13th EAVPT congress, Nantes

Monte Carlo Simulations in Veterinary Medicine

Dr. Ludovic Pelligand,
Senior Lecturer in Veterinary Anaesthesia and Pharmacology
The Royal Veterinary College

20/07/2015
Outline of the presentation

- What is Monte Carlo Simulation and what has it been used for so far in medical sciences?
- What is needed for a MCS?
- Application for veterinary antimicrobials and definition of veterinary clinical breakpoints
- Relevance and extension of Monte Carlo Simulations for veterinary pharmacology stakeholders
What is Monte Carlo simulation?

- Powerful mathematical tool to approximate solutions to a statistical problem impossible to solve with classical regressions

- Deals with complex and interacting uncertainties about real life scenarios to forecast outcome (model)

- Repetitive random sampling process from known distributions of model parameters (stochastic process)

- Presents data in a format easily understandable to inform decision
Stanislaw Ulam invented the expression
Risk analysis industries embraced Monte Carlo simulations

- Insurance, Finance, Aerospace, Environmental monitoring
- Present in every day life…
MC simulations in human pharmacology

- Introduced to the anti-infectious disease community by Drusano and Ambrose in 1998

- Applications of MC simulations in the field on antibiotic optimisation include:
  - Evaluation of adequacy of dosing regimens
  - Estimation of Antimicrobial susceptibility breakpoints
Monte Carlo simulations in veterinary medicine

Literature search

296 valid citations classified by topic:

- Physiology models: 4
- Animal Genetics (non-related to food production): 14
- Molecular biology for pathology: 1
- Ecology / wildlife (recapture for species census): 4
- Applied statistics mathematics: 9
- Pharmacology Withdrawal times - residues: 6
- Pharmacology Antimicrobials: 14
- Animal productions & risk of human exposure: 53
- Veterinary diagnostics improvement through simulation: 61
- Epidemiology Economic (benefit/cost measures): 87
- Epidemiology Infectious (temporal and spatial): 87
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Anti infective drug selection

Dose Justification

MIC breakpoint
Justification

Clinical trial simulation

Probability Density Functions

Clinical Data
Efficacy & Safety

Pharmacokinetics

Modeling & Simulation
“What if” scenarios

Pharmacodynamics

Infection models
or in vitro data
PK/PD indices best predicting therapeutic success

<table>
<thead>
<tr>
<th>Concentration-dependent</th>
<th>Co-dependent</th>
<th>Time-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}} &gt; \text{MIC}$</td>
<td>$\text{AUC}_{24h}/\text{MIC ratio}$</td>
<td>$T &gt; \text{MIC}$</td>
</tr>
<tr>
<td>Obj: Ratio &gt; 10-12</td>
<td>Obj: Ratio &gt; 125h</td>
<td>Obj: during 40-80%</td>
</tr>
</tbody>
</table>

![Concentration-dependent diagram](image)

![Co-dependent diagram](image)

![Time-dependent diagram](image)
MC simulation in antimicrobial PK/PD modelling

- Generate random PK and MIC values from dataset
- Calculate PK-PD Exposure Measure
- Plot results in a probability chart

Discrete distributions
Continuous distributions
Transformation
Random Number generator U (0, 1)
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Example 1: Probabilistic determination daily amoxicillin dose for calf pathogen

**PK:** Amoxicillin 15 mg/kg IM
- 10 calves, intensive PK sampling
- LC/MS measurement

**PD:** In vitro kill curve in serum (*M. haemolytica*)
- Calculation of $\text{AUC}_{24\,\text{h}}/\text{MIC}$ for bacteriostatic, bactericidal (3 log$_{10}$ reduction), eradication: 4 log$_{10}$ reduction)

MIC distribution

Data from Lees, Pelligand *et al.* 2014
Deterministic computation of the daily dose with single point estimates (mean clearance/F, MIC\textsubscript{90}) for amoxicillin \textit{M. haemolytica}.

\[ \text{Dose} = \frac{\text{Clearance}}{F(\%)} \times \frac{71.5 \times \text{MIC}}{f_u} \]

- Mean value = 419.6 mL/kg/h
- MIC\textsubscript{90} = 0.24 µg/mL
- f\textsubscript{u} = 0.68
- Average Dose = 10.6 mg/kg/d

PK/PD Breakpoint eradication
AUC\textsubscript{24h}/MIC (h)
Stochastic computation of the daily dose using Monte Carlo simulation for amoxicillin

Dose to Target Attainment Rate TAR = 90%?
Stochastic computation of the daily dose using Monte Carlo simulation for a amoxicillin

Observed Clearance distribution (mL/kg/h)

PK/PD Breakpoint eradication AUC_{24h}/MIC (h)

MIC: Observed distribution

Iteration #1
Dose 9.3 mg/kg/d
Stochastic computation of the daily dose using Monte Carlo simulation for a amoxicillin PK/PD Breakpoint eradication. AUC\textsubscript{24h}/MIC (h) Observed Clearance distribution (mL/kg/h) MIC: Observed distribution PK/PD Breakpoint eradication AUC\textsubscript{24h}/MIC (h)

Iteration #2
Dose 12.1 mg/kg/d
Stochastic computation of the daily dose using Monte Carlo simulation for a amoxicillin PK/PD Breakpoint eradication AUC$_{24\text{h}}$/MIC (h)

Observed Clearance distribution (mL/kg/h)

MIC: Observed distribution

PK/PD Breakpoint eradication AUC$_{24\text{h}}$/MIC (h)

Iteration #3
Dose 16.9 mg/kg/d
Stochastic computation of the daily dose using Monte Carlo simulation for a amoxicillin

Observed Clearance distribution (mL/kg/h)

PK/PD Breakpoint eradication AUC_{24h}/MIC (h)

MIC: Observed distribution

Iteration #10
Dose 5.5 mg/kg/d
Stochastic computation of the daily dose using Monte Carlo simulation for a amoxicillin

Observed Clearance distribution (mL/kg/h)

PK/PD Breakpoint eradication
AUC\textsubscript{24h}/MIC (h)

MIC: Observed distribution

Iteration #50

Not for Commercial Use

RVC
Stochastic computation of the daily dose using Monte Carlo simulation for a amoxicillin

Observed Clearance distribution (mL/kg/h)

PK/PD Breakpoint eradication AUC$_{24h}$/MIC (h)

MIC: Observed distribution

Iteration #50000
Final result of the Monte Carlo simulation and sensitivity analysis

- Limitations of this simplified example
Example 2: checking validity of breakpoints: Amoxicillin in pigs (Rey, Laffont et al. 2014)

- PK/PD index: Concentration > MIC for 40% of the dosing interval (> 9.6h for 24h dosing interval)
- Suggested CLSI breakpoint: 0.5 mcg/mL

PK/PD Cut-Off considered alongside epidemiological Cut-Off for consensus decision on clinical BP
VetCAST initiative

- VetCAST - EUCAST veterinary subcommittee on antimicrobial susceptibility testing on bacterial pathogens of animal origin and animal bacteria with zoonotic potential

- Define animal species-, bacterial species- and drug-specific MIC breakpoints

- Goal: limit the emergence of antimicrobial resistances while improving welfare and outcomes

- Collaboration encouraged to collate rich PK and PD datasets: we need you!
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Possibilities and extension of Bayesian statistics for antimicrobials

- **Field distributions known**
  - PD: multicentre distribution MIC wild type
  - Population PK model: parameters estimates + covariance matrix
  - Suitable PK/PD index

- **Monte Carlo simulation / Bayesian Approach**
  - Risk Tolerance: Target Attainment Rate (%)

- **Dose** for field trial
  - (drug companies)

- **PK/PD cut-off**
  - (laboratories, regulators, epidemiologists)

- **Licensed dose**

- **Individual covariates**
  - Demographics, Disease state, GFR
  - Measured Exposure

- **MIC measurement**

- **A priori TDM**
  - Targeted Therapy (dose, rate)

- **A posteriori TDM**
  - Tailored individual dose

- **ADDITIONAL PRIORS**
  - PK/PD cut-off (laboratories, regulators, epidemiologists)

- **PRIORS**
  - Field distributions known
  - PD: multicentre distribution MIC wild type
  - Population PK model: parameters estimates + covariance matrix
  - Suitable PK/PD index

- **PRIORS**
  - Licensed dose

- **PRIORS**
  - Individual covariates
    - Demographics, Disease state, GFR
    - Measured Exposure

- **PRIORS**
  - MIC measurement

- **PRIORS**
  - A priori TDM
  - A posteriori TDM

- **PRIORS**
  - Risk Tolerance: Target Attainment Rate (%)

- **PRIORS**
  - Dose for field trial
    - (drug companies)

- **PRIORS**
  - PK/PD cut-off
    - (laboratories, regulators, epidemiologists)
Conclusion

- Extension of Monte Carlo Simulations:
  - MCS to predict residue disposition and WT
  - MCS in clinical trial simulation / executive decision making
  - Markov Chain MC (SAEM algorithm in Monolix, NonMem 7): Bayesian implementation

- Versatile tool relevant to all veterinary pharmacology stakeholders
Thank you

- Coworkers

- VetCAST network
  (http://www.eucast.org/ast_of_veterinary_pathogens/)

- Animal Health Modeling and Simulation (AHM&S) Society (http://www.ahmss.com/)
Questions from the audience

Pascal Sanders: Recommended software and price

David Burch: We need to plan to collect MIC information for alternative sites: ie urine, CSF

Ludo: Only works for systemic exposure, not topical (skin and mammary)
### Winton Advert: Little Red Riding Hood

**Probability of Encountering a Wolf**

- **99.9%**

### 24HR Weather

<table>
<thead>
<tr>
<th>Time</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>16</td>
<td>Snowy</td>
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<tr>
<td>17</td>
<td>Snowy</td>
</tr>
<tr>
<td>18</td>
<td>Snowy</td>
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<tr>
<td>19</td>
<td>Snowy</td>
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### Projected Route

<table>
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<tr>
<th>Route</th>
<th>Distance</th>
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<tbody>
<tr>
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<tr>
<td>B</td>
<td>4.8KM</td>
</tr>
<tr>
<td>C</td>
<td>5.2KM</td>
</tr>
</tbody>
</table>

### Distance to Destination

- **4.63KM**

### Possessions

- **One Woven Basket**
  - **Contents:** Tea, Cake
  - **Weight:** 1.5kg

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