Model of non-inherited resistance and antibiotic treatment

We assume that within an infected patient, bacteria are of two states with respect to their inherent (genetic) susceptibility to a bactericidal antibiotic, susceptible and resistant. The extent to which the susceptible bacteria are killed by the antibiotic depends on the concentration of the drug, $A$ (µg/ml), and whether they are in an unprotected or protected state, $U$ and $P$, respectively. $U$ and $P$ in this model can be physically different sites within an infected host; one where they are replicating rapidly and are highly susceptible to the action of the antibiotic, $U$, and one in which they are replicating slowly and indifferent to antibiotic, $P$. The $P$ state can also be a slowing or non-dividing, persistent subset of a contiguous population of infecting bacteria. The densities of genetically sensitive and resistant bacteria in the $U$ state are, respectively $Su$ and $Ru$, and the corresponding densities in the $P$ state are $Sp$, and $Rp$ (bacteria per ml). Bacteria move (change states) from $U$ to $P$ and from $P$ to $U$ at rate $x$ and $y$ per cell per hour, respectively (Box figure in Levin and Rozen) and below.

![Diagram](image.png)

**Figure 1.** Two compartment model of antibiotic treatment. The susceptible bacteria in the $U$ (unprotected) compartment, at density $Su$, are rapidly killed by the antibiotic while those in the $P$ (protected) compartment, $Sp$, are somewhat refractory to the antibiotic. $A$ is the concentration of the antibiotic, which is the same in both compartments. $Ru$ and $Rp$ are the densities of genetically resistant bacteria in the $U$ and $P$ compartments, respectively. The parameters $x$ and $y$ are the rates of movement (change in state) between compartments.

In the absence of antibiotic, the $Su$ and $Sp$ populations grow at a maximum rates $vsu$ and $vsp$ hr$^{-1}$, respectively, and with or without the antibiotic the $Ru$ and $Rp$ populations grow at maximum rates, $vru$ and $vrp$ hr$^{-1}$. The total densities of bacteria
in these two states are regulated as logistic functions with carrying capacities $k_u$ and $k_p$, for the unprotected and protected states, respectively. While the rates of replication and mortality of $R_u$ and $R_p$ are independent of the concentration of the antibiotic, those of the $S_u$ and $S_p$ depend on the concentration as a Hill function. So that when the concentration of the antibiotic is $A$, the rate growth or death of $S_u$ and $S_p$ are respectively

\[
P(s_u) = (v_{s_u} - ((v_{s_u} - f_{s_u})(A/m_{i_u})^k)/((A/m_{i_u})^k - f_{s_u}/v_{s_u}))* (1-N_u/K_u)
\]

\[
P(s_p) = (v_{s_p} - ((v_{s_p} - f_{s_p})(A/m_{i_p})^k)/((A/m_{i_p})^k - f_{s_p}/v_{s_p}))* (1-N_p/K_p)
\]

Where $f_{s_u}$ and $f_{s_p}$ are the minimum growth (maximum death) rates in the U and P compartments, $m_{i_u}$ and $m_{i_p}$ are the minimum inhibitory concentrations of the antibiotic, MIC ($\mu$g/ml), in the U and P compartments and $k$ the Hill coefficient. $N_u$ and $N_p$ are the total densities of bacteria in that compartment, $N_u = S_u + R_u$, $N_p=S_p+R_p$. The effective concentration of the antibiotic, $A$ declines at rate $d$ per hour and every dose hours, $A_{max}$ ($\mu$g/ml) of the antibiotics is added. To allow for the change in the rate of conversion of $P$ to $U$ in the Box Figure of Levin and Rozen, we assume that after a specified amount of time, $y$ changes in value.

With these definitions and assumptions, at any given time, the rates of change in the densities of bacteria and the concentration of the antibiotic are given by,

\[
dS_u/dt = (P(S_u)*S_u - x*S_u + y*S_p)*(1-N_u/k_u)
\]

\[
dR_u/dt = (v_{r_u}*R_u - x*R_u + y*R_p)*(1-N_u/k_u)
\]

\[
dS_p/dt = (P(S_p)*S_p + x*S_u - y*S_p)*(1-N_p/k_p)
\]

\[
dR_p/dt = (v_{r_p}*R_p + x*R_u - y*R_p)*(1-N_p/k_p)
\]

\[
dA/dt = -d*A
\]

At a rate $\mu$ per cell per hour mutations can occur converting dividing susceptible bacteria into resistant. We neglect mutations in the reverse direction, but assume mutations can occur in the U and P states. We use a Monte Carlo protocol to simulate the mutation process. At each finite time interval $\Delta t$ a pseudo random number $x$ ($0 < x < 1$) from a rectangular distribution is generated. If that number is less than the product of the maximum replication rate, density of susceptible cells in that compartment, volume of the habitat, $v_{oU}$ and $v_{oR}$ and $t$ a mutation is generated and
the resistant bacteria in that compartment is augmented by 1/volU or 1/volP and the corresponding densities of susceptible bacteria reduced by that amount.

This model was programmed and run with Berkeley Madonna\textsuperscript{TM}, a differential equations-computer simulation package that can be downloaded from www.berkeleymadonna.com. You can run this program by patching the below code into the Berkeley Madonna file.

```
{Model of antibiotic decay, PD/PK with Two habitats}
{Protected habitat decays when TX > decay}
{In one habitat U, the bacteria replicate at a high rate and are done in by the antibiotic at a high rate}
{In the second habitat, P, the bacteria replicate at a low rate and are done in by the antibiotic at a low rate}
{We assume a Hill function PD and exponential decay of the antibiotic with periodic input for the PK}

METHOD EULER
STARTTIME = 0
STOPTIME=336
DT = 0.0001
DTOUT =0.50
init Su=1e6  {Initial density of sensitive bacteria U}
init Sp =1e5  {Initial density of sensitive bacteria P}
init Ru=0  {Initial density resistant bacteria U}
init Rp=0 {Initial density resistant bacteria P}
init Au=10 {initial concentration of the antibiotic U}
init Ap=10 {initial concentration of the antibiotic P}

{Note in runs made in Levin and Rozen, Au=Ap=A}
init TX=0 {Time indicator}

{Parameters}
vsu = 1.0 {Max growth rate sensitive U}
vsp = 0.01 {Max growth rate sensitive P}
vru = 0.9 {Max growth rate resistant U}
vrp = 0.009 {Max rowth rate resistant P}
fsu= -10 {Minimum growth rate sensitive U}
fsp=-0.01 {minimum growth rate sensitive P}
micu = 1. {MIC in U}
micp =1 {MIC in P}
{We are assuming the resistant bacteria are unaffected by the antibiotic}
ku =1e10 {Saturation of U}
kp=1e6 {Saturation of P}
k=1 {Hill Coefficient}
x = 1e-3 {Rate of migration U to P}
y = 1e-3 {Rate of migration P to U}
ycz =1e-3 {Rate of migration P to U when T>decay}
amaxu = 10 {Amount of the antibiotic added to U}
amaxp = 10 {Amount of the antibiotic added to P}
decay =120 {Decay in protected population starts at this time}
dpro = 0
du =.5 {Antibiotic decay rate U}
dp= .5 {Antibiotic decay rate P}
```
\[
\begin{align*}
\frac{d}{dt} (Au) &= -du\cdot Au + ADDu \quad \text{(change in the concentration of the antibiotic in U)} \\
\frac{d}{dt} (Ap) &= -dp\cdot Ap + ADDp \quad \text{(change in the concentration of the antibiotic in U)} \\
pu &= \frac{((vsu-fsu)\cdot(Au/micu)^k)}{((Au/micu)^k - fsu/vsu)} \\
pp &= \frac{((vsp-fsp)\cdot(Ap/micp)^k)}{((Ap/micp)^k - fsp/vsp)} \\

Nu &= Su + Ru \\
Np &= Sp + Rp \\
\frac{d}{dt} (Su) &= ((vsu - pu)\cdot Su - x\cdot Su + ykk\cdot Sp)\cdot(1 - Nu/ku) - GU/volU \\
\frac{d}{dt} (Ru) &= (vru\cdot Ru - x\cdot Ru + ykk\cdot Rp)\cdot(1 - Nu/ku) + GU/volU \\
\frac{d}{dt} (Sp) &= ((vsp - pp)\cdot Sp + x\cdot Su - ykk\cdot Sp)\cdot(1 - Np/kp) - GP/volP - Sp\cdot DK \\
\frac{d}{dt} (Rp) &= (vsp\cdot Rp + x\cdot Ru - ykk\cdot Rp)\cdot(1 - Np/kp) + GP/volP - Rp\cdot DK \\
\frac{d}{dt} (TX) &= 1 \\
\text{dose} &= 10 \quad \text{(Dosing interval Lambda)} \\
\text{init TT} &= 0 \\
\frac{d}{dt} (TT) &= 1 - GT^2 \\
ADDu &= \text{IF TT > dose THEN PULSE}(amaxu\cdot2, \text{TIME}, 21) \text{ ELSE 0} \\
ADDp &= \text{IF TT > dose THEN PULSE}(amaxu\cdot2, \text{TIME}, 21) \text{ ELSE 0} \\
GT &= \text{IF TT > dose THEN PULSE}(dose, \text{TIME}, 21) \text{ ELSE 0} \\

\{\text{Mutation routine}\} \\
volU &= 10 \quad \text{(Volume of U)} \\
volP &= 10 \quad \text{(Volume of P)} \\
u &= 0 \quad \text{(Mutation rate to resistance)} \\
bsu &= Su\cdot vsu\cdot DT\cdot u\cdot volU \\
rm &= \text{RANDOM} \ (0, \ 1) \\
GU &= \text{IF rm < bsu THEN PULSE \ (1,TIME,21) ELSE 0} \\
bsp &= Sp\cdot vsp\cdot DT\cdot u\cdot volP \\
rr &= \text{RANDOM} \ (0, \ 1) \\
GP &= \text{IF rr < bsp THEN PULSE \ (1,TIME,21) ELSE 0} \\

\{\text{Decay of protected habitat}\} \\
DK &= \text{IF TX < decay THEN PULSE \ (0,TIME,21) ELSE dpro} \\
ykk &= \text{IF TX < decay THEN PULSE \ (y,TIME,21) ELSE yzz}
\end{align*}
\]