

# Killer Yeast Vs. Sensitive Yeast

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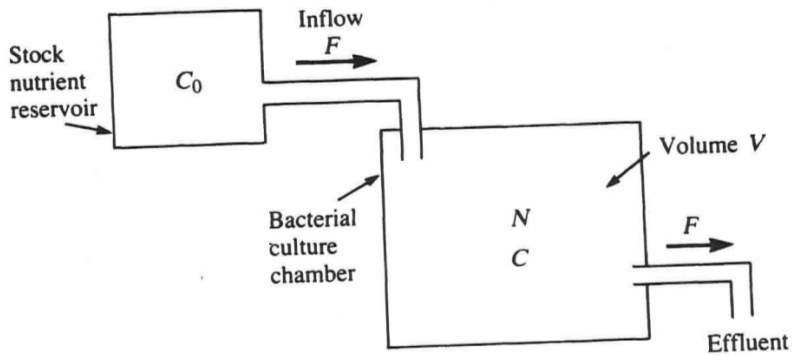
MATH 445 - Statistical, Dynamical, and Computational  
Modeling

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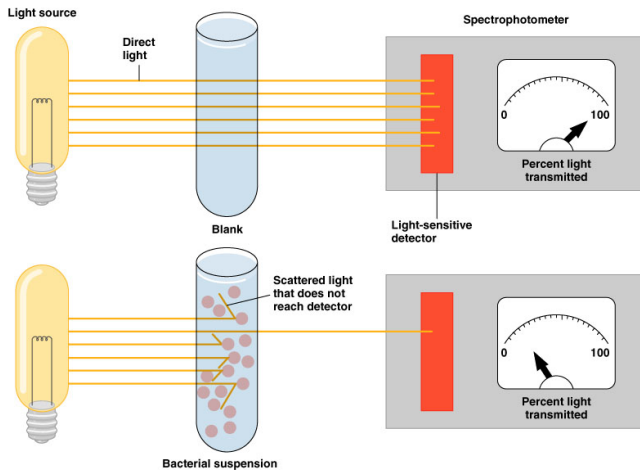
# Experiment

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



# 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,  $\alpha$  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  $\dot{N} = 0$ ,

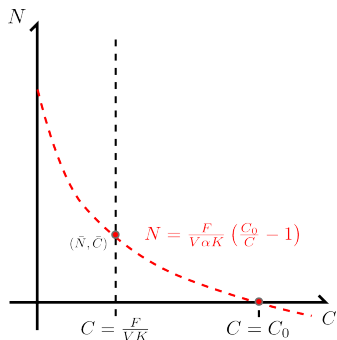
$$K\bar{C} = \frac{F}{V} \implies \bar{C} = \frac{F}{VK}. \quad (3)$$

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



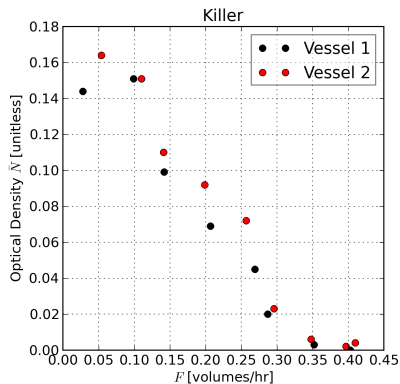
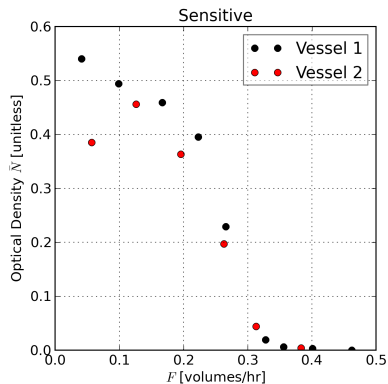
**Figure:** The  $\dot{C} = 0$  nullcline (dashed red) intersecting with the  $\dot{N} = 0$  nullcline (dashed black). The trivial and non-trivial steady-states  $(0, C_0)$  and  $(\bar{N}, \bar{C})$  are shown as red dots.

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

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

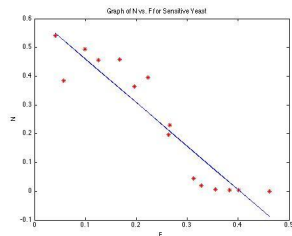
The unknown parameters in Eq (5) are  $\alpha$  and  $K$ . We can find these parameters by fitting Eq (5) to the data by non-linear least squares fitting  $\bar{N}_i$  at  $F_i$  for  $i = 1, \dots, n$ , where  $n$  is the number of observations.

# The Data



$$C_0 = 0.02$$

## Eq. (5) Fit for Sensitive Yeast

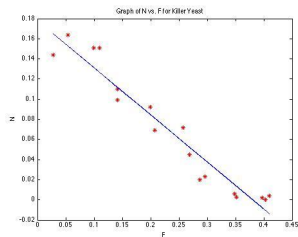


**Figure:** Sensitive yeast  $S$  steady-state best-fit line using Eq. (5).

	Estimates	SE	CI
$\alpha_S$	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  $K_L$ .

## Eq. (5) Fit for Killer Yeast



**Figure:** Killer yeast  $L$  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.

## What-If Scenario

Now that we have obtained estimates of the parameters for both the killer yeast  $L$  and sensitive yeast  $S$ , ( $\alpha_L$ ,  $\alpha_S$  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

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

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

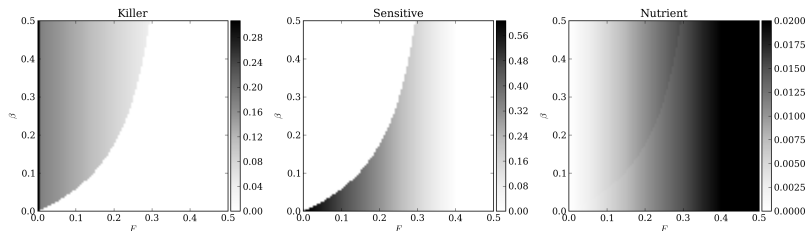
$$\frac{dC}{dt} = -\alpha_L K_L C L - \alpha_S K_S C S - \frac{F C}{V} + \frac{F C_0}{V}. \quad (8)$$



# What-if Scenario

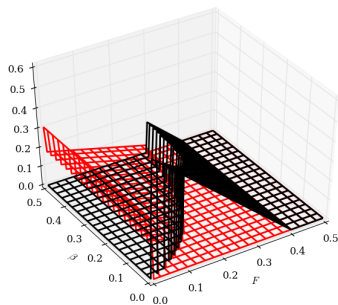
We can run the dynamic model (6), (7), and (8) to equilibrium. By letting  $\beta$  range from 0 to 0.5 (in units 1/time), and  $F$  range from 0 to 0.5 (in units volume/time), we can run the model for each  $\beta$  and  $F$  to determine the regions in the  $\beta, F$  plane where sensitive yeast 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

# What-if Scenario Results



**Figure:**  $250 \times 250$  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  $\Delta t$  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  $\beta$  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.

# Questions?

```
pf4d@pf4d-MacPro: ~  
  
1 [|||||100.0%]  
2 [|||||100.0%]  
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  
4951 pf4d 20 0 213M 31140 1968 R 100. 0.1 2:03.37 python killerYeas  
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 F3Search F4Filter F5Tree F6SortBy F7Nice -F8Nice +F9Kill F10Quit
```