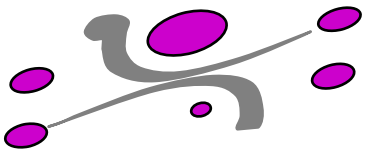

NATIONAL
VETERINARY
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PK/PD
MONTE CARLO SIMULATIONS

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The main goal of this exercise is to measure the impact of the main determinants of a kinetic via PK/PD Monte/Carlo simulations. To this end, you need the Excel file named "Monte Carlo" to perform the simulations. This workbook contains several sheets. The main sheet is the *balance sheet.* It contains the value of the PK/PD parameters that you need to change to complete the exercise. All the other sheets are only for computations.
All the PK parameters of this exercise are assumed to be log-normally distributed in the population. These assumptions are probably not realistic especially for the bioavailability. The distribution of bioavailability should be defined on [0 ; 1] but for convenience log-normality was kept and when a bioavailability was greater than 1 it was set to 1. Actually, the exact distribution of the PK parameters should be obtained by a pop PK study. The drug is given by an IM route and its kinetics is assumed to follow a mono compartmental model. The F9 key (in the top of the keyboard) allows to draw randomly 200 animals in the population. The first figure shows the kinetics of the drug obtained on these animals. You can change the value of the population PK parameters (mean and coefficient of variation).
The distribution of MIC can also be changed. It is represented on figure 2.
In the real life, the meeting between a pathogen and an animal is random. A simple way to simulate this meeting is to associate to each animal a MIC randomly selected from the distribution of MIC.
Two indices are calculated from this random meeting : AUC/MIC and C_{MAX} /MIC, where AUC and C_{MAX} are respectively the total area under the concentration-time curve of the animal and the maximum concentration of this curve.
When these indices are large, the animal has a large probability of cure. We assume that the thresholds above which the probability of cure is large enough are 125 and 8-10 for AUC/MIC and C_{MAX} /MIC respectively. Figure 3 and 4 respectively show the percentage of animals (over the 200 drawn from the population) with a AUC/MIC (resp. C_{MAX} /MIC) greater than the AUC/MIC (resp. C_{MAX} /MIC) given on the x-axis.

For sake of simplicity and time, this Excel file allows only simplified simulations that have to be refined to become realistic. We simply want to introduce the concepts and they are easy to understand. Enjoy yourself…

Exercise :

The first part of this exercise is devoted to the study of the influence of the bugs MIC in a *targeted antibiotherapy* (*ie* when the MIC of the bug is known).

PK	Pop. mean	Pop. CV %
Clearance (L/kg/h)	0.2	20%
Volume (L/kg)	1	15%
Ka (h^{-1})	0.5	15%
Bioavailability (%)	90%	10%
Dose (mg/kg)	10	

- Use the PK parameters of the table on the left
- What is the maximal MIC covered by this dose for 90% of animals?
- What dose would allow a correct exposure of 90% of animals for a MIC equal to 1µg/mL
- Set the MIC to 0.25 µg/mL
- What is the dose that allows a correct exposure of 90% of animals for a bioavailability of 50% and 10%.
- When the bioavailability decreases its dispersion usually increases. For a bioavailability of 50% with CV=30% and 10% with a CV=50% determine the dose that cover 90% of animals.
- What is the impact of variability ?

The aim of the second part of the exercise is to study the influence of the distribution of MIC in an *empirical antibiotherapy* (*ie* when the MIC of the bug is unknown before the treatment).

PK	Pop. mean	Pop. CV %
Clearance (L/kg/h)	0.2	20%
Volume (L/kg)	1	15%
Ka (h^{-1})	0.5	15%
Bioavailability (%)	60%	10%
Dose (mg/kg)	10	

MIC (µg/mL)	Distrib 1	Distrib 2	Distrib 3	Distrib 4
0.03125	10%	10%	10%	10%
0.0625	77%	0%	0%	0%
0.125	1%	78%	0%	0%
0.25	1%	1%	79%	0%
0.5	1%	1%	1%	80%
1	10%	1%	1%	1%
2	0%	9%	0%	0%
4	0%	0%	9%	0%
8	0%	0%	0%	9%

- What are the MIC_{90} of the four distributions given in the table ?
- Enter the PK data and the first MIC distribution in the balance sheet
- What percentage of animals reach a AUC/MIC ratio of 125 ?
- Same question for the three last MIC distributions
- Can the MIC distribution be summarised by the MIC_{90} ?
- Can the MIC distribution be summarised for PK/PD ?

Population PK can give you useful information about variability that can be incorporated in simulation. The animals considered in this study are dogs that may be roughly categorised into three formats : small, medium and large. Assume that the pop PK analysis evidenced a large influence of the format on the clearance. The sheet named "Clearance and Format" contains the mean and CV values of clearance per format as well as the percentage of the different formats in England. The last line entitled "population" gives the population mean and CV. The figure 5 shows the distribution of clearance by breed and in the population. As you can see on figure 5, a mixture of log-normal distributions is no longer a log-normal distribution. *In order to avoid intricate calculus, forget it, we only want here to obtain qualitative results.*

- Using the distribution of MIC and the PK parameters given hereafter determine the dose that covers 90% of dogs
- Using the same distribution of MIC and the same PK parameters (except clearance) determine the dose that covers 90% of the dogs in each breed.
- How do you explain the differences between these doses ?
- Assume that the distribution of the different format of animals is different in France. For example, assume that there are about 60% of small dogs and only 10% of large dogs. What would be the dose covering 90% of the french dogs ?
- Compare the dose you found in the first question to the dose you found in the previous question. How do you explain the difference ?

You can play with the "Clearance and Format" and see the impact on the population structure on the different indices. Only the numbers in yellow cells should be changed.

MIC (μg/mL)	0.03125	0.0625	0.125	0.25	0.5	1	2	4	8
percentage	0%	10%	50%	30%	0%	10%	0%	0%	0%

PK	Pop. mean	Pop. CV %
Clearance (L/kg/h)		
Volume (L/kg)	1	15%
Ka (h^{-1})	0.5	15%
Bioavailability (%)	60%	10%
Dose (mg/kg)		