Evaluating Exponential Integrators for Markov Chain Ion Channel Models

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Abstract

We evaluate the accuracy and efficiency of an exponential integrator method applied to a cardiac excitation model with numerically stiff Markov chain (MC) description of ionic channels, namely Ryanodine receptor (RyR) and L-type calcium channel $\mathrm{I}_{\mathrm{Ca(L)}}$*. If solved by explicit methods such as forward Euler (FE), the stability constraints for these MC models require very small time steps.*

We extend the idea of the Rush-Larsen method, originally developed for Hodgkin-Huxley type gate models, for MC models. The method is based on the assumption that the variation of the transitions of MC is small within one time step, so we can consider their values constant for the duration of the time step.

Our method allows 30-fold increase of the time step size, while providing reasonably accurate solutions and maintaining numerical stability. The reduction of computational cost is achieved by increasing time step size of the numerical integration.

1. Introduction

Electrophysiological description of cardiac cells includes models of ionic channels — large molecules incorporated into the cellular membrane. The simplest description of such channels is known as Hodgkin-Huxley (HH) type models, following their seminal paper [1]. This description hypothesises existence of imaginary "gates", which can close or open depending on the membrane voltage V, and lead to dynamic equations of the form

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \alpha(V)(1-y) - \beta(V)y \tag{1}$$

where y is the probability of a gate being open, and α and β are voltage-depending opening an closing rates.

HH models are generalised as Markov chain (MC) models,

$$\frac{\mathrm{d}\vec{x}}{\mathrm{d}t} = \boldsymbol{M}(V,c)\,\vec{x} \tag{2}$$

where the components of vector $\vec{x}$ are probabilities of a channel to be in different conformation states, including "open", "closed" or "inactivated" states. Transition rates between the states are defined by matrix $\boldsymbol{M}(V,c)$, and may depend on the membrane voltage V or ionic concentrations c.

Such system is solved on a computer by computing the states at discretized times $t_n = t_0 + n\Delta t$. The simplest time stepper for differential equations is the forward Euler (FE) method which defines the solution at the next time step $y(t_{n+1}) = y_{n+1}$ in terms of the same at the current time $y(t_n) = y_n$ as

$$y_{n+1} = y_n + \Delta t \frac{\mathrm{d}y_n}{\mathrm{d}t}. \tag{3}$$

The solution converges to the exact solution as the time step size reduces. When less accurate solution is acceptable the computing cost can be reduced by increasing the time step size. The maximum time step is limited by numerical instabilities, which are primarily due to fastest transition rates. So the stability conditions are most stringent in numerically stiff systems.

The instability issue can be addressed by using implicit solvers. Generic implicit solvers are complicated, and it often helps to exploit any specifics of a particular problem. Rush and Larsen [2] proposed a method specifically for the gate models of ionic channels. The method presumes the transition rates to be almost constant constant during one time step, and the corresponding equation with "frozen" coefficients gives an exact solution in terms of "steady-state" $\bar{y}(V_n)$ and "time constant" $\tau(V_n)$:

$$y_{n+1} = \bar{y}(V_n) - (\bar{y}(V_n) - y_n)\exp\left(-\frac{\Delta t}{\tau(V_n)}\right). \tag{4}$$

The MC often are a primary cause of instabilities in cellular models, as some of the MC transition rates can be much faster than other processes in the system. Hence explicit solvers require very small step size to avoid instability in such models. An example is the cardiac cell model published by Faber et al. [3] the use of which is somewhat limited by the stiffness of the MC models used in it, to which the Rush-Larsen method is not directly applicable.

In [4], we have described an extension of Rush-Larsen scheme for Markov chains. Briefly, we set

$$\vec{x}_{n+1} = \exp\left[\boldsymbol{M}(V_n, c_n)\,\Delta t\right]\,\vec{x}_n \tag{5}$$

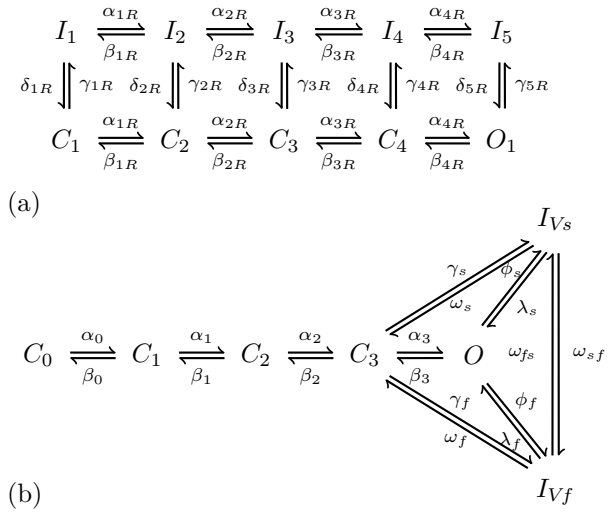

Figure 1. State diagrams of Markov chain models: (a) RyR receptor ; (b) $\mathrm{I_{Ca(L)}}$ channel.

where the matrix exponential is calculated using diagonalization and tabulated for the physiological ranges of the variables V, c. We considered there an implementation of this Matrix Rush-Larsen (MRL) scheme to a MC model of the $\mathrm{I_{Na}}$ current. In this report we describe application of the same method to the RyR and $\mathrm{I_{Ca(L)}}$ channels used in [3], with an aim to prevent instabilities due to the stiffness of MC and allow larger time steps. This application necessitated some adjustments of the method, according to the specifics of the MC. Here we focus on these adjustments, referring the reader to [4] for other details.

2. Methods

2.1. Cellular Model

We obtained the `C` source code of Faber's model from the Rudy Laboratory website [5]. This model contains two MC models: Ryanodine receptor and $\mathrm{I_{Ca(L)}}$ channel, see Fig. 1. All gated ionic channels in this model are simulated using Rush-Larsen method, which always yield stable solution. The forward Euler scheme is used for the integration of ionic concentrations ($[\mathrm{Ca^{2+}}]_\mathrm{i}$, $[\mathrm{Na^{+}}]_\mathrm{i}$, $[\mathrm{K^{+}}]_\mathrm{i}$) and membrane voltage V and, in the authors' code, also for the Markov chain models. The first action potential (AP) was initiated at $t = 1\,\mathrm{ms}$ to allow use of logarithmic time axis in the plots.

2.2. Ryanodine receptor

RyR is a calcium specific ion channel located in the sarcoplasmic reticulum (SR). During the excitation, the $\mathrm{Ca^{2+}}$ is released from SR to the intracellular sub-space, a thin compartment located under the cellular membrane.

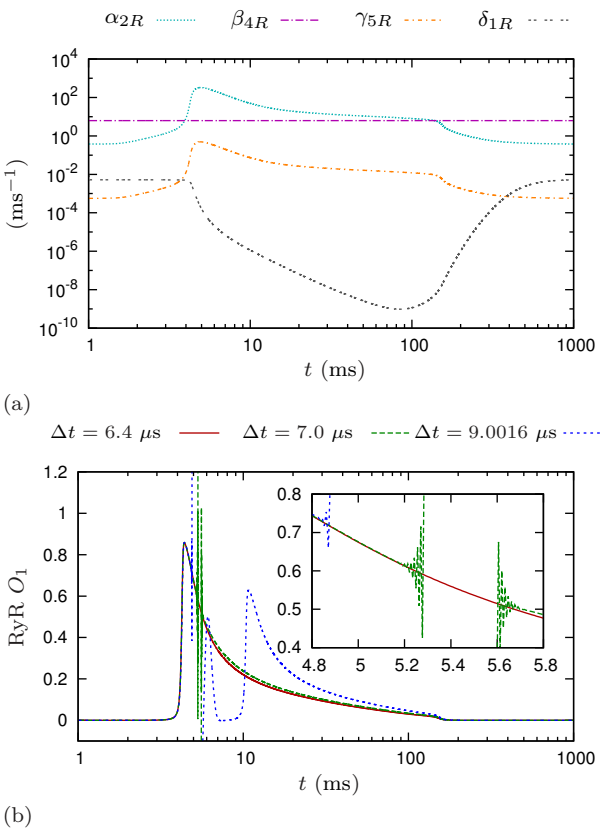

Figure 2. (a) Transition rates of RyR channel during an AP. (b) Numerical instability in by RyR model forward Euler integration at various time steps.

The RyR model contains 10 states located in 2 rows in the diagram Fig. 1(a), corresponding to inactivated (top row) and activated states (bottom row). The state O_1 is conductive, all other states are non-conductive.

Transition rates (TR) of the RyR can be divided into four groups (α, β, γ, δ), whose values are proportional. TR in group of β's are constant, α's and γ's depend on calcium concentration in sub-space $[\mathrm{Ca^{2+}}]_\mathrm{ss}$, and δ's are function of calsequestrin buffered calcium concentration $[\mathrm{CSQN}]$. Figure 2a shows the time evolution of the fastest representative of each group during one AP. The values of α's reach up to $\sim 10^2\,\mathrm{ms^{-1}}$, which puts an estimate for the maximal allowable step for the FE solver at $\sim 10^{-2}\,\mathrm{ms}$.

Direct application of the Matrix Rush-Larsen method as described in [4] is awkward here as the TRs depend on two variables ($[\mathrm{Ca^{2+}}]_\mathrm{ss}$, $[\mathrm{CSQN}]$) so tabulation would require large memory. However we note that all "vertical" TRs (γ's and δ's) are uniformly small and the "horizontal" TRs (α's and β's) only depend on $[\mathrm{Ca^{2+}}]_\mathrm{ss}$. Furthermore, the "horizontal" transition rates are identical in both rows. So, for this MC we can write $\vec{u} = (\vec{v}, \vec{w})$, where $\vec{v} = [I_1, I_2, I_3, I_4, I_5]^\top$, contains the states of the top row,

and $\vec{w} = [C_1, C_2, C_3, C_4, O_1]^\top$, containing the states of the bottom row, and the TR matrix is

$$\boldsymbol{M}([\mathrm{Ca}^{2+}]_{\mathrm{ss}}, [\mathrm{CSQN}]) = \left(\begin{array}{c|c} \boldsymbol{B} & 0 \\ \hline 0 & \boldsymbol{B} \end{array}\right) + \boldsymbol{C}$$

where $\boldsymbol{B} = \boldsymbol{B}([\mathrm{Ca}^{2+}]_{\mathrm{ss}}(t))$ represents the "horizontal" TRs and $\|\boldsymbol{C}(\dots)\| \lesssim 1\,\mathrm{ms}^{-1}$ represents the "vertical" TRs. Hence for this MC we use a mix of Matrix Rush-Larsen and FE using Lie-style operator splitting:

$$\begin{aligned} \vec{v}_{n+1/2} &= \exp\left(\Delta t\, \boldsymbol{B}(t_n)\right)\, \vec{v}_n \\ \vec{w}_{n+1/2} &= \exp\left(\Delta t\, \boldsymbol{B}(t_n)\right)\, \vec{w}_n \\ \vec{u}_{n+1} &= \vec{u}_{n+1/2} + \Delta t\, \boldsymbol{C}(t_n)\, \vec{u}_{n+1/2}. \end{aligned} \tag{6}$$

The matrix exponential $\exp(\Delta t \boldsymbol{B})$ is computed in advance, using eigenvalues and eigenvectors of $\boldsymbol{B}$, for a grid of the values of $[\mathrm{Ca}^{2+}]_{\mathrm{ss}}$. The $[\mathrm{Ca}^{2+}]_{\mathrm{ss}}$ ranges in five orders of magnitude, between 10^{-4} and $0.06\,\mathrm{mM}$, which would make a table for an evenly spaced grid of $[\mathrm{Ca}^{2+}]_{\mathrm{ss}}$ values computationally and memory expensive. So we use instead a grid with $\ln([\mathrm{Ca}^{2+}]_{\mathrm{ss}})$ evenly spaced from $\ln(10^{-5}\,\mathrm{mM})$ to $\ln(0.1\,\mathrm{mM})$ with the step 0.001.

The Lie substep taking care of the slow "vertical" transition rates is done with the FE scheme, which should work for $\Delta t \lesssim \|\boldsymbol{C}\|^{-1} \sim 1\,\mathrm{ms}$.

2.3. $\mathrm{I}_{\mathrm{Ca(L)}}$ channel

The $\mathrm{I}_{\mathrm{Ca(L)}}$ channel is controlled by two sorts of processes, characterised by transition rates that are functions of either voltage V or calcium concentration $[\mathrm{Ca}^{2+}]_{\mathrm{i}}$. The independence of those processes allows us to consider them separately. The $[\mathrm{Ca}^{2+}]_{\mathrm{i}}$-dependent regime factors out as a HH-type gate, leaving the simplified MC model for voltage dependent regime, which is shown on Fig. 1(b). The only conductive state of the MC model is the state O, however for the whole channel to be open, the $[\mathrm{Ca}^{2+}]_{\mathrm{i}}$-dependent HH-type gate must also be open.

TRs of this factored out V-dependent part of the $\mathrm{I}_{\mathrm{Ca(L)}}$ MC model do not provide a clear further separation into groups as was the case in RyR model, which makes operator splitting unusable. So we compute the MC using the straightforward MRL as specified by (5).

For tabulation, we use values of V evenly spaced from $-100\,\mathrm{mV}$ to $70\,\mathrm{mV}$ with the step $0.01\,\mathrm{mV}$.

3. Results

To study the numerical properties of the cellular model, we perform a number of simulations with different time step sizes. The suggested time step in the authors' code was of $\Delta t = 1\,\mu\mathrm{s}$. Increasing this value above $\Delta t \approx 6.7\,\mu\mathrm{s}$ causes instability as shown on Fig. 2(b). This instability first occurs in the state O_1 at the time, when the fastest TR reaches its maximum. This instability does not significantly affect the membrane potential up to the $\Delta t \approx 9\,\mu\mathrm{s}$; beyond that, the solution crashes as the calcium concentration reaches negative values. With the mixed MRL/FE method (6), the RyR model provides stable solution for all Δt we considered.

The instability in the FE scheme for the $\mathrm{I}_{\mathrm{Ca(L)}}$ model occurs also at the moment when the fastest TR reaches its maximum (not shown). At $\Delta t \approx 37\,\mu\mathrm{s}$ the method is stable, while at $\Delta t = 38\,\mu\mathrm{s}$ instability artefacts are observed in the state C_3. This hardly affects the overall solution as the state C_3 does not control the $\mathrm{I}_{\mathrm{Ca(L)}}$ current directly. However, at $\Delta t = 38.86$ the oscillations around the true solution propagate to $\mathrm{I}_{\mathrm{Ca(L)}}$ and cause a drift in $[\mathrm{Ca}^{2+}]_{\mathrm{ss}}$. Further increase of Δt leads to fatal numerical errors.

When using the MRL method for $\mathrm{I}_{\mathrm{Ca(L)}}$ model and the mixed MRL/FE method for RyR, the time step can be increased up to $\Delta t = 190\,\mu\mathrm{s}$ without losing stability. Figure 3 shows a comparison of the solutions obtained with the exponential integrators at various time steps. The reference solution is the FE with $\Delta t = 1\,\mu\mathrm{s}$. The results are consistent with the expected numerical convergence at $\Delta t \to 0$. The deviation of V is up to about $20\,\mathrm{mV}$ during the AP upstroke, which is equivalent to a less than $0.1\,\mathrm{ms}$ shift of the timing of the upstroke, and in the later phases reduces to less than $1\,\mathrm{mV}$ even for the highest time step.

Table 1 compares the computational costs of different methods. The timings are for pure calculations, without input/output or precomputing of the matrix exponentials. The blank spaces in the table represent unstable combination of computational method and time step. It is clear that both mixed MRL/FE and MRL schemes are computationaly more expensive than FE at the same time step. However, the advantage of exponential integrators is in the possiblity of increasing the time step above the stability threshold of the explicit solvers.

Table 1. Time in seconds used for a simulation of 100 beats with the cycle length of $1000\,\mathrm{ms}$ on an Intel Core i5-3470 3.2 GHz GNU/Linux box, separately for RyR and $\mathrm{I}_{\mathrm{Ca(L)}}$ Markov chains and for the whole cell model, comparing MRL/FE scheme (RyR) and MRL ($\mathrm{I}_{\mathrm{Ca(L)}}$) schemes with the original FE scheme.

	$\Delta t\,[\mu\mathrm{s}]$	1	6	35	180
RyR	FE	22.44	3.90		
	MRL/FE	41.68	6.93	1.198	0.2344
$\mathrm{I}_{\mathrm{Ca(L)}}$	FE	68.17	11.33	1.977	
	MRL	82.94	13.82	2.369	0.4619
total	FE	323.0	54.08		
	MRL/FE	346.8	57.84	9.937	
	MRL	342.8	57.21		
	MRL+MRL/FE	358.9	59.68	10.27	1.996

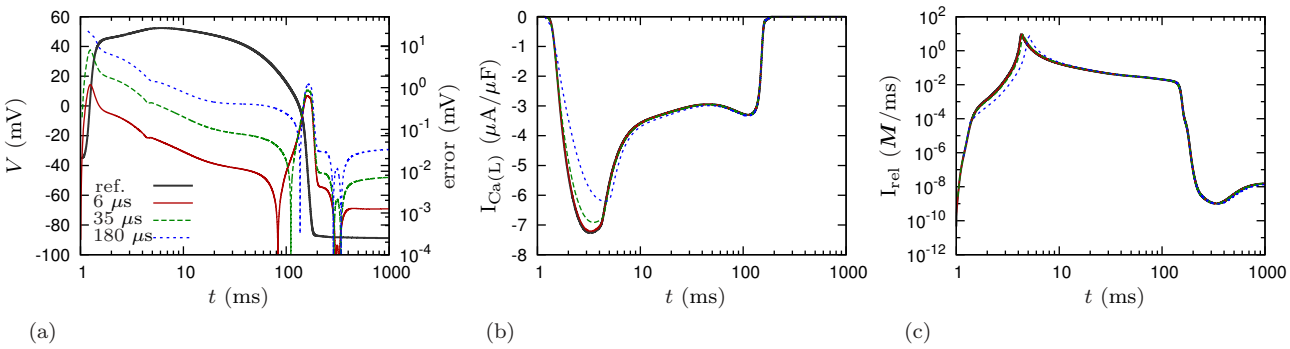

Figure 3. Comparison of the exponential integrators for RyR and $\mathrm{I_{Ca(L)}}$. Panel (a) shows the reference membrane potential: black line (left y-axis), and difference between the reference and a solution by exponential integrators (right y-axis); panel (b) shows the $\mathrm{I_{Ca(L)}}$ current; panel (c) shows RyR current.

4. Conclusions

The MRL method for $\mathrm{I_{Ca(L)}}$ combined with mixed MRL/FE method for RyR allow larger time steps, up to $\sim 180\,\mu$s, compared to $\sim 6\,\mu$s affordable for the original method, and the computation time reduces by a factor of 27. The instability at larger time steps occurs via intracellular concentrations $[\mathrm{Na}^+]_\mathrm{i}$ and $[\mathrm{K}^+]_\mathrm{i}$, which in any case are calculated by the FE scheme. As these concentrations are described by nonlinear equations coupled with other dynamical variables, we can not directly apply the MRL methods; see, however, [6].

The FE scheme with $\Delta t = 6\,\mu$s is stable for both Markov chain models. Further increasing of the step size requires MRL/FE scheme for the RyR Markov chain. For time steps above 37 μs, stability requires use of the MRL scheme for the $\mathrm{I_{Ca(L)}}$ Markov chain.

In implementing the idea of the Matrix Rush-Larsen method, we had to take into account specifics of the two Markov chains in question. In both cases, the problems were related to the dependence of the transition rates on different dynamic variables; and in both cases the problems were overcome by careful analysis of the structure of the transition rate matrices.

The main benefit of applying suggested methods, is the possibility to increase the time step size. This leads to the reduction of the computational cost, without the danger that the solver becomes unstable. An obvious disadvantage of higher time steps is loss of accuracy; however when stability of the MC components of the model is ensured, it opens the way to using higher-order schemes to improve the accuracy, say higher-order modifications of Rush-Larsen scheme (see e.g. [6]), for HH-type gates; their suitable matrix generalizations for Markov chains; and Runge-Kutta type methods for other components. This presents an interesting direction for further study.

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