Computational Sustainability

February 1st, 3rd, and 8th, 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:

Project 3. "Food Animal Systems-Based Mathematical Models of Antibiotic Resistance among Commensal Bacteria." Victoriya Volkova, Research Associate

1. Johne's Disease

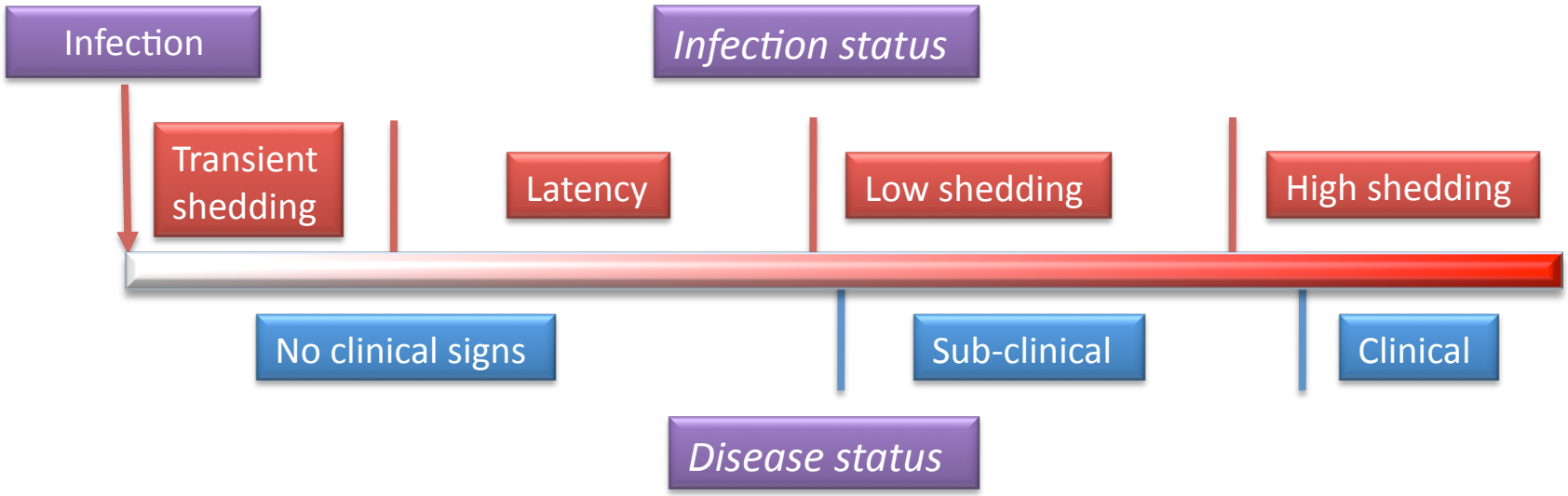
"Cost Effective Control Strategies for The Reduction of Johne's Disease on Dairy Farms"

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.

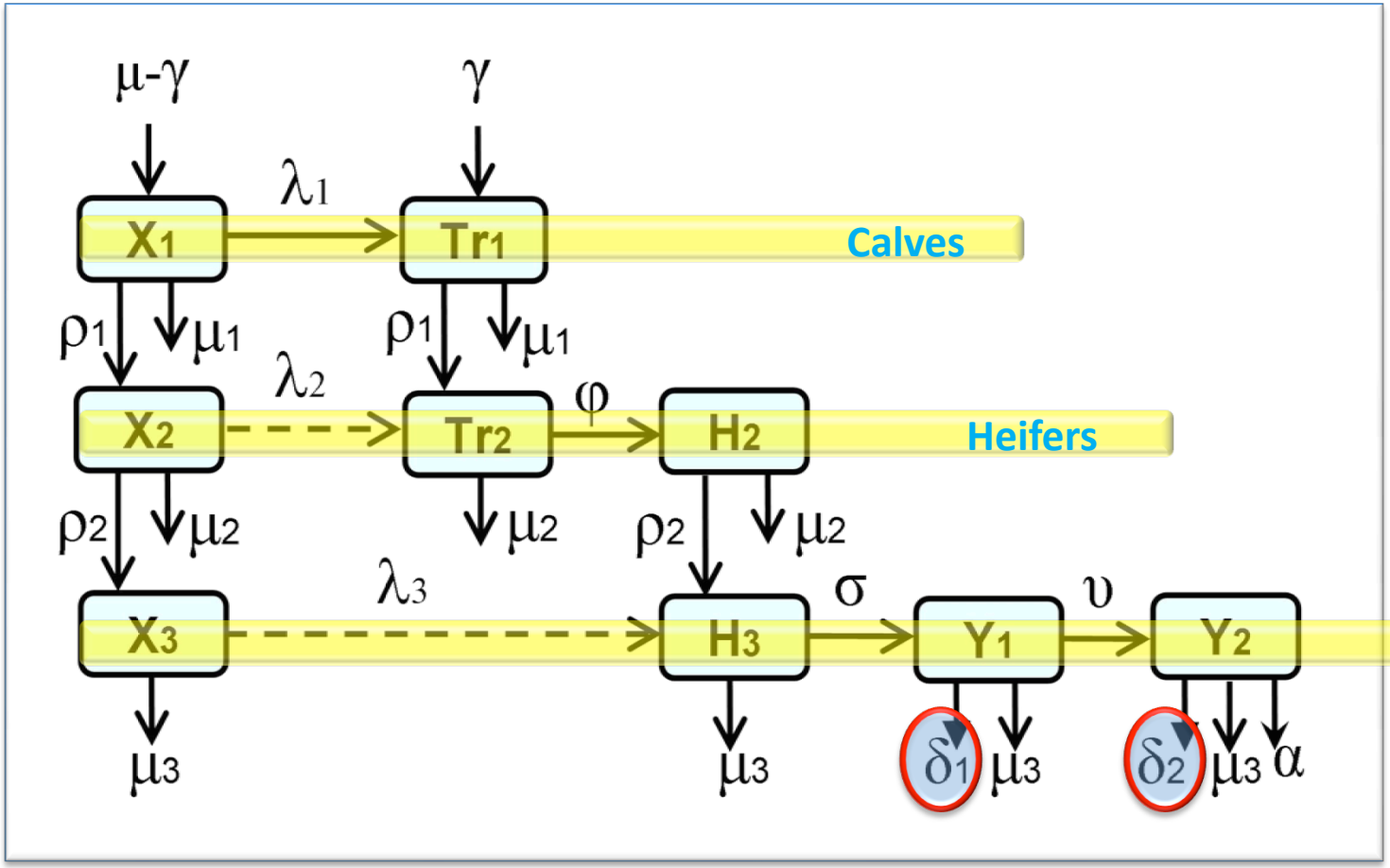
- Public health: a potential association between Johne's disease and human Crohn's disease has been debated.

- Control of Johne's disease:
  - *Test and cull strategies, i.e., to cull/remove infectious animals form 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

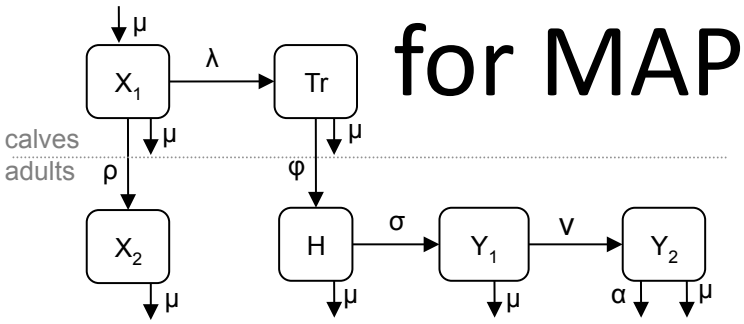
(Evaluation of effectiveness of test-based culling)



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

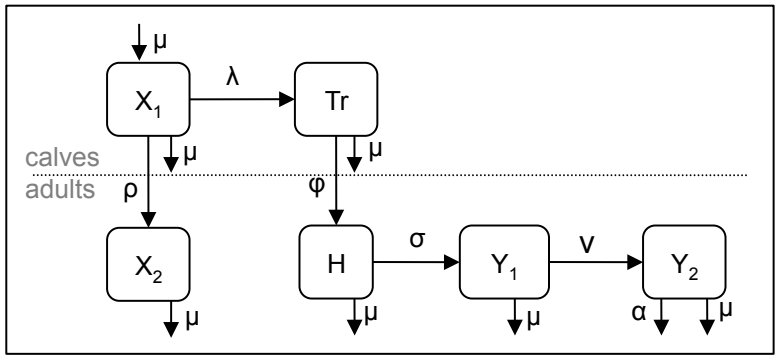
- Missing information:
  - Date of infection
  - Onset of low-shedding
  - Onset of high-shedding
  - True infection status (if all tests results were negative)

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


μ
X1
λ
Tr
calves
adults
μ
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X2
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μ
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μ
α
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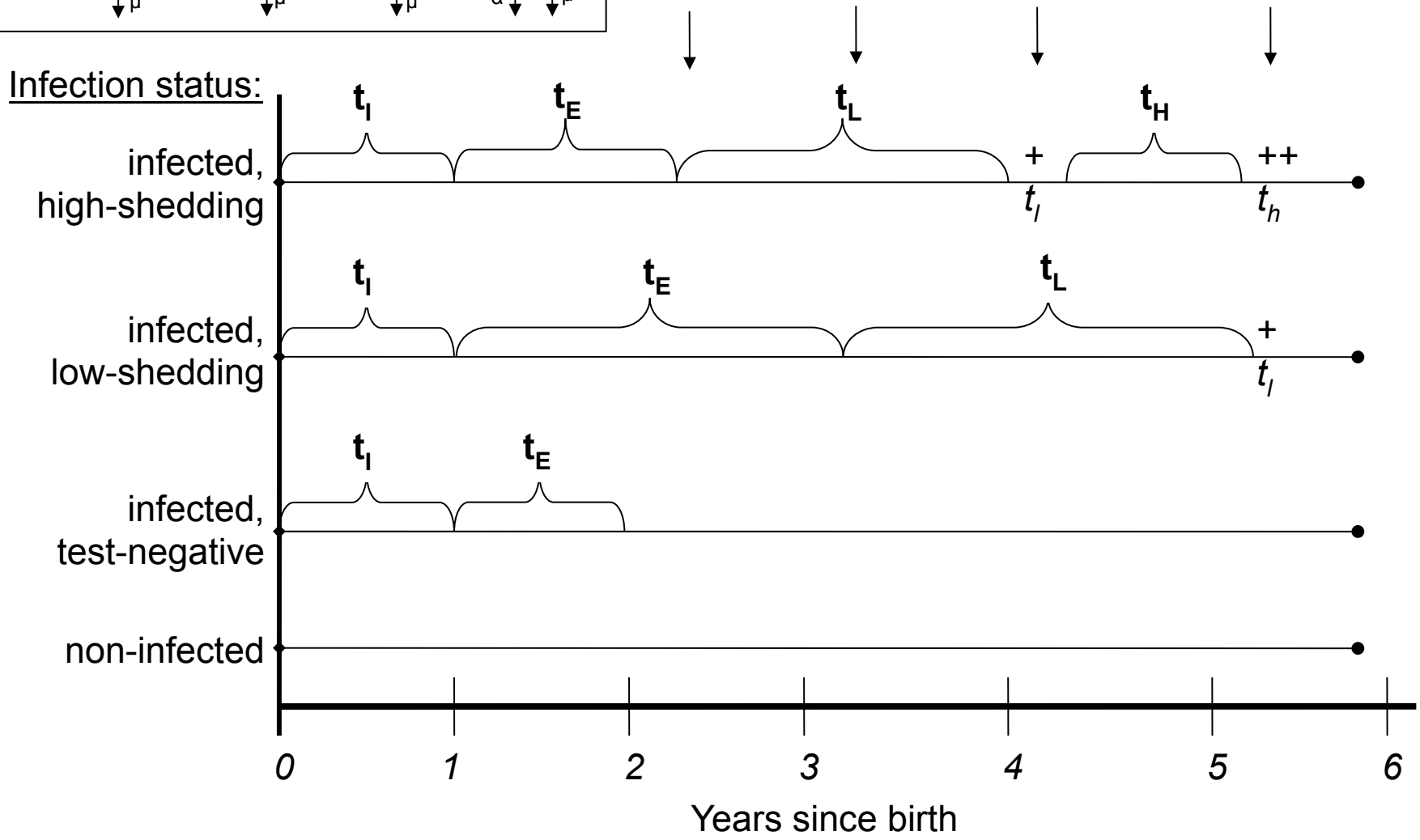
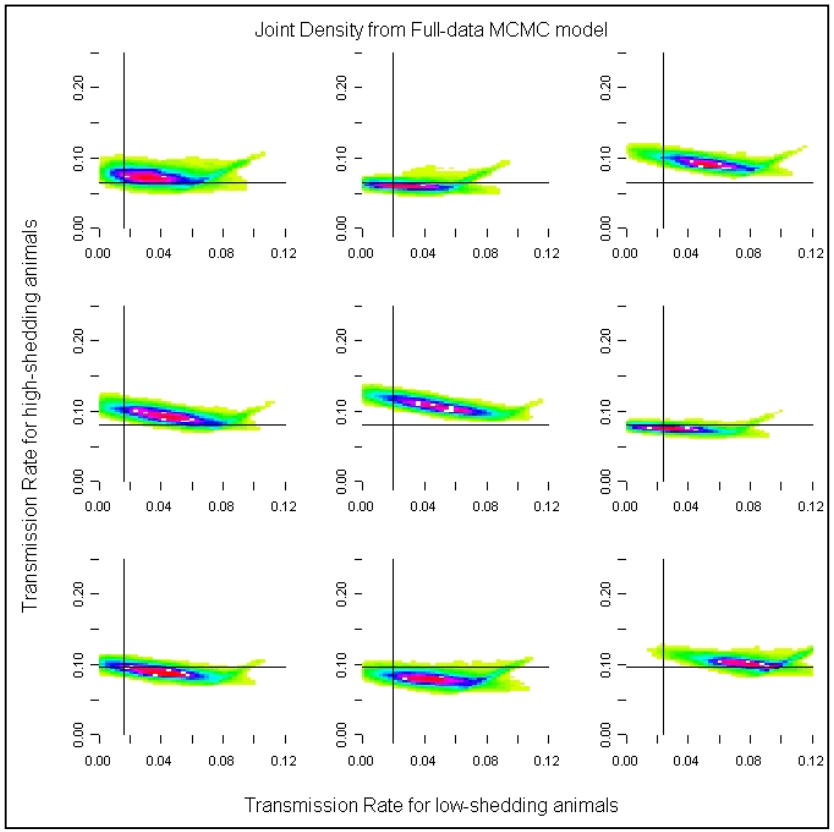

Infection status:
infected, high-shedding
infected, low-shedding
infected, test-negative
non-infected
tI
tE
tL
tH
+
++
tl
th
0
1
2
3
4
5
6
Years since birth

Validating MCMC models

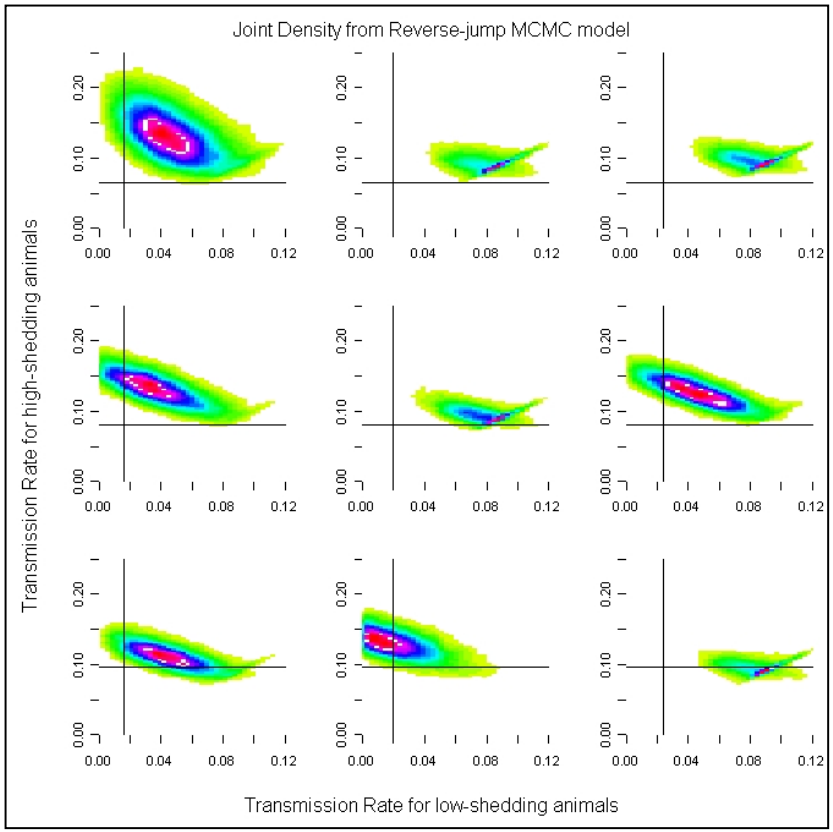
- In order to test that an MCMC model predicts the true parameter distribution, we feed it data simulated with known parameters
- In the case of the JD model, the full model requires individual animal data:
  - Infection status
  - Vaccination status
  - Dates of birth, compartment transitions, death
- We needed the individual-animal stochastic model

Validation Results: Transmission Rate Joint Posterior Density Function

Full Data

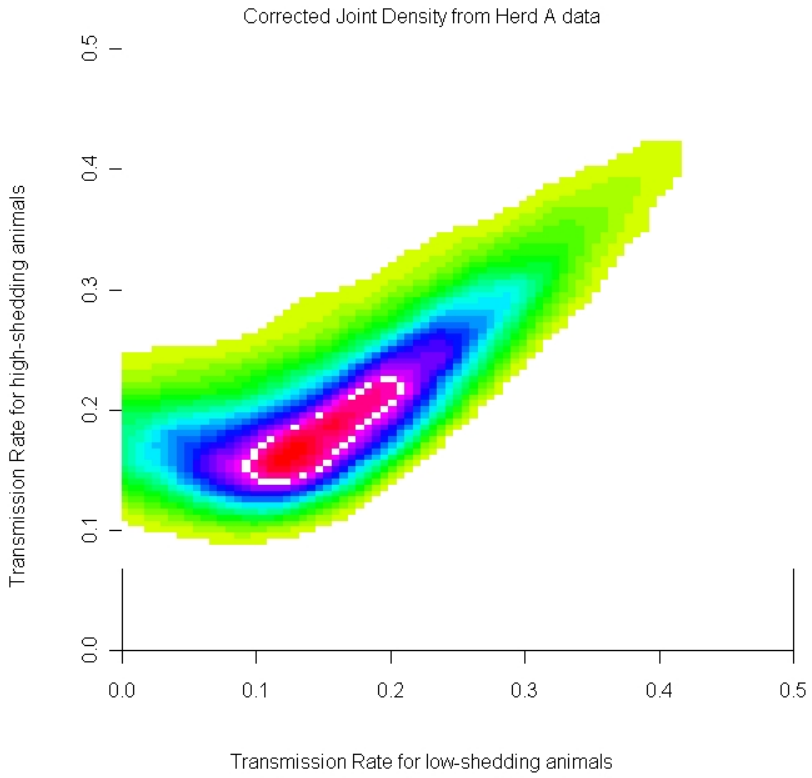


Reduced Data

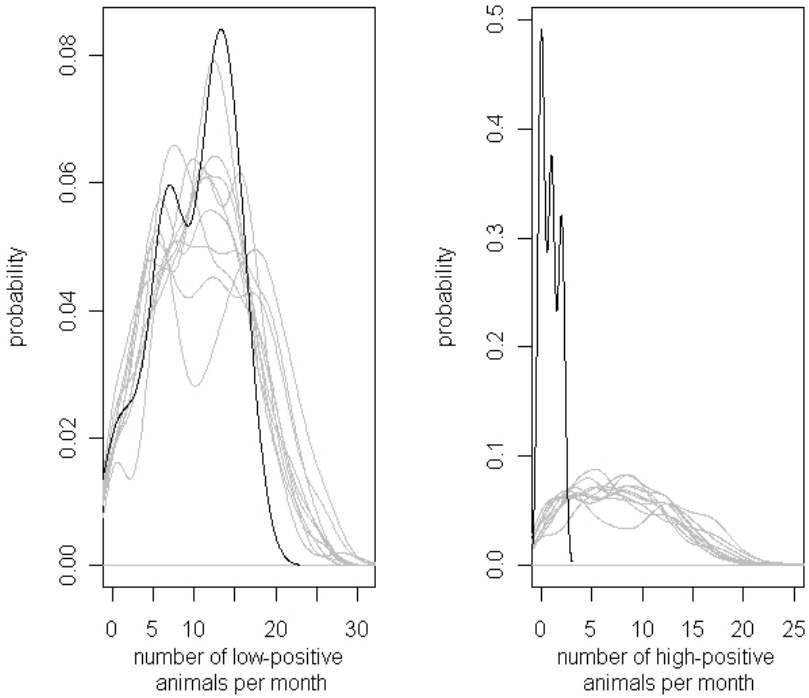


Real-world Application

Field Data Results



Cross-validation



Where could you help?

- Improved MCMC algorithms
  - Less data
  - Less time
  - More complicated models

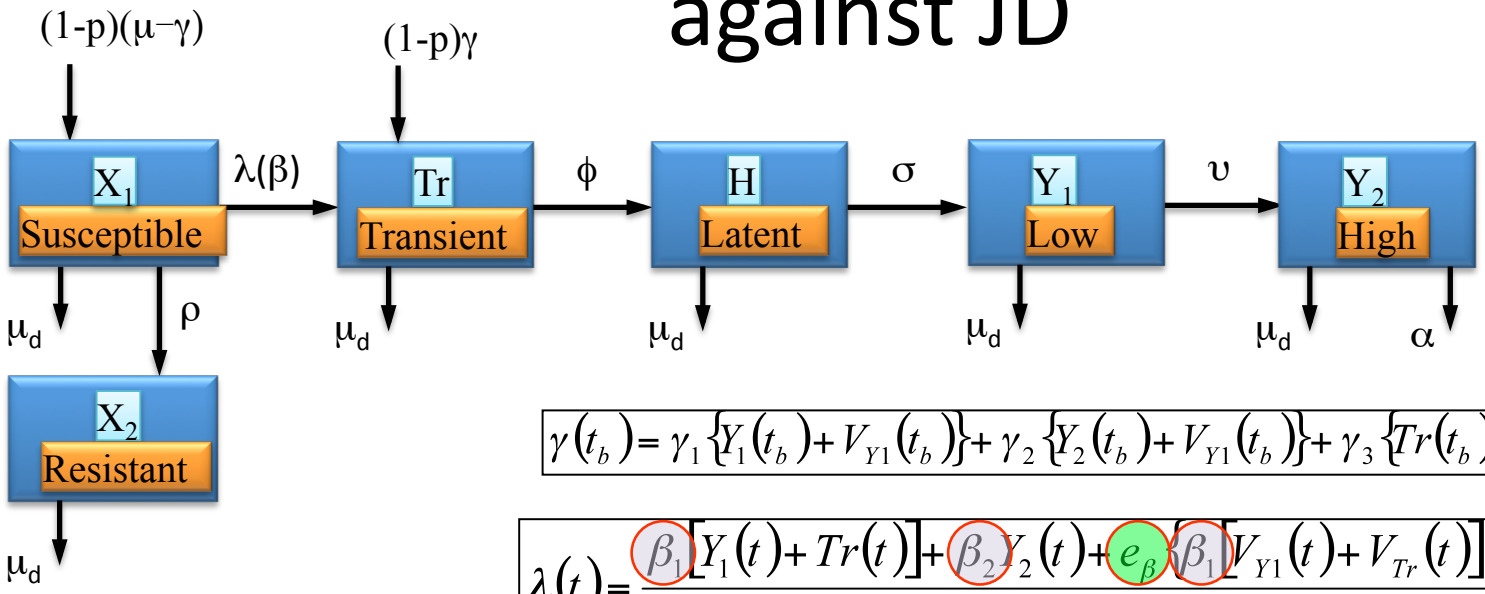
Modeling the efficacy of an imperfect vaccine with multiple effects

- 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

5 vaccine effects:

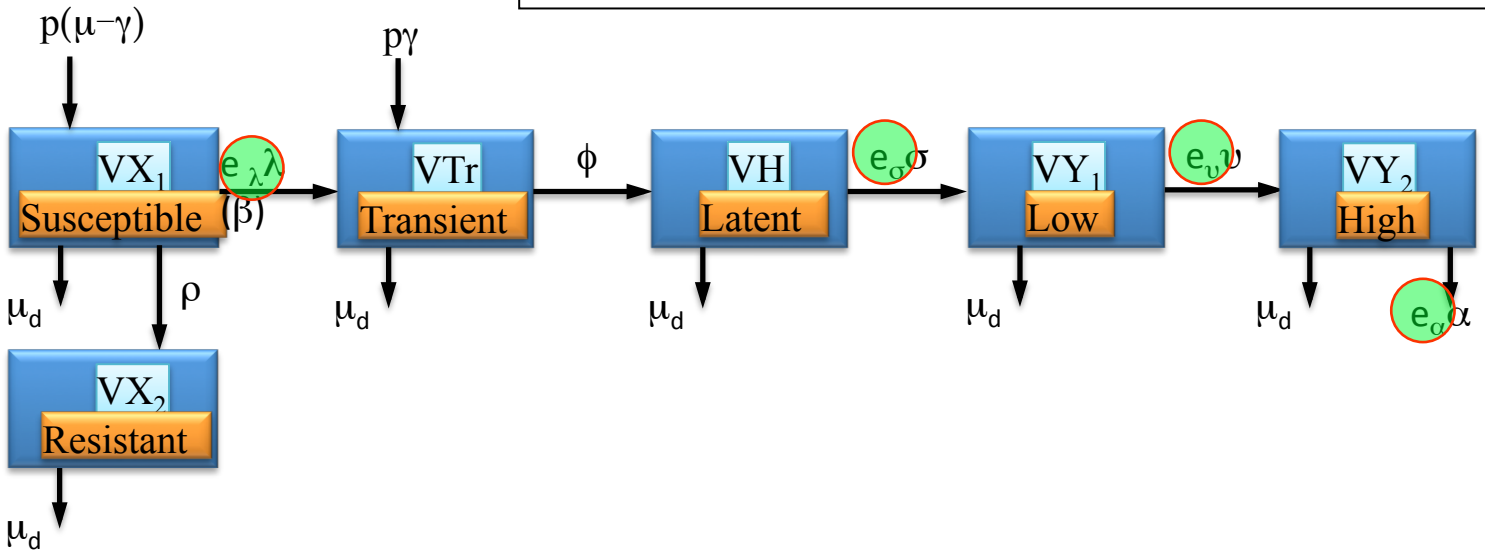
1. Horizontal transmission
   i. Susceptibility
   ii. Infectiousness
2. Duration of latency
3. Duration of low-infectious period
4. Progression of clinical symptoms

Next Step: Estimating vaccine efficacy against JD



$$\gamma(t_b) = \gamma_1\{Y_1(t_b) + V_{Y1}(t_b)\} + \gamma_2\{Y_2(t_b) + V_{Y1}(t_b)\} + \gamma_3\{Tr(t_b) + V_{Tr}(t_b)\}$$

$$\lambda(t) = \frac{\beta_1[Y_1(t) + Tr(t)] + \beta_2 Y_2(t) + e_\beta\{\beta_1[V_{Y1}(t) + V_{Tr}(t)] + \beta_2 V_{Y2}(t)\}}{N}$$



Optimal control models of Johne's disease in dairy farms

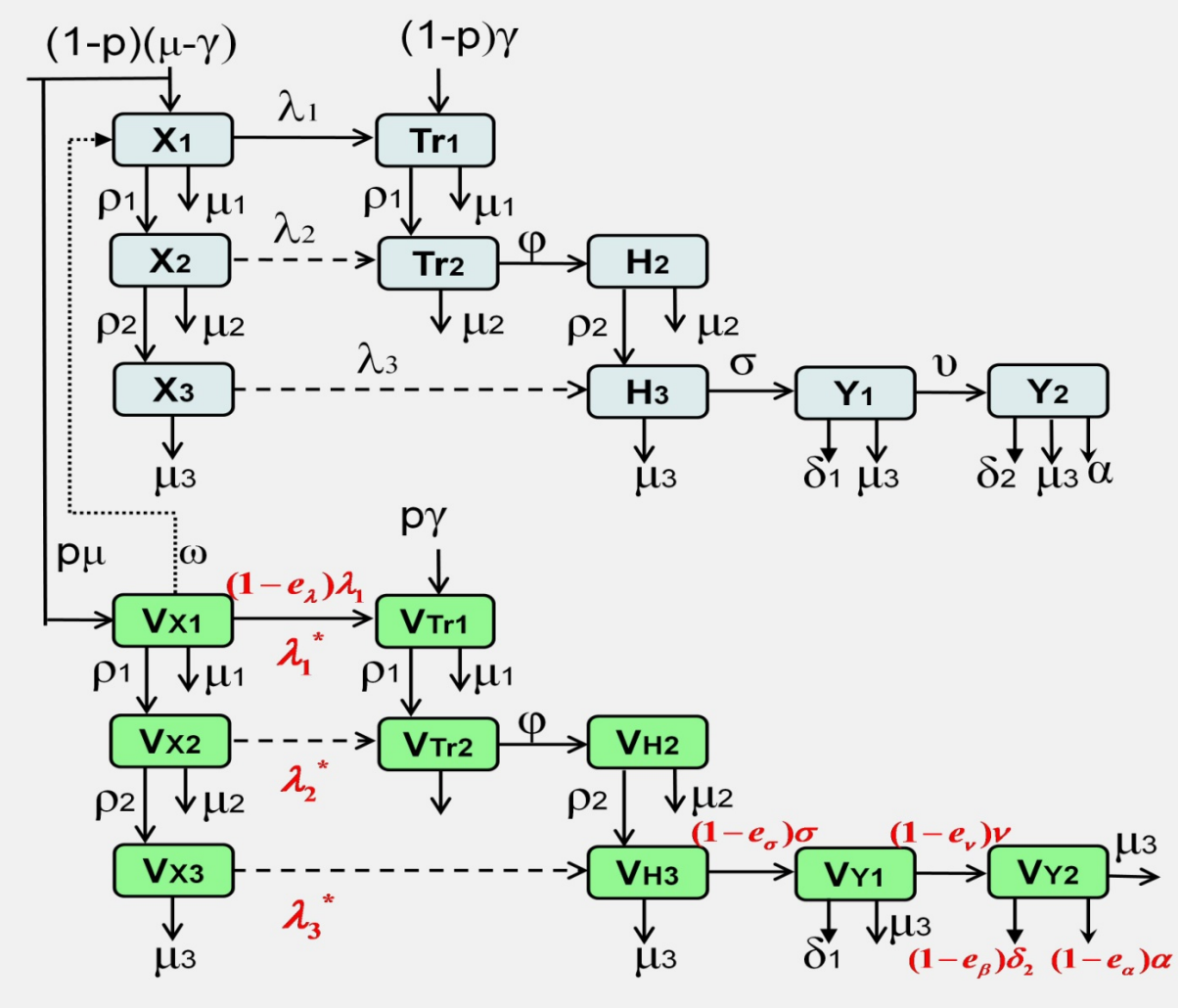
Control of Johne's disease

- 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:
  - 1st generation vaccines: whole cell based (Mycopar©).
  - 2nd 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):

$$\frac{dX_1}{dt} = (1-p)\mu N - (1-p)\mu_b\gamma(t)N - (\lambda_1(t) + \mu_1 + \rho_1)X_1 + \omega V_{X1} \quad \text{(A1)}$$

$$\frac{dX_2}{dt} = \rho_1 X_1 - (\mu_2 + \rho_2)X_2 \quad \text{(A2)}$$

$$\frac{dX_3}{dt} = \rho_2 X_2 - \mu_3 X_3 \quad \text{(A3)}$$

$$\frac{dTr_1}{dt} = \lambda_1(t)X_1 + (1-p)\mu_b\gamma(t)N - (\mu_1 + \rho_1)Tr_1 \quad \text{(A4)}$$

$$\frac{dTr_2}{dt} = \rho_1 Tr_1 - (\mu_2 + \phi)Tr_2 \quad \text{(A5)}$$

$$\frac{dH_2}{dt} = \phi Tr_2 - (\mu_2 + 2\rho_2)H_2 \quad \text{(A6)}$$

$$\frac{dH_3}{dt} = 2\rho_2 H_2 - (\mu_3 + \sigma)H_3 \quad \text{(A7)}$$

$$\frac{dY_1}{dt} = \sigma H_3 - (\mu_3 + \nu)Y_1 \quad \text{(A8)}$$

$$\frac{dY_2}{dt} = \nu Y_1 - (\delta_2 + \mu_3 + \alpha)Y_2 \quad \text{(A9)}$$

$$\frac{dV_{X1}}{dt} = p\mu N - p\mu_b\gamma(t)N - ((1-e_\lambda)\lambda_1(t) + \mu_1 + \rho_1)V_{X1} - \omega V_{X1} \quad \text{(A10)}$$

$$\frac{dV_{X2}}{dt} = \rho_1 V_{X1} - (\mu_2 + \rho_2)V_{X2} \quad \text{(A11)}$$

$$\frac{dV_{X3}}{dt} = \rho_2 V_{X2} - \mu_3 V_{X3} \quad \text{(A12)}$$

$$\frac{dV_{Tr1}}{dt} = \lambda_1^*(t)V_{X1} + p\mu_b\gamma(t)N - (\mu_1 + \rho_1)V_{Tr1} \quad \text{(A13)}$$

$$\frac{dV_{Tr2}}{dt} = \rho_1 V_{Tr1} - (\mu_2 + \phi)V_{Tr2} \quad \text{(A14)}$$

$$\frac{dV_{H2}}{dt} = \phi V_{Tr2} - (\mu_2 + 2\rho_2)V_{H2} \quad \text{(A15)}$$

$$\frac{dV_{H3}}{dt} = 2\rho_2 V_{H2} - (\mu_3 + (1-e_\sigma)\sigma)V_{H3} \quad \text{(A16)}$$

$$\frac{dV_{Y1}}{dt} = (1-e_\sigma)\sigma V_{H3} - (\mu_3 + (1-e_\nu)\nu)V_{Y1} \quad \text{(A17)}$$

$$\frac{dV_{Y2}}{dt} = (1-e_\nu)\nu V_{Y1} - ((1-e_\beta)\delta_2 + \mu_3 + (1-e_\delta)\alpha)V_{Y2} \quad \text{(A18)}$$

The culling rate δ_1 for low shedding animals was set to zero in the above differential equations. The forces of infection λ_1 and λ_1^*, vertical transmission rate γ, and the replacement rate μ are:

$$\lambda_1(t) = \beta_{Tr}(Tr_1 + Tr_2 + (1-e_\beta)(V_{Tr1} + V_{Tr2})) + \beta_{Y1}(Y_1 + (1-e_\beta)V_{Y1}) + \beta_{Y2}(Y_2 + (1-e_\beta)V_{Y2})$$

$$\lambda_1^*(t) = (1-e_\lambda)\lambda_1(t)$$

$$\gamma(t) = (\gamma_h(H_3 + V_{H3}) + \gamma_1(Y_1 + V_{Y1}) + \gamma_2(Y_2 + V_{Y2}))/N$$

$$\mu(t) = \mu_1 N_1(t) + \mu_2 N_2(t) + \mu_3 N_3(t) + (\delta_2 + \alpha)Y_2 + ((1-e_\beta)\delta_2 + (1-e_\alpha)\alpha)V_{Y2}$$

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

$$N = N_1(t) + N_2(t) + N_3(t)$$

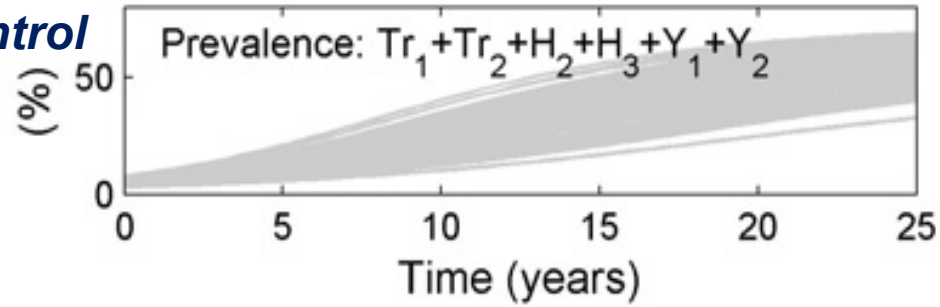
$$N_1(t) = X_1 + Tr_1 + V_{X1} + V_{Tr1}$$

$$N_2(t) = X_2 + Tr_2 + H_2 + V_{X2} + V_{Tr2} + V_{H2}$$

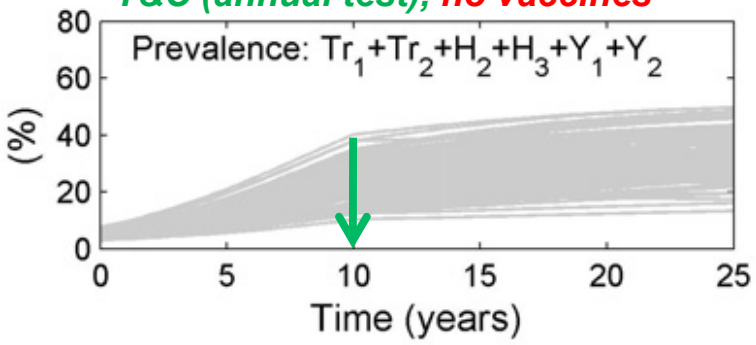
$$N_3(t) = X_3 + H_3 + Y_1 + Y_2 + V_{X3} + V_{H3} + V_{Y1} + V_{Y2}$$

Results: dynamics without/with controls

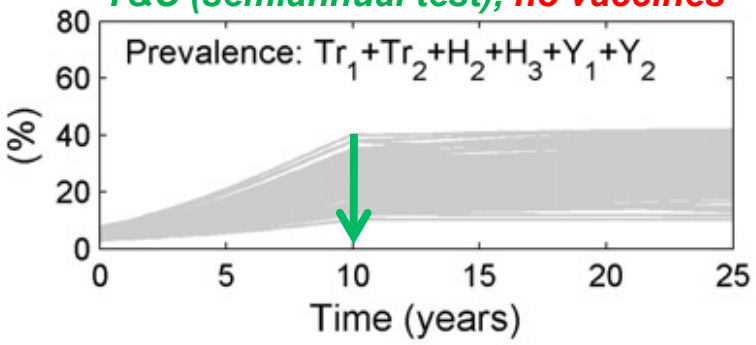
No control



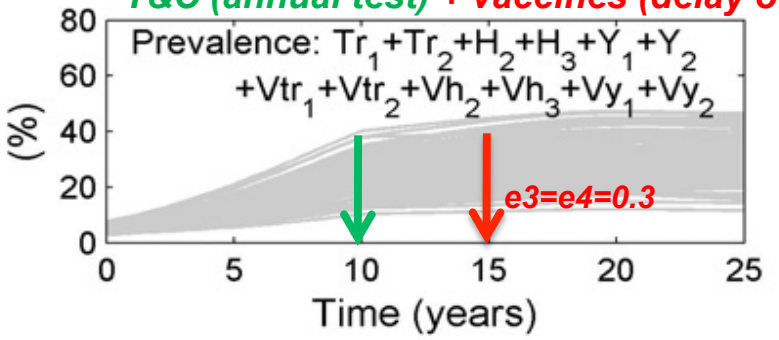
T&C (annual test), no vaccines

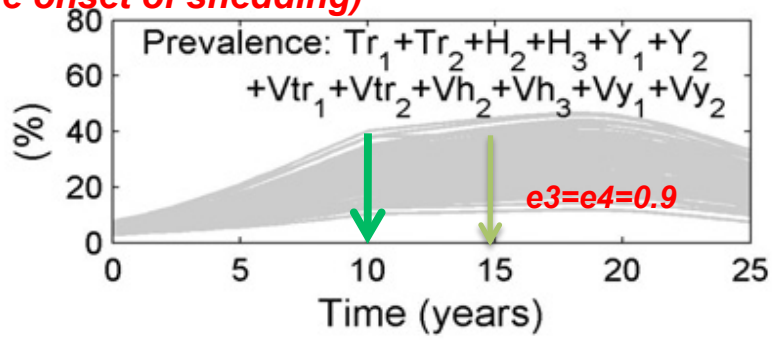


T&C (semiannual test), no vaccines



T&C (annual test) + vaccines (delay of the onset of shedding)

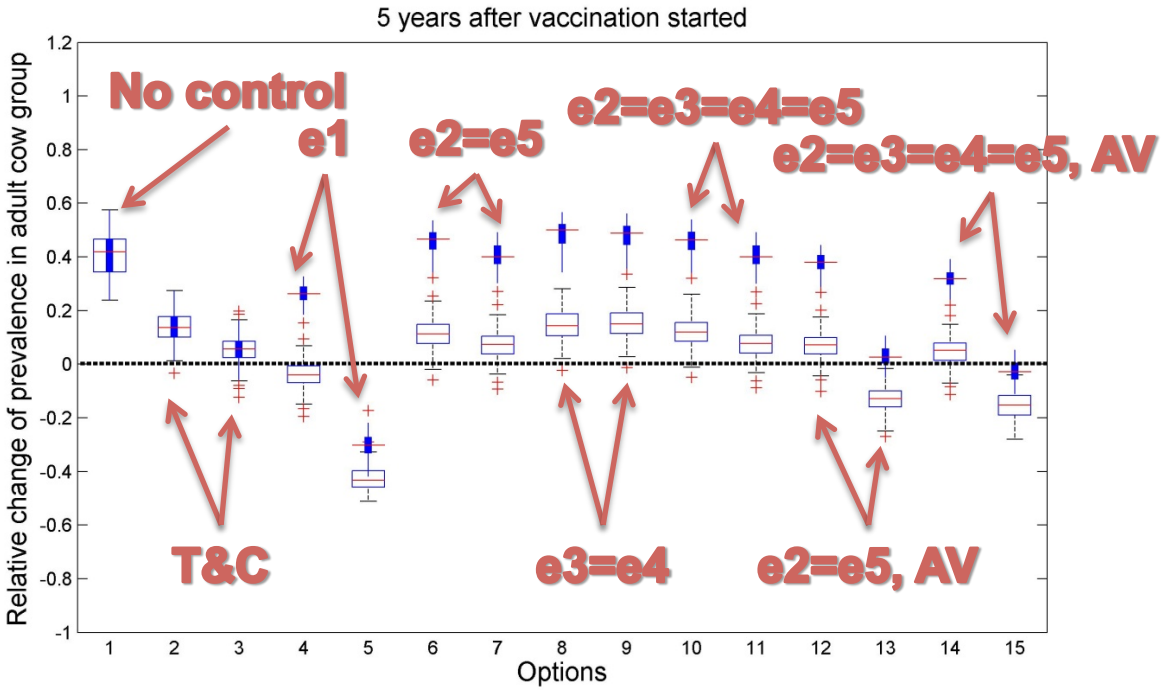


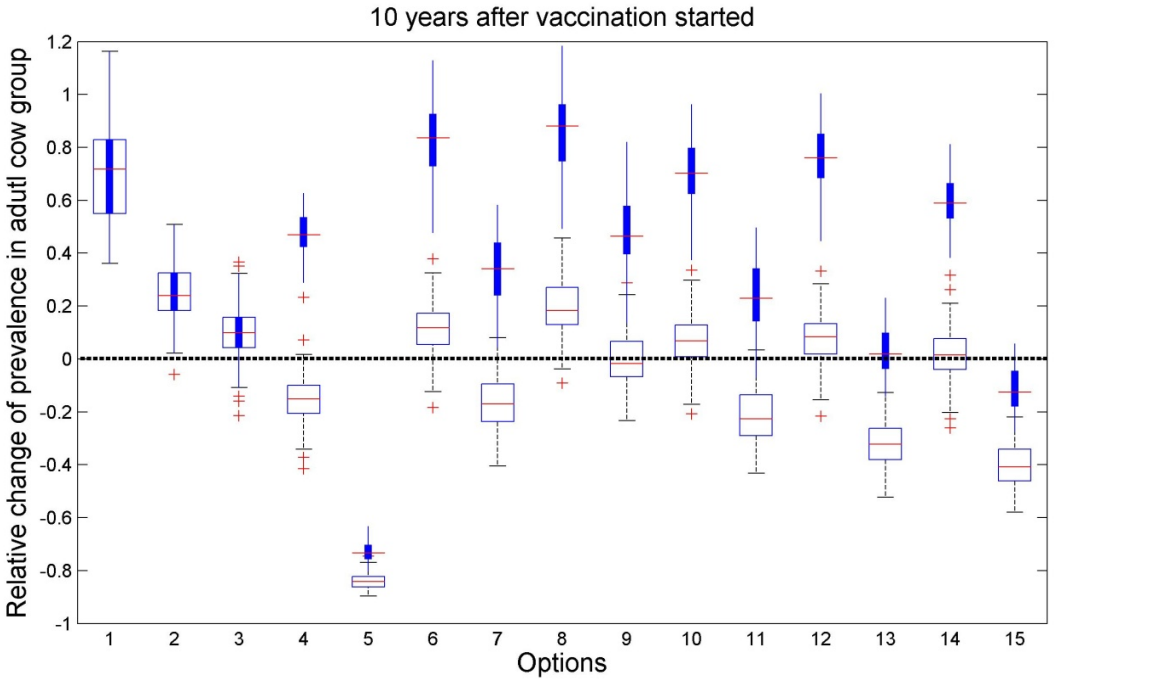


➢Relative change of prevalence in adult cow group at 5 and 10 years after vaccination started.

➢**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.

$$\min \int_{t=T_0}^{t=T_f} I_{\text{infected animals}}(t)dt$$

  - Optimal economic model.

$$\min \int_{t=T_0}^{t=T_f} e^{-rt}[AI_{\text{infected animals}}(t) + (B_\delta u_\delta^2 + B_\beta u_\beta^2 + B_v u_v^2) + \text{other terms}]dt$$

Control variables and constraints

- Control variables aimed at:
  - Test-based culling rates (u_δ).
  - Transmission rates (u_β).
  - 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 Prinicple

- *Optimal control applied to biological models*, by Suzanne Lenhart, and John T. Workman, 2007, CRC press, UK.

- *Optimal control of epidemics in metapopulations*, Robert E. Rowthorn, Ramanan Laxminarrayan, and Christopher A. Gilligan, J. R. Soc. Interfac (2009) 6, 1135-1144.

- *Optimal control for pandemic influenza: the role of limited antiviral treatment and isolation,* Sunmi Lee , Gerardo Chowell and Carlos Castillo-Chávez, J. Theo. Biol. 265, 136-150.

Then to our Mastitis research …

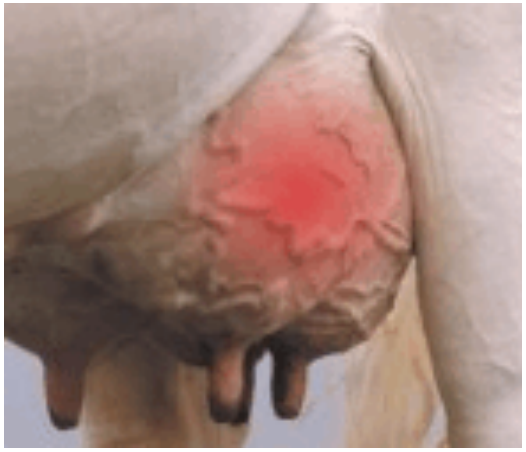
2. Modeling production and health:

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

<u>Our 1st example:</u>
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).



http://aps-dairycell.apstherapy.fr/html/DairyCell%20info%20mastitis%202008.htm

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:

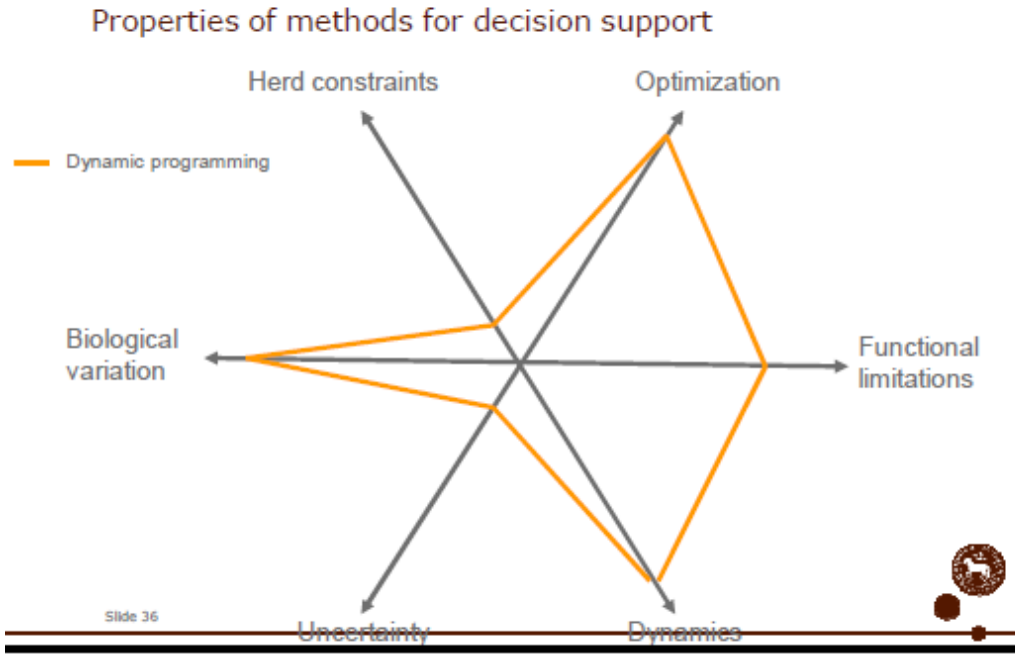
1. Calculate the cost of more than 3 different types of CM

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

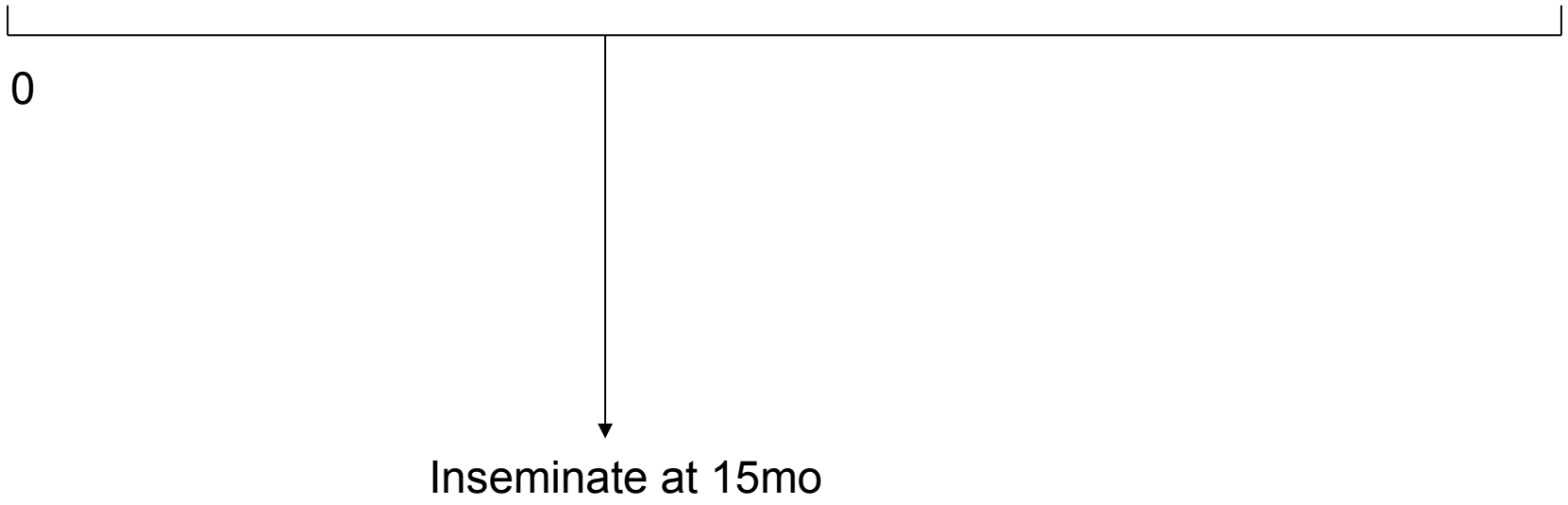
Life of a dairy cow

Heifer

0

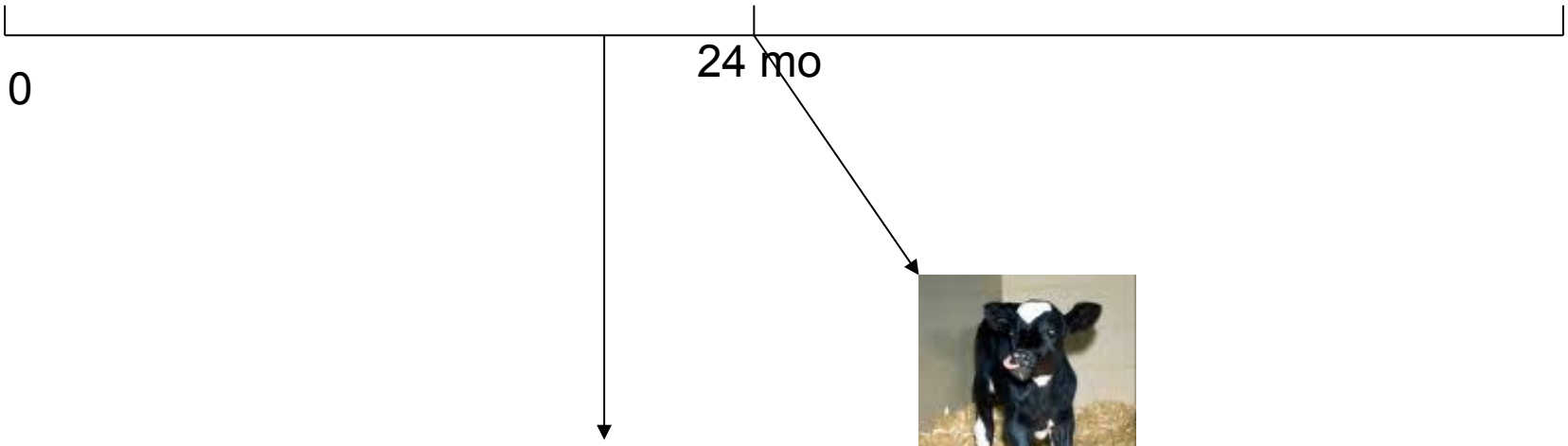
Life of a dairy cow

Heifer



Life of a dairy cow

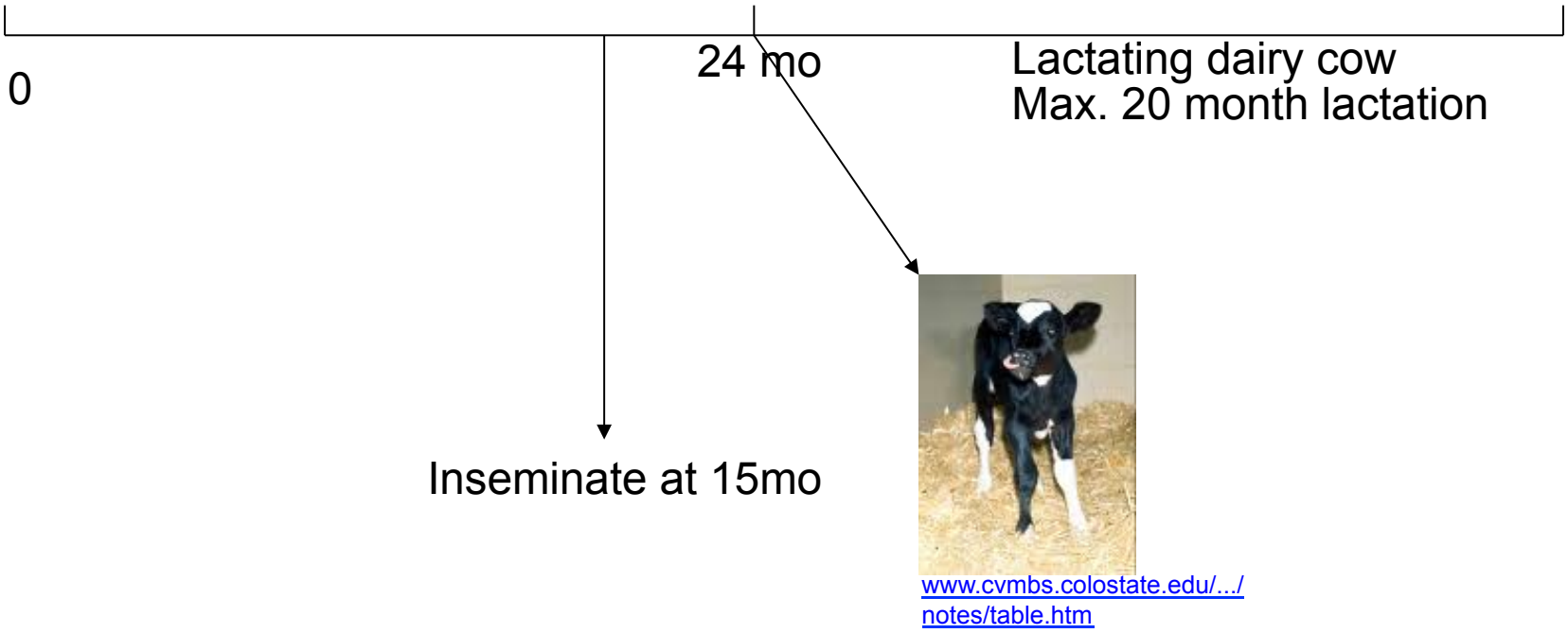
Heifer



www.cvmbs.colostate.edu/.../notes/table.htm

Life of a dairy cow

Heifer



www.cvmbs.colostate.edu/.../notes/table.htm

Life of a dairy cow

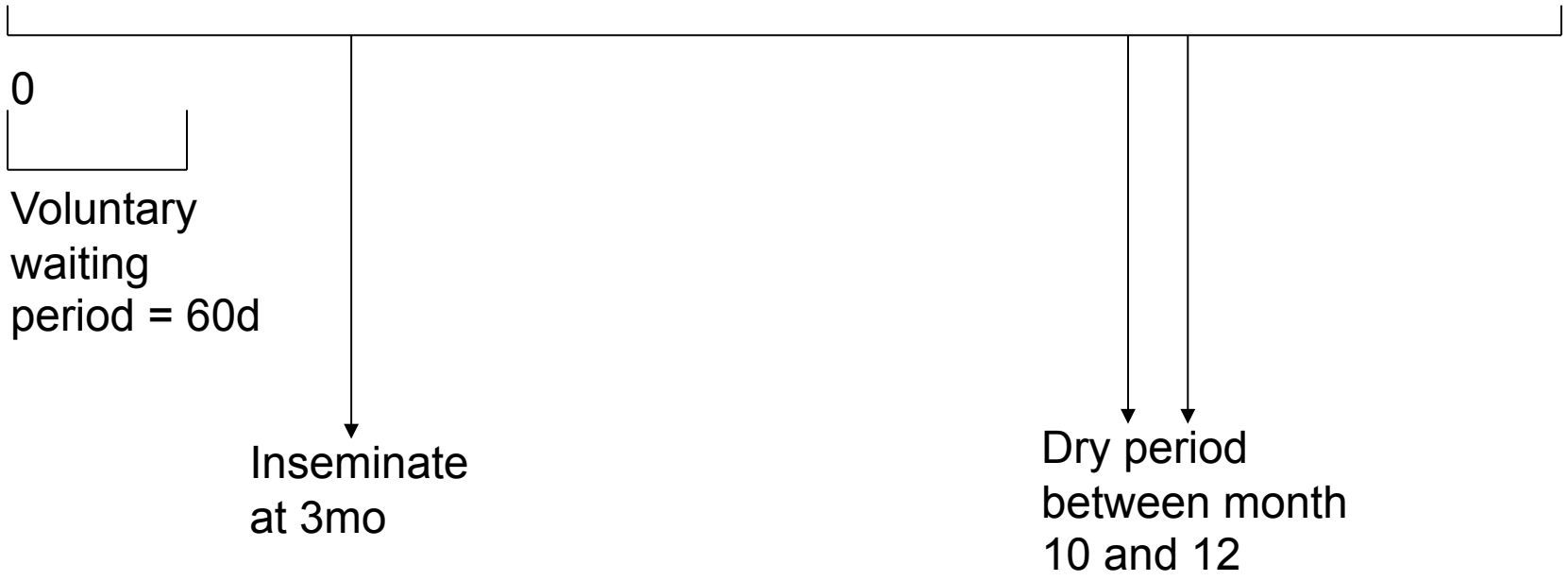
Lactating dairy cow

Life of a dairy cow

Lactating dairy cow

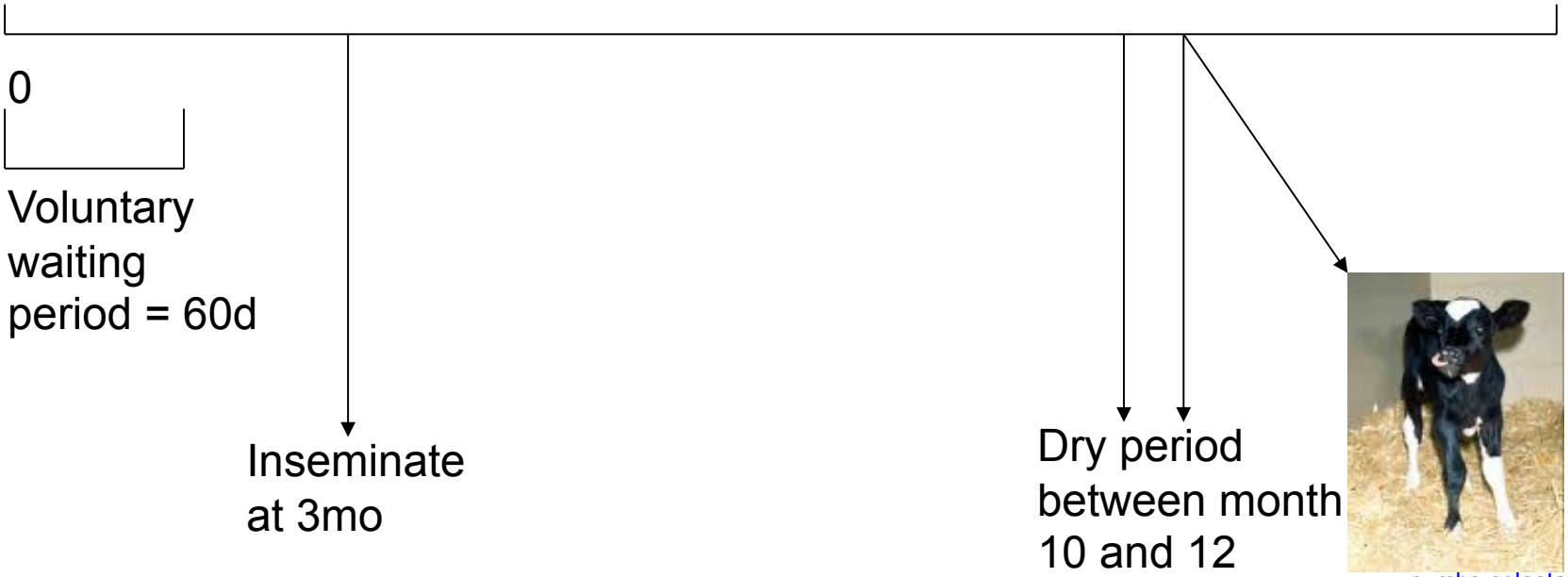
Life of a dairy cow

Lactating dairy cow



Life of a dairy cow

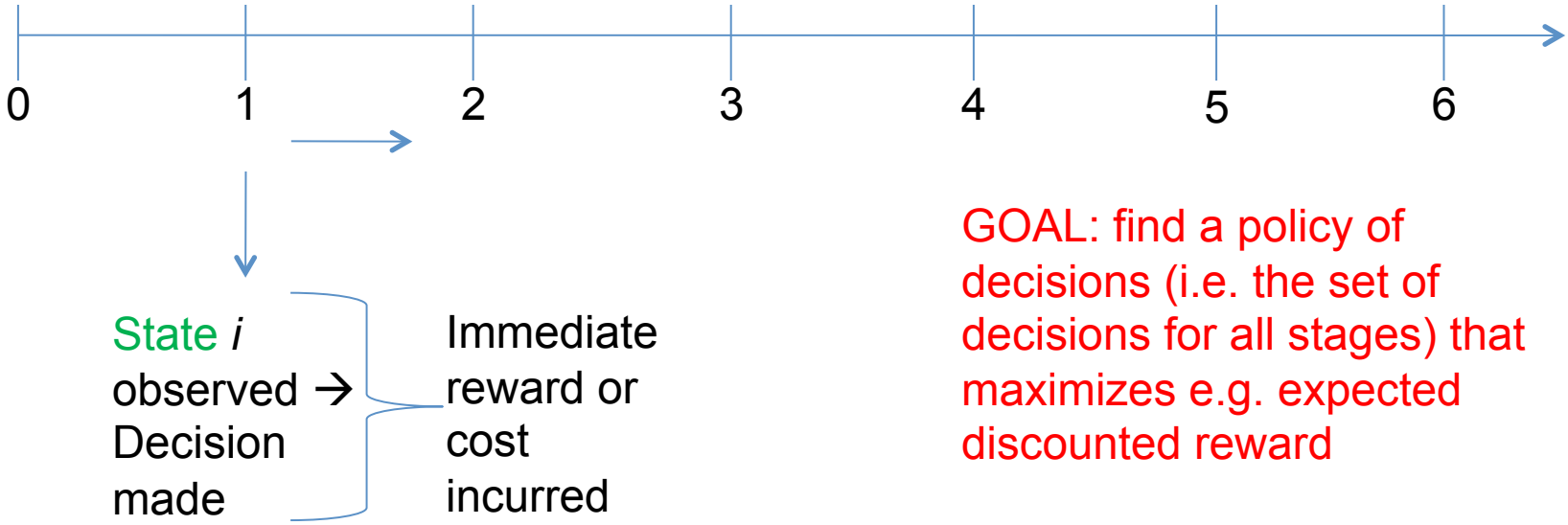
Lactating dairy cow



www.cvmbs.colostate.edu/.../notes/table.htm

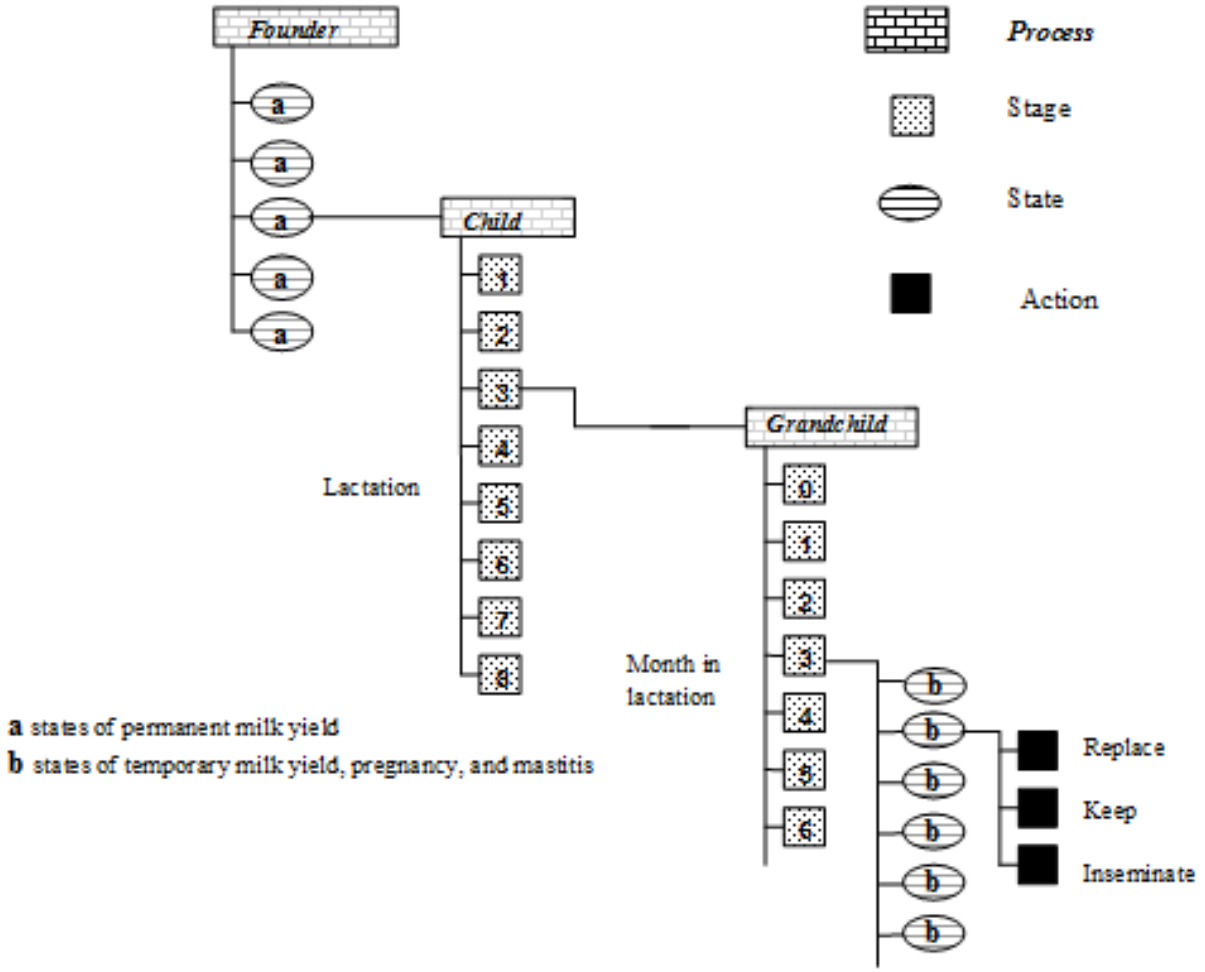
Fundamentals of DP

Stages *n* (monthly time intervals from calving)



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



Structure of the hierarchic Markov process optimization model:

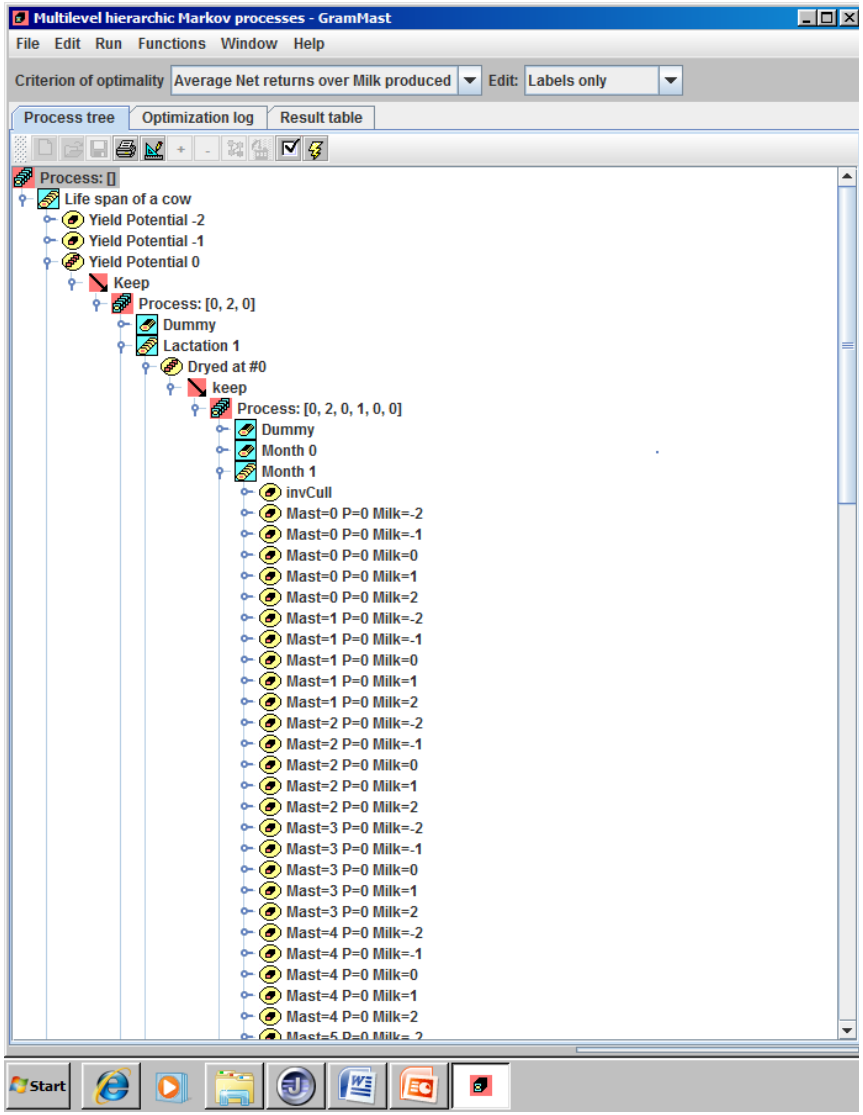
First level: **5 milk yield levels**

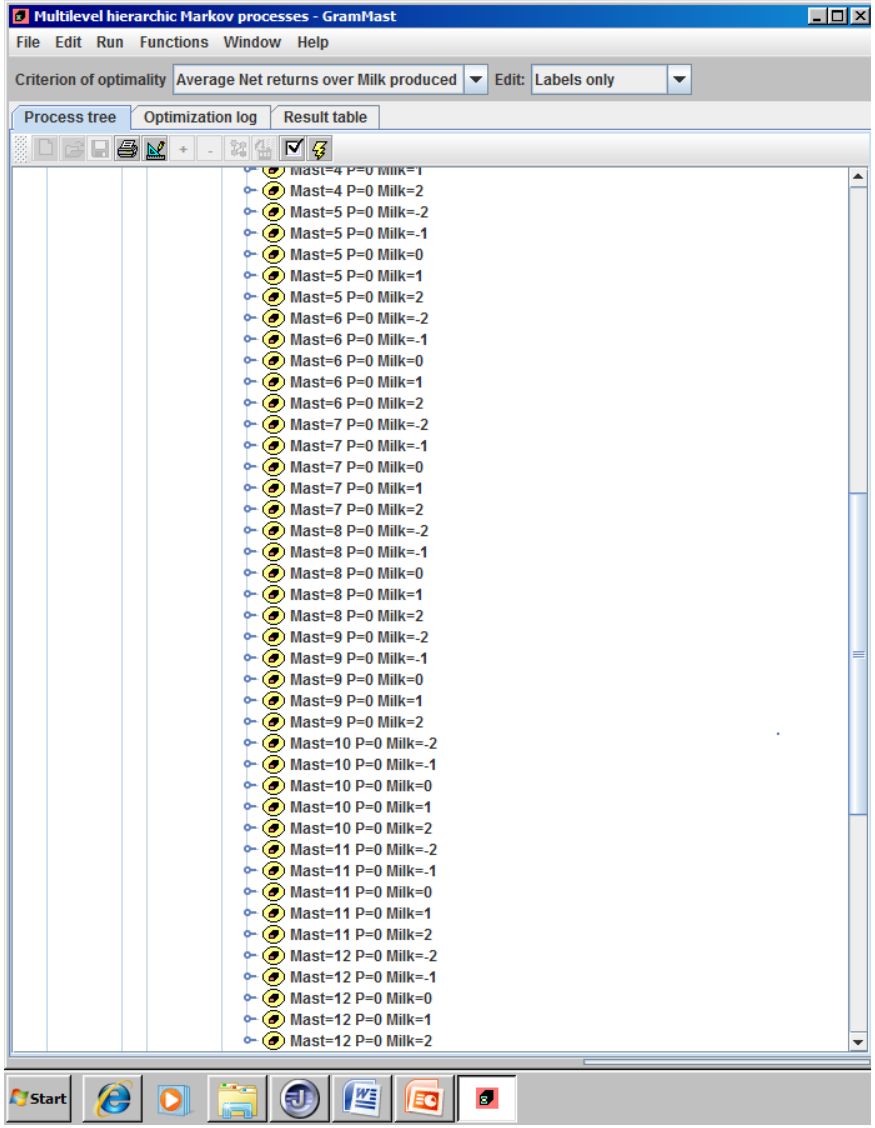
Second level: **8 possible lactations** and **2 carry-over mastitis states** from previous lactation (yes/no).

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

What our DP can do

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)

	Net return[a]	CM cases[b]	% of CM cases treated[c]	Average cost of CM	Average cost per case[d]
No CM [e]	426.05				
All [f]	357.35	44.3	93.6	68.70	155.08
Gram-negative and other [g]	374.20				
Only gram-positive [h]		12.6	93.1	16.85	133.73
Gram-positive and other	390.06				
Only gram-negative		15.5	93.1	32.71	211.03
Gram-positive and gram-negative	372.79				
Only other		16.2	94.6	15.44	95.31

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.

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

What our DP can do

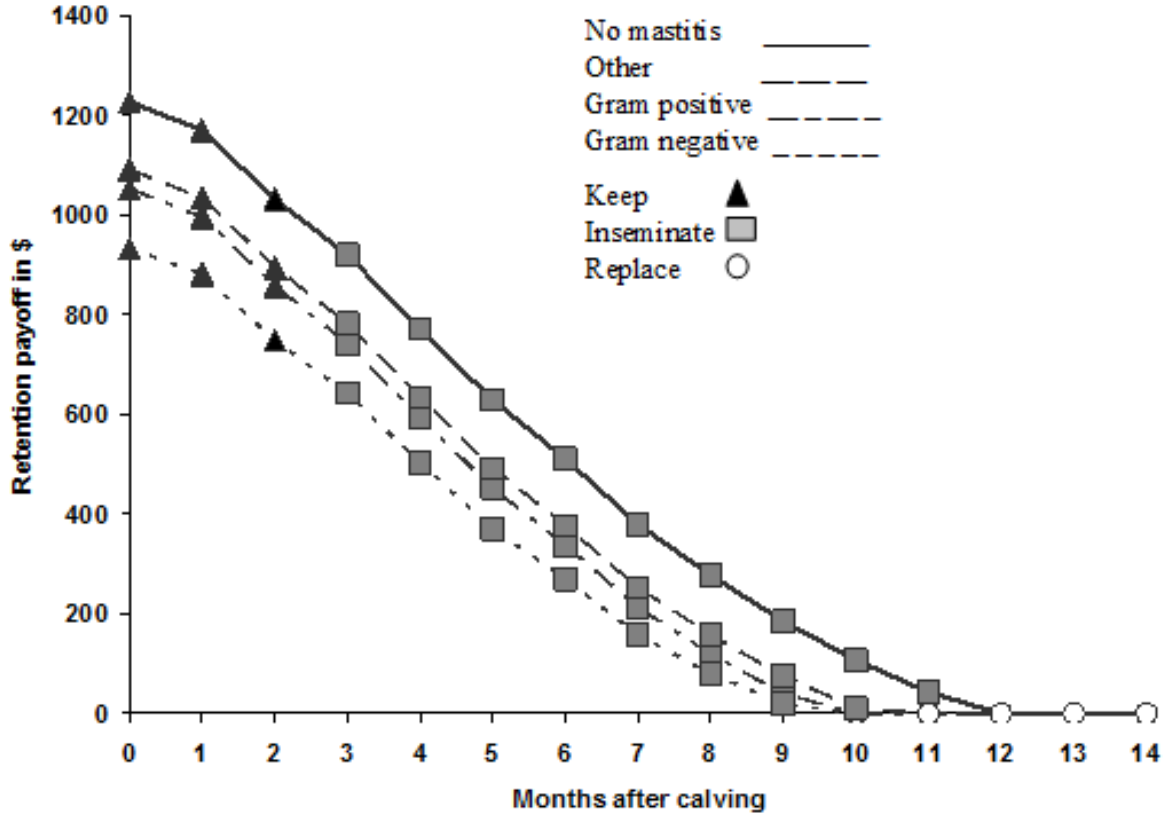


Figure 1. Retention payoffs under an optimal policy for hypothetically open (non pregnant) cows free of clinical mastitis (CM) and with different types of CM, specific to a second lactation cow with average milk yield per 305 day lactation.

What our DP can do

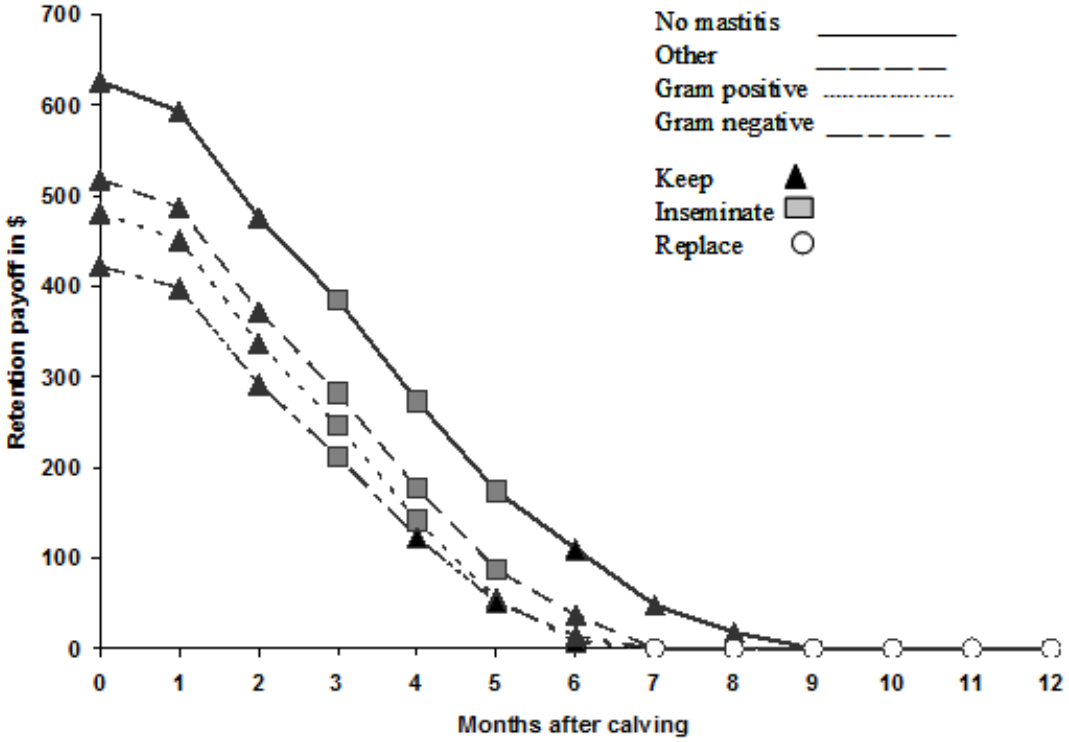


Figure 2. Retention payoffs under an optimal policy for hypothetically open (non pregnant) cows free of clinical mastitis (CM) and with different types of CM, specific to a second lactation cow with permanent milk yield of 1,500 kg per 305 day lactation less than the average in the herd (note: gram-positive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

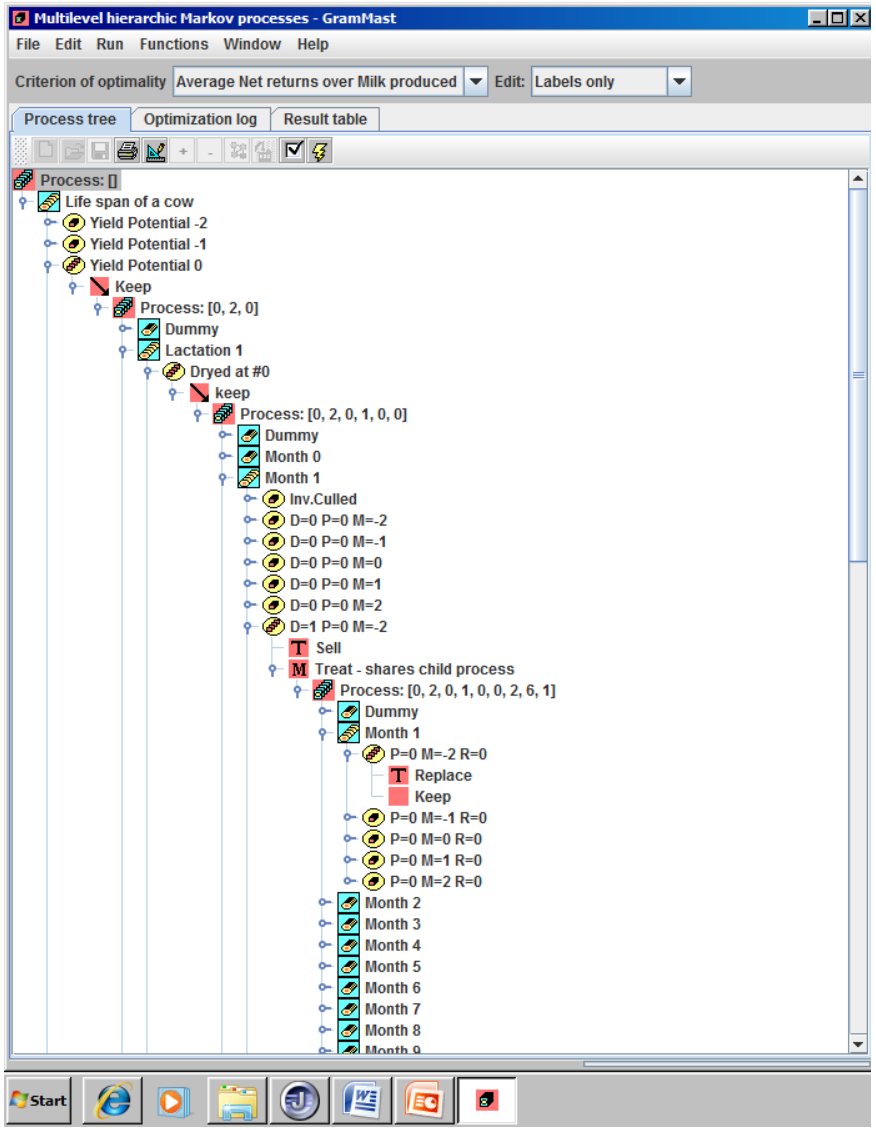
Application

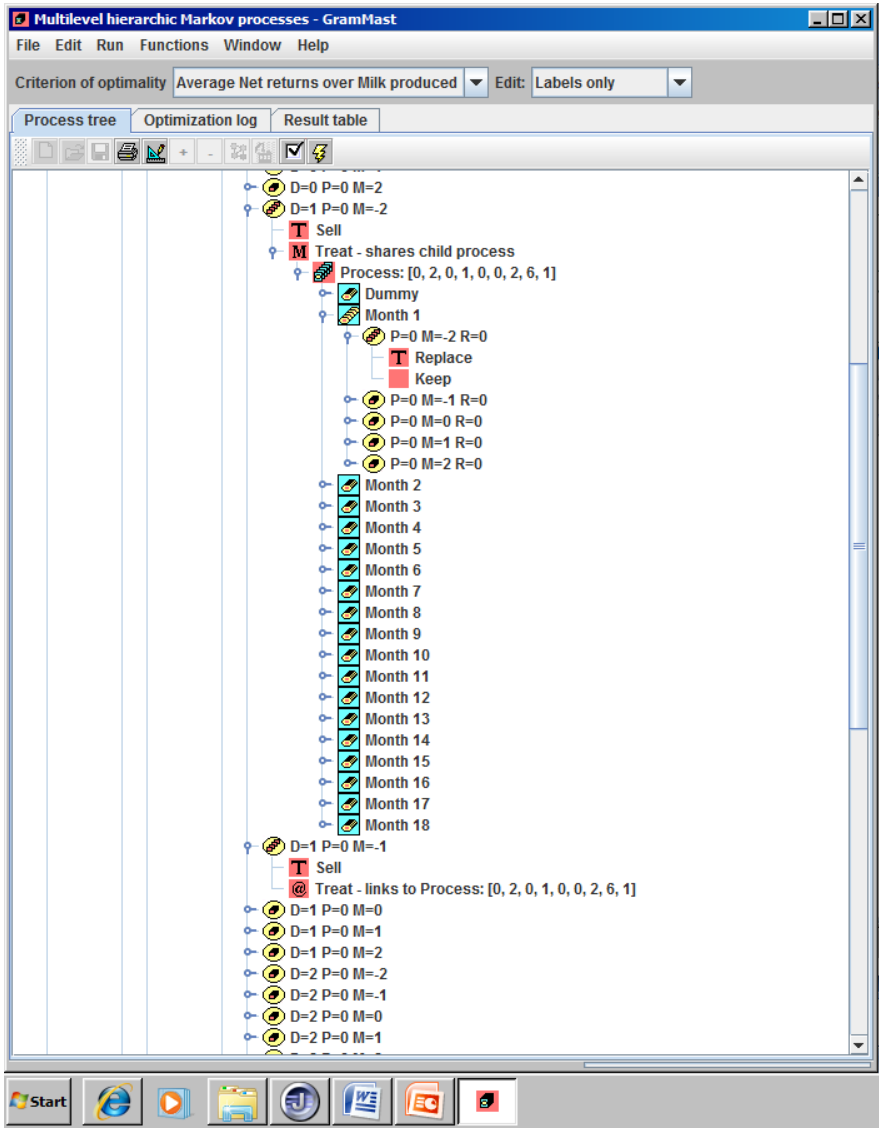
Farmers could run this program with parameters specific to their farm, and this information will be exported into their herd management program

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**.

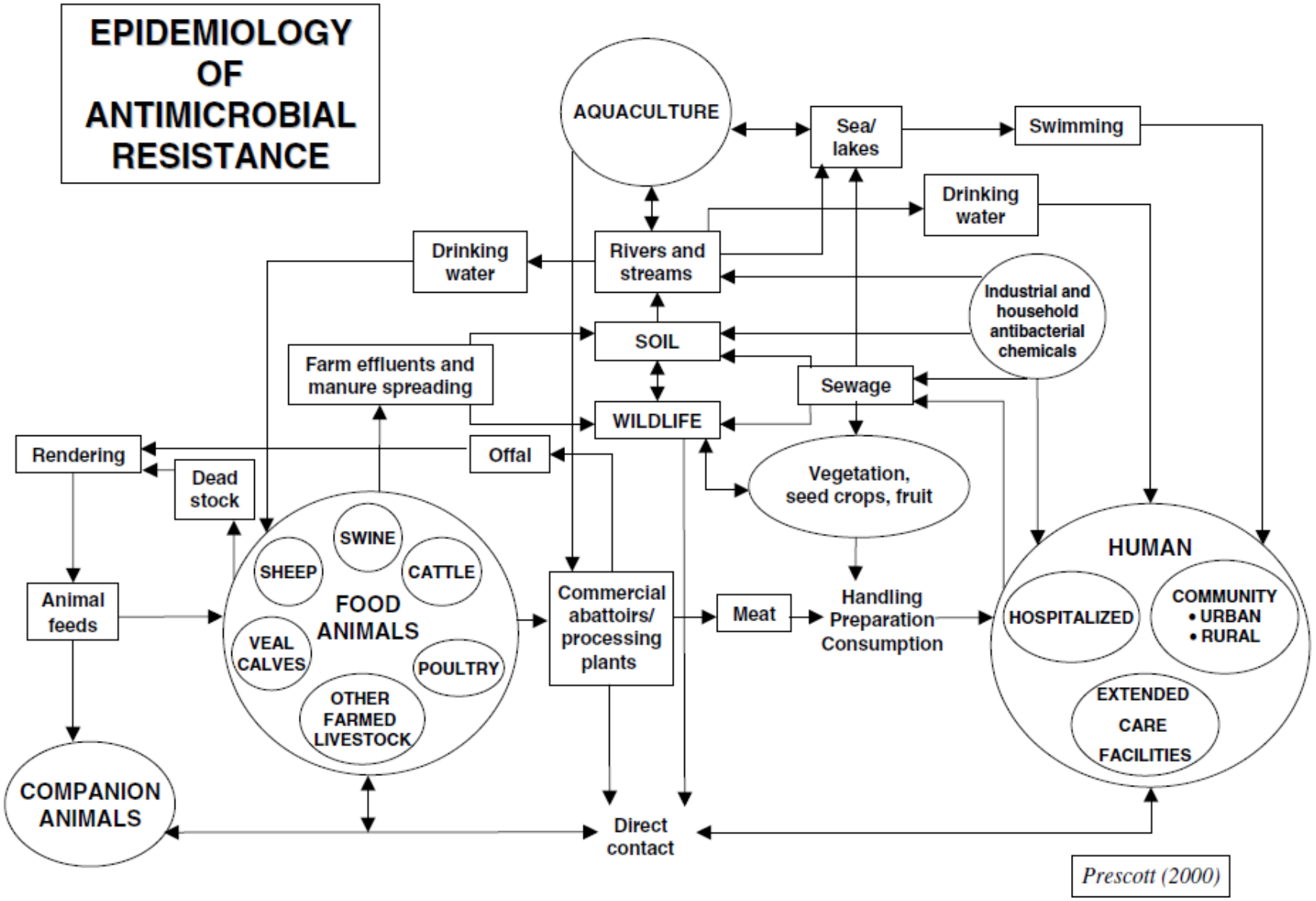
Where we need your help!

- Any ideas of how to further circumvent the COD??

Requests related to Antimicrobial Resitance

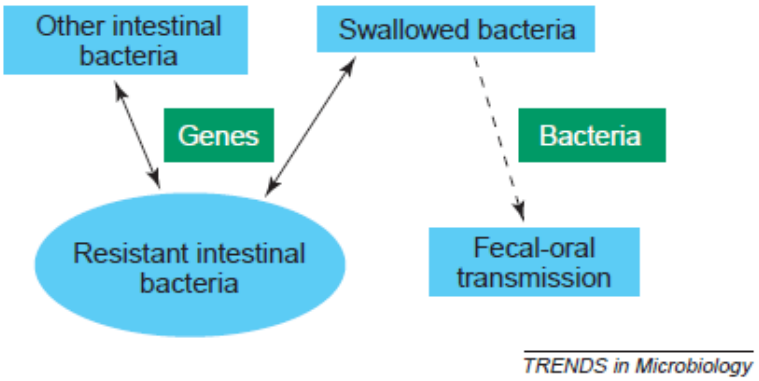
Project 3: “Develop, evaluate and improve food animal systems-based mathematical models of antimicrobial resistance among commensal bacteria”

Victoria Volkova , DVM, PhD, Research Associate

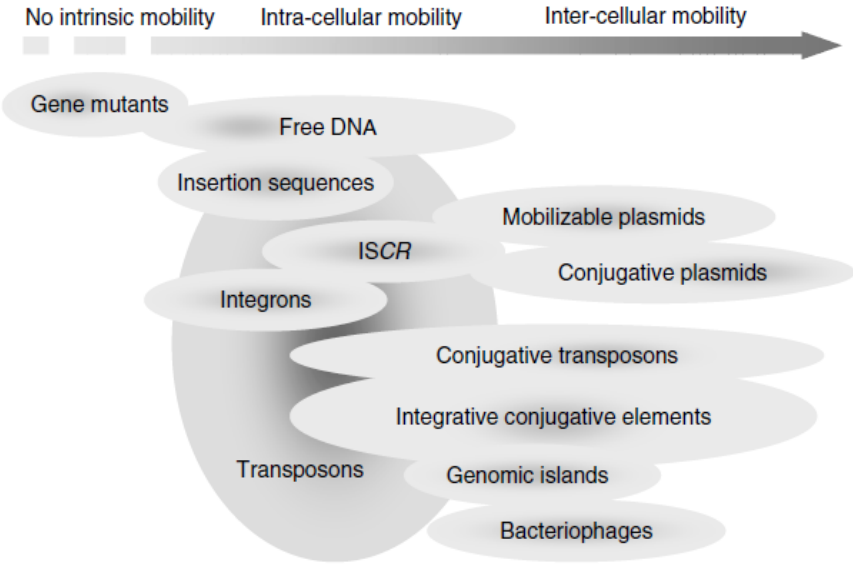

EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE
AQUACULTURE
Sea/ lakes
Swimming
Drinking water
Drinking water
Rivers and streams
Industrial and household antibacterial chemicals
SOIL
Farm effluents and manure spreading
Sewage
WILDLIFE
Rendering
Offal
Dead stock
Vegetation, seed crops, fruit
SWINE
SHEEP
CATTLE
FOOD ANIMALS
VEAL CALVES
POULTRY
OTHER FARMED LIVESTOCK
Animal feeds
Commercial abattoirs/ processing plants
Meat
Handling Preparation Consumption
HUMAN
HOSPITALIZED
COMMUNITY • URBAN • RURAL
EXTENDED CARE FACILITIES
COMPANION ANIMALS
Direct contact
Prescott (2000)

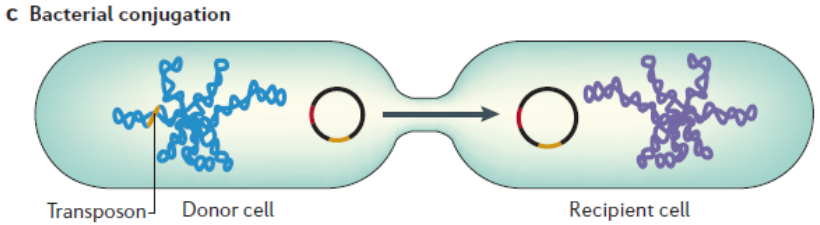
• Reservoirs of resistant genes are found in commensal bacteria in the human and animal gastrointestinal tracts (small intestine supports ~ 10^{10} bacterial cells/g) .

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



Salyers et al., 2004

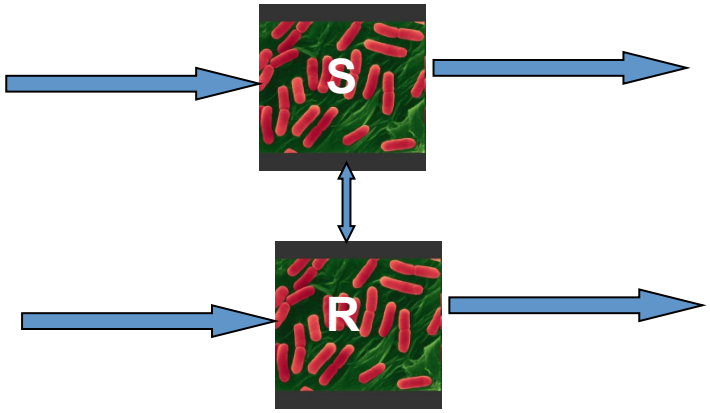




Molecular mechanisms involved in the spread of antimicrobial resistance. Inter-cellular movement (horizontal spread) is the main cause of acquisition of resistance genes.

Boerlin, 2008

WITHIN HOST



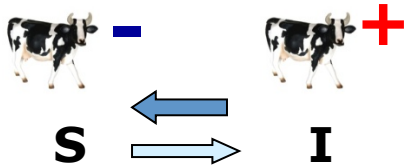
Population dynamics of antibiotic-sensitive and – resistant bacteria

Linked to antibiotic exposure

Emergence of resistance during antibiotic treatment

Fitness cost linked to microbial growth

BETWEEN HOSTS



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

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

$$\frac{dN_r}{dt} = r(1-\alpha)N_r - r(1-\alpha)\frac{(N_s + N_r)}{K}N_r + \beta\frac{N_s N_r}{N} - uE_d(C)N_r - r(1-\alpha)pN_r$$

Logistic Growth

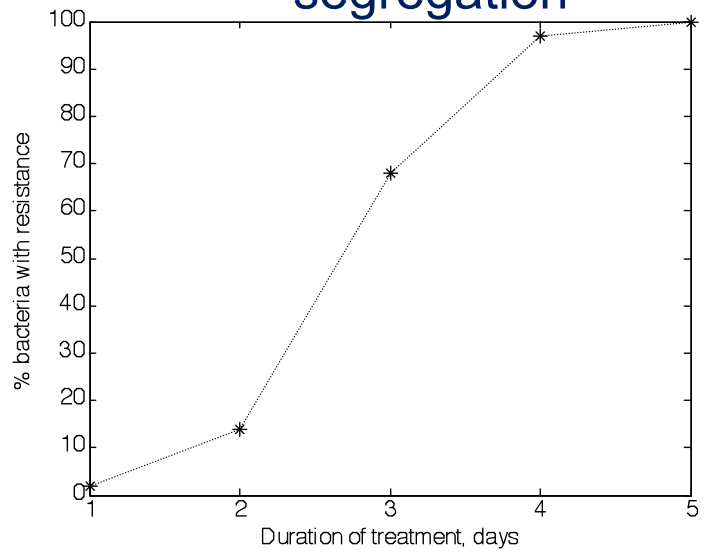
Plasmid transfer

Antibiotic effect

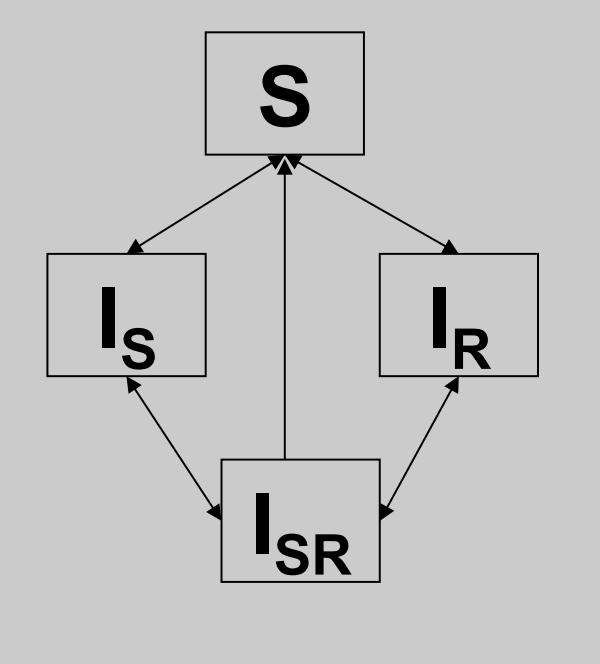
Plasmid loss during segregation

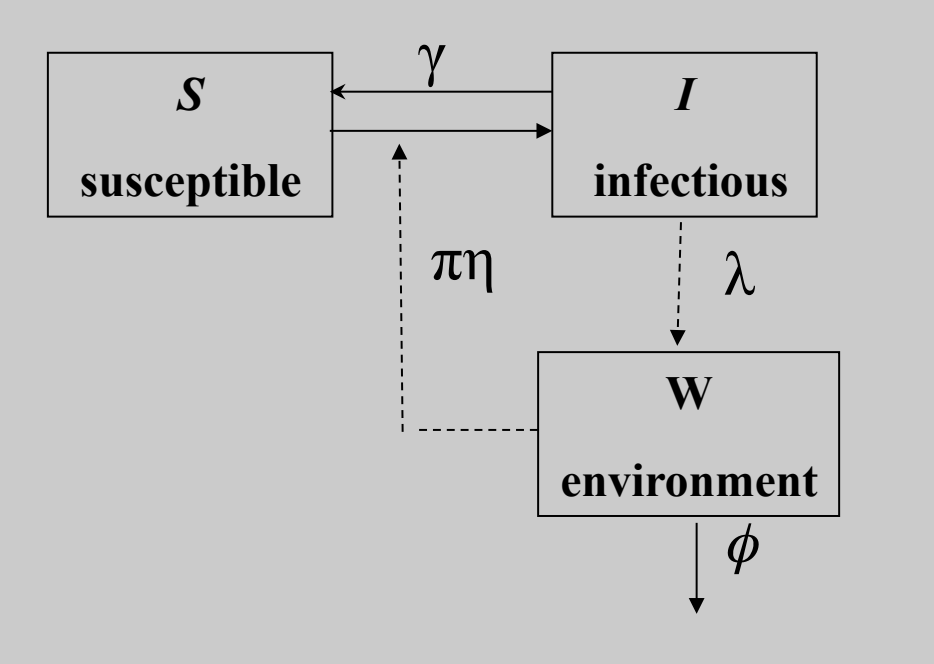
$$E_d(C) = 1 + \frac{E_{\max}\left(\frac{C}{MIC}\right)^H}{EC_{50}^H + \left(\frac{C}{MIC}\right)^H}$$

Percentage of resistant bacteria 24 h after the end of the antimicrobial treatment



Between host dynamics of antimicrobial resistance dissemination





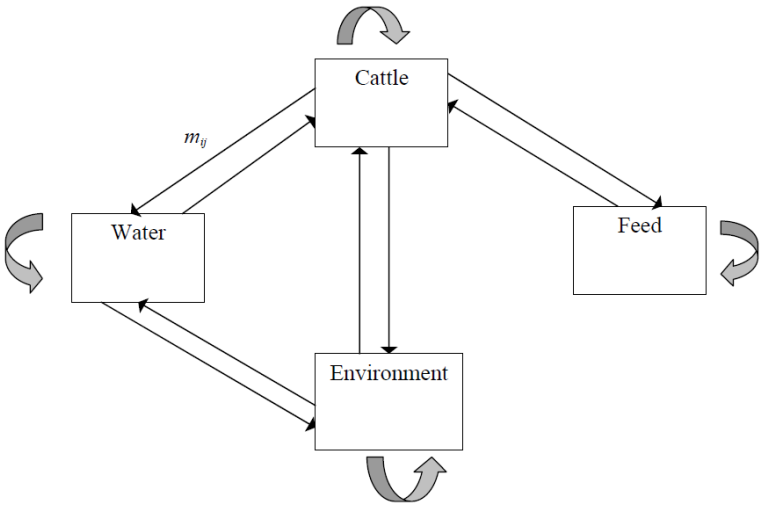
Integrating within and between host antimicrobial resistance dynamics

- 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.



$$\frac{dC}{dt} = r_c C\left[1 - \frac{C}{K_c}\right] - (\mu_c + p)C + m_{ec}E + m_{wc}W + m_{fc}F$$

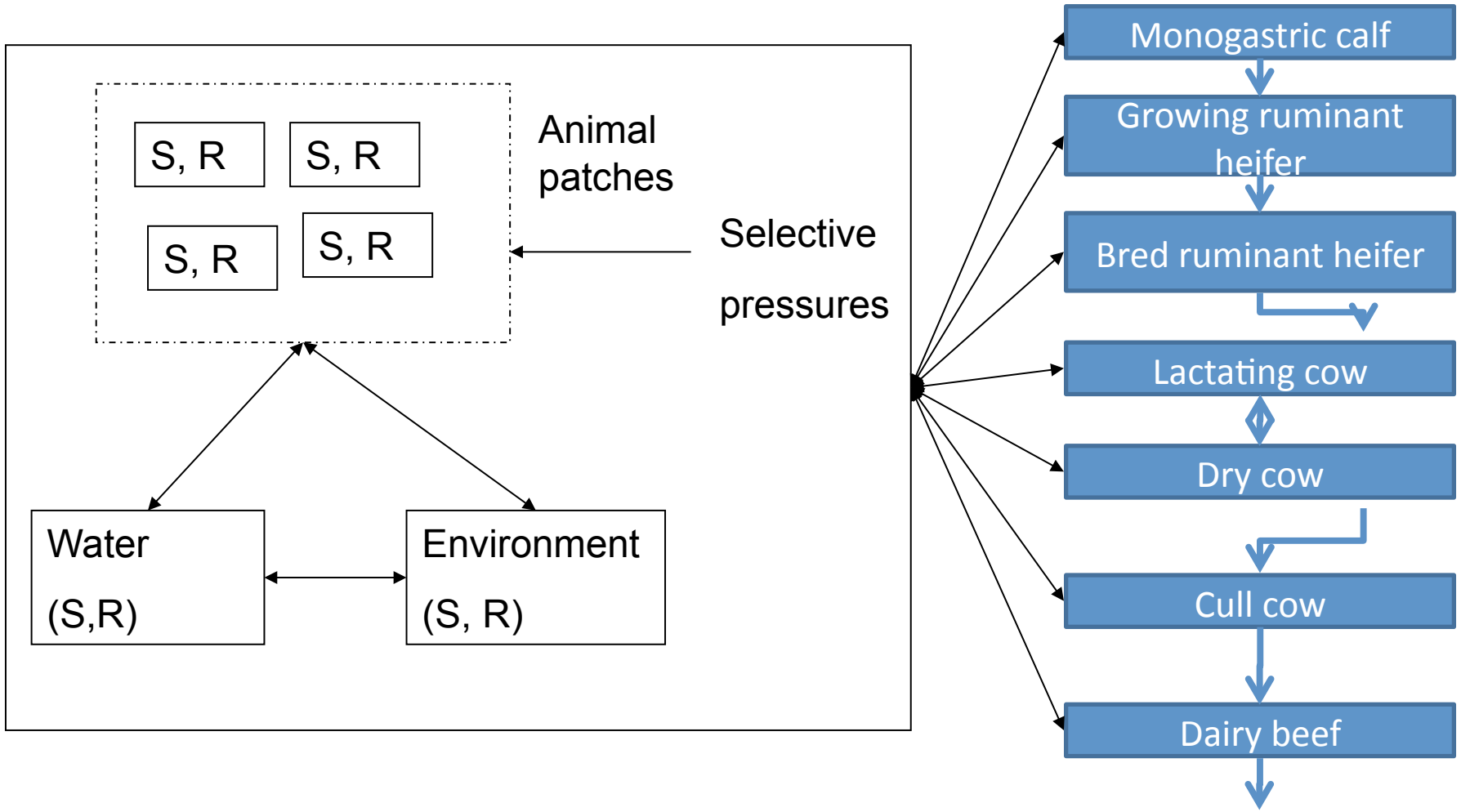
$$\frac{dW}{dt} = r_w W\left[1 - \frac{W}{K_w}\right] - (\mu_w + m_{wc} + m_{we})W + m_{ew}E + m_{cw}pC$$

$$\frac{dF}{dt} = r_f F\left[1 - \frac{F}{K_f}\right] + m_{cf}pC - (\mu_f + m_{fc})F$$

$$\frac{dE}{dt} = r_e E\left[1 - \frac{E}{K_e}\right] + m_{we}W + m_{ce}pC - (\mu_e + m_{ew} + m_{ec})E$$

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 *n* animals) and assuming indirect transmission (bacteria are transmitted to animals through water and environment):

For the *j* animal:

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

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

$$+ m_{wj} W_r + m_{ej} E_r - (m_{jw} + m_{je}) N_{rj}$$

Water patch:

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

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

Environmental patch:

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

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

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