Non-Tikhonov Asymptotic Properties of Cardiac Excitability

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Models of electric excitability of cardiac cells can be studied by singular perturbation techniques. To do this one should take into account parameters appearing in equations in non-standard ways. Physical reason for this is near-perfect switch behavior of ionic current gates. This leads to a definition of excitability different from the currently accepted one. The asymptotic structure revealed by our analysis can be used to devise simplified "caricature" models, obtain approximate analytical solutions, and facilitate numerical simulations.

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Self-organization in complex non-equilibrium dissipative systems is often understood in terms of "order parameters", i.e. a small number of essential quantities whose dynamics are much slower than all others in the system[1]. An important class of self-organized systems are excitable systems, found in such diverse areas as catalytical chemical reactions, nerves, heart, populations, liquid crystals, semiconductors and lasers [2, 3]. An excitable system has a "resting" state, which is stable against small perturbations, but an over-threshold perturbation produces a large "action potential" response before returning to rest. The classical FitzHugh-Nagumo[4, 5] way to understand excitable dynamics is in terms of a fast variable, called "activator" or "propagator", explicitly separate from one or more slow variables, called "inhibitors" or "controllers", and the dynamics of the activator may be bistable, depending on the instant state of the controller(s) [6].

In this Letter we provide a counterexample to this paradigm[4–6], by demonstrating that excitability of heart tissue is better understood in completely different terms. Earlier we demonstrated features of realistic heart models, incompatible with the FitzHugh-Nagumo description, such as dissipation of excitation fronts [7, 8] and characteristic shape of the action potentials [9]. Here we identify the details of heart excitation responsible for these features, and suggest a complete asymptotic description of heart excitability, consistent with these details. We do that for the first and the simplest cardiac excitation model by Noble [10]. We also propose a modified version of it, which has similar asymptotic properties and produces similar action potentials, but contains small parameters in the way that is more typical of other models of cardiac cells.

Simplified but adequate models are important for making massive numerical simulations of biological excitable systems more efficient. Development of such models has been via approximation of phase space dynamics [4, 11], imitation of action potentials and recovery dynamics [12, 13], *ad hoc* asymptotics [14, 15] or combination thereof [16–19]. Identification of typical asymptotic features of detailed models opens a regular and reliable way to do that by asymptotic methods.

The asymptotic techniques — The standard approach to "fast-slow" systems[20] is based on Tikhonov's 1952 [21] theorem. As it is well known, this theory operates with parametric families of systems of the form $\mathrm{d}x/\mathrm{d}t = f(x,y)$, $\epsilon\mathrm{d}y/\mathrm{d}t = g(x,y)$ (x and y are scalars or vectors), or equivalently $\mathrm{d}x/\mathrm{d}T = \epsilon f(x,y)$, $\mathrm{d}y/\mathrm{d}T = g(x,y)$, where $t = \epsilon T$ and ϵ is assumed small. In the limit $\epsilon \searrow 0$, the second (fast-time) system describes the fast variables y approaching their quasi-stationary values along the fast foliation of the phase space (x,y) determined by conditions $y = \mathrm{const}$, and the first (slow-time) system describes motion along the slow manifold defined by the condition $g(x,y) = 0$. An important assumption of Tikhonov's theorem is that the relevant attractors of the fast system are isolated, asymptotically stable equilibria.

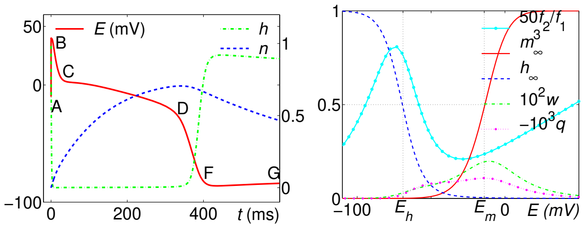
Mathematical models of real systems normally don't contain parameters that can conceivably tend to zero or infinity, thus asymptotic approaches to such systems are always based on artificially introduced small parameters. We call *parametric embedding* of a function $f(x)$ any function $\underline{f}(x;\epsilon)$ such that $\underline{f}(x,1) = f(x)$ for all $x \in \mathrm{dom}(f)$. A parametric embedding in the context of $\epsilon \to 0$ is called *asymptotic embedding*. An embedding of a system of differential equations corresponds to an embedding of its right-hand sides.

An artificial small parameter can be introduced in infinitely many different ways. To check that a particular embedding is reasonable, we use numerical simulation to see how its solutions behave in the limit $\epsilon \to 0$. Note this can be done prior to any analytical work.

The Noble-1962 model, after the standard adiabatic elimination of the m gate, can be written in the form

$$\begin{aligned}
\frac{\mathrm{d}E}{\mathrm{d}t} &= g_1(E)m_\infty^3(E)h + g_2(E)n^4 + g_3(E), \\
\frac{\mathrm{d}h}{\mathrm{d}t} &= f_1(E)\left(h_\infty(E) - h\right), \\
\frac{\mathrm{d}n}{\mathrm{d}t} &= f_2(E)\left(n_\infty(E) - n\right),
\end{aligned} \qquad (1)$$

where $g_1(E) = g_{Na}\left(E_{Na} - E\right)/C_M$, $g_2(E) = g_K\left(E_K - E\right)/C_M$, $g_3(E) = \left(g_{Na_1}(E)\left(E_{Na} - E\right) +\right.$



(a) (b)

FIG. 1: (color online) (a) The typical action potential solution of (1). This and all other AP solutions are calculated for initial conditions $E(0) = -10$, $h(0) = 1$, $n(0) = 0$. A–G: feature points referred to in further analysis. (b) Graphs of dimensionless functions of E whose properties are summarised in the assumptions A2–A7. Voltages E_m and E_h cut m_∞^3 and h_∞ on the level $1/2$.

$g_{K_1}(E)\,(E_K - E) + g_l\,(E_l - E))/C_M$, $f_1(E) = \tau_h^{-1}(E)$, $f_2(E) = \tau_n^{-1}(E)$, and further definitions of functions and parameters can be found in [9, 10]. Following [10] and [14], we raised the numerical coefficient at function $g_{K_1}(E)$ from 1.2 to 1.3, to make the system excitable rather than oscillatory. A typical AP solution of this system is shown on Fig. 1(a).

The asymptotic features of (1) are summarised in the following formal assumptions (see Fig. 1(b)):

A1 The maximal permittivity of the fast (gated) Na current is much larger than those of the other currents, $\max(g_K, g_{K_1}, g_{Na_1})/g_{Na} \lesssim 10^{-2}$. Thus we replace g_{Na} with $\underline{g_{Na}}(\epsilon) = \epsilon^{-1} g_{Na}$.

A2 The speed of h is comparable to E during the upstroke and definitely higher than the speed of n, so that $\max(f_2/f_1) \lesssim 10^{-2}$. Thus, we put $\underline{f_1}(E;\epsilon) = \epsilon^{-1} f_1(E)$.

A3 Function $m_\infty^3(E)$ is small for E below some E_m. Thus we replace $m_\infty^3(E)$ with $\underline{m_\infty^3}(E;\epsilon)$ which obeys $\lim\limits_{\epsilon\to 0} \underline{m_\infty^3}(E;\epsilon) = M(E)\theta(E - E_m)$ where $M(E) \approx m_\infty^3(E)$ for $E > E_m$. We use $\theta()$ for Heaviside function.

A4 Similarly, $h_\infty(E > E_h)$ is small so $\lim\limits_{\epsilon\to 0} \underline{h_\infty}(E;\epsilon) = H(E)\theta(E_h - E)$ where $H(E) \approx h_\infty(E)$ for $E < E_h$.

A5 From Fig. 1(b) we see that $E_m > E_h$.

A consequence of A3–A5 is that the specific permittivity of the "window current", defined as $w(E) = m_\infty^3(E) h_\infty(E)$, is small[24], i.e.

$$\lim_{\epsilon\to 0} \left[\underline{m_\infty^3 h_\infty}\right] = 0. \tag{2}$$

However, this small product is multiplied by a large factor g_{Na}, which makes it comparable to 1.

A6 Thus, we suppose $\lim\limits_{\epsilon\to 0} \left[\epsilon^{-1} \underline{m_\infty^3}(E;\epsilon) \underline{h_\infty}(E;\epsilon)\right] = W(E) > 0$, where $W(E) \approx w(E)$.

A7 In addition to (2), we assume that $q(E) = m_\infty^3 \mathrm{d}h_\infty/\mathrm{d}E$ is small, i.e. $\lim\limits_{\epsilon\to 0} \left[\underline{m_\infty^3}(E;\epsilon) \frac{\partial}{\partial E} \underline{h_\infty}(E;\epsilon)\right] = 0$.

So the asymptotic embedding of model (1) is

$$\begin{aligned}
\frac{\mathrm{d}E}{\mathrm{d}t} &= \epsilon^{-1} g_1(E) \underline{m_\infty^3}(E;\epsilon) h + g_2(E) n^4 + g_3(E) \\
\frac{\mathrm{d}h}{\mathrm{d}t} &= \epsilon^{-1} f_1(E)\left(\underline{h_\infty}(E;\epsilon) - h\right) \\
\frac{\mathrm{d}n}{\mathrm{d}t} &= f_2(E)\,(n_\infty(E) - n)\,.
\end{aligned} \tag{3}$$

Here only A1 and A2 are used explicitly. Examples of explicit embeddings $\underline{m_\infty}$ and $\underline{h_\infty}$ that satisfy A3–A7 are discussed in [22], here for brevity we only do the deductive analysis. For numerics, we set $E_m = -14$, $E_h = -69$ (so $m_\infty(E_m) \approx h_\infty(E_h) \approx 1/2$), $M = m_\infty$, $H = h_\infty$ and $W = w$.

The fast system — Changing the independent variable in (3) from t to $T = t/\epsilon$ and taking the limit $\epsilon \to 0$, gives, with account of A3 and A4,

$$\begin{aligned}
\frac{\mathrm{d}E}{\mathrm{d}T} &= g_1(E) M(E) \theta(E - E_m) h, \\
\frac{\mathrm{d}h}{\mathrm{d}T} &= f_1(E)\,(H(E)\theta(E_h - h) - h)\,, \\
\frac{\mathrm{d}n}{\mathrm{d}T} &= 0.
\end{aligned} \tag{4}$$

The first two right-hand sides are nonzero, thus we have two fast variables, E and h. This system coincides with the point system postulated in [7]. Its phase portrait is shown on Fig. 2(a); it does not depend on the slow variable n. The slow manifold is the set of equilibria of (4) and is defined by

$$M(E)\theta(E - E_m) h = 0, \tag{5}$$

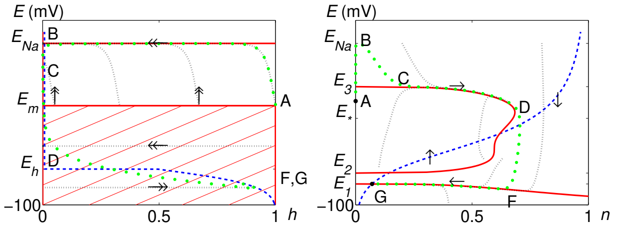
$$H(E)\theta(E_h - E) - h = 0, \tag{6}$$

since $g_1(E) > 0$, $f_1(E) > 0$ in the physiological range of E.

Substitution of (6) into (5) with account of A5 makes (5) an identity due to the product of two Heaviside functions. Thus we have a codimension 1 slow manifold, defined by equation (6). So, all the equilibria of the fast system, at any n, are not isolated, and Tikhonov's theorem is not applicable. The physical reason for this highly degenerate situation is the near-perfect switch behavior of $h_\infty(E)$ and $m_\infty(E)$[25].

System (4) is solvable in quadratures. For $E < E_m$, we have $\dot{E} = 0$ and the equation for $\dot{h}$ is separable. For $E > E_m$, we have $\frac{\mathrm{d}E}{\mathrm{d}h} = -g_1(E)M(E)/f_1(E)$ and a quadrature for $h(E)$ follows; substituted back to (4) it gives $h(T)$ and $E(T)$.

The threshold between excitatory and passive responses is the line $E = E_m$, at which the right-hand sides are non-analytical, and discontinuous if $M(E_m) \neq 0$. Even if $M(E_m) = 0$, this is not a locus of equilibria of the fast system. So, the nature of the threshold in this system is different from FitzHugh-type systems where the thresholds are unstable pieces of the slow manifold. We see also on Fig. 2(a) that each fast trajectory approaches the slow manifold only once,



(a) (b)

FIG. 2: (color online) Phase portraits of (a) fast system (4), (b) slow system (9). A–G: feature points defined at Fig. 1(a). Black dotted lines: trajectories of the fast (a) and slow (b) subsystem. Green large dots: projections of an action potential trajectory of the full system (1). Blue dashed lines: vertical isoclines, $\dot{h} = 0$ (a) or $\dot{n} = 0$ (b). Red solid lines: horizontal isoclines $\dot{E} = 0$. On (a), horizontal isocline includes *a region* $(E, h) \in (-\infty, E_m) \times [0, 1]$ (dashed rectangle). Thus, $\{\dot{h} = 0\} \subset \{\dot{E} = 0\}$, and the whole curve $\{\dot{h} = 0\} = \{h = H(E)\theta(E_h - E)\}$ consists of equilibria.

so there is no place for the classical interpretation of the excitability in terms of bistability of the fast dynamics.

The slow system — Consider system (3) in the original (slow) time, and focus on trajectories near the slow manifold, i.e. for $h \approx \underline{h_\infty}(E; 0)$. By re-arranging the second equation, and assuming that $\mathrm{d}h/\mathrm{d}t = O(1)$ (this is confirmed by the following result), we see that

$$h = \underline{h_\infty}(E; \epsilon) - \frac{\epsilon}{f_1(E)} \frac{\mathrm{d}h}{\mathrm{d}t} = \underline{h_\infty}(E; \epsilon) + O(\epsilon). \quad (7)$$

Differentiating this by t and substituting back into (7) gives

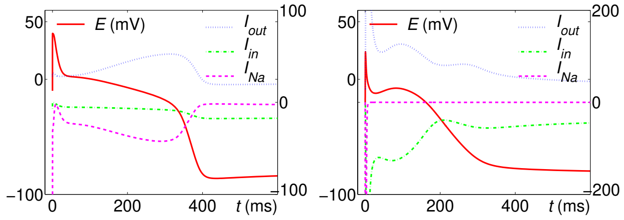
$$h = \underline{h_\infty}(E; \epsilon) - \frac{\epsilon}{f_1(E)} \frac{\partial \underline{h_\infty}}{\partial E} \frac{\mathrm{d}E}{\mathrm{d}t} + O(\epsilon^2). \quad (8)$$

Substituting this into the first equation, using A6 and A7 and taking the limit $\epsilon \to 0$ produces, in the leading order,

$$\begin{aligned} \frac{\mathrm{d}E}{\mathrm{d}t} &= g_1(E)W(E) + g_2(E)n^4 + g_3(E), \\ h &= H(E)\theta(E_h - E), \\ \frac{\mathrm{d}n}{\mathrm{d}t} &= f_2(E)\left(n_\infty(E) - n\right), \end{aligned} \quad (9)$$

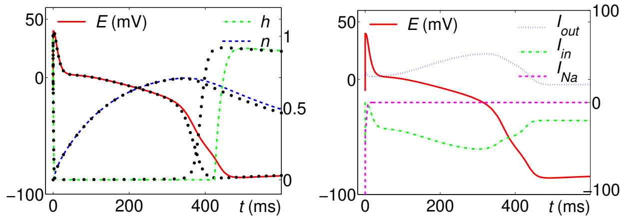
a system of two slow equations for E and n plus a finite equation for h defining the slow manifold. So we have a two-dimensional slow manifold, two slow variables, E and n, and a non-Tikhonov feature of variable E being both fast and slow.

System (9) was derived [26] and studied in detail in [14] In particular, it can be considered a fast-slow system itself, this time in the classical Tikhonov sense, with E as the fast variable and n as the slow variable. The small parameter of this secondary embedding is associated with a small dimensionless constant of the order of 10^{-1}. As both the fast and slow subsystems are one-dimensional, both admit solutions in quadratures. A phase portrait of (9) is shown on Fig. 2(b).



(a) (b)

FIG. 3: (color online) Transmembrane currents in (a) Noble model (1), $\mu\mathrm{A/cm}^2$, (b) Courtemanche et al. [23] model of a human atrial cell, pA. I_{Na}: the current component proportional to the product m^3h; I_{in}: the sum of all other inward currents; I_{out}: the sum of all outward currents; E: the action potential for reference. By the tradition accepted in physiology, currents that increase voltage are considered negative and called inward.



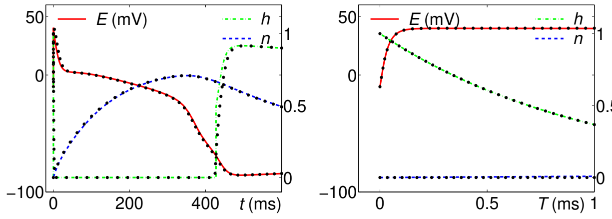
(a) (b)

FIG. 4: (color online) The modified Noble model (10). (a) The typical action potential solution. Black dots: solution of the original system for comparison. Agreement at the wake of AP can be improved by more careful choice of parameters and asymptotics in (9) [22]. (b) Currents making this action potential. Compare with Fig. 3.

Modified model — Noble's [10] model of heart Purkinje fibres is special (see Fig. 3) in that the action potential plateau is a balance between the outward potassium current I_{out} and the "window" component of the inward sodium current I_{Na} through poorly closed gates m and h, unlike other cardiac models, where balance is between I_{out} and other inward currents, and I_{Na} is neglible. This peculiar property of (1) is reflected by assumption A6, with $W(E) > 0$. In other models, we would have $W(E) = 0$. Then, in the leading order, $\underline{h_\infty}$ and $\underline{m_\infty}$ can be simply replaced with their limits, and the asymptotic embedding would have simple explicit form

$$\begin{aligned} \frac{\mathrm{d}E}{\mathrm{d}t} &= \frac{1}{\epsilon} g_1(E)M(E)\theta(E - E_m)h + g_2(E)n^4 + G(E), \\ \frac{\mathrm{d}h}{\mathrm{d}t} &= \frac{1}{\epsilon} f_1(E)\left(H(E)\theta(E_h - E) - h\right), \\ \frac{\mathrm{d}n}{\mathrm{d}t} &= f_2(E)\left(n_\infty(E) - n\right). \end{aligned} \quad (10)$$

where $G(E) = g_3(E) + g_1(E)W(E)$. Here we have chosen



(a) (b)

FIG. 5: (color online) Asymptotic embedding of the modified Noble model (10). Action potential solutions for $\epsilon = 10^{-3}$ (line choice as in Fig. 1) and $\epsilon = 1$ (black dots), (a) in the slow time $t \in [0, 600]$, (b) in the fast time $T = t/\epsilon \in [0, 1]$.

such right-hand sides that the fast and slow systems of this model exactly coincide with the fast (4) and slow (9) systems of the original model (1). Thus all the above asymptotic analysis of (1) applies to (10) as well. Note that the model postulated in [16] has structure similar to (10) but with $E_m = E_h$.

The modified model (10) approximates the original model (1), and has a structure more typical of other heart models, in that the window current is negligible during the plateau, and the balance is maintained by other currents, see Fig. 4(b). Its essential asymptotic features are captured by a simple explicit embedding, which gives a quantitatively good approximation, easily tested numerically, see Fig. 5. Thus it may serve as a prototype for simplified models for heart cells, by specifying appropriate phenomenology for the slow subsystem, as the fast subsystem in the form (4) is apparently quite generic. Indeed, we have found that an asymptotic embedding of model [23] similar to A1–A7 works well with $W(E) = 0$, and its fast subsystem is similar to (4); its slow subsystem is substantially more complicated than (9) and depends on a number of slow gates and ionic concentrations, but further progress is possible with identification of new small parameters.

In conclusion, the revealed asymptotic structure of the Noble-1962 model can be used to build simplified "caricature" models of excitability, which can be solved analytically and/or used for more efficient numerical simulations. We believe that our results can help to understand better excitability of heart. These results can also stimulate more adequate analysis of other excitable systems, both biological, e.g. neural, and non-biological, e.g. catalytical chemical reactions or semiconductors. Cardiac and nerve excitability models have features, such as near-switch behaviour of the ionic gates, that could not be described within Tikhonov formalism. Consideration of non-Tikhonov small parameters in other systems can provide new views and reveal unexpected aspects of known phenomena.

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[24] unless $E_m < E_h$ that is; $E_m = E_h$ as in [16] is a possibility, but then the fast system does not describe dissipation of fronts[8, 15]
[25] without factor ϵ^{-1} in the second equation of (3), the result is even more bizarre: the set of equilibria of the fast subsystem is the red set of Fig. 2(a), i.e. the slow set is not a manifold but consists of pieces of different dimensionality
[26] ignoring the fast upstroke, without approximating m_∞ or h_∞, and with reference to Tikhonov's theorem which we now see is inapplicable