Using detailed cellular morphology in modeling

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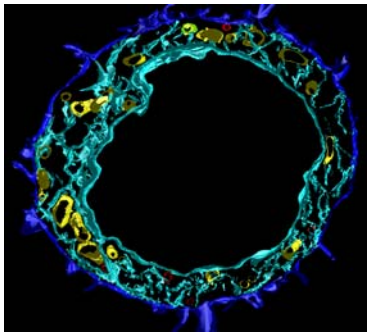
***Short Abstract* — The underlying mechanism in most allergic reactions is the release of inflammatory mediators by allergen-activated mast cells. We used a series of electron microscopy images to built a 3D reconstruction of a representative portion of an RBL-2H3 cell, a model mucosal mast cell. This 3D reconstrution was then used for modeling various aspects of mast cell activation, with an emphasis on stochastic effects and situations, where detailed spatial organization of intracellular organelles plays an important role.**

***Keywords* — mast cell, 3D reconstruction, stochastic modeling**

I. Introduction

THE underlying mechanism of type I hypersensitivity reactions is the activation of mast cell plasma membrane IgE receptors by allergen and the ensuing release of inflammatory mediators. A necessary step in the chain of events is the increase in intracellular calcium concentration mediated by its release from the intracellular ER stores by activated IP_3Rs and the secondary influx of extracellular calcium.



Here we used a 3D reconstruction of a rat basophilic leukocyte (RBL) to model the intermediate steps in the cascade, including the release of inositol trisphosphate (IP_3) by phospholipase γ (PLCγ) (activated after the IgE receptor activation by allergen), activation of the IP_3R calcium channels in the endoplasmic reticulum (ER) and release of calcium from the ER, as well as all the reactions and transport mechanisms involved in calcium signaling.

II. Methods

A series of electron microscopy images and software programs developed in UCSD and University of Colorado were used to build the 3D reconstruction [1,2]. Then a MATLAB program was written to populate the organelles with all the species involved (e.g. the IgE receptors, PLCγ, the IP_3Rs, plasma membrane and ER calcium pumps, calcium binding buffers, mitochondrial calcium transport mechanisms etc.). The species were distributed either randomly, or according to the available biological information. They were then allowed to diffuse, react and mediate membrane transport according to the equations and rates from previously published, mainly compartmental models [e.g. 3,4]. In order to keep these simulations PC-memory friendly, the space was discretized into cubic voxels with 28 nm edges.

For simplified simulations of single channel calcium release we used a spherical symmetry MATLAB PDE solver. Our program allows the channels to be placed to any selected (or random) place in the ER membrane. Channel environment was, in this case, represented in terms of radial distribution of volume fractions of individual organelles and membranes. The organelles were populated with all the major calcium signaling mechanisms. As IP_3Rs are feedback- regulated by released calcium, a stochastic model of IP_3R opening in response to local calcium concentration was applied (similar to our previous study [5]).

Compartmental models encoded in MATLAB, as well as in several ML platforms ([6]), were used for comparison.

III. Summary

We explored several possibilities to combine detailed spatial information with stochastic modeling in the complex case of calcium signaling, that includes highly nonlinear membrane transport mechanisms and very fast ion diffusion in combination with a relatively slow protein dynamics.

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