The Interaction of Calcium and Metabolic Oscillations in Pancreatic β-cells

UMBC REU Site: Interdisciplinary Program in High Performance Computing

Mary Aronne[1], Samantha Clapp[2], Soohwan Jung[3], Abigail Kramer[4], William Wang[5]

GA: Janita Patwardhan[1], Faculty mentor: Bradford E. Peercy[1], Client: Arthur Sherman[6]

[1]UMBC, [2]Georgia College and State University, [3]Edmonds Community College, [4]Kent State University, [5]Vanderbilt University, [6]NIH

Problem

Diabetes is a disease characterized by an excessive level of glucose in the bloodstream, which may be a result of improper insulin secretion. Insulin is secreted in a bursting behavior by pancreatic β-cells in islets, which is affected by oscillations of cytosolic calcium concentration. We used the Dual Oscillator Model to explore the role of calcium in calcium oscillation independent (CaI) versus calcium oscillation dependent (CaD) modes as well as the synchronization of metabolic oscillations.
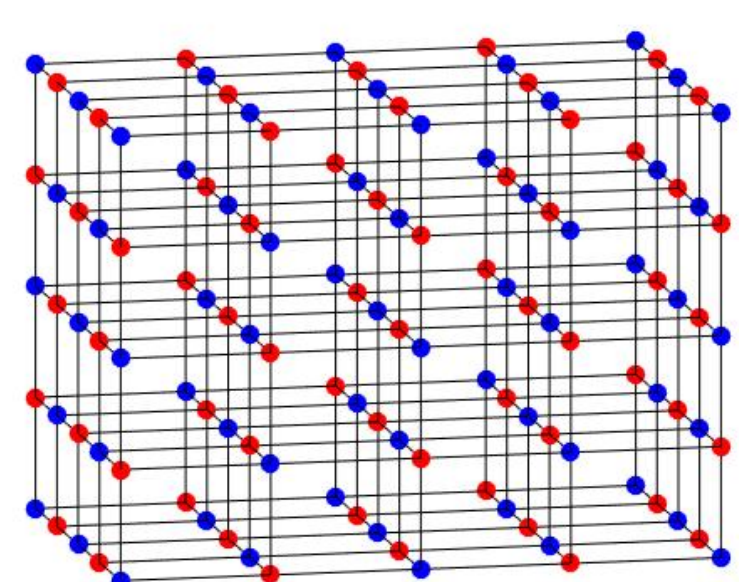
Biological Model
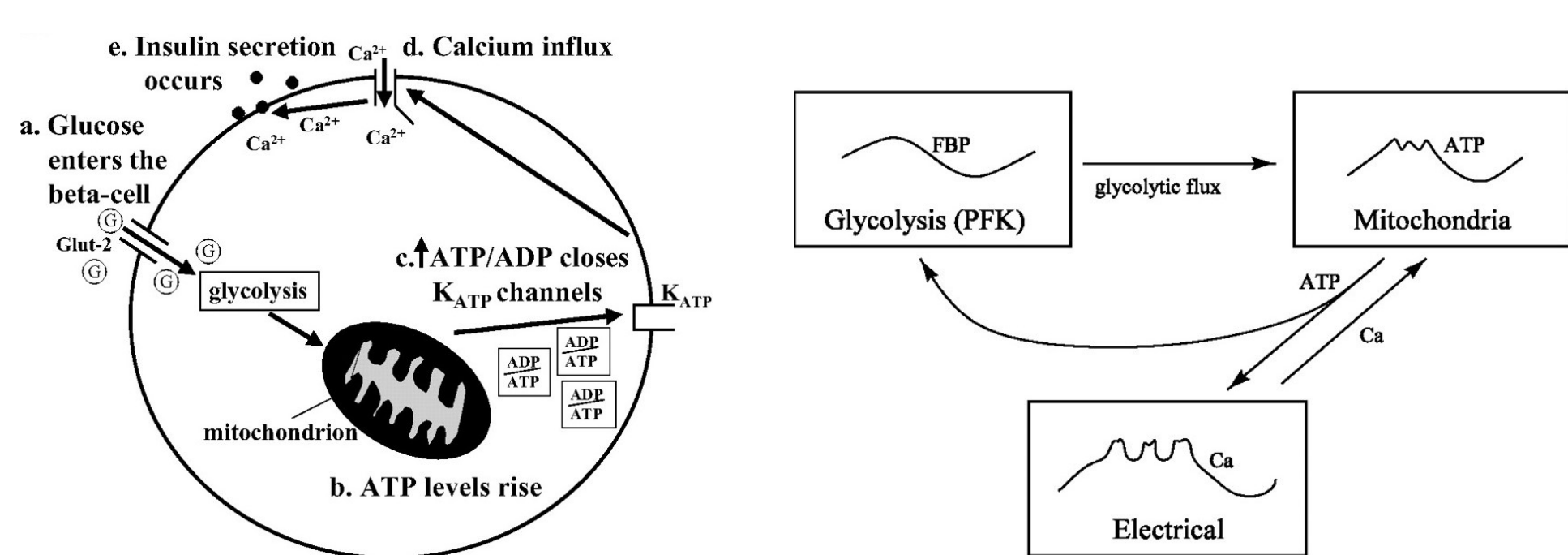
Dual Oscillator Model

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

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

$$\frac{d[Ca]}{dt} = f_{cyt}(J_{mem} + J_{er})$$

$$\frac{d[Ca_{er}]}{dt} = -\sigma_V f_{er} J_{er}$$

$$\frac{d[ADP]}{dt} = J_{hyd} - \delta J_{ANT}$$

$$\frac{d[G6P]}{dt} = k(J_{GK} - J_{PFK})$$

$$\frac{d[FBP]}{dt} = k(J_{PFK} - \frac{1}{2} J_{GPDH})$$

Coupling

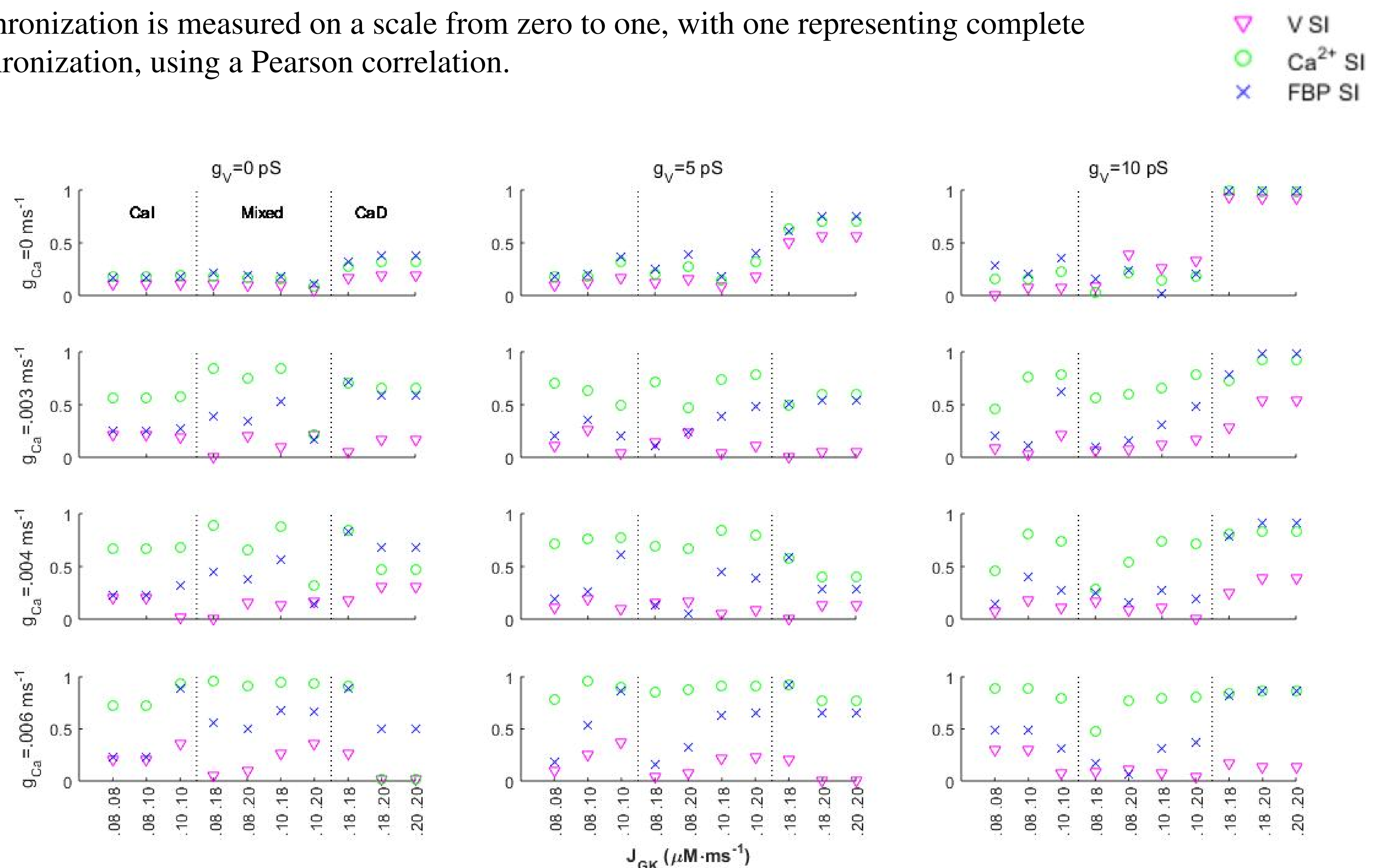The system of ODEs can be defined as

$$\frac{dy}{dt} = f(t, y) + Gy$$

where $f(t, y)$ represents the dynamics of each cell and Gy accounts for the impact of coupling on β-cells.

Islet Cube with equal distribution of two J_{GK} values
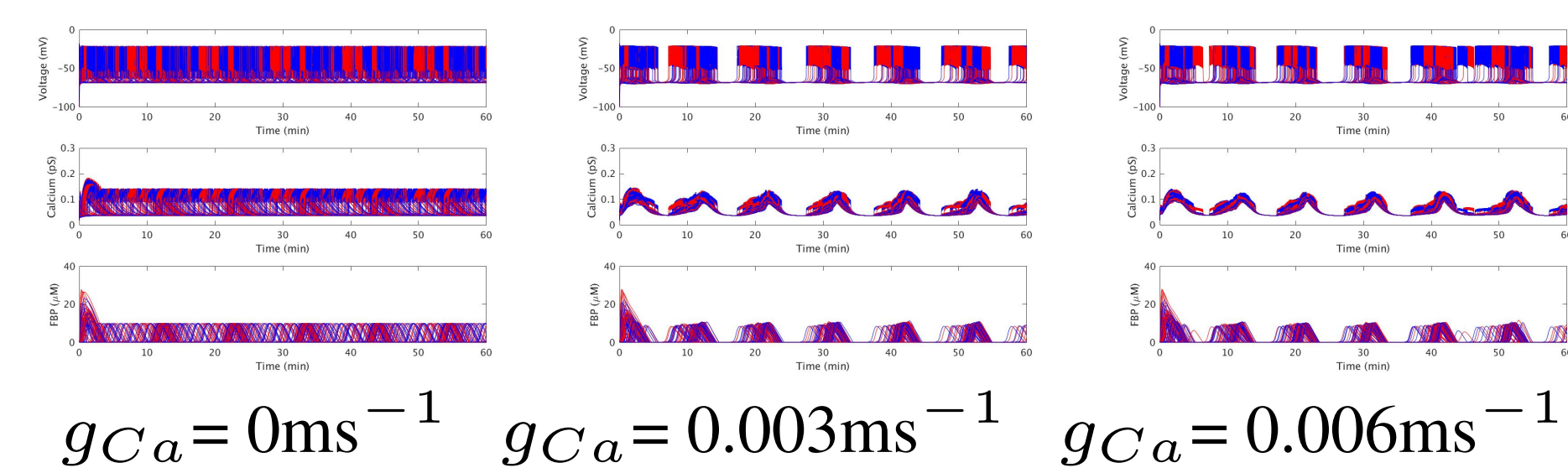
Synchronization Index

Synchronization is measured on a scale from zero to one, with one representing complete synchronization, using a Pearson correlation.

Simulations were run for one hour starting with a distribution of initial conditions with a 5×5×5 cube of cells, equal-50-percent bursting pattern, increasing voltage and calcium coupling, pairwise J_{GK} values in three different modes, CaI, CaD, and mixed CaI and CaD.
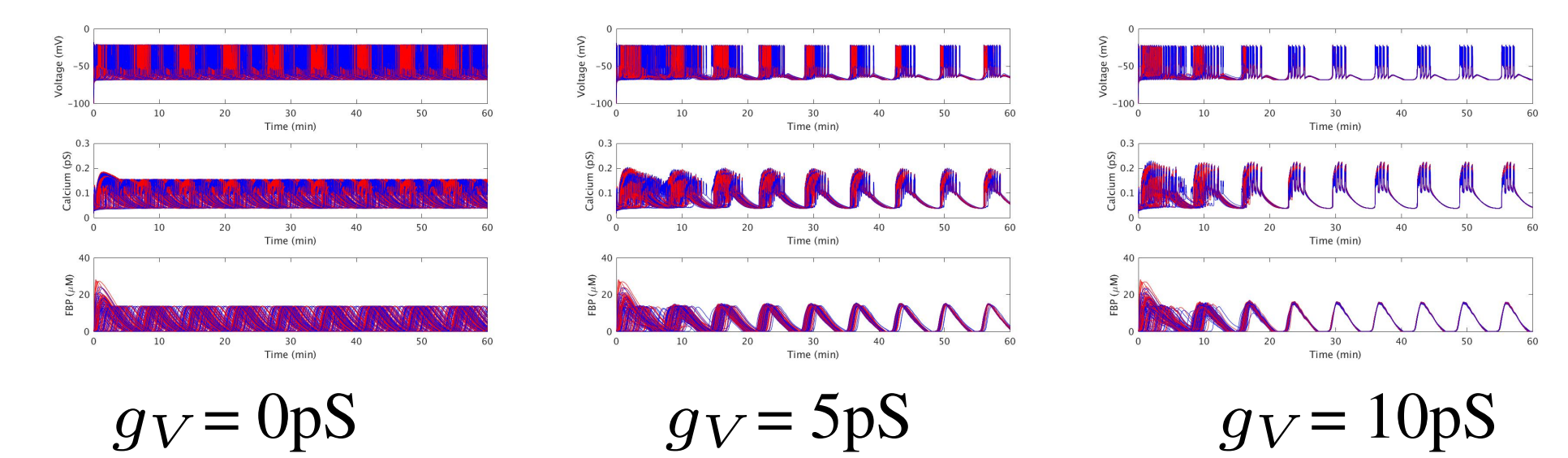
CaI Calcium Coupling Trend

In CaI regions increasing calcium coupling increases synchronization.

$g_{Ca} = 0$ms^{-1} $g_{Ca} = 0.003$ms^{-1} $g_{Ca} = 0.006$ms^{-1}

Simulations with 5×5×5 cube, $g_V = 0$pS, and J_{GK} is 0.08μM·ms^{-1} (blue) or 0.1μM·ms^{-1} (red)

CaD Voltage Coupling Trend

Increasing voltage coupling increases synchronization in CaD modes.

$g_V = 0$pS $g_V = 5$pS $g_V = 10$pS

Simulations with 5×5×5 cube, $g_{Ca} = 0$ms^{-1}, and J_{GK} is 0.18μM·ms^{-1} (blue) or 0.2μM·ms^{-1} (red)

Voltage & Calcium Coupling

In CaD regions increasing calcium coupling desynchronizes voltage.

$g_{Ca} = 0$ms^{-1} $g_{Ca} = 0.006$ms^{-1}
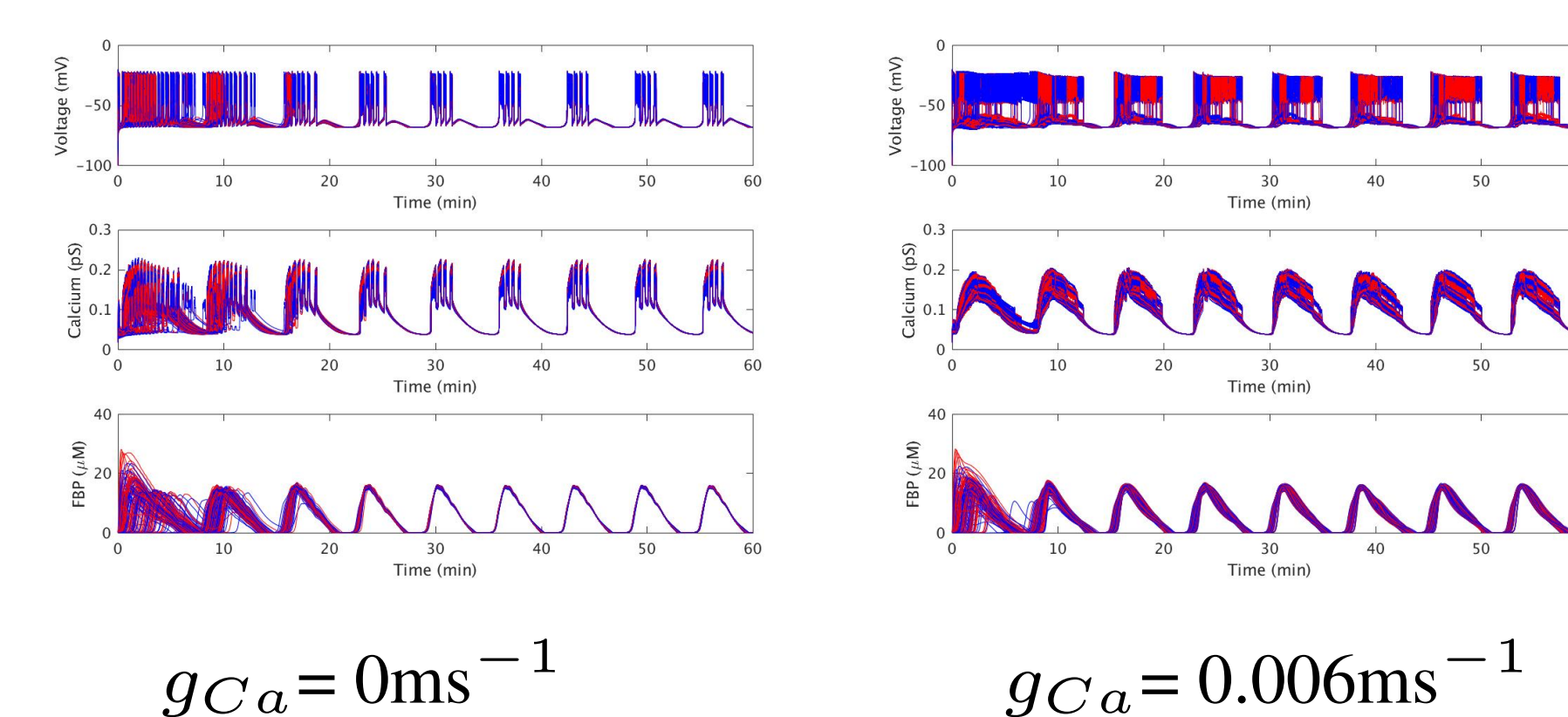
Simulations with 5×5×5 cube, $g_V = 10$pS, and J_{GK} is 0.18μM·ms^{-1} (blue) or 0.2μM·ms^{-1} (red)

Conclusions

Coupling complex cells together has interesting dynamic effects. When in CaI mode, increasing calcium coupling with no voltage coupling increases synchronization. In CaD modes, increased voltage coupling with no calcium coupling increases synchronization. However, in CaD modes, voltage coupling with high calcium coupling causes desynchronization in voltage. Mixed modes tend to behave like CaI modes.

References & Acknowledgments

- R. Bertram et al. *AJP-ENDO*, 2007.
- Technical report: HPCF–2016–14 hpcf.umbc.edu > Publications
- REU Site: hpcreu.umbc.edu
- NSF, NSA, DOD, UMBC, HPCF, CIRC