Seminars in Cancer Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Systems oncology: Towards patient-specific treatment regimes informed by multiscale mathematical modelling

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ARTICLE INFO

Keywords:
Hybrid multiscale model
Cell-cycle
Hypoxia
Chemotherapy
Radiation therapy

ABSTRACT

The multiscale complexity of cancer as a disease necessitates a corresponding multiscale modelling approach to produce truly predictive mathematical models capable of improving existing treatment protocols. To capture all the dynamics of solid tumour growth and its progression, mathematical modellers need to couple biological processes occurring at various spatial and temporal scales (from genes to tissues). Because effectiveness of cancer therapy is considerably affected by intracellular and extracellular heterogeneities as well as by the dynamical changes in the tissue microenvironment, any model attempt to optimise existing protocols must consider these factors ultimately leading to improved multimodal treatment regimes. By improving existing and building new mathematical models of cancer, modellers can play important role in preventing the use of potentially sub-optimal treatment combinations. In this paper, we analyse a multiscale computational mathematical model for cancer growth and spread, incorporating the multiple effects of radiation therapy and chemotherapy in the patient survival probability and implement the model using two different cell based modelling techniques. We show that the insights provided by such multiscale modelling approaches can ultimately help in designing optimal patient-specific multi-modality treatment protocols that may increase patients quality of life.

1. Introduction

Along with the rapid growth in acquisition of genetic, proteomic and other biochemical and biological data, there has been a parallel development from the theoretical side in terms of modelling. In particular, systems biology has emerged as a field of research over the past decade applied to a wide range of problems in the biomedical sciences. Systems biology seeks to bring to bear a range of inter-disciplinary skills and tools on complex biomedical problems. By adopting a holistic or integrative approach (as opposed to the more traditional reductionist logic), systems biology aims to predict emergent behaviour that will arise from complex biomedical systems i.e. behaviour that appears over time due to the interactions between genes, proteins, cells and tissues across a range of spatial and temporal scales. Given the complexity of most biomedical systems and their inherent nonlinearities, it is not possible to make accurate predictions without adopting some kind of "systems approach". Indeed, in the last few years, systems biology itself has evolved and further developed seeking not just to understand events at the separate biological scales in a qualitative manner, but also to develop mathematical models which are truly multiscale, leading to the emergence of "quantitative systems biology" or "quantitative integrative biology". This novel systems approach is now being brought to bear on cancer modelling and a related discipline of what may be termed systems oncology now exists in its own right to develop predictive multiscale models of cancer growth and spread. In this paper, we present a brief summary of previous cancer modelling over the past 15–20 years and then focus on two recent multiscale models of a solid tumour undergoing radio- and chemotherapy treatments. We show how simulation results can be used to optimize treatment regimes resulting in better clinical outcomes for individual patients.

2. Mathematical models in systems oncology

Decades of cancer modeling have produced established models representing all the key phases of solid tumour growth i.e. avascular growth [1,2], tumour-induced angiogenesis [3,4], the immune response to cancer [5,6], invasion and metastasis [7–11] and vascular growth [12,13]. New areas are also now being investigated concerning the spatio-temporal modelling of intracellular pathways associated with cancer such as p53-Mdmd2 [14,15]. A

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http://dx.doi.org/10.1016/j.semcancer.2014.02.003
1044-579X/

comprehensive overview of the field may be found in the review article of Lowengrub et al. [16]. In the past few years especially, multiscale models of solid tumour growth have been developed in order to account for the different spatial and temporal scales (from genes to tissues) that occur not only in cancer but in all biological systems [17–20]. A review of recent models in this area may be found in the paper of Deisboeck et al. [21]. There has also been a concerted effort to integrate mathematical models of cancer with real data in an attempt to develop quantitative, predictive models of cancer progression [22,23] and its treatment using chemotherapy [24–30], radiotherapy [31–33].

Most of the recent multiscale models of cancer growth and treatment adopt some kind of individual-based modelling approach where the individual cell is the initial focus of the model. Intracellular processes may be incorporated through systems of ordinary differential equations modelling processes in the cytoplasm and nucleus being associated with each individual cell. By simulating many interacting cells, insight into emergent tissue level phenomena can be achieved. In the next section we briefly review some of the cell-based modelling techniques currently being adopted before giving two specific examples of multiscale models of a solid tumour undergoing radio- and chemotherapy treatments.

3. Cell-based modelling techniques

Cancer is a complex disease involving many interrelated processes that occur across a wide range of spatial and temporal scales, from the intra-cellular level to the tissue level. Consequently, multiscale models are needed to capture these coupled processes. In the past 5 years or so, researchers have developed several mathematical and computational techniques that allow the study of how single-cell-based behaviours and local cell–cell and cell–ECM (extracellular matrix) interactions lead to emergent phenomena at the tissue level. These methods "trade off" the level of detail per cell against the number of cells per simulation. A key realisation that lies at the foundation of all these methods is that tissue development, homeostasis or disease are all driven by a fairly limited set of cellular behaviours. By growing, dividing, dying, adhering, secreting and absorbing chemicals or transducing signals and interacting with extracellular matrix, cells give rise to a whole range of tissue-level phenomena from healthy tissue development to cancer metastasis. Since cells live in a highly viscous environment all cell-based modelling methods assume some kind of relation between force (F) and cell velocity (v).

The simplest technique to implement (but not always the simplest to analyse) is the cellular automaton (CA) model which represents cells as single lattice points and encodes cellular behaviours in terms of transition probabilities of cells moving from one lattice location to another. Although defining rules and probabilities governing transitions in CA model is easy, linking these rules to forces or other physically measurable cellular characteristics is quite challenging. However simplifying single cell representations allows modellers to simulate large tissue fragments within reasonable computation times [34–36]. Another related approach is based on lattice-gas cellular automaton approach [37]. Center Models (CM) [38,39] relax the requirement of cells to be constrained to the grid points on a fixed lattice by representing cells as interacting points in space. Inspired by molecular dynamics, CMs solve force–velocity, F–v, equations for each of the model cells. CMs force- or energy-based formalism permits a much easier translation of measurable quantities into model parameters. Although CMs are computationally more challenging than cellular automaton models they provide more biophysical detail and also enable simulation up to the level of large tissue fragments. Sub-cellular Element Models (SEM) appear to be a natural extension of CMs and they represent an individual cell as a collection of interacting points in space. To faithfully represent a single cell morphology and to keep model cells unfragmented, SEM models apply "strong" interactions between points belonging to same cell and somewhat weaker interactions to points that are members of different cells. This separation of interaction strengths makes numerical integration of equations of motions more challenging [40] as compared to the simpler Center Model implementation. Regardless of this, numerical treatment of all center models (including SEM) is much simpler than molecular dynamics where one cannot assume a F–v relation. SEMs permit the detailed simulation of single cell morphology, shape changes, etc. but as anticipated, the average size of the simulation in terms of number of cells is several orders of magnitudes smaller than in the case of CA and CMs. The Cellular Potts Model (CPM) (or Glazier–Graner–Hogeweg (GGH) model) [41] is a stochastic method that approximates complex cell shapes as collections of pixels on a regular lattice and defines their behaviours and interactions through the local minimization of effective energies depending on cell and pixel configurations. By minimizing energy via the Modified Metropolis Algorithm, CPM recovers a linear relation between force and a cells velocity and by using an energy-based formalism it allows the translation of lab-measurable cellular characteristics into model parameters. The CPM embeds the F–v relation into a stochastic computational algorithm making it less explicit than in center models. Using a lattice makes CPM simulations faster than corresponding SEM simulations but not as fast as CA or simple center models. When details of single-cell representations are important, the finite element (FE) technique and immersed boundary (IB) method [42] provide viable alternatives to earlier methods but at much greater computation cost per cell. Ultimately, each simulation method should give the same results for the same biologically determined classes of objects, behaviours and interactions. Any observed discrepancies between methods can used to veto and/or improve modelling methods.

In the remainder of this paper, we focus on two recent multiscale models of a solid tumour undergoing radio- and chemotherapy treatments. We show how the computational simulation results can be used to optimize treatment regimes resulting in better clinical outcomes for individual patients.

4. A multiscale mathematical model of multimodality treatment

The growth and progression of a solid tumour mass depends critically on the responses of the individual cells that constitute the entire tumour mass. The evolution of each individual cancer cell and its decisions to grow, divide, remain inactive or die are usually influenced by cells spatial location within the tumour and intracellular interactions (e.g. the intracellular cell-cycle). These cellular responses are actively influenced by various extracellular signals from neighbouring cells as well as its dynamically changing microenvironment. Here, we discuss a multiscale mathematical model (and its two different mathematical implementations) for solid tumour progression incorporating such intracellular, cellular and microenvironmental factors. This model can be used to study the effects of cancer treatments and to optimize treatment regimes. The cell-cycle plays a critical role in most of the complex cellular processes that are involved in cancer progression (proliferation, cell division and DNA replication). Within a mammalian cell, the cell-cycle is controlled by a family of cyclin dependent kinases (CDK), whose activity is primarily dependent on association with a regulatory protein called cyclin [43,44]. Factors such as CDK inhibitors can act as negative regulators of the cell-cycle and tumour microenvironment [45]. In our cell-based model the growth and proliferation of each cancer cell is determined by its own internal cell-cycle

Please cite this article in press as: Powathil GG, et al. Systems oncology: Towards patient-specific treatment regimes informed by multiscale mathematical modelling. Semin Cancer Biol (2014), http://dx.doi.org/10.1016/j.semcancer.2014.02.003