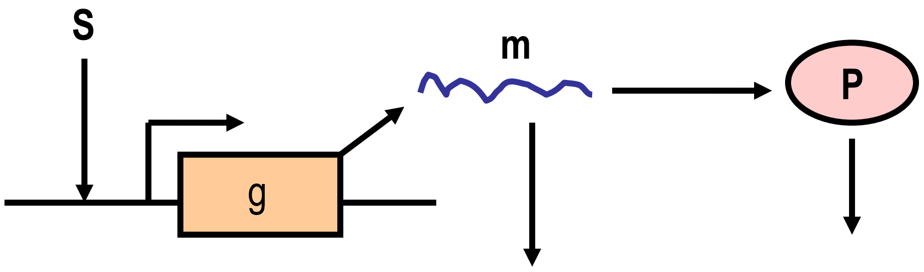
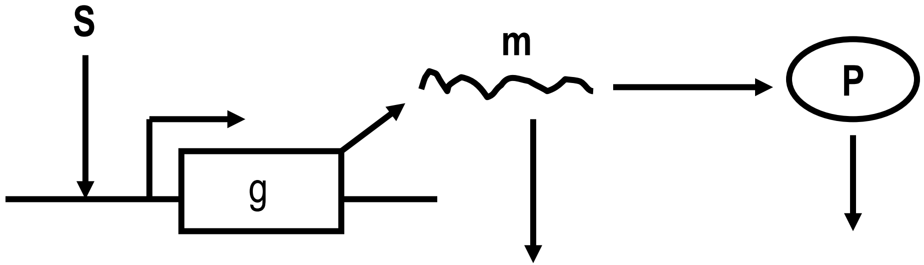


Modeling Molecular Processes-3

Expression of a protein

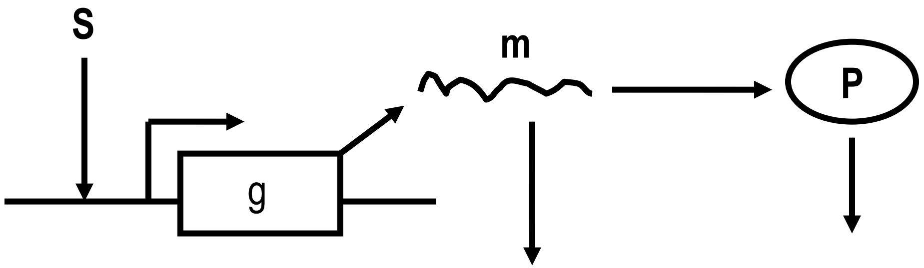
Involves transcription & translation



Simplest model:
Club multiple steps and represent just two processes, production and degradation of protein

$$\frac{d[P]}{dt} = k_s.S - k_d[P]$$

When simple model does not work



Some time:

Inducing signal has unique control dynamics

Stability of mRNA plays crucial role

Translation rate plays crucial role

We need to separate transcription and translation → Consider mRNA and protein as separate dependent variables

Control of transcription by a signal

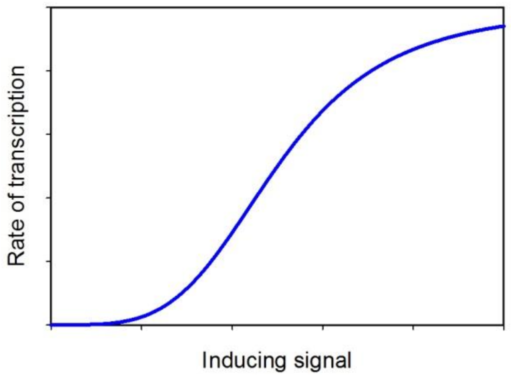
Rate of transcription is controlled by inducing or inhibitory signal

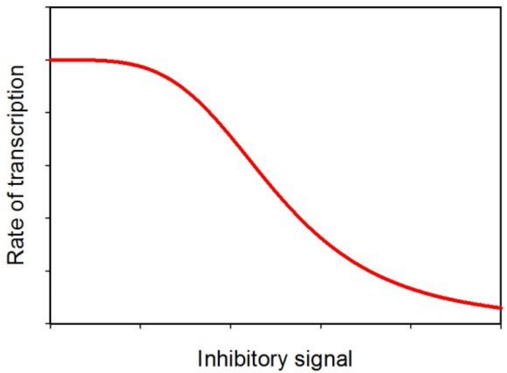
e.g.: IPTG controls the rate of transcription from lac operon/promoter system

$$\frac{d[m]}{dt} = k_1.S - k_2[m]$$

k_1: rate constant for transcription
k_2: rate constant for degradation of mRNA

Cooperativity among transcription factors → Input out-put of such control is often sigmoidal





A suitable sigmoid function

Must be simple and biologically meaningful

Hill function:

$$y = \frac{x^n}{K^n + x^n}$$

For $x \geq 0$

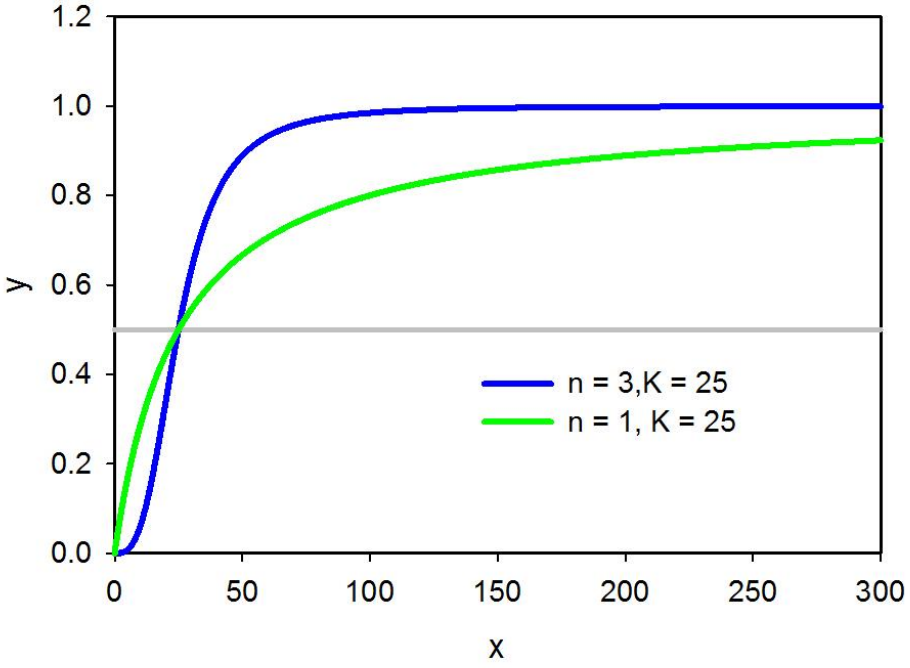
$$0 \leq y \leq 1$$

K : Hill constant → Position for half-saturation

n: Hill coefficient → Decides stiffness

n = 1 → Rectangular hyperbola

n > 1 → Sigmoid : Represents cooperativity



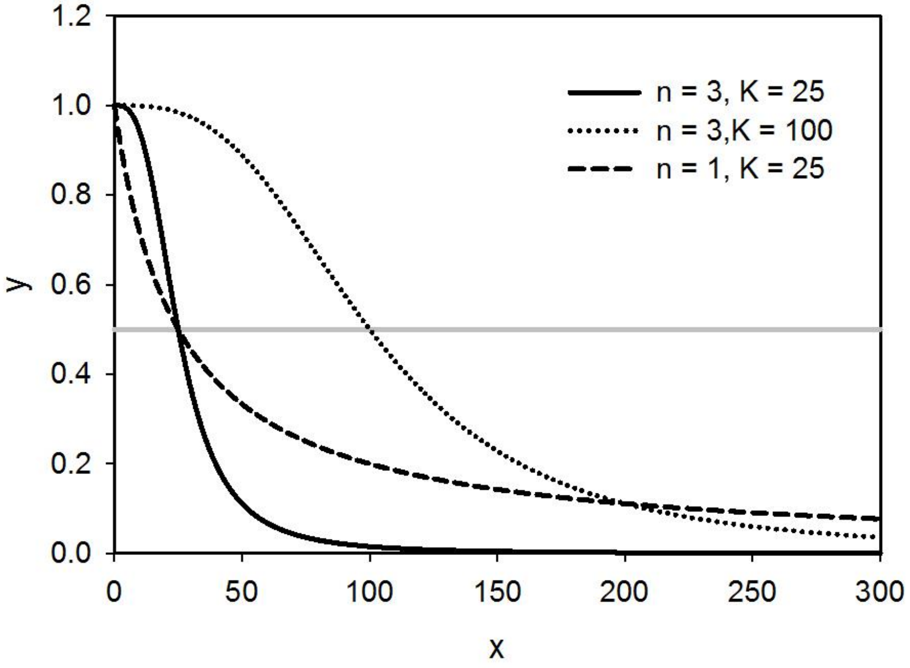
A suitable sigmoid function

Negative / Inverse Hill function:

$$y = \frac{K^n}{K^n + x^n}$$

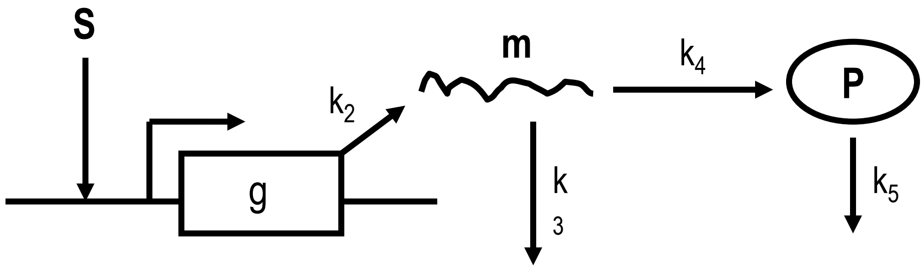
For $x \geq 0$

$0 \leq y \leq 1$



Used when the signal inhibits transcription

Modeling transcription and translation



$$\frac{d[m]}{dt} = k_2 . \frac{S^n}{K^n + S^n} - k_3 . [m]$$

$$\frac{d[P]}{dt} = k_4 . [m] - k_5 . [P]$$

If there is leaky expression:

$$\frac{d[m]}{dt} = k_1 + k_2 . \frac{S^n}{K^n + S^n} - k_3 . [m]$$

Modeling transcription and translation

$$\frac{d[m]}{dt} = k_1 + k_2 . \frac{S^n}{K^n + S^n} - k_3 .[m]$$

$$\frac{d[P]}{dt} = k_4 .[m] - k_5 .[P]$$

Reduce the system:

If transcription is much faster than translation

→ mRNA will reach steady state very fast

At steady state:

$$\frac{d[m]}{dt} = k_1 + k_2 . \frac{S^n}{K^n + S^n} - k_3 .[m] = 0$$

$$\Rightarrow k_3 .[m] = k_1 + k_2 . \frac{S^n}{K^n + S^n}$$

$$\Rightarrow [m] = \frac{k_1}{k_3} + \frac{k_2}{k_3} . \frac{S^n}{K^n + S^n}$$

Modeling transcription and translation

$$\frac{d[m]}{dt} = k_1 + k_2.\frac{S^n}{K^n + S^n} - k_3.[m]$$

$$\frac{d[P]}{dt} = k_4.[m] - k_5.[P]$$

Reduce the system:
If transcription is much faster than translation
→ mRNA will reach steady state very fast

At steady state:

$$[m] = \frac{k_1}{k_3} + \frac{k_2}{k_3}.\frac{S^n}{K^n + S^n}$$

$$\frac{d[P]}{dt} = k_4.(\frac{k_1}{k_3} + \frac{k_2}{k_3}.\frac{S^n}{K^n + S^n}) - k_5.[P]$$

$$\frac{d[P]}{dt} = \frac{k_4.k_1}{k_3} + \frac{k_4.k_2}{k_3}.\frac{S^n}{K^n + S^n} - k_5.[P]$$

$$\frac{d[P]}{dt} = k_b + k_i.\frac{S^n}{K^n + S^n} - k_5.[P]$$

$$k_b = \frac{k_4.k_1}{k_3} \quad \& \quad k_i = \frac{k_4.k_2}{k_3}$$

When signal inhibits transcription

Considering transcription and translation separately:

$$\frac{d[m]}{dt} = k_1 + k_2 . \frac{K^n}{K^n + S^n} - k_3 .[m]$$

$$\frac{d[P]}{dt} = k_4 .[m] - k_5 .[P]$$

Considering faster transcription and steady state for mRNA:

$$\frac{d[P]}{dt} = k_b + k_i . \frac{K^n}{K^n + S^n} - k_5 .[P]$$

Key points:

1. Protein production and degradation:
    1. mRNA and protein are considered as separate dependent variables
    2. Transcription and translation as separate processes.
2. This allows modeling the effect of inducer, stability of mRNA etc on level of protein
3. Transcription factors and inhibitors often have cooperativity.
4. Cooperativity leads to sigmoidal input-output relation.
5. Hill function and inverse Hill function is used for modeling such sigmoidal relation