

Glycogen Synthase Kinase-3 β Exploits Intracellular Noise to Regulate *Xenopus* Oocyte Maturation

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Many intracellular signal transduction networks rely on strong positive feedback to generate bistable, switchlike behavior. In eukaryotes, bistable switches are embedded within conserved signal transduction networks that specifically execute diverse cellular programs, suggesting that cellular context may impart functional diversity to cellular behaviors that incorporate switching. In the present study, we explore these ideas using *Xenopus* oocyte maturation as a model system. Within individual oocytes, progesterone induces a switchlike, irreversible transition from interphase (immature) to meiosis (mature) by altering the dynamics of a bistable network of intracellular kinases (Ref. 1, Fig. 1). Across oocyte populations, however, the average response to progesterone is remarkably graded. Here, we use a hybrid experimental-computational approach to implicate glycogen synthase kinase 3 β (GSK-3 β) in generating this graded population behavior. We report that inactivation of glycogen synthase kinase-3 β (GSK-3 β) defines a bistable, double-negative feedback loop within mature *Xenopus* oocytes. This loop regulates, but does not replace, the strong positive feedback that generates all-or-none meiotic commitment. Chemical inhibition of GSK-3 β abolishes the characteristic graded response of oocyte populations to progesterone, making it switchlike (Fig. 2). *In vivo*, GSK-3 β executes this control over population behavior in the absence of

extracellular communication; computational modeling shows that GSK-3 β amplifies intracellular noise to increase cell-to-cell variability. These results demonstrate that a bistable switch's composition of feedback can amplify or dampen biological variability, resulting in a population distribution that is specific to the switch's topology. Moreover, these observations suggest that apparently redundant signal transduction motifs may be dispensable for single cell behavior but crucial for establishing higher order organization across populations.

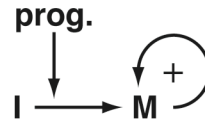


Fig. 1. Simplified model of *Xenopus* oocyte maturation.

Progesterone induces a switchlike transition from interphase (I) to M-phase (M). The all-or-none character of this cell-fate decision is owed to the non-linearity and strong positive feedback present during M-phase. This simple model captures single-cell behavior (Ref. 1) but not population behavior.

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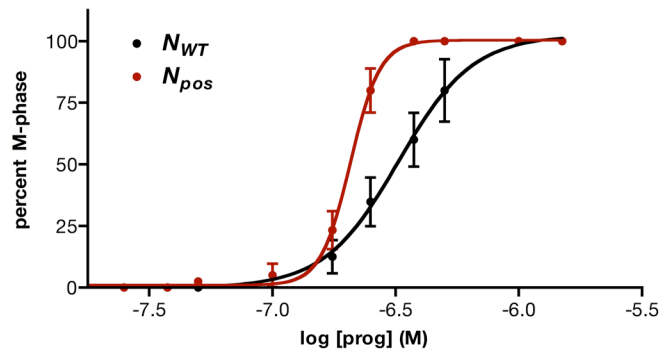
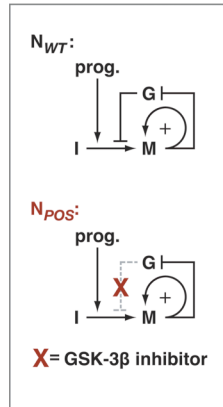


Fig. 2. Small-molecule Inhibition of GSK-3 β reduces cell-to-cell variability in progesterone response. Oocyte populations were incubated with progesterone, then maturation was scored. The black curve reflects the progesterone dose-response of the native system ($n_H=2.9$, $EC_{50}=325\text{nM}$, N_{WT} , depicted in the inset). Small-molecule inhibition of GSK-3 β results in an altered network topology (N_{POS} , the red curve) and concomitant decrease in cell-to-cell variability ($n_H=7.2$, $EC_{50}=207\text{nM}$).

Ref. 1. Ferrell, J.E. Jr. and Machleder, E.M. The biochemical basis of an all-or-non cell fate switch in *Xenopus* oocytes. *Science*, 1998. **280**: p. 895-898; Xiong, W. and Ferrell, J.E. Jr. A positive-feedback-based bistable 'memory module' that governs a cell fate decision. *Nature*, 2003. **426**: p. 460-465.