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A maximum likelihood estimator for parameter distributions in heterogeneous cell populations

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Abstract

In many biologically relevant situations, cells of a clonal population show a heterogeneous response upon a common stimulus. The computational analysis of such situations requires the study of cell-cell variability and modeling of heterogeneous cell populations. In this work, we consider populations where the behavior of every single cell can be described by a system of ordinary differential equations. Heterogeneity among individual cells is modeled via differences in parameter values and initial conditions. Both are subject to a distribution function which is part of the cell population model.

We present a novel approach to estimate the distribution of parameters and initial conditions from single cell measurements, e.g. flow cytometry and cytometric fluorescence microscopy. Therefore, a maximum likelihood estimator for the distribution is derived. The resulting optimization problem is reformulated via a parameterization of the distribution of parameters and initial conditions to allow the use of convex optimization techniques.

To evaluate the proposed method, artificial data from a model of TNF signal transduction are considered. It is shown that the proposed method yields a good estimate of the parameter distributions in case of a limited amount of noise corrupted data.

Keywords: Parameter estimation, cell population, likelihood, flow cytometry, convex optimization

1. Introduction

Most of the modeling performed in the area of systems biology aims at achieving a quantitative description of intracellular pathways within a "typical cell". Unfortunately, experimental data used to calibrate the models are in general obtained using averaged cell population data, e.g. western blot measurements. If the studied population is highly heterogeneous, meaning that there is a large cell-cell variability, fitting a single cell model to cell population data can lead to biologically meaningless results. In oder to understand the dynamical behavior of heterogeneous cell populations it is crucial to develop integrated cell population models, describing the whole population and not only a single individual.

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Modeling on the population scale has already been addressed by Mantzaris [1] and Munsky *et al.* [2]. These authors demonstrated that populations can show a bimodal response if stochasticity in biochemical reactions is considered. But besides stochasticity in biochemical reactions there are other reasons which can also lead to heterogeneity in populations. Examples are unequal partitioning of cellular material at cell division [1], or genetic and epigenetic differences [3].

For the purpose of this paper, heterogeneity in populations is modeled by differences in parameter values of the model describing the single cell dynamics [4, 5], whereas the network structure is assumed to be identical in all cells. The distribution of parameter values and initial conditions within the cell population of interest is described by a multivariate distribution function, which is part of the cell population model. This parametric approach is well suited for modeling of genetic and epigenetic differences.

In the following the problem of estimating the distribution function of the parameters is studied. Therefore, experimental data obtained via flow cytometry or cytometric fluorescence microscopy are considered. These measurement devices provide single cell data using fluorescently labeled antibodies [6].

To estimate the parameter distributions, in a first step, an appropriate population model has to be selected. In literature mathematical models of cell populations are either described as cell ensembles [2, 4], or as a non-linear partial differential equation (PDE) for the probability distributions of the state variables [1, 5, 7, 8]. In case of ensemble models, a differential equation is assigned to each cell. PDE models describing the time evolution of the distributions of the state variables are easy to handle from a theoretical point of view but hard to simulate for medium and large scale single cell models. Therefore, besides in [5] only low dimensional PDE models of populations have been studied in literature so far [1, 7, 9].

In this paper a model describing the state and output distribution functions within a heterogeneous cell population is derived. Therefore, a cell ensemble model is used in combination with classical density estimation [10]. With this approach, the state and output distribution within the population can be determined using only the single cell model and the parameter distribution.

Employing this efficient computation scheme for the population response a novel estimation method is developed. The joint likelihood of parameter distribution and data is derived, based on which the maximum likelihood estimate of the parameter distribution is determined. It is shown that the problem of determining the maximum likelihood estimate of the parameter distribution function is a convex problem and can be solved efficiently.

Compared to the classical approach for parameter estimation in populations [4, 5, 7, 9], the proposed method does not rely on the approximation of the output distribution at every measurement instance. Therefore, the proposed scheme can directly use the measured data without any approximation. This allows to obtain a good approximation of the parameter distribution with a smaller number of single cell measurements compared to the other approaches. Additionally, a very realistic measurement noise model is considered [5].

The paper is structured as follows. In Section 2, the problem of estimating the parameter distribution is introduced. In Section 3, we present the simulation model for state and output distribution. Section 4 describes the proposed identification procedure and in Section 5 the method is applied to a TNF signal transduction model.

2. Problem statement

For the purpose of this work, a model of a biochemical reaction network in a population of N cells is given by the collection of differential equations

$$\begin{aligned} \dot{x}^{(i)} &= F(x^{(i)}, p^{(i)}), \quad x^{(i)}(0) = x_0(p^{(i)}), \\ y^{(i)} &= H(x^{(i)}, p^{(i)}), \quad i \in \{1, \dots, N\} \end{aligned} \tag{1}$$

with state variables $x^{(i)}(t) \in \mathbb{R}^n_+$, measured variables $y^{(i)}(t) \in \mathbb{R}^m_+$, and parameters $p^{(i)} \in \mathbb{R}^q_+$. The vector field $F : \mathbb{R}^n_+ \times \mathbb{R}^q_+ \to \mathbb{R}^n$ is Lipschitz continuous and the functions $H : \mathbb{R}^n_+ \times \mathbb{R}^q_+ \to \mathbb{R}^m_+$ and $x_0 : \mathbb{R}^q_+ \to \mathbb{R}^n_+$ are continuous. In case concentration $x^{(i)}_k$ is measured via flow cytometry $y^{(i)} = H(x^{(i)}, p^{(i)}) = c x^{(i)}_k$, where c is a proportionality factor. The index i specifies the individual cells within the population. The parameters $p^{(i)}$ can be kinetic constants, e.g. reaction rates or binding affinities. Cell-cell interactions are assumed to be negligible for the considered pathway, which is the case in many *in vitro* lab experiments.

Heterogeneity within the cell population is modeled by differences in parameter values among individual cells. The distribution of the parameters $p^{(i)}$ is given by a probability density function $\Phi : \mathbb{R}^q_+ \to \mathbb{R}_+$, with $\int_{\mathbb{R}^q_+} \Phi(p) dp = 1$.

This density function Φ is part of the model specification, and the parameters of cell i are subject to the probability distribution

$$\Pr(p_1^{(i)} \leq p_1, \cdots, p_q^{(i)} \leq p_q) = \int_0^{p_1} \cdots \int_0^{p_q} \Phi(\tilde{p}) d\tilde{p}_1 \cdots d\tilde{p}_q. \tag{2}$$

In this paper measurement devices which provide single cell data

$$\mathcal{D}_i = \left(t_i, \bar{y}^{(i)}(t_i)\right), \quad i = 1, \ldots, M, \tag{3}$$

are considered, such as flow cytometry and flow fluorescence microscopy. Here $\bar{y}^{(i)}(t_i)$ is the measured output of the cell i at the time cell i is measured, t_i. M is the total number of measured cells. The complete set of data is denoted by

$$\mathcal{D} = \{\mathcal{D}_i\}_{i\in\{1,\ldots,M\}} = \left\{\left(t_i, \bar{y}^{(i)}(t_i)\right)\right\}_{i\in\{1,\ldots,M\}}. \tag{4}$$

Note that for the considered experimental devices, cells cannot be tracked over time, and are removed from the population in order to obtain the measurements. Thus, only one data point for each cell is taken, and in particular no single-cell time series data are available. On the other hand, the samples drawn from the cell population are independent and identically distributed. Contrary to previous work [5, 7], it is not assumed that M is large enough to determine an approximate of the output distribution.

Like most data also the considered single cell data are subject to noise. For the rest of the paper, noise consisting of a relative and an absolute component is considered,

$$\bar{y}^{(i)}(t_i) = \mathrm{diag}(\eta^1) y^{(i)}(t_i) + \eta^2, \tag{5}$$

in which $\bar{y}^{(i)}$ is the measured output, $y^{(i)}$ is the actual output, and $\eta^j \in \mathbb{R}^m$ is a vector of log-normally distributed random variables with probability density functions

$$f_{\eta_k^j}(\eta_k^j) = \begin{cases} \dfrac{1}{\sqrt{2\pi}\sigma_k^j \eta_k^j} \exp\left\{-\dfrac{1}{2}\left(\dfrac{\log \eta_k^j - \mu_k^j}{\sigma_k^j}\right)^2\right\} & \eta_k^j > 0 \\ 0 & \eta_k^j \leq 0 \end{cases}, \quad j = 1, 2, \ k = 1, \ldots, m, \tag{6}$$

yielding the joint probability density $f_{\eta^j}(\eta^j) = \prod_{k=1}^m f_{\eta_k^j}(\eta_k^j)$. The measurement noise distribution is chosen to be log-normal, which is a good model for the commonly seen noise distributions of the considered measurement device. Additionally, the property that all outputs are positive is conserved. For notational simplicity the measurement errors of the different outputs are assumed to be independent.

Given this setup the problem we are concerned with is:

Problem 1. *Given the measurement data $\mathcal{D}$, the cell population model* (1)*, and the noise model* (6)*, determine the parameter distribution Φ.*

Unfortunately, estimation of Φ using a cell population model (1) with a finite number of cells and discrete sampled data (4) is fairly difficult as no single cell trajectories are available. A more natural approach is to use a distribution description of the response of the cell population (1), in particular as the number of cells considered in a standard lab experiment is of the order 10^9 and hence nevertheless too large to be simulated on an individual basis. In the next section a model for the output distribution function of the cell population is introduced.

3. Modeling and simulation of heterogeneous cell populations

As outlined in the previous section, ensemble models are difficult to analyze in the context of cell population studies. Continuous statistical model in which states/outputs of the population are described by probability densities defined on the state/output space are preferable. Therefore, a model for the output distribution $\Upsilon(y|t, \Phi)$ is derived, with $\Upsilon : \mathbb{R} \times \mathbb{R}_+^m \times \ell^1 \to \mathbb{R}_+ : (t, y, \Phi) \mapsto \Upsilon(y|t, \Phi)$ and $\int_{\mathbb{R}_+^m} \Upsilon(y|t, \Phi) dy = 1 \ \forall t$, where Φ is the parameter distribution

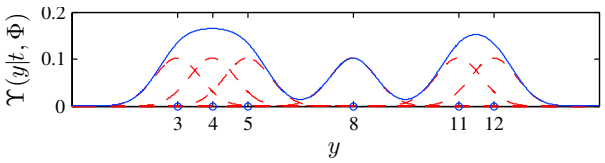

Figure 1: Kernel density estimate (—) of $\Upsilon(y|t,\Phi)$ for the measured outputs (o) and the associated kernels (– –).

within the model [5]. Based on this density function Υ, the probability of picking at random a cell from the population with outputs $y^{(i)}(t) \in \mathcal{Y} \subset \mathbb{R}^m$, where $\mathcal{Y}$ is an arbitrary set in the output space, is given by

$$\Pr(y^{(i)}(t) \in \mathcal{Y}) = \int_{\mathcal{Y}} \Upsilon(y|t,\Phi)dy. \tag{7}$$

For the computation of the output distribution $\Upsilon(y|t,\Phi)$ a kernel density estimator is used. Kernel density estimators are non-parametric approaches to estimate probability distributions from sampled data [10]. They are widely used and can be thought of as placing probability "bumps" at each observation, as depicted in Figure 1. These "bumps" are the kernel functions K, with $\int_{\mathbb{R}^m_+} K dy = 1$. In this work log-normal kernels,

$$K_k\left(y_k - y_k^{(i)}(t), h_k\right) = \begin{cases} \dfrac{1}{\sqrt{2\pi}h_k y_k} \exp\left\{-\dfrac{1}{2}\left(\dfrac{\log y_k - \log y_k^{(i)}(t)}{h_k}\right)^2\right\} & y_k > 0 \\ 0 & y_k \leq 0 \end{cases} \tag{8}$$

are used, as they conserve the positivity of the measured concentrations. The parameter h_k is the standard deviation and in the literature also often called smoothing parameter [10]. For the multivariate case, the multivariate kernel

$$K\left(y - y^{(i)}(t), h\right) = \prod_{k=1}^{m} K_k\left(y_k - y_k^{(i)}(t), h_k\right), \tag{9}$$

is chosen.

To compute the cell population response for a given parameter distribution $\Phi(p)$, S independent single cell trajectories $y^{(i)}(t)$ of the cell population (1) are calculated. The parameters for these cells are sampled from the parameter distribution Φ and the initial conditions computed according to $x_0(p^{(i)})$. Given this set of single cell trajectories an approximation of the output distribution of the cell population is given by

$$\Upsilon(y|t,\Phi) = \frac{1}{S}\sum_{i=1}^{S} K\left(y - y^{(i)}(t), h\right). \tag{10}$$

Similar approaches have also been employed in [4, 5].

Note that selection of the smoothing parameter h is crucial and depends strongly on S. There are rules-of-thumb available [10], as used here, but also the least-squares cross-validation method [11] can be employed.

4. Estimation of parameter distribution

In the previous section a method to determine the output distribution within the cell population is presented. Unfortunately, in order to simulate the population the parameter distribution Φ has to be known. Therefore, a maximum likelihood approach for estimating Φ is developed next.

4.1. Likelihood function and corresponding optimization problem

To determine an estimate of the actual parameter distribution $\Phi(p)$, at first the likelihood function $\mathcal{L}(\Phi)$, which gives the likelihood of a particular parameter distribution with respect to the data $\mathcal{D}$, is required. As the measurements are independently and identically distributed the likelihood of Φ is

$$\mathcal{L}(\Phi) = \prod_{i=1}^{M} f_\Phi(\mathcal{D}_i), \tag{11}$$

in which $f_\Phi(\mathcal{D}_i)$ is the conditional probability density function of measuring $\mathcal{D}_i = (t_i, \bar{y}_i)$ given Φ. For this system $f_\Phi(\mathcal{D}_i)$ is given by

$$f_\Phi(\mathcal{D}_i) = \int_{\mathbb{R}_+^m} f_y(\bar{y}^{(i)}) \Upsilon(y|t_i, \Phi) dy. \tag{12}$$

The conditional probability density $f_y(\bar{y}^{(i)})$ is the probability density of measuring $\bar{y}^{(i)}$ given y. According to the measurement noise model (5),

$$f_y(\bar{y}^{(i)}) = \prod_{k=1}^{m} f_{y_k}(\bar{y}_k^{(i)}), \tag{13}$$

in which $f_{y_k}(\bar{y}_k^{(i)})$ is the value of the line integral

$$f_{y_k}(\bar{y}_k^{(i)}) = \int_0^{\bar{y}_k^{(i)}/y_k} f_{\eta_k^1}(s) f_{\eta_k^2}(\bar{y}_k^{(i)} - y_k s) ds. \tag{14}$$

For this line integral no explicit solution has been found and therefore it is evaluated numerically using the adaptive Simpson quadrature method [12] implemented in `MATLAB`.

Given this formulation of the likelihood and the conditional probability distributions, the maximum likelihood estimate Φ^* of the parameter distribution is the solution of the constraint optimization problem

$$\begin{aligned} \underset{\Phi}{\text{maximize}} \quad & \sum_{i=1}^{M} \log f_\Phi(\mathcal{D}_i) \\ \text{subject to} \quad & \int_{\mathbb{R}_+^q} \Phi(p) dp = 1 \\ & \Phi(p) \geq 0 \quad \forall p \in \mathbb{R}_+^q. \end{aligned} \tag{15}$$

Here, the log-likelihood is maximized and the two constraints ensure that Φ is a probability density. Unfortunately, (15) is infinite dimensional and thus not computable numerically.

4.2. Parameterization of parameter distribution Φ

To avoid the infinite dimensional optimization problem (15), the parameter distribution Φ is parameterized according to

$$\Phi_\varphi(p) = \sum_{j=1}^{n_\varphi} \varphi_j \Lambda_j(p). \tag{16}$$

Here $\Lambda_j(p)$, $j = 1, \ldots, n_\varphi$ are ansatz functions for Φ, with $\Lambda_j : \mathbb{R}_+^q \to \mathbb{R}_+$ and $\int_{\mathbb{R}_+^q} \Lambda_i(p) dp = 1$. Note that not only Φ but also the ansatz functions Λ_j are probability density functions. The weighting vector for the ansatz functions is denoted by $\varphi \in [0, 1]^{n_\varphi}$ where n_φ is the number of ansatz functions. In this work, Gaussian distributions are used as ansatz function but the presented approach is independent of the exact choice of ansatz functions.

Given a parameterization of Φ_φ the output distribution can be written as

$$\Upsilon(y|t, \Phi_\varphi) = \sum_{j=1}^{n_\varphi} \varphi_j \Upsilon(y|t, \Lambda_j), \tag{17}$$

where $\Upsilon(y|t, \Lambda_j)$ is the output distribution obtained for simulation with a parameter distribution according to Λ_j. Equation (17) holds because the single cells are independent and the output distribution is the weighted sum of the kernel functions. Hence, it can be shown that the super position principle is fulfilled [5].

4.3. Simplification of the likelihood function and optimization problem

Based on the parameterization of the parameter distributions and the output distributions, the conditional probability density $f_\varphi(\mathcal{D}_i)$ can be written as

$$\begin{aligned} f_\varphi(\mathcal{D}_i) &= \int_{\mathbb{R}_+^m} f_y(\bar{y}^{(i)}) \Upsilon(y|t_i, \Phi_\varphi) dy \\ &= \int_{\mathbb{R}_+^m} f_y(\bar{y}^{(i)}) \sum_{j=1}^{n_\varphi} \varphi_j \Upsilon(y|t_i, \Lambda_j) dy \\ &= \sum_{j=1}^{n_\varphi} \varphi_j \int_{\mathbb{R}_+^m} f_y(\bar{y}^{(i)}) \Upsilon(y|t_i, \Lambda_j) dy. \end{aligned} \tag{18}$$

As the data $\mathcal{D}_i$, the conditional probability density $f_y(\bar{y}^{(i)})$, and the output distributions $\Upsilon(y|t, \Lambda_j)$ are known, the conditional probability $f_\varphi(\mathcal{D}_i)$ can be simplified to

$$\begin{aligned} f_\varphi(\mathcal{D}_i) &= \sum_{j=1}^{n_\varphi} \varphi_j c_j^{(i)} \\ &= \varphi^T c^{(i)} \end{aligned} \tag{19}$$

with $c^{(i)} = [c_1^{(i)}, \ldots, c_{n_\varphi}^{(i)}]^T$ and

$$c_j^{(i)} = \int_{\mathbb{R}_+^m} f_y(\bar{y}^{(i)}) \Upsilon(y|t_i, \Lambda_j) dy. \tag{20}$$

The values $c_j^{(i)}$ are determined using a Monte-Carlo based integration scheme [13].

Employing the parameterization of Φ and the reformulation of $f_\varphi(\mathcal{D}_i)$, the optimization problem (15) becomes

$$\begin{aligned} \underset{\varphi}{\text{maximize}} \quad & \sum_{i=1}^{M} \log\left(\varphi^T c^{(i)}\right) \\ \text{subject to} \quad & \mathbf{1}^T \varphi = 1, \\ & \varphi \geq 0, \end{aligned} \tag{21}$$

in which $\mathbf{1}^T = [1, \ldots, 1] \in \mathbb{R}^{n_\varphi}$. Note that problem (21) belongs to the class of nonlinear concave maximization problems with linear constraints [14]. For this class of problems efficient solvers exist, for instance interior-point methods. In this work, the `MATLAB` toolbox `cvx` for convex programming [15] has been used in combination with the solver `SDPT3` [16].

Remark 1. *As the optimization problem* (21) *is concave, the maximum likelihood estimate* Φ_φ^* *of the parameter distribution can also be computed efficiently also for* $n_\varphi \gg 1$.

5. Application to the TNF signal transduction

In order to illustrate the properties of the proposed scheme, a simple model of the tumor necrosis factor (TNF) signaling pathway will be analyzed in the following.

5.1. Model of TNF signaling

In multicellular organisms, the removal of infected, malfunctioning, or no longer needed cells is an important issue. To achieve this, TNF is able to induce programmed cell death, also called apoptosis, via the activation of the caspase cascade. On the other hand, it promotes cell survival via the inflammatory response, specifically activation of the NF-κB pathway [17]. Here, we study a simple model for the caspase and NF-κB activation in response to an external death receptor stimulus.

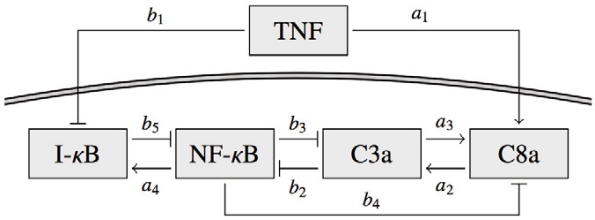

Figure 2: Graphical representation of the TNF signal transduction model.

Table 1: Nominal parameter values for the TNF signaling model (22).

j	1	2	3	4	5
a_j	0.6	0.2	0.2	0.5	
b_j	0.4	0.7	0.3	0.5	0.4

The considered model has been introduced in [18] and is based on known activating and inhibitory interactions among key signaling proteins. Besides active caspase 8 (C8a) and active caspase 3 (C3a), the nuclear transcription factor κB (NF-κB) and its inhibitor I-κB are considered in the model. A graphical representation of the system is shown in Figure 2. The model is given by the ODE system

$$\begin{aligned}
\dot{x}_1 &= -x_1 + \frac{1}{2}(\beta_4(x_3)\alpha_1(u) + \alpha_3(x_2)) \\
\dot{x}_2 &= -x_2 + \alpha_2(x_1)\beta_3(x_3) \\
\dot{x}_3 &= -x_3 + \beta_2(x_2)\beta_5(x_4) \\
\dot{x}_4 &= -x_4 + \frac{1}{2}(\beta_1(u) + \alpha_4(x_3)).
\end{aligned} \tag{22}$$

The state variables x_i, $i = 1, \ldots, 4$ denote the relative activities of the signaling proteins C8a, C3a, NF-κB and I-κB, in this order. The functions $\alpha_j(x_i)$ and $\beta_j(x_i)$ represent activating and inhibiting interactions, respectively. They are given by

$$\alpha_j(x_i) = \frac{x_i^2}{a_j^2 + x_i^2}, \quad j = 1, \ldots, 4 \tag{23}$$

and

$$\beta_j(x_i) = \frac{b_j^2}{b_j^2 + x_i^2}, \quad j = 1, \ldots, 5. \tag{24}$$

The parameters a_j and b_j are activation and inhibition thresholds, respectively, and take values between 0 and 1. The external TNF stimulus is denoted by u. All nominal parameter values are given in Table 1.

As seen from experimental cytotoxicity assays, the cellular response to a TNF stimulus is highly heterogeneous within a clonal cell population. Some cells die, others survive. However, the reasons for this heterogeneous behavior are unclear, but of great interest for biological research in TNF signaling. To understand the process at the physiological level it is crucial to consider the cellular heterogeneity, using for example cell population modeling. We model heterogeneity at the cell level via differences in the parameter b_3. This parameter has been selected as it models the inhibitory effect of NF-κB via the C3a inhibitor XIAP onto the C3 activity. As the amount of XIAP shows cell-cell variability, also variations in the associated inhibition strength in the model used here are likely.

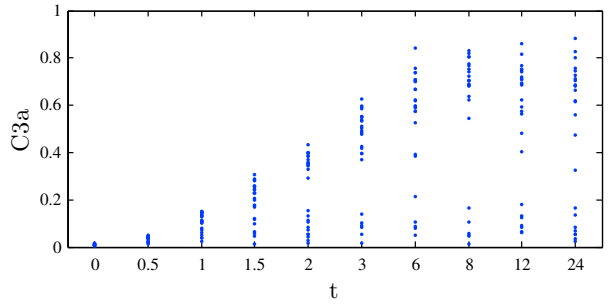

Figure 3: Single cell measurements (·) used for estimation of cell population heterogeneity.

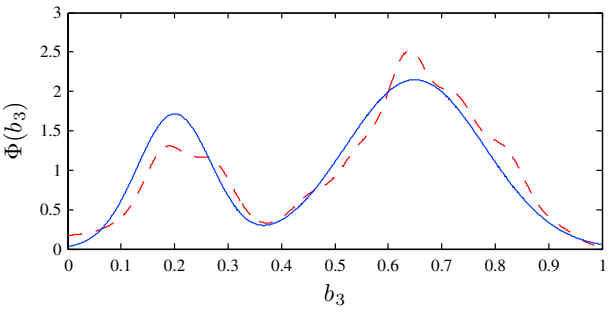

Figure 4: Actual (—) vs. estimated (– –) parameter distribution.

5.2. *Results of parameter distribution estimation*

For the evaluation of the proposed scheme, we consider an artificial experimental setup in which the caspase 3 activity is measured at ten different time instances during a sustained TNF stimulus, $u(t) = 1$. At each time instance the C3a concentration in 25 cells are measured with measurement noise according to Equation (5), where $\mu^1 = 0$, $\sigma^1 = 0.05$, $\mu^2 = \log(0.01)$, and $\sigma^2 = 0.3$. The obtained experimental data for a bimodal distribution in b_3 are depicted in Figure 3.

To estimate Φ from this data, the proposed likelihood-based method is applied. The ansatz function are chosen to be twelve Gaussian distributions with equally spaced center points. The results are shown in Figure 4.

It can be seen from Figure 4 that an accurate estimate of the parameter distribution is obtained, although the data are noisy and the amount of data is limited. Also the bimodal shape of $\Phi(b_3)$ does not cause any problems. Additionally, as the optimization problem (21) is concave, we can guarantee that the distribution Φ with the highest likelihood is reached.

6. Summary and Conclusion

In this paper a maximum likelihood approach for estimating the parameter distributions within cell populations is presented. The method uses a parameterization of the parameter distribution, convex optimization techniques, and can deal with realistic noise models. Compared to classical approaches, the method can deal with a small number of single cell measurements, as it does not rely on the approximation of the measured population response using a density estimator.

The properties of the proposed scheme are illustrated using artificial data. It could be shown that the proposed method yields good estimation results in case of a setup which is realistic in terms of noise and amount of available data. Also the estimation of bimodal parameter distributions does not cause any problems.

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