Synchronization and activation in a model of a network of β-cells *

J. G. Barajas Ramírez [a], E. Steur [b], R. Femat [a], H. Nijmeijer [b]

[a] *División de Matemáticas Aplicadas, IPICYT, Camino a la Presa San José 2055, Col. Lomas 4a Sección, C.P. 78216, San Luis Potosí, S. L. P., México*

[b] *Dept. Mechanical Engineering, Dynamics and Control Group, Eindhoven University of Technology, P.O.Box 513, 5600 MB, Eindhoven, The Netherlands*

Abstract

Islets of pancreatic β-cells are of utmost importance in the understanding of diabetes mellitus. We consider here a model of a network of such pancreatic β-cells which are globally coupled via gap junctions. Some of the cells in the islet are producing bursting oscillations while other cells are inactive. We prove that the cells in the islet synchronize if the coupling is sufficiently large and all cells are active (or inactive). If the islet consists of both active and inactive cells and the coupling is sufficiently large, an active cluster and an inactive cluster emerge. We show that activity of the islet depends on the coupling strength and the number of active cells compared to the number of inactive cells. If too few cells are active the islet becomes inactive.

Key words: Network synchronization, β-cells, Activation, Coupling

1 Introduction

Diabetes mellitus is a problem of world wide concern [14,15]. Dynamical analysis and control of pancreatic cells is one of its issues. The pancreas agglomerates cells in functional units called Langerhans islets. In particular, pancreatic β-cells play an important role in glucose homeostasis since they release insulin which is the hormone mainly responsible for the blood glucose regulation [1,4]. Experimental studies show that the insulin secretion in β-cell is directly related to spiking/bursting electrical activity of the cell membrane. For instance, the absence of the spiking or bursting indicates that the insulin secretion is inhibited [5,6,10]. Synchronization of bursting activity in Langerhans islets is expected to play an important role in the insulin secretion [4,10]. Moreover, there is experimental evidence that bursting electrical activity occurs when analyzing an islet as a whole, while when β-cells are analyzed in isolation, most of them are in an inhibited inactive state [4,12]. On the other hand,

if too many cells are inactive the islet might stop showing activity [6]. In this paper we consider a model of an islet with active and inactive β-cells and we study how many cells need to be active the let the islet show activity such that the insulin secretion will not be inhibited. A single β-cell will be described by a model proposed by Pernarowski [6] which is capable of reproducing the inactive state, bursting oscillations and continuous spiking. The behavior of the model can be changed by varying a single parameter. Each cell will interact with all other cells via gap-junctions, i.e. a coupling given by the difference in membrane potential of the cells multiplied by the coupling strength. Using machinery presented in [8,9] we prove that if the coupling is sufficiently strong an islet with all cells active (or inactive) synchronizes, and if the islet consists of both active and inactive cells we prove that an active cluster and an inactive cluster emerge. We show that the network will show activity as long as the islet contains a sufficient amount of active cells. It is well known that coupling between cells might influence the behavior of cells. In for instance [7,11] it is shown that certain systems that are inactive in isolation can produce stable oscillations when there are coupled. In the analysis it is first shown that solutions of the interacting systems are bounded, then it is shown that due to the coupling the equilibrium looses stability. In our analysis we show that, depending on the coupling

---

* This paper was not presented at any IFAC meeting. Corresponding author R. Femat. Tel. +52-444-8347215. Fax +52-444-8347271.

Email addresses: `jgbarajas@ipicyt.edu.mx` (J. G. Barajas Ramírez), `e.steur@tue.nl` (E. Steur), `rfemat@ipicyt.edu.mx` (R. Femat), `h.nijmeijer@tue.nl` (H. Nijmeijer).

strength, the equilibrium of the islet changes from un-
stable to stable when not enough cells are active which
in turn implies that the electrical activity of the islet dies
out and the insuline secretion is inhibited. The paper is
organized as follows. In section 2 the model of a single
cell is introduced and its dynamic behavior is briefly ex-
plained. Then in the next section we introduce the islet
of globally coupled β-cells and we present some theoret-
ical results concerning the synchronization of the activ-
ity in the islet. In section 4 we discuss when a islet stops
showing activity and we demonstrate our theoretical re-
sults using numerical simulations. Section 5 contains a
discussion on the results obtained in the paper.

2 A single β-cell

Consider a model of a β-cell [6]

$$\dot{y} = f(y) - z_1 - z_2, \tag{1}$$
$$\dot{z}_1 = w_\infty(y) - z_1, \tag{2}$$
$$\dot{z}_2 = \varepsilon\left(h(y) - z_2\right), \tag{3}$$

with $\dot{} := \frac{\mathrm{d}}{\mathrm{d}t}$, $y \in \mathbb{R}$ denotes the membrane potential
which is also the natural output of a cell, $z_1 \in \mathbb{R}$ a
channel activation variable, $z_2 \in \mathbb{R}$ is related to the
concentration of intracellular calcium and ADP, $\varepsilon \ll 1$ is
a small positive parameter and the polynomials $f(y) =
-f_3 y^3 + f_2 y^2 + f_1 y$, $w_\infty(y) = w_3 y^3 + w_2 y^2 - w_1 y - w_0$,
$h(y) = b\left(y + y_0\right)$. In the sequel we will use the following
parameters from [6]: $f_3 = \frac{1}{12}$, $f_2 = \frac{3}{8}$, $f_1 = \frac{37}{64}$, $w_3 = \frac{11}{12}$,
$w_2 = \frac{3}{8}$, $w_1 = 2\frac{27}{64}$, $w_0 = 3$, $\varepsilon = 0.0025$ and $b = 4$. If
$y_0 = 0.954$ the cell bursts; the cell shows activity and we
say the cell is active. On the other hand, if $y_0 = 1.375$
the solutions of (5),(6),(7) converge to an equilibrium
and we say the cell is inactive. Figure 1 shows the state
trajectories of an active cell and an inactive cell.

We will briefly recall the fast-slow analysis of the system
(1), (2), (3) as presented in [6] to explain how the model
generates the different behaviors depicted in Figure 1.
See also, for instance, Chapter 6 of [2] and Section 11.4
of [3]. We focus first on an active cell, i.e. $y_0 = 0.954$. On
the *fast t time scale*, the time scale dominating during
the bursts, the behavior of the cell is governed by letting
$\varepsilon = 0$ such that

$$\dot{y} = f(y) - z_1 - z_2, \quad \dot{z}_1 = w_\infty(y) - z_1, \tag{4}$$

with z_2 now a constant parameter. The bifurcation di-
agram is depicted in Figure 2. A family of stable limit
cycles starts at a Hopf bifurcation indicated by point B
in the diagram and terminates at the homoclinic bifur-
cation point C. The equilibria of the fast subsystem (4)
lie on $z_2 = S(y) := f(y) - w_\infty(y)$. The equilibria located
on the S-shaped curve $S(\cdot)$ between the left knee (point
A) and the Hopf bifurcation point B are unstable, the
other equilibria are stable. On the *slow $t^* := \varepsilon t$ time*
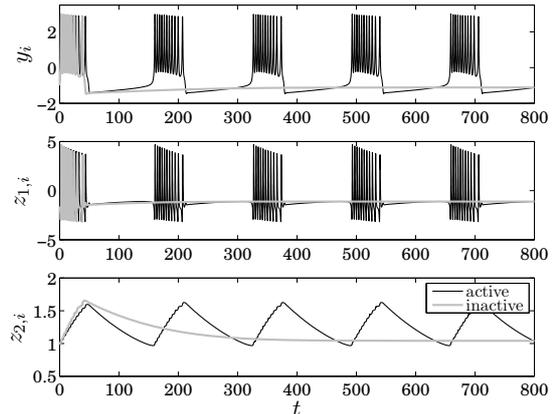
Figure 1. Numerical simulation of an isolated β-cell with
the parameters presented in the text and initial conditions
$(y_i(0), z_{1,i}(0), z_{2,i}(0)) = (-1, -2, 1)$. The black trajectories
correspond to an active bursting cell ($y_0 = 0.954$), the gray
trajectories represent an inactive cell ($y_0 = 1.375$). The single
burst in the beginning is due to the initial conditions.
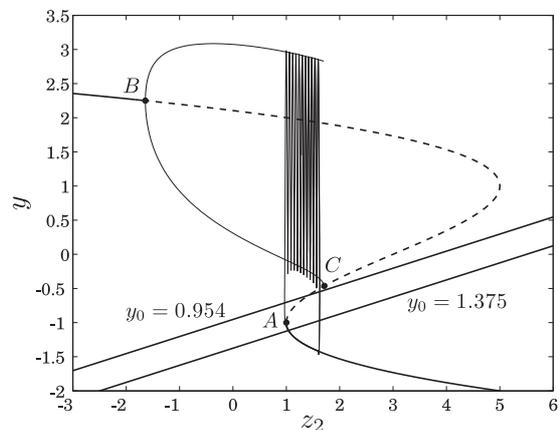
Figure 2. Fast-slow analysis and a projection of the trajec-
tories of an active cell onto the z_2-y plane.

scale the time between the bursts, the dynamics are given
by the equations $z_2 = S(y)$, $\frac{\mathrm{d}z_2}{\mathrm{d}t^*} = h(y) - z_2$. Between
the bursts the solutions of (1), (2), (3) follow the lower
branch of the curve $z_2 = S(y)$ with z_2 slowly decreasing
since this branch lies below the nulcline $z_2 = h(y)$. The
equilibrium of the system (1), (2), (3) is given by the in-
tersection of the S-shaped curve with the nulcline of the
slow system $h(y) = 0$. If $y_0 = 0.954$ the unique equilib-
rium is located at the unstable branch of $S(y)$. Suppose
that the initial conditions of (1), (2), (3) are chosen near
the lower branch of $S(y)$. Then the solutions follow the
lower branch with decreasing z_2 until the left knee (point
A) is reached. At this point stability is lost and the fast
subsystem starts to dominate. Hence the systems starts
to oscillate. During these oscillations z_2 will be slowly
increasing such that at a certain moment a homoclinic
bifurcation occurs (at point C) which forces the solu-
tions back to near the lower branch of $S(y)$. This proces
repeats over and over resulting in the stable bursting be-

havior. On the other hand, if $y_0 = 1.375$ the intersection of $S(y)$ and $h(y)$ is on the lower branch of $S(y)$ which implies that the equilibrium of (1), (2), (3) is stable.

3 An islet of β-cells

Consider an islet consisting of k coupled β-cells

$$\dot{y}_i = f(y_i) - z_{1,i} - z_{2,i} + u_i, \tag{5}$$
$$\dot{z}_{1,i} = w_\infty(y_i) - z_{1,i}, \tag{6}$$
$$\dot{z}_{2,i} = \varepsilon \left(b \left(y_i + y_{0,i} \right) - z_{2,i} \right), \tag{7}$$

with $i = 1, \ldots, k$ and $u_i \in \mathbb{R}$ is an input with which the cell is able to "communicate" with other cells. The islet consists of k_1 cells that are active while the remaining $k - k_1 =: k_2$ cells are inactive. Recall that the difference of a cell being active or inactive depends only on the value of $y_{0,i}$, i.e. $y_{0,i} = 0.954$ if a cell is active and $y_{0,i} = 1.375$ if the cell is inactive.

It is well known that β-cells couple via so-called gap junctions [10]. We assume that the cells are globally (all-to-all) coupled with uniform coupling strength. Hence the coupling for the ith cell is given by the equations

$$u_i = g_c \sum_{j=1, j\neq i}^{k} (y_j - y_i), \tag{8}$$

with coupling strength $g_c > 0$. The cells are called synchronized if $\lim_{t\to\infty} |x_i(t) - x_j(t)| = 0$ for all $i, j = 1, \ldots, k$ with $x_i := \text{col}(y_i, z_{1,i}, z_{2,i})$. Using the machinery presented in [8,13] we have the following two results.

Lemma 1 *The solutions of the cells* (5),(6),(7) *coupled via* (8) *are ultimately bounded.*

Theorem 2 *Consider an islet with k cells* (5),(6),(7) *coupled via* (8). *There exists a constant $\bar{g}_c > 0$ such that if $g_c k > \bar{g}_c$, then*

(1) if all cells are active ($k_1 = k$), all cells show synchronized bursting oscillations;
(2) if all cells are inactive ($k_2 = k$), all cells are synchronized but there are no oscillations;
(3) if $k_1 < k$ cells are active and $k_2 < k$ cells are inactive, the active cells synchronize and the inactive cells synchronize, but the active cells do not synchronize with the inactive cells.

The proofs of Lemma 1 and Theorem 2 are provided in the appendix. Lemma 1 states that all solutions of the interconnected cells enter some compact set in finite time and the solutions remain in that set thereafter. Note that this result is not trivial: it is well known that the solutions of interconnected systems might become unbounded even if the solutions of a system in isolation are bounded. This typically happens when the systems are non-minimum phase, cf. [7,13]. Theorem 2 states that if the coupling strength multiplied by the number of cells exceeds the threshold $\bar{g}_c$, i.e. the coupling is sufficiently strong and/or the number of cells is sufficiently large, a cluster of synchronized active cells and a cluster of synchronized inactive cells emerge. If all cells are either active or inactive then all cells in the islet synchronize when the coupling is sufficiently strong.

Remark 1 *Lemma 1 and Theorem 2 also hold for the biophysically plausible conductance based models of β-cells such as the models in [10,2]. See [13] for details.*

Remark 2 *Lemma 1 is also true for a general network topology, Theorem 2 can be generalized for a general network topology in case that all cells are either active or inactive. See [8,13] for details.*

4 An active or an inactive islet?

In this section we consider an islet of coupled cells (5), (6), (7), (8) of which k_1 cells are active and k_2 cells are inactive. In the remainder it is assumed that $g_c k \geq \bar{g}_c$ such that (as follows from Theorem 2) we end with a cluster of active cells and a cluster of inactive cells. Due to the interaction of the clusters two scenarios can occur:

(1) the active cluster "stimulates" the inactive cluster such that the cells in the inactive cluster start to produce oscillations;
(2) the inactive cluster suppresses the activity in the active cluster such that all activity in the islet dies out.

As one might imagine there will be two parameters that determine whether the islet will be active or inactive, namely the coupling strength $g_c k$ and the number of active cells relative to the number of inactive cells, i.e. the relative sizes of the clusters. Let η be the portion of active cells relative to the number of total cells, i.e. $\eta = \frac{k_1}{k}$. It follows that $1 - \eta$ represents the number of inactive cells relative to the number of total cells in the islet. In what follows we present estimates of the critical portion $\eta^* = \eta^*(g_c k)$ at which there is a change from activity of the islet to dead of all activity.

The dynamics of a cluster are given as

$$\dot{\zeta}_{1,m} = f(\zeta_{1,m}) - \zeta_{2,m} - \zeta_{3,m} + \nu_m, \tag{9}$$
$$\dot{\zeta}_{2,m} = w_\infty(\zeta_{1,m}) - \zeta_{2,m}, \tag{10}$$
$$\dot{\zeta}_{3,m} = \varepsilon \left(b \left(\zeta_{1,m} + y_{0,m} \right) - \zeta_{3,m} \right), \tag{11}$$

with $m = 1, 2$. Note that the equations describing the dynamics of the cluster are copies of the equations that describe the single cell. This is because the cells in a cluster are synchronized and share the same dynamics. We let $m = 1$ be the inactive cluster and $m = 2$ the
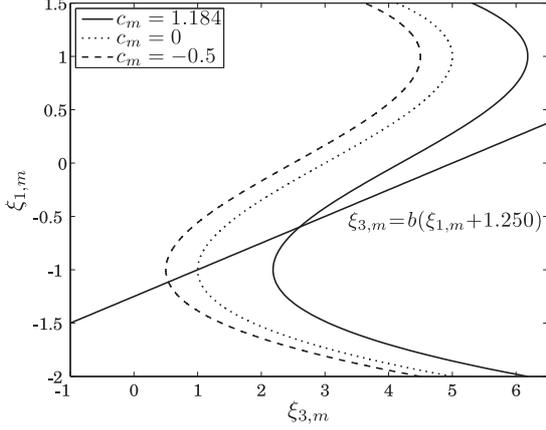
Figure 3. S-shaped curves of the uncoupled, i.e. $\tilde{\nu}_m = 0$, active cluster ($c_m = 1.184$) and inactive cluster ($c_m = -0.5$). Also presented are the S-shaped curve corresponding to $c_m = 0$ and the line $\xi_{3,m} = b(\xi_{1,m} + 1.250)$.

active cluster, i.e. $y_{0,1} = 1.375$ and $y_{0,2} = 0.954$. It is not difficult to see that the coupling between the clusters is given by the equations $\nu_1 = g_c k \eta (\zeta_{1,2} - \zeta_{1,1})$, $\nu_2 = g_c k (1 - \eta)(\zeta_{1,1} - \zeta_{1,2})$. We will use the machinery presented in Section 2 to determine the estimate of the critical portion η^*. First we introduce a change of coordinates: $\xi_{1,m} = \zeta_{1,m}$, $\xi_{2,m} = \zeta_{2,m}$ and $\xi_{3,m} = \zeta_{3,m} + c_m$ with $c_m := b(1.250 - y_{0,m})$, i.e. $c_1 = 1.184$ and $c_2 = -0.5$. Hence

$$\dot{\xi}_{1,m} = f(\xi_{1,m}) - \xi_{2,m} - \xi_{3,m} + c_m + \tilde{\nu}_m, \qquad (12)$$

$$\dot{\xi}_{2,m} = w_\infty(\xi_{1,m}) - \xi_{2,m}, \qquad (13)$$

$$\dot{\xi}_{3,m} = \varepsilon \left(b(\xi_{1,m} + 1.250) - \xi_{3,m} \right), \qquad (14)$$

and

$$\tilde{\nu}_1 = g_c k \eta (\xi_{1,2} - \xi_{1,1}), \qquad (15)$$

$$\tilde{\nu}_2 = g_c k (1 - \eta)(\xi_{1,1} - \xi_{1,2}). \qquad (16)$$

Figure 3 depicts the S-shaped curves of the fast subsystem of the uncoupled clusters and the line $\xi_{3,m} = b(\xi_{1,m} + 1.250)$. Again, the equilibrium of the clusters are given by the intersection of the S-shaped curve and the line. Note that the location of the equilibrium of the original model (1), (2), (2) (and thus that of a uncoupled cluster) is changed by varying y_0. In Figure 2 this corresponds to shifting the line $z_2 = h(y)$ up or down while keeping the S-shaped curve fixed. After the change of coordinates the location of the equilibrium still changes with y_0 since $c_m = c_m(y_0)$, but, as can be seen in Figure 3, this corresponds now to shifting the S-shaped curves to the left or right while keeping the line $\xi_{3,m} = b(\xi_{1,m} + 1.250)$ fixed. Let now the two clusters (12) – (14) be coupled via (15), (16). Due to the interaction the location of the S-shaped curves of the active and the inactive clusters change, hence the locations (and thus stability) of the equilibria change.

We now determine $\eta^*(g_c k)$ by estimating for which values of η, $g_c k$ and the equilibrium of the inactive cluster the equilibrium of the active cluster is at the left knee of its S-shaped curve. In particular we consider the two following extreme cases:

Case 1. The location of the equilibrium of the inactive cluster $(\xi^o_{1,1}, \xi^o_{2,1}, \xi^o_{3,1})$ does not change due to the interaction with the active cluster. This is the case when the portion of active cells is small, i.e. $\eta \to 0$. Let $(\xi^o_{1,2}, \xi^o_{2,2}, \xi^o_{3,2})$ be the equilibrium of the active cluster, then if the equilibrium is at the left knee we require

$$0 = \tilde{S}(\xi^o_{1,2}) - b\left(\xi^o_{1,2} + c_2\right)$$
$$+ g_c k(1 - \eta^*)(\xi^o_{1,1} - \xi^o_{1,2}), \qquad (17)$$

$$0 = \tilde{S}'(\xi^o_{1,2}) - g_c k(1 - \eta^*), \quad \tilde{S}''(\xi^o_{1,2}) > 0, \qquad (18)$$

where $\tilde{S}(\xi_{1,m}) := f(\xi_{1,m}) - w_\infty(\xi_{1,m}) + c_m$ and $'$ indicates the derivative with respect to $\xi_{1,m}$. Here (17) is the equilibrium equation for the active cluster and (18) is the condition that guarantees the equilibrium to be at the left knee. Solving (17), (18) for the given model parameters results in $g_c k(1 - \eta^*) = c$ with $c \approx 1.213$. Since $\eta^* \in [0, 1]$ it follows that $\eta^* = \max(0, 1 - \frac{c}{g_c k})$.

Case 2. The equilibria of both the active and inactive cluster are at the left knee of the S-shaped curve with $c_m = 0$. This happens if the coupling strength $g_c k$ is large. In Figure 3 this corresponds to shifting the S-shaped curve of the active (inactive) cluster to the *left* (*right*) by an amount of c_1 (c_2) such that the S-shaped curves of the active and inactive cluster coincide with the S-shaped curve with $c_m = 0$. Thus we require

$$0 = g_c k \eta^*(\xi^o_{1,2} - \xi^o_{1,1}) + c_1, \qquad (19)$$

$$0 = g_c k(1 - \eta^*)(\xi^o_{1,1} - \xi^o_{1,2}) + c_2, \qquad (20)$$

from which it follows that $\eta^* = \frac{c_1}{c_1 - c_2} \approx 0.297$.

Figure 4 summarizes the result. The estimated critical portion η^* is indicated by the thick gray line. The area in gray in the $(g_c k, \eta)$ plane indicates the region where we can guarantee that there is still activity of the islet. For instance, for large $g_c k$ at least 30% of the cells should be active to have any activity of the islet. The circles in Figure 4 indicate the critical portion obtained by numerical simulations of an islet with $k = 100$ cells. The analytical estimate approaches the numerical results well for small η and large $g_c k$.

Figure 5 shows the results of numerical simulations of a network consisting of $k = 7$ cells. The coupling strength $g_c = 1$. In Figure 5(a) $k_1 = 3$ cells are active and $k_2 = 4$ cells are inactive. As expected two clusters emerge and the network shows activity. In Figure 5(b) $k_1 = 2$ cells are active and $k_2 = 5$ cells are inactive. Again, as expected, two clusters emerge but now all activity dies out.
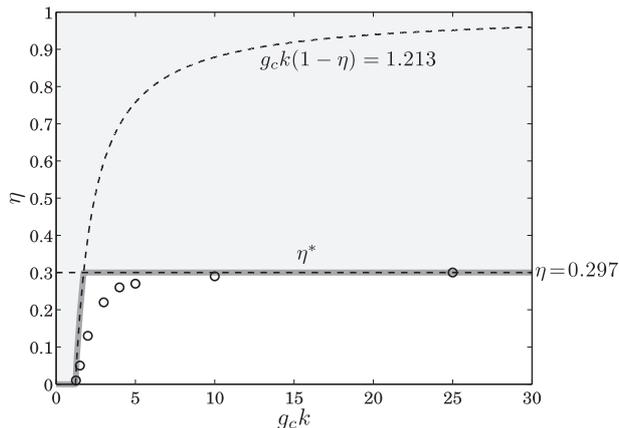
Figure 4. Analytical estimates of the critical portion (thick gray line) and the result of numerical simulations (circles).

5   Discussion

We have considered a model of an islet of globally coupled β-cells, where some are active and others are inactive. As stated in the introduction, the activity of an islet of β-cells is directly related to the blood glucose level, cf [5,6,10]. We have investigated here to what extent it is possible that coupled β-cells ultimately may exhibit active or inactive behavior. First we have proven that the solutions of all cells in the islet are ultimately bounded and we proved that if all cells are active or all cells are inactive, given that the coupling is sufficiently strong, all cells synchronize. Next we have proven that an active cluster and an inactive clusters emerge when the islet consists of both active and inactive cells and the coupling is sufficiently strong. Using stability analysis of the equilibria of the clusters an estimate of the critical portion $\eta^*(g_c k)$ is determined. If for some fixed coupling strength $g_c k$ the portion of active cells $\eta > \eta^*$, the islet will still show some activity. Results of numerical simulations show that the estimates of $\eta^*(g_c k)$ are accurate for small η and large $g_c k$.

In [6] the critical portion for an islet consisting of a large number $(O(\frac{1}{\varepsilon}))$ of cells that couple to their nearest neighbors is estimated to be 0.283. Although the analysis in [6] is different, the value of the estimated portion in the large islet with nearest neighbor coupling is close to the value we estimate for an globally coupled islet consisting of an arbitrary number of cells. Hence it would be interesting to study the influence of the topology of the network and the coupling strength in more detail.

References

[1]   E. M. Izhikevich. Neural excitability, spiking and bursting. *Int. J. Bif. Chaos*, 10(6):1171–1266, 2000.

[2]   J. Keener and J. Sneyd. *Mathematical Physiology*, volume 8 of *Interdisciplinary Applied Mathematics*. Springer-Verlag, New York, 1998.

(a)

(b)
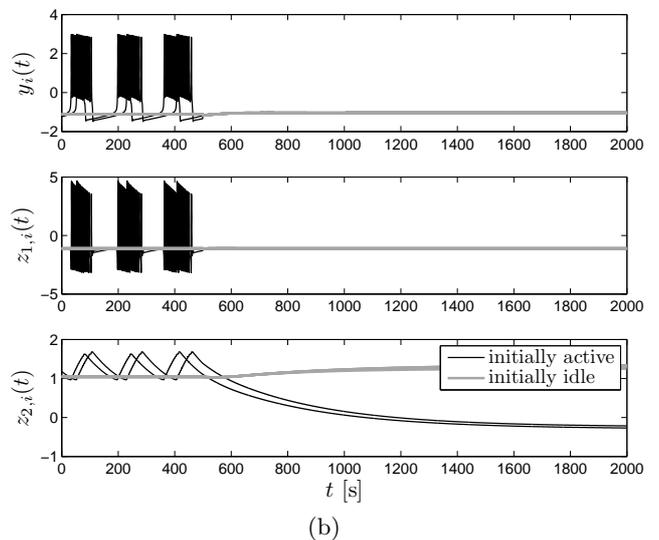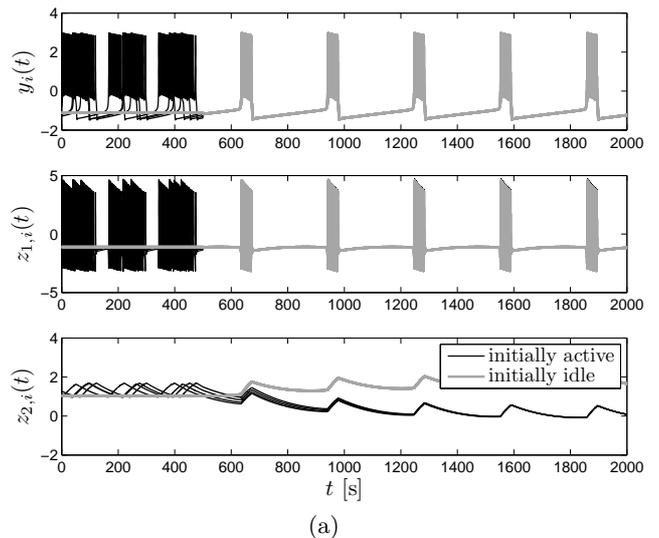
Figure 5. Numerical simulations of a network consisting of $k = 7$ cells coupled with strength $g_c = 1$: (a) three active and four inactive cells, (b) two active and five inactive cells.

[3]   H. K. Khalil. *Nonlinear Systems*. Prentice-Hall, 3 edition, 2002.

[4]   M. Pedersen, R. Bertram, and A. Sherman. Intra- and inter-islet synchronization of metabolically driven insulin secretion. *Biophys. J.*, 89:107–119, 2005.

[5]   M. Perez-Armendariz, C. Roy, D. C. Spray, and M. V. L. Bennett. Biophysical properties of gap juntions between freshly dispersed pairs of mouse pancreatic beta cells. *Biophys. J.*, 59:76–92, 1991.

[6]   M. Pernarowski. Fast and slow subsystems for a continuum model of bursting activity in the pancreatic islet. *SIAM J. Appl. Math.*, 58(5):1667–1687, 1998.

[7]   A. Pogromsky, T. Glad, and H. Nijmeijer. On diffusion driven oscillations in coupled dynamical systems. *Int. J. Bif. Chaos*, 9(4):629 – 644, 1999.

[8]   A. Pogromsky and H. Nijmeijer. Cooperative oscillatory behavior of mutually coupled dynamical systems. *IEEE Trans. Circuits Syst. I*, 48(2):152–162, 2001.

[9] A. Yu. Pogromsky. Passivity based design of synchronizing systems. *Int. J. Bif. Chaos*, 8(2):295 – 319, 1998.

[10] A. Sherman, J. Rinzel, and J. Keizer. Emergence of organized bursting in clusters of pancreatic beta cells by channel sharing. *Biophys. J.*, 54(3):411–425, 1988.

[11] S. Smale. A mathematical model of two cells via Turing's equation. In J. E. Marsden and M. McCracken, editors, *The Hopf bifurcation and its applications*, chapter 11, pages 354–367. Springer-Verlag, New York, 1976.

[12] P. Smolen, J. Rinzel, and A. Sherman. Why pancreatic islets burst but single β cells do not. the heterogeneity hypotesis. *Biophys. J.*, 64:1668–1680, 1993.

[13] E. Steur, I. Tyukin, and H. Nijmeijer. Semi-passivity and synchronization of diffusively coupled neuronal oscillators. *Physica D*, 238(21):2119–2128, 2009.

[14] S. Wild, G. Roglic, A. Green, R. Sicree, and H. King. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27:1047–1053, 2004.

[15] P. Zimmet, K.G. Alberti, and J. Shaw. Global and societal implications of the diabetic epidemic. *Nature*, 414:782–787, 2001.

A   Proofs

Proof of Lemma 1. Let $x_i := \mathrm{col}\,(y_i, z_{1,i}, z_{2,i})$ and consider the positive definite storage function $V_i(x_i) = \frac{1}{4}y_i^4 + \frac{1}{2w_3}z_{1,i}^2 + \frac{\mu}{2\varepsilon}z_{2,i}^2$ with a positive constant μ. Let the constants $\lambda_j \in (0,1)$, $j = 1,\ldots,4$, constant $\mu = \frac{1}{4f_3\lambda_1\lambda_3(1-\lambda_4)}$, then $\dot{V}_i = y_i^3 u_i - H_i$ with the function

$$
\begin{aligned}
H_i(x_i) &= \frac{\lambda_2}{w_3}\left(z_{1,i} + \frac{w_1}{2\lambda_2}y_i - \frac{w_2}{2\lambda_2}y_i^2\right)^2 \\
&+ \lambda_1 f_3\left(y_i^3 + \frac{1}{2\lambda_1 f_3}z_{2,i}\right)^2 + \mu\lambda_3\lambda_4\left(z_{2,i} - \frac{b}{2\lambda_4}y_i\right)^2 \\
&+ (1-\lambda_3)\mu z_{2,i}^2 - \mu b y_{0,i}z_{2,i} + (1-\lambda_2)\frac{1}{w_3}z_{1,i}^2 + \frac{w_0}{w_3}z_{1,i} \\
&+ (1-\lambda_1)f_3 y_i^6 - f_2 y_i^5 - f_1 y_i^4 - \frac{\mu\lambda_3 b^2}{4\lambda_4}y_i^2 \\
&- \frac{1}{4w_3\lambda_2}\left(w_1 y_i - w_2 y_i^2\right)^2 \quad\quad\quad\quad (A.1)
\end{aligned}
$$

which is positive for sufficiently large $|x_i|$. Let $W(x) := \sum_{i=1}^{k} V_i(x_i)$, $x := \mathrm{col}\,(x_1,\ldots,x_k)$, then $\dot{W} = \sum_{i=1}^{k} y_i u_i - H_i$. Note that $\sum_{i=1}^{k} y_i^3 u_i \leq \frac{g_c}{2}\sum_{i=1}^{k}\sum_{j=1,j\neq i}^{k} y_i^2(y_j^2 - y_i^2)$. Since $\sum_{i=1}^{k}\sum_{j=1,j\neq i}^{k}(y_j^2 - y_i^2) \leq 0$ and thus $\sum_{i=1}^{k} y_i^3 u_i \leq 0$ it follows that $\dot{W} = -\sum_{i=1}^{k} H_i \leq 0$ for sufficiently large $|x|$. The function W is radially unbounded since each function V_i is radially unbounded, hence there exists a constant c^* such that $\dot{W} < 0$ for each constant c and all x satisfying $W \geq c > c^*$. Thus the set $\left\{x \in \mathbb{R}^{3k} : W \geq c\right\}$ is a positively invariant compact set under the dynamics (5),(6),(7), (8) and all solutions exist and are bounded. $\qquad\square$

Proof of Theorem 2. We assume without loss of generality that the cells $i = 1,\ldots,k_1$ are active

and the cells $i = k_1 + 1,\ldots,k$ are inactive. We will prove that the active cells will synchronize with each other even in presence of coupling to the inactive cells. First, for notational convenience we define $z_i := \mathrm{col}\,(z_{1,i}, z_{2,i})$, $\dot{y}_i = a(y_i, z_i) + u_i$, with $a(y_i, z_i) = f(y_i) - z_{i,i} - z_{2,i}$ and $\dot{z}_i = q(y_i, z_i) := \mathrm{col}\,(w_\infty(y_i) - z_{1,i}, \varepsilon(b(y_i + y_{0,i}) - z_{2,i}))$. Define $\tilde{y}_1 = y_1, \tilde{y}_j := y_1 - y_{j+1}, \tilde{z}_1 = z_1, \tilde{z}_j = z_1 - z_{j+1}, j = 2,\ldots,k_1$, then $\dot{\tilde{y}}_j = a(y_1, z_1) - a(y_1 - \tilde{y}_j, z_1 - \tilde{z}_j) + u_1 - u_j$ and $\dot{\tilde{z}}_j = q(z_1, y_1) - q(z_1 - \tilde{z}_j, y_1 - \tilde{y}_j)$. Consider the Lyapunov function $V = \frac{1}{2}\tilde{y}^\top\tilde{y} + \frac{1}{2}\tilde{z}^\top P\tilde{z}$ with $\tilde{y} = \mathrm{col}\,(\tilde{y}_2,\ldots,\tilde{y}_{k_1})$, $\tilde{z} = \mathrm{col}\,(\tilde{z}_2,\ldots,\tilde{z}_{k_1})$ and

$$
P = \tilde{P} \otimes I, \quad \tilde{P} = \frac{1}{\varepsilon}\begin{pmatrix} \varepsilon & 0 \\ 0 & 1 \end{pmatrix}. \quad\quad (A.2)
$$

Note that $a(y_1, z_1) - a(y_j, z_j) = (a(y_1, z_1) - a(y_j, z_1)) + (a(y_j, z_1) - a(y_j, z_j))$. Using the ultimate boundedness of the states of all systems (Lemma 1), the triangle inequality and Lipschitz continuity of $a(\cdot,\cdot)$, it follows that there exist constants $c_0, c_1 \in \mathbb{R}_{>0}$ such that $\tilde{y}_j(a(y_1, z_1) - a(y_j, z_j)) \leq c_0|\tilde{y}_j| \cdot |\tilde{z}_j| + c_1|\tilde{y}_j|^2$. Similarly we have $\tilde{z}_j^\top\tilde{P}(q(z_1, y_1) - q(z_j, y_j)) \leq -|\tilde{z}_j|^2 + c_0|\tilde{y}_j|\cdot|\tilde{z}_j|$ for some constant $c_2 \in \mathbb{R}_{>0}$. Hence there exist positive constants C_0, C_1 such that $\dot{V} \leq -|\tilde{z}|^2 + C_0|\tilde{z}|\cdot|\tilde{y}| + C_1|\tilde{y}|^2 + \tilde{y}^\top\tilde{u}$ with $\tilde{u} := \mathrm{col}\,(u_1 - u_2,\ldots,u_1 - u_{k_1})$. Note that the constants C_0 and C_1 only depend on the bounds on the trajectories y_i and z_i and the functions $a(\cdot,\cdot), q(\cdot,\cdot)$ and not on the number of cells. Since the coupling is global we have

$$
u_1 = g_c(y_j - y_1) + g_c\sum_{\ell=2,\ell\neq j}^{k}(y_\ell - y_1), \quad (A.3)
$$

$$
u_j = g_c(y_1 - y_j) + g_c\sum_{\ell=2,\ell\neq j}^{k}(y_\ell - y_j), \quad (A.4)
$$

such that $\tilde{u}_j = -g_c k\tilde{y}_j$. Hence $\tilde{y}^\top\tilde{u} = -g_c k|\tilde{y}|^2$ such that if $g_c k \geq \bar{g}_c := \frac{C_0^2}{4} + C_1$ there exists a constant $\epsilon > 0$ such that $\dot{V} \leq -\epsilon V$. It follows that $\int_{t_0}^{t} -\dot{V}(\tau)\mathrm{d}\tau = V(t_0) - V(t) \leq V(t_0) < \infty$. Hence, using Barbalat's lemma (note that $\dot{V}$ is uniformly continuous), we can conclude that the active cells synchronize. Using the same machinery one can easily prove that the inactive cells will also synchronize with each other. On the other hand, the active cells will not synchronize with the inactive cells since the linear manifold corresponding to synchronization $\mathcal{M} := \{\mathrm{col}\,(x_1,\ldots,x_k) \in \mathbb{R}^{3k} : x_1 = \ldots = x_{k_1} = x_{k_1+1} = \ldots = x_k\}$, $x_i := \mathrm{col}\,(y_i, z_{1,i}, z_{2,i})$, is not invariant under the closed loop dynamics (5), (6), (7), (8). It follows immediately that all cells in the islet synchronize whenever $g_c k \geq \bar{g}_c$ provided that all cells are active ($k_1 = k$) or all cells are inactive ($k_2 = k$) such that $\mathcal{M}$ is invariant under the given dynamics. $\qquad\square$