Killer Yeast Vs. Sensitive Yeast

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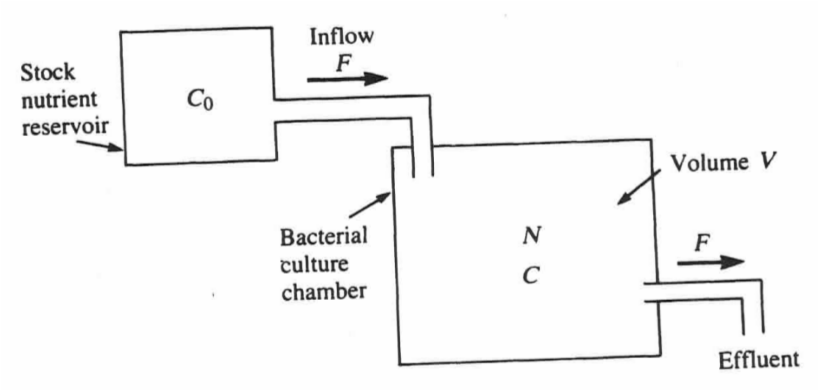
MATH 445 - Statistical, Dynamical, and Computational Modeling

December 11, 2013

Experiment

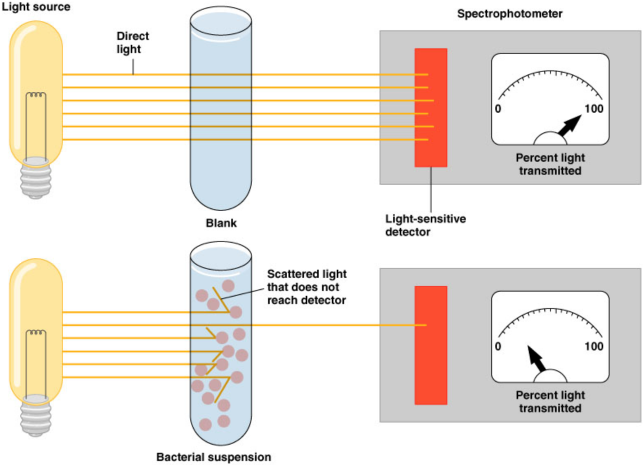
An experiment was conducted where an amount of yeast was grown in *chemostat* and allowed to come to equilibrium. The steady-state *optical density* of the yeast was recorded for a given flow rate F.

Chemostat



Stock
nutrient
reservoir
C_0
Inflow
F
Volume V
Bacterial
culture
chamber
N
C
F
Effluent

Optical Density



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:

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

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.

$k(C)$ and its Simplification

$k(C)$ is the reproduction rate for yeast in units 1/time with possible formula chosen such that $\lim_{C\to\infty} = k_{max}$, 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

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

with K in units 1/time.

New ODE

The equations we need to solve then become

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

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

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 $K\bar{C} = F/V$.

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

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

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

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

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

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

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

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

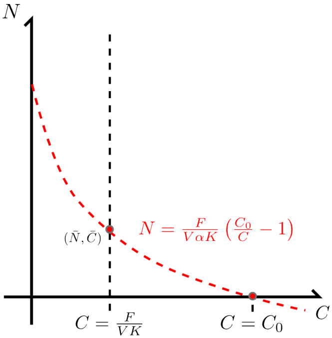


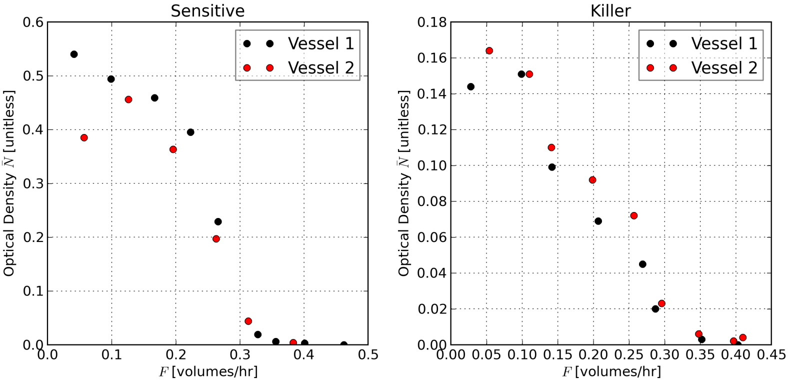
Figure: The $\dot{C} = 0$ nullcline (dashed red) intersecting with the $\dot{N} = 0$ nullcline (dashed black). The trivial and non-trivial steady-states $(0, C_0)$ and $(\bar{N}, \bar{C})$ are shown as red dots.

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

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

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.

The Data



$$C_0 = 0.02$$

Eq. (5) Fit for Sensitive Yeast

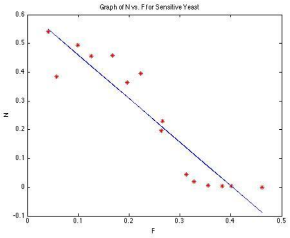


Figure: Sensitive yeast S steady-state best-fit line using Eq. (5).

	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

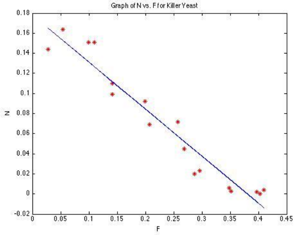


Figure: Killer yeast L steady-state best-fit line using Eq. (5).

	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

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

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

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

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 overtake the killer yeast L and vice versa.

What-if Scenario Results

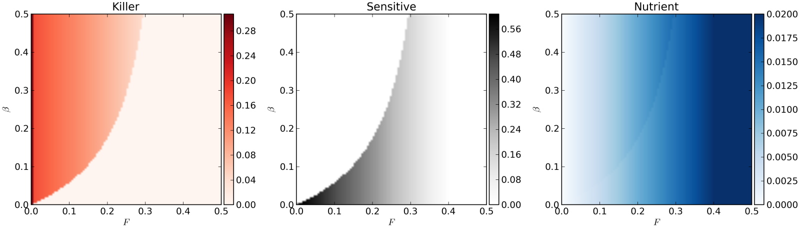


Figure: 250×250 steady-state optical density solution for killer yeast (left), sensitive yeast (middle) and nutrient (right) for a total run time of 40,000 hours. Equations (6), (7), and (8) were solved with the Dormand-Prince numerical integration algorithm with an absolute tolerance of 1e-6, relative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

What-if Scenario Results

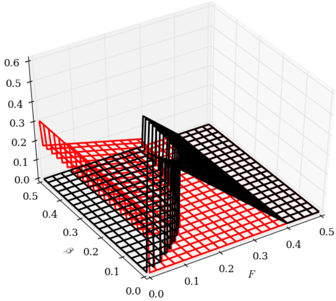
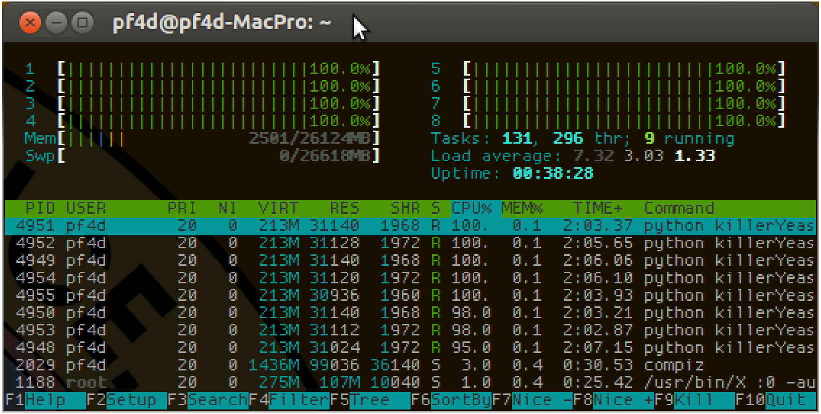


Figure: 3D solution depicting killer yeast (red) and sensitive yeast (black) steady-states.

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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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
4949 pf4d 20 0 213M 31140 1968 R 100. 0.1 2:06.06 python killerYeas
4954 pf4d 20 0 213M 31120 1972 R 100. 0.1 2:06.10 python killerYeas
4955 pf4d 20 0 213M 30936 1960 R 100. 0.1 2:03.93 python killerYeas
4950 pf4d 20 0 213M 31140 1968 R 98.0 0.1 2:03.21 python killerYeas
4953 pf4d 20 0 213M 31112 1972 R 98.0 0.1 2:02.87 python killerYeas
4948 pf4d 20 0 213M 31024 1972 R 95.0 0.1 2:07.15 python killerYeas
2029 pf4d 20 0 1436M 99036 36140 S 3.0 0.4 0:30.53 compiz
1188 root 20 0 275M 107M 10040 S 1.0 0.4 0:25.42 /usr/bin/X :0 -au
F1Help F2Setup F3SearchF4FilterF5Tree F6SortByF7Nice -F8Nice +F9Kill F10Quit