Asymptotic reduction of cardiac excitation models

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References and credits

Publications

- **Simitev, R.**, Biktashev, V.N., *Asymptotics of conduction velocity restitution in models of electrical excitation in the heart*, Bull. Math. Biol., 73(1), pp. 72–115, 2011.
- Biktashev, V.N., Suckley, R., Elkin, Y.E, **Simitev, R.**, *Asymptotic analysis and analytical solutions of a model of cardiac excitation*, Bull. Math. Biol., 70(2), pp. 517-554, 2008.

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Mathematical description

Typical electrophysiological models of cardiac excitation

In a one-dimensional, homogeneous and isotropic medium:

$$\frac{\partial E}{\partial t} = \sum_l I_l(E, \mathbf{y}), \tag{1a}$$

$$\frac{\partial \mathbf{y}}{\partial t} = \mathbf{F}_{\mathbf{y}}(E, \mathbf{y}), \tag{1b}$$

where $I_l(E, \mathbf{y})$ are ionic currents and $\mathbf{F}_{\mathbf{y}}(E, \mathbf{y})$ rate of change functions of gating variables.
These models summarize the best experimental knowledge of the electrophysiology of the cardiac cells.

Drawbacks

1. The equations are inherent very stiff.
2. The functional dependences in $I_l(E, \mathbf{y})$ and $\mathbf{F}_{\mathbf{y}}(E, \mathbf{y})$ are very messy.

Illustration: Noble model (1962)

Example: The simplest physiological model

$$\frac{\mathrm{d}E}{\mathrm{d}t} = g_1(E)\, m_\infty^3(E)\, \theta(E - E_m)\, h + g_2(E)\, n^4 + G(E) + \frac{\partial^2 E}{\partial x^2}, \tag{2a}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = f_h(E)\, \left(h_\infty(E) - h\right), \tag{2b}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = f_n(E)\, \left(n_\infty(E) - n\right), \tag{2c}$$

where

$$G(E) = g_1(E) W(E) + g_3(E), \quad W(E) = m_\infty^3(E) h_\infty(E)$$

$$g_1(E) = {C_M}^{-1} g_{Na}\,(E_{Na} - E)\,, \quad g_2(E) = {C_M}^{-1} g_K\,(E_K - E)\,,$$

$$g_3(E) = {C_M}^{-1}\left[g_{Na_1}\,(E_{Na} - E) + g_{K_1}(E)\,(E_K - E)\right],$$

$$g_{K_1}(E) = 1.2 \exp\left((-E - 90)/50\right) + 0.015\, \exp\left((E + 90)/60\right),$$

$$\mathbf{y}_\infty(E) = \alpha_y(E) / \left(\alpha_y(E) + \beta_y(E)\right), \quad y = h, n, m,$$

$$f_y(E) = \alpha_y(E) + \beta_y(E), \quad y = h, n,$$

$$\alpha_m(E) = \frac{0.1\, (-E - 48)}{\exp\left((-E - 48)/15\right) - 1}, \quad \beta_m(E) = \frac{0.12\, (E + 8)}{\exp\left((E + 8)/5\right) - 1},$$

$$\alpha_h(E) = 0.17\, \exp\left((-E - 90)/20\right), \quad \beta_h(E) = \frac{1}{\exp\left((-E - 42)/10\right) + 1},$$

$$\alpha_n(E) = \frac{0.0001\, (-E - 50)}{\exp\left((-E - 50)/10\right) - 1}, \quad \beta_n(E) = 0.002\, \exp\left((-E - 90)/80\right),$$

$$C_M = 12, \quad g_{Na} = 400, \quad g_K = 1.2, \quad g_{Na_1} = 0.14, \quad E_K = -110 \quad E_{Na} = 40.$$

Approaches to solution

Typical method of solution

Direct numerical computation

Drawback: Lack of conceptual understanding

Drawback: Difficult to isolate cause and effect

Drawback: Numerically expensive

Click to play ANIMATION of a 1D numerical solution

Proposed alternative

Techniques for asymptotic reduction

Advantage: Enhanced conceptual understanding

Advantage: Can address specific questions

Advantage: Simplified mathematical description; at times analytical results possible

Advantage: Mathematically sound approach

Parameter embeddings

Rationale

We introduce "auxiliary" parameters to achieve a well-defined mathematical approach to asymptotics.

Definition

A parametric embedding with parameter ϵ of a function $f(x)$ is any function $f(x;\epsilon)$ such that $f(x,1)=f(x)$. In the context of $\epsilon\to 0$ we say *asymptotic embedding*.

Parameter embedding - P1

Aim: To simplify the functional form of the model.

Justification: Complicated functional form is not always essential, especially for conceptual understanding.

Explicitly: Replace $f(x)$ by

$$f(x;\epsilon)=\epsilon f(x)+(1-\epsilon)g(x), \qquad \epsilon\in[0,1].$$

Example: Click to play ANIMATION

Parameter embedding - P2

Aim: To take into account intrinsic scale separation of the model.

Justification: Well-tested mathematical approach.

Explicitly: Replace $f(x)$ by

$$f(x;\epsilon)=\begin{cases}\epsilon f(x) & \text{if } f(x) \text{ relatively SMALL,}\\ \epsilon^{-1}f(x) & \text{if } f(x) \text{ relatively LARGE,}\end{cases} \qquad \epsilon\in[0,1].$$

Example of param embeddings: Noble model

A black art based on observations drawn from numerical experiments.

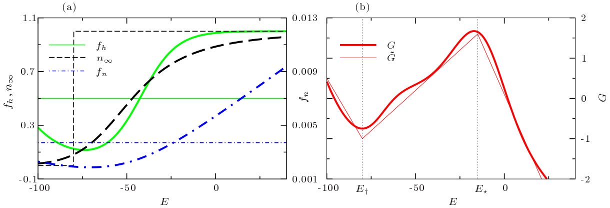

Figure: (a – b) The caricature approximations (thin lines) of the right-hand side functions of the Noble model (2) (thick lines).

Method To estimate relative magnitude define **scaling functions** $\tau_l(w_1, \ldots) \equiv |\mathrm{d}F_l/\mathrm{d}w_l|$ for a set of ODEs $\mathrm{d}w_l/\mathrm{d}t = F_l(w_1, \ldots w_N)$.

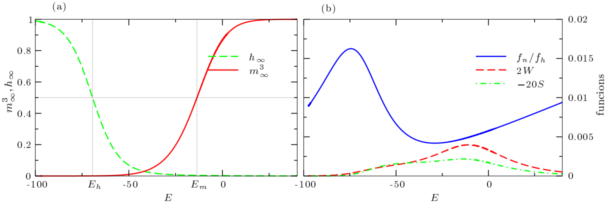

Figure: Main functions of E which determine the asymptotic properties of the Noble model.

Final result: The caricature Noble model

P1 Embed a first parameter μ to simplify functional form as shown above. Take the limit $\mu \to 0$. The functions of the caricature Noble model become:

$$\begin{gathered}
\tilde{g_2}(E) = g_{21}\theta(E_\dagger - E) + g_{22}\theta(E - E_\dagger), \qquad g_{21} = -2, \quad g_{22} = -9, \\
\tilde{G}(E) = \begin{cases} k_1(E_1 - E), & E \in (-\infty, E_\dagger), \\ k_2(E - E_2), & E \in [E_\dagger, E_*), \\ k_3(E_3 - E), & E \in [E_*, +\infty), \end{cases} \\
k_1 = 3/40, \quad k_2 = 1/25, \quad k_3 = 1/10, \quad E_1 = -280/3, \\
E_2 = (k_1/k_2 + 1)E_\dagger - E_1 k_1/k_2 = -55, \\
E_3 = (k_2/k_3 + 1)E_* - E_2 k_2/k_3 = 1, \\
F_h = 1/2, \quad F_n = 1/270, \quad E_{Na} = 40, \\
E_\dagger = -80, \quad E_* = -15, \quad G_{Na} = 100/3,
\end{gathered} \tag{3}$$

P2 Embed a second parameter ϵ to split scales of the problem. The equations of the caricature Noble model become

$$\frac{\partial E}{\partial t} = \frac{1}{\epsilon} G_{Na}\,(E_{Na} - E)\,\theta(E - E_*)\,h + \tilde{g_2}(E)\,n^4 + \tilde{G}(E) + \epsilon \frac{\partial^2 E}{\partial x^2}, \tag{4a}$$

$$\frac{\partial h}{\partial t} = \frac{1}{\epsilon} F_h\,\big(\theta(E_\dagger - E) - h\big), \tag{4b}$$

$$\frac{\partial n}{\partial t} = F_n\,\big(\theta(E - E_\dagger) - n\big), \tag{4c}$$

Exact analytical solution of the Caricature model

Success!

Functionall form is so simple that exact analytical solution in the case $\partial_x^2 E = 0$ can now be found!

Solution procedure

1. The equations for h and n are separable – find $h(t)$ and $n(t)$.
2. Upon substitution of $h(t)$ and $n(t)$ into the voltage equation it becomes a first-order linear ODE - solution easy to find.
3. Initial conditions $E(0) = E_\alpha > E_*, \quad h(0) = 1, \quad n(0) = 0.$
4. Natural continuity conditions at $E_\dagger$ and E_*.

Solution

$$n(t) = \begin{cases} 1 - \exp(-F_n t), & t \in [0, t_\dagger] \\ (\exp(F_n t_\dagger) - 1)\exp(-F_n t), & t \in [t_\dagger, \infty] \end{cases} \tag{5a}$$

$$h(t) = \begin{cases} \exp(-F_h t/\epsilon), & t \in [0, t_\dagger] \\ 1 - (1 + \exp(F_h t_\dagger/\epsilon))\exp(-F_h t/\epsilon), & t \in [t_\dagger, \infty] \end{cases} \tag{5b}$$

$$E(t) = \begin{cases} \overset{1}{E}(t) = \exp\left(\frac{G_{Na}}{F_h}\exp\left(-\frac{F_h t}{\epsilon}\right) - k_3 t\right) \times \Bigg[E_\alpha \exp\left(-\frac{G_{Na}}{F_h}\right) \\ \quad -k_3 E_3\, u(-k_3, t) - g_2^0 \sum_{l=0}^{4} (-1)^l \binom{4}{l} u\left((4-l)F_n - k_3, t\right) \\ \quad -\frac{G_{Na} E_{Na}}{\epsilon}\, u\left(\frac{F_h}{\epsilon} - k_3, t\right)\Bigg], & t \in [0, t_*] \\ \overset{2}{E}(t) = (E_* - w(t_*))\exp\left(k_2 (t - t_*)\right) + w(t), & t \in [t_*, t_\dagger] \\ \overset{3}{E}(t) = (E_\dagger - E_1)\exp\left(-k_1 (t - t_\dagger)\right) + E_1, & t \in [t_\dagger, \infty] \end{cases} \tag{5c}$$

Deviation of the exact solution from the original Noble model

Solution (cont.)

$$u(\varkappa, t) \equiv \frac{\epsilon}{F_h}\left(\frac{G_{Na}}{F_h}\right)^{-\frac{\varkappa\epsilon}{F_h}}\left[\Gamma\left(\frac{\varkappa\epsilon}{F_h}, \frac{G_{Na}}{F_h}\right) - \Gamma\left(\frac{\varkappa\epsilon}{F_h}, \frac{G_{Na}}{F_h}\ \exp\left(-\frac{F_h t}{\epsilon}\right)\right)\right],$$

$$w(t) \equiv E_2 - g_2^0 \sum_{l=0}^{4} (-1)^l \binom{4}{l} \frac{\exp\left(-l\, F_n\, t\right)}{k_2 + l\, F_n},$$

and $\Gamma(a, x)$ is the upper incomplete gamma function.

Measure of deviation

Advantage: The deviation of the parametric embedding (caricature model) from the original model (Noble) can be measured exactly via continuation in ϵ.

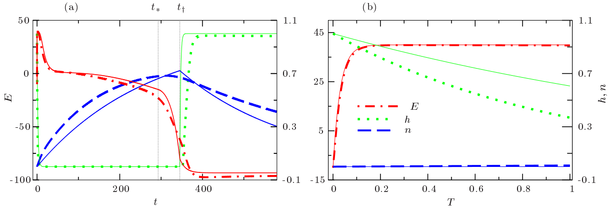

Figure: The numerical solution of the original Noble model (thick lines) in comparison with the analytical solution (5) of the caricature model (4) (corresponding thin lines) (a) in slow time $t \in [0, 600]$, for $\epsilon = 1$, , and (b) in fast time $T \in [0, 1]$, for $\epsilon = 10^{-3}$.

Applications

Some results

1. A consistent procedure for reduction of cardiac electrophysiological models.
2. Cardiac models have a non-Tikhonov asymptotic structure. Care is needed.
3. Successful application to the problem of CV-restitution curves.
4. Successful application to the problem of breakup-and self termination of propagating action potentials.

Some future problems

1. Initiation of propagating action potentials
2. Efficient numerical methods based on asymptotic reduction
3. Higher dimensions
4. More realistic models