Quorum Sensing Model

Quorum sensing is a cell-cell communication that detects and responds to cell population density by gene regulation. In our model, we aim to simulate the impact of the insertion of the two genes aiiA and ytnP on quorum sensing.

Formulas:

$$\frac{dR}{dt} = V_R \frac{P}{K_R + P} - k_R R + R_0, \tag{20}$$

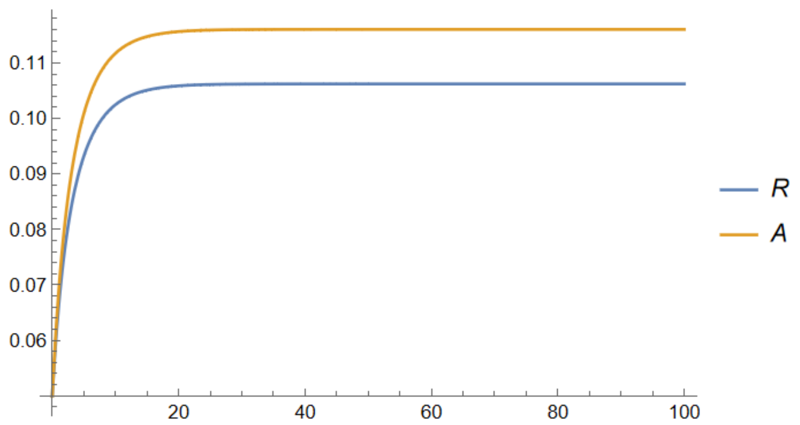
$$\frac{dA}{dt} = V_A \frac{P}{K_A + P} + A_0 - d(\rho) A, \tag{21}$$

where $P = \frac{k_{RA} R A}{k_P}$ and $d(\rho) = k_A + \frac{\delta}{\rho}\left(\frac{k_E(1-\rho)}{\delta + k_E(1-\rho)}\right)$.

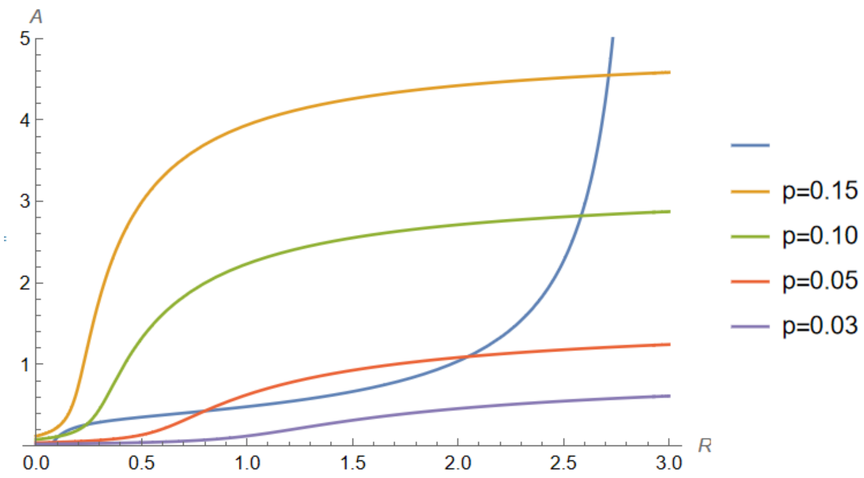
(Reference: Dockery JD, Keener JP. A mathematical model for quorum sensing in Pseudomonas aeruginosa. Bull Math Biol. 2001 Jan;63(1):95-116. doi: 10.1006/bulm.2000.0205. PMID: 11146885.)

Among the formulas above, A is 3-oxo-C12-HSL as an autoinducer, R is the LasR protein, P is the complex of A and R, ρ is the cell density, that is, cell volume/space volume.

Next, use the default parameters to solve the above system of equations, which results in the following picture:



We want to check how many equilibrium points are in the ode system. The picture below shows the stable line for this system, where the blue line indicates the stable line for equation (20), and the others indicate the stable line for equation (21) corresponds to different ρ. For example, the yellow line has only one common point with the blue one, which means that when ρ=0.15, there is only one equilibrium point in the ode system. There is only one equilibrium point when ρ is small. As ρ increases, the number of equilibrium points gradually becomes two, three, two, and eventually one.



Our purpose is to simulate the impact of the insertion of the two genes aiiA and ytnP on quorum sensing. The function of these two genes is to degrade AHLs, corresponds to the variable A mentioned above. Inserting these two genes is equivalent to increasing kA.

Purpose of our model: **Taking kA as a variable, try to deduce the relationship between the ρ and kA to reach the critical condition of a single equilibrium point.**

Model Construction:

With the equilibrium condition, we have $\frac{dR}{dt} = 0$, $\frac{dA}{dt} = 0$. Without loss of generality, assume that $\frac{k_{RA}}{k_P} = 1$. Then by (20), (21), we have

$$\frac{V_R R A}{K_R + R A} - k_R R + R_0 = 0;$$

$$\frac{V_A R A}{K_A + R A} - k_A A - \frac{\delta k_E (1-\rho)}{\rho\delta + \rho k_E (1-\rho)} A + A_0 = 0.$$

By elementary transformations, obtain:

$$-k_R A R^2 + (V_R A + R_0 A - K_R k_R) R + R_0 K_R = 0;$$

$$R = \frac{-A_0 K_A + K_A d(\rho) A}{V_A A + A A_0 - A^2 d(\rho)}.\ \text{where } d(\rho) = k_A + \frac{\delta k_E (1-\rho)}{\rho\delta + \rho k_E (1-\rho)}.$$

Substitute the second into the first equation, we get a 3 order polynomial of A as follow:

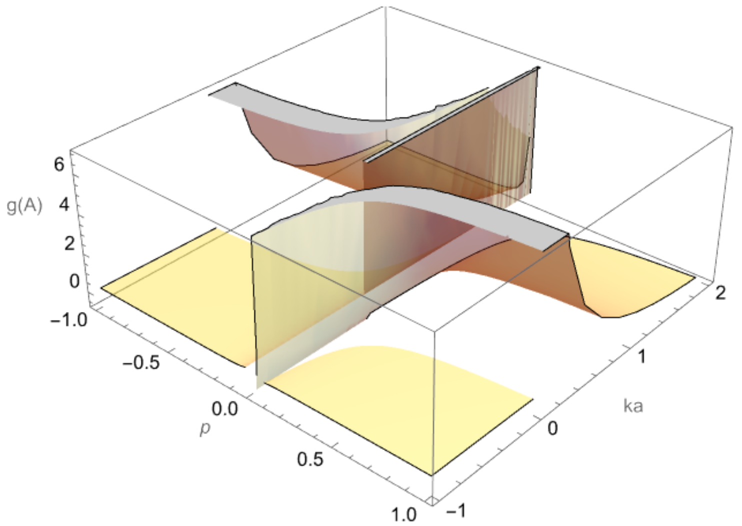
$$g(A) := \left(-d(\rho)^2 (V_R K_A + R_0 K_A + R_0 K_R)\right) A^3 + \left(d(\rho)^2 \left(-k_R K_A^2 + K_R K_A k_R\right) + d(\rho) (V_A V_R K_A + V_A R_0 K_A + A_0 V_R K_A + A_0 R_0 K_A + V_R K_A A_0 - 2 R_0 K_R V_A - 2 R_0 A_0 K_R)\right) A^2 + \left(d(\rho) (2 k_R A_0 K_A^2 - V_A K_R k_R - A_0 k_R K_R K_A - K_R k_R A_0 K_A) - V_A V_R K_A A_0 - V_R K_A A_0^2 + R_0 K_R V_A^2 + A_0^2 R_0 K_R + 2 V_A A_0 R_0 K_R\right) A + \left(-k_R A_0^2 K_A^2 + V_A K_R k_R A_0 K_A + k_R A_0^2 K_R K_A\right) = 0.$$

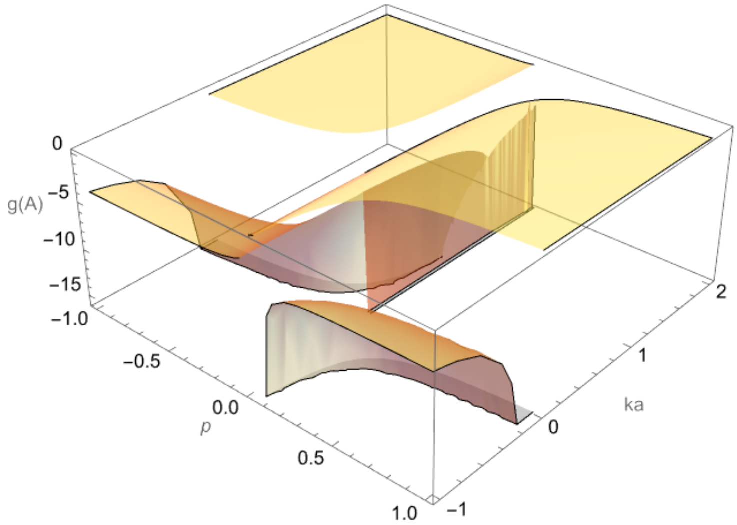
To find the relationship between the critical ρ and kA at a single equilibrium point, we are looking for the critical condition of only one real solution of g(A) greater than 0.

Solution:

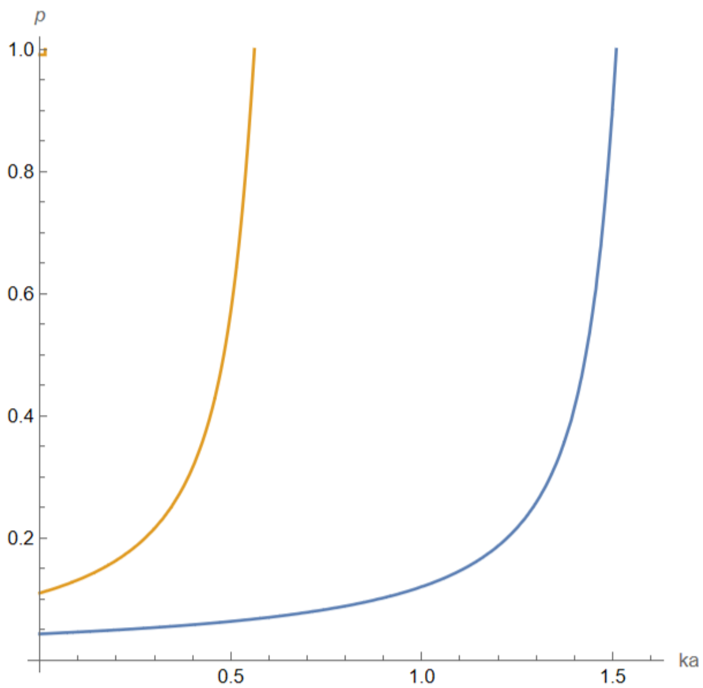
As g(A) is a cubic polynomial of A, according to the characteristics of the cubic equation, it is a function that is symmetric about the center of a certain point. Since the constant before the highest order is negative, this equation is negative infinity at positive infinity point and positive infinity at negative infinity point. What's more, g (0)=0.07>0. Also, the abscissa of the center point of the function is greater than zero. Let $g'(A) := a x^2 + b x + c$, then the abscissa of local maximum and minimum of g(a) are $\frac{-b+\left(b^2-4\,\mathrm{ac}\right)^{0.5}}{2\,a}$, $\frac{-b-\left(b^2-4\,\mathrm{ac}\right)^{0.5}}{2\,a}$; so in this way the critical condition is

$g\left(\frac{-b+\left(b^2-4\,\mathrm{ac}\right)^{0.5}}{2\,a}\right)=0$, or $g\left(\frac{-b-\left(b^2-4\,\mathrm{ac}\right)^{0.5}}{2\,a}\right)=0$. To solve these two critical conditions, we plot $g\left(\frac{-b+\left(b^2-4\,\mathrm{ac}\right)^{0.5}}{2\,a}\right)=0$ and $g\left(\frac{-b-\left(b^2-4\,\mathrm{ac}\right)^{0.5}}{2\,a}\right)=0$ with respect to ρ and ka as following:





By computing the contour of 0 on the two surfaces, the relationship between the critical ρ and kA to reach a single equilibrium point is deduced as shown in the figure below:



Conclusion:

As kA increases, *ρ* increases significantly.
Therefore, after the insertion of aiiA and ytnP, as kA increases, *ρ* also increases significantly. P. aeruginosa requires higher densities to activate the quorum sensing mechanism. (The quorum sensing effect also disappears faster when the density of P. aeruginosa decreases)

Coding Material:

In[ ]:=

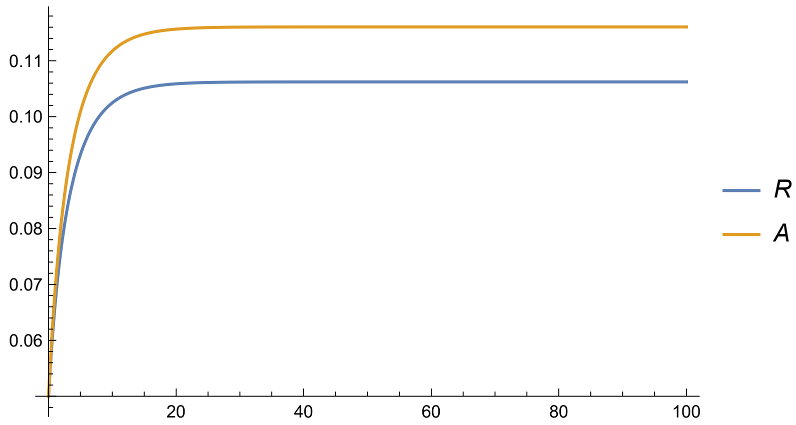
```
(*Set up parameters*)
Vr = 2;
Va = 2;
Kr = 1;
Ka = 1;
R0 = 0.05;
A0 = 0.05;
sigma = 0.2;
ke = 0.1;
kr = 0.7;
ka = 0.02;
kra = 1;
kp = 1;
end = 100;
p = 0.1;
(*Solve the ODE system, use the default parameter*)
solution = NDSolve[
```

$$\left\{R'[t] == Vr * \frac{\frac{kra*R[t]*A[t]}{kp}}{Kr + \frac{kra*R[t]*A[t]}{kp}} - kr * R[t] + R0,\right.$$

$$A'[t] == Va * \frac{\frac{kra*R[t]*A[t]}{kp}}{Ka + \frac{kra*R[t]*A[t]}{kp}} + A0 - A[t] * \left(ka + \frac{sigma}{p} * \frac{ke * (1 - p)}{sigma + ke * (1 - p)}\right),$$

```
    R[0] == R0, A[0] == A0}, {A, R}, {t, 0, end}
  ];
Plot[Evaluate[{R[t], A[t]} /. solution],
 {t, 0, end}, PlotRange → All, PlotLegends → {R, A}]
```

Out[ ]=



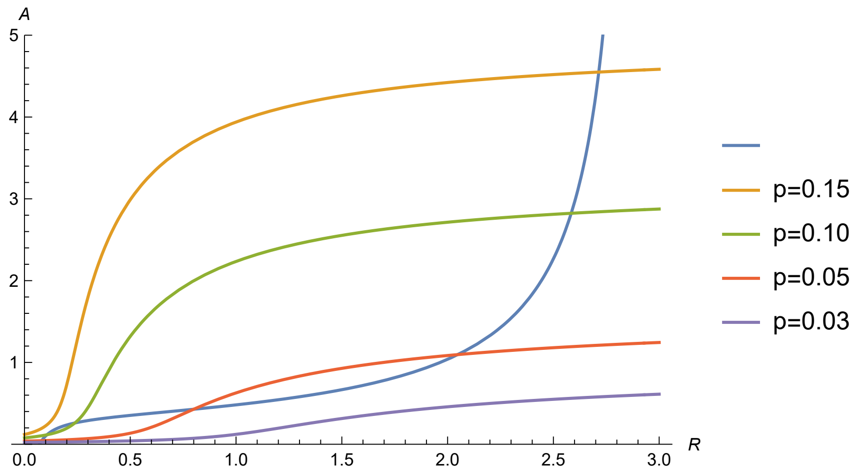
In[ ]:=
```
sol1 = Solve[
    Vr * (kra*R*A/kp)/(Kr + kra*R*A/kp) - kr * R + R0 == 0 , A
  ];

sol[p_] := Solve[Va * (kra*R*A/kp)/(Ka + kra*R*A/kp) + A0 - A * (ka + sigma/p * (ke * (1 - p))/(sigma + ke * (1 - p))) == 0 , A];

Plot[{Evaluate[A /. sol1], Evaluate[A /. sol[0.15][[2]]], Evaluate[A /. sol[0.1][[2]]],
   Evaluate[A /. sol[0.05][[2]]], Evaluate[A /. sol[0.03][[2]]]},
  {R, 0, 3}, PlotRange → {0, 5}, AxesLabel → {R, A},
  PlotLegends → {"", "p=0.15", "p=0.10", "p=0.05", "p=0.03"}]
```

Solve: Solve was unable to solve the system with inexact coefficients. The answer was obtained by solving a corresponding exact system and numericizing the result.

Out[ ]=



In[ ]:=
```
(*Find the critical relation when there is
 only one real solution beyond zero in the equation*)
ClearAll["Global`*"]

(*Set up parameters*)
Vr = 2;
Va = 2;
Kr = 1;
Ka = 1;
ke = 0.1;
kr = 0.7;
delta = 0.2;
A0 = 0.05;
R0 = 0.05;
```

$$f[p\_] := ka + \frac{delta\ ke\ (1-p)}{p\ (delta + ke\ (1-p))};$$

```
(*Obtain the equation*)
```

$$equation[A\_, p\_] = -f[p]^2\ (Vr\ Ka + R0\ Ka + R0\ Kr)\ A^3 + \left(f[p]^2\ \left(-kr\ Ka^2 + Kr\ Ka\ kr\right) + f[p]\ (Va\ Vr\ Ka + Va\ R0\ Ka + A0\ Vr\ Ka + A0\ R0\ Ka + Vr\ Ka\ A0 - 2\ R0\ Kr\ Va - 2\ R0\ Kr\ A0)\right) A^2 + \left(f[p]\ \left(2\ kr\ A0\ Ka^2 - Va\ Kr\ kr - A0\ Kr\ Ka\ kr - Kr\ kr\ A0\ Ka\right) - Va\ Vr\ Ka\ A0 - Vr\ Ka\ A0^2 + R0\ Va^2\ Kr + A0^2\ R0\ Kr + 2\ Va\ A0\ R0\ Kr\right) A + \left(-kr\ A0^2\ Ka^2 + Va\ Kr\ kr\ A0\ Ka + kr\ A0^2\ Kr\ Ka\right)$$

Out[ ]=

$$0.07 + A\left(0.005125 - 1.4\left(ka + \frac{0.02\ (1-p)}{(0.2 + 0.1\ (1-p))\ p}\right)\right) + A^2\left(0. + 4.0975\left(ka + \frac{0.02\ (1-p)}{(0.2 + 0.1\ (1-p))\ p}\right)\right) - 2.1\ A^3\left(ka + \frac{0.02\ (1-p)}{(0.2 + 0.1\ (1-p))\ p}\right)^2$$

In[ ]:=

$$\partial_A equation[A, p]$$

Out[ ]=

$$0.005125 + 2\ A\left(0. + 4.0975\left(ka + \frac{0.02\ (1-p)}{(0.2 + 0.1\ (1-p))\ p}\right)\right) - 1.4\left(ka + \frac{0.02\ (1-p)}{(0.2 + 0.1\ (1-p))\ p}\right) - 6.3\ A^2\left(ka + \frac{0.02\ (1-p)}{(0.2 + 0.1\ (1-p))\ p}\right)^2$$

In[ ]:=

```
a = -6.3 (ka + 0.02 (1 - p) / ((0.2 + 0.1 (1 - p)) p))^2;
b = 2 (4.0975 (ka + 0.02 (1 - p) / ((0.2 + 0.1 (1 - p)) p)));
c = 0.005125 - 1.4 (ka + 0.02 (1 - p) / ((0.2 + 0.1 (1 - p)) p));
characteristic = b^2 - 4 a c;
centralLine = -b / (2 a)
Reduce[{centralLine < 0, ka > 0, 1 ≥ p ≥ 0}, p, Reals]
```

$$a = -6.3 \left(ka + \frac{0.02\,(1-p)}{(0.2+0.1\,(1-p))\,p}\right)^2;$$

$$b = 2 \left(4.0975 \left(ka + \frac{0.02\,(1-p)}{(0.2+0.1\,(1-p))\,p}\right)\right);$$

$$c = 0.005125 - 1.4 \left(ka + \frac{0.02\,(1-p)}{(0.2+0.1\,(1-p))\,p}\right);$$

$$\text{characteristic} = b^2 - 4\,a\,c;$$

$$\text{centralLine} = \frac{-b}{2\,a}$$

Out[ ]=

$$\frac{0.650397}{ka + \frac{0.02\,(1-p)}{(0.2+0.1\,(1-p))\,p}}$$

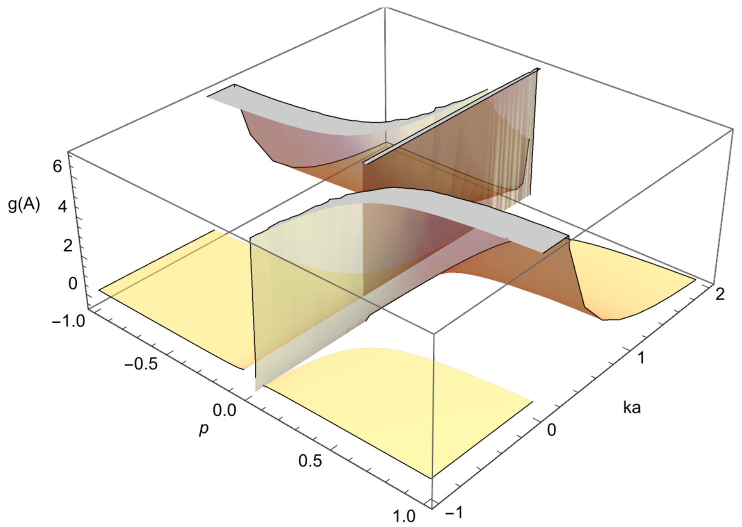
Reduce: Reduce was unable to solve the system with inexact coefficients. The answer was obtained by solving a corresponding exact system and numericizing the result.

Out[ ]=

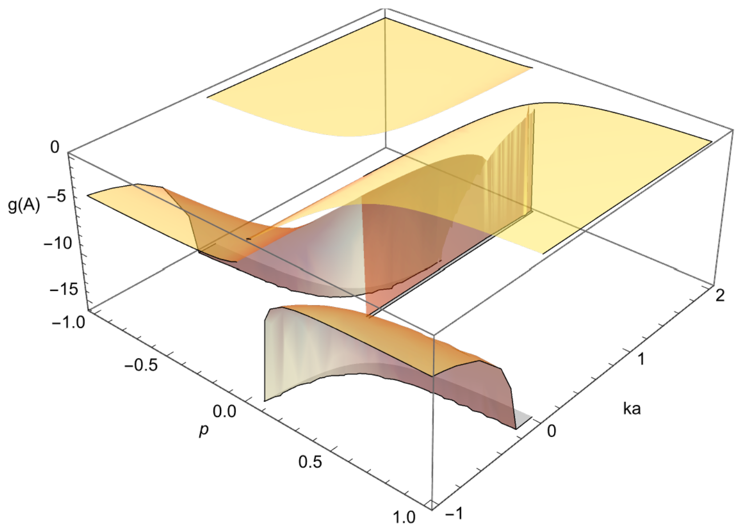
```
False
```

In[ ]:=
```
point1 = (-b - Sqrt[characteristic]) / (2 a);
point2 = (-b + Sqrt[characteristic]) / (2 a);
Plot3D[equation[point1, p], {p, -1, 1}, {ka, -1, 2}, AxesLabel → {p, ka, "g(A)"},
 PlotStyle → Directive[Opacity[.5], Orange, Specularity[White]], Mesh → None]
Plot3D[equation[point2, p], {p, -1, 1}, {ka, -1, 2}, AxesLabel → {p, ka, "g(A)"},
 PlotStyle → Directive[Opacity[.5], Orange, Specularity[White]], Mesh → None]
```

Out[ ]=



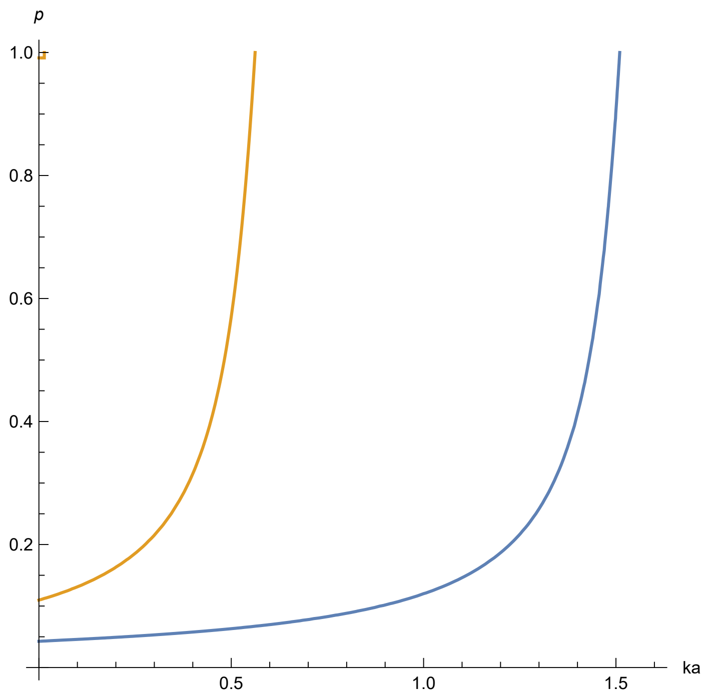
Out[ ]=



In[ ]:=

```
ContourPlot[{equation[point1, p] == 0, equation[point2, p] == 0},
  {ka, 0, 1.6}, {p, 0, 1}, Frame → False, Axes → True, AxesLabel → {ka, p}]
```

Out[ ]=



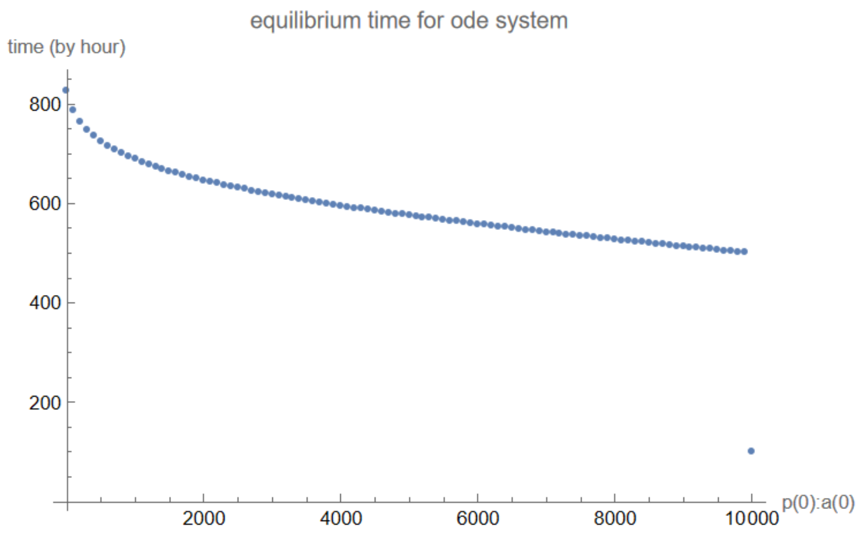
A Population Growth Model for P. aeruginosa

Purpose of the Model: Study the impact of the relative relationships of different initial variables on the growth curve. It comprises four independent parts that illustrate the pairwise relations within variables.
Basic Assumptions: The phage, wild-type P. aeruginosa, and phage-infected P. aeruginosa are uniformly distributed in space.

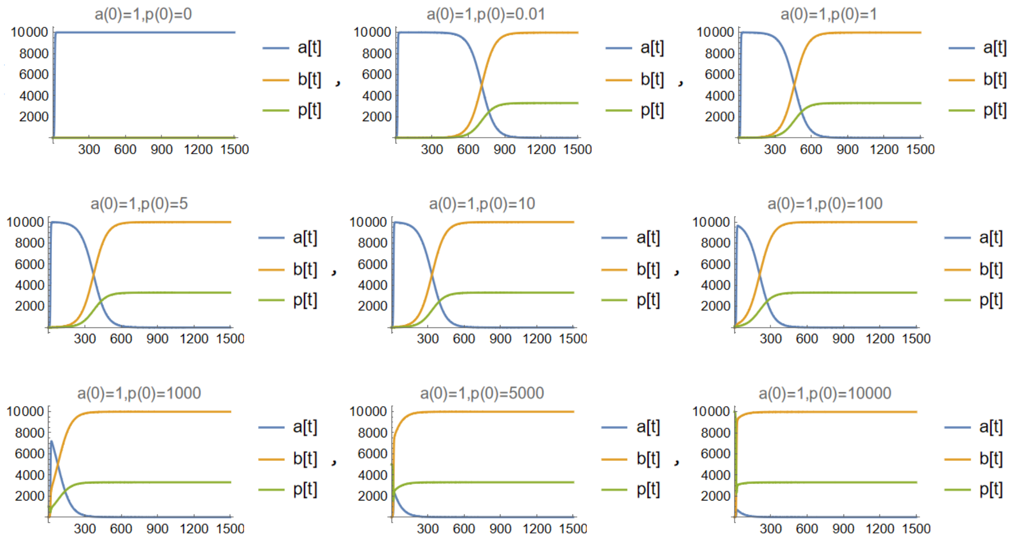
Task One: Explore the impact of the ratio p(0):a(0) on the time it takes for the growth curve to reach steady state.

Here, the concentration of wild-type P. aeruginosa changes with time as a(t), the concentration of phage-infected P. aeruginosa changes with time as b(t), the concentration of phage changes with time as p(t), and the environment accommodates is K, with a default value 10000.

Conclusions for task one: No matter how the ratio p(0):a(0) is selected, after a long enough time, the system will eventually reach its steady state, and a(t) tends to 0, p(t) tends to the environmental capacity K. This proves that mild phage therapy is theoretically feasible to treat P. aeruginosa in condition of different initial ratio p(0):a(0). In addition, the relationship between the time needed for the system to reach the steady state and p(0):a(0) is as follows, which shows that the larger the ratio of p(0):a(0), the lower the time to reach the steady state.



Here are also profiles for the growth curves when the ratio p(0):a(0) is equal to 0, 0.01, 1, 5, 10, 100, 1000, 5000, 10000, respectively to help better understand how the population changing over time:



Coding Material:

In[1]:=

```
(*Clear all to prevent chaotic in computation*)
ClearAll["Global`*"]
```

In[2]:=

```
(*paramerters setup*)
end = 1500; (*end time of ode system*)
ra = 0.5861175448479;
rb = 0.5861175448479;
K = 10 000;
u = 1 - 0.0769;
n = 1;
s = K / 3;
beta = 1;
alpha = 248;
v = 0.001;
```

In[12]:=
```
(*Plot the growth curves and compute the time required for the system to stable*)
solution[x_] := NDSolve[
  {a'[t] == ra * a[t] * ((K - a[t] - b[t])/K) - a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))),
   b'[t] == rb * b[t] * ((K - a[t] - b[t])/K) + a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))) - v * b[t],
   p'[t] == v * b[t] * alpha - beta * p[t] * ((a[t] + b[t])^n/(s^n + (a[t] + b[t])^n)), a[0] == 1,
   b[0] == 0, p[0] == x, WhenEvent[Abs[a[t]] < 0.1, Print[StringTemplate[
       "The equilibrium is `` for p(0)= ``"][t, x]]]}, {a, b, p}, {t, 0, end}
  ];
Table[Plot[Evaluate[{a[t], b[t], p[t]} /. solution[x]],
  {t, 0, end}, PlotLegends → {"a[t]", "b[t]", "p[t]"},
  Ticks → {{0, end / 5, end / 5 * 2, end / 5 * 3, end / 5 * 4, end}, Automatic},
  PlotLabel → StringTemplate["a(0)=1,p(0)=``"][x], PlotRange → All],
 {x, {0, 0.01, 1, 5, 10, 100, 1000, 5000, 10000}}]
```

```
The equilibrium is 1327.91 for p(0)= 0.01
The equilibrium is 1077.22 for p(0)= 1
The equilibrium is 989.576 for p(0)= 5
The equilibrium is 951.809 for p(0)= 10
The equilibrium is 825.846 for p(0)= 100
The equilibrium is 694.236 for p(0)= 1000
The equilibrium is 577.196 for p(0)= 5000
The equilibrium is 500.624 for p(0)= 10000
```

Out[13]=

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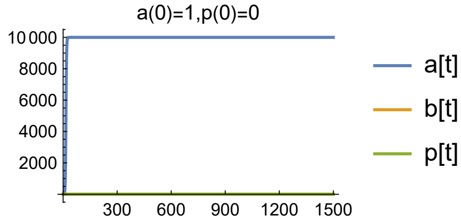

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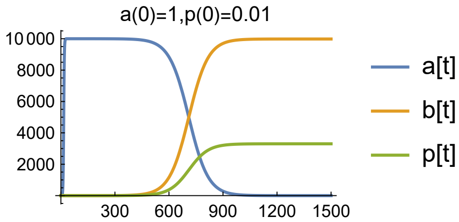

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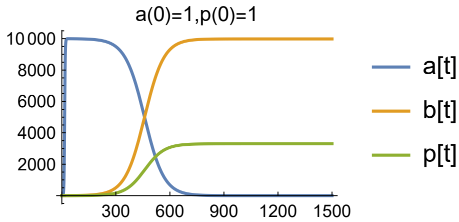

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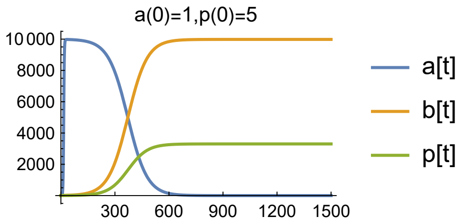

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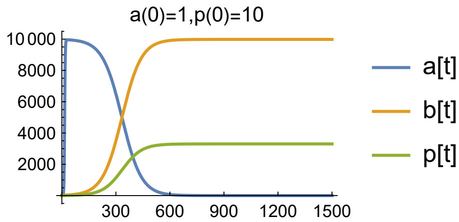

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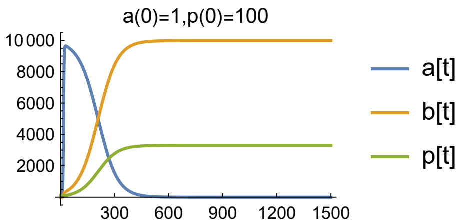

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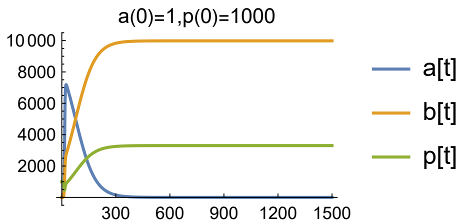

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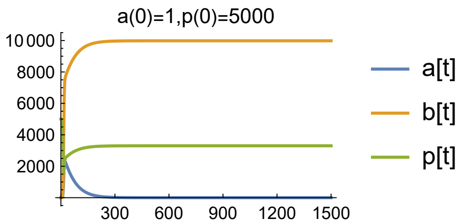

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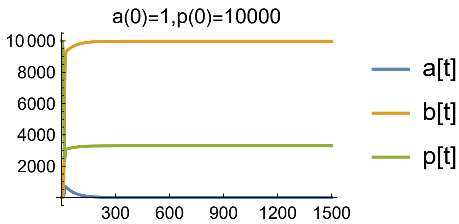


}

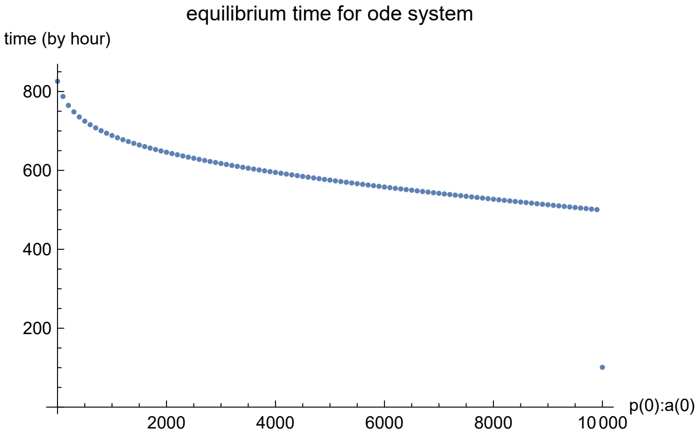
In[14]:=

```
equiTime = Array[# &, 101];
```

In[15]:=

```
Table[NDSolve[
  {a'[t] == ra * a[t] * ((K - a[t] - b[t])/K) - a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))),
   b'[t] == rb * b[t] * ((K - a[t] - b[t])/K) + a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))) - v * b[t],
   p'[t] == v * b[t] * alpha - beta * p[t] * ((a[t] + b[t])^n/(s^n + (a[t] + b[t])^n)), a[0] == 1, b[0] == 0,
   p[0] == x, WhenEvent[Abs[a[t]] < 0.1, equiTime[[x / 100]] = t]}, {a, b, p}, {t, 0, end}
 ], {x, Array[# &, 101, {0, 10000}]}];
ListPlot[Table[{x * 100 - 100, equiTime[[x]]}, {x, 1, 101}],
 PlotLabel → "equilibrium time for ode system",
 AxesLabel → {"p(0):a(0)", "time (by hour)"}]
```

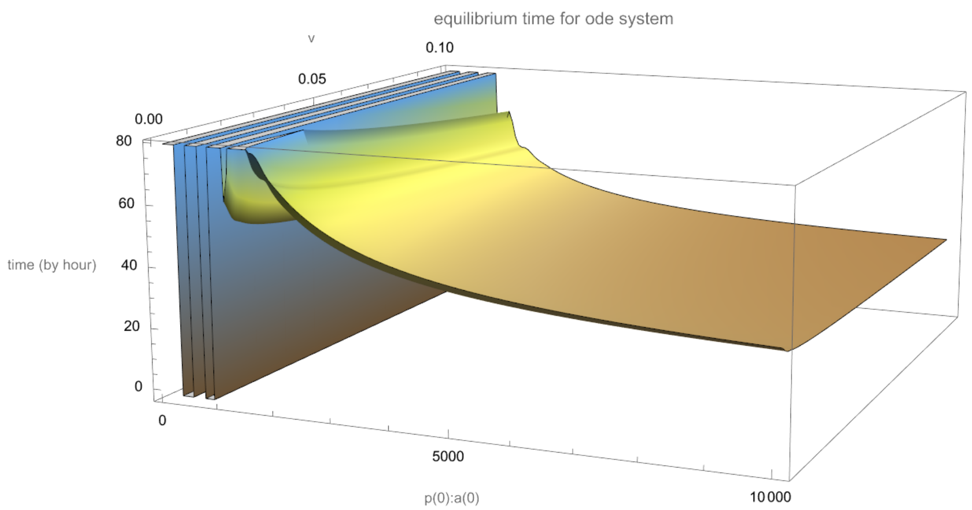
Out[16]=



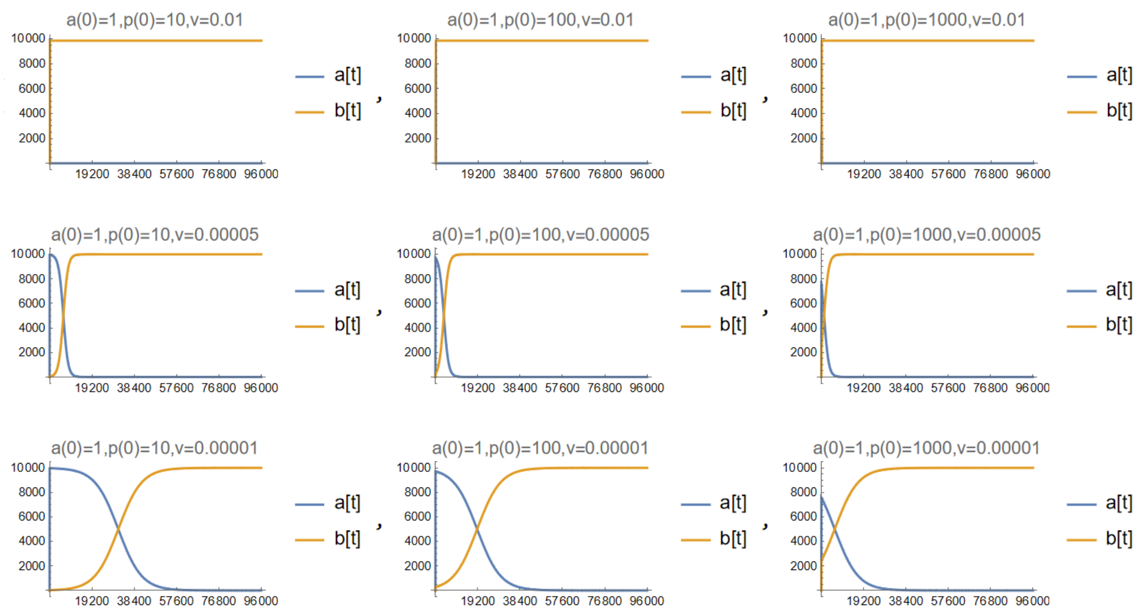
Task Two: Explore the impact of the selection of v and p(0):a(0) on the time needed for the growth curves reach steady state.

Recall that v is the lysis rate of lysogenic bacteria, the value range is $10^{-5} \sim 10^{-2}\ h^{-1}$.

Conclusions for task two: Within the reference range of v, after a long enough time, the system will eventually reach its steady state, and a(t) tends to 0, p(t) tends to the environmental capacity K. This proves that mild phage therapy is theoretically feasible to treat P. aeruginosa in the condition that v is in its reference range. In addition, the relationship between the time needed for the system to reach the steady state and p(0):a(0), v is as shown in the following picture, which indicates that generally, when v remains unchanged, the larger the ratio of p(0):a(0), the lower the time to reach the steady state; when p(0):a(0) remains unchanged, the larger v induces the lower time to reach the steady state. Note that when p(0):a(0)<2000, there are tremendous vibrations within the computation, so the equilibrium time in this region is non-convincing.



In addition, here are also profiles for the growth curves when the ratio p(0):a(0) is equal to 10, 100, 1000; v is equal to 0.01, 0.00005, 0.00001:

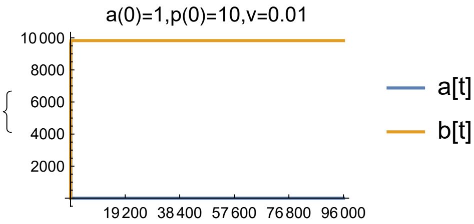


Coding Material:

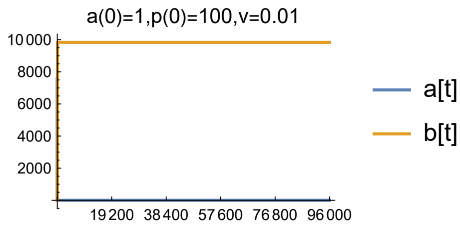
In[17]:=
```
end = 96 000;
solution[v_, x_] := NDSolve[
  {a'[t] == ra * a[t] * ((K - a[t] - b[t])/K) - a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))),
   b'[t] == rb * b[t] * ((K - a[t] - b[t])/K) + a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))) - v * b[t],
   p'[t] == v * b[t] * alpha - beta * p[t] * ((a[t] + b[t])^n/(s^n + (a[t] + b[t])^n)),
   a[0] == 1, b[0] == 0, p[0] == x}, {a, b, p}, {t, 0, end}
  ];
Table[Plot[Evaluate[{a[t], b[t]} /. solution[v, x]],
   {t, 0, end}, PlotLegends → {"a[t]", "b[t]"},
   PlotLabel → StringTemplate["a(0)=1,p(0)=``,v=``"][x, v],
   AxesStyle → Directive[ FontSize → 8],
   Ticks → {{0, end / 5, end / 5 * 2, end / 5 * 3, end / 5 * 4, end}, Automatic}],
  {v, {0.01, 0.00005, 0.00001}}, {x, {10, 100, 1000}}]
```

Out[19]=

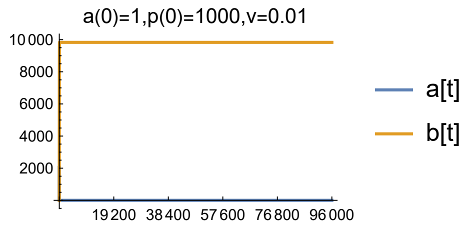
{{


a(0)=1,p(0)=10,v=0.01
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

,

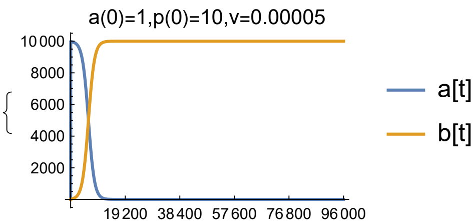

a(0)=1,p(0)=100,v=0.01
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

,

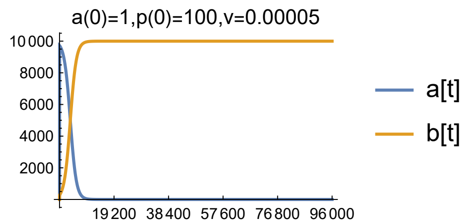

a(0)=1,p(0)=1000,v=0.01
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

},

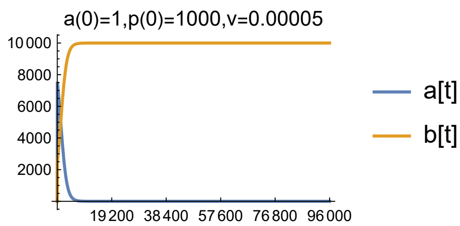
{


a(0)=1,p(0)=10,v=0.00005
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

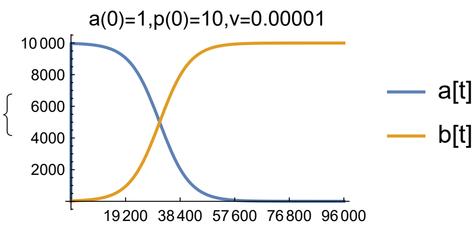
,


a(0)=1,p(0)=100,v=0.00005
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

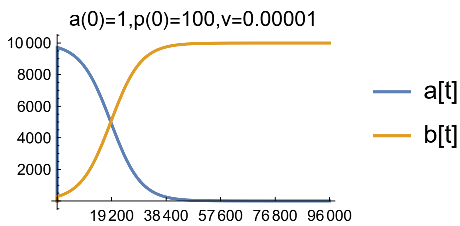
,


a(0)=1,p(0)=1000,v=0.00005
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

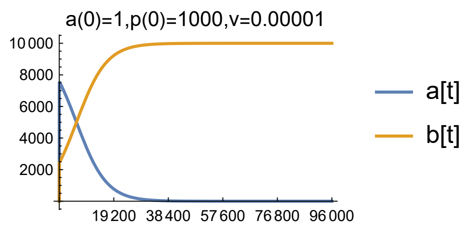
}, {


a(0)=1,p(0)=10,v=0.00001
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

,


a(0)=1,p(0)=100,v=0.00001
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

,


a(0)=1,p(0)=1000,v=0.00001
10 000
8000
6000
4000
2000
19 200 38 400 57 600 76 800 96 000
a[t]
b[t]

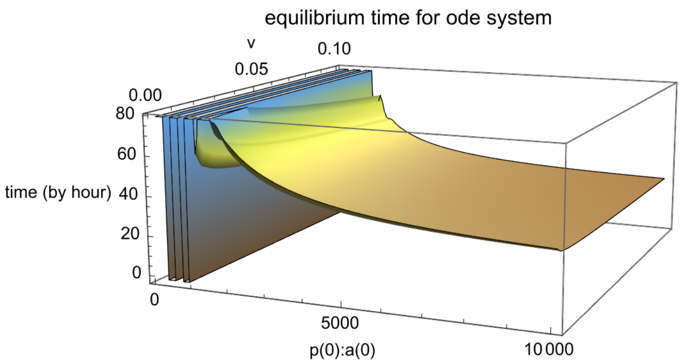
}}

In[77]:=
```
equiTime2 = Array[#1 &, {51, 51}];
apRatio = Array[# &, 51, {50, 10050}];
vArray = Array[# &, 51, {0.00001, 0.10001}];

Table[NDSolve[
  {a'[t] == ra * a[t] * ((K - a[t] - b[t])/K) - a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))),
   b'[t] == rb * b[t] * ((K - a[t] - b[t])/K) + a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))) - v * b[t],
   p'[t] == v * b[t] * alpha - beta * p[t] * ((a[t] + b[t])^n/(s^n + (a[t] + b[t])^n)),
   a[0] == 1, b[0] == 0, p[0] == x, WhenEvent[Abs[a[t]] < 0.1,
    equiTime2[[(x - 50) / 200 + 1]][[(v - 0.00001) / 0.002 + 1]] = t]}, {a, b, p}, {t, 0, end}
 ], {x, 50, 10050, 200}, {v, 0.00001, 0.10001, 0.002}];


data = Table[equiTime2[[(x - 50) / 200 + 1]][[(v - 0.00001) / 0.002 + 1]],
   {x, 50, 10050, 200}, {v, 0.00001, 0.10001, 0.002}];
S = ListPlot3D[data, PlotLabel → "equilibrium time for ode system",
  AxesLabel → {"p(0):a(0)", "v", "time (by hour)"}, Mesh → None, InterpolationOrder → 3,
  ColorFunction → "SouthwestColors", DataRange → {{50, 10050}, {10^-5, 0.1}}]
```

Out[82]=



Task Three: Explore the impact of alpha and the ratio p(0):a(0) selection on the time it takes for the growth curve to reach steady state.

Here alpha is the phage produced by lysis of unit bacteria, and the default value is 248.

Conclusions for task three: Ideally, as long as the value of alpha is large enough (greater than 12.6), a(t) will eventually tend to 0, and b(t) will ultimately grow to K; the default value of alpha is 248, which is much larger than the critical value of 12.6. As long as the alpha is regular, mild phage therapy is theoretically feasible to treat P. aeruginosa. When the alpha is large, an increase in alpha will decrease the time to reach stability. When alpha is near the critical value (which is equal to

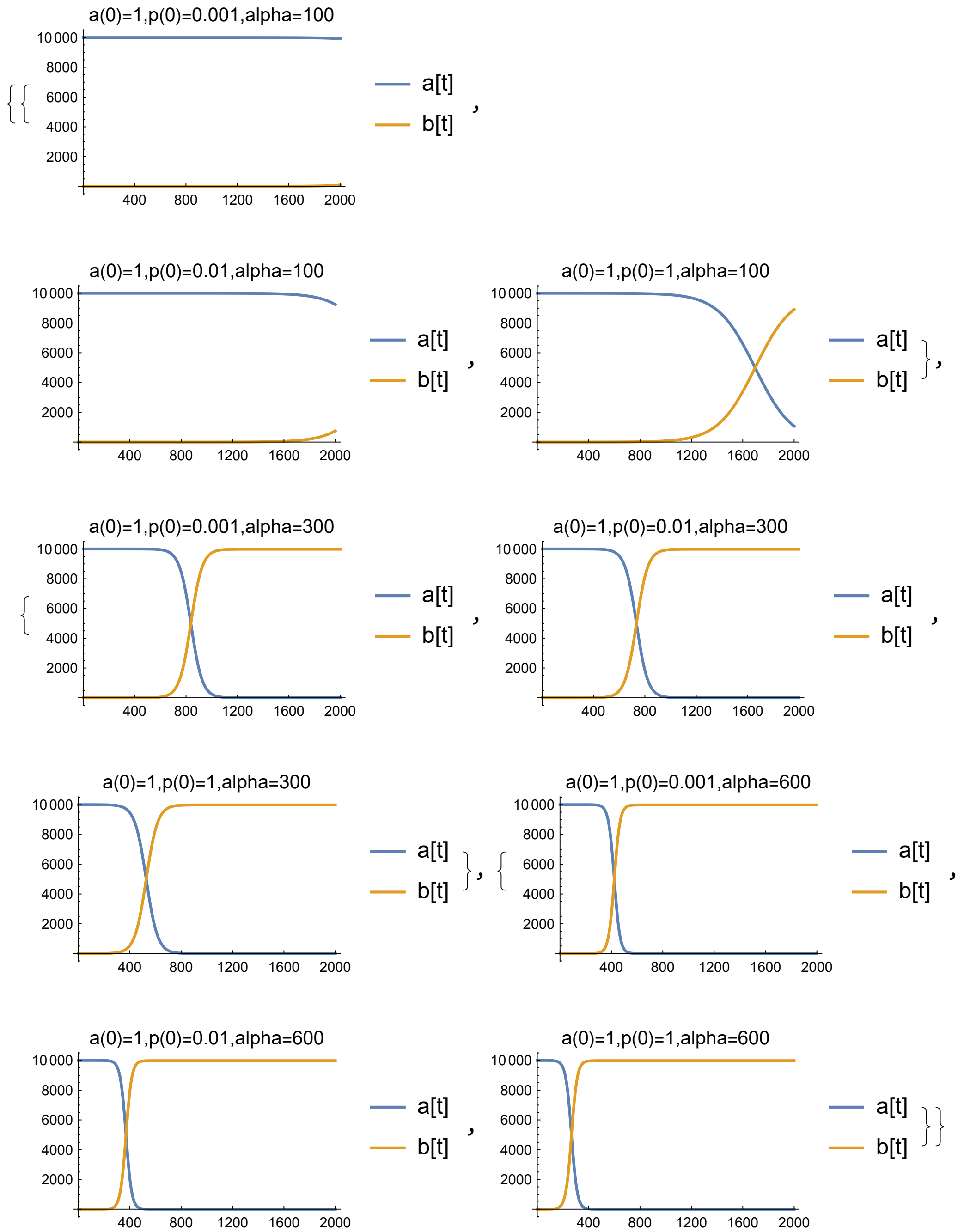
12.6), a(t) and b(t) will coexist stably.

Coding Material:

In[97]:=
```
end = 2000;
solution[alpha_, x_] := NDSolve[
  {a'[t] == ra * a[t] * ((K - a[t] - b[t])/K) - a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))),
   b'[t] == rb * b[t] * ((K - a[t] - b[t])/K) + a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1)/(s^n+(a[t]+b[t])^n)))) - v * b[t],
   p'[t] == v * b[t] * alpha - beta * p[t] * ((a[t] + b[t])^n/(s^n + (a[t] + b[t])^n)),
   a[0] == K, b[0] == 0, p[0] == x}, {a, b, p}, {t, 0, end}
  ];
Print["When alpha is relatively large (>12.6):"]
Table[Plot[Evaluate[{a[t], b[t]} /. solution[alpha, x]],
   {t, 0, end}, PlotLegends → {"a[t]", "b[t]"},
   PlotLabel → StringTemplate["a(0)=1,p(0)=``,alpha=``"][x, alpha],
   AxesStyle → Directive[FontSize → 8],
   Ticks → {{0, end / 5, end / 5 * 2, end / 5 * 3, end / 5 * 4, end}, Automatic}],
  {alpha, {100, 300, 600}}, {x, {0.001, 0.01, 1}}]
Print["When alpha is around critical value: "]
end = 100 000 000;
Table[Plot[Evaluate[{a[t], b[t]} /. solution[alpha, x]],
   {t, 0, end}, PlotLegends → {"a[t]", "b[t]"},
   PlotLabel → StringTemplate["a(0)=1,p(0)=``,alpha=``"][x, alpha],
   AxesStyle → Directive[FontSize → 8], Ticks → {{0, end / 2, end}, Automatic}],
  {alpha, {12.4, 12.5, 12.6}}, {x, {0.001, 0.01, 1}}]
```

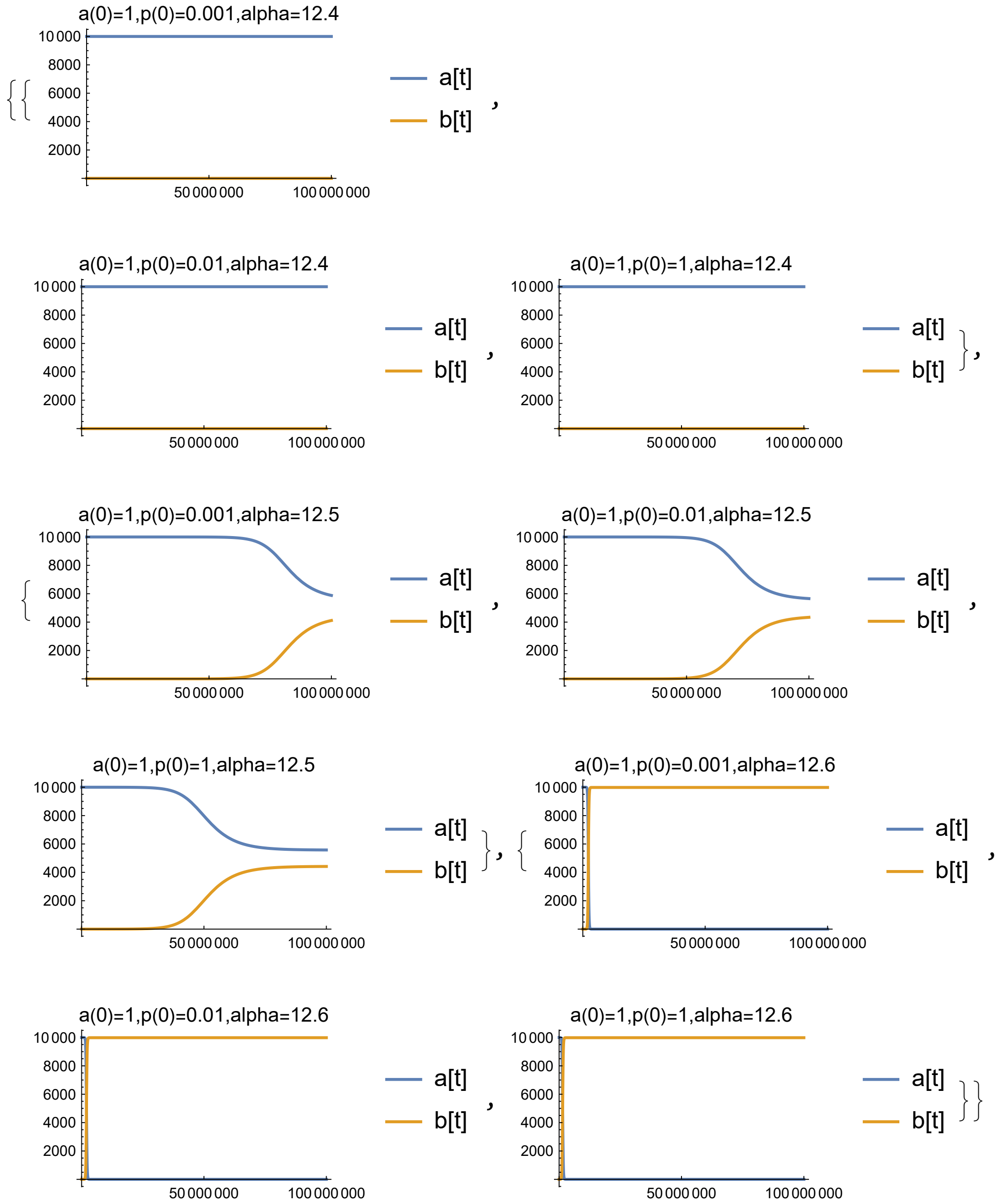
When alpha is relatively large (>12.6):

Out[100]=




```
When alpha is around critical value:
```

Out[103]=



Task Four: Explore the impact of the selection of u and p(0):a(0) on the time when the growth curve reaches steady state.

Here u is the probability of infection failure, and the default value is 1-0.0769=0.9231

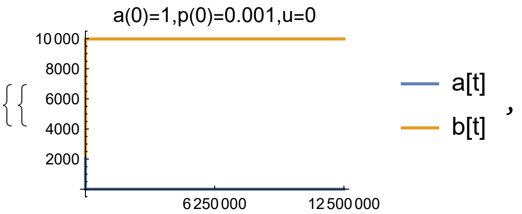
Conclusions for task four: Under default parameters, the critical value of u can be considered 0.996. When u is less than or equal to the critical value, the ideal state (which means that a(t) will eventually tend to 0, and b(t) will ultimately grow to K) can finally be reached, but the closer it is to the critical value, the longer it takes to reach the ideal state; when u is greater than the critical value, the ideal state cannot be reached. In the literature, the reference value of u is 0.9231 (less than 0.996), which means that mild phage therapy is theoretically feasible to treat P. aeruginosa in a regular u.

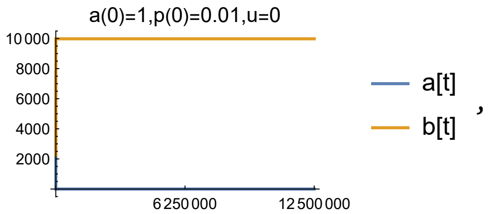
Coding Material:

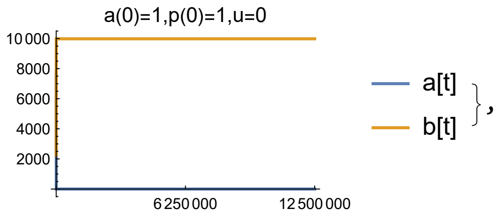
In[104]:=

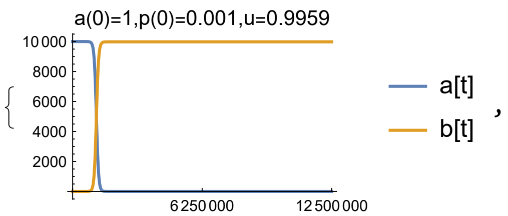
```
end = 12 500 000;
solution[u_, x_] := NDSolve[
   {a'[t] == ra * a[t] * ((K - a[t] - b[t]) / K) - a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1) / (s^n + (a[t]+b[t])^n)))),
    b'[t] == rb * b[t] * ((K - a[t] - b[t]) / K) + a[t] * (1 - u^(beta*p[t]*((a[t]+b[t])^(n-1) / (s^n + (a[t]+b[t])^n)))) - v * b[t],
    p'[t] == v * b[t] * alpha - beta * p[t] * ((a[t] + b[t])^n / (s^n + (a[t] + b[t])^n)),
    a[0] == K, b[0] == 0, p[0] == x}, {a, b, p}, {t, 0, end}
  ];
Table[Plot[Evaluate[{a[t], b[t]} /. solution[u, x]],
  {t, 0, end}, PlotLegends → {"a[t]", "b[t]"},
  PlotLabel → StringTemplate["a(0)=1,p(0)=``,u=``"][x, u],
  AxesStyle → Directive[FontSize → 8], Ticks → {{0, end / 2, end}, Automatic}],
 {u, {0, 0.9959, 0.99595, 0.996, 1}}, {x, {0.001, 0.01, 1}}]
```

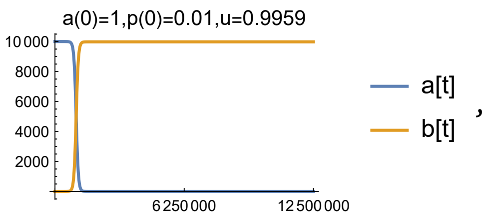
Out[106]=

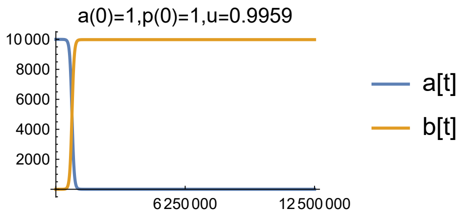


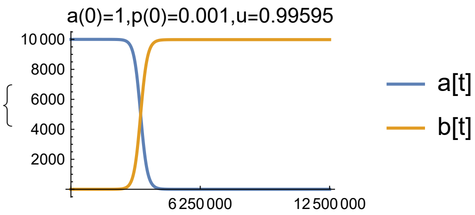


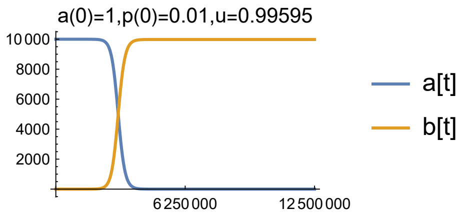


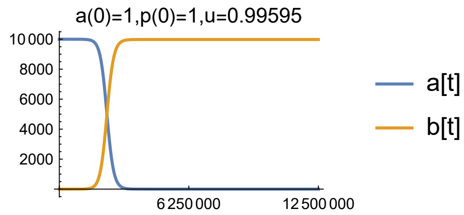


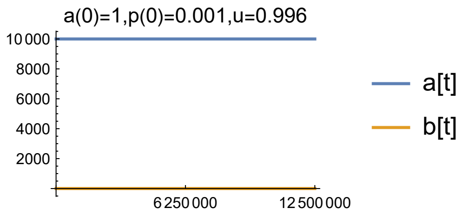


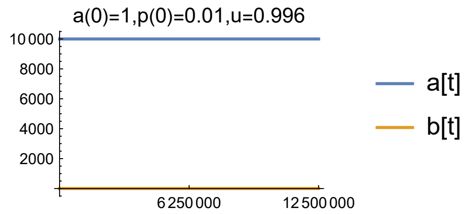


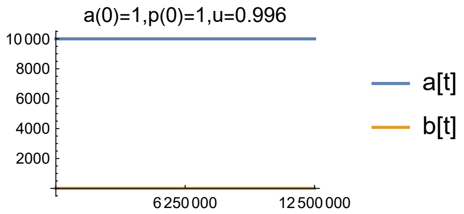


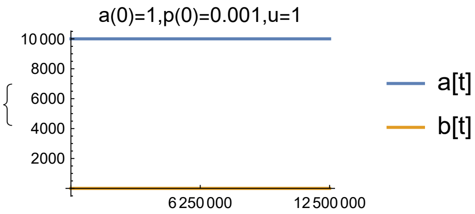


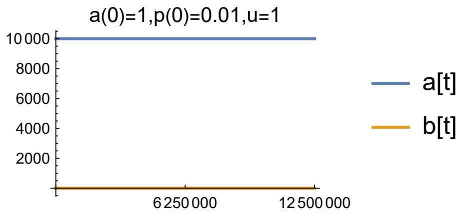


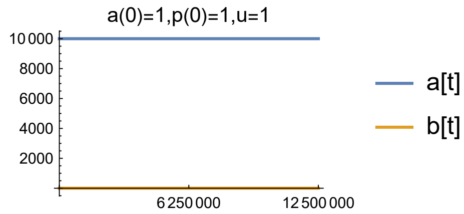












<u>Overall Conclusions</u>: <u>Mild phage therapy is theoretically feasible to treat P. aeruginosa.</u>