Journal of Computational Mathematics
Vol.30, No.1, 2012, 59–79.

http://www.global-sci.org/jcm
doi:10.4208/jcm.1110-m11si12

CRITICAL ISSUES IN THE NUMERICAL TREATMENT OF THE PARAMETER ESTIMATION PROBLEMS IN IMMUNOLOGY*

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Abstract

A robust and reliable parameter estimation is a critical issue for modeling in immunology. We developed a computational methodology for analysis of the best-fit parameter estimates and the information-theoretic assessment of the mathematical models formulated with ODEs. The core element of the methodology is a robust evaluation of the first and second derivatives of the model solution with respect to the model parameter values. The critical issue of the reliable estimation of the derivatives was addressed in the context of inverse problems arising in mathematical immunology. To evaluate the first and second derivatives of the ODE solution with respect to parameters, we implemented the variational equations-, automatic differentiation and complex-step derivative approximation methods. A comprehensive analysis of these approaches to the derivative approximations is presented to understand their advantages and limitations.

Mathematics subject classification: 34K29, 92-08, 65K10.
Key words: Mathematical modeling in immunology, Parameter estimation, Constrained optimization.

1. Introduction

Mathematical immunology represents a rapidly growing field of applied mathematics. The key features of the immune system that make call for the application of mathematical modeling tools are: physical complexity, compartmental structure, non-linear response, threshold-type of regulation, memory or time-lag effects, inter-clonal competition and selection, redundancy [3]. Most mathematical models of immune responses are not obtained from first principles and therefore the model structure usually has no a priori proof of validity. The key elements of the data- and science-driven application of mathematical modeling to immunology are:

(i) more than one model may correspond to a particular phenomenon;

(ii) the computational techniques permit, given data of appropriate quality, to discriminate between rival mathematical models.

Given a number of candidate models, one needs for each model to determine a set of actual parameters that is in a well-defined sense optimal and to order the resulting set of optimally parameterized models to indicate which is most appropriate, given the data [3].

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* Received February 9, 2011 / Revised version received May 29, 2011 / Accepted June 5, 2011 / Published online January 9, 2012 /

The last decade of research in immunology is characterized by a tremendous advance in the high-throughput experimental technologies yielding detailed information on the system state at various levels of resolution. This calls for a need to further advance the computational techniques for parameter estimation and a multiscale analysis of immunological phenomena. In our previous studies [4, 8–10, 14–16], we treated parameter estimation problems for models in immunology formulated by systems of ordinary, delay or partial differential equations, using different types of experimental data sets. Our experience led us to conclude that there is a set of rather common features of the parameter estimation problems in immunology:

(i) a lack of uniqueness of the solution to the inverse problem,

(ii) a high sensitivity to the errors in experimental data,

(iii) a poor practical identifiability of some of the model parameters.

The above difficulties, in part, result from an inconsistency between the information content of the data available and the ad hoc formulated parametric structures of the phenomenological mathematical models. The primary objective of this study is to propose an efficient computational technology for treating the parameter estimation problems appearing in mathematical immunology. Since the parameter estimation problem is essentially an optimization problem, the numerical accuracy and the computational cost of the evaluation of gradient, Jacobian- and Hessian matrices of the objective function represent the crucial factors. Therefore, an accurate and low-cost numerical approximation of the first and second derivatives of a model solution with respect to the model parameters are the key issues. So far, they have not been systematically addressed in the context of the inverse modeling in immunology.

In this study, we analyzed the existing approaches to derivative approximation: the conventional finite-differences method and the variational equations technique, which are broadly used since a long time, and the automatic differentiation (AD) and complex-step derivative approximation (CSD) methods, which came into focus of the numerical community only recently. We examined the efficiency and limitations of these methods in the context of the parameter estimation problems. The corresponding codes were implemented in Matlab. Note that during last years several AD packages have been introduced in Matlab [2]. The recently developed Matlab package PMAD [22] is meant for computing first derivatives of an analytic function by the CSD method. However, we are interested in developing a consistent and compact software which should be most efficient for solving the parameter estimation problems arising in immunology.

Most parameter estimation problems in mathematical immunology lead to minimization of a sum of squares of nonlinear functions subject to certain constraints on the estimated parameters. To solve the corresponding least-squares problems, we implemented the constrained Gauss-Newton method. To characterize the uncertainty in the parameter estimates, we used the variance-covariance and profile-likelihood-based methods. We show that the availability of the tools for computing accurate numerical derivatives allows one to perform a more thorough analysis of the parameter estimation problem, e.g. to examine the practical identifiability of the model parameters and their sensitivity to the data, to refine the model structure according to the data available.

In the next section we describe the key elements of the computational technology we propose for solving the parameter estimation problems arising in immunology. The numerical methods which can be used for approximating the derivatives of a model solution with respect to the model parameters are described in section 3. The comparative performance of the implemented