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

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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 $\beta$-cells

Pancreatic islet $\beta$-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

- $\beta$-cells are coupled to each other, forming a network
- The connectivity is important for normal function
- $\beta$-cells are percolated?
Natural history of T1D

Natural History of T1D

- $\beta$-cell mass
- $\beta$-cell function
- Clinical symptoms

Time

diagnosis
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: $p_c \sim 0.7 \times 0.3 = 0.21$

- Laboratory study: islet dysfunction at ~70% death or 70% cell cannot couple with others: $p_c \sim 0.7 \times 0.3 = 0.21$
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

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Percolation in $\beta$-cell network

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- Disease onset @ ~70% loss of $\beta$-cells: $p_c \sim 0.7 \times 0.3 = 0.21$
- Laboratory study: islet dysfunction at 70% death or 70% cell cannot couple with others: $p_c \sim 0.7 \times 0.3 = 0.21$
- 3D HCP (fcc): $p_c = 0.199$
Percolation in Hexgonal Closest Packing lattice (HCP, or fcc)
Oscillation synchronization transition

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

Plan to simulate ~1000 more around the critical point

Aparna Nittala

Serkan Guldal
Oscillation synchronization transition occurs around the critical point.
Bond percolation, additional to site percolation
Synchronization also depend on Bond strength

Rodent islet: $g_c \sim 100-300$ 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
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Percolation simulation in HCP
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Islet oscillation and multiscale modeling of glucose homeostasis
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HPC
An appropriate answer to the right problem is worth a good deal more than an exact answer to an approximate problem

John Tukey
“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 $\beta$-cells

There are $\sim 20$ members in the connexin family
utilization of connexin is tissue specific.
$\beta$ cells express only connexin-36

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

Importance β-cell coupling

Isolated β-cells

β-cells in intact islet
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

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

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

\[
\frac{dn}{dt} = \frac{1}{\tau_n} (n_\infty - n)
\]

\[
\frac{ds}{dt} = \frac{1}{\tau_s} (s_\infty - s)
\]

The currents

\[
I_{K_{ATP}} = g_{K_{ATP}} (V - V_K)
\]

\[
I_{Ca} = g_{Ca} m_\infty (V - V_{Ca})
\]

\[
I_{Kn} = g_{Kn} n_\infty (V - V_K)
\]

\[
I_{Ks} = g_{Ks} s_\infty (V - V_K)
\]

Steady state fraction of channel opening

\[
m_\infty = \frac{1}{1 + \exp((V_m - V)/s_m)}
\]

\[
n_\infty = \frac{1}{1 + \exp((V_n - V)/s_n)}
\]

\[
s_\infty = \frac{1}{1 + \exp((V_s - V)/s_s)}
\]

Computational demand

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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

Research

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

Obesity, T2D

T1D
β-cell network structure, is it simple cubic?
New HCP model: Hexagonal Closest Packing

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


unit-hcp
\[ n_c = 12 \text{ (3d)} \]
\[ n_c = 6 \text{ (2d)} \]

unit-scp
\[ n_c = 6 \text{ (3d)} \]
\[ n_c = 4 \text{ (2d)} \]
Numerical Investigation of Islet Structure with Islet Function

Islet Structure Space, \( S: (n_\beta, n_c, g_c) \)
\( n_\beta: [1-343], g_c: [0-1000pS], \) \( n_c: [0-12], \) over 1000 islet configurations simulated

Islet Function Space, \( F: (f_b, \lambda, T_b) \)
Insulin pulsatility

Ultradian frequency ~ hr

High frequency ~ min

Circadian: ~ day

Ultra high freq: ~ sec


Normal VS Diabetic

Sampling rate: 5min, diabetics: 1 insulin dose/day (T1D).
Normal meal and life style
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 $K_{\text{ATP}}$ 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. The 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.