HHS Public Access

Author manuscript

Trends Cell Biol. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Trends Cell Biol. 2015 August ; 25(8): 440–445. doi:10.1016/j.tcb.2015.04.005.

Fostering synergy between cell biology and systems biology

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Abstract

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 critical 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.

Keywords

systems biology; cell biology; modeling; networks; data integration

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,” where 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 of “how” when relating information encoded in the genome to resulting cellular composition and behavior (the genome-to-phenome relationship).

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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’ worth 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 more expansive structures and processes underlying many phenotypes and genome-scale measurements. Systems biology embodies the realization that certain systems are too large or complex to fully comprehend with empirical observations or even closed-form analytics. In these cases, characterizing mechanism and deriving 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 certain 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, along 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 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 critical 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 in order 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-phenome relationships observed. Systems biologists thus strive to combine and make sense of experimentally gained information, whether obtained from literature or 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 KEGG, DAVID, and 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 partially 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 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 of literature-based knowledge that would otherwise remain scattered and disconnected. For example, the first human metabolic network reconstruction incorporated information from over 1,000 peer-reviewed papers [6]. Community efforts continue to monitor and integrate new literature into an ever-improving, cohesive model [7].

Synthesizing annotated biological parts in structured, centralized resources not only provides information that can be used to guide modeling or experimental efforts, but also highlights gaps or poorly characterized areas of knowledge that can be consequently prioritized. Even in the case of systems (e.g., transcriptional regulatory or other large interaction networks) where complete experimental enumeration is presently infeasible, informative genome-scale models can be built and evaluated to generate new hypotheses [8,9]. Moreover, the basic task of defining what is known and unknown for a system can have far-reaching consequences, from guiding decisions of model or experimental design to proposing entirely new avenues of investigation.

Model development in the systems biology paradigm depends critically upon quantitative (often high-throughput) measurements. High-throughput technologies enable the simultaneous measurement of hundreds to thousands of biomolecules, paving the way for *in silico* model construction of increasingly large and diverse biological systems. In the age of

increasingly “big” biological data, computational analyses in systems biology also benefit from and help drive the annotation, centralization, standardization, and characterization of datasets—as well as the patterns they depict—within and across populations.

As the magnitude and scope of biological data grow exponentially, effectively harnessing “omics” experiments as organized and informative resources has become an increasingly valuable component of biological research programs. Notably, such resources also provide the opportunity to learn shared features and patterns across systems, including different cell types and contexts as well as model organisms—potentially accelerating the characterization of individual species and enhancing translation of discoveries across species.

Identifying mechanisms and themes through quantitative modeling

Systems biologists synthesize and integrate existing knowledge or data about biological systems to establish quantitative models for exploration of genome-to-phenome relationships. The end effect of many modeling studies is not necessarily a definitive target or mechanism. Instead, systems biology approaches often yield a reduced experimental search space or prioritized set of features to measure, novel hypotheses about the dynamics and regulation of a system, and broader themes and patterns that might go unnoticed when studying individual molecules in isolation. These outputs, while more modest, set the stage for follow-up investigation and an iterative cycle of experiment and computation. Importantly, the most useful models are typically those that effectively leverage existing knowledge or expertise in cell biology—whether incorporating literature or experimental measurements or collaborating directly with cell biologists.

Many systems models aim to describe the inter-conversion of biomolecules in networks that drive cell processes. Network models can represent encoded information between biological components and how these relationships contribute to emergent phenotypes. Metabolic networks, for instance, depict the rate of conversion of material through enzymatic reactions; information related to the synthesis and degradation of biomolecules in a cell can thus be traced from environmental inputs to system-level composition [10,11]. Interactions among components in signal transduction and regulatory networks are somewhat more abstract [12,13], being subject to absolute levels, post-translational states, spatial arrangement and location, and the duration of any particular action. In spite of this complexity, the development of quantitative signaling network models—a prevalent focus of systems efforts to date—highlights several advantages of model-centric synergy between cell and systems biologists [12].

Straightforward, verifiable deliverables of signaling models include quantitative predictions of concentrations, rates, and roles of specific molecules in a pathway or process [14–16]. For example, analysis of a mitogen-activated protein kinase (MAPK) signaling network [17] showed that increasing levels of MAPK phosphatase (MKP) (within a feedback loop) turn the MAPK/PKC system from a bistable on/off switch into a monostable proportional response system. These two states drive distinct biological responses utilizing a common upstream factor. In one state, low MKP expression results in sustained MAPK signaling, driving mitosis or development. Alternatively, higher MKP activity results in a more acute

MAPK response, driving other processes such as autocrine/paracrine signaling. Differences in network structure such as this are often the basis for differences in cell context. Several non-obvious impacts of modeling signaling networks have also been observed. For example, a computational tool for studying apoptotic signaling networks showed that the *dynamic range* of a particular signal—not the absolute strength of the signal—determined whether or not cells died [18]. In this case, integrative modeling highlights ways in which biological information and regulation can manifest beyond just rates and levels.

Systems biologists can also model biological networks that extend beyond the boundaries of the cell membrane—including interactions and molecular communication between cells—to better understand mechanisms that give rise to tissue-, organ-, or even organism-level function. For example, variability in cell responses to intercellular network signals can drive population-level phenomena. A combination of experiment and modeling showed that heterogeneity in cellular response to apoptotic ligands could be accounted for by fluctuations in proteins competing “for” or “against” a specific biological process [19]. The analysis posited that cell-to-cell variability enables an adaptive advantage to multi-cellular organisms by: (i) prevention of “half-dead” states that may result in pathology; (ii) finer regulatory control of death signals for a population of cells; and (iii) prevention of cells dying *en masse*, causing systemic failure. In a different context, careful experimentation has elucidated the gene regulatory networks responsible for many aspects of sea urchin development. Analysis of these networks has shown the structure/function relationships between specific genes, how these function together as developmental regulatory circuits, and how perturbing these circuits manifest in altered phenotypes at the organism level through the course of development [20].

Another impact of systems analysis of signaling networks has been the identification of themes that emerge from evaluating large numbers of models and model configurations. For example, profiling the dynamic properties of many possible network states revealed subsets of configurations that give rise to systems-level properties [21–23]. In a simple 3-protein network with over 16,000 possible wirings, it was shown that only two general configurations allowed perfect adaptation of the output response to a step-input signal [22]. By extension, numerous modeling studies have emphasized the general importance of network wiring or topology over specific rates and parameters [12]. For example, sensitivity analysis of an ErbB signaling model revealed that, despite degeneracy in parameter values across different fitting strategies, many relationships tend to be conserved between classes of parameters and the important features they influence [24]. Another model of c-Fos expression dynamics revealed how organization of feedforward loops in a cascade structure discriminates between transient and sustained signaling activities while remaining robust to parameter perturbation [25]. The importance of network structure has motivated the characterization and study of recurring network motifs [20,26,27] as well as attempts to quantify informative “differential network wiring” between phenotypes [28,29].

Not all biological processes are directly amenable to traditional network representations, where individual components are treated as nodes and the interactions between them as edges, For example, a computational model of translation initiation derived from next-generation sequencing data showed that ribosome density along an RNA transcript is a

function of gene length and rate of initiation [30]. This model helps to explain the 5′-to-3′ ramp of decreasing ribosome densities and suggests that this occurs due to rapid initiation of short genes rather than slow codons at the start of transcripts, as previously suggested. The model also showed how expression of a transgene could be improved by counter-intuitively reducing initiation rates. Even in non-network cases, systems approaches can help understand key questions of fundamental cell biology by integrating information about large numbers of variables or disparate data types.

Opportunities for synergy and iteration towards whole-cell understanding

Given the growing abundance, scale, and importance of data in biology, many of the tools and approaches of “data science” are being adopted. Likewise, core principles of data science also apply to data-driven analysis in systems biology. Quality data science emphasizes leveraging domain expertise to go beyond just machine learning or statistical inference [31], which can often be applied without context to the underlying biology. More importantly, rigorous data scientists typically prioritize the question being asked—rather than the tools applied—as the most fundamental determinant of success.

Collaboration with domain experts and experimental biologists can greatly facilitate analysis and modeling in systems biology. For example, given data from a strategically planned and controlled experiment (with sufficient sample size), a computational biologist can deduce potential causation from cleverly modeled correlation, time-series analysis, and/or leveraging of known biology in related systems. Conversely, experimental cell biologists with an intimate understanding of the biology and experimental design can often best understand the results of a systems analysis (and whether or not the findings are novel or informative).

Approaches to reverse engineer network structure or patterns from high-throughput datasets can be a fair target of skepticism, as over-fitting in these scenarios given small sample sizes is indeed a serious issue. However, such statistical inference can also be greatly informed and constrained by existing annotation and known biological mechanisms [31,32]. For example, methods built to infer gene regulatory networks increasingly leverage greater amounts and varieties of information and measurements beyond transcriptomics, the original data on which such models were typically trained [33]. Such studies aim to account for known transcription factor annotations, characterization of binding sites, or description of epigenetic states across a multitude of environmental conditions. Accounting for existing knowledge helps to elucidate regulatory dynamics that would be otherwise intractable by studying co-expression alone.

Opportunity for fruitful interaction also exists at early stages of data generation and analysis. Distinguishing meaningful signal from technical and biological noise presents a central challenge across high-throughput datasets. Noise and variability can be controlled for, in part, with strategies for experimental design and analysis. For example, including technical and biological replicates can help tease out discriminating patterns between experimental groups, relative to background heterogeneity. Similarly, careful selection and detailed descriptions of all subjects to be analyzed is essential for minimizing confounding variables

in the data. Sources of noise are often not intuitively obvious to either experimental or systems biologists, further motivating careful preliminary discussions or—when possible—analysis of pilot data.

As technology improves, biologists can directly measure more of the different data types that can be used to guide modeling and inference. Several such efforts have been accomplished with the ENCODE project. For example, the search for regulatory response elements was constrained to DNAse hypersensitivity regions when constructing transcription factor regulatory networks for human muscle regulation and mouse embryonic development. These reverse-engineered networks recapitulated well-described transcriptional regulatory networks generated with multiple experimental approaches. Extending this approach to several cell types revealed how different cell-type specific circuitry with the same genes can lead to different outcomes [34]. Numerous technical and computational challenges remain for integrating multiple types of large-scale information. Interaction between cell and systems biologists is essential to ensure that measurements and parameters are pertinent and sensible, experiments are statistically powered, and potential confounding factors are carefully considered.

Efforts to compile and synthesize existing knowledge of any biological system into a cohesive model lead to a consistent outcome: discovery of knowledge gaps, discrepancies, and errors. Characterizing these knowledge gaps is an important step in prioritizing research directions, and becomes possible even through initial steps of collecting and cataloging data. Attempts to reconcile *in silico* model predictions with experimental measurements take the gap identification process a step further. In this case, inconsistencies point not just to un- or mis-annotated molecular components, but also to inaccurate or incomplete representations of interactions and context-specific activity. Data- or model-derived candidates to understand context specificity and resolve gaps or inconsistencies present specific hypotheses to guide experimental studies.

A major effort that aligns systems biology goals with those of cell biology is the generation of whole-cell models—i.e., useful simplifications that aspire to fully represent the genome-to-phenome relationship of a cell. In the most extensive example to date, the “gene-complete” whole cell model of *Mycoplasma genitalium* [35] incorporates every known gene product to simulate the life cycle of a cell. Representations approaching this level of completeness remain out of reach in more complex systems, but there are substantial efforts in genome-scale modeling to encompass particular functions comprehensively (to the extent possible) within bacterial, archaeal, and eukaryotic cells [36–38]. In humans, such genome-scale metabolic networks have been further contextualized to explore characteristics of different cell types [39,40], cancers [41–43], and neurodegenerative diseases [44,45]. Meanwhile, efforts are ongoing to combine different genome-scale networks as multiple layers (e.g., metabolism with transcriptional regulation) into integrated models [46,47].

The iterative cycle of cataloging, modeling, and refining knowledge—enabled by the data and findings of cell biology and carried out through bottom-up and top-down approaches—can ultimately give rise to more comprehensive models that better capture genome-to-phenome relationships. In turn, whole-cell models typify the secondary benefits to be

derived from the iterative process, where the synthesis and systematic evaluation of existing knowledge is often as or more important than specific model predictions.

Concluding remarks

Understanding the multitude of mechanisms by which cell function arises from information in the genome will require significant advances in both cell biology and systems biology. The German philosopher Georg Wilhelm Friedrich Hegel proposed how a dialectic (thesis, antithesis, synthesis) can function to establish truth. Similarly, systems biology and cell biology can be viewed as complementary yet in some ways contrasting ideologies that, when considered together, advance understanding in both. By reconciling what we know about smaller systems with what we know about larger systems, we can create a framework in which to formulate hypotheses and ultimately translate knowledge of components to knowledge of cell mechanism.

The process of building models, making predictions, testing against experiment, and identifying knowledge gaps is an iterative process, with each step further advancing our collective understanding. This cycle will continue to benefit from greater and more active synergy between cell and systems biologists. Perhaps the most important ingredient for this synergy moving forward is a mutual respect for the strengths of each discipline—recognizing the value of systems to cell biology and vice versa helps researchers to better leverage each respective discipline. A culture of collaboration will better enable scientists together to deal with the massive complexity of the cell in order to describe mechanisms in practical terms.

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Highlights

Cell and systems biology share a goal in understanding mechanisms of cell function.

Systems biology provides tools to study complex cellular processes at larger scales.

Iteration between model building and experiment yields contributions to cell biology.

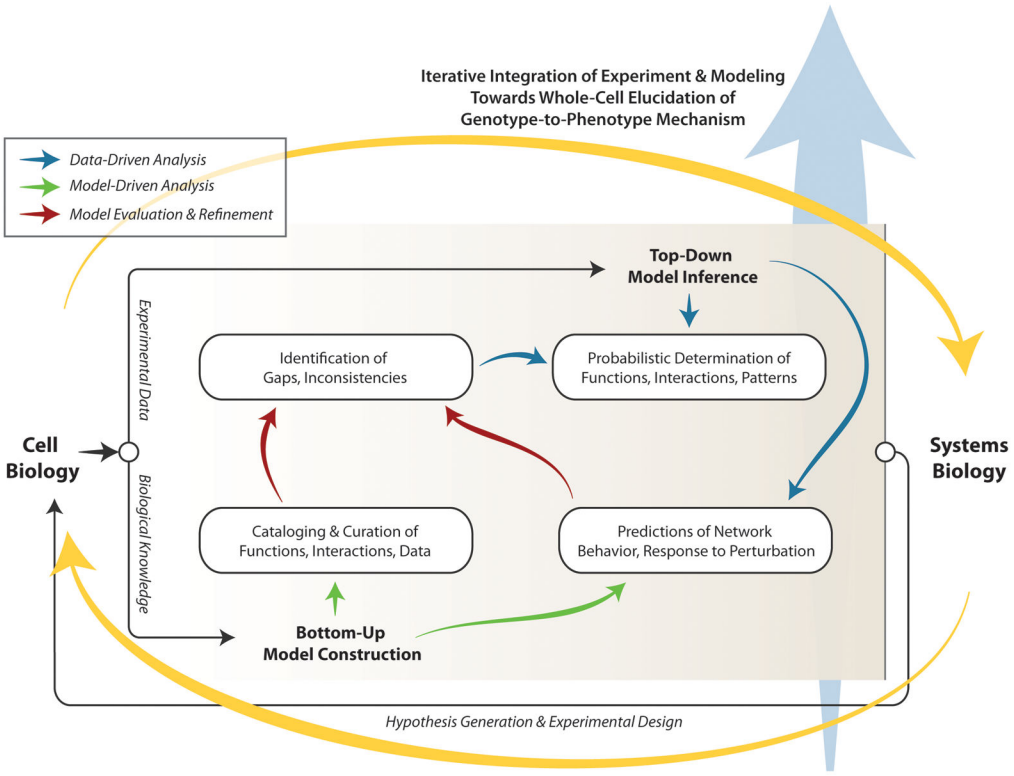

Figure 1. Systems biology gains from and contributes to cell biology through model building, analysis, and refinement

As cell biology continues to yield new advances and experimental discoveries, systems biology aims to further integrate this 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.