1. Consider the reactions where two substrates S and T compete for binding to an enzyme E to produce two different products P and Q:

$$E + S \underset{p_2}{\overset{p_1}{\rightleftharpoons}} ES \xrightarrow{p_3} P + E$$

$$E + T \underset{q_2}{\overset{q_1}{\rightleftharpoons}} ET \xrightarrow{q_3} Q + E$$

Assume that each reaction follows the Michaelis-Menten kinetics. Also, assume that that the initial enzyme concentration is $E_0 = [E] + [ES] + [ET]$.

(a) Derive rate equations for P and Q in this system in terms of $[ES]$ and $[ET]$. That is, determine $d[P]/dt$ and $d[Q]/dt$.

(b) Derive rate equations for ES and ET.

(c) Assume that the enzyme-substrate complexes reach equilibrium quickly: $d[ES]/dt \approx 0$ and $d[ET]/dt \approx 0$. Solve for $[E]$ in each of these equations.

(d) Equate the two expressions for $[E]$ from Part (c) and solve for $[ET]$.

(e) Solve for $[ES]$ by plugging your answers to Parts (c) and (d) into $E_0 = [E] + [ES] + [ET]$. You should not have $[E]$ or $[ET]$ in your final answer.

(f) Plug this into the original ODE for $d[P]/dt$.

(g) Derive an ODE for $d[Q]/dt$.

(h) Explain the effects of the competition occuring.

a) $\dfrac{d[P]}{dt} = p_3 [ES]$ $\qquad\qquad$ $\dfrac{d[Q]}{dt} = q_3 [ET]$

b) $\dfrac{d[ES]}{dt} = p_1 [E][S] - (p_2 + p_3)[ES]$

$\dfrac{d[ET]}{dt} = q_1 [E][T] - (q_2 + q_3)[ET]$

c) $0 = p_1 [E][S] - (p_2 + p_3)[ES] \Rightarrow [E] = \dfrac{(p_2 + p_3)[ES]}{p_1 [S]}$

$\Rightarrow [E] = \dfrac{(q_2 + q_3)[ET]}{q_1 [T]}$

d) $\dfrac{(q_2 + q_3)[ET]}{q_1 [T]} = \dfrac{(p_2 + p_3)[ES]}{p_1 [S]} \Rightarrow [ET] = \dfrac{q_1 (p_2 + p_3)[ES][T]}{p_1 (q_2 + q_3)[S]}$

e) $E_0 = [E] + [ES] + [ET]$

$E_0 = \dfrac{(p_2 + p_3)[ES]}{p_1 [S]} + [ES] + \dfrac{q_1 (p_2 + p_3)[ES][T]}{p_1 (q_2 + q_3)[S]}$

$E_0 p_1 [S](q_2 + q_3) = (p_2 + p_3)(q_2 + q_3)[ES] + [ES] p_1 [S](q_2 + q_3)$
$\qquad\qquad\qquad\qquad\qquad + q_1 (p_2 + p_3)[ES][T]$

$E_0 [S](q_2+q_3) = [\ \ ](\ \ )\ldots + [\ ](\ \ )\ldots + q_1(p_2+p_3)[T][ES]$

$$+q_1(P_2+P_3)[ES][T]$$

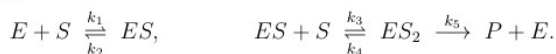$$E_0 p_1[S](q_2+q_3) = \left[(P_2+P_3)(q_2+q_3) + p_1[S](q_2+q_3) + q_1(P_2+P_3)[T] \right][ES]$$

$$[ES] = \frac{E_0 p_1[S](q_2+q_3)}{(P_2+P_3)(q_2+q_3) + p_1[S](q_2+q_3) + q_1(P_2+P_3)[T]}$$

f) $\dfrac{d[P]}{dt} = P_3 \left[\dfrac{E_0 p_1[S](q_2+q_3)}{(P_2+P_3)(q_2+q_3) + p_1[S](q_2+q_3) + q_1(P_2+P_3)[T]} \right]$

g) $\dfrac{d[Q]}{dt} = q_3 \left[\dfrac{E_0 q_1[T](P_2+P_3)}{(P_2+P_3)(q_2+q_3) + q_1[T](P_2+P_3) + P_1(q_2+q_3)[S]} \right]$

h) The rate will decrease for both since the rate is inversely related to the concentration of the other chemical.

2. The Hill equation is an approximation for multi-molecule binding and it assumes simultaneous binding of n-moecules of a substrate S to the enzyme E. Suppose that two molecules of the substrate S are undergoing a reaction with an enzyme in an ordered manner as follows:

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES, \qquad ES + S \underset{k_4}{\overset{k_3}{\rightleftharpoons}} ES_2 \xrightarrow{k_5} P + E.$$

Assume that the reaction follows the Michaelis-Menten kinetics and that the initial enzyme concentration is $E_0 = [E] + [ES] + [ES_2]$.

(a) Derive rate equations for P, ES, and ES_2.
(b) Assume that $d[ES_2]/dt \approx 0$ and solve for $[ES]$.
(c) Assume that $d[ES]/dt \approx 0$. Plug your answer to Part (b) into this and solve for $[E]$.
(d) Plug your expressions for $[E]$ and $[ES]$ back into $E_0 = [E] + [ES] + [ES_2]$ and solve for $[ES_2]$.
(e) Derive an ODE for $[P]$ of the form $d[P]/dt = f([S])$.
(f) Compare your answer to Part (d) to the Hill equation with Hill coefficient $n = 2$:

$$\frac{d[P]}{dt} = \frac{V_{\max}[S]^2}{K_m + [S]^2}.$$

When do these two equations become roughly the same, and why?

a) $\dfrac{d[P]}{dt} = k_5[ES_2]$ $\qquad \dfrac{d[ES_2]}{dt} = k_3[ES][S] - (k_4+k_5)[ES_2]$

$\dfrac{d[ES]}{dt} = k_1[E][S] - k_2[ES]$

$\dfrac{d[ES_2]}{dt} = k_3[ES][S] - (k_4+k_5)[ES_2]$

$\frac{d}{dt}$

b) $0 = k_3[ES][S] - (k_4+k_5)[ES_2] \Rightarrow [ES] = \frac{(k_4+k_5)[ES_2]}{k_3[S]}$

c) $0 = k_1[E][S] - k_2[ES] \Rightarrow \frac{k_2(k_4+k_5)[ES_2]}{k_1k_3[S]^2} = [E]$

d) $E_0 = [E] + [ES] + [ES_2]$

$E_0 = \frac{k_2(k_4+k_5)[ES_2]}{k_1k_3[S]^2} + \frac{(k_4+k_5)[ES_2]}{k_3[S]} + [ES_2]$

$[ES_2] = \frac{E_0 k_1 k_3 [S]^2}{k_1k_3[S]^2 + k_1[S](k_4+k_5) + k_2(k_4+k_5)}$

e) $\frac{d[P]}{dt} = \frac{k_5 E_0 k_1 k_3 [S]^2}{k_1k_3[S]^2 + k_1[S](k_4+k_5) + k_2(k_4+k_5)} = f([S])$

f) $V_{max} = E_0 k_1 k_3 k_5 \qquad K_m = \frac{k_2(k_4+k_5)}{k_1 k_3}$

$\frac{d[P]}{dt} = \frac{V_{max}[S]^2}{[S]^2 + \frac{k_4+k_5}{k_3}[S] + K_m}$

So if $\frac{k_4+k_6}{k_3} \approx 0$

Since each $k > 0$, this is only possible if $k_4+k_5 << k_3$
This would imply that $ES + S \rightarrow ES_2$ happens very fast