Hybrid spatial Gillespie and particle tracking simulation

Michael Klann*, Arnab Ganguly and Heinz Koeppl

1BISON Group, Automatic Control Lab, ETH Zurich, Switzerland

ABSTRACT

Motivation: Cellular signal transduction involves spatial-temporal dynamics and often stochastic effects due to the low particle abundance of some molecular species. Others, however, be of high abundances. Such a system can be simulated either with the spatial Gillespie/Stochastic Simulation Algorithm (SSA) or Brownian/Smoluchowski dynamics if space and stochasticity are important. To combine the accuracy of particle-based methods with the superior performance of the SSA, we suggest a hybrid simulation.

Results: The proposed simulation allows an interactive or automated switching for regions or species of interest in the cell. Especially we see an application if for instance receptor clustering at the membrane is modeled in detail and the transport through the cytoplasm is included as well. The results show the increase in performance of the SSA, we suggest a hybrid simulation.

Availability of Implementation: www.bison.ethz.ch/research/spatial_simulations/

Contact: mklann@ee.ethz.ch or koeppl@ethz.ch

Supplementary Information: Supplementary data are available at Bioinformatics online.

1 INTRODUCTION

Existing methods to model the spatial–temporal dynamics in signal transduction can be grouped into (i) partial differential equation (PDE) methods [Kholodnitska 2006; Stepchenko et al. 2003]; (ii) spatially resolved Markovian population models, often simulated with the SSA/Gillespie method [Ell et al. 2006; Gillespie 1976; Smoldyn and Damodar 2004] or other lattice-based methods (Anwer and Tompkin 2011) and (iii) particle-based methods such as Smolodyn [Andrews and Bray 2004], Greens function reaction dynamics (GFRD) [van Zon and Ten Wolde 2005] and others [Klang et al. 2010; Lapkova et al. 2011; Rumble and Simpson 2005; Persons et al. 2009].

Naturally, more detailed methods are computationally much more demanding, which requires careful selection of the right method for the biological problem in focus. Note that particle numbers and parameters are very heterogeneous in biological systems: molecule abundances range from 1 (gene) to several thousands of proteins of each class, similarly the size of the molecules and structures ranges from atoms/ions (< 1 nm) to molecular complexes (2 – 25 nm) and further to cellular sub-compartments and cytoskeleton structures (50 – 100 nm), whereas chemical interaction rate constants cover several orders of magnitude [Andrews et al. 2004a]. Hybrid methods can be employed to optimize the use of the computational resources in such a multi-scale environment [Hessche and Uhrmacher 2008].

*To whom correspondence should be addressed.

The present article aims at coupling a Brownian dynamics particle tracking method with the spatial Gillespie method to preserve the stochastic nature of the underlying signaling processes. Low-abundance species should for instance be always tracked as individual particles and high abundance species on the Gillespie level. Similarly subvolumes in focus of the simulation, e.g. receptor clustering on the plasma membrane, should be on the particle level. These two switches both on the species and the simulation volume level have to be accommodated in one simulation accordingly.

2 SYSTEM AND METHODS

We consider a reaction system consisting of M molecular species and K reaction channels with rate constants \( k = (k_1, \ldots, k_K)^T \). The reactions take place in reaction compartment \( D \) (the cell or a sub-compartment thereof). In the following, we describe how the time evolution of this system can be modeled either on the particle or the population level as well as the relation between the levels.

On the particle level, we track the position \( x(t) \) of the \( j \)-th molecule (\( j \in \mathbb{P} \subseteq \mathbb{Z}_+ \)), where the particles follow Brownian dynamics. The species map \( s(j) = i \) indicates that the \( j \)-th molecule is of species \( i \).

For a more coarse grained description, \( \mathbb{P} \) can be subdivided into \( U \) subvolumes of volume \( V_1, \ldots, V_U \). We denote the number of particles in subvolume \( v \) with \( N^v(t) = (N^v_1(t), \ldots, N^v_K(t))^T \). Time evolution on this population level follows Markovian dynamics in our simulator.

For conversion from particle level to population level of the \( j \)-th species in \( v \) we have to count all particles with corresponding species \( a_j(N^v(t)) \), called the propensity of reaction \( j \) within \( v \). The underlying assumption of the population dynamics model is that the \( N^v_j(t) \) molecules are uniformly distributed in \( V_v \).

In our hybrid simulation, we denote for every volume \( v \) which consists of species in particle or population mode. Let us denote the subset of species tracked on the population level as \( N \). For every reaction \( j \) within \( v \), its waiting time \( \tau^j \) is distributed exponentially with parameter \( a_j(N^v(t)) \), called the propensity of reaction \( j \) within \( v \). The waiting time \( \tau^j \) for any reaction to occur in \( v \) is exponentially distributed according to parameter \( a_j(N) = \sum_{i \in \mathbb{P}} a_i(N^i) \). Starting from a given time \( t \), the next event of reaction \( j \) in \( v \) is according to Gillespie’s algorithm (1976) at

\[
\tau^j = t + \tau^j; \quad \tau^j \sim \text{Exp}(a_j).
\]

(1)

Diffusion of species \( i \) with diffusion coefficient \( D_i \) into another volume \( \mu \) is translated into a first-order transport reactions with propensity \( a_i(N) = k_{ij}N^j_{ij} \). The corresponding rate constant can be expressed as follows:

\[
k_{ij} = \frac{D_i \times \mu^2}{t \times D_{ij} \times \mu^2} \times \frac{S_{ij}}{V_v},
\]

where \( S_{ij} \) is the surface/interface area of the cubic subvolumes. For convenience, we include these rates in \( \mu \) and thus \( a_i(N) \). A transport
reaction into $\mu$ at time $t'$ causes a state change $\tilde{N}^i(t) \rightarrow \tilde{N}^i(t')$, which according to Gillespie’s algorithm would require updating the precomputed waiting times $t_i^\nu$ in $\mu$. Anderson [2007] proved that the remaining fraction of the time to the next reaction can simply be stretched according to the changed propensity

$$t_i^\nu = t' + (\tilde{e}^\nu - t') \cdot \frac{a_i(\tilde{N}^i(t))}{a_i(\tilde{N}^i(t'))}$$

(3)

The remaining subset of $N^i(t)$ is given by counting the individually tracked particles that currently reside in $\nu$. Diffusion of the $j^{th}$ particle is modeled according to Brownian dynamics as a random walk

$$x_j(t + \Delta t) = x_j(t) + \sqrt{2D_{\nu}} \Delta t \xi$$

(4)

with $\xi$ a three-dimensional zero mean Gaussian random variable with unit variance. In the present algorithm based on Klann et al. [2011b], the particles of radius $\epsilon_j$ are allowed to overlap because signaling molecules normally are of low abundance, so that these rare events can be omitted. Modeling of a physiologically crowded cytoplasm with non-overlapping molecules is computationally much more demanding. Ridgway et al. [2008] obviously steps into cellular structures (plasma membrane, nucleus, cytoskeleton, etc.) are rejected (Klann et al. [2009]). Particles can interact with each other if their distance is smaller than their collision radius $\sigma_{ij} = r_i + r_j$ [cf. Algorithm 1], and a reaction based on the bimolecular rate constant $k_{ij}$ will be executed with probability (Lipková et al. 2011a)

$$P_{ij} = \frac{k_{ij} \Delta t}{4\pi \sigma_{ij}^3}$$

(5)

The time $t_j$ to its first order reaction is calculated for each molecule individually when it is created based on Equation (1) with the single molecule propensity $a_i^1 = a_i^1 = k_i^1 \times 1$, where $k_i^1$ is the sum of all first-order rate constants involving that species. The sequence of events of all molecules is then ordered, stored and updated as necessary Fig. 1. Aranyi and Tomita [2008] Byrne et al. [2010]. All first-order reactions up to current time $t$ will be executed in that sequence (Klann et al. [2011b]). The actual reaction $i$ that has to be executed out of the aggregate $k_i^1$ is found based on the probabilities $k_i^1$.

Note the following equality: The minimum of the waiting time of $N$ molecules, where each waiting time is calculated based on Exp(1), is Exp($N$) (cf. Fig. 1). Thus, the individual method on the particle level and the global method on the population level are equivalent. On the population level, each of the identical $N^i$ molecules would be the one with minimal waiting time with probability $1/N^i$. More generally, suppose that the waiting time for $j$-th reaction, $t_j^\nu$, is distributed as Exp($a_i$), $j = 1, \ldots, K$. Then the reaction is chosen with minimum waiting time with probability $a_i/a_0$. To see this observe that the required probability is given by

$$P(t_j \leq t_j, j \neq 1) = \int_0^\infty \prod_{j \neq 1} (1 - F_j(s)/\mu) \, ds = a_i/a_0.$$

Here, $F_1$ and $F_2$, respectively, denote the probability density function and the cumulative distribution function of Exp($a_i$).

### 3. Algorithm

With respect to coupling of Gillespie volume and individual particle tracking, we decided to partition the reaction set as follows:

1. First order reactions are stored on the species aggregation level, which is also used on the particle level for each species in each subvolume, i.e. one waiting time for each species. If no first-order reaction exists for species $i$, the waiting time $t_i^\nu = \infty$ (reaction times $t_j^\nu$, $j = 1, \ldots, M$).
2. Diffusion jumps are stored individually for each species in each subvolume (reaction times $t_j^\nu$, $j = M + 1, \ldots, 2M$).
3. Higher order reactions are stored for each of the $R_2$ higher order reactions in each subvolume (reaction times $t_j^\nu$, $j = 2M + 1, \ldots, 2M + R_2$).

These three groups match the behavior of the particle level, where first-order reactions are tracked along the molecules (of a species), diffusion jumps are triggered by the random walk process, and higher order reactions are triggered by (diffusion driven) collisions of molecules.

If we convert a subvolume from particle to Gillespie at $t$, all diffusion jump times and higher order reaction times will be initialized based on Equation (1). First-order reactions are treated differently, because each particle carries its next reaction time. The next reaction time of each species is therefore simply found by the minimum reaction time of all respective particles (cf. Fig. 1). The converted particles are then deleted.

The reverse conversion from Gillespie to particle creates $N^i$ particles uniformly distributed in the volume of the subvolume $\nu$ with individual properties inherited from the species properties. All predefined diffusion jump times and higher order reaction times are deleted because they will be triggered by the random walk of the molecules. The first-order reactions are, however, preserved in the following way:

* Arbitrarily, the first new particle of species $i$ inherits the next reaction time $t_i^\nu$. Note that all particles of one species are

```python
if particles[|x_i(t)−x_j(t)|] ≤ σ_{ij} then
    if $\xi_2 < P_{ij}$ with $\xi_2 \sim \mathcal{U}(0, 1)$ then
        execute reaction
end
```

**Algorithm 1:** Second-order (bimolecular) reactions on the particle level
if \( k_i \leq 1/N_i \mu \) with \( k_i \sim U(0, 1) \) then
   /* next reaction time goes with particle */
   \( t_i' = \min(t_i', t_i) \)
   \( t_i' = t_i' + t(a_i(N_i' - 1)) \)
else
   /* next reaction time stays in subvolume */
   \( t_i' = \min(t_i', t_i + t(a_i(1))) \)
   \( t_i' \) remains unchanged
end

Algorithm 2: Update scheme for the next first-order reaction after a jump from \( v \) to \( \mu \), where the exponentially distributed waiting time is calculated by the indicated number of particles: either the remaining particles in \( v \) or the one jumping from \( v \) to \( \mu \) identical, so the term ‘first particle’ just refers to the memory location.

- All other particles of that species initialize their next reaction times as \( t_i = t_i' + t(a_i) \) because their reaction has to be after the reaction of the first molecule accordingly.

The same approach is also followed for partial conversions of subvolumes, if not all but just a subset of the methods is converted between the levels. All affected jumps/higher order reaction waiting times on the Gillespie level are then updated based on Equation (3).

To be compatible with the above conversion approach, diffusion jumps also can carry the next first-order reaction time from subvolume \( v \) to the new subvolume \( \mu \). The next time \( t_i' \) belongs to the jumping particle of species \( i \) with probability \( 1/N_i' \). If a random number \( k_i \leq 1/N_i' \) (\( k_i \sim U(0, 1) \)), then the jumping particle is the next reacting particle. Algorithm 2 describes the executed process. The transferred time becomes the new time in the target volume \( \mu \) if it is the minimum time. All affected jumps/higher order reaction waiting times in both volumes on the Gillespie level are again updated based on Equation (3).

If particle \( i \) walks into a Gillespie level subvolume \( \mu \), then the next first-order reaction time there is likewise obtained by \( t_i' = \min(t_i', \xi) \). And if the diffusion jump out of Gillespie subvolume \( v \) leads into a particle volume, then accordingly a particle is created which obtains the next reaction time \( t_i' \) with probability \( 1/N_i' \) and otherwise calculates its time as in Algorithm 1. However as the target subvolume is particle based, no global waiting time is tracked there.

Especially, if we have just one particle in the system, its initially assigned first-order reaction time will be preserved throughout the simulation. This approach also ensures that frequent switching between particle and Gillespie volume tracking do not require too many re-initializations of the waiting times. Otherwise frequent switching could accumulate to a substantial error in the reaction rate if the switching intervals are in the range of the waiting times.

Thus, the suggested tracking and updating method on the Gillespie level ensures the compatibility with the particle tracking level but is not necessarily optimal with respect to its own performance due to the large number of stored reaction times and the time necessary to access and order them. As the Gillespie level still integrates time much faster than the particle level, this performance loss is, however, not relevant for the overall performance of the simulation.

Eventually also bimolecular reactions across the levels might occur in the simulation: let us assume that \( N_j \) molecules of species \( j \) are in the Gillespie subvolume with volume \( V_j \) and we have a bimolecular reaction with rate constant \( k_{ij} \) with species \( i \), which is tracked on the particle level. Concentration-based mass action kinetics requires that the reaction rate is \( k_{ij} \rho_j \rho_i = k_{ij} N_j V_j / V_i \), so the reaction can be treated as a first-order reaction with rate constant \( k_{ij} = k_{ij} N_j / V_j \). As this rate ‘constant’ depends on the time varying \( N_j \), we simulate these quasi first-order reactions in the classical particle-based scheme [cf. Andrews and Bray (2004); Klann et al. (2012)]: each molecule \( i \) in the volume \( v \) reacts with probability

\[
P_{ij} = 1 - \exp(k_{ij} \Delta t) = k_{ij} \Delta t
\]

in every timestep. This means, that a random number \( k_i \sim U(0, 1) \) is compared with \( P_{ij} \) for all molecules in every time step. This

/* requires ordered list of all subvolumes \( v \),
ordered smallest to largest by \( \min() \) */
while first_react_time() < \( \tau_0 \) do
\( j = \) first_react_in(\( v \))
\( t' = \) first_react_time()
update numbers in \( v \) based on scheme of \( j \)
for all products of \( j \) do
   if product species \( i \) is particle in \( v \) then
      create_particle(i, \( v', t' \))
      /\* species, location, initial time for its own first order reaction */
   end
if reaction \( j \) is a diffusion jump then
   /\* surfaces can have different weights */
   select \( \mu \) based on \( V/v/\sum_k=1^N/\mu_i, \mu_j \)
   update numbers in \( v \): \( N_j' \rightarrow N_j' + 1 \)
   transfer first order reaction time of that species \( i \)
   /\* see Algorithm 2. */
if species \( i \) is particle in \( \mu \) then
   create_particle(i, \( \mu, t' \))
else
   update affected waiting times in \( \mu \),
   except for the first order reaction of species \( i \)
   update the position of \( \mu \) in the ordered list
end
update affected waiting times in \( v \),
except for the first order reaction of species \( i \)
else
   /\* after reaction */
   update affected waiting times in \( v \)
end
set \( t_i' = t' + t(a_i) \)
update the ordered list of volumes

Algorithm 3: Algorithm of the Gillespie block. Note that particle conversions into Gillespie also change \( N_j \), which requires to update reaction times and the position of the volume in the ordered list. The exponentially distributed waiting time can be simply computed as \( \tau(a_i) = 1/a_i \log(1/\xi) \) using \( \xi \sim U(0, 1) \).
scheme also resembles the scheme of bimolecular reactions, where the probability is given by Equation (2) and Klann et al. (2011b) have extended it for dependent bimolecular reactions in a scaffold accordingly.

Algorithm 3 gives an overview of the complete simulation. Note that the steps (1)-(4) could be executed in any order. Visualization of the particles/volumes was done with BioInspire from ScienceVisuals, Lausanne, Switzerland (de Heras Ciechomski et al., 2010a) and POVray. 

4 IMPLEMENTATION AND PERFORMANCE

The method is implemented in Fortran, integrated into the functionality of the previously published particle-based methods Klann et al. (2011a, b, 2012). This includes first order \( A \rightarrow B \) and second order \( A + B \rightarrow \ldots \) mass action kinetics reactions, Michaelis–Menten enzyme kinetics \( E + S \rightarrow E + \ldots \) and binding and dissociation to/from plasma membrane, cytoskeleton and the nucleus. In particle mode, molecules can diffuse along the plasma membrane, the nucleus, through the cytoplasm or walk along the cytoskeleton. So far the simulation is not parallelized, but a parallel version in C/C++ is in preparation.

Here, we show the testcase \( A + B \rightarrow 0 \), where \( A \) starts from the plasma membrane and \( B \) from the nucleus with 20 000 molecules each in Figure 2. We run the simulation with both species in particle and Gillespie mode, and \( A \) as particle, whereas \( B \) is in Gillespie mode. Figure 2 shows no differences between the simulations however, the larger figure in the supplementary material shows that the particle-based simulation leads to slightly faster reaction rates in the initial mixing phase around 1.5 s. This could be an effect of local fluctuations that do not cancel out due to the nonlinearity and nonstationarity of the mixing.

![Fig. 2. Testcase with \( A + B \rightarrow 0 \), where \( A \) starts from the plasma membrane and \( B \) from the nucleus. The grid shows the discretization in x direction used for evaluation of the spatial distribution.](image)

5 DISCUSSION

Spatial and temporal effects can play a major role in signal transduction (Kholodenko et al., 2010). This holds especially for the transport of active signaling molecules from the plasma membrane where the signal is detected by receptors toward the nucleus, where it has to trigger gene activation. A common motive in signal transduction is the mitogen-activated protein kinase (MAPK) cascade, where the receptor and upstream components cluster together at the plasma membrane, and MAPK enters the nucleus. The active, phosphorylated form of MAPKpp is constantly deactivated in the cytoplasm. The fraction of active molecules reaching the nucleus, therefore, depends on the relationship between the speed of transport (diffusion) and the speed of the deactivation (reaction) (Kholodenko, 2006).

We simulated this process in a spherical cell with diameter 10 \( \mu \)m with a spherical nucleus (diameter 3 \( \mu \)m, located in the cell center) and a rate constant of 1.8 \( \mu \)m/s. A total of 10 000 MAPKpp molecules start initially from the plasma membrane with \( D_{\text{MAPK}} = 10 \mu \text{m}^2/\text{s} \) and can enter the nucleus with a rate constant of 1.8 \( \mu \)m/s (given the ‘concentration’ of the nuclear membrane in the cytoplasm, this leads to an effective nuclear import rate constant of 0.1 s\(^{-1}\)). A total of 30 577 phosphatase molecules
that reached the nucleus within 10s to the Gillespie area). A spherical symmetric radial distribution hides the sharp cutoff from the particle to the plasma membrane, whereas still the complete cell is tracked in 3D (Fig. 4).

(A) Initial phase of the MAPKpp molecules—correctly included in our simulation, because bimolecular rate constants in M⁻¹ s⁻¹ have to be divided by $V_i$ anyway for the Gillespie level (and an additional factor to convert from the liter in M=mol/l to the used length scale and single particles). For substrates $h$ and $i$ and length in μm

\begin{equation}
\frac{a_i^h(t)}{V_i} = \frac{k_i}{V_i} N_i(t) \phi(t) N^h_i(t)
\end{equation}

Diffusion, in contrast, is reduced by crowding. The jump rate constant on the Gillespie level [Equation (1)] likewise contains the properties of the volume. If the size of the obstacles becomes much smaller than $l$, such that the objects are uniformly/homogeneously distributed in the volume, however, both $V_i$ and $S_{mem}$ will be scaled by the same $\phi$. Thus, the effect cancels in Equation (1). Only if we go to a fine discretization of space, such that $S_{mem}$ becomes a random number with mean $\bar{\phi}$, then the crowding effect becomes visible in the resulting diffusion (cf. Fig. 4). These networks and the resulting diffusion can also be analyzed with percolation clusters (Gefen et al. 1983).

In the following, we want to analyze how far molecular crowding can be modeled on the Gillespie level. This was also investigated by Nicolau and Burridge 2009, Eschke and Uhrmacher 2008 and Lampoudi et al. 2009. Let $\phi$ denote the free volume fraction of the cytoplasm (i.e. the fraction which is accessible to the molecules of interest). Crowding leads to $\phi < 1$ and the reactants in the remaining volume $V_i' = V_i \phi$ have an effectively higher concentration, such that they react in bimolecular mass action kinetics with a faster rate. Klann et al. 2011a; Lampoudi et al. 2009. This effect is correctly included in our simulation, because bimolecular rate constants in M⁻¹ s⁻¹ have to be divided by $V_i$ anyway for the Gillespie level (and an additional factor to convert from the liter in M=mol/l to the used length scale and single particles).

| MAPKpp   | Phosphatase | Volumes (μl) | $T_{CPU}$ |
|----------|-------------|-------------|-----------|
| Always particle | Always particle | 5592 (L=20) | 174 min |
| Always particle | Always Gillespie | 872 (L=10) | 94 min |
| Always particle | N/A* | 5592 (L=20) | 41 min |
| Particle at membranes | Always Gillespie | 17488 (L=30) | 49 min |
| Particle at membranes | Always Gillespie | 5592 (L=20) | 13 min |
| Particle at membranes | Always Gillespie | 872 (L=10) | 15 min* |

Tested on a Win 7 Pro Intel i7 2600K at 3.5 GHz, 8GB RAM.

*Dephosphorylation is modeled by a first-order reaction with $k_p' = 1.5 \times 10^{-7}$ instead, which is the effective rate of the bimolecular reaction. This shows that the pair finding of the bimolecular reaction dominates $T_{CPU}$.

*Because of the more coarse grained grid, a bigger volume fraction along the plasma membrane was in particle mode, compared with the settings with more subvolumes.
Fig. 5. A Obstacles in the cell (from Transmission electron microscopy image) and simulation grid. B Resulting graph/network of the diffusion system, where the node and edge weight corresponds to the local free volume fraction. Note that the diffusion rate constant is given as the fraction of edge/source node weights, such that it can be different in the two directions along an edge. C Limit cases depending on the chosen discretization: all nodes/edges have the same (average) weight, e.g. if \( l \) is much larger than the length scale of the obstacles, or the resulting network becomes binary with weights 1 or 0 respectively if the obstacles have the same size like \( l \).

We tested this in an intracellular environment as shown in Figure 6 where the total diameter of 4.928 \( \mu \text{m} \) was divided into 94 subvolumes in each direction (4 million subvolumes in the sphere, requiring 1 GB of memory in the simulation). At this scale \( l = 52 \text{nm} \), which is 3 pixel of the original binarized transmission electron microscopy (TEM) image of Hiroi et al. (2011) we see a reduction in diffusion (cf. Fig. 2)). Still, the diffusion is only reduced to \( D_{\text{eff}} = 0.9D_0 \), whereas with particle tracking, we find \( D_{\text{eff}} = 0.7D_0 \) (Hiroi et al. 2012). The strong deviations in Figure 6 arise from the locally varying \( V_\nu \), apparently at \( x = 3 \mu \text{m} \) a big object reduces the available volume. This result underlines the fact that the reduced diffusion originates from the tortuosity of the structured volume: the particles do not move slower but have to go longer ways around the obstacles, which delays their arrival (Klann et al., 2011a).

Finally, it should be noted that reactions can be diffusion controlled (Morelli and Ten Wolde, 2008; Rice, 1985). Molecules cannot react faster than \( k_D = 4\pi\sigma D \) (where \( D \) is the sum of both diffusion coefficients). If \( k_j \) is close to \( k_D \), the observed rate is determined by the rate of collisions. Thus, if the subvolumes of the Gillespie method are too small, the method will not find enough pairs and underestimate the true reaction rate (Gillespie, 2009). Gillespie (2009) calculated the necessary correction factor.

In this low concentration and diffusion-controlled regime, particle-based methods still give correct results (Klann et al., 2011; Morelli and Ten Wolde, 2008). Therefore, we are planning to introduce a controller which switches from Gillespie to particle if the local concentration falls below the threshold. Note that particle tracking also is not expensive if just a few molecules have to be tracked, whereas the mean jump frequency grows with \( 1/l \) [cf. Equation (2)], making high-resolution spatial Gillespie simulations even more expensive.

In addition, we will develop a user interface to allow a better control of the simulation. This will also include interactive visualization of the molecules in the simulation (de Heras Ciechomski et al. 2009; Falk et al. 2010).

ACKNOWLEDGEMENT

We thank Pablo de Heras Ciechomski, Martin Falk and Preetam Nandy for valuable discussions.

Funding: M. Klann acknowledges funding by SystemsX.ch initiative and Swiss Confederation’s Commission for Technology and Innovation (CTI) project 12532.1 PFLS-L.S. H.Koeppl. and A. Ganguly acknowledge the support from the Swiss National Science Foundation, grant no. PP00P2_128503.

Conflict of Interest: none declared.
REFERENCES

Alberts,B. et al. (2002) Molecular Biology of the Cell. Garland Science, New York.
Andrews,S. and Bray,D. (2004) Stochastic simulation of chemical reactions with spatial resolution and single molecule detail. *Phys. Biol.*, 1, 137–151.
Angelescu,B. et al. (2012) Computational modeling of cellular signaling processes embedded into dynamic spatial contexts. *Nat. Methods.*, 9, 283–289.
Arjmand,S. and Tomlin,M. (2010) A new multicompartimental reaction-diffusion modeling method links transient membrane attachment of E. coli MinF to E-ring formation. *Molecules.*, 4, 35–53.
Byrne,M. et al. (2010) Cellular dynamic simulator: an event driven molecular simulation environment for cellular physiology. *Neuroinformatics*, 8, 63–82.
Costa,M. et al. (2009) Coupled stochastic spatial and non-spatial simulations of Edb1 signaling pathways demonstrate the importance of spatial organization in signal transduction. *PloS One.*, 4, e516. de Henas Ciechomski,M. et al. (2008) Two-phased real-time rendering of large neuron databases. 2008 International Conference on Innovations in Information Technology, Al Ain, United Arab Emirates, pp. 712–716.
Elf,J. et al. (2003) Mesoscopic reaction-diffusion in intracellular signaling. *Proc. SPIE*, 5110, 114–124.
Falk,M. et al. (2010) 3D visualization of concentrations from stochastic agent-based signal transduction simulations. In *Proceedings of the IEEE International Symposium on Biomedical Imaging: From Nano to Macro (ISBI 2010)*, IEEE, pp. 1301–1304.
Gelfen,Y. et al. (1983) Anomalous diffusion on percolating clusters. *Phys. Rev. Let.*, 50, 77–80.
Genes,F. et al. (2011) A computational analysis of the dynamic roles of talin, Dskl, and PIPKI for integrin activation. *PloS One.*, 6, e24808.
Gillespie,D. (1976) A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *J. Comput. Phys.*, 22, 403–434.
Gillespie,D. (2009) A diffusional bimolecular propensity function. *J. Chem. Phys.*, 130, 164108.
Hiroi,N. et al. (2011) Physiological environment indices quick response–slow exhaustion reactions. *Front. Physiol.*, 2.
Hiroi,N. et al. (2012) From microscopy data to in silico environments for in vivo oriented simulations. *EURASIP J. Bioinformatics Syst. Biol.*, 7.
Jeschke,M. and Uhrmacher,A. (2008) Multi-resolution spatial simulation for molecular crowding. In *Proceedings of the Winter Simulation Conference, 2008*. WSC 2008, Miami, USA, pp. 1384–1392.
Kholodenko, B. (2006) Cell-signalling dynamics in time and space. *Nat. Rev. Mol. Cell Biol.*, 7, 165–176.
Kholodenko,B. et al. (2010) Signalling bullet in space and time. *Nat. Rev. Mol. Cell Biol.*, 11, 414–426.
Klam,M. et al. (2009) Stochastic simulation of signal transduction: impact of the cellular architecture on diffusion. *Biophys. J.*, 96, 5122–5129.
Klam,M. et al. (2011a) Agent-based simulation of reactions in the crowded and structured intracellular environment: influence of mobility and location of the reactants. *BMC Syst. Biol.*, 11, e29645.
Klam,M. et al. (2011b) Improved reaction scheme for spatial stochastic simulations with single molecule detail. In *Proceedings of the 5th International Workshop on Computational Systems Biology (WCSB 2011)*, Tampere University, Tampere, Finland, 93–96.
Klam,M. et al. (2012) Spatial modeling of vesicle transport and the cytoskeleton: The challenge of hitting the right road. *PloS One.*, 7, e29645.
Lampoudi,S. et al. (2009) Effect of excluded volume on 2d discrete stochastic chemical kinetics. *J. Comput. Phys.*, 228, 3656–3666.
Lipkova,J. et al. (2011) Analysis of brownian dynamics simulations of reversible bimolecular reactions. *SIAM J. Appl. Math.*, 71, 714–730.
Morelli,M. and Ten Wolde,P. (2008) Reaction Brownian dynamics and the effect of spatial fluctuations on the gain of a pulse-pull network. *J. Chem. Phys.*, 129, 054112.
Mugler,A. et al. (2012) Membrane clustering and the role of rebinding in biochemical signaling. *Biophys. J.*, 102, 1089–1078.
Nickol,Jr,D. and Burrage,K. (2008) Stochastic simulation of chemical reactions in spatially complex media. *Comput. Math. Appl.*, 55, 1007–1018.
Plettenberg,S. and Slepchenko,B. (2008) ChemCell: A Particle-Based Model of Protein Chemistry and Diffusion in Microbial Cells. United States: Department of Energy.
Pogson,M. et al. (2006) Formal agent-based modelling of intracellular chemical interactions. *Biosystems*, 85, 37–45.
Rice,S. (1985) Diffusion-Limited Reactions. Amsterdam Elsevier.
Ridgway,D. et al. (2008) Coarse-grained molecular simulation of diffusion and reaction kinetics in a crowded virtual cytoplasm. *Biophys. J.*, 94, 3748–3759.
Slepchenko,B. et al. (2003) Quantitative cell biology with the Virtual Cell. *Trends Cell Biol.*, 13, 570–576.
Stamatakis,A. and Lander,E.S. (1996) Stochastic simulation of coupled reaction-diffusion processes. *J. Comput. Phys.*, 127, 196–207.
van Zon,J. and Ten Wolde,P. (2005) Simulating biochemical networks at the particle level and in time and space: Green’s function reaction dynamics. *Phys. Rev. Let.*, 94, 128103.