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Fostering synergy between cell biology and systems biology

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In the shared pursuit of elucidating detailed mechanisms of cell function, systems biology presents a natural complement to ongoing efforts in cell biology. Systems biology aims to characterize biological systems through integrated and quantitative modeling of cellular information. The process of model building and analysis provides value through synthesizing and cataloging information about cells and molecules, predicting mechanisms and identifying generalizable themes, generating hypotheses and guiding experimental design, and highlighting knowledge gaps and refining understanding. In turn, incorporating domain expertise and experimental data is crucial for building towards whole cell models. An iterative cycle of interaction between cell and systems biologists advances the goals of both fields and establishes a framework for mechanistic understanding of the genome-to-phenome relationship.

Systems biology: a toolbox for studying mechanism at the genome scale

In *Discovering Cell Mechanisms: The Creation of Modern Cell Biology*, William Bechtel frames cell biology as 'a quest to articulate mechanism' in which a mechanism is a structure performing a function in virtue of its component parts, component operations, and their organization [1]. Bechtel poses this view as a complement to historical endeavors to deduce generalizable lessons in cell biology. That is, in lieu of comprehensive schematics of all cellular components, cell biologists have successfully identified recurring themes and patterns (e.g., the Central Dogma or the cell cycle) that help to explain biological phenomena in different contexts. Goals of cell biology thus bridge both generalization (elucidating universal themes) and specification (characterizing detailed mechanism) to encompass the manifold answers to 'how' when relating information encoded in the genome to the resulting cellular composition and behavior (the genome-to-phenome relationship).

The genome-to-phenome relationship and mechanistic understandings of 'how' also lie at the heart of systems biology. Through modeling and data analysis, systems biology attempts to articulate and identify explanatory mechanisms from a collection of candidates. When mechanisms are difficult to fully resolve, systems biology can be used to integrate what is known about a cell scale system and provide probabilistic predictions. Systems biology also aims to address both fine-grained description and generalization: practitioners of the field strive to balance unifying themes and rules in biological systems with dynamic and condition-specific phenomena.

Systems biologists were not the first to consider molecules and biological processes in the context of systems. Nor were they the first to develop 'models' of systems. A model is nothing more than a useful simplification of a mechanism or collection of mechanisms. As exemplified by decades of process and pathway diagrams in biology papers, framing the activity of molecules in an explanatory model is a natural way to obtain a transferable understanding of that system. Simplified, qualitative models from empirical observations have been essential to our conceptual understanding of mechanistic biology; however, they lack the power to effectively capture the more expansive structures and processes that underlie many phenotypes and genome-scale measurements. Systems biology embodies the realization that some systems are too large or complex to fully comprehend via empirical observations or even closed-form analytics. In these cases, characterizing the mechanisms and deriving a generalizable understanding requires a specialized set of tools tailored for modeling systems at scale.

Systems biology aims to formalize model derivation – at scale – by combining quantitative experimental observation, theory, and computation [2]. Cell biology synthesizes and builds upon useful tools for studying cells, including those that existed before any formal definition of the field. Similarly, tools in mathematics or computer science can be useful in their own right when applied to particular biological data and questions. Systems biology extends these and other tools, integrates them into new frameworks, and adapts them to focus more effectively on cell scale systems.

Tantamount to technical implementation, systems biology – at its best – requires careful consideration and melding with the lessons and tools of cell biology; the value of a model is speculative without experimental characterization and validation of predictions. Nonetheless, the exercise of creating models can itself be highly informative. Building mechanistic models first requires cataloging what is known about the individual components and interactions, together with the data and observations specific to different contexts and conditions. With a model in hand, integration and quantification of information about a biological system can lead to predictions of mechanism as well as the identification of generalizable themes. Multiple points in the process of building and analyzing models – from experimental

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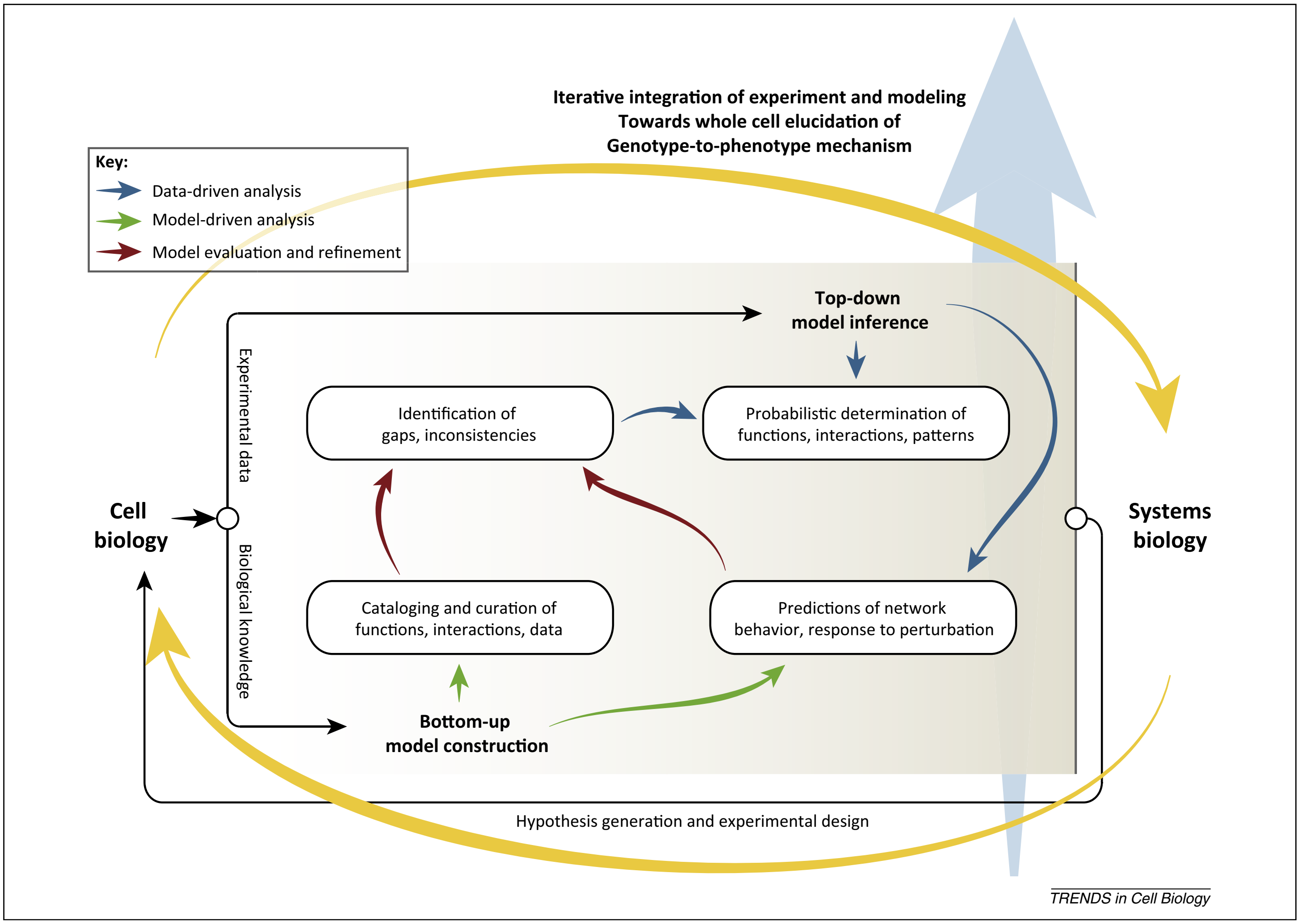

Figure 1. Systems biology gains from and contributes to cell biology through model building, analysis, and refinement. As cell biology continues to yield new advances and experimental discoveries, systems biology aims to further integrate these data and knowledge towards gaining a more comprehensive mechanistic understanding of the genome-to-phenome relationship. Importantly, the potential contributions of modeling efforts in systems biology benefit from both bottom-up and top-down approaches.

design to validating and interpreting results – can benefit greatly from interaction between cell and systems biologists. The iterative cycle of integrating domain expertise and experimental data, building and analyzing models, identifying gaps in understanding, and refining what is known, in our opinion, embodies systems biology (Figure 1). Moreover, this cycle captures both the intrinsic benefits and crucial requirements of building towards 'comprehensive' models of cells.

Integrating and cataloging data and knowledge

From pathways or circuits to genome-scale biological networks, depicting a system in any particular state or condition requires thorough enumeration of components and their possible significant interactions. As such, model-building efforts often begin with the identification (or creation) of a catalog of well-characterized biological information. Historically, reductionist biology – the analysis of a system through its breakdown into smaller pieces to determine the connections between components – has been essential to building our conceptual framework of mechanistic biology. Subsequently integrating this information presents increased opportunity to understand many of the genome-to-observed phenome relationships. Systems biologists thus strive to combine and make sense of experimentally gained information, whether obtained from the literature or from new measurements.

Reductionist approaches that carefully annotate a vast array of biological components collectively provide a 'parts list' for biological systems. These parts lists have given rise to databases of networks and pathways such as the Kyoto Encyclopedia of Genes and Genomes (KEGG), the Database for Annotation, Visualization, and Integrated Discovery (DAVID), and the Molecular Signatures Database (MSigDB) [3–5] that exist at a valuable interface between cell and systems biology. The information in these databases is largely compiled from decades of research in cell and molecular experimental biology, ranging from studies focusing on a single gene or protein (e.g., isolation, sequencing, biochemical characterization, perturbation) to high-throughput assays providing 'omics' measurements. In turn, the large-scale utilization of such databases is partly driven by the desire to perform systems-level analyses.

As systems biologists work to compile, connect, and quantify the many components of a system into a unified whole, they also can help to establish a valuable resource for cell biologists. Construction of pathway and genome-scale models for signal transduction or metabolism from the bottom up often involves the collation of vast amounts