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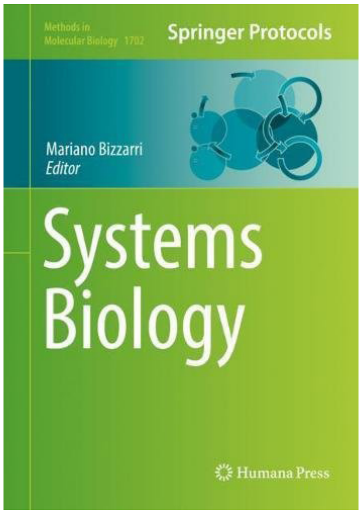

Systems Biology

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Systems Biology: insights into methodological challenges

Despite many explanations have been proposed to capture the hidden meaning of 'Systems Biology', definition of this 'new' discipline remains quite uncertain.

Currently two primary streams can be recognized within Systems Biology: 1) pragmatic Systems Biology, which emphasizes the use of large-scale molecular interactions, aimed at building huge signalling networks by applying mathematical modelling and thus showing how cells make decisions based on the 'information' flowing through their networks.

2) Theoretic Systems Biology which posits that the theoretical (and consequently the methodological) basis of biological study should be deeply modified.

Molecular Biology tries to explain the mysteries of the living being by exclusively considering it a consequence of a linear translation of the 'DNA code'. As originally formulated, the 'central dogma' posits that 'information' flows from DNA to proteins, and not the other way around.

However, environmental factors do change the genome, by both genetic as well as epigenetic mechanisms, and a number of both molecular and biophysical factors participate in shaping gene activity and cell functions.

Moreover, genomic functions are inherently interactive and biological processes flow along complex circuits, involving RNA, proteins and context-dependent factors (extracellular matrix, stroma, chemical gradients, and biophysical forces within which vital processes occur. Definitely, no simple, one to-one correspondence between genes and phenotypes can be made.

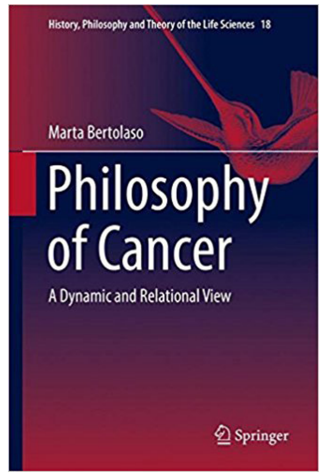
Reassessment of the fundamental concepts of biological science is therefore necessary. Namely, Authors participating to this volume do not believe Systems Biology should be considered a 'simple' 'gradual' extension of Molecular Biology. Systems Biology is indeed more than just a 'sum up' of different sciences, given that Systems Biology deals with 'systems', and it is concerned with the complex, emergent properties that arise from the relationship between molecules, cells and tissues. Functional properties are not yet in the 'molecules', instead they 'emerge' from a self-organized process, which shape geometrically the living structure into a system, characterized by hierarchical levels. Interaction among them lead to both top- and down-ward causation. Therefore, Systems Biology requires a new way to rethink biology, by promoting an integration of different kind of knowledge, not a simple collation of disciplines. There is no doubt that this challenging task need a new scientific methodology for the III millennium.

Many of these critical methodological issues are addressed in this volume. What kind of relationships exists among the lower levels (i.e., molecular) and the highest ones (cell, tissues, organs)? This question can be more precisely reframed as follows: how the intrinsic stochastic activity occurring at the genome level could ultimately end up into a deterministic behaviour, as such we observe at the cell or tissue level? Indeed, stochasticity in gene expression contributes in generating phenotypic heterogeneity from which the most suitable configuration can be explored by the cell to "make" appropriate decisions conferring it with remarkable phenotypic plasticity. Yet, gene and molecular activity regulation only partially rely on driving cues acting at the molecular, while they are strongly modulated by cues and constraints dependent on higher levels and tightly embedded within the specific biological field. Constraints and forces (including electromagnetic, gravity and cell-tissue-dependent mechano-transduced forces) mostly impose order in living systems by acting at higher levels than the molecular one.

Ultimately, phenotypic switching can result from stochastic (genetic and non-genetic) rather than by deterministic events alone (genetic), while higher order constraints altogether with the activation of specific regulatory network configuration will help in stabilizing the cell fate commitment. Systems Biology try to identify these factors by investigating the level in which this kind of interactions are likely to happen. The search for parameters than can help in describing biological process implies a double effort: a) identification of the minimum number of 'observables' required for a proper description of the system's behaviour, b) assessment of the relationships among variables in order to reconstruct a reliable mathematical model. That approach will likely enable us in inferring previsions from data as well as to detect critical transition points.

Furthermore, while Molecular biology taught us how some selected and 'compartmentalized' biochemical processes are mechanistically linked each other, nothing says about how the 'parts' are integrated in shaping the whole and, in turn, how the 'whole' drives and 'canalizes' biochemical pathways. This observation implies we have to rethink how the natural world is structured into hierarchical levels of organization, ranging from subatomic particles to molecules, ecosystems and beyond. Each level is both characterized and governed by emergent laws that do not appear at the lower levels of organization. Therefore, to explain the features and behaviour of a whole system, we require a theory that operates at the corresponding hierarchical level.

This volume focuses on these theoretical and methodological aspects, providing elements for a unified approach, with a robust and tailored experimental support. Chapters detail mathematical modelling, methodological issues, modulation of the collective behaviour, metabolic, dynamic profiling, and quantitative morphological studies. Written in the highly successful Methods in Molecular Biology series format, chapters include introductions to their respective topics, lists of the necessary materials and reagents, step-by-step, readily reproducible laboratory protocols, and tips on troubleshooting and avoiding known pitfalls.



Philosophy of Cancer
A Dynamic and Relational View
Editor(s): Marta Bertolaso
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Cancer: challenging theories

Since the 1970s, the origin of cancer is being explored from the point of view of the Somatic Mutation Theory (SMT), focusing on genetic mutations and clonal expansion of somatic cells. As cancer research expanded in several directions, the dominant focus on cells remained steady, but the classes of genes and the kinds of extra-genetic factors that were shown to have causal relevance in the onset of cancer multiplied. The wild heterogeneity of cancer-related mutations and phenotypes, along with the increasing complication of models, led to an oscillation between the hectic search of 'the' few key factors that cause cancer and the discouragement in face of a seeming 'endless complexity'. To tame this complexity, cancer research started to avail itself of the tools that were being developed by Systems Biology. At the same time, anti-reductionist voices began claiming that cancer research was stuck in a sterile research paradigm.

This alternative discourse even gave birth to an alternative theory: the Tissue Organization Field Theory (TOFT).

A deeper philosophical analysis shows limits and possibilities of reductionist and anti-reductionist positions and of their polarization.

This book demonstrates that a radical philosophical reflection is necessary to drive cancer research out of its impasses.

At the very least, this will be a reflection on the assumptions of different kinds of cancer research, on the implications of what cancer research has been discovering over 40 years and more, on a view of scientific practice that is most able to make sense of the cognitive and social conflicts that are seen in the scientific community (and in its results), and, finally, on the nature of living entities with which we entertain this fascinating epistemological dance that we call scientific research.

The proposed Dynamic and Relational View of carcinogenesis is a starting point in all these directions.