Overview of MCell Methods

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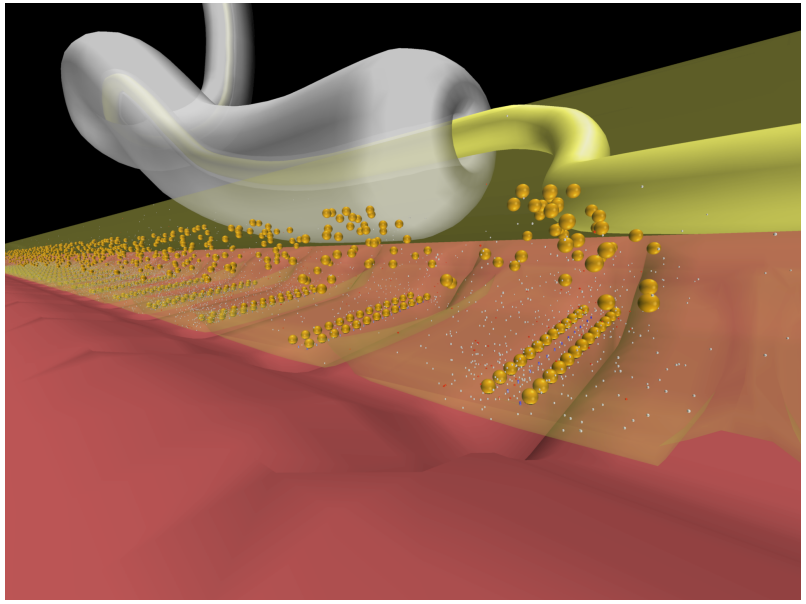
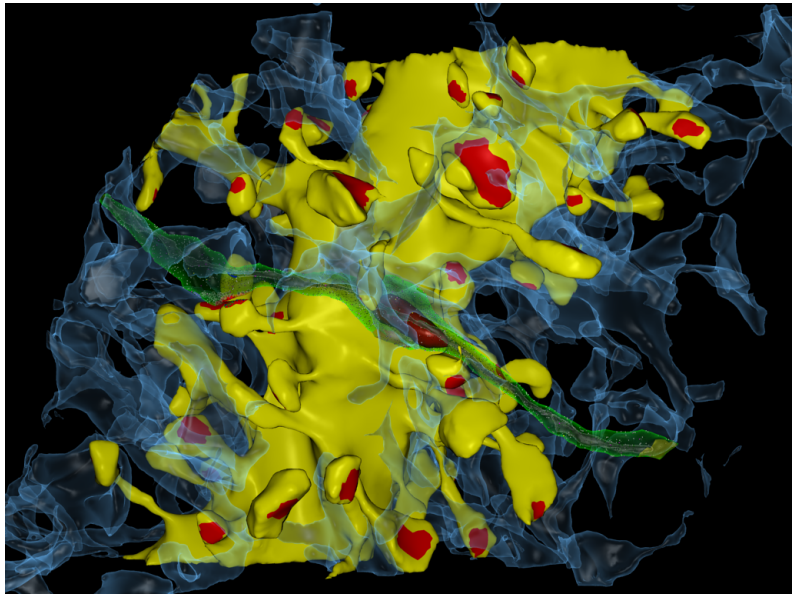
Computational Microphysiology





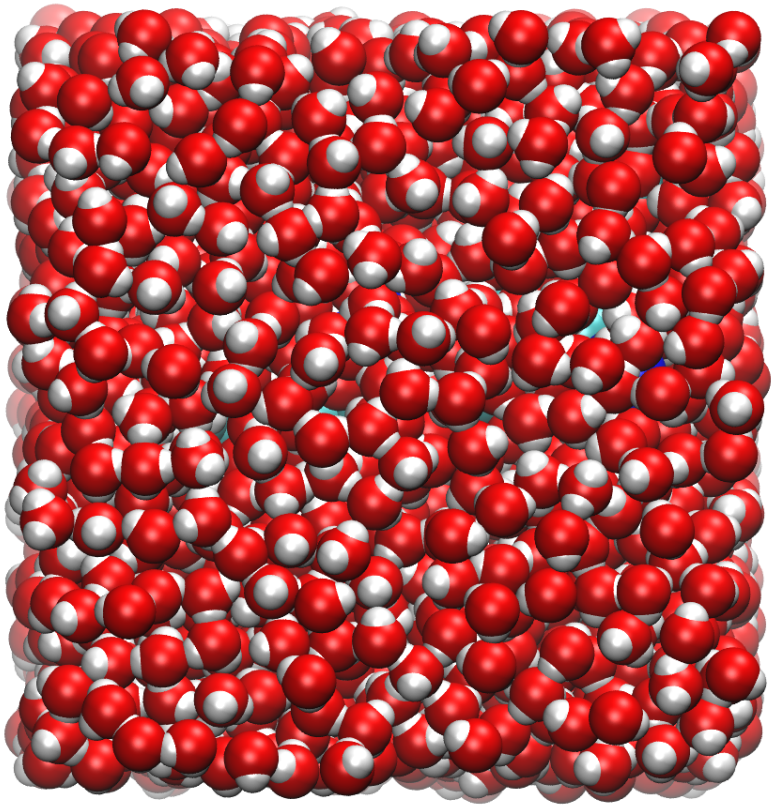
We want to simulate realistic 3D cellular microphysiology at length scales from *nm* and up and timescales of *ps* and longer.

References

Stiles, JR, and Bartol, TM. (2001). *Monte Carlo methods for simulating realistic synaptic microphysiology using MCell*. In: Computational Neuroscience: Realistic Modeling for Experimentalists, ed. De Schutter, E. CRC Press, Boca Raton, pp. 87-127.

Kerr R, Bartol TM, Kaminsky B, Dittrich M, Chang JCJ, Baden S, Sejnowski TJ, Stiles JR. (2008). *Fast Monte Carlo Simulation Methods for Biological Reaction-Diffusion Systems in Solution and on Surfaces*. SIAM J. Sci. Comput., 30(6):3126-3149.

Biomolecular Systems at the Molecular Level



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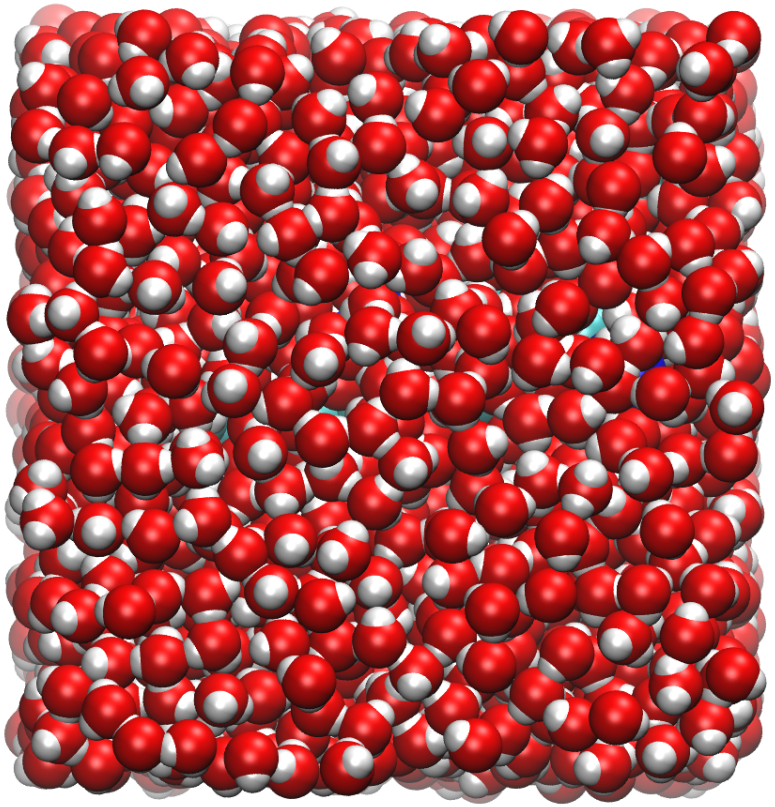

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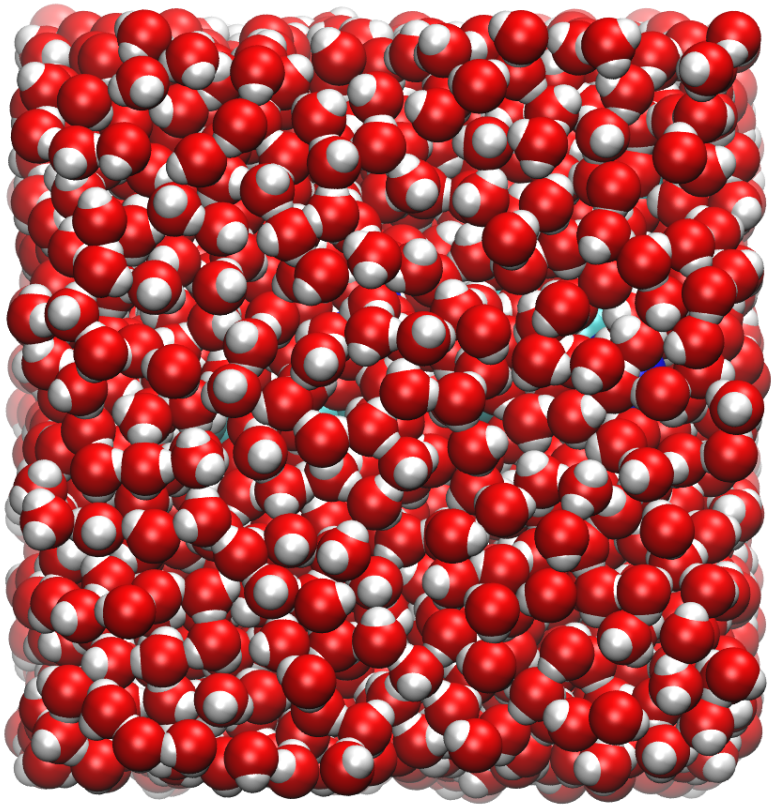


- To a first approximation, at the molecular level cells mostly consist of biomolecules solvated by (a large number of) water molecules.
- Relevant time and length scales are *fs* ($10^{-15}s$) and $\AA$ ($10^{-10}m$).
- From a computational modeling point of view molecular systems can be described using Newtonian equations of motion (molecular dynamics)

$$m_i \frac{d^2}{dt^2} r_i = -\frac{\partial}{\partial r_i} V(r_1, ..., r_N) \qquad (1)$$

Effective Description of Relevant Degrees of Freedom

Often, at the level of cellular events and biochemical reactions we are only interested in a much smaller number of degrees of freedom q_j, $M \ll N$ (e.g., center of mass motion). Phenomenologically, this can be written as (j = 1, 2, ..., M)

$$\mu_j \ddot{q}_j = -\frac{\partial}{\partial q_j} W(q_1, ..., q_M) - \gamma_j \dot{q}_j + \sigma_j \xi_j(t) \tag{2}$$

This is a stochastic differential equation, the *Langevin equation*. For single particles this can be written as

$$m\ddot{\mathbf{r}} = -\nabla W(\mathbf{r}) - \gamma \dot{\mathbf{r}} + \sigma \xi(\mathbf{t}) \tag{3}$$

In the strong friction limit $|\gamma \dot{\mathbf{r}}| \gg |m\ddot{\mathbf{r}}|$ (usually a good approximation if one considers time intervals $>$ 1ps) this becomes

$$\gamma \dot{\mathbf{r}} = -\nabla W(\mathbf{r}) + \sigma \xi(\mathbf{t}) \tag{4}$$

This equation underlies so called *Brownian Dynamics Simulations*.

Effective Description of Relevant Degrees of Freedom

In the absence of external forces acting on the particles

$$\gamma \dot{\mathbf{r}} = \sigma \xi(\mathbf{t}) \tag{5}$$

Instead of following the trajectories of particles via Eq. (5) directly we can also examine the time evolution of the conditional probability density $p(\mathbf{r}, t|\mathbf{r}_0, t_0)$. It can be shown that Eq. (5) corresponds to the Fokker-Planck equation

$$\partial_t p(\mathbf{r}, t|\mathbf{r}_0, t_0) = \frac{\sigma^2}{2\gamma^2} \nabla^2 p(\mathbf{r}, t|\mathbf{r}_0, t_0) \tag{6}$$

This is the celebrated *Einstein Diffusion Equation* describing microscopic transport of particles.

Diffusion Theory - Fick's 1st and 2nd Law

Developed by physiologist Adolf Fick in 1855.

Fick's 1st Law:

$$\mathbf{J}(\mathbf{r}, t) = -D \, \nabla C(\mathbf{r}, t) \tag{7}$$

Fick's 2nd Law:

$$\frac{\partial C(\mathbf{r}, t)}{\partial t} = \nabla \left(D \, \nabla C(\mathbf{r}, t) \right) = D \, \nabla^2 C(\mathbf{r}, t) \tag{8}$$

Eq. 2 is called the **Diffusion Equation**.

Here, J, diffusion flux [Mol length^{-2} time^{-1}], D, diffusion coefficient [length^2 time^{-1}, $cm^2 s^{-1}$], C concentration [Mol length^{-3}, $mol \ l^{-1}$].

Einstein Diffusion Equation - Solution

The solution to Einstein's Diffusion Equation provides the basis for MCell diffusion algorithm.

$$\frac{\partial p(\mathbf{r},t)}{\partial t} = D\ \nabla^2 p(\mathbf{r},t) \quad , \quad D = \frac{\sigma^2}{2\gamma^2} \tag{9}$$

In the neighborhood of a given molecule location, the probability p can be assumed to be radially symmetric, $p(\mathbf{r},t) \equiv p(r,t)$ and Eq. 3 simplifies to

$$\frac{\partial p(r,t)}{\partial t} = D\ \frac{1}{r}\frac{\partial}{\partial r} r^2 \frac{\partial p(r,t)}{\partial r} \tag{10}$$

Equation can be solved analytically for certain boundary conditions. E.g. for a point source of molecules the solution becomes

$$p(r,t) = \frac{1}{\lambda^3 \pi^{3/2}} e^{-r^2/\lambda^2} \quad , \quad \lambda = \sqrt{4Dt} \tag{11}$$

Eq. 5 can be directly converted into the fractional probability p_r for a displacement between r and $(r + dr)$ for a single diffusing molecule:

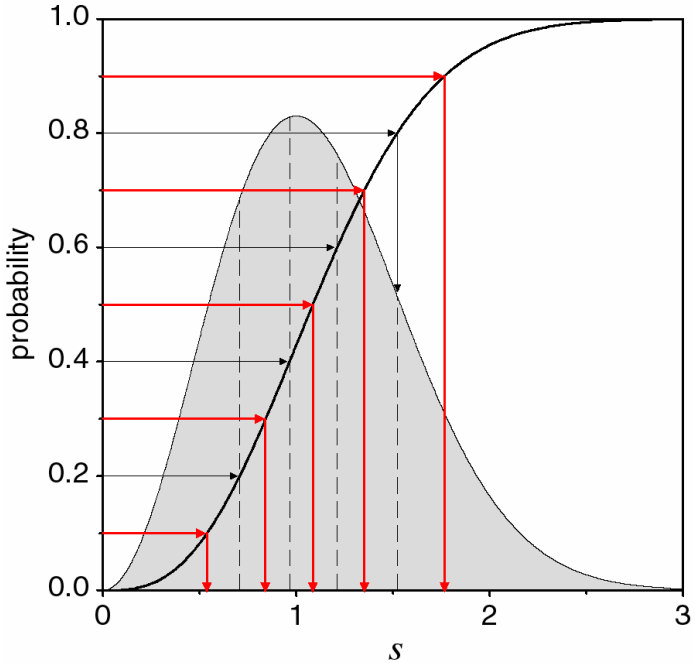
$$p_r = \frac{1}{\lambda^3 \pi^{3/2}} e^{-r^2/\lambda^2} (4\pi r^2) dr \tag{12}$$

$$p_s = \frac{4}{\sqrt{\pi}} s^2 e^{-s^2} ds \quad , \quad s = \frac{r}{\lambda} = \frac{r}{\sqrt{4Dt}} \tag{13}$$

Using Eq. 6 we can also compute the mean radial displacement $\bar{l}_r$

$$\bar{l}_r = \frac{2}{\pi} \lambda \sim \sqrt{t} \qquad (\bar{l}_\perp = \frac{\bar{l}_r}{2}) \tag{14}$$

Monte Carlo Probabilities For Diffusion in MCell

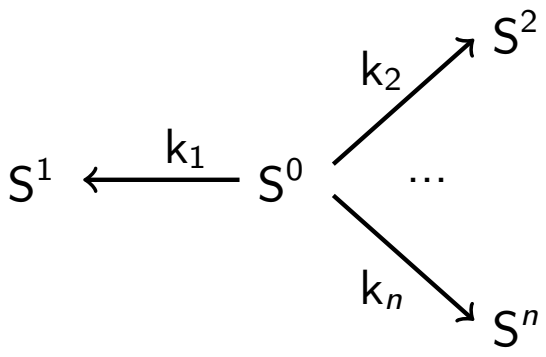


$$p_s = \frac{4}{\sqrt{\pi}} s^2 e^{-s^2} ds$$
$$s = \frac{r}{\sqrt{4Dt}}$$

To choose a radial distance R for diffusion we pick a random number X in $[0, 1]$ and solve

$$X = CDF(R) = \int_0^R p_s ds = erf(R) - \frac{2}{\sqrt{\pi}} R\ e^{-R^2} \qquad (15)$$

This can be efficiently computed during runtime of the simulation.



Unimolecular transition: Initial state S^0 can undergo one of n possible transitions to states S^1 through S^n with first order rate constants k_1, k_2, ... k_n.

We need to know the probability p_t that a molecule in state S^0 undergoes a transition. p_t is given by the fraction of $[S^0]$ that undergoes a transition during time t:

$$p_t = \frac{[S^1]_t + [S^2]_t + ... + [S^n]_t}{[S^0]_0} = 1 - \frac{[S^0]_t}{[S^0]_0} \tag{16}$$

From the rate equation we obtain

$$-d[S^0] = (k_1 + k_2 + ... + k_n)[S^0]dt = \left(\sum_{j=1}^{n} k_j\right)[S^0]dt \tag{17}$$

Eq. 17 can be integrated

$$\int_{[S^0]_0}^{[S^0]_t} \frac{d[S^0]}{[S^0]} = -\left(\sum_{j=1}^{n} k_j\right) \int_0^t dt \tag{18}$$

to yield

$$\frac{[S_0]_t}{[S_0]_0} = e^{-\sum_{j=1}^{n} k_j t} \tag{19}$$

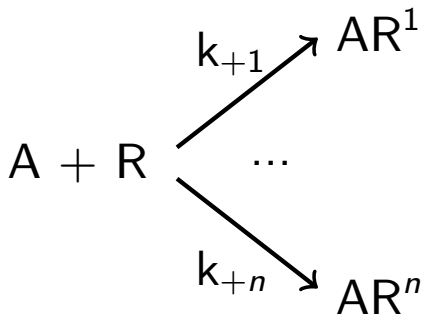
Substituting Eq. 19 into Eq. 16 then gives the probability p_t for unimolecular transitions as (here τ is the mean lifetime of S^0)

$$p_t = 1 - e^{-\sum_j k_j t} \quad , \qquad \tau = 1/\sum k_j \tag{20}$$

$$p_1 = p_t \frac{k_1}{\sum_j k_j}, \quad \ldots \quad p_n = p_t \frac{k_n}{\sum_j k_j}; \quad \sum_i p_i = p_t \tag{21}$$

Notes:

- The naïve way to choose unimolecular reactions is to compare a single random number in $[0, 1]$ to the cummulative probabilities $(p_1, p_1 + p_2, \ldots, 1)$.
- MCell3 instead computes the lifetime of each molecule from the exponential distribution of lifetimes $\rho(t) = \frac{1}{k} e^{-kt}$ and then uses its *scheduler* to schedule the unimolecular reaction to occur at the appropriate time.



Bimolecular Association: An example would be association between ligand A (volume molecule) and receptor R (surface molecule) with n possible binding sites.

We will derive a relation for p_b, the binding probability of ligand A to receptor R. The average rate of binding p_{bt} of A to R after N_H hits is given by

$$p_{bt} = 1 - (1 - p_b)^{N_H} \tag{22}$$

Next, we require that the *average binding rate* is equal to binding rate predicted by *mass action kinetics* given by

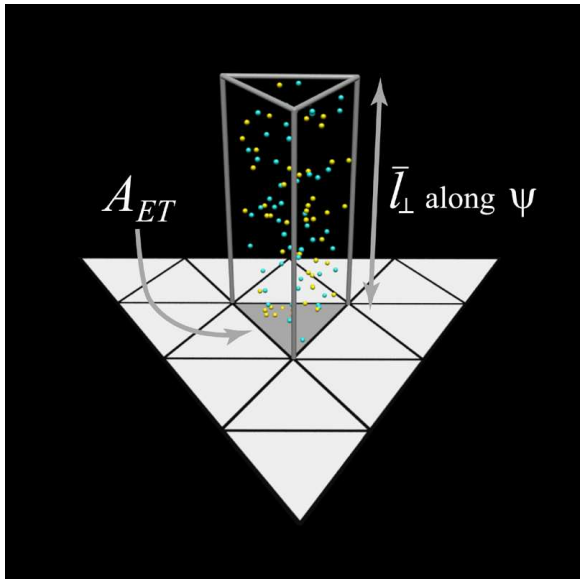
$$p_t = \sum_i k_{+i}[A]_0 \Delta t \quad , \quad \Delta t \to 0 \tag{23}$$

$$1 - (1 - p_b)^{N_h} = p_{bt} = p_t = \sum_i k_{+i}[A]_0 \Delta t \tag{24}$$

For small Δt, p_b and N_H approach zero and thus $(1 - p_b)^{N_H} \approx (1 - N_H p_b)$. Thus, Eq. 24 simplifies to

$$p_b = \sum_i k_{+i} \frac{[A]_0 \Delta t}{N_H} \quad , \quad \Delta t \to 0 \tag{25}$$

Next, we need to derive a relation for N_H the number of hits of A on R



The number of hits per unit time on a tile with surface area A_{ET} is given by

$$hits = N_a \frac{\bar{l}_\perp}{\Delta t} A_{ET} [A]_0 \tag{26}$$

This results in ($\Delta t \to 0$)

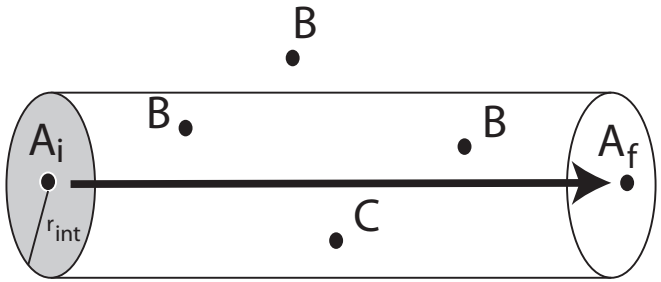
$$N_H = \int_0^{\Delta t} hits \; dt \approx N_a A_{ET} [A]_0 \left(\frac{4D\Delta t}{\pi} \right)^{1/2} \tag{27}$$

Eliminating N_H in Eq. 25 with 27 then yields the final expression for p_b

$$p_b = \sum_i k_{+i} \frac{1}{2N_a A_{ET}} \left(\frac{\pi \Delta t}{D} \right)^{1/2} \tag{28}$$

This can be efficiently computed at system initialization.

Monte Carlo Probabilities For Volume Reactions in MCell



A + B --> *products*

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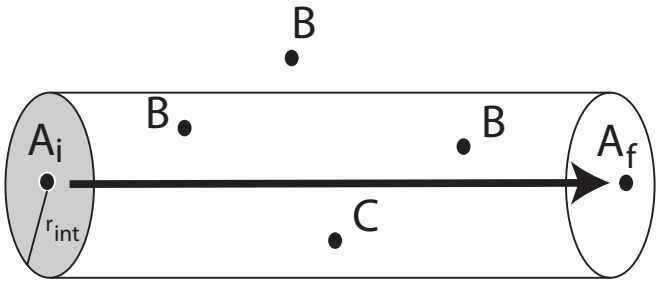

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- Volume molecules in MCell diffuse via ray-tracing along a randomly selected direction and diffusion step length computed as explained previously.
- Reaction partners are discovered and tested for reactions during ray marching. This unique approach provides good correlation between diffusive motion and location of reactants.

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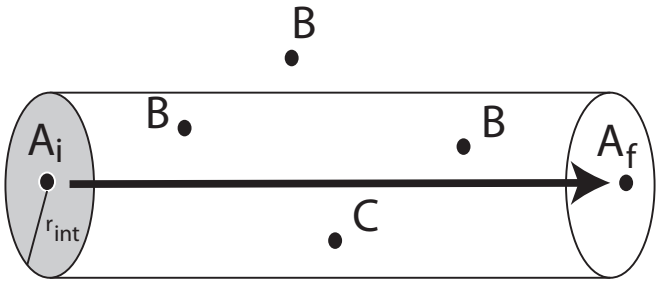

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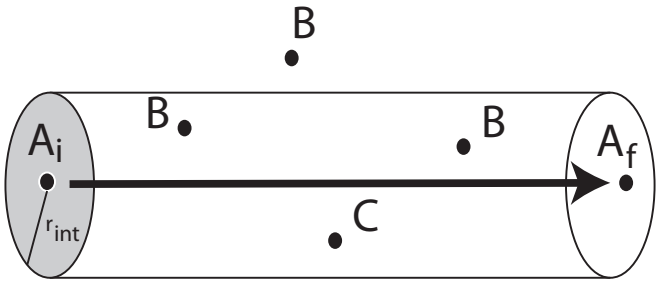

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Using an argument analogous to the one for bimolecular associations we can derive the following relation for the reaction probility between two diffusing volume molecules with diffusion constants $D1$ and $D2$:

$$p = \frac{k}{4A_{int}} \left(\frac{\pi \Delta t}{D_1 + D_2} \right)^{1/2} \tag{29}$$