Journal of Process Control 21 (2011) 1417–1425

Contents lists available at ScienceDirect

Journal of Process Control

journal homepage: www.elsevier.com/locate/jprocont

Analysis of heterogeneous cell populations: A density-based modeling and identification framework

Jan Hasenauer[a,*], Steffen Waldherr[a], Malgorzata Doszczak[b], Peter Scheurich[b], Nicole Radde[a], Frank Allgöwer[a]

[a] Institute for Systems Theory and Automatic Control, University of Stuttgart, Stuttgart, Germany
[b] Institute of Cell Biology and Immunology, University of Stuttgart, Stuttgart, Germany

ARTICLE INFO

Article history:
Received 1 December 2010
Received in revised form 28 June 2011
Accepted 28 June 2011
Available online 24 August 2011

Keywords:
Cell population
Parameter estimation
Density estimation
Convex optimization
Bootstrapping
Apoptotic signaling

ABSTRACT

In many biological processes heterogeneity within clonal cell populations is an important issue. One of the most striking examples is a population of cancer cells in which after a common, identical death signal some cells die whereas others survive. The reason for this heterogeneity is intrinsic and extrinsic noise.

In this paper we present a mechanistic multi-scale modeling framework for cell populations, in which the dynamics of every individual cell is captured by a parameter dependent stochastic differential equation (SDE). Heterogeneity among individual cells is accounted for by differences in parameter values, modeling extrinsic influences. Based on the statistical properties of the extrinsic noise and the SDE model for the individual cell, a partial differential equation (PDE) model is derived. This PDE describes the evolution of the population density. To determine the statistics of the extrinsic noise from experimental population data, a density-based statistical data model of the noise-corrupted data is derived. Employing this data model we show that the statistics of the extrinsic can be computed using a convex optimization. This efficient way of assessing the parameters allows for a so far infeasible uncertainty analysis via bootstrapping.

To evaluate the proposed method, a model for the caspase activation cascade is considered. It is shown that for known noise properties the unknown parameter densities in this model are well estimated by the proposed method.

1. Introduction

Most of the modeling performed in the area of systems biology aims at achieving a quantitative description of intracellular pathways. Hence, most available models describe a "typical cell" on the basis of experimental data. Unfortunately, experimental data are in general obtained using experiments which average over a cell population, e.g., western blotting. If the considered population is highly heterogeneous, meaning that there is a large cell-to-cell variability [1–3], fitting a single cell model to cell population data can lead to biologically meaningless results. To understand the dynamical behavior of heterogeneous cell populations it is crucial to develop integrated, mechanistic models for heterogeneous cell populations.

The general need for cell population models has been realized several decades ago. The first publications on that topic focused on the mathematical description of proliferating cell populations [4,5]. The corresponding models are called population balance models (PBMs) or age-structured models, and their dynamics are in general governed by a single one-dimensional partial differential equation (PDE) [4–9]. Although the PBMs are appealing from a theoretical point of view, the limited number of dimensions which can be handled by classical PDE solver restricted their use. Thus, only extremely simple single-cell models are employed or the single cell dynamics are neglected completely by assuming stationarity.

An alternative model class are the individual-based population models (IBPM). In this modeling framework, the given single cell model is simulated for a large number of cells, each with different parameters, initial conditions, and/or realizations of the intrinsic noise values, all specified in the model description [10–14]. The IBPMs allow for the study of complex single-cell dynamics but parameter estimation becomes more difficult.

In this work, we present a mechanistic multi-scale modeling framework for cell populations, in which the dynamics of each individual cell is captured by a parameter dependent stochastic differential equation (SDE). Thereby, we considered cell-to-cell variability introduced by intrinsic and extrinsic noise [1–3]. Intrinsic noise is generated by the stochastic dynamics of each individual cell which are due to stochasticity of the chemical reactions. Extrinsic noise and the other hand is modeled by differences in parameter values and initial conditions among cells, which are both subject to

* Corresponding author. Tel.: +49 71168567749; fax: +49 71168567735.
E-mail address: jan.hasenauer@ist.uni-stuttgart.de (J. Hasenauer).

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doi:10.1016/j.jprocont.2011.06.020