I. ANTIGEN EXTRACTION AS A FIRST PASSAGE PROBLEM

A. Stochastic differential equations of extraction dynamics

To describe the stochastic process of antigen extraction, we formulate competitive rupture of the two binding interfaces in a BCR-Ag-APC complex with a pair of Langevin equations coupled through the motion of the antigen molecule. The system state can be characterized by molecular displacements, \( x \) and \( y \), of the antigen and BCR molecules from their respective equilibrium positions, or alternatively by bond extensions, \( x_a \) and \( x_b \), of the Ag-APC association and the BCR-Ag attachment, respectively. These two sets of reaction coordinates are simply related through \( x_a = x \) and \( x_b = y - x \) (illustrated in Fig. S1).

In the \((x, y)\) coordinates of molecular displacements, the potential energy is given by

\[
U(x, y) = U_a(x) + U_b(y - x) - Fy, \tag{S1}
\]

where \( U_a(z) \) and \( U_b(z) \) represent interaction energies in the Ag-APC bond and the BCR-Ag bond, respectively, which depend on the separation \( z \) between molecules. A pulling force of magnitude \( F \) is exerted by a B cell on its BCR.

Equations of motion reflect a combined influence of molecular interactions, pulling force, frictional damping forces and thermal fluctuations. In the the over-damped regime, Langevin equations read

\[
\begin{align*}
\gamma_a \dot{x} &= -\partial_x U(x, y) + \xi_1 = -U'_a(x) + U'_b(y - x) + \xi_a, \\
\gamma_b \dot{y} &= -\partial_y U(x, y) + \xi_2 = -U'_b(y - x) + F + \xi_b,
\end{align*} \tag{S2}
\]
FIG. S1. Two systems of reaction coordinates equivalently characterize the state of a BCR-Ag-APC complex: molecular displacements and bond extensions. (A) Without pulling force, antigen and BCR molecules are fluctuating about their equilibrium positions, \( x_0 \) and \( y_0 \), respectively. (B) A pulling force \( F \) stretches the complex and causes displacements from the mean positions of the antigen and BCR molecules (\( x \) and \( y \)), which in turn alter the bond extensions of the Ag-APC and BCR-Ag interactions (\( x_a \) and \( x_b \)). Dissociation of the complex occurs when either bond extension reaches its rupture length, i.e., \( x = x_a = x_a^\ddagger \) or \( y - x = x_b = x_b^\ddagger \). Note that forces act on the receptor and antigen molecules (nodes) rather than on the bonds (springs).

where \( U'_a(z) = dU_a(z)/dz \) and \( U'_b(z) = dU_b(z)/dz \) are elastic forces. \( \gamma_a \) and \( \gamma_b \) are frictional constants setting the relaxation timescales. \( \xi_a \) and \( \xi_b \) are random forces due to collision of the Ag and BCR molecules with the ambient fluid particles, described as Gaussian white noises with zero mean and the following second moments (\( k_B \) being the Boltzmann constant and \( T \) the ambient temperature)

\[
\langle \xi_a(t)\xi_a(t') \rangle = 2k_BT\gamma_a\delta(t-t'), \quad \langle \xi_b(t)\xi_b(t') \rangle = 2k_BT\gamma_b\delta(t-t'), \quad \langle \xi_a(t)\xi_b(t') \rangle = 0.
\]

To provide a macroscopic description, one can specify the time evolution of the probability \( P(x, y, t) \) of finding the system in state \((x, y)\) using the corresponding Fokker-Planck equation

\[
\frac{\partial P(x, y, t)}{\partial t} = \mathcal{L}_{FP} P(x, y, t),
\]

where the Fokker-Planck operator \( \mathcal{L}_{FP} \) is given by

\[
\mathcal{L}_{FP} = -\sum_{i \in \{x, y\}} \frac{\partial}{\partial i} K_i + \sum_{i \in \{x, y\}} \sum_{j \in \{x, y\}} \frac{\partial^2}{\partial i \partial j} D_{ij}.
\]

Here \( K_i \) and \( D_{ij} \) are the drift and diffusion terms respectively defined by

\[
K_i(x, y, t) = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \langle i(t + \epsilon) - i(t) \rangle,
\]

\[
D_{ij}(x, y, t) = \frac{1}{2} \lim_{\epsilon \to 0} \frac{1}{\epsilon} \langle (i(t + \epsilon) - i(t))(j(t + \epsilon) - j(t)) \rangle.
\]

Specifically we find

\[
K = \begin{pmatrix}
\frac{1}{\gamma_a} \partial_y U(x, y), & -\frac{1}{\gamma_a} \partial_x U(x, y) \\
-\frac{1}{\gamma_b} \partial_y U(x, y), & \frac{1}{\gamma_b} \partial_x U(x, y)
\end{pmatrix}, \quad D = k_B T \begin{pmatrix}
1/\gamma_a & 0 \\
0 & 1/\gamma_b
\end{pmatrix}.
\]

Here the diffusion matrix is diagonal, because fluctuations in molecular displacements are decoupled.

Bond extensions, \((x_a, x_b)\), are the natural coordinates for specifying interaction potentials and rupture conditions. Transforming to the \((x_a, x_b)\) coordinates using the relations \( x = x_a \) and \( y = x_a + x_b \), the coupled Langevin equations (Eq. S2) become

\[
\gamma_a \dot{x}_a = -U'_a(x_a) + U'_b(x_b) + \xi_a, \quad \gamma_b (\dot{x}_a + \dot{x}_b) = -U'_b(x_b) + F + \xi_b.
\]
That is, Eq. 1 in the main text is recovered. Note that these equations of motion reflect a balance of forces acting on the molecules (nodes) rather than on the bonds (springs); see Fig. S1.

The associated Fokker-Planck equation has modified drift and diffusion terms

$$\frac{\partial P(x_a, x_b, t)}{\partial t} = \left( - \sum_{i \in \{a,b\}} \frac{\partial}{\partial x_i} \tilde{K}_i + \sum_{i \in \{a,b\}} \sum_{j \in \{a,b\}} \frac{\partial^2}{\partial x_i \partial x_j} \tilde{D}_{ij} \right) P(x_a, x_b, t). \tag{S5}$$

Explicitly, the components of the drift vector can be found by

$$\tilde{K}_a = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \left( x_a(t + \epsilon) - x_a(t) \right) = \frac{1}{\gamma_a} \partial x_a U(x_a, x_b) - \frac{1}{\gamma_a} \partial x_a U(x_a, x_b),$$

$$\tilde{K}_b = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \left( x_b(t + \epsilon) - x_b(t) \right) = -\frac{1}{\gamma_a} \partial x_a U(x_a, x_b) + \left( \frac{1}{\gamma_a} + \frac{1}{\gamma_b} \right) \partial x_b U(x_a, x_b),$$

where we used $\langle \xi_1 \rangle = \langle \xi_2 \rangle = 0$. Similarly, the elements of the diffusion matrix read

$$\tilde{D}_{aa} = \frac{1}{2} \lim_{\epsilon \to 0} \frac{1}{\epsilon} \left( (x_a(t + \epsilon) - x_a(t))^2 \right) = \frac{1}{2\gamma_a^2} \langle \xi_1 \xi_1 \rangle = \frac{k_B T}{\gamma_a},$$

$$\tilde{D}_{ab} = \tilde{D}_{ba} = \frac{1}{2} \lim_{\epsilon \to 0} \frac{1}{\epsilon} \left( (x_a(t + \epsilon) - x_a(t))(x_b(t + \epsilon) - x_b(t)) \right) = \frac{1}{2} \left( -\frac{1}{\gamma_a^2} \langle \xi_1 \xi_1 \rangle + \frac{1}{\gamma_b} \langle \xi_1 \xi_2 \rangle \right) = -\frac{k_B T}{\gamma_a^2},$$

$$\tilde{D}_{bb} = \frac{1}{2} \lim_{\epsilon \to 0} \frac{1}{\epsilon} \left( (x_b(t + \epsilon) - x_b(t))^2 \right) = \frac{1}{2} \left( \frac{1}{\gamma_a} \langle \xi_1 \xi_1 \rangle + \frac{1}{\gamma_b^2} \langle \xi_2 \xi_2 \rangle - \frac{2}{\gamma_a \gamma_b} \langle \xi_1 \xi_2 \rangle \right) = \frac{k_B T}{\gamma_a} + \frac{k_B T}{\gamma_b}.$$

Now that forces acting on the antigen molecule and the resulting movement will influence both bond extensions, the diffusion matrix acquires off-diagonal terms

$$\tilde{D} = k_B T \begin{pmatrix} 1/\gamma_a & -1/\gamma_a \\ -1/\gamma_a & 1/\gamma_a + 1/\gamma_b \end{pmatrix}. \tag{S6}$$

Components of the drift vector are related to those of the diffusion matrix through $\tilde{K}_i = \sum_j \tilde{D}_{ij} \partial x_j (\beta U(x_a, x_b))$ for $i, j \in \{a, b\}; \beta = 1/(k_B T)$.

Starting from equilibrium molecular positions hence zero bond extensions, i.e., $P(x_a, x_b, t = 0) = \delta(x_a) \delta(x_b)$, the probability distribution broadens and drifts, gradually leaking through the absorbing boundaries at the rupture lengths ($x_a = x_a^1$ and $x_b = x_b^1$).

**B. Extraction probability $\eta$ under specific potential profiles**

The chance of antigen extraction is determined by the relative dissociation rate of the Ag-APC bond compared to that of the BCR-Ag bond. Mathematically, this can be quantified by the fraction of the total integrated probability current leaking through the relevant absorbing boundary (here, the Ag-APC bond exceeding its rupture length).

As shown above, two bond extensions are coupled by the motion of antigen, we thus need to describe stochastic exploration of a two-dimensional state space, yielding a first passage problem with interfering absorbing boundaries.

Bond rupture occurs through activated dynamics, i.e., thermally aided escape from the bound state over an activation barrier. When activation barriers are high and pulling forces moderate, the extraction probability takes a simple intuitive form – how likely the BCR-Ag bond survives at least until the time when the Ag-APC bond breaks:

$$\eta = \int_0^\infty dt p_a(t) \int_t^\infty dt' p_b(t'), \tag{S7}$$

where the bond lifetime distributions $p_a(t)$ and $p_b(t)$ of the tethering and tugging interactions factor out. These are the first passage time distributions conditioned on exiting through the relevant absorbing boundary (rupture of the Ag-APC bond for the former and of the BCR-Ag bond for the latter) with the other boundary being reflective.

High activation barriers yield Poissonian rupture kinetics and hence exponential lifetime distributions with mean lifetimes, $\tau_a$ and $\tau_b$, respectively. It thus follows that, under constant moderate pulling forces, the extraction probability depends simply on the ratio of mean lifetimes between the tethering and tugging bonds:

$$\eta = \int_0^\infty dt \left( \int_t^\infty dt' \frac{1}{\tau_a} e^{-t'/\tau_a} \right) \frac{1}{\tau_a} e^{-t/\tau_a} = \frac{1}{1 + \tau_a/\tau_b}. \tag{S8}$$
Therefore, under moderate pulling, the extraction analysis becomes a calculation of mean first passage times (MFPTs) in the 2D state space. Whereas under strong pulling such that activation barriers are no greater than thermal noise, we estimate η by performing Brownian dynamics simulations of many independent extraction attempts on bound complexes and determining the success rate. Both approaches are carried out on the basis of the Langevin equations.

Below we demonstrate the calculation of MFPT and η for a number of specific potential energy profiles. We start with the widely used Bell’s phenomenological model of bond dissociation under force, where the force-free lifetime is fitted from measurements rather than being derived from microscopic dynamics. We then apply Talkner’s method based on Gauss theorem and the WKB approximation to deal with potentials with abrupt changes (e.g. cusp-harmonic potential). Lastly, we employ Langer’s multi-dimensional generalization of Kramers theory to calculate MFPTs on a linear-cubic potential surface – a general, smooth potential profile broadly applicable to molecular unbinding and unfolding. We finally arrive at a unified expression of η valid for all these potentials.

1. Bell’s phenomenological model

According to Bell, the force-dependent bond lifetime is given by

\[ \tau = \tau_0 e^{-\beta F x^4}, \]  

(S9)

where \( \tau_0 \) is the force-free bond lifetime, which is often determined by fitting to experimental data, rather than deriving from microscopic dynamics subject to a model potential profile. Using this formula for the APC-Ag bond and the BCR-Ag bond, respectively, one can get

\[ \eta = \left[ 1 + \frac{\tau_0}{\tau_b} e^{\beta F (x^a - x^b)} \right]^{-1}. \]  

(S10)

This simple model already suggests that the effect of force on extraction depends upon the difference between the tugging and tethering bonds. In particular, force can promote or suppress extraction depending on whether the APC-Ag bond is softer or stiffer than the BCR-Ag bond (main Fig. 2A).

Note that the MFPTs \( \tau_a \) and \( \tau_b \) in Bell’s model are decoupled. That is the BCR-Ag lifetime does not depend on the properties of the APC-Ag bond, and vice versa. To account for antigen-mediated coupling effect, landscape models that respond nonlinearly to force are necessary.

2. Cusp-harmonic potential

Consider a 2D cusp-harmonic potential with a minimum at \( x = y = 0 \) and cusp-like activation barriers at rupture boundaries \( x = x^a_b \) or \( y = x = x^b_b \), tilted by a constant force of magnitude \( F \) coupled to the BCR displacement \( y \):

\[ U(x, y) = \begin{cases} \Delta G^a_a \left( \frac{x}{x^a_b} \right)^2 + \Delta G^b_b \left( \frac{y}{x^b_b} \right)^2 - F y, & x \leq x^a_b \text{ and } y - x \leq x^b_b, \\ -\infty, & \text{otherwise}. \end{cases} \]  

(S11)

This potential has been used to describe ligand-receptor interactions and protein unfolding but was limited to 1D.

According to Talkner, the MFPT to escape a \( n \)-dimensional spatial region \( \Omega \) through the boundary \( \partial \Omega \) can be expressed in terms of a stationary probability distribution \( w \) from solving the Fokker-Planck equation \( Lw = 0 \) and the probability flux passing through the relevant boundary. Define the relative MFPT \( f(x) = \tau(x)/\tau_i \) along the escape pathway, where \( \tau_i(x) \) is the MFPT starting from an arbitrary position \( x \) and \( \tau_i \) the MFPT starting from the attractor. From the Gauss theorem,

\[ \int_{\Omega} w dxdy = -\int_{\partial \Omega_i} ds_i \cdot w \sum_j D_{ij} \frac{\partial \tau(x)}{\partial x_j} = -\tau_i \int_{\partial \Omega_i} ds_i \cdot w \sum_j D_{ij} \frac{\partial f(x)}{\partial x_j}, \]

where \( ds_i \) is the oriented surface element at the boundary \( \partial \Omega_i \). In our context, \( \partial \Omega_a \) denotes the boundary \( x = x^a_b \) and \( \partial \Omega_b \) denotes the boundary \( y - x = x^b_b \). For the boundary \( x = x^a_b \), we have \( ds_a = dy \); for the boundary \( y - x = x^b_b \), one shall use a linear combination of coordinates \( s_b = x + y \), so that \( ds_b \) is along the boundary. \( D = k_B T \text{diag}(1/\gamma_a, 1/\gamma_b) \) is the diffusion matrix. Index \( j \) runs through all degrees of freedom. This expression relates the volume integral of the
stationary distribution to a surface integral of the probability flux (driven by local gradients of the scaled MFPT), yielding the MFPT starting from the attractor as a ratio between the two:

$$\tau_i = \frac{\int_{\Omega} w \, dx \, dy}{-\int_{\partial\Omega} ds_i \cdot w \sum_j D_j \frac{\partial f}{\partial x_j}}.$$  \hspace{1cm} (S12)

To evaluate the integrals, one can simplify the form of $w(x)$ and $f(x)$ using WKB approximations. For example, given a potential with a high barrier separating the attractor and the boundary, a trajectory starting within $\Omega$ will typically first approach the attractor and stay in its neighbourhood for a long time until an occasional fluctuation brings it to the boundary. Thus we can assume that $f(x) = 1$ for all $x \in \Omega$ except for a thin layer $\Delta\Omega_i$ along the boundary $\partial\Omega_i$. That is, $f$ obeys the following conditions

$$L^f \left( \begin{array}{c} f(x) = 0, \ x \in \Delta\Omega_i; \\ f(x) = 0, \ x \in \partial\Omega_i; \\ f(x) = 1, \ x \in \Omega - \Delta\Omega_i. \end{array} \right.$$

Here $L^f$ is the adjoint operator of the Fokker-Planck operator. One can solve for $f(x)$ by means of the ansatz. In what follows we use Eq. S12 to calculate the MFPT for a cusp-harmonic potential.

We want to find the stationary probability distribution, $w$, as well as the form factor as a function of the starting position, $f(x)$, from the Fokker-Planck equation and the adjoint equation, respectively. Explicitly, the Fokker-Planck operator and its adjoint are given by

$$L = -\frac{1}{\gamma_a} \frac{\partial}{\partial x} [\kappa_a x - \kappa_b (y - x)] - \frac{1}{\gamma_b} \frac{\partial}{\partial y} [F - \kappa_b (y - x)] + \frac{k_b T}{\gamma_a} \frac{\partial^2}{\partial x^2} + \frac{k_b T}{\gamma_b} \frac{\partial^2}{\partial y^2},$$

$$L^f = -\frac{\kappa_a x + \kappa_b (y - x)}{\gamma_a} \frac{\partial}{\partial x} - \frac{F - \kappa_b (y - x)}{\gamma_b} \frac{\partial}{\partial y} + \frac{k_b T}{\gamma_a} \frac{\partial^2}{\partial x^2} + \frac{k_b T}{\gamma_b} \frac{\partial^2}{\partial y^2},$$

where $\kappa_a = \partial^2 U_a(x)|_A = 2 \Delta G_a^2/(x_a^4)$ and $\kappa_b = \partial^2 U_b(x)|_A = 2 \Delta G_b^2/(x_b^4)$ are local curvatures at the attractor. This corresponds to a multivariate Ornstein-Uhlenbeck process, characteristic of noisy relaxation.

The Fokker-Planck equation has a stationary solution in the form of Boltzmann distribution

$$L w = 0 \Rightarrow w = ce^{-\beta U(x,y)} = ce^{-\beta(\tfrac{1}{2} \kappa_a x^2 + \tfrac{1}{2} \kappa_b (y-x)^2 - Fy)}.$$  \hspace{1cm} (S13)

Here $U(x,y)$ is given by Eq. S11 and $c$ is a constant. Due to the Gaussian form, we can easily evaluate the numerator of Eq. S12 as follows

$$\int_{\Omega} w \, dx \, dy \approx \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} ce^{-\beta(\tfrac{1}{2} \kappa_a x^2 + \tfrac{1}{2} \kappa_b (y-x)^2 - Fy)} \, dx \, dy = c \cdot \frac{2\pi}{\beta \kappa_a \kappa_b} e^{\beta F}.$$  \hspace{1cm} (S14)

Here we extend the integration limits to infinity by considering a localized distribution near the attractor which is valid for high potential barriers.

In addition, the scaled MFPT (form factor) $f(x)$ is determined by the adjoint equation

$$L^f f = 0 \quad \text{or} \quad -\frac{1}{\gamma_a} [\kappa_a x + \kappa_b (y - x)] \frac{\partial}{\partial x} f - \frac{1}{\gamma_b} [\kappa_b (y - x) - F] \frac{\partial}{\partial y} f + \frac{1}{\gamma_a} k_b T \frac{\partial^2}{\partial x^2} f + \frac{1}{\gamma_b} k_b T \frac{\partial^2}{\partial y^2} f = 0.$$  \hspace{1cm} (S15)

with boundary conditions $f(x,y) = 0$ for $(x,y) \in \partial\Omega_i$ and $f(x,y) = 1$ for $(x,y) \in \Omega - \Delta\Omega_i$, where $i \in \{a,b\}$. In general Eq. S15 is hard to solve, but since $f(x,y)$ changes significantly only in a thin layer close to the boundary, we can Taylor expand the coefficients to the leading order near the “saddle point” for a cusp-harmonic potential, a saddle point is the position along the boundary where the potential energy is minimum and escape events are mostly likely to occur). Meanwhile, since $f$ is constant along the boundary, it is convenient to rotate the coordinates such that one is along the boundary and the other is perpendicular to it.

At the boundary $x = x_a^i$ (already parallel to the y-axis), one can evaluate the coefficients of Eq. S15 at the “saddle point” $(x_{S_a}, y_{S_a}) = (x_a^i, x_a^i + F/\kappa_b)$ to find

$$\frac{\partial^2 f}{\partial x^2} = \beta (\kappa_a x_a^i - F) \frac{\partial f}{\partial x}$$

and solve the equation with the boundary condition $f(x,y) = 0$ at $x = x_a^i$ and $f(x,y) \approx 1$ for $x \ll x_a^i$ to obtain

$$f(x,y) \approx 1 - e^{-\beta (\kappa_a x_a^i - F)(x_a^i - x)}, \quad \partial_x f|_{S_a} \approx -\beta (\kappa_a x_a^i - F), \quad \partial_y f|_{S_a} = 0.$$  \hspace{1cm} (S16)
We can see that \( f \) increases from 0 to 1 as \( x \) deviates from \( x_a^\dagger \) and the rate of change depends on the slope of the potential \( U(x,y) \) at the boundary, \( \kappa_a x_a^\dagger - F \). Here \( \partial_x f = 0 \) is expected because \( f \) vanishes along the boundary \( x = x_a^\dagger \).

With the stationary probability distribution (Eq. S13), scaled MFPT distribution (Eq. S16) and diffusion matrix (Eq. S4), we can calculate the MFPT using Eq. S12. In the denominator, we integrate along the boundary \( x \)

\[
- \int_{-\infty}^{\infty} \left. w \frac{k_B T}{\gamma_a} \frac{\partial f}{\partial x} \right|_{S_a} dy = - \int_{-\infty}^{\infty} ce^{-\beta(\frac{1}{2}\kappa_a(x_a^\dagger)^2 + \frac{1}{2}\kappa_a(y-x_a^\dagger)^2 - F y)} \frac{k_B T}{\gamma_a} (-\beta(\kappa_a x_a^\dagger - F)) dy
\]

\[
= e^{\kappa_a x_a^\dagger - F} \sqrt{\frac{2\pi}{\beta \kappa_b}} e^{-\beta(\frac{1}{2}\kappa_a(x_a^\dagger)^2 - F x_a^\dagger - x_a^\dagger^2)}
\]

Combining with Eq. S14 leads to

\[
\tau_a = \gamma_a \sqrt{\frac{2\pi}{\beta \kappa_a}} e^{\beta(\frac{1}{2}\kappa_a(x_a^\dagger)^2 - F x_a^\dagger + x_a^\dagger^2)}
\]

\[
= \gamma_a \sqrt{2\pi \Delta G_a^\dagger} \Delta G_a^\dagger \left( 1 - \frac{F x_a^\dagger}{2\Delta G_a^\dagger} \right) e^{\beta \Delta G_a^\dagger \left( 1 - \frac{F x_a^\dagger}{2\Delta G_a^\dagger} \right)}.
\]

(S17)

Two points are noteworthy. First, the exponential factor \( \Delta G_a^\dagger \left( 1 - \frac{F x_a^\dagger}{2\Delta G_a^\dagger} \right)^2 = \Delta G_a^\dagger - F x_a^\dagger + \frac{F^2}{2\kappa_a} \) is the minimal potential energy difference between the attractor \((x_A, y_A) = (F/\kappa_a, F/\kappa_a + F/\kappa_b)\) and the boundary \( x = x_a^\dagger \), i.e., corresponding to the activation barrier height. Second, the mean lifetime of the APC-Ag bond is not influenced by the properties or dynamics of the BCR-Ag bond in the limit of high activation barriers.

For the boundary \( y = -x_b^\dagger \), one can transform to new coordinates \( x' = (x - y)/\sqrt{2} \) and \( y' = (x + y)/\sqrt{2} \) using the rotation matrix \( R = \begin{pmatrix} \cos(\pi/4) & -\sin(\pi/4) \\ \sin(\pi/4) & \cos(\pi/4) \end{pmatrix} \). In this new coordinate system, we have \( \partial_y f = 0 \) since \( y' \) is parallel to the boundary. \( \partial_{x'} f \) can be found by converting Eq. S15 to the \( x'-y' \) coordinate and evaluating the coefficients at the “saddle point” \((x'_{S_b}, y'_{S_b}) = (-x_b^\dagger/\sqrt{2}, x_b^\dagger/\sqrt{2})\). After transformation, Eq. S15 becomes

\[
\frac{\partial^2 f}{\partial (x')^2} = -\sqrt{2}\beta(\kappa_b x_b^\dagger - F) \frac{\partial f}{\partial x^\dagger}
\]

which yields

\[
f(x', y') = 1 - e^{-\sqrt{2}\beta(\kappa_b x_b^\dagger - F)} (x' + \frac{x_b^\dagger}{2}) \quad \partial_{x'} f|_{S_b} = \sqrt{2}\beta(\kappa_b x_b^\dagger - F), \quad \partial_y f|_{S_b} = 0.
\]

S18

As \( x' \) increases (i.e. away from the boundary), \( f \) increases from 0 to 1, as expected. The diffusion matrix transforms accordingly

\[
D' = RDR^{-1} = k_B T \begin{pmatrix} (\gamma_a - 1 + \gamma_b - 1)/2 & (\gamma_a - 1 - \gamma_b - 1)/2 \\ (\gamma_a - 1 - \gamma_b - 1)/2 & (\gamma_a - 1 + \gamma_b - 1)/2 \end{pmatrix}
\]

Now we can evaluate the denominator of Eq. S12 using Eqs. S13, S18 and S19

\[
- \int_{-\infty}^{\infty} w \frac{k_B T}{2} \left( \frac{1}{\gamma_a} + \frac{1}{\gamma_b} \right) \frac{\partial f}{\partial x} \bigg|_{S_b} dy = e^{\gamma_a + \gamma_b} (\kappa_b x_b^\dagger - F) \sqrt{\frac{2\pi}{\beta \kappa_a}} e^{-\beta(\frac{1}{2}\kappa_a(x_a^\dagger)^2 - F x_a^\dagger + x_a^\dagger^2)}
\]

Combining with Eq. S14, we obtain

\[
\tau_b = \frac{\gamma_a}{\gamma_a + \gamma_b} \gamma_b \sqrt{\frac{2\pi}{\beta \kappa_b}} e^{\beta(\frac{1}{2}\kappa_a(x_a^\dagger)^2 - F x_a^\dagger + x_a^\dagger^2)}
\]

\[
= \frac{\gamma_a}{\gamma_a + \gamma_b} \gamma_b \sqrt{\frac{2\pi}{\beta \Delta G_b^\dagger}} \Delta G_b^\dagger \left( 1 - \frac{F x_a^\dagger}{2\Delta G_b^\dagger} \right) e^{\beta \Delta G_b^\dagger \left( 1 - \frac{F x_a^\dagger}{2\Delta G_b^\dagger} \right)}.
\]

(S20)

Like in Eq. S17, the exponential factor is the potential energy difference between the attractor and the saddle point. The prefactor also takes a similar form, except for an effectively reduced damping constant \( \gamma_a \gamma_b / (\gamma_a + \gamma_b) \), which
suggests that mobility of the antigen molecule reduce the expected lifetime of the BCR-Ag bond. Stronger damping of antigen motion (larger $\gamma$) would lead to slower diffusion and longer bond lifetimes.

The expressions of MFPT (Eqs. S17 and S20) provide intuition for understanding bond lifetimes in a chain structure. First, the lifetimes have an exponential dependence on the minimal activation energy to escape from the attractor to the boundary. Second, the prefactor is the potential gradient perpendicular to the boundary $(\kappa_a x_a^\dagger - F - \kappa_b x_b^\dagger - F)$, which determines how fast a Brownian particle leaves the saddle point. Third, the BCR-Ag bond lifetime $\tau_\beta$ depends on the frictional coefficient of the antigen molecule, implying that coupling between bond extensions does play a role.

Therefore, according to Eq. S7, extraction probability assumes the following form for a cusp-harmonic potential

$$\eta = \left[ 1 + \frac{\gamma_a + \gamma_b}{\gamma_b} \sqrt{\frac{k_b f_b - F}{\kappa_a f_a - F}} e^{(\Delta G_a^P(1-F/f_a)^2 - \Delta G_b^P(1-F/f_b)^2)} \right]^{-1},$$

where $f_a = 2\Delta G_a^P/x_a^\dagger$, $f_b = 2\Delta G_b^P/x_b^\dagger$; $\kappa_a = 2\Delta G_a^P/(x_a^\dagger)^2$, $\kappa_b = 2\Delta G_b^P/(x_b^\dagger)^2$. We can see that extraction probability only depends on the relative properties of the tugging and tethering interactions, subject to differential modulation by pulling force.

#### 3. Linear-cubic potential

While the Talkner’s method is general enough to treat potential profiles involving discontinuous changes, as we have seen above, the calculation is often extensive due to the generality. For any smooth potential, such as the linear-cubic potential representing a broad class widely applicable to biomolecular dissociation, Langer’s multi-dimensional generalization of Kramers theory provides a succinct and intuitive alternative for calculation of the MFPT.

For a two-dimensional smooth potential surface $U(x,y)$, Langer’s formula of the MFPT conditioned on exiting through boundary $i$ ($i \in \{a,b\}$) reads

$$\tau_i = 2\pi \frac{p_A}{p_{S_i}} = 2\pi \tau_i^+ \left( \frac{\det H_{S_i}}{\det H_A} \right)^{1/2} e^{\beta(U_{S_i} - U_A)}$$

Here $H_A$ and $H_{S_i}$ are Hessian matrices of the potential $U(x,y)$ describing local curvatures at the attractor and the saddle point on boundary $i$, respectively. $\tau_i^+$ is the unique positive root of the secular equation $\det (\beta D H_{S_i} + I/\tau_i^+) = 0$, where $D = k_B T \text{diag}(1/\gamma_a, 1/\gamma_b)$ is the diffusion matrix in $x$-$y$ coordinate and $I$ is the identity matrix; $\beta = 1/k_B T$. So $1/\tau_i^+$ can be found as the eigenvalue of matrix $-\beta D H_{S_i}$, representing the deterministic growth rate of a small deviation from the saddle point $S_i$. Therefore, $\tau_i^+$ is the characteristic time of leaving the saddle point. The probability $P_{S_i}$ to find the system at the saddle point $S_i$ can be approximated by expanding the potential near the saddle point, $p_{S_i} \propto \exp(-\beta U_{S_i})/\sqrt{\det H_{S_i}}$. Similarly, the probability to find the system at the attractor is given by $p_A \propto \exp(-\beta U_A)/\sqrt{\det H_A}$. Langer’s formula states that the escape rate $1/\tau_i$ is the deterministic growth rate $1/\tau_i^+$ of a small deviation from the saddle point times the relative frequency of finding the system at the saddle point $S_i$ rather than the at the attractor $A^2$.

Applying Langer’s formula to compute MFPTs, we get

$$\eta = \left[ 1 + \frac{\tau_i^+}{\tau_b^\dagger} \sqrt{\frac{\det H_{S_i}}{\det H_{S_b}}} e^{\beta(U_{S_a} - U_{S_b})} \right]^{-1}.$$

Note that the chance of extraction only depends on local structures near the competing saddle points $S_a$ and $S_b$, which is valid in the high-barrier/weak-noise regime.

To illustrate the method, we compute Eq. S23 explicitly. Consider a linear-cubic potential at both binding interfaces:

$$U_a(z) = \frac{3}{2} \Delta G_a^P \left( \frac{z - x_a^\dagger/2}{x_a^\dagger} \right) - 2\Delta G_a^P \left( \frac{z - x_a^\dagger/2}{x_a^\dagger} \right)^3,$$

$$U_b(z) = \frac{3}{2} \Delta G_b^P \left( \frac{z - x_b^\dagger/2}{x_b^\dagger} \right) - 2\Delta G_b^P \left( \frac{z - x_b^\dagger/2}{x_b^\dagger} \right)^3,$$

where $z$ is the bond extension. This potential has a minimum at $z = 0$ and a barrier at the bond rupture length, $z = x_a^\dagger$ for $U_a(z)$ and $z = x_b^\dagger$ for $U_b(z)$. The combined energy function under a constant pulling force $F$ in the $x$-$y$ coordinate is given by

$$U(x,y) = U_a(x) + U_b(y - x) - F y.$$
To apply Eq. S22, we first calculate the activation barrier and curvature at the attractor $A$ and the saddle point $S_a$. We can locate the attractor and saddle point by taking $\partial_x U = \partial_y U = 0$, which yields

$$(x_A, y_A) = \left( \frac{x_a^+}{2}(1 - \sqrt{1 - F/f_a}), \frac{x_b^+}{2}(1 - \sqrt{1 - F/f_a}) \right).$$

$$(x_{S_a}, y_{S_a}) = \left( \frac{x_a^+}{2}(1 + \sqrt{1 - F/f_a}), \frac{x_b^+}{2}(1 + \sqrt{1 - F/f_a}) \right).$$

where $f_a = 3\Delta G_a^1/2x_a^+$, $f_b = 3\Delta G_b^1/2x_b^+$. Without force, we have $(x_A, y_A) = (0, 0)$ at which the bonds are of natural lengths and $(x_{S_a}, y_{S_a}) = (x_a^+, x_b^+)$ where the APC-Ag bond is stretched while the BCR-Ag bond is relaxed. Force can displace both the attractor and the saddle point, reducing their separation (see main Fig. 1D for an example). Thus the activation barrier at saddle point $S_a$ is given by

$$U_{S_a} - U_A = \Delta G_a^1\left(1 - \frac{2Fx_a^+}{3\Delta G_a^1}\right)^{3/2}.$$

The Hessian matrix at the attractor is found readily

$$H_A = \begin{pmatrix} \frac{\partial^2 U}{\partial x^2} & \frac{\partial^2 U}{\partial x \partial y} \\ \frac{\partial^2 U}{\partial y \partial x} & \frac{\partial^2 U}{\partial y^2} \end{pmatrix} = \begin{pmatrix} \kappa_a + \kappa_b & -\kappa_b \\ -\kappa_b & \kappa_b \end{pmatrix},$$

where $\kappa_a = \frac{\partial^2 U_a(z)}{\partial x^2}|_A = \frac{4f_a}{x_a^+}\sqrt{1 - F/f_a}$ and $\kappa_b = \frac{\partial^2 U_b(z)}{\partial x^2}|_A = \frac{4f_b}{x_b^+}\sqrt{1 - F/f_b}$ are local curvatures of $U_a(z)$ and $U_b(z)$ at the attractor, respectively. Note that force reduces the curvatures. Similarly,

$$H_{S_a} = \begin{pmatrix} -\kappa_a + \kappa_b & -\kappa_b \\ -\kappa_b & \kappa_b \end{pmatrix}.$$  

Thus, $\det H_A = |\det H_{S_a}| = \kappa_a \kappa_b$. This results from the symmetric form of the linear-cubic potential – the curvature at the potential well equals the curvature at the barrier. Solving $\det(\beta DH_{S_a} + I/\tau^+_a) = 0$ for the characteristic time of leaving the saddle point $S_a$ yields

$$\tau^+_a = \frac{\gamma_a}{2\kappa_a} \left\{ 1 + \frac{\gamma_b}{\gamma_a} \left( 1 - \frac{\kappa_a}{\kappa_b} \right) + \sqrt{\left[ 1 + \frac{\gamma_b}{\gamma_a} \left( 1 - \frac{\kappa_a}{\kappa_b} \right) \right]^2 - 4\frac{\gamma_b}{\gamma_a} \kappa_a \kappa_b} \right\}.$$  

This shows that the larger the damping coefficient or the smaller the potential curvature, the longer it takes to leave the saddle point. Then the MFPT exiting through the boundary $x = x_a^+$ is given by

$$\tau_a = 2\pi\tau^+_a e^{\beta \Delta G_a^1(1 - F/f_a)^{3/2}}.$$  

Following the same procedure, we find the MFPT exiting through the boundary $y = x$ to be

$$\tau_b = 2\pi\tau^+_b e^{\beta \Delta G_b^1(1 - F/f_b)^{3/2}}$$

where

$$\tau^+_b = \frac{\gamma_b}{2\kappa_b} \left\{ 1 - \frac{\kappa_b}{\kappa_a} \left( 1 + \frac{\gamma_a}{\gamma_b} \right) + \sqrt{\left[ 1 - \frac{\kappa_b}{\kappa_a} \left( 1 + \frac{\gamma_a}{\gamma_b} \right) \right]^2 + 4\frac{\kappa_b}{\kappa_a} \gamma_a \gamma_b} \right\}.$$  

These expressions reduce to 1D Kramers form in certain limits:

- First, if $\kappa_b \gg \kappa_a$ (i.e., BCR and Ag being firmly attached to each other), $\tau_a \to 2\pi(\gamma_a + \gamma_b) e^{\beta(U_{S_a} - U_A)}/\kappa_a$, recovering 1D Kramers form except for an enhanced damping constant $(\gamma_a + \gamma_b)$. Meanwhile, $\tau_b \to 2\pi\frac{\gamma_a}{\gamma_a + \gamma_b} e^{\beta(U_{S_b} - U_A)}/\kappa_b$, which takes a similar Kramers form but with a reduced frictional coefficient $\gamma_a \gamma_b/((\gamma_a + \gamma_b)$.

- Second, if $\kappa_a \gg \kappa_b$ (a stiff APC-Ag bond), we have $\tau_b \to 2\pi\gamma_b e^{\beta(U_{S_b} - U_A)}/\kappa_b$, exactly recovering the 1D Kramers formula. In addition, $\tau_a \to 2\pi\gamma_a e^{\beta(U_{S_a} - U_A)}/\kappa_a$. Two bonds are effectively decoupled.
The pre-factor has the following force dependence which allow for a unified form of extraction probability:

\[
\eta = \left[ 1 + \frac{\tau_a^+}{\tau_b^+} e^{\beta (\Delta G^\dagger_a (1-F/f_a)^{3/2} - \Delta G^\dagger_b (1-F/f_b)^{3/2})} \right]^{-1}.
\]

The pre-factor has the following force dependence:

\[
\frac{\tau_a^+}{\tau_b^+} \propto \sqrt{\frac{f_b - F}{f_a - F}}.
\]

4. A unified form of \( \eta(F) \)

In summary, bond lifetimes subject to different potential functions can be written in the same form:

\[
\tau_a(F) = \tau_{a0}(F)e^{\beta \Delta G^\dagger_a \left( 1 - \frac{vFx_a^1}{\Delta G^\dagger_a} \right)^{2/3}},
\]

\[
\tau_b(F) = \tau_{b0}(F)e^{\beta \Delta G^\dagger_b \left( 1 - \frac{vFx_b^1}{\Delta G^\dagger_b} \right)^{2/3}},
\]

which allow for a unified form of extraction probability:

\[
\eta(F) = \frac{\tau_b(F)}{\tau_a(F) + \tau_b(F)} = \left[ 1 + \frac{\tau_{a0}(F)}{\tau_{b0}(F)} \exp \left\{ \beta \Delta G^\dagger_a \left( 1 - \frac{vFx_a^1}{\Delta G^\dagger_a} \right)^{2/3} - \beta \Delta G^\dagger_b \left( 1 - \frac{vFx_b^1}{\Delta G^\dagger_b} \right)^{2/3} \right\} \right]^{-1}.
\]

Here \( v = 1/2 \) corresponds to the cusp-harmonic potential and \( v = 2/3 \) represents the linear-cubic potential. Setting \( v = 1 \) would recover Bell’s model.

When comparing the expressions for \( \eta \) for the cusp-harmonic (Eq. S21) and linear-cubic (Eq. S26) potentials, two features are worth pointing out:

- Force application alters the barrier height at two saddle points to different extents; such changes depend both on binding affinity and bond stiffness (rupture length);
- Pulling force modifies the local curvature (linear-cubic) or gradient (cusp-harmonic) of the potential near the saddle point and the dependence on force takes the form of \( \tau_{a0}(F)/\tau_{b0}(F) \propto [(f_b - F)/(f_a - F)]^{1/v - 1} \), where \( f_a = \Delta G^\dagger_b/(vx_a^1), f_b = \Delta G^\dagger_b/(vx_b^1) \).

Therefore, if two bonds are identical (\( x_a^1 = x_b^1 \) and \( \Delta G^\dagger_a = \Delta G^\dagger_b \)), force has no effect at all. Furthermore, if \( \Delta G^\dagger_a \neq \Delta G^\dagger_b \) but \( f_a \approx f_b \), the Arrhenius (exponential) factor dominates the force dependence.

It should be noted that the expressions derived above only apply when the activation barrier is high compared to thermal noise even under force.

C. Dynamic force

Now we consider antigen extraction under a ramping force. The external force can be described by the gradient of a harmonic potential:

\[
V_{\text{pull}}(x,t) = \frac{1}{2} k_f (x - vt)^2,
\]

where \( k_f \) is the spring constant of the force. The pulling force modifies the local curvature or gradient of the potential near the saddle point and the dependence on force takes the form of \( \tau_{a0}(F)/\tau_{b0}(F) \propto [(f_b - F)/(f_a - F)]^{1/v - 1} \), where \( f_a = \Delta G^\dagger_b/(vx_a^1), f_b = \Delta G^\dagger_b/(vx_b^1) \).

Therefore, if two bonds are identical (\( x_a^1 = x_b^1 \) and \( \Delta G^\dagger_a = \Delta G^\dagger_b \)), force has no effect at all. Furthermore, if \( \Delta G^\dagger_a \neq \Delta G^\dagger_b \) but \( f_a \approx f_b \), the Arrhenius (exponential) factor dominates the force dependence.

It should be noted that the expressions derived above only apply when the activation barrier is high compared to thermal noise even under force.
and subject to ramping forces as quasistatic. For a soft effective spring with $k_f \ll 2\Delta G_i / \Delta x_i^2$ ($i = a, b$), the combined potential surface can be approximated as follows

$$U(x, y; t) = U_a(x) + U_b(y - x) - F(t)y,$$  

(S30)

where $F(t) = k_f vt$ ramps up linearly with time.

1. Extraction probability $\tilde{\eta}(r)$

We define $S(t)$ to be the survival probability of a bond chain at time $t$. For a BCR-Ag-APC complex, it reads

$$S(t) = S_a(t)S_b(t).$$  

(S31)

Note that $S(0) = 1$. Under the adiabatic approximation, the survival probability follows a first-order rate equation

$$\dot{S}_a(t) = -\frac{1}{\tau_a(F(t))} S_a(t), \quad \dot{S}_b(t) = -\frac{1}{\tau_b(F(t))} S_b(t),$$  

(S32)

where $\tau_a(F)$ and $\tau_b(F)$ are mean bond lifetimes under force $F$. Direct integration leads to

$$S(t) = \exp\left\{-\int_0^t dt' \left[ \frac{1}{\tau_a(F(t'))} + \frac{1}{\tau_b(F(t'))} \right] \right\}.$$  

(S33)

The term in the square bracket can be recognized as the inverse mean lifetime of the BCR-Ag-APC complex under pulling force $F$:

$$\tau(F) = \frac{\tau_a(F)\tau_b(F)}{\tau_a(F) + \tau_b(F)}.$$  

(S34)

With the survival probability (Eq. S33), we can compute the statistical properties of rupture dynamics, such as the rupture time distribution $p(t) = -dS(t)/dt$ and the rupture force distribution $p(F) = -dS/dF = -\dot{S}(t)/\dot{F}(t)$. The extraction probability $\tilde{\eta}$ under dynamic force $F(t)$ can be written as

$$\tilde{\eta} = \int_0^\infty dt p_a(t)S_b(t) = \int_0^\infty dt \frac{1}{\tau_a(F(t))} S(t)$$  

(S35)

To make contact with constant-force extraction dynamics studied earlier, we change variable from $t$ to $F$ for a linear ramping force $F(t) = rt$ where $r$ is the loading rate. This allows for an expression of the constant-speed extraction probability $\tilde{\eta}(r)$ as an average of the constant-force extraction probability $\eta(F)$ over the rupture force distribution $p(F|r)$ at a given loading rate $r$:

$$\tilde{\eta}(r) = \int_0^\infty dF \frac{\tau(F)}{\tau_a(F)} \frac{1}{r\tau'(F')} \exp\left\{-\int_0^F dF' \frac{1}{r\tau'(F')} \right\} = \int_0^\infty dF \eta(F)p(F|r),$$  

(S36)

where the constant-force extraction probability and the rupture force distribution are respectively

$$\eta(F) = \frac{\tau(F)}{\tau_a(F)}, \quad p(F|r) = \frac{1}{r\tau'(F')} \exp\left\{-\int_0^F dF' \frac{1}{r\tau'(F')} \right\}.$$  

Mean rupture force can be computed according to

$$\langle F \rangle_r = \int_0^\infty dF p(F|r) F.$$  

(S37)
2. Collapse dynamic-force data onto constant-force theory

The main Fig. 2A shows that extraction probability measured at different loading rates collapse onto the theoretical extraction curve under constant force, $\eta(F)$, over a wide range of force magnitude. Below we specify the condition under which this data collapse can be expected.

If the rupture force distribution is sharply peaked with respect to the gradual variation of $\eta(F)$ with force (to be justified below), we can Taylor expand $\eta$ around the mean rupture force $\langle F \rangle_r$:

$$\eta(F) = \eta(\langle F \rangle_r) + \frac{d\eta}{dF} \bigg|_{\langle F \rangle_r} (F - \langle F \rangle_r) + \frac{1}{2} \frac{d^2\eta}{dF^2} \bigg|_{\langle F \rangle_r} (F - \langle F \rangle_r)^2 + o(F - \langle F \rangle_r)^3. \quad (S38)$$

Hence

$$\tilde{\eta}(r) = \int dF \eta(F)p(F|r) \approx \eta(\langle F \rangle_r) + \frac{1}{2} \frac{d^2\eta}{dF^2} \bigg|_{\langle F \rangle_r} \sigma_F^2 \quad (S39)$$

where $\sigma_F^2 = \int (F - \langle F \rangle_r)^2 p(F)dF$ is the variance of the rupture force distribution. Therefore, extraction chance under ramping forces can be estimated using constant-force theory under the mean rupture force, provided that the following condition is met:

$$\eta(\langle F \rangle_r) \gg \frac{1}{2} \frac{d^2\eta}{dF^2} \bigg|_{\langle F \rangle_r} \sigma_F^2 \quad (S40)$$

We make two simplifying assumptions to obtain some analytical intuition: (1) force is modest so that Bell’s model gives reasonably accurate estimates for $\tau(F)$ and $\eta(F)$; (2) the rupture force distribution is predominantly determined by the weaker one between the tugging and tethering bonds, characterized by affinity $\Delta G^\dagger$ and bond length $x^\dagger$. Then we have

$$\eta(\langle F \rangle_r) = \left[ 1 + \frac{\tau a_0}{\tau b_0} e^{F \Delta x/k_B T} \right]^{-1}$$

and

$$\sigma_F^2 = \frac{\pi^2}{6} \left( \frac{k_B T}{x^\dagger} \right)^2.$$

Plugging these into Eq. S40, we find

$$\frac{\pi^2}{12} (1 - \eta) \cdot |1 - 2\eta| \cdot \left( \frac{\Delta x}{x^\dagger} \right)^2 \ll 1,$$

which is guaranteed if

$$|\Delta x| \ll x^\dagger. \quad (S41)$$

If the affinities of the APC-Ag bond and the BCR-Ag bond are similar, i.e., $\Delta G^\dagger_a \approx \Delta G^\dagger_b$, then the bond with a larger rupture length would be weaker. In this case, the condition becomes $|\Delta x| \ll \max(x^\dagger_a, x^\dagger_b)$. This appears indeed satisfied with realistic parameters of the tug-of-war complex; the difference in rupture lengths is typically only a small fraction of the rupture length per se.

3. Reconstruct $\eta(F)$ from rupture force histograms

In order to reconstruct $\eta(F)$, one needs to obtain and transform the rupture force histogram of both the APC-Ag-BCR complex and the APC-Ag bond (main Eq. 9). Consider rupture force histograms containing $n$ bins of width $\Delta F$ that start at $F_0$ and end at $F_n = F_0 + n\Delta F$. Let $C_i$ and $C_{a,i}$ be the count in the $i$-th bin of the APC-Ag-BCR histogram and the APC-Ag histogram, respectively. After normalization, the height in the $i$-th bin is respectively given by $h_i = C_i/ntot\Delta F$ and $h_{a,i} = C_{a,i}/n_{a,tot}\Delta F$, with $ntot$ and $n_{a,tot}$ being the total counts.
Thus, \( \tau(F) = \int_F^\infty p(f|r)df/(p(F|r)r) \) is measured as

\[
\tau(F_0 + (k - 1/2)\Delta F) = \frac{(h_k/2 + \sum_{i=k+1}^n h_i)\Delta F}{h_k r}.
\]

(S42)

Similarly, \( \tau_a(F) = \int_F^\infty p_a(f|r)df/(p_a(F|r)r) \) becomes

\[
\tau_a(F_0 + (k - 1/2)\Delta F) = \frac{(h_{a,k}/2 + \sum_{i=k+1}^n h_{a,i})\Delta F}{h_{a,k} r}.
\]

(S43)

Here \( r \) is the loading rate and the index \( k \) runs from 1 to \( n \).

Combining these two, we can reconstruct \( \eta(F) = \tau(F)/\tau_a(F) \) as follows

\[
\eta(F_0 + (k - 1/2)\Delta F) = \frac{(h_r/2 + \sum_{i=k+1}^n h_i)h_{a,k}}{(h_{a,k}/2 + \sum_{i=k+1}^n h_{a,i})h_k}.
\]

(S44)

In main Fig. 3, we obtain the rupture force histograms over three decades of loading rates from Brownian dynamics simulations and use Eq. S44 to reconstruct the relationship between \( \eta \) and \( F \).

D. Multiple binding interfaces

So far we have focused on a coarse-grained model complex consisting of two binding interfaces, to elucidate the essence of extraction dynamics. In reality, a greater number of molecular linkages connected in series (e.g. complement fragments and feedback antibodies) are likely involved in tethering the antigen to the surface of the APC. Moreover, B cells may pinch membrane vesicles from the APC while extracting antigens and fragments, making the APC membrane yet another link in the chain.

Now we generalize our formula of \( \eta \) to a chain of molecules composed of \( n \) tether bonds linked in series opposing the BCR-Ag bond. This system thus explores a \((n+1)\)-dimensional potential surface, \( U(x_1,..,x_n,x_b) \), where the reaction coordinates are the bond extension at each of the binding interfaces. In this setting, the chance of antigen extraction is the probability that at least one tether bond breaks while the BCR-Ag bond remains intact, namely,

\[
\eta = P(t_b > \min_{i \in \{1,...,n\}} t_{ai}) = 1 - \int_0^\infty dt_b p_b(t) \prod_{i=1}^n \int_t^\infty dt' p_{ai}(t'),
\]

(S45)

where the \((n+1)\)-fold integral computes the probability that all tether bonds are longer-lived than the BCR-Ag bond.

In the high-barrier/weak-noise regime, bond lifetime distributions \( \{p_{ai}(t)\} \) are nearly exponential with mean lifetimes \( \{\tau_{ai}\} \). It thus follows

\[
\eta = 1 - \int_0^\infty dt \frac{1}{\tau_b} e^{-\frac{t}{\tau_b}} \prod_{i=1}^n \int_t^\infty dt' \frac{1}{\tau_{ai}} e^{-\frac{t'}{\tau_{ai}}} = \frac{1}{1 + \tilde{\tau}_a/\tau_b}
\]

(S46)

where

\[
\tilde{\tau}_a = \left( \sum_{i=1}^n \frac{1}{\tau_{ai}} \right)^{-1}.
\]

Intuitively, \( \tilde{\tau}_a \) represents the effective mean lifetime of the entire tether complex subject to mechanical stress due to the pulling force, being limited by the weakest bond in the chain. Note that, like in the case of three-body complexes, force can differentially modulate the lifetime of different bonds, especially that the extent of barrier reduction depends on binding affinity and bond stiffness. Hence, as force applies, it is possible that the weakest bond shifts from the one with the lowest affinity to one with low stiffness.

On the other hand, under very strong pulling forces (such that rupture barriers vanish), complex rupture becomes reflective of a finite speed of stress propagation through the complex; as a result, tether bonds closest to the antigen would matter most to extraction with a given BCR.
II. SIMULATE THE GC REACTION: SUBJECTING EXTRACTION DYNAMICS TO ADAPTIVE EVOLUTION

A. Overview and computational program

By coupling the physical theory of tug-of-war antigen extraction to a computational model of stochastic GC reaction, we subject extraction dynamics to adaptive evolution, exploring the impact of force on selection pressure and evolutionary outcomes.

In existing GC reaction models in the literature, feedback is rarely considered. But increasing evidence suggests that antibodies secreted by plasma cells outside the GC can re-enter in the form of immune complexes, which might influence the strength of antigen tether and quality of antibody response. Our computational program aims to illuminate the effect of antibody feedback by contrasting two scenarios:

1. Without antibody feedback (constant antigen tether): Tether strength is limited by molecular interactions that remain unchanged on the timescale of affinity maturation (e.g. binding between complement receptors and ligands). Thus, tether properties (affinity and rupture length) are kept fixed throughout the GC reaction.

2. With antibody feedback (renewable antigen tether): The association between antigen and feedback antibody constitutes the weakest bond in the chain and sets the tether strength. Thus, tether properties are updated in sync with the feedback antibody pool in each GC cycle.

1. GC reaction without antibody feedback

• Step 0: Initialization

Upon antigen recognition, B cells rapidly proliferate without competition for several days. This pre-GC growth stage does not involve mutation or selection\(^{10}\). Only after the AID enzyme becomes activated and triggers somatic mutation in antibody-encoding genes, cycles of GC reaction ensue; alternating mutation and selection lead to B cell competitive expansion based on antigen extraction. Hence, we begin the simulation with a sizable clonal population of B cells, as a result of the non-competitive expansion, which is now subject to GC reaction. A GC starts with \(N_0=1000\) naive B cells with affinity \(\Delta G^b = 14k_B T\) and bond length \(x^b_\tau = 2\text{nm}\). The tether properties are fixed at affinity \(\Delta G^a = 14k_B T\) and bond length \(x^a_\tau = 1.5\text{nm}\). Initialize the plasma cell pool with a low-affinity B cell with \(\Delta G^b = 14k_B T\) and \(x^b_\tau = 2\text{nm}\), identical to the naive cells.

• Step 1: Antigen extraction

To determine the level of antigen extraction for each B cell, we first compute extraction probability \(\eta_i\) using the analytical expression (if the activation barrier is above \(3k_B T\)) or Brownian dynamics simulations (if the activation barrier is below \(3k_B T\)). We then draw the number of extracted antigen, \(n_{Ag,i}\), from the Binomial distribution \(B(C_{AgA}, \eta_i)\), where \(i\) indexes cells; \(C_{Ag} = 100/\mu m^2\) is the surface density of the APC-Ag-BCR complexes and \(A = 1\mu m^2\) is the contact area, both of which are assumed to be affinity-independent.

• Step 2: Death

Cells that fail to acquire any antigen \((n_{Ag,i} = 0)\) are removed. The remaining cells then undergo apoptosis with a uniform probability \(p_a = 0.3\).

• Step 3: Differentiation/Recycle

Each surviving B cell has a chance of \(p_d = 0.05\) to differentiate into a plasma or memory cell and enter the cumulative plasma pool. Plasma cells accumulate until a capacity of \(N_{c,\text{plasma}} = 5000\) is reached. Once the plasma pool is full, a random existing member is removed every time a newly differentiated cell joins the pool. The remaining B cells enter the next cycle of GC reaction.

• Step 4: Birth

B cells proliferate based on the amount of antigen they acquire from the APC. The reproductive fitness assumes a sigmoidal dependence on the level of extraction:

\[
\lambda_i = \lambda_{\text{max}} \frac{n_{Ag,i}}{n_0 + n_{Ag,i}},
\]
where $\lambda_{\text{max}} = 8/GC$ cycle is the maximum proliferation rate and $n_0 = 0.5C_{\text{Ag}}A$ the extraction level at half maximum proliferation.

The number of offspring is then drawn from a Poisson distribution, depicting a stochastic process of affinity-dependent logistic growth

$$n_i \sim \text{Pois}(\lambda_i(1 - N/N_c))$$

(S48)

where $N_c = 2000$ denotes the carrying capacity that accounts for resource and space limitations.

**Step 5: Mutation**

During proliferation, each daughter B cell can mutate with a probability $p_m = 0.5$. The affinity effect of mutation, $\delta G$, is assumed to be Gaussian distributed with zero mean and width $\sigma_G$, that is,

$$\Delta G_b^i = \Delta G_b^i + \delta G,$$

(S49)

with $\delta G \sim \mathcal{N}(0, \sigma_G)$. Here $\sigma_G = 0.1k_BT$ sets the mutation step size. The mutation effect is assumed to be symmetric for simplicity.

**Step 6: Iteration**

Repeat steps 1-5 until (a) all B cells die or (b) the maximum duration of $t_{\text{max}} = 300$ GC cycle is reached.

2. **GC reaction with antibody feedback**

To incorporate antibody feedback, two update steps are added:

- Prior to antigen extraction, we update candidate feedback antibodies with the current plasma pool. To capture the competition between antibodies for antigen binding, we draw plasma cells with the top-$K$ rank in affinity to form the new pool of feedback antibodies.

- In the step of antigen extraction, for each B cell, we randomly draw one feedback antibody from the updated pool and assign the antibody affinity to the tether while keeping the tether bond length unchanged. We then calculate the extraction probability $\eta_i$ and obtain the extraction level $n_{\text{Ag},i}$.

### TABLE I. Simulation parameters

| Parameters | Physical meaning                       | Value  | Ref. |
|------------|----------------------------------------|--------|------|
| $N_0$      | Number of founder B cells              | 1000   | 11   |
| $N_c$      | Germinal center capacity               | 2000   |      |
| $C_{\text{Ag}}$ | BCR-Ag-APC complex density          | 100/µm² | 2    |
| $A$        | Contact area                           | 1µm²   |      |
| $n_0$      | extraction level at half maximum proliferation | 50    |      |
| $\lambda_0$ | Maximum proliferation rate            | 8/GC cycle | 12  |
| $K$        | Feedback antibody pool size            | 100    |      |
| $\sigma_G$ | mutation step size                     | $0.1k_BT$ | 13  |
| $p_d$      | Probability of differentiation         | 0.05   | 11   |
| $p_a$      | Probability of apoptosis               | 0.3    | 14   |
| $p_m$      | Probability of mutation                | 0.5    | 11,15|
| $x_a^a$    | APC-Ag bond length                     | 1.5nm  |      |
| $x_b^a$    | BCR-Ag bond length                     | 2nm    |      |
| $\Delta G_{b0}$ | Naive B cell affinity              | 14k_BT |      |
### B. Adaptation rate under antibody feedback

Given that antibody feedback can lead to steady adaptation, it is useful to understand what determines the rate of affinity adaptation and, in turn, how these determinants are modulated by force. We show below that the Price equation provides a natural means of understanding by relating adaptation rate to statistical characteristics of population dynamics. To simplify the notation, we use $G_b$ to abbreviate the BCR-Ag binding affinity $\Delta G_b^2$.

The Price equation describes how the mean trait evolves due to changes in the population frequency of distinct trait values\textsuperscript{16}. Specifically, it states that the change in the mean value $Q$ of a trait $q$ in a population from one generation to the next, $\Delta Q$, is determined by

$$\Delta Q = \frac{1}{\bar{\lambda}} \text{Cov}(\lambda,q),$$

(S50)

where $\bar{\lambda}$ is the mean fitness across the population and $\text{Cov}(\lambda, q) = \sum_i (\lambda_i - \bar{\lambda})(q_i - \bar{q})$ is the covariance between the fitness and the trait; here the index $i$ runs through all individuals and the overbar indicates population average.

In the context of GC reaction, the trait of interest is the BCR binding affinity $G_b$ and the fitness is the per cell replication rate $\lambda$. Thus, the mean affinity evolves from one generation to the next (i.e. discrete GC reaction cycles) according to

$$\langle G_b(t+1) - G_b(t) \rangle = \langle \frac{1}{\bar{\lambda}} \text{Cov}(\lambda, G_b) \rangle.$$

(S51)

Here the ensemble average, indicated with angular brackets, over independent realizations of the GC reaction is performed since birth, death and mutation are stochastic.

For moderately large populations, we can approximate the sum over individuals in the covariance with an integral over the affinity distribution $p(G_b)$ to obtain

$$\text{Cov}(\lambda, G_b) \approx \int (G_b - \overline{G}_b)(\lambda(G_b) - \overline{\lambda})p(G_b)dG_b = \int G_b\lambda(G_b)p(G_b)dG_b - \overline{\lambda} \cdot \overline{G}_b.$$

(S52)

Further, if B cell affinities are localized near the mean value (valid for relatively large populations) such that fitness $\lambda(G_b)$ varies mildly over the width of $p(G_b)$, we can Taylor expand $\lambda(G_b)$ around mean affinity $\overline{G}_b$ to the leading order in deviation:

$$\lambda(G_b) = \lambda(\overline{G}_b) + \frac{\partial\lambda}{\partial G_b} \bigg|_{\overline{G}_b} (G_b - \overline{G}_b) + o(G_b - \overline{G}_b)^2.$$

Thus,

$$\int dG_b p(G_b) G_b \lambda(G_b) \approx \overline{G}_b \cdot \lambda(\overline{G}_b) + \left( \overline{G}_b^2 - \overline{G}_b^2 \right) \cdot \frac{\partial\lambda}{\partial G_b} \bigg|_{\overline{G}_b} \cdot \overline{G}_b.$$

In the last step we used the approximation $\lambda(\overline{G}_b) \approx \overline{\lambda}$, which again holds for a moderately large population. Taken together, we get

$$\nu_G \equiv \langle G_b(t+1) - G_b(t) \rangle \approx \langle \text{Var}(G_b) \alpha(\overline{G}_b) \rangle$$

(S53)

where

$$\alpha(G_b) \equiv \frac{d \ln \lambda}{d G_b} = \frac{\eta_0}{\eta(\eta_0 + \eta)} \frac{d \eta}{d G_b} = \frac{\eta_0(1 - \eta)}{\eta_0 + \eta} \frac{d \ln \tau_b}{d G_b}$$

(S54)

represents discrimination stringency (i.e. sensitivity of fitness to affinity changes) and characterizes selection strength.

Eq. S53 indicates that the expected adaptation rate is determined by the affinity variance and discrimination sensitivity; the former reflects the potential to generate higher-affinity mutants, and the latter quantifies the ability to select high-affinity clones for expansion. Using the expression of $\lambda$ in terms of extraction probability $\eta$ combined with the dependence of $\eta$ on BCR and tether affinities, one can evaluate the force dependence of $\alpha$ and hence of $\nu_G$, with the mean and variance of affinity extracted from simulations.
TABLE II. In vivo adaptation speed. Mean adaptation rate \( v_G \) is calculated from the fold change in association constant \( K_a \) or, equivalently, dissociation constant \( K_d \), that relates to affinity \( \Delta G^\ddagger_a \) through \( \Delta G^\ddagger_a = k_B T \ln(c_0 K_a) = k_B T \ln(c_0/K_d) \), where \( c_0 = 1\text{mol/L} \). Two GC cycles per day is assumed. We highlighted the result from Tas et al. because they measured the dissociation constant for antibodies isolated from individual GCs, which our simulation setup mimicks most closely.

| Antigen            | Duration   | fold change in \( K_a \) [M\(^{-1}\)] | change in \( \Delta G^\ddagger_a \) [k\(T\)] | mean \( v_G \) [k\(T\)/GC cycle] | Ref.                      |
|--------------------|------------|----------------------------------------|-----------------------------------------------|---------------------------------|---------------------------|
| Dinitrophenyl      | 3 weeks    | 2 – 50                                 | 0.69 – 3.91                                  | 0.016 – 0.093                   | Eisen et al.\(^{14}\)    |
| Dinitrophenyl      | 6 weeks    | 20 – 250                               | 3.00 – 5.52                                  | 0.036 – 0.066                   | Eisen et al.\(^{17}\)    |
| complex Ag         | 8 days     | 4 – 12                                 | 1.39 – 2.48                                  | 0.087 – 0.155                   | Kuraoka et al.\(^{18}\)  |
| complex Ag         | 16 days    | 48 – 80                                | 3.87 – 4.38                                  | 0.121 – 0.137                   | Kuraoka et al.\(^{18}\)  |
| chicken gamma globulin | 15 days | 3.5 – 14.5                             | 1.25 – 2.67                                  | 0.042 – 0.089                   | Tas et al.\(^{19}\)      |

C. B cell population dynamics

Our simulation begins at the time when the initial non-competitive expansion of a B cell population has finished. Starting with a sizable B cell population (\( N_0 = 1000 \)), mutation and selection begin in the first GC cycle (\( t = 1 \)). During GC reaction, apoptosis is the default B-cell fate\(^{14}\). That is, B cells are programmed to die unless receiving survival signal soon enough. Consequently, cell death and population collapse would occur if antigen extraction level is too low for B cell activation (upon receipt of T cell help), which can happen if pulling force is too strong. This is the basis of our reasoning that pulling strength should be bounded from above to avoid population extinction. Under moderate forces, instead, a population would recover following the initial decline, as beneficial mutations enable increasingly more efficient antigen extraction and presentation to T helper cells. Indeed, GCs induced in mice lacking T helper cells (thus lacking survival signal) only last for 3 days before all B cells undergo apoptosis\(^{20}\). Moreover, similar initial population decline and GC collapse also occur in previous models of affinity maturation\(^{21,22}\).

Tracking the time course of individual GCs is experimentally challenging. In existing studies, different GCs were typically harvested from lymph nodes taken from different mice; as a result, only snapshots were available, which revealed heterogeneity of GC size and the possibility of population collapse\(^{23}\). New advances in longitudinal imaging with “implantable windows”, recently developed for long-term imaging of growing tissues such as tumors\(^{24}\), hold the promise for revealing the entire life course of single GCs. This would make possible a direct test of our model predictions regarding force dependence of population dynamics.

D. Feedback antibodies as renewable antigen tethers

It has been known for over 100 years that both passively administered and actively produced antibodies can regulate immune responses – a phenomenon called antibody-mediated feedback regulation\(^{25}\). Feedback regulation can be positive or negative, either enhancing or suppressing specific antibody response. Moreover, \( \textit{in vitro} \) and \( \textit{ex vivo} \), antigens complexed to antibodies (IgG) are captured and presented by APCs more efficiently than antigen alone\(^{26}\). This mechanism leads to enhanced antibody response \( \textit{in vivo} \)\(^{27}\). These observations support a role of antibody binding to antigen (formation of immune complexes) in enhancing antigen presentation and elicited antibody response.

Further, \( \textit{in vivo} \) observations in Refs.\(^{28-30}\) are compatible with antibodies serving as FDC-antigen tethers. In Ref.\(^{28}\), antibodies of low, intermediate, or high affinities were injected to mice several days following immunization. Mice receiving higher affinity antibodies exhibited increased B cell apoptosis and faster production of higher-affinity IgG. This is in line with our model prediction that stronger tethers lead to lower antigen extraction, increased cell death, and stronger selection pressure for increased affinity. Ref.\(^{29}\) further showed that higher-affinity antibodies compete better in presenting antigens on FDCs, supporting the scenario in which antibodies play the role of FDC-antigen tethers and that higher antibody affinity results in greater tether strength.

In fact, these observations do not distinguish antigen masking from antigen tethering; both can modulate B cell selection against multi-epitope antigens by binding to the cognate epitope. But, our model makes a distinguishing prediction in terms of force dependence of population size. Antigen masking corresponds to fixed antigen tethers, for which our model predicts a \textit{force-independent} population size (Fig. 6B). In contrast, antigen tethering by endogenous antibodies with increasingly higher affinity is predicted to exhibit a \textit{force-dependent} population size (Fig. 6E).

Therefore, although it is not yet definitive to what extent endogenous antibodies serve as antigen tethers, with higher-affinity antibodies continuously replacing lower-affinity ones, we believe that it may constitute a plausible and interesting feedback mechanism that might enable self-adaptive selection pressure for sustained affinity maturation.
We also hope the distinguishing model predictions can motivate and guide new experiments which more closely and directly examine the role of antigen tether in regulating B cell selection.

E. Correlated evolution of rupture length and barrier height

For some antigen, mutation-induced changes in rupture length $x^+_b$ and barrier height $\Delta G^+_b$ are correlated. As shown for fluorescein$^{31}$, these changes can be in proportion (with a proportionality constant $c$), that is,

$$\frac{\delta x^+_b}{x^+_b} = c \cdot \frac{\delta \Delta G^+_b}{\Delta G^+_b},$$

(S55)

where $\delta x^+_b$ and $\delta \Delta G^+_b$ denote changes in rupture length and barrier height, respectively, due to a mutation. It follows that

$$x^+_b = x^+_b(0) \left( \frac{\Delta G^+_b}{\Delta G^+_b(0)} \right)^c.$$  

(S56)

Here symbols with a subscript 0 represent trait values of the founder B cell, and those without a subscript 0 correspond to trait values of the mutant. According to Schwesinger et al.$^{31}$, fitting to a variety of anti-fluorescein antibody mutants gives $c \approx 0.3$. In comparison, a constant rupture length is recovered when $c = 0$, whereas $c = 0.5$ if evolution retains a constant effective spring constant $K_b \propto \Delta G^+_b/\left(x^+_b\right)^2$.

We therefore relax the assumption of a constant rupture length and account for the observed correlated changes in barrier height and rupture length. As to be shown below, our conclusions remain qualitatively unchanged, compared to main Fig. 4 (force-induced expansion of affinity-discrimination range) and Fig. 6 (force dependence of affinity ceiling and adaptation rate). In addition, the range of optimal force magnitude remains quantitatively similar ($F \sim 10–20$pN).

1. Discrimination range

To the leading order in $F$, the barrier gap (main Eq. 6) is given by

$$U_{S_b} - U_{S_a} \approx \Delta G^+_b - \Delta G^+_a - F \left[ x^+_b(0) \left( \frac{\Delta G^+_b}{\Delta G^+_b(0)} \right)^c - x^+_a \right].$$

(S57)

Thus, for stiff tethers ($x^+_b(0) > x^+_a$), stronger forces reduce the barrier gap and suppress antigen extraction. With $c > 0$, suppression is enhanced as affinity improves, resulting in stretching of the extraction curve (similar to main Fig. 4A) and expansion of the discrimination range (like in main Fig. 4B). Such force-induced range expansion is stronger at larger $c$ values. Yet, for moderate forces, the absolute effect is modest (Fig. S2).

2. Affinity ceiling and adaptation rate

We simulate affinity maturation with correlated changes in barrier height and rupture length ($c = 0.3$). For each mutation-induced change in $\Delta G^+_b$, a corresponding change in $x^+_b$ is made, such that Eq. S56 is satisfied. As a result, rupture length increases (Fig. S3B,F) as affinity improves over time (Fig. S3A,E), aiding in maintaining selection pressure for higher affinity. Compared to affinity evolution with a constant rupture length (Fig. 6):

- Fixed tethers (Fig. S3 upper row):
  - Stronger suppression of antigen extraction at a given force magnitude yields a slightly deeper population bottleneck (panel C, $F=30$pN, red curve) and lower GC survival (panel D, near zero survival at $F \sim 30$pN).

- Renewable tethers (Fig. S3 lower row):
  - Stronger inhibition of antigen extraction results in increasing selection pressure as affinity improves, hence the population decline over time, especially under strong forces (panel G). Meanwhile, GC survival starts to fall at lower forces (panel H, red symbols) and the peak in adaptation rate shifts to slightly smaller forces (panel H, black symbols).
FIG. S2. Force-induced expansion of discrimination range under correlated evolution of barrier height $\Delta G^\dagger_\text{b}$ and rupture length $x^\dagger_\text{b}$. During evolution, changes in $\Delta G^\dagger_\text{b}$ and $x^\dagger_\text{b}$ are in proportion, with a proportionality constant $c$, according to Eq. S56. The range of distinguishable affinities (orange region) expands with increasing force magnitude; stronger expansion occurs at larger values of $c$. $c = 0$ (dotted) corresponds to the case of a constant rupture length as assumed in the main text. $c = 0.3$ (dashed) corresponds to a fit to a variety of anti-fluorescein antibody mutants performed by Schwesinger et al.\textsuperscript{31}. $c = 0.5$ (solid) corresponds to constant elasticity. Same parameters as in main Fig. 4.

FIG. S3. Force dependence of affinity ceiling and adaptation rate under correlated mutational changes in $\Delta G^\dagger_\text{b}$ and $x^\dagger_\text{b}$ ($c = 0.3$). During evolution, each mutation-induced change in rupture length is in proportion to the corresponding change in barrier height. (A-D) For fixed tethers, as cells pull more strongly, the ceiling affinity increases while the population bottleneck gets deeper. Comparing panel D to main Fig. 6C, affinity ceiling is slightly higher and GC collapse begins at slightly weaker pulling forces. (E-H) For renewable tethers, adaptation rate still exhibits a non-monotonic dependence on force magnitude, similar to main Fig. 6F, though the peak shifts to slightly lower forces. In the mean time, population extinction occurs under weaker pulling compared to the case of a constant rupture length. Note that, under strong pulling, population size falls over time (panel G). This is because the inhibition effect of force ($\sim Fx^\dagger_\text{b}$) increases with increasing rupture length. Left to right: trajectories of mean affinity, mean rupture length, population size, and force-dependence of ceiling affinity (upper)/adaptation rate (lower) and GC survival rate. Same parameters as in main Fig. 6.
FIG. S4. Force regulates extraction probability through differential modulation of the APC-Ag and BCR-Ag bond lifetimes, supporting main Fig. 2. Since \( x_b^\dagger < x_a^\dagger \), pulling incurs a stronger reduction in BCR-Ag bond lifetime (blue) than in APC-Ag bond lifetime (red). As a result, \( \eta \) (black) decreases with increasing pulling strength. Symbols are obtained from Brownian dynamics simulations. Solid lines are analytical results from Eqs. S17 and S20 for lifetimes and Eq. S21 for \( \eta \). Dashed lines are based on Bell’s model. Note that the slope of the log lifetime versus force is a direct measure of how the distance between the bound state and the transition state changes with force. The landscape model agrees much better with simulations than Bell’s model does; the latter underestimates bond lifetimes and extraction chance already under very modest forces. Under strong forces, analytical results deviate from simulations due to vanishing activation barriers. Since lifetimes are MFPTs conditioned on exiting through the relevant absorbing boundary in a 2D free energy landscape, the interfering boundary is treated as reflective in the simulations. A cusp-harmonic potential is used for both binding interactions. \( \Delta G^\dagger_a = \Delta G^\dagger_b = 10k_B T \), \( x_a^\dagger = 1.5\text{nm}, x_b^\dagger = 2\text{nm} \).

FIG. S5. Contour map of predicted mean lifetime \( \tau \) of 3-body complexes over relevant ranges of pulling force \( F \) and BCR-antigen affinity \( \Delta G^\dagger_b \). As expected, pulling force necessary to rupture a complex within a given time span increases with BCR-Ag affinity and saturates as it exceeds the tether strength. Note that optimal pulling forces of \( F \sim 10\text{–}20\text{pN} \) are sufficient to rupture a complex within 10 s. \( \Delta G_a = 14k_B T \), \( x_a^\dagger = 1.5\text{nm}, x_b^\dagger = 2\text{nm}, \gamma_a = \gamma_b = 10^{-5}\text{Ns/m} \).
FIG. S6. Large pulling forces strongly tilt the potential landscape and bend extraction trajectories towards the BCR-Ag rupture boundary. Typical extraction trajectories (red for success, green for failure) under varying force magnitudes (columns) against stiff (upper row, $x^a_\text{‡} = 1.5\text{nm}$) and soft (lower row, $x^a_\text{‡} = 3\text{nm}$) Ag-APC bonds. Solid black lines are deterministic trajectories. Histograms show distributions of the exit location (i.e. extension of the remaining bond when the competing bond breaks), obtained from 1000 Brownian dynamics simulations. Percentages indicate the fraction of trajectories that exit through the corresponding boundary. Rupture times $t_r$ are given in the form of mean±stdev. Dashed lines mark the absorbing boundaries at the rupture lengths. $\Delta G^a_\text{‡} = \Delta G^b_\text{‡} = 10k_B T$, $x^b_\text{‡} = 2\text{nm}$. A linear-cubic potential is used for both bonds.

FIG. S7. Ramping force further expands the discrimination range by causing affinity-dependent rupture force, related to main Fig. 4. (A) Extraction curves under ramping forces at different loading rates $r$. Higher loading rates yield a greater shift and stretching of the response curve (left to right). Curves are based on Eq. S36 (solid for landscape model, dashed for Bell’s model). Light gray lines mark equal-spacing shifts as reference. (B) Mean rupture force increases with BCR affinity until reaching saturation (when rupture occurs primarily on the Ag-APC side); rupture force at saturation increases with the loading rate. Curves are based on Eq. S37 (solid for landscape model, dashed for Bell’s model). Symbols are results from Brownian dynamics simulations. A cusp-harmonic potential is used for both bonds. Using a linear-cubic potential gives similar results. $\Delta G^a_\text{‡} = 20k_B T$, $x^a_\text{‡} = 1.5\text{nm}$, $x^b_\text{‡} = 2\text{nm}$.
FIG. S8. Landscape deformation expands the range of distinguishable affinities and raises affinity ceiling. (A) Comparison of evolutionary outcomes between using Bell’s model and a microscopic landscape model to compute extraction probability – a key input to GC simulations. Red symbols are the final affinity (circle) and survival rate (square) of GC populations at varying force magnitudes based on a microscopic landscape model. Black symbols are based on the phenomenological Bell’s model. Parameters are the same as in main Fig. 5C. (B) A schematic explaining the differences in (A). As shown in main Fig. 4B, the accessible affinities (indicated with the shaded areas here) range from the minimum affinity able to avoid population extinction to the maximum affinity distinguishable through antigen extraction. Landscape deformation under pulling (captured by the landscape model but missed by the Bell’s) stretches the response curve, allowing population survival under stronger pulling for a given naive cell affinity (blue dashed line) and resulting in a higher affinity ceiling (red vs black circles in panel A).

FIG. S9. GC reaction based on Bell’s model under antibody feedback. Compared to the results using a landscape model (main Fig. 6D-F), qualitative features remain: Population-mean affinity improves steadily over time (A), population size stabilizes to a force-dependent level (B), the rate of affinity increase shows a non-monotonic dependence on force magnitude until pulling is too strong to allow population survival (C). Quantitative differences are observed: Since Bell’s model neglects the nonlinear stretching effect (due to landscape deformation), population survival is possible up to a smaller force magnitude (below 20 pN), the steady population size is lower for a given pulling strength, and the adaptation rate peaks at a lower force magnitude. Curves in panels A and B and black symbols in panel C are averaging over 100 GC simulations for each value of $F$. In panel C, the grey solid line is the prediction from the Price equation (Eq. 11 in the main text) and the red symbols are the fraction of surviving GC populations. Parameters are the same as in main Fig. 6D-F.
FIG. S10. Population-mean probability of antigen extraction during affinity maturation with fixed (A) and renewable (B) antigen tether. Thick curves show the average over 100 realizations and the shade indicates variation among runs. (A) When the antigen tether has constant properties, extraction chance rises and saturates to a force-independent level. (B) With feedback antibodies renewing the tethers, extraction chance stabilizes to a force-dependent steady level. Simulation parameters are provided in Table I. Linear-cubic potential and top-K feedback rule are used.
FIG. S11. Feedback efficiency and strength influence the timing and rate of steady adaptation, supporting main Fig. 5. (A) Effect of delay in feedback. The top panel shows time evolution of B cell affinity under different amounts of delay time $T_d$ (i.e. the starting time of antibody feedback), suggesting that steady adaptation be reached at a later time given a longer delay in antibody feedback. The bottom panel shows the average affinity of antibodies in the feedback pool, which starts increasing soon after $t = T_d$. Solid curves are an average over 100 GCs. Shade indicates variation among GCs. The vertical dashed lines mark $T_d$. (B) Effect of feedback pool size. Before the capacity $K$ is reached, all plasma cells can enter the feedback pool. Once the feedback pool reaches its capacity (a new candidate joins the pool at the expense of a random current member), tether affinity starts increasing at the same rate as B cell affinity, resulting in steady adaptation. A larger capacity yields a smaller feedback strength and hence a lower adaptation rate.
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