



ISTITUTO ITALIANO  
DI TECNOLOGIA

## **STRATEGIC PLAN 2009-2011**

**Roberto Cingolani - April 2009**

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## **Part- A**

### **General Information**



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## A.1 INTRODUCTION

This document outlines the strategic plan of IIT for the period 2009-2011. The first section summarises the main results accomplished in the start-up phase of the institute, from December 2005 to December 2008 (part A). The second section presents the evolution of the original platforms Robotics, Neuroscience, Drug Discovery Development, and proposes the extension of the IIT scientific plan to a few new technology platforms, strictly connected to the on-going program, which may open important technology transfer opportunities in the near future. The scientific description of the strategic plan is given in part B.

### Results accomplished in the start up phase (strategic plan 2005-2008: months 0/36)

At present IIT has about 380 staff members (fig.1) whose profile is indicated in figure 2. One third are Italians reentering from abroad, while another third are foreigners from more than 30 countries.

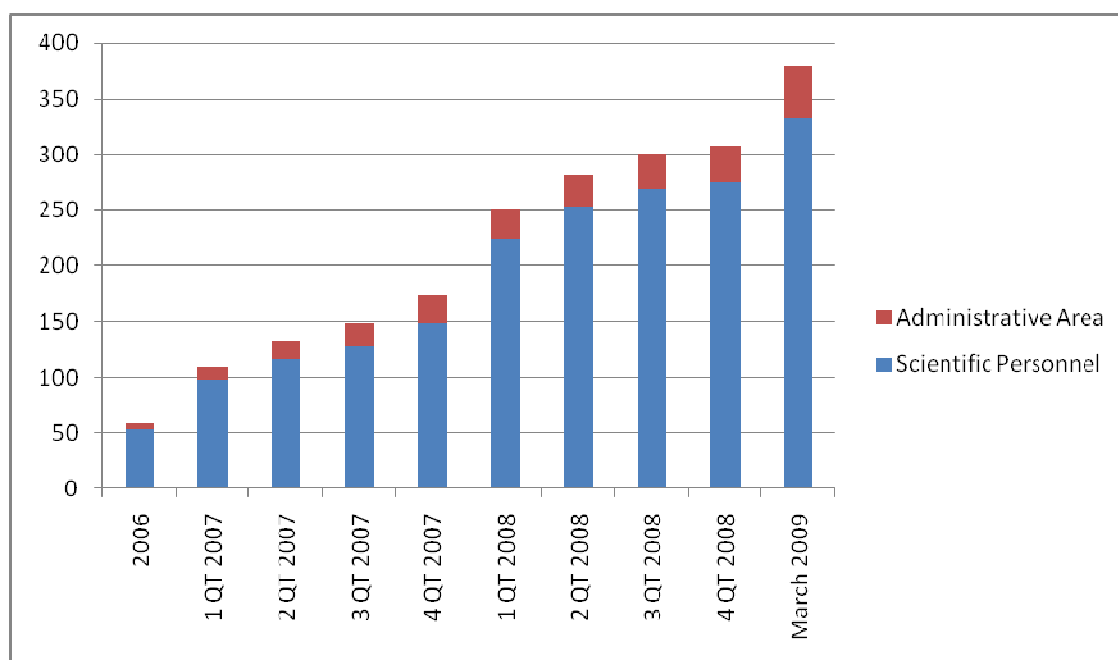


Figure 1-Employments for trimester up to March 2009

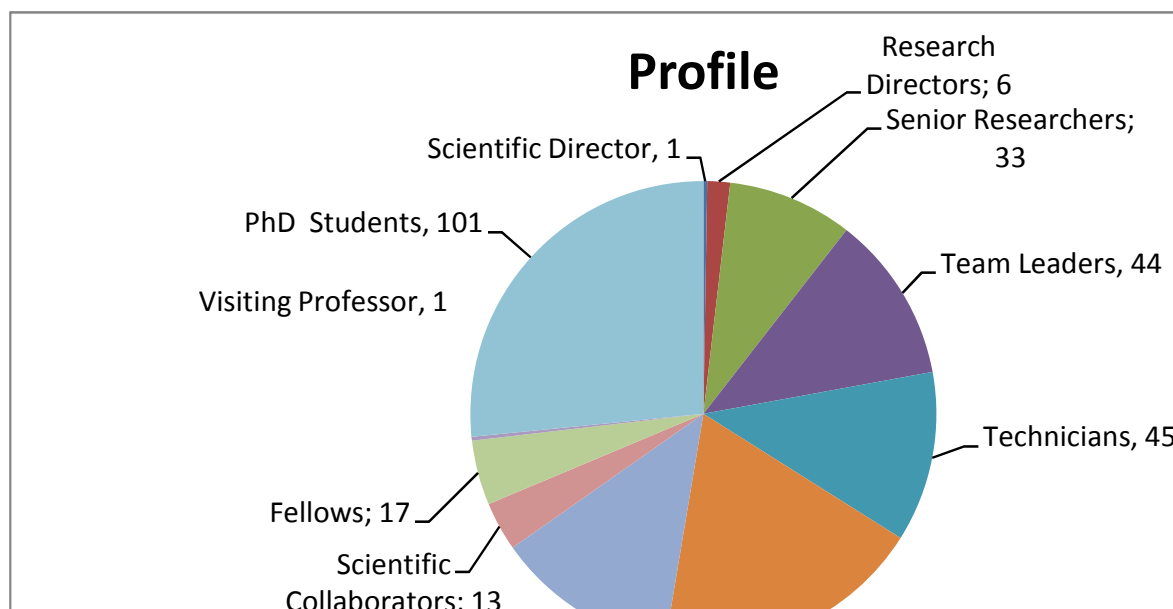


Figure 2-IIT staff profile

The IIT staff scientific profile reveals a wide interdisciplinary spread including: physicists, chemists, engineers, mathematicians, biologists, pharmacists, psychologists and physicians.

The staff was hired according to the IIT policy. Senior scientists are selected through international *calls* and interviews, by external panels of experts.

### *Platforms and Departments*

The research platforms of Robotics, Neuroscience and Drug Discovery and Development together with the shared facilities of Nanobiotechnology were established following the IIT Research Plan 2005-2008 (see [www.iit.it](http://www.iit.it)). Each platform is developed by one or more Departments and by external research units located throughout the country in the Multidisciplinary Research Network of IIT. The main body of the research activity is carried out at the Central Research Laboratories established in Genova-Morego, while a few collaborative projects are ongoing in selected research institutes with well established international reputations.

The Robotics platform is divided into 3 Departments: Robotics, Brain and Cognitive Sciences (RBCS), Advanced Robotics (AR) and Tele Robotics and Applications (TERA), each run by a research director, G. Sandini, D.Caldwell and J.G Fontaine respectively. The Neuroscience Platform is divided in 2 departments: Neuroscience and Brain Technologies (NBT), directed by F. Benfenati and the new Center for Neuroscience and Cognitive Systems (CNCS, under construction), focused on Primate studies, located in Parma, directed by J. Assad. The Pharmacology studies are developed in the Department of Drug Discovery and Development, in Genova-Morego directed by D. Piomelli.



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The research Directors were recruited from 6 different international research bodies: Harvard and Irvine ( USA), Paris (France), Manchester ( UK) and Genoa ( Italy). Moreover, starting from April 2009 the leader of the Nanobiotechnology Facilities is L. Manna, an Italian researcher recently returned from Berkeley (USA).

The shared facilities of Nanobiotechnology comprise ten interdisciplinary laboratories: the clean room, the electronic microscopy, animal research facility, chemistry, biology, polymers, spectroscopy, material science and the electric and mechanic workshops.

In addition, a multidisciplinary network of 9 centers was established nationwide :

- Trieste – SISSA
- Milano- Polytechnic
- Milano- IOE- IFOM
- Milano- S. Raffaele
- Pisa- Scuola Normale Superiore
- Pisa- Scuola Superiore S. Anna
- Roma- EBRI
- Napoli- CRIB
- Lecce- NNL National Nanotechnology Laboratory .

Such a multidisciplinary research network is carrying out a part of the IIT program according to a 50%-50% co-financing agreement. At present the IIT multidisciplinary research network's strategy involves approximately 300 researchers.

#### *Infrastructure*

The Central Research laboratory at Genoa is a facility of about 30000 sqm, which has been entirely restructured, and now hosts all the laboratories and facilities. Equipment and infrastructure costing approximately 40 Million Euro has already been installed and is functioning. The design of the laboratories, fixtures, fittings and spaces was entirely accomplished by IIT technical/scientific staff.

#### *Outreach/technology transfer*

Project management offices, technology transfer and patenting offices were established at IIT and specialized personnel were hired, recruited from the public and private sector and high-tech bodies. The patent portfolio contains 19 technologies and is continuously growing. There are numerous other ongoing contacts with enterprises such as Finmeccanica, Assofarmaceutica, Telecom Italia, STMicroelectronics, Centro Ricerche FIAT, and the industrial districts of Macerata (Lighting and plastic companies) and Bergamo (textile industry). Also, the i-CUB humanoid project, developed by the Robotics platform, has become the European standard for humanoid robots, within the ongoing European Framework Programme.

#### *Scientific Results*

IIT is present in the Web of Science and PubMed (the main scientific worldwide libraries), with around 390 international peer review publications (fig.3) and for the year 2009 we report till March a number of 64 articles published by the IIT researchers.



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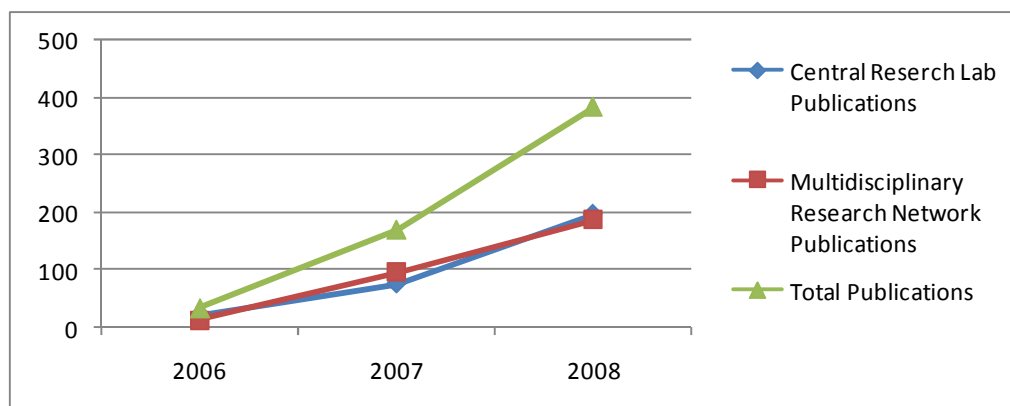


Figure 3- IIT international publications in last three years

#### *The IIT Scientific Offer*

On the basis of the actual organization and the scientific program approved by the IIT Board in October 2004, IIT can cover relatively a limited area of the relevant technologies strategic to the country, with technology transfer possibilities in the following areas:

- Robotics related areas/ automation/mechanics/ security/telecom - from Robotics Research Platform;
- Chemistry, material science - from Facilities;
- Life science/diagnosis/ disease treatment- from Neuroscience Research Platform;
- Drug Discovery which has considerable potential, will require hospital and other medical trials lasting up to 7 years

Though wide and important, such a technology spectrum is in reality still quite limited when compared to the national needs and the mission of the institute.

#### *Financial Resources*

The yearly allocated budget will increase to 100 million €/year starting from 2009. On the basis of the financial balance and the startup phase monitoring, the full operational costs of the Research Units and Facility (all including running costs, depreciation charge, personnel and other costs) is estimated to be approximately €50 million/year. Due to the closure of IRI Foundation and its assets being assigned to IIT, the Institute has now received the sum of approximately 140 Million €, half of which being financial products are under evaluation in light of recent financial market conditions. These funds have been earmarked for strengthening the research network and to widen the portfolio of technologies developed by IIT. Such a task is specifically addressed in the next section where we outline new strategic plan (2009-2011) of the Institute. In this frame, it is strongly recommended that the remaining resources are invested in strategic areas complementary and synergic to the ongoing research activity.

#### *Human Resources*

The main key to IIT's success is staff recruitment and selection:



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- Competitive hiring: based on international calls and direct interviews made by an evaluation board, looking for competences in order to fulfill the IIT development plan;
- Project based: contracts made following the milestones, deliverables and timetables of the scientific plan, startup budgets for laboratories and research teams;
- Meritocracy: yearly evaluation made by the Scientific Committee (the third one, independent and very high profile), with consequent MBO assignment;
- Competitiveness: wages and benefits at international (USA and European) standards.

It is important to highlight that the staff recruitment process is an exception in the actual national recruitment system, and it seems to be the only one that can guarantee competitiveness and re-launch national research.

We can conclude that to date IIT has fulfilled all its promises. Its technological portfolio should be expanded to fulfill the:

- Assigned mission;
- Available resources;
- Extremely high level of the Governance body (IIT Board).

On the other hand, it should be considered that:

- The possibility to hire staff using international criteria;
- The practice of transparent hiring criteria;
- The funding availability;
- The outstanding research infrastructure at Genoa;
- The high reputation staff and multidisciplinary network researchers,

make IIT highly attractive at an international level and an unprecedentedly strong at national level, comparable with the top international structures.



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## A.2 Overview of the Strategic plan 2009-2011

Extending IIT at a national level and strengthening the multidisciplinary research network is the way of choice to increase the technological offer and the international attractiveness of the Institute.

Based on the above analysis, immediate action is required starting from month 36 in order to capitalize on the outstanding capability developed by IIT in the start-up phase:

- Increase the technological portfolio through the development of existing research platforms and by establishing new ones. The new platforms, represent the natural evolution of the existing ones, and they are strictly connected to the on-going activities. Yet, they widen remarkably the horizon of the IIT program and open up technology transfer possibilities in fields so far not accessible to IIT;
- Consolidation of IIT's central research laboratory at Genoa Morego;
- Enhancement of the multidisciplinary technological network nationally;
- Launch a call for national IIT seeding research programs supporting the core IIT research platforms

These goals can be attainable in a short amount of time by further developing the pattern of a central laboratory with its network of international excellence distributed nationally. The technical scientific ideas and the implementation method of the strategy plan are briefly analyzed below. It is imperative that the broadening of the IIT technological areas follow these criteria:

- Compatibility with the existing IIT scientific program
- Sustainability with respect to the IIT know-how and infrastructure
- Competitiveness with the international scientific trend;
- Compatibility with future European programmes;
- Compatibility with the targets of Italian Research Plan;
- Relevance to the realities of Italian and international industry.

Prioritised technological platforms can be identified as:

1. **Energy**: portable energy sources, plastic solar cells, energy harvesting, energy storage, energy scavenging, fuel cell technologies (descending from the Robotics platform. Relevant to self-powered technologies, and of wide international and industrial interest);
2. **EHS (Environment, Health, Security)**: interaction of nanosystems with biological entities, in pharmacology, therapies, and any other human environment (descending from the Neuroscience platform, the Pharmacology platform and from the nanobiotech facilities. Relevant for future safety standards nanoscale currently targeted by US, Japan and EC and of great relevance for quality assessment in many fields such as new materials, environment, pharmacology, food and agriculture, new security standards for living creatures and human environment in the presence of nanosystems);
3. **Smart Materials**: lightweight nanocomposites, intelligent biocompatible surfaces, interface living systems/inorganic systems, textile/fiber engineering (descending from the Robotics platform and the nanobiotech facilities. Relevant for future non-metallic robots, and of wide international and industrial interest for environmentally friendly materials, biocompatible materials, new generation sensors, etc)
4. **4D (Diagnostic, Drug-Delivery Development)**: this is an extension and a completion of the existing drug discovery development platform (pursued by the D3 department) . In addition to the D3 activities, advanced diagnostic tools such as chip for genomic and proteomic analysis, nanocarrier for *in vivo* drug delivery will be developed.





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5. *Integrated Multiscale Computational Technology*: developing world-class open source software for advanced modeling of complex systems of interest to the above platforms (eg density functional methods for modeling at the atomic scale systems relevant to the above platforms).

It stands to reason that some of the presented themes are continuations of the research lines already started at IIT, while others, although synergic to the original plan, need new competences and structures.

#### *Implementation of the new research plan*

A short term sustainable development plan can be based only on multidisciplinary technological network enhancement together with the consolidation of the central research laboratory at Genoa Morego. The following preparatory activities could then be performed:

- To consolidate the existing Departments for the Robotics, Neuroscience and D3 platforms at Morego and Parma. To this end, the Directors have already developed strategic plans and budgets for the next 3 years. These have to be implemented immediately to ensure the consolidation of the existing research infrastructure.
- To reinforce the multidisciplinary research network country wide, on the basis of merit and responsibility criteria. A reference model is the Howard Hughes Foundation, USA, which ‘*hires out*’ for a period of 5-7 years the best US research structures, in specific interest areas. All activities are evaluated yearly by the international scientific Board and other internal evaluation bodies. The “poles” could transform from their actual state of associated projects labs to a full IIT research infrastructure, with IIT staff and equipment, as created at Parma. Each pole carries out specific research programs in the frame of one or more platforms of the strategic plan (see TAB 1). Emphasis is put on the possibility to extend the excellent researchers hiring model (calls in the international journals, international external evaluation panels, MBO wages and start-up budget competitive with the American and German system) to these poles. It is expected that this could result in a brain gain of approximately 500 units within a 3 year period.
- To launch yearly calls for IIT seeding-research projects, to explore high-risk, high-novelty ideas relevant to the IIT research plan, jointly with other institutions/researchers. This would simultaneously allow the growth of the national scientific community under the “scientific umbrella” of IIT and the identification of future poles of the networks.
- To boost the technology transfer capability of IIT by dedicated branches/offices of the institute. A main need is to create a market oriented branch of IIT, to deal with Intellectual Property and commerce related activities, to permit the scientific staff to be dedicated only to research.



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### Expected Results

From the action to be taken it is expected that there will be :

- Unprecedented *brain gain* within all IIT Research Units;
- A technological portfolio able to satisfy industrial requirements (materials and composites, automotive/aerospace, energy/environment, food/agronomy, electronics, computation/simulation), as well as the already present fields of robotics, pharmacy and neuroscience;
- Partnerships with industry (based on various collaborations already existing in the network centres, having a large geographic distribution)
- Correct and complete use of the budget;
- Capacity to tap into resources in the technical-scientific areas (e.g. energy 2.5 billion euro in the European Community in the next 5 years) and in the geographical areas ( e.g. Objective 1 , about 7 billion Euros in the next 5 years) in which IIT is not yet present;
- A real national dimension for the Institute;
- Strengthening of the top Italian research structures (bearing in mind the network pattern for the EIT – the European Institute of Technology);
- Fulfill the IIT original mission in relation to industrial development and national outcomes;

Scheme of research organisation in the IIT network for the period 2009-2011

TAB. 1

	Robotics	Neuro	D4	EHS	Smart Materials	Energy	Computation
RBCS – Sandini	X	X			X		X
AR – Caldwell	X						
TERA-Fontaine	X						X
NBT Benfenati	X	X		X	X		
Ge- Facilities & Nanochemistry			X	X	X	X	X
D3 Piomelli			X				X
NCS Parma		X			X		
NNL-LE	X		X	X	X	X	X
NEST-PI			X	X	X	X	X
PoliMi				X	X	X	
IFOM-Mi		X	X	X			
SSSA-Pi	X						
CRIB-NA			X	X	X		X
PoliTo*	X				X		

In **red** part of the IIT program is developed by the Multidisciplinary Research Network.

In **green** part of the IIT program is developed by the Central Research Lab at Morego

\*PoliTo is a new lab to be established at Politecnico di Torino. The scientific plans of the IIT poles are available separately.



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Main stream research lines carried out by departments and poles of IIT:

Robotics Brain and Cognitive Sciences Dept (Sandini)

- Humanoid robotics and cognition
- Human behavior, action, perception
- Human machine interaction

Advanced Robotics Dept (Caldwell)

- Actuation
- Haptic, telepresence
- Biomimetics
- Sensing
- Medical robotics
- Safety
- Demonstrators

TeleRobotics and Applications Dept. (Fontaine)

- Human mediated interaction
- Advanced computing/architectures/algorithms

Neuroscience and Brain Technologies(Benfenati)

- Neural Plasticity
- Genomics, postgenomics, connectomics
- Plasticity in neural networks
- Human central system diseases
- Bio-hybrid technologies

Facilities & Nanochemistry Genova

- Nanocarriers for drug delivery
- Nanofillers
- Image reconstruction
- Biomedical imaging reconstruction
- Nanostructured contacts, catalysis

Drug Discovery Development (Piomelli)

- Neurodegenerative disorders
- Pain and inflammatory disorders
- Carbon Monoxide discovery

Neuroscience and Cognitive Science Parma, (Assad)

- Perception and sensory motor integration
- Derangement of brain functions



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- Imaging in behaving animals
- Novel techniques for in-vivo monitoring of brain functions
- Nanotechnologies for neuroscience

#### POLIMI

- Artificial retina/eye
- Carbon nanocomposites
- Hybrid solar cells
- Fuel cells

#### IFOM-Mi

- Robotized, imaging based, high-throughput Screening Unit for cell based screening
- Empowering genomics-proteomics platforms for analysis of biological samples
- Development of next generation sequence technologies with electrochemical detection systems

#### NEST-Pi

- Lab on chip for ultrasensitive automated diagnostics
- Nanomedicine tools for diagnostics and therapeutics
- Nanoproducts and environmental safety assessment
- Energy storage/scavenging
- Modeling of biological/inorganic interfaces

#### SSSA-Pi

- Microrobotics

#### CRIB-NA

- Cell Instructive Materials
- Endothelial nanoshuttles
- 3D integrated platforms for high throughput and multiple detection

#### NNL-Le

- MEMs/new sensors for robotics
- Solid state genomics
- Interaction of biological structures with nanomaterials
- Smart surfaces, Responsive composites



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PoliTo

- Biocomposites
- Nanofibers
- Plastic solar cells, plastic lighting, Grezel cells
- Density functional software

- Robotics for aerospace
- Sensors & MEMS



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### *A.3 Further elements for future developments*

A few important issues need to be addressed by the IIT foundation in the near future:

1. IIT-PhD school. The proposal for the activation of an international IIT PhD school, independent of the National University system, will be proposed to the Ministry of Research and University in the next months, based on the present strategic plan. The IIT-PhD school will have strong multidisciplinary character, and will exploit the staff of IIT for the students education and training. The duration of the PhD will 4 years. The evaluation of the thesis will be done by international panels
2. SEED Projects. Based on the present Strategic plan, yearly calls for Seed Projects should be launched, in order to identify promising centers for future Networks nodes and to explore high-risk novel content topics, in collaboration with public and private research entities. The projects selection and evaluation will be performed by the Technical and Scientific Committee of IIT.
3. Evaluation. One approach for evaluation, modeled after the American academic system, is that senior and junior investigators can be evaluated individually based on their scientific productivity. Evaluation could be a two-stage process. The initial "screening" evaluation could be conducted by the IIT scientific administration. The second, more important evaluation should be by an external, international evaluation committee of peer scientists. The committee should be chosen to have an expert sense for the standards of productivity in a particular field. External review is the best mechanism to ensure the highest scientific standards at IIT. A purely internal evaluation could occur every years, and an external evaluation with external on-site visits and letters solicited, etc., at 3 years, and at 3-year intervals thereafter. Young investigators, particularly team leaders, must have potential at IIT to expand their scientific efforts. Thus successful evaluations could reward productive investigators with some sort of promotion, either in position (e.g., from team leader to senior scientist) and in terms of lab space, support or salary.
4. Tenure and contract length. IIT does not currently have a tenure system, but tenure does exist at most other academic institutions around the world, placing IIT at a disadvantage for recruiting the best scientists. However, short of its own tenure policy, there are other ways in which IIT can compete more effectively with institutions with permanent positions. One effective policy would be to increase contract length for young investigators. An excellent model is the Royal Society Fellowships in Great Britain, which offer fellowships as long as ten years. Longer contract length would allow young IIT scientists the scientific freedom and security to explore more innovative ideas, and could counterbalance offers of tenure-track positions at other institutions.

## **Part- B**

### **Scientific Plan**



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## **B.1 ROBOTICS PLATFORM**

**Operating structures:** RBCS-Ge, NBT-Ge, AR-Ge, TERA-Ge, SSSA-Pi, PoliTo, NNN-Le

### **General introduction to the platform activity**

Robotics is a highly diversified area of research focused in all aspects of engineering (primarily electronics and mechanical) and computer science, but strongly influenced (and influencing) developments in areas such as neuroscience, physiology, psychology, mathematics, physics, chemistry and biological science. This highly diversified nature of the research forms one of the great opportunities and challenges of robotics and it is at these various interfaces that many of the key developments in humanoid (human and machine) theory are being studied.

The “Robotics Platform” is composed of three Departments

- Robotics, Brain and Cognitive Science
- Advanced Robotics
- TeleRobotics and Applications.

Each of these Departments has distinct and unique areas of specialism that provide an immense depth of knowledge and understanding, but through collaboration there is also a breadth to the research that is already being recognised as unique.

Central to this understanding is the high level of interdepartmental co-operation and collaboration both at a strategic and individual level. Evidence of this can be seen through joint internal activities and increasingly co-participation in externally funded projects.

This section provides a strategic overview of the platform and of each Department, highlighting their current and future plans. It clearly demonstrates the specialisms inherent in each Department, yet through research on common platforms it also shows collaboration and synergy that provide one of the great strengths of IIT.





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## DEPARTMENT RBCS: ROBOTICS BRAIN AND COGNITIVE SCIENCES

### Introduction

The RBCS platform will consolidate the on-going research program on “human” systems along three main research streams:

- humanoid robotics with a focus on cognition,
- human behavioral studies with a focus on action and perception,
- human-machine communication and interaction with a strong emphasis on the technological and scientific advancement of bidirectional direct interface to the nervous systems.

Common to all three streams will be the focus on learning and development and, in general, on the dynamics of knowledge acquisition and update. These streams of research are carried out with two objectives:

1. to advance knowledge and technologies in the area of artificial systems by performing targeted investigation of human motor and perceptual abilities and by implementing autonomous humanoid robots able to learn from experience and interacting naturally with humans;
2. to investigate how the merging of robot technologies with systems neuroscience research can contribute to the improvement of the quality of life, particularly of the weak components of our society.

### Humanoid robotics with a focus on cognition

The main focus of the Cognitive Humanoids activity is in the implementation of biologically sound models of cognition in robots of humanoid shape. This has the two-fold aim of

- i) improving the understanding of brain functions, and
- ii) realizing robot controllers that can learn and adapt from their mistakes.

The activities follow two main lines of research that can be approximately identified with the hardware and software of the robot. On the hardware side, the general plan is to consolidate the activities related to the development of the ICub humanoid platform, and, simultaneously, to strengthen the development of the next generation humanoid robots based on soft adaptable materials (for sensing as well as for processing) and hybrid systems (*soft-robotics*). As to the consolidation and development of the ICub, the effort devoted to hardware development will be reduced percentagewise due to the relative maturity of the robot platform.

On the software side, much effort will be dedicated to the enhancement of the cognitive skills of the humanoid robot. Though broad, such a research has a clear target also in industrial applications. In particular, humanoid robots can be imagined as helpers in manufacturing, office or home environments. In this respect, for example, we address safety in human-machine interaction (at the cognitive, control, and hardware level). Finally, participation in international projects that will add language skills to the ICub and development of new microelectronic sensors for actuation and processing will be pursued.

In the following, a list of topics of research is reported:

- Consolidation of the ICub platform:

- Force Control: e.g. sensing forces and compliant control strategies
- Electronics performance/networking methods, parallel/distributed computation
- Use of improved actuators, new gears, etc. for improved compliance/smoothness of movement
- Machine learning & development
- Motor control, learning, representation
- Planning and control of complex motor actions: manipulation and affordances
- Perception: attention, motivations, and action selection
- Language, Speech
- Safe, Natural Interaction with humans and robots

As to the hardware activity will focus on the development of key technologies improving current platforms and forming the basis of the next generation of “soft bodied” robotic systems. For example:

- Touch Sensors:
  - POSFET (polymer-oxide-semiconductor FET) based high density tactile sensing arrays
  - TFTs (thin film transistors) embedded in organic or elastomeric substrates
  - Piezoelectric-based MEMS for touch, shear and force (also on polymer surface)
  - Large surface touch sensors based on capacitive measures
- Spun composite nanofibers and yarns for mechanical and electrical transduction in robots
- Novel actuation mechanisms for artificial muscles: from nano to macro
- Carbon material transparent films for flexible electronics and sensing
- Dielectric Elastomer-based Actuators
- Neuromorphic visual sensors

Licensing & spin-off: the development of the robotic technologies and the cognitive control of the robots will draw a balance between openness and patenting. Specific solutions will be evaluated for patenting (and or selling/generating revenues) while the more global project of the platform will maintain the current Open Source licensing schema. The aim is to generate interest both for the research community and to industry (which might demonstrate to be fundamental for the future of humanoid robotics both for production and for the creation of targeted applications).

The laboratory will continue to promote his role as one of the main “player” in Humanoid Robotics both in Europe and worldwide.

### **Human behavioral studies with a focus on action and perception**

Research in this stream will focus on three interrelated lines offering the possibility of understanding aspects of human behavior and perception which, besides their scientific value, are essential for the implementation of complex behaviors in artificial systems and new motor rehabilitation devices. All the research aspects addressed have in common the goal of understanding not only the motor and/or perceptual “process” per se but also how the processes adapt, learn and develop as a consequence of interaction with the environment and other human beings.

#### *Physiology of Action and Perception*

The main focus of the scientific activities is to advance the understanding of the mechanisms involved in the production of goal oriented actions. The working hypothesis is that action and perception processes are strongly linked. Consequently action production is studied by considering both motor command and perceptual feedback. Plasticity of sensory and motor cortical areas in addition to action and to perception coupling is also studied after i) a period of inactivity through immobilization and ii) retraining sequences based on implicit motor imagery and observational relearning nonuse and retraining. **Perception** is investigated through several new experimental paradigms based on the idea of online mental simulation of the observed action: a) Role of vision and proprioception in imitation, motor resonance (motor contagion) and learning by observation; b) Motion inference process and visual permanence of biological movement, that corresponds to the performance of an observer that is asked to estimate the final position of hand trajectory that suddenly vanishes behind a wall. **Action** is studied by considering simple (arm) and whole body movements, where **empirical observations** are associated to **numerical simulations**. Among several specific questions that are addressed we try to understand how the gravity force field is represented at the different levels of the CNS. **A potential cognitive representation** is studied using the recorded kinematic and muscle activity of simple arm reach to grasp movement performed in a real or a virtual environment. **A sensorimotor representation** is also considered by studying the multi-joint body mechanical system during a whole body reach to grasp motion. The existence and the combination of specific motor primitives is investigated in the frame of our understanding of the coordination of reaching and equilibrium sub-goals inherent to this complex task. The plasticity of action production is investigated after hypo activity and learning. Functional (motor efficiency through kinematic analysis) and structural (brain plasticity through transcranial magnetic stimulation SEP and MEP recording) experiments are conducted simultaneously.

### *Motor Learning and Rehabilitation*

In relation to the studies on human behavior, we will continue to investigate aspects of human motor control (i.e. goal oriented movements and equilibrium functions), and perception which have a potential to suggest new technologies for the realization of autonomous robotics systems. The purpose of this research is the development of a robotic technology in terms of mechanics and control that can be used to facilitate and speed up the acquisition of novel motor skills or recover the motor ability after brain injuries. This will focus on the cognitive and neural mechanisms underlying the acquisition of a variety of motor skills that involves the upper limb and the hand, including tool use, the generation of complex sequences of movements, and the cooperation of multiple end effectors. In general, we will aim at understanding the way physical assistance affects movement performance and motor learning.

Among these studies, particular emphasis will be devoted to designing robotic systems which, besides being used in scientific investigations, have potential applications in several fields, from rehabilitation of neurological patients to operator training in advanced man-machine systems and in harsh environment such as in space. The focus of the studies on human perception will be on haptic and visuo-haptic perception and development.

Primary application of this technology is robotic rehabilitation by which different control implementations are used to study and characterize brain recovery after stroke or other pathologies; the control system is implemented in a way to be capable of continuously regulating assistance in terms of the observed performance and of the neural and cognitive correlates of adaptation, monitored in real-time by kinematics and dynamics acquisition or through EEG and other noninvasive recordings of brain activity.



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The knowledge acquired in the design of 'optimal', adaptive assistive strategies for neuromotor rehabilitation will be extended and applied for a rational, principled approach to the design of new classes of human-robot interaction mechanisms, including advanced prosthetic devices.

In particular:

- Motor control and modeling : from physiology to robotics and vice e versa
- Analysis of complex motor tasks that include a focal component (upper limb) and a postural component (lower limb)
- Action and perception coupling : Psychophysics, EEG, TMS and fMRI approaches
- Analysis of complex tasks that involve proximal and distal as well as bimanual movements.
- Integration of a modular haptic bimanual robot: arm+wrist+hand.
- Neural Correlates of motor learning and imitation of biological motion
- Adaptive/optimal control mechanisms in human/robot and robot/human interaction.
- Robot-training & Robot-learning for skill acquisition and sensorimotor rehabilitation
- Integration of assistance and performance evaluation in robot therapy of neurological patients
- Development of visuo-haptic perception and multimodal integration in humans

#### *Visual-Haptic Perception in adults and during development*

All senses provide simultaneous information about our environment and this information needs to be combined into a single percept. A powerful framework in which to study integration is the *Bayesian approach* that suggests that information should be combined in a statistically optimal manner that can change dynamically as conditions change. During the next years we propose to study unimodal perception and multimodal integration of different kind of signals (in particular visual and tactile flow signals and visual haptic size and orientation signals and visual-haptic search) to understand the rules that govern fusion and how the intention to move signals (corollary discharge) and a prior knowledge modulate the fusion; This knowledge is important to be able to reproduce the human ability in artificial systems. In addition the interest of our research will be extended at the analysis of the dynamic of these perceptual capacities during development in normally sighted children and considering patients with visual disabilities.

Five principal topics will be investigated:

1. Visual and tactile motion perception during accelerating and constant speed stimuli: we found that a tactile pedestal facilitated a visual test and vice versa, indicating facilitation between modalities and supporting the hypothesis that the thresholding of these signals occurs at high levels after cross-modal integration and that a supramodal system of analysis may be present. By following this field of research we propose to investigate different spatial and temporal characteristic of these signals, adaptation effect and aperture problems between modalities for constant and transient visual and tactile flows.
2. Development of cross modal integration: in our studies we showed that prior to eight years of age, integration of visual and haptic spatial information is far from optimal, with either vision or touch dominating totally, even in conditions where the dominant sense is far less precise than the other. By eight-ten years, the integration becomes statistically optimal, like in adults. In line with this kind of study we propose to investigate the object constancy during development and to repeat the visual tactile size integration experiment by decreasing the haptic reliability (i.e. by producing haptic noise).



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3. Facilitation of haptic information on visual perception. Preliminary data show that unstable perception, like rivalry between oriented gratings, is stabilized by presenting congruent haptic information. The effect is not due to attention or to prior-knowledge, indicating that is probably a consequence of the fusion of the two sources of information. We plan to extend these preliminary observations to determine if the fusion is optimal and to determine the selectivity and tolerance for the spatial and temporal congruency between the two sources of information.
4. A new line of experiment will be initiated aiming to study haptic-visual integration in a more natural condition and behaviour, like during simultaneous exploration with eye and hand movements. The experiment will consist in detecting the presence of a small (visual and haptic) target embedded in noise on simple object like a sphere. The object surface will be presented in virtual reality, while the same object will be manipulated with both hands in open loop. Scan eye movements will be recorded in presence and absence of the haptic information with the aim to evaluate how the search strategy is changed during haptic search. Eye-movement scan path are simulated well with an ideal observer model. We predict that the same model can be applied to the haptic and the visual-haptic search.
5. Motion perception in low vision patients: Perception of the spatio-temporal properties of the environment is essential for everyday life and anomalies related to motion perception have recently been observed in low vision people. We propose to investigate motion perception in low vision patients (by measuring direction discrimination thresholds with gratings and dots in motion as a function of spatial frequency, luminance, speed, duration of the stimulation, and different levels of eccentricity). Moreover since there are many studies that suggest that facilitation and interaction between modalities are present we also propose to study the tactile perception of motion and the presence of cross modal facilitation in this kind of patients.

## Human Machine Interfacing and Interaction

### *Brain Machine Interface*

The main effort in this area will be devoted to the study of chronically implantable Brain Machine Communication devices in humans. In particular the main focus of this long term goal is to implement bidirectional and “ad-hoc” interfaces. By this we mean interfaces that can be adapted to the residual functional abilities and the morphology of individual patients (up to the shape of the “connector”) and that can support bidirectional flow of information between the nervous system and the artificial device. Along this line we will consolidate the ongoing activities on microelectrodes arrays development, microelectronics, brain signal analysis and studies on functional localization of goal-directed movements in humans and start the activities related to the mechanical (tissue) interface between the human body and the artificial system. Particular attention will be addressed to significantly improve the signal-to-noise ratio, to explore the possibility of epicortical mid-impedance recordings, to improve the biocompatibility of implants and therefore their temporal stability.

In particular:

- Carbon nanotubes and conductive polymers composites for high performance, moldable electrodes for in-vivo neural recording
- Microelectronics for signal conditioning and processing of bidirectional brain signals
- Optimal and stable extraction of information from brain signals (local fields and action potentials)
- Mapping of motor/premotor functions in individual brains
- Study and implementation of in-vivo techniques for bidirectional communication with the nervous system
- fMRI studies to study the structural and functional organization of cortical and subcortical motor areas
- “open” fMRI scanner for functional brain analysis of humans in a standing or sitting position
- Study of the bio-compatibility of implanted devices, also through the investigation of the possibility of covering the implants with adult glial cells (in collaboration with NBT).

### *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.

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 cavity of 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. In contrast the ideal scanner for a motor functional study should allow the subject to sit or stand in a most natural position, with unobstructed



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sight of the surroundings and unimpeded arm movements; the field intensity should be high and the stray field minimal. A project, started in 2006 and carried on in the past two year has examined the feasibility of such an “open” fMRI scanner and has laid the basis of its practical implementation.

The main effort in the coming years will be devoted to the finalization of the project of the magnet. It will be a “C” superconductive magnet with a field intensity of 1.5 T oriented along a horizontal axis. The project is highly innovative from the point of view of the magnet structure since it comprises a complete field recirculation within the structure. As a consequence the stray field will only be determined by the presence of the opening and it will be comparable to that of current shielded, tunnel shaped magnets. The design departs from conventional practice since it is based on non-circular and sometimes non-planar windings that although not common in the realization of MRI magnets, have many times been used in different fields, like high energy physics. A relevant part of the project will deal with the optimization of the structure, to make it easier to transfer to cost sensitive applications such as conventional clinical imaging; another significant area is represented by the field compensation techniques that will merge with the design of the gradient coils.

Two types of superconductor are currently under consideration: conventional NbTi alloy wire that would require a liquid Helium cooling or the recently developed MgBr superconductors capable of working at around 20°K that would permit the use of a cryocooler and to dispense with liquefied gases. In both cases the techniques and the tooling for the realization of the windings will have to be specially designed and engineered.

In parallel to the fMRI scanner design a close eye will be kept on the development of the Near Infrared Spectroscopy (NIRS). It is a complementary technique that offers, with respect to fMRI, a worse spatial resolution but presents the advantage of a much lighter equipment and could become, once fully developed, a valuable complement to MRI.

### *Tissue Engineering*

One of the IIT main technological goals is to move ahead from traditional humanoids with mechanical hands and legs (hard-bodied systems) toward next generation hybrid systems realized with soft materials, artificial muscles, tendons, growing tissues, bio-sensors (soft-bodied systems). This ambitious goal requires a deep investigation of soft, functional, anisotropic materials mimicking our skin, tendons and bones but also development of self-repairing, evolvable materials. By endowing such materials with appropriate biocompatible and functional properties, highly efficient interfaces between biological systems and artificial devices may be created, allowing the development of innovative prosthetic devices. To this end, during the years 2009 - 2011, a Tissue Engineering Laboratory will be established in Morego relying on the direct collaboration of researchers from the IIT Network that have a well established record of achievement in this field.

The very first topic that will be addressed will be the coupling of structural elements of artificial limbs with bone tissue. Many pre-clinical and also clinical reports demonstrate that poor scaffold design and inadequate tissue culture condition are currently the major problems in bone tissue engineering that may prevent its successful applications. To overcome these limitations, novel biomaterials and better processes are needed capable of sustaining and guiding tissue regeneration. This task will be pursued by the integration of novel bio-hybrid synthetic techniques, nanotechnologies and advanced material processing technologies to obtain scaffolds able to guide and control tissue growth, differentiation and proliferation.

Within the IIT Network and the Morego Central Laboratories all the appropriate multidisciplinary expertise to achieve this goal can be found, creating the unique pool of knowledge that can give rise to relevant breakthroughs: state-of-the art

clinical know-how and prostheses development, biocompatible materials design and bio-reactor based tissue engineering and testing, nanobiotechnology materials design and robotics engineering.

The role of the Tissue Engineering Laboratory will be to bring into contact, motivate and coordinate towards the common aim of interfacing biological systems to artificial devices all the involved Research Units.

### **Collaborations with other Departments in the IIT Network and with external Institutions**

The activities carried out at RBCS have complementary as well as collaborative aspects with other departments of the robotics as well as neuroscience platform of IIT. In particular there are very strong synergies in exploiting the use of the hydraulic/pneumatic actuators developed in the AR department (Darwin Caldwell) in the control strategies implemented in our robots. Similarly we are collaborating strictly with the Telerobotics and Applications dept. (Jean Guy Fontaine) to investigate the transfer of the results obtained in the Human Behavior Lab. to the use in tele-operation and virtual reality environments (e.g. how to improve the sense of presence by optimizing the perceptual interface with the human operators). Finally an ongoing collaboration activity with the Neuroscience and Brain Technology Department (Fabio Benfenati) within the Brain Machine Interface project is based on the sharing of microelectronics and microelectrode technologies and their future development with, broadly speaking, RCBS addressing in-vivo aspects of brain machine communication and NBT addressing mostly aspects of network formation and processing in in-vitro experiments. Moreover, still in the framework of the BMI project, NBT (optical imaging) and RCBS (electrophysiology) will collaborate to the study of motor representations in rats premotor cortex. As to the collaboration with the IIT network, we expect to continue our collaboration with the **Milano Polytechnic** and **SISSA** in the Brain Machine Interface project (along with Universities of Ferrara, Modena and with the Udine Hospital).

With **Scuola Superiore S. Anna** (SSSA) in Pisa (Paolo Dario) we plan to continue and develop joint activities along the following research lines:

1. Humanoid robots: SSSA is a partner of the RobotCub project and we intend to continue our collaboration in updating and maintaining the robotic platform and to extend the cognitive research aspects to include social behavior as well as safety and robustness targeting humanoid-human interface and interaction. As to the “bodyware” components particular emphasis will be devoted to joining forces in the study of tactile sensors as well as micro-fabricated sensors.
2. Technologies for micro-actuation and micro-locomotion to be used, among other applications, to control the positioning of recording and stimulating electrodes and micro-surgical tools in the framework of Brain Machine Interface. In particular the following approaches will be jointly investigated:
  - wireless actuation exploiting the interaction between static or slowly variable magnetic fields;
  - active (nano)fibers to be embedded into miniaturised devices for generating a sort of active material;
  - muscular cells interfaced with an artificial device in a sort of bio-hybrid actuator with the compliance and the typical behaviour of actual muscles.
3. Hand prosthetic devices.





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In the area of *soft-robotics*, we will continue our recently started collaboration with **National Nanotechnology Lab (NNL)** in Lecce in different areas of robot sensor's design (tactile, force) as well as flexible materials for tendons and artificial muscles. Also with NNL and **Centro di Ricerca Interdipartimentale sui Biomateriali (CRIB)** in Naples we will foster the start of a joint inter-network project for the investigation of biocompatible materials that can be used as electrical interface and mechanical connection (and support) with the human body for the development of advanced hybrid prostheses directly communicating with the nervous system.



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## DEPARTMENT AR: ADVANCED ROBOTICS

### Introduction

The research within the Department of Advanced Robotics combines activities from both the hard (mechanical/ electrical design and fabrication, sensor systems, actuation development etc.) and soft (control, computer software, human factors etc) systems areas of robotics. Overall the balance of activities is focused towards the hardware end of this spectrum with a balance of 70% hardware and 30% software. The activities have synergy with the activities of the other robotics dept. and there is increasing interaction with the other non-robotic departments, particularly Neuroscience. Within the Department the research activities are ordered in terms of:

- core scientific/technological research aimed at providing core competences needed to develop the robotic and humanoid technology and
- advanced research demonstrators that provided large focused research projects that integrate the core sciences.

### Core Scientific Research

Within the core scientific research there are activities based on

#### *Actuation and Power/energy systems*

Strategically this research is aimed at developing and using new actuation and revitalised traditional actuation technologies to solve the power issues that can limit the operation of robotics. In particular the current strategic direction is looking at

- compliant actuation with robots having the ability to deal with contacts in a manner that is safe both for the robot and for humans who may be in contact with the robot.
- Power weight performance to improve the ability of robots to operate in non-conventional environments
- Enhanced control of novel pneumatic and hydraulic (including water) technologies
- New energy generation and storage systems including fuel cells, Stirling engines and energy technologies.

#### *Haptic, Telepresence and Interaction systems*

The strategic aim of this research is the development of high fidelity user interfaces based on touch. The work activities are currently focused on:

- Tactile sensing and feedback
  - High precision tracking
- This work will interface with other research across the spectrum of research in the Department and is particularly aimed at producing a telepresence – teleoperational interface that can rival the human hand in terms of manipulating dexterity.

#### *Biomimetic Systems*

This activity draws inspiration from the natural world and combines these with advanced engineering concepts to develop cutting edge robotic systems.

iv). Advanced Structures – Within this core technology the goal is the development of novel mechanical structures eg advanced high dexterity humanoid hands with sensory capacity to permit effective interaction with a manipulative environment, robotic feet to study the effects of foot construction on robotic (and ultimately human) locomotion, medical rehabilitation (and in the future surgical) interfaces. This work will also address issues of novel materials and their use in robotic application eg composite material, MRF etc.



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#### *Sensor technology*

strategically this will look at the whole remit of sensory technologies that are of relevance to humanoid robotics and human robot interfacing. Efforts are focusing initially on human sensory modalities (eg touch, audition) but future research will extend this to non-human modalities.

#### *Medical Robotics*

During the initial stages of research at IIT medical research has focused on what might be termed paramedical activities such as rehabilitation, training/simulation and medical instrumentation. Recent appointments have strengthened our core capacity in surgical robotics and this is seen as one of the key strategic developments for the next 3 years. It is also considered that developing robotic activities to aid future aging populations should form a developmental focus that can be strengthened and further expanded.

#### *Energy and safety*

One aspect that could form a future strategic direction is development of a novel manufacturing paradigm for food production. The production of food products is labour and energy intensive (and wasteful) and has significant risk of contamination. Work in this area would focus on the development of a novel production scenario that could vastly reduce energy, water and pollution while enhancing food safety.

### **Demonstration Technologies**

Tangentially with these core scientific technologies are key advanced demonstrators that provide a large integrated and focused showcase for the research. The advanced demonstrator projects include:

#### *Humanoid Robotics*

At present the production of the iCub humanoid is already a largely IIT based activity (jointly between AR and RCBS). Future strategic plans in Advanced Robotics will look to very significantly enhance the hardware and control performance of this robot leading to future generations of the iCub. The research demonstrators will develop new activities including, miniature dextrous hand, modular legs and arms, composite based construction, novel actuator technologies with enhanced performance to permit walking and ultimately running and jumping (perhaps even a fully athletic robotic), active sensing skins, anatomically accurate feet etc.

#### *Advanced Haptic and Telepresence Interface*

This demonstrator will integrate research in manipulator design, tactile sensing, motion control, multimodal tactile feedback, high precision hand manipulation to form a telepresence based human robotic interface with a capacity to manipulate object in a manner comparable with (and in future superior to) normal direct human manipulation.

#### *Human Performance Augmentation Systems*

This demonstrator will combine research in actuators, power systems, mechanical/structural design, computation to provide an advanced human interface for enhanced physical performance.

#### *Advanced Medical Systems*

Current demonstrators in medical scenarios are at present based on several small projects. This has a useful role, however, with future developments in medical work the goal would be to integrate larger groups to form more challenging projects. This will be a significant aspect of the future strategy in this area.

### *Quadruped Robotics*

The development of the quadrupedal robotic project aims to draw together further core technologies in a manner similar to those for the humanoid but with different operational targets and goals.

### **Collaborations with other Departments in the IIT Network and with external Institutions**

The activities within the Advanced Robotics Dept. have a high level of collaboration. This collaboration has interfaces with

- i) Other IIT robotics Departments. There is strong collaboration with the RBCS on the development of the iCub humanoid platform, the modified icub developed for the University of Karlsruhe, new actuation technologies, novel exoskeletal structures and recently a joint participation in a new EU framework programme Viactors. With the TERA group there is collaborative work in quadrupeds, composite materials for robotic design and haptic systems with applications in telepresence.
- ii) Other departments within IIT. There are growing activities with the neuroscience department of F. Benfenati looking at microrobotics for biomanipulation. Again this collaboration has recently been strengthened with the award of an EU grant OCTOPUS.
- iii) External bodies. The Advanced Robotics Dept. has developed collaborative research links with other institution Universities of Manchester, Sheffield, Bangor, and King's College London in the UK, UPC (Barcelona), Spain, University of Karlsruhe, Germany, Università degli Studi di Napoli Federico II, Naples, North Carolina State University, USA and membership of the Network of Fluid Power Centres.

## DEPARTMENT TERA: TELE ROBOTIC AND APPLICATIONS

The Department of TeleRobotic and Applications (TERA), is meant to provide short term technology solutions to the increasing demand of automation and robotics worldwide. As such the TERA department targets the development of specific applications in the field of:

- Security: Design of safe and secure links for Tele-robotics activities. Collaborative environments and multi robots based systems under real time constraints (eg Home care, tele work etc.)
- Energy: Low power consumption embedded computer (eg by solar cells or fuel cells).
- Spatial sciences: Crew assistants and crewless devices under remote control and optimal architectures design dealing with micro-gravity and non-linear phenomena's.
- New devices: Artificial skin for underwater applications (i.e. "like fish" robots).

To this aim, the TERA department will develop an R&D strategy based on the study of Human mediated Interaction Research and Advanced Computing Architectures and Algorithms.

### Human mediated interaction research

This activity is carried out to better understand humans in terms of capabilities and behavior when achieving mediated and "distant" interactions (tele-operation). Namely, we continue our efforts in creating interfaces enabling human(s)-robot(s) co-operation regardless to distance, to scale and to physical constraints. In particular we focus on human intentions and commands (capture and interpretation), and synthesis of understandable representations of working worlds (what and how to display remote worlds). With such interfaces we target to minimize users' workload, to immerse them within various worlds (conventional or nonconventional like in space, underwater, etc) and to act through various vectors (anthropomorphic and non anthropomorphic robots).

The main stream lines of such activities are:

- Human intention extraction (through gesture, speech, emotions, etc...) and understanding:
  - Development of non invasive measurement tools and technologies to extract explicit commands,
  - Allowing multimodal control of semi-autonomous robots or agents.
- Non conventional interactions:
  - Development of concepts and VR-AR based technologies to immerse within nonconventional worlds,
  - Enabling people to interact (manipulate and navigate) naturally within nano-macro scales environments, in space and underwater.
- Immersive collaborative environments:
  - Development of networking technologies and immersive shared VR-AR-MR worlds
  - Enabling groups of people to share common working environments for gaming, learning or home care, etc...
- Complex robots' systems management:
  - Development of advanced management tools to abstract robots' groups mobility and sensing capabilities,
  - Allowing simplified tele-operation of multi-robots systems for surveillance, environment monitoring, etc...



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### **Advanced Computing Architectures and Algorithms**

Teleoperation is to consider the tele-operated robotic systems as locally fully autonomous systems, such as a spacecraft, wherein human interaction with the machine takes place at the highest level of task definition/modification. In order to achieve systems with local autonomy, we plan to develop and demonstrate a set of necessary capabilities.

- **Advance Reasoning System**  
An autonomous system needs to handle uncertainty and updates its understanding of the task and environment while pursuing a specific mission. The objective of this research effort is to develop breakthrough algorithms and highly parallel, special-purpose computing architectures for efficient and practical implementation of advanced reasoning systems, based on the Truth Maintenance Systems (TMS).

Assumption-based Truth Maintenance Systems (ATMS) represents the most complete and systematic approach to truth maintenance. Due to its unique features, an ATMS can be potentially a core element of any intelligent system that needs to handle uncertainty, inconsistency, and delays in the information it must process, or more generally for systems that must reason under changing conditions, e.g., when assumptions once valid can later be retracted.

A combination of new algorithms, suitable for massively parallel implementation, and the computing power offered by new architectures would then enable efficient and *practical* implementation of ATMS. Such an efficient implementation could enable an entirely new classes of applications including, but not limited to, robotics reasoning and advanced control and execution, natural language processing, speech recognition, computer vision, hypothesis-exploration engines, machine discovery systems, design systems, diagnosis systems, and planners.

- **Self Awareness Capability**  
An autonomous system need to be able to analyze its current capability and internal state, predict its future ones, and adapt to changes its in capabilities while pursuing its mission. To provide such a Self Awareness capability, we plan to leverage our previous experience and develop and demonstrate monitoring, diagnosis, prognosis, and adaptive control technologies.
- **Low Power, Lightweight, Supercomputer Architecture**

Achieving local autonomy requires a massive computing power to process various sensory data, transform data into information, analyze information, reason about the task and environment, etc. The technical challenge resides in the fact that our target systems are severely limited in terms of weight and power consumption. Our specific objective is to develop novel, massively parallel, low-power embed computing architectures for various processing task. Two specific and current objectives are:

- Embedded supercomputing architecture for image processing
- Special-purpose computing architecture for reasoning based Assumption-based Truth Maintenance System (ATMS)

We plan to identify other needed computing capabilities, e.g. for motion control and optimization, and develop appropriate computing architecture.

### **Collaborations with other Departments in the IIT Network and with external Institutions**



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The activities carried out at TERA have complementary as well as collaborative aspects with the other departments operating in the central research laboratory of Morego and with the NNL-LE pole

- Investigations on Human behavior (motor control and modeling) for Human intention understanding and non-conventional interactions (RBCS LAB)
- Multi bodies, high mobility systems and interfaces (haptic devices), micro-robotics applications (AR LAB)
- New interfaces (haptic and augmented reality based) for micro-manipulation (NBT),(AR LAB)
- Advanced test-benches: automatic modeling and interactive planning (D3)
- Development of new MMS and sensors (NNL-LE)

## **B.2 PLATFORM: THE NEUROSCIENCE PLATFORM**

**Operating units/Dept.:** RBCS-Ge, NBT-Ge, NCS-Pr, IFOM-Mi

### **General Introduction to the Platform Activity**

Neuroscience research at IIT is divided between two departments, the Department of Neuroscience and Brain Technologies (NBT) in Genova and that for Neuroscience and Cognitive Systems (NCS) in Parma. While the two groups are collaborative in their study of brain function, their approaches are broadly complementary, increasing IIT's intellectual and technical "coverage" of brain science.

The brain is still considered the best performing computational device. It exhibits astonishing properties, including a highly complex, hierarchic organization, input integration, parallel computation, emergent properties, and functional and structural adaptation (plasticity). Abilities that the brain accomplishes effortlessly and flexibly, such as identifying objects, controlling fine movements, and learning and adapting to new environments, have proven extremely difficult to implement in artificial systems. The neuroscience centers at IIT are dedicated to investigating brain function at all levels – from molecules, synapses and neurons to large-scale, multi-areal neural circuits in the intact brain. Only this integrated view can reveal the



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true richness of brain function. The longitudinal view of neuroscience is also at the heart of understanding and alleviating neurological and psychiatric disorders of brain function, such as Parkinson's and Alzheimer's disease, epilepsy, schizophrenia, autism, depression and addiction. Disorders of brain function originate in derangements of molecules, synapses and single neurons, but are manifested in the abnormal function of large-scale, dynamic neural circuits. Moreover, a global understanding of brain function is essential for developing brain-machine interfaces, such as neural prosthetics for treating paralysis and sensory deficits, and for bio-hybrid biomimetic systems to allow bidirectional communication between neural tissue and robotic devices.

The focus of research at NBT is the elucidation of the molecular mechanisms of neurotransmission and synaptic plasticity, from individual synapses to synaptic circuits up to brain diseases and to interfacing the brain with electronic chips. The strength of a connection between two neurons can be enhanced or depressed, and these changes span a wide range of time windows, from milliseconds to years. These mechanisms are believed to be the basis of the modifications in information flow and processing induced by epigenetic factors, and eventually lead to learning and memory. NBT research will be aimed at elucidating the mechanisms of neural plasticity, and examining the mechanisms and neural strategies for adaptation, learning and memory. NBT is also broadly interested in understanding the pathogenetic mechanisms of brain disorders such as epilepsy, schizophrenia, autism, addiction and neurodegenerative diseases. We are interested in applying the knowledge we gain to implementing innovative neurocomputer prototypes based on *in vitro* neural networks interfaced with electronic chips, and in developing biological/ robotic actuators with potential application as biosensors and neuroprosthetics.

The focus of the NCS is large-scale neuronal circuits in the brain and the way that those neuronal circuits mediate behavior. While NBT is more focused on *in vitro* and other reduced systems and in small animal models, the work at NCS will focus on the function of the intact, *in vivo* brain, and will encompass experiments both with human subjects and with animals, including non-human primates. Scientists at NCS will broadly examine the *in vivo* neural circuits mediating the brain's remarkable transition from sensation to action, including sensory perception, motor and executive control, attention, decision, and short- and long-term adaptation. Understanding these neural circuits is also essential to elucidating brain disorders, such as Parkinson's disease, that are fundamentally derangements in the interaction of multiple, widely-extending brain areas. A major emphasis of NCS will be the development of new tools for monitoring brain function *in vivo*. This is extraordinarily fertile ground for cross-disciplinary collaboration with other groups at IIT, including NBT and IIT's nanotechnology group.





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## DEPARTMENT NBT: OF NEUROSCIENCE AND BRAIN TECHNOLOGIES

### Neural Plasticity: Studying Information Processing in the Brain and Interfacing Neural Networks with the External World

The brain is still considered the best performing computation device known so far. It exhibits astonishing properties including highly complex and hierarchic organization, input integration, parallel computation, emergent properties, functional and structural adaptation (plasticity). The latter phenomenon is believed to be the basis of higher brain functions and, at the same time, to be precociously impaired in brain diseases.

The focus of the NBT research is the elucidation of the molecular mechanisms of neurotransmission and synaptic plasticity, from individual synapses to synaptic circuits up to brain diseases and to interfacing brain with chips. The strength of a connection between two neurons can be either enhanced or depressed and these changes span a wide range of time windows from milliseconds to years. These mechanisms are believed to be the basis of the modifications in information flow and processing induced by epigenetic factors and eventually lead to learning and memory.

In addition, the central nervous system is the new “scientific paradigm” for information technologies and the concept of “embodied brain” inspires humanoid robots. This has greatly stimulated the attempts to create bio-hybrid/biomimetic devices in which brain tissue is interfaced with electronic chips and to embody neuronal networks by bidirectionally connecting them to robotic bodies.

The main aims of the NBT research will be:

- elucidating of the mechanisms of neural plasticity;
- understanding the mechanisms and neural strategies for adaptation, learning and memory;
- understanding the pathogenetic mechanisms of brain diseases such as epilepsy, schizophrenia, autism, addiction and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases;
- applying this knowledge to the implementation and testing of innovative neurocomputer prototypes;
- creating chronically active artificial networks in vitro to be interfaced with electronic chips and external biological/ robotic actuators with potential application in the biosensors and neuroprosthesis fields.

### Basic Neuroscience Research: genomics, postgenomics and connectomics

#### Study of the molecular bases of the formation and plasticity of synaptic connections in developing neural networks

##### *Formation of synaptic connectivity in developing networks.*

The first assembly of neuronal networks is driven by genetic factors, i.e. by the size of the physiological targets and the expression of chemotactic and/or cell adhesion “recognition” proteins whose genes are specifically transcribed and translated by the various neuronal populations. Formation of synaptic connections during development and their modifications by experience are important steps in the wiring of the brain. These processes require molecular recognition cues - cell adhesion, neurotrophins and extracellular matrix molecules - to guide interactions between the growth cones and environment, through which they navigate. In the last decade, advances in molecular and cellular biology combined with the development of fluorescence microscopy tools to visualize synapses and synaptic molecules in live neurons have revealed many intriguing and unexpected findings regarding the dynamics of synapses formation. The planned research is targeted to identify recognition molecules involved in formation of specific subtypes of synapses, to dissect their functional roles and use this knowledge for discovery of drug-like compounds capable to compensate impaired synaptic functions in animal models of major neurological and psychiatric disorders. Another important advance for the analysis of the synaptic basis of systemic



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functions would be to design a system in which synaptic transmission or plasticity at defined synapses can be specifically turned on and off. This goal will be achieved via the transgenic expression of heterophilic adhesion molecules, which would accumulate at the synapses of interest and will be coupled with appropriate effector domains influencing synaptic function in a predictable manner.

#### *Role of microRNAs in neurogenesis and synaptic plasticity*

MicroRNAs (miRNAs) are short noncoding RNAs that regulate protein expression by suppressing translation and destabilizing messenger RNAs with specific target sequences. Hundreds of miRNAs are expressed in mammalian brain and recent studies suggest a possible role of miRNAs in neurogenesis and synaptic function. It has been shown that synaptic plasticity is critically dependent upon regulation of specific protein synthesis near or within the pre- and/or post-synaptic sites. Numerous components of the microRNA machinery, including dicer are expressed within dendrites and mature miRNAs and their precursors are detected in nerve terminals. It has been suggested that synaptic stimulation can trigger local processing of pre-miRNAs by dicer, leading to the regulation of mRNAs targeted by these miRNAs. Since a single miRNA may target hundreds of mRNAs including global regulators of translation, it is possible that synaptic miRNAs play a profound role in synaptic plasticity.

#### *Molecular and cellular determinants of synaptic plasticity and information processing in neural networks*

Neuronal networks are capable of adaptation and learning, although a thorough study of circuit activity has been hindered by the complexity of mammalian networks. Network plasticity can be defined as the shaping of network morphology and function primarily induced by experience. This process is based on complex activity-dependent changes in neurons that modulate the ability of the neural network to transfer, elaborate and store information. We propose to clarify the mechanisms underlying synaptic transmission and plasticity in networks of live neurons with the purpose of understanding the changes in the information flow and processing involved in higher brain functions. The investigations on the molecular basis of synaptic plasticity will include the molecular analysis of the neurotransmitter release machinery, the functional characterization of key synaptic proteins and of the roadmap of signal transduction and protein phosphorylation processes that mediate the changes in the efficiency of synaptic transmission. These studies will be carried out using leading edge biotechnologies, including viral-infected neuronal cell cultures, live imaging of neuronal cells coupled to patch-clamp recordings as well as generation and phenotypic characterization of genetically-altered mice lacking specific neuronal proteins.

#### *Astrocyte-to-neuron signaling and synaptic plasticity*

Astrocytes are profoundly involved in the dynamics of synaptic transmission. Preliminary experiments show that cortical astrocytes control the activity of neuronal NMDA receptors, a key receptor involved in many forms of plasticity. The focus of this work will be to determine the role of astrocytes in one model of NMDAR-dependent plasticity *in vivo*, ocular dominance plasticity. By using a combination of two-photon microscopy, electrophysiology and the use of an astrocyte-specific transgenic mouse model, this project will investigate astrocytic physiology during ocular dominance plasticity. In particular, this study will test the hypothesis that astrocytes respond to visual stimulation, that they undergo ocular dominance shift after monocular deprivation and that, by regulating NMDA receptors, they control ocular dominance plasticity *in vivo*.

#### **Induction of plasticity in neural networks by chronic environmental stimuli**

Synaptic strength can be finely tuned over a short-to-long time scale by a combination of factors including previous activity of the network, generation of second messengers, functional changes in pre- and post-synaptic proteins as well as regulation of the expression of genes implicated in growth, survival and synaptic transmission. These changes profoundly affect the processing between input and output information and, ultimately, shape the information flow within the network. We propose to subject random and engineered neuronal networks obtained from wild-type or genetically altered mice to chronic, spatially-defined, patterns of electrical stimulation in the presence or absence of controlled changes in the extracellular environment (ions, neurotransmitters, lipid messengers, hormones, etc). During and after the conditioning sessions, the functional and structural changes induced by experience will be evaluated by live imaging coupled with electrophysiology, in



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order to define a constellation of environmental stimuli with negative/positive influences on neural development and plasticity and capable to modify neural connectivity and information processing through the network. Photic stimulation paradigms will also be employed through the localized application of light stimuli with high spatio-temporal resolution. Systems entail photoreceptive neurons of retinal origin or cerebral neurons rendered light-sensitive by transfection of specific light-sensitive ion channels or ion transporters.

### **Study of experience-dependent plasticity in ex-vivo and in-vivo models**

#### *Synaptic basis of experience-dependent plasticity in vivo*

We will investigate the functioning and plasticity of excitatory and inhibitory microcortical circuits in the intact brain by focusing on the visual cortex of mammals as an anatomically and functionally well-characterized model system. To this aim, we will estimate excitatory and inhibitory synaptic conductances by recording voltages while injecting different currents intracellularly in vivo. This approach will be complemented by recordings of the spike activity of genetically labelled interneurons and by the study of the effects of monocular deprivation using intracellular blockers of inhibitory neurotransmission. This knowledge is crucially lacking and is absolutely required for any attempt to recover cortical function after lesion through the use of brain-machine interfaces.

#### *Cross-modal plasticity in vivo*

We will study if cortical neurons in area V1 receive subthreshold inputs from other sensory modalities (somatosensory, acoustic) that affect visually driven spiking responsiveness when the different sensory stimulations are presented simultaneously. We will investigate this issue in normal animals, in animals subjected to a generalized increase of sensory stimulations (environmental enrichment) or to the opposite condition, a lack of visually evoked activity from birth (dark rearing). We will also investigate the presence of mirror neurons in the prefrontal cortex of rodents (in collaboration with the BMI project coordinated by Luciano Fadiga and the RBCS-Sandini). These results will be of utmost importance due to the possibility of studying receptive field modifications in genetically-modified animals.

#### *Synaptic correlates of behavioural plasticity*

The overall goal is to understand how specific molecular pathways in the brain modulate synaptic plasticity to produce behavioural changes. The main focus will be on the mechanisms underlying learning of goal-directed behaviours, the flexible use of actions and how they become habitual. This is of particular interest given the proposed dysfunction of habitual control over behaviour under pathological conditions, including Parkinson's disease and drug addiction.

### **Applications to the understanding of human central nervous system diseases**

The basic properties of information processing at the synapse are precociously altered in an array of human central nervous system diseases and many synaptopathies are believed to be underlie the early stages of the pathogenesis of epilepsy, neurodegenerative diseases (such as Parkinson's or Alzheimer's diseases), autism, schizophrenia, etc. Main goal of this project is to investigate key neuropathological mechanisms of neurodegenerative diseases, with the view of understanding the pathological processes and identifying potential novel targets for drug discovery. The main diseases that will be studied mostly using genetically altered mice will include:

- epilepsy, to understand the mechanisms of epileptogenesis and its relationships with an array of epilepsy-associated mutations involving pre- and post-synaptic proteins;
- neurodegenerative diseases with special reference to Alzheimer's disease, Down syndrome, tauopathies, synucleinopathies and autosomal dominant leukodystrophy, by focusing on: (i) the mechanisms mediated by  $\beta$ -amyloid aggregates and neuroinflammation, (ii) the potential role of adult neurogenesis; (iii) dysfunction and aggregation of other neuronal proteins such as the microtubule-associated protein tau, mutated  $\alpha$ -synuclein and the nuclear protein lamin B1;



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- autism, with special reference to the mutations in synaptic proteins found to be associated with the abnormal neural connectivity that is believed to underlie such disease;
- schizophrenia and Parkinson's disease, attention deficit hyperactivity disorders (ADHD) and depression, with special reference to the associated dysfunctions of monoaminergic systems, including novel systems using trace amines as neurotransmitters.

## **Applications to bio-hybrid and bio-inspired technologies**

### *Set-up of neuroelectronic interfaces for high-efficiency coupling*

#### *Generation of artificial networks*

Attention will be paid to the optimization of the cell-solid state interaction, in order to achieve long-lasting conditions of cell survival and an optimal transfer of forward and backward signals from neurons to the solid-state device. We plan to obtain targeted positioning of neuronal terminals, oriented cell motion and neurite outgrowth, which would allow us to record signals related to pathfinding and stabilization of organized contacts and networks. This will be obtained through the development of new solid-state substrates favoring neuronal growth along specific pathways and the optimization of cell solid-state interfacing by micropatterning of various guidance proteins. We also intend to develop 3D neuronal cultures by growing neurons onto porous membranes or on scaffold-like polymeric substrates.

#### *High-resolution microelectrode devices for recording and stimulating individual neurons*

We aim at the design, realization and testing of novel neuroelectronic interfaces based on micro/nano-fabrication technologies and CMOS integrated systems. We will also design and implement experimental platforms for interfacing the realized devices and for exploiting the enabled features in the analysis of multi-dimensional electrophysiological data. We will also apply post-processing technologies for improving the electrode-neuron interface (e.g. carbon nanotubes coating). Similar strategies will be applied also to electrodes for in vivo recordings in order to improve the electrode biocompatibility and the signal-to-noise ratio in long-term recordings, such as coating the electrode surface with autologous glial or neuronal cells in order to prevent the scar-induced long-term loss of electrode sensitivity (collaboration with RBCS Dept.).

#### *Exploration of alternative non-invasive electro-optical signal transduction mechanisms for the optical readout of neuronal activity.*

Towards the development of a kilo- to mega-pixel recording array with embedded optical sensors (e.g., voltage-sensitive dyes or refractive materials) that respond to changes in membrane potential. Resolution will only be limited by spatio-temporal camera characteristics. The main advantages will be arbitrary sampling of neural activity at any location within the network, high stability of the sensor units and enhanced biocompatibility.

#### *Heterologous synaptic sniffers for biosensing*

Currently, the electrodes used for non-invasive long-term recordings provide information about changes in the focal field and spiking activity of neurons, but not on excitatory and inhibitory currents or synaptic concentration of neurotransmitters. Since several cell adhesion molecules are sufficient to trigger formation of functional presynaptic structures, we will use them to develop a new generation of adhesive sensors which will function as heterologous synapses, thus allowing recording of synaptic currents. To this aim, we will reconstitute adhesion molecules together with neurotransmitter receptors in artificial membranes on the surface of metal electrodes or use commercially available dopamine and glutamate sensors and modify



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these by coverage with appropriate adhesion molecules sufficient for formation of heterologous synapses. These adhesive sensors will provide a new tool for long-term recording of synaptic activity in cultures, with the potential for recordings in cultures and freely moving animals.

#### *Planar patch chips*

Multiple site recordings is limited to extracellular electrodes and is hindered by the low sensitivity to subthreshold changes and the population-type of information that is obtained. To record the activity of single neurons and native synapses, we will develop new planar chips for long-term patch-clamp recordings. The gigaOhm seal will be obtained using various strategies, from microfluidics to the specific expression in genetically engineered neurons of an adhesive interface near to the recording hole made by proteins mediating tight junctions or docking of myelin sheets.

#### *Embodied networks and bidirectional neurorobotic interfaces*

Learning capabilities in complex neuronal systems usually require a two-way interaction with the environment (i.e. a closed loop architecture) and the contribution of specialized and coordinated activity of large neuronal assemblies. We will develop efficient neuroelectronic interfaces allowing a bidirectional interaction between “the brain” and artificial devices. The research will investigate the mechanisms which allow to reliably modify synaptic connections in neuronal preparations by using the technology of multi-electrode arrays and efficient coding and decoding schemes. In vitro neurons from different brain areas, extracted from rat/mouse embryos and plated onto microelectrode arrays will be interconnected to external entities (e.g. a computer, a virtual environment, a robot or a biological actuator such as the octopus arm), thus allowing real-time closed-loop interactions. The software tools for the on-line/off-line analysis of the behavior of the neurorobotic system will be also developed and the built hybrid system will be used for studying the computational properties of biological neuronal networks and for investigating the mechanisms underlying complex behaviors such as learning at network level.

#### *Simulation and design of neuromimetic information processing devices*

The deep knowledge of the elementary properties of information processing and transmission in single synapses and neuronal networks will be used for the initial design and simulation of neuromimetic optoelectrical hardware architectures using parallel computing and wiring/volume modalities of information transfer.



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## DEPARTMENT (NCS) :NEUROSCIENCE AND COGNITIVE SYSTEMS, PARMA

### Introduction

NCS will be broadly concerned with studies of *in vivo* neuronal systems and circuits in animal models, and cognitive systems approaches in both humans and animal models. Systems and cognitive neuroscience is the study of large-scale neuronal circuits in the brain and the way that those neuronal circuits mediate behavior. Simply put, an “understanding” of brain function ultimately entails a description from the systems-neuroscience perspective. Systems and cognitive neuroscience can also critically inform the development of sophisticated robotics applications and brain-machine interfaces for control systems and for human therapeutics. In addition, many brain disorders, such as Parkinson’s disease, epilepsy, and autism, are at their heart derangements in the function of brain circuitry. Systems-neuroscience approaches are thus essential for understanding and ultimately alleviating these diseases.

The specific research projects at NCS will be determined in detail as the scientific staff is recruited over the next year. However, our research will be directed on the following broad areas:

(a) Human studies of perception and sensory-motor integration. Several groups in the center will focus on research with human subjects to examine mechanisms of perception and sensory-motor integration. These studies will include examinations of cue integration, for example, how observers derive the perception of depth from the visual scene from multiple cues, such as motion and stereoscopic cues. We will also examine how active movements of the sensory apparatus, such as saccadic eye movements, affect or enhance sensory processing, and how multiple sensory cues or actions are integrated, such as during reaching toward visual targets. These studies could have important applications to robotics, and are fertile areas for collaboration with other researchers at NCS who are working with animal models.

(b) Studies of derangements of brain function. A group in the center will focus on inferring brain function by the study of brain derangements, such as in stroke patients. For example, understanding important brain mechanisms such as attention is facilitated by examining patients with lesions in specific brain locations, such as parietal cortex. In addition, we will study the effect “virtual” lesions using the technique of transcranial magnetic stimulation (TMS) to safely and reversibly inactivate specific brain areas. We will also explore the possibility of using TMS as a rehabilitative tool in for the lesioned brain.

(c) Neurophysiological and imaging studies of sensorimotor and cognitive function in behaving animals. The main goal of the center is to use understand brain function by recording the electrical activity of neurons in animals trained to perform specific trained tasks. We will use both non-human primates and rodent models for these studies, and we will also be open to studies with model invertebrate organisms. We intend to use both neurophysiological and imaging approaches. Studies will emphasize a parallel and integrated approach to brain function, for example examining both cortical and subcortical structures in the mammalian brain, and investigating how multiple brain areas interact to mediate perception and behavior. The types of questions that we will explore include:

- I. Examining brain mechanisms of sensory-motor integration and sensory cue integration in animals trained to navigate toward or reach toward visual targets.
- II. Exploring cognitive function in behaving animals, using trained tasks to reveal abilities such as selective attention, on-line plasticity of function, mechanisms of decision and reward reinforcement, and formation of cognitive “rules” and strategies.



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iii. Studying aspects of movement control, in particular the initiation of movement and the relationship to disorders of movement control, such as in Parkinson's disease.

(d) Development of novel techniques for monitoring brain function in vivo. A critical adjunct to our animal studies is the development of innovative new tools for monitoring activity in the intact brain, and for assessing connectivity in neural circuits. Present techniques for recording brain activity are greatly limited in spatial and/or temporal domains. We are planning collaborations with our colleagues in the IIT nanotechnology group and elsewhere to develop new molecular sensors that can detect functions such as neuronal firing and neurotransmitter release with spatial precision and high temporal fidelity, but also in a massively parallel manner among many neurons or brain areas. We will test these reagents in animal models, and we intend to ultimately employ them in our experiments on brain function. These technical developments could have a high potential for medical application.

#### **Applications of our research to medicine and industry**

Our work is primarily basic research directed toward understanding fundamental aspects of brain function, but there are important potential applications to medicine, science and industry:

(a) Our basic studies on perception, action, and integration could be useful in informing robotics applications, and we intend to collaborate closely with our robotics colleagues in Genova in this regard.

(b) Our studies of derangements of brain function are at their core directed at developing therapeutic and rehabilitative approaches for patients with brain damage. For example, we intend to test whether TMS can be used to relieve unilateral motor, sensory, and attentional deficits in stroke patients.

(c) Our neurophysiological studies in animals could have important applications to evaluating or treating human patients. For example, neurophysiological approaches are used in the emerging field of brain-machine interfaces, such as neural prosthetics, and in applications such as deep-brain stimulation, a rapidly developing treatment for Parkinson's disease and other central disorders.

(d) Perhaps most importantly, our efforts to develop new molecular probes for monitoring brain activity and connectivity could have critical application in medical diagnosis and treatment. For example, development of reagents for massively parallel monitoring of neuronal activity could facilitate more detailed and less invasive long-term monitoring of brain function, such as in pre-operative epilepsy patients.

#### **Exploration of Nanotechnology Applications to Systems Neuroscience**

Systems neuroscience is the study of how large-scale neuronal circuits in the brain mediate behavior. Simply put, an "understanding" of brain function ultimately requires a description from the systems-neuroscience perspective, using *in vivo* studies. Many brain disorders, such as Parkinson's disease, are at their heart derangements in the function of brain circuitry; systems-neuroscience approaches are thus essential for understanding and ultimately alleviating these diseases. Moreover, systems neuroscience lies at the heart of developing brain-machine interfaces for control systems and human therapeutics.

Despite the importance of systems neuroscience, the tools for *in vivo* studies remain severely limited. Much of what we know about brain function comes from decades of research using metal electrodes that record either gross electric or magnetic





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signals from the surface of the brain (EEG or MEG), or using microelectrodes that record electrical activity from single neurons or small groups of neurons inside the brain. While metal electrodes generally have excellent temporal resolution, on par with the underlying electrophysiological activity, they provide either a very spatially restricted picture of brain activity (e.g., single unit recording with microelectrodes) or they provide an overly coarse signal representing superimposed activity from millions of neurons simultaneously (e.g., EEG and MEG). Moreover, electrodes cannot provide information about the *types* of neuron recorded nor on the inputs to and outputs from the neuron(s) under study.

More recently, functional imaging has been added to the armamentarium of techniques for studying the brain *in vivo*. By far the main approach is functional magnetic resonance imaging (fMRI). fMRI has the advantage that it is non-invasive, so that humans can be studied as well as animal subjects. In addition, functional imaging gives a view of “activity” throughout the entire brain simultaneously, which will be essential for understanding the circuitry mediating brain function. However, fMRI in its present form is severely limited. The main problem is that fMRI does *not* provide a direct read-out of neuronal activity; rather, almost all fMRI experiments rely on a *hemodynamic* response. When neurons are activated in a part of the brain, their increased metabolism triggers a release of oxygen from local blood vessels. Since oxyhemoglobin and deoxyhemoglobin differ in their magnetic susceptibility, changes in blood oxygenation causes the magnetic signal variation that is imaged with fMRI. fMRI is thus a very coarse, slow measurement. For example, when the brain is activated by a visual signal to the eyes, neurons in the visual cortex “turn on” within tens of *milliseconds* (as measured directly with microelectrodes), but the fMRI signal from visual cortex rises over several *seconds*-- nearly a thousand times more slowly than the actual neuronal signals. Moreover, the physiological control over blood oxygenation levels is spatially far less localized than the pattern of activation of neurons. Thus fMRI could be tremendously improved if there were ways to image neuronal activity more directly; indeed, such an approach would be a real breakthrough.

In the broadest terms, systems neuroscience desperately needs new techniques that allow precise measurements with *high temporal resolution* from as *many neurons* as possible, from as *many parts of the brain* at once. Only this approach will allow the essential integrated view of how the brain solves problems such as perception, memory and control of movement. There are some newer techniques that begin to address these needs. For example, optical imaging of brain activity can allow measurements from hundreds of individual neurons at once, but is presently limited to only the outermost surface of the brain (a few hundred microns of neocortex), and generally relies on indirect measurements of neuronal activity, such as intracellular calcium-ion accumulation as a proxy for neuronal firing.

Our understanding of *in vivo* brain function could be enormously improved by integrating systems neuroscience with nanotechnology. This inter-disciplinary approach will also spur the development of new reagents for medical diagnosis and treatment. In both cases IIT may be in a unique position worldwide to stimulate and guide such efforts. Among various new ideas to be developed, we mention:

#### *New “smart” microelectrode technologies,*

Using new materials, multi-functional microelectrodes could be designed that incorporate different electrically- or magnetically-sensitive reagents along their length to allow recording from many neurons simultaneously. Present metal microelectrodes only provide signals from one or a few neurons located near the uninsulated tip of the electrode (tens of microns); the rest of the electrode’s shaft is insulated to prevent electrical shunting. If instead the electrode could record signals from all along its length (several millimeters or more), the activity of many more neurons (potentially hundreds or more) could be recorded. For example, this approach could be used to record activity throughout the entire depth of a neocortical functional column. (Multi-contact conventional electrodes have been developed for this purpose, but they have generally performed poorly, they require cumbersome and fragile individual leads and amplifiers, and they can only record from a few neurons at most.) The challenge for any “smart” electrode would be to disambiguate the signals from the many neurons that are recorded, and in this regard, one can envision materials that provide “carrier” signals with different properties that can be multiplexed and then disambiguated with appropriate electronic discrimination.





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#### *New generation voltage-sensitive dyes.*

Voltage-sensitive dyes are optically sensitive molecules that incorporate into cellular plasma membranes and changes their optical properties in response to the large changes in transmembrane electrical potential that are the basis of neuro-electric signaling. Voltage-sensitive dyes have the advantage that they can be used to image electrical signals from many neurons simultaneously, but they are limited in that they generally provide weak signals and are often toxic to cells. Nanotechnology provides new optically active materials that could provide greatly improved voltage-sensitive dyes. For example, quantum dots are inorganic semiconductor crystals that have remarkable optical characteristics broad excitation bandwidth, exceedingly narrow and tunable emission spectra, and high quantum yields. Their optical properties can also be strongly affected by external electric fields (Stark effects), such as the enormous electric fields ( $\sim 10^6$  V/m) that exist across neuronal cell membranes. Quantum dots could be functionalized with appropriate hydrophobic organic molecules to incorporate into neuronal cell membranes and act as voltage-sensitive dyes. In principle, quantum dots should also be much less toxic than conventional voltage-sensitive dyes, since their high quantum yield should reduce the formation of reactive free radical molecules.

#### *Reagents for fMRI that provide direct neuronal signals.*

Paramagnetic nanoparticles could be developed that provide a direct read-out of neuronal activity for fMRI. Iron oxide nanoparticles are presently used for improving contrast for anatomic MRI applications and for enhancing hemodynamic fMRI signals. These particles could also be functionalized to provide a magnetic signal that reports the membrane potential of neurons. Analogous to voltage-sensitive dyes, magnetic nanoparticles could be complexed with amphipathic molecules that target them to cell membranes. With changes in neuronal membrane potential (such as action potentials), these magnetic complexes could change their disposition within the cell membrane, providing an activity-dependent variation in magnetic signals detectable by fMRI. A challenge to this approach is having particles that can cross the blood-brain barrier so that they can be introduced via the blood stream. Nanotechnology could also provide a solution to this problem, by the development of “carrier” materials to transport reagents across the blood-brain barrier. This could provide a more general means for transporting other molecules into the brain, such as drugs.

#### *New methods for detecting neurotransmitters in vivo.*

A critical question in neuroscience is the *in vivo* action and dynamics of neurotransmitter molecules. For example, an important group of neurotransmitters are those of the “diffuse ascending systems”, which include dopamine, noradrenaline, serotonin, and acetylcholine. These modulatory molecules are hypothesized to play important roles in learning and attention, and derangements of these neurotransmitter systems have been implicated in pathological conditions such as Alzheimers and Parkinson’s disease, schizophrenia, and addiction. Nonetheless, very little is known about the spatiotemporal pattern of neurotransmitter release *in vivo*. New nanomaterials could revolutionize this important area of research. For example, miniaturized biosensors based on localized surface plasmon resonance (LSPR) could be used to optically detect the binding and dynamics of specific neurotransmitters molecules. Surface plasmons are electromagnetic waves propagated at the interface of metals (such as noble metal nanoparticles) and a dielectric (such as the saline extracellular environment of the brain). The optical behavior of the interface is extremely sensitive to the binding of molecules to the surface. If specific molecular “receptors” are complexed to the surface, the binding of particular ligands, such as neurotransmitters, could be detected optically by monitoring changes in the index of refraction of the interface. SPR is the basis for sensitive new biosensors for detection of molecules *ex vivo*. Miniaturizing an LSPR system using nanotechnology could provide extremely precise and localized sensing of neurotransmitters *in vivo*.

#### *Improved materials for identifying neurons.*



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One of the biggest challenges of systems neuroscience is identifying the *types* of neurons from which signals are recorded. Electrophysiological recording *in vivo* is almost always done “blind”: one cannot identify whether a particular neuron is a projection neuron or a local circuit interneuron. It is also extremely difficult to determine where a neuron “sits” in a neuronal circuit – from where it receives input and to where it projects. Nanotechnology can offer approaches to these critical questions. For example, nanoparticles could be developed that can be injected into a part of the brain and then be retrogradely transported back to the cell bodies of neurons that specifically project to that injected area. The particular nanoparticles could be engineered to provide a signal – optical, magnetic, etc. -- in the cell body that can be detected by physiological methods or fMRI to determine whether neurons in an particular part of the brain are projection neurons of a specific type. In addition, nanoparticles could be complexed with molecular ligands that are taken up specifically by particular classes of neurons, such as interneurons that express and absorb specific neurotransmitters. If the nanoparticles provided a detectable “signature”, the cell types could be identified. Approaches of this sort could revolutionize our understanding of neural circuits, and could help to elucidate how derangements in neural circuits cause brain disorders.



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### **B.3 PLATFORM: DRUG DISCOVERY, DEVELOPMENT AND DIAGNOSTICS (D4)**

**Operating Departments/Units: D3-Ge, NC-Ge, CRIB-NA, NNL-Le, NEST-Pi, IFOM-Mi**

#### **General Introduction on the platform activity**

D4 is the new platform being developed by IIT, combining the large scale facility of the Department of Drug Discovery and Development (D3) with the remarkable know-how in new tools for medical and biological diagnostics developed by the bionanotech facility of IIT. The basic concept is to combine the D3 mission, to discover innovative medicines for human diseases, with the solid state bio-chips technologies for genomics and proteomics and the nanoparticle-based technologies for intelligent drug delivery and labeling in optical and magnetic diagnostics, either in vivo or in vitro.

Concerning the D3 Department, its mission stems from three key ideas:

*It is important to discover innovative drugs.* As noted above, the pharmaceutical industry aims most of its current research efforts at low-risk programs, leaving often unattended the quest for high-risk innovative medicines – those that target mechanisms never tested before in man. These are, however, more likely to achieve both significant therapeutic advance and impressive financial reward<sup>5</sup>. The D3 will dedicate its research efforts to the pursuit of such drugs.

*It is possible to discover new drugs outside the pharmaceutical industry.* Half of the medicines in the market today were discovered outside the pharmaceutical industry. This fact highlights how drug discovery can benefit from the creative environment found in academic labs. While maintaining alive such an environment, the D3 will also provide the infrastructure, resources and know-how that are necessary to validate scientific advances and capture their full societal and economic value.

*The collaboration with private partners is a key to success in drug discovery.* Only the private enterprise can transform innovative medical discoveries into successful pharmaceutical products. To facilitate this transition, the D3 will encourage and promote the collaboration with private partners (venture capital funds, pharmaceutical companies) at various stages of the discovery process and on specific projects of common interest.

The pursuit of the innovative drug discovery is a complex, multi-level task, which IIT has started through three complementary approaches:

1. Designing research labs that combine access to state-of-the-art facilities with an environment that fosters scientific collaboration. Our labs are currently under construction.
2. Launching a recruitment campaign aimed at achieving a balance between highly creative academic scientists and seasoned pharmaceutical researchers experienced in drug discovery and early development.
3. Implemented a matrix-based organization in which scientists from different technical backgrounds (computational and synthetic chemistry, molecular and system pharmacology, etc.) can interact freely and productively on specific target-oriented projects.

At the outset, the D3 will focus its research activity on two areas of significant unmet medical need: neurodegenerative disorders, such as Alzheimer's disease, and pain and inflammatory disorders.

- New magnetic/fluorescent beads for cell sorting/counting
- New polymer shells for drug delivery activated by nano magnets
- Solid state chips/labs-on-chip devices for genomics, proteomics and cellomics



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- New fluorophores (molecular and/or inorganics) and ultra high resolution optical imaging
- New electrical detection schemes for modification, toxicity and interactions of cells and biological entities (up to single event sensitivity)

The fourth D (from D3 to D4) in the Acronym D4, stands for Diagnostics and includes all the new technology solutions developed by the nanobiotech laboratories in the IIT network. These encompass:

The combination of these technologies, which are unique in the IIT network, with the D3 Department places the entire D4 platform at the leading edge of the research in the field.



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### DEPARTMENT DRUG DISCOVERY AND DEVELOPMENT (D3)

The Activity of the Drug Discovery Development department encompasses the following mainstream lines:

-Neurodegenerative disorders. Over the next two decades, the number of patients affected by Alzheimer's disease – the most common type of neurodegenerative disorder – will increase, in the United States alone, from 5 to 10 million. By 2050, estimates range as high as 16 million Alzheimer's patients in the United States. This impending crisis creates a huge need for safe and effective medicines that can slow down Alzheimer's progression. A study authored by John Vernon, PhD, for the advocacy group ACT-AD, estimated that a therapy that delayed onset of Alzheimer's disease for only one year could result in a benefit of more than one trillion US dollars<sup>7</sup>.

-Pain and inflammatory disorders. Pain, particularly of inflammatory and neuropathic origins, is both underestimated and underserved. Like Alzheimer's disease, inflammatory disorders are on the rise. Analysts believe that just one type of inflammation, osteoarthritis, affects at present more than 20 million individuals in the United States, but that number is expected to rise to 40 million by 2020. Estimates of prevalence of neuropathic pain vary widely, but a realistic range is between 30 and 60 million patients worldwide<sup>8</sup> Endocannabinoid Discovery Team,

- Carbon Monoxide Discovery. This activity will focus on the discovery of novel anti-inflammatory and anti-neurodegenerative agents targeting the carbon monoxide signaling pathway.

#### The endocannabinoid system as a target for novel analgesics.

Cannabinoid receptors – the cell-surface receptors activated by the active principle of *Cannabis*,  $\mu^9$ -tetrahydrocannabinol ( $\mu^9$ -THC) – are the centerpiece of a signaling system of previously unsuspected biological importance. This signaling system has three key components. The first is represented by the cannabinoid receptors themselves, two subtypes of which have been molecularly characterized – the CB<sub>1</sub>, which is found almost everywhere in the body, but is most abundant in the central nervous system; and the CB<sub>2</sub>, which is primarily expressed in immune cells. The second is constituted by the endocannabinoids, lipid biomolecules 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. These interrelated elements are employed by cells to execute a variety of short-range signaling tasks – from synaptic communication in the brain to cell-to-cell signaling in the vasculature. At a mechanistic level, there are three different ways to interfere with endocannabinoid signaling to achieve a therapeutic goal – blockade of CB<sub>1</sub> receptors, activation of peripheral CB<sub>1</sub> and CB<sub>2</sub> receptors, and inhibition of endocannabinoid deactivation. The D3 will utilize the latter two approaches to discover new analgesic drugs.

#### Cannabinoid receptors activation.

Activation of cannabinoid receptors causes profound analgesic effects in animal models of inflammatory and neuropathic pain, two conditions that do not respond well to standard analgesic therapy. Enticing clues of efficacy in human pain states have also been reported in the literature – for example, a *Cannabis* preparation (Sativex®) recently received regulatory approval by Health Canada for the treatment of neuropathic pain in multiple sclerosis. The problem is whether cannabinoid analgesia can be dissociated from the unwelcome costs of CB<sub>1</sub> receptor activation and, in particular, from the mind-altering effects sought after by marijuana users and heavily guarded by regulatory authorities in the USA and Europe. This difficulty, which has stopped all previous efforts to develop cannabinoid-based analgesics, may no longer be insurmountable. Evidence suggests three possible ways to circumvent it: the first is to target CB<sub>1</sub> receptors located on nerve fibers that carry pain sensation to the brain; the second is to exploit the pain-modulating actions of a different cannabinoid receptor subtype,



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the CB<sub>2</sub>, which is not expressed in brain neurons; finally, as evidence emerges for the existence of new cannabinoid receptors, such proteins might be targeted for therapeutic purposes.

#### *Peripherally restricted CB<sub>1</sub> receptor agonists.*

The ability of cannabinoid agonists to reduce pain by acting outside the central nervous system (i.e., through a peripheral mechanism) has been confirmed by studies in non-human primates and human volunteers. Additional support comes from a placebo-controlled clinical trial of the synthetic cannabinoid CPL7075 (Cervelo Pharma), also known as ajulemic acid. CPL7075 is a chemical derivative of  $\mu^9$ -THC, which activates CB<sub>1</sub> receptors but has more limited brain access and slightly higher therapeutic index than standard cannabinoid agonists. Neuropathic pain patients treated for one week with CPL7075 reported significantly less pain than did placebo-treated patients, as assessed using a visual analog scale. This effect was associated, however, with a greater incidence of adverse events such as transient dry mouth and tiredness, indicating that the compound was still able to enter the brain in significant amounts. The D3 plans to develop novel peripherally restricted CB<sub>1</sub> receptor agonists also through a partnership with venture capital firms.

**Endocannabinoid deactivation inhibitors.** The biological actions of the two main endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are terminated through a two-step process consisting of transport into cells followed by intracellular hydrolysis.

**Endocannabinoid transport.** Endocannabinoid uptake is structurally specific, displays classical saturation kinetics, and is selectively inhibited by anandamide analogs such as AM404. These compounds are very useful experimental tools but, being highly flexible and subject to multiple metabolic transformations, offer little in the way of drug development. So the identification of a second generation of endocannabinoid transport inhibitors critically depends on the discovery of novel drug-like leads. Research in this area has been slowed down, however, by the elusive nature of the endocannabinoid transport system, whose molecular identity has long remained undefined. The identification of potent and selective inhibitors of anandamide transport and their validation as analgesic agents is a key area of investigation for the D3 (recently, an anandamide transporter has been cloned and purified in the Piomelli lab at the University of California, Irvine). Efforts in this area have already started through collaboration between the Computational Chemistry group at the D3 and at UCI.

**Anandamide hydrolysis.** Anandamide is hydrolyzed by fatty-acid amide hydrolase (FAAH), an intracellular membrane-bound serine hydrolase that also cleaves non-cannabinoid lipid amides, while 2-AG is hydrolyzed by monoacylglycerol lipase (MGL), a cytosolic serine hydrolase that converts 2- and 1-monoacylglycerols into fatty acid and glycerol. In the rat brain, neurons that express FAAH are usually found in proximity of axon terminals containing CB<sub>1</sub> receptors, providing important evidence for a role of FAAH in anandamide deactivation. Moreover, mutant mice lacking the gene encoding for FAAH cannot degrade anandamide and show signs of an exaggerated endocannabinoid tone, such as reduced pain sensation. These findings suggest that selective FAAH inhibitors could enhance the actions of anandamide in brain regions in which this lipid mediator is physiologically important – for example, those engaged in the processing of pain and emotion. The increased anandamide tone produced by blocking FAAH may result in a more restricted spectrum of pharmacological effects than those produced by direct-acting CB<sub>1</sub> agonists and, possibly, in fewer adverse events. This concept has been validated in animals. For example, the compound URB597, which is potent at inhibiting FAAH activity both in vitro and in vivo, increases anandamide levels in the brain without mimicking the spectrum of responses produced by direct CB<sub>1</sub> agonists. Thus, at doses that abrogate brain FAAH activity, the drug does not produce immobility, hypothermia or overeating – three hallmarks of cannabinoid intoxication. Nevertheless, URB597 is highly effective in animal models of pain, anxiety and depression. The D3 is currently exploring the feasibility of a program oriented to the development of novel FAAH inhibitors with improved drug-like properties.

**2-AG hydrolysis.** Based on what we know about the function of 2-AG, selective blockers of this cytosolic serine hydrolase would complement FAAH inhibitors in a variety of therapeutic areas, including analgesia and neuroprotection. The D3 will initiate a drug discovery effort on MGL and other 2-AG-hydrolyzing enzymes that might be discovered in the future.



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**Hydrolysis of other endocannabinoids.** In addition to anandamide and 2-AG, the body produces other endocannabinoid-like substances, including palmitoylethanolamide (PEA). When administered as a drug, PEA exerts profound analgesic and anti-inflammatory effects, which are mediated by activation of the nuclear receptor PPAR- $\alpha$ . Its actions are terminated by an enzyme called N-acyl ethanolamide acid amidase (NAAA), which is structurally different from both FAAH and MGL. The identification of potent and selective NAAA inhibitors and their validation as anti-inflammatory and analgesic agents is another key area of investigation for the D3. Efforts in this area have already started through collaboration between the Structural Biophysics team at the D3 and the University of California, Irvine.

### **Innovative strategies for the treatment of Alzheimer's disease.**

Alzheimer's disease (AD) stands out among neurodegenerative diseases as the fourth leading cause of death in Western countries, and the most common cause of acquired dementia in elderly people. In line with an increase in average life expectancy, the number of affected persons will triple by 2050, with immense economic and personal tolls. The pathogenesis of AD is thought to involve a complex interplay of genetic, environmental, and biochemical factors. This multifactorial nature, along with the lack of a real clinical efficacy of currently available drugs, calls for innovative approaches to drug discovery. One possible strategy is based on the concept that a single multifunctional compound might be deployed to hit multiple targets that cooperate in the neurodegenerative process underlying AD. Such a strategy would prevent unwanted compensation among interacting pathogenic pathways, and could represent a practical alternative to the use of cumbersome drug cocktails.

One of the first examples of multifunctional compound is represented by memoquin, a molecule developed by the Project Director at the University of Bologna. Memoquin is a bis-diamino-benzoquinone derivative that affects several mechanisms relevant to AD: i) it reduces formation of reactive oxygen species (ROS), ii) it interferes with the aggregation of the amyloid  $\beta$  peptide ( $A\beta$ ), and iii) it inhibits acetylcholinesterase (AChE) and  $\alpha$ -secretase 1 (BACE-1) enzymatic activities in the nanomolar range. In animal models, memoquin causes a remarkable decrease in the formation of key AD neurodegenerative hallmarks such as  $A\beta$  plaques and neurofibrillary tangles (deposits of hyperphosphorylated  $\tau$  protein), and a reversal of behavioral deficits, as assessed using the object recognition test. Based on our initial work with memoquin, the D3 plans, in partnership with the University of Bologna, to preclinically develop memoquin and to create a second generation of multifunctional AD therapeutics.

### **Multifunctional therapeutics.**

**Memoquin optimization.** A campaign of lead optimization on memoquin will be performed. The main aim of such campaign is the improvement of the pharmacokinetic, toxicological, and ADME properties of memoquin, thus creating a second generation of memoquin analogs with enhanced drug-like properties. All moieties of memoquin – spanning from the quinone core and the length of the alkylic chain to the solubilizing moieties, i.e., the protonable amino group – will be systematically modified. In addition, the ortho-methoxy group of memoquin will be replaced by different substituents to investigate the structure-activity relationships. To this aim, electron-donating and electron-withdrawing substituents in ortho, meta, and para positions will be inserted onto the new derivatives. All new derivatives will be tested for their activity as inhibitors of the AChE and BACE-1 enzymes. The antioxidant properties will be assessed by molecular and cellular assays, while their activity as  $A\beta$  aggregation inhibitors will be tested by using the thioflavin T fluorescence and circular dichroism-based assays. Selected compounds will eventually be tested *in vivo* using the APPsw transgenic mice (Tg2576). *In vivo* studies will be carried out in collaboration with the Neuroscience and Brain Technologies Department of IIT.

**Novel multifunctional compounds.** In light of the promising *in vitro* and *in vivo* profiles of memoquin, novel multifunctional drug candidates will be designed, synthesized and tested. To this aim: i) chemically tractable combinations will be carefully identified; ii) new molecules bearing the desired biological profile against multiple targets (ROS,  $A\beta$ , AChE, BACE-1, etc.) will





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be designed and synthesized by merging pharmacophoric functions and/or fragments responsible for the biological activities towards each target; iii) selected lead compounds will be optimized into clinical candidates that combine the desired multifunctional activities with a drug-like pharmaceutical profile.

**Pathway-based drug candidates.** Multifunctional compounds represent the first step towards an increased complexity in drug discovery. Indeed, reductionistic paradigms 'one-disease-one-target' and 'one-target-one-drug' have turned out to be very weak in providing innovative and efficacious drug candidates, particularly in the field of neurodegenerative diseases. With this in mind and starting from multifunctional compounds, D3 plans to definitively move away from the target-based approach towards pathway-based strategies. In this respect, aimed at obtaining innovative anti-AD drug candidates, Wnt has very recently emerged as a promising pathway to modulate. In particular, acting on the glycogen synthase 3 (GSK3) level could represent a very promising approach to novel anti-AD drug candidates. Indeed, besides to be a pivotal downregulator of the Wnt pathway, GSK3 is involved in the hyperphosphorylation of the  $\tau$  protein, the main component of neurofibrillary tangles.

**Self-activating small organic molecules.** The central nervous system is purposefully endowed with a set of powerful antioxidant enzymes that maintain the cellular redox balance and are promptly induced upon exposure to oxidant (e.g., ROS) and stress stimuli. The concerted expression of these enzymes is finely controlled at transcriptional level by the specific activation of the nuclear factor Nrf2 that under normal conditions is retained in the cytoplasm in a 'silent' form by its repressor Keap1. Nrf2 activates the antioxidant responsive element (ARE) of a series of antioxidant/phase 2 detoxification genes. Heme oxygenase-1 (HO-1) and NADPH:quinone oxidoreductase (NQO1) are the typical prototypes of inducible enzymes whose expression depends strictly on the activation of Nrf2. Both enzymes and their catalytic products (carbon monoxide/bilirubin and ubiquinol, respectively) are critical systems employed by cells and tissues to counteract ROS-mediated damage. Notably, certain small organic molecules (primarily compounds with electrophilic properties) known to act as powerful inducers of HO-1 and NQO1 possess the ability to disrupt the Keap1-Nrf2 complex.

In this scenario, the specific aims of this part of the project are: i) to identify and characterize new small molecules that disrupt the Nrf2-Keap1 pathway leading to a strong and persistent expression of specific cytoprotective genes (HO-1 and NQO1); ii) to implement a truly innovative design strategy for the identification of self-activating small organic molecules with drug-like profile. These are hybrid compounds carrying both a moiety able to potently stimulate Nrf2-mediated HO1 and NQO1 expression, and a substrate scaffold (heme- or quinone-containing), which can be promptly utilized by the enzymes to provide an additional and effective antioxidant action; iii) to test the new pharmacological intervention strategy in cellular and in vivo models of neurodegeneration.

### **The heme oxygenase/carbon monoxide pathway as a novel target for drug discovery**

Heme oxygenase enzymes, which exist in constitutive (HO-2) and inducible (HO-1) isoforms, are the rate-limiting steps in the degradation of heme to carbon monoxide (CO) and bilirubin. Research conducted in the last decade has demonstrated that HO-1 and its products exert important protective actions in a variety of disease models. In addition, the identification of the first human case of HO-1 deficiency has corroborated the notion that HO-1 is an obligatory pathway in the preservation of tissue integrity against oxidative stress and prevention of vascular- and inflammatory-related disorders. Studies in humans have also shown that moderately high levels of plasma bilirubin correlate with decreased risk of cardiovascular disease and cancer, and are associated with improved inflammatory and lipid profiles in diabetic patients. The signaling and anti-inflammatory effects of CO as well as the powerful antioxidant properties of bilirubin are central to the protective activities mediated by HO-1. Intensive research has also focused on understanding the mechanisms involved in the regulation of the HO-1 gene. The findings emerging so far indicate that the transcription factor Nrf2 and the nuclear repressor Bach1 are the main regulators of tissue HO-1 expression. Based on this knowledge, targeting the heme oxygenase/CO pathway for the development of useful pharmacological therapies appears of great relevance in drug discovery. Our project will focus on three main approaches aimed specifically at amplifying HO-1 activity and maximizing the physiological function of its products. The principal areas of application will be inflammation and neurodegenerative diseases. We will first design and





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characterize novel CO-releasing molecules (CO-RMs), based on our original discovery that transition metal carbonyls liberate controlled amounts of CO to cells and tissues. Secondly, amplification of HO-1 expression by natural and synthetic compounds (curcumin and porphyrin derivatives, respectively) that selectively target the transcription factor Nrf2 and the repressor Bach1 will be pursued. Finally, we will work on the design of molecules that maintain high levels of circulating bilirubin by specifically inhibiting UDP-glucuronosyltransferase activity, the enzyme responsible for bilirubin clearance in the body.

**Carbon monoxide-releasing molecules (CO-RMs).** The discovery that transition metal carbonyls act effectively as CO-releasing molecules (CO-RMs) in biological systems highlights the potential of developing pharmaceuticals that deliver CO for the treatment of pathophysiological disorders. We were the first to show that lipid-soluble CO-RMs promote relaxation of blood vessels, inhibit coronary vasoconstriction and markedly reduce acute hypertension *in vivo*. Subsequently, we synthesized the first prototypic water-soluble CO-RM (CORM-3) and demonstrated its pharmacological properties against myocardial infarction, cardiac graft rejection, platelet aggregation and smooth muscle cell proliferation. In search of other classes of CO-RMs, we discovered that a boron-based compound (CORM-A1) liberates CO in a pH-dependent manner and that, under physiological conditions, releases CO at a slower rate compared to CORM-3. CORM-A1 reduces systemic vascular resistance and elicits cerebroprotective effects against seizure-induced vascular injury. Recently, we found that CO-RMs mitigate the inflammatory response in macrophages and microglia cells stimulated with endotoxin and cytokines both *in vitro* and *in vivo*. Thus, we have assembled a portfolio of biologically compatible CO carriers possessing different chemical and bioactive features. The D3 plans to develop novel CO-RMs derivatives (both boron- and metal-based) to improve their pharmacokinetic and toxicological properties and test their efficacy in *in vitro* and *in vivo* models of inflammation and neurodegenerative diseases (i.e. Alzheimer's). This project will be conducted in partnership with Alfama, a pharmaceutical firm based both in Portugal (Lisbon) and USA (Cambridge, Massachusetts). Although the pleiotropic actions of CO are gradually emerging and cellular targets are being proposed, the exact mechanism(s) of action by which "small amounts" of CO offer protection against inflammation and oxidative stress is unknown. Consequently, our efforts at the D3 will also concentrate on the identification of novel molecular targets of this endogenous gas.

**Transcriptional regulation of HO-1.** Another way to increase the intracellular production of CO and bilirubin is to amplify the expression of the HO-1 gene by selectively enhancing its transcription. Two molecular targets are central to the expression of HO-1 protein: Nrf2 and Bach1.

**Targeting Nrf2.** Nrf2 is a nuclear transcription factor that binds to a DNA consensus sequence known as "antioxidant responsive element" (ARE). This highly conserved sequence is present in the promoter region of several genes encoding for detoxifying and antioxidant enzymes, including HO-1. Under normal conditions, Nrf2 is retained in the cytoplasm in a 'silent' form by its repressor Keap1; however, the Nrf2-Keap1 complex is disrupted by oxidative stress leading to a rapid translocation of Nrf2 into the nucleus and a prompt expression of defensive genes. Loss of Nrf2 (Nrf2-deficient mice) is associated with a marked reduction of HO-1 resulting in increased susceptibility to oxidant- and inflammation-mediated cellular damage. We have reported that small molecules bearing electrophilic character such as the natural compounds curcumin and caffeic acid phenethyl ester (CAPE) can markedly induce HO-1 via Nrf2 activation resulting in increased protection against oxidative stress. We have shown that similar effects can be elicited by chalcones, naturally occurring flavonoids that contain chemical motifs also present in curcumin and CAPE. The scaffold of these naturally occurring compounds will form the basis for the design and synthesis of novel and more potent activators of Nrf2. The pharmacological activity and efficacy of the most promising Nrf2 inducers will be tested in established models of inflammation and neurodegenerative diseases.

**Targeting Bach1.** Contrary to Nrf2, which activates HO-1 expression, Bach1 is a recently discovered repressor of the HO-1 gene. This nuclear protein binds to the promoter region of HO-1 thus preventing gene expression by transcription factors. Bach1 contains heme binding motifs that, upon interaction with heme, lead to a conformational change and a decrease in Bach1-DNA binding activity. Thus, the repressor effect of Bach1 is lost in the presence of heme or other protoporphyrins and emerging evidence indicates that inhibition of Bach1 attenuates atherosclerosis and vascular inflammation through over-



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expression of HO-1. Notably, Bach1 deficient mice exhibit constitutively high levels of HO-1 in various organs under normal physiological conditions. Our plan is to exploit this mechanism of repression by designing porphyrin-like molecules or identifying new classes of agents that efficiently derepress Bach1 enabling the amplification of the HO-1 pathway. The most effective Bach1 inhibitors will be tested and validated (alone or in combination with Nrf2 activators) as anti-inflammatory and protective agents in our established models of disease.

**Inhibition of UDP-glucuronosyltransferase activity.** Bilirubin, one of the most important antioxidants formed in mammals, is eliminated following glucuronidation by UDP-glucuronosyltransferases, enzymes involved in the detoxification and excretion of xenobiotics in intra-hepatic and extra-hepatic tissues. UGT1A1 is the enzymatic isoform primarily responsible for the clearance of bilirubin. Therefore, a pharmacological approach that can be utilized to mimic the protective action of the HO-1 pathway is to induce moderately high levels of circulating bilirubin by inhibiting UGT1A1 activity. The idea finds a strong rationale in the fact that humans affected by Gilbert syndrome, a hereditary condition where a mild unconjugated hyperbilirubinemia is caused by mutations in the UGT1A1 gene, exhibit a reduced risk of developing cardiovascular disease and cancer. Interestingly, diabetic patients affected by Gilbert syndrome have a significantly lower prevalence of hypertension and decreased levels of glycated hemoglobin A1, triglycerides and C-reactive protein indicating that increased bilirubin is strongly associated with reduced vascular complications and inflammation. Our team will implement a program for identifying and validating small molecules that act as inhibitors of UGT1A1 activity. The assessment of these inhibitors as potential pharmaceuticals will be initially conducted in models of neuroinflammation; however, because of the reported beneficial activities of bilirubin in alleviating vascular dysfunction, the effectiveness of UGT1A1 inhibitors will also be explored in diseases where both vascular and neuronal components are equally important (i.e. diabetic neuropathy).

#### **Predicting biomolecular interactions.**

Protein-protein, protein-DNA, protein-lipid and protein-ligand interactions – especially binding – are crucial microscopic events both physiological and pathological biochemical pathways build upon. The free energy of interaction, calculated along some reaction coordinate, is the observable that describes this kind of events and connects the microscopic to the macroscopic frameworks. It inherently accounts for the complex interplay of the occurring physical mechanisms, the most ubiquitous and important ones being totally or partly electrostatic in nature. In fact, polar and Coulomb interactions, hydrogen bonding, hydrophobic forces and, more in general, solvent mediated interactions have a large electrostatic component. A detailed modeling of electrostatics and its effects is therefore essential to design molecules apt to disrupt, stabilize or compete with any given interaction and, ultimately, to interfere with any biochemical process. An accurate description of the electrostatic free energy of interaction in the previously mentioned examples of biological interest, however, is truly a challenging task, especially in aqueous environment. This is due to the difficulty in modeling electron density in the classical atomistic framework, the only one compatible with the simulation timescales typical of the biological processes. The complexity becomes exceeding in the modeling of electron redistribution – due either to molecule distortion or to the reaction to an external field – since the mechanisms that are involved are intrinsically quantum-mechanical in nature. On the other hand, free energy estimation is *per se* a challenging task, due to the intrinsic difficulty in simulating a biochemical system long and accurately enough to sample all its relevant configurations.

**Specific Aims.** This project will be devoted to the task of bringing the accuracy of the free interaction energy calculation to a level that can be comparable with experiments, building an enabling tool to be used in rational Drug Design. The activity will focus on the two following crucial aspects:

- i) the modeling of electrostatic and non-bonded interactions among biomolecules,
- ii) the refinement of already existing and promising “enhanced sampling” techniques to improve free energy estimation along a biochemical process.



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Methods used will range from *ab initio* techniques aimed at the calculation of electron density on a quantum-mechanical basis to advanced statistical techniques aimed at exploring new functional forms for the various kind of forces involved. The electrostatic potential will be mapped onto the molecular surface, as well as other possible observables of interest. This formulation should allow for fast resolution of Poisson Boltzmann equation over large systems via the Boundary Element method, and for an interesting surface based approach on rapid large-scale affinity estimation. As for point ii), the refined version of the enhanced sampling technique will be implemented in a specialized hardware architecture such as CELL BE, for which we already started a collaboration with the University of Bologna. The speedup provided by this implementation could be spent in a more thorough exploration of the configurational space and in the utilization of a more accurate, and potentially more computationally demanding, force field, as the one obtained from point i). The developed knowledge will serve both to in depth understand the nature of a biomolecular interaction of biological interest, and to design or screen small organic molecules aimed at disrupting or stabilizing a given interaction. This set of studies is intended to be general and will be tested on different classes of biomolecular partners, such as, for instance, transcription factors involved in the regulation of inflammatory and neurodegenerative disorders.

## DIAGNOSTICS

Concerning the diagnostic part, the main stream lines of the activity are described in the following.

### Multifunctional nanocarriers for biomedical applications

#### *Development of magnetic-fluorescent sub-micrometer beads for cell sorting applications.*

The early diagnosis of tumors (i.e. by detection in biological liquids of low concentrations of tumour markers) is a challenge that can be tackled by developing magnetic-fluorescent nanotools for cell sorting. A magnetic-fluorescent nano-system would perform at the same time separation and detection of cells or analytes while its nanoscale size would offer higher surface to volume ratio, thus higher sensitivity should be achieved. The aim of this research line is to develop magnetic fluorescent nanobeads (MFNBs) with specific requirements for cell sorting and multiplexing detection, such as: i) the beads must accumulate promptly to a magnet (within a few minutes); ii) the size of the beads must be within a few hundreds of nanometers to ensure high sensitivity; iii) the beads must have good stability in aqueous media, iv) it must be possible to include within the structure code molecules able to achieve multiplexing analysis. These MFNBs will be based on magnetic inorganic nanocrystals and on fluorophore molecules, the latter including either standard organic dyes, or oligothiophenes, or even quantum dots (QDs). The magnetization of the beads will be tuned by controlling the assembly of magnetic nanoparticles (MNPs) in small clusters using an amphiphilic polymer. The type of fluorophore inclusion in the MFNBs will depend on their nature: whereas organic molecules can be linked to the polymer used for clustering the MNPs, QDs can be clustered together with the MNPs. Optical and magnetic properties, colloidal stability and biocompatibility of the MFNBs will be studied and the beads will be explored in cell studies. First they will be tested non-specifically on tumor cells to evaluate their magnetic and fluorescent performance. Then their functionalization with specific vitamins (i.e. folic acid) and antibodies (i.e. CD44<sup>+</sup>/CD24<sup>-</sup>) will allow to assess the specific tumor cell recognition and separation efficacy of the MFNBs. The systems developed will be compared to commercial magnetic systems, for which no cell sorting tool that is both magnetic and fluorescent is available at present. Indeed for the commercial systems post fluorescent labeling is needed after the separation step to confirm the presence within the sample of certain cell populations.

The MFNBs will be of great use for isolating and identifying cells (like cancer stem cells) on a real patient biopsy. Based on the evidences that radiation therapy and chemotherapy both fail in the long run treatments (as they cannot kill sub-population of tumor-initiating cells), the existence of cancer stem cells has been hypothesized, and the existence of mammary stem cells has been demonstrated (the latter have been identified by their surface antigen expression, CD44<sup>+</sup>/CD24<sup>-</sup>). Those population have shown a resistance to both radio and chemo therapy. Therefore the ability to isolate and identify cancer stem cells within a tissue sample will be of great value in order to develop treatments that aim to eliminate cancer stem cells. We will apply the same type of nanosystems to isolate also other target molecules and cells from other biological samples (i.e. gastric liquids).



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#### *Magnetic stimulus-responsive carriers for controlled release of various agents.*

We will develop nanocarriers for a multivalent approach to cancer therapy. These will be based on magnetic nanoparticles (MNPs) combined with nanostructures that act as nanocontainers, which are able to encapsulate drugs and to release them under defined stimuli. The nanostructures will be designed for specific targeting and

treatment of tumor cells. The following key objectives will be targeted: a) Synthesis of size, shape, and composition controlled MNPs or magnetic nanobeads (MNBs), as described in research line 3A. They will be the active tools for hyperthermia tumor treatment, imaging and induction of the stimuli. b) Preparation of various types of stimulus-responsive polymeric nanocontainers for drug encapsulation, protection, and transport. c) Assembly of MNPs or MNBs with nanocontainers in order to merge in a single nano-object the two individual sub-units, each of them able to perform its task. d) Drug encapsulation and functionalization of the nanostructure's surface with specific ligands for targeting tumor cells. e) Characterization of magnetic performance and drug release of such nanostructures in tumor cell cultures in vitro.

We will prepare **stimulus-responsive polymeric nanocontainers** for drug encapsulation. Current chemotherapy treatments could be far more efficient if they could deliver the drugs selectively to the tumor. We will explore different polymeric nanometer-sized vectors (PNVs), which can act as nanocontainers for encapsulation, protection, and transport of chemotherapeutic agents. Issues related to the controlled drug release as a response to external stimuli will be addressed. **pH and thermosensitive hydrogels** for instance are polymeric nano-beads used as vesicles for controlled drug release. They are able to undergo volume changes under the effect of physical and chemical stimuli. Polymers that shows 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 tumor cells is highly acidic. We will develop nano-vectors that will swell at acidic pH. We will evaluate the best performing systems under the typical pH values of tumor cells. Challenging issues will be the control of the size of the vectors below 300 nm size, the drug encapsulation and the fusion of such polymeric nanocontainers with MNPs in order for them to be exploited in combined hyperthermia and drug release experiments. To fabricate magnetic hydrogel nanovectors (MHNVs) we will follow different strategies: a) We will exploit the swelling behaviour of the polymeric nanovectors to encapsulate both the MNPs and the drug; under the response to the external stimuli we will control the release of both the nanoparticle and the drug; b) We will coat the surface of the as-synthesized MNPs (either the MNBs synthesised in the research line 3A or the individual nanoparticles) with priming "polymer-brush" molecules. In a second step, a polymerization reaction will be promoted by initiator molecules (such as radical species). c) We will attempt the preparation of MHNVs by following a layer-by-layer method for the deposition of MNPs on top of pre-formed hydrogel nanovectors. Alternatively, on the MNBs synthesized above a layer by layer methodology will be developed for the encapsulation of the drug within polyelectrolyte layers. This procedure will allow tuning the number of MNPs entrapped within the nano-vectors, so that for instance it will be possible to build MHNVs that are strongly responsive to external magnetic fields. Such strategy should therefore lead to MHNVs that will be easily directable to a specific body site under the effect of a magnetic field, and/or that could show enhanced magnetic-field-mediated hyperthermia for drug delivery. We will encapsulate the drugs in such MHNVs by varying the pH and/or the temperature of the system. The MHNV with a magnetic core and a polymer outer shell can be exploited as template for the preparation of hollow stimulus-responsive materials for drug release. The magnetic core will be chemically dissolved and we will study the drug loading capability of the hollow nanovector.

#### *Development of fluorescent beads based on oligothiophenes.*

Many areas of clinical diagnosis, molecular imaging and molecular sensing require fluorescent probes that are stable, brighter than traditional fluorophores, non toxic and that can perform multiplexing analysis, making the development of



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optical code technology increasing attractive. We will develop polymer barcodes based on new emerging types of organic fluorophores, such as oligothiophenes (OTFs). These are oligomer structures of thiophene rings, with structure-dependent emission spectra (i.e. related to the number of rings and to their functionalization). The choice of OTFs has been suggested by their features that make them a viable alternative to traditional organic dyes in biomedical applications. OTFs, besides being characterized by high photochemical stability and low toxicity, have broad excitation spectra and therefore it is possible to excite with the same source different OTFs molecules emitting at different colours, allowing for easy multiplexing analysis. To increase the number of colours available for multiplexing analysis, different OTFs molecules at different concentration ratios can be encapsulated within the same polymer beads. The resulting beads should exhibit a broader range of emission colours and higher stability compared to the initial OTFs. The effect of the encapsulation over the optical stability, the optical performance of the fluorescent beads as barcode system, the cell interaction and cell imaging are all issues that will be addressed.

### **Solid State Nanobiotechnology Devices for diagnostics**

The increasing demand for discovering new biomarkers of human diseases in diagnostics, as well as molecular mechanisms which are at the basis of diseases, require new technological efforts ranging from biochips technology (possibly integrated with microarray platforms) to single molecules analyses, focusing on the development of specific assays for high-throughput, multiplexed biomolecules detection. Furthermore, the production of new biochips leading to increased multiplexed capability and sensitivity may open up new frontiers in the fields of clinical diagnostics and biomarker discovery.

This research area aims at the development of innovative technological approaches, allowing the production of new biodevices for genomic and proteomic applications. We will exploit several nano-biotechnological strategies, by combining top-down and molecular self-assembly approaches, with molecular biology tools, along with the production of high-density biomolecules arrays and static plastic chips. Micro- and nano-patterning of biomolecules onto different inorganic and plastic substrates, combined to innovative molecular biology approaches (including production of engineered proteins, construction and screening of biomolecular probes by phage display technique) will be also investigated in order to realize innovative hybrid interfaces to be applied for genomic and/or proteomic analyses. We will investigate the immobilization and localization of specific bio-molecules (such as oligonucleotides, proteins, cells) onto suitable substrates, with very precise spatial control, while ensuring a good density, uniformity and functionality of the immobilized biomolecules. Such approaches will exploit molecular interactions onto nanostructured substrates by combining several nanofabrication techniques (such as optical and E-beam lithography, soft lithography, molecular self-assembly), leading to the formation of highly packed “bioactive interfaces” (in terms of density of probe molecules) to be applied for bio-recognition of target species. The bioactive substrates (micro- and nano-arrays of DNA, proteins, peptides, membrane receptors, etc.) may be particularly promising for performing highly parallel analyses (high throughput screening) of target molecules, such as DNA, antigens and ligands. Moreover, the possibility to localize single biomolecules onto nanostructures, while maintaining functionality, may also lead to the development of novel and powerful investigation tools, that allow a deeper insight into some specific biological processes or molecular mechanisms. A wide range of different materials (e.g., silica, glass, quartz, plastic materials) will be investigated for the realization of biochips for analytical and diagnostic applications. Particularly, we will focus on the development of suitable and reliable chemical surface strategies (i.e., silane-based chemistry, avidin-streptavidin chemistry, etc) for biomolecules patterning onto plastics. Plastic materials show advantages for low cost and in-batch manufacturing as they can be easily processed by various nanotechnological techniques (such as standard or soft lithography) and integrated into microfluidics platforms.

Another aim of the project is the realization of plastics substrates for DNA and protein arrays and biocompatible plastic devices for genomics and proteomic analyses (i.e. real-time PCR, tumor markers biorecognition). The possibility to exploit specific properties of plastics (e.g., as resist materials or in combination with colloidal nanoparticles) may also allow the realization of “smart plastic material” to be used as tailored integrated platforms for bio-recognition and detection of





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biomolecules. Such approaches will be exploited for the realization of arrays of functional membrane receptors (for instance, GPCRs receptors) to be applied for highly parallel screening of analytes/drugs/ligands by using microfluidics networks. Such analytical set-up, combined with optical detection systems for multiplexing and real-time analyses of binding events (using fluorescent ligands and displacement processes), and integrated into plastic chip connected to microfluidic networks will be compared, in terms of efficiency and sensitivity, with conventional analytical methodologies. All these studies will be supported by molecular biology techniques such as production of properly engineered recombinant proteins and realization of suitable probes by phage display technique. Such strategies, along with the development and implementation of high-density molecule arrays, will be supported by innovative optical imaging techniques recently developed within the IIT network, which allow, under particular conditions, to obtain a significant increase of the emission signal of fluorescent markers (thus improving the detection sensitivity), and to perform real-time studies of biomolecular interactions. In this frame, we will further exploit the use of nanopatterned metallic substrates suitable for MEF or SERS applications, to be applied for DNA and protein microarray technology.

#### **Lab-on-a-chip for ultrasensitive automated diagnostics**

The goal for this activity is the design and realization of handheld, battery-operated biochips based on surface-acoustic-wave (SAW) driven micropumps suitable for automated, high-throughput, cost-effective diagnostics.

The chip will couple the SAW-induced pumping mechanism we recently demonstrated (IIT-patent T02007A000554) with original ultra-high sensitivity detection protocols that are being developed within IIT. This combination will constitute a novel enabling technology for large-scale clinical screening with extreme resolution, down to single-molecule, single-interaction detection and monitoring. Full portability and automation will make these devices suitable for point-of-care and even independent patient use. In a different configuration, these systems will also make it possible to carry out cell-level high-sensitivity molecular-level studies for drug and general biological testing that will not require laboratory animal sacrifice.

Handheld lab-on-a-chip systems will be realized that are based on surface-acoustic-wave (SAW) driven on-chip micropumps. We recently demonstrated that, using a smart-device configuration, SAWs can lead to very efficient fluid motion into microchannels, paving the way to battery-operated Lab-on-a-Chip devices. This technology guarantees true portability and avoids the need for complex pumping systems that severely limits the exploitability of traditional lab-on-a-chip architectures. The present IIT-patented approach will be developed into high-density micro/nanofluidic networks and coupled with ultrasensitive detection protocols that are currently being demonstrated within IIT. The overall result will be portable, fully automated systems allowing highly-sensitive biosample analyses down to single molecule and/or single interaction resolution. These molecule-level studies will also be made possible in highly controlled cellular cultures for drug testing or other molecular biology/medicine investigations that will not require live laboratory animals.

This research activity will target the three separate functional blocks needed for the implementation of the diagnostic systems:

- 1) **Fluidics:** Multichannel geometry will be realized exploiting full biocompatible, inert materials. The fluidic path will drive extremely small quantity of fluids (down to fl) toward diagnostic active areas by the interaction with SAWs. For sake of example, the network could include: conduits with lateral dimension ranging down to less than 1  $\mu\text{m}$ ; micro-chambers for mixing and collecting; active and passive micro-mixers along the channels; active and passive valves for addressing fluids to specific diagnostic paths. Chip biocompatibility will enable the integration of bioreactors designed for living cell and tissue high-resolution analyses. These systems will allow monitoring single-molecule behavior in selected living cells in parallel and under highly controlled physico-chemical conditions.
- 2) **Biomaterials:** A vast range of biocompatible and/or biodegradable substrate materials and geometries will be made available for integration with the fluidic networks. For sake of example, thermoplastic polymers and copolymers



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[examples are polystyrene (PS), polylactic acid (PLA)] and non-conventional nanolithography techniques (i.e. nanoimprint lithography, hot-embossing, electrospinning) will be tested for optimized fabrication protocols yielding 2D/3D scaffolds with controlled nanotopography and rigidity. Additionally, the bottom layer will be integrated with nano-electrodes in order to provide local electrical control and/or detection over selected cellular regions for the study of the biological/biomedical action of specific molecules.

- 3) **Immobilization:** Selective, high-resolution chemical functionalization will be provided to the host substrate and to the micro-/nano-channel walls. Chemical functionalization will benefit from the smart diagnostic nanotools being developed within IIT. These highly specific nano-sensors will be positioned on the chips surfaces with high-spatial resolution (down to less than 100 nm), leading to original recognition protocols within microfluidic chips. Functionalized areas may also include: binding sites for selected biomolecules, adhesion proteins, guiding chemical cues, cell-repellant molecules etc.

The three described technological platforms will be eventually applied in a synergic way to obtain functional chips.

### **Nanomedicine tools for smart diagnostics and therapeutics**

Nanomedicine, i.e. the use of nanometric materials for specific diagnostic and/or therapeutic purposes, represents the future strategy for improving human health. The market of nanomedicine is expected to amount to more than \$3.4 billion in 2015. Yet, the concept of an independent nanodevice that can selectively recognize the source of a pathology at the intracellular level is still in its infancy. Following this perspective, the project goal is the development of an array of nanomedicine tools. Once in the body, these devices will be able to deliver to specific cells “molecular machine” (*payload*) that can recognize one or more biomolecular targets of malignant origin, and act thereupon removing the cause of pathology. This general strategy is expected to lead to non-conventional therapies tailored to patients’ diseases with low or null side-effects. Due to the inherent long term character of such a study, we expect this program to exceed the length of the present strategic plan. We thus expect to build the knowledge basis of the field in the next three years, and then to target at some clinical application. Namely, within the next 3 years we plan to identify the structure of the nanodevice and all its sub-module, then to demonstrate the nanodevice functionality in cultured cells (year 6) and, finally, to make these tool available for clinical trials as non-conventional diagnostic/therapeutic tool for a relevant pathology (year 10).

The architecture of these tools will be modular in order to allow for different cellular/molecular targets and intracellular activities (e.g.: signaling, triggering apoptosis, etc...). Accordingly, these nanosystems will comprise some or all of the following elements:

- a) a shell/coating/bound motif capable of interacting with the cell membrane and allowing the translocation of the payload to the cytoplasm upon (i) external (e.g., electromagnetic drive) or (ii) local-environment (e.g., enzymatic hydrolysis) stimuli;
- b) a recognition molecular motif capable of addressing the nanosystem to its final destination in the living organism;
- c) a recognition molecular motif capable of biding the nanosystem to the domain of interest within the cell;
- d) a *payload* (drug, multifunctional probe for diagnosis and reporting).

We envision 3 main R&D research lines:

**Shell engineering.** Molecules will be designed and engineered that can act as nanocarriers for the intracellular delivery of selected payloads. The focus will be devoted to: a) cell-permeating peptides based on lysine/arginine-enriched structures; b) polymeric materials, especially of bio-erodible/biodegradable nature; c) semiconductor/metal nanostructures, capable of highly selective and efficient interaction with externally-applied electromagnetic fields. Particular attention will be devoted to engineered molecular sequences, of organic or inorganic origins, that can modify their properties upon local or external stimuli.



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*Biomolecular target identification and recognition.* Specific biomolecular targets (e.g. proteins, DNA sequences, membrane components, organelles) linked to specific pathologies will be selected. Particular attention will be devoted to multiprotein complexes, whose involvement in the evolution of pathologies and cell degeneracy is

increasingly acknowledged in molecular biology. Accordingly, the formation and function of the selected multiprotein complexes will be studied at single-molecule level by high-resolution biophysical methods. The second step will address the engineering of new compounds that are capable of recognizing these target biomolecular complexes at cellular level. Here, the approach will involve: a) *in silico* screening and “maturation” of recognition sequences, mostly derived from natural compounds (e.g.: antibodies), b) molecular-evolution methods, to tailor the recognition affinity, c) *in vivo* (cultured cells and whole organisms) assays to test high-recognition affinity.

*Payload.* An array of organic or inorganic molecular nanostructures will be designed and engineered: a) diagnostic probes sensitive to structural change/activity/interaction-complexing of cell biomolecules (e.g.: fluorescent reporter molecules, semiconductor nanostructures, contrast agents); b) compounds capable of triggering cell death or protein repair upon local or external stimuli; c) bioactive molecules with high therapeutic activity. We shall particularly focus on methods that can amplify the recognition signal, for example by boosting the local concentration of active nanostructure (e.g.: dendrimer-based systems). Additionally, the efficiency of payload delivery and its capability to exert its diagnostic/therapeutic activity will be investigated by state-of-art single-molecule imaging techniques and high-resolution biophysical methods.





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## **B.4 PLATFORM: ENVIRONMENT HEALTH AND SAFETY**

**Operating units/departments:** NC-Ge, NBT-Ge, NNL-Le, NEST-Pi, IFOM-Mi, PoliMi, CRIB-NA

### **General overview of the platform activity**

Nanotechnology has become an opportunity for big companies, University spin-off and start-up companies to develop new products for applications that are meant to replace in many cases conventional materials/devices. Indeed, nanotechnology results in an enabling platform technology for applications impacting all industrial sectors from Chemical Industry to Semiconductors, from Pharmaceutical to Automotive. Nanotechnology production processes and products, however, also pose potential risks, since the extreme miniaturization requires an unprecedented level of accuracy in terms of process and quality control. Indeed functionality in these systems depends on nanosized features and nanosize control is therefore a crucial requirement. Consequently a need emerges for a multidisciplinary effort aimed at assessing the biosafety characteristics and environmental impact of nanomaterials and their production processes. Lately, the debate about these issues has become vigorous and rather controversial: the safety in the use of nanostructured materials indeed has to face the limited knowledge of the mechanisms of biological recognition occurring at the nanometric interface between materials and cell. The nanometric size of the material may activate mechanisms of cellular uptake different from those already known of fago- and pino-cytosis and these mechanisms may be activated/modulated by the size, shape and charge of the nanometric material. It is largely agreed that a better understanding of the mechanism of cellular uptake is required both to assess the real biological risks coupled with the use of nanomaterial (nanopathology and nanotoxicology) and to engineer carriers able to improve the medical practice. As a matter of fact, all the most advanced countries in the G8 plan to have a standard safety certification and a risk management strategy for nanoproducts in the next 5-10 years.

In this framework IIT is in a unique leading position to drive a coordinated effort by different laboratories in the network, merging nanotechnology, biochemistry, medicine and characterization expertise, in order to set the future standard for nano-safety. Indeed, the present platform aims at the development of an array of nanotechnology essays to recognize potential biosafety and environmental-unfriendly risks connected to nanotechnology products. The platform has a strong multidisciplinary character, as the understanding of material properties at nanoscale entails different aspects of their interactions with living organisms and the environment. The interaction of nanomaterials with biological bodies (cells) will be particularly considered, as it represents the first step towards the biosafety assessment. For this platform IIT will exploit the combined knowledge of the nanotechnology and life science laboratories in the network, together with the D3 and Neuroscience Departments to set up a program that covers the entire range of activities, from the nanoparticle synthesis to the in-vivo risk assessment

It is forecast that over the next 5 years this research activity will help: 1) the development of the market for qualitative nano-production in Italy, 2) the prevention of mistakes by users of nano-products, 3) the rejection of products that could cause harm to the user or contain a potential threat to the user's health or the environment and 4) to set up the standard for methodology, quality and risk assessment.

The main research needs to be addressed are:

- instruments, metrology to bonols and analytical methods for detection of nanomaterials in biological systems, and their interactions and mutual modifications.
- Assess the size, shape, concentration and composition dependence of the biochemical interactions between nanosystem and cells.
- Assess the process of absorption of nanomaterials in the human body, and the uptake mechanisms versus the shape, size, type of contact (ingestion, respiration, skin-diffusion etc.).



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- Develop standard assay both in-vitro and in-vivo with representative classes of nanoparticles to simulate most typical environmental conditions for uptake (eg C-based particles for traffic, metal particles for heavy-working environment, oxide particles for cosmetics etc.).
- Understand the interaction mechanisms between the nanosystem and the body at molecular, cellular and tissue level.
- Understand the nanoparticle-environment relationship.
- Assess the human-environmental exposure.
- Build a risk management strategy and a nano-safety standard.

Clearly, this platform benefits from the interdisciplinary know-how within IIT, particularly the combination of nanotechnology expertise in nanoparticles specimens synthesis, the advanced characterisation tools for detection and the life science know how (Neuroscience and D3) for assessment of biological interactions in-vitro and in-vivo. The platform activity will be based on the following research lines:

#### *Detection in biological matrices*

The research activity will be focused on the development of standard procedures of nanomaterial characterization and the identification of some nanostructures that could be employed as reference materials for in-vitro and in-vivo essays. This activity will make use of state-of-the-art instrumentation that is meant to provide the complete physical, chemical, and biochemical parameters related to the nanocompounds to be analyzed. In particular, attention will be devoted to methods aiming at the identification of purity, size, poly-dispersion, nanofabrication yields, conductivity, diffusion parameters in biological fluids and air, surface adhesion properties, degradation in environmentally-simulated conditions, interaction with biomolecules (proteins, DNA, RNA, membrane lipids), and activation of biological pathways potentially leading to pathologies.

In addition, methods to detect nano-objects in biological matrices, in the environment and in the working place will be developed to accomplish the highest sensitivity and resolution in the measurements.. This encompasses both characterisation in cells, and particle identification in various environments, including optical methods, magnetic methods, advanced microscopies, size and composition assessment, both in-vitro and in-vivo. In this context, several innovative detection techniques, such as MEF, SERS, FRET, FLIM, 2-photon and holographic microscopy, AFM imaging and force spectroscopy, along with the development of suitable nanomaterials, will play a fundamental role. Development of new fluorophores for high yield emission, either molecular or inorganic with low toxicity and high biocompatibility, will be a primary issue to enable ultra low signal detection in different environments. Also, new magnetic nanoprobe and advanced NMR and fMRI tools will play an important role for in-vivo assessment of the nanoparticle-cell interaction.

Biosensing devices monitoring the thermal, mechanical and electrical characteristics of cells in the presence of different nanoparticles will also be developed, along the line of the lab-on-chip technologies investigated within the D4 platform. Overall, this activity should provide a systematic and broad understanding of the interaction of nano-objects with cells, in-vitro and in-vivo, versus the size, shape, composition and surface functionality of the particle. Also it should elucidate how the intake, the degradation and the uptake of the particles is modified by the chemical and physical properties of the cellular environment.

#### *Intake and interaction at cellular level*

This activity relies on animal models to study the different intake processes, eg respiration, skin diffusion, ingestion, of particles with different shape, size, composition and surface functionality, exploiting relevant classes of nanoparticles representative of major environmental conditions. The target is to evaluate the response of the immune system to the nanomaterial and to investigate the various biological pathways leading to diseases and mutation at the DNA level. The complex scenario of the bio-nano interactions in living systems is multi-parametric, so that the in-vivo studies will be performed systematically with nanoparticles having different size, shape, composition, functionality and aggregation state.



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Though a wide in-vitro experimental activity will be performed in all the laboratories involved in the platform, the in-vivo studies will be concentrated in the animal facility of the central research laboratory of Genova.

These studies should create the knowledge basis for the second phase of the program, which presumably will involve companies, industries or universities interested in the assessment of their nanotechnological products. These entities will provide their end-process nanoproducts accompanied by documents reporting the related properties, the employed production process, and the in-house performed experiments on both the nanoproduct functionalities and the bio-safety character. The nanoproducts will then start their analytical pathway in our research unit.

A series of tailored activities and initiatives will follow:

- Assessment that the warranted characteristics really exist, that the nanoproduct is really constituted by nano-active elements having some peculiar property and that the application results are “safe” from toxicological aspects and that it is “biosafe”;
- Assessment of the production protocol (nanoproduct yield, presence of contaminants, the role of these contaminants from a health-care point of view, disposal and safety of the materials required for the nano-synthesis etc.), obtaining a reliable standard for the safety of products and processes. To this aim the nanochemistry facility at Genova Central Research Laboratory and the chemistry and biology facilities in the network (NNL-Le, NEST-Pi), will play a crucial role in identifying and synthesising prototype nanosystems for the in-vitro and in-vivo essays.
- Extensive analysis of the nanoparticle/cell interaction will be undertaken, on prototype cell lines (encephalic cells, epathic cells, lung cells) with representative classes of nanoparticles (oxides, metals, carbon), to reproduce typical uptake and environmental conditions met by humans in typical environments (living, working etc.). This activity will exploit the biochemical and biological laboratories and the advanced physical, chemical and biochemical characterisation laboratories existing in the IIT network. In-vivo experiment to be carried out at the animal facility of the Central Research Laboratory will complete this fundamental assessment work.

### *Risk Assessment and Management*

The above activity has quite a potential for industrial consultancy. We forecast the following activities as a fall out of the assessment risk phase described above:

- Provide consultancy to producers on the nanomaterials use (including assistance to manufacture and export of domestic, competitive nano-industry products), support in acquire knowledge on materials characteristics, enable this way an increased visibility of nanoproduct properties (active marketing), .
- Bio-safety studies, to guarantee that the interaction of nanoparticles with living tissues is sufficiently characterized to certify their safety and lack of secondary effects.
- Determination of the procedures related to safe disposal of these nanomaterials at the end of their life-cycle in order to evaluate and minimize their impact on the environment.

Owing to their special relevance, the assessment of the interactions of supplied nanomaterials with biological bodies (e.g. cells) will comprise a key part of the research activity. Here, we envisage two major steps:

1) Verification of possible cytotoxic effects on the cells/tissues directly exposed to the particles. To do this, we shall make use of the cell/whole organism imaging platforms developed by NEST and involving the realization of fluorescent or light-active probes localized regioselectively in the biological specimen and providing a sensing activity at high spatio-temporal resolution.

2) Verification of hidden secondary effects caused by the entrance of the nanomaterial into long range transport systems that might deliver the particles to locations far away from the site of entrance, and therefore cause bioeffects in unexpected targets. Note that an important long range transport system is constituted by nerve tracts that potentially could uptake and transport the nanoparticles to the peripheral and central nervous systems, causing remarkable brain alteration and disease.

In a typical scenario, we shall apply a multi-tiered strategy based on both *in-vitro* and *in-vivo* model systems. Cellular assays will be based on the usage of the appropriate primary cultures where cytotoxicity can be assayed in a variety of conditions.



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When appropriate, we shall develop high- throughput screenings based on fluorescent reporters of cellular function to test cells viability in a large variety of conditions in a short period of time. If the integrity of the tissue is desirable, in-vivo testing can be performed. The technology that will enable the application of fluorescent probes/nanomaterials will be the in-vivo two photon microscopy. This gives low invasivity and excellent penetration within living tissue. This will be crucial to study the secondary effects due to the transport of the nanomaterials to different body regions. It is worth stressing that, since the transport from the olfactory epithelia is an avenue of access through the blood-brain barrier, particular attention will be devoted to interaction of the nanocompounds with this cellular family



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## B.5 PLATFORM: SMART MATERIALS

**Operating Departments/Units:** RBCS-Ge, NC-Ge, NBT-Ge, NCS-Pr, NNL-Le, NEST-Pi, PoliMi, CRIB-Na, PoliTo

### Introduction – Composite Materials

The technological development points towards a synergic performance of a combination of different materials.

The combination of distinct materials, with so far well studied and established properties, appropriately merged together, are expected to lead to novel materials that can preserve the properties of the individual components, but furthermore will exhibit characteristics that would not be possible individually. Such composite materials impact upon many areas, including transport, bioengineering and medical instrumentation, civil engineering, mechanical tools, fashion, packaging, fire-retardant electrical enclosures, and sport.

The fundamental materials essential to make all the aforementioned applications possible are plastics and nanostructures. The plastics are polymeric materials of high molecular weight that exhibit inherently excellent processing characteristics together with good mechanical properties. They are lightweight and low cost. These characteristics make them ideal candidates for manufacturing and product design. They are classified in different ways according to the property that is relevant for technological developments. Examples include thermoplastic and thermoset resins, electrically conductive polymers, polymeric fibers, and biodegradable or biocompatible plastic materials, etc. All these classes of plastics form a common starting point for composite materials when combined with a vast variety of nanofillers. By preserving the inherent capability of the plastics for processing and manufacturing, without sacrificing their mechanical properties, and without adding excessive weight, the resulting composite materials combine unique desirable properties unavailable in the matrix or filler material alone.

The integrated strategy of IIT relies on the unique combination of nanochemistry and material science, which places the Institute at the leading edge in this field. The growth of nanostructures and nanocrystals of complex shapes (dots, wires, branched nanostructures) and compositions (i.e. bimagnetic nanoparticles, magnetic-fluorescent nanoparticles, core/shell nanoparticles, inorganic nano-barcodes) is carried out by different methods such as solution techniques (both under conventional, i.e. heated batch-type flask reactor, as well as supercritical, hydrothermal, and microwave irradiation conditions), sol-gel approaches and chemical vapour deposition. The growth facility benefits of the large scale characterisation laboratories for advanced structural and compositional analysis of such nanostructures (X-ray diffraction, HRTEM, HAADF, TEM energy filtered imaging, spatially resolved EDS, electron tomography, XPS, X-ray absorption spectroscopy) and for optical, magnetic and transport characterization. The material science laboratories will exploit the nanofillers to develop composite materials and nanostructured systems with customised chemical, mechanical and biological properties. Using these components, the smart material platform can tackle a wide range of material science oriented problems, ranging from robotics to aerospace. The mainstream research lines will be the following:

#### *Composites of polymers with nanoparticles and fibers: Nanoparticle Composites*

Over the past 50 years the need for lightweight, but strong and resistant materials in many fields (e.g. aviation and aerospace), has led to the very successful use of carbon fiber reinforced plastics. These compounds consist of rigid and high-strength carbon fibers bonded into a polymer matrix, to give a combined material that is extraordinarily tough and lightweight. Nevertheless, the need for further improvement of the performances of the manufactured products combined with numerous new desired properties, has led to significant efforts to find new synthetic approaches for nanoscale structures that form new components for nanocomposite materials.

The most promising candidates for **nanofillers** in the nanocomposites materials are the **colloidal nanoparticles**. They can change their chemical composition, shape, and size by inducing small variations in the synthetic process, and therefore, they can be tailored very precisely according to the desired application. The control over the synthesis of the colloidal



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nanoparticles gives a great variety of possibilities in terms of properties (optical, thermal, mechanical, electronic, magnetic) that can be tuned over large ranges. The properties of nanocomposite materials depend not only on the properties of their individual components but also on their interfacial characteristics. This is another strong advantage in the use of colloidal nanoparticles as nanofillers in the nanocomposite materials since their surface properties, and thus their interface with the plastic matrix, can also vary. Indeed, during the preparation of the nanoparticles their stabilization is achieved using organic molecules, ie the surfactants. This surface modification of the nanoparticles decreases their surface free energy, and thus reduces their tendency for aggregation. Preventing the nanofillers agglomerate forming before their mixing with the plastics is possibly the most important step in order to achieve good dispersion, and thus, homogeneity of the final nanocomposite material. In addition, the nanoparticles interact with the polymeric molecules through the surfactants bound to their surface. Therefore, the proper choice of surfactants compatible with the matrix is essential for the enhancement of the interfacial adhesion between the plastic matrix and the nanofillers, through non-covalent bonding (van der Waals forces, hydrophilic interactions), that naturally promotes a better degree of dispersion of the nanocrystals into the resin.

The use of nanocomposites with colloidal nanocrystals as filling materials is targeted at producing mechanically reinforced, lightweight components, that can simultaneously exhibit electrical or thermal conductivity or magnetic response, depending on the application. Such materials are expected to be used extensively in a variety of diverse fields such as robotics, construction, sports, defense, products for uses in housing, dental fillings, transportation etc. Specific examples that describe the benefits of the nanocomposites follow: Concerning the *transportation industry*, the substitution of the classical compounds based on metals or on traditional composites by the improved lighter nanocomposite materials, will result in a better fuel economy. Moreover, the use of nanocomposites in vehicle parts is expected to improve processing ability, manufacturing speed, and dimensional stability to environmental and thermal changes. Another example is related to the *storage of information* where nanocomposite with fillers having magnetic properties can be used as high density magnetic storage media, that are easily processable and with highly increased areal bit density. In the case of electronic devices, such as *photovoltaics or light emitting displays* the performances of conjugated polymers can be improved by using conductive or semiconductive nanoparticles as fillers, to increase the power conversion efficiencies. For such applications the capping molecules of the nanoparticles should be carefully tailored in order to not insulate the particles from the matrix. Furthermore, nanocomposites could be used as repeated *self-protective materials*. In the case of cracks introduced into the material, the nanoparticles could migrate to the cracks, potentially restoring the mechanical properties of the composites. The driving force for this behavior could be the entropy of the system, since the polymeric chains can gain greater conformational degrees of freedom by driving the particles into the cracks. The nanocomposite system is expected to behave autonomously, localizing the nanoparticles at the damaged or defective sites. At the same time nanocomposites can also be *self-repairing materials*. Using capsules with monomeric fluid and catalysts dispersed throughout the polymeric material, they can burst and the induce fluid flow into the crack region, where a propagating crack encounters the dispersed capsules. In collaboration with the catalyst that can initiate a polymerization reaction, a polymeric patch can be introduced into the crack.

Nanocomposites can also be employed as coating materials, changing the surface properties of different systems. Such coatings can be used as flammability retarders. Another possibility is hydrophobic enhancement of a nanocomposite surface, that can diminish the extent to which water would be transmitted to an underlying material. Such a property, combined with possible gaseous barrier properties, due to various gas-nanoparticles interactions, can result in the use of nanocomposite-based composites as packaging materials in future years.

#### *Nanofiber composites*

Another class of nanomaterials that exhibit unique structural and chemico-physical properties, and could be fundamental fillers in nanocomposite systems are the one-dimensional (1D) nanostructures **polymer nanofibers**. The nanofibers are promising candidates for the structural reinforcement of their polymeric matrices as they increase significantly the degree of interaction between the fillers and the surrounding matrices with respect to conventional, micrometer-size fibers. They also can exhibit intriguing characteristics concerning their radar absorption properties. To act as efficient scattering/absorption centers for radar/microwave radiation (frequency in the range of 2-12 GHz), particles must exhibit an aspect ratio between  $10^2$  and  $10^3$ , which is well matched by nanofibers with diameters in the range of tens to hundreds of nanometers and with





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lengths of 50-100 micrometers. The ultra-high surface/weight ratio of polymer nanofibers (up to  $10^3 \text{ m}^2/\text{g}$ ), which is practically the state-of-the-art for high-volume processable nanomaterials, further contributes to effective absorption properties. It is also expected that upon incorporation in a matrix of polymeric nanofibers in a completely random configuration, they can effectively act as a sound-absorbing medium in a wide range of sound frequencies (especially below  $10^3 \text{ kHz}$ ). Nanofibers exhibit unique structural and chemico-physical properties, finding applications in a variety of fields. In recent years, one-dimensional (1D) nanostructures such as polymer nanofibers have seen increasing interest, because of their smart properties which make them useful for many applications, including textiles, micro-electro mechanical systems, sensing and filtering elements, microfluidics, artificial tissues, and optoelectronic. Nowadays, also the flame retardant character of nanocomposite materials embedded in networks of nanoscale particles and fibers is well-established.

More specifically, nanofibers prepared by electrospinning can be used as light and flexible building blocks of high-performance devices and nanocomposites, filtration membranes, and scaffolds for tissue engineering. In fact, while polymer nanofibers can be fabricated by diverse methods, including polymerization, in nanoporous templates, dip-pen lithography and nanofluidics, only electrospinning assures low cost and high throughput production. This technique uses the electrostatic repulsion between surface charges to continuously reduce the diameter of a viscoelastic jet. Electrospinning is indeed the technology of choice for realizing nanofibers for its simplicity and versatility (it can be tailored –by using new architectures of capillaries or suitable processing parameters) in order to control the deposition and the orientation of the nanofibers, their integration with microfabricated surfaces and the realization of superstructures. In particular, polymer nanofibers realized by conjugated polymers are well-suited to incorporation in thermoplastic or thermosetting resins for the realization of nanocomposite materials, with significantly increase the degree of interaction between the fillers and the surrounding matrices with respect to conventional, micrometer-size fibers. Nanofibers are excellent building blocks for structurally reinforced materials. Another important feature relies on their moderate conductivity characteristics (especially when realized by conjugated conductive polymers). Typical measured conductivity values, up to  $10^{-3} \text{ S cm}^{-1}$ , enable the effective absorption by the nanomaterials, while higher, metal-like conductivities would preferably result in light-reflecting surfaces, thus allowing a wide tailoring of the resulting electromagnetic properties. For analogous reasons, and due to the typical random configuration taken by electrospun nanofibers in mats samples, they can effectively act as a sound-absorbing medium in a wide range of sound frequencies. Within this activity a primary target is to reduce the surfacedefects and to increase the reproducibility of the fiber. To achieve this electrospinning processes have to be developed in an inert atmosphere, controlled in terms of oxygen content, temperature and humidity. In addition, both the experimental set-up and the process parameters will be implemented to control both the deposition and the orientation of the fibers, and hence manage the resulting porosity of the filtration membranes. In the facility, polymeric fibers can be produced with an average diameter in the range 50-1000 nm. These can be characterised by high-resolution scanning electron microscopy to evaluate all the morphological features (i.e. diameter distribution, porosity degree on the single fiber surface, average resulting porosity of the membrane, and surface roughness of the polymer interfaces) and by infrared spectroscopy to define the chemical composition before and after electrospinning. The single fibers, mats, tissues, and assembled nanocomposites can also be characterized by scanning electron and atomic force microscopy, force-distance, and optical spectroscopy in order to determine the best processing parameters in terms of applied electrospinning bias, interelectrode distance and geometries, environmental conditions, and solution parameters (concentration, viscosity, conductivity, etc.) for realizing smart and switchable elements and surfaces, and next-generation optoelectronic and nanoelectronic devices, including solid-state lasers and field-effect transistors. In particular, the fibers orientation will represent the crucial point to employ the carbon nanofibers as fillers for the structural and functional reinforcement of the polymeric compounds both in the microelectronic industry for the generation of low voltage and high-output currents, and in the textile, housebuilding and implants fields. The nanofibers will combine the excellent properties of the polymeric nanofibers in terms of simplicity, low processing cost, high surface/volume ratio, and high mechanical resistance, with the versatility and the electric conductivity of porous materials which are excellent candidates for sensing, catalytic and electric applications. In particular, the unusual combination of high mechanical strength, high surface/volume ratio and electric conductivity, will render the nanofibers excellent candidates as materials employable in; the energy-saving field as anodes for rechargeable batteries and superconductors, the synthetic



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and rubber industries as building blocks for opto- and microelectronics, for tissue-engineering, and as supports for filtering and high temperature catalysis.

#### *Composites of polymers with responsive fillers: Responsive Composites*

In the case of the smart composites the plastic materials will no longer exhibit the usual passive behavior, but instead, they respond to external stimuli such as humidity, temperature, solvent polarity, light, pH, or electric field. In addition, this response can be reversed and the materials can recover their initial properties, as soon as the stimulus is reversed or disappears. To create these smart composite materials the plastics should be combined with responsive organic molecules or inorganic nanocrystals, that can transfer their reversible properties directly or indirectly to the host matrix.

One of the most important applications of the responsive composites deals with the conversion of the input stimulus into mechanical work. Such systems are targetted at the operation of MEMS, artificial muscles, and robotic systems, that are conventionally built by wiring microcomponents with external electronics where actuation occurs by the conversion of electrical to mechanical energy. The use of lightweight but robust plastic materials for these applications, where metallic parts are typically used, would improve significantly the processing ability and the operational capability of the systems. Responsive molecules that can be used as the fillers in the polymeric matrices are the photochromic or thermochromic molecules. Photochromism or thermochromism are defined as a reversible transformation of chemical species, induced by electromagnetic radiation or heat, respectively, between two states (isomers) having different structures, and thus, light absorption bands in distinctly different regions. When photochromic or thermochromic molecules are incorporated in a polymeric matrix the chains of the polymers respond to the structural change of the molecules in such a way that the macroscopic dimensions of the plastics change reversibly. Responsive composite strategies can also be designed by imitating some biological systems. A recent research example is inspired by the sea cucumber's self-protection strategy. The inner dermis of the sea cucumber is composed of collagen nanofibers in a viscoelastic matrix of fibrillin microfibers and, upon danger, the animal produces chemicals that trigger the formation of interactions between the nanofibers, making the sea cucumber stiff. A polymer nanocomposite architecture mimicking such an organism, was made of nanofibers embedded in a copolymer matrix, with the degree of interaction between them being modulated by using a water-based solvent. In the absence of such a solvent the material becomes rigid, whereas upon addition of the solvent that forms hydrogen bonds with the nanofibers the fibers interactions are disrupted, and the material becomes soft. Similar strategies whether inspired by biological systems or other mechanisms are planned for the development of novel responsive composites.

These responsive composites can be used also as coatings for the fabrication of "smart" surfaces with switchable wetting properties having practical applications, in biosensors, microfluidic devices, intelligent membranes, and multifunctional coatings. A class of strategies for the design of dynamically modifiable surfaces is the use of plastic coating with organic molecules confined to their near surface, that exploit geometry and dipole moment changes due to conformational transitions upon externally applied stimuli, such as light irradiation, electrical potential, temperature, solvent, or pH. Another approach towards more pronounced and switchable wettability changes would be the use of nanocomposites with semiconductor oxides nanofillers, such as  $\text{TiO}_2$ ,  $\text{ZnO}$ ,  $\text{WO}_3$ , and  $\text{V}_2\text{O}_5$ , that exhibit increased hydrophilicity upon band-gap photoexcitation, due to photogeneration of holes that create oxygen vacancies at the semiconductor surface. These defects are then able to promote dissociative adsorption of atmospheric water, which ultimately leads to an increase in surface hydroxylation. Under dark ambient conditions, a recovery of the starting properties occurs, as molecular oxygen replaces the UV-grafted hydroxyl moieties. These inorganic materials offer clear advantages over stimuli-responsive organic molecules in terms of structural and photochemical stability, low toxicity, and significantly larger wettability changes.

#### *Composites of polymers with biological molecules: Biocomposites*

Plastic materials are possibly the most promising candidates for custom-made biomaterials for specific medical applications. Tissue engineering techniques can be used on plastics with a target to design spare human body parts, or to deliver drugs in a fully controllable manner. For these kinds of applications the polymeric materials should be biocompatible





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and biodegradable and be combined with biological molecules. For example plastic materials can be used as scaffolds for engineering functional tissues, due to the high processability of the plastic materials. 3-D polymeric scaffolds will be designed and developed by the materials science team, with controlled porous architecture networks, needed for cell migration, nutrient diffusion, and vasculature, for the successful growth of human tissues such as skin, cartilage, blood vessels, and nerves. The scaffolds can incorporate proteins that are known as growth factors and could guide and support tissue in-growth. The idea is that as the biodegradable scaffolds degrade inside the body the proteins will be slowly released. The growth factors attract blood vessels from the healthy surrounding tissues that flood the damaged area, bringing nutrients that the new tissue requires to survive. In this way, the usual problem of providing blood in the implantable organs can be solved since surrounding cells and blood vessels are encouraged by the proteins to grow into the new organs. Tissue growth is facilitated by a three-dimensional framework with properties that encourage favorable cell responses. Also stem cells could be combined with the growth factors in seeding the plastic scaffolds to grow new organs. An important issue in tissue engineering using biocomposite polymeric scaffolds is the tuning of the polymers so that they disintegrate at the same rate as the new tissue is developed. It should be possible in the future to use multilayered polymers that release a series of growth factors necessary for healing an ailing part at predetermined time rates and intervals.

Another very important application of the polymeric composites with biological molecules that this platform will target are the drug delivery systems. For example, a DNA vaccine could have advantages over conventional ones that use weakened or inactivated pathogens in that if a DNA encoding a protein antigen is introduced directly into cells, they would produce the antigen, eliciting an immune response. Unfortunately, naked DNA is readily degraded in the body and it cannot be introduced directly into cells. For this reason spherical polymeric particles of specific size can be used for the **encapsulation of the DNA**. These particles can be taken up by cells and slowly degrade in the weakly acidic pH environment of the cell, releasing the DNA vaccine. The same technique can be used for delivering, into specific sites of human bodies or materials, repairing molecules encapsulated into polymeric microcapsules.

### **Self Assembled Structures, Surface Topography and Chemistry Control**

#### *Self-Assembly of colloidal nanocrystals for new coatings and smart surfaces*

This activity targets the exploitation of colloidal nanocrystals as building blocks for engineered self assembly architectures in applications 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. The path to these architectures will exploit concepts that are amenable to large scale deposition and parallelization. The reproducible, high yield fabrication of colloidal nanocrystals with narrow size and shape distributions with different materials will be targeted first. Emphasis will be on a combined approach, using fabrication techniques borrowed from different realms (from the 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. In this context, assembly of nanocrystals with different degrees of order can be used for coating a vast variety of materials in order to change their surface properties in a controllable manner. Applications of such technologies include self cleaning surfaces, antflammable surfaces and controlled wettability surfaces. In particular novel titanium oxide (TiO<sub>2</sub>) nanorod structures developed by the Nanochemistry facility have been used as coatings for complete, homogenous coverage of numerous substrates having different initial surface properties, such as silicon, polymers, glasses, and gold. By changing various properties and characteristics of the nanorods, such as preparation method, length, storage conditions etc., the formed coatings can exhibit changeable surface properties. In this way, the surface of the samples can be easily tuned towards hydrophobic and superhydrophobic behaviors with photo-induced reversible changes in their wettability upon UV irradiation. In particular, after absorption of UV photons, the nanorod-coatings change dramatically their wetting properties and become very hydrophilic.



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The wettability variations (more than 100°) can be further improved by surface nanopatterning of the substrate. For example the intrinsic random surface roughness, and thus the initial hydrophobicity of the polymeric substrates, can be further enhanced by photo-patterning in pillar geometries with different spacing. The surface of these pillar structures are subsequently covered by TiO<sub>2</sub> nanocrystals, that further affect the initial hydrophobicity with respect to the uncovered surfaces.

## **Novel Materials for Advanced Sensing Devices**

### *Nitride piezo-electrics for energy harvesting and micro and nano actuators*

This activity deals with another class of novel material, the III-Nitrides (GaN, AlN) having striking piezoelectric properties and excellent mechanical and thermal robustness. The properties of piezoelectric materials rely on the asymmetric nature of their crystalline unit cell. In these materials the application of a mechanical stress leads to a creation of an electric field and vice versa. If these asymmetric crystals can be synthesized and controlled at micro and nanoscale, micro and nano energy generators can be created to be used as power supplies for remote electronics, sensors for robotics and automotive vehicles, and also biocompatible in-vivo microactuators and micromotors for drug delivery or advanced prognostics and diagnostics.

Aluminium nitride (AlN) is the best candidate for these applications being synthesized and structured in suspended architectures, that are more sensitive to mechanical displacement. A combined approach to the synthesis of nitride compounds and on the design, simulation and fabrication of complete devices through micro and nanostructuring of the nitride heterostructures including membranes, bridges and cantilevers architectures opens up the following applications fields.

- Energy harvesting in membrane and cantilever structures;
- inertial sensors based on the direct piezoelectric response of a nitride-membrane to 3-D deformation,
- shock sensors, based on the direct piezoelectric response of a nitride-cantilever deflection,
- micro-actuators, based on the inverse piezoelectric effect acting on a nitride-cantilever (used also as a peristaltic pump for liquid analytes in lab-on-chip applications),
- arrays of sensors for tactile applications.

These classes of devices are relevant for robotics, as well as for other manufacturing fields such as automotive, aerospace, biomedical equipment, measurement tools and metrology etc. The activity will be developed exploiting the MOCVD and magnetron sputtering facilities available within the IIT network.

Parallel to the III-N materials the III-V group materials (InGaAs/GaAs) exhibit interesting mechanical, optical and electronic properties that will be exploited to realise new compact-integrated gyroscopic sensors for equilibrium control of robots (somewhat inspired by the integrated vestibular system in the humans).

This is designed to be an *Integrated Laser Gyroscope*. Optical gyroscopes are widely used in several industrial and military applications such as in spacecrafts, aircrafts and satellites. Active and passive optical ring interferometers are exploited in optical gyroscopes by typically using fiber optic components. However the integration of these devices in compact systems still calls for a smaller size and weight, and lower power consumption. A miniature integrated optical sensor for gyroscopes can in principle possess these properties and high enough sensitivity even on a millimeter scale. The principle of operation of our optical gyroscope is based on the Sagnac effect in which a beam of light is split and the two beams follow trajectories in opposite directions and interfere close to the point of entry. The position of the interference fringes is dependent on the angular velocity of the setup. A boost in the sensitivity of optical gyros can be obtained in highly dispersive media, such as electromagnetically induced transparency systems obtained by a sequence of coupled high-Q optical resonators in which



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large optical dispersion and slow group velocity of light is achieved.

## Artificial Systems for Humanoid Technology and Robotics

### *Developing Artificial Retina*

The retina is a complex and sophisticated image detector that converts incoming light from an image into a set of highly processed sub-images. Creating an actual implantable artificial retina is a long-range project which includes a multi-disciplinary challenge and many intermediate steps. In spite of its risk and difficulty, the impact of such an enterprise, even with the intermediate milestones, is huge and involves a broad range of areas, including physics, biology, chemistry, engineering and medicine. Spin-offs are in robotics, security, imaging and neuro-sciences. The expected advances are not only in technology and applications, but also in basic science, such as understanding how the retinas of humans and primates turn incoming light into coded messages communicated to the brain, how neurons communicate and how ionic transport and other biological solutions to data communication work at a molecular level.

We have selected organic semiconductor technology, as it offers several advantages with respect to inorganic options, particularly in terms of biocompatibility and biostability. Besides conjugated polymers and molecules are easily processable, can be chemically engineered, can be deposited onto flexible substrates, and can also be manufactured using ink-jet printing techniques. The project has three main research lines, each aimed at specific targets and constituting intermediate steps to the final goal. The effort is supported by collaboration with researchers in many complementary disciplines, including photo-physics, organic electronics, bio-engineering, robotics and humanoid technology and vision scientists.

*Micro Array for Retinal Visual Elaboration:* development of an artificial visual system (AVS), sensitive to the visible and to the near infrared part of the electromagnetic spectrum (approximately in the range 360-1200nm), based on variable geometry organic photo-detector arrays. The AVS we propose is strongly inspired by natural solutions to the tasks of vision and mobile target tracking. Its realization would bring innovative cameras for warning and tracking, with distinct features for the perception of motion, artificial systems for machine vision and ultimately retina implantation.

*The interface between nerve cells and artificial devices:* non-invasive connections between the human nervous system and prostheses and instruments with unprecedented flexibility, compactness and reliability. Although light signals have previously been transmitted to nerve cells using silicon, nano-engineered materials promise far greater efficiency and versatility. The research tasks are the compatibility with living cells and the ability to turn light into tiny electrical currents that can produce responses in nerves or to read-out neuronal activity. In particular organic semiconductors or other substrates used in organic technology, provide a natural environment for neuronal growth and thus a potential interface for establishing a contact between artificial and biological worlds.

### *Organic Colorimetry*

This activity is a fall-out of the retina project. It aims at realizing an organic photodiode system based on the tri-stimuli approach for color sensitivity. While the long range goal is the realization of an artificial color sensitive retina working on similar principles to natural ones, the short term goal is colorimetry for industrial purpose, and color science. The main tasks are the selection of organic semiconductors that allow building photodiodes with the proper spectral function, the realization of stable devices and their integration into a colorimeter for commercial use. Side activities concern color science and the study of image processing and color sensitivity based on tailored photoreceptors spectral functions.

## B.6 PLATFORM: ENERGY

Operating Departments/Units: NC-Ge, NNL-Le, NEST-Pi, PoliMi



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## Introduction

The goal of this platform is to tackle the increasing demand for *portable, alternative* energy sources in very important industrial areas such as automation and robotics, portable electronics and automotive. We envisage that IIT will be able to provide strategic technological solutions in both directions using nanostructured materials and devices, developing novel concepts and approaches for storing energy or harvesting it from the surrounding environment. **Portability** and **environmental impact** will be two of the major issues affecting the choice and development of future portable energy sources at the moment mainly based on chemical batteries which are marred by limited lifetime and costly disposal procedures.

With these demands, we performed a careful analysis of the scientific and industrial scenario of alternative energy conversion devices, reaching the conclusion that the main tasks for IIT are the development of new low-cost plastic materials for portable photovoltaic systems and nano-engineered interfaces for advanced energy harvesting and storage devices. The approach chosen is therefore that of developing organic and nanostructured materials, and to engineer surfaces and nanoparticles, integrating their multiple capabilities together, to improve the performances of a multiplicity of energy conversion devices. These encompass:

- Energy storage devices
- Photovoltaic devices
- Novel fuel cells
- Energy harvesting devices
- Energy scavenging devices

## Energy Storage

### *Nanostructured materials for electrical energy storage devices*

Nanostructured materials are promising candidates for the preparation of highly efficient energy storage devices. Compared to bulk materials, nanoscale electrodes show higher surface areas for the electrochemical reaction to take place. The small dimensions shorten the distances for mass and charge diffusion, theoretically improving simultaneously ionic and electronic conductivities as well as minimizing the mass and volume of electrode required to achieve high energy capacities. Finally, they introduce an increased degree of freedom for volume change that accompanies for instance Li-ion intercalation in the electrode crystal lattice, improving battery's cycle life. Some successful attempts to decrease the size of the electrode particles have been reported in recent years and show improvements in the device performance. However, dimensions below 1micron are rarely achieved, and always use polycrystalline powders of aggregated particles where no shape and size control is accomplished.

The aim of this activity is to develop new nanocomposite materials for rechargeable battery devices, based on lithium ions, to improve the present energy storage capabilities. The research activity will focus on novel architectures for electrodes based on nanowires/nanocrystals of low-cost and environmentally-friendly electro-active materials, exploiting the nanochemistry facility existing at the Central Research Lab. in Genova. In particular:

**a)** Synthesis of nanocrystals/nanowires of various mixed *lithium-transition metal phosphates* and *intercalation vanadium oxide* and *manganese oxide* structures with control of their structure/stoichiometry, to be used as components of the cathode (lithium *intercalation electrodes*). These "cathode" materials is expected to become the most convenient in terms of cost, material availability, safety and environmental issues. The reduced and controlled dimensions of nanoparticles and their shape control will be key for the optimization of Li ion intercalation/de-intercalation processes (which will influence both capacity and conductivity of the device).

**b)** Synthesis of nanocrystals and nanowires of various *non-layered transition metal oxides* with control of their crystalline structure and stoichiometry to be used as components of either the cathode or the anode in conversion

electrodes. These show promising reversible  $\text{Li}^+$  uptake activity accompanied by the transition metal ion reduction and formation of  $\text{Li}_2\text{O}$ . The group includes copper, tin, iron and manganese oxides, which are usually treated as anode materials, as alternatives to metallic alloys or graphitic carbons which show problems of cyclic stability and lower theoretical capacities.

c) Supervalent/multivalent ion doping of above mentioned nanocrystals and formation of hybrid metallic-electroactive nanocrystals. In this way the electronic conductivity of the electroactive material will be enhanced, overcoming one of the main limitations of active materials for energy storage. With the same aim, coating of nanostructures/assemblies with materials as molecular compounds, conductive polymers, graphitic carbon and metallic/semiconductor inorganic materials will be performed, which additionally are expected to improve the characteristics of the electrode/electrolyte interface.

d) Assembly of the building blocks on substrates starting from solution-processable blends as well as by direct growth will be explored. Solution-phase growth of nanowires on substrates patterned with metal seeds acting as catalysts as well as vapor phase approaches will be developed as direct growth methods.

e) Fabrication and characterization of simple prototype storage devices based on the various materials. We aim at reducing electron transport pathways from the electro-active materials to the electron collectors and reducing  $\text{Li}^+$  ion diffusion pathways through the electrolyte between the two electrodes. Bottom-up synthesis procedures will enlarge the amount of available nanocrystalline materials useful for the battery design, and surface and molecular chemistry will improve stability and properties, overcoming potential disadvantages of such nanostructured systems. Assembly techniques will be exploited in order to arrange such nanocrystal-based composites in the device, with the aim of optimizing efficiency.

#### *New approaches to Energy Storage*

Capacitors represent the most natural alternative to batteries as a means to store electric energy in applications requiring moderate power and compatible with relatively frequent re-charging cycles (laptops, cell-phone, etc.). Standard technologies, however, result in short discharge times and/or bulky components when high output powers are needed. Recently, however, a new generation of components termed “supercapacitors” or “ultracapacitors” has hit the market using electrolytic solutions and porous carbon electrodes for high surface areas. These are starting to be considered in hybrid vehicles as a complement to batteries (to answer fast power demands) but are not yet compatible with stand-alone solutions for instance in portable electronics. Nanowires, carbon nanotubes (CNT), and graphene are now the object of intense research in a variety of configurations as new capacitor elements to boost the energy storage capabilities. There are already very promising results. A group at MIT has claimed, this year, to have reached an energy density of 25 % of that attainable with Li-ion batteries in a CNT-based capacitor, while the first graphene ultracapacitor has been reported recently at The University of Texas. Recently it was shown that a sandwich of just two graphene layers can create a nanopump able to increase the inter-layer  $\text{H}_2$  pressure achieving the DOE volumetric storage target at moderate external  $\text{H}_2$  pressures and room temperature. Here the challenge will be to create such graphene nanopumps exploring different methods for large-scale graphene deposition and optimizing the inter-layer graphene distance for H-storage by visualizing, measuring and theoretically modeling H-graphene interaction with single-atom resolution. Under the framework of this activity, key phenomena such as storage capability, desorption and adsorption processes need to be fully understood and measured experimentally. Further research will include peptide nanotubes for the electrodes and nanoporous oxide membranes as insulating materials. An important avenue to be examined though is also related to the development of novel architectures for the device design that could allow a better usage of the storage space.

#### **Photovoltaic cells**

The advancement of low cost photovoltaic (PV) devices is a key step towards portable and clean future energy technology. The novel chemical, physical, optical and electronic properties of nanocomposites and of polymeric materials will enable photovoltaic technologies to reach in the long term high levels of performance and cost effectiveness that could never be paralleled by the existing traditional technologies. This can succeed if novel devices based on nano-structured materials can



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be made in a cost effective manner. For example, flexible solar cells, much like a plastic sheet, could be envisioned as highly cost effective roll-to-roll manufacturing. The target of this research line is to develop novel nanocomposite and polymeric materials for plastic solar cells having different architectures.

- Hybrid organic-inorganic solar cells
- Dye sensitized solar cells (DSSC)
- Organic TANDEM solar cells

#### *Hybrid Organic Inorganic Solar Cells*

The aim of this research line is the development of photovoltaic cells based on organic/inorganic hybrid nanocomposites. This research couples the low cost and high processability of the organic materials with the unsurpassed stability of inorganic compounds. Key elements for such technology will be Cd-free nanocrystals (of low environmental impact) synthesized in the Nanochemistry facility. The following strategies will be pursued:

- 1- assembly of inorganic nanocrystals (NCs) in organic matrices,
- 2- synthesis of new nanocomposites based on NC with tailored shapes and sizes and new functional organic ligands.
- 3- totally inorganic active systems based on colloidal NCs, deposited in liquid phase by cheap methods such as spin coating, printing, etc .

The long term target of this activity is the fabrication of stable solar cells with efficiency in the range of 10% , long lifetime and low degradation.

We will develop synthesis procedures for size-, shape-, and composition-controlled nanoparticles based on a wide range of materials, to be used in blends with oligomers, polymers and tailored ligand molecules. The assembly and interfacing will be controlled at the nanoscale level and will be extended. 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. Emphasis will be put on toxicity and impact on the 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<sub>2</sub>S<sub>3</sub>, 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.

We will also assemble and interface nanocrystals with organic molecules, which will act both as spacers and as ligands, to achieve optimal film forming, blending, light absorption in a well defined energy window, exciton generation, highly efficient hole-transport, and charge separation at the organic-inorganic interface. One example is oligothiophenes (OTs) functionalized with tailored moieties in order for their efficient anchorage to nanocrystals. Depending on the active layer and device architecture, all these organic components will have to ensure good electrical contact with any additional small molecule/oligomer that will be evaporated/spin coated on the nanocrystal layer. Other relevant properties of OTs include their potential for forming liquid-crystalline phases.

Isolated networks of interlinked nanocrystals, as well as blends of polymers and networks of nanocrystals will be exploited to induce the formation of networks of interlinked particles. This should result in a direct electrical contact for a large number of nanocrystals creating percolating networks for electrons thus reducing dead-ends in electron transport (which is a typical drawback of traditional hybrid nanocomposite films for organic photovoltaics).

#### *Dye sensitized Solar Cells(DSSC)*





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DSSC are presently the best performing plastic solar cell devices. Efficiencies in the range of 10% on small areas (0.3 sqmm), and 7% on wide areas (1 sqcm) have been demonstrated, with lifetimes exceeding 10000hrs. The objective of this activity is the development and optimization of low cost DSSC devices suitable for mass production. To achieve this aim our research will target the optimization of the photo-anode, which is one of the key components of these emerging PV technologies. This is formed essentially by nanostructured transition metal oxides (i.e.  $\text{TiO}_2$ ) and has to satisfy several requirements that are much more demanding than for photocatalysis: thickness in the order of 10 microns, porosity higher than 50%, high surface area available for dye chemisorption, low defect density, high electron mobility. In addition to these material requirements, new features are being recognized by the scientific community as necessary for enhancing conversion performance, such as optimized light trapping and electron conduction architectures. Efforts are now being devoted to optimizing electron injection in the  $\text{TiO}_2$  conduction band, and also exploiting novel  $\text{TiO}_x$  nanostructures and optimized dye compounds. Future directions are towards all-solid-state DSC, employing solid electrolyte solutions, and the integration of the DSSC in light trapping devices. This kind of photo-anode is in principle interesting also for other solar cell schemes, such as Hybrid Organic-Inorganic Solar Cells in which the absorber-donor layer is a semiconducting polymer and the acceptor layer is an oxide. The technology issues are similar to DSC, with the added difficulty of infiltrating polymers into a mesoporous material.

#### *Organic TANDEM solar cells*

The high cost of conventional Si-based photovoltaic systems (3-6€/Wp) has increased the demand for cheap fully plastic solar cells based on organic compounds, with low environmental impact and low production cost. A credible target for this technology is to accomplish fully organic solar cells with production costs in the range of 1€/Wp, with the additional benefit of being mechanical flexible and integratable in glass or plastic surfaces of any curvature and shape. To achieve this, IIT will pursue a research line on plastic solar cells based on low-molecular weight molecules which are fabricated by simple thermal evaporation methods. These materials enable fabrication of multilayer devices, including doping for p-i-n structures. The TANDEM configuration based on vertically stacked cells is the architecture of choice for devices with optimised solar absorption efficiency, with estimated efficiency in the range of 10%, a cost of less than 1€/Wp and a lifetime greater than 20 years. Figures of merit of this kind should be accomplished in a timespan of about 5-7 years.

#### *Novel mesostructured TCO for photovoltaics.*

The terrific increment in efficiency of crystalline Si solar cells (cSi) (from  $\approx 15\%$  up to  $\approx 26\%$ ) is mainly due to optimized light trapping and carrier diffusion schemes. Unfortunately, the texturing strategies used for cSi are not replicable on polycrystalline and amorphous materials, but are still urgently required in order to increase efficiency. Thus, novel approaches are needed. Among the different possibilities an interesting approach is the three dimensional patterning of the Transparent Conducting Oxide (TCO). This approach has not been extensively explored in the literature but holds promise for those PV technologies where the main limitation arises from the compromise between optical absorption and carriers transport. In contrast, by realizing optical micro-cavities with integrated photonic crystals it would be possible, in principle, to separate the two paths, yielding large absorption volumes with reduced absorber thickness, resulting in shorter diffusion lengths. This technology would be of great technological interest since TCO coated glasses or plastics could be used for any of the above mentioned organic plastic devices. Furthermore, an increased absorption volume with reduced absorber material thickness could translate in faster processing time using existing production processes and machines.

#### **Fuel cells components**

##### *Novel catalysts materials based on nanocomposites for the water gas-shift reaction.*



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The aim of this line is to develop new catalysts for CO abatement in hydrogen-rich gases for fuel cells. In polymer electrolyte fuel cells, due to their low operational temperature, the platinum catalyst is likely to be poisoned by carbon monoxide (CO), and the performance of the unit is degraded when CO is present in the reformed gas at concentrations beyond a few ppm. In general, a CO removal unit is provided downstream of the reforming unit which produces the reformed gas rich in hydrogen, and CO is selectively converted through a **water gas shift** reaction so that the concentration of CO in the reformed gas is usually <10-50 ppm. Typical catalysts for CO conversion are based on Cu-Zn, CeO<sub>2</sub>-Au, Fe<sub>3</sub>O<sub>4</sub>-Au. The nano-soldering process developed at the NC-Ge facility should be easily extendable to the preparation of porous networks made of branched metal oxide nanocrystals/metal domains. These porous networks are expected to exhibit catalytic activity (for instance towards the water gas shift reaction). The main tasks in this research activity will be: **(a)** Synthesis of various metal-metal oxide (MO) based nanostructures (by employing both non-hydrolytic and hydrolytic methods), that promote the elementary reaction steps towards the CO oxidation and H<sub>2</sub>O dissociation with the help of the metal (*A*). Here *A* = Au, Cu, Pt, Pd. **(b)** Synthesis of *A*-MO heterostructures using rod, multipod, hyper-branched MO nanocrystals, followed by selective growth of metal domains on their tips. Assembly of these *A*-MO heterostructures via the nano-soldering process will yield porous networks, which will be exploited as catalysts. **(c)** Tests on water gas shift reactions to check the efficiency of the fabricated catalysts.

#### *Novel electrode materials for solid oxide fuel cells.*

Solid Oxide Fuel Cells (SOFC) use a solid ceramic inorganic oxide as its electrolyte rather than a liquid electrolyte and work at high temperatures (500-1000°C). Here the anode and the cathode must be stable in a reducing and in oxidizing atmosphere, respectively. Also, they must be electronically conducting, porous in structure and stable at high operating temperature. Numerous metal/oxide composites (cermets) and doped oxides have been studied in the literature as electrode materials. Commercialized materials are synthesized using solid-state reactions, which yield materials in the micron size regime. Nanostructured materials with high surface energy and low sintering temperature may become promising candidates for such applications. A few perovskites-based nanocomposites (manganite, cobaltite, etc.) have been proposed recently as electrode materials. We will therefore aim at exploring novel nanocomposite materials based on various classes of nanocrystals and assembly techniques. Some of the electrode materials that look promising and that will be tested are: La<sub>1-x</sub>Sr<sub>x</sub>CoO<sub>3</sub>, La<sub>1-x</sub>Sr<sub>x</sub>MnO<sub>3</sub>, SrCoO<sub>3-δ</sub>, Sm<sub>1-x</sub>Sr<sub>x</sub>CoO<sub>3-δ</sub>, etc. (where 0 ≤ *x* ≤ 1) (cathode materials), and nickel/yttria stabilized zirconia cermet, LaSrCrTiO<sub>3</sub>, SrTiNbO<sub>3</sub> (anode materials). In this context the main tasks of the activity will be: **(a)** Synthesis of various electrode materials in the nanometer regime and the exploitation of their electrochemical properties and **(b)** searching for alternative electrolyte materials having better performance and lower cost.

#### *Advanced composite materials for H<sub>2</sub> and methanol fuel cells*

Traditional FC technology, such as the Proton Exchange Membrane Fuel Cell (PEMFC) suffers from the major disadvantage of needing a pure H<sub>2</sub> feed. This raises several critical issues for production and storage. Direct methanol fuel cell technology (DMFC) is a further more recent development of the polymer electrolyte fuel cell that is particularly promising for portable and vehicular applications, thanks to the advantage of a liquid feed. Nevertheless, technical challenges remain unresolved: performance and production cost. The scientific and technical literature agrees that the major cause of the lower performance and higher cost of DMFC compared to PEMFC, is methanol permeation through the polymeric membrane (cross-over). In fact, methanol cross-over causes fuel wasting and a reduction in the catalyser efficacy at the cathode. Usually, to mitigate these effects membrane thickness and catalyst loading at the cathode are increased with respect to the PEMFC adversely affecting the production cost. The other fundamental issue in DMFC is the slow methanol electro-oxidation at the anode. The research aims at developing novel hybrid metal-polymer fuel cell architectures, that integrate support, electrolyte and catalytic layers. The heart of the novel device is an innovative nanostructured Pd-based selective barrier with controlled composition, crystalline structure and porosity at the nanoscale. This barrier is designed to selectively block methanol molecules, while preserving high proton conductivity. One of the goals is an even more selective membrane, able to





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control water permeation. This novel architecture is expected to have a very high potential in reducing methanol cross-over in DMFC and in overcoming the major DMFC shortcomings, thus fostering their commercialisation. Moreover, the envisioned architecture may be further developed to obtain enhanced water management in hydrogen fed PEMFC. This is a critical issue for their performance and longevity.

### *Bio-fuel cells*

Conventional fuel cells rely on expensive non-renewable metal catalysis at the electrodes and are limited to hydrogen and methanol fuels, and high-temperature applications. The so-called biofuel cells (BFs) utilize enzymes as catalysts, thus eliminating the dependence on precious metal catalysts. With respect to abiotically-catalyzed FCs, BFs can offer high reactant specificity and high catalytic activity, making them very suitable as amperometric sensors. As a consequence of the catalyst specificity, BFs can also be miniaturized as they do not require proton exchange membranes. Yet, they still suffer from the limited stability of the enzymes (in the order of weeks) which makes long term operation difficult. Current research focused on immobilization technologies enhance the enzyme stability and the electronic communication with the electrodes. Within this technique, highly-controlled laminar flows, delivered by microfluidic technologies, can be crucial in enhancing both miniaturization and stability of this strategic class of devices. A major challenge relates to the provision of highly regulated fluidic conditions, and of improvements to the (bio)catalyst longevity through the investigation of innovative conductive matrices for enzyme immobilization at micro- and nano-scale.

The main task of this research activity will be to combine FC technology within microfluidic devices by fabricating microfluidic fuel cells that work under continuous flow. In general, the functional lab-on-a-chip devices required for FC (bio)chemical processes will require diverse on-chip building blocks, which may often be three-dimensional, such as fluid injectors, filters, pumps, valves, mixers, separation elements, detectors, etc.. These may often include optical, electrical and mechanical elements, and therefore will present significant challenges for micro- and nano-engineering. For example, a large variety of fluid pumping schemes have been proposed, including pressure-driven, pneumatic, piezoelectric, electrostatic, electromagnetic, surface tension, and electrokinetic effects, but no fabrication standard has yet been established. Integration of functional elements is also a challenge. Ideally, functional microfluidic FC devices should be able to carry out a complex laboratory process. Major objectives of will be: i) The realization, and the on-chip integration, of electrodes for capillary electrophoresis, single-use and multi-use valves, mechanical pumps and valves, active and passive mixers and heating elements and temperature sensors; ii) The realization of diffusive-based fluidic devices with different filtration geometries, and the investigation of the dependence of performances on the viscosity, interfacial free energies, flow rates, and geometries. Furthermore, the development of nano-engineered substrates with an unprecedented level of flexibility will be carried out by the integration of patterning approaches (photo- and soft lithographies) working at the micrometer-scale (for the definition of microchannels), and nanolithographies, such as electron-beam lithographies and nanoimprinting, allowing one to reach 100-nm and sub 100-nm scale resolution. This will allow the definition of the fine structures within the different capillary walls. These techniques will be specifically implemented to realize complex nanoengineered interfaces using a top-down approach. Multilevel nanopatterning will also allow us to print layers of functional molecules in a controllable and reproducible fashion for interface control of the desired regions of the microchannels.

### **Energy Scavenging**

The possibility of harvesting energy from the environment is particularly interesting way for low-power, portable electronics to supplant rechargeable batteries. Opportunities are particularly interesting for the conversion of vibrations into electric energy using piezoelectric nanostructures, for which power densities of the order of one–two hundred mW/cm<sup>2</sup> were predicted. This value compares very favorably with those typical of Li-ion batteries that average in the tens of mW/cm<sup>2</sup> range. Thermal energy is another potentially exploitable energy form. Using the thermoelectric effect, powers comparable to those of rechargeable batteries can be extracted from temperature differences of about 10 degrees. In both the above research directions



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nanowires present a very promising solution due to their clear one-dimensional character. Strongly piezoelectric oxide nanowires can be grown in very high densities on a variety of substrates while semiconductor nanowires have already been used to study thermoelectric effects.

It is likely though that for real applications a combination of strategies would be required. Nanowires are indeed especially suitable for this approach, as they offer a common platform for many different functionalities that is largely substrate independent. Furthermore, they provide a possible path towards integration with high-efficiency photovoltaic technologies since III-V nanowire photonic devices can be seamlessly realized on Si.



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## **B.7 PLATFORM: Integrated Multiscale Computational Technology**

**Operating Departments/Units:** RBCS-Ge, TERA-Ge, NC-Ge, D3-Ge, NNL-Le, NEST-Pi, CRIB-Na

We aim at developing a new computational infrastructure for advanced modeling of systems of interest for the Drug-Discovery-Development-and-Diagnostic (D4), Environment-Health-and-Safety (EHS), Smart-Materials (SM), and Energy platforms.

Research activities in all these diverse fields need tools and models for the quantitative description and control of structure and dynamics at the nanoscale. Computational methods bear the promise of being able to address these fields within a unified approach, enabling the rational design of novel drugs and molecular machines for nanomedicine, devices for optoelectronics, biophysics, and new smart materials. The fields of Computational Material-/Nano-/Bio-Sciences are rapidly growing not only thanks to the constant increase of the available computational power, but also due to the development of new theoretical methods and optimized algorithms. Nowadays, several computational approaches and advanced algorithms are available worldwide to perform calculation on systems of different sizes (from small molecules to solvated proteins, from bulk to hybrid-interfaces) and with different accuracy (from highly-correlated wavefunction methods to semiempirical tight-binding, from atomistic approaches to coarse-grained methods). Different commercial/open-sources codes are available to cover specific interests of the well-separated fields of quantum chemistry (GAUSSIAN, TURBOMOLE, MOLPRO, NWCHEM, etc.), solid-state physics (European Theoretical Spectroscopic Facility, CPMD, CP2K, QUANTUM-ESPRESSO, etc.), molecular-dynamics (AMBER, GROMACS, NAMD, DL-POLY, etc.), small organic molecules docking (AutoDock, Gold, ICM, etc.), protein-protein docking (HADDOCK, ROSETTA DOCK, etc.), coarse-grained and mesoscopic effects (ESPRESSO, DL-POLY, RedMD, etc.), and commercial multiscale environment (Accelrys Material Studio). Nowadays, a first-principles Density-Functional Theory (DFT) calculation of a system with one hundred atoms or simulations of oligopeptide folding via molecular-dynamics can be routinely performed on a standard PC, while only ten years ago a dedicated super-computing centre was required.

Despite these impressive advances in specific fields, much less attention has been paid to the multiscale integration of all these techniques, because strong interdisciplinary competences in chemistry, physics, biology, and computer science are required.

A general computational tool for nanobiotechnology is still lacking, which should have the following characteristics:

- 1) Multiscale in space, including ab initio, molecular mechanics, and coarse-grain methods;
- 2) Multiscale in time, including semiclassical/classical dynamics;
- 3) Able to treat different environments (gas phase, isotropic and anisotropic solutions, surfaces, and solid state)
- 4) User friendly, flexible, and open to developments;
- 5) Suitable for the new emerging multicore architectures.

The development and validation must be done in close collaboration with the leading experimental groups participating to experimental platforms in order to check results and develop interpretative models close to experimentalist needs. Particular attention has to be paid to the following applicative targets, which represent challenging open problems:

- A1) inorganic nanocrystals and their interaction with biological systems;
- A2) free energy calculation of protein-ligand binding;
- A3) multiscale modeling of photovoltaic cells;
- A4) design of smart molecular machines for medicine and biology.

### **A1) Inorganic nanocrystals and their interaction with biological systems**



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Inorganic nanocrystals are at the forefront of the present revolution in nanoscience and nanotechnology. Typical inorganic nanocrystals are composed by a metal (Au, Ag, etc.), magnetic-oxide ( $\text{Fe}_3\text{O}_4$ ,  $\text{CoPt}_3$ , etc.) or semiconductor ( $\text{TiO}_2$ , CdS, ZnSe, CdTe, etc.) core surrounded by organic surfactants. The inorganic core can be of complex shapes (e.g. rods, tetrapods, or core-shell systems, etc.), with different dimensions (from 5 nm to 100 nm), and moreover complex hybrid hetero-nanostructures can be realized. Such systems can contain several hundred thousands of atoms, therefore quantum-chemistry methods can be applied only to model the smallest systems, while plane-wave approaches can hardly be applied due to the absence of any periodicity in these systems. Thus, the structural properties of systems of real dimensions have been investigated only using continuum-elasticity or force-field approaches, while electronic and optical properties are mainly studied using standard envelop-function approximation methods (for semiconductor nanocrystals) or electromagnetic approaches (for metal nanoparticles). Moreover, all these modeling approaches are mainly focused on a single non-interacting nanocrystal.

A theoretical modeling of the interactions of nanocrystals among themselves will allow the understanding of self-assemblies and can guide the fabrication of well defined nano-surfaces. Moreover, nanocrystals can be used in biomedical applications, and therefore the modeling of interaction with proteins or biological systems is of fundamental importance. However, no general approach is currently available to investigate such nanocrystal-biomolecule complex systems. A full non-periodic multiscale approach is required, ranging from coarse-grain for the interaction between mesoscopic objects, down to atomistic simulation of the inorganic/surfactant interface.

This activity is of foremost importance for the EHS, SM, and D4 platforms.

## **A2) Free energy calculation of protein-ligand binding**

The theoretical estimate of ligand-protein binding free energy plays a pivotal role in drug discovery as it could drive the design of novel drug candidates for subsequent chemical syntheses and biological assays. Indeed, a-priori knowledge of free interaction energy would enormously facilitate and enhance the drug discovery process. In fact, the free energy calculated along some reaction coordinates is the observable that best describes ligand-protein binding events, and that connects the microscopic to the macroscopic world, as it would allow an accurate prediction of ligand-protein binding affinity. Nowadays, several computational methods are available for free energy estimation of ligand-protein binding. These are commonly used within computational docking protocols, where ligands are tried to be fitted at a protein binding pocket. Empirical figures of merit are then used to compare the efficacy of binding of different molecules (scoring phase). This approach, although computationally very efficient, fails in taking into account the detailed interaction. In particular, three major issues need to be faced:

- 1) Docking methods fail to properly describe the response of ligands and proteins in terms of intrinsic flexibility that may significantly alter the free energy of binding. Such a behavior is nowadays widely recognized, and can be described according to two paradigms named induced- and selected-fit;

- 2) At present, standard docking methods fail to catch and estimate the energetics of barriers experienced by a ligand that approaches the protein binding site;

- 3) Finally, the scoring functions used to estimate the protein-ligand binding energy fail to properly account for polarization effects, which are crucial during the recognition and binding processes.

For these reasons, the implementation of new computational approaches within this activity is of foremost importance for the D4 platform.

## **A3) Multiscale modeling of photovoltaic cells**

Organic solar-cells have attracted strong interest for low cost photovoltaics. In a full plastic solar cell, a donor (D) and an acceptor (A) organic layer are sandwiched together between two electrodes. The photocurrent generation requires the generation of an exciton, which can be a direct, photoinduced charge transfer exciton at the D/A interface, or more likely a molecular exciton formed either in the donor or in the acceptor layer, which then migrates and dissociates at the D/A interface. The probability of the electron transfer from the donor to the acceptor is one of the key parameters for optimizing



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the solar cell efficiency. A predictive modeling is of fundamental importance to design better devices. So far, theoretical modeling studies have focused on the optimization of the optical absorption (computational electromagnetism) and of the photocurrent (drift-diffusion methods). On the other hand, ab-initio atomistic methods have mainly been applied to model the electron-transfer in organic/TiO<sub>2</sub> heterointerfaces (dye-sensitized solar cells). To accurately investigate charge-transfer effects in donor-acceptor systems, a full ab-initio quantum-mechanical treatment of the excited state, inside an anisotropic polarizable environment (the surrounding organic molecules) is required. Time-Dependent Density-Functional Theory (TD-DFT) methods could be well suited for the size of systems under investigation (about one hundred atoms for a typical donor-acceptor system), but more accurate exchange-correlation functionals must be developed to avoid the shortcoming local-density-approximation, which also limits the application of plane-wave approaches.

Another key issue for improving the efficiency of solar cells is the energy-level alignment for the organic-metal interface which controls the charge injection. Standard first-principles plane-wave methods cannot easily treat large molecules or disorder effects due to the very large supercell required, and moreover they cannot treat efficiently the non-local exchange. A Gaussian-based method with a proper embedding scheme is more appropriate to model such complex organic/metal interfaces.

Finally, complex hybrid hetero-nanostructures for photovoltaics are rapidly growing. A full multiscale approach to model optical absorption of nanostructures and charge-transfer at hybrid interfaces is strongly required.

This activity is of the foremost importance for the Energy platform.

#### **A4) Design of smart molecular machines for medicine and biology**

Current research for novel diagnostic and therapeutic tools involves the design and development of smart and biocompatible molecular machines, able to reach given intracellular compartments, recognize specific biomolecular targets, and subsequently produce a detectable signal, or perform some action (e.g. drug release) upon local or external stimuli, either in whole organisms or in explanted primary cells. A pivotal role in the rational design of these systems will be played by computational techniques. Modeling the interaction between macromolecules and the cellular membrane will guide the design of cellular vectors such as peptides, dendrimers, and lipids. The integration of all-atom and coarse-grain molecular dynamics will enable detailed investigation of membrane permeation phenomena, and assist the design of best performing delivery systems. Moreover, fluorescent probes (fluorescent proteins, organic markers, fluorescent nanocrystals) sensitive to and activated by structural changes or to local environmental factors (pH, concentration of ionic species, solvent polarity), will provide the means for external detection. The rational design of these fluorescent modules will depend on accurate prediction of spectroscopic properties within the appropriate embedding, and on simulating conformational changes upon recognition.

This activity will greatly benefits the D4 platform.

#### **Modules**

To tackle all these challenging problems, different methodological advances beyond the current state of the art must be pursued. The main development goals of this platform are organized in four-modules:

M1) Embedding Approaches

M2) Free Energy Calculations and Molecular Dynamics

M3) Coarse Grain Methods

M4) Spectroscopy

#### **M1) Embedding Approaches**

The reference framework of this module is a mixed quantum-mechanics/molecular mechanics (QM/MM) model. Starting from the observation that most physical-chemical phenomena have a local nature (i.e. they occur in a limited region of



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space), it is expedient to partition the system under study in several spatial regions (at least two), namely an internal one, where the process occurs and where the most intense computational effort must be concentrated by sophisticated QM methods, and an external region, described by empirical MM force fields and atomic charges. Moreover, the bulk of the system can be described by finite elements methods (like the polarizable continuum model, PCM) or, generally, by mean field (MF) continuum models. It is to be stressed that MF models are not limited to isotropic solutions (their original field of application), but have been extended with considerable success to anisotropic situations (e.g. liquid crystals), membranes, and metals. This computational approach is nowadays well established, but its effective implementation requires further work, especially when polarizable force fields are sought, which become mandatory for polar or charged systems. Furthermore, the determination of atomic charges and other parameters of the MM part requires the development of effective optimization tools employing combined strategies (e.g. simplex, Newton-Raphson and genetic algorithms) and the definition of the most suitable partitioning of the electronic density taking into account the averaging by molecular motions. However, QM/MM methods can be not sufficiently accurate in situations where it is not possible to neglect the electronic interaction between the core of the phenomenon to be described and the rest of the system (hereafter broadly referred to as bulk). It becomes thus necessary to develop more effective embedding procedures based on the so called frozen density approach where the interaction potential between the core and the bulk is built starting from a zero-order electron density delivered by a simplified density functional theory (DFT), usually an orbital-free DFT. However, for surfaces or nanosystems, the zero order density could be obtained as well by periodic computations of a suitable regular model (e.g. a surface without defects or the solid corresponding to the infinite nanosystem). The state of the art in this connection is represented by some modules linked to the MOLCAS (multireference post-Hartree-Fock) and Demon (conventional DFT) codes, together with the Embed code using periodic boundary conditions (PBC) results obtained by the Crystal program. However, the first two implementations are not general and not freely distributed, while the third one is too complicate and specific for general use. A general module implementing embedding approaches of increasing complexity is thus timely and should be linked to computations enforcing PBC with localized basis functions, which allow the best compromise between accuracy (e.g. use of hybrid functional) and computational efficiency. This is the reason why a PBC implementation is also sought. The same approach can be generalized from static computations to ab-initio molecular dynamics (AIMD). Since an AIMD QM/MM/MF module based on localized basis functions will be developed within the same general project, we should have at our disposal an integrated computational tool able to combine the different theoretical approximations in order to allow the static and dynamic study of realistic nanostructures with accuracy comparable to that of experiments. The methodological advances of this module will be of fundamental importance for applications A1, A2, and A3.

## **M2) Free Energy Calculations and Molecular Dynamics**

We aim at accurately estimating the ligand-protein binding free energy to enhance and facilitate the drug discovery process. To this aim, we will face the two major drawbacks of currently available structure-based drug design methods: i) the sampling and the entropy estimation; ii) the enthalpy estimation and the scoring. The activity will focus on the two following aspects:

i) The development of enhanced sampling techniques (and algorithms) based on the molecular dynamics scheme to improve the sampling, and therefore the free energy estimation along a suitably chosen ligand-protein interaction coordinate;

ii) The modeling of electrostatic and non-bonded interactions established between drugs and targets.

As for point i), a new enhanced sampling technique will be developed and implemented in next generation multicore hardware architecture, for instance graphical processor unit (GPU) or CELL broadband engine (BE). The speedup provided by this implementation (up to 50x) could be spent in a more thorough exploration of the configurational space and in the utilization of a more accurate, and potentially more computationally demanding, force field, as the one obtained from point ii).

As for point ii), methods will range from ab initio techniques (mainly at the DFT level of theory), used for the calculation of the electron density, to advanced statistical techniques, such as kernel methods aimed at exploring new functional forms for the various types of forces involved. The electrostatic potential will be mapped onto the molecular surface, as well as other possible observables of interest. This formulation allows for fast resolution of the Poisson Boltzmann Equation over large systems via the Boundary Element method, and for an interesting surface-based approach on rapid large scale affinity





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estimation.

The most natural way of performing ab-initio dynamical computations for solutions employing localized basis functions involves the replacement of standard periodic boundary conditions by suitable non-periodic ones. Besides the success of continuum solvent models, an explicit representation of the solvent becomes mandatory to correctly describe dynamical solvent effects (the relaxation after an electronic excitation or a charge transfer, just to quote some important examples). Our recent applications also confirm this perspective. The forecasted developments regard the generalization of our GLOB model in order to describe thermodynamic ensembles other than the original NVT one, the consistent combination with several QM's and MM partitions, and implementation for Born-Oppenheimer dynamics. With this method, a number of pilot applications will be performed, ranging from the computation of spectroscopic properties for flexible biomolecules in solution and to DNA photophysics.

Methods of this module will be used for applications A1 and A2.

### M3) Coarse Grain Methods

Coarse Grain (CG) can be done at many different resolution levels. Depending on the application, CG developers devised schemes ranging from the “united atoms” model (i.e. a “soft” coarse graining, where interacting “beads” are small functional groups such as methyls) to the so-called mesoscale models, where entire domains or proteins are considered as single interacting centers. After the resolution level is fixed, the particular CG model is further defined by the choice of the force field. In general, the task of combining structural accuracy and predictive power in a CG model is not straightforward, since many complex interactions must be included in a few force field parameters. The quality of a CG force field depends on the choice of the functional form, and on the parameterization, which can be based on: i) single structures (Network and Go models); ii) including structural properties from a statistical set of experimental structures (via the Boltzmann inversion method); iii) based on the matching of the forces from higher resolution simulations (Force Matching methods); iv) including *a priori* knowledge and thermodynamic or kinetic data. A combination of these methods is also possible. Thus, while the goal of building CG models that are as much general, transferable and accurate as possible remains the ultimate task of the CG force field developers, at the moment a variety of different recipes or compromise solutions are available.

For instance “one-bead” models, representing proteins and nucleic acids on an amino-acid or nucleotide base are advantageous as their resolution coincides with that of low-resolution structural techniques, such as cryo-electron microscopy. Existing models for biological membranes and organic polymers at equivalent resolution can be easily combined and integrated with those for bio-molecules in order to simulate, for instance, delivery systems, molecular actuators or interfaces.

In CG models, the strictly related issues of embedding and multi-scale simulations arise spontaneously: in fact, the CG modeling itself is apt to treat the system at different resolutions. In general, multi-scale approaches can be divided in two classes: the “parallel” approaches and the “serial” approaches. Parallel approaches entail the already discussed embedding problem, involving the description with two or more different resolutions at the same time. While very effective in describing single-point properties (such as spectroscopic features), the parallel multiscale models suffer from a common limitation in simulating molecular dynamics: the rate limiting step is always the highest resolution part of the system.

The “serial” schemes consist in approaching the whole system with different resolution methods subsequently. This in principle enables longer time scales in simulations and extensive exploration of the configuration space (with the low-resolution representation). When necessary, high-resolution simulations are performed starting from selected configurations obtained from the low-resolution trajectory. Clearly, this resolution transition requires global “thermodynamic” consistency: the system must explore equivalent free-energy surfaces when represented with the different resolutions. This condition is naturally achieved when the low-resolution models (e.g. the CG) are parameterized based on the Boltzmann inversion of a statistical set of structures taken from the high-resolution (e.g. atomistic) simulation. Serial approaches are more recent and less standard than parallel embedding. Efficient implementation of these schemes must address: i) the uniformity of input/output for different resolution configurations; ii) the implementation of the Boltzmann inversion or force matching procedure to parameterize the force fields.

The tasks of this module will be to solve the described problems and to build standards for serial multi-scale simulations, with a focus on the coarse-grained and meso-scale models.



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Methods of this module will be used for applications A1, A2, and A4.

#### **M4) Spectroscopy**

Spectroscopy characterization is a fundamental tool to study the properties of the nanosystems. Recently, the European Physics community has launched the European Theoretical Spectroscopy Facility (ETSF) with the aim to predict the absorption and photoemission properties of periodic systems such as bulk and surfaces. Aim of this module is to investigate the optical properties on non-periodic systems such as molecules and nanosystems.

Characterization of the structural and dynamic properties of complex systems and/or of unstable species is based on spectroscopic techniques of increasing power and sophistication. However, the outcome of spectroscopic studies is rarely interpretable without the help of QM computations providing a link between electronic structure and spectroscopic properties. The development of reliable methods based on DFT and TD-DFT has revolutionized this field, providing a very satisfactory compromise between reliability and cost (especially scalability) of the computations.

Further development of density functional will be carried out in order to improve their effectiveness and to solve some remaining problems connected with charge-transfer transition. Moreover, a proper comparison with experiments will require inclusion of other effects, ranging from computations of new properties, to proper treatment of environment and inclusion of nuclear motions.

Time independent approaches to nuclear motions require wider considerations, since they play the double role of allowing reproduction of IR and Raman spectra and to provide the underlying data for vibrational averaging of other spectroscopic parameters. Here, previous experience on anharmonic force fields and for vibronic contributions to electronic spectra will be used to develop effective linear-scaling approaches. Furthermore, the computation of other spectroscopic parameters, related to resonance-Raman, circular dichroism, and 2D-IR will be also taken into account.

The computational Spectroscopy is not only limited to organic molecules. Optical characterization is also important for semiconductor and metal nanocrystals. For the latter, a brute force TD-DFT approach is still out of reach. To model the absorption and scattering of large semiconductor and metal nanoparticle, envelop function approximations or electromagnetic approaches will be used.

Methods of this module will be used for application A1, A3.

#### **Technological Delivery**

##### **The MUSICA (MultiScale Integrated Computational Approach) software suite for Nano-Bio-Technology**

The previous methodological advances can be obtained using and/or further developing standard computational software. However, to include in a rationalized fashion integrated multiscale computational technologies, all the methods must be combined together in a new independent code. The idea of the **MUSICA** code for Nano-Bio-Technology is the interconnection between methods at different levels of accuracy, towards the development of innovative integrated software for computational Material-/Nano-/Bio-sciences. We will concentrate on the development, validation, and applications of an integrated multiscale approach in which different space and time scales are treated at different levels and combined to allow reliable descriptions of complex systems.

The MUSICA code will be endowed with the following main features:

- It will be tuned for next generation multi-core architectures (GPU and CELL BE), thus it will be vectorized and parallelized;
- It will be open-source, which is a key-point to attract other national or international computational groups which could add new and advanced features;
- It will include well defined protocols and interfaces to exchange parameters at the different computational levels;

Finally, we will develop a web-based IIT portal for launching MUSICA applications through a GRID-computing infrastructure between the IIT computational nodes.