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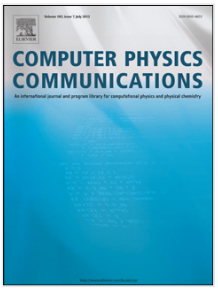

Reducing complexity: An iterative strategy for parameter determination in biological networks

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Reducing complexity: an iterative strategy for parameter determination in biological networks

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Abstract

The dynamics of biological networks are fundamental to a variety of processes in many areas of biology and medicine. Understanding of such networks on a systemic level is facilitated by mathematical models describing these networks. However, since mathematical models of signalling networks commonly aim to describe several highly connected biological quantities and many model parameters cannot be measured directly, quantitative dynamic models often present challenges with respect to model calibration. Here, we propose an iterative fitting routine to decompose the problem of fitting a system of coupled ordinary differential equations describing a signalling network into smaller sub-problems. Parameters for each differential equation are estimated separately using a Differential Evolution algorithm while all other dynamic quantities in the model are treated as input to the system. The performance of this algorithm is evaluated on artificial networks with known structure and known model parameters and compared to a conventional optimisation procedure for the same problem. Our analysis indicates that the procedure results in a significantly higher quality of fit and more efficient reconstruction of the true parameters than the conventional algorithm.

Keywords: Parameter estimation; Signalling network; Biology; Differential evolution

1. Introduction

A quantitative description of biological networks is critical to an understanding of biological processes at different scales. In particular, signalling networks regulate a plethora of biological systems [1] and play a key role in the control of immune functions, e.g. in intracellular signal transduction like T cell receptor signalling or intercellular communication by a network of cytokines [2]. While the interactions between the constituents of such biological networks are often unknown, there is an increasing amount of quantitative data on their dynamics. The complex behaviour that can emerge even from simple interactions [3] has motivated increasing interest in dynamic models of signalling networks (see [4, 5, 6] and references therein).

In the common case where quantitative knowledge about the underlying kinetic properties of modelled reactions is missing, either due to a lack of data or because there is no direct physical equivalent, model parameters have to be estimated by fitting the model output to suitable data. This problem usually involves the minimisation of a function measuring the disagreement between model output and data. Although this problem is well-studied [7], parameter estimation can be challenging, as biological data are often noisy, contain measurement errors and are incomplete. Furthermore, especially in the case of signalling networks, the systems under study can be too complex. Even parameter estimation problems in simplified network models can be high-dimensional and almost inevitably have multiple local minima.

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