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.

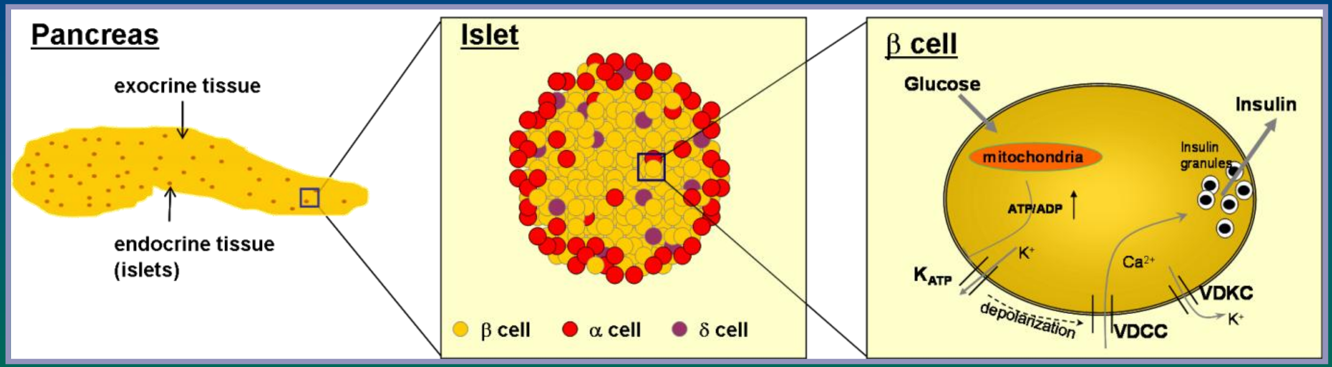
Type 1 Diabetes

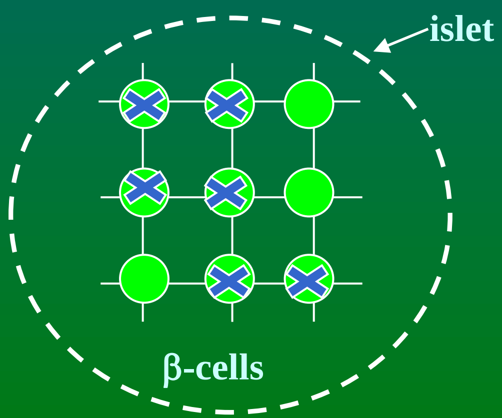
T1D: results from loss of pancreatic islet β-cells

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

Insulin: the primary hormone that regulates glucose

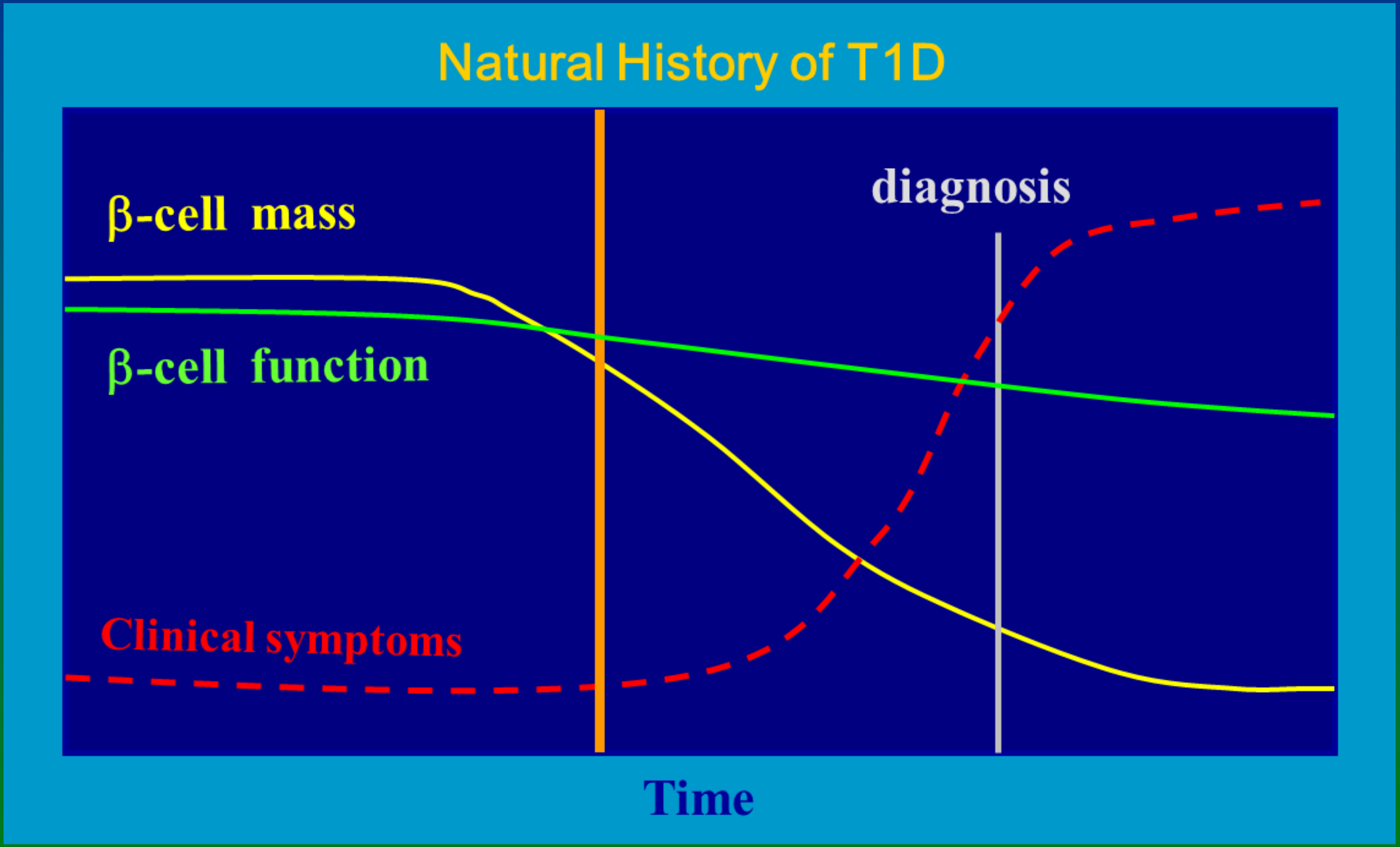
Glucose homeostasis: the process that provide energy to every cell in our body



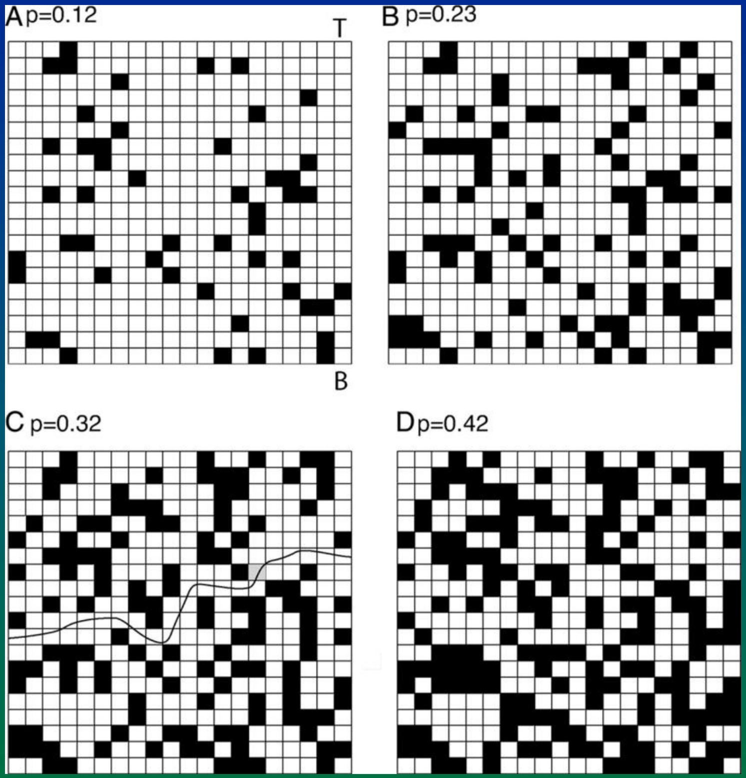


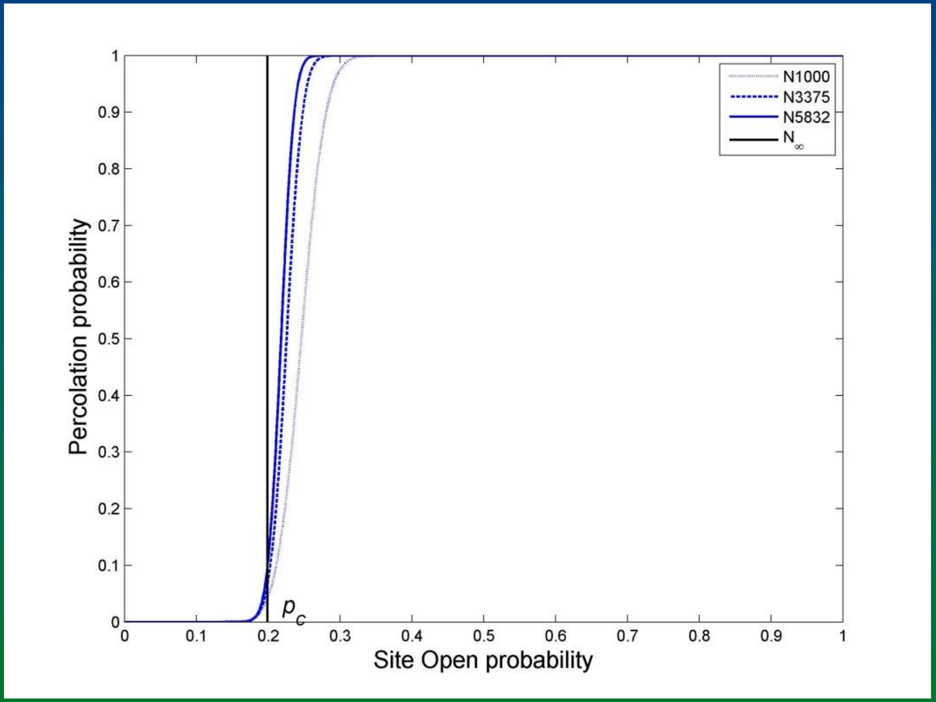
- **β-cells are coupled to each other, forming a network**
- **The connectivity is important for normal function**
- **β-cells are percolated?**

Natural history of T1D



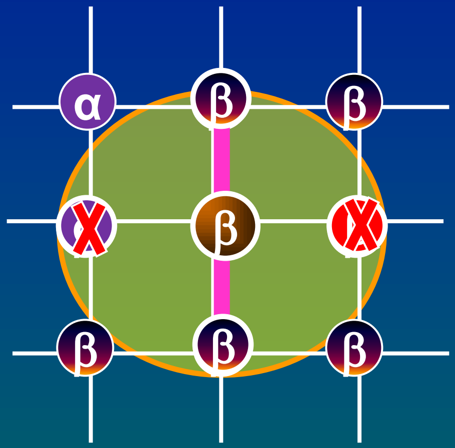
What is Percolation





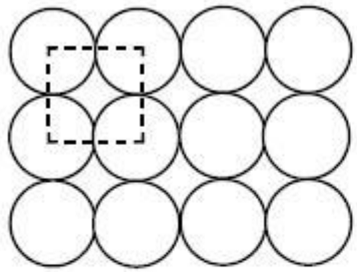
PNAS. 2009 4;106(31):12634-9

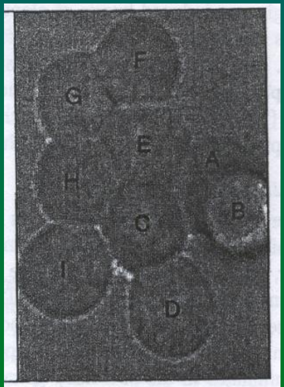
Percolation in β-cell network

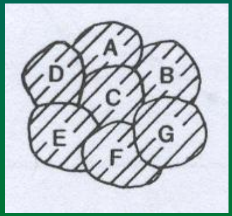


- **3D cube: p_c=0.316**
- **Normal islet: ~70% are β-cells, site open probability p~0.7>p_c, percolated**
- **Disease onset @ ~70% loss of β-cells: p_c~0.7*0.3=0.21**
- **Laboratory study: islet dysfunction at 70% death or 70% cell cannot couple with others: p_c~0.7*0.3=0.21**

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





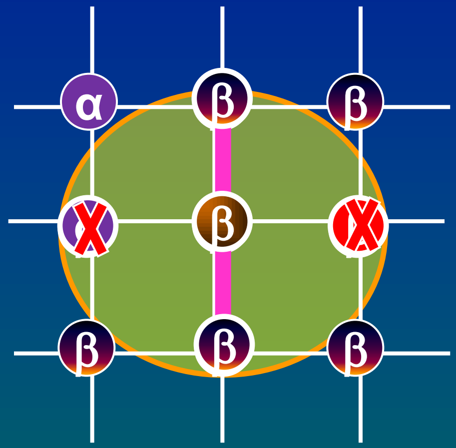


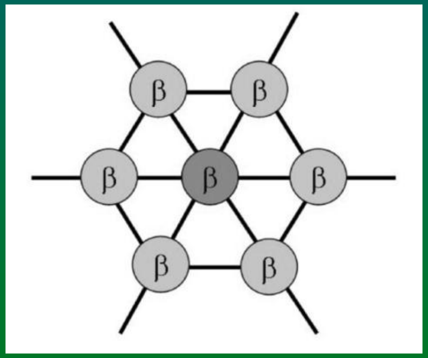
We were the first to introduced the hexagonal lattice model to study the β-cell network

<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





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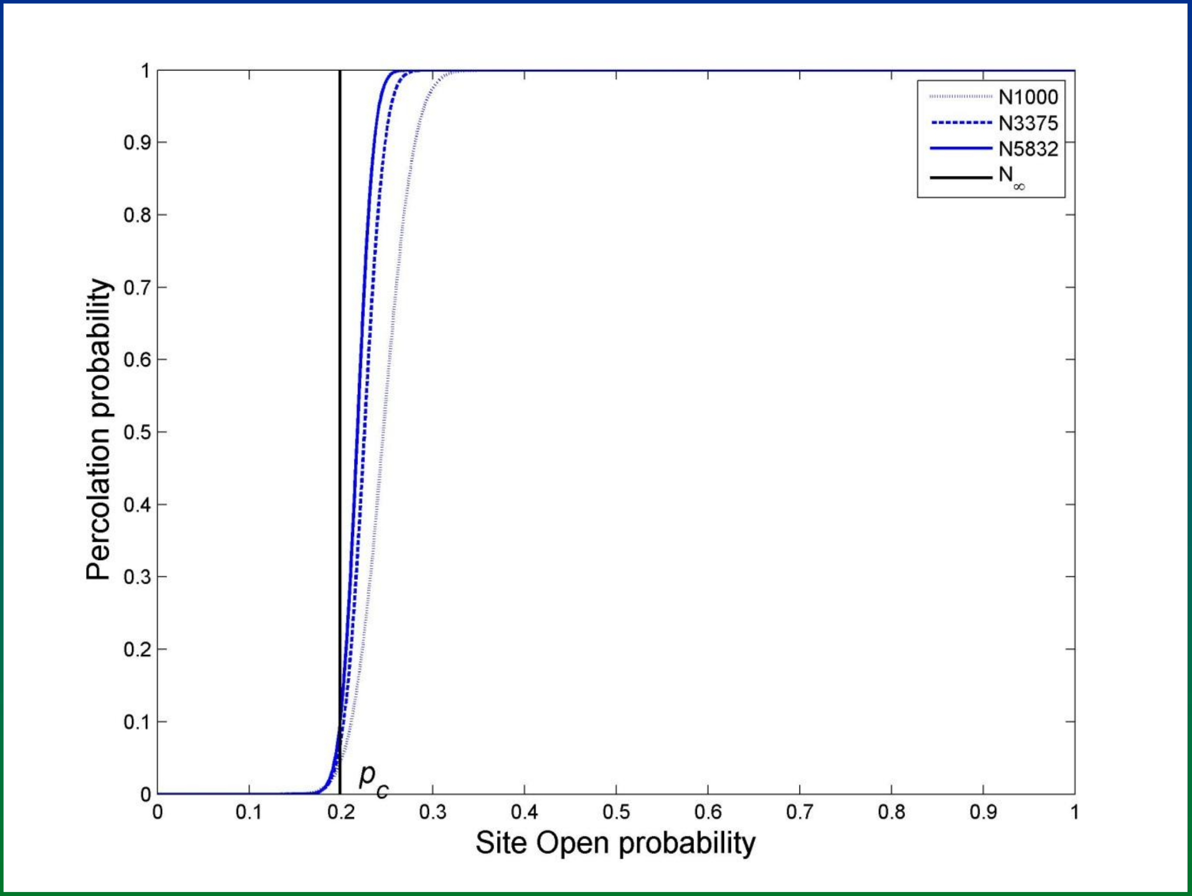
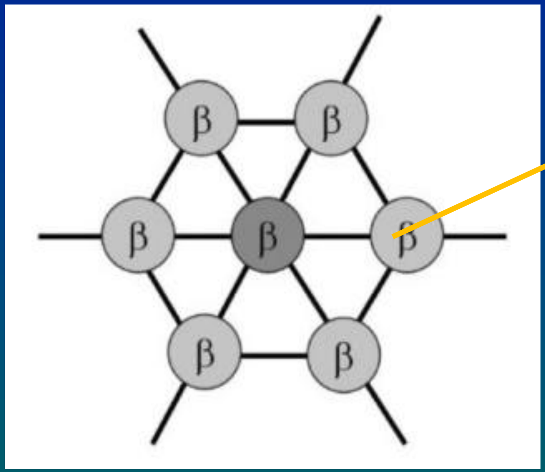
- 3D HCP (fcc): p_c=0.199

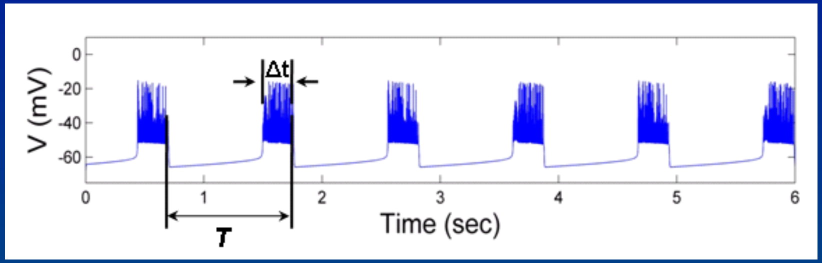
Percolation in Hexgonal Closest Packing lattice (HCP, or fcc)



Elais Jackson
Johanna Stamper

Oscillation synchronization transition





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

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)

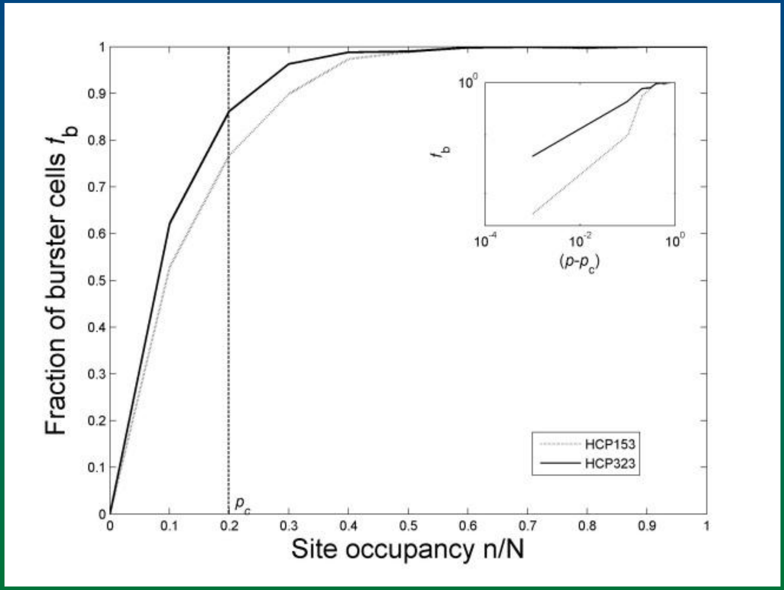
1000 islet configurations simulated, using a cluster Zeke (45 node), ~ 1 month

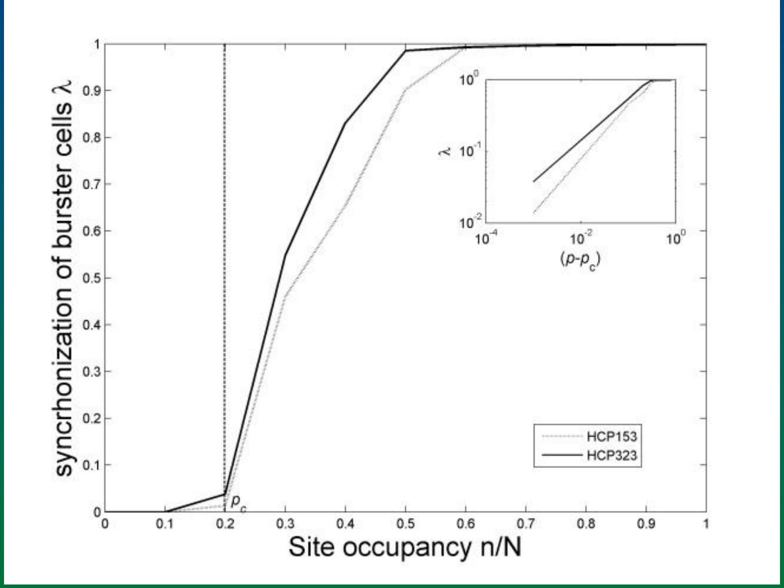
Aparna Nittala

Plan to simulate ~1000 more around the critical point

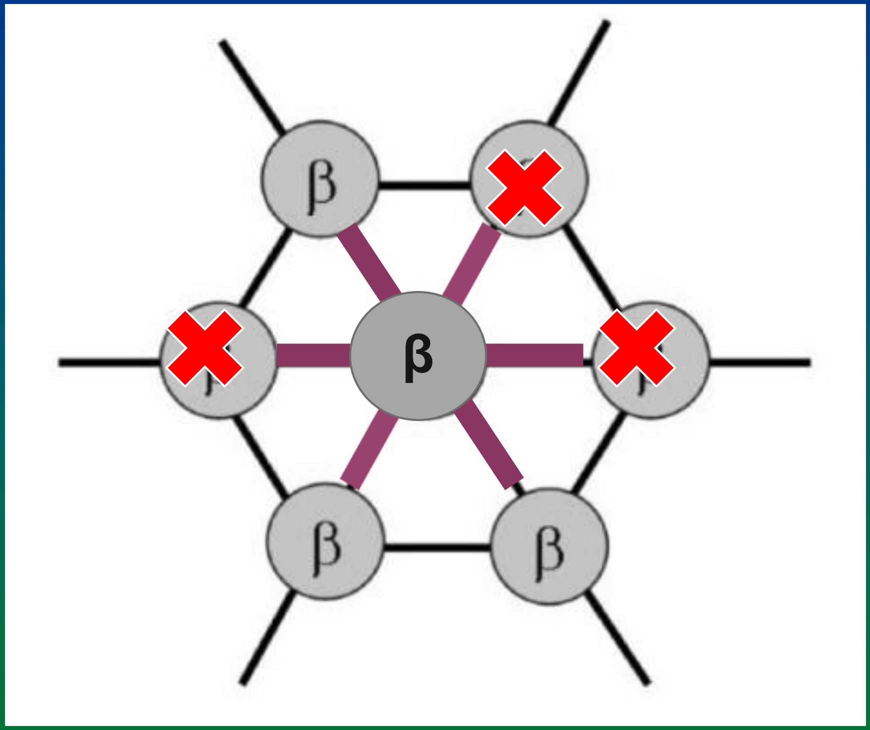
Serkan Guldal

Oscillation synchronization transition occurs around the critical point

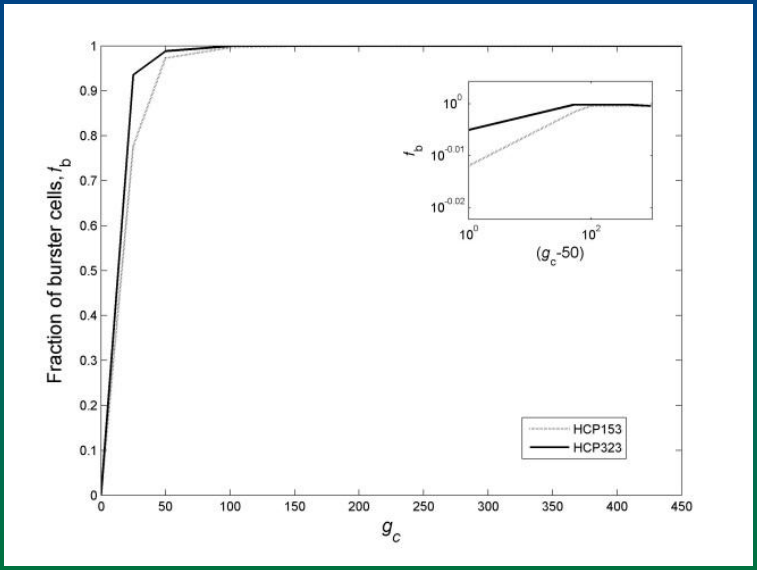


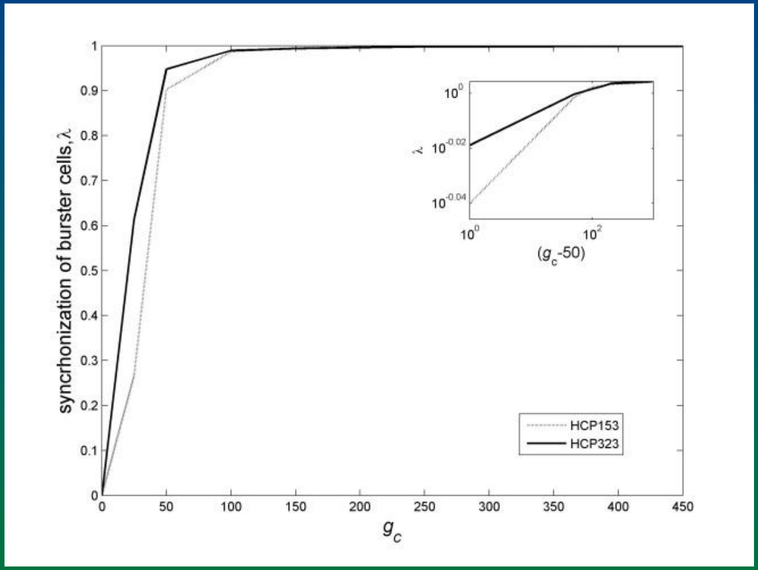


Bond percolation, additional to site percolation



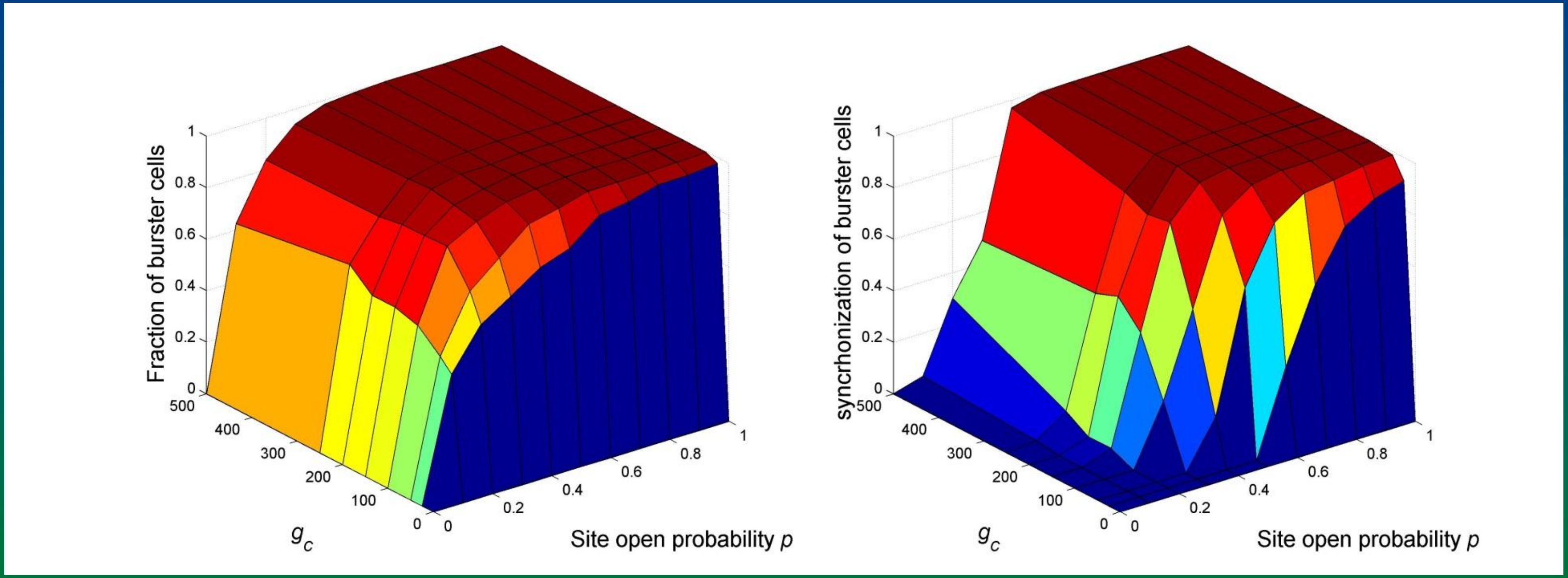
Synchronization also depend on Bond strength





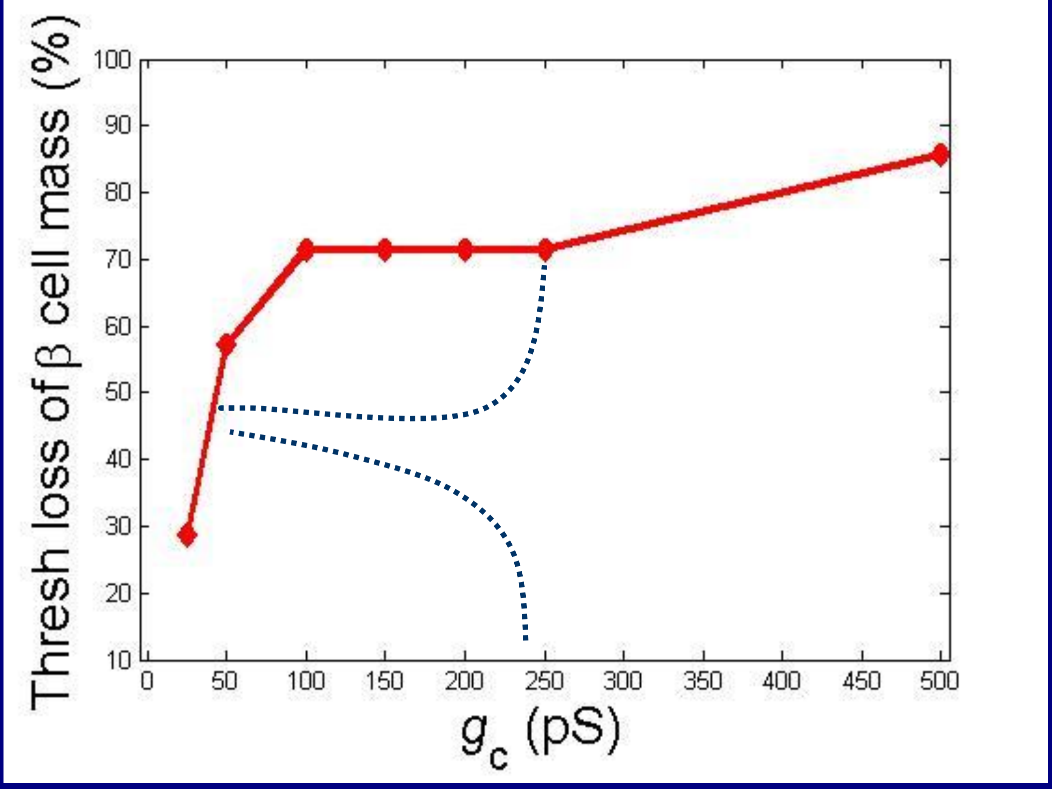
Rodent islet: g_c~100-300 pS.

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