

Killer Yeast Vs. Sensitive Yeast

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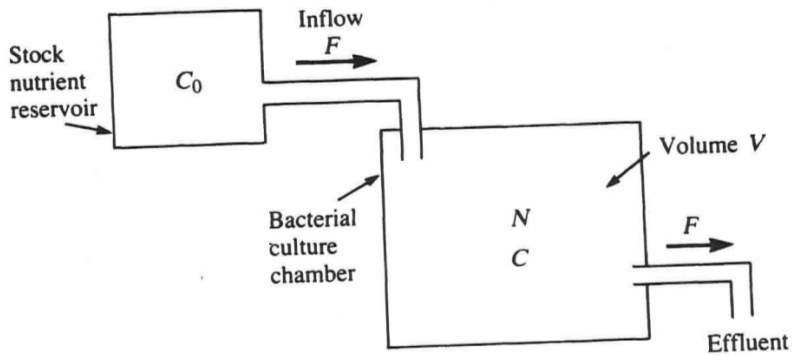
MATH 445 - Statistical, Dynamical, and Computational
Modeling

December 9, 2013

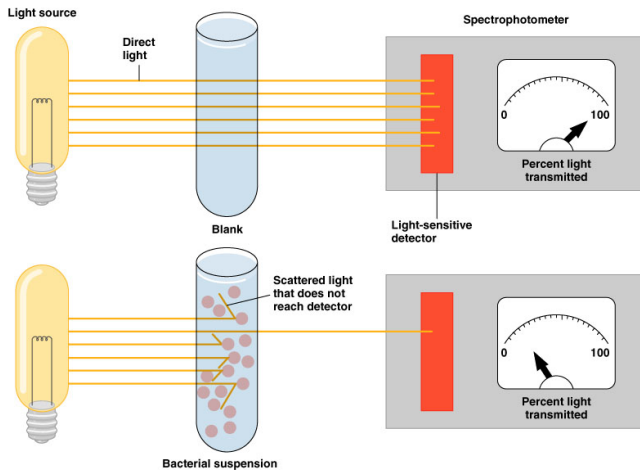
Experiment

An experiment was conducted where an amount of yeast was grown in *chemostat* and allowed to come to equilibrium. The steady-state *optical density* of the yeast were recorded for a given flow rate F .

Chemostat



Optical Density



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ODE

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, α is a unitless inverse of the yield constant, and $k(C)$ is the reproduction rate for yeast in units 1/time.

$k(C)$ and its Simplification

$k(C)$ 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

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

with K in units 1/time.

New ODE

The equations we need to solve then become

$$\frac{dN}{dt} = KCN - \frac{FN}{V}, \quad (1)$$

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

Steady States

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

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

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

which is zero for $\bar{N} = 0$ or $K\bar{C} = F/V$.

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

$$\frac{dC(\bar{N}, \bar{C})}{dt} = -\alpha K \bar{C} \bar{N} - \frac{F \bar{C}}{V} + \frac{F C_0}{V} = 0,$$

which is zero for $\alpha K \bar{C} \bar{N} + \frac{F \bar{C}}{V} = \frac{F C_0}{V}$.

Determination of (\bar{N}, \bar{C})

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

$$K\bar{C} = \frac{F}{V} \implies \bar{C} = \frac{F}{VK}. \quad (3)$$

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

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

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

Determination of (\bar{N}, \bar{C})

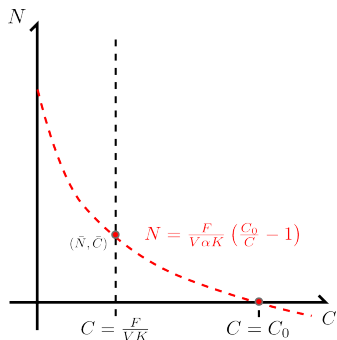


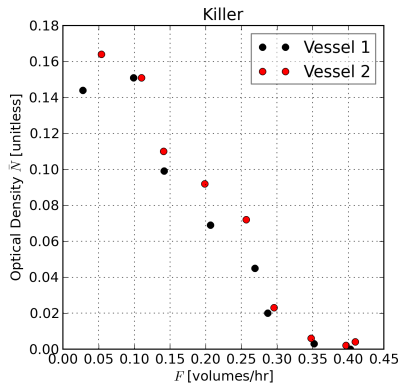
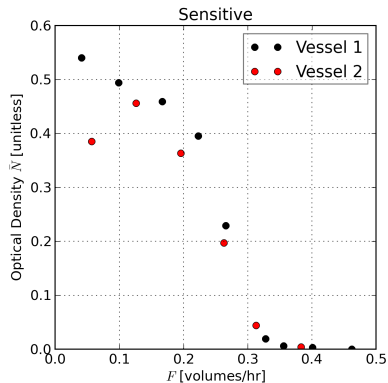
Figure: The $\dot{C} = 0$ nullcline (dashed red) intersecting with the $\dot{N} = 0$ nullcline (dashed black). The trivial and non-trivial steady-states $(0, C_0)$ and (\bar{N}, \bar{C}) are shown as red dots.

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

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

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

The Data



$$C_0 = 0.02$$

Eq. (5) Fit for Sensitive Yeast

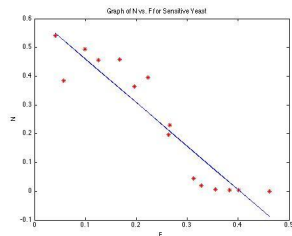


Figure: Sensitive yeast S steady-state best-fit line using Eq. (5).

	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 .

Eq. (5) Fit for Killer Yeast

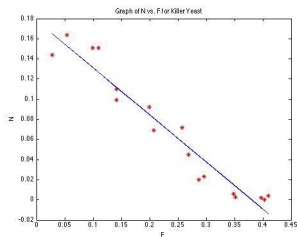


Figure: Killer yeast L steady-state best-fit line using Eq. (5).

	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.

What-If Scenario

Now that we have obtained estimates of the parameters for both the killer yeast L and sensitive yeast S , (α_L , α_S and K_L , K_S respectively), we model a “what if” scenario whereby we place both species of yeast, sensitive and killer, into one chemostat. The differential equations we use to solve this three-species model is

$$\frac{dL}{dt} = K_L C L - \frac{F L}{V}, \quad (6)$$

$$\frac{dS}{dt} = K_S C S - \frac{F S}{V} - \beta S L, \quad (7)$$

$$\frac{dC}{dt} = -\alpha_L K_L C L - \alpha_S K_S C S - \frac{F C}{V} + \frac{F C_0}{V}. \quad (8)$$

What-if Scenario

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.

What-if Scenario Results

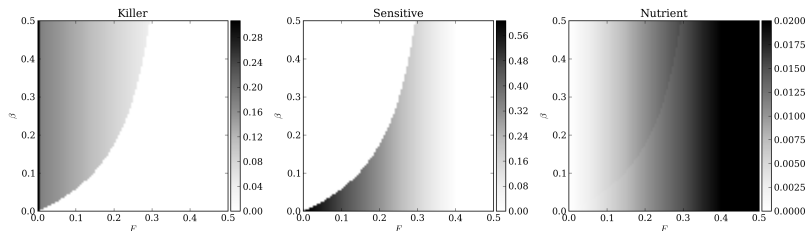


Figure: 250×250 steady-state optical density solution for killer yeast (left), sensitive yeast (middle) and nutrient (right) for a total run time of 40,000 hours. Equations (6), (7), and (8) were solved with the Dormand-Prince numerical integration algorithm with an absolute tolerance of $1e-6$, relative 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. In order to keep the total time to complete the simulation minimized, parallel processing was required.

What-if Scenario Results

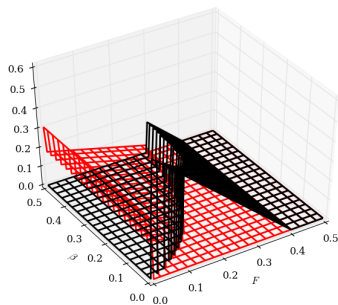


Figure: 3D solution depicting killer yeast (red) and sensitive yeast (black) steady-states.

Notice 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.

Questions?

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3 [|||||100.0%]  
4 [|||||100.0%]  
Mem[|||||2581/26124MB]  
Swp[0/26618MB]  
5 [|||||100.0%]  
6 [|||||100.0%]  
7 [|||||100.0%]  
8 [|||||100.0%]  
Tasks: 131, 296 thr; 9 running  
Load average: 7.32 3.03 1.33  
Uptime: 00:38:28  
  
PID USER PRI NI VIRT RES SHR S CPU% MEM% TIME+ Command  
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4952 pf4d 20 0 213M 31128 1972 R 100. 0.1 2:05.65 python killerYeas  
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