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14. ABSTRACT
A group of theoretical and mathematical biologists met to establish the fundamental principles of mathematical biology and set the course for the field in the future. The theme that emerged was stochasticity, and its effects on the availability and storage of information. Living beings cope with or capitalize on noise through networks compartmentalization, outsourcing of tasks other organisms, and by

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Statement of the problem studied

A group of theoretical and mathematical biologists gathered in Salt Lake City on Dec 13-14, 2015 to take on the official charge of establishing the fundamental principles of mathematical biology and set the course for the field for the remainder of this century.

Summary of the most important results

The theme that emerged was that of stochasticity, whether rightly called noise, variability, or unpredictability, and its effects on the availability and storage of information. This variability is rarely just unstructured noise imposed by the external environment. Some is generated by organisms or cells themselves, for example when plants modulate the rates and magnitudes of system-resetting fires, or when cells use stochasticity in production of RNA transcripts or protein molecules to generate phenotypic diversity in their genetically identical descendents. Furthermore, variability has structure in the form of predictable ranges of temporal frequencies and spatial scales, as with ocean waves, pulses of odor in a turbulent plume, and daily or seasonal cycles. The sizes of organisms and cells and the temporal scales at which they function determine how the stochastic and predictable variation in their world affects them, and which they in turn can affect.

The challenges and opportunities of noise and variability influence all living beings, including the mathematical biologists who think about them. Clear thinking about how life persists and flourishes in a noisy world demands that we develop new methods to capture these mechanisms without being overwhelmed by real or apparent complexity.

We discussed many ways that living beings cope with or capitalize on noise, each of which raises new challenges for modelers. Networks can be compartmentalized to contain error propagation, tasks can be outsourced to other organisms, such as our gut bacteria, to let them suffer the consequences of errors, and dynamics can be tuned, through such newly understood mechanisms like miRNA, to produce novel forms of robustness. Responding appropriately depends on gathering information from a recalcitrant world, with many mechanisms falling under an umbrella related to the Brownian ratchet, searching physical or information space through a random walk, but with periodic evaluation to effectively control randomness, and organismal control over the timing and magnitude of steps. For example, small organisms can capitalize on micro-scale information in fluids and biochemistry, and cells can use diffusion as a source of information when patterns are sharpened through filters and positive feedbacks.

As scientists, we must formulate principles and models that capture stochasticity as part of the process, rather than as extrinsic noise. In some sense, like all organisms, we must continually solve inverse problems, extracting information even when we know that details and specific mechanisms are non-identifiable or lost in the haze of the past. The ease of collecting huge biological datasets at all scales raises an acute problem: what mechanistic parameters can, even in principle, be determined and from what types of data? We cannot simply assume that sufficient data can resolve any biological problem, because there are already examples of massive data collection efforts that are provably unable to distinguish between alternative underlying processes. Mathematically, we can approach these challenges with methods to predict the dynamics of distributions, not just individuals, and ideally understanding informative underlying patterns such as the relationship of sample means to sample variances. Alternatively, we can seek simplicity amidst the complexity through finding how networks are built from relatively simple network motifs to create robust dynamics.

These issues have implications beyond basic scientific understanding. If ensembles, ranging from groups of cells to collections of individuals, provide one way to cope with noise and integrate information, they create problems of their own regarding maintenance of cooperation, including avoiding the tragedy of the commons and breakdown of collective regulation, such as in cancer. The hidden potential of those individuals can backfire, such as when cancer cells recall the tricks they used as single-celled organisms to survive the challenges of an unpredictable environment to evade the controls of the whole organism.

Addressing these challenges demands not just new techniques or even new ways of thinking, but also new structures to support progress and new ways to frame the goals of our enterprise. We tend to think of scientific success in terms of identifying a novel mathematical approach that makes sense of stochasticity and making predictions that could not be made before, ideally while simultaneously elucidating new mechanisms and proposing new experiments. The meeting concluded with a discussion of new approaches to these challenges, ranging from working more closely with engineering methods to high throughput data.

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