

SYSTEMS BIOLOGY AS A SUB-COMPONENT OF “LIVING SYSTEMS BIOLOGY”

– An Internal Position Paper from a Sub-Committee of the Biology Directorate Advisory Committee

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Charge

At the November 2-3, 2006 meeting of the Biology Directorate Advisory Council (BIO-AC), Division Director James Collins requested that the BIO-AC provide perspective for the funding of Systems Biology, broadly defined. During the delivery of the charge, there was discussion about how Systems Biology might be more broadly expanded to a Living Systems Biology concept. A subcommittee of four BIO-AC members was created, with the goal of producing an internal position paper on Systems Biology and Living Systems Biology.

Introduction

“Systems Biology” is one of the most exciting biological frontiers of the 21st century. It was started in order to develop a qualitative and quantitative understanding of complex biological systems, by combining theory and computational and mathematical modeling with the extremely large sets of data being generated at molecular and cellular levels. But the future of Systems Biology will extend far beyond this early goal, as it becomes the model for a broadly applicable synthetic approach to some of the largest and traditionally most difficult questions in biology as a whole. The purpose of this internal position paper is to offer an interpretation (not a binding definition) of Systems Biology, and to fit this field into the larger context of “Living Systems Biology”.

Semantics

Current practice defines Systems Biology largely in terms of the molecular/genomic/cellular domain. It attempts to understand and even predict higher order phenomena by making use of the large volumes of data generated as a result of the various genome projects. There has been some rather strong “branding” through the incorporation of “Systems Biology” into the naming of centers and institutes with a distinctly molecular emphasis. This suggests to us that rather than attempting to rename molecular/cellular level activities, or

redeploy the term “Systems Biology” in an expanded, unfamiliar and perhaps even confusing manner, we should develop new terminology to encompass studies that bring the approaches of Systems Biology to bear on a broader set of biological problems. We propose that NSF consider funding science that is related to, but broader in scope than, Systems Biology alone. The terminology we propose, to expand Systems Biology beyond its current meaning, is “Living Systems Biology”. One aspect of Living Systems Biology is that bi-directional movement, both up and down the continuum of biological organization is included.

How Does Systems Biology Fit Into the Living Systems Biology?

Systems Biology emphasizes the study of the interaction of components, and the networks between components, primarily at the molecular level, leading to the recognition of the emergent properties of the system.

For much of its history, biology has been divided into two general camps: descriptive or synthetic biologists on the one hand and reductionist biologists on the other. Another way these camps can be described (in an admittedly somewhat simplistic way) is as field biology versus test tube biology, or ecosystem/organismal biology versus molecular biology. The reason for the division was practical; not enough was known of the molecular components of very complex systems to really study their interactions, and then to develop an understanding of consequences of their interactions at a higher level.

The combination of extremely large and comprehensive data sets, as well as ever improving technology--ranging from molecular imaging to the developing NEON system--are redefining what can be done in biology, and offering the exciting potential for the first time in history, to integrate the two camps we described above under the banner of Living Systems Biology. The potential advances that could emanate from such an integration of biological information presents a very exciting prospect, and will likely form the centerpiece of much of the exciting biology of the future.

A common view of Systems Biology is that it is performed at the level of molecular and cellular biology with an eye to predicting components and their interactions at higher organizational levels. This “directional bias” is ameliorated in Living Systems Biology, whose practitioners may potentially contribute to more reductionist insights (down) as well as more synthetic insights (up) along the organizational hierarchy of life. That is, Living Systems Biology will allow predictions of cellular processes from molecular events (the Systems Biology component) as well as the inverse, which involves, for example, predictions of physiological processes from behaviors.

The goal of Living Systems Biology, including the Systems Biology sub-component, should not be confused with the techniques or approaches of these

disciplines. Living Systems Biology is the study of biology vertically along multiple hierarchical levels, but it is not merely the “horizontal” interdisciplinary use of modeling/simulation, computation, etc. That is, using modeling to understand the function of a protein in the ribosome is neither Systems Biology nor Living Systems Biology, but rather a horizontal study that uses the outcomes of modeling to understand the role of proteins in regulating cell function.

Who “Does” Systems Biology and Living Systems Biology?

Because of the integrative nature of Living Systems Biology and its subcomponent, Systems Biology, an investigator or investigative team working solely at one hierarchical level in the atoms to planets continuum, with one experimental approach, is thus contributing to, but not necessarily doing, Systems Biology/Living Systems Biology. In fact, only by taking one’s findings and placing them in the context that extends to a higher or lower organizational level is one truly participating in the science of Living Systems Biology, which is an essential component of Integrative Biology.

Conclusion and Recommendations to NSF Biology Directorate

We offer the following recommendations:

- Assemble in workshop format diverse groups of scientists (e.g., biologists, theorists, mathematical and computational modelers), to identify specific areas where an NSF investment would most effectively advance the integrative biology envisioned as part of a "Living Systems Biology" initiative.
- Create a funding initiative that is clear, concise, and emphasizes the core values of the Living Systems Biology Initiative, making clear the ways in which this initiative does and does not intersect with Systems Biology.
- Emphasize a simultaneously horizontal and vertical integrative approach that includes multiple approaches and/or levels of biological organization within a single team’s (or, more rarely, a single PI’s) approach.