Computational Sustainability
February 1\textsuperscript{st}, 3\textsuperscript{rd}, and 8\textsuperscript{th}, 2011 at 2:55PM – 4:00PM
315 Upson Hall

Optimizing Intervention Strategies in Food Animal Systems: modeling production, health and food safety

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Perhaps I should start with “a disclaimer”…

If I understood correctly, your approach is to assume the model is 'correct', then optimize the system.

As veterinarians, our responsibility is to build a model based on subject matter representing reality.

Of course, our goal is to find the optimal way to control disease (not necessarily eradication). And sometimes we need to learn the economically optimal way to coexist with them.
Food Supply Veterinary Medicine
....all aspects of veterinary medicine's involvement in food supply systems, from traditional agricultural production to consumption.

Modeling production, health and food safety:

1. Optimizing health and management decisions

2. Mathematical modeling of zoonotic infectious diseases (such as L. monozytogenes, E. coli, MDR salmonella and paratuberculosis).
Three examples ...

1. Modeling production and health:

Project 1. “Cost Effective Control Strategies for The Reduction of Johne’s Disease on Dairy Farms.” Zhao Lu, Research Associate and Becky Smith’s PhD research

Project 2. “Optimal Clinical Mastitis Management in Dairy cows.” Elva Cha’s PhD research

2. Modeling Food Safety:

1. Johne’s Disease

“Cost Effective Control Strategies for The Reduction of Johne’s Disease on Dairy Farms”

Zhao Lu, PhD, Research Associate, and Becky Smith, DVM, PhD student
Johne’s disease (paratuberculosis)

- Johne’s disease is a chronic, infectious, intestinal disease caused by infection with *Mycobacterium avium* subspecies *paratuberculosis* (MAP).

- Infection process of *paratuberculosis* in a dairy cow:
Issues of Johne’s disease

• Economic loss: > $200 million per year (Ott, 1999) due to the reduced milk production, lower slaughter value, etc.

• Public health: a potential association between Johne’s disease and human Crohn’s disease has been debated.

• Control of Johne’s disease:
  – Test and cull strategies, i.e., to cull/remove infectious animals from herd by test-positive results using diagnostic testing methods, such as culture and ELISA tests.
  – Improved hygiene management;
  – Vaccination.

However, it is difficult to control JD spread:
  – Long incubation period;
  – Low diagnostic test sensitivity for animals shedding low levels of MAP;
  – Cross reactivity of Johne’s disease vaccines with tuberculosis (TB) tests.
A stochastic multi-group model for MAP in a dairy herd

(Evaluation of effectiveness of test-based culling)
Coupled model for MAP in a dairy herd

• We asked for an agent-based model that could handle demographics and produce cow-specific information
  – Births
  – Milk production
  – Reproduction
  – Culling
    • Based on value of milk and reproductive status
    • Can use test status
Estimating transmission parameters for MAP with field data

- **Known information:**
  - birth date
  - death date
  - annual test dates and results
  - vaccination status

- **Missing information:**
  - Date of infection
  - Onset of low-shedding
  - Onset of high-shedding
  - True infection status (if all tests results were negative)

To estimate MAP parameters, missing information must also be estimated
Estimating parameters with Markov Chain Monte Carlo models

MCMC models are Bayesian statistical models, useful for disease modeling because they

• Can account for nonlinear systems
  – parameters may be inter-related

• Can account for time-dependence
  – i.e. infectious pressure

• Have a mechanism for missing-data imputation:
  – Missing information can be estimated probabilistically, given a set of parameters drawn from a prior distribution
  – The full dataset can then be used to determine the relative likelihood of a different set of parameters drawn from the prior
    • The new set of parameters may be accepted or rejected, based on its relative likelihood
  – This process is iterated until it converges on a posterior distribution for all parameters
Validating MCMC models

• In order to test that an MCMC model predicts the true parameter distribution, we feed it data simulated with known parameters

• In the case of the JD model, the full model requires individual animal data:
  – Infection status
  – Vaccination status
  – Dates of birth, compartment transitions, death

• We needed the individual-animal stochastic model
Validation Results: Transmission Rate
Joint Posterior Density Function

Full Data

Reduced Data
Real-world Application

Field Data Results

Corrected Joint Density from Herd A data

Cross-validation

Transmission Rate for low-shedding animals

Transmit rate for low-shedding animals

number of low-positive animals per month

number of high-positive animals per month

Probability
Where could you help?

• Improved MCMC algorithms
  – Less data
  – Less time
  – More complicated models
Modeling the efficacy of an imperfect vaccine with multiple effects

• Vaccines are often imperfect
  – They may not prevent all infections
  – They may have effects other than decreasing susceptibility

• Efficacy can be considered as the proportional effect on a rate in a compartmental model

<table>
<thead>
<tr>
<th>5 vaccine effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Horizontal transmission</td>
</tr>
<tr>
<td>i. Susceptibility</td>
</tr>
<tr>
<td>ii. Infectiousness</td>
</tr>
<tr>
<td>2. Duration of latency</td>
</tr>
<tr>
<td>3. Duration of low-infectious period</td>
</tr>
<tr>
<td>4. Progression of clinical symptoms</td>
</tr>
</tbody>
</table>
Next Step: Estimating vaccine efficacy against JD

\[ \gamma(t_b) = \gamma_1 \{Y_1(t_b) + V_{Y_1}(t_b)\} + \gamma_2 \{Y_2(t_b) + V_{Y_2}(t_b)\} + \gamma_3 \{T_{tr}(t_b) + V_{tr}(t_b)\} \]

\[ \lambda(t) = \frac{\beta_1 [Y(t) + T_{tr}(t)] + \beta_2 Y_2(t) + e_\rho \beta_1 [V_{Y_1}(t) + V_{tr}(t)] + \beta_3 Y_2(t)\}}{N} \]
Optimal control models of Johne’s disease in dairy farms
Control of Johne’s disease

• **Test-and-cull:**
  – Diagnostic tests using fecal culture, ELISA, and PCR methods.
  – Culling of test-positive high shedding cows.

• **Improved hygiene management:**
  – Calf rearing management.

• **Vaccination of calves:**
  – 1\textsuperscript{st} generation vaccines: whole cell based (Mycopar©).
  – 2\textsuperscript{nd} generation, subunit-based, DNA-based, or DNA-based vaccines.
  – MAP vaccines are imperfect, and multiple vaccine efficacies have been observed.
Modeling of imperfect *Mycobacterium avium* subspecies *paratuberculosis* (MAP) vaccines on a dairy herd
A deterministic model

The deterministic ordinary differential equations for MAP vaccination model of Figure 1 are described as follows (parameters are defined in Table 1):

\[
\frac{dX_1}{dt} = (1 - p)\mu N - (1 - p)\mu_1 x(t)N - (\lambda_1(t) + \mu_4 + \rho_1)X_1 + \omega V_{r1}
\]  
(A1)

\[
\frac{dX_2}{dt} = \rho_1 X_1 - (\mu_3 + \rho_2)X_2
\]  
(A2)

\[
\frac{dX_3}{dt} = \rho_2 X_2 - \mu_3 X_3
\]  
(A3)

\[
\frac{dT_{r1}}{dt} = \lambda_1(t)X_1 + (1 - p)\mu_1 x(t)N - (\mu_1 + \rho_1)T_{r1}
\]  
(A4)

\[
\frac{dT_{r2}}{dt} = \rho_3 T_{r1} - (\mu_2 + \phi)T_{r2}
\]  
(A5)

\[
\frac{dH_1}{dt} = \phi T_{r2} - (\mu_2 + 2\rho_3)H_1
\]  
(A6)

\[
\frac{dH_2}{dt} = 2\rho_3 H_1 - (\mu_3 + \phi)H_2
\]  
(A7)

\[
\frac{dY_1}{dt} = \sigma H_1 - (\mu_4 + \omega)Y_1
\]  
(A8)

\[
\frac{dY_2}{dt} = \omega H_2 - (\delta_2 + \mu_4 + \alpha)Y_2
\]  
(A9)

\[
\frac{dV_{r1}}{dt} = p\mu N - p\mu_2 x(t)N - (1 - e_2)\lambda_4(t) + \omega_4 V_{r2} - \omega V_{r1}
\]  
(A10)

\[
\frac{dV_{r2}}{dt} = \rho_4 V_{r1} - (\mu_4 + \rho_2)V_{r2}
\]  
(A11)

\[
\frac{dV_{r3}}{dt} = \rho_3 V_{r2} - \mu_3 V_{r3}
\]  
(A12)

\[
\frac{dV_{r4}}{dt} = \lambda_3(t)W_{r3} + p\mu x(t)N - (\mu_4 + \rho_3)W_{r4}
\]  
(A13)

\[
\frac{dV_{r5}}{dt} = \rho_4 V_{r4} - (\mu_4 + \phi)W_{r5}
\]  
(A14)

\[
\frac{dV_{r6}}{dt} = \phi V_{r5} - (\mu_2 + 2\rho_2)W_{r6}
\]  
(A15)

\[
\frac{dV_{r7}}{dt} = 2\rho_2 V_{r6} - (\mu_2 + (1 - e_2)\sigma)W_{r7}
\]  
(A16)

\[
\frac{dV_{r8}}{dt} = (1 - e_4)\sigma W_{r7} - (\mu_3 + (1 - e_4)\omega)W_{r8}
\]  
(A17)

\[
\frac{dV_{r9}}{dt} = (1 - e_4)\omega W_{r8} - ((1 - e_4)\delta_2 + \mu_2 + (1 - e_4)\alpha)W_{r9}
\]  
(A18)

The culling rate \(\delta_4\) for low shedding animals was set to zero in the above differential equations. The forces of infection \(\lambda_4\) and \(\lambda_4'\), vertical transmission rate \(\gamma\), and the replacement rate \(\mu\) are:

\[
\lambda_4(t) = \beta_3(T_{r1} + T_{r2} + (1 - e_2)(V_{r4} + V_{r5})) + \beta_4(Y_1 + (1 - e_4)V_{r7}) + \beta_5(V_1 + (1 - e_5)V_{r5})
\]

\[
\lambda_4'(t) = (1 - e_4)\lambda_4(t)
\]

\[
\gamma(t) = (\gamma_1(H_1 + V_{r1}) + \gamma_2(Y_1 + V_{r2}) + \gamma_3(V_1 + V_{r3})) / N
\]

\[
\mu(t) = \mu N_1(t) + \mu N_2(t) + \mu N_3(t) + (\delta_2 + \alpha)Y_2 + ((1 - e_4)\delta_2 + (1 - e_4)\omega)Y_{r2}
\]

The herd size \(N\) and the group sizes \(N_1\), \(N_2\), and \(N_3\) are:

\[
N = N_1(t) + N_2(t) + N_3(t)
\]

\[
N_1(t) = X_1 + T_{r1} + V_{r1} + V_{r2}
\]

\[
N_2(t) = X_2 + T_{r2} + H_2 + V_{r2} + V_{r3} + V_{r4}
\]

\[
N_3(t) = X_3 + H_3 + Y_1 + Y_2 + V_{r3} + V_{r4} + V_{r5} + V_{r6}
\]
Results: dynamics without/with controls

No control

T&C (annual test), no vaccines

T&C (semiannual test), no vaccines

T&C (annual test) + vaccines (delay of the onset of shedding)
Relative change of prevalence in adult cow group at 5 and 10 years after vaccination started.

Filled boxplots: No Test and cull.

Unfilled boxplots: with Test and cull.
Optimal control models of Johne’s disease

- Objective functional:
  - Elimination of MAP infection.
    \[ I_{\text{infected animals}}(t = T_f) = 0 \]
  - Control of MAP transmission.
    \[ \min_{t = T_0} \int_{t = T_f} I_{\text{infected animals}}(t) dt \]
  - Optimal economic model.
    \[ \min_{t = T_0} \int_{t = T_f} e^{-rt} [AI_{\text{infected animals}}(t) + (B_\delta u_\delta^2 + B_\beta u_\beta^2 + B_v u_v^2) + \text{other terms}] dt \]
Control variables and constraints

- Control variables aimed at:
  - Test-based culling rates ($u_\delta$).
  - Transmission rates ($u_\beta$).
  - Vaccine efficacy parameters ($u_v$).

- Constraints:
  - A system of ordinary differential equations.
  - Compartment model providing numbers of calves, heifers, and cows in each compartment, which are needed in the objective functional.
We need your help

- Deterministic optimal control models:
  - Formulation of the optimal control models using Pontryagin’s maximal principle.
  - Development of computer codes for the optimal control models.
  - Finding the optimal control strategies and solutions of the dynamic systems.

- Stochastic optimal control model.
  - Stochastic differential equations.
  - Individual-based (agent-based).
References using Pontryagin’s Maximal Principle


Then to our Mastitis research ...

2. Modeling production and health:

Our overall goal is to develop a comprehensive economic model, dynamic model (DP), to assist farmers in making treatment and culling decisions.

Our 1st example:
Elva Cha’s PhD research: “Optimal Clinical Mastitis Management in Dairy cows”
Clinical Mastitis (inflammation in mammary gland which can be observed)

Common, costly disease (major losses: milk yield, conception rates, and culling).

Cost of Clinical Mastitis

• The cost of clinical mastitis (CM) **varies greatly** for individual cows, depending on

  • performance of the cow
  • age (lactation, month in lactation)
  • pregnancy status
  • type of CM
Objectives:

1. Calculate the cost of more than 3 different types of CM

2. To determine the economically optimal amount of information needed to make CM treatment decisions
Current CM classification

• There are many different bacteria that can cause CM in dairy cows
• Our model has categorized these into 3 groups
  – Gram-positive
  – Gram-negative
  – Other
• Due to us being limited by how many diseases we can include in our model
What DP can and cannot do:

Capabilities:
- Provides a guide for decision support

Limitations:
- Not for individual animals
- There is no memory

Taken from slides of ‘Advanced Herd Management Course 2010’ by Anders Ringgaard Kristensen http://www.prodstyr.ihh.kvl.dk/vp/2010/plan.htm
Fundamentals of DP

- Cow’s life is represented as a sequence of discrete stages
- Each stage associated with states that describe various characteristics of a cow
Life of a dairy cow

Heifer
Life of a dairy cow

Heifer

Inseminate at 15mo
Life of a dairy cow

Heifer

Inseminate at 15mo

www.cvmbs.colostate.edu/.../notes/table.htm
Life of a dairy cow

Heifer

0 24 mo  Lactating dairy cow
Max. 20 month lactation

Inseminate at 15mo

www.cvmbs.colostate.edu/.../notes/table.htm
Life of a dairy cow

Lactating dairy cow

Voluntary waiting period = 60d
Life of a dairy cow

Lactating dairy cow

0

Voluntary waiting period = 60d

Inseminate at 3mo
Life of a dairy cow

Lactating dairy cow

Voluntary waiting period = 60d

Inseminate at 3mo

Dry period between month 10 and 12
Life of a dairy cow

Lactating dairy cow

Voluntary waiting period = 60d

0

Inseminate at 3mo

Dry period between month 10 and 12

www.cvmbs.colostate.edu/.../notes/table.htm
Fundamentals of DP

Stages $n$ (monthly time intervals from calving)

State $i$ observed $\rightarrow$ Decision made

Immediate reward or cost incurred

GOAL: find a policy of decisions (i.e. the set of decisions for all stages) that maximizes e.g. expected discounted reward
Structure of our DP

- Founder
  - a
  - a
  - a

- Child
  - a
  - 2
  - 3
  - 4

- Grandchild
  - 3
  - 4
  - 5
  - 6

- Lactation
  - Month in lactation

- Process
  - Stage
  - State
  - Action

- a: states of permanent milk yield
- b: states of temporary milk yield, pregnancy, and mastitis

- Replace
- Keep
- Inseminate
Structure of the hierarchic Markov process optimization model:

**First level:** 5 milk yield levels

**Second level:** 8 possible lactations and 2 carry-over mastitis states from previous lactation (yes/no).

**Third level:** 20 lactation stages (max calving interval of 20 months).

5 temporary milk yield levels (relative to permanent milk yield),
9 pregnancy status levels (0=open, 1-7 months pregnant, and 8=to be dried off), one involuntary culled state

13 mastitis states:
0=no mastitis
1 = 1st occurrence of CM (observed at the end of the stage),
2, 3, 4 = 1, 2, 3 and more months after 1st CM,
5 = 2nd CM,
6, 7, 8 = 1, 2, 3 and more months after 2nd CM,
9 = 3rd CM,
10, 11, 12 = 1, 2, 3 and more months after 3rd CM,
CM events > 3 assigned same penalties as if they were 3rd occurrence.

After deleting impossible stage-state combinations, the model described 560,725 stage-state combinations.
Structure of our DP
Fundamentals of DP

• Curse of dimensionality (COD)
  – Effect of adding states
  – Way to address this: hierarchical Markov process
    • A series of child processes (finite time) built into the founder process (infinite time)
    • Advantage
      – Reduce state space as age of the cow can be omitted
Table 1  The effects of different types of clinical mastitis (CM) (gram-positive, gram-negative, other) on net return, CM cases, % of CM cases treated, average cost of CM and average cost per case, following an optimal replacement policy (all costs in USD)

<table>
<thead>
<tr>
<th></th>
<th>Net return</th>
<th>CM cases</th>
<th>% of cases treated</th>
<th>CM</th>
<th>Average of CM</th>
<th>Average cost per case</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CM</td>
<td>426.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>357.35</td>
<td>44.3</td>
<td>93.6</td>
<td>68.70</td>
<td>155.08</td>
<td></td>
</tr>
<tr>
<td>Gram-negative and other</td>
<td>374.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only gram-positive</td>
<td>370.06</td>
<td>12.6</td>
<td>93.1</td>
<td>16.85</td>
<td>133.73</td>
<td></td>
</tr>
<tr>
<td>Gram-positive and other</td>
<td>390.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only gram-negative</td>
<td>372.79</td>
<td>15.5</td>
<td>93.1</td>
<td>32.71</td>
<td>211.03</td>
<td></td>
</tr>
<tr>
<td>Gram-positive and gram-negative</td>
<td>372.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only other</td>
<td>372.79</td>
<td>16.2</td>
<td>94.6</td>
<td>15.44</td>
<td>95.31</td>
<td></td>
</tr>
</tbody>
</table>
What our DP can do

Table 2 Effects of increasing and decreasing milk price replacement cost and treatment cost by 20%, halving the incidence of all 3 different types of clinical mastitis (CM) and increasing pregnancy rate by 20% on CM cases and the average cost/case for all CM, and each different type of CM.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>All (^a) CM cases (^c)</th>
<th>Average cost/case (^d)</th>
<th>Gram-positive (^b) CM cases (^c)</th>
<th>Average cost/case (^d)</th>
<th>Gram-negative CM cases (^c)</th>
<th>Average cost/case (^d)</th>
<th>Other CM cases (^c)</th>
<th>Average cost/case (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk price +20%</td>
<td>43.5</td>
<td>173.23</td>
<td>12.4</td>
<td>145.36</td>
<td>15.1</td>
<td>240.63</td>
<td>15.9</td>
<td>105.08</td>
</tr>
<tr>
<td>Milk price -20%</td>
<td>45.3</td>
<td>137.91</td>
<td>12.8</td>
<td>123.49</td>
<td>15.9</td>
<td>183.37</td>
<td>15.9</td>
<td>90.10</td>
</tr>
<tr>
<td>Replacement cost +20%</td>
<td>45.1</td>
<td>163.23</td>
<td>12.8</td>
<td>138.70</td>
<td>15.8</td>
<td>225.15</td>
<td>16.5</td>
<td>99.05</td>
</tr>
<tr>
<td>Replacement cost -20%</td>
<td>43</td>
<td>148.67</td>
<td>12.3</td>
<td>130.58</td>
<td>15</td>
<td>200.06</td>
<td>15.8</td>
<td>93.13</td>
</tr>
<tr>
<td>Treatment cost +20%</td>
<td>44.2</td>
<td>164.97</td>
<td>12.6</td>
<td>147.60</td>
<td>15.5</td>
<td>218.57</td>
<td>16.2</td>
<td>104.10</td>
</tr>
<tr>
<td>Treatment cost -20%</td>
<td>44.3</td>
<td>145.59</td>
<td>12.6</td>
<td>120.13</td>
<td>15.5</td>
<td>203.96</td>
<td>16.2</td>
<td>86.84</td>
</tr>
<tr>
<td>Halving incidence of all 3 different types of CM</td>
<td>29.6</td>
<td>155.45</td>
<td>14.4</td>
<td>137.80</td>
<td>7.5</td>
<td>216.84</td>
<td>7.7</td>
<td>98.47</td>
</tr>
<tr>
<td>Increasing pregnancy rate by 20%</td>
<td>45.7</td>
<td>150.35</td>
<td>12.9</td>
<td>131.55</td>
<td>16.1</td>
<td>205.90</td>
<td>16.7</td>
<td>92.70</td>
</tr>
</tbody>
</table>
What our DP can do

Figure 1. Retention payoffs under an optimal policy for hypothetically open (non pregnant) cows free of clinical mastitis (CM) and with different types of CM, specific to a second lactation cow with average milk yield per 305 day lactation.
What our DP can do

Figure 2. Retention payoffs under an optimal policy for hypothetically open (non pregnant) cows free of clinical mastitis (CM) and with different types of CM, specific to a second lactation cow with permanent milk yield of 1,500 kg per 305 day lactation less than the average in the herd (note: gram-positive and gram-negative CM graphs overlap from month 5).
What our DP can do

• Allows for parameters such as *production costs*, *economic values* and *disease frequencies* to be altered

• Thus, this can provide farmers economically optimal guidelines *specific* to their individual cows
Application

Farmers could run this program with parameters specific to their farm, and this information will be exported into their herd management program.
What we are currently doing

1. Restructuring of our DP to circumvent the COD
   - Testing
Restructuring
Background to restructuring

• Previously, we added a state variable with 4 classes for each disease
  – This means a new disease increases the state space by a factor of 4
Background to restructuring

• By adding the hierarchy
  – The state space is smaller
  – The number of child processes corresponds to the number of diseases
    • Additive effect
  – Still need to add new state at the parent level (but not 4) for each new disease
  – Sharing child processes
Next step

1. Add more diseases to our DP, such that we study >3 different types of mastitis
A request for “an optimal DP” structure:

- 7 permanent milk levels
- 8 lactations
- 20 lactation stages
- 9 pregnancy states
- 5 temporary milk levels
- About 36 disease states (4 mastitis types with 4 stages, 3 lameness types with 3 stages, 6 calving disease with 1 state, 2 fertility disorders with 2 stages, and a healthy state)
If we were able to overcome the curse of dimensionality ...

No longer only *generic guidelines for the generic cow.*

The *DP recommendations* could be tailored to the *individual cow in real time* according to her cow characteristics and economics of the herd.
Where we need your help!

• Any ideas of how to further circumvent the COD??
Requests related to Antimicrobial Resistance

Project 3: “Develop, evaluate and improve food animal systems-based mathematical models of antimicrobial resistance among commensal bacteria”

Victoria Volkova, DVM, PhD, Research Associate
EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE

AQUACULTURE
- Sea/lakes
- Drinking water

Rivers and streams
- Drinking water

SOIL
- Industrial and household antibacterial chemicals
- Sewage

WILDLIFE
- Vegetation, seed crops, fruit

FOOD ANIMALS
- SWINE
- CATTLE
- PIGS
- VEAL CALVES
- OTHER FARMED LIVESTOCK

COMPANION ANIMALS
- Animal feeds
- Rendered deadstock

COMMUNITY
- Urban
- Rural

HUMAN
- Hospitalized
- Extended care facilities

Meat
- Handling, preparation, consumption
- Direct contact

Prescott (2000)
• Reservoirs of resistant genes are found in commensal bacteria in the human and animal gastrointestinal tracts (small intestine supports ~ 10^{10} bacterial cells/g).

• Commensal bacteria can transfer mobile genes coding antimicrobial resistance among themselves and to pathogen bacteria (e.g. plasmid transfer between Salmonella and E. coli)

Molecular mechanisms involved in the spread of antimicrobial resistance. Inter-cellular movement (horizontal spread) is the main cause of acquisition of resistance genes.

Salyers et al., 2004

Boerlin, 2008
Population dynamics of antibiotic-sensitive and – resistant bacteria
Linked to antibiotic exposure
Emergence of resistance during antibiotic treatment
Fitness cost linked to microbial growth

The host population is divided according its epidemiological status (e.g. susceptible, infectious)
“Binary response”: Animal carries the bacteria carrying the resistance or not
Transmission of resistant clones
Individuals colonized with either susceptible or resistant strains
Within host dynamics of antimicrobial resistance dissemination

Microbial growth for sensitive and resistant strains with horizontal gene transfer

\[
\frac{dN_s}{dt} = rN_s - r \frac{(N_s + N_r)}{K} N_s - \frac{N_s N_r}{N} - uE_d(C)N_s
\]

\[
\frac{dN_r}{dt} = r(1 - \alpha)N_r - r(1 - \alpha) \frac{(N_s + N_r)}{K} N_r + \frac{N_s N_r}{N} - uE_d(C)N_r - r(1 - \alpha)p N_r
\]

Logistic Growth

Plasmid transfer

Antibiotic effect

Plasmid loss during segregation

\[
E_d(C) = 1 + \frac{E_{\text{max}} \left( \frac{C}{\text{MIC}} \right)^H}{EC_{50}^H + \left( \frac{C}{\text{MIC}} \right)^H}
\]

Percentage of resistant bacteria 24 h after the end of the antimicrobial treatment
Between host dynamics of antimicrobial resistance dissemination
Integrating within and between host antimicrobial resistance dynamics

• Interventions to minimize the dissemination of antimicrobial resistance can be applied at different organizational levels (e.g. within host/between hosts and environment):
  • Optimize antimicrobial dosage regimes to mitigate the dissemination of antimicrobial resistance within enteric commensal bacteria.
  • Reduce the exposure of animals to antimicrobial resistant bacteria.

• Mathematical approaches that integrate within and between host dynamics are necessary to optimize mitigation strategies acting at different hierarchical scales:
  • Agent-based/Individual-based models
  • Dynamic nested models
Modeling On-farm *Escherichia coli* O157:H7 population dynamics

- Metapopulation models has allowed us to investigate the potential role of non-bovine habitats (i.e., water troughs, feedbunks, and the surrounding pen environment) on the persistence and loads of *E. coli* O157:H7 in feedlots.

- O157:H7 survive and reproduce in water troughs, feed, slurry, pen floors.

\[
\begin{align*}
dC/dt &= r_c C \left[ 1 - \frac{C}{K_c} \right] - (\mu_c + p) C + m_{ec} E + m_{wc} W + m_{fc} F \\
dW/dt &= r_w W \left[ 1 - \frac{W}{K_w} \right] - (\mu_w + m_{wc} + m_{we}) W + m_{ew} E + m_{cw} p C \\
dF/dt &= r_f F \left[ 1 - \frac{F}{K_f} \right] + m_{cf} p C - (\mu_f + m_{fc}) F \\
dE/dt &= r_e E \left[ 1 - \frac{E}{K_e} \right] + m_{we} W + m_{ce} p C - (\mu_e + m_{ew} + m_{ec}) E 
\end{align*}
\]

Ayscue et al., Foodborne Pathog Dis, 6:461-470 (2009)
This metapopulation approach is suitable for modeling the dynamics of antimicrobial resistance dissemination. Pharmacokinetics and pharmacodynamics and biological fitness of antimicrobial resistance can be integrated.
Assuming three types of ecological patches (water, environment and animals) and assuming indirect transmission (bacteria are transmitted to animals through water and environment):

For the $j$ animal:

\[
\frac{dN_{sj}}{dt} = r_j N_{sj} - r_j \frac{(N_{sj} + N_{rj})}{K_j} N_{sj} - \beta \frac{N_{sj} N_{rj}}{N_j} N_{sj} - u_j E_d (C) N_{sj} + m_{wj} W_s + m_{ej} E_s - (m_{jw} + m_{je}) N_{sj} + m_{wj} W_r + m_{ej} E_r - (m_{jw} + m_{je}) N_{rj}
\]

\[
\frac{dN_{rj}}{dt} = r_j (1 - \alpha) N_{rj} - r_j (1 - \alpha) \frac{(N_{sj} + N_{rj})}{K_j} N_{rj} + \beta \frac{N_{sj} N_{rj}}{N_j} N_{rj} - u_j E_d (C) N_{rj} - r_j (1 - \alpha) p N_{rj}
\]

**Water patch:**

\[
\frac{dW_s}{dt} = r_w W_s - r_w \frac{(W_s + W_r)}{K_w} W_s - \beta \frac{W_s}{W} W_r - u_w W_s + \sum_{j=1}^{j=n} m_{jw} N_{sj} + m_{ew} E_s - \sum_{j=1}^{j=n} m_{wj} W_s - m_{we} W_s
\]

\[
\frac{dW_r}{dt} = r_w (1 - \alpha) W_r - r_w (1 - \alpha) \frac{(W_s + W_r)}{K_w} W_r - \beta \frac{W_s}{W} W_r - u_w W_r + \sum_{j=1}^{j=n} m_{jw} N_{rj} + m_{ew} E_r - \sum_{j=1}^{j=n} m_{wj} W_r - m_{we} W_r - r_w (1 - \alpha) p W_r
\]

**Environmental patch:**

\[
\frac{dE_s}{dt} = r_e E_s - r_e \frac{(E_s + E_r)}{K_e} E_s + \beta \frac{E_s}{E} E_r - u_e E_s + \sum_{j=1}^{j=n} m_{je} N_{sj} + m_{we} W_s - \sum_{j=1}^{j=n} m_{ej} E_s - m_{ew} E_s
\]

\[
\frac{dE_r}{dt} = r_e (1 - \alpha) E_r - r_e (1 - \alpha) \frac{(E_s + E_r)}{K_e} E_r + \beta \frac{E_s}{E} E_r - u_e E_r + \sum_{j=1}^{j=n} m_{je} N_{rj} + m_{we} W_r - \sum_{j=1}^{j=n} m_{ej} E_r - m_{ew} E_r - r_e (1 - \alpha) p W_e
\]
Potential students projects

• Application of optimal control to evaluate strategies in metapopulation models
• Development of agent based models to address antimicrobial resistance dissemination.
• Optimization in agent based models
• Optimization in hierarchical models