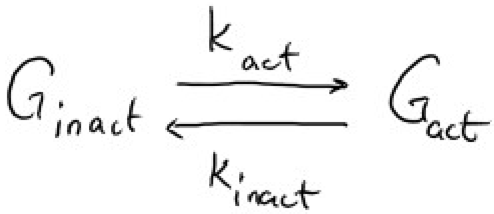
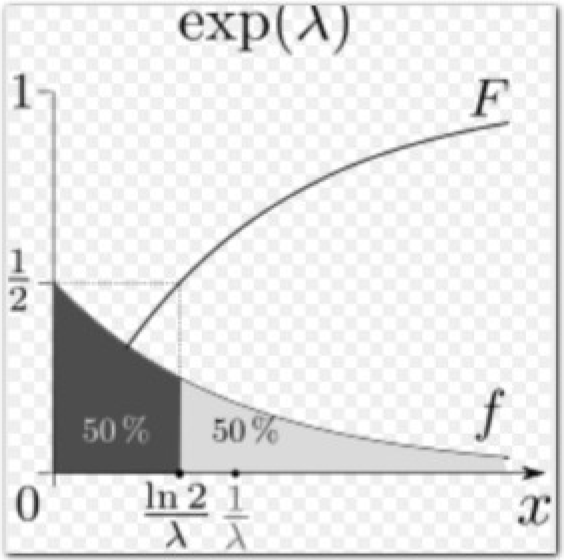
Stokastik gen ekspresyonu





Uniform probability of activation over the time:

probability density function

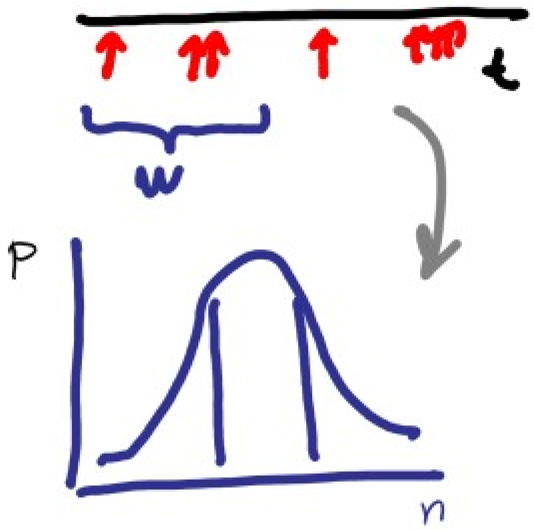
$f(t) = e^{-t/b}/b$

cumulative density function

$F(t) = 1 - e^{-t/b}$

b : mean time between events

$t_{1/2} = \ln 2\, b = 0.693\, b$



Activation as first order reaction:

$$G_{inact} \xrightarrow{k_{act}} G_{act}$$

⇝

$$\frac{dG_{act}}{dt} = k_{act} \cdot G_{inact}$$

$k_{act} = 1/6$

$k_{act} = \ln 2 / t_{1/2}$

ACTIVATION:

G_{inact} : 0

G_{act} : 1

0 → 1 switch probability: $k_{act} = 1/6 = k_1$

$k_{act} \propto$ ploidity

INACTIVATION:

- removal of transcriptional activator
- binding of transcriptional inhibitor

$$k_{inact} = k_{act\text{-}off} + k_{inh\text{-}on}$$

fraction of time G_{act}:

$$= k_{act} / (k_{act} + k_{inact})$$

($\approx$ fraction of cells in which G_{act} at any given time) activated gene produces product P (1° kinetics)

& product decays at a rate $\propto$ [P]

$$\frac{dP}{dt} = k_3\, G_{act} - k_4 P$$

diploid cell :

$$\frac{dP}{dt} = k_3 (G_{1act} + G_{2act}) - k_4 P$$

[P] fluctuates with stochastic variation in G_{act}

 [P] fluctiation amplitude :

- $t_{1/2}$ of G_{act} & G_{inact}
- synthesis & destruction rate of P

small k_{act} & k_{inact} $\rightsquigarrow$ long $t_{1/2}$ for activation/inactivation

large P synthesis & decay rate

$\Longrightarrow$ LARGE FLUCTUATION in [P]

large k_{act} & k_{inact} $\rightsquigarrow$ short $t_{1/2}$ for act/inact

$\Longrightarrow$ SMALL FLUCTUATIONS in [P]

$$[P]_{mean} = (G_{1act} + G_{2act})\, k_{act}\, k_3 \,/\, (k_{inact}\, k_4 + k_{act}\, k_4)$$

$$[P]_{mean} = \frac{k_3 (G_{1act} + G_{2act}) k_{act}}{k_4 (k_{inact} + k_{act})}$$

$$T_{G_{act}} = \frac{k_{act}}{k_{act} + k_{inact}}$$

Fraction of time G is activated

$$\frac{dP}{dt} = k_3 (G_{1act} + G_{2act}) - k_4 P \qquad \text{Eq 4}$$

Synthesis: $k_3 (G_{1act} + G_{2act})$

degradation: $-k_4 P$

(Eq 5)

$$[P]_{mean} = \frac{k_3 (G_{1act} + G_{2act})}{k_4} \cdot \frac{k_{act}}{k_{act} + k_{inact}}$$

- $k_3 (G_{1act} + G_{2act})$: P synthesis
- k_4: P degradation
- $\frac{k_{act}}{k_{act} + k_{inact}}$: T_{Gact}

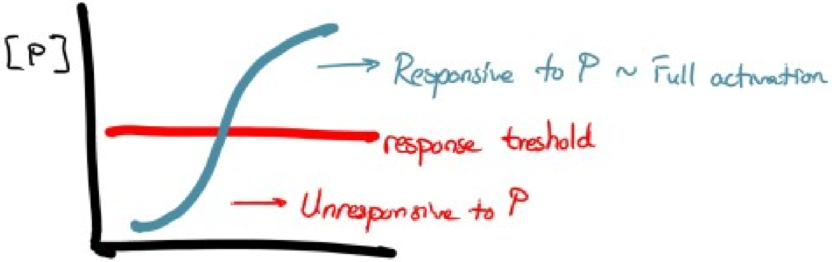
Two Patterns of Stochastic Gene Expression:

1. Stochastic initiation ⟹ Expression will eventually become homogenous in all cells
2. $0 \rightleftharpoons 1$ transition between alternative states in different cells ⟹ Salt & pepper pattern

k_{act} ↓ k_{inact} ↓
OR
k_3 ↑ k_4 ↑

$[P]_{mean}$ remains unchanged
however, system spends increased time @ $[P]_{min}$ & $[P]_{max}$ or $[P]_{1/2}$

Transition between high/medium/low ~ RANDOM



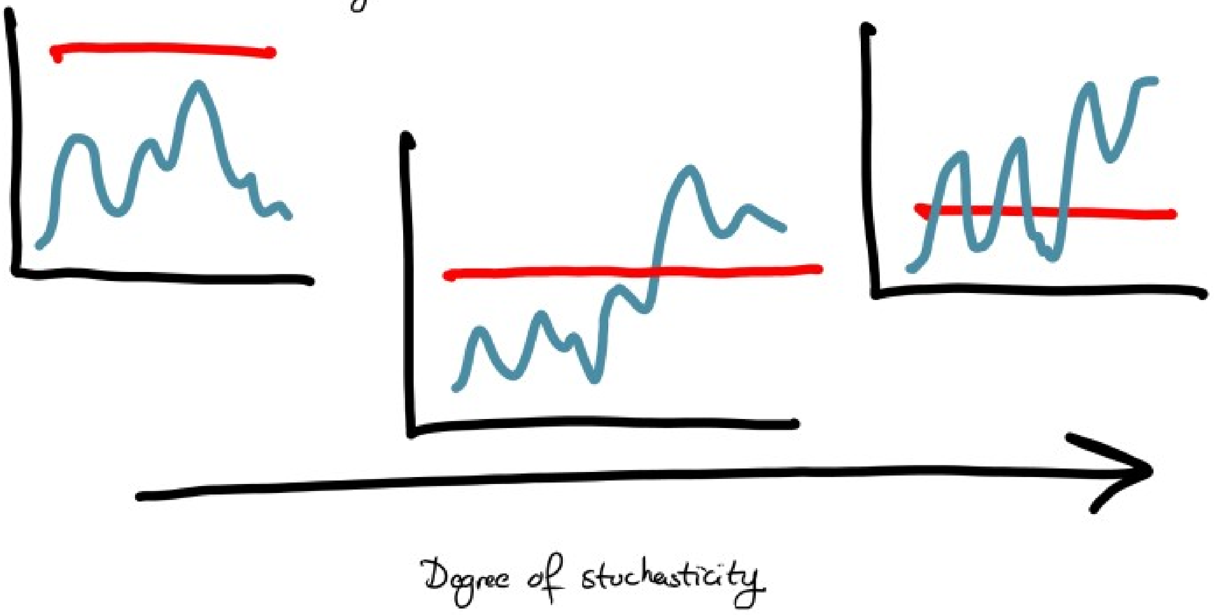
response treshold determines the fraction of population that express the phenotype

$$G_{inact} \underset{}{\overset{k_{act}}{\rightleftharpoons}} G_{act}$$

$$G_{inact} \xrightarrow{k_{act}} G_{act}$$

$$\frac{dG_{act}}{dt} = k_{act} \cdot G_{inact}$$

high treshold vs low treshold



Let P act as an inhibitor of inactivation reaction:

$G_{inact} \xrightarrow{k_{act}} G_{act}$

(Eq 7)

$\frac{dG_{act}}{dt}$

$$\frac{dG_{act}}{dt} = k_{act}G_{inact} - k_{inact}G_{act}/P$$

$\frac{dG_{inact}}{dt}$

$G_{inact} \xleftarrow{k_{inact}} G_{act}$

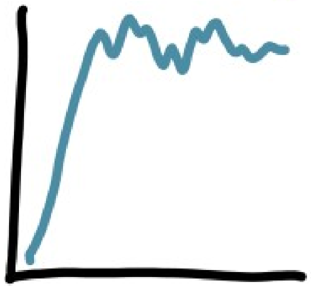
SIMILAR EFFECTS!

Let P act as a activator of activation reaction:

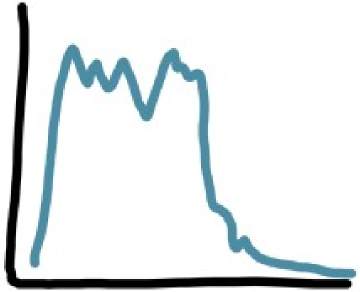
(+) feedback

(Eq 8)

$$\frac{dG_{act}}{dt} = P \cdot k_{act}G_{inact} - k_{inact}G_{act}$$



(+) fb → G_{act}



(+) fb of P to G_{act} is not strong

→ permanent inactivation

For a diploid system:

$$\frac{dG_{1act}}{dt} = P k_{act} G_{1inact} - k_{inact} G_{1act} / P$$

$$\frac{dG_{2act}}{dt} = P k_{act} G_{2inact} - k_{inact} G_{2act} / P$$

Synthesis

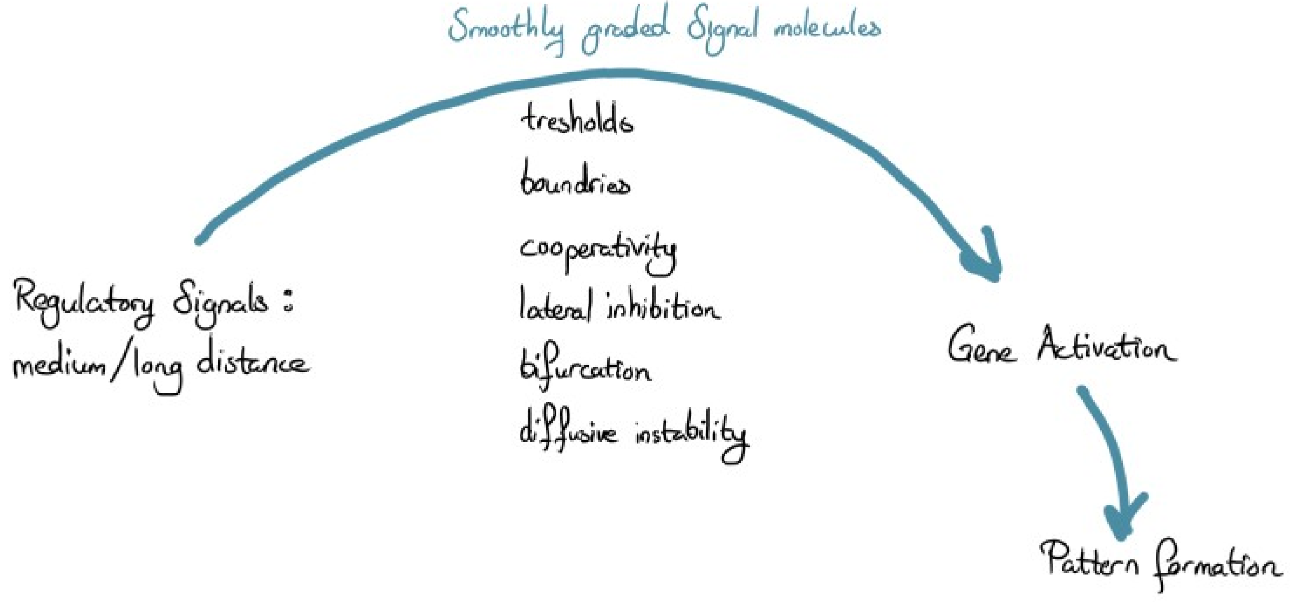
$$\frac{dP}{dt} = k_3 \left(G_{1act} + G_{2act} \right) - k_4 P$$

Degradation

Hill coefficient : measure of cooperativity in binding process
Used to estimate the nb of ligand molecules required to bind to a receptor to produce a functional effect

1 : independent binding

>1 : Cooperative binding



Graded Signal

Slow Cycle vs Fast Cycle

$0 \rightleftarrows 1$

activation / inactivation

RESPONSE : Gene Activation

P production

Temporal & spatial distribution of stochastic response

- Stochastic permanent gene inactivation
- kept active with high probability

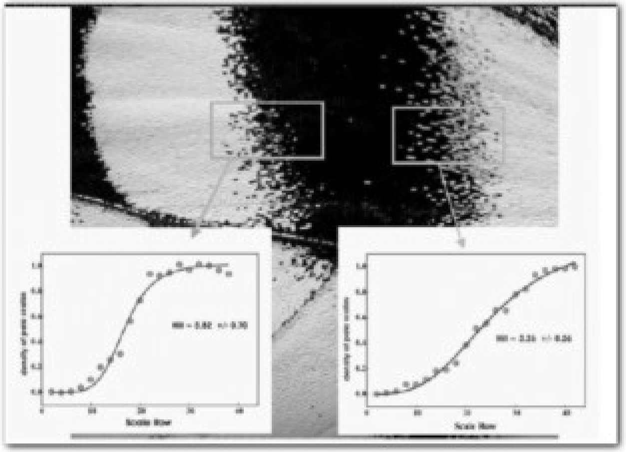
1 OR 0

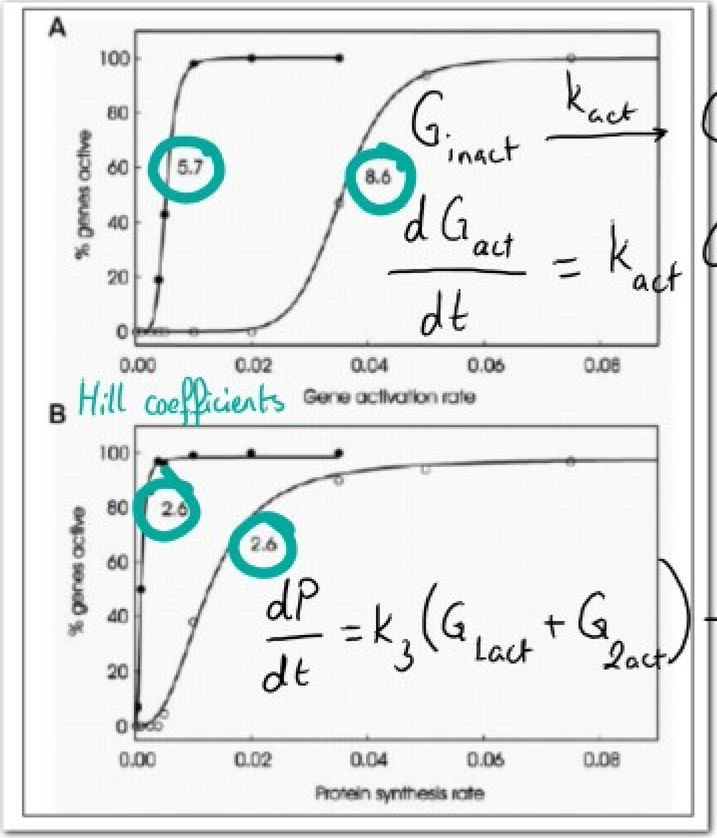
depending on :

- transcriptional activator levels
- product synthesis & decay rates

Smooth Gradients of Signal Molecules

Spatial variation in the probability that the genes in given cell will be activated / inactivated





$$G_{inact} \xrightarrow{k_{act}} G_{act}$$

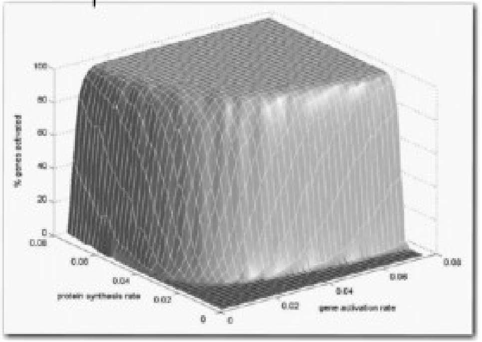
$$\frac{dG_{act}}{dt} = k_{act} G_{inact}$$

$$\frac{dP}{dt} = k_3 (G_{1act} + G_{2act}) - k_4 P$$

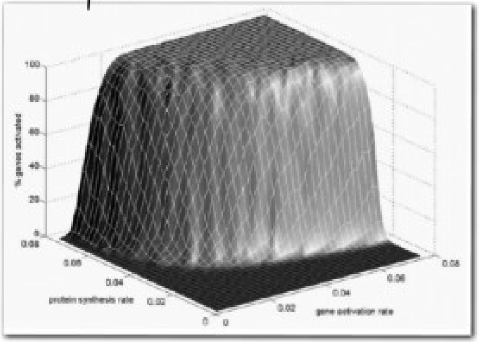
Response of stochastic gene activation system to

(A) a linear gradient of transcriptional activator activity

(B) linear gradient in the product synthesizing enzyme activity params : 0.05



params : 0.075



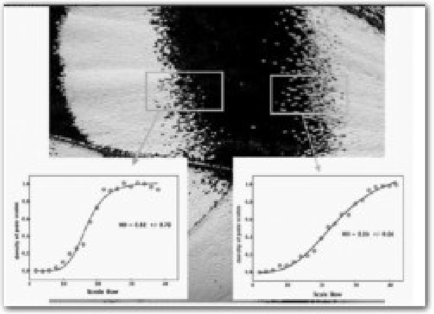
the gene represented in Y-axis provides genetic background for the gene represented by x-axis

Bivariate plots :

transcription factor activity → % G_{act} → Protein Synthesis

- transitions are always sigmoid
- params affect midpoints & tresholds : Sharp/switch-like OR gradual

Stochastic gene expression without feedback regulation produces treshold-like response to graded input signals

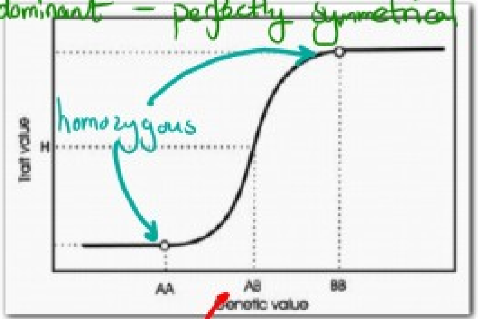


Stochastic expression at boundaries — regulation of tresholds

Genetic value → Sigmoidal relation → Phenotypic value

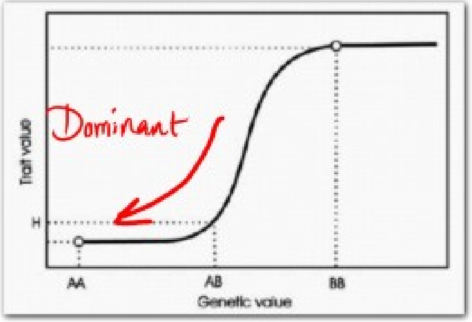
Nonlinear

Codominant – perfectly symmetrical

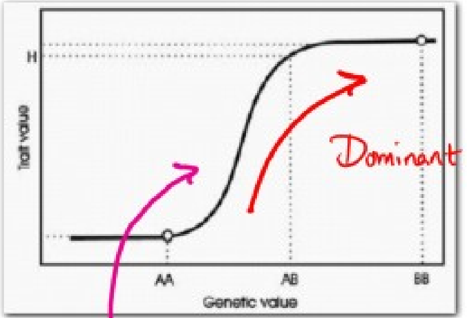


homozygous

heterozygous

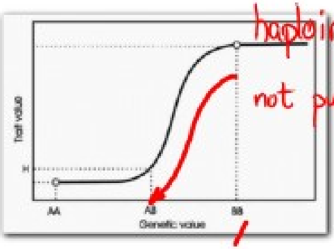


Dominant



Dominant

← mutation in alleles →



haploinsufficiency : remaining allele can not pull trait value beyond mid-point

change in genetic background

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Change in shape of curve — slope & inflection point of sigmoid