Case Study: Interpreting Flow Cytometry Data with Stochastic Dynamical Models

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RESEARCH ARTICLE Open Access

Emergence of bimodal cell population responses from the interplay between analog single-cell signaling and protein expression noise

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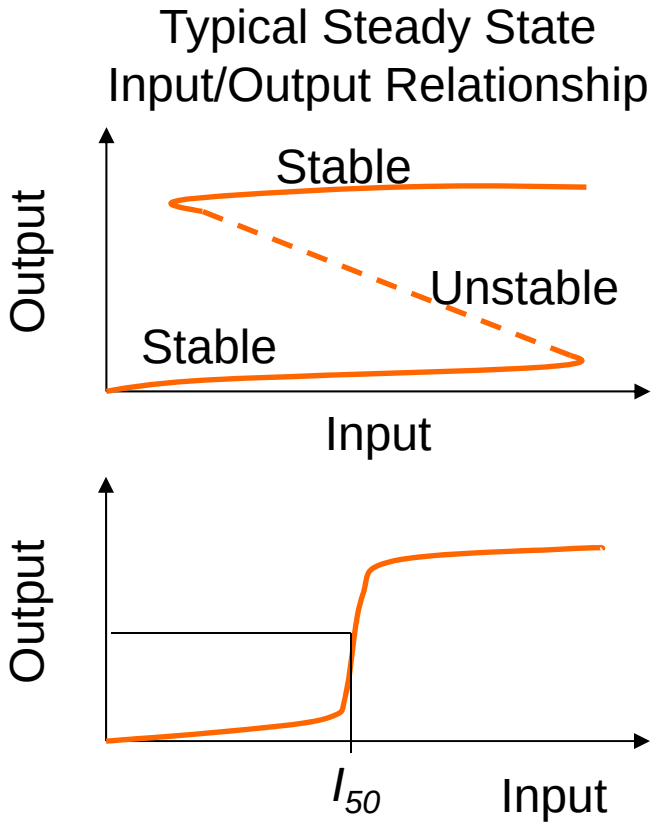
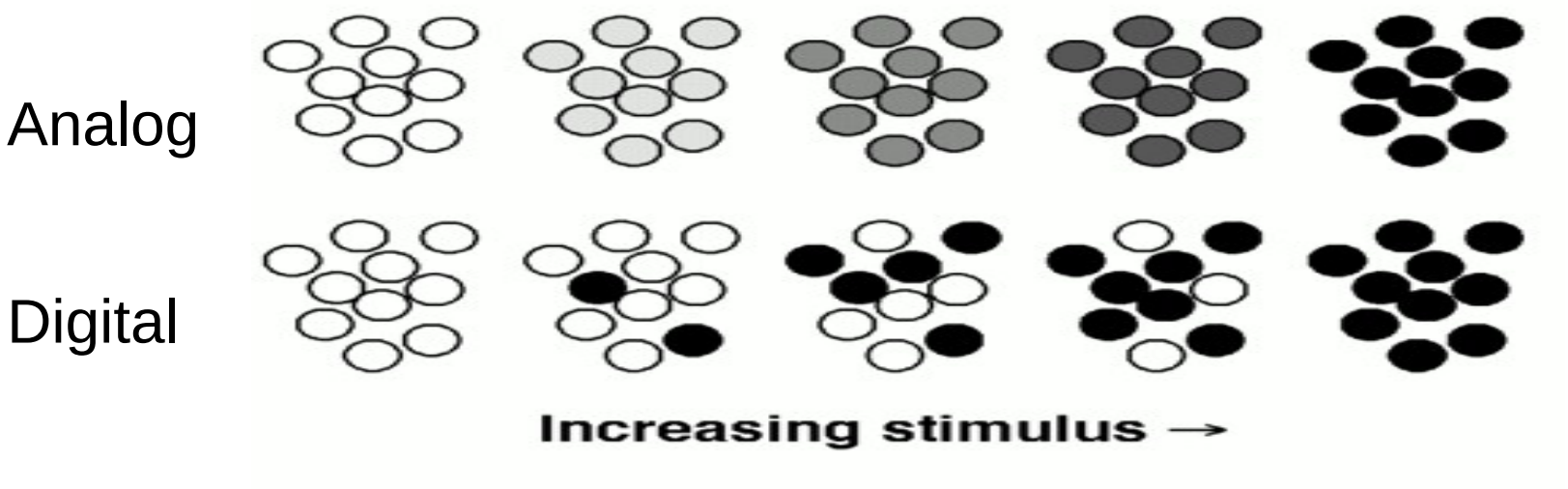
Switch-like Signal Transduction

- Bistable System
  - Hysteresis is a common characteristic
  - Examples:
    - Dual modification cycle (Markevich et al., 2004)
    - Protein modification cycle with “destabilizing feedback” (Ferrell, 2002)
- Ultrasensitive System
  - $$Output = \frac{(Input)^n}{(I_{50})^n + (Input)^n};\ n > 1$$
  - Examples:
    - Saturated enzyme-”Zero-order ultrasensitivity” (Goldbeter et al., 1984)
    - Multi-modification cycles (Goldbeter et al., 1981)

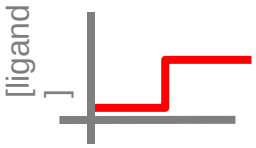


Single Cell Measurements are Needed to Observe Switch-Like Responses

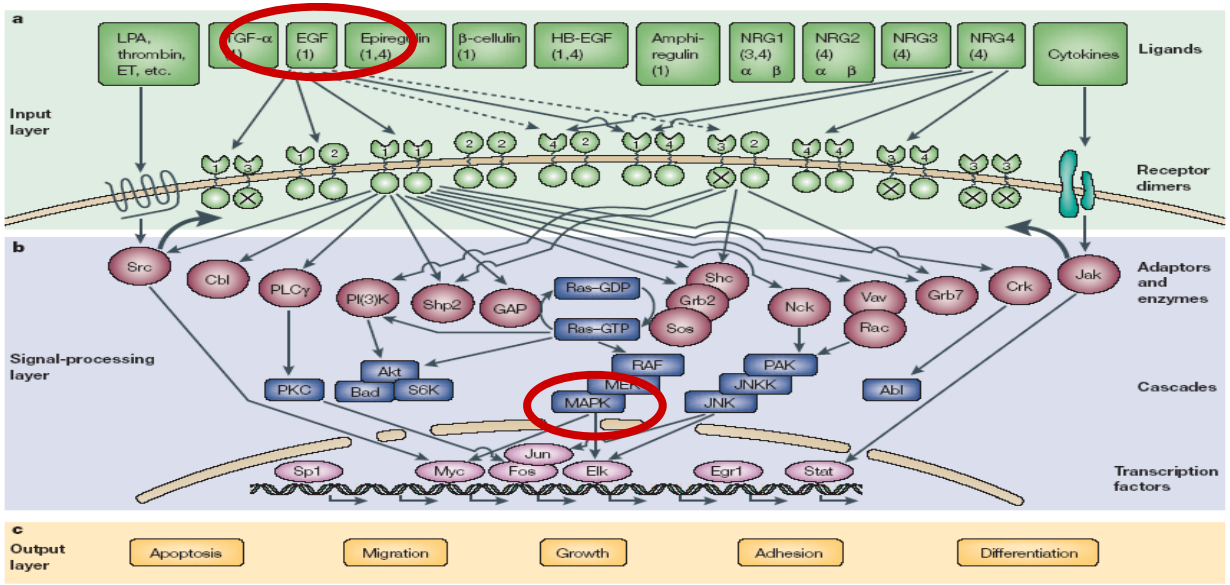


Ferrell and Machleder, 1998. *Science* 280, 895-8

Use Flow Cytometry to Measure Responses in Single Human Embryonic Kidney (HEK) 293 Cells

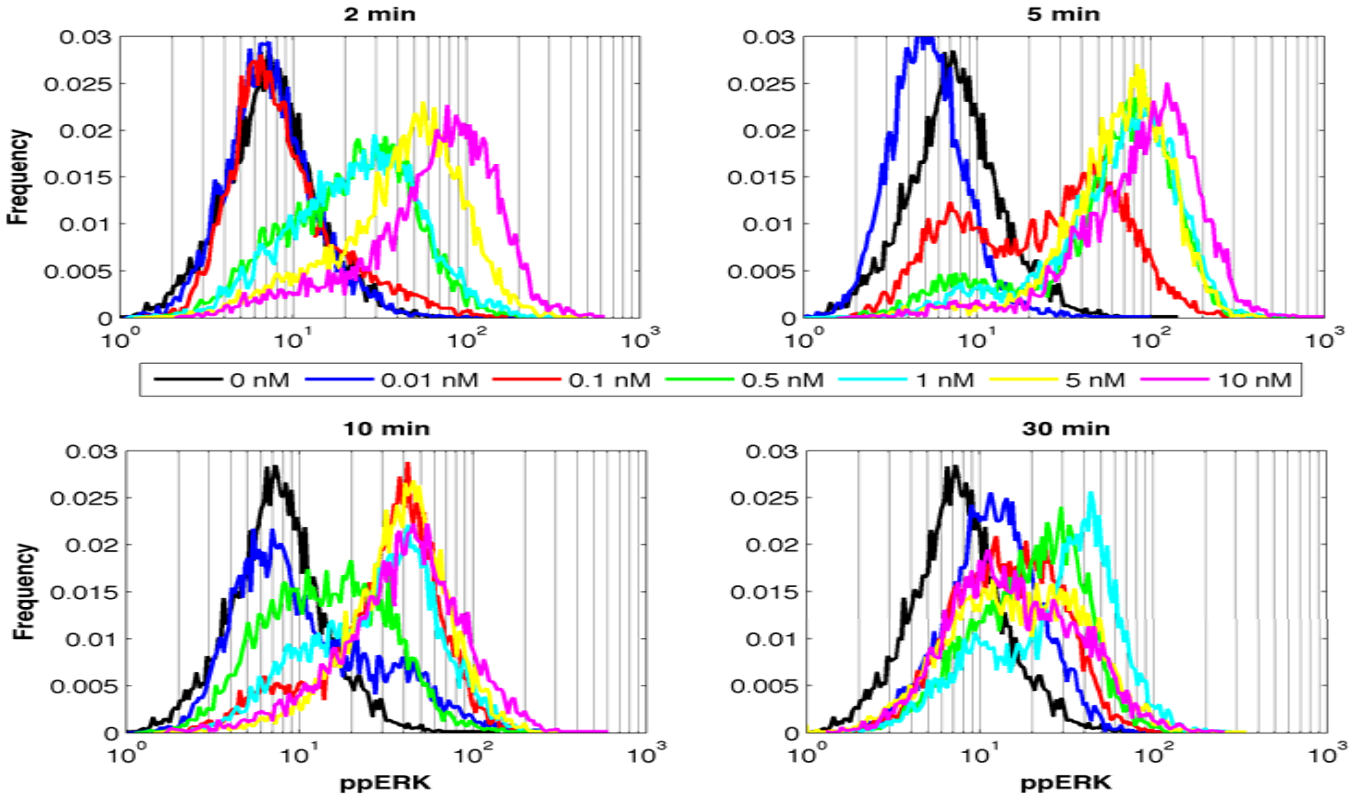


0.01, 0.1, 0.5, 1, 5, 10 nM

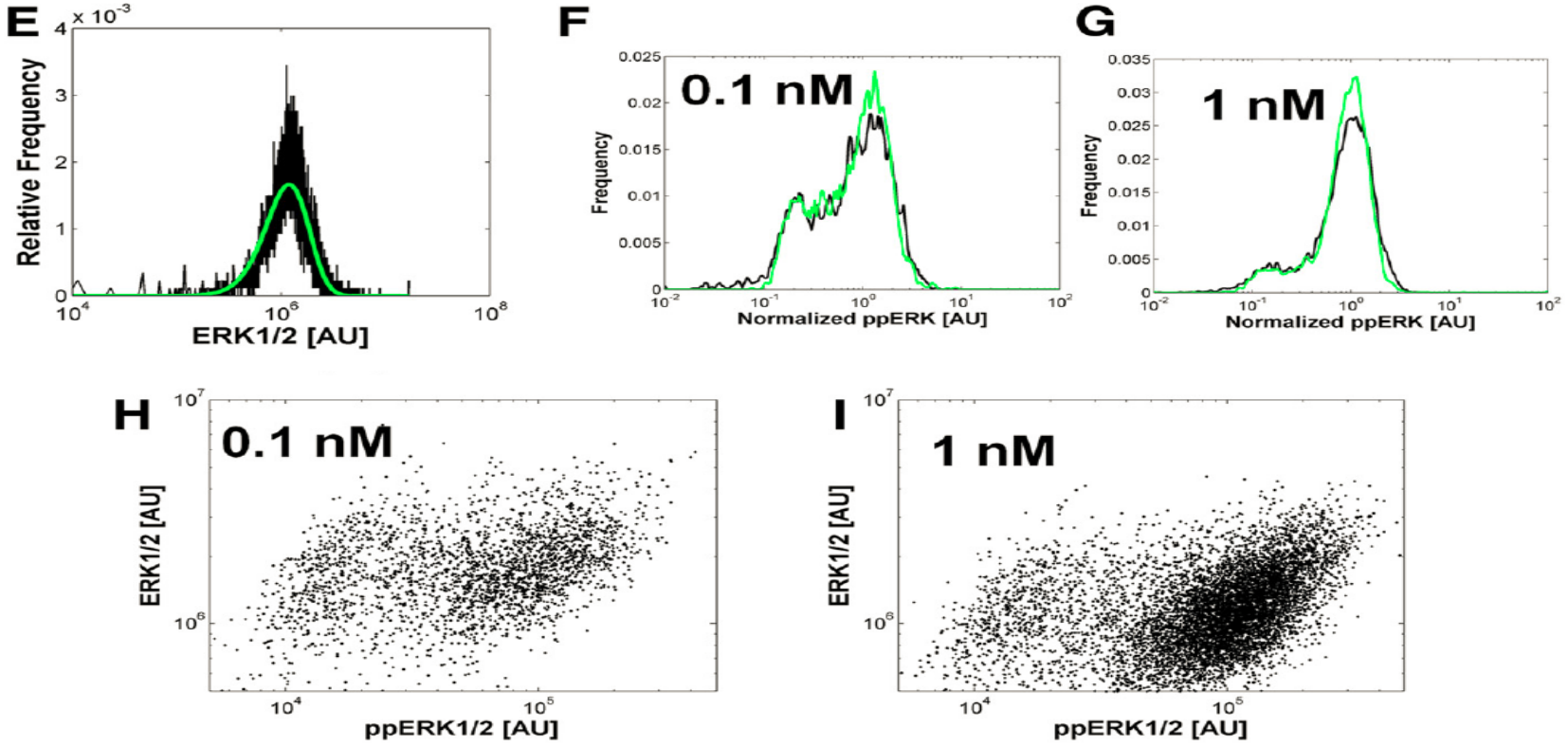


2, 5, 10, 30 min

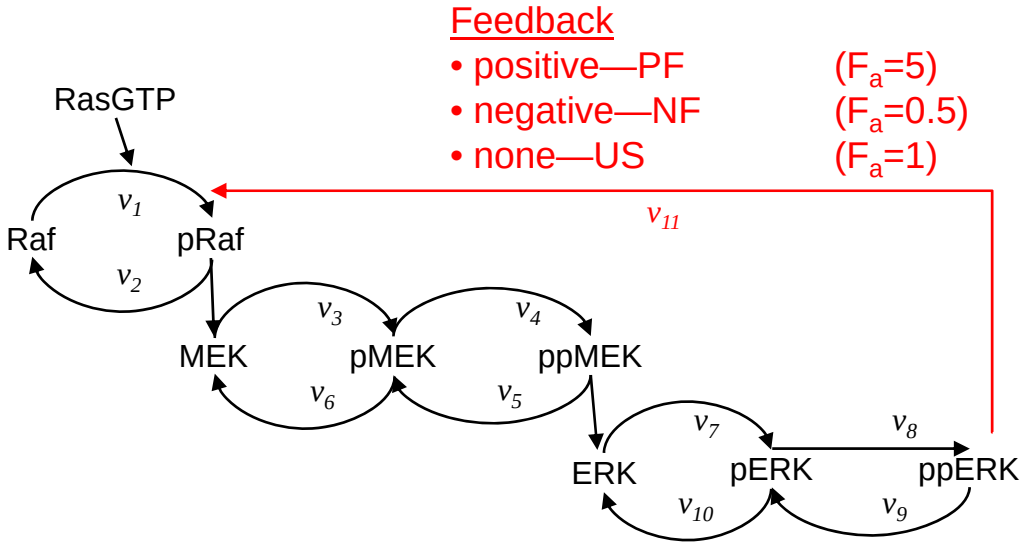
ERK Activation Responses to EGF



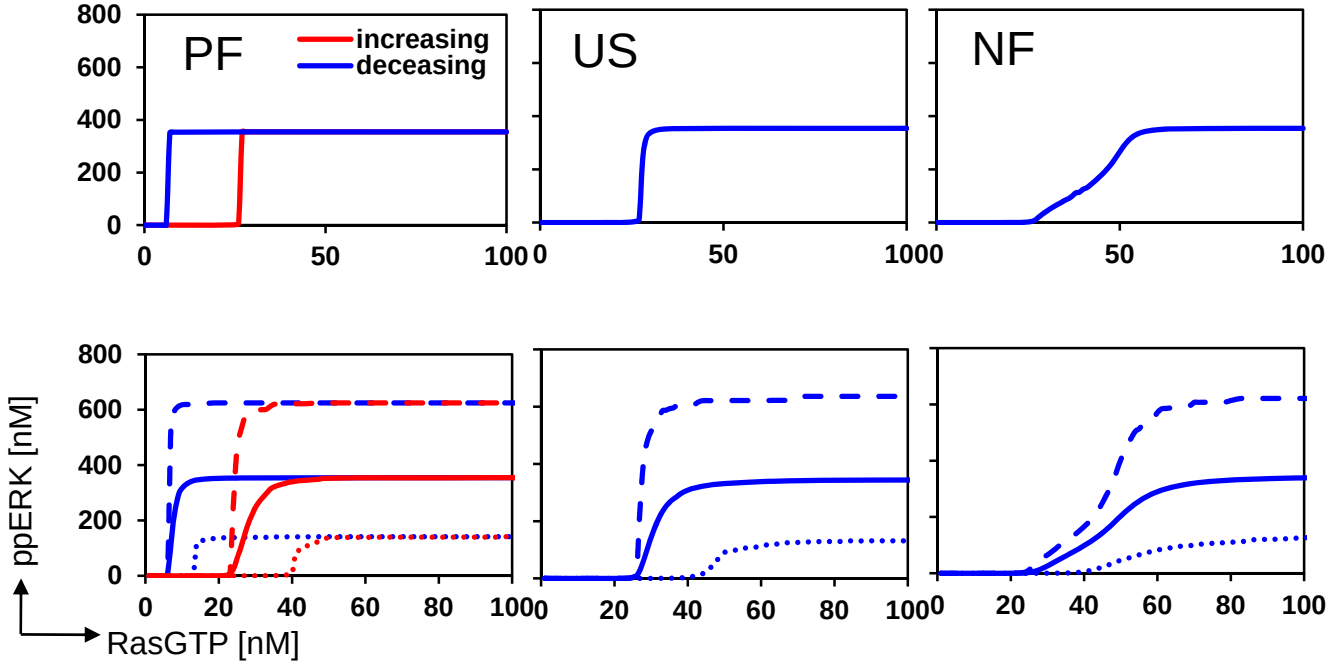
Total ERK Expression Variability Doesn't Cause the Bimodality



What Kind of ERK Cascade Model Can Reproduce This Mixed Analog-Digital Behavior?



Steady-State Dose Responses

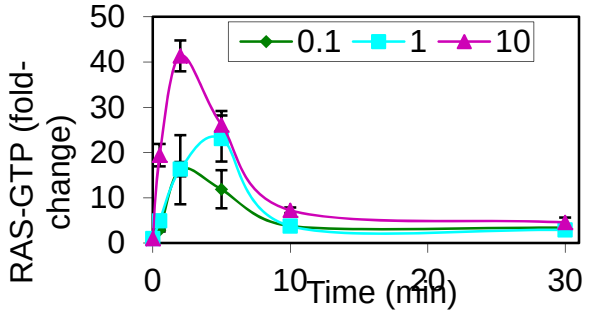


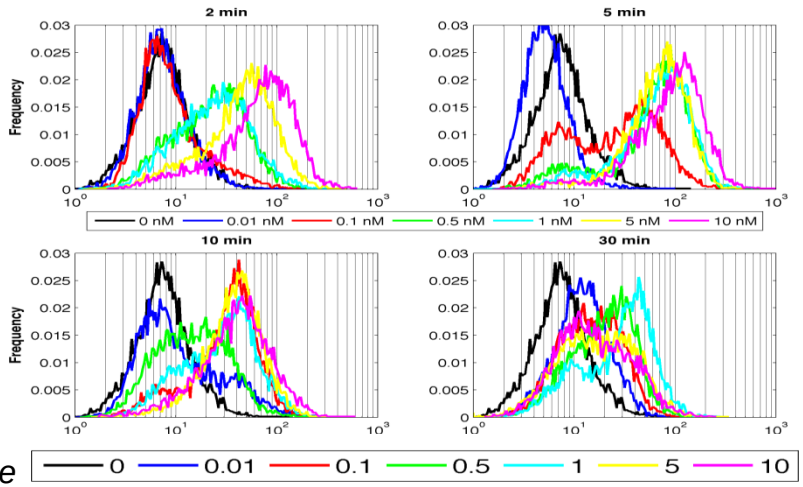
No protein expression noise

Raf, MEK, and ERK levels sampled from a gamma distribution**

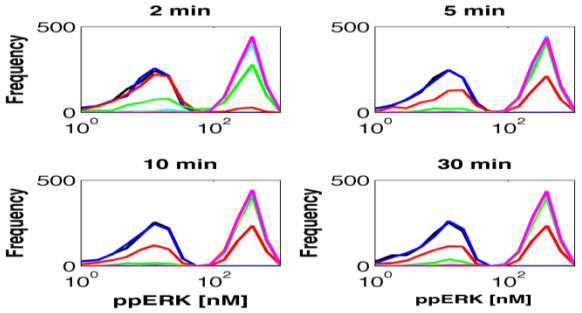
**Birtwistle et al., Mammalian protein expression noise: scaling principles and the implications for knockdown experiments, Mol Biosystems, 2012

Dynamic Responses

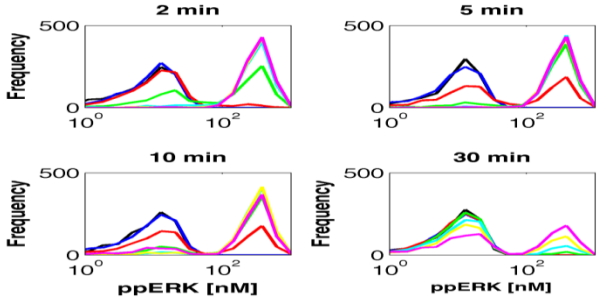




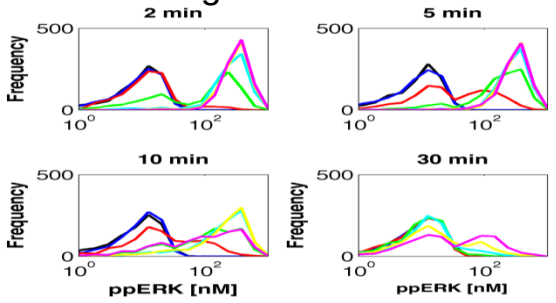
Positive Feedback



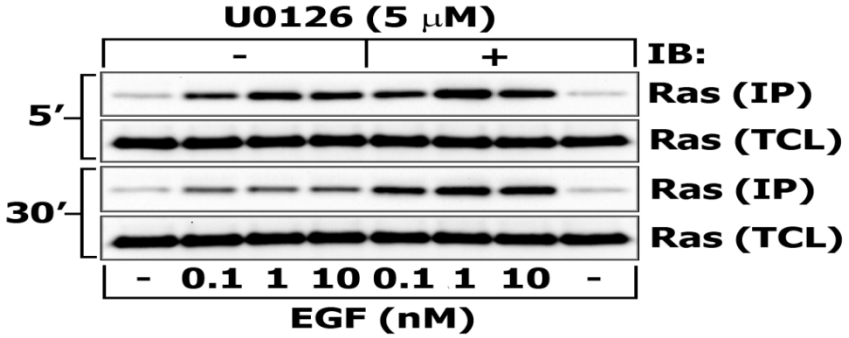
No Feedback



Negative Feedback



Confirming the Negative Feedback Behavior



Mixed Analog-Digital Behavior Arises From Protein Expression Variability Combined Threshold-linear Responses