

# Mathematical modelling in biology

## Some models

Giacomo Fantoni

telegram: @GiacomoFantoni

Github: <https://github.com/riacchiappando/mathematical-modelling-in-biology>

June 9, 2023

## Contents

<b>1</b>	<b>The bathtub</b>	<b>2</b>
1.1	Constant input . . . . .	2
1.2	Constant input and no output . . . . .	4
1.3	Varying input . . . . .	4
1.4	Output flux but no input . . . . .	4
<b>2</b>	<b>Malthus equation</b>	<b>5</b>
<b>3</b>	<b>The logistic equation</b>	<b>6</b>
3.1	Solution . . . . .	7
3.2	Equilibria and stability . . . . .	9
<b>4</b>	<b>Logistic equation with periodic carrying capacity</b>	<b>10</b>
4.1	Solution . . . . .	10
4.2	Equilibria . . . . .	11
<b>5</b>	<b>Predator-Prey system</b>	<b>11</b>
5.1	Equilibrium points . . . . .	12
5.2	Stability . . . . .	14
<b>6</b>	<b>Epidemiological models</b>	<b>15</b>
6.1	Normalization . . . . .	16
6.2	Vaccination rate and temporary immunity . . . . .	16
6.3	Equilibria . . . . .	17
6.3.1	Structuring the equilibria . . . . .	18
6.4	Stability . . . . .	19

---

<b>7</b>	<b>Enzymatic reactions</b>	<b>20</b>
7.1	Reactant abundance . . . . .	21
7.1.1	Equilibrium points . . . . .	22
7.2	Slower time-scale . . . . .	22
7.3	Michaelis Menten's Law . . . . .	24
7.4	Enzymatic reaction with reversible production . . . . .	26
7.4.1	Normalization . . . . .	26
7.4.2	Equilibrium points . . . . .	27
7.4.3	Quasi-equilibrium . . . . .	27
7.5	Enzymatic inhibition . . . . .	29
7.5.1	Normalization . . . . .	30
7.5.2	Quasi-equilibrium . . . . .	30
7.5.3	Rate of production of the product . . . . .	32
7.6	Cooperativity . . . . .	34
7.6.1	Normalization . . . . .	34
7.6.2	Changing timescale . . . . .	35
7.6.3	Rate of production of the product . . . . .	37
<b>8</b>	<b>Molecular networks</b>	<b>39</b>
8.1	Signal-response mechanism . . . . .	39
8.1.1	Linear response . . . . .	39
8.1.2	Hyperbolic response . . . . .	40
8.2	Adapted response . . . . .	40

## 1 The bathtub

Imagine a container in which there exists an input of water  $I(t)$  and an output  $O(t)$ . Let  $V(t)$  be the volume of water in the bathtub. The variation in time of the volume of water is:

$$\frac{dV(t)}{dt} = I(t) - O(t)$$

### 1.1 Constant input

Assume that the input is constant  $I(t) = \Lambda$  and that the output depends on  $V(t)$  through a constant  $\gamma$ . The problem then becomes:

$$\frac{dV(t)}{dt} = \Lambda - \gamma V(t)$$

This can be solved thorough the variation of constants method. First solve the associated homogeneous equation:

$$\begin{aligned}
\frac{du(t)}{dt} &= -\gamma u(t) \\
\frac{du(t)}{u(t)} &= -\gamma dt \\
\int \frac{du(t)}{u(t)} &= -\gamma \int dt \\
\ln(u(t)) &= -\gamma t + c \\
u(t) &= e^{-\gamma t + c} \\
u(t) &= Ce^{-\gamma t}
\end{aligned}$$

Then we can write  $V(t) = C(t)e^{-\gamma t}$ . Computing its derivative:

$$\frac{dV(t)}{dt} = \frac{dC(t)}{dt}e^{-\gamma t} - \gamma C(t)e^{-\gamma t}$$

Posing it equal to the starting one:

$$\begin{aligned}
\Lambda - \gamma V(t) &= \frac{dC(t)}{dt}e^{-\gamma t} - \gamma C(t)e^{-\gamma t} \\
\Lambda - \gamma V(t) &= \frac{dC(t)}{dt}e^{-\gamma t} - \gamma V(t) \\
\frac{dC(t)}{dt} &= \Lambda e^{\gamma t} \\
C(t) &= \int \Lambda e^{\gamma t} dt \\
C(t) &= \frac{\Lambda}{\gamma} e^{\gamma t} + c
\end{aligned}$$

So that the solution then becomes:

$$\begin{aligned}
V(t) &= \left[ \Lambda \frac{e^{\gamma t}}{\gamma} + c \right] e^{-\gamma t} \\
&= \frac{\Lambda}{\gamma} + ce^{-\gamma t}
\end{aligned}$$

The same thing can be done using an integrating factor:

$$\begin{aligned}
\frac{dV(t)}{dt} &= \Lambda - \gamma V(t) \\
\frac{dV(t)}{dt} + \gamma V(t) &= \Lambda \\
e^{\int \gamma dt} \frac{dV(t)}{dt} + \gamma e^{\int \gamma dt} V(t) &= \Lambda e^{\int \gamma dt} \\
e^{\gamma t} \frac{dV(t)}{dt} + \gamma e^{\gamma t} V(t) &= \Lambda e^{\gamma t} \\
\frac{d}{dt} [e^{\gamma t} V(t)] &= \Lambda e^{\gamma t} \\
e^{\gamma t} V(t) &= \int \Lambda e^{\gamma t} dt \\
e^{\gamma t} V(t) &= \frac{\Lambda}{\gamma} e^{\gamma t} + c \\
V(t) &= \frac{\Lambda}{\gamma} + ce^{-\gamma t}
\end{aligned}$$

## 1.2 Constant input and no output

In the case in which there is no output the problem then becomes:

$$\frac{dV(t)}{dt} = \Lambda$$

This is easy to solve:

$$V(t) = \Lambda t + c$$

## 1.3 Varying input

Let now the input be a function of time  $I(t) = \Lambda(t)$ . The equation becomes:

$$\frac{dV(t)}{dt} = \Lambda(t)$$

The solutions of this is found by integrating both sides:

$$V(t) + \int_0^t \Lambda(u) du + c$$

## 1.4 Output flux but no input

Let now the input be a function of time  $O(t) = \gamma V(t)$ . The variation in time becomes:

$$\frac{dV(t)}{dt} = -\gamma V(t)$$

This does not explicitly depends on  $t$ : it is autonomous. This can be solved through the separation of variable methods:

---


$$\begin{aligned}
\frac{dV(t)}{dt} &= -\gamma V(t) \\
\frac{dV(t)}{V(t)} &= -\gamma dt \\
\int \frac{dV(t)}{V(t)} &= -\gamma \int dt \\
\ln(V(t)) &= -\gamma t + c \\
V(t) &= e^{-\gamma t + c} \\
V(t) &= e^{-\gamma t} e^c \\
V(t) &= k e^{-\gamma t}
\end{aligned}$$

$k$  in this context is the volume in the bathtub at time 0, which could be computed if the volume at time 0 was given:

$$\begin{cases} \frac{dV(t)}{dt} = -\gamma V(t) \\ V(0) = V_0 \end{cases}$$

So that  $V(0)$  can be computed:

$$\begin{aligned}
V(0) &= k e^{-\gamma \cdot 0} \\
V(0) &= k
\end{aligned}$$

## 2 Malthus equation

The Malthus equation is a model for the growth of a population. It neglects difference among individuals and migrations. It represents a population through its size that will increase through reproduction and decrease through death:

$$\frac{dN(t)}{dt} = B(t) - D(t)$$

The number of births and deaths are linked to the current population. A death rate  $\mu$  can be introduced ( $\frac{1}{\mu}$  is the average lifespan) and a birth rate  $\beta$  (the average number of newborn generated during a lifespan). Both are non-negative constants:

$$\begin{aligned}
\frac{dN(t)}{dt} &= \beta N(t) - \mu N(t) \\
\frac{dN(t)}{dt} &= (\beta - \mu) N(t) \\
\frac{dN(t)}{dt} &= r N(t)
\end{aligned}$$

Where  $r = \beta - \mu$  is the instantaneous growth rate or Malthus parameter or biological potential of the population. The equation can be solved through the separation of variables method:

---


$$\begin{aligned}
\frac{dN(t)}{dt} &= rN(t) \\
\frac{dN(t)}{N(t)} &= rdt \\
\int \frac{1}{N(t)} dN(t) &= \int rdt \\
\ln(N(t)) &= rt + c \\
N(t) &= e^{rt+c} \\
N(t) &= ke^{rt} \\
N(t) &= ke^{(\beta-\mu)t}
\end{aligned}$$

Where  $k$  is the population size at time 0. If  $r < 0$  the population will go extinct, while if  $r > 0$  it will grow exponentially. If  $r = 0$  the population is constant. The basic reproduction number  $R_0 = \frac{\beta}{\mu}$  can be considered.  $r < 0$  is equivalent to  $R_0 < 1$ , while  $R_0 > 1$  is equivalent to  $r > 0$ . Now, the equilibria and stability can be computed:

$$\begin{aligned}
rN(t) &= 0 \\
N(t) &= 0
\end{aligned}$$

This is the only equilibrium point.

### 3 The logistic equation

The logistic equation introduces into the Malthus' one a term that limits the growth of the population. The simplest way to do so is to modify the rates, supposing that fertility decreases and mortality increases linearly with  $N(t)$ :

$$\begin{aligned}
\beta(N(t)) &= \beta_0 - \tilde{\beta}N(t) \\
\mu(N(t)) &= \mu_0 + \tilde{\mu}N(t)
\end{aligned}$$

Where  $\beta_0, \tilde{\beta}, \mu_0, \tilde{\mu}$  are positive constants. Now the equation becomes:

$$\begin{aligned}
 \frac{dN(t)}{dt} &= \beta(N(t))N(t) - \mu(N(t))N(t) \\
 &= (\beta_0 - \tilde{\beta}N(t))N(t) - (\mu_0 + \tilde{\mu}N(t))N(t) \\
 &= \beta_0N(t) - \tilde{\beta}N^2(t) - \mu_0N(t) - \tilde{\mu}N^2(t) \\
 &= N(t) \left[ \beta_0 - \tilde{\beta}N(t) - \mu_0 - \tilde{\mu}N(t) \right] \\
 &= N(t) \left[ (\beta_0 - \mu_0) - (\tilde{\beta} + \tilde{\mu})N(t) \right] \\
 &= N(t)(\beta_0 - \mu_0) \left[ 1 - \frac{N(t)(\tilde{\beta} + \tilde{\mu})}{\beta_0 - \mu_0} \right]
 \end{aligned}$$

Now  $(\beta_0 - \mu_0) = r$ , the Malthus parameter, and  $\frac{(\beta_0 - \mu_0)}{(\tilde{\beta} + \tilde{\mu})} = K$ , the carrying capacity:

$$\frac{dN(t)}{dt} = rN(t) \left[ 1 - \frac{N(t)}{K} \right]$$

If both  $\tilde{\beta}$  and  $\tilde{\mu}$  are 0 the equation goes back to the Malthus one. For very large  $N(t)$  and  $\tilde{\beta} > 0$ , the birth rate could go negative. This does not cause mathematical problems and the conditions are which it happens do not occur, so it is neglected. Generally it is assumed that  $r > 0$ , since the population is growing over time. So if  $r > 0$ , and considering all the other assumptions  $K > 0$ .

### 3.1 Solution

To solve the equation we solve for its reciprocal:

$$u(t) = \frac{1}{N(t)}$$

This implies that:

$$\begin{aligned}
 \frac{du(t)}{dt} &= -\frac{1}{N^2(t)} \frac{dN(t)}{dt} \\
 &= \frac{-rN(t) \left[ 1 - \frac{N(t)}{K} \right]}{N^2(t)} \\
 &= \frac{-r \left[ 1 - \frac{N(t)}{K} \right]}{N(t)} \\
 &= -r \left[ \frac{1}{N(t)} - \frac{1}{K} \right] \\
 &= -ru(t) + \frac{r}{K}
 \end{aligned}$$

This is a linear non-homogeneous differential equation that can be solved with the variation of constants method. Solving first the associated homogeneous problem through separation of variables:

$$\begin{aligned}
\frac{du(t)}{dt} &= -ru(t) \\
\frac{du(t)}{u(t)} &= -r dt \\
\int \frac{1}{u(t)} du(t) &= \int -r dt \\
\ln(u(t)) &= -rt + c \\
u(t) &= e^{-rt+c} \\
u(t) &= Ce^{-rt}
\end{aligned}$$

Let  $C$  be a function of  $t$ :

$$u(t) = C(t)e^{-rt}$$

And derive it:

$$\frac{du(t)}{dt} = C'(t)e^{-rt} - rC(t)e^{-rt}$$

Considering that:

$$\frac{du(t)}{dt} = -ru(t) + \frac{r}{K}$$

So that:

$$\begin{aligned}
-ru(t) + \frac{r}{K} &= \frac{dC(t)}{dt}e^{-rt} - rC(t)e^{-rt} \\
\cancel{-rC(t)e^{-rt}} + \frac{r}{K} &= \frac{dC(t)}{dt}e^{-rt} - \cancel{rC(t)e^{-rt}} \\
\frac{dC(t)}{dt}e^{-rt} &= \frac{r}{K} \\
\frac{dC(t)}{dt} &= \frac{r}{K}e^{rt} \\
C(t) &= \frac{r}{K} \int e^{rt} dt \\
C(t) &= \frac{r}{K} e^{rt} + c \\
C(t) &= \frac{1}{K} e^{rt} + c
\end{aligned}$$

Substituting back into  $u(t)$ :



$$u(t) = \left[ \frac{e^{rt}}{K} + c \right] e^{-rt}$$

$$u(t) = \frac{1}{K} + ce^{-rt}$$

So that:

$$N(t) = \frac{1}{\frac{1}{K} + ce^{-rt}}$$

Now, solving the Cauchy problem where  $N(0) = N_0$ :

$$\frac{1}{\frac{1}{K} + ce^{-r0}} = N_0$$

$$\frac{1}{\frac{N_0}{K} + cN_0} = 0$$

$$\frac{N_0}{K} + cN_0 = 1$$

$$cN_0 = 1 - \frac{N_0}{K}$$

$$c = \frac{1}{N_0} - \frac{1}{K}$$

So that, substituting:

$$N(t) = \frac{1}{\frac{1}{K} + \left[ \frac{1}{N_0} - \frac{1}{K} \right] e^{-rt}}$$

$$= \frac{K}{1 + \left[ \frac{K-N_0}{N_0} \right] e^{-rt}}$$

### 3.2 Equilibria and stability

Assume  $r > 0$  and  $K > 0$ :

$$rN(t) \left[ 1 - \frac{N(t)}{K} \right] = 0$$

$$N(t) = 0 \quad \wedge \quad N(t) = K$$

The first equilibrium is unstable, since the population is growing, while the second is stable.

---

## 4 Logistic equation with periodic carrying capacity

The logistic model can be modified by assuming that the carrying capacity  $K$  is a periodic, always positive function of  $t$ . For example:

$$k(t) = K_0(1 + \epsilon \cos(\omega t)) \quad 0 < \epsilon < 1$$

The model then becomes:

$$\begin{aligned} \frac{dN(t)}{dt} &= rN(t) \left[ 1 - \frac{N(t)}{K(t)} \right] \\ &= rN(t) \left[ 1 - \frac{N(t)}{K_0(1 + \epsilon \cos(\omega t))} \right] \end{aligned}$$

Which makes the equation not autonomous anymore.

### 4.1 Solution

The equation can be solved with the same reciprocal trick:

$$\begin{aligned} u(t) &= \frac{1}{N(t)} \\ \frac{du(t)}{dt} &= -\frac{1}{N^2(t)} \frac{dN(t)}{dt} \\ &= \frac{-\cancel{rN(t)} \left[ 1 - \frac{N(t)}{K(t)} \right]}{N^{\cancel{2}}(t)} \\ &= \frac{-r \left[ 1 - \frac{N(t)}{K(t)} \right]}{N(t)} \\ &= -r \left[ \frac{1}{N(t)} - \frac{1}{K(t)} \right] \\ &= -ru(t) + \frac{r}{K(t)} \end{aligned}$$

Now this can be solved with the Variation of constants. Solving the associated homogeneous problem:

$$u(t) = Ce^{-rt}$$

Now let  $C$  a function of  $t$  and compute the derivative:

$$\frac{du(t)}{dt} = \frac{dC(t)}{dt} e^{-rt} - rC(t) e^{-rt}$$

So now, substituting what we now:

$$\begin{aligned}
 \frac{dC(t)}{dt}e^{-rt} - rC(t)e^{-rt} &= -ru(t) + \frac{r}{K(t)} \\
 \frac{dC(t)}{dt}e^{-rt} - rC(t)e^{-rt} &= -ru(t) + \frac{r}{K(t)} \\
 \frac{dC(t)}{dt}e^{-rt} - \cancel{rC(t)e^{-rt}} &= \cancel{-rC(t)e^{-rt}} + \frac{r}{K(t)} \\
 \frac{dC(t)}{dt}e^{-rt} &= \frac{r}{K(t)} \\
 \frac{dC(t)}{dt} &= \frac{r}{K(t)}e^{rt} \\
 C(t) &= r \int \frac{e^{rt}}{K(t)} dt \\
 C(t) &= r \int \frac{e^{rt}}{K_0(1 + \epsilon \cos(\omega t))} dt \\
 C(t) &= \frac{r}{K_0} \int \frac{e^{rt}}{1 + \epsilon \cos(\omega t)} dt
 \end{aligned}$$

Which has no analytical solution. So now:

$$u(t) = e^{-rt} \frac{r}{K_0} \int \frac{e^{rt}}{1 + \epsilon \cos(\omega t)} dt$$

And:

$$N(t) = \frac{e^{rt} K_0}{r \int \frac{e^{rt}}{1 + \epsilon \cos(\omega t)} dt}$$

## 4.2 Equilibria

Assuming still  $r > 0$  and  $K_0 > 0$ , the equilibria can be computed:

$$\begin{aligned}
 rN(t) \left[ 1 - \frac{N(t)}{K(t)} \right] &= 0 \\
 N(t) = 0 \quad \wedge \quad N(t) &= K(t)
 \end{aligned}$$

The first equilibria is unstable. The second is an asymptotically stable periodic equilibria with period  $T = \frac{2\pi}{\omega}$ .

## 5 Predator-Prey system

The predator-prey system is a non-linear system of two differential equations:

$$\begin{cases} \frac{dH(t)}{dt} = rH(t) \left[ 1 - \frac{H(t)}{K} \right] - \alpha H(t)P(t) \\ \frac{dP(t)}{dt} = -\mu P(t) + \gamma \alpha H(t)P(t) \end{cases}$$

Estimating now the parameters:

$$\begin{cases} \frac{dH(t)}{dt} = 2H(t) [1 - H(t)] - 2H(t)P(t) \\ \frac{dP(t)}{dt} = -\frac{1}{2}P(t) + 3H(t)P(t) \end{cases}$$

### 5.1 Equilibrium points

$$\begin{cases} 2H(t) [1 - H(t)] - 2H(t)P(t) &= 0 \\ -\frac{1}{2}P(t) + 3H(t)P(t) &= 0 \end{cases}$$

$$\begin{cases} H(t) = 0 &\wedge & H(t) = 1 - P(t) \\ -\frac{1}{2}P(t) + 3H(t)P(t) &= 0 \end{cases}$$

There are two solution for the first equation. Considering the first:

$$\begin{cases} H(t) &= 0 \\ -\frac{1}{2}P(t) + 3H(t)P(t) &= 0 \end{cases}$$

$$\begin{cases} H(t) = 0 \\ -\frac{1}{2}P(t) &= 0 \end{cases}$$

$$\begin{cases} H(t) = 0 \\ P(t) &= 0 \end{cases}$$

So the first equilibrium point is  $E_1 = (0, 0)$ .  
Considering now the second:

$$\begin{aligned}
 & \begin{cases} H(t) &= 1 - P(t) \\ -\frac{1}{2}P(t) + 3H(t)P(t) &= 0 \end{cases} \\
 & \begin{cases} H(t) &= 1 - P(t) \\ -\frac{1}{2}P(t) + 3(1 - P(t))P(t) &= 0 \end{cases} \\
 & \begin{cases} H(t) &= 1 - P(t) \\ -\frac{1}{2}P(t) + 3P(t) - 3P^2(t) &= 0 \end{cases} \\
 & \begin{cases} H(t) &= 1 - P(t) \\ P(t) \left[-\frac{1}{2} + 3 - 3P(t)\right] &= 0 \end{cases} \\
 & \begin{cases} H(t) &= 1 - P(t) \\ P(t) &= 0 \end{cases} \quad \wedge \quad P(t) = \frac{5}{6}
 \end{aligned}$$

So there are two equilibrium points:  $E_2 = (1, 0)$  and  $E_3 = (\frac{1}{6}, \frac{5}{6})$ . The vector field will be enriched adding the equilibrium points and the null isoclines, the curves where the derivatives are posed equal to zero one at a time:

$$\begin{aligned}
 2H(t) [1 - H(t)] - 2H(t)P(t) &= 0 \\
 H(t) = 0 \quad \wedge \quad H(t) &= 1 - P(t)
 \end{aligned}$$

And:

$$\begin{aligned}
 -\frac{1}{2}P(t) + 3H(t)P(t) &= 0 \\
 P(t) \left[-\frac{1}{2} + 3H(t)\right] &= 0 \\
 P(t) = 0 \quad \wedge \quad H(t) &= \frac{1}{6}
 \end{aligned}$$

Furhtermore the phase plane will be filled with vectors having components:

$$[f(H(t), P(t)), g(H(t), P(t))]$$

Solutions will be tangent to these vectors, although there will not be any information about the evolution in time (there is no  $t$  axis). The three equilibrium will be consant in time. Since now the objective is qualitative it is enough, instead of evaluating the points, to study the sign of the derivatives in the regions identified by the isoclines. In each region the sign will be constant: the isoclines are points in which derivatives change sign, so:

$$\begin{aligned}
 \frac{dH(t)}{dt} &> 0 \\
 2H(t)[1 - H(t)] - 2H(t)P(t) &> 0 \\
 2H(t) - 2H^2(t) - 2H(t)P(t) &> 0 \\
 H(t)[2 - 2H(t) - 2P(t)] &> 0 \\
 (H(t) > 0 \wedge 2 - 2H(t) - 2P(t) > 0) \vee (H(t) < 0 \wedge 2 - 2H(t) - 2P(t) < 0) &> 0
 \end{aligned}$$

Since the second solution is not compatible with the biological domain,  $\frac{dH(t)}{dt} > 0$ :

$$H(t) > 0 \wedge H(t) < 1 - P(t)$$

Now, considering the second equation:

$$\begin{aligned}
 \frac{dP(t)}{dt} &> 0 \\
 -\frac{1}{2}P(t) + 3H(t)P(t) &> 0 \\
 P(t) \left[ -\frac{1}{2} + 3H(t) \right] &> 0 \\
 (P(t) > 0 \wedge -\frac{1}{2} + 3H(t) > 0) \vee (P(t) < 0 \wedge -\frac{1}{2} + 3H(t) < 0) &> 0
 \end{aligned}$$

The second solution is again not compatible with the biological domain,  $\frac{dP(t)}{dt} > 0$ :

$$P(t) > 0 \wedge H(t) > \frac{1}{6}$$

From this the direction field can be populated with vectors with unitary coordinates and negative horizontal when over the  $H(t) + 1 - P(t)$  isocline and positive under it. Moreover vectors to the left of  $H(t) = \frac{1}{6}$  will have negative vertical component and positive to the right. All vectors on an isocline will have the corresponding component equal to 0. From this  $E_1$  and  $E_2$  are unstable, while it is hard to make predictions about  $E_3$ .

## 5.2 Stability

To compute the stability of the equilibria first the Jacobian needs to be computed:

$$\begin{aligned}
 J &= \begin{bmatrix} \frac{\partial f}{\partial H(t)} & \frac{\partial f}{\partial P(t)} \\ \frac{\partial g}{\partial H(t)} & \frac{\partial g}{\partial P(t)} \end{bmatrix} \\
 &= \begin{bmatrix} 2 - 4H(t) - 2H(t) & -2H(t) \\ 3P(t) & -\frac{1}{2} + 3H(t) \end{bmatrix}
 \end{aligned}$$

Now inserting the value of the equilibrium in the Jacobian. For  $E_1$ :

$$J = \begin{bmatrix} 2 & 0 \\ 0 & -\frac{1}{2} \end{bmatrix}$$

It has eigenvalue  $\lambda_1 = 2$  and  $\lambda_2 = -\frac{1}{2}$ , so  $S(A) = 2 > 0$ , then this equilibrium is unstable.

For  $E_2$ :

$$J = \begin{bmatrix} -2 & -2 \\ 0 & \frac{5}{2} \end{bmatrix}$$

This is a triangular matrix, so it has eigenvalues  $\lambda_1 = -2$  and  $\lambda_2 = \frac{5}{2}$ , so  $S(A) = \frac{5}{2} > 0$ , then this equilibrium is unstable.

For  $E_3$ :

$$J = \begin{bmatrix} -\frac{1}{3} & -\frac{1}{3} \\ \frac{5}{6} & 0 \end{bmatrix}$$

To not compute the eigenvalues the Routh-Hurwitz criteria are used. It can be computed that  $\det(A) > 0$  and  $\text{tr}(A) < 0$ , so  $S(A) < 0$ , then this equilibrium is asymptotically stable.

## 6 Epidemiological models

They are used to simulate the spread of an epidemic across a population. A simple one is the SIR one, that categorizes the population into:

- $S$ : the susceptible: when they come into contact with an infectious individual they contract the disease and transition to the infectious compartment.
- $I$ : the infectious individuals: they have been infected and can infect the susceptible.
- $R$  the removed (immune) individuals: they have been infected and have recovered, and entered the removed compartment.

The compartments are linked via different rates:

- The birth rate  $\mu$  feeds people into  $S$ , with dynamics that depends on the total number of people  $N = S + I + R$ .
- Infections  $S \rightarrow I$  happen with a contact rate  $\beta$  and are modelled with mass action dynamics.
- Natural deaths can occur in all groups with rate equal to the one of births  $\mu$  and with dynamics that depends on the number of people in the compartment.
- Infected people recover with a recovery rate  $\gamma$ , with dynamics that depend on the total number of infected people.

Each SIR variable has the number of people as dimension, while rates  $\frac{1}{t}$ : the derivatives will have dimension  $\frac{\text{people}}{t}$ . The system governing the dynamics is:

$$\begin{cases} \frac{dS(t)}{dt} &= -\beta S(t) \frac{I(t)}{N} - \mu S(t) + \mu N \\ \frac{dI(t)}{dt} &= \beta S(t) \frac{I(t)}{N} - \gamma I(t) - \mu I(t) \\ \frac{dR(t)}{dt} &= \gamma I(t) - \mu R(t) \end{cases}$$

Since  $N = S(t) + I(t) + R(t) \Rightarrow R(t) = N - S(t) - I(t)$ , the system can be rewritten as:

$$\begin{cases} \frac{dS(t)}{dt} = -\beta S(t) \frac{I(t)}{N} - \mu S(t) + \mu N \\ \frac{dI(t)}{dt} = \beta S(t) \frac{I(t)}{N} - \gamma I(t) - \mu I(t) \end{cases}$$

## 6.1 Normalization

The system can be modified further by considering the fraction of people in each compartment instead of the total number introducing:

$$X(t) = \frac{S(t)}{N} \quad Y(t) = \frac{I(t)}{N}$$

Dividing all terms in both equations by  $N$ . It is expected that  $0 \leq X(t), Y(t) \leq 1$ . Considering the derivatives:

$$\begin{aligned} \frac{dS(t)}{dt} \frac{I(t)}{N} &= \frac{d \frac{S(t)}{N}}{dt} \\ &= \frac{dX(t)}{dt} \end{aligned}$$

And:

$$\begin{aligned} \frac{dI(t)}{dt} \frac{I(t)}{N} &= \frac{d \frac{I(t)}{N}}{dt} \\ &= \frac{dY(t)}{dt} \end{aligned}$$

So that the normalized system becomes:

$$\begin{cases} \frac{dX(t)}{dt} &= -\beta X(t)Y(t) - \mu X(t) + \mu \\ \frac{dY(t)}{dt} &= \beta X(t)Y(t) - \gamma Y(t) - \mu Y(t) \end{cases}$$

## 6.2 Vaccination rate and temporary immunity

It can be assumed that immunity is temporary and people in  $R$  can flow back in  $S$  with rate  $\sigma$ , and that there is a vaccination rate  $p$  at birth, so that a fraction  $p$  of the births is automatically immune and  $1 - p$  feeds  $S$ . The previous system described the case in which  $p = 0 \wedge \sigma = 0$ . Now the system becomes:

$$\begin{cases} \frac{dS(t)}{dt} &= -\beta S(t) \frac{I(t)}{N} - \mu S(t) + \mu(1 - p)N + \sigma R(t) \\ \frac{dI(t)}{dt} &= \beta S(t) \frac{I(t)}{N} - \gamma I(t) - \mu I(t) \\ \frac{dR(t)}{dt} &= \gamma I(t) - \mu R(t) - \sigma R(t) + \mu pN \end{cases}$$

It is still true that  $R = N - S - I$ , so again the third equation can be not considered:



$$\begin{cases} \frac{dS(t)}{dt} &= -\beta S(t) \frac{I(t)}{N} - \mu S(t) + \mu(1-p)N + \sigma(N - I(t) - S(t)) \\ \frac{dI(t)}{dt} &= \beta S(t) \frac{I(t)}{N} - \gamma I(t) - \mu I(t) \end{cases}$$

Then introduce  $X(t) = \frac{S(t)}{N}$  and  $Y(t) = \frac{I(t)}{N}$  to normalize the system:

$$\begin{cases} \frac{dX(t)}{dt} &= -\beta X(t)Y(t) - \mu X(t) + \mu(1-p) + \sigma(1 - X(t) - Y(t)) \\ \frac{dY(t)}{dt} &= \beta X(t)Y(t) - \gamma Y(t) - \mu Y(t) \end{cases}$$

### 6.3 Equilibria

To find the equilibria let's first put the derivatives equal to zero:

$$\begin{aligned} \begin{cases} -\beta X(t)Y(t) - \mu X(t) + \mu(1-p) + \sigma(1 - X(t) - Y(t)) &= 0 \\ \beta X(t)Y(t) - \gamma Y(t) - \mu Y(t) &= 0 \end{cases} \\ \begin{cases} -\beta X(t)Y(t) - \mu X(t) + \mu(1-p) + \sigma(1 - X(t) - Y(t)) &= 0 \\ Y(t)(\beta X(t) - \gamma - \mu) &= 0 \end{cases} \\ \begin{cases} -\beta X(t)Y(t) - \mu X(t) + \mu(1-p) + \sigma(1 - X(t) - Y(t)) &= 0 \\ Y(t) = 0 \wedge X(t) &= \frac{\gamma + \mu}{\beta} \end{cases} \end{aligned}$$

Discussing first for  $Y(t) = 0$ :

$$\begin{aligned} \begin{cases} Y(t) &= 0 \\ -\beta X(t)Y(t) - \mu X(t) + \mu(1-p) + \sigma(1 - X(t) - Y(t)) &= 0 \end{cases} \\ \begin{cases} Y(t) &= 0 \\ -\mu X(t) + \mu(1-p) + \sigma(1 - X(t)) &= 0 \end{cases} \\ \begin{cases} Y(t) &= 0 \\ -\mu X(t) + \mu(1-p) + \sigma - \sigma X(t) &= 0 \end{cases} \\ \begin{cases} Y(t) &= 0 \\ -(\mu + \sigma)X(t) &= -\mu(1-p) - \sigma \end{cases} \\ \begin{cases} Y(t) &= 0 \\ X(t) &= \frac{\mu(1-p) + \sigma}{\mu + \sigma} \end{cases} \end{aligned}$$

So the first equilibrium, or disease free equilibrium  $DFE$  is:

$$E_1 = DEF = \left( \frac{\mu(1-p) + \sigma}{\mu + \sigma}, 0 \right)$$

Now discussing for  $X(t) = \frac{\gamma + \mu}{\beta}$ :

$$\begin{aligned}
 & \begin{cases} X(t) & = \frac{\gamma+\mu}{\beta} \\ -\beta X(t)Y(t) - \mu X(t) + \mu(1-p) + \sigma(1-X(t)-Y(t)) & = 0 \end{cases} \\
 & \begin{cases} X(t) & = \frac{\gamma+\mu}{\beta} \\ -\beta X(t)Y(t) - \mu X(t) + \mu(1-p) + \sigma - \sigma X(t) - \sigma Y(t) & = 0 \end{cases} \\
 & \begin{cases} X(t) & = \frac{\gamma+\mu}{\beta} \\ (\beta X(t) + \sigma)Y(t) & = -\mu X(t) + \mu(1-p) + \sigma - \sigma X(t) \end{cases} \\
 & \begin{cases} X(t) & = \frac{\gamma+\mu}{\beta} \\ (\beta X(t) + \sigma)Y(t) & = -(\mu + \sigma)X(t) + \mu(1-p) + \sigma \end{cases} \\
 & \begin{cases} X(t) & = \frac{\gamma+\mu}{\beta} \\ Y(t) & = \frac{-(\mu+\sigma)X(t) + \mu(1-p) + \sigma}{(\beta X(t) + \sigma)} \end{cases} \\
 & \begin{cases} X(t) & = \frac{\gamma+\mu}{\beta} \\ Y(t) & = \frac{-(\mu+\sigma)\frac{\gamma+\mu}{\beta} + \mu(1-p) + \sigma}{\left(\beta\frac{\gamma+\mu}{\beta} + \sigma\right)} \end{cases} \\
 & \begin{cases} X(t) & = \frac{\gamma+\mu}{\beta} \\ Y(t) & = \frac{\mu(1-p) + \sigma - (\mu+\sigma)\frac{\gamma+\mu}{\beta}}{\gamma + \mu + \sigma} \end{cases}
 \end{aligned}$$

So, the second equilibrium, or endemic equilibrium  $EE$  is:

$$E_2 = EE = \left( \frac{\gamma + \mu}{\beta}, \frac{\mu(1-p) + \sigma - (\mu + \sigma)\frac{\gamma+\mu}{\beta}}{\gamma + \mu + \sigma} \right)$$

From an epiemiological point of view the quantity  $R_0$ , the average number of individuals infected by a newly infected individual over all its infecious period:

$$R_0 = \frac{\beta}{\mu + \gamma} \quad X = \frac{1}{R_0}$$

Using  $R_0$  the endemic equilibrium can be reformulated:

$$E_2 = EE = \left( \frac{1}{R_0}, \frac{\mu(1-p) + \sigma - \frac{1}{R_0}(\mu + \sigma)}{\mu + \gamma + \sigma} \right)$$

### 6.3.1 Structuring the equilibria

Consider now the case of no vaccination and permanent immunity ( $p = 0$ ,  $\sigma = 0$ ). The equilibria now become:

$$E_1^* = DFE^* = (1, 0) \quad E_2^* = EE^* = \left( \frac{1}{R_0}, \frac{\mu \left(1 - \frac{1}{R_0}\right)}{\mu + \gamma} \right)$$

While  $DFE^*$  is always feasible,  $EE^*$  is feasible only if  $R_0 > 1$ : if not  $Y$  will either go to zero if  $R_0 = 1$  (which is not compatible with this equilibrium), or it will reach negative numbers if  $R_0 < 1$  (which is not compatible with biology).

## 6.4 Stability

To check for the stability of the equilibria, first write the Jacobian matrix:

$$J = \begin{bmatrix} -\beta Y(t) - \mu - \sigma & \beta X(t) - \sigma \\ \beta Y(t) & \beta X(t) - \gamma - \mu \end{bmatrix}$$

Then it is evaluated at the equilibria. Start with  $DFE = \left( \frac{\mu(1-p)+\sigma}{\mu+\sigma}, 0 \right)$ :

$$J_{DFE} = \begin{bmatrix} -\mu - \sigma & -\beta \frac{\mu(1-p)+\sigma}{\mu+\sigma} \\ 0 & \beta \frac{\mu(1-p)+\sigma}{\mu+\sigma} - \gamma - \mu \end{bmatrix}$$

This is a triangular matrix, so it has eigenvalues:

$$\begin{aligned} \lambda_1 &= -\mu - \sigma \\ \lambda_2 &= \beta \frac{\mu(1-p)+\sigma}{\mu+\sigma} - \gamma - \mu \end{aligned}$$

$\lambda_1$  is always negative, while to discuss  $\lambda_2$  introduce:

$$R_c = \frac{\beta}{\mu + \gamma} \frac{\mu(1-p) + \sigma}{\mu + \sigma} = R_0 \frac{\mu(1-p) + \sigma}{\mu + \sigma}$$

It can be seen that:

$$\begin{aligned} \lambda_2 &= R_c(\mu + \gamma) - \gamma - \mu \\ &= R_c(\mu + \gamma) - (\gamma + \mu) \end{aligned}$$

So that:

$$\begin{aligned} \lambda_2 &> 0 \\ R_c(\mu + \gamma) - (\mu + \gamma) &> 0 \\ R_c &> \frac{\mu + \gamma}{\mu + \gamma} \\ R_c &> 1 \end{aligned}$$

The  $DFE$  will be unstable if  $R_c > 1$  ( $S(A)$  positive) and asymptotically stable if  $R_c < 1$  ( $S(A)$  negative).

Now, to discuss the stability of  $E_2 = EE = \left( \frac{1}{R_0}, \frac{\mu(1-p)+\sigma-\frac{1}{R_0}(\mu+\sigma)}{\mu+\gamma+\sigma} \right)$ . Remember that the  $EE$  is well defined only if  $R_0 > 1$  and remembering  $R_0 = \frac{\beta}{\mu+\gamma}$ , the Jacobian will be:

$$\begin{aligned} J &= \begin{bmatrix} -\beta \frac{\mu(1-p)+\sigma-\frac{1}{R_0}(\mu+\sigma)}{\mu+\gamma+\sigma} - \mu - \sigma & -\beta \frac{1}{R_0} - \sigma \\ \beta \frac{\mu(1-p)+\sigma-\frac{1}{R_0}(\mu+\sigma)}{\mu+\gamma+\sigma} & \beta \frac{1}{R_0} - \gamma - \mu \end{bmatrix} \\ &= \begin{bmatrix} -\beta \frac{\mu(1-p)+\sigma-\frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} - \mu - \sigma & -\beta \frac{\mu+\gamma}{\beta} - \sigma \\ \beta \frac{\mu(1-p)+\sigma-\frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} & \beta \frac{\mu+\gamma}{\beta} - \gamma - \mu \end{bmatrix} \\ &= \begin{bmatrix} -\beta \frac{\mu(1-p)+\sigma-\frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} - \mu - \sigma & -\mu - \gamma - \sigma \\ \beta \frac{\mu(1-p)+\sigma-\frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} & \mu + \gamma - \gamma - \mu \end{bmatrix} \\ &= \begin{bmatrix} -\beta \frac{\mu(1-p)+\sigma-\frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} - \mu - \sigma & -\mu - \gamma - \sigma \\ \beta \frac{\mu(1-p)+\sigma-\frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} & 0 \end{bmatrix} \end{aligned}$$

To discuss the stability consider the Routh-Hurwitz criterion for square matrices. First consider the trace of the matrix:

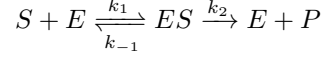
$$\begin{aligned} Tr(J) &= -\beta \frac{\mu(1-p) + \sigma - \frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} - \mu - \sigma + 0 \stackrel{?}{<} 0 \\ &= -\beta\mu + \beta\mu p + \beta\sigma + \beta \frac{\mu+\gamma}{\beta} \mu + \beta \frac{\mu+\gamma}{\beta} \sigma - \mu^2 - \sigma\mu - \gamma\mu - \sigma\mu - \gamma\sigma - \sigma^2 \stackrel{?}{<} 0 \\ &= -\beta\mu + \beta\mu p + \beta\sigma + (\mu+\gamma)\mu + (\mu+\gamma)\sigma - \mu^2 - \sigma\mu - \gamma\mu - \sigma\mu - \gamma\sigma - \sigma^2 \stackrel{?}{<} 0 \\ &= -\beta\mu + \beta\mu p + \beta\sigma + \cancel{\mu^2} + \cancel{\gamma\mu} + \cancel{\mu\sigma} + \cancel{\gamma\sigma} - \mu^2 - \cancel{\sigma\mu} - \cancel{\gamma\mu} - \sigma\mu - \gamma\sigma - \sigma^2 \stackrel{?}{<} 0 \\ &= \underbrace{-\beta\mu + \beta\mu p}_{p < 1} + \beta\sigma - \sigma\mu - \sigma^2 \stackrel{?}{<} 0 \end{aligned}$$

$Tr(J) < 0$

So  $Tr(J) < 0$ . Now consider the determinant. For a  $2 \times 2$  matrix the determinant is:  $x_{11}x_{22} - x_{12}x_{21}$ . From the computation of the trace  $x_{11} < 0$  and  $x_{22} = 0$ , while  $x_{21} > 0$  and  $x_{12} < 0$ . So the  $det(J) > 0$ . From this it can be concluded that the Endemic equilibrium  $EE$  is asymptotically stable, when it exists.

## 7 Enzymatic reactions

An enzymatic reaction follows:



By assuming a law of mass action dynamics (the rate of each reaction is proportional to the concentration of the reactants), this scheme can be transformed into a set of differential equations. Let  $s = [S]$ ,  $e = [E]$ ,  $c = [SE]$  and  $p = [P]$ :

$$\begin{cases} \frac{ds(t)}{dt} = -k_1 s(t)e(t) + k_{-1}c(t) \\ \frac{de(t)}{dt} = -k_1 s(t)e(t) + (k_{-1} + k_2)c(t) \\ \frac{dc(t)}{dt} = k_1 s(t)e(t) - (k_{-1} + k_2)c(t) \\ \frac{dp(t)}{dt} = k_2 c(t) \end{cases}$$

The first three equations do not depend on  $p$ , so the last equation can be excluded as:

$$p(t) = k_2 \int_0^t c(s) dt$$

Then the system becomes:

$$\begin{cases} \frac{ds(t)}{dt} = -k_1 s(t)e(t) + k_{-1}c(t) \\ \frac{de(t)}{dt} = -k_1 s(t)e(t) + (k_{-1} + k_2)c(t) \\ \frac{dc(t)}{dt} = k_1 s(t)e(t) - (k_{-1} + k_2)c(t) \end{cases}$$

Additionally it can be noted how  $\frac{de(t)}{dt} + \frac{dc(t)}{dt} = 0$ , meaning that:

$$\frac{d}{dt}[e(t) + c(t)] = 0 \rightarrow e(t) + c(t) = k = e_0$$

Given that  $\frac{de(t)}{dt}$  can be recovered when  $\frac{dc(t)}{dt}$  is known, computing  $e(t) = e_0 - c(t)$ , the second equation can be excluded from the system:

$$\begin{cases} \frac{ds(t)}{dt} = k_{-1}c(t) - k_1 s(t)(e_0 - c(t)) \\ \frac{dc(t)}{dt} = k_1 s(t)(e_0 - c(t)) - (k_{-1} + k_2)c(t) \end{cases}$$

Now consider  $s(0) = s_0$ ,  $c(0) = 0$  and  $p(0) = 0$  and normalize the system by:

$$x(t) = \frac{s(t)}{s_0} \quad \wedge \quad y(t) = \frac{c(t)}{e_0}$$

## 7.1 Reactant abundance

Assume a negligibly small concentration of enzyme:

$$\epsilon = \frac{e_0}{s_0} \ll 1$$

Now normalizing the system, note that  $\frac{ds(t)}{dt} \rightarrow \frac{ds(t)}{dt} \frac{1}{s_0} = \frac{d \frac{s(t)}{s_0}}{dt}$  and  $\frac{dc(t)}{dt} \rightarrow \frac{dc(t)}{dt} \frac{1}{e_0} = \frac{d \frac{c(t)}{e_0}}{dt}$ . So that the normalized system:

$$\begin{cases} s_0 \frac{dx(t)}{dt} = k_{-1}y(t)e_0 - k_1x(t)s_0(e_0 - y(t)e_0) \\ e_0 \frac{dy(t)}{dt} = k_1s_0x(t)(e_0 - e_0y(t)) - e_0y(t)(k_{-1} + k_2) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} = k_{-1}y(t)\frac{e_0}{s_0} - k_1x(t)s_0\frac{e_0}{s_0}(1 - y(t)) \\ \frac{dy(t)}{dt} = k_1s_0x(t)(1 - y(t)) - y(t)(k_{-1} + k_2) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} = k_{-1}y(t)\epsilon - k_1x(t)s_0\epsilon(1 - y(t)) \\ \frac{dy(t)}{dt} = k_1s_0x(t)(1 - y(t)) - y(t)(k_{-1} + k_2) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} = \epsilon[k_{-1}y(t) - k_1x(t)s_0(1 - y(t))] \\ \frac{dy(t)}{dt} = k_1s_0x(t)(1 - y(t)) - y(t)(k_{-1} + k_2) \end{cases}$$

Since it was assumed that  $\epsilon \approx 0$ :

$$\begin{cases} \frac{dx(t)}{dt} = 0 \\ \frac{dy(t)}{dt} = k_1s_0x(t)(1 - y(t)) - y(t)(k_{-1} + k_2) \end{cases}$$

So  $x(t)$  is a constant. Moreover, given that  $x(t) = \frac{s(t)}{s_0}$ , and that  $s_0$  is a constant, then  $s(t)$  is constant. This means that it never changes from its initial value, so  $x = \frac{s(t)}{s_0} = \frac{s_0}{s_0} = 1$ . Then a single ODE remains in the system:

$$\frac{dy}{dt} = k_1s_0(1 - y(t)) - y(t)(k_{-1} + k_2)$$

### 7.1.1 Equilibrium points

Analyzing the equilibrium points of the system:

$$\begin{aligned} k_1s_0(1 - y(t)) - y(t)(k_{-1} + k_2) &= 0 \\ k_1s_0 - k_1s_0y(t) - y(t)(k_{-1} + k_2) &= 0 \\ (k_1s_0 + k_{-1} + k_2)y(t) &= k_1s_0 \\ y(t) &= \frac{k_1s_0}{k_1s_0 + k_{-1} + k_2} \end{aligned}$$

## 7.2 Slower time-scale

In a lower time-scale the system cannot be approximated into a single equation.  $t$  is replaced by a smaller unit  $\tau$  such that:

$$\tau = \epsilon t$$

So that when  $\epsilon$  is very small, also  $\tau$  is very small and the timescale is slowed down. Using the chain rule:

$$\frac{d}{d\tau} = \frac{d}{dt} \frac{dt}{d\tau}$$

And since  $t = \frac{\tau}{\epsilon}$ :

$$\begin{aligned} \frac{d}{d\tau} &= \frac{d}{dt} \frac{dt}{d\tau} \\ &= \frac{d}{dt} \frac{1}{\epsilon} \end{aligned}$$

Applying this in  $x(t)$  and  $y(t)$ :

$$\begin{aligned} \frac{d}{d\tau} x(\tau) &= \frac{d}{dt} \frac{1}{\epsilon} x(\tau) \\ &= \frac{1}{\epsilon} \frac{dx(t)}{dt} \end{aligned}$$

$$\begin{aligned} \frac{d}{d\tau} y(\tau) &= \frac{d}{dt} \frac{1}{\epsilon} y(\tau) \\ &= \frac{1}{\epsilon} \frac{dy(t)}{dt} \end{aligned}$$

So the system can be switched to the slower time scale by dividing by  $\epsilon$ :

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= \frac{1}{\epsilon} [k_{-1}y(\tau) - k_1x(\tau)s_0(1 - y(\tau))] \\ \frac{dy(\tau)}{d\tau} &= \frac{1}{\epsilon} [k_1s_0x(\tau)(1 - y(\tau)) - y(\tau)(k_{-1} + k_2)] \end{cases}$$

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= k_{-1}y(\tau) - k_1x(\tau)s_0(1 - y(\tau)) \\ \frac{dy(\tau)}{d\tau} &= \frac{1}{\epsilon} [k_1s_0x(\tau)(1 - y(\tau)) - y(\tau)(k_{-1} + k_2)] \end{cases}$$

Switching back to the fast timescale for the second equation:

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= k_{-1}y(\tau) - k_1x(\tau)s_0(1 - y(\tau)) \\ \frac{dy(t)}{dt} = \epsilon \frac{dy(\tau)}{d\tau} &= [k_1s_0x(\tau)(1 - y(\tau)) - y(\tau)(k_{-1} + k_2)] \end{cases}$$

But, since  $\epsilon \approx 0$ :

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= k_{-1}y(\tau) - k_1x(\tau)s_0(1 - y(\tau)) \\ 0 &= [k_1s_0x(\tau)(1 - y(\tau)) - y(\tau)(k_{-1} + k_2)] \end{cases}$$

The second equation allow to extract the equilibrium value  $\tilde{y}$  for  $y(t)$  in the slower timescale:

$$\begin{aligned}
 [k_1 s_0 x(\tau)(1 - \tilde{y}(\tau)) - \tilde{y}(\tau)(k_{-1} + k_2)] &= 0 \\
 k_1 s_0 x(\tau) - k_1 s_0 x(\tau) \tilde{y}(\tau) - \tilde{y}(\tau)(k_{-1} + k_2) &= 0 \\
 (k_1 s_0 x(\tau) + k_{-1} + k_2) \tilde{y}(\tau) &= k_1 s_0 x(\tau) \\
 \tilde{y}(\tau) &= \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2}
 \end{aligned}$$

So that it can be substituted in the first equation:

$$\begin{aligned}
 \frac{dx(\tau)}{d\tau} &= k_{-1} \tilde{y}(\tau) - k_1 x(\tau) s_0 (1 - \tilde{y}(\tau)) \\
 &= k_{-1} \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} - k_1 x(\tau) s_0 \left( 1 - \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} \right) \\
 &= k_1 x(\tau) s_0 \frac{k_{-1}}{k_1 x(\tau) s_0 + k_{-1} + k_2} - k_1 x(\tau) s_0 \left( 1 - \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} \right) \\
 &= k_1 x(\tau) s_0 \left[ \frac{k_{-1}}{k_1 x(\tau) s_0 + k_{-1} + k_2} - 1 + \frac{k_1 x(\tau) s_0}{k_1 x(\tau) s_0 + k_{-1} + k_2} \right] \\
 &= k_1 x(\tau) s_0 \left[ \frac{k_{-1} + k_1 x(\tau) s_0}{k_1 x(\tau) s_0 + k_{-1} + k_2} - 1 \right] \\
 &= \frac{(k_1 x(\tau) s_0)^2 + k_{-1} k_1 x(\tau) s_0 - k_1 x(\tau) s_0 [k_1 x(\tau) s_0 + k_{-1} + k_2]}{k_1 x(\tau) s_0 + k_{-1} + k_2} \\
 &= \frac{\cancel{(k_1 x(\tau) s_0)^2} + \cancel{k_{-1} k_1 x(\tau) s_0} - \cancel{(k_1 x(\tau) s_0)^2} - \cancel{k_{-1} k_1 x(\tau) s_0} - k_2 k_{-1} k_1 x(\tau) s_0}{k_1 x(\tau) s_0 + k_{-1} + k_2} \\
 &= \frac{k_2 k_1 x(\tau) s_0}{k_1 x(\tau) s_0 + k_{-1} + k_2}
 \end{aligned}$$

Solving this equation  $\tilde{x}(\tau)$ , an approximate solution for  $x(\tau)$  can be obtained. This can be used in the identity of  $\tilde{y}(\tau)$  to obtain an approximate equation for  $y(\tau)$ , approximating a solution for the whole system.

This is called quasi-equilibrium approximation: the timescale is changed to a slower one, and then one equation is reverted back to the quicker time scale that will be equal to 0. In this way that equation is solved so that the solutions for the two equations can be found.

### 7.3 Michaelis Menten's Law

Consider now the product:

$$\frac{dp(t)}{dt} = k_2 c(t)$$

Since  $y(t) = \frac{c(t)}{e_0}$ :

$$\frac{dp(t)}{dt} = k_2 e_0 y(t)$$



Changing to the slow timescale:

$$\frac{dp(\tau)}{d\tau} = \frac{k_2 e_0 y(t)}{\epsilon} = k_2 s_0 y(\tau)$$

Assume to have applied the quasi-equilibrium approximation and found a value  $\tilde{y}(\tau)$  that can be replaced in there. Remembering:

$$\tilde{y}(\tau) = \frac{k_1 x(\tau) s_0}{k_1 x(\tau) s_0 + k_{-1} + k_2}$$

So:

$$\begin{aligned} \frac{dp(\tau)}{d\tau} &= k_2 s_0 \frac{k_1 x(\tau) s_0}{k_1 x(\tau) s_0 + k_{-1} + k_2} \\ &= \frac{k_1 k_2 x(\tau) s_0^2}{k_1 x(\tau) s_0 + k_{-1} + k_2} \end{aligned}$$

And remembering that  $x(t) = \frac{s(t)}{s_0}$ :

$$\frac{dp(\tau)}{d\tau} = \frac{k_1 k_2 s(\tau) s_0}{k_1 s(\tau) + k_{-1} + k_2}$$

Now, multiplying by  $\epsilon$  to go to the fast timescale:

$$\begin{aligned} \frac{dp(t)}{dt} &= \epsilon \frac{dp(\tau)}{d\tau} = \epsilon \frac{k_1 k_2 s(t) s_0}{k_1 s(t) + k_{-1} + k_2} \\ &= \frac{e_0}{s_0} \frac{k_1 k_2 s(t) \cancel{s_0}}{\cancel{s_0} k_1 s(t) + k_{-1} + k_2} = \frac{\cancel{k_1} k_2 s(t) e_0}{\cancel{k_1} s(t) + \frac{k_{-1} + k_2}{k_1}} \\ &= \frac{k_2 s(t) e_0}{s(t) + \frac{k_{-1} + k_2}{k_1}} \end{aligned}$$

Given that  $k_2$  and  $e_0$  are constants, introduce  $m = k_2 e_0$ , the same for  $\frac{k_{-1} + k_2}{k_1} = s_h$ , or the half saturation constant so that the Michaelis Menten's Law is obtained:

$$\frac{dp(t)}{dt} = \frac{ms(t)}{s(t) + s_h}$$

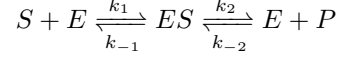
Where:

- $m = k_2 e_0$
- $s_h = \frac{k_{-1} + k_2}{k_1}$

This law links the speed at which the product of an enzymatic reaction is produced to the concentration of substrate. The half saturation constant  $s_h$  is the value of the concentration of  $S$  such that the rate of production of the product is half of its maximum. The rate of production will increase until saturation with maximum value  $m$  as the concentration of substrate grows to infinity.

## 7.4 Enzymatic reaction with reversible production

An enzymatic reaction with reversible production follows:



The system is:

$$\begin{cases} \frac{ds(t)}{dt} &= -k_1 s(t)e(t) + k_{-1}c(t) \\ \frac{de(t)}{dt} &= -k_1 s(t)e(t) + k_{-1}c(t) + k_2c(t) - k_{-2}p(t)e(t) \\ \frac{dc(t)}{dt} &= k_1 s(t)e(t) - k_{-1}c(t) - k_2c(t) + k_{-2}p(t)e(t) \\ \frac{dp(t)}{dt} &= k_2c(t) - k_{-2}p(t)e(t) \end{cases}$$

It can be seen that:

$$\begin{aligned} \frac{d}{dt}[e(t) + c(t)] &= 0 \Rightarrow e(t) + c(t) = k = e_0 \\ \frac{d}{dt}[s(t) + c(t) + p(t)] &= 0 \Rightarrow s(t) + c(t) + p(t) = k = s_0 \end{aligned}$$

Given that at any instant  $e(t)$  can be recovered from  $c(t)$  and  $p(t)$  from  $s(t)$  and  $c(t)$ , the system can be reduced to:

$$\begin{cases} \frac{ds(t)}{dt} &= -k_1 s(t)(e_0 - c(t)) + k_{-1}c(t) \\ \frac{dc(t)}{dt} &= k_1 s(t)(e_0 - c(t)) - k_{-1}c(t) - k_2c(t) + k_{-2}(s_0 - s(t) - c(t))(e_0 - c(t)) \end{cases}$$

### 7.4.1 Normalization

$$x(t) = \frac{s(t)}{s_0} \qquad y(t) = \frac{c(t)}{e_0} \qquad \epsilon = \frac{e_0}{s_0} \ll 1$$

$$\begin{aligned}
 \begin{cases} s_0 \frac{dx(t)}{dt} &= -k_1 s_0 x(t)(e_0 - e_0 y(t)) + k_{-1} e_0 y(t) \\ e_0 \frac{dy(t)}{dt} &= k_1 s_0 x(t)(e_0 - e_0 y(t)) - k_{-1} e_0 y(t) - k_2 e_0 y(t) + k_{-2} (s_0 - s_0 x(t) - e_0 y(t))(e_0 - e_0 y(t)) \end{cases} \\
 \begin{cases} \frac{dx(t)}{dt} &= -k_1 s_0 \frac{e_0}{s_0} x(t)(1 - y(t)) + k_{-1} \frac{e_0}{s_0} y(t) \\ \frac{dy(t)}{dt} &= k_1 s_0 x(t)(1 - y(t)) - k_{-1} y(t) - k_2 y(t) + k_{-2} s_0 (1 - x(t) - \frac{e_0}{s_0} y(t))(1 - y(t)) \end{cases} \\
 \begin{cases} \frac{dx(t)}{dt} &= -k_1 s_0 \epsilon x(t)(1 - y(t)) + k_{-1} \epsilon y(t) \\ \frac{dy(t)}{dt} &= k_1 s_0 x(t)(1 - y(t)) - k_{-1} y(t) - k_2 y(t) + k_{-2} s_0 (1 - x(t) - \epsilon y(t))(1 - y(t)) \end{cases} \\
 \begin{cases} \frac{dx(t)}{dt} &= \epsilon [-k_1 s_0 x(t)(1 - y(t)) + k_{-1} y(t)] \\ \frac{dy(t)}{dt} &= k_1 s_0 x(t)(1 - y(t)) - k_{-1} y(t) - k_2 y(t) + k_{-2} s_0 (1 - x(t) - \epsilon y(t))(1 - y(t)) \end{cases} \quad \epsilon \approx 0 \\
 \begin{cases} \frac{dx(t)}{dt} &= 0 [-k_1 s_0 x(t)(1 - y(t)) + k_{-1} y(t)] \\ \frac{dy(t)}{dt} &= k_1 s_0 x(t)(1 - y(t)) - k_{-1} y(t) - k_2 y(t) + k_{-2} s_0 (1 - x(t) - 0 y(t))(1 - y(t)) \end{cases} \\
 \begin{cases} \frac{dx(t)}{dt} &= 0 \\ \frac{dy(t)}{dt} &= k_1 s_0 x(t)(1 - y(t)) - k_{-1} y(t) - k_2 y(t) + k_{-2} s_0 (1 - x(t))(1 - y(t)) \end{cases}
 \end{aligned}$$

So  $x(t)$  is a constant. Assuming  $x(t) = x = 1$ :

$$\frac{dy(t)}{dt} = k_1 s_0 (1 - y(t)) - k_{-1} y(t) - k_2 y(t)$$

#### 7.4.2 Equilibrium points

$$\begin{aligned}
 k_1 s_0 (1 - y(t)) - k_{-1} y(t) - k_2 y(t) &= 0 \\
 k_1 s_0 - k_1 s_0 y(t) - k_{-1} y(t) - k_2 y(t) &= 0 \\
 (k_1 s_0 - k_{-1} - k_2) y(t) &= k_1 s_0 \\
 y(t) &= \frac{k_1 s_0}{k_1 s_0 + k_{-1} + k_2}
 \end{aligned}$$

#### 7.4.3 Quasi-equilibrium

Switching to slower timescales:

$$\tau = \epsilon t$$

$$\begin{aligned}
 \frac{d}{d\tau} x(\tau) &= \frac{d}{dt} \frac{1}{\tau} x(\tau) = \frac{dx(t)}{dt} \frac{1}{\epsilon} \\
 \frac{d}{d\tau} y(\tau) &= \frac{d}{dt} \frac{1}{\tau} y(\tau) = \frac{dy(t)}{dt} \frac{1}{\epsilon}
 \end{aligned}$$

$$\begin{cases} \frac{dx(\tau)}{d\tau} = \frac{dx(t)}{dt} \frac{1}{\epsilon} &= \frac{1}{\epsilon} [-k_1 s_0 x(\tau)(1 - y(\tau)) + k_{-1} y(\tau)] \\ \frac{dy(\tau)}{d\tau} = \frac{dy(t)}{dt} \frac{1}{\epsilon} &= \frac{1}{\epsilon} [k_1 s_0 x(\tau)(1 - y(\tau)) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0(1 - x(\tau) - \epsilon y(\tau))(1 - y(\tau))] \end{cases}$$

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= -k_1 s_0 x(\tau)(1 - y(\tau)) + k_{-1} y(\tau) \\ \frac{dy(\tau)}{d\tau} &= \frac{1}{\epsilon} [k_1 s_0 x(\tau)(1 - y(\tau)) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0(1 - x(\tau) - \epsilon y(\tau))(1 - y(\tau))] \end{cases}$$

Now applying the quasi-equilibrium condition and reverting to the fast timescale for the second:

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= -k_1 s_0 x(\tau)(1 - y(\tau)) + k_{-1} y(\tau) \\ \frac{dy(\tau)}{d\tau} = \epsilon \frac{dy(\tau)}{d\tau} &= \cancel{\frac{1}{\epsilon}} [k_1 s_0 x(\tau)(1 - y(\tau)) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0(1 - x(\tau) - \epsilon y(\tau))(1 - y(\tau))] \end{cases}$$

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= -k_1 s_0 x(\tau)(1 - y(\tau)) + k_{-1} y(\tau) \\ \frac{dy(\tau)}{d\tau} = \epsilon \frac{dy(\tau)}{d\tau} &= \cancel{\frac{1}{\epsilon}} [k_1 s_0 x(\tau)(1 - y(\tau)) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0(1 - x(\tau))(1 - y(\tau))] \end{cases}$$

$\epsilon \approx 0$

$$\begin{cases} \frac{dx(\tau)}{d\tau} &= -k_1 s_0 x(\tau)(1 - y(\tau)) + k_{-1} y(\tau) \\ 0 &= k_1 s_0 x(\tau)(1 - y(\tau)) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0(1 - x(\tau))(1 - y(\tau)) \end{cases}$$

Now extracting  $\tilde{y}(\tau)$ :

$$\begin{aligned} k_1 s_0 x(\tau)(1 - y(\tau)) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0(1 - x(\tau))(1 - y(\tau)) &= 0 \\ k_1 s_0 x(\tau) - k_1 s_0 x(\tau)y(\tau) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0(1 - x(\tau) - y(\tau) + x(\tau)y(\tau)) &= 0 \\ k_1 s_0 x(\tau) - k_1 s_0 x(\tau)y(\tau) - k_{-1} y(\tau) - k_2 y(\tau) + k_{-2} s_0 - k_{-2} s_0 x(\tau) - k_{-2} s_0 y(\tau) + k_{-2} s_0 x(\tau)y(\tau) &= 0 \\ [-k_1 s_0 x(\tau) - k_{-1} - k_2 - k_{-2} s_0 + k_{-2} s_0 x(\tau)]y(\tau) &= -k_1 s_0 x(\tau) - k_{-2} s_0 - k_{-2} s_0 x(\tau) \\ y(\tau) &= -\frac{k_1 s_0 x(\tau) + k_{-2} s_0 + k_{-2} s_0 x(\tau)}{-k_1 s_0 x(\tau) - k_{-1} - k_2 - k_{-2} s_0 + k_{-2} s_0 x(\tau)} \\ y(\tau) &= \frac{k_1 s_0 x(\tau) + k_{-2} s_0 + k_{-2} s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} s_0 x(\tau)} \end{aligned}$$

At this point it can be plugged into the equation for  $\frac{dx(\tau)}{d\tau}$ :

$$\frac{dx(\tau)}{d\tau} = -k_1 s_0 x(\tau)(1 - y(\tau)) + k_{-1} y(\tau)$$

$$\begin{aligned}
 1 - y(\tau) &= 1 - \frac{k_1 s_0 x(\tau) + k_{-2} s_0 + k_{-2} s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} x(\tau)} \\
 &= \frac{\cancel{k_1 s_0 x(\tau)} + k_{-1} + k_2 + \cancel{k_{-2} s_0} - \cancel{k_{-2} s_0 x(\tau)} - \cancel{k_1 s_0 x(\tau)} - \cancel{k_{-2} s_0} - \cancel{k_{-2} s_0 x(\tau)}}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} s_0 x(\tau)} \\
 &= \frac{k_{-1} + k_2}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} s_0 x(\tau)}
 \end{aligned}$$

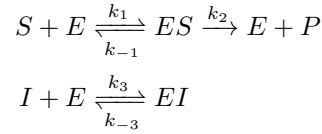
So that:

$$\begin{aligned}
 \frac{dx(\tau)}{d\tau} &= \frac{-k_1 s_0 x(\tau)(k_{-1} + k_2)}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} s_0 x(\tau)} + \frac{k_{-1} k_1 x(\tau) s_0 + k_{-1} k_{-2} s_0 - k_{-1} k_{-2} s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} s_0 x(\tau)} \\
 &= \frac{-\cancel{k_1 k_{-1} s_0 x(\tau)} - k_1 k_2 s_0 x(\tau) + \cancel{k_{-1} k_1 x(\tau) s_0} + k_{-1} k_{-2} s_0 - \cancel{k_{-1} k_{-2} s_0 x(\tau)}}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} s_0 x(\tau)} \\
 &= \frac{-k_1 k_2 s_0 x(\tau) + k_{-1} k_{-2} s_0 - k_{-1} k_{-2} s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2 + k_{-2} s_0 - k_{-2} s_0 x(\tau)}
 \end{aligned}$$

In order to apply Tikhonov's theorem, the equation has to be solved, finding  $\tilde{x}(\tau)$ , then it would be plugged into  $\tilde{y}(\tau)$  to obtain  $\bar{y}(\tau)$ . At this point for  $\epsilon \rightarrow 0$  the exact solution converges to the degenerate  $(\tilde{x}(\tau), \tilde{y}(\tau))$ .

## 7.5 Enzymatic inhibition

An inhibitory molecule may decrease the rate at which an enzymatic reaction occurs. Considering competitive inhibition, let  $I$  be the inhibitory molecule, then the competitive inhibition is schematized as:



Let  $s = [S]$ ,  $e = [E]$ ,  $i = [I]$ ,  $c_1 = [SE]$ ,  $c_2 = [IE]$  and  $p = [P]$ :

$$\begin{cases}
 \frac{ds(t)}{dt} &= -k_1 s(t)e(t) + k_{-1} c_1(t) \\
 \frac{de(t)}{dt} &= -k_1 s(t)e(t) + (k_{-1} + k_2) c_1(t) - k_3 i(t)e(t) + k_{-3} c_2(t) \\
 \frac{dc_1(t)}{dt} &= k_1 s(t)e(t) - (k_{-1} + k_2) c_1(t) \\
 \frac{dp(t)}{dt} &= k_2 c_1(t) \\
 \frac{di(t)}{dt} &= -k_3 i(t)e(t) + k_{-3} c_2(t) \\
 \frac{dc_2(t)}{dt} &= k_3 i(t)e(t) - k_{-3} c_2(t)
 \end{cases}$$

No equation depends on  $p$ , so it can be eliminated. Moreover:

$$\frac{d}{dt}[e(t) + c_1(t) + c_2(t)] = k = e_0 \quad e(t) = (e_0 - c_1(t) - c_2(t))$$

So  $\frac{de(t)}{dt}$  can be eliminated from the system. Finally  $[I]$  is assumed so large that its variation on time are negligible:  $\frac{di(t)}{dt} = 0$ . Now the constant value of  $i$  can be recovered:

$$\begin{aligned} \frac{di(t)}{dt} &= -k_3 i(t) e(t) + k_{-3} c_2(t) = 0 \\ k_3 i(t) (e_0 - c_1(t) - c_2(t)) &= k_{-3} c_2(t) \\ i &= \frac{k_{-3} c_2(t)}{k_3 (e_0 - c_1(t) - c_2(t))} \end{aligned}$$

With these assumptions the system becomes:

$$\begin{cases} \frac{ds(t)}{dt} &= -k_1 s(t) (e_0 - c_1(t) - c_2(t)) + k_{-1} c_1(t) \\ \frac{dc_1(t)}{dt} &= k_1 s(t) (e_0 - c_1(t) - c_2(t)) - (k_{-1} + k_2) c_1(t) \\ \frac{dc_2(t)}{dt} &= k_3 i (e_0 - c_1(t) - c_2(t)) - k_{-3} c_2(t) \end{cases}$$

### 7.5.1 Normalization

Introduce:

$$x(t) = \frac{s(t)}{s_0} \quad y_1(t) = \frac{c_1(t)}{e_0} \quad y_2(t) = \frac{c_2(t)}{e_0} \quad \epsilon = \frac{e_0}{s_0} \ll 1$$

$$\begin{cases} s_0 \frac{dx(t)}{dt} = -k_1 s_0 x(t) (e_0 - e_0 y_1(t) - e_0 y_2(t)) + k_{-1} e_0 y_1(t) \\ e_0 \frac{dy_1(t)}{dt} = k_1 s_0 x(t) (e_0 - e_0 y_1(t) - e_0 y_2(t)) - (k_{-1} + k_2) e_0 y_1(t) \\ e_0 \frac{dy_2(t)}{dt} = k_3 i (e_0 - e_0 y_1(t) - e_0 y_2(t)) - k_{-3} e_0 y_2(t) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} = -k_1 \frac{e_0}{s_0} s_0 x(t) (1 - y_1(t) - y_2(t)) + k_{-1} \frac{e_0}{s_0} y_1(t) \\ \frac{dy_1(t)}{dt} = k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) - (k_{-1} + k_2) y_1(t) \\ \frac{dy_2(t)}{dt} = k_3 i (1 - y_1(t) - y_2(t)) - k_{-3} y_2(t) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} = -k_1 \epsilon s_0 x(t) (1 - y_1(t) - y_2(t)) + k_{-1} \epsilon y_1(t) \\ \frac{dy_1(t)}{dt} = k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) - (k_{-1} + k_2) y_1(t) \\ \frac{dy_2(t)}{dt} = k_3 i (1 - y_1(t) - y_2(t)) - k_{-3} y_2(t) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} = \epsilon [-k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) + k_{-1} y_1(t)] \\ \frac{dy_1(t)}{dt} = k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) - (k_{-1} + k_2) y_1(t) \\ \frac{dy_2(t)}{dt} = k_3 i (1 - y_1(t) - y_2(t)) - k_{-3} y_2(t) \end{cases}$$

### 7.5.2 Quasi-equilibrium

Assume a slower timescale  $\tau = \epsilon t$ :

$$\begin{aligned} \frac{d}{d\tau}x(\tau) &= \frac{dx(t)}{dt} \frac{1}{\epsilon} & \frac{d}{d\tau}y_1(\tau) &= \frac{dy_1(t)}{dt} \frac{1}{\epsilon} & \frac{d}{d\tau}y_2(\tau) &= \frac{dy_2(t)}{dt} \frac{1}{\epsilon} \\ \begin{cases} \frac{dx(\tau)}{d\tau} &= -k_1 s_0 x(\tau)(1 - y_1(\tau) - y_2(\tau)) + k_{-1} y_1(\tau) \\ \frac{dy_1(\tau)}{d\tau} &= \frac{1}{\epsilon} [k_1 s_0 x(\tau)(1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau)] \\ \frac{dy_2(\tau)}{d\tau} &= \frac{1}{\epsilon} [k_3 i(1 - y_1(\tau) - y_2(\tau)) - k_{-3} y_2(\tau)] \end{cases} \end{aligned}$$

Reverting back to the fast timescale the last two equations:

$$\begin{aligned} \begin{cases} \frac{dx(\tau)}{d\tau} &= -k_1 s_0 x(\tau)(1 - y_1(\tau) - y_2(\tau)) + k_{-1} y_1(\tau) \\ \epsilon \frac{dy_1(\tau)}{d\tau} &= k_1 s_0 x(\tau)(1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) \\ \epsilon \frac{dy_2(\tau)}{d\tau} &= k_3 i(1 - y_1(\tau) - y_2(\tau)) - k_{-3} y_2(\tau) \end{cases} \\ \epsilon &\approx 0 \\ \begin{cases} \frac{dx(\tau)}{d\tau} &= -k_1 s_0 x(\tau)(1 - y_1(\tau) - y_2(\tau)) + k_{-1} y_1(\tau) \\ 0 &= k_1 s_0 x(\tau)(1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) \\ 0 &= k_3 i(1 - y_1(\tau) - y_2(\tau)) - k_{-3} y_2(\tau) \end{cases} \end{aligned}$$

The last two equations can now be solved:

$$\begin{aligned} k_1 s_0 x(\tau)(1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) &= 0 \\ k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_1(\tau) - k_1 s_0 x(\tau) y_2(\tau) - k_{-1} y_1(\tau) - k_2 y_1(\tau) &= 0 \\ [k_1 s_0 x(\tau) + k_{-1} + k_2] y_1(\tau) &= k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_2(\tau) \\ y_1(\tau) &= \frac{k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_2(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} \end{aligned}$$

This still depends on  $y_2(\tau)$ , so we need to solve the last equation:

$$\begin{aligned}
& k_3 i (1 - y_1(\tau) - y_2(\tau)) - k_{-3} y_2(\tau) = 0 \\
& k_3 i \left( 1 - \frac{k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_2(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} - y_2(\tau) \right) - k_{-3} y_2(\tau) = 0 \\
& k_3 i - \frac{k_3 i (k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_2(\tau))}{k_1 s_0 x(\tau) + k_{-1} + k_2} - k_3 i y_2(\tau) - k_{-3} y_2(\tau) = 0 \\
& \quad - \frac{k_3 i k_1 s_0 x(\tau) y_2(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} + k_3 i y_2(\tau) + k_{-3} y_2(\tau) = k_3 i - \frac{k_3 i k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} \\
& \frac{-k_3 i k_1 s_0 x(\tau) + k_3 i (k_1 s_0 x(\tau) + k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)}{k_1 s_0 x(\tau) + k_{-1} + k_2} y_2(\tau) = \frac{k_3 i (k_1 s_0 x(\tau) + k_{-1} + k_2)}{k_1 s_0 x(\tau) + k_{-1} + k_2} + \\
& \quad - \frac{k_3 i k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} \\
& \frac{(-k_3 i k_1 s_0 x(\tau) + k_3 i k_1 s_0 x(\tau)) + k_3 i k_{-1} - k_3 i k_2 + k_{-3} k_1 s_0 x(\tau) + k_{-3} k_{-1} + k_{-3} k_2}{k_1 s_0 x(\tau) + k_{-1} + k_2} y_2(\tau) = \frac{k_3 i k_{-1} + k_3 i k_2}{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)} \\
& \quad - \frac{k_3 i k_1 s_0 x(\tau)}{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)} \\
& y_2(\tau) = \frac{k_3 i k_{-1} + k_3 i k_2}{k_3 i k_{-1} - k_3 i k_2 + k_{-3} k_1 s_0 x(\tau) + k_{-3} k_{-1} + k_{-3} k_2} \\
& \tilde{y}_2(\tau) = \frac{k_3 i (k_{-1} + k_2)}{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)}
\end{aligned}$$

Now, replugging into  $y_1(\tau)$ :

$$\begin{aligned}
y_1(\tau) &= \frac{k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_2(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} \\
&= \frac{k_1 s_0 x(\tau) \left( 1 - \frac{k_3 i (k_{-1} + k_2)}{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)} \right)}{k_1 s_0 x(\tau) + k_{-1} + k_2} \\
&= \frac{k_1 s_0 x(\tau) \frac{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2) - k_3 i (k_{-1} + k_2)}{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)}}{k_1 s_0 x(\tau) + k_{-1} + k_2} \\
&= \frac{\frac{k_1 s_0 x(\tau) k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)}{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)}}{k_1 s_0 x(\tau) + k_{-1} + k_2} \\
\tilde{y}_1(\tau) &= \frac{k_1 s_0 x(\tau) k_{-3}}{k_3 i (k_{-1} + k_2) + k_{-3} (k_1 s_0 x(\tau) + k_{-1} + k_2)}
\end{aligned}$$

In order to apply Tikhonov's theorem, the two solutions will be plugged into  $\frac{dx(\tau)}{\tau}$ , solving the differential equation and plugging the values of  $x(\tau)$  into the two solution.

### 7.5.3 Rate of production of the product

Now, since the objective is to find an explicit way to track the rate of production of the product and considering:



$$\frac{dp(t)}{dt} = k_2 c_1(t) \quad \wedge \quad \frac{dp(t)}{dt} = k_2 y_1(t) e_0$$

And transitioning to the slow timescale"

$$\begin{aligned} \frac{dp(\tau)}{d\tau} &= \frac{dp(t)}{dt} \frac{1}{\epsilon} \\ &= \frac{k_2 y_1(\tau) e_0}{\epsilon} \\ &= k_2 y_1(\tau) s_0 \end{aligned}$$

Plugging the value for  $\tilde{y}_1(\tau)$ :

$$\begin{aligned} \frac{dp(\tau)}{d\tau} &= k_2 s_0 \frac{k_1 (s_0 x(\tau)) k_{-3}}{k_{-3} (k_{-1} + k_2 + k_1 s_0 x(\tau)) + k_3 i (k_{-1} + k_2)} \\ &= \frac{k_2 s_0 k_1 s(\tau) k_{-3}}{k_{-3} (k_{-1} + k_2 + k_1 s_0 x(\tau)) + k_3 i (k_{-1} + k_2)} \end{aligned}$$

And going back to the fast timescale:

$$\begin{aligned} \epsilon \frac{dp(\tau)}{d\tau} &= \frac{dp(t)}{dt} = \frac{\epsilon k_2 s_0 k_1 s(\tau) k_{-3}}{k_{-3} (k_{-1} + k_2 + k_1 s_0 x(\tau)) + k_3 i (k_{-1} + k_2)} \\ &= \frac{k_2 e_0 k_1 s(t) k_{-3}}{k_{-3} (k_{-1} + k_2 + k_1 s_0 x(t)) + k_3 i (k_{-1} + k_2)} \\ &= \frac{\frac{k_2 e_0 k_1 s(t) k_{-3}}{k_1 k_{-3}}}{\frac{k_{-3} (k_{-1} + k_2 + k_1 s_0 x(t)) + k_3 i (k_{-1} + k_2)}{k_1 k_{-3}}} \\ &= \frac{\frac{k_2 e_0 \cancel{k_1} s(t) \cancel{k_{-3}}}{\cancel{k_1} \cancel{k_{-3}}}}{\frac{\cancel{k_{-3}}}{\cancel{k_1} \cancel{k_{-3}}} (k_{-1} + k_2 + \cancel{k_1} s(t)) + \frac{k_3 i}{k_1 k_{-3}} (k_{-1} + k_2)} \\ &= \frac{k_2 e_0 s(t)}{\frac{k_{-1} + k_2}{k_1} + \frac{\cancel{k_1} s(t)}{\cancel{k_1}} + \frac{k_3 i}{k_1 k_{-3}} (k_{-1} + k_2)} \\ &= \frac{k_2 e_0 s(t)}{\frac{k_{-1} + k_2}{k_1} + s(t) + \frac{k_3 i}{k_1 k_{-3}} (k_{-1} + k_2)} \end{aligned}$$

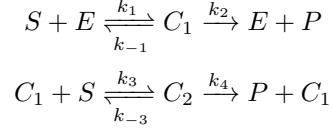
Now setting  $m = k_2 e_0$ ,  $s_h = \frac{k_{-1} + k_2}{k_1}$  and  $s_i = \frac{k_3 i}{k_1 k_{-3}} (k_{-1} + k_2)$ :

$$\frac{dp(t)}{dt} = \frac{ms(t)}{s_h + s(t) + s_i}$$

Which is the speed of production of  $p$ . So adding an inhibitor will increase the half saturation constant from  $s_h$  to  $s_h + s_i$ , decreasing the reaction rate when the substrate is not abundant. When it grows to infinity, the enzyme is still capable of reaching its maximum speed  $m$ .

## 7.6 Cooperativity

In cooperativity an enzyme can bind up to two substrate molecules. The reaction scheme is:



This happens when the binding of the first molecule changes the enzyme configuration and changing the rate at which further binding occurs. An extreme degree happens when  $k_1$  is very low and  $k_3$  is very high. On the other hand independence means that  $k_1 = 2k_3$  and  $k_{-3} = 2k_{-1}$ . Moreover independence implies that  $k_4 = k_2$ . The ODE system is:

$$\begin{cases} \frac{ds(t)}{dt} &= -k_1 s(t)e(t) + k_{-1}c_1(t) - k_3c_1(t)s(t) + k_{-3}c_2(t) \\ \frac{de(t)}{dt} &= -k_1 s(t)e(t) + k_{-1}c_1(t) + k_2c_1(t) \\ \frac{dc_1(t)}{dt} &= k_1 s(t)e(t) - k_{-1}c_1(t) - k_2c_1(t) - k_3c_1(t)s(t) + k_{-3}c_2(t) + k_4c_2(t) \\ \frac{dc_2(t)}{dt} &= k_3c_1(t)s(t) - k_{-3}c_2(t) - k_4c_2(t) \\ \frac{dp(t)}{dt} &= k_2c_1(t) + k_4c_2(t) \end{cases}$$

$p$  appears in only one equation, so it can be recovered from other quantities. Moreover:

$$\frac{d}{dt}[e(t) + c_1(t) + c_2(t)] = 0 \Rightarrow e(t) + c_1(t) + c_2(t) = k = e_0$$

So that the dynamics of  $e$  can be expluded. So the system becomes:

$$\begin{cases} \frac{ds(t)}{dt} &= -k_1 s(t)(e_0 - c_1(t) - c_2(t)) + k_{-1}c_1(t) - k_3c_1(t)s(t) + k_{-3}c_2(t) \\ \frac{dc_1(t)}{dt} &= k_1 s(t)(e_0 - c_1(t) - c_2(t)) - (k_{-1} + k_2)c_1(t) - k_3c_1(t)s(t) + k_{-3}c_2(t) + k_4c_2(t) \\ \frac{dc_2(t)}{dt} &= k_3c_1(t)s(t) - k_{-3}c_2(t) - k_4c_2(t) \end{cases}$$

### 7.6.1 Normalization

Let:

$$x(t) = \frac{s(t)}{s_0} \quad y_1(t) = \frac{c_1(t)}{e_0} \quad y_2(t) = \frac{c_2(t)}{e_0} \quad \epsilon = \frac{e_0}{s_0} \ll 1$$

Then the system becomes:

$$\begin{cases}
s_0 \frac{dx(t)}{dt} &= -k_1 s_0 x(t)(e_0 - e_0 y_1(t) - e_0 y_2(t)) + k_{-1} e_0 y_1(t) - k_3 e_0 y_1(t) s(t) + k_{-3} e_0 y_2(t) \\
e_0 \frac{dy_1(t)}{dt} &= k_1 s_0 x(t)(e_0 - e_0 y_1(t) - e_0 y_2(t)) - (k_{-1} + k_2) e_0 y_1(t) - k_3 e_0 y_1(t) s_0 x(t) + k_{-3} e_0 y_2(t) + k_4 e_0 y_2(t) \\
e_0 \frac{dy_2(t)}{dt} &= k_3 e_0 y_1(t) s_0 x(t) - k_{-3} e_0 y_2(t) - k_4 e_0 y_2(t)
\end{cases}$$

$$\begin{cases}
\frac{dx(t)}{dt} &= -k_1 s_0 x(t) \frac{e_0}{s_0} (1 - y_1(t) - y_2(t)) + k_{-1} \frac{e_0}{s_0} y_1(t) - k_3 \frac{e_0}{s_0} y_1(t) s(t) + k_{-3} \frac{e_0}{s_0} y_2(t) \\
\frac{dy_1(t)}{dt} &= k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) - (k_{-1} + k_2) y_1(t) - k_3 y_1(t) s_0 x(t) + k_{-3} y_2(t) + k_4 y_2(t) \\
\frac{dy_2(t)}{dt} &= k_3 y_1(t) s_0 x(t) - k_{-3} y_2(t) - k_4 y_2(t)
\end{cases}$$

$$\begin{cases}
\frac{dx(t)}{dt} &= -k_1 s_0 x(t) \epsilon (1 - y_1(t) - y_2(t)) + k_{-1} \epsilon y_1(t) - k_3 \epsilon y_1(t) s(t) + k_{-3} \epsilon y_2(t) \\
\frac{dy_1(t)}{dt} &= k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) - (k_{-1} + k_2) y_1(t) - k_3 y_1(t) s_0 x(t) + k_{-3} y_2(t) + k_4 y_2(t) \\
\frac{dy_2(t)}{dt} &= k_3 y_1(t) s_0 x(t) - k_{-3} y_2(t) - k_4 y_2(t)
\end{cases}$$

$$\begin{cases}
\frac{dx(t)}{dt} &= \epsilon [-k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) + k_{-1} y_1(t) - k_3 y_1(t) s(t) + k_{-3} y_2(t)] \\
\frac{dy_1(t)}{dt} &= k_1 s_0 x(t) (1 - y_1(t) - y_2(t)) - (k_{-1} + k_2) y_1(t) - k_3 y_1(t) s_0 x(t) + k_{-3} y_2(t) + k_4 y_2(t) \\
\frac{dy_2(t)}{dt} &= k_3 y_1(t) s_0 x(t) - k_{-3} y_2(t) - k_4 y_2(t)
\end{cases}$$

### 7.6.2 Changing timescale

Let:

$$\tau = \frac{t}{\epsilon}$$

Then:

$$\begin{cases}
\frac{dx(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dx(t)}{dt} &= -k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) + k_{-1} y_1(\tau) - k_3 y_1(\tau) s(\tau) + k_{-3} y_2(\tau) \\
\frac{dy_1(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dy_1(t)}{dt} &= \frac{1}{\epsilon} [k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) - k_3 y_1(\tau) s_0 x(\tau) + k_{-3} y_2(\tau) + k_4 y_2(\tau)] \\
\frac{dy_2(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dy_2(t)}{dt} &= \frac{1}{\epsilon} [k_3 y_1(\tau) s_0 x(\tau) - k_{-3} y_2(\tau) - k_4 y_2(\tau)]
\end{cases}$$

$$\begin{cases}
\frac{dx(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dx(t)}{dt} &= -k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) + k_{-1} y_1(\tau) - k_3 y_1(\tau) s(\tau) + k_{-3} y_2(\tau) \\
\frac{dy_1(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dy_1(t)}{dt} &= \frac{1}{\epsilon} [k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) - k_3 y_1(\tau) s_0 x(\tau) + k_{-3} y_2(\tau) + k_4 y_2(\tau)] \\
\frac{dy_2(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dy_2(t)}{dt} &= \frac{1}{\epsilon} [k_3 y_1(\tau) s_0 x(\tau) - k_{-3} y_2(\tau) - k_4 y_2(\tau)]
\end{cases}$$

Switching to fast timescale for the last two equation:

$$\begin{cases}
\frac{dx(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dx(t)}{dt} &= -k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) + k_{-1} y_1(\tau) - k_3 y_1(\tau) s(\tau) + k_{-3} y_2(\tau) \\
\frac{dy_1(\tau)}{d\tau} = \frac{dy_1(t)}{dt} &= k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) - k_3 y_1(\tau) s_0 x(\tau) + k_{-3} y_2(\tau) + k_4 y_2(\tau) \\
\frac{dy_2(\tau)}{d\tau} = \frac{dy_2(t)}{dt} &= k_3 y_1(\tau) s_0 x(\tau) - k_{-3} y_2(\tau) - k_4 y_2(\tau)
\end{cases}$$

$\epsilon \approx 0$

$$\begin{cases}
\frac{dx(\tau)}{d\tau} = \frac{1}{\epsilon} \frac{dx(t)}{dt} &= -k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) + k_{-1} y_1(\tau) - k_3 y_1(\tau) s(\tau) + k_{-3} y_2(\tau) \\
0 &= k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) - k_3 y_1(\tau) s_0 x(\tau) + k_{-3} y_2(\tau) + k_4 y_2(\tau) \\
0 &= k_3 y_1(\tau) s_0 x(\tau) - k_{-3} y_2(\tau) - k_4 y_2(\tau)
\end{cases}$$

To find quasi-equilibria solve first for  $y_2(\tau)$ :

$$\begin{aligned}
k_3 y_1(\tau) s_0 x(\tau) - k_{-3} y_2(\tau) - k_4 y_2(\tau) &= 0 \\
[k_{-3} + k_4] y_2(\tau) &= k_3 y_1(\tau) s_0 x(\tau) \\
y_2(\tau) &= \frac{k_3 y_1(\tau) s_0 x(\tau)}{k_{-3} + k_4}
\end{aligned}$$

Then for  $y_1(\tau)$ :

$$\begin{aligned}
k_1 s_0 x(\tau) (1 - y_1(\tau) - y_2(\tau)) - (k_{-1} + k_2) y_1(\tau) - k_3 y_1(\tau) s_0 x(\tau) + k_{-3} y_2(\tau) + k_4 y_2(\tau) &= 0 \\
k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_1(\tau) - k_1 s_0 x(\tau) y_2(\tau) - (k_{-1} + k_2) y_1(\tau) - k_3 y_1(\tau) s_0 x(\tau) + k_{-3} y_2(\tau) + k_4 y_2(\tau) &= 0 \\
[-k_1 s_0 x(\tau) - k_{-1} - k_2 - k_3 s_0 x(\tau)] y_1(\tau) &= k_1 s_0 x(\tau) y_2(\tau) - k_{-3} y_2(\tau) - k_4 y_2(\tau) - k_1 s_0 x(\tau) \\
[(k_1 + k_3) s_0 x(\tau) + k_{-1} + k_2] y_1(\tau) &= (k_{-3} + k_4 - k_1 s_0 x(\tau)) y_2(\tau) + k_1 s_0 x(\tau) \\
y_1(t) &= \frac{(k_{-3} + k_4 - k_1 s_0 x(\tau)) y_2(\tau) + k_1 s_0 x(\tau)}{(k_1 + k_3) s_0 x(\tau) + k_{-1} + k_2}
\end{aligned}$$

Now, substituting  $y_2(\tau)$ :

$$\begin{aligned}
y_1(t) &= \frac{(k_{-3} + k_4 - k_1 s_0 x(\tau)) \frac{k_3 y_1(\tau) s_0 x(\tau)}{k_{-3} + k_4} + k_1 s_0 x(\tau)}{(k_1 + k_3) s_0 x(\tau) + k_{-1} + k_2} \\
y_1(t) &= \frac{\cancel{(k_{-3} + k_4)} \frac{k_3 y_1(\tau) s_0 x(\tau)}{\cancel{k_{-3} + k_4}} - k_1 s_0 x(\tau) \frac{k_3 y_1(\tau) s_0 x(\tau)}{k_{-3} + k_4} + k_1 s_0 x(\tau)}{(k_1 + k_3) s_0 x(\tau) + k_{-1} + k_2} \\
y_1(t) &= \frac{k_3 y_1(\tau) s_0 x(\tau) - \frac{k_1 k_3 y_1(\tau) s_0^2 x^2(\tau)}{k_{-3} + k_4} + k_1 s_0 x(\tau)}{(k_1 + k_3) s_0 x(\tau) + k_{-1} + k_2} \\
[k_1 s_0 x(\tau) + k_3 s_0 x(\tau) + k_{-1} + k_2] y_1(t) &= k_3 s_0 x(\tau) y_1(\tau) - \frac{k_1 k_3 s_0^2 x^2(\tau) y_1(\tau)}{k_{-3} + k_4} + k_1 s_0 x(\tau) \\
[k_1 s_0 x(\tau) + \cancel{k_3 s_0 x(\tau)} + k_{-1} + k_2 - \cancel{k_3 s_0 x(\tau)} + \frac{k_1 k_3 s_0^2 x^2(\tau)}{k_{-3} + k_4}] y_1(t) &= +k_1 s_0 x(\tau) \\
\tilde{y}_1(\tau) &= \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_2 + k_{-1} + \frac{k_1 k_3 s_0^2 x^2(\tau)}{k_{-3} + k_4}}
\end{aligned}$$

So now, in  $y_2(\tau)$ :

$$\begin{aligned}
\tilde{y}_2(\tau) &= \frac{k_3 \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_2 + k_{-1} + \frac{k_1 k_3 s_0^2 x^2(\tau)}{k_{-3} + k_4}} s_0 x(\tau)}{k_{-3} + k_4} \\
&= \frac{k_3 k_1 s_0^2 x^2(\tau)}{(k_{-3} + k_4) \left( k_1 s_0 x(\tau) + k_2 + k_{-1} + \frac{k_1 k_3 s_0^2 x^2(\tau)}{k_{-3} + k_4} \right)} \\
&= \frac{k_3 k_1 s_0^2 x^2(\tau)}{(k_{-3} + k_4) (k_1 s_0 x(\tau) + k_2 + k_{-1}) + k_1 k_3 s_0^2 x^2(\tau)}
\end{aligned}$$

To solve Tikhonov those values would be fed into  $\frac{dx(\tau)}{d\tau}$  to obtain an equation from which to derive  $\bar{x}(t)$  and use it to derive  $\bar{y}_1(t)$  and  $\bar{y}_2(t)$ .

### 7.6.3 Rate of production of the product

Since the interest is in the rate of production of the product, consider:

$$\frac{dp(t)}{dt} = k_2 c_1(t) + k_4 c_2(t)$$

Applying the normalizations:

$$\frac{dp(t)}{dt} = k_2 e_0 y_1(t) + k_4 e_0 y_2(t)$$

And transitioning to the slow time-scale:

$$\begin{aligned}
\frac{dp(\tau)}{d\tau} &= \frac{dp(t)}{dt} \frac{1}{\epsilon} \\
&= k_2 y_1(\tau) \frac{e_0}{\epsilon} + k_4 \frac{e_0}{\epsilon} y_2(\tau) \\
&= k_2 y_1(\tau) s_0 + k_4 y_2(\tau) s_0
\end{aligned}$$

Plugging the values for  $\tilde{y}_1(\tau)$  and  $\tilde{y}_2(\tau)$ :

$$\begin{aligned}
\frac{dp(\tau)}{d\tau} &= k_2 s_0 \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2 + \frac{k_1 k_3 s_0^2 x^2(\tau)}{k_{-3} + k_4}} + k_4 s_0 \frac{k_1 k_3 s_0^2 x^2(\tau)}{(k_{-3} + k_4) (k_1 s_0 x(\tau) + k_2 + k_{-1}) + k_1 k_3 s_0^2 x^2(\tau)} \\
&= k_2 s_0 \frac{k_1 s(\tau)}{k_1 s(\tau) + k_{-1} + k_2 + \frac{k_1 k_3 s^2(\tau)}{k_{-3} + k_4}} + k_4 s_0 \frac{k_1 k_3 s^2(\tau)}{(k_{-3} + k_4) (k_1 s(\tau) + k_2 + k_{-1}) + k_1 k_3 s^2(\tau)} \\
&= \frac{k_1 k_2 s_0 s(\tau) (k_{-3} + k_4)}{(k_{-3} + k_4) (k_1 s(\tau) + k_{-1} + k_2) + k_1 k_3 s^2(\tau)} + \frac{k_1 k_3 k_4 s_0 s^2(\tau)}{(k_{-3} + k_4) (k_1 s(\tau) + k_2 + k_{-1}) + k_1 k_3 s^2(\tau)} \\
&= \frac{k_1 k_2 s_0 s(\tau) (k_{-3} + k_4) + k_1 k_3 k_4 s_0 s^2(\tau)}{(k_{-3} + k_4) (k_1 s(\tau) + k_{-1} + k_2) + k_1 k_3 s^2(\tau)}
\end{aligned}$$

Going back to the fast time-scale:

$$\begin{aligned}
\epsilon \frac{dp(\tau)}{d\tau} &= \frac{dp(t)}{dt} = \epsilon \frac{k_1 k_2 s_0 s(t)(k_{-3} + k_4) + k_1 k_3 k_4 s_0 s^2(t)}{(k_{-3} + k_4)(k_1 s(t) + k_{-1} + k_2) + k_1 k_3 s^2(t)} \\
&= \frac{e_0}{s_0} \frac{k_1 k_2 s_0 s(t)(k_{-3} + k_4) + k_1 k_3 k_4 s_0 s^2(t)}{(k_{-3} + k_4)(k_1 s(t) + k_{-1} + k_2) + k_1 k_3 s^2(t)} \\
&= \frac{k_1 k_2 e_0 s(t)(k_{-3} + k_4) + k_1 k_3 k_4 e_0 s^2(t)}{(k_{-3} + k_4)(k_1 s(t) + k_{-1} + k_2) + k_1 k_3 s^2(t)}
\end{aligned}$$

So depending on the value of the constants this last expression can correspond to different shapes of the function. If the binding sites are independent,  $k_1 = 2k_3 \wedge k_{-3} = 2k_{-1} \wedge k_4 = 2k_2$ :

$$\begin{aligned}
\frac{dp(t)}{dt} &= \frac{k_1 k_2 e_0 s(t)(k_{-3} + k_4) + k_1 k_3 k_4 e_0 s^2(t)}{(k_{-3} + k_4)(k_1 s(t) + k_{-1} + k_2) + k_1 k_3 s^2(t)} \\
&= \frac{4k_3 k_2 e_0 s(t)(k_{-1} + k_2) + 4k^2 k_3 k_2 e_0 s^2(t)}{(2k_{-1} + 2k_2)(2k_3 s(t) + k_{-1} + k_2) + 2k_3 k_3 s^2(t)} \\
&= \frac{2k_3 k_2 e_0 s(t)(2k_{-1} + 2k_2) + 2k_3 k_3 2k_2 e_0 s^2(t)}{2(k_{-1} + k_2)(2k_3 s(t) + k_{-1} + k_2) + 2k_3 k_3 s^2(t)} \\
&= \frac{4k_3 k_2 e_0 s(t)(k_{-1} + k_2 + k_3 s(t))}{2[2k_{-1} k_3 s(t) + k_{-1}^2 + k_{-1} k_2 + 2k_2 k_3 s(t) + k_{-1} k_2 + 2k_2^2 + k_3^2 s^2(t)]} \\
&= \frac{2k_3 k_2 e_0 s(t)(k_{-1} + k_2 + k_3 s(t))}{2[2k_{-1} k_3 s(t) + k_{-1}^2 + 2k_{-1} k_2 + 2k_2 k_3 s(t) + 2k_2^2 + k_3^2 s^2(t)]} \\
&= \frac{2k_3 k_2 e_0 s(t)(\cancel{k_{-1} + k_2 + k_3 s(t)})}{2(k_{-1} + k_2 + k_3 s(t))^2} \\
&= \frac{2k_3 k_2 e_0 s(t)}{2(k_{-1} + k_2 + k_3 s(t))} \\
&= \frac{2k_2 e_0 s(t)}{\frac{k_{-1} + k_2}{k_3} + s(t)} \\
k_1 &= 2k_3 \\
&= \frac{2k_2 e_0 s(t)}{\frac{2(k_{-1} + k_2)}{k_1} + s(t)}
\end{aligned}$$

If the sites are totally dependent  $k_1 \ll 1$  and  $k_3 \gg 1$ . The terms with only  $k_1$  can be sent to  $\infty$ :

---


$$\begin{aligned}
\frac{dp(t)}{dt} &= \frac{k_1 k_2 e_0 s(t) \cancel{(k_{-3} + k_4)} + k_1 k_3 k_4 e_0 s^2(t)}{(k_{-3} + k_4) \cancel{(k_1 s(t))} + k_{-1} + k_2 + k_1 k_3 s^2(t)} \\
&= \frac{k_1 k_3 k_4 e_0 s^2(t)}{(k_{-3} + k_4)(k_{-1} + k_2) + k_1 k_3 s^2(t)} \\
&= \frac{k_4 e_0 s^2(t)}{\frac{(k_{-3} + k_4)(k_{-1} + k_2)}{k_1 k_3} + \cancel{\frac{k_1 k_3}{k_1 k_3}} s^2(t)} \\
&= \frac{k_4 e_0 s^2(t)}{\frac{(k_{-3} + k_4)(k_{-1} + k_2)}{k_1 k_3} + s^2(t)}
\end{aligned}$$

Introducing now:

$$K = \frac{(k_{-3} + k_4)(k_{-1} + k_2)}{k_1 k_3}$$

Then the equation becomes:

$$\frac{dp(t)}{dt} = \frac{k_4 e_0 s^2(t)}{K + s^2(t)}$$

Or the Hill equation, which is an example of sigmoidal rate equations: the binding of an additional substrate becomes more efficient if there is already a substrate interacting with the enzyme. This converges to  $k_4 e_0$ .

## 8 Molecular networks

Molecular networks consist of a large number of molecular species with complex patterns of interactions. Now reaction loops will be considered, networks with two molecular species, each acting on the rates of synthesis and decay of the other. There are three possible cases:

- Each molecular species has a positive effect on the other (mutual activation),  $++$  positive loop.
- Each has a negative effect on the other (mutual inhibition),  $--$  negative loop.
- One has a positive effect, while the other has a negative (activation-inhibition),  $+-$  negative loop.

### 8.1 Signal-response mechanism

How the concentration of a substance responds to a stimulus that increase its synthesis rate.  $S$ , the concentration of some substance favouring the synthesis of  $X$  is the signal, while the equilibrium concentration of  $X$  is the response.

#### 8.1.1 Linear response

The concentration of  $S$  promotes linearly the production of  $X$ .  $X$  has a basal production rate  $k_0$ , the ODE governing the system will be:

$$\frac{dX(t)}{dt} = k_0 + k_1 S(t) - k_2 X(t)$$

The response is the concentration of  $X$  at equilibrium:

$$\begin{aligned} k_0 + k_1 S(t) - k_2 X_{eq} &= 0 \\ X_{eq} &= \frac{k_0 + k_1 S(t)}{k_2} \end{aligned}$$

### 8.1.2 Hyperbolic response

The molecule  $X$  can be present in an active state  $X_a$  and inactive  $X_i$ .  $S$  promotes the transition towards the active state.  $S$  and  $X_i$  participate to the production of  $X_a$ :

$$\frac{dX_a(t)}{dt} = k_1 S(t) X_i(t) - k_2 X_a(t)$$

Introducing  $X_T = X_a + X_i$ :

$$\frac{dX_a(t)}{dt} = k_1 S(t) (X_T - X_a(t)) - k_2 X_a(t)$$

Computing now the equilibrium:

$$\begin{aligned} k_1 S(t) (X_T - X_a(t)) - k_2 X_a(t) &= 0 \\ k_1 S(t) X_T - k_1 S(t) X_a(t) - k_2 X_a(t) &= 0 \\ (k_1 S(t) - k_2) X_a(t) &= k_1 S(t) X_T \\ X_a(t) &= \frac{k_1 S(t) X_T}{k_1 S(t) - k_2} \end{aligned}$$

## 8.2 Adapted response

There are several physiological systems that give a constant response, independent of the strength of the signal. The ODEs are:

$$\begin{cases} \frac{dX(t)}{dt} = k_{01} + k_1 S(t) - k_2 X(t) Y(t) \\ \frac{dY(t)}{dt} = k_{02} + k_3 S(t) - k_4 Y(t) \end{cases}$$

Assuming that in the absence of  $S$  there is no production:

$$\begin{cases} \frac{dX(t)}{dt} = k_1 S(t) - k_2 X(t) Y(t) \\ \frac{dY(t)}{dt} = k_3 S(t) - k_4 Y(t) \end{cases}$$

The response is the concentration at equilibrium:



$$\begin{aligned}
&\begin{cases} k_1 S(t) - k_2 X(t)Y(t) &= 0 \\ k_3 S(t) - k_4 Y(t) &= 0 \end{cases} \\
&\begin{cases} k_2 X(t)Y(t) &= k_1 S(t) \\ Y(t) &= \frac{k_3}{k_4} S(t) \end{cases} \\
&\begin{cases} k_2 X(t) \frac{k_3}{k_4} S(t) &= k_1 S(t) \\ Y(t) &= \frac{k_3}{k_4} S(t) \end{cases} \\
&\begin{cases} X(t) &= \frac{k_1 k_4}{k_2 k_3} \\ Y(t) &= \frac{k_3}{k_4} S(t) \end{cases}
\end{aligned}$$

So the concentration of  $X$  is independent of  $S$ : its response is independent of the signal if it is not null. In that case the system is:

$$\begin{cases} \frac{dX(t)}{dt} &= -k_2 X(t)Y(t) \\ \frac{dY(t)}{dt} &= -k_4 Y(t) \end{cases}$$

And at equilibrium:

$$\begin{cases} -k_2 X(t)Y(t) &= 0 \\ -k_4 Y(t) &= 0 \end{cases} // \begin{cases} X(t) &= 0 \\ Y(t) &= 0 \end{cases} //$$