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Building a genetic transistor in yeast: How protein sequestration generates a tunable ultrasensitive or all-or-none response

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Protein sequestration, where an active protein (A) is bound in an inactive complex by an inhibitor, is a common molecular mechanism in natural regulatory circuits. The inhibitor serves as a molecular sink that can buffer and titrate low concentrations of A. If sufficient protein A is produced, then the sink is saturated and A will exhibit an ultrasensitive or all-or-none response. Theory demonstrates that this ultrasensitivity grows both as a function of inhibitor concentration and increased binding affinity. Although protein sequestration can theoretically generate tunable ultrasensitive responses, this regulatory principle has never been tested experimentally. We used a synthetic genetic circuit in budding yeast to show that sequestration of a basic leucine zipper transcription factor (C/EBPa) by a dominant-negative inhibitor converts a graded transcriptional response into an ultrasensitive response, with apparent Hill coefficients up to 12. We developed a simple quantitative model for this genetic network that demonstrates how the threshold and degree of ultrasensitivity depend upon the abundance of the inhibitor, exactly as observed in our experimental results. Many proteins in natural regulatory networks involve the formation of inactive protein-protein complexes, e.g. stoichiometric inhibitors of kinases and dominant-negative inhibitors of transcription factors. Our results demonstrate that protein sequestration can provide potent and tunable ultrasensitivity in genetic networks. Ultrasensitive or all-or-none responses are critical for robust bistable or oscillatory genetic networks, and our findings suggest that protein sequestration might play an unappreciated role in facilitating the evolution of bistable or oscillatory circuits in natural systems.