Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute

Parameter Estimation by Simulated Annealing for Models of Whole-Blood Infection Assays with *Candida Albicans*

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Summary

The precise estimation of a priori unknown model parameters reveals insight into the relative importance of individual processes in complex biological systems. We simulate time-resolved data obtained from human whole blood infection assays with *Candida albicans* by numerically solving a mathematical model in terms of coupled differential equations. The optimal set of model parameters is obtained from a self-written algorithm that performs Simulated Annealing based on the Metropolis Monte Carlo scheme. The algorithm randomly explores the space of rate parameters and searches for a solution with minimal *weighted Least Squared Error* (*wLSE*) compared to experimental data. Two different procedures of error evaluation have been implemented: the *individual procedure* and the *joint procedure*. The mathematical model aims at elucidating the relative importance of different routes in the immune response against *C. albicans*.

Method

Modeling using Differential Equations

Model:

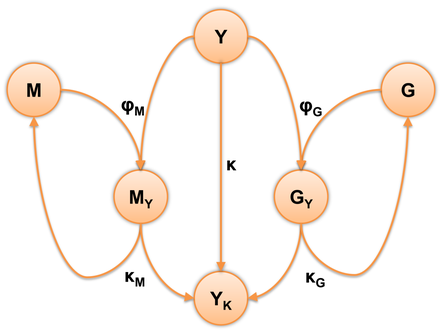


Figure 1: Depiction of processes describing the immune defense against *C.albicans* in human blood.

Legend:

- Y living, free *C. albicans* yeast cell
- M monocytes without a yeast cell
- G granulocytes without a yeast cell
- M_Y monocytes which phagocytosed a yeast cell
- G_Y granulocytes which phagocytosed a yeast cell
- Y_K killed yeast cells

Differential Equation System

$$\dot{Y} = -\phi_M \cdot Y(t) \cdot M(t) - \phi_G \cdot Y(t) \cdot G(t) - -\kappa \cdot Y(t)$$

$$\dot{M} = -\phi_M \cdot Y(t) \cdot M(t) + \kappa_M \cdot M_Y(t)$$

$$\dot{G} = -\phi_G \cdot Y(t) \cdot G(t) + \kappa_G \cdot G_Y(t)$$

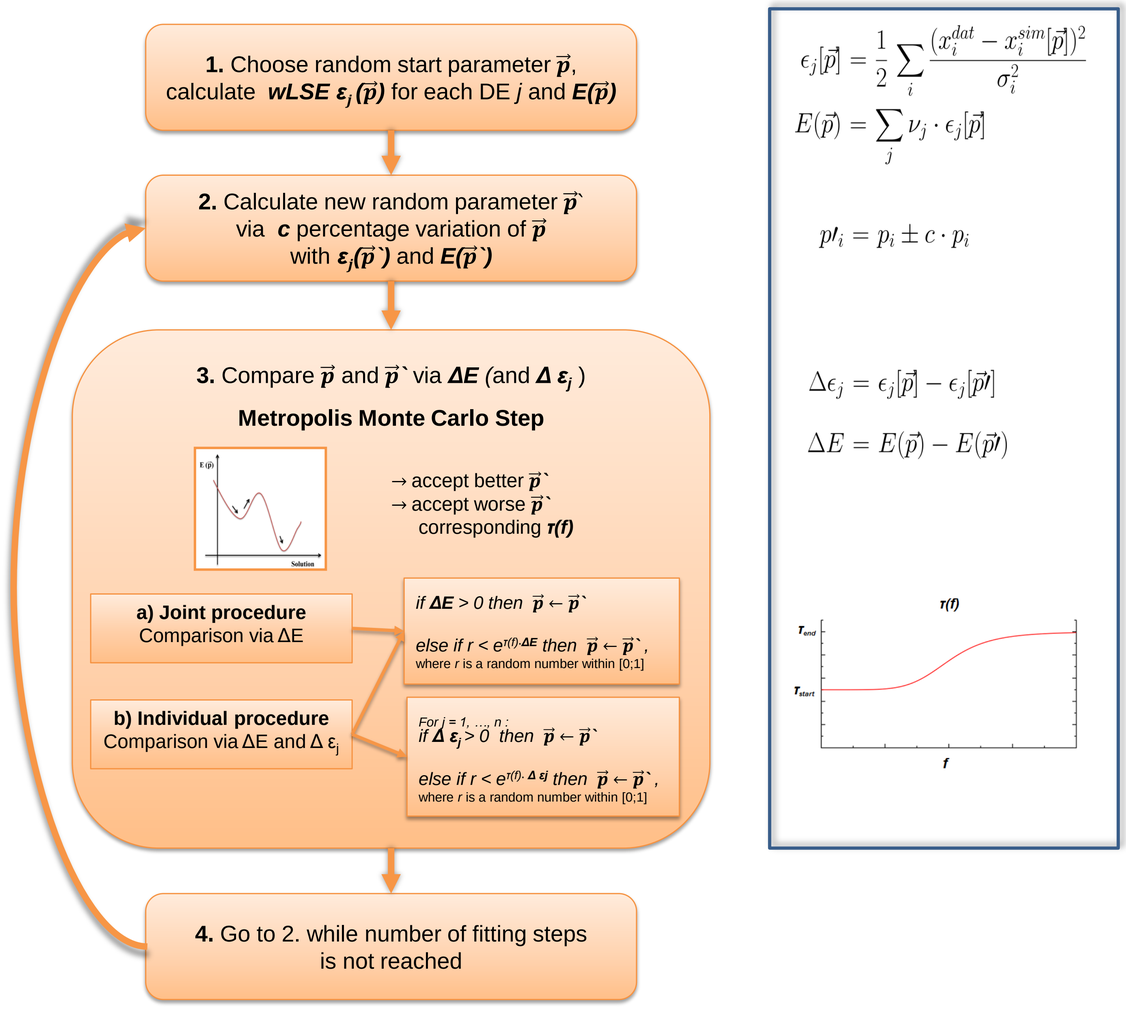
$$\dot{M_Y} = -\kappa_M \cdot M_Y(t) + \phi_M \cdot Y(t) \cdot M(t)$$

$$\dot{G_Y} = -\kappa_G \cdot G_Y(t) + \phi_G \cdot Y(t) \cdot G(t)$$

$$\dot{Y_K} = \kappa \cdot Y(t) + \kappa_M \cdot M_Y(t) + \kappa_G \cdot G_Y(t)$$

A priori unknown parameter
κ, κ_M, κ_G, ϕ_M, ϕ_G

Parameter Estimation using Simulated Annealing



$$\epsilon_j[\vec{p}] = \frac{1}{2} \sum_i \frac{(x_i^{dat} - x_i^{sim}[\vec{p}])^2}{\sigma_i^2}$$

$$E(\vec{p}) = \sum_j \nu_j \cdot \epsilon_j[\vec{p}]$$

$$p\prime_i = p_i \pm c \cdot p_i$$

$$\Delta\epsilon_j = \epsilon_j[\vec{p}] - \epsilon_j[\vec{p\prime}]$$

$$\Delta E = E(\vec{p}) - E(\vec{p\prime})$$

Figure 2: Scheme of the self-written Metropolis Monte Carlo algorithm which performs Simulated Annealing.The algorithm can be described in four steps, where step 2-4 were repeated corresponding the number of fitting steps *f*. Equations applied in the algorithm are listed in the blue box on the right.

Experimental Data

Whole blood infection assays of *C. albicans* deliver time resolved data of immune defense by monocytes and granulocytes as well as the complement system.

Experimental Way:
Inoculation of *C.albicans* into human blood probes at 10 different time points, where interesting cell types were measured using *Facs* (fluorescence activated cell sorting) and Killing plates. Observed experimental data are displayed in Figure 3.

Method	Measured cell types
Facs	Y, M, G, M_K, G_K
Killing plates	Y_K

Table 1: Experimental methods and measured cell types. Abbreviations are explained in the Method part.

Results

We applied the self-written Metropolis Monte Carlo algorithm to estimate the a priori unknown parameters of the mathematical model which describes the human immune defense against *C. albicans*.

Algorithm Settings

- Joint procedure
- 15 % parameter variation
- without individual penalty ν
- 4000 fitting steps
- 10 runs

Resulting Parameter Values

parameter	mean	sd
ϕ_M	$0.016\ \mu l/s$	26.5 %
ϕ_G	$0.015\ \mu l/s$	2.9 %
κ_M	$0.38\ 1/s$	25.0 %
κ_G	$0.12\ 1/s$	2.9 %
κ	$0.0\ 1/s$	0.0 %

Table 2: Resulting values of a priori unknown parameter.

Resulting Curves

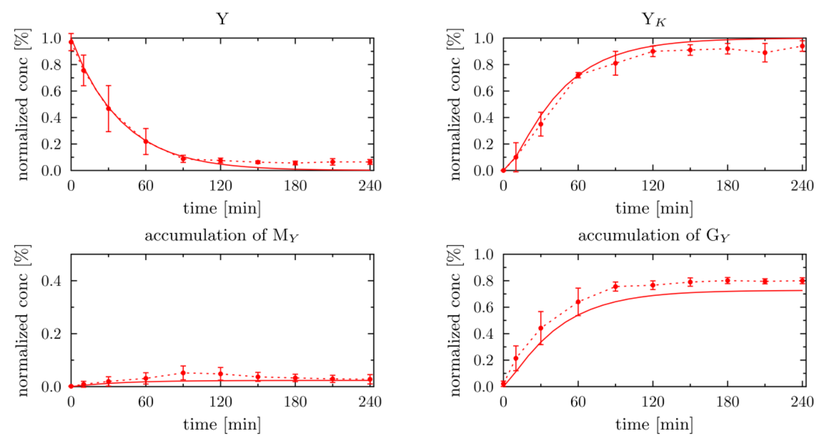


Figure 3: Resulting experimental and simulated data generated using parameter values which were estimated applying the presented algorithm. Dashed red lines denote experimental data and continuous red lines represent simulated data.

Outlook

In future, we will extend the model for including the impact of antimicrobial factors generated by granulocytes with regard to activation of the complement system.

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