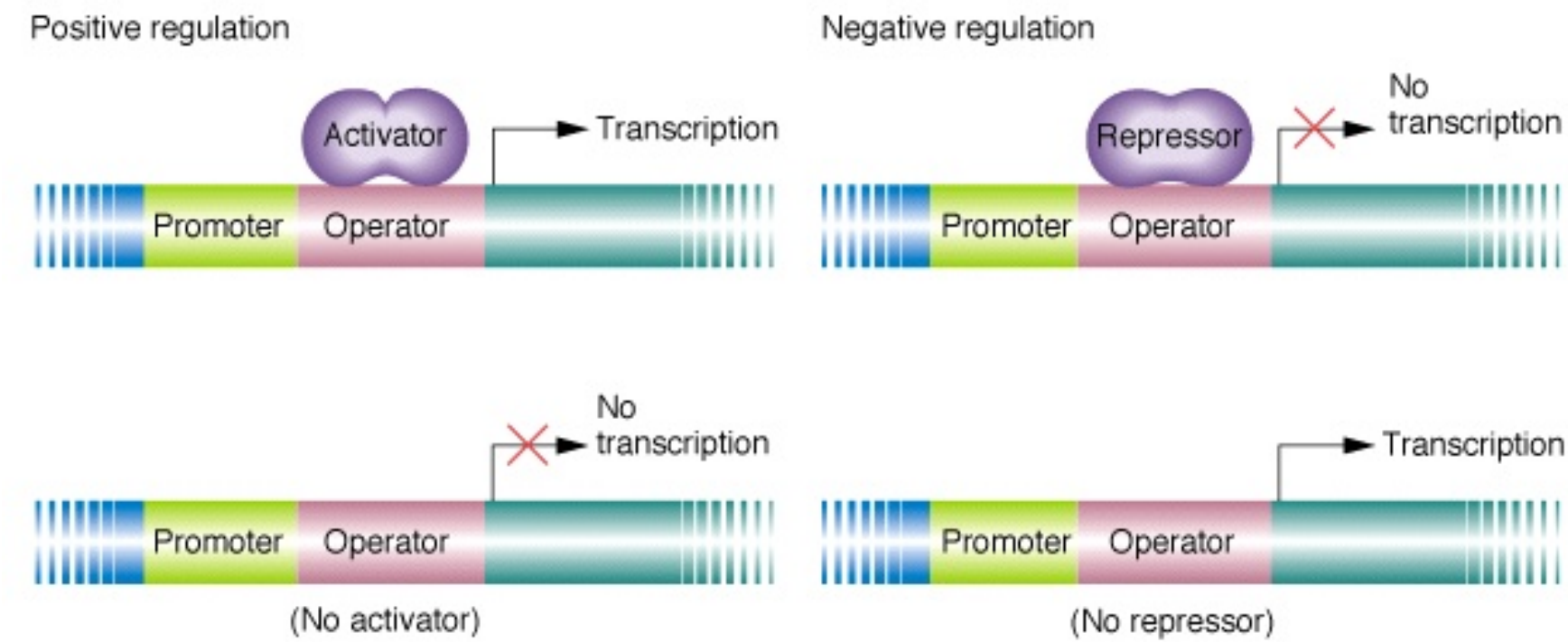
BME 5742 Biosystems Modeling and Control

Lecture 28
Gene Regulatory Networks
Part 2
Regulated Gene Expression Model

Potential Gene Expression Regulation Targets

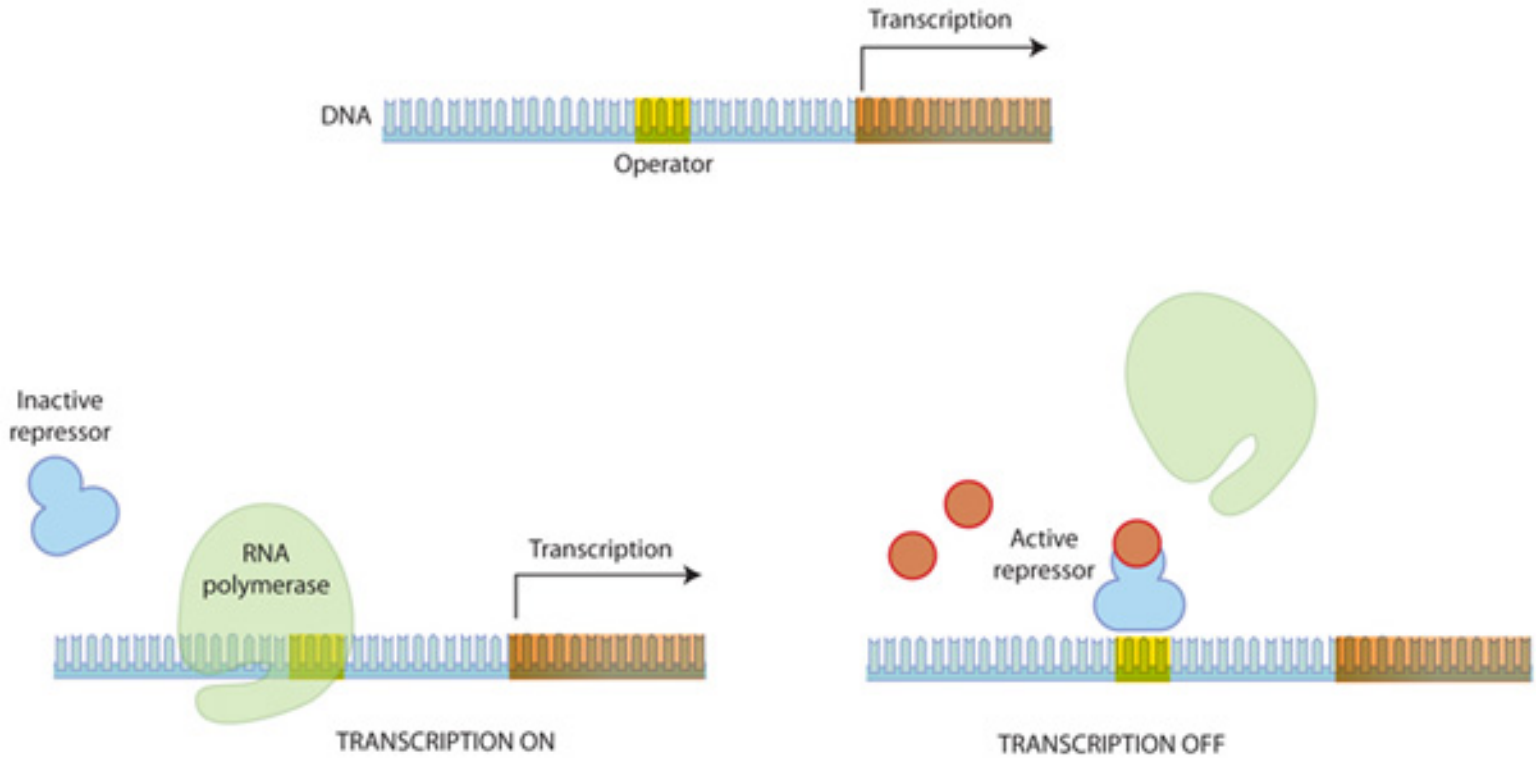
- RNA Polymerase binding (i.e. initiation of the transcription)
- The elongation (i.e. creation) of the mRNA strand
- Translational initiation (i.e. mRNA-ribosome binding)
- Polypeptide elongation (i.e. the initial synthesis of the protein)
- Direct degradation of the mRNA molecule
- Direct degradation of the protein molecule

Transcription Factors: Activators and Repressors



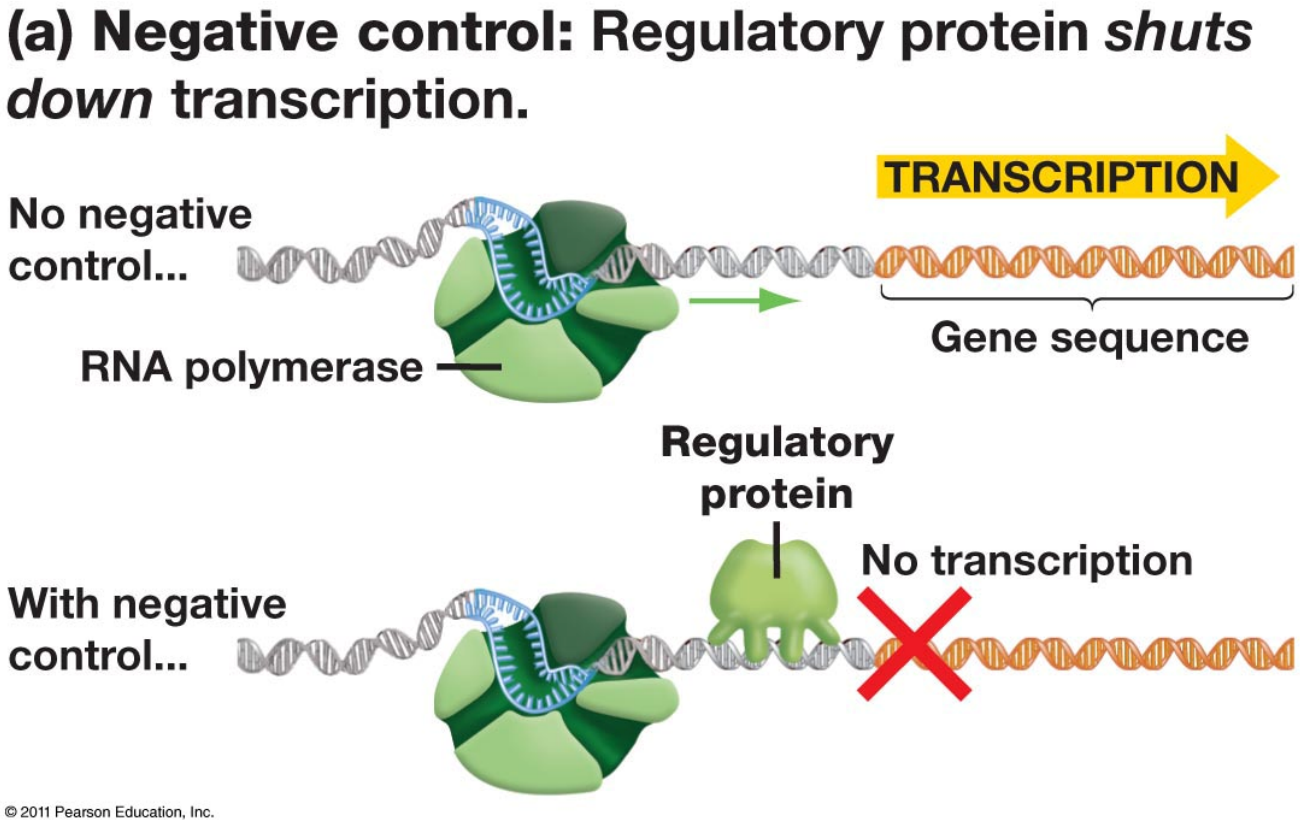
Operator regions are typically close to the promoter regions

Active Repressor prevents the binding of mRNA Polymerase to the promoter



- In the above the operator region equals the promoter region

Example to another repression mechanism where reading of the DNA is blocked



Transcription Factor Binding to an Operator

$$O + P \underset{d}{\overset{a}{\rightleftarrows}} OP$$

- O = the unbound operator
- P = the transcription factor (TF) protein
- OP = the bound operator
- Operator-TF equilibrium is faster than gene transcription

Transcription Factor Binding to an Operator – Equilibrium Conditions

$$\varepsilon = \frac{[OP]}{[O]+[OP]} = \frac{\frac{[O][P]}{K}}{[O]+\frac{[O][P]}{K}} = \frac{\frac{[P]}{K}}{1+\frac{[P]}{K}} = \frac{P}{K+[P]}$$

- K = d/a
- Fraction of bound operators = ε

$$O + P \underset{d}{\overset{a}{\rightleftarrows}} OP$$

Rate of Transcription from Regulated Gene if Transcription Factor is an Activator

$$\cancel{\frac{dm(t)}{dt} = k_0 - \delta_m m(t)}$$

$$\boxed{\frac{dm(t)}{dt} = \alpha_0 + \alpha \frac{\frac{[P]}{K}}{1 + \frac{[P]}{K}} - \delta_m m(t)}$$

- The rate of transcription from a regulated gene depends on the promoter's occupancy
- If TF P is an activator, the rate of gene transcription is proportional to the promoter's occupancy

Rate of Transcription from Regulated Gene if Transcription Factor is an Activator

$$\frac{dm(t)}{dt} = \alpha_0 + \alpha \frac{\frac{[P]}{K}}{1 + \frac{[P]}{K}} - \delta_m m(t)$$

- Maximal transcriptional rate = α
- Basal transcription rate = α_0

Rate of Transcription from Regulated Gene if Transcription Factor is a Repressor

$$\frac{dm(t)}{dt} = \alpha_0 + \alpha \frac{1}{1 + \frac{[P]}{K}} - \delta_m m(t)$$

- The rate of transcription from a regulated gene depends on the promoter's occupancy
- If TF P is a repressor, the rate of gene transcription is proportional to the promoter's fraction of unbound operators

Gene Regulated by Two Transcription Factors

- Consider a promoter with two non-overlapping operator sites
- O_A binds transcription factor A
- O_B binds transcription factor B
- Promoter may have 4 states:
  - O: A and B unbound
  - OA: A bound at O_A, B unbound
  - OB: B bound at O_B, A unbound
  - OAB: Both A and B are bound

Gene Regulated by Two Transcription Factors (Chemical Notation)

$$O + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OA$$

$$O + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OB$$

$$OB + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OAB$$

$$OA + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OAB$$

Assuming that binding events at O_A and O_B are independent of one another

Equilibrium: Fractions of Promoters in each State

$$O + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OA$$

$$O + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OB$$

$$OB + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OAB$$

$$OA + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OAB$$

$$K_A = \frac{d_1}{a_1}$$

$$K_B = \frac{d_2}{a_2}$$

$$(fraction_O) = \frac{1}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B}}$$

$$(fraction_OA) = \frac{\frac{[A]}{K_A}}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B}}$$

$$(fraction_OB) = \frac{\frac{[B]}{K_B}}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B}}$$

$$(fraction_OAB) = \frac{\frac{[A]}{K_A}\frac{[B]}{K_B}}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B}}$$

Gene Regulated by Two Repressors A and B

$$O + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OA$$

$$O + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OB$$

$$OB + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OAB$$

$$OA + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OAB$$

If the binding of both repressors is needed to block polymerase binding →

Transcription occurs from all promoter states except for OAB

Gene Regulated by Two Repressors A and B, if both need to block polymerase binding

$$O + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OA$$

$$O + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OB$$

$$OB + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OAB$$

$$OA + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OAB$$

$$K_A = \frac{d_1}{a_1}$$

$$K_B = \frac{d_2}{a_2}$$

$$Transcription_Rate = \alpha_0 + \frac{\alpha\left(1 + \frac{[A]}{K_A} + \frac{[B]}{K_B}\right)}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B}}$$

There can be other combinations

- For instance, A may be an activator, and B may be a repressor
- If we assume that B completely blocks polymerase binding, and no expression happens unless A is bound →
- → Transcription requires promoter state OA only.

Cooperativity in Transcription Factor Binding

- Positive cooperativity → Rate of second event is reduced by a factor $K_Q < 1$.
- The reduced K indicates an increased affinity

Fractions of Promoters in each State, if A and B have positive cooperativity

$$O + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OA$$

$$O + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OB$$

$$OB + A \underset{d_1}{\overset{a_1}{\rightleftarrows}} OAB$$

$$OA + B \underset{d_2}{\overset{a_2}{\rightleftarrows}} OAB$$

$$K_A = \frac{d_1}{a_1} > K_A K_Q$$

$$K_B = \frac{d_2}{a_2} > K_B K_Q$$

$$(fraction_O) = \frac{1}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

$$(fraction_OA) = \frac{\frac{[A]}{K_A}}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

$$(fraction_OB) = \frac{\frac{[B]}{K_B}}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

$$(fraction_OAB) = \frac{\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B} + \frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

A and B have strong positive cooperativity

$$(fraction_O) = \frac{1}{1+\frac{[A]}{K_A}+\frac{[B]}{K_B}+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

$$(fraction_OA) = \frac{\frac{[A]}{K_A}}{1+\frac{[A]}{K_A}+\frac{[B]}{K_B}+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

$$(fraction_OB) = \frac{\frac{[B]}{K_B}}{1+\frac{[A]}{K_A}+\frac{[B]}{K_B}+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

$$(fraction_OAB) = \frac{\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}{1+\frac{[A]}{K_A}+\frac{[B]}{K_B}+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

States OA and OB will be negligible.

$K_Q << 1$

$$1+\frac{[A]}{K_A}+\frac{[B]}{K_B}+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q} \approx$$

$$\approx 1+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}$$

A and B have strong positive cooperativity

$$(fraction_O) \approx \frac{1}{1+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

$$(fraction_OAB) \approx \frac{\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}{1+\frac{[A]}{K_A}\frac{[B]}{K_B K_Q}}$$

A and B have strong positive cooperativity: Particular Case A=B=P

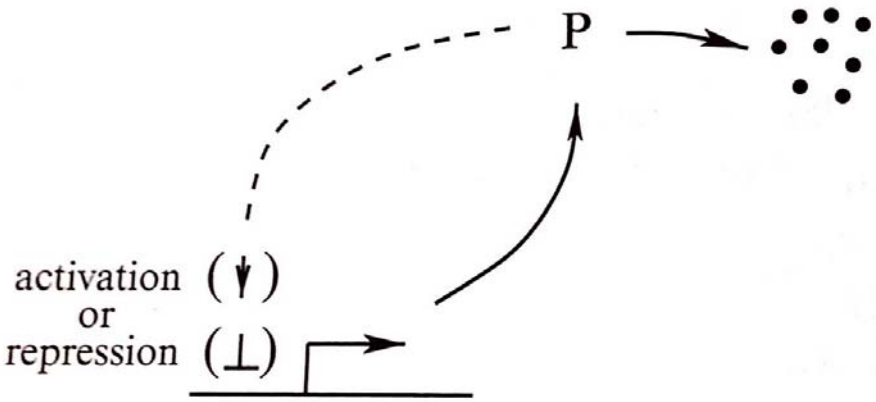
$$(fraction_O) \approx \frac{1}{1+\frac{[P]^2}{K_P{}^2 K_Q}}$$

Hill function with N=2

$$(fraction_OAB) \approx \frac{\frac{[P]^2}{K_P{}^2 K_Q}}{1+\frac{[P]^2}{K_P{}^2 K_Q}}$$

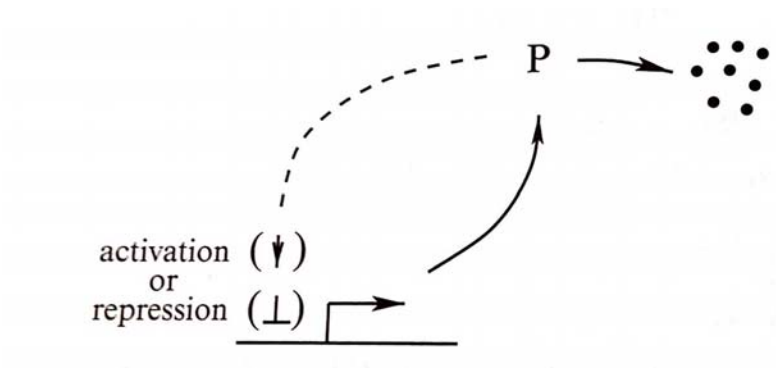
Whenever cooperativity is not that strong, N may be between 1 and 2.

Genes that regulate their own activity



- If the gene's protein product enhances expression, the gene is called autoactivator
- If the product inhibits expression the gene is called autoinhibitor

Simple Model of an Autoinhibitor



$$\frac{dp(t)}{dt} = \alpha \frac{1}{1 + \frac{p(t)}{K}} - \delta_p p(t)$$

- We assume that the mRNA is in quasi-steady-state.
- We also assume that the transcription factor P binds to a single operator site.
- [P]=p

Comparison of Unregulated and Autoinhibited Gene

$$\frac{dp(t)}{dt} = \alpha \frac{1}{1 + \frac{p(t)}{K}} - \delta_p p(t) \qquad \frac{dp(t)}{dt} = \alpha_0 - \delta_p p(t)$$

- Autoinhibition decreases the sensitivity to variations in the maximal expression rate α.
- In order to reach the same steady-state p_∞ the maximal expression rate α must be larger than the unregulated expression rate α_0

Steady-State Protein Level in Unregulated and Autoinhibited Gene

$$\frac{dp(t)}{dt} = \alpha \frac{1}{1+\frac{p(t)}{K}} - \delta_p p(t) = 0$$

$$\frac{dp(t)}{dt} = \alpha_0 - \delta_p p(t) = 0$$

$$p_\infty = \frac{\sqrt{K^2 + 4\alpha \frac{K}{\delta_p}} - K}{2}$$

$$p_\infty = \frac{\alpha_0}{\delta_p}$$

- In order to reach the same steady-state p_∞ the maximal expression rate α must be larger than the unregulated expression rate α_0

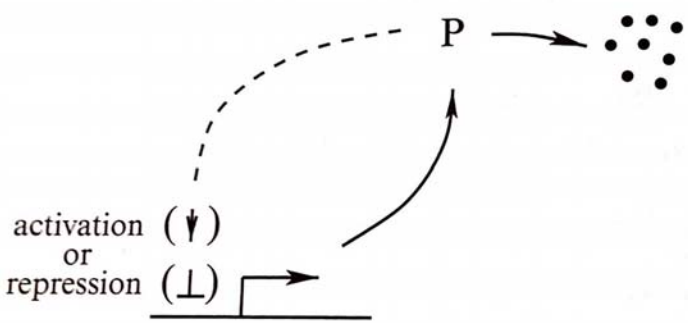
$$p_\infty = \frac{\sqrt{K^2 + 4\alpha \frac{K}{\delta_p}} - K}{2} = \frac{\alpha_0}{\delta_p} \qquad \alpha = \frac{\alpha_0^{\ 2} + \alpha_0 K \delta_p}{K \delta_p}$$

Autoinhibited Gene Expression is Faster than Unregulated Gene Expression

$$p_\infty = \frac{\sqrt{K^2 + 4\alpha \frac{K}{\delta_p}} - K}{2} = \frac{\alpha_0}{\delta_p} \qquad \alpha = \frac{\alpha_0{}^2 + \alpha_0 K \delta_p}{K \delta_p}$$

- As a consequence of the larger maximal expression rate, autoinhibited genes can respond much quicker to changes in protein level demands.

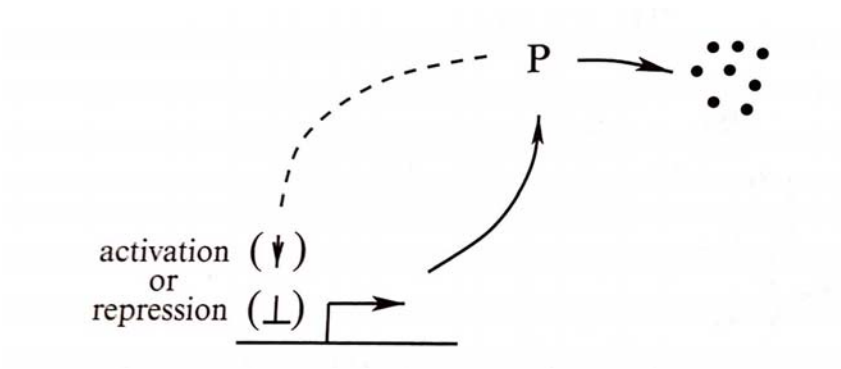
Simple Model of an Autoactivator



$$\frac{dp(t)}{dt} = \alpha \frac{\frac{p(t)}{K}}{1+\frac{p(t)}{K}} - \delta_p p(t)$$

- Such a scalar model may be simply analyzed using phase-plane.
- There are two equilibrium points: $p_\infty=0$ and $p_\infty=(\alpha/\delta_p)-K$

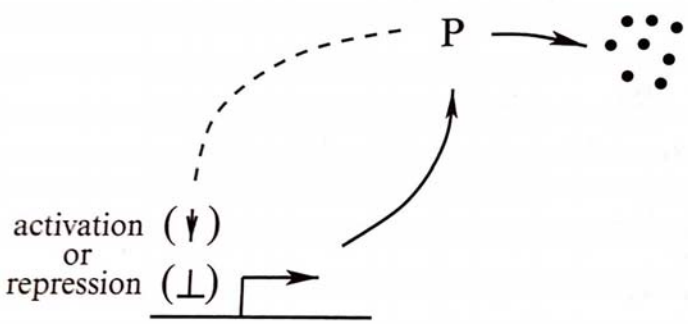
Single Operator Site Autoactivator



$$\frac{dp(t)}{dt} = \alpha \frac{\frac{p(t)}{K}}{1+\frac{p(t)}{K}} - \delta_p p(t)$$

- There are two equilibrium points: $p_\infty=0$ and $p_\infty=(\alpha/\delta_p)-K$
- Case 1: α is small – there is only one physical equilibrium $p_\infty=0$ and it is stable. (Gene is OFF)

Single Operator Site Autoactivator



$$\frac{dp(t)}{dt} = \alpha \frac{\frac{p(t)}{K}}{1+\frac{p(t)}{K}} - \delta_p p(t)$$

- There are two equilibrium points: $p_\infty=0$ and $p_\infty=(\alpha/\delta_p)-K$
- Case 2: α is large : $p_\infty=0$ is unstable and $p_\infty=(\alpha/\delta_p)-K$ is stable quick convergence to a state in which gene is expressing at a high rate

Autoactivators that bind cooperatively at M operator sites

$$\frac{dp(t)}{dt} = \alpha \frac{(\frac{p(t)}{K})^N}{1+(\frac{p(t)}{K})^N} - \delta_p p(t)$$

- N ≤ M and of course N is not necessarily an integer.
- Such a model may exhibit bi-stability where both OFF and ON states are stable
- For most initial conditions the gene is ON but under certain conditions it may turn OFF.