Metabolic and Electrical Oscillations: Partners in Controlling Rhythmic Islet Activity

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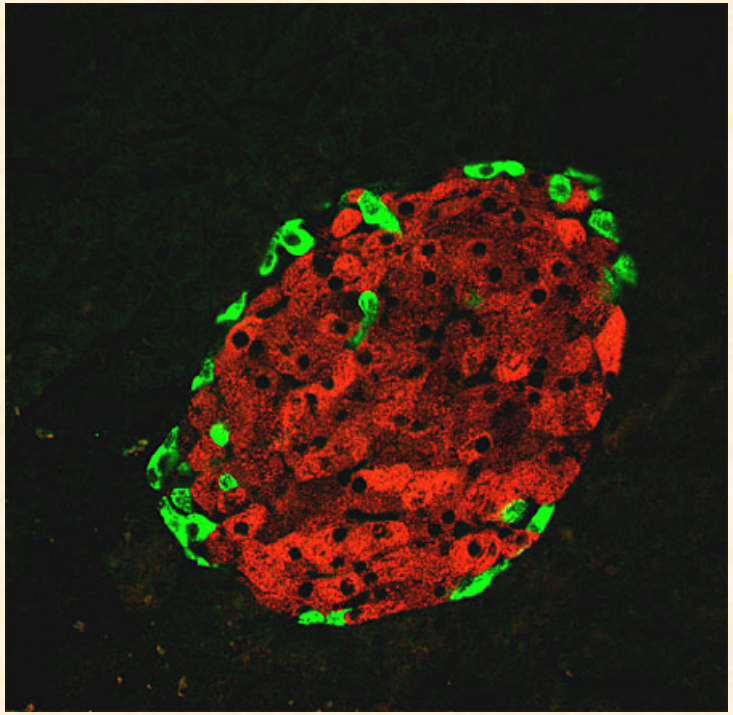
National Science Foundation, Division of Mathematical Sciences

What is an Islet?

Cluster of hormone-secreting cells. These clusters are located in the pancreas.

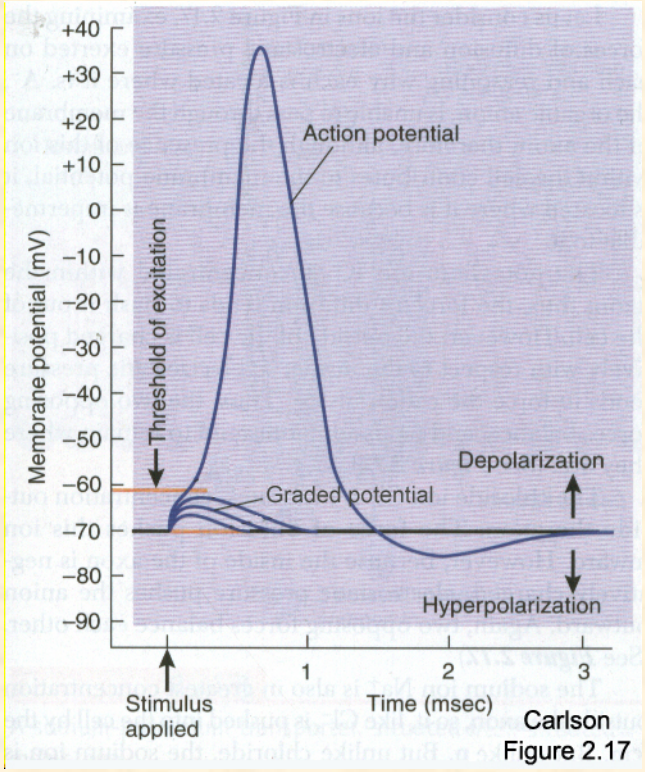


Courtesy of Rohit Kulkarni

Immunostained for glucagon (green) and insulin (red)

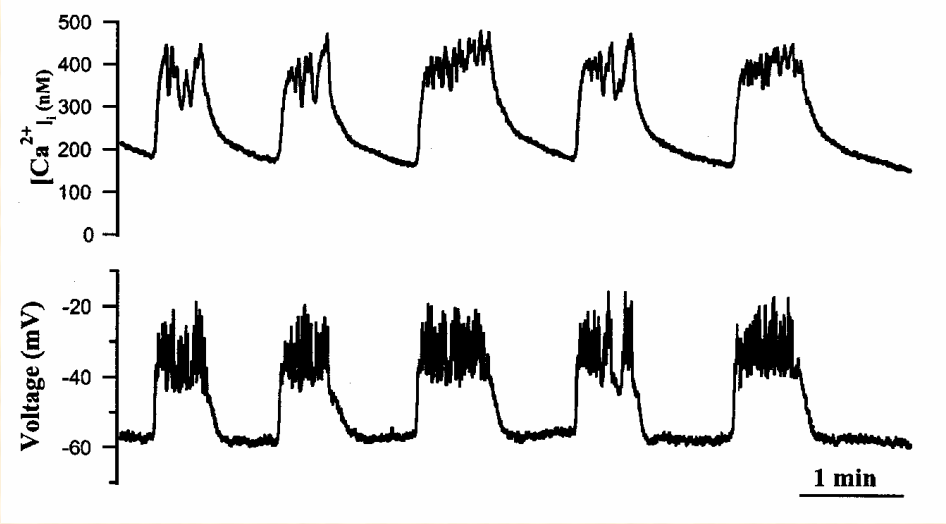
Islets are Electrically Excitable

Islets are like nerve cells in that they produce electrical impulses. During an upstroke of an impulse Ca^{2+} enters the cells, causing insulin to be released.



Islets Have Characteristic Patterns of Electrical Activity

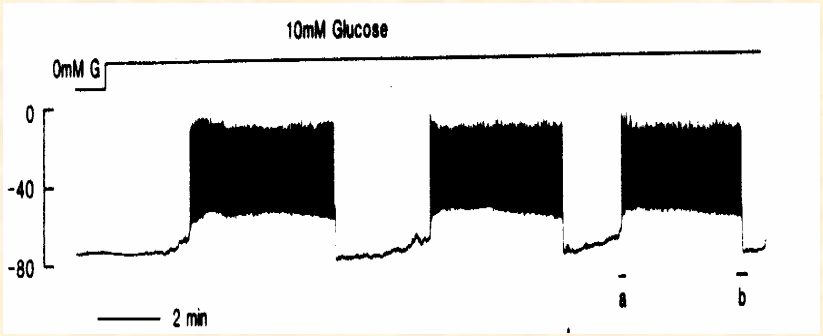
Fast Bursting Oscillations



Simultaneous fast Ca^{2+} and voltage measurements from a mouse islet in 11.1 mM glucose. From Zhang et al., *Biophys. J.*, 84:2852, 2003

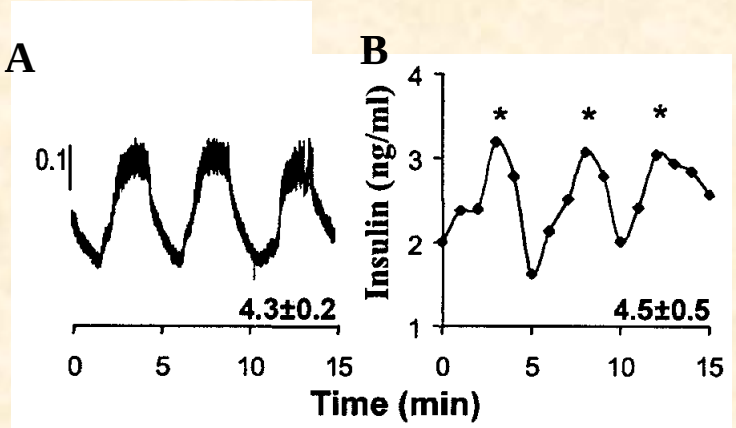
Slow Bursting Oscillations

Slow oscillations of Ca^{2+} and voltage from an islet...



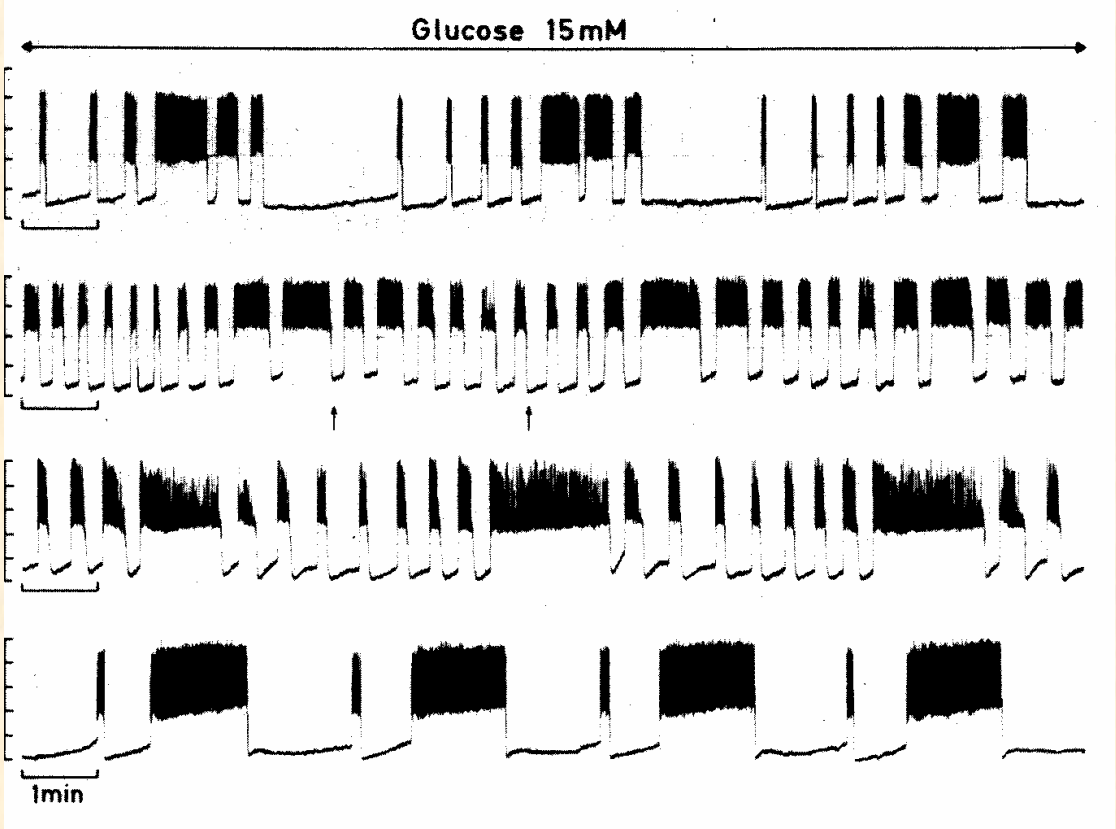
Smith et al., *FEBS Lett*., 261-187, 1990

Zhang et al., *Biophys. J*., 84:2852, 2003



…have period similar to slow insulin oscillations measured from a mouse in vivo (Nunemaker et al., Diabetes, 54:3517, 2005)

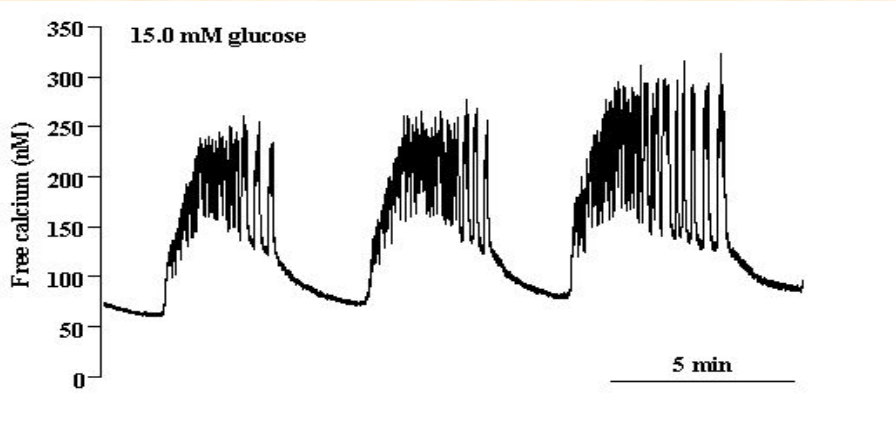
Compound Bursting Oscillations



Henquin et al., Eur. *J. Physiol*., 393:322, 1982

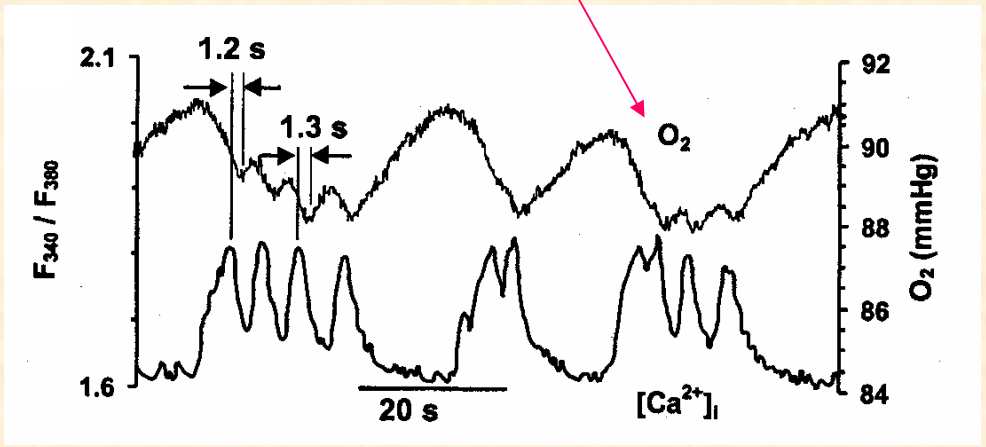
Bursting oscillations superimposed on a slow wave of activity

More Evidence of Compound Oscillations



Compound Ca^{2+} oscillations (Zhang et al., *Biophys. J.*, 84:2852, 2003)

Compound O_2 oscillations (Kennedy et al., *Diabetes*, 51:S152, 2002)



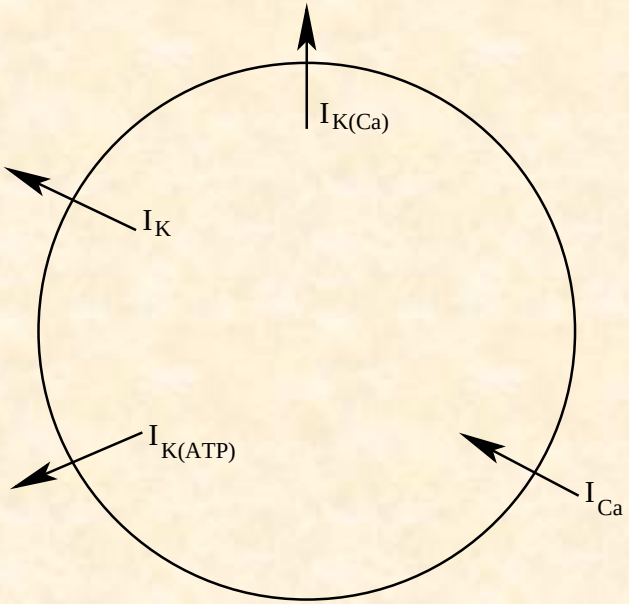
Goal: Develop a Mathematical Model That Can Reproduce the Various Patterns of Activity

The Dual Oscillator Model

Central Hypothesis

Fast, slow, and compound oscillations can all be produced by a mechanism that includes Ca^{2+} feedback onto ion channels (for the fast component of the oscillation) and glycolytic oscillations (for the slow component). This mechanism is the basis for our recent **Dual Oscillator Model** (DOM) for β-cell activity.

Electrical Component of the DOM



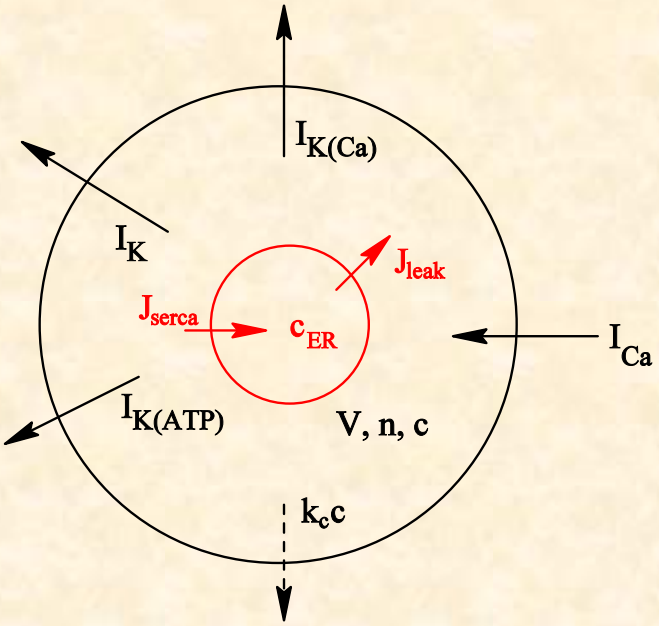
$$\dot{V} = -(I_{Ca} + I_K + I_{K(Ca)} + I_{K(ATP)})/C_m$$

$$\dot{n} = (n_\infty(V) - n)/\tau_n$$

Voltage equation reflects Kirchoff's current law

Second equation describes dynamics of the K^+ activation variable *n*. This depends on the voltage.

Electrical/Calcium Components of the DOM



$$\dot{V} = -(I_{Ca} + I_K + I_{K(Ca)} + I_{K(ATP)})/C_m$$

$$\dot{n} = (n_\infty(V) - n)/\tau_n$$

$$\dot{c} = f(J_{leak} - J_{serca} - \alpha I_{Ca} - k_c c)$$

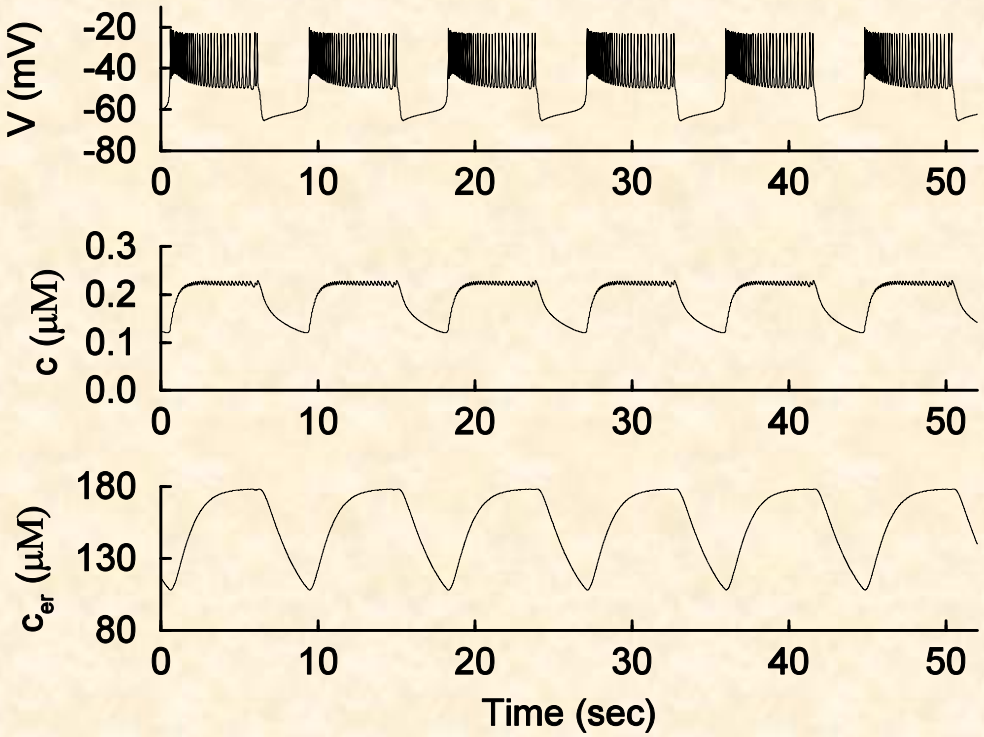
$$\dot{c}_{ER} = f_{ER}(V_{cyt}/V_{ER})(J_{serca} - J_{leak})$$

ER is the Endoplasmic Reticulum

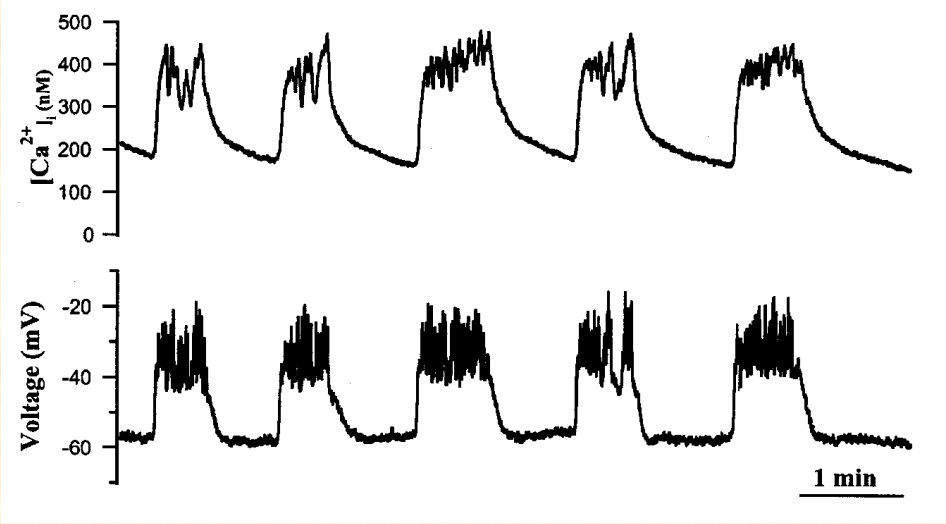
Ca^{2+} enters the cell through L-type Ca^{2+} channels. The free cytosolic Ca^{2+} activates K(Ca) channels. Thus, there is mutual feedback between the electrical and Ca^{2+} components.

Fast Oscillations with the DOM

When glycolysis is non-oscillatory, the DOM produces fast bursting oscillations, due to the electrical/calcium components of the model.

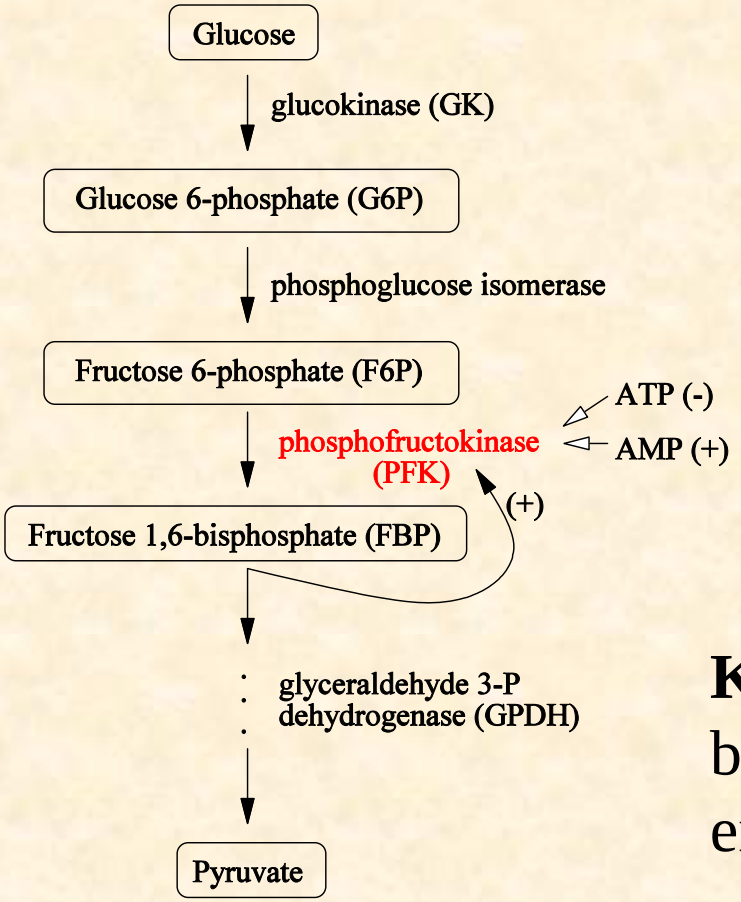


Fast Oscillations in Islets



Simultaneous fast Ca^{2+} and voltage measurements from a mouse islet in 11.1 mM glucose. From Zhang et al., *Biophys. J.*, 84:2852, 2003

Glycolytic Component of the DOM



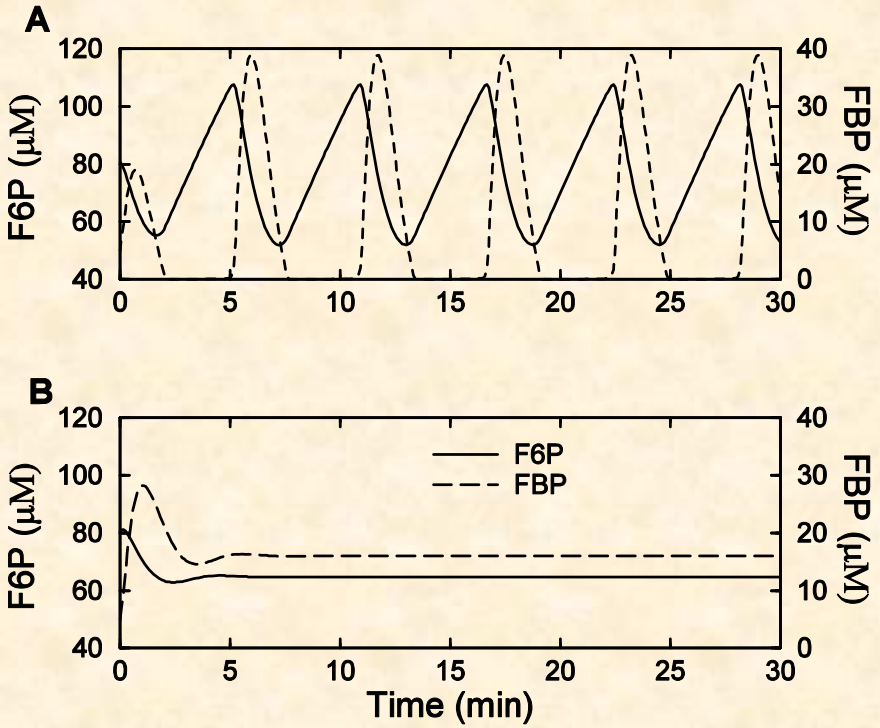
$$\frac{d\,F6P}{d\,t} = \lambda(J_{GK} - J_{PFK})$$

$$\frac{d\,FBP}{dt} = J_{PFK} - 0.5J_{GPDH}$$

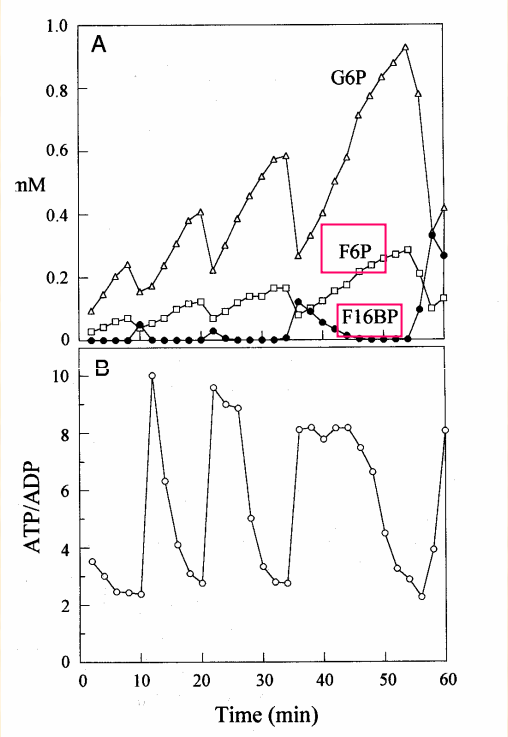
Key feature: The product FBP feeds back positively onto the allosteric enzyme PFK.

Glycolytic Oscillations Produced if Glucokinase Rate is in the Right Range

Solid-F6P, Dashed-FBP



(A) Intermediate J_{GK}
(B) High J_{GK}

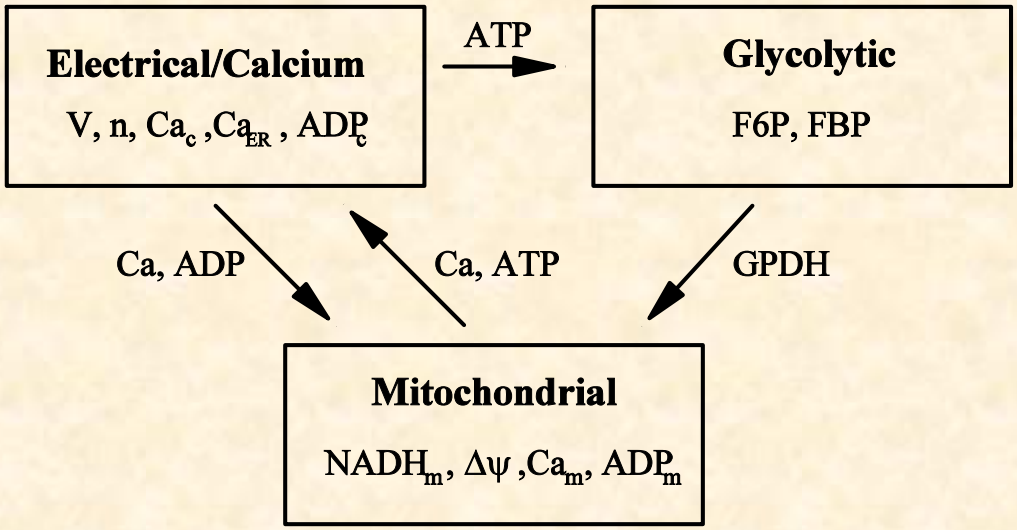


Glycolytic oscillations in muscle extracts (Tornheim, *Diabetes*, 46:1375, 1997)

Mitochondrial Component

Includes equations for mitochondrial NADH concentration, inner membrane potential, Ca^{2+} concentration, and ADP/ATP concentrations.

Final 3-compartment model:

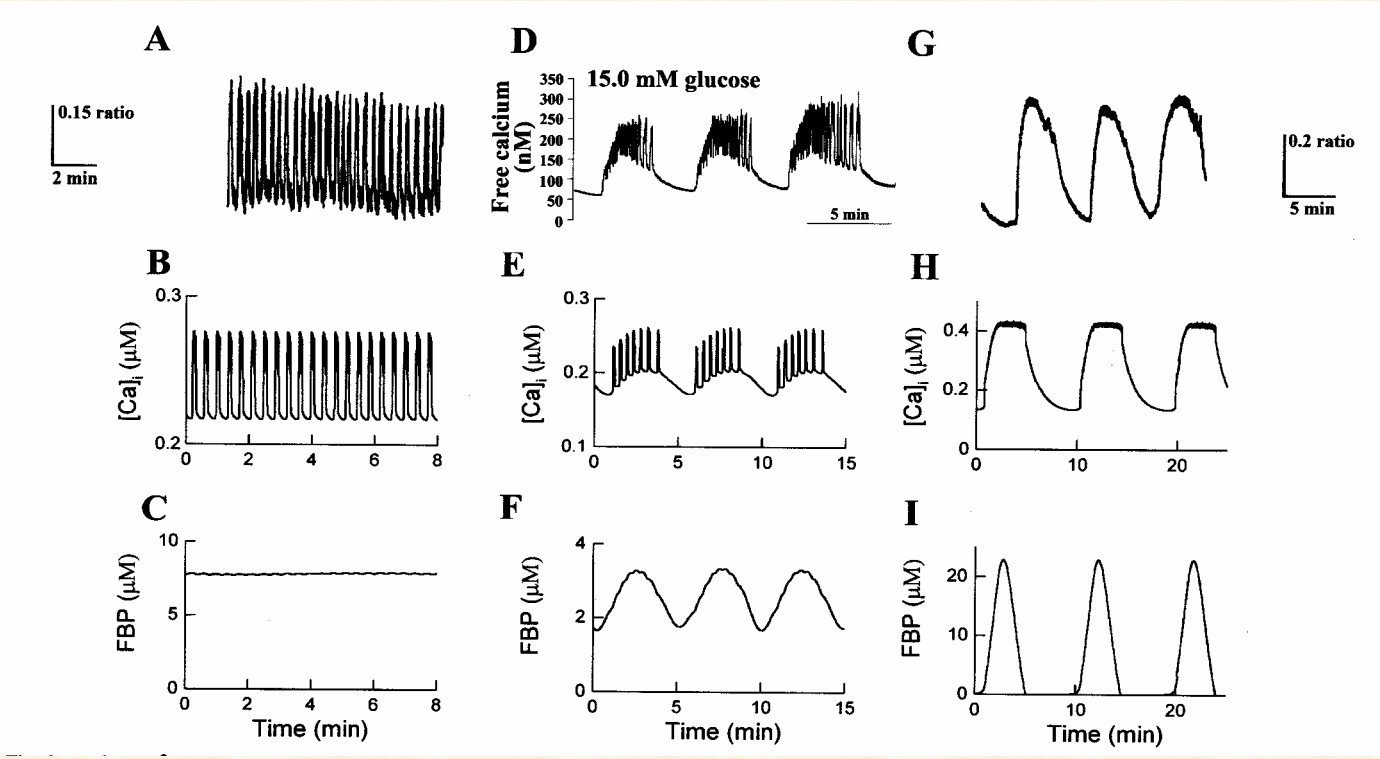


The Three Types of Activity Can Be Reproduced by the Model

No glycolytic oscillations

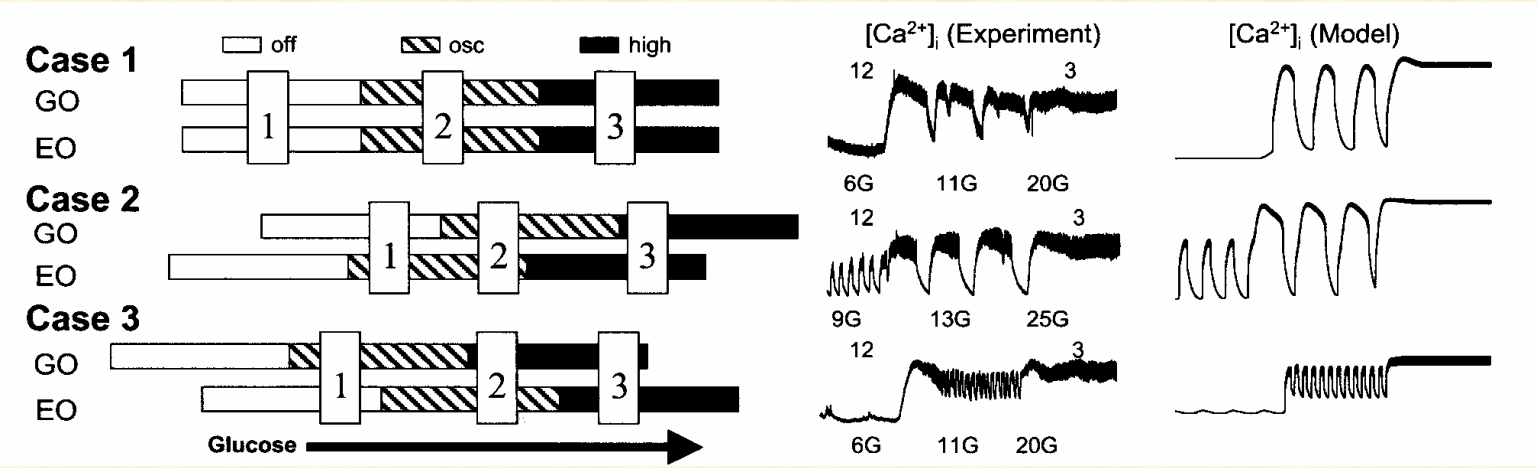
With glycolytic oscillations

With glycolytic oscillations



Bertram et al., *Am. J. Physiol.*, 293:E890, 2007

Glucose Response Can Be Explained with a Sliding Bar Diagram

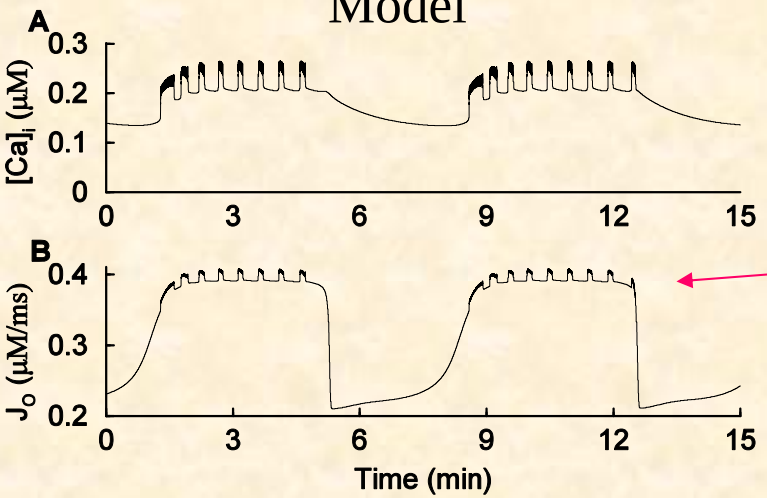


Bertram et al., *Am. J. Physiol.*, 293:E890, 2007

Model reproduces the islet response to changes in the glucose level, the primary hormone affecting islets.

DOM Reproduces the Slow Rhythm and "Teeth" in O_2 Consumption

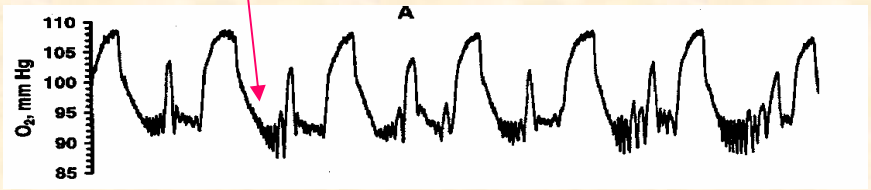
Model



Teeth in oxygen consumption

Teeth in oxygen concentration

O_2 measured
with O_2 electrode

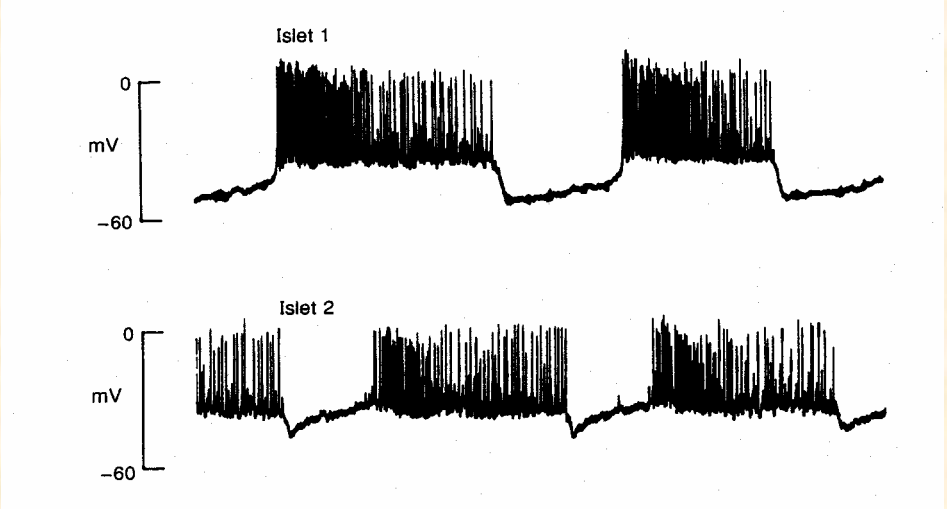


Jung et al., *BBRC*, 259:331, 1999

In Vivo Bursting Found To Be Asynchronous

***In vivo* synchronous membrane potential oscillations in mouse pancreatic β-cells: lack of co-ordination between islets**

M. Valdeolmillos, A. Gomis and J. V. Sánchez-Andrés

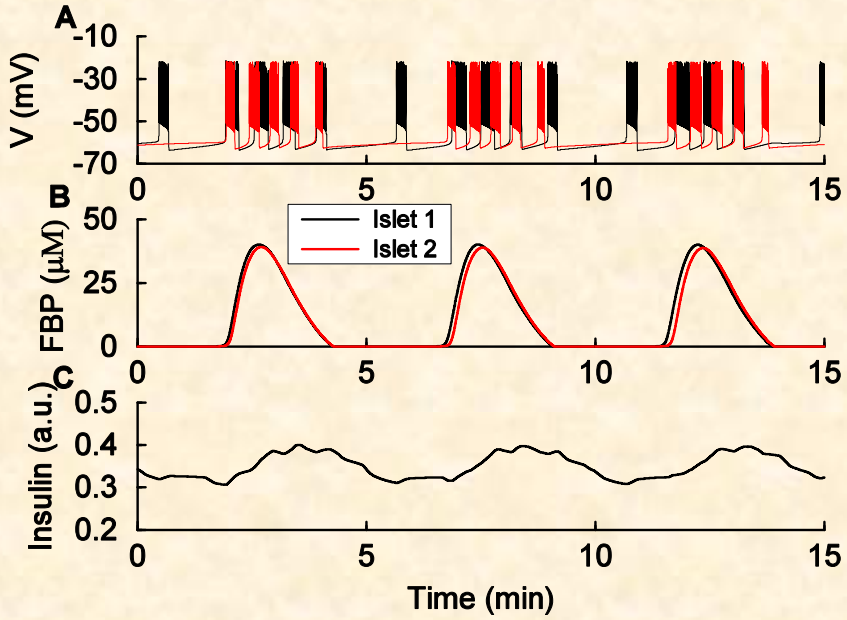


J. Physiol., 493:9, 1996

Electrical recordings from two islets *in vivo* show that islet bursting is not synchronized

Electrical Synchronization Not Required

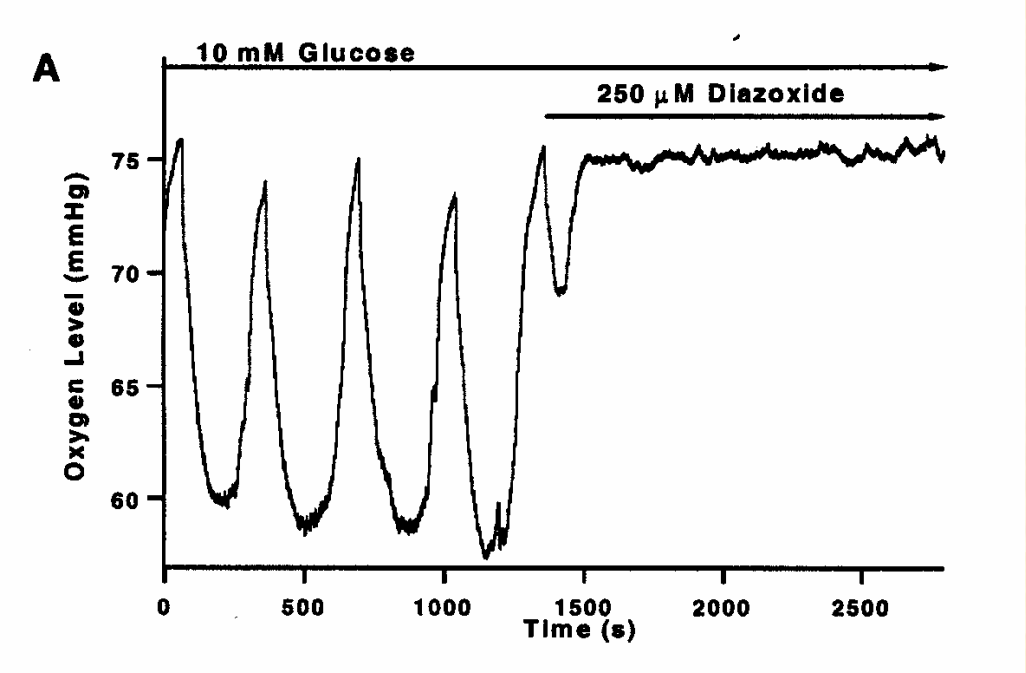
The DOM predicts that insulin secretion oscillations within an islet population can be synchronized even if the individual fast bursts are not synchronized. That is, only the glycolytic oscillations need be synchronized.



This can account for *in vivo* data from Valdeolmillos et al. (J. Physiol., 493:9, 1996) showing that bursting oscillations in two islets were not synchronized.

Terminating Bursting Terminates Metabolic Oscillations in Islets

Oxygen consumption in an islet, measured with an oxygen electrode.



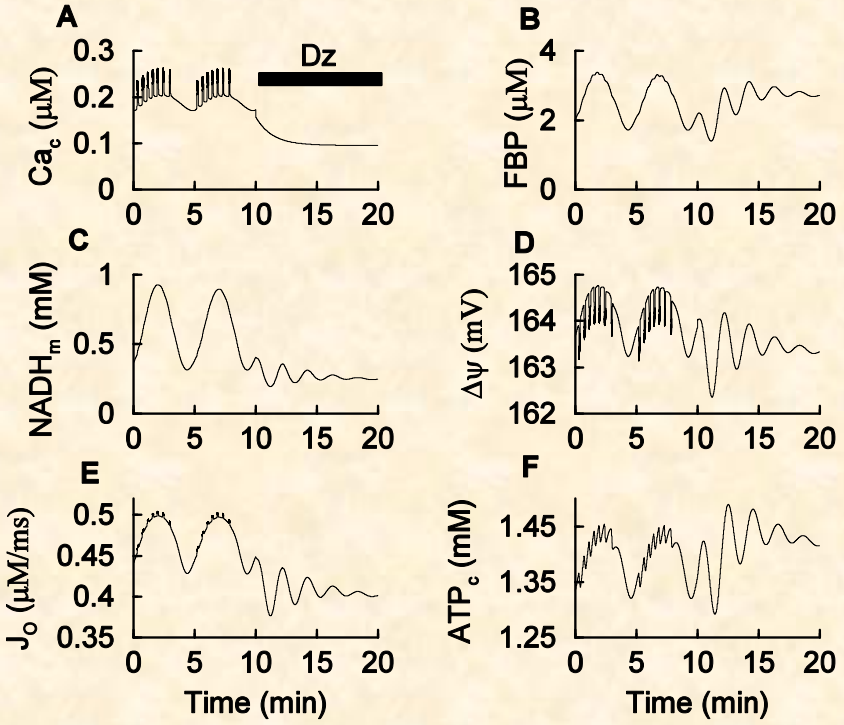
Kennedy et al., *Diabetes*, 51:S152, 2002

Diazoxide hyperpolarizes the islet, terminating electrical activity.

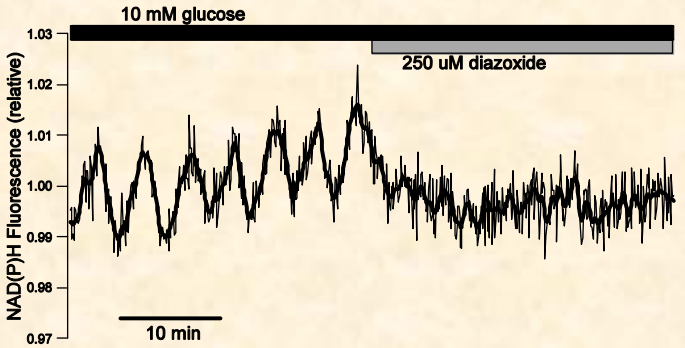
Kennedy Data Consistent with the DOM

Opening K(ATP) channels with diazoxide (Dz) can terminate the oscillations in glycolysis, and thus the metabolic oscillations. Explains O_2 recordings from Kennedy's lab and our own NAD(P)H data.

Model



NAD(P)H autofluorescence



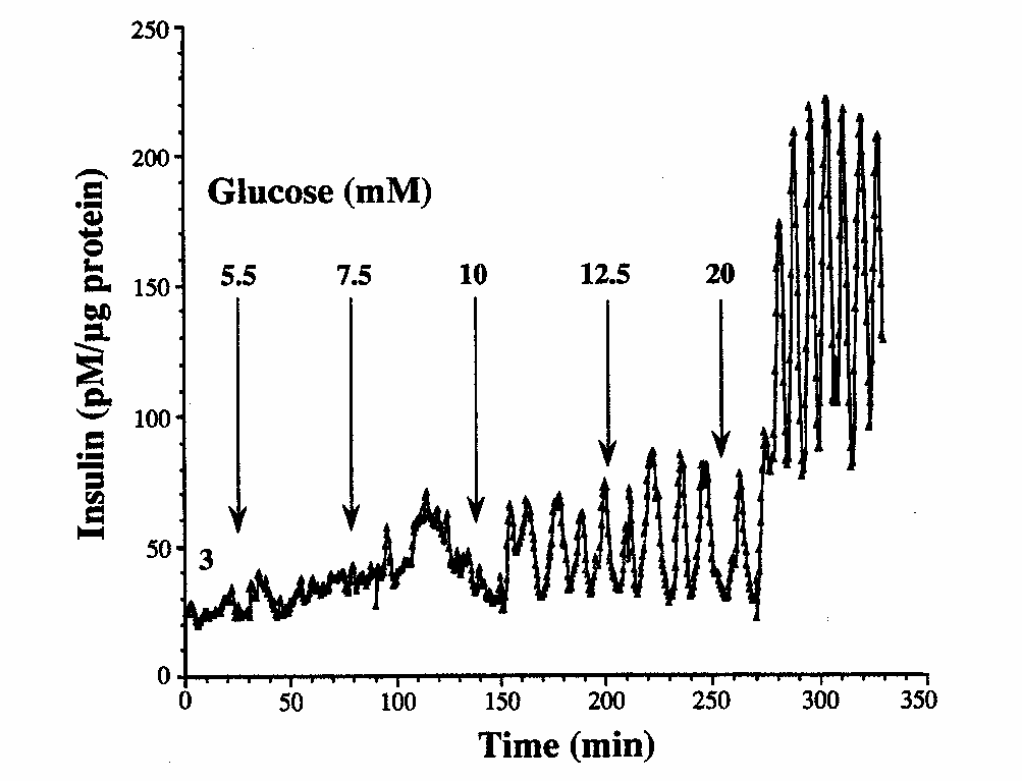
Bertram et al., Biophys. J., 92:1544, 2007

Dz hyperpolarizes membrane, lowering cytosolic Ca^{2+}, reducing ATP usage by Ca^{2+} ATPases, elevating cytosolic ATP concentration, inhibiting PFK.

Why Compound Oscillations?

Increasing Glucose Primarily Increases Insulin Oscillation Amplitude

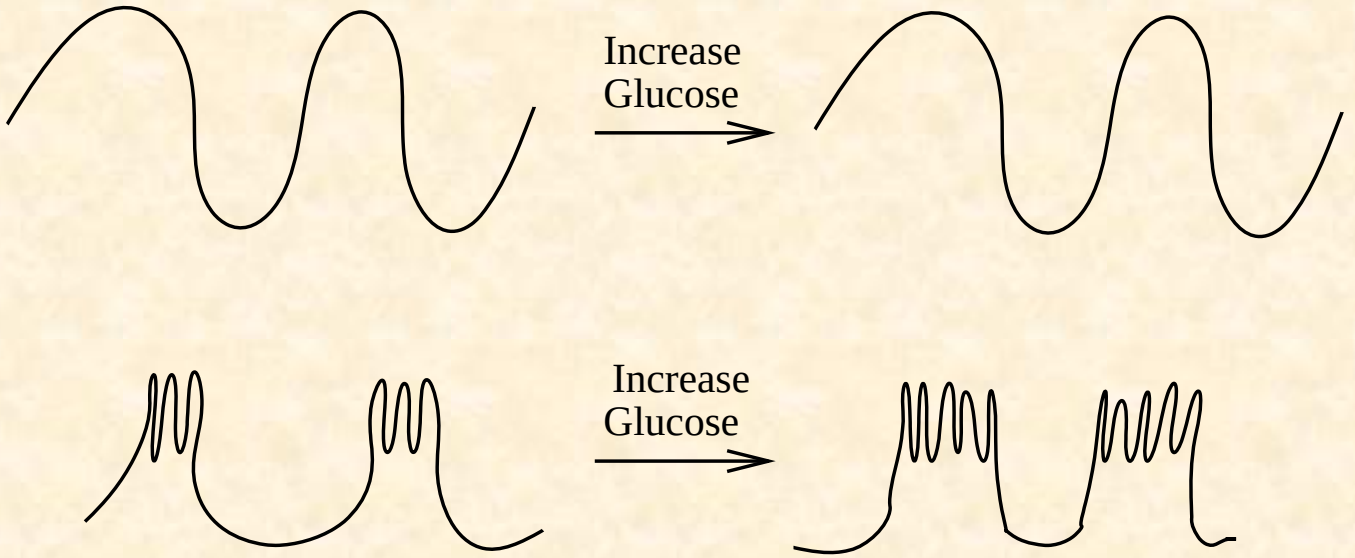
Perifused islets



Cunningham et al., *Am. J. Physiol.*, 271:E702, 1996

Data from several labs have shown that increasing glucose primarily increases the amplitude of insulin oscillations. The change in frequency is more modest.

Metronome Hypothesis



The frequency of glycolytic oscillations in the DOM is only moderately sensitive to the glucose concentration. However, the plateau fraction (i.e., duty cycle) of the inner bursts is very sensitive to glucose. When glucose is increased, the plateau fraction increases. This amplifies the amplitude of the insulin oscillation, while the effect on frequency is smaller.

Thank You!