# Mathematical modeling of insulin secretion from a network of coupled islet β-cells via glucose-induced changes in membrane potential, intracellular calcium, and insulin granule dynamics

I. Johanna Stamper[1,2], Xujing Wang[3]
[1]Department of Physics, University of Alabama at Birmingham, Birmingham, Alabama, 35294
[2]The Comprehensive Diabetes Center, University of Alabama at Birmingham, Birmingham, Alabama, 35294
[3]Bioinformatics and Systems Biology Core, Systems Biology Center, National Heart, Lung and Blood Institute, NIH, Bethesda, MD 20892, USA

Tel: 301-451-2862

In this study we present a new mathematical model of the biphasic insulin secretion and β-cell mass. It is built on two of our previous models: an inter-cellular Hodgkin-Huxley (H-H) type model of a hexagonally closed packed (HCP) network of electrically connected pancreatic islet β-cells (Plos One, 2007), and an intra-cellular model of glucose-induced insulin secretion based on insulin granule dynamics (J. Theo. Bio 2013). In order to couple these two models we assume that the rate at which the primed and release-ready insulin granules fuse at the cell membrane increases with the intracellular calcium concentration, one of the variables in the HH model. Moreover, by assuming that the fraction of free $K_{ATP}$ -channels decreases with increasing glucose concentration, we are able to take into account the effect of glucose dose on membrane potential and, indirectly via the effect on the potential, on intracellular calcium. Numerical analysis of our model shows that a single step increase in glucose concentration typically yields the characteristic biphasic insulin release often seen experimentally. Our model's biphasic response can be either oscillatory or non-oscillatory in nature depending on the glucose-concentration; at high concentrations the oscillations tend to vanish due to a constantly elevated membrane potential of the β-cells. Furthermore, with increasing glucose dose, the area under the insulin curve increases, as does the plateau fraction (the time that the β-cells spend in their active firing phase). To our knowledge our model is the first to explicitly connect insulin secretion from intracellular insulin granules to glucose-stimulated intercellular electrical activity within a network of coupled β-cells.