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Editors

New Challenges for Cancer Systems Biomedicine

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New Challenges for Cancer Systems Biomedicine

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Preface

The future of oncology has a name: Molecular Medicine (MM). Molecular Medicine is a new science based on three pillars. Two of them are well known and evident in its very name: medical science and molecular biology. However, there is a general unawareness that MM is firmly based on a third but equally important pillar: Systems Biomedicine. Currently this term mainly evokes Bioinformatics and modern Applied Statistics, but increasingly it shall have to include (as in part it already does) the interacting complex of scientific fields such as Mathematical Biology, Systems Biology, Theoretical Biophysics.

The data from MM of tumors are complex and heterogeneous (e.g. clinical data paired with -omics data) but – and this is their most important feature - are unified by their dynamical nature. Indeed, cancers are a family of dynamic diseases, endowed by multiple temporal and spatial scales, and their polymorphic macroscopic instances are emergent properties originating from a wide number of microscopic interplays at intracellular and intercellular level. The complexity of these multiscale data cannot be deciphered by natural language reasoning, or by classical data analysis based on static data mining and model-unrelated time series analysis. These classical tools no longer suffice to cope with MM data in order to understand them and to produce meaningful and useful predictions.

As a consequence, it is mandatory to build mechanistic mathematical models of biomedical phenomena with complex outputs. These models could allow a deeper understanding of the "internal dynamics" of single patients or classes of patients, hopefully opening the road for tailored therapies. This is a huge challenge at the frontier of contemporary mathematical modeling, since dynamic modeling in MM is what allows to bridge the bench to the bedside, and in perspective it will be increasingly instrumental in aiding the cure of patients. By no means this implies that future medical doctors will be like electronic engineers, skilfully using special software to cure patients. Nevertheless, in a realistic perspective, future generation of oncologists will be more similar to cardiologists that rely on basic knowledge of the physics of heart and circulation, and use devices from bioengineering in their everyday clinical work.

Strict collaboration between biomedical researchers and Systems Biomedicine scientists is mandatory to make these hypotheses true in the future. What is the current state of this collaboration? A small number of outstanding experimental groups are seriously collaborating with biomathematicians, physicists and computer scientists, still maintaining separate competences. This is an important phenomenon. However, what is happening mainly in Systems Biology is even more interesting. An increasing number of inter-disciplinary groups are forming thanks to a new generation of group-leaders whose undergraduate background is in biomedical sciences. This trend leads to a far closer contact between two worlds quite separate in the past, and to the use of a common language. Many life scientists then become – in different degrees – confident and aware of the Systems Biomedicine potential. As an example of this potential, we can mention the possible role of mathematical modeling in drug development. Post-genomic drug discovery is indeed revealing serious shortcomings in the current way of performing clinical trials, which appears inadequate to face the age of personalized medicine. Systems Biomedicine, in the future generation of clinical trials, could thus play a fundamental role in shaping cancer treatments for single patients or groups of patients.

Many are the challenges that Systems Biomedicine of cancer must face. We have the responsibility of showing to the Life Sciences community that the potential of this discipline may become reality.

The present book has been inspired by the ideas underlying the Workshop Mathematical Oncology: New Challenges for Systems Biomedicine, held at the Ettore Majorana Centre for Scientific Culture in Erice (Italy), September 26–30, 2011.

The aim of this book is not only to illustrate the state of the art of tumor systems biomedicine, but also (and especially) to explicitly capture and collect results of the above-mentioned collaborative trends. Indeed, this volume is characterized by a well-structured presence of a large number of life scientists working directly in Systems Biomedicine, and a number of mathematical biology researchers working in biomedical institutions. With this book we wish to provide a coherent view of tumor modeling, based on the concept that mathematical modeling is the third pillar of molecular medicine. We hope that these features give to this work an unprecedented tone, providing an original interdisciplinary insight into the biomedical applications. We also hope the book may foster and encourage new fruitful communications and cooperations.

The present volume covers five basic topics of interest in oncology: comprehensive theories of cancer growth, systems biology of cancer, basic mechanisms of tumor progression, tumor-immune system interplay and immunotherapy, computational methods for improving chemotherapies. All the scales are so addressed, from the intracellular molecular networks to the therapy of patients. Moreover, relevance is given to recent mathematical methodologies such as nonlinear analysis, control and optimization theory, cellular automata and cellular-Potts modeling, agent-based modeling, and formal methods of computer science.

We wish to thank Professor Nicola Bellomo for the kind invitation to edit this book as part of the new SIMAI-Springer Series, and for his constant encouragement. We also wish to thank Professor Zvia Agur for her effort as co-organizer in setting the scientific shape of the Erice Workshop, and for the help in defining the project of this book.

Milan, Pisa, Rome, May 2012

Alberto d'Onofrio
Paola Cerrai
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Combining Game Theory and Graph Theory to Model Interactions between Cells in the Tumor Microenvironment

Attila Csikász-Nagy, Matteo Cavaliere, and Sean Sedwards

Abstract Mathematical concepts of graph theory and game theory both influence models of biological systems. We combine these two approaches to understand how game-like interactions influence the cellular topology of a planar tissue. We review the literature on the role of cell to cell interactions in tumourigenesis and survey the mathematical approaches that have been used to simulate such cell-cell interactions. We present how this game-graph approach can be used to simulate epithelial tissue growth and how it can foster our understanding of the role of cell-cell communication in the early stages of cancer development. We present computational models that we use to test how cooperating and non-cooperating cells build planar tissues and compare the simulated tissue topologies with literature data. We further discuss how such system could be used to model microenviromental communications between cancer cells and the surrounding tissue.

1 Introduction

Mathematical approaches to investigate cellular behaviour have a long history [10, 11, 20, 25, 86]. Game theory and graph theory have both provided extensive contri-

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bution to our biological knowledge [15, 57, 76, 89, 104, 109]. Game theory investigates the interactions between 'players', while graph theory focuses on the large scale topology of an interaction network. Tissues of an organism are made up of highly organized spatial interactions of individual cells. In this chapter we investigate how such interactions can influence the large scale cytoarchitecture (cell to cell interaction network topology) of the tissue. First we review the corresponding biological literature and the published mathematical modelling approaches. We then introduce a method where game and graph theory are combined to treat a tissue as a dynamical graph that is updated based on the local interactions of individual cells.

2 Role of Social Interactions in Complex Biological Systems

Multicellular organisms emerged from individual cells cooperating to deal with the changes in their environment [105], while currently existing single celled slime moulds reunite to form fruiting bodies if food sources are limited [111]. This complex structure helps the survival of some of the cells in the population but requires other cells to sacrifice their proliferation capacity. Biofilm formation is another example where the individual cells pay some cost (produce adhesive factors) for the benefit of the whole population (better reach of resources) [87]. In both of these cases, cheaters (defectors) can emerge in the population which do not pay the cost of sacrificing themselves or producing adhesive factor, but still benefit from the 'public good' (i.e., they always take part of the fruiting body or enjoy the elevated resources in a biofilm). As these cheaters save energy by not working towards the public good, they can reproduce faster than their cooperating neighbours. The uncontrolled proliferation of cheaters can cause the entire population to collapse [106]: cooperators are outgrown by cheaters, but they cannot maintain the nurturing environment. Such population collapses can happen without any external influence, since cheaters can arise from genetic mutation of regular cooperators. Indeed, there is an evolutionary benefit to cheat as long as many cooperators provide public good to the population [89]. Individual cells of the human body can also be viewed as cooperators: somatic cells cannot pass on their DNA but help germ cells pass on their genetic material. However, cheaters can also appear in the human body: mutations can lead to the emergence of cancer cells that proliferate as long as nutrients and oxygen are present; their uncontrolled proliferation eventually leading to the collapse of the population of cells when the organism dies. Cooperation between individual cells can happen through cell to cell interactions. Direct membrane-bound signalling molecules can send information between cells or diffusible signalling molecules may be secreted by a cell and picked up by the receptors of neighbouring cells. These receptors induce some response in the receiver cell and may lead to the release of another extracellular signalling molecule. Such complex signalling crosstalk between neighbouring cells is needed to keep a cooperating tissue intact. A mutated cell might lose some of the controls from its environment and can behave differently. The nature of communication between normal and mutated cells (such as those found in cancer) is not

well understood [55]. Cell to cell interactions influence tissue topology and tissue architecture feeds back to influence microenviromental cell to cell communications. Here we discuss how ideas from systems biology, evolutionary game theory, mathematical biology and computer science can help to uncover the details of cell to cell interactions.

2.1 Cell to Cell Interactions in the Tumour Microenvironment

The fate of a cell is determined by signals received from its environment [61, 66]. This is true for cells in a developing tissue, for quiescent cells and also for proliferating malignant cells. It was observed a long time ago that the neighbouring cells of cancer cells behave differently to the same cells in a normal context, but recently it has also been proposed that they can play an active role in controlling the behaviour of cancer cells [72, 101]. As Cairns stated [21] "Survival of rapidly renewing tissues of long-lived animals like man requires that they be protected against the natural selection of fitter variant cells (that is, the spontaneous appearance of cancer)." He went on to propose that stem cells and tissue architecture might be important for tumour suppression. In the following year Nowell established the evolutionary view of cancer development [92]. Recently, by combining these ideas with newer results on tumour microenvironments, the concept has emerged that cancer is an evolutionary ecological process [51, 80]. Recent reviews discuss what type of interactions might happen between different cells and give examples demonstrating the presence of almost all types of possible ecological interactions [129] between mammalian cells [55, 80, 84, 100]. The question remains as to which of these interactions might be important for mutated cells to spread in an otherwise homogenous tissue. Microenvironmental regulation is a sum of cell to cell and cell-extracellular matrix interactions. The role of microenvironmental signalling during metastasis is crucial, since malignant cells can only colonize tissues where they can find a supporting microenvironment [18, 55, 60]. As distal metastasis is most often established by a single clonal tumour cell, the initial signals it receives when it first reaches a homeostatic tissue might play a crucial role. There is evidence for the role of cell-cell competition during the development of the Drosophila wing disc [74], as well as recent research suggesting that a similar process occurs between normal and cancer cells [14, 64, 84]. Cell to cell contact inhibiton is another layer, where cells can control their neighbour's behaviour. How cells sense and signal when they are closely packed is only partially understood [114, 115], while the failure of this cell to cell signalling is a critical step in tumour formation [54]. Over-proliferating cancer cells reach a state where they are limited for oxygen and nutrients, forcing them to compete for resources with other cancer cells and with the neighbouring tissue [3]. The results in Drosophila suggest competition for growth factors occurs even in a normal tissue: "Winner" cells survive and divide to fill up the space left over by dead "loser" cells [84]. Other researchers [13, 18, 29] instead suggest that mutated cells might cooperate: they aid the survival and proliferation of each other by producing complementary growth factors. Genetic heterogeneity of tumours [75] is usu-

ally explained as the winner clone developing genetic instability; but at a previous stage, this clone might have interacted with other genetically heterogeneous cancer cells [51]. When the clonal population of the winner clone reaches a critical size, it stops proliferating as it cannot obtain enough oxygen and nutrients. It needs to secrete VEGF that induces angiogenesis [54]. The process of angiogenesis is complex and cancer cells might activate it indirectly by inducing neighbouring normal cells to secret VEGF by competing with them for oxygen and resources [72]. Thus, there could be both altruistic and competitive interactions between neighbouring cells during the different stages of cancer progression.

3 Tissue Topology Dynamics

One of the early results [69] on tissue topology research was the discovery that in an epithelial tissue, cells are packed in a specific way in a quasi 2D monolayer. Development of the Drosophila wing is widely used to understand epithelial tissue patterning [70]. In the wing disc most cells have six direct neighbours, but cells with four or nine neighbours are also observed [48]. Importantly, other epithelial tissues show very similar distribution of sidedness (number of neighbours) [48, 68]. Several theoretical ideas have appeared to explain how this observed distribution emerges, using elasticity theory [41], mechanics [2, 117], or simple mathematical models [48, 98]. Furthermore, as mentioned above, competition also plays a crucial role, suggesting that there might be multiple levels of control working to determine the complex cytoarchitecture of living tissue. It has been shown that during mitosis the number of neighbours changes and the directionality of the cell division plane has also been investigated [49], but the dynamic changes in tissue topology in the presence of competing cells were not followed in detail. Similar investigations have not yet been performed on mammalian tissues, although it is reasonable to assume that epithelial tissue topology (at least in single layer, simple epithelia) looks quite similar to the ones observed in other organisms [40, 88]. Graph rewriting [110], an extension of L-systems [109], is widely used to model plant development [104]. In this generative paradigm, fractal structures are created by the iterative and recursive application of a finite set of elementary rewriting rules. These rules determine how an initial simple graph is transformed into a more complex one. Similar concepts have been used to reproduce the patterning of seashells [77] and to model plant epithelial tissue development [79, 120]. Below we present an approach that combines graph rewriting with game theory to model cell to cell interactions in epithelial tissues.

4 Evolutionary Dynamics of Graphs

The dynamics of complex networks have recently been investigated through evolutionary game theoretic models [97, 118, 122], while the evolution of cooperation has