Mathematical models of β-cell cluster dysfunction via IAPP-induced membrane pores

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β CELL PHYSIOLOGY

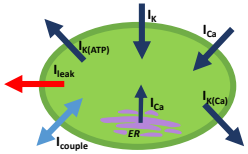
β cells function

- Blood glucose levels in the body are controlled by the pancreas
- The pancreas is made up of clusters if known as the Islets of Langerhans
- One cell type in these islets, β cells, are responsible for releasing insulin, the primary hormone involved in blood glucose regulation
- Insulin release exhibits a characteristic bursting pattern and is dependent on concentrations of Ca^{2+} and K^+

Mechanism of secretion in β cells

- ATP-inactivated K^+ channels prevent the buildup of K^+ in the cytosol
- When blood glucose is high, the cell produces ATP which inactivates the K_{ATP} channels, allowing K^+ to build up, electrically polarizing the cell
- This polarization activates the voltage-gated Ca^{2+} channels to open allowing Ca^{2+} to flow into the cell The endoplasmic reticulum also contributes to this depolarization via Ca^{2+} from the IP3R pathway.
- Ca^{2+} binds to receptor proteins on the insulin containing vesicles. This activates a docking mechanism between the secretory vesicles and the plasma membrane causing the secretion of the insulin
- Ca^{2+} also activates K^+ channels causing K^+ efflux, depolarizing the cell

An important characteristic of healthy insulin secretion is the synchronization of bursting by all the β cells within an islet. Cell clusters achieve this synchrony via gap junctions which allow ions to flow between the cytosol of adjacent cells, ultimately enhancing insulin release and facilitating insulin regulation.



Diabetes

- Insulin resistance in bodily tissues leads to high blood sugar.
- β cells are still functional and enter a state of relative hypersecretion in response to abnormally high blood glucose levels
- This leads to hyperplasia and hypertrophy, and eventually hypoplasia and hypotrophy
- Islet amyloid polypeptide (IAPP), also known as amylin, is co-secreted with insulin and has been shown to be cytotoxic.
- The aggregation of IAPP, specifically human IAPP, has been linked the formation ion channels or pores which can lead to membrane disruption and ion dysregulation.
- Membrane disruption can hinder cell coupling and ultimately lead to cell death via apoptosis.

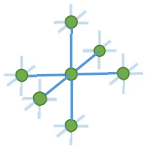
MATHEMATICAL MODELS OF IONIC CURRENTS AND β CELL BURSTING

Mathematical modeling can be used to simulate the function of the pancreatic β cells. The Hodgkin-Huxley model, which simulates nerve cell function has been applied to models for insulin secretion. The action potential physiology of impulse propagation is similar to the physiology of insulin secretion. The model shows the electric potential of a cell as function of time. However, the equation itself is based on a series of differential equation that take into account current flowing into and out of the cell via ion influx and efflux. Each component is further dependent on the instantaneous potential of the cell and other variables. Bursting frequencies for individual cells may be altered by modifying their conductance (g).

$$\frac{dV}{dt} = \frac{(I_{Ca} + I_K + I_{K(ATP)} + I_{K(Ca)} + I_{couple} + I_{leak})}{Cm}$$

$$I_{leak} = g_{leak}(V - V_{Ca})$$

$$I_{couple} = \sum_{i \in N} g_{couple}(V - V_i)$$



Where N = set of adjacent cells (max 6)

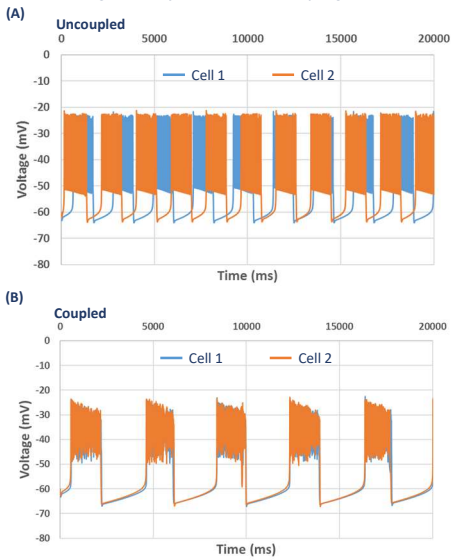
Using a model for a single cell, we developed one that simulates a cluster of cells. Each cell has an additional current that couples it to adjacent cells. Our primary cluster model simulated a 3x3x3 cell matrix. Simulations were run using the 190-core parallel computing cluster at LMU

Synchronization Index

To quantify the degree of synchronicity within the cluster we used a synchronization index which reports the lowest mean correlation coefficient for a cell to it neighbors.

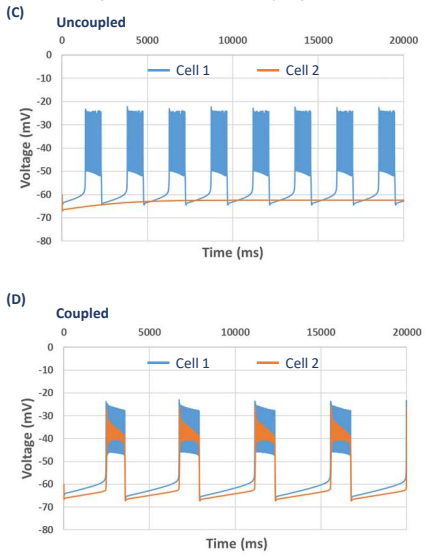
VOLTAGE TRACINGS FOR TWO CELLS IN A 3X3X3 CLUSTER

Bursting can be synchronized via coupling between cells



(A) The two cells are uncoupled and burst at different frequencies (Cell 1 = 2.76 bursts·min^{-1} , Cell 2 = 3.12). (B) Once coupled, the two cells are synchronized (Cell 1 = 1.68, Cell 2 = 1.68)

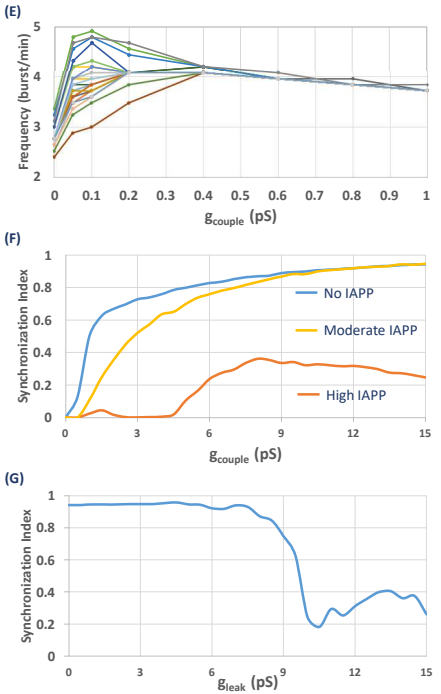
Bursting can be induced via coupling between cells



(C) The two cells are not electrically coupled. Cell 1 exhibits normal bursting behavior. Cell 2 remains in a non-bursting, polarized state. (D) When coupling is introduced, Cell 2 begins bursting in sync with Cell 1.

EFFECT OF IAPP-INDUCED PORES ON CLUSTER SYNCHRONY

IAPP-induced leak currents reduce cluster synchrony



The magnitude of g_{leak} correlates to the permeability of the membrane due to IAPP. The magnitude of g_{couple} correlates to the connection between cells. (E) For a 3x3x3 cluster of healthy cells, increasing the conductance of the coupling currents between cells, causes the bursting frequency of the cells to align. (F) Cluster synchrony decreases as IAPP affliction increases. Heavy affliction can nullify the effects of strong coupling. (G) Increasing the conductance of leak currents decreases cluster synchrony.

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