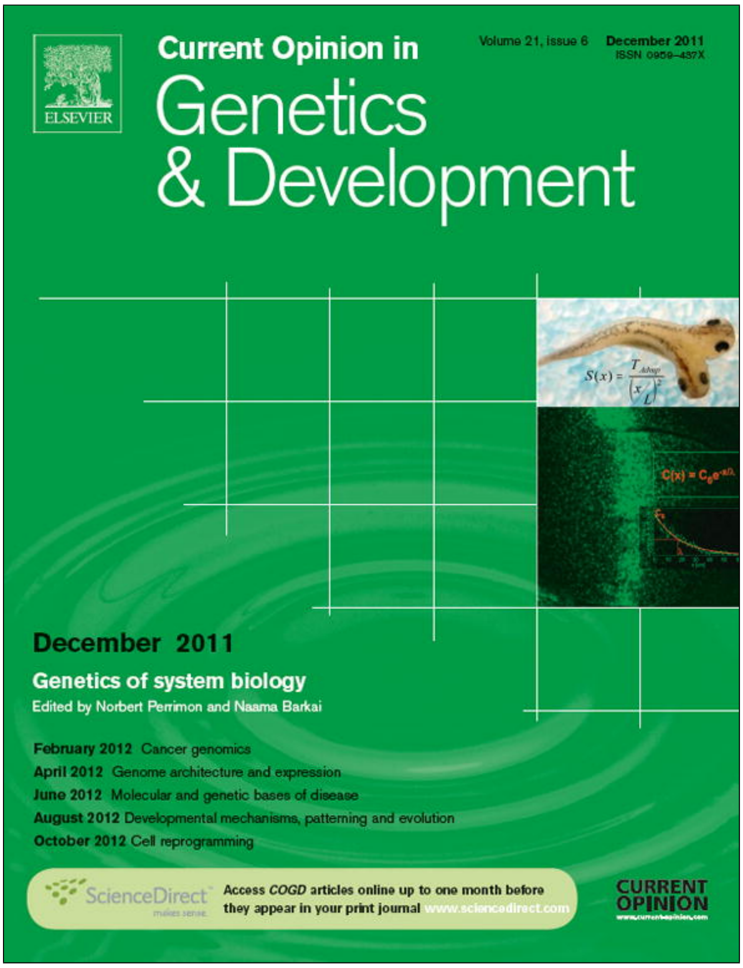
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The era of systems developmental biology

Editorial overview

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Norbert Perrimon is Professor of Genetics at Harvard Medical School and an Investigator with the Howard Hughes Medical Institute. He is interested in the organization and function of signaling pathways involved in developmental processes and homeostasis. In recent years, his group has implemented large-scale approaches of high-throughput RNAi screens and proteomics to analyze signaling networks systematically.

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Developmental biologists are concerned with a myriad of biological questions that address problems as diverse as egg formation and fertilization, development and patterning of the embryo, cellular differentiation, morphogenesis, metamorphosis, tissue and organ formation, regeneration and homeostasis, control of animal size and aging. Early experimental studies, using primitive methods based on today's criteria, led to fundamental concepts, such as of organizing activity and morphogen gradient, pluripotency and cell differentiation. Developmental biology was quickly transformed when the tools of genetics and molecular biology were used to identify the molecules and mechanisms underlying developmental processes. Today, after more than thirty years of intense studies, the molecules and pathways that control pattern formation, cellular interactions, cell migration, and differentiation, have been identified, and many of these findings have had major impact on our understanding of the basis of diseases, including congenital disorders and cancer. Further, a number of exciting applications, for example for tissue repair and stem cell therapies, are emerging as a direct consequence of our basic understanding of developmental processes.

Developmental biology, fueled by advances in genomics, proteomics, imaging, and applications of physics and mathematical modeling, is yet undergoing another renaissance – entering the era of 'Systems Developmental Biology'. The availability of complete genome sequences has led us to think about applying systematic and unbiased methods to identify all the genes involved in a specific process. Astounding progresses in chip-based arrays and sequencing technologies, together with sophisticated methods to perturb and control gene activities, now allow us to address the function of virtually any gene in any cells and at any time points. Further, advances in imaging, and fluorescent proteins in particular, allow us to probe the subcellular localization of proteins and follow their spatial and temporal dynamics. Finally, advances in proteomics allow us to identify with great accuracy protein–protein interactions and post-translational modifications. Altogether, these flurries of technical advances allow us to describe both wild-type and mutant phenotypes at unprecedented detailed levels, genome-wide and importantly in some instances quantitatively.

The goal of 'Systems Developmental Biology' is to go beyond our current understanding of what single gene, or a few connected parts, do in a biological context. The challenge is to become more systematic, unbiased and quantitative in the analysis of developmental questions. Thus, we now want to identify all the parts and pathways involved and quantify some of the key parameters to build mathematical and computational models that describe and predict the behavior of the systems. Further, detailed knowledge of signaling pathways enables us to start addressing seminal questions regarding their functionalities: How is patterning reproducible from one embryo to the next, despite fluctuations in the levels of signaling components, temperature differences, variations in size, or unequal distribution of components between daughter cells? Are there underlying mechanisms that assure a reproducible response? Are these mechanisms conserved across species, similar to the signaling pathways they control? Our ability to identify using genetics and proteomics most components involved in a process, together with our ability to describe phenotypes quantitatively has allowed mathematical models to go beyond abstract conceptual frameworks, and as such provide tools to generate biological hypotheses and identify emerging properties of systems, which is a prerequisite to fully understand the logic behind animal development.

The reviews in this issue illustrate some of the exciting work being done in today's 'Systems Developmental Biology'. They encompass a very diverse set of model systems and topics that exemplifies how developmental biologists, using a combination of experimental and mathematical tools, study for example the complex patterning of tissues, the detailed molecular mechanisms of morphogen action, and the collection of genome-wide data sets to obtain network level understanding.

A central paradigm in developmental biology is that of morphogen gradients. Morphogens are molecules that instruct cells to adopt particular cell fates in a concentration-dependent manner. Key outstanding questions are how morphogen gradients are formed and interpreted by responding cells to induce their differentiation. Several reviews in this volume are concerned with properties of morphogen gradients, with particular emphasis on the well-studied family of Bone morphogenetic protein (BMP) ligands. Xie and colleagues describe the mechanism controlling the production of the BMP ligand Decapentaplegic (Dpp) in the niche of the *Drosophila* ovary. In this context, Dpp production, diffusion and signaling are precisely orchestrated and act only within one cell diameter. This short range signaling activity is necessary to maintain a stable germline stem cell pool. Dpp also acts during patterning the *Drosophila* wing disc, which is the subject of the review by Wartlick and González-Gaitán. In this disc, Dpp regulates both patterning and growth. Wartlick and González-Gaitán discuss how Dpp could instruct cell divisions, which is a key for understanding how a spatial gradient of Dpp regulates uniform growth.

BMP ligands also play a key role during vertebrate development. De Robertis and colleagues describe how the BMP gradient is formed in the early Xenopus embryo. A combination of quantitative experiments and theoretical modeling revealed that formation and maintenance of this gradient involves a flow of BMP ligands towards the ventral size, a mechanism predicted to increase the robustness of the gradient and enable its scaling with embryo size. The issue of scaling, namely the ability to adjust the morphogen gradient with embryo size, is also discussed by Shilo and colleagues who describe a simple network motif ('expansion–repression') that naturally accounts for scaling. Recent results suggest a specific implementation of this mechanism in the scaling of the Dpp gradient in the *Drosophila* wing imaginal disc.

The challenge of how morphogen gradients are interpreted is the subject of three additional reviews in this volume. Wunderlich and DePace describes insights that can be gained from quantitative studies of transcriptional regulatory networks. Focusing on the early *Drosophila* embryo they illustrate how a systems approach help model the Bicoid morphogen gradient, how quantitative *in situ* hybridization methods can be used to build a modeling framework that addresses the function of cis regulatory element sequences, and how a statistical model can be used to predict the expression patterns of candidate cis regulatory element sequences. Shvartsman and colleagues analyze the formation and readout of the EGFR activation gradient in patterning the follicular epithelium surrounding the *Drosophila* oocyte. They show how combining quantitative imaging, theoretical modeling and experimentations can generate new hypothesis about the underlying mechanisms. Finally, Lander and colleague provide a complementary perspective on morphogen gradient interpretation. While the classical view is that morphogen concentrations are compared with fixed concentration thresholds, this review discusses recent results suggesting that Hedgehog and other morphogens are interpreted dynamically, integrating the concentrations levels as they are being established.

A second patterning principle complementary to that of morphogen gradients is that of symmetry breaking. Here, pattern is formed through dynamic interactions between equivalent quantities. One example, which is the subject of the review by Shaya and Sprinzak is lateral inhibition mediated by the Notch–Delta pathway. Lateral inhibition is used repeatedly in development, an example being the selection of sensory precursor cells out of a cluster of equivalent cells. Here, random process leads to the selection of one cell in the cluster, which subsequently inhibits its neighbors. This inhibition occurs in trans; Delta ligand from the selected cells binds to the Notch receptors in neighboring cells. Yet, Delta binds Notch also in cis, in the same cells. Shaya and Sprinzal describe recent experimental and theoretical data that emphasize the role of this cis interaction in the patterning mechanism.

A complementary aspect of symmetry breaking is that of choosing cell polarity. While polarity cues are often predisposed, cells can polarize spontaneously and this inherent ability is critical for ensuring efficient polarization also in the presence of a pre-set cue. The review by Lew and colleagues describe theoretical and experimental progresses in understanding the mechanism of cell polarity in the single budding yeast cell. In multicellular organisms, polarity needs to be coordinated along full tissues and organs. The review by Eaton and Julicher discusses how such coordination is achieved during the development of the pupal *Drosophila* wing. In particular, they emphasize the role of mechanical stresses exerted on the tissue and of the oriented cell divisions and neighbor exchanges.

Notably, the initiation of symmetry breaking relies on some stochastic (noisy) events. Loewer and Lahav discuss the cause and consequence of stochastic events in individual mammalian cells. Reuven and Eldar further expand on the consequence of such stochastic variability, focusing this time on adaptive responses in bacteria to conflicting challenges. An interesting angle explored in this review is the opportunity it provides for social interactions that enable sharing the benefits of the different fates but also allowing the emergence of 'cheater' cells. From yet a different perspective, Balaban discusses the role of stochastic events in the resistance of bacteria to antibiotics. She discusses how bacteria randomly transit between 'normal' and 'persistent' states, the later showing reduced sensitivity to antibiotics, highlighting recent progress elucidating environmental factors that effect those transitions, as well as the network motifs enabling co-existence of persistent and non-persistent cells within the same population.

Our ability to study problems genome-wide and the technologies available is discussed by Van Nostrand and Kim who review state-of-the-art methods to systematically characterize mRNA expression profiles, transcription factors binding sites, and nucleosome positioning to study gene regulation at the tissue and single cell levels. In the context of transcription, integration of these datasets provides insights into novel gene regulatory circuits. The conceptual framework of networks to help interpret large datasets is further discussed by Gunsalus and Rhrissorrakrai who describe how molecular interaction networks that integrate physical interactions and genetic dependencies between genes, transcripts, and proteins, can be used to study robustness, modularity, feedback loops, dynamics, and responses to perturbations.

Understanding how organs are built and function at the systems level ultimately requires the integration of information at multi levels. These issues are discussed by Tusscher and Scheres who review the importance of feedback and integration during plant development, both within a process (transition to floral development, lateral root initiation) and between processes and levels of organization (cell differentiation, orientation, division, auxin transport, mechanics). Similarly, in the olfactory response, a systems level description of cellular networks is necessary to understand how responses are achieved. Leinwand and Chalasani, reviewing the organization and connectivity of the olfactory network comprised of sensory neurons and interneurons, provide a striking example of how cellular networks are organized to mediate responses to olfactory cues.

The articles in this issue provide a number of examples of the success of looking at biological problems globally and quantitatively. The approach of studying developmental questions in more quantitative and systematic manners is quickly becoming the norm. As thus, to facilitate progress, it will become critical to empower students entering the field with a rigorous curriculum that teaches developmental biology, mathematics and physics.