ENABLING PHYSIOLOGICALLY REPRESENTATIVE SIMULATIONS OF PANCREATIC BETA CELLS

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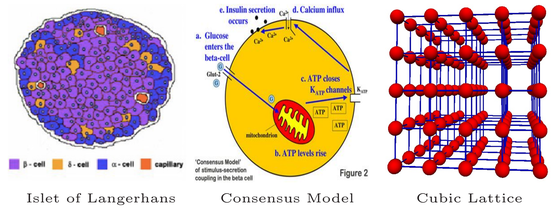
Abstract

Within the endocrine system of the pancreas lie clusters of cells called islets of Langerhans. Each islet is composed of four cell types - the most prevalent of which being the beta cell. We aim on continuing the development of a computational islet and simulating the behavior of these cells. There exist set of deterministic Ordinary Differential Equations (ODEs) that models insulin secretion within beta cells. We consider cell dynamics on a cubic lattice of on average 1000 heterogeneous cells with key parameters including ionic fluxes, calcium handling, metabolism, and electrical coupling. By using sophisticated software, careful consideration of robust numerical methods, and efficient programming techniques, physiologically representative simulations of pancreatic beta cells become feasible.

We provide an extensible, efficient, and functional computational islet simulator to aid research in beta cell dynamics. In particular, we adapt an existing dual electrical and glycolytic oscillator model into a numerically robust, modular set of Matlab files.

Background



Islet of Langerhans | Consensus Model | Cubic Lattice

The islets of Langerhans are islands of β-cells within the pancreas. The metabolic and electrical activities of these islets are closely related with the islets' insulin secretion. Each beta-cell can be categorized as slow or fast based on the insulin secretion rate.

Consider an N^3 grid of β-cells, each coupled to its nearest neighbors, as shown above. Let v represent the current voltage. The (i,j,k) cell voltage in $\mathbb{R}^3$ is found by:

$$\begin{aligned} V_{i,j,k} = f_V(V^{i,j,k};p^{i,j,k}) + g_j^A(V^{i+1,j,k} - V^{i,j,k}) \\ +g_j^B(V^{i-1,j,k} - V^{i,j,k}) + g_j^C(V^{i,j+1,k} - V^{i,j,k}) \\ +g_j^D(^{i,j-1;k} - V^{i,j,k}) + g_j^E(V^{i,j,k+1} - V^{i,j,k}) \\ +g_j^F(V^{i,j,k-1} - V^{i,j,k}) \end{aligned}$$

Implementing the model involves solving 7 time dependent ODEs by using Matlab's stiff ode15s solver for each of the cells in this lattice. The sheer number of degrees of freedom and time-steps used by the ode15s solver makes the implementation of this model computationally complex and requires the use of the sophisticated software.

Numerical Methods

Extensibility

- Output to file
- Coupling of beta cells through any variables
- Modify coupling constant depending on variable(s)
- Set up to modify slow/fast bursting parameter allocation scheme
- Restructured code for ease of usability

Efficiency

- Added parallelization
- Modified Matlab's stiff ODE solver - Ode15s

N	DOF	No modifications	modifications
2	56	00:00:51	00:00:51
3	189	00:01:37	00:01:18
4	448	00:05:41	00:03:19
5	875	00:21:32	00:13:07
6	1512	01:02:44	00:34:31
7	2401	02:40:18	01:25:38
8	3584	06:22:46	03:46:10
9	5103	14:09:50	08:37:59
10	7000	27:36:36	18:32:40

Table 1: $n_s = 7$, DOF $= N^3 n_s$

It is evident from the table above that we have enabled the model to be more efficient with the modifications.

Model

We simulate the glycolytic oscillator model of the β-cell using a deterministic model developed by Chay and Keizer (1983) and updated by Sherman et al., including voltage data by Rorsman and Trube (1986). This original model characterizes the dual oscillatory behavior of a representative β-cell as an intact islet of Langerhans

$$\frac{dV}{dt} = \frac{-(I_K + I_{Ca} + I_{K(Ca)} + I_{K(ATP)})}{C_m} \quad (1)$$

$$\frac{dn}{dt} = \frac{(n_\infty - n)}{\tau_n} \quad (2)$$

$$\frac{d[Ca^{2+}]}{dt} = f_{cyt} \cdot (J_{mem} + J_{er}) \quad (3)$$

$$\frac{d[Ca^{2+}_{er}]}{dt} = -\sigma_V \cdot f_{er} \cdot J_{er} \quad (4)$$

$$\frac{d[G6P]}{dt} = \kappa \cdot R_{GK} - R_{PFK}) \quad (5)$$

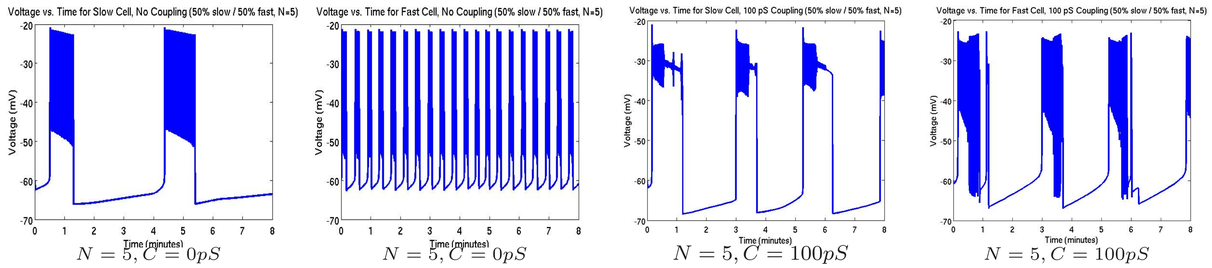
$$\frac{d[FBP]}{dt} = \kappa \cdot (R_{PFK} - 0.5 \cdot R_{GPDH}) \quad (6)$$

$$\frac{d[ADP]}{dt} = \frac{[ATP] - [ADP] \cdot \exp\left\{(r+\gamma)\left(1 - \frac{[Ca^{2+}]}{r_1}\right)\right\}}{\tau_a} \quad (7)$$

In equation (1), the independent variable V is membrane potential. In equation (2), the variable n is the open fraction of voltage-gated K + channels. These variables generate the spikes during active phases.

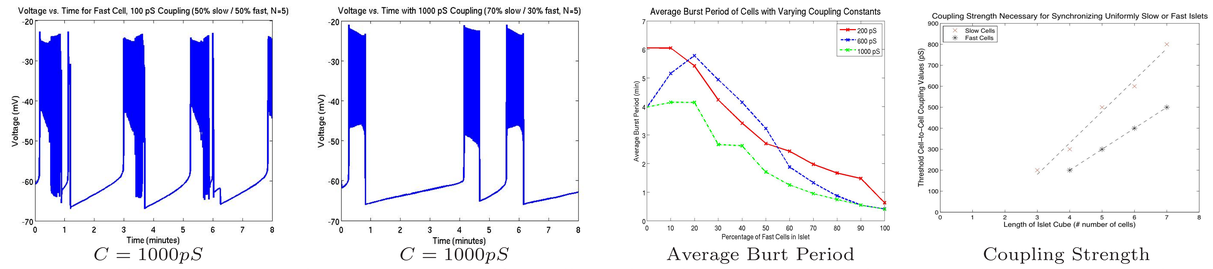
Application Results

Bursting Period: 50% **slow**/50%**fast** β**-cells**



$N = 5, C = 0pS$ | $N = 5, C = 0pS$ | $N = 5, C = 100pS$ | $N = 5, C = 100pS$

Bursting Periods, Average Burst Period,Coupling Strength



$C = 1000pS$ | $C = 1000pS$ | Average Burt Period | Coupling Strength

- In weak and strong coupling, an increase of fast cells tends to lessen the average burst period. However, in midrange coupling, the fast cells act by first increasing the period -actually slowing down the oscillations and making the coupling of the slow cells more pronounced, before falling into this similar pattern.
- The coupling strength at which synchronicity is achieved in either all fast cell or all slow cell islets exehibits a positive correlation to N ,the number of cells per islet.

Aknowledgement

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