BIOS3036 – Computer Modelling in Science: Applications
Model Fitting and Sensitivity Analysis Practical
Dov Stekel

Semester 1 2023/24

This is an assessed practical.

In this exercise, we will consider an antimicrobial resistance model for bacteria in a slurry tank of a farm. **Before doing the practical, please listen to the slides on antimicrobial resistance that are available on Moodle.**

The model is given by the equations:

$$\frac{dS}{dt} = r\left(1 - \frac{N}{N_{max}}\right)E_S S - \delta S - \frac{\beta SR}{N}$$
$$\frac{dR}{dt} = r(1-\alpha)\left(1 - \frac{N}{N_{max}}\right)E_R R - \delta R + \frac{\beta SR}{N}$$
$$\frac{dA}{dt} = -\delta_A A$$
$$E_S = 1 - \frac{E_{max}A^H}{MIC_S^H + A^H}$$
$$E_R = 1 - \frac{E_{max}A^H}{MIC_R^H + A^H}$$
$$N = R + S$$

S is the concentration of sensitive bacteria (CFU/l), R is the concentration of resistant bacteria and A is the concentration of antibiotic. r is the maximal growth rate, N_{max} is the carrying capacity, E_S and E_R are the effects of antibiotic on growth of sensitive and resistant bacteria respectively, δ is the death rate of sensitive and resistant bacteria, β is the rate of horizontal gene transfer, α is the fitness cost of carrying resistance genes and δ_A is the decay rate of antibiotics. In the E equations, E_{max} is the maximal antibiotic inhibition, H is a Hill coefficient equal to 2, and MIC_S and MIC_R are the minimal inhibitory concentrations of antibiotic on the sensitive and resistant strains respectively.

The data you are given are placed in the file **amrdata.txt**

They represent samples from the slurry tank each week. At the start of the experiment, a large volume of antibiotic is added to the tank, and the antibiotic decays in time. No further antibiotic is added. Each week, the microbiologists cultured 100 bacterial strains, and worked out how many of them are resistant to the antibiotic. The first column is the time in hours, and the second column is the number of resistant strains of the 100 isolates tested. This can be thought of as equal to:

$100\ R/(R+S)$

You will need to estimate three parameter values from the data:

β, the horizontal transfer rate
α, the fitness cost of carrying the resistance
δ_A, the rate of decay of the antibiotic

You have the following information about these three parameters:

β is expected to be small, but could be anywhere between 10^{-2} and 10^{-11}
α must be bigger than 0 and less than 1
δ_A is the rate of decay (1 / mean lifetime of antibiotics).. It is thought that the mean life time is about 2-3 weeks, based on other studies, but might be outside this range in slurry as the chemical conditions are different.

For the sake of this exercise, the other parameters are fully known. They can be assumed to be:

Parameter	Value
r – maximal growth rate	$0.5\ h^{-1}$
N_{max} – carrying capacity	10^7 CFU/L
δ – death rate	$0.025\ h^{-1}$
E_{max} – maximal inhibition	2
H – hill coefficient	2
MIC_S – MIC sensitive	8 μg/L
MIC_R – MIC resistant	2000 μg/L
S(0) – initial sensitive population	9×10^6 CFU/L
R(0) – initial resistant population	10^5 CFU/L
A(0) – initial antibiotic concentration	5.6 μg/L

For the Assessment

Please create a Word (or equivalent) document into which to place your write-up.

1. Implement the ODE model in Python. You can use one of the existing MCMC Python codes that I have given you as a starting point. Please copy and paste the ODE model function into your write-up.

   [15%]

2. Implement the MCMC scheme and use it to find out as much as you can about the parameter values of the model. You may need to run some short simulations to optimize the proposal distributions. For your write-up, please include:

    i. A description of what you have done and why
    ii. All your program code
    iii. Suitable figures and tables showing the results of your MCMC
    iv. A description of what your results mean

    [60%]

3. The maximum value of the resistant population can be worked out using the function np.max() . For example, if the resistant cells are in a variable called out produced by a call to a simulation of the model, this would be:

```
max_R = np.max(out[:,1])
```

   Use sensitivity analysis to identify which of the parameters β, α and δ_A the maximum level of resistance is most sensitive to. Include a suitable graph in your answer. What impact do you think this output has on data fitting?

   [25%]