Research, Education, and Outreach at the Interface of Math and Biology

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University of Tennessee

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Outline

- Beginning of my career and starting to work on math biology
- REU program in UT Math Dept.
- Math Ecology at UT as a concentration in Math PhD program
- Work at Oak Ridge National Laboratory
- Work at NIMBioS

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Starting at U of Kentucky

- Started working with Tom Hayden and Phil Crowley on a biological modeling course at UK
- Dissertation Work at UK in partial differential equations as the first student of Craig Evans
- Went straight to University of Tennessee in 1981 after PhD at UK
- Hayden connected me with Curtis Travis at Oak Ridge National Lab and helped with find a collaborator in applications of ODEs and delay equations in biology

Beginning at UT

- Continued to do PDEs and began to do more math biology and more optimal control
- David Adams was a good mentor
- Got involved with Research Experiences in Undergraduates program at UT in 1987, one of the first NSF REU programs
- Became the director of this program in 1989 and continued for 15 years. Working with undergraduates on research projects has been an important part of my career.

Continuing

- Started to work as a part-time researcher at Oak Ridge National Lab in 1987. Found an amazing collaborator, Vladimir Protopopescu. Oak Ridge National Lab is a Dept. of Energy Lab.

- Wrote book on Optimal Control applied to Biological Models

- Wrote book on Mathematics for the Life Sciences, for freshman biology students

- Advised 20 PhD students and 28 masters students; their job placement includes small colleges, Intel, Office of Economic Accountability, IBM, Navy Surface Weapons Center, Tennessee Valley Authority

ORNL project: Cardiopulmonary Resuscitation

Each year, more than 250,000 people die from cardiac arrest in the USA alone. Despite widespread use of CPR the survival of patients recovering from cardiac arrest remains poor.

The rate of survival for CPR performed out of the hospital is 3%, while for patients in the hospital, the rate of survival is 10-15%.

Here, we consider a model for CPR allowing chest and abdomen compression and decompression.

We apply the optimal control strategy for improving resuscitation rates to a validated circulation model developed by Babbs.
Reference: Babbs, Circulation 1999.

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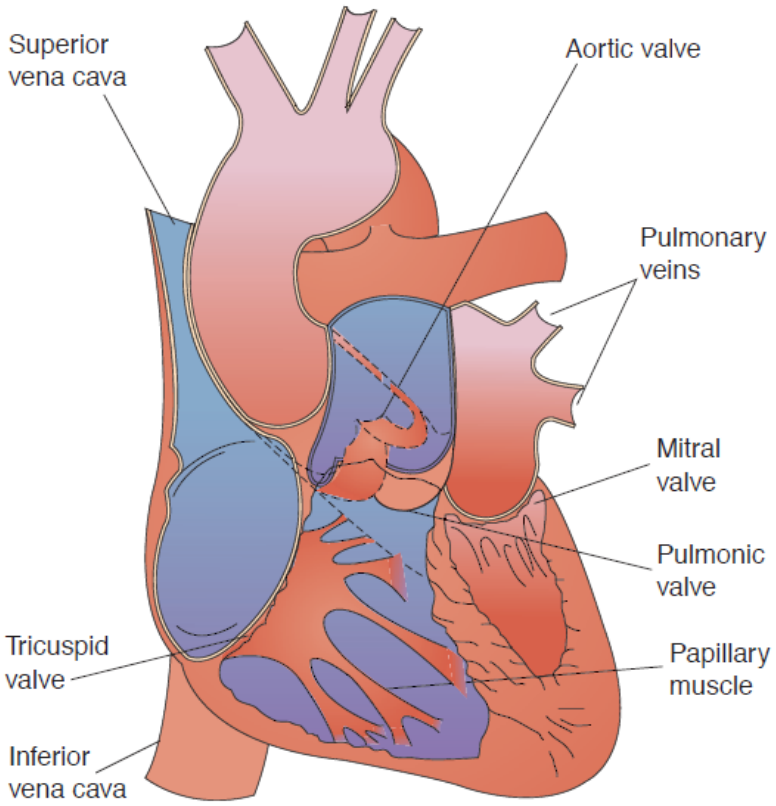
Improving CPR



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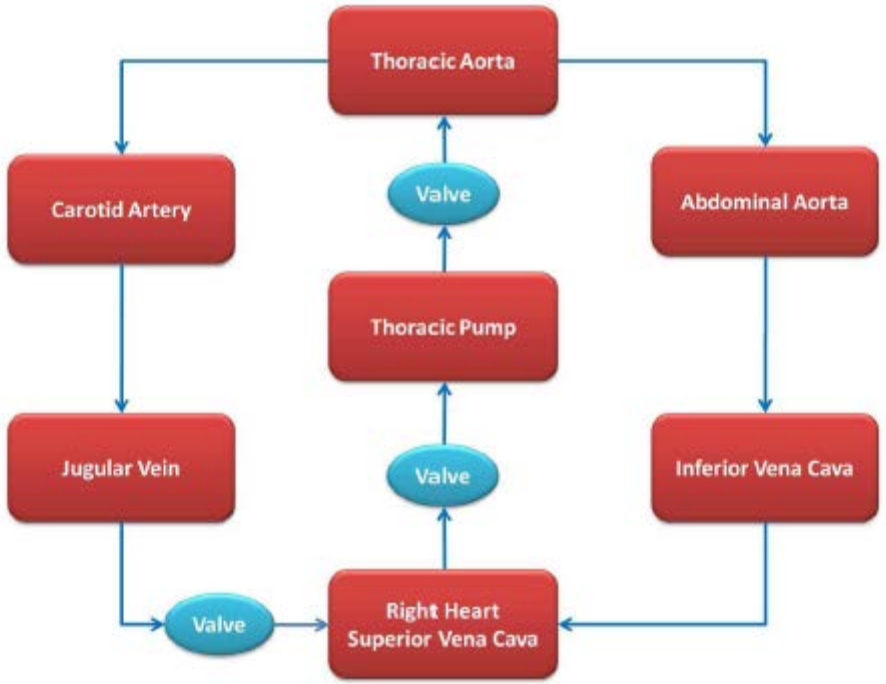
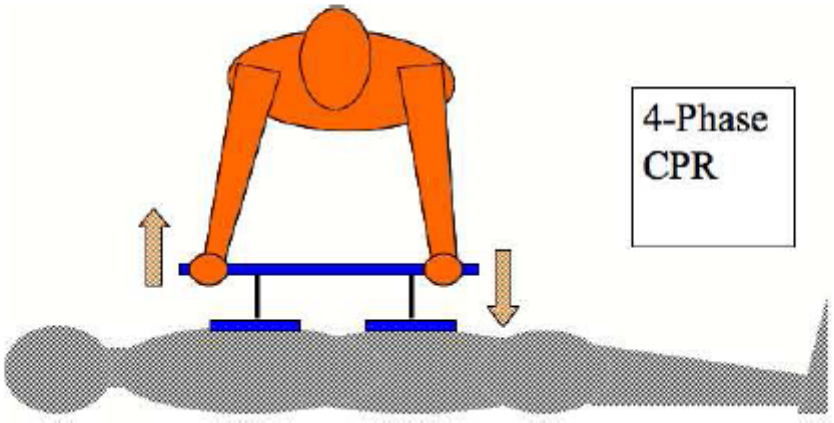
Circulation Diagram



Lifestick



Pressure Functions

As controls, we choose the the pattern of the external pressure on the chest and on the abdomen. The pressure state variables are as follows:

P_1 pressure in abdominal aorta
P_2 pressure in inferior vena aorta
P_3 pressure in carotid artery
P_4 pressure in jugular vein
P_5 pressure in thoracic aorta
P_6 pressure in right heart, superior vena cava
P_7 pressure in thoracic pump and left heart.

Model Setup

The chosen CPR model consists of seven difference equations, with time as the discrete underlying variable.
At the step n, when time is $n\Delta t$, the pressure vector is denoted by:

$$P(n) = (P_1(n), P_2(n), ..., P_7(n)).$$

We assume that the initial pressure values are known, when $n = 0$.
To make the chest pressure profiles medically reasonable, assume
i.e., $u_i(0) = u_i(N-1)$.

$$u_1 = (u_1(0), u_1(1), ..., u_1(N-2), u_1(0)),$$
$$u_2 = (u_2(0), u_2(1), ..., u_2(N-2), u_2(0)),$$

Difference Equations Model

for $n = 1, 2, ..., N-1$ (in vector notation)

$$P(1) = P(0) + T_1(u_1(0)) + T_2(u_2(0)) + \Delta t F(P(0)), \quad (1)$$

$$P(n+1) = P(n) + T_1(u_1(n) - u_1(n-1)) \quad (2)$$

$$+ T_2(u_2(n) - u_2(n-1)) + \Delta t F(P(n)), \quad (3)$$

$$T_1(u_1(n)) = (0, 0, 0, 0, t_p u_1(n), t_p u_1(n), u_1(n)),$$

$$T_2(u_2(n)) = (u_2(n), u_2(n), 0, 0, 0, 0, 0).$$

Interactions between compartments in function F

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Interaction Terms

Note that the calculation of the pressures at the next time step requires the values of the controls at the current and previous time steps.

Show function $F(P(n))$ by showing the last equation (thoraric pump) of the system:

$$P_7(n+1) = P_7(n) + u_1(n) - u_1(n-1)$$

$$+\Delta t \left[\frac{1}{R_i} V(P_6(n) - P_7(n)) - \frac{1}{R_o} V(P_7(n) - P_5(n)) \right]$$

where the valve function is defined by
$V(s) = s$ if $s \geq 0$
$V(s) = 0$ if $s \leq 0$.

Three valves: between compartments 4 - 6 AND 5 - 7 AND 5 - 6.

Goal

Choose the control set $U \subset \Re^{2N}$, defined as:

$$U = \{(u_1, u_2) | u_i(0) = u_i(N-1)$$

$$-K_i \leq u_i(n) \leq L_i, i = 1, 2, n = 0, 1, \ldots, N-2\}.$$

NEED positive and negative values due to compression and depression!

We define the objective functional $J(u_1, u_2)$ to be maximized

$$\sum_{n=1}^{N} [P_5(n) - P_6(n)] - \sum_{n=0}^{N-2} [\frac{B_1}{2} u_1^2(n) + \frac{B_2}{2} u_2^2(n)] \qquad (4)$$

Key Feature

The calculation of the pressures at the next time step requires the values of the controls at the current and previous time steps. We use extension of the discrete version of PMP.

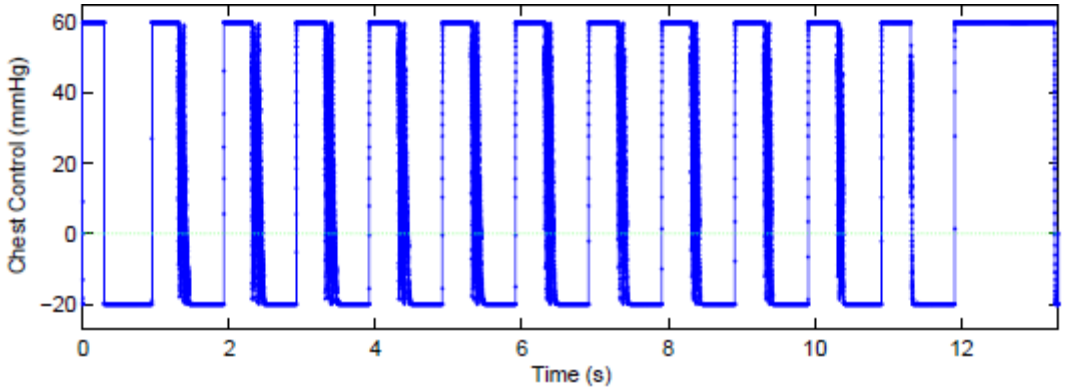
Use derivative of the map from controls-to-states to form the sensitivity equations. Use the sensitivity operator and the the objective functional to find the adjoint system.

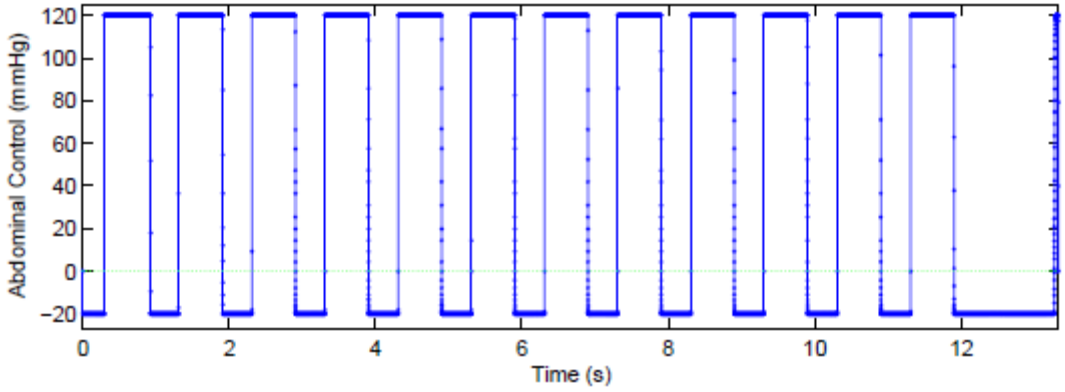
Use the adjoint system to simplify the quotient below and obtain OC characterizations

$$0 \geq \lim_{\epsilon \longrightarrow 0^+} \frac{J(u^* + \epsilon l) - J(u^*)}{\epsilon}$$

Numerical method: iterative method with forward-backward sweeps

Optimal controls for Lifestick





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Conclusions: CPR project

We can increase the pressure difference across the thoracic aorta and the right heart by about 25 percent.

We received a US government patent for the idea of optimal control of CPR models. (Vladimir Protopopescu and Eunok Jung)

This procedure with RAPID compression and decompression cycles has recently been recommended by several medical groups. (use a device)

Reference: IMA Journal Mathematical Medicine and Biology 25, 2008, 157-170.

Math Biology Graduate Education at U of Tennessee

- Math Ecology concentration in the PhD Mathematics program
- Graduate two semester course in Math Ecology
- Advanced Topics course
- Math Biology seminar runs each semester

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Math Biology Undergraduate Education at UT

- Freshmen course: Mathematics for the Life Sciences, with one semester of discrete math and one semester of calculus……
- 160 students per semester in this course for biology, animal science, pre-vet majors
- Math Modeling course
- Models in Biology course

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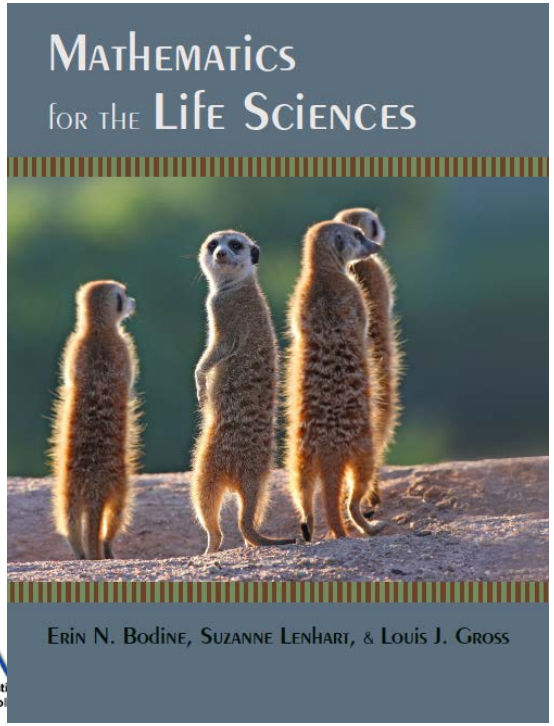
Mathematics for the Life Sciences – Princeton U. Press

Rule of Five- **different learning styles to meet needs of diverse students: Symbolically, Graphically, Numerically, Verbally, Data-driven**

descriptive statistics (regression, semi-log, log-log), matrix models, discrete probability, basic calculus, emphasizing data and hypothesis formulation.



Erin Bodine, Lou Gross and S. Lenhart

Outreach

- Work with Association for Women in Mathematics
- Outreach…visit Bearden High School once a week for the last 14 years… visited Vine Middle School for 4 years before that
- New phase of my work, retired from Oak Ridge National Lab and became Associate Director of NIMBioS

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Lessons from Research, Education and Outreach at NIMBioS

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Vision

- Foster new collaborative efforts to investigate fundamental and applied questions arising in biology using appropriate mathematical and computational methods
- Enhance the essential human capacity to analyze complex biological questions and develop necessary new mathematics
- Encourage broader public appreciation of the unity of science and mathematics.

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Specific Methods

- Focused research projects (**Working Groups**) to build collaboration among diverse communities.
- Building collaborations through more open-ended general problems (**InvestigativeWorkshops**).
- Skill and methods-based programs (**Tutorials**) that foster a broader understanding of applications of modern math and computational science in biology.
- An expansive set of **education-linked-to-research**endeavors from elementary through post-doctoral level that provide diverse opportunities at interface.
- Short term and long term visitors and post-docs add to the collaborations.
- Community driven with 500 visitors a year

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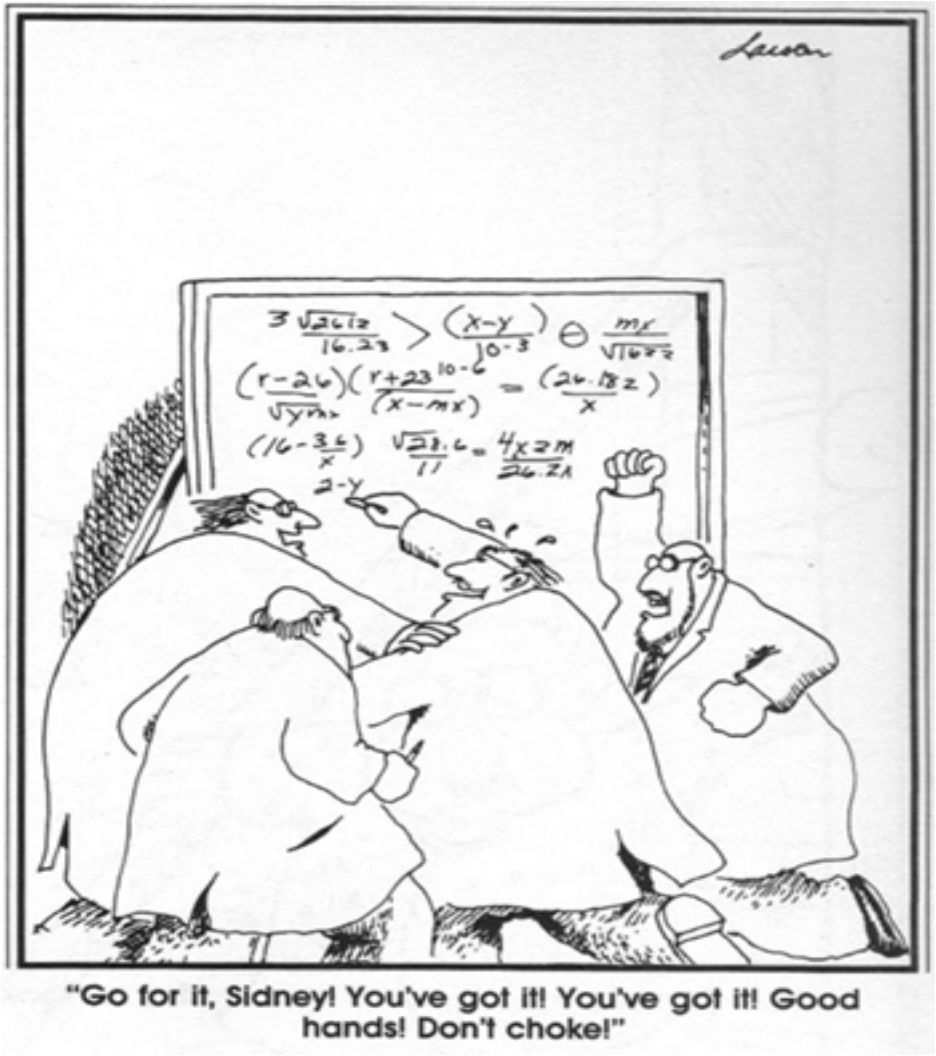
Working Group

- Relatively small size (10-15 people)
- Focus on a well-defined topic.
- Well-defined goal

Ex. Software, databases, and publication



"Go for it, Sidney! You've got it! You've got it! Good hands! Don't choke!"

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Investigative Workshop

- Relatively larger size (30-40 people).
- Inclusion of visitors, post-docs, and graduate students.
- Focus on a broader topic or set of related topics.
- Summarize state-of-the-art and identify future directions.
- Potential for leading to future working group (s).

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Undergraduate Students:

Undergraduates Research Conference at the Interface of Biology and Math Conference
November 11 – 12, 2017

Summer Research Experience for Undergraduates and Teachers Program, 8 weeks

*Students majoring in Mathematics/Biology or related fields, pre-service teachers and high school teachers

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Teachers, Students (K-12)

- Summer middle school STEM camp, during the days of one week
- Teachers will be invited to attend the undergraduate conference and can participate in our summer program.
- Curriculum materials, science folios and modules will be developed for educational resources and teacher workshops at the Great Smoky Mountains National Park.

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Biology in a Box Project

A science education outreach project of
Department of Ecology & Evolutionary Biology,
Division of Biology, University of Tennessee

Dr. Susan Riechert, Project leader

•This project provides teachers student-active learning materials and exercises that can be used each year in the classroom to enrich science and math contents in a wide variety of contexts.

Available Themes:

1 Fossils **5 It's in Your Genes** **9 Forestry**

2 Of Skulls & Teeth **6 Animal Kingdom** **10 Behavior**

3 Fur, Feathers, Scales: Insulation **7 Backyard Naturalist**

4 Simple Measures **8 Everything Varies**

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http://web.bio.utk.edu/biologyinbox/default.htm

Graduate Education

- NIMBioS funds some research assistantships for graduate students

- Visiting Fellowships for Graduate Students

- Graduate Student Summer Workshops with MBI and CAMBAM

- PEER, NIH program for under-represented groups

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GSMNP

Great Smoky Mountains National Park

- biodiversity hotspot, imperiled species hotspot
- international context:
  - Wildlife Heritage Site, proposed non-stationary NEON sites
  - International Biosphere reserve


knoxnews.com

Home › GoSmokies › GoSmokies News

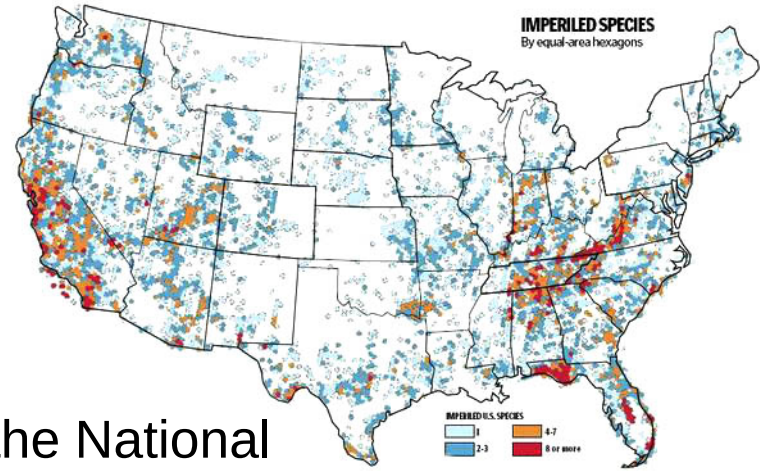
As Smokies species inventory exceeds expectations over decade, officials focus on keeping project afloat

By Morgan Simmons (Contact)
Thursday, May 29, 2008

Related information

It has been 10 years since the Great Smoky Mountains National Park launched the most ambitious biodiversity study ever attempted.

The goal of the All Taxa Biodiversity Inventory was to catalog the vast storehouse of living organisms in the park - no small feat, considering



- role as a ‘prototype’ park within the National Park Service
- Organizing sessions at teacher workshops and student science camps

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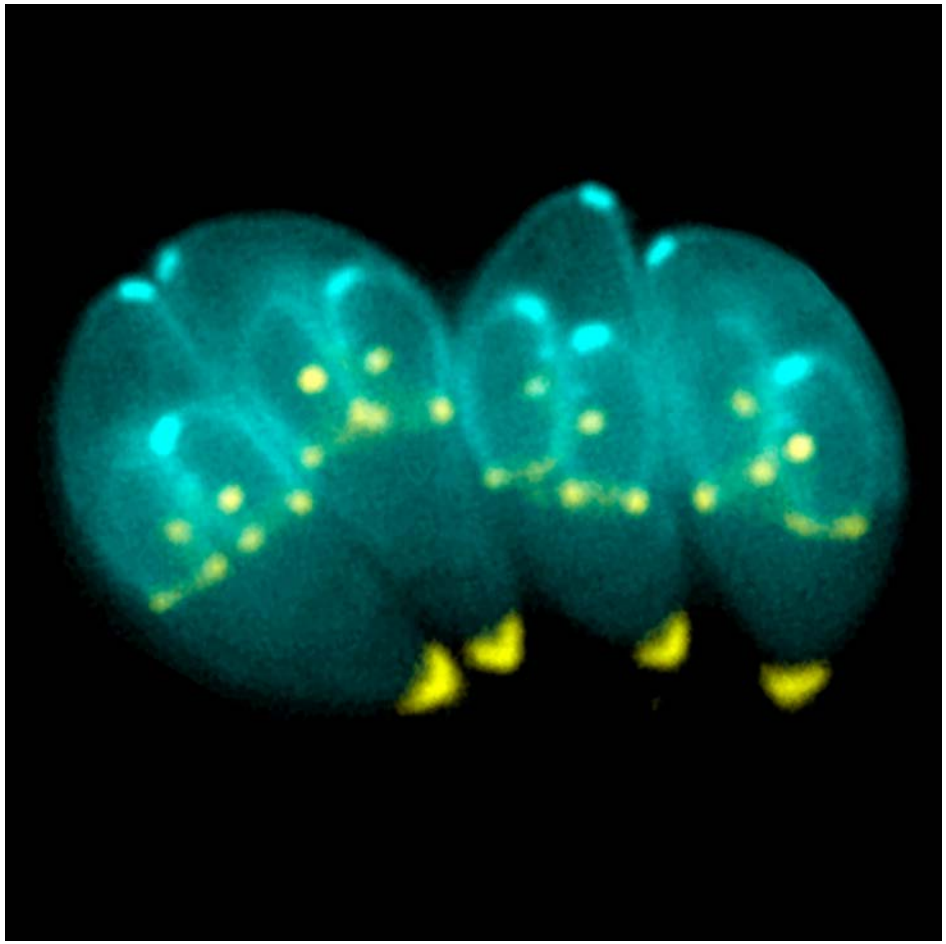
Understanding the Biological Properties of the World's Most Successful Parasite



T. gondii constructing daughter scaffolds within the mother cell

(Hu& Murray)

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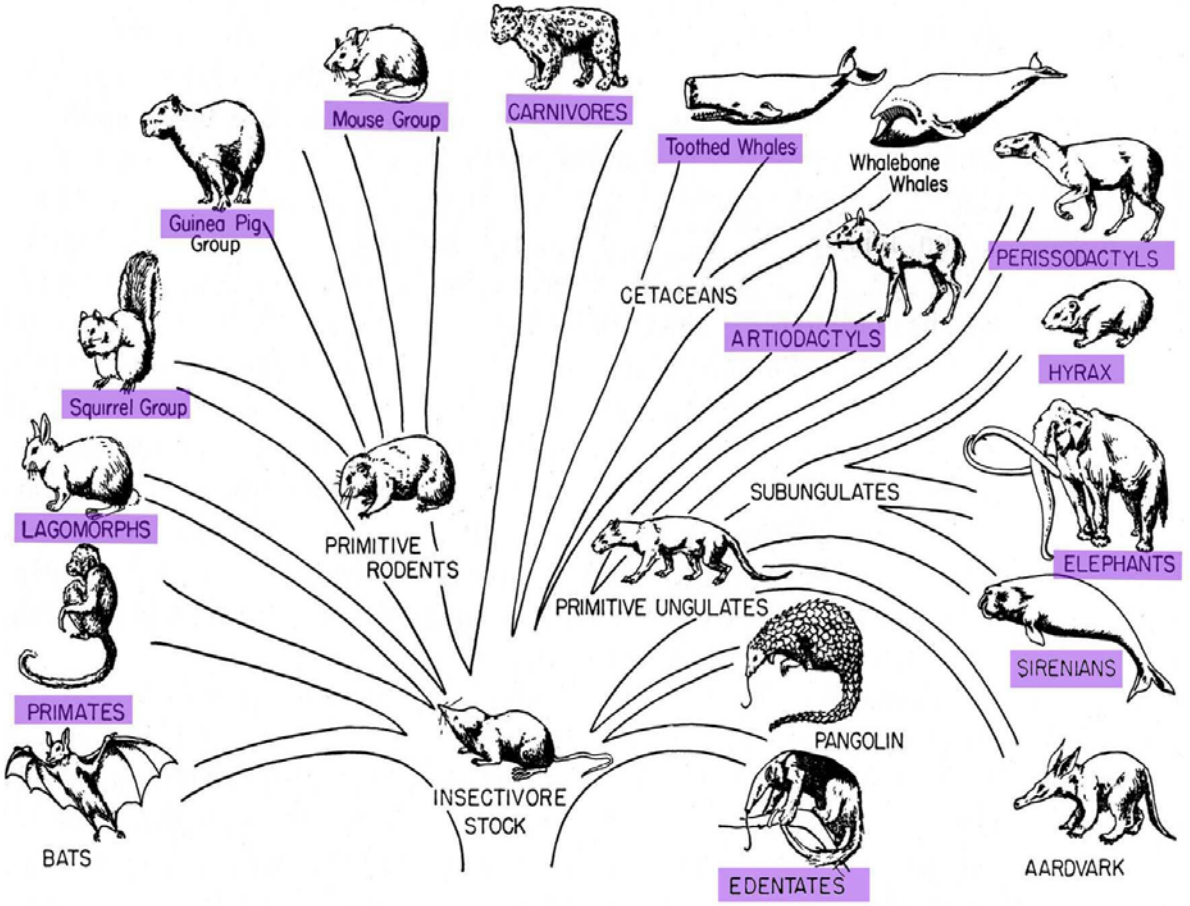
Known Hosts for *Toxoplasma gondii*



Mammals

Birds

Most infections asymptomatic
Abortion (sheep and goats)
Acute pulmonary toxoplasmosis (pigs)

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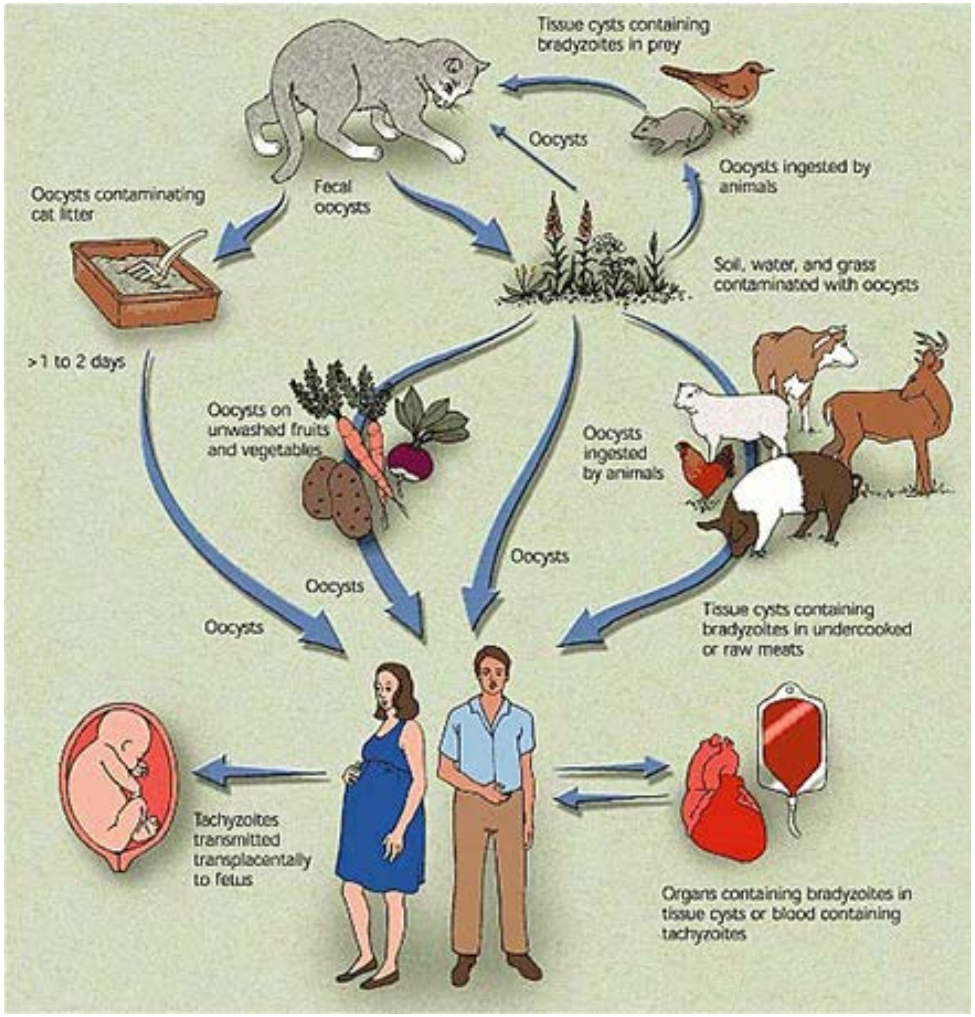
Life Cycle of Toxoplasma



Jones et al. 2003 AFP

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Toxoplasmagondii
protozoa parasite

- **Wide range of possible hosts**
  - Definitive hosts, DHs (sexual reproduction) = Felines, often domestic cats
  - Intermediate hosts, IHs (asexual reproduction) = Rodents, but also virtually all warm blooded animals.

- **Different routes of transmission**

- **Manipulation of the behavior of infected rodents**

  Attraction toward cat odors.

- **Zoonosis**

  Severe consequences in fetuses and immunocompromised patients

Behavior Change due to *Toxoplasma* Infection

Infected mice are drawn to rather than fearful of the scent of cats

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How Your Cat is Making You Crazy

- Toxo is strongest environmental factor implicated in schizophrenia.
- The parasite may trigger schizophrenia in genetically susceptible people – alters dopamine levels.
- Mental illness occurs 2-3x more often in people who have parasite.

(Torrey and Yolken, 2003)

- Toxo disconnects fear circuits in the brain & instead causes a type of sexual attraction to normally aversive cat odor.

(House, Vyas, Sapolsky, 2011)

- Parasite may also increase risk of suicide *(Pedersen, et. al., 2012)*

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T. Gondii in Humans

Human Infection

- World-wide prevalence (10% - 80%)
- Range of impacts on individuals:

Asymptomatic chronic infection

Ocular

Damage to fetus

Severe acute disseminated toxoplasmosis

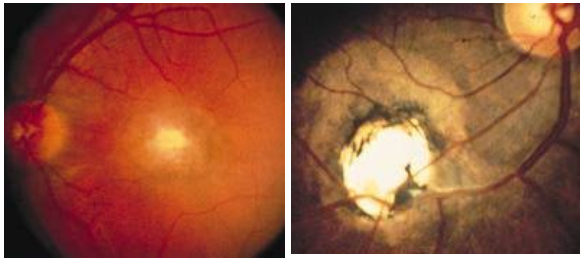
-- caused by atypical strains

- Immunocompromised patients (AIDS, etc.):

Encephalitis

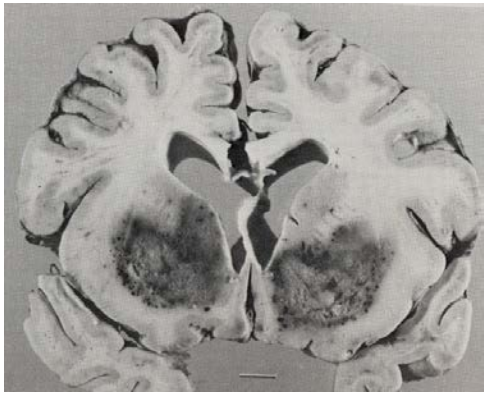
Ocular Toxoplasmosis

Active Chronic

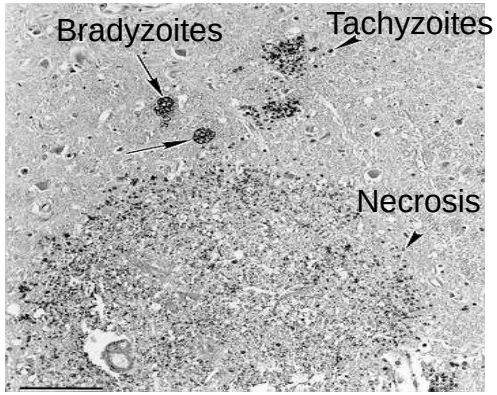


(www. revoptom.com/handbook/sect5i.htm)

Toxoplasmic Encephalitis



(Dubey JP & Beattie CP. 1988)



gsbs.utmb.edu/microbook/ch084.htm

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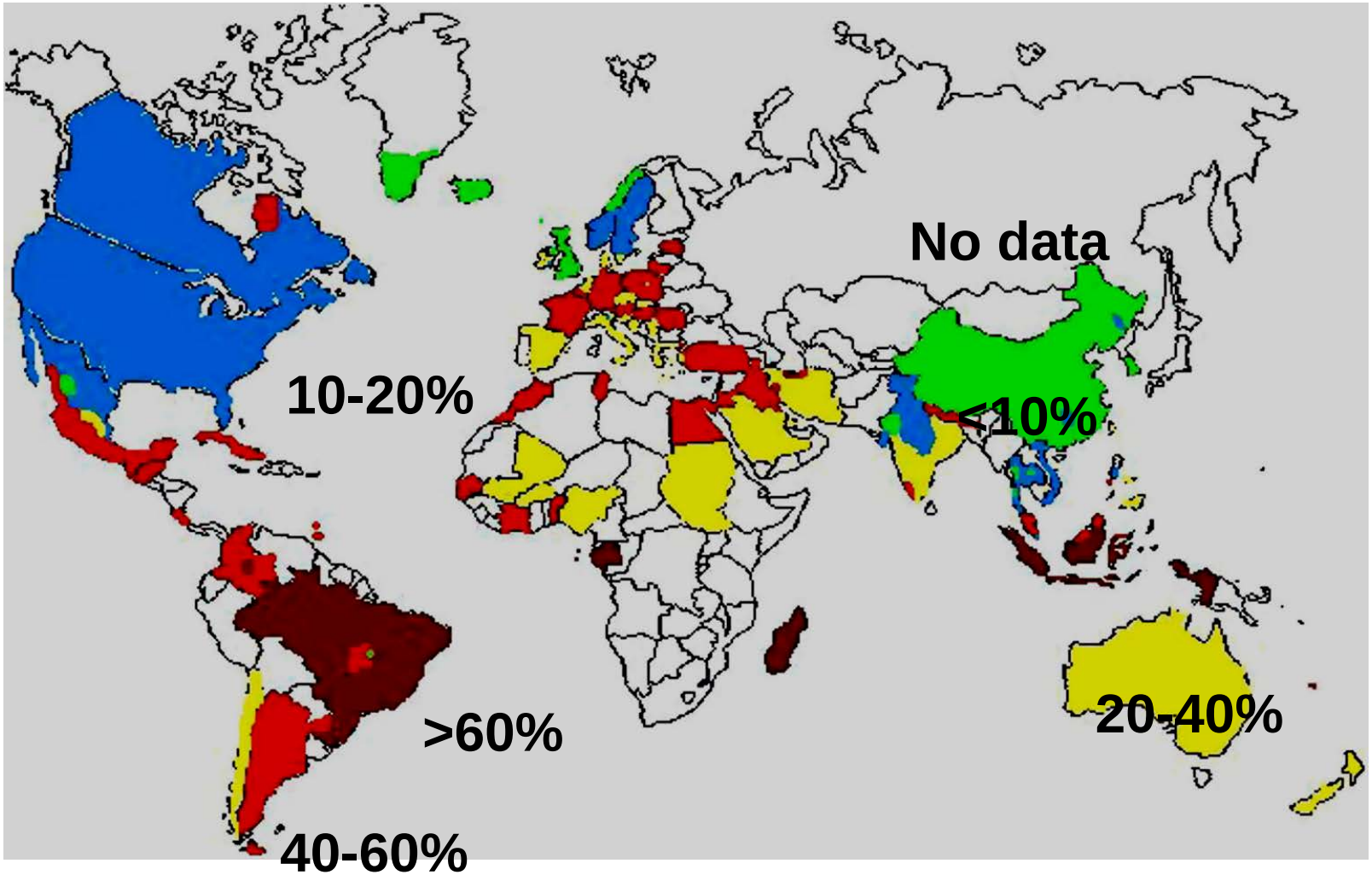
Toxoplasma seroprevalence in women of childbearing age



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Pappas et al., Int. J. Parasitol. 2009. 39:1385-1394.

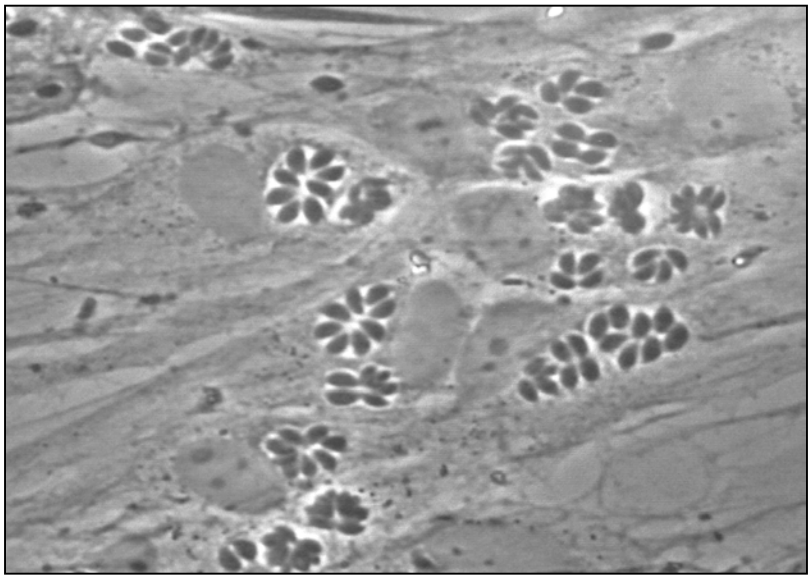
Table ES-1: Annual Disease Burden Caused by 14 Foodborne Pathogens

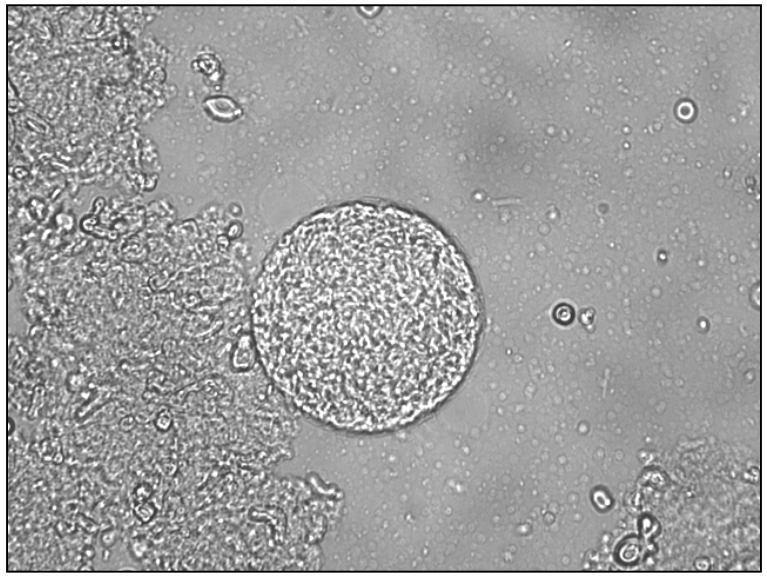
Pathogen	Combined Rank*	QALY loss	Cost of Illness ($ mil.)	Illnesses#	Hospital-izations#	Deaths#
Salmonella spp.	1	16,782	3,309	1,027,561	19,336	378
Toxoplasma gondii	2	10,964	2,973	86,686	4,428	327
Campylobacter spp.	3	13,256	1,747	845,024	8,463	76
Listeria monocytogenes	3	9,651	2,655	1,591	1,455	255
Norovirus	5	5,023	2,002	5,461,731	14,663	149
E.coli 0157:H7	6	1,565	272	63,153	2,138	20
Clostridium perfringens	6	875	309	965,958	438	26
Yersinia enterocolitica	8	1,415	252	97,656	533	29
Vibrio vulnificus	8	557	291	96	93	36
Shigella spp.	10	545	121	131,254	1,456	10
Vibrio other+	11	341	47	57,616	210	4
Cryptosporidium parvum	12	149	107	52,228	183	12
E.coli non-O157 STEC	13	327	26	112,752	271	0
Cyclospora cayetanensis	14	10	2	11,407	11	0
Total		61,461	14,114	8,914,713	53,678	1,322

QALY=quality adjusted life year

Growth Phase Switch

In mouse brain





Tachyzoites
(acute phase)

Bradyzoites
(chronic phase)

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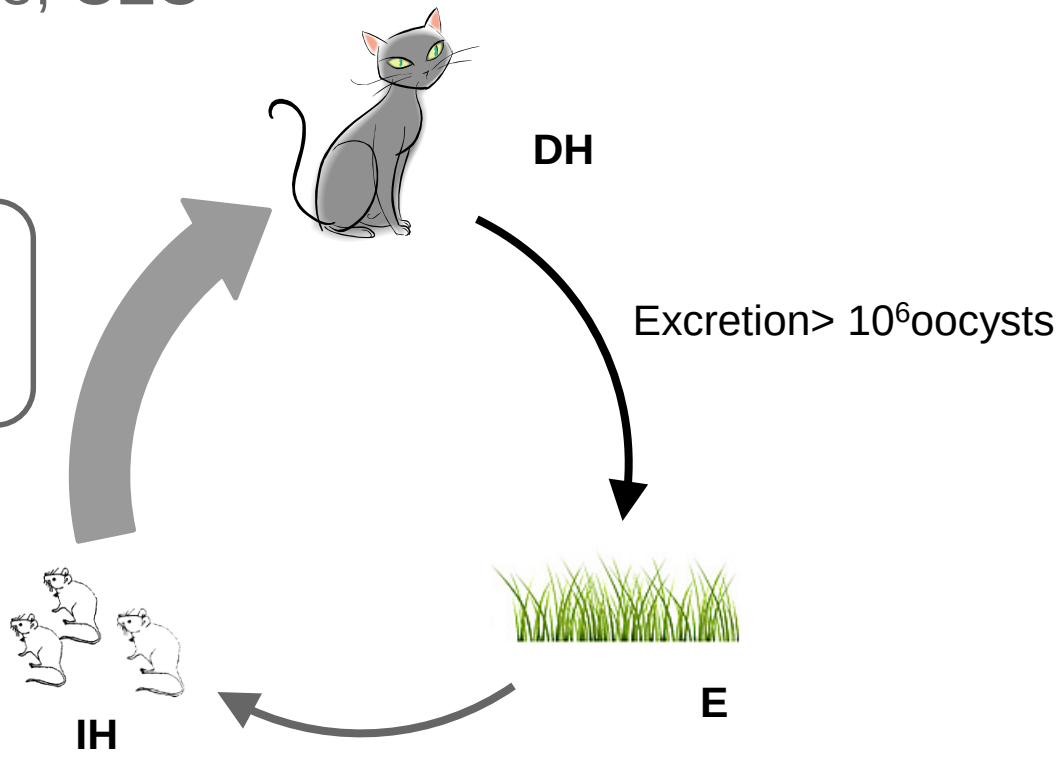
Toxoplasmagondii
life cycle

Complex Life Cycle, **CLC**

IH behavioral manipulation



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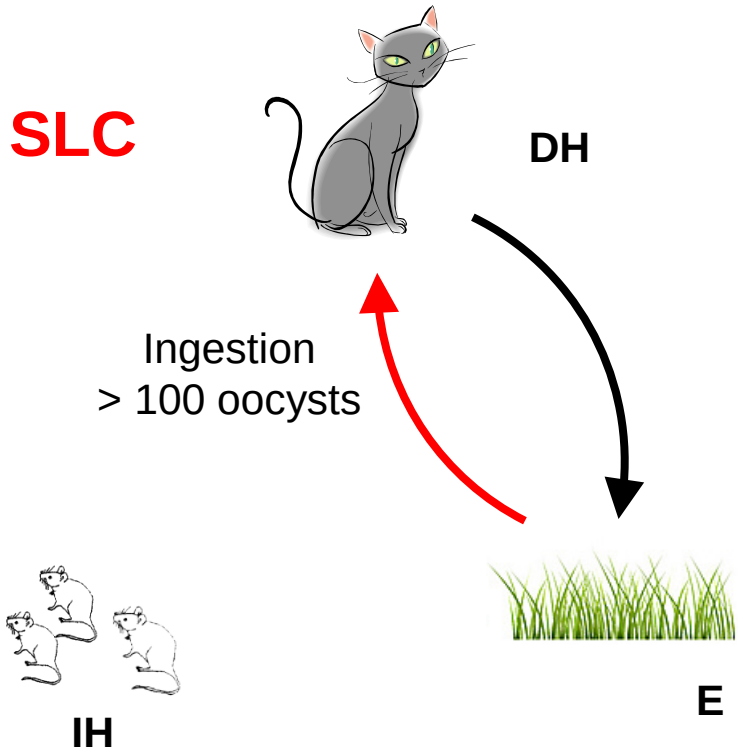
Modeling *Toxoplasma gondii* life cycle

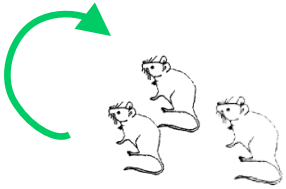
Simple Life Cycle, **SLC**



Modeling *Toxoplasma gondii* life cycle

IH-IH Cycle

DH



IH

E

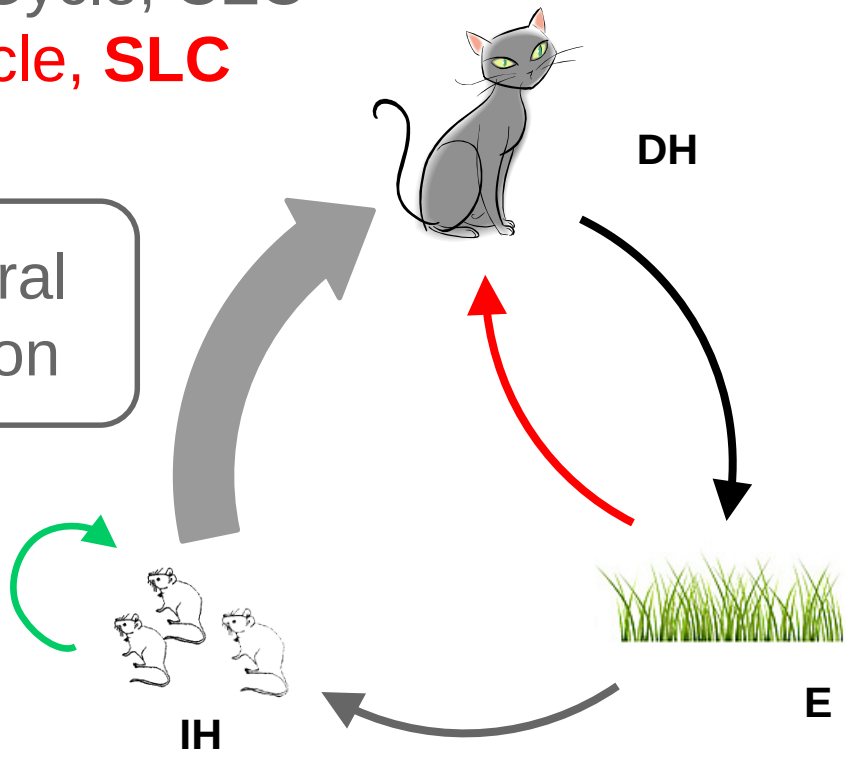
Modeling *Toxoplasma gondii* life cycle

Complex Life Cycle, **CLC**

Simple Life cycle, **SLC**

IH-IH Cycle

IH behavioral manipulation



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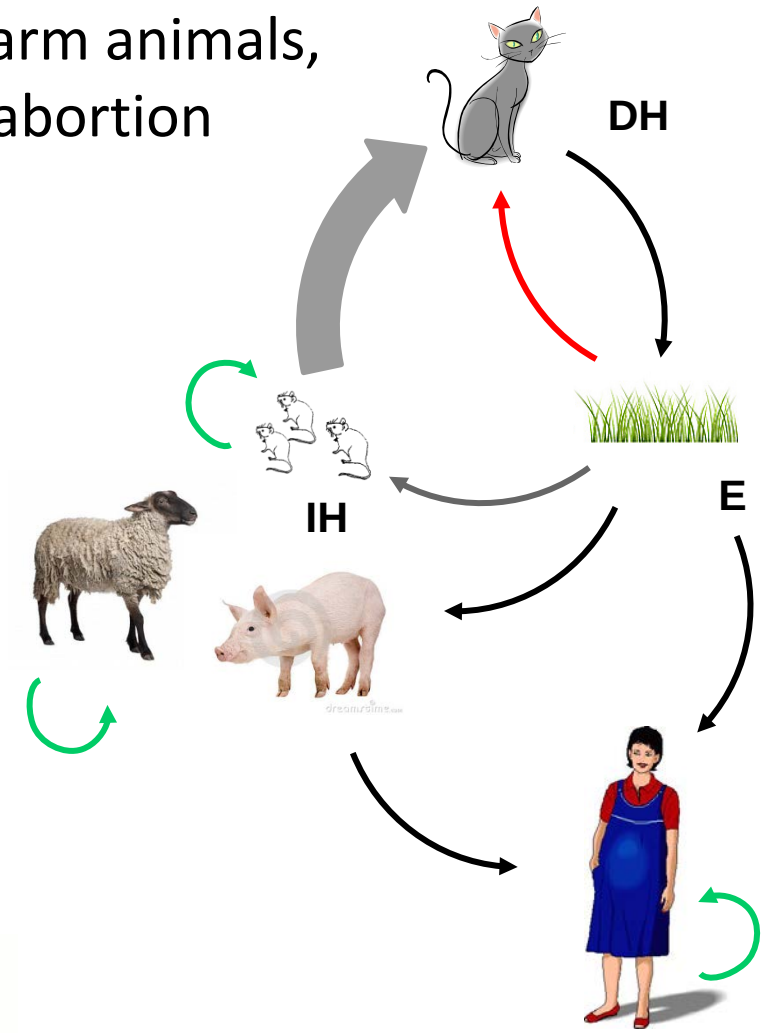
Modeling *Toxoplasma gondii* life cycle

Can infect farm animals, causes abortion



Zoonosis with severe consequences on fetuses, immunocompromised persons

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Goals of modeling studies on *T. gondii*

- **Transmission dynamics of *T. gondii***

What are the contribution of the SLC and CLC to *T. gondii*transmission along a gradient of host densities?

- **Evolution of *T. gondii*transmission routes**

Should manipulation evolve with vertical transmission?

How host densities impact the evolution of different transmission routes?

Dr. Maud Lélu
NIMBioS Postdoc

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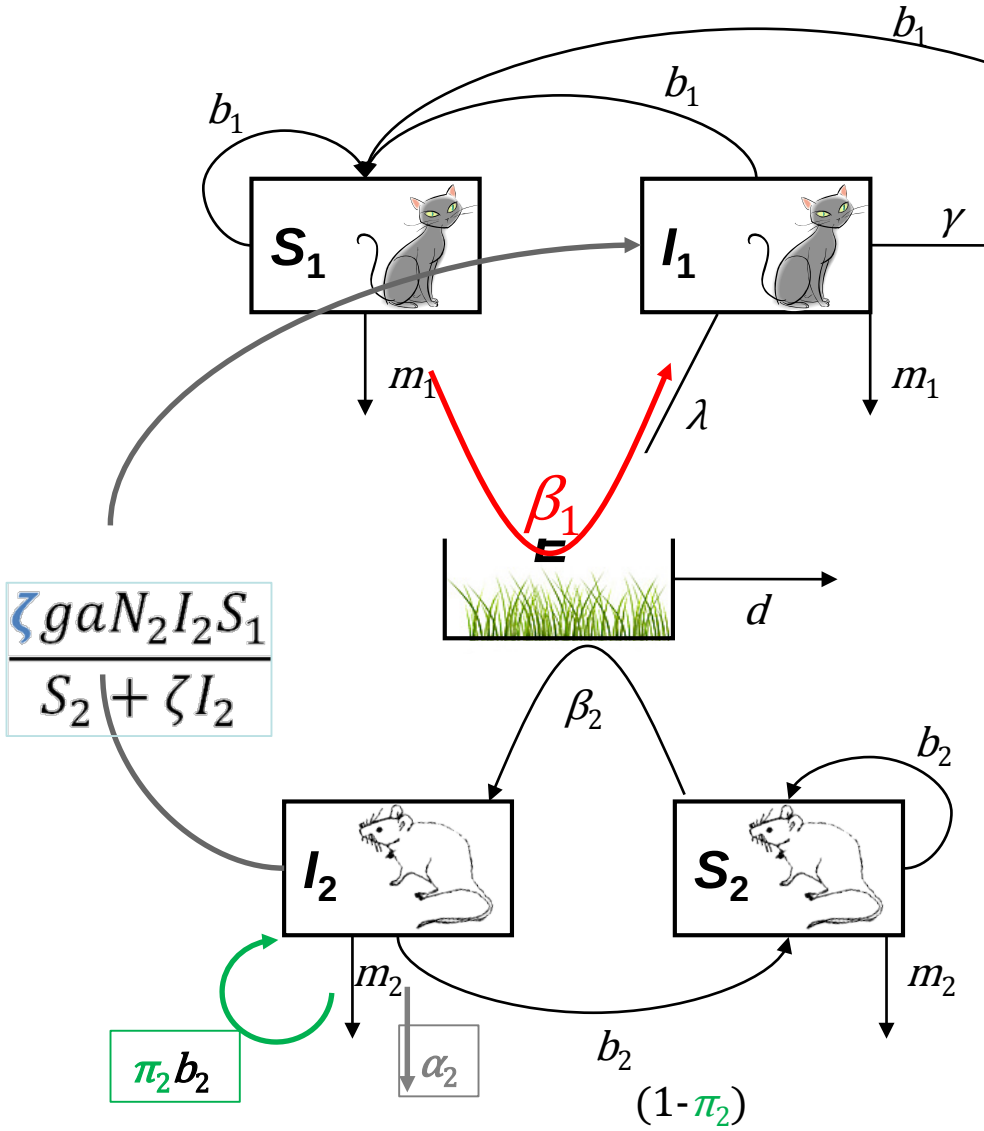
Epidemiological model



β_1,Oocyst to cat transmission rate

ζ, Manipulation coefficient

π_2, proportion of vertical transmission

α_2, virulence rate

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Epidemiological model

$$\dot{S}_1 = b_1 N_1 - (m_1 + k_1 N_1) S_1 - \left(\frac{\zeta g a N_2 I_2}{S_2 + \zeta I_2} + \beta_1 E \right) S_1$$

$$\dot{I}_1 = \left(\frac{\zeta g a N_2 I_2}{S_2 + \zeta I_2} + \beta_1 E \right) S_1 - (m_1 + k_1 N_1 + \gamma) I_1$$

$$\dot{R}_1 = \gamma I_1 - (m_1 + k_1 N_1) R_1$$

$$\dot{E} = \lambda I_1 - dE$$

$$\dot{S}_2 = b_2 S_2 + (1 - \pi_2) b_2 I_2 - \left(m_2 + k_2 N_2 + \frac{a N_2 K_1}{S_2 + \zeta I_2} \right) S_2 - \beta_2 E S_2$$

$$\dot{I}_2 = \beta_2 E S_2 + \pi_2 b_2 I_2 - \left(m_2 + k_2 N_2 + \frac{\zeta a N_2 K_1}{S_2 + \zeta I_2} + \alpha_2 \right) I_2$$

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Conclusions of modeling on *T. gondii*

Combination of different transmission routes can result in endemic outcome:

CLC + SLC increase the possibilities of *T. gondii* spread in environments with low host densities.

However, it can also result in conflict between transmission routes:

Manipulation of IH behavior could be disadvantageous for strains highly efficient in vertical transmission.

The high variability in host densities among environments (e.g., urban, rural) colonized by cats may impact the evolution of different transmission routes and could favor generalist strains. (leader Xiaopeng Zhao)

Summer Research Experiences for Undergraduates and Teachers

Projects for math and biology majors
(broadly interpreted) and math/science teachers.

Also accept international students in college in US

Frequently have topics using local data and scenarios

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Motivation

- Recent outbreak of Canine Distemper Virus (CDV) in local shelters resulting in depopulation
- Vaccine breaks
- New strain of CDV

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Canine Distemper Outbreak Modeled in an Animal Shelter

Ashley Dantzler, Margaux Hujoel, Virginia Parkman, Ayana Wild, Suzanne Lenhart, Benjamin Levy, and Rebecca Wilkes

Paper appeared in Letters in Biomathematics in 2016

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Goal

Model the spread of a Canine Distemper Virus (CDV) outbreak in a shelter in order to investigate possible transmission routes and various control methods.

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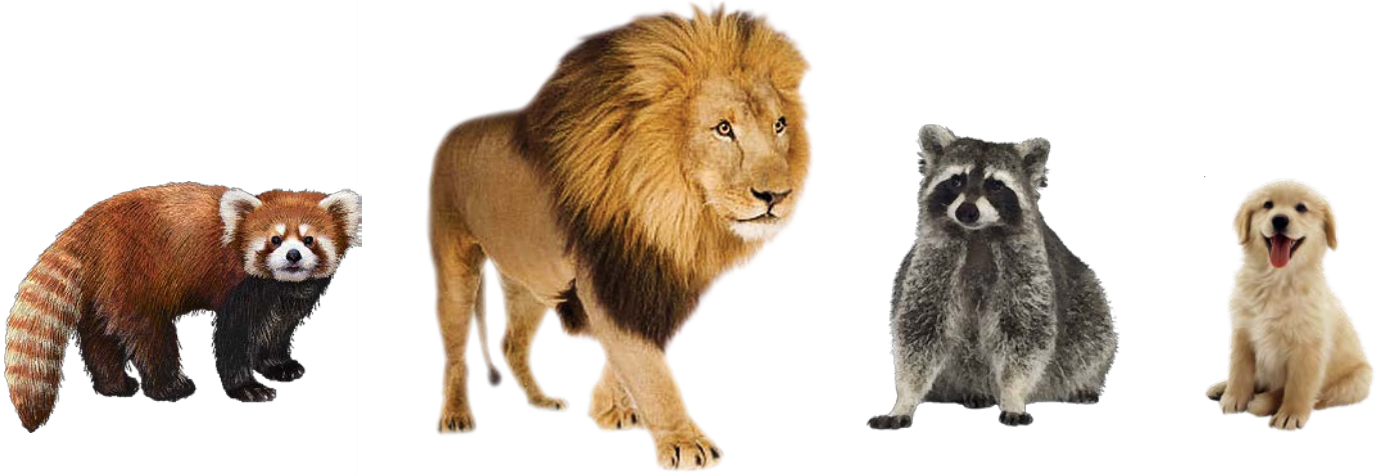
Introduction

- Canine Distemper Virus (CDV)
  - Highly contagious
  - Affects a wide range of animals



  - Severity of infectiousness similar to measles in humans

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Symptoms

- Respiratory
  - Coughing
  - Sneezing
- Gastrointestinal
  - Vomiting
  - Diarrhea
- Neurological -Seizures
  - Encephalitis

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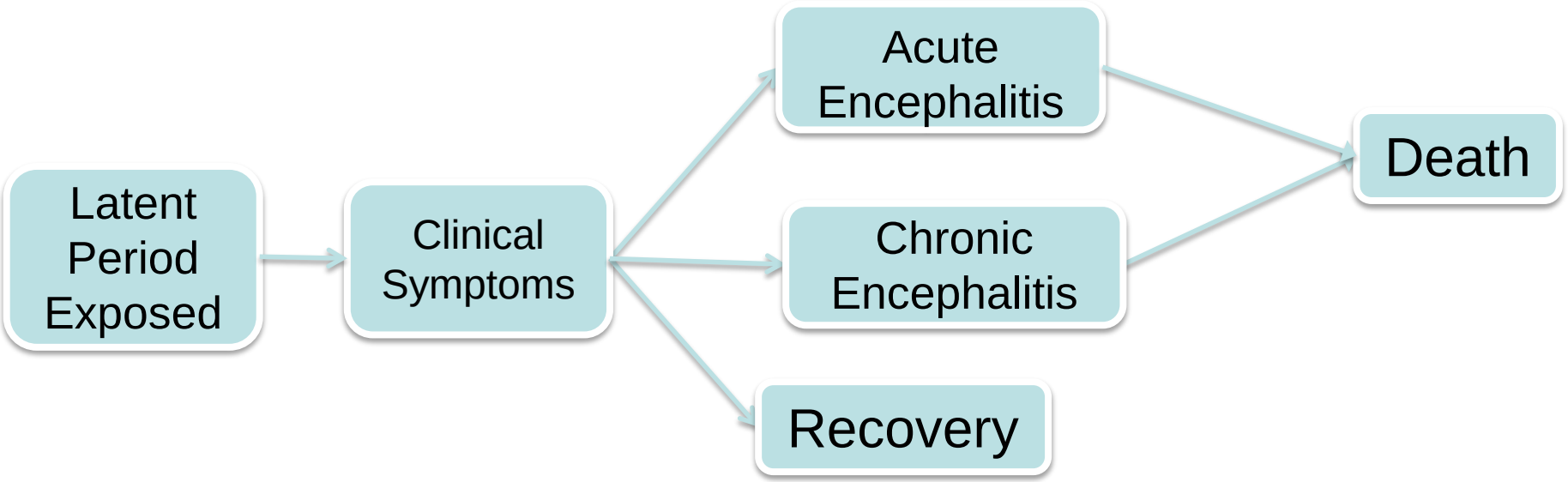
Disease Manifestations



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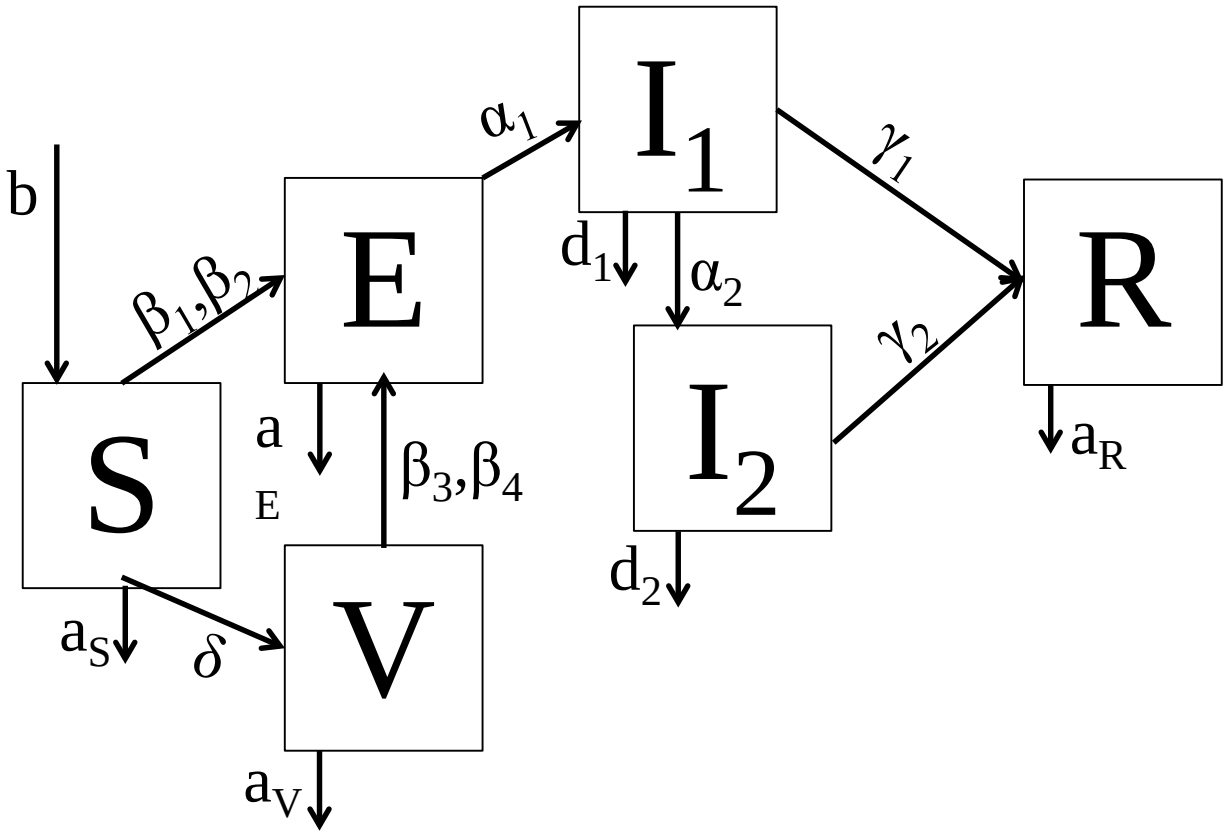
Epidemiological Model



- S: susceptibles
- E: exposed
- I_1: acutely infected
- I_2: chronically infected
- R: recovered
- V: vaccinated

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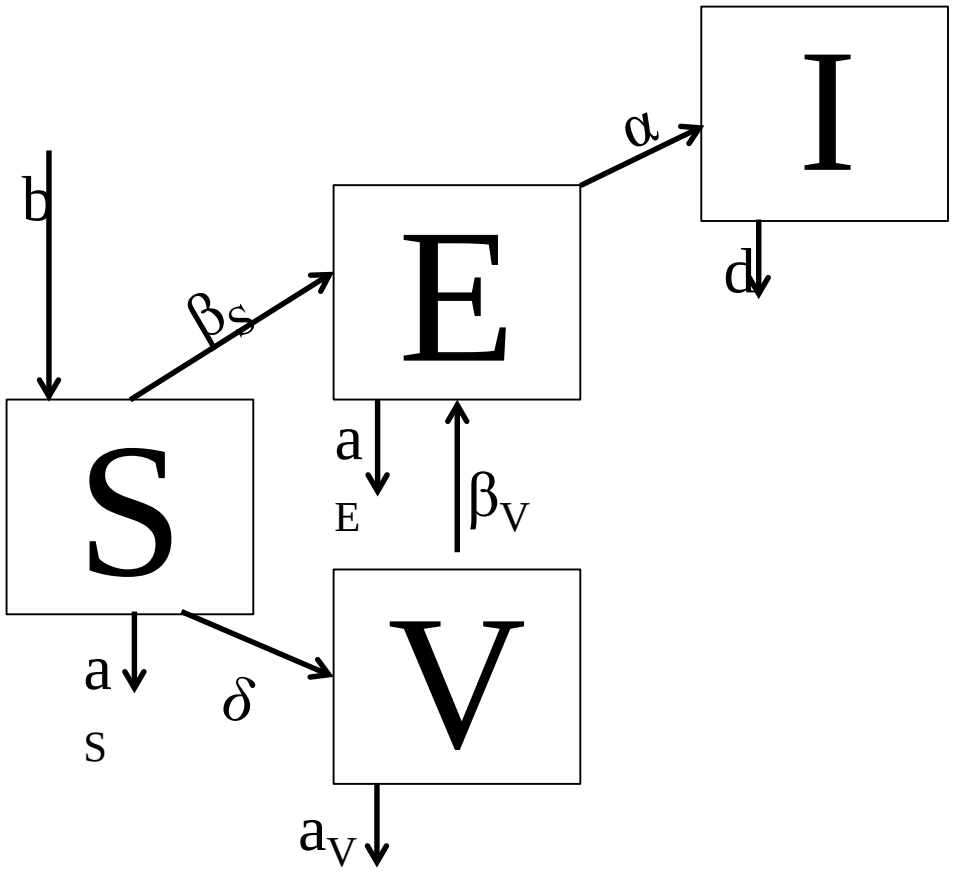
Shelter Model

Structured from a local shelter

- S: susceptibles
- E: exposed
- I: acutely infected
- V: vaccinated



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Local Shelter

- On average, the shelter houses 230 dogs.
- May
  - 485 dogs were received at the shelter
  - 339 dogs were adopted from the shelter
- Procedure upon infection
  - Clinical Symptoms noticed
  - Test completed
    - CDV test results in 1 day
  - Euthanization if positive

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Conclusions

- Prevention methods for shelters similar to the modeled local shelter:
  - Euthanizing infected dogs promptly
  - Increasing adoptions
  - Limiting interactions
- Simulations on the full model:
  - Euthanasia rate plays a large role in disease persistence




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Thank You!

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What is Johne's disease?

- Caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP);
- Chronic and progressive inflammatory gastrointestinal disease;
- Primarily affects ruminants, including cattle.

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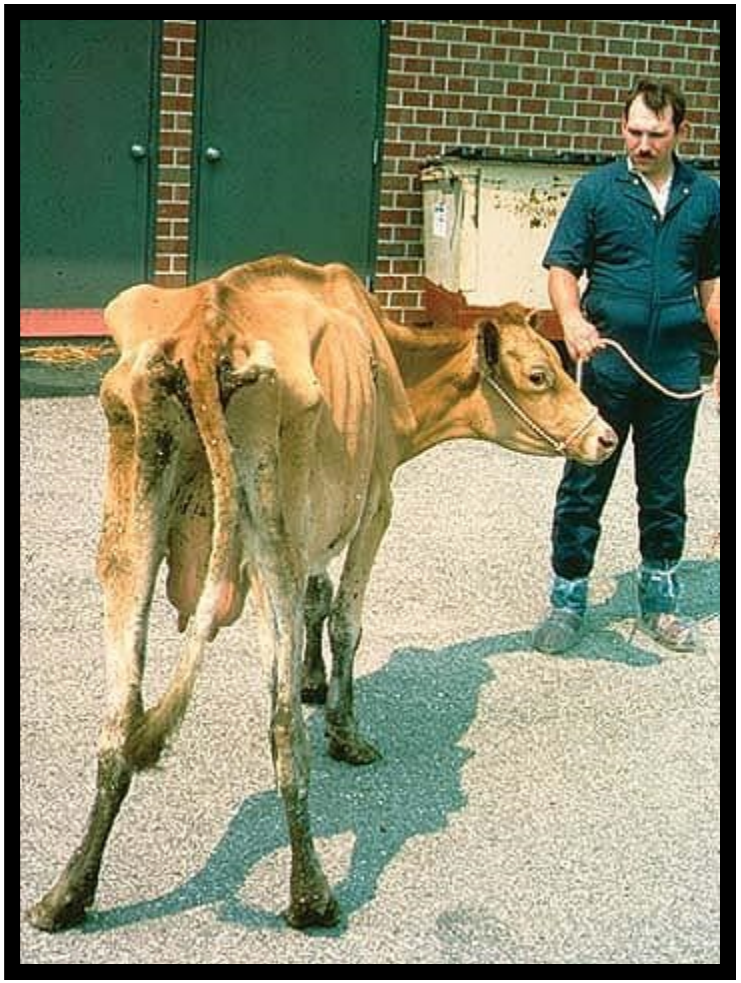
Clinical signs

- Chronic diarrhea;
- Emaciation;
- Weight loss despite a normal appetite;
- Decreased milk production.



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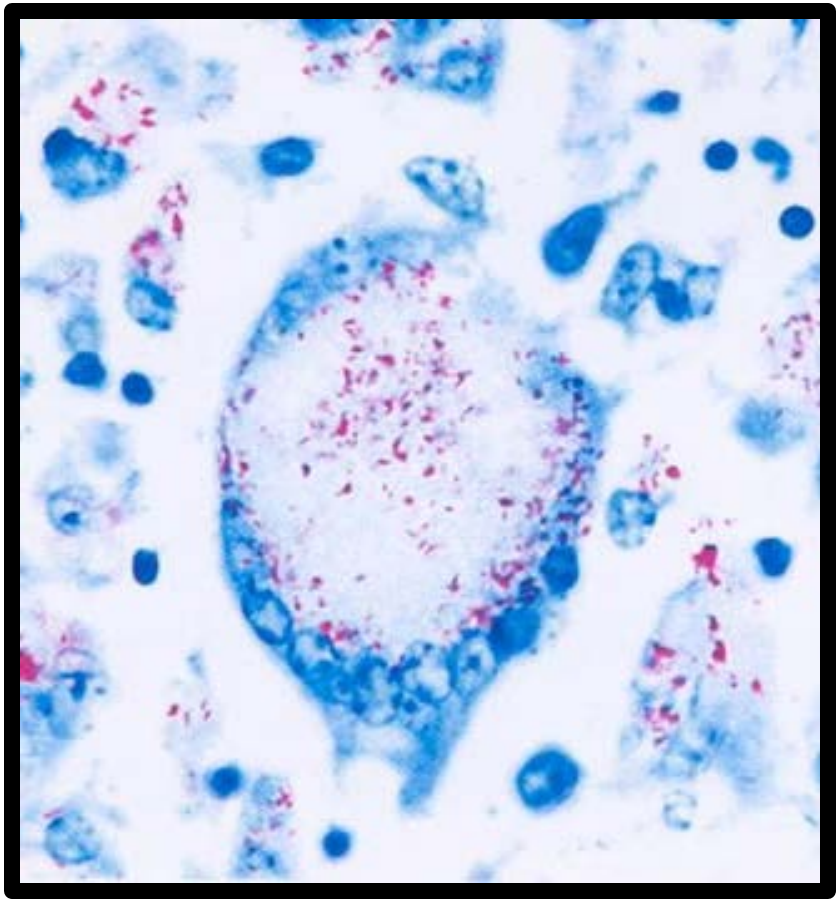
Mycobacterium avium subsp. *paratuberculosis* (MAP)



- Slow-growing bacteria;
- Invades intestinal mucosal surfaces;
- Resists destruction by macrophages;
- Re-enters the environment through shedding;
- Bacteria are spread via feces, milk, and colostrum;
- Bacteria can also spread from dam to fetus via amniotic fluid (vertical transmission).

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Impacts of Johne's disease

Highly prevalent worldwide; in the US, Africa, Australia, New Zealand and Europe.

MAP was found in 68% of US dairy herds and actual prevalence was estimated to be over **90%**.

Annual loss of more than **$200 million** to the US dairy industry. These loss are mainly due to reduced milk production and early culling.

The causative bacteria of Johne's disease is suspected to cause or worsen a **human disease**, called Crohn's disease

Obstacles in Johne's disease control

Antibiotics are expensive and require a long course of treatment: not a practical option for the livestock industry.

Vaccines have had limited success.

So, current management is based on:
Diagnosis and culling of infected animals.

However …

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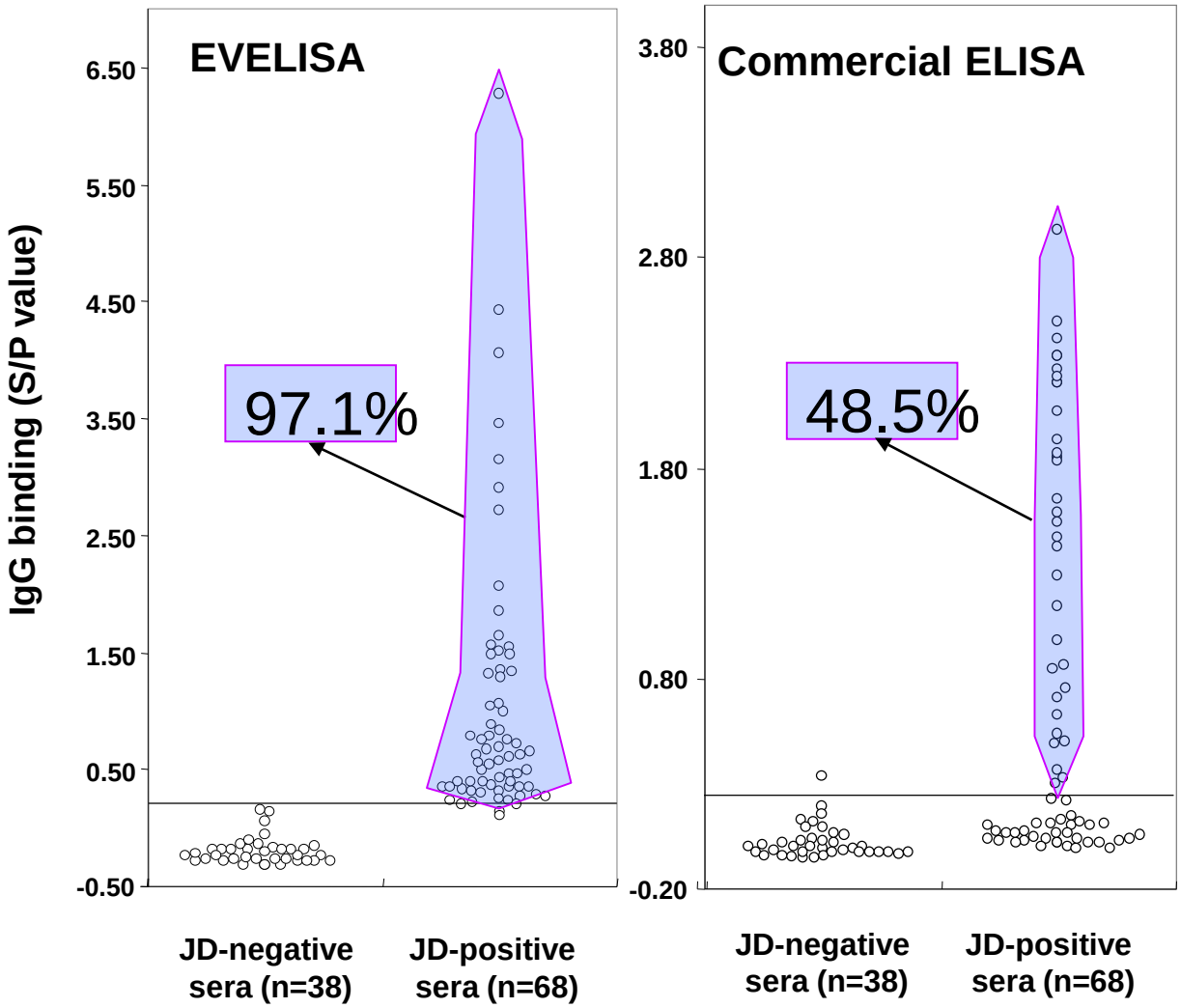
Problems in Johne's disease diagnosis

- **Detection of bacteria in feces**
  a. Culture
     Time consuming -- up to 4 months
     Expensive -- $20/sample
  b. DNA detection (PCR)
     Labor intensive – requires a skilled examiner
     Expensive -- $25/sample

- **Detection of antibodies in serum ELISA test**
  Rapid -- Half a day ---get results in a week
  Cheap -- $5/sample
  Easy -- **but very low sensitivity**

Sensitivity of EVELISA (1)



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Our Age Classes

- Calves:
  - 0-2 months old;
- Heifers:
  - 2-24 months old;
- Adults:
  - 24+ months old.

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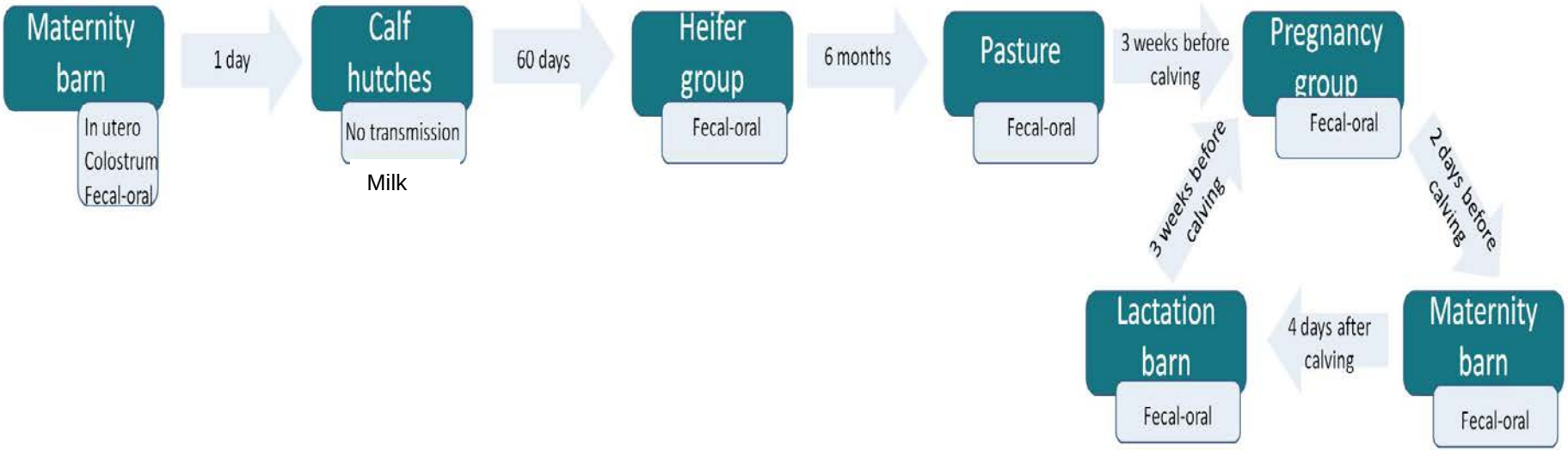
Cattle management model (contact structure)



The scheme by which individuals move through different spatial compartments.

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Two REU projects

Johne's disease epidemiology model was programmed based on the contact structure in the previous slide.

Difference equation model and agent-based model were implemented using R and NetLogo, respectively.

Using the model population dynamics, transmission (prevalence), and economics were analyzed.

In the economic analysis, cost-effectiveness of current diagnostic test (ELISA) and improved test (EVELISA) were compared.

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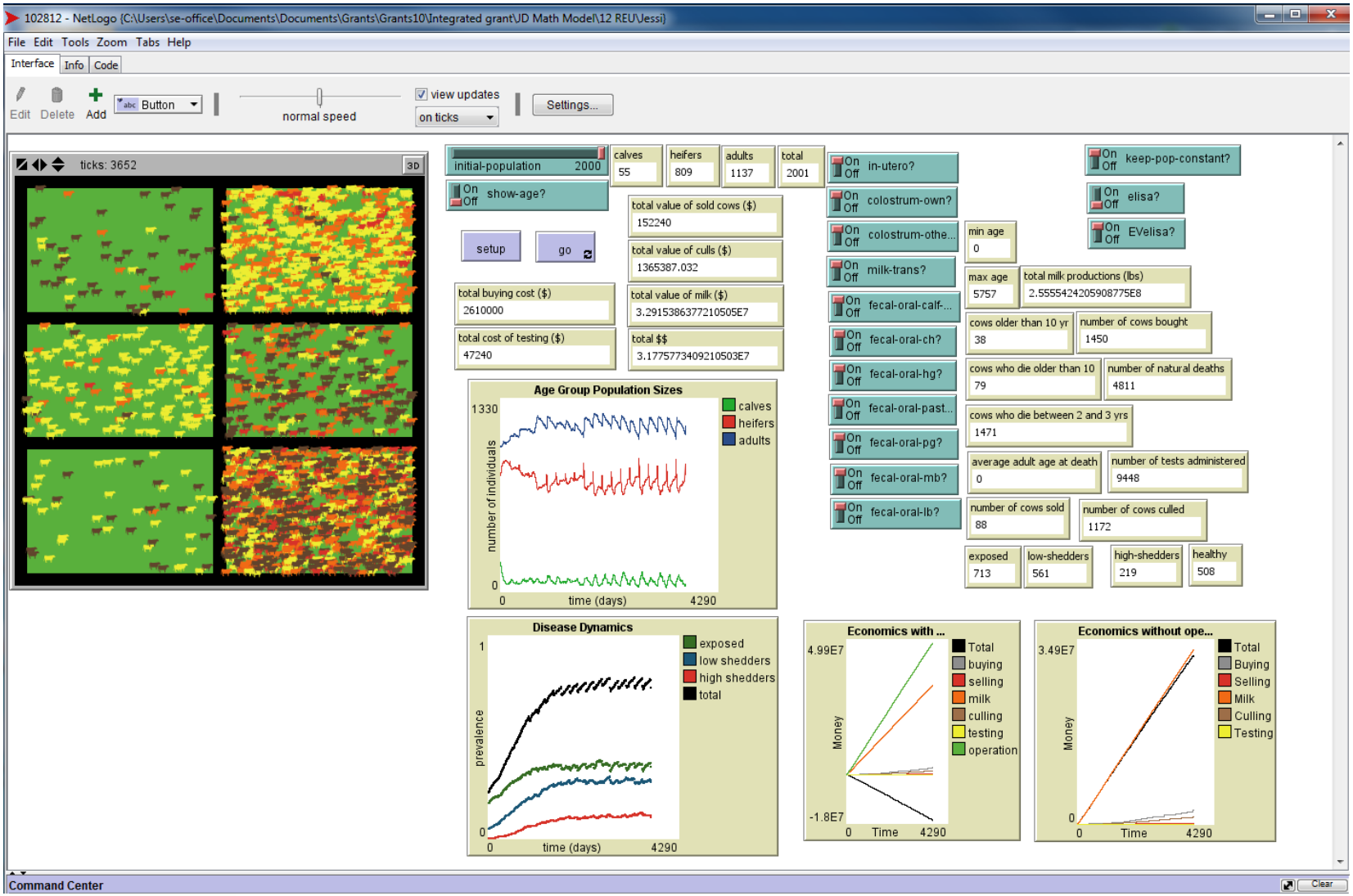
Johne's disease model implicated with NetLogo



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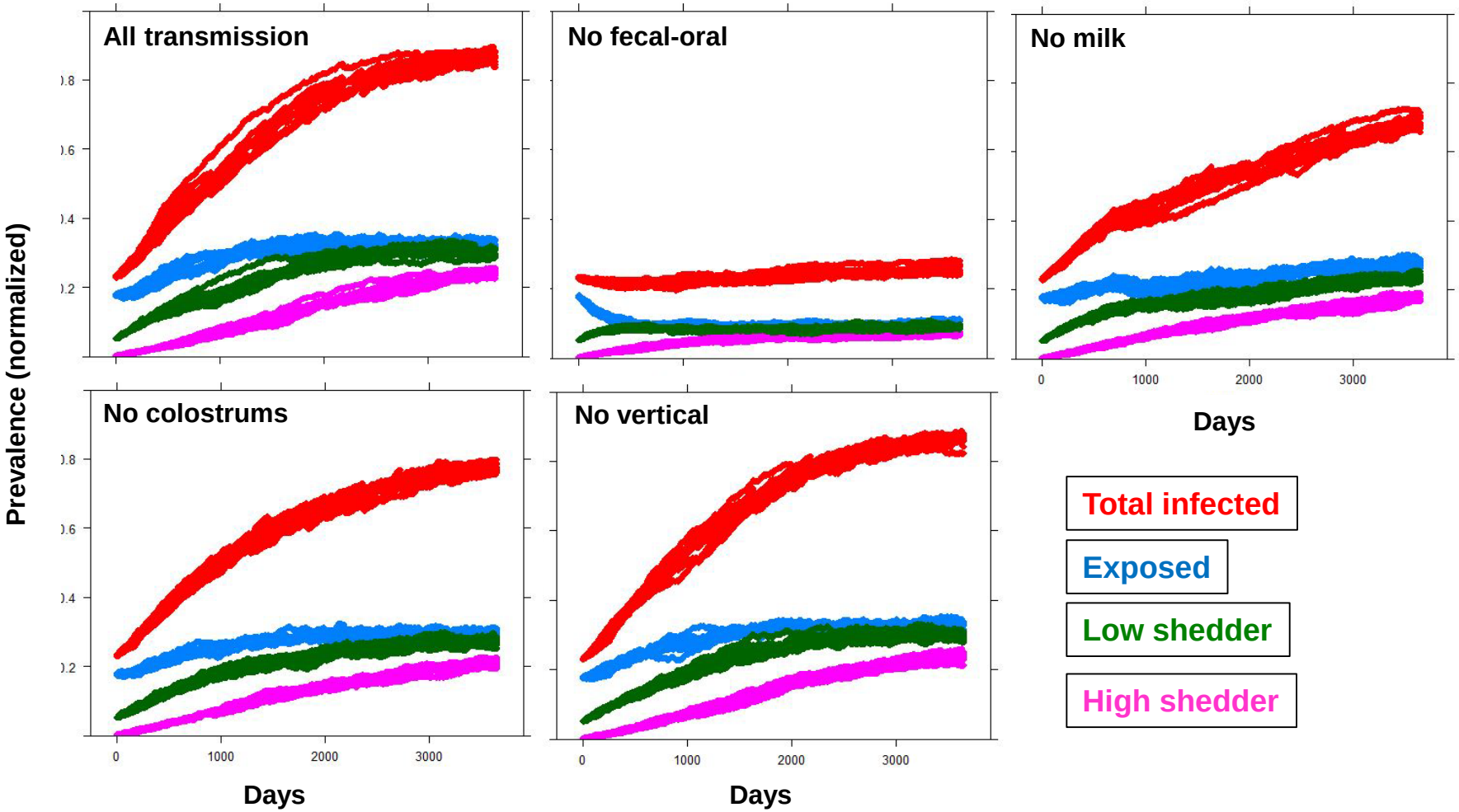
Population dynamics of JD in a dairy farm simulated by the JD agent-based model



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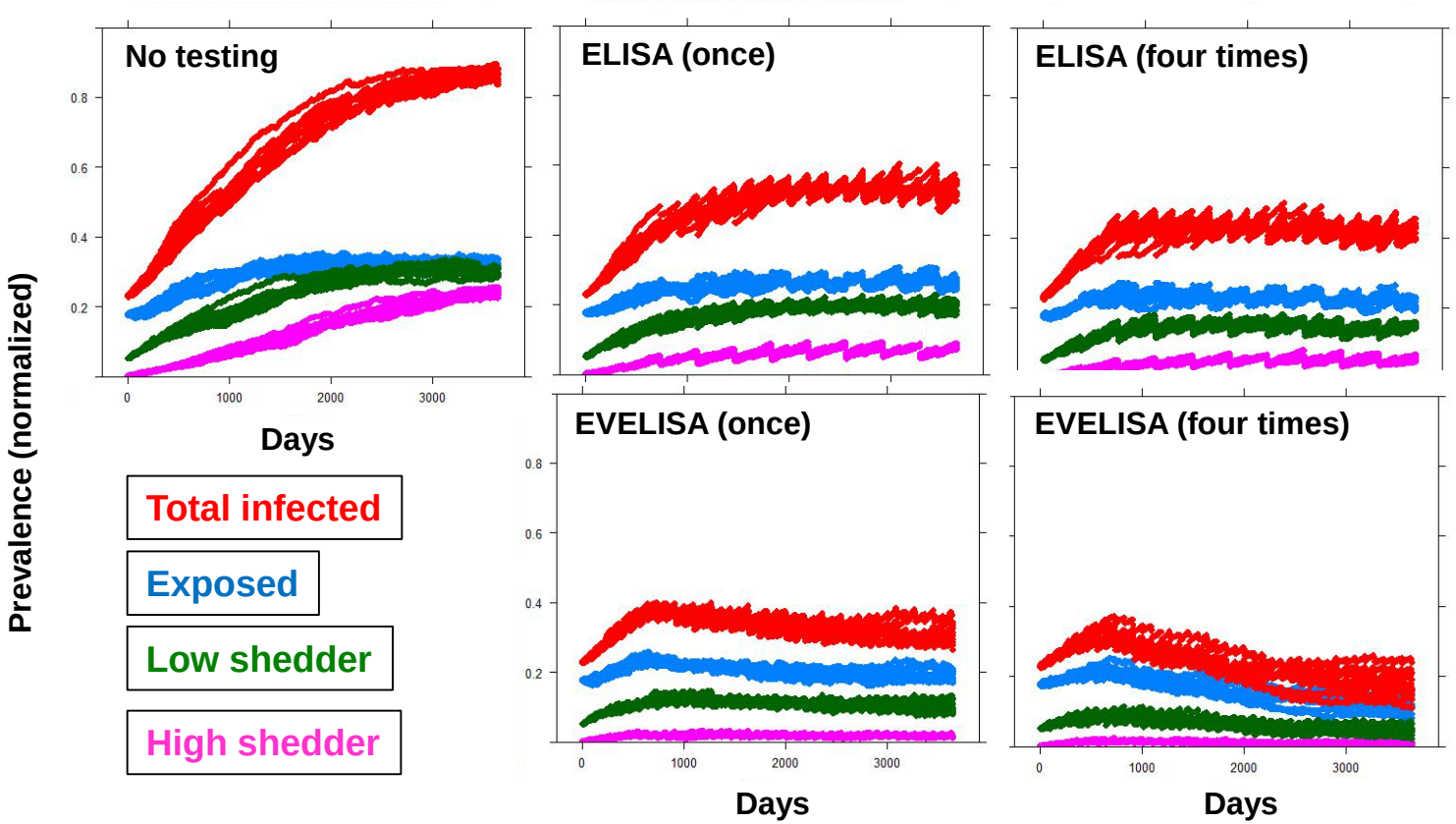
Population dynamics of JD in a dairy farm simulated by the JD agent-based model



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Conclusions from Johne's epidemiological models

EVELISA-based Johne's disease control was predicted to reduce MAP infection in a dairy farm and to be more cost-effective than ELISA-based control. However, even after the control, MAP infections persisted in the dairy herd.

Currently, Johne's disease screening is conducted only once a year, which may be a cause of the persistence of MAP infections.

Collaborators: S. Eda, Tyler Massaro, Jessica Robins and several other undergraduates and Vet students

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Johne's disease

Etiologic agent --- Acid fast gram positive bacteria, *Mycobacterium aviumsubsp. paratuberculosis*(MAP)

Host --- Primarily ruminants in livestock and wildlife. Many other animals can be carriers or sporadically infected.

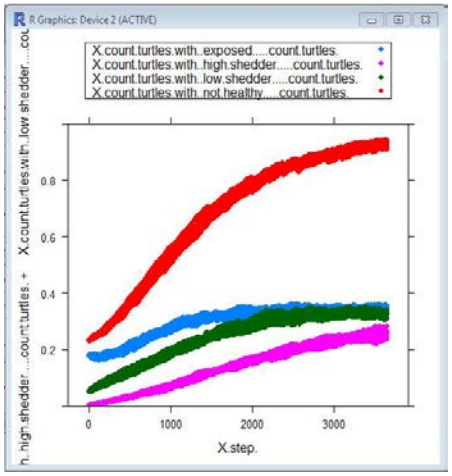
Infection --- The primary site of infection is small intestine (esp. ileum). MAP bacilli survive in macrophages and cause formation of granulomas. After a long incubation time, the bacteria break out of the macrophages and contaminate feces and milk.

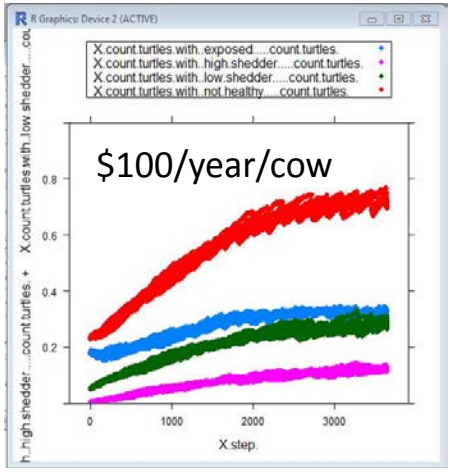
Transmission --- Oral-fecal transmission, contaminated colostrums/milk

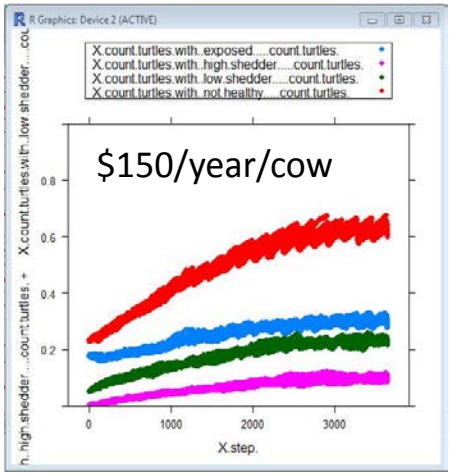
Signs --- Chronic diarrhea, weight loss, and decreased milk production.

Outputs of agent-based model

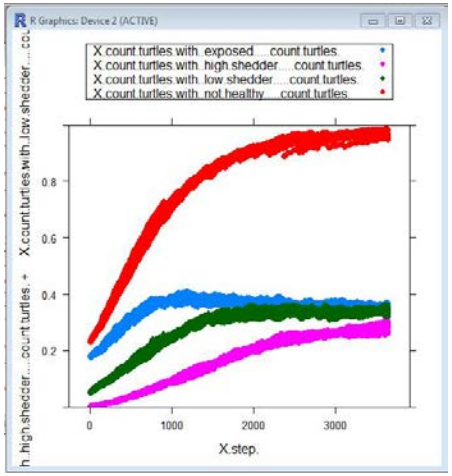
Low fecal oral transmission

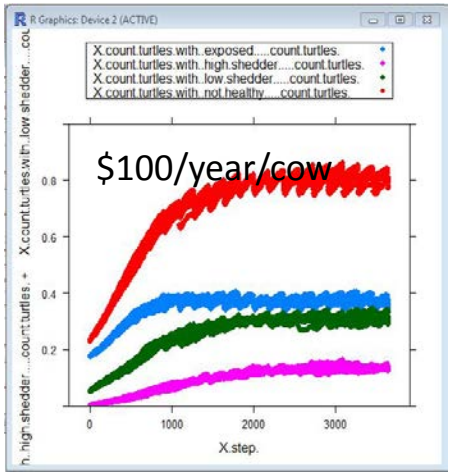


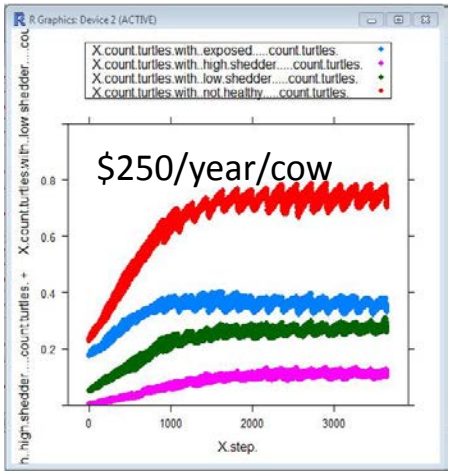




High fecal oral transmission







No testing ELISA EVELISA