MORPHOGEN DIFFUSION

$$\underbrace{\frac{\partial M}{\partial t} = D \frac{\partial^2 [M]}{\partial x^2}}_{\text{DIFFUSION EQ.}} - \gamma [M] \qquad \text{REACTION-DIFFUSION EQ.}$$

DEGRADATION

DIFFUSION TERM
SMOOTHES DISTRIBUTION

BOUNDARY CONDITIONS:

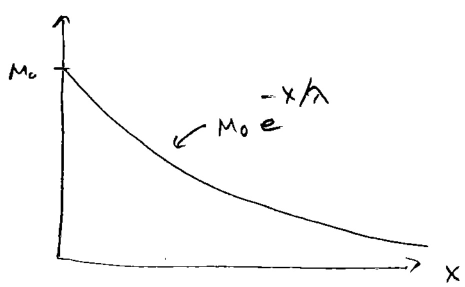
$x = 0$: $M(x) = M_0$ (STEADY CONCENTRATION AT MORPHOGEN SOURCE)

$x \to \infty$: $M(\infty) = 0$ (FAR AWAY ALL MORPHOGEN IS DEGRADED)

STEADY STATE $\partial M/\partial t = 0$:

$$D \frac{d^2}{dx^2} [M]_{ss} - \gamma [M]_{ss} = 0$$

$$\Rightarrow \underline{[M]_{ss} = M_0 e^{-x/\lambda}, \quad \lambda = \sqrt{D/\gamma}}$$



GENE REGULATION:

$$[\dot{m}] = \alpha_m \frac{[g_{ON}]}{[g_{TOT}]} + \alpha_0 - \gamma_m[m]$$

$$[\dot{P}] = \alpha_p[m] - \gamma_p[P]$$

α_m: PRODUCTION RATE

g_{ON}/g_{TOT} : FRACTION OF GENE THAT IS ON

α_0 : LEAKY PRODUCTION

GENE ACTIVATION

$$g_{OFF} + nA \underset{k_-}{\overset{k_+}{\rightleftharpoons}} g_{ON}$$

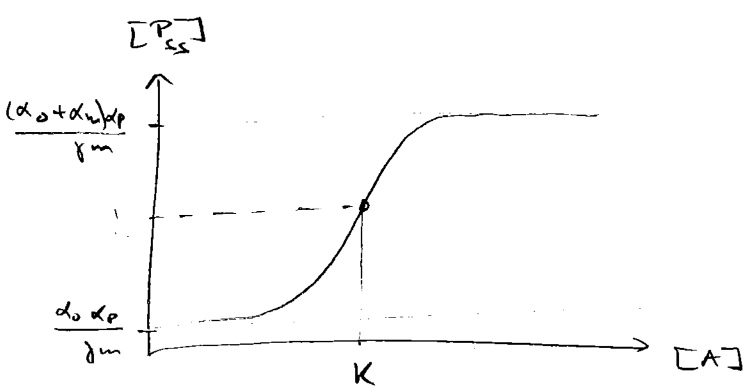
$$\dot{g}_{ON} = k_+[g_{OFF}][A]^n - k_-[g_{ON}] \overset{!}{=} 0 \quad \text{(STEADY STATE)}$$

$$\Rightarrow [g_{OFF}] = \frac{k_-}{k_+}[g_{ON}]/[A]^n$$

$$\Rightarrow [g_{TOT}] = [g_{ON}] + [g_{OFF}] = 1/(1+[A]^n/K^n)[g_{ON}] \qquad k_-/k_+ = K^n$$

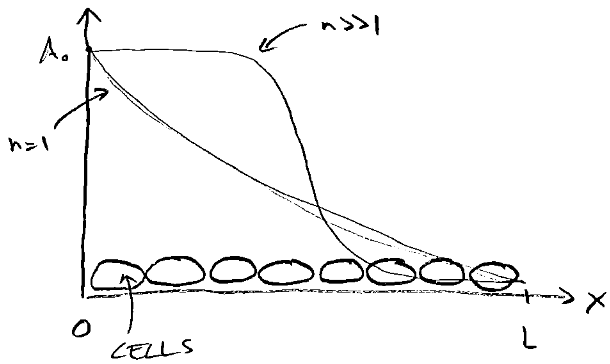
$$[\dot{m}] = \alpha_m \frac{([A]/K)^n}{1+([A]/K)^n} + \alpha_0 - \gamma_m[m] \overset{!}{=} 0 \quad \text{(STEADY STATE)}$$

$$\Rightarrow [\dot{P}] = \frac{\alpha_p\alpha_m}{\gamma_m} \frac{([A]/K)^n}{\underbrace{1+([A]/K)^n}_{P_A}} + \frac{\alpha_0\alpha_p}{\gamma_m} - \gamma_p[P]$$



$$\overset{\alpha_0=0}{[P]_{ss}} = \underbrace{\frac{\alpha_p\alpha_m}{\gamma_m\gamma_p}}_{P_0} \frac{[A]^n}{K_A^n + [A]^n}$$

ASSUME A IS A MORPHOGEN WITH A LOCALIZED SOURCE:



$$[P]_{ss} = P_0 \frac{[A]^n}{K_A^n + [A]^n}$$

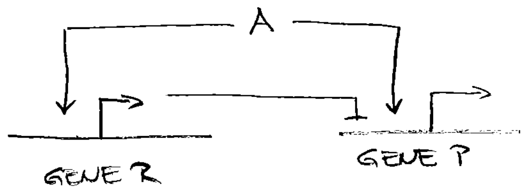
HIGH COOPERATIVITY CAN RESULT IN A STEEP SPATIAL THRESHOLD!

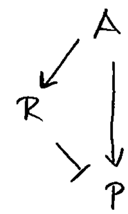
GENE NETWORKS

CONSIDER $\alpha_0 = 0, \quad n = 1$

$$P_A = \frac{[A]}{K_A + [A]}$$: PROB. THAT A IS BOUND TO GENE

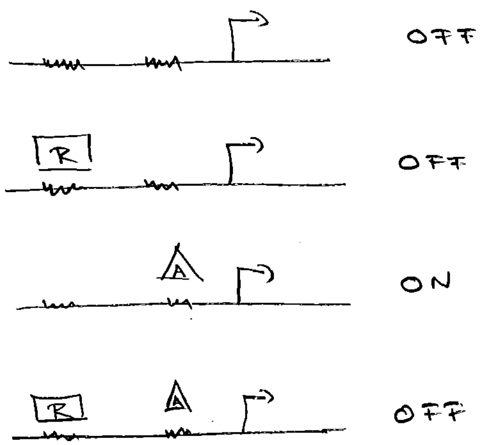
INCOHERENT FEED-FORWARD LOOP





BINDING SITES FOR A, R ARE INDEPENDENT.

POSSIBLE STATES OF THE PROMOTER



$$\text{PROB (A BOUND, R NOT BOUND)} = \frac{[A]}{K_A + [A]} \cdot \frac{K_R}{K_R + [R]}$$

$$[P]_{ss} = P_0 \frac{[A]}{K_A + [A]} \cdot \frac{K_R}{K_R + [R]}$$

$$= P_0 \frac{[A]}{K_A + [A]} \cdot \frac{K_R}{K_R + R_0 \dfrac{[A]}{K_{A2} + [A]}}$$

$K_{A2} >> [A]$

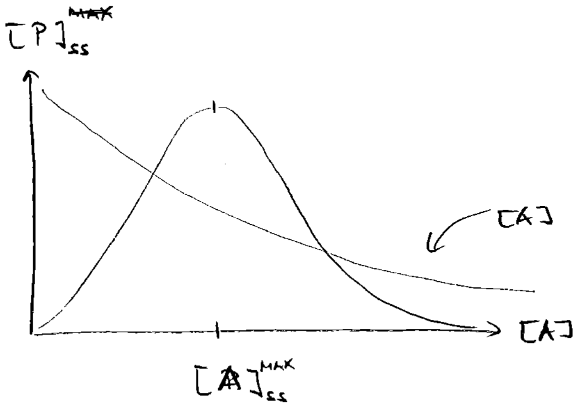
$$= P_0 \frac{[A]}{K_A + [A]} \cdot \frac{K_R}{K_R + R_0 [A] / K_{A2}}$$

$[A] = 0 : [P]_{ss} = 0$

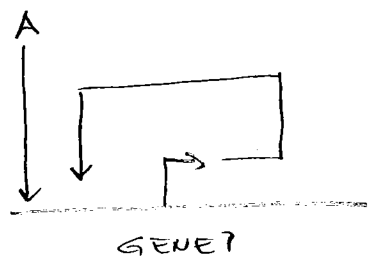
$[A] \gg K_A : [P]_{ss} = 0$ (NOT REALLY VALID)

IN BETWEEN? COMPUTE $d[P]_{ss}/d[A] = 0 \Rightarrow [P]_{ss}$ HAS MAX

$$[A]^{MAX} = \sqrt{K_A K_P K_{A2}/R_1}$$



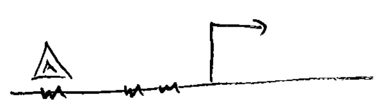
POSITIVE FEEDBACK AND BISTABILITY



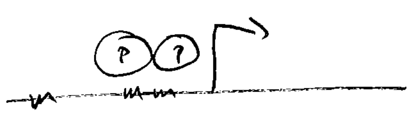
ASSUME P BINDING IS COOPERATIVE, $n=2$

A NON-COOPERATIVE, $n=1$

OFF INDEPENDENT SITES



ON



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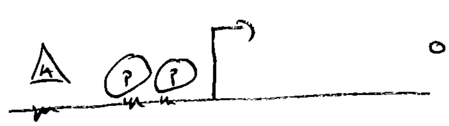


ON

$$Pr(A \text{ OR } B \text{ BOUND}) = 1 - \overbrace{\left(1 - Pr(A)\right)}^{\text{PROB. FOR A NOT BOUND}} \overbrace{\left(1 - Pr(B)\right)}^{\text{PROB. FOR B NOT BOUND}} = Pr(P) + Pr(A)\left(1 - Pr(B)\right)$$

$$Pr(A) = \frac{[A]}{K_A + [A]}$$

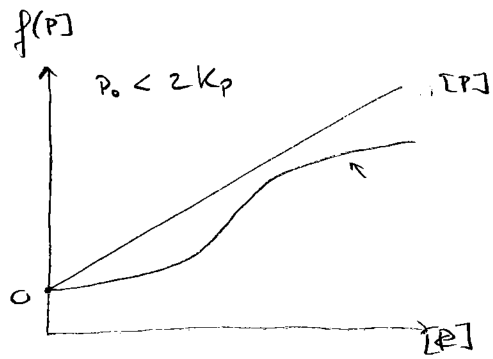
$$Pr(P) = \frac{[P]^2}{K_p^2 + [P]^2}$$

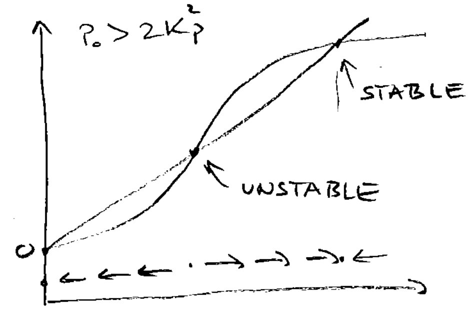
$$\frac{d[P]}{dt} = P_0 \gamma \left(\frac{[P]^2}{K_p^2 + [P]^2} + \frac{[A]}{[A] + K_A} \cdot \frac{K_p^2}{K_p^2 + [P]^2} \right) - \gamma [P]$$

FIRST CONSIDER $[A] = 0$:

$$\frac{d[P]}{dt} = \gamma \left(P_0 \frac{[P]^2}{K_p^2 + [P]^2} - [P] \right) \stackrel{!}{=} 0$$

WHAT ARE POSSIBLE STEADY STATE VALUES OF P?





$$[P] \left(\frac{P_0 [P]}{K_p^2 + [P]^2} - 1 \right) = 0 \Rightarrow [P] = 0$$

$$\text{OR} \quad [P]^2 - P_0[P] + K_p^2 = 0 \Rightarrow [P]_\pm = \frac{1}{2}\left(P_0 \pm \underbrace{\sqrt{P_0^2 - 4K_p^4}} \right)$$

$\Rightarrow P_0 > 2K_p^2$ FOR SOLUTION TO EXIST

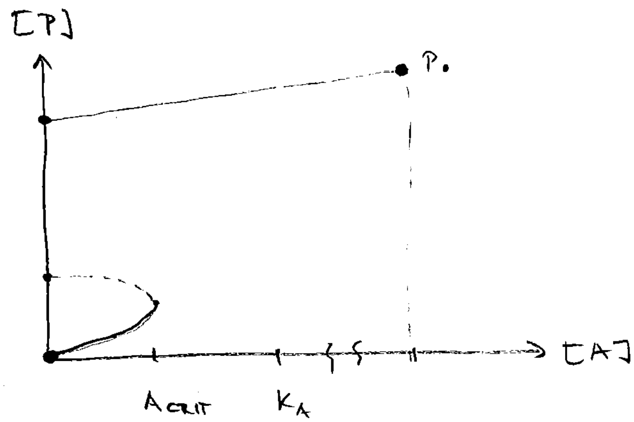
THREE FIXED POINTS.

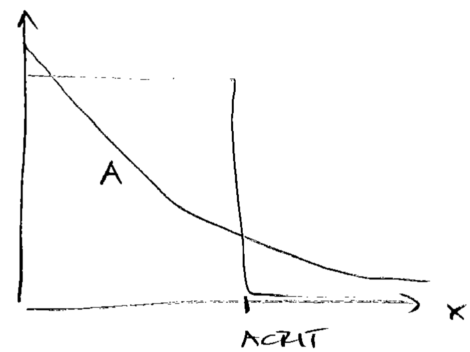
NOW CONSIDER $[A] \gg K_A$

$$\frac{d[P]}{dt} = P_0 \gamma \left(\frac{[P]^2}{K_p^2 + [P]^2} + \left[1 - \cancel{\frac{[P]^2}{K_p^2 + [P]^2}} \right] \right) - \gamma_P [P]$$

$$= P_0 \gamma - \gamma_P [P]$$

$\Rightarrow [P]_{ss} = P_0$: ONE FIX POINT





PATTERN IS MAINTAINED EVEN WHEN A DISAPPEARS