

Cellular-level simulation

Heejo Choi, Jasmine Johnson, Raj Raina
March 8, 2017

Model internal organization of a cell over time

How does the shape of two cells coming together affect their adhesion?

How does cell shape affect the spatial and temporal dynamics of cell signaling?

“Which molecules interact at which place and in which sequence, in order to orchestrate a specific cellular function?”

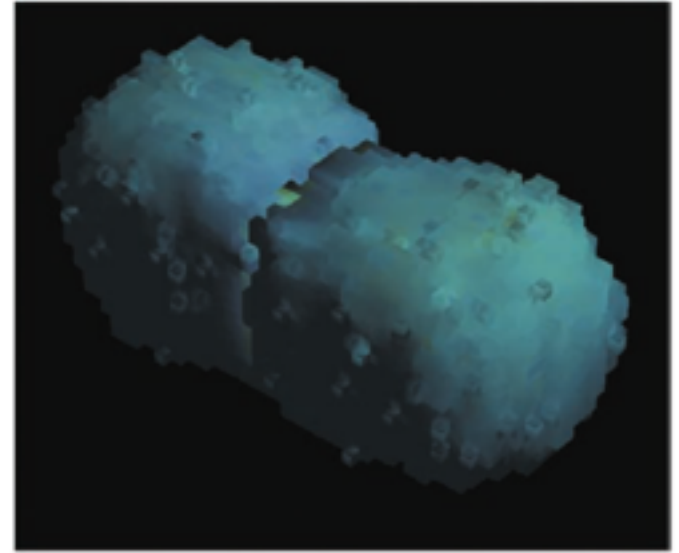
Computational approaches for reaction-diffusion simulation

Simmune	Virtual Cell	ReaDDy
continuum	continuum	particle-based

- Divide space into voxels
- Monitor concentration of each molecule type
- Update concentrations according to reactions and diffusion

- Particles represent molecules
- Particles diffuse and react

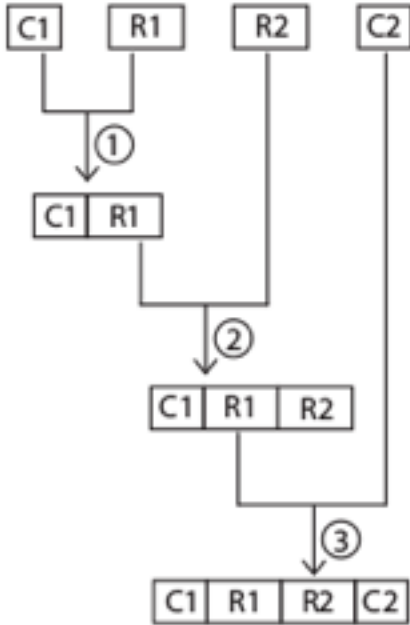
Computational modeling of cellular signaling processes embedded into dynamic spatial contexts



Bastian R Angermann, Frederick Klauschen, Alex D Garcia, Thorsten Prustel, Fengkai Zhang, Ronald N Germain & Martin Meier-Schellersheim | Nature Methods | March 2012
National Institutes of Health

Heejo Choi

Simmune: software for reaction-diffusion simulations



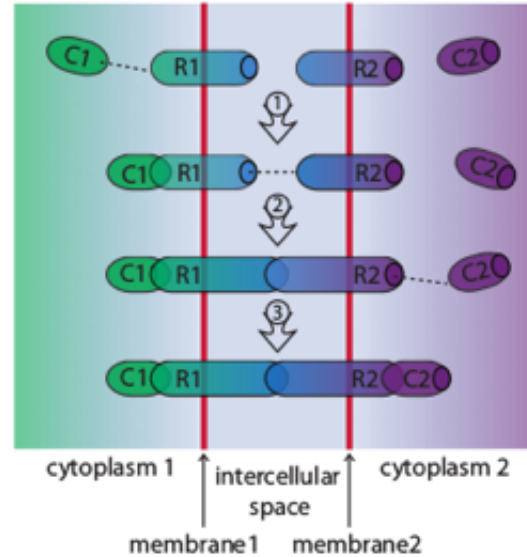
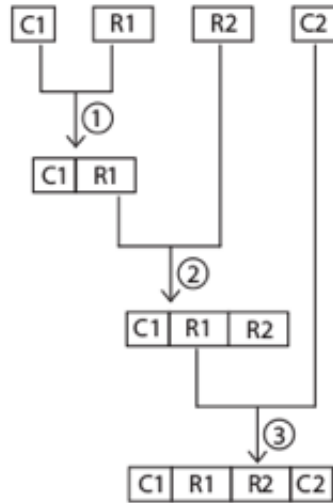
Version 1 (2006)

- User-provided rule-based interactions
- Space discretized into cubic volume elements
- Each species represented by their concentration
- At each timestep: perform local reactions & diffusion

Version 2 (2012)

- Automatic generation of local reaction-networks
- Dynamic membrane geometries

Motivating automatic network generation: converting from nonspatial to spatial modeling increases complexity



- cytosolic 1 cytosolic 2 ■
- intracellular membrane-bound ■
- extracellular membrane-bound ■

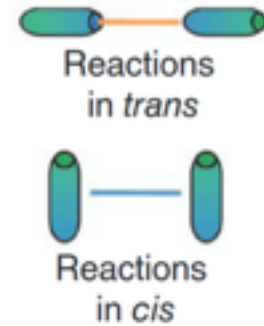
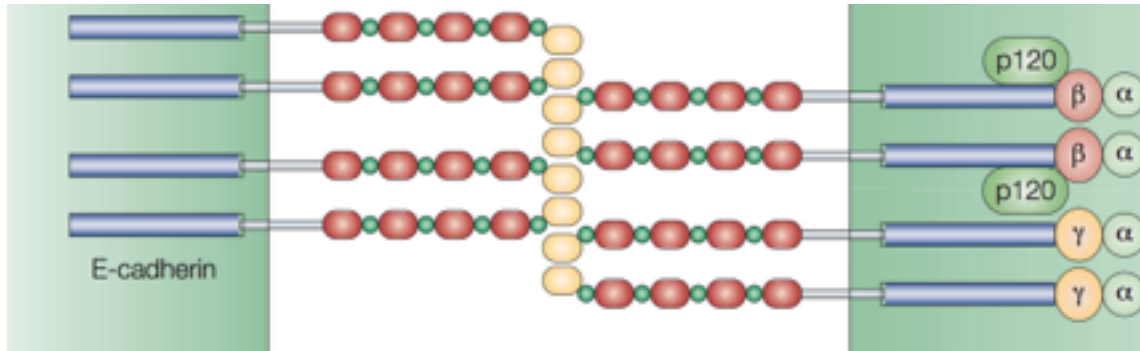
Authors' claim:

“Here we introduce an approach to address these challenges by automatically generating computational representations of complex reaction networks based on simple biomolecular interaction rules embedded into detailed, adaptive models of cellular morphology”

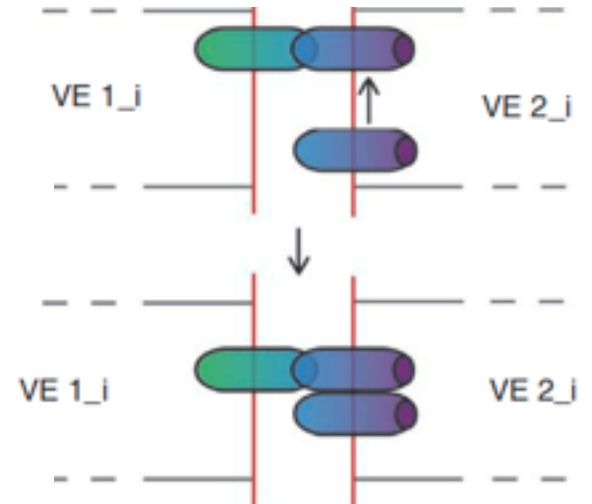
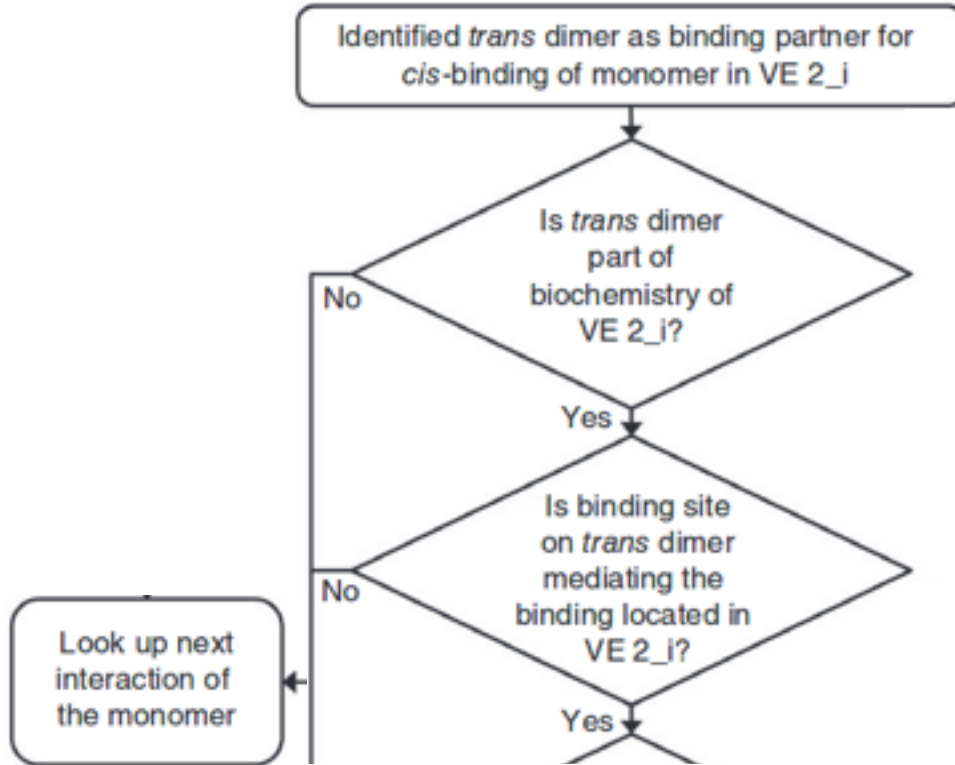
Cellular
adhesion

MAPK activation
in yeast

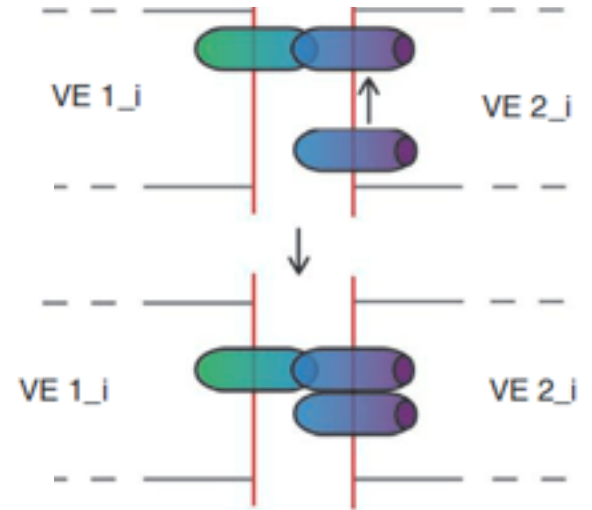
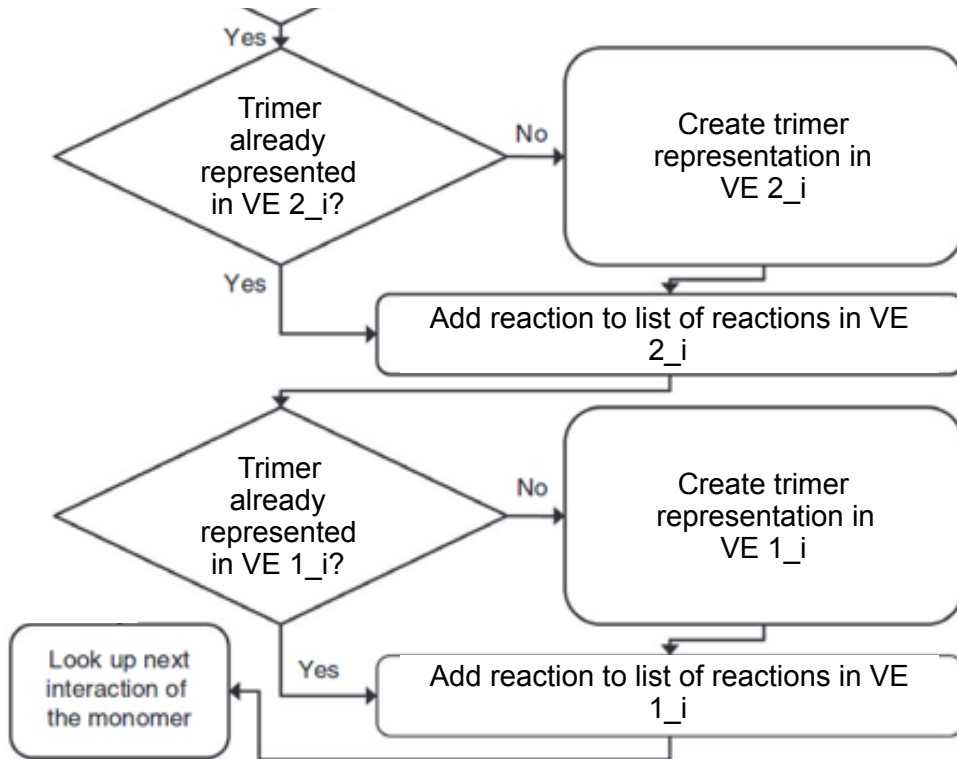
Cadherins facilitate cell-cell adhesion



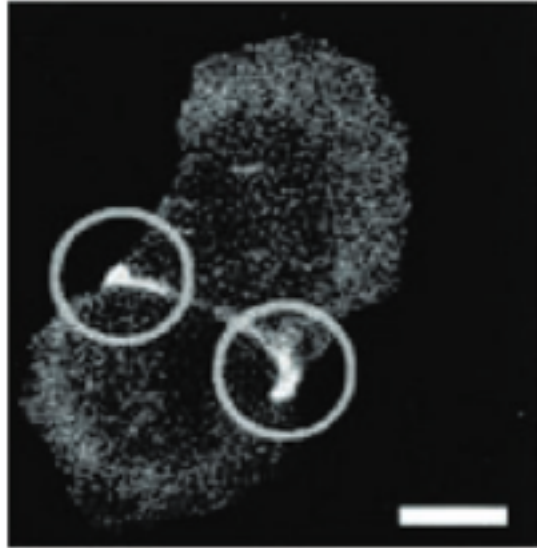
Automatic local network generation (one step)



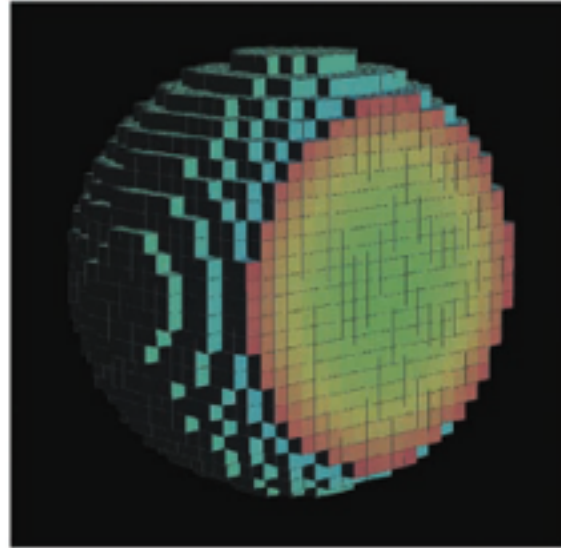
Automatic local network generation (one step)



Simulation agrees with experimentally observed E-cadherin accumulation on periphery of morphologically static cells

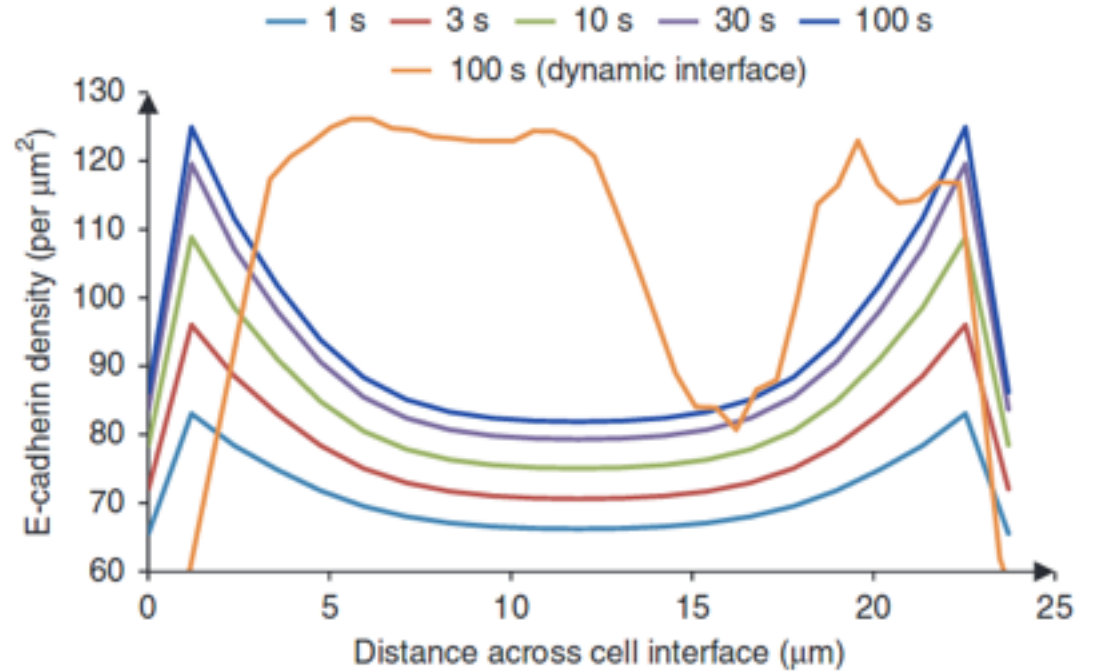
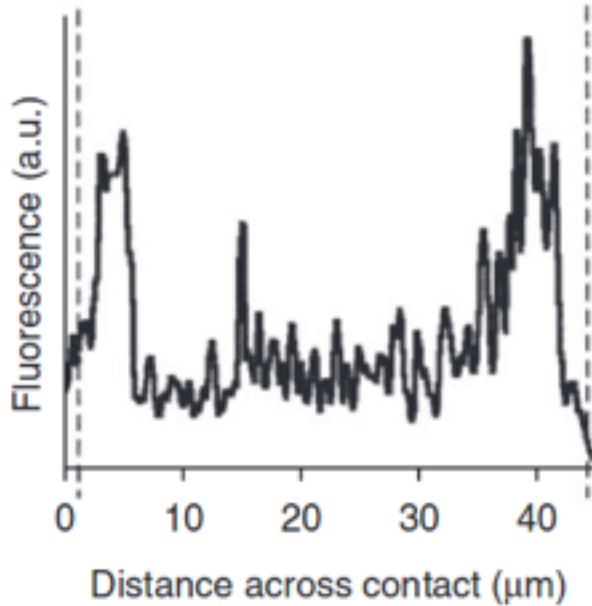


GFP-labeled E-cadherin
peripherally accumulated

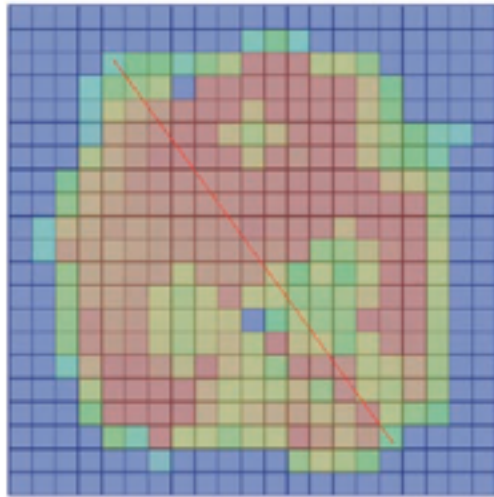


low vs **high**
E-cadherin concentration

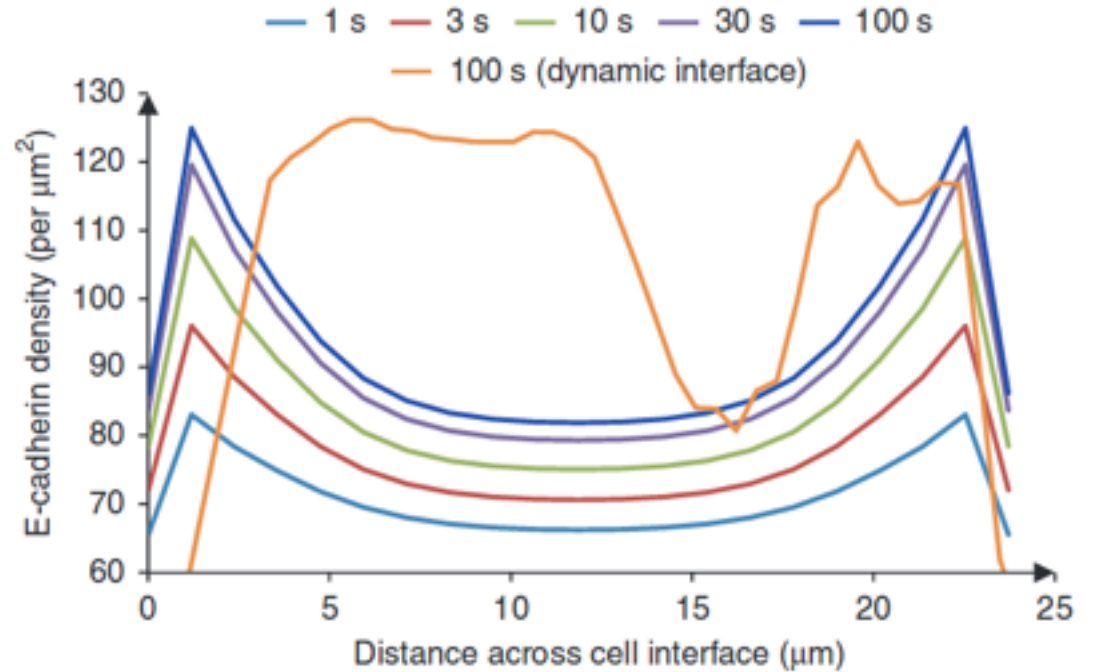
Simulation agrees with experimentally observed E-cadherin accumulation on periphery of morphologically static cells



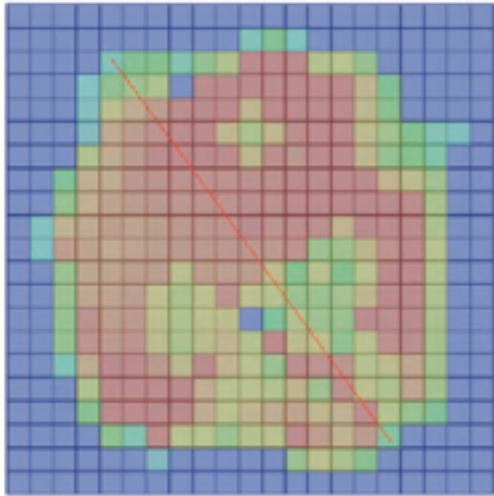
Dynamic simulation shows increased E-cadherin density in central contact zones



low vs high
E-cadherin concentration



Dynamic simulation shows increased E-cadherin density in central contact zones → biological insight



low vs **high**
E-cadherin concentration

Hong et al identified existence of active removal of E-cadherin from central contact sites (2010)

Simulations show:

- E-cadherin quickly accumulates to growing contact points
- E-cadherin has a rapid diffusion (relative to time-scale of growing contact)
- Simulations suggest: rather than passive diffusion (model assumption) active transport of E-cadherin from central contact zone → generate adhesive ring at cell periphery

Conclusions

Solved technical modeling issues by automatic generation of reaction-diffusion networks

a solution

Made details of local dynamics accessible

available

Provides framework for creating custom simulations aimed at combining reaction-diffusion and morphological dynamics

yes, for projects of similar scale

Suggestions

Heightened focus on theory

Expand discussion of modeling improvements from Version 1

Demonstration of model limits

Apply method to large-scale biological system

Meier-Schellersheim Lab's current work

Cheng et al. *BMC Systems Biology* 2014, **8**:70
<http://www.biomedcentral.com/1752-0509/8/70>



SOFTWARE

Open Access

NetworkViewer: visualizing biochemical reaction networks with embedded rendering of molecular interaction rules

Hsueh-Chien Cheng^{1,2*}, Bastian R. Angermann³, Fengkai Zhang¹ and Martin Meier-Schellersheim³

THE JOURNAL OF CHEMICAL PHYSICS **141**, 194115 (2014)

Rate coefficients, binding probabilities, and related quantities for area reactivity models

Thorsten Prüstel^(a) and Martin Meier-Schellersheim^(b)

Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA

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This paper is available on line at <http://www.mcponline.org>

Targeted Proteomics-Driven Computational Modeling of Macrophage S1P Chemosensing*

Nathan P. Manes[‡], Bastian R. Angermann[‡], Marijke Koppenol-Raab[‡], Eunkyung An^{‡¶},
Virginie H. Sjoelund^{‡||}, Jing Sun[‡], Masaru Ishii[§], Ronald N. Germain[‡],
Martin Meier-Schellersheim[‡], and Aleksandra Nita-Lazar^{‡**}

Decoding Information in Cell Shape

Raj Raina

Introduction and Motivation

What affects cell signaling?

Lipid rafts in plasma membrane, cytoskeleton network, scaffolding proteins, etc.

What about the topology of the cell shape?

Cell Shape = Repository of information

Central hypothesis: cell shape can control signal transduction at the plasma membrane

* **All pictures taken from** Padmini Rangamani, Azi Lipshtat, Evren U. Azeloglu, Rhodora Cristina Calizo, Mufeng Hu, Saba Ghassemi, James Hone, Suzanne Scarlata, Susana R. Neves, Ravi Iyengar, Decoding Information in Cell Shape, Cell, Volume 154, Issue 6, 12 September 2013, Pages 1356-1369, ISSN 0092-8674.

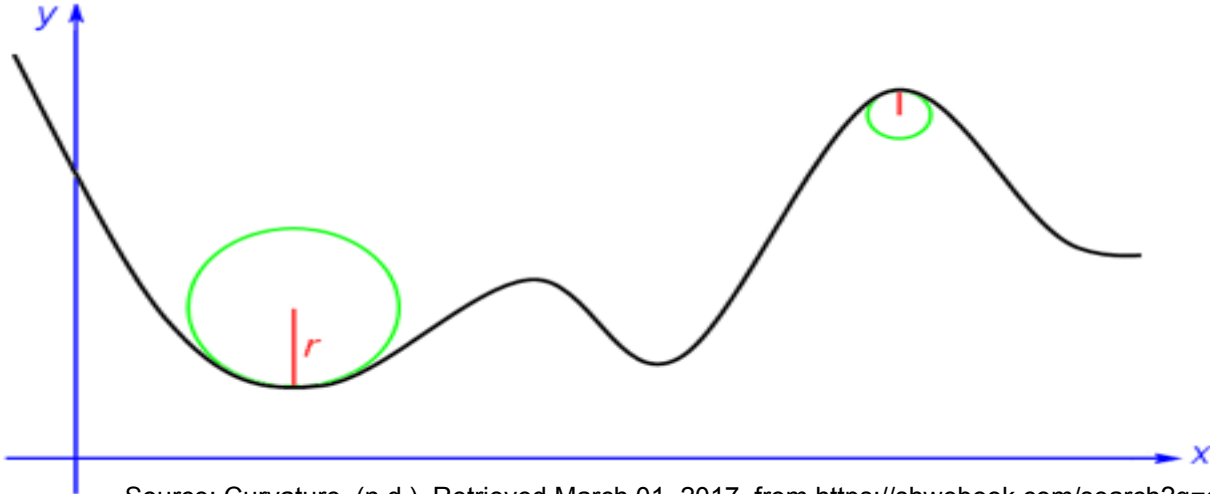
Unless otherwise noted

Introduction and Motivation

Important notes:

Must use mathematical modeling

2D \leftrightarrow 3D



Mathematical Model Setup

A is a component in the solution (cytoplasmic or extracellular) and X is in membrane

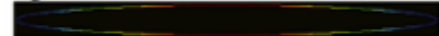
Initial Distribution of A in the volume and B on the membrane



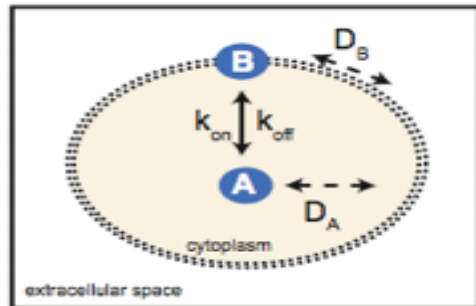
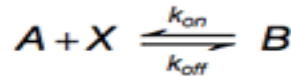
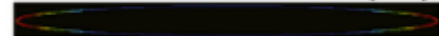
C_A at 30 s



N_B at 30 s



Reaction rate at the membrane (30 s)



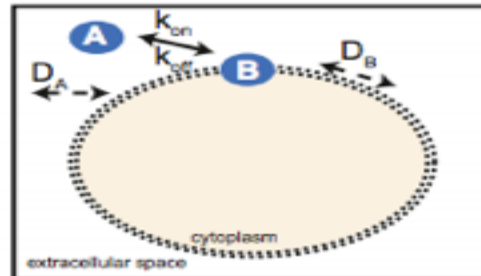
C_A at 30 s



N_B at 30 s



Reaction rate at the membrane (30 s)



Mathematical model

B and X can diffuse across the membrane

$$\frac{\partial N_X}{\partial t} = D_X \nabla^2 N_X - k_{on} C_A|_{\partial\Omega} N_X + k_{off} N_B$$

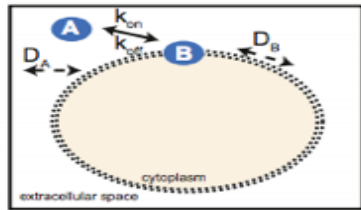
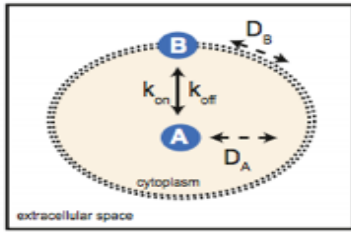
$$\frac{\partial N_B}{\partial t} = D_B \nabla^2 N_B + k_{on} C_A|_{\partial\Omega} N_X - k_{off} N_B$$

Dynamics of A in the cytoplasm (extracellular space)

$$\frac{\partial C_A}{\partial t} = D_A \nabla^2 C_A$$

Mathematical Model Results

Spatial results

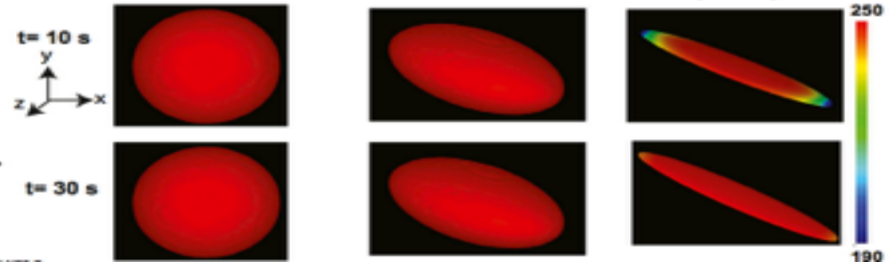


(ii) 3D simulations

$a=5.16, b=5.16, c=5.16$

$a=7.4, b=3.2, c=5$

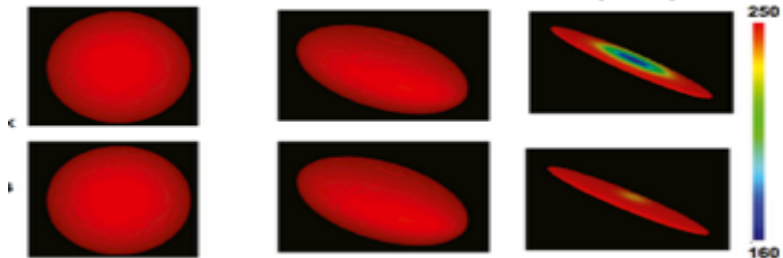
$a=23.1, b=1.0, c=5$



$a=5.16, b=5.16, c=5.16$

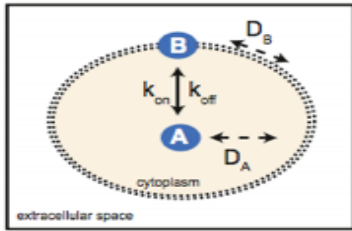
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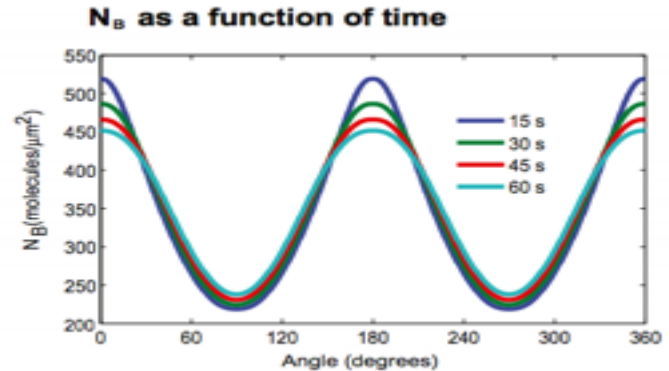
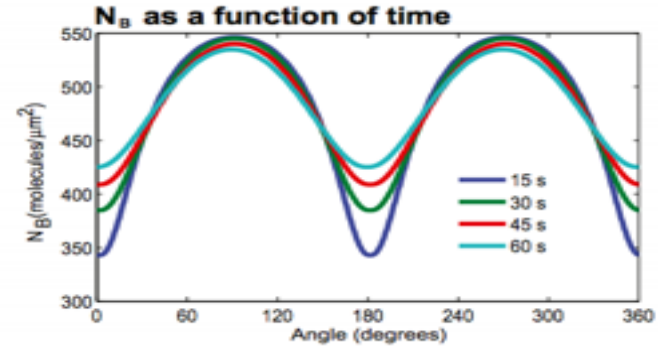
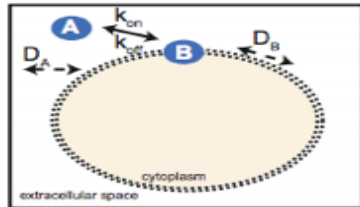


Mathematical Model Results

Temporal results



Mathieu Functions



Real Life Results

Three predictions based on our mathematical results

- (1) A circular cell shape will have a homogeneous spatial activation
- (2) Spatial differences at the plasma membrane can affect downstream reactions
- (3) The effect of local curvature may also be seen in the cell nucleus

Real Life Results

- (1) A circular cell shape will have a homogeneous spatial activation

Bradykin receptor on circular + ellipse shaped cells

(2) Spatial inhomogeneity affects downstream reactions

EGFR affects MAPK1,2 activation

MAPK uniform in cytoplasm, concentration higher in ellipses

Same results for nucleus (3)

Further Work/Conclusions

Try to mathematically model more complex interactions aside from $A+X=B$

This is way too simple of a model

Figure out how to isolate just cell shape

Test different downstream reactions

Final thoughts

ReaDDy - a software for particle based reaction diffusion dynamics

Jasmine Johnson
CS 371



Particle-based reaction-diffusion algorithms facilitate the modeling of the **diffusional motion of individual molecules and the reactions** between them in cellular environments.

Introduction

Biological function relies on molecular reactions

Particles need to be in close proximity > forms encounter complex (EC)

With a certain probability, the EC reacts to:

- form products

- dissociates again by diffusion

Probability of a reaction depends on many parameters:

- Chemical and physical interactions between educt molecules

- Properties of the molecular transport process (diffusion)

- Environment (crowding and obstructing cellular geometry)

Simulating particle-based reaction diffusion

In order to simulate spatiotemporal processing, we need:

- Single particle resolution
 - Are concentration based approaches sufficient?
- Diffusion
 - Can we assume the species to be well mixed?
- Interaction potentials
 - How do molecules attract or repulse each other?
- Cellular geometry
 - How does cellular shape and container affect reactions?
- Reactions
 - How do molecules change?

Many approaches exist that try to tackle particle-based reaction-diffusion but they are **lacking 1 of the 5 conditions**

Why is ReaDDY Important?

In order to simulate spatiotemporal processing, we need:

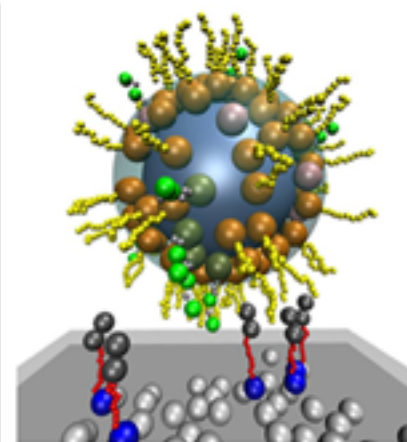
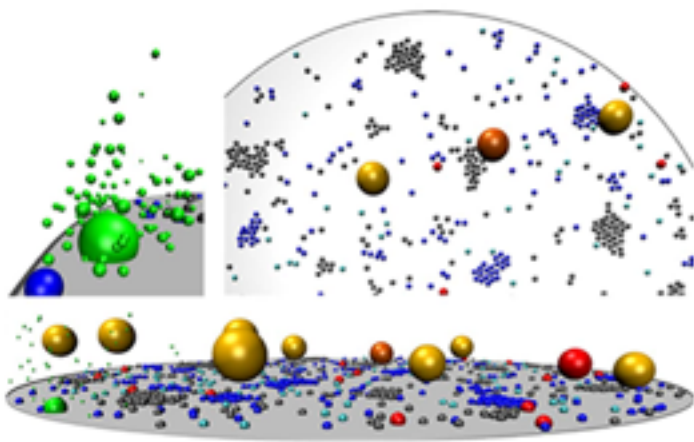
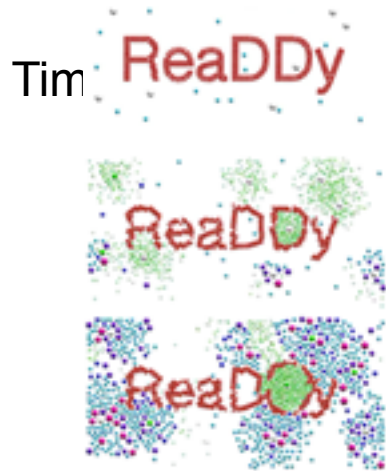
- Single particle resolution
 - Are concentration based approaches sufficient? No..
- Diffusion
 - Can we assume the species to be well mixed? No...
- **Interaction potentials**
 - **How do molecules attract or repulse each other?**
- Cellular geometry
 - How does cellular shape and container affect reactions?
- Reactions
 - How do molecules change?

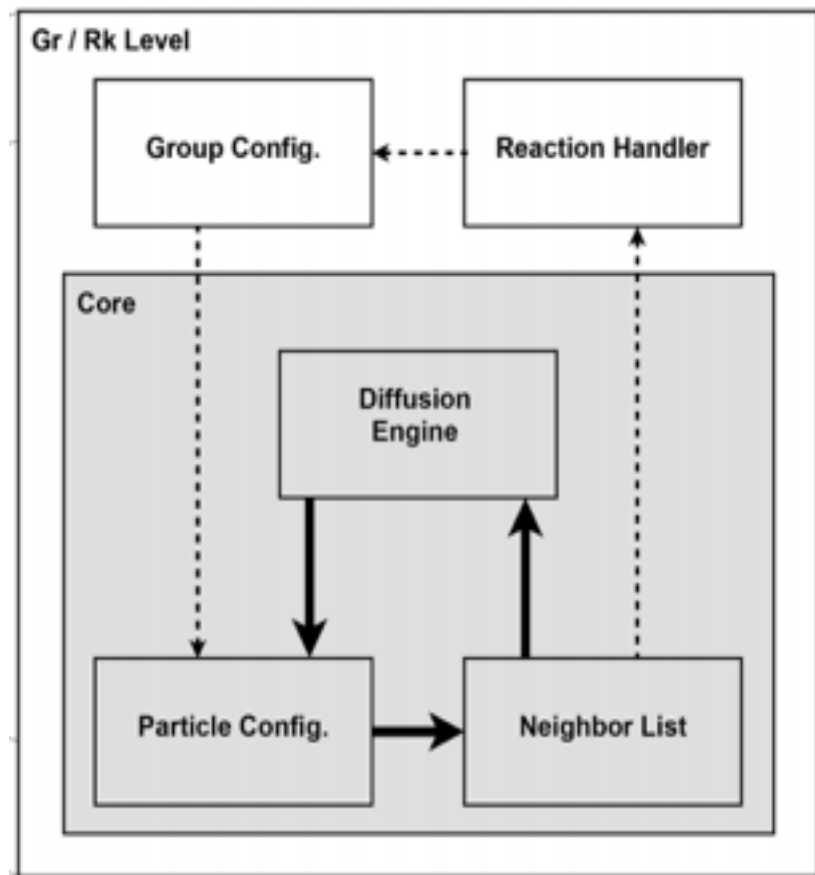
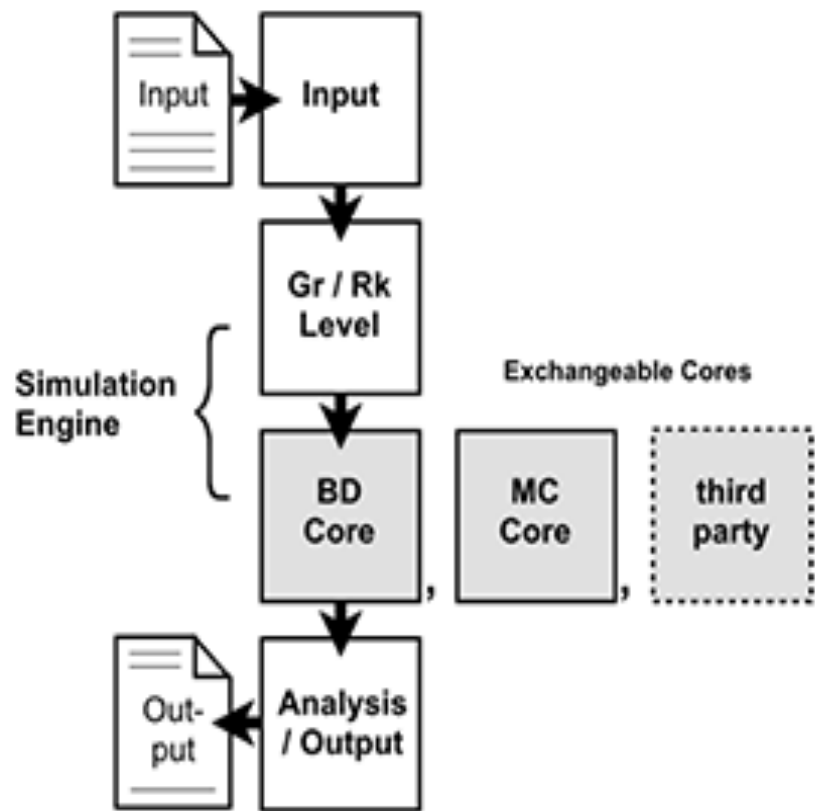
Quick Facts about ReaDDY - **R**eaction **D**iffusion **D**ynamics

Open source java library

Source code provided: <https://github.com/readdy>

Runtime scales linearly





Algorithm simulation

Given an initial particle configuration, for each time step:

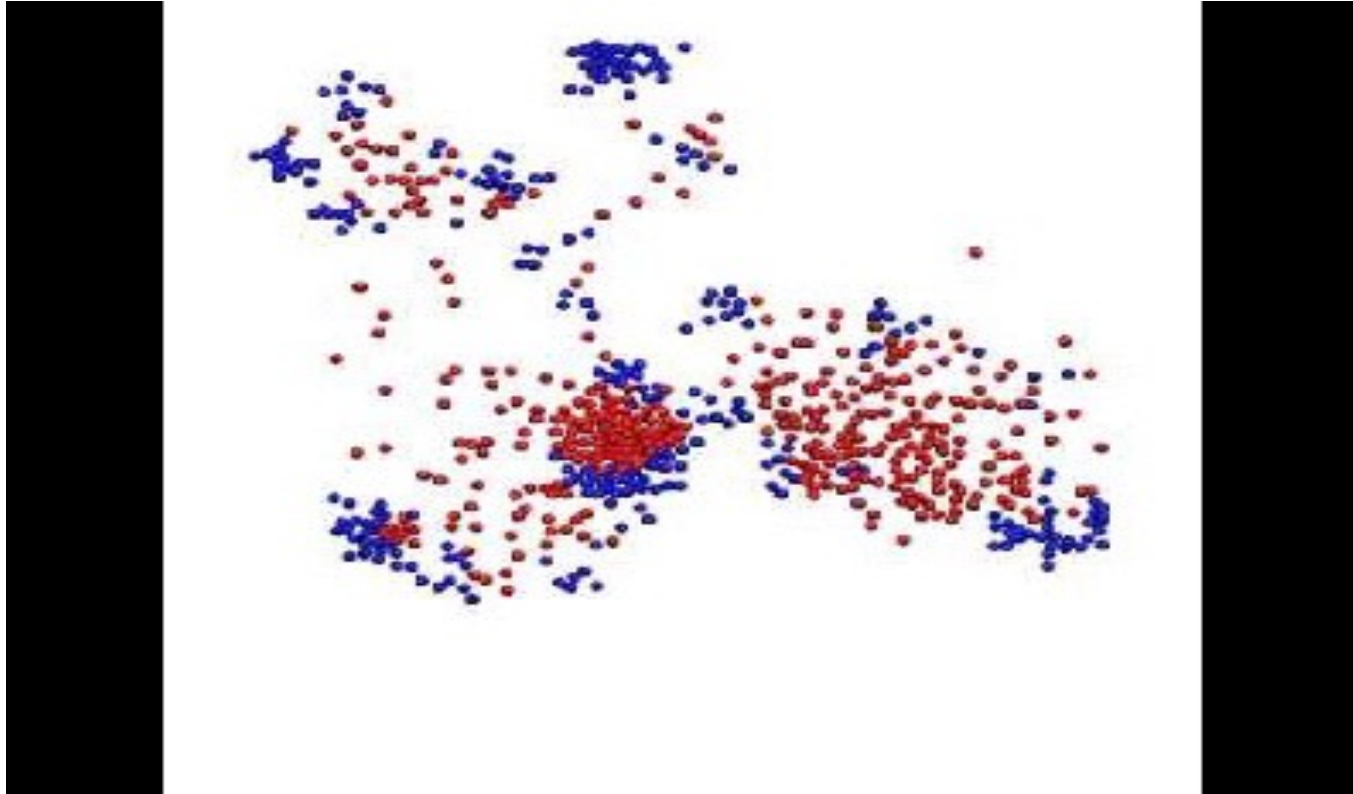
The software performs two actions:

- (1) a brownian dynamic step of all particles
- (2) a reaction step that may change particle types and numbers.

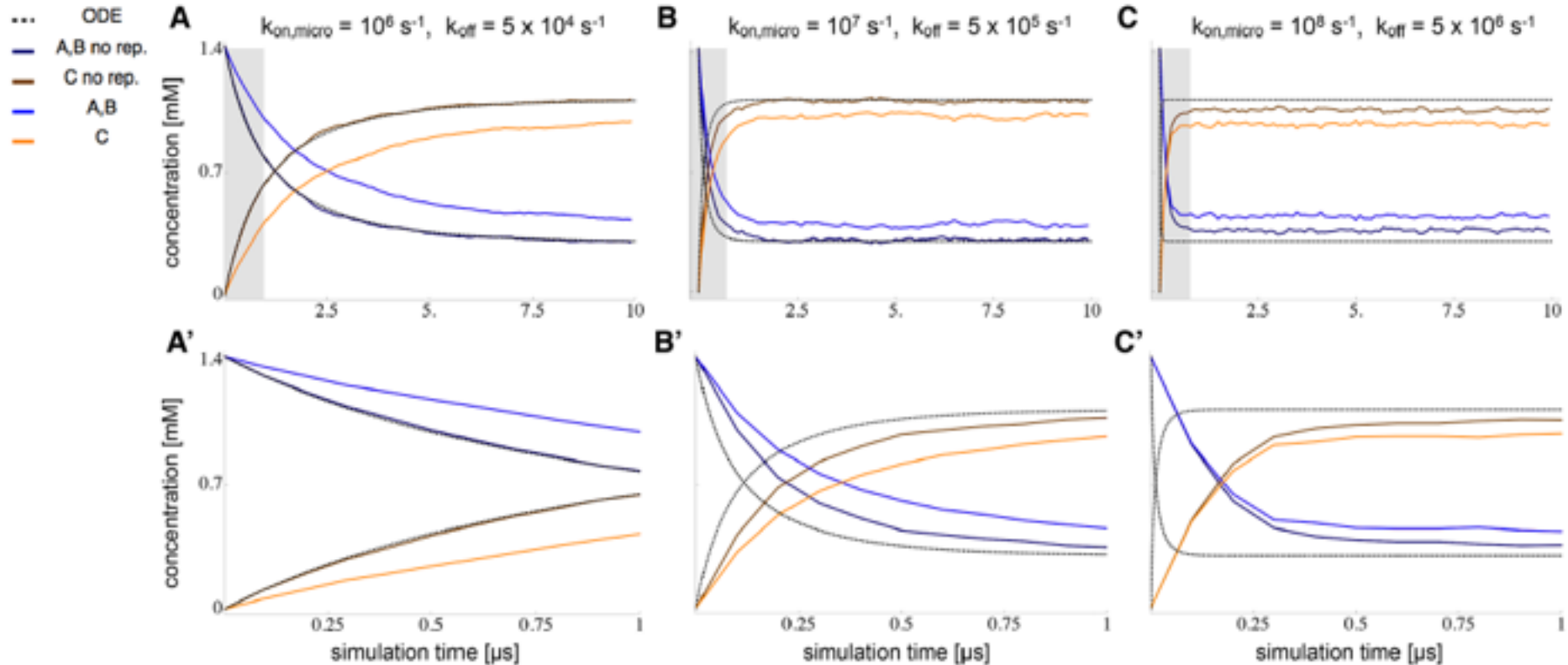
Pairwise distances between particles are updated

Time is updated before a new cycle is started.

Predator-Prey Simulation Model



Comparison of ODE reaction kinetics with ReaDDy



Conclusion

Biological Applications

Allows a microscopic, particle-based reaction-diffusion simulation to be combined with particle interaction potentials

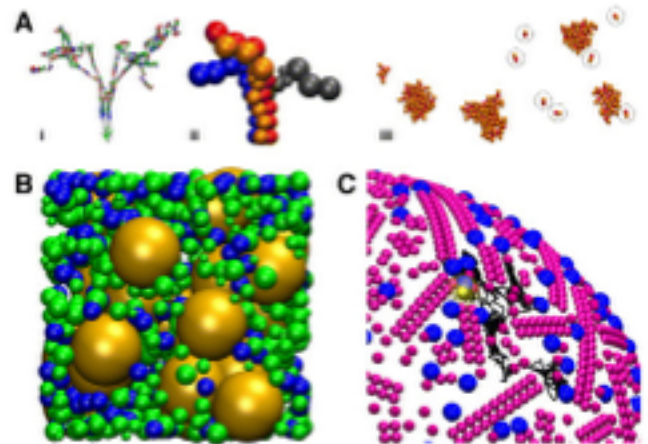
Vesicle fusion and rod cell phototransduction

Critique

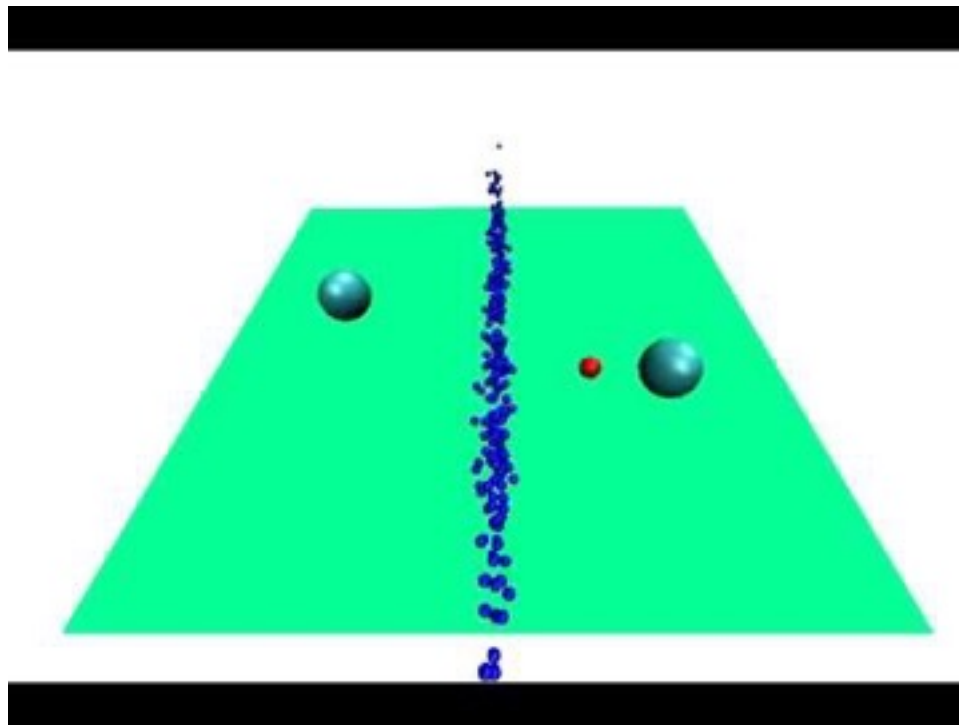
Hard to identify comparison to other software

Computationally expensive

Procedural limitations to simulation



ReaDDy Tennis



Benchmark

