# Coarse-Grained Brownian Dynamics Simulation of Rule-Based Models

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# Motivation

**Aim**: impact of complexes (rings) stability for signalling cascades, etc.

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**Rule-based modelling**

- Cope with the combinatorics of potential complexes.
- Compact and non-redundant specification of reactions.

**Spatial simulation**

- Decompose diffusion (Brownian motion) and reaction.
- Finer expression of reaction probabilities.
- Impact of non-homogeneity.

**Coarse grain**

- Approximated stochastic simulation.
- Simple parameterization.

Contribution: combine the three ingredients, in a comprehensive manner.

# Overview

**Use of ruled-based paradigm**

- Never expand the rules: directly look for and apply rule embeddings.
- Enforce *atomic* rules: only one single modification at a time, arity $\leq 2$.

**Reaction probabilities refinement**

- Distinguish bindings occurring within a complex vs between complexes.
- Emerging behaviour: rings become very stable.

**Approximations**

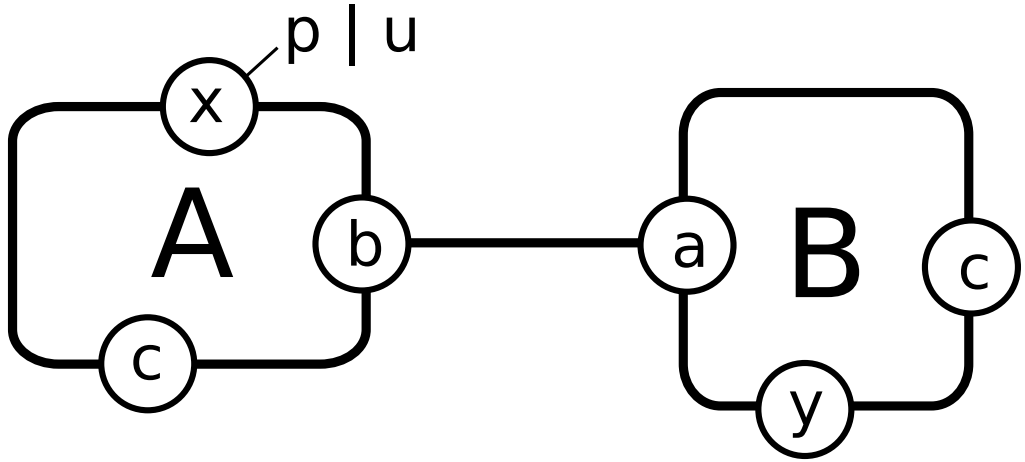
- Spherical approximation of complexes; ignore rotation, etc.
- Discrete-time simulation (approximation of Poisson distribution).

**Proof of concept**

- Initiation of the yeast pheromone response signalling cascade.
- Impact of the binding rates rules for the stability of the Ste5 scafold.

# Rule-based modelling

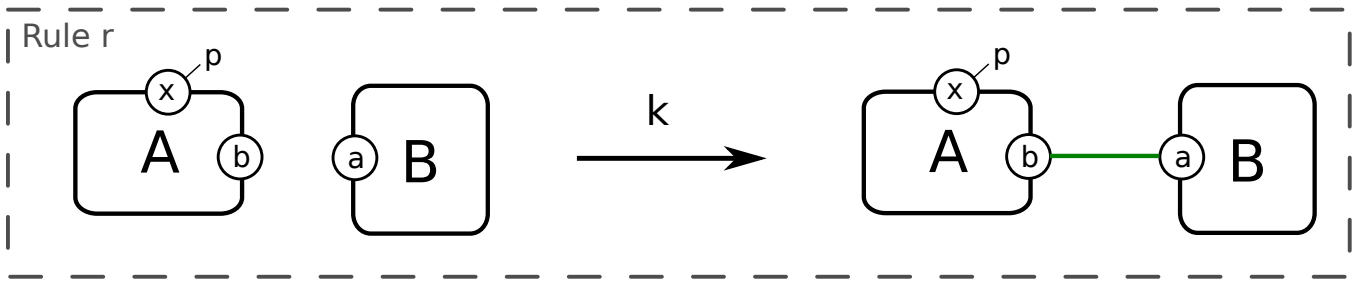
## Syntax

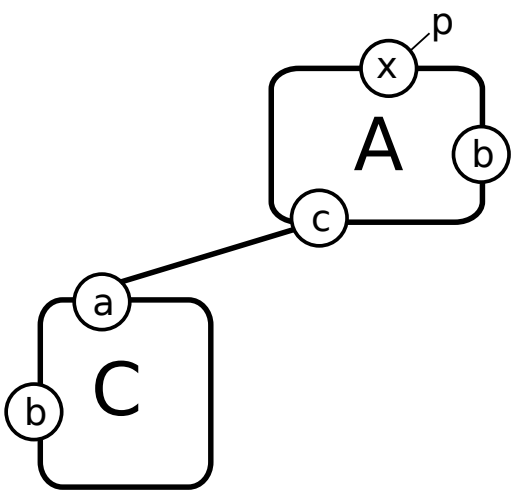



- Agents: e.g., $A$, $B$.
- Sites: e.g., $A.x$, $A.b$, $A.c$, $B.a$, $B.c$, $B.y$
- A site can have values: e.g., $p$, $u$.
- A site can be bound to another site of a different agent instance.

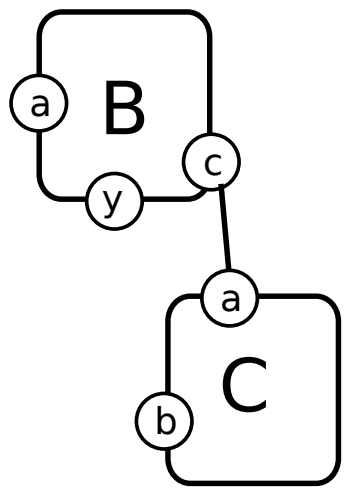
# Rule-based modelling

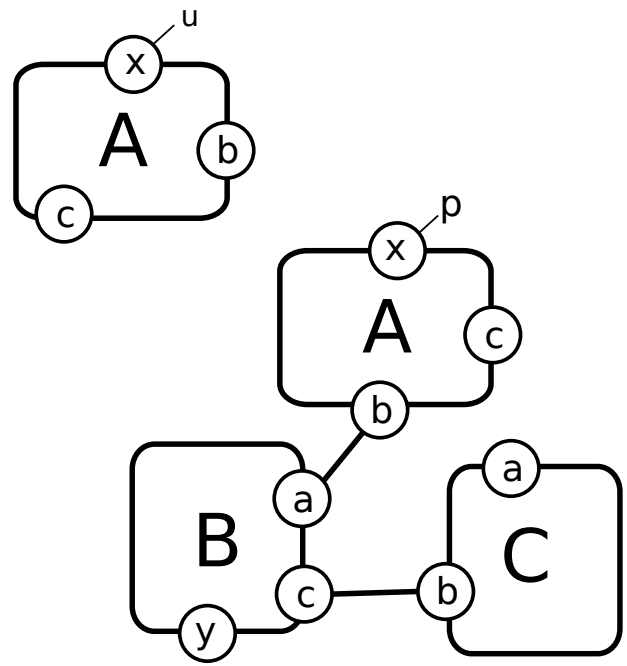
## Rule application



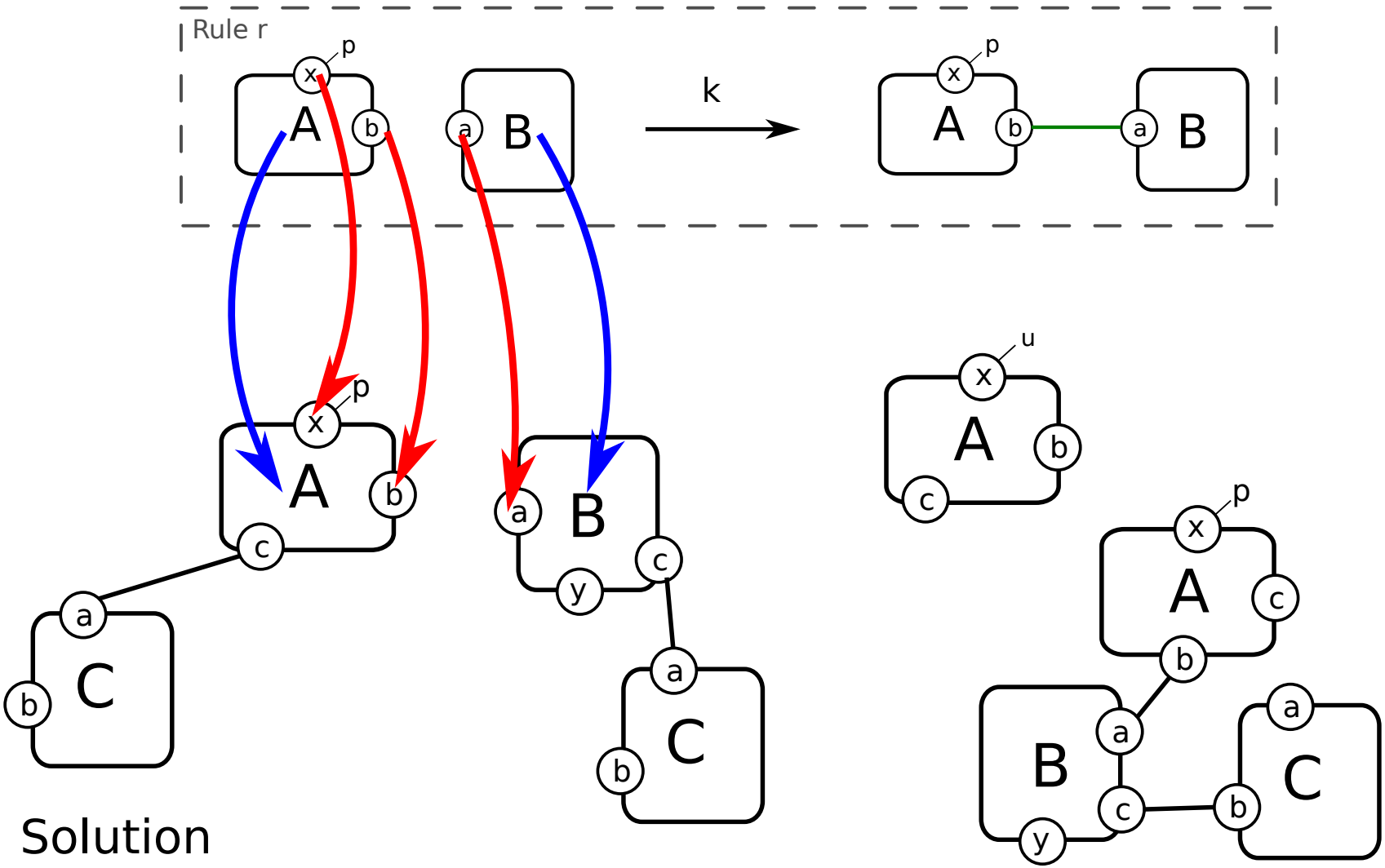

Solution



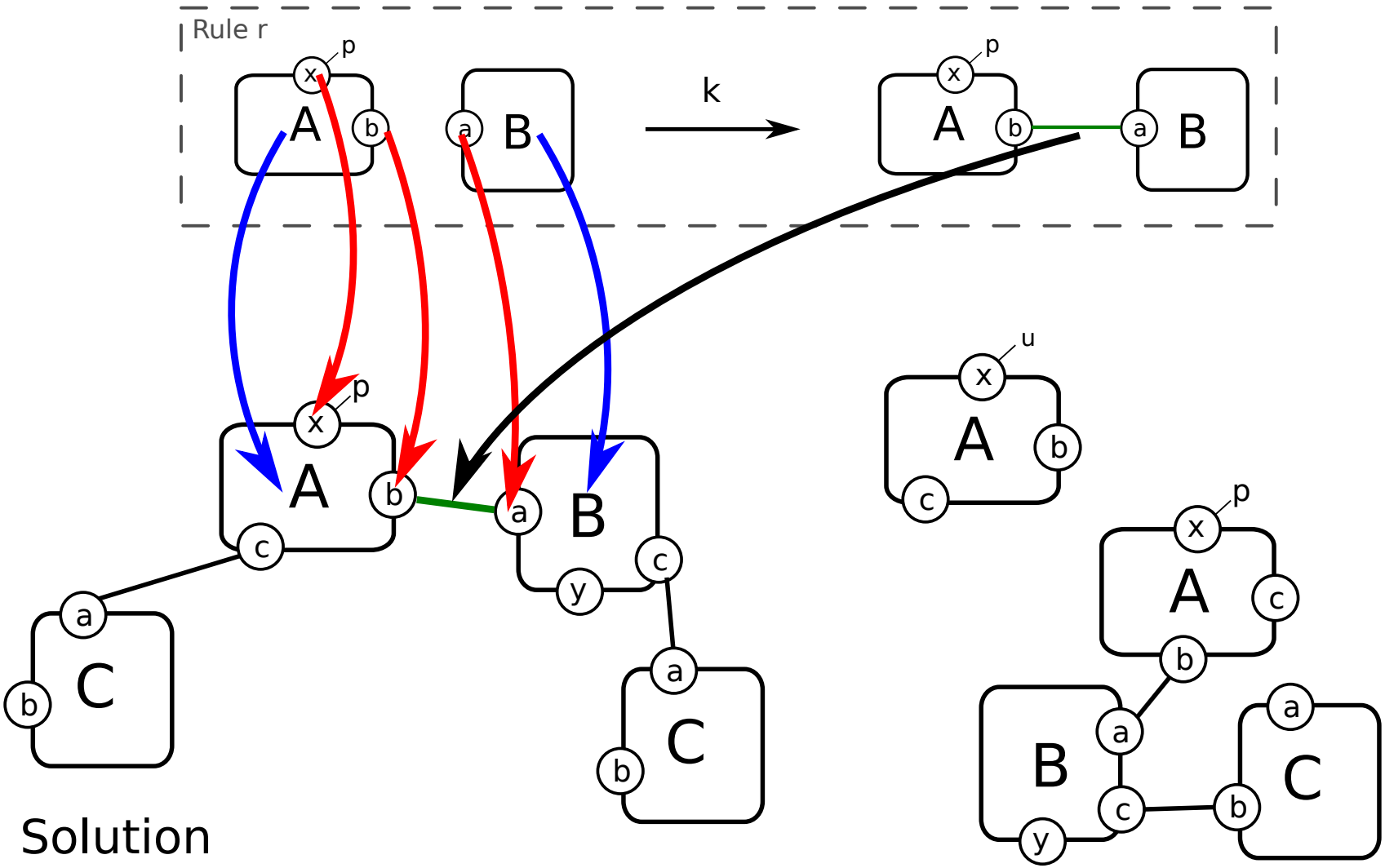
# Rule-based modelling

## Rule application



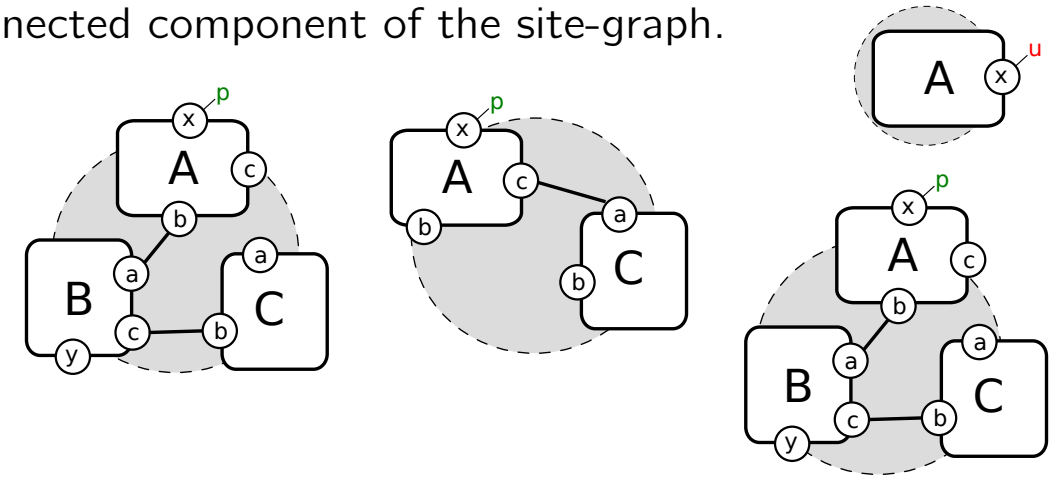
# Rule-based modelling

## Rule application



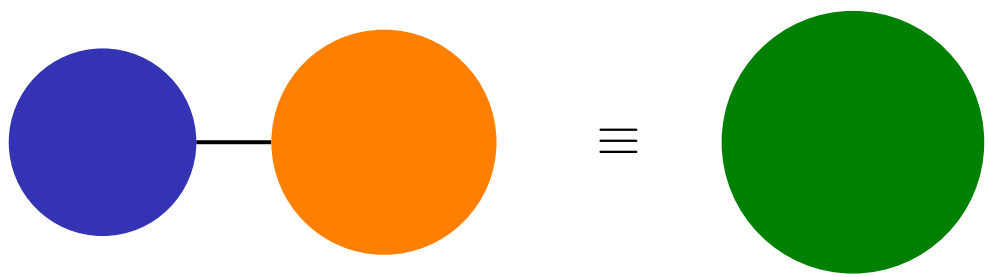
# Coarse-graining complexes

Complex ≡ connected component of the site-graph.




**Spherical approximation**

- No orientation, no rotation (considered as occurring on a much faster scale).
- Radius of agent $a$: $r_a$
- Radius of complex $C_i$: $\texttt{rad}(C_i) = \left(\sum_{v \in C_i} r^3_{\texttt{type}(v)}\right)^{1/3}$



# Brownian diffusion

Each complex instance is tracked individually (particle-based simulation).

Discrete time continuous space random walk for diffusion

$$\mathbf{x_i}(t + \Delta t) = \mathbf{x_i}(t) + \boldsymbol{\xi}\sqrt{2D_i\Delta t}$$

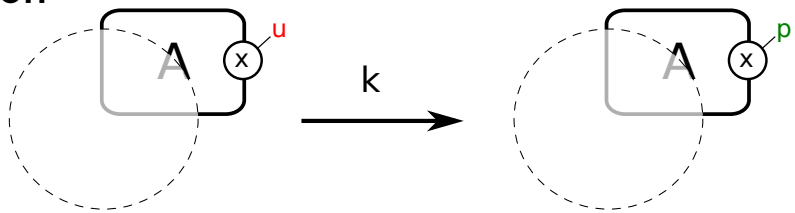
- $x_i(t)$: position of complex $i$ at time $t$.
- $\boldsymbol{\xi}$: standard normal random variable.
- $D_i$: diffusion coefficient of complex $i$ (derived using Stokes-Einstein equation)

$$D_i = \frac{D_0 r_0}{\mathtt{rad}(C_i)}$$

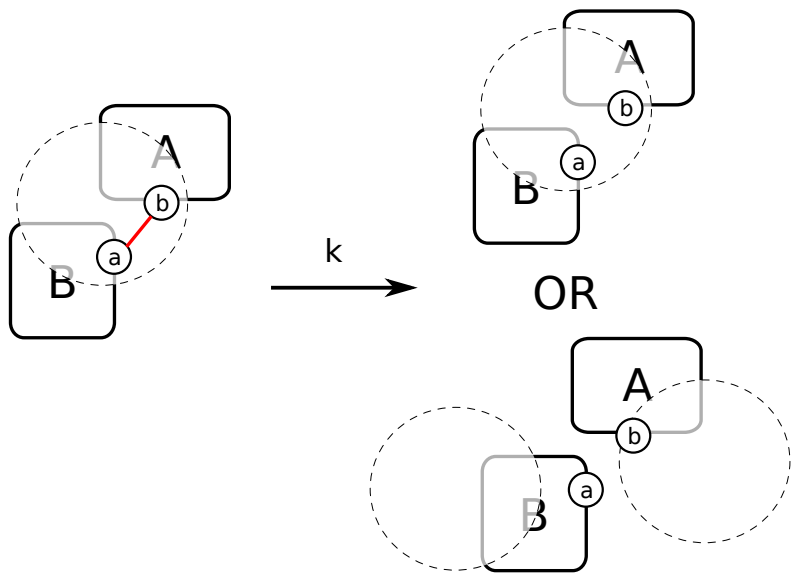
# Rules probability

## Modifcation / unbinding

**State modification**




**Unbinding**



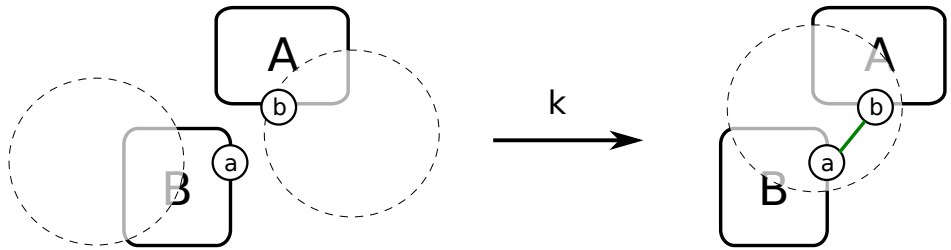

$\Rightarrow \texttt{prob}(\{C_1\}, \texttt{rule}, \Delta t) \approx k\Delta t$

# Rules probability

## Binding within/between complexes

One rule, two different instanciantions.

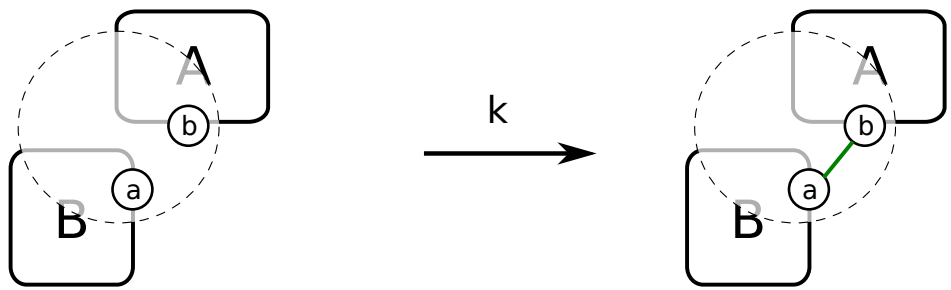
**Binding between two complexes**




$$\Rightarrow \texttt{prob}(\{C_1, C_2\}, \texttt{rule}, \Delta t) \approx \frac{3}{4\pi(\texttt{rad}(C_1)+\texttt{rad}(C_2))^3} k\Delta t$$

Only when collision!

**Binding within a complex**




$$\Rightarrow \texttt{prob}(\{C_1\}, \texttt{rule}, \Delta t) \approx \frac{3}{4\pi(r_A+r_B)^3} k\Delta t$$

Always active!

# Stochastic abstract machine

**Machine term**

| | |
|---|---|
| $M ::= (t, C, X, \mathcal{R})$ | Time $t$, complex maps $C$ and $X$, rules $\mathcal{R}$ |
| $C ::= \{i_1 \mapsto \mathcal{G}_1, \cdots, i_N \mapsto \mathcal{G}_N\}$ | Map from a complex $i$ to its site-graph $\mathcal{G}$ |
| $X ::= \{i_1 \mapsto \mathbf{x}_1, \cdots, i_N \mapsto \mathbf{x}_N\}$ | Map from a complex $i$ to its position $\mathbf{x} \in \mathbb{R}^3$ |

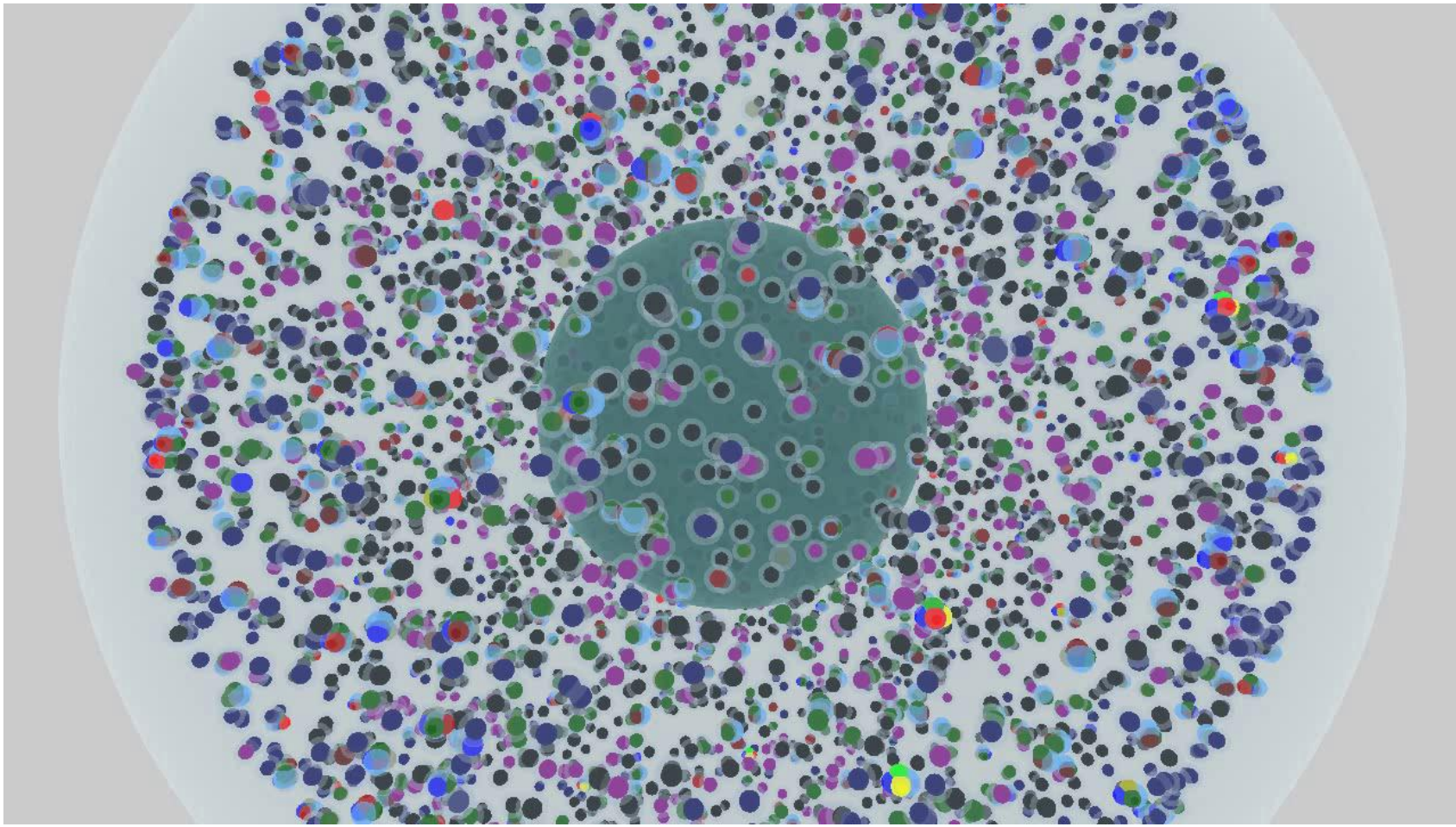
$i_1, \cdots, i_N$ are the complex identifiers, assumed all distinct.

**Execution**

$$\frac{\begin{aligned} X' &= \texttt{diffuse}(C, X, \Delta t) \\ (C', X'') &= \texttt{react}(C, X', \mathcal{R}, \Delta t) \end{aligned}}{(t, C, X, \mathcal{R}) \to (t + \Delta t, C', X'', \mathcal{R})}$$

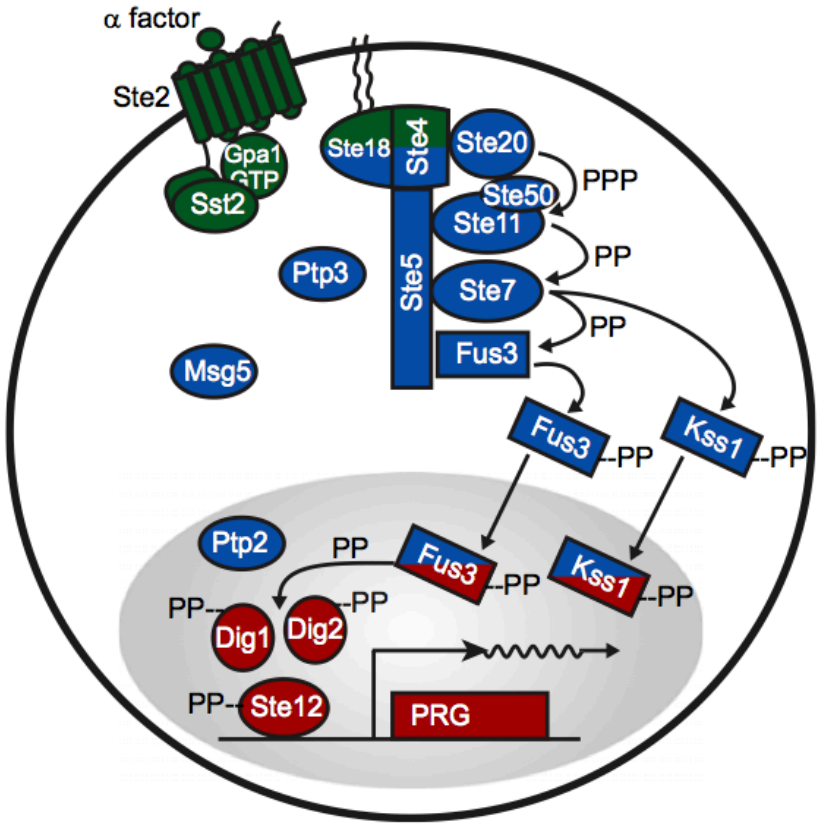
`diffuse`: Brownian diffusion
`react`: apply unary reactions and binary reactions restricted to collisions. Probability scaled by $\Delta t$.

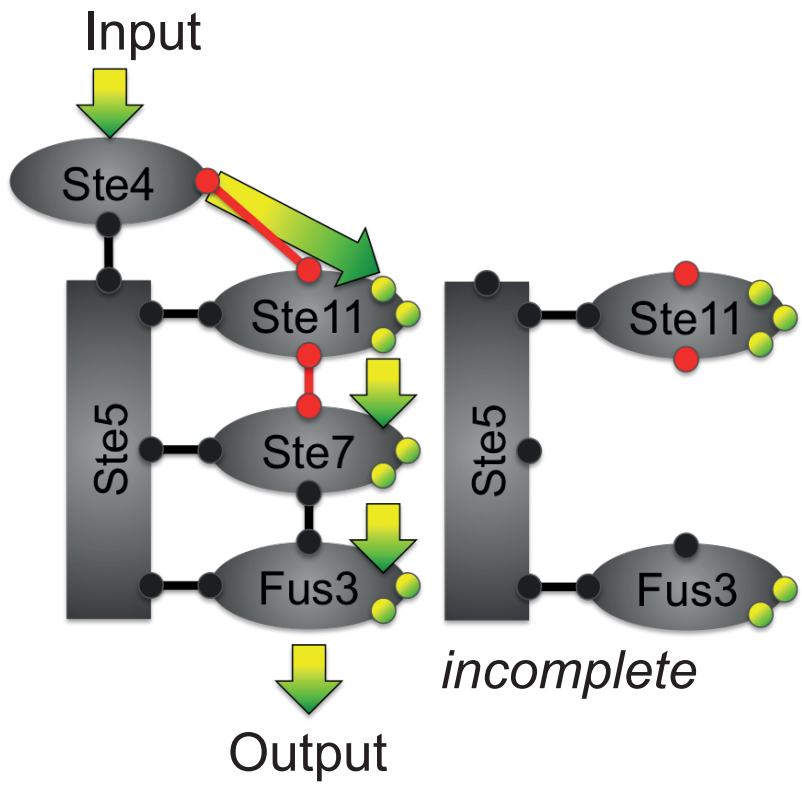
## Movie



# Application: Ste5 scafold

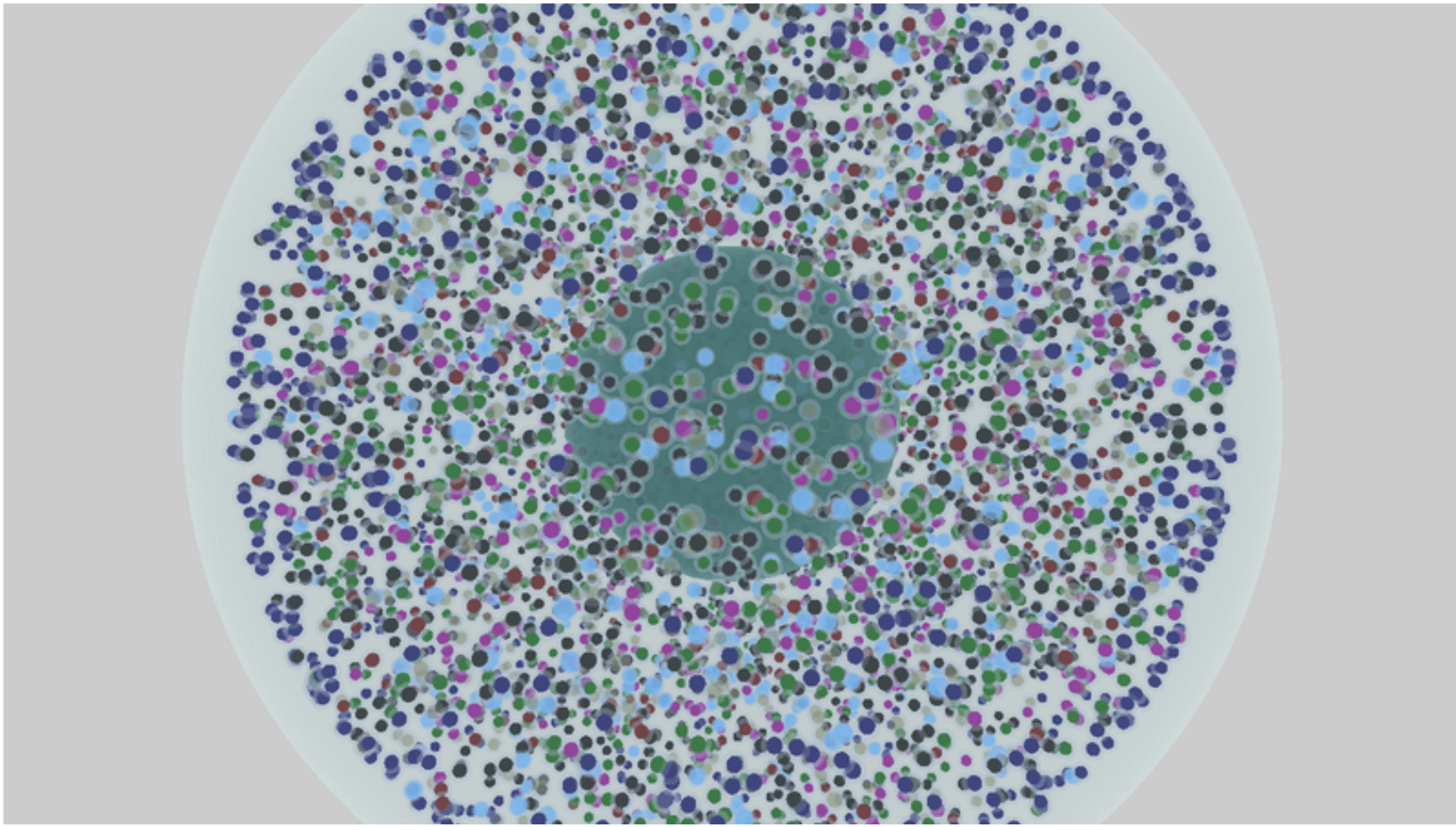
**Initiation of the Ste5/MAPK signalling cascade**



# Application: Ste5 scafold

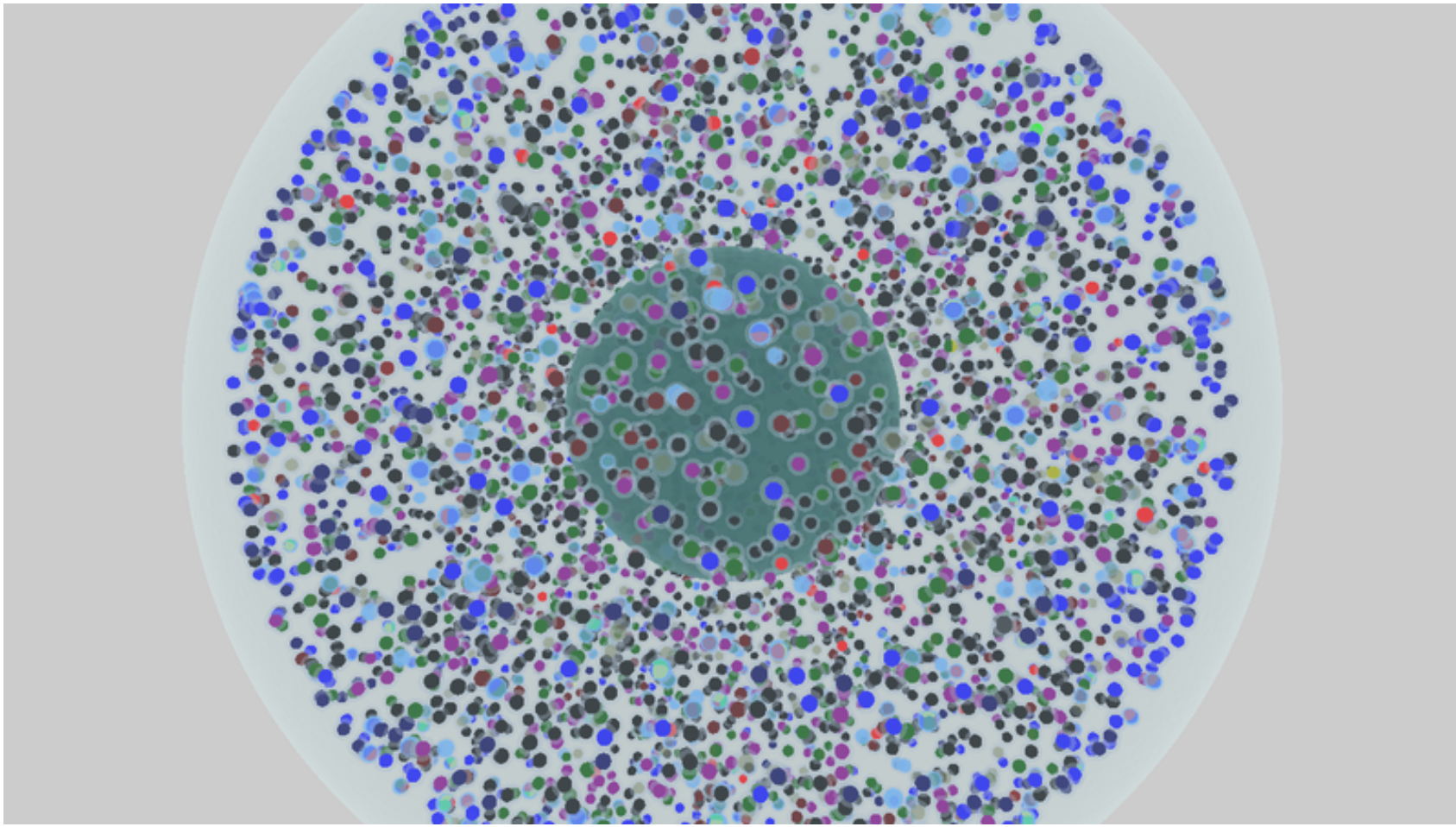
## Flipbook



t=1s Ste4=blue, Ste11=red, Ste7=yellow, Fus3=green

# Application: Ste5 scafold

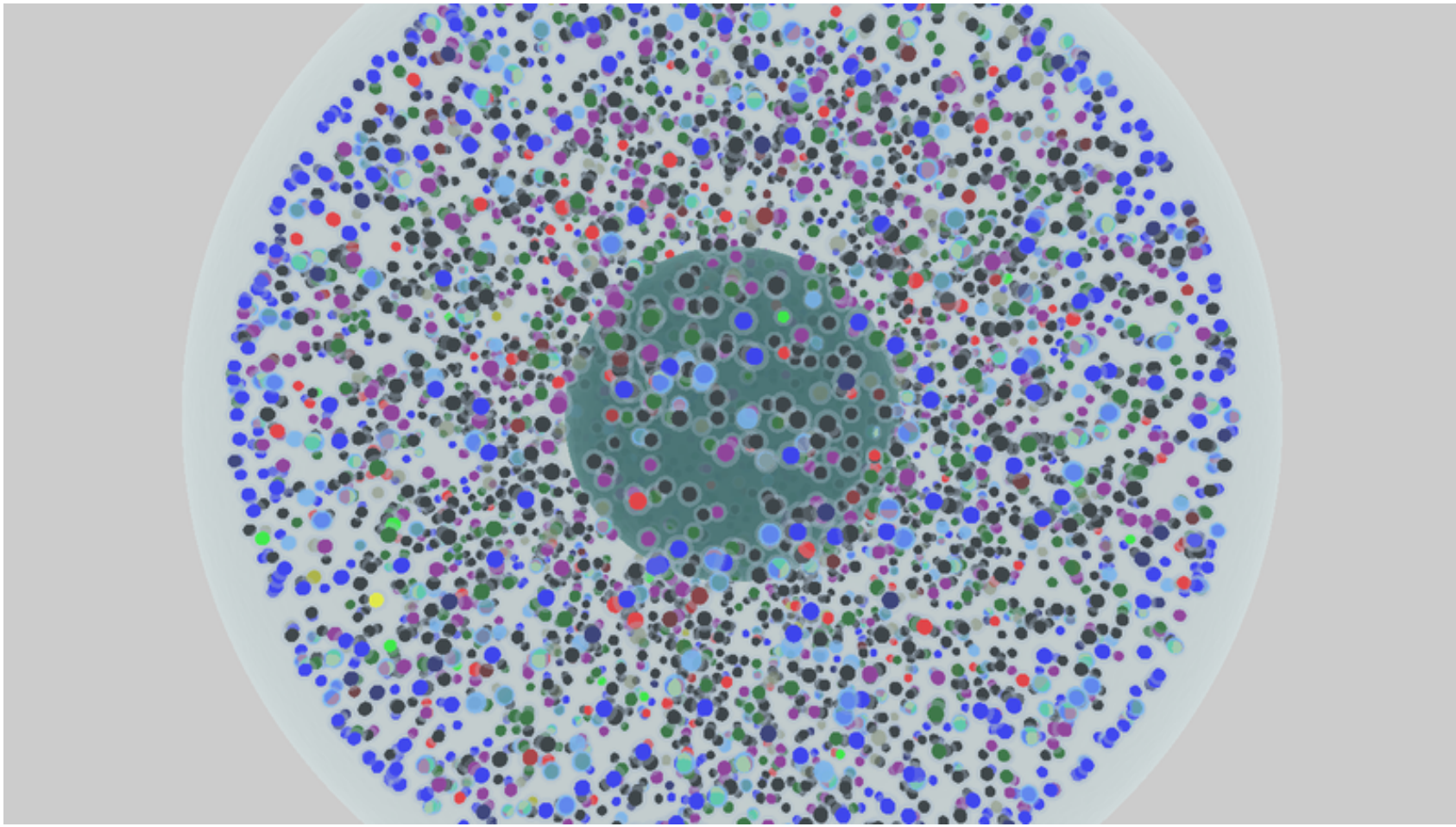
## Flipbook



t=25s Ste4=blue, Ste11=red, Ste7=yellow, Fus3=green

# Application: Ste5 scafold

## Flipbook



t=60s Ste4=blue, Ste11=red, Ste7=yellow, Fus3=green

# Application: Ste5 scafold

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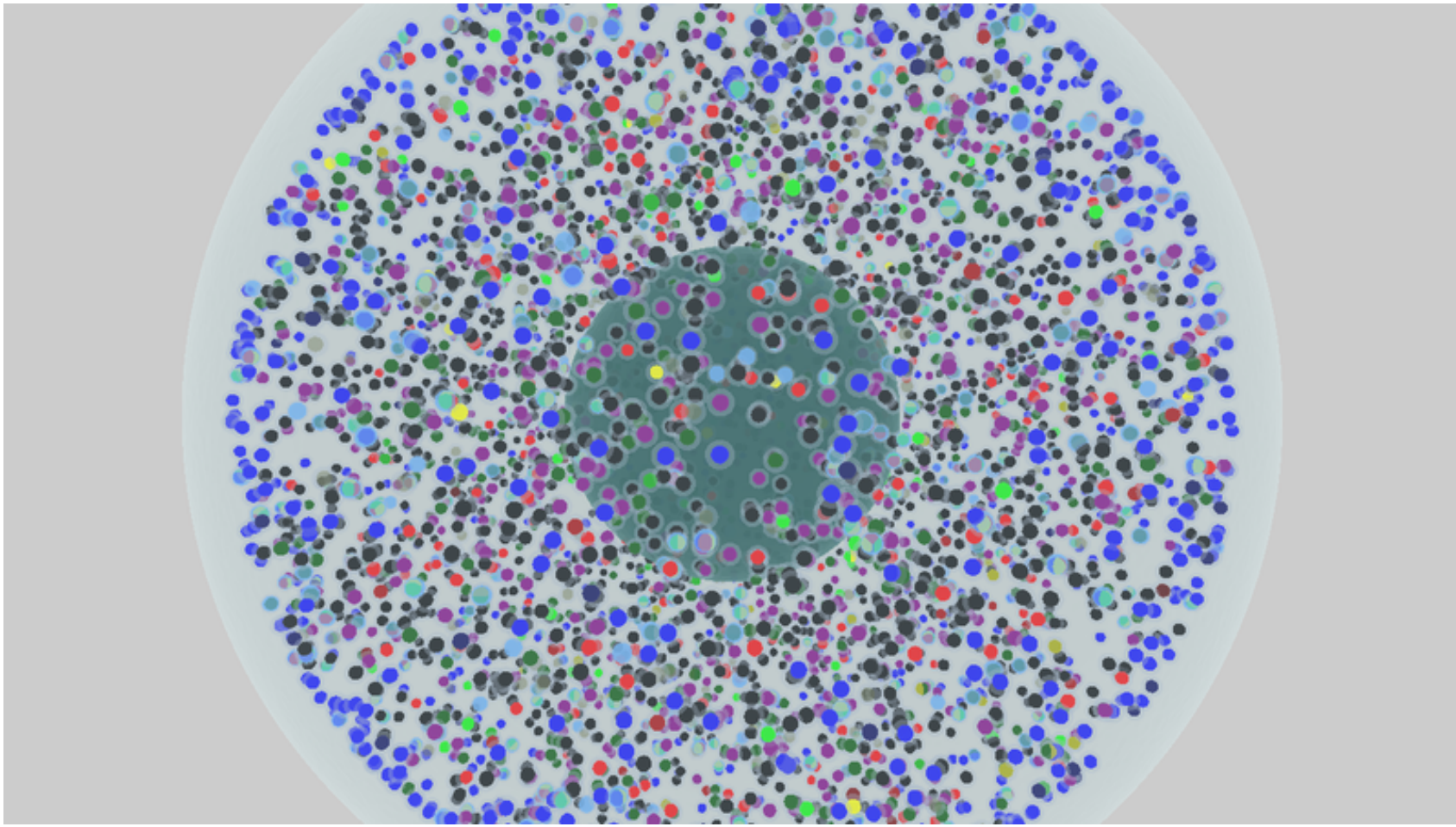
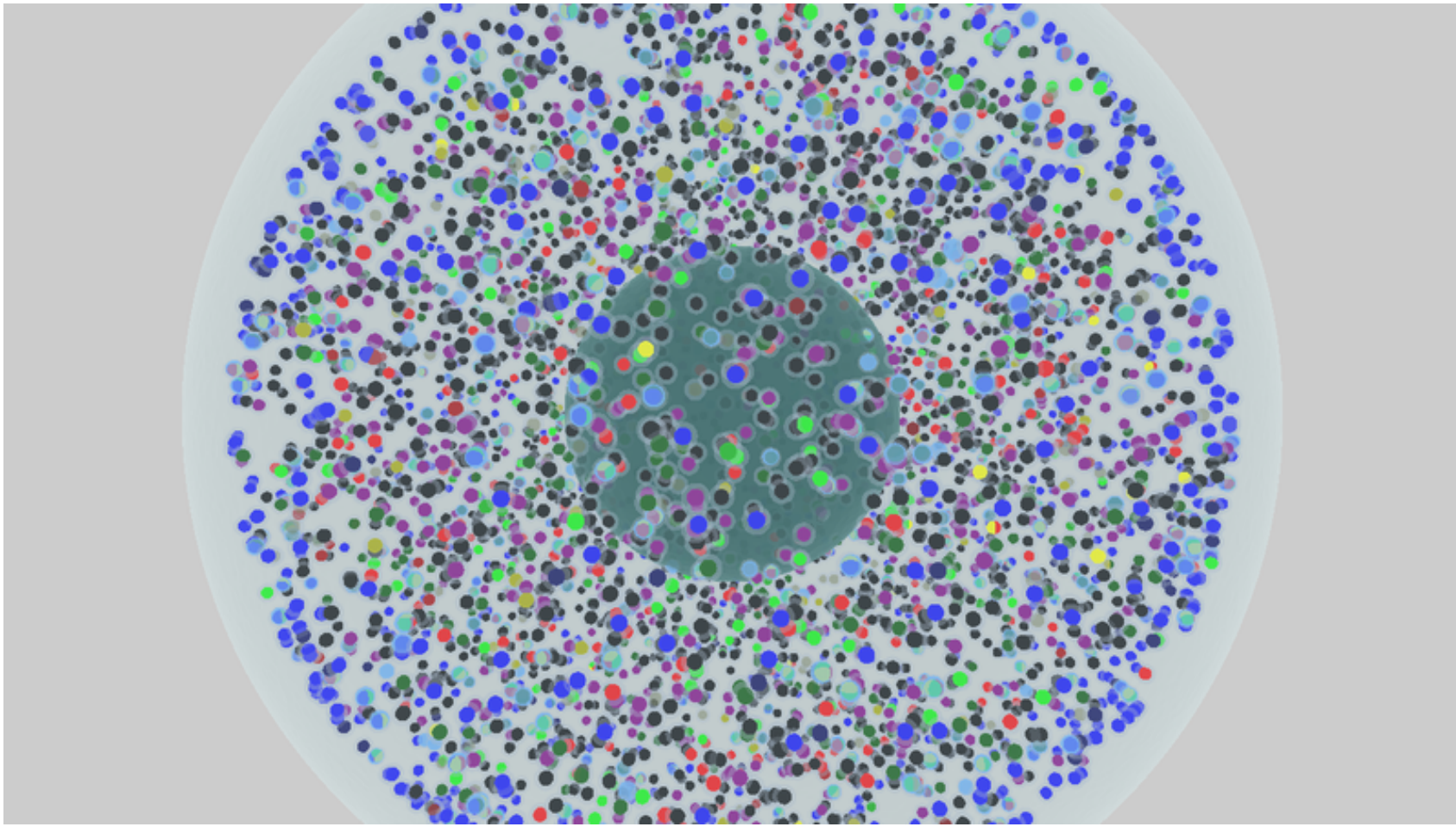


t=120s Ste4=blue, Ste11=red, Ste7=yellow, Fus3=green

# Application: Ste5 scafold

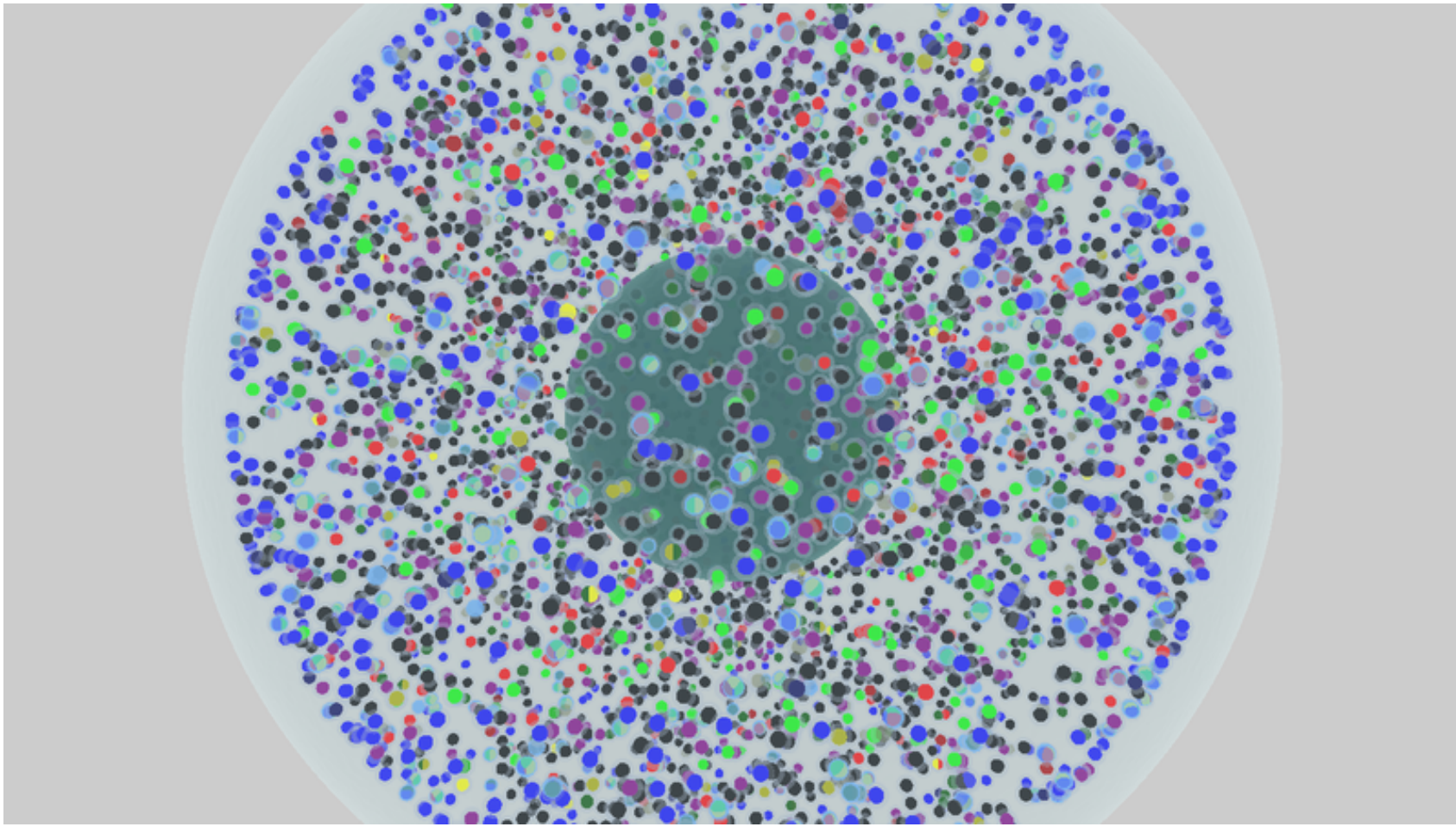
## Flipbook



t=180s Ste4=blue, Ste11=red, Ste7=yellow, Fus3=green

# Application: Ste5 scafold

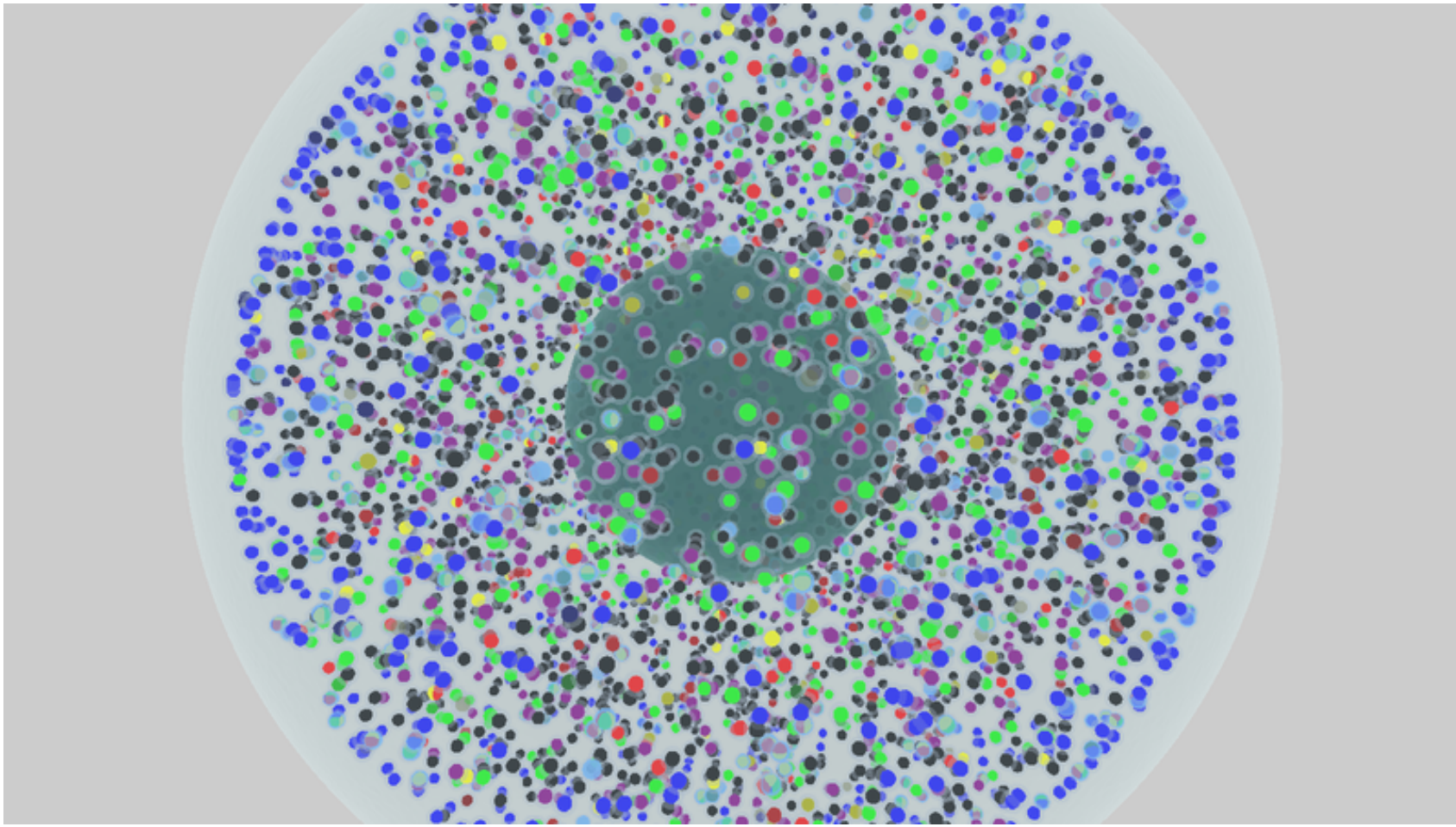
## Flipbook



t=240s Ste4=blue, Ste11=red, Ste7=yellow, Fus3=green

# Application: Ste5 scafold

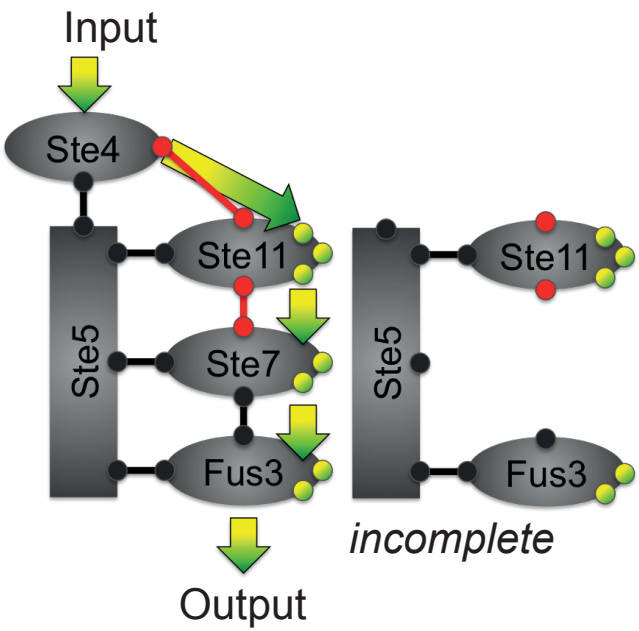
## Flipbook

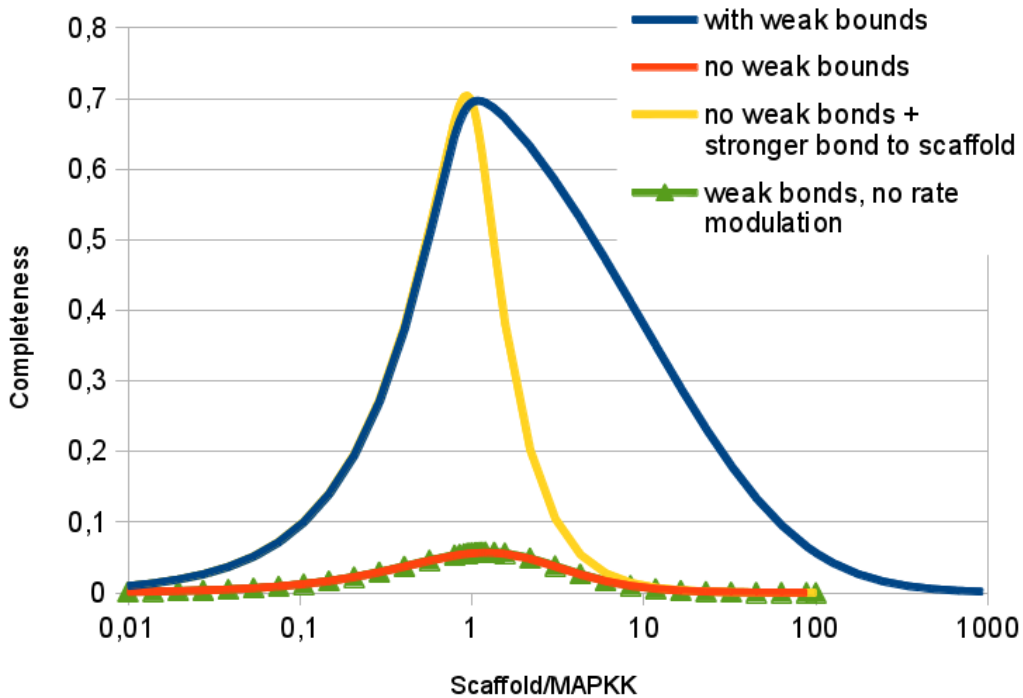


t=500s Ste4=blue, Ste11=red, Ste7=yellow, Fus3=green

# Application: Ste5 scafold

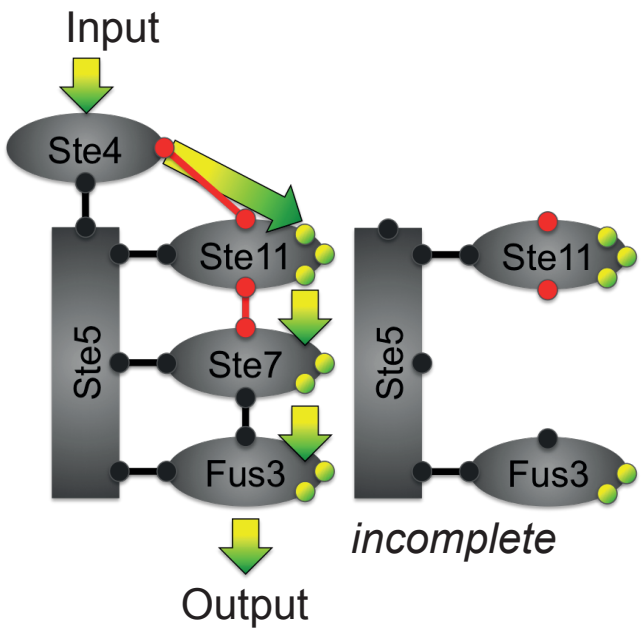
## Scafold stability



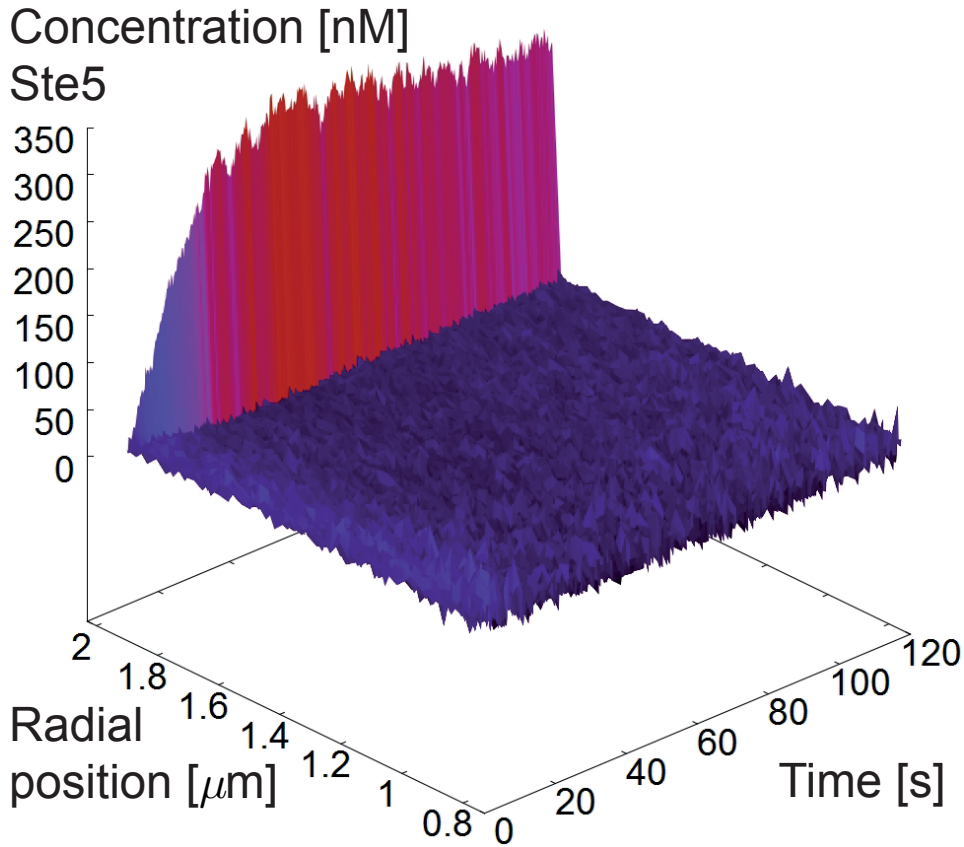



# Application: Ste5 scafold

## Impact on concentration gradients




Ste4: membrane-bound protein.



# Conclusion

**Stochastic simulation framework** combining three ingredients:

- Rule-based modelling: scale with the species combinatorics.
- Particle-based simulation: decompose diffusion and reaction.
- Approximate simulation: discrete time step.

**Coarse-grained Brownian dynamics**

- Spherical approximation of complexes.
- Spatial dimension: take into account concentration gradients
- Proof-of-concept: influence of weak bonds on scafold stability.

**Further work**

- More modulation of rates *(paper)*
- Constrained diffusion (membrane-bound complexes, etc.) *(appendix)*
- Geometric constraints *(related work)*

Thank you for your attention.