

Expression of Interest for Network of Excellence called ESBIGH

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- The **German Projektträger Jülich (PTJ)** <http://www.fz-juelich.de/ptj>
- The **Dutch National Organisation for Scientific Research (ALW-NWO)** <http://www.nwo.nl>
- The **Austrian Bureau Intl. Research & Technology Cooperation (BIT)** <http://www.bit.ac.at>

Full and 'live' information: <http://www.systembiology.net/esbigh/>

Title: **European Systems Biology Initiative: Genomics for Health**

Acronym: **ESBIGH**

Subject of this "Expression of Interest" (EoI) is the establishment of a pan-European "Supra Network of Excellence" (SoE) to maximise the benefits to human health from Systems Biology (SB) and functional genomics.

1. ESBIGH Mission

ESBIGH *will catalyse the integration of all the first rate European expertise available in SB to explore the full potential of genomics for human health.* It will open up novel perspectives in the diagnosis, prevention, monitoring, and treatment of human diseases. The ESBIGH SoE will *provide tools* for the study of, and for the development of improved therapies for human disorders, including monogenic and *multifactorial diseases*, such as those caused by a combination of genetic and environmental factors. ESBIGH will help to *integrate experimental science* (functional genomics) *with theoretical science* (mathematical biology/integrative bioinformatics) in such studies. ESBIGH will also *promote the optimisation of biotechnological processes in industry*, thus contributing to the high-yield production of recombinant pharmaceuticals and to *sustainable production processes*. ESBIGH will strongly *promote the training of young scientists* by coordinating *European graduate schools and courses*. Following the initial period of EC funding for ESBIGH, a suitable platform will be established for a European non-profit organisation on SB for genomics and health. This non-profit organisation will be financially independent through membership fees from companies and the licensing of expertise and technologies.

2.1. Rationale: What do we know about Life?

The complete sequencing of genomes from several organisms has generated a mass of information unimaginable just a few years ago. The majority of cellular components (macromolecules) of living cells and organisms, including man, are now well-understood at the DNA level. Despite these tremendous achievements, we are still a long way from solving the puzzles of life and still fail to understand complex living systems as wholes - a knowledge which could allow us to cure most diseases. Although we are confronted with severe and life-threatening diseases such as cancer, diabetes and cardio-vascular disorders, we fail to provide effective diagnosis and therapies in many instances. At this point, we are just collecting the parts of the puzzle (whole-genome sequences) and, although we know the structure and the sequence of genes, many associated functions remain to be discovered. Hence, functional genomics and molecular biochemistry are needed to unravel the functions of the single components in the context of living cells.

If we knew the shape and function of every cellular macromolecule, would we understand life, and would this understanding bring us closer to causal therapies for remaining diseases? The answer will certainly be disappointing as long as we keep ignoring very important aspects. Imagine a list of all the components of a TV set and their individual technical data. Would this information be sufficient to understand how the whole TV set works? Obviously not, as long as the wiring (i.e. the interconnections of all the electronic parts) is unknown. A single misconnection can cause a TV to fail. *Similar additional information about the connections* is indispensable in order to understand how complex biological systems such as living cells work. In other words, knowing how the macromolecules are connected and how that specific connectivity generates biological functions will provide a key to the understanding of life. This idea is the driving force behind a

newly emerging *multidisciplinary scientific discipline termed Systems Biology*. It was recently identified as a "hot topic" in the media, perhaps due to the general understanding that we are entering a new era in biology, involving scientists who are seeking the fundamental mechanisms that control the phenomena of life and health, as well as lead to the occasional failure of biological processes, i.e. disease.

Systems Biology (SB) thus focuses on the *real time study of the organisation and functional interaction of all molecules in living cells and organisms*. In the past, SB was hampered by a lack of sufficient molecular data on living organisms. During the last decade, this situation has dramatically improved due to the immense increase in the (i) rate at which such data are generated, (ii) completeness of the dataset, and (iii) the progress in information technologies that brought about the development of superior methods and computer tools for pathway simulation, data storage and processing. The next quantum leap in biomedical research will be achieved by *joining these data and tools in a multidisciplinary SB approach*. This approach will *embrace different concepts and expertise* from fields like molecular biology, biophysics, biochemistry, genomics, informatics, mathematics, systems engineering and molecular medicine. It will also bring the much needed integration of Mathematical and Experimental work. In this manner, the "Systems Biology meets Genomics" endeavour will pave a new way to a much improved understanding and more successful treatment of human diseases. *Therefore, this proposal is dedicated to a European Initiative on Systems Biology in the service of Genomics and Health (ESBIGH).*

2.2. Rationale: Why now, why Europe?

Europe holds a strong and propitious position in the field of SB and its implementation in functional genomics because it can rely on excellent and research expertise in the biosciences. SB evolved as a branch of theoretical biology and is just beginning to blossom in Europe, reviving major research traditions in areas such as self-organisation, metabolic control and non-equilibrium thermodynamics/bioenergetics. Bioinformatics and mathematics are also based on solid scientific fundamentals throughout Europe. *However, Europe has not yet become a common research area*. At present, the lack of coherence between diverse national scientific programmes hampers the *effective concerted actions* and the *integration of the European research community* that are exquisitely needed for Systems Biology *vis-a-vis* Genomics and Health, as a counterbalance to the dominant US scientific community.

US science has long been focusing on components rather than systems. Consequently, Europe has many competitive edges in Systems Biology. As Europe is naturally better in carrying out research collaborations once they have been put in place, Europe will become the leader in the SB/Genomics field provided its national excellences can be integrated. Several US institutions and initiatives are being dedicated to SB, some of which focus on human health (e.g. Institute for Systems Biology in Seattle). However, these initiatives are compromised by the ultra-competitiveness of traditional US research. *The integrative approach proposed here for the European research area is unique world-wide and will place Europe at the forefront of both Systems Biology and medically-oriented applied functional genomics.*

3. Objectives

- Create **synergy between the European networks and national initiatives** on SB
- **Establish a virtual Research institute** with **all European excellence** relevant for Health
- **Focus** European Systems Biology on genomics and health
- **Organisation of new research** to stimulate synergy between IPs, NPs and NoEs
- **Organisation and funding** of projects to bring SB and genomics closer to application to health
- **Window function** to industry and non-European research
- **Training** of a new generation of students in SB for genomics and health
- **Attracting** mathematicians, bioinformaticians, biologists and clinicians to ESBIGH.
- **Through the above: obtain exciting new results in Genomics and SB**
- **Through the above: new and successful applications of Genomics and SB**
- **Through the above: finally make Genomics work for human health**

As umbrella over European Systems Biology and Genomics, ESBIGH will contribute to quite a few thematic areas of FP6 research. These include (1.1.1) Genomics and biotechnology for health (1.1.1.i: *Advanced Genomics and its applications for health; Fundamental knowledge and basis tools for functional genomics; Gene expression and proteomics; Comparative Genomics and population genetics; Bioinformatics; Multidisciplinary functional genomics approaches to basis biological processes; Technological platforms for developments in the fields of new diagnostic, prevention and therapeutic tools* | 1.1.1.ii *Combating major diseases*), (1.1.5.) Food Quality and Safety, and (1.1.6) Sustainable development [bio-motor fuels].

4.1. General approach: A Network of Networks

The integration of pan-European research is beneficial given that only the outstanding expertise of each country is recruited and actively involved in the network. Most of the coordinators of the EoI involved in **ESBIGH** are renowned scientists from the different fields relevant to SB and genomics. The active support and general interest of all these scientists in the idea of **ESBIGH** - confirmed in the Annex - indicates that *Europe is ready to think and act in a multidisciplinary mode at a systems-level!* We therefore propose to follow a unique and ambitious approach with **ESBIGH**: European Networks of Excellence (NoEs), Integrated Projects (IPs) and national programmes (NPs) will each focus on their own identifiable modules of SB relevant for medical genomics and molecular medicine. If these NoEs were to act as individual consortia, most of the results and conclusions from these networks would probably remain "hidden" from the scientific community and potential applicants (except for publications in peer journals and EU reports). In contrast, *ESBIGH will create synergy between the different NoEs, providing the necessary infrastructure to collect, present and transfer findings* to other networks and scientists not directly involved in the SoE by means of a web-based platform (<http://www.systembiology.net/>), printed materials, electronic newsletters, scientific consultancy by ESBIGH coordinators, and frequent **ESBIGH** meetings.

One of the most important and demanding challenges for SB is the requirement to satisfy the need for standardised data through *standard operating procedures (SOP)*. It is absolutely mandatory that data are reproducible and thus suitable for modelling and computer-based simulation. **ESBIGH** will therefore offer workshops to *provide training* on essential requirements of data collection, processing and other techniques relevant for SB. **ESBIGH** will *coordinate* and *cooperate* with individual NoEs to start sharing expertise, protocols and software platforms from an early stage. This joint approach will be unique and highly beneficial for all participating teams, but also for the general scientific community in related fields. Hence, **ESBIGH** will establish central databases that will be *freely accessible to the entire scientific community*. In this context, **ESBIGH** will provide know-how and experience emanating from the participating IPs, NoEs and NPs. Furthermore, by bringing together the very best scientists in the field of SB and genomics, **ESBIGH will set up SOPs for SB** which ensure standardised protocols and high quality data of the utmost reproducibility. The individual NoEs, IPs and NPs that are partners in **ESBIGH** will focus on their own areas of SB for genomics and health. An essential activity of **ESBIGH** is therefore to organise communication and integration between these areas and between individual areas and applications. **ESBIGH** will accomplish this through calls for proposals, evaluations and funding of research activities that bridge the participating NoEs, IPs and NPs. **ESBIGH** will also *emphasise the integration and promotion of young scientists* in(to) the ESBIGH area through *training networks, dedicated European graduate schools*, and continuous student exchange among various NoEs, IPs, NPs and research teams. SB for genomics and health is an attractive research topic for PhD students and postdocs from various disciplines. **ESBIGH** will organise seminars, workshops, as well as student lecture courses through established European granting agencies such as *FEBS, NATO, EMBO* and *EC*.

4.2. General approach: Training and Teaching

The teaching of SB for genomics and health will be organised in three modes and co-ordinated by an ESBIGH teaching committee to be appointed by the SSC:

1. European Graduate schools on **ESBIGH**. These will be formed by integrating existing national research schools on the topic. The first such school is already in existence, *i.e.* the European Graduate school BCA-GKB, between the BioCentrum Amsterdam and the Graduierten Kolleg Berlin-Dynamics and Evolution of Cellular Processes, funded by NWO and DFG.
2. Transnational courses.
3. Short-term (2-4 week) training and research training of up to six months for graduate students and postdocs from one research group or another within **ESBIGH**.

4.3. General approach: organisation

ESBIGH will be based on *clear, manageable and open organisational structures*. First, the *Scientific Steering Committee (SSC)* will be the independent, decision-making panel of international (European) experts that will supervise, control and coordinate the SoE. The SSC supports the successful establishment and development of **ESBIGH**. One SSC member will be appointed by the EC, three members by the scientific advisory board (see below), and one member by the industrial partners. The SSC will elect a chairperson out of its own ranks for each period of three years.

Second, the *Scientific Advisory Board (SAB)* will consist of the coordinators of the participating NoEs, IPs, NPs and industrial biotechnology partners. On the basis of conclusions from SAB meetings, integration projects will be redirected, public calls for new proposals for IPs and projects formulated, and external groups invited to join **ESBIGH**. As possible in FP6, **ESBIGH** will announce dedicated calls for proposals. The board

will discuss funding of research proposals submitted after the calls, using external peer review to provide an objective basis. The final decision will be made by the SSC.

The **Organisational Board (OB)** will consist of the coordinators from the three (or more) *core institutions* involved in the technical organisation of the SoE and an EC representative.

5. Need, and relevance for Genomics and Health

Because of its rational implementation of molecular systems biology ESBIGH will have important spin-off for the areas Food Quality and Safety and Sustainable development, global change and ecosystems. Yet, ESBIGH focuses on the priority area Genomics and Biotechnology for Health. As the function of all living cells depends upon dynamic interactions between all cellular macromolecules (i.e. proteins, DNA, RNA), a **molecule-to-system approach** will greatly enhance the **understanding of the human organism and its diseases** and will enable the **effective exploitation of genomics** for the improvement of human health. Multidisciplinary research is necessary to translate the data accumulating from genomics into applications of molecular medicine. Accordingly, the incorporation of SB into genomics is multifaceted and cannot be covered by a single NoE. Several NoEs, IPs and large-scale NPs, each devoted to well-defined aspects of SB, will therefore be integrated in an overall context called the **"European Initiative on Systems Biology in the Service of Genomics and Health" (ESBIGH)**. ESBIGH will bring about maximum synergy between the individual consortia through the transfer and integration of data and know-how, the sharing of common databases, the organization and funding of cross-connecting research activities, a common teaching programme and the establishment of general **Standard Operating Procedures (SOP)**.

6. Excellence, feasibility and critical mass

ESBIGH will **unite and permanently integrate** various **"Networks of Excellence" (NoE), Integrated Projects (IP)**, as well as other recently initiated **national programmes (NP)** dedicated to SB. The criteria for including a new NoE, IP or NP in ESBIGH will be **(i) its importance for Systems Biology, (ii) its importance for the routes from Genomics to human Health, (iii) its scientific excellence, and (iv) likely synergy with the other consortia in ESBIGH**. This way, ESBIGH will not only serve as a **"crystallisation nucleus"** for further activities, but will also detect deficiencies that prevent the appropriate development of SB for Genomics and Health. Essential aspects of ESBIGH include:

- Integrative Genomics, i.e. parallel acquisition of diverse parameters relevant for genomics (e.g. transcriptome, proteome, metabolome) because function requires integration.
- Complex Systems, focusing on the emergence of properties from non-linear interactions of molecules.
- Entering the Living Cell; experimental determination of molecular properties in living cells.
- Integrative Bioinformatics, combining all data of the above experimental strategies with those from databases to calculate relevant implications.
- Silicon Life, i.e. making computer replica of living cells and organisms.

The **Annex lists prospective NoEs and IPs that will join ESBIGH** if they can acquire sufficient EC funding. It also lists the large national SB programmes that are already funded and have committed themselves to ESBIGH. Together these will amply supply the expertise and technology needed to address the above aspects.

7. Integration and structuring effect

The explicit aims of ESBIGH are to integrate and to structure: ESBIGH will integrate its IPs, NoEs and NPs and will therewith structure the European field of Systems Biology and Genomics. ESBIGH will create added value for advanced genomics in the context of human health by **creating synergy** between the NoEs, IPs and NPs. ESBIGH will **remain open** to new NoEs, IPs, and NPs and will even catalyse the formation of new NoEs and IPs. ESBIGH will actively **invite interested researchers, research institutions** and suitable organisations, on the premise of their excellent research performance. The structure of ESBIGH will facilitate the continuous integration of partners because each "member **consortium**" acts in parallel as an autonomous **module**. Many European countries are excellent with regard to individual technologies related to SB, but none of them does well in all the SB fields that need to be integrated to make SB work for Genomics and Health. Thus, we propose to link the top European expertise in SB relevant to functional genomics through a SoE termed ESBIGH. This SoE will **integrate the various subdisciplines** of SB, molecular and cell biology, and the novel platform technologies (including transcriptomics proteomics, metabolomics bioinformatics, functional genomics). It will therewith optimally **exploit the "data pool" of genomics**. The strength of this novel branch of research is the **joining of forces of different scientific disciplines**: It is generally accepted today that substantial progress can be made at the intersections of different scientific disciplines. We expect many **tremendous scientific and economic benefits**, e.g. through **in silico models** of major biological phenomena in living cells and organisms (**artificial models of life**), from the synergistic strength of such a SoE. The outcome

of **ESBIGH** will be relevant for applied science and industrial applications in biotechnology and molecular medicine. *Virtual cells* for example will facilitate drug development, studies on drug metabolism and drug detoxification will reduce animal experiments. The biotech and pharmaceutical industries (both SME and big pharma) will participate as cooperation partners in **ESBIGH**. **ESBIGH** will *implement an industrial platform*, providing for the rapid transfer of know-how to biotechnology applications. **ESBIGH** will also help manage individual intellectual property rights of its partners.

Annex: Composition of ESBIGH: IPs, EoIs, NPs, Institutes, Companies & Non-Profit Organizations

(1) Participating European Networks (NoE) and Integrated Projects (IP) include:

- **YSIC**, Yeast Silicon Cell (**Alberghina**, Milano/Westerhoff, Amsterdam I/NL) **IP**
- **3D Genomics** (**Van Driel**, Amsterdam; NL) **IP**
- **Hierarchical Concepts** (**Gilles**, Magdeburg, DE) **IP**
- **Virtual Biotechnology: in Silico Simulations of Cells and Animals as Novel Tools for Biology and Toxicology** (VISION) (**Moore & Allen**, Plymouth, UK) **IP**
- **Omic united**; a systems biology perspective from the genome to the physiome (**Wolkenhauer**, Manchester, UK) **IP**
- **Biosimulation** - A New Tool for Drug Development (**Mosekilde**, Lyngby, DK) **NoE**
- **Nerve Cell Simulation** (**Cattaneo, Arisi**, Rome, IT) **IP**
- **ABC-RescEU** (**Kuchler**, Vienna, AT) **NoE**
- **Microgravity and Life Sciences** (**Jack van Loon**, Amsterdam, NL) **NoE**
- **BioTools** (**Hans Söderlund**, FI) **NoE**
- **ESBCC: European alliance for Systems Biology applied to Cell Division and Cancer** (**Serrano, Barbacid, Wodak**, Heidelberg, Madrid, Brussels, DE, ES, BE) **IP**
- **From the virtual cell to the real patient** (**De Meyts**, Novo Nordisk, DK) **IP**
- **Building an integrated network; open source, compatible bioinformatics databases & SB tools** (**Kuiper**, Gent, BE) **NoE**
- **Interaction Proteome**. Functional Proteomics: towards defining the interaction proteome (**Hartl**, Martinsried, DE) **IP**
- **Cellular Signaling Networks in Tumor Biology and Immunology** (**Höfer & Heinrich**, Berlin, DE)
- **Cellicium**. From bio-array imaging to morphogenesis (**Demongeot**, Grenoble, FR) **NoE**
- **CROWD**. Proteins in cells: structure, folding and interactions in crowded environments (**Pons**, Barcelona, ES) **IP**
- **DYNAMO**. Platforms for Monitoring of Dynamics of Cellular Processes (**Ruzgas/Emnéus/Owman**, Lund, SE) **IP**
- **EUTERS**. Unifying Theoretical and Experimental Research in SB (**Kummer/Wade**, Heidelberg, DE) **IP**
- **STYFF**. Signal Transduction in Yeasts and Filamentous Fungi (**Johan Thevelein**, Leuven, BE) **NoE**
- **E-Plant**. European Plant Systems Biology Network (**Ferda Mavituna**, Manchester, UK) **NoE**
- **FEPACS**: Fuel Ethanol Production from Alternative Carbon Sources (**Richard**, Helsinki, FI) **IP**
- **PROTEUS**. Functional genomics; symbiotic & pathogenic alpha proteobacteria (**Jean-Jacques Letesson**, Namur, BE) **IP**
- **BITOPIA-FUGE** BioInformatics Tools Optimised Prediction & Integrative An. Funct. GEN" (**Heeringa**, London) **IP**
- **The Living Soil**. Biotrophic indicators of soil health, usage & habitat restor. (**V Veen**, Heteren, NL) **IP**

(2) Contributing large national programs (NPs) include:

The Amsterdam-centered Silicon Cell (SiC) programme aiming at the generation of precise replica of living cells and living organisms and provides a [web-based model 'data' base](#).

The German **"Systems of Life - Systems Biology"** activity supporting multidisciplinary research teams integrated in a competence network with a focus on the human hepatocyte.

The UK **Network for Systems Theory & Genomics (Genetic Systems)**, funded by EPSRC, coord.: Wolkenhauer.

The **Swedish national systems biology initiative**, coordinated by Hohmann

The **French** CNRS National program **Energy from Biomass**, coordinated by Gerard Goma

The **French network ARC CPBIO**, Cooperative Research Initiative; Biological Processes & Process Calculi, coord: Fages

The **Greek National Initiative on Structural Genomics** coordinated by Mike Kokkinidis

(3) Interested individual research groups/institutes. Individual groups and institutes will be associated to ESBIGH through consortia that affiliate to ESBIGH. A list of interested groups: <http://www.systembiology.net/>

(4) Companies The companies supporting or involved in the IPs, NoEs and NPs that compose ESBIGH (see above) will be invited to take part in the industrial board of ESBIGH. Large multinationals and SMEs have expressed interest in the steering of ESBIGH through its SAB (see above). For further information see <http://www.systembiology.net/>

(5) Non-profit organizations Non-profit organizations such as public research institutes or evaluation centers have expressed their interest to join ESBIGH: see <http://www.systembiology.net/>.

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