

## Updating The Two Signal theory of T cell Activation with a Cellular Calculus

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T and B-lymphocytes process affinity, co-stimulatory signals, and secreted cytokines to reach decisions about the strength and type of response to follow after challenge. By combining direct cell imaging, genetic manipulation and computer modelling we examine cells making decisions under different stimulation combinations. Our results reveal surprisingly simple rules for cellular calculation for both B and T cells. Typically cells simply count through a series of divisions, stop and die. Varying the stimulation strength alters the proportion of cells entering the autonomous program without changing division, differentiation or survival rates. In T cells IL-2 extends the number of divisions reached in a concentration dependent manner without altering time between divisions. These results give an insight into how complex immune responses evolved from simpler pathways and suggest a signal integration calculator can be developed to dissect the influence of changes caused by drugs, or genetic polymorphisms.