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A termination criterion for parameter estimation in stochastic models in systems biology

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ABSTRACT

Parameter estimation procedures are a central aspect of modeling approaches in systems biology. They are often computationally expensive, especially when the models take stochasticity into account. Typically parameter estimation involves the iterative optimization of an objective function that describes how well the model fits some measured data with a certain set of parameter values. In order to limit the computational expenses it is therefore important to apply an adequate stopping criterion for the optimization process, so that the optimization continues at least until a reasonable fit is obtained, but not much longer. In the case of stochastic modeling, at least some parameter estimation schemes involve an objective function that is itself a random variable. This means that plain convergence tests are not a priori suitable as stopping criteria.

This article suggests a termination criterion suited to optimization problems in parameter estimation arising from stochastic models in systems biology. The termination criterion is developed for optimization algorithms that involve populations of parameter sets, such as particle swarm or evolutionary algorithms. It is based on comparing the variance of the objective function over the whole population of parameter sets with the variance of repeated evaluations of the objective function at the best parameter set. The performance is demonstrated for several different algorithms. To test the termination criterion we choose polynomial test functions as well as systems biology models such as an Immigration-Death model and a bistable genetic toggle switch. The genetic toggle switch is an especially challenging test case as it shows a stochastic switching between two steady states which is qualitatively different from the model behavior in a deterministic model.

1. Introduction

Parameter estimation is very important for the analysis of models in systems biology. Computational modeling is a central approach in systems biology for studying increasingly complex biochemical systems. Progress in experimental techniques, e.g. the possibility to measure small numbers of molecules in single cells, Raj and van Oudenaarden (2009) highlights the need for stochastic modeling approaches. Simulation methods for stochastic processes are being developed for decades since (Gillespie, 1976) and nowadays exist with a lot of variants (Pahle, 2009). Parameter estimation for stochastic models is still in the early phase of development.

A stochastic model as used in this study describes the time evolution of its species as a Markov jump process. A time course can be simulated using the Gillespie algorithm (Gillespie, 1976) which explicitly considers every single reaction iteratively. The counterpart is deterministic models – most commonly modeled with ODEs – which are deterministic except for measurement noise. The most common choice for an objective function in ODE modeling is the least squares functional. In stochastic modeling an objective function might also be based on the likelihood function. However, when stochastic simulations are used for its evaluation the objective function is itself stochastic. This leads to the fact that multiple evaluations at the same point can lead to (slightly) different function values. The article will focus on this kind of objective function which leads to stochastic optimization problems. The term stochastic optimization problems are used for optimization problems with stochastic objective functions. These optimization problems can be tackled amongst others with global optimization algorithms.

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Some recently developed parameter estimation approaches for time series data of stochastic models use stochastic simulations. Due to the Markov property of the time series the likelihood function factorizes into the product of transition probabilities. These transition probabilities are generally unknown in stochastic modeling. They can be estimated using stochastic simulations. This can be done with density estimation methods (Tian et al., 2007; Poovathingal and Gunawan, 2010). Another approach is the use of a reversible jump algorithm (Boys et al., 2008) in combination with Bayesian methods or a stochastic gradient descent (Wang et al., 2010). Using approximations (Henderson et al., 2010; Zimmer and Sahle, 2012, 2015) is faster from a computational point of view. Another approximation is suggested in form of an approximate maximum likelihood method (Reinker et al., 2006), where also a singular value decomposition likelihood method is described. A second class of methods focuses on a numerical solution of the chemical master equation (CME) (Andreychenko et al., 2012) or moment-closure methods (Gillespie, 2009; Gillespie and Golightly, 2009). All the simulation based approaches lead to stochastic optimization problems.

The solution of the stochastic optimization problems is computational intensive due to the use of stochastic simulations for the evaluation of the objective function. Therefore it is especially important to have a well suited termination criterion. This article will introduce a termination criterion which takes the properties of stochastic models into account.

Theoretical remarks on stochastic optimization problems can be found in Morton (1998). Despite the large amount of literature on global stochastic optimization methods, Moles et al. (2003) and references therein, the issue of termination criteria for global optimization algorithms applied to stochastic optimization problems has yet not been in the focus of discussion.

This article suggests a termination criterion that is applicable to optimization methods that are based on populations of parameter sets. Examples include particle swarm and evolutionary/genetic methods. It works by comparing the variance of the objective function values in the population with the variance of a multiple evaluation of the best value. Using this criterion allows the algorithm to terminate as soon as the “noise” of the stochastic evaluation of the objective function dominates the shape of the underlying average landscape. This reduces computation time drastically which is especially important as solving stochastic optimization problems is very time consuming. It should be noted that while we discuss this concept in the context of parameter estimation for stochastic models, it is actually applicable whenever a global optimization of a function including noise is required. The methods section of this article shortly introduces the three optimization algorithms for which the proposed criterion has been implemented and tested: particle swarm, a Genetic Algorithm and Evolutionary Programming. Then it explains the new termination criterion in detail. Finally, it describes the objective function that was used for parameter estimation in the test cases. The results section presents performance tests with the proposed termination criterion on two noisy polynomials, an Immigration-Death model and a genetic toggle switch model. Since for all test cases the true solution is known, the accuracy of the estimation can be evaluated as a function of the applied termination criterion. Global optimization algorithms such as the ones used in this study typically have several parameters that can be used to tune the performance of the algorithms. The choice of these parameters will generally have an impact on the convergence speed and reliability and usually it is left to the user of parameter estimation software to provide these settings. The convergence test proposed here is independent of the specific settings of the optimization algorithms. Therefore the effect of these parameters was not systematically studied. Instead, the parameters were set so that optimization runs were successful in all cases.

2. Methods

2.1. Optimization algorithms

Optimization algorithms mostly perform a search starting from a start domain, then iteratively moving toward regions with better function values until finally converging to an optimum. Global optimization algorithms work without the use of derivatives. The objective function takes a parameter value as input and – almost like a black box – yields back a function value.

- *Particle swarm:* An initial set of points is distributed randomly on the start domain. In every iteration the points are moved in a direction which composed of the best result each individual point has reached and the best result which the swarm has reached so far. The algorithm conventionally terminates if the following two conditions are satisfied: the variance of the function values of the swarm is small and the variance of the points of the swarm is small as well. Fig. 1 shows the detailed structure of the particle swarm (Kennedy and Eberhart, 1995) implemented in the software COPASI (Hoops et al., 2006).
- *Genetic algorithms (GA):* GA transform the number representation of points in the search space in a bit string representation. An initial set of bit string points is chosen randomly on a start domain. Then GA comprises a mutation, recombination and selection step. The mutation step changes some bits of the bit string. Parts of bit strings of the mutated population are then combined with parts of other bit strings of the mutated population. The next generation is drawn randomly according to the relative fitness of each bit string in the mutated and recombined population. Although in general possible there is no special termination criterion suggested for EP in its original article (Bäck and Schwefel, 1993; Bäck et al., 1997) or in the COPASI implementation (Hoops et al., 2006). This means that the user chooses a number of iterations after which the algorithm terminates.
- *Evolutionary Programming (EP):* An initial set of points is distributed randomly over a start domain. Each iteration comprises a mutation step and a selection step. In contrast to other evolutionary algorithms, EP does not have a recombination step. The mutation step changes every point by adding a normally distributed random number to it. The selection step compares each old and new point with a certain number of other points with respect to its function value and assigns a score to it. According to the score, the best 50% of the points is chosen for the next iteration. Although in general possible there is no special termination criterion suggested for EP in its original article (Bäck and Schwefel, 1993; Bäck et al., 1997) or in the COPASI implementation (Hoops et al., 2006). This means that the user chooses a number of iterations after which the algorithm terminates.

2.2. New termination criterion

When treating stochastic optimization problems the objective function is a random variable which means that two evaluations of the same parameter might have (slightly) different outcomes. Now consider a situation in which the population has settled, which means that all individual parameter sets in the population are confined to a small region in parameter space. In this case the variance of the objective function evaluations StdDev(F(individuals)) will be dominated by the stochasticity of the objective function F rather than the variance of the parameter sets in the population. Therefore the standard deviation of the function evaluations will not reflect