Supplementary Information 1

Membrane-mediated interactions

The interaction between a T cell and an APC is mediated by several molecular components, especially the cells plasma membranes and the LFA1-ICAM1 and TCR-pMHC adhesion bonds connecting them. In our simulations, we focus on the dynamics of the TCR-pMHC bonds and for this purpose we need to calculate the membrane-mediated interactions that they experience due to the deformation of the membrane of the T cell. To this end, the state of a system that includes all the relevant components, *except for the TCR-pMHC bonds*, is taken as a reference. In this reference state, which is shown schematically in Fig. S1a, the distance between the cells is set by the length of the LFA1-ICAM1 bonds (~ 41 nm). The deformation energy of the T cell membrane can be described by the Helfrich effective Hamiltonian [1]

$$\mathcal{H} = \int \frac{1}{2}\left[\kappa\left(\nabla^2 h\right)^2 + \gamma h^2\right] d^2\mathbf{r}, \tag{1}$$

where $h(\mathbf{r})$ is the membrane's height profile relative to the reference plain state at $h = 0$. The first term in eq. (1) is the curvature energy of the membrane, characterized by a bending modulus κ. The second term is a harmonic confining potential of strength γ. This term accounts for various influences that surpress the membrane thermal undulation around $h = 0$, e.g., the interaction of the membrane with the actin cytoskeleton (residing underneath the T cell membrane in Fig. S1a) and the glycocalyx (not shown explicitly). Fig. S1b depicts the same system with the TCR-pMHC included. These pull the T cell membrane toward the APC and locally set the inter-cell separation to 14 nm, thereby deforming the T cell membrane a distance $h_0 = 41 - 14 = 27$ nm from the minimum of the harmonic confining potential. The resulting deformation energy is minimized when the TCR-pMHC bonds aggregate, which is the origin of the attractive membrane-mediated interactions between them. In principle, these interactions are described by a many-body potential of mean force (PMF) that depends on the instataneous coordinates of all TCR-pMHC bonds. In practice, for dilute systems the PMF is well-approximated by the sum of pairwise interactions that depend only on the distance r between the adhesion bonds [2]. The

PMF between two TCR-pMHC bonds, $\Phi_{\rm att}(r)$, can be derived from the partition function

$$Z_A = \int \mathcal{D}\left[h(\mathbf{r})\right] e^{-\beta\mathcal{H}} \delta\left(h(0) - h_0\right) \delta\left(h(r) - h_0\right), \tag{2}$$

which involves statistical averaging over all membrane configurations whose height at the locations of the bonds ($r_1 = 0, r_2 = r$) is fixed at $h_0 = 27\,\mathrm{nm}$. The height constraints are represented in eq. (2) by the two δ-functions. The partition function can be calculated using standard statistical-mechanics techniques for handling multidimensional Gaussian integrals. The PMF is related to Z_A by $\Phi_{\rm att}(r) = -k_{\rm B}T \ln Z_A$, where $k_{\rm B}$ is the Boltzman constant and T is the temperature. It is given by (see eqs.(5) and (7) in ref. [3])

$$\frac{\Phi_{\rm att}(r)}{k_{\rm B}T} = \left(\frac{h_0}{\Delta}\right)^2 \frac{\frac{4}{\pi}\mathrm{kei}\left(\frac{r}{\xi}\right)}{1 - \frac{4}{\pi}\mathrm{kei}\left(\frac{r}{\xi}\right)}, \tag{3}$$

where kei(x) is the Kelvin function [4], $\xi = (\kappa/\gamma)^{1/4}$ and $\Delta^2 = k_{\rm B}T/8\sqrt{\kappa\gamma}$. Both ξ and Δ have units of length. For T cells, their values are roughly given by $\xi \simeq 100\,\mathrm{nm}$ and $\Delta \simeq 8\,\mathrm{nm}$ [3]. The PMF, $\Phi_{\rm att}/k_{\rm B}T$ (expressed in units of the thermal energy), is depicted by the solid line in Fig. S2 as a function of the normalized pair distance r/ξ, for the aformentioned values of the systems parameters ξ, Δ and h_0. The attractive pair-potential has a strength of a few $k_{\rm B}T$ for $r \simeq \xi$, and is screened at somewhat larger distances.

At separations smaller than ξ, one has to take into account direct excluded volume (hard core) interactions between the TCR-pMHC bonds. Since these are missing in the calculation of the partition function, a purely repulsive potential diverging for $r \to 0$ must be added to $\Phi_{\rm att}$. The full pair potential between TCR-pMHC bonds is reminiscent of a Lennard-Jones potential, i.e., repulsive at very short distances and attractive at an intermediate finite range. Domain formation under the influence of this type of potentials can be conviniently studied within the framework of the classical discrete lattice-gas (Ising) model where each lattice site can be occupied by at most one lattice point (in order to account for the short range repulsion), and with nearest-neighbor attraction of strength ϵ. Setting the lattice spacing to ξ, we take $\epsilon = \Phi_{\rm att}(r = \xi) \simeq -4.5\ k_{\rm B}T$. We do not consider next-nerarest-neighbor interactions, despite

of the fact that the $\Phi_{\rm att}$ does not fully decay at $r = \xi$. The reason for this decision is the many-body nature of the membrane-mediated PMF, which becomes important at the onset of the formation of adhesion clusters. In high density domains, each adhesion bond interacts with the proximal bonds in the first surrounding shell, whose very presence screens the interactions with the slightly more distant bonds in the next shells [5].

Another important note about the many-body membrane-mediated PMF between TCR-pMHC bonds is that, in principal, it should also be dependent on the density of the LFA1-ICAM1 bonds since their presence is the source of effective attraction between the TCR-pMHC bonds. Here, the LFA1-ICAM1 bonds are not modeled explicitly but are represented by the uniform harmonic potential in eq. (1). The utility of this approach was demonstrated in a previous study [3], employing a lattice model with a microscopic spacing of 5 nm and an explicit representation of the membrane. In that work we calculated the phase diagram of the system, which exhibits a two-phase region including semi-dilute domains with densities of about 100 bonds per μm^2. These densities are comparable to the estimated density of TCR-pMHC bonds in the IS, and correspond to a typical distance of $\xi = 100$ nm between them. Thus, the uniform harmonic confining potential correctly captures the influence of the LFA1-ICAM1 bonds in inducing the aggregation of the TCR-pMHC bonds in the system. Based on the success of eq. (1) to capture the thermodynamics of the system within a model of finer resolution, we here present a coarser model with lattice spacing ξ, an set the pairwise interactions between TCR-pMHC bonds at this separation to $\epsilon = -4.5\ k_{\rm B}T$, according to eq. (3) (which has been derived from eq. (1)).

In addition to the membrane-mediated interactions between TCR-pMHC bonds, we also need to calculate the pair PMF between the TCR-pMHC bonds and proteins that pin the T cell membrane to the actin cytoskeleton. These interactions are obviously repulsive due to the large differences in the height of the membrane at the locations of these two proteins ($h = 0$ at the pinning sites compared to $h = h_0 = 27\,$nm at the sites of the TCR-pMHC bonds). The repulsive pair PMF can be derived from the partition function

$$Z_B = \int \mathcal{D}\left[h(\mathbf{r})\right] e^{-\beta\mathcal{H}} \delta\left(h(0) - h_0\right) \delta\left(h(r)\right), \tag{4}$$

which differs from eq. (2) by one height constraint. The resulting repulsive pair PMF is given by

$$\frac{\Phi_{\rm rep}(r)}{k_{\rm B}T} = \frac{1}{2}\left(\frac{h_0}{\Delta}\right)^2 \frac{\left(\frac{4}{\pi}\right)^2 \mathrm{kei}^2\left(\frac{r}{\xi}\right)}{1-\left(\frac{4}{\pi}\right)^2 \mathrm{kei}^2\left(\frac{r}{\xi}\right)} \tag{5}$$

and is depicted by the dashed line in Fig. S2 for similar values of system parameters. From Fig. S2 it is clear that $\Phi_{\rm rep}$ is a purely repulsive potential of range $r \simeq \xi$ that quickly decays to zero at larger separations. For $r < \xi$, $\Phi_{\rm rep}$ sharply increases similarly to an excluded volume potential. We thus conclude that the membrane curvature itself serves as a source of repulsion between TCR-pMHAC bonds and pinning proteins, which renders the addition of explicit excluded volume (hard core) interactions unnecessary in this case. In the lattice simulations with lattice constant ξ, this strong membrane-mediated repulsion is accounted for by the standard demand that each lattice site can be occupied by no more than a single lattice point.

References

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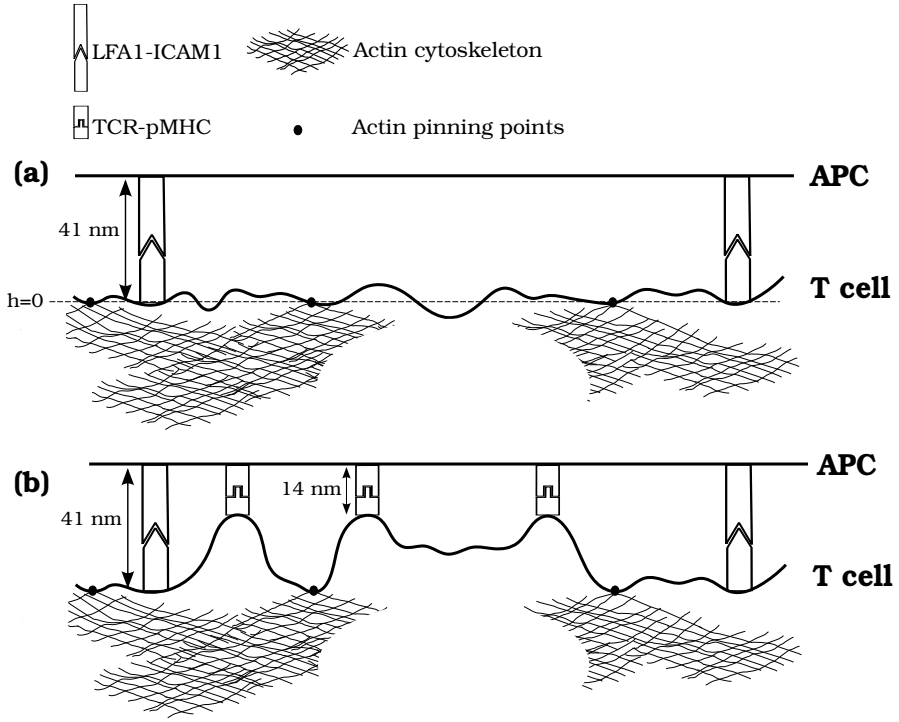

Figure S1: Schematics of the contact area between the membranes of the T cell and the APC. The two membranes are connected by two types of adhesion proteins: LFA1-ICAM1 and TCR-pMHC with bond lengths of 41 nm and 14 nm, respectively. The T cell's membrane is attached to the cytoskeleton by a set of actin pinning proteins. (a) shows all of the system components except from the TCR-pMHC bonds. The latter, which are present in (b), pull the T cell membrane away from its reference state.

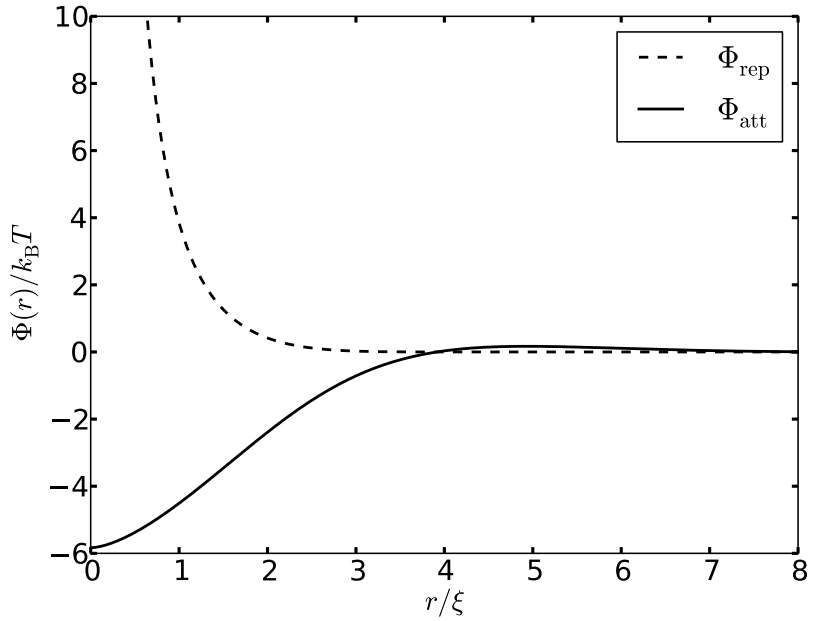

Figure S2: Curvature-induced interactions: the solid line depicts the curavture-induced attraction between two TCR-pMHC bonds, while the dashed line stands for the curvature-induced repulsion between a TCR-pMHC bond an a membrane-cytoskeleton pinning point.