Mathematical modelling in biology

Some models

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Contents

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 varation 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 γ. The problem then becomes:

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

This can be solved thorugh 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:

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

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:

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

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 thourgh the separation of variable methods:

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

k in this context is the volume in the bathtub at time 0, wich could be computed if the volme 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:

$$V(0) = kre^{-\gamma 0}$$
$$V(0) = k$$

2 Malthus equation

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

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

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

$$\frac{dN(t)}{dt} = \beta N(t) - \mu N(t)$$
$$\frac{dN(t)}{dt} = (\beta - \mu)N(t)$$
$$\frac{dN(t)}{dt} = rN(t)$$

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

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

Where k is the population size at time 0. If $r < 0$ the population will go extint, 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:

$$rN(t) = 0$$
$$N(t) = 0$$

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 decreses and mortailtiy inreases inearly 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:

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

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 mathamtical 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-homoeneous differential euqation that can be solved with the variation of constants method. Solving first the associated homogeneous problem thorugh sepration of variables:

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

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:

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

$$C(t) = \frac{1}{K}e^{rt} + c$$

Subsitituting 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 $N(0) = N_0$:

$$
\begin{aligned}
\frac{1}{\frac{1}{K} + ce^{-r0}} &= N_0 \\
\frac{1}{\frac{N_0}{K} + cN_0} &= 0 \\
\frac{N_0}{K} + cN_0 &= 1 \\
cN_0 &= 1 - \frac{N_0}{K} \\
c &= \frac{1}{N_0} - \frac{1}{K}
\end{aligned}
$$

So that, substituting:

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

3.2 Equilibria and stability

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

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

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 assomng that the carrying capacity K is a periodic, always positive function of t. For example:

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

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:

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

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

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 analyitical 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:

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

The first equlibria 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:

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

5.1 Equilibrium points

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

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

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:

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

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

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

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

$$\begin{cases} H(t) & = 1 - P(t) \\ P(t) & = 0 \qquad \wedge \qquad P(t) = \frac{5}{6} \end{cases}$$

So there are two equilibrium points: $E_2 = (1, 0)$ and $E_3 = \left(\frac{1}{6}, \frac{5}{6}\right)$. 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:

$$2H(t)\left[1 - H(t)\right] - 2H(t)P(t) = 0$$
$$H(t) = 0 \qquad \wedge \qquad H(t) = 1 - P(t)$$

And:

$$-\frac{1}{2}P(t) + 3H(t)P(t) = 0$$
$$P(t)\left[-\frac{1}{2} + 3H(t)\right] = 0$$
$$P(t) = 0 \qquad \wedge \qquad H(t) = \frac{1}{6}$$

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 enouch, 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 comptaible 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. Morever vectors to the left of $H(t) = \frac{1}{6}$ wil 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, whie it is hard to make predictions about E_3.

5.2 Stability

To compute the stability of the equilibria first the Jaciobian 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 critera are used. It can be computed that $det(A) > 0$ and $tr(A) < 0$, 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 infectd 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 linnked via different rates:

- The birth rate μ feeds people into S, with dynamics that depends on the total number of people $N = S + I + R$.
- Natural deaths can occur in all gropups with rate equal to the one of births μ and with dynamics that depends on the number

of people in the compartment.

- Infections $S \to I$ happen with a contact rate β and are modelled with mass action dynamics.

- Infected people recover with a recovery rate γ, with dynamics that depend n the total number of infecte people.

Each SIR variable has the number of people as dimension, while rates $\frac{1}{t}$: the derivatives will have dimenison $\frac{people}{t}$. 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 comparment instead of the total number introducing:

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

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

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

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:

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

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

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

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

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

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

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

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

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

So the first equilibrium, or desease free equilibrium DFE is:

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

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

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

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

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

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

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

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

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

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:

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

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:

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

While DFE^* is always feasible, EE^* is feasible only if $R_0 > 1$: if not Y will eighter 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:

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

λ_1 is always negative, while to discuss λ_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-Hurzwitz criterion for square matrices. First consider the trace of the matrix:

$$Tr(J) = -\beta \frac{\mu(1-p)+\sigma-\frac{\mu+\gamma}{\beta}(\mu+\sigma)}{\mu+\gamma+\sigma} - \mu - \sigma + 0 \overbrace{<}^{?} 0$$

$$-\beta\mu + \beta\mu p + \beta\sigma + \cancel{\beta}\frac{\mu+\gamma}{\cancel{\beta}}\mu + \cancel{\beta}\frac{\mu+\gamma}{\cancel{\beta}}\sigma - \mu^2 - \sigma\mu - \gamma\mu - \sigma\mu - \gamma\sigma - \sigma^2 \overbrace{<}^{?} 0$$

$$-\beta\mu + \beta\mu p + \beta\sigma + (\mu+\gamma)\mu + (\mu+\gamma)\sigma - \mu^2 - \sigma\mu - \gamma\mu - \sigma\mu - \gamma\sigma - \sigma^2 \overbrace{<}^{?} 0$$

$$-\beta\mu + \beta\mu p + \beta\sigma + \cancel{\mu^2} + \cancel{\gamma\mu} + \cancel{\mu\sigma} + \cancel{\gamma\sigma} - \cancel{\mu^2} - \cancel{\sigma\mu} - \cancel{\gamma\mu} - \sigma\mu - \cancel{\gamma\sigma} - \sigma^2 \overbrace{<}^{?} 0$$

$$\underbrace{\overbrace{-\beta\mu + \beta\mu p}^{<0}}_{p<1} + \beta\sigma - \sigma\mu - \sigma^2 \overbrace{<}^{?} 0$$

$$Tr(J) < 0$$

So $Tr(J) < 0$. Now consider the determinant. For a 2×2 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:

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

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 equaiton can be excluded as:

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

Then the system becomes:

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

Addutionally 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:

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

7.1 Reactant abundance

Assume a negligibly small cocnentration 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:

$$\begin{cases} s_0\frac{dx(t)}{dt} = k_{-1}y(t)e_0 - k_1 x(t)s_0(e_0 - y(t)e_0) \\ e_0\frac{dy(t)}{dt} = k_1 s_0 x(t)(e_0 - e_0 y(t)) - e_0 y(t)(k_{-1} + k_2) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} = k_{-1}y(t)\frac{e_0}{s_0} - k_1 x(t)s_0\frac{e_0}{s_0}(1 - y(t)) \\ \frac{dy(t)}{dt} = k_1 s_0 x(t)(1 - y(t)) - y(t)(k_{-1} + k_2) \end{cases}$$

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

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

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

$$\begin{cases} \frac{dx(t)}{dt} = 0 \\ \frac{dy(t)}{dt} = k_1 s_0 x(t)(1 - y(t)) - y(t)(k_{-1} + k_2) \end{cases}$$

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:

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

7.1.1 Equilibrium points

Analyzing the equilibrium points of the system:

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

7.2 Slower time-scale

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

$$\tau = \epsilon t$$

So that when ϵ is very small, also τ is very small and the timescale is slowed done. 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 ϵ:

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

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

Switching back to the fast timescale for the second equation:

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

But, since $\epsilon \approx 0$:

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

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 subsituted 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 ϵ to go to the fast timescale:

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

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:

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

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 Ssuch that the rate of production of the product is hal 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:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E + P$$

The system is:

$$\begin{cases} \frac{ds(t)}{dt} &= -k_1 s(t)e(t) + k_{-1}c(t) \\ \frac{de(t)}{dt} &= -k_1 s(t)e(t) + k_{-1}c(t) + k_2 c(t) - k_{-2}p(t)e(t) \\ \frac{dc(t)}{dt} &= k_1 s(t)e(t) - k_{-1}c(t) - k_2 c(t) + k_{-2}p(t)e(t) \\ \frac{dp(t)}{dt} &= k_2 c(t) - k_{-2}p(t)e(t) \end{cases}$$

It can be seen that:

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

$$\frac{d}{dt}[s(t) + c(t) + p(t)] = 0 \Rightarrow s(t) + c(t) + p(t) = k = s_0$$

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:

$$\begin{cases} \frac{ds(t)}{dt} &= -k_1 s(t)(e_0 - c(t)) + k_{-1}c(t) \\ \frac{dc(t)}{dt} &= k_1 s(t)(e_0 - c(t)) - k_{-1}c(t) - k_2 c(t) + k_{-2}(s_0 - s(t) - c(t))(e_0 - c(t)) \end{cases}$$

7.4.1 Normalization

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

$$\begin{cases} s_0 \frac{dx(t)}{dt} &= -k_1 s_0 x(t)(e_0 - e_0 y(t)) + k_{-1}e_0 y(t) \\ e_0 \frac{dy(t)}{dt} &= k_1 s_0 x(t)(e_0 - e_0 y(t)) - k_{-1}e_0 y(t) - k_2 e_0 y(t) + k_{-2}(s_0 - s_0 x(t) - e_0 y(t))(e_0 - e_0 y(t)) \end{cases}$$

$$\begin{cases} \frac{dx(t)}{dt} &= -k_1 s_0 \frac{e_0}{s_0} x(t)(1 - y(t)) + k_{-1}\frac{e_0}{s_0} y(t) \\ \frac{dy(t)}{dt} &= k_1 s_0 x(t)(1 - y(t)) - k_{-1}y(t) - k_2 y(t) + k_{-2}s_0(1 - x(t) - \frac{e_0}{s_0} y(t))(1 - y(t)) \end{cases}$$

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

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

$$\epsilon \approx 0$$

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

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

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:

$$\tau = \epsilon t$$

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

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

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

Now applying the quasi-equilibrium conditiona nd reverting to the fast timecale for the second:

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

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

$$\epsilon \approx 0$$

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

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

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

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:

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

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 $\epsilon \to 0$ 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:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$
$$I + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} EI$$

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:

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

So $\frac{de(t)}{dt}$ can be elimintaed 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:

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

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:

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

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

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

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

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

7.5.2 Quasi-equilibrium

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

$$\frac{d}{d\tau} x(\tau) = \frac{dx(t)}{dt} \frac{1}{\epsilon} \quad \frac{d}{d\tau} y_1(\tau) = \frac{dy_1(t)}{dt} \frac{1}{\epsilon} \quad \frac{d}{d\tau} y_2(\tau) = \frac{dy_2(t)}{dt} \frac{1}{\epsilon}$$

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

Reverting back to the fast timescale the last two equations:

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

$$\epsilon \approx 0$$

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

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:

$$
\begin{aligned}
k_3 i \left(1 - \frac{k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_2(\tau)}{k_1 s_0 x(\tau) + k_{-1} + k_2} - y_2(\tau)\right) - k_{-3} y_2(\tau) &= 0 \\
k_3 i - k_3 i \frac{k_1 s_0 x(\tau) - k_1 s_0 x(\tau) y_2(\tau)}{k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2} - y_2(\tau) - k_{-3} y_2(\tau) &= 0 \\
k_3 i - k_3 i \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2} + \frac{k_1 s_0 x(\tau) y_2(\tau)}{k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2} - y_2(\tau) - k_{-3} y_2(\tau) &= 0 \\
\left[\frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2} - 1 - k_{-3}\right] y_2(\tau) &= k_3 i - k_3 i \frac{k_1 s_0 x(\tau)}{k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2} \\
y_2(\tau) = \frac{k_3 i (k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2 - k_1 s_0 x(\tau))}{k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2} & \frac{k_1 s_0 x(\tau) + k_3 i k_{-1} + k_2}{k_1 s_0 x(\tau) - k_1 s_0 x(\tau) - l_3 i k_1 - k_2 - k_{-3} k_1 s_0 x(\tau) - k_{-3} k_3 i k_{-1} - k_{-3} k_2}
\end{aligned}
$$