Synchronization and transitions in β-cells networks

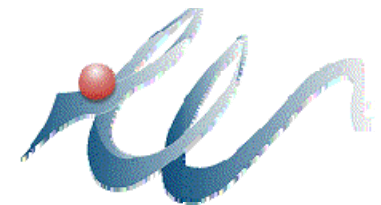*Ricardo Femat*

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In collaboration with

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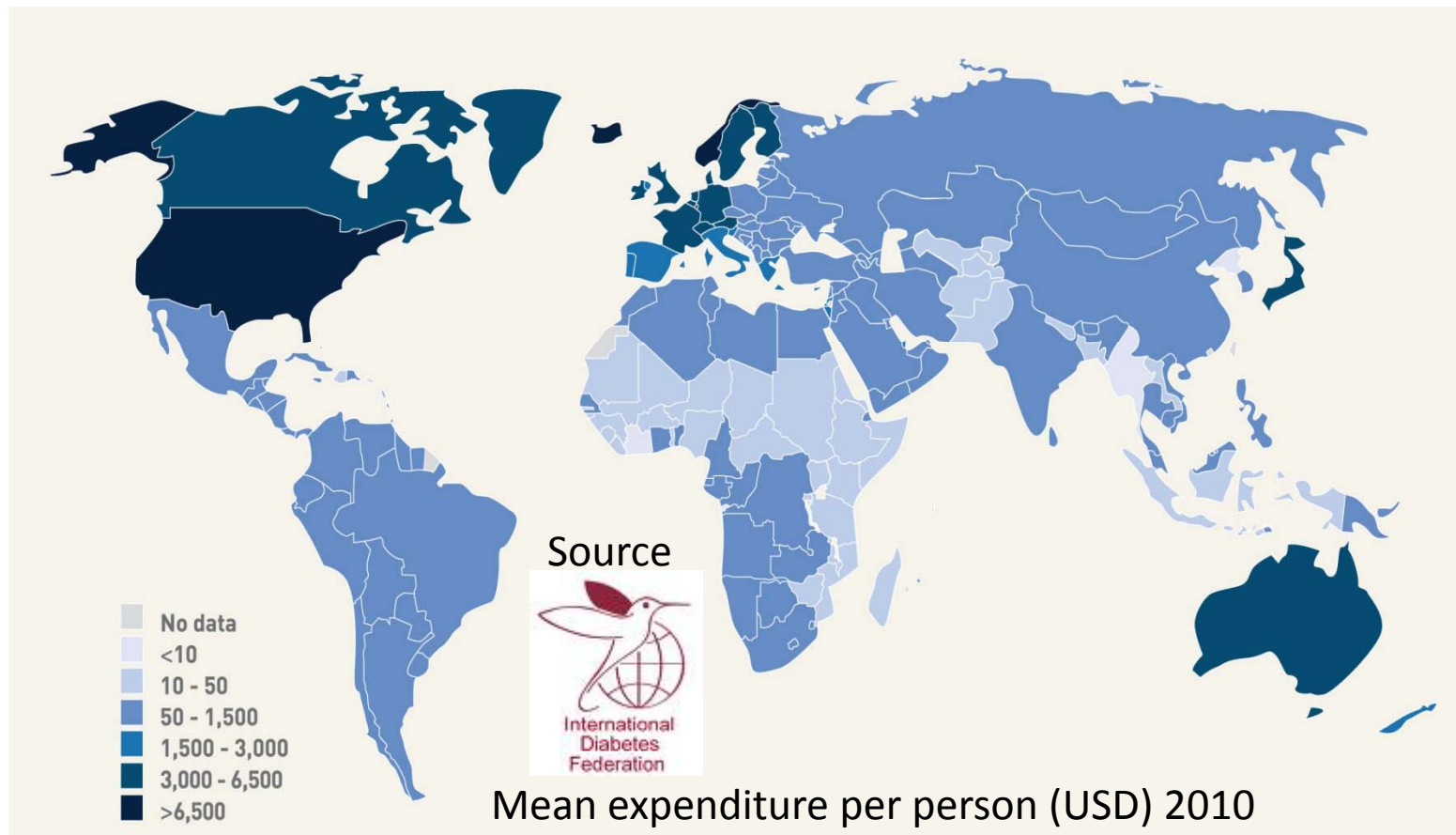IPICYT

I will chat with you about …

- A semipassivity-based approach to claim synchrony

  - **On semipassive properties of the electrical activity of an isolated β-cell.**
  - **On conditions for synchrony in terms of semipassivity.**

- Conditions for the emergence of bounded complex solutions

  - **On how changes on specific topological aspects produce transitions among bounded behaviors of dynamical networks.**

The complete version of results can be found at:
1. *Automatica , year 2011, Vol. 47, pags 1243-1248,*
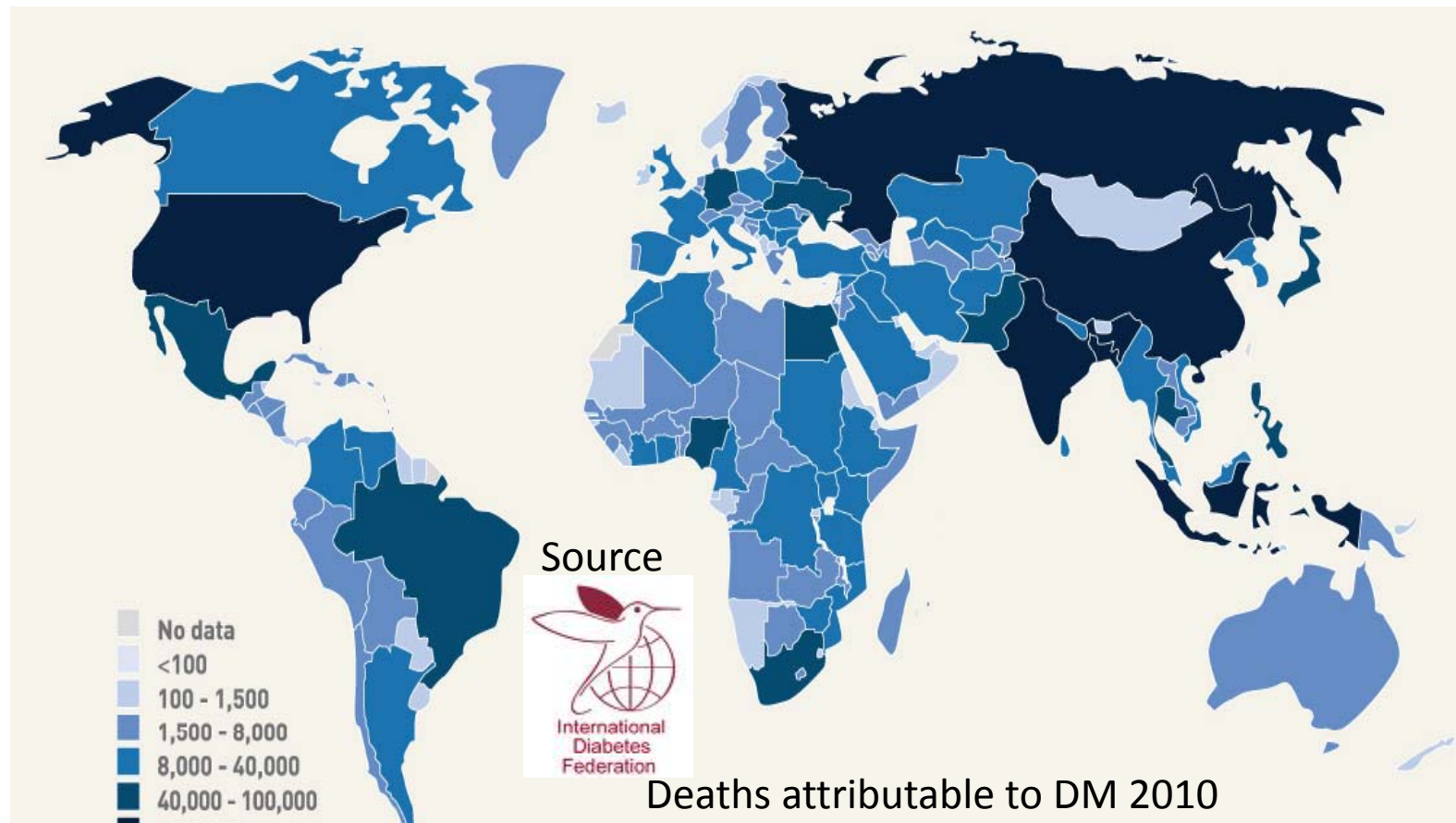2. *Int. J. Systems Science, year 2011, i-first 569585.*

But, before that, let me address briefly the relevance on this topic

Some problems seems unconnected to Chaos Theory: Diabetes Mellitus is an example

Source

International Diabetes Federation

No data
<10
10 - 50
50 - 1,500
1,500 - 3,000
3,000 - 6,500
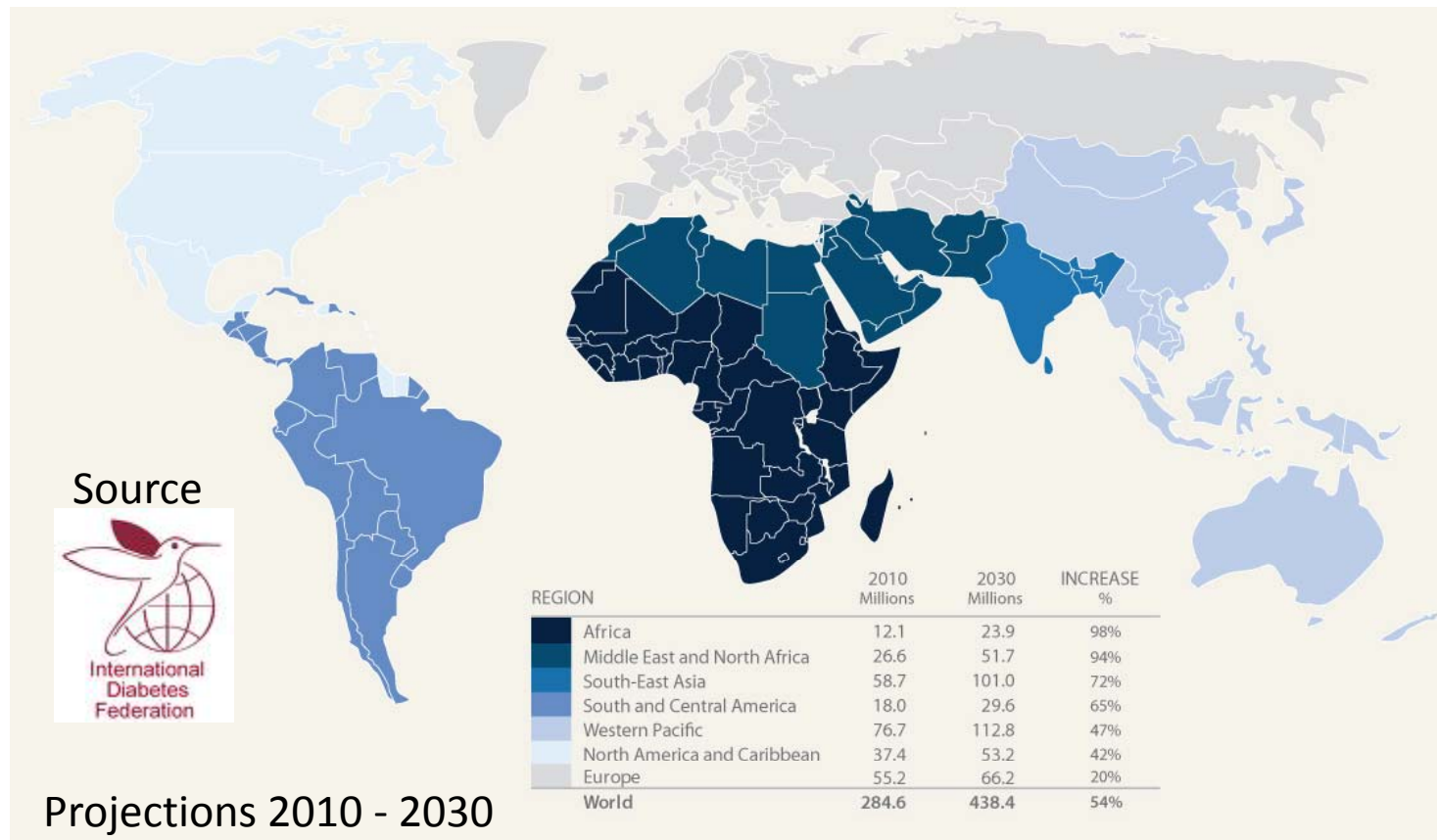>6,500

Mean expenditure per person (USD) 2010

But, before that, let me address briefly the relevance on this topic

Some problems seems unconnected to Chaos Theory: Diabetes Mellitus is an example

Source

International Diabetes Federation

No data
<100
100 - 1,500
1,500 - 8,000
8,000 - 40,000
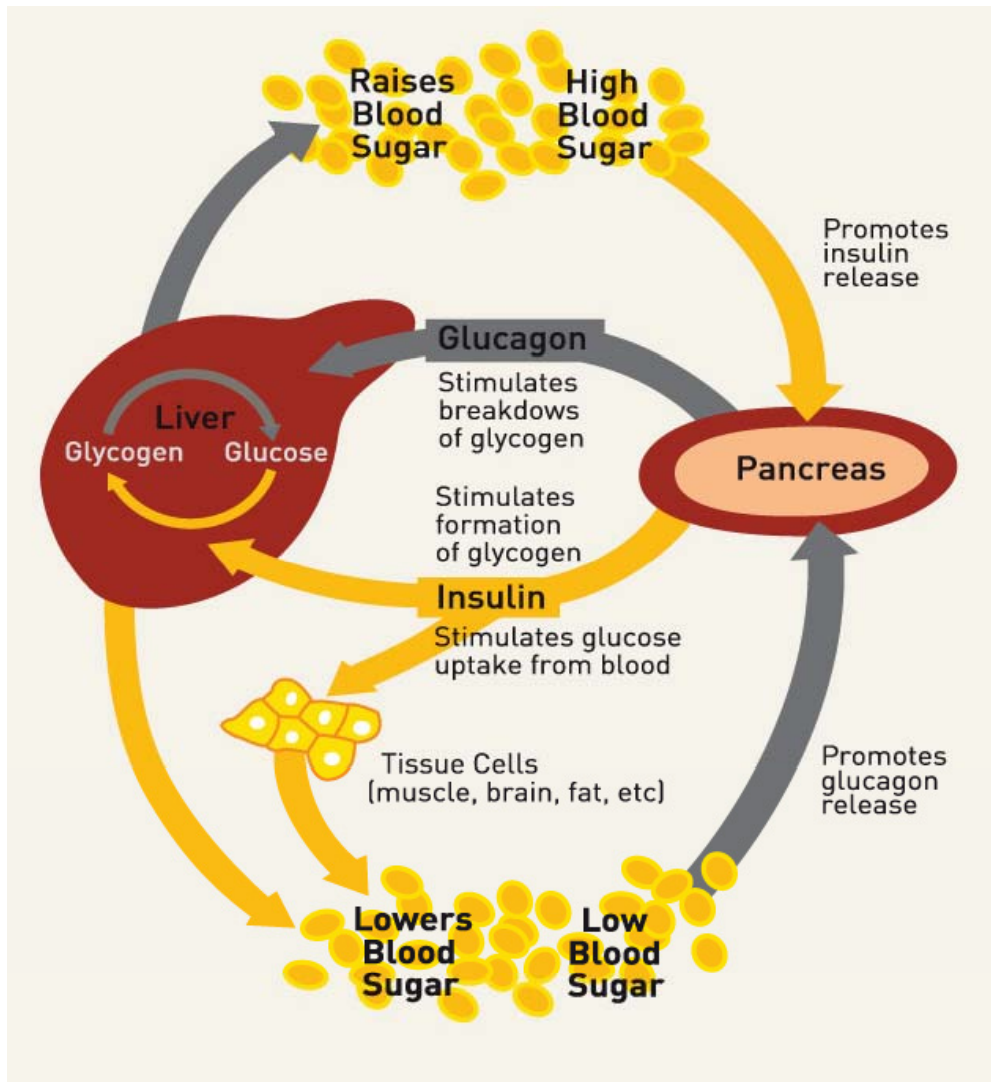40,000 - 100,000

Deaths attributable to DM 2010

But, before that, let me address briefly the relevance on this topic

Some problems seems unconnected to Chaos Theory: Diabetes Mellitus is an example

Source

International Diabetes Federation

REGION	2010 Millions	2030 Millions	INCREASE %
Africa	12.1	23.9	98%
Middle East and North Africa	26.6	51.7	94%
South-East Asia	58.7	101.0	72%
South and Central America	18.0	29.6	65%
Western Pacific	76.7	112.8	47%
North America and Caribbean	37.4	53.2	42%
Europe	55.2	66.2	20%
World	284.6	438.4	54%

Projections 2010 - 2030

Now, about relation between DM and complex networks

In Diabetes Mellitus, Pancreas is miss-functioning
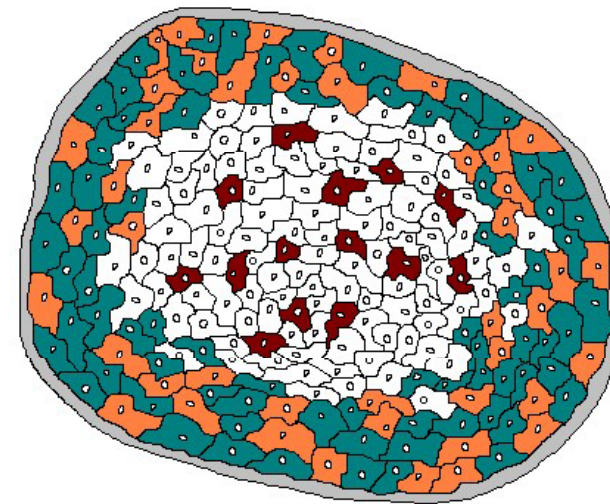
The β-cell activity plays "the role" in using glucose for glucose hemeostasis

These facts lead us to observe shared premises and questions

Premises:

  1.- Chaos theory can explain and model nonlinear phenomena

  2.- Biodynamical phenomena related to glucose regulation are nonlinear (possibly chaotic)

Current questions linking Chaos - Diabetes problems :

  1.- Is the pancreatic islet of β-cell behavior synchronous ?

  2.- Since each β-cell islet are very important in glucose regulation, Does the synchrony phenomena make sense on them?

Next, the semipassivity-based approach for complex networks synchrony

In this part, we used the semipassivity framework to determine synchrony conditions for networks of β-cells under two different situations:

- *(i) homogeneous*: networks of activated β-cells where we determine under what conditions synchronization is achieved

- *(ii) heterogeneous*: networks where we consider that before coupling some β-cells are activated while the others are inhibited.

A model for a single β-cell

The model used this contribution corresponds to the electrical activity of a Beta cell [Pernarowski (1998)]

$$\frac{du}{dt} = f(u) - w - k(c)$$
$$\frac{dw}{dt} = \frac{1}{\bar{\tau}}(w_\infty(u) - w) \qquad\qquad (4)$$
$$\frac{dc}{dt} = \varepsilon(h(u) - c).$$

where

u stands for the membrane potential,
w denotes the ionic channel activation, and
c refers to the concentration of agents that regulate bursting electrical activity of the cell (as glucose, Ca^{+2}, etc.).

A model for a single β-cell
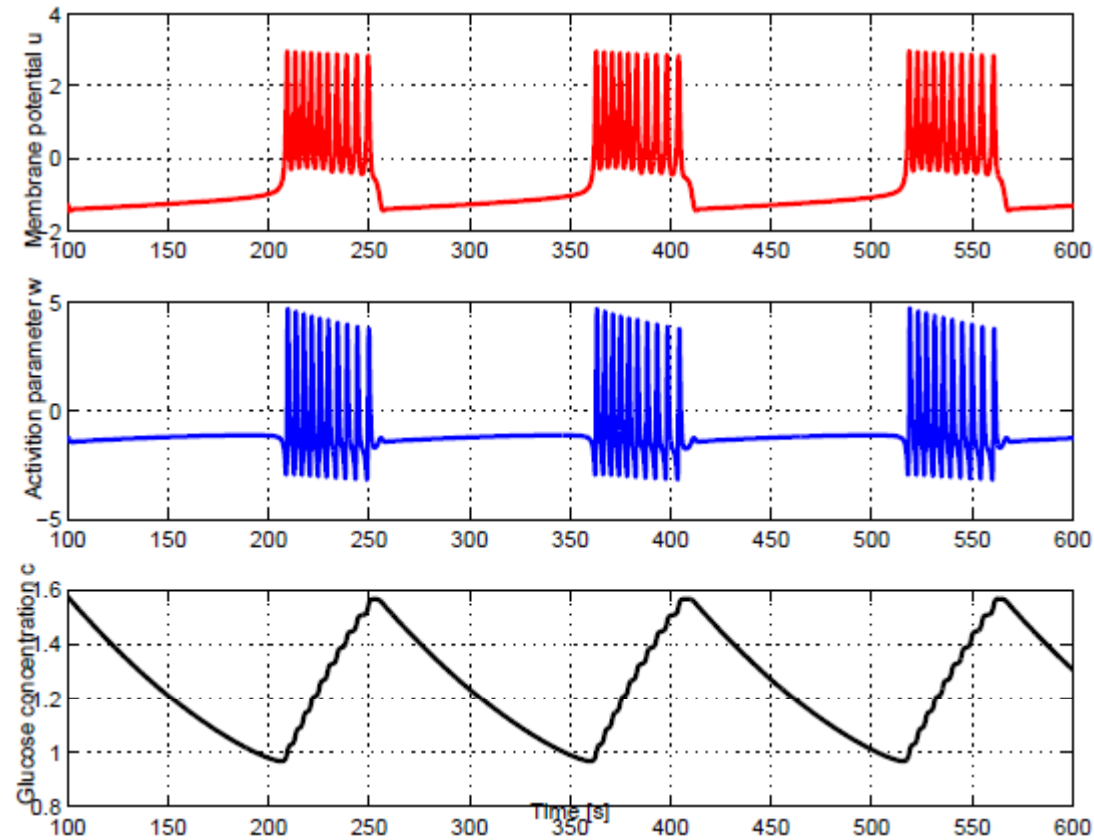
Figure 1. *u, w* and *c* of an activated β-cell in isolation.

Let us depart on semipassivity of β-cells

$$\dot{x}(t) = F(x(t)) + \Gamma u(t)$$

$$u(t) = g_c \sum_{j=1}^{M} a_{1j} y_j(t) = g_c(a_{1,2}(y_1(t) - y_2(t))$$

$$+ a_{1,3}(y_1(t) - y_3(t)) + \ldots + a_{1,M}(y_1(t) - y_M(t)))$$

where $y_i(t) = Cx_i(t) = [1, 0, 0]x_{i1}(t) = x_{i1}(t)$, for $i = 1, 2, \ldots, M$; and $a_{ij} < 0$, for $i \neq j$.

A result on semipassivity of β-cells

The system in (6) is called semipassive if there exists a storage function $V \in \mathcal{C}^1$, $V : \mathbf{R}^3 \to \mathbf{R}_+$, with $V(0) = 0$; and $\underline{\alpha}, \bar{\alpha} \in \mathcal{K}_\infty$ two *class-k* functions, such that

$$1. \qquad \underline{\alpha}(\|x(t)\|) \leq V(x(t)) \leq \bar{\alpha}(\|x(t)\|), \text{ and}$$

$$2. \qquad \dot{V}(x(t)) = \frac{\partial V(x(t))}{\partial x(t)} f(x(t), u(t)) \leq y(t)u(t) - H(x(t))$$

where the scalar function $H(x(t)) : \mathbf{R}^3 \to \mathbf{R}$ is nonnegative for $x(t)$ lying outside some ball $\mathcal{B} \subset \mathbf{R}^3$; that is, there exists a number $r \in \mathbf{R}$ and some non-negative function $q : \mathbf{R}^3 \to \mathbf{R}$ defined for $\|x(t)\| \geq r$, such that:

$$H(x(t)) \geq q(\|x(t)\|), \text{ for } \forall \, \|x(t)\| \geq r$$

First, we show each β-cell is semipassive

Lemma 3.2 *Each β-cell in the pancreatic islet described in (4) is strictly semi-passive.*

$$\dot{x}(t) = F(x(t)) + Bu(t)$$

where the input is given by

$$u(t) = g_c \sum_{j=1}^{M} a_{1j} y_j(t) = g_c(a_{1,2}(y_1(t) - y_2(t))$$

$$+ a_{1,3}(y_1(t) - y_3(t)) + \dots + a_{1,M}(y_1(t) - y_M(t)))$$

with $y_i(t) = Cx_i(t) = [1, 0, 0]x_{i1}(t) = x_{i1}(t)$, and $B = \Gamma$.

$$V(x(t)) = \tfrac{1}{2}(x_1^2(t) + \mu x_2^2(t) + \tfrac{1}{\varepsilon\beta} x_3^2(t))$$

The time derivative of the storage function along trajectories is given by

$$
\begin{aligned}
\dot{V}(x(t)) &= x_1(t)\left[f(x_1(t)) - x_2(t) - k(x_3(t)) + u(t)\right] + \mu x_2(t)\left[\tfrac{1}{\tau}(\omega_\infty(x_1(t)) - x_2(t))\right] \\
&\quad + \tfrac{1}{\varepsilon\beta}x_3(t)\left[\varepsilon(h(x_1(t)) - x_3(t))\right] \\
&= y(t)u(t) - H(x(t))
\end{aligned}
$$

Using the Pernarowski's model

$$
\begin{aligned}
H(x(t)) &= \tfrac{1}{\beta}x_3(t)^2 + v_\beta x_3(t) - f_2 x_1(t)^3 - \mu\omega_0 x_2(t) \\
&\quad - f_3 x_1(t)^4 - \mu\omega_2 x_1(t)^2 x_2(t) \\
&\quad + \mu x_2(t)^2 - (\mu\omega_1 - 1)x_1(t)x_2(t) \\
&\quad - f_1 x_1(t)^2 - \mu\omega_3 x_1(t)^3 x_2(t)
\end{aligned}
$$

$$
\begin{aligned}
\dot{V}(x(t)) &= x_1(t)\left[f(x_1(t)) - x_2(t) - k(x_3(t)) + u(t)\right] \\
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&\quad + \tfrac{1}{\varepsilon\beta}x_3(t)\left[\varepsilon(h(x_1(t)) - x_3(t))\right] \\
&= y(t)u(t) - H(x(t))
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&\quad - f_3 x_1(t)^4 - \mu\omega_2 x_1(t)^2 x_2(t) \\
&\quad + \mu x_2(t)^2 - (\mu\omega_1 - 1)x_1(t)x_2(t) \\
&\quad - f_1 x_1(t)^2 - \mu\omega_3 x_1(t)^3 x_2(t)
\end{aligned}
$$

$$
\mathcal{B} = \left\{
\begin{array}{l}
x(t) \in \mathbf{R}^3 \; : \; \|x_1(t)\| > \|\tfrac{f_2}{f_3\lambda_1}\|, \|x_2(t)\| > \left\|\dfrac{\mu\omega_0}{(\mu\lambda_2 + \frac{\mu^2\omega_2^2}{4f_3(1-\lambda_1)})}\right\|, \text{ and} \\[4mm]
\|x_3(t)\| > \|\beta v_\beta\|
\end{array}
\right\}
$$

Lemma 2. Consider the network of N nodes linearly and diffusively coupled described by (21). If each node in the network is a semipassive system such that (18)-(20) are satisfied, the solutions of all the connected systems in the network, independently from the initial conditions, will eventually end up within some ball $\mathcal{B}$ of the state space of the network.

Theorem 3 Consider an islet with k β-cells coupled. There exists a constant $g_c{}^* > 0$ such that if $g_c k > g_c{}^*$ and the islet consists of

(1) k_1 active cells and k_2 inactive cells, then the active cells synchronize with each other and the inactive cells synchronize with each other but the active cells do not synchronize with the inactive cells;

(2) k active cells or k inactive cells, i.e. all β-cells are either active or inactive, then all cells synchronize.

But, as ussual, systems can be more complicated … from here, the dynamical transitions …

Lyapunov exponents

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

$$h_1 \geq h_2 \geq h_3.$$
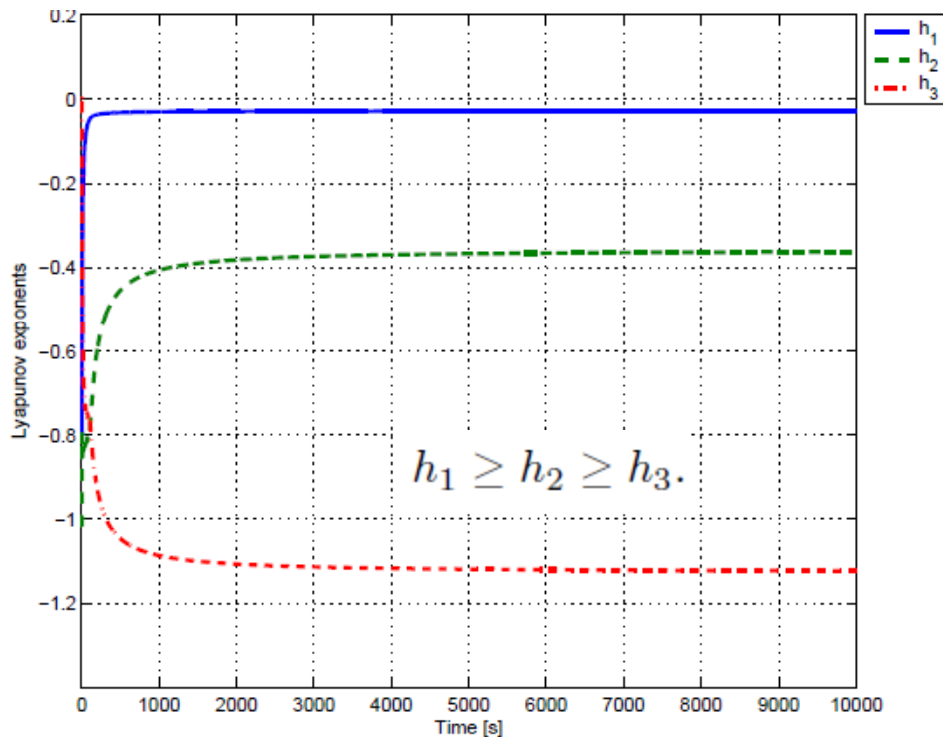
This means that the single cell activity is inhibited.

We are interested in showing how the connections of the network can synchrony a cluster of inhibited Beta cells.

But, as ussual, systems can be more complicated … from here,
the dynamical transitions …

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

Connectivity Matrix

$$\mathbf{A} = (a_{ij}) \in \mathbb{R}^{N \times N}$$

is such that

$$0 = \lambda_1 > \lambda_2 \geq \lambda_3 \geq \ldots \geq \lambda_N.$$

According to [Wu and Chua (1995)] if

$$\lambda_2 \leq -\frac{T}{c}$$

zero is an exponentially stable point of a node in isolation.

But, as ussual, systems can be more complicated … from here, the dynamical transitions …

- The tLe's of a network of identical systems are determine from the Lyapunov exponents of a node in isolation (h_i) and the eigenvalues of the connectivity matrix (λ_k) as [Barajas-Ramírez and Femat (2008)]

$$\mu_i(\lambda_k) = h_i + c\lambda_k$$

with $\mu_i(\lambda_k)$ as the tLe associated to the i-th local direction of a single cell and the k-th node along the corresponding eigenvector of the coupling matrix A.

But, as ussual, systems can be more complicated … from here, the dynamical transitions …

- The synchronized solution of the network is stable if all the transverse direction are contracting.

- The smallest value of c such that this occurs is when the largest tLe becomes positive, i. e., $\mu1(N) > 0$ or equivalently

$$\frac{h_1}{\lambda_N} > |c|$$

- The emergence of chaotic solutions require an extra condition, to ensure that all the trajectories of that move away from the unstable synchronized solution remain bounded.

Lemma 1. [13, 14] If there exists a positive definite symmetric matrix $\mathbf{R}^{m \times m}$ such that all eigenvalues $\lambda_i(Q)$ of the symmetric matrix

$$Q(x(t), u(t)) = \frac{1}{2} \left[P \left(\frac{\partial f}{\partial x(t)}(x(t), u(t)) \right) + \left(\frac{\partial f}{\partial x(t)}(x(t), u(t)) \right)^{\top} P \right]$$

are negative and separate from zero, *i. e.*, there exists a $\delta > 0$ such that

$$\lambda_i(Q) \leq -\delta < 0 \text{ for } i = 1, ..., m; \text{ and } \forall x(t) \in \mathbf{R}^m \text{ with } u(t) \in \mathcal{D}$$

Then, the system in (14) is convergent in the class $\mathcal{D}$.

- According to [Barajas-Ramírez and Femat (2008)] , this is expected when the overall sum of tLes associated with each node are negative, i.e.,

$$\sum_{i=1}^{m} \mu_i(\lambda_k) < 0, \text{ for any } k$$
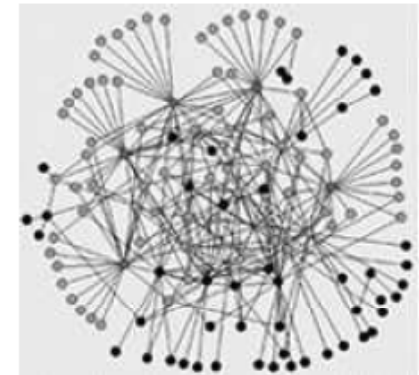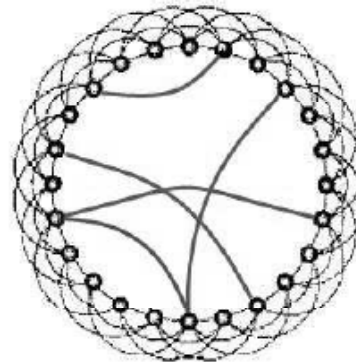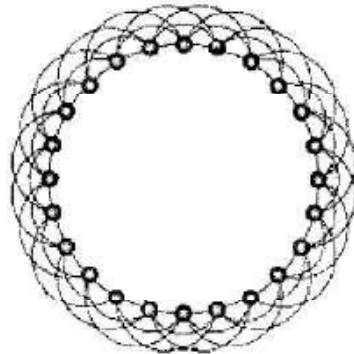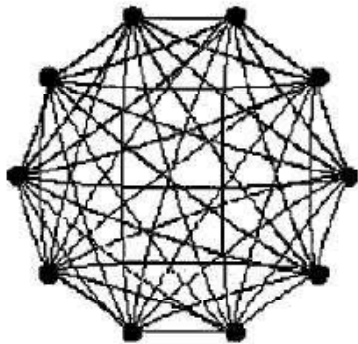
Firstly a system as benchmark: Lorenz
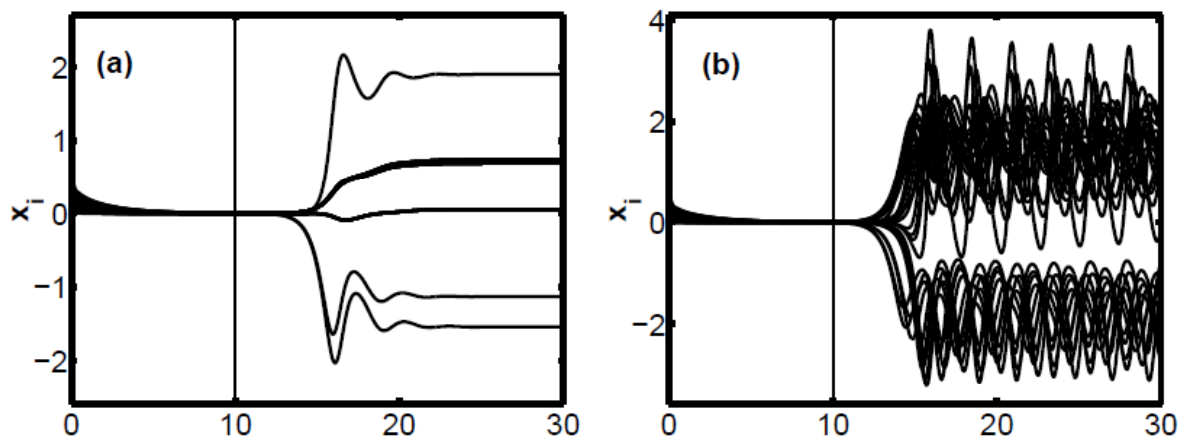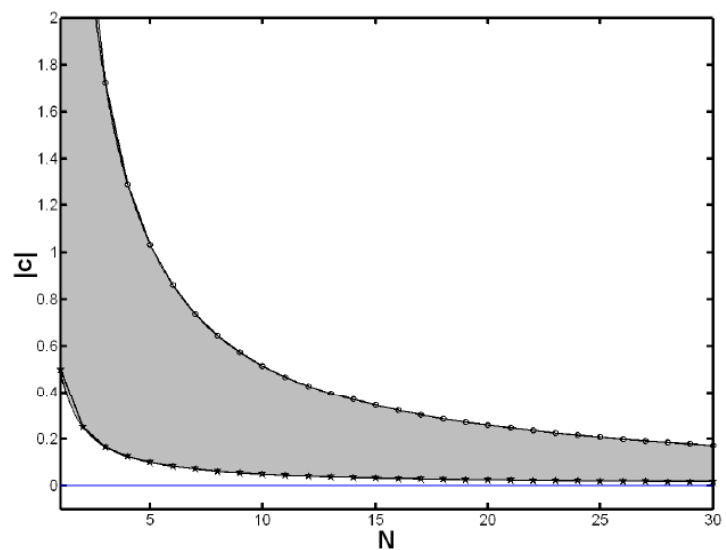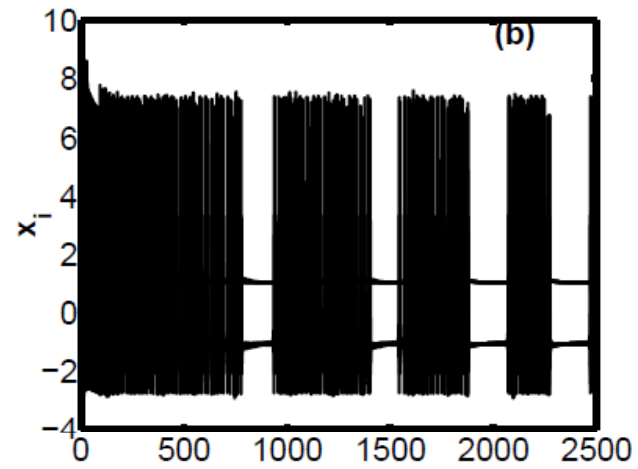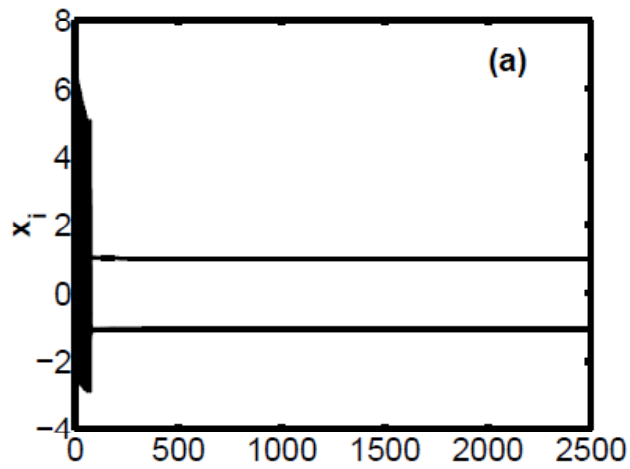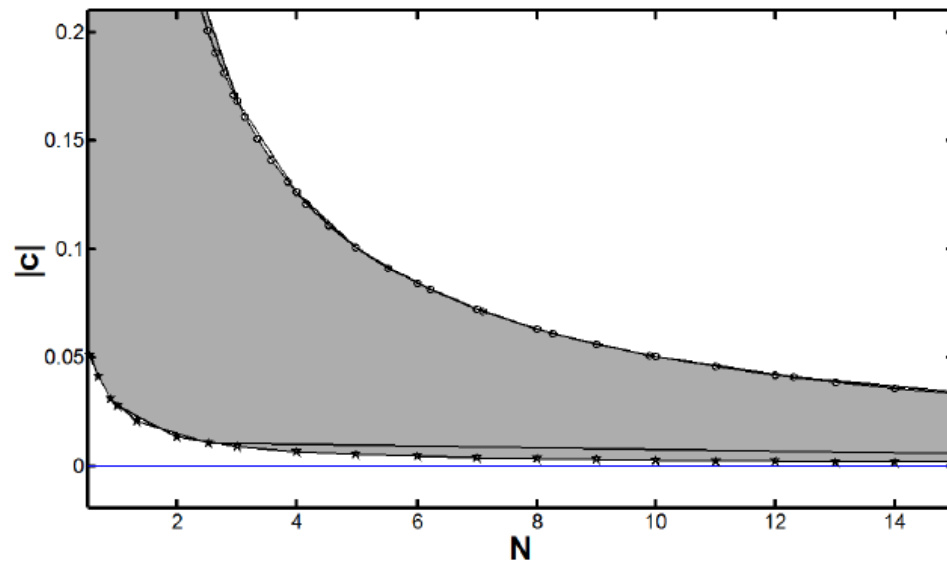
The estimated critical portion η^* is indicated by the thick gray line. The gray area indicates the region where we can ensure that there is still activity of the islet.

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.

Coming back to b-cells problem
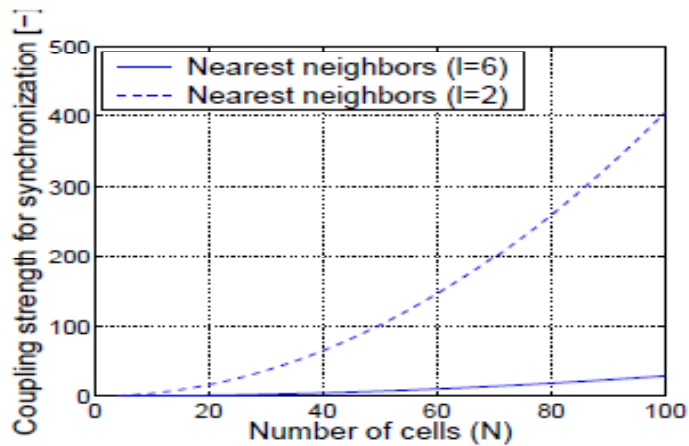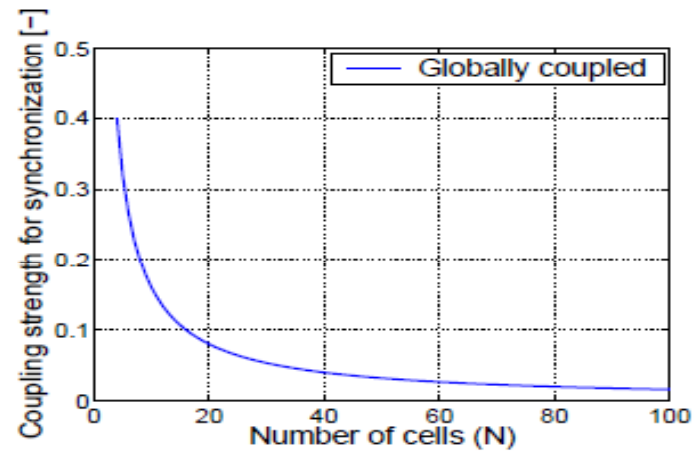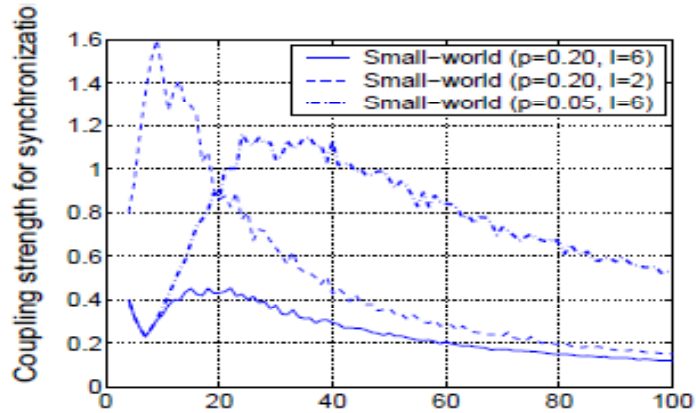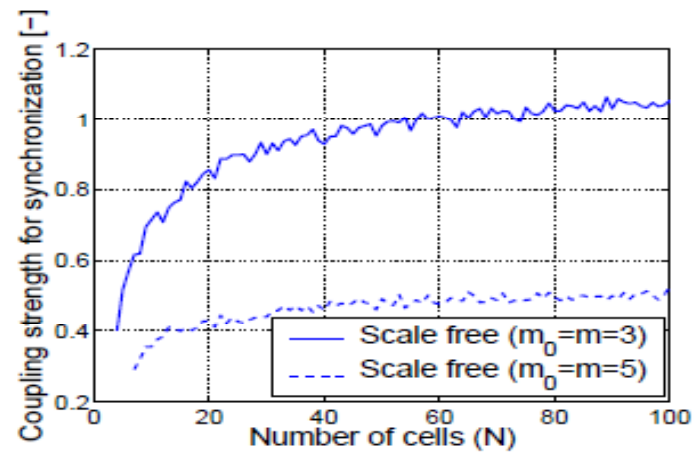
Minimum coupling strength needed for synchronization of β-cells on different network topologies: (a) Nearest-neighbor, (b) Globally coupled, (c) Small-world, and (d) Scale-free
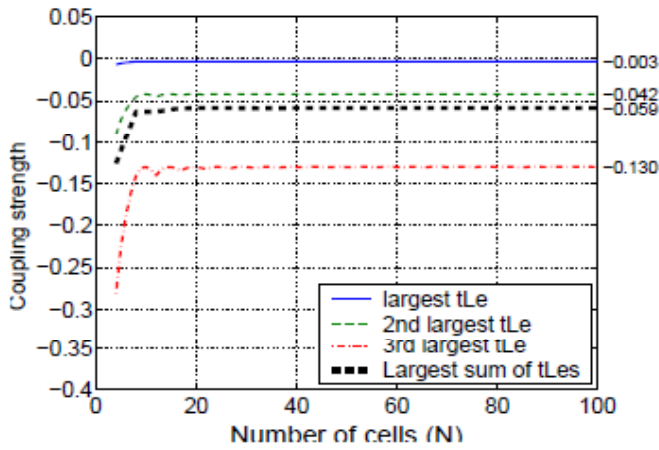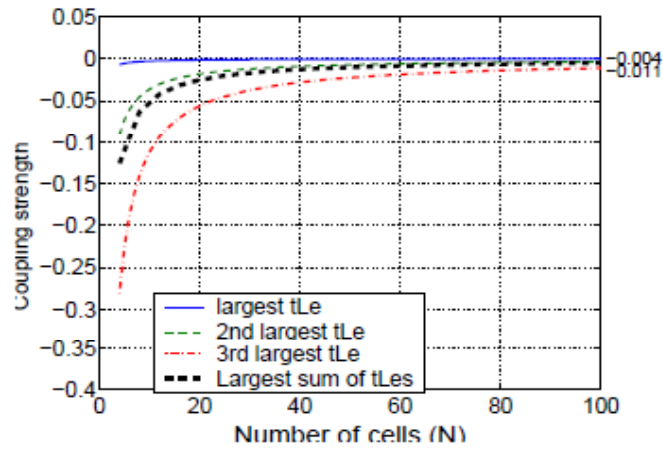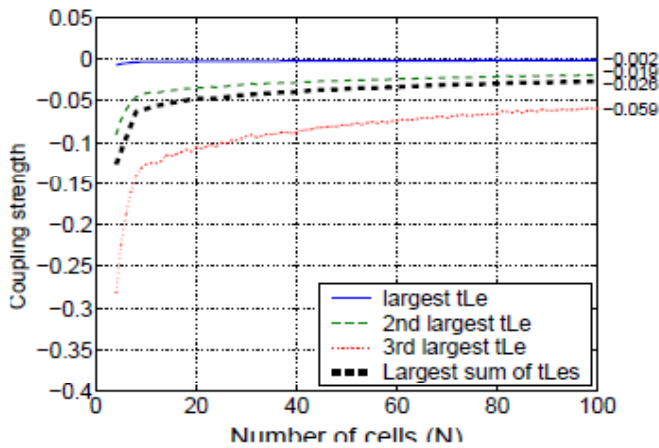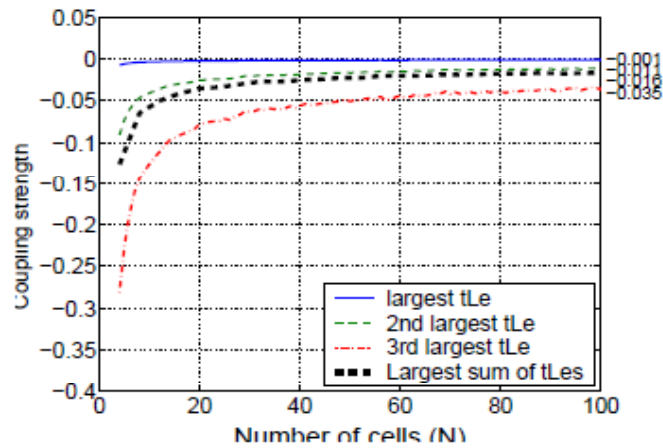
First three largest tLes for a) Nearest neighbor (l = 6), b) Globally coupled, c) Small-world (p = 0.05, l = 6) and d) Scale-free (m = 3).

Case 1. The location of the equilibrium of the inactive cluster $(\xi_{1,1}^o, \xi_{2,1}^o, \xi_{3,1}^o)$ 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 $(\xi_{1,2}^o, \xi_{2,2}^o, \xi_{3,2}^o)$ be the equilibrium of the active cluster, then if the equilibrium is at the left knee we require

$$0 = \tilde{S}(\xi_{1,2}^o) - b\{\xi_{1,2}^o + c_2\}$$
$$+ g_c k(1 - \eta^*)(\xi_{1,1}^o - \xi_{1,2}^o), \tag{31}$$
$$0 = \tilde{S}'(\xi_{1,2}^o) - g_c k(1 - \eta^*), \tilde{S}''(\xi_{1,2}^o) > 0, \tag{32}$$

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 (31) is the equilibrium equation for the active cluster and (32) is the condition that guarantees the equilibrium to be at the left knee. Solving (31), (32) 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 $\eta^* = \max(0, 1 - \frac{c}{g_c k})$.
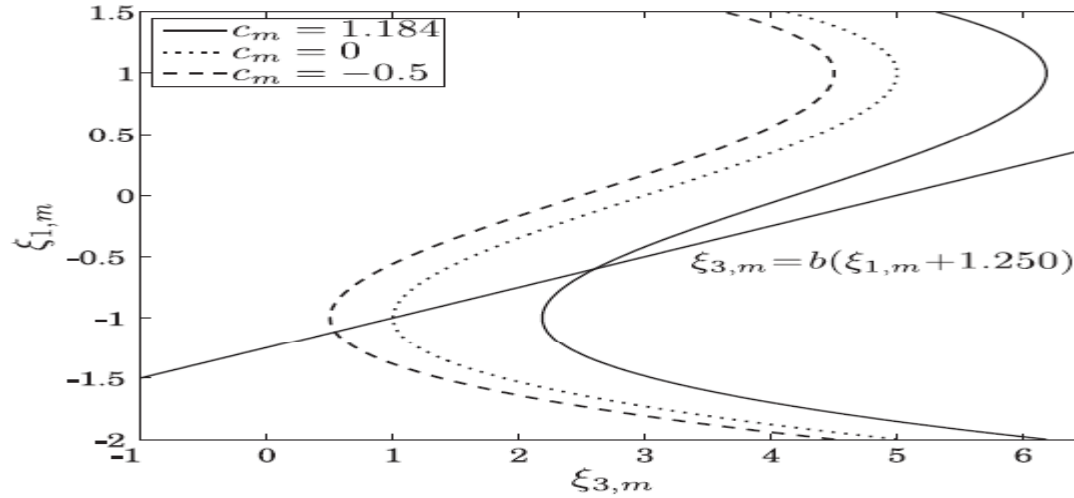


S-shaped curves of the uncoupled, i.e. $\tilde{\nu}_m = 0$, active cluster ($c_m = 1.184$) and inactive cluster ($c_m = -0.5$). Also presented are the S-shaped curve corresponding to $c_m = 0$ and the line $\xi_{3,m} = b(\xi_{1,m} + 1.250)$.

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   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
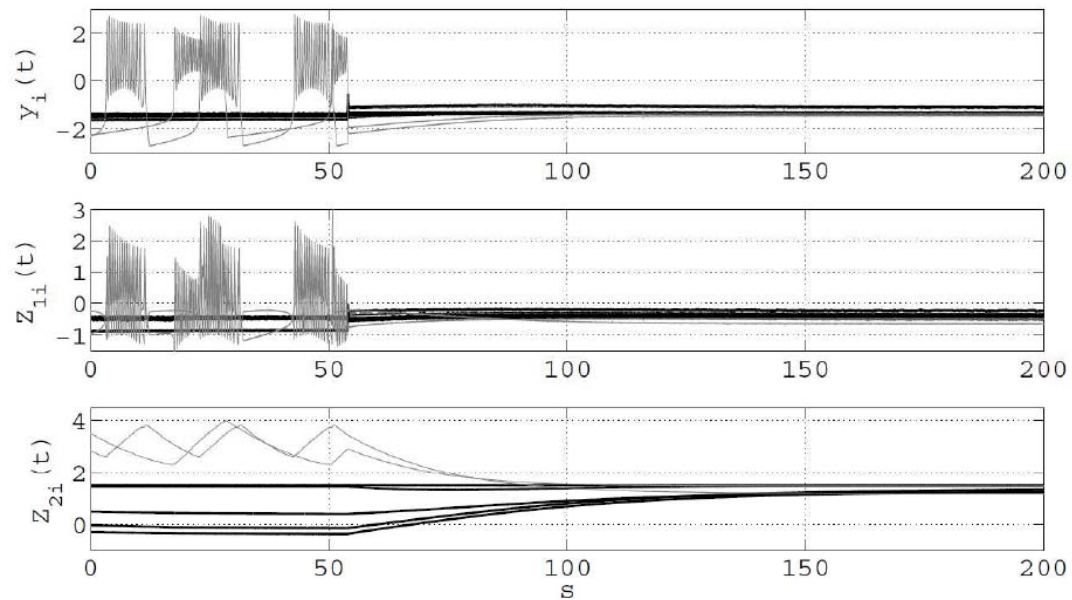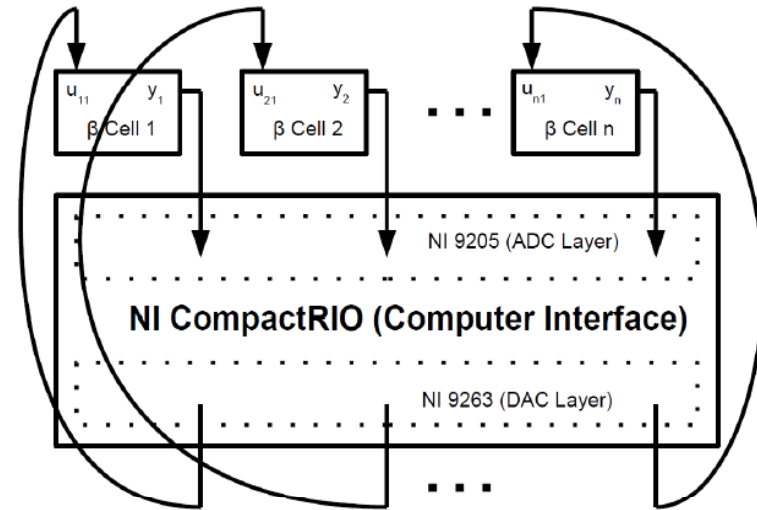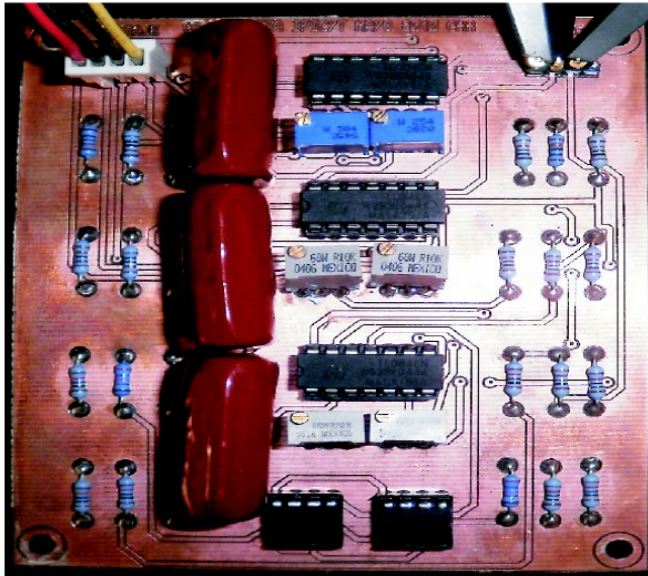
$$0 = g_c k \eta^* (\xi_{1,2}^o - \xi_{1,1}^o) + c_1,$$
$$0 = g_c k (1 - \eta^*)(\xi_{1,1}^o - \xi_{1,2}^o) + c_2,$$

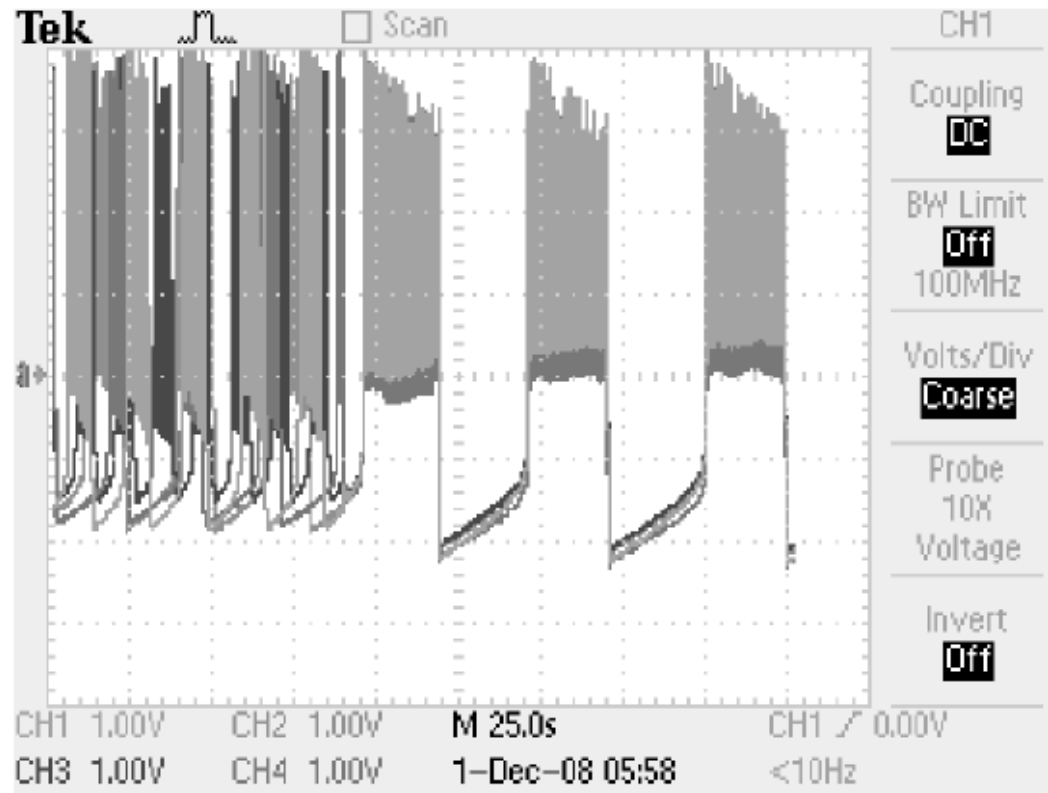from which it follows that $\eta^* = \frac{c_1}{c_1 - c_2} \approx 0.297$.
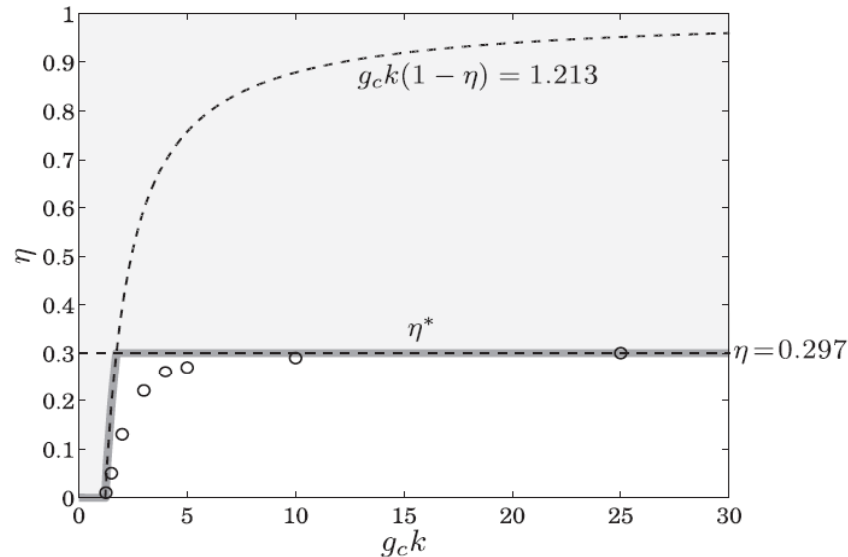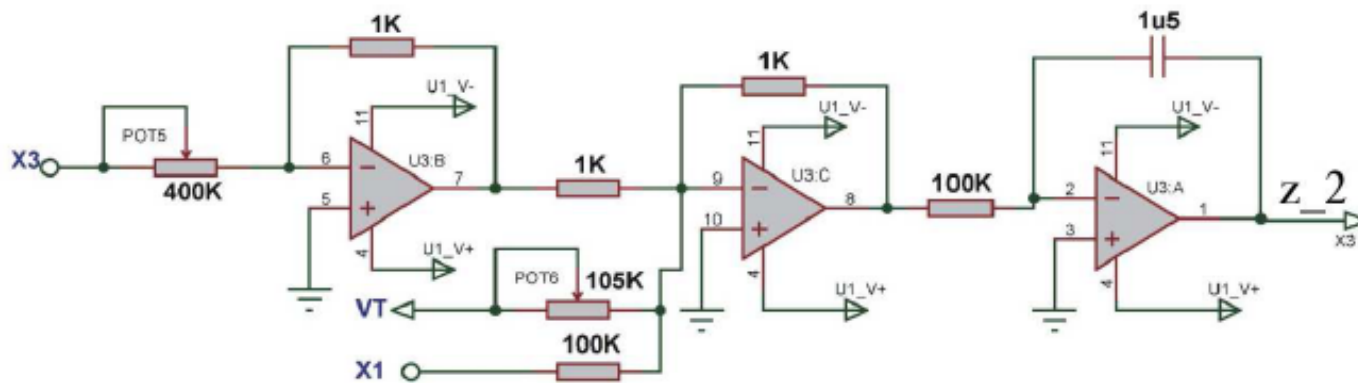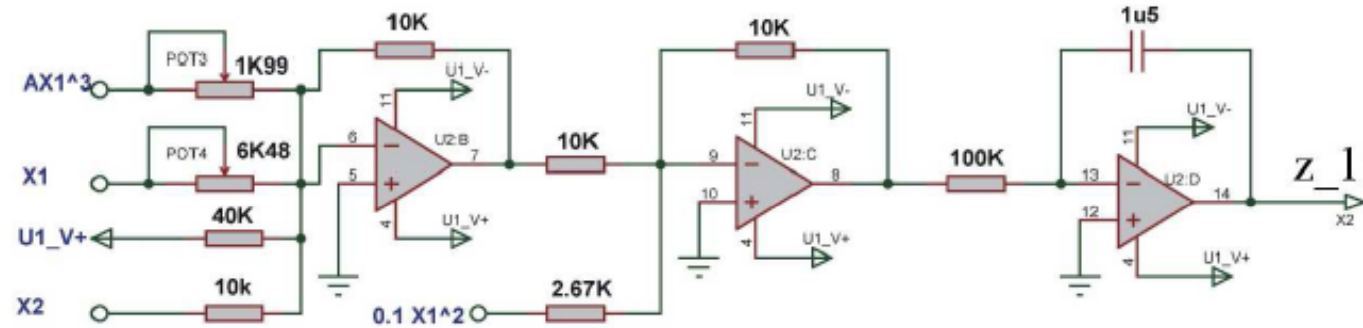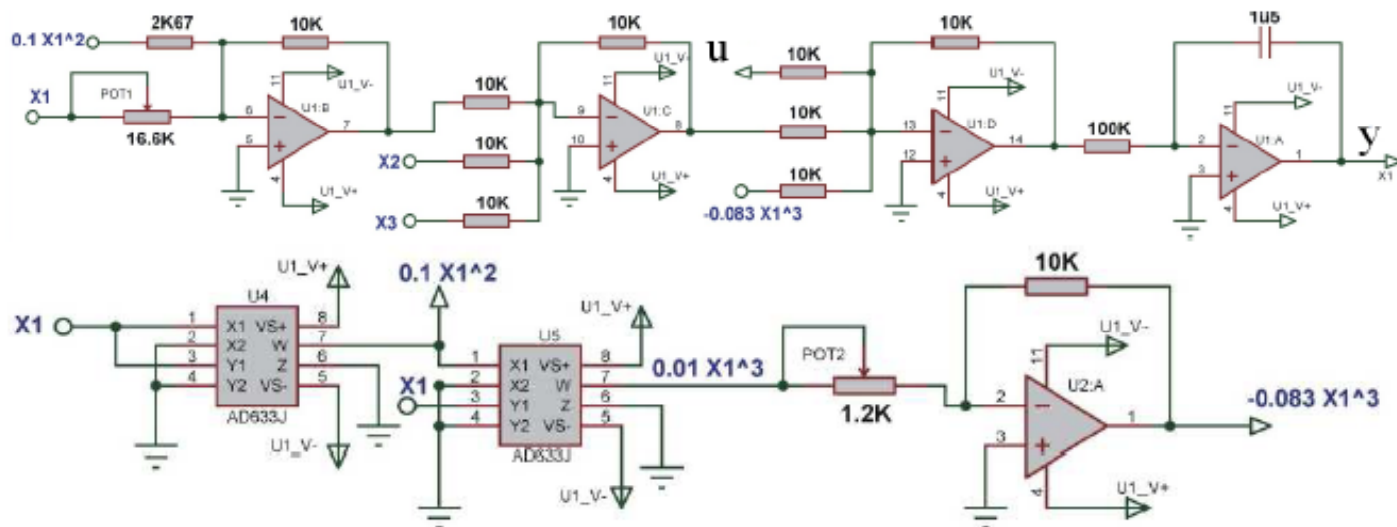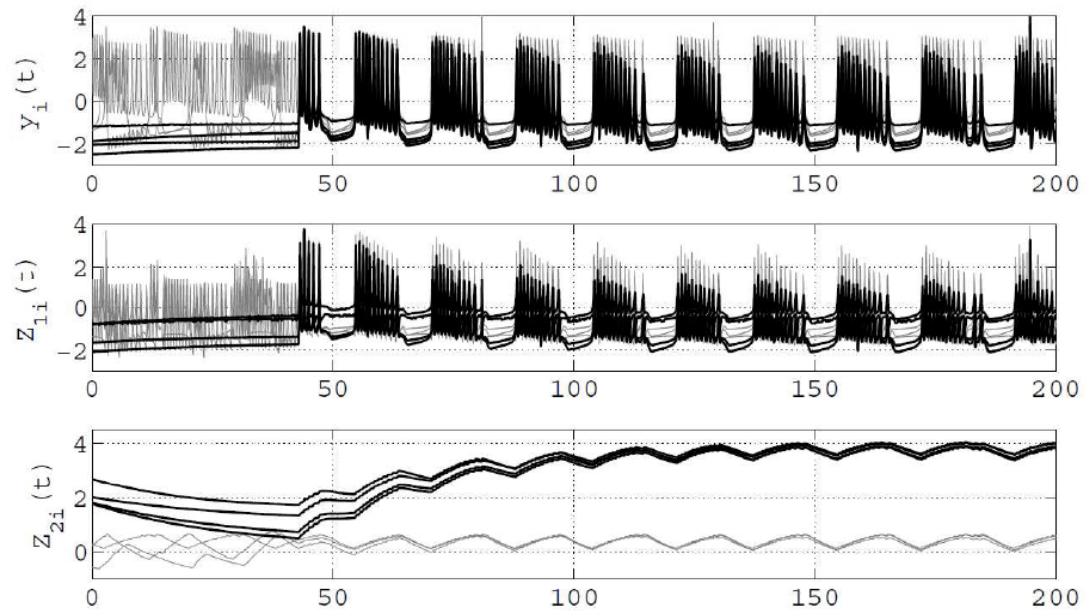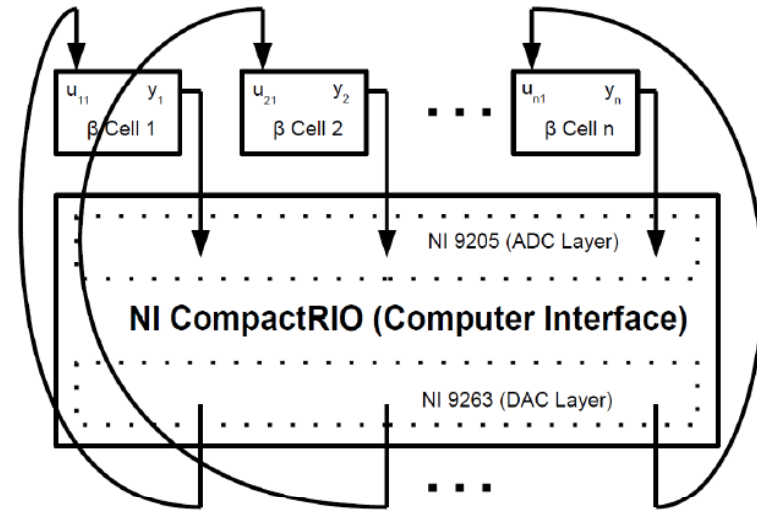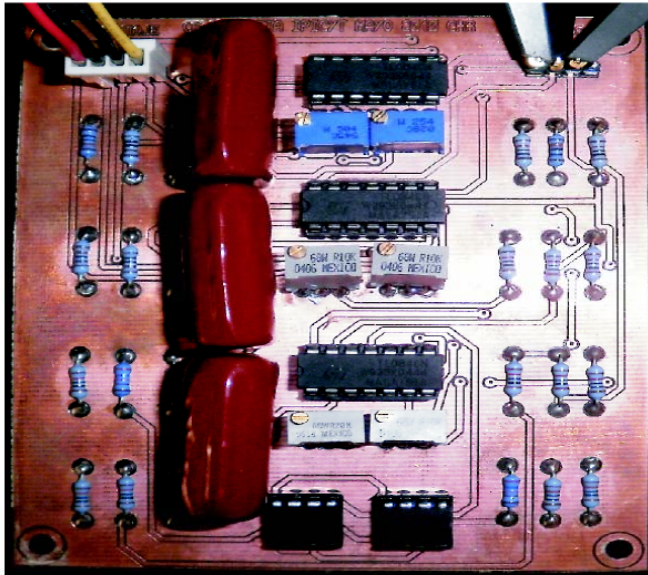
Experimental realization of the synchronization of a globally coupled network of seven cells with coupling strength c = 0.6. Here we show only the number of inputs in an oscilloscope.

Final Remarks

- We used four different network topologies for ensembles of β-cell models and investigated conditions for synchronization and emergence of chaotic bursting on activated and inhibited cells, respectively.

- An electronic setup to experimentally validated the theoretical results was successfully realized. The results presented have potential applications on explaining some aspects of biological processes.

- In particular, the electronic realization may help physicians with experimental setups of β-cells, due to its ease of interpretation and manipulation.

Final Remarks

- For future research, it maybe possible to have different coupling strengths for different connections.

- Although this might give a more accurate representation of the real coupling between -cells in the Langerhans islet, it will also be more difficult to analyze.

- Another remark is that partial synchronization, that is, where only a part of the network synchronizes, was observed numerically and experimentally for coupling strengths smaller than the coupling strength needed for complete synchronization.

- Further knowledge about this phenomenon maybe of significance for some specific biological purpose, however, this will be subject for future research

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