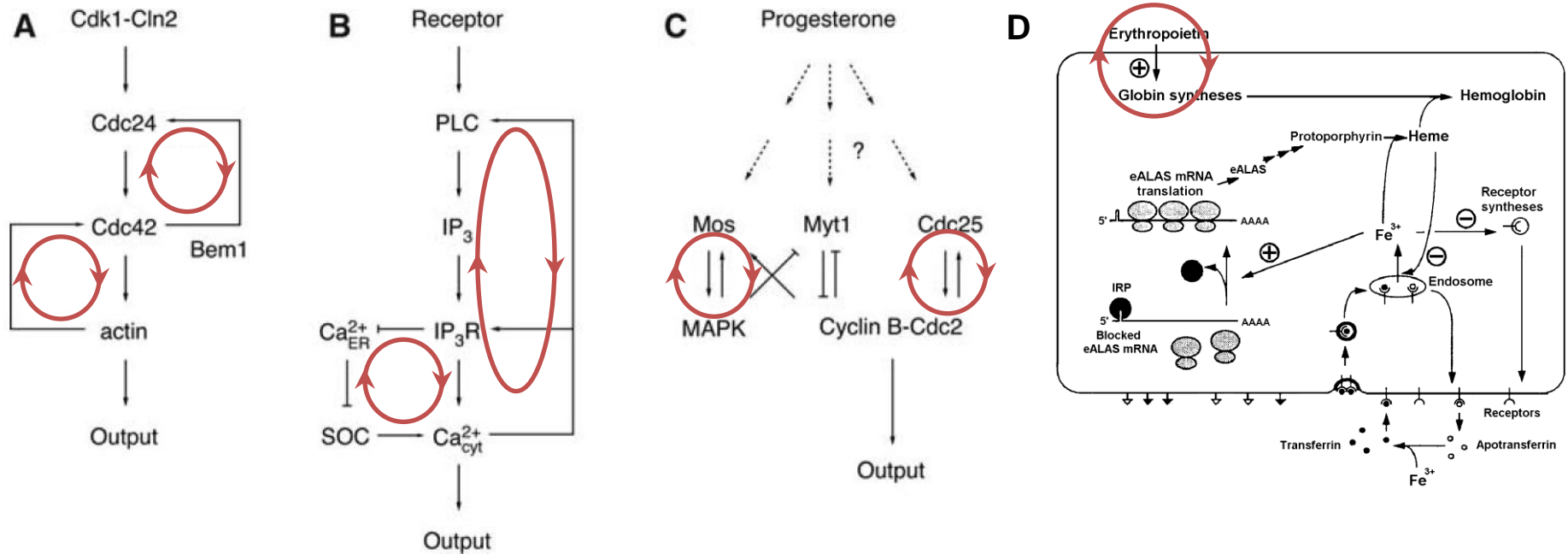


Биомолекулярные системы с асимметричными положительными обратными связями

ASymmetrically Self-UpREgulated (ASSURE) biomolecular systems

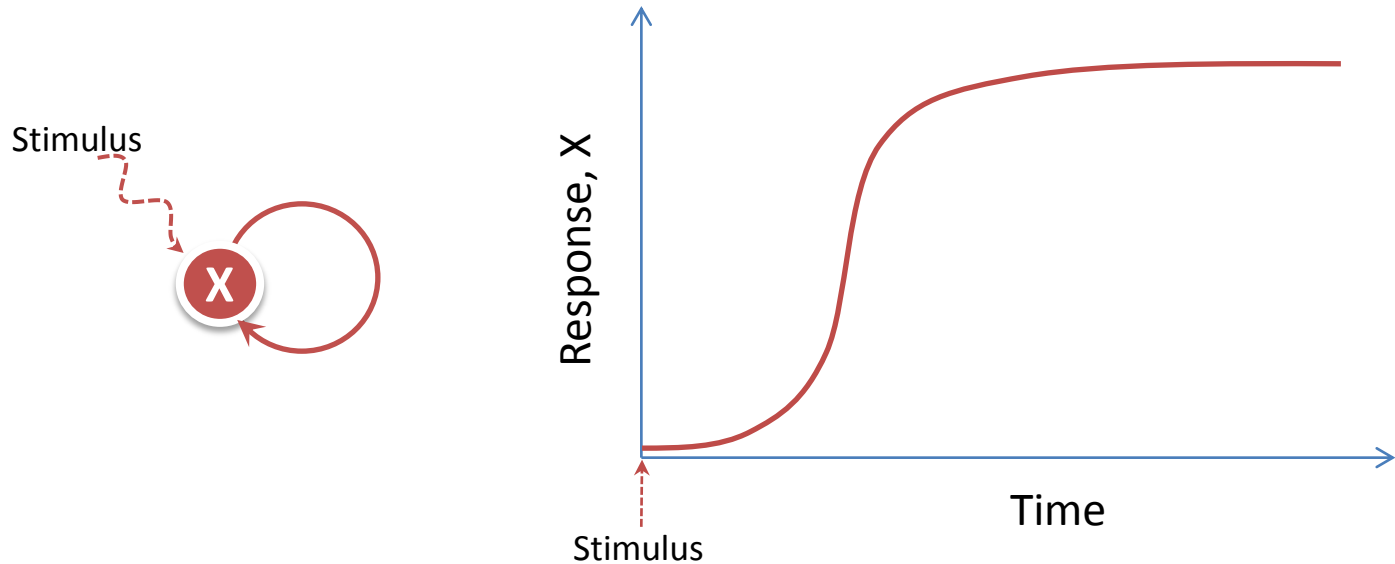
Александр Ратушный

Positive feedback systems



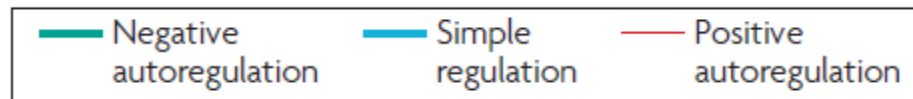
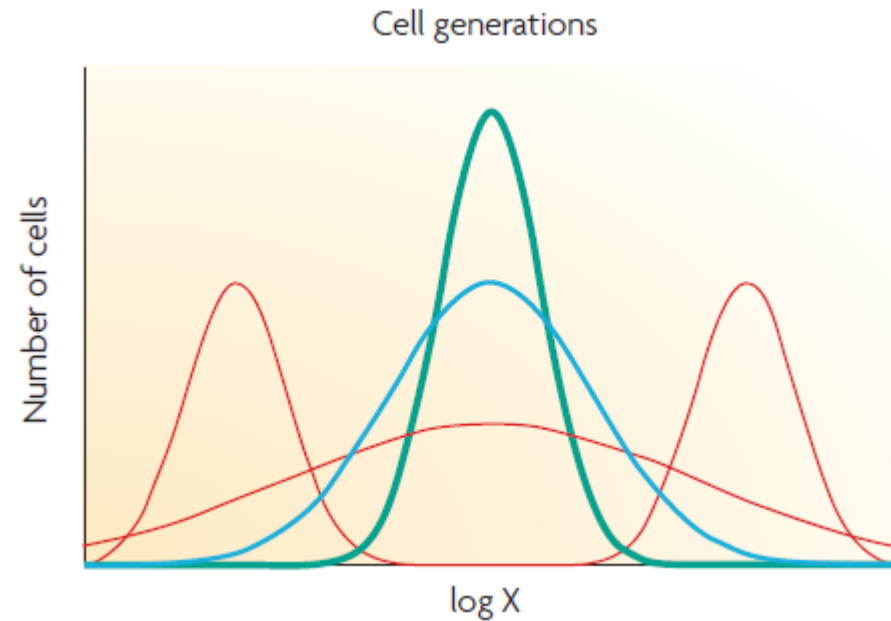
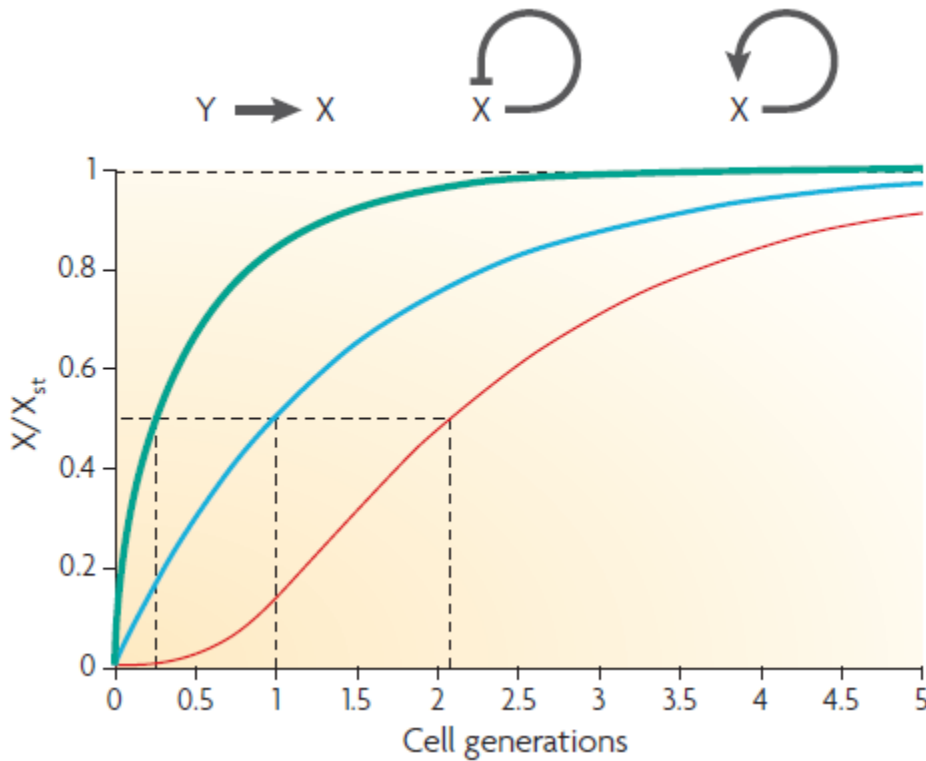
(A) Establishment of polarity in budding yeast. (B) Mammalian calcium signal transduction. (C) Xenopus oocyte maturation. (D) Erythroid cell differentiation.

Positive feedback systems



In positive feedback systems, input signals trigger a chain of signaling or regulatory events, which loop back and amplify the system response.

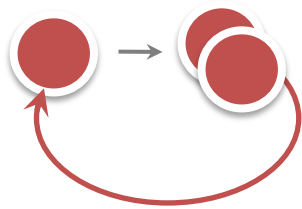
Positive vs. negative feedback systems



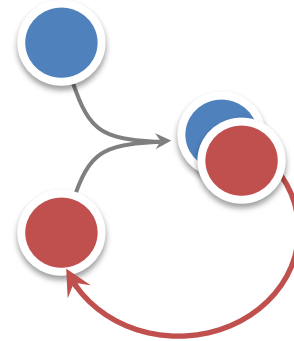
Positive feedback system characteristics

- Positive feedback is one of the main causes of **instability** in dynamical systems.
- Positive feedback **amplifies** changes in state and is the force behind population explosions.
- Positive feedback can also create unstable **breakpoints** or **thresholds** in dynamical systems.

Asymmetry in positive feedback systems



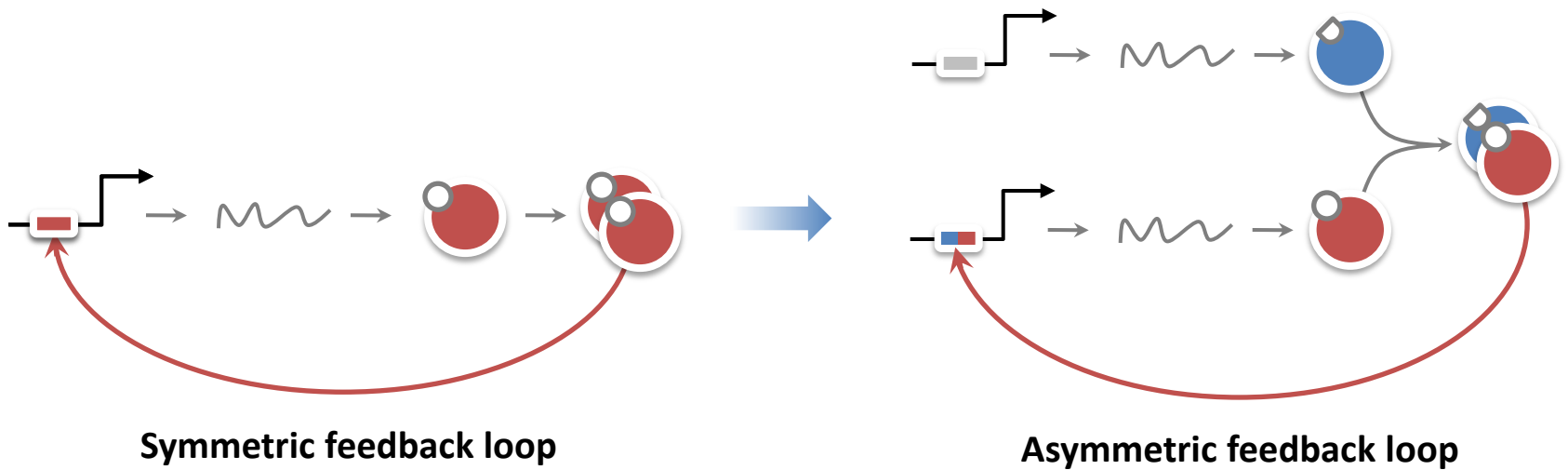
Symmetric feedback loop



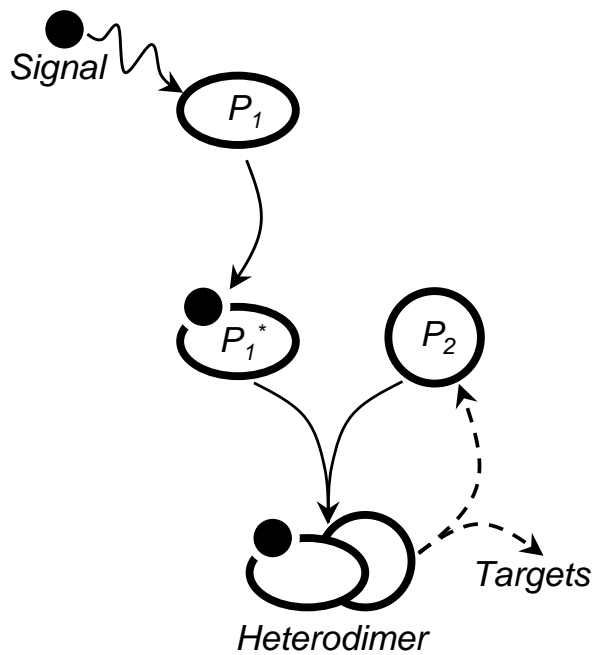
Asymmetric feedback loop

ASymmetric Self-UpREgulation (**ASSURE**) network motif

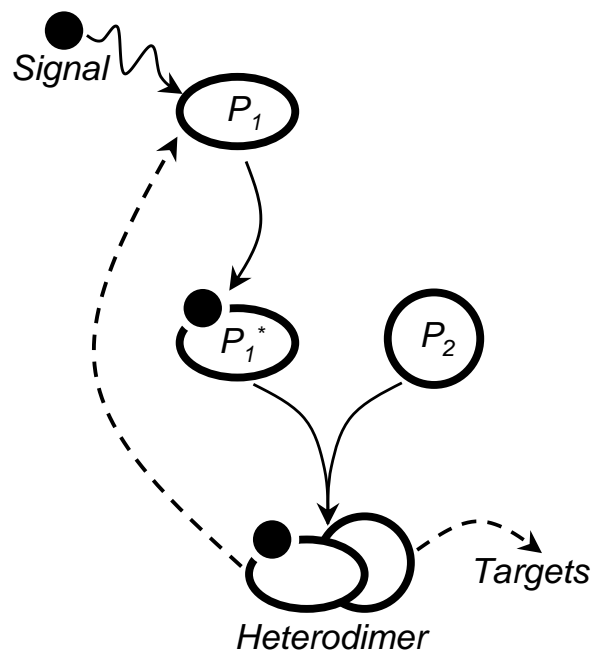
Possible evolution of positive feedback systems



ASSURE I&II

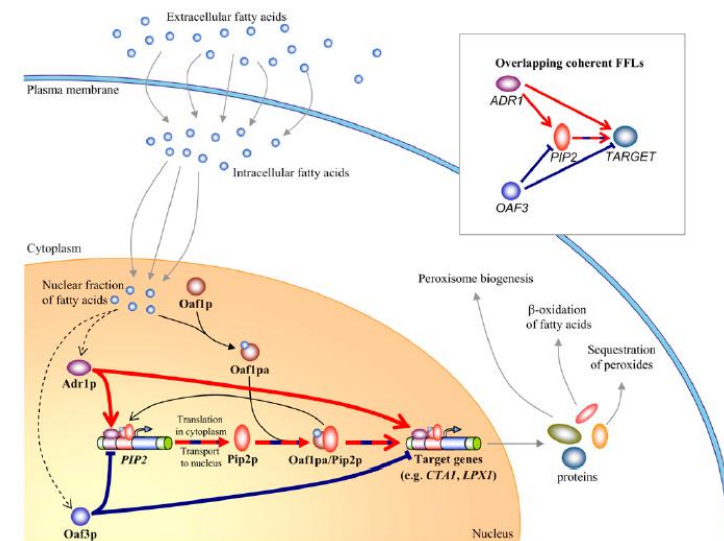
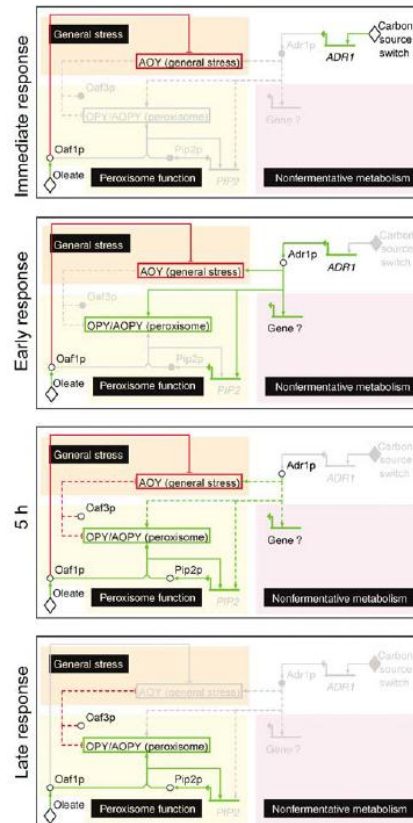
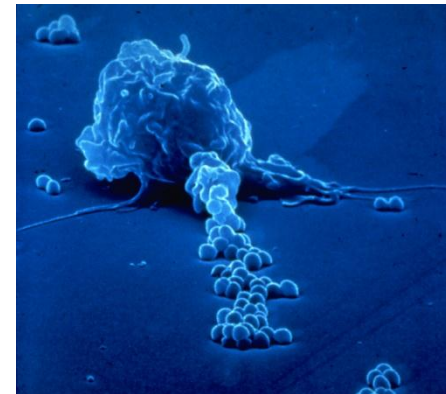
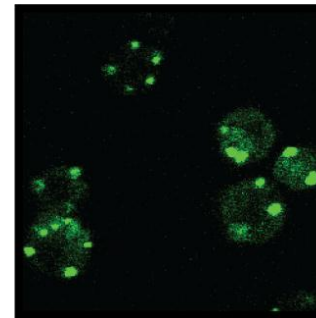
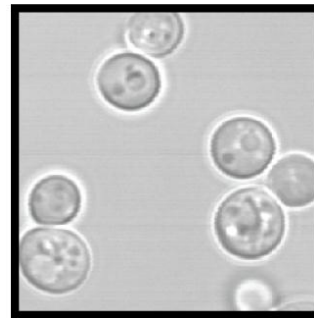
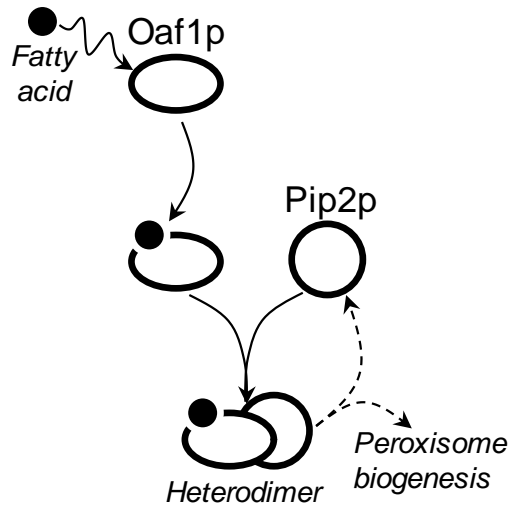


ASSURE I



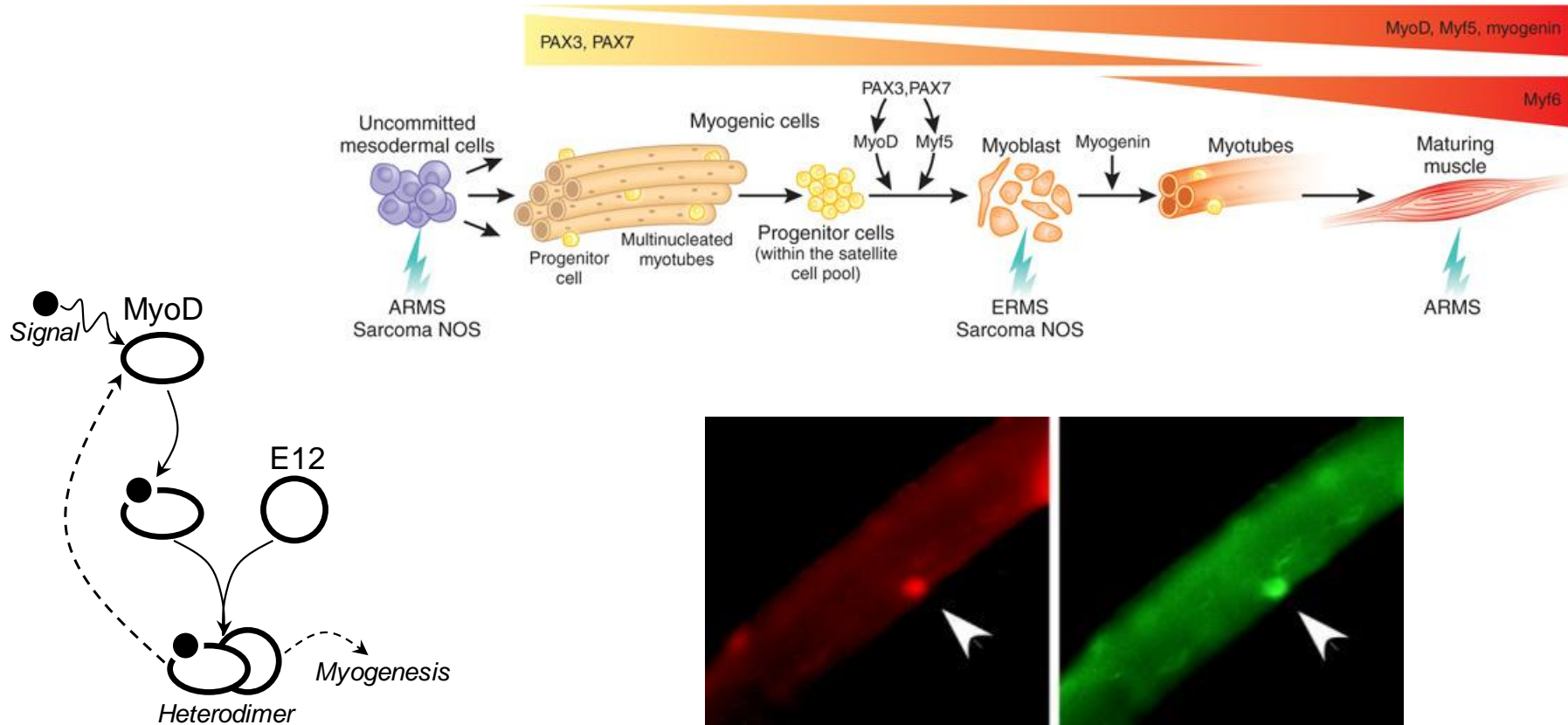
ASSURE II

Fatty acid response and peroxisome biogenesis in *S. cerevisiae*



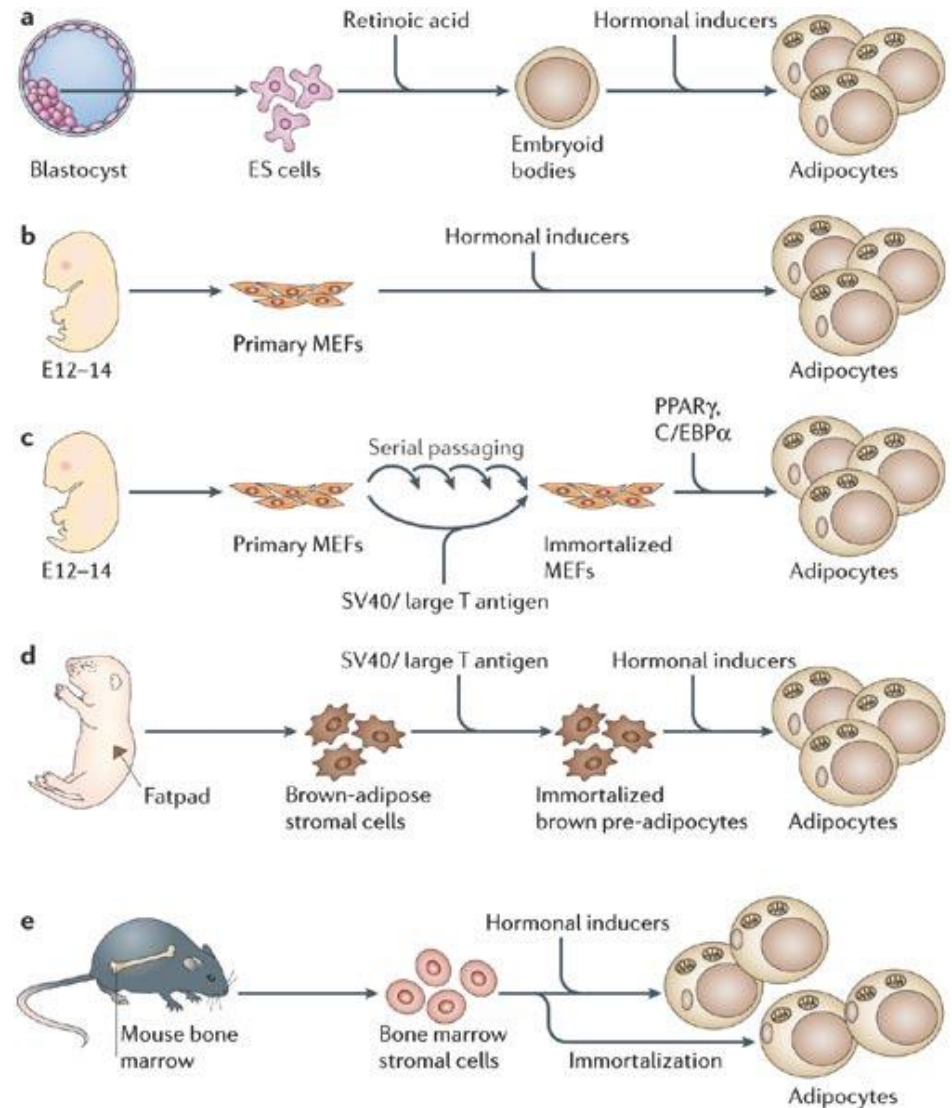
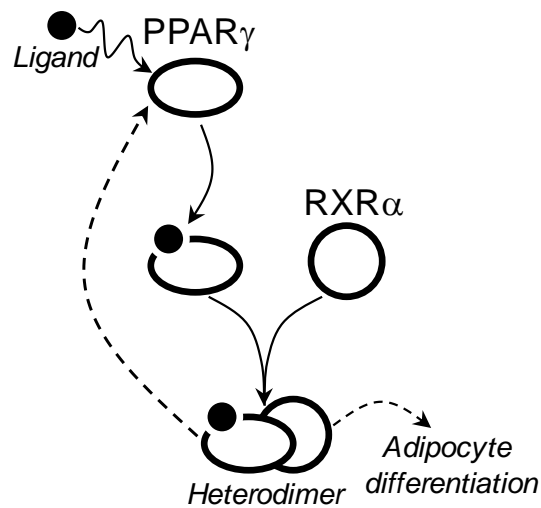
Smith et al., 2007
Ratushny et al., 2008
Saleem et al., 2010

Myogenesis



Benayoun et al., 1998
 Hettmer and Wagers, 2010
 Zhang, K., et al. 2010

Adipocyte differentiation

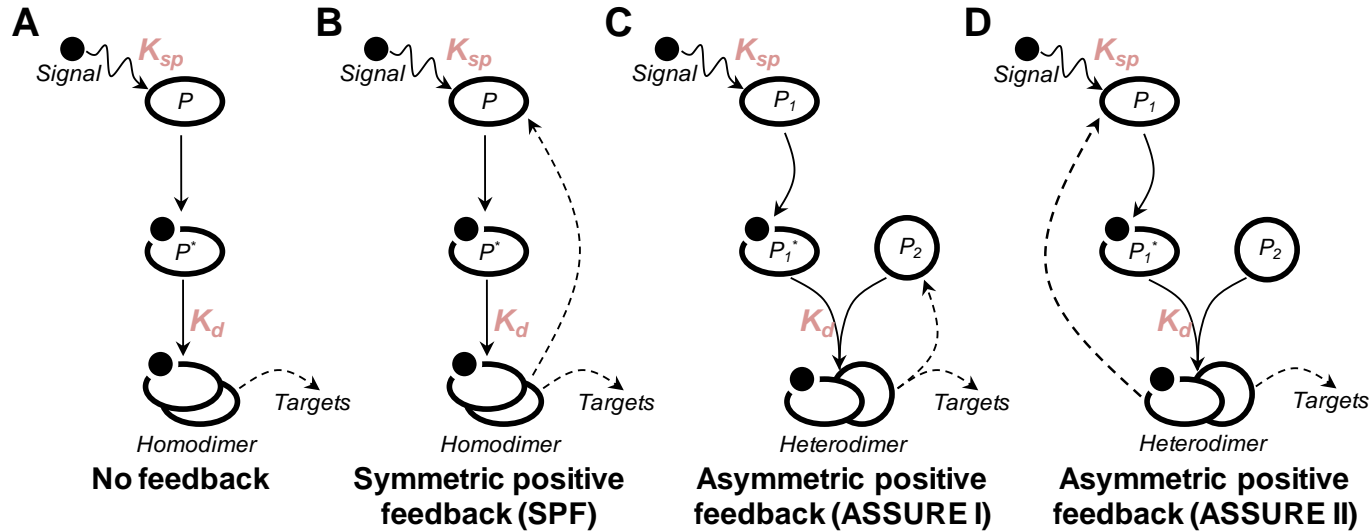


Examples of regulatory networks with the ASSURE motif

System	Asymmetric positive feedback
Fatty-acid-response and peroxisome biogenesis in budding yeast	Fatty-acid + Oaf1p → Oaf1p* Oaf1p* + Pip2p → heterodimer → upregulation of PIP2 gene
Adipocyte differentiation	Agonist + PPAR γ → PPAR γ * PPAR γ * + RXR α → heterodimer → upregulation of PPAR γ gene
Cholesterol homeostasis in human macrophages	Agonist + LXR α → LXR α * LXR α * + RXR α → heterodimer → upregulation of LXR α gene
Early development and differentiation (human)	Agonist + RAR β → RAR β * RAR* + RXR → heterodimer → upregulation of RAR gene
Early development and differentiation (mice)	Agonist + RAR → RAR* RAR* + RXR → heterodimer → upregulation of RAR gene
Early development and differentiation (zebrafish)	Agonist + RAR → RAR* RAR* + RXR → heterodimer → upregulation of RAR gene
Cellular antiviral defense	Signal/virus + IRF3 → IRF3* Signal/virus + IRF7 → IRF7* IRF3* + IRF7* → heterodimer → upregulation of IFN β gene → IFN β → STAT1, STAT2 and IRF9 → upregulation of IRF7 gene
Myogenesis	Signal + MyoD → MyoD* MyoD* + E12 → heterodimer → upregulation of MyoD gene
Control of the synaptic plasticity in Drosophila	Signal + Fos → Fos* Signal + Jun → Jun* Fos* + Jun* → heterodimer → upregulation of CREB gene CREB → upregulation of CREB and Fos genes
Filamentous growth regulation in yeast	Signal (low nitrogen, butanol, etc.) + Tec1 → Tec1* Signal + Ste12 → Ste12* Tec1* + Ste12* → upregulation of TEC1 gene (and filamentous genes)
Cell proliferation and growth (Myc system)	Myc -- miRNA-22 -- MYCBP → Myc+MAX → upregulation of target genes
Antioxidant response (HepG2 cells)	ROS → KEAP1-Nrf2 → Nrf2 → Nrf2-small Maf → upregulation of p62 expression → p62 level → upregulation of Nrf2 expression
Response to xenobiotics: reduction of arsenic-induced cytotoxicity (HeLa cells)	iAsIII → Nrf2 activation (KEAP1-Nrf2 → Nrf2) → Nrf2-small Maf → Upregulation of HO-1 expression → HO-1 level → Upregulation of Nrf2 expression
White-opaque phenotypic switching in Candida albicans	Signal (loss of the mating type locus heterozygosity) → Wor1; Wor1 + Mcm1 → upregulation of WOR1 and other target genes (induction of the white-opaque phenotypic switching)
Cell cycle (G ₁ → S phase transition) and tumor suppression control	E2F1 + DP1 → E2F1-DP1 E2F1-DP1 + pRB → pRB-E2F1-DP1 Growth stimulatory signals → pRB-E2F1-DP1 → E2F1-DP1 + pRB → upregulation of E2F1 gene

What are predominant features that may be responsible for **evolutionary advantages** of the **ASSURE** network motif and its consequent **widespread** use in biology?

Mathematical models



$$\text{A: } \frac{d\gamma}{dt} = k_s f_{d(d(s,P,K_{sp}), d(s,P,K_{sp}), K_d)} - k_u \gamma, \forall \gamma \in \{Target\}$$

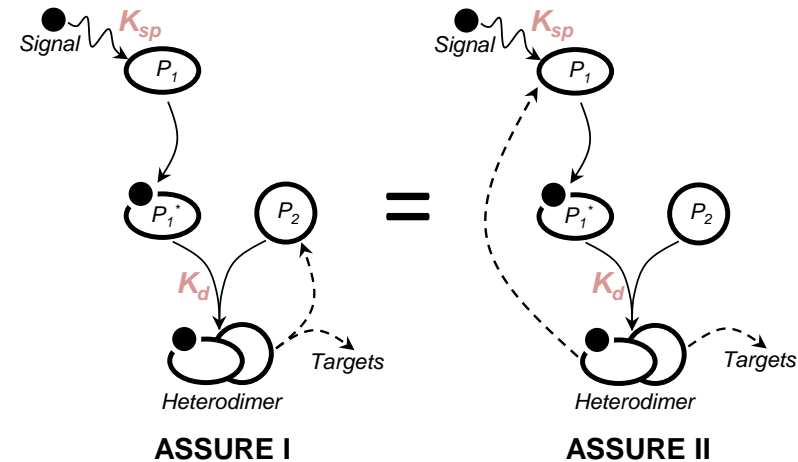
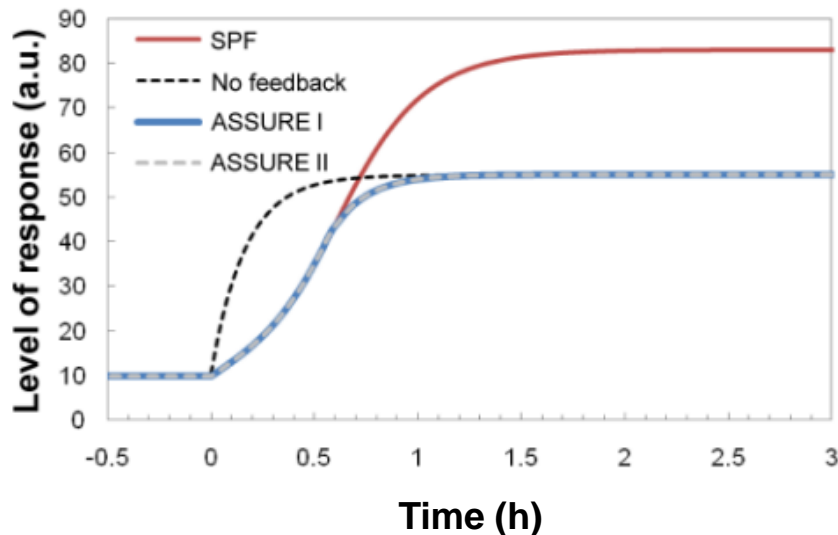
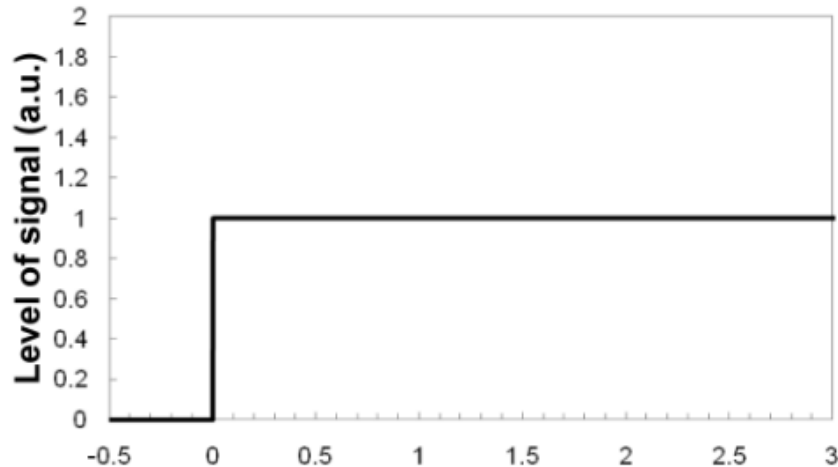
$$\text{B: } \frac{d\gamma}{dt} = k_s f_{d(d(s,P,K_{sp}), d(s,P,K_{sp}), K_d)} - k_u \gamma, \forall \gamma \in \{P, Target\}$$

$$\text{C: } \frac{d\gamma}{dt} = k_s f_{d(d(s,P_1,K_{sp}), P_2, K_d)} - k_u \gamma, \forall \gamma \in \{P_2, Target\}$$

$$\text{D: } \frac{d\gamma}{dt} = k_s f_{d(d(s,P_1,K_{sp}), P_2, K_d)} - k_u \gamma, \forall \gamma \in \{P_1, Target\}$$

$$\text{where } f_x = \frac{k_0 + \left(\frac{x}{k_a}\right)^h}{1 + \left(\frac{x}{k_a}\right)^h}, \quad d(y, z, K) = \frac{K}{2} \left(1 + \frac{y+z}{K} - \sqrt{\left(1 + \frac{y+z}{K}\right)^2 - \frac{4yz}{K^2}} \right)$$

Equivalence condition for the ASSURE I&II responses



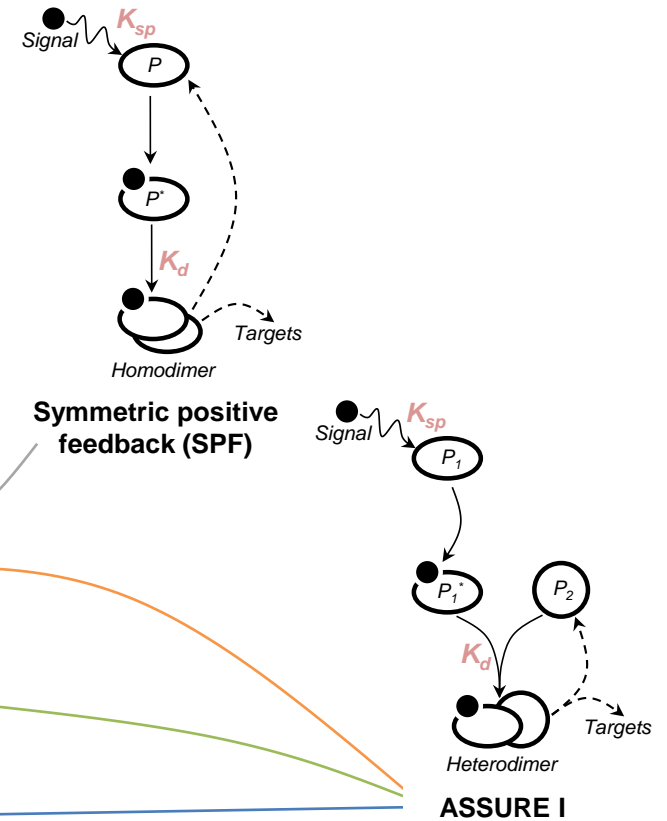
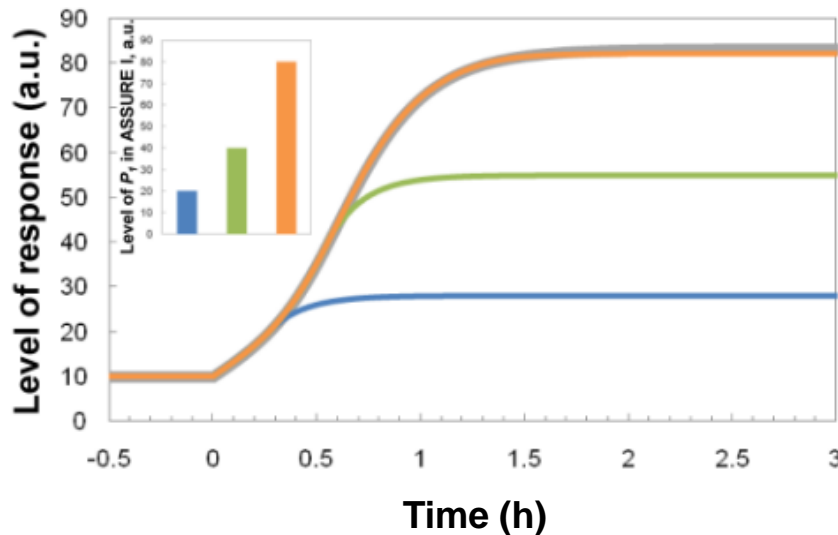
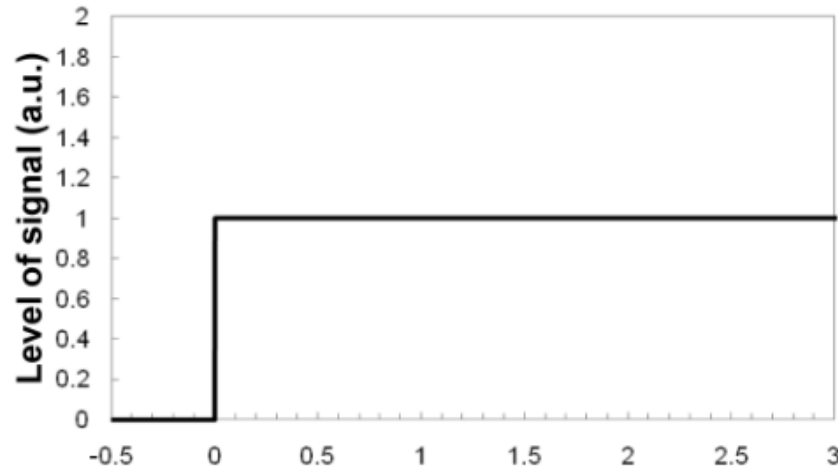
$Signal \gg P_1$ and/or $K_{sp} \rightarrow 0$
 typical physiological conditions

$K_{sp} = 1.65 \times 10^{-8}$ M for Oaf1/oleate

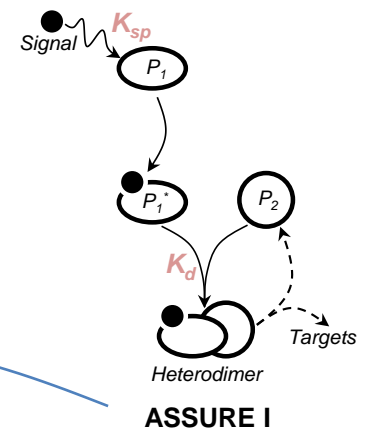
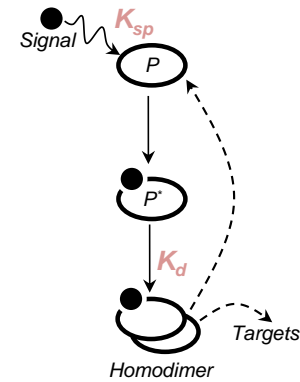
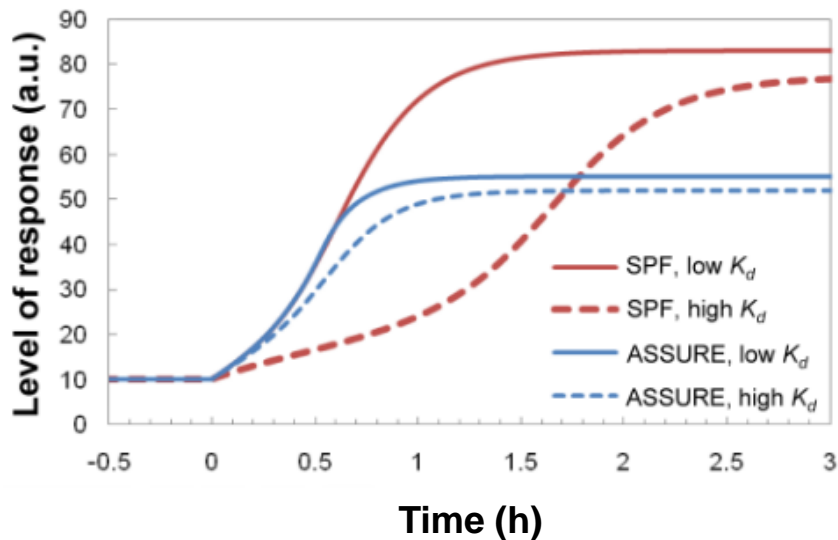
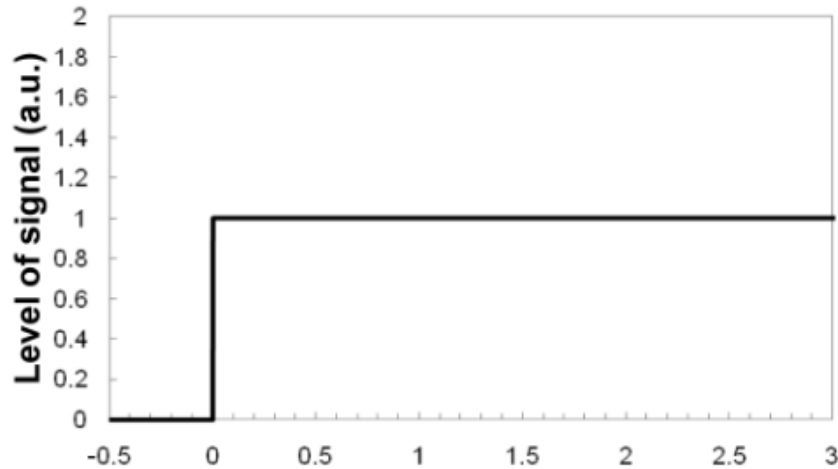
$K_{sp} = 1.33 \times 10^{-7}$ M for PPAR γ /nitrolinoleic acid

$K_{sp} = 1.33 \times 10^{-7}$ M for LXR α and 22(R)-hydroxycholesterol

ASSURE precisely controls the response level



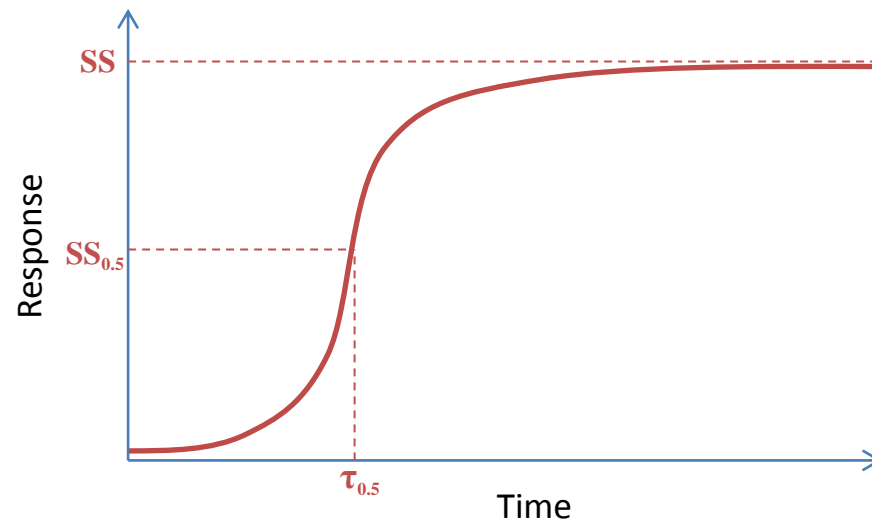
ASSURE is robust to parameter changes



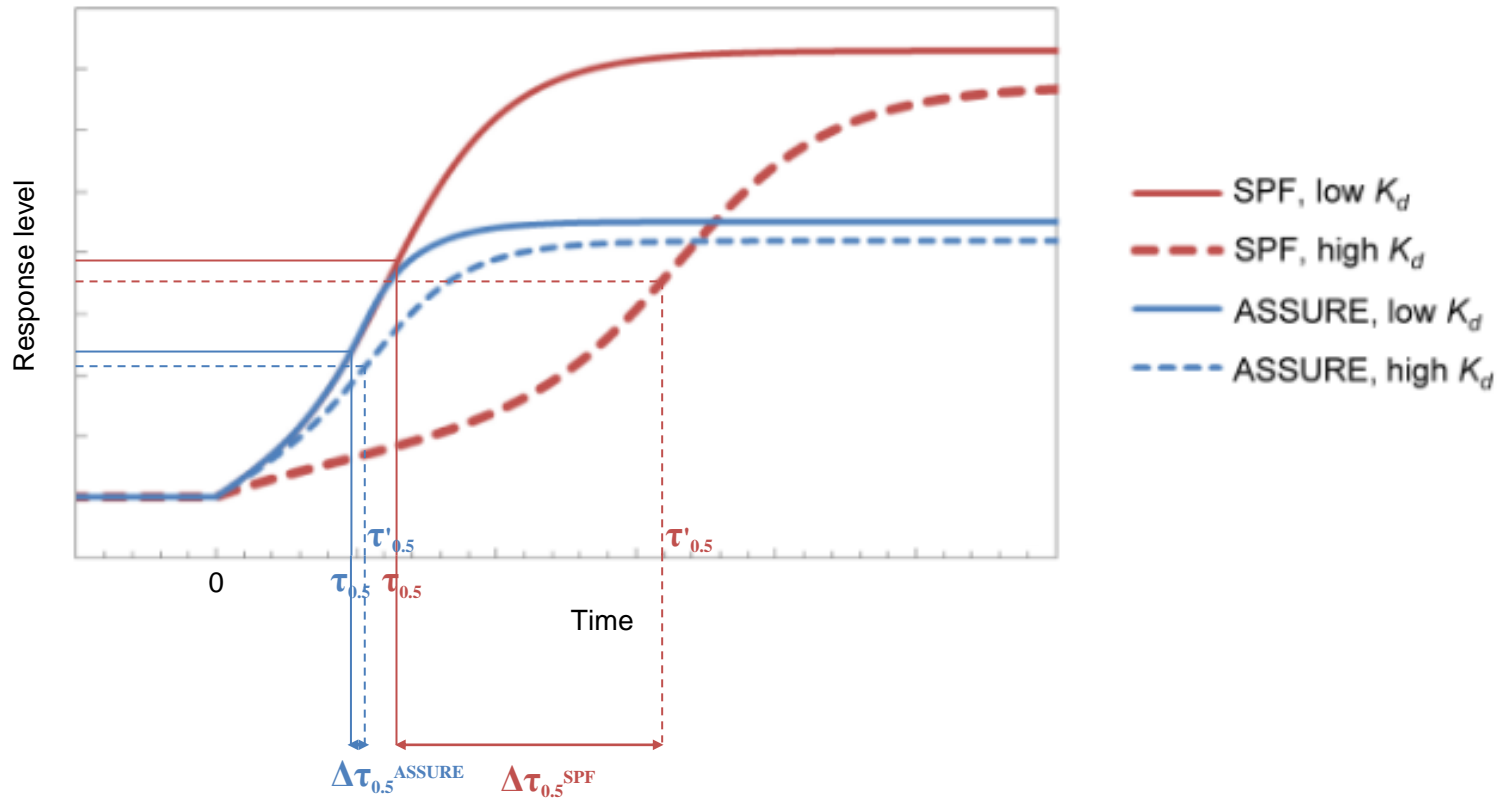
low $K_d = 10^{-5}$ a.u. and high $K_d = 1$ a.u.

$Signal \gg P_1$ and/or $K_{sp} \rightarrow 0$

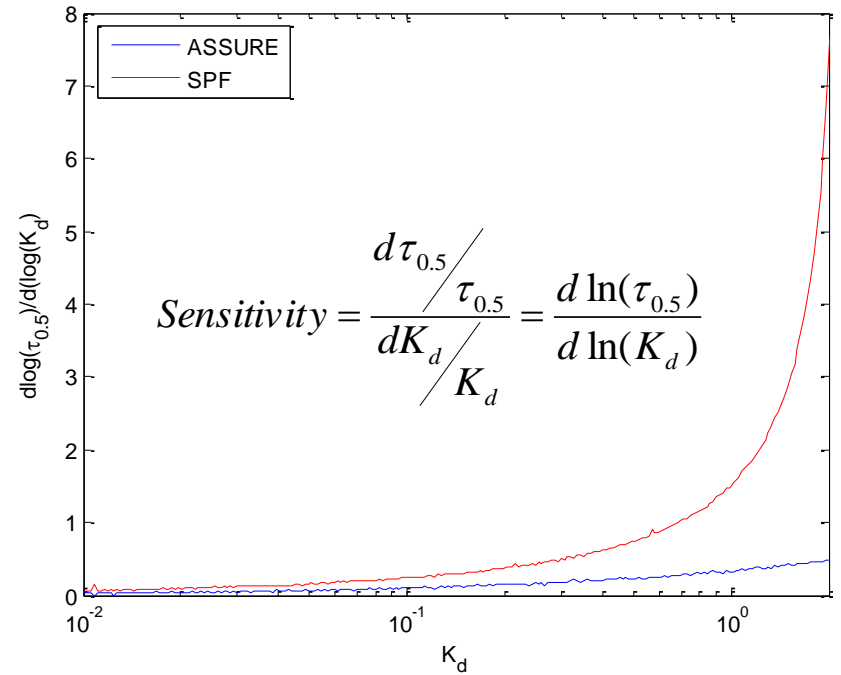
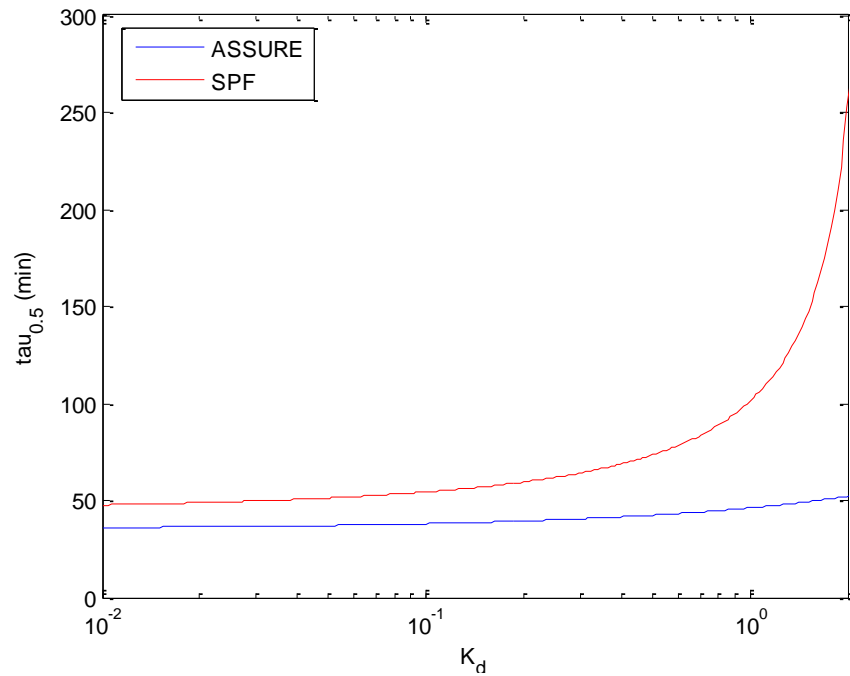
Response time ($\tau_{0.5}$)



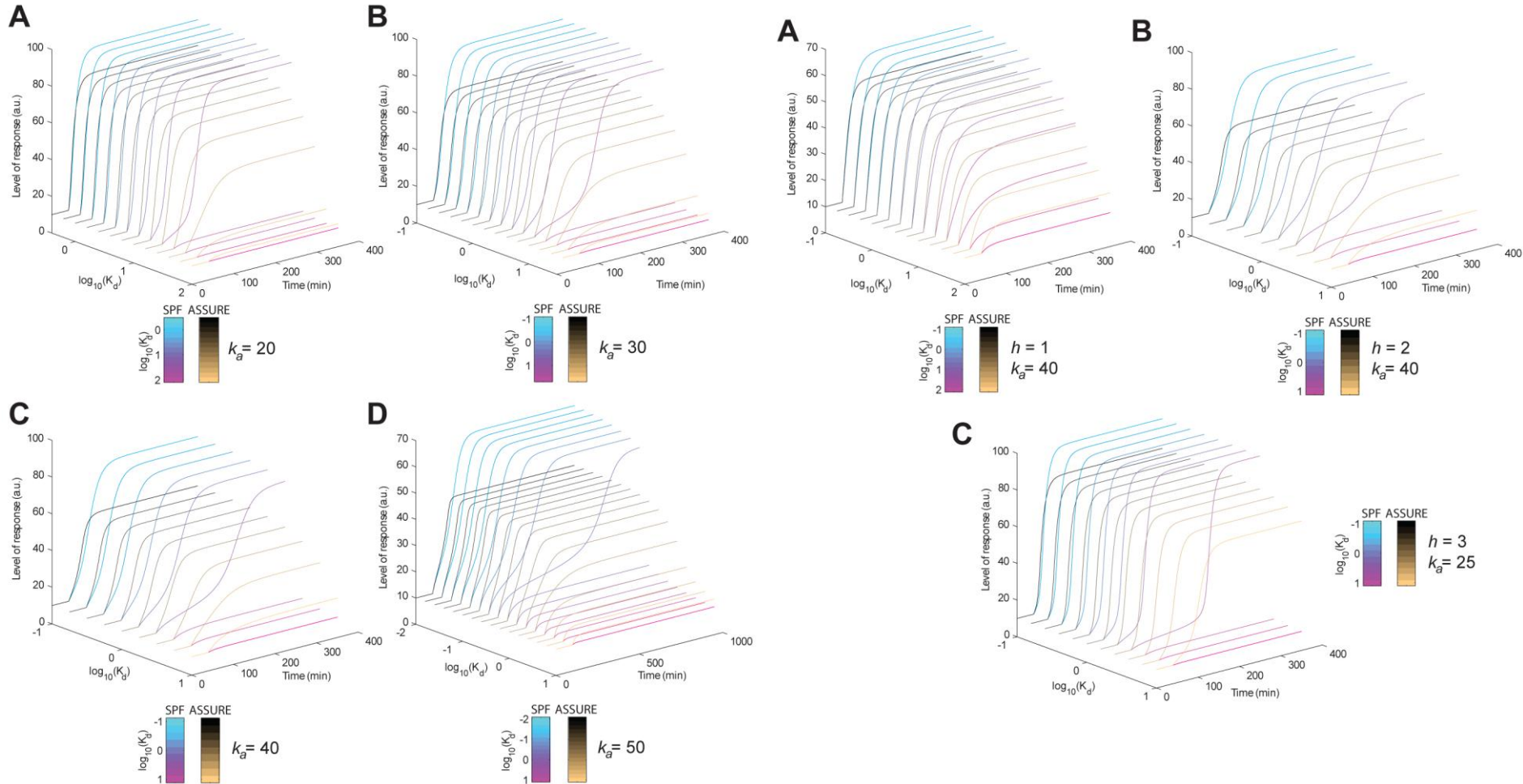
Response time of the ASSURE and SPF systems



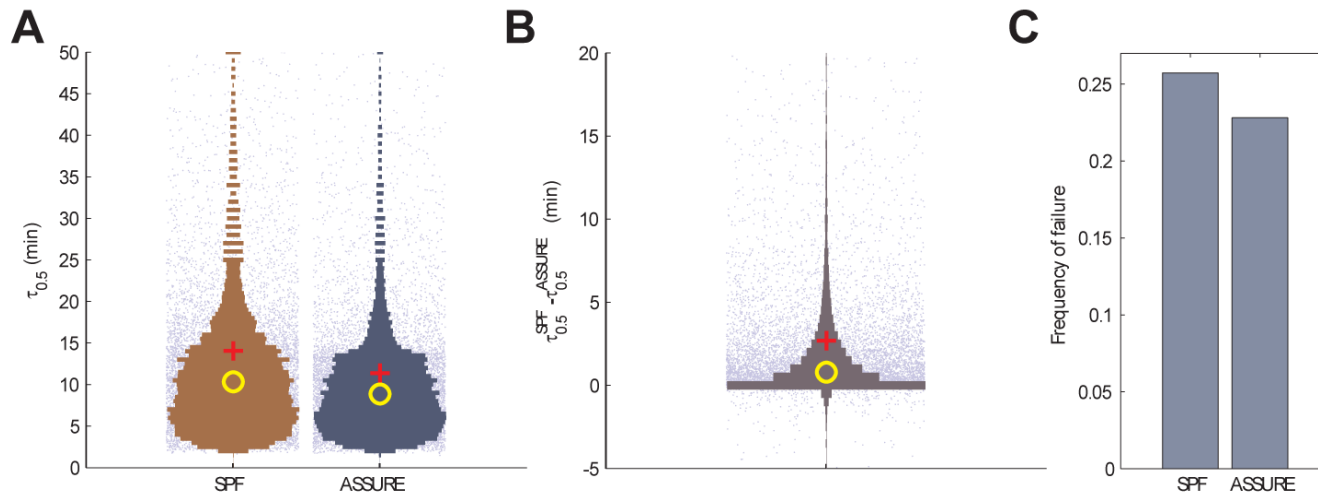
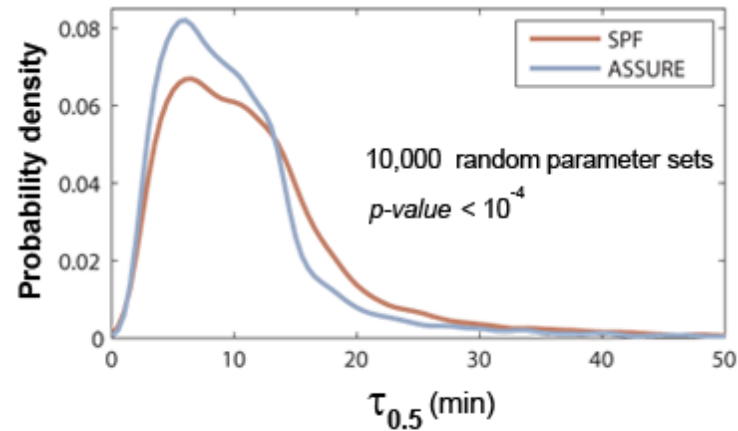
Sensitivity analysis of the ASSURE and SPF responses



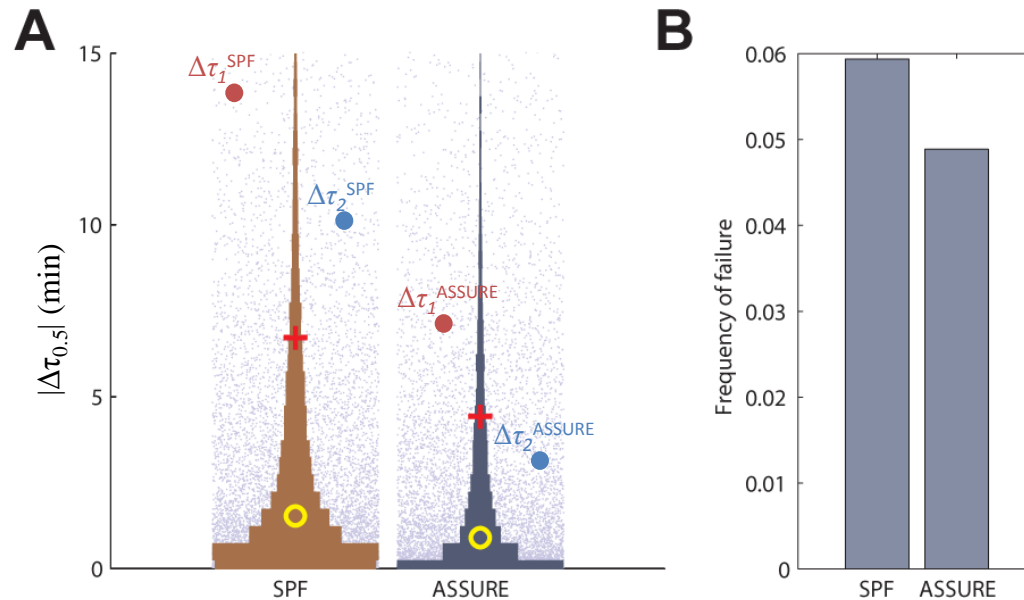
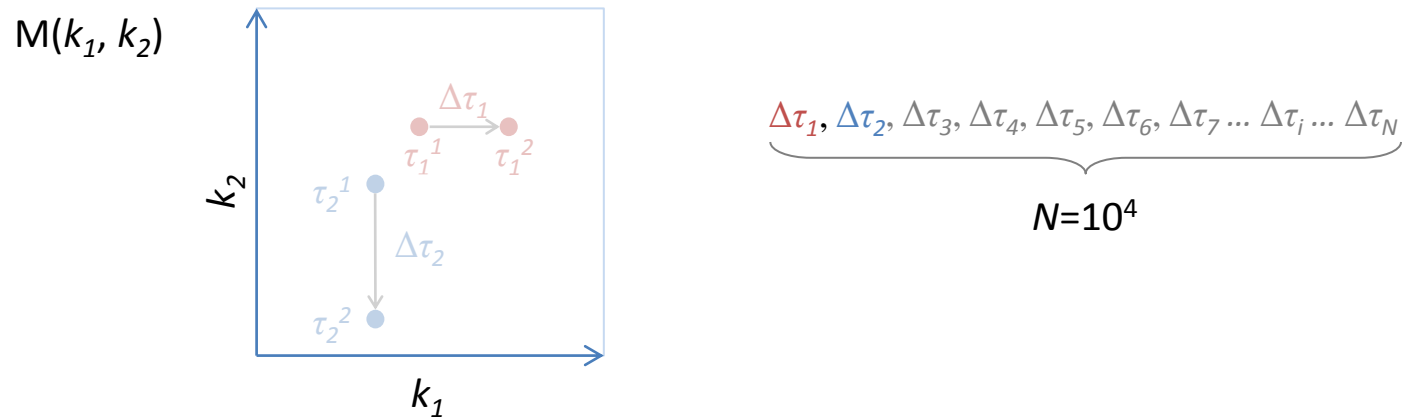
Exploration of the effects of changing multiple model parameters on the SPF and ASSURE temporal responses



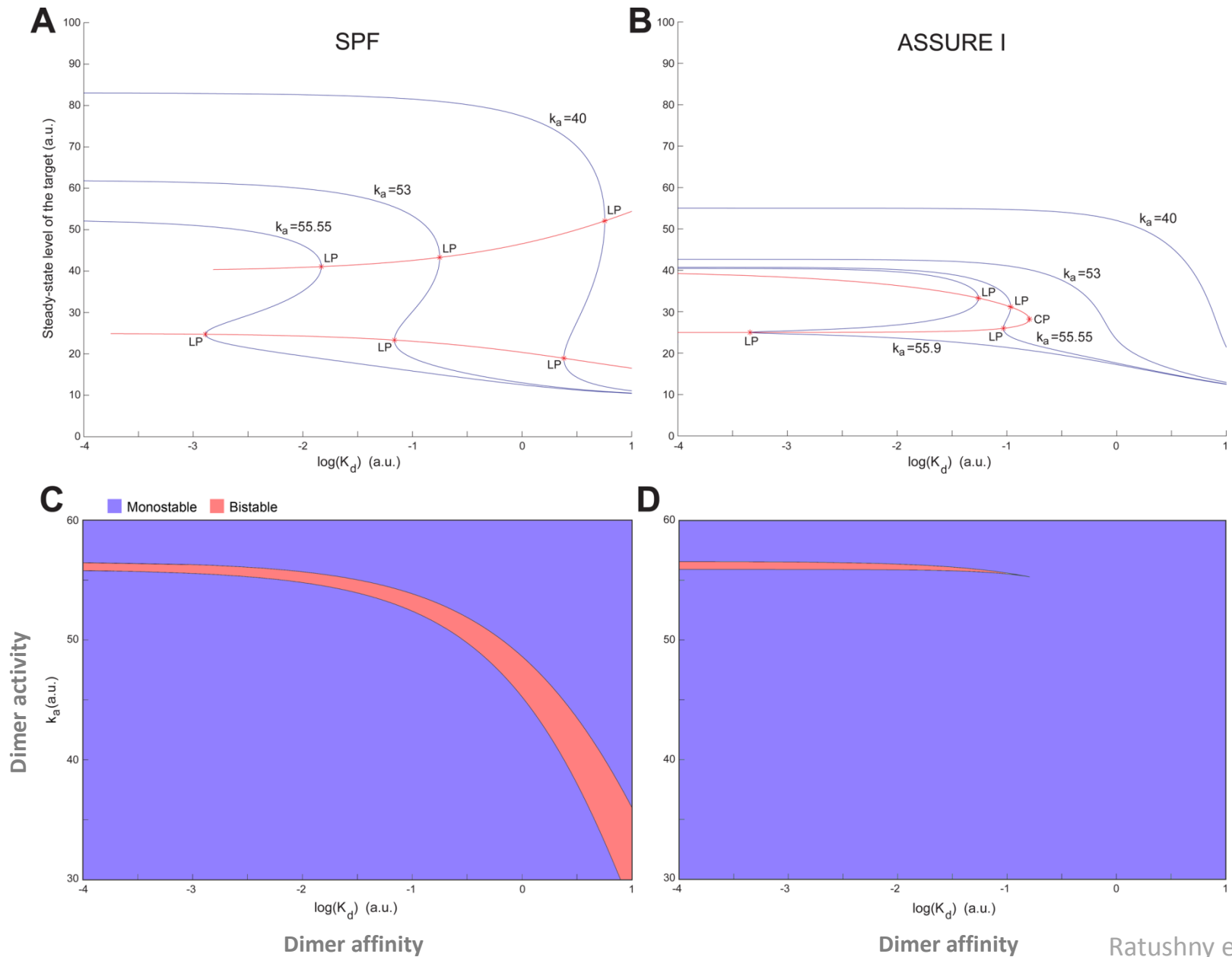
Randomly parameterized SPF and ASSURE models



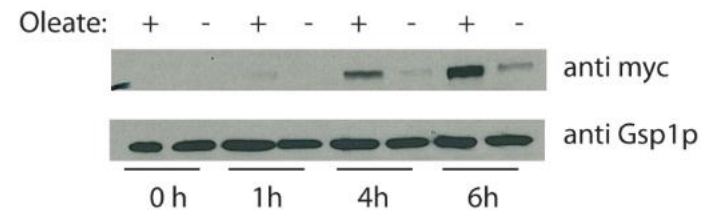
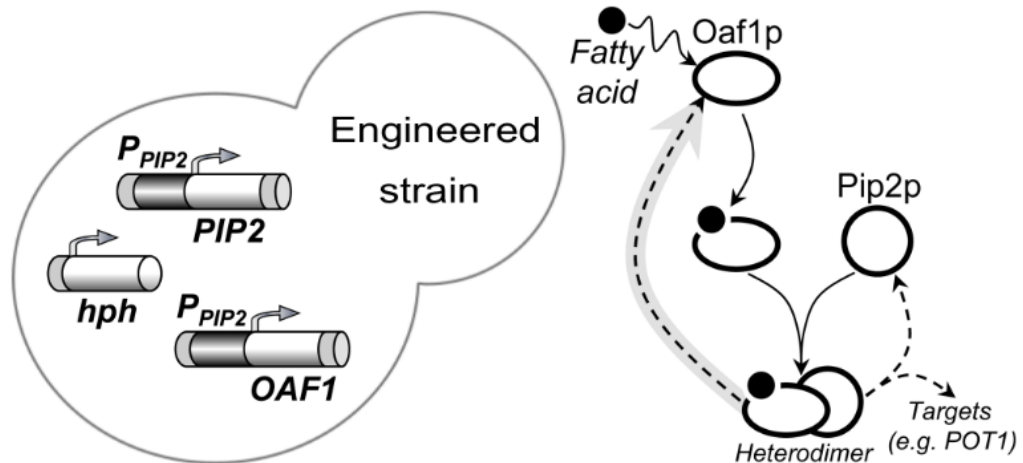
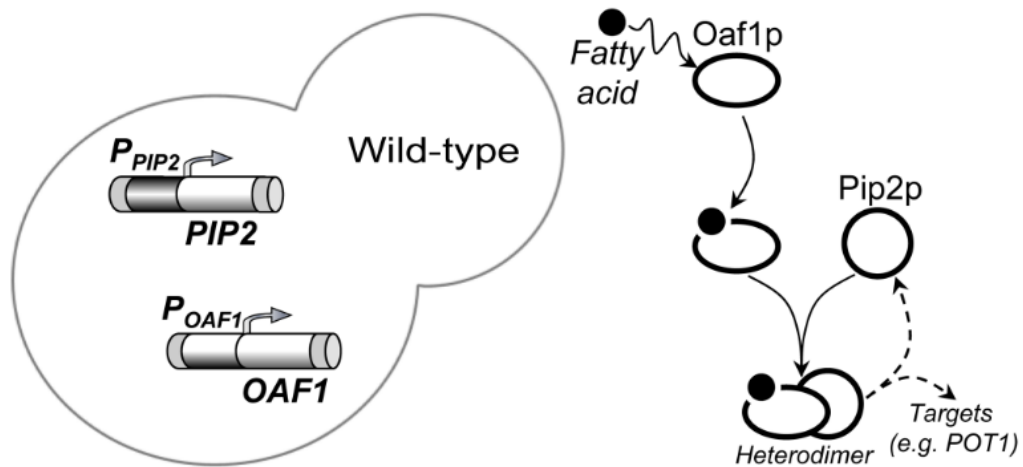
Evolution of the randomly parameterized SPF and ASSURE models



Bifurcation analysis

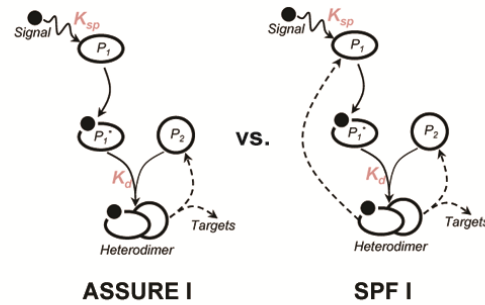


Experimental validation: engineered strain construction

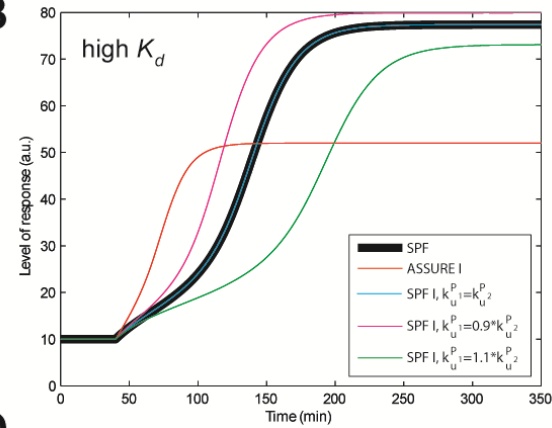


Comparison of the SPF, ASSURE I and SPF I systems

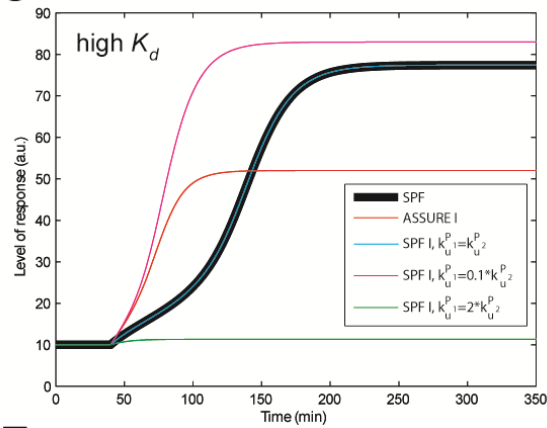
A



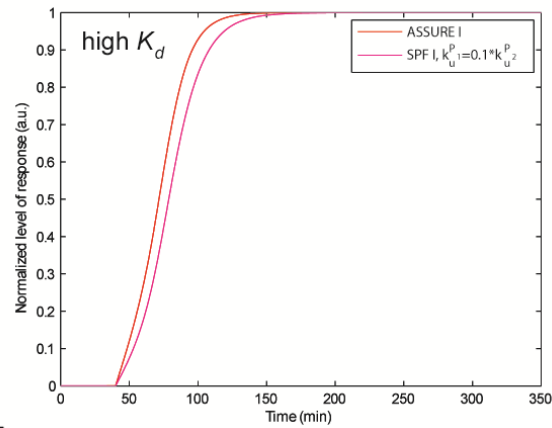
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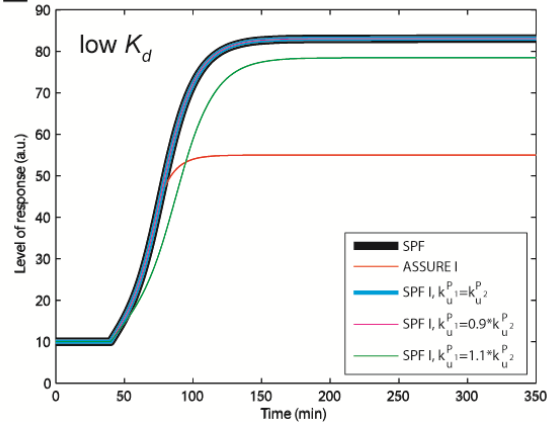
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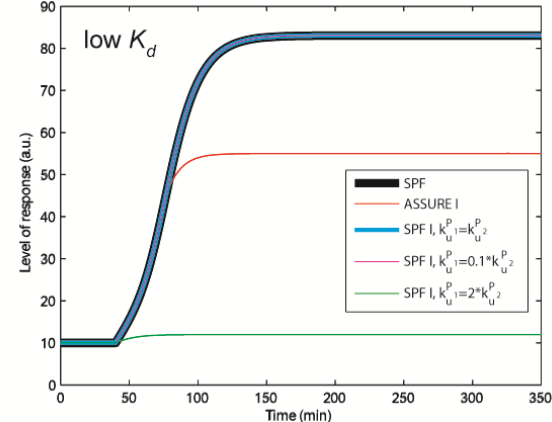
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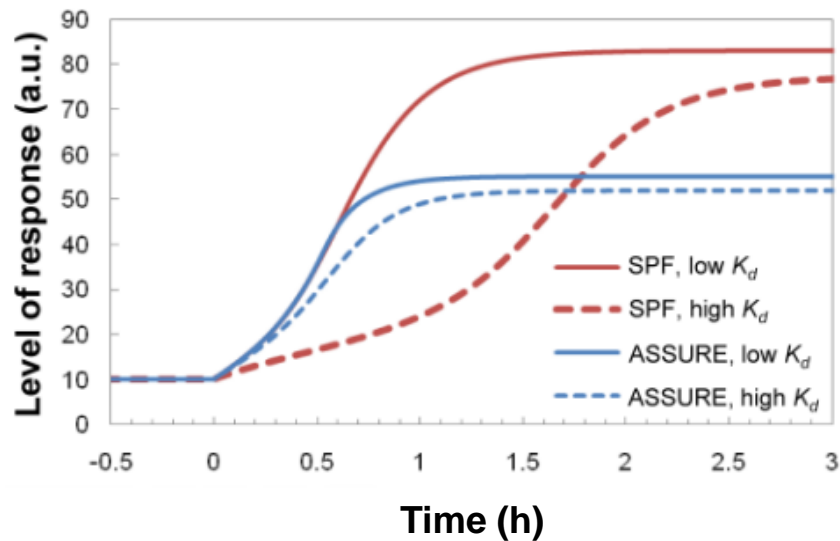
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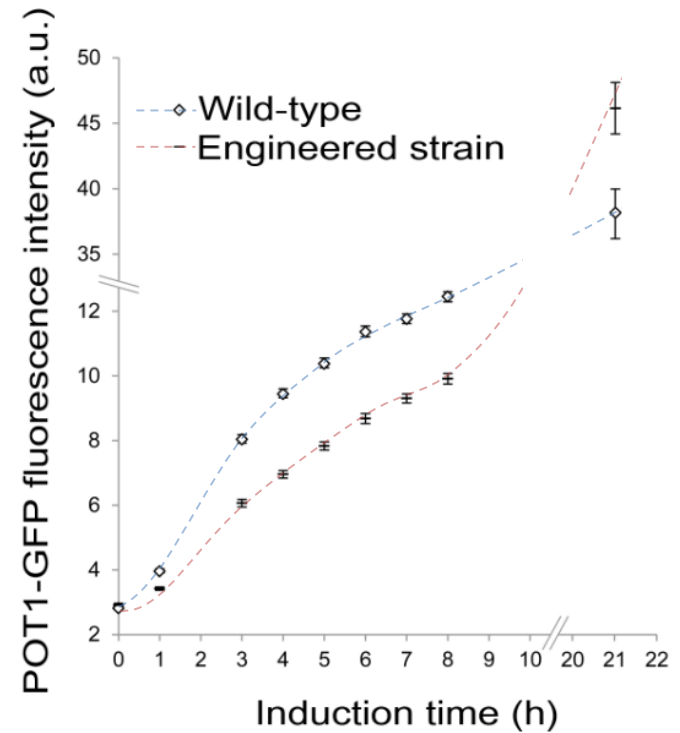
F



Experimental validation: rapid and controlled response of the ASSURE

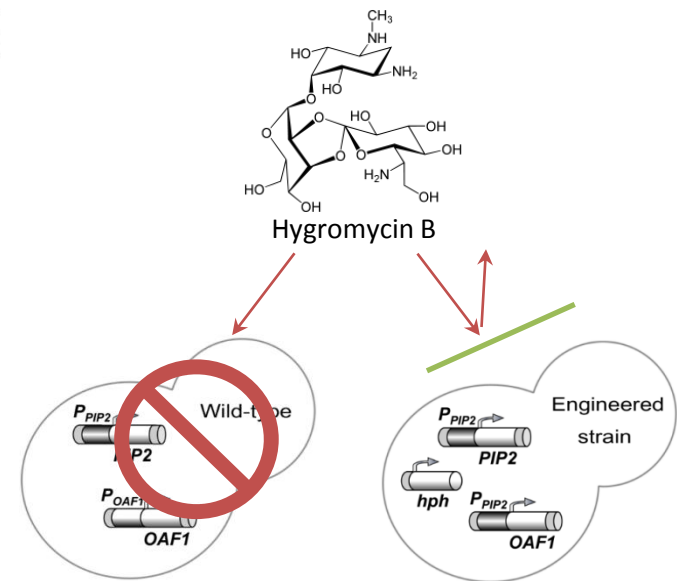
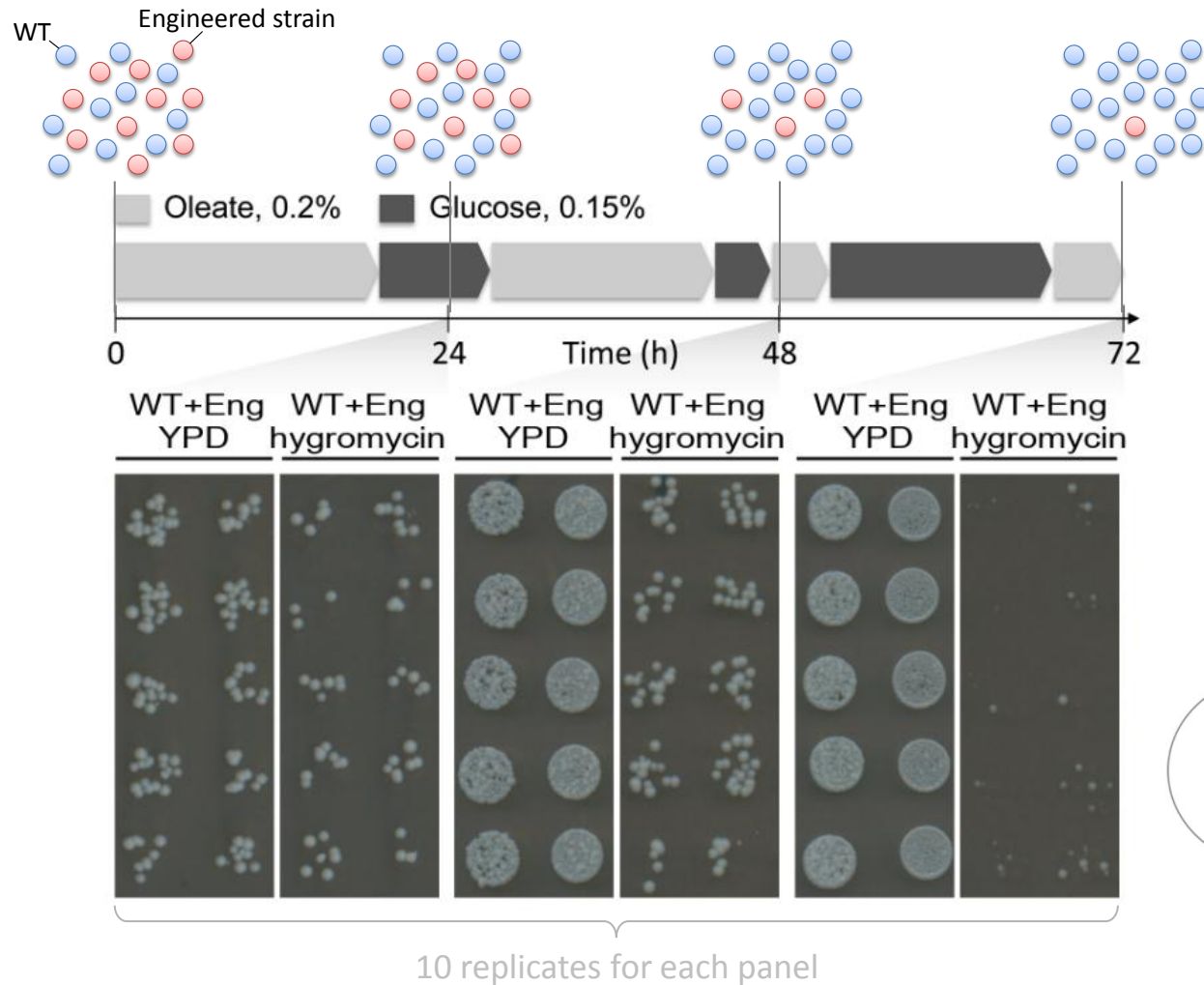


Theoretical prediction



Experimental validation

Experimental validation: competitive advantage of the ASSURE



If $\frac{[(WT+Eng) \text{ in hygromycin}]}{[(WT+Eng) \text{ in YPD}]} = 0.5 \Rightarrow$ there is no competitive advantage for any of these two strains

Summary

Many important biological systems rely on regulation by dimers of proteins which upregulate the transcription of numerous targets, including one, and only one, of the dimer pair. This is termed asymmetric self-upregulation.

ASymmetric Self-UpREgulated (ASSURE) networks confer rapid induction of their targets and their network behaviors are robust to parameter variation—both features appear to have contributed to the prevalence of the network across widely different biological systems.

Likely evolutionary precursors to ASSURE networks are symmetrically self-upregulated network mediated by homodimers. *In silico* and experimental studies demonstrate that the ASSURE network confers a competitive advantage over its symmetrical counterpart.

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