

Adaptive Mechanical Proofreading Toward Robust yet Tunable Humoral Immunity

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To reliably transmit information, cells exploit nonequilibrium drives to reduce errors. Kinetic proofreading is a classic mechanism that sharpens ligand discrimination by T lymphocytes, yet it remains unclear whether adaptive immunity relies on kinetic proofreading alone to achieve high fidelity. Here, we propose an alternative: an enhanced form of mechanical proofreading (MPR), in which adaptive force generation during dynamic cell-cell contact enables faithful selection of high-affinity B lymphocytes. Using a coarse-grained model validated by experiments, we show that adaptive MPR, characterized by mechanical feedback between force exertion and contact formation, supports robust discrimination of receptor quality regardless of ligand quantity. While MPR generally balances tradeoffs between speed and fidelity, a negative scaling of contact duration with ligand abundance reveals the presence of feedback. By modulating interactions among distinct ligands that share mechanical load at membrane contacts, adaptive MPR may help mitigate autoimmunity or enhance multivalent vaccines. Overall, this work generalizes proofreading to include cellular designs that operate across scales to reconcile competing functional demands at the systems level.

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I. INTRODUCTION

One basic characteristic of life is the ability to operate with extraordinary fidelity. Key processes responsible for propagating inheritable information inside living cells—protein translation, RNA transcription, and DNA replication—are known to have far lower error rates than expected at thermal equilibrium. It is thus believed that cells utilize nonequilibrium drives to detect and correct errors through a kinetic proofreading mechanism [1–4]. This dissipative mechanism reduces errors by amplifying the effect of binding energy differences between competing molecular substrates, via a cascade of enzymatic reactions (proofreading steps) that slow the progress toward the product. Thus, speed is traded for accuracy.

Vital to organismal survival, natural immunity demands efficiency no less than fidelity—to contain self-amplifying threats (invasive agents or cancerous cells). Although the ability of T lymphocytes to exquisitely discriminate self from nonself peptides is considered a classic example of kinetic proofreading (KPR) [5], it is unclear if the adaptive immune system relies solely on KPR for fidelity-enhancing purposes.

Here, we suggest an alternative possibility: humoral immunity—constantly renewed through clonal diversification and selection—can employ an enhanced form of mechanical proofreading (MPR) at the cellular scale to enable efficient and faithful selection of high-affinity B lymphocytes at the

organismic level, yielding robust yet tunable responses that are not directly selected for. In contrast to KPR in which the proofreading steps are downstream of receptor binding inside the cell, MPR takes effect through the dynamic junction formed between mutually engaged cells—intracellular forces organize interfacial patterns of force-sensitive receptor-ligand species and modulate information transfer by deforming opposing membranes and molecular complexes.

Using a minimal construction of force schemes that distills the distinctive feature of MPR, we contrast schemes that differ in their ability to adapt to the system state. We find that, when force can sense and adapt to the contact pattern organized under force, such mechanical feedback leads to reduced contact duration with increasing ligand abundance, opposite to when force turns on after a predetermined delay. This feedback allows for robust discrimination of receptor quality against variations in ligand concentration. The same feedback causes ligand antagonism, a phenomenon by which nonagonists alter immune responses to co-presented agonists. Hence, despite being similar to allostery-based proofreading [6] by causing conformational changes in molecular complexes, adaptive MPR is a many-body mechanism in which the manner of force exertion may alter the relationship between molecular species that share load at membrane interfaces. This mechanism has intriguing implications for mitigating autoimmunity and enhancing the efficacy of multivalent vaccines.

We propose that adaptive mechanical proofreading at cell-cell contact can enhance the fidelity of clonal selection while satisfying competing functional demands, and that this mechanism extends beyond adaptive immunity. Our results point to a generalized proofreading paradigm in which cellular processes operating under dynamic feedback produce robust yet tunable responses at the systems level, suggesting an evolutionary origin of proofreading across biological scales.

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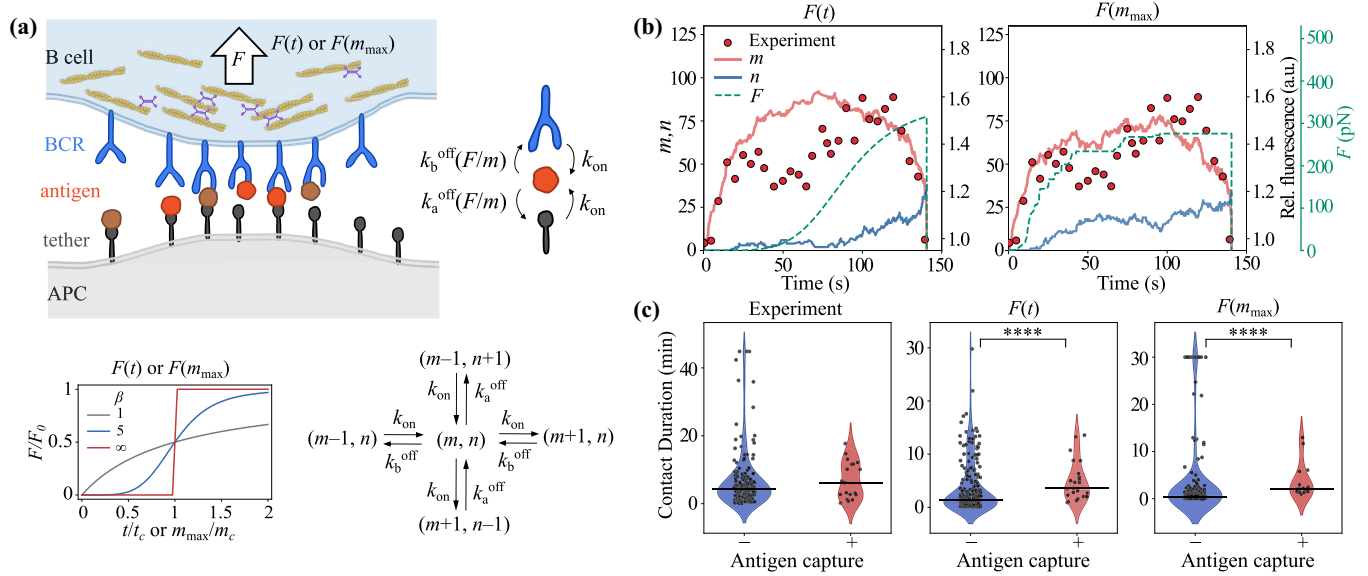


FIG. 1. B cells apply dynamic forces to control antigen extraction: model validation with independent experiments. (a) B cell uses its BCRs to bind antigens tethered to an APC, forming localized clusters of BCR-Ag-tether complexes. The contractile cytoskeleton exerts dynamic pulling forces on individual clusters and drives antigen extraction. Force influences the system state by altering the off-rates k_a^{off} and k_b^{off} of the complexes that share load. An inert force $F(t)$ turns on with a preset delay t_c , whereas an adaptive force $F(m_{\max})$ compares the maximum cluster size reached, $m_{\max}$, to the onset threshold m_c . The system state, specified by the instantaneous cluster size m and the number of BCR-bound antigens n , evolves via stochastic binding/unbinding on either side of the molecular tug-of-war; see Eq. (1). (b), (c) Model captures the observed extraction dynamics. (b) Simulated trajectories of (m, n) and applied force F for each scheme. Cluster size in both schemes (red lines) matches the experimental trend of antigen fluorescence [7] (red symbols). (c) Distributions of contact duration for low/high extraction B cells (“-”/“+”) in both schemes (right two panels) match experimental data [8] (left panel). High-extraction B cells show a larger median (higher black bar), whereas lower-extraction B cells are skewed toward brief contacts with a tail toward long durations. The difference in distributions between the two groups is statistically significant (two-sided Mann–Whitney U test, $p < 0.0001$). Parameters: $L_0 = 100$, $k_{\text{on}} = 0.05 \text{ s}^{-1}$, $E_a = 12.6 k_B T$, $E_b = 13.3 k_B T$, $x_a = 1.5 \text{ nm}$, $x_b = 2 \text{ nm}$, $\beta = 5$; (b) $F_0 = 350 \text{ pN}$, $t_c = 1.5 \text{ min}$, $m_c = 60$; (c) middle: $F_0 / \text{pN} \sim \mathcal{U}(250, 900)$, $t_c / \text{min} \sim \text{LogUniform}(0.1, 15)$; right: $F_0 / \text{pN} \sim \mathcal{U}(300, 900)$, $m_c \sim \mathcal{U}(20, 80)$.

II. MODEL

Within the transient microenvironment called germinal centers (GCs), B lymphocytes improve their antigen recognition capability through a rapid Darwinian process known as affinity maturation [9–11]. In a cyclic fashion, GC B cells diversify their receptor encoding genes during replication via somatic hypermutation and compete for limited survival signals provided by T helper cells. Ideally, B cells expressing higher affinity receptors (BCRs) compete better and expand preferentially.

The key step that translates the affinity excess of a B-cell clone to its competitive advantage is a vigorous physical process of antigen extraction [7,8,12,13]: through a dynamically organized intercellular junction (immunological synapse), a B cell actively acquires antigens from an antigen presenting cell (APC) using cytoskeletal forces and presents the acquired antigens in a processed form on its surface. T helper cells then discern BCR affinity according to the surface density of presented antigens [14,15]. Consequently, antigen extraction dynamics—tunable through force exertion—control, and potentially limit, the fidelity of clonal selection.

Upon binding of a BCR to an antigen (Ag) tethered to the surface of an APC, a BCR-Ag-tether three-body complex forms. Productive binding deforms the B-cell membrane and drives clustering of BCRs, initiating a series of BCR-Ag interactions. These interactions in turn trigger cytoskeletal

remodeling inside the B cell and generation of contractile forces needed to pull Ags away from the APC. Successful Ag extraction occurs when the BCR-Ag bond withstands the forces longer than the Ag-tether bond within a three-body complex. Once all complexes in a cluster are disrupted, the B cell locally detaches from the APC, concluding one extraction attempt.

Previous models [16–18] assume pre-formed clusters subject to constant loads, only depicting the rupture stage. Here, we describe the entire process of an extraction attempt—from initial binding and subsequent cluster growth to complete dissociation—under the influence of dynamic forces throughout, as demonstrated in experiments combining live-cell imaging and sensitive force measurements [19,20]. This allows us to explore the functional role of mechanical feedback through which force not only alters the system state but can adjust to the altered state. Such feedback was shown [21] to be able to stabilize a multifocal synaptic pattern comprising segregated BCR-Ag clusters, characteristic of GC B cells undergoing affinity maturation [19]. We thus focus on antigen extraction via one localized cluster [Fig. 1(a)].

A. Antigen extraction dynamics

Assume that a limited amount L_0 of antigens is available along with a large abundance of BCRs; both are uniformly

distributed without spatial specificity. Changes in the quantities of the BCR-Ag-tether complexes (m), BCR-Ag complexes (n), and Ag-tether complexes ($L_0 - m - n$) resemble the turnover of chemical species due to stochastic reactions (here, binding/unbinding events). At each moment, the pair (m, n) fully specifies the state of the system, where m represents the cluster size and n the number of BCR-bound Ags; the value of n at final dissociation corresponds to the amount of extracted antigen, n_{Ag} . The probability of occupying the state (m, n) evolves according to a set of one-step master equations:

$$\begin{aligned} \frac{dP(m, n; t)}{dt} = & [(\xi^{1,-1} - 1)mk_a + (\xi^{1,0} - 1)mk_b \\ & + (\xi^{-1,1} - 1)nk_{\text{on}} + (\xi^{-1,0} - 1)(L_0 - m - n)k_{\text{on}}]P(m, n; t). \end{aligned} \quad (1)$$

Here $\xi^{i,j}$ is the step operator defined through $\xi^{i,j}G(m, n) = G(m + i, n + j)$ for any function $G(m, n)$. Note that $0 \leq m + n \leq L_0$. The first two terms on the right hand side of Eq. (1) represent breaking of the three-body complex at the Ag-tether interface and the BCR-Ag interface, respectively. The latter two terms correspond to the reverse association processes. Sample trajectories of (m, n) are shown in Fig. 1(b) (red and blue lines).

Ag acquisition assumes a tug-of-war architecture [17], in which kinetics of competitive bond rupture between the tethering (Ag-tether) and tugging (BCR-Ag) interactions govern the likelihood and speed of antigen extraction [16]. We assume that two binding interfaces share the same constant on-rate k_{on} but have different off-rates [Fig. 1(a)]. These off-rates depend on affinity and vary with the applied force according to Bell's phenomenological model [22]:

$$\begin{aligned} k_a^{\text{off}}(m) &= k_0 e^{-(E_a - \frac{F x_a}{m})/k_B T}, \\ k_b^{\text{off}}(m) &= k_0 e^{-(E_b - \frac{F x_b}{m})/k_B T}. \end{aligned} \quad (2)$$

Here F is the total force exerted on the cluster that we set to be dynamic (see below). The evenly distributed force per bond F/m is key to extraction dynamics. E_a and E_b are binding free energies of the Ag-tether and BCR-Ag interactions, while x_a and x_b are the corresponding bond lengths, each indicating the distance between the potential minimum and the energy barrier to bond rupture along the reaction coordinate. k_0 is the basal rate of dissociation, aggregating the effect of additional factors that are not explicitly modeled, including membrane fluctuations and hydrodynamics.

B. Dynamic force schemes

Cytoskeletal forces may sense and adjust to cluster size (though size-dependent assembly of the pulling machinery) or turn on after a predetermined delay (via a reaction cascade propagating receptor signals). A minimal construction of force schemes that encodes the essence of inert and adaptive MPR is given by

$$F(t) = F_0 \frac{t^\beta}{t^\beta + t_c^\beta}, \quad F(m_{\text{max}}) = F_0 \frac{m_{\text{max}}^\beta}{m_{\text{max}}^\beta + m_c^\beta}. \quad (3)$$

Both schemes are three-parameter families with tunable magnitude (F_0), nonlinearity (β), and onset threshold (t_c or m_c).

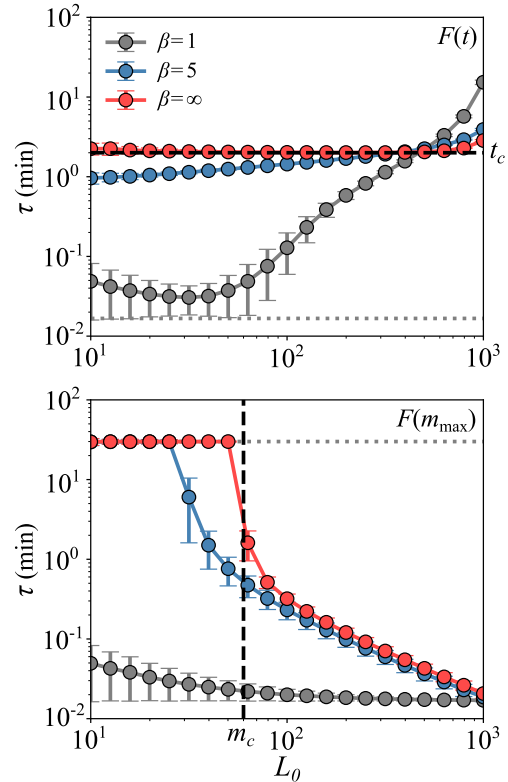


FIG. 2. Inert and adaptive forces produce opposite scaling of contact duration with antigen quantity. At each antigen quantity L_0 , contact duration τ (i.e., cluster lifetime) is averaged over 1000 independent runs. τ is limited to a realistic range $[t_{\text{min}}, t_{\text{max}}]$ as indicated by the dotted lines. Under $F(t)$, contact typically prolongs as the amount of presented antigens increases. Under $F(m_{\text{max}})$, contact duration decreases with increasing antigen abundance. $k_{\text{on}} = 0.05 \text{ s}^{-1}$, $E_a = 12.6 k_B T$, $E_b = 15 k_B T$, $F_0 = 4000 \text{ pN}$, $t_c = 2 \text{ min}$, $m_c = 60$, $t_{\text{min}} = 1 \text{ s}$, $t_{\text{max}} = 30 \text{ min}$.

The onset threshold m_c specifies the typical BCR-antigen cluster size required to initiate the extraction force, whereas t_c represents the time lag between receptor signaling and actomyosin assembly. The nonlinearity parameter β captures cooperativity in myosin motor recruitment and activation, as well as in BCR clustering. In principle, m_c and t_c can be inferred from joint live-cell imaging and sensitive force measurements that resolve the timing and cluster size at force onset. β can be estimated from the measured scaling of contact duration with antigen abundance (Fig. 2), as discussed below.

The major difference between two schemes is whether the extraction force adapts to system state: inert force $F(t)$ rises to the half-maximum magnitude after a fixed lag t_c , whereas adaptive force $F(m_{\text{max}})$ adjusts to the maximum cluster size $m_{\text{max}}(t) = \max_{t' \leq t} [m(t')]$ ever reached until a given time t . This choice reflects the ratchetlike nature of the contractility apparatus [23,24], such that force scales with the maximum cluster size so far accessed and is insensitive to instantaneous fluctuations. By exploring the parameter space of both force schemes, we will identify the dynamic regimes accessible to the extraction system and determine key functional consequences of adaptive force application.

III. RESULTS

Immune cells appear to be able to fulfill seemingly incompatible functional demands: rapid antigen detection, high-fidelity affinity discrimination, and robustness to variations in antigen abundance. We show that adaptively controlled tugging forces can provide a common physical solution to these competing objectives. Our model thus offers a window into how B cells selectively expand high-quality clones while balancing speed, robustness, and flexibility.

A. Model captures observed extraction dynamics

Significant experimental progress over the past decades has characterized B-cell–APC interactions and visualized subsequent antigen extraction and internalization [7,8,12,19,25–27]. In their seminal work, Batista and Neuberger proposed that B cells extract antigens by exerting mechanical forces [12,25]. More recently, direct evidence has shown that B cells physically pull on BCR-antigen-tether complexes at synaptic contacts, leading to affinity-dependent acquisition of BCR-Ag microclusters [7,19,28].

Our model largely recapitulates the observed extraction dynamics (see Supplemental Material (SM) [29] for simulation details). As shown in Fig. 1(b), the simulated trajectory of cluster size (red line) closely matches the temporal data of antigen fluorescence (red dot) [7] both in the initial stage of steady cluster growth and at the final stage toward complete dissociation—when force becomes strong enough to trigger a cascade of bond rupture. This cascade reflects load-sharing among three-body complexes: as more bonds break, the remaining complexes bear a larger force per bond, hence an accelerated dissociation. Note that despite distinct force trajectories (green dashed lines), both schemes capture the essential characteristics of cluster formation and dissociation. Dynamics at intermediate times are more complex, with nonmonotonic variations in cluster size that may arise from dynamic competition between in-plane contractile forces and out-of-plane pulling forces exerted by the cytoskeleton, which may alternately dominate during synapse formation. Capturing this behavior would require explicit coupling among membrane deformations, receptor binding kinetics, and cytoskeletal force generation in both lateral and normal directions, as explored in more detailed mechanistic models (e.g., Ref. [30]).

An independent validation can be obtained from the conditional distribution of contact duration. To seek correlations between contact duration and antigen capture among B cells, Suzuki *et al.* [8] sorted the measured duration based on whether or not a detectable amount of Ag was acquired [Fig. 1(c), each symbol being a B cell]. Both force schemes reproduce the key features of each group: The negative group is strongly skewed toward short durations below 2 min, while having a long tail that extends beyond 30 min. In contrast, the positive group shows a narrower range with a higher median (black bar). The limited range in the positive group reflects that productive Ag extraction imposes constraints on F_0 , such that it is neither too high to allow cluster growth nor too low to trigger dissociation. Importantly, capturing the broad distributions of contact duration observed experimen-

tally requires substantial cell-to-cell heterogeneity in force parameters (Figs. S1(A)–S1(D) [29]): the long tail arises from small force magnitudes and large onset thresholds, whereas brief contacts correspond to the opposite regime. In contrast, with homogeneous force parameters, contact durations in the model tightly cluster around the median, especially under $F(t)$ (Fig. S1(E) [29]).

The speed of cluster extraction is crucially dependent on the timing at which the rupture cascade is triggered. It is thus useful to ask whether a tipping point underlies this loss of stability, or it is merely a result of stochasticity in binding/unbinding kinetics. A bifurcation analysis of the deterministic dynamics indicates that, as the total force F increases, two steady states, m_s^{low} and m_s^{high} , get closer and eventually merge and annihilate at a tipping point (F^*, m^*) , beyond which cluster size vanishes (Fig. S2 [29]). The critical value F^* is determined by the weaker side of the tug of war [29]. Since m_s^{high} is stable whereas m_s^{low} is not, if the cluster and force develop gradually, then the system would approach m_s^{high} and fluctuate around it until force exceeds F^* triggering dissociation. If, instead, m falls below m_s^{low} early on, then the rapid increase in force per bond would cause the cluster to dissolve immediately. This bifurcation underlies the constraints on F_0 described above.

Then, what measurement can distinguish the underlying force scheme? Interestingly, our model predicts that the scaling relationship between the mean contact duration τ and ligand quantity L_0 can tell apart inert and adaptive forces (Fig. 2). Under $F(t)$, a larger abundance of ligand leads to a longer contact, whereas under $F(m_{\text{max}})$, the extraction proceeds faster as the amount of ligand increases—a desirable feature for timely containment of insults. Moreover, the nonlinearity β of force onset influences the sensitivity of τ to changes in L_0 depending on the force scheme; stronger nonlinearity increases the sensitivity under $F(m_{\text{max}})$ but decreases the sensitivity under $F(t)$. These differences reflect distinct conditions to be met to dissociate the cluster (see SM [29] for details). Under $F(t)$, the contact duration is set by the time taken to reach the bifurcation point. That is, $F(\tau) = F^* \propto L_0$, leading to

$$\tau \sim L_0^{1/\beta}. \quad (4)$$

Under $F(m_{\text{max}})$, for a step force ($\beta = \infty$), the contact lasts until the cluster grows to the critical size that triggers force, i.e., $m(\tau) = m_c$, resulting in

$$\tau \sim L_0^{-1}. \quad (5)$$

These predictions agree well with simulations (Fig. 2) and could be tested by measuring the antigen-dose dependence of the mean duration of contact. Such an experiment will inform the dynamic characteristics of force that B cells employ to probe their receptor quality.

B. Optimal force scheme for faithful clonal selection

Efficient selection of high-affinity B-cell clones relies on a faithful mapping from an excess in BCR affinity to a competitive advantage in acquiring limited T-cell help [31]. T-help acquisition is determined by the amount of antigen presented on the B-cell surface [14,15] and, in turn, by the

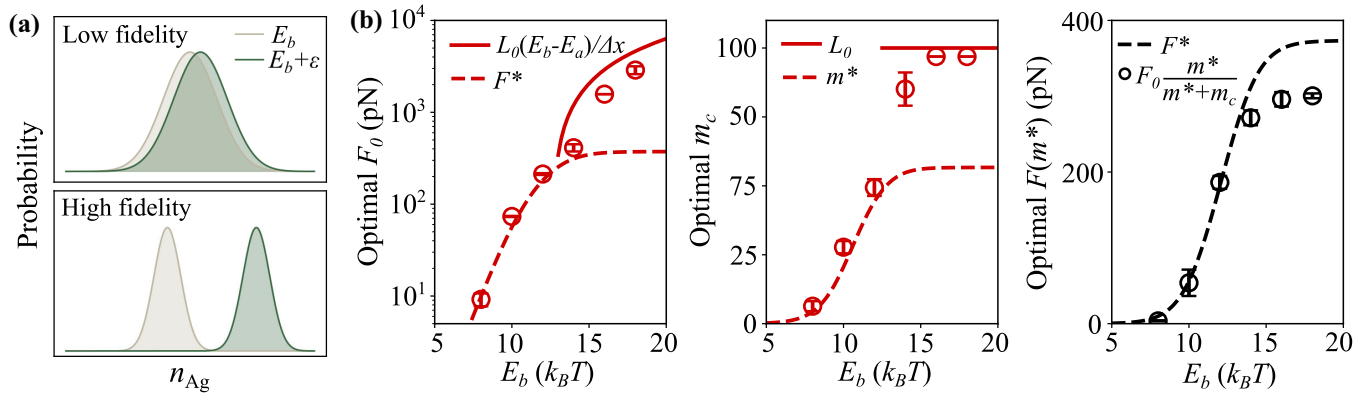


FIG. 3. Optimal force scheme for faithful selection depends on BCR affinity. (a) Selection fidelity is determined by distinguishability of readout (here, extraction level n_{Ag}) distributions between similar BCR affinities ($\epsilon \ll E_b$). (b) Optimal parameters F_0 and m_c of an adaptive force that maximizes the ranking fidelity ξ (shown by symbols) vary with BCR affinity. At low E_b , they correspond to the bifurcation point (dashed line). At high E_b , they close the affinity gap under a step force (solid line). The left two panels (red) are for step force $F(m_{\text{max}}; \beta = \infty)$ and the right panel (black) is for linear force $F(m_{\text{max}}; \beta = 1)$. Parameters: $k_{\text{on}} = 0.05 \text{ s}^{-1}$, $L_0 = 100$, $E_a = 12.6 k_B T$, $\epsilon = 0.5 k_B T$, $x_a = 1.5 \text{ nm}$, $x_b = 2 \text{ nm}$.

extraction level n_{Ag} . Stochastic extraction dynamics yield noisy affinity readouts (here, n_{Ag}) and hence unreliable clonal selection. We therefore quantify the fidelity of clonal selection, ξ , as the probability that a B cell with a higher affinity $E_b + \epsilon$ extracts a larger amount of antigen than a peer with affinity E_b , representing the chance of correct ranking:

$$\xi = \text{Prob}[n_{\text{Ag}}(E_b + \epsilon) > n_{\text{Ag}}(E_b)]. \quad (6)$$

As such, selection fidelity is limited by the distinguishability between readout distributions with similar affinities [18], as illustrated in Fig. 3(a). At one extreme, if two distributions do not overlap, then $\xi \approx 1$; at the other extreme, with two identical distributions, $\xi = 0.5$, indicating that cells drawn from either distribution have an equal chance of extracting more antigen and being selected. Often the distribution of n_{Ag} is not analytically tractable, then ξ can be estimated from the rate of correct ranking among many simulated B-cell pairs (with E_b vs $E_b + \epsilon$). In cases where n_{Ag} follows a Gaussian distribution, with mean μ_n and variance σ_n^2 both dependent on affinity, the fidelity to the leading order in ϵ (i.e., in the hard discrimination regime) is given by

$$\xi \approx \frac{1}{2} + \frac{1}{2\sqrt{\pi}\sigma_n} \frac{d\mu_n}{dE_b} \epsilon. \quad (7)$$

It follows that selection is faithful when the mean extraction level is sensitive to changes in affinity (large $d\mu_n/dE_b$) and/or the variance in extraction is low (small σ_n). This allows us to understand how cellular forcing dynamics influence selection fidelity in cell populations through their impact on the moments of the extraction level distribution, $P(n_{\text{Ag}})$.

To quantify the contribution from different stages of the extraction process, we express the distribution as

$$P(n_{\text{Ag}}) = \sum_{m_{\text{tot}}=0}^{L_0} P(m_{\text{tot}}) P(n_{\text{Ag}}|m_{\text{tot}}). \quad (8)$$

Here the distribution of m_{tot} , the total number of distinct antigens visited by BCRs in one extraction attempt, encodes the dynamic accessibility of antigens on the APC and character-

izes the stage of cluster formation. The conditional probability $P(n_{\text{Ag}}|m_{\text{tot}})$ is governed by the rupture stage in which antigen extraction occurs with the following success chance (treating rupture of the BCR bond and the tether bond as independent):

$$\eta(f_r) = \frac{k_a^{\text{off}}}{k_a^{\text{off}} + k_b^{\text{off}}} = \frac{1}{1 + e^{-(E_b - E_a - f_r(x_b - x_a))/k_B T}}. \quad (9)$$

Note that η depends on the force per bond f_r just before rupture and f_r , in turn, depends on total force and the number of remaining three-body complexes, both of which change over time. Therefore, antigen extraction can be viewed as a series of m_{tot} Bernouli events with varying success chances η due to varying rupture forces [29], leading to simplified expressions of the moments:

$$\begin{aligned} \mu_n &= \langle m_{\text{tot}} \bar{\eta} \rangle \approx \langle m_{\text{tot}} \rangle \langle \bar{\eta} \rangle, \\ \sigma_n^2 &\approx \langle m_{\text{tot}} \rangle \langle \bar{\eta} - \bar{\eta}^2 \rangle. \end{aligned} \quad (10)$$

Here, $\langle \cdot \rangle$ represents an ensemble average (over stochastic binding/unbinding events) and $\bar{\eta}^\alpha = \int_0^\infty \eta^\alpha(f_r) P(f_r) df_r$ denotes the α th moment of the extraction chance, averaged over the distribution $P(f_r)$ of rupture force per bond. A relatively narrow distribution of m_{tot} factorizes the ensemble average. Clearly, both cluster formation and dissociation contribute to the sensitivity

$$\frac{d\mu_n}{dE_b} \approx \langle \bar{\eta} \rangle \frac{d\langle m_{\text{tot}} \rangle}{dE_b} + \langle m_{\text{tot}} \rangle \frac{d\langle \bar{\eta} \rangle}{dE_b}, \quad (11)$$

reflecting that B cells of different affinities engage with different amounts of antigen during cluster growth (first term) and dissociate at disparate extraction chances (second term). Two stages dominate the fidelity gain at low and high affinities, respectively (Fig. S3 [29]).

We can now identify the dynamic force scheme that optimizes selection fidelity. By varying the force magnitude F_0 and the onset threshold m_c under different nonlinearities β , we determine the highest fidelity achievable at various BCR affinities. A notable switch in behavior occurs [Fig. 3(b)]: at high BCR affinities ($E_b > E_a$), a step force ($\beta = \infty$) of

magnitude $F_0 \sim L_0(E_b - E_a)/\Delta x$ yields the optimal fidelity (red solid lines), whereas at low BCR affinities ($E_b < E_a$), fidelity is maximal when $F(m^*) = F^*$ is satisfied (dashed lines).

Here is some physical intuition. At high BCR affinities, the number of antigens visited is primarily limited by E_a (the weaker bond in the three-body complex), resulting in low sensitivity of m_{tot} to E_b during cluster formation. Hence, fidelity at high E_b is mainly determined by the rupture stage (see Fig. S3(C) [29]). To optimize fidelity, both a large m_{tot} and a high $d\eta/dE_b$ are desired. A large m_{tot} can be obtained via a step force with a large onset threshold m_c , allowing time for cluster growth. $d\eta/dE_b$ reaches its maximum when $k_b^{\text{off}} = k_a^{\text{off}}$ [18], which occurs when the rupture force closes the affinity gap between the BCR bond and the tether bond:

$$F \Delta x / m \sim E_b - E_a, \quad (12)$$

where m is the instantaneous cluster size and $\Delta x = x_b - x_a$ is the difference between bond lengths. The optimal F_0 and m_c found in simulations indeed match this gap-closing condition (red solid lines in Fig. 3(b) and Fig. S4(A) [29]).

At low BCR affinities, a force that regulates cluster growth is key to optimizing fidelity. The optimal scheme is found to meet a general criterion:

$$F(m^*) = F_0 \frac{(m^*)^\beta}{(m^*)^\beta + m_c^\beta} = F^*, \quad (13)$$

as shown by dashed lines in Fig. 3(b) (also the blue line in Fig. S4(A) [29]). This condition results from the strong sensitivity of cluster formation, i.e., large dm_{tot}/dE_b , near the bifurcation point (F^*, m^*) , where a small increment in E_b significantly alters system dynamics (see Fig. S3(B) [29]). An optimal inert force $F(t)$ shows a similar trend of dependence of F_0 and t_c on E_b [comparing Fig. S4(B) [29] to Fig. 3(b)].

Although it is not immediately clear how B cells infer the exact force that closes the affinity gap or matches the tipping point, our results suggest a compelling possibility: B cells may switch the force application strategy (hence discriminatory regime) as they evolve from below to above E_a during affinity maturation—potentially through sensing the tether strength.

C. Speed-fidelity tradeoff in extraction-based affinity discrimination

Intuitive speed-accuracy tradeoffs have been reported for various information-processing systems that involve kinetic proofreading (e.g., Refs. [32,33]). Does mechanical proofreading based on active, physical signal acquisition experience similar tradeoffs?

Tradeoffs manifest as a Pareto front along which one trait cannot improve without deteriorating the other [34]. To reveal the Pareto front, we explore the parameter space of dynamic forces and present the speed and accuracy of many “force variants” over a wide dynamic range. We use the inverse

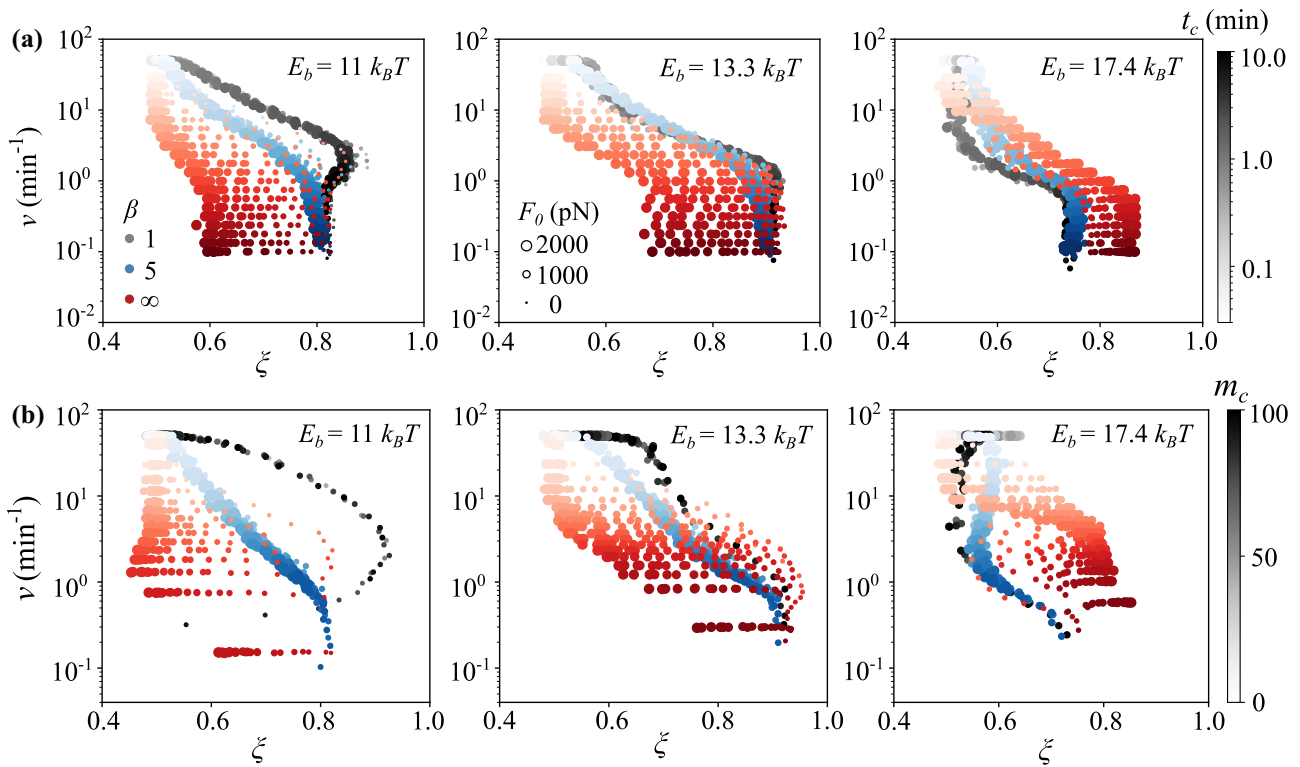


FIG. 4. Speed-fidelity tradeoff in discrimination of BCR affinity based on antigen extraction. Extraction speed and ranking fidelity are displayed simultaneously for each set of force parameters β , F_0 , and t_c (or m_c), represented by symbol color, size, and shading, respectively. Each symbol is an average over 4000 replicate simulations. (a) is under $F(t)$ and (b) is under $F(m_{\text{max}})$. Three columns correspond to different BCR affinities, $E_b = 11 k_B T$, $13.3 k_B T$, and $17.4 k_B T$ from left to right. At low E_b , a linear force (grey) defines the Pareto front, whereas at high E_b , a step force (red) optimally balances the trade-off. A further delay beyond the turning point (the elbow) substantially slows extraction while providing, at best, a modest gain in fidelity. Parameters: $L_0 = 100$, $k_{\text{on}} = 0.05 \text{ s}^{-1}$, $E_a = 12.6 k_B T$, $\epsilon = 0.5 k_B T$.

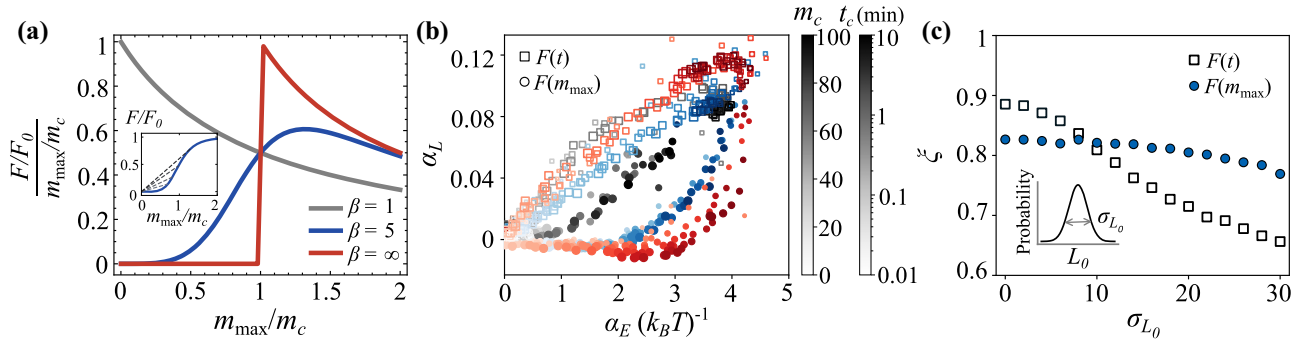


FIG. 5. Absolute discrimination can be achieved with nonlinear adaptive force. (a) Scaled force per bond is plotted against scaled maximum cluster size according to the definition of an adaptive force Eq. (3). For $\beta > 1$, force per bond increases with maximum cluster size before the total force saturates, providing a negative feedback that limits cluster growth. The inset shows $F(m_{\max}, \beta = 5)$, where the slope of the dash lines represents force per bond. (b) Sensitivity of mean extraction level to changes in ligand quantity, α_L , against sensitivity to changes in BCR affinity, α_E Eq. (14). Force parameters β , F_0 , and t_c (or m_c) are represented by symbol color, size, and shading, respectively. α_L and α_E are averaged over 5000 independent runs for each set of force parameters. Under $F(t)$, α_L always increases with α_E . Under $F(m_{\max})$, especially with a strong nonlinearity, there is a regime where α_E reaches larger values while α_L stays near zero, i.e., absolute discrimination. (c) Ranking fidelity is calculated for 6000 pairs of B cells, each seeing a different ligand number sampled from a Gaussian distribution with mean L_0 and standard deviation σ_{L_0} . $F(m_{\max})$ allows robust discrimination against strong variations in ligand number. Parameters: (b), (c) $L_0 = 100$, $k_{\text{on}} = 0.05 \text{ s}^{-1}$, $E_a = 12.6 k_B T$, $E_b = 13.3 k_B T$, (b) $F_0 = 100\text{--}1000 \text{ pN}$ with a spacing of 100 pN, (c) $F_0 = 800 \text{ pN}$, $t_c = 1 \text{ min}$, $m_c = 60$, $\beta = 5$.

cluster lifetime (from initial contact to dissociation) to represent speed and identify accuracy with selection fidelity. As shown in Fig. 4, for each given nonlinearity β , the Pareto front is associated with a particular force magnitude F_0 ; varying the onset threshold t_c or m_c moves the system along the front.

Two distinctive features emerge in both force schemes. First, the shape and nature of the Pareto front depend strongly on affinity. At low affinity, a linear force onset ($\beta = 1$, gray symbol) yields the best performance, whereas at high affinity a steplike force ($\beta = \infty$, red symbol) becomes favorable. In the low-affinity regime, a linear force suppresses clustering of weak BCRs while allowing higher-affinity receptors to assemble sizable clusters prior to extraction, enabling rapid discrimination. By contrast, at high E_b , a step force supports rapid cluster growth and confers higher fidelity for a given m_{tot} by closing the affinity gap. At intermediate E_b , Pareto fronts corresponding to different β largely overlap.

Second, optimal performance occurs at an intermediate delay of force onset—further delays yield only modest gains in fidelity while substantially slowing extraction. At low E_b , there exists a parameter regime where speed and fidelity improve simultaneously; the turning point (elbow) corresponds to maximum fidelity, arising from enhanced sensitivity near the tipping point. At high E_b , instead, the turning point marks the condition under which a later force onset dramatically reduces speed with only marginal improvement in fidelity.

In sum, the turning point in the speed-fidelity Pareto front designates the optimal force dynamics that best enable rapid and faithful discrimination of BCR affinity through antigen extraction.

D. Robust discrimination under adaptive force

A desirable feature of affinity discrimination is robustness to variations in ligand concentration. For T lymphocytes, a kinetic proofreading cascade supplemented by negative

feedback (mediated by the SHP-1 phosphatase) enables the detection of a few foreign ligands against a large excess of self-ligands [35–37]. This capacity to distinguish ligand quality independently of ligand quantity was termed absolute discrimination [38].

Analogously, as germinal center B cells migrate through the follicular dendritic cell network and sample heterogeneously distributed antigens [8,39], the amount of antigen they extract should reflect BCR quality rather than local antigen concentration. Can B cells achieve absolute discrimination through mechanical control?

To probe the enabling conditions, we vary the force parameters and compute the sensitivity of the extraction level to small changes in receptor affinity (α_E) and antigen quantity (α_L), respectively:

$$\alpha_E = \frac{1}{\sigma_n} \frac{d\mu_n}{dE_b}, \quad \alpha_L = \frac{1}{\sigma_n} \frac{d\mu_n}{dL_0}. \quad (14)$$

As shown in Fig. 5(b), only nonlinear adaptive forces [$F(m_{\max})$, red and blue circles] generate a regime of absolute discrimination, where α_L remains near zero while α_E reaches large values. In contrast, inert forces that are indifferent to the clustering state [$F(t)$, squares] fail to decouple receptor quality from ligand quantity: α_E and α_L remain positively correlated.

In essence, extraction forces that activate once Ag/BCR clusters reach a critical size implement a physical form of negative feedback: A nonlinear adaptive force yields a stronger force per bond as cluster size increases [Fig. 5(a)], thereby suppressing dose dependence of the extraction level. In contrast, an inert force lacking negative feedback reduces the mean force per bond during contact formation (Fig. S7(C) [29]), allowing clusters to grow larger before extraction and leading to higher overall extraction with increased sensitivity to L_0 . Supporting evidence is shown in Figs. S5–S7 [29].

Lastly, we examine how variations in ligand concentration affect selection fidelity ξ . To mimic spatial inhomogeneity or

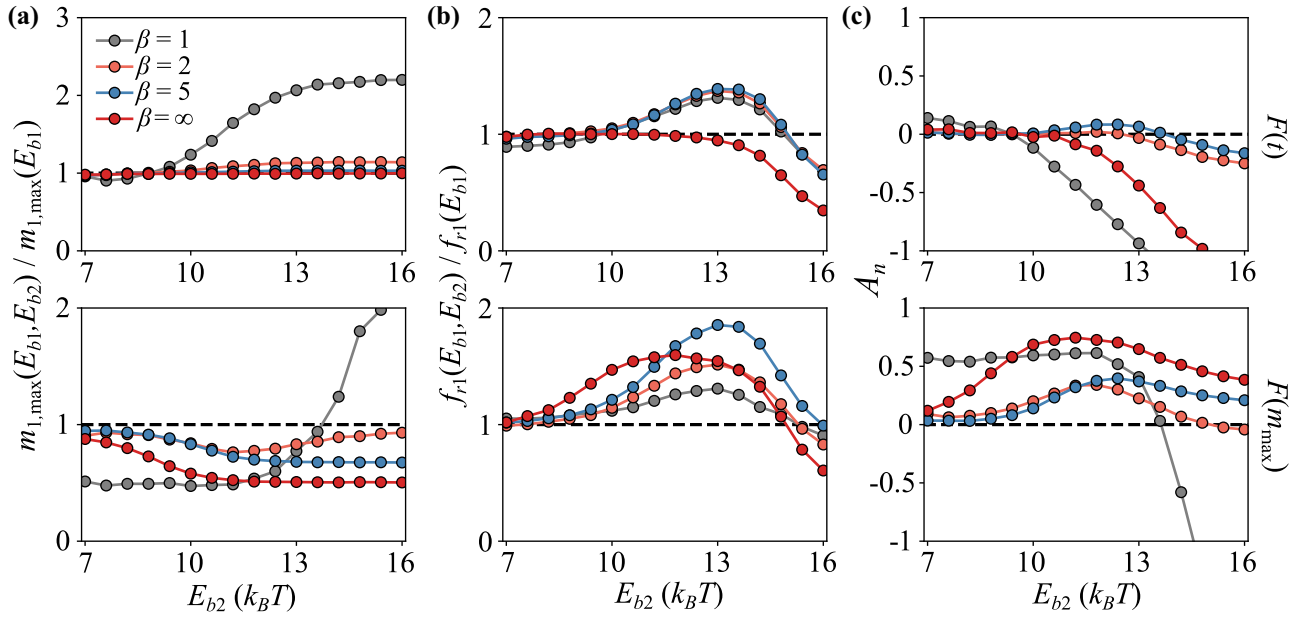


FIG. 6. Antagonism due to load sharing in the presence of a second antigen type. The ratio of the maximum agonist cluster size $m_{1,\max}$ (a) and that of the mean rupture force per agonist bond f_{r1} (b), between cases with and without antagonists, combine to determine the strength of antagonism A_n (c), as defined in Eq. (15). The top/bottom row corresponds to an inert/adaptive force. All results are averaged over 1000 replicate simulations. Under $F(t)$, mixed antigens are largely cooperative ($A_n < 0$) due to larger agonist clusters attained. Under $F(m_{\max})$, mixed antigens are mostly antagonistic ($A_n > 0$), caused by restricted growth of agonist clusters combined with stronger rupture force per agonist bond that lowers the chance of successful antigen extraction. $L_{10} = L_{20} = 40$, $k_{\text{on}} = 0.05 \text{ s}^{-1}$, $E_a = 12.6 k_B T$, $E_{b1} = 15 k_B T$. Top: $F_0 = 700 \text{ pN}$, $t_c = 1 \text{ min}$. Bottom: $F_0 = 500 \text{ pN}$, $m_c = 40$.

temporal fluctuations in antigen abundance, ligand quantity is drawn from a Gaussian distribution $\mathcal{N}(L_0, \sigma_{L_0})$. As shown in Fig. 5(c), fidelity declines with increasing σ_{L_0} under the inert force $F(t)$, whereas discrimination remains robust under the adaptive force $F(m_{\max})$. That is, adaptive forces effectively buffer fluctuations in antigen concentration and preserve high selection fidelity.

Therefore, dynamic forces that adapt to the clustering state provide a negative feedback that minimizes dependence on ligand quantity during extraction, enabling absolute discrimination in part of the parameter space.

E. Ligand antagonism due to load sharing

Upon natural infection or vaccination, antigens are often presented as mixtures, comprising distinct viral mutants or cocktails of related antigenic variants. Experimental studies have shown that both B and T cells exhibit ligand antagonism—a phenomenon in which ligands below the activation threshold (antagonists) alter responses to agonists [40–43]. Antagonism can cause immune evasion [44–46] and reduce vaccine efficacy [47]. Conversely, elucidating its mechanistic origins may offer strategies to counter autoimmune responses by antagonizing faulty cellular decisions [48], and inform better designs of multivalent vaccines.

To detect antagonism of a physical origin, we examine agonist extraction in the presence of antagonists of varying affinities, contrasting $F(t)$ with $F(m_{\max})$. We quantify antagonism by the relative reduction in agonist extraction when

mixed with antagonists (well-mixed in equal quantities):

$$A_n \equiv \frac{\mu_n(E_{b1}) - \mu_n(E_{b1}, E_{b2})}{\mu_n(E_{b1})}, \quad (15)$$

where $\mu_n(E_{b1})$ and $\mu_n(E_{b1}, E_{b2})$ denote, respectively, the mean extraction level of the agonists (of affinity E_{b1}) in the absence and presence of antagonists (of affinity E_{b2}). Without antagonism, $A_n = 0$.

Collecting statistics from simulated extraction trajectories, we find that the two force schemes yield opposing behaviors [Fig. 6(c)]. Under $F(t)$, ligand interactions are largely cooperative, resulting in negative antagonism. By contrast, extraction under $F(m_{\max})$ exhibits pronounced antagonism. With nonlinear force onset, antagonism is maximal at intermediate antagonist affinities, whereas under linear onset, weak antagonists most strongly suppress agonist extraction. This behavior is analogous to that of artificial neural networks performing ligand classification under adversarial perturbations [49].

This contrasting behavior between force schemes arises from how ligand mixing alters the maximum attainable agonist cluster size $m_{1,\max}$ [Fig. 6(a)] and the mean rupture force per agonist bond f_{r1} [Fig. 6(b)]. Under $F(t)$, agonists can form larger clusters because antagonists share the load and support continued growth. Under $F(m_{\max})$, antagonists trigger an additional load, which suppresses agonist cluster growth. In both schemes, the mean rupture force per agonist bond peaks when antagonists have subthreshold affinities ($E_{b2} \leq E_{b1}$). In this regime, both ligands contribute to cluster growth and activate a strong total force, but toward dissociation, antagonist bonds break sooner, leaving agonists alone to bear a high force

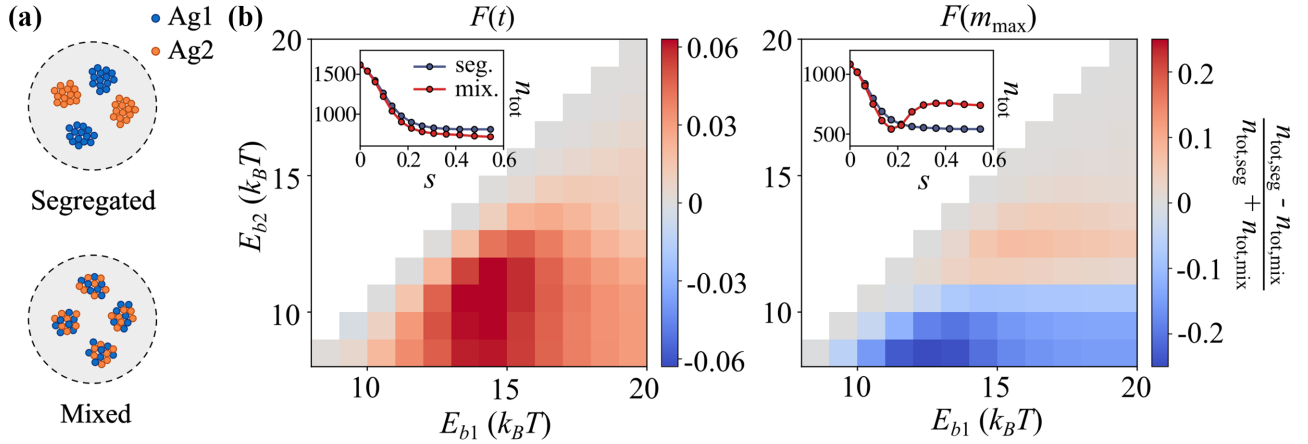


FIG. 7. Preferred configuration of multitype antigen presentation depends on B cell specificity. (a) We examine two extreme scenarios of multitype antigen presentation: fully segregated (top) and well-mixed (bottom). (b) Heatmaps show the scaled difference in total antigen extraction per cell ($n_{\text{tot}} = n_{\text{Ag1}} + n_{\text{Ag2}}$) between segregated and mixed presentation scenarios. We assume every cell has 20 clusters with 100 antigens each. Insets show the total extraction level in each scenario with respect to specificity $s = (E_{b1} - E_{b2}) / (E_{b1} + E_{b2})$. s is varied by keeping E_{b1} fixed at $17 k_B T$ while varying E_{b2} from $17 k_B T$ to $5 k_B T$. All results are averaged over 6000 independent runs. Under $F(t)$, segregation of different antigen types promotes extraction by specific and cross-reactive cells alike. Under $F(m_{\max})$, mixing is preferred for specific cells, while segregation remains favorable for cross-reactive cells. Parameters: $k_{\text{on}} = 0.05 \text{ s}^{-1}$, $E_a = 12.6 k_B T$, $F_0 = 600 \text{ pN}$, $t_c = 1 \text{ min}$, $m_c = 40$, $\beta = 5$.

per bond (see Fig. S8 [29] for representative trajectories). Together, these effects account for the extraction outcomes in Fig. 6(c): ligand cooperativity ($A_n < 0$) under inert forces and antagonism ($A_n > 0$) under adaptive forces.

Importantly, absolute discrimination and ligand antagonism share a common origin: negative feedback generating inhibitory coupling among receptors.

An intriguing implication follows: extracting antigens under a shared load provides a mechanism to select against self-reactive B cells. Under nonlinear adaptive forces, loss of self-reactivity through BCR mutation reduces antagonism, enhancing extraction of foreign antigens and acquisition of survival signals from T helper cells. This may explain clonal redemption, observed in mice and humans [50,51], where dual self-/foreign-binding B cells are rescued by mutation away from self-reactivity [52]. Our results suggest that negative selection of auto-reactive B cells can occur via positive selection of B cells that no longer bind self-antigen, highlighting a GC tolerance mechanism based on load-sharing antigen extraction and competition for T cell help.

F. Spatial organization of multitype antigens tunes response specificity

We finally assess how the spatial organization of multiple antigen types influences total extraction. This is needed for understanding immune responses to multivalent vaccines, where all variant antigens are foreign. We anticipate that sorting different types into separate clusters may enhance or reduce overall extraction depending on forcing dynamics and B-cell specificity.

Consider extreme scenarios of multitype antigen presentation [Fig. 7(a)]: complete segregation versus perfect mixing, for the same total dose. In Fig. 7(b), we show how the relative efficiency of total extraction between these scenarios varies with B-cell specificity. The two force schemes yield markedly

different outcomes. Under $F(t)$, well-mixed presentation always reduces extraction, because mixing leads to a lower force on weaker antigens and a much higher force on stronger antigens, with the latter dominating due to nonlinear force effects.

Under $F(m_{\max})$, the preferred spatial arrangement depends on specificity. Cross-reactive B cells ($E_{b1} \approx E_{b2}$) favor segregation, as under $F(t)$, whereas specific cells ($E_{b1} > E_{b2}$) benefit from mixing. This benefit occurs because weaker antigens, though barely extracted, help distribute stronger antigens into smaller clusters and modulate force dynamics, enabling more efficient engagement with BCRs (Fig. S10 [29]). Consequently, response specificity could be tuned by spatially patterning antigen mixtures on the presenting surface.

IV. DISCUSSION

Nonequilibrium proofreading reactions enable a strong reduction of errors in biological recognition. Here we generalize proofreading to cases where the drive and the effect operate on vastly different scales: force-generating assemblies within individual cells regulate the selective expansion of cell lineages over many generations. As in conventional kinetic proofreading, MPR relies on kinetic complexity in reaction pathways to be effective. Unique to MPR, the ability of intracellular forces to actively pattern the cell-cell interface is exploited to propagate information across organizational scales. Although we demonstrate MPR through adaptive immunity, the ubiquity of contractile force ratchets and force-sensitive receptor-ligand interactions suggests that this mechanism may operate broadly wherever cells communicate through physical engagement.

We examined the capacity of MPR to enhance selection fidelity by studying antigen extraction under dynamic forces. Our results show that elucidating the form and effect of

mechanical feedback is essential for understanding clonal selection, as the mapping from receptor affinity excess to clonal competitive advantage is strongly shaped by force dynamics. Both inert forces, which activate after a preset delay, and adaptive forces, which adjust to the clustering state, are biologically plausible and supported by experimental data (Fig. 1). Notably, our model identifies a clear signature of mechanical feedback: adaptive forces allow faster detection of larger antigen abundance, whereas inert forces yield the opposite trend (Fig. 2). The predicted contrast in the scaling of contact duration with ligand quantity provides a direct experimental test to distinguish between these force schemes.

By quantifying contributions from distinct stages of force-driven extraction, we identify affinity-dependent regimes of discrimination and the corresponding optimal force schemes (Fig. 3). At low BCR affinities, a ramping force that steers cluster growth toward the bifurcation point is the key to optimizing discrimination. At high affinities, a step force that closes the affinity gap between BCR and tether bonds maximizes fidelity. In addition, we find that the optimal balance of speed and accuracy occurs at an intermediate delay in force onset—longer delays only marginally improve accuracy while dramatically slowing extraction (Fig. 4). Faster antigen extraction is expected to promote more efficient accumulation of survival signals, which may amplify selective differences and enhance clonal selection fidelity across generations.

An intriguing feature of the MPR mechanism is ligand antagonism (Fig. 6). Conceptually, sequential assembly reactions combined with negative feedback—here provided by nonlinear adaptive forces—generate inhibitory coupling between agonists and nonagonists, in close analogy to the biochemical counterpart in early T-cell activation [37]. This suggests the possibility of a unifying framework for biological recognition that generalizes antagonism under adversarial perturbations (structured variations in ligand background) [49]. Practically, sub-threshold nonagonists produce maximum antagonism, implying that negative selection of auto-reactive B cells can occur via positive selection of cells that no longer bind self-antigen, as loss of self-binding enhances foreign binding by reducing antagonism. Furthermore, our model predicts that under adaptive forces, presenting distinct antigens in separate clusters can increase total extraction by cross-reactive cells but reduce extraction by specific cells (Fig. 7), suggesting that vaccine response specificity could be tuned by spatially patterning antigens on presenting surfaces, such as nanoparticles.

One might expect that maintaining clonal diversity would compromise selection fidelity, as it likely caps the expansion of high-affinity clones to preserve lower-affinity ones. Our results suggest that MPR offers a way around this apparent tradeoff. As we showed previously [17], force exertion in a tug-of-war configuration engages additional internal

degrees of freedom in the BCR-Ag-tether complex, allowing a wide spectrum of binding phenotypes to coexist. The present analysis further indicates that diversity gained through this physical route is not incompatible with faithful selection. Instead, pattern-sensing adaptive forces can robustly amplify the most potent clones in response to the current challenge, while preserving the phenotypic breadth needed for future threats.

Furthermore, we argue that the adaptive immune system likely deploys complementary kinetic and mechanical proofreading mechanisms to secure reliable information transfer across different developmental stages and organization levels of the response. Recent theoretical work [53] proposed that, in the face of exponentially replicating antigens, kinetic proofreading is necessary for the selective expansion of high-affinity naive B cells that seed affinity maturation. Here, we suggest that mechanical proofreading may instead dominate during affinity maturation, sustaining selection pressure as affinities improve. Indeed, naive and germinal center B cells exhibit pronounced differences in contact pattern and force utilization, pointing to a potential switch in proofreading mode [19,27].

Perhaps most remarkably, enhancing the fidelity of clone selection via mechanical feedback yields functional properties that appear mutually incompatible and are unlikely to be directly selected for. Negative feedback under adaptive MPR buffers against variations in ligand concentration (Fig. 5) while simultaneously enabling tunable interactions between distinct ligands through differences in relative affinity (Fig. 6) or spatial organization (Fig. 7). These observations lead us to postulate that MPR might have evolved under selection for efficient clonal expansion: By enhancing ranking fidelity, MPR increases the collective reproductive fitness of selected clones. The resulting boost in population growth would favor the expansion of clones that possess MPR. Once mechanical feedback emerges, the functionalities it carries can add further selection pressure to maintain it. An interesting avenue for future work is to model clonal dynamics driven by the emergence, expansion, and inheritance of mechanical feedback, which may help uncover an evolutionary origin of proofreading across scales.

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DATA AVAILABILITY

The data that support the findings of this article are openly available [59].

- [1] J. Ninio, Kinetic amplification of enzyme discrimination, *Biochimie* **57**, 587 (1975).
- [2] J. J. Hopfield, Kinetic proofreading: a new mechanism for reducing errors in biosynthetic processes requiring high specificity, *Proc. Natl. Acad. Sci. USA* **71**, 4135 (1974).
- [3] M. Ehrenberg and C. Blomberg, Thermodynamic constraints on kinetic proofreading in biosynthetic pathways, *Biophys. J.* **31**, 333 (1980).
- [4] A. Murugan, D. A. Huse, and S. Leibler, Discriminatory proofreading regimes in nonequilibrium systems, *Phys. Rev. X* **4**, 021016 (2014).

- [5] T. W. McKeithan, Kinetic proofreading in t-cell receptor signal transduction, *Proc. Natl. Acad. Sci. USA* **92**, 5042 (1995).
- [6] R. Phillips, *The Molecular Switch: Signaling and Allostery* (Princeton University Press, Princeton, NJ, 2020).
- [7] E. Natkanski, W.-Y. Lee, B. Mistry, A. Casal, J. E. Molloy, and P. Tolar, B cells use mechanical energy to discriminate antigen affinities, *Science* **340**, 1587 (2013).
- [8] K. Suzuki, I. Grigorova, T. G. Phan, L. M. Kelly, and J. G. Cyster, Visualizing B cell capture of cognate antigen from follicular dendritic cells, *J. Exp. Med.* **206**, 1485 (2009).
- [9] H. N. Eisen and G. W. Siskind, Variations in affinities of antibodies during the immune response, *Biochemistry* **3**, 996 (1964).
- [10] G. D. Victora and M. C. Nussenzweig, Germinal centers, *Annu. Rev. Immunol.* **30**, 429 (2012).
- [11] G. D. Victora and M. C. Nussenzweig, Germinal centers, *Annu. Rev. Immunol.* **40**, 413 (2022).
- [12] F. D. Batista, D. Iber, and M. S. Neuberger, B cells acquire antigen from target cells after synapse formation, *Nature (London)* **411**, 489 (2001).
- [13] H. C. W. McArthur, A. T. Bajur, M. Iliopoulou, and K. M. Spillane, Antigen mobility regulates the dynamics and precision of antigen capture in the B cell immune synapse, *Proc. Natl. Acad. Sci. USA* **122**, e2422528122 (2025).
- [14] A. Lanzavecchia, Antigen-specific interaction between T and B cells, *Nature (London)* **314**, 537 (1985).
- [15] G. D. Victora, T. A. Schwickert, D. R. Fooksman, A. O. Kamphorst, M. Meyer-Hermann, M. L. Dustin, and M. C. Nussenzweig, Germinal center dynamics revealed by multiphoton microscopy with a photoactivatable fluorescent reporter, *Cell* **143**, 592 (2010).
- [16] H. Jiang and S. Wang, Immune cells use active tugging forces to distinguish affinity and accelerate evolution, *Proc. Natl. Acad. Sci. USA* **120**, e2213067120 (2023).
- [17] H. Jiang and S. Wang, Molecular tug of war reveals adaptive potential of an immune cell repertoire, *Phys. Rev. X* **13**, 021022 (2023).
- [18] H. Jiang and S. Wang, Physical extraction of antigen and information, *Proc. Natl. Acad. Sci. USA* **121**, e2320537121 (2024).
- [19] C. R. Nowosad, K. M. Spillane, and P. Tolar, Germinal center B cells recognize antigen through a specialized immune synapse architecture, *Nat. Immunol.* **17**, 870 (2016).
- [20] J. Wang, F. Lin, Z. Wan, X. Sun, Y. Lu, J. Huang, F. Wang, Y. Zeng, Y.-H. Chen, Y. Shi, W. Zheng, Z. Li, C. Xiong, and W. Liu, Profiling the origin, dynamics, and function of traction force in B cell activation, *Sci. Signaling* **11**, eaai9192 (2018).
- [21] M. Knežević, H. Jiang, and S. Wang, Active tuning of synaptic patterns enhances immune discrimination, *Phys. Rev. Lett.* **121**, 238101 (2018).
- [22] G. I. Bell, Models for the specific adhesion of cells to cells, *Science* **200**, 618 (1978).
- [23] F. M. Mason and A. C. Martin, Tuning cell shape change with contractile ratchets, *Curr. Opin. Genet. Dev.* **21**, 671 (2011).
- [24] J. E. Komianos and G. A. Papoian, Stochastic ratcheting on a funneled energy landscape is necessary for highly efficient contractility of actomyosin force dipoles, *Phys. Rev. X* **8**, 021006 (2018).
- [25] F. D. Batista and M. S. Neuberger, B cells extract and present immobilized antigen: implications for affinity discrimination, *EMBO J.* **19**, 513 (2000).
- [26] C. D. C. Allen, T. Okada, H. L. Tang, and J. G. Cyster, Imaging of germinal center selection events during affinity maturation, *Science* **315**, 528 (2007).
- [27] K. Kwak, N. Quizon, H. Sohn, A. Sanicee, J. Manzella-Lapeira, P. Holla, J. Brzostowski, J. Lu, H. Y. Xie, C. Xu, K. M. Spillane, P. Tolar, and S. K. Pierce, Intrinsic properties of human germinal center B cells set antigen affinity thresholds, *Sci. Immunol.* **3**, eaau6598 (2018).
- [28] K. M. Spillane and P. Tolar, B cell antigen extraction is regulated by physical properties of antigen presenting cells, *Biophys. J.* **112**, 126a (2017).
- [29] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/vfqt-t3b9> for details of the bifurcation analysis and stochastic simulations, calculation of the scaling relationship of contact duration with ligand quantity, description of the readout distribution and its moments, analysis of conditional distributions of contact duration, and characterization of absolute discrimination, which includes Refs. [54–58].
- [30] T. Wong, T. Chou, S. Shankar, and S. Wang, Mechanical activity enables patterning and discrimination at the immune synapse, *arXiv:2510.18771*.
- [31] A. D. Gitlin, Z. Shulman, and M. C. Nussenzweig, Clonal selection in the germinal centre by regulated proliferation and hypermutation, *Nature (London)* **509**, 637 (2014).
- [32] B. Wang and O. K. Dudko, A theory of synaptic transmission, *eLife* **10**, e73585 (2021).
- [33] W. Cui and P. Mehta, Identifying feasible operating regimes for early T-cell recognition: The speed, energy, accuracy trade-off in kinetic proofreading and adaptive sorting, *PLoS One* **13**, e0202331 (2018).
- [34] O. Shoval, H. Sheftel, G. Shinar, Y. Hart, O. Ramote, A. Mayo, E. Dekel, K. Kavanagh, and U. Alon, Evolutionary trade-offs, pareto optimality, and the geometry of phenotype space, *Science* **336**, 1157 (2012).
- [35] G. Altan-Bonnet and R. N. Germain, Modeling t cell antigen discrimination based on feedback control of digital erk responses, *PLoS Biol.* **3**, e356 (2005).
- [36] O. Feinerman, R. N. Germain, and G. Altan-Bonnet, Quantitative challenges in understanding ligand discrimination by $\alpha\beta$ T cells, *Mol. Immunol.* **45**, 619 (2008), Special section: Theories and Modelling of T Cell Behaviour.
- [37] P. François, G. Voisinne, E. D. Siggia, G. Altan-Bonnet, and M. Vergassola, Phenotypic model for early T-cell activation displaying sensitivity, specificity, and antagonism, *Proc. Natl. Acad. Sci. USA* **110**, E888 (2013).
- [38] P. François and G. Altan-Bonnet, The case for absolute ligand discrimination: Modeling information processing and decision by immune T cells, *J. Stat. Phys.* **162**, 1130 (2016).
- [39] A. Martinez-Riano, S. Wang, S. Boeing, S. Minoughan, A. Casal, K. M. Spillane, B. Ludewig, and P. Tolar, Long-term retention of antigens in germinal centers is controlled by the spatial organization of the follicular dendritic cell network, *Nat. Immunol.* **24**, 1281 (2023).
- [40] J. W. Schrader, Antagonism of B lymphocyte mitogenesis by anti-immunoglobulin antibody, *J. Immunol.* **115**, 323 (1975).
- [41] J. F. Kearney, M. D. Cooper, and A. R. Lawton, B lymphocyte differentiation induced by lipopolysaccharide: III. Suppression of B cell maturation by anti-mouse immunoglobulin antibodies, *J. Immunol.* **116**, 1664 (1976).

- [42] S. C. Jameson and M. J. Bevan, T cell receptor antagonists and partial agonists, *Immunity* **2**, 1 (1995).
- [43] J. Ruppert, J. Alexander, K. Snoke, M. Coggeshall, E. Herbert, D. McKenzie, H. M. Grey, and A. Sette, Effect of T-cell receptor antagonism on interaction between T cells and antigen-presenting cells and on T-cell signaling events, *Proc. Natl. Acad. Sci. USA* **90**, 2671 (1993).
- [44] P. Klenerman, S. Rowland-Jones, S. McAdam, J. Edwards, S. Daenke, D. Laloo, B. Köppe, W. Rosenberg, D. Boyd, A. Edwards, *et al.*, Cytotoxic T-cell activity antagonized by naturally occurring HIV-1 gag variants, *Nature (London)* **369**, 403 (1994).
- [45] U.-C. Meier, P. Klenerman, P. Griffin, W. James, B. Köppe, B. Larder, A. McMichael, and R. Phillips, Cytotoxic T lymphocyte lysis inhibited by viable HIV mutants, *Science* **270**, 1360 (1995).
- [46] T. N. Schumacher and R. D. Schreiber, Neoantigens in cancer immunotherapy, *Science* **348**, 69 (2015).
- [47] S. J. Kent, P. D. Greenberg, M. C. Hoffman, R. E. Akridge, and M. J. McElrath, Antagonism of vaccine-induced HIV-1-specific CD4 T cells by primary HIV-1 infection: potential mechanism of vaccine failure, *J. Immunol.* **158**, 807 (1997).
- [48] B. Vanhove, N. Poirier, F. Fakhouri, L. Laurent, B. 't Hart, P. H. Papotto, L. V. Rizzo, M. Zaitsu, F. Issa, K. Wood, *et al.*, Antagonist anti-CD28 therapeutics for the treatment of autoimmune disorders, *Antibodies* **6**, 19 (2017).
- [49] T. J. Rademaker, E. Bengio, and P. François, Attack and defense in cellular decision-making: Lessons from machine learning, *Phys. Rev. X* **9**, 031012 (2019).
- [50] Z. Sabouri, P. Schofield, K. Horikawa, E. Spierings, D. Kipling, K. L. Randall, D. Langley, B. Roome, R. Vazquez-Lombardi, R. Rouet, *et al.*, Redemption of autoantibodies on anergic B cells by variable-region glycosylation and mutation away from self-reactivity, *Proc. Natl. Acad. Sci. USA* **111**, E2567 (2014).
- [51] J. H. Reed, J. Jackson, D. Christ, and C. C. Goodnow, Clonal redemption of autoantibodies by somatic hypermutation away from self-reactivity during human immunization, *J. Exp. Med.* **213**, 1255 (2016).
- [52] D. L. Burnett, J. H. Reed, D. Christ, and C. C. Goodnow, Clonal redemption and clonal anergy as mechanisms to balance B cell tolerance and immunity, *Immunol. Rev.* **292**, 61 (2019).
- [53] R. Morán-Tovar and M. Lässig, Nonequilibrium antigen recognition during infections and vaccinations, *Phys. Rev. X* **14**, 031026 (2024).
- [54] D. T. Gillespie, Exact stochastic simulation of coupled chemical reactions, *J. Phys. Chem.* **81**, 2340 (1977).
- [55] D. F. Anderson, A modified next reaction method for simulating chemical systems with time dependent propensities and delays, *J. Chem. Phys.* **127**, 214107 (2007).
- [56] K. M. Spillane and P. Tolar, B cell antigen extraction is regulated by physical properties of antigen-presenting cells, *J. Cell Biol.* **216**, 217 (2017).
- [57] S. K. Norman, L. Johnson, and A. W. Kemp, *Univariate Discrete Distributions* (John Wiley & Sons, Hoboken, NJ, 2005).
- [58] R. Eisinga, M. Grotenhuis, and B. Pelzer, Saddlepoint approximation for the sum of independent non-identically distributed binomial random variables, *Stat. Neerl.* **67**, 190 (2013).
- [59] Q. Xu, sunchi7/Adaptive-MPR, <https://github.com/sunchi7/Adaptive-MPR>.