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Integrating multiple signals into cell decisions by a network of protein modification cycles

Cell responses to internal and external stimuli are governed by protein interactions. The enzymatic activity and biological function of proteins is modulated by reversible post-translational modifications such as phosphorylation, acetylation, methylation, ubiquitination, sumoylation, etc. Here we present a general model of reversible protein modifications and show that such system can integrate multiple input signals into digital-like responses, representing robust cellular decisions. Consequently, proteins modified by multiple enzymes can function as complex switches, playing a similar role in cellular information processing as neurons in the brain. We develop an analytical approach for constructing the phase diagram of such systems from the structure of the protein modification network, determining how switching between distinct responses take place. This method can be applied to a broad class of protein modification systems and provides an alternative to numerical approaches that give limited insight when the number of unknown parameters is large.