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SYMPOSIUM

Systems Biology: New Institute and Applications

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The Yale Systems Biology Institute (YSBI†) sponsored its first symposium at the university's West Campus in October 2010. The symposium served to provide Yale's scientific community with a glimpse into the wide range of research at the forefront of this interdisciplinary field. YSBI was conceived less than a year ago, and the event was the perfect forum for its debut, both at Yale and in the U.S. scientific community. This article includes a brief overview of the different topics presented at the symposium, followed by a discussion of the advantages and challenges of practical application of systems biology.

Systems biology focuses on understanding and characterizing organizational relationships and interactions of entities within biological systems. This involves a combination of disciplines, including physics, statistics, mathematics, engineering, and biology. The similarly interdisciplinary Yale Systems Biology Institute (YSBI) was conceived less than one year ago, and Günter Wagner, the Alison Richard Professor of Ecology and Evolutionary Biology at Yale, was appointed the chair of its Faculty Advisory Committee. He describes systems biology as "an outgrowth of molecular biology. After taking biology apart for so long, it is about time to put things together again and study biological systems as it should be, a whole." Wagner envisions the YSBI as a scientific research hub at Yale, "to bring together faculties from across different departments, particularly those with a keen interest in interdisciplinary research." He feels that systems biology can be pursued at three levels: a) the macro-level, or the dynamics of the biological systems of cells, tissues, and organs, as opposed to conventional, static, single-gene or single-protein snapshots of biological processes; b) the micro-level, or biological interactions at the molecular level; and, most importantly, c) the development of methodologies and research tools. It is in these directions that Wagner is guiding the YSBI.

The first YSBI symposium in October 2010 at Yale's West Campus was divided

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†Abbreviations: YSBI, Yale Systems Biology Institute; ETH, Eidgenössische Technische Hochschule; GSMM, genome-scale metabolic model.

into four thematic sessions. The first examined the logic processing, structure, and evolution of gene regulatory networks in different species, a highly investigated area of systems biology. The second segment was more applications based, exploring the coupling of high-throughput technology, such as large-scale microarrays and next-generation sequencing, with synthetic biology and computational modeling. Systems biology has already been put to prognostic use to assess tumor progression, analyze the interactome in human diseases, and predict patient outcomes. The third session examined systems biology approaches to elucidating physiological functions, moving beyond the fragmented view provided by traditional molecular studies of specific physiological components in isolation. Researchers specifically discussed how current technology can be used to quantitatively analyze the proteome, the immune system, and the mammalian genome. Finally, the fourth and last section highlighted synthetic biology and molecular systems and advocated the engineering and design of novel biological circuits derived from natural systems.

The symposium covered breadth with considerable depth in the relatively new field of systems biology. It is imperative to note that the idea of systems biology has a relatively long history, with Ludwig von Bertalanffy introducing his general systems theory in 1928. However, the ideas have only recently been institutionalized and popularized [1], primarily due to the maturation of biotechnology, improved data availability, and the promise of biomedical applications. As an emergent field, it is intriguing that systems biology is already showing huge practical potential. Speakers Jorg Stelling, Professor at the Department of Biosystems and Engineering at ETH Zurich, and Jens Nielsen, Professor of Systems Biology at Chalmers University, Sweden, attributed the cause of this "hastened" transition, from basic research to practical applications, to synthetic biology.

Synthetic biology is the creation of non-natural biological components or systems to aid in the study of their natural counterparts [2,3]. Hence, systems biology and synthetic biology can be viewed as complementary. The synthesis of new systems requires a deep understanding of how biological networks and sub-cellular components are wired. Conversely, analyses of natural systems enhance researchers' capacity to create novel systems. Stelling proposed application-driven approaches to study biological circuits, as opposed to a conventional knowledge-driven approach, which requires detailed hypotheses, observations, and data analyses. Such an application-driven approach tailors experiments to solve specific problems. This extension from biology into engineering expands the repertoire of scientific tools and propels both fields forward [4].

Stelling compared biological circuits to electronics. While both generally behave according to a set of "rules," biological circuits are often not as predictable as electrical circuits. Complexity and uncertainty constitute the main challenges in designing biological circuits. Complexity increases with size and biological circuit dynamics. More specifically, biological circuits can adapt, mutate, evolve, change, or have graded outcomes, bestowing even more complexity. To investigate uncertainty and stochasticity in cell signaling, Stelling's group has developed ensemble modeling [5,6]. This method enables enumeration of the different configurations that a circuit can adopt due to varying degrees of uncertainty. This configuration space also can be explored to reduce prediction errors.

While Stelling designs models, he is also interested in another arm of synthetic biology that designs tools exclusively for engineering biological components [7]. A very prominent and influential example is the Massachusetts Institute of Technology registry of Standard Biological Parts (http://partsregistry.org), a repository of modularized biological components that provide standardized nomenclature for biological network construction.

Meanwhile, Nielsen focuses on commercial applications. As a consultant for several and founder of four biotechnology

and pharmaceutical companies, he has melded ideas from systems and synthetic biology into commercial innovations. His group has developed cell factories for the sustainable production of drugs, bio-fuels, high-value bio-chemicals, and recombinant proteins [8,9] and has improved the efficiency of existing cell factories based on yeast [10,11] and *aspergilli* [12]. Metabolic engineering lies at the core of these innovations. In systems biology, an organism's metabolism is represented by the evolutionarily optimized network formed through the interactions of genes and proteins. The effects of the network can be manipulated by inserting new pathways and eliminating undesirable ones.

To try to achieve this, Nielsen implemented a genome-scale metabolic model (GSMM) of cell factories. Many modeling techniques, such as physicochemical and kinetic ones, describe biological systems with mathematical equations and strive to obtain dynamic predictions of each component through calculations. Consequently, bigger models require a large number of parameters to feed the equations. GSMM is advantageous because it is a constraint-based model that uses a rule-based approach, imposing restrictions on its components to derive a global outcome, without requiring parameters. For example, to increase growth factor production in an organism, positive regulatory pathways in the metabolic network must be enhanced while negative regulatory pathways are simultaneously suppressed. Different constraints are applied until components achieving the desired effects are found by *in silico* analyses, followed by experimental verification. Nielsen's group has successfully induced exogenous succinate production in *Saccharomyces cerevisiae* using this method. However, limitations in biological knowledge hamper the extensive usage of the GSMM approach. For instance, reconstruction of a complete metabolic map requires a well-characterized genome, as well as knowledge of the link between gene and metabolic reaction, both of which may be difficult to establish.

In sum, the YSBI symposium covered a wide spectrum of research, increased awareness of the field and its practical applications, and set the stage for the YSBI's debut. The latter is rapidly growing, having just recruited two new faculty members from the Yale School of Medicine. As more researchers join the ranks of the YSBI, more collaboration will be fostered, pulling together Yale's scientific community, while future symposia will help to encourage collaboration beyond Yale as well.

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