

Supplementary Material

1 MEAN FIELD THEORY

We implement the mean field (MF) theory for adhesion system, wherein cell membrane adheres to planar supported bilayer containing mobile ligand molecules. We start with the grand-canonical ensemble in which the concentrations of adhesion proteins and lipid rafts are determined by the chemical potentials μ_p and μ_r , respectively. The grand-canonical Hamiltonian is then given by

$$\mathcal{H} = \mathcal{H}_{\text{ad}} - \sum_i \mu_r^+ n_i^+ - \sum_i (\mu_p^+ m_i^+ + \mu_p^- m_i^-) \quad (\text{S1})$$

where \mathcal{H}_{ad} is the total energy of canonical ensemble as given in main text. The superscript $+, -$ distinguishes the upper cell membrane and lower supported bilayer. Transforming raft variables $n_i^+ = 0, 1$ to spin variables $s_i^+ = 2n_i^+ - 1 = \pm 1$, and using MF approximation $s_i^+ s_j^+ \approx \langle s_i^+ \rangle s_j^+ + \langle s_j^+ \rangle s_i^+ - \langle s_i^+ \rangle \langle s_j^+ \rangle$ with the average $s = \langle s_i^+ \rangle = \langle s_j^+ \rangle$, we obtain MF Hamiltonian

$$\begin{aligned} \mathcal{H}_{\text{MF}} &= \mathcal{H}_{\text{me}} + \mathcal{H}_{\text{R-L}} + \\ &\sum_i \left[\epsilon_r^+ - U_{\text{effr}} s_i^+ - \frac{u_a}{2} (s_i^+ + 1) m_i^+ - \mu_p^+ m_i^+ - \mu_p^- m_i^- + V_b m_i^+ m_i^- \right] \end{aligned} \quad (\text{S2})$$

with $\epsilon_r^+ = \frac{1}{2} [u(s^2 - 1) - \mu_r^+]$, $U_{\text{effr}} = u(1 + s) + \frac{1}{2} \mu_r^+$. Then the grand-canonical partition function is obtained as

$$\begin{aligned} \mathcal{Z}_{\text{MF}} &= \left[\prod_i \int_0^\infty dl_i \right] \left[\prod_i \sum_{s_i^+ = \pm 1} \sum_{m_i^- = 0, 1} \sum_{m_i^+ = 0, 1} \right] e^{-\beta \mathcal{H}_{\text{MF}}} \\ &= e^{-N\beta \epsilon_r^+} \left[\prod_i \int_0^\infty dl_i \right] \left[e^{-\beta \mathcal{H}_{\text{me}}} \prod_i \sum_{\sigma^+ = \pm 1} w_{\sigma^+}(l_i) \right] \end{aligned} \quad (\text{S3})$$

with $\beta = (k_B T)^{-1}$ and

$$\begin{aligned} w_{\sigma^+}(l_i) &= \left[e^{\beta U_{\text{effr}} \sigma^+} + e^{\beta (U_{\text{effr}} \sigma^+ + \mu_p^-)} \right. \\ &\left. + e^{\beta (U_{\text{effr}} \sigma^+ + \frac{1}{2} u_a (\sigma^+ + 1) + \mu_p^+)} + e^{\beta (U_{\text{effr}} \sigma^+ + \frac{1}{2} u_a (\sigma^+ + 1) + \mu_p^+ + \mu_p^- + u_b \theta(l_b/2 - |l_i - l_c|)} \right] \end{aligned} \quad (\text{S4})$$

By defining $A_{\sigma^+} = w_{\sigma^+}(l_i)|_{\theta(l_b/2 - |l_i - l_c|) = 0}$ and $B_{\sigma^+} = w_{\sigma^+}(l_i)|_{\theta(l_b/2 - |l_i - l_c|) = 1}$, the partition function given by Eq. (S3) can be rewritten as

$$\mathcal{Z}_{\text{MF}} = e^{-N\beta \epsilon_r^+} \left[\sum_{\sigma^+ = \pm 1} A_{\sigma^+} \right]^N \left[\prod_i \int_0^\infty dl_i \right] e^{-\beta [\mathcal{H}_{\text{me}} + \sum_i V_{b,\text{eff}}(l_i)]} \quad (\text{S5})$$

where the effective binding potential $V_{b,\text{eff}}(l_i) = -U_{b,\text{eff}}\theta(l_b/2 - |l_i - l_c|)$ is a square-well potential with the same width l_b and location l_c as the R-L binding potential in Eq. (2) in the main text. The effective binding strength takes the form

$$U_{b,\text{eff}} = k_B T \ln \frac{\sum_{\sigma^+} B_{\sigma^+}}{\sum_{\sigma^+} A_{\sigma^+}} \quad (\text{S6})$$

which is a function of parameters $u_b, u_a, u, \mu_p, \mu_r$ and T . The free energy density is determined as

$$\mathcal{F} = -\frac{k_B T}{N} \ln \mathcal{Z}_{\text{MF}} = \epsilon_r^+ - k_B T \ln \left[\sum_{\sigma^+ = \pm 1} A_{\sigma^+} \right] + \mathcal{F}_0 \quad (\text{S7})$$

where

$$\mathcal{F}_0 = -\frac{k_B T}{N} \ln \left\{ \left[\prod_i \int_0^\infty dl_i \right] e^{-\beta [\mathcal{H}_{\text{me}} + \sum_i V_{b,\text{eff}}(l_i)]} \right\} \quad (\text{S8})$$

is the free energy density for two *homogeneous* membranes with Hamiltonian $\mathcal{H}_0 = \mathcal{H}_{\text{me}} + \sum_i V_{b,\text{eff}}(l_i)$.

Phase separation occurs if the free energy density \mathcal{F} shows two equal minima separated by a maximum, implying that the first-order partial derivative $\partial\mathcal{F}/\partial s = 0$ has three roots s_1, s_2 , and s_3 , and the second-order partial derivative $\partial^2\mathcal{F}/\partial s^2$ is negative for one of the roots and positive for the other two. We can then obtain the self-consistent equation using the condition $\partial\mathcal{F}/\partial s = 0$

$$s = P_b \frac{\sum_{\sigma^+} \sigma^+ B_{\sigma^+}}{\sum_{\sigma^+} B_{\sigma^+}} + (1 - P_b) \frac{\sum_{\sigma^+} \sigma^+ A_{\sigma^+}}{\sum_{\sigma^+} A_{\sigma^+}} \quad (\text{S9})$$

where $P_b = -\partial\mathcal{F}_0/\partial U_{b,\text{eff}} = \langle \theta(l_b/2 - |l_i - l_c|) \rangle_{\mathcal{H}_0}$ is the equilibrium fraction of bound membrane patches with $l_c - l_b/2 < l_i < l_c + l_b/2$ in the reference system, i.e., the so-called contact probability. P_b is determined by MC simulations for homogeneous membrane system with Hamiltonian \mathcal{H}_0 . We then identify the phase transition points by numerically solving Eq. (S9) under the condition $\mathcal{F}(s_1) = \mathcal{F}(s_3)$.