KINETIC MODEL

SIMPLEST KINETIC MODEL

Consider the different state probabilities for a specific virus particle:

- $P_0(t)$: the CD4-attached complex that will serve as the initial condition. This state is achieved by exposing the host cells to HIV for a long time while maintaining a low temperature.
- $P_1(t)$: the activated CD4-attached complex. Once temperature is raised, the CD4-bound state transitions into an activated state that has not yet bound to CCR5 but that is receptive to subsequent CCR5 binding.
- $P_2(t)$: the CD4-CCR5 complex. Once the state described by $P_1(t)$ binds CCR5, it is described by $P_2(t)$.
- $P_3(t)$: the activated CD4-CCR5 complex. Once CCR5 has bound, the system transitions into the prehairpin complex.
- Q: the membrane-fused state. The prehairpin complex can then initiate membrane fusion and viral entry. $Q(t)$ represents the probability that the viral as entered the host cell.

The kinetic equations for the probabilities can be written as

$$\begin{aligned}
\frac{\mathrm{d}P_0(t)}{\mathrm{d}t} &= -k_0P_0 + q_1P_1 \\
\frac{\mathrm{d}P_1(t)}{\mathrm{d}t} &= k_0P_0 - (k_1+q_1)P_1 + q_2P_2 \\
\frac{\mathrm{d}P_2(t)}{\mathrm{d}t} &= k_1P_1 - (k_2+q_2)P_2 + q_3P_3 \\
\frac{\mathrm{d}P_3(t)}{\mathrm{d}t} &= k_2P_2 - (k_\mathrm{f}+q_3)P_3 \\
\frac{\mathrm{d}Q(t)}{\mathrm{d}t} &= k_\mathrm{f}P_3
\end{aligned} \tag{1}$$

In the above, k_0, k_1, k_2, and k_f represent rates at which the CD4-bound complex is activated, the rate at which CCR5 binds, the rate at which the CD4-CCR5 complex transitions

into the prehairpin complex, and the rate of membrane fusion, respectively. The CCR5 binding rate k_1 would be a function of the available CCR5 or CCR5 binding site concentration. The parameters q_i are simply the associated backward rates. For example, q_2 is the rate of CCR5 detachment.

When agonists and fusion inhibitors are administered, the rates will change. For example, depleting CCR5 will decrease k_1, while administration of T20 would decrease k_2 and/or k_f.

Solutions to Eq. 1 can be explicitly found when $q_i = 0$ and the viral entry process is irreversible. We can Laplace transform Eqs. 1 and find

$$\tilde{Q}(s) = \frac{k_0 k_2 k_2}{s(s+k_0)(s+k_1)(s+k_2)(s+k_\mathrm{f})}. \tag{2}$$

For constant rates (no inhibitor added), the solution for the fraction of the initial CD4-bound virus in the special irreversible case is

$$\begin{aligned} Q(t) = 1 + k_\mathrm{f} k_0 k_1 k_2 \Bigg[& \frac{e^{-k_\mathrm{f} t}}{k_\mathrm{f}(k_\mathrm{f}-k_0)(k_\mathrm{f}-k_1)(k_\mathrm{f}-k_2)} + \frac{e^{-k_0 t}}{k_0(k_0-k_\mathrm{f})(k_0-k_1)(k_0-k_2)} \\ & + \frac{e^{-k_1 t}}{k_1(k_1-k_\mathrm{f})(k_1-k_0)(k_1-k_2)} + \frac{e^{-k_2 t}}{k_2(k_2-k_\mathrm{f})(k_2-k_0)(k_2-k_1)} \Bigg]. \end{aligned} \tag{3}$$

where $t = 0$ corresponds to the time at which temperature is instantly raised.

The fraction of initial CD4-bound virus that enter up to time $T_\mathrm{m} \approx 48$hrs is given by

$$F = Q(T) + k_\mathrm{f} \int_T^{T_\mathrm{m}-T} P_3(t)\mathrm{d}t \approx Q(T) + k_\mathrm{f} \int_T^{\infty} P_3(t)\mathrm{d}t, \tag{4}$$

where $P_3(t > T)$ is determined by the solution to $P_3(t = T)$ before k_1 is set to zero and the last approximation assumes T_m is much longer than any other timescale in the problem. We now consider three possible mechanisms of action for timed viral entry inhibitor experiments.

CCR5 antagonist: $k_1 = 0$ at time T

Suppose Maraviroc is administered at time $t = T$. We assume its effective mechanism is to bind to and "sequester" the available CCR5. Thus, for a perfect and instantaneous depletion of CCR5, we set $k_1 = 0$ starting at time T. If we assume irreversibilty and the limit $T_\mathrm{m} \to \infty$, the expression 4 for the fraction of viruses entered becomes

$$F \approx Q(T) + P_2(T) + P_3(T) = 1 - \left(\frac{k_1 e^{-k_0 T} - k_0 e^{-k_1 T}}{k_1 - k_0} \right). \tag{5}$$

Thus, for experiments where only Maraviroc is administered at time T, we fit the relative infection to the two-parameter result for F. However, since Eq. 5 is symmetric in k_0, k_1, both k_0 and k_1 cannot be independently obtained. Thus, we need an independent estimate for one of k_0, k_1.

A simple parameter consistency check is to compaere the peak of the derivative $\mathrm{d}F/\mathrm{d}T$ to that found from the data. The time T_d defined by $\mathrm{d}^2F/\mathrm{d}T^2|_{T=T_\mathrm{d}} = 0$ is

$$T_\mathrm{d} = \frac{1}{k_0 - k_1} \ln\left(\frac{k_0}{k_1}\right), \tag{6}$$

which provides a symmetric relationship between k_0 and k_1 given an observed T_d.

Late stage T20: $k_\mathrm{f} = 0$ at time T Now, consider experiments in which T20 is applied and assume that it acts by preventing the final fusion step. At and after time T, we set $k_\mathrm{f} = 0$. The total fraction entered in this case is predicted to be $F = Q(T_\mathrm{m}) \approx Q(\infty) = Q(T)$ given by Eq. 3 above evaluated at $t = T$.

If k_0 and k_1 can be estimated for a specific strain by the Maraviroc experiment, these parameter values can be used in Eq. 3 and F can be fit to T20 data to estimate k_2 and k_f.

Early stage T20: $k_2 = 0$ at time T

If T20 prevents the transition described rate k_2, we set $k_2 = 0$ after $t = T$, Eq. 4 becomes

$$F = Q(T) + k_\mathrm{f} P_3(T) \int_T^{T_\mathrm{m}-T} e^{-(k_\mathrm{f}+q_3)(t-T)} \mathrm{d}t \approx Q(T) + \frac{k_\mathrm{f} P_3(T)}{k_\mathrm{f} + q_3}, \tag{7}$$

where $P_3(T)$ is determined by solving Eqs. 3 before k_2 is set to zero. It will depend on all the rates k_i, q_i.

Again, in the irreversible case $q_i = 0$, we find

$$F \approx Q(T) + P_3(T) = 1 - \frac{k_0 k_2 e^{-k_1 T}}{(k_1 - k_0)(k_1 - k_2)} - \frac{k_1 k_2 e^{-k_0 T}}{(k_0 - k_1)(k_0 - k_2)} - \frac{k_0 k_1 e^{-k_2 T}}{(k_2 - k_0)(k_2 - k_1)}, \tag{8}$$

which is independent of k_f and adds the additional parameter k_2 into the fitting of T20 data.