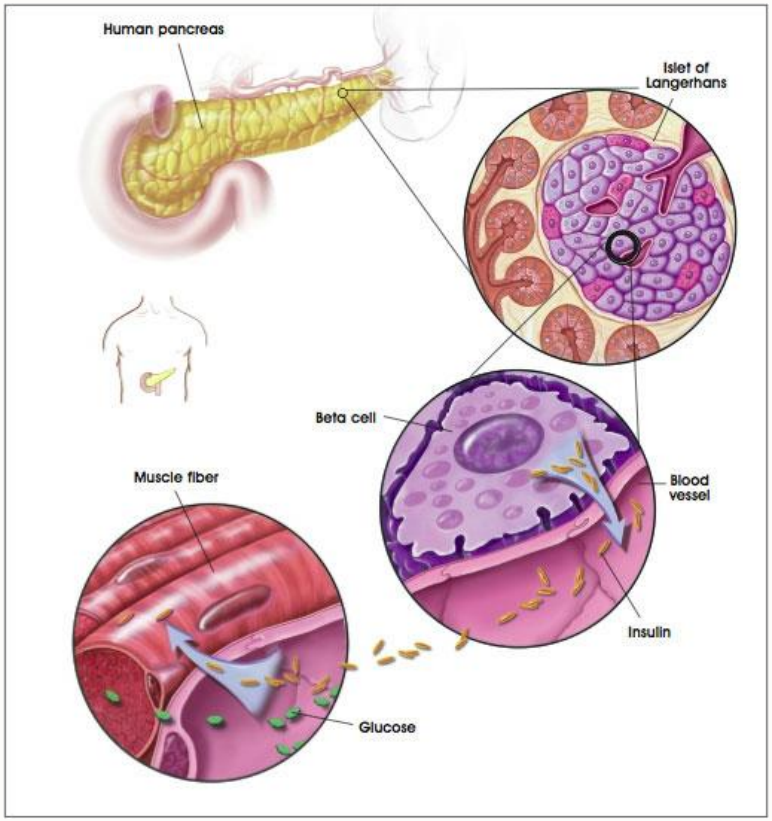
Models of cellular and network activity in the pancreas

Looking ahead towards pancreatic transplants

Pranay Goel
IISER Pune

ICTS
13th June 2017

Pancreatic physiology



Terese Winslow, Lydia Kibiuk
http://stemcells.nih.gov

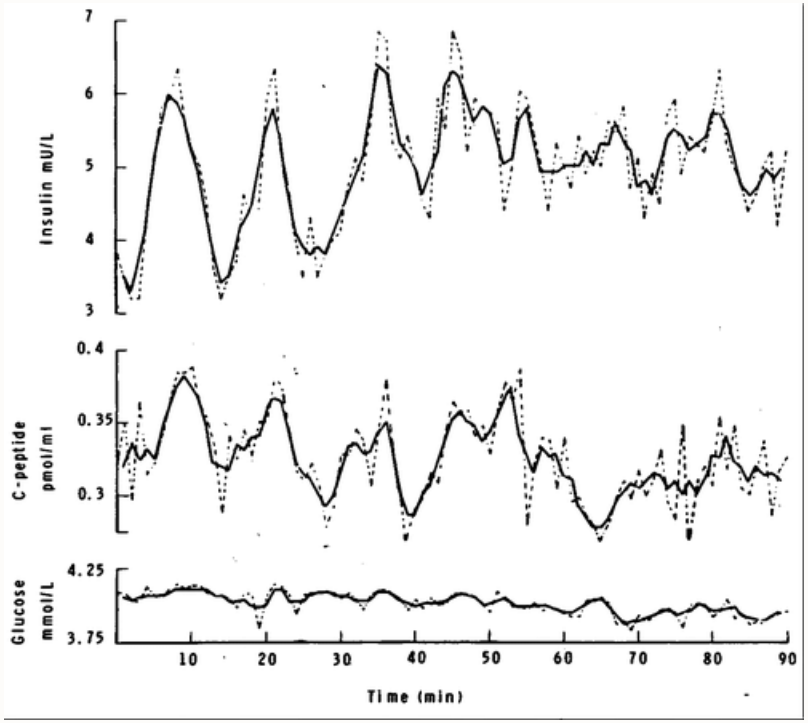
Bioengineering artificial pancreas

- Two approaches to artificial pancreas (for Type 1 diabetes)
    - Insulin pump systems
    - Islet transplantation
- Edmonton protocol: Cadaverous islets are placed into the liver; takes some time for vascularization and insulin secretion
- Success rates: The Collaborative Islet Transplant Registry reported in 2009 that 70% of adults with were free of insulin injections at one year, 50% at two years, and 35% at three years
- Challenges
    - Sourcing of islet cells (human, porcine, differentiating various precursors)
    - Engraftment; oxygen and blood supply
    - Immunoprotection/suppression
    - How do they influence diabetic complications?

Theme

GSIS: The origin of insulin pulsatility

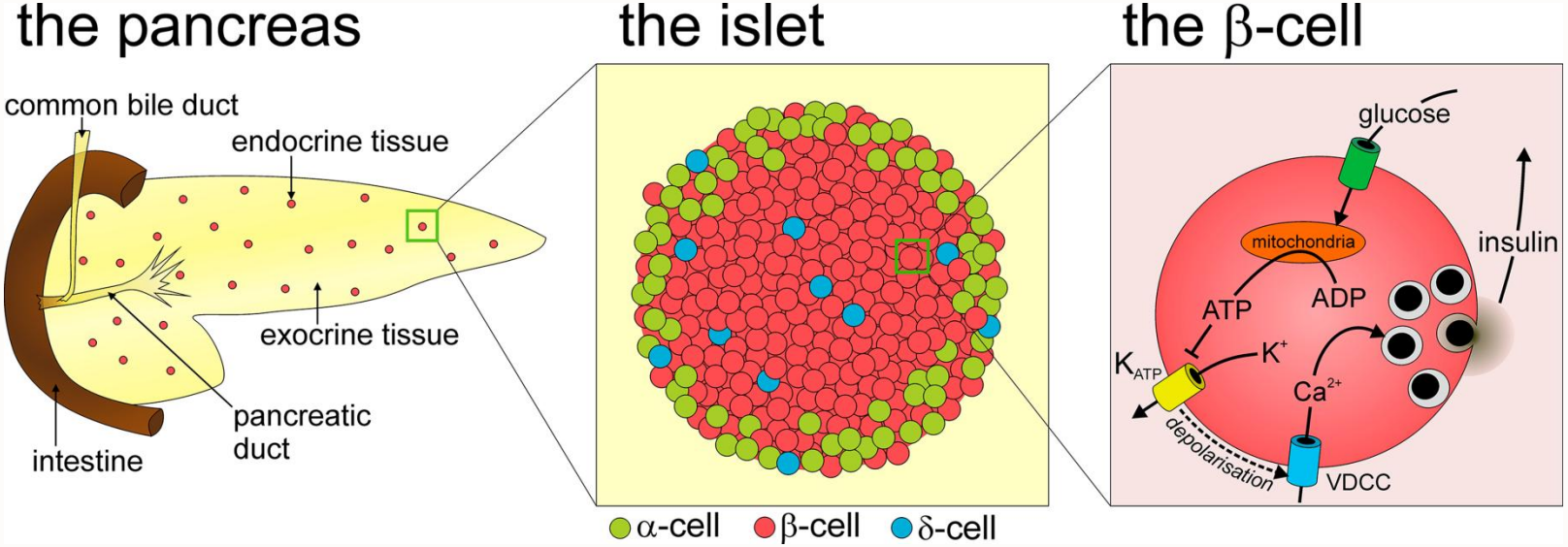
Insulin pulsatility in type 2 diabetes



Measurements from a peripheral vein in a fasted human subject, Lang et al.

- Insulin pulsatility is disrupted in diabetes (reduced amplitude)
- Early marker of disease:
  - Observed in pre-diabetics, and in
  - First-degree relatives of diabetic patients
- Pulses more effective at
  - Suppressing hepatic glucose production and
  - Glucose uptake by peripheral tissue

GSIS: The consensus model



Electrical oscillations in beta-cells

- Bursting in islets. (A-B) A simultaneous recording of electrical activity (A) and [Ca2+]i (B) illustrates islet bursting (Zhang and Satin, unpublished example). The periodic firing of action potentials results in corresponding changes in [Ca2+]i, which is also reflective of insulin secretion. (C) A description of the components of a burst.

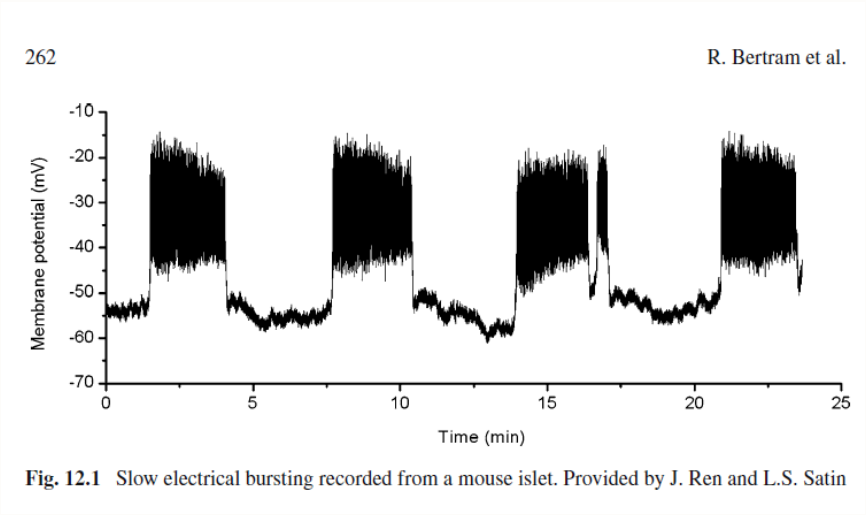
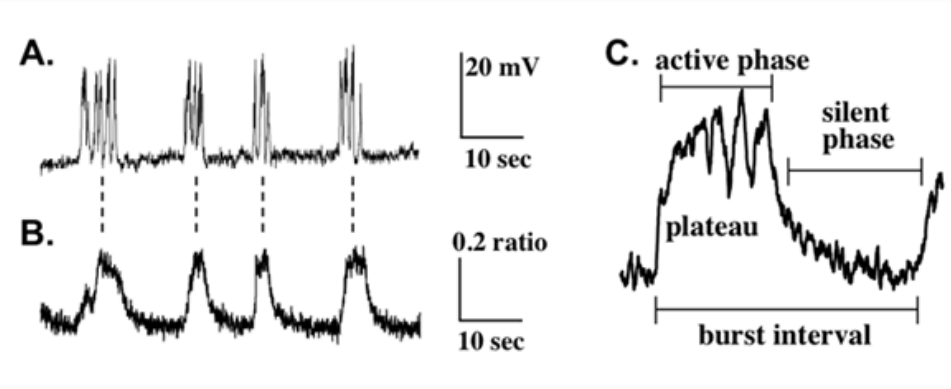


Fig. 12.1 Slow electrical bursting recorded from a mouse islet. Provided by J. Ren and L.S. Satin

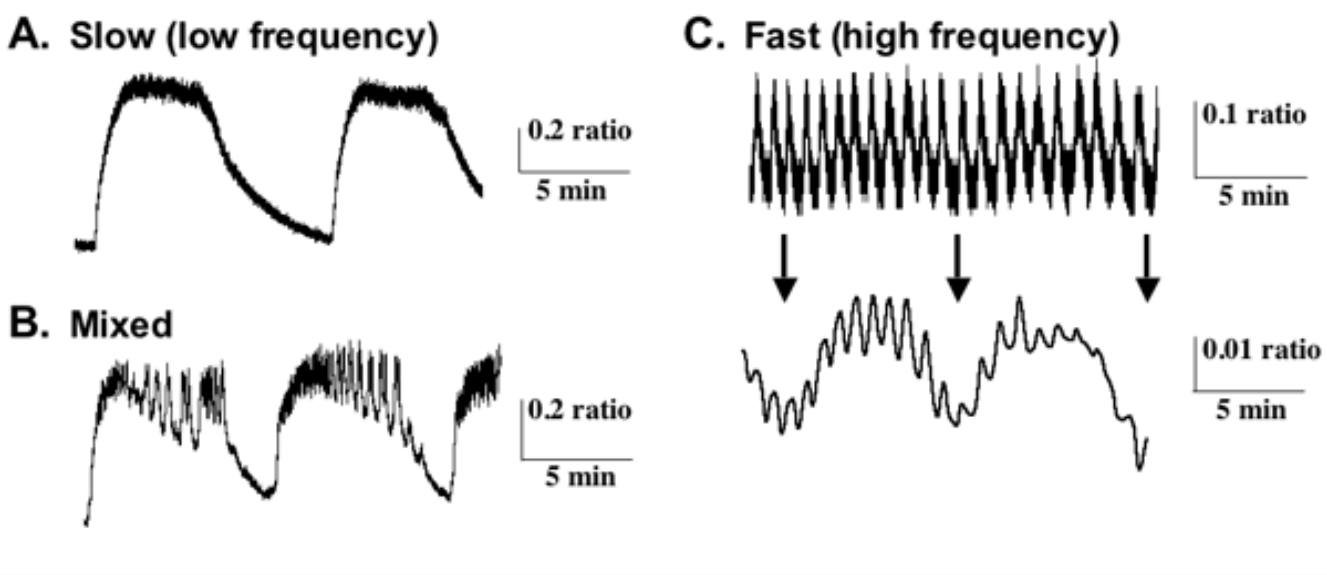
Transmembrane Voltage



Intracellular calcium

Multiple bursting patterns in β-cells

- Examples of the multiple modes of oscillations in [Ca2+]i, including purely slow oscillations (A), a mixture of fast and slow (B), and fast (C, top) with an underlying slow oscillations revealed (C, bottom) by signal averaging. [Ca2+]i traces from unpublished data, Nunemaker and Satin.



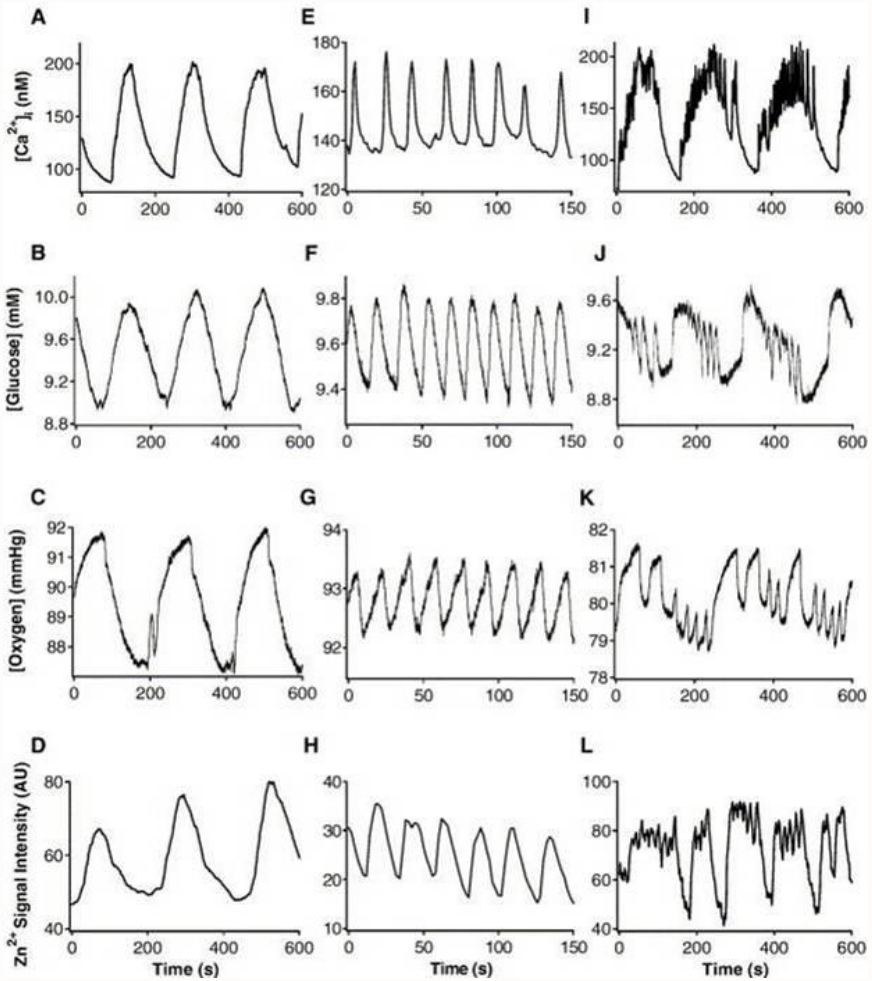
A (very) brief history of GSIS models

- Atwater I, Dawson CM, Scott A, Eddlestone G, Rojas E. The nature of the oscillatory behaviour in electrical activity from pancreatic beta-cell. Horm Metab Res Suppl. 1980;(Suppl 10):100–107.
- Chay TR, Keizer J. Minimal model for membrane oscillations in the pancreatic beta-cell. Biophys J. 1983;42(2):181–190.
- Two-timescale analysis: Rinzel J. Bursting oscillations in an excitable membrane model. In: Sleeman BD, Jarvis RJ, editors. Ordinary and partial differential equations, lecture notes in mathematics, 1151. New York: Springer; 1985. pp. 304–316.
- Bertram R, Sherman A. Negative calcium feedback: the road from Chay–Keizer. In: Coombes S, Bressloff PC, editors. Bursting: the genesis of rhythm in the nervous system. Singapore: World Scientific; 2005. pp. 19–48.
- And finally…the DOM (Bertram et al.)…

Modern developments in stimulus-secretion coupling in beta-cells

- The "old" theory held ion channels to be essential to bursting behavior:
  - Driven by V,n,Ca
- Recent data indicates the behavior is richer: implicates a direct involvement of metabolism
- The puzzle: Incompatible timescales!

Metabolic oscillations in beta-cells



Slow, Fast, and Mixed Metabolic Oscillations, Dahlgren, Kauri, Kennedy, BBA 1724:23 2005

- Recent confirmations of glycolytic oscillations
  - Merrins MJ, Bertram R, Sherman A, Satin LS (2012) Phosphofructo-2-kinase/Fructose-2,6-bisphosphatase Modulates Oscillations of Pancreatic Islet Metabolism. PLoS ONE 7(4): e34036. doi:10.1371/journal.pone.0034036
  - Direct measurements of oscillatory glycolysis in pancreatic islet β-cells using novel fluorescence resonance energy transfer (FRET) biosensors for pyruvate kinase M2 activity, Merrins MJ1, Van Dyke AR, Mapp AK, Rizzo MA, Satin LS. J Biol Chem. 2013 Nov 15;288(46):33312-22. doi: 10.1074/jbc.M113.508127. Epub 2013 Oct 7.

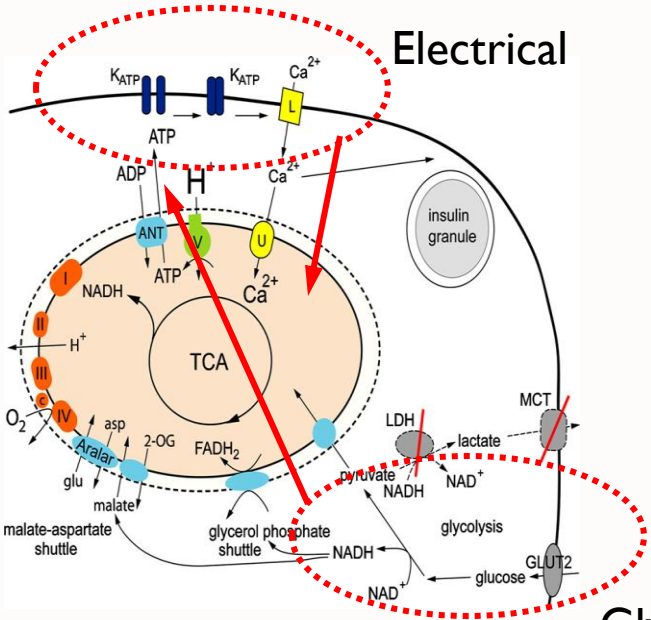
The Systems Biology of GSIS

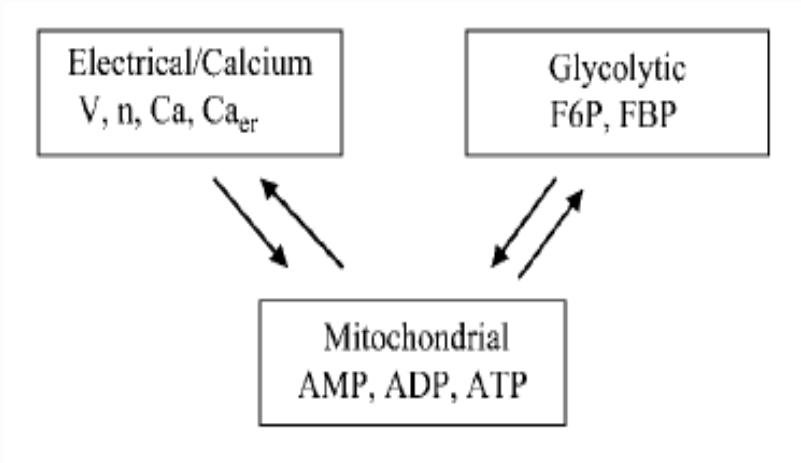
- Glycolysis/mitochondrial metabolism and ion-channel mediated calcium influx are both ancient systems.
- Beta cells are the *only* cells in the body that not only utilize glucose for respiration, but also secrete insulin, and thereby regulate glucose uptake by other cells.
- It is plausible that beta-cells may have evolved by coupling glycolytic and electrical systems together to achieve gluco-regulation.

The Dual-Oscillator Model (DOM)

- The DOM has been recently proposed that incorporates the effects of glycolysis into the electrical bursting model.

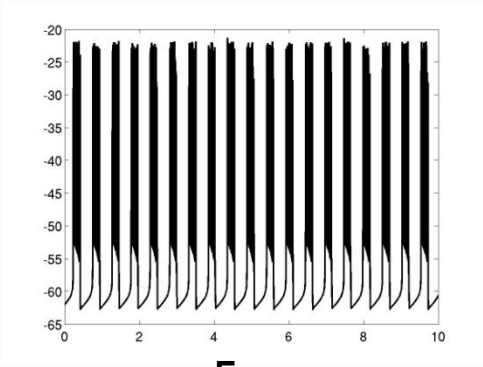
  Reference: *Bertram, R., L. Satin, M. Zhang, P. Smolen, and A. Sherman. 2004. Calcium and glycolysis mediate multiple bursting modes in pancreatic islets. Biophys. J. 87:3074–3087.*



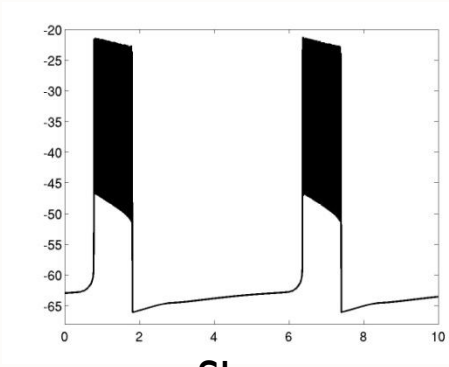


Patterns of activity in beta-cells

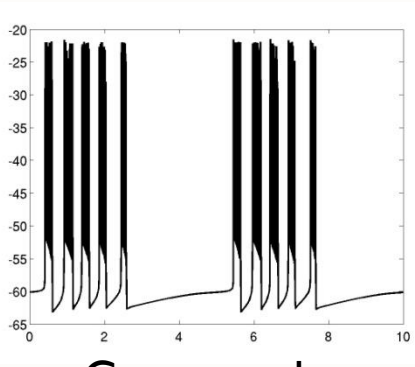
- The DOM reproduces experimentally observed bursting patterns:



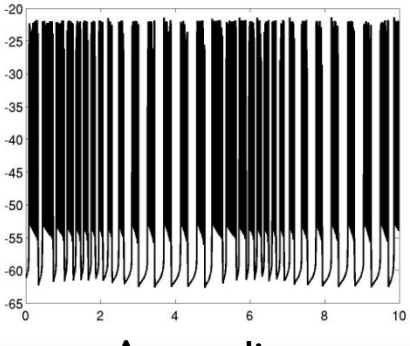
Fast



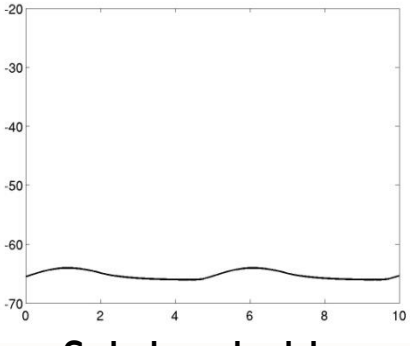
Slow



Compound



Accordion



Subthreshold

Dynamics of the beta-cell: electrical activity coupled to glycolysis

Pranay Goel and Arthur Sherman, *The Geometry of Bursting in the Dual Oscillator Model of Pancreatic beta-cells*, SIADS (2009)

The Dual-Oscillator Model

- V,n,Ca_i:

$$I_K = \bar{g}_K n(V - V_K)$$

$$I_{Ca} = \bar{g}_{Ca} m_\infty(V)(V - V_{Ca})$$

$$I_{K(Ca)} = g_{K(Ca)}(V - V_K)$$

$$I_{K(ATP)} = g_{K(ATP)}(V - V_K) \quad ,$$

$$MgADP^- = 0.165ADP \, , \; ADP^{3-} = 0.135ADP \, , \; ATP^{4-} = 0.05ATP$$

$$o_\infty(ADP, ATP) = \frac{0.08\left(1 + \frac{2MgADP^-}{17\mu M}\right) + 0.89\left(\frac{MgADP^-}{17\mu M}\right)^2}{\left(1 + \frac{MgADP^-}{17\mu M}\right)^2\left(1 + \frac{ADP^{3-}}{26\mu M} + \frac{ATP^{4-}}{1\mu M}\right)}$$

$$m_\infty(V) = \frac{1}{1 + e^{-(20+V)/12}}$$

$$n_\infty(V) = \frac{1}{1 + e^{-(16+V)/5}}$$

$$g_{K(Ca)} = \bar{g}_{K(Ca)}\left(\frac{Ca^2}{K_D^2 + Ca^2}\right) \quad , \quad g_{K(ATP)} = \bar{g}_{K(ATP)} o_\infty(ADP, ATP)$$

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

$$C_m \frac{dV}{dt} = -(I_K + I_{Ca} + I_{K(Ca)} + I_{K(ATP)})$$

- Ca_i, Ca_{ER}:

$$J_{mem} = -(\alpha I_{Ca} + k_{PMCA} Ca)$$

$$J_{er} = J_{leak} - J_{SERCA}$$

$$J_{leak} = p_{leak}(Ca_{er} - Ca)$$

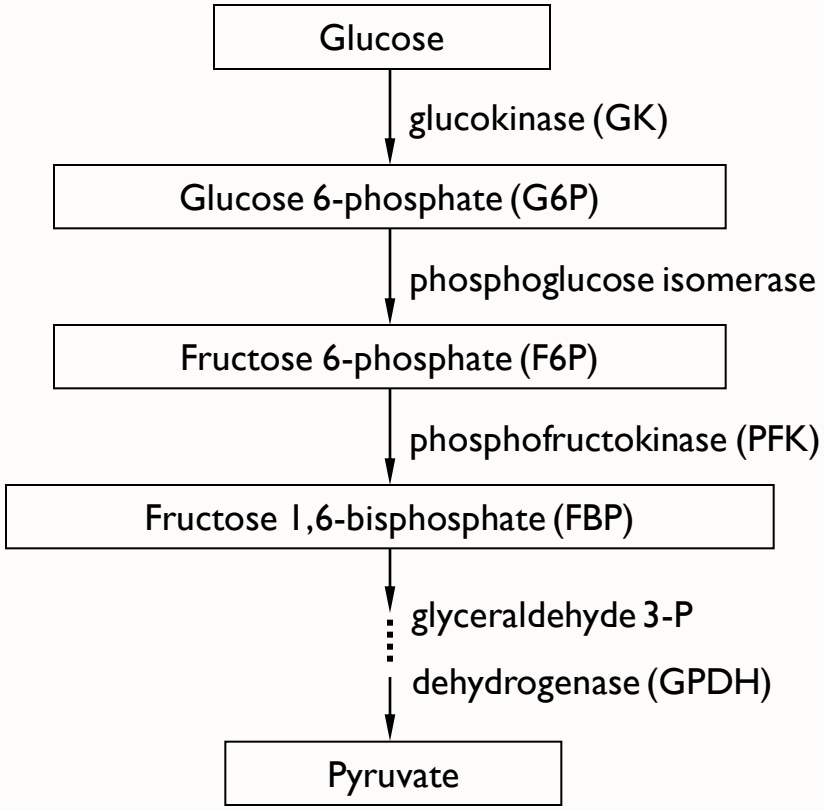
$$J_{SERCA} = k_{SERCA} Ca$$

$$\frac{dCa_{er}}{dt} = -f_{er}(V_{cyt}/V_{er})J_{er}$$

$$\frac{dCa}{dt} = f_{cyt}(J_{mem} + J_{er})$$

The Dual-Oscillator model

- Glycolysis: ADP, FBP, G6P:



$$J_{PFK} = V_{max} \frac{(1-\lambda) w_{1110} + \lambda \sum_{ijl} w_{ijl1}}{\sum_{ijkl} w_{ijkl}},$$

where l, j, k, l take value 0 or 1, and

$$w_{ijkl} = \frac{1}{f_{13}^{ik} f_{23}^{jk} f_{41}^{il} f_{42}^{jl} f_{43}^{kl}} \left(\frac{AMP}{K_1}\right)^i \left(\frac{FBP}{K_2}\right)^j \left(\frac{F6P}{K_3}\right)^k \left(\frac{ATP}{K_4}\right)^l$$

FBP (+)
AMP (+)
ATP (-)

$$J_{GPDH} = 0.2\sqrt{\frac{FBP}{1\,\mu M}}.$$

$$F6P = 0.3\,G6P$$

$$AMP + ADP + ATP = A_{tot}$$

$$AMP = \frac{ADP^2}{ATP} \qquad \gamma = \frac{v_\gamma R_{GPDH}}{k_\gamma + R_{GPDH}}$$

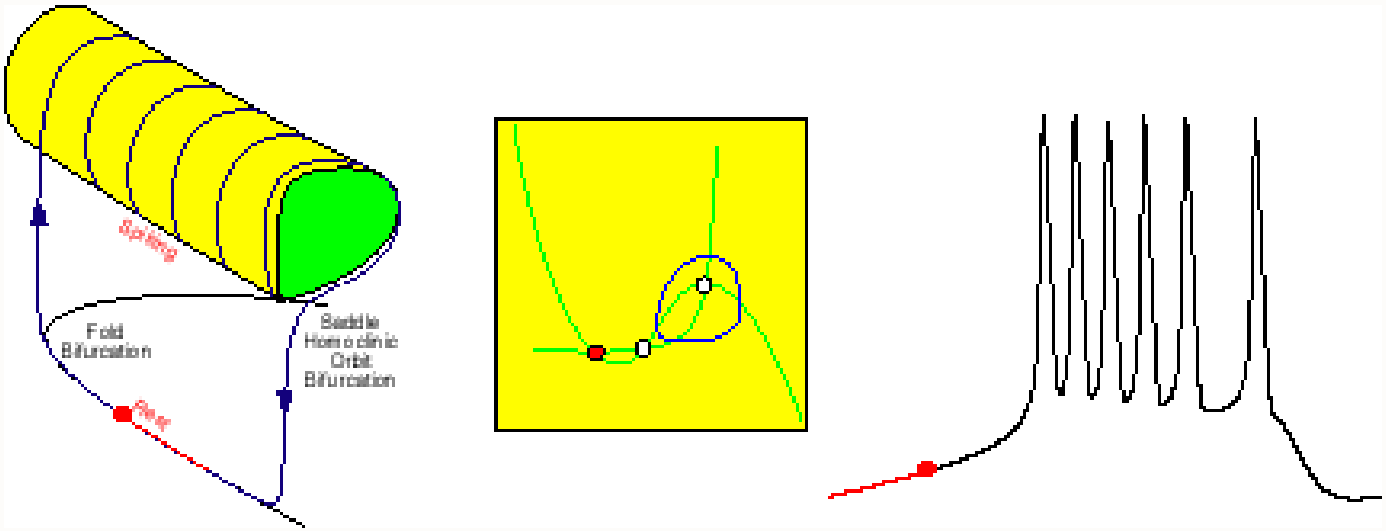
$$\frac{d\,ADP}{dt} = \left(ATP - ADP \exp\left[(r+\gamma)(1 - Ca / r_1)\right]\right) / \tau_a$$

$$\frac{d\,G6P}{dt} = \lambda (R_{GK} - R_{PFK})$$

$$\frac{d\,FBP}{dt} = \lambda \left(R_{PFK} - \frac{1}{2} R_{GPDH}\right)$$

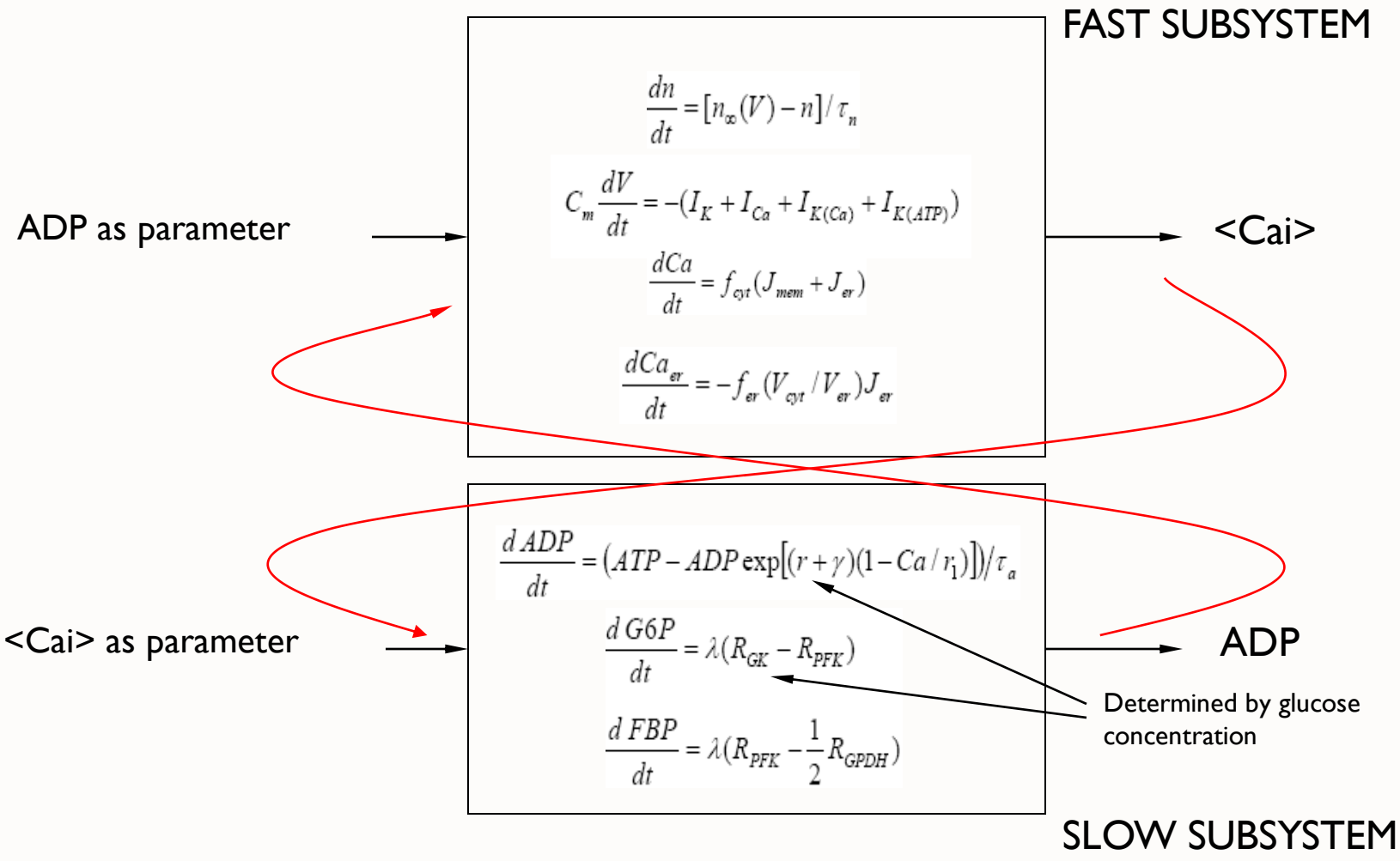
Classical bursting: Fold/homoclinic

- The beta-cell is a square-wave burster:



from Izhikevich (2006), Scholarpedia, 1(3):1300

A Multiscale Approach: the Electrical-Glycolysis partition

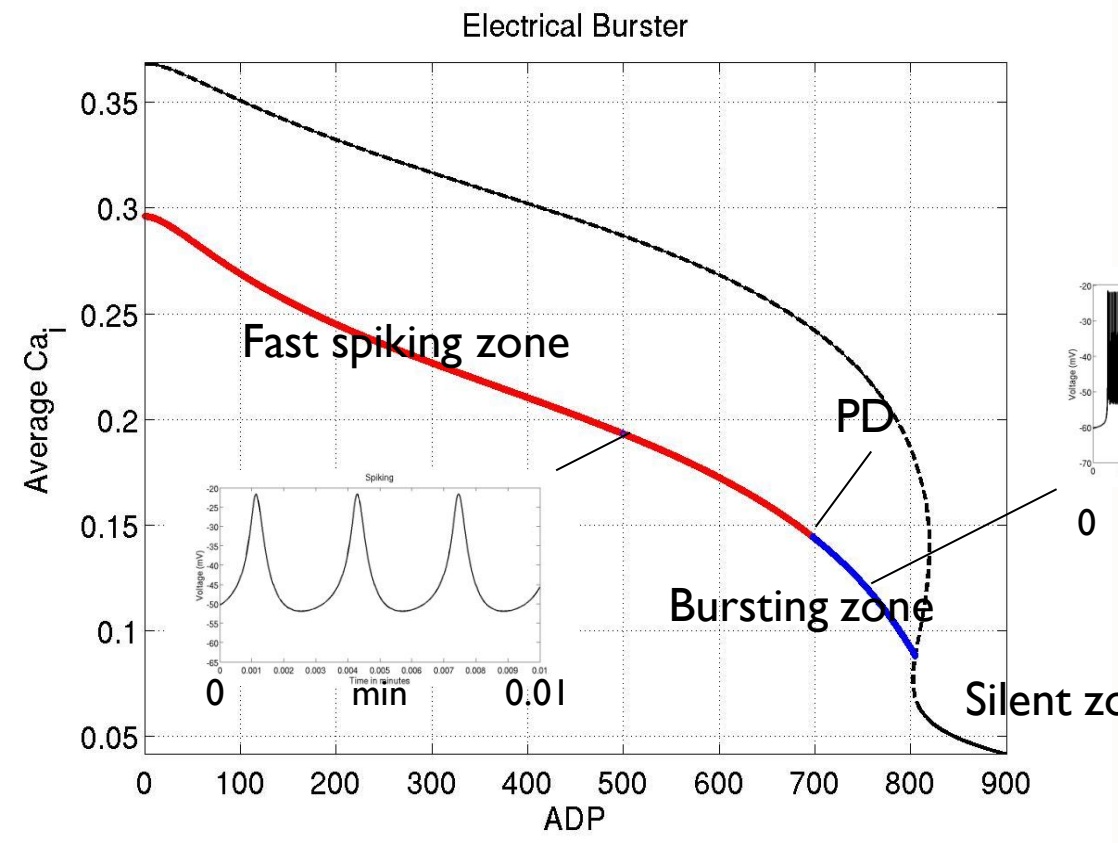


Electrical bursting: the Fast subsystem

- Invariant manifolds of the fast subsystem. ADP parameterizes the slow manifold of the full system:

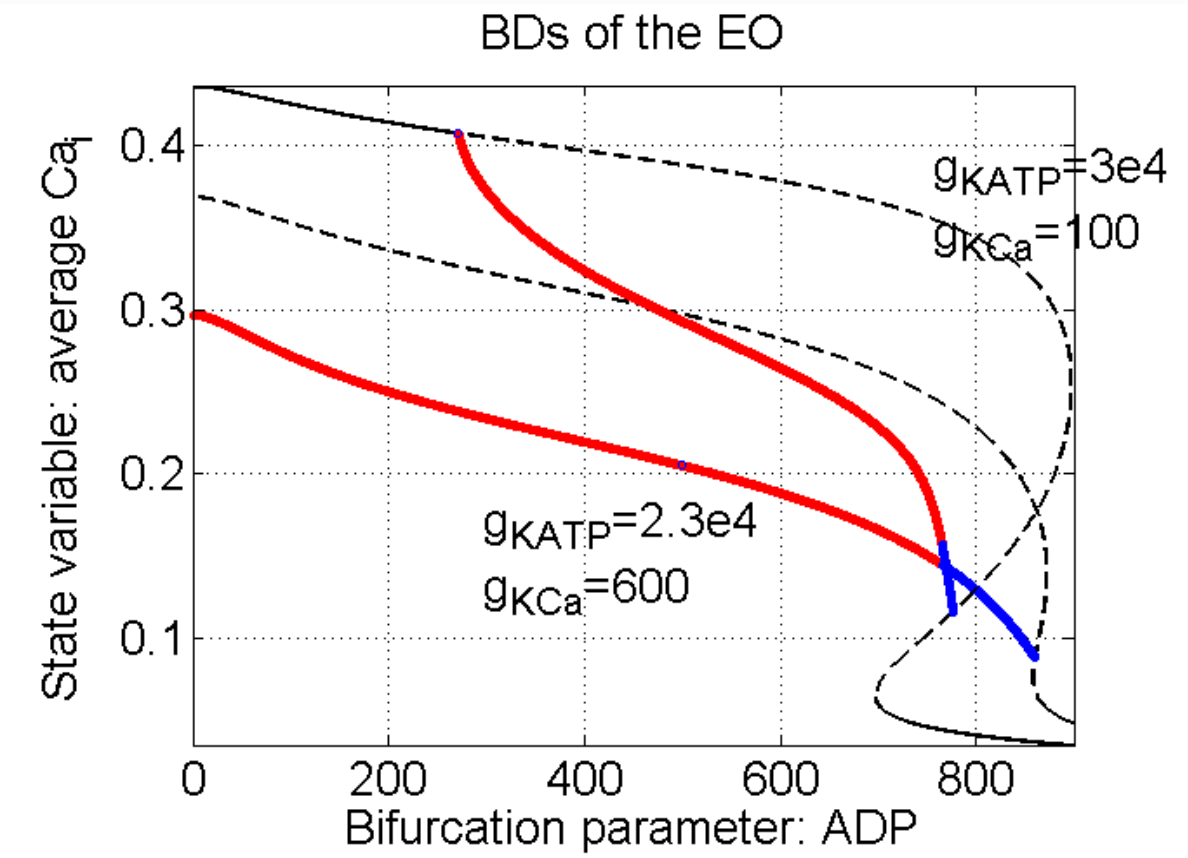
Fast system

V,n,CaER,Ca



The EO-BD

- Potassium channels influence the EO:

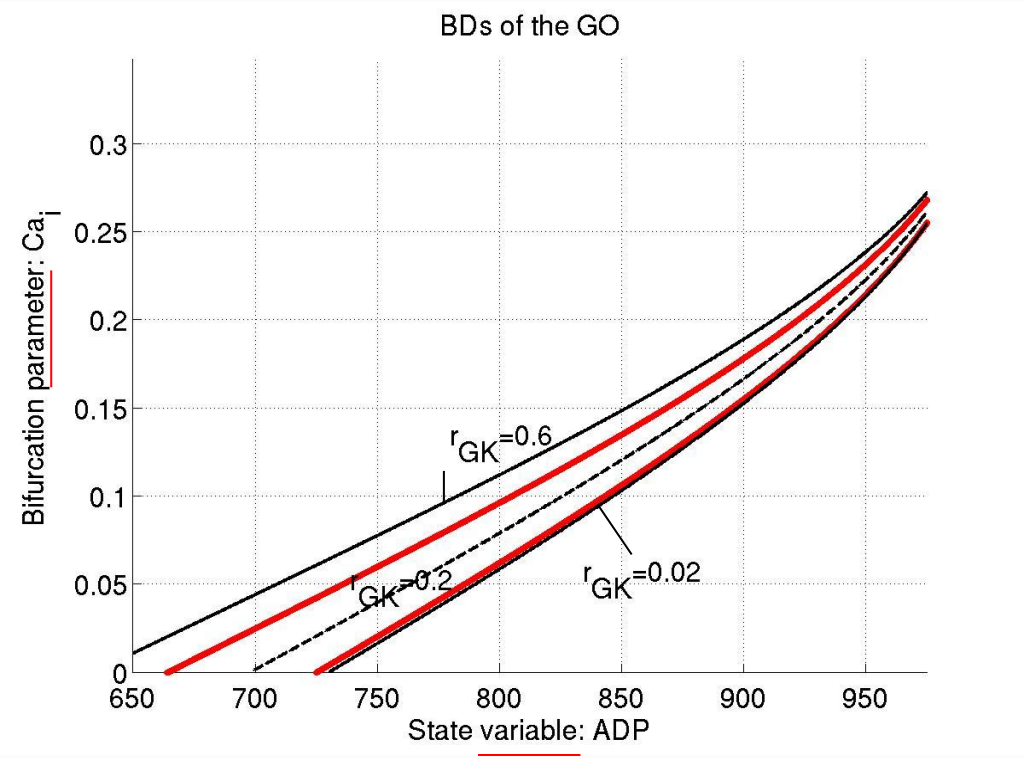


Glycolysis: the Slow subsystem

- Invariant manifolds of the slow subsystem. These are target manifolds in the full system. Parameterized by average Ca.

Slow system

FBP,G6P,ADP



Fast bursting in the DOM

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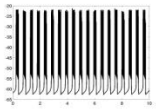

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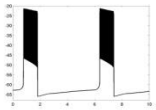

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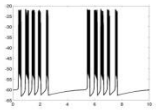
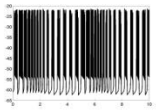


A



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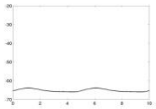
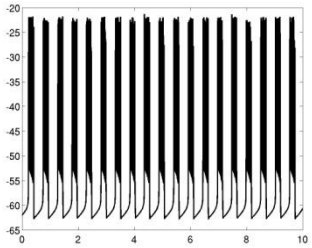
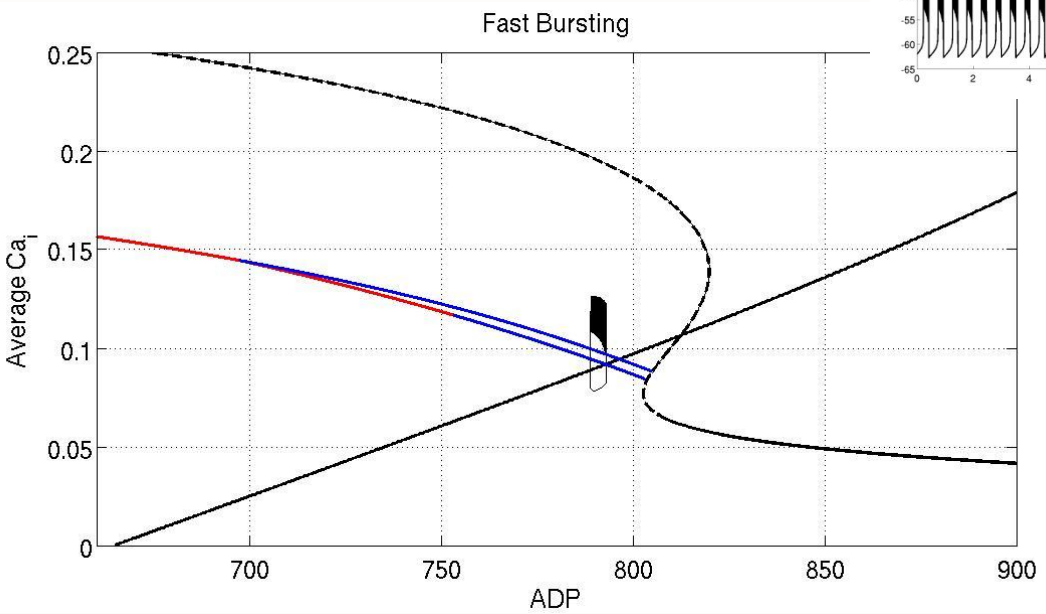


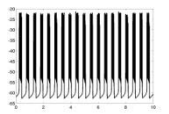




The Overlapped Bifurcation Diagrams (OBDs) predict the trajectory of the full system

Slow bursting

F



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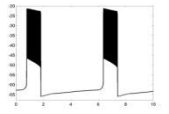

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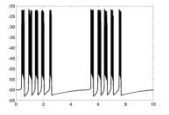

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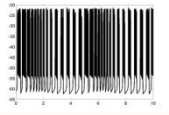

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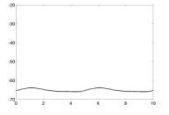
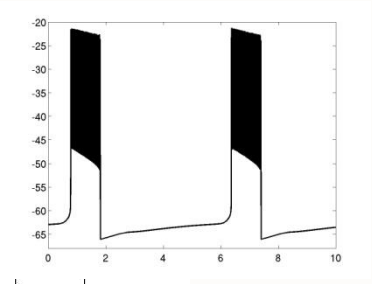
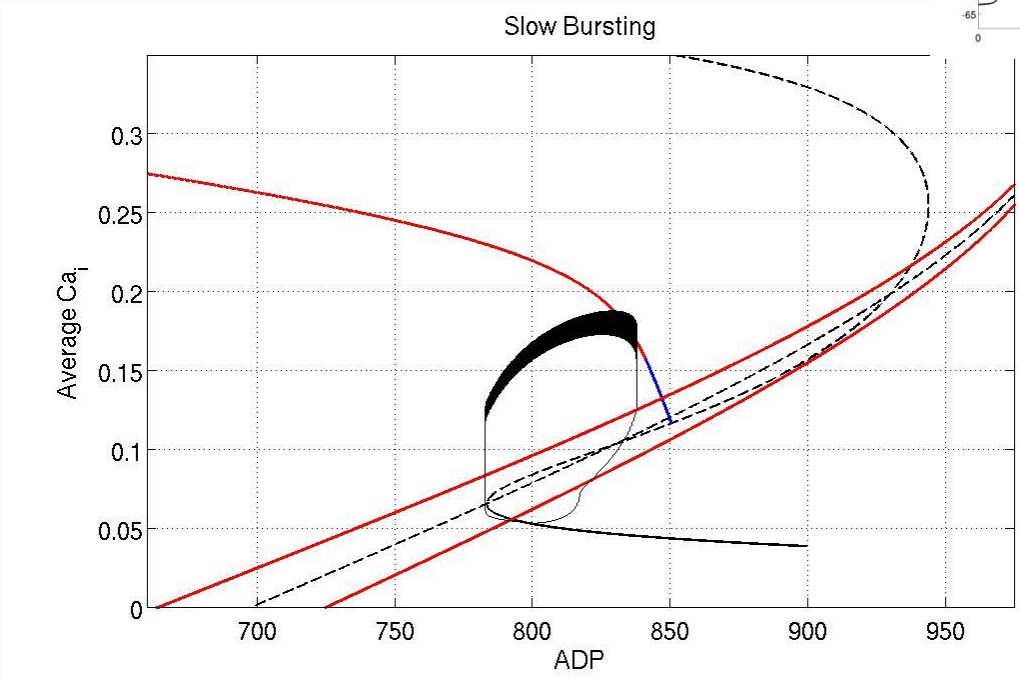
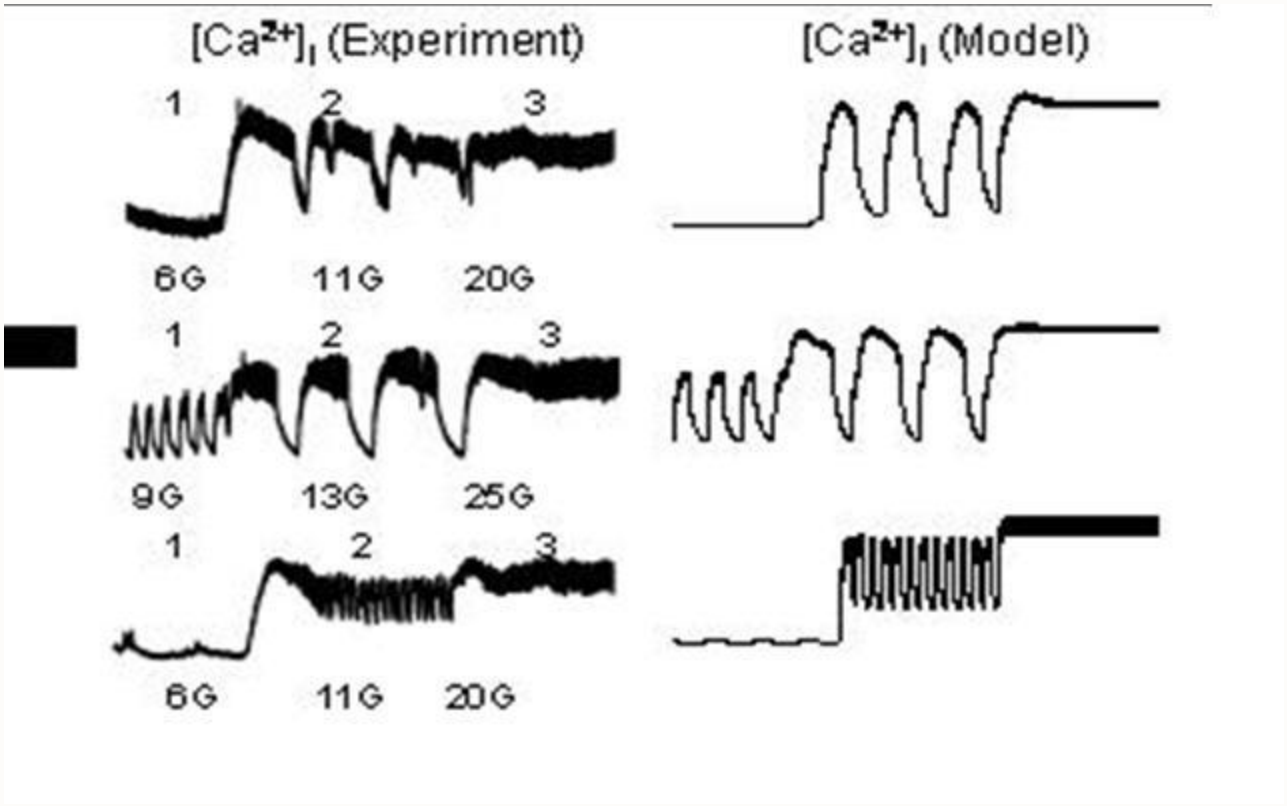






Glucose stimulated islet oscillations

- After Nunemaker et al., Biophys. J., 2006:



Implications for BAP

- Insulin pulsatility could be very important in islet transplants:
  - Pulsed insulin therapy
  - If pulsatility plays a functional role, that could relate to the long-term health of the transplanted tissue
- We understand glucose-stimulated insulin secretion
- We understand how islets can be pulsatile
- What about insulin pulsatility…in say, the graft?

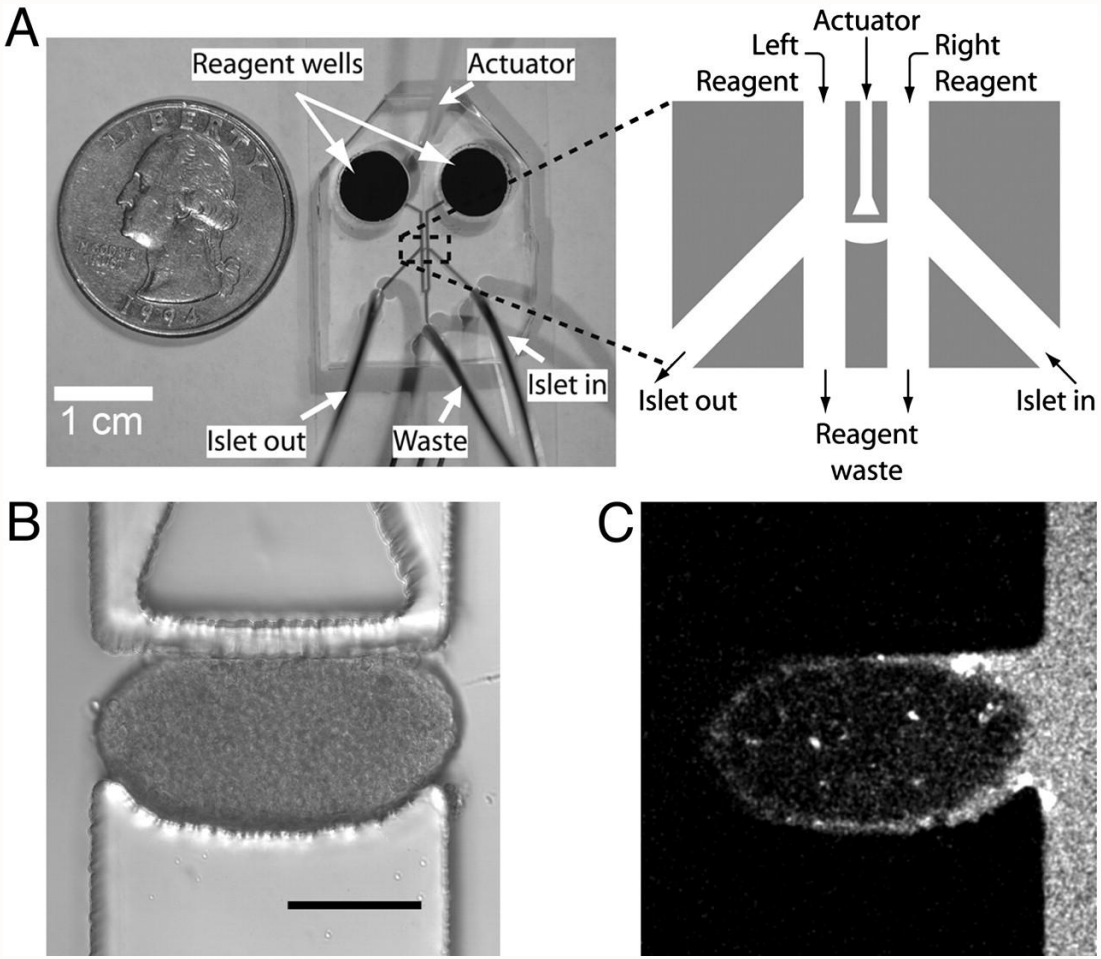
The coupling of beta-cells within islets

Amlan Barua and Pranay Goel, *Isles within islets: The lattice origin of small-world networks in pancreatic tissues*, Physica D, 315 (2016), 49-57.

Gap junctions in islets

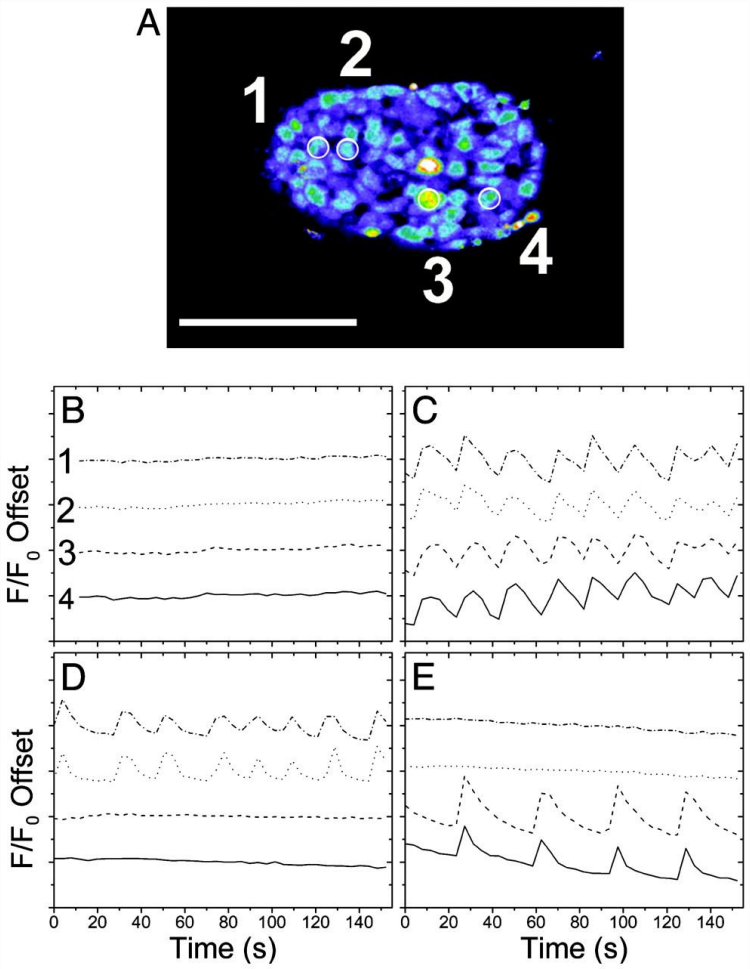
- Beta-cells are coupled by gap junctions of conductance about 100-300 pS - very strong!
- Traditional theory: strong gap junctions presumably synchronize beta-cells, so the islet secretion can be phasic.
- This has been challenged recently…

The Rocheleau experiment



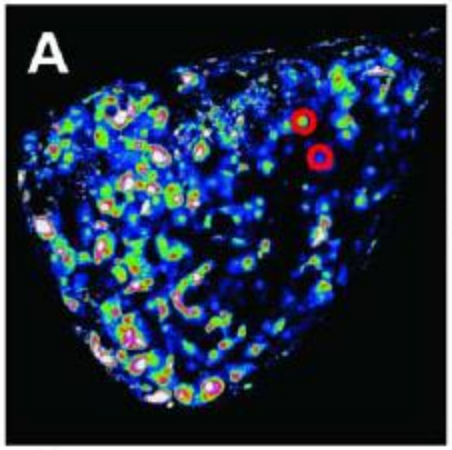
Microfluidic glucose stimulation reveals limited coordination of intracellular Ca^{2+} activity oscillations in pancreatic islets, Rocheleau J V et al. PNAS 2004;101:12899-12903

The Rocheleau experiment

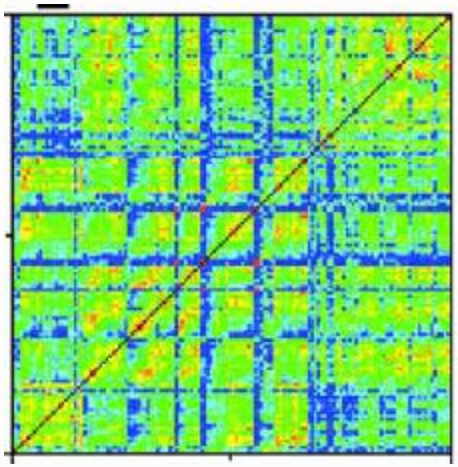


Microfluidic glucose stimulation reveals limited coordination of intracellular Ca^{2+} activity oscillations in pancreatic islets, Rocheleau J V et al. PNAS 2004;101:12899-12903

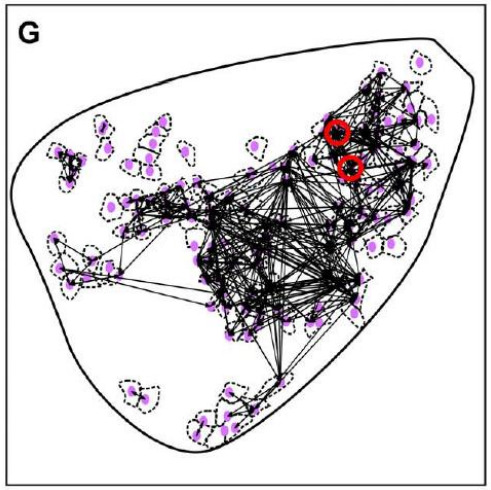
Stozer et al., 2013



Intensity of fluorescence signal



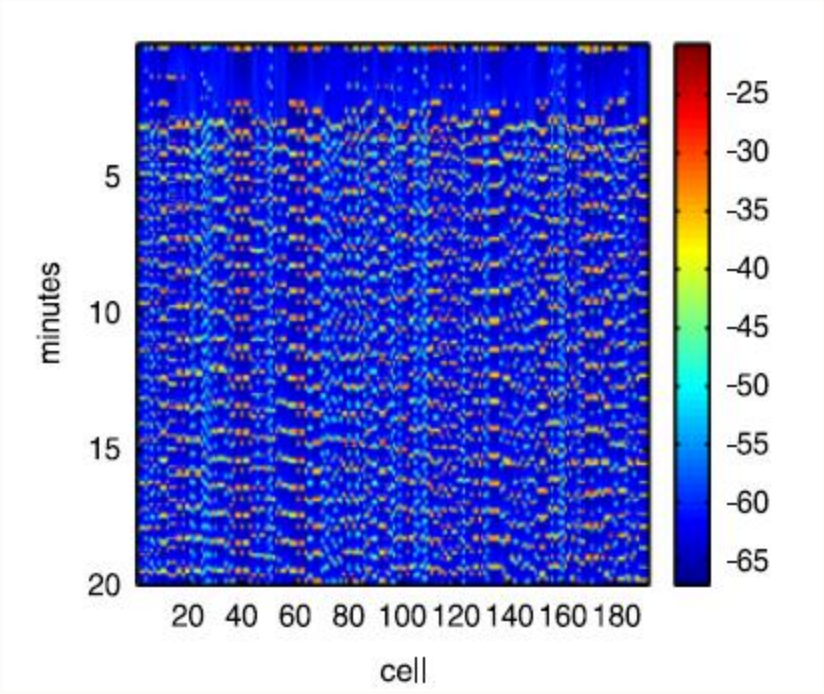
Correlation matrix of pairwise correlation



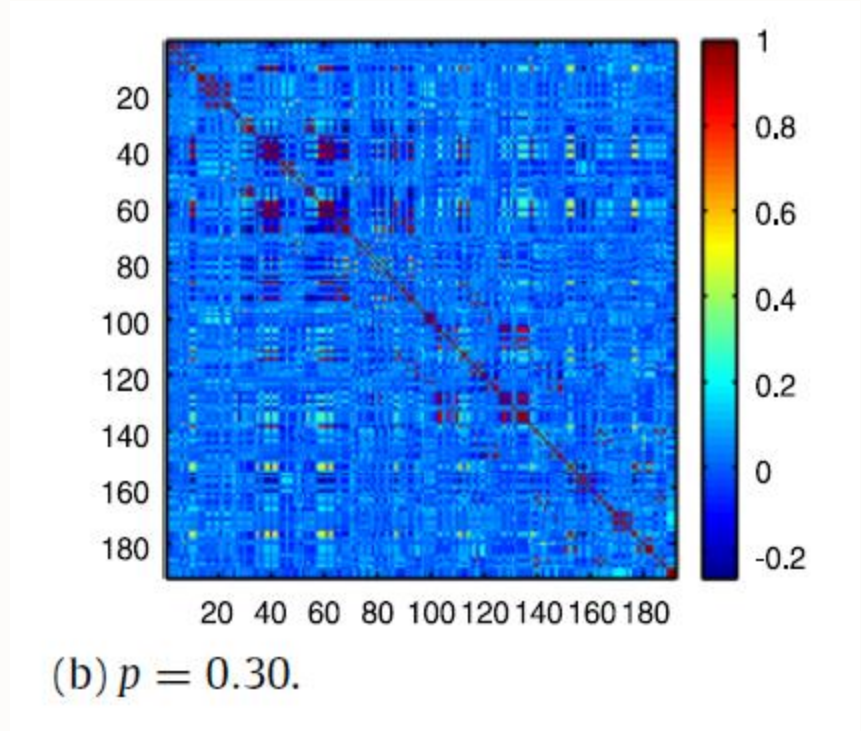
Connectivity map

Stožer A, Gosak M, Dolenšek J, Perc M, Marhl M, et al. (2013) Functional Connectivity in Islets of Langerhans from Mouse Pancreas Tissue Slices. PLoS Comput Biol 9(2): e1002923. doi:10.1371/journal.pcbi.1002923

An 8x8x3 islet with partial gap junction connectivity



Raster plot of the membrane potential



The connectivity matrix

Small world-ness in islets?

A comparison of clustering coefficient (C_{avg}) and global efficiency of the functional network (E_{glob}) against a random network (C_{rand} and E_{rand})

p	C_{avg}	C_{rand}	$\frac{C_{avg}}{C_{rand}}$	E_{glob}	E_{rand}	$\frac{E_{rand}}{E_{glob}}$	S
0.40	0.84	0.47	1.79	0.49	0.73	1.49	1.20
0.35	0.78	0.25	3.12	0.28	0.61	2.18	1.43
0.30	0.72	0.11	6.55	0.11	0.50	4.55	1.44
0.25	0.62	0.05	12.4	0.05	0.4	8.0	1.55
Stozer:	0.67		5.59	0.29		1.41	3.96

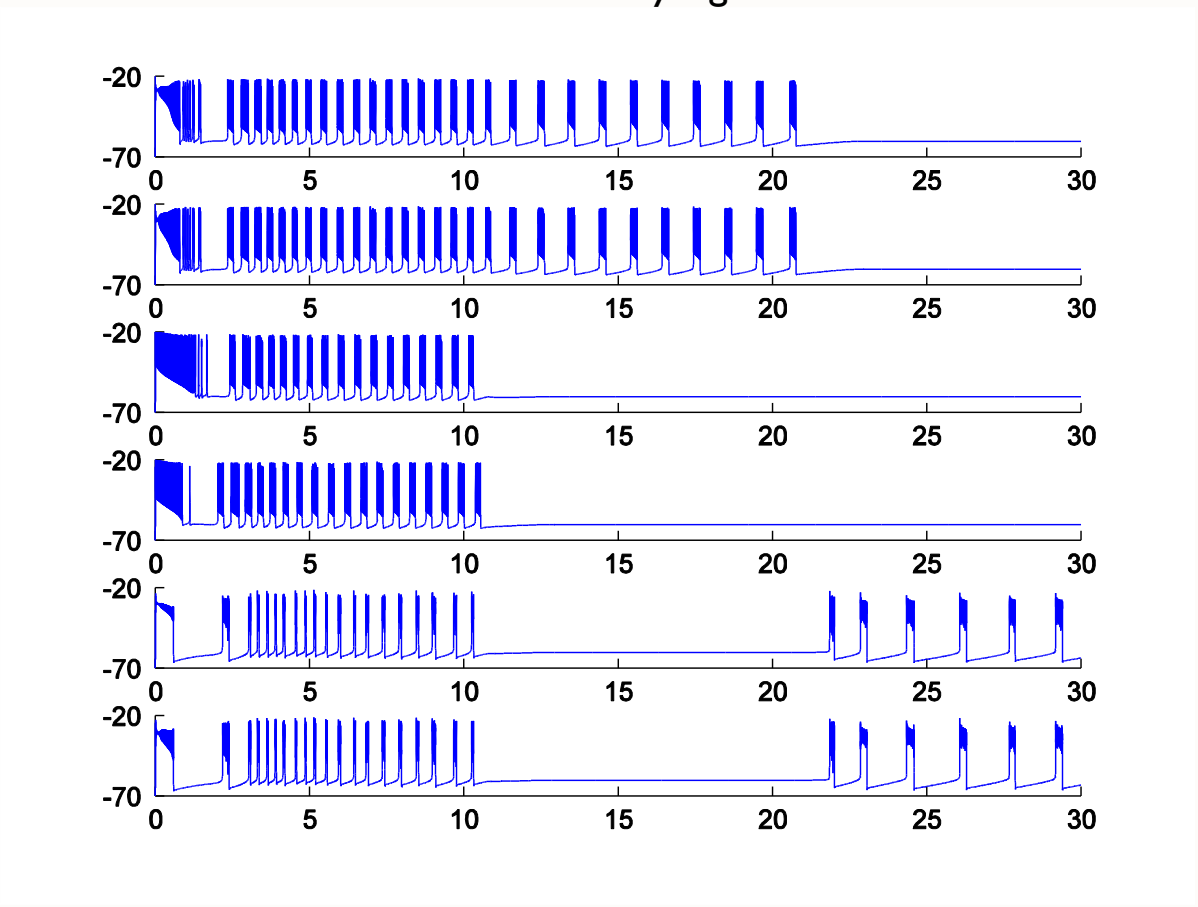
$S = (C_{avg}/C_{rand})/(E_{rand}/E_{glob})$

For small-world: $C_{avg}/C_{rand} > 1$ and $E_{rand} \sim E_{glob}$ so that $S > 1$.

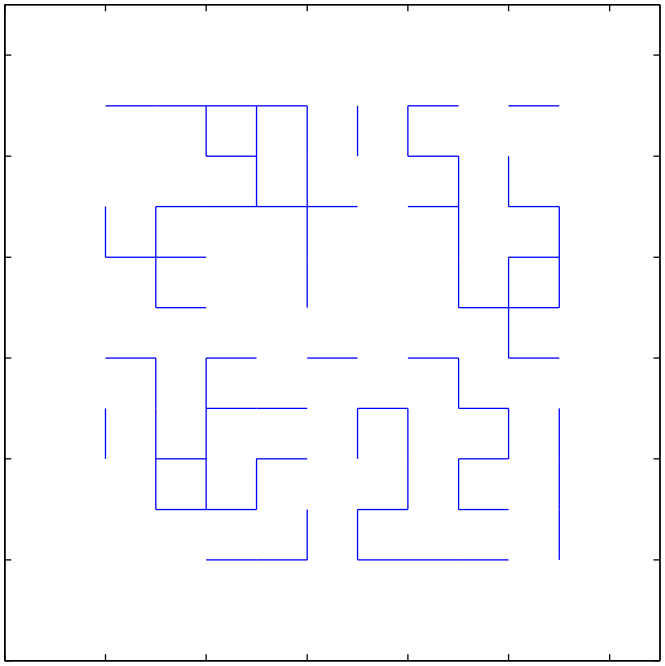
agrees with Stozer et al.

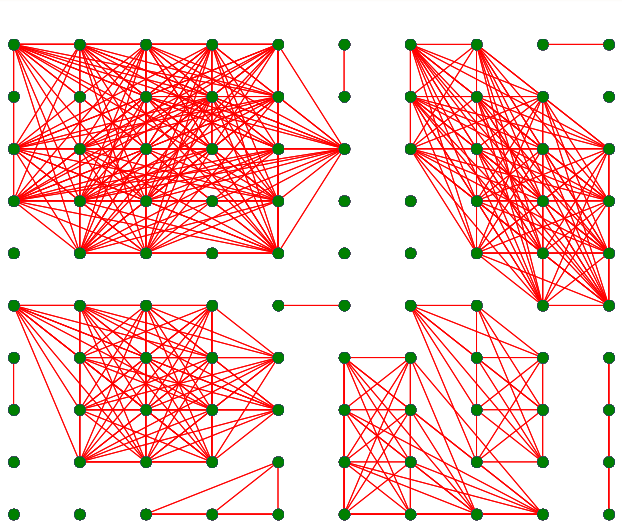
The Rocheleau protocol

- 8x8x8 islet: Subjected to uniformly high glucose for first 10 minutes, for next 10 minutes only left face was excited and for last 10 minutes only right face was excited.



Explanation: Gap junctional connection and its functional network in a 2D slice (with p = 0.45)





Summary idea: Implications for BAP

- Insulin pulsatility is probably not due to intrinsic synchronization
- It is more likely to be **due to glucose entrainment…**

Theme

Theoretical models of diabetogenesis

Pranay Goel, *Insulin resistance or hypersecretion? The βIG picture revisited* Journal of Theoretical Biology, 2015

the Topp model

2.1 The Topp model

The original Topp model is:

$$\frac{dI}{dt} = \sigma \frac{G^2}{\alpha + G^2} \beta - kI \tag{1}$$

$$\frac{dG}{dt} = R - (E + S_I I)G \tag{2}$$

$$\frac{d\beta}{dt} = (-d_0 + r_1 G - r_2 G^2)\, \beta, \tag{3}$$

with parameters as in [15].

[15] B. Topp, K. Promislow, G. deVries, R. M. Miura, and D. T. Finegood. A model of beta-cell mass, insulin, and glucose kinetics: pathways to diabetes. *J. Theor. Biol.*, 206(4):605–619, Oct 2000.

the Topp model: geometry

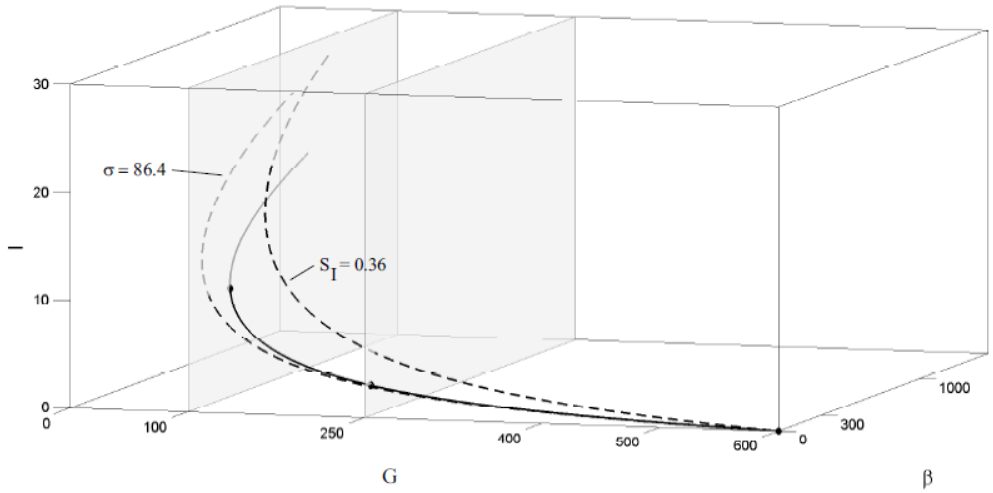
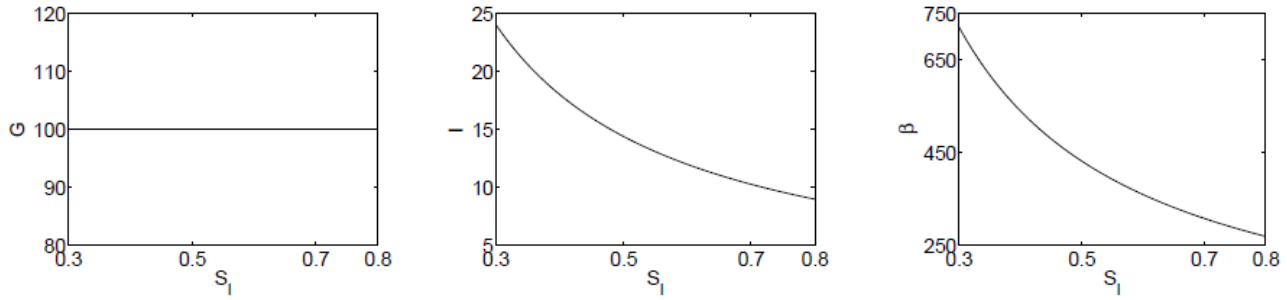


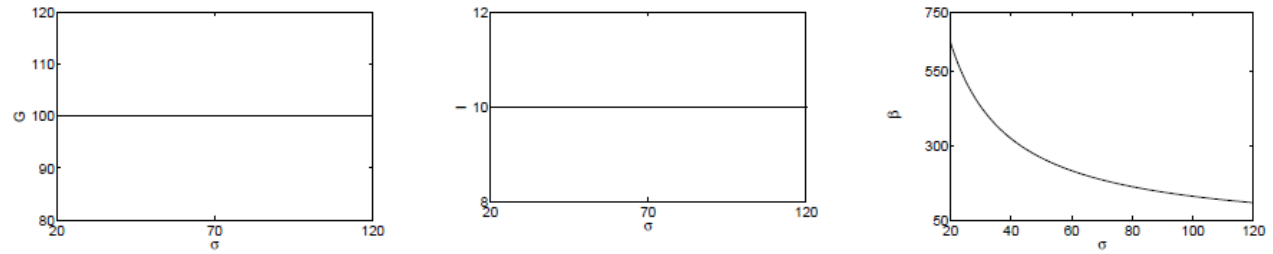
Figure 1: The geometry of the Topp model. The slow manifold of the original system is shown as a curve in $\beta - I - G$ phase space. Fixed points of the model are also shown, in black circles. The healthy, stable glucose state is at $G^* = 100$. The fixed points are alternately stable, unstable and stable, corresponding to $G^* = 250$ and $G^* = 600$ (pathological). The slow manifold for a lower insulin sensitivity, $S_I = 0.36$, is shifted upward towards a higher β and I (black curve). The slow manifold with secretion, σ, twice the basal value, 86.4, is pushed out towards lower β.

the Topp model: behavior



(a) G^* (b) I^* (c) β^*

Figure 2: S_I does not alter the G^* for the healthy steady state in the model, but it does change the corresponding I^* and β^*.



(a) G^* (b) I^* (c) β^*

Figure 3: σ does not alter the G^* and I^* for the healthy steady state in the model, but it does change the corresponding β^*.

the Topp-IR model

2.2 The Topp-IR model

The Topp model, modified to study dependence on the insulin resistance parameter, S_I, is:

$$\frac{dI}{dt} = \sigma \frac{G^2}{\alpha + G^2}\,\beta - kI \tag{4}$$

$$\frac{dG}{dt} = R - (E + S_I I)G \tag{5}$$

$$\frac{d\beta}{dt} = (-d_0 + r_1 G - r_2 G^2 - d_I I)\,\beta \tag{6}$$

The major difference relative to the Topp model is the inclusion of the I-dependent term in the β' equation. That is, we argue that just as glucose influences mass in the original Topp equations, so does insulin. We assume the simplest such interaction between insulin and mass: an increasingly available plasma insulin suppresses increases in mass.

The parameters that have been modified from the Topp model are $d_0 = 3.93 \times 10^{-2}$, $d_I = 1.82 \times 10^{-3}$ and $r_2 = 2.65 \times 10^{-6}$.

the Topp-IR model geometry

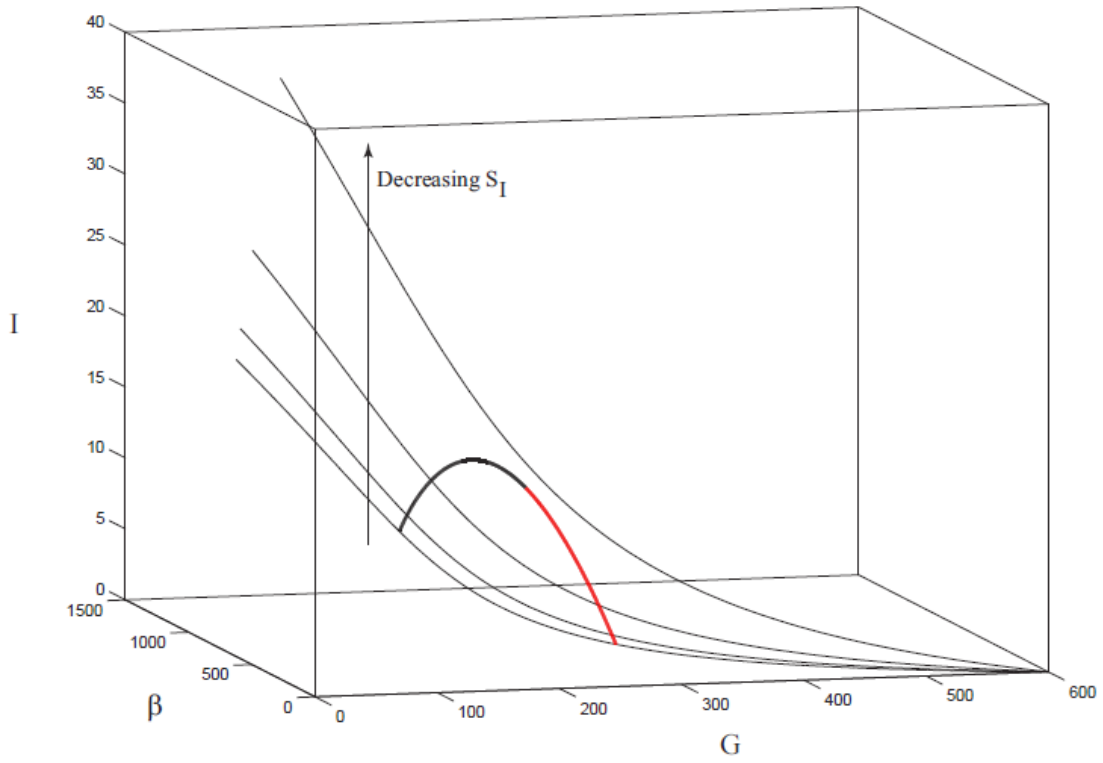


Figure 5: The geometry of the Topp-IR model. Decreasing insulin sensitivity, S_I, alters the fixed points. Several slow manifolds are shown, for S_I=0.72, 0.6, 0.4 and 0.2. The physiological (black curve) and unstable (red curve) fixed points coalesce in a fold bifurcation at $S_I = 0.23$ with $\beta = 203.5$, $I = 13.25$, $G = 193.2$.

the Topp-IR model features

- Insulin resistance increases resting glucose and insulin
- A natural explanation of IFG
- Transition by way of bifurcation = inevitability
- Slow passage close to the bifurcation explains why people can stay in IFG for a long time

The Topp-HS model

2.3 The Topp-HS model

The Topp-HS model extends the Topp-IR model further. It considers that insulin sensitivity changes in reponse to secretory capacity, $S_I \equiv S_I(\sigma)$:

$$\frac{dI}{dt} = \sigma \frac{G^2}{\alpha + G^2} \beta - kI \tag{7}$$

$$\frac{dG}{dt} = R - (E + S_I(\sigma)\, I)G \tag{8}$$

$$\frac{d\beta}{dt} = (-d_0 + r_1 G - r_2 G^2 - d_I I)\, \beta, \tag{9}$$

where $S_I(\sigma) = -8.33 \times 10^{-3}\, \sigma + 1.079$, while the other parameters are as in the Topp-IR model above.

Topp-HS model geometry

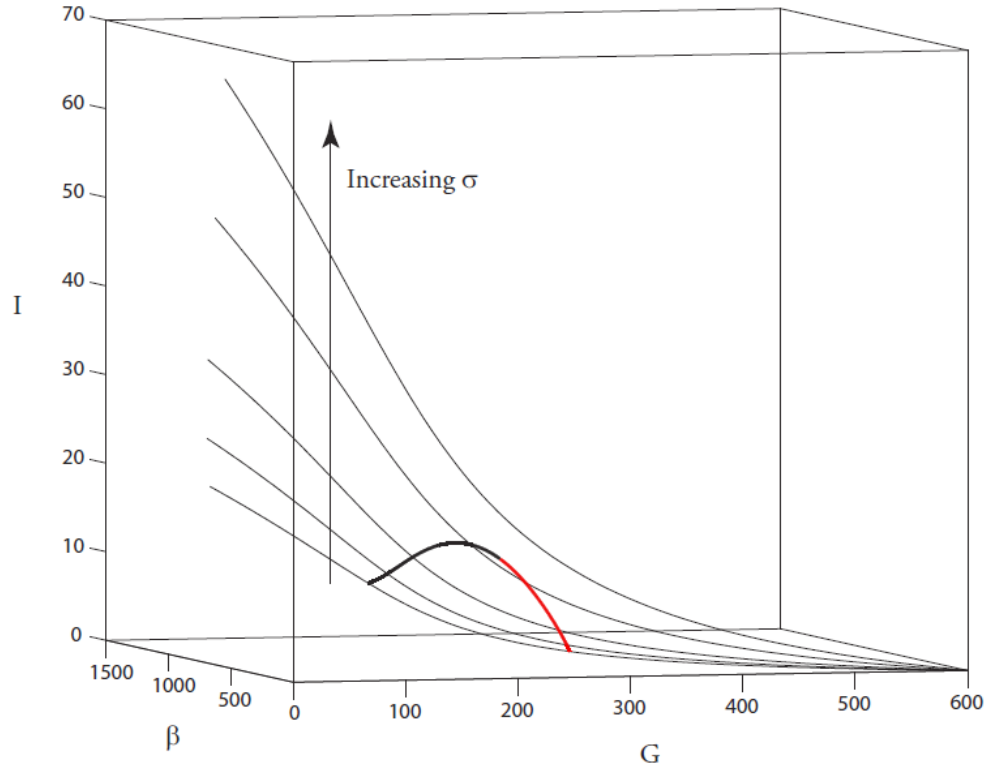


Figure 6: The geometry of the Topp-HS model. The secretion parameter, σ, alters the fixed points structure of the model. Slow manifolds are plotted for σ=43.2, 60, 80, 100 and 110. The physiological (black curve) and unstable (red curve) fixed points coalesce in a fold bifurcation at $\sigma = 102.1$ with $\beta = 86.1$, $I = 13.25$, $G = 193.2$.

Topp-HS model features

- A mathematical model of the hypersecretion theory
- A key assumption: Elevations in peak insulin drives insulin resistance
- Hyperinsulinemia is a *consequence*. Corrects the hypersecretion theory thus:

to resistance. The casual sequence of events is not *hypersecretion* → *hyperinsulinemia* → *insulin resistance*, but *hypersecretion* → *transient hyperinsulinemia* → *insulin resistance* → *persistent hyperinsulinemia* instead. That is, insulin resistance develops in response to transient, not sustained hyperinsulinemia.

Implications for BAP

- The models of insulin control in (type 1) diabetes are essentially G-I models
- Long term G-I dynamics is influenced by mass changes, among other things. We therefore need good G-I+Mass models
- It will be interesting to ask how to adapt *βIG* models to islet transplant scenarios

Thank you