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Coarse-graining and hybrid methods for efficient simulation of stochastic multi-scale models of tumour growth

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ABSTRACT

The development of hybrid methodologies is of current interest in both multi-scale modelling and stochastic reaction–diffusion systems regarding their applications to biology. We formulate a hybrid method for stochastic multi-scale models of cells populations that extends the remit of existing hybrid methods for reaction–diffusion systems. Such method is developed for a stochastic multi-scale model of tumour growth, i.e. population-dynamical models which account for the effects of intrinsic noise affecting both the number of cells and the intracellular dynamics. In order to formulate this method, we develop a coarse-grained approximation for both the full stochastic model and its mean-field limit. Such approximation involves averaging out the age-structure (which accounts for the multi-scale nature of the model) by assuming that the age distribution of the population settles onto equilibrium very fast. We then couple the coarse-grained mean-field model to the full stochastic multi-scale model. By doing so, within the mean-field region, we are neglecting noise in both cell numbers (population) and their birth rates (structure). This implies that, in addition to the issues that arise in stochastic-reaction diffusion systems, we need to account for the age-structure of the population when attempting to couple both descriptions. We exploit our coarse-graining model so that, within the mean-field region, the age-distribution is in equilibrium and we know its explicit form. This allows us to couple both domains consistently, as upon transference of cells from the mean-field to the stochastic region, we sample the equilibrium age distribution. Furthermore, our method allows us to investigate the effects of intracellular noise, i.e. fluctuations of the birth rate, on collective properties such as travelling wave velocity. We show that the combination of population and birth-rate noise gives rise to large fluctuations of the birth rate in the region at the leading edge of front, which cannot be accounted for by the coarse-grained model. Such fluctuations have non-trivial effects on the wave velocity. Beyond the development of a new hybrid method, we thus conclude that birth-rate fluctuations are central to a quantitatively accurate description of invasive phenomena such as tumour growth.
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1. Introduction

Cells behaviour within tissues respond to a number of stimuli. Their behaviour result from a complex network of interactions between genes and gene products which ultimately regulates gene expression. Such systems of gene regulation are often modelled as non-linear, high-dimensional dynamical systems whose structure has been moulded in the course of biological evolution. In addition to such intracellular complex dynamics, cells are also influenced by 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 occur at whole-tissue level [3,61,47,51,50,19,58,39]. These and other factors contribute towards a highly complex dynamics in biological tissues which is an emergent property of all the layers involved. To tackle such complexity, a number of multi-scale models of biological systems, particularly in the context of tumour growth, have been developed [3,40,61,47,51,59,72,9,46,50,60,19,55,73,20,58,70,13,15,64,39,74].

Many current multi-scale models of tumour growth formulated so far are individual-based, i.e. cells are individually resolved and their response to different types of cues (chemical, mechanical, etc.) is explicitly described by models of cell behaviour of varying levels of complexity [3,40,61,50,19,55,58,70,15,39]. Further to the individual-based approach to multi-scale modelling of biological cell populations, we have recently introduced new stochastic models that allow to analyse the effects of fluctuations, both at the intracellular level (intrinsic noise in signalling pathways and gene regulatory networks) and at the level of the birth-and-death dynamics of cells [32,17].

Multi-scale approaches have been shown to have both strengths and limitations. Among the latter, it prominently features the computational intensity of these models. The level of detail they involve implies that large scale simulations are computationally costly, which limits the scope of such models. In order to simulate growth in a wider range of conditions, along with model development, algorithms and analytic methods must be developed that enable us for more efficient analysis and simulation of such models. The formulation of hybrid methods for multi-scale models of tumour growth [44,42,43] is one such development. The basis of hybrid methodologies is to use models at different resolutions in different regions of the simulation domain, whereby cells (or other structures such as vessels in models of angiogenesis) are individually resolved in some region of interest. Away from such region, the system is described by a lower-resolution, coarse-grained model, obtained for example by means of homogenisation methods [12,65,54,52,53,48]. Such homogenised model describes the system at a reduced level of detail but with the benefit of a much smaller computational cost. The challenges involved in these hybrid methodologies include defining criteria to identify the different domains, derive coarse-grained models consistent with their individual-based counterparts, and formulate the appropriate boundary conditions between the individual-based and coarse-grained regions.

A similar situation arises in a different area in which fair progress has been made: stochastic reaction–diffusion systems. Such systems are also costly to simulate using standard methods (i.e. variations of the Gillespie method [68,6,21]), so it is often necessary to resort to hybrid methods [49]. The rationale for a hybrid method is that noise levels, roughly associated with the local population or number of particles, is not uniform over the whole system, resulting in regions where fluctuations have more severe effects than in others. An archetypic example of this situation is the propagation of fronts such as travelling waves [7,8,49,14]. In such systems, the population behind the propagating front approaches the carrying capacity of the system. If the carrying capacity is large enough, fluctuations in the region behind the front will be relatively small, so that the system may be described by the mean-field limit of the system. By contrast, at the front and ahead of it fluctuations dominate system behaviour and therefore the full stochastic description is needed. Such inhomogeneities in the noise level have been exploited to formulate hybrid simulation methods. According to this methodology, the mean-field limit of the system is used in low-noise regions which are then coupled to the full stochastic dynamics describing the high-noise regions. The coupling between both descriptions is achieved by means of appropriately defined boundary conditions at the interface(s) between mean-field and stochastic regions [49,22,34,23,62,67,75,71].

In this paper, we extend and further develop the hybrid method formulated by Spill et al. [67] for stochastic reaction–diffusion systems to stochastic multi-scale models of tumour growth. Such models [32,17] consider fluctuations regarding both number of cells (*population* noise) and the intracellular (cell-cycle) dynamics (*structure* noise), and consequently any attempt to formulate a hybrid method for such systems must find a way to accommodate both types of noise. Structure noise is associated with noise at the intracellular level and it manifests itself in fluctuations of the birth rate. We show in our analysis that this source of noise is at least as important as the population noise on the behaviour of the system. In particular, we show that the speed of propagation of travelling wave solutions is heavily affected by birth rate fluctuations at the leading edge of the front. More specifically, when a model in which the intracellular dynamics is coarse-grained (i.e. fluctuations of the birth rate are averaged out) is considered, the speed of the travelling wave front is over-estimated by a rather significant percentage. However, when the coarse-grained mean-field model is coupled to the full stochastic multi-scale population-dynamical model, the deviation travelling wave speed is very much rectified and a much more accurate result is obtained. This result demonstrates the usefulness of such hybrid approaches: they can recover accurately the behaviour predicted by the more detailed models whilst, by averaging out some of those details in regions where they are not necessary, their computational performance is much improved.

The paper is organised as follows. In Section 2, we present a summary of the stochastic multi-scale model. For an in-depth presentation, the reader is referred to de la Cruz et al. [17]. Section 3 contains a multiple scale asymptotic analysis which concludes with the derivation of versions of both the full stochastic model and its mean-field limit where the intracellular dynamics (i.e. age-structure) has been coarse-grained. The resulting models are described by the growth rate

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