

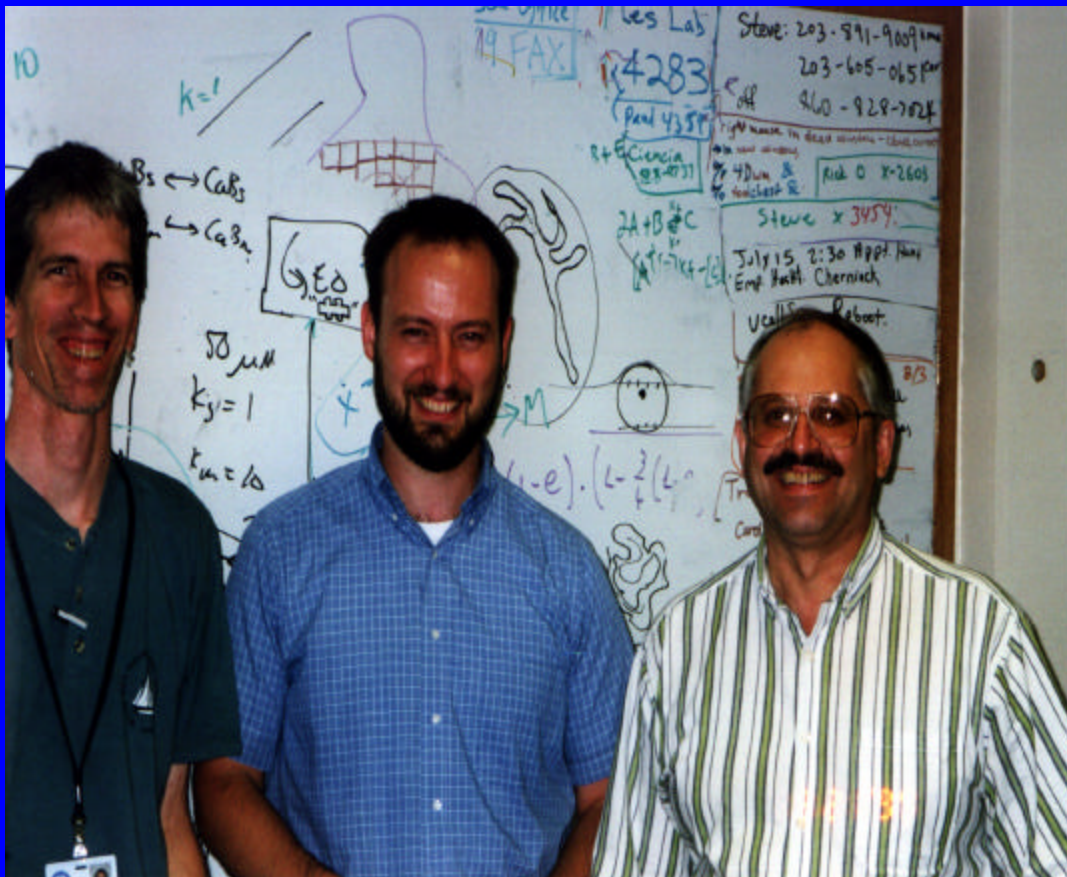
"Every attempt to employ mathematical methods in the study of biological questions must be considered profoundly irrational and contrary to the spirit of biology.

"If mathematical analysis should ever hold a prominent place in biology - an aberration which is happily almost impossible - it would occasion a rapid and widespread degeneration of that science"

-- Auguste Comte, Philosophie Positive, 1830

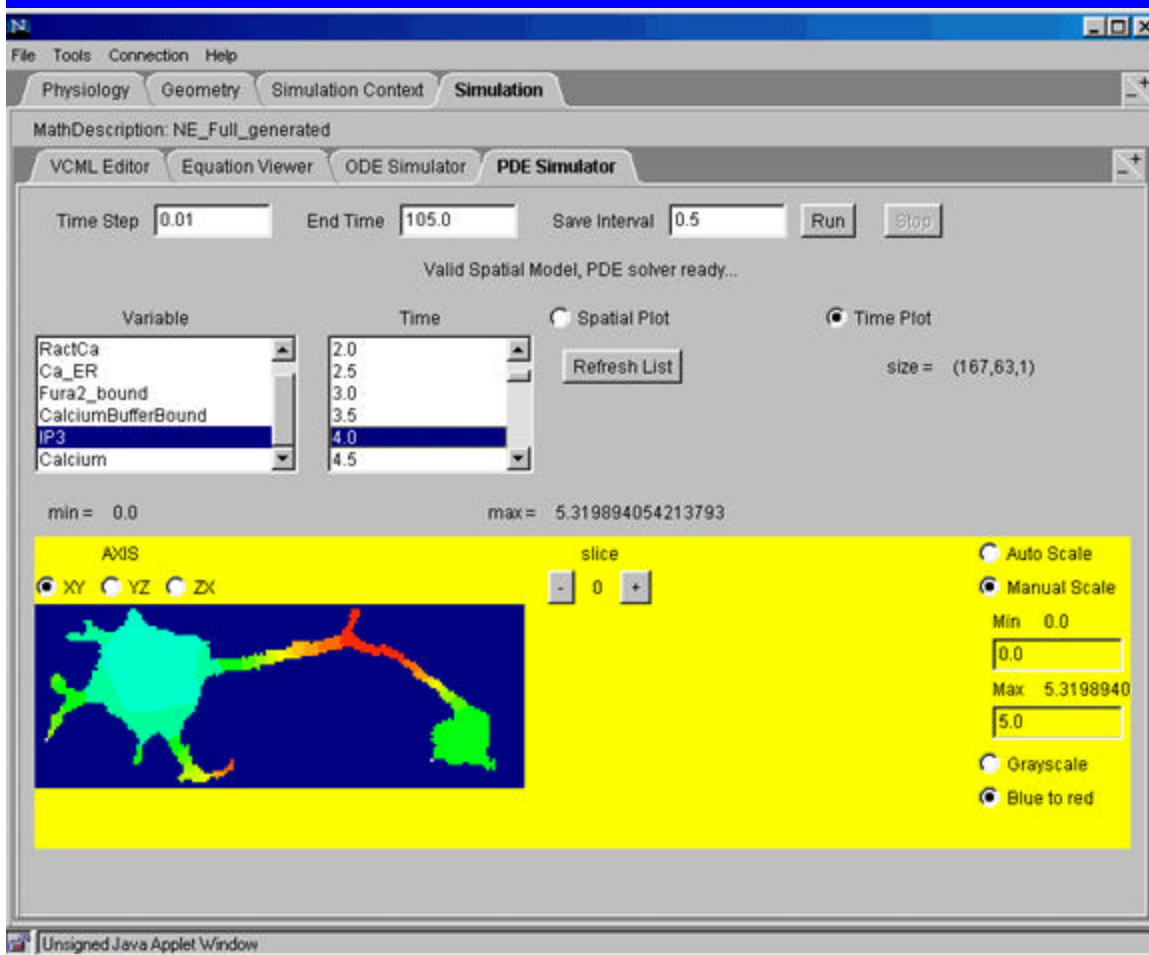
The Virtual Cell Project

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Features of the VC Modeling Environment



- Designed to be used Interactively with Experiment
- Enables Construction and Testing of Complex Models of Rapid Investigation of Simple Hypotheses
- Geometry from Experimental Images
- Math, Physics, and Numerics are Transparent to an Experimentalist while fully Accessible to a Theorist

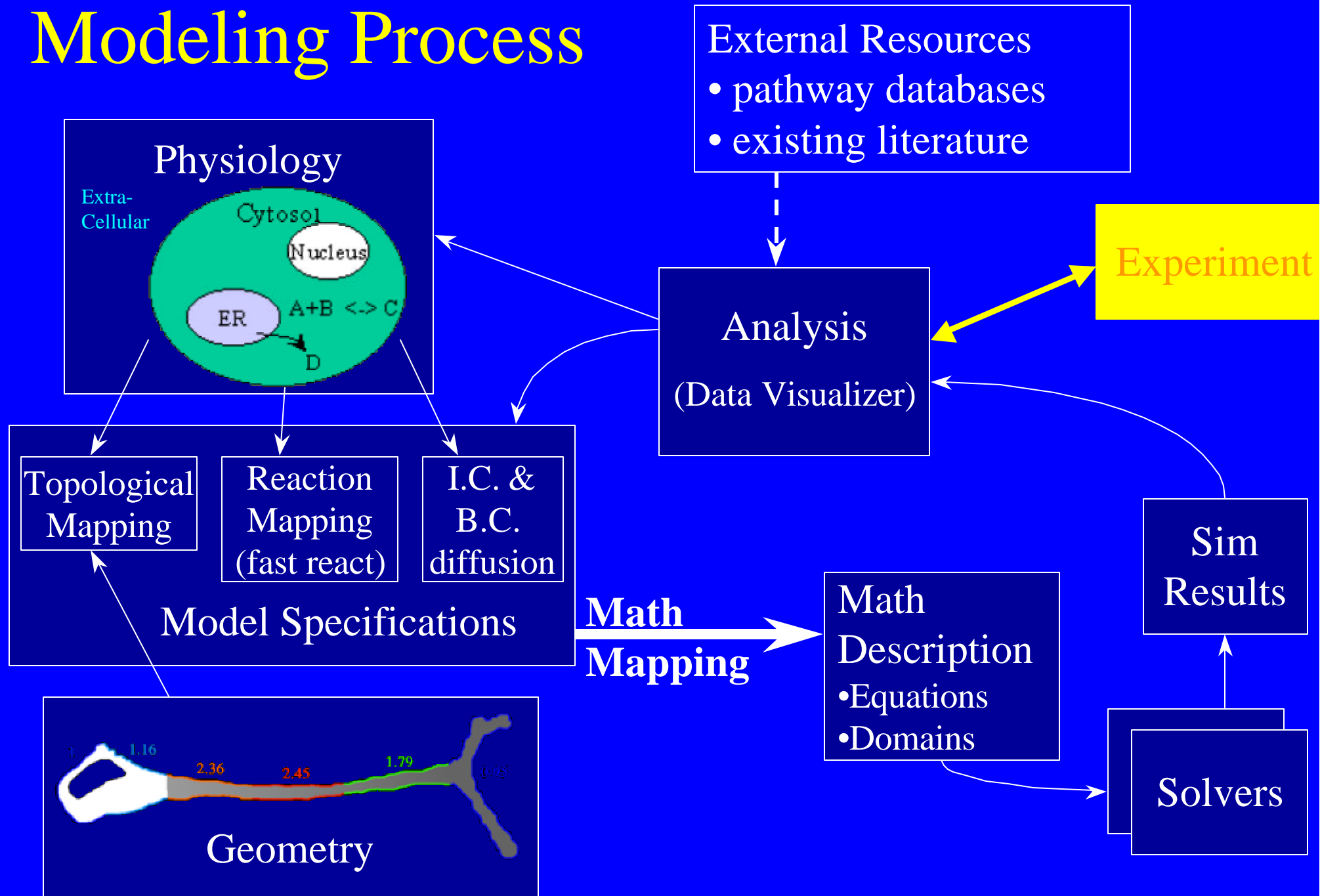
Math and Physics

$$\mathbf{F}_i = -D_i \nabla C_i - z_i m_i C_i \nabla \Phi, \quad m_i = \frac{D_i F}{RT}$$

$$A + B \xrightleftharpoons[k_{-1}]{k_1} C, \quad R_i = k_1 [A] [B] - k_{-1} [C]$$

$$\frac{\mathcal{I} C_i}{\mathcal{I} t} = -\operatorname{div} \mathbf{F}_i + R_i$$

Modeling Process

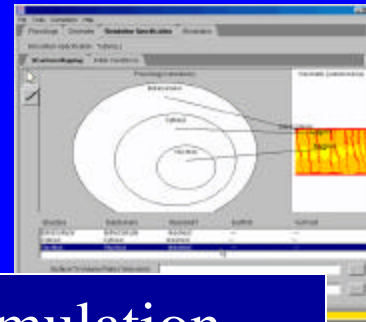


Virtual Cell Database

Physiological
Model



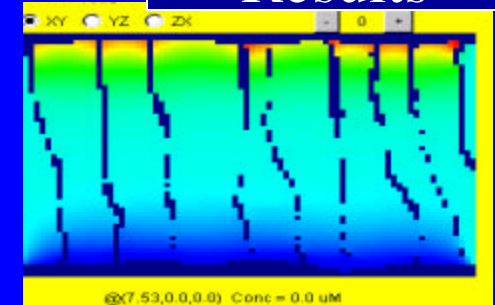
Simulation
Specification



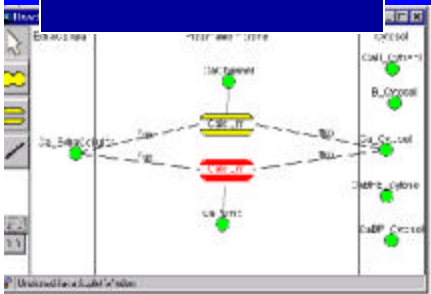
Math
Description

$$\frac{d_Calcium}{dt} = 220.0 \cdot \nabla^2 Calcium$$
$$Calcium_initial = (1000.0 \cdot (y < 5.7) + 0.1 \cdot (y > 5.7))$$

Simulation
Results



Reactions



Geometry



Images

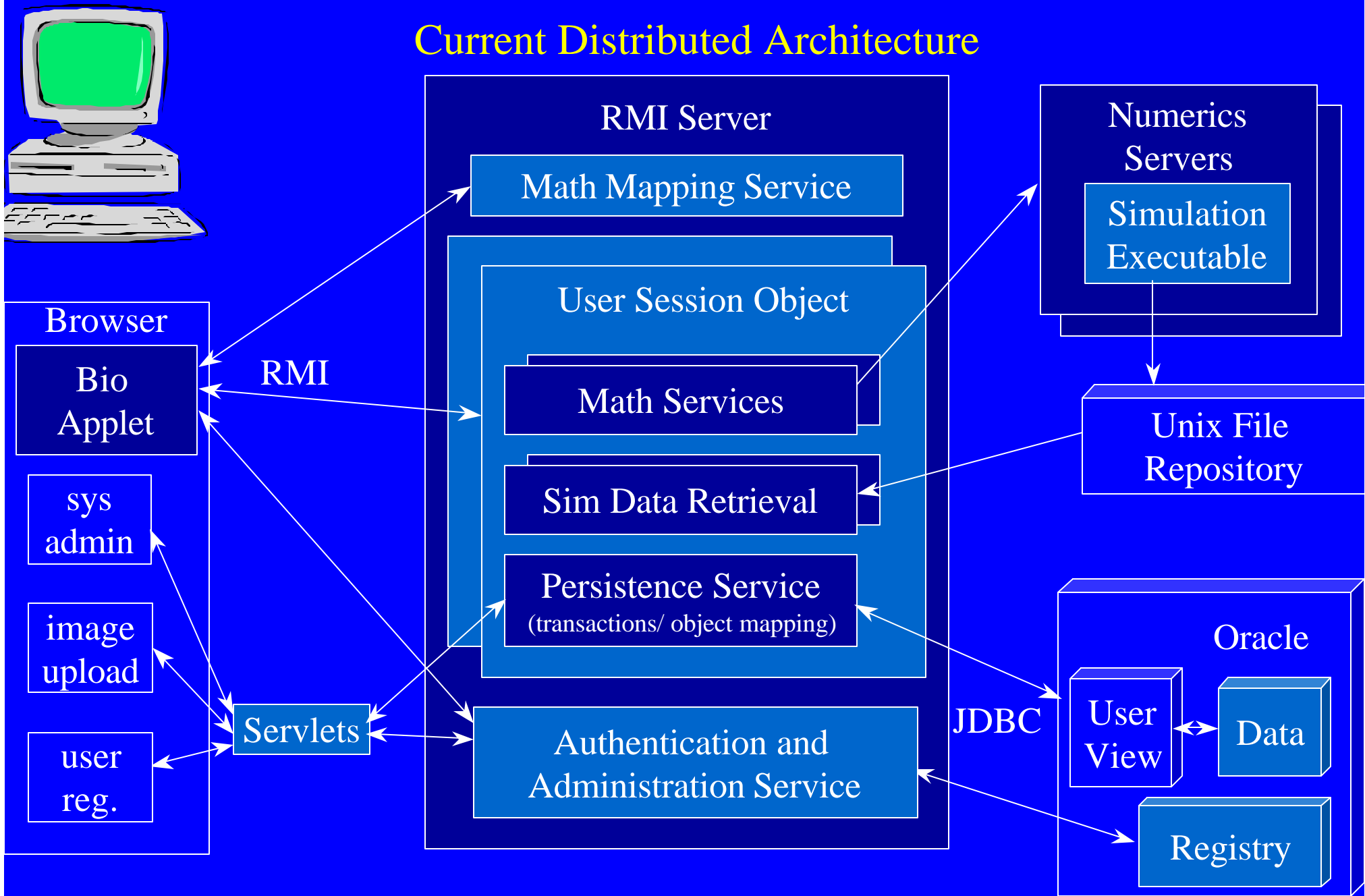
Persistence of evolving models and data (versioning, sharing)

Allows future integration with WWW accessible resources

- Pathway databases (EcoCyc, KEGG, EMP)
- Other modeling tools

Requires development of standard vocabularies for modeling entities.

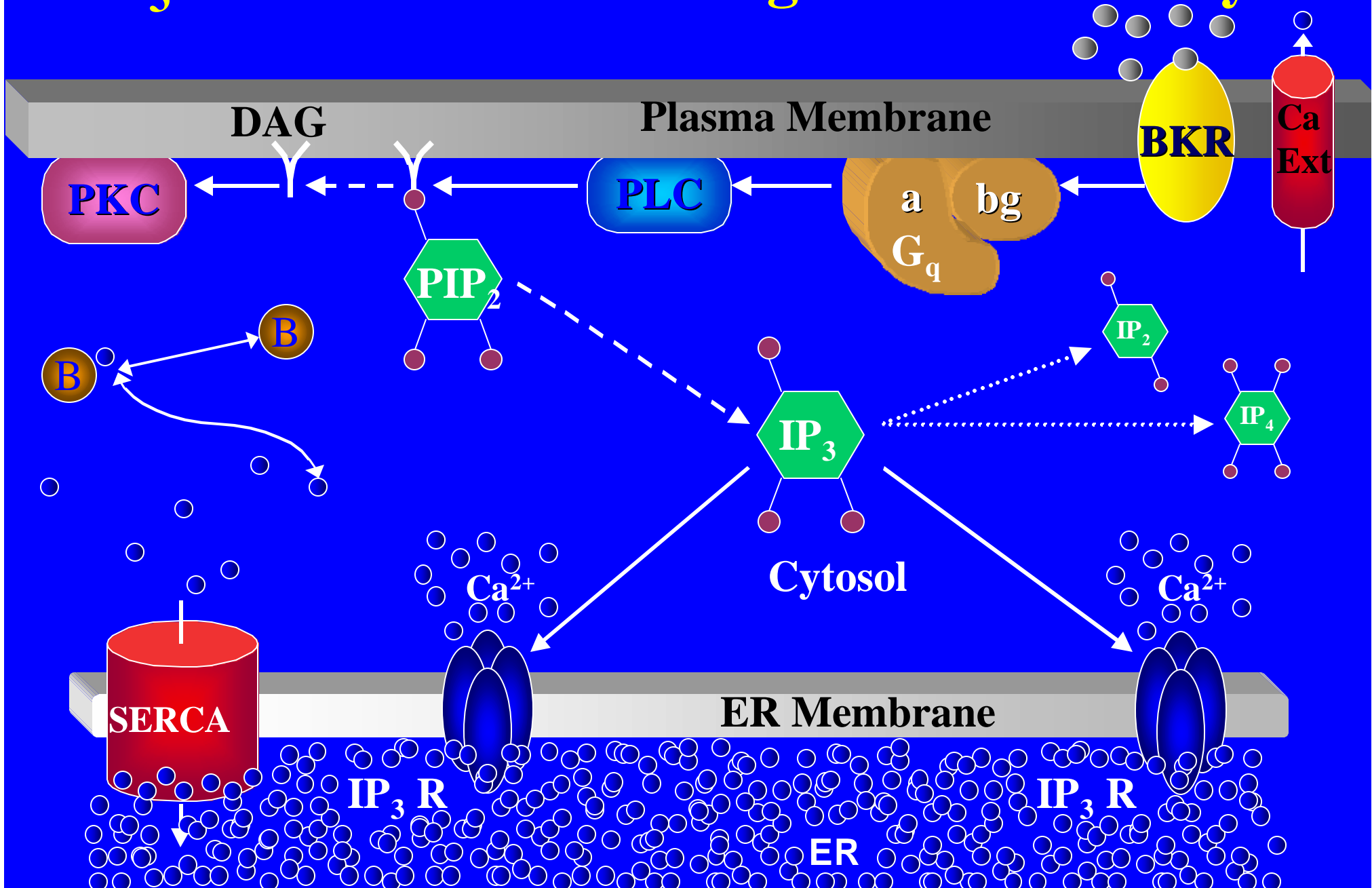
Current Distributed Architecture



Why?

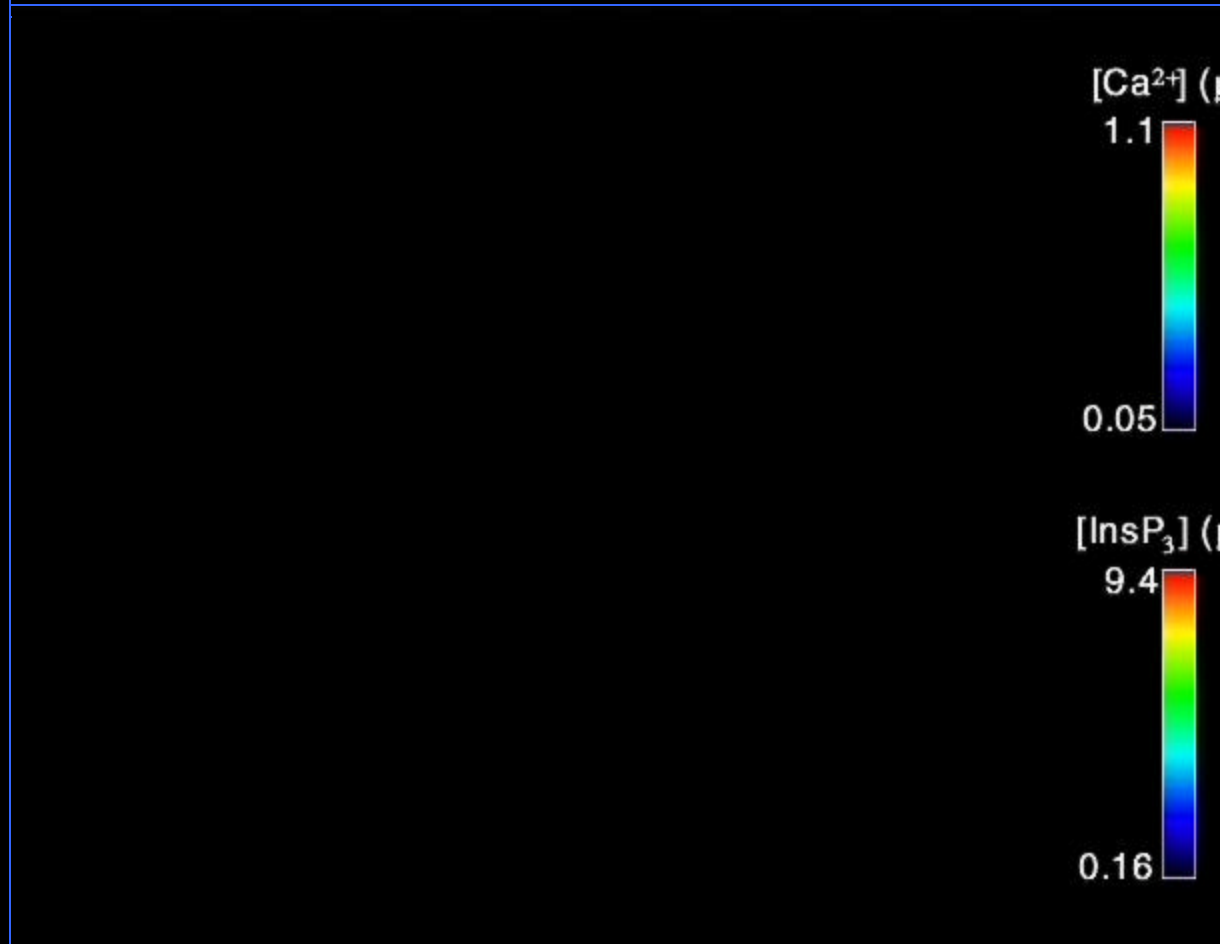
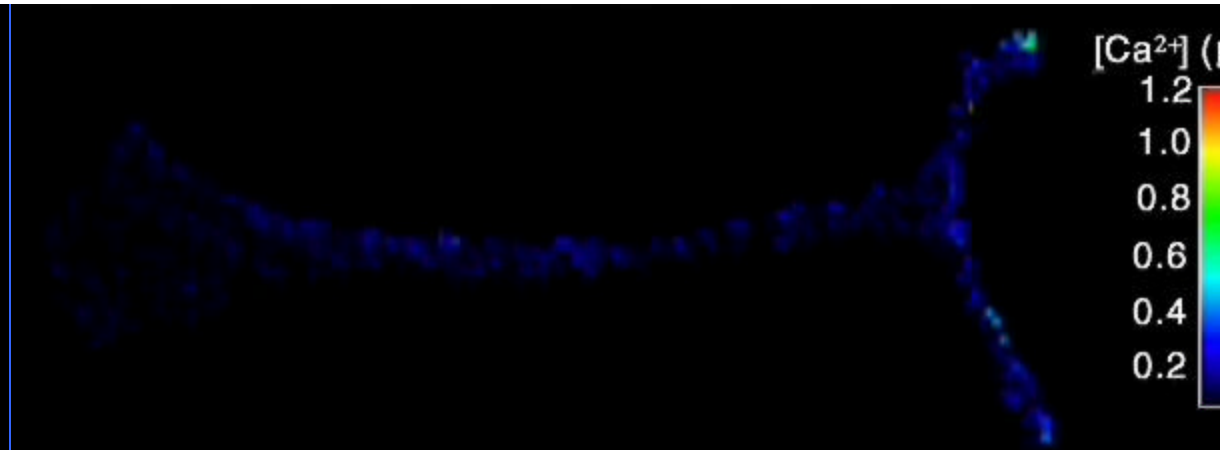
- Explore the fit of mechanistic hypotheses
- Make new predictions that can be tested experimentally
 - Results could either strengthen a model or force us to modify hypotheses
- Show species that can't be visualized experimentally
- Examples: calcium wave in a neuronal cell, long term depression in cerebellar Purkinje cells, fertilization-wave in frog egg, mitochondrial respiration, RNA granule trafficking, nuclear envelope breakdown, epithelial cell transport.

IP₃ Production / Ca²⁺ Regulation Pathways

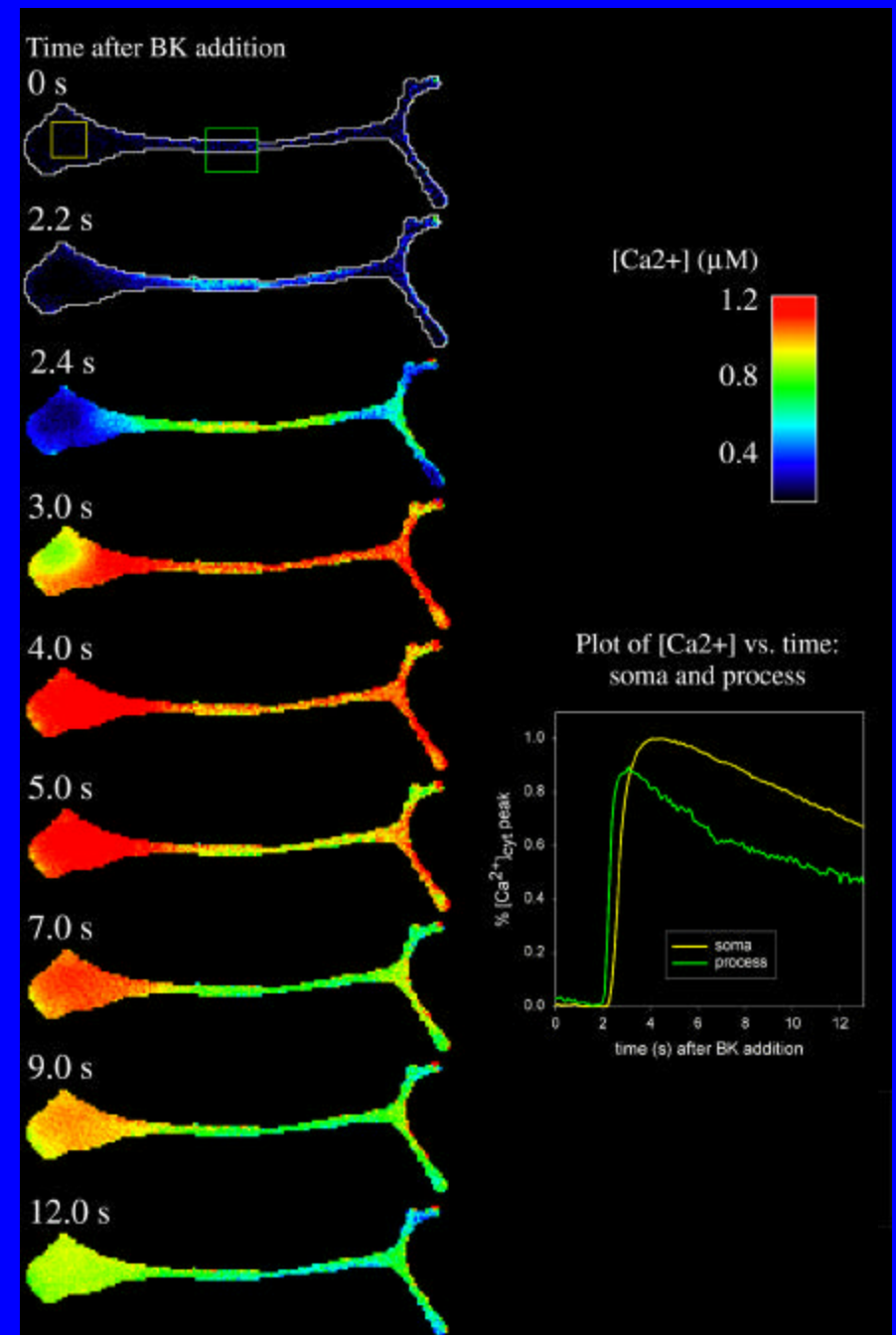
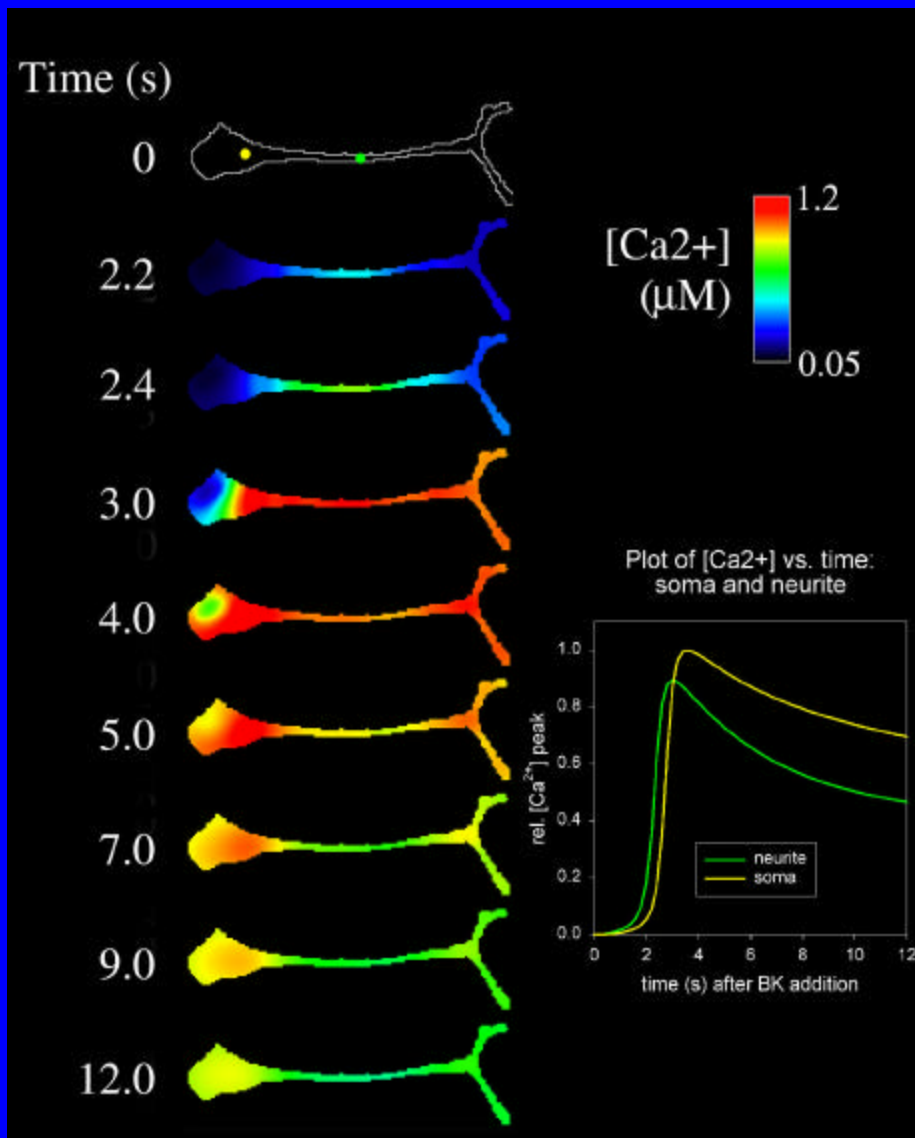


Bradykinin Induced Calcium Wave in a Neuroblastoma Cell

Modeling Result for
 Ca^{2+} and InsP_3



Comparison of Simulation and Experiment



"What are we to do with the enormous cornucopia of genes and molecules we have found in living cells? How can we see the wood for the trees and understand complex cellular processes? Although we poor mortals have difficulty manipulating seven things in our head at the same time, our silicon protégés do not suffer this limitation. ...The data are accumulating and the computers are humming. What we lack are the words, the grammar and the syntax of the new language." -- Dennis Bray, 1997