

# Use of information far from steady-state by signal transduction systems.

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**W**e present a mechanism that enables signaling systems to discriminate between different levels of extracellular signals that saturate receptors at equilibrium. This mechanism, which we called PRESS, for Pre Equilibrium Sensing and Signaling, operates when the kinetics of ligand receptor binding is slower than a transient downstream signaling step. This dynamic coupling between slow receptor binding and fast downstream transduction enables sensing systems to use information about the initial rate of receptor occupation, which is proportional to ligand concentration, even at concentrations that yield almost complete and practically indistinguishable levels of occupied receptors. We provide experimental and modeling evidence that PRESS is involved in the directional budding of yeast cells in gradients of mating pheromone. We further show by mathematical modeling that PRESS is not limited to plasma membrane receptor signaling: it can also operate at other levels, such as cycles of phosphorylation and dephosphorylation, provided that a slow activation step couples to a faster downstream step.

PRESS expands and shifts the dynamic range of sensing systems, allowing cells to generate distinct responses to ligands or signaling components concentrations so high that cannot be distinguished by the levels of binding site occupation at steady-state. Published kinetic data for receptor ligand interactions in mammalian systems suggests that PRESS operates in many cell-signaling systems throughout biology.