

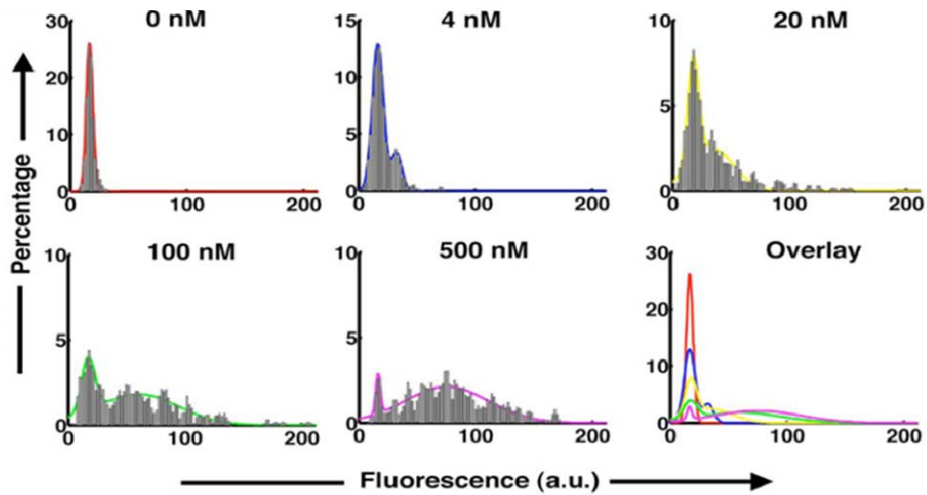
# Mathematical modeling for hybrid gonadotrope biosynthetic response to gonadotropin-releasing hormone

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This paper addresses biosynthetic responses of gonadotropes, which utilizes several signal transduction pathways to mediate gonadotropin-releasing hormone (GnRH)-mediated signaling from brain. These pathways are required for mammalian reproduction, and we have specifically focused on the MAPK signaling pathway which induces phosphorylation of extracellular-regulated kinase (ERK), and *egr1* mRNA and protein production. Experimental studies for the biosynthetic response of the gonadotrope to varying GnRH concentrations showed that the overall average level of ERK activation in populations of cells increased non-cooperatively with increasing GnRH and did not show evidence of either ultra-sensitivity or bistability. However, it is observed from the single-cell responses that individual gonadotropes exhibited two response states, inactive and active, while both the probability of activation and the average response in activated cells increased with increasing GnRH concentration (*cf.* Figure 1). These data indicate a hybrid single-cell response having both digital (switch-like) and analog (graded) features as shown in Figure 2. In order to provide a plausible mechanism for the hybrid response, we have employed mathematical modeling approach based on the detailed kinetic mechanism, and it was found that the hybrid response can be explained by cell-to-cell variations for total concentrations of proteins involved in the signal transduction pathway as well as indirect thresholding of ERK activation resulting from the distributed structure of the GnRH-modulated network. In addition, on the basis of the developed model, we investigated the propagation of cell to cell response variation through this pathway and found that the noise scales in proportion to the average response as observed in the experimental data.

**Figure 1:** Distributions of single-cell pERK responses to varying GnRH concentrations. Fittings of experimental data (solid lines) with two Gaussian distributions are shown. a.u., arbitrary units.



**Figure 2:** Three possible single-cell response models consistent with the signaling and gene induction data. Top, graded (analog) single-cell response pattern with similar responses in all cells. Middle, binary (digital, switch-like) single-cell response with all-or-none responses. Bottom, hybrid digital/analog model with both switching to an active state and varying levels of activation seen with increasing GnRH levels.

