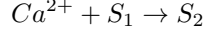


There are a total of 54 reactions that involve  $Ca^{2+}$  binding to a state of the sensor and forming a different state.



Let  $R_i$  be the event that in period of  $\Delta T$ , the  $i$ th reaction takes place at least once.

$$r_i \Delta T = P(R_i) = k_i [Ca^{2+}] [S_i] \Delta T$$

Let  $B_N$  be the event that exactly  $N$  reactions occur in  $\Delta T$ .

Probability that no reactions occur in  $\Delta T$ :

$$P(B_{N=0}) = \lim_{K \rightarrow \infty} (1 - \sum_i r_i \epsilon)^K = e^{-\Delta T R_{tot}}$$

Let  $r_{bind} = \sum r_i$ , the sum of all the binding reaction rates.

Now,

$$P(R_i | B_{N=0}) = \frac{P(R_i \cap B_{N=0})}{P(B_{N=0})} = 0$$

Similarly we can calculate  $P(B_{N=1})$ :

$$\begin{aligned} P(B_{N=1}) &= \sum_i P(R_i) \lim_{K \rightarrow \infty} [1 - \sum_{j \neq i} r_j \epsilon]^K \\ &= \sum_i r_i \Delta T e^{-\Delta T (r_{bind} - r_i)} \\ P(R_l | B_{N=1}) &= \frac{P(R_l \cap B_{N=1})}{P(B_{N=1})} \\ &= \frac{r_l \Delta T e^{-\Delta T (R_{bind} - R_l)}}{\sum_i r_i \Delta T e^{-\Delta T (r_{bind} - r_i)}} \\ &= \frac{k_l [S_l]}{\sum_i k_i [S_i] e^{-\Delta T (r_l - r_i)}} \end{aligned}$$

We can approximate the exponential to one.

This extends to  $N = 2$  as follows:

$$\begin{aligned}
P(B_{N=2}) &= \sum_{i,j} P(R_i)P(R_j) \lim_{K \rightarrow \infty} \left[1 - \sum_{k \neq i,j} r_k \epsilon\right]^K \\
&= \sum_{i,j} r_i r_j \Delta T e^{-\Delta T(r_{bind} - r_i - r_j)} \\
P(R_m, R_n | B_{N=2}) &= \frac{r_m r_n (\Delta T)^2 e^{-\Delta T(R_{bind} - R_m - R_n)}}{\sum_{i,j} r_i r_j (\Delta T)^2 e^{-\Delta T(R_{bind} - r_i - r_j)}} \\
&= \frac{k_m k_n [S_m][S_n]}{\sum_{i,j} k_i k_j [S_i][S_j] e^{-\Delta T((r_m + r_n) - (r_i + r_j))}} \\
&\approx \frac{k_m k_n [S_m][S_n]}{\sum_{i,j} k_i k_j [S_i][S_j]}
\end{aligned}$$

We can similarly extend this to higher  $N$ s. In extremely rare circumstances,  $N=5$  can occur. We are assuming the independence of the  $R_i$ s.