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Parameter Estimation of Non-linear Dynamical Models – A Web Based Application

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Abstract

This paper presents a web application that provides a tool for numerical parameter estimation. It utilizes ADFIT (Automatic parameters estimation of mathematical models tool) that can solve mathematical models containing systems of ordinary differential equations. It uses both finite-difference and adjoint sensitivity analysis for introduced models. The numerical methods used to solve such equations are Euler and Runge-Kutta methods. There has been created the web application for this tool, where the user with access provides experimental data into the program. Then objective function and its gradient are calculated. The user can choose the method of solving differential equation, determining the gradient and minimization algorithm, choose integration step and use genetic algorithm if necessary. In order to increase program efficiency and improve the execution time, all calculations are made externally. At first, the program generates a file with C code and then compiles it to special MEX file and such a file is sent for calculations. The tool focuses on solving complicated non-linear and high-dimensional models. It can also deal with rare in time and irregular measurement data. The main advantage of the program is the ability to solve in a fast way models containing up to even 30 ordinary differential equations. One more novelty is ability to estimate the initial conditions for each equation in the system. It is very important since medical data usually lacks initial conditions. Such a tool can play an important role in analyzing medical data. The program is executing externally, so the performance time does not depend on computational capabilities of user's computer. Moreover, tasks are automatically queued so user does not need to wait to send data till previous task is terminated.

Keywords: parameter estimation, ordinary differential equations, sensitivity analysis, automatic differentiation

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Introduction

Numerical parametric estimation is a complex problem that occurs in various applications, including medical data analysis, signal processing, telecommunication, control theory and even opinion polls.

Despite of the fact that numerical parameter estimation is widely used in various fields of science, it still represents a challenge. The data is often characterized by a huge noise or uncertainty. Medical data are usually lacking of initial conditions. The results are strongly susceptible to errors and manifest strong dependence of the initial point of estimation.

Apart from problems with obtaining reasonable results, a major problem is a speed of calculations caused by high computational efficiency. Some problems may have many non-linear ordinary differential equations and the calculations last long time.

One of the most widely-used environments to perform advanced calculations and simulations is Matlab. However, its scripts are written in high-level language that is not time-efficient. Because of that, the parametric estimation, when executed on home computers, may take many hours. The presented web application responds to the problems with performance time and complexity of the model.

The great advantage of the web application is the fact that calculations can be executed regardless of user's computer performance. Moreover, many calculations can be queued or made simultaneously or large computing cluster.

The presented website uses ADFIT – a tool that can solve mathematical models containing systems of ordinary differential equations based on discrete in time experimental data (Łakomiec, 2014). ADFIT is a set of scripts written in Matlab code. To improve computational efficiency, it used so-called adjoint sensitivity analysis (Fujarewicz, 2007) in order to compute the gradient of the objective function. It also uses MEX files to generate low-level C code that is more time-efficient that Matlab M-files and uses genetic algorithm to avoid the dependence of results of the initial point of estimation.

The presented web application has user-friendly GUI that generates input file and send it to ADFIT parser on the server. Obtained solution from numerical parametric estimation is returned back to the web application. When calculations are finished, the user will see values of estimated parameters and graphs that fit obtained results to experimental data.

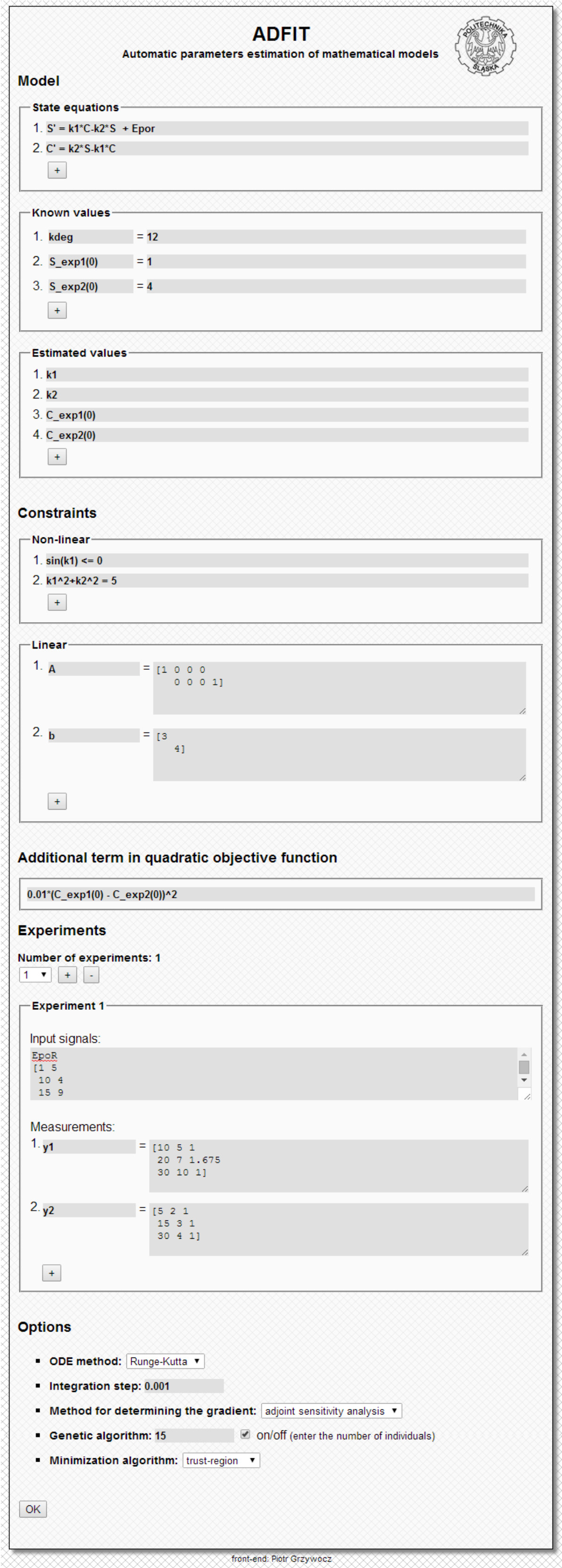
Using the presented GUI is intuitive and only minimum technical knowledge is required.

Graphical User Interface

The website is divided into two subpages. The first view is used to insert all the data that is necessary to perform calculations. The second view is responsible for delivering information about current state of the task, and when the estimation is terminated, it presents the results. Fields in the first view are as follows:

- *State equations* – differential equations describing relations between state variables,
- *Known values* – values that are known and do not require estimation (parameters, initial values),
- *Estimated values* – parameters to be estimated,
- *Constraints* – we can add both non-linear constraints in algebraic (implicit or explicit) form, and linear ones in a matrix form,
- *ODE Method* – user can choose between Euler and Runge-Kutta numerical methods,
- *Integration step* – a decimal number used in ODE methods,
- *Method of determining the gradient* – there are two options: finite difference method and adjoint sensitivity analysis,
- *Genetic algorithm* – user can turn on/off genetic algorithm. When selected, the number of its individuals must be given,
- *Minimization algorithm* – there are three nonlinear optimization algorithms to choose: trust-region, active set and interior point,
- *Experiments* – this part is used to add experimental data. This application enables to add any number of experiments. The "input signals" field accepts data in matrix form where the first column is time and the second column has rows with values of excitation signal in particular time. The "measurements" field requires $n \times 3$ matrix where the first column is time and the next two are: measured value and weight.

Figure 1. *Graphical User Interface*



Moreover, there are two additional options:

- *Load from file* - user can send an input file with mathematical model and experimental data directly to server without using the form.
- *Check my task* - displays the status of the task that has been previously queued. After clicking on the link, user will be asked for the number of the task.

After clicking "OK" button, an initial validation of data is performed. If some field is empty, user will be asked for filling it. Otherwise, the second subpage is displayed. The second view is responsible for delivering information about task status, and when calculations are finished, presenting results or errors if any occur.

Depending on the amount of tasks in a queue and the complexity of the mathematical model, the performance may last several hours. A user does not need to keep the website open all the time. A unique number is assigned to every estimation task and can be used to identify it.

Moreover, it is not necessary to refresh the webpage because of using Ajax (Asynchronous JavaScript and XML) technology. The information about current state of calculations is refreshed every second and tells whether the task waits in queue, the task is being calculated or calculations are terminated.

The input file to the ADFIT tool is also displayed.

After finishing the task, unless any errors occur, a user will see the following information:

- the values of estimated parameters,
- the final value of objective function,
- plots depicting graphical model fit after estimation to experimental data.

Back-end

The back-end of the web application has been implemented in PHP programming language and was supported by bash commands. It has been adapted to Linux/Unix operating systems.

After sending to the server, tasks are queued using TORQUE Resource Manager. This tool is adapted to manage time-consuming tasks and provides ability to handle larger computing clusters with tens of thousands of nodes and jobs. For smaller projects, it helps in separating of tasks between cores, allows to set maximum time of performance and even enables to send e-mails when calculation is finished. The job can be also suspended or cancelled. It can be easily configured by the server administrator.

The ADFIT engine is implemented in Matlab. It is a set of M-file scripts from which we can distinguish parser of input data and parametric estimation algorithms. Moreover, to obtain better execution speed, MEX files have been utilized. These files contain subprogram written in C language to provide better computational efficiency than standard M-files.

Example of Application

In this section we will do the study and show the results of parameter estimation for the enzymatic reaction. Such reaction may be modeled (Robert, 2001) using four non-linear ordinary differential equations.

During the enzymatic reaction the conversion of the substrate *S* into the product *P* is catalyzed by the enzyme *E*. The substrate binds to the enzyme and a temporal complex *C* is created:

$$E + S \underset{k_1}{\rightarrow} C$$

(1)

which may break apart:

$$C \underset{k_2}{\rightarrow} E + S$$

(2)

or the conversion may take place and the complex break apart into the enzyme and the product:

$$C \underset{k_3}{\rightarrow} E + P$$

(3)

Merging reactions (1–3) we obtain the reaction:

$$E + S \underset{k_2}{\overset{k_1}{\rightleftarrows}} C \underset{k_3}{\rightarrow} E + P$$

(4)

Reactions (1–3) take place with speeds k_1SE, k_2C and k_3C respectively, which leads to following system of four non-linear ordinary differential equations:

$$\begin{cases} \dot{S} = -k_1SE + k_2C \\ \dot{E} = -k_1SE + (k_2 + k_3)C \\ \dot{C} = k_1SE - (k_2 + k_3)C \\ \dot{P} = k_3C \end{cases}$$

(5)

where k_1, k_2 and k_3 are parameters to be estimated.

The model (5) has been simulated for 10 seconds and used to generate “artificial” data in 5 time moments: 2, 4, 6, 8 and 10 seconds for all four variables *S*, *E*, *C* and *P*.

Figures 2 and 3 show results of parameter estimation by using presented in this article tool for free enzyme (*E*) and substrate (*S*).

One can see almost perfect fit of the model with estimated parameters to measurements. The estimation process gave the same values of the parameters as used for data generation and the objective function approached zero. This was possible because the artificial data was not noisy. Of course in real experiments such perfect fit is not possible. Nevertheless, presented example demonstrated precision and usefulness of the web-based parameter estimation tool.

Figure 2. *Concentration of the Free Enzyme* (*E*): *Solid Line – Simulation of the Model after Parameter Estimation, Dots – the Data used for the Estimation.*

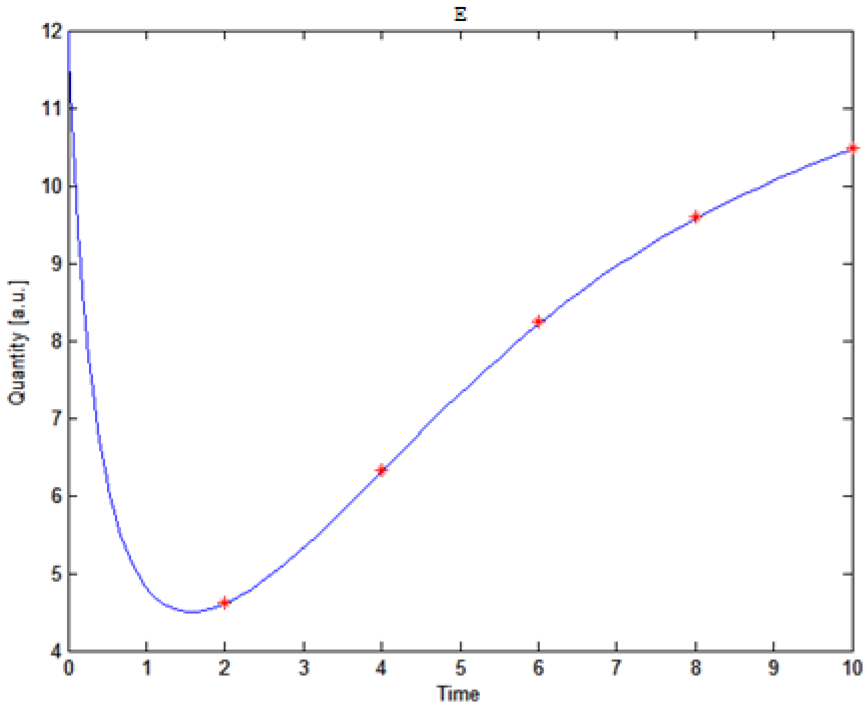
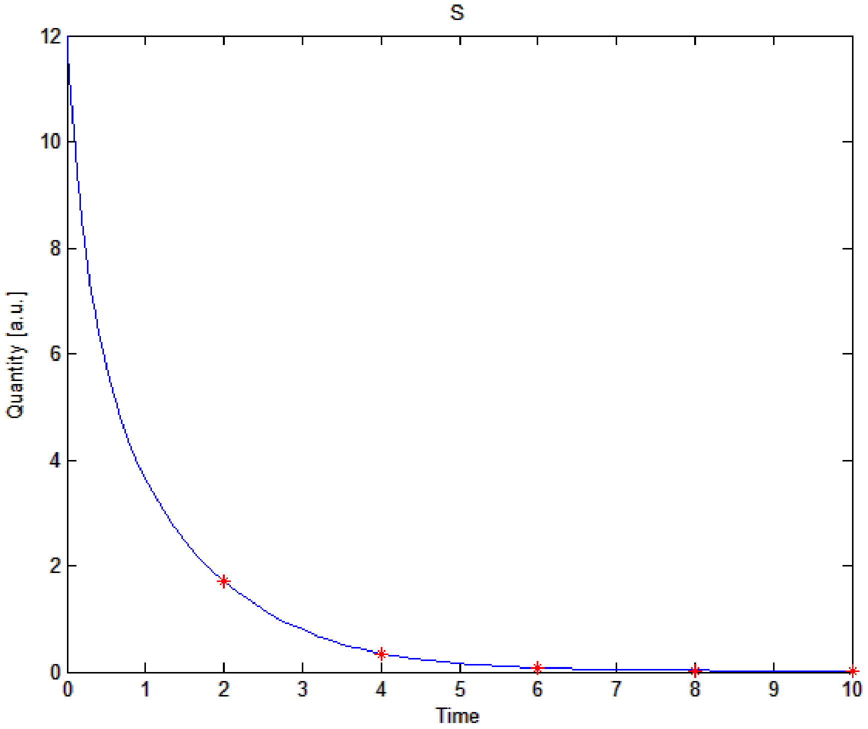


Figure 3. *Concentration of the Substrate* (*S*): *Solid Line – Simulation of the Model after Parameter Estimation, Dots – the Data used for the Estimation.*



Availability

The web-based application described in this paper may be accessed through the web page: www.cellab.polsl.pl/index.php/software.

Conclusions

This paper presented the web application for ADFIT tool – a tool which estimates parameters for the mathematical models based on experimental data, for example biological data. It is the tool which is highly recommended for finding the parameters of systems of complicated non-linear, ordinary equations, because the application sends the data to the computer with has really big computational power. What is more, the tool uses the MEX files to improve the speed of calculations and use the adjoint sensitivity analysis to minimize the impact of numerical errors.

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