INtegral BIOmathics Support Action

Work programme topic addressed
8.10 Identifying new research topics, Assessing emerging global S&T trends in ICT for future FET Proactive initiatives

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Proposal abstract

Research roadmaps in computational systems biology, autonomic computing and communications target the enrichment of knowledge and technology transfer between (analytic) life sciences and (synthetic) engineering sciences. However, we claim that it is impossible to make significant progress in this transdisciplinary field without a breakthrough paradigm change towards *biologically driven* mathematics and computation. Turing Machines used in biology and elsewhere in science today are Newtonian in a broad sense because they deal exclusively with syntax and inference rules based on discrete logic in absolute space and time to deliver predictable behaviour. Despite this approach being *extraordinarily* useful in engineering human processes, the interactions within the real world has proven to be vague and relational in many ways. A profoundly new understanding of the role of biology in natural and engineering sciences needs to be set out. Our driving argument is that living systems have fundamentally different notions of self-organization from those in engineering sciences. We therefore propose a research programme to investigate the imperatives of mathematics and computation in a cardinal new way by comprehending the fundamental principles of emergence, development and evolution in biology. The goal will be a set of novel mathematical formalisms capable of addressing the multiple facets of an integral model and a general theory of biocomputation within an adequate frame of relevance. Its base will be a long-term fundamental research programme in mathematics, systems biology and computation that we call *Integral Biomathics*. The proposed support action has the goal of identifying, consolidating and organizing transdisciplinary research in Europe around this focus with the objectives: i) to devise a set of challenges for future FET research at proactive initiative level; ii) to produce a position paper motivating the need for action and reflecting the impact on science, technology and society.

> Our goal is to prepare a research cooperation infrastructure that will transform and boost mathematics and computation, robotics and cognitive systems, which are priority research topics in FP7, upon the foundations of mathematical modeling.

1. Concept

In past centuries, physics was engaged with applying general statistical mechanics for understanding distinct system states. This approach was inherited in biology and computer science (Bohm, 1980). Although now a special case in modern physics, Newton's world picture still dominates computer science (Blum, 2004), engineering (Lee et al., 2005) and biology (Bower, 2005). Turing Machines used in biology and elsewhere in science today are Newtonian in the broad sense that they deal exclusively with syntax and inference rules based on discrete logic in absolute space and time to deliver predictable behaviour. Extraordinarily useful though this has proven for planning tasks which include people and machines, this approach has been much less successful for tasks which require direct interaction with the real world which has come true to be vague and relational in many ways.
Over 50 years ago Rashevsky pointed out that "the relation between physics and biology may lie on a different plane from the one hitherto considered" (Rashevsky, 1954). He supposed that while the physical phenomena are the manifestations of the metric properties of the four-dimensional universe, biological phenomena may reflect some localized topological properties of that universe which we might interpret as effects that only occur at very small distances (e.g. reconformation of ion channels due to high voltage gradients across cellular membranes or quantum effects in microtubules). [Recent research in scale relativity and integrative systems biology (Auffray & Nottale, 2008; Nottale & Auffray, 2008) continue this line of thought.] Realizing that biology needs stable fundamentals such as those of post-Newtonian physics, his goal was to develop a set of principles which connect the different "physical phenomena expressing the biological unity of the organism and of the organic world as a whole". Therefore, a profoundly new understanding about the role of biology in analytical natural sciences and synthetic engineering sciences has to be set out. Recent research roadmaps both in computational systems biology and autonomic computing and communications target the perpetuation and enrichment of the knowledge, technology and methodology transfer between analytic life sciences and synthetic engineering sciences. However, we dare to question the firmness of the bridge between converging sciences and claim that it is impossible to make any significant progress in this multidisciplinary field of research without inaugurating a *breakthrough paradigm change towards biologically driven mathematics and computation*.

> Our driving argument is that living systems have fundamentally different notions for self-organization from those conceived in engineering sciences today. Whereas artifacts are designed and programmed to serve human needs as tools and mechanisms, organisms are beings whose sole purpose is to maintain, survive and reproduce in a changing environment. The former are closed deterministic systems that conform to the laws of physics; the latter are open non-deterministic systems that also follow the patterns of biology. Therefore, when devising the plan for future converging sciences, one should be aware of the limits of engineering and of the fact that various relations within organisms are outside the scope of metric mathematical biology and contemporary science (Rashevsky, 1954-1955). This holds also for computer science which still suffers from the inertness of exclusively bounded syntactic and mechanistic computing models.
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> Further, to achieve a conceptual breakthrough both in biology and computation "a new paradigm is needed for a complex biological phenomenon beyond the current parameters of networks and of systems" (Mesarovic & Sreenath, 2006).

Modern physics provides through thermodynamics and quantum mechanics new model bases for biology and computation. While thermodynamics connects to development, QM connects to vagueness and internalism. Realizing that the one constraint on science, as on all thought, is (conventional) logic, if we wish to go beyond it, the only possibility at present is to address *vagueness*, not algorithms. Hence, it is not a question of inventing yet another novel approach to computing, but one that integrates the multiple levels of organization and activity in a living system, and beyond that, one that evolves autonomously by extending and refining the model, thus mimicking the system itself.

Yet, it is not possible to have a realistic concept and understanding of a natural system by sticking to the limited capabilities of reductionist models. This is exactly what Feynman had in mind when he said he was not happy with using numeric computation in quantum research (Feynman, 1982).

> Therefore, we need to investigate the biological imperatives of mathematics and computation in a profoundly new way. It should be based on understanding the premises for, and the fundamental characteristics of emergence, organization, development and evolution in biology, in particular with an emphasis on the so far widely neglected perspective on internalism (Matsuno, 1989; Salthe, 1993; Salthe & Matsuno, 1995; Rössler, 1998; Coen, 2000; Noble, 2008).
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> Its goal should be a set of novel mathematical formalisms capable of addressing the multiple facets of an integral model and a general theory for biocomputation within an adequate engineering frame of relevance. One possible way forward is through category theory (Nomura, 2006; Ehresmann and Vanbremeersch, 2007-2009). The base of the research should be a long-term fundamental theoretical research in mathematics, system biology and computation. We call this research field *Integral Biomathics* (Simeonov, 2010).

Present day systems engineering relies on specifying deterministic systems programmed to execute its tasks with pre-defined responses to each case. If there is no programmed response to a specific combination of external signals, there is no response or (usually) an inappropriate response to them. The system fails. Yet, as the world for which we build systems becomes increasingly nuanced, complex and unpredictable it becomes even more difficult to map within a limited set of specifications. There will inevitably be new interaction possibilities introduced into the system or its environment will generate new situations and the system will always have gaps, conflicts or ambiguities in its own knowledge and capabilities. The system's semantic and semiotic analysis of overwhelming amounts of (often ambiguous) sensor data to select or *invent* an appropriate response will become in future an insurmountable obstacle if we do not develop a new paradigm and discover a profoundly new way to engineer and deploy systems.

We do not have a logic and formalization of information processing to match this challenge. But natural systems such as neuronal networks and multi-cellular organisms provide the resource for studying and understanding true *bio*-logic based on different premises from the logic of today's engineered systems (Elsasser, 1981; Conrad, 1989; Hong, 1992; Simeonov, 2007a; Smith, 2008).

> A first step towards performing such a transformation is to bring together and organize the activities of *a non-mainstream scientific research community* working in this area. This target group of distinguished individuals has not obtained sufficient attention and support by either national or European research programmes because of the long-term nature of their research. The research of these unconventional and passionate people lies outside the borders of current mainstream industrialized product-oriented science.
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> The INBIOSA initiative is intended
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> - to mobilize multidisciplinary research in a variety of fields in mathematics and natural sciences towards a paradigm change in computational systems biology;
> - to collect ideas and proposals for devising future research in Integral Biomathics into specific research fields, topics and roadmaps for dissemination to the EC;
> - to offer an open platform for recognized experts to meet, exchange ideas and debate on issues of interest, as well as to enable them to venture adequate research actions;
> - to provide the base for an international collaboration network in the field of Integral Biomathics.

2. Objectives

The INBIOSA project pursues two *primary objectives*:

I. **to devise a set of challenges for future EU FET research** at proactive initiative level, and

II. **to release a position paper (white paper)** in collaboration with the Scientific Advisory Council of the project, a panel of distinguished world-class experts, motivating the need for action, reflecting the impact foreseen in science, technology and society and defining goals, directions and a roadmap for future research in Integral Biomathics until 2020-2025. This document will be delivered to the EC to establish a future agenda for research covering the related disciplines and areas and develop new plans for ICT FET programmes.

INBIOSA has the following *secondary objectives* which can be directly observed:

1. **Steering and support of research activities in Integral Biomathics** by providing appropriate communication and exchange tools, as well as feedback and reporting mechanisms to the EC and the research community to ensure the provision of open and broad eco-technological directives for scientific investigation in the field.
2. **Creation of a pan-European Integral Biomathics "metalogue",** (Bateson, 1972), to ensure that the foundational scientific and exploratory investigations in this field lead to cooperative and synergetic knowledge exchange between the computation engineering and natural science communities that can derive deployable design principles for sustainable techno-social environments within the FET 2020-2025 timeframe.
3. **Creation of a European based world-wide community of scientific and technical experts** that will be able in collaboration with other international research programmes and initiatives to investigate important areas in Integral Biomathics, as well as to study the fundamental architecture and design principles of biocomputation and produce a structured and cohesive vision of the future natural and biosynthetic ecosystems.

The **driving principles** of the INBIOSA initiative are:

- focusing on "off-road" scientific research in mathematics and computation engineering targeting a synergetic integration and exchange with natural and life science disciplines;
- enforcing holistic multidisciplinary approaches to investigation;
- identifying research areas which are crucial for accelerated, yet balanced, transformation of the future information society towards eco-awareness (Bateson, 2002).

Within this context, INBIOSA pursues the following *sub-objectives*:

- to set up a discourse infrastructure for scientists from a variety of fields to meet and exchange ideas. Correspondence will be realized electronically in both asynchronous and synchronous modes (email, data exchange, teleconferencing, etc.) using standard tools integrated into and managed by a WWW platform that will be used by all members.
- to organize monthly virtual meetings of the consortium members and the Scientific Advisory Board to discuss scientific issues, current problems and future needs of the project. There will be two general technical workshops. They will deliver reports on anticipated future research developments. The main part of the project work will be performed during these meetings. Additionally, some smaller ad-hoc and interim meetings could be organized to support specific activities.
- to ask distinguished experts to propose scientific fields for investigation and define goals, tasks and roadmaps for their realization.

These sub-objectives will be realized through extensive consultations on the strategic orientation and focal points of the INBIOSA initiative with the Scientific Advisory Board represented by outstanding world class researchers.

Although INBIOSA is initially focusing on promoting European research, its ambition is to become a world-wide scientific forum. As such, non-European leading researchers will be also invited to join the collaboration network and participate in the meetings.

In practice, INBIOSA will be responsible for

- covering the general costs for organizing the collaboration and communication platform and the virtual and real meetings, as well as for publishing the results (e.g. by providing website and document server to help on keeping record on the progress of the initiative)
- funding the meetings and other administrative support

The above objectives will comply with the long-term goals of the IST FET proactive initiatives as they:

1. Will promote and raise awareness of the Integral Biomathics (IB) research framework by
    - supporting research efforts in identified technology fields and promoting interoperability between them;
    - elaborating synergetic relationships and interdependencies between research initiatives, institutions and individuals in ICT and other fields of physical and life sciences.
2. Will provide a highly competitive and widely known world-wide forum in which current issues, problems and solutions in the research, development and deployment of IB systems can be freely debated, discussed and resolved by
    - organizing Integral Biomathics relevant research in Europe and the world;
    - drawing in and integrating previous research from related areas and disciplines;
    - identifying areas of critical importance for the broader EU IST and global community and focusing research work in these areas;
    - preparing the milestones of a curriculum program for teaching and training in Integral Biomathics and supporting the students and trainee integration in the research community.
3. Will disseminate the INBIOSA vision and strategy by means of:
    a) an international symposium on Integral Biomathics. This conference will be carried out in Europe with two satellite subconferences in USA and Japan.
    b) scientific publications of the IMBIOSA members
    c) a WWW information and collaboration platform, newsletters, press releases, etc.

3. Approach

A central issue of the Integral Biomathics work programme will be computation beyond the Turing limit (Siegelmann, 1995). Current approaches to biologically inspired computing take neural membranes, neurons, or assemblies of neurons like cortical columns, and attempt to implement these directly as electronic or software components or as some mixture of these (Hong, 2005ab). Although this research has had some success (for example in artificial neural networks, or in novel image sensors), nothing that could remotely be described as intelligent has actually been produced. *Why is this?* Is it because the systems that have been produced are too simple (and don't have enough components or enough accuracy in their modeling or neurons or membranes or enough adaptability), or is there some critical aspect being omitted from the jigsaw? Grossberg (2008) suggests that what is required is an all-out onslaught on the whole of brain-based computing in order to produce autonomous systems. Simeonov (2007a) discusses a number of possible approaches, and Hong (1992) discusses the idea that the very mechanics of biochemical reactions might lie at the base of the difference between silicon and biochemical informatics. Smith (2008) has suggested that it is the crossing of engineering levels that is partly responsible for the effectiveness of biological approaches. But **what *is* clear is that something is missing.**

How then should we aim to produce autonomous systems? Purely computational approaches tend to be brittle; fuzzy and/or neural (in the sense of neural network) approaches can provide relief from brittleness. Truly biological systems integrate the sensors, actuators and processing in ways that we simply cannot manage technologically. But we do not know what it is that really makes the difference. Therefore, we are interested to understand **organism-machine disanalogy** (Conrad, 1989; Pattee, 2002; Zeigler, 2002; Simeonov, 2007a; Smith, 2007) and aim to take the first steps towards answering the question of *what it is that makes biological systems different*: to this end one might consider, for example, the simplest of independent organisms (for example, single-celled amoeba-like organisms like *Paramecium*), and examine the difference between different types of detailed models of such a system and the system itself.

> To take-off in this direction, we need a new paradigm to work with, providing a unique frame for exploring the biological foundations of computation at the frontiers of science. The attained knowledge can be used in the design of biosynthetic systems which go beyond Turing's discrete computation model and von Neumann's self-replicating automata, thus unleashing science to grow towards new horizons.
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> Therefore, INBIOSA will investigate how such a new paradigm can be developed.

Currently, there is little dialogue between researchers from different fields in life sciences (biophysics, biochemistry, genetics, zoology, molecular and system biology and other) investigating living systems at different levels, and engineers and computer scientists building artificial systems that (according to them) are inspired from or mimic the biological ones. The models of the underlying systems are often different and specific, addressing a particular view or set of problems. But living systems are skilled at demonstrating emergent properties of the whole which are more than the parts, such as cognition and consciousness, and we cannot understand with just a single view or model. We need integral superposed models of such systems which can only come into being if multiple models at different scales are reconciled and adjusted to generate a more adequate picture. The proposed project brings together researchers in these different areas, forcing them to relate and adjust their work to the researchers in other areas.

> Integral Biomathics is envisioned to discover and establish new relationships and deliver new insights into the interaction and interdependence between natural and artificial (human-created) phenomena for a number of scientific fields. It is expected to invent and develop new mathematical formalisms and provide a generalized epistemological framework and ecology for symbiotic research in life, physical, social and engineering sciences.

> *Our objective is to unify classical mathematical biology with biomathics or biological mathematics (the study of mathematics as it occurs in biological systems) with system biology on the way to genuine biological system engineering.* Our approach is a systemic one. It is about asking what is computing and cognition, and about understanding where the biological imperatives for them come from and lead to, rather than being about replicating some isolated aspects of them. In this regard, our goal differs from most present day efforts of biomimetics in automata and computation design such as neuromorphic engineering (Mead, 1990; Jung et al., 2001) to develop autonomic systems by emulating a limited set of "organic" features using traditional mathematical methods and computational models.
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> We will develop a profoundly new theoretical framework integrating systems biology into computation and capable to answer such questions as:
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> - What is computation? – within the biological context, because there is "no computer into which we could insert the DNA sequences to generate life, other than life itself" (Noble, 2010).
> - How useful is computation? – for living systems, where "usefulness" is studied from the viewpoint of the entity performing the computation.
> - To what extent can a computation be carried out? – in an organism or an ecosystem, with the available resources (energy supply, time, number of 'computing' elements, etc.).

To face these issues, it is mandatory to revise the conceptual framework of contemporary computing and communication theory, rather than addressing other issues such as computability which are essentially irrelevant to biology. Since historical contingency prevents classical Turing computability in dissipative systems, including the biological ones, alternative theoretical approaches to defining biocomputability in line with those in (Hogarth, 1994; MacLennan, 2003) are required.

This research will be carried out both from the perspective of traditional (analytic) life and physical sciences, as well as from that of mathematical and engineering (synthetic) sciences. Thereby, classical information theory (Shannon, 1948) should be also developed along the same line of research in order to obtain an authentic picture of natural biological systems (Rashevsky, 1954-1955; Rosen, 1958-1959) that will enable the creation of artificial ones. This viewpoint has certainly become an important issue in the design of complex networked systems deploying large numbers of distributed components with dynamic exchange of information in the presence of noise and under power and bandwidth constraints in the areas of telecommunications, transport control and industrial automation. What is important for the design of naturalistic systems in this areas is the perception of signaling and information content (including their processing and distribution) from the *internal* perspective of biological systems (Miller, 1978) and in correlation with autonomous regulation of power consumption and other life maintaining mechanisms. This topic has not been addressed sufficiently by present research in either natural or artificial systems. Therefore, it should become an integral part of the models and methods for approaching naturalistic computation.

We anticipate that the focus of this research will meet the interests of and (eventually) find broad acceptance in the scientific community. The project is expected to deliver answers to such questions as: (i) *what is computation?* – in biological context; (ii) *how useful is a computation?* – for living systems, where "usefulness" is studied from the viewpoint of the entity performing the computation; (iii) *to what extent can a computation be carried out?* – in an organism or an ecosystem, with the available resources (power, time, number of computing elements, etc.).

4. Outcomes

To address these issues the research team is going to revise the conceptual framework of contemporary computing and communication theory. The constituent fields and the entire multidisciplinary research area Integral Biomathics will benefit from the INBIOSA initiative by the establishment of a widely known and recognized discourse and collaboration forum for discussing, streamlining and organizing research in themes of major interest and importance for the scientific community and information society. In particular, the implementation of the project objectives will yield the following results that will consolidate and foster research in this area:

- **Strategic research manifesto, position paper and reports** as an outcome of these think tank meetings, aiming at the fulfillment of primary objectives I and II. These manifesto and position paper will be the direct outcome of the discussions and debates invoked by the INBIOSA think tank meetings. The consensus nature of these outcomes, together with the anticipated high quality of the attendance producing these outcomes, is expected to give them the legitimacy required for the impact they claim for. It is the task of INBIOSA to appropriately record and disseminate these results.
- **Web presence and Advanced Online Scientific Community Service (AO-SCS),** (Simeonov, 2007b), as tools for establishing an electronic discussion forum and disseminating selected publications, presentations and other multimedia content, including feedback collected from the larger community, aiming at secondary objectives 1-3. It will be possible to register to an emailing list in order to receive INBIOSA newsletters and reports automatically, subscribe to RSS feeds on news and reports.
- **Highly focused research magazine issues** as a means for distributing and discussing selected highlights of state-of-the-art research in a peer reviewed manner, aiming at supporting primary objective I.

5. Individual participants

JSRC: Plamen L. Simeonov

JSRC is an ICT innovation & research consultancy for physical and life sciences established in 2006. Its scientific activities comprise a number of frontier research areas such as Artificial Life, Neurocomputing & Cognitive System Architectures. The JSRC current research is situated in three major domains: i) mathematical models, methods and algorithms inspired from physical & life sciences, ii) advanced distributed computing techniques, and iii) biomolecular, nano- and quantum-scale information & communication systems.

Plamen L. Simeonov, received both his Ph.D. degree in computer science and M.Sc. degree in electronic engineering from the Technology University Ilmenau, Germany in 2002 and 1986 respectively. He is currently free researcher, ITC & nanobiotech evaluator, industry & VC advisor. His experience includes a variety of fields in industry and academia during the past 25 years such as Director Research, Distributed AI Laboratory, Technical University Berlin (2004-2007) and Director Active Multimedia, CTO, Siemens Mobile Division (1999-2001).

Next to mainstream telecommunications and multimedia technology his research interests include information theory and formal methods, self-organizing and self-assembling dynamic distributed information systems, neuroscience and biocomputation. He has 7 inventions and patents in the area of intelligent multimedia telecommunications and over 80 research papers and reports in the areas of VLSI design, image processing, visual interfaces, system modeling, software engineering, formal system design and verification.

Dr. Simeonov coined the term *Integral Biomathics* in an extensive interdisciplinary research survey (2006-2010) and is the initiator of the INtegral BIOmathics Support Action (INBIOSA). To his responsibility belong the overall project coordination in WP1 and the development of its communication infrastructure and services in WP3. He will also participate in the scientific discourse in WP2.

University of Stirling: Leslie S. Smith

The University of Stirling was established in 1967. The Department of Computing Science and Mathematics has a long history of research in biologically inspired computing, working both with other departments within the University, and with other institutions. The Department held early European Workshops on Neuromorphic Computing, and more recently has become part of the Scotland-wide "pooling initiative" in Computing, SICSA. This has brought all the Scottish Computing Departments together for research, providing a large research base, particularly in biologically inspired computing.

Professor Leslie Smith (PhD, SMIEEE) is the key staff member for this project. He has been working on the boundaries of Computing and Neurophysiology since the mid 1980's. Prof. Smith has worked with neuroscientists in Glasgow, Edinburgh and Newcastle. He helped set up the UK CARMEN project, which brought together Neuroscientists and Informaticians in 11 UK Universities to develop techniques for archiving and re-using electrophysiological neural measurement.

Professor Smith is principal investigator on a project developing a novel biologically inspired Neuromorphic microphone. Working on biologically inspired systems for 25 years has convinced him that the tools that we currently use are not sufficient for making the kind of steps forward that really would come from a better integration of neural and computer systems. This has led him to take part in Artificial General Intelligence conferences, as well as giving seminars on what it is that might really help link these areas together. Professor Smith will lead the scientific discourse in WP2. He is also deputy leader of WP1.

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