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On analytical and numerical approaches to division and label structured population models

H.T. Banks[a,*], Kevin B. Flores[a], Suzanne S. Sindi[b]

[a] *Department of Mathematics, Center for Quantitative Sciences in Biomedicine, Center for Research in Scientific Computation, North Carolina State University, Raleigh, NC 27695, United States*

[b] *Department of Applied Mathematics, School of Natural Sciences, University of California, Merced 5200 N Lake Rd, Merced, CA 95343, United States*

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ABSTRACT

Even among cells in the same population, the concentration of a protein or cellular constituent can vary considerably. This heterogeneity can arise from several sources, including differences in kinetic rates between cells and distribution of cellular constituents through cell division. Compartmental models have been used to describe the distribution of the number of divisions undergone by cells in a population. More recently, such models have been coupled with the dynamics of intracellular labels and analytical solutions to the division and label structured population equations have been found. However, such approaches have thus far focused on simple models of intracellular dynamics such as the decay of an intracellular label. In this work, we demonstrate that analytical solutions are possible for more general forms of intracellular dynamics offering the promise to lend mathematical insight into population dynamics in more realistic biological settings.

1. Introduction

Mathematical modeling has a long history of providing insights into biological processes through comparisons with experimental data [1–3]. With advancing techniques in molecular and cellular biology, it is possible to obtain highly accurate quantitative longitudinal data on the concentration of intracellular molecular constituents. However, such experiments are typically performed on populations of cells and, as such, mathematical models of these experimental time courses must consider not only the dynamics of constituents inside the cells, but the growth and division of the cells themselves.

Structured population models are commonly used to describe populations of individuals according to some continuously structured variable, such as age, size, levels of fluorescent label, or spatial location [4]. In

* Corresponding author.
E-mail addresses: htbanks@ncsu.edu (H.T. Banks), kbflores@ncsu.edu (K.B. Flores), ssindi@ucmerced.edu (S.S. Sindi).

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some experimental settings like flow cytometry, it is possible to obtain data on both the physical properties of cells as well as properties of their molecular constituents. When modeling this type of data, it may be necessary to keep track of the number of discrete generations (cell-divisions) a cell has undergone since the start of the experiment. For example, this occurs when the production or degradation rate of an intracellular molecule varies as a function of cell generation. Thus, structured populations models have been developed to simultaneously track both the dynamics of intracellular states and cell age, i.e., generation number [5–7].

Most mathematical approaches of division structured populations have considered only simple models for the dynamics of molecular constituents such as a decaying cellular label [5,8,9]. In these cases, explicit analytical solutions are possible for a partial differential equation (PDE) governing the intracellular label concentration, enabling the fast and accurate computation of model solutions necessary for efficient comparisons with experimental data. Since many biological scenarios arise in which proteins or other molecular constituents undergo complex dynamics, e.g., due to continued synthesis and feedback control, there is the need to develop general methods for computing analytical solutions for more sophisticated PDE models of intracellular dynamics.

In this manuscript, we demonstrate that analytical solutions are possible for division and label structured population models incorporating intracellular molecular dynamics more complex than just label decay. These results illustrate how mathematical researchers can employ division and label structured population models to problems of increasing biological fidelity and complexity without sacrificing the ability to estimate parameters from experimental data and develop a predictive understanding of these systems.

2. Division and intracellular concentration structured population model

2.1. Population and cellular dynamics

We model a single intracellular constituent distributed in a growing population of cells. Within a single cell, we assume the intracellular concentration evolves according to an ordinary differential equation (ODE) depending on its current state, y, and a parameter vector $\boldsymbol{\theta}$. Let $y(t)$ be the intracellular concentration in a cell t minutes after dividing, then

$$\frac{dy}{dt} = f(y, \boldsymbol{\theta}) \tag{1}$$

where $y(0) = y_0$ and $\boldsymbol{\theta}$ represents the kinetic parameters governing the intracellular processes.

With the intracellular differential equation defined, we describe a model for the intracellular-structured density of a population of dividing cells by formulating a system of weakly-coupled PDEs — with one PDE representing each cell generation i up to some maximum generation number M

$$\begin{aligned}
&\frac{\partial N_0}{\partial t} + \frac{\partial \left(f(y,\boldsymbol{\theta})N_0(t,y)\right)}{\partial y} = -\left(\alpha_0(t) + \beta_0(t)\right) N_0(t,y)\\
&\frac{\partial N_1}{\partial t} + \frac{\partial \left(f(y,\boldsymbol{\theta})N_1(t,y)\right)}{\partial y} = -\left(\alpha_1(t) + \beta_1(t)\right) N_1(t,y) + R_1(t,y)\\
&\vdots\\
&\frac{\partial N_M}{\partial t} + \frac{\partial \left(f(y,\boldsymbol{\theta})N_M(t,y)\right)}{\partial y} = -\left(\alpha_M(t) + \beta_M(t)\right) N_M(t,y) + R_M(t,y).
\end{aligned} \tag{2}$$

The intracellular structured density $N_i(t,y)$ represents the density of cells at time t with intracellular constituent level y that have undergone i divisions since the start of the experiment ($t = 0$). The rates $\alpha_i(t)$ and $\beta_i(t)$ are the time varying division and death rates, respectively, for cells that have undergone i divisions. The influx of cells to population i due to the division of cells from population $i-1$ is given by

$$R_i(t,y) = 2\gamma\alpha_{i-1}(t)N_{i-1}(t,\gamma y),$$