CELL POPULATION DYNAMICS DURING APOPTOTIC STIMULATION VIA MATHEMATICAL MODELING

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Abstract

In order to investigate induced apoptosis in heterogeneous cancer cell populations, mathematical population models are developed. An important issue is to estimate underlying population parameters with help of experimental data. In this work, an approach is presented for the comparison of experimental information with simulations of population models. Considered data include measurements of apoptotic cells over time during a treatment with an apoptosis-inducing ligand. This data can not be directly compared to the population model. Hence, a simple minimal system of ordinary differential equations is developed for the description of cell number dynamics. In an example, results from own data are compared to a previously published individual-based population model. The presented work is important for further applications, especially because realistic estimations of population parameters during apoptotic treatment are crucial for the development of a predictive model.

Keywords

Population Modeling, Cell Population Dynamics, Apoptosis.

Introduction

Several population models that describe the response to an induction of programmed cell death (apoptosis) were published in the last years (Stamatakis and Zygourakis, 2010). One challenge is to estimate appropriate values for parameters describing the cell population dynamics. The presented work describes a novel approach for integrating information about apoptotic cells from flow cytometry data into mathematical population models. A minimal system of ordinary differential equations (ODEs) is constructed as simplified model, and applied to extract key information from experimental data which is not directly being measured. An individual-based population model (Imig et al., 2015) is compared and adapted to results gained from experiments, leading to a model-based hypothesis for alteration of the growth rate during apoptotic treatment.

The work is embedded in the BMBF-funded project "PREDICT" where results from different modeling levels should be connected, in order to gain a holistic understanding of a drug treatment. A goal is to combine insights from the cell population level with modeling of vascular tumor growth (Perfahl et al., 2011).

Minimal system of ordinary differential equations

Surviving (N(t)) and apoptotic (A(t)) cells were determined over time via flow cytometry measurements of the membrane integrity (see Vermes et al., 2000). For normalization, several steps of data processing were necessary. As population models usually only consider dead cells which is the sum of apoptotic and disintegrated (removed) cells (R(t)), the number of disintegrated cells has to be approximated. In order to estimate related rates, a minimal system of ordinary differential equations that describes the flux from cells that are alive to disintegrated cells, is developed. A representation of the model is given in Figure 1.

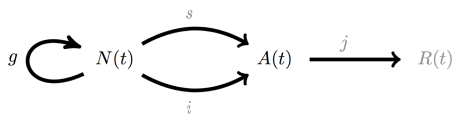

Figure 1: Schematic representation of minimal ODE system

Cells grow with growth rate g and can become apoptotic with rate s, representing spontaneous apoptosis occurring without apoptotic stimulation. Rate i represents induced apoptosis by e.g. TRAIL. Apoptotic cells are removed with rate j. Assuming first order kinetics, this results in three ODEs:

$$\frac{dN(t)}{dt} = g\,N(t) - (s+i)\,N(t) \quad (1)$$

$$\frac{dA(t)}{dt} = (s+i)\,N(t) - j\,A(t) \quad (2)$$

$$\frac{dR(t)}{dt} = j\,A(t) \quad (3)$$

In the following, limits for j are approximated. A first constraint is that j must be greater than zero, resulting in a lower bound. Secondly, the control experiment where no additional apoptosis is induced by TRAIL can be considered. Here, the biologically motivated assumption of a constant ratio

$$Q = \frac{A(t)}{N(t)} \quad (4)$$

is made. With Equations (1) and (2) and i=0 this leads to

$$j = \frac{g-a}{Q} - a \quad \text{with} \quad a = \frac{1}{t}\ln\frac{N(t)}{N(0)} \quad . \quad (5)$$

The parameter a stands for an effective growth rate that can be estimated by fitting an exponential function to the measured values for N(t) in the control experiment. Given a fixed ratio Q and measurements of growth rate g of surviving cells in the control experiment, j can be approximated. It is reasonable to assume that the value of j is the same in control and stimulation experiments. Hence, the number of dead cells D(t) can be estimated in the stimulated case as sum of apoptotic and disintegrated cells:

$$D(t) = A(t) + j\int_0^t A(t)\,dt \quad . \quad (6)$$

D(t) must be increasing, leading to a constraint for j if A(t) decreases with time.

Example: Comparison to a cell population model

In the individual-based population model (Imig et al., 2015), a large number of cells with the same apoptotic signaling pathway is simulated. Surviving cells over time are adapted to measured HCT-116 cells during stimulation with a TRAIL-based drug. Next, simulated dead cells are compared to a conservative lower bound of dead cells that was approximated (Fig. 2). The number of dead cells in the simulation falls below the approximated lower bound, indicating that population parameters must be corrected.

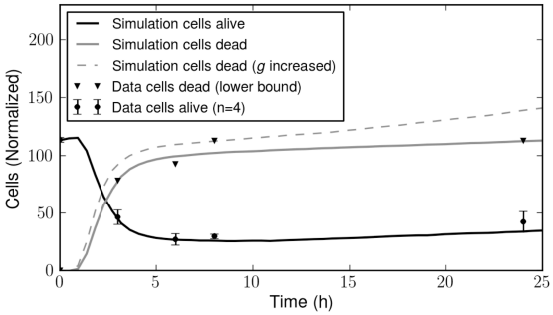

Figure 2: Comparison of simulations and experiments

A model hypothesis to improve the data fit is that the growth rate of cells is dynamically altered with the TRAIL input. Hints for this can be found for example in Levina et al., 2008. In the example above, a TRAIL-induced decrease of the mean cell cycle length in the model leads to reaching the lower bound of dead cells (Fig. 2).

Conclusions

We present how data of apoptotic and surviving cells obtained from flow cytometry experiments can be used to determine the absolute number of cells that died during the experiment. This can be used for model comparison and gives useful information for estimating model parameters.

Acknowledgments

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