

# Killer Yeast Vs. Sensitive Yeast

Evan Cummings      Intizor Aliyorov  
Malachi J. Cryder

MATH 445 - Statistical, Dynamical, and Computational Modeling

December 11, 2013

The differential equation we may use for modeling the growth of yeast is the same as that used for bacterial growth in a chemostat:

$$\begin{aligned}\frac{dN}{dt} &= k(C)N - \frac{FN}{V}, \\ \frac{dC}{dt} &= -\alpha k(C)N - \frac{FC}{V} + \frac{FC_0}{V},\end{aligned}$$

with initial conditions  $C(0) = C_i$  and  $N(0) = N_i$ ,  $N$  is the unitless optical density of yeast in the chamber,  $C$  is the unitless optical density of nutrient in the chamber,  $C_0$  is the unitless optical density of nutrient in the reservoir,  $F$  is the in/out volume flow rate with units volume/time,  $V$  is the volume of the chamber,  $\alpha$  is a unitless inverse of the yield constant, and  $k(C)$  is the reproduction rate for yeast in units 1/time with possible formula chosen such that  $\lim_{C \rightarrow \infty} k(C) = k_{max}$ , and  $k_{max}$  represents the maximum possible reproduction rate:

$$k(C) = \frac{k_{max}C}{C_n + C}.$$

where  $C_n$  is chosen such that  $k(C_n) = k_{max}/2$ . Because the concentration in the tank  $C(t)$  is related to the concentration in the reservoir by  $C(t) \leq C_0$ ,  $C_0$  may be chosen sufficiently small such that

$$k(C) = \frac{k_{max}C}{C_n + C} \approx \frac{k_{max}C}{C_n} = KC,$$

where  $K$  has units density/time. The equations we need to solve then become

$$\frac{dN}{dt} = KCN - \frac{FN}{V}, \tag{1}$$

$$\frac{dC}{dt} = -\alpha KCN - \frac{FC}{V} + \frac{FC_0}{V}. \tag{2}$$

The quantitative measurement for fitness is a unitless measurement of optical density at steady state ( $N$ ) at a given flow rate ( $F$ ) in volumes/hr. In order to find the steady states, we have to find the intersections of the null-clines at equilibrium points  $(\bar{N}, \bar{C})$ , i.e.  $dN(\bar{N}, \bar{C})/dt = 0$  and

$$dC(\bar{N}, \bar{C})/dt = 0:$$

$$\begin{aligned}\frac{dN(\bar{N}, \bar{C})}{dt} &= K\bar{C}\bar{N} - \frac{F\bar{N}}{V}, \\ &= \bar{N} \left( K\bar{C} - \frac{F}{V} \right) = 0,\end{aligned}$$

which is zero for  $\bar{N} = 0$  or  $K\bar{C} = F/V$ . Solving the other equation gives us the other steady-states:

$$\frac{dC(\bar{N}, \bar{C})}{dt} = -\alpha K\bar{C}\bar{N} - \frac{F\bar{C}}{V} + \frac{FC_0}{V} = 0,$$

which is zero for  $\alpha K\bar{C}\bar{N} + \frac{F\bar{C}}{V} = \frac{FC_0}{V}$ .

In order to evaluate these null-clines, we need to evaluate the non-trivial cases, here for  $\dot{N} = 0$ ,

$$\begin{aligned}K\bar{C} &= \frac{F}{V} \\ \Rightarrow \bar{C} &= \frac{F}{VK}.\end{aligned}\tag{3}$$

Likewise, for  $\dot{C} = 0$ ,

$$\begin{aligned}\alpha K\bar{C}\bar{N} + \frac{F\bar{C}}{V} &= \frac{FC_0}{V} \\ \Rightarrow \bar{N} &= \frac{FC_0}{V\alpha K\bar{C}} - \frac{F}{V\alpha K} = \frac{F}{V\alpha K} \left( \frac{C_0}{\bar{C}} - 1 \right).\end{aligned}\tag{4}$$

This intersects the  $\bar{N} = 0$  nullcline at  $\frac{F}{V\alpha K} = 0$  or  $\frac{C_0}{\bar{C}} = 1$ . However, because  $F$  is never 0, we can disregard the first equation, and we know that the only trivial steady-state is located at  $\bar{N} = 0$ ,  $\bar{C} = C_0$ .

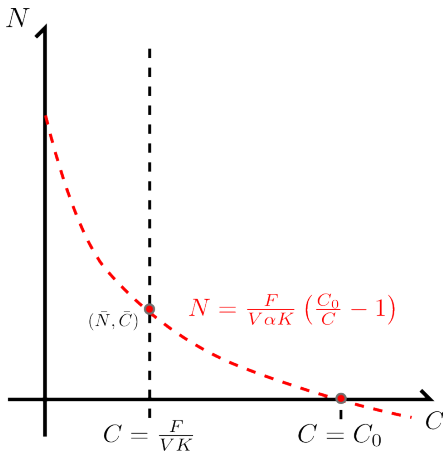


Figure 1: The  $\dot{C} = 0$  nullcline (dashed red) intersecting with the  $\dot{N} = 0$  nullcline (dashed black). The trivial and non-trivial steady-states  $(0, C_0)$  and  $(\bar{N}, \bar{C})$  are shown as red dots.

By placing Eq. (3) inside Eq. (4), we can find the non-trivial steady-state, the intersection of null-clines:

$$\begin{aligned}\bar{N}(\bar{C}) &= \frac{FC_0}{V\alpha K\bar{C}} - \frac{F}{V\alpha K} \\ &= \frac{FC_0}{V\alpha K \frac{F}{VK}} - \frac{F}{V\alpha K} \\ &= \frac{C_0}{\alpha} - \frac{F}{V\alpha K} = \frac{1}{\alpha} \left( C_0 - \frac{F}{VK} \right).\end{aligned}\tag{5}$$

The unknown parameters in Eq (5) are  $\alpha$  and  $K$ . We can find these parameters by fitting Eq (5) to the data by non-linear least squares fitting  $\bar{N}_i$  at  $F_i$  for  $i = 1, \dots, n$ , where  $n$  is the number of observations.

After we obtain estimates of these parameters for both the killer yeast  $L$  and sensitive yeast  $S$ , ( $\alpha_L$ ,  $\alpha_S$  and  $K_L$ ,  $K_S$  respectively), we can model a “what if” scenario whereby we place both species of yeast, sensitive and killer, into one chemostat. The population of sensitive yeast  $S$  will be negatively impacted by the amount of toxin the killer yeast  $K$  can produce, so we add the term  $-\beta KL$  to the differential equation describing population  $S$ . The differential equations we use to solve this three-species model is

$$\frac{dL}{dt} = K_L CL - \frac{FL}{V}, \quad (6)$$

$$\frac{dS}{dt} = K_S CS - \frac{FS}{V} - \beta SL, \quad (7)$$

$$\frac{dC}{dt} = -\alpha_L K_L CL - \alpha_S K_S CS - \frac{FC}{V} + \frac{FC_0}{V}. \quad (8)$$

The data we are provided with include two sets of two separate runs, along with the concentration of nutrient in the reservoir,  $C_0 = 0.02$ :

## 1 K1 Run

### Vessel One :

Volumes/Hr	0.028	0.099	0.142	0.207	0.269	0.287	0.352	0.403
Optical Density at Steady State	0.144	0.151	0.099	0.069	0.045	0.02	0.003	0

### Vessel Two :

Volumes/Hr	0.054	0.11	0.141	0.199	0.257	0.296	0.348	0.397	0.41
Optical Density at Steady State	0.164	0.151	0.11	0.092	0.072	0.023	0.006	0.002	0.004

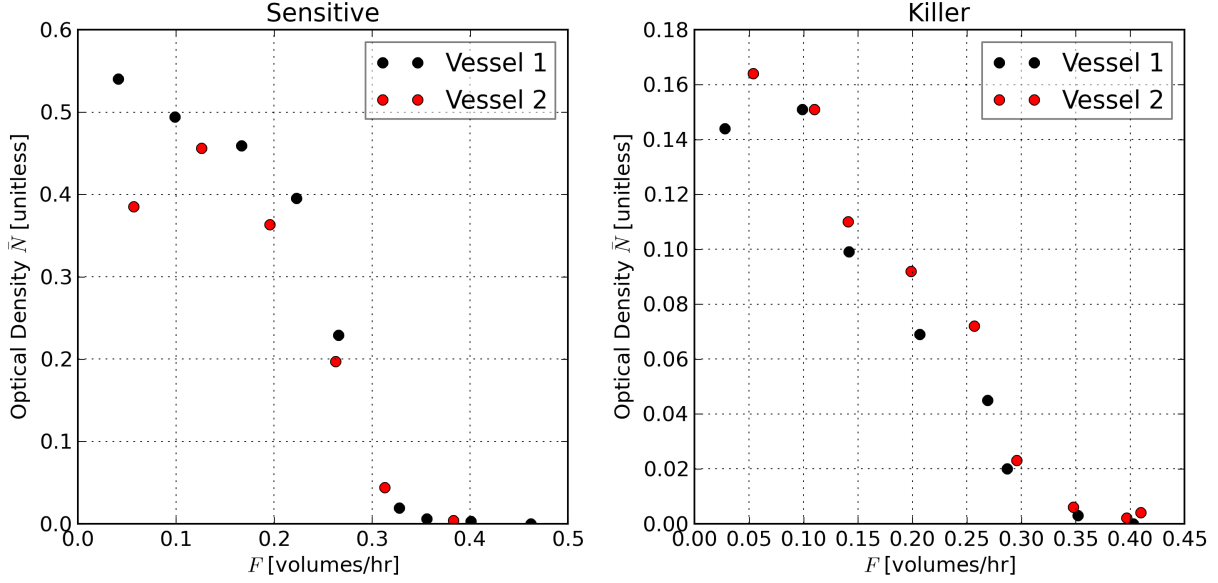
## 2 Sensitive Run

### Vessel One :

Volumes/Hr	0.041	0.099	0.167	0.223	0.266	0.328	0.356	0.401	0.462
Optical Density at Steady State	0.54	0.494	0.459	0.395	0.229	0.019	0.006	0.003	0

### Vessel Two :

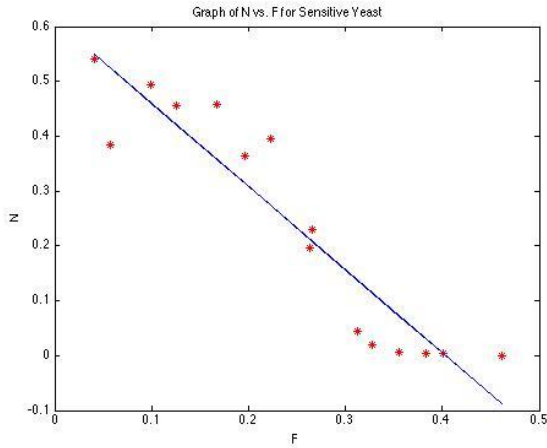
Volumes/Hr	0.0571	0.126	0.196	0.263	0.313	0.383
Optical Density at Steady State	0.385	0.456	0.363	0.197	0.044	0.004



The data provided does not include the volume of the chamber,  $V$ . In order to solve Eq. (5), this quantity is needed. Here we have dimensional analysis of the problem:

$$\begin{aligned}
 \frac{dN}{dt} &= KCN - \frac{FN}{V} \\
 &\equiv \left[ \frac{1}{\text{time}} \right] \equiv \left[ \frac{1}{\text{time}} - \frac{\text{volume}}{\text{time}} \cdot \frac{1}{\text{volume}} \right] \equiv \left[ \frac{1}{\text{time}} \right], \\
 \frac{dC}{dt} &= -\alpha KCN - \frac{FC}{V} + \frac{FC_0}{V} \\
 &\equiv \left[ \frac{1}{\text{time}} \right] \equiv \left[ -\frac{1}{\text{time}} - \frac{\text{volume}}{\text{time}} \cdot \frac{1}{\text{volume}} + \frac{\text{volume}}{\text{time}} \cdot \frac{1}{\text{volume}} \right] \equiv \left[ \frac{1}{\text{time}} \right].
 \end{aligned}$$

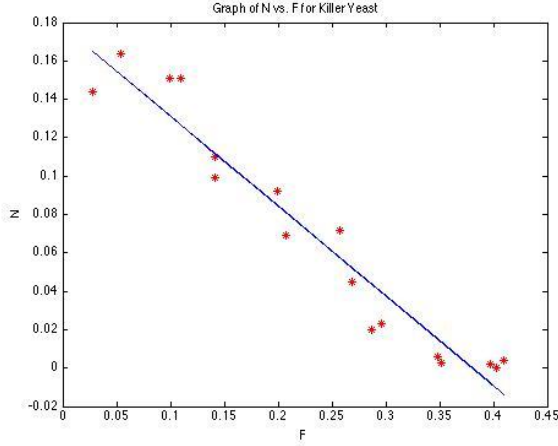
Taking  $V = 1$ , we can solve Eq. (5) using MatLab's `nlinfit` function. The results of this are shown below for both sensitive and killer yeast.



	Estimates	SE	CI
$\alpha_S$	0.0325	0.0024	(0.0255, 0.0399)
$K_S$	20.1818	1.0802	(16.9281, 23.4356)

The results on the left show that there may be a better fit to the data than Eq. (5). Notice that elimination of the last few data points corresponding to high  $F$  may be removed; this would reduce the standard error and hence provide a better estimate for  $\alpha_L$  and  $K_L$ .

Figure 2: Sensitive yeast  $S$  steady-state best-fit line using Eq. (5).



	Estimates	SE	CI
$\alpha_L$	0.1124	0.0053	(0.0969, 0.1279)
$K_L$	19.0288	0.6367	(17.1526, 20.905)

The best-fit line on the left shows that steady-state data follows a fairly linear relationship with flow, and as such we can be confident our estimates for  $\alpha_L$  and  $K_L$  are correct.

Figure 3: Killer yeast  $L$  steady-state best-fit line using Eq. (5).

Now that we have estimates for all values of  $\alpha$  and  $K$  (for both killer and sensitive yeast) we can run the dynamic model (6), (7), and (8) to equilibrium. By letting  $\beta$  range from 0 to 0.5 (in units 1/time), and  $F$  range from 0 to 0.5 (in units volume/time), we can run the model for each  $\beta$  and  $F$  to determine the regions in the  $\beta, F$  plane where sensitive yeast  $S$  overtakes the killer yeast  $L$  and vice versa.

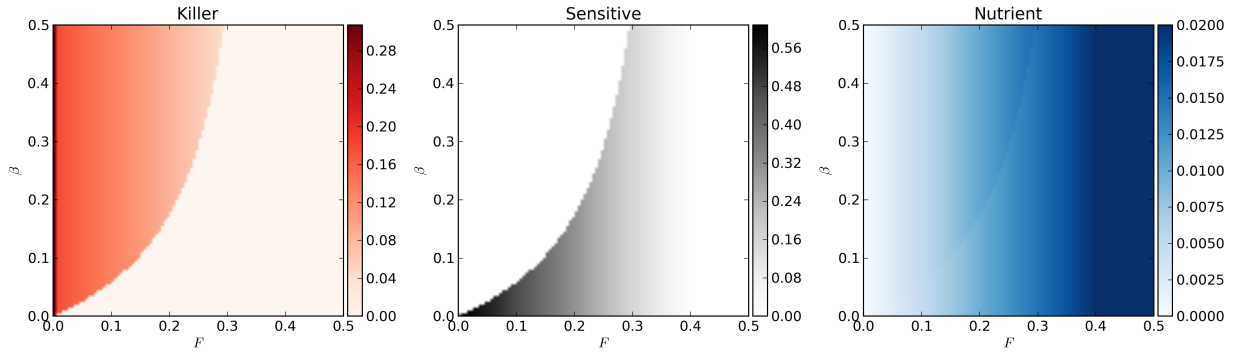


Figure 4:  $100 \times 100$  steady-state optical density solution for killer yeast (left), sensitive yeast (middle) and nutrient (right) for a total run time of 40,000 hours. Equations (6), (7), and (8) were solved with the Dormand-Prince numerical integration algorithm with an absolute tolerance of  $1e-6$ , relative tolerance of  $1e-6$ , and timestep  $\Delta t$  of 500 hours. The timestep was kept high due to the  $100 \times 100 = 10,000$  simulations required to complete the figure. Parallel processing was also implemented to speed up the simulation.

Notice in Figure 4 that as  $\beta$  increases the killer yeast dominates and sensitive yeast eventually dies off, while as  $F$  increases the sensitive yeast dominates and the killer yeast eventually dies out. The sensitive yeast are flushed from the container at around  $F = 0.4$  volumes/hr.

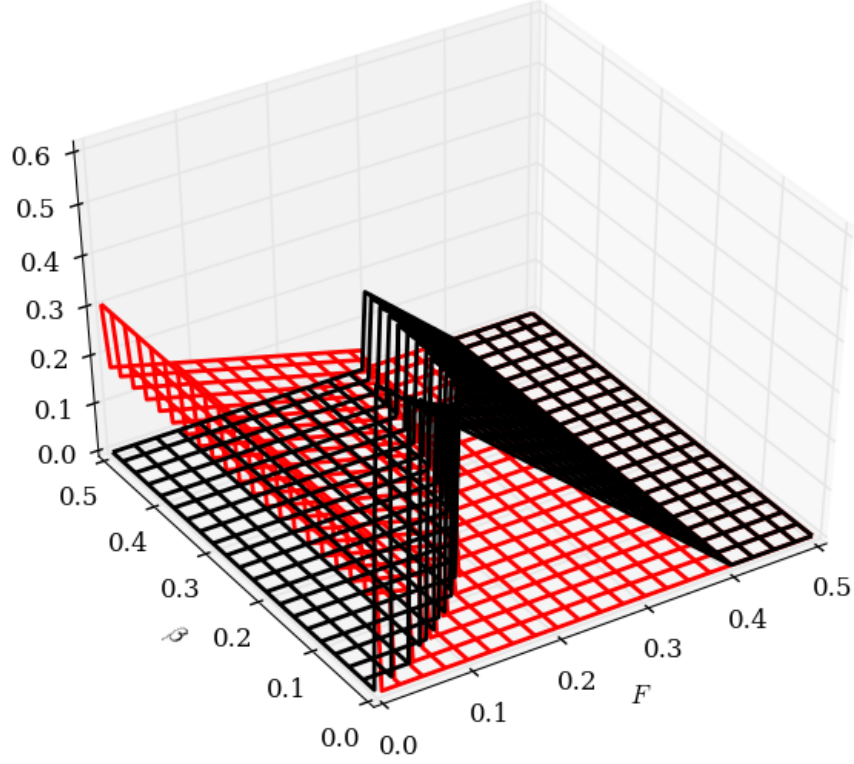


Figure 5: 3D solution depicting killer yeast (red) and sensitive yeast (black) steady-states.

## Steady-State regions

In order to evaluate the steady-state solutions, we need to equate Equations (6), (7), and (8) to zero and solve:

$$\frac{d}{dt}L(\bar{L}, \bar{S}, \bar{C}) = K_L \bar{C} \bar{L} - \frac{F \bar{L}}{V} = 0, \quad (9)$$

$$\frac{d}{dt}S(\bar{L}, \bar{S}, \bar{C}) = K_S \bar{C} \bar{S} - \frac{F \bar{S}}{V} - \beta \bar{S} \bar{L} = 0, \quad (10)$$

$$\frac{d}{dt}C(\bar{L}, \bar{S}, \bar{C}) = -\alpha_L K_L \bar{C} \bar{L} - \alpha_S K_S \bar{C} \bar{S} - \frac{F \bar{C}}{V} + \frac{F C_0}{V} = 0. \quad (11)$$

From Eq. (9), we see that  $\bar{L}(K_L \bar{C} - F/V) = 0$ , and thus  $\bar{L} = 0$  or  $\bar{C} = F/(K_L V)$ . For each of these steady-states, we will evaluate Equations (10) and (11) to find the qualitative behavior of the steady-states.

### 1 $\bar{L} = 0$ :

From (10),  $\bar{S}(K_S \bar{C} - F/V - \beta \bar{L}) = 0$ , so  $\bar{S} = 0$  or  $\bar{C} = \frac{F/V + \beta \bar{L}}{K_S} = \frac{F}{K_S V}$ .

1.  $\bar{S} = 0$ :

From (11),

$$\begin{aligned} -\alpha_L K_L \bar{C} \bar{L} - \alpha_S K_S \bar{C} \bar{S} - \frac{F \bar{C}}{V} + \frac{F C_0}{V} &= 0 \\ -\frac{F \bar{C}}{V} + \frac{F C_0}{V} &= 0, \quad F/V \neq 0. \end{aligned}$$

Thus  $\bar{C} = C_0$ , and the first steady-state is  $(0, 0, C_0)$ , where both species of yeast are flushed out. Call this **Steady-State I**.

2.  $\bar{C} = \frac{F}{K_S V}$ :

From (11),

$$\begin{aligned} -\alpha_S K_S \left( \frac{F}{K_S V} \right) \bar{S} - \frac{F}{V} \left( \frac{F}{K_S V} \right) + \frac{F C_0}{V} &= 0 \\ -\alpha_S \left( \frac{F}{V} \right) \bar{S} - \frac{F}{V} \left( \frac{F}{K_S V} \right) + \frac{F C_0}{V} &= 0 \\ \alpha_S \left( \frac{F}{V} \right) \bar{S} &= \frac{F}{V} \left( \frac{F}{K_S V} \right) - \frac{F C_0}{V} \\ \alpha_S \bar{S} &= \frac{F}{K_S V} - C_0 \\ \bar{S} &= \frac{F}{K_S V \alpha_S} - \frac{C_0}{\alpha_S}. \end{aligned}$$

Therefore, the second steady-state is  $\left( 0, \frac{F}{K_S V \alpha_S} - \frac{C_0}{\alpha_S}, \frac{F}{K_S V} \right)$ , where only the sensitive species of yeast survives. Call this **Steady-State II**.

**2**  $\bar{C} = \frac{F}{K_L V}$ :

From (10),

$$\begin{aligned} \bar{S} \left( K_S \bar{C} - \frac{F}{V} - \beta \bar{L} \right) &= 0 \\ \bar{S} \left( K_S \frac{F}{K_L V} - \frac{F}{V} - \beta \bar{L} \right) &= 0. \end{aligned}$$

So  $\bar{S} = 0$  or  $\bar{L} = \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta}$ .

1.  $\bar{S} = 0$ :

From (11),

$$\begin{aligned}
-\alpha_L K_L \bar{C} \bar{L} - \alpha_S K_S \bar{C} \bar{S} - \frac{F \bar{C}}{V} + \frac{F C_0}{V} &= 0 \\
-\alpha_L \left( \frac{F}{K_L V} \right) \bar{L} - \frac{F}{V} \left( \frac{F}{K_L V} \right) + \frac{F C_0}{V} &= 0 \\
\alpha_L \left( \frac{F}{V} \right) \bar{L} &= \frac{F C_0}{V} - \frac{F}{V} \left( \frac{F}{K_L V} \right) \\
\alpha_L \bar{L} &= C_0 - \frac{F}{K_L V} \\
\bar{L} &= \frac{C_0}{\alpha_L} - \frac{F}{K_L V \alpha_L}.
\end{aligned}$$

Thus third steady-state is  $\left( \frac{C_0}{\alpha_L} - \frac{F}{K_L V \alpha_L}, 0, \frac{F}{K_L V} \right)$ , where only the killer species of yeast survive. Call this **Steady-State III**.

2.  $\bar{L} = \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta}$ :

From (11),

$$\begin{aligned}
-\alpha_L K_L \bar{C} \bar{L} - \alpha_S K_S \bar{C} \bar{S} - \frac{F \bar{C}}{V} + \frac{F C_0}{V} &= 0 \\
-\alpha_L K_L \left( \frac{F}{K_L V} \right) \left( \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta} \right) - \alpha_S K_S \left( \frac{F}{K_L V} \right) \bar{S} - \frac{F}{V} \left( \frac{F}{K_L V} \right) + \frac{F C_0}{V} &= 0.
\end{aligned}$$

Solving for  $\bar{S}$ ,

$$\begin{aligned}
\Rightarrow \alpha_S K_S \left( \frac{F}{K_L V} \right) \bar{S} &= \frac{F C_0}{V} - \alpha_L K_L \left( \frac{F}{K_L V} \right) \left( \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta} \right) - \frac{F}{V} \left( \frac{F}{K_L V} \right) \\
\alpha_S K_S \left( \frac{1}{K_L} \right) \bar{S} &= C_0 - \alpha_L K_L \left( \frac{1}{K_L} \right) \left( \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta} \right) - \frac{F}{K_L V} \\
\frac{\alpha_S K_S}{K_L} \bar{S} &= C_0 - \alpha_L \left( \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta} \right) - \frac{F}{K_L V} \\
\bar{S} &= \left( \frac{K_L}{\alpha_S K_S} \right) C_0 - \alpha_L \left( \frac{K_L}{\alpha_S K_S} \right) \left( \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta} \right) - \left( \frac{K_L}{\alpha_S K_S} \right) \left( \frac{F}{K_L V} \right) \\
\bar{S} &= \frac{K_L C_0}{\alpha_S K_S} - \frac{\alpha_L F}{\alpha_S V \beta} + \frac{\alpha_L K_L F}{\alpha_S K_S V \beta} - \frac{F}{\alpha_S K_S V} \\
\bar{S} &= \frac{K_L C_0}{\alpha_S K_S} + \frac{F}{V} \left( \frac{\alpha_L K_L}{\alpha_S K_S \beta} - \frac{\alpha_L}{\alpha_S \beta} - \frac{1}{\alpha_S K_S} \right).
\end{aligned}$$

Therefore, the fourth and final steady-state is  $\left( \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta}, \frac{K_L C_0}{\alpha_S K_S} + \frac{F}{V} \left( \frac{\alpha_L K_L}{\alpha_S K_S \beta} - \frac{\alpha_L}{\alpha_S \beta} - \frac{1}{\alpha_S K_S} \right), \frac{F}{K_L V} \right)$ , where both species survive. Call this **Steady-State IV**.

## Non-Trivial Steady State Evaluation

Looking at **Steady-State IV**:



$$\begin{aligned}
\bar{L} &= \frac{K_S F}{K_L V \beta} - \frac{F}{V \beta} \\
\bar{S} &= \frac{K_L C_0}{\alpha_S K_S} + \frac{F}{V} \left( \frac{\alpha_L K_L}{\alpha_S K_S \beta} - \frac{\alpha_L}{\alpha_S \beta} - \frac{1}{\alpha_S K_S} \right) \\
\bar{C} &= \frac{F}{K_L V}.
\end{aligned}$$

First, assume that both  $\bar{L}$  and  $\bar{S}$  are greater than zero. Then

$$\begin{aligned}
\frac{K_S F}{K_L V \beta} - \frac{F}{V \beta} &> 0 \\
\frac{F}{V \beta} \left( \frac{K_S}{K_L} - 1 \right) &> 0,
\end{aligned}$$

and thus because  $F > 0$  and  $\beta > 0$ ,  $\frac{K_S}{K_L} > 1$  and hence  $K_S > K_L$ . Next,

$$\begin{aligned}
\frac{K_L C_0}{\alpha_S K_S} + \frac{F}{V} \left( \frac{\alpha_L K_L}{\alpha_S K_S \beta} - \frac{\alpha_L}{\alpha_S \beta} - \frac{1}{\alpha_S K_S} \right) &> 0 \\
\frac{F}{V} \left( \frac{\alpha_L K_L}{\alpha_S K_S \beta} - \frac{\alpha_L}{\alpha_S \beta} - \frac{1}{\alpha_S K_S} \right) &> -\frac{K_L C_0}{\alpha_S K_S} \\
\frac{\alpha_L K_L}{\alpha_S K_S \beta} - \frac{\alpha_L}{\alpha_S \beta} - \frac{1}{\alpha_S K_S} &> -\frac{V}{F} \cdot \frac{K_L C_0}{\alpha_S K_S} \\
\frac{\alpha_L K_L}{\beta} - \frac{\alpha_L K_S}{\beta} - 1 &> -\frac{V}{F} \cdot K_L C_0 \\
\frac{1}{\beta} (\alpha_L K_L - \alpha_L K_S) &> 1 - \frac{V}{F} \cdot K_L C_0 \\
\beta &< \frac{\alpha_L K_L - \alpha_L K_S}{1 - \frac{V}{F} \cdot K_L C_0}.
\end{aligned}$$

A similar procedure also produces

$$\beta > \frac{\frac{F}{V} (\alpha_L K_S - \alpha_L K_L)}{C_0 K_L - \frac{F}{V}}.$$

Because  $K_S > K_L$ , we know that the numerator is negative. Also, because  $\beta > 0$ , we know that the numerator must also be negative, i.e.,

$$\begin{aligned}
\frac{V}{F} \cdot K_L C_0 &< 1 \\
K_L C_0 &< \frac{F}{V}.
\end{aligned}$$

## Source Code:

```
from scipy.integrate._ode      import ode
from scipy.io                 import savemat
from pylab                   import *
from mpl_toolkits.mplot3d     import Axes3D
from multiprocessing         import Queue, cpu_count, Process
from mpl_toolkits.axes_grid1 import make_axes_locatable

#-----
# ODE function to be integrated
def dLdt(L, S, C, params):
    """
    INPUT:
        L - population of killer yeast.
        S - population of sensitive yeast.
        C - population of nutrient.
        params - dLdt equation parameters.
    OUTPUT:
        dLdt - time derivative of L.
    """
    K_L = params[0]
    F = params[1]
    V = params[2]
    dLdt = K_L*C*L - F*L/V
    return array(dLdt)

def dSdt(L, S, C, params):
    """
    INPUT:
        L - population of killer yeast.
        S - population of sensitive yeast.
        C - population of nutrient.
        params - dSdt equation parameters.
    OUTPUT:
        dSdt - time derivative of S.
    """
    K_S = params[0]
    F = params[1]
    V = params[2]
    beta = params[3]
    dSdt = K_S*C*S - F*S/V - beta*S*L
    return array(dSdt)

def dCdt(L, S, C, params):
    """
    INPUT:
        L - population of killer yeast.
        S - population of sensitive yeast.
        C - population of nutrient.
        params - dCdt equation parameters.
    OUTPUT:
        dCdt - time derivative of C.
    """
    a_L = params[0]
    a_S = params[1]
    K_L = params[2]
    K_S = params[3]
    F = params[4]
    V = params[5]
    C_0 = params[6]
    dCdt = -a_L*K_L*C*L - a_S*K_S*C*S - F*C/V + F*C_0/V
    return array(dCdt)

def f(t, y, dLdt, dSdt, dCdt, L_params, S_params, C_params):
    """
    INPUT:
```

```

t          - time array
dLdt       - function
uSdt       - function
dCdt       - function
L_params   - parameters for dLdt
S_params   - parameters for dSdt
C_params   - parameters for dCdt
OUTPUT:
    ydot[0] = time derivative of y[0],
    ydot[1] = time derivative of y[1],
    ydot[2] = time derivative of y[2].
"""
L = y[0]
S = y[1]
C = y[2]
rhs1 = dLdt(L, S, C, L_params)    # right hand side 1st eqn
rhs2 = dSdt(L, S, C, S_params)    # right hand side 2nd eqn
rhs3 = dCdt(L, S, C, C_params)    # right hand side 3rd eqn
return array([rhs1, rhs2, rhs3])

def model(F, beta, y0, ta, dt):
    """
    Run model for given volume flow rate <F> and toxin coef <beta> for total
    time array <ta> in hours at timestep <dt>, also in hours. Returns the
    last solution 3-tuple for L, S, and C.
    """
    # Additional parameters being passed to the ODE function
    a_L = 0.1124
    a_S = 0.0325
    K_L = 19.0288
    K_S = 20.1818
    V = 1.0
    C_0 = 0.02

    L_params = [K_L, F, V]
    S_params = [K_S, F, V, beta]
    C_params = [a_L, a_S, K_L, K_S, F, V, C_0]

    # Call function that integrates the ODE:
    r = ode(f)
    r.set_integrator('dopri5', atol=1e-6, rtol=1e-5)
    r.set_initial_value(y0, ta)
    r.set_f_params(dLdt, dSdt, dCdt, L_params, S_params, C_params)

    sol = []
    sol.append(y0)
    for t in ta[:-1]:
        r.integrate(r.t + dt)
        sol.append(r.y)
    sol = array(sol).T

    return sol[:, -1]

class solveProcess(Process):
    """
    Process to solve the model function.
    """
    def __init__(self, i, queue, beta_a, F_a, y0, ta, dt, p):
        """
        Initialize the Process with ID <i>, processing queue <queue>, beta array
        <beta_a>, flow array <F_a>, time array <ta>, timestep <dt>, and number of
        parameters <p>.
        """
        Process.__init__(self)
        self.i = i
        self.q = queue
        self.beta_a = beta_a

```

```

self.F_a      = F_a
self.y0       = y0
self.ta       = ta
self.dt       = dt
self.m        = len(beta_a)
self.n        = len(F_a)
self.p        = p

def run(self):
    """
    solve the differential equations for all beta_a and F_a.
    """
    p = self.p
    m = self.m
    n = self.n

    SS_L = zeros((m,n))
    SS_S = zeros((m,n))
    SS_C = zeros((m,n))

    for i, beta in enumerate(self.beta_a):
        for j, F in enumerate(self.F_a):
            print 'Process %i solving: beta=%f, F=%f' % (self.i, beta, F)
            sol = model(F=F, beta=beta, y0=self.y0, ta=self.ta, dt=self.dt)
            SS_L[i,j] = sol[0]
            SS_S[i,j] = sol[1]
            SS_C[i,j] = sol[2]

    self.q.put(array([SS_L, SS_S, SS_C])) # add the result to the queue.

def plot_sol(ax, f, extent, tit, cmap='Greys'):
    """
    plot the 2D solution <f> to axes <ax>.
    """
    im      = ax.imshow(f[:,-1,:], extent=extent, cmap=cmap)
    divider = make_axes_locatable(ax)
    cax     = divider.append_axes("right", size="5%", pad=0.05)
    ax.set_title(tit)
    ax.set_ylabel(r'$\beta$')
    ax.set_xlabel(r'$F$')
    colorbar(im, cax=cax)

# parameters :
m = 100      # number of beta discretizations.
n = 100      # number of F discretizations.
p = 3        # number of parameters
t0 = 0.0     # initial time
tf = 40000   # final time
dt = 500     # time step

# Initial conditions
y0 = [0.3, 0.3, 0.001]

# range of beta, flow, and time to model :
betaMin = 0.0
betaMax = 0.5
Fmin     = 0.0
Fmax     = 0.5

beta_a   = linspace(betaMin, betaMax, m)
F_a      = linspace(Fmin, Fmax, n)
ta       = arange(t0, tf+dt, dt)

# multiprocessing data structures :
solvers = []
queue    = []
numCpus  = cpu_count()
Fs       = array_split(F_a, numCpus)

```

```

# create a solver for each processor and begin solving each :
for i in range(numCpus):
    q = Queue()
    queue.append(q)
    solver = solveProcess(i, q, beta_a, Fs[i], y0, ta, dt, p)
    solvers.append(solver)
    solver.start()

# wait until solver (started above) finishes :
for s in solvers:
    s.join()

# retrieve the results :
sols = []
for q in queue:
    while q.empty() == False:
        sols.append(q.get())

# put the results from the individual cores back together :
for i, s in enumerate(sols):
    if i == 0:
        L_sol = s[0]
        S_sol = s[1]
        C_sol = s[2]
    else:
        L_sol = hstack((L_sol, s[0]))
        S_sol = hstack((S_sol, s[1]))
        C_sol = hstack((C_sol, s[2]))

Flow, Beta = meshgrid(F_a, beta_a)

data = {'Beta' : Beta,
        'Flow' : Flow,
        'L_sol' : L_sol,
        'S_sol' : S_sol,
        'C_sol' : C_sol}
savemat('../..../killer_yeast/data/results.mat', data)

# plot the results :
fig = plt.figure()
ax = fig.add_subplot(111, projection='3d')

ax.plot_wireframe(Flow, Beta, L_sol, color='r', lw=2.0, rstride=5, cstride=5)
ax.plot_wireframe(Flow, Beta, S_sol, color='k', lw=2.0, rstride=5, cstride=5)
ax.set_ylabel(r'$\beta$')
ax.set_xlabel(r'$F$')
show()

fig = plt.figure(figsize=(15,5))
ax1 = fig.add_subplot(131)
ax2 = fig.add_subplot(132)
ax3 = fig.add_subplot(133)

extent = [Fmin, Fmax, betaMin, betaMax]
plot_sol(ax1, L_sol, extent, r'Killer', cmap='Greys')
plot_sol(ax2, S_sol, extent, r'Sensitive', cmap='Greys')
plot_sol(ax3, C_sol, extent, r'Nutrient', cmap='Greys')
tight_layout()
savefig('../..../killer_yeast/doc/images/sols.png', dpi=300)
show()

```