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Peter Donnell, Stephen A. Baigent, Murad Banaji. Monotone dynamics of two cells dynamically coupled by a voltage-dependent gap junction. *Journal of Theoretical Biology*, 2009, 261 (1), pp.120. 10.1016/j.jtbi.2009.07.012 . hal-00554637

**HAL Id: hal-00554637**

**<https://hal.science/hal-00554637>**

Submitted on 11 Jan 2011

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# Author's Accepted Manuscript

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PII: S0022-5193(09)00325-7  
DOI: doi:10.1016/j.jtbi.2009.07.012  
Reference: YJTBI5630

To appear in: *Journal of Theoretical Biology*

Received date: 7 May 2009  
Revised date: 7 July 2009  
Accepted date: 8 July 2009

Cite this article as: Peter Donnell, Stephen A. Baigent and Murad Banaji, Monotone dynamics of two cells dynamically coupled by a voltage-dependent gap junction, *Journal of Theoretical Biology*, doi:[10.1016/j.jtbi.2009.07.012](https://doi.org/10.1016/j.jtbi.2009.07.012)

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# Monotone dynamics of two cells dynamically coupled by a voltage-dependent gap junction

Peter Donnell\*, Stephen A. Baigent†, Murad Banaji‡

July 7, 2009

## Abstract

We introduce and analyse a simple model for two non-excitable cells that are dynamically coupled by a gap junction, a plaque of aqueous channels that electrically couple the cells. The gap junction channels have a low and high conductance state, and the transition rates between these states are voltage-dependent. We show that the number and stability of steady states of the system has a simple relationship with the determinant of the Jacobian matrix. For the case that channel opening rates decrease with increasing trans-junctional voltage, and closing rates increase with increasing trans-junctional voltage, we show that the system is monotone, with tridiagonal Jacobian matrix, and hence every initial condition evolves to a steady state, but that there may be multiple steady states.

**Keywords:** Dynamic coupling, monotone dynamics, gap junction.

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# 1 Introduction

A number of mathematical models in cardiophysiology and neuroscience are emerging which describe how cells are electrically coupled into networks via gap junctions (Cai et al., 1984, Henriquez et al., 2001; Ermentrout, 2006; Coombes and Zachariou, 2009; Lewis and Rinzel, 2000), plaques of ion channels that provide a direct passage for ions to move between cells. The passage of ions across the junction is diffusive, and depends linearly on the voltage difference across the junction. The majority of these models look at the collective dynamics of electrically excitable cells – which oscillate when isolated – and the typical questions are: How does the system behaviour change as the gap junction coupling strength increases? Do the cells continue to oscillate, do they synchronise, do spatial patterns emerge in large networks?

With the exception of Henriquez et al. (2001), these models assume that the conductance of the gap junction is fixed, but in reality it is dynamic: each channel can reside in multiple states and noise causes the channels to constantly switch between different conductance states. The energy barrier between these conductance states typically depends on the trans-junctional voltage (Harris et al., 1981), and hence the rate of transition between states is voltage-dependent.

There is a small literature on models of coupled non-excitable cells where the gap junction is dynamic. In Baigent et al (1997) and Baigent (2003) the authors look at a simple model for two cells linked by a junction with channels that could reside in one of three states. This model, being low dimensional, can be partially analysed. At the other end of the scale, is the model of action potential propagation in a line of cells (Henriquez et al., 2001) that incorporates the dynamic gap junction model in Vogel and Weingart (1998). The model of Henriquez et al. (2001), however, is complex and presents a major challenge analytically. Even for the simple model for two non-excitable cells coupled by a gap junction described in Baigent et al. (1997), a complete mathematical analysis of the model dynamics has not

yet been achieved, although the steady states and their stability have been classified. In the absence of excitability in the cells, it is intuitive that when diffusively coupled, the cell pair should relax to a steady state, but a rigorous proof ruling out periodic orbits in the model and any small perturbation of it is so far unavailable.

Here we provide an analytically tractable model of two cells electrically coupled via a *dynamic* gap junction. As in Baigent et al. (1997) we consider non-excitable cells. The model presented is a simplification of that in Baigent et al. (1997), although its steady state properties are largely the same. The key difference is that we replace the two-gate model of Baigent et al. (1997) (see also Vogel and Weingart (1998), Chen-Izu, Y. et al. (2001)) with a simpler one-gate model with two conductance states, a low-conductance “closed” state, and a high-conductance “open” state. The transition rates between the two states are voltage-dependent, as in Baigent et al. (1997). Thus the new 2-state model for the gap junction, while simpler, still retains some of the dynamical features of the 3-state model. The benefit in the simpler model is that there is just one variable for the junction state, taken here to be the fraction of closed channels.

In essence, the model discussed here consists of a thermodynamic part – the model for the ionic current flow, which is simply an RC circuit – and a ‘gating’ part which models the dynamics of the gap junction. If the channel were static, the electrical energy in the circuit would provide a suitable Lyapunov function, from which it would follow that all initial states end up at a (not necessarily unique) steady state. However, when the ion channel has dynamics that depend on the voltage across it, there is no obvious Lyapunov function. For such a model, the typical form is

$$\begin{aligned} C\dot{\varphi} &= -\frac{\partial\Phi(\varphi, x)}{\partial\varphi} \\ \dot{x} &= \Psi(\varphi, x), \end{aligned} \tag{1}$$

where  $\varphi$  is a vector of potentials,  $x$  a coupling strength variable (typically the fraction of channels

in a given state of conductance),  $C$  is capacitance, and  $\Phi$  the dissipation function. When  $\Psi \equiv 0$  we obtain gradient dynamics, but when the coupling is allowed to vary dynamically  $\Psi \neq 0$ , the dynamics is potentially more complex. It is worth noting that the class of systems (1) appears often in electrophysiology models. For example, the Hodgkin-Huxley model for the nerve axon (Hodgkin and Huxley, 1952) can be written in the form of (1). The essential difference is that in the Hodgkin-Huxley model the gating dynamics occurs in the cell membranes, and is central to cell excitability, whereas here the gating dynamics occurs in the junction providing diffusive coupling between cells.

## 2 Biological background

Gap junctions are plaques of specialised ion channels that electrically and metabolically couple adjacent cells (see Bennett and Verselis (1992) for an introduction to the biophysics of gap junctions). These junctions are found connecting a very wide variety of cells, and among their many roles they

- electrically couple cardiac myocytes in the heart facilitating action potential propagation (Henriquez et al., 2001);
- provide coupling between various cells in the nervous system (Coombes, 2008; Coombes and Zachariou, 2009);
- provide a nutrient supply route to cells in the lens, where transparency is needed and vessel-based supply would block light (Vaghefi et al., 2008);
- enable synchronisation of beating pancreatic beta cells (Smolen et al., 1993).

(Here we have elected to provide references to mathematical models, rather than detailed biological references.) Each gap junction channel consists of two hemi-channels, one from each cell membrane,

that dock together to form a continuous aqueous pore that links the cell cytoplasm directly. In turn each hemi-channel is a barrel of 6 proteins known as *connexons*. In most cases the hemi-channels provided by each cell membrane are identical, since they are made from the same connexons, and the junction formed is *homotypic*. In some cases, however, such as when membranes of different cell types become close, *heterotypic* junctions are formed where the connexons in each hemi-channel are not the same.

The aqueous channels in the junction are large enough to allow the diffusive passage of ions and small metabolites up to 100 kDa. However the permeability of the channels depends on the average configuration of the stochastically changing proteins lining the channels. It is widely documented that the transition rates between the various permeability states of the channels depend on the voltage difference across the channel (see, e.g. Harris et al. (1981)). A standard model for the gap junction is thus a Markov chain with a voltage dependent transition matrix.

As might be expected, whereas homotypic junctions function symmetrically, heterotypic junctions may show asymmetries, such as rectification (Vogel and Weingart, 1998; Chen-Izu, Y. et al., 2001).

### 3 Model formulation

In Baigent et al. (1997) a simple model was developed to describe the flow of ions between two cells connected by a gap junction. This first model treated each gap junction channel as having three gating configurations, two of low conductance and one of high conductance. We showed that the voltage-dependence of the gap junction led to the possibility of multiple steady states. However, we were unable to show that all initial conditions of the four-dimensional model evolved to one of the steady states, except under special conditions, namely that ionic current was made up of small ions, an assumption that meant the long-term dynamics was essentially two-dimensional (Baigent, 2003).

Here we consider a simplification of the model in Baigent et al. (1997) that produces a new model whose dynamics can be completely analysed. This is achieved by simplifying the gap junction model – which originally had three gating configurations – to one with just two gating configurations, namely open and closed. The new model still has the same potential for multiple steady states demonstrated by the model in Baigent et al. (1997). Moreover, the new model is three dimensional, since it has one less gating configuration, and we show that reasonable monotonicity assumptions for the voltage-dependence of the channel opening and closing rates lead to a complete analysis of the model dynamics. The present model is composed of an electrical circuit as shown in Figure 1, in which the flow of ions between the cells and the outside environment (taken to be earthed) and between the cells via the junction is modelled as a current. Each cell  $i = 1, 2$  is represented by a capacitor  $C_i$  in parallel with an EMF  $e_i$  and a resistance  $R_i$  in series. This means that we have assumed that the cell membrane has linear voltage-current characteristics. The EMF represents the cell resting potential. Without loss of generality we may assume  $e_1 \geq e_2$  (else we simply relabel the cells).

The two cells are linked by a further resistor which models the gap junction and whose conductance is  $g(x(t))$  where  $x(t)$  is the current fraction of channels of the junction in the closed (low conductance) configuration. The corresponding fraction in the open (high conductance) configuration is then  $1 - x$ . The conductance of the junction is thus given by

$$g(x) = g_{\min}x + g_{\max}(1 - x),$$

where  $g_{\min} > 0$  is the *non-zero* conductance of the gap junction when all channels are closed, and  $g_{\max} > g_{\min}$  the conductance of the gap junction when all channels are open.

The channels open and close according to Markovian dynamics:

$$\dot{x} = -\alpha(V)x + \beta(V)(1 - x), \tag{2}$$



where  $V = \varphi_1 - \varphi_2$  and  $\alpha(V) > 0$  is the probability per unit time that a channel opens (usually called the opening rate) and  $\beta(V) > 0$  is the probability per unit time of a channel closing (the closing rate).

The full set of equations for the model read:

$$C_1 \dot{\varphi}_1 = -\frac{1}{R_1}(\varphi_1 - e_1) - g(x)(\varphi_1 - \varphi_2) = f_1(\varphi_1, \varphi_2, x) \quad (3)$$

$$C_2 \dot{\varphi}_2 = -\frac{1}{R_2}(\varphi_2 - e_2) + g(x)(\varphi_1 - \varphi_2) = f_2(\varphi_1, \varphi_2, x) \quad (4)$$

$$\dot{x} = -\alpha(\varphi_1 - \varphi_2)x + \beta(\varphi_1 - \varphi_2)(1 - x) = f_3(\varphi_1, \varphi_2, x). \quad (5)$$

We will assume that the opening and closing rates  $\alpha, \beta$  are  $C^1$  functions and satisfy

$$V\alpha'(V) < 0, \quad V\beta'(V) > 0 \quad \text{for all voltages } V \neq 0. \quad (6)$$

It turns out that these conditions are sufficient to ensure that all orbits converge to a steady state.

Although further assumptions are possible on physical grounds, including saturation of the opening and closing rates for large  $V$ , we do not require such assumptions for the results presented here.

The precise functional forms of  $\alpha, \beta$  determine the number of steady states, but we stress that, as we will show later, convergence of each orbit is guaranteed when (6) is satisfied.

Before proceeding to the main analysis, let us first consider the special case where  $e_1 = e_2 = E$ , say.

Let  $\phi_i = \varphi_i - e_i$ . Then the equations for the evolution of  $\phi = (\phi_1, \phi_2)^T$  can be written as  $C\dot{\phi} = M(x)\phi$  where  $M(x)$  is a  $2 \times 2$  negative definite matrix and  $C$  is the diagonal matrix with diagonal elements  $C_1, C_2$ . Thus

$$\frac{1}{2} \frac{d}{dt} |C^{\frac{1}{2}} \phi|^2 = \phi^T C \frac{d}{dt} \phi = \phi^T M(x) \phi \leq 0$$

with equality if and only if  $\phi = 0$ . Hence  $\phi(t) \rightarrow 0$  as  $t \rightarrow \infty$  for all initial  $\phi$  *regardless* of how  $x(t)$  evolves, i.e. each  $\varphi_i(t) \rightarrow E$  as  $t \rightarrow \infty$ . Moreover, using the results of Markus relating to asymptotically autonomous differential equations (Markus, 1956), we can justify simply taking equation (5) with  $\varphi_i = E$ , to study the asymptotic behaviour of  $x$ , and hence conclude that  $x(t) \rightarrow \frac{\beta(0)}{\alpha(0) + \beta(0)}$  as  $t \rightarrow \infty$ .

## 4 Model Analysis

In the following subsections we provide the mathematical details behind the analysis of the model. We analyse the orbits of the system (3) - (5), by which we mean, setting aside rigorous mathematical definitions, the evolution of  $(\varphi_1(t), \varphi_2(t), x(t))$  for  $t \geq 0$  for each choice of initial state  $(\varphi_1(0), \varphi_2(0), x(0))$ .

In non-mathematical terms, we do the following:

P1 *Prove all orbits are bounded* (Lemma 1). In other words the voltages and fraction of closed channels cannot grow indefinitely. Physically this is obvious, but actually we also show that *the voltage difference between the cells eventually has fixed polarity*, and since we may relabel the cells if necessary, we may arrange that after sufficient time the voltage of cell 1 remains greater than that of cell 2. This eventual ordering of the voltages is crucial to identifying (3) - (5) as a monotone dynamical system (see P3 below). In fact we show that whatever the initial voltages and fraction of closed channels, the vector of voltages and fraction of closed channels eventually enters and remains inside the interior of a bounded convex set (where  $\varphi_1 > \varphi_2$ ). This result is an important foundation for the application of more technical results later.

P2 *Show that there is at least one steady state, find a condition which will guarantee a unique steady state, and determine whether steady states are stable or unstable* (Lemmas 2-4 and Corollary 1).

The technical investment of P1 enables us to immediately conclude that for all parameter values there must be at least one state where the cell voltages and fraction of closed channels remain steady. There may be one or more steady states, and we find an easily checkable condition which guarantees a unique steady state. We also investigate whether each steady state is locally stable or unstable. By a locally asymptotically stable steady state we mean that a small (transient) perturbation to the system when in this steady state decays, so that the system relaxes back

to that same steady state. For an unstable steady state, by contrast, small perturbations may initially grow, and may result in the system relaxing to a different state. When there are multiple steady states, they must alternate in stability when ordered by increasing steady trans-junctional voltage. This means, as for the model discussed in Baigent et al. (1997), that when there are multiple steady states, switching between stable states is possible via loops in parameter space, such as for example, slow variations in the number of gap junction channels, or slow variations in cell resting potentials. In particular, when there are two stable steady states, and one unstable steady state, as in Baigent et al. (1997), we find that one stable steady state has a low trans-junctional voltage and high gap junctional conductance, and the other has a high trans-junctional voltage and low gap junctional conductance.

P3 *Show that all orbits converge to steady states* (Theorem 1). Having analysed the steady state regime in P2, we next show that no matter what the initial voltages of the cells and the fraction of closed channels in the junction, the system will eventually evolve to a steady state if left undisturbed. In particular no closed orbits are possible. When there are multiple steady states, which steady state the system ends up at depends on the initial state. Crucially it is our biologically reasonable assumption that the channel opening rate decreases, while the closing rate increases, with increasing positive trans-junctional voltage which places the model in the important class of *monotone dynamical systems*. The assumptions on the opening and closing rates imply that *the rate of change of closed channel fraction is an increasing function of trans-junctional voltage*, and the theory of monotone dynamical systems enables us to identify this feature of the gap junctional coupling that precludes any dynamical behaviour other than convergence to steady state.

#### 4.1 All orbits are bounded

Following the comment at the end of the previous section, we suppose  $e_1 > e_2$ . Define  $\Delta \equiv \{(\varphi_1, \varphi_2, x) \in \mathbb{R}^3 : \varphi_1, \varphi_2 \in [e_2, e_1], x \in [0, 1]\}$ , and  $T = \{(\varphi_1, \varphi_2, x) \in \Delta : \varphi_1 \geq \varphi_2\}$ .

**Lemma 1** *All orbits of (3) - (5) eventually enter the interior of the compact, convex set  $T$ .*

Proof: Compactness and convexity of  $T$  are immediate from its construction. First we show that all orbits of (3) - (5) enter the interior of the cuboid  $\Delta$ . Now suppose that  $\delta \geq 0$  is given and consider the region of a plane  $S_1$  defined by  $\varphi_1 = e_2 - \delta$ ,  $\varphi_2 \in [e_2 - \delta, e_1 + \delta]$  and  $x \in [0, 1]$ . Then on  $S_1$  we have  $\varphi_2 \geq \varphi_1$  and  $\varphi_1 - e_1 = e_2 - e_1 - \delta < 0$ , which gives  $\dot{\varphi}_1 > 0$  on  $S_1$ . If  $S_2$  is similarly defined by  $\varphi_2 = e_2 - \delta$ ,  $\varphi_1 \in [e_2 - \delta, e_1 + \delta]$  and  $x \in [0, 1]$  then on  $S_2$  we have  $\varphi_2 \leq \varphi_1$  and  $\varphi_2 - e_2 = -\delta < 0$  and so  $\dot{\varphi}_2 > 0$ . Similarly we may define  $S_3$  via  $\varphi_1 = e_1 + \delta$ ,  $\varphi_2 \in [e_2 - \delta, e_1 + \delta]$ ,  $x \in [0, 1]$ , and  $S_4$  by  $\varphi_2 = e_1 + \delta$ ,  $\varphi_1 \in [e_2 - \delta, e_1 + \delta]$ ,  $x \in [0, 1]$ . We find that  $\dot{\varphi}_1 < 0$  on  $S_3$  and  $\dot{\varphi}_2 < 0$  on  $S_4$ . For each  $\delta \geq 0$  the regions  $S_1$  to  $S_4$  together with the planes  $x = 0$  and  $x = 1$  bound a cuboid  $S_\delta$ . Then for each  $\delta \geq 0$ , we have shown that orbits enter the interior of  $S_\delta$ . Thus all orbits eventually enter the interior of  $\Delta = S_0$ . Now consider how orbits cross the planar section  $\Pi_\delta$  defined by the intersection of  $\Delta$  with the plane defined by  $\varphi_1 = \varphi_2 - \delta$ . Then when  $\delta > 0$ , on  $\Pi_\delta$  we have  $C_1\dot{\varphi}_1 = -\frac{1}{R_1}(\varphi_1 - e_1) + g(x)\delta > 0$  since  $\varphi_1 \leq e_1$  and  $g(x) > 0$ . Similarly  $C_2\dot{\varphi}_2 = -\frac{1}{R_2}(\varphi_2 - e_2) - g(x)\delta < 0$ .

We have thus shown that once orbits have entered  $\Delta$ , they also cross each plane  $\varphi_1 = \varphi_2 - \delta$  in the direction of increasing  $\varphi_1 - \varphi_2$  when  $\delta > 0$ . When  $\delta = 0$  we have  $C_1\dot{\varphi}_1 = -\frac{1}{R_1}(\varphi_1 - e_1) \geq 0$  with equality if and only if  $\varphi_1 = e_1$  and similarly  $C_2\dot{\varphi}_2 = -\frac{1}{R_2}(\varphi_2 - e_2) \leq 0$  with equality if and only if  $\varphi_2 = e_2$ . When  $\varphi_1 = \varphi_2 = e_1$  we have  $\dot{\varphi}_1 = 0$  and  $C_2\dot{\varphi}_2 = -\frac{1}{R_2}(e_1 - e_2) < 0$ , and when  $\varphi_1 = \varphi_2 = e_2$  we have  $\dot{\varphi}_2 = 0$  and  $C_1\dot{\varphi}_1 = -\frac{1}{R_1}(e_2 - e_1) > 0$ . Hence orbits also cross  $\Pi_0$  in the direction of increasing  $\varphi_1 - \varphi_2$ . Thus all orbits eventually enter the interior of the prism  $T$ .  $\square$

In particular this means that if  $e_1 \neq e_2$  there can be no steady states on the boundary of  $T$ .

## 4.2 Existence and local stability of steady states

The previous section showed that the system (3) - (5) is dissipative, that is to say that all orbits eventually enter the interior of a compact set  $T$ . By continuous time analogues of the Brouwer fixed point theorem, since  $T$  is compact, convex and forward invariant, there exists at least one steady state in  $T$  (Spanier, 1981).

Steady states  $(\varphi_1^*, \varphi_2^*, x^*)$  must satisfy

$$\begin{aligned} 0 &= -\frac{1}{R_1}(\varphi_1 - e_1) - g(x)(\varphi_1 - \varphi_2) \\ 0 &= -\frac{1}{R_2}(\varphi_2 - e_2) + g(x)(\varphi_1 - \varphi_2) \\ 0 &= -\alpha(\varphi_1 - \varphi_2)x + \beta(\varphi_1 - \varphi_2)(1 - x). \end{aligned}$$

Combining the first two relations gives

$$0 = -V + e - Rg(x)V, \quad (7)$$

where  $V = \varphi_1 - \varphi_2$ ,  $R = R_1 + R_2$  and  $e = e_1 - e_2$ .

Introduce  $V_H = \frac{e}{1+Rg_{\min}}$ ,  $V_L = \frac{e}{1+Rg_{\max}}$ . From (7), if  $V^* = \varphi_1^* - \varphi_2^*$  is a steady state trans-junctional voltage for (3) - (5) then

$$V_L < V^* < V_H.$$

To determine the local stability of steady states we compute the Jacobian for (3) - (5):

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial \varphi_1} & \frac{\partial f_1}{\partial \varphi_2} & \frac{\partial f_1}{\partial x} \\ \frac{\partial f_2}{\partial \varphi_1} & \frac{\partial f_2}{\partial \varphi_2} & \frac{\partial f_2}{\partial x} \\ \frac{\partial f_3}{\partial \varphi_1} & \frac{\partial f_3}{\partial \varphi_2} & \frac{\partial f_3}{\partial x} \end{pmatrix} = \begin{pmatrix} -\frac{1}{R_1 C_1} - \frac{g}{C_1} & \frac{g}{C_1} & -\frac{g'(x)V}{C_1} \\ \frac{g}{C_2} & -\frac{1}{R_2 C_2} - \frac{g}{C_2} & \frac{g'(x)V}{C_2} \\ Z & -Z & -\alpha(V) - \beta(V) \end{pmatrix}. \quad (8)$$

where  $Z = -\alpha'(V)x + \beta'(V)(1 - x)$ .

**Lemma 2** *The matrix  $J = Df$  is stable if and only if  $|J| < 0$ .*

Proof: We recall the Routh-Hurwitz conditions for a  $3 \times 3$  matrix  $J$  to be stable:

$$\begin{aligned} \operatorname{tr}(J) &< 0 \\ |J| &< 0 \\ \operatorname{tr}(J)(|J_{11}| + |J_{22}| + |J_{33}|) - |J| &< 0, \end{aligned} \quad (9)$$

where  $\operatorname{tr}(J)$  is the trace of  $J$ , and  $J_{ii}$  is the submatrix of  $J$  obtained by deleting the  $i$ th row and column. Note first that by inspection  $\operatorname{tr}(J) < 0$ . To ease the calculations we make the following substitutions:  $r = 1/R_1$ ,  $u = 1/R_2$ ,  $\tau = (g_{\max} - g_{\min})V$  and  $w = \alpha + \beta$ . These parameters and variables are all positive by assumption. In this new notation we have

$$|J| = \frac{1}{C_1 C_2} ((r + u)\tau Z - guw - rgw - wru). \quad (10)$$

We also have

$$|J_{11}| = \frac{1}{C_1(r + u)} (r^2 w - C_1 C_2 |J|) \quad (11)$$

$$|J_{22}| = \frac{1}{C_2(r + u)} (u^2 w - C_1 C_2 |J|) \quad (12)$$

$$|J_{33}| = \frac{1}{C_1 C_2} (ru + gr + gu) \quad (13)$$

Finally we compute

$$\begin{aligned} \operatorname{tr}(J)(|J_{11}| + |J_{22}| + |J_{33}|) - |J| &= -w(|J_{11}| + |J_{22}| + |J_{33}|) \\ &\quad - \left( \frac{r + u}{C_2} \right) (|J_{11}| + |J_{33}|) - \left( \frac{r + g}{C_2} \right) (|J_{22}| + |J_{33}|) - \frac{g}{C_2} |J_{22}| - \frac{g}{C_1} |J_{11}| - \frac{ruw}{C_1 C_2} \end{aligned} \quad (14)$$

Clearly  $|J_{33}| > 0$ . Now we note that when  $|J| < 0$  then  $|J_{11}|, |J_{22}| > 0$  and we check that all terms in (14) are negative giving (9), as required.  $\square$

**Lemma 3** *Let  $J = Df$ . If  $|J| < 0$  in  $T$  then (3) - (5) has a unique steady state in the interior of  $T$ .*

Proof: We use degree theory to show this. By definition, for each  $c \in \mathbb{R}^3$  such that (i)  $f(z) \neq c$  on the boundary of  $T$ , and (ii) all points  $z \in f^{-1}(c)$  are such that  $|J(z)| \neq 0$ , the degree  $\deg(f, \text{int}(T), c) = \sum_{z \in f^{-1}(c)} \text{sgn}|J(z)|$ . Now, there are no steady states on the boundary of  $T$ , and  $|J| \neq 0$ , so we have  $\deg(f, \text{int}(T), 0) = -|f^{-1}(0)|$ , i.e. minus the number of zeros in the interior of  $T$ . On the other hand the vector field  $f = (f_1, f_2, f_3)^T$  points inwards on the boundary of the convex compact set  $T$ , so that  $\deg(f, \text{int}(T), 0) = -1$ , minus the Euler characteristic of the unit sphere. Hence there is precisely one steady state in the interior of  $T$ .  $\square$

**Lemma 4** *Let  $F(V) = (e - V)/R$  and  $G(V) = V \left( \frac{g_{\min}\beta(V) + g_{\max}\alpha(V)}{\alpha(V) + \beta(V)} \right)$ . Consider  $H(V) = F(V) - G(V)$ . Then at a steady state,  $H(V) = 0$  and  $\text{sgn}(H'(V)) = \text{sgn}(|J|)$ .*

Proof: It is easy to check that at a steady state  $H(V) = F(V) - G(V) = 0$ . Also

$$H'(V) = -\frac{G}{V} - (g_{\max} - g_{\min}) \frac{V(\beta\alpha' - \alpha\beta')}{(\alpha + \beta)^2} - \frac{1}{R}.$$

At steady state this becomes

$$H'(V) = \frac{V - e}{RV} - (g_{\max} - g_{\min}) \frac{V(\beta\alpha' - \alpha\beta')}{(\alpha + \beta)^2} - \frac{1}{R}$$

On the other hand,

$$|J| = \frac{1}{R_1 R_2 C_1 C_2} [(g_{\max} - g_{\min})RZV - (1 + gR)(\alpha + \beta)],$$

where

$$Z = -\alpha'x + \beta'(1 - x) = \frac{-\beta\alpha' + \beta'\alpha}{\alpha + \beta}$$

Hence

$$H'(V) = \frac{1}{R(\alpha + \beta)} \left( \frac{(V - e)}{V}(\alpha + \beta) + R(g_{\max} - g_{\min})ZV - (\alpha + \beta) \right)$$

At steady state  $RVg = e - V$  and hence

$$H'(V) = \frac{1}{R(\alpha + \beta)} (R(g_{\max} - g_{\min})ZV - (1 + Rg)(\alpha + \beta)) = \frac{R_1 C_1 R_2 C_2}{R(\alpha + \beta)} |J| \quad \square.$$

**Corollary 1** *If the system (3) - (5) has  $2n + 1$  hyperbolic steady states ordered by their voltages  $V_1 < \dots < V_{2n+1}$ , then the  $V_k$  are locally asymptotically stable for odd  $k$  and unstable for even  $k$ .*

Proof: We simply have to check the sign changes of  $|J|$ . At the lowest steady state  $V_1$  (which might be the only one) since  $G$  is increasing from zero and  $F$  is decreasing, we see that  $H'(V_1) < 0$ , which implies  $|J| < 0$ , and hence  $V_1$  is locally stable. At the next steady state  $H'$  must change sign and hence the next steady state is unstable, and so on.  $\square$

### 4.3 Monotonicity: Global convergence of orbits

Note that  $V > 0$  in the interior of  $T$  and so our earlier assumption that  $V\alpha'(V) < 0, V\beta'(V) > 0$  gives that  $\alpha' < 0, \beta' > 0$ . Since  $x \in [0, 1]$ ,  $Z > 0$  in the interior of  $T$ .

By inspection, we see that all elements of the Jacobian (8) eventually have the fixed sign structure

$$J = \begin{pmatrix} - & + & + \\ + & - & - \\ + & - & - \end{pmatrix}. \quad (15)$$

since eventually orbits enter the interior of  $T$ . However, it pays dividends to study (3) - (5) in a new set of coordinates. This will allow us to prove our main theorem:

**Theorem 1** *Every orbit of (3) - (5) converges to a steady state.*

Proof: For definiteness, we assume that the membrane time constants  $\tau_i = R_i C_i$  satisfy  $\tau_1 > \tau_2$  and introduce new coordinates:

$$\psi = C_1 \varphi_1 + C_2 \varphi_2, \quad V = \varphi_1 - \varphi_2.$$



Here  $\psi$  can be interpreted as the total charge stored by the capacitances of the two membranes. (If  $\tau_2 > \tau_1$  we define  $\psi = -C_1\varphi_1 - C_2\varphi_2$  and the arguments below work equally well.) In the coordinates  $(\psi, V, x)$ ,  $T$  is transformed to a new set in  $\mathbb{R}^3$  which we can term  $T'$ , and the Jacobian becomes

$$\begin{pmatrix} -\left(\frac{R_1 + R_2}{R_1 R_2 (C_1 + C_2)}\right) & \frac{\tau_1 - \tau_2}{R_1 R_2 (C_1 + C_2)} & 0 \\ \frac{\tau_1 - \tau_2}{(C_1 + C_2)\tau_1\tau_2} & -\frac{1}{C_1 + C_2} \left[ \frac{C_2}{\tau_1} + \frac{C_1}{\tau_2} - \left( \frac{1}{C_1} + \frac{1}{C_2} \right) g(x) \right] & -\left( \frac{1}{C_1} + \frac{1}{C_2} \right) V g'(x) \\ 0 & -\alpha'(V)x + \beta'(V)(1-x) & -\alpha(V) - \beta(V) \end{pmatrix}$$

We have already shown that after a sufficiently long time all orbits of (3) - (5) enter the interior of  $T$ , and so all orbits of the recoordinated system enter the interior of  $T'$ , where the Jacobian matrix has sign structure:

$$\begin{pmatrix} - & + & 0 \\ + & - & + \\ 0 & + & - \end{pmatrix}. \quad (16)$$

Notice that the Jacobian matrix in (16) has tridiagonal structure. Moreover, the off-diagonal elements are all strictly positive in the interior of  $T'$  (where  $V > 0$ ). A system with Jacobian of the form (16) is termed a “strictly cooperative tridiagonal” system. Smillie has shown that for such a system defined on an open set, each bounded orbit converges to a steady state (Smillie, 1984). Thus in the new coordinates, all orbits enter the interior of  $T'$  (an open set), where the dynamics is tridiagonal and strictly cooperative, and hence all orbits converge to steady states.  $\square$

Note that strictly cooperative tridiagonal systems are a special case of *monotone dynamical systems* (see Hirsch and Smith (2005) for an introduction to monotone dynamical systems). Monotone systems preserve some ‘ordering’ in phase space. One immediate consequence of monotonicity is that there can be no stable periodic orbits in any forward invariant open set (such as the interior of  $T'$  as defined

above).

### Remark

If  $\tau_1 = \tau_2 = \tau_0$ , say, we may show that each orbit of (3) - (5) converges to a steady state, but now *we need no assumptions on the signs of the derivatives  $\alpha', \beta'$* . In this case, the system in  $(\psi, V, x)$  coordinates decouples and becomes

$$\dot{\psi} = -\frac{1}{\tau_0}(\psi - (C_1 e_1 + C_2 e_2)) \quad (17)$$

$$\dot{V} = -\frac{1}{\tau_0}(V - e) - \left(\frac{1}{C_1} + \frac{1}{C_2}\right)g(x)V \quad (18)$$

$$\dot{x} = -\alpha(V)x + \beta(V)(1 - x). \quad (19)$$

This system inherits the boundedness properties of the full system: all orbits eventually enter a compact set, and hence all orbits have compact closure. The first equation is easily solved and shown to be globally convergent to  $\psi = C_1 e_1 + C_2 e_2$ . Notice that the Jacobian matrix for (18), (19) has trace  $-\frac{1}{\tau_0} - \left(\frac{1}{C_1} + \frac{1}{C_2}\right)g(x) - \alpha(V) - \beta(V) < 0$ , and hence by the autonomous convergence theorem (Smith, 1986; also corollary 2.9 in Li and Muldowney (1995)) every orbit converges to one of the steady states - regardless of the functional forms of  $\alpha, \beta$  provided that  $\alpha, \beta \geq 0$ . However, the number of steady states will depend on these functional forms.

## 5 Discussion

Here we have analysed a model of two cells dynamically coupled by a gap junction. We have simplified the two cell model studied in Baigent et al. (1997), treating the junction as a single voltage-sensitive gate which can be open or closed. By making biologically reasonable assumptions about the monotonicity of changes of the gap junction channel opening and closing rates with trans-junctional voltage, we

have shown (i) that the local stability of hyperbolic steady states depends solely on the sign of the determinant of the Jacobian matrix at the steady state, and (ii) all initial states of the model evolve to a steady state using monotone dynamical systems theory.

By using new coordinates, we identified the model as a monotone dynamical system. The tendency towards convergence of tridiagonal monotone dynamical systems can also be understood in terms of sensitivities of velocities to the phase space variables, i.e. the entries of the Jacobian matrix  $J$  above. For example we can see how  $\dot{x}$  evolves by computing  $\frac{d}{dt}\dot{x} = \frac{\partial \dot{x}}{\partial \psi}\dot{\psi} + \frac{\partial \dot{x}}{\partial V}\dot{V} + \frac{\partial \dot{x}}{\partial x}\dot{x} = (-\alpha'(V)x + \beta'(V)(1-x))\dot{V} - (\alpha(V) + \beta(V))\dot{x}$ . If at some time  $\dot{x} = 0$ , we have  $\frac{d}{dt}\dot{x} = (-\alpha'(V)x + \beta'(V)(1-x))\dot{V}$ , which show that  $\dot{x}$  next goes positive if  $V$  is currently increasing, or goes negative if  $V$  is currently decreasing, since the assumptions on  $\alpha, \beta$  ensure  $-\alpha'(V)x + \beta'(V)(1-x) > 0$  in the interior of  $T'$ . So, although the junction channels may currently be opening at  $V = V_0$  (i.e.  $\dot{x}(V_0) < 0$ ), if the voltage then goes through a sustained increase, the channels will eventually start to close, since eventually  $\dot{x}(V) > 0$  for  $V$  large enough. Conversely, if  $V > 0$  decreases from some  $V_1$ , where  $\dot{x}(V_1) > 0$ , then  $\dot{x}$  will decrease, so that eventually  $\dot{x}(V) < 0$  and the channels open.

The nice feature of tridiagonal monotone systems is that when considering the possible velocity changes for all variables, one finds that the feasible changes constrain the system in such a way that eventually, after sufficient time, each velocity has a fixed sign. In the context of the present model, this means that eventually  $\psi, V, x$  are individually increasing or decreasing with time. Since we also know that the voltages and fraction of closed channels are bounded, this means that  $(\psi, V, x)$  must tend to a steady vector - a steady state. The key step in applying this theory to our model is that we require  $\partial \dot{x} / \partial V > 0$ , which is the embodiment of the experimentally-supported assumption that “increasing trans-junctional voltage leads to decreases in gap junctional conductance”.

The assumption on the opening and closing rates that leads to  $\partial \dot{x} / \partial V > 0$  for  $V > 0$  also has

implications for multiple steady states. Indeed, suppose that we had completely the opposite behaviour:  $\alpha'(V) > 0, \beta'(V) < 0$  for  $V > 0$ . Now  $Z < 0$  and hence every term in  $|J|$  is negative in (10) giving  $|J| < 0$ , so that by lemma 3 there is a unique steady state which by lemma 2 is locally asymptotically stable. Hence in this opposite case - which we concede is not biologically realistic in this context since channels open with increasing voltage - there can be no switching between steady states. For multiple steady states to exist (keeping the same linear cell membrane properties), we must have  $\partial \dot{x} / \partial V > 0$  for some interval of values of  $V > 0$ .

More complex models treat the channels as having two voltage-sensitive gates, one in each connexon (Harris et al., 1981; Baigent et al., 1997; Vogel and Weingart, 1998; Chen-Izu, Y. et al., 2001). For such models, various gating mechanics have been proposed. Independent gating proposes that the two gates can open and close independently of each other. By contrast contingent gating supposes that if one gate is closed the other must be open (Harris et al., 1981; Baigent et al. 1997), so that both gates cannot be simultaneously closed. Not surprisingly, the more complex two-gate models can capture more of the dynamical behaviour observed experimentally, and, in particular, the temporary increase in conductance following a change in polarity of trans-junctional voltage, which comes about due to the channels passing through the high conductance open-open state in order to switch between the low conductance open-closed or closed-open states. In these more complex models we can find no simple equivalent of  $\partial \dot{x} / \partial V > 0$  for the gating dynamics which now is described by two gating variables, typically the fraction of high conductance open-open channels together with the fraction of low conductance open-closed channels. Nevertheless, our simplified model does incorporate the major feature of the drop in conductance with increasing magnitude of trans-junctional voltage, and also picks out the same steady state voltages as the two-gate model in Baigent et al. (1997).

As mentioned above, we have not yet succeeded in showing that the more complex model of Baigent et

al. (1997) is a monotone dynamical system, which would rule out stable periodic orbits on the interior of phase space and, with mild additional assumptions, guarantee generic convergence to the set of equilibria. Thus the question of whether a dynamic junction with a sufficiently complicated response to changes in the trans-junctional voltage can give rise to stable oscillations in a two-cell system remains open. It is also unclear whether the analysis presented here extends naturally to larger networks of coupled cells. These are interesting questions for future work.

## 6 Acknowledgments

PD was funded by EPSRC/MRC grant to the MIAS IRC (GR/N14248/01), and MB by EPSRC grant EP/D060982/1.

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Figure 1:

Figure 1 here

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Caption for figure 1:

Equivalent electrical circuit model for 2 cells linked by a gap junction. Each cell is a capacitor in parallel with an EMF and fixed resistor. The gap junction is represented by a variable resistor of conductance  $g$ .

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