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4/5/4

Lecture 1

- the advantage of being dimensionless
- simplifying problems by comparing scales
- analyzing steady-state behavior
- re~~qutal~~l equations for gene regulation
- exhibiting self control ~~control one's self~~ : autoregulation

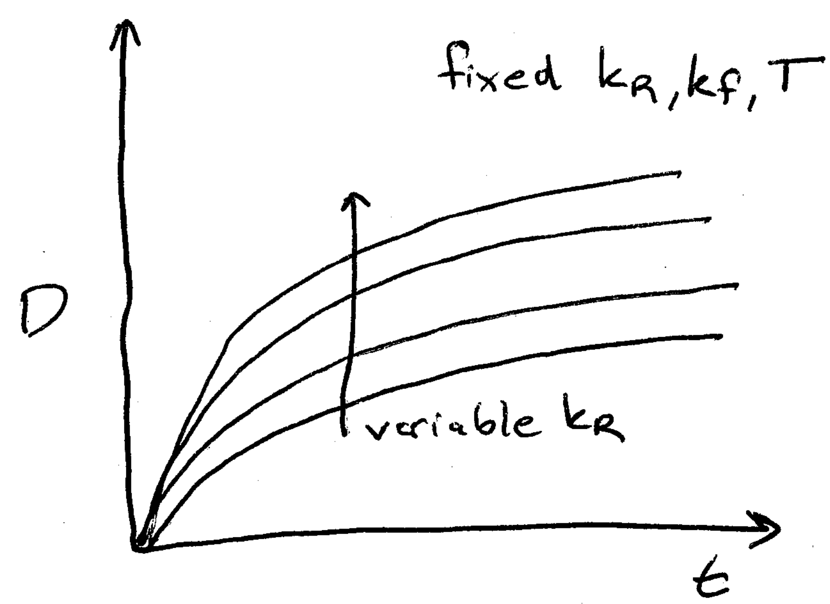
Dimerization

$$2A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} D$$

$$\frac{1}{2}\frac{dA}{dt} = -k_f A^2 + k_r D$$

$$\frac{dD}{dt} = -k_R D + k_F A^2$$

$$T = 2D + A$$



- varying k_R, k_f, T would require a book to convey system behavior
- use intuition to ~~reduce number~~ combine ~~of~~ parameters

STEP 1: Identify all dimensions

A : c	T : c
D : c	k_R : $1/s$
t : s	k_F : $\frac{1}{c\,s}$

BOOKKEEPING: variables ↑ (A, D, t) parameters ↑ (T, k_R, k_F)

STEP 2 : Introduce dimensionless variables

$$\alpha \equiv \frac{A}{T} \qquad \beta \equiv \frac{P}{T} \qquad \tau \equiv t \cdot k_R$$

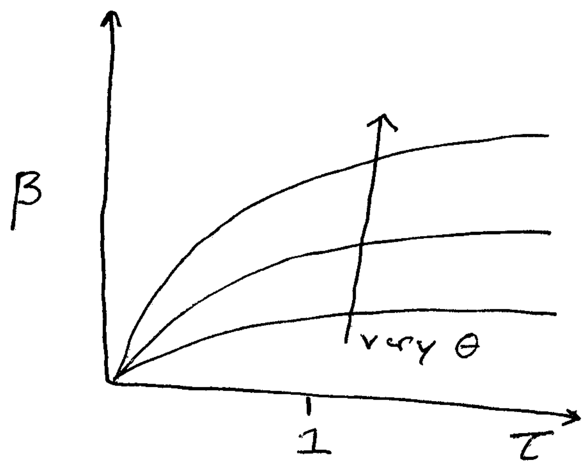
STEP 3 : Substitute

$$\frac{dD}{dt} = k_R D - k_F A^2$$

$$k_R T \frac{d\beta}{d\tau} = k_R T \beta - k_F T^2 \alpha^2$$

$$\frac{d\beta}{d\tau} = \beta - \underbrace{\frac{k_F T}{k_R}}_{\theta} \alpha^2$$

$$\boxed{\begin{aligned} \frac{d\beta}{d\tau} &= \beta - \theta \alpha^2 \\ \alpha + \beta &= 1 \end{aligned}}$$



$\tau_{\text{special point}}$

$$1 = \tau_s = t_s k_R$$

timescale of rxn :

$$t_s = \frac{1}{k_R}$$

if $k_R = 1/s \Rightarrow t \sim$ seconds

$k_R = 0.01/s \Rightarrow t \sim$ minutes

We were lucky, dimerization is relatively easy

more formal definition

$$t_s \sim \frac{f_{max} - f_{min}}{\left| \frac{df}{dt} \right|_{max}}$$

Example: Degradation

$$A \xrightarrow{k} \text{nothing}$$

$$\frac{dA}{dt} = -kA \Rightarrow A(t) = A_0 e^{-kt}$$

BC: @ $t=0$, $A = A_0$

$$f_{max} = A_0 \qquad f_{min} = 0 \qquad \left|\frac{dA}{dt}\right|_{max} = kA_0$$

$$t_s = \frac{A_0 - 0}{kA_0} = \frac{1}{k}$$

Mixing of Reactive Gasses:

Ozone reactions: nanoseconds

Wind: weeks to months

- from the perspective of the reactions, the wind is still
- from the perspective of the wind, the reactions are always over

How can this be used to simplify problems?

Michaelis-Menton Kinetics

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} P$$

$$\frac{dS}{dt} = k_{-1}C - k_1 ES$$

$$\frac{dC}{dt} = k_1 ES - k_{-1}C - k_2 C$$

velocity
$$v = \frac{dP}{dt} = k_2 C \qquad E_0 = E + C$$

- common assumption : C is at quasi-steady-state

$$\frac{dC}{dt} = k_1 E_0 S - k_1 C S - k_{-1} C - k_2 C = 0$$

$$= k_1 E_0 S - (k_1 S + k_{-1} + k_2) C$$

$$C = \frac{k_1 E_0 S}{k_{-1} + k_2 + k_1 S} = \frac{E_0 S}{K_m + S} \qquad K_m \equiv \frac{k_{-1} + k_2}{k_1}$$

$$v = \frac{dP}{dt} = \frac{k_2 E_0 S}{K_m + S} \qquad \text{familiar form}$$

when is this assumption valid?

wind S   C "sees" constant S (S_0)

~~Prep~~ ozone C   To S, C is always finished

~~C changes so fast~~

an argument of scale:

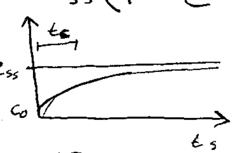
$$t_c \ll t_s$$

- constant $S = S_0$

$$\frac{dC}{dt} = k_1 E_0 S_0 - (k_1 S_0 + k_{-1} + k_2) C$$

form of solution $C(t) = C_{ss}\left(1 - e^{(k_1 S_0 + k_{-1} + k_2) t}\right)$

$$t_c \sim \frac{1}{k_1 S_0 + k_{-1} + k_2} = \frac{1}{k_1 (S_0 + K_m)}$$



- C is always finished $\left(\frac{dS}{dt}\right)_{qss} = -\left(\frac{dP}{dt}\right)_{qss}$ (mass conservation)

~~[illegible]~~

$$t_s = \frac{S_0 - 0}{\frac{k_2 E_0 S_0}{K_m + S_0}} = \frac{K_m + S_0}{k_2 E_0} \Leftarrow \left|\frac{dS}{dt}\right|_{max,qss} = \frac{k_2 E_0 S_0}{K_m + S_0}$$

Can now state conditions when qss is valid

$$t_c \ll t_s$$

$$\boxed{\frac{1}{k_1(S_0+K_m)} \ll \frac{K_m+S_0}{k_2E_0}}$$

- t_s can be used to dedimensionalice the system

The steady state behavior can be used to determine ~~the behavior~~ where the equations will "end up"

Autocatalysis

eg, Prions

$$A + B_0 \underset{k_R}{\overset{k_F}{\rightleftharpoons}} 2A$$

constant B_0

$$\frac{dA}{dt} = k_F A B_0 - k_R A^2$$

$$\alpha = A/B_0 \qquad \tau = t B_0 k_R$$

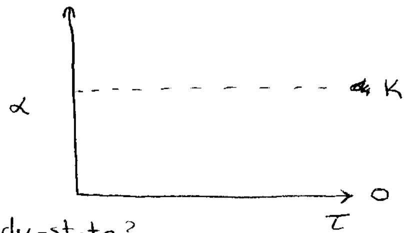
$$k_R B_0^2 \frac{d\alpha}{d\tau} = k_F B_0^2 \alpha - B_0^2 k_R \alpha^2$$

$$\frac{d\alpha}{d\tau} = K\alpha - \alpha^2 \qquad K \equiv \frac{k_F}{k_R}$$

at steady-state

$$0 = K\alpha - \alpha^2$$

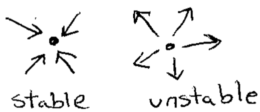
$$\alpha_1 = 0 \qquad \alpha_2 = K$$



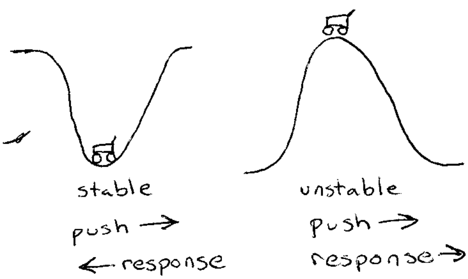
- How do the solutions look around the steady-state?

~~questio~~

1-dimensional problem has two options:



- How can we tell if a steady-state is stable or unstable?



Need to nudge the steady-state mathematically "acceleration" of equations

$$\frac{\partial}{\partial \alpha}\left(\frac{d\alpha}{d\tau}\right) = K - 2\alpha$$

~~at a specific point~~

at $\alpha = K$

$$\left.\frac{\partial}{\partial \alpha}\left(\frac{d\alpha}{d\tau}\right)\right|_{\alpha=K} = K - 2K = \underbrace{-K}_{\text{negative}}$$

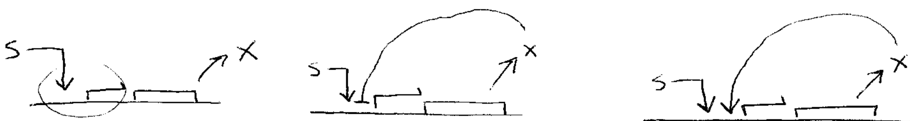
negative
responds in opposite direction than the push
stable

$$\left.\frac{\partial}{\partial \alpha}\left(\frac{d\alpha}{d\tau}\right)\right|_{\alpha=0} = \underbrace{K}_{\text{positive}}$$

positive
unstable

timescale of the response $t_R \sim \dfrac{1}{\frac{\partial}{\partial \alpha}\left(\frac{d\alpha}{d\tau}\right)}$

Analysis of Regulatory Circuits



CASE 1 CASE 2 CASE 3

Modeling promoters:

Shea-Ackers
(Activator)

1 ______ $\Delta G_1 = 0$ $K_1 = 1$

2 ___(S)___ ΔG_2 $K_2 = e^{-\beta \Delta G_2}$

$$P_2 = \frac{K_2 S}{1 + K_2 S}$$

(looks a little like the grand canonical p

(repressor)

1 ______

2 ___(S)___

3 ___(X)___

$$P_2 = \frac{K_2 S}{1 + K_2 S + K_3 X}$$

1 ______

2 ___(S)___

3 ___(S) (X)___

~~4 ___(X) (S)___~~

~~$P_{(2\text{ or }4)} = \dfrac{K_2 S + K_4 X S}{1 + K_2 S + K_3 X + K_4 X S}$~~

$$P(2\text{ or }3) = \frac{K_2 S + K_3 X}{1 + K_2 S + K_3 X}$$

$$\frac{dX}{dt} = \beta_x P_o - \gamma_x X$$

$$x = \frac{X \gamma_x}{\beta_x} \qquad \tau = t \gamma_x$$

$$\beta_x \frac{dx}{d\tau} = \beta_x P_o - \beta_x x$$

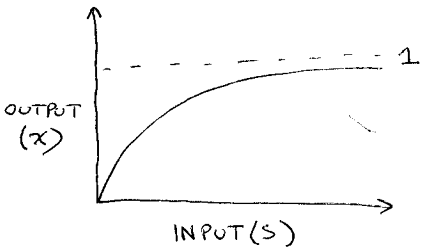
$$\frac{dx}{d\tau} = P_o - x$$

CASE 1 (no autoregulation)

$$\frac{dx}{d\tau} = \frac{K_2 S}{1 + K_2 S} - x$$

at steady-state

$$x = \frac{K_2 S}{1 + K_2 S}$$



stability

$$\frac{\partial}{\partial x}\left(\frac{dx}{d\tau}\right) = -1 \qquad \text{stable}$$

CASE 2 (negative autoregulation)

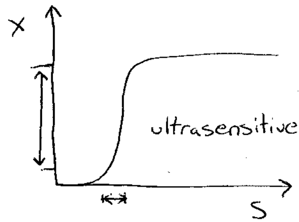
$$\frac{dx}{d\tau} = \frac{K_2 S}{1 + K_2 S + K_3 X} - x$$

$$\frac{\partial}{\partial x}\left(\frac{dx}{d\tau}\right) = \underbrace{-\frac{K_3 K_2 S}{(1 + K_2 S + K_3 X)^2}}_{\text{Additional stability}} - 1$$

(timescale of response is also faster)

CASE 3 (positive autoregulation)

$$\frac{dx}{d\tau} = \frac{K_2 S + K_3 X}{1 + K_2 S + K_3 X} - \cancel{\gamma} X$$



ultrasensitive switch

steady state

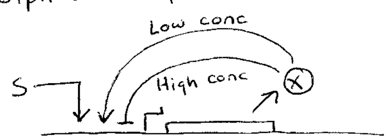
$\frac{dx}{d\tau} = 0$, some simple algebra

$$\frac{\partial}{\partial x}\left(\frac{dx}{d\tau}\right) = \frac{K_3 + \cancel{K_2 K_3 S} + \cancel{K_3^2 X} - \cancel{K_3 K_2 S} - \cancel{K_3^2 X}}{(1 + K_2 S + K_3 X)^2} - 1$$

$$= \underbrace{\frac{K_3}{(1 + K_2 S + K_3 X)^2}}_{\text{always positive}} - 1$$

How to regain stability?

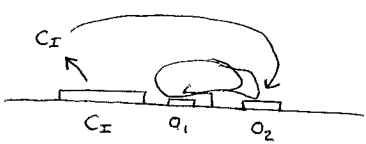
biphasic response

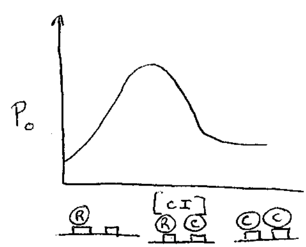


examples

~~Spor~~ Transcription factors

cI in λ phage





when C_I is bound to O_2, it recruits RNAP

" O_1, it blocks RNAP