BIOMATH 201

Deterministic Models in Biology

Ideas:

- Units
- comparing sizes (physics)
- conservation

ODEs, integral transforms, (Laplace)

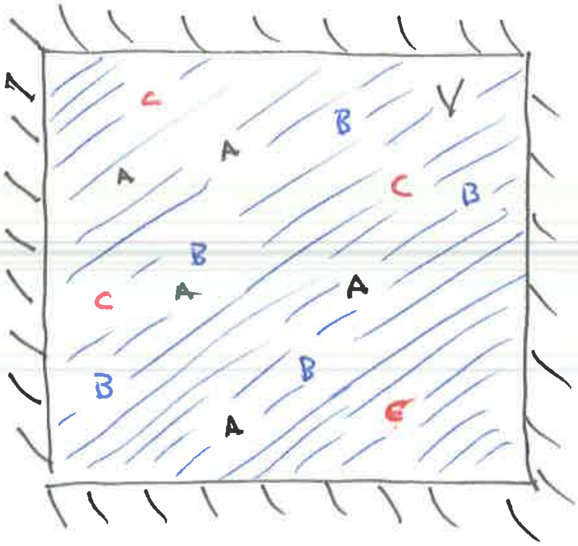
Linear algebra, some PDEs

Can use any classical Mathematical Biology text

"Mass-action" kinetic models (chemical species, populations, etc)

$A + B \rightleftharpoons C$

- C spontaneously dissociates into $\overset{\text{one}}{\vee}$ A and $\overset{\text{one}}{\vee}$ B
- A and B have to "touch" to have a chance to bind together and form C



expected number : $N_A(t) = \frac{1}{J}\sum_{j=1}^{J} N_A^{(j)}(t)$ as $J \to \infty$

Deterministic limit:

for one realization j:

$$\hat{N}_A^{(j)}(t+\Delta t) - \hat{N}_A^{(j)}(t) = \text{net number change in } \Delta t \text{ (deterministic value)}$$

$$\boxed{\approx 0, \pm 1 \text{ for } \Delta t \to 0}$$

* average over realizations and assume "molecular chaos"

$$\lim_{J\to\infty} \frac{1}{J}\sum_{j=1}^{J}\left[\hat{N}_A^{(j)}(t+\Delta t) - \hat{N}_A^{(j)}(t)\right] \longrightarrow N_A(t+\Delta t) - N_A(t)$$

continuous number

take $\Delta t \to 0$. RHS $\propto \Delta t$;

$$-\underbrace{\overset{\circledast}{P_{AB}(t)}}_{\text{probability A \& B are in contact}} N_A(t)\,\underbrace{\omega\,\Delta t}_{\text{rate of rxn} \cdot \Delta t \text{ given A \& B are in contact}} + k_d N_c(t)\,\Delta t$$

$\omega \Delta t$ = prob of rxn in Δt

$k_d \Delta t$ = prob. of dissociation in time Δt

⊛ well-mixed assumption (prob. of contact, N_A, and prob. of rxn are all independent)

$$P_{AB}(t) \equiv \frac{N_B(t)\, v_{AB}}{V}$$

$$\boxed{\frac{v_{AB}}{V} = \text{prob. that B is near A} \quad \text{fraction of volume that is reactive}}$$

$$\boxed{\frac{N_A(t+\Delta t) - N_A(t)}{\Delta t} = -\frac{v_{AB}}{V} N_B N_A \omega + k_d N_c}$$

$\Delta t \to 0$

$$\frac{1}{V}\frac{dN_A(t)}{dt} = -(\nu_{AB}\omega)\left(\frac{N_B(t)}{V}\right)\frac{N_A(t)}{V} + k_d\frac{N_c(t)}{V}$$

$$\Rightarrow \quad \frac{dc_A(t)}{dt} = -\underbrace{(\omega\nu_{AB})}_{\to k_a} c_A(t)\,c_B(t) + k_d\, c_c(t)$$

where $c_A \equiv \frac{N_A}{V}$ is a concentration

Units ω, k_d : $1/\text{time}$ (rate)

$c_{A,B,c}$: concentration $= \frac{\#}{L^d} \equiv \frac{\#}{V}$

$$\boxed{k_a : \ 1/\text{time} \cdot \text{volume}}$$

$$\boxed{\frac{dc_A}{dt} = -k_a\, c_A(t)\, c_B(t) + k_d\, c_c(t)}$$ mass-action kinetics

Can also show
$$\frac{dc_B}{dt} = -k_a c_A c_B + k_d c_c$$

$$\frac{dc_c}{dt} = -k_d c_c + k_a c_A c_B$$

Bilinear form is ubiquitous.

What about "3-body" reaction?

$$\frac{dc_1}{dt} = -\overset{\frac{1}{\text{time}}\cdot(\text{volume})^2}{k}\, c_1 c_2 c_3$$

3 different types of particles must simultaneously overlap

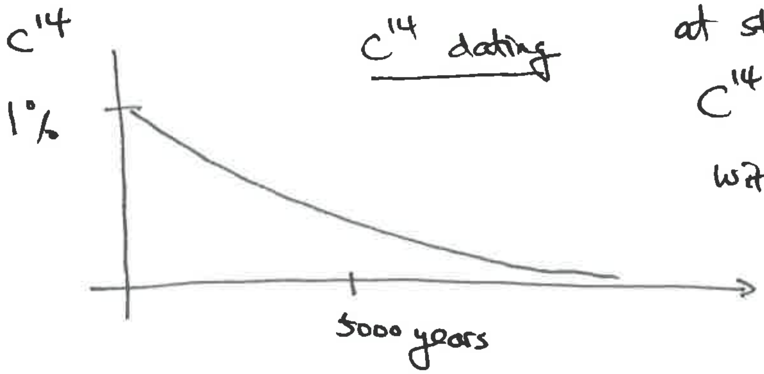
typically occurs through intermediate: $c_1 + c_2 \rightleftharpoons D$, $D + c_3 \rightleftharpoons$ product

Simple decay

$A \xrightarrow{k} B$ $\qquad \frac{dc_A}{dt} = -k c_A,$ initial condition:

$c_A(t=0) \equiv c_A(0)$

$$\int_{c_A(0)}^{c_A} \frac{dc_A'}{c_A'} = -\int_0^t k\, dt' \Rightarrow c_A(t) = c_A(0)\, e^{-kt}$$



C^{14} dating

at steady state, about 1% of C is C^{14} isotope. After death, no exchange with C^{14} carbon and only decay occurs. Loss of C^{14} measures time since death

- 1% is typically a huge number.
- For smaller numbers, go back to discrete numbers & probabilities:

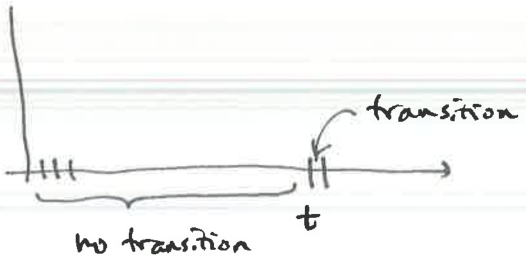
$\bullet \xrightarrow{k} \circ$ $\qquad$ Probability of a transition in time dt

$\equiv k\, dt$

prob. of transition at time t

$= (1 - k\,dt)^N\, k\,dt$ (Markov)

$t \equiv N\,dt$



$= \left(1 - \frac{kt}{N}\right)^N k\,dt = e^{-kt}\, k\,dt$

prob. of transition before t: $\int_0^t k\, e^{-kt'} dt' = 1 - e^{-kt}$

Prob. of no transition up to time t : "survival probability"

$$P_s(t) = e^{-kt}$$

Starting with No particles, prob. that n exist at time t:

$$\binom{N_0}{n} P_s^n(t) \left(1 - P_s(t)\right)^{N_0-n}$$

<u>binomial distribution</u>

(each particle behaves independently)

Note that $\sum_{n=0}^{N_0} \binom{N_0}{n} P_s^n(t) \left(1-P_s(t)\right)^{N_0-n} \equiv 1$

mean (expected) number surviving at time t:

$$\sum_{n=0}^{N_0} n \underbrace{\binom{N_0}{n} P_s^n(t) \left(1-P_s(t)\right)^{N_0-n}}_{P_n(t)} = N_0 P_s(t) = N_0 e^{-kt}$$

Consider $\underbrace{\binom{N_0-1}{n-1}}\; P_s^{n-1}(t) \left(1-P_s(t)\right)^{N_0-1-(n}$

$$\frac{1}{P_s(t)}\left(\frac{n}{N_0}\right) \underbrace{\frac{N_0!}{(N_0-n)!\; n!} P_s^n \left(1-P_s\right)^{N_0-n}}_{\text{sums to } 1}$$

* within volume V;

$\frac{N_0}{V} e^{-kt}$ matches 'meanfield' result for concentration

Second order rxns

$A + B \xrightarrow{k}$ Product P $\qquad \frac{dP}{dt} = k\, C_A C_B$

each step consumes one A & one B, they are tied together

define $y \equiv$ extent of rxn: ($\equiv$ product if $P_0 = 0$)

$$\frac{dy}{dt} = k\,(C_A(0) - y)(C_B(0) - y) \qquad \left(\text{units of } k = \frac{1}{\text{conc. time}}\right)$$

$$\Rightarrow \int_{y(0)}^{y} \frac{dy'}{(C_A(0)-y')(C_B(0)-y')}$$ and if $C_A(0) \neq C_B(0)$,

$$\frac{1}{C_A(0) - C_B(0)}\left[\int_0^y \frac{dy'}{C_A(0)-y'} - \int_0^y \frac{dy'}{C_B(0)-y'}\right] = kt$$

$$\ln\left(\frac{C_A(0)-y}{C_A(0)}\right) - \ln\left(\frac{C_B(0)-y}{C_B(0)}\right) = [C_A(0) - C_B(0)]\,t$$

$$\frac{C_A(0)-y}{C_B(0)-y}\,\frac{C_B(0)}{C_A(0)} = e^{(C_A(0)-C_B(0))t}$$

$$\Rightarrow \boxed{y(t) = \frac{C_A(0)\left(e^{(C_A(0)-C_B(0))t} - 1\right)}{\frac{C_A(0)}{C_B(0)}\, e^{(C_A(0)-C_B(0))t} - 1}}$$

when $C_A(0) = C_B(0) = C_0 \Rightarrow$ L'Hopital's rule $\Rightarrow y(t) = \frac{C_0^2 kt}{C_0 kt + 1}$

Enzyme Kinetics (mass-action)

$\text{Substrate} \xrightarrow{k} \text{product}$

$\underset{k_2 \text{ faster pathway}}{\longrightarrow}$

mediated by
catalyst (enzyme)

* Simple enzyme and substrate rxn:

Sugar → CO_2

(can go on further)

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

(net rxn S → P, which by itself is too slow)

$$\boxed{C \equiv S \cdot E}$$

substrate-enzyme complex

Concentrations $\underset{s}{\underset{\equiv}{[S]}}$, $\underset{e}{\underset{\equiv}{[E]}}$, $\underset{c}{\underset{\equiv}{[C]}}$, $\underset{p}{\underset{\equiv}{[P]}}$ in a closed system $\frac{\#}{\text{volume}}$

mass-action equations

$$\frac{ds}{dt} = -k_{+1}\, se + k_{-1} c$$

$$\frac{de}{dt} = -k_{+1}\, se + (k_{-1} + k_2) c$$

"degenerate"

$$\frac{dc}{dt} = k_{+1}\, se - (k_{-1} + k_2) c$$

$$\frac{dp}{dt} = k_2 c \quad \text{(slaved to } c\text{)}$$

Note that k_{-1} and k_2 are "first order" rates with units $1/\text{time}$

k_{+1} has units of $\frac{1}{t \cdot \text{concentration}} = \frac{\text{Volume}}{t}$

Quasi-Steady-State Approximation

assume k_2 is "small", compared to what? k_{-1}?
(k_{+1} has different units)

let's just be sloppy and assume $c(t)$ is "slowly" changing:

$$\frac{dc}{dt} \approx 0 = k_1 s e - (k_2 + k_{-1}) c \Rightarrow c \approx \frac{k_1 s e}{k_2 + k_{-1}}$$

Now, for a closed system free enzyme: $e = e_0 - c$

initial enzyme concentration ≡ total enzyme conc.

free substrate:

$$s = s_0 - c - p$$

initial substrate

$$c \approx \underbrace{\left(\frac{k_1}{k_2 + k_{-1}}\right)}_{\frac{1}{K_m}} s e = \frac{(s_0 - c - p)(e_0 - c)}{K_m}$$

$$K_m c = s_0 e_0 - s_0 c - e_0 c + c^2 - e_0 p + c p$$

$$= s_0 e_0 - (s_0 + e_0 - p) c + c^2$$

concider short/intermediate times where $p << s_0$;

also $c^2 << s_0 c$ because $e_0 << s_0$,

$$K_m c \approx s_0 e_0 - (s_0 + e_0) c \Rightarrow \frac{s_0 e_0}{s_0 + \cancel{e_0} + K_m} \approx c$$

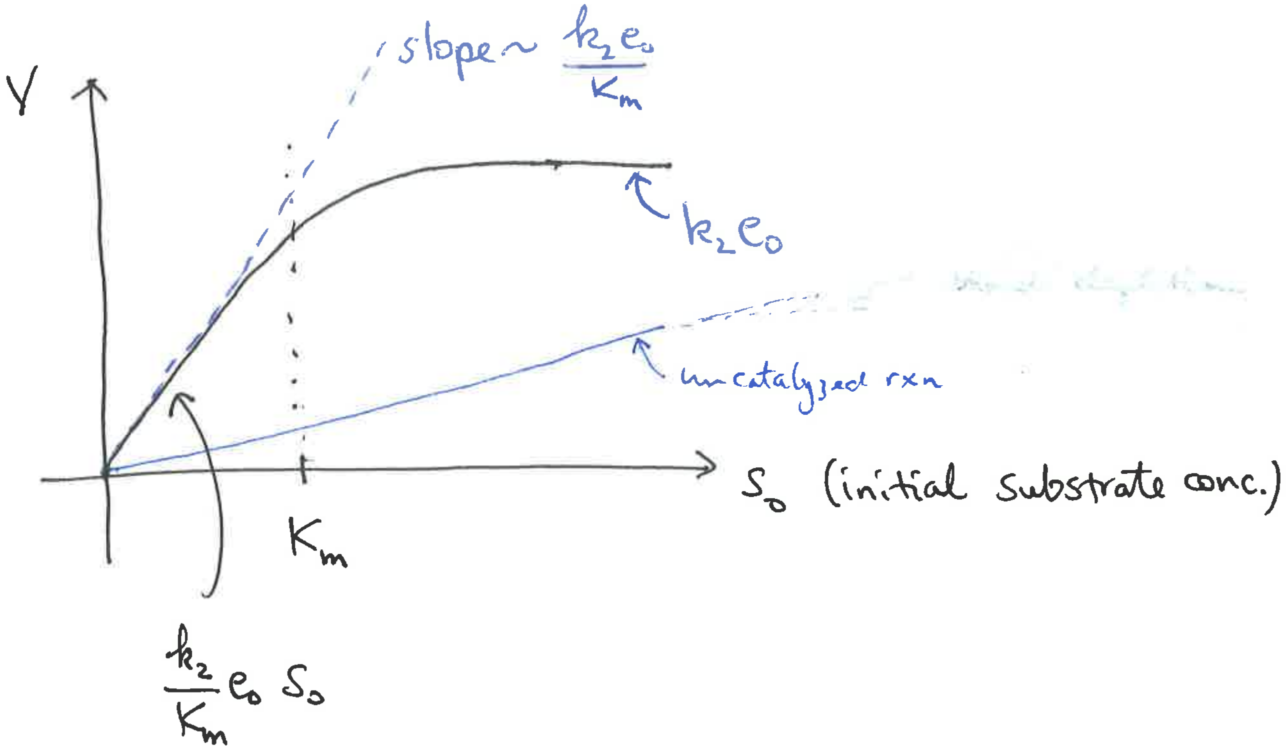
$$\approx \boxed{\frac{s_0 e_0}{s_0 + K_m}}$$

$$\boxed{\frac{dp}{dt} = k_2 c \approx \frac{k_2 s_0 e_0}{s_0 + K_m} \equiv V}$$

$$K_m = \frac{k_2 + k_{-1}}{k_1} = \text{concentration}$$

* If $s_0 \ll K_m$, $V \approx \frac{k_2}{K_m} e_0 s_0 \propto s_0$

* If $s_0 \gg K_m$, $V \approx k_2 e_0$ independent of substrate



for $S_0 \gg K_m$, substrate saturates enzyme and velocity depends on enzyme e_0

for $S_0 \ll K_m$, e_0 is not limiting, substrate is limiting.

Approx assumes $p \ll s_0$, but steady-state assumption requires later times, where p can accumulate.

Need a more systematic approximation:

Singular perturbation math (review)

Consider roots of $\varepsilon x^3 - x^2 + 1 = 0$ for $\varepsilon \to 0^+$

Seek series solution $x = x_0 + \varepsilon x_1 + \varepsilon^2 x_2 + \dots$

$$\varepsilon (x_0 + \varepsilon x_1 + \varepsilon^2 x_2 + \dots)^3 - (x_0 + \varepsilon x_1 + \varepsilon^2 x_2 + \dots)^2 + 1 = 0.$$

order by order:

$$\left.\begin{array}{ll} \mathcal{O}(\varepsilon^0): & -x_0^2 + 1 = 0 \Rightarrow x_0 = \pm 1 \\ \mathcal{O}(\varepsilon^1): & \varepsilon x_0^3 - 2 x_0 \varepsilon x_1 = 0 \\ & x_0^2 - 2x_1 = 0 \Rightarrow x_1 = \frac{1}{2} \end{array}\right\} x = \pm 1 + \frac{\varepsilon}{2} + \mathcal{O}(\varepsilon^2)$$

But the true problem has 3 roots. Power series w/o rescaling misses the "singular" root.

Use 2-term dominant balance

Is $\varepsilon x^3 \sim 1$? if so, $x \sim \frac{1}{\varepsilon^{1/3}}$, and $x^2 \sim \frac{1}{\varepsilon^{2/3}} \gg 1$,

So we cannot neglect x^2 term for 1,

Is $\varepsilon x^3 \sim x^2$? if so, $x \sim \frac{1}{\varepsilon}$, so $\varepsilon x^3, x^2 \gg 1$ OK ✓

this suggests rescaling $x = y/\varepsilon$,

$$\varepsilon \left(\frac{y}{\varepsilon}\right)^3 - \left(\frac{y}{\varepsilon}\right)^2 + 1 = 0 \Rightarrow y^3 - y^2 + \varepsilon^2 = 0,$$

now assume a power series solution for y:

$$\mathcal{O}(\varepsilon^0): \quad y_0^3 - y_0^2 = 0 \Rightarrow y_0 = 0, 0, 1$$

$$\mathcal{O}(\varepsilon^1): \quad 3y_0^2 y_1 - 2y_0 y_1 = 0 \Rightarrow ?, ?, 0$$

$\mathcal{O}(\varepsilon^2)$: $\quad 3y_0y_1^2 + 3y_0^2y_2 - y_1^2 - 2y_0y_2 + 1 = 0$

$$\left.\begin{array}{l} \text{for } y_0 = 0, \quad y_1^2 = 1 \Rightarrow y_1 = \pm 1 \\ \text{for } y_0 = 1, y_1 = 0, \quad y_2 = -1 \end{array}\right\} \quad y = \begin{array}{l} 0 + \varepsilon + \dots \\ 0 - \varepsilon + \dots \\ 1 - \varepsilon^2 + \dots \end{array}$$

$\therefore \quad x = 1 + \dots, \quad -1 + \dots, \quad \frac{1}{\varepsilon} - \varepsilon + \dots$

Now consider singular perturbation of ODE using matched asymptotic expansions:

Consider solving $\quad \varepsilon y''(x) + (1+x)y'(x) + y = 0$

$y(0) = y(1) = 1, \quad$ as $\varepsilon \to 0^+$

for $\varepsilon \to 0^+$, first consider "outer solution" valid for $\varepsilon y''(x) <<$ other terms

$y_{out} = y_0 + \varepsilon y_1 + \dots$, $\quad y_{out}$ expansion in eqn:

$\mathcal{O}(\varepsilon^0)$: $(1+x)y_0'(x) + y_0 = 0$, assume that $y_0(1) = 1$ (guess) (only 1 B.C. can be satisfied!)

$\Rightarrow y_0(x) = \frac{2}{x+1}$

$y_{out}(1) = y_0(1) + \varepsilon y_1(1) + \dots = 1$

$\mathcal{O}(\varepsilon^1)$: $\quad \varepsilon y_0'' + (1+x)\varepsilon y_1' + \varepsilon y_1 = 0, \quad y_1(1) = 0$

$\Rightarrow \quad y_1(x) = \frac{2}{(x+1)^3} - \frac{1}{2(x+1)}$

$$\boxed{y_{out}(x) \simeq \frac{2}{x+1} + \varepsilon\left[\frac{2}{(x+1)^3} - \frac{1}{2(x+1)}\right] + \mathcal{O}(\varepsilon^2)}$$

at $x=0$, $y_{out} \simeq 2 + \frac{3\varepsilon}{2}$, Only one B.C. can be satisfied

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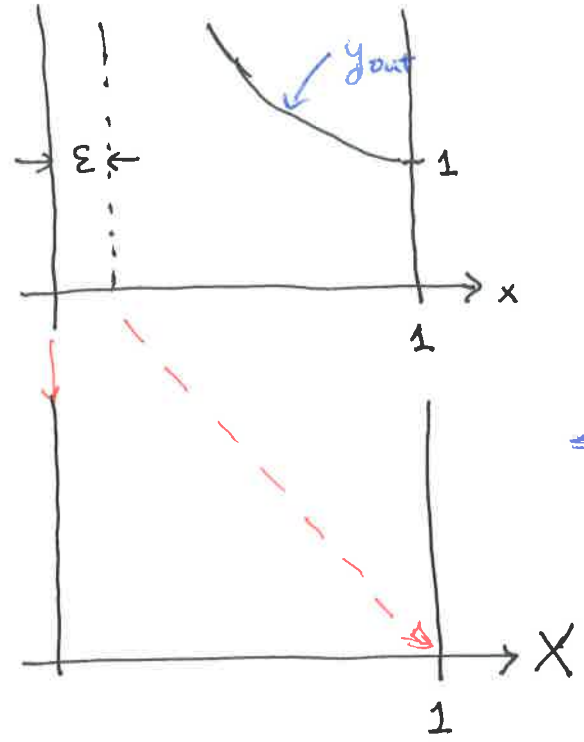
Now, consider region where $\varepsilon \underbrace{y''(x)}$ cannot be neglected.

$y''(x)$ is large, "Boundary layer"

Rescaling

$X = \frac{x}{\varepsilon}$, and consider $y(X)$:

$\frac{d}{dx} = \frac{1}{\varepsilon}\frac{d}{dX}$, ODE becomes



$$\varepsilon \frac{1}{\varepsilon^2}\frac{d^2y}{dX^2} + \frac{(1+\varepsilon X)}{\varepsilon}\frac{dy}{dX} + y = 0$$

$$y(X=0) = 1.$$

This is the "inner solution"

$$\Rightarrow y_{in}(X) = Y_0(X) + \varepsilon Y_1(X) + \varepsilon^2 Y_2(X) + \dots$$

$\mathcal{O}(\varepsilon^0)$: $Y_0'' + Y_0' = 0$, $Y_0(0) = 1$

$$Y_0(X) = A_0(e^{-X} - 1) + 1$$

↑ free parameter remains to "match"

$\mathcal{O}(\varepsilon^1)$: $Y_1(X) = -X + A_0\left(-\frac{X^2}{2}e^{-X} + X\right) + A_1(e^{-X} - 1)$

Matching order by order   assume $x \to 0$, but $X \to \infty$

$\mathcal{O}(\varepsilon^0)$: $\left.\begin{array}{l} Y_0(X\to\infty) \longrightarrow 1 - A_0 \\ y_{out} \approx y_0(x\to 0) \longrightarrow 2 \end{array}\right\} A_0 = -1$

$\mathcal{O}(\varepsilon^1)$: $\left.\begin{array}{l} Y_{in}(X\to\infty) \longrightarrow 1 - A_0 + \varepsilon\left[\overbrace{-X + A_0 X}^{-(2\,[illegible])X} - A_1\,[illegible]\right] \quad - A_1\varepsilon \\ y_{out}(x\to 0) \longrightarrow \frac{2}{x+1} + \frac{3}{2}\varepsilon + \dots \approx 2 - 2\varepsilon X + \frac{3}{2}\varepsilon + \dots \end{array}\right\} A_1 = -3/2$

Uniformly valid solution

$$y_{unif} = y_{out}(x) + y_{in}(X) - y^* \quad , \text{ where}$$

the matching solution $y^* \equiv y_{out}(x \to 0) = y_{in}(X \to \infty)$

$$\boxed{y_{unif}(x) \simeq \left(\frac{2}{x+1} - e^{-x/\varepsilon}\right) + \varepsilon\left[\frac{2}{(x+1)^3} - \frac{1}{2(x+1)} + \left(\frac{(x/\varepsilon)^2}{2} - \frac{3}{2}\right)e^{-x/\varepsilon}\right] + \dots}$$

Systematic analysis of Michaelis-Menten Kinetics:

$$\frac{ds}{dt} = -k_{+1}\,s\,(e_0 - c) + k_{-1}\,c$$

$$\frac{dc}{dt} = k_{+1}\,s\,(e_0 - c) - (k_{-1} + k_2)\,c$$

nondimensionalize:

$\bar{s} = \frac{s}{s_0}$, $\bar{c} = \frac{c}{e_0}$

$\tau = k_{+1} e_0 t$

$$\frac{d\bar{s}}{d\tau} = -\bar{s}(1-\bar{c}) + \overbrace{\left(\frac{k_{-1}}{k_{+1}s_0}\right)}^{\alpha}\bar{c} \quad ; \quad \underset{\ll 1}{\overbrace{\left(\frac{e_0}{s_0}\right)}^{\varepsilon}}\frac{d\bar{c}}{d\tau} = \bar{s}(1-\bar{c}) - \overbrace{\left(\frac{k_{-1}+k_2}{k_{+1}s_0}\right)}^{K}\bar{c}$$

To lowest order, <u>outer solution</u>: $\bar{c} \simeq \frac{\bar{s}}{\bar{s}+K}$,

$$\frac{d\bar{s}}{d\tau} = \frac{(\alpha - K)\bar{s}}{\bar{s}+K} \equiv \frac{-\lambda\bar{s}}{\bar{s}+K} \Rightarrow \int_{\bar{s}_-}^{\bar{s}}\left(1 + \frac{K}{\bar{s}'}\right)d\bar{s}' = -\lambda\int_{\boxed{\tau_-}}^{\tau} d\tau'$$

cannot be 0

$$\bar{s} + K\ln\bar{s} = \boxed{A} - \lambda\tau$$

integration constants

use to match inner solution

Inner solution

rescale time $T = \frac{\tau}{\varepsilon}$; $\frac{d}{d\tau} = \frac{1}{\varepsilon}\frac{d}{dT}$; inner solns: $\bar{C}$ and $\bar{S}(T)$

$$\frac{d\bar{S}(T)}{dT} = -\varepsilon \bar{S}(1-\bar{C}) + \varepsilon\alpha\bar{C}$$

$$\frac{d\bar{C}}{dT} = \bar{S}(1-\bar{C}) - K\bar{C}$$, lowest order in $\bar{C}, \bar{S}$;

$$\frac{d\bar{S}}{dT} \approx 0, \Rightarrow \bar{S}(T) \simeq \frac{s(0)}{s_0} = 1$$

$$\therefore \quad \frac{d\bar{C}}{dT} = 1-(K+1)\bar{C}, \quad \bar{C}(0) = 0$$

$$\bar{C}(T) = \frac{1}{1+K}\left[1 - e^{-(K+1)T}\right]$$

Matching $\bar{C}_{out} \simeq \bar{C}(T\to\infty) \Rightarrow \bar{S}_{out}(\tau\to 0) \simeq 1$

$$\bar{S} + K\ln\bar{S} \simeq A \Rightarrow A = 1$$

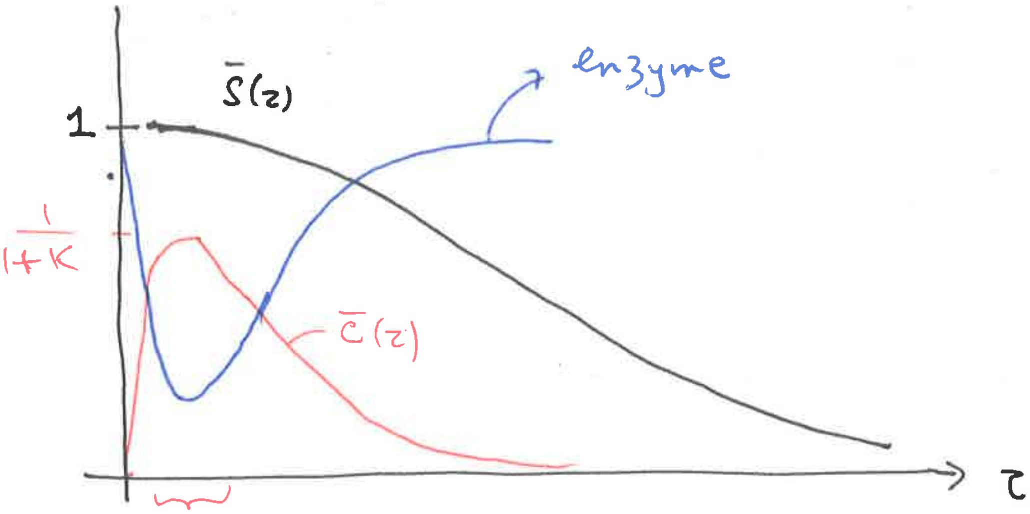
$\therefore$ outer soln for $\bar{S}_{out}(\tau)$ is determined implicitly by

$$\boxed{\bar{S}(\tau) + K\ln\bar{S}(\tau) = 1 - \lambda\tau}$$

This is both inner & outer solution and is uniform

$$\bar{C}_{unif}(\tau) = \bar{C}_{out}(\tau) + \bar{C}(T) - \overset{\frac{1}{1+K}}{C_m^*}$$

$$= \frac{\bar{S}(\tau)}{\bar{S}(\tau)+K} - \frac{e^{-(K+1)\tau/\varepsilon}}{K+1}$$



Michaelis-Menten only reasonable with short window of time