

### Three-way reactions in MCell

The rate of reaction of a molecule that can engage in a three-way reaction with reactants  $I$  and  $J$  at concentrations  $\rho_I$  and  $\rho_J$  is  $\kappa\rho_I\rho_J$ . Suppose that a single molecule moves a distance  $R$  while sweeping out an interaction area  $A$ . Then the expected number of hits, assuming that the concentration of  $I$  and  $J$  is low, is

$$n_{\text{hits}} = RA\rho_I \cdot RA\rho_J$$

Thus, the expected number of hits for a molecule with a diffusion length constant of  $\lambda$  is

$$n_{\text{hits}} = \int_0^\infty \rho_I\rho_J A^2 R^2 \frac{4\pi R^2}{\pi^{3/2}\lambda^3} e^{-R^2/\lambda^2} dR = \frac{3}{2}\rho_I\rho_J A^2 \lambda^2$$

If we let  $p$  be the probability of reaction, then

$$\kappa\rho_I\rho_J\Delta t = p \cdot n = p \cdot \frac{3}{2}\rho_I\rho_J A^2 \lambda^2$$

Solving for  $p$  gives

$$p = \frac{\kappa}{6DA^2}$$

assuming that  $\Delta t$  is the time step for the moving molecule. If we let all three reactants move and react—let us number them 1, 2, and 3—then we matching the total rate gives

$$\kappa\rho_1\rho_2\rho_3\Delta t = \frac{3}{2}\rho_1\rho_2\rho_3 A^2 \left( p_1 \frac{\Delta t}{\Delta t_1} \lambda_1^2 + p_2 \frac{\Delta t}{\Delta t_2} \lambda_2^2 + p_3 \frac{\Delta t}{\Delta t_3} \lambda_3^2 \right)$$

where in general the individual molecules may move with custom timesteps  $\Delta t_i$ . We let  $p_1 = p_2 = p_3 = p$  to give

$$p = \frac{\kappa}{6(D_1 + D_2 + D_3)A^2}$$

This solution also works for the cases where some of the reactants can't move (as  $D_i$  will be zero and will drop out of the equation).

Now suppose that the reaction takes place near a surface such that for a fraction  $a$  of the distance, the molecule sweeps out  $A^* < A$  of area instead of  $A$ . The expected number of hits is then

$$n_{\text{hits}}^* = R\rho_I ((1-a)A + aA^*) R\rho_J ((1-a)A + aA^*)$$

which we can rewrite as

$$n_{\text{hits}}^* = n_{\text{hits}} \left( (1-a)^2 + 2a(1-a)\frac{A^*}{A} + a^2 \left( \frac{A^*}{A} \right)^2 \right)$$

where the first term occurs when both hits are in the unconstrained space, the second when one target molecule is in the unconstrained space and one is in the constrained space, and the third when both targets are in the constrained space. If we multiply the probability of reaction by the inverse of the fractional areas for each target, i.e., by  $A/A^*$  if one target is in the constrained space and  $(A/A^*)^2$  when both are in the constrained space, we then find that the total rate of reaction is

$$pn_{\text{hits}} \left( (1-a)^2 \cdot 1 \cdot 1 + 2a(1-a)\frac{A^*}{A} \cdot 1 \cdot \frac{A}{A^*} + a^2 \left( \frac{A^*}{A} \right)^2 \cdot \frac{A}{A^*} \cdot \frac{A}{A^*} \right) = pn_{\text{hits}}$$

That is, the reaction rate is unchanged, which is exactly what we want. Since  $a$  is arbitrary, we can make  $a$  differentially small and thus the result holds for arbitrary restrictions of the swept area.

### 3-way reactions plus a surface in MCell

If we have three reactants but one of them is on a surface, we can calculate the probability of the moving molecule both striking the surface and hitting the other reactants. If the molecule is a distance  $h$  above the surface, then the probability of hitting the surface is

$$p_{\text{surfhit}} = \frac{1}{2} \int_h^\infty dr_z \cdot \frac{1}{\pi^{1/2}\lambda} e^{-r_z^2/\lambda^2}$$

But the molecule also diffuses in the  $xy$  plane, and this determines the length of the collision cylinder. If the diffusion distance is  $r_{xy}$  in that plane, then the total diffusion length is  $r = \sqrt{r_{xy}^2 + r_z^2}$  and the swept volume is  $A\sqrt{r_{xy}^2 + r_z^2}$ . For a given  $r_z$ , then, the probability of hitting another free molecule is

$$p_{\text{freehit}} = \int_0^\infty dr_{xy} \cdot \frac{2\pi r_{xy}}{\pi\lambda^2} e^{-r_{xy}^2/\lambda^2} \cdot \left( A\sqrt{r_{xy}^2 + r_z^2} \right) \cdot \rho_1$$

where  $\rho_1$  is the density of the other free molecule. Thus, the probability of hitting the surface from distance  $h$  and also hitting a diffusing partner is

$$\begin{aligned} p_{\text{hit}}(h) &= \frac{1}{2} \int_h^\infty dr_z \frac{1}{\pi^{1/2}\lambda} e^{-r_z^2/\lambda^2} \int_0^\infty dr_{xy} \cdot \frac{2\rho_1 A}{\lambda^2} r_{xy} \sqrt{r_{xy}^2 + r_z^2} \cdot e^{-r_{xy}^2/\lambda^2} \\ &= \frac{\rho_1 A}{\pi^{1/2}\lambda^3} \int_h^\infty dr_z \cdot e^{-r_z^2/\lambda^2} \int_0^\infty dr_{xy} \cdot r_{xy} \sqrt{r_{xy}^2 + r_z^2} e^{-r_{xy}^2/\lambda^2} \end{aligned}$$

The inner integral evaluates to  $\frac{\lambda^2}{2} r_z + \frac{\pi^{1/2}\lambda^3}{4} e^{r_z^2/\lambda^2} \text{erfc}\left(\frac{r_z}{\lambda}\right)$ , giving

$$p_{\text{hit}}(h) = \frac{\rho_1 A}{2\pi^{1/2}\lambda} \int_h^\infty dr_z \cdot \left( r_z e^{-r_z^2/\lambda^2} + \frac{\pi^{1/2}\lambda}{2} \text{erfc}\left(\frac{r_z}{\lambda}\right) \right)$$

The outer integral works out to  $\lambda^2 e^{-h^2/\lambda^2} - \frac{\lambda h \pi^{1/2}}{2} \text{erfc}\left(\frac{h}{\lambda}\right)$ :

$$p_{\text{hit}}(h) = \frac{\rho_1 A}{2\pi^{1/2}} \left( \lambda e^{-h^2/\lambda^2} - \frac{h \pi^{1/2}}{2} \text{erfc}\left(\frac{h}{\lambda}\right) \right)$$

which we can integrate over the entire column above a surface molecule of area  $B$  to get the expected number of hits:

$$n_{\text{hit}} = \int_0^\infty dh \cdot B \cdot \rho_2 \cdot p_{\text{hit}}(h) = \frac{\rho_1 A \rho_2 B}{2\pi^{1/2}} \cdot \frac{3\lambda^2 \pi^{1/2}}{8} = \frac{3}{16} \lambda^2 \rho_1 \rho_2 A B$$

Since  $n_{\text{hit}} \cdot p_{\text{rx}}$  should be equal to the bulk reaction rate  $\kappa \rho_1 \rho_2 \Delta t$ , we have

$$p_{\text{rx}} = \frac{4\kappa}{3DAB}$$

if only species 2 diffuses (note that  $\lambda^2/\Delta t = 4D$ ). If both volume molecules diffuse, the total number of hits in a time  $\Delta t$  is

$$\frac{\Delta t}{\Delta t_1} n_{\text{hit},1} + \frac{\Delta t}{\Delta t_2} n_{\text{hit},2} = \frac{3}{16} (4D_1 + 4D_2) \rho_1 \rho_2 A B \Delta t$$

so that

$$p_{\text{rx}} = \frac{4\kappa}{3AB(D_1 + D_2)}$$

If the surface can be hit from either side, the number of hits doubles, so the reaction rate should be halved:

$$p'_{\text{rx}} = \frac{2\kappa}{3AB(D_1 + D_2)}$$

### Three-way reactions with two surface components

The standard computation for the number of hits against a single surface is

$$n_{\text{hit}} = \frac{\rho_1 A \lambda}{2\sqrt{\pi}}$$

and the probability that a grid element is filled with an appropriate surface molecule is  $\sigma_i A$  so that if we demand that we strike the first surface molecule directly and the second is adjacent, then the productive hit rate is (keeping in mind that either of the two surface molecules can be the initial target)

$$n_{\text{productive}} = \frac{3\rho_1\sigma_2\sigma_3A^3\lambda}{\sqrt{\pi}}$$

The desired number of reactions is  $\kappa\rho_1\sigma_2\sigma_3\Delta t$  (if appropriate units are used for the rate constant), so that

$$p_{\text{rx}} = \kappa \frac{\sqrt{\pi}}{3A^3v}$$

If hybrid units are used, one factor of  $A$  may drop out (as it does for the standard single-surface-molecule case). In contrast, if one of the components is the surface itself and the other is the molecule, the number of productive collisions drops by a factor of six (no neighbors, and only one target), giving

$$p'_{\text{rx}} = \kappa \frac{2\sqrt{\pi}}{A^3v}$$

### Three-way reactions with all surface components

If all components are in the surface, the total number of reactions per timestep for a single molecule should be  $\kappa\sigma_2\sigma_3\Delta t$  and the actual probability of finding the appropriate neighbors is  $3\sigma_2A \cdot 2\sigma_3A$ . Thus the reaction probability should be

$$p_{\text{rx}} = \frac{\kappa}{6A^2}\Delta t$$

### N-way reactions in MCell

Generalizing to  $N + 1$  reactants (one moving and  $N$  targets), where  $N$  is a positive integer, we find that the collision rate is

$$n_{\text{hits}} = \int_0^\infty dR \cdot \prod_{i=1}^N \rho_i \cdot (RA)^N \cdot \frac{4\pi R^2}{\pi^{3/2}\lambda^3} e^{-R^2/\lambda^2} = \prod_{i=1}^N \rho_i \cdot \frac{2\lambda^N A^N}{\sqrt{\pi}} \Gamma\left(\frac{N+3}{2}\right)$$

and the bulk rate is  $\kappa \cdot \prod_{i=1}^N \rho_i \cdot \Delta t$ , so equating probabilities gives

$$p = \frac{\kappa \sqrt{\pi} \Delta t}{2 \lambda^N A^N \Gamma\left(\frac{N+3}{2}\right)}$$

Note that  $\Gamma(N) = (N-1)!$  and  $\Gamma(N + \frac{1}{2}) = \sqrt{\pi} \cdot 2^{-2N} \cdot (2N)!/N! = \sqrt{\pi} \cdot \prod_{i=1}^N \frac{2i-1}{2}$ . If we have multiple moving molecules,

$$\kappa \cdot \prod_{i=1}^{N+1} \rho_i \cdot \Delta t = \prod_{i=1}^{N+1} \rho_i \cdot \frac{2A^N}{\sqrt{\pi}} \Gamma\left(\frac{N+3}{2}\right) \cdot \sum_{i=1}^{N+1} p_i \frac{\Delta t}{\Delta t_i} \lambda_i^N$$

so that, if we set all the  $p_i$  to be equal,

$$p = \frac{\kappa \sqrt{\pi}}{2 \Gamma\left(\frac{N+3}{2}\right) A^N \sum \frac{\lambda_i^N}{\Delta t_i}}$$

By induction on the result for pairs of targets in the 3-way case, we also see that if a target  $i$  is hit in a restricted space, the reaction probability should be multiplied by  $A/A_i^*$ .

### Higher order reactions with single surfaces

The primary equation for  $p_{\text{hit}}(h)$  remains the same for higher-order reactions except that  $\rho_1 A r$  turns into  $\prod_{i=1}^{N-1} \rho_i A r$  (recall that  $r = \sqrt{r_{xy}^2 + r_z^2}$ ). Otherwise the integration is the same. The general formulae for such integrals is rather tricky, but the first few values for  $n_{\text{hit}}$  are listed here:

$$\begin{aligned} n_{\text{hit}}^{(N=2)} &= \frac{3}{16} \lambda^2 A B \prod_{i=1}^N \rho_i \\ n_{\text{hit}}^{(N=3)} &= \frac{1}{2\sqrt{\pi}} \lambda^3 A^2 B \prod_{i=1}^N \rho_i \\ n_{\text{hit}}^{(N=4)} &= \frac{15}{32} \lambda^4 A^3 B \prod_{i=1}^N \rho_i \\ n_{\text{hit}}^{(N=5)} &= \frac{3}{2\sqrt{\pi}} \lambda^5 A^4 B \prod_{i=1}^N \rho_i \\ n_{\text{hit}}^{(N=6)} &= \frac{105}{64} \lambda^5 A^5 B \prod_{i=1}^N \rho_i \\ n_{\text{hit}}^{(N=7)} &= \frac{6}{\sqrt{\pi}} \lambda^6 A^5 B \prod_{i=1}^N \rho_i \end{aligned}$$

The author conjectures that the formula for even  $N$  is

$$\frac{(N+1)!}{4 \cdot 2^{3N/2} (N/2)!} \lambda^N A^{N-1} B \prod_{i=1}^N \rho_i$$

and for odd  $N$  is

$$\frac{((N+1)/2)!}{4\sqrt{\pi}} \lambda^N A^{N-1} B \prod_{i=1}^N \rho_i$$

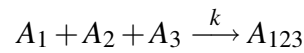
These have been checked up to  $N = 12$  in Maple 10, but these formulae have not been proven.

## Higher order reactions with multiple surface components

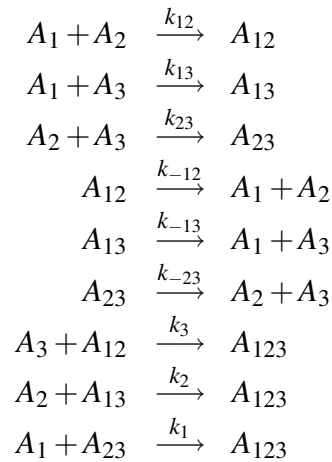
Each time one adds a molecular surface component, one adds a factor of  $\frac{1}{A}$  the first time (if one is already hitting a surface and a molecule needs to be there also),  $\frac{1}{3A}$  the second time,  $\frac{1}{2A}$  the third time, and  $\frac{1}{A}$  the fourth time. More than four molecules cannot be found by adjacent search; if this is generalized to a wider search, then if the extra partner can be found in one of  $n$  places, the reaction probability changes by  $\frac{1}{nA}$ . In addition, if there are  $k$  possible surface targets total, the reaction probability should be multiplied by an additional  $\frac{1}{k}$ .

## Converting 3-way reactions to 2-way reactions

Suppose we have a three-way reaction



which we wish to approximate by nine bimolecular reactions:



At quasi-steady state, we want to match rate of entry in to the  $A_{123}$  state:

$$kA_1A_2A_3 = k_1A_1A_{23} + k_2A_2A_{13} + k_3A_3A_{12} \quad (1)$$

And we also wish to keep the quasi-steady state concentrations of the intermediates  $A_{12}$ ,  $A_{13}$ , and  $A_{23}$  low compared to the starting materials. In general, we will have

$$\frac{d}{dt}A_{hi} = -k_jA_jA_{hi} - k_{-hi}A_{hi} + k_{hi}A_hA_i \approx 0$$

so that

$$A_{hi} \approx \frac{k_{hi}A_hA_i}{k_{-hi} + k_jA_j}$$

If we want this to be roughly independent of the concentration of  $A_j$  then we require  $k_{-hi} \gg k_jA_j$  and can rewrite this as

$$A_{hi} \approx \frac{k_{hi}}{k_{-hi}}A_hA_i \left(1 - \frac{k_jA_j}{k_{-hi}}\right)$$

If we further require that  $A_{hi}$  be small compared to  $A_h$  and  $A_i$ , we also require  $\frac{k_{hi}}{k_{-hi}} \ll \frac{1}{\max(A_h, A_i)}$ . Let  $A_+$  be the largest value of any of the  $A_i$  during a simulation. Furthermore, let us set all  $k_j$  to be  $k^*$ , all  $k_{hi}$  to be  $k^\dagger$  and all  $k_{-hi}$  to be  $k^\ddagger$ . Then our constraints require that  $k^\ddagger \gg k^* A_+$  and  $k^\dagger \ll k^\ddagger \frac{1}{A_+}$ ; taken together,  $k^\dagger \approx k^*$  is a valid solution, so we may as well make the two the same,  $k'$ . Thus, we have a forward reaction rate  $k'$  for all binding reactions and a backward reaction rate  $k^\ddagger$  for dissociation of the intermediates.

Thus, equation (1) becomes

$$kA_1A_2A_3 \approx k'A_1\frac{k'}{k^\ddagger}A_2A_3 + k'A_2\frac{k'}{k^\ddagger}A_1A_3 + k'A_3\frac{k'}{k^\ddagger}A_1A_2 = 3\frac{k'^2}{k^\ddagger}A_1A_2A_3$$

with a first-order error term

$$-\frac{k'^3}{k^{\ddagger 2}}A_1A_2A_3(A_1 + A_2 + A_3)$$

If we let  $k^\ddagger = \alpha k'$ , where  $\alpha \gg A_+$ , we then have

$$k \approx \frac{3}{\alpha}k' - \frac{A_1 + A_2 + A_3}{\alpha^2}k'$$

Thus,

$$k_1 = k_2 = k_3 = k_{12} = k_{13} = k_{23} = k' \approx \frac{1}{3}\alpha k$$

and

$$k_{-12} = k_{-13} = k_{-23} = k^\ddagger \approx \frac{1}{3}\alpha^2 k$$

Note that our fractional error is approximately  $1/\alpha$ , i.e. if we let  $\alpha = 100A_+$  our fractional error would be under 1%.