# Affinity Discrimination in B Cells Requires Kinetic Proofreading

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***Short Abstract* — The strength of the B cell response to antigen is proportional to the affinity of the B cell for antigen, a process known as affinity discrimination. The mechanisms of B cell affinity discrimination are not currently known. In this work, we use a stochastic, agent-based model to propose that B cell affinity discrimination requires a process similar to kinetic proofreading. We show optimal affinity discrimination requires an antigen dwell time of ~10 seconds before cytosolic signaling molecules can bind the the B cell receptor and initiate signaling.**

***Keywords* — Affinity discrimination, B cells, kinetic proofreading, intracellular signaling, B cell receptor, B cell activation, agent-based modeling, dwell time.**

## I. INTRODUCTION

B cells are activated by the binding antigen (Ag) to the B cell receptor (BCR). Binding of antigen to the BCR results in the initiation of an intracellular signaling cascade that leads to antibody production and differentiation into memory B cells. The strength of B cell signaling in response to stimulation by antigen is known to depend on the affinity of the B cell receptor for antigen, a process known as affinity discrimination [1-3]. The precise mechanisms by which B cells sense antigen affinity are still the subject of current investigations. Recent research shows that antigen fragments presented on the surface of antigen presenting cells (dendritic cells, follicular dendritic cells or macrophages) are potent stimulators of B cells [4].

Further studies show that during contact between B cells and antigen presenting cells, BCR initially encounters antigen along protrusions on the B cell surface, resulting in the formation of micro-clusters of BCR/Antigen complexes [5]. These micro-clusters are thought to be signaling-active, as they trigger a spreading of the B cell surface which leads to increased micro-cluster formation at the leading edges [3]. Because the strength of the B cell spreading response is a function of the affinity of the BCR for antigen [3], it is likely that the strength of BCR signaling within the micro-clusters is also dependent on antigen affinity. However, very little is known about how B cells discriminate between antigens of varying affinity at the micro-cluster level.

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## II. RESULTS

In this work, we use an agent-based, kinetic Monte Carlo model of B cell surface dynamics and intracellular signaling to show that affinity discrimination at the level of BCR/Antigen micro-clusters requires a kinetic proofreading-type mechanism. We show that if Src-family kinases such as Lyn can bind to the Igα/β subunits of BCR immediately after the latter binds an antigen molecule, the strength of B cell signaling decreases monotonically with affinity. This indicates serial triggering, as the number of BCRs with phosphorylated Igα/β subunits is solely dependent on the rate of BCR-antigen encounters, which is greater at higher $k_{off}$ values (i.e. at lower affinity). Adding a dwell time requirement brings in kinetic proofreading, which favors high-affinity interactions. The number of BCRs with phosphorylated Igα/β subunits is no longer solely dependent on the rate of BCR-antigen encounters, but also on the length of time that a BCR has bound antigen, which increases with higher affinity. With a dwell time of ~1 second, signaling strength reaches a maximum at mid-range affinity values and then decreases with increasing affinity. However, we find that a dwell-time of ~10 seconds results in a monotonic increase in signaling with increasing antigen affinity, in line with experimental investigations of B cell signaling [1-3].

## III. CONCLUSIONS

We find that affinity discrimination in B cells requires a kinetic proofreading-type mechanism. Our modeling results show that B cell affinity discrimination is optimal with an antigen dwell time of ~10 seconds, and sharply deteriorates as the value of the dwell times deviates form this number.

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