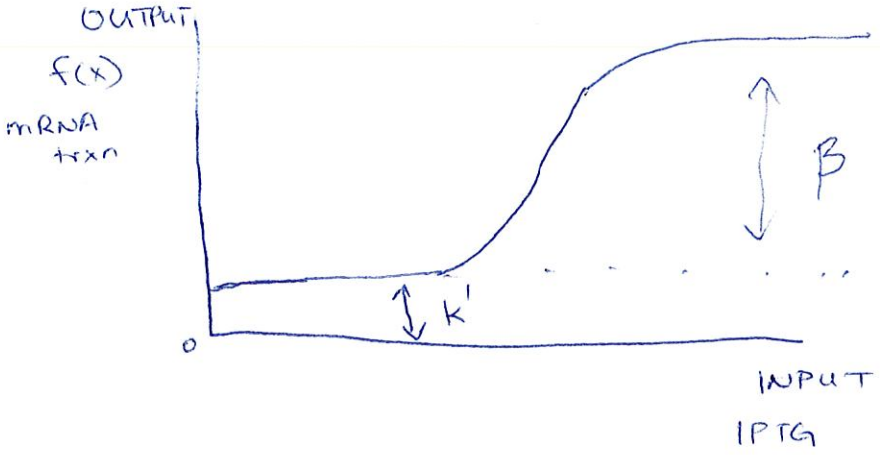
QUANTITATIVE PROPERTIES OF BIOLOGICAL SYSTEMS

9/11/2018

Recall: Parts have properties that control function



Hill eqn

$$f(x) = k' + \beta \frac{x^n}{K^n + x^n}$$

(saturation kinetics)

$K^n + x^n$ ranges from 0 → 1

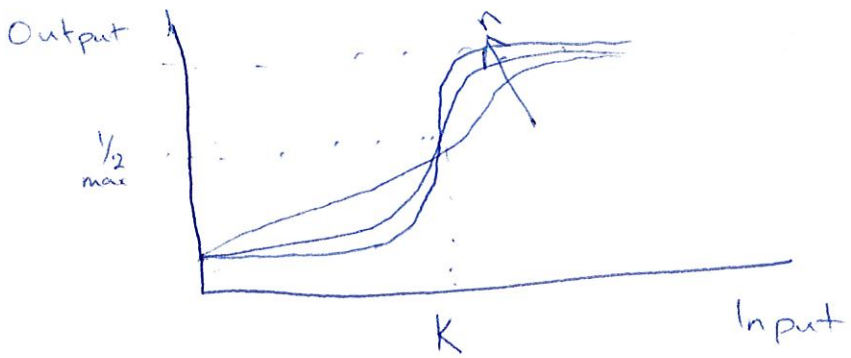
x = Input e.g. ligand concentration
↳ lactose / IPTG

k' = background exp.

β = max exp. change

K = concentration @ which expression is half maximum

n = Hill coefficient



as $n \uparrow$, system becomes more binary (ON/OFF) or ~~ultrasensi~~ ultrasensitive

Background Exp. (k')

T7 < TetR < araC < lacI

"Tight" ⟶ "leaky"

Strength (fold change β/k')

lacI < araC < TetR < T7

What do these parameters mean physically?

K^n is a fn of binding affinity

- weaker binding ↑ K^n
  - ↳ more slowly saturate promoter (slower output changes w/ input)

$K^n \propto K_d$

Hill coefficient → fn of ~~the~~ binding intxn

↳ $\propto$ # binding events

- cannot be higher the # of binding sites available

lacI - tetramer binds 2 operator sites

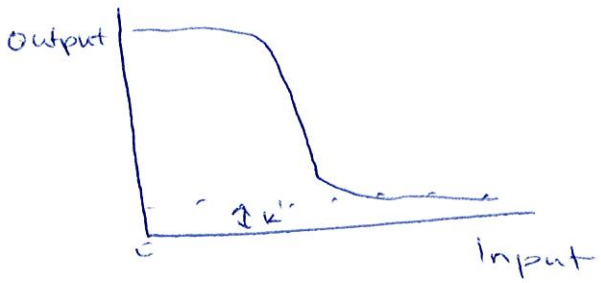
$n < 2$

tetR/araC dimers $n \sim 2$

$\beta + k'$ maximal expression

↳ correlated w/ gene copy #, cellular resources, RNAP affinity for promoter, etc.

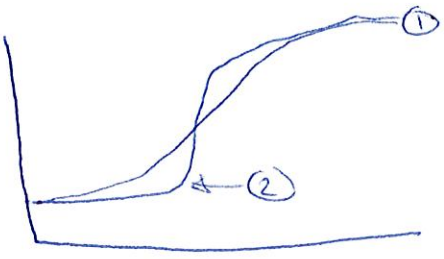
Gene Repression



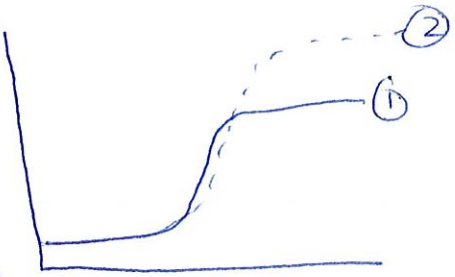
$$f(x) = k' + \beta \frac{K^n}{K^n + x^n}$$

How do I . . . .

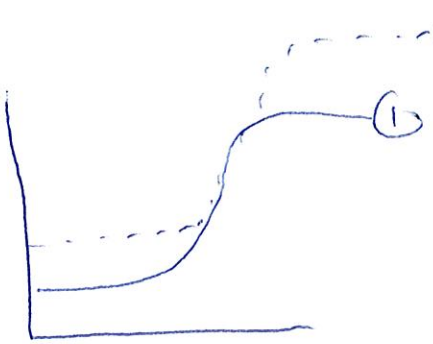
↑ steepness
↳ ↑ n, change regulatory protein



↑ vertical scaling, Gain
↳ ↑ β
- change regulatory protein, ↑ RNAP
. . .

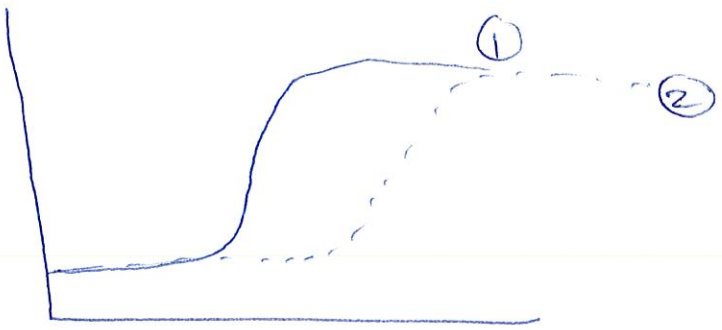


Vertical shift
↳ ↑ k', ↑ copy #



Horizontal Scaling

↳ ↑K, decreasing binding affinity



Are there other knobs to tune?

Mass balance; Accumulation = Gen. − Consumption

m = mRNA conc.

k_{dm} = degradation rate of mRNA

μ = dilution due to growth

$$\frac{dm}{dt} = f(\text{ligand}) - g(m)$$

$$= k' + \frac{\beta x^n}{K^n + x^n} - (k_{dm} + \mu)m$$

$\mu \to 0$, $k_{dm} \gg 0$

P = protein conc.

k_d = degradation rate of protein

$$\frac{dP}{dt} = f(mRNA) - g(P)$$

$$= \alpha m - (k_d + \mu)P$$

@ SS $\quad \frac{dP}{dt} = \frac{dm}{dt} = 0$

$$m_{ss} = \underbrace{\frac{k'}{k_{dm}}}_{A} + \underbrace{\frac{\beta}{k_{dm}}}_{B} \frac{x^n}{K^n + x^n}$$

$$= A + B\frac{x^n}{K^n + x^n}$$

$$\frac{dP}{dt} \rightarrow 0 = a m_{ss} - (k_d + \mu) P_{ss}$$

$$P_{ss} = \frac{a m_{ss}}{\mu + k_d} = \frac{a}{\mu + k_d}\left(A + \frac{B X^n}{K^n + X^n}\right)$$

Can control protein conc. by changing

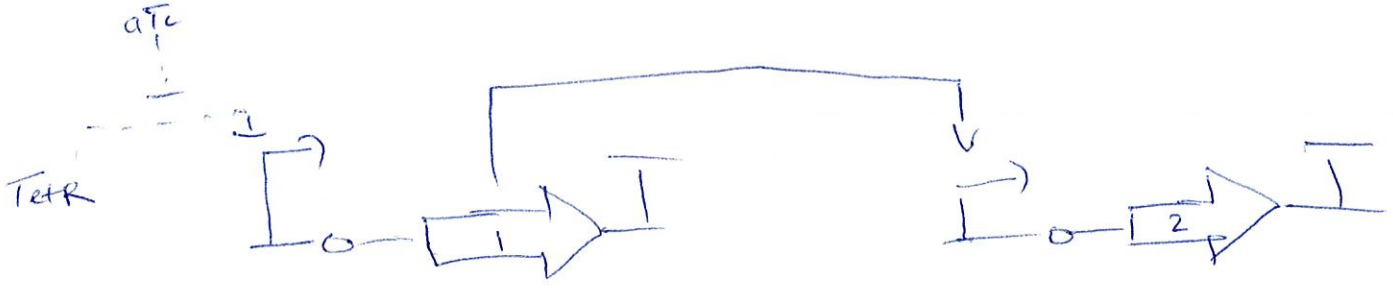
$a \rightarrow$ trsln rate $\propto$ ribosome availability (e.g. O-ribosomes)

$\mu \rightarrow$ change growth rate
- ↳ growth rate in chemostat set by flow rate/ dilution rate
- ↳ Monod growth ⇒ nutrient supply

$k_d \rightarrow$ e.g. degradation by proteasome

ClpXP for degradation, ubiquination, etc

What happens when we combine systems?



Gene 2 $= f(atc) = ?$

m_1 P_1
m_2 P_2
X

$$\frac{dP_1}{dt} = a m_1 - (\mu + k_d) P_1 \Rightarrow P_{1ss} = \frac{a m_1}{\mu + k_{d_1}}$$

$$\frac{dm_1}{dt} = k_1' + \frac{\beta_1 X^n}{k_1^n + X^n} - k_{dm_1} m_1 \Rightarrow m_{1ss} = \frac{k_1' + \beta_1 X^n}{k_{dm_1}(k_1^n + X^n)}$$

$$\frac{dm_2}{dt} \Rightarrow m_{2ss} = \frac{k_2'}{k_{dm_2}} + \frac{\beta_2 P_1^{n_2}}{k_{dm_2}(K_2^{n_2} + P_1^{n_2})}$$

$$\frac{dP_2}{dt} \Rightarrow P_{2ss} = \frac{a_2 m_{2ss}}{\mu + k_{d_2}}$$

activators in series.

β & n multiply

↓ amplifies the signal

↓ more binary (ON/OFF)

evolution selects for cascades due to