Instabilities in an asymptotic model of cardiac excitation

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Abstract

We outline the regions in the parameter space of a model of cardiac excitation where normal 1:1 response, alternans 2:2 response and further instabilities occur during repeated stimulation with a dynamic restitution pacing protocol. To this end we consider a version of the classical model of Purkinje fibers (Noble, J. Physiol. 160:317, 1962) simplified by a well-justified asymptotic embedding approach to a "caricature model" (Biktashev *et al.*, Bull. Math. Biol. 70:517, 2008). The caricature is amenable to analytical study but at the same time preserves the essential features of contemporary ionic models of cardiac excitation unlike models of FitzhHugh-Nagumo type or typical ad-hoc simplifications of cardiac models. We derive an explicit discrete "restitution" map which specifies the action potential duration as a function of the preceding diastolic interval. We then study the bifurcations of equilibria of this map to determine the regions the parameter space where normal response and alternans occur. We find explicit parametric representations of both the normal and the alternans equilibrium branches of the restitution map. The theoretical results are compared to direct numerical simulations.

Keywords action potential; singular perturbations; alternans; instability; restitution curve.

Contents

1 Introduction

Under the so-called *dynamic restitution pacing protocol* a (space-clammed) cardiac cell periodically receives an external stimulus at a fixed interval know as the Basic Cycle Length (BCL), until it settles into a stable periodic response [9]. A variety of periodic responses have been observed in experiments [5, 13]. For example, every stimulus may excite an action potential (AP, see section 2.3 and figure 1) and all APs may be identical (1:1 response). Under certain conditions only every second stimulus may excite an AP and all APs may be identical (2:1 response). Under different conditions every stimulus may excite an AP but even and odd APs may be different (alternans 2:2 response, see figure 1). It is commonly thought that the 1:1 response represents the healthy function of the cardiac cell while the other responses are viewed as "instabilities" of the normal response that may progressively lead to the onset of cardiac arhythmias including in tissue e.g. [2, and references within]. It has been suggested [4, 8] that these instabilities can be studied using discrete iterative maps, hereafter called *APD restitution maps*, that relate the duration of an action potential (APD) to the duration of the preceding action potential, or equivalently to the preceding diastolic interval (DI) if the BCL is kept fixed, see equation (**??**) below for an example.

With this motivation, here we derive APD restitution maps to various orders of accuracy for a "caricature Noble model" under repeated stimulation with a dynamic restitution protocol and study their equilibrium branches and bifurcations. The caricature Noble model represents an important example in the theory of cardiac electrical excitability. The caricature Noble model is a version of the classical model of Purkinje fibers [7] simplified by a well-justified asymptotic embedding approach [1, 12]. The asymptotic embedding procedure is specifically designed to preserve the generic properties of cardiac excitability so that the caricature has all of the essential features of contemporary ionic models of cardiac excitation. In contrast, other typical simplifications of cardiac models are either ad-hoc and thus suitable only for a particular application, or are modifications of FitzhHugh-Nagumo equations that are relevant to nerve tissue but do not describe cardiac tissue well. We remark in passing that the caricature Noble model has a non-Tikhonov asymptotic structure essentially different from those of the latter types of models, for detailed discussion see [1, 12]. In a recent series of works [1, 10–12], we have studied various features of the caricature Noble model, and the present paper adds a critical mass of results to the theory of this unique example.

The structure of the paper is as follows. ....

2 Mathematical formulation

We consider an idealized model of an isolated cardiac cell excited by applying a periodic external stimulus in order to study the resulting periodic responses. In this section we define the governing model equations, describe their typical behaviour under ....

2.1 The Caricature Noble model

We consider the following set of equations [1, 12],

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \frac{1}{\epsilon_1\epsilon_2} G_{Na}\left(E_{\mathrm{Na}} - E\right) H(E - E_*)\, h + \frac{1}{\epsilon_2}\Big(\tilde{g}_2(E)\, n^4 + \tilde{G}(E)\Big), \tag{1a}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \frac{1}{\epsilon_1\epsilon_2} F_h \left(H(E_\dagger - E) - h\right), \tag{1b}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = F_n(E)\left(H(E - E_\dagger) - n\right), \tag{1c}$$

where $H(\cdot)$ is the Heaviside step function and the remaining terms represent properties of ionic currents and gating variables

$$\tilde{g}_2(E) = g_{21} H(E_\dagger - E) + g_{22} H(E - E_\dagger), \qquad g_{21} = -2, \quad g_{22} = -9,$$

$$\tilde{G}(E) = \begin{cases} k_1(E_1 - E), & E \in (-\infty, E_\dagger), \\ k_2(E - E_2), & E \in [E_\dagger, E_*), \\ k_3(E_3 - E), & E \in [E_*, +\infty), \end{cases} \tag{1d}$$

$$k_1 = 3/40, \quad k_2 = 1/25, \quad k_3 = 1/10,$$

$$E_1 = -280/3, \quad E_2 = (k_1/k_2 + 1)E_\dagger - E_1 k_1/k_2 = -55, \quad E_3 = (k_2/k_3 + 1)E_* - E_2 k_2/k_3 = 1,$$

$$F_h = 1/2, \quad F_n(E) = f_n\big(r\, H(E_\dagger - E) + H(E - E_\dagger)\big), \qquad r = 1, \quad f_n = 1/270,$$

$$E_{\mathrm{Na}} = 40, \quad E_\dagger = -80, \quad E_* = -15, \quad G_{Na} = 100/3.$$

In the following we refer to equations (1) as the Caricature Noble model. It is obtained from the authentic Noble model of Purkinje fibers [7] using a set of verifiable assumptions and well defined simplifications as detailed in [1, 12]. The main features of equations (1) which make them an appropriate model system are:

(a) They reproduce exactly the asymptotic structure of the authentic Noble model [7], which is guaranteed by the embedding of the artificial small parameters $0 < \epsilon_1, \epsilon_2 \ll 1$. The authentic Noble model is the prototype of all contemporary voltage-gated cardiac models, and for this reason we believe that the asymptotic structure of (1) is rather generic in this class. Realistic voltage-gated cardiac models do not have explicit small parameters already present in them; or, rather, they have so many parameters that it is not a straightforward task which of them to use for asymptotic reduction. Hence we employ a procedure of embedding artificial small parameters, as discussed e.g. in [1, 12].

(b) Equations (1) have the simplest possible functional form consistent with property (a). Most functions in the right-hand side are replaced by constants as justified in [1, 12]. This allows analytical solutions to be obtained in closed form [1] which makes it possible to rigorously validate asymptotic reductions in this case. This is valuable from a theoretical point of view and also as an estimate for the errors introduced by asymptotic reductions in other realistic ionic models where analytical solutions are not available.

We complement equations (1) by the following initial conditions

$$E(0) = E_{\mathrm{stim}}, \quad h(0) = 1, \quad n(0) = 0. \tag{2a}$$

and apply a "pacing" condition with basic cycle length B

$$E(kB) = E_{\mathrm{stim}}, \qquad k \in \mathbb{N}. \tag{2b}$$

The significance and choice of these conditions is discussed in section 2.3 below.

2.2 Asymptotic reduction

At $\epsilon_1 = \epsilon_2 = 1$ the solutions of the caricature Noble model (1) agree closely with the solutions of the authentic Noble model [7] as demonstrated in [1]. For this reason, we regard equations (1) as a contemporary detailed ionic model. In the limits $\epsilon_1, \epsilon_2 \to 0^+$ the model simplifies to a hierarchy of asymptotically reduced systems amenable to analytical work which provide much insight into the dynamics of the full model.

Superfast-time system Consider a "super-fast" time scale $t \sim \epsilon_1\epsilon_2$, or equivalently $T \sim (\epsilon_1\epsilon_2)^{-1}$, in the limits $\epsilon_1, \epsilon_2 \to 0^+$, or in fact at a finite value of ϵ_2. The essential dynamical variables are E and h and their evolution is governed by

$$\frac{\mathrm{d}E}{\mathrm{d}T} = G_{Na}\,(E_{\mathrm{Na}} - E)\,H(E - E_*)\,h, \tag{3a}$$

$$\frac{\mathrm{d}h}{\mathrm{d}T} = H(E_\dagger - E) - h. \tag{3b}$$

This "superfast-time" subsystem is obtained from equations (1) by stretching time to $T = t/(\epsilon_1\epsilon_2)$, taking the limit $\epsilon_1 \to 0^+$ and neglecting the equation for n which decouples from the rest. This system describes the upstroke stage of the action potential.

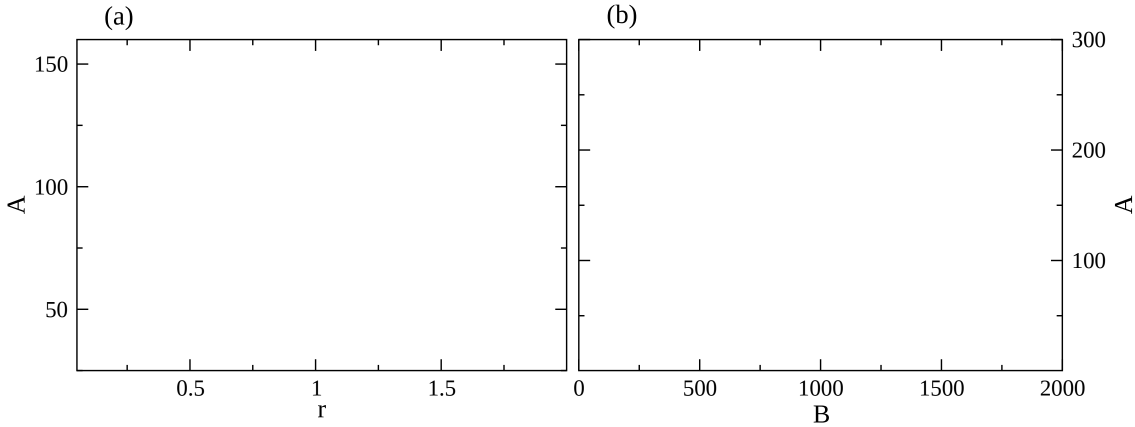

Figure 1: (color online) A Sequence of Action potentials with related notation; Typical examples of alternans 2:2 response. A_k and D_k intervals are denoted to introduce notation. a) Alternans at $\epsilon = 1$, $\epsilon_2 = 1$ b) Alternans at $\epsilon = 0$, $\epsilon_2 = 0.1$

Slow-time system Consider a “slow” time scale $t \sim \epsilon_2$, or equivalently $\tau \sim (\epsilon_2)^{-1}$, in the limit $\epsilon_1 \to 0^+$ and at a finite value of ϵ_2. The essential dynamical variables are E and n and their evolution is governed by

$$\frac{\mathrm{d}E}{\mathrm{d}\tau} = \tilde{g_2}(E)\, n^4 + \tilde{G}(E), \tag{4a}$$

$$\frac{\mathrm{d}n}{\mathrm{d}\tau} = \epsilon_2 F_n(E) \left(H(E - E_\dagger) - n\right). \tag{4b}$$

This “slow-time” subsystem is obtained from equations (1) by rescaling time to $\tau = t/\epsilon_2$, and taking the limit $\epsilon_1 \to 0$. Equation (1b) then implies $h \to H(E_\dagger - E)$. Hence the first term of equation (1a) is proportional to a product of non-overlapping Heaviside functions $H(E-E_*)H(E_\dagger-E) = 0$ which vanishes in the limit $\epsilon_1 \to 0$ despite the large factor ${\epsilon_1}^{-1}$ in front of it and we are left with system (4). This system describes the post-overshoot drop, the plateau, repolarization and recovery stages of the of the action potential. It is a Tikhonov fast-slow system in its own right.

Fast-slow-time system Consider the “fast-slow” time scale $t \sim \epsilon_2$, or equivalently $\tau \sim (\epsilon_2)^{-1}$, but in this case in the limits $\epsilon_1 \to 0^+$ and $\epsilon_2 \to 0^+$ simultaneously. The essential dynamical variable is E and its evolution is governed by

$$\frac{\mathrm{d}E}{\mathrm{d}\tau} = \tilde{g_2}(E)\, n^4 + \tilde{G}(E), \tag{5a}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = 0. \tag{5b}$$

This “fast-slow-time” subsystem is obtained directly from equations (4) by taking the additional limit $\epsilon_2 \to 0^+$. This system describes the post-overshoot drop and the repolarization stages of the of the action potential.

Slow-slow-time system Consider the “slow-slow” time scale $t \sim 1$ in the limits $\epsilon_1 \to 0^+$ and $\epsilon_2 \to 0^+$. The essential dynamical variable is n and its evolution is governed by

$$0 = \tilde{g_2}(E)\, n^4 + \tilde{G}(E), \tag{6a}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = F_n(E) \left(H(E - E_\dagger) - n\right). \tag{6b}$$

This “slow-slow-time” subsystem is obtained directly from equations (1) by taking the limit $\epsilon_1 \to 0^+$ and $\epsilon_2 \to 0^+$ simultaneously, or equivalently by rescaling back to $t = \epsilon_2\tau$ in system (4) and then taking the additional limit $\epsilon_2 \to 0^+$. This system describes the plateau and the recovery stages of the of the action potential.

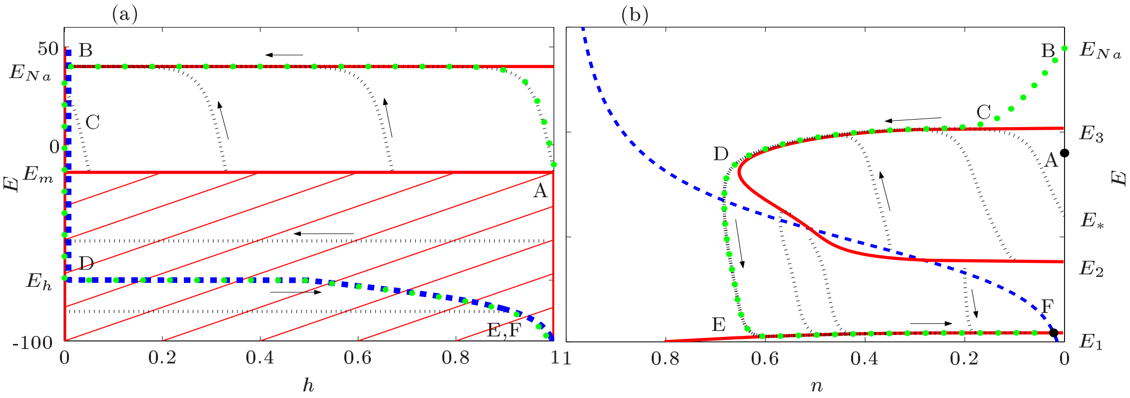

Figure 2: (color online) Phase portraits of (a) the fast system (3) and (b) the slow system (4) of the caricature Noble Model. Blue dashed lines represent vertical nulclines $\mathrm{d}h/\mathrm{d}t = 0$ in (a) and $\mathrm{d}n/\mathrm{d}t = 0$ in (b). Solid red lines and the cross-hatched region in (a) represent horizontal nulclines $\mathrm{d}E/\mathrm{d}t = 0$. Thin dotted black lines with attched arrows represent trajectories. The thick dotted green line corresponds to initial conditions (2a). The letters A-F designate feature points of the solution. Notice that the blue set in (a) is a subset of the red set, so it is a continuous set of equilibria in the fast subsystem. Replace this plot with the actual phase portraits of (3) and (4) in the same format as these plots.

2.3 Phase portraits and AP sequence

Action Potentials A solution of equations (1) that exhibits a significant deviation from the global equilibrium $(E, h, n) = (E_1, 1, 0)$ is known as an *Action Potential (AP)*; examples are shown in figure 1. We now construct a typical AP starting from initial conditions (2a) using the phase portraits of the asymptotic subsystems of (1).

Phase portrait of the supperfast-time system The phase portrait of the superfast-time system (3) is shown in figure 2(a). Equations (3) and figure 2(a) demonstrate that E_* acts as a threshold with $E_{\text{stim}} > E_*$ leading to excitation of a superfast upstroke, while if $E_{\text{stim}} < E_*$ the super-fast-time system is not activated and the AP may be generated by the slow-time system alone; see also the discussion in [1]. This superfast-time subsystem does not make a significant contribution to the duration of APs.

Phase portrait of the slow-time system The phase portrait of the slow-time system (4) is shown in figure 2(b). Equation (6a) defines the super-slow manifold,

$$n = \mathcal{N}(E) = \left(-\tilde{G}(E)/\tilde{g}_2(E)\right)^{1/4}, \tag{7a}$$

and in $t \sim 1$ equation (6b) describes the motion along this manifold. As illustrated in figure 2(b) the super-slow manifold is split into two parts by the condition $n^4 \geq 0$, namely the "diastolic" branch $E \in (-\infty, E_1]$ and the "systolic" branch for $E \in [E_2, E_3]$. The stability of the fast-slow equilibria is determined by the sign of $\partial\dot{E}/\partial E$ which coincides with the sign of $\mathcal{N}'(E) = \mathrm{d}\mathcal{N}/\mathrm{d}E$: the stable branches of the super-slow manifold correspond to regions in (n, E) plane where its graph has a negative slope, i.e. $\mathcal{N}'(E) < 0$. These are the regions of the entire diastolic branch and the upper part of the systolic branch, in the range $E \in (E_*, E_3]$. Here E_* is the root of the equation $\mathcal{N}'(E_*) = 0$, where the super-slow gating variable n takes it maximal value,

$$n_* = \left(k_2(E_2 - E_*)/g_{22}\right)^{1/4}. \tag{7b}$$

These considerations determine the excitability properties in terms of the slow-slow-time subsystem (6). As seen in figure 2(b) a trajectory starting from $E_{\text{stim}} > E_2$ will be repelled by the lower systolic branch and attracted by the upper one, thus making a relatively large excursion if,

$$n(t_0) < n_{\text{thr}} \equiv \left(k_2(E_2 - E_{\text{stim}})/g_{22}\right)^{1/4} = n_*\left((E_2 - E_{\text{stim}})/(E_2 - E_*)\right)^{1/4}, \qquad n_{\text{thr}} \in [0, n*). \quad (8)$$

This will be followed by a slow movement along the upper systolic branch, then a jump to the diastolic branch at E_* and then another slow movement along the diastolic branch approaching the global equilibrium, $(E_1, 1, 0)$, where the motion would eventually stop unless another superthreshold external stimulus is applied, in which case the entire cycle is repeated.

Periodic pacing protocol In this paper, we wish to consider the latter scenario of a repeated stimulation leading to the excitation of an AP sequence as illustrated in the examples of figure 1. In physiological experiments cells are paced by applying an external stimulus current in the form of an train of period B composed of rectangular impulses of amplitude J_{stim} and duration δ, i.e.

$$I_{\text{stim}}(t) = J_{\text{stim}}\left[\frac{1}{4}\,\mathrm{sgn}\left(\sin\frac{2\pi t}{B}\right)\mathrm{sgn}\left(\sin\frac{2\pi(t - B/2 + \delta)}{B}\right)\right].$$

In the experimental literature such forcing is often called *dynamic restitution pacing protocol* [9]. If the impulse duration is short compared to other time scales $\delta \ll \epsilon_1, \epsilon_2$, the current may be consistently incorporated in our asymptotic formulation by adding a forcing term $\delta^{-1}I_{\text{stim}}(t)$ to the RHS of equation (1a). To avoid non-essential complications to the analysis we impose the pacing condition (2b), instead.

3 APD restitution maps

Examples of AP sequences excited by the periodic pacing condition (2b) are shown in figure 1. It is desirable to describe the properties of such sequences using quantities that can be readily measured in experiments and without recourse to the complete voltage trace. It was first proposed in [8] that this can be accomplished using a map, henceforth called *APD restitution map*, that relates the durations of subsequent APs, and is usually written in one of the following variants

$$\begin{aligned} A_{k+1} &= \Phi(A_k) && (9)\\ &= \Phi(B - D_k) = F(\tilde{\mathbf{a}}, A_k) = F(\mathbf{a}, B - A_k). \end{aligned}$$

Here $\tilde{\mathbf{a}} = [\mathbf{a}, B]^T$ is a vector of model parameters and, for completeness, we define the *action potential duration (APD)*, A_k and the *diastolic interval (DI)*, D_k of the k-th AP as follows.

Definition 1 *Consider an AP sequence generated in model (1,2). Let the beginning of the k-th AP be at time kB, and let $t_{\dagger k}$ be the first subsequent moment such that $E(t_{\dagger k}) = E_\dagger$. We define*

$$A_k = t_{\dagger k} - (k-1)B, \qquad D_k = kB - t_{\dagger k}, \qquad k \in \mathbb{N}. \quad (10)$$

The role of the “cut-off” value may be assigned to any voltage value, $E_\dagger$ being a convenient choice in model (1). In direct numerical simulations and in physiological measurements 90% of the maximal voltage is often chosen. It is not obvious that the k-th AP is generated at kB as this depends on the type of response to the periodic stimulation as discussed below.

Typical responses to periodic stimulation (2b) may now be represented using map (9).

1:1 response A normal 1:1 response is one where every stimulus excites an AP and all APs are identical. It can be represented by a superthreshold, stable fixed point $\overline{A} = F(\overline{A})$ of map (9),

$$\overline{A} = F(\mathbf{a}, B - \overline{A}), \quad (11a)$$

$$\left|\left[\partial_A F(\mathbf{a}, B - A)\right]_{\overline{A}}\right| < 1, \quad (11b)$$

$$B > \overline{B}_{\text{thr}}. \quad (11c)$$

The first condition requires that $A_k = A_{k+1}$ which is true for a sequence of identical APs. The second condition asserts that this fixed point must be stable to be physically realizable. The third condition is a “threshold” condition for excitation of such an AP sequence.

2:2 response (alternans) A 2:1 response also known as *alternans* is one where every stimulus excites an AP but even and odd APs are different. Analogously, it can be represented by a suprathreshold, stable fixed point of the composed second-generation map $\Phi^2 \equiv \Phi \circ \Phi$, i.e. a 2-cycle of Φ,

$$\overline{\overline{A}} = F\big(\mathbf{a}, B - F(\mathbf{a}, B - \overline{\overline{A}})\big), \tag{12a}$$

$$\left|\Big[\partial_A F\big(\mathbf{a}, B - F(\mathbf{a}, B - \overline{\overline{A}})\big)\Big]_{\overline{\overline{A}}}\right| < 1, \tag{12b}$$

$$B > \overline{\overline{B}}_{\mathrm{thr}}. \tag{12c}$$

2:1 response A 2:1 response is one where only every second stimulus excites an AP and all APs are identical. Since every second stimulus fails to initiate an AP, the BCL between successful APs is effectively doubled to $2B$ and this case can be represented by

$$\widetilde{A} = F(\mathbf{a}, 2B - \widetilde{A}), \tag{13a}$$

$$\left|\Big[\partial_A F(\mathbf{a}, 2B - \widetilde{A})\Big]_{\widetilde{A}}\right| < 1, \tag{13b}$$

$$2B > \overline{B}_{\mathrm{thr}}. \tag{13c}$$

Further instabilities Other periodic responses can de described in a similar way.
Conditions such as (11), (12) and (13) may be used to partition the parameter space $\tilde{\mathbf{a}}$ of the APD map (15), thus providing a direct correspondence between values of model parameters and types of response. Controlling parameter values, e.g. pharmacologically, offers the hope that cells may be steered to a regime of “healthy” function.

In the rest of this section we derive APD restitution maps of various accuracy apply and these ideas to the caricature Noble model (1).

3.1 A simple APD restitution map from the slow-slow-time system

Map The simplest APD restitution map of (1) is obtained in the limits $\epsilon_1, \epsilon_2 \to 0^+$ as follows.

Lemma 1 *For an AP sequence generated in problem* (6)–(2)

$$A_k = a(n_{k-1}), \qquad a(x) \equiv {f_n}^{-1} \log\big((1-x)/(1-n_*)\big), \tag{14a}$$

$$D_k = d(n_k), \qquad d(x) \equiv (r f_n)^{-1} \log(n_*/x), \tag{14b}$$

$$n_k \equiv n(kB), \quad k \in \mathbb{N}.$$

Proof The result follows by integration of equation (6b) along the systolic branch of the super-slow manifold,

$$A_k = \int_{(k-1)B}^{(k-1)B+A_k} \mathrm{d}t = \frac{1}{f_n} \int_{n((k-1)B)}^{n_*} \frac{\mathrm{d}n}{1-n} = -\frac{1}{f_n}\Big[\log(1-n)\Big]_{n((k-1)B)}^{n_*} = \frac{1}{f_n} \log\left(\frac{1-n_{k-1}}{1-n_*}\right),$$

$$D_k = \int_{(k-1)B+A_k}^{kB} \mathrm{d}t = B - A_k = -\frac{1}{r f_n} \int_{n_*}^{n(kB)} \frac{\mathrm{d}n}{n} = -\frac{1}{r f_n}\Big[\log(n)\Big]_{n_*}^{n(kB)} = \frac{1}{r f_n} \log\left(\frac{n_*}{n_k}\right).$$

The crucial observation in deriving expressions (14) is that in this limit the end of any plateau phase coincides with the beginning of the next recovery stage when the slow gating variable n takes its maximal value (7b) on the systolic branch of the super-slow manifold (7a), e.g. $n((k-1)B + A_k) = n(kB + A_{k+1}) = n_*$ for any $k \in \mathbb{N}$. This is well illustrated by the phase portrait in figure 2(b). ■

Proposition 1 *An APD restitution map relating* A_{k+1} *to* A_k *is given by*

$$\begin{aligned} A_{k+1} &= \Phi(A_k), \\ \Phi(A) = F(\tilde{\mathbf{a}}, A) = F(\mathbf{a}, B - A) &= \frac{1}{f_n} \log\left(\frac{1 - n_* \exp\big(-r f_n\,(B - A)\big)}{1 - n_*}\right), \end{aligned} \tag{15}$$

where $\tilde{\mathbf{a}} = [\mathbf{a}, B]^T = [r, f_n, n_*, B]^T$ *is a vector of parameters.*

Proof The result is obtained by eliminating n_k between expression (14a) written for A_{k+1} and expression (14b) written for $D_k = B - A_k$. ∎
Lemma 1 gives a parametric representation of the APD restitution map and the Proposition gives an equivalent explicit representation.

Fixed points We can now proceed to find the fixed points of Φ and Φ^2 corresponding the 1:1- and 2:2-responses discussed above as follows.

Proposition 2 *The equation* $\overline{A} = \Phi(\overline{A})$ *has a unique solution branch given in parametric form by*

$$\overline{A} = a(\overline{n}), \qquad \overline{D} = d(\overline{n}), \tag{16}$$

with a parameter $\overline{n} \in [0, n_{\text{thr}}]$.

Proof Rather than solving the transcendental equation $\overline{A} = \Phi(\overline{A})$ directly, we use the equivalent parametric representation of Lemma 1. In a 1:1 response $A_k = A_{k+1}$ and $D_k = D_{k+1}$, equivalent by (14) to $a(n_{k-1}) = a(n_k)$ and $d(n_k) = d(n_{k+1})$, respectively. By the bijectivity of the logarithmic function, solutions are $n_{k-1} = n_k \equiv \overline{n}$ and $n_k = n_{k+1} \equiv \overline{n}$, respectively. It follows that in a 1:1 response all APs start from identical values of the n gate, $\overline{n}$, thus expressions (16) hold. Obviously, the parameter $\overline{n}$ is a gating variable hence $\overline{n}$ must be in the range $[0, 1]$. Furthermore, no AP can be excited above n_{thr} so $\overline{n} \in [0, n_{\text{thr}}]$. ∎

Proposition 3 *The equation* $\overline{\overline{A}} = \Phi \circ \Phi(\overline{\overline{A}})$ *has three solution branches: the first one is identical to* (16)*, and the other two are given in parametric form by*

$$\overline{\overline{A}}_{\text{even}} = a(\alpha n_b), \qquad \overline{\overline{D}}_{\text{even}} = d(n_b), \tag{17a}$$

$$\overline{\overline{A}}_{\text{odd}} = a(n_b), \qquad \overline{\overline{D}}_{\text{odd}} = d(\alpha n_b), \tag{17b}$$

$$n_b = \left(\alpha^{1/r} - 1\right) / \left(\alpha^{(r+1)/r} - 1\right), \tag{17c}$$

with a parameter $\alpha \in [1, \infty)$.

Proof Again, rather than solving the transcendental equation $\overline{\overline{A}} = \Phi \circ \Phi(\overline{\overline{A}})$ directly, we use the equivalent parametric representation of Lemma 1. In a 2:2 response, $A_k = A_{k+2}$ and $A_{k+1} = A_{k+3}$ as well as $D_k = D_{k+2}$ and $D_{k+1} = D_{k+3}$. Applying expressions (14), we find $n_{k-1} = n_{k+1} \equiv n_a$ and $n_k = n_{k+2} \equiv n_b$. Since the BCL, B is fixed we also require

$$B = A_k + D_k = A_{k+1} + D_{k+1} \Leftrightarrow a(n_a) + d(n_b) = a(n_b) + d(n_a), \tag{18}$$

and explicitly $\log\big((1 - n_a)/(1 - n_b)\big) = r^{-1} \log\big(n_b/n_a\big)$. By the bijectivity of the logarithm and after the change of variable $n_a = \alpha n_b$ this equation reduces to $\alpha(1 - \alpha n_b)^r = (1 - n_b)^r$ with exact solution (17). Equations (17a) and (17b) follow immediately. To establish the range of α note that (18) is invariant with respect to exchanging n_a and n_b, so without loss of generality we may consider only the case $n_a \geq n_b$, and since n_a and n_b are positive it follows that $n_a/n_b = \alpha \in [1, \infty)$.

Finally, a fixed point of Φ is also a fixed point of $\Phi \circ \Phi$, hence (16) is a third solution branch of $\overline{\overline{A}} = \Phi \circ \Phi(\overline{\overline{A}})$.

We remark that solutions (16) and (17) can, of course, be verified by back-substitution into $\overline{A} = \Phi(\overline{A})$ and $\overline{\overline{A}} = \Phi \circ \Phi(\overline{\overline{A}})$, respectively. ∎

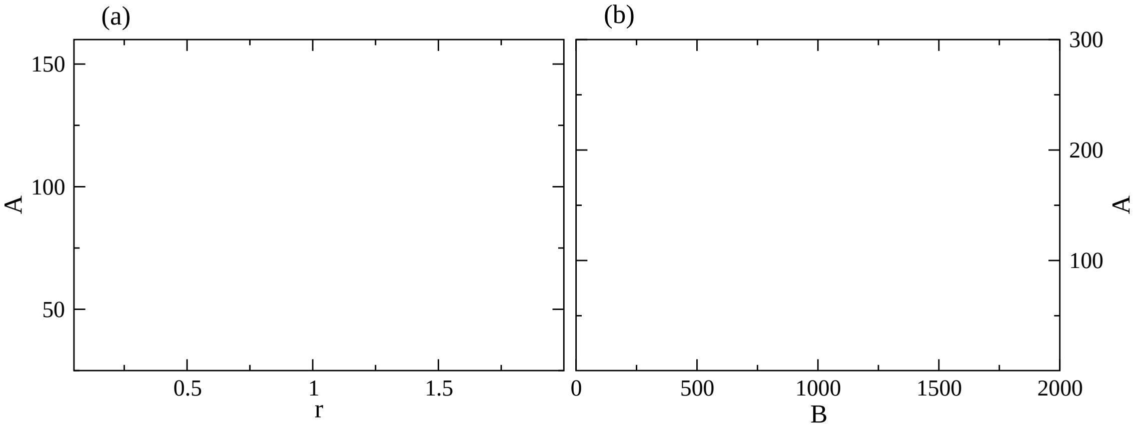

Figure 3: (color online) Plot of solutions (16) and (17) illustrating (a) supercritical; and (b) subcritical flip bifurcation at parameter values ...

Figure 3 illustrates equilibria (17).

Perturbation solution of $\overline{A} = \Phi(\overline{A})$ We remark in passing that it is also possible to find an explicit approximation to the solution of $\overline{A} = \Phi(\overline{A})$ by using a regular perturbation approach. First, note that equation (11a) is exactly solvable in the case $r = 1$. Expand the unknown $\overline{A}$ in a Taylor series near $r = 1$,

$$\overline{A} = \sum_{m=0}^{\infty} (1-r)^m \mathcal{A}_m.$$

Upon substitution of the expansion in equation (11a), collecting powers of the small quantity $(1-r)$, and solving for the expansion coefficients $\mathcal{A}_m$, we find, e.g. to order $O\big((1-r)^2\big)$

$$\overline{A} = B - \frac{1}{f_n}\log(\gamma)\left(1 + \frac{n_*}{\gamma}(1-r)\right) + O\big((1-r)^2\big), \tag{19}$$
$$\gamma = \big(1 - \exp(Bf_n)\big)n_* + \exp(Bf_n).$$

Figure figure 4 shows comparisons between the exact solution (16) and the perturbation solutions with variation of r and the order p of the approximation $O\big((1-r)^p\big)$. Remarkably, the perturbation solution is a good approximation far beyond the asymptotic limit $r \to 1$.

Stability and bifurcations of equilibria We now impose conditions (11b) and (12b) to establish the stability properties of 1:1- and 2:2-responses.

Proposition 4 *The equilibrium* (16) *of the APD restitution map* (15) *loses stability in a flip (period-doubling) bifurcation at*

$$n_{\mathrm{bif}} = 1/(1+r) \tag{20a}$$

or in terms of the BCL, alternatively at

$$B_{\mathrm{bif}} = \frac{1}{f_n}\log\left(\frac{r\, {n_*}^{1/r}(1+r)^{(1-r)/r}}{(1-n_*)}\right). \tag{20b}$$

Proof On substitution of (16) in (11b), the latter yields,

$$\overline{n} = n_{\mathrm{bif}} = 1/(1+r) \in (0,1) \quad \text{if} \quad \Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = -1$$

or

$$\overline{n} = n_{\mathrm{bif}} = 1/(1-r) \in (-\infty,0) \cup (1,\infty) \quad \text{if} \quad \Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = 1.$$

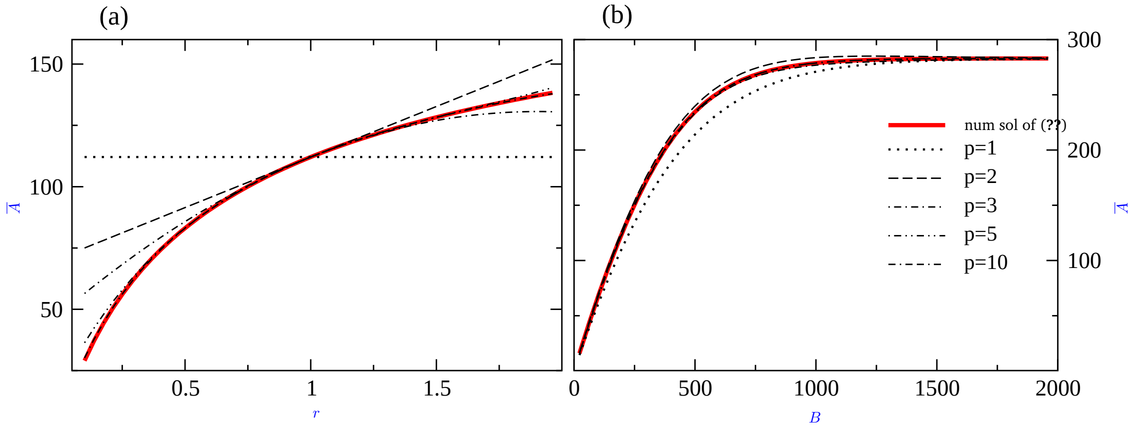

Figure 4: (color online) Comparison between direct numerical and perturbation solutions of equation (11a). (a) as a function of r for defalut balues of the parameters and $B = 200$. (b) as a function of B for $r = 1.4$ and default values of the other parameters. The defalut parameter values are listed in (1). The order of accuracy $O\big((1-r)^p\big)$ and the type of lines is denoted in the legend which is common to (a) and (b). The line with $p = 1$ corresponds to expression (19).

The second solution must be rejected since it is outside the interval $[0, 1]$ where gating variables are defined. The first solution is valid and since it is obtained at

$$\Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = -1,$$

stability is lost in a flip bifurcation of the APD restitution map (15), see e.g. [3].

Evaluating (16) at $n_{\text{bif}} = 1/(1-r)$ we then find

$$A_{\text{bif}} = a(n_{\text{bif}}) = {f_n}^{-1} \log\big((1/(1+r) - 1)/(n_* - 1)\big), \tag{21a}$$

$$B_{\text{bif}} = a(n_{\text{bif}}) + d(n_{\text{bif}}) = \frac{1}{f_n} \log\left(\frac{r{n_*}^{1/r}(1+r)^{(1-r)/r}}{(1-n_*)}\right). \tag{21b}$$

■

Proposition 5 *The equilibria* (17) *of the second-generation map* $\Phi \circ \Phi$ *bifurcate from the equilibrium* (16) *of the APD restitution map* (15) *at* (20) *and lose their stability at* $r = 1$.

Proof To confirm that equilibria (17) bifurcate from equilibrium (16) it is enough to evaluate (17c) at $\alpha = 1$, the value where (17) first emerges. Since

$$n_b(\alpha = 1) = 1/(1+r) = n_{\text{bif}},$$

(16) and (17), indeed intersect at n_{bif}.

Rather than using (12b) directly, we recall that a flip bifurcation for Φ is a pitchfork bifurcation for the second generation map $\Phi \circ \Phi$, see e.g. [3]. A pitchfork bifurcation (and the corresponding flip bifurcation) can be either subcritical if $[\partial^3_A \Phi \circ \Phi]_{A_{\text{bif}}} < 0$ or supercritical if $[\partial^3_A \Phi \circ \Phi]_{A_{\text{bif}}} > 0$. Substituting (21) into $[\partial^3_A \Phi \circ \Phi]_{A_{\text{bif}}} = 0$ and solving this equation for r we find that $r = 1$ is the boundary between the sub- and the supercritical cases. The subcritical case is characterised by one stable branch on one side and no branches on the other side of the bifurcation point. The superctitical case is characterised by one stable branch on one side and two stable and one unstable branch on the other side of the bifurcation point. ■

Figure 3 illustrates further the stability of equilibria.

Thresholds We now impose the threshold conditions (11c) and (12c).

Proposition 6 *The threshold value of BCL for excitation of a 1:1 response is*

$$\begin{aligned}\overline{A}_{\text{thr}} &= a(n_{\text{thr}}) = {f_n}^{-1} \log\big((1-n_{\text{thr}})/(1-n_*)\big),\\ \overline{D}_{\text{thr}} &= d(n_{\text{thr}}) = (rf_n)^{-1}\log(n_*/n_{\text{thr}}),\\ \overline{B}_{\text{thr}} &= A_{\text{thr}} + D_{\text{thr}}.\end{aligned} \tag{22}$$

Proof Recall that the k-th AP can be only be excited by a super-threshold stimulus $E_{\text{stim}} > E_2$ for which $n_{k-1} < n_{\text{thr}}$ where n_{thr} is given by (8). The result then follows by evaluation of (16) at $\overline{n} = n_{\text{thr}}$. ■

Proposition 7 *The threshold value of BCL for excitation of a 2:2 response is*

$$\overline{\overline{B}}_{\text{thr}} = a\big(n_{\text{thr}}\big) + d\big(n_{\text{thr}}\alpha(n_{\text{thr}})\big) = a\big(n_{\text{thr}}\alpha(n_{\text{thr}})\big) + d\big(n_{\text{thr}}\big), \tag{23a}$$

where $\alpha(n_{\text{thr}})$ is the solution of the transcendental equation

$$n_{\text{thr}} = \left(\alpha^{1/r} - 1\right) / \left(\alpha^{(r+1)/r} - 1\right). \tag{23b}$$

Proof Again, excitation of the k-th AP requires a super-threshold stimulus $E_{\text{stim}} > E_2$ for which $n_{k-1} < n_{\text{thr}}$ where n_{thr} is given by (8). The result then follows by evaluation of (17) at $\overline{n} = n_{\text{thr}}$. Clearly, in this case n_{thr} needs to be used a parameter and equation (17c) must be inverted. ■
Perturbation solution of equation (23b) Because we failed to find an exact solution of equation (23b) for α, we present here an approximation obtained by regular perturbations about $r = 1$. First, it is useful to look closely at the exact solutions at $r = 1$. We find two roots, namely $\alpha_1 = 1$ and $\alpha_2 = (1-n_{\text{thr}})/n_{\text{thr}}$. While the first solution α_1 is constant, and the particular constant is the value of the left end of the interval of definition of α, the other solution α_2 varies as a function of n_{thr} and we find that $\alpha_1 = \alpha_2$ exactly at $n_{\text{thr}} = [1/(1+r)]_{r=1} = n_{\text{bif}}$. This implies that α_1 and α_2 are not two different solutions at the same value of n_{thr} but, in fact, two branches bifurcating from each other at $n_{\text{thr}} = n_{\text{bif}}$. This could have been expected as the 2:2 solution does not exist below n_{bif}. So we now only need to find α_2. We expand the unknown α_2 in a Taylor series near $r = 1$,

$$\alpha_2 = \sum_{m=0}^{\infty} (1-r)^m \beta_m.$$

Upon substitution of the expansion in equation (23b), collecting powers of the small quantity $(1-r)$, and solving for the expansion coefficients β_m, we find, e.g. to order $O\big((1-r)^2\big)$

$$\alpha(n_{\text{thr}}) = \begin{cases} 1, & \text{if } n_{\text{thr}} \ge n_{\text{bif}} = 1/(1+r),\\ \dfrac{1-n_{\text{thr}}}{n_{\text{thr}}} - (1-r)\dfrac{1-n_{\text{thr}}}{1-2n_{\text{thr}}}\log\left(\dfrac{1-n_{\text{thr}}}{n_{\text{thr}}}\right) & \\ \qquad\qquad\qquad\qquad + O\big((1-r)^2\big), & \text{if } n_{\text{thr}} < n_{\text{bif}} = 1/(1+r), \end{cases} \tag{24}$$

We remark that the threshold for excitation of a 2:2 AP sequence was determined incorrectly in [6], where it was claimed that 2:2 sequence exists until the threshold condition (22) for a 1:1 response is violated.

==

Synthesis We have proven the following Theorem

Theorem 1 *The bifurcation set of problem* (6)–(2) *where transitions between the 1:1-response* (16), *2:2-response* (17) *and 2:1-response occurs and where stability is gained or lost consists of surfaces $\overline{B}_{\text{thr}}$ given by* (22), *$\overline{\overline{B}}_{\text{thr}}$ given by* (23), *B_{bif} given by* (20b), *and $r = 1$ (see Figure 5).*

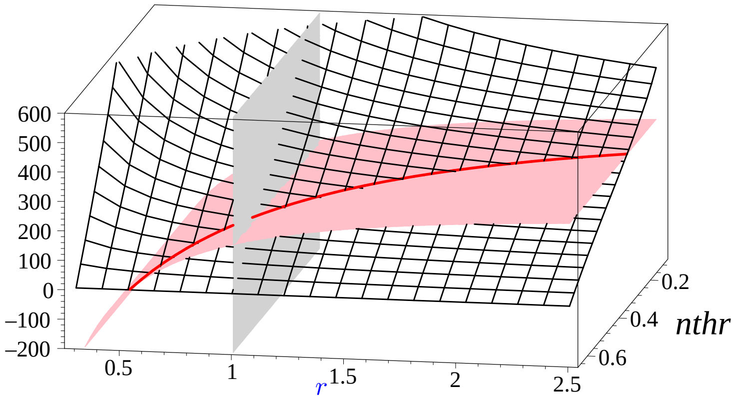

Figure 5: Some surfaces
`/rswork1/02_Papers_Proposals/052AlternansInCaricNobel/01CodesCalcs/02Map01-2014-04-23/10regions.M`

Theorem 2 *(Stability and bifurcations of equilibria) This following formulation is awkward. Try to formulate the result as a description of figure 5. The APD restitution map* (15) *exhibits a flip (period-doubling) bifurcation from equilibrium* (16) *to equilibria* (17) *at* $n_{\rm thr} = 1/(1+r)$ *which is subcritical for* $r < 1$*, and supercritical for* $r > 1$*. More precisely, USE 3D FIGURE map* (15) *has*

1. *a unique stable equilibrium branch in the region*

$$\begin{aligned}\mathcal{R}_{1:1} =& \Big\{(r, n_{\rm thr}, B) \;\big|\; r > 0,\ n_{\rm thr} \in [0, 1/(1+r)),\ B > B_{\rm thr}\Big\}\\ &\cup \Big\{(r, n_{\rm thr}, B) \;\big|\; r > 0,\ n_{\rm thr} \in [0, n_*),\ B > B_{\rm bif}\Big\}.\end{aligned} \tag{25a}$$

2. *an unstable 2-cycle in the region*

$$\mathcal{R}^u_{2:2} = \Big\{(r, n_{\rm thr}, B) \;\big|\; r \in ((1-n_*)/n_*, 1),\ n_{\rm thr} \in (1/(1+r), n_*),\ B \in (B_{\rm thr}, B_{\rm bif})\Big\}, \tag{25b}$$

   and a stable 2-cycle in the region

$$\mathcal{R}^s_{2:2} = \Big\{(r, n_{\rm thr}, B) \;\big|\; r \in (1, \infty),\ n_{\rm thr} \in (1/(1+r), n_*),\ B \in (B_{\rm thr}, B_{\rm bif})\Big\}, \tag{25c}$$

   where

$$B_{\rm bif} \equiv \frac{1}{f_n} \log\left(\frac{r\, {n_*}^{1/r}(1+r)^{(1-r)/r}}{(1-n_*)}\right), \tag{25d}$$

3. *a stable 2:1 response in the region*

$$\mathcal{R}_{2:1} = U/(\mathcal{R}_{1:1} \cup \mathcal{R}^s_{2:2}), \tag{25e}$$

   where U *is the universe of possible values of* $r, n_{\rm thr}, B$*.*

Proof

Use parametric representation.. 21parsol.M

The conditions for a stable equilibrium, i.e. $A_k = A_{k+1} = \overline{A}$, of (**??**) are

$$\overline{A} = F(\mathbf{a}, \overline{A}), \tag{26a}$$

$$\Big|\Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}}\Big| < 1. \tag{26b}$$

The *bifurcation set*, i.e. the set of values of A and $\mathbf{a}$ where bifurcation occurs, is found by replacing the inequality with an equal sign. A parametric solution of (26a) is given by

$$\overline{A} = {f_n}^{-1} \log\big((\overline{n} - 1)/(n_* - 1)\big), \quad \overline{D} = (r f_n)^{-1} \log(n_*/\overline{n}), \quad B = \overline{A} + \overline{D}, \tag{27}$$

where the role of a parameter is played by $\overline{n}$, the value of the primary dynamical variable of the slow-slow-time system at the fixed point. This solution is obtained from (**??**) and (14b) noting that at a fixed point and for all sufficiently large values of k, $D_k = D_{k+1} = \overline{D}$ and $B = \overline{A} + \overline{D}$, as well, so one can introduce $\overline{n} = n(kB)$. Solution (27) can be verified by backsubstitution into (26a). This solution is obviously unique.

On substitution of (27) in (26b), the latter yields,

$$\overline{n} = n_{\text{bif}} = 1/(1+r) \in (0,1) \quad \text{if} \quad \Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = -1$$

or

$$\overline{n} = n_{\text{bif}} = 1/(1-r) \in (-\infty,0) \cup (1,\infty) \quad \text{if} \quad \Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = 1$$

The second solution is rejected since it is outside the interval $[0,1]$ where gating variables are defined. Note that the first valid solution requires

$$\Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = -1$$

so stability is lost in a FLIP bifurcation of the APD restitution map (**??**), see e.g. [3].

Finally, for the equilibrium branch to remain stable until it ceases to exist, we must have $A_{\text{bif}} < A_{\text{thr}}$ and comparing (27) and (**??**) we find

$$n_{\text{thr}} < n_{\text{bif}} = \frac{1}{1+r}.$$

Conversely, if the reverse inequality holds, then the equilibrium solution (27) loses stability before it ceases to exist so there are a range of values of B such that (21b) holds true.

A flip bifurcation for Φ is a pitchfork bifurcation for the second generation map $\Phi \circ \Phi$, see e.g. [3]. A pitchfork bifurcation (and the corresponding flip bifurcation) can be either subcritical if $[\partial^3_A \Phi^2]_{A_{\text{bif}}} < 0$ or supercritical if $[\partial^3_A \Phi^2]_{A_{\text{bif}}} > 0$. Solving

$$[\partial^3_A \Phi^2]_{A_{\text{bif}}} = 0,$$

$$A_{\text{bif}} = {f_n}^{-1} \log\big((1/(1+r) - 1)/(n_* - 1)\big), \qquad B_{\text{bif}} \equiv \frac{1}{f_n} \log\left(\frac{r{n_*}^{1/r}(1+r)^{(1-r)/r}}{(1-n_*)}\right),$$

we find that

$$r = 1$$

is the boundary between $\mathcal{R}^u_{2:2}$ and $\mathcal{R}^s_{2:2}$.

Explicit parametric solution for the 2 stable branches of the pitchfork bif- yes! see “parmsol.M”

■

Strength-duration curve Derive formula. Plot graph. Comment on fixing n_{thr}

A similar procedure is applied in [6] to derive an APD map in an unrelated simplified model.

Proposition 8

$$n_b(\alpha = 1) = 1/(1+r),$$

where n_b *is defined in* (17).

Remark 1 *Consider a dynamic stimulation protocol with stimuli such that* $E_{\text{stim}} > E_2$ *and BCL sufficiently small so that for the* k*-th AP* $n(kB) > n_{\text{thr}}$*. Then stimulus number* k *fails to excite an AP. The* n *gating variable continues to recover until this condition is ultimately satisfied. The next stimulus will then excite an AP - 2:1 response. The equilibrium is ... Basis of attraction too narrow.*

This proves the following result about the regions in the parameter space where various responses occur.

Theorem 3 *(Parameter regimes) Formulate results in terms of figure* 5*.*

3.2 Comparison with DNS

===========Below is some text that I may discard =============

4 An APD restitution map derived from the exact solution (of the slow-time system)

The caricature Noble model (1) allows an closed-form analytical solution derived in [1] and that can be used to derive an exact APD restitution map. We remark that an exact solution of the model discussed in [6] is not known.

The main question is how the fast subsystem affects the APD map. Probably via the threshold properties.

Exact solution of the full caricature

Exact solution of the slow-time system

5 Bifurcations in the simple APD restitution map

5.1 Bifurcation sets

Conditions for instability of the 1:1 response are

$$\Phi(A) = A,$$
$$|\Phi'(A)| = 1, B = B_{\mathrm{thr}}.$$

Solution of this set of equations gives

$$F21 = -\frac{F22\ (n_{\mathrm{thr}} - 1)}{n_{\mathrm{thr}}}.$$

This can be written as

$$n_{\mathrm{thr}} = \frac{1}{1+r},$$

where $r = F21/F22$. This is the same expression as in Mitchell [6].

5.2 2:2 alternans responses

Conditions for sub and supercritical pitchfork bifurcations In addition to condition (5.1), the boundary between sub- and supercritical pitchfork bifurcation is

$$\Phi'''(A) = 0.$$

Solution of this set of equations gives the line

$$F22 = F22 \quad (\text{i.e.} \quad r = 1), \qquad n_{\mathrm{thr}} \in [0, 1/2),$$

This is the same result as in Mitchell [6], as well.

6 Interpretation

We should address the following questions.

1. How accurate are results of the bifurcation analysis of the simple map. I.e., do we see alternans when $F22/F22 > 1$ etc ..?
2. Derive conditions as a function of B.

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7 More

- CRN-3? APD map with memory?
- Ensemble Karman Filter for APs. Idea. Use a simple model e.g. the caricature and fit its parameters using Toni's data. Then try to do analytical work.

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Proposition 9 *The APD restitution map* (15) *exhibits a flip (period-doubling) bifurcation from equilibrium* (16) *to equilibria* (17) *at* $n_{\rm bif} = 1/(1+r)$ *which is subcritical for* $r < 1$*, and supercritical for* $r > 1$*. Corollary*

$$B_{\rm bif} \equiv \frac{1}{f_n} \log\left(\frac{r\, {n_*}^{1/r}(1+r)^{(1-r)/r}}{(1-n_*)}\right), \tag{28}$$

Proof On substitution of (16) in (11b), the latter yields,

$$\overline{n} = n_{\rm bif} = 1/(1+r) \in (0,1) \quad \text{if} \quad \Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = -1$$

or

$$\overline{n} = n_{\rm bif} = 1/(1-r) \in (-\infty, 0) \cup (1, \infty) \quad \text{if} \quad \Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = 1.$$

The second solution must rejected since it is outside the interval $[0,1]$ where gating variables are defined. The first solution is valid and since it is obtained at

$$\Big[\partial_A F(\mathbf{a}, A)\Big]_{\overline{A}} = -1,$$

stability is lost in a FLIP bifurcation of the APD restitution map (**??**), see e.g. [3].

Next, for the equilibrium branch to remain stable until it ceases to exist, we must have $A_{\rm bif} < A_{\rm thr}$ and comparing (27) and (**??**) we find

$$n_{\rm thr} < n_{\rm bif} = \frac{1}{1+r}.$$

Conversely, if the reverse inequality holds, then the equilibrium solution (27) loses stability before it ceases to exist so there are a range of values of B such that (21b) holds true.

A flip bifurcation for Φ is a pitchfork bifurcation for the second generation map $\Phi \circ \Phi$, see e.g. [3]. A pitchfork bifurcation (and the corresponding flip bifurcation) can be either subcritical if $[\partial_A^3 \Phi^2]_{A_{\rm bif}} < 0$ or supercritical if $[\partial_A^3 \Phi^2]_{A_{\rm bif}} > 0$. Solving

$$[\partial_A^3 \Phi^2]_{A_{\rm bif}} = 0,$$

$$A_{\rm bif} = {f_n}^{-1} \log\big((1/(1+r) - 1)/(n_* - 1)\big), \qquad B_{\rm bif} \equiv \frac{1}{f_n} \log\left(\frac{r{n_*}^{1/r}(1+r)^{(1-r)/r}}{(1-n_*)}\right),$$

we find that

$$r = 1$$

is the boundary between $\mathcal{R}^u_{2:2}$ and $\mathcal{R}^s_{2:2}$.

Finally, in order to confirm that solution (16) bifurcates to (17) and not something else it is enough to evaluate (17c) at $\alpha = 1$, the value where (17) first emerges. Since

$$n_b(\alpha = 1) = 1/(1+r) = n_{\rm bif},$$

is precisely what we need.

Explicit parametric solution for the 2 stable branches of the pitchfork bif- yes! see “parmsol.M” ■