Dynamics Reading Group

Dynamical Properties of Markov Chain Cardiac Ion Channel

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1. Model Definition
   - Cellular Membrane
   - Ion Channel
   - Sodium Channel Markov Chain
2. Motivation
   - Numerical Instability Issues
   - Exponential Time Differentiation – Rush, Larsen (1978)
3. Methods
   - Generalized Rush-Larsen (gRL)
   - Tabulation (tab.)
   - Hybrid method (hyb.): Operator Splitting
4. Results

Cellular Membrane

Cellular membrane potential governed by equation:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{1}{C_m}\left[I_{\mathrm{stim}}(t) - \sum_{k=1}^{N} I_k(V, \vec{X}, P_{\mathrm{open}})\right] \tag{1}$$

- V – membrane potential
- C_m – membrane capacitance
- $I_{\mathrm{stim}}(t)$ – external stimulation current
- $I_k(V, \vec{X}, P_{\mathrm{open}})$ – specific ion current
- $\vec{X}(t)$ – ionic concentrations

Ion Channel (1/2)

From the Ohm's law:

$$I_k = G_k P_{\mathrm{open}}(t)[V(t) - E_k(X_k)] \tag{2}$$

- G_k – maximum conductance of specific ion current
- $E_k(X_k)$ – equilibrium voltage for specific ion (Nerst potential)
- $P_{\mathrm{open}}(t)$ – open probability defined by one of the following ion channel models:
  - Gate model
  - Markov chain model

Ion Channel (2/2)

- Gate model – Hodgkin, Huxley (1952)

$$\frac{\mathrm{d}y_i}{\mathrm{d}t} = \alpha_{yi}(V)(1 - y_i) - \beta_{yi}(V)y_i \tag{3}$$

$$P_{\mathrm{open}}(t) = \prod_{i=1}^{N} y_i(t) \tag{4}$$

where y_i represents hypothetical gates; and transition rates ($\alpha_{yi}(V)$, $\beta_{yi}(V)$) are determined experimentally.

- Markov chain model

$$\frac{\mathrm{d}\vec{u}}{\mathrm{d}t} = \boldsymbol{A}(V)\vec{u} \tag{5}$$

$$P_{\mathrm{open}}(t) = u_1(t) \tag{6}$$

where u_1 is open (conductive) state; and transition rates matrix ($\boldsymbol{A}(V)$) is determined experimentally.

Sodium Channel Markov Chain (1/2)

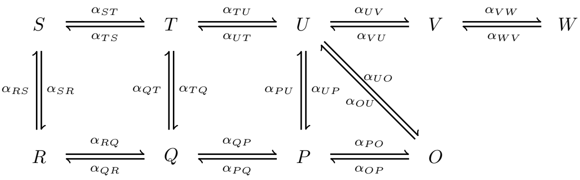


Figure : I_{Na} Markov chain model: 9 interconnected dynamical states, state O denotes to conductive open state (u_1).

Standard	Our
O	O
C_1	P
C_2	Q
C_3	R
IC_3	S
IC_2	T
IF	U
IM_1	V
IM_2	W

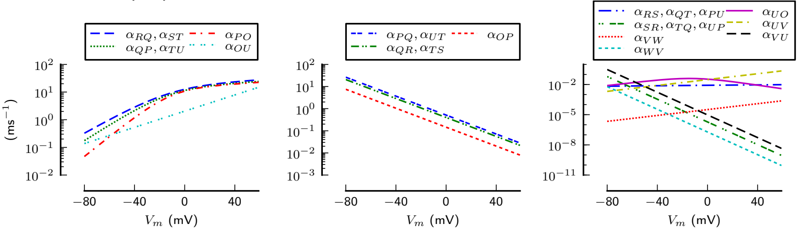
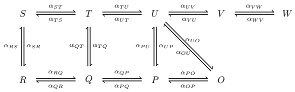


Figure : Transition rates in the range of physiological potentials.

Sodium Channel Markov Chain (2/2)



$$
\begin{aligned}
\frac{\mathrm{d}O}{\mathrm{d}t} &= \alpha_{PO}P + \alpha_{UO}U - (\alpha_{OP} + \alpha_{OU})O \\
\frac{\mathrm{d}P}{\mathrm{d}t} &= \alpha_{QP}Q + \alpha_{UP}U + \alpha_{OP}O - (\alpha_{PQ} + \alpha_{PU} + \alpha_{PO})P \\
\frac{\mathrm{d}Q}{\mathrm{d}t} &= \alpha_{RQ}R + \alpha_{TQ}T + \alpha_{PQ}P - (\alpha_{QR} + \alpha_{QT} + \alpha_{QP})Q \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \alpha_{SR}S + \alpha_{QR}Q - (\alpha_{RS} + \alpha_{RQ})R \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= \alpha_{TS}T + \alpha_{RS}R - (\alpha_{ST} + \alpha_{SR})S \\
\frac{\mathrm{d}T}{\mathrm{d}t} &= \alpha_{QT}Q + \alpha_{ST}S + \alpha_{UT}U - (\alpha_{TQ} + \alpha_{TS} + \alpha_{TU})T \\
\frac{\mathrm{d}U}{\mathrm{d}t} &= \alpha_{TU}T + \alpha_{PU}P + \alpha_{VU}V + \alpha_{OU}O - (\alpha_{UT} + \alpha_{UP} + \alpha_{UO} + \alpha_{UV})U \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= \alpha_{UV}U + \alpha_{WV}W - (\alpha_{VU} + \alpha_{VW})V \\
\frac{\mathrm{d}W}{\mathrm{d}t} &= \alpha_{VW}V - \alpha_{WV}W
\end{aligned}
$$

Numerical Instability Issues

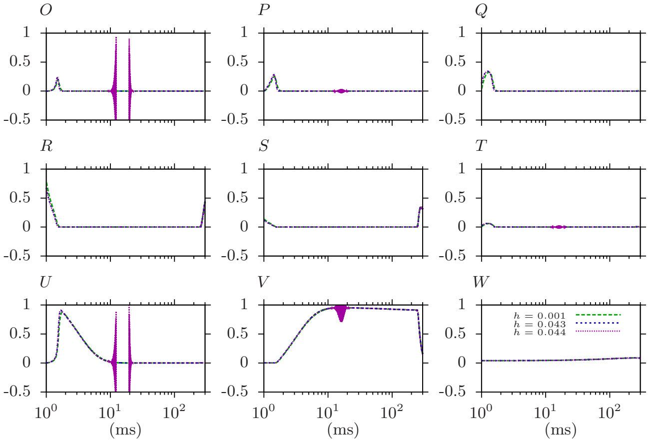


Figure : MC I_{Na} ion channel simulation driven by Action potential (V) at time step $h = 0.001, 0.043$ and 0.044 ms.

Exponential Time Differentiation – Rush, Larsen (1978)

The exponential time differentiation scheme developed by Rush and Larsen (1978) is efficient method for solving gate model:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \alpha(V)(1-y) - \beta(V)y \tag{7}$$

considering $\alpha(V)$ and $\beta(V)$ constants we can obtain analytical solution:

$$y^{n+1} = y_\infty(V) - [y_\infty(V) - y^n]\exp(-h/\tau) \tag{8}$$

where

- $y_\infty(V) = \alpha(V)/[\alpha(V) + \beta(V)]$ – "steady-state" solution
- $\tau = 1/[\alpha(V) + \beta(V)]$ – "time constant"
- $h = t_{n+1} - t_n$ – time step
- $y^n = y(t_n)$

Generalized Rush-Larsen (gRL)

We can extend the exponential time differentiation for given Markov chain $\mathrm{d}\vec{u}/\mathrm{d}t = \boldsymbol{A}(V(t))\vec{u}$ as:

$$\vec{u}^{n+1} = \exp\left[\boldsymbol{A}(V(t_n))h\right]\vec{u}^n = \boldsymbol{T}(V)\vec{u}^n \tag{9}$$

Matrix $\boldsymbol{T}$ can be expanded using the definition of the exponential:

$$\boldsymbol{T} = \exp(\boldsymbol{A}h) = \sum_{j=0}^{\infty}\frac{(\boldsymbol{A}h)^j}{j!} = \sum_{j=0}^{\infty}\frac{(\boldsymbol{S\Lambda S}^{-1})^j h^j}{j!} = \sum_{j=0}^{\infty}\frac{(\boldsymbol{S\Lambda S}^{-1}\boldsymbol{S\Lambda S}^{-1}\ldots\boldsymbol{S\Lambda S}^{-1})h^j}{j!} =$$

$$= \boldsymbol{S}\left(\sum_{j=0}^{\infty}\frac{(\boldsymbol{\Lambda}h)^j}{j!}\right)\boldsymbol{S}^{-1} = \boldsymbol{S}\exp(\boldsymbol{\Lambda}h)\boldsymbol{S}^{-1} \tag{10}$$

where matrix $\boldsymbol{S}(V)$ is composed of eigenvectors concatenated as column vectors; and matrix $\boldsymbol{\Lambda}(V)$ contains eigenvalues placed on the corresponding places on diagonal, such that $\boldsymbol{A}(V) = \boldsymbol{S}(V)\boldsymbol{\Lambda}(V)\boldsymbol{S}(V)^{-1}$.

Tabulation (tab.)

Because finding eigenvalues and eigenvectors is computationally expensive:

- we save the matrices $\boldsymbol{S}(\tilde{V})$ and $\boldsymbol{\Lambda}(\tilde{V})$ for a fine grid of physiological potentials: $\tilde{V} = (-100, 70)$ mV with the step 0.01 mV.
- before numerical solution we pre-compute: $\boldsymbol{T}(\tilde{V}) = \boldsymbol{S}(\tilde{V})\exp(\boldsymbol{\Lambda}(\tilde{V})h)\boldsymbol{S}(\tilde{V})^{-1}$
- The numerical solution:

$$\vec{u}^{n+1} = \boldsymbol{T}(\tilde{V}_{j(n)})\vec{u}^{n} \tag{11}$$

where $\tilde{V}_{j(n)} \approx V(t_n)$; and $\boldsymbol{T}(\tilde{V}_{j(n)})$ is quickly substituted during the solution.

Hybrid method (hyb.): Operator Splitting (1/2)

In our system $\mathrm{d}\vec{u}/\mathrm{d}t = \boldsymbol{A}(V(t))\vec{u}$, the transition rates matrix can be divided according to the transition rates speeds:

$$\boldsymbol{A}(V) = \boldsymbol{A_0(V)} + \boldsymbol{A_1(V)} + \boldsymbol{A_2(V)}$$

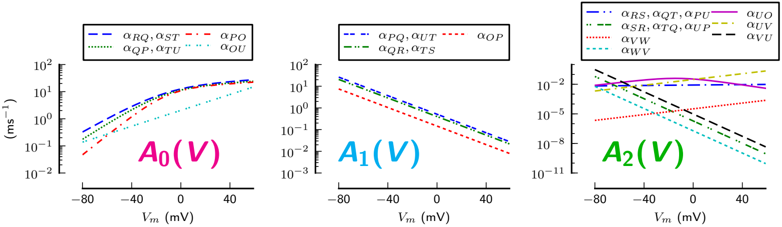


Figure : Transition rates of I_{Na} Markov chain model.

Hybrid method (hyb.): Operator Splitting (2/2)

Then the solution can be split into three steps:

$$\vec{u}^{n+1/3} = \exp(h\boldsymbol{A}_0(t_n))\vec{u}^{n} \tag{12}$$

$$\vec{u}^{n+2/3} = \exp(h\boldsymbol{A}_1(t_n))\vec{u}^{n+1/3} \tag{13}$$

$$\vec{u}^{n+1} = \vec{u}^{n+2/3} + h\boldsymbol{A}_2(t_n)\vec{u}^{n+2/3} \tag{14}$$

- $\vec{u}^{n+1/3}$ – contribution from the $\boldsymbol{A}_0(t)$
- $\vec{u}^{n+2/3}$ – contribution from the $\boldsymbol{A}_0(t) + \boldsymbol{A}_1(t)$
- $\vec{u}^{n+1}$ – final solution at the time t_{n+1}

Hybrid method (hyb.): Solution for $A_0(V)$ (1/2)

$$\frac{\mathrm{d}O}{\mathrm{d}t} = \alpha_{PO}P - \alpha_{OU}O \tag{15}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \alpha_{QP}Q - \alpha_{PO}P \tag{16}$$

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \alpha_{RQ}R - \alpha_{QP}Q \tag{17}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = -\alpha_{RQ}R \tag{18}$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha_{ST}S \tag{19}$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \alpha_{ST}S - \alpha_{TU}T \tag{20}$$

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \alpha_{TU}T + \alpha_{OU}O \tag{21}$$

Hybrid method (hyb.): Solution for $A_0(V)$ (2/2)

$$
\begin{aligned}
O = & O_0\mu_{OU} + P_0\left[\frac{\alpha_{PO}(\mu_{PO}-\mu_{OU})}{\alpha_{OU}-\alpha_{PO}}\right] + \\
& + Q_0\left[\frac{\alpha_{PO}\alpha_{QP}(\mu_{QP}-\mu_{OU})}{(\alpha_{PO}-\alpha_{QP})(\alpha_{OU}-\alpha_{QP})} - \frac{\alpha_{PO}\alpha_{QP}(\mu_{PO}-\mu_{OU})}{(\alpha_{PO}-\alpha_{QP})(\alpha_{OU}-\alpha_{PO})}\right] + \\
& + R_0\left[-\frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{QP}-\mu_{OU})}{(\alpha_{QP}-\alpha_{RQ})(\alpha_{PO}-\alpha_{QP})(\alpha_{OU}-\alpha_{QP})} + \right. \\
& + \frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{PO}-\mu_{OU})}{(\alpha_{QP}-\alpha_{RQ})(\alpha_{PO}-\alpha_{QP})(\alpha_{OU}-\alpha_{PO})} + \\
& + \frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{RQ}-\mu_{OU})}{(\alpha_{QP}-\alpha_{RQ})(\alpha_{PO}-\alpha_{RQ})(\alpha_{OU}-\alpha_{RQ})} - \\
& \left. - \frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{PO}-\mu_{OU})}{(\alpha_{QP}-\alpha_{RQ})(\alpha_{PO}-\alpha_{RQ})(\alpha_{OU}-\alpha_{PO})}\right]
\end{aligned}
\qquad (22)
$$

- O_0, P_0, Q_0, R_0 – initial conditions at t_0
- $\mu_{jk} = \exp(-\alpha_{jk}(t-t_0))$

Results (1/2)

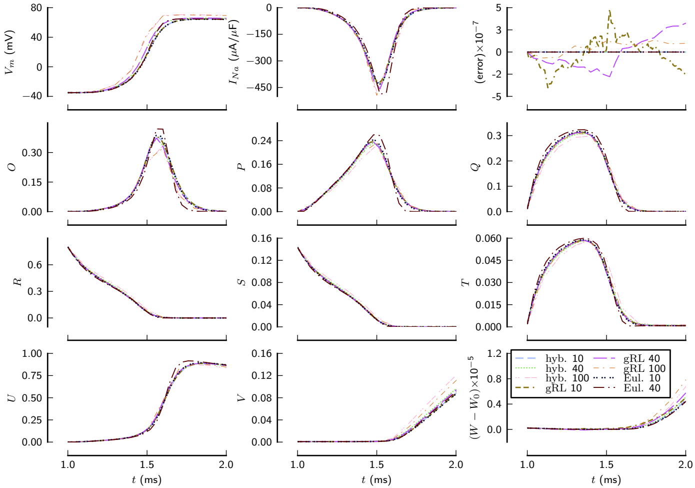


Figure : Cardiac excitation simulations with I_{Na} Markov chain model.

Results (2/2)

Table : Computational cost [s] during 100 pulses with cycle length of 1 s.

	$h = 10\ \mu s$		$h = 40\ \mu s$		$h = 100\ \mu s$	
I_{Na} Model	I_{Na}	Total	I_{Na}	Total	I_{Na}	Total
Eul.	5.44	24.01	1.29	6.02		
Eul. (tab.)	2.74	21.38	0.69	5.36		
gRL (tab.)	4.79	24.36	1.23	6.23	0.54	2.45
hyb.	9.51	28.13	2.22	7.04	0.79	2.83
hyb. (tab.)	2.89	21.71	0.77	5.49	0.37	2.21

A. L. Hodgkin and A. F. Huxley.
A quantitative description of membrane current and its application to conduction and excitation in nerve.
J Physiol, 117(4):500–544, Aug 1952.

S. Rush and H. Larsen.
A practical algorithm for solving dynamic membrane equations.
IEEE Trans Biomed Eng, 25(4):389–392, Jul 1978.

C. E. Clancy and Y. Rudy.
Na^+ channel mutation that causes both Brugada and long-QT syndrome phenotypes: a simulation study of mechanism.
Circulation, 105(10):1208–1213, Mar 2002.