

# Systems Biology: Its Past, Present and Potential

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## Abstract

**T**his review considers Systems Biology currently as a network of disciplines rather than as an already well integrated field. The diverse views of “what Systems Biology is” are traced to particular challenges and successes in evolving “systems level views” of biological processes within each discipline. The interaction of the different disciplines within this network is already contributing to each discipline’s development and “focussed subnetworks” which could lead to a higher integration level are emerging. The potential impact of Systems Biology in medicine, drug discovery as well as education in the sciences is briefly outlined. The initial activities and successes in initiatives such as SMILES at UP Diliman as well as upcoming challenges for Systems Biology in the Philippines are described. Systems biology could be an important step towards a theory of biology.

## 1. What is Systems Biology?

Systems Biology has rapidly emerged since 2000 as one of the leading paradigms for the life sciences in the early 21<sup>st</sup> century. The year 2000 was significant for the field’s emergence not only because of the completion of the Human Genome Project, but also due to three pioneering efforts: the founding of the Institute for Systems Biology in Seattle (headed by Leroy Hood), the occurrence of the First International Conference on Systems Biology in Tokyo (chaired by Hiroaki Kitano) and the initiation of activities for SBML (Systems Biology Mark-up Language) mainly led by John Doyle at Caltech. The integrative approach has captured the imagination of biologists and the wider scientific culture. Its growing influence has led to the establishment or re-focus of many research groups and institutes, including Harvard Medical School’s establishment of a Department of Systems Biology—it’s first entirely new one in 20 years—with a substantial investment in resources and facilities. PhD study programs in Systems Biology, led by 3 top US universities—MIT, Harvard and Princeton were established already in 2004. A plethora of new scientific events and journals

with “Systems Biology” in their titles have emerged and established ones added significant subsections devoted to the field. National and international initiatives for Systems biology, coupled with the provision of substantial funding, have been started worldwide.

Given this importance, it may be surprising to discover that, as even the ISB admits “at present, there is no universally accepted all-encompassing definition of systems biology, even among scientists at the [institute]” (ISB 2009). Some proponents emphasize the use of high throughput “omics” technologies and use data covering the whole system for a “top down” approach (Ideker et al 2001), others prefer a “bottom up” method from molecules to functional modules (Hartwell et al 1999), (ESF 2005). A third group views Systems Biology as the “New Physiology” (Noble 2008) and has adopted in pioneering work on heart models a “middle-out” strategy, starting from tissue models (“middle level”), incrementally extending to the organ and “higher” levels as well as “down” to molecular detail (Noble 2006). Others see that “Systems Biology offers an opportunity to study how the phenotype is generated from the genotype and with it a glimpse of how evolution has crafted the phenotype” (Kirschner 2005). Practitioners with an engineering background prefer the formula “Systems biology is the application of dynamical systems theory to biology”. In addition, various other names such as “quantitative biology”, “digital biology”, “predictive biology” or “integrative biology” have been suggested. However, despite all these differences, a certain “set of premises that characterize the approach” exists (ISB 2009). C. Priami (Priami 2009) has identified “at least four characteristic concepts” in all definitions as follows: “Systems Biology is a transition

1. from qualitative biology towards a quantitative science from reductionism to systems level understanding of biological phenomena

2. from structural, static descriptions to functional, dynamic properties
3. from descriptive biology to mechanistic/causal biology”

A compact description of these core aspects is provided by the following “working definition” from (Kirschner 2005): “However if forced to provide some label for systems biology, I would simply say that systems biology is the study of the behaviour of complex biological organization and processes in terms of its molecular constituents.” (see also Mendoza 2005). The work of the EraSys project (<http://www.erasysbio.net>) also provides a careful characterization of the field, which is acceptable to

## 2. The Roots of Systems Biology

### 2.1 The view from Biology

Most biologists view Systems Biology as the “next level” of molecular biology. In their influential essay “From molecular to modular cell biology”, L. Hartwell et al argue for the recognition of functional modules as a critical level of biological organization as follows: “Much of twentieth-century biology has been an attempt to reduce biological phenomena to the behavior of biological

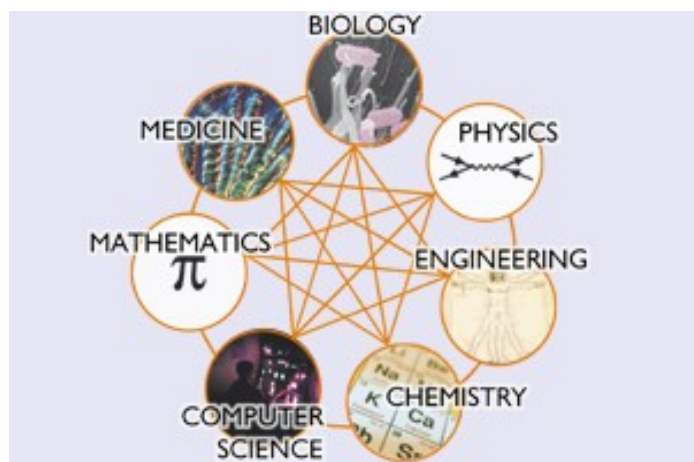


Figure 1. Systems Biology: a network of disciplines.

a range of funders across Europe.

While a certain degree of diversity in direction is “normal” in dynamic, emerging fields, I will argue below that the current situation in Systems Biology is closely related to the field’s key research requirements/strategies 1) the extremely broad multidisciplinary scope or approach and 2) tight integration of the work of experimenters and computational modellers. These two key characteristics stem directly from the underlying complexity of biological systems: Figure 1 (originally from ISB website in 2003) illustrates Systems Biology as a “network of disciplines”, of which the seven most important ones are listed: biology, (bio)chemistry, medicine, engineering, physics, computer science and mathematics. Similarly, NIH (2007) sees the field as “a discipline at the intersection of biology, mathematics, engineering and the physical sciences ...” In the following section, we trace the roots of Systems Biology in the individual disciplines in order to understand the current diversity and attempt to identify potential paths of integration at different levels (cf. also the discussion in Section 5.2).

Table 1a. Adapted from Figure 1 (Westerhoff and Palsson 2004).

Year	Event/Trend
1944	DNA, the genetic material
1953	DNA structure
1960-1980	Recombinant technology
1976-1990	Automated sequencing
1990-2000	High-throughput at genome scale, “data rich” biology
2001	Human genome sequenced

molecules...Despite the enormous success of this approach, a discrete biological function can only be rarely attributed to an individual molecule...In contrast, most biological functions arise from interactions of many components” (Hartwell et al 1999). Some of the key events of this “mainstream” development were discussed by H. Westerhoff and B. Palsson (Westerhoff and Palsson 2004) and listed in Table 1A.

This view of the evolution of systems biology is clearly echoed by the following statement on the ISB website: “Delineation of a species’ genes is the starting point for systems biology. The genes, and the proteins they encode, constitute a “parts list” for any said species. Once the parts are in hand, a focused, yet global, investigation of how their molecular interactions engender the distinctive properties of the species becomes more tractable and more exciting”. (ISB 2009).

Westerhoff and Palsson also discuss “a lesser known effort that constantly focussed on the formal analysis of new functional states that arise when multiple molecules interact simultaneously”, with key events as listed in Table 1B. In effect, they argue that, from early on, “systems level thinking” was present in the field, though not as prominent

or dominant. P. Wellstead (Wellstead 2005) also confirms this “duality”: he noted that E. Schrödinger, the famous physicist, expounded two “big ideas” in his Dublin lectures (later compiled in his influential book, “What is Life?”, 1944): the first one was his discussion of individual molecules in determining biological events, with which he, together with other physicists such as M. Delbruck, significantly contributed to the nascent field of molecular biology. The second big idea was what would now termed “a systems approach to life.” It is interesting to note that this line of development in molecular biology has significant overlap with biochemistry (highlighted in yellow).

M. Kirschner (Kirschner 2005) notes, that while systems biology is built on molecular biology, it also derives key concepts from other subdisciplines, such as physiology (e.g. adaptive states of the cell), developmental biology (e.g. the importance of a succession of physiological states in a process) and on evolutionary biology and ecology, especially “for the appreciation that all aspects of the organism are products of selection, a selection we rarely understand on a molecular level”.

towards scaling up to larger networks consisted in transitioning from mechanistically-based functions (e.g. Michaelis-Menten rate law) to approximate canonical models, e.g. power laws in BST (Chou and Voit 2009). While MCA was mainly restricted to metabolic networks, BST techniques were applied to other biological networks, such as gene regulatory networks beginning in the late eighties. Another significant development –the reconstruction of genome-scale stoichiometry-based metabolic networks--was pioneered largely by B. Palsson’s Lab at UC San Diego. By considering various constraints on the stoichiometric matrix of the large network, they were able to deduce important properties without having to use kinetic information (Palsson 2006).

The historical connection between medicine and systemic approaches has been strongest through physiology. This is not surprising, since physiology was formerly often called “experimental medicine.” The French physiologist Claude Bernard (1813-1878) , whom D. Noble recently portrayed as the first systems biologist ( Noble 2008), entitled his major discourse on the scientific method, “An Introduction to the Study of Experimental Medicine” (1865). Bernard not only did trailblazing experimental work, but also foresaw clearly the need to use mathematical methods to advance his field’s research. His concept of “milieu interieur” formed the basis for Walter Cannon’s “homeostasis” approach at Harvard Medical School (1933).

The work of A. Hodgkin and A. Huxley (1951-52) marks a further milestone in physiology’s contribution to systems biology. Their model, which quantitatively describes how a cellular behaviour (i.e. propagation of action potentials along an axon) emerges from the interaction between two different molecular components (i.e. a potassium and a sodium channel) has been recently appraised as marking the beginning of computational systems biology (le Novère 2007). However, this praise should not detract from their painstaking experiments (based on voltage-clamp methods) and insightful analysis of the data which formed the basis of the model (a complex set of differential equations). The model has been uniquely influential, not only in neuroscience, but also in other fields of physiology, e.g. the cardiovascular system (Cronin 1987).

The physiological view of Systems biology emphasizes a multi-level (and hence multi-scale view) of systems biology, with the higher levels serving as constraints. For example, the cells and organs of the body produce many different messengers, mostly small molecules such as hormones or transmitters, to transmit such influences. In Figure 2 , the small arrows (going upward) denote what Noble calls the “reductionist causal chain”, while the large arrows emphasize the constraining role of the higher levels.

Table 1b. Adapted from Figure 1 (Westerhoff and Palsson 2004).

Year	Event/Trend
1931	Non-equilibrium thermodynamics
1952	Self-organization
1957	Feedback mechanism in metabolism
1958-63	Analog simulation, bioenergetics, lac operon
1970-1980	Large-scale simulators of metabolic dissipative structures, energy coupling, MCA (Metabolic Control Analysis) and BST (Biochemical Systems Theory)
1980-1995	“Data poor” in silico biology, models of viruses, red blood cells
1995-2000	Genome-scale models and analysis, large-scale kinetic models

## 2.2 The views from (Bio)chemistry and (Bio) medicine

Molecular biology and Biochemistry have always been closely related—as can be seen from various professional organizations for experts in both areas, including the Philippine Society for Biochemistry and Molecular Biology—so that the overlaps in Table 1B are not surprising. Underlying the pioneering work in the 70’s of both Metabolic Control Analysis (mainly in Europe) and Biochemical Systems Theory (mainly in the US) for modelling and analysis of metabolic networks were the advances in enzyme kinetics, which began with the work of Michaelis and Menten in 1913. An important step

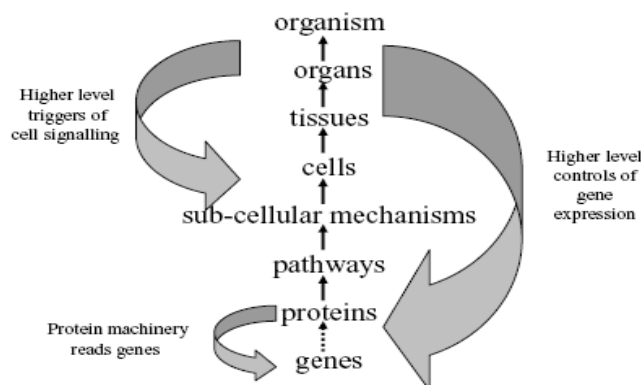


Figure 2. Interactions between various levels of biological organization (from Noble 2008).

## 2.3 The view from Engineering

Biologists are often surprised when they learn that the term “Systems Biology” was introduced by an engineer at the Case Institute of Technology (now Case Western Reserve University), Michaelo Mesarovic, some forty years ago. This is documented in the proceedings of the International Symposium on Systems Theory and Biology, which were published by J. Wiley and Sons. In fact, a review in *Science* (Vol. 161, No. 3836, July 1968) entitled "A Means Towards a New Holistic" concluded with the statement, "A field of systems biology with its own identity and its own right" has been launched. Hence, in its original sense, systems biology was understood to be “the application of systems theory to biology”. Two points of clarification are important here: First, dynamical systems theory (rather than the traditional study of “linear systems” for reverse engineering) is meant here, particularly with its emphasis on studying non-steady states. The second point is that Mesarovic himself, being conscious of the complexity of the task, was more cautious and prescient when he wrote ““The real advance in the application of systems theory to biology will come about when biologists start asking questions which are based on system-theoretic concepts....then, we will have a field of systems biology with its own identity and in its own right” Mesarovic 1968). Indeed, it would take more than thirty more years before the field blossomed around the turn of the century.

The manifold roots of Systems Theory itself and the evolution of its relations to biology are well documented in Wellstead’s essay on Erwin Schrödinger (Wellstead 2005). The paper (Wolkenhauer et al 2003) was the first comprehensive introduction of the re-emergent field to the engineering community. Table 2 is a synopsis of some of the key events mentioned in Section 5 “The Rise of Systems Theory” in that essay and (Wolkenhauer 2001) .

I have found it important in discussions with biologists to emphasize the past contributions of engineering to the development of systems biology. Its continuing importance is even more highlighted by the rapid development of areas such as “synthetic biology”. It is however important to stress that, in the simple sounding formula “systems biology is the application of systems theory to biology”, systems theory refers to the theory of dynamical systems. Though less well known outside of engineering disciplines, this view would (at least conceptually) integrate the results of practitioners of the other discipline. For example, the study of complex networks in terms of their degree distributions or “cliquishness”, which belongs to the tradition of statistical physics, would be a part of the evolving theory of dynamical systems. A second important comment is that biological systems are evolved systems and not designed ones, and hence an engineering-inspired approach to such systems is not trivial (Alon 2003) , (Way and Silver 2007).

Table 2. Key Events in Systems Theory.

Year	Event/Trend
1900-1930	Black box descriptions of electrical circuit modules, characterization thru input signals, based on work of O. Heaviside (1850-1925)
1930-1945	Invention of negative feedback amplifier, math theory of feedback systems by H. Nyquist (1932) and H.W. Bode (1945) based on previous work by Maxwell, Routh etc
1930-1945	Mathematical characterization of signals, particularly for noise reduction and signal recovery (Lee, Wiener, Kolmogorov, Shannon)
1948	The field of cybernetics is established (N. Wiener)
1948	L. Bertalanffy proposes systems view of biology
1950-1965	Application of electrical engineering work to more general systems (Olsen, Paynter)
1968	M. Mesarovic develops systems theoretic approach to biology and coins the term “systems biology”
1970-	Development of the field of biomedical engineering in close connection with systems and control theory
1980-1995	Work by R. Rosen on “relational biology”
1990-2000	Emerging systems approach to biology (e.g. Kordon 1993)

## 2.4 The view from Physics

The key role of physicists such as E. Schrödinger in establishing molecular biology and systems approaches to life also highlights the very diverse and indirect ways that the discipline has contributed to systems biology. Even Biophysics-the discipline’s most explicit interface to the life sciences-exhibits a tremendous variety of work and achievements . For example, Wikipedia’s entry on the field (Wikipedia 2009) lists the following “Famous Biophysicists” in Table 3:



## 2.5 The view from Mathematics

However, from this and an adjoining list of “Other notable Biophysicists”, only 5 out of over 40 have clearly identifiable contributions to systems approaches, pointing to the dominance of reductionist approaches (as in molecular biology) in the field. The part of Theoretical Biophysics using statistical physics approaches are of course another exception. It was from this vantage that the study of complex, dynamic networks developed in the late 90’s (e.g. work of S. Strogatz, A. Barabasi and others) that

Table 3. Famous Biophysicists (from Wikipedia 2009).

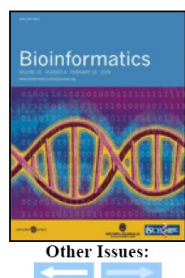
Scientist	Major Achievement
Luigi Galvani	Discovery of bioelectricity
Hermann van Helmholtz	First measurement of the velocity of nerve impulses, studies of hearing and vision
Alan Hodgkin & Andrew Huxley	Mathematical theory of how ion fluxes produce nerve impulses
Georg von Bekesy	Research on the human ear
Bernard Katz	Discovery of how synapses work
Hermann J. Muller	Discovery of how X-rays cause mutations
George Pallade	Electron microscopy studies of protein secretion and cell ultra-structure
Linus Pauling & Richard Corey	Co-discovery of the alpha helix and beta sheet structures of proteins
J.D. Bernal	X-ray crystallography of plant viruses and proteins
R. Franklin, M. Wilkins, J. Watson & F. Crick	DNA crystallography and discovery of the structure of DNA
Max Perutz & John Kendrew	Pioneering work in protein crystallography
Sir John Randall	X-ray and neutron diffraction of proteins and DNA

a further significant contribution to systems biology from the physics community emerged (Barabasi 2002).

Moreover, especially in the earlier years, the dividing line between Biophysics and other scientific areas (e.g. Physiology) was not clear, especially when persons such as A. Hodgkin, A. Huxley and Bernard Katz, who are more widely known as physiologists, are listed as “biophysicists”. One important area of contribution though is the development of new experimental techniques and instrumentation – this is definitely Physics and extremely important for many advances in biological research.

Many mathematical structures and relations are applied in mathematical model construction and analysis, the most popular formalism being systems of differential equations. Most of these applications, particularly in cellular and molecular biology, have been done by practitioners of non-mathematical disciplines (rather than “card carrying” mathematicians). In fact, there are a number of examples where within such application efforts, mathematical results have been re-invented, e.g. biochemists introduced sets of T-invariants of Petri nets under various names in the context of stoichiometry-based analysis of biological networks. Why this anomaly? Hans Westerhoff, a leading European systems biologist, offers the following explanation: “Stereotypical mathematicians do not like biology, nor do they like chemistry. They have learned to accept physics, and indeed the real-world side in their studies has always been physics, never biology. This has been because physics was reductionist, reducing problems to simpler ones that could actually be solved mathematically. Biology was considered impure, [with] a large number of special cases, where no analytical solution would be possible because it was too complex, too nonlinear” (Westerhoff 2007).

Underlying this “culture” was of course the transformation of mathematical practice after the foundational crisis in mathematics in the first third of the 20<sup>th</sup> century. Pure mathematics, as particularly encouraged by the influential French Bourbaki school, became a completely axiomatized body of knowledge and no longer seen as “a language of nature”. A more or less formal derivation from the axioms (“proof”) was the main (or even sole) measure of the quality of results and little attention was given to “applicability” or “correspondence with” with natural phenomena. In their insightful book “The Biology of Numbers”, G. Israel and A. Millan Gasca point out that the “Biomathematics” of the eminent Italian mathematician Vito Volterra in the late 30’s could “be seen in this sense as an anomaly to a general trend....He [Volterra] was really interested in empirical evidence for his theory.” (Israel and Gasca 2002). The two decades between 1920 and 1940 are often called “the Golden Age of Theoretical Biology” with the advances in conceptual application of mathematics to biology, as in the works of D Arcy Thompson, A. Lotka, R. A. Fisher and V. Volterra. The statistically-oriented work of J.B.S. Haldane and S. Wright in population genetics was another important area in the then emerging field. Although Mathematical Biology drifted away from the mainstream of mathematics, there were still individual achievements, particularly on the organismic, physiological and ecological levels, (some of which were even awarded Nobel Prizes) and which are beautifully documented in textbooks such as “Mathematical Biology” by J. Murray.



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Figure 3. Systems Biology: a section of the "Bioinformatics" journal.

The biology-inspired study of stochastic processes is becoming a major contribution of mathematics to systems biology. Statistical methods have been applied, too, and refined primarily in the context of high-throughput "omics" methods, e.g. for the inference of gene regulatory networks. Most of the stochastic modelling techniques rely on variants of Markov processes – an excellent introduction is given in D. Wilkinson's book [WILK06] and an original overview (in the form of a "family tree") in (Ullah and Wolkenhauer 2007). One should also not forget the contributions of a remarkable mathematician: John von Neumann. In the 40's he introduced both the concept of cellular automata, which has widespread use in the modelling of tissues, in particular of tumors as well as together with an economist, Oskar Morgenstern, Game Theory. A further development of the latter, Evolutionary Game Theory, has been the basis of the field of Evolutionary Dynamics and is increasingly integrated in the modelling of intra- and intercellular biological processes, particularly in the context of agent-based modelling.

Despite these ventures, Westerhoff (a Vice-President of the European Society for Mathematical and Theoretical Biology) nevertheless points out that "much of the growth in Systems Biology has bypassed the Mathematical and Theoretical Biology community". He sees the root cause in the following attitude of Mathematical Biologists: "Yet many of them kept searching for general mathematical principles in highly idealised or simplified models, thereby foregoing the essence of Systems Biology. They did not

want to descend to the details of molecular biology and its nonlinearities" (Westerhoff 2007).. He ends his article with an urgent appeal to the community no longer to "avoid the issue of what "Life" here and now is" and contribute to a new Mathematical Systems Biology.

## 2.6 The view from Computer Science/Informatics

The subdiscipline of Computer Science (or Informatics) that has contributed most to Systems Biology is Bioinformatics, which emerged in the late 80's, in parallel to the ambitious Human Genome Project. The term "Computational Biology" is often used as a synonym, although others would say that the latter is the larger field and would include computational approaches to models arising in Mathematical Biology. According to Wikipedia "The term *bioinformatics* was coined by Paulien Hogeweg in 1978 for the study of informatic processes in biotic systems. Bioinformatics nowadays entails the creation and advancement of databases, algorithms, computational and statistical techniques, and theory to solve formal and practical problems arising from the management and analysis of biological data. Many computer scientist view the computational side of Systems Biology (or "Computational Systems Biology" for short) as the "next level" of bioinformatics, though research methods and educational approaches are substantially different from those of "traditional" Bioinformatics. The leading journal in the field, also called *Bioinformatics* now includes "Systems Biology" among its subsections (Figure 3 ).

Another area of Computer Science which has recently grown in importance in Systems Biology is the theory of concurrent systems. The earliest such theory, Petri Nets, which dates back to the mid-sixties, was also the first to be applied to biological networks (Reddy et al 1993). C.A. Petri himself already considered applications of a similar approach to chemical networks as early as 1939. Various extensions of the basic place/transition nets for applications in engineering, business management, software development have also been applied to all kinds of biochemical networks.

Other concurrency approaches, such as process algebras or state charts, particularly in their stochastic variants, have also been successfully applied to biological systems. The Nature essay "Cells as computation" by A. Regev and E. Shapiro provides a succinct summary of these modelling methods (Regev and Shapiro 2002), which will be discussed in next section under the heading of "algorithmic" or "executable" Systems Biology (Priami 2009), (Fisher and Henzinger 2007).

### 3. The Current Impact and Potential of Systems Biology

Viewing Systems Biology as a “network of disciplines” not only explains the diversity in scoping the field but also in assessing its current impact and potential. While in the previous section, we showed how the important contributions of each discipline have shaped its particular view of systems biology, in this part we will provide examples of how the challenges and opportunities of the broadly interdisciplinary field are already impacting or will in the near future impact the various disciplines.

#### 3.1 Towards Predictive and Personalized Medicine

Its potential impact on medicine and healthcare—most clearly expressed by Leroy Hood in his vision of a new P4 Medicine - with the predicates “predictive, preventive, personalized and participatory”—is the major factor in the shift of research funding to the field. The 7<sup>th</sup> Framework Program of the European Union, which comprises the most important supranational research funding in the region between 2007 and 2013, dedicates its Health and Life Sciences sector funding mainly to two themes: Systems Biology and Translational Medicine. The vision is already resulting in tremendous changes in the life sciences and health industries. “Systems Medicine” or “People Medicine” are also terms used in this context (Russell 2007).

Indeed, the tremendous advances in genomics in the last decade have fuelled the concept of “personalized medicine” independent of systems biology. New areas of healthcare such as “consumer genomics” or “personal health information services”—with Internet heavyweights such as Google, Microsoft and IBM entering the fray—have emerged in the last two years. However, it is only its synergy with the predicates “predictive” and “preventive” which has the promise of a new kind of proactive (rather than today’s reactive) medical practice. The individual’s active “participatory” role in deciding on the possible analytic and therapeutic alternatives then becomes imperative because of the far-reaching consequences of such knowledge.

L. Hood et al provide the following summary of their vision in a *Science* viewpoint essay (Hood et al 2004):

“The medicine of today is reactive, with a focus on developing therapies for preexisting diseases, typically late in their progression. Over the next 10 to 20 years, medicine will move toward predictive and preventive modes. New technologies will allow individuals to have the

relevant portions of their genomes sequenced, and multiparameter informative molecular diagnostics via blood analysis will become a routine procedure for assessing health and disease status. During this period, there will also be extensive correlations of genetic variations with disease, and this combination of advances will allow for the determination of a probabilistic future health history for each individual.

Preventive medicine will follow as disease-perturbed networks can be used to identify drug targets—first for therapy and later for prevention. Pharmacological intervention will focus on preventing disease-mediated transitions, as well as reversing or terminating those that have occurred. This will require building a fundamental understanding of the systems biology that underlies normal biological and pathological processes, and the development of new technologies that will be required to achieve this goal.

Predictive and preventative medicine will lead naturally to a personalized medicine that will revolutionize health care. Drug companies will have the opportunity for more effective means of drug discovery guided by molecular diagnostics, although the paradigm will shift to partitioning patients with a particular disease into a series of therapeutic windows, each with smaller patient populations but higher therapeutic effectiveness. Health care providers will move from dealing with disease to also promoting wellness (prevention). Finally, the public must be educated as to their roles in a very different type of medicine, as must the physicians who practice it.

Voit and collaborators (Voit and Brigham 2008) have begun to develop conceptual tools towards this vision and applied them to health and disease scenarios. The concept of a “health simplex” provides an intuitive visualization and efficient quantification of delineating health and disease conditions in a personalized manner (s. Figure 4 from (Voit 2009)).

The recent European Science Foundation (ESF) Science Policy Briefing entitled “Advancing Systems Biology for Medical Applications” (ESF 2008) is particularly valuable as it identifies promising application areas for mathematical modelling and formulates specific recommendations how to address this potential. The five areas identified are cancer, the link between cancer and ageing, inflammatory diseases, chronobiology and chronotherapy and last not least, disorders of the central nervous system. Initial projects are underway in these areas in order to implement the first steps recommended.



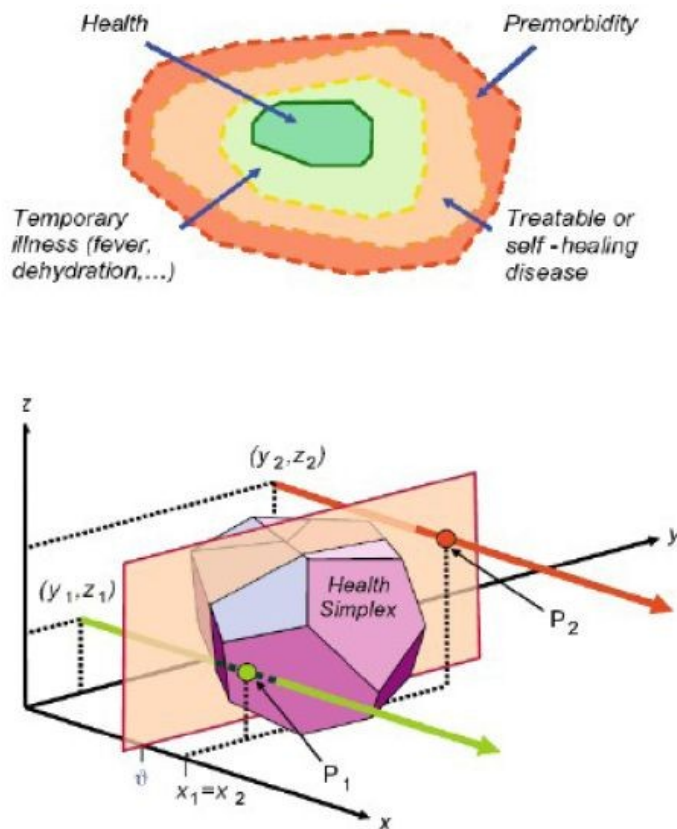


Figure 4. The "health simplex" concept (from Voit, 2009).

### 3.2 Synthetic Biology – are the engineers taking over the lab?

In the Top Ten Breakthroughs of the Year 2005, *Science* magazine lists "Systems Biology Signals Its Arrival" as No. 8 and the article's first sentence reads: "Make room in the labs, molecular biologists. The engineers have arrived". While "molecular biologists have spent decades tearing apart cell signalling pathways... engineers have excelled in understanding complex systems..." and strive towards a dynamic (rather than static) view of these systems. The emergence of synthetic biology can be viewed as epitomizing the growing influence of engineering approaches in biology.

What is synthetic biology? A typical definition one encounters is the following: "Synthetic biology is concerned with applying the engineering paradigm of systems design to biological systems in order to produce

predictable and robust systems with novel functionalities in nature" (NEST 2008). Figure 5 illustrates this focus succinctly.

A question that immediately comes to mind is: is this not just biotechnology or its further development? The NEST document seems to confirm this view in the following example: "Designed microorganisms might be capable of producing pharmaceutical compounds that are extremely challenging for existing methods of chemical and biological synthesis. While several pharmaceuticals are already produced biotechnologically using genetically engineered organisms, the capacity to design complex synthetic pathways into such organisms could greatly expand the repertoire of products that could be made this way." The difference between traditional biotechnology and synthetic biology is between the former's "ad hoc and empirical" approach compared with the latter's "rational design and redesign of living systems at a deeper and more complex level". An impressive example of this is the work of Jay Keasling's at UC Berkeley which has developed semisynthetic artemisinin and is thus opening the prospect of inexpensive malaria cure (Amyris et al 2008).

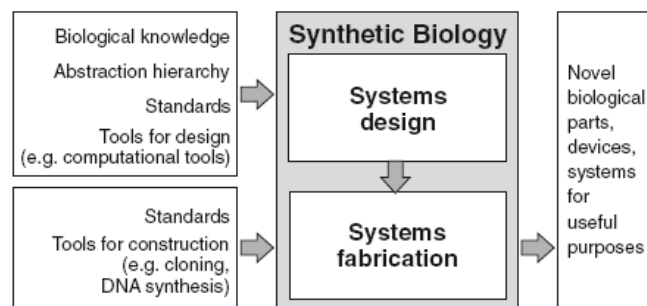


Figure 5. Synthetic Biology in context (from Heinemann and Panke 2006).

One should note though, that, as with systems biology, there are different viewpoints regarding the scope of the field: S. Benner and M. Sismour perceive two broad classes of synthetic biologists: those who use "unnatural molecules to reproduce emergent behaviors from natural biology, with the goal of creating artificial life" and those that "seek interchangeable parts from natural biology to assemble into systems that function unnaturally" (Benner and Sismour 2005). A further question often debated is: is synthetic biology a part of systems biology or not? Synthetic biologists more often than not stress the novelty and "independence" of their approaches (vs. systems biology) and new journals (such as IET's Synthetic Biology or Springer Verlag's "Systems and Synthetic



Biology”) seem to confirm this. On the other hand, the well-established engineering framework includes both a reverse engineering approach (with its typical recursive loop of systems modelling-systems simulation-systems reasoning-systems discovery) and a forward engineering aspect (modification and construction of systems with desired properties). Synthetic biology can hence be considered as the “design counterpart” of systems biology since its practitioners share the same holistic perspective” and use many insights of systems biologists for their design.

R. Weiss’ group at Princeton sees the tremendous impact of synthetic biology “as a new engineering discipline” in that it already shows the need to extend the classical engineering strategies of standardization, decoupling and abstraction. In their view, inherent characteristics of biological subsystems imply that, for example “the notion of cellular context in the functional definition of devices and modules as well as the use of rational redesign and direction evolution for system optimization, and focus on accomplishing tasks using populations rather than just individual cells.” (Andrianantoandro et al 2006)

Control theory is another area of engineering which is profiting tremendously from the study of complex biological systems. In particular, the non-linear character of the biological control systems has highlighted the need to go beyond the usual linear theory in engineering (Sontag 2005), (Wellstead et al 2008).

### 3.3 Impact on Physics and Chemistry

The impact in the fields of Physics and Chemistry (and related engineering activities) is most evident in the burgeoning fields of Bionanotechnology and Nanobio-technology. The former thrives more in the tradition of biomimetics (or *Bionik*, its established name in German), where bio-inspired methods are used in effecting nanotechnological advances. The latter discipline on the other hand uses advances in nanoscience and nanotechnology to study biological processes. One of the most important and successful fields here is the broad area of Bioimaging, including techniques from microscopy and spectroscopy for *in vivo* studies (producing data on dynamics so essential for modelling in systems biology) but on the other hand has provided many challenges for experimental physical scientists to further develop their methods (e.g. microscopy beyond the Abbe limit).

The emerging field of “Structural Systems Biology” is another example of the impact of Systems Biology in Physics and Chemistry, specifically in Biophysics (of molecular motors) and Quantum Chemistry. Structural Biology formerly focuses on understanding in detail (primarily through X-Ray crystallography) the structure of individual proteins or tightly coupled complexes (e.g. molecular motors). Advances in Cryo-Electron Microscopy have in recent years provided snapshots of the dynamics of such complexes. Structural Systems Biology then uses computational techniques (and lots of supercomputing power) such as molecular dynamics or coarse-grained methods to bridge the angstrom-quality (static) crystallographic pictures to the nanometer EM-snapshots, enabling impressive demonstrations of mechanistic details of complex motors such as the ribosome or even bacterial photosynthetic factories.

A further example is the emergence of graduate courses and research groups in the new area of “Systems Biophysics” which target the extension of biophysical techniques (typically applied to single or few molecules) to study complex systems, cf. <http://www.biosystems.physik.lmu.de/>. Some groups see a convergence with Structural Systems Biology (e.g. S. Rice group at Northwestern University).

### 3.4 Impact on computer science

The application of concurrency theory methods to biological systems was already introduced as an important recent contribution of computer science. The initial successes have encouraged the community to propose a distinct “algorithmic” or “executable” approach to Systems Biology. Figures 6a and 6b compare the “Algorithmic/Executable” (AlEx) and “Equational/ mathematical (EMa) modeling processes (adapted from (Fisher and Henzinger 2007). A perceived advantage of the “AlEx” approach is the availability of addition model validation techniques such as model checking. C.Priami perceives a big opportunity for computer science in further developing these methods (Priami 2009).

Evolutionary computing is another area of computer science increasingly applied in systems biology, particularly in network inference and estimation of parameters. (Chou and Voit 2009) provide a comprehensive overview of evolutionary computational methods currently used in the context of canonical ODE models. Other areas of growing importance are various information mining approaches, including data and text mining (Ananiadou et al 2006) and information systems supporting various forms of collaboratories (Olson et al 2008).

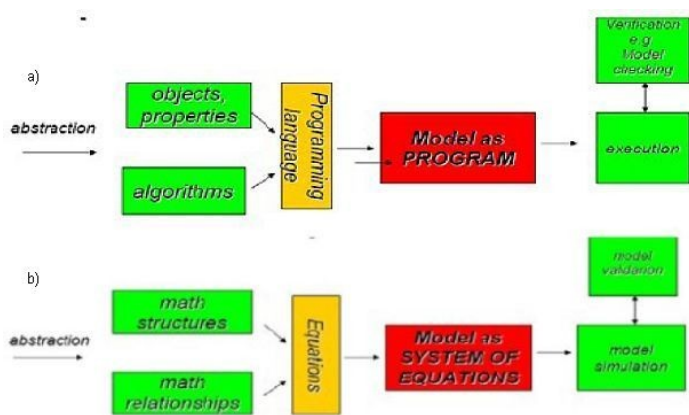


Figure 6. a) Algorithmic/Executable (AIEx) b) Equational/Mathematical (EMa) (from Fisher and Henzinger 2007)

### 3.5 Challenges of Systems Biology

As we near the end of the first decade of Systems Biology’s resurgence, it is useful to take a step back and reflect not only on the its impact on its constituent disciplines but also on the open questions and challenges facing the field as a whole. D. Noble ( Noble 2008) has summarized his reflections in a set of Ten Principles, which we have collected in Table 4 .

Table 4. Noble’s 10 Principles.

No	Principles of Systems Biology
I	Biological functionality is multilevel
II	Transmission of information is not one way
III	DNA is not the sole transmitter of inheritance
IV	There is no privileged level of causality (theory of biological relativity)
V	Gene ontology will fail without higher level insight
VI	There is no genetic program
VII	There are no programs on any other level
VIII	There are no programs in the brain
IX	The self is not an object
X	There are many more to be discovered, a genuine “theory” of biology does not exist

It would take us to far afield to discuss each of these principles in detail (the reader should read D. Noble’s lively—and slightly polemic—article for that). I restrict myself here to comments on two key computational aspects:

the first is the challenge of multilevel or multiscale modelling. I am not aware of a mathematically comprehensive and computationally efficient framework currently available for large, complex biological systems. It may well be that a single mathematical formalism will suffice, but rather a combination (engineers and computer scientists use the term “hybrid) of mathematical methods might be needed to adequately model such complex systems. The example of persistent infection (e.g. tuberculosis) was recently discussed by D. Kirschner and collaborators in this context (Young et al 2008) , (Blaser and Kirschner 2007).

The majority of current models do not address a further important aspect of biological systems, which is its spatial organization and dynamics (at each level). Not only location but “compartmentalization” is an important aspect in this regard and biological organization at various levels abounds with mechanisms that regulate these characteristics. Takahashi et al provide an excellent mini-comparison of current methods available for spatial modeling (Takahashi et al 2005).

The theory of Multi-Agent Systems (MAS), which originated in Artificial Intelligence research within Computer Science), provides an interesting approach to both the multi-scale and spatial aspects discussed above. There is in fact a partial re-invention of these approaches in the form of Agent-Based Modeling (ABM) through ecologists and biologists, but little synergy between the techniques actually applied (e.g. game theory is widely applied in MAS, but still scarce in ABM models). The relationship between MAS and process calculi or algebras in my view still needs to be better understood – traditionally, the two communities have not interacted too much, with the former more inclined to publish in software engineering/Artificial Intelligence journals and the latter in those of Theoretical Computer Science. Thus the former is more focussed on engineering aspects while the latter is judged by its suitability to mathematical analysis. The MAS community, for example, emphasizes the concepts of “objectives” and “beliefs” of an agent, which are not present or at least not explicit in a process (though these could be formalized with epistemic/modal logics). The computational efficiency of MAS is also an issue, as a recent study of the US Defence Department (an extensive user of MAS models for strategic planning) emphasized (Carley 2006).

Despite the current low impact of Systems Biology in Mathematics (e.g. Westerhoff’s recent call to action to the European Mathematical Biology community), I see a great potential for synergy between the two fields. A number of research institutes have been established to explicitly address the interface between Mathematics and Biology, and these are increasingly venturing into mathematical aspects of Systems Biology. Leading mathematicians such

D. Mumford (Brown University) and M. Gromov (IHES) have championed various aspects of the field as a rich source of mathematical challenges. As Systems Biology “grows up” beyond its initial “molecular” (i.e. intracellular) focus into multilevel/multiscale scenarios, the strengths of traditional Mathematical Physiology can also be combined appropriately with molecular detail.

A particular interesting field in my view consists of discovering novel methods for modelling biological membranes. On one hand, there is a strong tradition of using particle-based methods among theoretical biophysicists for detailed 3D-models on the small scale (hundreds of nanometer and nanoseconds) (Burrage et al 2007). On the other hand, computer scientists (the above

Perelman and others of the Poincare Conjecture (2003) and Thurston’s Geometrization Conjecture (2003-2006).

In my opinion, problems from Systems Biology provide an excellent opportunity to revive the legacy of Vito Volterra to test the validity of many of the new mathematical theories of the last 50 years as “a language of nature”.

### 3.6 Systems Biology and Research & Development Organization

Systems Biology demands effective communication between researchers on two levels: i) between the constituent disciplines and ii) between experimental and modelling/computational “mindsets”. Both tasks are not easy, given the strong tradition of specialization in the sciences and the innate complexity of biological phenomena. As I discussed in an earlier publication (Mendoza 2005), at many institutions, a two-level organizational approach has been implemented to address these challenges: besides the project-oriented activities in formal research centers, a level of “semi-organized networking”-distinct from “informal networking” is needed. The most prominent Systems Biology example is the Computational and Systems Biology Initiative at MIT (CSBi @ MIT). CSBi began in mid-2002 as a bottom-up initiative of young faculty members from Biology & Bioengineering. Despite the strong tradition of MIT in interdisciplinary work and the plethora of such research centers there, these researchers felt that they still could not leverage their individual expertise in collaborative projects on complex biological systems. With the support of several insightful department and center heads, they developed their ideas for an initiative “...designed as a virtual organization, a community of practice, built around a shared vision linking science and technology”. It was launched with the 1<sup>st</sup> CSBi Symposium in January 2003. CSBi membership is open to all MIT researchers from graduate students up, a current list of 105 affiliated faculty and PIs from 14 departments can be found at <http://csbi.mit.edu/index.html>.

An important factor for CSBi’s continuing success has been the development of an institute-wide technology infrastructure, the CSBi Technology Platform, that provides MIT researchers with access to complex technologies. CSBi has identified several technologies that will be required to advance systems biology at MIT. Each technology is treated as a core competency distributed across multiple facilities and labs. When integrated, these core competencies will serve as an enabling research infrastructure, including fee-for-service facilities and technology development centers. The Platform is actively managed by a group of faculty and supported by a

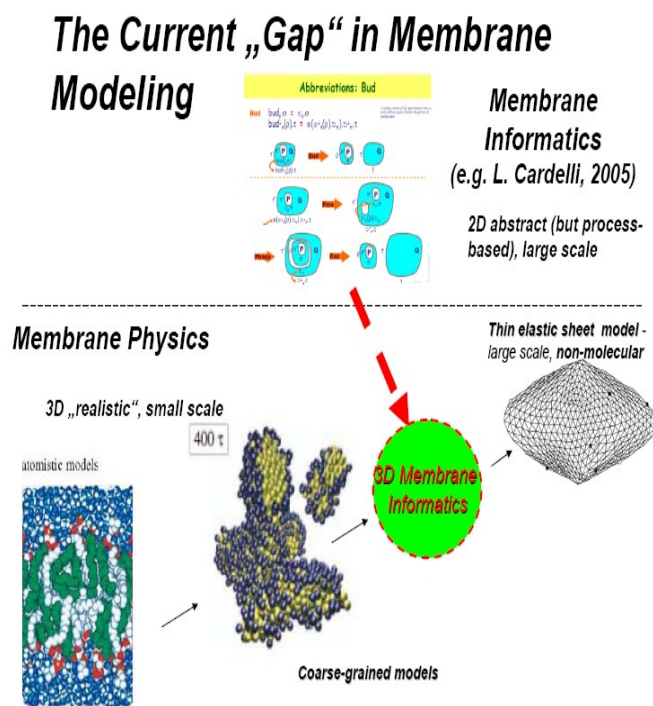


Figure 7: Membrane Modeling Approaches.

mentioned “algorithmic” community) have started to build the basis for a “Membrane Informatics” with a plethora of scalable (but only 2D so far) modelling approaches (Busi and Zandron 2007). The obvious gap (s. Figure 7) could be filled with a new “3D Membrane Informatics”, which could try to develop older “elastic membrane” methods by adapting the vast amount of deep mathematical concepts developed in 3D topology and geometry developed in the last 15 years which have culminated in the proofs by G.



network of CSBi Research Staff who act as links among the disparate computational and experimental facilities and engage in systems biology research and training. CSBi hence serves as a “collaboratory” in two aspects: as a community of practice and a provider of shared instruments (Bos et al 2008).

Novel approaches in drug discovery and development provide an interesting example of the impact of Systems Biology in industrial research and development. In viral

thinking” in drug discovery is H. Kitano’s proposal for a robustness-based approach. Particularly interesting is his framework relating “use of dynamics” and “number of components” in drug design (s. Figure 8).

Systems Biology is also causing changes in the drug discovery and development process itself. “Predictive Biosimulation” with Entelos’ software platform “PhysioLab” is beginning to enable pharmaceutical mainstays such as Pfizer and Johnson & Johnson, to substantially increase their drug discovery and development productivity (Bangs 2005). Innovative companies such as Merrimack Pharmaceuticals have even revolutionized their discovery and development processes through integration of computational and experimental approaches already. In parallel to these commercial (and hence proprietary) endeavors, projects in academia such as the Physiome Project of the International Union of Physiological Sciences (IUPS) and the EU-supported EuroPhysiome Network, have begun to focus on disease-relevant aspects, which will in the future contribute to drug discovery and development (Hunter and Borg 2003). Thus one can expect various paths of convergence between the commercial and academic efforts.

### 3.7 Impact on education

The active community of practice also enabled MIT to establish the first PhD program in Systems Biology in 2004. Like its counterparts at Harvard and Princeton (announced soon afterwards), it focuses on a few core subjects and stresses a systematic rotation among the participating laboratories. This allows the students to establish important contacts as well as orient themselves in the “network of disciplines” involved. Such an approach heightens the educational value of a common Technology Platform such as the one developed by CSBi, too.

The impact of Systems Biology on undergraduate education will be even be more pronounced, especially for the biosciences. M. Casman and collaborators, who conducted a worldwide survey on Systems Biology in 2005 noted in a Nature commentary (WTEC 2005) that “Unfortunately the translation of systems biology to a broader approach is complicated by the innumeracy of many biologists. Some modicum of mathematical training is required, reversing the trend in the past 30 years, during which biology has become a discipline for people who want to do science without learning mathematics”. On the other hand, serious collaboration between modelers and experimenters can only happen if the computational side learns enough biology to be able to communicate and interact productively. Princeton University, under the guidance of David Botstein, has started a fully interdisciplinary program for freshman students of biology,

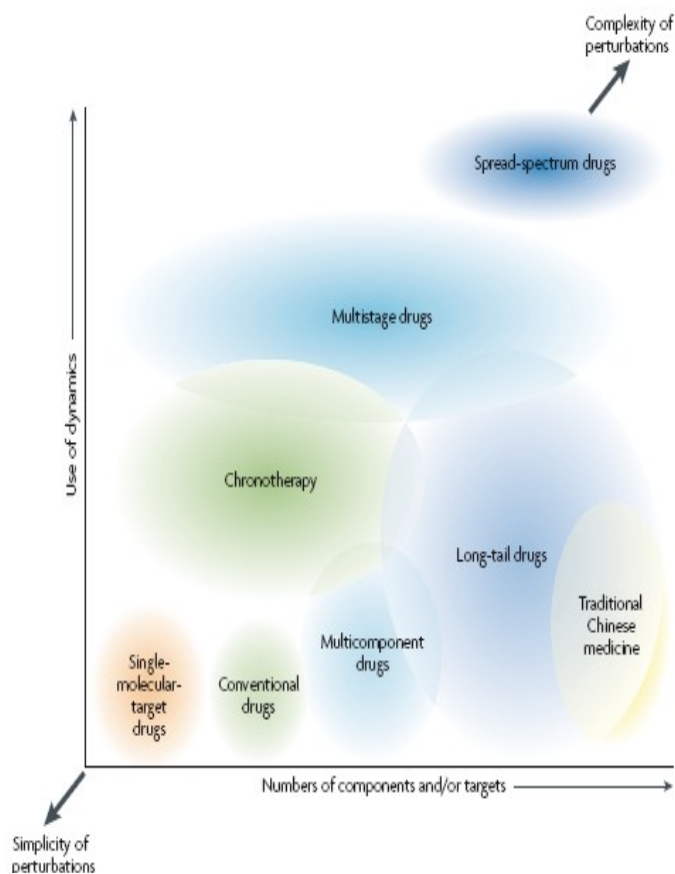


Figure 8. Robustness-based drug discovery in context (from ( Kitano 2007)).

infections, for example, drugs have traditionally targeted virally encoded enzymes that are essential for viral replication. But with the propensity of viruses to develop drug resistance on one hand and the increasing availability of data on virus-host cell interactions on the other, the alternative strategy of host-oriented anti-viral treatment is gaining ground-some authors call this a “paradigm shift” already (Tan et al 2007). Pfizer’s Selzentry/ Celsentri (maraviroc) is an example of a recently approved drug of this kind--it targets the human CCR5 receptor for anti-HIV therapy. Another example of systems biology-inspired “re-

chemistry, physics, mathematics and computer science, with the goal that each student will take subjects in all these disciplines but be specialized enough so that each could continue in their junior year in the standard course of that discipline. Prior to the program, an interdisciplinary group purged the curricula of all the disciplines of all contents “that were not 21<sup>st</sup> century vintage”. The program is voluntary and admittedly targeted at only the better half of beginning freshman students.

#### 4. Systems Biology activities in the Philippines

My focus on modelling biological systems developed from an interest in the theory of complex adaptive systems, which in turn arose from the rather mundane task of trying to manage a large, distributed IT consulting organization (Mendoza 2008). I was lucky to meet a few “right people at the right time” during a short visit to Manila in May 2002: this convinced me that the emerging field of “Systems Biology” (I had discovered Kitano’s influential overview paper in the March 1, 2002 issue of *Science* in the meantime) offered tremendous opportunities for Filipino researchers, particularly on the computational side and led me to initiate some of the activities described below.

##### 4.1 The SMILES<sup>□</sup> Initiative

The SMILES<sup>□</sup> (Statistics, Mathematics and Informatics in the Life and Environmental Sciences) initiative is an evolving multi-disciplinary “community of practice” of experimental and computational researchers and students at UP Diliman (UPD). The Mathematics Department initiated in January 2003 a series of lectures on “Mathematical and Computational Biology” by UPD researchers interested in identifying collaboration opportunities. After six weeks, a sufficient number of Joint Experimenter-Modeller (JEM) projects in the broader field of “Life Sciences” were identified and the “Mathematical Life Sciences Initiative” (MLSI) was established on March 20, 2003. In the ensuing period, besides the projects, a number of graduate courses related to the research topics were offered. Researchers and students from the Department of Computer Science as well as the School of Statistics joined the projects and broadened the basis for the research and at the same time, the applications also broadened to ecological and environmental areas. After two years, on the way to establishing formal tracks in the Graduate Studies in Mathematics and Computer Science, MLSI transformed into SMILES<sup>□</sup>.

While SMILES<sup>□</sup> is focussed on computational aspects, it is based on JEM projects and mandates that research-at all levels- be done in very close cooperation with

experimental partners. Due to constraints in resources for experimental work in the Philippines, partnerships with foreign groups have been forged from the very beginning, given the advantages of the Internet to do eScience. A maximum use of software standards (both established and emerging) and an emphasis on building reusable software (as much as possible based on open source or freely accessible components) are also targeted.

From the very beginning, SMILES<sup>□</sup> researchers agreed that their target was (in compliance with UPD standards) to publish in high-impact journals indexed by Thomson’s Institute of Scientific Information (“ISI journals”). This focus is an important element of the vision to become “by 2011, an internationally recognized research community active in applying Statistics, Mathematics and Informatics to the Life and Environmental Sciences and a leading innovator in interdisciplinary JEM project execution and Life & Environmental Sciences education in the region.”. SMILES<sup>□</sup>’s scorecard (Figure 9) as well as the very successful 10<sup>th</sup> International Conference on Molecular Systems Biology (Feb 25-28, 2008 at UP Diliman) attest to the progress made towards this vision.

### SMILES Scorecard (Q1 09)

#### • Research Publications:

- **ISI:** 15 (12 published, 3 in press), 2 accepted, 1 submitted, 5 for submission in the next 3-4 months
- numerous conf papers & posters

#### • Education at UPD

- **3 PhD (EE, Math) 6 MS Math, 6 MS CompSci completed**
- **Students:** PhD: 2 Math, MS: 1 Math, 2 CompSci

#### • Other:

- **5 Postdoc fellowships, 8 PhD scholarships and numerous research visits abroad**



Figure 9: SMILES after 6 years

Currently, SMILES<sup>□</sup> has 3 Focus Areas in research: MOLES (MOdelling networks in the Life and Environmental Sciences), WINKS (Web-based INTeGrated Knowledge-oriented and Systems) and DIMPLES (Digital IMage Processing in the Life and Environmental Sciences).

MOLES targets what is often called the core of “Computational Systems Biology”, particularly on the molecular and cell biological level. Modelling methods used vary from qualitative approaches (e.g. stoichiometric models, Petri nets, pi calculus) to quantitative methods (ordinary /partial differential equations, stochastic models), depending on the kind of data available from the experimental partner. Particularly important is the use of methods which are most easily understood by the experimental partners, to enable the intensive interaction needed for useful and predictive models. Petri nets (for qualitative models) and power-law approximations such as S- and GMA-systems (for ODE models) are examples of such approaches ((Rodriguez et al 2007), (Gonzalez et al 2007)). Interesting contributions to the systems biology of halophilic archaea and circadian systems were published during this period (del Rosario et al 2007), (Gonzalez et al 2008), (Roenneberg et al 2008)).

Data integration is a further important part of building the right infrastructure for systems biology. This line of research should be viewed as a further development of the data-oriented achievements of traditional bioinformatics. Experimental data from various –omics technologies and traditional methods, a variety of information from external sources as well as repositories of mathematical and computational models need to be integrated in a useful way for both experimenters and modellers. The emerging WINKS<sup>□</sup> strategy is a focus on Community-Oriented Information (CORI) Systems, that is, through close cooperation a particular Systems Biology research community, establish a customized, integrative system, which would also be sustained by the community. A first example of such a project is EUCLIS, the information system being built for the EUCLOCK research network, a 5-year Integrated Project of the EU 6<sup>th</sup> Framework Program, but envisioned as an information infrastructure for the worldwide (Systems) Chronobiology community ((Batista et al 2007)).

A further CORI-system VirhoLex (Virus-host interaction Lexicon) will be developed within the Manila Bay Research Corridor (MBaRC) initiative between DLSU Manila, UP Manila and Mapua. The architecture of such systems will evolve into a digital-library based Common Information Space (or “Collaboratory”) in order to effectively handle the diverse multimedia objects dealt with by broadly multidisciplinary systems biology research (Santos and Mendoza 2008). A different approach is taken by the WeP project, which adds a qualitatively new level of investigation to biomedical studies through systematic use of the Web (cf. <http://www.thewep.org> ).

In the past few years, digital image processing has become an important tool in many areas of biology and medicine, as imaging techniques allow non-invasive *in vivo* study of systems dynamics. These techniques allow

the extraction of time-series data needed for the kinetic modelling of biological processes. They also allow the substitution of less expensive and more precise techniques for “wet lab” processes. Within DIMPLES, an interesting collaboration with the University of Montreal on using images to assess marine environmental complexity has started (Botin et al 2009). An earlier project attempted to use digital pathology software to analyze coral reef images (Betty et al 2007).

On the education side, individual graduate courses were incrementally introduced at the Mathematics Department (now Institute of Mathematics) starting in the second semester of AY 2002-2003. In addition, multi-disciplinary Lecture Series were conducted regularly to update and broaden the awareness of mathematical and computational applications in the Life and Environmental Sciences. The graduate courses MATH 235 (Mathematical Models in Population Biology) and MATH 236 (Mathematics in Biological Processes) are now offered annually. In addition, MATH 298 courses on Selected Topics in Systems Biology are offered regularly. At the Department of Computer Science, at least one CS 297 course per semester focuses on Computational Systems Biology. In order to encourage talented BS graduates to stay on for graduate studies, SMILES<sup>□</sup> also established a Research Assistant Program. The goals of the program are to provide graduate students:

- experience with semi-professional software use and development in joint experimenter-modeller projects in the life sciences
- a computational basis for research theses (chosen to be related to the bio-scientific area addressed in the software development)

## 4.2 Challenges and Opportunities in the next 3 Years

The recent 10<sup>th</sup> International Conference on Molecular Systems Biology (ICMSB 2008), one of the established events in the field, organized by the UPD Department of Computer Science (H. Adorna, J. Caro and P. Naval) and competently supported by UP ITTC, was a big success and hence a fitting celebration of the achievements of the first 5 years of SMILES<sup>□</sup> as well as a contribution to UP’s Centennial Year. It highlighted progress in Filipino research in Computational Systems Biology (first authors of 35% of papers presented were Filipinos) and established closer contacts with leading researchers such as A. Friedman (Ohio State University), E. Voit (Georgia Tech), M. Tomita (Keio University) A. Dress (PICB Shanghai) and O. Wolkenhauer, Rostock University) as well as other Asian scientists in the field.



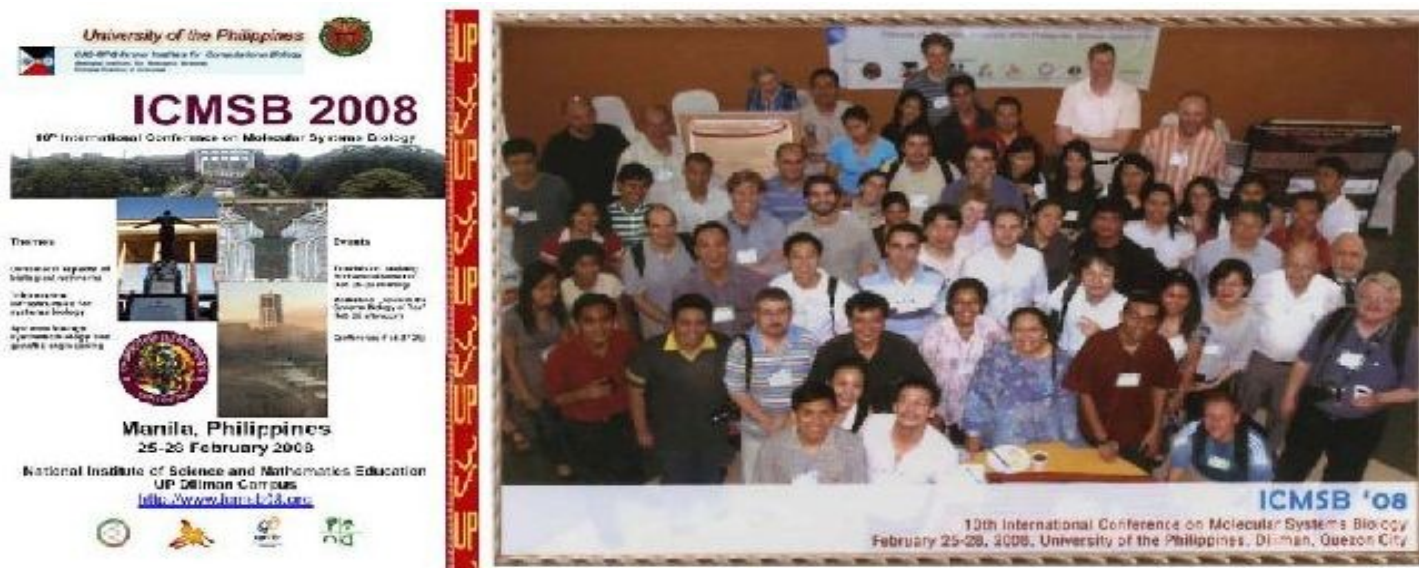


Figure 10. ICMSB 2008 poster and poster session participants.

Nevertheless, the community faces important challenges moving forward:

- A substantial expansion of collaboration with local experimental groups. The community has encountered a number of stumbling blocks in the past, including the lack of quantitative data needed for modeling as well as serious intellectual property issues. Aspects of scientific culture such as the lack of persistence (resignation after the rejection of the first paper submission) and lack of motivation for interdisciplinary work have also surfaced in a number of projects.
- Incremental establishment of a research environment for the broad multidisciplinary approaches required for successful systems biology and sorely needed to attract promising Filipino researchers to return or at least actively collaborate with the local scientists, both experimental and computational
- Further attraction of talented students to do research in this promising but intellectually challenging field

Despite these challenges, there are many reasons for optimism, not only because of the achievements of the first 5 years but also because new opportunities have emerged and evolved in the same period:

- A substantial increase in research funding has materialized in the last 2 years (in my view, mainly thanks to an initiative of the Philippine-American Academy of Science and Engineering (PAASE) driven to a large extent by scientists-and somewhat later,

engineers-of UP Diliman. The nearing completion of the National Science Complex greatly expands the needed experimental infrastructure, in particular, the facilities for bioimaging. The new flagship project “PharmaSeas” of the Department of Science and Technology (DOST) includes an NMR and LC-MS/MS facilities for serious high-throughput measurements. This is complemented by the ambitious Engineering Research and Development for Technology (ERDT) which will boost engineering research at 7 lead institutions in the country. The new “TeleHealth” project will also provide bridges to medical application on a large scale. Not only will this experimental infrastructure generate the data enabling systems biology approaches to be applied to local problems, it will also enable collaboration with foreign groups on the “next” level.

- The trend to “chip-oriented” approaches (nano- and almost nanotechnology) such as microfluidics) in the Life Sciences will drive down prices, again allowing greater participation of labs in developing countries in leading-edge research
- New services on the Internet are already enabling practicable (and inexpensive) eScience collaboration on research projects, so Filipinos here and abroad can start to build effective virtual communities for research. SMILES has, for example, in the last 2 years effectively used Skype sessions for efficient project meetings, research mentoring (including theses defenses) and advanced graduate courses. This will alleviate some of the current lack of competent mentors in different areas in the country. This can be

coupled to a more effective BalikScientist Program, leading not only to more “balik nang balik” scientists but probably to something like an “OFR” (Overseas Filipino Researchers) program, where Filipino scientists abroad collaborate continuously with competent local counterparts, so that ideas and innovations are not only “remitted” in one direction, but are mutually exchanged.

Finally, SMILES<sup>□</sup> researchers now have the opportunity to share their knowhow and experience with other academic institutions as well as with innovative companies. Initial examples of this within the MBarC (Manila Bay Research Corridor) initiative are the evolution of the Munich-Atlanta-Diliman (MAD) cooperation to 2 member universities in Manila (now “MADMan”) and building the VirhoLex system on the same basis as the EUCLIS system. This broader basis will enable Filipino researchers not just to hold on but even to expand their “foothold” in this important area of 21<sup>st</sup> century research.

## 5. Beyond Systems Biology?

### 5.1 Integrating Biological Subdisciplines

The growing impact of Systems Biology in the biological sciences is also reflected by a “wave” of terms prefixed by “Systems” and suffixed by “biology”. Notable examples include the 2005 report by the American Academy of Microbiology entitled “Systems Microbiology: Beyond Microbial Genomics,” which outlined potential applications ranging from improvements in the management of bacterial infections to the development of commercial-scale microbial hydrogen generation. The report was based on the findings of a colloquium convened by the Academy in Portland, Oregon, in June 2004, where a group of distinguished scientists gathered to examine the power of applying a systems approach to microbiology. *Nature Reviews Microbiology* has begun to publish papers in a series entitled “Systems Microbiology”. Similarly, the newly formed “World Alliance for Systems Chronobiology” (WATCH) has formulated its mission as follows: “WATCH promotes systems biology approaches to study biological timing, particularly the 24-hour circadian clock. WATCH proposes the circadian clock as a paradigm to understand the design principles of dynamic biological systems, across species and scales of organisation, and so to advance the field of systems biology in many research areas”.

Similarly, one now finds many biology groups which define their research focus with a prefix or suffix of “Systems Biology”, e.g. “Cancer Systems Biology” or “Systems Biology of Yeast”. This reflects in my view, beyond just a use of a “hype word” for attracting better

funding, the process of re-thinking and transforming from a primarily reductionist culture to one oriented to “systems-level understanding”.

### 5.2 Paths to Integration: Focussed Subnetworks of Disciplines

A big disadvantage of the portrait of Systems Biology as “a network of disciplines” is its static character. Not every interaction is active in a particular scenario. However, there are many successful examples of “subnetworks of disciplines” integrating different competencies to provide focussed solutions “on a system level”. Emerging subfields such as “Structural Systems Biology”, which brings structural biologists, physical chemists, biophysicists and computer scientists together to use molecular dynamics and coarse-grained approaches in advanced computing environments for simulating dynamics and thereby bridging system snapshots taken with electron microscopy, is a good example of such an integrating subnetwork. Another interesting subfield is NanoSystems Biology, which targets using the advances of nanoscience and nanotechnology to develop novel experimental and computational techniques to eventually address the “holy grail” of real-time *in vivo* measurements of complex biological systems. In my view, the paths for the integration of the disciplines will result from such “partial networks”, though the challenges of Systems Biology discussed in 3.5 are likely to demand the concerted effort of nearly all the disciplines in the network.

It is interesting to note that already today, one finds Professors of Systems Biology in all the disciplines in the network. It is also easy to identify pioneers, who have contributed to the field’s re-emergence in 2000, in all of the networked disciplines.

### 5.3 Systems Biology – a step towards a Theory of Biology?

Although a journal with the predicate “Theoretical Biology” is well established, prominent biologists have often highlighted the current lack of a “theory of biology”. There is also a lack of appreciation in general of the work of theoretical biologists, who are often seen as the same as “mathematical biologists”. The disciplines of physics and chemistry provide a strong contrast: there is a strong consensus that is an established core of theory and the cycle of theory and experiment is practised in many labs (often by the same person). There is also a clear differentiation between theoretical and computational approaches and peer respect between experimentalists and theorists is part of the community culture.

In biology, another response to the question “is there a theory of biology?” is yes, and that’s the theory of evolution. I tend to agree with Dennis Noble’s disagreement with this position: “The Theory of Evolution is not a theory in the sense in which I am using the term. It is more a historical account, itself standing in need of explanation. We don’t even know yet whether it consists of events that are difficult, if not impossible, to analyse fully from a scientific perspective, or whether it was a process that would homed into the organisms we have, regardless of the conditions. My own suspicion is that it is most unlikely that, if we could turn the clock right back and let the process run again, we would end up with anything like the range of species we have today on earth”. J. Way and P. Silver in fact see a role of Systems Biology in elucidating an emerging question in evolutionary biology: there is growing evidence “that organisms are, in some ways, poorly designed and don’t function as well as they could. Systems Biology should ask the question why biological systems work the way they do” (Way and Silver 2007). Indeed, the search of general or design principles – including the logic by which the organisms we find today have succeeded in the competition for survival –is an important goal of systems biology, which could lay the foundations for a future theory of biology. As B. Aguda remarked (private communication), as a physicist/chemist, he begins “with the assumption that the fundamental physical and chemical theories need to be augmented with biological constructs or concepts to create a theory of living systems.”

A recent book “Systems Biology: Philosophical Foundations” (Bogeerd et al 2007) documents the pioneering work of scientist, philosophers at the Vrije Universiteit in Amsterdam and their collaborators on related issues and questions. One of their conclusions is the need to transcend the status of the Philosophy of Science still being mainly Physics-focussed and to develop a Philosophy of Systems Biology.

#### 5.4 The Need for a Socio-Ethics of Systems Biology

In a rapidly developing disruptive technology such as Systems Biology, optimism about its impact on science and society naturally (and rightly) prevails. According to the Institute of Systems Biology’s website (ISB 2009), “Predictive, preventive, personalized and participatory medicine will be the most obvious impact. But other transformations will occur: for example, in the development of alternative sources of food and energy. Likewise, a much deeper understanding of the biological basis of human behavior may, in the future, lead to efforts to predict and control it“. In a recent interview, Lee Hood predicted that “the digitalization of biology and medicine

will constitute a far greater revolution than the digitalization of information technologies.”

The ethical, social, legal and political implications of systems biology and its applications, are significant and ought not be ignored or underappreciated by the research community. There are initial efforts in the area of Synthetic Biology, but more comprehensive approaches and studies are needed, as O’Malley et al stress in (O’Malley et al 2007).

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