Modelling the effect of overuse of antimicrobials on antibiotic resistance

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Introduction

Over-prescribing of antibiotics has arguably led to an epidemic of drug resistant microbes that increases morbidity and mortality among humans, Thus, although antibiotic use may be beneficial to the individual, excessive use can be detrimental to the community. Limiting the use of antibiotics is predicted to address the problem.

When the goals of the individual conflict with the goals of the community, a ‘‘tragedy of the commons’’ may result. Under such circumstances, individual incentives lead to the overuse and destruction of a shared resource, whereas restrictions to limit use would benefit all individuals

Objectives

- Analyse the conflict of interest between the individual and society using two compartmental models of treatment and drug resistance.
- Assess when antibiotic use becomes a tragedy of the commons by analysing the conflict of interest between the individual and society as a mathematical game.
- Explore under what conditions antibiotic use becomes sub-optimal for society, despite the benefits to the individual.

Methods

We analyse two simple compartmental models of disease transmission and drug resistance.

MODEL 1: The first model includes transmissible drug-resistant strains or organisms and the development of resistance during treatment. (SIS Model)

MODEL 2: The second model extends the first to include a mild early stage of colonization, infection or disease, and a more severe later stage of infection or disease. (SIS Model)

Process

1. Develop a Markov model representing the transitions of an arbitrary individual in the population.
2. Derive the corresponding population model by summing the state variables over all individuals.

Individual case

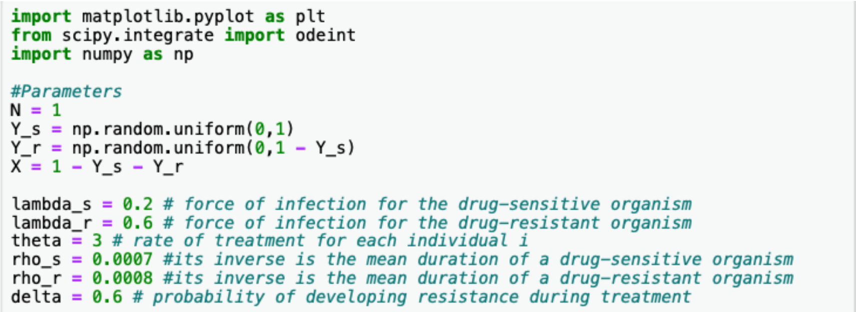
1. Each individual may choose its own treatment rate for infection (in Model 1), or for mild/severe infection (in Model 2).
2. The payoff of each individual depends on the strategy chosen, and the choices of all other individuals.
3. Analyse the outcome subject to exogenous forces of infection

Population case

1. Assume a large population and sum the probabilities for each state to approximate the expected number of individuals in each state at the population level.
2. At the population level, the forces of infection are not exogenous, but determined by the overall prevalence of drug-sensitive and drug-resistant organisms.

Code-Models

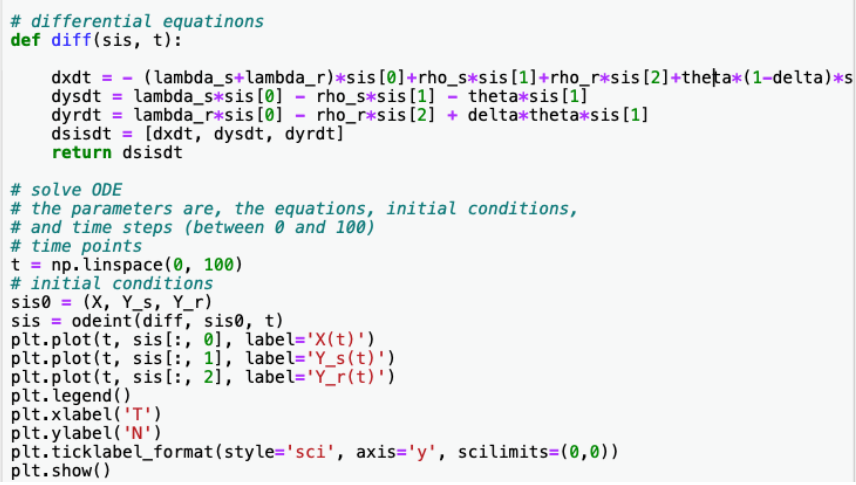
Model 1 – Individual Case



```
import matplotlib.pyplot as plt
from scipy.integrate import odeint
import numpy as np

#Parameters
N = 1
Y_s = np.random.uniform(0,1)
Y_r = np.random.uniform(0,1 - Y_s)
X = 1 - Y_s - Y_r

lambda_s = 0.2 # force of infection for the drug-sensitive organism
lambda_r = 0.6 # force of infection for the drug-resistant organism
theta = 3 # rate of treatment for each individual i
rho_s = 0.0007 #its inverse is the mean duration of a drug-sensitive organism
rho_r = 0.0008 #its inverse is the mean duration of a drug-resistant organism
delta = 0.6 # probability of developing resistance during treatment
```



```
# differential equatinons
def diff(sis, t):

    dxdt = - (lambda_s+lambda_r)*sis[0]+rho_s*sis[1]+rho_r*sis[2]+theta*(1-delta)*s
    dysdt = lambda_s*sis[0] - rho_s*sis[1] - theta*sis[1]
    dyrdt = lambda_r*sis[0] - rho_r*sis[2] + delta*theta*sis[1]
    dsisdt = [dxdt, dysdt, dyrdt]
    return dsisdt

# solve ODE
# the parameters are, the equations, initial conditions,
# and time steps (between 0 and 100)
# time points
t = np.linspace(0, 100)
# initial conditions
sis0 = (X, Y_s, Y_r)
sis = odeint(diff, sis0, t)
plt.plot(t, sis[:, 0], label='X(t)')
plt.plot(t, sis[:, 1], label='Y_s(t)')
plt.plot(t, sis[:, 2], label='Y_r(t)')
plt.legend()
plt.xlabel('T')
plt.ylabel('N')
plt.ticklabel_format(style='sci', axis='y', scilimits=(0,0))
plt.show()
```

- Standard parameters for a SIS-model (susceptible, infected, susceptible).
- Code block solves differential equations, obtains a 50x3 matrix, with each position representing the probability of the individual being in that state at that particular time. Then plots a line graph to reveal changes over time.

Model 1 – Population Case

- The risk of infection is determined by the population prevalence and may be considered exogenous when modelling the experience of a single individual =>introduction of transmission coefficients since we no longer assume constant forces of infection.
- Treatment Rates are not the same for each individual in the population case.
- We now run through each individual in the population and add the corresponding 50x3 matrix to a list.
- Then we construct a 50x3 matrix as the sum of each individual matrix to obtain a suitable object that can be plotted in the same fashion as the individual case.

Model 2 – Individual Case

The second model extends the first to include a mild early stage of colonization, infection or disease, and a more severe later stage of infection or disease. In terms of implications for the code, we now have 5 states, and our resulting solution matrix will have dimension 50x5. There are also many more parameters that can be changed relating to the increase in stages.

Model 2 – Population case

From a simplicity standpoint, fortunately the population/community level for Model 2 extends by exactly the same logic as Model 1, explained previously.

Findings - Sensitivity Analysis

We started by defining a base scenario with population N=1000. Our basis scenario, which our work is based upon, was given by the parameters provided by the following table on the research paper. From there onwards, we conducted a pure sensitive analysis.

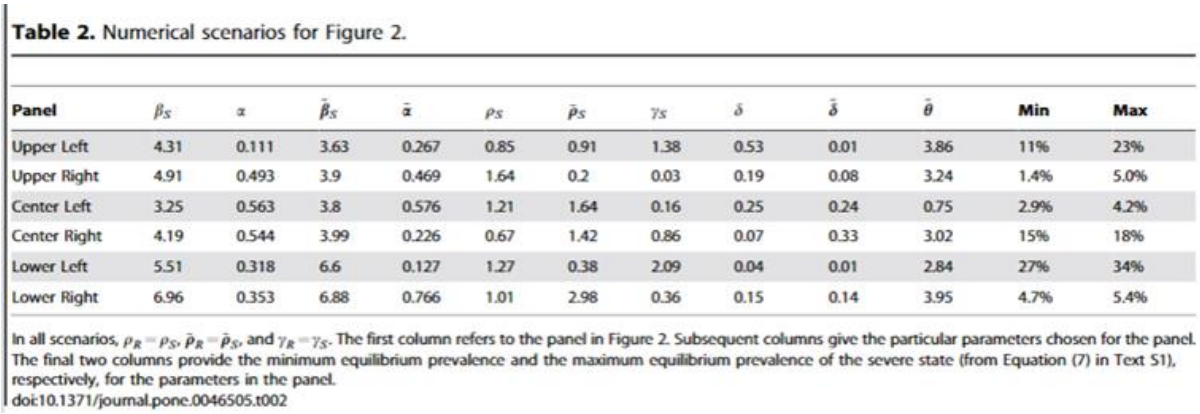


Table 2. Numerical scenarios for Figure 2.

Panel	β_S	α	$\tilde{\beta}_S$	$\tilde{\alpha}$	ρ_S	$\tilde{\rho}_S$	γ_S	δ	$\tilde{\delta}$	$\tilde{\theta}$	**Min**	**Max**
Upper Left	4.31	0.111	3.63	0.267	0.85	0.91	1.38	0.53	0.01	3.86	11%	23%
Upper Right	4.91	0.493	3.9	0.469	1.64	0.2	0.03	0.19	0.08	3.24	1.4%	5.0%
Center Left	3.25	0.563	3.8	0.576	1.21	1.64	0.16	0.25	0.24	0.75	2.9%	4.2%
Center Right	4.19	0.544	3.99	0.226	0.67	1.42	0.86	0.07	0.33	3.02	15%	18%
Lower Left	5.51	0.318	6.6	0.127	1.27	0.38	2.09	0.04	0.01	2.84	27%	34%
Lower Right	6.96	0.353	6.88	0.766	1.01	2.98	0.36	0.15	0.14	3.95	4.7%	5.4%

In all scenarios, $\rho_R = \rho_S$, $\tilde{\rho}_R = \tilde{\rho}_S$, and $\gamma_R = \gamma_S$. The first column refers to the panel in Figure 2. Subsequent columns give the particular parameters chosen for the panel. The final two columns provide the minimum equilibrium prevalence and the maximum equilibrium prevalence of the severe state (from Equation (7) in Text S1), respectively, for the parameters in the panel.

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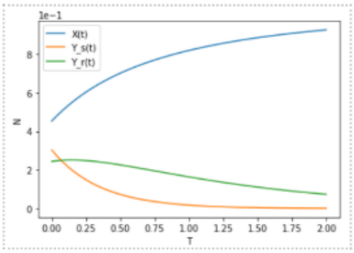
Findings- Model 1

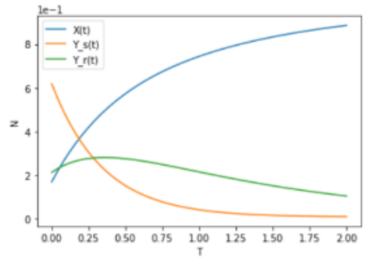
In Model 1, individuals are classified into three states: susceptible (uninfected), infected by drug-sensitive organisms, and infected by drug-resistant organisms. For each individual i, i~1, ... ,N, denote the probability of being susceptible at time t by X(i) , the probability of being infected by the drug-sensitive organism by Y(i)_S , and the probability of being infected by the drug-resistant organism by Y(i)_R

Let's compare upper left for model 1:

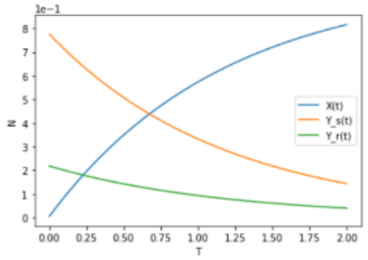
1. N=1000



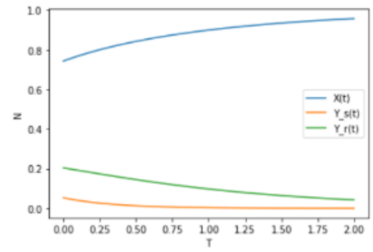
N=100



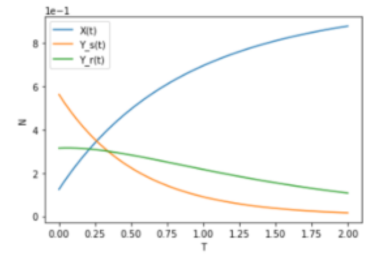
Delta=0.89



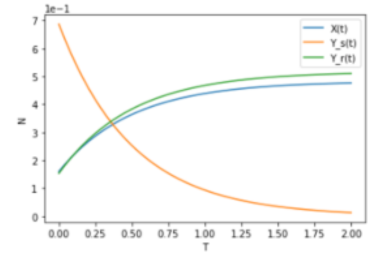
Alpha= 0.025



Beta_S=9.5



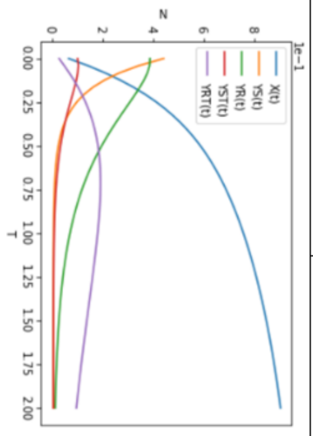
Rho_s=0.0017



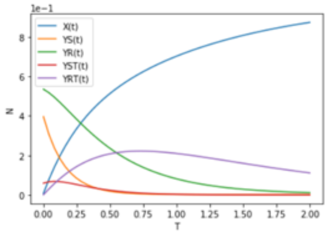
Findings - Model 2

We divided the analysis as on the table while changing every time one parameter and everything else remaining constant, so that we could conduct some sensitive analysis. Being our base scenario N=1000.

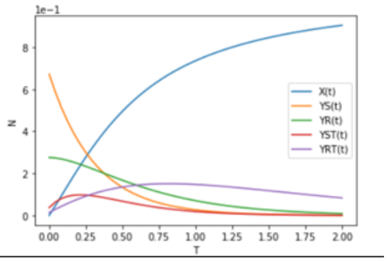
N=1000



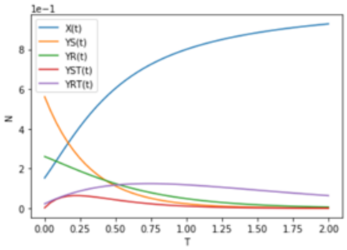
N=100



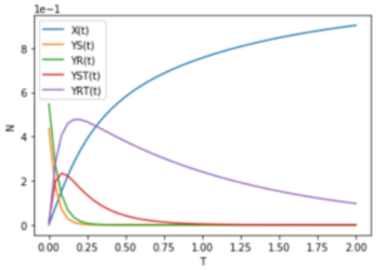
Delta=0.89



Tild_theta = 4.99



Gama=17.37



Optimal Strategies, Model 2

Assuming each member of the community chooses a single treatment rate for the mild state, we assess the fraction of time spent in the severe stage for any individual choosing a different strategy from that of the community (for the mild state).

Different parameter choices in Model 2 lead to very different outcomes, as shown by specific numerical examples on the previous slides. We present the same six scenarios as before to illustrate the range of behaviour when choosing to take different parameters, through the treatment strategy lens.

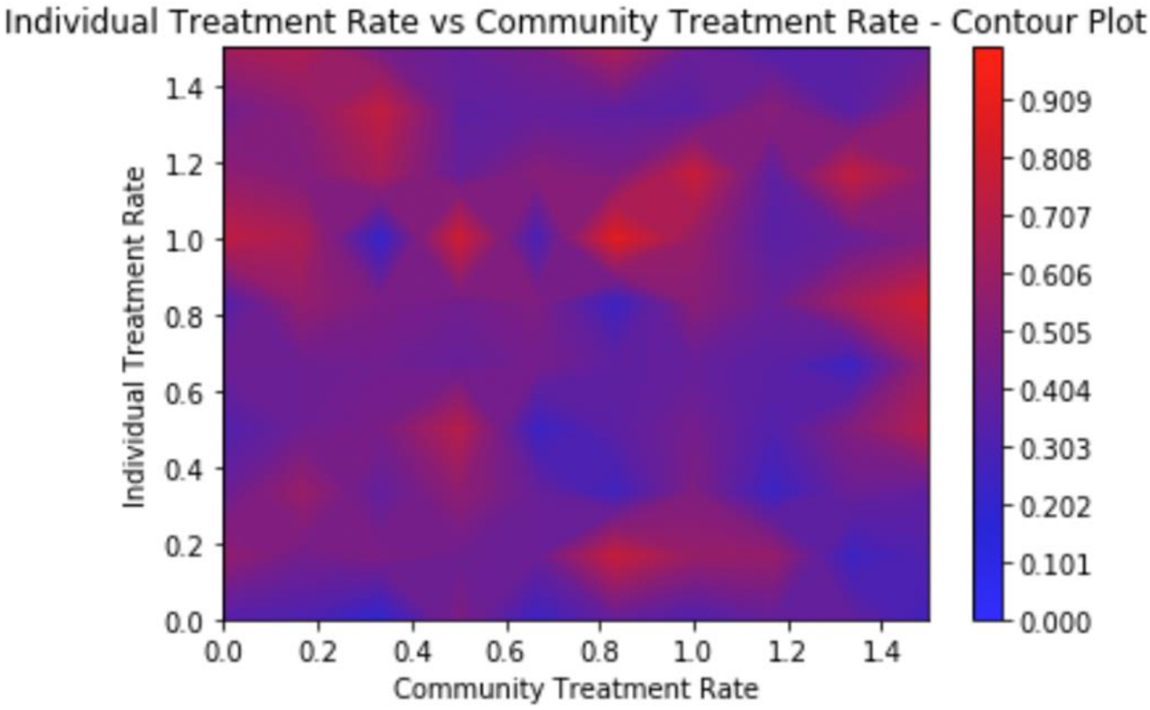
The strategy chosen by the specific individual of interest is given on the vertical axis, while the community level of treatment is shown on the horizontal axis. For each set of parameter values, we computed the fraction of time an individual spent in the severe state.

The resultant graphs are contour plots, with the colour band ranging between 0 and 1.

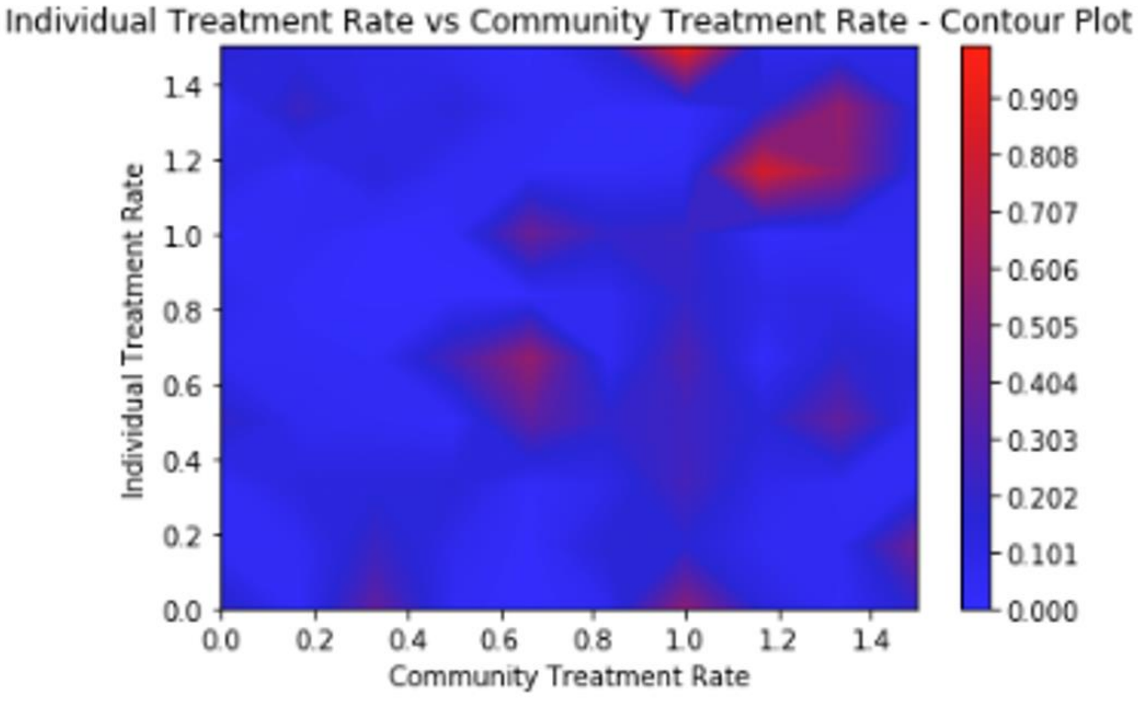
We are limited by computational power, this could be the reason our results are not completely aligned with that of the paper, but we feel the results to sufficiently support those of the paper.

```
for w in range(N):
    for i in range(N):

        if i==w:
            thetas_j[i]=thetas_j[i]
        else:
            thetas_j[i]= community[i]

        YS_j[i] = np.random.uniform(0,0.8)
        YR_j[i] = np.random.uniform(0,1-YS_j[i])
        YST_j[i]=np.random.uniform(0,1-YS_j[i]-YR_j[i])
        YRT_j[i]=np.random.uniform(0,1-YST_j[i]-YS_j[i]-YR_j[i])
        X_j[i] = 1 - YS_j[i] - YR_j[i]-YRT_j[i]-YST_j[i]
        lams = (beta_s*YS_j[i]+tildbeta_s*YST_j[i])/N
        lamr = (beta_r*YR_j[i]+tildbeta_r*YRT_j[i])/N
        individsol =(odeint(diff, (X_j[i],YS_j[i],YR_j[i],YST_j[i], YRT_j[i]), t))
        indisis.append(individsol)
        indith.append(thetas_j[i])
        commth.append(community[i])
        n=sum(individsol[:, 3])
        m=sum(individsol[:, 4])
        l=sum(individsol[:, 0])
        o=sum(individsol[:, 1])
        p=sum(individsol[:, 2])
        z = (n+m)/(n+m+l+o+p)
        yylist.append(indith[w])
        xxlist.append(commth[w])
        zlist.append(z)
```

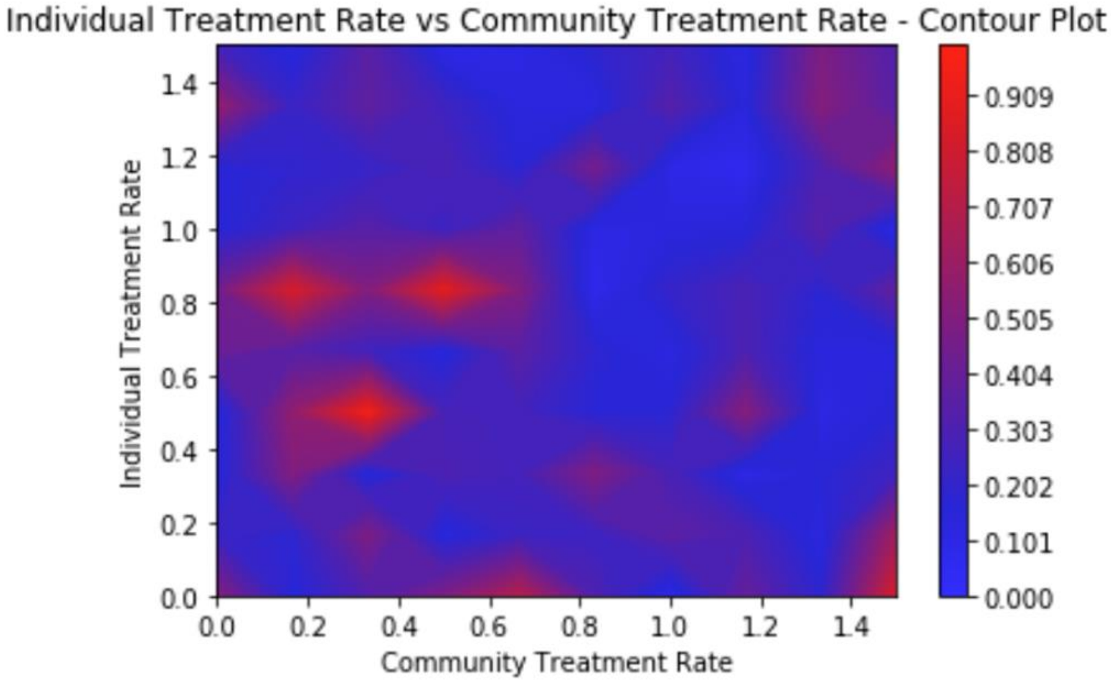
The first plot shows increasing treatment whilst in the mild state causes more resistance for a chosen individual no matter what the community treatment rate is. As you can see, with the community treatment rate at 0, if an individual increases treatment rate, they will spend more time being severely ill due to drug resistance. So, the best option in this case is to choose no treatment with the community choosing high treatment. Here, treatment of the community reduces how prevalent the disease is, so no treatment is the best choice.



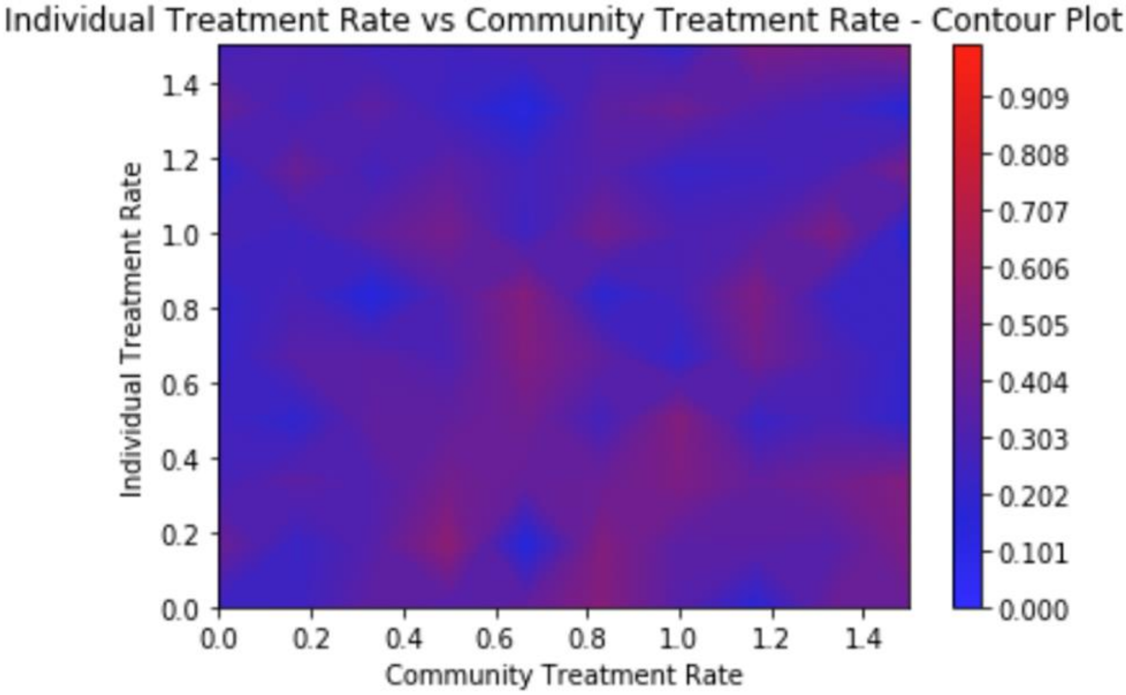
In this situation, an individual who increases their treatment rate whilst in the mild state is worse off as a result. Also, the amount of time spent in the severe state increases in the community as the community treatment rate during the mild state increases. Here, the individual's treatment rate choice does not matter as a high community treatment rate will always causes severe infections. So, an individual who chooses treatment is worse off if they are in a mild state and the whole community is worse off if the community rate increases.



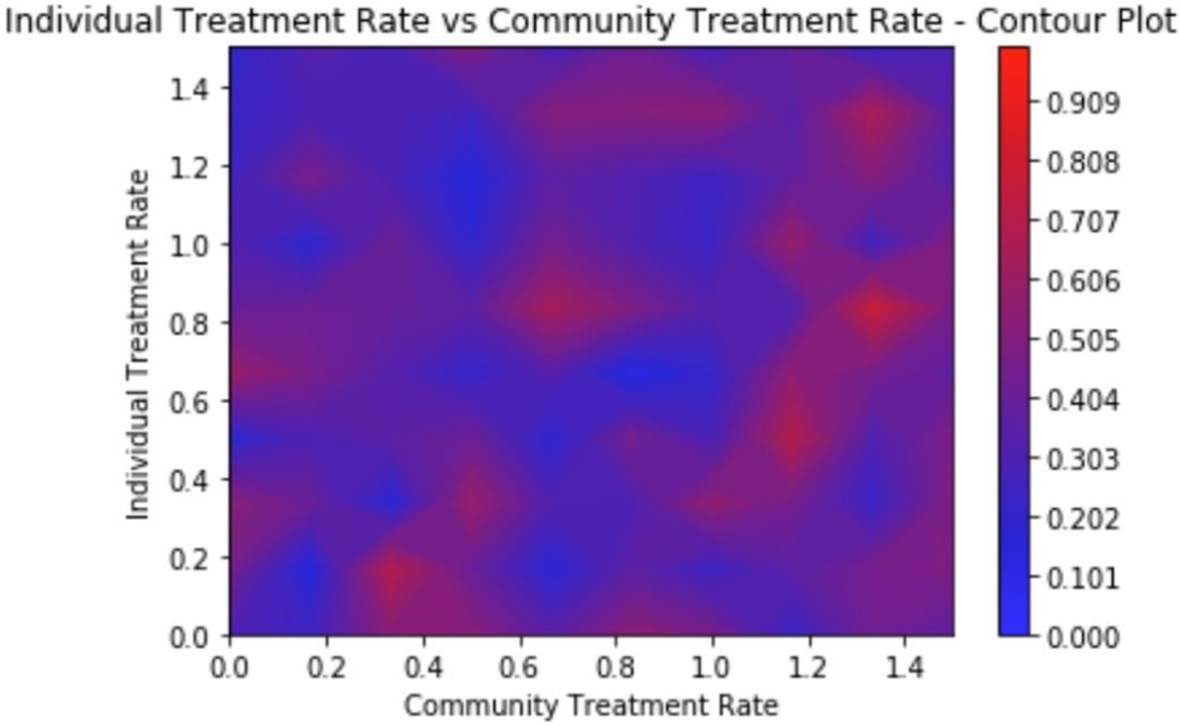
In this scenario both the individual and the community benefit from increased treatment whilst in the mild state. Here, increasing treatment of the mild state creates an increasing level of drug resistance. However, the drug resistance is outweighed by the reduction in overall disease that results from treatment.



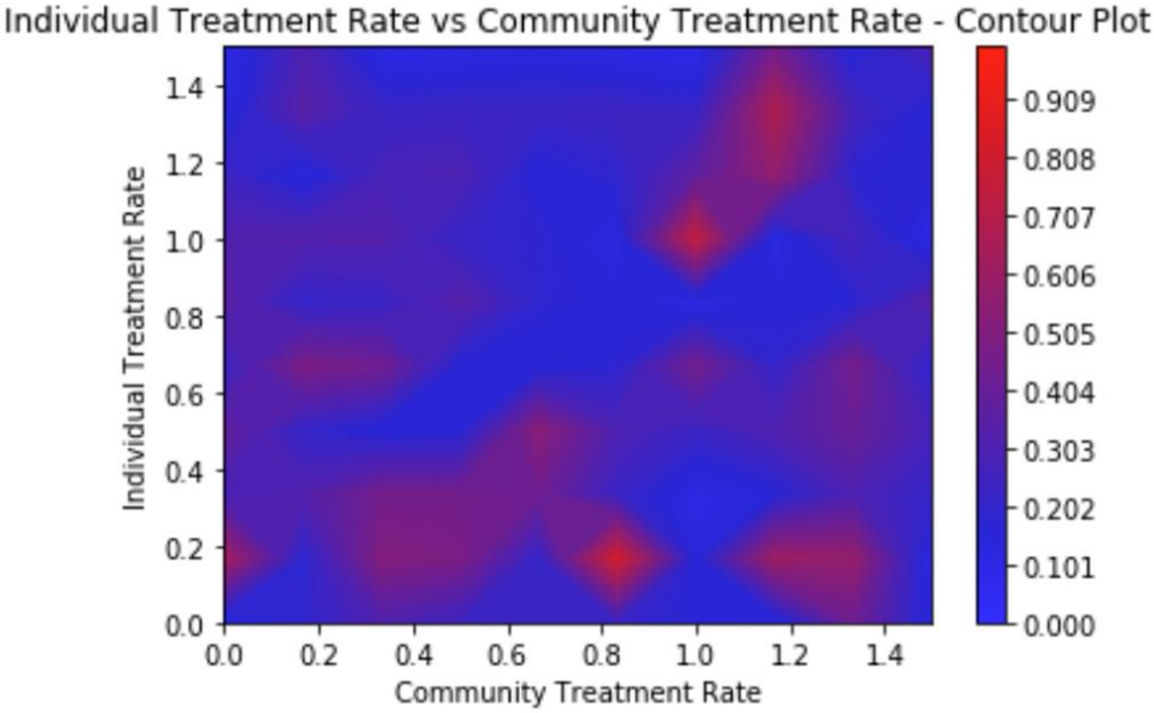
This one is quite similar to the one above however, in this case at higher community treatment rates for the mild disease, infection is still really strong with the similarities being the left sides of the graphs. The community suffers with the more treatment they take and the drug resistant infection completely outweighs the drug sensitive infection so the community is worse off as a result.



In this graph, an individual would always benefit from an increasing treatment rate whilst in the mild state regardless of the community treatment rate. However, if the community treatment rate were to increase then the individual would be worse off. However, individuals who increase their treatment rate for the mild state spend less time in the severe state. Unfortunately, community prevalence of the disease increases as the community rate increases too. Here an individual and the community do not have aligning interests. This describes a tragedy of the commons.



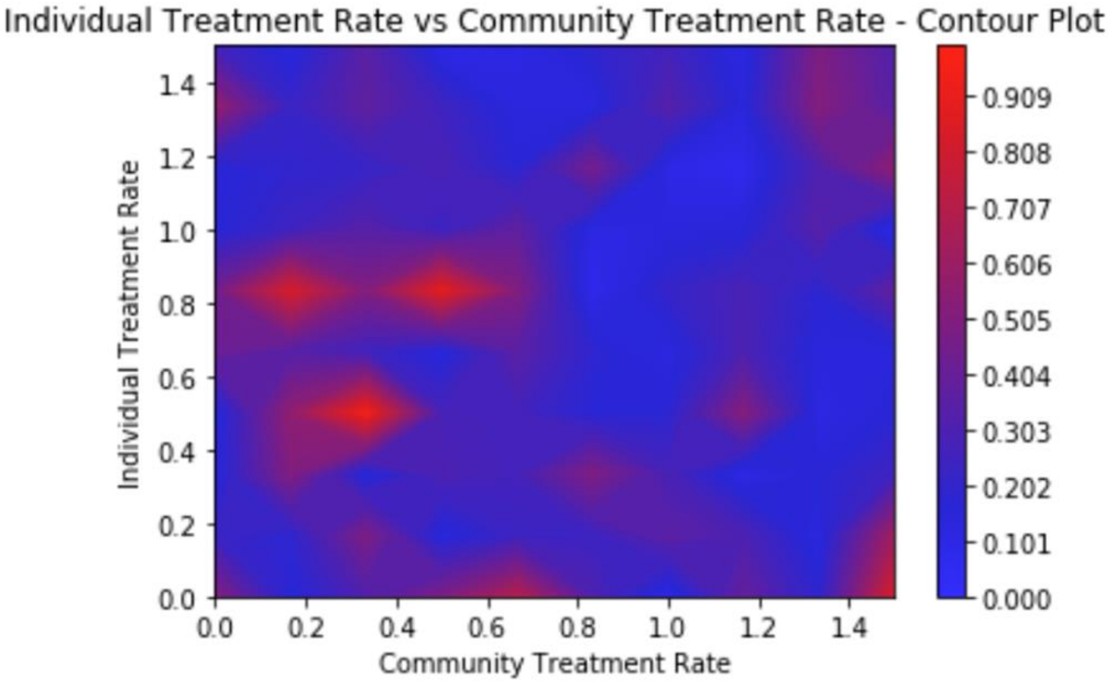
Our last scenario is similar to the previous for low treatment levels. When community treatment rates are low, an individual is better off choosing higher treatment rates. However from the bottom right of the graph we can see that if the community treatment rates are high, an individual is better of choosing a lower treatment rate whilst in a mild state of infection. Overall the community is worse off choosing higher treatment rates. This happens because the force of infection for the resistant disease is big enough such that those who recover from the sensitive version get re-infected by the resistant version of the organism.



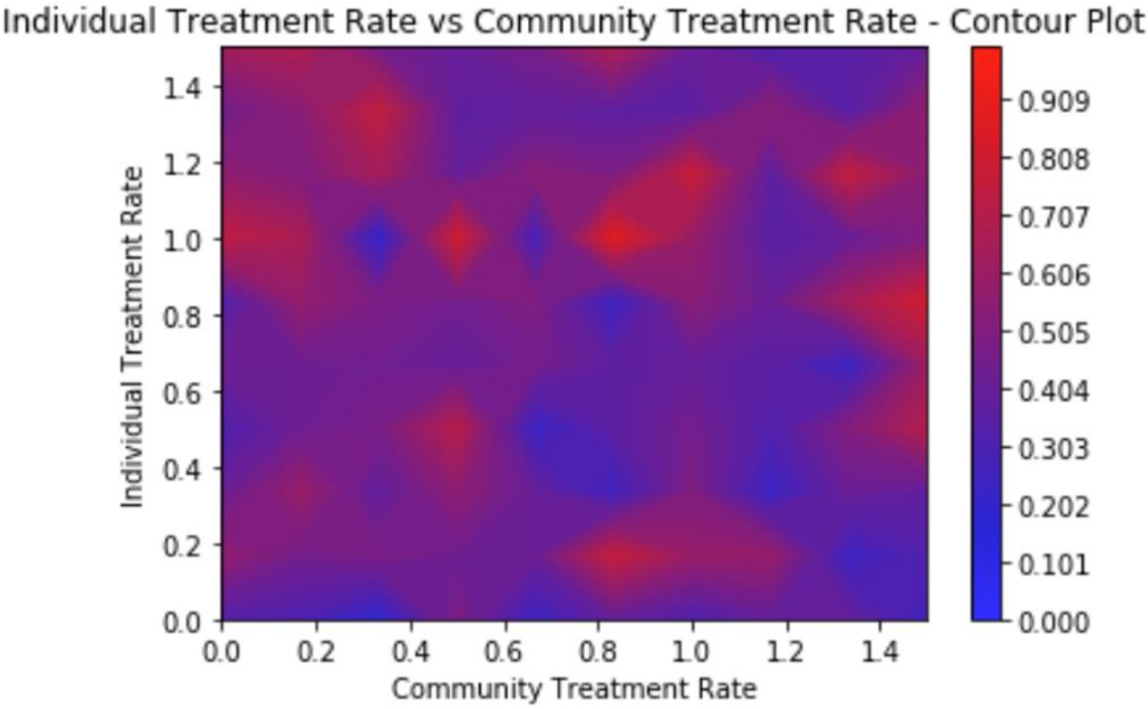
Conclusions

A conflict of interest may indeed result, though not in all cases.

1. Increased use of antibiotics by individuals benefits society under certain circumstances, despite the amplification of drug-resistant strains or organisms.
    - Here both the individual and the community benefit from increased treatment whilst in the mild state.

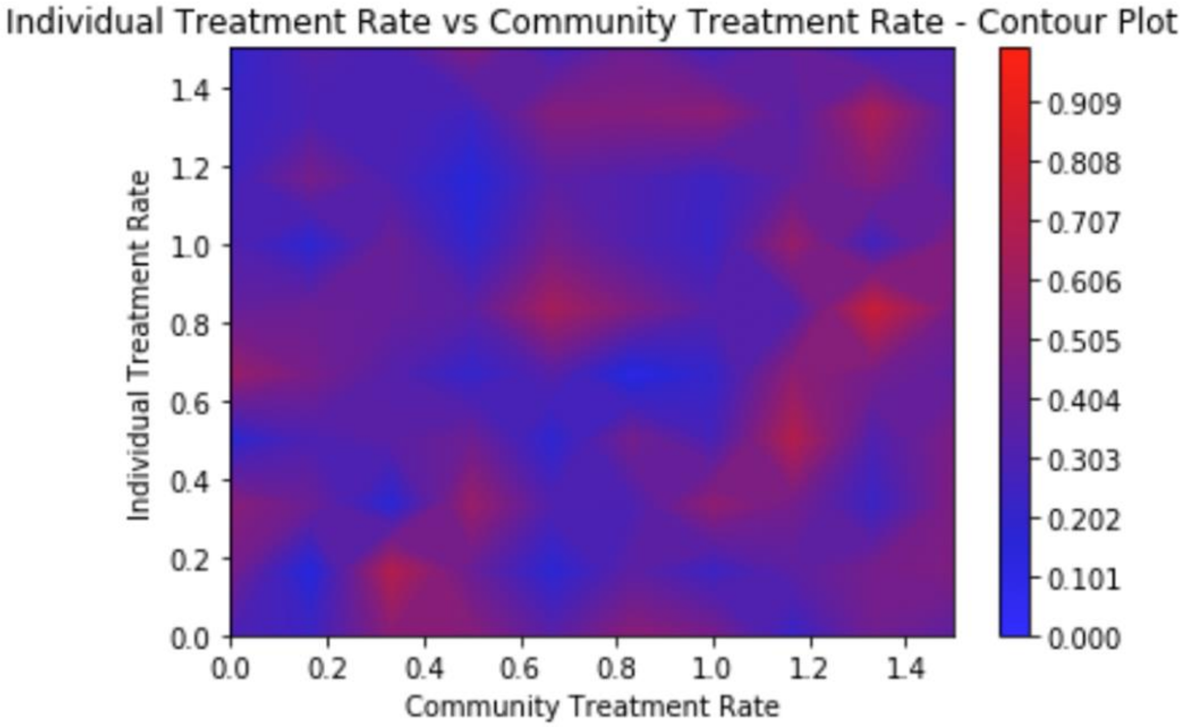


2. In situations where increased use of antibiotics leads to less favourable outcomes for society, antibiotics may be harmful for the individual as well.
    - With the community treatment rate at 0, if an individual increases treatment rate, they will spend more time being severely ill due to drug resistance.



3. For other scenarios, where a conflict between self-interest and society exists, restricting antibody use would benefit society.

- Here, individuals who increase their treatment rate for the mild state spend less time in the severe state. However, if the community treatment rate were to increase then the individual would be worse off.



Overall, one should assess when antibiotic use becomes a tragedy of the commons by analysing the conflict of interest between the individual and society as a mathematical game.

Limitations

- Analyses are based on equilibrium comparative statics and assume perfect information. In reality, decisions would be made with partial information in real time, leading to a dynamic game theoretic problem
- We have also assumed a large population (so that stochastic effects may be neglected)
- The model contains the following simplifying assumptions:
    - lack of immunity
    - absence of coinfection
    - linear dependence of the force of infection on the prevalence fraction
    - availability of only a single drug
    - assumption of a homogeneously mixing population in which network structure is ignored
- Further studies which included these features could search for a conflict of interest on a case-by-case basis