Killer Yeast Vs. Sensitive Yeast

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Proposal

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

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

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, α 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 $\lim_{C\to\infty} = k_{max}$, 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 1/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 $\dot{N} = 0$,

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

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

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

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 $\bar{N} = 0$, $\bar{C} = C_0$.

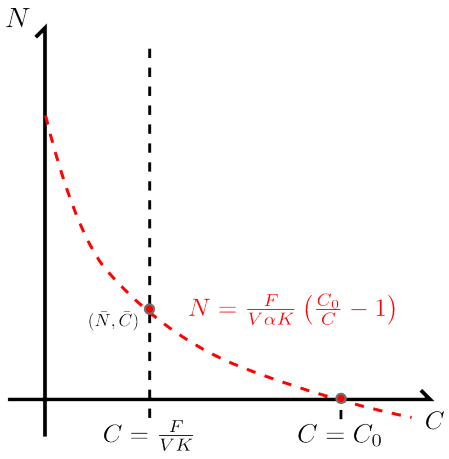


Figure 1: The $\dot{C} = 0$ nullcline (dashed red) intersecting with the $\dot{N} = 0$ nullcline (dashed black). The trivial and non-trivial steady-states $(0, C_0)$ and $(\bar{N}, \bar{C})$ are shown as red dots.

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 α 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 $i = 1, \ldots, n$, where n is the number of observations.

After we obtain estimates of these parameters for both the killer yeast L and sensitive yeast S, (α_L, α_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

$$\frac{dL}{dt} = K_L CL - \frac{FL}{V}, \tag{6}$$

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

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

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

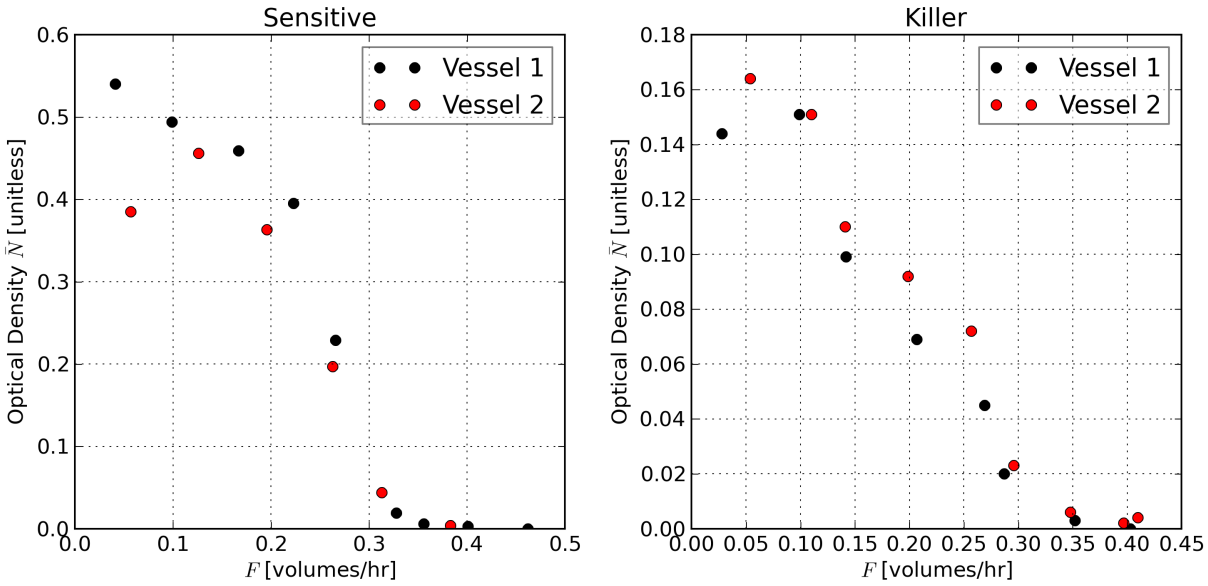
2 Sensitive Run

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 :

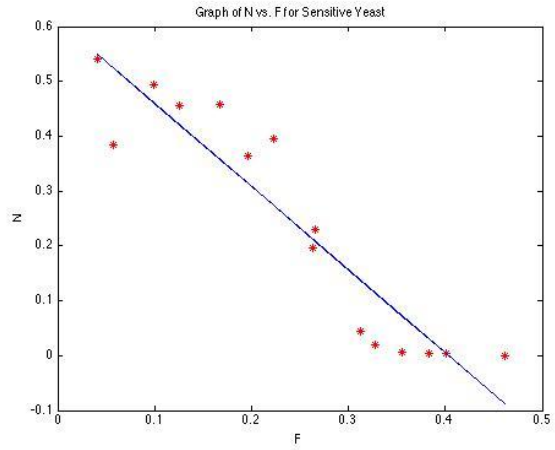
Volumes/Hr	0.0571	0.126	0.196	0.263	0.313	0.383
Optical Density at Steady State	0.385	0.456	0.363	0.197	0.044	0.004



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:

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

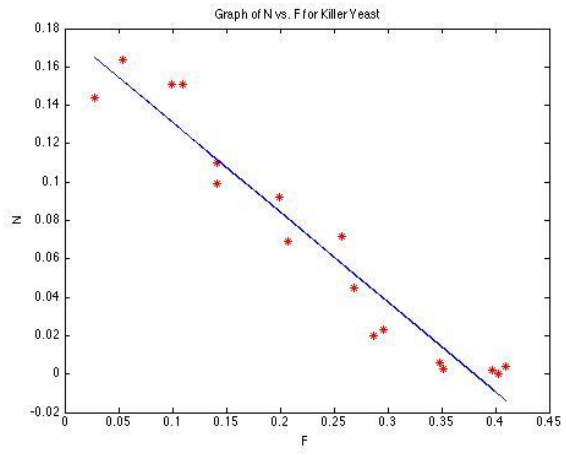
Taking $V = 1$, we can solve Eq. (5) using MatLab's `nlinfit` function. The results of this are shown below for both sensitive and killer yeast.



	Estimates	SE	CI
α_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 α_L and K_L.

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



	Estimates	SE	CI
α_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 α_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 α and K (for both killer and sensitive yeast) we can run the dynamic model (6), (7), and (8) to equilibrium. By letting β 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 β and F to determine the regions in the β, F plane where sensitive yeast S overtakes the killer yeast L and vice versa.

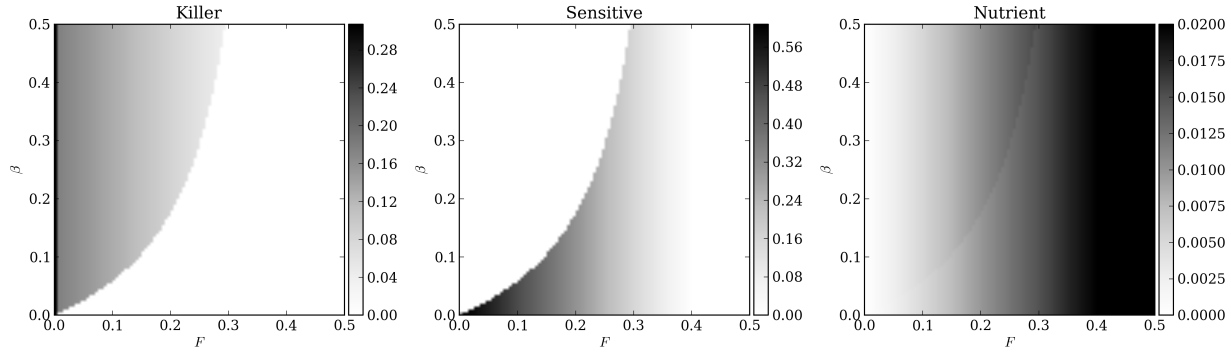
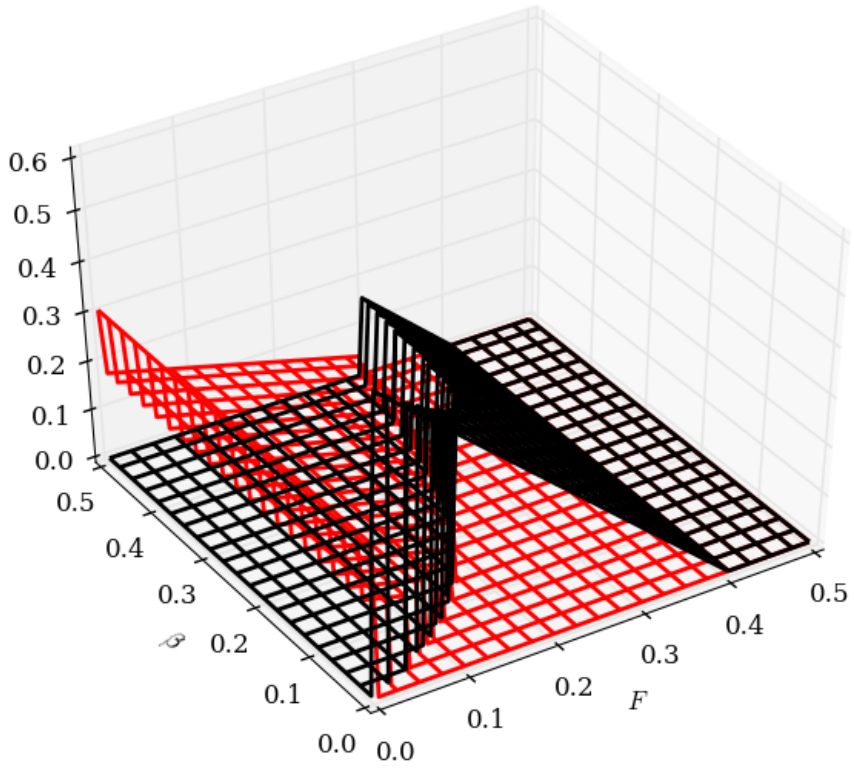


Figure 4: 250×250 steady-state optical density solution for killer yeast (left), sensitive yeast (middle) and nutrient (right) for a total run time of 40,000 hours. Equations (6), (7), and (8) were solved with the Dormand-Prince numerical integration algorithm with an absolute tolerance of 1e-6, relative tolerance of 1e-6, and timestep Δt of 500 hours. The timestep was kept high due to the $250 \times 250 = 62,500$ simulations required to complete the figure, while parallel processing was also implemented to speed up the simulation.

Notice in Figure 4 that as β 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.



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  = 250     # number of beta discretizations.
n  = 250     # 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 = 1.0
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()

# retrive 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]))

Beta, Flow = meshgrid(beta_a, F_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(Beta, Flow, L_sol, color='r', lw=2.0, rstride=5, cstride=5)
ax.plot_wireframe(Beta, Flow, 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 = [betaMin, betaMax, Fmin, Fmax]
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()
```