Catch bonds at T cell interfaces: Impact of surface organization and membrane fluctuations

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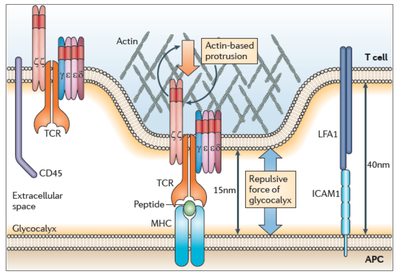
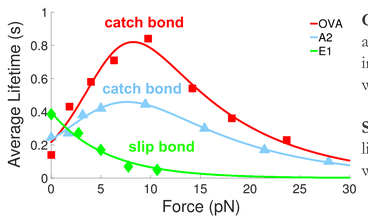
T cells orchestrate adaptive immunity

T lymphocytes use the T cell receptor (TCR) complex to engage membrane-presented ligands (pMHCs) on the surfaces of other cells as they scan for antigens. An outstanding question in immunology is: How can the T cell reliably distinguish between self and foreign ligands while being sensitive to even a single antigenic ligand?



The TCR-pMHC bond is shorter than many other surface molecules (SMs) in the intercellular junction. Image adapted from Dustin and Depoil (2011) [1].

Recent studies have shown that TCRs can exhibit catch-bond behavior when engaged with stimulatory ligands [2].



Catch bond: average lifetime initially increases with increasing force

Slip bond: average lifetime decreases with increasing force

Force-dependent lifetime data (points) for the OT1 TCR bound to three different ligands. Data points are from Liu et al. [2]. Solid lines are nonlinear least squares fits using standard catch- and slip-bond models.

Membrane-associated proteins experience forces at cell interfaces

Many factors influence the formation and dissociation of TCR-pMHC complexes at the T cell interface, including forces that arise from membrane undulations, cell motion, and active cytoskeletal processes. Additionally, it is energetically unfavorable to bend membranes over short length scales, and the coupling of protein size exclusion to membrane bending mechanics can lead to deformations of the membrane, a large-scale reorganization of the membrane, and a time-dependent force on a single TCR-pMHC bond [3].

It is unclear how small numbers of catch bonds at a cell-cell interface are influenced by membrane shape changes, reorganization of surface molecules, and thermal fluctuations. We consider a computational framework that accounts for small numbers of bonds at the interface of a T cell and an antigen-presenting cell.

Model

Two apposed membranes are connected by one or more static intermembrane bonds. The membrane shape and distribution of surface molecules (SMs) evolve in time in response to the presence of bonds. The energy of the system is

$$E[z, C_{\mathrm{SM}}] = \iint dx\, dy \underbrace{\left(\frac{\kappa}{2}\left(\nabla^2 z\right)^2\right)}_{\text{Bending Energy}} + \underbrace{C_{\mathrm{SM}} E_p}_{\text{SM deformation}}$$

Membrane shape and concentration of surface molecules

$$E_p(x, y, t) = k_p (z_p - z)^2 / 2$$

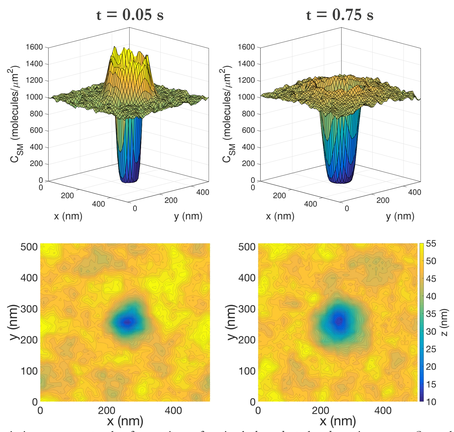
The concentration of surface molecules changes according to

$$\frac{\partial C_{\mathrm{SM}}}{\partial t} = D\nabla^2 C_{\mathrm{SM}} + \frac{D}{k_{\mathrm{B}}T}\nabla \cdot \left(C_{\mathrm{SM}} \nabla E_p\right)$$

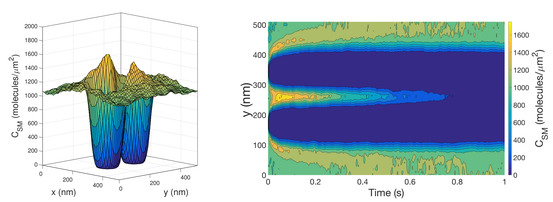
We use a hybrid computational scheme to characterize the dynamics of the intermembrane distance profile (z) and the concentration profile of surface molecules (C_{SM}): The concentration profile of SMs is propagated forward in time using the drift-diffusion equation. The membrane is then allowed to relax to an equilibrium configuration using Metropolis Monte Carlo simulations. This process is repeated.

Bond formation drives membrane reorganization

The formation of an intermembrane bond causes a response in the membrane shape and in the distribution of surface molecules.



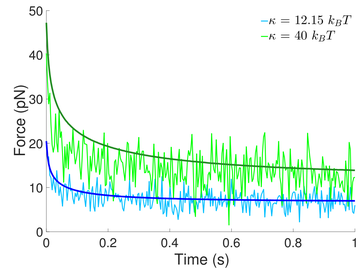
Characteristic response to the formation of a single bond at the domain center: Snapshots of the surface molecule concentration (top) and the intermembrane distance (bottom).



Response of surface molecules to the formation of two bonds: Snapshot at 0.75 s (left) and kymograph of a one-dimensional slice containing both bonds (right).

Bonds experience a time-dependent tension

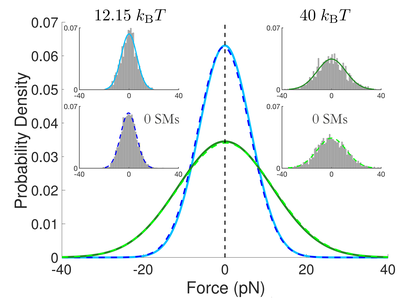
When a bond forms, the membrane shape and surface organization alter the energy profile near the bond, leading to a time-dependent force on the bond. As the system evolves toward more energetically favorable configurations, the average tension on the bond decreases.



Average bond tension as a function of time. The average tension at each time point is calculated by averaging the tension from ten independent simulation trajectories. Trajectories without fluctuations are shown in darker shades.

Force fluctuations are driven by membrane shape fluctuations

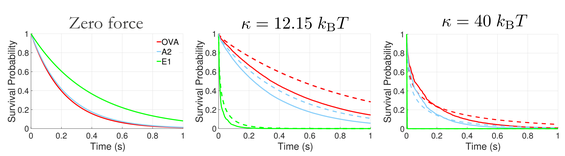
Fluctuations in z in the region surrounding the bond give rise to fluctuations in the bond tension, with the characteristic size of the force fluctuations similar to the characteristic size at an undeformed interface.



Gaussian fits of the probability densities for the mean-centered forces obtained from simulations with and without surface molecules present. Histograms of mean-centered force data are included as insets for cases with (solid) and without (dashed) surface molecules.

Catch bonds enhance lifetimes

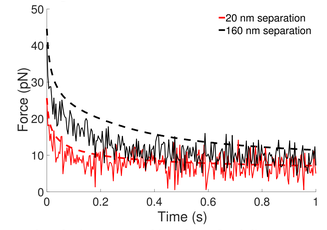
Given the forces calculated above, stimulatory catch bonds are more likely to remain intact than the slip bond. Thermal fluctuations of the membrane shape enhance the decay of the average force on a bond, but also lead to fluctuations of the force. These fluctuations promote bond rupture, but the effect is buffered by catch bonds.



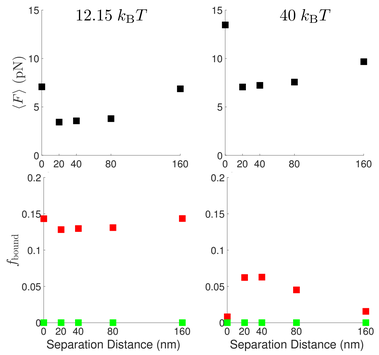
Survival probabilities for different ligands with (solid) and without (dashed) thermal fluctuations. At zero applied force, the slip bond (E1) exhibits the longest average lifetime.

The spatial distribution of bonds impacts bond lifetimes

At the T cell interface, multiple TCRs are likely to engage pMHCs and mutually influence each other's behavior. When more than one bond is present, the bonds experience reduced average forces that depend on their relative positions, leading to changes in bond lifetimes. When three or more bonds are present, some of bonds can experience compressive forces.



Average force on a bond when a second bond is a fixed distance away. Results with (solid) and without (dashed) thermal fluctuations. The average bond tension increases with increased separation.



Average force (top) and fraction of bonds remaining at 1 s (bottom) as a function of the separation between two bonds. The separation distance of zero corresponds to a single bond.

Conclusions and future direction

A growing body of work has revealed the importance of forces in T cell activation. Our results indicate that agonist catch bonds are more likely to remain intact than an antagonist slip bond when the bonds experience a time-dependent and fluctuating force. This is suggestive from a mechanistic standpoint, as force-dependent regulation of TCR-pMHC binding times provides a physical mechanism that could help T cells discriminate between self and foreign peptides.

Future directions: Receptor mobility and organization, actin-mediated forces, dynamic membrane responses, and stochastic reaction kinetics. Development of hybrid stochastic-deterministic algorithms.

References

1 Dustin ML and Depoil D (2011) *Nat. Rev. Immunol.* **11**, 672-684.
2 Liu B et al. (2014) *Cell.* **157**, 357-368.
3 Allard JF et al. (2012) *Biophys. J.* **102**, 1265-1273.