Numerical investigation of phase transition in a cellular network and disease onset

Xujing Wang, Associate Professor

Dept of Physics

xujingw@uab.edu

934-8186

The question: Is (chronic) disease onset a phase transition

Evidence:

- Disease development is a slow process, onset is abrupt, and irreversible

Significance:

- Allows the identification of control parameters that, when altered, could reverse a pathophysiological process
- Can lead to a better understanding of disease dynamics, and hence better prediction of disease risk, prognosis, and treatment protocols.

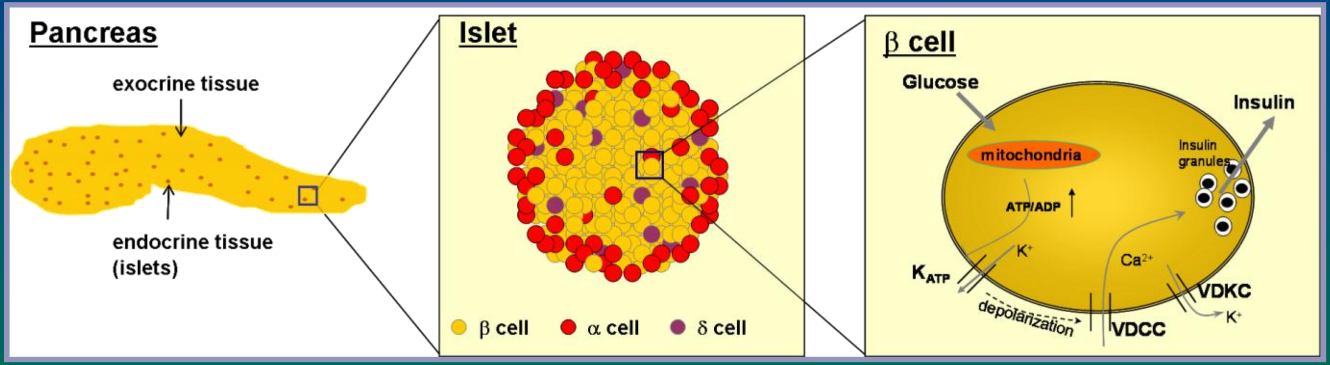
Type 1 Diabetes

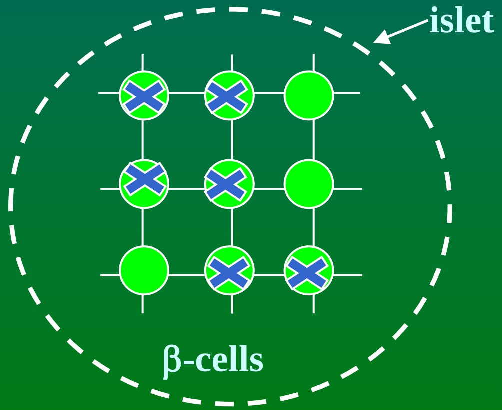
T1D: results from loss of pancreatic islet β-cells

Pancreatic islet β-cell: the only cell type that produce and release insulin

Insulin: the primary hormone that regulates glucose

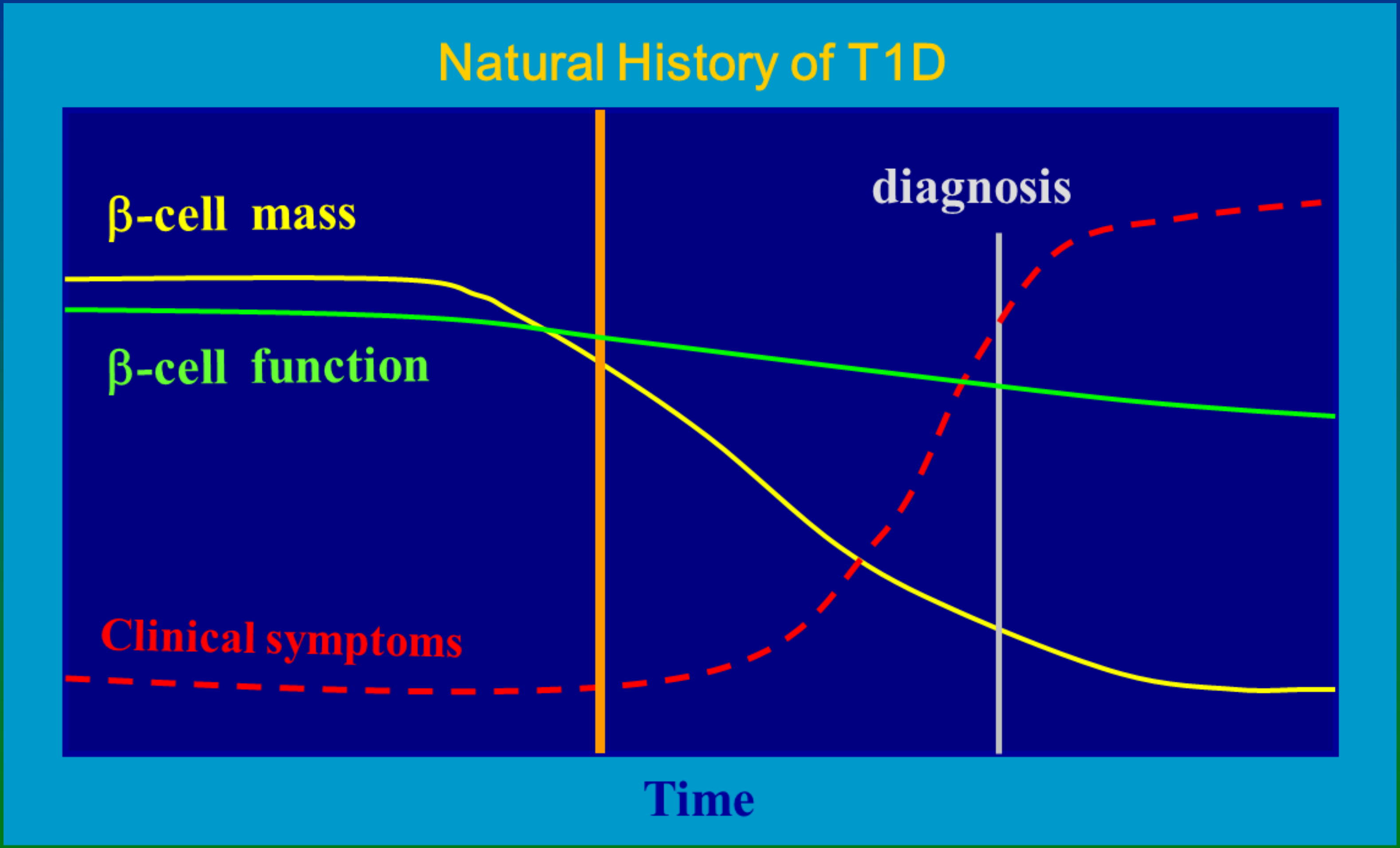
Glucose homeostasis: the process that provide energy to every cell in our body



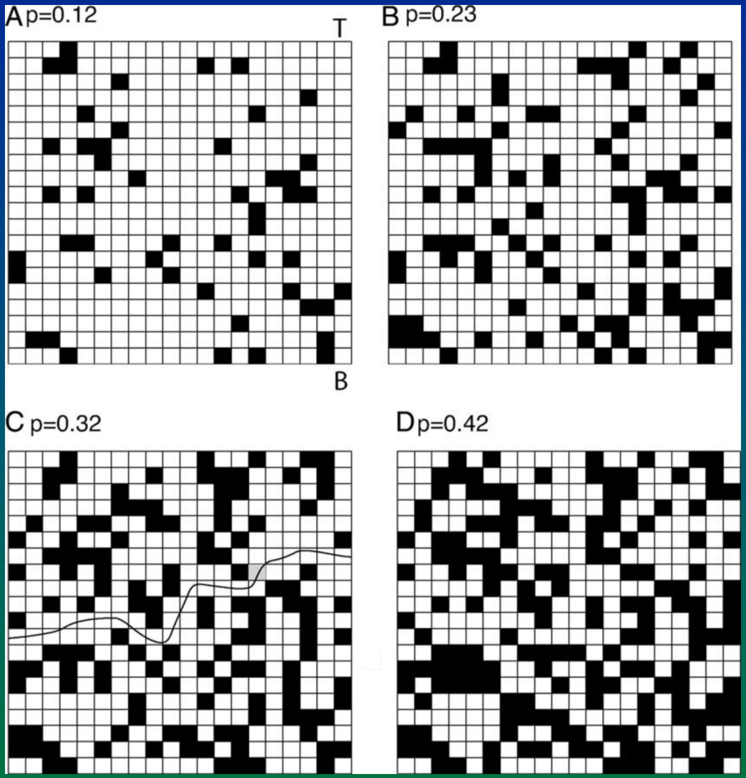


- **β-cells are coupled to each other, forming a network**
- **The connectivity is important for normal function**
- **β-cells are percolated?**

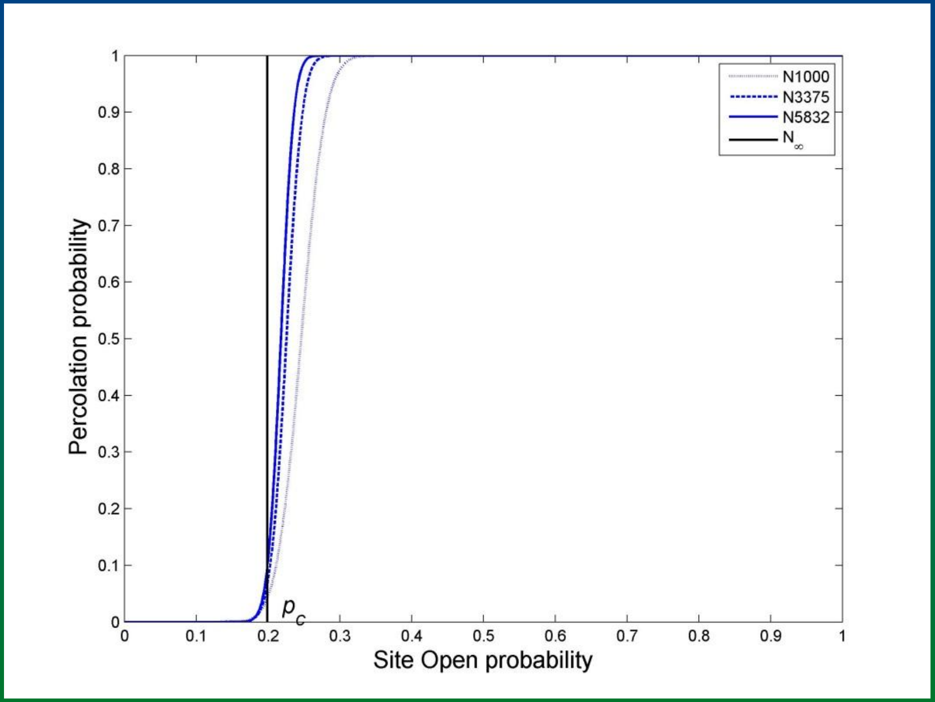
Natural history of T1D



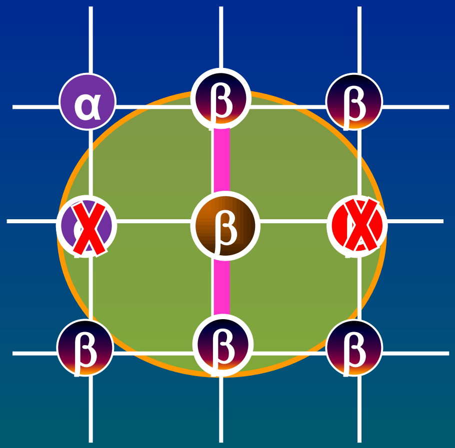
What is Percolation



PNAS. 2009 4;106(31):12634-9

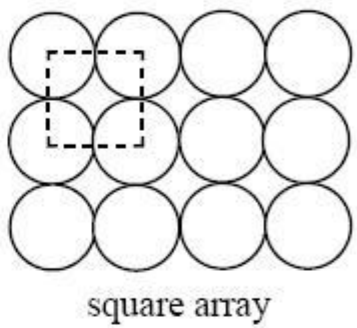


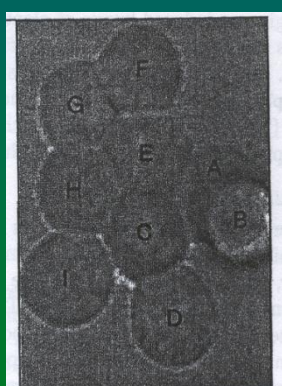
Percolation in β-cell network

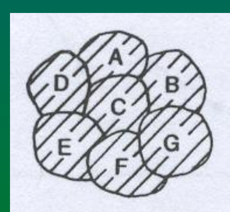


- 3D cube: $p_c=0.316$
- Normal islet: ~70% are β-cells, site open probability $p \sim 0.7 > p_c$, percolated
- Disease onset @ ~70% loss of β-cells: $p_c \sim 0.7*0.3=0.21$
- Laboratory study: islet dysfunction at 70% death or 70% cell cannot couple with others: $p_c \sim 0.7*0.3=0.21$

β-cell network structure, is hexagonal, not simple cubic





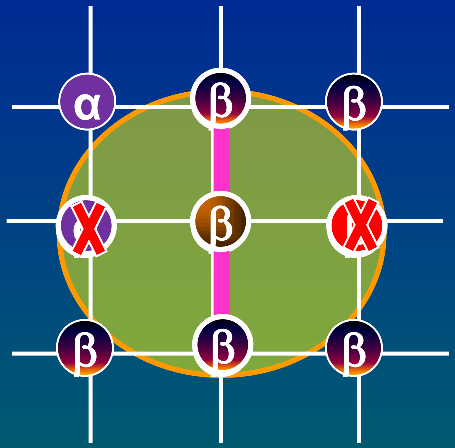


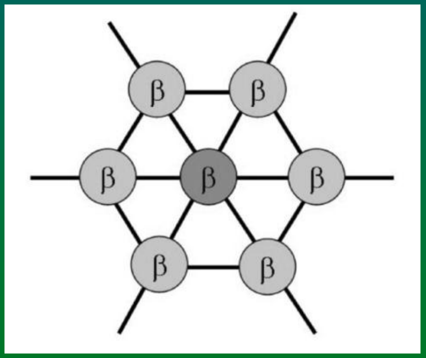
We were the first to introduced the hexagonal lattice model to study the β-cell network

<u>PLoS ONE</u> 2(10): e983, 2006

B. Hellman, et al. Diabetologia, 1994. 37 Suppl 2: S11-20.
E. Gylfe,et al. Ups J Med Sci, 2000. 105(2): 35-51

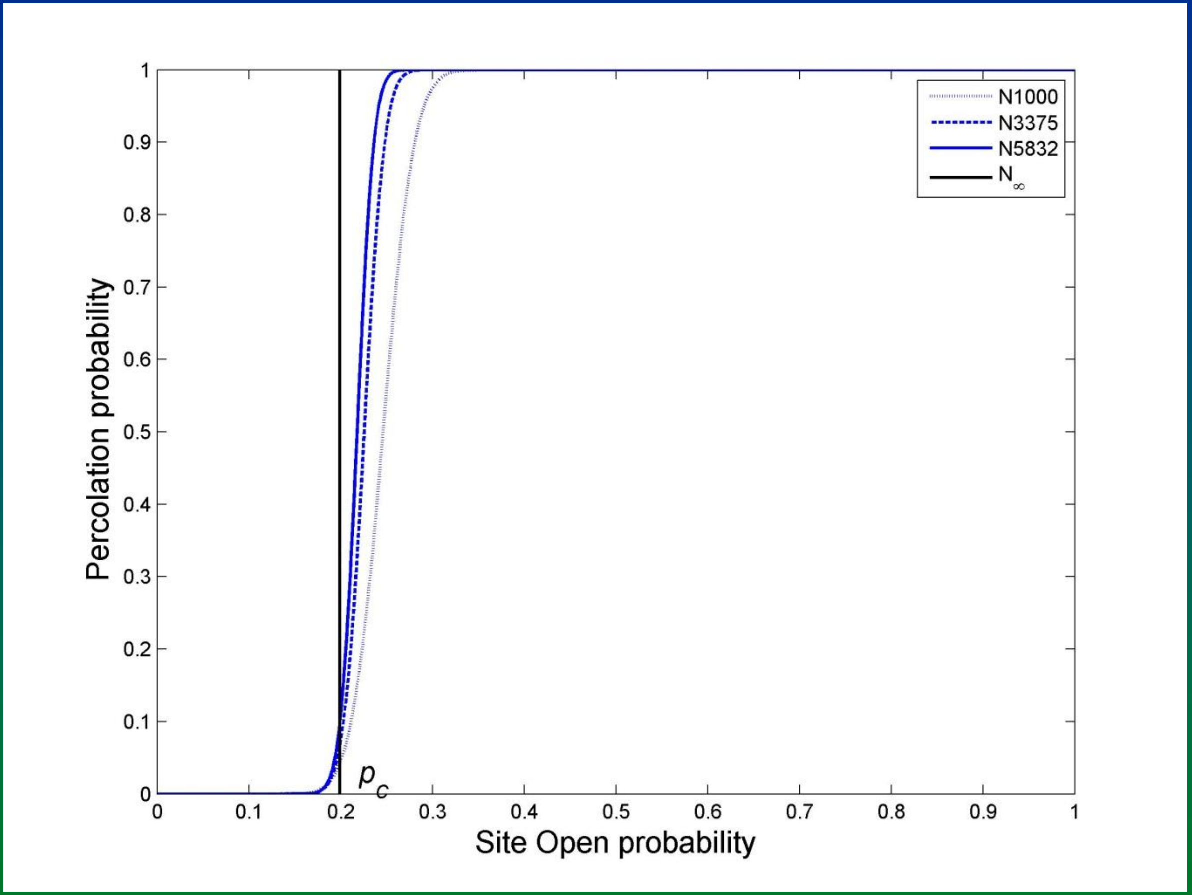
Percolation in β-cell network





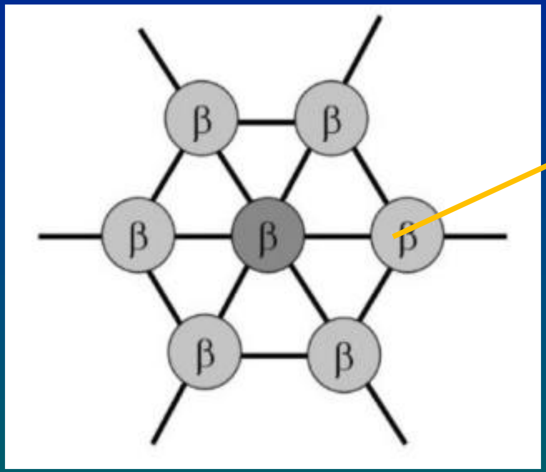
- 3D cube: <u>p_c=0.316</u>
- Normal islet: ~70% are β-cells, site open probability p~0.7
- Disease onset @ ~70% loss of β-cells: <u>p_c~0.7*0.3=0.21</u>
- Laboratory study: islet dysfunction at 70% death or 70% cell cannot couple with others: <u>p_c~0.7*0.3=0.21</u>
- 3D HCP (fcc): <u>p_c=0.199</u>

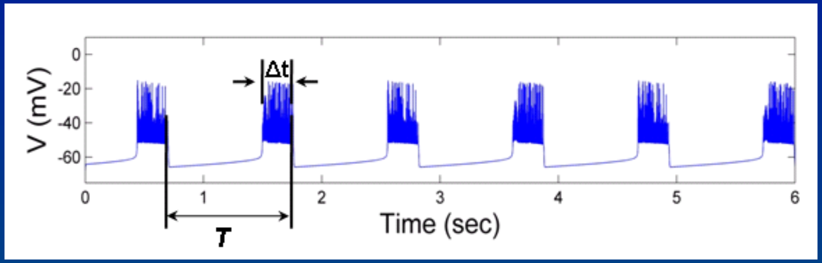
Percolation in Hexgonal Closest Packing lattice (HCP, or fcc)



Elais Jackson
Johanna Stamper

Oscillation synchronization transition





$$C_{m,i}\frac{dV_i}{dt} = -(I_{Ca,i} + I_{K_{ATP},i} + I_{K,i} + I_{s,i}) - \sum_{j=\text{all cells coupled to } i} g_c\left(V_i - V_j\right)$$

For a cluster of 100 cells, 60 million evaluations of the 400 equations (4 ODE each cell), It took a few hours on a Dell OptiPlex GX620 PC with dual 3 GHz CPU and 2 GB of Ram.

(Human islets ~ 10^3 cells; rodent islets ~ 10^2 cells)

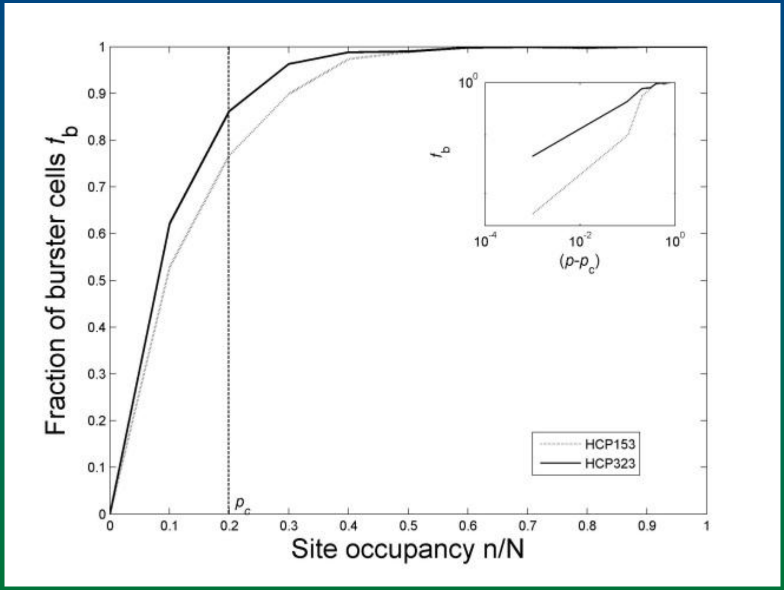
1000 islet configurations simulated, using a cluster Zeke (45 node), ~ 1 month

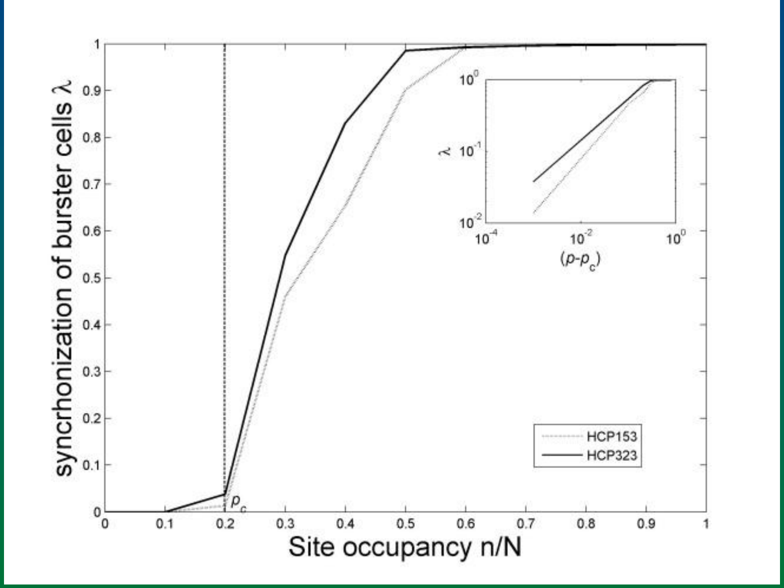
Aparna Nittala

Plan to simulate ~1000 more around the critical point

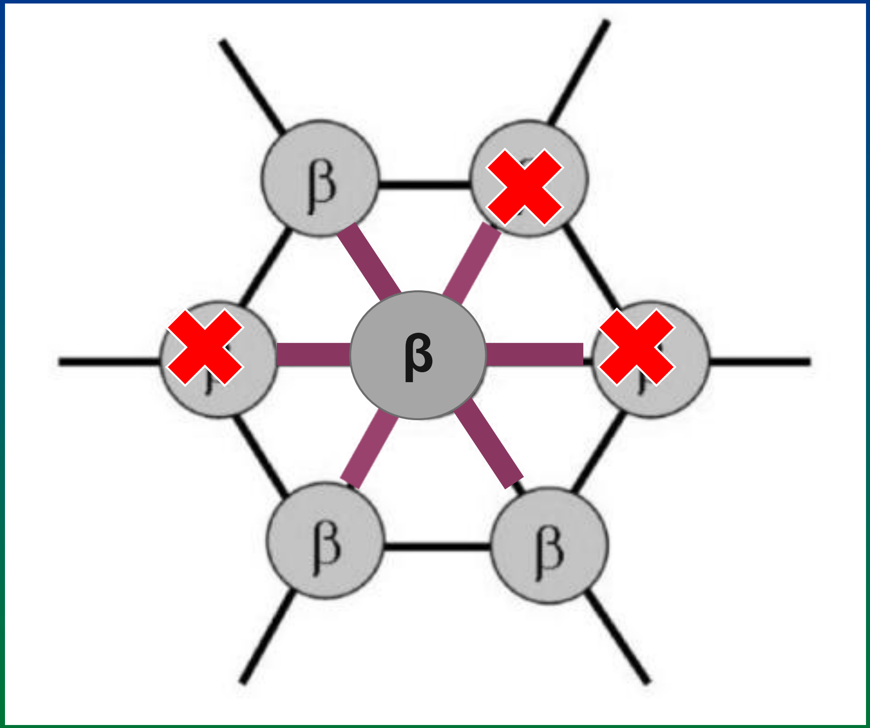
Serkan Guldal

Oscillation synchronization transition occurs around the critical point

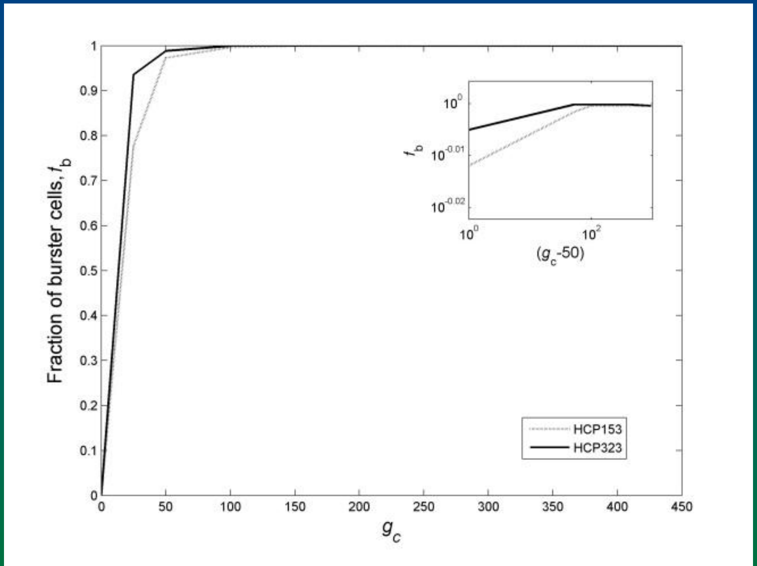


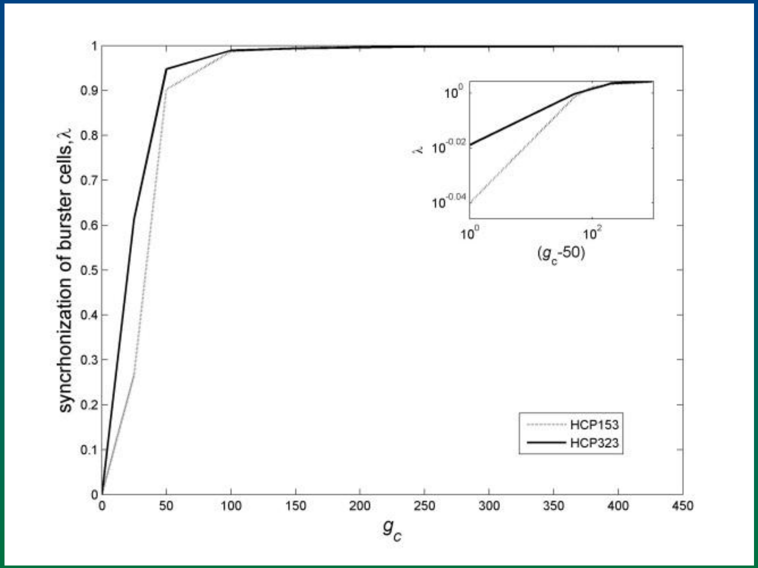


Bond percolation, additional to site percolation



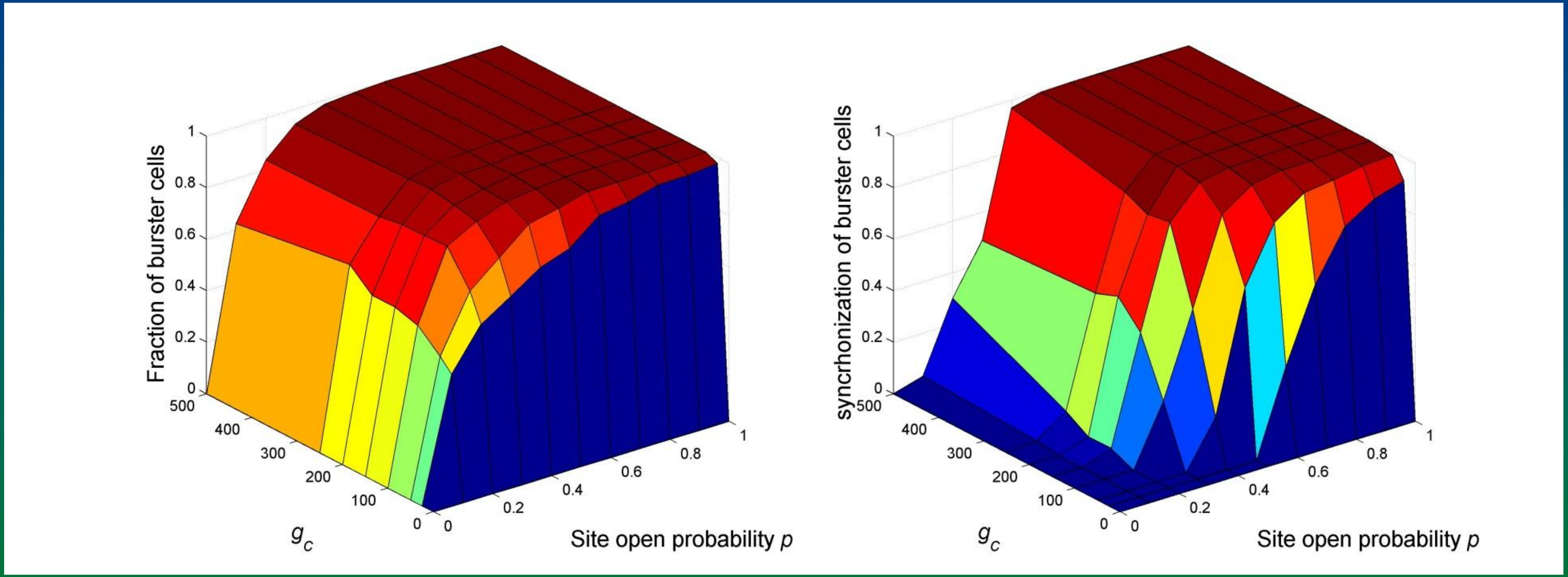
Synchronization also depend on Bond strength





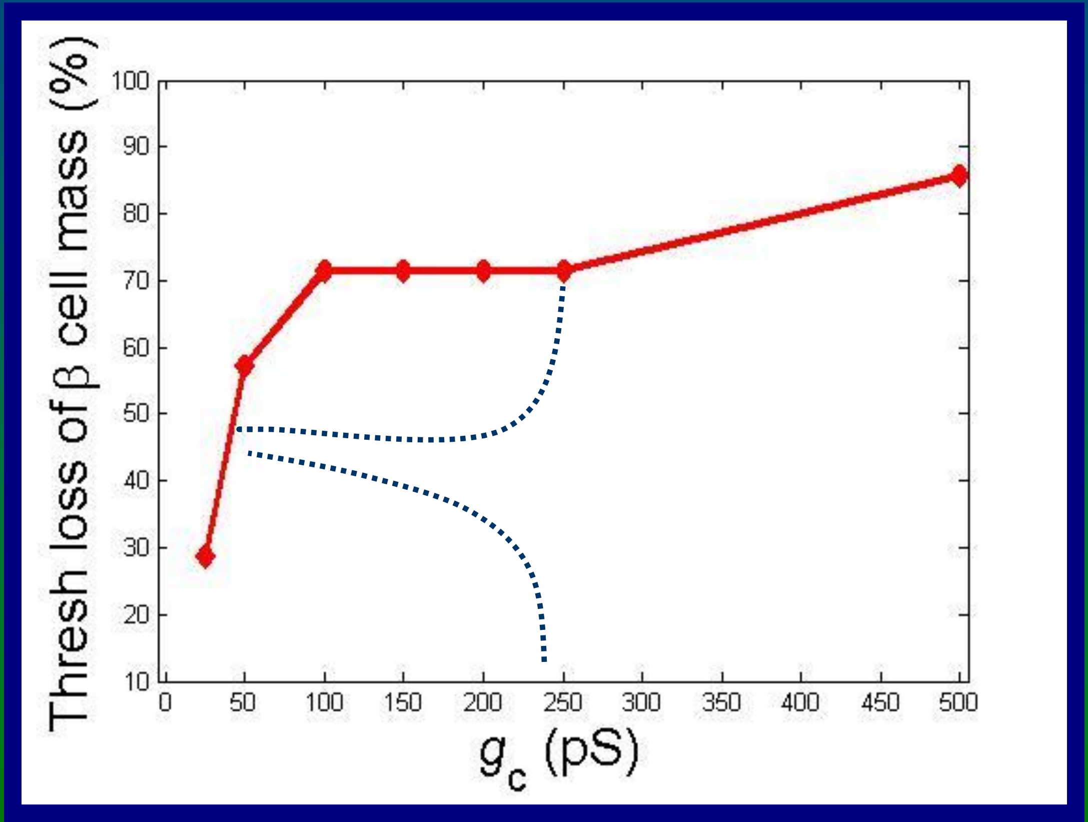
Rodent islet: g_c~100-300 pS.

Interplay between site and bond percolation



The honeymoon phenomenon after T1D onset: a transient recovery

Right after disease onset, many people experienced a transient relapse, where endogenous insulin secretion is re-established (islets can oscillate and secret insulin again).
Mechanism not known, dynamics not studied



Summary

- Normal islet β-cell network is percolated
- The onset of T1D occurs near the critical point of the percolation phase transition of the β-cell network
- Around this critical point, β-cell network also undergo synchronization transition
- The synchronization transition depends on bond strength in addition to site percolation
- The critical behavior of the β-cell network reproduce the disease dynamics, including a long time mystery in T1D: the Honeymoon phenomenon

- Onset of type 1 diabetes could be due to a (geometric) phase transition of the β-cell network in pancreatic islets, due to loss of percolation

Acknowledgement

Percolation simulation in HCP

Elais Jackson (Computer Science)

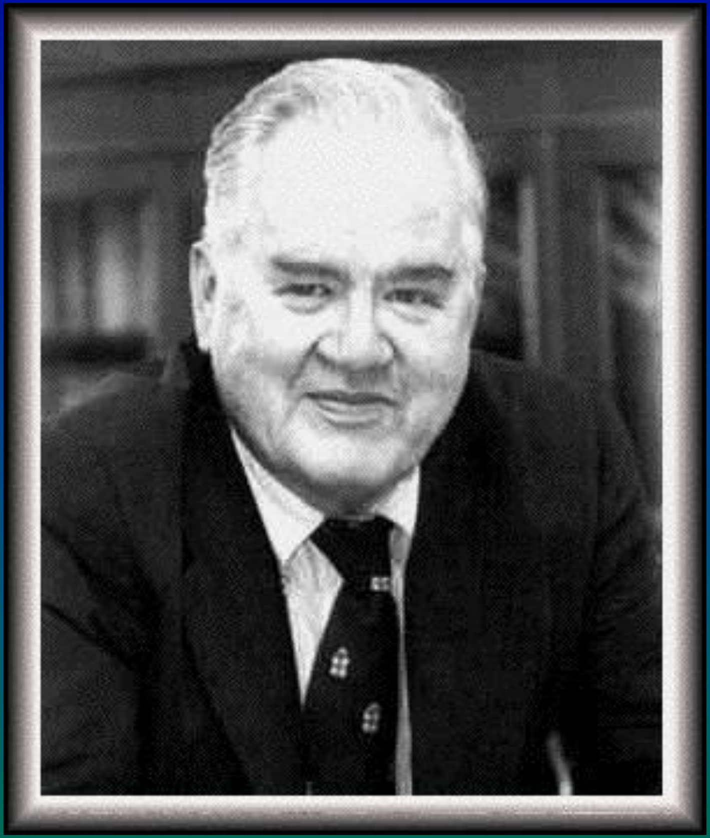
Islet oscillation and multiscale modeling of glucose homeostasis

Serkan Guldal (physics)
Johanna Stamper (physics)

Aparna Nittala (Marquette, MCW, now at GE)

Collaborators

Yuefan Deng (SUNY Stony Brook) HPC



An appropriate answer to the right problem is worth a good deal more than an exact answer to an approximate problem

John Tukey

Structure & function

“If structure does not tell us anything about function, it only means we have not looked at it correctly.”

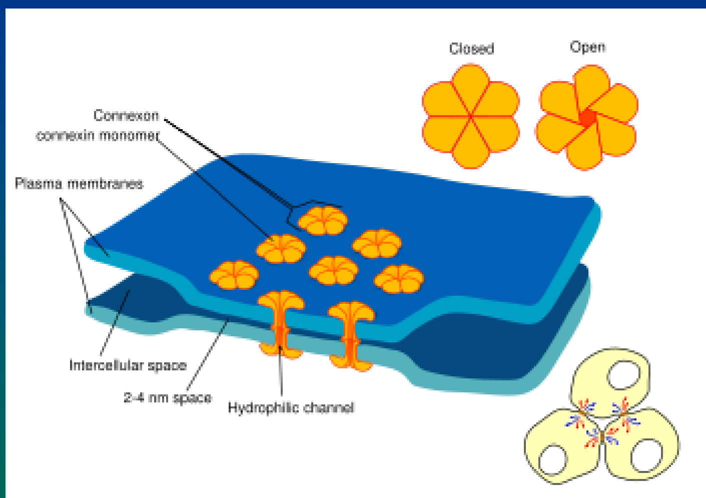
– Albert Szent-Györgyi

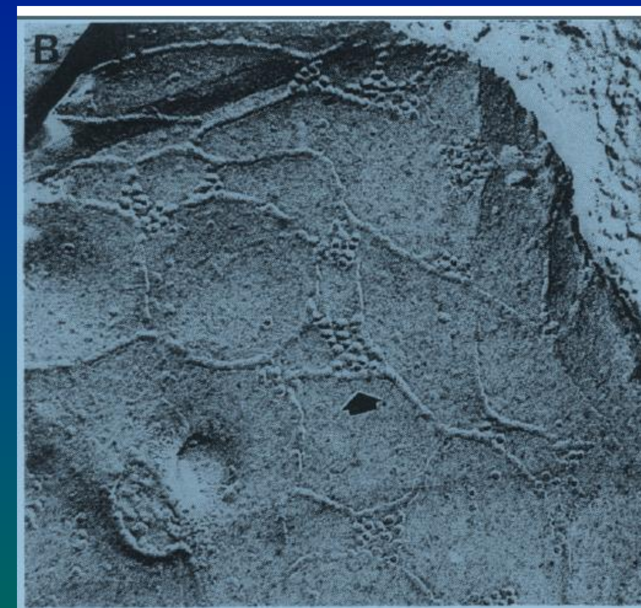
Percolation

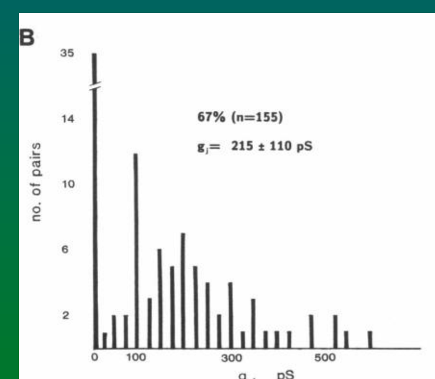
- . The spread of forest fires ref 16, the transmission of infectious diseases and the impact of immunization [1-3][83-85], the emergence of life [4][86], and the formation of a city [5][87] are but a few of the modeling applications. Percolation is a measure of network connectivity. More precisely, in a network of infinite size, percolation occurs abruptly above a critical threshold of node connectivity. This means that for a low degree of node connectivity, the network only features isolated small clusters, while for sufficiently large connectivity there exists a large connected cluster spanning across the whole network . The occurrence of percolation is due to a geometric phase transition of the network structure that has profound impact on network dynamics and function.
-

Gap junction: coupling between β-cells

$$C_{m,i}\frac{dV_i}{dt} = -(I_{Ca,i} + I_{K_{ATP},i} + I_{K,i} + I_{s,i}) - \sum_{j=\text{all cells coupled to } i} g_c\left(V_i - V_j\right)$$



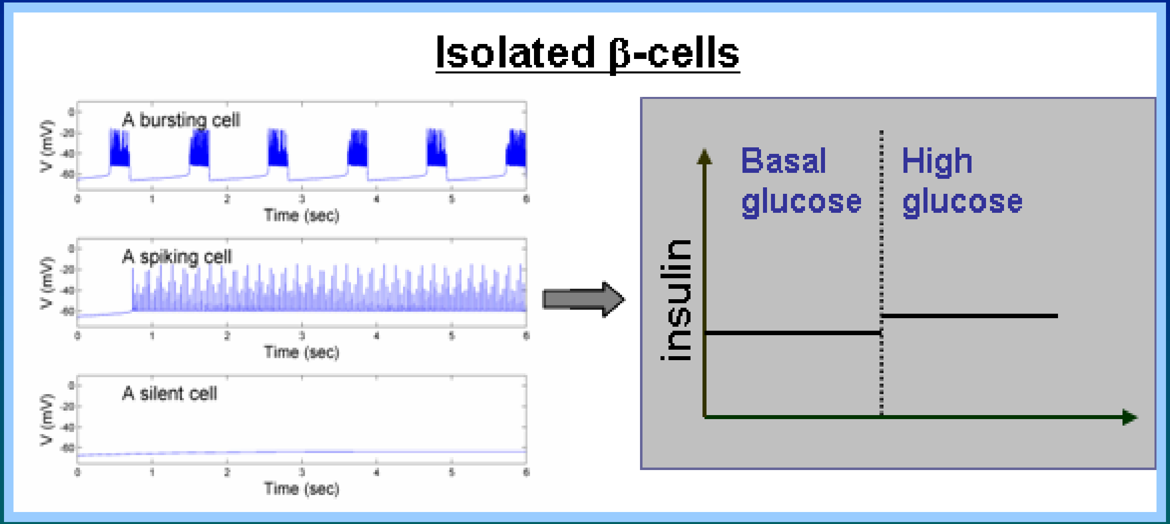


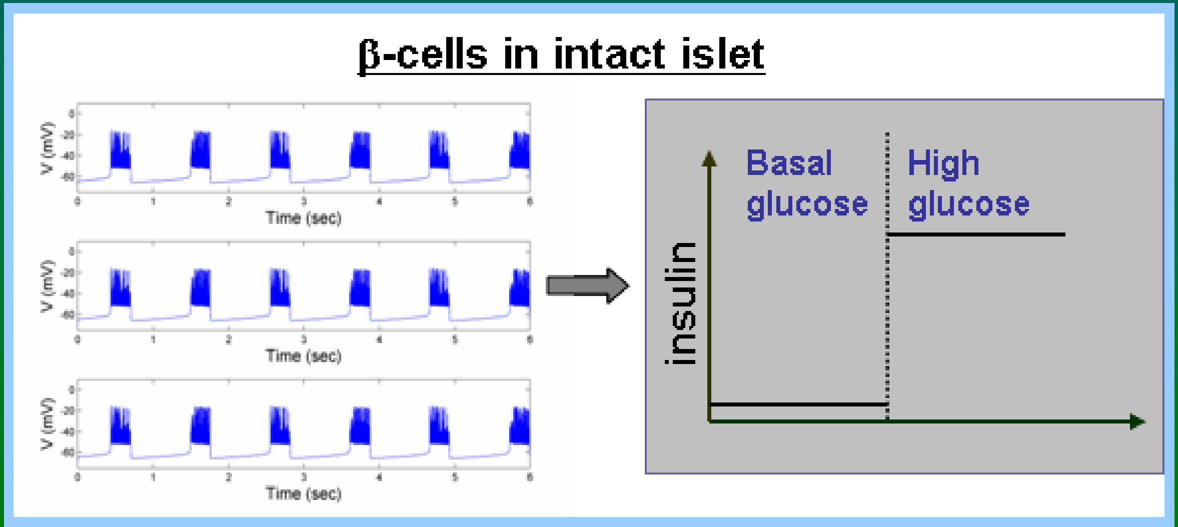


- There are ~20 members in the connexin family
- utilization of connexin is tissue specific. β cells express only connexin-36

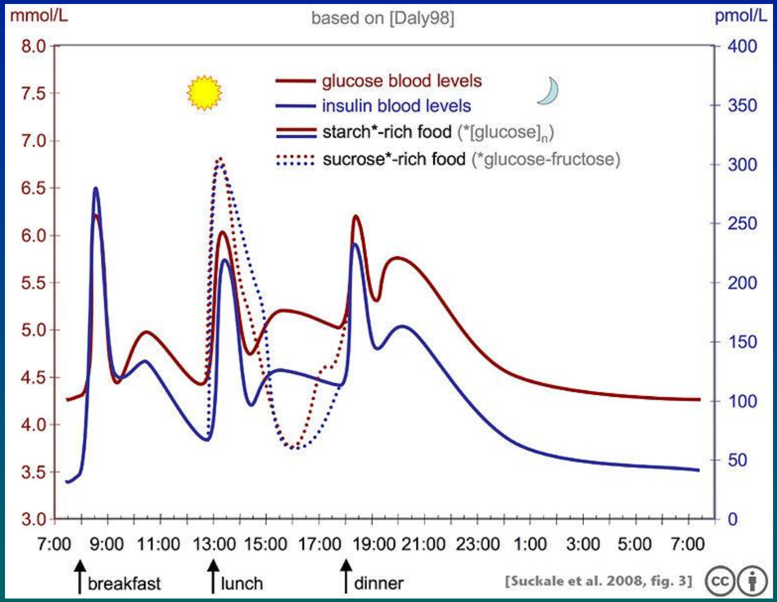
M. Perez-Armendariz, C. Roy, D.C. *properties of gap junctions between freshly dispersed pairs of mouse pancreatic beta cells.* Biophys J, 1991. 59(1): 76-92.

Importance β-cell coupling





Glucose homeostasis



Chronic excursions from the normal range lead to diabetes

Epidemic of diabetes:

US: 23.6 million (7.8%).
5.7 million are undiagnosed

Worldwide:
1985: 30 million
2005: 230 million
2025: 350 million (projected)

- **Diabetes reduce life-span by 10-15 y**
- **Pre-onset development of disease is often long-term (up to ~decade), no efficient way of detection**
- **Chronic hyperglycemia, even of mild degree, can cause organ damage**
- **After disease, need efficient measures of management quality, risk for complications, etc (current method: HbA1c)**

Why?

- on identifying control parameters that, when altered, could reverse a pathophysiological process, could ultimately lead to a better understanding of disease dynamics and yield greater potential for development of successful treatments .
- Similar studies

Investigation of islet function versus structure

Box 1. Formulation of β-cell oscillation

The ODEs

$$C_{m,i}\frac{dV_i}{dt} = -(I_{Ca,i} + I_{K_{\mathrm{ATP}},i} + I_{Kn,i} + I_{Ks}) - \sum_{j=\{\text{all cells coupled to } i\}} g_c\left(V_i - V_j\right)$$

$$\frac{d[Ca^{2+}]_i}{dt} = -\alpha_i I_{Ca,i} - k_{Ca,i}[Ca^{2+}]_i$$

$$\frac{dn}{dt} = \frac{1}{\tau_n}\left(n_\infty - n\right)$$

$$\frac{ds}{dt} = \frac{1}{\tau_s}\left(s_\infty - s\right)$$

The currents

$$I_{K_{\mathrm{ATP}}} = g_{K_{\mathrm{ATP}}}\ (V - V_K)$$

$$I_{Ca} = g_{Ca}\cdot m_\infty\left(V - V_{Ca}\right)$$

$$I_{Kn} = g_K n\ (V - V_K)$$

$$I_{Ks} = g_S s\ (V - V_K)$$

Steady state fraction of channel opening

$$m_\infty = \frac{1}{1+\exp\left((V_m - V)/s_m\right)}$$

$$n_\infty = \frac{1}{1+\exp\left((V_n - V)/s_n\right)}$$

$$s_\infty = \frac{1}{1+\exp\left((V_s - V)/s_s\right)}$$

A. Nittala, S. Ghosh,X. Wang, *Investigating the Role of Islet Cytoarchitecture in Its Oscillation Using a New beta-Cell Cluster Model.* PLoS ONE, 2007. 2(10): e983.

Computational demand

For a cluster of 100 cells, 60 million evaluations of the 400 equations (4 ODE each cell), It took a few hours on a Dell OptiPlex GX620 PC with dual 3 GHz CPU and 2 GB of Ram.

(Human islets ~ 10^3 cells; rodent islets ~ 10^2 cells)

- 1000 islet configurations simulated, using a cluster Zeke (45 node), ~ 1 month

OPEN ACCESS Freely available online
PLoS one

Investigating the Role of Islet Cytoarchitecture in Its Oscillation Using a New β-Cell Cluster Model

Aparna Nittala, Soumitra Ghosh, Xujing Wang*

Theoretical Biology and Medical Modelling
BioMed Central

Research

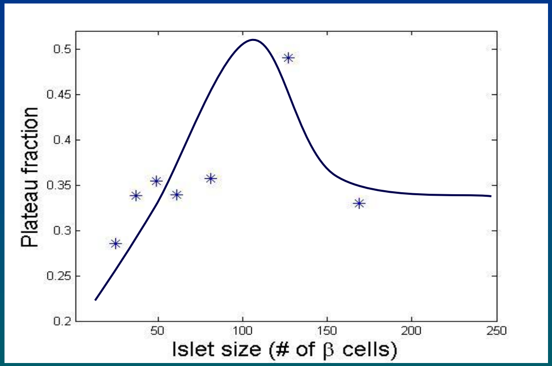
Open Access

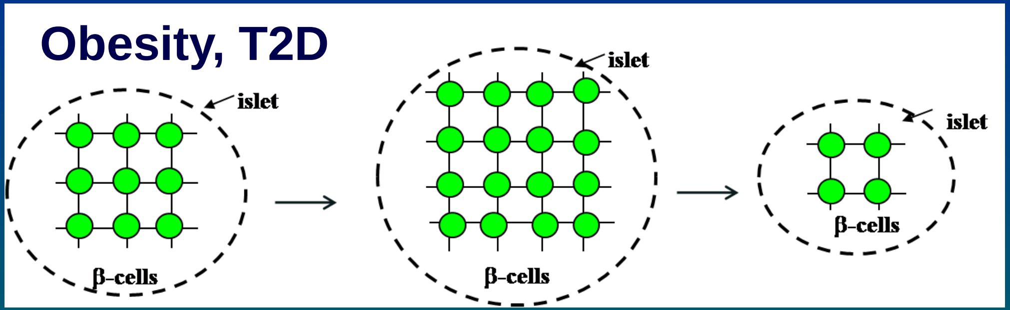
The hyperbolic effect of density and strength of inter beta-cell coupling on islet bursting: a theoretical investigation

Aparna Nittala and Xujing Wang*

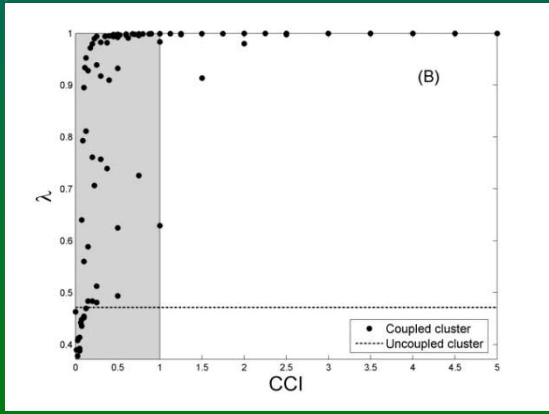
β-cell function versus mass

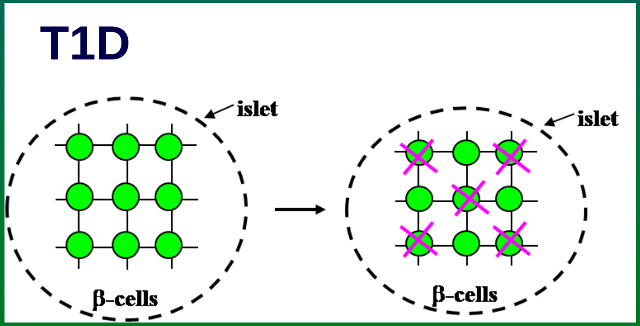
β-cell function depends on total amount of mass



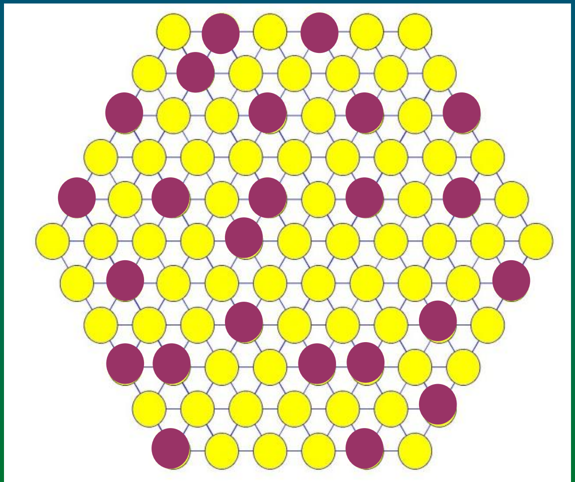


Also depends on structural organization of mass





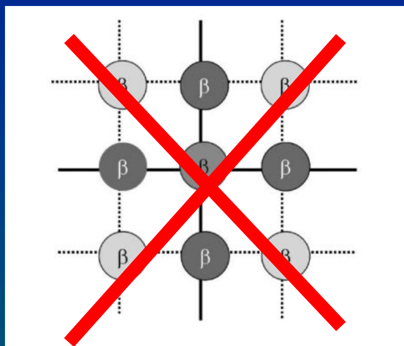
β-cell network structure, is it simple cubic?

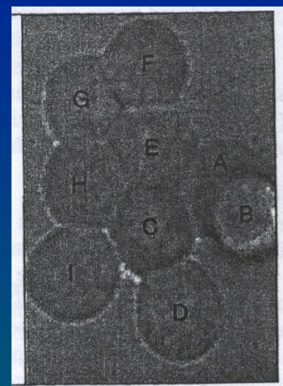


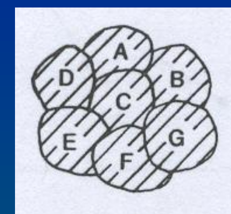
β cells Non-β or damaged β cells

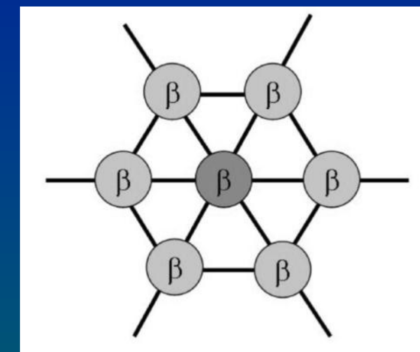
New HCP model: Hexagonal Closest Packing

$$C_{m,i}\frac{dV_i}{dt} = -(I_{Ca,i} + I_{K_{ATP},i} + I_{K,i} + I_{s,i}) - \sum_{j=\text{all cells coupled to } i} g_c\left(V_i - V_j\right)$$





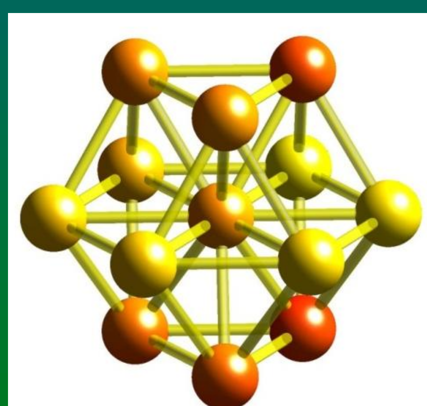


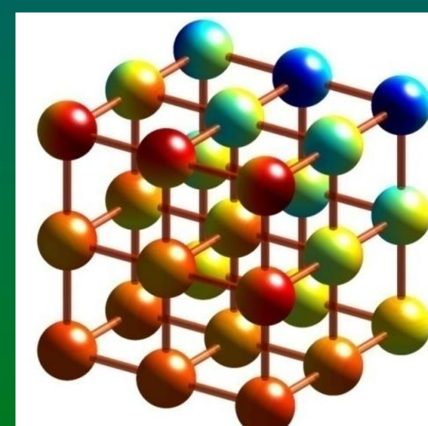


B. Hellman, et al. Diabetologia, 1994. 37 Suppl 2: S11-20.
E. Gylfe,et al. Ups J Med Sci, 2000. 105(2): 35-51

unit-hcp

n_c = 12 (3d)
n_c = 6 (2d)

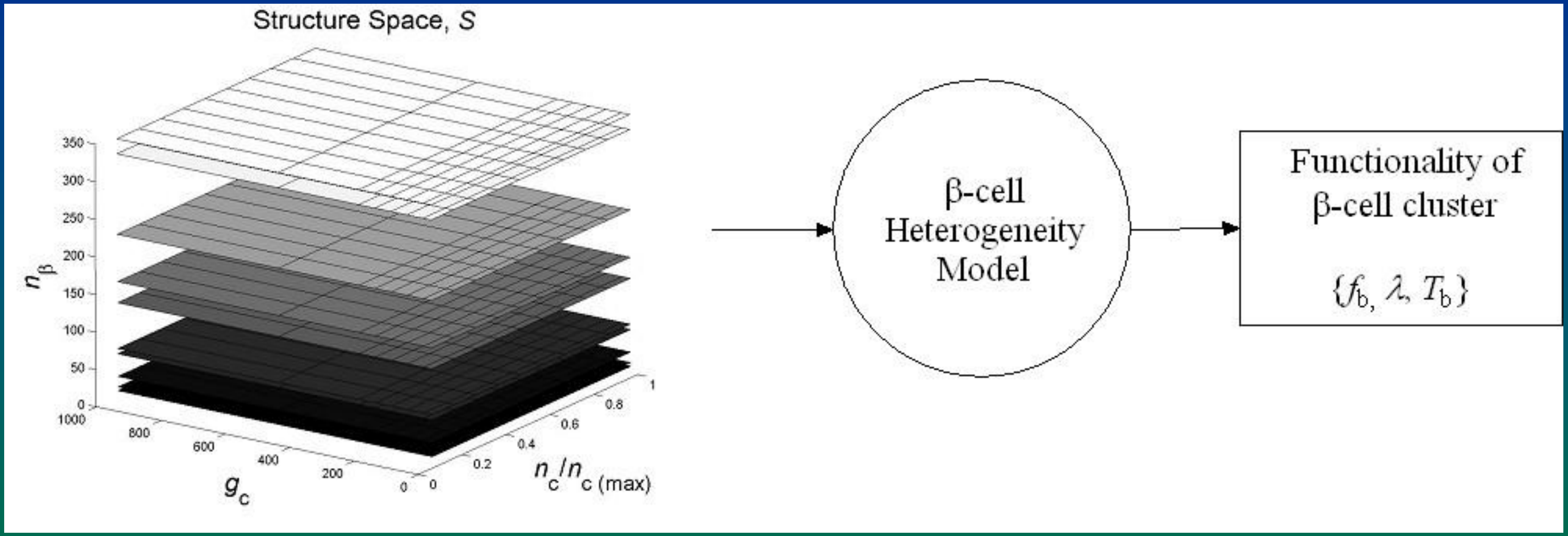




unit-scp

n_c = 6 (3d)
n_c = 4 (2d)

Numerical Investigation of Islet Structure with Islet Function



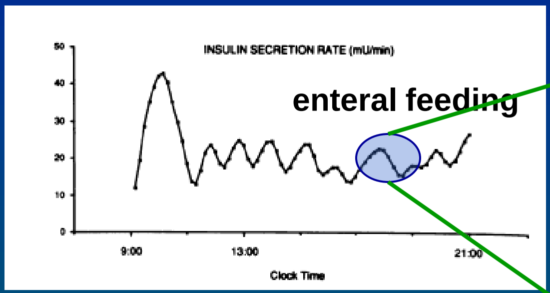
Islet Structure Space, S: (n_β, n_c, g_c)

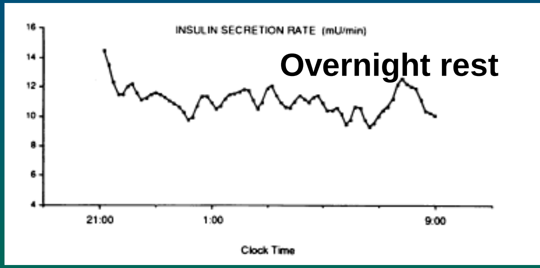
n_β: [1-343], g_c : [0-1000*pS*], n_c: [0-12], over <u>1000</u> islet configurations simulated

Islet Function Space, F: (f_b, λ, T_b)

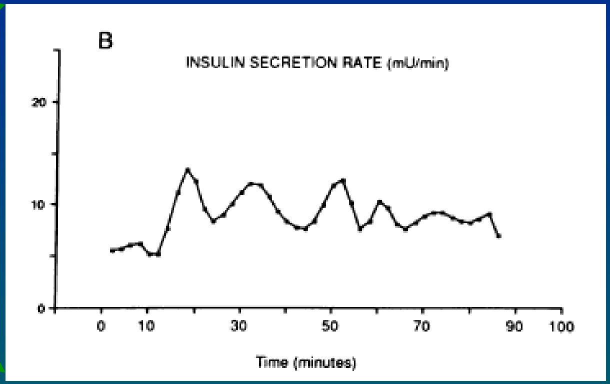
Insulin pulsatility

Ultradian frequency ~ hr



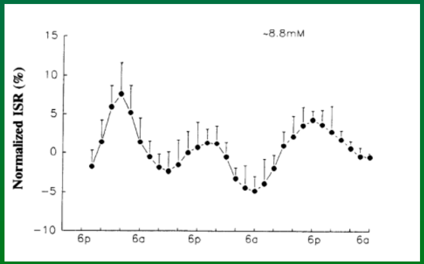


High frequency ~min



Sonnenberg, G.E., et al., J Clin Invest, 1992. 90(2): p. 545-53.

Circadian: ~day



Ultra high freq: ~sec

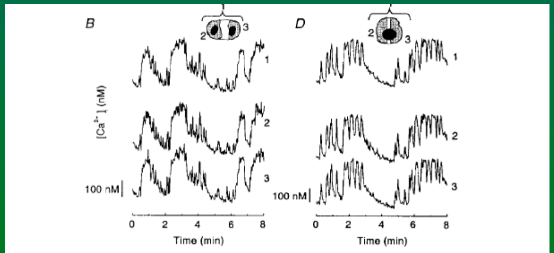
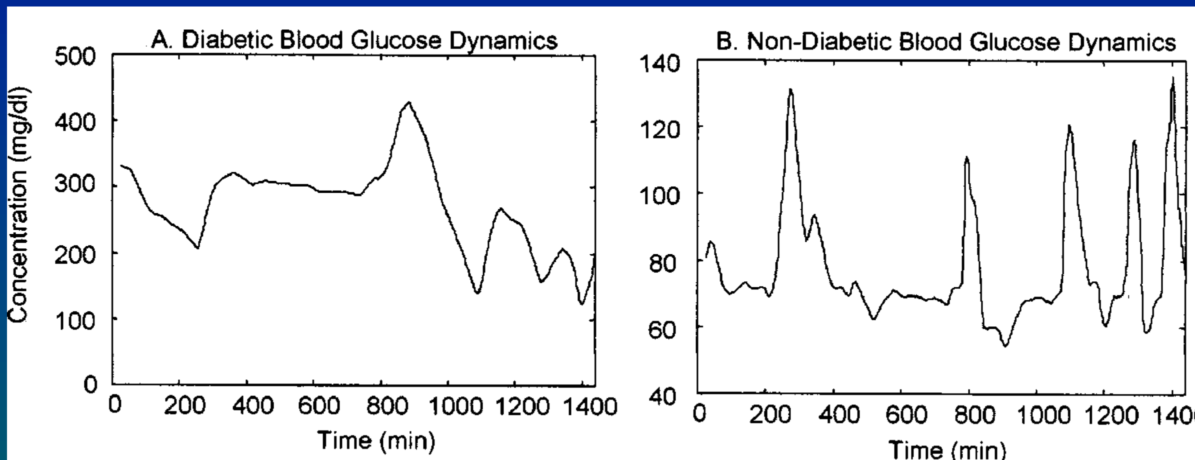


Figure 4. Synchrony of $[Ca^{2+}]_i$ oscillations in clusters of cells from mouse pancreatic islets during continuous stimulation with 15 mM glucose

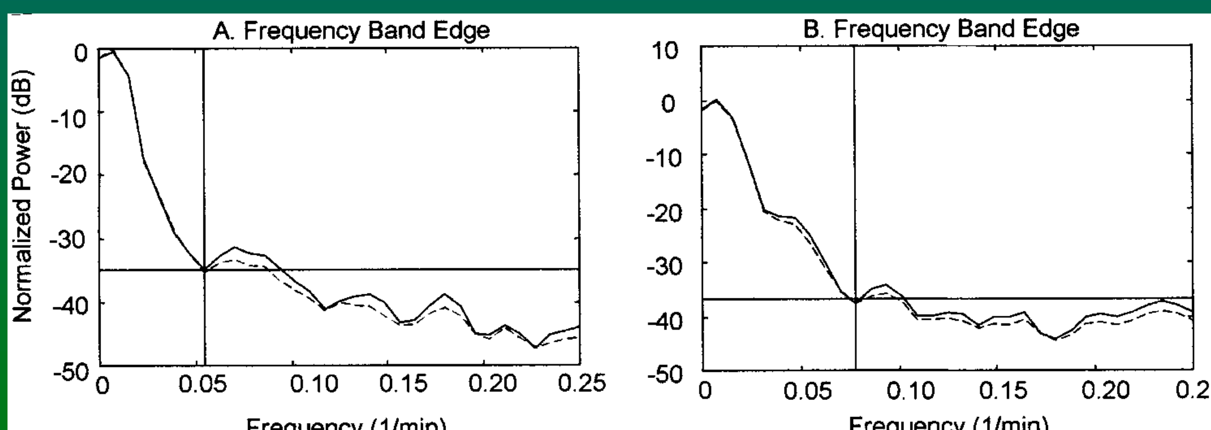
F.C. Jonkers, et al,. J Physiol, 1999. 520 Pt 3: 839-49.

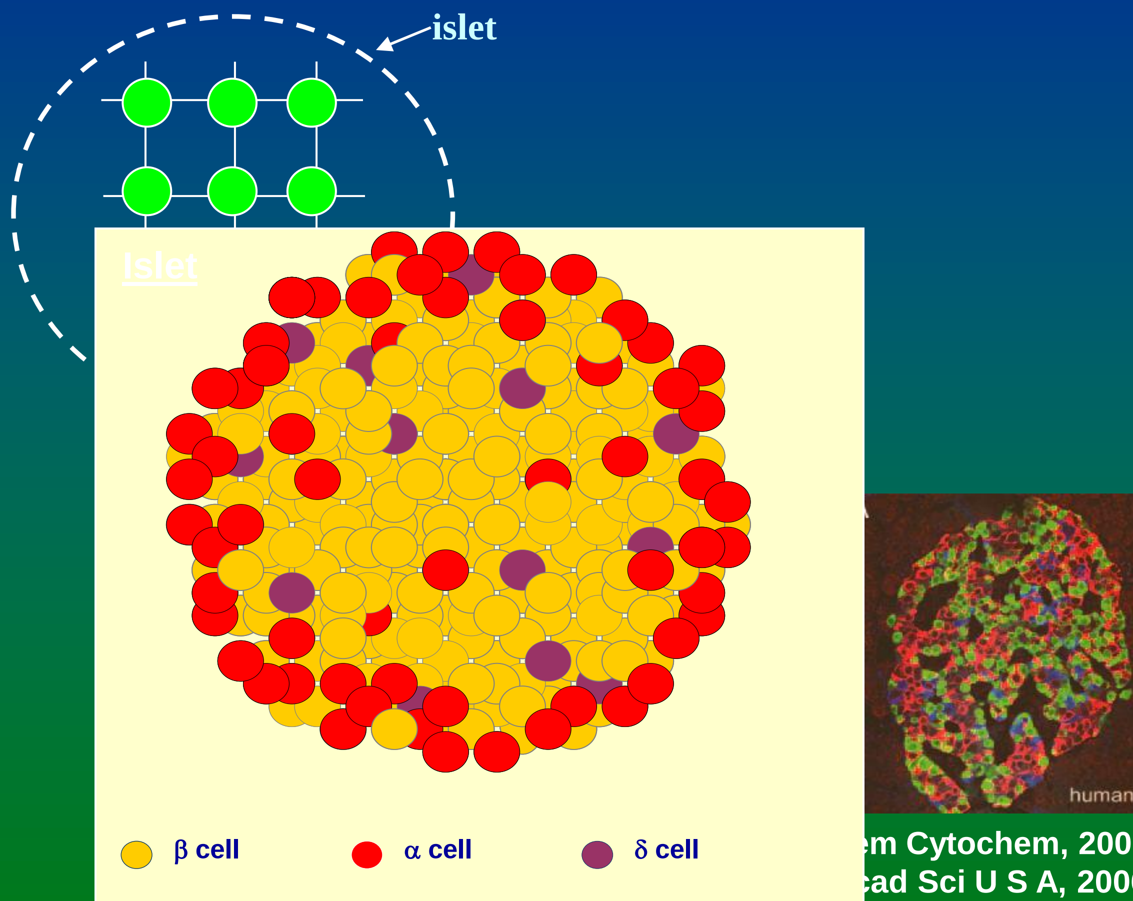
Boden, G, et al Am J Physiol. 1996 Aug;271(2 Pt 1):E246-52.

Normal VS Diabetic



Sampling rate: 5min, diabetics: 1 insulin dose/day (T1D). Normal meal and life style





em Cytochem, 2005. 53(9): 1087-97.

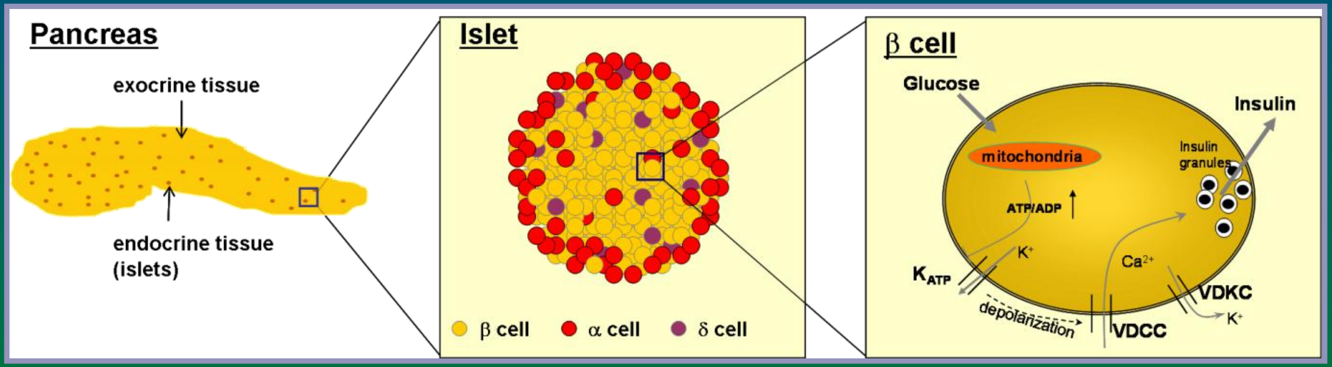
cad Sci U S A, 2006. 103(7): 2334-2339

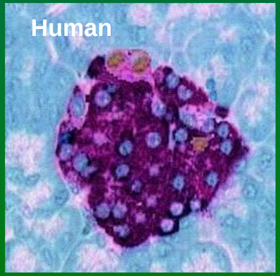
Complex (biological) networks: An example

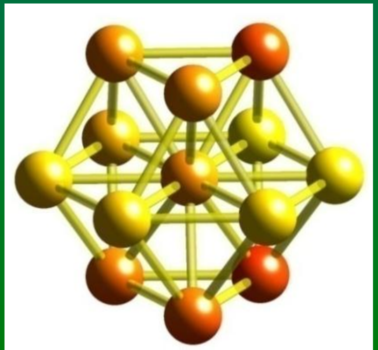
Glucose homeostasis:
the process that provide energy to every cell in our body
glucose need to be in a narrow range (chronic excursion lead to serious health problem: hypoglycemia, diabetes, cardiovascular, etc

Insulin: the primary hormone that regulates glucose

Pancreatic islet β-cell: the only cell type that produce and release insulin



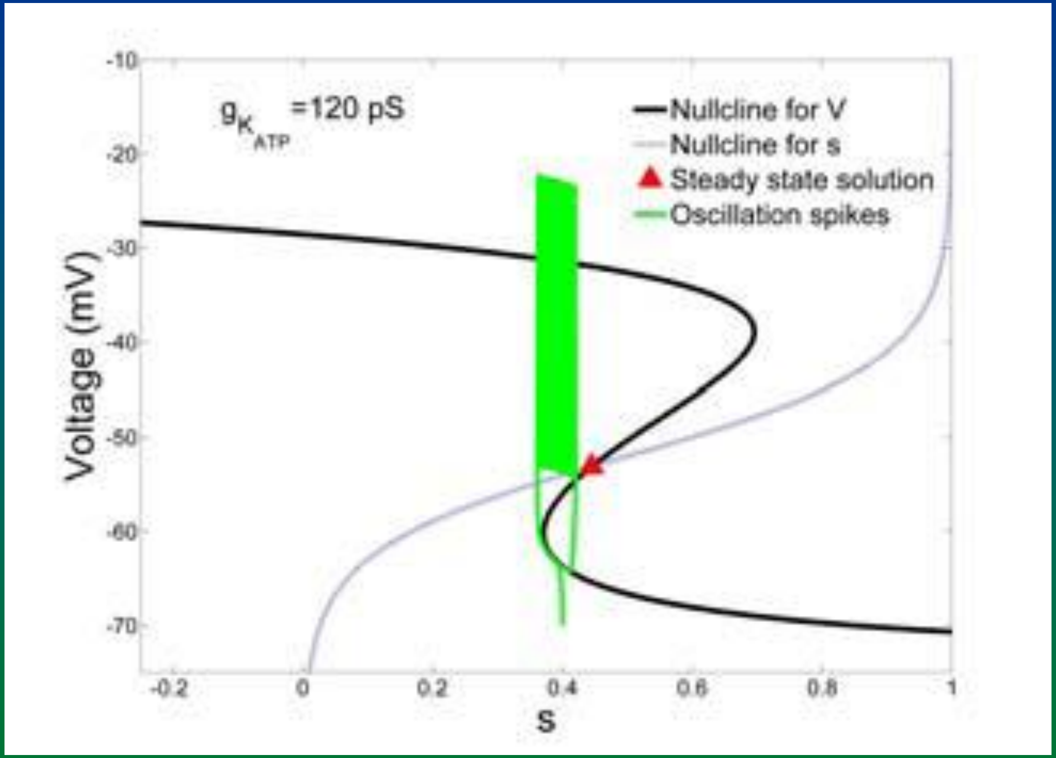




unit-hcp

n_c = 12 (3D)

Mathematical studies:
Phase diagram



electrical excitability of β-cells, at normal K_{ATP} channel activation.

Abstract

- From a dynamic perspective, the onset of a chronic diseases resembles the phase transition in a complex system. Recently we examined this idea in a special case, the onset of type 1 diabetes (T1D). T1D results from autoimmune destruction of the β-cells, which is the only cell type that produces and releases insulin, the primary regulating hormone of glucose homeostasis. Inside a pancreatic islet, the β-cells are electrically coupled to each other and can be mathematically modeled as a network of coupled nonlinear chaotic oscillators. We show that the critical percolation probability p_c of the β-cell network predicts a critical value of β-cell loss leading to functional failure, which is consistent with laboratory and clinical observations. Numerical simulations confirm that around the critical point, the β-cells lose their ability to synchronize, and that the critical behavior of network captures the disease dynamics around onset. T he results indicate that the onset of T1D could be the result of a geometric phase transition of the islet β-cell network due to loss of percolation.