

Computational Systems Biology in Cancer: Modeling Methods and Applications

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Abstract: In recent years it has become clear that carcinogenesis is a complex process, both at the molecular and cellular levels. Understanding the origins, growth and spread of cancer, therefore requires an integrated or system-wide approach. Computational systems biology is an emerging sub-discipline in systems biology that utilizes the wealth of data from genomic, proteomic and metabolomic studies to build computer simulations of intra and intercellular processes. Several useful descriptive and predictive models of the origin, growth and spread of cancers have been developed in an effort to better understand the disease and potential therapeutic approaches. In this review we describe and assess the practical and theoretical underpinnings of commonly-used modeling approaches, including ordinary and partial differential equations, petri nets, cellular automata, agent based models and hybrid systems. A number of computer-based formalisms have been implemented to improve the accessibility of the various approaches to researchers whose primary interest lies outside of model development. We discuss several of these and describe how they have led to novel insights into tumor genesis, growth, apoptosis, vascularization and therapy.

Keywords: cancer, computational systems biology, simulation, modeling, cellular automata

Background

Living organisms are complex systems. Nowhere is this complexity more evident than in the genesis and development of cancer. While cancer may originate from genetic and molecular changes that occur in a single cell, the subsequent proliferation, migration and interaction with other cells is crucial to its further development. In their landmark paper, Hanahan and Weinberg described six hallmarks they thought necessary for the transition from normal cells to invasive cancers (Hanahan and Weinberg, 2000). These included: 1) self-sufficiency in growth signals, 2) insensitivity to growth inhibitory signals, 3) evading apoptosis, 4) limitless replicative potential, 5) sustained angiogenesis, and 6) tissue invasion and metastasis. While genetic instability was not explicitly included in this list, it was included as an implicit enabling alteration that might start a normal cell down a mutagenic pathway leading to the acquisition of one or more of these essential characteristics.

The molecules that govern the cell growth and division cycle in response to external and internal signals are numerous and interact through complex, multiply-connected pathways over a wide range of temporal and spatial scales. Tumors reflect this complexity in that they are composed of several different cell types that interact to create malignant growth (Burkert et al. 2006). Despite the widespread acceptance of this complexity, the majority of biological and biomedical studies still utilize a strictly reductionist approach, focusing on the interactions of at most a few genes or proteins in each experiment. Systems biology, an integrative discipline that attempts to describe and understand biology as systems of interconnected components, has arisen partly as a response to these traditional reductionist approaches. Systems biology is a young field made possible by the explosion of data from genomic, transcriptomic, proteomic and metabolomic techniques developed within the last decade (Hollywood et al. 2006; Bugrim et al. 2004; Jares, 2006).

Computational systems biology, which is a sub-discipline of systems biology, has developed both as a tool supporting the processing of these massive amounts of data and as a modeling discipline, building upon this "omic" data in order to predict biological behavior (Ideker et al. 2001a; Alberghina et al. 2004). Not surprisingly, both experimental and computational systems biology approaches have provided fruitful insights into cancer.

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Computational Systems Biology Chapter 19 Applications In Cancer Research Mathematical Models Of Apoptosis

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Computational Systems Biology Stefan M. Kallenberger, Stefan Legewie, Roland Eils, 2013-11-26 Apoptosis is a form of cellular suicide central to various aspects in biology including tissue homeostasis and embryonic development It is typically dysregulated in cancer Understanding the apoptotic signal transduction network is thus a central goal of cancer research Quantitative modeling approaches provided valuable insights into determinants of cell fate decisions and promise to become a valuable tool to optimize therapeutic strategies In this chapter we summarize modeling approaches used in systems biology of apoptosis In addition we give an overview of apoptosis related research questions that can be addressed by modeling Moreover we review top down and bottom up modeling approaches applied to apoptosis and particularly focus on ordinary differential equation ODE modeling We describe bistability temporal switching crosstalk between death and survival and discuss approaches to model cell to cell variability

Computational Systems Biology Andres Kriete, Roland Eils, 2013-11-26 This comprehensively revised second edition of *Computational Systems Biology* discusses the experimental and theoretical foundations of the function of biological systems at the molecular cellular or organismal level over temporal and spatial scales as systems biology advances to provide clinical solutions to complex medical problems In particular the work focuses on the engineering of biological systems and network modeling Logical information flow aids understanding of basic building blocks of life through disease phenotypes Evolved principles gives insight into underlying organizational principles of biological organizations and systems processes governing functions such as adaptation or response patterns Coverage of technical tools and systems helps researchers to understand and resolve specific systems biology problems using advanced computation Multi scale modeling on disparate scales aids researchers understanding of dependencies and constraints of spatio temporal relationships fundamental to biological organization and function

Computational Systems Biology Roland Eils, Andres Kriete, 2013-11-26 *An Introduction to Computational Systems Biology* Karthik Raman, 2021-05-30 This book delivers a comprehensive and insightful account of applying mathematical modelling approaches to very large biological systems and networks a fundamental aspect of computational systems biology The book covers key modelling paradigms in detail while at the same time retaining a simplicity that will appeal to those from less quantitative fields Key Features A hands on approach to modelling Covers a broad spectrum of modelling from static networks to dynamic models and constraint based models Thoughtful exercises to test and enable understanding of concepts State of the art chapters on exciting new developments like community modelling and biological circuit design Emphasis on coding and software tools for systems biology Companion website featuring lecture videos figure slides codes supplementary exercises further reading and appendices <https://github.com/SysBioBook> An Introduction to Computational Systems Biology Systems Level Modelling of Cellular Networks is highly multi disciplinary and will appeal to biologists engineers computer scientists mathematicians and others

Genome Research, 2007 **Index Medicus**, 2002 Vols for 1963 include as pt 2 of the Jan issue Medical

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