Binary to graded response conversion in autoregulated genes: transcriptional leakage vs. noise

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Micro and Macro Systems in Life Sciences
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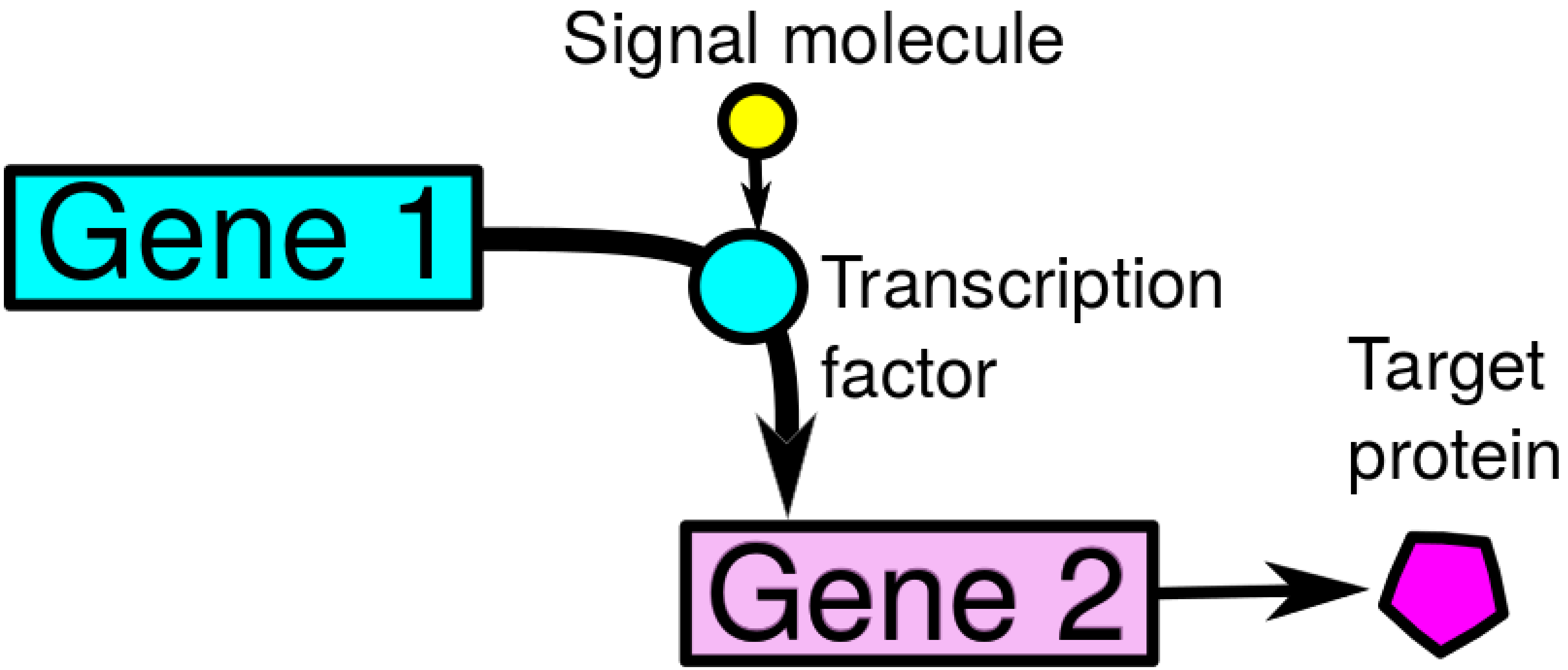
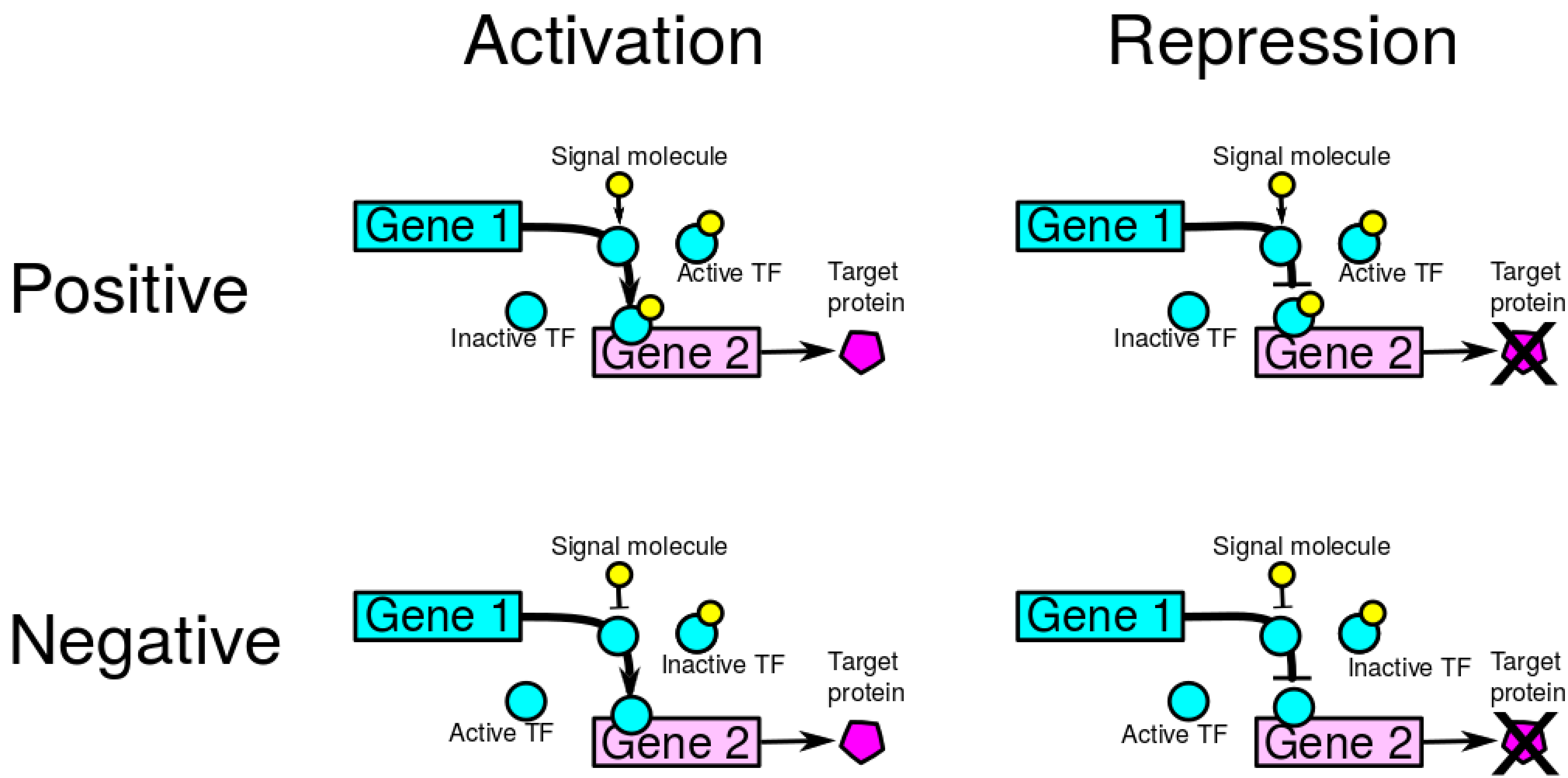


Signal molecule
Gene 1
Transcription
factor
Target
protein
Gene 2



Activation
Repression
Positive
Negative
Signal molecule
Gene 1
Active TF
Inactive TF
Target protein
Gene 2
Signal molecule
Gene 1
Active TF
Inactive TF
Target protein
Gene 2
Signal molecule
Gene 1
Inactive TF
Active TF
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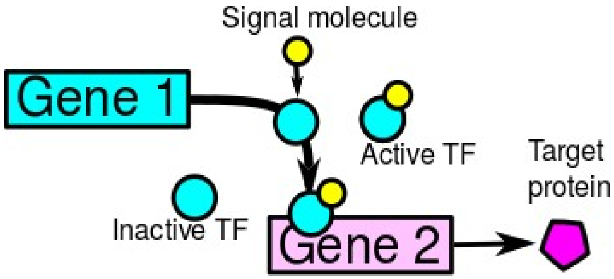
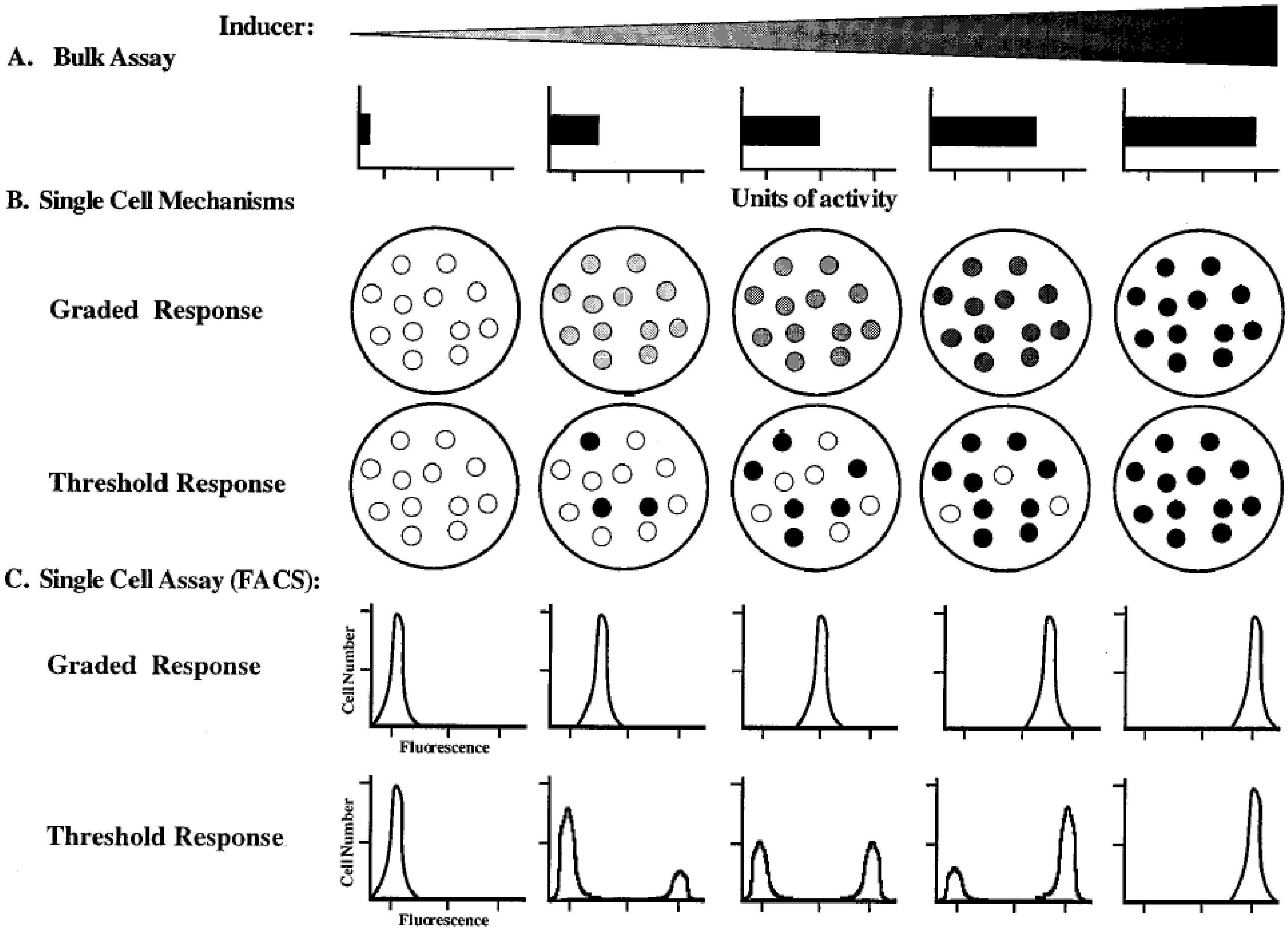


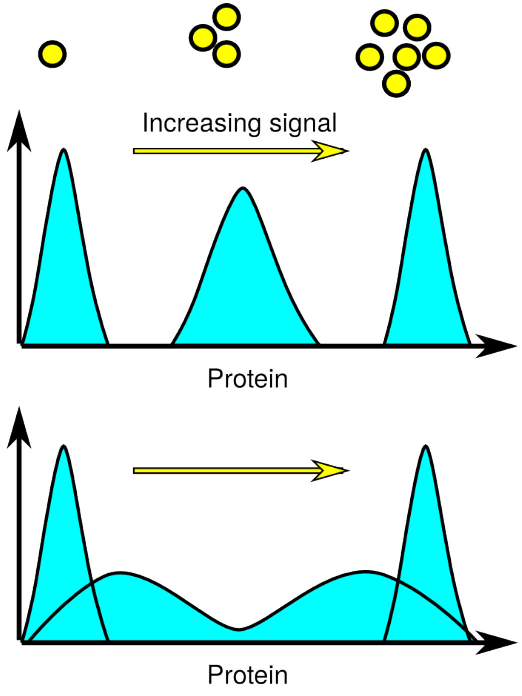
Binary / graded response



Kringstein, AM (1998) PNAS 95(23), 13670–5

Possible functions of binary/graded responses

- Graded: Precise
- Binary: Bet hedging

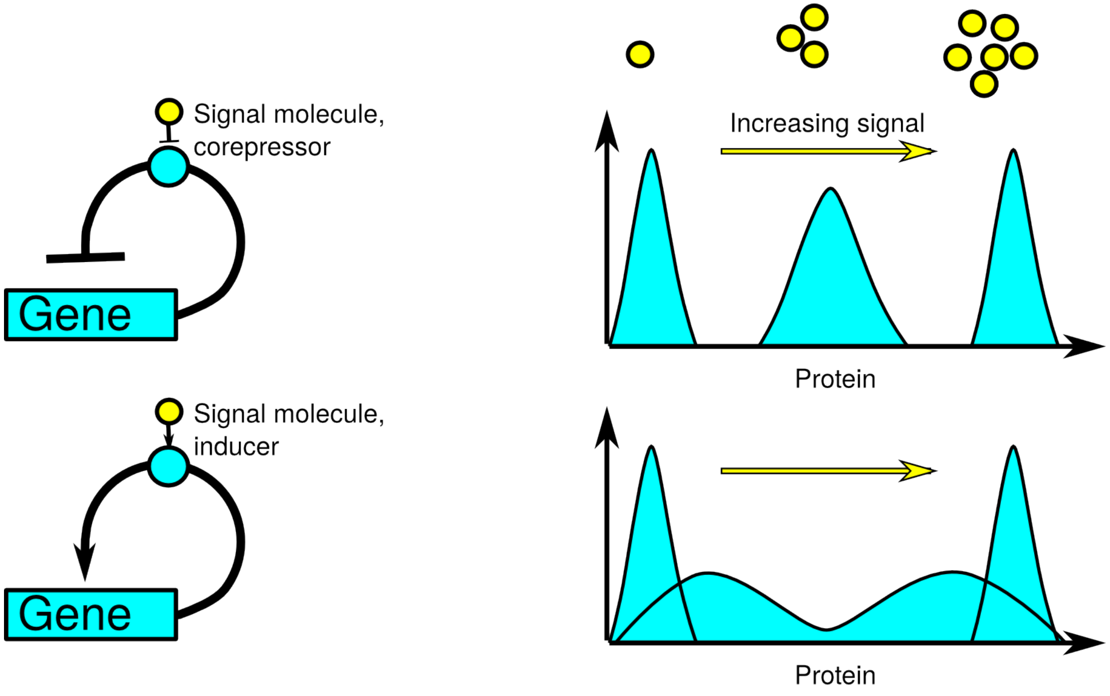


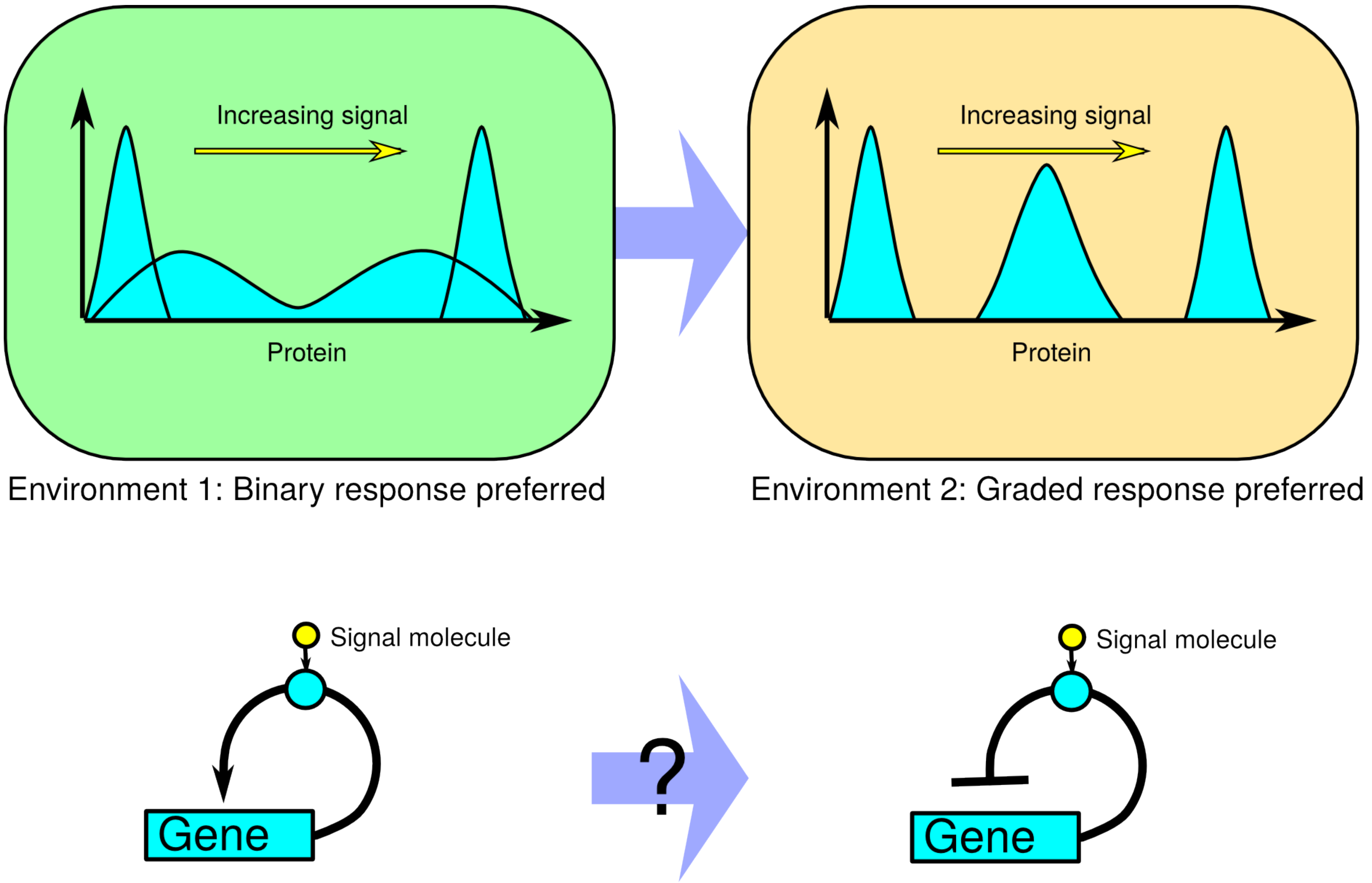
Self-regulation

- Common knowledge:

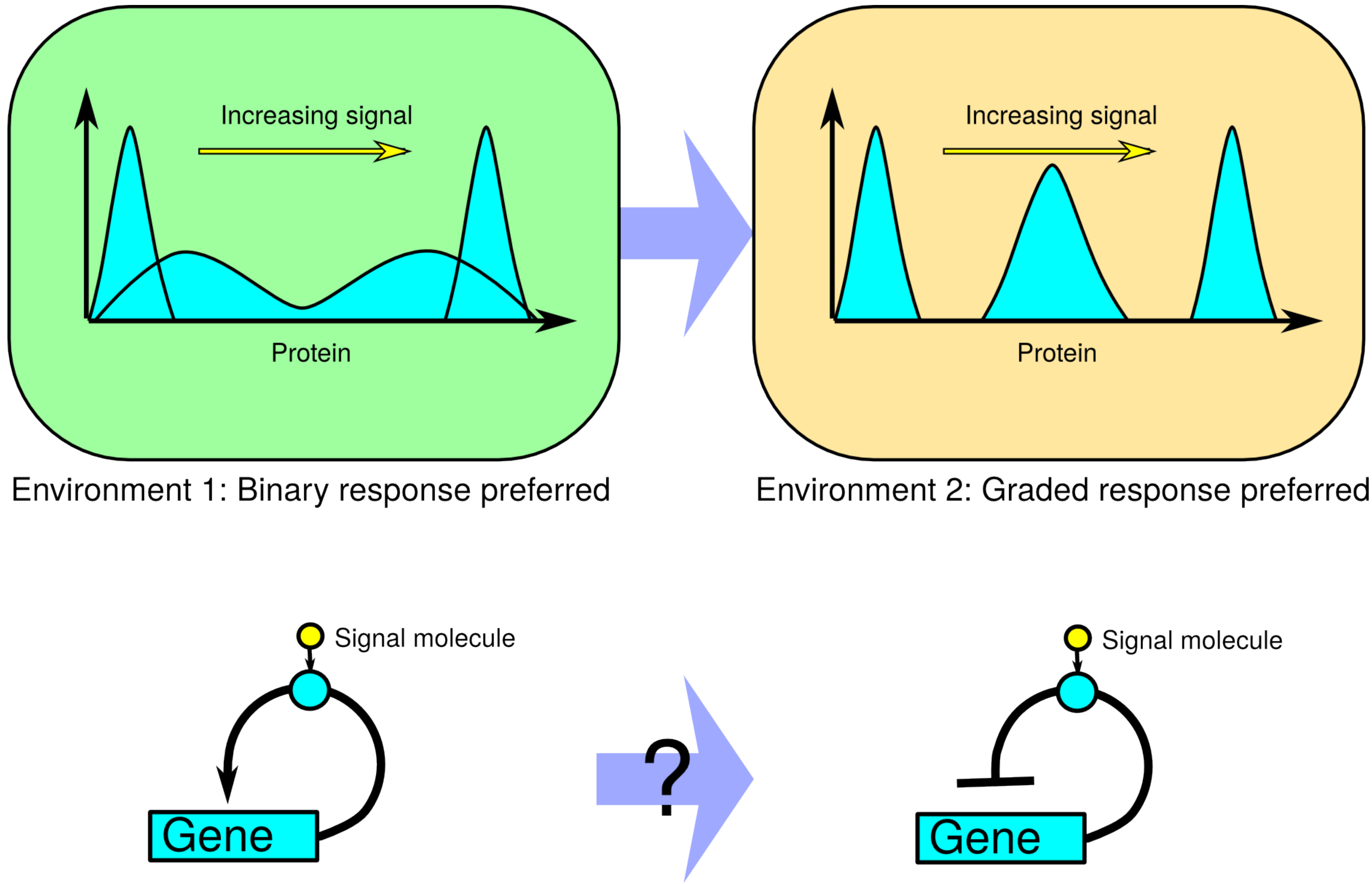
  Negative autoregulation → unimodal distributions → graded response

  Positive autoregulation → bimodal distributions → binary response?





Increasing signal
Protein
Environment 1: Binary response preferred
Increasing signal
Protein
Environment 2: Graded response preferred
Signal molecule
Gene
?
Signal molecule
Gene


Increasing signal
Protein
Environment 1: Binary response preferred
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Protein
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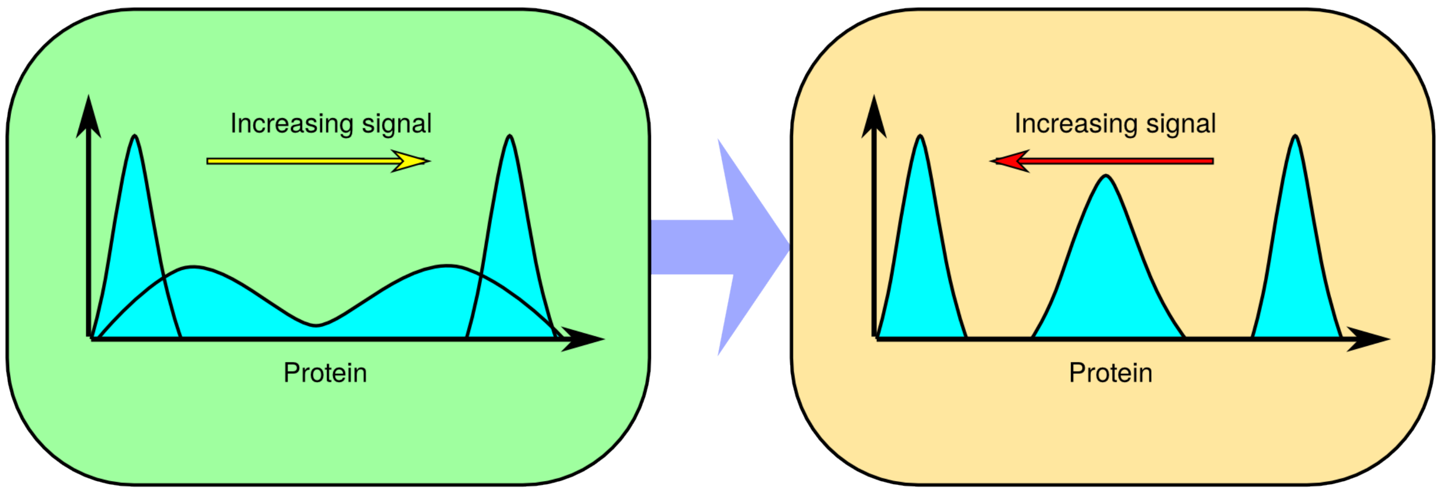
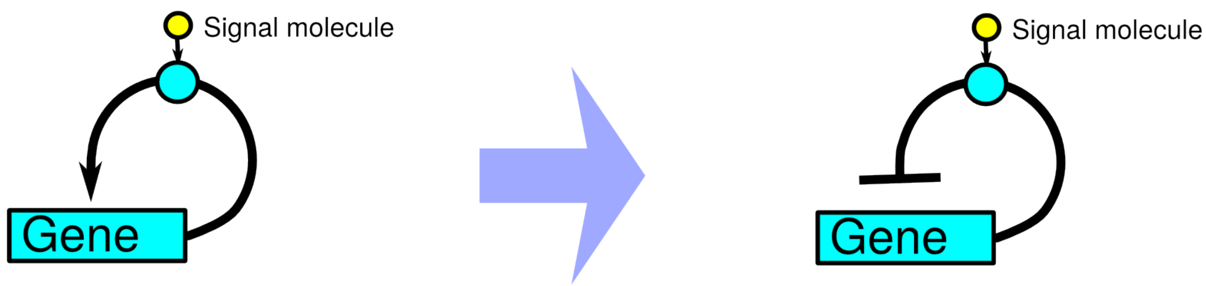
Signal molecule
Gene
?
Signal molecule
Gene

Not so easy!



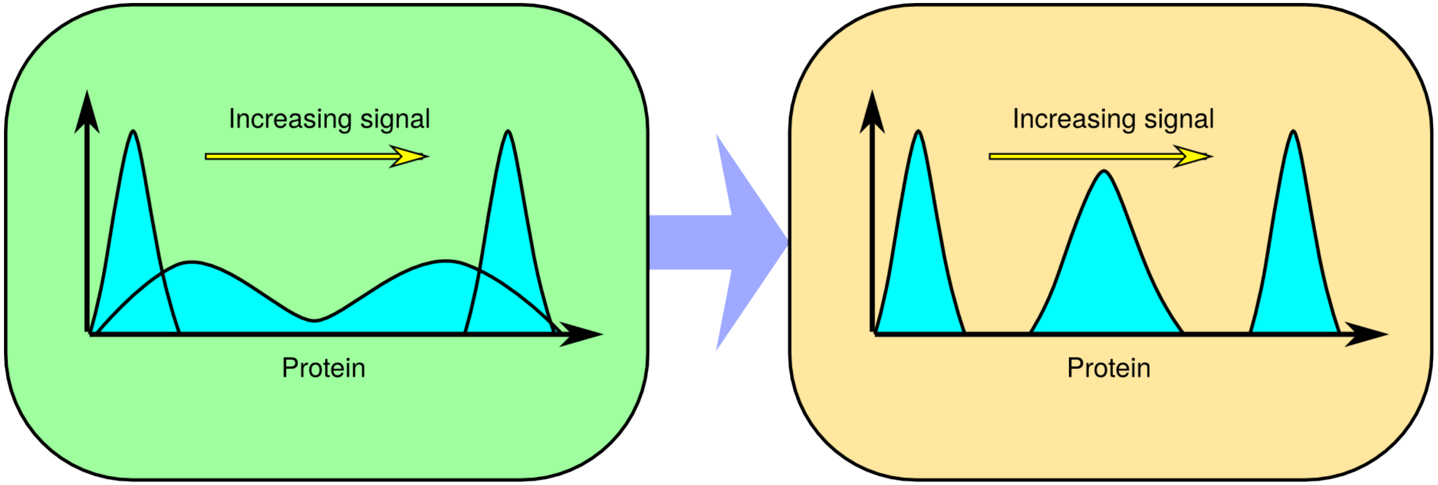
Environment 1: Binary response preferred

Environment 2: Graded response preferred



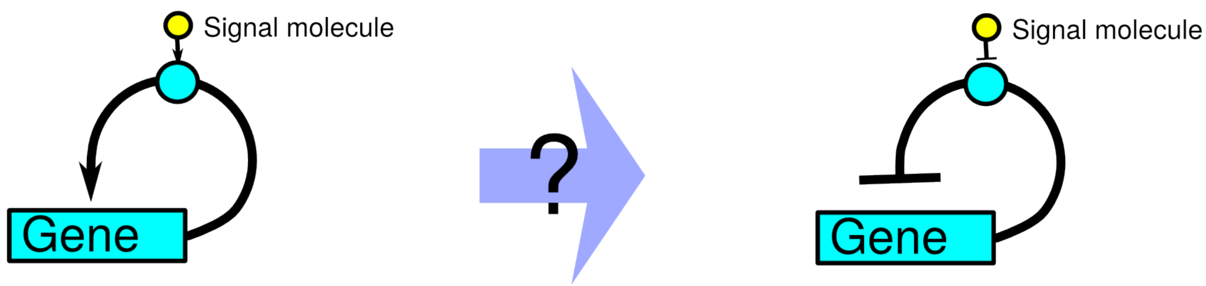
More effectors →
better transcription factor binding →
more activation

More effectors →
better transcription factor binding →
more repression



Environment 1: Binary response preferred

Environment 2: Graded response preferred



More effectors →
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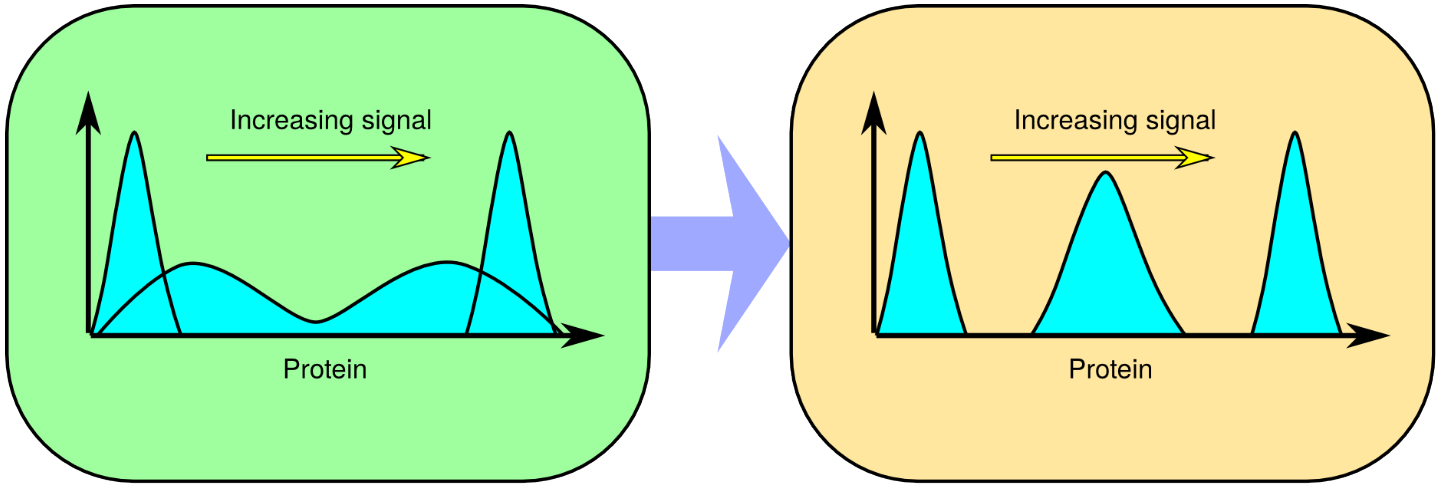
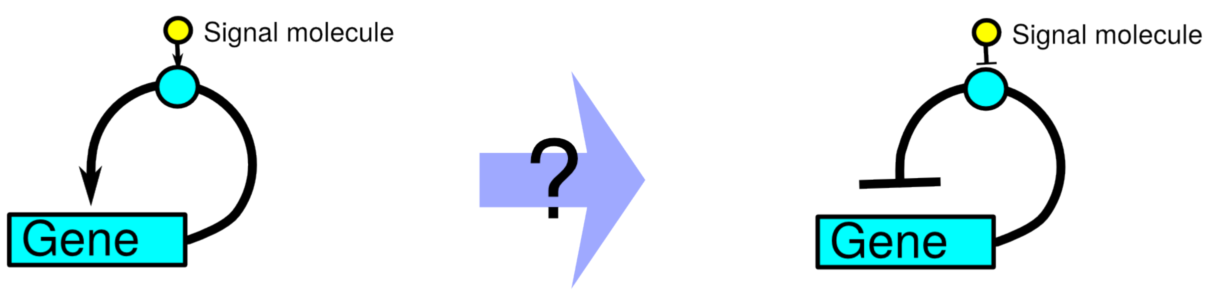
more activation

More effectors →
worse transcription factor binding →
less repression



Environment 1: Binary response preferred

Environment 2: Graded response preferred



More effectors →
better transcription factor binding →
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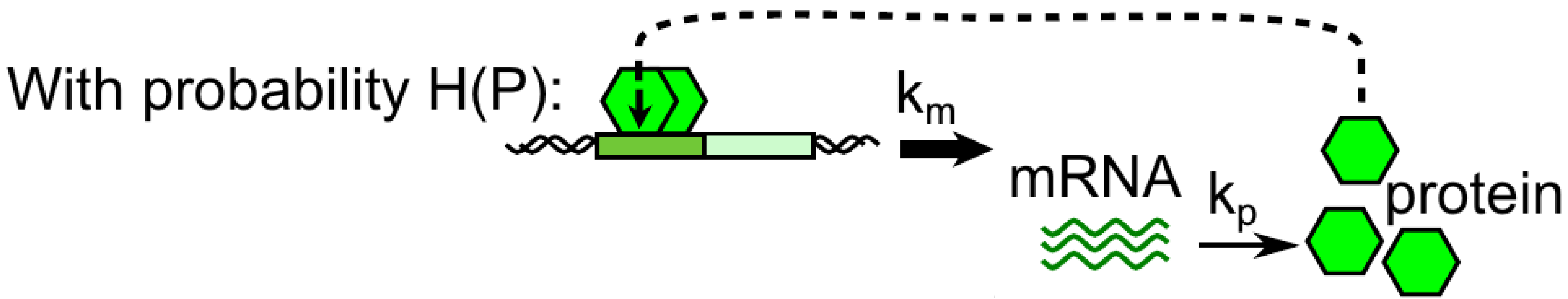
More effectors →
worse transcription factor binding →
less repression

Multiple mutations needed:

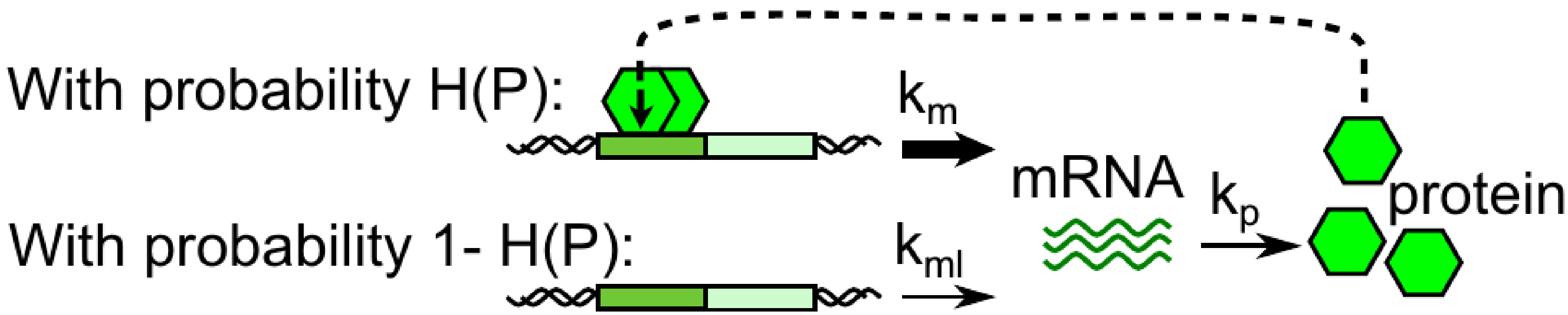
- Transcription factor: Activator → repressor
- Effector: Inducer → corepressor

Transcriptional leakage (basal expression)



Ochab-Marcinek, Tabaka (2015) Phys Rev E, 91, 012704

Transcriptional leakage
(basal expression)



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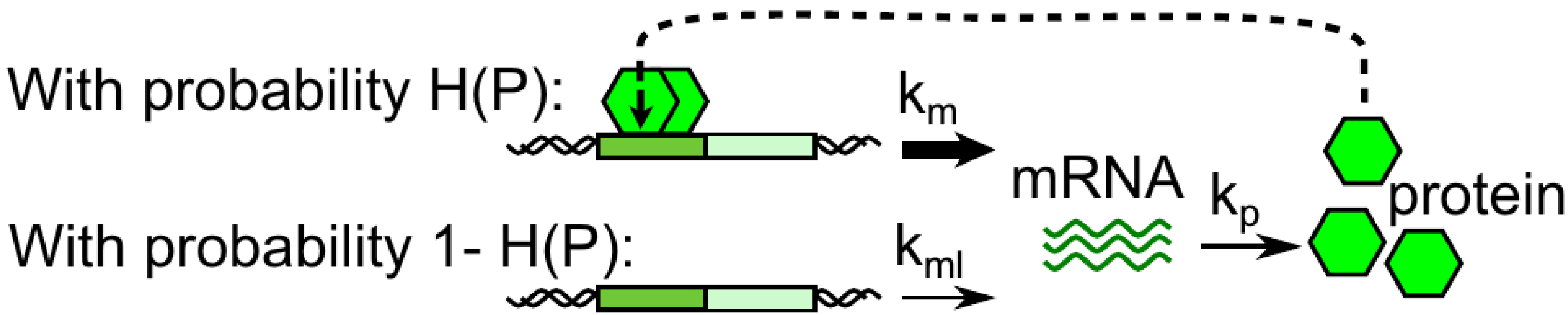
Transcriptional leakage (basal expression)



- No tight control over the promoter.
- Some level of transcription is maintained even when the promoter is in the *off* state.
- To date, the role of transcriptional leakage has been underappreciated.
- Most often described as unfavorable (for an experimenter).
- Is it favorable for cells?

Deterministic description of an autoregulated gene

- Rate equations:

$$\frac{dM}{dt} = k_m h(P) - k_{dm} M, \qquad \frac{dP}{dt} = k_p M - k_{dp} P$$

- Transcription rate: $h(P) = k_m H(P) + k_{ml}(1 - H(P)) =$

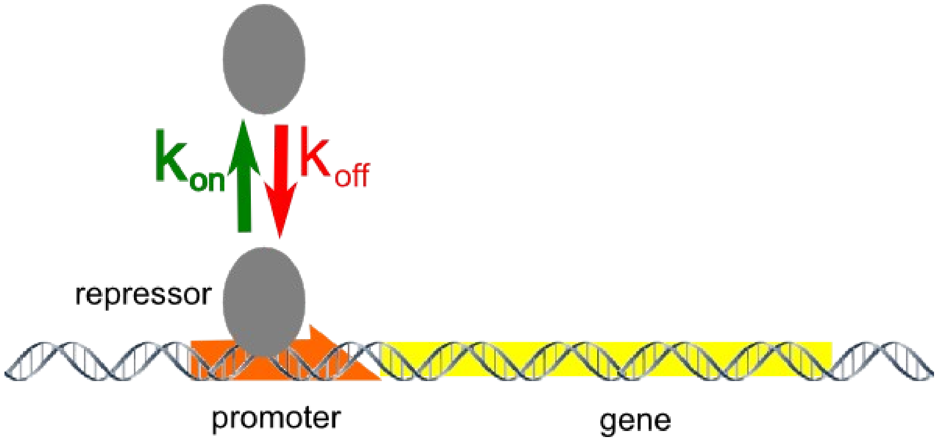
$$= H(P)\left(1 - \frac{k_{ml}}{k_m}\right) + \frac{k_{ml}}{k_m} =$$

$$= H(P)(1-\epsilon) + \epsilon$$

- Transcription factor binding governed by Hill kinetics:

$$H(P) = \frac{1}{1 + cP^n}$$

Hill / Michaelis-Menten kinetics

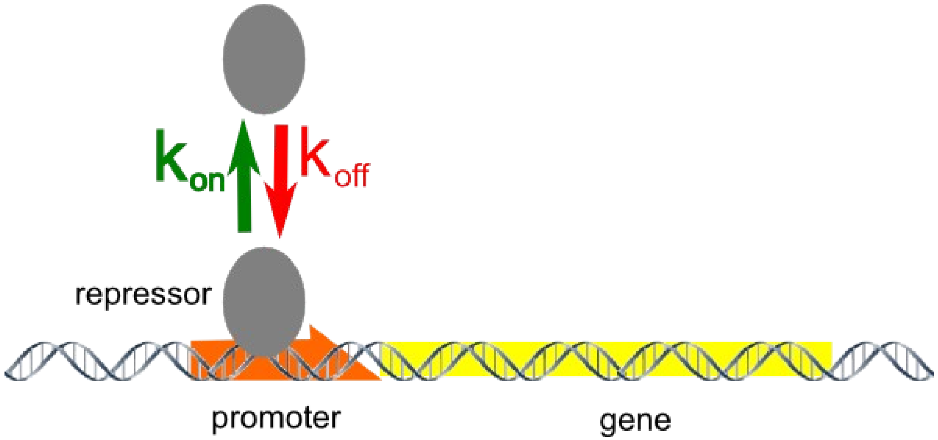


Repression:
Transcription when the operator is free

$$\frac{dM}{dt} = k_m O - k_{dm} M$$

O: probability that the operator is free

Hill / Michaelis-Menten kinetics



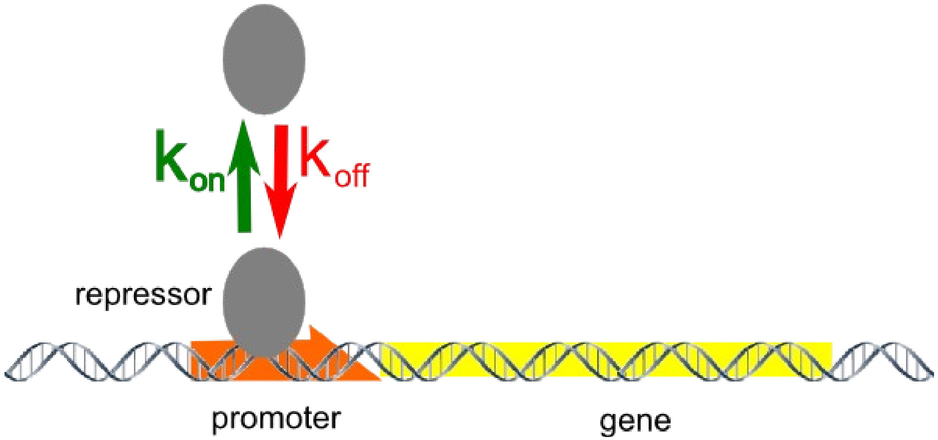
O: probability that the operator is free

O_R: probability that the operator is occupied

At steady state:

$$k_{on} \cdot R \cdot O = k_{off} \cdot O_R \quad \rightarrow \quad O_R = \frac{k_{on}}{k_{off}} R \cdot O$$

Hill / Michaelis-Menten kinetics



$$O + O_R = 1$$

$$O\left(1 + \frac{k_{on}}{k_{off}} R\right) = 1$$

$$O \equiv h(R) = \frac{1}{1 + \frac{k_{on}}{k_{off}} R}$$

Hill kinetics, n binding sites

- Detailed balance

$$k_{\text{on}}^1 R \cdot O = k_{\text{off}}^1 RO, \quad \ldots, \quad k_{\text{on}}^n R \cdot R_{n-1} O = k_{\text{off}}^n R_n O$$

- Probabilities sum up to 1

$$O + R \cdot O \frac{k_{\text{on}}^1}{k_{\text{off}}^1} + \ldots + R \cdot R_{n-1} O \frac{k_{\text{on}}^n}{k_{\text{off}}^n} = 1$$

- Full dose-response function

$$h(R) = \left(1 + \frac{k_{\text{on}}^1}{k_{\text{off}}^1} R + \cdots + \frac{k_{\text{on}}^1 \cdot \ldots \cdot k_{\text{on}}^n}{k_{\text{off}}^1 \cdot \ldots \cdot k_{\text{off}}^n} R^n\right)^{-1}$$

- At strong cooperativity, Hill function:

$$h(R) = \left(1 + \frac{k_{\text{on}}^1 \cdot \ldots \cdot k_{\text{on}}^n}{k_{\text{off}}^1 \cdot \ldots \cdot k_{\text{off}}^n} R^n\right)^{-1}$$

Deterministic description of an autoregulated gene

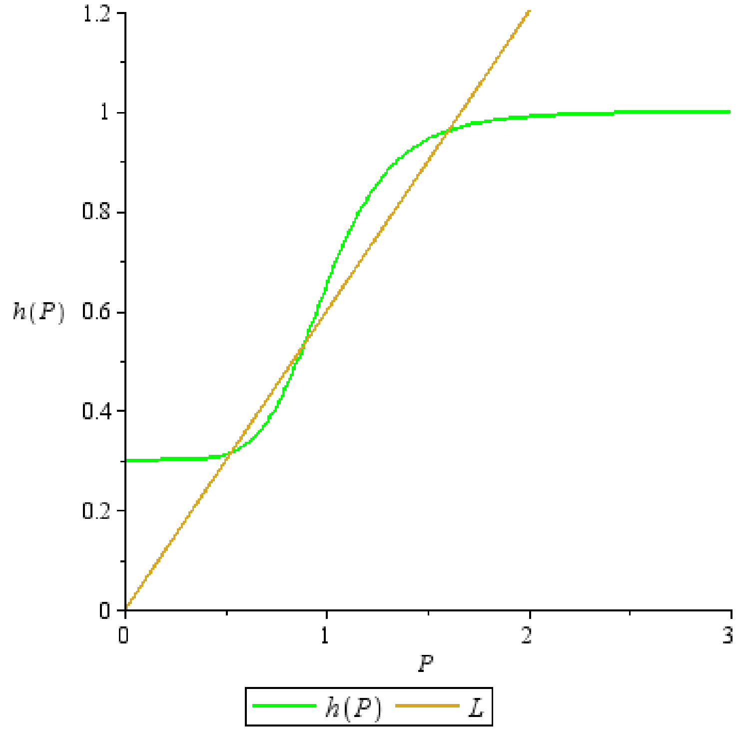
- Rate equations:

$$\frac{dM}{dt} = k_m h(\boldsymbol{P}) - k_{dm} M, \qquad \frac{dP}{dt} = k_p M - k_{dp} P$$

- Steady states: $H(P)(1-\epsilon) + \epsilon = \frac{1}{\alpha\beta} P$

$\alpha = k_m / k_{dp}$

$\beta = k_p / k_{dm}$



Stochastic description

$$\frac{\partial p(P)}{\partial t} = \frac{\partial}{\partial P}\left[k_{dp}\ P\ p(P)\right] + k_m \int_0^P dP'\ w(P,P')\ p(P')$$

- Hybrid model (Friedman, PRL 2006)
- Deterministic degradation
- Production in stochastic bursts
- Exponential distribution of burst sizes

Stochastic description

- Steady state solution with leakage (Friedman, PRL 2006; Ochab-Marcinek, Tabaka, PRE 2015):

$$p(P) = AP^{-1} e^{-P/\beta} e^{\alpha \int dP\, h(P)/P}$$
$$= AP^{\alpha-1} e^{-P/\beta} H(P)^{\alpha(1-\epsilon)/n}$$

- Maxima and minima given by an analogous geometric construction

$$H(P)(1-\epsilon) + \epsilon = \frac{1}{\alpha\beta} P + \frac{1}{\alpha}$$

Stochastic description

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Noise term

Stochastic description

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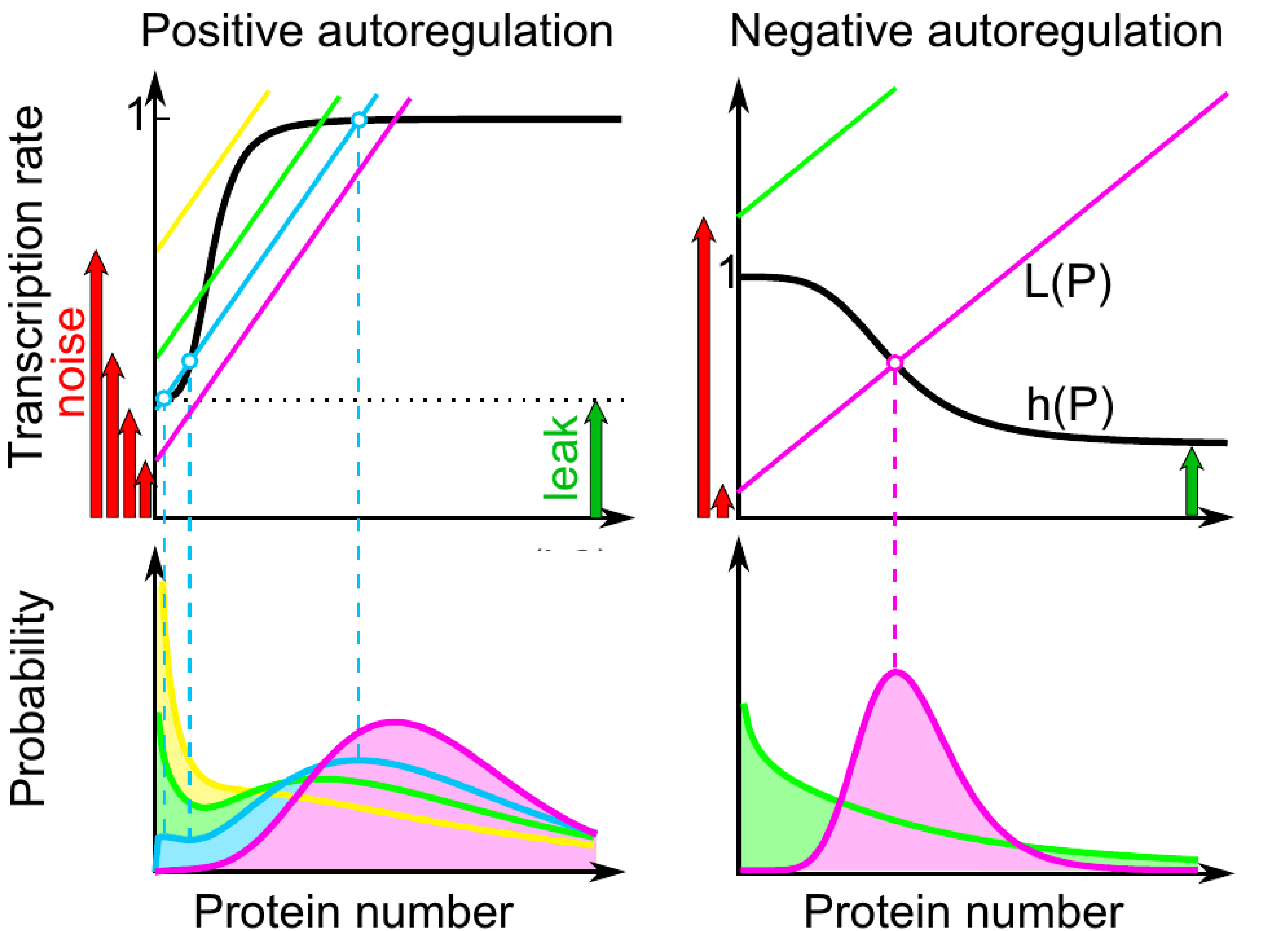
- Maxima and minima given by an analogous geometric construction

$$H(P)(1-\epsilon)+\epsilon = \frac{1}{\alpha\beta}P + \frac{1}{\alpha}$$

Noise term

$\alpha = k_m/k_{dp}$ Maximal frequency of protein bursts (when gene is at its maximum espression)



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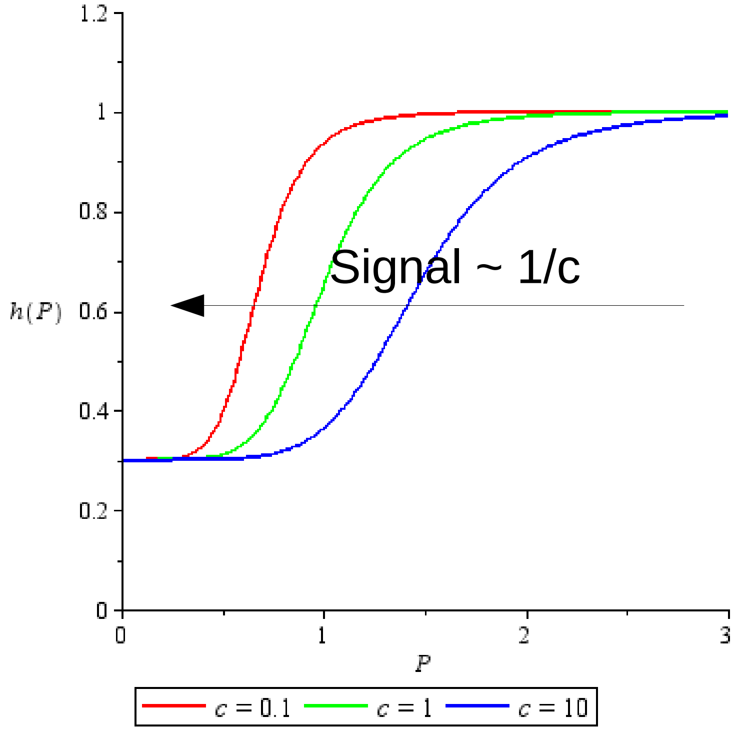
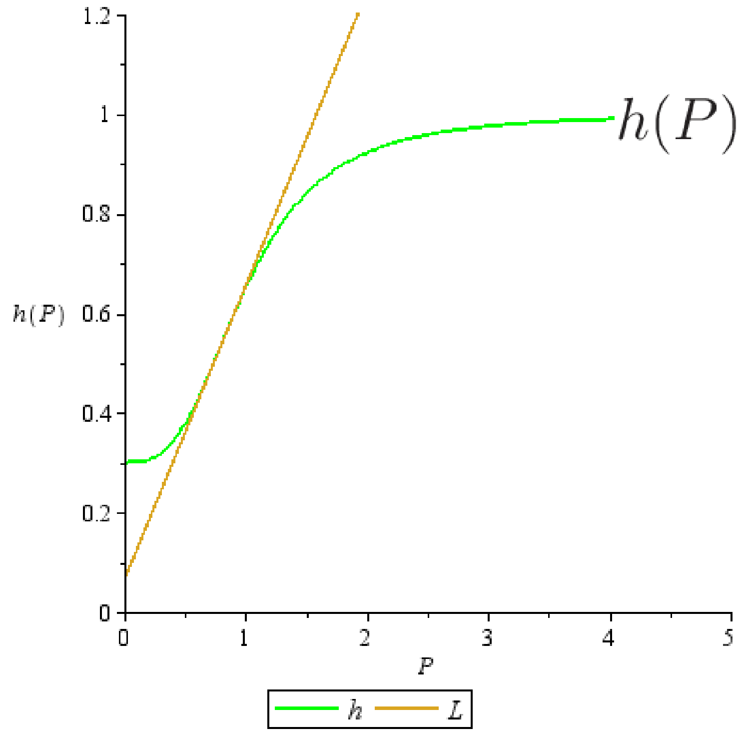
How signal changes the Hill function

- Slope increases as *c* decreases $H(P) = \frac{1}{1 + cP^n}$, n<0



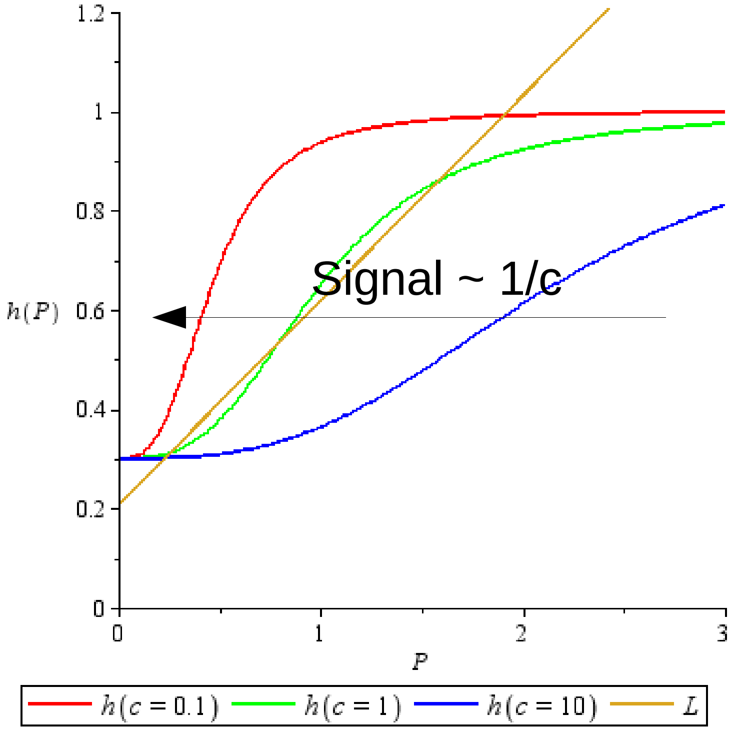
- We have certain α, β such that they define L(P) = $\dfrac{1}{\alpha\beta}P + \dfrac{1}{\alpha}$
- There exists c=c* such that L(P) intersects h(P) in its inflection point

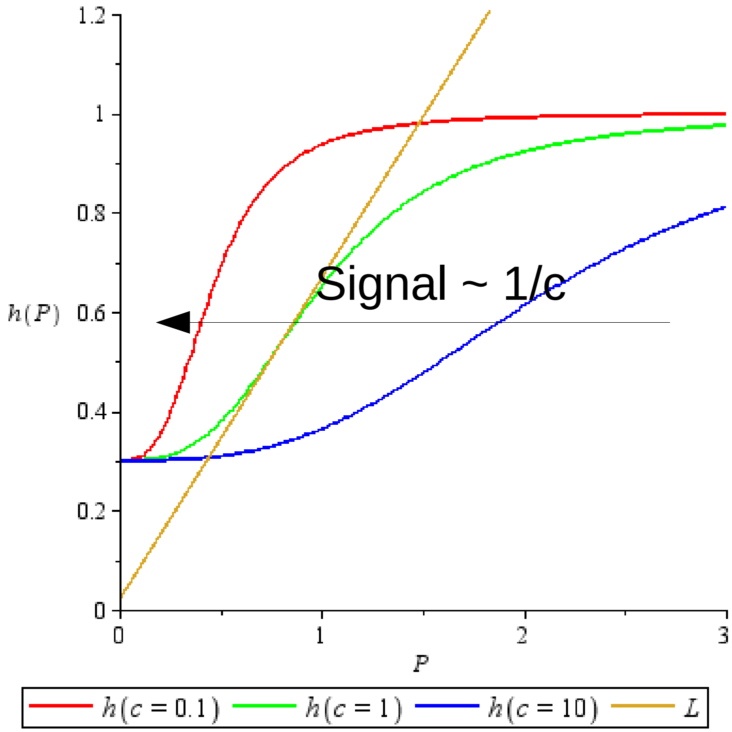


$$h(P) = \frac{1}{1 + c^{*}P^{n}}(1-\epsilon) + \epsilon$$

Binary or graded response

- L(P) intersects h(P) in its inflection point
- L(P) slope < h(P) slope in inflection point → binary response
- L(P) slope > h(P) slope in inflection point → graded response





Condition for graded response

- At c=c*, L(P) intersects h(P) in its inflection point P_p

$$h(P_p, c^*) = \frac{1}{\alpha\beta} P_p + \frac{1}{\alpha}$$

← intersection at P_p

$$\frac{d}{dP_p} h(P_p, c^*) < \frac{1}{\alpha\beta}$$

←L(P) slope > h(P) slope in inflection point

Nice properties of Hill function

$$H(P) = \frac{1}{1 + cP^n} \qquad h(P) = H(P)(1-\epsilon) + \epsilon$$

- Inflection point: $P_p = \left(\frac{n-1}{c(n+1)}\right)^{1/n}$
- Value at inflection point: $H(P_p) = \frac{n+1}{2n}$
- Slope at inflection point: $H'(P_p) = -\frac{n^2-1}{4n\ P_p}$

Condition for graded response

$$h(P_p, c^*) = \frac{1}{\alpha\beta} P_p + \frac{1}{\alpha}$$ ← intersection at P_p

$$\frac{d}{dP_p} h(P_p, c^*) < \frac{1}{\alpha\beta}$$ ← L(P) slope > h(P) slope in inflection point

---

Dependence on β, c* and P_p will disappear!

Condition for graded response

$$h(P_p, c^*) = \frac{1}{\alpha\beta} P_p + \frac{1}{\alpha}$$ ← intersection at P_p

$$\frac{d}{dP_p} h(P_p, c^*) < \frac{1}{\alpha\beta}$$ ← L(P) slope > h(P) slope in inflection point

---

$H(P_p)$

$$\frac{1}{\alpha\beta} = \frac{1}{P_p}\left((1-\epsilon)\boxed{\frac{n+1}{2n}} + \epsilon - \frac{1}{\alpha}\right)$$

$$(1-\epsilon)\boxed{\frac{-(n^2-1)}{4n\ P_p}} < \frac{1}{P_p}\left((1-\epsilon)\frac{n+1}{2n} + \epsilon - \frac{1}{\alpha}\right)$$

$H'(P_p)$

Condition for graded response

$$h(P_p, c^*) = \frac{1}{\alpha\beta} P_p + \frac{1}{\alpha}$$

← intersection at P_p

$$\frac{d}{dP_p} h(P_p, c^*) < \frac{1}{\alpha\beta}$$

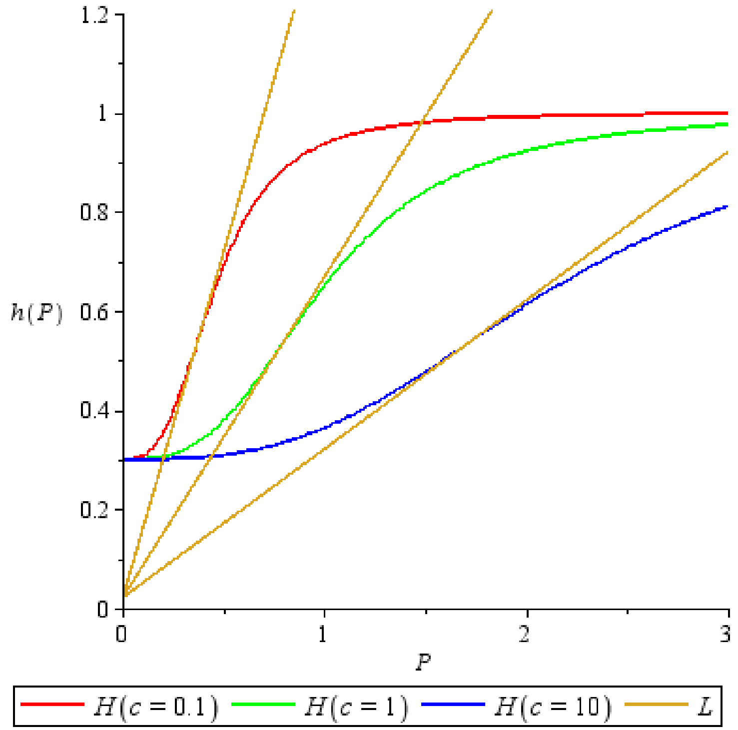
← L(P) slope > h(P) slope in inflection point

$$\frac{1}{\alpha\beta} = \frac{1}{P_p}\left((1-\epsilon)\frac{n+1}{2n} + \epsilon - \frac{1}{\alpha}\right)$$

$$(1-\epsilon)\frac{-(n^2-1)}{4n\ \cancel{P}_p} < \frac{1}{\cancel{P}_p}\left((1-\epsilon)\frac{n+1}{2n} + \epsilon - \frac{1}{\alpha}\right)$$

One more nice property of Hill function

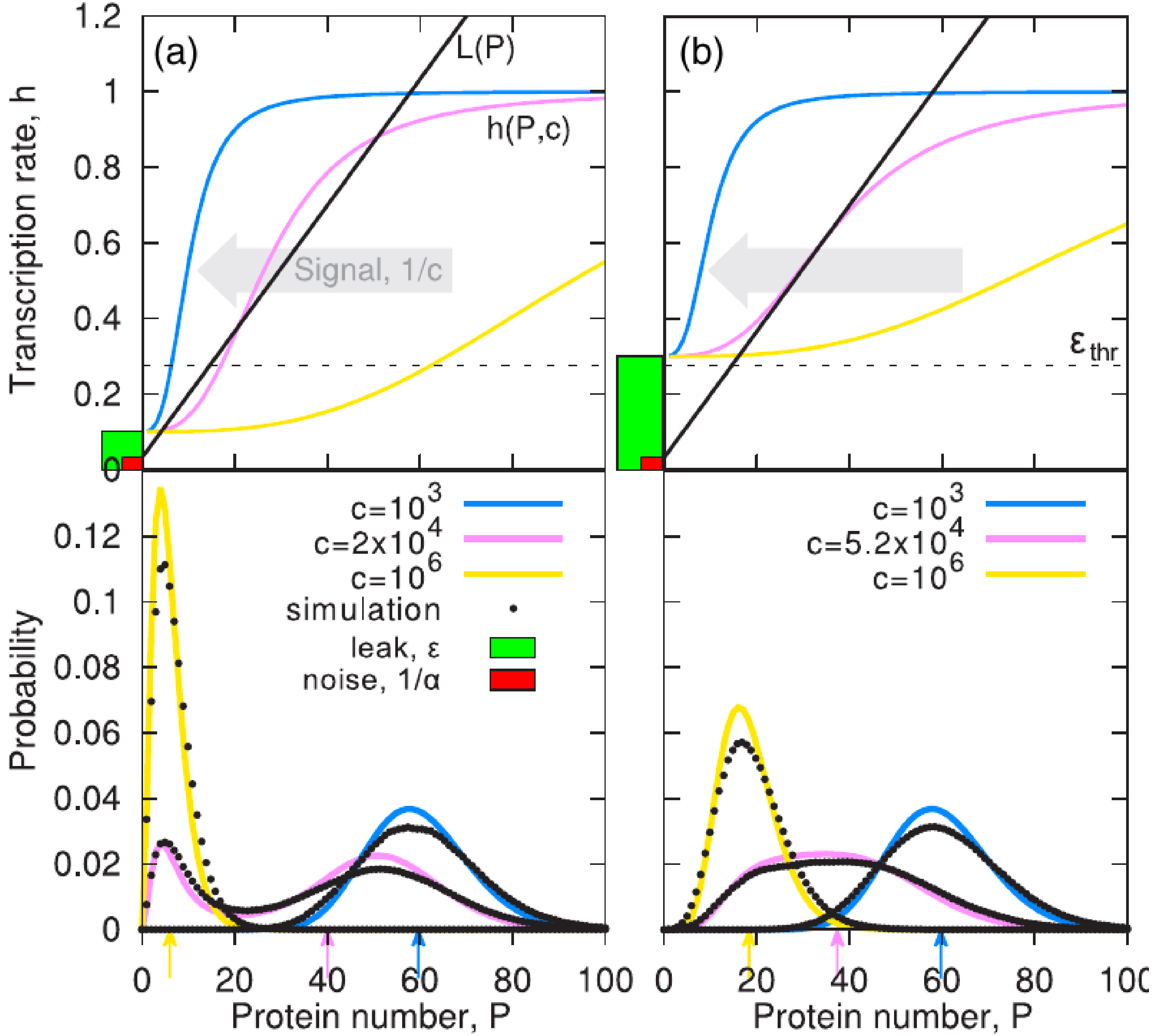
- Tangents to Hill function in its inflection point always meet at the same point



Condition for graded response

$$\epsilon > \frac{1}{\alpha}\frac{(-4n)}{(n-1)^2} + \frac{(n+1)^2}{(n-1)^2} \equiv \epsilon_{thr}$$

- If transcriptional leakage ε is greater than the threshold ε_{thr}, then the positively autoregulated gene will produce a graded response.
- For the leakage below that threshold, the response will be binary.



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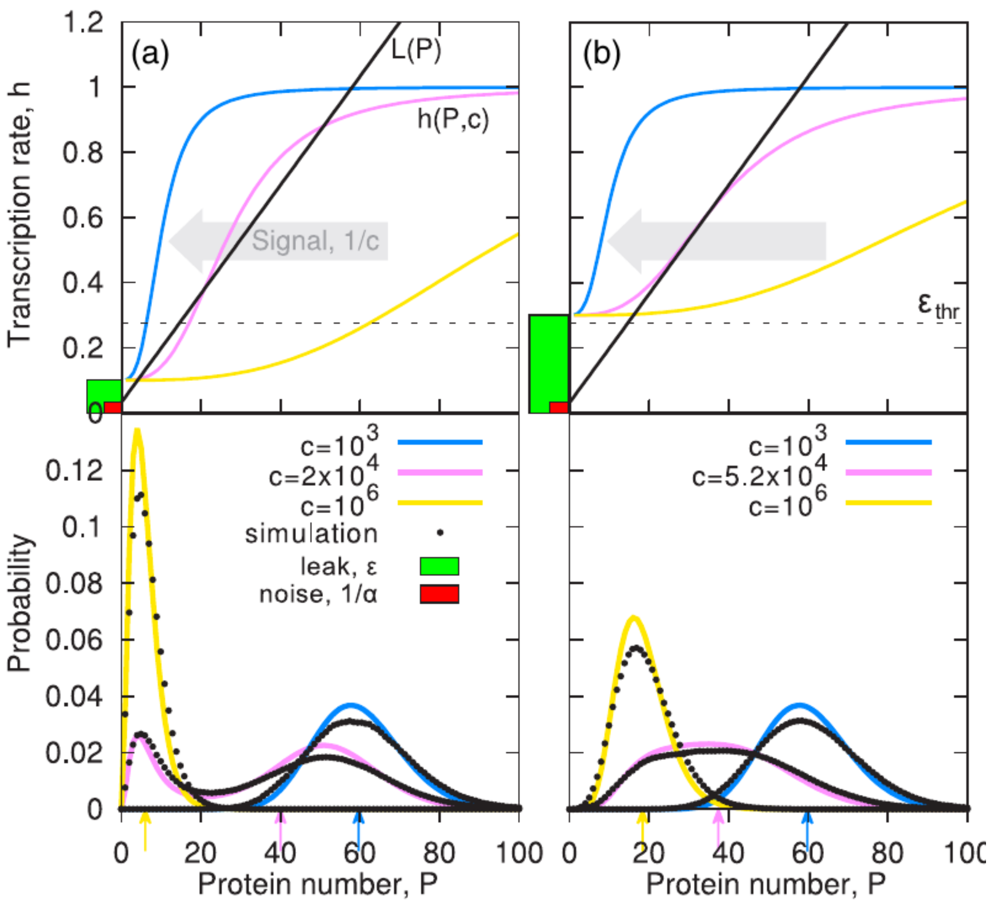
In a positively autoregulated gene, leakage acts against noise

$$\epsilon > \frac{1}{\alpha}\frac{(-4n)}{(n-1)^2} + \frac{(n+1)^2}{(n-1)^2} \equiv \epsilon_{thr}$$

- Increasing noise induces binary response
- Increasing leakage recovers graded response



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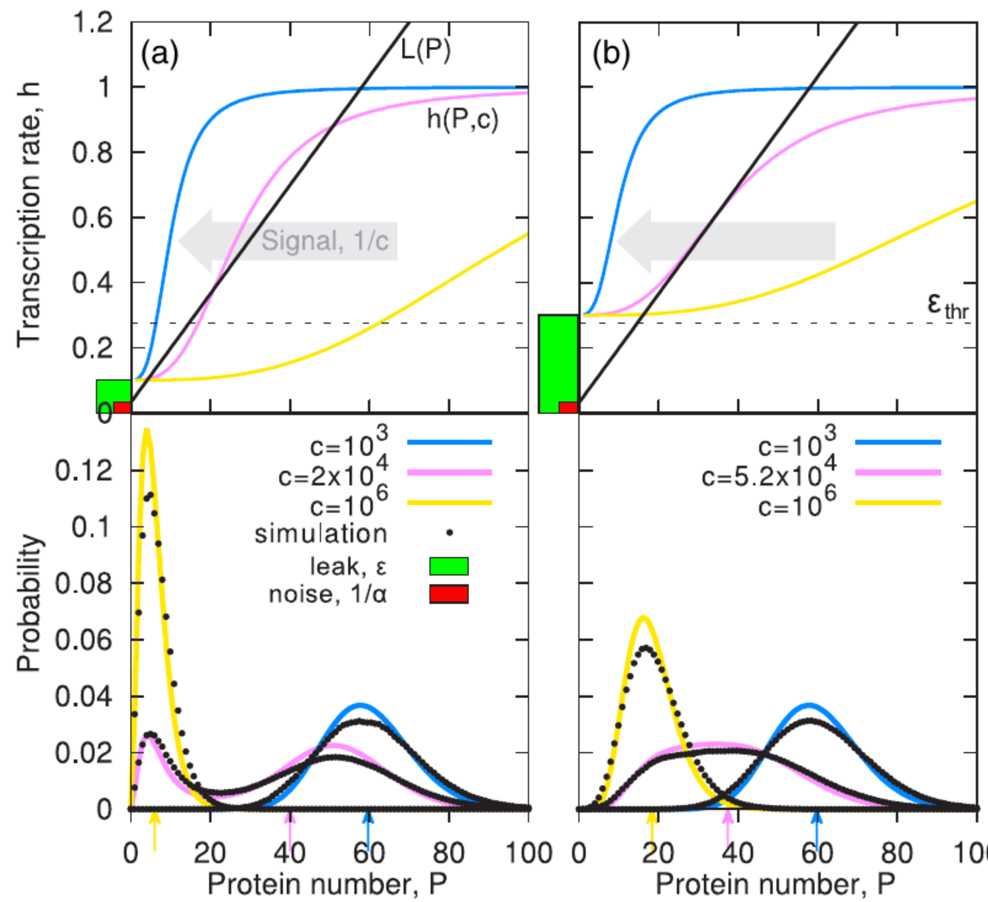
In a positively autoregulated gene, leakage acts against noise

$$\epsilon > \frac{1}{\alpha}\frac{(-4n)}{(n-1)^2} + \frac{(n+1)^2}{(n-1)^2} \equiv \epsilon_{thr}$$

- Low cooperativity: Low conversion threshold, low noise needed to obtain graded response
- High cooperativity: High conversion threshold, strong leakage needed to obtain graded response

Lowest possible threshold, for zero noise:

n	-2	-3	-4	-6
ε_{thr}	0.11	0.25	0.36	0.51



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Summary

- Change in leaky transcription: Single mutations in the promoter (E.g. influencing RNA polymerase recruitment or binding of other TFs)

- Conversion from positive to negative autoregulation: Multiple mutations
(activator → repressor, inducer → corepressor)

- Existence of leaky transcription can be an evolutionary adaptation which facilitates conversion between binary and graded response to signal

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