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Stochastic multi-scale models of competition within heterogeneous cellular populations: Simulation methods and mean-field analysis

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HIGHLIGHTS

- Analysis and numerical simulations of a model based on an age-dependent stochastic process.
- Optimal path theory and the quasi-steady state approximation show properties related to fluctuations.
- Dynamics of a stochastic heterogeneous population under resource limitation conditions.
- Explore the effects of noise-induced heterogeneity on the emergence of drug resistance.

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ABSTRACT

We propose a modelling framework to analyse the stochastic behaviour of heterogeneous, multi-scale cellular populations. We illustrate our methodology with a particular example in which we study a population with an oxygen-regulated proliferation rate. Our formulation is based on an age-dependent stochastic process. Cells within the population are characterised by their age (i.e. time elapsed since they were born). The age-dependent (oxygen-regulated) birth rate is given by a stochastic model of oxygen-dependent cell cycle progression. Once the birth rate is determined, we formulate an age-dependent birth-and-death process, which dictates the time evolution of the cell population. The population is under a feedback loop which controls its steady state size (carrying capacity): cells consume oxygen which in turn fuels cell proliferation. We show that our stochastic model of cell cycle progression allows for heterogeneity within the cell population induced by stochastic effects. Such heterogeneous behaviour is reflected in variations in the proliferation rate. Within this set-up, we have established three main results. First, we have shown that the age to the G1/S transition, which essentially determines the birth rate, exhibits a remarkably simple scaling behaviour. Besides the fact that this simple behaviour emerges from a rather complex model, this allows for a huge simplification of our numerical methodology. A further result is the observation that heterogeneous populations undergo an internal process of quasi-neutral competition. Finally, we investigated the effects of cell-cycle-phase dependent therapies (such as radiation therapy) on heterogeneous populations. In particular, we have studied the case in which the population contains a quiescent sub-population. Our mean-field analysis and numerical simulations confirm that, if the survival fraction of the therapy is too high, rescue of the quiescent population occurs. This gives rise to emergence of resistance to therapy since the rescued population is less sensitive to therapy.

1. Introduction

Global cell traits and behaviour in response to stimuli, the so-called phenotype, results from a complex network of interactions between genes and gene products which ultimately regulates gene expression. These networks of gene regulation constitute non-linear, high-dimensional dynamical systems whose structure has been shaped up by evolution by natural selection, so that they exhibit properties such as robustness (i.e. resilience of the phenotype against genetic alterations) and canalisation (i.e. the ability

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for phenotypes to increase their robustness as time progresses). These properties are exploited by tumours to increase their proliferative potential and resist to therapies (Kitano, 2004). In addition to complex, non-linear interactions within individual cells, there exist intricate interactions between different components of the biological systems at all levels: from complex signalling pathways and gene regulatory networks to complex non-local effects where perturbations at whole-tissue level induce changes at the level of the intra-cellular pathways of individual cells (Alarcón et al., 2005; Ribba et al., 2006; Macklin et al., 2009; Osborne et al., 2010; Deisboeck et al., 2011; Powathil et al., 2013; Jagiella et al., 2016). These and other factors contribute towards a highly complex dynamics in biological tissues which is an emergent property of all the layers of complexity involved.

To tackle such complexity, multi-scale models of biological systems as diverse as cardiac systems (Smith et al., 2004; McCulloch, 2009; Hand and Griffith, 2010; Land et al., 2013), systems of developmental biology (Schnell et al., 2008; Oates et al., 2009; Hester et al., 2011; Setty, 2012; Walpole et al., 2013), and tumour growth systems (Alarcón et al., 2005; Jiang et al., 2005; Ribba et al., 2006; Macklin et al., 2009; Owen et al., 2009; Preziosi and Tosin, 2009; Tracqui, 2009; Byrne, 2010; Lowengrub et al., 2010; Osborne et al., 2010; Rejniak and Anderson, ; Deisboeck et al., 2011; Perfahl et al., 2011; Travasso et al., 2011; Durrett, 2013; Powathil et al., 2013; Szabo and Merks, 2013; Chisholm et al., 2015; Curtius et al., 2015; Scott et al., 2016; Jagiella et al., 2016) have been developed. In parallel to the model development, algorithms and analytic methods are being developed to allow for more efficient analysis and simulation of such models (Alarcón, 2014; Spill et al., 2015; de la Cruz et al., 2015; Spill et al., 2016).

In the case of cancer biology, the multi-scale interactions of intracellular changes at the genetic or molecular pathway level and tissue-level heterogeneity can conspire to generate unfortunate effects such as resistance to therapy (Merlo et al., 2006; Gillies et al., 2012; Greaves and Maley, 2012; Chisholm et al., 2015; Asatryan and Komarova, 2016). Heterogeneity plays a major role in the emergence of drug resistance within tumours and can be of diverse types. There is heterogeneity in cell types due to increased gene mutation rate as a consequence of genomic instability and other factors (Merlo et al., 2006; Greaves and Maley, 2012; Chisholm et al., 2015; Asatryan and Komarova, 2016). Heterogeneity can also be caused by the complexity of the tumour microenvironment (Alarcón et al., 2003; Gillies et al., 2012; Chisholm et al., 2015), in which diverse factors such as tumoural or immune cells (Kalluri and Zeisberg, 2006, Grivennikov et al., 2010), or the extracellular matrix and its physical properties (Spill et al., 2016), strongly influence cancer cell behaviour. Note that hypoxia is also known to change the tumour microenvironment (Spill et al., 2016). In either case, heterogeneity within the tumour creates the necessary conditions for resistant varieties to emerge and be selected upon the administration of a given therapy.

The main aim of this paper is to analyse the properties of heterogeneous populations under the effects of fluctuations both within the intracellular pathways which regulate (individual) cell behaviour and those associated to intrinsic randomness due to finite size of the population. To this purpose, we expand upon the stochastic multi-scale methodology developed in Guerrero and Alarcón (2015), where it was shown that such a system can be described by an age-structured birth-and-death process, instead of a branching process (Danesh et al., 2012; Durrett, 2013). The coupling between intracellular and the birth-and-death dynamics is carried out through a novel method to obtain the birth rate from the stochastic cell-cycle model, based on a mean-first passage time approach. Cell proliferation is assumed to be activated when one or more of the proteins involved in the cell-cycle regulatory pathway hit a threshold. This view allows us to calculate the birth rate as a function of the age of the cell and the extracellular oxygen in terms of the associated mean-first passage time (MFPT) problem (Redner, 2001). The present approach differs from that in Guerrero and Alarcón (2015) in that our treatment of the intracellular MFPT is done in terms of a large deviations approach, the so-called optimal path theory (Freidlin and Wentzell, 1998; Bressloff and Newby, 2014).

This methodology allows us to explore the effects of intrinsic fluctuations within the intracellular dynamics, in particular a model of the oxygen-regulated G1/S which dictates when cells are prepared to divide, as a source of heterogeneous behaviour: fluctuations induce variability in the birth rate within the population (even to the point of rendering some cells quiescent, i.e. stuck in G0) upon which a cell-cycle dependent therapy acts as a selective pressure.

This paper is organised as follows. Section 2 provides a summary of the structure of the multi-scale. In Section 3, we give a detailed discussion of the intracellular dynamics, i.e. the stochastic model of the oxygen-regulated G1/S transition, and its analysis. In Section 4, we summarise the formulation of the age-structured birth-and-death process, the numerical simulation technique, and the mean-field analysis of a homogeneous population. In Section 5, we discuss how noise within the intracellular dynamics induces heterogeneity in the population and analyse the stochastic dynamics of competition for a limited resource within such heterogeneous populations. In Section 6 we further study the effects of noise-induced heterogeneity on the emergence of drug resistance upon administration of a cell cycle-specific therapy. Finally, in Section 7 we summarise our results and discuss our conclusions as well as avenues for future research.

2. Summary of the multi-scale model

Before proceeding with a detailed discussion of the different elements involved in the formulation of the stochastic multi-scale model, it is useful to provide a general overview of the overall structure of the model, which is closely related to that of the model proposed in Alarcón et al. (2005).

The model we present in this article integrates phenomena characterised by different time scales, as schematically shown in Fig. 1. This model intends to tackle the growth and competition of cellular populations under the restriction of finite amount of available resources (in this case, oxygen) supplied at a finite rate, $\bar{S}$.

The general approach used in this model is a natural generalisation of the standard continuous-time birth-and-death Markov process and its description via a Master Equation (Gardiner, 2009). As we will see, the consideration of the multi-scale character of the system, i.e. the inclusion of the physiological structure associated with the cell-cycle variables, introduce an age-structure within the population: the birth rate depends on the age of cell (i.e. time elapsed since last division) which determines, through the corresponding cell-cycle model, the cell-cycle status of the corresponding cells.

The evolution of the concentration of oxygen, $c(t)$, (*resource scale*, see Fig. 1) is modelled by:

$$\frac{dc}{dt} = \bar{S} - \bar{k}c \sum_{i=1}^{N_T} N_i(t) \tag{1}$$

where N_T is the number of cellular types consuming the resource c, and $N_i(t)$, $i = 1, \ldots, N_T$, is the number of cells of type i at time t. Note that, in general, $N_i(t)$ is a stochastic process, and, therefore, in principle Eq. (1) should be treated as a stochastic differential equation (Oksendal, 2003).

The second sub-model considered in our multi-scale model,