

# Mesososcopic methods for noisy biochemical processes (II)



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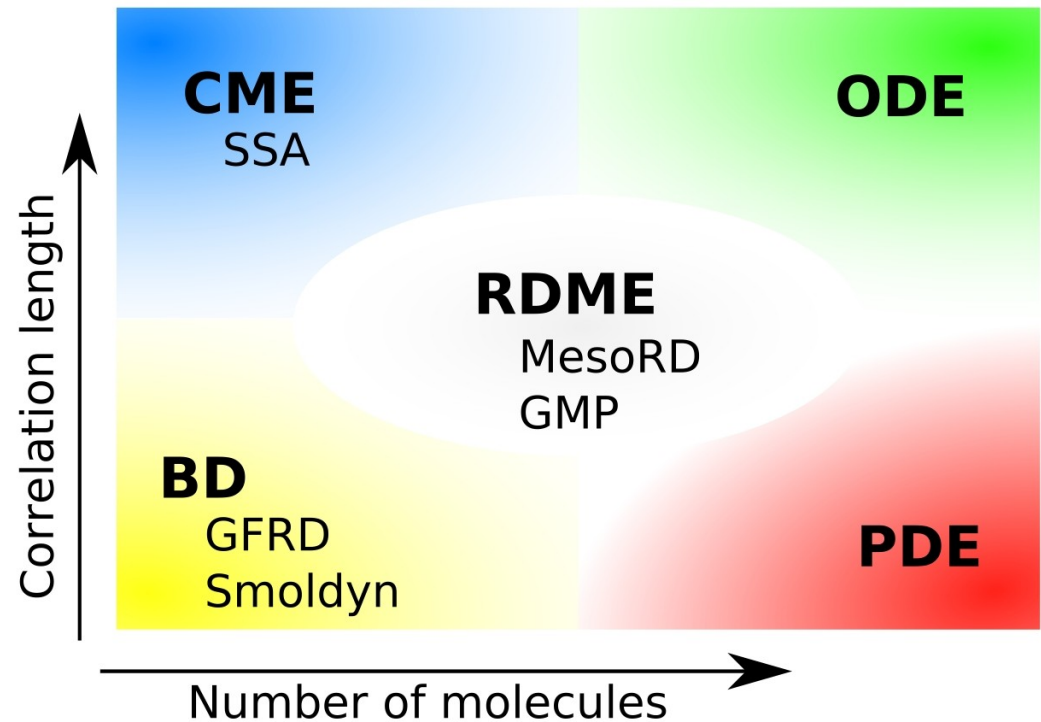
# Outline

Mesoscopic methods:  
Brownian dynamics  
Reaction-diffusion  
master equation

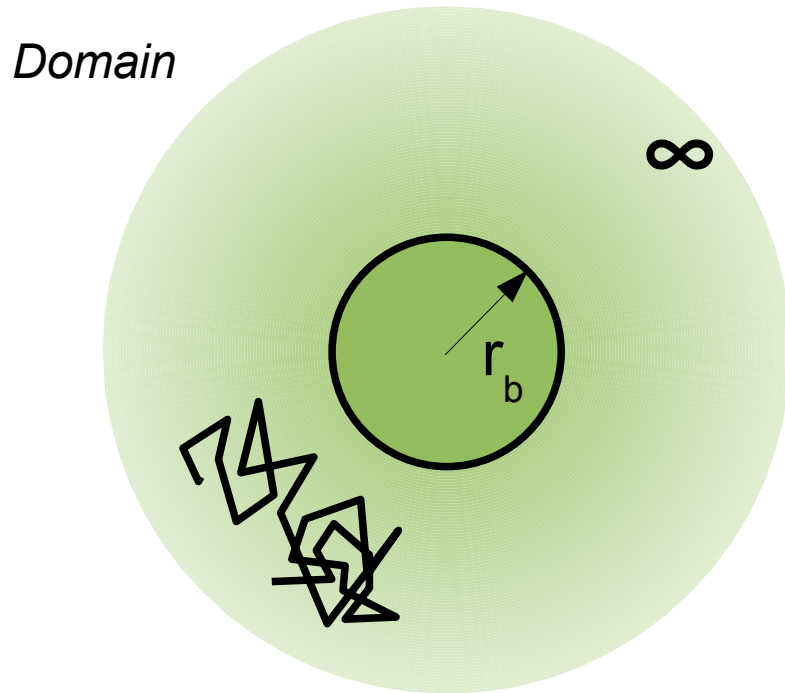
Comparison for the gene  
expression model

Explaining different behavior

Practical issues:  
input parameters  
complexity



# BD – chemical reactions



Random walk  
+  
reactions

Reversible reaction:  $A + B \leftrightarrow C$

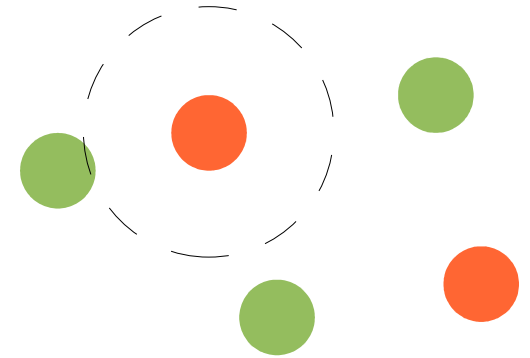
$$\text{flux at } r = r_b \sim -K_r + K_d$$

# BD – implementations

## GFRD

- Brownian motion + reaction
- one pair can react per  $\Delta t \Rightarrow$  variable  $\Delta t$
- **not a package!**

J van Zon & PR ten Wolde, J.Chemical Physics 123, 2005

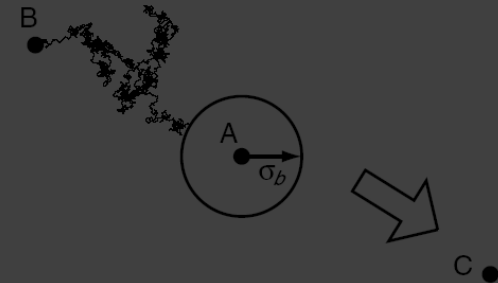


## Smoldyn

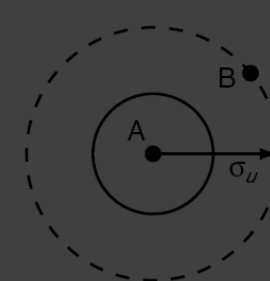
- fwd reaction rate  $\Rightarrow$  distance
- binding / unbinding radius
- fixed  $\Delta t$
- **usable tool!**

S Andrews & D Bray, Physical Biology 1, 2004

Forward reaction:  $A + B \rightarrow C$



Back reaction:  $C \rightarrow A + B$

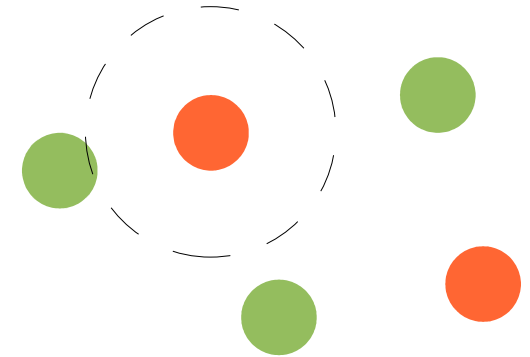


# BD – implementations

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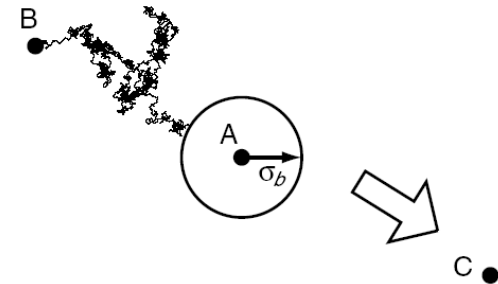


## Smoldyn

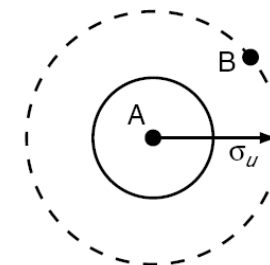
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# RDME – implementations



## Chemical Master Equation: Stochastic Simulation Alg. – Gillespie

Gillespie, J. Physical Chemistry, 81 (25), 1977

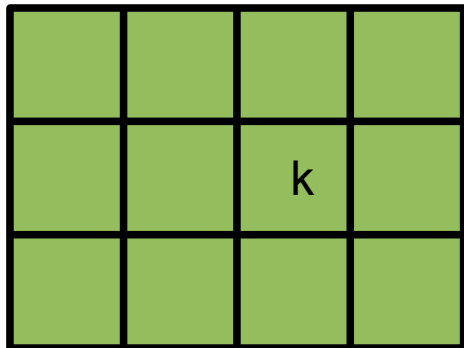
## Speed-ups:

$\tau$ -leap, next-reaction method

Gillespie, J. Chemical Physics, 115 (4), 2001

Gibson and Bruck, J. Physical Chemistry A, 104, 2000

# RDME – implementations



## Chemical Master Equation: Stochastic Simulation Alg. – Gillespie

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## Reaction-Diffusion Master Equation: MesoRD – next sub-volume method

Hattne et al., Bioinformatics 21 (12), 2005

Elf and Ehrenberg, Systems Biology 1 (2), 2004

## GMP – splitting reaction-diffusion

Vidal et al., Bioinformatics, 2006

# Test case

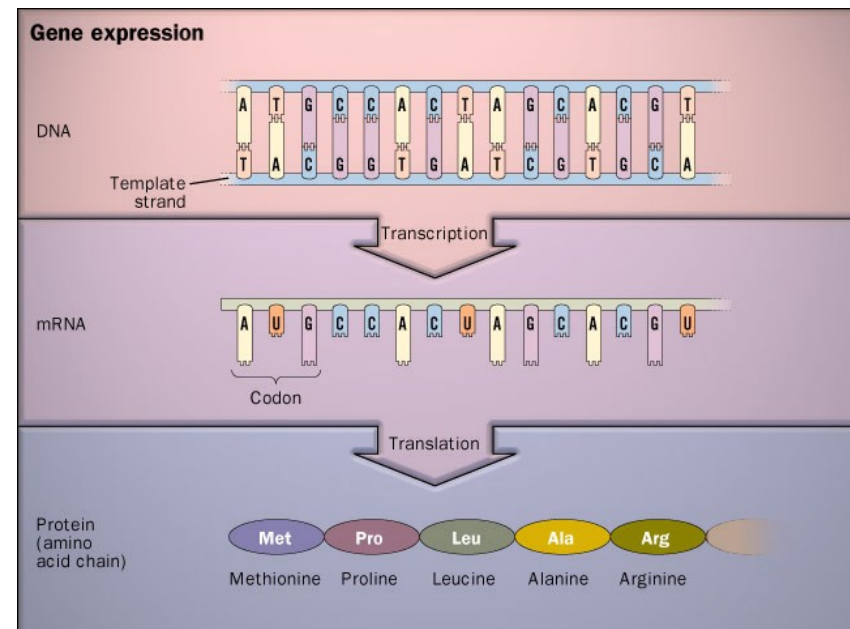
DNA + RNAP  $\leftrightarrow$  Complex

Complex  $\rightarrow$  DNA + RNAP + Protein

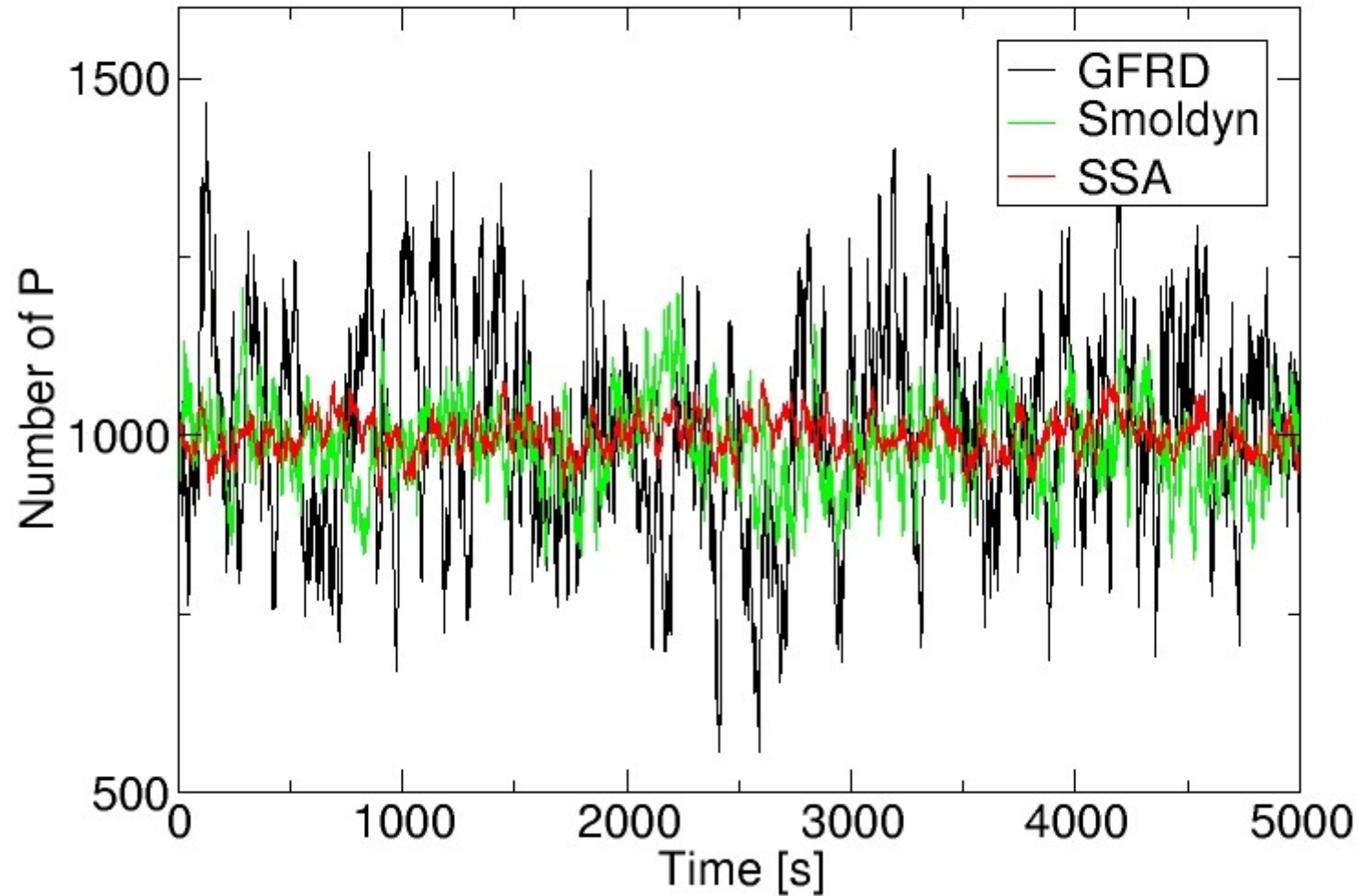
Protein  $\rightarrow \emptyset$

Measurements:  
average protein number

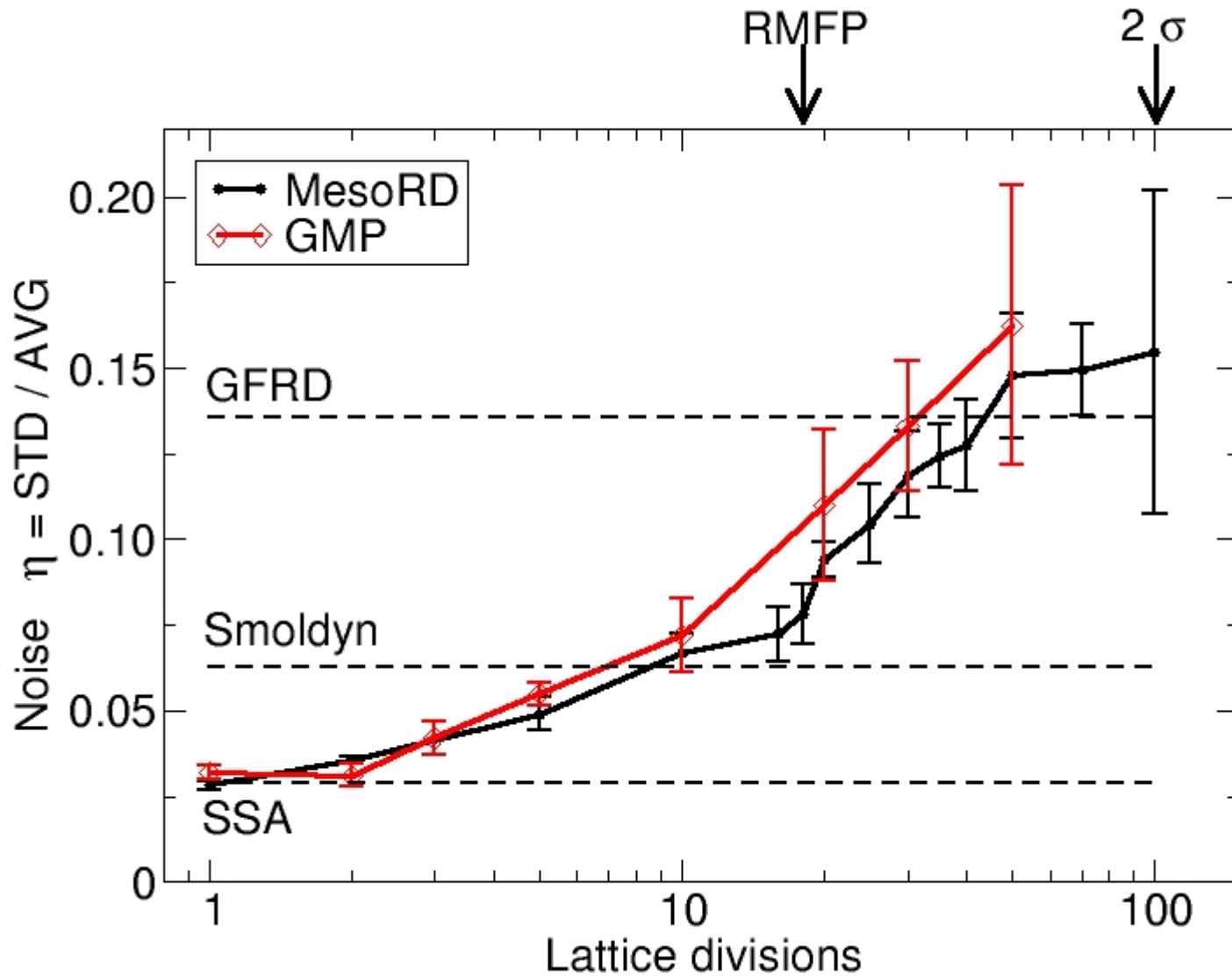
noise: STD / Mean



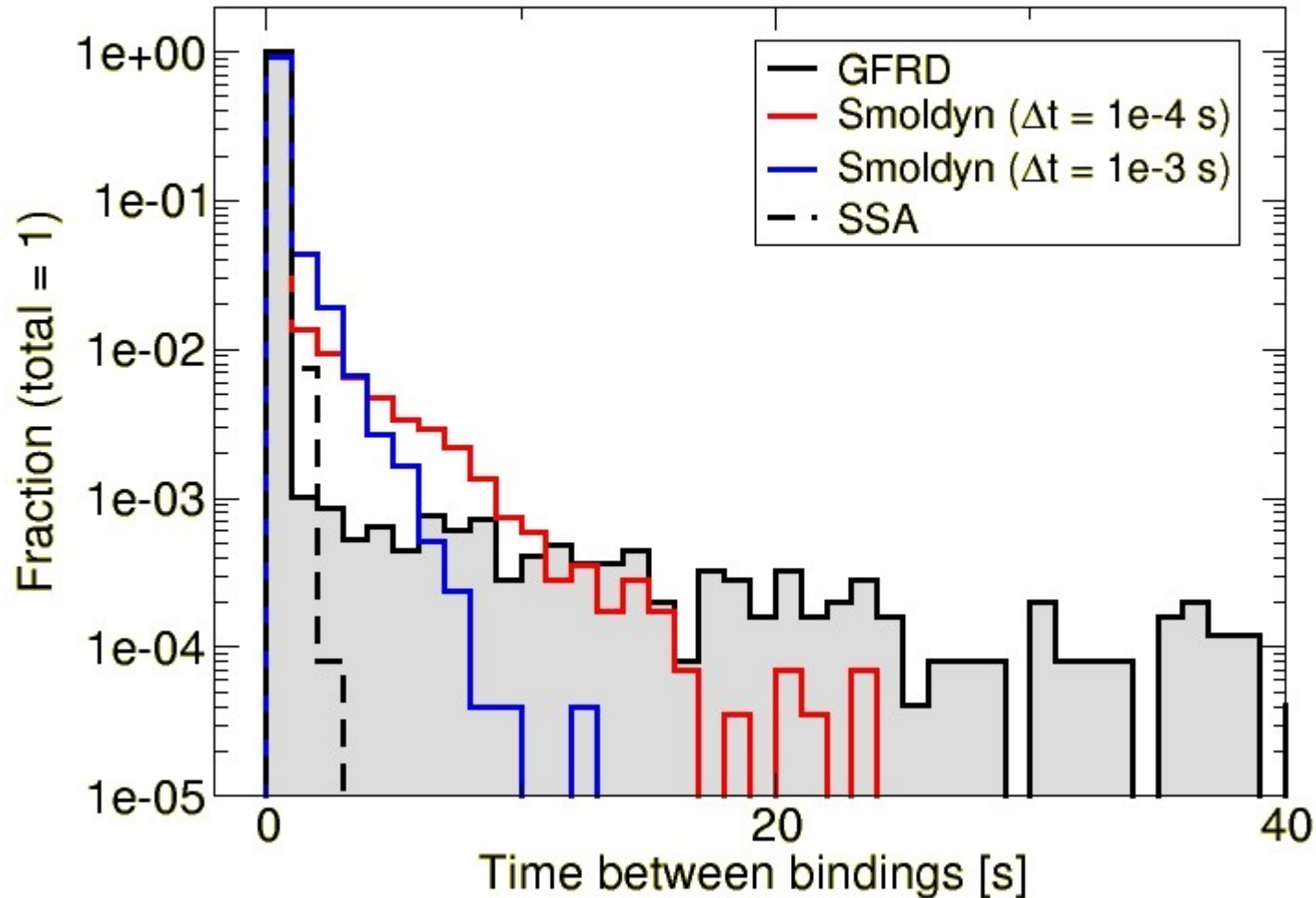
# Time trajectories



# Noise vs lattice size

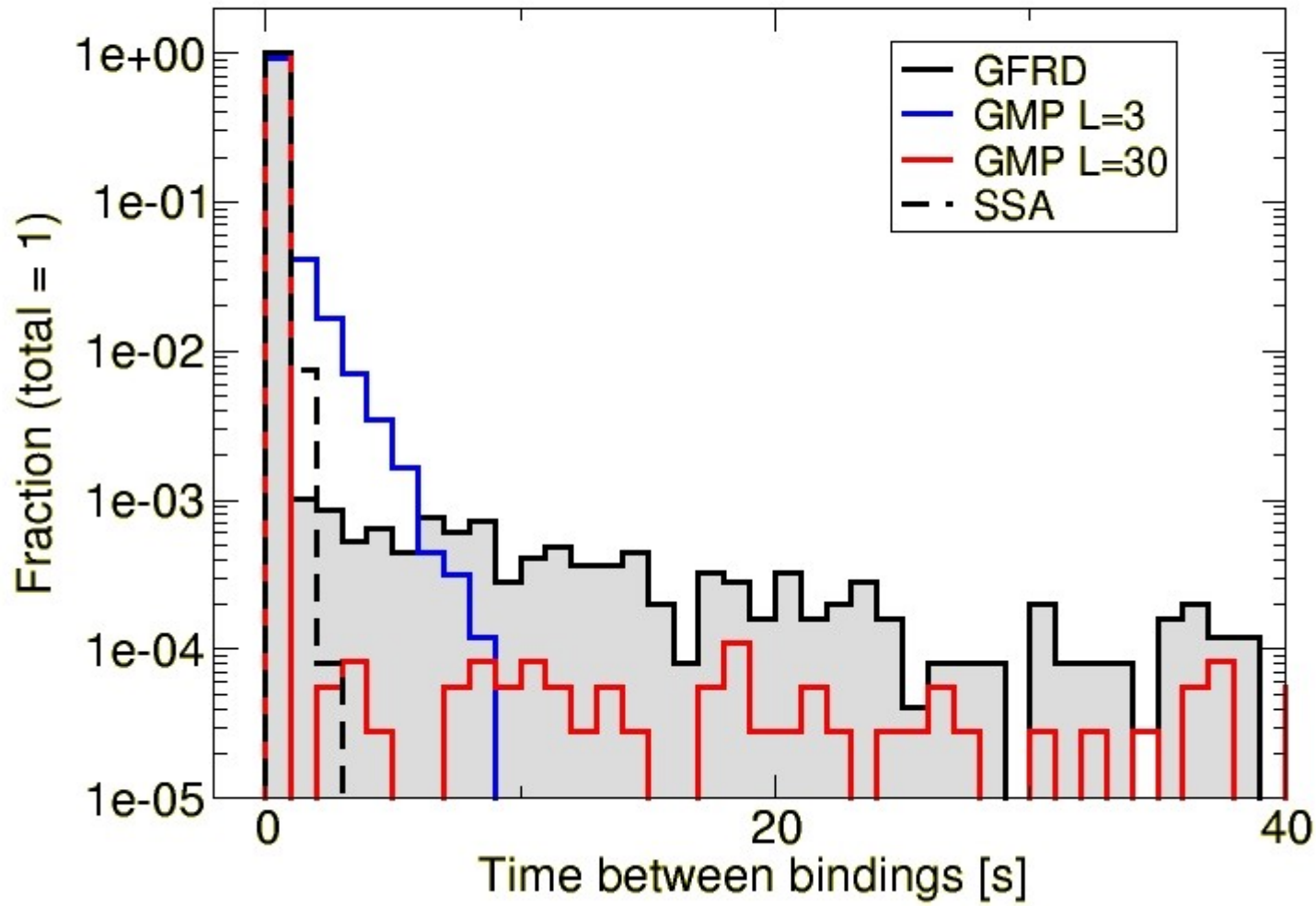


# Isolated pair – reversible reaction



Same average, different higher moments!

# Isolated pair (II)



# Input parameters

All methods:

- diffusion constants
- reaction rates
- geometry

GFRD:

- size of the molecules

Smoldyn:

- binding + unbinding radii
- time step

RDME (GMP, MesoRD, etc.):

- lattice size

# Complexity

## GFRD:

- scales with number of molecules
- advantage over classical BD (analytical propagator)  
 $\Delta t \sim 10^{-10} \text{ s} \Rightarrow 10^{-6} - 10^{-4} \text{ s}$

## Smoldyn:

- scales with number of molecules
- fixed  $\Delta t$  (typically  $\sim 10^{-4} \text{ s}$ )

## RDME:

- scales with:
  - ✓ number of sub-volumes
  - ✓ number of reaction channels & reactive species
- MesoRD: efficient for sparse systems (next sub-vol.)
- GMP: efficient for large systems (distributions)

# Conclusions

## GFRD:

- properly models diffusion-limited reactions
- need to be tailored

## Smoldyn:

- not able to reproduce proper fluctuations
- reversible reactions  $\Rightarrow$  binding / unbinding radii

## RDME (GMP, MesoRD, etc.):

- properly accounts for spatial effects
- correct results for lattice size  $\sim$  size of molecules
- RMFP lattice size yields  $\sim 20\%$  error

Q: low no. of molecules + short corr. length of compartment  
– existing biological regime?

# Acknowledgments

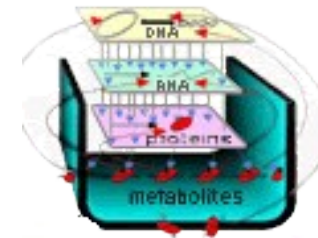
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