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# STRATEGIC PLAN 2012-2014

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**The Strategic Plan 2012-2014**
**Executive Summary**


1. Introduction
2. Scientific Guidelines: Continuity, Evolution, Exploration
3. The Scientific Program (see also Technical Annex I)
4. The Inter-departmental Projects (see also Technical Annex II)
5. The Technology Transfer (see also Technical Annex III)
6. The Career Track
7. The Internationalization Program
8. The Education/training Program
9. The Evaluation Program (see also Technical Annex IV)
10. The Management Processes and ICT
11. Deliverables of the main platforms

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**INTRODUCTION**

Since its start-up, IIT has been constantly and progressively evolving. The first Strategic Plan (2005-2008) was dedicated to the construction of the central research laboratory and of the humanoid technology program based on 4 technology platforms. The second Strategic Plan (2009-2011) has consolidated the research program with the activation of 3 new technology platforms and with the launch of the national network of IIT laboratories. Overall the growth of the international reputation and of the visibility of IIT in the scientific community has been very encouraging, making it attractive to young researchers from all over the world and appealing as a partner for long-term, cutting-edge research collaborations for many institutions worldwide.

Today, after five and half years of activity and according to the original plan, IIT has successfully created the large scale infrastructure in Genova, a network of 10 state of the art laboratories countrywide, recruited an international staff of about 1000 people from more than 30 countries. The scientific output is also quite good. About 2000 publications and about 60 patents authored by IIT in the period 2006-2011 (including the first 3 years of start up dedicated to the construction of the laboratories and to the recruiting), more than 30 European projects approved and funded, about 60 national and international bilateral collaboration programs involving IIT, and an increasing number of grants form agencies and industries, witness the quick qualitative and quantitative growth of the Institute at international level (data at December 2011). This is also reflected by the Scimago International Ranking, which ranks the quality of the IIT research output among the top 380 research Institutions in the world (those awarded of the "green label of excellence" out of 2833) and among the top 15 in Italy (out of 124), for the observation period 2004-2008 (despite IIT started the scientific activity on December 2005). Similarly, the international database Web of Science Thomson Reuter ranks the director of the chemistry facility of IIT among the top 25 in chemists in the world (despite the very young age of 39). With such premises the next strategic plan has to consolidate the reputation of the institute and to put the basis for the future long term development of the IIT research.

Therefore, the next Strategic Plan (2012-2014) has a multi-fold target:

- To consolidate the excellent work accomplished by IIT during the previous scientific plans (2005-2008, 2009-2011);
- To reinforce the impact and the transfer of the results produced by the Institute to the international market;
- To reinforce the interdisciplinary nature of the research;
- To elicit a long-term vision, towards ambitious "*trip-to-the-moon-like*" programs, which will become the scientific *manifesto* of IIT at the international level;
- To enhance the internationalization of the Institute.

To do this the Strategic Plan has to properly balance *continuity, evolution* and *exploration*. Individual departmental activities must be continued towards curiosity-driven research, while joint interdepartmental research has to be reinforced to pursue high-risk ideas and long-term programs exploiting the unique interdisciplinary nature of IIT. Shared, ambitious objectives for the future will drive IIT forward in the next decade, enhancing synergies among research units (departments and network centers) and scientists from different backgrounds. Necessarily, such an evolution has to be smooth and progressive, and the present Strategic Plan is conceived to create the right conditions with which to start. This is sustainable both in terms of the overall evolution of IIT research, and of the completion of *all* research units. In 2015, indeed, the network of laboratories will finish its first life-cycle and evaluation phase, so that the Institute will be ready for a further integration and focus of the overall activity involving all its research units.

Exploration of new ideas and their transfer to society is part of the mission of IIT. Therefore great attention will be paid to constantly developing innovative partnerships with industry. In the context of the seven well-established IIT research platforms, these partnerships could include the following:

- **Robotics**, emphasizing mechatronics, human assistance, cognition, and security, will target automotive companies, rehabilitation/hospital structures, electronics and hardware companies.
- **Neuroscience**, devoted to cognition, diseases, and brain technologies, will target therapeutics (medical community), bio-diagnostic industries, and pharmaceutical industries.

- **Drug Discovery and Development** will target biotechnology, biochemistry and pharmaceutical industries.
- **Smart Materials** will target industries producing new functional materials, chemicals, polymers, and surfaces, as well as those engaged in functionalization of organic and inorganic materials.
- **Environment, Health and Safety**, focusing on issues related to the interactions between living systems and inorganic nanostructures, will target certification companies and international regulatory organizations.
- **Energy**, focusing on plastic photovoltaic and other portable low-cost energy-production devices will target automotive, computer, and electronics industries.
- **Computation** will target companies involved in security and automation, and will provide general support for design and modelling at IIT.

A notable by-product of the above activities will be the development *on-site at IIT* of new instrumentation for measurement, characterization and diagnosis, which has promising commercial potential for Technology Transfer (TT). On-site TT activity has already started through the establishment of joint programs with Leica and Nikon, two world-leading companies in optics and imaging.
Other important pillars of the Strategic Plan 2012-2014 are:

- The launch of selected high-profile international collaborations,
- The development of an advanced and diversified career track for the IIT staff,
- The consolidation of the evaluation of scientific and managerial activity,
- The reinforcement of the educational activities (IIT PhD program).

Based on the above points, the Strategic Plan 2012-2014 will be organized as follows:

1. An executive summary briefly outlining the vision of IIT for the future, the research activities of the Departments and Research Centers, the joint interdepartmental projects and the rationale for the new proposed national and international initiatives and managerial ideas.
2. Technical annex I: describing in detail the research activities carried out by the Departments and Research Centers, in continuation of the previous scientific plan (2009-2011). The evolution of the department activities naturally continues the ongoing research according to the mainstream lines of the Institute. Such research lines preserve a curiosity-driven character, though with strong focus on the development of transferrable technologies.
3. Technical annex II: describing the guidelines to enhance joint interdepartmental programs. Here we also propose a few high-risk, visionary, cross-disciplinary problems, exploiting the wide spread of expertise existing at IIT.
4. Technical Annex III: summarizing the key issues of the technology-transfer strategy.
5. Technical Annex IV: describing the key issues of the evaluation strategy and methodology.

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**SCIENTIFIC GUIDELINES: CONTINUITY, EVOLUTION AND EXPLORATION**

Current welfare has to face tremendous challenges and its sustainability is at stake in our private, social, economic, urban and physical environments. A great challenge comes from the ageing of the population. In fact, in 40 years nearly 35 per cent of the western population is projected to be over 60 years old. Paradoxically the positive outcome of welfare, i.e. an increase in life expectation, is now creating new challenge, namely: how to provide an ageing society with sustainable solutions in order to remain active, creative, productive, and above all, independent. We envisage that to achieve sustainable welfare will require a new class of machines and linked technologies, operating *inside, outside* and *aside* humans. These have to perform a multitude of assistive roles for humanity thanks to their capabilities to act and interact, physically, socially and safely with humans, in an ubiquitous yet unobtrusive, user-friendly and safe manner. Such a "robot ecosystem" will extend the active independent lives of citizens, bolster the labor force, preserve and support human capabilities and experience, provide key services in our cities, aid us to cope with natural and man-made disasters and maintain our planet.
To achieve this ambitious goal, IIT has to continue to develop the visionary scientific strategy initiated less than 6 years ago: robotics becomes an arena for science and an active technology provider to advance and validate natural principles and to translate them into synthetic ones. This vision is based on the systematic and federated contribution and continuous involvement of several disciplines and communities (represented by our platforms) that synergistically develop: Matter, Body, Brain and Mind, keeping in mind the future needs of our society. Matter includes nanotechnology, material science, and tissue engineering supporting a new *bodyware*; biomaterials, and micro- and macro-scale cell biology, for developing bioartificial hybrid systems; nanofabrication technologies for energy storage, production and harvesting. Body: includes sensing, actuation and the construction of new compliant, light yet strong morphologies. Brain addresses neuroscience, in particular systems neuroscience for understanding the design principles of the brain and the processes underlying its evolution, development, adaptation and maintenance in the real world; social neuroscience, cognition and sentience. Mind: includes the development and validation of the theoretical framework of sentience, communication, perception, cognition, emotion and action; the principles of human-human, human-robot and robot-robot interaction; principles of knowledge accumulation and expression.

With such a vision in mind, the Strategic Plan for 2012-2014 has to set up the IIT road map for the next 10 years, while establishing short- and mid-term milestones to be accomplished during the work. Setting up a visionary road map with robust and well-conceived intermediate milestones will help also to identify credible industrial partners. The key idea of the plan is schematized in Fig. 1. IIT is a cross-disciplinary institute. The merging of different cultural profiles in its teams allows IIT the unique ability to develop architectures . Developing architectures means adapting and elaborating different degrees of complexity according to the needs of the end users. Evolution is the most striking example of adaptive architectures. To fight off a viral infection we do not need arms, to lift a weight we need arms and eyes, to interact at different levels of behavioral sophistication we need an increasing level of awareness, i.e., increasingly sophisticated sensing networks with expanded computational capability. There is no interruption in nature in the chain that links single-celled organisms to humans; there is only a strong increase in architectural complexity, resulting in a functional form tailored to an organism's particular ecological niche. IIT has the know-how to create a new functional "ecosystem" of sophisticated architectures (from molecules to robots), whose increasing complexity covers the entire scale of living architectures existing in nature. We envision that these architectures could fulfil many future needs of humans.
Following the architecture/complexity axis of Fig.1, one can see different domains of such an ecosystem:

- Biochemically driven architectures (or biochemical robots), operating inside the body, will function as diagnostic and therapeutic aids to humans. This is the domain of the simplest architectures, based on nanochemistry and material science in combination with biochemistry, pharmacology and medicine.
- Animal-like robots, at mm scale or bigger, will support humans in exploration, services and low-complexity operations, exploiting basic interactive capabilities and sensing networks. In this case the architecture will grow towards more sentient and interactive machines.

- Humanoids pave the way towards sentient machines, where the most complex architecture requires a sophisticated integration of state-of-the-art multi-sensory networks, brain/cognitive models, biomimetic materials, etc. Here the grand challenge is the integration of brain and body, at the top of the architecture.
- Wearable robots (e.g., exoskeletons) will be one of the possible different architectures to be developed. The extent to which these will be interconnected to the central nervous system (e.g., for prostheses) or independently operated, will be again a matter of architecture.

Our ecosystem is thus *human-centric*; it includes artificial architectures operating inside the body, outside the body or beside the body. These systems will be profoundly different in size, composition, operational mechanism and functionality, self-awareness and sentient capability. However, they will all share the common characteristics of being:
*1) human-safe and human friendly*
*2) ethical*
*3) architecturally adaptive (i.e., capable of evolving)*

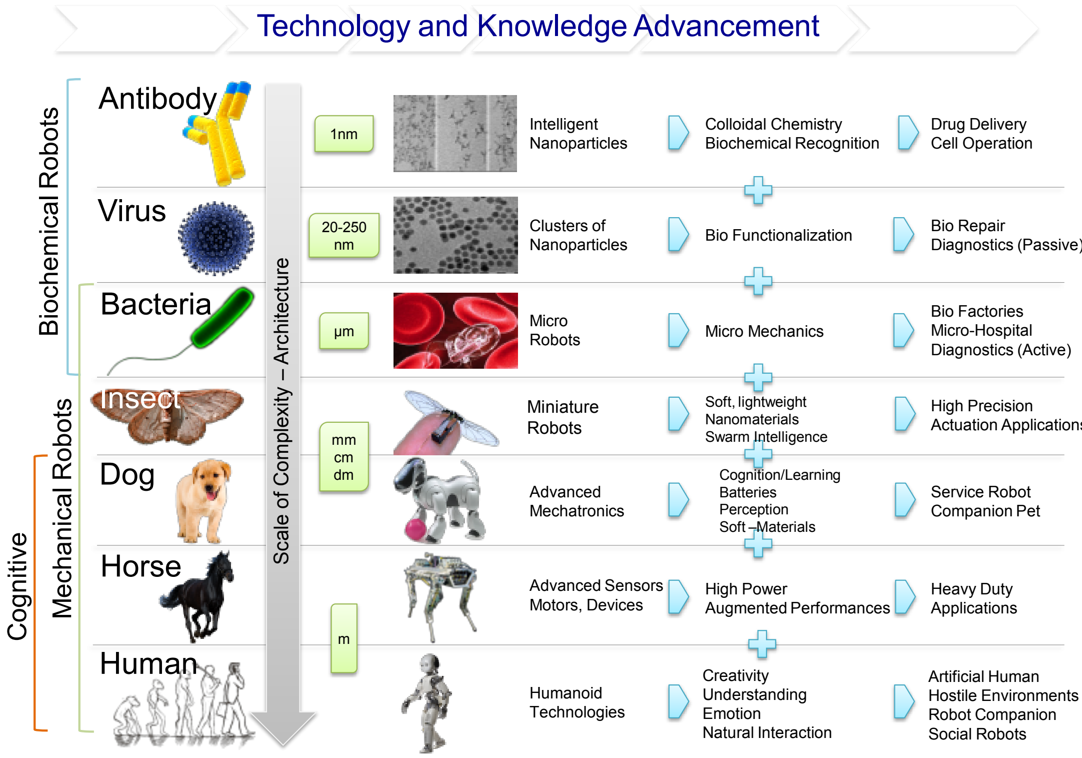


*Fig.1 The overall vision of the plan relies on the idea that, for the first time, robotics becomes an active technology provider rather than a passive technology use. The plan is based on the systematic and federated contribution and continuous involvement of many different disciplines and communities, such as: chemistry and biochemistry for new molecules and nanoscale structures of different functionalities; robotics and the morphology-behaviour relationship in living systems; nanotechnologies, material science and tissue engineering for new body-ware; biomaterials, and micro- and macro-scale cell biology, for developing biological-artificial hybrid systems (e.g.,. bio-hybrid sensors and actuators, such as artificial muscles); nano-fabrication technologies for energy storage, production and harvesting; neuroscience for understanding organizing principles of sensory-motor systems at multiple scales (cell-scale, tissue-scale, system-scale); systems neuroscience for understanding generic design principles of brains and the processes that allow their evolution, development, adaptation and maintenance in the real world; social neuroscience for*

understanding cognition and principles of human-human, human-robot and robot-robot interaction.
*It is expected that in about 10 years new body-ware and mind-ware technology will be transferred and applied to the development of several new embodiments, such as a powered suit, advanced prostheses or a legged vehicle for environmental exploration and rescue. These technologies will specifically target emergent societal challenges, such as the sustainability of urban services, environmental care and monitoring, natural disasters, and the general safety of the population.*

With these key ideas in mind we can build the vision depicted in Fig.1. The vertical axis sets up the road map of the architecture/complexity needed for a specific task. The horizontal axes define the technical and scientific domains that are relevant for the accomplishment of a specific architecture, as well as some potential end users. This scheme should help in identifying companies, killer applications and measurable milestones. There is of course a risk of dispersion. However, we are firmly convinced that the combined efforts of more than 1000 researchers, distributed across 10 state-of-the art-laboratories, will provide the greatest benefit to society by *directly* confronting large-scale challenges rather than by adhering to safe, circumscribed projects, with companies and universities advancing incrementally. Large-scale, ambitious projects are the trend worldwide, both in major research institutions and leading funding agencies. For example, the EU is launching the new "flagships" programs, 10-year projects that tackle extremely ambitious and high-risk ideas, such as artificial brains, "guardian-angels" nanosystems, graphene technologies, future information and communications technology (ICT), medical ICT, and robot companions (which is represented by IIT).

As a concluding point, Fig.2 shows the actual mapping of the IIT research platforms onto the scientific vision described above. Here it can be seen that the new long-term scientific strategy evolves naturally from the 7 platforms of the previous scientific plan.

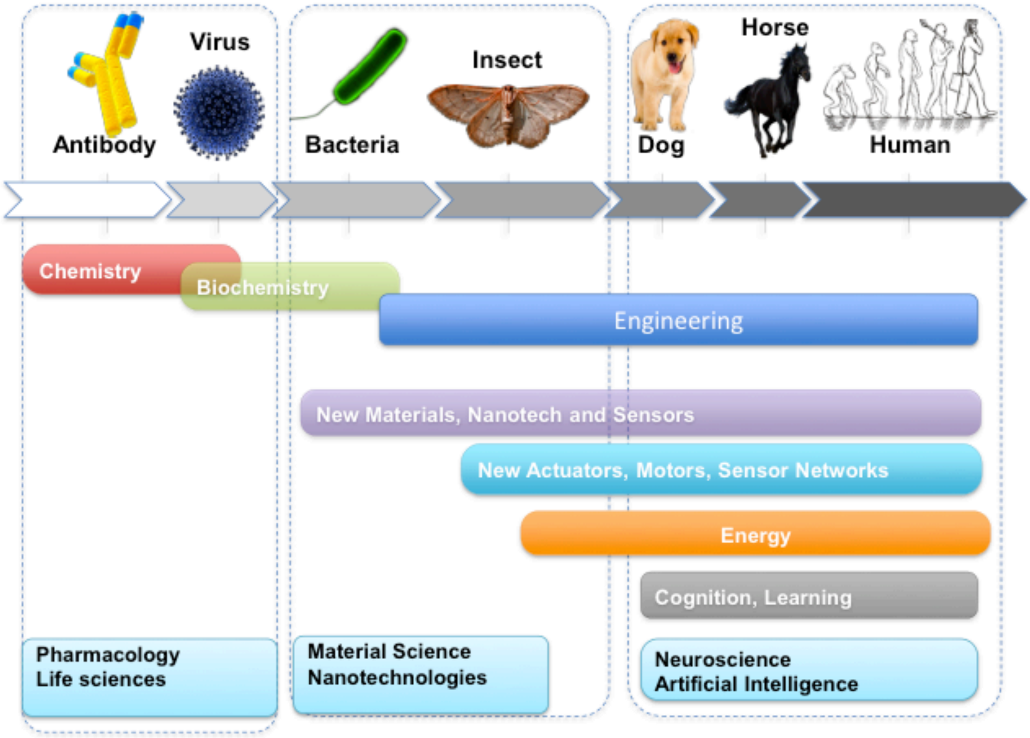


*Fig.2 Mapping of the IIT research platforms on the future scientific vision. Robotics spans the second and third columns.*

**3. THE SCIENTIFIC PROGRAM**

In this section we briefly summarize the main activities carried out by the IIT research units within the framework of the technology platforms (grouped into thematic macro-areas: **robotics**, **life sciences** and **nanobiotech**). A detailed description of the scientific activity is given in the Technical Annex 1.

- **The Robotics Platform**

Robotics at IIT has a world-leading position, which has to be maintained and even enhanced. The scientific plan for 2012-2014 aims at further improving and consolidating IIT's leadership in the field. The strategy for the next three years is based on the following points:

1. The two departments, Robotic Brain and Cognitive Sciences (RBCS Sandini) and Advanced Robotics (ADVR, Caldwell) will continue their scientific activities and ongoing research programs in the field of mind-ware (brain, cognition, behaviour, learning, etc.) and body-ware (mechatronics, motors, physical performances, etc.), respectively
2. A new, shared facility, mainly consisting of a selected team of engineers and researchers from both departments, will take charge of a common platform (iCub) that will consolidate the most promising research achievements obtained by the robotics platform at large. The iCub team will deliver regular releases of new versions of the humanoid, with improved cognitive and physical performances. This new organization of the robotics platform has the advantage of continuing the independent, curiosity-driven research of the two departments, while supporting a third body responsible for merging and integrating new technologies developed at IIT into a common humanoid platform. We expect to generate regular releases of a new, improved version of iCub every few years. The new releases will reinforce the iCub platform in the international community, and will keep the iCub ahead of its competitors. The shared robotics facility is also a candidate for a robotics spin-off of IIT, in light of the increasing worldwide demand for iCub humanoids and components.
3. The robotics platform will continue to reinforce interdepartmental collaborations, both in the neuroscience area (for cognition and behavior) and in the nanotechnology and material-science area (for bodyware and new materials). These collaborations will help to provide higher performance technology solutions for future versions of iCub.

The activity of RBCS and ADVR are briefly summarized in the following.

**RBCS (Robotics, Brain and Cognitive Sciences):**

The general theme of the research activity of RBCS will be "Motor Cognition and Interaction". This is in turn divided into three main research streams:

i) Cognitive Robotics (with a focus on actions in close contact with humans),
ii) Human Cognition (with an emphasis on manipulation-related skills),
iii) Human-Human and Human-Machine Interaction and Interfacing

These streams of research are characterized by an interdisciplinary, human-centric approach aimed at advancing knowledge in the area of artificial systems. This will be achieved by 1) investigating human motor and perceptual abilities and 2) implementing the ability to learn and interact naturally with humans in an autonomous humanoid robot (the iCub).

The RBCS approach will follow these guidelines:

- Human-centric research and technology addressing the level of complexity of the humans and their (social) behaviour for future integration in humanoid robots.

- Sharing science and engineering objectives by addressing topics of mutual interest to neuroscientists studying the human brain and body, and engineers implementing artificial cognitive robots.
- Studying robot actions in close contact and interaction with humans (such as motor and sensory rehabilitation).
- Focus on systems that can learn and develop (not only execute actions).

Following these guidelines, RBCS researchers will investigate human manipulation and interaction abilities and will implement realistic models in humanoid robots, with a focus on the interaction and interfacing of humans and machines. The central rationale of RBCS's interdisciplinary research plan is that there is much to discover about the human ability to explore the world manually and to interact through gestures and speech, and that the knowledge that is gained of these human abilities will drive developments in robotics.To achieve this goal, RBCS's new research plan, built on the "three streams" structure of the past plan (i.e., robots, humans, interaction), is organized as much as possible around research topics explicitly spanning *across* the three streams. The new research plan is structured along four main themes:

1. **Manual and postural actions**. This research theme is devoted to the study of the execution and understanding of goal-directed actions, in particular mono- and bi-manual exploration, in both humans and humanoids. Reference sub-topics are: computational motor control, variable compliance, sensorimotor learning, motor synergies and syntax, oculomotion and spatial attention, hand design.
2. **Perception during action**. This theme will investigate how sensory information is exploited during actions to stress the unitary nature of perception and action during development, learning, motor execution and motor understanding. Reference sub-topics are: perception of self and space, attention, perception of time, object's affordance, sensorimotor development, perceptual rehabilitation and sensory aids, computational principles and neuromorphic sensor technologies.
3. **Interaction between and with humans**. This theme will investigate how humans interact and how machines can interact meaningfully and safely with humans on the basis of a shared representation of goal-directed actions (including speech). It will also examine how shared representations are built during sensorimotor and cognitive development. Reference sub-topics are: action mirroring and imitation, speech perception and understanding, grammatic structures shared by action and language, interpersonal physical interaction, neuromotor rehabilitation and related technologies.
4. **Interfacing with the human body**. The activity here is the continuation and expansion of the work on brain machine interfaces carried out in recent years. This activity will evolve along different research paths, some of which are carried out in close collaboration with other IIT research units, such as the Neuroscience and Brain Technologies Department. Reference sub-topics are: neural computation, neural correlates of motor cognition, electrophysiology of bidirectional neural interface, neural rehabilitation and technologies for neural interface, tissue engineering.

**ADVR (Advanced Robotics):**
The research in the Department of Advanced Robotics (ADVR) is currently arranged into four themes.

i) Humanoid Technologies,
i) Biological Inspired Technologies,
ii) BioMedical and Micromanipulation Technologies,
iii) Haptics and VR Technologies.

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The Humanoid technologies will have as a primary focus the development of innovative hardware for the new generations of iCub, capable of running, jumping, climbing, etc. This requires the development of both new actuators and motors and of new components and mechanisms (feet, legs, etc.). Sensing and locomotion control will be developed in order to provide the robots with locomotion capabilities that are as dextrous and accurate as possible.
The biologically inspired technologies will be based on the development of quadrupeds (animal-like robots) exploiting new motors, hydraulic technologies and new architectures, to be used in different heavy-duty applications.
Finally, teleoperation, exoskeletons and haptics will also be developed to provide a complete portfolio of technologies to the humanoid platform.

**iCub central facility**
Following the success in establishing the iCub platform as a reference humanoid for robotics research worldwide, IIT will form an interdepartmental development unit to accelerate and coordinate the integration of new components/technologies into the iCub platform. For the start-up the central facility will be guided by a steering board composed of representatives of different IIT research units, coordinated by a RBCS senior scientist. The facility will include all activities and people previously allocated to the development, production and maintenance of the iCub platform. The steering board will establish milestones for the development of the iCub, and will decide on the integration of new materials and technologies. All research activities related to the implementation of robot cognition in the iCub will remain part of the RBCS plan, together with certain research activities on the iCub mechanics related to manipulation. New hardware/bodyware will come primarily from ADVR, according to the architectural design agreed by the facility. Details are reported in Technical Annex II.
The activities of the Robotics Platform will be supported by the research carried out in the nanobiotech facilities (PAVIS and Nanophysics) and in the network, particularly in the centers at Politecnico di Milano (new materials and artificial eyes), at Politecnico di Torino (aerospace robotics), at Scuola Superiore S. Anna (microrobotics), at Lecce University (smart materials) and at Napoli (bio materials and artificial tissues).

- **<u>The life science platforms: Neuroscience and Drug Discovery, Development and Diagnostics</u>**

Life science activities at IIT are carried out through two platforms: *Neuroscience*, represented by the Neuroscience and Brain Technology (NBT) Department and several network centers, and *Drug Discovery, Development and Diagnostics (D4)* represented by the Departments of Drug Discovery and Development (D3), Nanochemistry, Nanophysics, Nanostructure, PAVIS and by a few network centers.
Neuroscience has a threefold target: i) to develop cognition, learning, behaviour and intelligence-related topics for robotics, ii) to improve basic knowledge in neurophysiology and neurodegenerative diseases, and iii) to explore new technologies to study the brain and advance brain-machine interfaces (neurotech). The pharmacology activity deals with the discovery and the development of new molecules for pain killers, anti-inflammatory drugs and neurodegenerative diseases, with a strong orientation towards market transfer and start up. Both platforms develop and make use of advanced diagnostic tools, either biochemical or instrumental, which are common to various research programs (drug delivery, early diagnosis, single bioevent detection, bioimaging, etc.).
Following the rapid growth of the Neuroscience platform, the next scientific plan aims at consolidating the basic scientific work carried out so far, and at reinforcing technology-oriented activities, through strong interdisciplinary projects involving different centers and departments in collaboration with NBT. Concerning D3, whose activity started in the early 2010, the main target is to consolidate its international reputation and to start technology-transfer activities based on new drugs discovered by the department.

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The activities of the Neurosciences and D4 platforms will be supported by the research carried out in the network, particularly in the centers at Trento (cognitive neuroscience and psychophysics), Parma (cognition), Politecnico in Milano (new materials and artificial eyes), IFOM-IEO Campus (diagnostics, genomics), NEST - Scuola Normale Superiore (drug delivery, bionanotechnologies), Roma La Sapienza (Diagnostics and biotech), Lecce University (nanotoxicology), and Napoli (Drug delivery).
In what follows we shortly summarize the activities to be carried out by the two departments.

**NBT (Neuroscience and Brain Technologies):**

According to the recent revision of the NBT department, it has been decided to reduce fragmentation of the activities, to reinforce some technology-oriented research and consolidate some excellent programs/results achieved so far. Therefore the activity of NBT will be split in two main areas, the Synaptic Neuroscience coordinated by F. Benfenati and the Advanced Neurotechnologies coordinated by J. Assad. The Synaptic Neuroscience will face very fundamental topics, and will be mainly focused on three main research lines:

- Molecular mechanisms of synaptic plasticity and computation
- In-Vivo neurophysiology, plasticity and behavior
- Mechanisms and early markers of brain diseases

The Advanced Neurotechnologies area will develop a few explorative, high-risk programs with strong high-tech content, in collaboration with the Synaptic Neuroscience area and with other technology oriented research units of IIT. The main lines will be:

- Reverse engineering of the brain
- Optointerfaces and new optogenetic probes
- Technologies for sampling, manipulating and stimulating neural activity and coding schemes

**D3 (Drug Discovery and Development):**

D3 was created with the ambitious target of bridging the gap between academic and industrial research in drug discovery, with specific attention to strategic therapeutic areas such as pain, inflammation and neurodegeneration. To achieve the objective of creating a research environment conducive to innovative drug discovery, in the first 18 months since the start of its activities, D3 has recruited scientists with both industrial and academic backgrounds, and has implemented a matrix-based organization in which scientists from different functions interact productively on specific goal-oriented projects.

The three main functions are:

- Computational chemistry and biophysics
- Medicinal chemistry
- Pharmacology

These are functional to three classes of projects:

· *Advanced Projects* have as their objectives (1) the optimization of "lead" compounds; (2) the identification of suitable candidates for preclinical development; or (3) the coordination and performance of preclinical "de-risking" activities (e.g., toxicological, pharmacokinetic or pre-formulation studies). These include: FAAH inhibitors for pain and NAAA inhibitors for inflammation. Though extremely early, these projects have already yielded important results – including publications in high-impact journals such as Nature Neuroscience and PNAS, patent applications and early success in preclinical development activities.

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DI TECNOLOGIA

· *Exploratory Projects* aim at the identification, validation and characterization of potential disease targets (enzymes, receptors, biological pathways). These comprise: FLAT inhibitors, NAPE-PLD modulators, Dual FAAH-Cox inhibitors, Clock modulators and Dual NR2B/AchE inhibitors.

· *Enabling Projects* have as their objective the creation of novel computational tools for drug discovery. These tools are utilized to advance D3's research, and will eventually be made available to the scientific and pharmaceutical community. The most relevant Enabling projects are: Electrostatic modelling of biomolecular systems, Free energy of protein-ligand binding and next-generation 3-dimensional QSAR.

- **The nanotechnology and materials science platforms: Smart Materials, Energy, Environment Health and Safety (EHS)**

These platforms were launched in the 2009-2011 scientific plan with the aim of supporting the evolution of the robotics, neuroscience and diagnostic activities of IIT. To achieve this aim, four facilities , Nanochemistry, Nanophysics, Nanostructures and Computer Vision (collectively called the "Nanobiotech facilities") were created, providing a complete, state-of–the-art scientific and instrumental background to the Institute. After less than three years the facilities have gained an impressive international reputation, as evidenced by a large number of high impact publications, grants, and patents. The facilities have demonstrated the capability to combine independent research at the cutting edge of their respective fields, with the production of methods, instruments and tools useful to the entire IIT community. Due to their central role in the interdisciplinary vision of IIT and to the excellence reached in their own research programs, the facilities will play an increasingly important role of *glue* in the scientific vision of IIT, and of *accelerators* of the new high-risk ideas in the 2012-2014 scientific plan. In what follows we summarize the mainstream activities of the Nanobiotech facilities.

**NANOSTRUCTURES:**

The Nanostructures research group has recently reported outstanding results (e.g., two papers in the Nature publishing group during the start-up phase) in the very innovative and strategic field of investigating molecules and nanosystems with ultimate spatial and chemical resolution. This opens the way to a brand new stream of applications that span the entire Institute, including biomedical imaging, drug delivery, material characterization, and instrument development. The backbone of the nanostructures research activity is based on the idea that the entire research pipeline of novel devices, including design, fabrication, chemical and physical characterization and application to specific domains, will be carried out *within* the facility.

The prototype areas where this general approach is followed are:

1) Devices for control of efficient delivery and exchange of energy to the nanoscale (including transport properties).

2) Design and development of new instrumentation (based on nanoscale technologies), for obtaining physical, chemical and biological information with spatial resolution between 10 nm and 1000 nm. Spectroscopies under development include SERS, SEIRA, THz scanning-probe based, CARS, and RRS.

3) Devices for single molecule detection from highly diluted solutions in single and complex component mixtures based on super hydrophobic substrates.

4) Devices for single molecule detection from biological systems such as living cells and tissues.

5) Nanodevices with low background noise to enable optogenetic studies down to single molecule excitation.

6) Microfluids and optofluidics for the development of novel devices that combine optical tweezers and microfluidics, applied to cellomic studies (such as Circulating Cancer Cells, for *in vivo* enrichment of serum for early cancer detection and drug delivery based on nanoparticles.

7) Numerical simulations for device design and for numerical problem solving, for all IIT departments.

8) Metal-semiconductor hybrid nanosystems.

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**NANOCHEMISTRY:**
Nanochemistry has been growing extremely quickly during the past few years, becoming one of the world-leading labs in the field of chemical nanotechnologies. The state-of-the-art facility for colloidal chemistry and biochemistry allows IIT to synthesize almost all class of colloidal nanoparticles (oxides, semiconductors, metals) with highly controlled shape, size and composition, enabling new applications relevant to all platforms. For the next Strategic Plan Nanochemistry will develop a strong interdisciplinary program targeting three main fields:

1. Nanoparticles for intelligent drug delivery
2. Nanoparticles for energy
3. Novel self assembled nano-materials

Each of these fields represents a "hot spot" of international research in which IIT has a leading role. Each also provides a unique opportunity to feed research activities in other IIT departments and network centers, including intelligent drug delivery in collaboration with D3 and NBT, energy in collaboration with Robotics, and new nanocomposite materials in collaboration with several centers of the network (e.g., at Politecnico di Milano, Lecce University) and with Nanopyhsics and Nanostructures.

**NANOPHYSICS:**
The strongly interdisciplinary scientific activity of the Nanophysics laboratories is spread across several strategic programs of the Institute. The planned activities for 2012-2014 focus on two main streams:

- Nanocomposite (smart) materials: from nanoparticle synthesis to 3D scaffolds
- Novel nanoscopy-devices and instruments for accessing the nanoscale, from tissue/organ size (cm) to single molecule precision (nm).

The first research line has a predominantly material-science character and exploits the Nanophysics group's expertise in material physics and chemistry of surfaces, polymer nanocomposites and hybrid materials. The second research line targets the design and realization of new concept devices and instrumentation for nanometer-resolution spectroscopy of living matter. In both cases the general aim is to develop new materials and instruments of relevant industrial interest, to be applied to "human" problems such as toxicology, neuro-tech implantable devices, new multifunctional and "tunable" materials (actuators, sensors, portable/converting energy), nanocarriers and scaffolds for smart drug delivery (actively/passively triggered), intelligent (bio)probes, implantable (bio)substitutes, early stage detections of diseases and "therapeutic" nanodevices.
The activities of the Energy, Smart Materials, EHS and Computation platforms will be supported by the research carried out in the network, particularly in the centers at Politecnico di Milano (organic materials), at Politecnico di Torino (materials and energy), at Lecce University (nanotechnologies and energy) and at Napoli (new materials).

**PAVIS (Pattern Analysis & Computer Vision):**
The research pursued by the Pattern Analysis and Computer Vision (PAVIS) facility deals with computer vision and pattern recognition/machine learning topics, with applications to video surveillance, biomedical imaging, neuroimaging and pattern analysis (bioinformatics). Based on the department's expertise in probabilistic and statistical techniques, learning and inference, classification and clustering, geometric and 3D data management, PAVIS cans deal naturally with the analysis of images, video sequences, and other types of structured and unstructured, so allowing it to cope with many application scenarios.
The activity will be useful to many research activities at IIT, such as vision and recognition for robotics,

biomedical imaging for neuroscience, image analysis for microscopy, optical and structural nano-characterizations and scanning-probe imaging.

**4. THE INTER-DEPARTMENTAL PROJECTS**

The interdepartmental projects will be the basic instrument to cross-fertilize the research activities of IIT in different fields and to develop the long-term, high-risk program described in the introduction. The progressive merging of the mainstream research lines into the long-term vision of IIT has to be sustainable and compliant with regard to the individual requirements and expectations of all our research units. As such the strategy for the construction of a strong interdepartmental program of activities will be based on the following criteria:

- Bottom-up construction of a portfolio of joint ideas/programs (interdepartmental and/or involving network centers) consistent with the development of the long-term IIT vision.
- Selection of a limited number of joint ideas/programs through dedicated internal calls (every year), under the supervision of the scientific director with the help of the Scientific Technical Committee (STC).
- Support of the program (max on a two year basis) through dedicated postdoctoral positions co-tutored by two scientists belonging to different research centers/departments
- External peer-evaluation of the results, aimed at establishing whether the exploratory joint programs might generate longer term interdisciplinary research activities to be incorporated into the next scientific plan (or into a revised version of the present one).

The joint programs must have an inherent exploratory, high-risk, long-term character, and must exploit the interdisciplinary characteristics of IIT involving at least two different departments/research units. Also, the rationale for an interdepartmental project has to match with the IIT vision. If successful, the shared postdoc positions will also provide highly interdisciplinary junior researchers for the future recruitment of IIT. Also, the ability to propose and successfully develop high quality joint interdepartmental programs that are well integrated into the overall vision of IIT will become a key element for the evaluation of the scientific activity of the departments/research units.

A preliminary, non-exhaustive compilation of possible joint ideas/research programs is given in Technical Annex II. This is expected to evolve quickly in time, depending on the results of the departmental activities and on the increased interdepartmental communication/exchange of ideas generated by the initiative. We point out that the iCub central facility is also described in Technical Annex II, even though this should not be considered an exploratory project but an interdepartmental infrastructure.

**5. THE TECHNOLOGY TRANSFER**

Technology Transfer will have a key role in the scientific plan 2012-2014, concomitant with the completion of the Technology Transfer Office, which will be fully functional by the end of 2011. According to the guidelines of the Technology Transfer recently approved by the IIT Foundation, the following high priority actions are envisaged:

- Set up of a web-portal for direct contact and dissemination of information about inventions and patents generated at IIT, for public demand.
- Start up of new companies based on IIT intellectual property, involving participation by IIT researchers.
- Launch of pre-clinical studies of new drugs.
- Creation of a network of investors and companies interested in the IIT activities through public-IIT events (twice a year).
- Creation of new joint laboratories with national/international companies.

The strategic guidelines of the Technology Transfer are summarized in Technical Annex III, according to the guidelines approved by the IIT Foundation in 2010.

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## 6. THE CAREER TRACK

The offer of a viable career track will be a key element to maintain the international attractiveness of IIT in recruiting and retaining top scientific talent. The international benchmarks for prestigious scientific institutions include world-class scientific excellence, state-of-the-art facilities, international scientific environment and appealing job opportunities. In the early phase of IIT the scientific staff has been recruited based on a conventional three-level scheme:

- 5-year contracts for the senior positions (researchers, team leaders, senior scientists and coordinators). These positions are evaluated yearly with part of the salary variable.
- 2+2 years for the postdoctoral positions.
- 3 years for the PhD positions.
- Technicians and administrators have been recruited based on a standard employee contract, which may turn into a permanent position after three years.

All scientific positions have European-standard salary, including an objective-related bonus, and are evaluated periodically by an international panel. Contract renewal and career progress depends solely on the evaluation, as described in detail in the evaluation policy of IIT.

The IIT staff at the end of 2011 consists of about 1000 researchers, with a clear pyramidal structure. About 50% of the researchers are at PhD and postdoc level, thus guaranteeing high turnover on a 2-year basis and low average age (around 33 years for the entire IIT in 2011). Researchers, team leaders and senior scientists comprise ~300 staff members of higher seniority, along with ~80 technicians and ~120 administrative staff members. For the senior positions there is also turnover, albeit on a longer time scale. Thus IIT has the need to retain a selected number of top scientists, and to attract internationally acknowledged researchers from prestigious institutions worldwide.

A typical problem to be faced is the recruitment of researchers who have a tenure/permanent position elsewhere, or the retention of IIT scientists for periods longer than the maximum leave of absence allowed by the institution of origin (in other words, top-level scientists are unlikely to abandon a permanent position to join IIT for 5 years). For the future, the following career options could be proposed and developed, in addition to the already existing job offer menu at IIT:

- Joint appointments → for senior levels, building specific agreements with universities to have IIT researchers keep part-time professor appointments at their university of origin. IIT will provide the extra salary and the research budget, the University will provide retirement fees and health insurance and part-time salary with permanent appointment. The researcher will develop the research activity entirely at IIT, with some teaching duty at the university.
- 10 years contracts → A limited number of long contracts (about 10%) to attract talented young scientists or very clever senior researchers at the end of their career, with long term appointment (not renewable).
- Permanent positions → IIT has the possibility to turn 10% of its scientific staff positions into permanent appointments in the future (at steady state). A first call for such positions could be launched in the period 2012-2014.

## 7. INTERNATIONALIZATION PROGRAM

To date IIT has more than 60 bilateral scientific agreements with international research institutions, some of which could grow strategically. In most cases these agreements aim at encouraging the exchange of young researchers between groups/departments with a longstanding tradition of collaboration. To enhance the rapid growth of IIT's international reputation, further effort is needed to create an international network of high-level institutions that share IIT's vision.

International programs should be built based on a reciprocal assessment of scientific interest in specific research areas. This requires a careful confidence-building process, based on existing collaborative track record, direct knowledge among key scientists and principal investigators, and mutual institutional knowledge based on official bilateral meetings/workshops involving the top level management of the two institutions.

The specifics of the international agreements will depend primarily on the nature of the partner institution: academic institutions might have more focus on education and exchange of junior staff, whereas pure research institutions might focus more on joint research labs/programs or particular areas of research. Funding scheme, IP rules and program governance could thus change substantially and should be tailored to the specific initiative. However, it is expected that a selected number of agreements with world-class institutions could definitely boost the international visibility of IIT.

To date a few preliminary contacts are established with the following institutions:

1. University of Irvine California. Scientific area: pharmacology, drug discovery.
2. Max Planck Gesellschaft. Scientific area: instrument development for spectroscopy, nanoscopy, biological applications.
3. Harvard University. Scientific area: neuroscience.
4. Massachusetts Institute of Technology. Scientific area: vision, machine learning, human machine interface.

**8. THE EDUCATION AND TRAINING PROGRAM**

Education and training is a very important issue for IIT, because PhD students and internships are crucial to the development of the research and the vitality of the insitution. After a positive evaluation of the IIT-PhD school by the Comitato Universitario Nazionale, the IIT proposal is now under examination by the ANVUR (Agenzia Nazionale per la Valutazione del sistema Universitario e della Ricerca).

In order to consolidate the training proposal currently underway at IIT, the Foundation aims to establish the IIT International PhD School, called Scuola Internazionale di Perfezionamento on "HIGH TECHNOLOGY APPLIED TO HUMAN AND HUMANOID SYSTEMS" as a first-class, post-graduate studies program open to graduates from around the world.

Since the beginning of its activities, IIT has actively contributed to the training of young graduates, supporting and directing the training of over 200 students, thanks to specific agreements with universities and institutes of excellence. The proposal of the IIT PhD School "Scuola Internazionale di Perfezionamento" organised and run entirely by IIT allows the introduction of important new aspects of training:

- **interdisciplinary approach:** this is essential to promote synergy between seemingly unrelated fields, such as medicine and engineering, structural and cell biology, biochemistry, mathematics, physics, materials science, psychophysics and computational calculus. The educational programs of the School will expose students with different backgrounds to the various disciplines, allowing them to converse with each other and to carry out collaborative work. This type of approach has already been tried successfully in other countries and is the general direction followed by several European and North American schools.

- **the close link between basic and applied research:** this is a key element in ensuring the immediate acquisition of specific know-how and the learning of the basics of scientific experimentation, such as designing and conducting independent research projects, solving experimental and technological problems, and implementing and applying new technologies. Training at the School should therefore include rotations in different research laboratories as a necessary aspect of training.

- **the international dimension:** the School offers the fundamental opportunity of international scientific exchanges through the organization of international seminars, study periods and work abroad.

During the 4-year course at the School, students can access state-of-the-art instrumentation and intellectual resources typical of a multidisciplinary and international centre. Interaction, cooperation and mobility between IIT centres will be encouraged to train scientists who are able to study problems from a non-traditional perspective and to solve them in an original way.

One of the main goals of the PhD School is to engender a highly interdisciplinary field in which scientists contribute to the discovery of new technologies in different sectors as well as the implementation of new artificial hybrid systems (i.e., bionic). These could deal with topics as diverse as early diagnosis of neurodegenerative diseases, energy conservation to preserve the environment, support for an aging population, and improvement of the quality of life for the disabled (e.g., development of prosthetics and rehabilitation therapies).

The ultimate purpose of the PhD School is the training of a scientific elite that will rise to the senior level in academic research centres, in clinical centres of excellence and in a wide-spectrum of technological industries (from nanotechnology to the biomedical industry, and from aerospace to the energy sector).

**Structure of courses**

The proposed courses will be organised following the training model developed in previous cycles and depending on the general structure:

1. Basic (elementary/core): aimed at creating a common foundation in students with different training. The courses will focus on issues of importance such as engineering/robotics, neuroscience, materials science, biochemistry/biology, and nanotechnology.
2. Advanced: focused on the state-of-the-art of core research areas of the School.
3. Practical: centred on the application of the various disciplines. This offers students the possibility to hone their practical skills through the realisation of products, designs, or specific experiments (e.g., becoming familiar with a particular instrument or technique).
4. Seminars: a series of lectures given by qualified scientists in various disciplines on topics of particular interest, or to provide students updates in particular areas (e.g., intellectual property, patenting, funding opportunities).

**Basic elements of the training**

- The placement of students in the experimental research process, through the design and performance of a research project;
- The introduction of new subjects of study which form the technological core of modern science in its entirety, such as nanotechnology, materials science, proteomics, high-throughput screenings, imaging, drug design, as well as humanoid robotics;
- The teaching of elements of financial management, patenting, intellectual and industrial property;
- The presence of foreign students and teachers: the course of specialisation will draw on the contribution of foreign teachers, both on the basis of specific agreements with foreign scientific institutions and in a personal capacity.
- The use of English as the official language of courses.

## 9. THE EVALUATION PROGRAM

Evaluation is a key issue in quality assessment at IIT. The 2012-2014 plan relies on the constant and careful assessment of the scientific activities made over the last years. Namely:

- Department Evaluations by the Scientific Technical Committee panels:
- *Dec 2008:* panel for Robotics (members from Karlshrue, Stanford, MIT) → Outcome Very Positive
- *Jul 2010: special assessment* panel for Department of Telerobotics and Applications (members from Stanford, MIT, Berkeley) → Outcome negative, Department closed
- *Sept 2010:* panel for Robotics (members from NIH, MIT, Stanford) → Outcome Very Positive
- *Sept 2010:* panel for Neuroscience (members from Roche, Harvard, MIT, ETH-Zurich, NIH, Yale) → Outcome overall positive with recommended changes in the strategy. A dedicated international Advisory Board has been constituted to this aim, which completed the job in June 2011.
- *Planned: on site visits*
- *Nov 2011:* panels for the nanobiotech facilities (MIT, Tokyo University, Munich University, Brown University)
- *June 2012* : panels for D3 (to be formed)
- General Institute evaluations
- *June 2007*: Ministry Evaluation Committee (members from ISI/Torino and Harvard →confidential report to the Ministry. Oral report to the scientific director of IIT, president of IIT and Ministry of Finance very positive → The Institute was funded entirely after such evaluation.
- *June 2008/May 2009*: 1° Evaluation Committee (members from McKinsey, Weizman Inst., Università di Napoli, Avago Technologies Ltd, Roche pharma) → Outcome very positive
- *May 2011-May 2012:* 2° Evaluation Committee (members from EPFL, Università di Milano, STMicroelectronics, Usi-Lugano, Weizman Inst., MIT)
- *Nov 2011* ANVUR has started the evaluation of IIT

The above evaluations have been important to identify the weak points of the scientific strategy, to apply the needed corrections and to consolidate the vision of the institute as presented in the 2012-2014 plan.

In 2012 the procedures for the evaluation of the scientists, managers, employees and research units will be standardized in order to have uniform criteria and ranking methods. This is particularly difficult due to the different nature of the research activities carried out in our research units, and the different evaluation parameters characteristic of the disparate (e.g., robotics vs. life sciences). However, the considerable experience gained in the past few years, with the yearly evaluation and the on-site visits by external panels, will help in producing a second updated release of the "Documento Unico di Valutazione", where the evaluation schemes will be improved in a quantitative manner. A new custom-tailored data base for the publications analysis is presently under test and will be operational by January 2012, in order to avoid multiple searches on different public databases. The program will also generate basic bibliometric indicators and will enable author/topic/affiliation/date search directly, thus facilitating the departmental/staff evaluation. By 2012 this database will become the official repository of the output of IIT's research for both

public and internal use.
The standard evaluation procedure based on the yearly individual assessment by the STC for the directors (or by the group leaders for more junior profiles) will be supported by a quantitative evaluation model allowing normalization of different sectors and uniform ranking. A similar evaluation scheme will be set up for the administration profiles. This activity will benefit the new organization of the HR office, which will be operational by November 2011.
The agenda of the on-site evaluation by external panels will be planned in detail, so as to have well-identified milestones/deliverables for the future.
In addition to the internal evaluation program, IIT is expected to be evaluated by the ANVUR in 2012, and by the Comitato di Valutazione della Fondazione in 2012.

**10. MANAGEMENT PROCESSES AND ICT**

IIT has finalized its start-up phase and is rapidly shifting towards a more mature and complex organization. The rapid growth of the infrastructures, headcount, the creation of new IIT centers distributed throughout the country are challenging the organization's ability to maintain excellence, both in core scientific activities and in support processes. The success of organizational growth is therefore heavily dependent upon the quality of the processes, policies and supporting tools.

As a result we are envisaging a new internal project aimed at reviewing all existing processes within the administrative and scientific environment in order to develop a new blueprint that will enable:

- Alignment of strategic vision, operations, people and information technology
- Stronger integration between research, administration and management
- Extensive use of cutting-edge information technology in order to maximize focus on value-adding activities
- Enhancement of the knowledge base
- Greater availability of data for analysis and performance evaluation (KPI - Key Performance Indicators) of the overall organization, single organizational units and individuals)

The overall project will be implemented in 3 main phases:

1. Phase 1 will focus on the analysis and design of the process model and technological architecture
2. Phase 2 will be devoted to the implementation of standard functionalities (Accounting & Finance, Procurement and logistics, Fundraising)
3. Phase 3 will focus on the implementation of innovative and highly customized deliverables (e.g., impact factor evaluation, scientific infrastructure usage and maintenance support, lab-operations scheduling and performance monitoring, etc.).

The time framework will be aligned to the Strategic Plan. This activity will be under the coordination of the General Director.

## 11. DELIVERABLES OF THE MAIN PLATFORMS

Table 1: Platforms deliverables are meant to provide measurable macro-objectives to the Foundation, useful to test the advancement of the scientific activity. They originate by the synergistic accomplishment of the scientific milestones of different research units involved in the platform, as described in the technical annexes (see Table II). The time frame (the quarter of the year) is indicative.

| | 2012 | 2012 | 2012 | 2013 | 2013 | 2013 | 2014 | 2014 | 2014 |
|---|---|---|---|---|---|---|---|---|---|
| **Robotics** | Humanoid Walking prototype<br><br>Simple Object Manipulation | Quadruped 12 km/h<br><br>iCub with full skin<br><br>Wrist robot for rehabilitation | Human robot interaction including manipulation and speech<br><br>Initial results from paediatric robot rehabilitation<br><br>Video analysis tools for human behavior analysis (single and 2-person interaction) | Human-robot interaction with learning<br><br>Adult size robot | Self powered humanoid<br><br>Humanoid with some flexible component<br><br>First prototypes of event-coded sensors | Human-Robot Cooperation (simple tasks):<br><br>1.Perception of objects on the iCub, their affordances using machine learning<br><br>2.Variable stiffness control on the iCub<br><br>Video analysis tools for human behavior analysis (groups and crowd) | Proof of clinical utility of pediatric robot rehabilitation | New material Robot<br><br>Event coded sensors installed in iCub | Human-robot interaction with action and speech:<br><br>Learning abilities for objects and their properties, safe exploration and learning via interaction with humans (from demonstration)<br><br>Video analysis tools for people reidentification |

| | 2012 | 2012 | 2012 | 2013 | 2013 | 2013 | 2014 | 2014 | 2014 |
|---|---|---|---|---|---|---|---|---|---|
| **Neuro** | Twofold NBT organization fully operational | Cellular system mechanism for experience dependent neural plasticity<br><br>Study of perception in disabled children<br><br>Development of advanced optical imaging and stimulation methods | Diagnostic tools<br><br>First results of bidirectional interface with rat brain<br><br>First prototypes of perceptual aids for disabled<br><br>Development of improved methods for understanding neuronal interactions and dynamics in vivo and in vitro | Artificial retina implant in vivo<br><br>Significant results on brain signal encoding and decoding<br><br>Significant results on multimodal sensing in humans and robots<br><br>Identification of molecular mechanisms and markers for neurologic and psychiatric disorders | Early markers for neurodegenrative diseases<br><br>Experimental Stations to study human manipulation and perceptual skills (clinical use)<br><br>Identification of genes involved in normal and abnormal cognitive states, and characterization of animal models | Functional Bi-directional interface with rat brain (1 degree of freedom)<br><br>Experimental results of perceptual aids and second generation tools | Development of novel wireless methods and reagents for monitoring and manipulating large neuronal populations in vivo | Sensors actuators for brain homeostasys<br><br>Development of novel functional reagents for enhanced functional magnetic resonance imaging<br><br>Development of advanced methods for imaging and measuring neuro-active substances in vivo | Functional programming for neuronal transplantation therapy<br><br>Functional Bi-directional interface with rat brain (2 degrees of freedom)<br><br>Application of advanced genomics to reveal genetic and epigenetic mechanisms of brain development, function, and disease |
| **D4** | AC inhib. for cancer (validation) | FLAT inhib. for pain (validation) | PST inhib. for age-related diseases (validation) | Periph. FAAH inhib. (preclinic) | Global FAAH inhib (optimization) | Global NAAA inhib (optimization) | Dual FAAH/cox inhib. for cancer (validation) | Uptake and in vivo test of new chromophores for diagnostics<br><br>Global NAAA inhib (preclinic) | FLAT inhib. for pain (optimization) |
| **SmartMat** | Antibacterial multifunctional composites | AFM/STED microscope | PH/temperature responsive nanomagnets for drug delivery | Single molecule device platform for optogenetics | Testing new nanomagnetic particles as contrast agents and dual mode chromophores | SuperB design<br><br>Prototypes of Hybrid materials for prostheses | Soft polymer actuators<br><br>Prototype chip on diamond device | Microfluidic/tweezer cell sorting device platform for diagnostics | SuperB tender<br><br>In vivo drug delivery by responsive nanoparticles |
| **EHS** | TUV collaboration for safety protocols | Phenotype of mutated animals by nanoparticle uptake | | | Safety Protocol for Metallic nanoparticles | | | Safety Protocol for oxide nanoparticles | |
| **Energy** | Metal sulphide and ternary oxide NP for batteries electrodes | Gretzel solar cells with 10% efficiency | New catalytic nanostructures | Printing technology for plastic solar cells | Wide area Gretzel solar cells (square meter) | Nanostructured contacts for Low Temperature fuel cells | | Selective CO oxidation by nanostructured metal metal oxide nanostructures | Prototypes of inorganic nanoparticle solar cells without Cd |

| | 2012 | 2012 | 2012 | 2013 | 2013 | 2013 | 2014 | 2014 | 2014 |
|---|---|---|---|---|---|---|---|---|---|
| **Computation** | Software Tools delivery | | Video analysis algorithms for human detection and tracking | Software Tools delivery for density functional | Clustering tools for bioinformatics | Software algorithms for multi-sensory surveillance and monitoring | Software Tools delivery for multi scale analysis of nanostructures | Software algorithms for neuroimaging data analysis | Software tools for nanoimaging |
| **ICub facility** | | Facility up and running | iCub 2.0 release (currently at an advanced stage of design/fabrication) | | iCub 2.5 release: basic walking, skin, vision and grasping | | iCub software release (including skills derived from "robotics platform") | | iCub 3.0 release including variable impedance, sensorized foot, some energy autonomy, increased robustness |
| **Tech Transf** | Spin off neuro<br><br>Patent portal ready<br><br>Fully functional IIT-Gaslini Joint lab on robot rehabilitation | Start prototyping photovoltaic cells production process<br><br>Initatives with companies in the field of micro-nano electronics<br><br>Initatives with companies in the field of energy<br><br>Activation Italian Drug Discovery Network | Joint labs on smart materials relative to surfaces and fibres treatment<br><br>IIT/VC open day<br><br>Develop a joint lab with primary industry operator on the iCub platform | Outlicensing/start up FAAH inhibitor | Outlicensing/start up on new single molecule detection devices | IIT/VC open day | | Spin off robotics<br><br>Outlicensing NAAA inhibitors | IIT/VC open day |
| **Management** | | Processes/ functions survey | | | New basic Informatic system for management and control | | | Advanced informatics system | |
| **International** | MPI/IIT agreement | MIT/IIT agreement<br><br>Harvard/IIT agreement | Harvard/IIT agreement<br><br>Super B agreement | | | | | | |
| **Education** | | IIT PhD expected approval from Anvur | PhDcall total around 80 positions | | | PhDCall Total around 80 positions | | | PhDCal Total around 80 positions l |
| **Inter Dept** | | Call for proposal | | | Call for proposal | | | Call for proposal | |

| | 2012 | 2012 | 2012 | 2013 | 2013 | 2013 | 2014 | 2014 | 2014 |
|---|---|---|---|---|---|---|---|---|---|
| **Evaluation** | Bibliometric/publication database | Panel D3 evaluation<br><br>Comitato valutazione IIT | Anvur evaluation completed | Network evaluation | Network evaluation | Panel NBT evaluation | | | Panel Robotics evaluation |

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**TECHNICAL ANNEX I → SCIENTIFIC ACTIVITY OF RESEARCH UNITS**

## ADVR DEPARTMENT: ADVANCED ROBOTICS
## (PROF. D. CALDWELL)

**Introduction**

The research in the Department of Advanced Robotics (ADVR) is currently arranged into four themes.

i) Humanoid Technologies,
ii) Biological Inspired Technologies,
iii) BioMedical and Micromanipulation Technologies,
iv) Haptics and VR Technologies.

The strategic plan presented here will outline in detail key proposed developments in the areas of Humanoid, and Biologically Inspired Technologies, with a short (and much less detailed) reference to Haptic Technologies at the end of this document.

**Humanoid Technologies**

Humanoid Technologies headed by Dr. Tsagarakis is the largest and most established of the research areas within the Dept. of Advanced Robotics. During the first three years of IIT (2005-2009) the research was focused around the development of a lower body for three variants of the iCub. Variant 2 is the current iCub lower body. Since 2009 and the finish of the RobotCub project, work has concentrated on the development of new compliant robots such as the ComPARM (Compliant robot arm), a humanoid designated as COMAN, and the component technologies and controllers for these systems: AwAS (Actuator with Adjustable Stiffness), AwAS II, AwAS III, CompAct (Compliant Actuator) and VPDA (Variable Physical Damping Actuator).

While the primary focus in this thematic area has been on the development of innovative hardware technologies for humanoid systems in the past year there has been a strong growth in the development of control and locomotion systems for gait generation. The ability of the robot to walk, walk quickly, run, jump, climb etc (especially over uneven terrain) will form one of the key areas of development for the next 3-5 years.

Although the development of "cognitive" robots is not a core part of the research efforts of the Department, there is small amount of research focused on the ability to provide the robots with easier more intuitive programming and skills development techniques. It is believed that this will allow the transfer of practical skills from humans to robots. This research is based around demonstration by imitation and reinforcement learning.

The research structure is arranged as shown in figure 1. Within this area the core activity is the mechatronic (mechanical, electronic and control) development of systems for future generations of humanoid robot. This covers activities in Actuation and Power Systems, Mechanisms and Structures, Sensing and Locomotion and Control. This activity will provide new solutions and bodyware components for the interdepartmental facility which will develop the future new versions of iCub. The final aspect of activities in this area focuses on machine learning with particular focus on learning by imitation and reinforcement learning. These machine learning activities are focused around a practical need to provide methods of improving the motion and locomotion skills of the robot and are not geared towards studies of human like cognitive abilities or architectures.

**Biologically Inspired Technologies**

The Bio. Insp. Tech. theme started as a small project to develop a quadrupedal robot of dimensions similar to a goat, with locomotive skills that could equal such an animal. This platform was also seen as a test bed for novel hydraulic actuator technologies that were not being developed for the humanoids, but which might ultimately prove useful. In many respects the work on this quadruped robot called HyQ is extremely complimentary to the humanoid technologies. As can be seen from figure 2 showing the research strategies within this area, there is once again a concentration on:

- Actuation (in this instance hydraulic power is used with a similar focus on the need to provide compliant interaction through joint torque control,
- Mechanisms and Structures (with a goal to achieve very dynamic high speed running and jumping in the short to medium term),
- Sensing- most of the sensory technologies used in humanoid systems can be applied to the quadruped and vice versa,
- Locomotion and control – by focusing on a more intrinsically stable four legged platform rather than two legs, work in the Bio. Insp. Tech. can study the gaits needed for generation of locomotion but can more quickly move on to the planning stage for accurate understanding of the terrain for outdoor operation, path and motion planning and navigation, foot placement, map building etc without such a great need for concern over issues of balance, stability etc. This research will of course feed back into the humanoids program,
- Machine Learning – Within this theme the learning activity is directed towards the development of gait planning and navigation in support of "Locomotion and Control".

In considering plans for the future it can be very useful to consider the Humanoid Technology, and the Bio. Insp. Tech. together as there are many useful synergies and the capacity to compare hardware and software on bi- and quadrupedal systems provides a unique research tool. All this will play an important role in the developmente of the European Flagship "Robot Companion".

**Long Term Research Scenarios**

**(Humanoid Tech.)**

The long term goal within the humanoid technology area is the development of a humanoid with physical, motion and locomotion abilities similar to, and ultimately better than human performance. As an example of a potential 10 year goal for the development of the "bodyware" aspects of the humanoid program, a target for a humanoid could be: *completion of a military style assault course involving, walking on rough, uneven, wet and broken terrain, running on similar terrain, jumping up and across objects, climbing (ropes, ladders), crawling etc.* The capacity to complete a course of this type would allow humanoid robots to be deployed in disaster situations, earthquake rescue, hazardous areas (chemical/biological/radiation leaks). In these scenarios the robot would not be required to demonstrate extensive cognitive skills. Simple actions would be understood by the robot but in most instances the intelligence processes would be relayed to a remote operator who would plan the cognitive actions. This would be a more complex version of the Mars rover control where the robots are responsible for local manoeuvring, balance etc but the path planning etc is controlled from earth.

**(Bio. Insp. Tech).**

For the Bio. Insp. Tech area the goals are similar to the humanoids, however, the nature of the platform allows testing of different scenarios. The development of autonomous operation in remote and difficult terrains will be a particular focus, as will the development of highly dynamic motions (running at >20kph), jumping and bounding, terrain identification and gait management.

**Planned Technology Developments**

***Actuation and Power Sources***

Actuators and Power sources are one of the primary "failure" areas for humanoid and mobile robots especially when required to operate out of doors or away from an electrical supply. Further, they are critical during interactions with people yet the current nature of robot design makes them "hard" and therefore safety

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in Human-Robot interaction (HRI) is one of the biggest concerns for actuation. Issues to be addressed include:

***Electric Motors*** – Most robots (humanoids) use electric drives either brushed or brushless dc. While the power/weight and power/volume ratio of these motors has increased in the past 20 years they are still inadequate. Better performance could be achieved by approaching manufacturers and getting motors designed for purpose. Higher specification and performance may already exist for military applications but these are hard to source. New lighter materials with highly magnetic properties perhaps may also provide improvements. Compliant actuation to address the safety issues in HRI for future generations of service robots is now a very "hot" topic in robotics. At IIT there has been a strong focus on improving actuator performance and a number of new compliant actuation systems have been developed. Several of these have been patented. These variable compliance actuators (now trademarked as ComPACT) form joints for the limbs of a new humanoid with the capacity to interact with humanoids more safely, to absorb impacts and therefore jump and to store energy and provide efficiency previously not possible with humanoid technology. This is a very exciting new phase of development with distinct commercial possibilities.

***Hydraulic Motors*** – Hydraulic actuation works well for robots in external environments where the technology for excavators can easily be adapted, although it is large, heavy, dirty, noisy etc. Research to improve this technology and make it suitable for robots is important but not a very active research domain as the hydraulics industries believes it already has the "right" actuators and power sources for its target audience. Typically systems require a compressor and peripherals and are powered by internal combustion engines. These are effective but again noisy, heavy, hot, dirty etc. New technology and developments are needed to miniaturize these and there may be unknown innovative solutions from the car and aerospace industries. The hydraulic oils are dirty and polluting – we in ADVR have undertaken limited research on water as the operating fluid. This has many advantages including better performance and cleanliness but water is a much more difficult fluid to use. The ability to control the high forces in hydraulic systems (compliance regulation) is not commonly required outside robotic applications but will be vital if robots are to make widespread use of hydraulics. Work at IIT has demonstrated excellent force control in the HyQ robot and this could have important application in the future.

***Gears*** – Gears are needed for electric drives, however, the current best solution (Harmonic Drives) are expensive, have control issues when used in torque controlled modes and most importantly are at their operational limit with currently available motors and will be exceeded by the new motors mentioned above. New gearbox technologies must be found or developed through new designs, better materials in traditional designs, or some other approach.

***Energy Storage*** – For electric drives energy is usually obtained from batteries. The power density is improving annually but the performance is still very inadequate. Fuel cell technology holds promise but never seems to be able to deliver. Combustion sources have high energy density but are noisy, polluting etc. Hydrogen engines would not be polluting as would those running on LPG, CNG, LNG, but they are still noisy and hot and have not yet been tried in robotics. Pure chemical sources are possible (e.g. hydrogen peroxide) but most sources have unpleasant associated problems, e.g. toxins, cost, temperature etc. The issue of energy storage and use is critical to future humanoid and quadruped technology but remain unresolved although solutions may already exist (at least in part) in other domains.

***Mechanisms and Structures***

***New materials -*** Most robotic structures are made of steel or aluminium. State of the art robots such as the KUKA LWR and the IIT ComPARM use carbon fiber, but there is little development or knowledge of advanced materials beyond these. Collaborative, multi-disciplinary research on the use of new stronger, lightweight, high performance materials could prove to be one of the key research

ISTITUTO ITALIANO
DI TECNOLOGIA

developments in robotics in the next 5-10 years. In this area there is a real potential for more and stronger interactions with the nanobiotech laboratories at IIT Genova and with the materials science centers of the IIT network (Lecce, Napoli, Milano).

***Robustness -*** Linked with the issues of new materials is physical robustness and resilience of the robotic structure. Cars, while having a protective skin/bodywork, are not supposed to collide with anything. If a collision occurs only very low energy impacts can be accommodated without the need for repair. On the other hand, humans and animals fall or collide with objects quite regularly, and therefore it seems likely that human-like and animal-like robots will also fall. However, when a human falls damage is either limited or when more severe the system will repair itself naturally or with medical help. Building robustness in some form will be an important future step for robots. In the first instance "skins" should have energy absorbing characteristics. These could be sacrificial components with the primary goal of preventing damage to the main/critical component but ultimately the skin and other structure may have some aspects of self healing perhaps. Here once again collaboration with the materials centers could be very useful.

***Sensory skins -*** The development of tactile skins has been a goal of robotic researchers for more than 30 years but it still remains an unresolved problem. Many solutions have been proposed, and tested, but nothing comes close to the capacity for sensing and protection provided by human skin. The failure to develop a truly useful skin for the whole body and the fingertips in particular is perhaps the greatest failing of researchers in the "bodyware" aspect of robots and without it there will always be a limitation to the learning capacity of any autonomous robot. The development of a truly effective skin while appearing rather simplistic is one of the "grand challenges" of robotics yet it seldom receives any great effort comparable with other similar "grand challenges".

***Novel Structures (Foot, Wrist, Hands) -*** Humanoid robots and advanced animal inspired robots already exist but certain key often very complex physical structures have been ignored and over simplified in even the most advanced designs. The peripheral limbs are primary among the most critical and obvious of these "oversights".

***Hand*** – Many dextrous robotic hands have been developed including at IIT. Often these hands have motion capacities and kinematics not far short of the human hand, however, the application of this technology to achieve effective grasping and manipulation is still limited. These limitations are often due to factors already mentioned as key future research topics: power and actuation, sensing, materials and robustness, but are also due to issues such as complexity of control: a hand is effectively 5 small robots operating in parallel. Similar robustness issues can be applied to the wrist of dexterous hands when lifting heavier objects or worse still supporting the body mass eg crawling.

***Foot*** – Most humanoids have a solid metal foot (plate) with little or no compliance or flexibility. COMAN has a fully sensorised ankle and foot with compliant toes making it one of the most complex feet on any biped, however, this still falls very short of the capacity of the human foot. Further, humanoid feet and ankles (and indeed human feet) are heavy structures which makes high foot speed (fast running) difficult because of high inertias. Reductions in foot mass for COMAN and HyQ can be achieved with new materials but also new design. For instance an ostrich, a biped, which is broadly comparable to a human in mass and height can run with peak speeds of over 90kph, but the majority of the mass of the leg is close to the body with only comparatively light feet. Redesigns of the HyQ foot and possibly the COMAN foot could have significant speed benefits. By adding a sensing skin to detect surface contacts and a more flexible design with multiple articulation the foot can form a key part of coping with motion over very uneven surfaces eg rocks, fields.

***Sensing***

Sensing within robotic systems is one of the key requirements particular if there is a need to allow for cognitive abilities. Vision systems currently (at the sensory level as opposed to the data processing) achieve good performance and while improvements are always beneficial they are not vital. Similar comments apply to Audio technology. Smell and Taste sensing have been researched and possibly could be useful in a number of applications but at this time seem to be less critical. Tactile sensing as already mentioned is one critical area that still remains unsolved and will ultimately hamper developments.

> ***Data Rates and Wiring* – In future** problems will be encountered as the number of sensors increases. At this time the sensors in most robots are typically only joint level position sensors, however, COMAN which has compliance adds both extra position and increased torque level detection more than doubling the sensory load. It is predictable that in future systems, with much higher joints sensing capacity and tactile skins, that the data rates and wiring (using conventional approaches) will become extreme in terms of bandwidth, size of wiring bundles and the mass of those bundles. Wireless systems will reduce the wiring problem and prevent increases in mass due to cable bundle weight. Fibre optics links would also be possible. New data processing designs may become necessary with greater local processing (based perhaps on biological models). At this time the issues of data and wiring do not receive great attention in the robotics community typically following the trends in computer systems without ever trying to take a lead and define the future demands. While robotics may never be able to lead this technology greater understanding of the future requirements would be a significant and easily achieved advance.

***Locomotion and Control***

The development of the locomotion (gait generation) capabilities in both the bi and quadrupedal systems will be a key research target for the future. In addition it will be important to identify scenarios in which legged locomotion will have a critical defining advantage over wheeled and tracked vehicles. One such scenario could be in security and rescue eg the nuclear disaster at Fukushima, where legged robots potentially had assess to areas impossible for even wheeled or tracked systems. Key identified goals for the future will include:

> ***Balance -*** Developing balance controllers and stabiliser is one of the key requirements in a biped. The current IIT robot COMAN, by combining, passive and active compliance regulation is one of the most successful in this respect coping with high force impacts and even kicks, however, future bipeds will need to achieve balanced motion in all terrains and this will require new control algorithms (that may take biological inspiration) combined with greater sensory data, inertial system, tactile data from feet, vision processing of terrain profile, joint data etc. Falling will be a distinct possibility and fast controller will be needed with robust design for survival when a fall does occur.
>
> ***Walking, running, jumping, climbing, swinging -*** At this time biped robots are capable of walking, some limited running and a little jumping. Quadruped performance is better in most of these areas due to the lesser requirements to concentrate on balance. However, apart from Big Dog, even few of the quadrupeds venture from specially prepared surfaces. None are certainly capable of the range of locomotive techniques commonly exhibited by humans or animals. In terms of locomotion the medium to long term goal will be the development of a humanoid (and animal) that can achieve the speeds and range of motion formats common for humans. This will move far beyond the current state of the art eg climbing will involve coordinated whole body efforts with support transfer from hand to foot etc. Controllers and gait generators for these activities do not currently exist.
>
> ***Energy Efficiency*** – The issues of actuator and power system design have been highlighted previously and it has been mentioned that there need to be improvements in their performance. However, the energy available within many humanoids already far exceeds that produced by humans and therefore the issue is not just actuation/power systems but also how the energy is used and the efficiency of this use. Although some very successful work has been undertaken in passive walkers

there is generally limited study of the efficient use of power in robots. This started with current industrial robot arms that typically use kW of energy to lift and manoeuvre weights commonly handled by humans. The better use of energy through hardware developments and improved algorithms should become a key research topic in the next 10 years if humanoids are to achieve any of their potential.

***Multi-Terrain Operation*** – All bipedal and most quadrupedal robots currently walk on carefully prepared almost fully flat, stable surfaces, however, one of the key quoted benefits of legged locomotion is the potential for motion over broken terrain however, this has never been demonstrated for a biped and there are few good examples for quadrupeds. These outdoor multi terrain environments remote from conventional power supplies will prove one of the most testing and hopefully most productive areas advanced robotic development. Development in this area will require the combination of all previous mentioned systems ie power, actuation, locomotion, sensing, structure, materials and will form one of the key testing grounds.

***Machine Learning***

This is a relatively new aspect of humanoid technology for ADVR and is related to the practical acquisition and transfer of skills. This work seeks to allow robots to learn new tasks without the need for experienced operator programming and enables normal training based on observation of a task and replication with correction of any anomalies.

***Learning of simple operations by demonstration and imitation -*** Traditional methods of robot programming are time consuming and typically require a high level of skill. At the same time humans daily “train” other humans in new tasks without any advanced programming skills and at the end of the process the trainee often achieves a level of performance that exceeds that trainer by continuing to learn and optimise that which has been taught. The goal of learning by demonstration is not emulation of the human cognitive system, nor development of a cognitive architecture, it is a pragmatic approach to the need to transfer skills from human to machine. The development and enhancement of these skills could be an important process for robotic development in the short to medium term.

***Optimisation of locomotive and motion behaviours-*** The training of locomotion profiles, at present, is usually based on off-line gaits generated in simulation by a researcher, with the goal of ensuring movement that is stable and of course effective. While this does produce motions it is rather ad hoc and cannot refine these motions to optimise a given parameter or parameters eg energy consumption, speed. Work at IIT has started to show learning applied in walking with energy reductions of almost 20% with only short training walks. It is believed that these techniques could be developed much further to allow the robot to explore its own motion limits and enhance the motion profiles in a way that cannot easily be achieved by conventional human programming.

***Teleoperation***

Within ADVR the primary focus is on the development of the mechatronic system, and its successful operation, with limited reference to intelligence and machine learning as outlined above. Yet the complex structures to be developed will need to be controlled in an “intelligent” manner such that real world tasks can be solved. Our preferred approach is to ensure human in the loop control whereby a human operator provides the overarching intelligence and hence the ability to solve unresolved and unexpected problems. When a previously unrehearsed action is encountered the robot would be teleoperated through this scenario using a programming be imitation core. The robot would be able to complete the task controlled by the human and at the same time would “learn” the core actions needed to undertake the same or a similar task in the future. To achieve this level of human control in a natural intuitive manner the approach within ADVR would be based on exoskeletal systems with high fidelity vision, audio and particularly haptic feedback.

***Exoskeletons -*** Work within the Humanoids Theme will develop a new generation of full body

(Legs, Arms and Hands) exoskeletons powered by compliant actuators for safety and comfort. These exoskeletons will be multipurpose having application in medical rehabilitation, human performance augmentation and control of complex humanoid systems. As with the robotic/Humanoid systems these exoskeletons will draw on research in new materials, actuators, power systems, structures, controller etc as outlined for the humanoid/animal robots above.

***Haptics -*** A key aspect of the telepresence control of the human will be the ability to manipulate accurately and safely. On the robot side as already mentioned this will involve the development of complex dextrous hands, and accurate tactile sensing. On the user side there will be a need for accurate sensing of the users finger motions and high fidelity feedback of tactile sensations.

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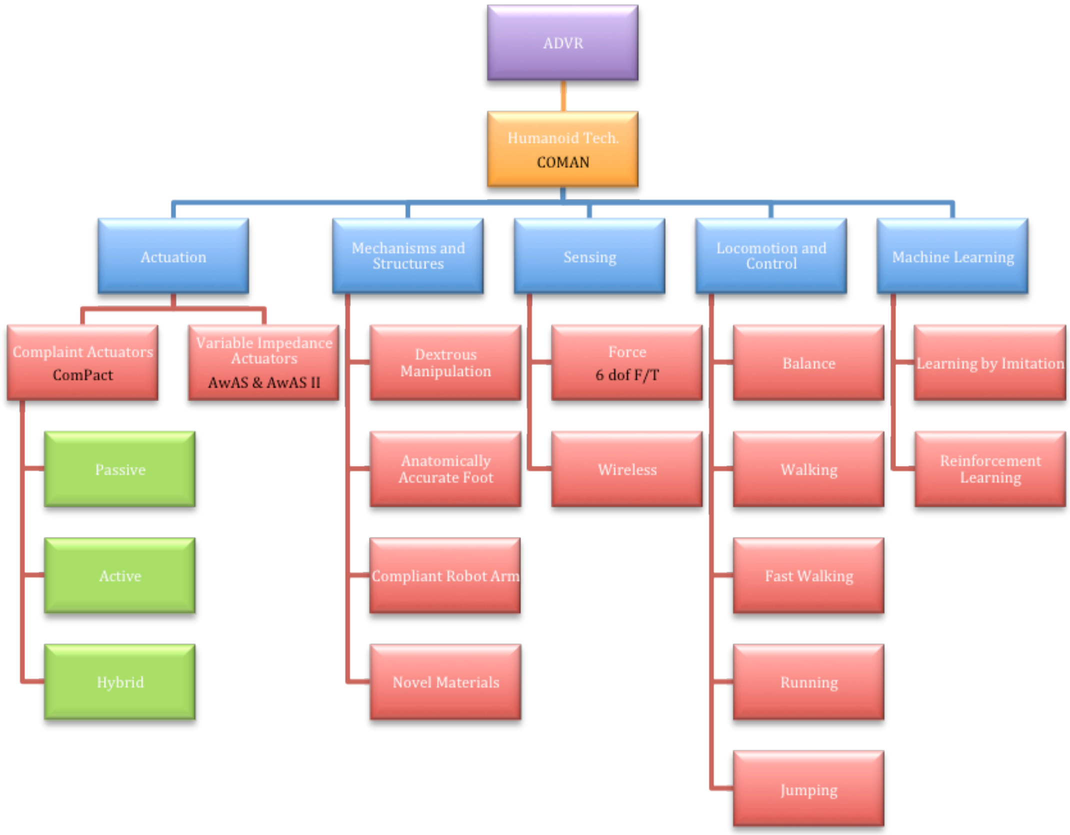


*Figure 1. Research Structure in Humanoid Technologies Theme.*

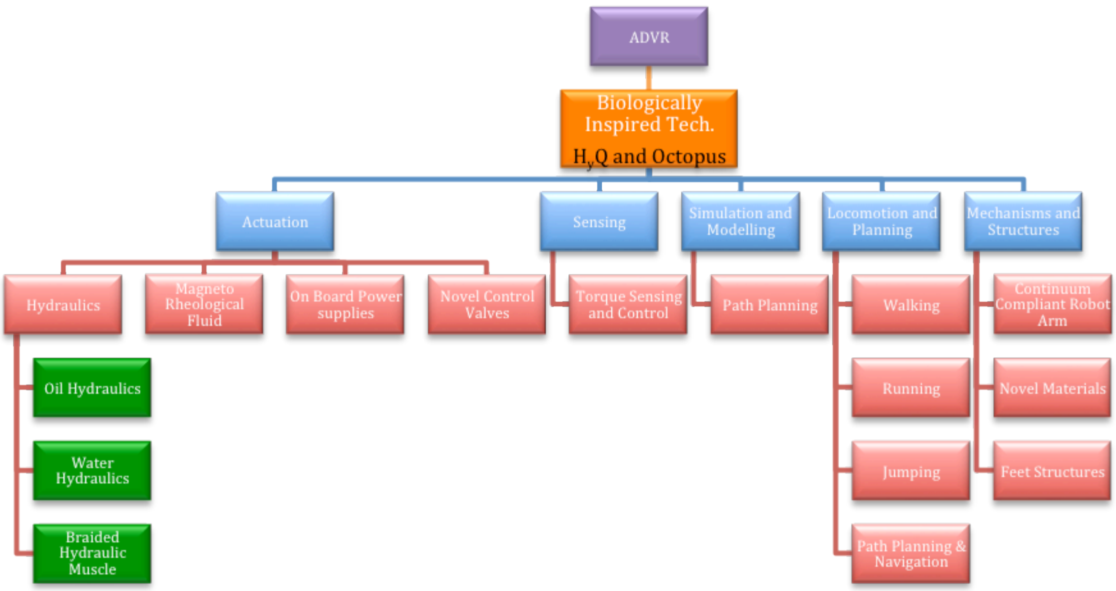


*Figure 2. Research Structure in Biologically Inspired Technologies Theme.*

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**RBCS DEPARTMENT: ROBOTICS, BRAIN AND COGNITIVE SCIENCES**
**(PROF. G. SANDINI)**

## 1 Introduction

The central theme of the research activity of RBCS will be "Motor Cognition and Interaction" along three main streams: Cognitive Robotics with a focus on actions in close contact with humans, Human Cognition with emphasis on manipulation related skills, Human-Machine Interaction and Interfacing.
These streams of research are characterized by an interdisciplinary, human-centric approach aimed at:

1. advancing knowledge in the area of artificial systems by performing targeted investigation of human motor and perceptual abilities and by implementing the abilities required to learn from experience and to interact naturally with humans in an autonomous humanoid robot (the iCub);
2. Investigating how the development and merging of the related technologies can contribute to the improvement of the quality of life, particularly of the weak components of our society.

Scientifically, the RBCS approach will follows these guidelines:

- Human-centric research addressing the level of complexity of the human being in understanding our (social) behavior and in advancing useful technologies. All the technological approaches will be characterized by bio-compatibility and possibility of integration.
- Sharing science and engineering objectives by addressing topics of mutual interest to neuroscientists studying the human brain and body and engineers implementing artificial cognitive robots.
- Studying robot actions in close contact and interaction with humans (including motor and sensory rehabilitation)
- Focus on learning systems and development (not only executing)

The outcome of these activities will lead to scientific as well as technological advancements in the areas of robotics, systems neuroscience and material sciences.
Following the success of RBCS in developing and establishing the iCub platform as a reference humanoid for robotics research worldwide it has been decided to strengthen the involvement of all interested IIT research unit through the integration of HW and SW components on the iCub platform. This activity will continue under the responsibility of a dedicated central facility guided by a scientific board composed of representatives of different IIT's research unit and led by Giorgio Metta. The dedicated facility will include all activities and persons previously allocated to development of the iCub platform and responsible of the iCub production and maintenance.
All research activities (hardware and software) related to the implementation of robot cognition in the iCub will remain part of the RBCS plan as they represent RBCS approach to guide and foster multidisciplinary research. More specifically the targeted scenarios of the iCub for the next years can be summarized as follows:

- 2012: learning to manipulate objects of various shapes through autonomous exploration of the environment.
- 2013: human-robot interaction behaviours (simple version) including certain speech recognition abilities.
- 2014: integration of variable stiffness controllers with manipulation and various machine learning methods.

- 2015: Considerable learning abilities for objects and their properties, safe exploration or learning via interaction with humans.
- 2016: a new platform using some of the developmental/cognitive modules implemented earlier, with passive variable stiffness actuators, and their control for manipulation of objects.

Within this framework the research plan described in the remainder of the document addresses the following topics: learning and adaptation, multimodal perception and affordance, motor control and learning, natural and social interaction, attention and recognition. In the following a brief outline of RBCS research plan for the period 2012-2014 is presented.

## 2 RBCS Research Plan

There is still very much to discover about the principles behind human ability to explore the world manually, to use tools and to collaborate and communicate with others through contact and non-contact interaction (in spite of the fact that social behavior is largely mediated by non-verbal communication). Similarly, only very simple behaviors have been implemented in artificial systems in relation to manual exploration, tools use and gestural communication. Moreover, very rarely these implementations involve physical interactions between a human and a robot. RBCS aims at advancing the knowledge in this field by investigating human abilities, implementing models in humanoid robots and developing technologies for human-machine interaction and interface. The scientific results and possibly new technologies will be exploited in other areas and made available to the IIT community and worldwide to fully exploit the potential of multidisciplinary research.
To this goal, the future RBCS research plan, though keeping the "three streams" structure of the past (i.e. robots, humans, interaction), will be organized around research topics spanning across the three streams.
The outline of the RBCS's research plan is presented in the following table where the columns represent the RBCS organizational structure and the rows the research activities.

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| | | | Robot (iCub) Cognition | | | | Human Cognition | | | | Interaction/Interface | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Perception | Cognitive Architecture | Acting and Control | Body and Material | Physiology of Action and Perception | Motor Learning and Rehabilitaton | Multi-Modal and Time Perception | Dynamic Touch and Interaction | Mirror Neurons and Interaction | Brain Machine Interface | Neural Computation | Tissue Engineering |
| | | | Natale | Metta | Nori | Metta, Ricci | Pozzo | Morasso, Masia | Morrone, Burr, Sandini, Gori | Boud-Bovy | Fadiga | Fadiga, Vato, Ricci, Panzeri | Panzeri | Ricci |
| Manual and Postural Actions | 2.1.1 | Computational Motor Control, Variable Compliance and Actuators | | | ** | * | * | * | | * | | | | * |
| | 2.1.2 | Object Manipulation, Perception and Interaction | * | | | | | * | * | ** | | * | * | |
| | 2.1.3 | Motor Synergies and Motor Syntax | | * | * | | * | * | | | | ** | * | |
| | 2.1.4 | Oculomotion and Spatial Attention | | * | | | | | ** | | | ** | | |
| | 2.1.5 | Sensorimotor Learning | | | * | | | ** | * | | | | | |
| | 2.1.6 | Hand's Design | | ** | * | * | | | | * | | | | |
| Perception during Action | 2.2.1 | Perception of Self and Attention | | | | | ** | | ** | | | | | |
| | 2.2.1 | Visual and Haptic Perceptual Stability | | | | | | | ** | * | | | | |
| | 2.2.3 | Representarion of Peripersonal Space | * | ** | | | | | * | | * | | | |
| | 2.2.4 | Perception of Time, Duration and Synchronicity | * | | | | * | | ** | | * | | * | |
| | 2.2.5 | Computational Principles of Multisensory Perception | * | | | | * | | * | | * | | ** | |
| | 2.2.6 | Sensorimotor Development and Cross-Sensory Calibration | | | | | | | ** | | | | | |
| | 2.2.7 | Neuromorphic Sensors | * | ** | | * | | | * | | | | * | * |
| Interaction Between and with Humans | 2.3.1 | Action Mirroring, Understanding and Imitation | | * | | | * | | * | | ** | | | |
| | 2.3.2 | Speech Perception and Understanding | | * | | | | | | | ** | | * | |
| | 2.3.3 | Neuromotor and Perceptual Rehabilitation | | | * | | * | ** | * | * | * | | | |
| | 2.3.4 | Haptic Technologies and Robot Rehabilitation | | | | | | ** | | * | | | | |
| | 2.3.5 | Interpersonal Physical Interacton | | | * | | | ** | | | | | | |
| Interfacing with the Human Body | 2.4.1 | Inferring Neural Correlates from Non-Invasive Measures of Brain Activity in Humans During Motor Cognition and Interaction | | | | | * | * | | * | | * | ** | |
| | 2.4.2 | Electrophysiology of Bidirectional BMI | | | | | | * | | | | ** | * | * |
| | 2.4.3 | BMI systems for Neural Rehabilitation | | | | | | * | * | | | ** | | |
| | 2.4.4 | Technologies for Brain Machine Interface | | | | | | | | | | * | * | ** |
| | 2.4.5 | Open fMRI and Brain Imaging | | | | | * | | | | | ** | | |
| | 2.4.6 | Bridging the Gap in the Brain (with Fabio Benfenati at NBT) | | | | | | | | | | with NBT | | |
| | 2.4.7 | Neuronal Reprograming and Regeneration (with Fabio Benfenati at NBT) | | | | | | | | | | with NBT | | |
| | 2.4.8 | Tissue Engineering (with Nanotech Units) | | | | | | | | | | | | with Ntech |
| iCub Central Facility | | iCub Body - HW Integration | * | * | * | | * | * | * | * | * | | | * |
| | | iCub Body - SW Integration | * | * | * | | * | * | * | * | * | | * | |
| | | iCub Production | | | | | | | | | | | | |

The research activity is organized in four main themes addressing the study of:

1. Manual and postural actions
2. Perception during action
3. Interaction between and with humans
4. Interfacing with the human body

## 2.1 Manual and Postural Actions

This theme of research is devoted to study in humans and implement in the iCub the execution and understanding of goal-directed actions. Considering that RBCS robotic platform is a full humanoid robot, it will be possible to study complex actions in terms of their specificity as well as commonalities. Specific target of the studies will be manipulative actions (mono- and bi-manual), and the whole body coordination (e.g. reaching outside the peripersonal space, crawling etc.). As for the iCub, this includes the study of learning methods and procedures for skill acquisition and the general topic of the control of movement (e.g. using force and impedance control, modularity and whole body movements). The goals are: the implementation of force control and dynamics compensation/shaping, the development of whole body movements (crawling, balancing) and inverse kinematics schemas. This broad area can be subdivided in many sub-topics of which the most relevant are listed below.

**Computational Motor Control, Variable Compliance and Actuators**

Different approaches (such as optimal and intermittent control) to the study of neural control of complex, goal-directed movements will be investigated and compared by performing behavioral experiments, developing theoretical models, and implementing adaptive behaviors in the iCub. A common approach will be the exploitation of sensory information (specifically haptic and visual) to guide and control movements and to understand the role of compliance and haptic sub-modalities (force, position, velocity, distributed/local tactile sensing) and vision-derived depth information (stereo, vergence, shape, texture etc.) in planning goal directed movements and in reducing the effect of uncertainties (see also the activities specifically devoted to "perception during action"). Targeted actions will be mono- and bi-manual reaching and grasping (while standing), two hands manipulation with particular emphasis on actions performed inside (or close to) the peripersonal space, force and impedance control in grasping, prehension strategies in multi-finger grasps, and the problem of how to generalize reaching and grasping from hand-based synergies to whole-body synergy formation (using different control architectures such as the so called "Passive Motion Paradigm" or PMP). The hardware part of this research theme is concerned with the design, realization and testing of innovative actuators for robotic manipulation, with specific focus on compliant/soft actuation and push-pull mechanisms. Research in the emerging technology of plastic lightweight solid electrochemical actuators will be also carried out aiming at a proof of principle of large scale actuator based on a collection of microactuators. The goal is to study feasible solutions for the construction of variable stiffness actuators for the iCub.

**Object Manipulation, Perception and Interaction**

Object manipulation is a crucial skill in many goal-directed actions (e.g., opening a door, hammering, writing) as well as in many explorative behaviors (e.g., feeling the weight of an object, finding an object in a bag, etc.). The difficulty that current robots face in tasks involving the manipulation of objects beyond a simple reach-grasp-lift-and-hold task is a perfect illustration of the challenges that humans somehow routinely and apparently effortlessly solve. These difficulties can be related to the lack of a sophisticated sense of touch and force in robots, which is crucial for the manipulation of objects, and to the necessity to control the contacts and interaction forces together with motion, which presents considerable theoretical challenges that are not always obvious to neuroscientists. The general objective of this topic is to advance our knowledge of human manipulatory skills beyond reaching and grasping, and to suggest plausible models to be implemented on humanoid robots.

Research activities include:

- As noted above, the simultaneous control of force and motion rises significant challenges, in particular if the object is fixed or partially constrained such as when using a tool or opening a tool (see section 2.1.1 Computational Motor Control, Variable Compliance and Actuators). This research activity will investigate the contribution of tactile, kinaesthetic and visual inputs to movement and force control as well as the role of gaze for the planning and execution of movements (see also 2.1.4 Oculomotion and Spatial Attention). One goal here is to extend the simple touch/no-touch approach toward a more continuous trade-off of force and motion to move from free movements to (partially) constrained movements and, more generally, compare the validity of intermittent and continuous control models.

- One of the main goals of manual exploration is to provide sensory information about object's shape, mass, solidity, texture, material with the goal of supporting object's recognition, categorization and use as tools. The integration of all these haptic-derived features into a unified representation and its link with the corresponding visual derived features is the goal of this research activity. .Specifically the strategies used by humans to actively explore objects by coordinating finger movements, contact forces, gaze direction will be investigated to advance out knowledge on human perception and to suggest plausible models to be implemented on the iCub. The impact of manual exploration on perceptual (visual and haptic) stability are investigated elsewhere (see 2.2.2 Visual and Haptic Perceptual Stability).
- The developmental approach can shed light about the stages that precede the emergence of complex behaviors that integrate many different processes (see 2.2.5 Sensorimotor Development and Cross-Calibration). So far, the study of sensorimotor development of fine motor skills of pre-school children has focused on the development reaching and grasping behavior. One goal here is to understand how children use multiple sources of sensory information to guide their action. Another goal is to investigate the development of the motor strategies used to explore the object properties.
- We will investigate the neuronal correlates of the relationship between the observation of object's geometrical properties, motor imagery and the preparation of motor synergies in humans (with TMS) and in monkeys (by single-neuron recordings). We know that object observation activate the parieto-frontal circuits necessary for grasp planning and execution. However, it is not clear whether such activation is functionally limited to those relatively high-level motor areas or it extends to primary motor and spinal components (see 2.1.3 Motor synergies and Motor Syntax). It is also not clear whether object observation or motor imagery alone can activate complex motor synergies to a high level of detail and specificity and the extent to which such a process might depend on proper stimulation of the sensory peripheral system.
- Design of sensorized objects based on custom-developed tactile sensing technologies (see 2.2.6 Neuromorphic sensors) and ad-hoc experimental set-ups to selectively limit and control the type of manipulation possible (see 2.3.4 Haptic Technologies and Robot Rehabiliation).

**Motor Synergies and Motor Syntax**

Our brain is able to control the highly redundant structure of the human body to perform basic motor primitives and to combine them effectively to produce complex actions. We call the patterns of muscle activation that best describe, using the minimal number of variables, different types of complex movements "motor synergies" and we refer to "motor syntax" when dealing with the combination of motor primitives to produce complex, task specific motor action[1]. The main target of this activity will be: i) to investigate action production of simple and hyper redundant musculoskeletal system at the level of motor synergies, ii) complex goal directed actions, and iii) to implement in robots the coordination of multijoint movement synergies and the rules at the basis of motor syntax. Activities in this stream will develop in the framework of action representation,

[1] The concept of motor syntax is based on the involvement of Broca's area (a "classical" speech area of the human brain) not only in syntactic processing of language, (a well know finding) but also in action execution and during the observation of actions performed by others (a recent finding related to the so-called mirror neuron system).

synergy formation & goal directed reasoning to understand how 'task specific' motor actions are generated. Similarities between the syntax of actions, language and music will be investigated to understand the common bases of communication. Targeted actions for the iCub will be tools use, whole body synergy formation and control, and complex task-specific actions obtained by combining motor primitives inside the peripersonal space. Part of this research effort will be devoted to understanding how the established principle of muscular synergies can be ported to complex robotic tasks (e.g. iCub whole body motions).

**Oculomotion and Spatial Attention**

Among the processes traditionally considered to be 'high level' or cognitive, selective visuospatial attention is one of the most important. It refers to the capability of selecting a particular stimulus according to its physical/visual properties, way of presentation, or previous contingencies and instructions. After selection, the stimulus is processed and, if convenient for the individual, acted on. The traditional view is that selective attention is controlled by a supramodal system 'anatomically separate from the data processing systems'. Like the sensory and motor systems, this 'attention system' performs operations on specific inputs. It interacts with other centers of the brain but maintains its own identity.

Another view of selective attention is that it derives from mechanisms that are intrinsic to the circuits underlying perception and action: attention is modular and there is no need to postulate control mechanisms anatomically separate from the sensorimotor circuits. This account of selective attention, which we deeply favor, is rooted in the idea that the coordinate frame in which space is coded depends on the motor requirements of the effectors that a given circuit controls. Given this strict link between space coding and action programming, visuospatial attention is a consequence of an activation of those brain circuits that are involved in the transformation of visuospatial information into eye movements. The main assumption of this view is that the motor programs for acting in space, once prepared, are not immediately executed. The condition in which action is ready but its execution is delayed corresponds to what is introspectively called visuospatial attention. In other words, any time attention is directed to a target, an oculomotor program toward that target is prepared.

For these reasons, the goal of this stream of research is to (1) model a sensorimotor system for oculomotion to be integrated in the iCub; (2) model a working controller for the iCub which allows to bidirectionally activate the same oculomotor system: from perception to action (i.e. from visual signals to eye movements) to move the eyes, from action to perception (i.e. from oculomotor programs to backwords activation of sensory circuits) to enhance the perceptual salience of an incoming stimulus. We will further study how this visuomotor representation can be acquired through learning and development and during the interaction of the robot with the environment.

**Sensorimotor Learning**

Although learning is a pervasive topic of research in RBCS, the specificity and relevance of sensorimotor learning calls for a dedicated topic. The focus will not be on the symbolic issues that are the main stream of research on learning but on the sub-symbolic processes and sensorimotor primitives that are called into action when the learning agent (whether human or robotic) is engaged in a physical interaction with the teacher and environment, in the framework of a specific task. We concentrate here on the modes of learning as a kind of dynamical process rather than specifically on the way information for learning is obtained as for example in learning by imitation. The environment through which motor learning is studied can be virtual (i.e. based on virtual visual stimuli and robotics devices capable of exerting controlled forces during movements), or natural (such as with real objects and tools). In all these cases compliance and force/torque control is the main medium for retrieving sensory information during explorative behaviors. When action is concerned as opposed to exploration (e.g. using a tool), stiffness becomes the counterpart of compliance and proper force regulation strategies becomes fundamental for successfully learning the task.

**Hand's Design**

The improvement of the hardware of iCub hand in terms of its kinematic structure, the number of degrees of freedom, the sensorization (skin, force, etc.) and reliability/dependability will be synergic to the study of manual exploration and tactile sensing. As in the design of the first iCub, the hand is the crucial component that determines subsequently the design of the whole body of the robot. This prominence is justified by the crucial role of manipulation in the development of cognition. In the short term, improvements are foreseen primarily in the accuracy of control and sensorization;

## 2.2 Perception During Action

There are still many aspects to investigate in relation to the use of sensory information during actions. From the visual information required to plan a goal directed movement to the kind of haptic information required to interact gently and safely with a human being. By investigating specifically the peculiarity of perception DURING action we want to stress the unitary nature of perception and action in supporting each other during development, learning, motor execution and understanding. The roadmap of these activities is approximately organized along the roadmap of human development, starting from basic sensorimotor coordination and evolving towards more exquisite human skills as for example language. Along this way we touch attention, reaching in peripersonal space, affordances, multisensory integration and perception, imitation, speech and language and eventually the perception of time.

The broad area of "perception during action" can be subdivided in many sub-topics of which the most relevant are listed below.

**Perception of self and attention**

Where and what to attend to during action is a fundamental aspect to investigate as it is related not only to perception but, more importantly for the aims of RBCS plan, to the learning and monitoring of action execution. In this activity we want to stress the "body of the actor (the "self") during actions as the target of attention as opposed to the external environment. We consider the specificity of attentional mechanisms during action execution as very peculiar and relevant. The control of attention during action is driven not only by external (environmental) parameters which are, in some sense passively perceived, but also by our ability to predict the sensory and motor outcome of goal-directed actions on the basis of contingent sensorimotor information and past experience. This implementation in humans is worth investigating for example during object exploration and the execution of reaching, grasping and manipulatory actions. Furthermore, among all perceptual aspects, we want to highlight the role of self-perception during learning manipulative skills and at the basis of inter-individual interaction and communication. In the context of learning manipulation, in fact, "self-perception" does not only refer to the classical concept of motor proprioception providing the body with the feedback signals necessary to control movement, but the active observation of our own body during learning. This is required to build the internal representation of the sensory experience of goal directed actions. The sensory experience is fundamental to anticipate and monitor the correct execution of motor actions as well as to "resonate" during actions performed by others

**Visual and Haptic Perceptual Stability**

Perception of space is a fundamental ingredient to plan goal-directed movements and, conversely, goal directed actions are important sources of information about space. Considering the emphasis of RBCS plan on manipulative, exploratory and whole body actions, the perception of peripersonal space and the integration (merging) of visual, haptic, and auditory spaces are particularly important. Topics of relevant research about space perception that will be investigated are:

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- how space representation is built and maintained through active exploration by integrating visual, auditory and haptic information (and its sub-modalities)
- how space representation is processed to maintain perceptual (visual and haptic) stability during active exploration of the environment (e.g. across saccadic eye movements)
- how space perception and representation is exploited to anticipate the evolution of perceptual information during actions (predictive remapping of visual and haptic receptive fields)
- what is the impact of manual movements on the stability of the haptic perception of the object properties (e.g. mass, size)? How do these percepts emerge from continuously time-varying sensory signals?

Previous studies showing how transient remapping of neural receptive fields mediates visual perceptual stability will be extended to haptic perception in the specific case of object's manipulation. Questions like: "how do we perceive the shape and solidarity of an object when we explore it with continual finger movements?" will be experimentally investigated in humans and the most promising models will be tested in the iCub humanoid to implement haptic exploration of the peripersonal space and manual exploration and recognition skills.

**Representation of the Peripersonal Space**

Empirical evidence from neuroscience is showing that the control of reaching in humans and animals is correlated with the activation of several neural pathways, where touch, proprioception, and vision are intertwined with motor information in a multisensory representation of the space around the body. This multimodal convergence of information provides the brain with a multimodal spatial map where spatial positions around the body are mapped as sensorimotor targets and not according to a specific geometric coordinate system. This multimodal map implicitly solves the problem of the transformation of coordinates between the different motor effectors (e.g. eye-related retinotopic coordinates into hand centered ones). By this way, the peripersonal space becomes an extension in the space of the body surface, thanks to the integration of tactile, vuisual and motor signals. The goal of this stream of research is to model these multiple neural pathways in the form of a working controller for the iCub, taking into account vision, proprioception and tactile information. We will study how this multisensory representation can be acquired through learning and development during the interaction of the robot with the environment.

**Perception of Time, Duration and Synchronicity**

Mounting evidence suggests that in humans space and time perception are linked, and associated with the action system. Recent pilot studies showed a dependence of perceived time on changes of body posture as if active movements contributed to resetting our internal clock. Audition leads the other sensory modalities in case of conflicting time-related sensory stimuli. In spite of these findings there is still missing evidence on how we perceive the synchronicity of multimodal events and the duration of perceptual events during action execution. Along this line, we plan to extend these studies to intersensory stimuli aimed at understanding the extent to which event timing may share some basic principles and mechanisms across different sensory modalities, and how clocks within modalities may be synchronized to yield a supramodal estimate of duration. Conversely, the construction of asynchronous architectures for the control of robots in real-time is a hot topic of research particularly for systems with the motor and sensory complexity of humanoid robots where different modalities have computational loops with different periodicity. In this respect we intend to investigate the construction of asynchronous architectures for computation and sensory integration, and the comparison between intermittent control and continuous control models. Moreover, in the current framework of Perception during Action, time cannot be dissociated from action duration and an important question to ask is "what is the cost of time for action production and duration?" The brain selectively and implicitly adjusts this quantity suggesting that movement time is related to cost or reward functions. A general computational model for predicting what should be the "natural" movement durations will be set up. In robotics, reaching movement duration is provided "by hand" while modelling action duration seems crucial to develop autonomous and adaptive robots. A specific goal will be to suggest mathematical principles to predict the optimal movement duration on the basis of the reward (e.g. to reach a target) and the effort we expect to spend in the unit time. Based on the empirical results and the developed models, this studies should contribute to propose robotic implementation dedicated to assist robots in action selection and decision making process.

**Computational Principles of Multisenory Perception**

In order to plan and perform complex cognitive and motor acts, subjects need to gather, integrate and then combine or select multiple sources of information from several senses and from motor planning signals. However, little is yet known about how the cerebral cortex collects, represents and then processes all these types of information needed to produce a behavioral act. One possibility about integration of contribution from multiple sources is that at any given moment there tends to be a leading source of information orchestrating the oscillatory dynamics that form the electrophysiological representation of the processing of that particular source of neural information. For instance in multisensory perception, there could be at any given time, a 'leading' sense enabling a concerted control of excitability in cortical areas processing modality-specific properties of multisensory environments, thereby resulting in low-level multisensory interactions and an efficient merging of information at higher levels of processing. Merging sensory and motor information could proceed along the same lines. We aim to investigate the principles of integration of multisensory and motor information by developing data analysis methods able to investigate, from neurophysiological and/or neuroimaging recordings, how the different streams of information are reflected and then integrated in the temporal pattern of activity of single or multiple cortical areas. We plan to use models of neural networks to explore the neural architectures behind these representations. Then, these algorithms and these principles will be transferred in robots endowed with multiple-modality sensors to enhance multisensory motor cognition.

**Sensorimotor Development and Cross-Sensory Calibration**

RBCS research investigated the sensorimotor development in both normal and sensory deprived children. This paradigm of development has also been used as a guideline for the evolution of intelligent behavior in the iCub humanoid. A distinctive stream of research in RBCS to explain the development of multisensory perception in human children is the so-called "cross-calibration" theory. According to this theory, which has been demonstrated in normally developing children and later confirmed in sensory deprived children, different sensory modalities calibrate each other during development to achieve "adult-like" performance. Each sensory modality leads the others in relation to specific sensory features and their intrinsic strength. For example vision is used to calibrate the perception of haptic orientation while in the measure of size haptic perception is used to calibrate visual estimation of size. These findings may explain how the integration of multimodal information develops in humans and may give important suggestions on how to implement this process in artificial systems. In the following years we intend to continue along this line of research to extend this research by investigating how the impairment of motor functions (e.g. in children with Dyskinetic Cerebral Palsy) affects visual estimate of size and by measuring sensitivity for time and space discriminations in congenitally blind and deaf children. The application of these findings to rehabilitation of dyskinetic, non-sighted and deaf children will be described later. From the robotics perspective, the integration and cross-calibration of visual and haptic information will be investigated on the iCub exploiting its multimodal sensory system during manual exploration of the environment.

**Neuromorphic Sensors**

A promising approach for the successful hardware implementation of a computational theory of multisensory perception on robotic platforms is the neuromorphic technology, exploiting the fine temporal accuracy of diverse event-driven sensors. Therefore we plan to invest dedicated effort to the development of neuromorphic sensors and processing. In particular, we would like to capitalize on the early success of event-based cameras to develop a new chip for the iCub which implements various sensing modalities: change detection, intensity, motion, etc. The layout of the photoreceptors will be space variant mimicking the structure of the human retina. As for iCub's tactile sensing, artificial skin represents a paradoxical situation where softness is needed for high sensitivity while simultaneously a high stiffness of the material is required for durability. For this reason, even within the neuromorphic computational framework described above, the focus initially will be on new materials and sensing principles. The skin is also paradigmatic of systems solutions because it needs to be flexible and stretchable, it requires pre-processing and embedded electronics and it has to minimize the number of wires. We will continue the development of the flexible POSFET, the collaborations on the study of piezoelectric materials for sensing and the more traditional capacitive sensing. In parallel we will investigate, using the iCub skin developed so far, the "event driven" approach for tactile sensing and multimodal integration.

### 2.3 Interaction Between and with Humans

The ability to interact meaningfully and safely with humans is a fundamental resource of our society and a strong requirement for future robots. Since the discovery of Mirror and Canonical Neurons it has become evident that interpersonal communication and interaction requires mutual understanding and is based on a shared representation of goal directed actions. The main focus of this activity is the understanding of the representation of goal directed actions is built during sensorimotor and cognitive development, and then updated and exploited during action execution and understanding. Furthermore, in a task related to human-human and human-robot interaction, speech production and understating is a fundamental ability to investigate (also refer to section on "motor syntax" to understand the similarities we intend to stress between action execution and speech production). Finally, the peculiarities of interpersonal physical interaction through direct contact or mediated by external objects (e.g. during collaborative tasks) will be investigated. In all the research activities related to human-robot interaction the anthropomorphic shape of the iCub body will be exploited

**Action Mirroring, Understanding and Imitation**

By action mirroring we mean the process, based on interpersonal bodily and neural similarity between an observer and an actor, whereby the observer maps the actor's perceived movements onto her/his own motor repertoire. Along this line of research basic questions that will be investigated are:

- how motor activities, elicited by action observation, are modulated by the task the observing participant is engaged with
- the role of action mirroring for inter-individual communication, imitation and social functions
- the granularity (detail of representation) and plasticity of action mirroring induced by training.

From the robotics perspective a first attempt will be made to identifying which visual parameters, measured during action observation, are more promising to index the representation of the corresponding action in the iCub's internal vocabulary of action.

**Speech Perception and Understanding**

Speech perception has been shown to activate the motor system of the listener. This motor activation is somatotopically organized such that listening to tongue-produced sounds (i.e. [r] or [l] sounds) activate the tongue motor representation. All the above-mentioned studies however, cannot define the role of the motor system in speech perception. In fact, such motor activations may be simply correlated discharges that are not related with the real process of speech sound decoding. Recently, we demonstrated that the selective interference with speech production centers proved effective in altering subject's performance in speech discrimination tasks. All together these data suggest that the motor system is causally related to the perception of speech. To better understand the causal role of the motor system in speech perception, we will verify whether the motor involvement becomes more critical when dealing with inter-speaker variability. Within this framework specific areas of investigations will be:

- **Multiple speakers variability as a tool to extract speech invariants**. We will measure which between acoustic or motor distances between own production and auditory samples is the critical in perceptual discrimination. Moreover, the effect of temporary inactivation of motor cortex during phonological discrimination tasks will be employed to assess the degree of involvement of the motor system during speech perception.
- **Motor attention as a predictive cue for perception**. Here we will investigate the contribution of 'motor' attention to speech perception. It is well known, in fact, that the human brain has the capability to extract speaker's information even in very noisy environments or in multiple-speakers contexts. This is, at present, impossible for artificial recognizers. Our hypothesis is that this extraction of information is allowed by feed-forward predictive mechanisms, motor in origin, activated by the listener through an attentional activation.
- **Segmentation**. We will investigate both with perceptual and neurophysiological (TMS) experiments and with elaboration of artificial models how the brain segments individual words (or pseudo-words) starting from a stream of continuous speech.
- **Automatic speech recognition.** From the robotics point of view we intend to investigate methods for automatic speech recognition (ASR) that use principles derived from neuroscientific findings and in particular results obtained with TMS. The involvement of motor signals in segmentation and recognition of speech is specifically investigated.

**Neuromotor and Perceptual Rehabilitation**

We intend to systematically investigate the common links between the studies on motor learning and imitation and the development of efficient robot-based rehabilitation techniques in neuromotor impairments. The field is still characterized by empirical approaches and we intend to ground it by exploiting the analogy between new skill acquisition and functional recovery. The envisaged role of the robot is to mediate and facilitate a three-ways interaction: patient - human therapist - robot therapist. Therefore, the standard rehabilitation techniques will be extended to include controlled forces and perceptual stimuli able to elicit the activation of the motor resonance system. Also intelligent monitoring modules of biomechanical features and neural correlates, known to evolve during learning/functional recovery, will be included. In particular, during the next period we intend to focus on:

- Rehabilitation tasks involving not only proximal but also distal movements (including the hand);
- Integration of sensory (proprioceptive) training and motor training

- Online evaluation of the modulation of sensorimotor variables, like end-point stiffness and limb position sense, and physiological variables related to attention;
- The crucial role on cortical plasticity of action observation and production (hypo activity/immobilization or learning tool manipulation) and its possible use as an innovative, and decisive clinical tool/technology for sensory motor rehabilitation.

The recovery following dedicated rehabilitation programs (e.g., using mirror neurons properties and multimodal stimulation) will be investigated at the functional (motor efficiency, body schema, peripersonal space etc…) and the structural (FMri, Transcranial Magnetic Stimulation and EEG) levels.
From the clinical point of view we plan to extend our target patients from stroke & multiple sclerosis to cerebral palsy & ataxic children. These activities will be carried out also thanks to the Joint-Lab recently established at the Pediatric Hospital "Giannina Gaslini" for "Clinical Research in Robotic Rehabilitation"
In the area of sensory rehabilitation we will base out activities on the observation that the studies of cross-modal calibration and development performed with the contribution of dyskinetic, non-sighted and deaf children, can give rise to the development of rehabilitation procedures as well as assistive devices. Thanks to an ongoing collaboration with the Institute for Blind Children "Davide Chiossone " and the "Stella Maris" Hospital in Pisa, we intend to continue and strengthen our activity in this area. Finally the collaboration with the IIT labs in Lecce on the development of a tactile display for blind will be continued

**Haptic Technologies and Robot Rehabilitation**

An important outcome of the studies on motor learning and rehabilitation and a technological goal by itself is the development of devices and the related rehabilitation protocols that can be used both in the clinical practice and at home. In the past years, such devices have been developed for our "robotic gym" and preliminary pilot studies with patients have been performed. In the future we intend to strengthen these activities by expanding the 'robotic gym' in the sense of modularity, three-dimensionality, bimanuality, sensorized objects/toys; exoskeletal vs. serial robotics. Also a dedicated activity to investigate the feasibility of Delivering Home Therapy by means of "soft" robotics will be carried out. Finally, an important activity deriving from the execution of behavioral experiments in humans and robots is the design and implementation of ad-hoc sensorized and actuated components to be used as stimuli and/or probes of perceptual performance, such as: devices to measure force, compliance and motor impedance during exploratory movements, tactile, visual and haptic stimulators. RBCS plan to develop the most successful such devices into experimental set-ups that can be exploited for clinical applications as well as rehabilitation tool.

**Inter-Personal (Physical) Interaction**

The role of physical interaction in interpersonal collaboration and during teaching by guiding will be investigated in human-human and human-robot scenarios. Collaborative tasks requiring mutual physical interaction will be investigated and the relationship with the control of movement and compliance will be studied. Specific attention will be devoted to understand how the dual concepts of passive compliance and active force production are tuned on the basis of on the task to be performed. In a sense, the goal will be to understand how the task specifications regulate the active (i.e. guiding) and the passive (i.e. being guided) counterparts of inter-personal physical interactions. In this contest a special case of interpersonal interaction that will be addressed is that established between patient and robot-therapist.

## 2.4 Interfacing with the Human Body

The activity here is the continuation and expansion of the work on Brain Machine Interface carried out in the last years. This activity will evolve along different research paths some of which carried out in close collaboration with other IIT's research units such as the Neuroscience and Brain Technologies Department. The aim is to identify technological research paths that can effectively lead to the development of artificial connection between the human brain and an external device or between different areas of the human brain disconnected by a pathologic process (i.e. ictus, trauma, etc.). During the previous scientific period we achieved new results allowing the recording from stimulated multiple brain sites in awake human patients. Among these results are a multichannel microdrive for intracortical recordings, multichannel arrays of microcontacts for epicortical recordings, a multichannel microstimulator. Among the most relevant technological progresses, the covering of the surfaces of contact with carbon nanotubes (CNTs), alone or associated with gold or polymers, allowed us to significantly improve the signal-to-noise ratio. The details of the activities planned during the next period are outlined below.

### Inferring Neural Correlates from Non-Invasive Measures of Brain Activities in Humans During Motor Cognition and Interaction

Although information is exchanged at the single neuron level, neural activity in human subjects performing tasks can only be recorded with non-invasive signals, such as Electroencephalograms (EEGs), Magnetoencephalograms (MEGs) and functional Magnetic Resonance Imaging (fMRI), that all measure neural activity only indirectly. Understanding how the human brain performs motor cognition and interaction requires therefore being able to map explicitly the time course of neuroimaging responses onto the underlying dynamics of the neural computations implementing these functions. Only when this is achieved we are able to map the experimental data in quantitative mathematical models that can be implemented in robots.

The Neural computation group will contribute to these aims by investigating in details, by means of mathematical models and mathematical analysis tools, the relationship between the temporal dynamics of EEGs fMRI signals and that of the true underlying neural spiking activity that can be recorded only with invasive experiments in animals or human patients. Revealing the precise contribution of different components of neural spiking activity to variations of BOLD and EEGs signal will be central to a better interpretation of many of the experiments proposed in other parts of this project. For example, this knowledge will be crucial to map observed coordinated changes across brain locations of EEG/fMRI signals during learning to changes of causal interactions and effective connectivity of the underlying neural populations.

### Electrophysiology of Bidirectional Brain Machine Interface

The main goal of the activities describe here is to study how to establish a bidirectional communication channel between the nervous system and an artificial device (e.g. a robotic limb or a computer cursor) with the purpose of investigating how the brain control actions and, in a longer term, how to realize the technologies requires to improve the quality of life of patients with sensory and motor disabilities. By using in-vivo techniques, we will focus our efforts on: i) developing and testing new bidirectional chronically implantable devices and low-power wireless recording systems to collect and process the information flow and in ii) exploring computational algorithms to decode the neural activity to interact with an artificial device and, on the other direction, to encode the signals collected from the external environment to be feed directly to the nervous system. The experimental activity is organized in two main research streams with the goal of.

- Understanding the role of the feedback in a bidirectional brain machine communication system
- Developing a closed-loop bidirectional brain communication system taking inspiration from how the spinal cord of vertebrates mediates communication between the brain and the limbs.

In the first research stream we will continue to investigate how to use intracortical microstimulation patterns (ICMS) to provide the brain with information collected by the environment, establishing in this way an artificial sensory channel. Using microwire arrays chronically implanted in the sensory representation of the whiskers in the barrel cortex of behaving rodents, we are investigating which electrical parameters of the stimulation pulse train should be used to evoke an artificial sensation similar to the natural one produced by the whiskers while interacting with an object.
In the second research stream, by establishing a bidirectional interface with a sensory and a motor area of the cortex, the brain interacts with a simulated dynamical system generating a family of trajectories converging upon a selected equilibrium point. The goal of this research is to lay the foundation for the development of a new family of bidirectional closed-loop brain machine communication systems taking inspiration on how the spinal cord organizes coordinated patterns of muscle forces driving the limbs along dynamically stable trajectories

**BMI Systems for Neural Rehabilitation**

One of the most challenging applications of Brain Machine Communication (BMC) systems consists in using this technology as complement of the traditional rehabilitation techniques. It has been demonstrated that patients suffering from post-stroke motor disorders or affected by Parkinson's disease or epilepsy, could benefit by using BMC systems that provide supplemental feedback to the robotic rehabilitation apparatus. In this clinical context is worth investigating how BMC systems could induce neural plasticity by providing a neuro-feedback related to the brain activity during the rehabilitation process. Theoretical framework based on Hebbian theory and experimental evidences of the presence of plasticity processes occurring during stroke recovery, makes this new applications of the BMC systems very promising in terms of increasing the performances of the rehabilitation process. Based on the Hebbian theory, BMC systems will be used in the context of restoring the connection between the sensorimotor cortex and the peripheral muscles by detecting the motor intention and providing corresponding haptic sensory stimulation. To achieve this challenging goal will be crucial the choice of the neural states to be used as feedback and the modality of how such feedback is provided to the patients. The neuro-feedback will be also used as supplemental information in shaping the rehabilitation strategy modulating the passive and active-assisted movements.

**Technologies for Brain Machine Interface**

The activities aimed at improving the recording and processing performance of BMI devices will continue on the following topics:

- exploring new types of impedance-lowering techniques, such as the association of CNTs+PEDOT, synterized microspheres, other types of stable nanostructured coatings for simultaneous ultra-low noise neural recordings and high current density stimulation
- improving the biocompatibility by covering the active contacts with some human-derived conductive layers (e.g. fibrine glue).
- realizing high density flexible integrated electrodes and electronics for in-situ signal conditioning
- realizing conformable, variable stiffness material based electrodes for enhanced tissue biocompatibility and long term implantation
- Studying new methods of signal analysis allowing a single trial-based discrimination of motor commands and sensory percepts on the basis of surface, epicortical, recordings.

Both intracortical and epicortical devices will be developed with tailored designs for specific experimental scenarios, at first tested in-vivo on animals and finally fully certified for clinical use on humans. Direct metalizzation of conformable medical grade polymers via excimer laser pre-treatment on 2D and 3D surfaces will be carried in collaboration with the micromachining Laboratory at the Nanophisycs Facility in IIT@Morego (Dr. Fernando Brandi).

**Open fMRI Machine and Brain Imaging**

Functional analysis of cerebral activity is today almost a synonym of functional Magnetic Resonance Imaging (fMRI). This technique is in principle applicable to any MR scanner but the requirements of image rate, spatial resolution and sensitivity make it practical only in high field (>1.5 T) scanners. The study of the functional response of the motor cortex during the programming, execution and mental representation of voluntary movements is of great relevance; given the high integration of the visuo-motor, sensory feedback and proprioceptive systems, it is important to be able to evaluate it in conditions that closely approximate the real ones. As of today the availability of a scanner capable of BOLD-fMRI acquisitions in humans that allows the subject to maintain an erect stance (at least for the trunk), the direct observation of the surroundings and sufficient limb freedom to afford the execution of simple motor tasks is still a dream. The necessary field intensities of at least 1.5 T over volumes of a few tens of cm are today achieved only within cylindrical superconductive magnets with a useful cavityof less than 1 meter diameter. Open MRI scanners are limited to field values inferior to 1 T and their shape only allows the patient to assume a prone/supine position with limited limb movement capability. After many attempts, the quest for an fMRI system to devote to the study of the human motor cortex has reached a final solution for the magnetic configuration. After an extensive analysis of many competing alternatives an axi-symmetric disposition of coils has been found, that offers good advantages in terms of simplicity, homogeneity, stray field and field stress on the conductors. The configuration chosen is easily adaptable to different uses as well, like an operating theater version to be employed in neurosurgery or a small scale primate version. In fact preliminary analysis have been made for a few possible scenarios:

- a human scale system for a sitting human leaving enough space for small objects manipulation (about 80 cm shoulder to shoulder) at a 2 T field
- a "surgical" system at lower field and smaller gap (50-60 cm) for neurosurgery application
- a small scale, medium-high field (gap 40 cm, field of view 10-15 cm) for a primate lab
- a 1.5 T "conventional" open clinical system.

That said all four alternatives appear to be technically feasible and will be investigated.

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**NBT DEPARTMENT: NEUROSCIENCE AND BRAIN TECHNOLOGIES**
**(PROF. J. ASSAD, PROF. F. BENFENATI)**

Following the recent reorganization, the NBT department will focus on two main areas of research: the Synaptic Neuroscience, coordinated by F. Benfenati, and the Advanced Neurotechnologies coordinated by J. Assad. The former will pursue basic neurophysiology studies started in the previous scientific plan, in addition to the development of new cellular neurotechnologies, whereas the latter will mostly focus on more technology oriented activities. The following description summarizes the main research lines pursued by the two research teams. The topic organization is not rigid as several activities will be carried out in collaboration between the two areas.

## SYNAPTIC NEUROSCIENCE

### A. Molecular mechanisms of synaptic plasticity and computation

**1. Molecular determinants of cortical circuit development and wiring.** We will investigate the effects of neurotrophins, GABAergic transmission and their intracellular pathways on neuronal maturation, polarization and cortical wiring. We will also study the potential consequences of defective GABAergic transmission and cortical mis-wiring in developmental disorders such as epilepsy, focal cortical dysplasia, schizophrenia and Down or Rett syndromes. To achieve these goals, optimization of the newly patented electroporation device able to target *in utero* different brain areas will be achieved in the attempt to unravel similarities and differences in neuronal development of the diverse brain areas.

**2. Epigenetic control of homeostatic plasticity.** We will investigate various forms of homeostatic plasticity that are induced by hyperexcitability and that depend on the induction of a Repressor Element Silencing Transcription Factor (REST). REST silences transcription of a broad variety of neural genes, such as ion channels, synaptic vesicle proteins, and neurotransmitter receptors. We plan to investigate the signaling pathway linking neuronal hyperexcitability to REST. We will also characterize how changes in REST expression affect neurotransmitter release and synaptic transmission and test its effectiveness as a protective factor against epilepsy. There is also emerging evidence that miRNAs could play a key role in regulation of local protein synthesis at the synapse and thus mediate adaptive mechanisms. We have identified a set of dendritically enriched miRNAs, the abundance of which is changed in response to prolonged synaptic inactivity. We found that one of these miRNAs, miR-218, is involved in the translational regulation of GluR2 receptor and of many other key synaptic proteins potentially implicated in schizophrenia, epilepsy and other neurological diseases. We will search for further evidence of miR-218 involvement in the molecular pathophysiology of synaptic plasticity and test the hypothesis that pre-miRNA containing exosomes are part of the mechanism coordinating pre- and postsynaptic changes in synaptic strength.

**3. Presynaptic control of excitability and excitation/inhibition balance by synaptic vesicle trafficking.** The research will focus on the role of presynaptic proteins in the definition of the functional properties of central synapses, their heterogeneity and plastic responses to environmental stimuli. We will study the differential expression and distribution of specific presynaptic proteins and the changes in synaptic vesicle cycling and short-term plasticity associated with their genetic deletion of with the activation of specific classes of kinases. Moreover, we will concentrate our interest on the pathophysiology of mutations in presynaptic proteins associated with epilepsy or autism and affecting synaptic vesicle trafficking including synapsins, Rab3 or TBC1D24/ARF6. In particular, we are interested in elucidating the molecular and cellular mechanisms by which mutated synapsins generate the pathological phenotype in humans and in understanding the differences between mutations that generate the sole epileptic phenotype and those associated with ASD or mixed ASD/epileptic phenotype.

**4. Targeting and Reconstitution of Brain Extracellular Matrix.** We will focus on the signalling cascades controlled by (peri)synaptic ECM and associated cell surface receptors, visualization of ECM and synapse remodelling, and development of new technologies for conditional genetic and pharmacological manipulations of ECM in time-, space- and/or activity-dependent manner. We will also attempt to reconstitute brain ECM by generation of artificial three-dimensional multi-component ECM scaffolds, which would be populated in a controlled fashion by reprogrammed human neurons of defined subtypes. This could facilitate the development of artificial human-derived brain tissue for human cellular neurophysiology studies, transplantation studies and fabrication of neuron-based chips.

**5. Interplay between glutamatergic and GABAergic systems in the control of excitability**

We will focus on the influence of receptor lateral diffusion on post-synaptic plasticity at GABAergic synapses by resolving the trajectories of individual synaptic GABA and glutamate receptors by single particle tracking. We will optimize the illumination based on plasmonic resonance and used it to activate individual photoswitchable channels linked to quantum dots to test whether the conformational state of extrasynaptic glutamate or $GABA_A$ receptors affects the diffusional properties of these receptors, their interaction with scaffold proteins, and their modulation following receptor activation. The interactions between glutamatergic and GABAergic systems will also be studied at both striatal and neocortical levels. Impairment in the function of fast-spiking striatal interneurons (FSI) may contribute to motor and cognitive disorders. Using *in vitro* electrophysiological techniques, we will investigate the role of cortically evoked synaptic excitation on FSI co-activation and decoupling mediated by gap-junctions. We will also use optogenetic tools to stimulate several FSIs simultaneously, in order to decipher the interaction of multiple electrical synapses acting in concert during burst activity at the population level. At the neocortical level, we will identify biological mechanisms responsible for the interictal state and ictal onset in focal temporal lobe epilepsies using a mouse models of Severe Myoclonic Epilepsy of Infancy, bearing loss-of-function mutations in the $Na_V1.1$ channel that is highly enriched in cortical interneurons.

**6. Genetic reprogramming of skin fibroblasts into functional dopaminergic and GABAergic neurons.**

Genetic reprogramming of adult somatic cells into functional neurons is a promising therapeutic strategy for treating disorders such as Parkinson's disease and epilepsy. We plan to test electrophysiological properties of reprogrammed cells transplanted in mice brains. We will record synaptic activity and intrinsic firing properties of fibroblast-derived dopaminergic and GABAergic reprogrammed neurons in slices. We also will detect postsynaptic currents induced by laser photostimulation of reprogrammed neurons transfected with bacterial channelrhodopsins (ChR2). The data will provide evidence for functional integration of reprogrammed cells in control animals, as well as in models of Parkinson's disease and epilepsy.

**B. In vivo neurophysiology, plasticity and behavior**

**1. Neuronal polarity and neurogenesis.** We have reported that the pan-neurotrophin receptor $p75^{NTR}$ is a key polarity regulator that localizes asymmetrically in differentiating neurons in response to neurotrophins and transduces polarity signals for specification of the future axon. We will continue investigating the role of $p75^{NTR}$ in transducing signals for axonal specification. In addition, although the lifelong genesis of new mammalian neurons is well documented, the regulation of these neurons is largely unknown. However, microRNAs are rapidly emerging as candidate regulators of neurogenesis. Our previous work indicated that early stages of embryonal development are less dependent on miRNAs function than later stages. Our current work uses genome-wide profiling and acute *in vivo* target validation as an approach to identify novel miRNA-targets involved in developing mouse neocortex. We will apply this approach to discover the role of miRNAs in adult neurogenesis. This will be initially implemented *in vitro* and then validated *in vivo*.

**2. Functional in vivo imaging and cellular determinants of rhythmogenesis**. We will develop a camera-based, two-photon holographic microscope for fast *in vivo* functional imaging. When combined with calcium indicators, this technique allows the monitoring of the activity of cellular networks *in vivo* with high spatial and temporal resolution. Using ChR2 and halorhodopsin expression in subpopulations of layer II/III and layer V neurons in anesthetized and freely moving animals, we are examining the contribution of various subpopulations of cortical neurons to the generation and propagation of slow cortical oscillations.

**3. Physiology and plasticity of cortical circuits.** The focus of will be on the role of connections emanating from identified cell types within cortical circuits in simple forms of sensory-driven behaviour, and their modifications upon changes by sensory experience. This will be done at the level of local microcircuits, by exploring the differential plasticity of identified neuronal populations in clinically-relevant models of focal sensory deprivations or cortical lesions using two-photon targeted patch-clamp recordings in rodent visual cortex. This will be key to understanding how this circuitry is modified by modality-specific sensory deprivation during development. We will also address the unsolved mystery of the functional role of cortical minicolumns. To this aim, we will attempt to image the spiking activity of the clusters of dendrites formed by retrogradely labelled layer 5 cells receiving input from a common subcortical target. In addition, the function of cortico-tectal projecting neurons on simple forms of visually-driven behaviour will be explored.

**4. Neuromodulatory pathways and functional connectivity.** We will focus on the mechanisms regulating the functional connectivity between the cortex and subcortical regions (dorsal and ventral striatum), which plays a major role in sensory-motor integration and in learning of stimulus-response associations. We will analyse the functional cross-talk between dopamine and endocannabinoid-mediated signalling in modulating synaptic and behavioural plasticity at cortico-striatal circuits under physiological and pathological conditions. Synchronized cortico-striatal oscillatory activity is believed to be required for optimal execution of reward-guided motivated behaviour. We will investigate how the oscillatory activity between the cortex and defined striatal subregions influences the acquisition and expression of goal-directed/habitual behaviour.

**5. Genetics and epigenetics of sleep.** We will identify novel genomic and epigenomic targets for sleep and cognition, create mouse mutant models, characterize behavioral, physiological and molecular phenotypes and create a model of the functional role of sleep in cognition. The establishment of large archives of DNA from the F1 progeny of ENU-mutagenised mice will allow for systematic, genotype-based screens for mutations within specific genomic fragments. In addition, approximately 8000 genes have already been targeted in ES cells and are ready to be injected to generate mouse mutants. These targeting constructs have been generated in a way that they can initially be used to knockout the gene completely, but they also have the potential to be converted into conditional knockouts. A list of 15 selected gene mutants will be generated/rederived. Full knockouts will be phenotyped using primary screening batteries. Only relevant sleep/cognitive mouse lines will be selected to import in our facilities to perform targeted experiments.

**6. Physiology and pharmacology of monoamines and trace amines.** Monoamines, such as dopamine, are key CNS neurotransmitters regulating behavior and motor activity. Dysfunction of monoaminergic systems is related to Parkinson's Disease, schizophrenia, depression and ADHD. We will study dopamine function using mutant mice deficient in key components of dopamine homeostasis. We will also characterize mice carrying mutations in the dopamine-transporter (DAT) gene that have been recently identified in patients with Dopamine Transporter Deficiency Syndrome. To model theories of schizophrenia, we will develop a DAT knockout (to model hyperdopaminergia) and NR1 knockdown rat (to model hypoglutamatergia). To understand the physiological roles of a new family of monoaminergic receptors, trace amine associated receptors (TAARs), we will apply in vitro and in vivo approaches in knockout mice to characterize TAAR1/5/6 receptors, their transduction mechanisms and their effects on motor functions in intact mice and models of PD, such as 6-OHDA mouse model developed in TAAR5 and TAAR6 knockout mice.

**C. Mechanisms and early markers of brain diseases.**

**1. Detecting early molecular mechanisms of neurodegeneration.** Intraneuronal accumulation of the microtubule-associated tau protein and of β-amyloid (Aβ) is a hallmark of Alzheimer disease (AD) and other neurodegenerative disorders. In transgenic mice overexpressing human mutant tau protein or mutant APP, alterations of neuronal function occur before formation of inclusions. We will focus on the functional and molecular changes typical of initial stages of neurodegeneration to dissect the contributions of abnormal tau and Aβ oligomers to such events. Moreover, we will exploit the ‘biosensing’ properties of microglia to identify early pathological mechanisms triggered by Aβ aggregates and tau accumulation. The identification of initial molecular alterations of pathological cascades will help in developing disease-modifying therapies and biomarkers of potential clinical value in AD diagnosis and monitoring of therapy.

**2. Polyglutamine and motor neuron diseases.** Polyglutamine diseases are a family of neurodegenerative diseases caused by expansion of the CAG repeat encoding glutamine in the coding region of certain genes. Despite the widespread distribution of polyglutamine proteins throughout the CNS, specific populations of neurons degenerate in each disease, suggesting that the polyglutamine tract cannot be the only determinant of disease pathogenesis. Rather, we will study whether selective neuronal vulnerability may arise from the interplay between the polyglutamine tract and intrinsic properties of each mutant protein. Second, SBMA and ALS are neurodegenerative diseases characterized by the selective loss of motor neurons and skeletal muscle atrophy. Our goal is to identify altered signaling pathways that may be involved in these diseases.

**3. Identification of alpha-synuclein and amyloid beta neuronal targets.** We will investigate whether amyloid beta- and α-synuclein induce alterations of actin cytoskeleton dynamics and calcium homeostasis, which could play a role in the pathogenesis of Alzheimer and Parkinson's disease. We will dissect the intracellular pathways involved in amyloid beta and α-synuclein action and analyze the differential effects of the intracellularly or extracellularly delivered α-synuclein, searching for a putative receptor at the neuronal plasma membrane that may activate the intracellular pathways and affect cytoskeletal dynamics. Actin cytoskeleton is fundamental in the modulation of neurite outgrowth during growth and regeneration after injury. Our hypothesis is that amyloid beta and α-synuclein may inhibit or retard regeneration of injured axons. We will determine the possible effect of amyloid beta and α-synuclein on axonal re-growth following axonal transection and determine if their action is due to the binding to the external membrane surface.

**4. Etiology of neurodevelopmental behavioral disorders.** Mutant mice bearing targeted mutations of schizophrenia-susceptibility genes are unique tools to elucidate the neurobiological basis of this devastating disorder. Using genetically modified mice for genes relevant to schizophrenia, we will then employ a combined approach beginning at the behavioral level and culminating at the cellular and molecular levels. To develop effective tools for detecting high-risk individuals and prodromal stages, we will characterize neurobehavioral features of our genetically modified mice during critical developmental periods equivalent to adolescence/young adulthood in humans by assessing the timing of appearance of the behavioral abnormalities and the early neurochemical/synaptic dysfunctions within prefrontal cortex circuits.

## ADVANCED NEUROTECHNOLOGIES

Advanced Neurotechnologies starts with the aim to boost high-risk exploratory research in neuroscience with a strong interdisciplinary and technological content. There are a few areas growing at international level which are of interest for IIT, namely:

One area deals with innovative optical approaches for imaging the structure and function of the nervous system and for selectively perturbing the nervous system with light, especially in vivo. Innovative approaches include techniques for multiple-area *in vivo* imaging of neural structure and activity, innovative approaches for imaging of deep cortical layers or subcortical structures, enhanced optogenetics techniques for activating or inactivating specific neural populations, and advanced techniques for imaging live structures at a scale below the diffraction limit of visible light. Nanophysics and Nanostructures would be important collaborators in these efforts. In addition to optical approaches, the development of reagents that can be read-out or manipulated by non-visible electromagnetic radiation or ultrasound, for non-invasive or deep-brain monitoring and manipulation of neuronal populations, is also very promising. For example, nanoscale "antennas" conjugated to cell-specific markers could allow for read-out or manipulation of specific cell types in vivo (in collaboration with Nanochemistry).

2. Approaches for monitoring and manipulating neuronal populations in freely moving, behaving animals are also very promising for brain studios. This could include cable-free optical systems for optical imaging and miniaturized closed-loop stabilization methods (e.g., with laser interferometry) to allow for long-term recordings (in collaboration with Nanophysics, Nanostructures, Computer imagining and Robotics)

3. An important area is in developing innovative techniques for electrical measurements of neural activity, especially in vivo. These could include miniaturized multi-electrode arrays, autonomous, wireless devices for

in vivo recording, and new reagents or techniques for *intra*cellular recording *in vivo* (in collaboration with the Nanobiotech facilities).

Most of these ideas require nanochemistry-based reagents and techniques, including innovative devices for real-time measurement of neuro-active molecules *in vivo*, new reagents for functional imaging (such as "smart" magnetic particles for enhanced functional magnetic resonance imaging based on real-time neuronal signals rather than slow metabolism), and new chemical reagents for labeling and tracing specific neural populations. Another key component to many of the aforementioned projects is the interfacing of molecular biology with innovative nano-scale reagents. Molecular biology provides unprecedented ability to identify and manipulate specific neural cell types and circuits, and could be used to direct exogenous reagents to desired targets. For example, innovative nanoscale reagents can be directed to specific neuronal cell types by functionalizing the reagents to bind to specific cell-surface molecules. In addition, new viral technology can allow gene transfer and specific cell expression in non-genetic-model organisms. All these efforts will require high expertise and innovation in molecular biology, and underscore the importance of recruiting a world-class molecular biologist to IIT.

The following main research lines will be developed:

**A. Reverse engineering of the brain.** Brain processing involves anatomical and functional dynamics occurring over a wide range of spatial and temporal scales. Conventional techniques used to investigate brain processing are limited to specific scales as well as to distinct observation of anatomical processes, electrophysiological signalling or neurochemical changes. This technological frontier is a major constraint for unravelling how information is processed by brain circuits. Our approach focuses on the development of instrumentation based on array-integrated neuroelectronic devices realized by micro-/nano-technologies and bio-mimetic approaches to observe and interact with large neuronal circuits at cellular/sub-cellular resolution and converging multi-modal imaging, as well as neurocomputational methods to describe both anatomical and functional architectures. Based on our recent development of a high-resolution electrodei array platform, this electrode-based approach will be further developed to observe neuronal signalling from in-vitro neuronal circuits, up to acute tissue preparations and in-vivo animal models. This will allow us to develop interfacing hardware and software tools for analysis, and computational modelling to ultimately allow for real-time closed-loop 3D interfacing and analysis of brain circuits in vivo.

**B. Optointerfaces and new optogenetic probes.** Interfacing artificial functional materials and living neuronal tissues is at the forefront of bio-nano-technology. We have reported the successful interfacing of an organic blend to a network of primary neurons, opening the way to the implementation of efficient opto-neural interfaces and retinal prosthetic devices. We will proceed toward the generation of a polymer-retina interface on retinal explants and in vivo implants in mouse/rat models of photoreceptor degeneration. A novel application of the optogenetic technology is the modulation of signaling. We are planning to implement a range of new opto-probes using the light-oxygen-voltage (LOV) domains to modulate protein-protein interactions and control gene expression at either transcriptional or post-transcriptional level. We also plan to engineer bi-functional proteins composed of both a sensor and an actuator, sensing intracellular/extracellular stimuli (pH, $K^+$, $Ca^{2+}$ or membrane potential variations) and inducing appropriate adaptive responses in the electrical or metabolic state of the target neurons.

**C. Technologies for sampling, manipulating and simulating neural activity and coding schemes.** We will focus on the development of implantable, tissue-adaptive *polymeric microelectrode arrays* as multimodal (electrical, optical, microfluidic) *in vivo* recording and stimulation devices with multiple transduction sites for epicortical, deep brain and cardiac electrophysiology for basic neuroscience, diagnostics, neuroprosthetics and *in vivo* drug evaluation. Key objectives will be: (i) the development and optimization of rapid prototyping and production schemes for specific device geometries and electrode layouts; (ii) research into multifunctional materials to support device placement and long-term tissue integration or timed drug delivery; (iii) integration of optical approaches for microscopy with concurrent optical electrophysiology and manipulation. We will also design a *neuromimetic hardware architecture*

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mimicking the well-characterized nervous system of the nematode *C. elegans* to test our understanding of information processing in neural networks, and to aid in the creation of a new class of highly parallel and configurable architectures to address computational challenges that are still beyond reach for most current *von Neumann*-based information and communication technologies.

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## D3 DEPARTMENT: DRUG DISCOVERY AND DEVELOPMENT (PROF. D.PIOMELLI)

### Introduction

In the period between 1985 and 2000, the pharmaceutical industry has been a leader in financial performance and value creation, providing average annual returns that exceeded those of any other industrial sector – including information technology and telecommunication. The business model that led to this success is straightforward: new products are discovered through research and development, while patents protect high revenues for 10 to 12 years after product launch. Intellectual property plays a crucial role: a new class of drugs is typically covered by only one or a few patents, which control in turn markets ranging from US$0.5 billion to $10 billion per year. But since the end of the 1990's, this model has come under attack and top pharmaceutical companies have suffered considerable losses in shareholder value. There are several possible causes for this reversal of fortune. Nevertheless, experts agree that a major factor driving the crisis is a long term decline in productivity experienced by pharmaceutical research and development. This decreased productivity is certainly not related to available budgets, which have increased 30-fold since 1970, but rather to a 'perfect storm' generated by an increase in costs, enhanced pricing pressure and a toughening of the regulatory environment. A consequent wave of mergers and acquisitions has lead to increased bureaucracy and overhead spending. These elements, and particularly the latter, have conspired to stifle innovation and steer research toward low-risk projects. It is not surprising, therefore, that a significant fraction of the development portfolio in the largest pharmaceutical firms is currently in-sourced from academic labs and start-up companies.

The ability of these small entities to create innovation has never been examined quantitatively, but is generally considered to be very high. One important problem limits, however, the impact that academic research can exert on drug discovery. Publicly funded labs usually lack the mind-set and resources needed to advance basic discoveries toward the creation of new products. They tend to concentrate their efforts on making and publishing important discoveries, while paying little attention to the need of protecting the intellectual property generated or validating their findings as a source of economic growth. The process of validation, or 'de-risking', is essential to capture the full economic and societal value of a scientific advance. In the pharmaceutical field, the de-risking of a discovery consists in determining its potential therapeutic use (e.g., by conducting proof-of-concept experiments in animal models of disease), evaluating its liabilities (e.g., by performing preclinical toxicological studies), resolving technological problems (e.g., by developing appropriate drug formulations), and building a strong intellectual property portfolio.

The early stages in the de-risking process are not prohibitively expensive, yet they allow one to decide whether to propel a promising technology toward the market or, conversely, to halt its commercial development. Passing such stages successfully requires specific experience, know-how and resources that most academic labs do not have**. Our mission is to fill this gap while advancing knowledge. Our objective is to discover transformative drugs and facilitate their progression toward the clinic and the market.**

### Organization

To achieve this objective, in the first 18 months since the start of its activities, D3 has strived to create a research environment that is conducive to innovative drug discovery. Fostering such an environment is a complex task, which we have addressed at two different levels. First, **our recruitment efforts have targeted scientists with both industrial and academic backgrounds**. As of today, 5 of our 9 team leaders and 3 of our 4 senior scientists come from the pharmaceutical industry. This choice helped us to create an environment that balances experience in drug discovery with out-of-the-box thinking. Second, **we have implemented a matrix-based organization** in which scientists from different **Functions** interact productively on specific goal-oriented **Projects.**

The primary role of a **Function** is to provide resources and technologies needed to accomplish the goals of all Projects. The Head of Function acts as project facilitator and is accountable for the seamless working of the resources she/he oversees as well as for the development of the technological know-how of the Function. We have presently three Functions, each of which is headed by a senior scientist who serves as Function Head:

· *Computational Chemistry and Biophysics (*directed by Dr. Andrea Cavalli). Andrea received his PhD in Pharmaceutical Sciences from the University of Bologna and did postdoctoral work at SISSA (Italy) and ETH (Switzerland).

· *Medicinal Chemistry* (directed by Dr. Tiziano Bandiera). Tiziano obtained his PhD in chemistry from the University of Pavia (Italy) and worked at Farmitalia-Carlo Erba, Pharmacia, Pfizer and Nerviano Medical Sciences.

· *Pharmacology* (directed by Dr. Angelo Reggiani). Angelo received his PhD in experimental pharmacology from the University of Milan (Italy) and worked at Zambon, Glaxo-Smith-Kline and Schering-Plough.

On the other hand, **Projects** are temporary research endeavors that are undertaken to achieve specific objectives and milestones. The long-term goal of a Project is to identify one or more optimized lead compounds suitable for preclinical development and final progression to clinical trials. The Project's main champion is the Project Leader, who is accountable for defining objectives and timelines, monitoring progress and resources, etc. We distinguish 3 different types of Projects:

· *Advanced Projects* have as objectives (1) the optimization of 'lead' compounds; (2) the identification of suitable candidates for preclinical development; or (3) the coordination and performance of preclinical 'de-risking' activities (e.g., toxicological, pharmacokinetic or preformulation studies). These projects are highly structured, have stringent milestones and yield technology packages that can be licensed to or partnered with the pharmaceutical industry. They are expected to last for a maximum of three years and are constantly monitored by the Research Director of D3 supported by a panel of external advisors from the pharmaceutical community.

· *Exploratory Projects* are aimed at the identification, validation and characterization of potential disease targets (enzymes, receptors, biological pathways). These projects have flexible structure and variable duration, and are subjected to periodic progress reviews. They provide a pool from which Advanced Projects are selected.

· *Enabling Projects* have as objective the creation of novel computational tools for drug discovery.

These tools are utilized to advance D3 research and are eventually made available to the scientific and pharmaceutical community using appropriate venues (open source or licensing).

In addition to these departmental projects, D3 is working with the laboratory of Nanochemistry, directed by Dr. Liberato Manna, to start an interdisciplinary new project named BIOTACK., also listed in Technical Annex II.

**Advanced Projects**

**The endocannabinoid system as a target for novel analgesics**

The endogenous cannabinoid system modulates a range of physiological processes in the central nervous system and periphery, including pain, inflammation, mood and anxiety disorders. This signaling system has three key components. The first is represented by the CB1 and CB2 cannabinoid receptors, the cell-surface receptors that are activated by the active principle of cannabis, D9-tetrahydrocannabinol (D9-THC). The second is constituted by the endocannabinoids arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), lipid molecules that are generated on demand by cells, activate cannabinoid receptors, and are rapidly eliminated. The third component is represented by the proteins – enzymes and transporters – involved in endocannabinoid formation and deactivation. The biological actions of endocannabinoids are terminated through a two-step process consisting of transport into cells followed by intracellular hydrolysis. The major degrading enzymes for anandamide and 2-AG are the fatty-acid amide hydrolase (FAAH) and monoglyceride lipase (MGL), respectively.

Activation of cannabinoid receptors causes profound analgesic effects in animal models of pain. However, globally acting cannabinoid agonists, such as D9-THC, produce a spectrum of motor and psychotropic side effects, which are mediated by the central cannabinoid CB1 receptors. On the contrary, increasing the levels of anandamide by genetic deletion or pharmacological inhibition of FAAH reduces pain sensitivity in mice with a more restricted spectrum of side effects than those produced by direct-acting CB1 agonists.
Selective FAAH inhibitors represent potential new drugs for the treatment of pathological conditions where an increase in the endocannabinoid tone may be beneficial, such as pain and central nervous system diseases. At the D3, we are currently optimizing globally-acting as well as peripherally restricted FAAH inhibitors.
Another approach to sustain anandamide levels consists in blocking the transmembrane transport system. The molecular identity of this transporter has long remained unknown. We recently discovered a key protein component of anandamide transport, which we named FLAT (FAAH-Like Anandamide Transporter), and we have identified a small molecule inhibitor of the transporter that we are now investigating.

*Peripheral FAAH inhibitors for post-operative and visceral pain* (Project Leader: Tiziano Bandiera, Senior Scientist). Anandamide is produced in peripheral injured tissues and activates cannabinoid receptors on pain-sensing terminals, which prevent the access of pain-carrying signals to the brain. The compound ARN354 stops the degradation of anandamide, caused by the enzyme fatty acid amide hydrolase (FAAH), and by doing so produces profound analgesic effects in animal models of pain. ARN354 does not enter the brain and spinal cord, yet its analgesic actions are equal or superior to those of centrally active analgesics. We are optimizing ARN354 to identify a suitable candidate for preclinical development, which we expect to position for post-operative pain and/or other nociceptive pain states.
*Global FAAH inhibitors for smoking cessation and sleep disorders* (Project Leader: Tiziano Bandiera, Senior Scientist). In parallel with the development of ARN354, D3 is optimizing brain-penetrating FAAH inhibitors for the treatment of central nervous system diseases, such as nicotine addiction and sleep disorders, in which preclinical and clinical evidence suggest a role for anandamide. This project is partially supported by a 5-year grant from the US National Institutes of Health.

**PEA signaling pathway**

Palmitoylethanolamide (PEA), the amide of palmitic acid and ethanolamine, is a naturally occurring bioactive signaling molecule in a remarkable number of cellular events. PEA was isolated from plant and animal tissues over 50 years ago. Soon after, PEA was shown to reduce allergic reactions and inflammation in animals, and was briefly used to treat influenza symptoms in humans.
The recent years have seen a significant increase of interest on the PEA pathway as target for novel drugs, mainly due to the finding that when PEA is given as a drug it has profound analgesic and anti-inflammatory effects in rodents and attenuate skin inflammation in humans via activation of nuclear receptor PPAR-α. Interestingly, available data seems to suggest that PEA could be part of an endogenous mechanism to keep inflammatory mediators release under control thus disregulation of PEA signaling can lead to the development of a pathological state. Consistent with this hypothesis we found that proinflammatory stimuli can reduce PEA levels in innate immune cells of rats and mice as a possible consequence of a reduced biosynthesis which makes less PEA available to keep the pathway active. Similar PEA level reduction were observed in man in synovial fluid from rheumatoid arthritis and osteoarthritis patients, compared to healthy control subjects.
Following up these initial discoveries, we have initiated a research effort to identify the best way to correct PEA signaling disregulation under pathological conditions. PEA is primarily formed by catalytic cleavage of N-acylated phosphatidylethanolamine (NAPE) *via* a membrane-associated NAPE-phospholipase D (NAPE-PLD) and is primarily inactivated by enzymatic cleavage *via* a N-acylethanolamine-hydrolyzing acid amidase (NAAA), a lipid amidase that is localized in lysosomes and is highly expressed in inflammatory cells such as macrophages. The current strategy includes an advanced project targeting NAAA with molecules active as covalent inhibitors (restoration of PEA levels by blocking degradation) and an

exploratory project to study the biological effect of NAPE-PLD modulation.
*NAAA inhibitors for chronic inflammatory disorders* (Project Leader: Angelo Reggiani, Senior Scientist). Initial studies by our group have identified the first class of small-molecule inhibitors of intracellular NAAA activity and have shown that these agents can restore the reduced PEA signalling and blunt inflammatory responses both in vitro and in vivo. The current projects aims at developing a 2nd generation of NAAA inhibitors for the treatment of different inflammatory disease states. In animal models, these compounds were shown to be highly effective at reducing inflammation, and to lack the side effects typical of steroidal and non-steroidal anti-inflammatory drugs. We have identified a potent lead compound and are currently optimizing it with the objective of identifying a suitable candidate for preclinical development. Available preclinical data suggest that these compounds may find use in chronic inflammatory conditions such as rheumatoid arthritis and asthma.

**Exploratory Projects**
*FLAT inhibitors* (Project Leader: Giovanni Bottegoni, Post Doc). Using an *in silico* approach we identified a small molecule competitive inhibitor that selectively interacts with this protein. The compound, called ARN272, blocks anandamide deactivation and causes profound analgesia in mouse models of pain. This project combines computational methods and classical structure-activity relationship analyses to define pharmacophores for FLAT inhibition, improve on the scaffold of ARN272, and eventually identify potent and selective FLAT inhibitors. Based on available data, we hypothesize that FLAT will offer an innovative target for neural inflammation, drug addiction and neuropathic pain.
*NAPE-PLD modulators* (Project Leader: Gianpiero Garau, Team Leader).This project utilizes a variety of biophysical methodologies (X-ray crystallography, NMR etc) to investigate the structural properties of NAPE-PLD and identify small-molecule modulators of its activity. This project is partially supported by a Marie Curie fellowship.
*Dual FAAH-Cox inhibitors* (Project Leader: Marco De Vivo, Team Leader). The simultaneous inhibition of the anandamide-degrading enzyme FAAH and the prostaglandin-generating enzyme cyclooxygenase (COX) may produce greater pharmacological efficacy and fewer side effects than either mechanism alone.
This project integrates computational and biophysical methods to discover dual-target FAAH/COX inhibitors with potential application in cancer and chronic inflammation.
*Clock Modulators* (Project Leader: Benedetto Grimaldi, Team Leader). The activities of our body follow cycles of repeated oscillations, which are regulated by a circadian biological clock. We hypothesize that small molecules acting on specific component of the clock machinery may provide a promising approach for pharmacological intervention in neurodegenerative disorders such as Alzheimer's Disease. To test this hypothesis, in this project we use molecular biological and computation approaches to search for molecules acting on a series of clock elements such as CRY, PER and REV-ERB.
*Dual inhibitors for Alzheimer's disease* (Project Leader: Andrea Cavalli, Senior Scientist). Alzheimer's is a multifactorial disease, where a complex interplay of genetic and biochemical events takes place. Standard of care for the treatment of the disease is the use of a combination of two drugs, memantine (an NMDA receptor antagonist) and a cholinesterase inhibitor (i.e. galantamine, donepezil, rivastigmine). A novel possibility to contrast the multifaceted nature of Alzheimer's disease is the development of multitarget drugs, namely single chemical entities able to tackle the neurodegenerative pathways at multiple key points.
In a first project, we aim to identify dual-target compounds – inhibitors of the enzyme acetylcholinesterase (AChE), and antagonists of the extrasynaptic NMDA receptor channels NR2B. Preclinical and clinical evidences suggest that such compounds might interact synergistically to improve cognition. In particular, AChE inhibitors can slow down the cognitive impairment associated with the disease by stimulating the cholinergic system. NR2B antagonists can tackle the NMDA-induced neurodegeneration, thus prolonging the neurons survival, and in turn prolonging the beneficial effects related to the stimulation of the cholinergic system. This project has identified a first series of chemical hits in this class and is currently optimizing these

compounds and testing their pharmacological effects in vitro and in vivo.
In a second project, we aim to identify dual inhibitors of the enzymes BACE-1 and GSK-3b. BACE-1 is an aspartic-acid protease responsible for the formation of the Ab peptide, the major component of b-amyloid plaques, which are one of the two histopathological hallmarks of Alzheimer's disease. GSK-3b is a protein kinase involved in the hyperphosphorylation of the tau protein, and the formation of neurofibrillary tangles, the other histopathological hallmark of AD. Here, we use state-of-the-art drug discovery technologies to identify BACE-1/GSK-3b combined inhibitors in order to demonstrate that dual-target compounds hitting proteins on complementary pathways (amyloid and tau cascades) could offer a significant step forward with respect to single-target molecules. If successful, the new molecules would represent the first example of compounds rationally designed to tackle the two major characteristic and pathological lesions of Alzheimer's disease. The project has identified the first series of fragments able to bind either to BACE-1 or to GSK-3b. These are new chemical scaffolds that we intend to use for designing fused or hybrid dual-target inhibitors to be then synthesized.

**Enabling Projects**
Computational methods have permeated all aspects of modern drug discovery. However, these in silico approaches still suffer from some major limitations that require novel algorithms to be developed. In structure-based drug design, the ligand-protein binding free energy, which can be used to predict the affinity of a new drug for its biological counterpart, is still estimated with an unacceptable level of approximation. In ligand-based drug design, the need to generate a structural alignment of a set of compounds to be subsequently used to generate statistical models, has limited the predictive power of conventional QSAR and 3D QSAR methodologies. Aimed to overcome the major limitations of conventional structure- and ligand-based computational tools, D3 computer scientists are involved in the development of novel algorithms for drug discovery. Three major enabling projects are carried out at D3: Electrostatic modeling of biomolecular systems; Free energy estimation of protein-ligand binding; Next generation 3-dimensional QSAR.
Furthermore, Andrea Cavalli (Senior Scientist) coordinates the activity of the IIT Platform "Integrated Multiscale Computational Technology". The goal of the platform is the multiscale integration of different computational approaches toward the development of novel software to utilize in different fields, spanning from life sciences and nanobiotechnology, to material sciences. The platform focuses on the following applicative issues which represent challenging open problems:

- Inorganic nanocrystal and their interaction with biological systems;
- Multiscale modeling of photovoltaic cells;
- Design of smart molecular machines for medicine and biology.

*Electrostatic modeling of biomolecular systems* (Project Leader: Walter Rocchia, Team Leader). Theoretical and computational obstacles make extremely difficult the quantitative description and prediction of the electrostatic properties of proteins and other biomolecules. Yet, such properties are of paramount importance. The goal of this project is to create enabling tools for the investigation of the electrostatic potential in systems of size ranging from the nanoscale to the microscale, with particular attention to those of biomedical interest (e.g proteins, nucleic acids, lipid membranes, etc.). This project is supported by a 5-year grant from the US National Institutes of Health.
*Free energy of protein-ligand binding* (Project Leader: Andrea Cavalli, Senior Scientist). A critical problem that limits the predictability of structure-based drug design methods is the inadequate accuracy of free energy estimations of the protein-ligand binding process. The goal of this project is to bring the estimation close to the experimental accuracy. We generate new algorithms based on enhanced sampling techniques, which can provide an accurate estimate on of thermodynamic quantities related to rare events, such as ligand-protein binding. Ad hoc strategies for improving the scalability and efficiency of new codes on highly parallel hardware architectures are developed to extend the capabilities of current simulation techniques.

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*Next-generation 3-dimensional QSAR* (Project Leader: Walter Rocchia, Team Leader). The goal of this project is to improve the predictability of quantitative structure-activity relationship analysis (QSAR), which are widely utilized in ligand-based drug design. To achieve this, we apply state of the art data-mining and machine learning and shape analysis techniques, which proved useful in extracting informative patterns from complex datasets, to the outcome of quantum mechanical calculations of molecular electronic properties. The resulting new generation of tools for statistical analysis will increase the predictability of biological and pharmacological features responsible for the drug-candidate efficacy and toxicity.

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**THE CROSS-DISCIPLINARY FACILITIES**
**NANOSTRUCTURES**
**(PROF. E. DI FABRIZIO)**

The scientific activity at Nanostructure department evolves from the original facility-scheme into a highly focused, high risk transversal research program which will accelerate the growth of IIT in different fields, thanks to the implementation of novel technologies and devices of general interest. The activity focuses on the design and fabrication of new-concept nano-devices and their use for facing basic and applied problems of modern science. The key issue is to find a solution to the long standing problem of **delivering Energy at Nanoscale.**

Such a general theme deals with the optimization of the interaction of a macroscopic source of energy with a nanostructure. This problem is the starting point of many others in different fields, such as nanospectroscopy, design of efficient fotovoltaic systems, opto energy transfer in biology, novel concepts of nanolithography (also applied to biological materials) etc. The general unified approach that we will follow relies on the optimized design and fabrication of nanostructrures, enabling the generation of localized or propagating Surface Plasmon Polaritons (SPP), which will allow the delivery of energy at nanoscale. In this sense Plasmonics is the "trait de union" between all activities in the department, as in most cases, the new tools designed for nanoscale studies will be based on Plasmon propagation. The development of advanced novel instrumentation for enhanced nanospectroscopy will follow this approach and will be treated as a problem of energy delivering at Nanoscale. SERS (Surface Enhanced Raman Spectroscopy) based on continuous wave Laser source, or CARS (Coherent Anti Stokes Raman Scattering) or the more advanced RRS (Resonant Raman Scattering) based of ultrafast sources, will be mediated by a nanostructure, in order to obtain, at the same time, chemical resolution and spatial resolution at nanoscale. This opens up the way to a few new interdisciplinary applications, which will bring IIT at the forefront of the international competition in different strategic fields, namely:

**1.Novel devices for Single Molecule Detection**

Biologists and neuroscientists study cells, neurons and tissues to understand molecular mechanisms underlying biological events. However, very rarely they deal with or are able to detect single molecules and their understanding of molecular events is blurred by the poor experimental resolution.

Single molecules can be detected and their motion followed when they are labeled with an appropriate tag, such as a fluorescent label i.e. the green fluorescent protein (GFP) and/or quantum dots, combined with the molecule of interest by genetic engineering or chemical manipulation. Manipulation of single molecules as well as the measurements of several important mechanical properties can be performed with optical tweezers (OT) and atomic force microscopy (AFM). Biologists dream of a miniaturized chemical probe or microscope which could be moved around and inside a cell, able to detect, visualize, characterize and identify a single or a small number of molecules. Future breakthroughs in the understanding of fundamental biological processes and of molecular events causing major diseases require a miniaturized chemical probe or microscope, which could be moved around and inside a cell, able to detect and identify a single or a small number of molecules. The complete characterization (mechanical and spectroscopic) of a single unknown molecule will be applied to study processes of biological and medical interest such as the chemical composition and physical properties of membrane receptors, and molecules involved in cancer development and metastasis. In addition these new devices will allow the acquisition of THz images, paving the way for the use of such spectral region for biomedical scanning.

Direct characterisation for label-free detection of biological molecules such as proteins, nucleic acids or etiological agents of specific diseases is of real importance since it avoids the use of an intermediary molecular species. Such a direct characterisation is possible by the use of vibrational spectroscopies. Indeed, vibrational spectroscopies (IR absorption and Raman scattering) are powerful tools for label-free characterisation of biological species since the vibrational modes are actual fingerprints of both the whole molecule (chemical bonds, conformation, 3D structure…) but also its local interaction with other molecules (binding between two molecules…). Unfortunately, IR absorption and Raman scattering cross-sections in common experimental set ups are far low and require a large amount of sample. However, observations of surface plasmon resonance in metallic nanostructures have demonstrated the existence of large enhancement of the electromagnetic field on the local scale.

The field enhancement created in the vicinity of a metallic nanostructure surface can be controlled through the physical parameters and optical properties (localised surface plasmon resonance…) of the particles and this field enhancement can reach several orders of magnitude. Exploiting such field enhancement in vibrational spectroscopy, surface enhanced Raman scattering (SERS) and surface enhanced IR absorption (SEIRA), have indicated the way towards extreme amplification of the vibrational signal (enhancement factor of $10^{14}$ for SERS1 and $3x10^{5}$ for SEIRA) and have allowed the observation of a very low amount of molecules (around 100 000 molecules in SEIRA) or even the single-molecule sensitivity in SERS.

**2. Novel methods and devices for Opto genetics studies**

This activity aims at the development of a novel generation of biologically inspired molecular devices (MDs), exploiting new photonic tools based on Polariton technology, enabling focused light spots of diameter around 10 nm. We will also develop new light sensitive molecules that will be selectively activated by our new photonic tools. Such a technological innovations will provide a way to control activation of *single* light sensitive molecules and will allow the investigation of molecular computation in a biological environment with unprecedented resolution.

**3. Metal-Semiconductor Hybrid Nanosystems**

Metal nanostructures are very good conductors and can strongly interact with light in the visible and infrared spectral regions due to the presence of free electrons inducing plasmon oscillations. In semiconductor nanocrystals the band gap and consequently, the optical and electrical properties, depend strongly on their size, shape and composition.

The aim of this activity is to couple the light emitted by semiconductor nanocrystals into metallic nanostructures via plasmonic effects. This will allow us to reduce the spatial extension of the optical signal by one order of magnitude, resulting in remarkable light field enhancement and in miniaturizing of optical communication circuits.

Another approach is based on the controlled manipulation of the electrical conductivity of complex metal-semiconductor network structures by plasmonic excitation in the metal particles. Typically, on a metal-semiconductor interface a Schottky barrier is formed that hinders transport of charge carriers. The plasmonic resonance of metal nanoparticles integrated into a semiconductor nanostructure network represents a controllable tool to manipulate the Schottky barrier and to control the conductance.

The strong size dependence of the optical properties of the metal and semiconductor nanostructures enable multiplexed switching via different wavelengths of the exciting light beams.

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## NANOCHEMISTRY
## (DR. L. MANNA)

The Nanochemistry facility has been growing exceptionally fast over the last three years, becoming one of the world leading labs in the field of chemical nanotechnologies. Both the international acknowledgment of its results, and the strategic value of the colloidal nanoparticles for many different IIT activities, make the nanochemistry facility a pillar of the institute. For the next strategic plan Nchemistry will develop a strong interdisciplinary program targeting three main fields:

1. Nanoparticles for Intelligent drug delivery
2. Nanoparticles for energy
3. Nanoparticles for Novel Self-Assembled Materials

Each one of these fields represents a challenge for the international community in which IIT has a leading role, and a unique opportunity to feed other research programs/activities carried out in other departments and network centers, namely the intelligent drug delivery is in collaboration with D3 and NBT, energy with the robotics, and the new materials with several centers of the network and with Nphysics and nanostructures.

### 1. Nanoparticles for Intelligent Drug Delivery

#### A. Development of multifunctional polymeric sub-micrometer beads for cell sorting, cell detection and cell manipulation applications

The early diagnosis of tumours requires the detection and the isolation in biological liquids of low concentrations of tumor markers or cells. Also based on the evidences that radiation therapy and chemotherapy both fail in the long run treatments as they cannot kill sub-populations of tumor-initiating cells, the ability to isolate, identify and study cancer stem cells within a tissue sample will be of great value in order to develop treatments that aim to target and eliminate cancer stem cells.

To this aim it is challenging to develop suitable nano-tools able to detect, sort and manipulate cells. A magnetic-fluorescent nano-system would perform at the same time separation and detection of cells or analytes while its nanoscale size would offer a high surface to volume ratio for the derivatization of the nanostructure surface with specific ligands for targeting tumour cells or cancer stem cells.

At IIT we have recently developed magnetic-fluorescent nanobeads based on cluster of superparamagnetic nanoparticles and fluorescent inorganic nanocrystals having different advantages:

i) they can accumulate promptly to a magnet (within a few minutes);
ii) their size is kept below a few hundreds of nanometers for ensuring high sensitivity;
iii) they show a good stability in aqueous media;
iv) they include within the structure fluorescent probes (including standard organic dyes, photosensitizers, quantum dots, QDs, lanthanide nanocrystals) able to achieve multiplexing analysis;
v) the bead surface can be easily functionalized with tailored molecules for specific targeting;
vi) the surface charge of the beads can be engineered in order to make it responsive to the pH thus allowing the loading and the release of polycationic or polyanionic molecules associated to the bead surface;
vii) Additional polymeric layer having thermo-responsive or pH-responsive behaviour, or acting as protecting layer with biodegradable properties, can be associated to them;

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These multifunctional platforms will be exploited for different purposes, including:

a) the isolation of cancer cells (including cancer stem cells);
b) their exploitation as delivery tools of growth factors to promote the cell survival and adhesion in vitro;
c) their use as control delivery carriers of siRNAs/amiRNAs release to tumour cells, in order to pave the way to new therapeutic approaches based on gene therapy;
c) their exploitation as fluorescent tags for studying the interaction of those cells with other cell populations in 3D culturing;
d) Their exploitation as contrast agents in molecular resonance imaging for the *in vivo* tracking of specific cell populations (such as stem cells);

**B. Stimuli-responsive magnetic carriers for controlled release of various agents**

In current chemotherapies a critical drawback is related to the non specific delivery of drug compounds not only to malignant cells but also to healthy cells. As a direct consequence, the use of large doses of drugs, with severe side effects, is required. Existing treatments could be by far more efficient if the drugs could be associated to nanoconatiners and they could be delivered selectively to the tumour site under defined stimuli.
*pH AND TERMOSENSITIVE HYDROGELS* are polymeric nano-beads that are able to undergo volume changes and thus drug incorporation and release under the effect of physical and chemical stimuli, like heat or pH.
Our ongoing activity at the nanochemistry department at IIT has highlighted the feasibility to combine hydrogel materials with different types of inorganic nanocrystals having interesting features for therapeutics or imaging purposes. For instance, the inclusion of magnetic nanoparticles within the hydrogels will allow additional tasks: it will facilitate the delivery and the detection under a magnetic field to a tumour site and at the same time it will act as a hyperthermia agent to heat locally the nanostructure and trigger the drug release.

We will develop biodegradable hydrogel nanocarriers for combining hyperthermia mediated by inorganic nanoparticles with stimuli-responsive drug carriers for a multivalent approach to cancer therapy. Challenging issues will be the control of the size of the vectors below a threshold of 300 nm in size, the identification of the right magnetic nanoparticles with the most performing features, the drug encapsulation, the biodegradable nature of the polymer materials and the fusion of such polymeric nanocontainers with the magnetic nanoparticles.
The following key objectives will be targeted:

a) Synthesis of controlled magnetic nanoparticles whit high efficiency for hyperthermia treatment will be performed and the materials will be magnetically characterized. Also, procedures to control the clustering of those nanoparticles in anisotropic shape will be developed. Magnetic characterization will be carried out in order to compare the effect of the assembly on the magnetic properties.
b) Preparation of magnetic nanobeads (MNBs), as described in research line 1, based on magnetic nanocrystals having the most efficient heat performance. Both the individual magnetic nanocrystals and the magnetic beads will be exploited as the active tools for hyperthermia tumour treatment, imaging and induction of the stimuli.
c) Development of procedures to growth various types of biodegradable stimuli-responsive polymer at the surface of both individual magnetic nanoparticles and magnetic nanobeads.

d) Preparation of pH-responsive and thermo-responsive biodegradable nanocontainers and their assembly with magnetic nanoparticles in order to merge in a single nano-object the two individual sub-units, each of them able to perform specific tasks. Polymers that exhibit a volume transition temperature above 37 °C are ideal candidates for controlled drug release. The shell would therefore protect the drug and release it only when undergoing a volume transition caused by application of a heat stimulus. Also pH-responsive nano-vectors that respond to an acidic pH are interesting systems because the intracellular environment of tumour cells is highly acidic. We will develop nano-vectors that will swell at acidic pH.
e) Layer-by-layer methods for the deposition of biodegradable pH-responsive polymer shell at the surface of magnetic nanobeads will be developed and the encapsulation of drug molecules within the polyelectrolyte layers will be study.
f) Study of the encapsulation and of the controlled release of a wide variety of antitumoral agents including drugs approved by the FDA and now used in chemotherapy; polycationic antimicrobical agents; polyanionic short interfering RNA for siRNA therapy; photosentitizer molecules will be carried out.
g) Linking of drug molecules to the magnetic nanoparticle surface through linker molecules (thermo or pH sensitive);
h) Functionalization of the nanostructure's surface with specific ligands for selective targeting towards tumour cells.
i) In vitro study on tumour cells of the stimuli-responsive drug release and of the chemotherapeutic effects.

**C. Synthesis of heterostructures by exploiting bacteria**

Magnetotactic bacteria are organisms able to naturally synthesise magnetic nanocrystals called magnetosomes. The magnetosomes are crystals of either magnetite ($Fe_3O_4$), or greigite ($Fe_3S_4$) coated by a membrane layer. The production of magnetosome is the natural route to fix iron compounds and store them for ages. The magnetosomes are among the most efficient nanoparticles available for hyperthermia. The aim of this research line is to exploit these bacteria as bioreactors for the preparation of complex inorganic nanostructures. To such purpose we will trigger the uptaking of preformed nanocrystals by exploiting the natural uptaking pathway of iron compounds. Synthesis of nanostructure and characterization of the materials will be carried out.

**2. Nanoparticles for Energy**

**A. Nanocrystal-based electrode materials for Li –ion batteries**

Metal sulfides and phosphides nanocrystals of different shapes such as flakes, rods and disks will be synthesized and investigated for use as possible anode materials in $Li^+$ ion batteries. In general, a wide range of transition metal oxides (often anisotropic shapes) will also be explored. For cathode materials, lithiated metal (M=Fe, Co, Zn, Mn and Ni) ternary (*for example* $LiCoPO_4$) nanocrystals will be studied.
The following key objectives will be targeted:
Synthesis: Primarily, colloidal synthesis approaches based on hot injection in coordinating solvents, will be used to prepare those nanocrystals because by these approaches it is possible to fine tune not only the size but also the shape of the nanoparticles, due to the presence of surfactant molecules capable to selectively stabilize specific facets of the nanocrystals. This represents an important aspect in the $Li^+$ ion battery, as $Li^+$

ion diffusion is largely assisted by the exposed crystals planes. In some cases, however, other synthetic methods, such as microwave, solvothermal and chemical vapor deposition will also be employed.
The interface between the electrode/electrolyte is often identified as one of the factors that determines the cycling behavior of the cells, but this prone to undergo side reactions with nanocrystals due to the increased surface area and high chemical reactivity. Alternatively, the $Li^+$ ions conductors as solid polymer electrolytes will be more suitable for achieving a stable and robust interface. Therefore, various solid polymer electrolytes *(for example doped PVDF, PEO, PVA)* will be explored.
Lithiation and de-lithiation (*upon charge/discharge*) processes on nanocrystals based electrodes will thoroughly be investigated by cyclic voltammetry and impedance spectroscopy. Finally, the cell performance in both half and full cells will be evaluated by assembling 2032 coin type cells Swagelok cells. Possible modification in the cell assembly and design will also be considered for better performance.
In addition to the above goals, there is an ongoing cooperation with TU Delft, where L. Manna has a part-time professor position, aiming at developing new generations of batteries based on $Li_2S$ and lithium-air technology.

**B. Advanced nanoparticles for heterogeneous catalysis**

As heterogeneous catalysis is (like the homogeneous and enzymatic counterparts) a nanoscale phenomenon, the use of nanoparticles enhances heterogeneous catalyst efficiency and selectivity. Colloidal nanoparticles can be heterogenized by dispersing them onto an inorganic matrix like silica, alumina or other oxides. The present catalysis research line aims at applying colloidal nanoparticles (NPs) to technological and energetic relevant gas phase reactions for the purification of hydrogen, namely the water gas shift reaction (WGSR) and the CO preferential oxidation (CO-PROX).
Generally speaking, in heterogeneous catalysts the active sites are metal nanoparticles but the metal/support boundary was often proven to play a role in the catalytic reaction. We will focus especially on multidomain nanoparticles made of a noble or a transition metal (or a metal alloy) domain epitaxially connected to a metal oxide domain. The latter should act as a “nano-support” with two fundamental functions: the metal nanoparticle stabilization and the exploitation of the eventual so-called strong metal support interaction (SMSI) that could enhance the catalytic activity of the overall system. A number of different formulations, both in terms of active metal and metal oxide domains will be tested. The nanoparticle synthesis procedure will be addressed to grow domains with different shapes, therefore exposing preferentially determined crystallographic planes; the effect on the catalytic activity and stability will be studied. The choice of the dispersion matrix will also be critical: a comparison will be made between reducible oxides that could also take part in the catalytic process and relatively inert supports, namely silica and, to a lesser extent, alumina.
The targets will be the preparation of active and stable catalytic systems for both selected processes and to and to perform an extended catalyst characterization. A great attention will be devoted also to the study of the reaction mechanism. Many aspects of the influence of catalyst features on reaction mechanism are still controversial and very difficult to clarify.
The first year could be devoted to the preparation and characterization of noble metal based catalysts giving good performances in terms of activity and stability; the second year could be spent in optimizing the catalyst formulation, studying the mechanism related aspects and starting to work on some non noble metal based catalytic system. During the third year the reaction path will be studied more in depth.

**C. Nanoparticles in advanced photovoltaic applications**

The aim of this line is to develop nanocomposite materials for hybrid organic-inorganic solar cells, by optimizing architectures based on ensembles of nanocrystals. The assembly and interfacing will be controlled at the nanoscale level and will extend over the large areas required for the potential mass-production. The aim is to enhance the photovoltaic conversion by tailoring the electronic properties of the nanostructures, and by exploiting their energy barriers. We will fabricate size-, shape-, and composition-controlled nanoparticles based on a wide range of materials. Emphasis will be put on toxicity and impact on environment through the investigation of InP and Cu-, Cu-In-based chalcogenides. This same concern will guide novel synthesis of IR-active nanocrystals, to replace standard toxic materials like InAs, Pb-chalcogenides and HgTe. Bi- and Sn-chalcogenides are potentially environmentally friendlier candidates. We will optimize synthetic strategies for $Bi_2S_3$ ,BiTe and SnTe nanoparticles. Candidates for infrared optical applications are also Ge chalcogenides, such as GeTe, whose bulk fundamental band gap energy is close to 200 meV.

One exciting direction in photovoltaics will to combine plasmonics with colloidal quantum dot- based photovoltaics. We will develop plasmon-enhanced photovoltaic cells operating in the NIR, by exploiting various types of plasmonic nanoparticles, such as the recently synthesized $Cu_{2-x}Se$ nanocrystals (developed at IIT), which exhibit a plasmon band tunable in the NIR depending on the degree of copper deficiency in the lattice.

Another important approach of this research line is the development of colloidal nanocrystal inks for low-cost photovoltaics. Here the traditional, high-cost step of thin film deposition based on vacuum techniques is being replaced by low-cost alternatives such as ink-jet printing. We will pursue environmental friendly synthetic routes for the preparation of ternary and quaternary copper indium gallium sulfides/selenides (CIGS) nanoparticles, as well as of ternary and quaternary copper zinc tin sulfide/selenides (CZTS), with controlled composition and crystallographic structure. Nanocrystals with the appropriate crystallographic phase would be highly desirable to ensure homogeneity and set an exact starting point for ink formulation and for the definition of the sintering process, preventing posterior reliability problems as those presumably associated with actual solution processing pilot lines.

## 3. Nanoparticles for Novel Self-Assembled Materials

### A. Assembly of colloidal nanocrystals into various types of nanocomposite architectures with advanced properties

This line intends to advance the exploitation of colloidal nanocrystals as building blocks for engineered self assembly architectures across multiple length scales, from the molecular level up to the macroscopic world. The aim is to develop new strategies of nanocrystal assembly able to create various types of nanoparticle architectures, and to discover collective properties stemming from them. Also here, the path to these architectures will exploit concepts that are amenable to large scale deposition and parallelization. The advanced fabrication of colloidal nanocrystals with narrow size and shape distributions, of a variety of materials will be targeted first. Emphasis will be on a combined approach, using fabrication techniques borrowed from different realms (from solution phase and additionally from the vapour phase). An example will be the seeded-growth method, which has been successfully exploited for the fabrication of shape-controlled nanocrystals with narrow distributions of shapes. These will all aim at tailoring various properties (i.e. energy range of light absorbed/emitted, polarization and quantum yield of emission, capability for charge separation) in each nanostructure.

We will then assemble these nanocrystals into both ordered and disordered superstructures: ordered superstructures will be achieved using assembly concepts that are amenable to large scale production and parallelization (i.e. self-assembly at interfaces between immiscible fluids, by Langmuir-Blodgett techniques, by phase segregation, by slow de-wetting, by depletion forces, by slow variation of the polarity and/or Hamaker constant of the solvent). Narrow distributions of shapes will be the key for large scale ordered assembly. We will prepare various types of assemblies on different substrates. Both ordered and disordered superstructures of nanorods and branched nanocrystals will be realized. We also aim at composites of polymers and assemblies of nanocrystals. The polymers will be chosen in order to realize nanocomposites with improved mechanical or conductive properties (or both). It will be important to control both efficient incorporation of the assemblies in the polymer phase so as to prevent phase segregations effects, which will negatively affect the mechanical properties but also the rheological properties of the polymer. We will characterize the properties of both ordered and disordered assemblies. In ordered structures of semiconductor nanoparticles, electron transport and phototransport properties of monolayers and multilayer structures for instance should be strongly anisotropic. Nanoparticle coupling effects can be revealed both by optical spectroscopy and by scanning probe techniques. Multi-layers of close-packed semiconductor nanoparticles should exhibit amplified stimulated emission (ASE), which is critical for fabricating nanoparticle-based lasers. Semiconductor-metal assemblies will be interesting because of strong local optical field associated with plasmon modes in the metallic nanostructures, which can be useful in light-harvesting and conversion devices. Multi-layers of vertically stacked semiconductor nanoparticles should show strong anisotropy in the direction of emitted light, which can be useful in solar concentrators.

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# NANOPHYSICS

## (PROF. A. DIASPRO)

The Nanophysics department grew comparatively fast in the last 2 years focusing on activities mainly related to: 1) nanocomposite materials design and characterization; 2) design and construction of new instruments with ultimate resolution for imaging, microscopy and spectroscopy; 3) nano-bio-technological applied and fundamental studies. The scientific activity is based on a strong interdisciplinary approach, facilitated by the IIT environment, and on goals and results at the best of the current international state of the art. The planned activities for the 2012-2014 years focus on two main stream lines, namely:

**1) Nanocomposite (smart) materials: from nanoparticle synthesis to 2D/3D materials (films/scaffolds).**

**2) Novel nanoscopy-devices and instruments: accessing the nanoscale from tissue/organ size (cm) to single molecule precision (nm)**.

The former research line has a predominant material science character and exploits the well established expertise in development of hybrid multifunctional materials with emphasis on physics and chemistry of surfaces, bulk thermo/mechanical properties, electromagnetic properties of composite systems, interaction of biological molecules with carefully designed surfaces. The latter, targets the design and realization of new concept devices and instrumentation for nanometer resolution microscopy and spectroscopy of living matter and materials, including the possibility of photo-nano-structuring. In both cases the general aim is to develop new approaches at high technological content for smart materials and advanced instruments of relevant industrial interest, to be applied to "human" problems such as nanotoxicology, neuro-tech implantable devices, new multifunctional and "tunable" materials (actuators, sensors, portable/converting energy), nanocarriers and scaffolds for smart drug delivery (actively/passively triggered), intelligent (bio)probes, implantable (bio)substitutes, early stage detections of diseases and "therapeutic" nanodevices. NPhys activities exploit the vaste cross disciplinary know how existing at IIT in different Department and network Centers, particularly with NBT, Nanostructures, Nanochemistry, D3, and the NETWORK centers of IIT@PoliMi, IIT@SEMM-IFOM-IEO in Milano, IIT@LaSapienza in Roma, IIT@NEST in Pisa, IIT@UniLe in Lecce and IIT@CRIB in Napoli.

### 1) Nanocomposite materials: from nanoparticle synthesis to 2D/3D materials (films/scaffolds).

The research approach is related to activities covering the full research chain from nanoparticles production to development of new nanocomposite materials with tailored surface and bulk properties. We move from biological applications, using the nanoparticles as diagnostic (probes) and therapeutic agents, or growing cells on well designed surfaces, towards energy and transport applications by developing light-weight, functional materials with enhanced electrical, magnetic, mechanical and thermal properties.

As a general strategy we plan to use inorganic and organic nanofillers (nanoparticles, nanorods, nanowires, functional molecules, monomers, oligomers etc.) into polymeric matrices, or as additives into nanostructured, membrane-like, or non-woven materials, realizing new hybrid systems having, for example, tailored mechanical, electromagnetic, surface (from self-cleaning to superhydrophilic) and electrical tunable properties. Substantial effort will be made in developing new strategies for the homogeneous dispersion of such nano-objects and the characterization of the resulting novel materials, to be used in (not exhaustive list):

- reinforced nanocomposites based on resins for aerospace,
- innovative nanocomposite resins for dental materials,

- sensing surfaces and polymeric wires for robotics,
- 2D/3D Laser Micromachining, Patterning and Scaffolding for model system investigations, prosthetic and lab-on-a-chip devices,
- 2D/3D biodegradable or permanent films/scaffolds as bio-substitues and lab-on-a-chip implantable analytical devices,
- 2D/3D light driven nanoactuators based on photo-nanocomposite materials,
- 3D optical data storage devices.
- 2D/3D bio-chip patterned nanodevices integrated with multi-electrode array for both recording and stimulation of 3D neuronal networks.
- Non-toxic antibacterial films based on natural polymers for food preservation

The surface properties of nanocomposite materials will be extensively studied in order to finely tune their wettability according to the desired application. The tailoring of the wettability of the surfaces will be done using different methods such as light-induced changes, micro/nano-structuring, in situ formation of nanoparticles etc. For biological/medical applications, interfacing the nanostructured material with biological matter will be a key issue. A particular emphasis will be given in optimizing cell adhesion and biocompatibility. This research line will produce specific knowledge in those mechanisms related to neurodegenerative and oncological diseases and, the very same time, will allow the development of biologically optimized surfaces for hybrid bio-devices and smart drug delivery systems, tunable neural network patterning, etc.. Apart from the biology oriented applications, also other domains will be targeted in this research activity, such as environmental pollution, by the development of smart and self-cleaning materials for reducing sea water pollution due to oil contamination, or food preservation, by the preparation of moisyure barrier films with antibacterial properties.

A different form of nanostructured material will also be explored, consisting of a solid inorganic porous matrix of nanoporous alumina, filled with a polymer and/or different functional macromolecules or nanoparticles fed into its pores. Such material can be used alternatively as scaffold for the growth of different types of cells.

Within the 3D scaffolding activity, an innovative fully computer controlled excimer based stereolithography system is being developed aiming at the efficient production of structures with controlled micrometer porosity for tissue engineering application. The use of high-power reliable excimer laser, widely used in many industrial processes, will increase the fabrication throughput, thus bringing stereolithography technique from the rapid-prototyping arena to actual production processes. A parallel high-tech improvement will be related to the adoption of a RESOLFT-like (REversible Saturable OpticaL Fluorescence Transitions) approach. The produced 2D patterned surfaces and 3D scaffolds find key applications in advanced tissue engineering for bone and/or cartilage repair as well as in brain-machine interface.

As a highly promising new material Silicon-on-Diamond will be investigated for applications spanning from lab-on-chip devices to human-machine interface. The capability of interfacing biological systems (e.g., neuronal networks) on the Diamond surface to electronic systems on the silicon surface opens new exciting perspectives due to the unique characteristics of Diamond (high mechanical strength coupled with low chemical reactivity, optical transparency and large electrochemical potential window). Specifically, laser micromachining techniques will be investigated for the fabrication of conductive through-SoD-vias, and 2D/3D direct laser writing of conductive graphitic channels in Diamond.

On the nanoparticles side, different approaches will be developed or optimized for their generation and fine control. Different nanoparticles are already used for a variety of applications such as bio-imaging, antiseptic metal ion release, cancer treatment, UV-protection, photo-catalytic effects, scratch-resistance and corrosion protection. But the availability of nanoparticles with high purity is still lacking in particular for biomedical applications. For this reason we will use light driven **"green"** production of nanoparticles (silicon, germanium, silver, gold, nickel, iron oxide) with high flexibility in functionalization using pulsed laser ablation in liquid. The applications will be oriented to smart drug delivery systems covering dimensions from 4 nm to 10 nm, fluorescence nano-marker, conducting films, antibacterial materials, magnetically actuated materials, etc. Optimization of the nanoparticle synthesis by this "green" method will be investigated aiming at the demonstration of efficient production rate to trigger industrial interest. Biocompatibilty improvement of these nanoparticles is predicted due to their restricted surface contamination, since the synthesis is carried out in water or in a solution of biocompatible ligand. Next, photocatalytic production of gold nanorods, at tunable aspect ratios, based on a new procedure developed at IIT labs, will be oriented to diagnostic and therapeutic applications following specific functionalization. Finally, in situ formation of nanoparticles directly into polymer matrices starting from the precursors of the nanoparticles, opens the way to a huge variety of applications since the size, density and localization of the nanoparticles can be precisely controlled.

Nanoparticles and nanocomposite materials will be characterized by means of several techniques aiming to validate and test their properties including working conditions: TEM, SEM, SPM, pump and probe spectroscopy, dynamic light scattering, dynamic mechanical analysis, differential scanning calorimetry, thermogravimetric analysis, nanoindentation, and AFM advanced mechanical analysis (force modulation, friction force microscopy, nanoDMA).

Furthermore, we will work on nanoparticle interactions with biosystems requiring the evaluation of the potential cytotoxic effects and related implications to human health. In fact, the uniqueness of nanoparticles and nanomaterials requires a new experimental methodology for nanotoxicity studies to complement the conventional techniques of traditional toxicology. Understanding the nanoparticle-induced defects in biological membranes is among the major challenges of nanotoxicology. Research on nanoparticle/nanomaterial–membrane interactions needs to go toward understanding the mechanism of interaction which could lead to less hazardous nanotechnologies. Manufactured nanoparticles are potentially capable of inducing defects in cell membranes such as physical disruptions, formation of holes, thinned regions, and may affect essential cellular processing, such as ion transport or signal transduction. Moreover, internalization of nanoparticles may interact with different cell compartments such as organelles, cytoskeleton or cell nuclei. The localization of nanoparticles in living cells will be studied by advanced microscopy techniques. Scanning probe microscopy will applied to investigate changes in plasma membranes and in cell physical properties such as cell stiffness, and the cell adhesion capabilities and coupled to optical nanoscopy approaches towards protein dynamics in the cell. Our department has the unique potential of having all the scientific and technological steps in the very same place coupled to the strong interactions with other Departments and Centers of the network (mainly Lecce and Milan).

**2) Novel technologically advanced devices and instruments: accessing the nanoscale from tissue/organ size (cm) to single molecule precision (nm).**

IIT aims at becoming a world leading institution in the design and development of ultra high resolution imaging equipment, including UHV-STM/SPM and super-resolution microscopes. Part of this activity will be carried out in the frame of the agreements for the development of new optical super-resolution approaches based on single- and multiphoton interactions with Leica Microsystems and Nikon, leading companies in the optical microscopy market, and of JPK, Nanonics and Bruker, leaders in scanning probe microscopy.

Furthermore, functional (including chemical) and structural imaging with resolution at the nanoscale under ambient conditions can significantly advance our understanding of biological and physical processes at the molecular/nanoparticle level, for example, towards the elucidation of the early stages of Alzheimer's disease and of lung cancers. Here, the knowledge of molecular mechanisms is essential for early detection of diseases, to improve the efficacy of therapeutic drugs and to evaluate the real impact of nanomaterials/nanoparticles to health and safety. In production processes, the ability to reveal defects with nanometer imaging resolution is critical for robust quality control of 'industrially important' products e.g. organic photovoltaic devices, antimicrobial textiles and functional coatings on biomedical implants.

One of the 3-years-term goal is to develop a super resolution microscope, operating in the range of 5-50 nm, utilizing different combined modalities for achieving nm resolution with the goal of being a potential substitute of the electron microscope in biological applications allowing measurements on living samples, in vivo in perspective. Such a development will combine targeted and stochastic approaches utilizing linear and non-linear excitation of fluorescence. The approach will be extended to label free methods including shift to infrared wavelengths and oriented to the realization of an endoscopic approach. Nevertheless, a strong multidisciplinary departmental activity will lead to the realization of the first "Living miniaturized supermicroscope". Such a microscope will be realized using the ability of making lab-on-a-chip 3D scaffolds including lenses and mirrors. Within such a miniaturized supermicroscope, it will be realized a micro laser cavity using as active substance fluorescent molecules as GFP expressed by cells contained in the device and/or by new class of fluorescent/luminescent molecules realized by the Nanochemistry department. The active part of the cavity will be recharged by means of a microfluidic integrated pathway. As further long term objective (3rd year), such a device could be included in an endoscopic system to allow in vivo investigations at high resolution. Such a system can also be used, as active device, for ultra high-resolution lithography. This will be the smallest living supermicroscope. (Interested companies: Leica Microsystems, Nikon Instruments, Coherent).

In parallel, we aim at continuing the development of an architecture that combines different super resolution approaches, including FRET and lifetime methods, from localization methods to optical nanoscopy, from label free methods to non-linear interactions (multiphoton excitation, high-order harmonic generation). Such an architecture will allow to detect and track single molecules when they are labeled with an appropriate tag, such as a fluorescent label i.e. the green fluorescent protein (GFP) and/or quantum dots/nanoparticles or exploiting label free luminescent properties. This will enable the detection of biological molecules such as proteins, nucleic acids or etiological agents of specific diseases. This activity requires to realize a new microscope chamber, tunable phase plates, 3D image processing and restoration approaches for large number of frames (40.000-80.000) and single molecules (1.5-2 million) per plane, new class of functionalized nanoparticles. The main application will be High-resolution morphological and functional brain mapping.

As further development super resolution microscopy will be coupled to atomic force microscopy to allow for in-vivo mechanical- functional correlation properties during different cell life cycles or by application of external stimuli, for which an Expression of interest from the world leader scanning probe companies (JPK, Nanonics, Bruker) already exists." Moreover, a Super resolution Microscopy Platform will be realized in the IR within a new FP7 granted project (LANIR, Label Free Nanoscopy Using Infra Red). Such an architecture will allow to perform label free nanoscopy of smart an bio-materials (70 nm in xy, 500 nm along z for an investigating spectral range shifted to 0,3 microns, 10 microns in deep) by exploiting vibrational spectroscopy based imaging tools such as Infra-Red (IR) and Raman microscopy complemented by a reversible saturable optical transitions approach, as the one typical for STED nanoscopy.

An important development in the “optical suitcase” containing the most advanced solutions in optical microscopy is represented by the development of label free methods in non linear optical microscopy towards tissue engineering and elucidation of neurodegenerative and oncological diseases having important impact on the Society. Such developments constitute a crucial aspect of next years investigations in bioimaging for high demanding applications. New approaches to capture signals from unlabeled biological molecules may finally fullfill the promise of practical label-free microscopy with molecular specificity. For example, an important aim of tissue engineering is to provide a three-dimensional structure mimicking some of the extracellular matrix features, and it remains unclear whether the pattern and the molecular structure of the newly tissue might be differentt and labelling may perturb the function of biomolecules, the use of label-free approaches results particularly powerful. Label-free microscopy methods rely on a variety of different photophysical processes to generate light signals from biological macromolecules, among them we focus on non linear interactions like the ones related to two-photon excitation microscopy and second harmonic generation (SHG) microscopy. Two-photon excitation (TPE) microscopy can detect some prevalent autofluorescent molecules and SHG methods allow to distinguish fibrillar sturctures. We aim to understand the mechanisms of image formation when using TPE and backward/forward SHG and to use them for the comprhension of scaffold geometry dependent differences in collagen fiber concentration and organization within newly formed tissues in unloading vs. loading conditions. The most intriguing concept is obtaining materials able to mimic a specific eventually pre-existing microenvironment, thus priming the natural processes of bone regeneration driven by cells. Within this framework, it is still unclear, whether the pattern and the molecular structure of the newly formed tissues might grow in different ways, based on the chemico-physical cues, for example, given by scaffold design. TPE and SHG approaches will be focused to elucidate such mechanisms.

Closing the circle, within a “Swiss army knife” multifunctional and multimodal approach for the realization of a powerful microscopy platform, a compact harmonic phase-dispersion microscope, based on the principles of second-harmonic interferometry, will be also developed. The common-path geometry of the second-harmonic interferometer allows for an easy integration into standard transmission microscopic devices, while its high-sensitivity and high-speed allow to acquire high-resolution images of samples much faster compared to typical Mach-Zender interferometer similar devices. Either biological or inorganic (e.g, film or nanoparticles) thin transparent samples can be imaged. Since such an instrument is self calibrating for phase measurements, absolute measurement of optical dispersion can be performed.

ISTITUTO ITALIANO
DI TECNOLOGIA

**PAVIS - PATTERN ANALYSIS & COMPUTER VISION**
**(PROF. V. MURINO)**

The research pursued by the Pattern Analysis and Computer Vision (PAVIS) department deals with **Computer Vision** and **Pattern Recognition/Machine Learning** with applications to **video surveillance**, **biomedical imaging, neuroimaging** and **pattern analysis (bioinformatics)**. The activity is based on the expertise in the probabilistic and statistical techniques, learning and inference, classification and clustering, geometric and 3D data management. This makes PAVIS a transversal facility to deal with image analysis, video sequences, and other types of structured and unstructured data, coping with various applications of interest for different research units.

**Video surveillance & monitoring**

Concerning video surveillance, PAVIS tackles most of the relevant topics of the field such as tracking, detection, re-identification, and other issues, targeting the analysis of behavior in general, with some specific peculiar features to be highlighted. The final objective is the development of a surveillance framework able to detect and classify, possibly predict, situations of interest (e.g., threats) on line, while allowing the identification of the responsible subjects. The most relevant aspect in this study regards the explicit involvement and exploitation of social cues. **Social signal processing** is in fact a recent multi-disciplinary area aimed at detecting and recognizing socially relevant signs for the **analysis of human behavior**, either at the individual, dyadic or group levels. This will allow to develop more robust and reliable methods for the understanding (detection, recognition, interpretation, prediction) of socially relevant situations by means of the investigation of the nonverbal human behavior.

In particular, PAVIS will investigate *Vocal Behavior* (everything else than words in speech), *Face and Eyes Behavior* (expressions, gaze, head pose, etc.), *Gesture and Posture* (bodily movements, conscious and unconscious gestures, orientation with respect to others, etc.), and *Space and Environment* (mutual distances, spatial organization of people, territoriality, geometric constraints, etc.). These methods, taking inspiration and utilizing findings from the psychology, anthropology, ethology and other social sciences, will push much further the studies on abnormal behavior analysis.

Another issue deals with **biometrics**, mainly non cooperative face detection and recognition (and at distance), but also other less used characteristics like the gait. Particularly interesting is the exploitation of *soft biometrics* in other tasks like, for instance, the re-identification, which consists in recognize the same person in different places and times. Characterizing a pedestrian using not only features derived from the clothing, but also from biometric traits like the gait, height, the presence of beard/mustache, glasses, etc. may help in discriminating better among different subjects.

A more technological aspect, regards the use of **multi-sensory** devices and the related **data fusion** and **integration**. Actually, most of the surveillance tasks are accomplished using video cameras, and little has been done beyond these devices. PAVIS plans to employ different types of sensors like microphones (freely installed in the environment or organized in an array), thermo-cameras, and 3D sensors, possibly RFID, and to develop algorithms targeted at the same tasks as for the normal optical cameras, so as to increase the reliability, robustness and applicability of the surveillance system to several environmental conditions. The use of (multi-sensorial) distributed devices also implies to cope with the problem of their coordination and cooperation so as to increase the whole system effectiveness, hence the security, of large monitored areas. This topic is known under the name of **sensors networks**. The use of these sensors, distributed in a large zone, not all and necessarily visual, communicating among them and utilized in a cooperative and complementary way, is one of the main novel direction in the context of the automatic surveillance.

Generalizing the concept of distributed sensors networks, PAVIS also plans to utilize **fleet of robots** for surveillance tasks in the field. Actually, in the context of social & service (& rescue) robotics, the idea is to exploit off-the-shelf (fleet of) robots (or with a minimum customization) for tasks related to environment exploration and service activity for clients. A possible objective could be the reconstruction of an unknown environment in the fastest and more accurate way using a fleet of robots going around the area. Another example may consists in using accompanying robots to direct clients to specific places in an area following their commands, or to interact with a person trying to limit his/her movements (as for security problems). From the technical point of view, this requires developing algorithms for reconstruction from uncalibrated images and videos, distributed visual SLAM, pedestrian detection, part-based human body modeling, action recognition, and distributed mobile sensors' coordination.

**Biomedical Imaging, Neuroimaging, and Pattern Analysis**

Computational methods have proved to be largely used also for the analysis of biomedical data, images in particular. They are typically used for diagnostic purposes and in general to better figure out the data produced by the increasing number of **biomedical imaging** instrumentation available nowadays (e.g., MRI, PET, SPECT, MEG, TMS). A significant branch of this research is also devoted to the processing of images for the support of the surgeon during an intervention (*image-guided surgery*).

Overall, the main goal is to provide objective (as opposed to subjective) tools supporting the biomedical professionals in their activities, either for the diagnosis of a disease, during a surgery intervention, to discover a new gene, or for better understanding the effects of a new drug on a protein. In this context, PAVIS research will focus on providing rigorous data analysis methods (in terms of accuracy and reproducibility) to different research groups at IIT and beyond. The main activity in this area will focus on the analysis of **neuroimaging** data, targeting several tasks as related to human brain mapping, brain engineering, clinical applications, also related to cognitive, affective and social neurosciences. Possible activities can be focused to the analysis of MRI brain images of normal and pathological subjects to figure out the possible differences in terms of structure and functions. Despite the simplicity of the problem statement, this requires a specific work to identify (a statistical significant amount of) subjects, acquiring images, identify the same regions of interest in all the brain images, devise and extract effective features, and design classification methods which could actually perform a reliable categorization. If this analysis is carried out considering schizophrenic or autistic patients, two of the major behavioral diseases, it can be associated to the analysis of expressive behavior of the subjects in order to identify (explicit) behavioral profiles (or markers) to be possibly linked to the inner (brain) disfunctions, so increasing the understanding of such pathologies. To this end, a possible field of study can be in collaboration with the Nanomedicine division of IIT@NEST in Pisa for the analysis of MRI (fMRI in particular) data.

In general, all these kinds of tasks require the design of specific image analysis and computer vision methods up to the definition of high-level pattern recognition/machine learning algorithms which match well with the activities carried out for the video surveillance applications. Such activities may be made more and more complex if one considers the different modalities of the biomedical instrumentation which can be utilized, so implying issues related to *image registration*, *data fusion*, and *reasoning* using multiple and integrated information.

Finally, the design of a physiological and behavioral system for the assistance of blind patients will be addressed. This activity aims at modeling the physical and cognitive status of human subjects while they acquire spatial knowledge, by jointly estimating their physiological and behavioral features. Together with adopting multi-modal low-level features to infer how subjects "behave" or "feel" when navigating in unknown spaces, more covert measures, coming from body signals, can provide complementary information which may lead to more robust models. A further step can be the joint modeling of physiological and behavioral signals into novel high-level structures, which can be related to a normal or abnormal behavior of the subjects. The output of the project is the robust modeling of the behavior of several subject categories, as well as the monitoring of aged subjects or patients with motor and cognitive diseases.

Similar considerations hold for the **bioinformatics** domain. The analysis of biological patterns, not necessarily images, often subsumes classification and clustering problems for which state-of-the-art methods are often not sufficient. So, there is the need to address the addressed problems from also a chemical, physical and biological perspective so as to envisage and design the most proper computational method. These activities are mainly in collaboration with the D3 department.

**Activities of the Network Centers**

The activities of the network centers are carried out according to the original plan started in 2010, and they are fully integrated in the scientific strategy of the Institute. In what follows, we briefly summarize the main stream lines of the centers with minor updates aimed at the fine tuning of the research with respect to the new scientific plan.

**CENTER FOR SPACE HUMAN ROBOTICS@PoliTo**
**PROF. F. PIRRI**

Platforms: Robotics, Smart Material, Energy

Mission: The Centre's mission is to study, to design and to realize/assemble demonstrators of the future generation of materials, processes and components for space human robotics. Locomotion and manipulation, sensing/perception, intelligence and ability to communicate with the humans are the basic requirements for space robotics. The development of these basic functions demands several technologies and structural/functional components, sensor/actuator MEMS and NEMS devices and compact and flexible energy supply systems, all based on new structural and functional materials with related process technologies that can also be fruitfully used for the development of the next generation of terrestrial robotics systems and several industrial applications.

**Robotics**

The activities have the aim to develop the basic components for human robotics concept and related technologies for the space utilization and to foster all related spin-offs for terrestrial applications. The mainstream research lines are focused on the development of smart exoskeleton components, according to the following subjects:

1) Development of new metallic alloys and polymeric multifunctional materials;

2) Development of components for the exoskeleton control through surface physiology parameters;

3) Development of distributed sensors for humanoid robotic components;

In particular, a demonstrator of a robotic glove exoskeleton based on new metal alloys and polymers, with distributed sensing skin and an EMG feedback control, is planned. The activities of Robotics Platform are performed in collaboration with the Robotics, Brain and Cognitive Sciences Department and the **Center for Biomolecular Nanotechnologies.**

**Smart Materials**

The activities are focused on the development of materials and technologies for micro/nano-sensors and actuators based on MEMS and NEMS technology. The following items are investigated:

1) Lead free metal-oxide based piezoelectric materials, piezoresistive materials, piezoelectric nanostructures, hybrid and nanocomposite materials, nanostructured multifunctional polymers (in particular all these materials will be investigated for sensing and energy applications, including devices for mechanical harvesting);

2) New nanostructured materials for energy applications: polymeric electrolytes and new materials for electrodes with a particular focus on metal oxides and carbon based structures;

ISTITUTO ITALIANO
DI TECNOLOGIA

3) Innovative processing techniques/ for device fabrication;

The investigated materials will be obtained through several low cost techniques: thin film deposition (CVD and sputtering), ink jet deposition, chemical synthesis (hydrothermal, microwave assisted and wet processes), electrochemical synthesis (anodic oxidation), surface functionalization (with specific molecules, thus easily expanding the materials functions in sensing or energetic direction).The activities of Smart Materials Platform is performed in collaboration with the **Center for Biomolecular Nanotechnologies, the Center for Advanced Biomaterials for Health Care and the Center for Nano Science and Technology.**

**Energy**
The activities are focused on the development of technologies for portable energy sources to be used in space human robotics applications, also exploitable in very important industrial areas such as automation and robotics, portable electronics and automotive.
The research is organized in two main directions:
1)Innovative systems for energy production: innovative flexible solar cells based on polymeric electrolytes; third generation solar cells with innovative design and electrodes; investigation of new materials for innovative membranes for fuel cells and hydrogen production

2) Innovative systems for energy storage: application of polymeric materials, solid electrolytes and nanostructured electrodes in flexible batteries and supercapacitors.

The efforts are focused on the development of demonstrators of solar cell systems based on new materials, structures and design. An attempt will be also made for applying the new electrolytes and nanostructured contacts in flexible batteries for energy storage. The activities of Energy Platform are performed in collaboration with the **Center for Biomolecular Nanotechnologies and the Center for Nano Science and Technology.**

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DI TECNOLOGIA

**CENTER FOR NANO SCIENCE AND TECHNOLOGY@ PoliMi**
**PROF. G. LANZANI**

Platforms: Energy, Smart Materials

Mission: The Center is to foster innovation in the area of portable energy conversion and humanoid technology by devising and implementing new materials and new device concepts. The research is framed by the energy and the smart materials IIT platforms. The strategy is exploiting new fundamental knowledge in nano science, as acquired by experimental and theoretical research, for application in nanotechnology. The Center has lab facilities and competences in material science, including molecular synthesis, material growth and characterization. The Center also has state of the art tech facilities in molecular electronic, printed electronics and plastic electronics that are dedicated to testing and validating tech innovation.

**Energy**
The platform aims to design new approaches to light energy harvesting and light energy conversion, develop market technology based on printed electronic and to understand fundamental principles and mechanism of third generation solar cells. The mainstream research lines are:
1) Synthesis of new organic molecules for light harvesting, charge transfer and charge transport in solid state DSSC and polymer cells;

2) Growth of semiconducting nano structures as new electrodes, light harvesting antennae or components in third generation solar cells;

3) Fabrication techniques based on ultrafast lasers (femto second micro-machining);

4) Developing the processing of organic semiconductors and metals in solution for printed electronics, including large area plastic solar cells. This activity will soon begin also within a join lab IIT-OMET, a leading industry in the printing technology market and in collaboration with Center for Space Human Robotics@PoliTo

5) Morphological, structural and photo physical studies; modeling for the molecular and extended states properties. The activities will be performed in collaboration with Nanochemistry Department and with **Center for Biomolecular Nanotechnologies.**

**Smart Materials**
The platform aims to develop a new technology platform for interfacing artificial and living systems, based on an interface capable of information transfer between an organic artificial detector and a living neuron network, investigation on organic based technology for retina implantation and to develop new hybrid bio-organic materials and other nano materials with smart functions. The mainstream research lines are:
1) Study of bio-organic interfaces for Humanoid technology, artificial retina, neuron stimulation and neuron diagnostic and communication. The activities will be performed in collaboration with NBT Department;

2) Realization and study of hybrid solid liquid interfaces and new devices. The activities will be performed in collaboration with University of Bologna;

3) Realization of bio mimetic organic photodetectors for humanoid technology and robotics. The activities will be performed in collaboration with RBCS Department;

4) Synthesis of new organic carbon polyconjugated photochromic molecules and their integration in device components;

5) Studies of new materials such as photochromic/ nanotubes blends, bio-materials, quantum dots, ecc.

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DI TECNOLOGIA

## CENTER FOR GENOMIC SCIENCE OF IIT@SEMM
**PROF. B. AMATI**

Platforms: D4, Computation

Mission: the Center focuses on cancer genomics and on the de-convolution of the genetic alterations and mechanisms underlying disease progression using two parallel approaches: "next-generation" DNA sequencing, for the integrated analysis of DNA (genome), chromatin (epigenome) and RNA (transcriptome); high-throughput cell-based phenotypic screens, based on an integrated robotic platform and advanced light microscopy.

### D4
The mainstream research lines are:
1) Genome and Epigenome evolution in Cancer progression-*Genomic Unit (GU)*
This research project aims at testing the hypothesis that cancer-causing mutations, as well as environmental factors and lifestyles, promote cancer by provoking specific epigenomic changes in cancer-initiating cells. Indeed, beyond being a DNA-packaging device, the epigenome is a complex regulatory platform that can permanently alter genome activities. Genome, epigenome and transcriptome alterations will be profiled in a variety of mouse tumor models, and under environmental or physio-pathological stress. Further research will establish the role of relevant epigenomic and/or transcriptomic changes as determinants of tumor progression, as well as their value as molecular markers. This will eventually allow the development of novel therapeutic or early-cancer detection programs. The activities will be performed in collaboration with IFOM and IEO.

2) High-throughput and high-content phenotypic screens- *Screening Unit* (SU)
This program aims at de-convoluting cancer-associated pathways based on genetic and chemical screens. The SU will adapt the assays to high-throughput format and will run the screens, leading to the identification of key small molecules or gene products for further study. Emphasis will be placed on disease-associated mechanisms and on the identification of prospective therapeutic targets, paving the way to innovative drug development. The activities will be performed in collaboration with D3, IFOM and IEO.

### Computation
The mainstream research lines are:
1) Acquisition, storage, processing and analysis of large-scale next-generation sequencing datasets, as well as on the implementation of new algorithms and analytical strategies of the genomic projects;

2) Developing automated image analysis software and other algorithms required for the development and execution of genetic screens.
The activities will be performed in collaboration with Computational Department in Morego.

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**CENTER FOR NEUROSCIENCE AND COGNITIVE SYSTEMS@UniTn**
**PROF. J. ASSAD**

Platforms: Neuroscience, Computation

Mission: The broad goal is to understand how neuronal circuits in the brain mediate behavior. The research activity includes experiments in both animal models and human subjects, spanning systems neuroscience and cognitive science. Systems neuroscience and cognitive science can critically inform the development of robotics applications and brain-machine interfaces for human therapeutics. In addition, because many brain disorders, such as Parkinson's disease and schizophrenia, are at their heart derangements in the function of brain circuitry, systems- and cognitive-neuroscience approaches are essential for understanding and ultimately alleviating these diseases. Innovative new probes for monitoring brain function will be developed.
The main research lines are:
1) Human studies of perception and sensori-motor integration
The research focuses on behavior studies and computational modeling to mimic the behavior of the visual system.The activities will be performed in collaboration with Advanced Robotics, Nanofabrication, Robotics, Brain and Cognitive Sciences and Computational Department.

2) Innovative studies and tool development in systems and cellular neuroscience
The research activity develops cutting-edge techniques in systems neuroscience, including techniques for monitoring, perturbing and analyzing large-scale neuronal activity in vivo, such as advanced optical techniques. The activities will be performed in collaboration with Nanophysics, Nanochemistry Department and Center for Biomolecular nanotechnologies.

3) Neurocognitive function in the normal and diseased human brain
The research activity studies neurocognitive function in the normal and the diseased human brain. To achieve this goal we use quantitative psychophysical techniques, functional magnetic resonance imaging (fMRI), and noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation.

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DI TECNOLOGIA

**CENTER FOR NANOTECHNOLOGY INNOVATION@NEST**
**DR. A. BIFONE**

Platforms: D4, EHS, Energy, Computation

Mission: IIT@NEST is an interdisciplinary R&D center dedicated to the investigation and exploitation of phenomena at the nanoscale. The activity of the Center is organized in three research divisions:
• Nanomedicine, focusing on the development of novel tools for molecular diagnostics and targeted delivery of imaging probes and therapeutics (D4 and Computation platforms);
• Nanoscale Processes and Tools, targeting the development of an array of nanoscale assays for quality control and for the recognition of potential biosafety and environmental risks connected to nanotechnology products (EHS and Computation platforms);
• Power Nanosystems, aiming at the fabrication of nanoscale devices for energy storage and harvesting (Energy platform).

**D4**
The mainstream research lines are:
1) Design and realization of a hand-held, battery operated lab-on-a-chip based on Surface-Acoustic-Waves (SAW) driven micropumps suitable for automated, high-throughput diagnostics;
2) Development of modular, nano-engineered devices able to target selected tissues and cellular compartments, sense the micro-environment, and deliver imaging probes and drugs. An emphasis will be put on brain-penetrant agents, and on mechanisms that enable translocation through the Blood Brain Barrier (BBB) and to intracellular compartments. Consistent with the modular structure of this nanodevice, the activities are organized in:
- targeting and recognition: cell penetrating peptides and aptamers (single stranded oligonucleotides) will be developed to enable penetration of the BBB (through receptor-mediated mechanisms), translocation to intracellular compartments, and escaping from endosomal trapping.
- scaffold engineering: biodegradable polymer and lipid nanoparticles will be designed and engineered to act as nanocarriers, thus concentrating payload in the compartment of interest and protecting the cargo from clearance by the immune system.
- sensing: environment-sensitive fluorescent probes and MR contrast agents will be developed to detect physico-chemical environmental parameters (e.g polarity) and specific enzymatic activity (e.g. proteolysis).
- controlled and conditional release: linkers will be developed to enable efficient release of the payload upon photoactivation (e.g. through photocleavable systems) and/or in the presence of environmental conditions (e.g. pH, enzymatic activity).
3) Imaging methods: advanced imaging approaches will be developed to enable high-sensitivity, high-resolution mapping of diagnostic probes. Specifically, fluorescence nanoscopy methods based on correlation analysis will be applied to the detection of molecular events in living cells. A Magnetic Resonance Imaging facility is now operational for pre-clinical in vivo studies, and will focus on imaging of the CNS, and on brain functional imaging in the presence of pharmacological or optogenetic stimulation. The activities will be performed in collaboration with D3, NBT and Nanophysics;

**Computation**
The mainstream research lines are:
1) In silico modeling will be applied to guide the synthesis of molecular components of the nanodevices described in the previous section. More specifically, photoactivatable and photocleavable linkers will be modeled using ab initio approaches to predict structure and properties. Coarse-grained methods will be applied to study the folding of oligonucleotides in the presence of non-natural substitutions, in order to

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DI TECNOLOGIA

support in silico optimization of lead structures.
2) A bioinformatics approach based on heuristic algorithms will be deployed to select novel peptides with favorable cell penetrating properties;
3) An image analysis platform supporting fluorescence nanoscopy and MR imaging will be established, with a focus on multivariate and correlation analysis of image time-series. The activities will be performed in collaboration with IMT and Morego.

**EHS**
The mainstream research lines are:
1) Development of assays to study the interactions of naonmaterials with living cells, and the mechanisms leading to toxic or inflammatory responses. More specifically, these assays will focused on cell models of the Immune and Central Nervous Systems (CNS). Nano-safety information from CNS cells (neurons, glia and micro-glia, the CNS resident immune system) will provide directions for the development of brain-targeted nanodevices. Imaging approaches (MRI and 2-photon fluorescence imaging) will be applied to assess potential toxicity and inflammatory responses *in vivo*.
2) Several novel techniques for the characterization of nanostructured materials and their interactions with cells and tissues will be implemented. Specifically, precession electron diffraction will be installed on the TEM to help solve the structure of nanocrystals and to perform texture analysis. Coherent Anti-Stokes Raman Spectroscopy (CARS) will be applied to perform label-free imaging of live cells and tissues, and to determine in real time the penetration of drugs and nanoparticles. Together with the existing facilities at CNI, these new techniques will represent an enabling platform for a complete characterization of structure and properties of nanomaterials, and will provide the basis for interactions with the industrial sector of nanobiotechnology.

**Energy**
The activities are focused on the development of graphene-based devices for hydrogen storage. A facility for production of high-quality graphene, based on Chemical Vapour Deposition, will be operational shortly. The effects of doping, intercalation or mechanical deformation on hydrogen-graphene interactions will be investigated via STM/STS and microRaman spectroscopy to device strategies for efficient hydrogen adsorption/desorption.

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DI TECNOLOGIA

**CENTER FOR MICRO-BIO ROBOTICS@SSSA**

**D.SSA B. MAZZOLAI**

Platforms: Robotics, Smart Materials

Mission: CMBR aims at developing innovative methodologies and robotictechnologies, new materials, and advanced components, for the design and development of high performance bio-inspired machines and systems at the micro/mesoscale, and for the development of devices for biomedical, environmental, and rescue applications. The mission of the Center is to generate and promote new scientific and technological knowledge in the field of microbiorobotics, which is fully deployed by inventions deriving from an interdisciplinary approach to the issues tackled. The micro/mesoscale domain shows dramatic potential for giving rise to new science and new technology, and for offering innovative engineering solutions to many practical application issues. Artefacts can be developed by observing, analyzing, and modelling phenomena and strategies used by living creatures in order to achieve motion and propulsion, and to efficiently and adaptively interact with the environment.

**Robotics**

The activities are focused on the investigation of the different aspects at the micro/mesoscale, including the design and development of new devices, actuation, sensing, reactive control and powering.The mainstream research lines are:

1) Soft-microrobots and endoscopic solutions for biomedical applications

The privileged application field of this research line is the biomedical sector. The development of untethered and tethered biomedical micro/millirobots with potential applications in targeted delivery and mininvasive diagnosis and therapy is pursued. The Central Nervous System has been identified as a remarkable domain due to the many deriving human disabling pathologies. In this context, the development of a dexterous endoscope for diagnosis and intervention within the ventricular system is being addressed. In parallel, CMBR is using magnetic fields to propel soft bodied microstructures in 3D liquid environments, and it is investigating new strategies for the development of autonomous microrobots. Moreover, transport of drugs within biofluids (as the cerebrospinal fluid) is also being investigated.

2) Robotic systems and components inspired by plants

The Plant Kingdom represents an amazing source of inspiration for designing and developing smart solutions in different fields. Mimicking plants requires deep investigation of new materials, mechanisms, sensors, actuators, and control schemes, and it can lead to breakthrough technology accomplishments. CMBR is investigating innovative artificial approaches in order to develop a robot inspired by plant roots, the so-called *Plantoid*. Plant inspired actuation (mainly based on the osmotic principle), sensing (touch, humidity), and collective behaviour are also investigated. The final goal of this research line is to develop in three years a full robotic artefact inspired by plant roots for soil and environment exploration.

From the Plant Kingdom, unicellular algae organisms (*Chlamydomonas reinhardtii*) are also studied and used as a puller model in the microworld, as an innovative approach as opposed to already known swarm behaviour strategies.

3) Bio-inspired adhesion mechanism

New artificial adhesion mechanism is under development, drawing inspiration from the suckers of the *Octopus vulgaris*. Octopus uses suckers for efficiently anchoring its body to the substratum or for grasping and manipulating objects. From an engineering point of view, this study offers potential cues for the development of innovative, bioinspired artificial adhesion strategies and devices able to outperform the ones currently available. With this in mind, CMBR has the goal to develop a revolutionary and innovative

ISTITUTO ITALIANO
DI TECNOLOGIA

adhesion mechanism, both passive and active, with an interesting perspective from an industrial (a new product) and scientific view point. Moreover, the octopus arm is also under study as a source of inspiration for robotic arms, called "Continuum Robots", which feature a continuous central structure and omnidirectional mobility. On this research topic, CMBR has established scientific collaboration with the NBT Department of IIT.

**Smart Materials**

Bioinspired approaches for developing robots require new mechanisms, materials, and technological solutions, including micro/nanofabrication, to create the final morphology of the components. Different classes of materials are explored as building blocks for developing novel microrobots and, more in general, novel Smart Materials. The mainstream research lines are:

1) Functional Nanofilms

Nanofilms (or nanosheets) are polymer-based films with a very large area (up to tens of $cm^2$) and with a thickness in the order of few tens – hundreds of nanometers. The peculiar properties of these structures make them suitable for different applications, such as electrochemical devices, and chemical, biological as well as nanomechanical sensors. CMBR research aims at developing new nanocomposite films with magnetic, conductive, and piezoelectric properties that can be used for novel integrated microrobots and devices for biomedical applications.

2) Smart polymer actuators

Smart polymers, with their almost infinite capability to be modified for the precise "tuning" of desired properties and with their generally easier and cheaper processing, represent key enabling technologies for microrobotics. CMBR research is mainly focused on studying new paradigms for actuation at the microscale, based on composites of electronic-ionic conductive polymers and liquid crystal elastomers.

3) Smart Bio-Interfaces

This project aims at investigating the interaction of micro-nanostructured environments and materials with living cells and tissues. Several key aspects are investigated, including: micro-nanostructured scaffolding (based on polymeric nano-composite), and bio-nanotransducers (such as Boron Nitride Nanotubes, $BrTiO_3$ ZnO) for the development of bio-hybrid systems (artificial muscles, Merkel cells), regenerative medicine (stem cells, neural cells, bone tissues) and nanomedicine.

4) Smart Soft Tactile Systems

The sense of touch is particularly important, because it allows a robot to interact with the surrounding environment. New materials are today being more and more employed in tactile sensing solutions. The CMBR goal is twofold. The first aspect consists in developing sensor systems that can encode dynamic and static tactile information, such as the one related to both texture and contact forces, in a smart microrobot. The second aspect relates to integration of both sensors and electronics in new materials, in order to achieve full flexibility, compliance, extensibility, and robustness of the whole integrated system.

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DI TECNOLOGIA

**CENTER FOR ADVANCED BIOMATERIALS FOR HEALTH CARE@CRIB**
**PROF. P. NETTI**

Platforms: Smart Materials, EHS, D4, Computation

Mission: The Center uses cutting edge technologies to engineer novel bio-logically inspired materials that perform specific and programmable functions through the hybridizations of synthetic polymeric backbones with bioactive molecular and biophysical signals. Research activities are focused on the understanding the molecular and cellular mechanism of signal recognition occurring within hybrid matrices, the identification of relevant biological and biophysical signals and the development of strategies to encode these signals with controlled spatio-temporal features. The group possesses the know-how on signal presentation at the cell-material interface and has a consolidated expertise in tailoring biochemical and biophysical cues to elicit specific cell responses or to recruit or deliver specific molecular moieties.

**Smart Materials**
The main objective of this activity is the design and realization of novel material platform (CIMs – Cell Instructive Materials) able to control and guide specific cell function. CIMs can be programmed to elicit specific cell or tissue responses both *in vivo* and *in vitro*. The development of CIMs which direct and guide cell fate represents a relevant step towards tissue and organ regeneration *in vitro* and *in vivo*. One of the greatest obstacles, however, that has hampered the development of such bioactive platforms concerns our limited knowledge on the basic biological principles that govern cell-signal and cell-material interactions. Therefore, an improved understanding on the effects of molecular and physical signals on cell behaviour is of fundamental relevance for developing novel and smart bioactive materials that are able to trigger specific cell functions according to predefined schemes. The research project aims at defining the most relevant biochemical-biophysical signals for eliciting specific cell activities and developing strategies to encode these signals onto synthetic platforms with a tight control on their spatial arrangement and temporal evolution.
The activities of this platform is developed in collaboration with the Centre for Space Human Robotics.

**EHS**
Nanometric particles interact with cells, tissue and organs at a molecular level. For these reasons they present potential interest as molecular medicine shuttles for advanced therapy and diagnosis. However, along with the excitement that has driven the development of novel nanomaterials, there have been increasing concerns regarding the risks these nanoparticles may elicit. Therefore, as these nanostructures are intentionally engineered to target specific cells, it is important to ensure that these enhancements do not trigger adverse effects. The activities in this platform aim at enlightening the molecular mechanism involved in nanoparticle cellular uptake with particular emphasis on the role of nanoparticle shape, surface chemistry and charge. The project aims at the definition the optimal chemical-physical and morphometrical parameters for designing and producing safe nanometric carriers that are able to cross part to part the cell membrane. The intended goal is to produce novel devices which effectively cross the blood brain barrier and deliver drugs in a controlled fashion.
The activities of this platform is developed in collaboration with the Center for Biomolecular Nanotechnologies

**D4**
Biotechnology tools, inspired by natural screening processes, can be greatly helpful in providing recognition motifs toward target biomolecules. On the other end, recent advances in materials science have provided innovative processing procedures that allow a tight control over material chemical, physical and morphological properties Furthermore, nanotechnologies have proved the feasibility of encoding signals at a molecular level and with high spatial resolution onto material platforms. The aim of this program is to

exploit such synergistic strategy for the creation of sensing devices characterized by high sensitivity and throughput. This body of knowledge may be helpful in the field of proteomic, genomics and post genomics, offering solutions to tackle important practical aspects: cost reduction; improve the consistency of the analyses; increase data throughput; enhance spatial resolution. Research activities include the determination of innovative and specifically screened molecules to be used as sensor moieties toward customized biomolecules, the development of technologies for the integration of such molecular sensors into scaffolding materials especially designed for their effective presentations and advanced tools for the read-out of the reporter molecules.
The activities of this platform are developed in collaboration with the Centre for Space Human Robotics.

**Computation**

Decrypting cell-cell and cell-material communications requires the understanding of the mechanisms underlying molecular recognition events. The investigation of these phenomena can strongly advantage of molecular modelling, as this allows to view, interact, calculate, and modify the chemical elements involved in the recognition. To date, there are no established computational methodologies dealing with these issues. The research aims to develop synergistic combination of theoretical and experimental approaches allowing to understand and to dissect the subtle structure-property relationships that influence the effectiveness and the specificity of the system of interest. By pursuing the aim of a direct comparison between experiments and simulations, the activity aims at developing a valuable tool for supporting the interpretation of ambiguous laboratory outputs and for driving the design of new materials toward new experimental directions.

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DI TECNOLOGIA

**CENTER FOR BIOMOLECULAR NANOTECHNOLOGIES@UniLe**
**DR. P. P. POMPA**

Platforms: Computation, EHS, Energy, Robotics, Smart Materials

Mission: The Center establishes a large scale facility for bio-molecular and organic materials and nanoscale biomolecular interactions. The main target is the development of nanostructured materials with advanced mechanical, chemical and electronic functionalities and the investigation of the cellular toxicity of such nanostructured compounds, in view of future nano-safety standards of certification. The activity of the center is highly interdisciplinary. Exploiting a wide range of molecular and biomolecular compounds, as well as metrologically assessed engineered nanomaterials, the center aims at performing state of the art research in the field of functional and responsive nanocomposite materials, nanotoxicity screening of nanomaterials and development of reliable in-vitro and in-vivo models, organic materials for low-cost energy sources, and advanced materials modeling.

**Smart Materials**

This platform deals with the development of new composite materials pointing towards a synergistic performance of the different materials combined together. The platform studies different potential techniques to merge together distinct materials, with so far well studied and established properties, in order to fabricate novel materials that can preserve the properties of the individual components, but most importantly exhibit enhanced characteristics that would not be possible otherwise. The focus is on composites that have as basic component polymeric materials that exhibit inherently excellent processability, good mechanical properties, a huge range of surface properties, they are lightweight and low cost. Intense research activity is focused on biodegradable, biocompatible or even natural polymers. Such polymers are the common starting point for the composite materials, combined with a vast variety of nanofillers. As nanofillers we use custom tailored inorganic nanoparticles of various shapes (rods, wires, branched nanostructures, etc.), and diverse compositions leading to different properties, i.e. magnetic, fluorescent, conducting etc., or molecules responsive to external stimuli, i.e. photochromic, thermochromic, electrochromic etc. With those components available, the Smart Materials platform can develop composite materials and nanostructured systems with desirable chemical, mechanical, thermal, surface, optical, and biological properties, tackling a number of material science oriented problems, spanning from robotics to aerospace. The activities will be performed in collaboration with Center for MicroBiorobotics, Nanochemistry and Nanophysics Department

**EHS**

The research activities of the EHS platform are in the field of nanotoxicology and intensively focus on understanding the interaction between nanoscale materials (engineered nanoparticles and nanostructured substrates) and living systems. The primary aim is the identification of the key parameters affecting the biological responses (size, shape, surface area, charge, coating, etc.) and the development of reliable "nano dose-metrics" and "nanotoxicity factors" of specific nanomaterials, based on their accurate physical/chemical characterization. An in-depth investigation of the interaction mechanisms is performed by applying systematic multidisciplinary approaches which foresee the combined use of several analytical techniques, nanotoxicogenomics, nanoproteomics and advanced imaging tools. Both cell lines and simple animal models are explored in this respect, in order to develop appropriate metrological tools that can provide a general assessment of potential toxicity of nanoparticles. Eventually, procedures and protocols developed for metrological assessment will be compared to the international regulatory rules.
In this frame, a natural expansion and integration of these research lines is the development of innovative nanovectors for nanomedicine applications (once assessed their biocompatibility), the implementation of

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DI TECNOLOGIA

antibacterial coatings based on toxic nanomaterials (in collaboration with the Smart Materials Platform) and the fabrication of nanomaterial-based diagnostic devices.
The activities will be performed in collaboration with Nanophysics and D3 Department, **Center for Advanced Biomaterials for Health Care, Center for Space Human Robotics and Center for Nanotechnology Innovation.**

**Energy**

Research activities of Energy Platform in IIT-CBN are focused on two main lines:
L1) Devolopment of Dye Sensitised Solar Cells (DSSC) on glass and flexible substrates;
Research line L1 aims at fabricating DSC cells with conversion efficiency (CE) >12% and their integration in smart photovoltachromic panels. Novel device structures (also exploiting flexible substrates) and materials will be explored.
L2) Development hybrid solar cells based on polymers and colloidal inorganic semiconductor shaped nanocrystals Research line L2 aims at developing hybrid cells based on different class of polymers and colloidal nanocrystals, namely, IR absorbing and Cd-free nanoparticles. Novel device structures exploiting doping technology will be explored aiming at CE > 5%. Collaborations with IIT@polito, IIT@polimi and IIT-Genoa are currently active.

**Robotics**

By virtue of their extremely small size, high performances, low power consumption, low cost and possible integration, MEMS technology and devices are being increasingly exploited in robotics. Biomimetic and biological inspired systems are being feasible because of the possible convergence in MEMS of smart materials, micro and nanoelectronics and energy generation and storage. MEMS technology can, therefore, enable both the embedding of novel, compact and accurate sensors arrays in-vivo, in humanoid or animal robots and the fabrication of micro and miniature robots at relatively low unit cost. Robots with improved awareness of the external environment through MEMS sensors will both expand their capabilities and make possible hazardous missions, or duties presently unimaginable. The activities of the MEMS group will develop new advanced micro/nanotechnologies and devices for humanoid hypersensing applications (hearing, touch, smell and taste) to be embedded either in robots or in-vivo and their interface with neuronal networks. As a byproduct, the developed technologies will be applied to micro and nanoactuators, to prosthetics, to energy harvesting, to biomimetic and advanced devices.
The research activities related to the humanoid applications will be extended also to smell- and taste-based sensing strategies.
The activities will be performed in collaboration with RBCS, CNCS and Nanochemistry Department, **Center for Advanced Biomaterials for Health Care, Center for Space Human Robotics and Center for Nanotechnology Innovation.**

**Computation**

The research activity aims to develop a three-level multiscale approach based on the Frozen Density Embedding (FDE): i) the energy relevant part will be described using correlated wavefunction, hybrid Density Functional Theory (DFT) methods and/or the GW approach; ii) a surrounding region using semi-local functional and new non-empirical approximation will be developed, also to better describe quasi-2D systems; iii) the remainder part of the system (e.g. the environment) by novel electrostatic embedding approaches, based on the fast-multipole-method and/or finite difference approaches.
The mainstream research lines are:
1) Modeling of metal nanoparticles as additional activity
2) Modeling of organic-inorganic interfaces
3) Development of embedding schemes

The activities will be performed in collaboration with D3 and Nanochemistry Department, Center for Nanotechnology Innovation and Center for Advanced Biomaterials for Health Care.

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**CENTER FOR LIFE NANO SCIENCE@Sapienza** (under construction)
**PROF. G. RUOCCO**

Platform: D4, Smart Materials, Computation

Mission: The Center focuses on Life Nanosciences and covers different technological aspects of common interest: the development of advanced instrumentation; new techniques for structural determination and molecular imaging; methodologies for drug delivery and new genomic, proteomic and cellular diagnostics and therapies. The Center develops biomedical researches activities where technological innovation is key to reach the goals and is organized in the following laboratories:
Nanoscience Lab
The scientific activity of the life nanoscience laboratory is devoted to interdisciplinary research targeting two major biomedical areas through the application of innovative technologies.The first biomedical area covers neurodegenerative disorders, hereditary and sporadic conditions characterized by progressive nervous system dysfunction. The project will study the molecular, cellular and tissutal processes underlying nervous system homeostasis and differentiation and their misregulation. The second area focuses brain tumours: primary aims is understand the interplay between Cancer Stem Cells (CSC) and neoangiogenesis, the dynamics of the CSC population and the set-up of pharmacological screenings of available small drug and natural products libraries as well as of innovative immunotherapeutic strategies. At the same time the project will employ and further develop *in vivo* molecular imaging technologies to improve tumour detection. The mainstream research lines are:
1) Novel Nanotech-Based Approaches for the Study and Treatment of Neurodegenerative diseases;
2) Novel strategies for the imaging and treatment of brain tumours through targeting cancer stem cell-specific signalling pathways

Genomics & Bioinformatics Lab
The mainstream projects are: High-throughput sequencing;libraries preparations; sequencing informatics

Microscopy & Tracking Lab
Single molecule imaging aimed at investigating macromolecular distribution and traffic at the intracellular level will be developed. The mainstream research lines are:
- Development of digital holographic microscopy
- Development of CARS microscopy
- Development of total reflection microscopy
- New scanning techniques"standard" confocal and/or multiphotons microscopy
- Development of single molecule trapping techniques based on infrared radiation
- Development of a ready-to-use intracellular Raman single molecule detection system based on a plasmonic antenna
- Development of integrated AFM/spectomicroscopy based on photonic and plasmonic nanostructures for single molecules in both the intra and extra cellular context
- Development of integrated spectro-photometric systems for multi spectra analysis
- Development of new nano-phosphorous labels which allow to go beyond the blinking and bleaching problems associated to fluorescent and nano-dots dyes
- Development of techniques (software and hardware) for tracking and image reconstruction

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DI TECNOLOGIA

**BRAIN CENTER FOR NANO SOCIAL AND MOTOR COGNITION@UniPr**
(PROF. G. RIZZOLATTI)
Platform: Neuroscience
Mission: The Center aims to unravel the mechanisms that are at the basis of the different aspects of social cognition as well as to study their possible interactions. This objective will be attained by (a) investigating these different mechanisms in humans, using instrumental (high density EEG, TMS and fMRI) and behavioural techniques; (b) extending our knowledge on the mirror mechanism and on its role in action and emotion understanding in non-human primates; (c) examining the dysfunction of the mirror mechanism and the other mechanisms involved in social cognition in patients with diseases like autism and schizophrenia. The mainstream research lines are:
1) To elucidate the mirror neuron circuitry in non-humans primates, describing the laminar organization of the area F5 and the temporal relationship between the responses of mirror neurons and those of other types of neurons located in this area;

2) To extend our knowledge on the role of the “chained” motor act organization of the frontal and parietal lobe in understanding motor intention both in non-human primates and in humans;

3)To establish the mechanism underlying the understanding of motor intentions, including the dispositional moods (“vitality forms”) which characterize object-directed and communicative actions both in healthy humans and in autistic and schizophrenic patients;

4) To assess the existence of the mirror mechanism in rodents;

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DI TECNOLOGIA

| Research Unit | Robotics | Neuro | D4 | EHS | Smart Mat | Energy | Computation |
|---|---|---|---|---|---|---|---|
| ADVR | X | | | | | | |
| RBCS | X | X | | | X | | |
| NBT | | X | | | X | | |
| D3 | | | X | | | | X |
| NACH | | | X | | X | X | |
| NASTR | | X | X | | X | | X |
| NAPH | | | X | X | X | | |
| PAVIS | X | | | | | | X |
| CSHR@PoliTo | X | | | | X | X | |
| CNST@PoliMi | | | | | X | X | |
| CGS@SEMM | | | X | | | | X |
| CNCS@UniTn | | X | | | | | X |
| CNI@NEST | | | X | X | | X | X |
| CMBR@SSSA | X | | | | X | | |
| CABHC@CRIB | | | X | X | X | | X |
| CBN@UniLe | X | | | X | X | X | X |
| CLNS@SAPIENZA | | | X | | X | | X |
| SMC@UniPr | | X | | | | | |

Distribution of the main activities carried out by the IIT research units on the technology platforms The distribution is indicative, as all research units have several minor and/or joint activities on other platforms. Activities do not have necessarily similar size and might involve teams of different dimension. Updates and revisions of the network centers will be decided between 2012 and 2013 according to the output of the external evaluation panels.

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DI TECNOLOGIA

**TECHNICAL ANNEX II →INTERDEPARTMENTAL JOINT PROJECTS**

The purpose of this technical annex is:

- to provide a framework for facilitating inter-departmental collaborations within IIT;
- to present the iCub central facility;
- to present a few ideas for future interdepartmental research.

IIT has a very high potential – perhaps unique in the world – to carry out interdisciplinary research that can drive innovation in science. For one, IIT neuroscientists work under the same roof with researchers in nanochemistry, nanostructures, nanophysics, drug discovery, robotics and imaging. Proximity alone lowers the energy barrier for productive interactions between departments. In addition, IIT is making a commitment to interdisciplinary research at a time when traditional funding agencies are shying away from supporting early-stage, innovative interdisciplinary research. IIT thus has a tremendous opportunity to become a leader in interdisciplinary research related to different fields of science. A second important feature is that IIT is a "Human Centric Technology Institution", with the main objective of developing technologies to improve the quality of live of the human society in a sustainable way (from molecules to humanoids). This has a very high social, cultural and ethical value. This is beyond the simple concept of " "Projects", as there is no unique, identifiable final destination, and it is closer to a collective, multidisciplinary and adaptive exploration program that we like to identify as *trip to the moon* enterprise. To accomplish valuable results, the interdepartmental collaboration, and the interdisciplinary research has to be constantly encouraged and nurtured.

Over the previous three years, IIT departments have focused on their consolidation and accomplishment of important basic research goals. In the next three years we should bring increased interaction between departments. **The question is how to best invigorate such interactions within the IIT research structures**. This annex outlines a few criteria and a few ideas on how IIT could actively foster interdepartmental collaborations. In the next section the emphasis is on the *process* for encouraging interdepartmental collaborations. Then we will present the layout of the iCub central facility discussed in Annex I and in the Executive Summary of the scientific plan 2012-2014. Finally, we will present some general ideas that serve as examples of the kinds of interdisciplinary projects to be developed in the future.

*1-General Guidelines to foster interdisciplinary research between IIT departments.*

**1. The key element to successful interdepartmental projects is to *dedicate* young scientists (postdocs or PhD students) to specific interdepartmental projects, under the guidance of two senior scientists.** Collaborative projects will develop from bottom-up discussions between researchers, who will then work together to identify and recruit appropriate postdocs or students for the project. These "hybrid" fellows will be the point persons for the collaborations. The hybrid fellows would most likely be experts (or trainees) in one of the relevant technology fields of the project, but should also become knowledgeable about the others relevant to their technology development. Initially they will work primarily in the core laboratory involved in the collaboration, then they progressively move towards other laboratories to cross fertilize the activity. This arrangement will require close supervision and communication between the senior scientists (the supervisors). The growth of such initiative will become a critical success factor and an evaluation parameter of increasing importance in the future.

**2. It is critical that funding for the personnel of the interdepartmental projects should not be taken from the main budget of the departments. Rather, it would be wise for IIT to establish a separate budget for interdepartmental collaborations, specifically dedicated to these pilot actions.** This budget would fund the salaries of the hybrid fellows and could partially defray operating expenses for the collaborative projects. This is critical for two reasons. First, we must acknowledge that investigators -- particularly young investigators -- will be cautious about using their limited research resources on innovative projects, which are inherently risky. By setting up separate cost centers for interdisciplinary research, under the supervision of the scientific direction, the institution assumes at least some of the risk of interdisciplinary projects. Second, it will be difficult for IIT investigators to obtain external funding for such risky projects without preliminary results. However, IIT funding in the initial stages of these projects could be expected to leverage future funding, especially from European funding agencies that support collaborative projects.

**3. To ensure the quality of cross-departmental projects, the hybrid fellowships could be awarded on the basis of a competitive process within IIT.** This could involve one or two calls for proposals every year. Proposals could be brief outlines of the motivation and research plan for the project. Evaluation should be made by the scientific and technical committee (eventually supported by external experts), which will help in the review process and provide advice.

**4. To encourage interdepartmental projects, evidence of interdisciplinary research could be one criterion for evaluation of scientific staff,** in addition to publication record, ability to obtain external funding, etc.

**5. To stimulate brainstorming between IIT scientists, IIT should organize in-house symposia or retreats between departments.** This is especially important for junior investigators to learn about activities in other departments. A remarkably effective approach in this regard is for many fields of science to present a challenge of a specific, seemingly intractable technical problem in their area of research, and then open the floor for brainstorming.

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DI TECNOLOGIA

*2-The iCub central facility*

This section describes the plan and organization of the iCub central facility. The goal of this new unit is that of maximizing the impact of the iCub platform as the IIT flagship in robotics research. This includes integrating hardware and software of the iCub into a coherent platform, of providing support to the iCub users (internally and externally), fostering community building, and implementing the transfer of iCub-derived technologies to industrial exploitation should the opportunity arise in the future.

**Evolution of the iCub Platform**

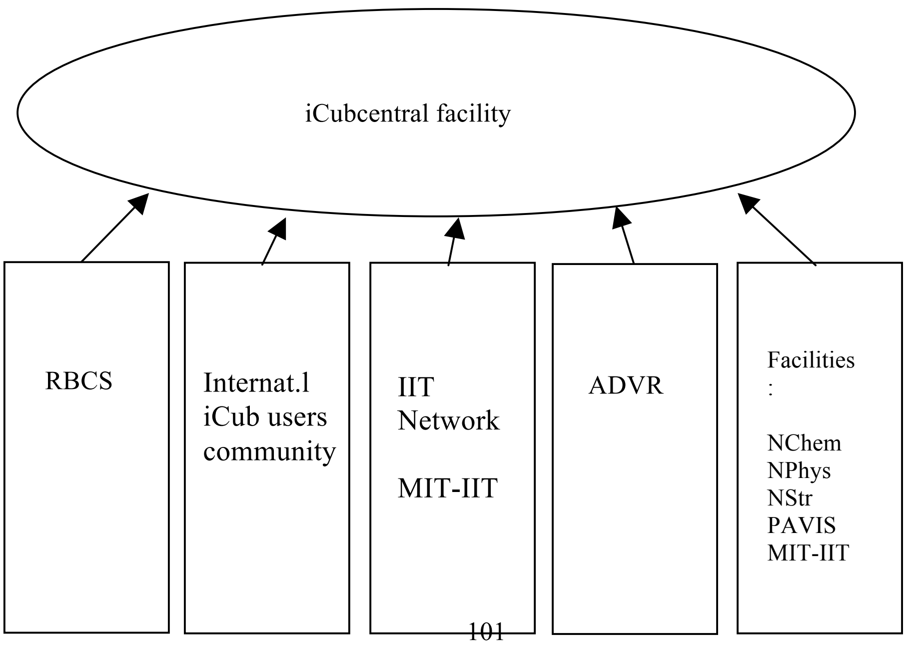
After a considerable momentum in the development of the iCub owing to the guidance of the RobotCub project, due to the cohesion of the RobotCub Consortium, and the continuation of the effort inside IIT also through the new activities of several FP7 EU-funded projects, the iCub community has been enlarging but simultaneously defocusing. In spite of the fact that several iCubs are available in Europe, the amount of research and contributions to the common repository is somewhat diminishing. Conversely, we might need to scale up the effort in order for IIT to play a major role in the worldwide arena of humanoid robotics and in the development of the robotic platforms for the future European Flagship (hoping that the proposal of RoboCom Flagship will be successful in 2012). This defocusing might occur even inside IIT, as the development of new technologies and solutions for bodyware, mindware, new materials by the deputed research units is hard to synchronize. This is because new discoveries and developments occur with timing dictated by the international competition in the scientific community, whereas system integration in a reliable and robust robotic platform such as the iCub is a much longer process, since the iCub is distributed worldwide to a well-established, demanding community of users. In other words, inventing/developing a new individual component at the state of the art does not necessarily mean that it can be immediately integrated in the humanoid to improve its performance. Rather this might require so many system-wide changes to the point of making improvement pointless (or to make it less convenient). Even though IIT has already developed several components and technologies for the upgrade of the present version of the iCub, their integration is not straightforward: e.g. it is difficult to integrate *a posteriori* variable impedance actuators and the new compliant legs, in materials there is still a lot of problems for the development of the iCub skin, and in software the bipedal locomotion modules have yet to be integrated with cognitive tasks. This is a well-known problem manifesting itself when a state of the art technology moves from the level of prototype to the level of worldwide reference technology. The leap from a single state of the art humanoid to a community of iCub users requires reliability and reproducibility, even though the humanoid platform is still a basic research tool. IIT thus needs to synchronize and facilitate the synergistic integration of new technologies produced by the different departments in the next iCub versions, without limiting the exploratory research carried out independently by the research units in their respective fields. This is the only way for IIT to:

- Produce outstanding research results, staying ahead of the international competitors;
- Enlarge the user basis and the number of developers of the iCub, manage the open source community and support it effectively;
- Release periodically upgraded versions of the iCub with improved mechanics, electronics, and software;
- Ensure quality and reliability for both hardware and software;
- Envisage (in case of success) a start-up company in humanoid robotic in the future;
- Guide dissemination and publicity about the iCub maximizing the impact of the iCub in the research community.

The integration of cognitive components and of mechatronic development is thus the main motivation for establishing the iCub central facility. A long term planning of the activity should lead to an *evolutionary road map* for the iCub, the central iCub facility being the “*atelier of design*” preparing such road map. With clear deliverables for the next 10 years, it is possible to set up the strategies for enhancing the collaboration among the research units, optimizing the synchronization of the iCub-related developments, and ensuring the integration and compatibility of all new components (body, cognition, software, etc.) in the future. In this way the departments’ activities will continue according to their respective scientific plans, on a more curiosity driven basis (triggered by the international competition in the different fields and to a certain extent by the facility road map) while the iCub facility, will be responsible for the identification of the technologies to be transferred to the iCub, their integration and the release of the new iCub versions.

In addition the iCub facility will have the possibility of exploiting the results developed by the external community of users, who continuously produce new code (software) and hardware solutions in a competitive way. To enable integration of all these results in an advanced artificial cognitive system such as the iCub, a solid infrastructure is needed, where people can collaborate and, simultaneously, compete and where effort is never wasted. To speed up the selection process tools for fast development and debugging must be provided. More important, the process of testing and evaluation of the software has to be fast and efficient. The iCub facility would take a pivotal role in providing these services, a software repository to the community and in supervising and leading the process of software integration and validation.

Having set the basis for *integration of new technologies within the road map*, the next step is to provide a platform where users can experiment wildly. That is, the result of this integration process will be a better iCub that scientists (at IIT and worldwide) can use to test and demonstrate the advancement of their scientific goal and the maturity of related technologies. The iCub is going to be an ever-evolving hardware/software system, which constantly valorizes the investment of IIT in robotics, neuroscience, new materials, etc. and integrates new solutions in new versions released periodically to the international iCub community. The release of new iCub versions will be targeted approximately every two years, requiring management of versions, maintenance, debugging, etc. In terms of software the pace could be even faster with applications being developed quickly and providing new functionalities to the iCub. Clearly this sets the basis for the transition from a research device to a worldwide accepted platform with increasing industrial characteristics. The quality of solutions for robotics (not necessarily a whole humanoid) developed by IIT should become the main attractor for industry. In a longer time frame, we think that humanoid robots would make appearance as complete applications. Initially they will work as generic helpers and, later, as heavy duty systems operating in dangerous places or physically assisting a person in difficulty. The development of such a vision clearly points towards a joint venture with world-class companies (very likely automotive) to further develop the iCub and a brand new "robotic companion" market.



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**Structure**

The iCub central facility places itself at the intersection of various ongoing activities as exemplified by the figure above. It acts as a collector of scientific results and facilitates the creation of new results, mixing them to accelerate the evolution of the iCub. In the language of biological evolution, integration of solutions represents the cross-over of genes (cross-over makes the whole process of evolution particularly efficient). Similarly, we plan for an environment where this can happen smoothly and where the competitive selection takes place at a reasonable pace. The role of the facility is:

- To define the road map for the iCub evolution (timing of the new versions, their release and main objectives to be accomplished by each version);
- To guarantee that appropriate tools are developed by the departments and that results and corrective actions are taken whenever needed'
- To coordinate and agree all the technical aspects related to the integration, compatibility and quality of the new technologies incorporated in the iCub;
- To coordinate the incorporation of the new software produced by the open source community of the iCub.

This is obtained by defining and implementing the following tasks (T):

- T1: continuous integration of the iCub mechatronics, this includes e.g. fixed and variable stiffness actuation, robust and safe mechanical interaction with the environment, skin, new visual sensors, new distributed electronics, Ethernet connectivity, battery module for power autonomy;
- T2: continuous development of the software infrastructure, which includes e.g. the software middleware of the iCub and all development tools required to foster collaboration across the iCub community (servers, distributions, packaging, etc.), standardization;
- T3: integration of skills and controllers developed by various departments and units into coherent and mutually compatible modules and libraries including sharing the coordination of large-scale experiments on the iCub;
- T4: support of iCub users and owners, including the maintenance of the software and hardware of the iCubs, generic support for troubleshooting, documentation maintenance, teaching, etc.;
- T5: management and guidance of the open source community, as for example dissemination, publicity and external website maintenance;
- T6: production, i.e. the construction of prototypes and full robots as needed;
- T7: technology transfer. If possible, the creation of collaboration with industry for iCub-based technologies in synergy with IIT's research units.

The main contributors of technological solutions are expected to be RBCS, ADVR, PAVIS, IIT-MIT, several network centers (IIT@ Unile, IIT@MIT,IIT@PoliTo, IIT@PoliMi), and the community of users of the iCub (for software).

The management of the iCub facility is demanded to a steering committee initially composed of three members (one from RBCS, one from ADVR and one from the nanobiotech facilities), one of the three acting as coordinator and responsible person. The steering committee might be extended in the future (maximum 6-7 people) in order to accommodate a varying degree of participation of other IIT's units. A dedicated budget will be made available to support and supervise the integration of the new technologies developed by the different research units and to maintain a common repository of the iCub. Quality control and optimization of the iCub platform will be responsibility of the facility, which will coordinate all the needed extra engineering to adapt and integrate components coming from different departments/units.

**Resources**

The iCub facility will need at steady state about 30 people, most of which will be moved from RBCS. The facility will have teams for the development of iCub hardware and software, iCub production, maintenance and test groups, namely:

- The iCub platform infrastructure (a team covering software, hardware and materials);
- The iCub platform production. This group is already existing in RBCS and might need only a minor integration if needed;
- The infrastructure of the facility. This is the informatics and server structure of the iCub facility. It includes the compile farms, the web access, software testing and documentation infrastructure;
- 1 Administrative Point of Contact.

The construction of several prototypes and one/two full iCubs to be maintained as reference platforms is foreseen.

**Milestones**

Needless to say that a project of this size and vision requires a startup phase for the preparation of the infrastructure and hiring of new people, and later a steady state phase where the full set of results is achieved. In terms of personnel, the increment during the first 18-24 months is of about 10 people, reaching quickly the steady state (most people are already available at RBCS). The idea is to start with an agile structure that grows over a period of time of about five years especially if external funding becomes available.

During the first 18-24 months we expect to grow up to about 30 people, in addition to IIT people contributing voluntarily to the project. Our approach is to make yearly adjustments and therefore to tailor the investment to the actual requirements. The timeline for integration is not very different from the planned activities within the departments and is summarized in the following:

2012, Construction of parts employing new technologies (compliant actuation), validation, tentative design of sub-groups (e.g. head, hands, legs) using the new technologies (for the iCub). Improved robustness and enhanced motor performance for better physical interaction and safety. Refinement and consolidation of the iCub 2.xx (e.g. new version of the skin, integration of new lower leg/foot mechanics to permit bipedal locomotion).

Scenario: first draft of the integration activity. Sensorimotor coordination in a human populated environment (the lab); human-robot interaction (physical and speech-based).

What to integrate:

- Basic walking/steering modules, simple gait stabilization (ADVR);
- Modules required for motor control and vision for objects, e.g. attention, reaching and grasping (RBCS);
- Simple speech recognition module (RBCS);
- New control electronics (RBCS/ADVR);

2013-2014, Start the development of parts of the “flexible robot” as evolution of the iCub and tentative merging with new technologies (in particular, passive fixed or variable stiffness actuators).

Scenario: integration of whole body control (e.g. simultaneous reaching and balancing) with manipulation and various machine learning methods.

What to integrate:

- Modules required for multimodal perception of objects (RBCS, MIT);

- Machine learning modules (RBCS/MIT);
- Modules required for planning movement and impedance profiles during interaction (control only), RBCS/ADVR.
- Custom motor design (RBCS);
- People detection and tracking for social interaction, detection of people is learned (PAVIS).

2015, New integrated version of the iCub (version 3.0) including variable impedance actuators (type and shape to be determined as well as their location in the body), body protection and skin, joint protection (rubber, plastic, wiring redesign), force control, an enhanced fully sensorized foot permitting human like walking and power autonomy (batteries). First release of an integrated layer of software libraries for the iCub control including vision, learning, sensorimotor coordination, force control, walking, foot planning over uneven terrains, body stabilization to disturbances, and the respective debugging tools.

Scenario: a new release of the iCub with increased robustness, body & skin protection for impact and force/impedance control (integrated version of year 2012-2014). Increased interaction with people (social and physical) in indoor environments.

What to integrate:

- Human body modelling with pictorial structures modules, social awareness (PAVIS);
- 3D world modelling modules, navigation, object detection (RBCS/PAVIS/MIT);
- Integrated low-level control modules (ADVR/RBCS);
- Motion planners for footholds over uneven surfaces (ADVR);
- Body stabilization and reaction step planning under large disturbances (ADVR);
- Modules required for acquisition of affordances via learning (RBCS);
- Skin (RBCS/Material);
- Neuromorphic cameras (RBCS);

2016-2017, Robustification of previous achievements especially consistent integration of testing and debugging into the iCub development in version 3.0. Inclusion of new software modules and libraries to improve social interaction (recognition of people), learning abilities for new objects and people (possibility of extending the iCub database via training procedures), walking, and improvements for energy autonomy (e.g. custom designed Li-polymer batteries). Start new design on alternative materials as e.g. carbon fibre and other composite materials.

Scenario: iCub being able to understand simple spoken commands, plan an opportune set of actions to satisfy the request. Examples are requests to fetch an object in a room and bring it back.

What to integrate:

- Re-identification of known people module (PAVIS);
- Some cognitive planning modules for interaction and manipulation (RBCS);
- Robust low-level behaviours including walking and control of the upper body modules, balance stabilization while carrying a load (RBCS/ADVR);
- Energy modules (photovoltaic, batteries, etc.) (Smart Materials);

2018, New release of the iCub (version 4.0) including the use of new materials whenever possible and limp designs based on dynamics optimization, energy autonomy and a new release of the skin on flexible materials. Second release of integrated software libraries for the iCub including all the behaviours demonstrated in year 2016-2017.

Scenario: yet another iCub release with energy autonomy, optimization of weight and mass distribution (particularly for legs) using new materials and running all the software modules identified in the previous four years into an integrated demonstration.

What to integrate:

- All the above described modules (2012-2017)
- Energy modules including batteries, plastic photovoltaic cells, controllers (Smart Materials);
- New materials for increased weight optimization (Smart Materials/RBCS/ADVR);
- New arm/legs designs with optimum weight and mass distribution for better dynamic performance (RBCS/ADVR);
- More continuous/incremental learning of new situations (people/objects/interactions) (RBCS/PAVIS/MIT);

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*3 - Ideas for interdepartmental projects*

In what follows we list a preliminary, non-exhaustive list of ideas eligible for future interdepartmental projects. Based on these ideas, more structured short proposals will be submitted to the scientific committee in the next months for selection and funding. Due to the inherent explorative nature of these programs, it is expected that new ideas for interdepartmental collaborations will be generated continuously. A periodic internal call with well defined rules for the selection will be set up during the first quarter of 2012.

1. **RBCS-NBT-Nanobiotech: Bridging the Gap in the Brain: permanent brain stimulator for rehabilitation**

2. **RBCS-Nanobiotech-IIT@CRIB-UniNa-IIT@UniLe: Tissue Engineering: the problem of interconnecting an artificial system to a living system**

3. **RBCS-NBT:** neuronal reprogramming and regeneration.

4. **D3-Nanochemistry:** nanomedicines capable of selectively delivering special pharmacological agents to their target tissues.

5. **NBT - Nanophysics - Nanochemistry:** 3D neuron growth**.**

6. **NBT/Synaptic Neuroscience - IIT@PoliMi:** opto-neural interfaces (organic polymers and artificial retina).

7. **NBT/Synaptic Neuroscience - IIT@NEST-Pisa:** genetically-encoded actuators

8. **NBT/Synaptic Neuroscience – IIT@NEST-Pisa:** genetically encoded "CLOSED-LOOP" sensor-actuator PROBES .

9. **NBT/Synaptic Neuroscience – NANOSTRUCTURES:** focusing single molecule probes for cellular integration and computation of signals.

10. **NBT/Synaptic Neuroscience – RBCS:** neuronal reprogramming and regeneration.

11. **NBT Synaptic Neuroscience - NANOSTRUCTRES:** neuromimetic computational devices.

12. **12) PAVIS – D3**: methods and analysis of biological data using pattern recognition techniques.

13. **13) PAVIS – NBT**: designing and applying advanced computer vision and pattern recognition techniques to the understanding of the functional behavior of cellular neural networks**.**

14. **14) PAVIS –NANOPHYSICS:** image analysis tools for nanoscopy.

15. **15) PAVIS – iCub Facility:** algorithms adapted to be used in the iCub for visual tasks.

TECHNICAL ANNEX III → THE TECHNOLOGY TRANSFER

**Strategic aims and priority choices of the Institute**

Technology transfer is a strategic objective of the IIT and is an important yardstick of its success. The IIT Technology Transfer strategy, whose general guidelines are included in the development of long term activity plans should be based on the constant refinement of the level of technical excellence and scientific credibility of the institute at the national and international level.

The strategic guidelines for organisation of Technology Transfer by the IIT and the main types of activity expected in relation to different markets and the different partnerships of interest are outlined in the IIT policy approved by the Board of Trustees.

**Summary of the strategic plan**

The strategic plan of the IIT consists of seven "technological platforms" of strategic interest to the country and the international scientific community. Each platform contains a selection of related subjects of considerable practical interest (in the short-medium term) and fundamental (long term) that is being developed synergistically by the research facilities of the IIT. The seven platforms build a long-term visionary path and bring together for the first time the hard sciences and life sciences for the development of human and humanoid technologies ranging from humanoid robotics to "intelligent drug delivery". The platforms are (Fig.1):

- Robotics
- Neuroscience
- Drug Discovery Development and Diagnostics
- Portable Energy
- Environment Health and Safety
- Smart Materials
- Computation

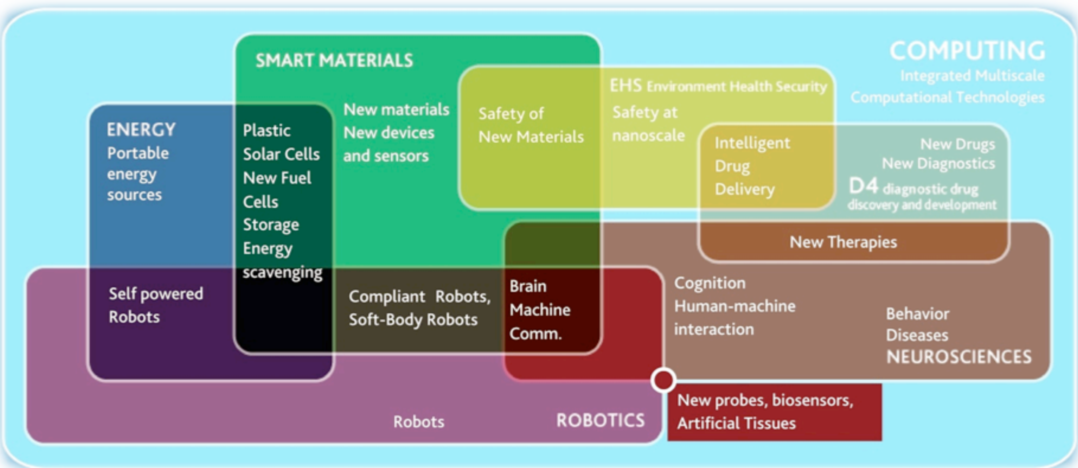


*Fig 1: Scientific Plan*

The overlaps in Fig.1 between the platforms show the spaces of interdisciplinary nature on which the technological convergences of the IIT are developed, for instance: new sensors developed by the smart materials platform are adopted to strengthen the cognitive capacity of a robot while the robot itself is used for the motor rehabilitation of humans. Synthetic nano-structures developed for composite materials are used

as carriers to transport and release new drugs. Constant and synergistic development of the platforms generates a scientific circuit in which "hard" and "wet technologies" concur on the development of an integrated project that has technologies for mankind as final target.
World-class scientific expertise and state of the art equipment contribute to the development of a wide-ranging, multidisciplinary scientific programme, strengthening the competitiveness of the national technological system through collaboration with national public and private organisations.

**Models of Technology Transfer**
The opportunities for TT of the Institute, similarly to what happens in other research institutions of worldwide importance, can be summarised as follows:
**Consulting and feasibility studies**
This is a type of TT generally based on small-scale projects: consulting services and feasibility studies for SMEs and enterprises. The type of project is annual, targeted to the study of problems of technological and/or manufacturing, with rather small innovative content in view of resolving problems with short term effects. Usually it does not have strong implications for intellectual property (IP) rights and low cost. It requires concentration of resources in the short term (staff is especially distracted from the activities of institutional research on which it is assessed) and is dispersed over many different and extensive issues. An institute like the IIT is already the subject of numerous and frequent requests, potentially in conflict with the indications of the Board to make a threshold for small projects. Just because in Italy there are few companies that invest more than a few percent of annual turnover in R&D and about 70% of them are SMEs, it is reasonable to assume that most of these requests could fall below the minimum threshold of acceptability of the Institute.
*For this type of activity, the Foundation has substantially to verify the technical and scientific interest and the opportunity to support a project of a small size within the framework of the overall strategies, properly filtering the requests coming from the world of production.*

**Industrial Projects**
These are agreements of joint research between the research institution and a company aimed at developing prototypes/technology or knowledge of primary interest to the company. The basic requirements of these programmes are the duration of the order of two or three years and the risk margin higher than the previous type of short projects. In general the activity is too long to merit the term domestic investment by the company but sufficiently innovative to be developed by the body. They generally grow with the times and methods dictated by business needs, which are more stringent than a typical programme of basic research. The issues relating to intellectual property are negotiated from time to time, although often adopt criteria for ownership of patents under exclusive license to use the company for its core business applications. Agreements of intellectual property not shared in relation to the resources invested by the parties and the weight of prior knowledge made available for programme development are also acceptable.
*For this type of activity, and compatibility with the strategic plan, the Foundation must ensure the sustainability of the project in terms of resources invested in relation to those acquired.*
Projects of this kind, besides bringing prestige, however, require a degree of flexibility that is in the DNA of the IIT.

**Laboratories shared with companies**
This is an action of long-term partnerships with larger companies that can invest resources and personnel in R&D. Researchers from the IIT and those working in the same environment, with common targets and agreed road maps. These activities require adequate logistics solutions, large laboratories and a very advanced I.P. management. In general, the programmes to be developed must be sufficiently long-term to be of interest to the research institute and highly target-oriented to be of interest to the company.

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The mixed team creates interdisciplinary professionals in great demand, and if well managed, it gives excellent results both of the research, which can finalize its work on real projects in technology, both the company can develop processes, products and ideas otherwise not developed internally. The possibility of establishing joint labs are also maximised by offering expertise and infrastructure issues across multiple platforms, and network structure on multiple sites, as proposed in the Strategic Plan 2009-2011. A typical I.P. management scheme envisages joint ownership of patents, exclusive license for the industry in areas related to its core business, and the opportunity for the institute to exploit the inventions in applications other than the core business of the partner company (possibly reserving it the right of first option).
*For this type of activity, the Foundation has substantially to verify the sustainability of the project in terms of resources invested to those acquired, its compatibility with the strategic plan and with logistics.*

**Spin-offs and exploitation of the internal I.P.**
This is the best known type of TT and so also the most debated. From the institutional point of view, the spin-off of a body of research is almost never an operation oriented to the profit of the institution that forms it, but an operation of building value and the effects of socio-economic research products. In this case spin-offs do not produce profits that come in addition to the budget of the research, if not in due proportion to the institution itself if it decides to participate as a partner in the corporate structure of the spin off, or in the form of royalties from licensing. The growth of many spin off initiatives is to be considered as an indicator of very positive impact for a research institute, as it creates quality jobs and economic growth based on the products of research (the so-called value chain of research). In this context it should be noted that the concept of spin-off is generic and changes greatly according to the disciplines and specific applications (also related to more or less relevant issues of intellectual property). Sectors with low infrastructure costs, such as software, have reduced start-up costs and the possibility of higher revenues. Hardware-based initiatives require substantial initial investment, which move the breakeven point much further ahead and increase the risk with the same competition. A particular case is pharmaceutical research, noted for its significant initial investment (ranging from $ 0.5 million seed financing to up to $ 25 million of series A financing), the high risk (10% success rate) and high return on investment in case of success (10-100x). It is essential that for every spin-off idea the potential and its categorisation are qualified as soon as possible. This allows you to define the investment plan and the arrangements for the transfer of intellectual property, which play a crucial role and vary by industry and the centrality of the I.P. in the company set up.
From the perspective of the IIT, it is reasonable to assume that there are many ideas that potentially can be developed, some of which are very likely to succeed and bring revenues (typically enterprise value of the order of 20x compared to the initial investment after a few years and as such can be a candidate for P.I.O. and for sale to established Italian and foreign companies), to which must be added many ideas for spin-offs that could lead to a relatively modest increase in value (2x-3x after a few years) but still sufficient to create jobs and allied industry outside the walls of the institute, provided that the wager on the pharmaceuticals remains an important priority of the D3 department. The list of ideas largely protected by patents is constantly growing, both quantitatively and from the point of view of maturation of the prototypes.
The main problems of high-tech spin-offs concern the start-up phase, which almost always needs seed funds in the first two to three years in order to maximise the spin-offs and to obtain external funding and evaluations by higher potential investors. The role of the IIT in this area is very clear: the Institute can provide initial support to spin-offs in terms of infrastructure and equipment necessary for the development of the idea/product that otherwise would require an unsustainable initial investment, participating in the company structure of the spin-off as a founding member.
This is a multi-step process in which the Foundation must have a role of supervision and control over:

- Identification of ideas that can lead to spin-off by management.
- Qualification of the ideas from the management, assisted by a small group of experts in the VC field, to extract ideas from a selected set of results, patents, and initiatives that could lead to external financing or the

exploitation of IP by sale to established companies.

- Determination of the involvement of the IIT (funding, participation on the board of directors, industrial relations, transfer of IP) and selection of management that will cover the spin-off. The people involved will be both internal and external. At this stage it is essential to accurately determine the boundaries between the IIT and the spin-off and regulate possible conflicts of interest.
- Determination of exit strategies and their timing in collaboration with external financers.

The management of relationships with researchers who become entrepreneurs and in particular, the management of conflicts of interest is a delicate point and must be regulated appropriately. These rules vary greatly depending on the institution (universities, public research centers, private research centers, industry).

- *For universities in the USA*, the rules envisage a sharing of revenues from patents by the researcher with the University (among the most generous, Berkeley is at 50%), the possibility of granting an "industrial leave of absence" for two years that is renewable at the discretion of the department and the governing bodies of the University, the opportunity to work with the company in days of consulting (in the U.S.A, on average one day per week), the possibility of sharing in the ownership of the spin-off company independently of the patents granted in use or transferred permanently. The most frequent cases in which conflicts of interest originate arise when a company, in which the scientist has an equity interest or from which he receives fees in excess of a certain amount (typically $ 5,000 per year) is also financing research in universities, or even if research results are transferred in a privileged way. In any case, conflicts of interest are regulated by a special internal committee.

  Virtuous behavior by the researcher, if it remains so, is highlighted by the evaluation mechanism of his work. If the researcher has his scientific production reduced due to his participation in the company, his promotion and advancement in his career are greatly affected.
  In no case is the I.P. developed by the enterprise in the course of its business transferred to the University.

- *In the IIT*, in view of its institutional mission and similarly to what happens in the best international research institutions taken as reference, the researcher must be enhanced and encouraged in his efforts to transfer technology, consistent with the role and commitment that the Institute has and with the scientific findings on which it is assessed. There will be a transition period in which the researcher after having produced an idea of spin-off (the result of his research) will have to work alongside other partners and investors to make the idea transferable into a product. In this phase, the researcher will continue to operate as an IIT researcher, keeping his commitments, and at the same time will be an entrepreneur of himself. There is no conflict of interest in this temporary situation since the researcher, regarding his scientific work, is monitored by the Director of his structure. Also, while operating partially as an entrepreneur of himself, the researcher works in a facility where the IIT is a founding partner, with a clear sharing of interests and objectives. The researcher will also be a partner in the spin-off and therefore he will have a direct participation and share responsibility.

  At the end of the transition period (typically 3 years), if the spin-off is successful, both the role of the researcher and the participation of the IIT in the company society will be discussed again and agreed.

  The case in which the spin-off sees the director of a scientific structure (e.g. Department head) directly involved is different. In this situation it is necessary to ensure that in the interests of the IIT the structure is not distracted from its institutional aim (carrying out research according to the lines of the strategic plan) and is not entirely used as the base for the research and development activities of the spin-off.
  One is obviously dealing with particular cases that are to be individually assessed and monitored, usually

with the help of special technical commissions of control.

*For this type of activity, the Foundation must essentially check: (i) its compatibility with the strategic plan, (ii) the sustainability of the project in terms of resources invested compared with resources acquired, (iii) the type of corporate and strategic implications related to creation of a spin-off, its governance and its corporate structure, (iv) the financing plan and its implications for the future of the IIT, (v) relations with the scientific staff and possible conflicts of interest.*

**Models of incubators**
This model is designed to bring together in one "catalogue" of "custom tailored" products all the technological breakthroughs of the IIT that individually do not justify a spin-off, or that can lead to a small spin-off (of the spin-off 2x type mentioned before). The establishment of a company seeded from the IIT with a start-up investment fund (obtained possibly with the involvement of business angels, banks, and savings fund management) could accelerate the micro-processes of technology transfer that the institute often has the chance to deal with. These would be components, inventions or devices to be produced with advanced technology owned by the IIT, in small numbers and with a specific design, taking on the features of occasional orders with no prospect of a continuous market, or of custom tailored technology, always varied over time. This is the case of about 50 rotation sensors for mechanical joints or of the many iCub robots already ordered by several laboratories all over the world.

An important example is that of Siena Nanotech a spin-off of the SNS (Scuola Normale Superiore) with shareholding by the Monte dei Paschi di Siena Foundation. The Foundation participates in the initiative with its capital while the SNS gives the company (a joint stock company) patents and projects. A structure of this type could then operate as a branch of the IIT on the market, and could also meet the needs of SMEs (see "Consulting and feasibility studies") by simplifying the tasks of the research institute.

*For this type of activity, the Foundation must essentially build an innovative governance model designed for the specific domain of application.*

**Joint Ventures with corporates and external I.P.**
These are spin-offs where the IIT is not the scientific or technical driver or they are investments in initiatives in which the IIT is a member of a team with other public and private institutions (this is the case of the R&I Foundation recently established). In these initiatives the IIT may reasonably participate as a partner with highly relevant expertise in various fields as well as being a governmental research organisation.

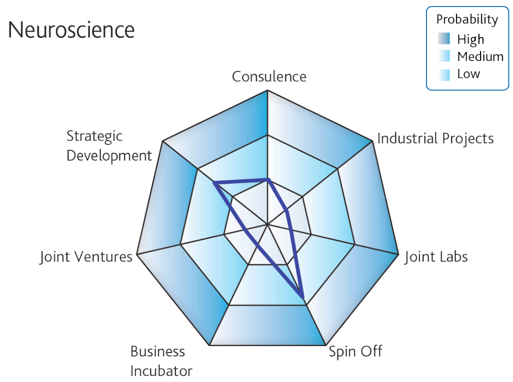
*As in the case of spin-offs previously analysed, for this type of activity, the Foundation must essentially check: (i) its compatibility with the strategic plan, (ii) the sustainability of the project in terms of resources invested compared with resources acquired, (iii) the implications of corporate and strategic type related to the establishment of a start-up, its governance and its corporate structure, (iv) the financing plan and its implications for the future of the IIT, (v) relationships with the scientific staff and potential conflicts of interest.*

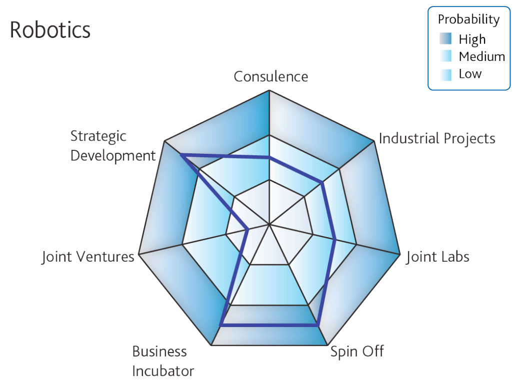
**Development of instrumentation**
This is a common process of transferring technologies that are developed to prototype level in laboratories for internal use, and which can then be transferred to commercial instruments for their upgrading (for example in areas such as metrology, detection, sensors, motors). Usually the companies interested in upgrading their equipment install high-end equipment in the IIT free of charge on which researchers adapt and develop dedicated technology solutions. Thus the IIT acquires expensive equipment for free and

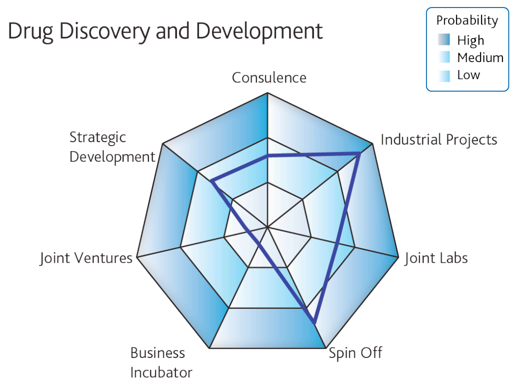
businesses can put equipment into their catalogues quickly which are updated with the latest technology (with an excellent advertising effect for the IIT). This is the case of a couple of international companies, which installed equipment at the Nanobiotech facility of the IIT for the implementation of a specific prototype tool in their commercial equipment. In other cases it is the IIT that installs its robots for rehabilitation in hospitals, with strong potential for clinical development.

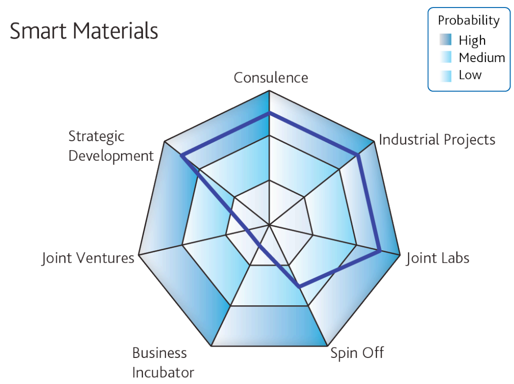
*In general this type of activity is very decisive for the institute, it is consistent with the activities of the strategic plan and easily sustainable within the approved scientific programming and it does not require very complex planning.*

**Forecasts of types and sectors of technology transfer by platform**
The following graphical representations show examples of the forecasts of models of technology transfer expectations for the results of the different platforms. The internal sector has a low probability, while the external sector is highly likely.



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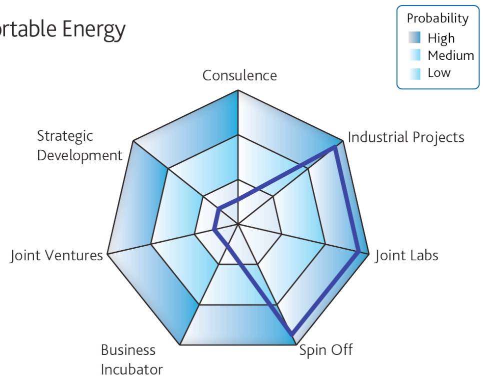
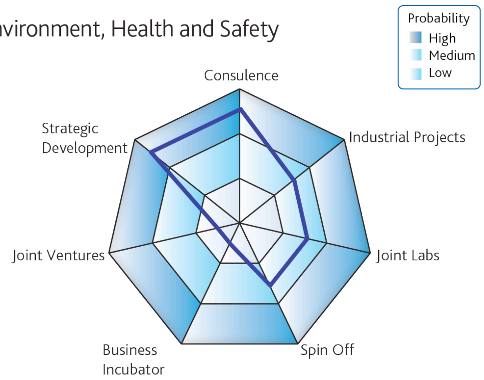
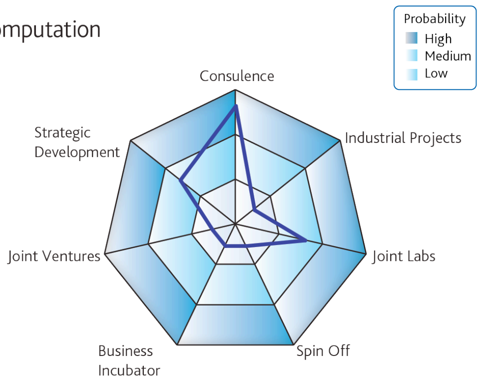
### Portable Energy



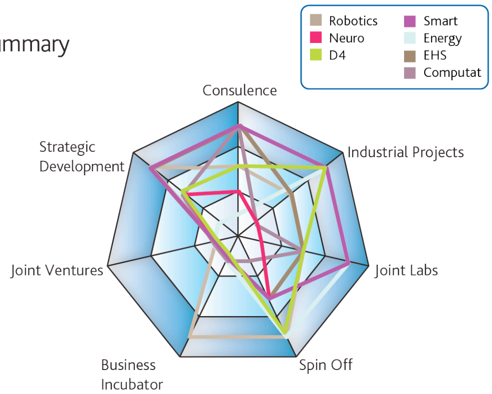

### Environment, Health and Safety




### Computation




### Summary



| | Food | Pharma | Hospitals | Biotec Diagnostics | Road/Air Transport | Manufacture Materials | Electronics/ICT | Military |
|---|---|---|---|---|---|---|---|---|
| Robotics | | | ■ | | ■ | ■ | ■ | ■ |
| Neuro | | ■ | ■ | ■ | ■ | | | ■ |
| D4 | ■ | ■ | ■ | ■ | | | | |
| Energy | | | | | ■ | ■ | ■ | ■ |
| Smart Materials | ■ | | | ■ | ■ | ■ | ■ | ■ |
| EHS | ■ | ■ | ■ | ■ | | ■ | | ■ |
| Computation | ■ | ■ | | ■ | ■ | ■ | ■ | ■ |

*Table - Analisys of potential and foreseeable markets*

**Implementation Programme**
The Implementation Programme is detailed in IIT "Guideline for Technology Transfer, which gets deeper into the following themes:

- **OBJECTIVES**
- **ACTIVITIES**
  - ✓Policy
  - ✓Training
  - ✓Technological scouting
  - ✓Relations with companies and investors
  - ✓Communication
  - ✓Territorial observatories (impact on regions)
- **ORGANISATIONAL STRUCTURE**
- **DECISION MAKING PROCESSES**
- **BENCHMARK**

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## TECHNICAL ANNEX IV → THE EVALUATION PROGRAM

**Standard evaluation indicators in connection with the peculiarities of IIT:**

a) The performance indicators of a scientific research institute are of two types:

- *quantitative* (Impact factor - IF, Citation Index - CI, h-factor, number of patents, spin-offs, international events, attractiveness for foreigners, fund raising capacity, licensing of IP).

- *qualitative* (leadership skills, management capability, international acknowledgement and reputation, facility/lab organisation and management, qualification of the young people, placing on the market of young post Ph.D., training, communication etc...).

The former are derived from parameters available on the Web of Science (or equivalent database) or based on financial/management parameters. The latter are mainly related to a subjective assessment, usually delegated to external experts. There is therefore a need, common to all scientific institutions, to combine an evaluation using an algorithm (by objective parameters) with one of individual type, typically obtained from a panel of external experts and on-site visits with interviews.

b) A critical aspect of the scientific evaluation of a multidisciplinary institute like the IIT is the fact that the performance indicators above mentioned do not have the same weight in different areas (platforms). For example, for neuroscience, IF and CI are by far more significant parameters than industrial fund raising or licensing and patenting. Diametrically opposite considerations apply to robotics. Therefore, it is not possible to elaborate universal algorithms and evaluation schemes. There is thus the need to introduce appropriate "weight functions" to adjust the value of both quantitative and qualitative indicators to the peculiarities of the different platforms. This in fact is equivalent, on the one hand, to tracing the principles and guidelines of assessment common to all platforms, and on the other, to developing a capacity to adapt these criteria to the different disciplines.

From the points raised it is clear therefore that assessment is a complex process that must take account of the institute's target and that must have *a strong subjective component (panel evaluation) grafted on an objective basis, customised to the field of research.* The evaluation process should therefore consist of a series of steps:

1. Identification of items of general interest to the foundation (system of objectives), and their weight functions by thematic area.
2. Identification of objective algorithms (if any) customised to the different thematic areas.
3. Identification of the panel of mixed, external experts, who are able to assess not only scientific aspects but are also able to harmonise points 1 and 2 even with subjective assessments (e.g. leadership skills or the potential value of young recruits).

In this sense, the role of the Scientific Technical Committee (STC) is fundamental both as advisor in the set up of the mid and long term goals, as well as a driver of the assessment. The STC establishes the external evaluation panels for the assessment, guides their activities, and helps in the implementation of reports and suggestions that emerge from the on-site visits.

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**Evaluation method**

On the basis of the points above, it is therefore necessary to proceed with the construction of a methodology for assessment, shared by the bodies of the Foundation and the scientific component (directors of departments and centers), that amalgamates the objective and subjective indicators and their relative weight functions for the various thematic areas. From this must stem the guidelines that the evaluation panel should follow in the years ahead. Based on established international practice the evaluation panel should be proposed by the STC and appointed by the Executive Committee. The panel should be made up of both members of the STC and of outside experts chosen from the international community, selected *ad hoc* and from time to time, with interdisciplinary profiles suitable for assessment of all aspects of the Institute activities.

The evaluation will assess the scientific and technical staff in its entirety, with specific attention:
*on an annual basis* to the determination of the variable part of salary for team leaders, senior scientists, research directors, technicians and administrative staff;

*on a base of several years (every two-three years in start-up, every three four years in full scale operation*) to the strategy and international positioning of the research units (departments and centers of the network).

As discussed in the previous section, the assessment must take account both of scientific results and achievement of the expected scientific objectives, as well as the capacity of fund raising and technology transfer and leadership skills.
The research directors should be evaluated not only for scientific and technological excellence and fund raising but also for their ability to manage and guide their scientific infrastructure and to develop an interdisciplinary approach.
The administrative staff and management should be evaluated for their ability to create an environment that, compatibly with regulations and laws, would allow researchers to develop their research quickly and effectively.

*Assessment on an annual basis*

On an annual basis, the assessment is done through the preparation of a self-appraisal by each staff member, which shows all the quantitative and qualitative indicators for the activity of the previous year. The self appraisal is delivered to the staff members immediate superior (e.g. senior scientists for team leaders, director for the senior scientist) who in turn will draw up an individual assessment report in which, quantitative, qualitative parameters and the staff members objectives achievement will be evaluated. The MBO (Money by Objective) proposed percentage for the past year shall also be indicated in the individual report.

The research directors deliver their self appraisal to the STC chairman. The evaluation will be carried out by all the members of the STC.
All assessment forms and MBO proposals are also examined by the scientific director.

The scientific director prepares the annual evaluation report for the STC and the Board of Trustees.

*Assessment on a multi-year basis*

The general assessment of the research structures instead is carried out on the basis of two or three years during the start-up phase and four-five years later. It is conducted by a panel of experts appointed by the STC for the on-site visit. The panel must evaluate both the quantitative and qualitative aspects properly weighted, as described in Section 1, it should interview the researchers to assess the real excellence and leadership skills and to assess the international scientific positioning, the vision and the scientific strategy for each IIT structure.

**Technology Transfer**

The Technology Transfer (TT) activities remain a key aim of the IIT activity, therefore they represent an important yardstick of its success evaluation. However, it is necessary to analyse the opportunities and the possibilities offered by domestic and international markets to envisage from the beginning what might be a reasonable expectation of success (revenues) in TT. To this aim it must first be remembered that 70% of the SMEs which constitutes the industrial backbone of our country is broadly speaking a user of medium-low technology and in the rare cases of high-tech activities it has a limited investment power. Large domestic firms (including multinationals with an Italian centre of gravity) invest percentages varying between 10 and 15%in R & D, with a predominance of the D part rather than R. Furthermore, in most cases they resort to more public support via Italian law 297, *PON* (National Operative Programmes) or *Industria 2015* to which IIT cannot have access (or can access only in part), effectively making them an unattractive partner regardless of their quality. In this context, the presence of IIT centres in the South of Italy, or the participation of IIT on national and district structures, which have the right to access programme agreements with the regions, may play an important role. In any case, these possibilities are merely marginal and geographically localised.

From the international point of view, although IIT begins to be attractive as a partner for high-tech companies, it is necessary to consider the difficulty due to the young reputation of the institute and to the competition coming from other well established research giants (e.g. Fraunhofer, Max Planck, MIT, Weizmann etc.).

It is therefore absolutely essential to be completely aware that TT cannot be and will never become the main source of revenue of the IIT (just as it is not for the MIT or Weizmann). IIT approved guidelines and policies illustrate the integrated strategy of TT, prepartory for the IIT success.

Beyond the general nature of the term, Technology Transfer is based on scientific excellence (which remains the main objective of the IIT) and on new products and new research ideas, and takes time, seriousness and credibility. The measures briefly described must be implemented in parallel, especially at a time of general crisis in which the already low propensity for risk of our companies is exacerbated by market conditions.

From the point of view of assessment it must be clear that these results are a combination of a growing reputation and international visibility along with a well-organised national and international network of relations with companies, which develops through a constant work of scientific quality and seriousness of the institute. This takes time, like any other process of confidence building in the international market and cannot be improvised. Therefore, the role of evaluation is that of encouraging actions that go in this direction and to stop everything that is not functional for this difficult and challenging process.

**Fund raising capacity**

While being another important objective parameter of the appraisal process, the ability to attract funding is "environment-dependent” and as such requires a conscious capacity discernment on the part of the evaluator.

ISTITUTO ITALIANO
DI TECNOLOGIA

At present, the IIT can procure funds for research through the following channels:

- European projects
- private funds, grants and Industrial Technology Transfer
- public funds via State tenders
- other options (donations, foundations, local authorities etc.)

For European projects the IIT is absolutely state of the art with a high success rate, superior to almost all other European institutions. However, as we know, European projects do not finance infrastructures and equipment but only research and personnel costs. So they cannot in any shape or form be considered as a primary source of income (average size less than a million Euros in three years).

For private funds the considerations of the previous point are valid so it is unthinkable in the short term to have an IIT substantially supported by industrial funds. For public funds the IIT has a competitive disadvantage upstream, since due to its legal nature it is prevented from participating in most of the ministry's calls to tender (MIUR, FIRB, PRIN, authority tenders etc. that also have low budget and periodicity is not guaranteed). The other options in Italy are marginal both for social and fiscal reasons.

Therefore, it is clear that for the purposes of a meaningful and high-level assessment, the weight of the "fund raising capability" parameter should be appropriately weighted by the factor of "actual fund raising opportunities". Needless to say that such assessments cannot be based on simple algorithms, but must go through a complete evaluation by an expert and high-profile panel of independent third parties, but not necessarily consisting of only foreigners.

*It is reasonable to deem that a fund raising capacity between 20% and 30% of the budget allocation of a department (staff, consumables, durables, travel, services) should be considered an excellent performance for the IIT, which is comparable to the best international technology institutes.*

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DI TECNOLOGIA

**IIT Indicators and Strategic Objectives**

From all the foregoing discussion it appears that the system of evaluation is closely related to the definition of both qualitative and quantitative goals that are clearly defined and measurable, albeit with the necessary flexibility linked to the non-deterministic nature of the activities which a research institute carries out. In this sense we can propose the following qualitative and quantitative objectives for the Institute activities :

***Quality objectives***

1) SCIENTIFIC VISIBILITY: internationalisation of IIT, measurable through the construction of international, bi/multilateral, industrial and project based agreements The world of science and technology only accepts first-tier partners, therefore important partnerships are good indicators of correct technical and scientific choices and of credibility in the medium and long term.

2) SCIENTIFIC ASSESSMENT: external panels for the assessment of (short-term, fixed frequency) both the quality of researchers and the general activities of IIT, with constant attention to the international state of the art.

3) PUBLIC PERCEPTION: this is a random but also very crucial indicator. For example: public awareness of IIT, relations with the ministries, relationships with other research bodies, ability to innovate and operate in the context of research minimizing antibodies and conflicts but preserving the quality and the prerogatives of the foundation, independence from politics and high-level communication.

4) MANAGEMENT SKILLS: administrative and management efficiency, problem-solving approach to bureaucratic problems, speed and fairness of the procedures.

5) HUMAN RESOURCE MANAGEMENT: procedures for high-level hiring, career paths for researchers, an international staff, IIT researchers' satisfaction and sense of belonging.

6) IIT INTERNATIONAL POSITIONING: to date, in the five-year period of reference 2005-2008 for the start up and 2009-2011 for the new strategic plan, substantial resources have been invested on seven platforms:

- Robotics
- Neuroscience
- Drug Discovery Development and Diagnostics (D4)
- Environment Health and Safety (EHS)
- Smart Materials
- Portable Energy
- Computation

forming multinational teams of scientists in research units of the highest international level, spread throughout Italy. The assessment of the international positioning of such teams requires a few years. However it can be partially deduced from worldwide rankings periodically published by international scientific data –bases and from the acknowledgement of the Institute in the scientific community (e.g. invited oral presentation at congresses, presence of IIT scientific outputs at conferences).

ISTITUTO ITALIANO
DI TECNOLOGIA

***Quantitative Indicators***

1) GROWTH OF THE IIT BRAND: performance of the IIT network at the national and international level, (measurable with publications, patents, contracts, impact factor, citation index and fund raising).

2) FUNDING (national, international, public and private grants), bearing in mind the considerations of previous sections.

3) TECHNOLOGY TRANSFER: set up of a high-level system of technology transfer, setting up of spin-offs, licensing and royalties. Main actions of technology transfer:

- Transfer of products of IIT research to the clinical world from D4, EHS, Neuro
- Transfer of products of IIT research to the pharmacological and diagnostics industry from D4 and EHS
- Transfer of products of IIT research to manufacturing and high tech industries (transport, ICT, electronics etc) from Energy, Smart Materials, Computation and Robotics
- Creation of Spin-offs
- Divulgation
- Creation of joint laboratories with companies