Brownian dynamics simulations of the B-cell activation

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The binding between B cell receptors (BCRs) and their ligands is a fundamental step in the B cell activation. This binding consists of a series of states and processes which include: diffusion, orientation and molecular binding [1] (see Fig.1).

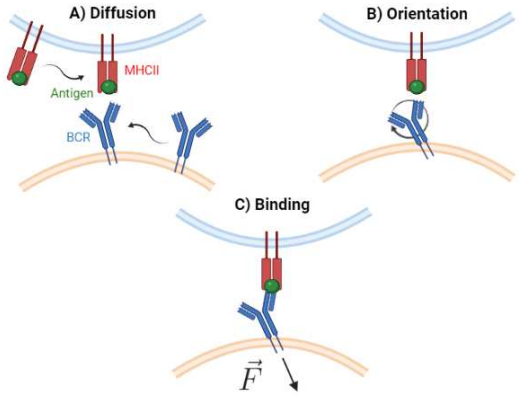

Fig. 1. **Three steps of binding**. **a)** Membrane diffusion, **b)** Orientation and **c)** Molecular binding.

Once the bond is formed, it is mechanically stressed by tensile forces coming from the environment and the internal reorganization of the cell membrane. Interestingly, it has been observed in many biological systems that the applied force changes the bond mean lifetime. Naively, one could expect that the larger the force, the shorter the time (as the two molecules are *pulled* away). This mechanism is called slip-bond unbinding. However, it has been empirically observed that for some systems, the opposite happens (at least for small tensions). This is called catch-bond mechanism, and it has been reported in a wide variety of systems, from elastic fibers to T-cells [2].

Microscopically, the three steps in Fig. 1 are stochastic in nature due to thermal fluctuations at the protein level. In this work, we model all those previous processes as Brownian motions, either in a cell membrane (diffusion), extracellular space (orientation), or a potential landscape (binding rupture). Using Montecarlo simulations, we investigate the so-called "Two-pathways model" of the catch bond [3] and

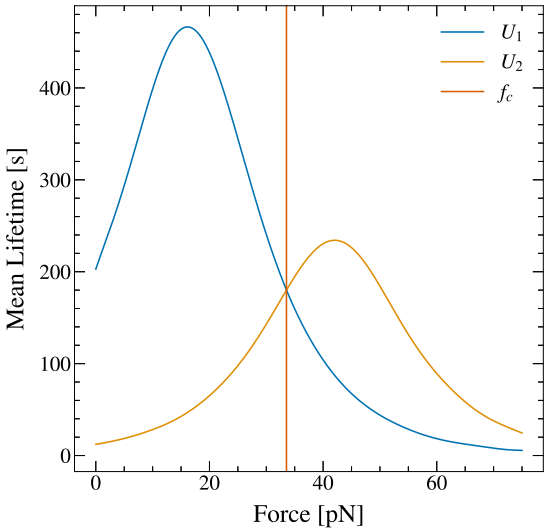

Fig. 2. **Catch behavior of two bonds**. In solution ($f = 0$), the affinity of one bond is much greater than the other. As from a critical force (f_c), the rank in the affinity of both bonds is interchanged.

reproduce the orientation and catch bond dynamics. We find that the affinity of two BCRs with an antigen can drastically change if it is measured in solution (absence of force, $f = 0$) or in a cell-to-cell set up as in physiological conditions (see Fig.2).

Our results highlight the dangers of uncontrolled in-vitro experiments to rank the affinity of antibodies as those experiments are unable to capture the true underlying kinetic rates and, thus, can mislead the quest to find specific therapeutic treatments based on antibodies.

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[2] O. V. Prezhdo, Y. V. Pereverzev, *Theoretical Aspects of the Biological Catch Bond*, Accounts of Chemical Research, **42** (6) (2009).

[3] V. K. Gupta, *Brownian dynamics simulation of catch to slip transition over a model energy landscape*, J. Biological Systems, **24** (2016).