

# High-throughput whole-cell spatial modeling

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Robert F. Murphy

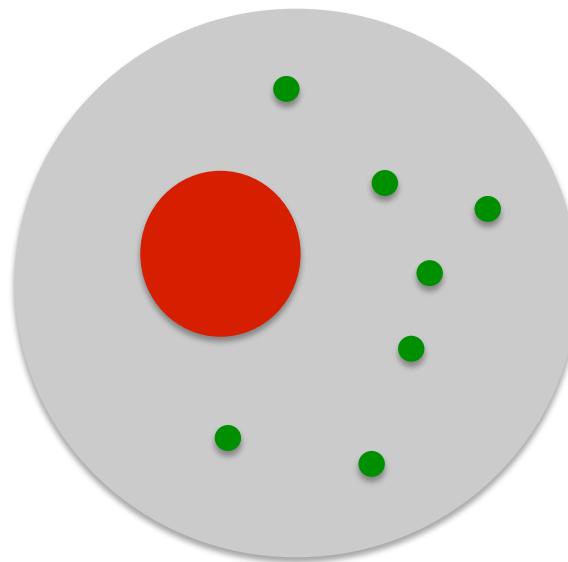


# Motivation

- Modeling cellular dynamics provides key insight into cellular response and behavior
- Spatially resolved approaches increase model accuracy and may reveal novel responses
- Spatially driven dynamics may help in identifying, understanding, and treating phenotypes

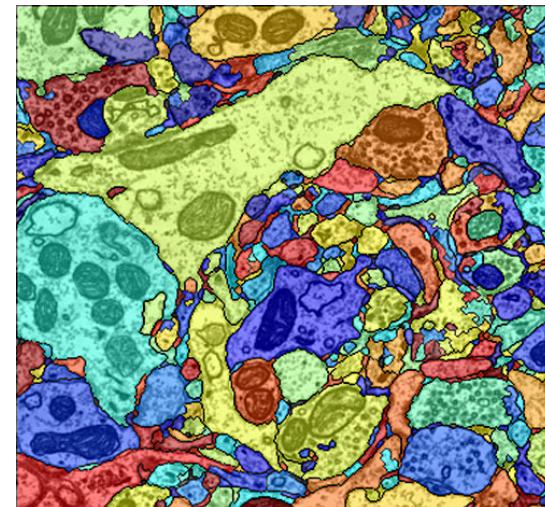
# Spatially resolved modeling: Previous approaches

Vastly simplified geometries



Manual segmentation

Neuronal EM<sup>1</sup>

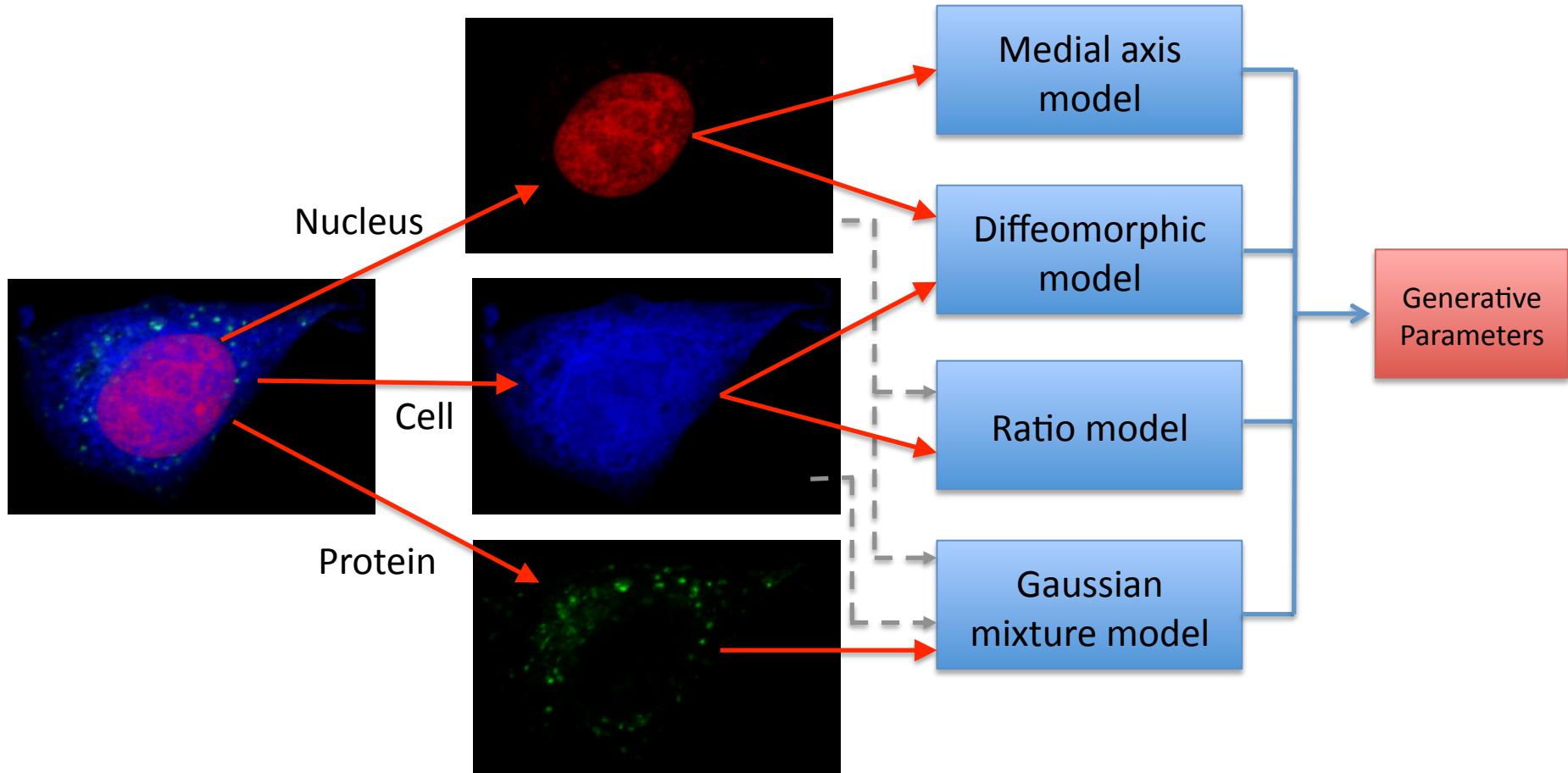


1. Vazquez-Reina, A., Gelbart, M., Huang, D., Lichtman, J., Miller, E., & Pfister, H. 2011<sup>3</sup>

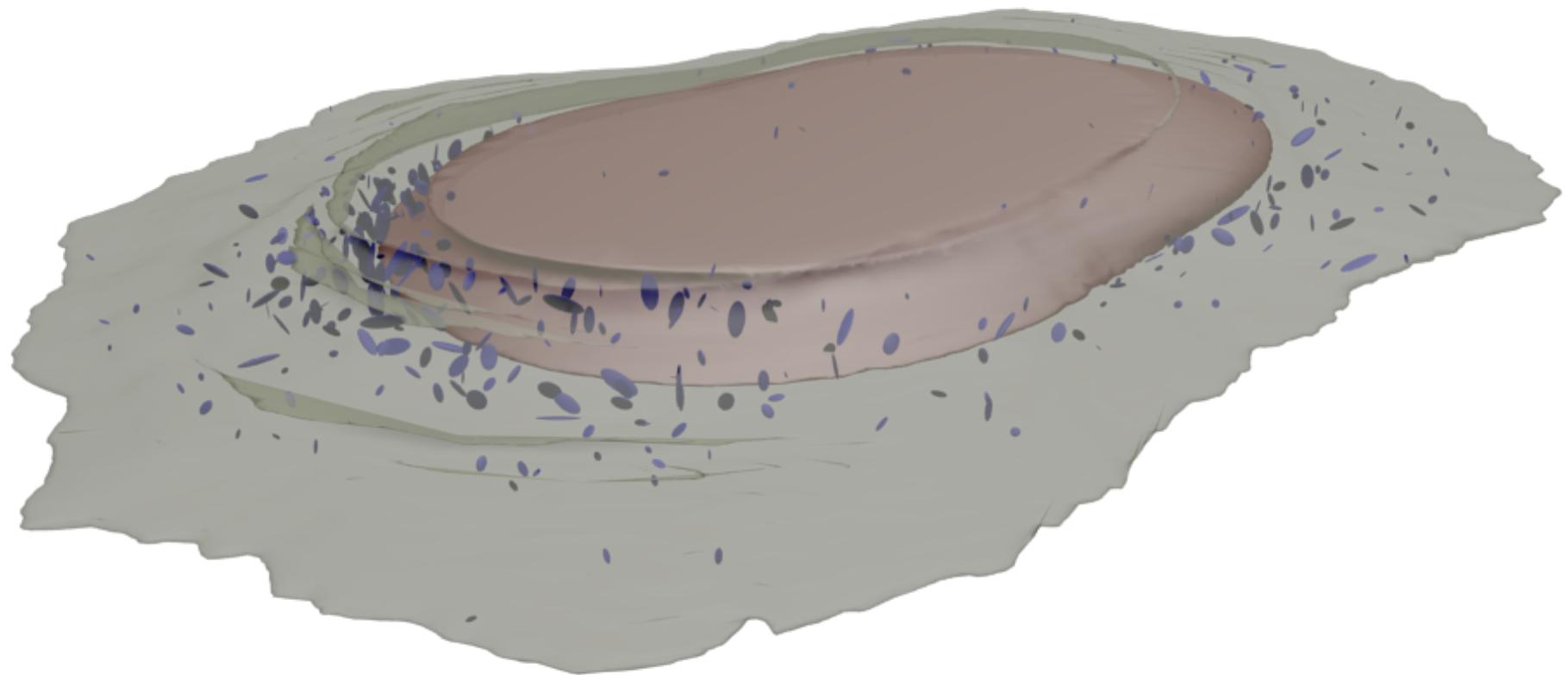
# Benefits of generative models

- Represents organelle localization, size and shape in a conditionally dependent way
- Provides a continuous space for synthesizing and subsequently analyzing changes in cell geometries

# Training generative models of subcellular organization

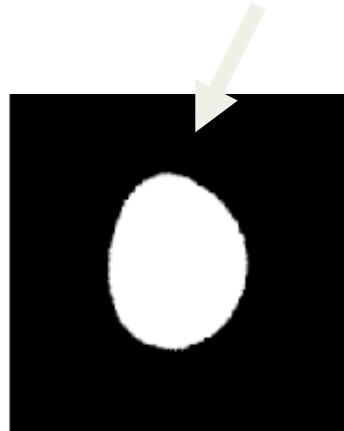


# Creating synthetic cells

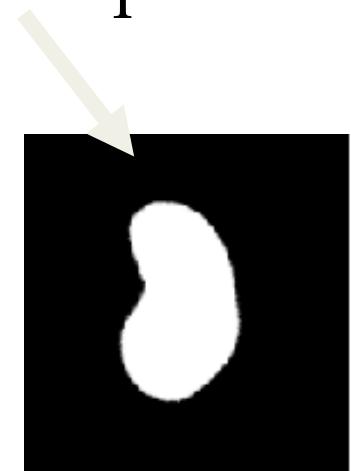


# Diffeomorphic model learning: Non-rigid image registration

Starting shape

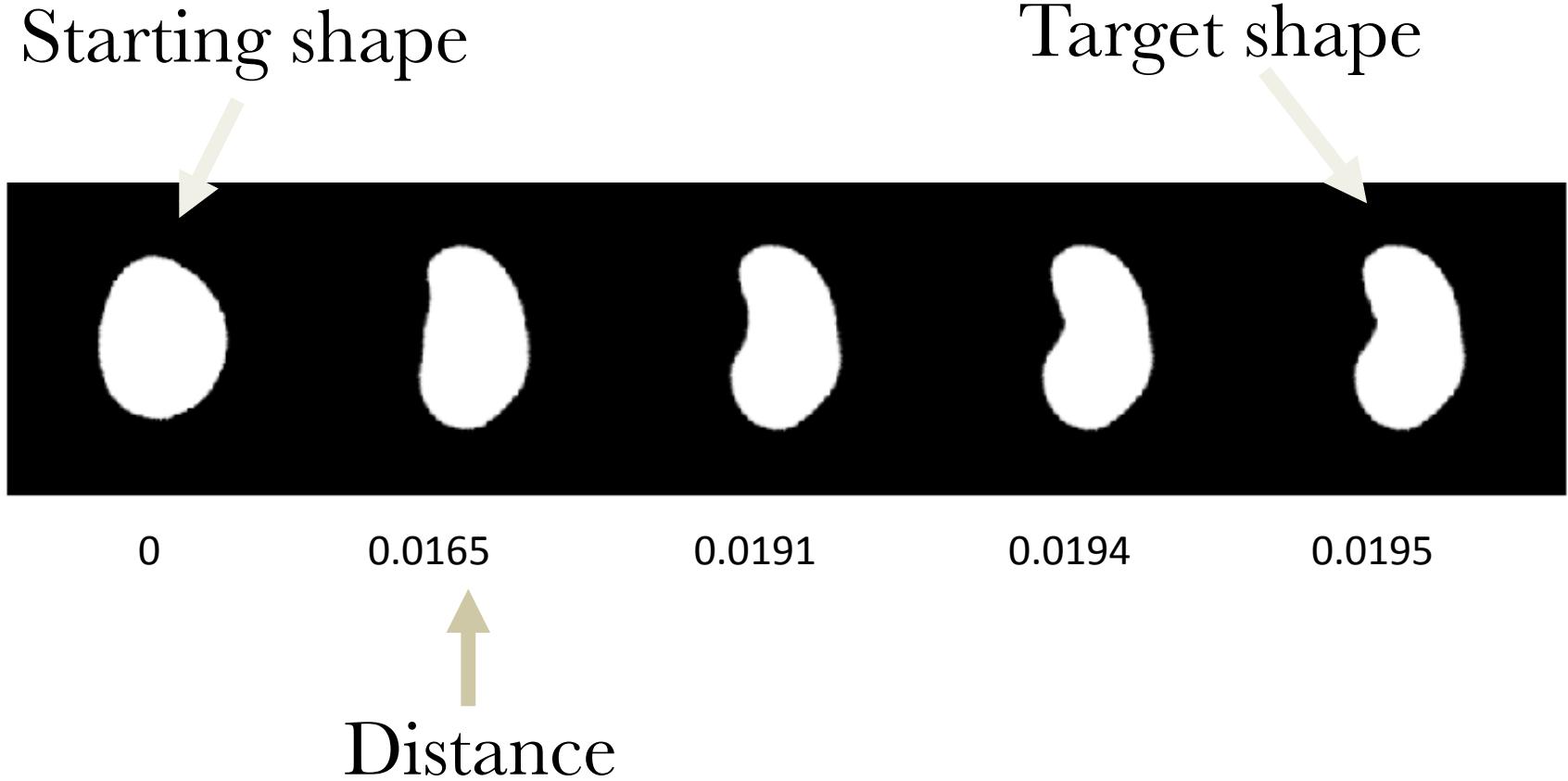


Target shape



1. Rohde G. K., Wang W., Peng T., and Murphy R.F. (2008).

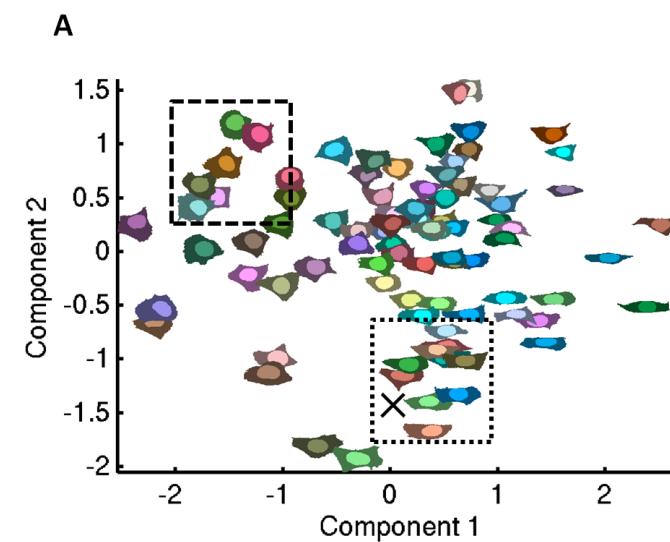
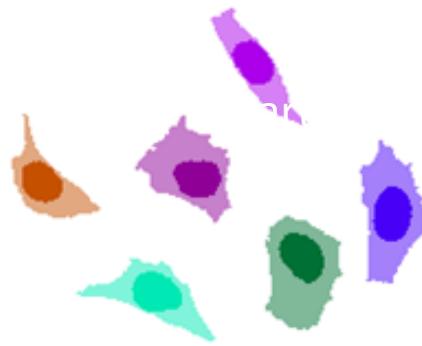
# Diffeomorphic model learning: Non-rigid image registration



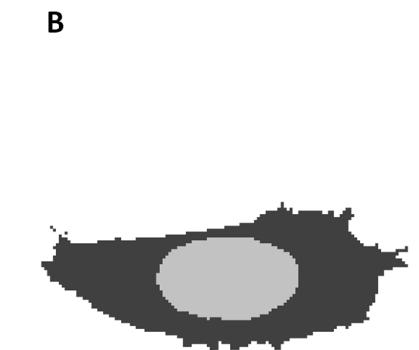
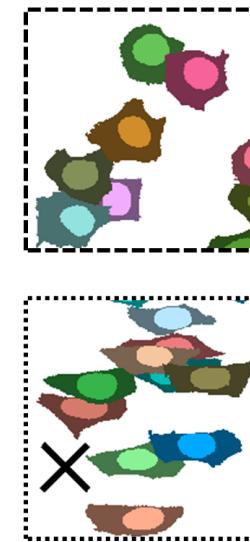
1. Rohde G. K., Wang W., Peng T., and Murphy R.F. (2008).

# Generating synthetic cells

- Use multi-dimensional scaling to create “shape space”
- Sample a point in this shape space
- Generate synthetic cell by deforming nearby cells

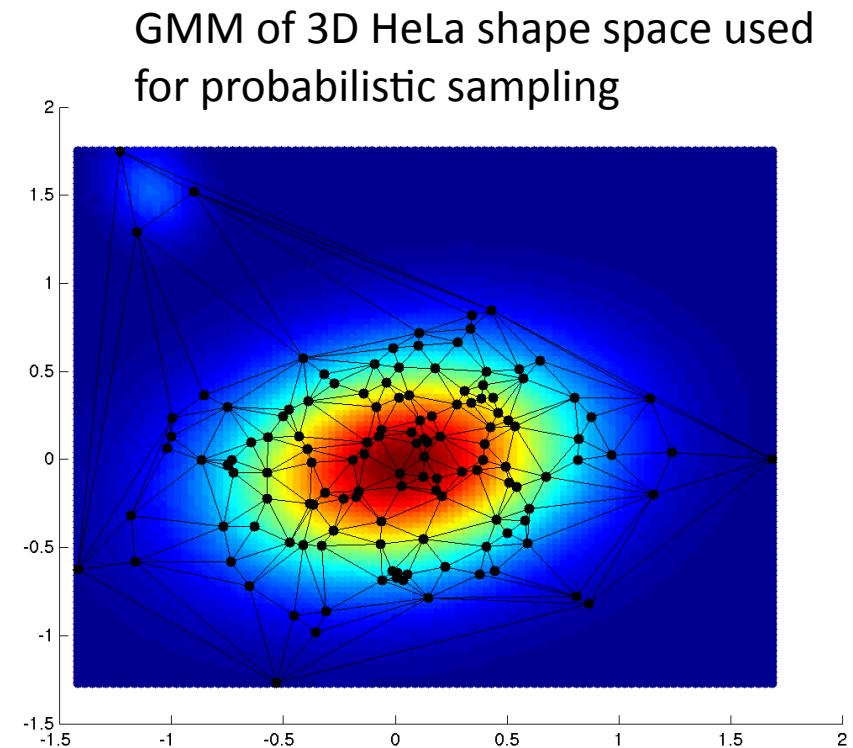


Cellular and nuclear  
shapes



# Exploring cellular parameter space

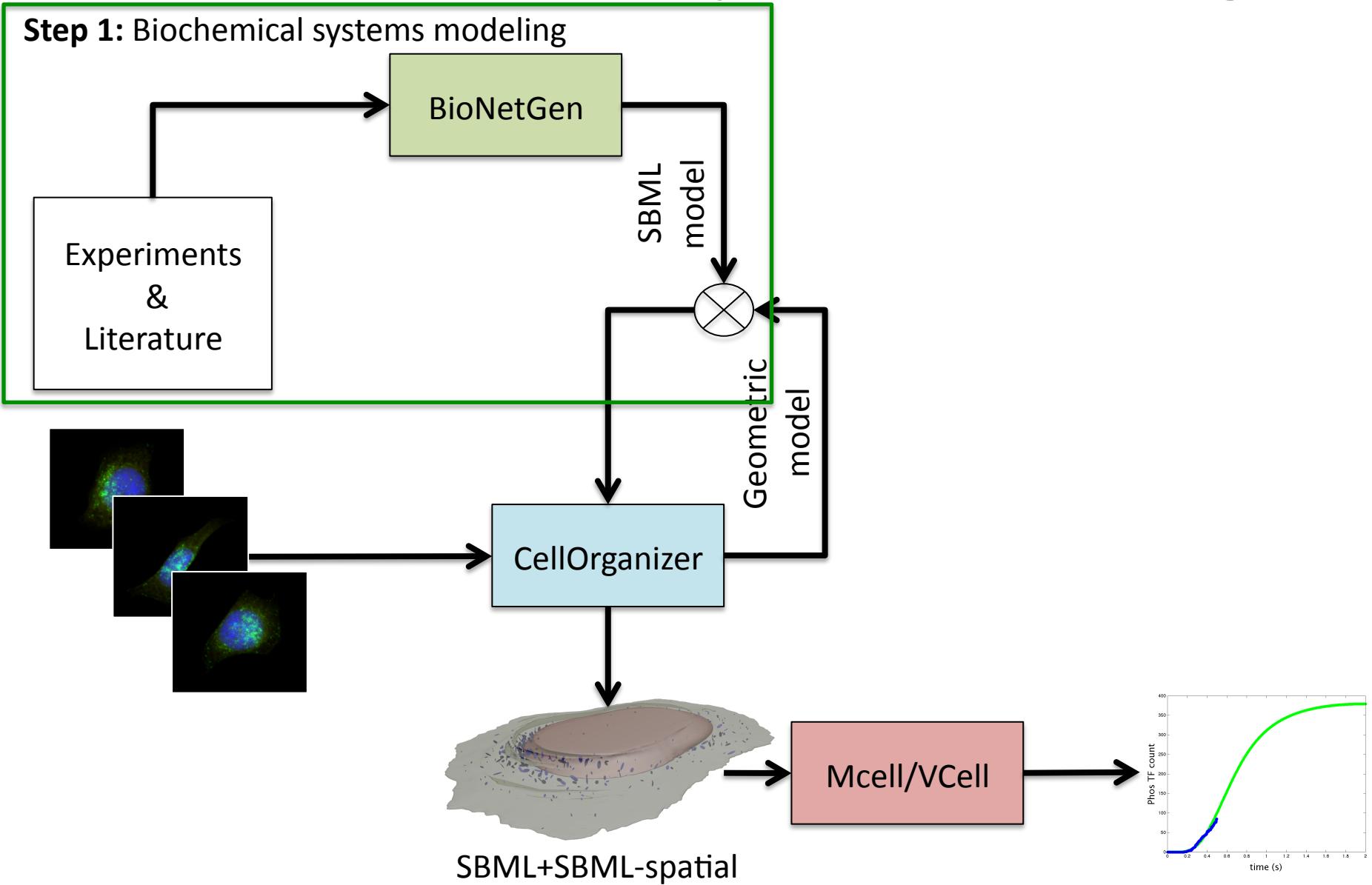
- Sample modal instances
- Sample outlier instances
- Sample a sequence of instances



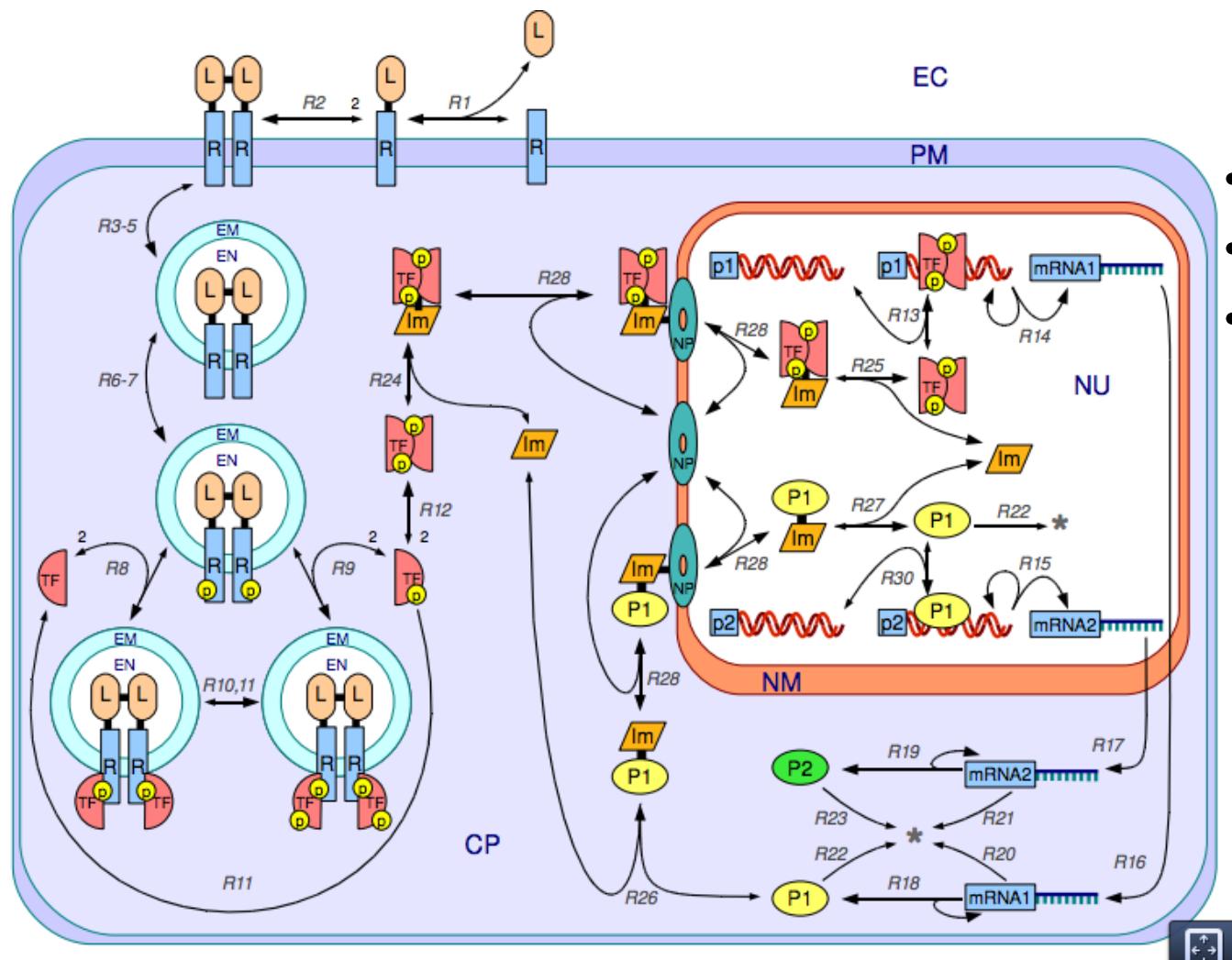
# High-throughput spatially realistic simulations

- Study the effects of spatial variance caused by
  - Cell cycle
  - Diseases
  - Drugs
  - Inherent cell variance
- Model large systems with high spatial realism
- Validate generative model accuracies

# Automation of spatial modeling



# Example system



- 354 reactions
- 78 species
- 7 “compartments”

# Compact rule-based models

## Traditional Modeling

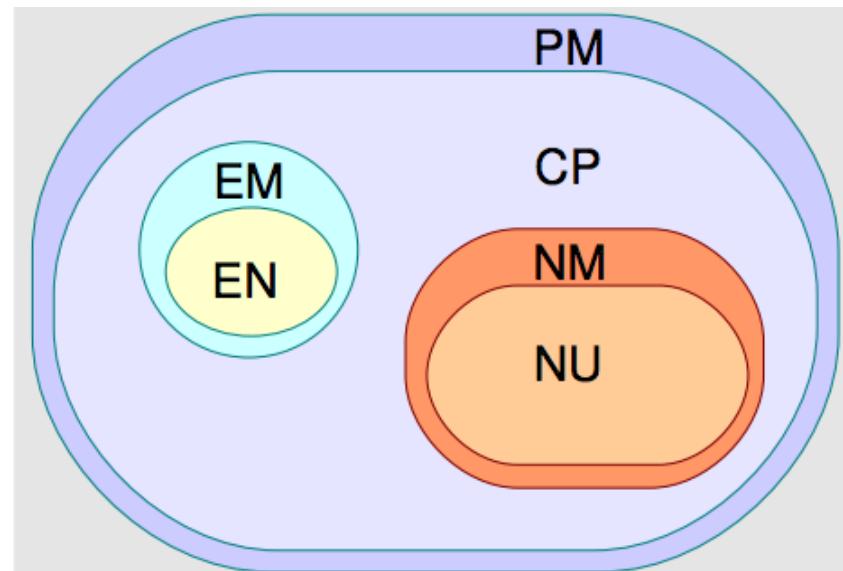
354 reactions

78 species

## Rule-Based Modeling

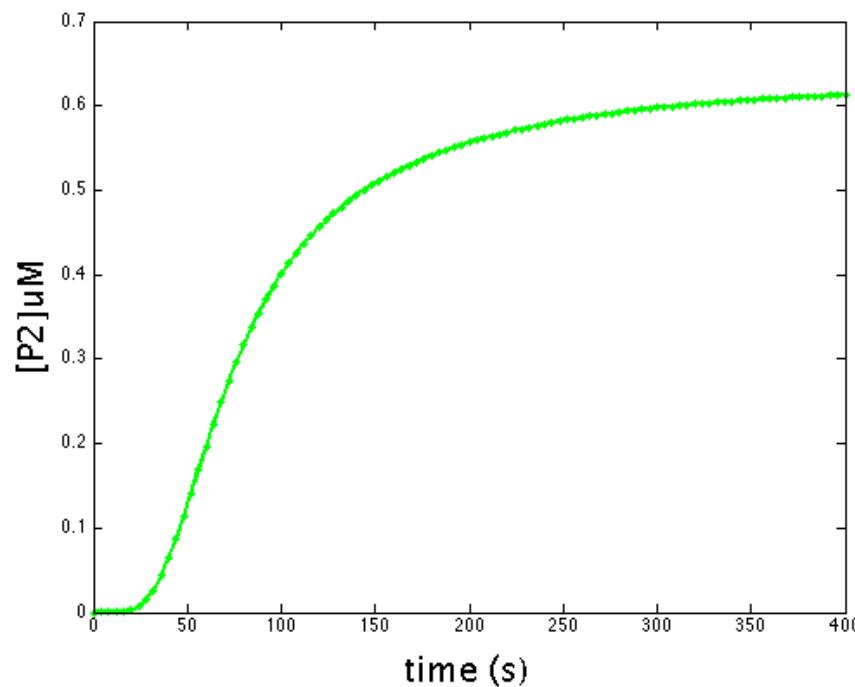
30 rules

10 molecule types

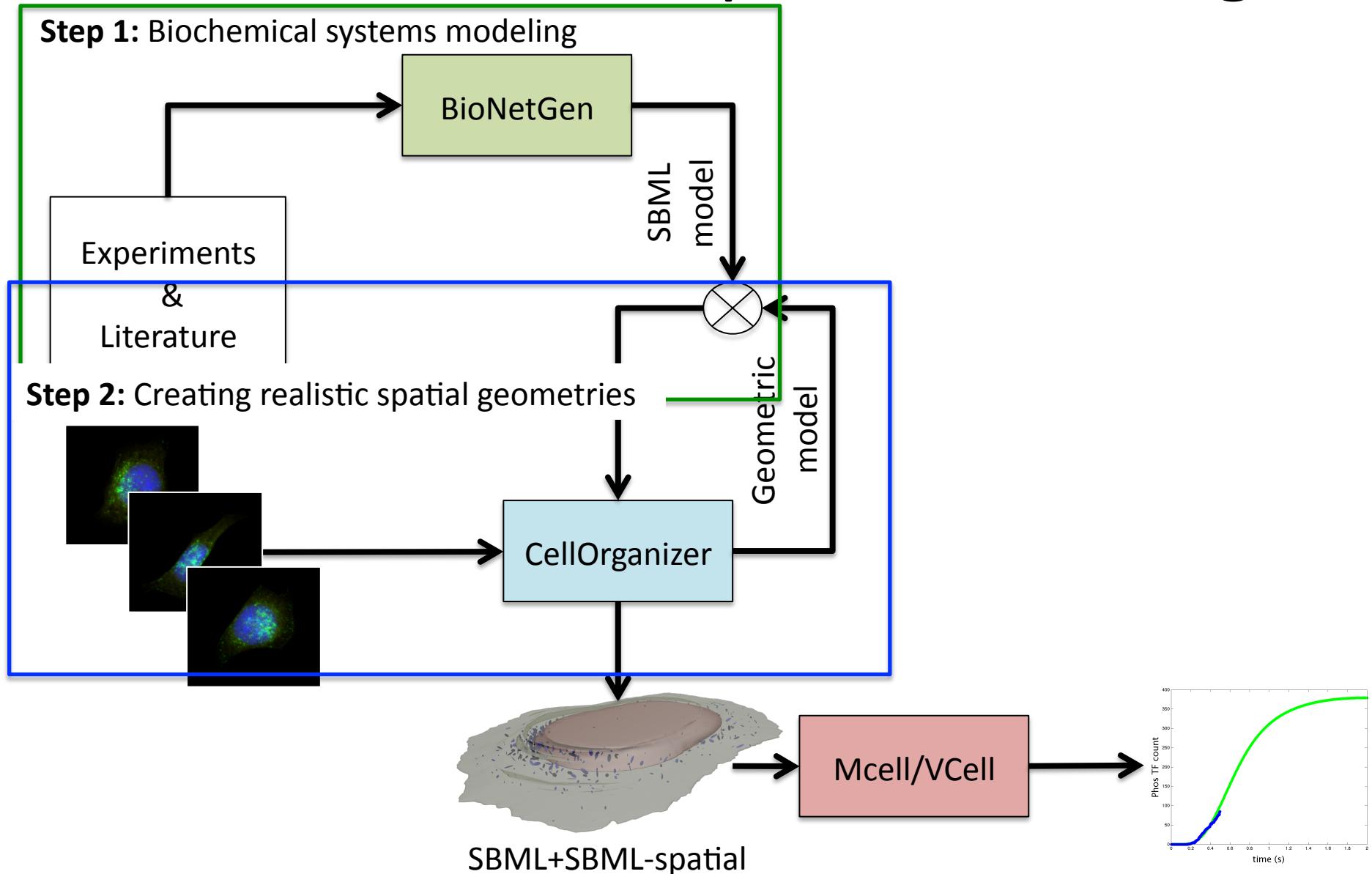


# ODE modeling

- Obtain a general idea of system behavior
- Check simulation to confirm “reasonable” parameters/behaviors

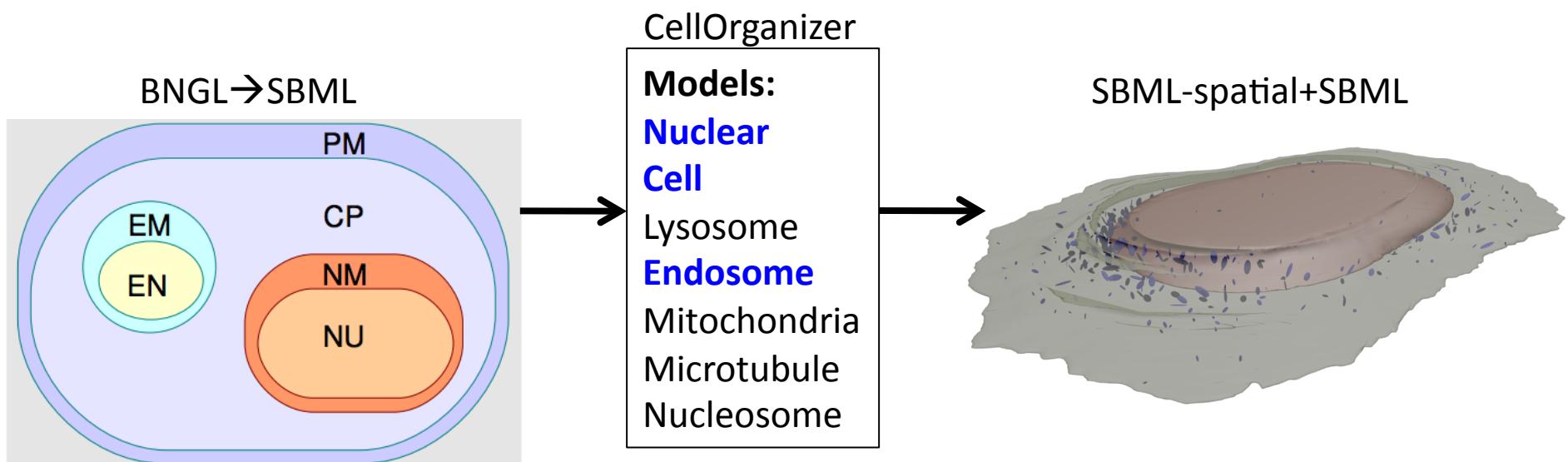


# Automation of spatial modeling

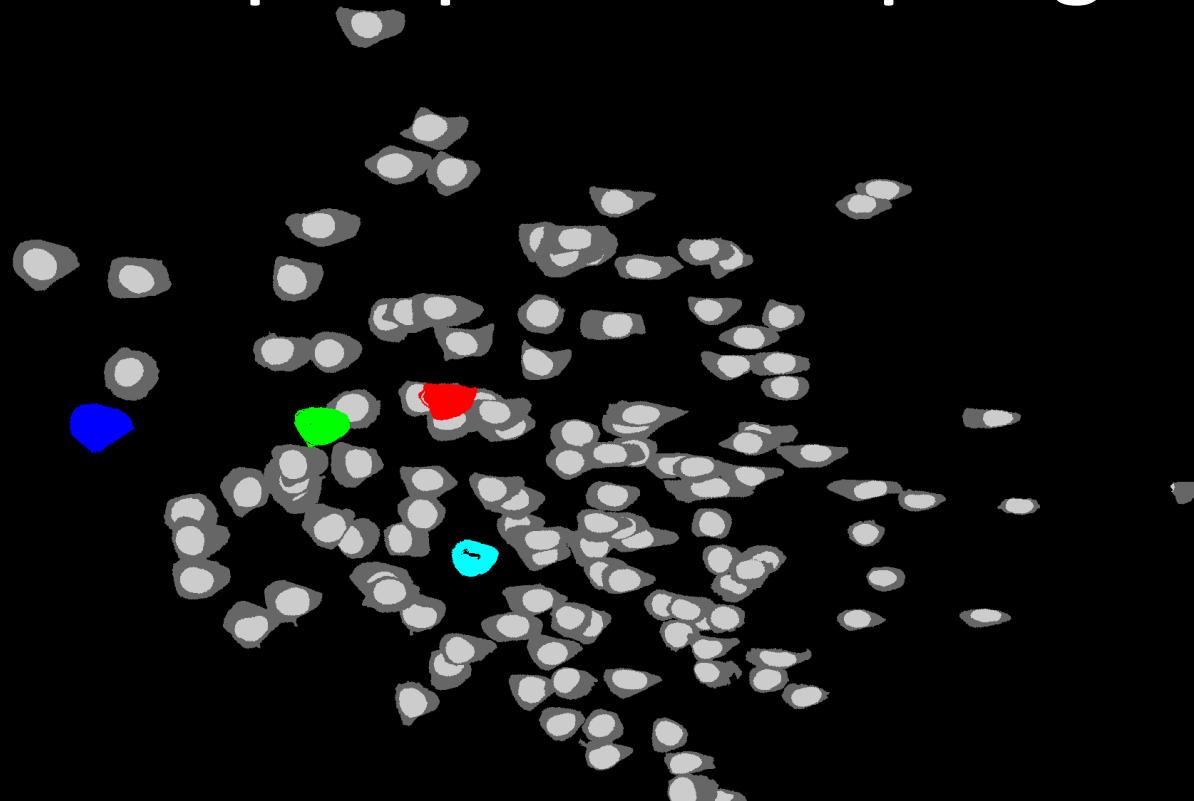


# Identifying compartments

- Extract compartment information from SBML
- Identify relevant models using string matching
- Generate SBML-spatial instances with biochemistry and necessary geometries

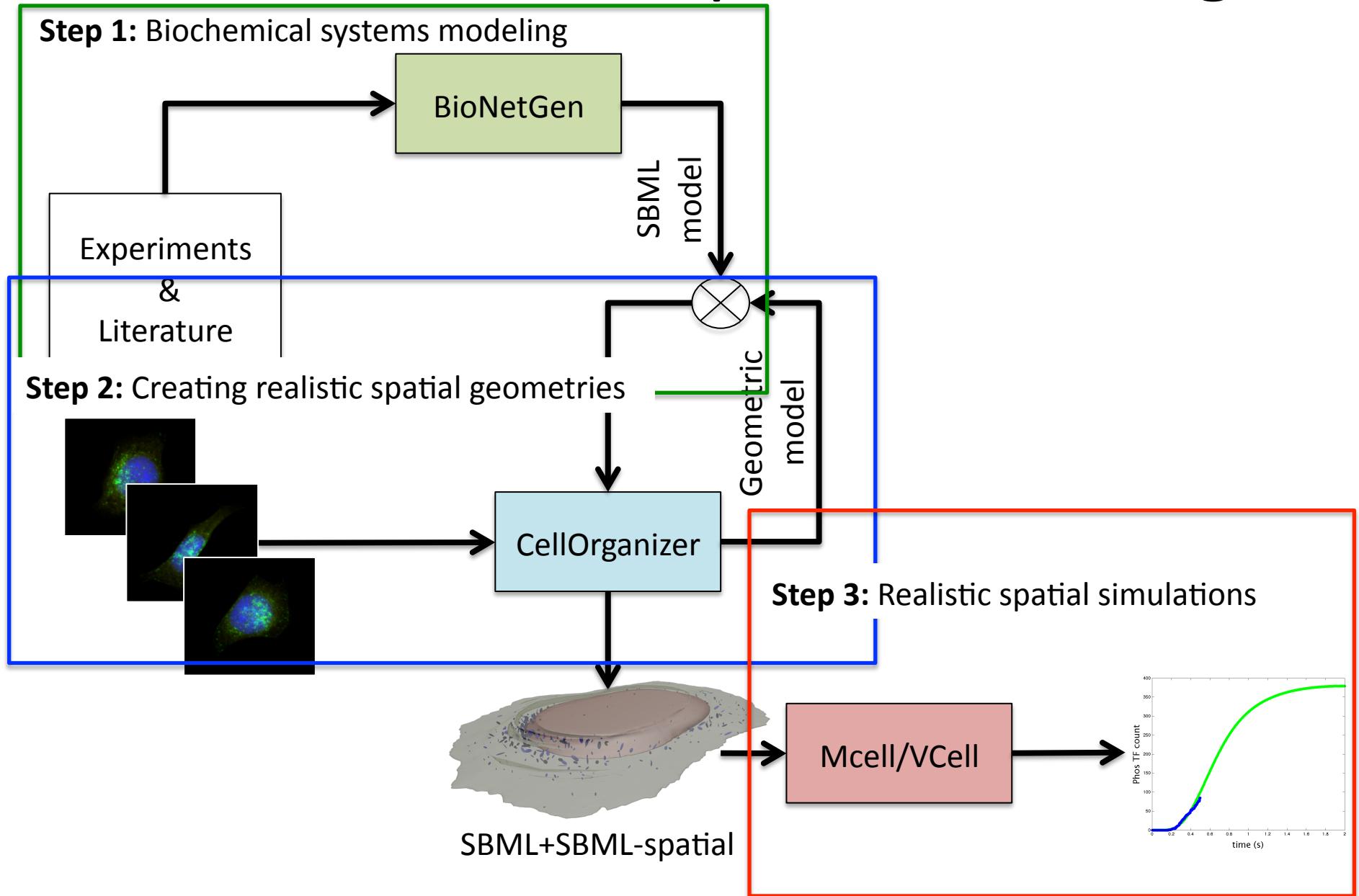


# Shape space sampling



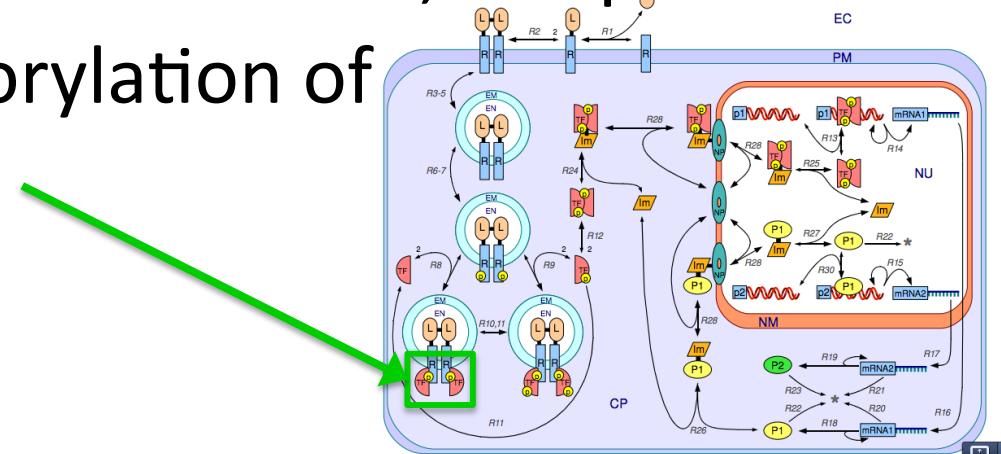
Grey – Experimentally observed  
Colored – Simulated synthetic cells

# Automation of spatial modeling



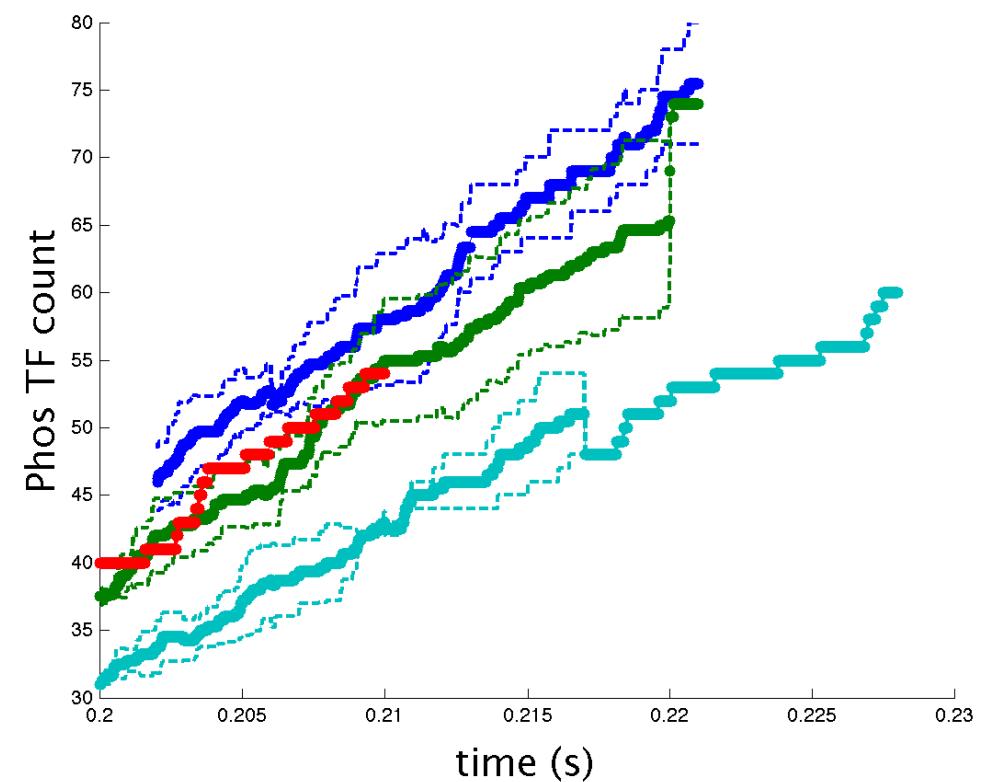
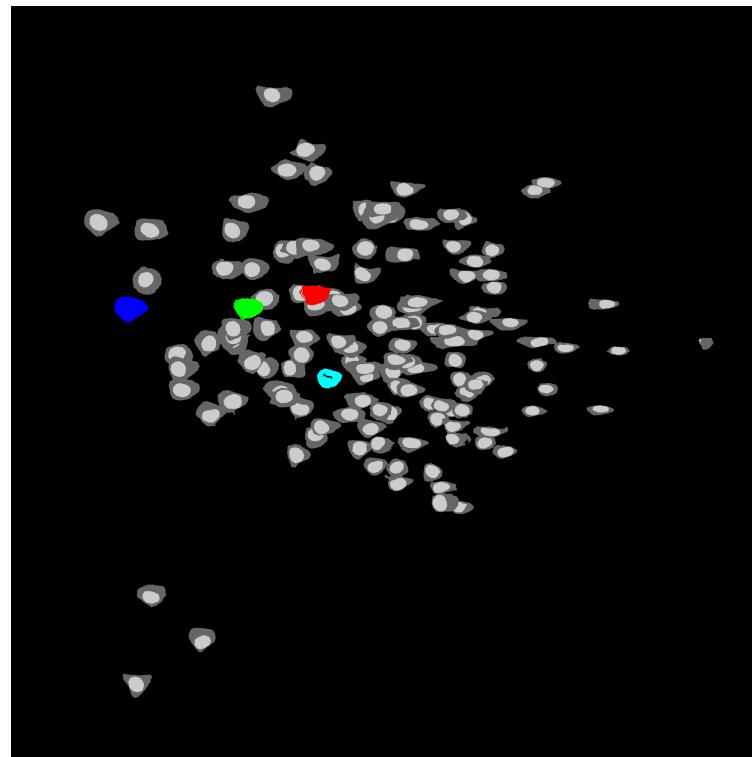
# MCell simulation results

- “Prime” simulation to 0.2 seconds using compartmental ODE model
- Export as SBML file
- Append geometric data using SBML-spatial
- Import into MCell/CellBlender
- Run full cell model 354 reactions, 78 species
- Analyze the phosphorylation of transcription factors



# Cell-shape dependent dynamics

- Cells that are closer in shape space responded more similarly than distant cells



# Conclusions

- SBML/SBML-multi can be used to encode compact rule-based models for complex biochemical networks using BNGL
- CellOrganizer can be used to read SBML files and generate the necessary realistic geometries when models are available
- SBML-spatial can be used to export these spatially resolved biochemical systems from CellOrganizer
- Spatially resolved simulations can be performed in high-throughput using tools such as MCell to study the impact of cellular organization on response

# Acknowledgments

## Automation of simulations

- Jose Juan Tapia
- Markus Dittrich
- Rohan Arepally
- Jacob Czech

## CellOrganizer

- Gregory Johnson
- Ivan Cao-Berg

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Robert F. Murphy

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# **Shameless Plug**

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- Students create R03 style grant proposals
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- Students conduct research and provide progress reports

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