NATIONAL SCIENCE FOUNDATION
2415 EISENHOWER AVENUE
ALEXANDRIA, VIRGINIA 22314

NSF 19-054

Dear Colleague Letter: Models for Uncovering Rules and Unexpected Phenomena in Biological Systems (MODULUS)

April 3, 2019

Dear Colleague:

The National Science Foundation (NSF) Division of Mathematical Sciences (DMS), in collaboration with the Division of Molecular and Cellular Biosciences (MCB), seeks to promote interdisciplinary research that enables novel mathematical and computational approaches that capture and explore the full range of mechanisms and biological variability needed to better understand biological systems behavior across multiple scales. The development of replicative or descriptive models for complex biological systems remains challenging. Models that move beyond replication into the realm of prediction and ultimately becoming indispensable tools for discovery-driven biology are severely lacking. A paradigm shift in the current, oftentimes conservative approach to interdisciplinary mathematical biology is needed to promote the realization of modeling platforms that facilitate discovery of novel biological phenomena, rules, and theories. As part of the effort, funding opportunities are available in fiscal years FY2019 and FY2020 to provide support for proposals from interdisciplinary teams comprised of mathematical, computational, and biological scientists to develop **MOD**els for **U**ncovering Ru**l**es and **U**nexpected Phenomena in Biological **S**ystems (**MODULUS**). This Dear Colleague Letter (DCL) is to encourage researchers involved in the biosciences and the mathematical sciences to collaborate formatively in biological investigations using novel mechanistic mathematical models to guide biological exploration and discovery of new rules in living systems.

BACKGROUND

The development of new research tools has revolutionized the ability to interrogate, manipulate and engineer biological systems at the molecular scale and to measure their multiscale response to changing environments. The ability to generate data across molecular and cellular scales has far outpaced the capacity for multiscale data integration and development of mechanistic mathematical models capable of discovering emergent

phenomena and novel biological principles. Simultaneously, there is a need for innovative mathematical approaches that capture the full range of mechanisms and biological variability needed to recapitulate biological systems behavior across scales. The current biological modeling challenge is assimilation of burgeoning multi-omics information into causal, predictive models capable not only of replicating observed phenomena but also guiding further exploration and driving discovery in areas such as systems and synthetic biology, cellular dynamics and function, and genetic mechanisms. As an example, forming a systems-scale understanding of the interplay between chromatin structure, epigenetics, environment and genetic regulation may require novel combinations of mathematical methods that enable exploration of these interactions across interdependent scales. Similarly, connecting myriad environmental, biomechanical, and biochemical cues to formulate systems-based rules modulating embryogenesis requires innovation in multiscale mathematics to enable complex spatiotemporal simulation and visualization.

With an emphasis on deep integration across disciplines and inspired by challenging biological questions and pressing societal needs, the DMS and MCB Divisions at NSF are interested in proposals that jump-start community thinking and development of integrated mathematical approaches and novel modeling platforms for complex biological systems at the molecular and cellular scales. Such platforms should be a tool for discovery-driven science that addresses compelling systems-scale biological questions. The expectation is that innovative mathematics will emerge from confronting the need to elegantly incorporate the full range of pertinent biological variability and variety of length and time scales into mechanistic models capable of generating new biological understanding.

DESCRIPTION OF THE OPPORTUNITY

Proposals funded through this DCL are anticipated to cultivate innovative modes of collaboration among researchers working at the interface of mathematics and molecular and cellular biology, with an emphasis on systems-scale integration. Each proposal submitted in response to this DCL should address a current state-of-the-research challenge and describe a strategy for formative integration of mathematical and biological understanding to address the challenge. In addition, the proposal should describe the unique interdisciplinary training opportunity for graduate students and postdoctoral researchers working on the project.

Competitive proposals are expected to address clearly stated biological questions or hypotheses, make a case for and develop innovative mathematical methods or integrate disparate mathematical fields, and articulate a well-defined plan for the mathematics to drive biological discovery within the funded period. The most competitive proposals will outline a strategy to use causal, principled models as a central tool to guide further experimental exploration and new discovery on rules of life. It is expected that many proposals will be high-risk/high-reward; successful projects will demonstrate a capacity to adapt to and make progress, with possibly unexpected outcomes resulting in novel discoveries. This DCL

specifically encourages proposals from nascent collaborative teams that include expertise from both the mathematical and biological sciences focused on the development of highly innovative approaches that address the challenges outlined in this DCL.

Opportunities for participation, co-mentoring and/or exchange of graduate students and postdoctoral fellows between participating labs to facilitate integrated projects are welcomed. Projects that include efforts to broaden participation of underrepresented groups in science are encouraged.

Proposals in response to this DCL should be submitted to either DMS via the Mathematical Biology Program Description or the MCB solicitation, NSF 18-585, directed to the Systems and Synthetic Biology program (8011). The proposal title should be prefaced with "MODULUS:". The MCB solicitation accepts proposals to core programs or to a Rules of Life (RoL) track. Submission to either track is permissible given that the guidance as detailed in the solicitation (NSF 18-585) for each is followed. For proposals submitted to MCB and targeted for the RoL track, a second program in another BIO Division **must** also be identified. Neither Division puts limits on proposal budgets and expects budgets to be appropriate for the scope of the project proposed.

The MCB solicitation accepts proposals without deadline. In order to ensure adequate time for review of proposals, proposals should be received prior to June 1, 2019 to be considered for FY 2019 funding and be received prior to April 1, 2020 to be considered for FY 2020 funding. Proposals submitted to DMS via the Mathematical Biology Program must be submitted during the normal submission window for the program.

For further information, please contact:

- Dr. Elebeoba E. May, BIO/MCB, emay@nsf.gov
- Dr. James Powell, MPS/DMS, jpowell@nsf.gov
- Dr. David Alexander Rockcliffe, BIO/MCB, drockcli@nsf.gov
- Dr. Junping Wang, MPS/DMS, jwang@nsf.gov

Sincerely,

Joanne Tornow
Assistant Director for Biological Sciences

Anne Kinney
Assistant Director for Mathematical and Physical Sciences