



NATIONAL SCIENCE FOUNDATION
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NSF 21-069

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

April 19, 2021

Dear Colleagues:

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 complex and nonlinear behavior across multiple biological systems and scales. The development of replicative or descriptive models for complex biological systems remains a challenging task, yet 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 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 FY2021 and FY2022 to provide support for proposals from interdisciplinary teams comprised of mathematical, computational, and biological scientists to develop *MODEls for Uncovering Rules and Unexpected Phenomena in Biological Systems (MODULUS)*. This Dear Colleague Letter (DCL) is to encourage researchers involved in the biosciences and the mathematical sciences to collaborate in a substantive manner in biological investigations using novel mechanistic mathematical models to guide biological exploration and discovery of new rules, phenomena, and theories 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 multiple 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 gene regulation may require novel use 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 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 supporting 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 mathematical and computational models capable of generating new biological understanding, as well as models based on statistical and machine/deep learning methods that capture mechanism-driven behavior of biological systems.

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. Successful proposals are anticipated to include a strategy that uses 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.

There will be an annual grantees' conference (one day if in person or two days if virtual) for sharing of successes, challenges and future plans, and for NSF program officers to review progress. All PIs and co-PIs from each award will be invited to participate. Proposers can include costs of participating in their budgets.

Proposals in response to this DCL should be submitted to either DMS via the [Mathematical Biology Program](#) or the MCB solicitation, [NSF 21-509](#), directed to the Systems and Synthetic Biology program (8011). The proposal title should be prefaced with "MODULUS:". 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.

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Sincerely,

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