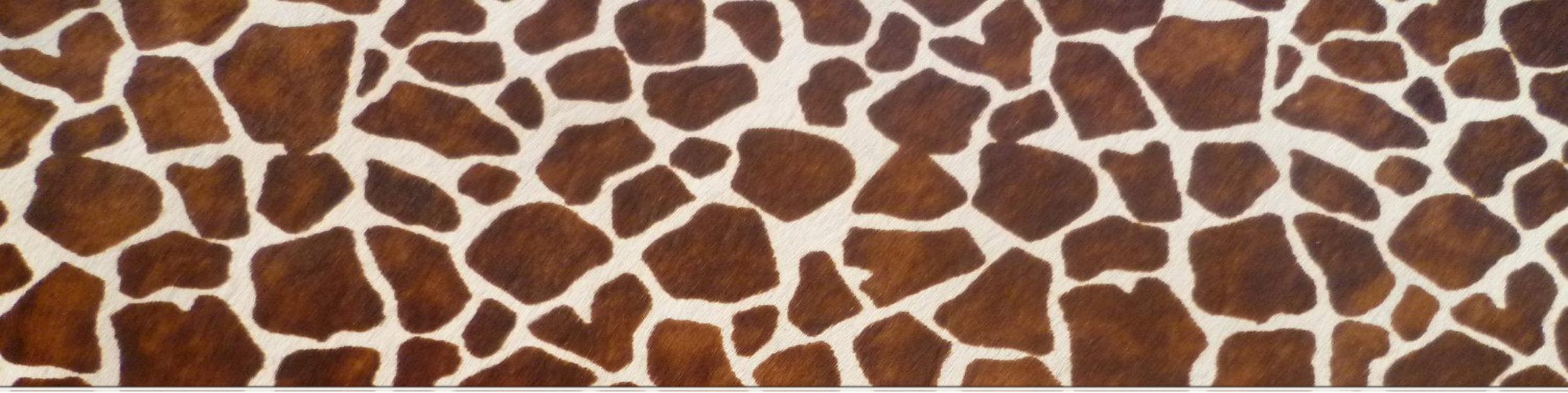
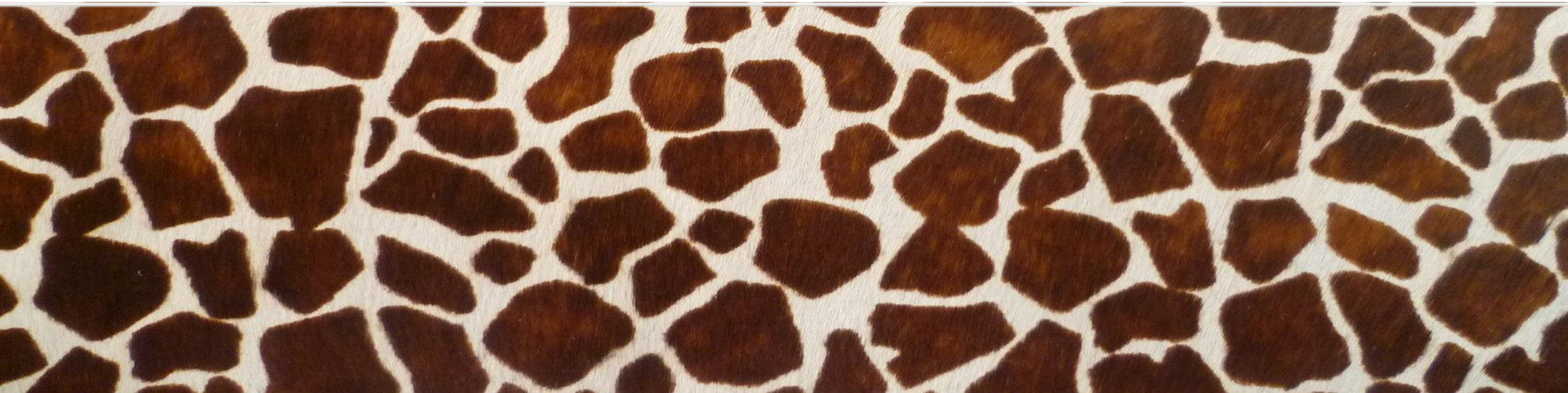


Mathematical Biology - Lecture 4 – biochemical kinetics



molecular and cellular biology

- molecular and cellular biology – frontier between the physical siences and the life sciences
- kinetics of chemical processes: metabolism, information transmission, defence mechanisms, transport of essential substances, mechanical work
- complexity in biochemical reactions – conventional wisdom about equilibrium – Prigogine – complexity possible when far from equilibrium – metabolism

chemical kinetics

law of mass action: Guldberg, Waage and van't Hoff

$$A + B \leftrightarrows \mathrm{C} + \mathrm{D}$$

chemical affinity or reaction force: $\alpha[A]^a[B]^b$
developed a dynamical view of the chemical reaction based on chemical affinity but too complicated – so study of equilibrium conditions

at equilibrium, forward and backward reactions go at a rate such that there is no more change:

$$k_+[A][B] = k_-[C][D]$$

dynamics of chemical processes

$$A + B \rightarrow \mathrm{C}$$

$$\frac{d[C]}{dt} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A][B]$$

$$A + B \leftrightarrows \mathrm{C}$$

$$\frac{d[C]}{dt} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k_{+}[A][B] - k_{-}[C]$$

Michaelis-Menten kinetics

Victor Henri – chemistry of enzyme reactions – Michaelis and Menten – hydrolysis of sucrose and fructose catalysed by invertase

substrate S, enzyme E, complex C, product P

$$E + S \leftrightarrows \mathrm{C} \rightarrow \mathrm{P} + \mathrm{E}$$

forward rates: k_1, k_2
backward rate: k_{-1}

$$\frac{dS}{d\tau} = k_{-1}C - k_1SE; \quad \frac{dE}{d\tau} = (k_{-1} + k_2)C - k_1SE$$

$$\frac{dC}{d\tau} = k_1SE - (k_{-1} + k_2)C; \quad \frac{dP}{d\tau} = k_2C$$

Michaelis-Menten kinetics

$$\frac{d(E+C)}{d\tau} = 0; \;\; E + C = E_0$$

E_0- conservation of total amount of enzyme in free and bound state

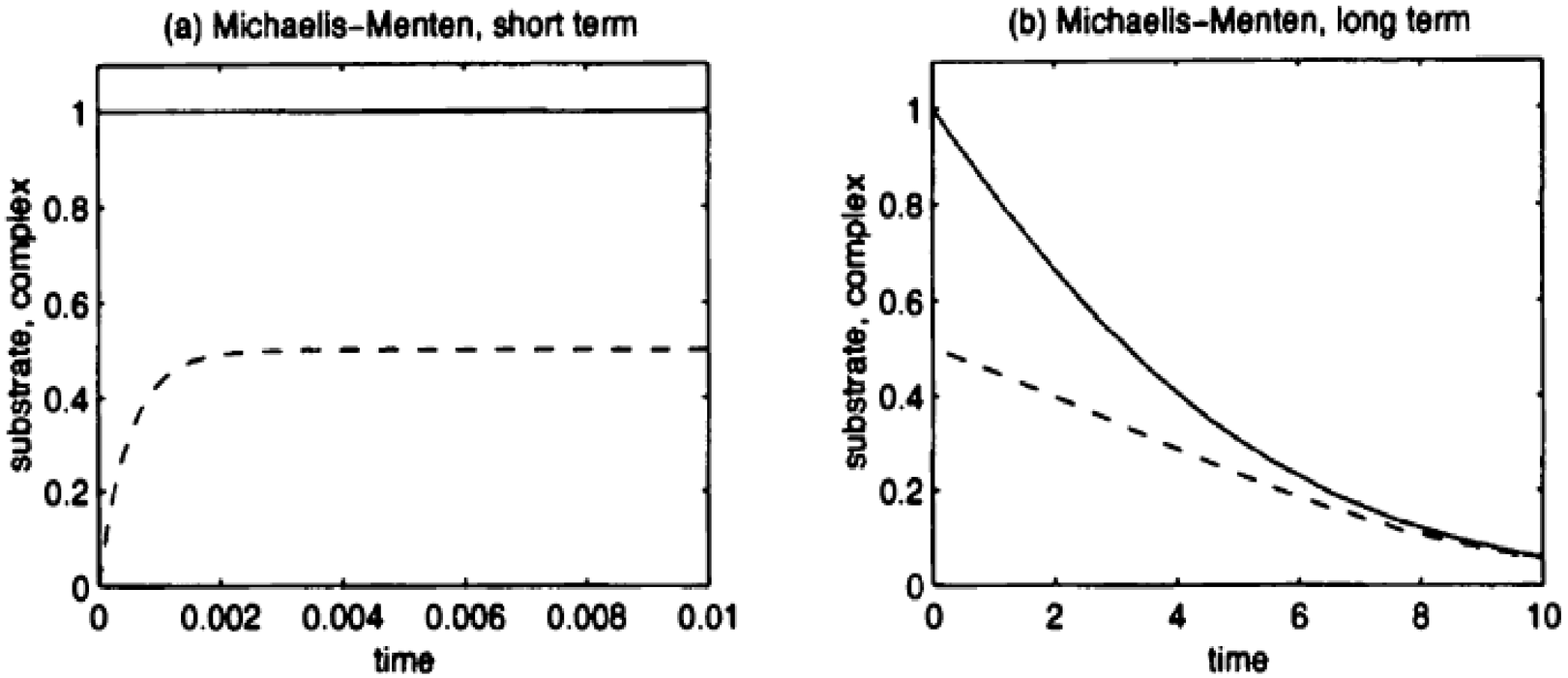
$$\frac{d(S+C+P)}{d\tau} = 0; \;\; S + C + P = S_0$$

S_0 - conservation of substrate as itself, complex or product; enzyme is only a catalyst

Michaelis-Menten kinetics

$$\frac{dS}{d\tau} = k_{-1}C - k_1 S(E_0 - C); \frac{dC}{d\tau} = k_1 S(E_0 - C) - (k_{-1} + k_2)C$$

$$S(0) = S_0; E(0) = E_0; C(0) = P(0) = 0$$



Hydrolysis of benzoyl-L-arginine ethyl ester by trypsin

quasi-steady-state

different time scales of the reaction and different concentrations

concentration of complex rises very fast, substrate remains unchanged
concentrations of substrate and complex change at a slower time scale

Assuming $\frac{dC}{d\tau} = 0$, we can solve for the equilibrium concentration of complex

$$C = \frac{k_1 S E_0}{k_1 + k_2 + k_1 S} = \frac{S E_0}{K_m + S}$$

$$\frac{dS}{d\tau} = -k_2 C = -\frac{V_m S}{K_m + S}, V_m = k_2 E_0;\ K_m = \frac{k_{-1} + k_2}{k_1}$$

quasi-steady-state

saturation function: $\mathrm{Y}(S) = \frac{C}{E+C} = \frac{S}{K_m+S}$

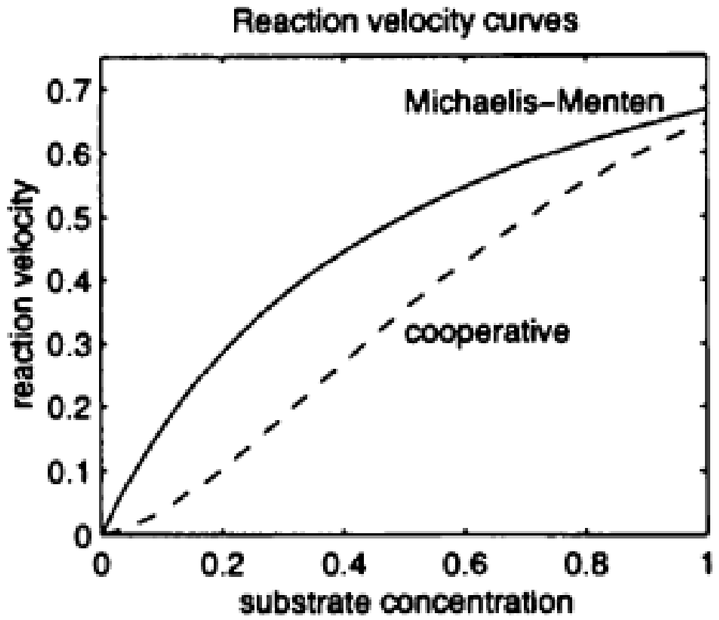
overall rate of the reaction $\frac{dP}{d\tau} = V_m Y(S) = \frac{V_m S}{K_m+S}$ - Michaelis-Menten rate equation

in more complicated cases, we use a technique of matched asymptotic expansions

exercise in non-dimensionalising

Hill function

$$\frac{dx}{dt} = f(x;\theta) = \frac{ax^n}{\theta^n + x^n}$$



Reaction velocity curve sigmoidal in many cases – co-operative phenomenon

Several identical binding units – protomers and one binding site for each ligand for each protomer

dimer: $E + S \underset{k_{-1}}{\overset{2k_1}{\rightleftharpoons}} C_1 \overset{k_3}{\rightarrow} E + P, \quad C_1 + S \underset{2k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} C_2 \overset{2k'_2}{\rightarrow} C_1 + P.$

Hill function

$$\frac{dS}{d\tau} = -2k_1ES - k'_1C_1S + k_{-1}C_1 + 2k'_{-1}C_2$$

$$\frac{dE}{d\tau} = -2k_1ES + k_{-1}C_1 + \mathrm{k_2C_1}$$

$$\frac{dC_1}{d\tau} = 2k_1ES - k_2C_1 - k'_1C_1S - k_{-1}C_1 + 2k'_{-1}C_2 + 2\mathrm{k'_2C_2}$$

$$\frac{dC_2}{d\tau} = k'_1C_1S - 2k'_{-1}C_2 - 2k'_{-1}C_2$$

$$\frac{dP}{d\tau} = k_2C_1 + 2k'_2C_2$$

$$E + C_1 + C_2 = E_0; S + C_1 + 2C_2 + P = S_0$$

Hill function

saturation function $Y(S) = \frac{C_1+2C_2}{2(E+C_1+C_2)} = \frac{S(K'_m+S)}{K_mK'_m+2K'_mS+S^2}$

$$V = \frac{dP}{d\tau} = \frac{2E_0S(k_2K'_m + k'_2S)}{K_mK'_m + 2K'_mS + S^2} = V_mY(S)\ if\ k_2 = k'_2$$

Limiting case: Very little of the first complex present but non-negligible quantities of free enzyme and second complex

$$K'_m \ll S \ll K_m,;\ \ K^2 = K_mK'_m$$

$$V = V_mY(S) = \frac{V_mS^2}{K^2 + S^2}$$