Kinetic Models

By: Team iGEM amsterdam 2015: [Photo]synthetic romance

The models for substrate dependencies are based on the Monod equation. We created models for a consortium with a single dependency of *E. coli* on a substrate *Synechocystis* produces, for a consortium with a substrate interdependency, in which *Synechocystis* is also dependent on a substrate *E. coli* produces, and for a consortium in which *Synechocystis* is growing light limited. For each of these consortia we created a model for a turbidostat environment and for batch cultures. In this handout we will show you the model we created for a substrate interdependent consortium in a turbidostat environment and we will show you the results.

1 Turbidostat model for a substrate interdependent consortium

If we want to model the consortium in a turbidostat, we have to account for the fact that both *Synechocystis* and E. coli are increasing the OD as they grow. This means that the dilution rate is dependent on the biomass of *Synechocystis* as well as that of E. coli. For simplicity we make the assumption that there is a constant flow through the system, instead of only diluting when the threshold is reached. To understand this we first look at the case of a single strain, called b. In a chemostat the growth rate of the organism would become equal to the dilution rate. In a turbidostat however, an organism can grow at its maximal growth rate, but the amount of biomass must still become constant. This means the following:

$$\frac{db}{dt} = \mu \cdot b - D \cdot b = 0 \tag{1}$$

Where b is the amount of biomass of the strain b, mu is the growth rate and D the dilution rate.
In a chemostat it would mean that $D < \mu_{max}$ is a chosen dilution rate and that μ becomes equal to D due to substrate limitation. In a turbidostat however, D becomes equal to μ_{max}, because the species in not growing limited.
In the case where there are two strains, strain a and b, that share a turbidostat, the differential equations that then describe the system looks like the following:

$$\frac{da}{dt} = f(a, b, t) - Da \tag{2}$$

$$\frac{db}{dt} = g(a, b, t) - Db \tag{3}$$

Herein are f and g functions that describe the growth of the organisms a and b respectively. D is again the dilution rate. Now in a shared turbidostat it holds that $a + b = k$, where k is a constant amount of biomass. This implies:

$$D = \frac{g + f}{a + b} \tag{4}$$

For the turbidostat we then arrive at the following set of differential equations:

$$\frac{d\mathrm{syn}}{dt} = \mu_{syn} \cdot \mathrm{syn} - D \cdot \mathrm{syn} \tag{5}$$

$$\frac{d\mathrm{ec}}{dt} = \mu_{ec} \cdot \mathrm{ec} - D \cdot \mathrm{ec} \tag{6}$$

$$\frac{d[S_1]}{dt} = \frac{1}{y_{syn/S1}} \cdot \mu_{syn} \cdot \mathrm{syn} - \frac{1}{y_{ec/S1}} \cdot \mu_{ec} \cdot \mathrm{ec} - D \cdot [S_1] \tag{7}$$

$$\frac{d[S_2]}{dt} = Qp_{S2/ec} \cdot \mathrm{ec} - \frac{1}{y_{syn/S2}} \cdot \mu_{syn} \cdot \mathrm{syn} - D \cdot [S_2] \tag{8}$$

where

$$D = \frac{\mu_{syn} + \mu_{ec}}{\mathrm{syn} + \mathrm{ec}} \tag{9}$$

$$\mu_{syn} = \mu_{max,syn} \frac{[S_2]}{k_{s2,syn} + [S_2]} \tag{10}$$

$$\mu_{ec} = \mu_{max,ec} \frac{S_1}{k_{s1,ec} + [S_1]} \tag{11}$$

Herein is syn the amount of biomass of *Synechocystis* and ec the amount of biomass of *E. coli*. The μs are growth rates. μ_{max} is the maximal growth rate (equal to the growth rate at unlimited growth), and $[S]$ the concentration of substrate. k_S is the concentration of $[S]$ at a rate $\frac{1}{2}\mu_{max}$. In this case there are two μ and two μ_{max} values, one for *Synechocystis* and one for *E. coli*. There are also two substrates. $[S_1]$ can be seen as acetate. It is being produced by *Synechocystis* and consumed by *E. coli*. Its production is growth coupled. S_2 could be arginine, It is produced by *E. coli*, not in a growth coupled way, and consumed by *Synechocystis*. $y_{syn/S1}$ is the substrate yield of *Synechocystis*. Since in this model the substrate is only formed when *Synechocystis* forms biomass, per amount of biomass formed, there is a constant amount of substrate formed. The yield is usually expressed in gram dry weight mole substrate *used*. In this case we mean gram dry weight mole substrate *formed*. So to find the amount of substrate that is formed per amount of biomass that is formed we simply take $\frac{1}{y_{syn/S1}}$. $y_{ec/S1}$ and $y_{syn/S2}$ are biomass yields.

1.1 Parameters

To simulate the interdependency on substrates, we needed a lot more parameters. For some of the parameters we had no good measurements, so we estimated them. The general behavior stays generally the same under variations in parameters, although exact outcomes may differ.

$\mu_{max,syn}$ (h^{-1})	0.075
$\mu_{max,ec}$ (h^{-1})	0.08
$k_{s1,ec}$ (mM)	0.02
$k_{s2,syn}$ (mM)	0.02
$y_{\frac{s1}{syn}}$ ($\mathrm{mmol} \cdot \mathrm{gDW}^{-1}$)	0.40
$y_{\frac{ec}{s}}$ ($\mathrm{gDW} \cdot \mathrm{mmol}^{-1}$)	0.031
$y_{\frac{s2}{syn}}$ ($\mathrm{mmol} \cdot \mathrm{gDW}^{-1}$)	0.1
$Q_{p,ec}mmol$ ($\mathrm{mmol} \cdot \mathrm{gDW}^{-1} \cdot \mathrm{h}^{-1}$)	0.13

Table 1: Measured and estimated parameters for the substrate interdependent model.

2 Results

Here we will show you some results of the simulations of a consortium with a substrate dependent photoautotroph in a turbidostat. The model we used is described in equations 5 to 11 in section 1. The parameters used are given in table 1 In a turbidostat it is expected that the total amount of biomass, so that if *E. coli* and *Synechocystis* combined would stay constant. To test this, we have plotted the total amount of biomass under different initial conditions. The result is show in figure 2, and we can see that this is indeed constant.
This however, does not mean that the amount of biomass of each species stays the same. In figure 1 several examples of the amount of biomass in time of *Synechocystis* and *E. coli* are given.

Now we can once again look at the biomass ratio to see if this converges. In figure 5 the biomass ratio in time is given under different initial conditions.

We can see that indeed the biomass ratio converges. Also if we look at the values for μ in figure 6 in time, we can see that the growth rates converge. In a turbidostat the dilution rate will become equal to the final growth rate to which the growth rates converge. We can also conclude that this system stabilizes in time and that it is robust with respect to the initial conditions.

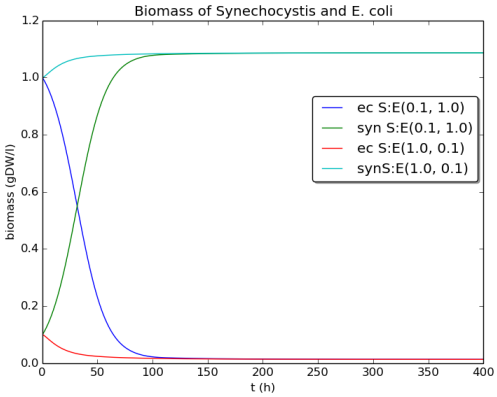

Figure 1: Biomass of *Synechocystis* and *E. coli* in time in a turbidostat. Even thought the total amount stays the same, the amount of each species varies in time.

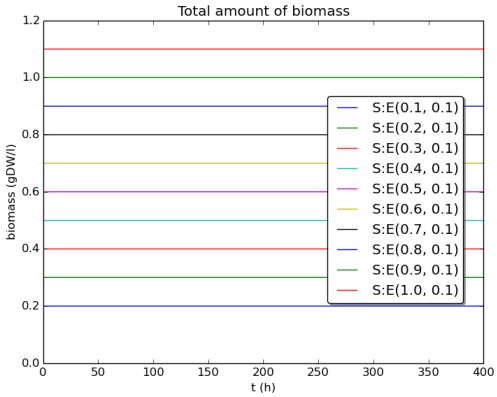

Figure 2: The added biomass of *Synechocystis* and *E. coli* in a turbidostat. Like expected this amount stays constant.

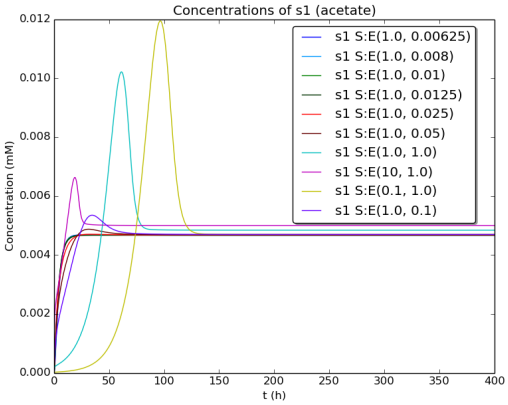

Figure 3: Concentration of acetate, or S_1 in the model in time under different initial conditions. After an initial spike it stabelizes.

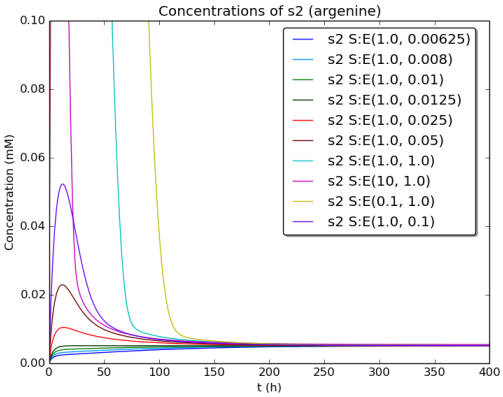

Figure 4: Concentration of argenine, or S_2 in the model in time under different initial conditions. After an initial spike it stabelizes

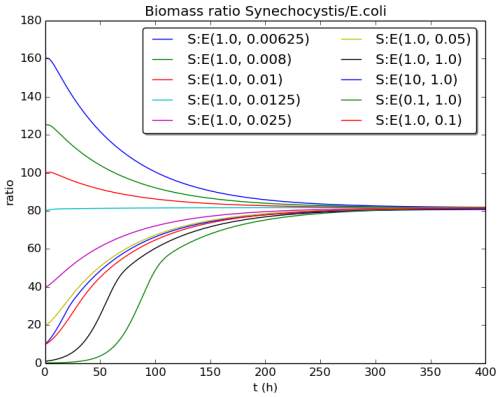

Figure 5: Ratio of the biomass of *Synechocystis* and *E. coli* under several different initial conditions (shown in legend in $gDW \cdot l^{-1}$) in a turbidostat. The biomass ratio of *Synechocystis* and *E. coli* converge to the same value for each initial condition. The model is given by equations 5 to 11. Parameters are given by table 1.

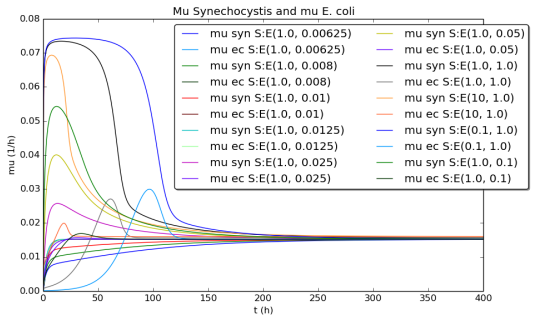

Figure 6: μ_{ec} and μ_{syn} in time in a turbidostat. μ_{ec} and μ_{syn} both converge to the same value, this value is equal to the dilution rate D. The model is given by equations 5 to 11. Parameters are given by table 1.