Parameter Identification for Calcium Release in a Heart Cell with Modified Patankar–Runge–Kutta Schemes

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Simulation of calcium release in heart cells requires the solution of a complex three-dimensional model, which involves a large number of parameters, whose values are crucial for a realistic simulation. To identify biophysically meaningful parameters, studying a one-dimensional model for several hundred parameter values is instructive. The goal of this process is to capture the general model behavior and to maintain physical principles like positivity for all time step sizes. We use time adaptive modified Patankar–Runge–Kutta (MPRK) schemes to solve the one-dimensional models for various parameter values. These schemes ensure unconditional positivity and capture the model behavior also for large time steps. The adaptive MPRK schemes are very efficient for crude tolerances, which enables fast and meaningful solutions of the one-dimensional problems, and hence, fast parameter identifications.

1 Introduction

Long time simulation of calcium release in heart cells is a challenging task, which requires the solution of a system of non-linear partial differential equations with probabilistic calcium source term in three dimensions for large final times [1]. The corresponding model is based on several parameters and it is vitally important to work with reasonable parameter values, to obtain biophysically meaningful model properties.

To identify sound parameter values for the complex three-dimensional model, it can be instructive to solve a simplified one-dimensional model [2] instead. After a discretization of the parameter space, the 1-D model equations are solved several hundred times for different parameter values to find biophysically meaningful parameters. This identification process does not demand very accurate simulations as only the principal behavior is of interest. Hence, methods that allow for large time steps, while maintaining important solution properties, like positivity, are favorable. One class of methods which is interesting in this regard are modified Patankar–Runge–Kutta (MPRK) schemes.

MPRK schemes were introduced for the time integration of positive and conservative production–destruction systems, see [3–5] for a detailed introduction. They ensure unconditional positivity and conservation irrespective of the time step size. Hence, they are especially useful to compute meaningful approximations for large time step sizes, where classical methods fail due to stability restrictions or divergence of the non-linear solver. The MPRK43I and MPRK43II schemes introduced in [5] are of third order and require the computation of a second order approximation as Patankar–weight denominator within each solution step. Of course, these second order approximations can additionally be used to estimate the local truncation error, which allows an easy adaptive implementation of the above mentioned MPRK43 schemes.

Figure 1 shows that adaptive MPRK43 schemes are competitive, when crude tolerances are acceptable. In situations where the error estimator allows for large time steps, and classical schemes must take smaller steps due to stability or solver issues, the MPRK43 schemes can prevail. Usually coarse tolerances are already sufficient to capture the general system behavior.

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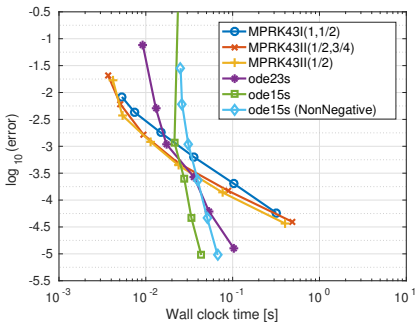

Fig. 1 Comparison of different adaptive time integration schemes applied to solve the stiff Robertson problem with final time 10^{11}, see [5] for the system of ODEs. Three different MPRK43 schemes are compared to the solvers `ode23s` and `ode15s` implemented in MATLAB. For `ode15s` errors are shown with and without the the `NonNegative` feature. The approximations were computed for relative tolerances on the error estimator ranging from 10^{-1} to 10^{-6}. The absolute tolerance was set to the relative tolerance times 10^{-3}. The errors were computed with respect to a reference solution obtained with `ode15s` and tolerances 10^{-12}. The computation of time step sizes followed the usual strategy, when different order approximations are available. We see that the MPRK43 schemes are efficient for practically relevant tolerances.

2 Governing equations

A three-dimensional model for the calcium release in heart cells is given by the diffusion–reaction system

$$\begin{aligned} \frac{\partial c}{\partial t} &= \nabla \cdot (\mathbf{D}_c \nabla c) + \gamma \sum_{i=1}^{2} R_i(c, b_i, B_i) + \gamma (J_{CRU}(c, \mathbf{p}) - J_{pump}(c) + J_{leak}) \\ \frac{\partial b_i}{\partial t} &= \nabla \cdot (\mathbf{D}_{b_i} \nabla b_i) + R_i(c, b_i, B_i), \quad \frac{\partial B_i}{\partial t} = \nabla \cdot (\mathbf{D}_{B_i} \nabla B_i) - R_i(c, b_i, B_i), \qquad i = 1, 2, \end{aligned} \tag{1}$$

where c denotes the concentration of calcium in the cytosol, and b_i and B_i, $i = 1, 2$, represent the free and bound concentration of buffer species in the cytosol, respectively. See [6] for a description of all occurring parameters and the definition of the reaction terms. In particular, the term J_{CRU}, which depends on various parameters collected in the parameter vector $\mathbf{p}$, models the injection of calcium into the cell as point sources. Once the injection of calcium starts, it continues for 5 ms, before it stops for 100 ms. To simulate this behavior efficiently requires the use of adaptive time stepping techniques.

The model used for parameter identification is the one-dimensional analogue of (1). After a discretization in space by the finite volume method we end up with a non-conservative production–destruction system (PDS). Although MPRK schemes were developed for conservative PDS, we can apply the method to non-conservative PDS as well. The MPRK scheme can then be written as

$$\begin{aligned} y_i^{(k)} &= y_i^n + \Delta t \sum_{\nu=1}^{k-1} a_{k\nu} \left(p_{ii}^{(\nu)} - d_{ii}^{(\nu)} \frac{y_i^{(k)}}{\pi_i^{(k)}} \right) + \Delta t \sum_{\nu=1}^{k-1} a_{k\nu} \sum_{j=1, j\neq i}^{N} \left(p_{ij}^{(\nu)} \frac{y_j^{(k)}}{\pi_j^{(k)}} - d_{ij}^{(\nu)} \frac{y_i^{(k)}}{\pi_i^{(k)}} \right), \\ y_i^{n+1} &= y_i^n + \Delta t \sum_{k=1}^{s} b_k \left(p_{ii}^{(k)} - d_{ii}^{(k)} \frac{y_i^{n+1}}{\sigma_i} \right) + \Delta t \sum_{k=1}^{s} b_k \sum_{j=1, j\neq i}^{N} \left(p_{ij}^{(k)} \frac{y_j^{n+1}}{\sigma_j} - d_{ij}^{(k)} \frac{y_i^{n+1}}{\sigma_i} \right), \end{aligned} \tag{2}$$

where $p_{ij} = d_{ji}$ contain the conservative parts for $i \neq j$ and p_{ii} and d_{ii} are the non-conservative production and destruction parts of the ith equation, respectively. As in the conservative case, this method is unconditionally positive. The choice of the Patankar–weight denominators $\pi_i^{(k)}$ and σ_i is essential for the convergence order of the scheme. Order conditions for conservative production–destruction systems were derived in [4, 5] and remain valid in this more general case.

3 Numerical results

Application of the MPRK scheme (2) to the one-dimensional model showed that the biophysical behavior was captured well even for a coarse tolerance of 10^{-1}. The reference solution was obtained with `ode15s` and tolerance 10^{-10}. This indicates that adaptive MPRK schemes might be well suited for a wider class of parameter identification problems.

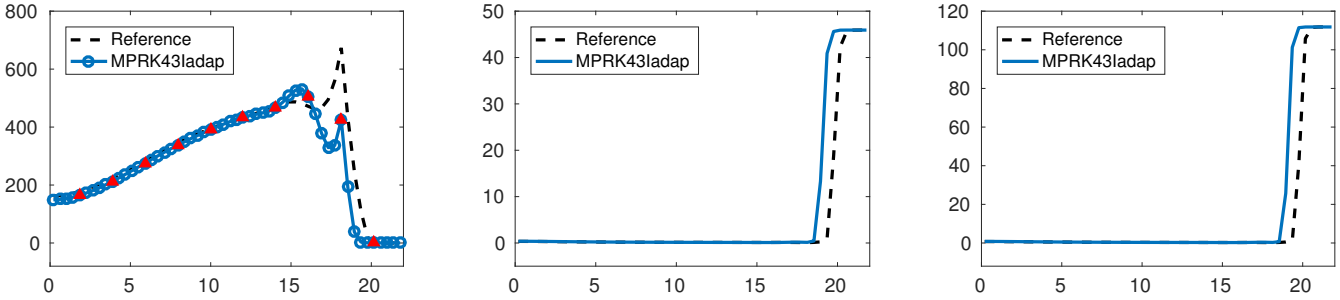

Fig. 2: Calcium concentration (left), free florecent dye b_1 (middle), and free contractile protein b_2 (right) at time $t = 38.1$ ms. The MPRK43I approximations agree well with the reference solution, and the positivity of b_1 and b_2 is preserved.

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