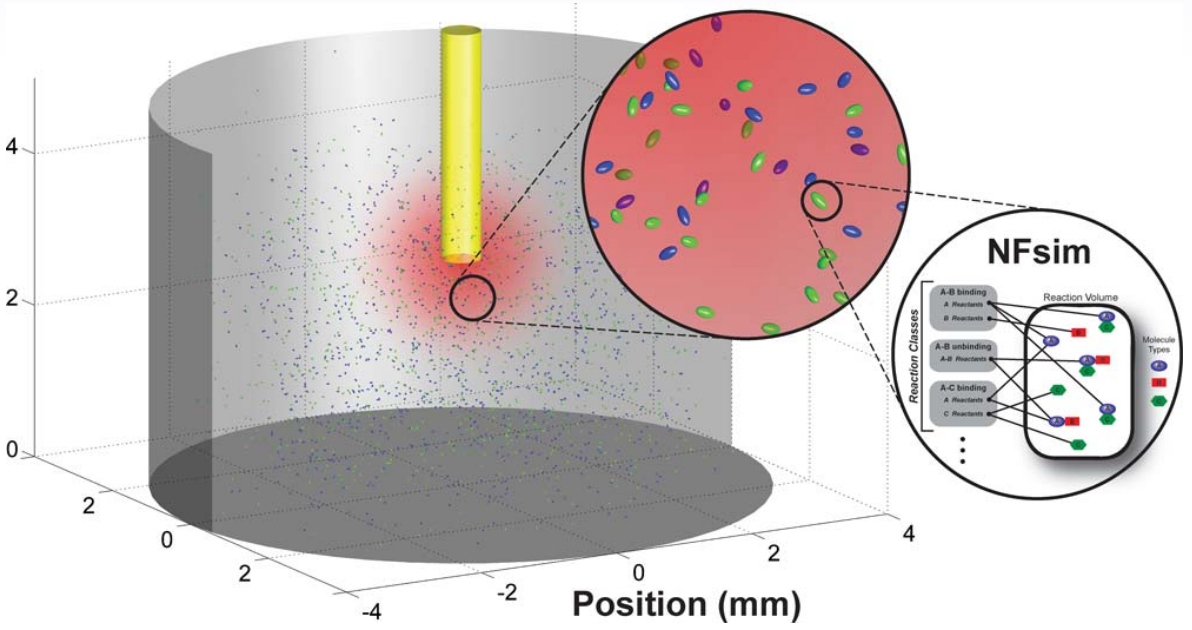
NFsim: A Novel, Agent-based, Stochastic Simulator for Biology

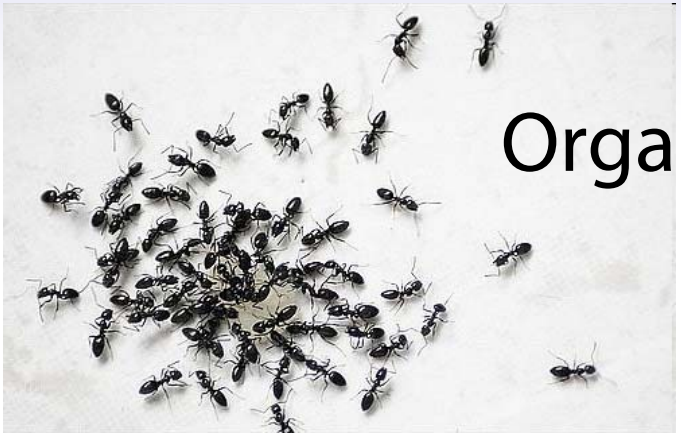
Michael Sneddon
Emonet Lab
Yale University

Swarmfest '09

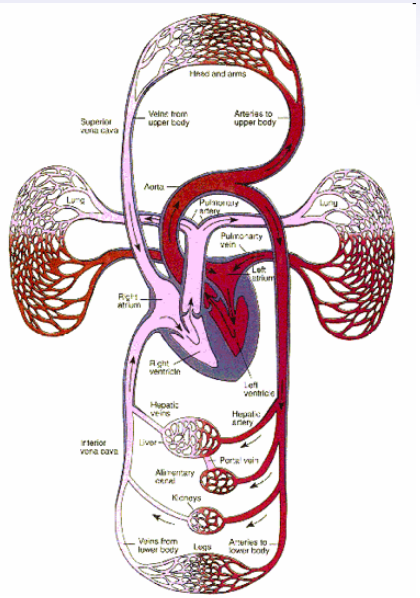


Agents at all Scales of Biology

Populations

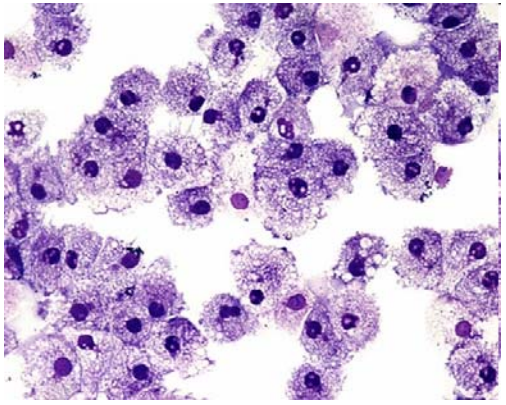


Organisms

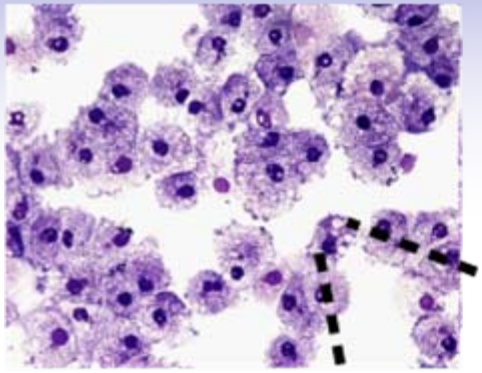


Organs & Tissues

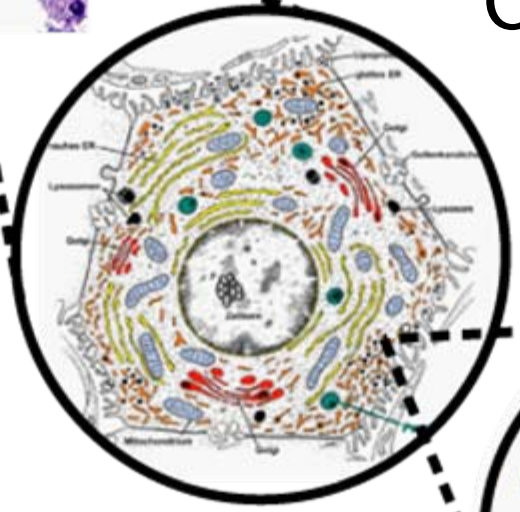
Individual Cells



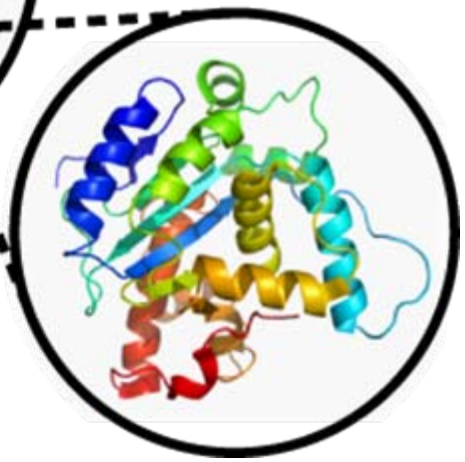
Agents at all Scales of Biology



Cells as Agents



Organelles as Agents



Molecules as Agents

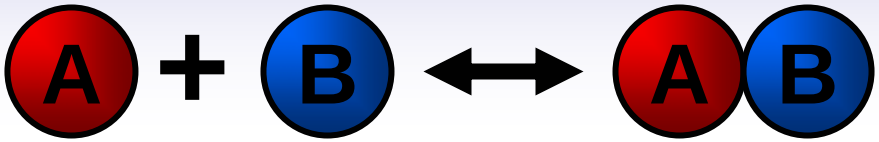
Goal: Multiscale Agent-based, simulation of biological systems, building up from the stochastic molecular level

Cell and Population Level Behavior

Molecular Level Interactions

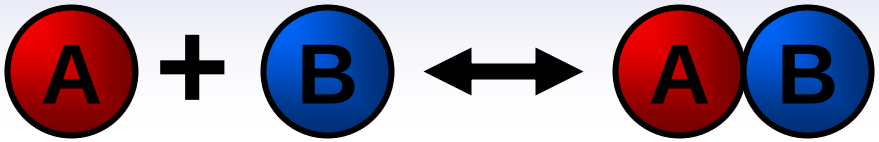
Combinatorial Complexity in Biochemistry

Binding Reaction

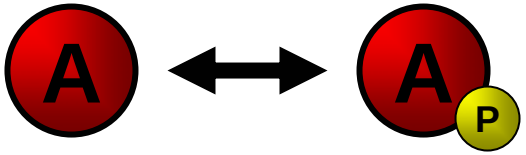


Combinatorial Complexity in Biochemistry

Binding Reaction

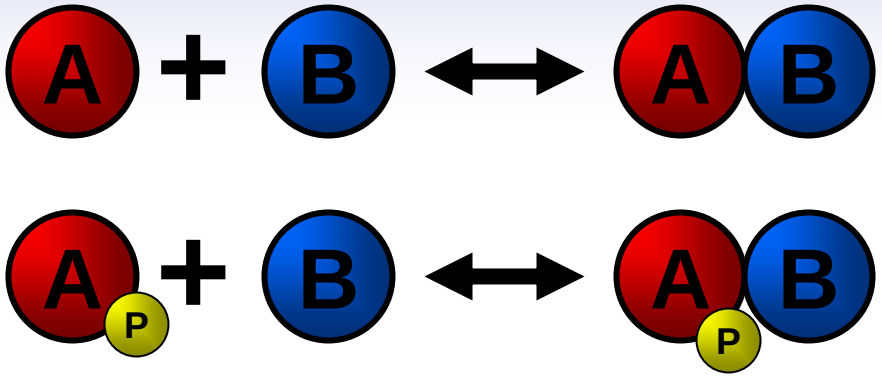


Phosphorylation Reaction

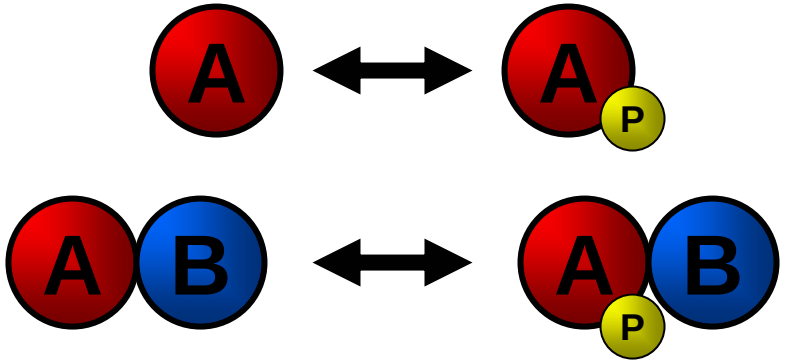


Combinatorial Complexity in Biochemistry

Binding Reaction

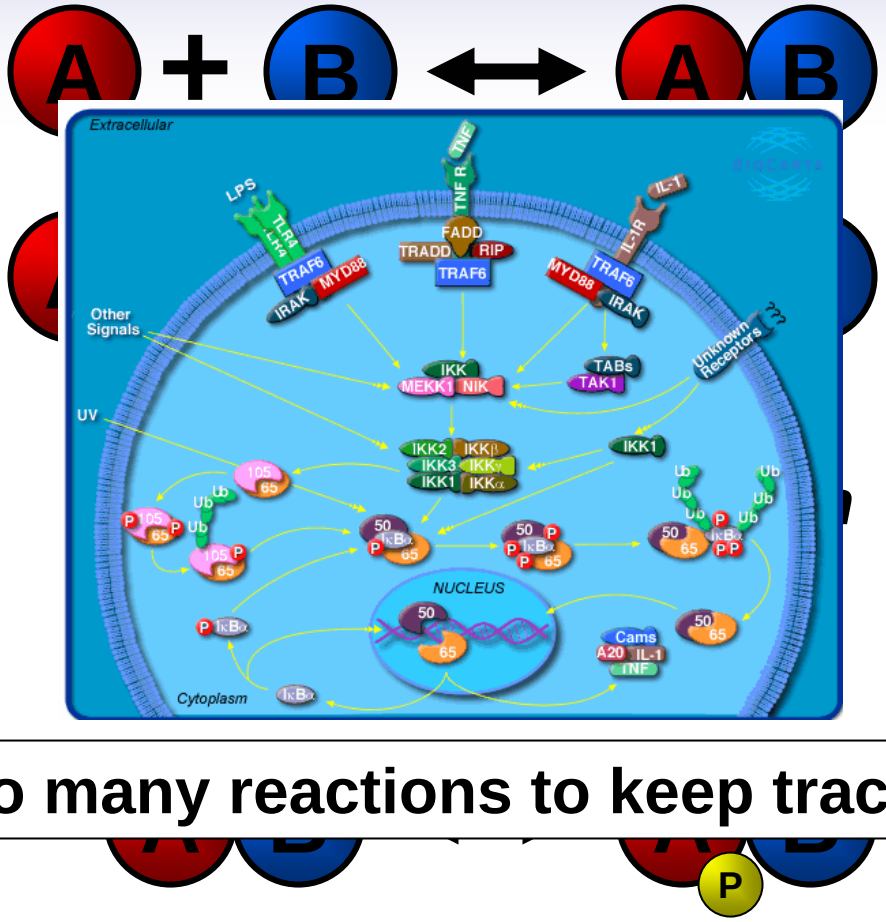


Phosphorylation Reaction



Combinatorial Complexity in Biochemistry

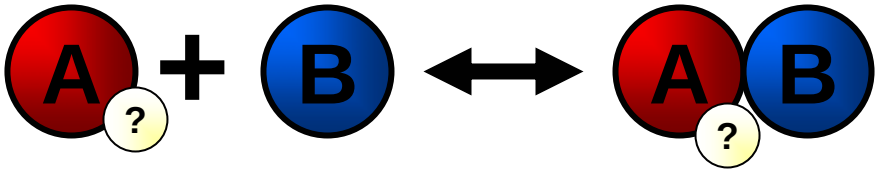
Binding Reaction



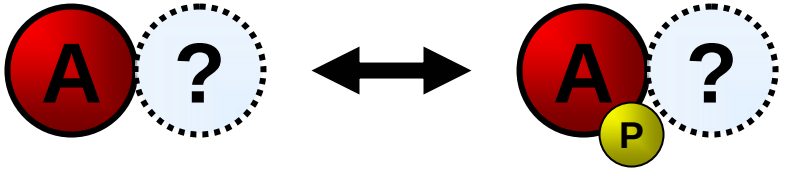
Too many reactions to keep track of!

Rules can Simplify Complexity

Binding Reaction Rule



Phosphorylation Reaction Rule



Rules and the BioNetGen Language

Jim Faeder
University of Pittsburgh

begin molecule types

```
A(b,p)
B(a)
```

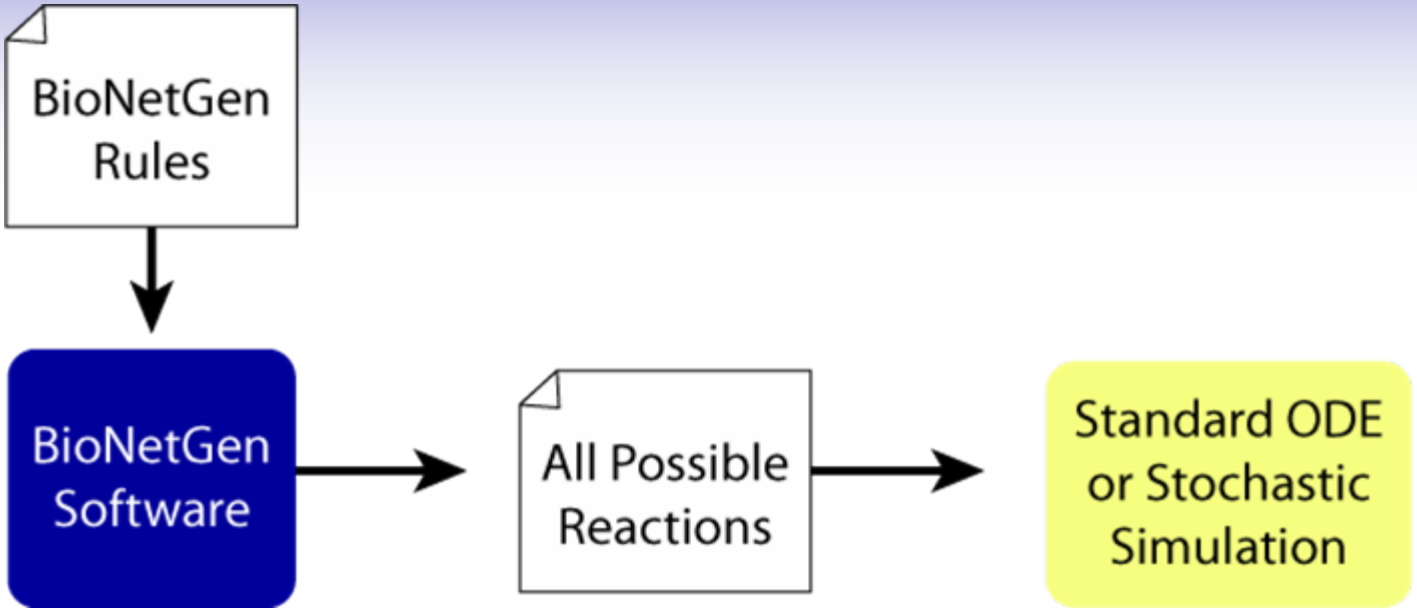
end molecule types

begin reaction rules

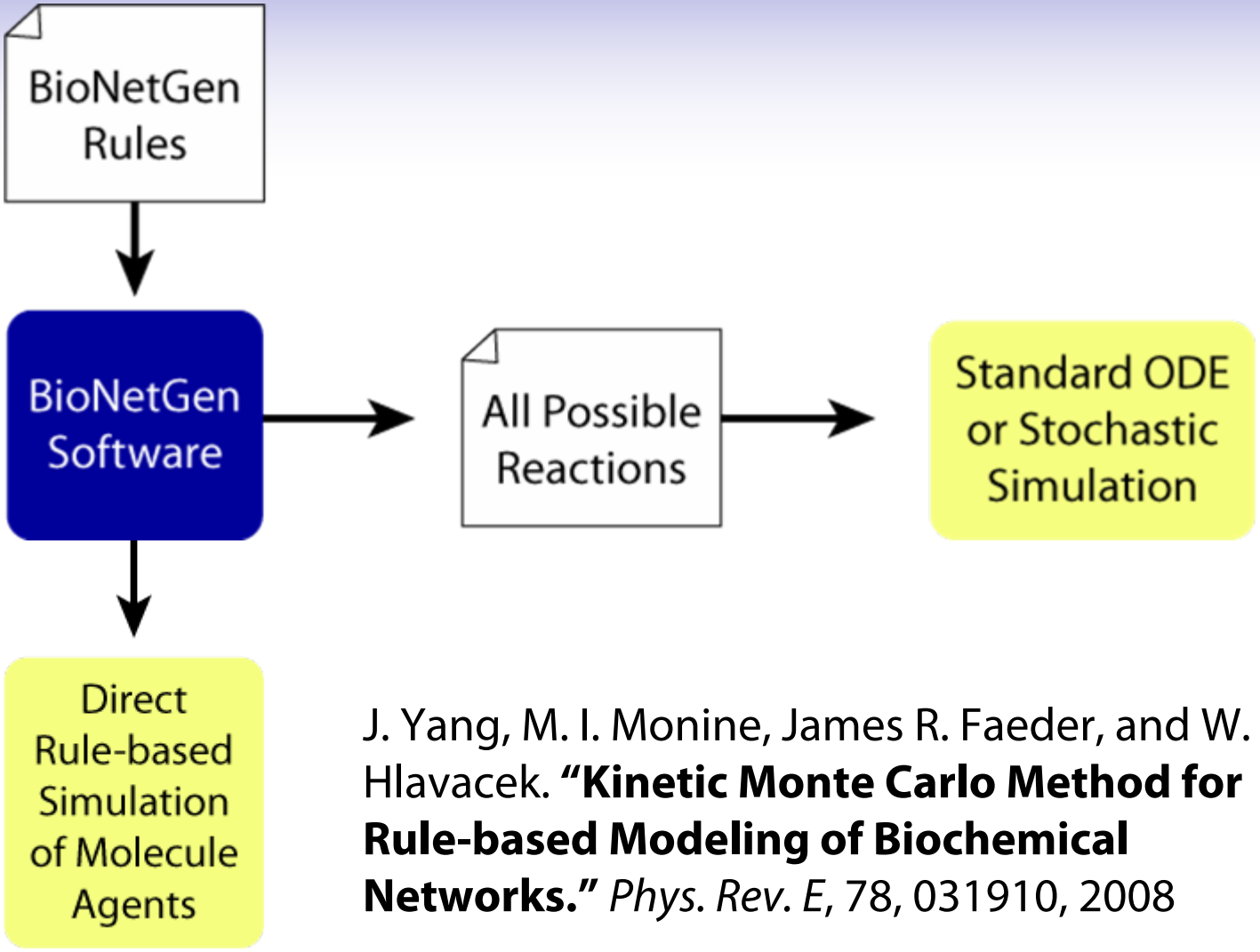
```
A(b) + B(a) -> A(b!1).B(a!1)
A(p~U) -> A(p~P)
```

end reaction rules

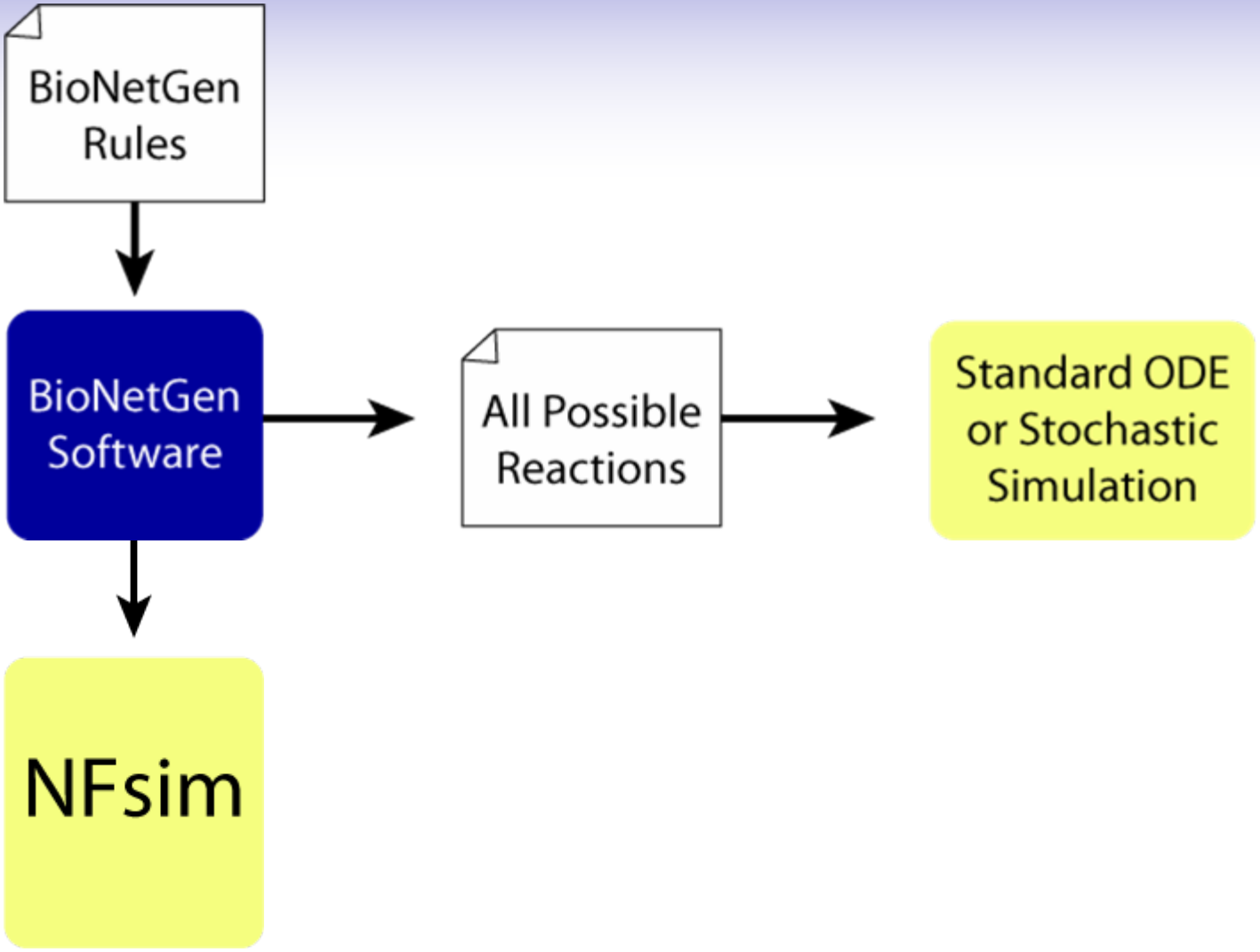
Faeder JR, Blinov ML, Hlavacek WS **Rule-Based Modeling of Biochemical Systems with BioNetGen.** In *Methods in Molecular Biology: Systems Biology*, (2008) Ed I. V.



Not Always Possible!



J. Yang, M. I. Monine, James R. Faeder, and W. S. Hlavacek. **"Kinetic Monte Carlo Method for Rule-based Modeling of Biochemical Networks."** *Phys. Rev. E*, 78, 031910, 2008


BioNetGen
Rules
BioNetGen
Software
All Possible
Reactions
Standard ODE
or Stochastic
Simulation
NFsim

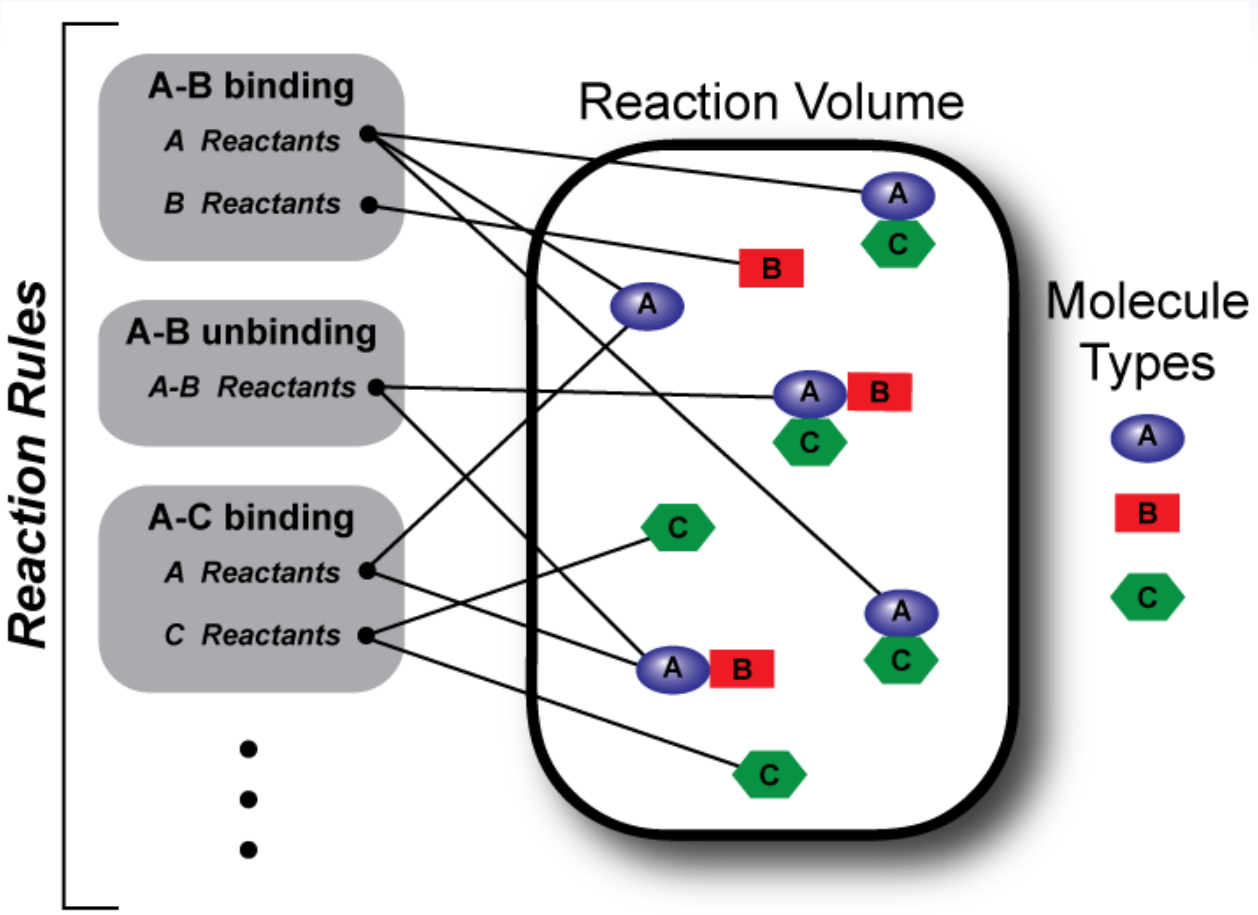
NFsim

The Network-Free Stochastic Simulator

1) Treat molecules as Agents that can be connected together.

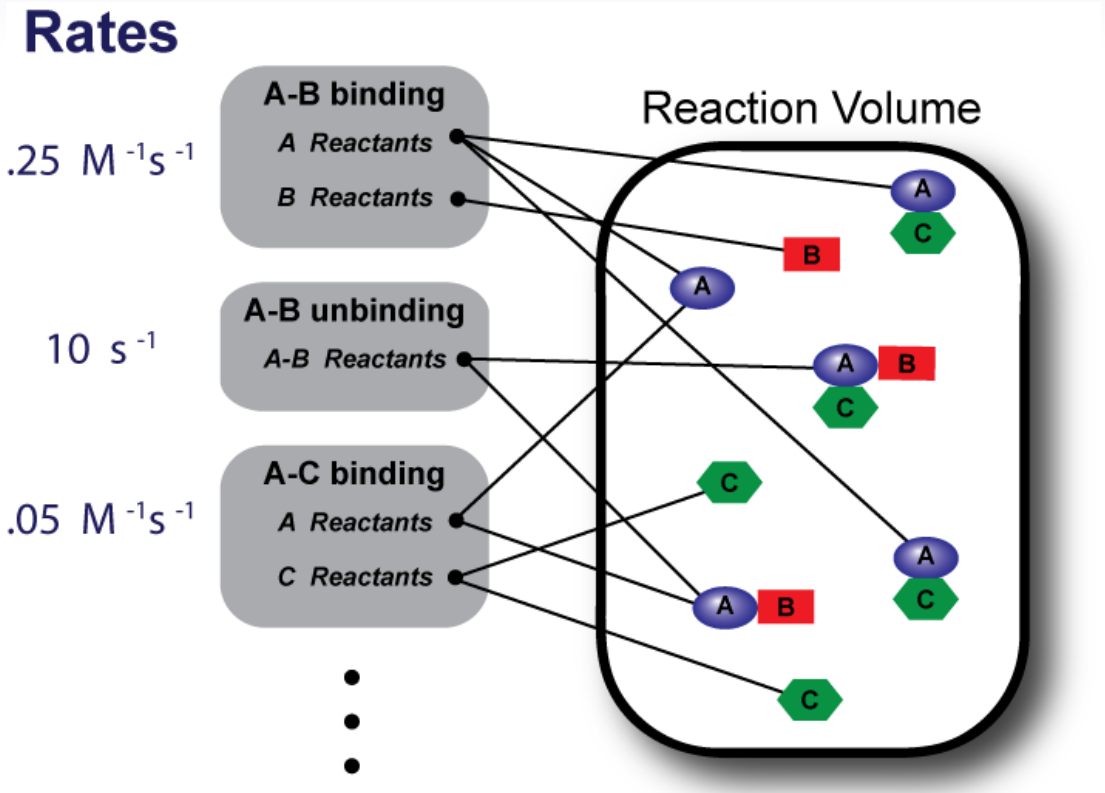
2) Use reaction rules to define interactions.

3) Simulate with an Agent-based extension to the Gillespie Algorithm



The Event Scheduler

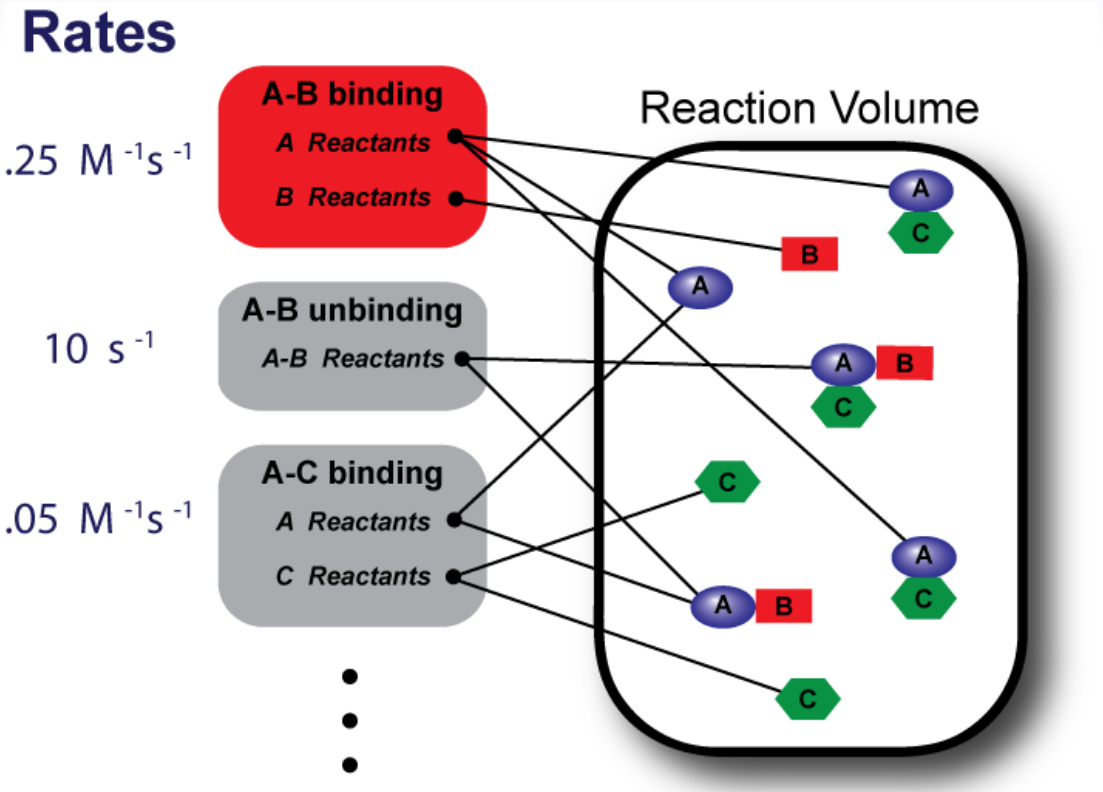
An Agent-based Extension to the Gillespie Algorithm



Every possible reaction event is stored by the Rule-Reactant Pointers

The Event Scheduler

An Agent-based Extension to the Gillespie Algorithm

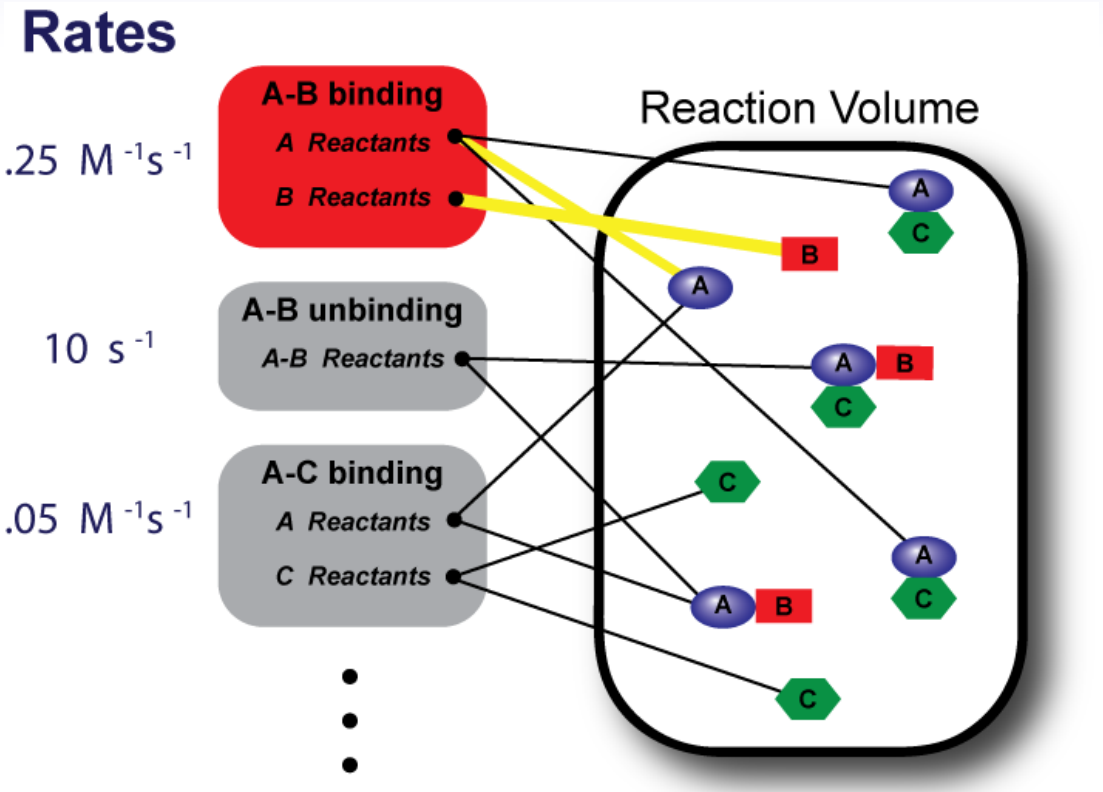


As in Gillespie, the waiting time to the next event is sampled.

Here, the next RULE is chosen stochastically (not the next reaction).

The Event Scheduler

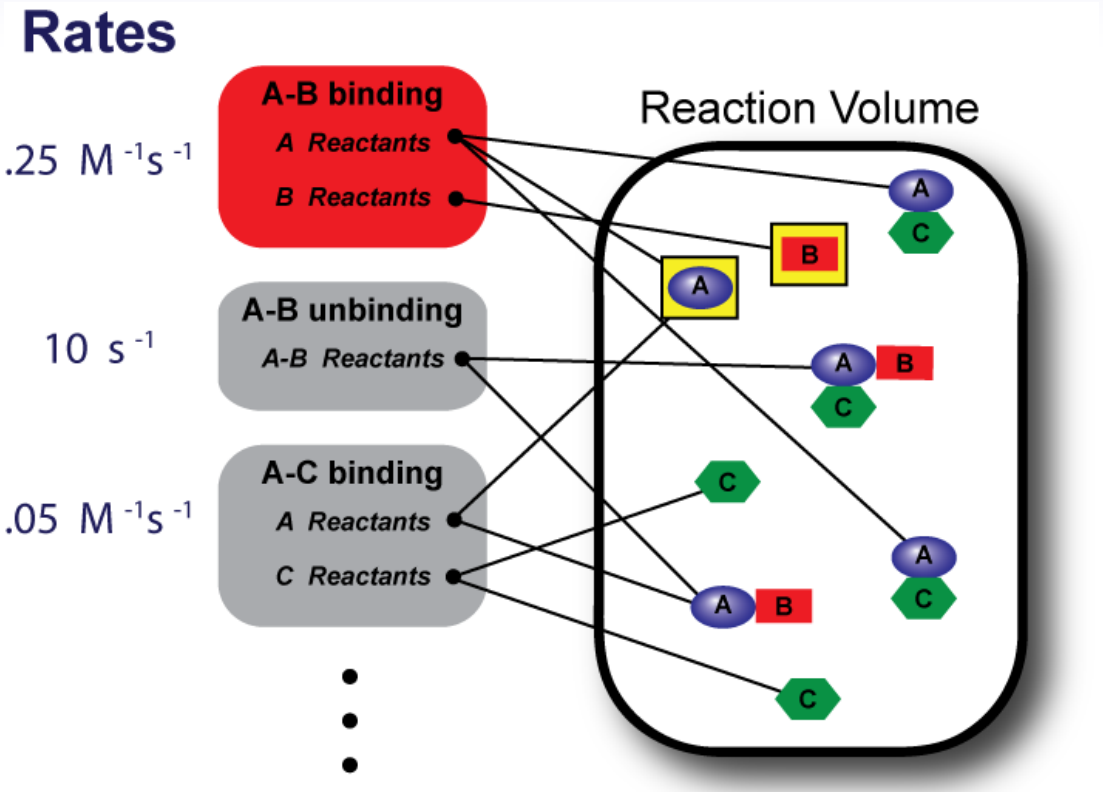
An Agent-based Extension to the Gillespie Algorithm



The molecule Agents that will react are randomly selected.

The Event Scheduler

An Agent-based Extension to the Gillespie Algorithm



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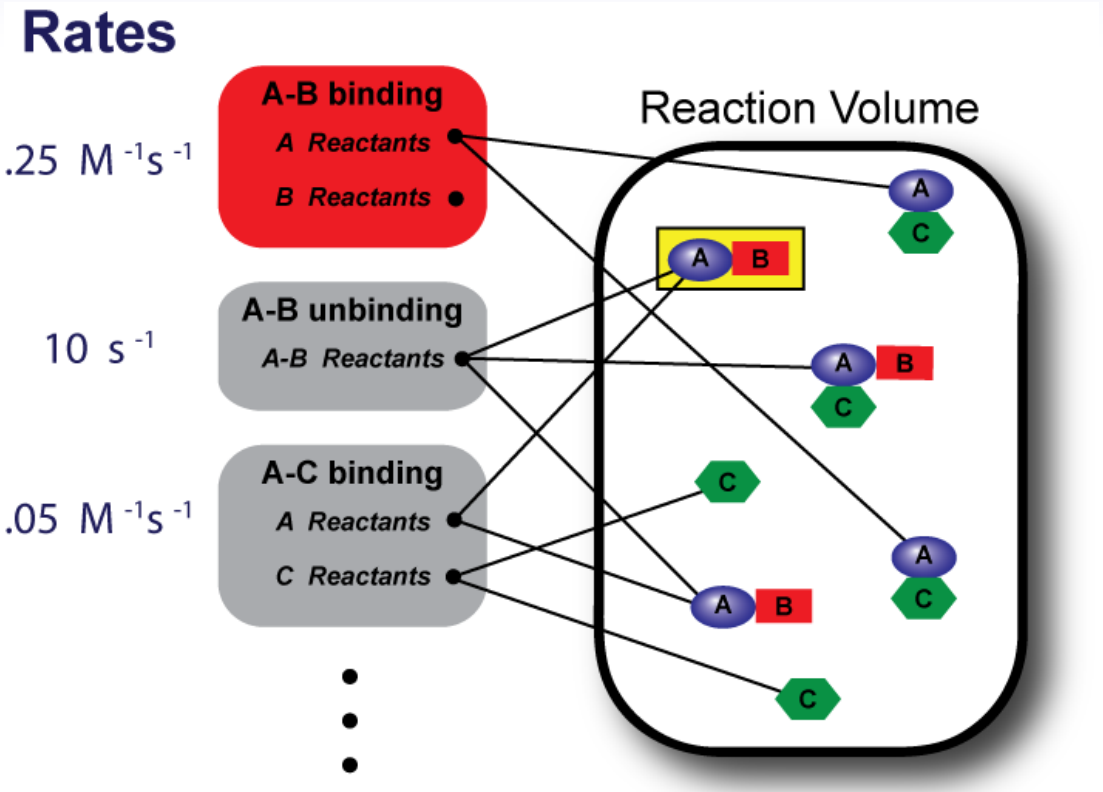
The Event Scheduler

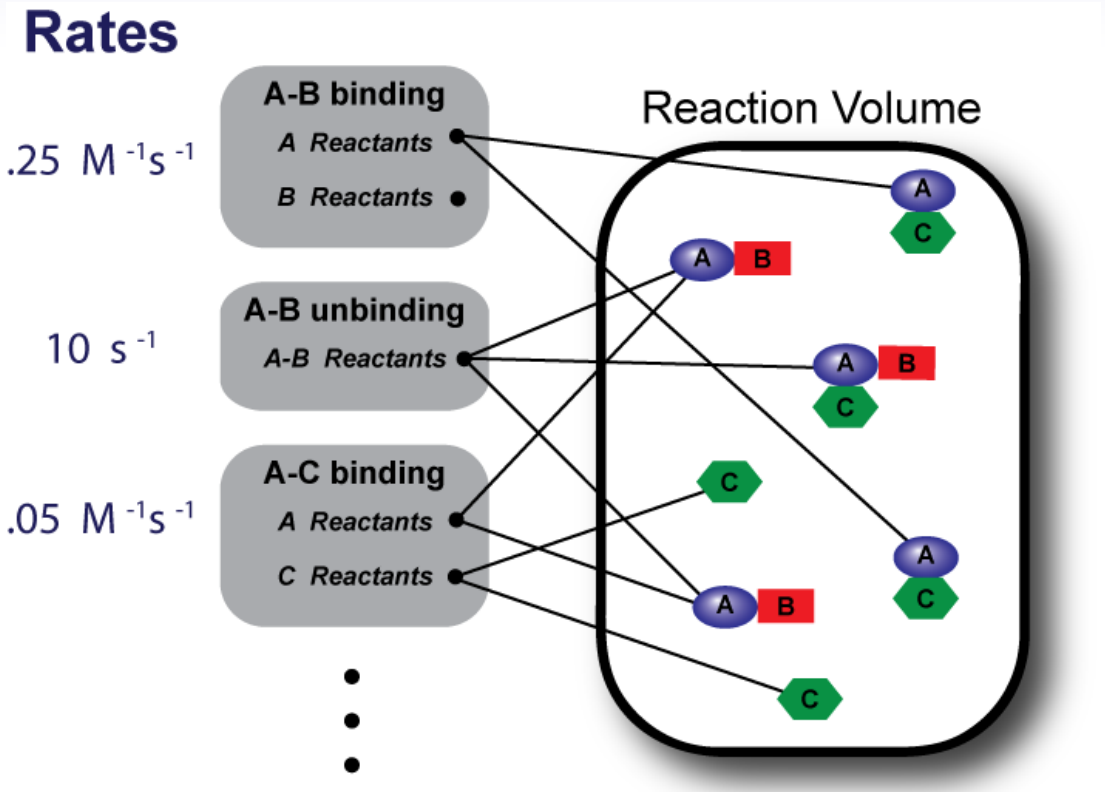
An Agent-based Extension to the Gillespie Algorithm



The molecule Agents update themselves and "reschedule" themselves by updating their Rule-Reactant Pointers.

The Event Scheduler

An Agent-based Extension to the Gillespie Algorithm



The system is advanced by the sampled time.

NFsim Core Simulator Features

1) New code base, and the first Agent-based simulator that produces exact trajectories of the chemical master equation

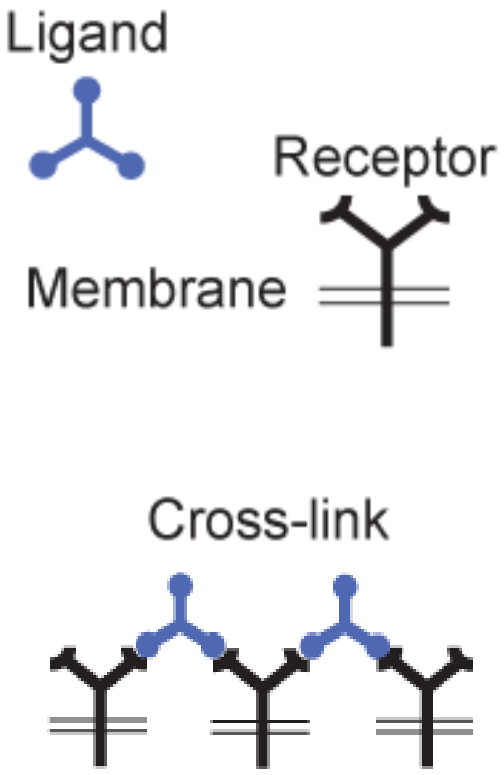
2) Efficiently solves the problem of combinatorial complexity

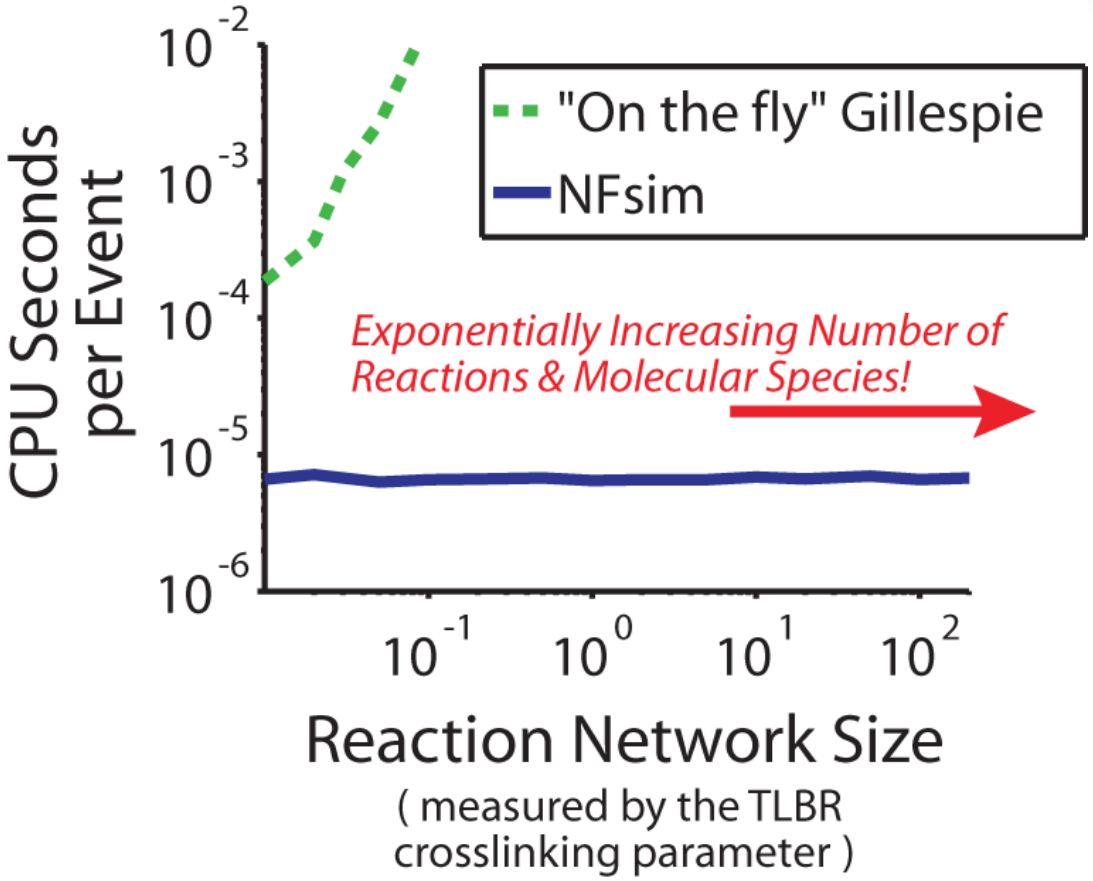
3) Operates seamlessly with BioNetGen

4) Functional definition of rate laws, extended BioNetGen Language.

NFsim's Performance

Trivalent Ligand, Bivalent Receptor (TLBR) System

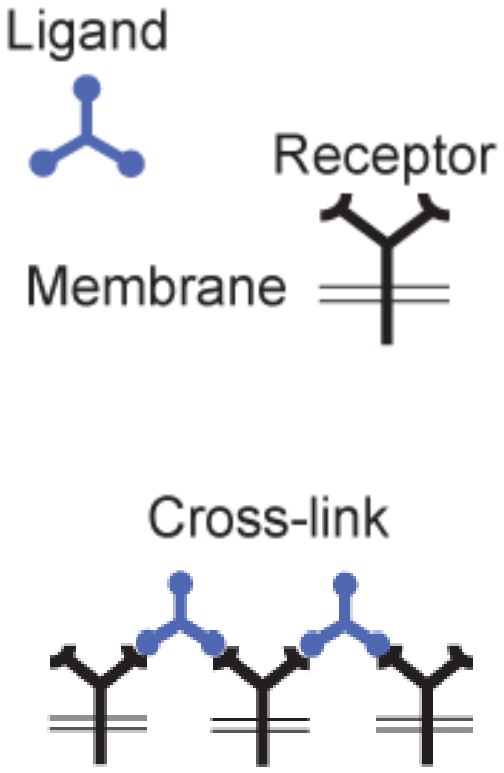


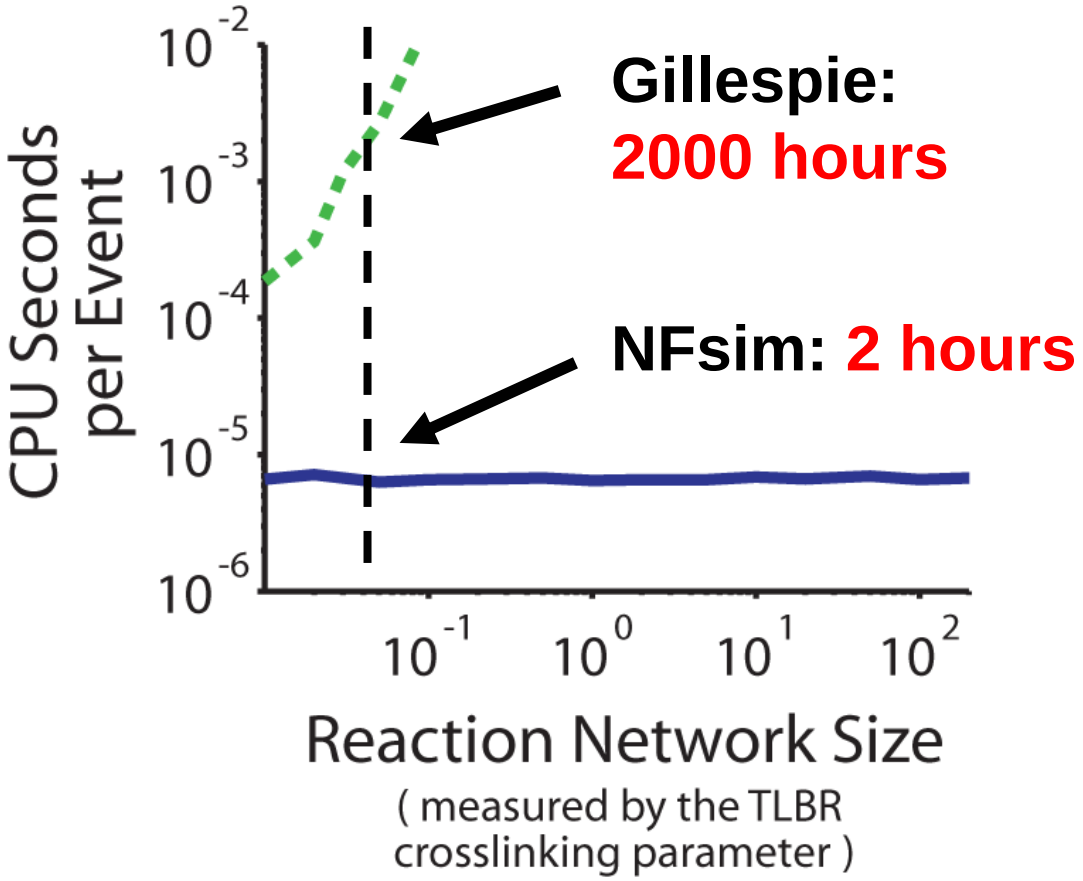


3000 Receptors, 10,000 Ligands

NFsim's Performance

Trivalent Ligand, Bivalent Receptor (TLBR) System





3000 Receptors, 10,000 Ligands

The StochSim Approach

BIOINFORMATICS APPLICATIONS NOTE Vol. 17 no. 6 2001 Pages 575–576

StochSim: modelling of stochastic biomolecular processes

Nicolas Le Novère* and Thomas Simon Shimizu

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Received on November 11, 2000; revised on February 27, 2001; accepted on March 1, 2001

StochSim, 1998

Bray Lab

University of Cambridge

Systems biology

Simulation of large-scale rule-based models

Joshua Colvin[1], Michael I. Monine[2], James R. Faeder[3], William S. Hlavacek[2,4], Daniel D. Von Hoff[5], and Richard G. Posner[1,6*]

[1]Computational Biology Division, Translational Genomics Research Institute, Phoenix, AZ 85004, USA

[2]Theoretical Division and Center for Nonlinear Studies, Los Alamos National Laboratory, Los Alamos, NM 87545, USA

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[5]Clinical Translational Research Division, Translational Genomics Research Institute, Phoenix, AZ 85004, USA

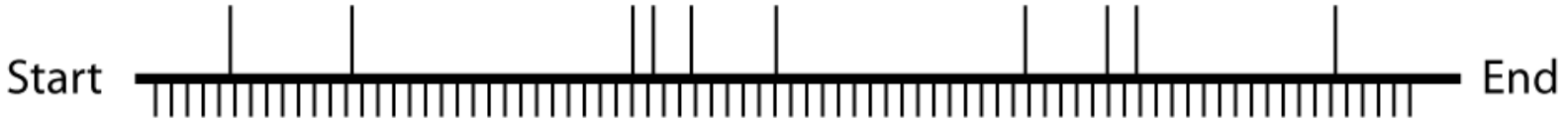
[6]Department of Biological Sciences, Northern Arizona University, Flagstaff, AZ 86011, USA

DynStoc, 2009

Posner Lab

Northern Arizona Univ.

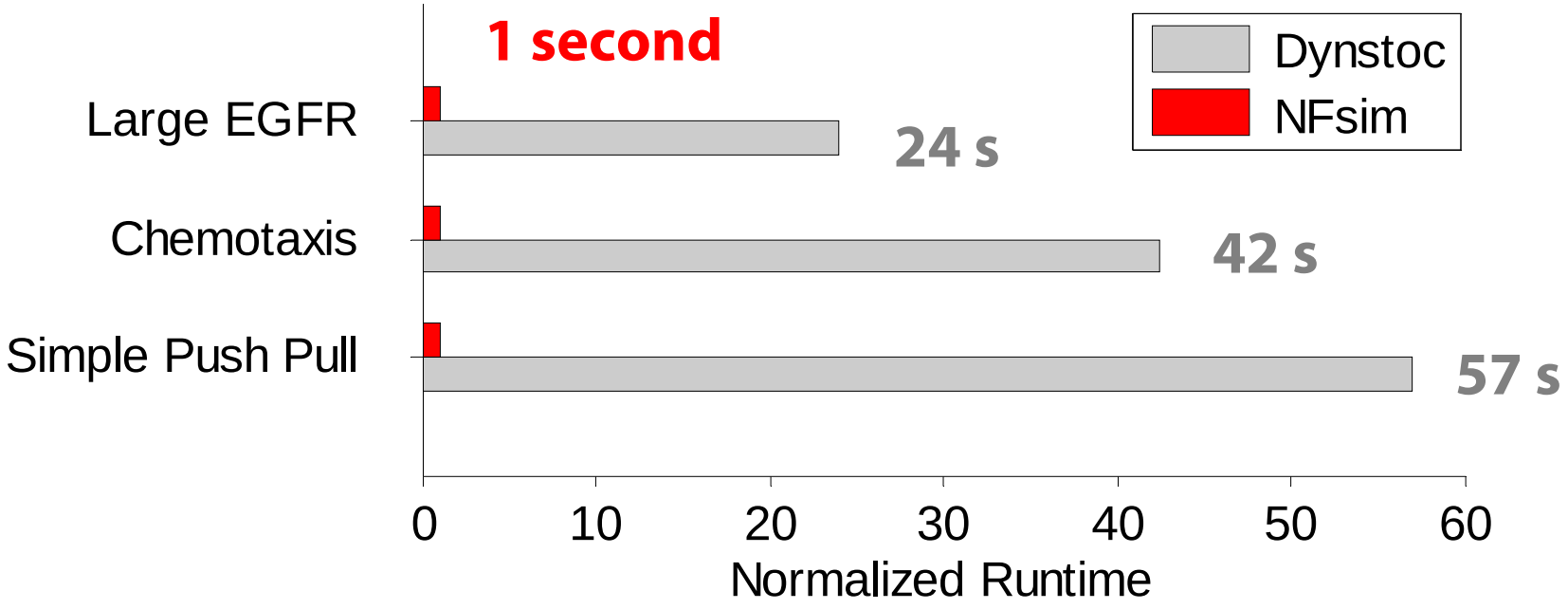
NFsim: Event-driven, slower updates

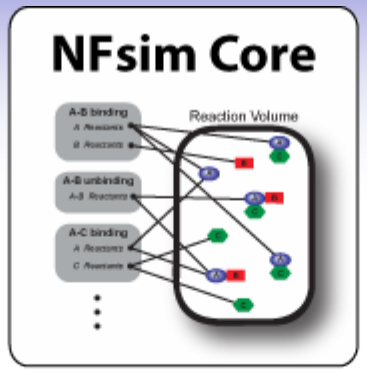


StochSim: Fixed time step, fast updates

NFsim's Performance

Comparison to the StochSim / Dynstoc Approach





Emonet Lab
Yale University

BioNetGen Interface, Simulation Methods

Faeder Lab
University of Pittsburgh

Parallel Computing

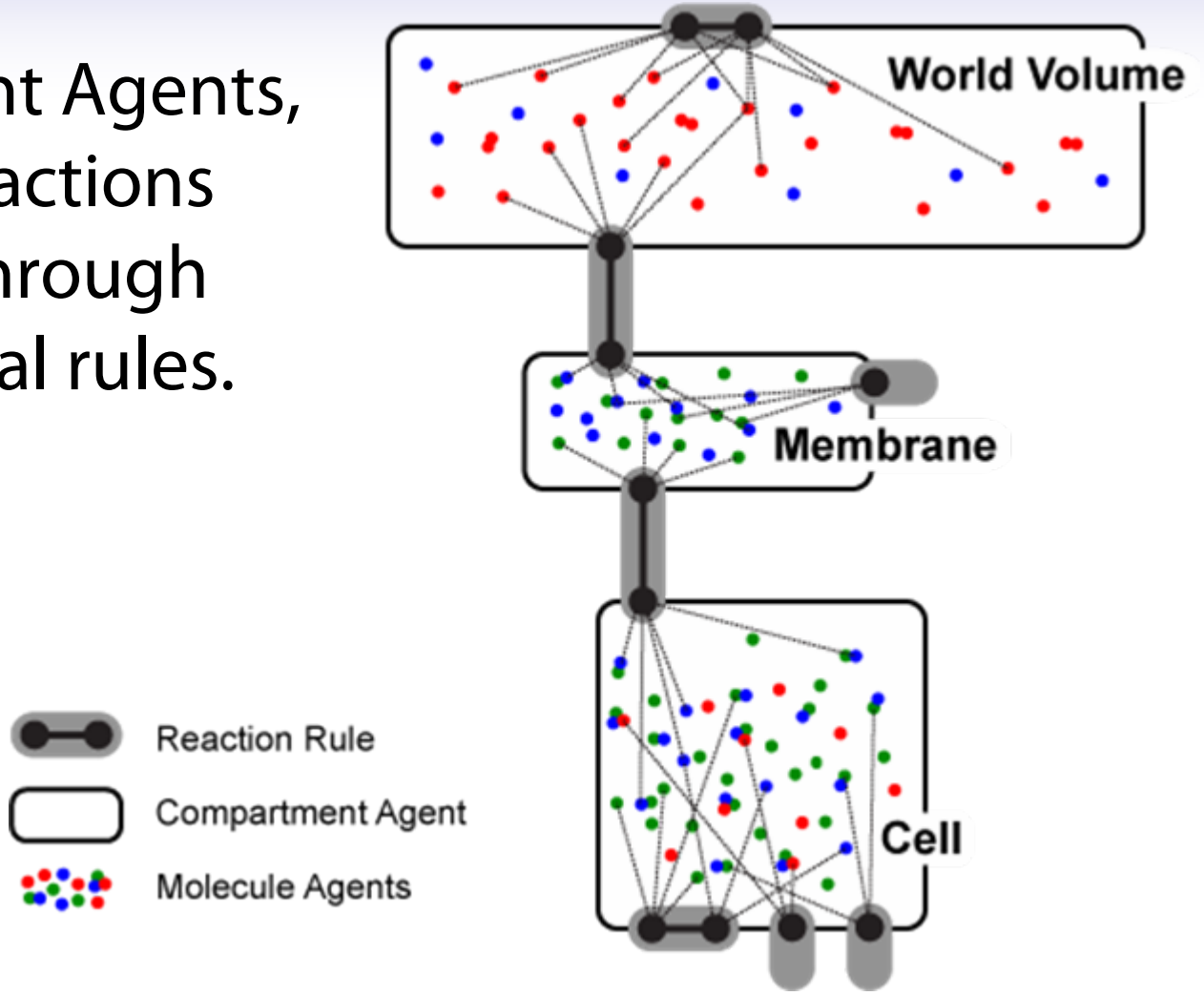
Rick Stevens Group
Argonne National Lab

Applications to Medicine, Knowledge Representation

Gary An Lab
Northwestern University

Current Development

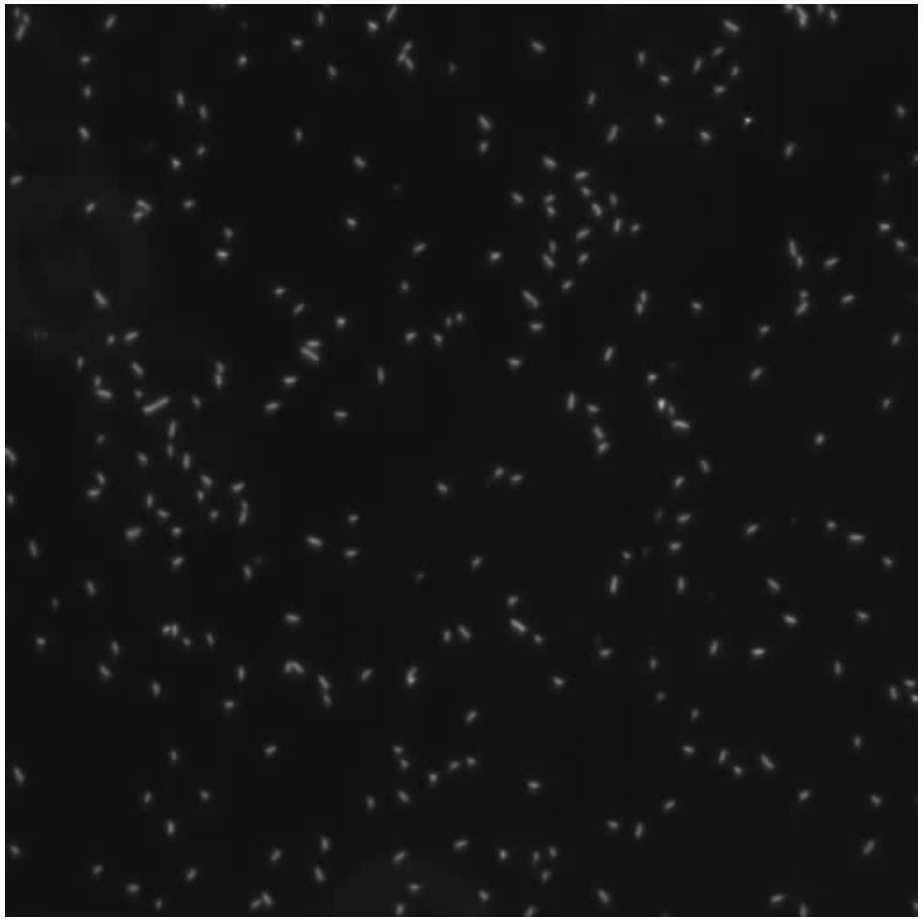
Compartment Agents, with interactions defined through biochemical rules.



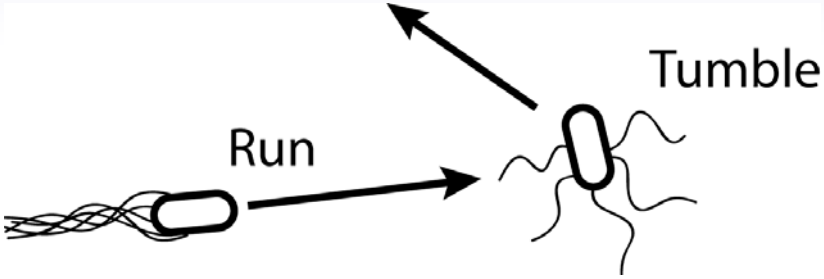
Applications to Complex Systems

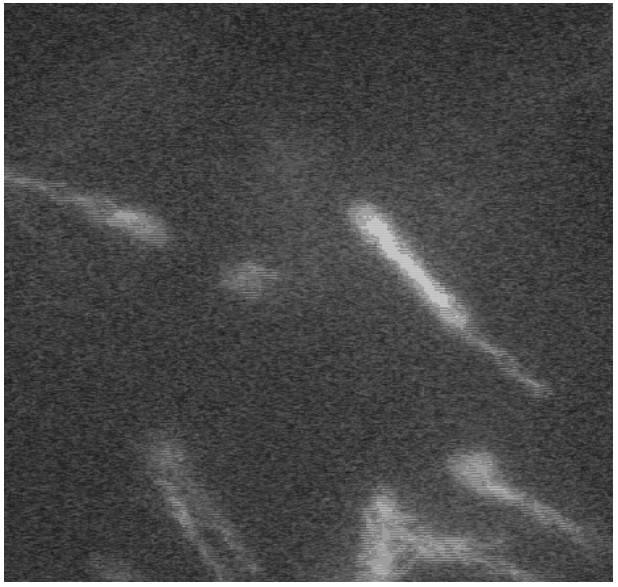
Bacterial Chemotaxis:

A model system for signal transduction



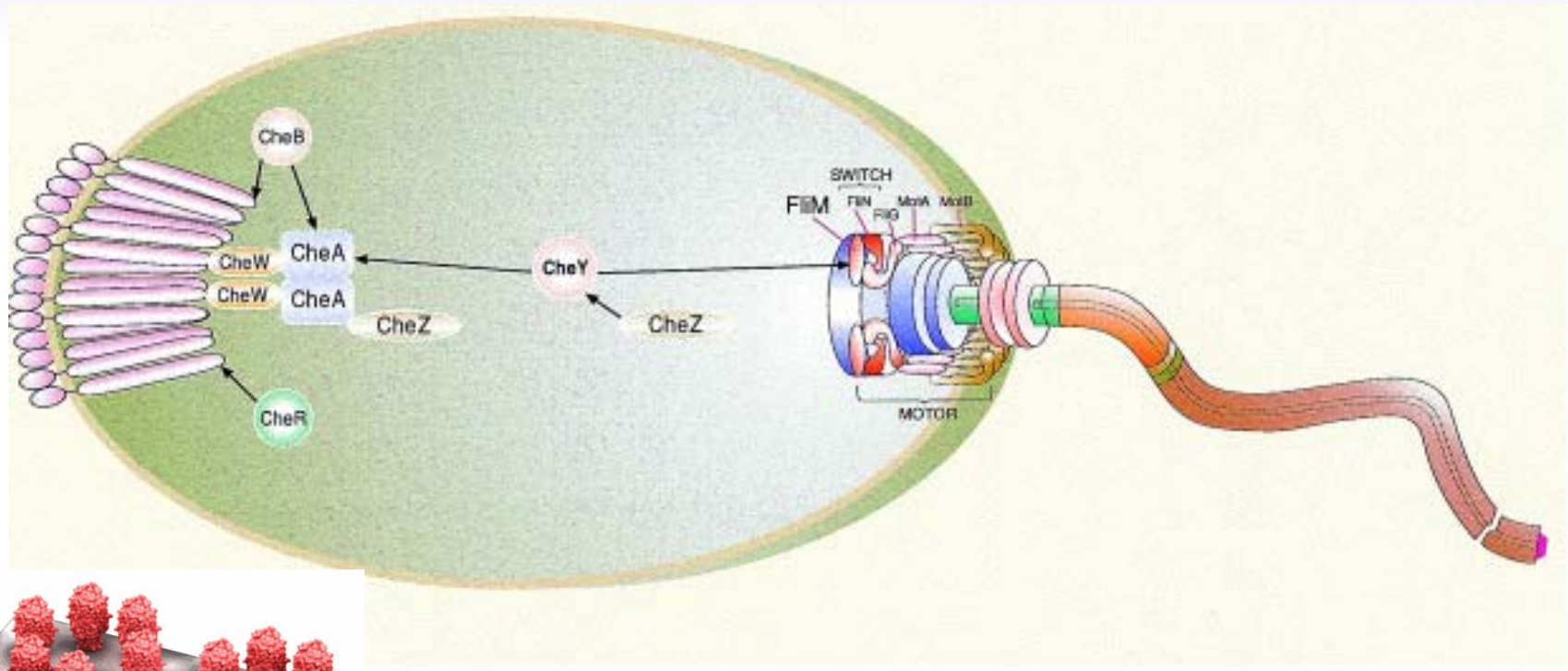
Emonet Lab

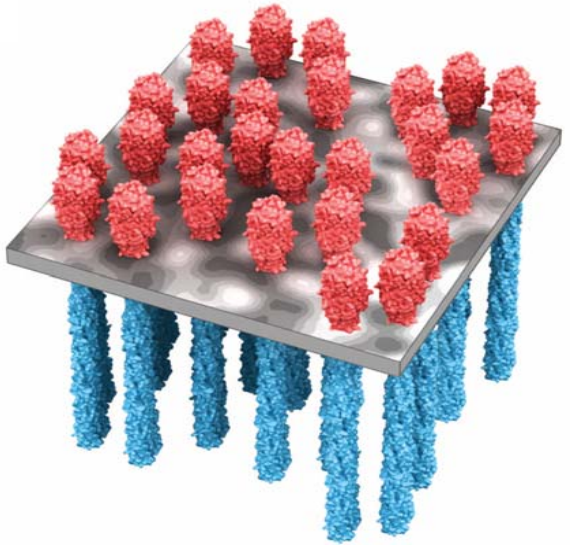




Berg Lab

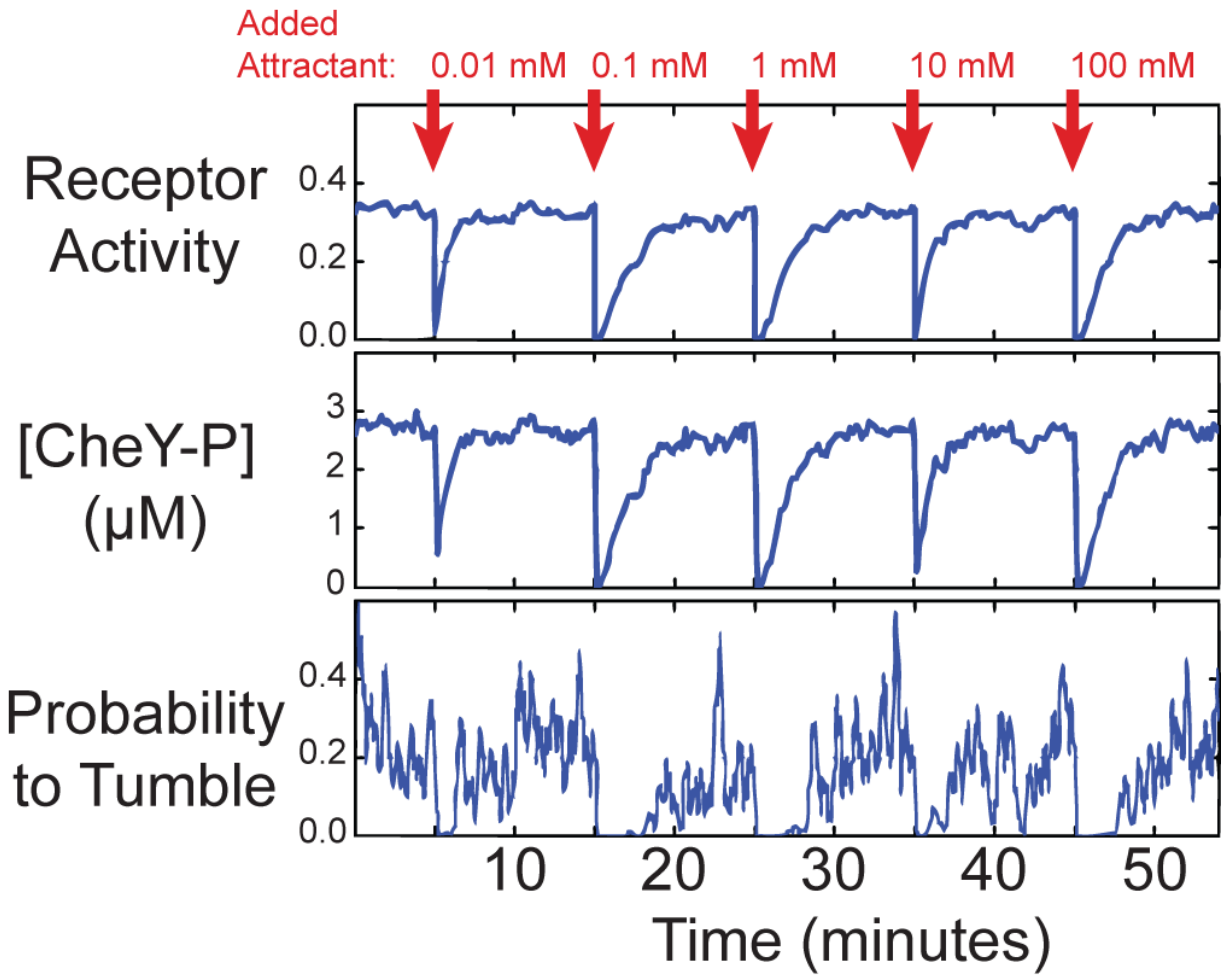
Complexity in Chemotaxis Signaling



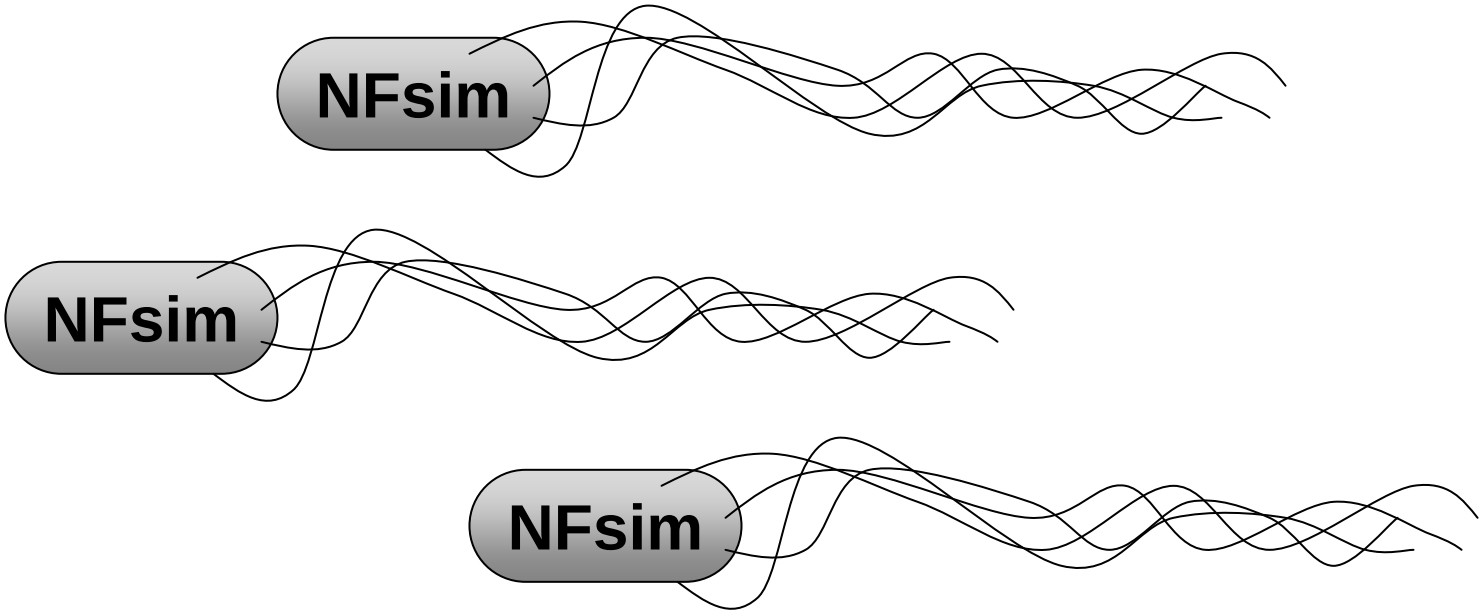


Receptor aggregation makes simulation difficult

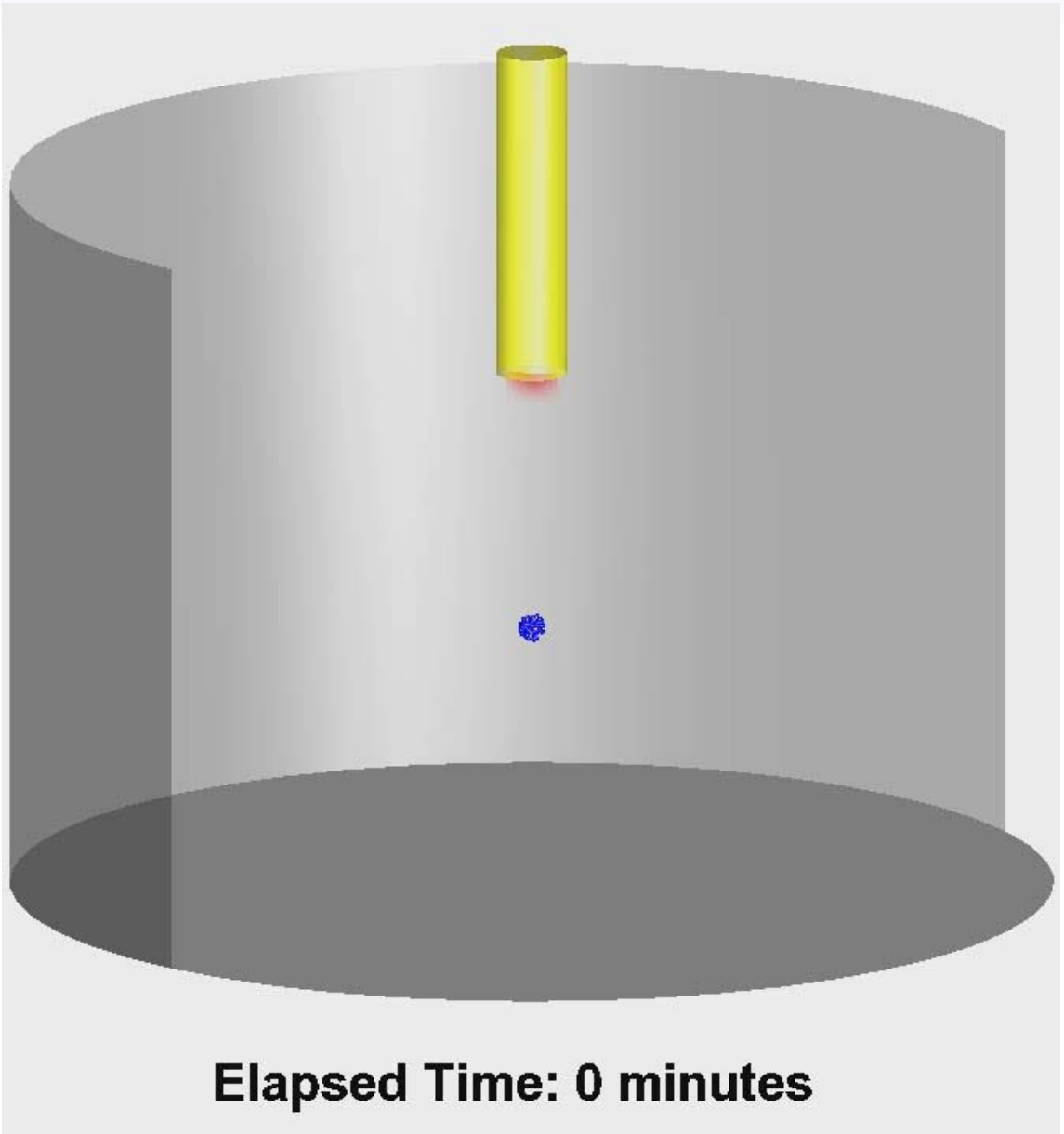
Complexity in Chemotaxis Signaling



NFsim can be embedded into other higher level agents



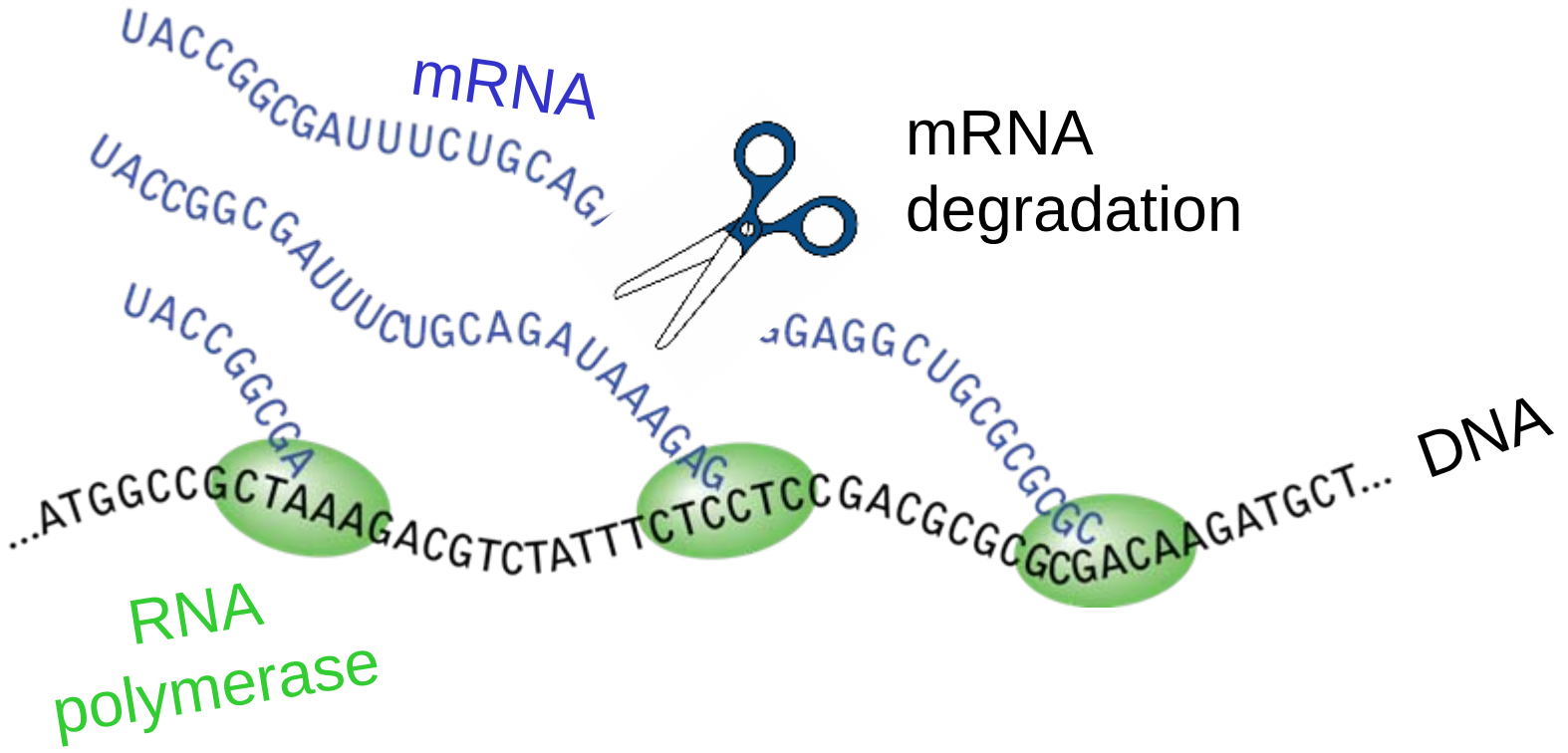
Digital Chemotaxis Experiments



200 *E. coli* Cells
2mm from Capillary
10mM Attractant

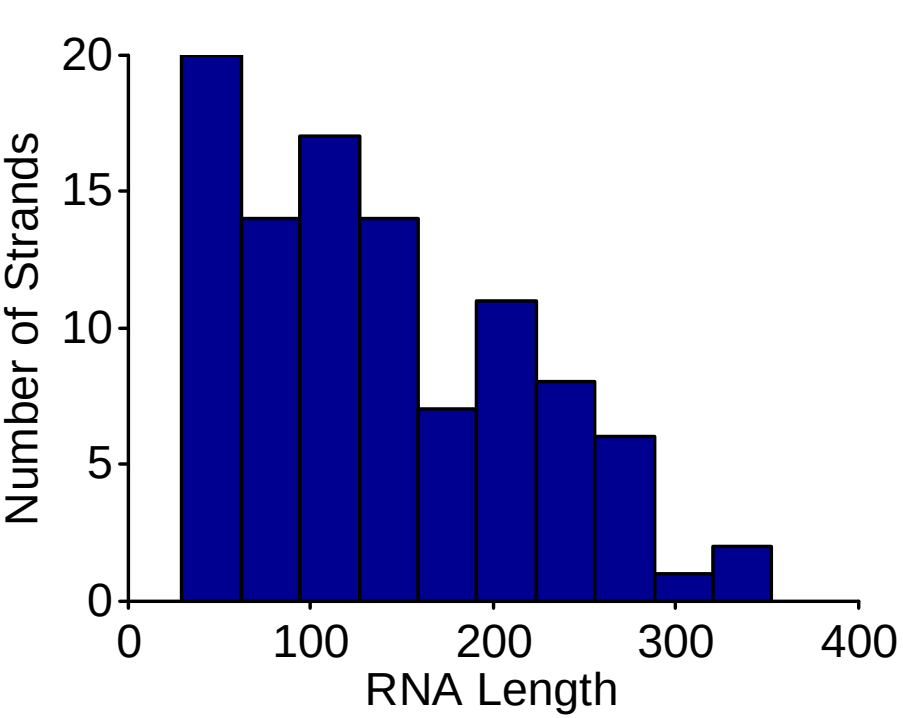
40 min simulation

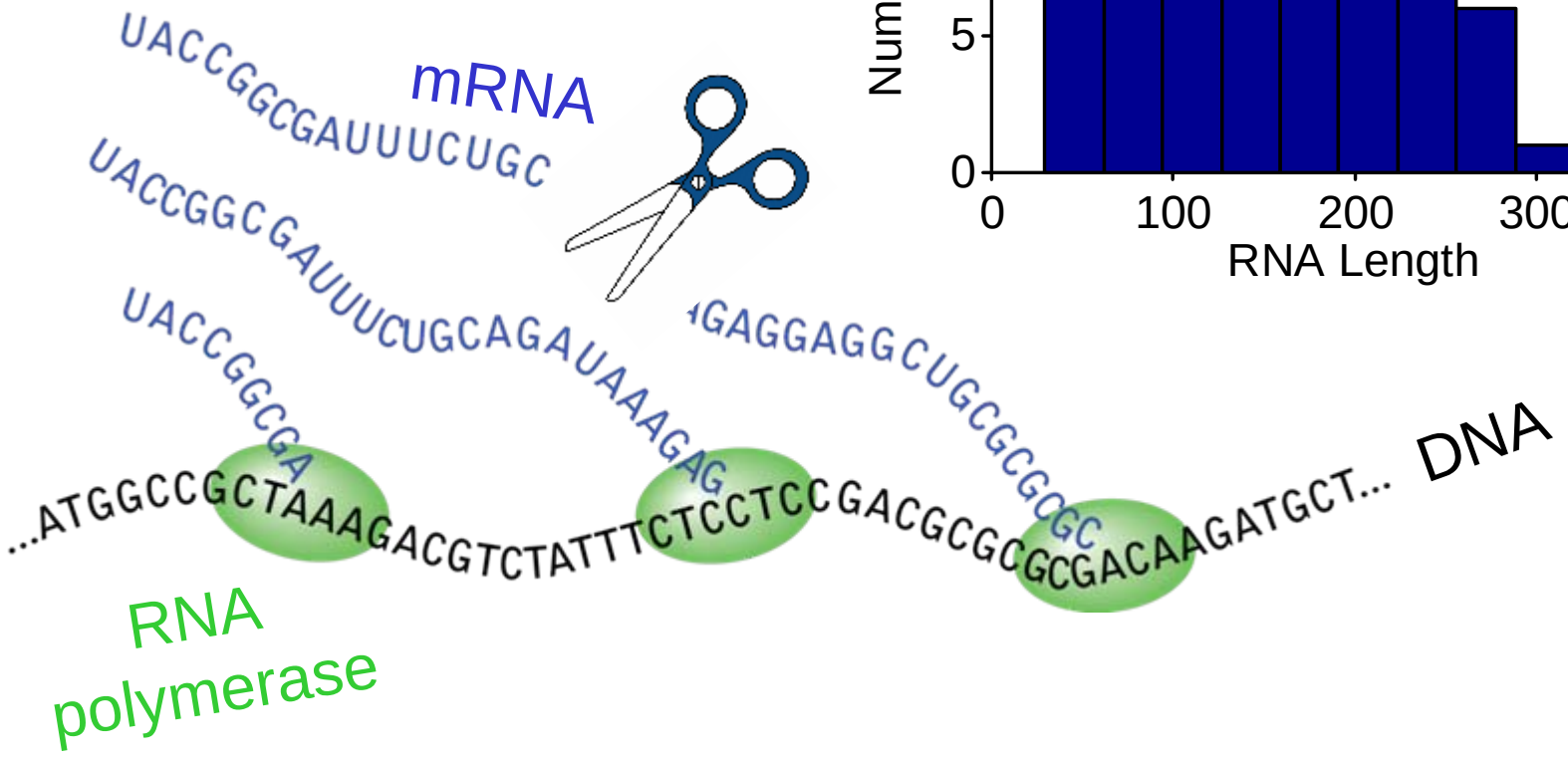
RNA Transcription



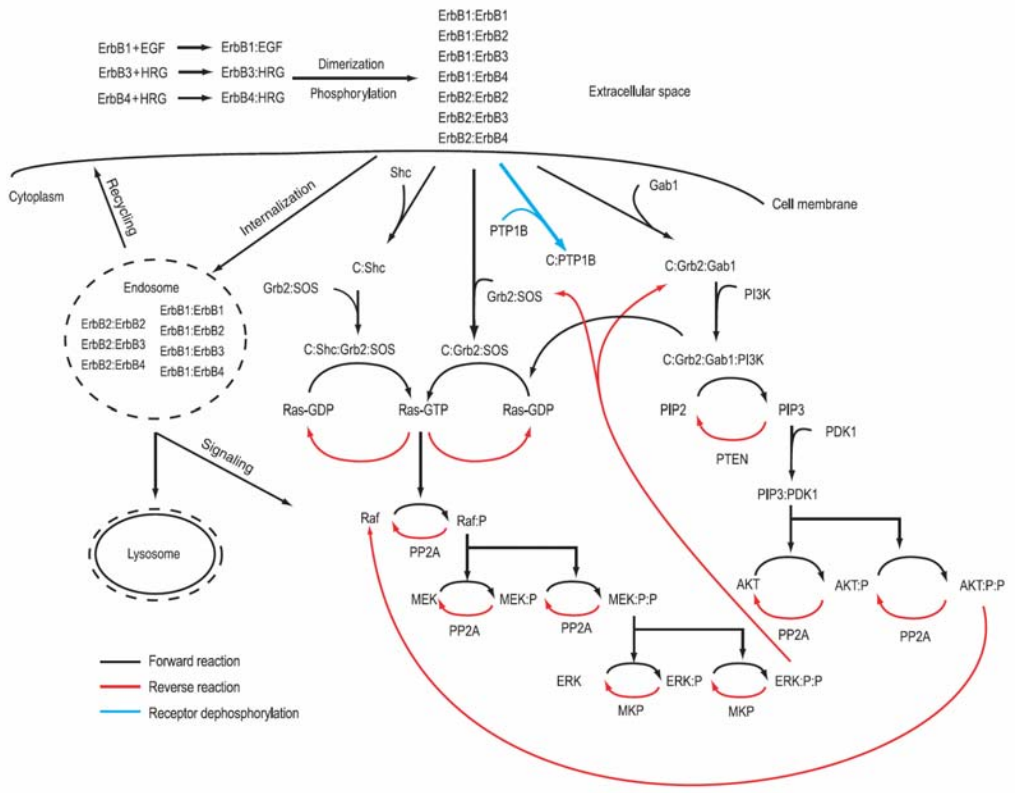
RNA Transcription

NFsim allows you to model complex polymer formation easily with a few rules…





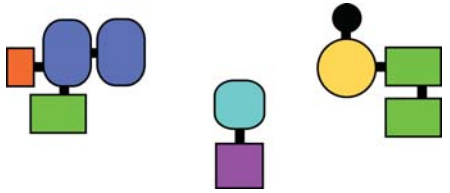
Epidermal Growth Factor (EGF) Signaling System



Chen, *et al, Molecular Systems Biology* (2009) 5, 239

~20 Different "Types" of Molecules

Millions of possible Molecular Species



How do I get NFsim?

NFsim is open source. The public release and manuscript for the core simulator is in preparation, and will be available here:

http://emonet.biology.yale.edu/nfsim

Email me to try out NFsim now:

michael.sneddon@yale.edu

Open Challenges and Current Development

1) **Addition of Spatial Compartments**
   Need to handle multiple cells, membranes, cell movement, and cell division in a single cohesive simulation

2) **Simulation of Compartments in Parallel**

3) **Dynamic Agent Compression**
   Agent-based methods for biochemical simulation are limited by the number of agents stored in memory.
   (NFsim: ~10 million agents in 4GB of memory)

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