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An age structured cell cycle model with crowding

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ABSTRACT

We study a two compartment, nonlinear, age structured model for the cell cycle. The phases of the cell cycle G_1, S, G_2 and M are grouped into two phases, which we call Phase 1 and Phase 2, where Phase 1 consists of the phase G_1 and Phase 2 consists of the phases S, G_2 and M. It is assumed that Phase 1 has a variable duration while the duration of Phase 2 is fixed. The model consists of a system of nonlinear PDEs describing the number densities $n_i(t,\tau)$, $i=1,2$, of cells in Phase i of age τ (counted from when the cell entered the phase) and time t, together with initial and boundary conditions for n_i. We first prove that this initial and boundary value problem is equivalent to solving a system of integral equations. We then prove existence and uniqueness of this system of integral equations, and hence also of the original PDE system. Qualitative behaviour of solutions with small initial and input data is studied, and an application to quorum sensing is discussed. Finally, some simple numerical examples are computed using the derived integral equations.

1. Introduction

In this paper, we study an age structured model for the cell cycle. The cell cycle consists of the four phases G_1, S, G_2, and M, and our model is a system of partial differential equations describing the number density of cells at time t and of age τ in each of these phases. Age structured cell cycle models have previously been studied in many papers, including [24,19,4,23,16,8,10,9,6,5]. Other cell cycle models are structured according to size or DNA content instead of age, see e.g. [1–3,10,14,15], and such models have the advantage that size and DNA content can be more easily measured experimentally than age. The main reason for studying an age structured model is that in cancer therapies, specific phases of the cell cycle are targeted by blocking or delaying the progress through one or more phases. Therefore, the progress of the cells around the cell cycle must be taken into account. A recently developed technique, Fluorescent ubiquitination-based cell cycle indicator (FUCCI) can be used for keeping track of the amount of time individual cells spend in the phases

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G_1 and $S/G_2/M$, respectively [21,22], and it is expected that this and similar techniques will improve the availability of data needed also for the study of age-structured models.

Our model has two compartments, Phase 1 (corresponding to G_1), and Phase 2 (corresponding to S, G_2 and M). The length of the cell cycle for individual cells is highly variable, and most of this variability is accounted for by the variability in the G_1 phase [18]. In this model, we therefore assume that Phase 2 has a fixed duration, and that the variable length of Phase 1 is described by a cumulative distribution function F, so that the proportion $F(\tau)$ of the cells that entered Phase 1 (at age 0) has transferred to Phase 2 at age τ or younger. This is also supported by experiments for an age-structured linear model in [7], where a cumulative distribution function for the phases S and $S/G_2/M$ was determined experimentally.

Space limiting or quorum sensing is modelled by means of a function $f : [0,\infty) \to [0,1]$, which describes the proportion of cells that divide after Phase 2 as a function of population size. In the case of space limiting, $f(p)$ is chosen to be small when p is large, and in the case of quorum sensing, $f(p)$ is small for p small. Age structured one compartment models where overcrowding is taken into account have previously been studied in [13,10].

Our model does not consider some aspects of the cell cycle, like quiescence for example, but these aspects can be included, and the result will be a more complicated model with the same structure.

The paper is organised as follows:

- In Section 2, we present the mathematical model as a system of PDEs with initial and boundary conditions, and which leads up to Theorem 1, stating that this PDE system is equivalent to a system of two integral equations in terms of $M(t)$, the number density of cells before cell division at time t, and $P(t)$, the total population size at time t.
- In Section 3, we present a proof of Theorem 1.
- The rest of the paper is devoted to the study of the system of integral equations, and in Section 4, we prove the existence of a unique local solution which extends to a global solution defined for all $t \geq 0$.
- In Section 5, we study the existence of steady state distributions, and in Section 6, we study the qualitative behaviour of solutions when the initial and input conditions are small.
- Finally, in Section 7 we present numerical simulations of solutions of the system of integral equations, and present some open problems.

2. The mathematical model

In this paper, we study a two compartment age structured model. Phase 1 corresponds to the phase G_1 of the cell cycle, and Phase 2 corresponds to the phases S, G_2 and M.

For $i \in \{1,2\}$, we let $n_i(t,\tau)$ denote the number density of cells per age unit in Phase i at time t and age τ (so that the unit of n_i is that of $(\text{time} = \text{age})^{-1}$). Let T_i be the maximum time that the cells can stay in each phase. We assume that T_1 and T_2 are finite. Let D be the operator defined by

$$Dn_i(t,\tau) = \lim_{\epsilon \to 0} \frac{n_i(t+\epsilon, \tau+\epsilon) - n_i(t,\tau)}{\epsilon}. \tag{1}$$

If n_i describes the number density of cells in Phase i of age τ at time t, then Dn_i is the rate of change of this population in time. Of course, if $n_i \in C^1$, then $Dn_i = \partial n_i/\partial t + \partial n_i/\partial \tau$. We will however deal with functions n_i which are not necessarily C^1 (and sometimes not even continuous), and so this identification is not always possible. It is always possible however, to interpret Dn_i as the (classical) directional derivative along the vector $(1,1)$.

Let $T > 0$ be arbitrary. We assume that the cells leave Phase 1 and enter Phase 2 with a transition rate $h(\tau)$, i.e. n_1 satisfies the differential equation