LECTURE EIGHT: Gene Expression, Trafficking Dynamics and catalysis

This lecture covers: Approach to steady state and receptor trafficking, Inorganic and enzyme catalysis and their properties; kinetics of heterogeneous catalytic reactions; adsorption isotherms, derivation of rate laws; and Langmuir-Hinshelwood kinetics

1. **Gene Expression and Trafficking Dynamics**

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

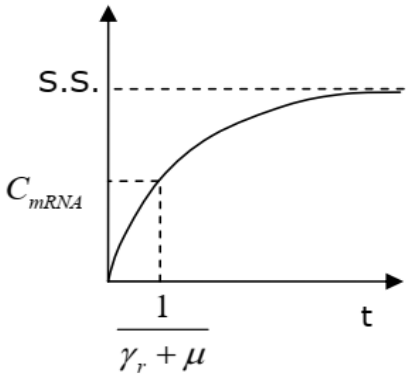

Figure 1. Concentration of C_{mRNA} versus time. At long times steady state is approached.

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

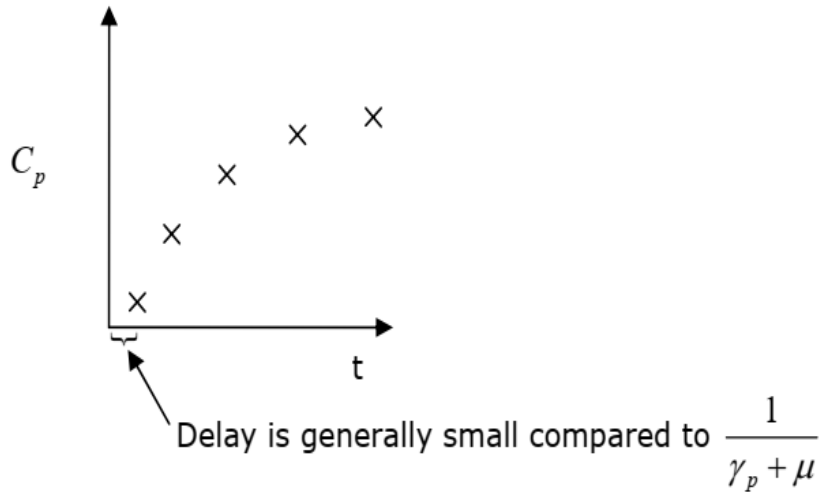

Figure 2. Concentration of protein versus time.

However, the delay can dramatically destabilize feedback loops.

Cellular compartmentalization

$C_{p,1} \rightarrow C_{p,2}$ where $C_{p,1} \equiv C_p$ for compartment 1, and $C_{p,2} \equiv C_p$ for compartment 2

rate = $K_{transport} C_{p,1}$

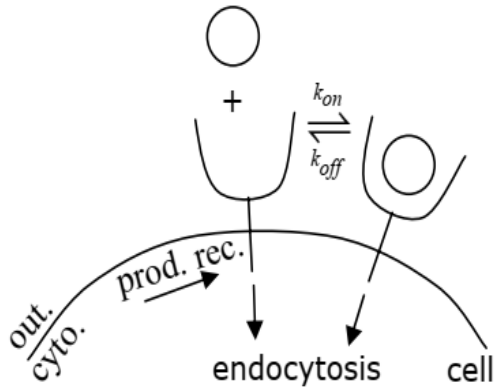

Figure 3. Diagram of protein-ligand binding on the cell surface.

2. **Catalysis**

What initiates the reaction?

$A + B \rightarrow$ starts upon mixing

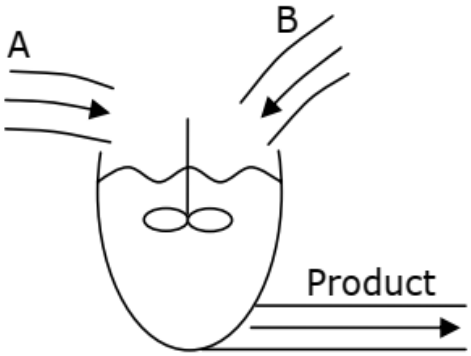

Figure 1. Bi-molecular reaction in a CSTR.

Temperature drastically increases reaction rate.

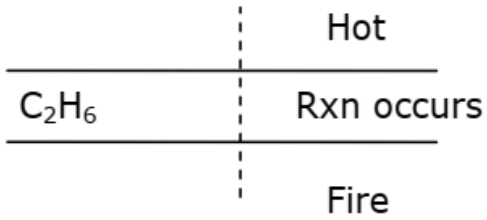

Figure 2. Schematic of tube reactor.

Catalyst dramatically increases reaction rate.

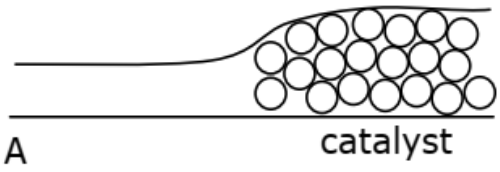

Figure 3. Schematic of packed bed reactor.

Catalyst: Accelerates rate of reaction but is not consumed

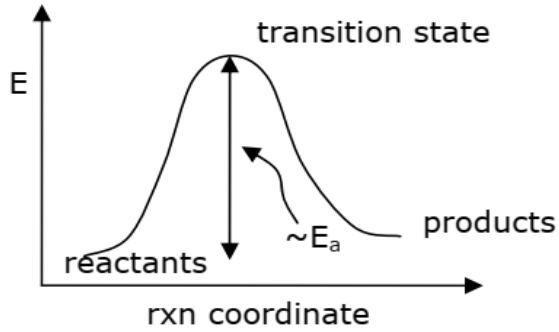

Figure 4. Reaction diagram.

rate constant:

$$k = \frac{k_B T}{h} \exp\left[-\frac{(G_{\text{ts}} - G_{\text{reactants}})}{RT} \right]$$

$$G = H - TS$$

$$e^{-G/RT} = e^{-H/RT} e^{S/R}$$

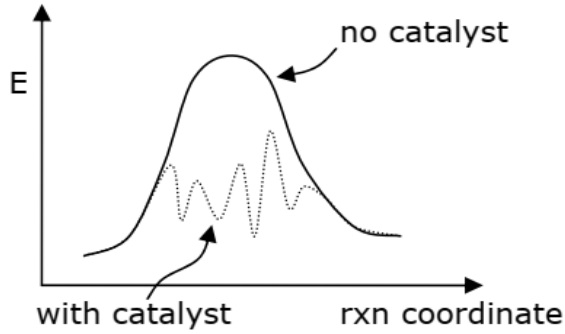

Figure 5. Reaction diagram with and without catalyst.

The reaction forms many intermediates. A catalyst lowers the energy of these intermediates.

Acid/Base catalysis

$$\boxed{ROR + H_2O \rightarrow 2ROH}$$

$$ROR + H^{\oplus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{H}{\underset{\oplus}{ROR}}$$

$$\overset{H}{\underset{\oplus}{ROR}} \xrightarrow{k_2} ROH + R^{\oplus}$$

$$R^{\oplus} + H_2O \xrightarrow{k_3} ROH + H^{\oplus}$$

QSSA $\overset{H}{ROR}^{\oplus}$, $R^{\oplus}$

$$O \approx \frac{d\left[\overset{H}{ROR}^{\oplus}\right]}{dt} = k_1\left[H^+\right][ROR] - (k_{-1}+k_2)\left[\overset{H}{ROR}^{\oplus}\right]$$

$$\left[\overset{H}{ROR}^{\oplus}\right]_{QSSA} = \frac{k_1}{k_{-1}+k_2}\left[H^+\right][ROR]$$

$$\frac{d[ROH]}{dt} = 2k_2\left[\overset{H}{ROR}^{\oplus}\right]_{QSSA}$$

$$\frac{d[ROH]}{dt} \approx \frac{2k_1k_2}{k_{-1}+k_2}\left[H^+\right][ROR] = r$$

$r_A \sim [A]$

$r_A \sim [\text{catalyst}]$ (where $\sim$ denotes "proportional to")

$$\left[H^+\right] + \left[\overset{H}{ROR}^{\oplus}\right] + \left[R^+\right] = \frac{N_{H^+\,added}}{V} = \left[H^+\right]_{added}$$

$$\left[H^+\right]\left(1 + \frac{k_1[ROR]}{k_1+k_2} + \frac{k_1k_2[ROR]}{k_3(k_{-1}+k_2)[H_2O]}\right) = \left[H^+\right]_{added}$$

$$r = \frac{k_{eff}[ROR]\left[H^+\right]_{added}}{1+k[ROR]}$$

$$r = \frac{k[\text{catalyst}][A]}{1+k_A[A]+k_B[B]+\ldots}$$

All the things that the catalyst binds to

Langmuir-Hinshelwood: all reagents bind to catalyst, bound forms react

Eley-Rideal: one reagent binds, 2nd reagent reacts with bound form

$$\frac{dN_A}{dt} = Vr_A \leftarrow f\left([A],\left[H^+\right]\right)$$

$$\frac{dN_A}{dt} = (\text{area of metal}) r_A''$$

r_A'': moles / area s

$f(\theta_A)$

where $\theta_A = \dfrac{N_{A\ bound}}{N_{\substack{total\ sites \\ on\ surface}}}$