Investigating Oscillation Loss in Computational Islets

UMBC REU Site: Interdisciplinary Program in High Performance Computing
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Problem and Motivation

Diabetes mellitus is a group of diseases characterized by insulin resistance or insulin deficiency. Pancreatic beta cells, located in islets of Langerhans, exhibit electrical bursting and metabolic oscillations that correlate with insulin secretion. This behavior depends on coupling strengths in the islet and varies from one beta cell to another.

- We confirm the loss of slow metabolic oscillations, which have been simulated in a two-cell model, in computational islets with larger cell counts coupled metabollically and electrically.
- We simulate open mutated K(ATP) channels and analyze bursting behavior in islets with various percentages of mutated cells.

Model

We represent a computational islet with N^3 cells arranged in a cube. Our model is a stiff system of seven ordinary differential equations (ODE's) per cell describing rates of change of voltage (V), the fraction of open K^+ channels (n), and five chemical species (Ca, Ca_{er}, ADP, G6P, and FBP). We couple cells through voltage and through the two metabolites glucose 6-phosphate (G6P) and fructose 1-6-bisphosphate (FBP).

Mutated K(ATP) channels are simulated by manipulating the current

$$I_{\mathrm{K(ATP)}} = g_{\mathrm{KATP}}(V - V_{\mathrm{K}}),$$

where $g_{\mathrm{KATP}} = \overline{g}_{\mathrm{K,ATP}} o_\infty([\mathrm{ADP}])$ and $\overline{g}_{\mathrm{K,ATP}}$ maximizes g_{KATP}.
This current affects $\frac{dV}{dt}$, defined as

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

where I_{K}, I_{Ca}, and $I_{\mathrm{K(Ca)}}$ are other currents in the islet [1].

We set $o_\infty([\mathrm{ADP}])$ to be constantly 0.0075 to model channels that are always open.

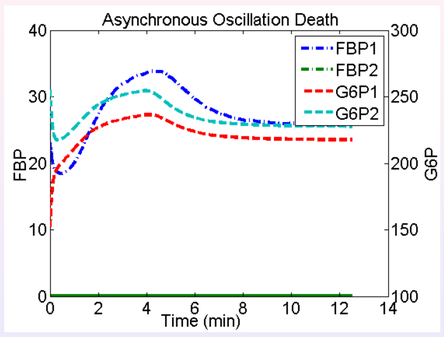
Numerical Study

We use a memory-modified version of Matlab's stiff ODE solver ode15s and supply a sparse Jacobian derived analytically by the automatic differentiation software ADiMat [3].

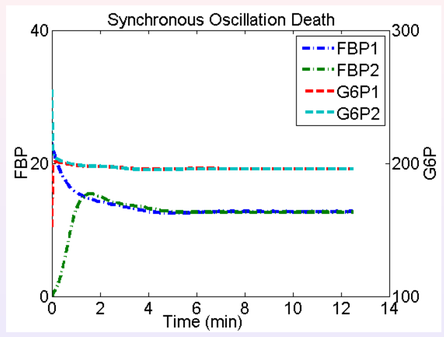
Wall clock time in HH:MM:SS for coupling (V) 75 pS, (G6P) 0.01 ms^{-1}, (FBP) 0.001 ms^{-1} with ADiMat for 200,000 ms in the 'grouped' distribution.

N	Original ode15s	Memory-Modified ode15s
3	00:00:28	00:00:21
4	00:01:38	00:00:33
5	00:04:07	00:00:46
6	00:10:02	00:01:14
7	00:24:26	00:01:45
8	00:32:52	00:02:47
9	00:48:47	00:04:51
10	01:11:58	00:07:48

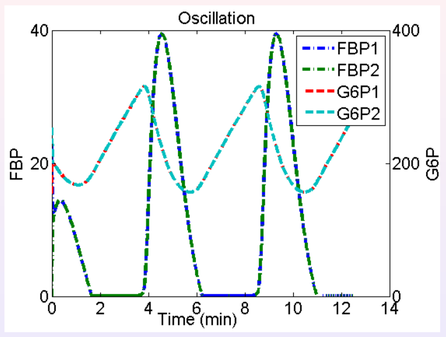
Classes of Metabolic Behavior



(V) 75 pS, (G6P) 0.01 ms^{-1}, (FBP) 0.001 ms^{-1}



(V) 75 pS, (G6P) 0.1 ms^{-1}, (FBP) 0.001 ms^{-1}

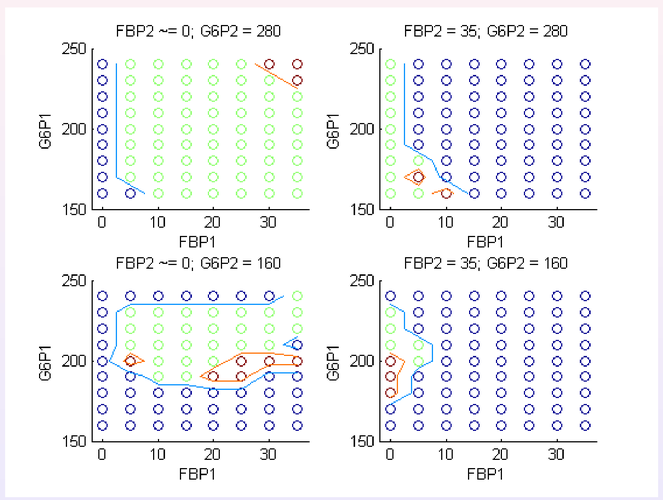


(V) 75 pS, (G6P) 1 ms^{-1}, (FBP) 0.1 ms^{-1}

Three types of behaviors exhibited by heterogeneous cells at differing coupling strengths and initial conditions: (left) asynchronous oscillation death, (center) synchronous oscillation death, and (right) continued oscillation.

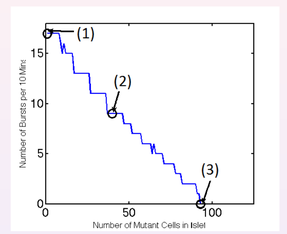
Results

Initial Conditions at Which Loss Occurs

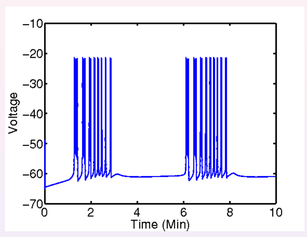


Coupling strengths kept constant at (V) 75 pS, (G6P) 0.01 ms^{-1}, and (FBP) 0.001 ms^{-1}. Blue regions describe continuing oscillations, green regions describe asynchronous oscillation death, and red regions describe synchronous oscillation death.

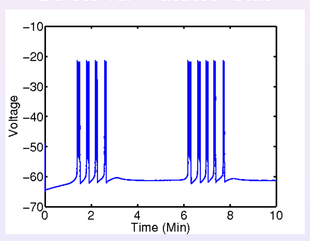
Open Mutations and Voltage Bursting



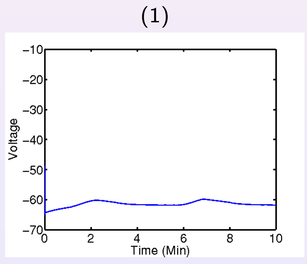
Bursts vs. Mutated Cells



(1)



(2)



(3)

Coupling strengths kept constant at (V) 75 pS, (G6P) 0 ms^{-1}, and (FBP) 0 ms^{-1}. As the number of cells with open K(ATP) channel mutations increases, the number of voltage bursts gradually decreases. Voltage bursts disappear when 93 of the 125 cells are mutated.

Conclusions

- Given set coupling strengths and initial concentrations of G6P and FBP, we can predict the class of solution of our multicellular islet. Providing a perturbation sufficient to alter the concentrations of the two metabolites so that they lie in a different basin of attraction, we can switch between bistable solutions; this extends a result in coupled cells from [2] to the multicellular islet.
- Electrical bursting in a 125-cell islet reduces with the addition of cells with mutant open K(ATP) channels and disappears altogether when the count of mutated cells reaches 74 percent. This behavior is independent of strength of electrical and metabolic coupling. Runs with a 27-cell islet also have a 74 percent threshold, suggesting islet size independence. Mutant cell arrangement within the islet also did not affect threshold.

References and Acknowledgments

1. Full technical report: HPCF–2013–14 at `www.umbc.edu/hpcf` > Publications.
2. Tsaneva-Atanasova, Zimliki, Bertram, and Sherman, *Biophysics Journal*, 90:3434–3446, 2006.
3. Khuvis, Gobbert, and Peercy, *Journal of Mathematical Biosciences*, submitted.

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