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# A spatially extended model of B cell receptor cluster signaling

The process of B cell activation is initiated by the clustering of B cell receptors (BCR) upon specific engagement and cross-linking with antigens (Ag). A BCR-Ag microcluster must comprise a minimum number of receptors ($\sim$ 10-20) in order to create an immunon – the smallest signaling unit capable of triggering intracellular signaling leading to the development of immunogenic response.

We have approached the kinetic simulation of early signaling events within a two-dimensional cellular automaton in which the plane representing a region of the B cell membrane is discretized using the hexagonal tiling. Transmembrane molecules of BCR and membrane-tethered Src-family kinases (represented in our study by single kinase Lyn) diffuse over the tiles while Ag ligands are placed in trigonal cells of a dual lattice. We assume that the Y-shaped extracellular part of the BCR (mIg) can bind up to two Ag, that may have higher valency. Movements of Ag-bound BCR are limited: singly linked BCR can move only to the cells that are adjacent to Ag, and BCR is immobilized when bound twice. Lyn may bind to the cytoplasmic part of BCR either by its unique domain (week binding) or by SH2 domain (strong binding to phosphorylated BCR), resulting in the creation of complexes that by convention occupy a single hexagonal cell of the plane. Associated Lyn can phosphorylate the neighboring BCR or Lyn. Every binding reaction is reversible and molecules undergo spontaneous dephosphorylation. The process is coded in software in the way that ensures the exact state-to-state dynamics: reaction and diffusion events are selected from the catalog of possible events and are fired at random with their propensities proportional to corresponding rate constants.

We found that when the receptors are freely moving over the surface (in the absence of ligands) the system exhibits only small basal activity – characteristic for unstimulated cells. In the presence of ligands BCR form clusters which enhance the effective interaction rate and triggers kinase activity. Trivalent ligands are much more effective than bivalent ones in building dense, signaling-efficient, BCR clusters. Due to the positive feedback in mutual receptor and kinase activation (phosphorylation of receptor stabilizes kinase binding and autophosphorylation) clusters exhibit switch-like activation. The cluster inactivation propensity decreases with the the size of the cluster, and clusters of ten or more receptors activate virtually persistently.

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