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## Appendix

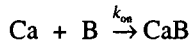
### Relationship between deterministic rate constants and probability of binding

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Here we derive the probability of binding for the Monte Carlo algorithm corresponding to a given macroscopic rate constant. The key steps are to interpret what probability means in this context and to convert units carefully, since deterministic rates are typically expressed in terms of concentration, whereas stochastic rates are expressed in terms of numbers of molecules or ions. We illustrate for the case of  $\text{Ca}^{2+}$  binding to buffer, but the same approach applies to the vesicle binding sites.

Diffusion is accounted for already by the random walk aspect of the algorithm, and we consider only the forward reaction



The rate for the deterministic case is

$$[1] \quad k_{\text{on}} [\text{Ca}] [\text{B}]$$

which has units of concentration per time. In order to compare with the stochastic case, we use eq. 1 to calculate the number of binding events per time step in the volume of one microcube (that is, in a cube of length  $\Delta x$  centered on a lattice point). That unitless number,  $N_{\text{D}}$ , comes out to

$$[2] \quad N_{\text{D}} = k_{\text{on}} [\text{Ca}] [\text{B}] \Delta t \Delta x^3$$

For the stochastic case, we define two random variables,  $N_{\text{Ca}}$  and  $N_{\text{B}}$ , the number of  $\text{Ca}^{2+}$  and buffer ions, respectively, in the microcube. These numbers take on only the values 0 or 1, but the more relevant quantities for comparison with the deterministic case are the expected values, obtained by averaging over runs. The expected values are related to macroscopic concentrations by

$$[3] \quad \langle N_{\text{Ca}} \rangle = [\text{Ca}] \Delta x^3$$

and similarly for  $N_{\text{B}}$ . Then,  $N_{\text{D}}$  can be rewritten as

$$[4] \quad N_{\text{D}} = k_{\text{on}} \frac{\langle N_{\text{Ca}} \rangle \langle N_{\text{B}} \rangle}{\Delta x^3} \Delta t$$

Now, in the stochastic case, the expected number of binding events per time step is

$$[5] \quad N_{\text{S}} = p \langle N_{\text{Ca}} N_{\text{B}} \rangle$$

where the quantity in parentheses is the number of Ca–B pairs (see Gillespie 1977). If  $N_{\text{Ca}}$  and  $N_{\text{B}}$  are independent random variables, then  $\langle N_{\text{Ca}} N_{\text{B}} \rangle \approx \langle N_{\text{Ca}} \rangle \langle N_{\text{B}} \rangle$ . This is a reasonable approximation if the reaction is not diffusion limited. Assuming this approximation, we equate  $N_{\text{D}}$  and  $N_{\text{S}}$  to obtain

$$[6] \quad p = \frac{k_{\text{on}} \Delta t}{\Delta x^3} = \frac{\overline{k_{\text{on}}} \overline{\Delta t}}{\overline{\Delta x}^3 (6.02 \times 10^5)}$$

where the barred quantities have the units and values in Table 1, and  $\Delta x = 5$  nm, giving a final result of  $p \approx 0.2$ .

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### Reference

Gillespie, D.T. 1977. Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.* **81**: 2340–2361.