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# Conditions for synchronization and chaos in networks of $\beta$ -cells

J.M.W. van de Weem\* J.G. Barajas Ramírez\*\* R. Femat\*\*  
H. Nijmeijer\*

\* *Eindhoven University of Technology, PO Box 513, 5600 MB  
Eindhoven, The Netherlands.*

\*\* *Instituto Potosino de Investigación Científica y Tecnológica,  
IPICYT, Camino a la Presa San José 2055, Col. Lomas 4a. sección,  
San Luis Potosí, San Luis Potosí, 78216, México*

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**Abstract:** The insulin producing and releasing pancreatic  $\beta$ -cells play a key role in glucose homeostasis. The proper function of these cells is characterized by a spiking-bursting activity in their membrane potential. It is known that these cells are coupled with each other and that this coupling can induce synchronization. This fact maybe relevant in the mechanisms of blood glucose regulation. However, not much is known about conditions of synchronization, nor about the topology of real-world  $\beta$ -cell network. Also about the conditions for the emergence of chaotic bursting in networks of  $\beta$ -cells not much is known. We investigate these phenomena in terms of complex network theory as model of  $\beta$ -cells networks, in which synchronization and emergence of chaotic bursting occurs.

*Keywords:* Coupled systems; Pancreatic  $\beta$ -cells; Complex networks, Chaos, Synchronization.

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## 1. INTRODUCTION

The spiking-busting activation of pancreatic  $\beta$ -cells is associated with their insulin secreting and the overall glucose homeostasis. In isolation, a single  $\beta$ -cell can be on an activated state, in which bursting periodically occurs. Alternatively, the isolated  $\beta$ -cell can be inhibited with no spiking-busting behavior. Both activated and inhibited  $\beta$ -cells are naturally electrically-coupled via gap junction channels within the pancreatic islets of Langerhans, studies available in the literature have related the periodic bursting of the entire ensemble of  $\beta$ -cells to the synchronization of the network of  $\beta$ -cells [Smolen et al. (1993)]. In other studies, the synchronization of electrical bursting and metabolic oscillations have been mainly associated with electrical coupling between the cells [Pedersen et al. (2005)]. However, there is not much known about the topology and coupling strengths between  $\beta$ -cells, nor about conditions for chaotic behavior on  $\beta$ -cell networks. So we ask, Can the coupling between  $\beta$ -cells induce chaos, and when is such network in synchrony? Using knowledge of complex networks might help to get a deeper comprehension on these phenomena.

In this paper we are interested in conditions for which  $\beta$ -cells synchronize or produce chaotic behavior. Our particular interests lie in numerical and experimental modeling of these cells.

## 2. A SINGLE $\beta$ -CELL

The model that is used in this research to simulate the bursting behavior of  $\beta$ -cells was designed by Pernarowski. The equations for this model are [Pernarowski (1998)]

$$\begin{aligned}\frac{du}{dt} &= f(u) - w - k(c) \\ \frac{dw}{dt} &= \frac{1}{\bar{\tau}}(w_\infty(u) - w) \\ \frac{dc}{dt} &= \varepsilon(h(u) - c).\end{aligned}\tag{1}$$

In equation 1,  $u$  refers to the membrane potential,  $w$  refers to an ionic activation and  $c$  refers to the glucose concentration of the cell. The terms  $f(u)$ ,  $k(c)$ ,  $h(u)$  and  $w_\infty$  that are used in above formulas are defined as

$$\begin{aligned}f(u) &= f_3 u^3 + f_2 u^2 + f_1 u \\ f_3 &= -\frac{a}{3} \\ f_2 &= a\hat{u} \\ f_1 &= \frac{1}{\bar{\tau}} - a(\hat{u}^2 - \eta^2) \\ h(u) &= \beta(u - u_\beta) \\ k(c) &= \bar{\tau}c \\ w_\infty(u) &= w_3 u^3 + w_2 u^2 + w_1 u + w_0 \\ w_3 &= \bar{\tau} - \frac{a}{3} \\ w_2 &= a\hat{u} \\ w_1 &= \frac{1}{\bar{\tau}} - a(\hat{u}^2 - \eta^2) - 3\bar{\tau} \\ w_0 &= -3\bar{\tau}\end{aligned}\tag{2}$$

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<sup>1</sup> e-mail: j.m.w.v.d.weem@student.tue.nl

<sup>2</sup> e-mail: jgbarajas@ipicyt.edu.mx

<sup>3</sup> e-mail: rfemat@ipicyt.edu.mx

<sup>4</sup> e-mail: h.nijmeijer@tue.nl

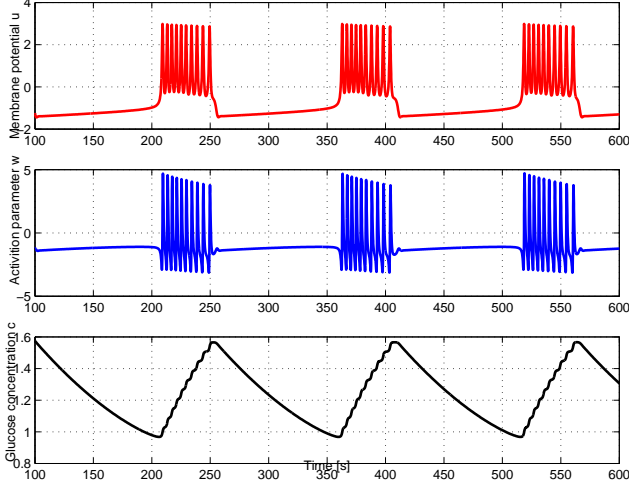


Fig. 1. States  $u, w$  and  $c$  of a bursting  $\beta$ -cell.

with parameters

$$\begin{aligned} a &= \frac{1}{4}, \eta = \frac{3}{4}, \hat{u} = \frac{3}{2}, \beta = 4, \\ u_\beta &= -0.954, \varepsilon = 0.0025, \bar{\tau} = 1. \end{aligned} \quad (3)$$

The trajectories of single  $\beta$ -cell model are shown in Fig. 1. A measure for chaotic behavior of a cell in isolation is the Lyapunov exponent. It describes the long-term development of a direction in the phase space of a system, where a positive exponent represents expansion and a negative exponent represents contraction. When there exists at least one positive Lyapunov exponent, the system can be considered as chaotic, with the magnitude of the exponent reflecting the time scale on which the system dynamics become unpredictable [Wolf et al. (1985)]. The Lyapunov exponents are calculated by

$$h_i = \lim_{t \rightarrow \infty} \frac{1}{t} |J(t, x_0) u_i|, \quad i = 1, 2, 3 \quad (4)$$

where  $h_i$  is the  $i$ th Lyapunov exponent of the isolated cell along the direction  $u_i$ ;  $J(t, x_0)$  is the Jacobian matrix of equations (1) evaluated at a randomly selected initial condition  $x_0$  and  $\{u_1, u_2, u_3\}$  is a set of orthonormal vectors in the tangent space of the system.  $h_i$  is ordered as

$$h_1 \geq h_2 \geq h_3. \quad (5)$$

To check if a  $\beta$ -cell produces chaotic behavior, the Lyapunov exponents can be determined for the inhibited cell, i.e. when the cell doesn't produce bursting. For the  $\beta$ -cell system this is the case when the parameter  $u_\beta = -1.3$ . The three exponents, representing the directions of  $u$ ,  $w$  and  $c$ , are plotted in Fig. 2 over 10,000 seconds to attain the final values  $h_1 = -0.0277$ ,  $h_2 = -0.3621$  and  $h_3 = -1.1233$ . All exponents are negative, meaning that a  $\beta$ -cell is not chaotic.

System (1) was implemented on an electronic circuit to get more realistic results, in this case all cells are different due to uncertainties in the electronics.

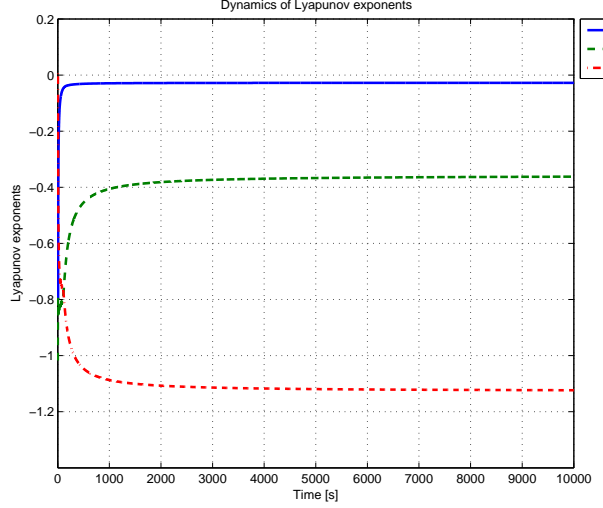


Fig. 2. Lyapunov exponents for a  $\beta$ -cell

### 3. COMPLEX NETWORKS AND THE SYNCHRONIZATION CRITERION

The  $N$  node networks that will be discussed are diffusively coupled only in their first state variable ( $u$ ), i.e. the coupling between a pair of cells is dependent on the difference in output voltage of these cells. Then, the entire network can be written as [Wang and Chen (2002)]

$$\dot{\mathbf{x}}_i = f(\mathbf{x}_i) + c \sum_{j=1}^N a_{ij} \Gamma \mathbf{x}_j, \quad i = 1, 2, \dots, N \quad (6)$$

where  $\mathbf{x}_i = (u_i, w_i, c_i)$  are the state variables of node  $i$ , the constant  $c > 0$  represents the coupling strength, and the internal coupling matrix equals  $\Gamma = \text{diag}(1, 0, 0)$  in our situation. If there is a connection between node  $i$  and node  $j$  ( $i \neq j$ ), then  $a_{ij} = a_{ji} = 1$ ; otherwise,  $a_{ij} = a_{ji} = 0$ .  $a_{ii}$  can be defined using the degree  $k_i$  of node  $i$ , which is the total number of connections of node  $i$ :

$$a_{ii} = -k_i = - \sum_{j=1, j \neq i}^N a_{ij}, \quad i = 1, 2, \dots, N. \quad (7)$$

A coupling matrix  $\mathbf{A} = (a_{ij}) \in \mathbb{R}^{N \times N}$  can be created, which represents the coupling configuration of the network. There are no isolated clusters considered inside the network, meaning that  $\mathbf{A}$  is a symmetric, irreducible matrix having a zero eigenvalue with multiplicity 1 and all other eigenvalues strictly negative:

$$0 = \lambda_1 > \lambda_2 \geq \lambda_3 \geq \dots \geq \lambda_N. \quad (8)$$

#### 3.1 Synchronization

According to [Wu and Chua (1995)], a network will synchronize if the largest non-zero eigenvalue  $\lambda_2$  of  $\mathbf{A}$  is negative enough, i.e.

$$\lambda_2 \leq -\frac{T}{c}. \quad (9)$$

where  $c > 0$  is the coupling strength of the network and  $T > 0$  is a positive constant such that zero is an exponentially stable point of the  $n$ -dimensional system.

### 3.2 Chaotic behavior

Lyapunov exponents are used to characterize chaotic behavior of a single cell, while eigenvalues of the coupling matrix are used to say something about synchronization of the network. These can be combined in transverse Lyapunov exponents (tLes) to determine chaotic behavior of a network [Barajas-Ramírez and Femat (2008)]:

$$\begin{aligned} \mu_i(\lambda_k) &= h_i + c\lambda_k \\ i &= 1, 2, 3; \quad k = 1, 2, \dots, N. \end{aligned} \quad (10)$$

with  $\mu_i(\lambda_k)$  the tLe of the  $i$ th Lyapunov exponent of a single cell  $h_i$  and the  $k$ th eigenvalue  $\lambda_k$  of the coupling matrix  $\mathbf{A}$ . The coupling strength  $c < 0$ , because instead of synchronization, chaos is wanted. The tLes are sorted as

$$\begin{aligned} \mu_1(\lambda_k) &\geq \mu_2(\lambda_k) \geq \mu_3(\lambda_k) \\ \mu_i(\lambda_N) &\geq \mu_i(\lambda_{N-1}) \geq \dots \geq \mu_i(\lambda_2) \geq \mu_i(\lambda_1) \end{aligned} \quad (11)$$

so  $\mu_1(\lambda_N)$  is the largest tLe and  $\mu_3(\lambda_1)$  is the smallest tLe. Considering only inhibited  $\beta$ -cell, every cell in the network will go to the same stable equilibrium point if the largest tLe is negative, which means in our case ( $h_1 < 0$ ) that

$$\frac{h_1}{\lambda_N} > |c|. \quad (12)$$

Extra conditions are presented in [Barajas-Ramírez and Femat (2008)] to make distinction between chaotic and unbounded solutions. Bounded chaotic solutions can be expected when the largest tLe is positive, i.e.

$$\frac{h_1}{\lambda_N} < |c| < \frac{h_\tau}{\lambda_T}, \quad (13)$$

$$\tau = 2, 3; \quad T = 1, 2, \dots, N - 1.$$

but the remaining tLes compensate for this in order to avoid unbounded solutions, i.e. the sum of tLes for any node is negative:

$$\sum_{i=1}^m \mu_i(\lambda_k) < 0, \text{ for any } k. \quad (14)$$

Nevertheless, these are not concrete boundaries: bounded chaotic behavior may also occur when more than one tLe is positive and the largest sum of tLes is negative. Furthermore, bounded chaotic behavior may occur even when only the largest tLes is positive. Nevertheless, the compensation of the positive tLes plays a major role in chaotic behavior.

This theory can be used to have a guideline when  $\beta$ -cells may produce continuous bursting, a behavior which may lead to exhaustion and failures in the cells.

## 4. NETWORK TOPOLOGY MODELS

To get an answer on the questions stated in the introduction, some benchmark network topologies will be studied.

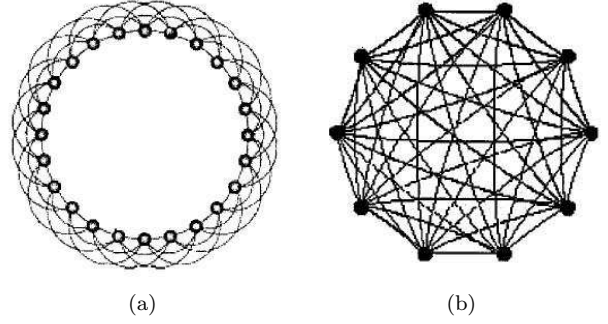


Fig. 3. Regular networks: a) Nearest neighbor topology: each cell is connected to its  $l=6$  nearest cells. b) Globally coupled topology: all cells are connected to each other. [Wang and Chen (2002)]

These are the regular nearest-neighbor and globally coupled models and the complex small-world and scale-free models.

### 4.1 Nearest-neighbor coupled

In the nearest-neighbor coupled model (Fig. 3a), a network of  $N$  cells is arranged in a ring, where each cell is connected to its  $l$  nearest cells, with  $l > 0$  being an even integer. The largest non-zero eigenvalue of this model is [Wang and Chen (2002)]

$$\lambda_{2nn} = -4 \sum_{j=1}^{l/2} \sin^2 \left( \frac{j\pi}{N} \right), \quad (15)$$

which means that  $\lambda_{2nn}$  goes to zero for large networks such that the nearest-neighbor network will be very difficult to synchronize when the number of nodes is large.

### 4.2 Globally coupled

In the globally coupled model, all cells are directly connected to each other. The coupling matrix for this network has all non-zero eigenvalues equal to  $-N$ , where  $N$  is the total number of cells in the network.

The requirement for synchronization is

$$\lambda_{2gc} = -N \leq -\frac{T}{c} \quad (16)$$

so the network synchronizes easier when the network is large.

### 4.3 Small-world

A transition between above regular networks and random networks is the small-world model designed by Newman and Watts (Fig. 4a). The starting point for this model is the nearest-neighbor model. New connections are added between cells with a probability  $p$  with the constraints that a pair of cells can not be connected more than once and a cell can not have a connection with itself [Wang and Chen (2002)].

The largest non-zero eigenvalue of the coupling matrix is

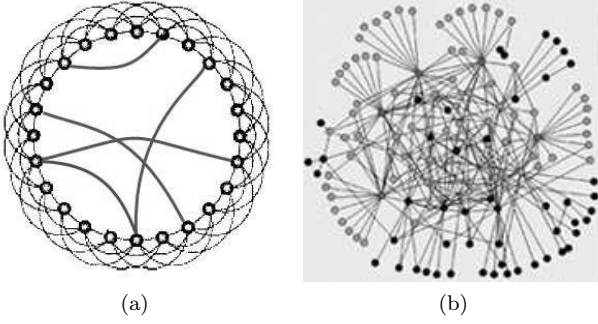


Fig. 4. Complex networks: a) Small-world topology: Nearest neighbor topology, but with random extra connections. b) Scale free topology: Each new cell is connected to  $m$  existing cells. [Wang and Chen (2003)]

dependent on both the probability and the number of cells in the network:

$$\lambda_{2sw}(p, N) \leq -\frac{T}{c}. \quad (17)$$

When  $p = 0$ , this model reduces to the nearest-neighbor network and for  $p = 1$  it becomes a globally coupled network.

#### 4.4 Scale-free

Another complex network can be found in the scale-free model of Barabási and Albert (Fig. 4b). The starting point is a small number of cells  $m_0$ . At every time step is a new node introduced and connected to  $m \leq m_0$  already-existing cells. This happens with preferential attachment: the probability  $\Pi_i$  that a new cell is connected to already-existing cell  $i$  depends on the degree  $k_i$  of cell  $i$  related to the total number of connections in the network:  $\Pi_i = k_i / \sum_j k_j$  [Wang and Chen (2003)].

This network will consist of a few cells having many connections (“hubs”) and many cells with only a few connections. There is no analytical formula present for calculating the eigenvalues, the only thing that can be said for this network is that the largest non-zero eigenvalue is dependent on  $m_0$  and  $m$ :

$$\lambda_{2sf}(m_0, m) \leq -\frac{T}{c}, \quad (18)$$

where  $m$  is often chosen equal to  $m_0$ .

The above topologies can also be applied experimentally with the use of multiple cells on a circuit board and a computer connecting the cells.

## 5. RESULTS

### 5.1 Synchronization

The threshold value of the system is numerically determined as  $T = 1.6$ . Because there are no analytical formulas present to calculate  $\lambda_2$  for some network topology models, they are determined numerically and the minimum coupling strength for synchronization is calculated. This is done 20 times for network sizes of 4 to 100 cells of each

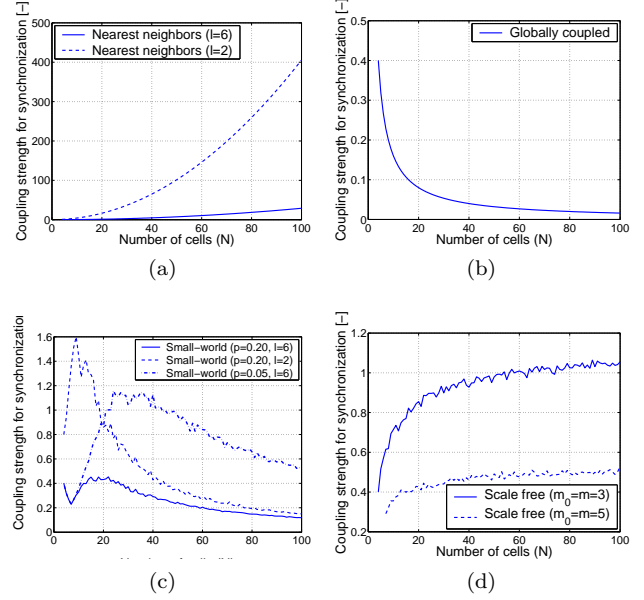


Fig. 5. Minimum coupling strength needed for dynamical synchronization of the specific network a) Nearest-neighbor, b) Globally coupled, c) Small-world and d) Scale-free network

topology to get a good average.

As expected, the minimum coupling strength to synchronize a nearest-neighbor network increases rapidly when the network grows (Fig. 5a). For  $l = 2$ , this results in a coupling strength  $c = 405.4$  for a network of 100 cells. The needed coupling strength is reduced significantly to  $c = 29$  when each cell is connected to its six nearest neighbors, but is still very large.

From equation (16), it would be expected that the coupling strength of a globally coupled network is inversely proportional to the number of cells. This is verified by Fig. 5b, where a network of 4 cells needs  $c = 0.4$  to synchronize and  $c = 0.016$  is enough for a network of 100 cells.

In general, the small-world topology is showing a decreasing line with respect to the number of cells (Fig. 5c). Reducing the number of nearest-neighbors in this model will give a different result mainly in small networks: a stronger coupling is needed. But when the network is sufficiently large, it can be noticed that the network with  $l = 2$  gets close to the network with  $l = 6$  when the network is sufficiently large. On the other side, reducing the probability of a new connection significantly increases the coupling strength needed for synchronization. In Fig. 5c you can see the differences between  $p = 0.20$  and  $p = 0.05$ , where  $c = 0.12$  and  $c = 0.55$  respectively are needed for synchronization of a network of 100 cells.

The scale-free network shows an increasing coupling strength which remains constant for sufficiently large networks. This is interpretable because addition of a new cell doesn’t change the topology of the network significantly when it is sufficiently large. Increasing the number of connections per newly added cell from  $m = 3$  to  $m = 5$  decreases the needed coupling strength from 1.05 to 0.5 (Fig. 5d).

It can be concluded that all topologies behave differently. While the minimum coupling strength for the nearest-neighbor and the scale-free topologies increases for net-

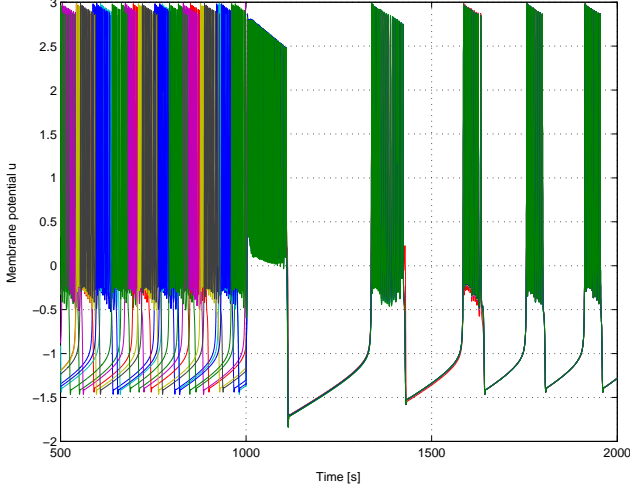


Fig. 6. A nine-cell globally coupled network synchronizes when a coupling of  $c = 0.18$  is introduced after 1000 seconds

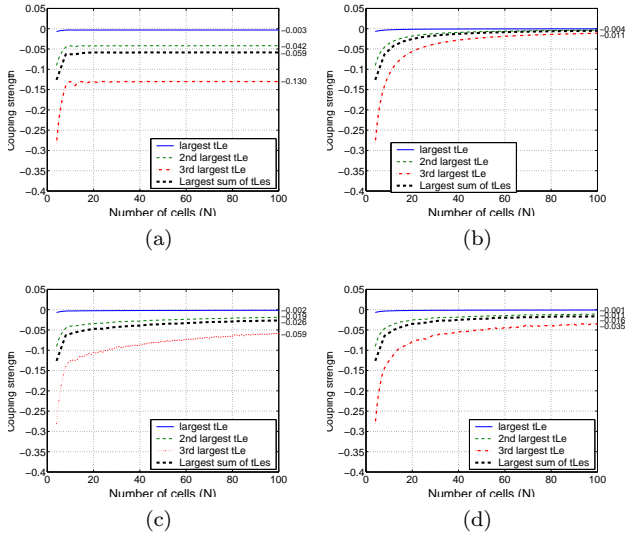


Fig. 7. 1st-, 2nd- and 3rd-largest tLes and the line when the largest sum of tLes is zero for different topologies of networks ranging from  $N = 4$  to  $N = 100$ . a) Nearest neighbor ( $l = 6$ ), b) Globally coupled, c) Small-world ( $p = 0.05, l = 6$ ) and d) Scale-free ( $m_0 = m = 3$ ).

work size, the opposite happens for the globally coupled and small-world topologies.

Fig. 6 is an example of the bursting of a network consisting of nine cells. Initially, the cells are uncoupled and bursting is asynchronous. The cells are globally coupled after 1000 seconds with  $c = 0.18$ , which is stronger than the minimum coupling strength of  $c \geq -\frac{1-6}{9} = 0.1778$ . The resulting bursting behavior is equal to that of a single cell (fig. 1). Interesting is that this happens within two bursting periods while the coupling strength is only slightly stronger than necessary for synchronization.

## 5.2 Chaotic behavior

To have guidelines for chaos in networks of  $\beta$ -cells, the values of the coupling strength when the largest sum of

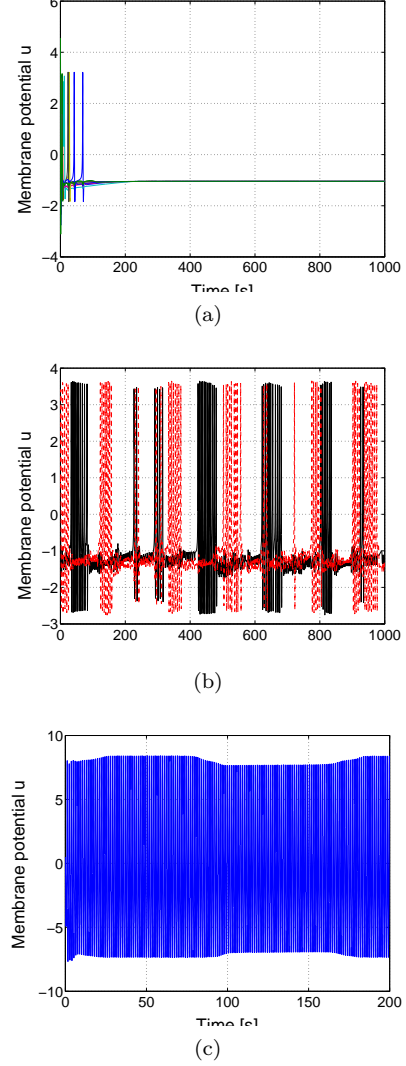


Fig. 8. Trajectories of a globally coupled network of nine cells for different coupling strengths. a) all cells go to the equilibrium point for  $c = -0.03$ , b) asynchronous bursting at  $c = -0.08$  (two cells shown) and c) continuous bursting at  $c = -0.50$  (one cell shown).

tLes equals zero and when the tLes are zero, are calculated for examples of the different topologies.

These values get constant for the nearest-neighbor network in an early stage of the network growing process (Fig. 7a). Following the guidelines of subsection 3.2, synchronization to the equilibrium point would be expected till a very small coupling strength of  $c = -0.003$  for all network sizes of the 6-nearest-neighbor topology. Bounded chaotic behavior can be expected between  $c = -0.003$  and  $c = -0.042$ , whereupon for smaller values unbounded behavior may exist. The largest sum of tLes gets positive at  $c = -0.059$ . These values get closer to zero when the number of nearest-neighbors is increased.

In the globally coupled model, the tLes get more easily positive for large networks (Fig. 7b). The coupling strength needed to get the first tLe, the second tLe and the largest sum of tLes positive, converges to  $c = -0.004$  for a network of 100 cells. The third tLe gets positive for  $c = -0.011$  in the same network.

The results for the small-world model (Fig. 7c) look similar

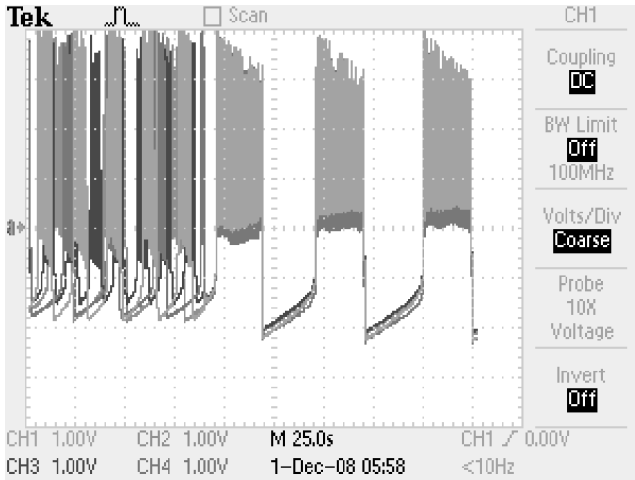


Fig. 9. Example of a real time globally coupled network of six cells with coupling strength  $c = 0.6$ . Four cells shown due to limited input of the oscilloscope and a time scaling is applied for viewing purposes

to the previous model. The coupling values when the tLes become positive are more separated and need a more negative coupling strength to get chaotic in this example. But a higher probability for new connections or more nearest-neighbors in the initial network will result in less negative tLes and thus are more similar to the globally coupled network.

Also the scale-free model behaves the same as the previous two models: when the network is larger, it is easier to get chaotic behavior (Fig. 7d). When the number of connections for a newly introduced cell is increased, the tLes will be less negative.

In overall, it can be concluded that it is easier to attain chaotic behavior for a large network with many connections than for a small network with few connections. The results of all topologies are very close to each other, especially for large networks. The only exception is the nearest-neighbor model.

The globally coupled network of nine cells is again mentioned to visualize the different kinds of chaotic bursting. The largest-, second largest- and third largest tLe become positive at  $c = -0.003$ ,  $c = -0.04$  and  $c = -0.125$  respectively. The largest sum of tLes is positive for values below  $c = -0.058$ .

It would be expected that all cells go to the equilibrium point until the largest tLe becomes positive. However, this behavior is still encountered till  $c = -0.034$  (Fig. 8a). The oscillatory responses during the first seconds are due to the choice of the initial values.

Asynchronous bursting is found for  $c = -0.035$  and below (Fig. 8b). The bursting period and amplitude increase for more negative values of  $c$  till eventually all cells continuously burst (fig. 8c), but the network stays always bounded.

This example illustrates that the tLe method can create certain regions to predict chaos, but it doesn't give concrete boundaries.

### 5.3 Experimental results

The advantage to use electronic cells is that the coupling of cells is easier and all cells are different because of

uncertainties in the electronic components. The result of seven globally coupled cells is shown in Fig. 9 as illustration. A coupling strength  $c = 0.6$  was used to get a satisfactory synchronization. This is three times as high as theory says and the result is a larger bursting period and no *perfect* synchronization. This is due to the differences and uncertainties between the cells.

## 6. DISCUSSION

In this report we used four different network topologies for ensembles of  $\beta$ -cell model and investigated conditions for synchronization and emergence of chaotic behavior. Also an electronic setup is successfully created to simulate these networks. This shows potential for explaining biological processes and especially the electronic setup may help biologists with experiments on  $\beta$ -cells, because it is much easier interpret than numerical simulations.

It has been decided to only mention general coupling for this contribution, i.e. the coupling strength for all connections is equal and the heterogeneity of a network is only caused by its topology. For future research, it is possible to have different coupling strengths for different connections. Although this might give a more accurate representation of the real coupling between  $\beta$ -cells, it will also be more difficult to analyze.

Another remark is that it is possible to have partial synchronization for certain coupling strengths, smaller than the coupling strength needed for complete synchronization, where only a part of the network synchronizes. Knowledge is absent if this is wanted in this specific biological purpose, but it may be subject for future research.

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