Computational Models of Calcium Signaling in the Pancreas - Temporal and Spatial Regulations

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1 Introduction

The major function of exocrine pancreas (pancreatic acinar cells) is the secretion of digestive enzymes. This process is regulated by neurotransmitters and hormones, both of which utilize Ca^{2+} as a principal signaling molecule. Ca^{2+} signals exhibit various temporal (transient/oscillatory) and spatial (local/global) patterns depending on the agonists and the strength of the stimulations. It has been known that the patterns rise from the interactions between Ca^{2+} transporters, second messengers (IP_3, cADPR, and NAADP) and Ca^{2+}-stores (the endoplasmic reticulum, mitochondria and the nuclear envelop) and we have been investigating what interactions can generate or affect particular patterns of Ca^{2+} signals. We developed computational models of Ca^{2+} signaling in the pancreatic acinar cells to obtain detailed quantitative information from experimental data as well as to improve the theoretical understanding of the processes, particularly Ca^{2+} oscillations.

2 The Model

The computational model was created on FEMLAB, a MATLAB-based software environment for modeling mathematical problems based on a system of coupled partial differential equations. The model was composed of (1) membrane transports and (2) cell geometry. The former underlies the generation of Ca^{2+} signals and the latter defines their localization.

2.1 Membrane Transports (Figure 1)

The model considered the transports of Ca^{2+} between two compartments, the cytoplasm and the endoplasmic reticulum (ER) that is the major Ca^{2+} store in the pancreatic acinar cell. IP_3 receptors and ER Ca^{2+}-ATPases in the ER membrane release Ca^{2+} from ER (J_{re}) and uptake Ca^{2+} into ER (J_{SERCA}), respectively. We also considered Ca^{2+} extrusion from the cytosol by plasma membrane Ca^{2+}-ATPase (J_{PMCA}) and the passive leak Ca^{2+} from ER (J_{leak}). The mathematical models for each transport mechanism were from [3].

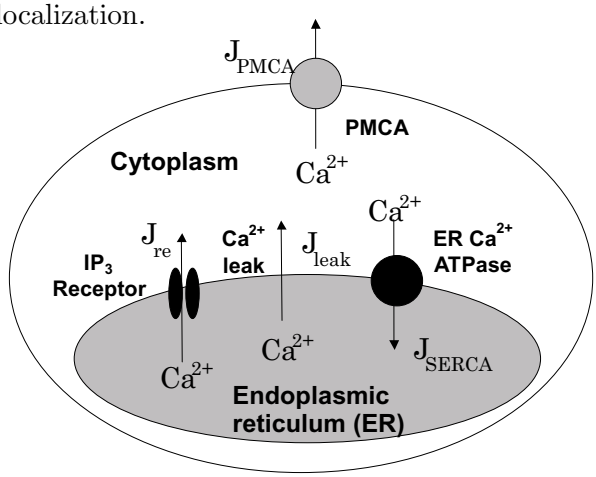

Figure 1: Intracellular compartments and membrane transport mechanisms in the pancreatic acinar cell model.

2.2 Geometry (Figure 2)

The geometry of the model represented the polarized structure of the pancreatic acinar cell, which has apical region (proximal to the pancreatic duct) which contains secretory granules and the majority of IP_3 receptors, basal region (proximal to the blood vessels) largely filled with ER, and "belt" region separating the apical and basal region. Both the cytosolic and ER compartments were present in all

the regions and Ca^{2+} could diffuse in both compartments. To reflect the heterogeneity of ER [1], the ER compartment in the model had following geometrical constraints; (1) the density of ER was higher in the basal region than apical or belt region, (2) diffusion of Ca^{2+} in the basal region was faster when it was parallel to the plasma membrane than when the diffusion was perpendicular to it, (3) densities of IP_3 receptor and ER Ca^{2+}-ATPases were higher in the apical region than the basal region.

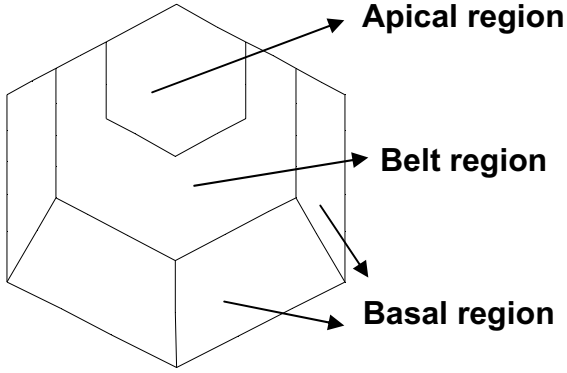

Figure 2: Subdomains in the acinar cell model.

3 Simulation of Localized Cytosolic Ca^{2+} Oscillations

It has been shown that physiological concentration of neurotransmitters or hormones induce cytosolic Ca^{2+} oscillations localized in the apical and belt regions and we reproduced them using the model shown above (Figure 3 and 4). We observed the strong dependency of the amplitude and the frequency of the Ca^{2+} oscillations on ER Ca^{2+} in the simulations as we observed in the experiments [2] and the qualitative behaviors of the oscillations was consistent with the experimental data. We found that a variety of geometrical parameters, such as the cell shape, volume of intracellular Ca^{2+} stores and the size of the apical region, altered the Ca^{2+} oscillations. We suggest that our computational models are usable for the analysis of the possible effects of cell geometry on Ca^{2+} oscillations in pancreatic acinar cells.

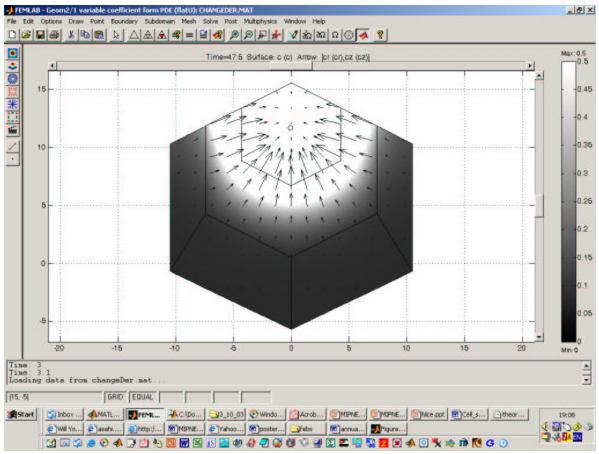

Figure 3: Distribution of cytosolic Ca^{2+} during the localized Ca^{2+}oscillations in the acinar cell model on FEMLAB.

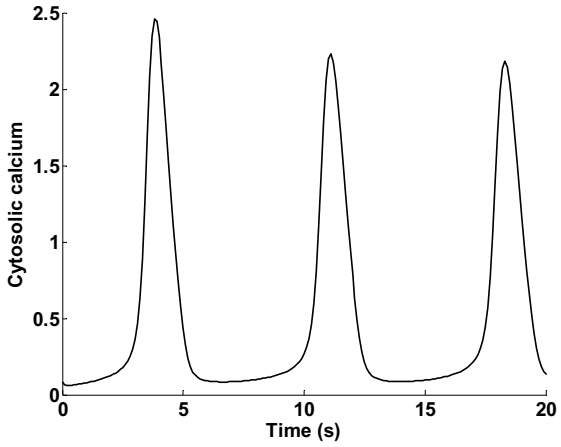

Figure 4: The simulated pattern of cytosolic Ca^{2+} oscillations in the apical region of the acinar cell.

References

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