10.37 Chemical and Biological Reaction Engineering, Spring 2007
Prof. K. Dane Wittrup
Lecture 15: Gene Expression and Trafficking Dynamics

This lecture covers: Approach to steady state and receptor trafficking

Central dogma of molecular biology:

DNA → mRNA → protein
transcription translation

Material balance on one specific mRNA

Accumulation = synthesis – degradation

$$C_{mRNA} \equiv \frac{\text{moles mRNA}}{\text{cell volume}}$$

$$K_r \equiv \frac{\text{mol mRNA}}{(\text{time})(\text{cell volume})}$$, transcription (function of gene dosage, inducers, etc.)

$$\mathrm{V}_i \equiv \frac{\text{cell volume}}{\text{vessel volume}}$$

$$\frac{d\left(C_{mRNA}\mathrm{V}_i\right)}{dt} = K_r\mathrm{V}_i - \gamma_r C_{mRNA}\mathrm{V}_i$$

$\gamma_r \equiv$ first order rate constant for mRNA degredation
$\mathrm{V}_i \equiv$ a function of time (cells grow, divide)
→ can't pull out of the derivative

Do the chain rule:

$$C_{mRNA}\frac{d\mathrm{V}_i}{dt} + \mathrm{V}_i\frac{dC_{mRNA}}{dt} = K_r\mathrm{V}_i - \gamma_r C_{mRNA}\mathrm{V}_i$$
$$\frac{dC_{mRNA}}{dt} = K_r - \gamma_r C_{mRNA} - C_{mRNA}\frac{1}{\mathrm{V}_i}\frac{d\mathrm{V}_i}{dt}$$

simplify: $\frac{1}{\mathrm{V}_i}\frac{d\mathrm{V}_i}{dt} = \mu$ (specific growth rate in exponential growth)

$$\frac{dC_{mRNA}}{dt} = K_r - \gamma_r C_{mRNA} - \underbrace{\mu C_{mRNA}}$$

dilution by growth term
(b/c concentration is on a per-cell volume basis)

$$\frac{dC_{mRNA}}{dt} = K_r - (\gamma_r + \mu)C_{mRNA}$$

at steady-state:

$$C_{mRNA,\,SS} = \frac{K_r}{(\gamma_r + \mu)}$$

transient case, analytical solution (just integrate)

$$C_{mRNA} = \frac{K_r}{(\gamma_r + \mu)}\left(1 - \underbrace{e^{-(\mu+\gamma_r)t}}\right)$$

independent of the transcription rate constant K_r

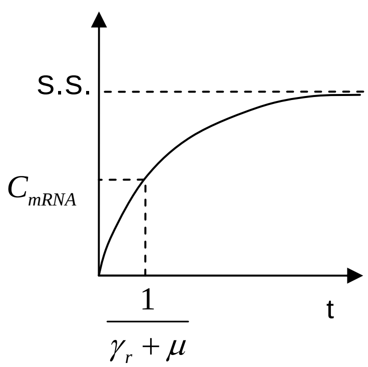

Figure 1. Concentration of C_{mRNA} versus time. At long times steady state is approached.

Similar rate expression for the protein:
(again, per-cell volume basis, analogous constants)

$$\frac{dC_p}{dt} = K_p C_{mRNA} - (\gamma_p + \mu)C_p$$

function of time, solved for above

$$\frac{dC_p}{dt} = K_p \frac{K_r}{(\gamma_r + \mu)}\left(1 - e^{-(\gamma_r+\mu)t}\right) - (\gamma_p + \mu)C_p$$

steady-state: $\frac{d}{dt} = 0$, $t \to \infty$

$$C_{p,\,SS} = \frac{K_r K_p}{(\gamma_r + \mu)(\gamma_p + \mu)}$$

$$\frac{C_{p,SS}}{C_{mRNA,SS}} = \frac{K_p}{\gamma_p + \mu}$$

Note: K_p, γ_p vary from protein to protein and condition to condition

Integrate $\frac{dC_p}{dt}$:

$$C_p = C_{p,SS}\left(1 + \frac{(\gamma_r + \mu)e^{-(\gamma_p+\mu)t} - (\gamma_p + \mu)e^{-(\gamma_r+\mu)t}}{\gamma_p - \gamma_r}\right)$$

Usually, $\gamma_p \ll \gamma_r$

in E. coli $\frac{\ln 2}{\gamma_r} \sim 7$ minutes on average.

for most proteins, $\frac{\ln 2}{\gamma_p} \sim$ hours to days.

also, $\gamma_r \gg \mu$

Apply assumptions to get:

$$C_p = \frac{K_p K_r}{\gamma_r(\gamma_p + \mu)}\left(1 - e^{-(\gamma_p+\mu)t}\right)$$

Delays in synthesis

	time (seconds)		
	E. coli	Yeast	Mammals
mRNA – 1 kb gene	10-20	30-50	30-50
Protein – 400 a.a.	20	20	60-400

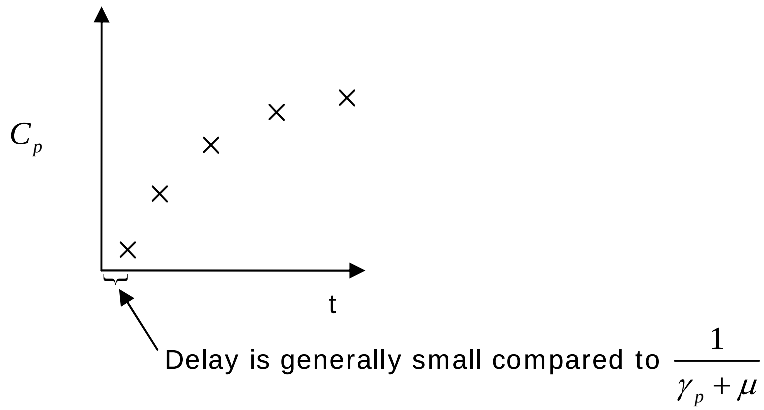

Figure 2. Concentration of protein versus time.

However, the delay can dramatically destabilize feedback loops.

Cellular compartmentalization

$C_{p,1} \to C_{p,2}$ where $C_{p,1} \equiv C_p$ for compartment 1, and $C_{p,2} \equiv C_p$ for compartment 2
rate = $K_{transport} C_{p,1}$

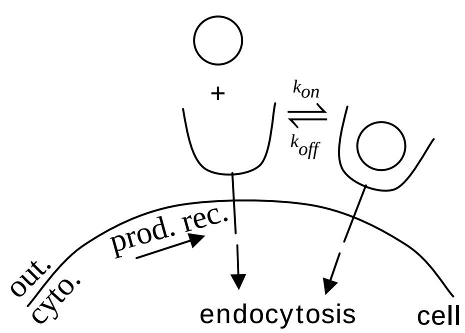

Figure 3. Diagram of protein-ligand binding on the cell surface.