Report of the National Centers for Systems Biology External Review Committee
January 2016

The overarching goal of the **National Centers for Systems Biology (NCSB)** Program has been to "promote institutional development of pioneering research, training, and outreach programs focused on systems level analysis of biological phenomena of biomedical importance within the NIGMS mission." Thus, as currently implemented, NCSB Programs involve significant components of training and outreach in addition to the pursuit of systems-level biomedical research. In December 2014 NIGMS convened a group of scientists to:
- assist in determining the overall success of the Program in meeting its stated goal
- determine whether the field has matured to the point that the initiative is no longer needed
- recommend Program adjustments if it is to be continued

Specific questions posed by the NIGMS Director and staff at the outset of the meeting concerned:
- Whether to separate the training and research aspects of the Program
- Whether existing training mechanisms such as T32 grants would do as good a job for training
- Whether to retain the NCSB budgetary set-aside or instead to mainstream the research component and if so through what sort of mechanism(s) (e.g. P50 vs. R01, multi-investigator R01, P01, P30, etc.).

The committee was comprised of Brenda Andrews, Andrea Califano, Mark Chance, Jay Dunlap, Garret FitzGerald, Rick Horwitz, and Marian Walhout. The committee was provided initially with the following materials: a quantitative "map of science" analysis of the influence of Center grants on Systems Biology, a description of the Center Program and the 10-year anniversary brochure, and a series of questions intended to guide the evaluation, including influence on the field, role in training and education, effectiveness of dissemination and outreach, and role in NIGMS portfolio. On-site presentations were from Paul Sheehy, on setting the stage, Kevin Boyak, on the map of science based data analysis, Peter Lyster, on the overall program, John Lorsch, on the Committee charge, and 4 additional presentations from NCSB Awardees: Bridget Wilson (UMN), Ron Weiss (MIT), Peter Sorger (Harvard), and Lee Hood (ISB). At the end of the meeting, power point presentations were sent to the review committee.

During its deliberations, the committee requested additional information to address:
1. Retrospective data on publications, including
    a. the number and impact as assessed by citations, attributed to each center as a function of research dollars
    b. citations and publications/grant $ as compared to the general NIGMS pool and to other RPGs (P01s, or R01s) involving systems biology
2. The perception of the community of non-participant system biologists on the value of the NCSB Program
3. Evaluation of how distinctive and essential the NIGMS-supported NCSB Program is now that several other NIH institutes are funding NCSB-like programs and centers. While some data regarding this were provided, the committee consensus was that the search definition applied

for screening the overall NIH portfolio had been too restrictive and as a result significant investment in systems biology elsewhere within NIH had been missed.
4. A census of what NCSBs felt were their most important contributions
5. An overview of the magnitude and stability of systems biology funding mechanisms

Evaluation of the evaluation mechanism
The quantitative analyses provided by SciTech Strategies, Inc. were largely a text mining exercise in which publications were clustered based on similarity of vocabulary and mutual citation, foci containing "systems biology" were identified, and then the degree to which P50 centers anticipated the general growth of the field evaluated. This analysis revealed that the field has grown in parallel with the Center initiative, is increasingly interdisciplinary, and extends beyond the NIGMS funded centers. However, all of these data are correlative and for the most part, neither surprising nor readily interpretable. In contrast, the Awardee presentations, solicited data, and reviewers' knowledge of the field were generally viewed as more informative.

Executive Overview
Overall the committee expressed unanimous agreement that "Systems Biology" as a discipline is not yet mature and instead is just beginning to hit its stride. There is general consensus that Systems Biology remains a potentially transformative field and that the National Center Program excels at integrating the diverse elements of research, training and outreach that can achieve a fully developed vision for the field. However, some reductions in overall funding to the NCSB program may be achieved by narrowing the focus and limiting the number of awards during each funding cycle.

In general the panel feels that

- *NCSBs greatly contributed to the origins of the field of Systems Biology and continue uniquely to contribute to their development, and therefore it is premature to terminate the entire mechanism.*

- *NCSBs excel as centers integrating research, training, and outreach elements, but should evolve in a structure appropriate to current opportunities and challenges and the pool of potential outstanding applications.*

- *NCSBs are not as cost-efficient as P01s and R01s in the production or publication of some kinds of data, and therefore are not be the best mechanism to support every kind of Systems Biology research.*

- *The prospect for broadening opportunities for applications of Systems Biology emphasizes the catalytic role NCSBs will have in influencing the rate at which the discipline penetrates the practice of science and medicine.*

- *NCSBs represent a 15 year sustained effort in training of junior investigators skilled in Systems Biology, and the panel recommends that this training mission be sustained*

and possibly enhanced by encouraging additional innovative combinations of training and outreach in the context of necessary workforce development.

These points are more fully developed below.

- *NCSBs contributed to the origins of the field of Systems Biology and continue uniquely to contribute to their development, and therefore it is premature to sunset the entire mechanism. Because Systems Biology is still evolving and not mature, we recommend preserving the best aspects of the NCSB program along with judicious trimming consistent with conscientious resource stewardship and size and quality of the applicant pool. The NCSB program is supporting a new science that is transformative and catalytic, developing new ways of thinking about how to approach problems in the Life Sciences. In discussing this field, the panel makes the distinction between systematic biology, which seeks to assemble and query large data sets in search of correlations, and Systems Biology, which also often deals with large data sets but seeks to extract emergent organizing principles and develop predictive models, and to validate these principles and models through perturbation and experimentation. To achieve this, Systems Biologists need to access, combine, and often to create, tools and approaches not commonly used by other biologists, most particularly using a combination of mathematics, statistics, computer science, and engineering, as well as being able viscerally to absorb biological data and concepts. This breadth is uncommon and requires a new kind of training and execution that includes interdisciplinary team science; this has been slow to permeate research.*

  Whereas the goals of the NSCB program are to nurture the evolution of Systems Biology and to promote its broad acceptance within the Life Sciences, the panel noted that to date, the NCSBs are mostly silos within individual institutions charged with local development of expertise. Moving forward the panel favors de-emphasis of such silos in favor of experimentation with multi-organizational or multi-institutional consortia that might have virtual characteristics, perhaps including partners from the private sector when appropriate, sharing a focus, as a way of accelerating the distribution of new ways of thinking. Such centers, and indeed NCSBs as a whole, should be clearly focused on this new science, and the panel favors tightening review criteria and reducing the number of NCSBs funded annually better to match the pool of outstanding Systems Biology.

- *NCSBs excel as Centers integrating research, training, and outreach elements, and should evolve in structure appropriate to current opportunities and challenges. This evolution may require a specific set aside in the NIGMS budget. NCSBs have been successful in achieving the program goal and have helped to develop quantitative advances for basic science research not achievable through other mechanisms. In particular, the P50 Centers have exhibited a strong training mission, promoted team science with a trans-disciplinary culture, and have displayed a discovery orientation in the context of high-level biological hypothesis testing. This provides a unique resource and blueprint for the biomedical science community and has moved Systems Biology from a niche specialty to a potentially important player in the landscape of biomedical research. However, while the Centers*

have permitted Systems Biology to have "a seat at the table", its voice is still not large. Moving forward, and as noted above, the panel advises that NIGMS specifically encourage the centers to develop into inter-institutional (virtual) consortia, possibly including public/private partnerships, breaking out of the restrictive expertise extant in any one institution and harvesting talents from a broader landscape. Such a development will also enhance the capability of the training and outreach activities of the centers to permeate more broadly biomedical science.

- *NCSBs are not as cost-efficient as P01s and R01s in the production or publication of some kinds of data, and therefore are not the best mechanism to support every kind of Systems Biology research. The data collected by the panel shows that R01s and to some extent P01s are more cost effective as ranked by cost per publication or per citation and are comparable in terms of citations per publication* (Figure 1)*. Some reservation was, however, expressed as to the interpretation of such data and how they might relate to important scientific discoveries. Moreover, this speaks to the salient nature of Systems Biology in general, but not to the distinction between NCSBs and "smaller science" mechanisms. NCSBs are not solely meant research engines like R01s and P01s; rather they are mechanisms whereby, through training and outreach as well as by promulgation of novel tools and ways of thinking drawing from a broader and more diverse community of scientists, the prosecution of all science will be changed. Given these diverse and to some extent divergent goals it is not surprising that pure research engines are more cost efficient in doing research. However, the data for 2004-2012 also show that nearly 30% of NCSB publications fall within the top 10% for citations within their ESI category* (Figure 2)*; NCSB published highly cited software, tools, and databases at a rate 5 times that of R01s/P01s* (Figure 3)*: This is highly visible work impacting the way in which science is done, not just providing data. Transformations in the way in which science is approached, however, are rarely fast.*

	Activity	Cost per Publication	Cost per Citation	Citations per Publication
National Centers for Systems Biology (NCSB) (NIGMS)	P50	$160,000	$5,500	32
Physical Science - Oncology Centers (PS-OC) (NCI)	U54	$132,500	$6,000	25
National Centers for Biomedical Computing (NCBC) (Roadmap)	U54	$131,000	$5,500	32
Integrative Cancer Biology Program (ICBP) (NCI)	U54/U56	$187,000	$5,500	37
Quantitative Approaches to the Analysis of Complex Biological Systems (PA98-077) (NIGMS)	R01/P01	$111,000	$2,500	48

Figure 1. Comparator publication analysis for NIH-supported Systems Biology research. P50 data from 2002 to 2014; numbers rounded to nearest $500.

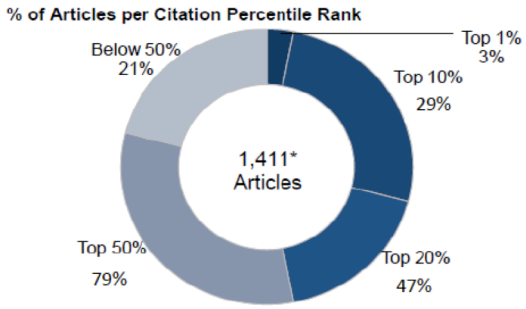

Figure 2. Citation Impact of publications arising from NCSB-supported research between 2004 and 2012.

Type of Product	NCSB Publications	PA98-077 Publications
Software	72	16
Dataset/database	53	8
Web Tool	4	1

Figure 3. Comparator analysis of software, tools and databases arising from NIGMS-funded Systems Biology-related grants, 2002-2014.

- *A corollary of this is that the panel perceived substantial variation in the apparent productivity and the quality of the research and outreach being done by different NCSBs, and therefore would encourage greater scrutiny of programs prior to funding, including reductions in funding for new grants within individual grant cycles if the requisite standards are not met. The panel acknowledges the problems with peer review of proposals where the actual goal is to develop a cadre of peers capable of such review, and sees how proposals might score well in such peer review, even if they represent great science rather than great Systems Biology. However, NCSBs should represent the very best of Systems Biology in consortia that will move the field forward, not just pursue normal science, and this means that new proposals should be clearly in the superior range of the previously funded ones, not simply the best of what is there at one time. With an eye to broadening involvement of researchers in Systems Biology, the panel favors additional scrutiny of NCSB proposals at institutions that have previously been home to an NCSB.*

Activity Code	Closed Announcement	Open Announcement	Total
F30	2		2
P01	1		1
P50	4	1	5
P60	1		1
R01	13	2	15
R21	4		4
Supp	1		1
T32	2	1	3
U01	1	1	2
U19	3		3
U24	1		1
U54	1		1
Grand Total	34	5	39

Figure 4. NIH System Biology FOAs 2008 – 2015. Institutes supporting these included NCI, NHLBI, NIA, NIAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIMH as well as NIGMS.

Funding Agency	*Closed Announcement*	*Open Announcement*
Air Force -- Research Lab	1	
Air Force Office of Scientific Research	9	
Chicago Service Center	4	
CSREES	1	
DARPA - Biological Technologies Office		1
DARPA - Defense Sciences Office	3	
Defense Advanced Research Projects Agency	1	
Defense Threat Reduction Agency	1	
Department of Commerce	1	
Dept of the Army -- Materiel Command	3	2
Dept. of the Army -- USAMRAA	14	6
Environmental Protection Agency	1	
National Institute of Food and Agriculture	2	1
National Institute of Standards and Technology	6	
National Institutes of Health	34	5
National Science Foundation	5	
NAVAL MEDICAL LOGISTICS COMMAND	1	
Office of Naval Research	3	
Office of Science	7	
Grand Total	97	15

Figure 5. System Biology FOAs across the federal government, 2008-2015.

- *The data revealed a picture of eroding support for Systems Biology at a time when sustained engagement is paramount: data from 2008 to 2015 show that at both the federal and NIH level only 15% of grant mechanisms "relevant to Systems Biology" remain active* (Figures 4 and 5). *The panel encourages sustained support of NCSBs, judiciously focused so as to maximize impact and distinction from typical investigator-initiated science, accepting that this may entail a reduction in the number of centers. If the number of outstanding centers falls below a critical threshold, the mechanism could be merged into a broader mechanism that funds, "center-sized", interdisciplinary, collaborative research and training in quantitative biology.*

- *The prospect for broadening opportunities for applications of Systems Biology emphasizes the catalytic role NCSBs will have in influencing the rate at which the discipline penetrates the practice of science.*
  - *Because "Systems Biology" is broadly defined and relatively new, meaningfully sourcing federal funding is challenging. Due to its interdisciplinary nature, drawing on computation, high- throughput screens, statistical analysis, computational modeling, bioinformatics etc., it usually employs interdisciplinary teams. Consequently, the scope of R01, and even P01 projects is limited because of budgetary constraints, even with non-modular budgets. Therefore, the classic R01 and P01 mechanisms, while powerful, provide only a limited source of Systems Biology funding. Another main asset of a "center" mechanism is that it provides sufficient levels of support for a large team of scientists, as well as the support for highly integrative discovery-based and tool-oriented projects that are not supported by R01 and P01 mechanisms.*
  - *NIGMS is in a special position within all Federal Institutions, either within the NIH or NSF, because its PIs are of the greatest scientific diversity, facilitating bridges between translational medicine, basic science, engineering, and mathematics. Because the NIGMS covers all biomedical research in a general way, it is particularly powerful as a catalyst and, we believe, responsible for further enabling the field of Systems Biology to develop and expand its reach in the most efficient, effective, and far-reaching manner.*

- *NCSBs represent a 14 year sustained effort in training of junior investigators skilled in Systems Biology, and the panel recommends that this training mission be enhanced by encouraging additional innovative combinations of training and outreach in the context of workforce development. While training in Systems Biology within the existing NIGMS T32 framework is essential and consistent with expanding Big Data needs, the integrated training within the NCSBs has considerable additional value. Historically, the NCSB training mission has included extensive outreach to a wide range of scientific communities, enhancing the reach, the reputation and the development of systems approaches. Junior investigators specifically funded within the Centers (including graduate students and post-doctoral fellows) have experienced a unique training environment that includes training in interdisciplinary Big Data team science, a quantitative focus and exposure to various modeling strategies. In addition, the Centers have had an impact on developing relevant curricula and educational resources, typically in the context of websites, for Systems Biology. These are examples of opportunities not consistently available with T32-supported programs.*
  - *The Center contributions to the development of the science of Systems Biology have now positioned the field well for extension into the development of predictive paradigms of disease evolution and drug response that are central to the concept of Precision Medicine. This will involve the development of novel informatics tools to integrate diverse data sets reflective of genomic, epigenomic, lipidomic, metabolomic, microbiomic and imaging based networks from the single cell to population levels and also to integrate data derived from model systems and from deep phenotyping in humans. Thus, the Centers now have an opportunity further to advance the "basic science" of the field while providing training, outreach and impact to foster and accelerate translational science.*

- *Continued investment in training, particularly in the context of a comprehensive Center framework, will also expand the critical mass and the diversity of scientific background of individuals capable of leading NCSBs and other important Systems Biology initiatives in the future.*