Supporting Material

A Simple Model of Multivalent Adhesion and Its Application to Influenza Infection

Derivation of Eqs. 16–18

We present here the outline of the derivation of Eqs. 16–18. These equations estimate the affinity of adhesion mediated by a range of different receptors, each with a different binding affinity to the ligand. Suppose that there are N_i receptors of type $i = 1,2,\ldots,m$ with binding free energy $\Delta G_i = RT \ln K_i' \equiv RT \ln(K_i V_{\text{eff}})$. We can write down the grand canonical partition function of the system as

$$Z = \frac{1}{\prod_i N_i! N_L!} \sum_{\{n_i\}} \binom{N_i}{n_i} \binom{N_L}{n_1\ n_2 \cdots n_m} \prod_i n_i! \exp\left(-\frac{1}{RT} \sum_i n_i \Delta G_i\right). \quad \text{(S1)}$$

Following the derivation of Eqs. 1 and 2 in the text, we obtain the equilibrium condition

$$\frac{(N_i - \bar{n}_i)(N_L - \sum_i \bar{n}_i)}{\bar{n}_i} \approx K_i V_{\text{eff}}, i = 1,2,\ldots, \quad \text{(S2)}$$

and the probability of breaking all connections (i.e., $n_i = 0\ \forall i$)

$$\ln p_0 = \ln \frac{1}{\prod_i N_i! N_L!} - \ln Z$$

$$\approx \sum_i N_i \ln \frac{N_i - \bar{n}_i}{N_i} + N_L \ln \frac{N_L - \sum_i \bar{n}_i}{N_L} + \sum_i \bar{n}_i\ . \quad \text{(S3)}$$

Defining $\bar{n} \equiv \sum_i \bar{n}_i$, and taking the continuous limit by replacing the summation with the integral, we obtain Eqs. 16 and 17.

From Eq. S2, we have

$$\bar{n}_i = N_i \left(1 + \frac{K_i V_{\text{eff}}}{N_L - \bar{n}}\right)^{-1}, i = 1,2, \ldots, \tag{S4}$$

Summing over i, and taking the continuous limit, we obtain Eq. 18 in the text.

Derivation of Eqs. 31 and 32

We derive here Eqs. 31 and 32, which account for the cooperativity in the binding of SA molecules to monomers within a HA trimer. If the binding of k = 1,2,3 SA molecules to the same HA trimer corresponds to the free energy change of ΔG_k, the partition function of the system is

$$Z = \frac{1}{3^{N_{\text{HA}_3}} N_{\text{HA}_3}! N_{\text{SA}}!} \sum_{n_1,n_2,n_3} \binom{N_{\text{HA}_3}}{n_1\ n_2\ n_3} \binom{N_{\text{SA}}}{n} n! \binom{3}{1}^{n_1} \binom{3}{2}^{n_2} \binom{3}{3}^{n_3} \cdot$$

$$\exp(-(n_1 \Delta G_1 + n_2 \Delta G_2 + n_3 \Delta G_3)/RT)$$

$$= \sum_{n_1,n_2,n_3} \frac{3^{n_1+n_2-N_{\text{HA}_3}}}{(N_{\text{HA}_3} - n_1 - n_2 - n_3)! n_1! n_2! n_3! (N_{\text{SA}} - n)!} \exp(-(n_1 \Delta G_1 + n_2 \Delta G_2 + n_3 \Delta G_3)/RT), \tag{S5}$$

where $\binom{N_{\text{HA}_3}}{n_1\ n_2\ n_3}$ is the number of ways to choose n_k HA trimers to bind k = 1,2,3 SA molecules, $\binom{3}{k}$ accounts for the number of ways of choosing k monomers out of each HA trimer, and $n = n_1 + 2n_2 + 3n_3$ is the total number of SA molecules bound to HA. $N_{\text{HA}_3} = N_{\text{HA}} / 3$ is the total number of HA trimers.

As before, we approximate Z with the largest term in the summand, which is given by

$$\frac{p_{n_1+1}}{p_{n_1}} = \frac{3(N_{\text{HA}_3} - n_1 - n_2 - n_3)(N_{\text{SA}} - n)}{n_1 + 1} \exp\left(-\frac{\Delta G_1}{RT}\right)$$

$$\approx \frac{3(N_{\mathrm{HA}_3}-n_1-n_2-n_3)(N_{\mathrm{SA}}-n)}{n_1}\exp\left(-\frac{\Delta G_1}{RT}\right) \approx 1$$

$$\frac{p_{n_2+1}}{p_{n_2}} = \frac{3(N_{\mathrm{HA}_3}-n_1-n_2-n_3)(N_{\mathrm{SA}}-n)(N_{\mathrm{SA}}-n-1)}{n_2+1}\exp\left(-\frac{\Delta G_2}{RT}\right)$$

$$\approx \frac{3(N_{\mathrm{HA}_3}-n_1-n_2-n_3)(N_{\mathrm{SA}}-n)^2}{n_2}\exp\left(-\frac{\Delta G_2}{RT}\right) \approx 1$$

$$\frac{p_{n_3+1}}{p_{n_3}} = \frac{(N_{\mathrm{HA}_3}-n_1-n_2-n_3)(N_{\mathrm{SA}}-n)(N_{\mathrm{SA}}-n-1)(N_{\mathrm{SA}}-n-2)}{n_3+1}\exp\left(-\frac{\Delta G_3}{RT}\right)$$

$$\approx \frac{(N_{\mathrm{HA}_3}-n_1-n_2-n_3)(N_{\mathrm{SA}}-n)^3}{n_3}\exp\left(-\frac{\Delta G_3}{RT}\right) \approx 1. \quad \text{(S6)}$$

The largest term thus corresponds to the equilibrium numbers of HA trimers bound to 1, 2, or 3 SA molecules, satisfying

$$\frac{3(N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3)(N_{\mathrm{SA}}-\bar{n})}{\bar{n}_1} \approx \exp\left(\frac{\Delta G_1}{RT}\right)$$

$$\frac{3(N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3)(N_{\mathrm{SA}}-\bar{n})^2}{\bar{n}_2} \approx \exp\left(\frac{\Delta G_2}{RT}\right)$$

$$\frac{(N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3)(N_{\mathrm{SA}}-\bar{n})^3}{\bar{n}_3} \approx \exp\left(\frac{\Delta G_3}{RT}\right)$$

$$\bar{n} = \bar{n}_1 + 2\bar{n}_2 + 3\bar{n}_3. \quad \text{(S7)}$$

The probability of breaking all connections (i.e., $n_1 = n_2 = n_3 = 0$), is

$$\ln p_0 = \ln \frac{1}{3^{N_{\mathrm{HA}_3}} N_{\mathrm{HA}_3}! N_{\mathrm{SA}}!} - \ln Z$$

$$\approx N_{\mathrm{HA}_3} \ln \frac{N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3}{N_{\mathrm{HA}_3}} + N_{\mathrm{SA}} \ln \frac{N_{\mathrm{SA}}-\bar{n}}{N_{\mathrm{SA}}} + \bar{n}$$

$$-\bar{n}_1\left(\ln \frac{3(N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3)(N_{\mathrm{SA}}-\bar{n})}{\bar{n}_1} - \frac{\Delta G_1}{RT}\right)$$

$$-\bar{n}_2\left(\ln\frac{3(N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3)(N_{\mathrm{SA}}-\bar{n})^2}{\bar{n}_2}-\frac{\Delta G_2}{RT}\right)$$

$$-\bar{n}_3\left(\ln\frac{(N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3)(N_{\mathrm{SA}}-\bar{n})^3}{\bar{n}_2}-\frac{\Delta G_3}{RT}\right)$$

$$\approx N_{\mathrm{HA}_3}\ln\frac{N_{\mathrm{HA}_3}-\bar{n}_1-\bar{n}_2-\bar{n}_3}{N_{\mathrm{HA}_3}}+N_{\mathrm{SA}}\ln\frac{N_{\mathrm{SA}}-\bar{n}}{N_{\mathrm{SA}}}+\bar{n}. \tag{S8}$$

Eqs. S7 and S8 are Eqs. 32 and 31 in the text.

Derivation of Eqs. 33 and 34

We outline here the derivation of Eqs. 33 and 34, which describe the inhibition of adhesion when there is cooperativity in the binding of SA molecules to different monomers within a HA trimer.

Denoting m_i as the number of HA trimers that have i = 0,1,2,3 inhibitors bound, and n_{ij} as the number HA trimers that have i inhibitors and j SA molecules bound, we can write the partition function of the system as

$$Z=\frac{1}{3^{N_{\mathrm{HA}_3}}N_{\mathrm{HA}_3}!N_{\mathrm{SA}}!}\sum_{\{m_i\}}\binom{N_{\mathrm{HA}_3}}{m_1\ m_2\ m_3}\binom{3}{1}^{m_1}\binom{3}{2}^{m_2}\exp\left(-\frac{(m_1+2m_2+3m_3)\Delta\mu}{RT}\right)\cdot$$

$$\sum_{\{n_{ij}\}}\binom{m_0}{n_{01}\ n_{02}\ n_{03}}\binom{m_1}{n_{11}\ n_{12}}\binom{m_2}{n_{21}}\cdot\binom{3}{1}^{n_{01}}\binom{2}{1}^{n_{11}}\binom{3}{2}^{n_{02}}\binom{N_{\mathrm{SA}}}{n}n!\cdot$$

$$\exp\left(-\frac{(n_{01}+n_{11}+n_{21})\Delta G_1+(n_{02}+n_{12})\Delta G_2+n_{03}\Delta G_3}{RT}\right). \tag{S9}$$

In Eq. S9, we assume that the inhibitors are in excess of the HA, such that the solution concentration of inhibitor [I] does not change with $\{m_i\}$, and we assume that the affinity of

inhibitor-HA binding does not depend on the presence or absence of other inhibitor-HA or SA-HA complexes.

The largest term in the summand corresponds to the equilibrium condition

$$\binom{3}{i}\frac{\bar{m}_0-\sum_{j=1}^{3}\bar{n}_{0j}}{\bar{m}_i-\sum_{j=1}^{3-i}\bar{n}_{ij}}=\left(\frac{K_I}{[I]}\right)^i, i=1,2,3$$

$$\binom{3-i}{j}\frac{\bar{m}_i-\sum_{k=1}^{3-i}\bar{n}_{ik}}{\bar{n}_{ij}}=\frac{\exp\left(\frac{\Delta G_j}{RT}\right)}{(N_{\mathrm{SA}}-\bar{n})^j}, i=0,1,2,3;\ \ j=1,\ldots,3-i$$

$$\bar{m}_0+\bar{m}_1+\bar{m}_2+\bar{m}_3=N_{\mathrm{HA}_3}$$

$$\sum_{i=0}^{3}\sum_{j=1}^{3-i} j\,\bar{n}_{ij}=\bar{n}, \tag{S10}$$

and the probability of breaking all HA-SA connections (i.e., $n_{ij} = 0$ for $j > 0$), is

$$\ln p_0=\ln\left(\frac{1}{3^{N_{\mathrm{HA}_3}}N_{\mathrm{HA}_3}!N_{\mathrm{SA}}!}\sum_{\{m_i\}}\binom{N_{\mathrm{HA}_3}}{m_1\ m_2\ m_3}\binom{3}{1}^{m_1}\binom{3}{2}^{m_2}\exp\left(-\frac{(m_1+2m_2+3m_3)\Delta\mu}{RT}\right)\right)-\ln Z$$

$$=\ln\left(\frac{1}{3^{N_{\mathrm{HA}_3}}N_{\mathrm{HA}_3}!N_{\mathrm{SA}}!}\left(1+\exp\left(-\frac{\Delta\mu}{RT}\right)\right)^{3N_{\mathrm{HA}_3}}\right)-\ln Z$$

$$\approx N_{\mathrm{HA}_3}\ln\frac{\bar{m}_0-\bar{n}_{01}-\bar{n}_{02}-\bar{n}_{03}}{N_{\mathrm{HA}_3}/(1+\frac{[I]}{K_I})^3}+N_{\mathrm{SA}}\ln\frac{N_{\mathrm{SA}}-\bar{n}}{N_{\mathrm{SA}}}+\bar{n}. \tag{S11}$$

The last line is the result of replacing Z by the largest term in the summand, applying the Stirling approximation, and substituting in the equilibrium condition in Eq. S10. Eqs. S10 and S11 are Eqs. 34 and 33 in the text.

Adhesion of influenza virus to a cell population with variable numbers of receptors

Different cells have different SA densities on their surfaces, and thus different numbers of receptors at the interface. Here we analyze the effect of this variability on adhesion. Assuming that the expression and surface presentation of each individual receptor molecule is independent of other receptor molecules on the surface of a cell, the number of receptors at the interface in a cell population follows the Poisson distribution:

$$\chi(N_R) = \bar{N}_R{}^{N_R} \exp(-\bar{N}_R) / N_R!, \tag{S12}$$

where $\bar{N}_R$ is the average number of interface receptors in the cell population. The viral concentration bound to cells with N_R number of receptors, $[CV](N_R)$, satisfies

$$\frac{[CV](N_R)}{[V]} = [C](N_R) K_{D,\mathrm{ad}}{}^{-1}(N_R) = [\mathrm{cell}]\chi(N_R) K_{D,\mathrm{ad}}{}^{-1}(N_R). \tag{S13}$$

The total fraction of viral particles bound to cells is thus given by

$$f = \frac{\sum_{N_R}[CV](N_R)}{[V] + \sum_{N_R}[CV](N_R)} = \left(1 + \frac{1}{[\mathrm{cell}] \sum_{N_R} \chi(N_R) K_{D,\mathrm{ad}}{}^{-1}(N_R)}\right)^{-1}. \tag{S14}$$

Typically, $K_{D,\mathrm{ad}}{}^{-1}(N_R)$ increases rapidly with N_R around $\bar{N}_R$, while $\chi(N_R)$ decreases rapidly with $N_R > \bar{N}_R$, and their product sharply peaks at a maximum near $N_{R,\max} \approx \bar{N}_R$. The summation over N_R in Eq. S14 can thus be well approximated by the term $\chi(N_{R,\max}) K_{D,\mathrm{ad}}{}^{-1}(N_{R,\max})$, and Eq. S14 then reduces to Eq. 19, but with [cell] scaled by $\chi(N_{R,\max})$. This suggests that the conclusions drawn for adhesion to an individual cell remain largely unchanged for adhesion to a population of cells with variable receptor densities.

To explore the quantitative difference resulting from the variability in N_R, we computed the $K_{D,\max}$ that corresponds to the HA-SA affinity at which half of the viral particles are bound (see

the discussion on the viable range of binding affinity in the main text), assuming the value $\bar{N}_R = N_{SA}$ (in Table 1), and assuming the other parameter values in Table 1. Solving Eq. S14 for K_D with $f = 0.5$ yields $K_{D,\max} = 10.5$ mM, which is essentially the same as the value obtained for adhesion to cells with a uniform number of receptors (see main text).