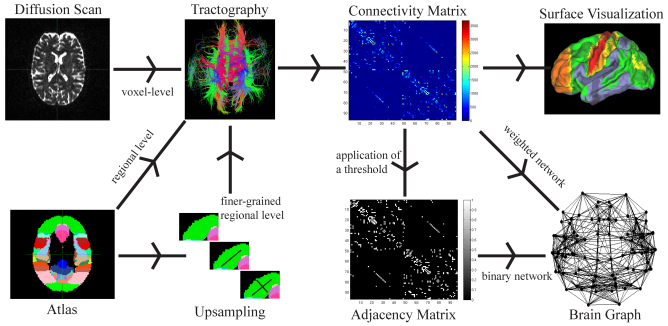
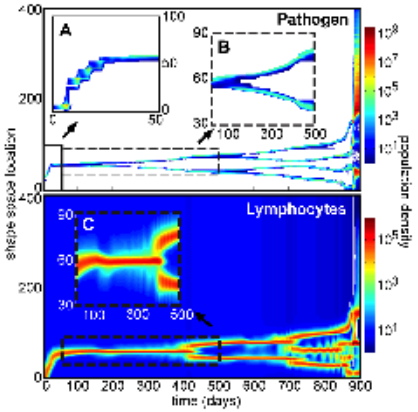
# Complex Systems @ UCSB

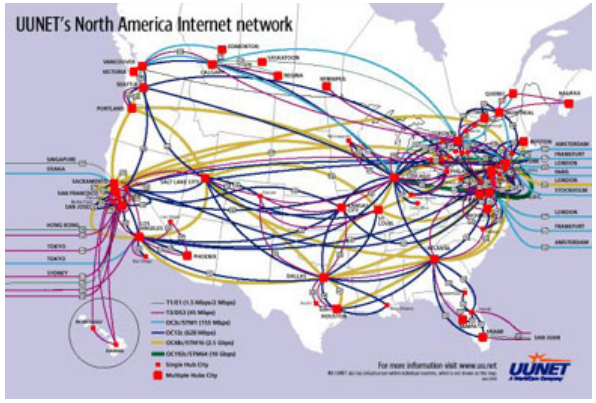
Jean Carlson, Department of Physics

## Robustness Tradeoffs, Dynamics, and Multi-scale Modeling in Geological, Ecological, Biological, and Technological Networks

Tools and applications:




**Data driven network and dynamic network ID: brain structure/function relationships, state switching, learning, aging, machine learning for high resolution medical imaging.**

**Mechanistic models: cellular materials, adaptive immunity, microbiome: dynamics, robustness, co-evolution, population structure, dynamic response**

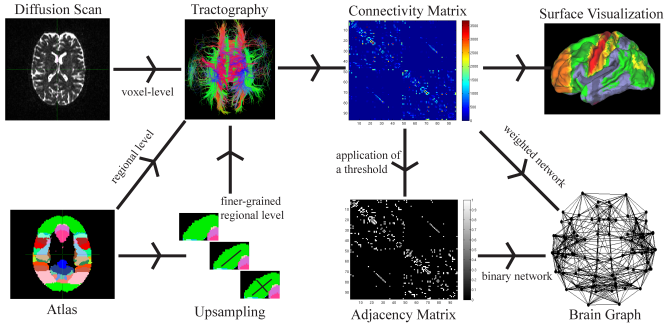
**Technological/social networks, natural disasters: dynamic resource allocation protocols, collective decision making, information diffusion**

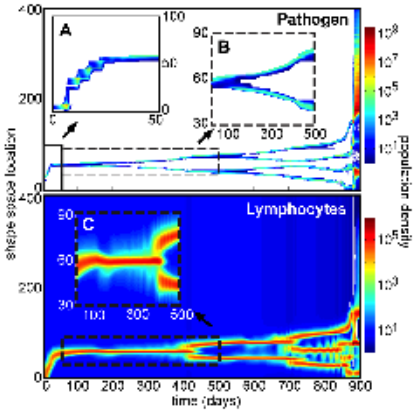
# Why am I here today?

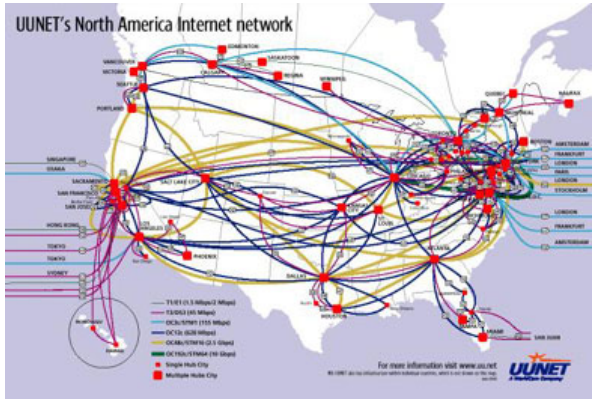
Jean Carlson, Department of Physics

## Robustness Tradeoffs, Dynamics, and Multi-scale Modeling: Host Pathogen (co)Adaptation, Diversification, and Age

Tools and applications:

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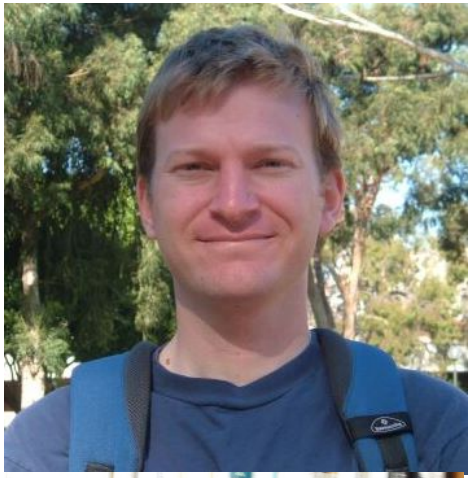
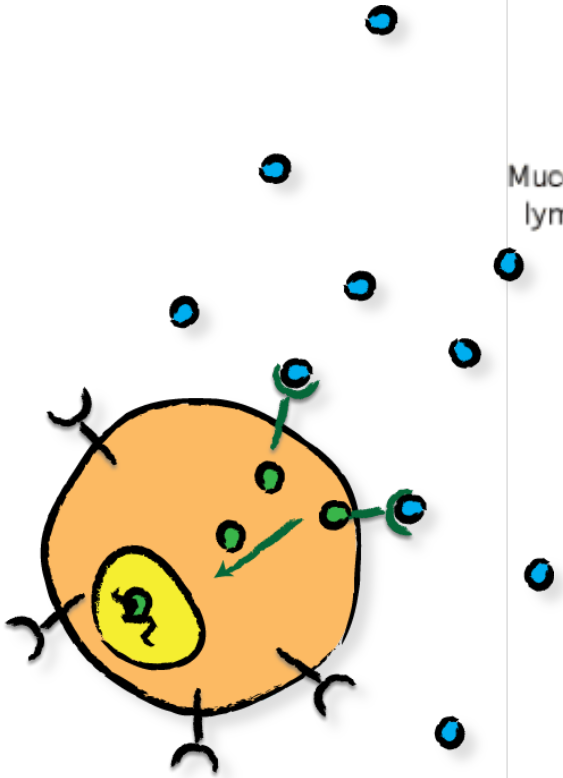
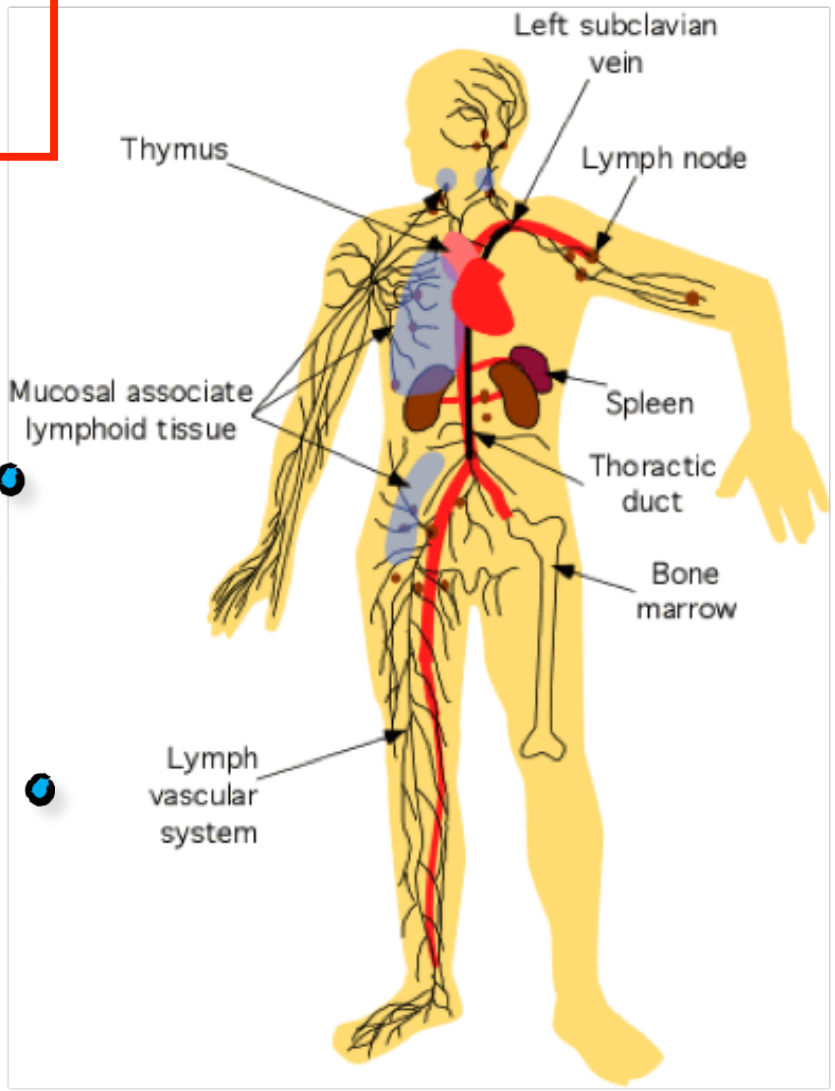
# Robustness and Fragility in the Adaptive Immune System: Immunosenescence and host-pathogen coevolution

*Jean Carlson, Sean Stromberg,*
*Kimberly Schlesinger, UCSB Physics*
http://www.physics.ucsb.edu/~complex







# Aging in the Adaptive Immune System

The immune system has resource constraints in the total number of cells that compose the system. It also allocates its resources to be more efficient at fighting diseases it has already encountered.

**Robust** to uncertainties

-- that are common,

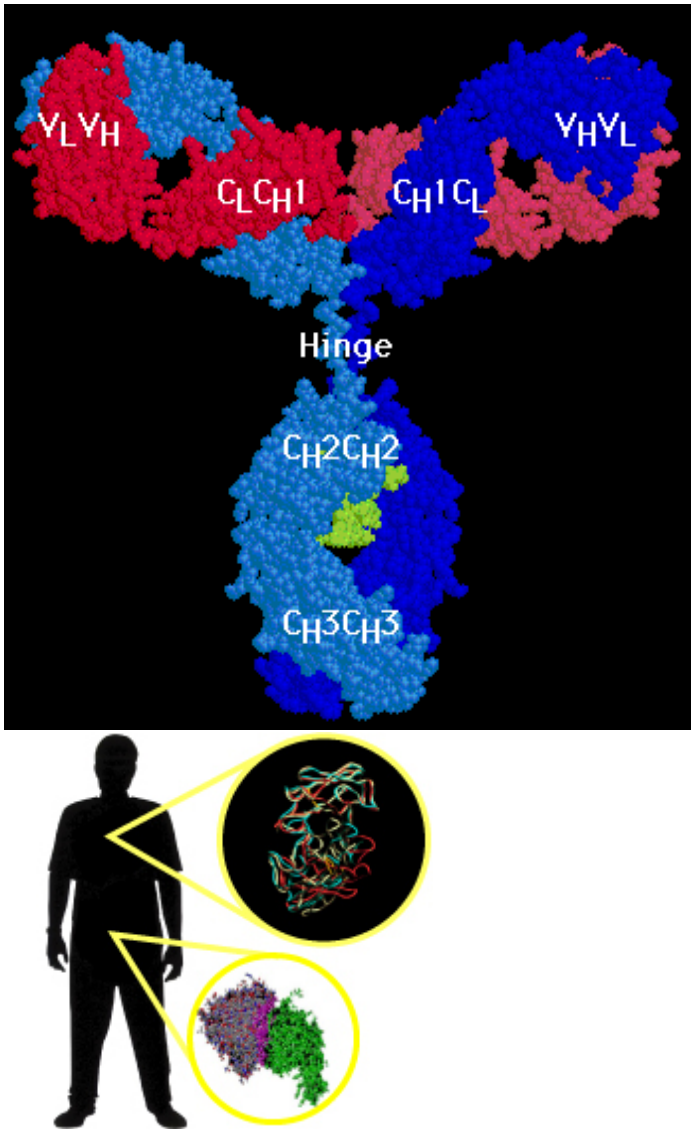
-- the system was designed for, or

-- has evolved to handle,

…yet **fragile** to unknown

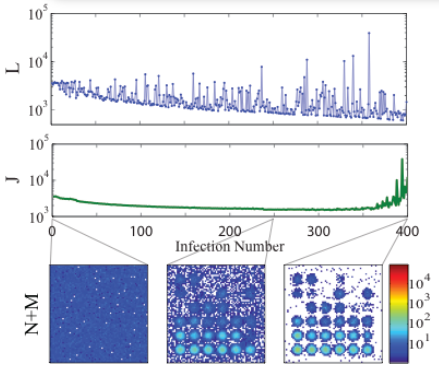
-- or rare events **(HOT!)**

Focus on consequences of adaptive mechanisms, rather than breakdown of cellular function.

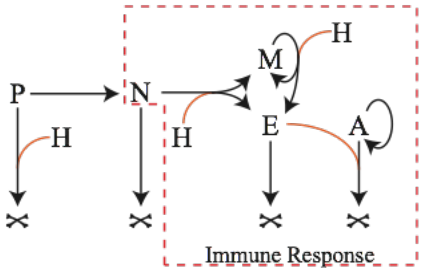


## Approach:

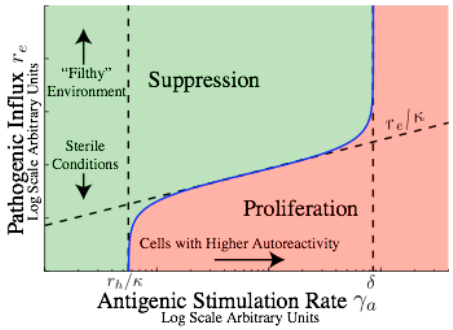
- Dynamical models of immune system behavior based on the mechanics of individual cell types.
- The models are used to:
  - Understand how the immune system solves problems
  - Predict failures that will result from these problem solving mechanisms



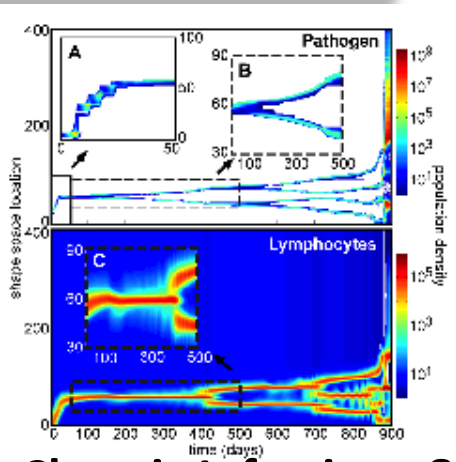

**Adaptation, Aging, Overspecialization**




**Cross Reactivity, Antigenic Sin & Negative Selection**




**Passive Attrition & Hygiene Hypothesis**




**Chronic Infections & Immune Escape**

All of these reflect different fragilities associated with a dynamic (arrow of time), systems level view of adaptive mechanisms that evolved for robustness

# Approach:

- Dynamical models of immune system behavior based on the mechanics of individual cell types.
- The models are used to:
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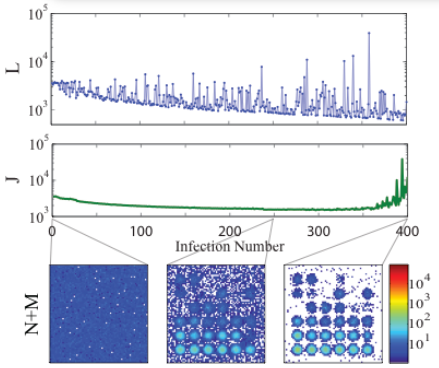
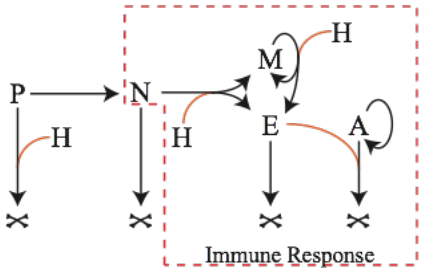


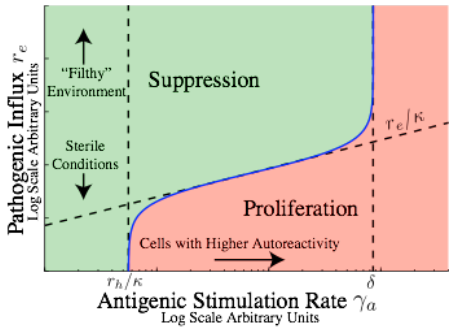

**Aging of the Immune System**

Immunosenescence
organism lifetime



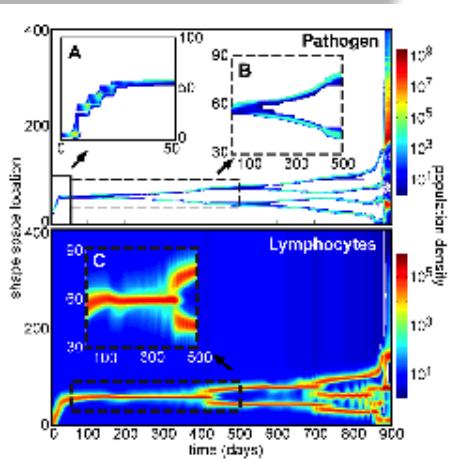

**Antigen evades Immune response**

Tolerance
Immunosuppresive




**Tuning immune system depends on exposure**

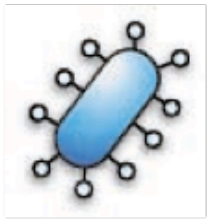
Environmental factors
sterile vs. filthy



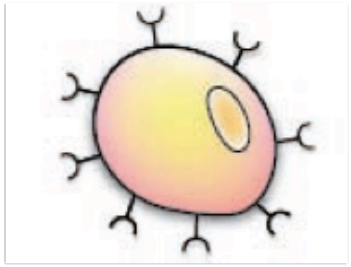

**Immune/pathogen coevolution**

Mutation & diversity
"arms race"

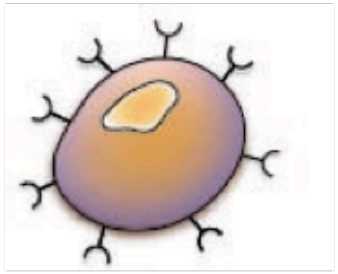
# Cells in Immune Response Model



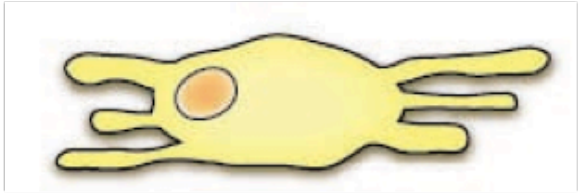
Antigen - A



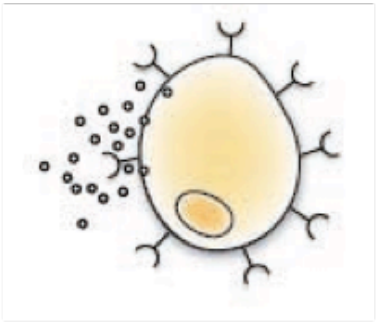
Naive Cell - N



Memory Cell - M



Dendritic Cells - F and F*



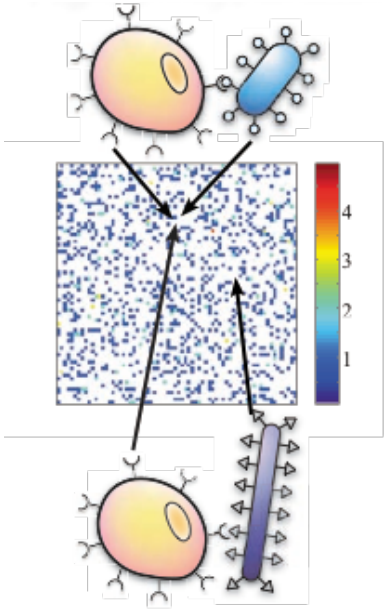
Effector Cell - E

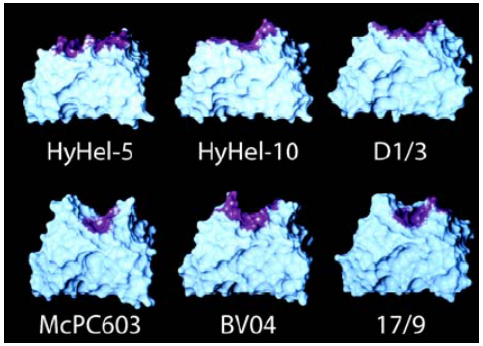
Stromberg and Carlson, Robustness and Fragility in Immunosenescence. PLOS Comp. Bio. 2, e160 (2006).

# Shape Space

- Because the lymphocyte population is so diverse we need a method to organize the distribution of lymphocyte affinities for different antigens
- We use the generalized shape space of Oster and Perelson (1979)
  - Lymphocyte($\vec{y}$) and antigen($\vec{x}$) binding characteristics are described by vectors in the shape space
  - The binding affinity is a decaying function of the distance between vectors:

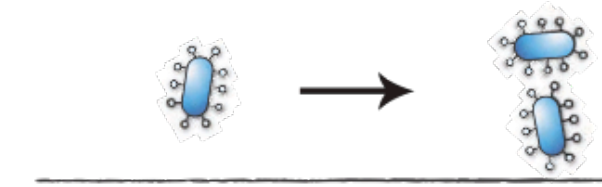
$$\gamma(\vec{x},\vec{y}) = \gamma_m e^{-(\vec{x}-\vec{y})^2/2b^2}$$




*(shape, charge, size, hydrophobicity…)*

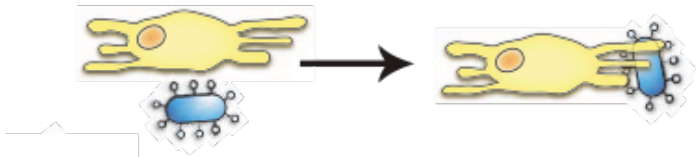
# Reactions in Immune Response



**Antigen Growth**

- Coupled to pathogen division

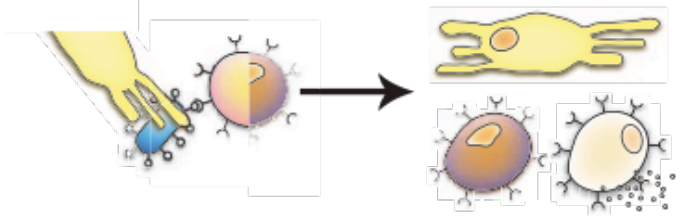
Reaction Rate: $\beta A$



**Antigen Capture**

- $F \rightarrow F^*$
- $F + F^* = \text{const.}$

Reaction Rate: $\rho FA$



**Lymphocyte Stimulation**

- Both $N$ and $M$
- Divide into $E$ and $M$
- E with fraction f, M with fraction 1-f.
- Affinity Dependent
- $F^* \rightarrow F$

Reaction Rate: $\alpha\gamma F^*(M+N)$

**Antigen Removal**

- Affinity dependent

Reaction Rate: $\gamma EA$

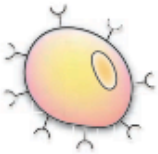
**Effector Cell Death**

Reaction Rate: $\delta E$

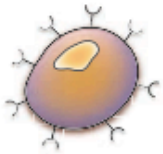
# Immune Response Equations

$$\frac{\partial A(\vec{x})}{\partial t} = \underbrace{\beta A(\vec{x})}_{\text{Division}} - \underbrace{A(\vec{x}) \int \gamma(\vec{x},\vec{y}) E(\vec{y}) d\vec{y}}_{\text{Removal}} - \underbrace{\rho F A(\vec{x})}_{\text{Capture}}$$

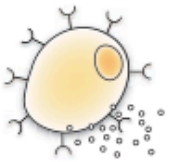
$$\frac{\partial F^*}{\partial t} = \underbrace{\rho F A(\vec{x})}_{\text{Capture}} - \underbrace{\alpha \int \gamma(\vec{x},\vec{y}) F^* (M+N)(\vec{y}) d\vec{y}}_{\text{Stimulation}}$$



$$\frac{\partial N(\vec{y})}{\partial t} = \underbrace{-\alpha \gamma(\vec{x},\vec{y}) F^* N(\vec{y})}_{\text{Stimulation}}$$



$$\frac{\partial M(\vec{y})}{\partial t} = \underbrace{(2-2f)\alpha\gamma(\vec{x},\vec{y}) F^* N(\vec{y})}_{\text{Stimulation}} + \underbrace{(1-2f)\alpha\gamma(\vec{x},\vec{y}) F^* M(\vec{y})}_{\text{Stimulation}}$$

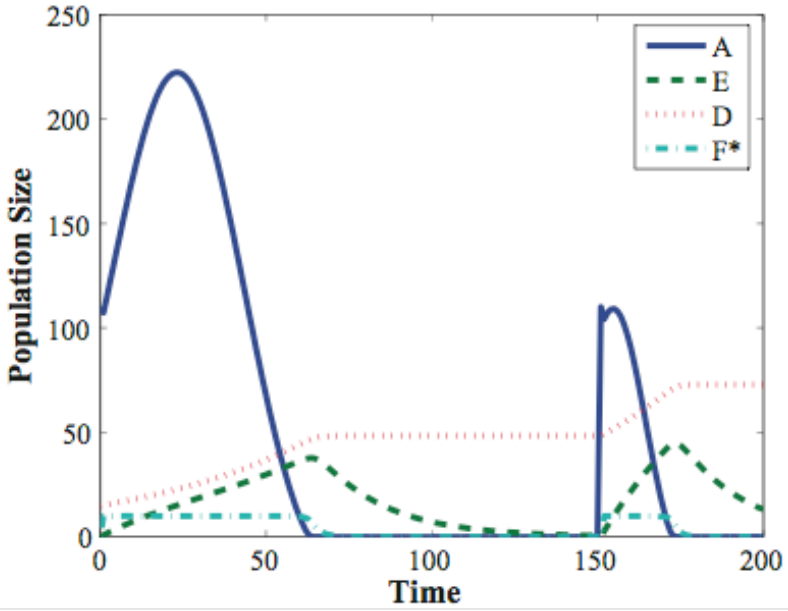


$$\frac{\partial E(\vec{y})}{\partial t} = \underbrace{2f\alpha\gamma(\vec{x},\vec{y}) F^* (M+N)(\vec{y})}_{\text{Stimulation}} - \underbrace{\delta E(\vec{y})}_{\text{Death}}$$

# Loss

- To quantify the severity of an infection (Loss) we take the integral of the antigen pulse
- This is proportional to the amount of damage the infection will do to tissues of the body and to the amount of toxin that would be released
- Repeat of the same or similar infection results in less severe response due to long-lived memory cells

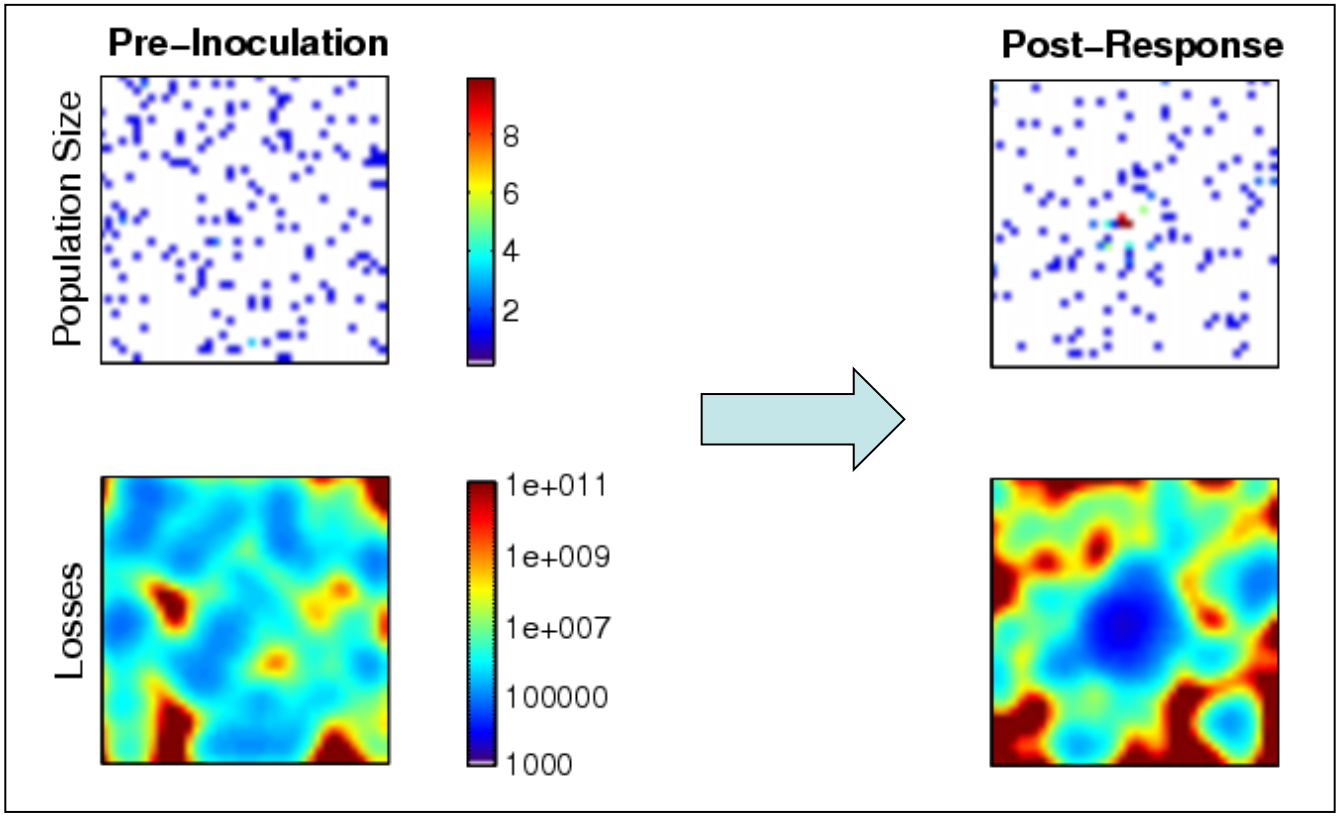
Two exposures, same infection



•The cells that were stimulated by an antigen and aided in its removal, remain as long lived memory cells.

•Other cells are called naïve, are short lived and are constantly recycled.

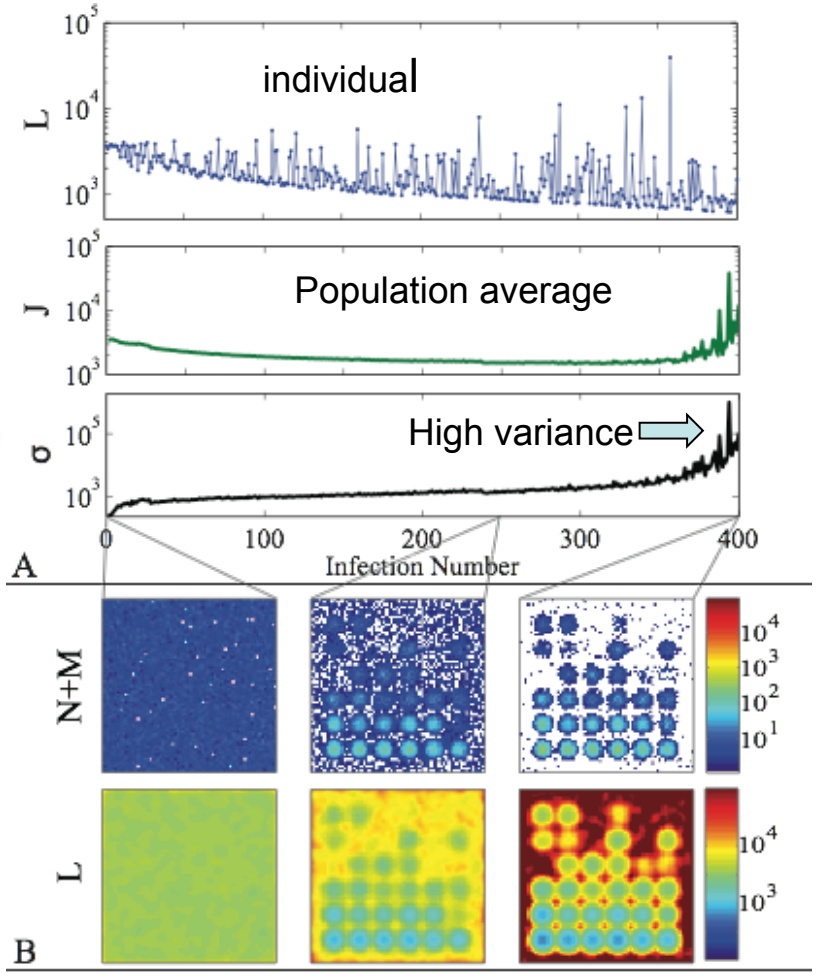
•The sum of memory and naïve is kept constant.




•The Naïve for Memory tradeoff corresponds to a fast secondary response with a cost of more vulnerability in outlying areas, “Robust Yet Fragile,” a key feature of HOT *(Carlson and Doyle)*.

# Overspecialization with Age

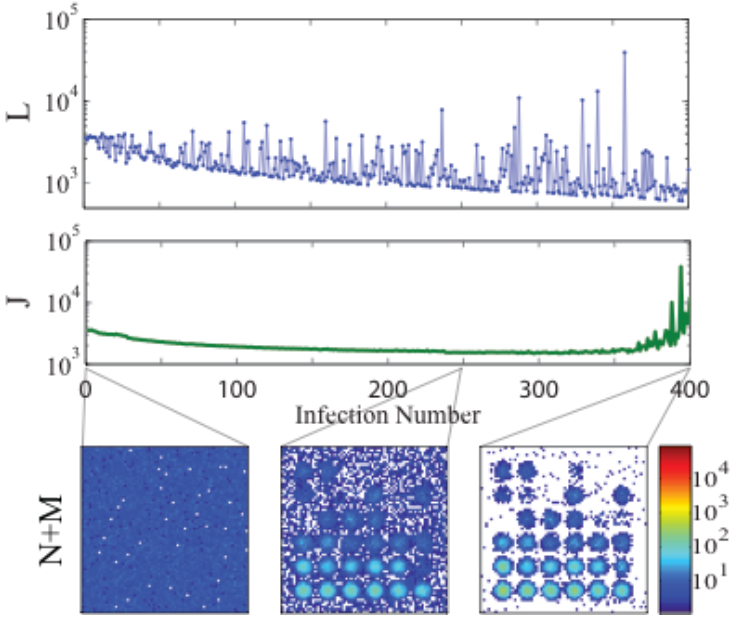
- We randomly choose from a skewed probability distribution 1 of 36 infections
- Between each infection the naive population experiences attrition, loosing randomly chosen cells
- Memory accumulates over time
- Eventually the system over-adapts

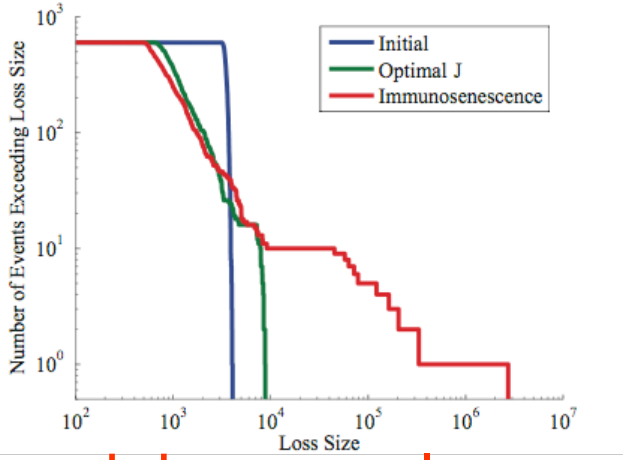


# Robust Yet Fragile: Adaptation, Complexity, and Age

Immunosenescence:

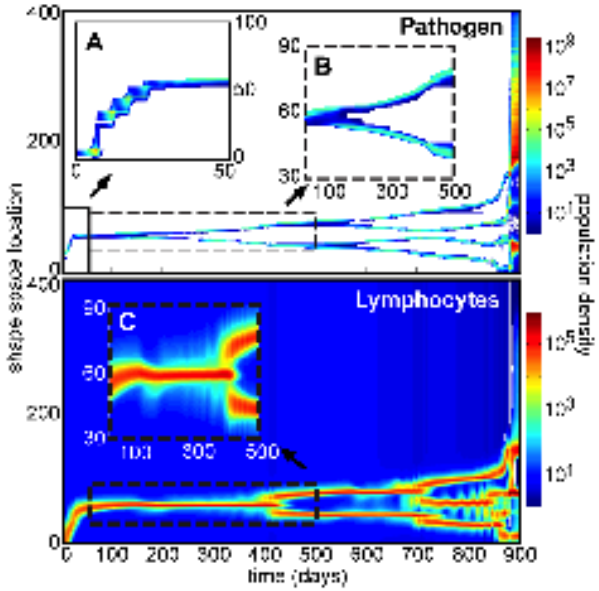
- Robustness: The adaptive immune system acquires memory to past infections. In this way it adapts to its environment.
- Fragility: With resource constraints (#cells) it over-adapts and has few resources for new diseases with age.




Immunosenescence overspecializes, going beyond the power law (which coincides with the optimal fitness) – excess large losses

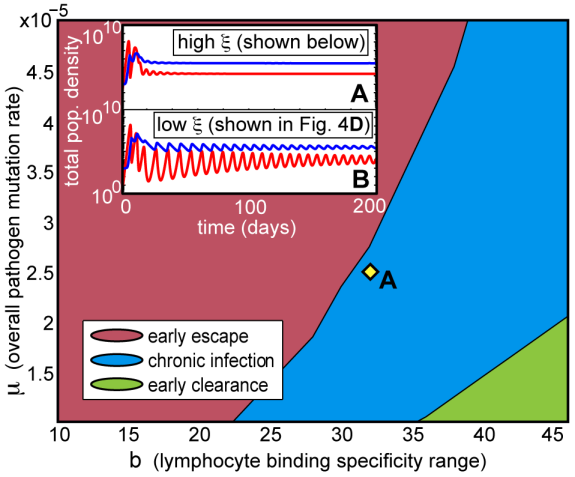
# Mutation, diversity, and immunosurveilance:




**Chronic Infections & Immune Escape**

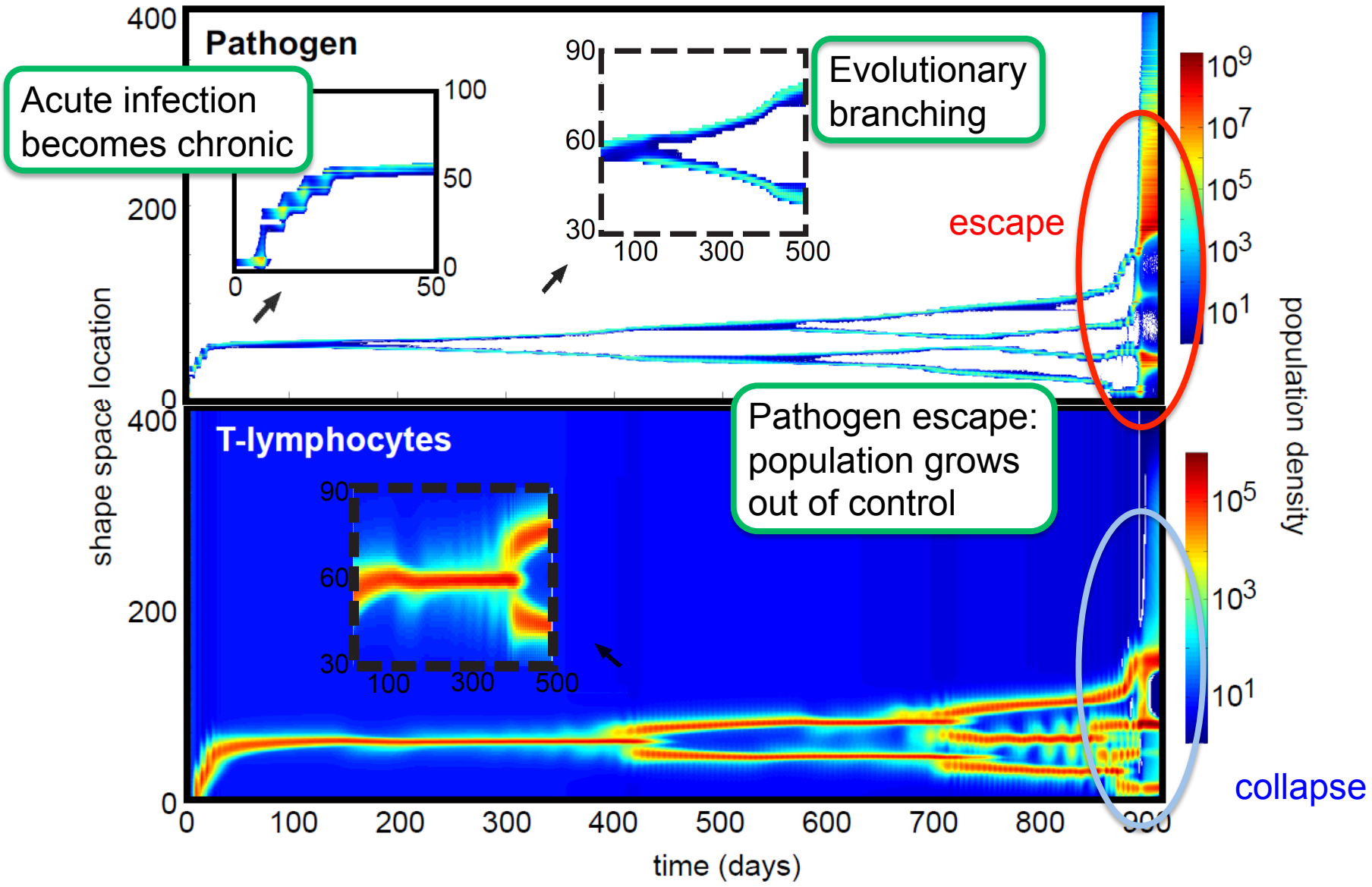
- Host/pathogen co-evolution in shape space (1d)
- Adaptive immune system: same as before (naïve, effector, memory)
- Add pathogen mutation

## Consider single infection



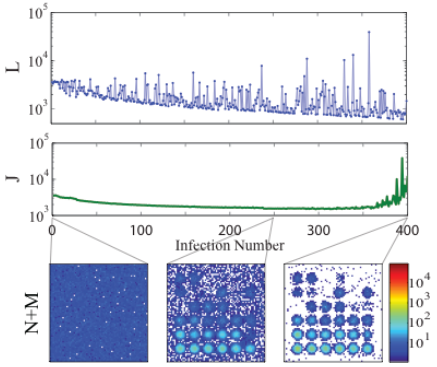

- Infection outcomes: elimination, chronic infection, escape
- Diversity of responses; average result depends on specificity and mutation rate

# Dynamics of chronic infections: Host-pathogen co-evolution leads to resource thinning and sudden pathogen escape

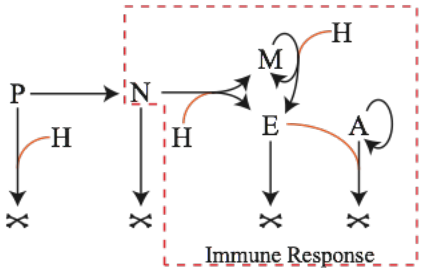


# Cellular population dynamics in adaptive immunity:

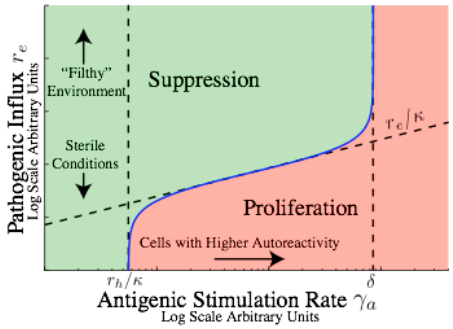
- The immune system is a complex dynamical system with cellular binding specificity and adaptation on observable time scales
- Robustness mechanisms give rise to immune system vulnerabilities



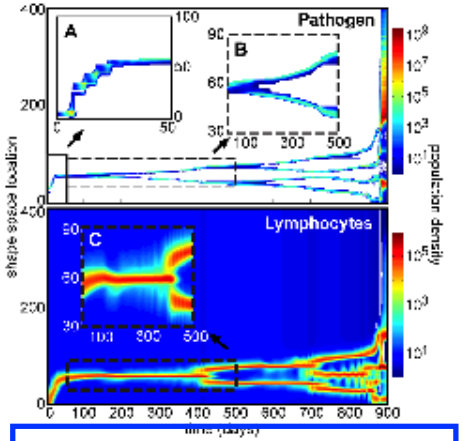

Adaptation & Overspecialization




Cross Reactivity, Antigenic Sin & Negative Selection




Passive Attrition & Hygiene Hypothesis

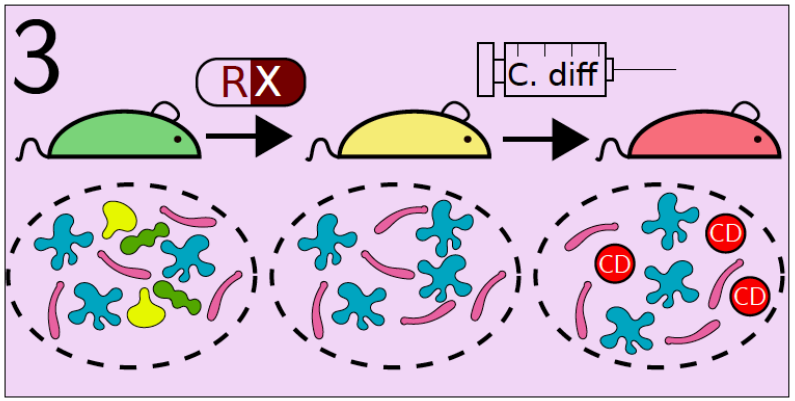



Chronic Infections & Immune Escape

More recently, my group's work in this area (population dynamics and ecological modeling) has focused on the microbiome: data-driven interaction network between microbes

# Microbiome: two models systems

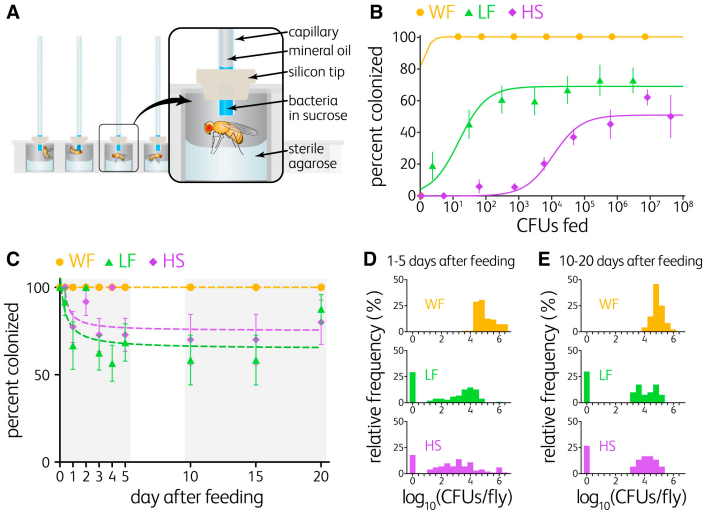
Eric Jones: UCSB




**Mouse microbiome:**
ecological modeling, antibiotics,
C Diff infection, FMT

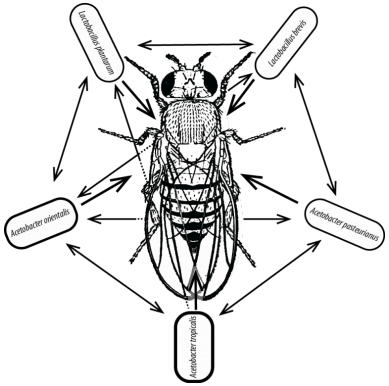
*(Buffie and Pamer; Stein, et al)*

Will Ludington: Carnegie Institute for Science
http://mcb.berkeley.edu/labs/ludington/



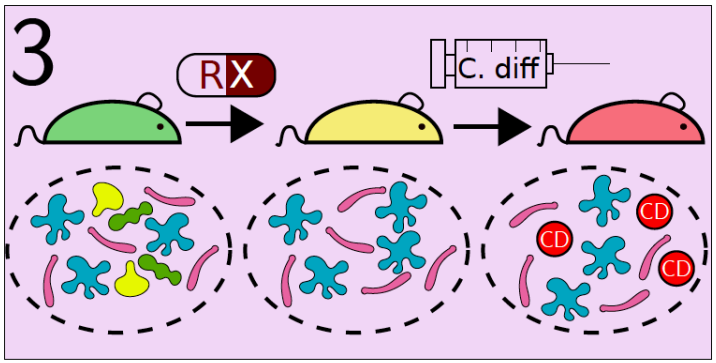

*(Obadia et al.)*

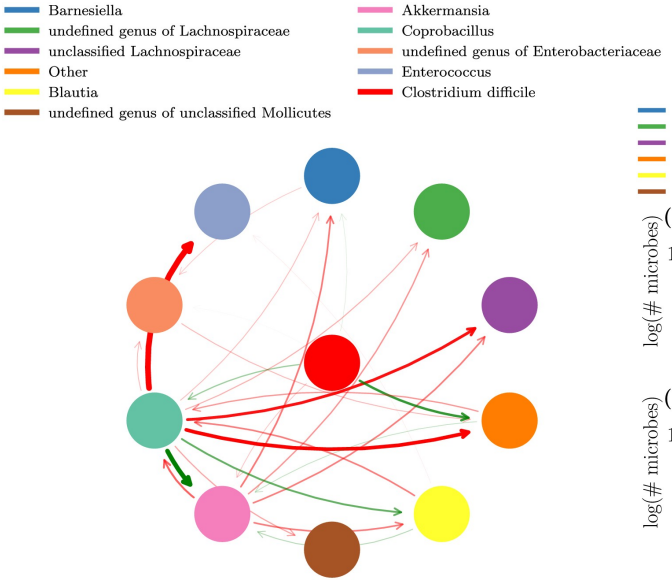
**Fly Microbiome:**
5 microbial species,
Gut diversity: impact on aging, health reproduction, etc

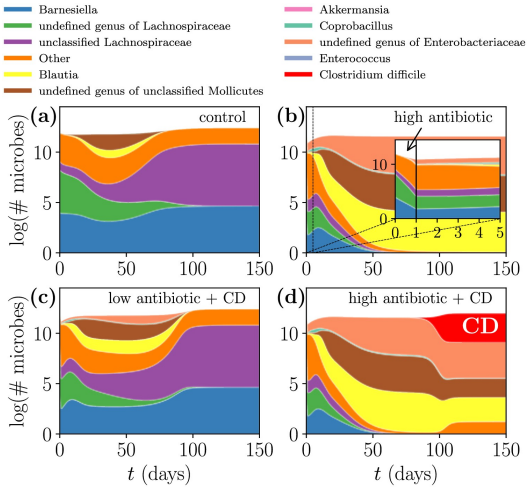


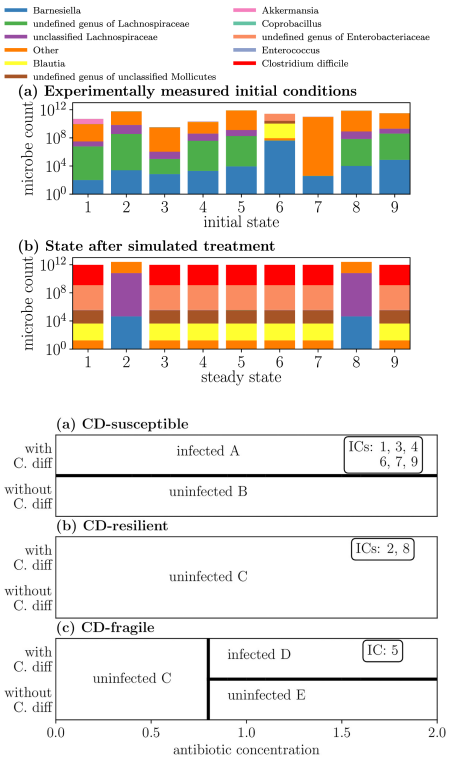
# Mouse Microbiome:

- Use ecological model to reverse engineer diversity of outcomes



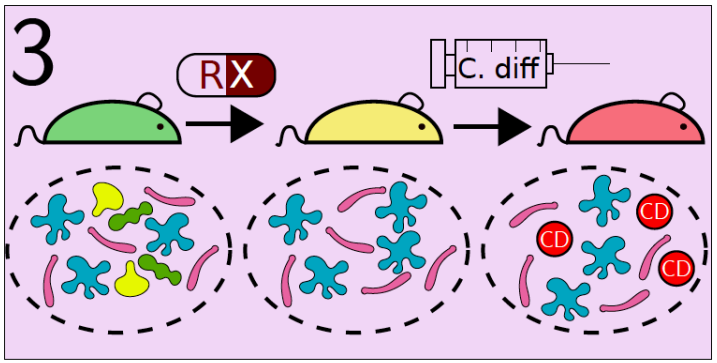

Data-driven GLV model

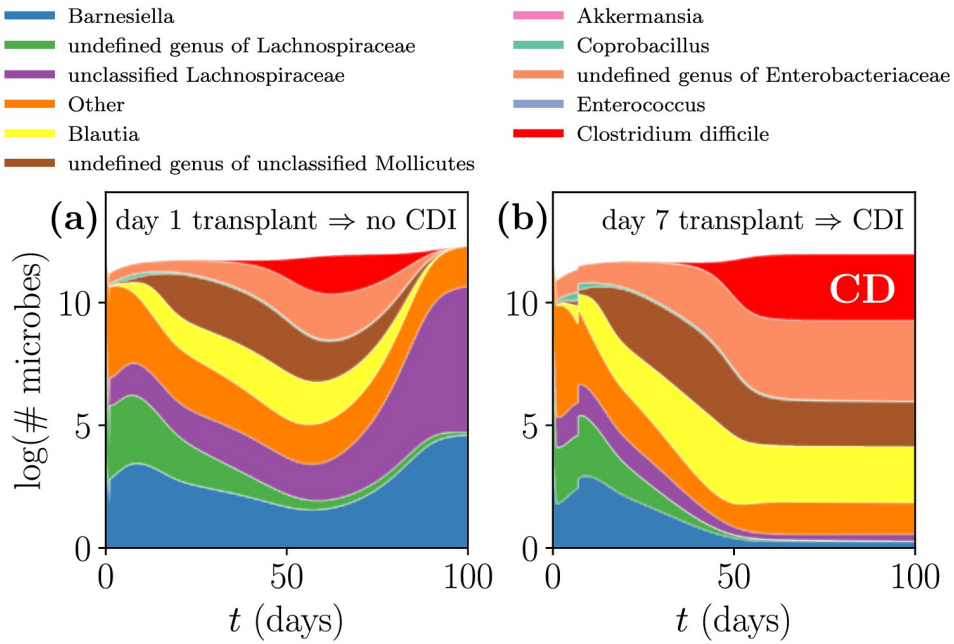
Time trajectories

Variable outcomes

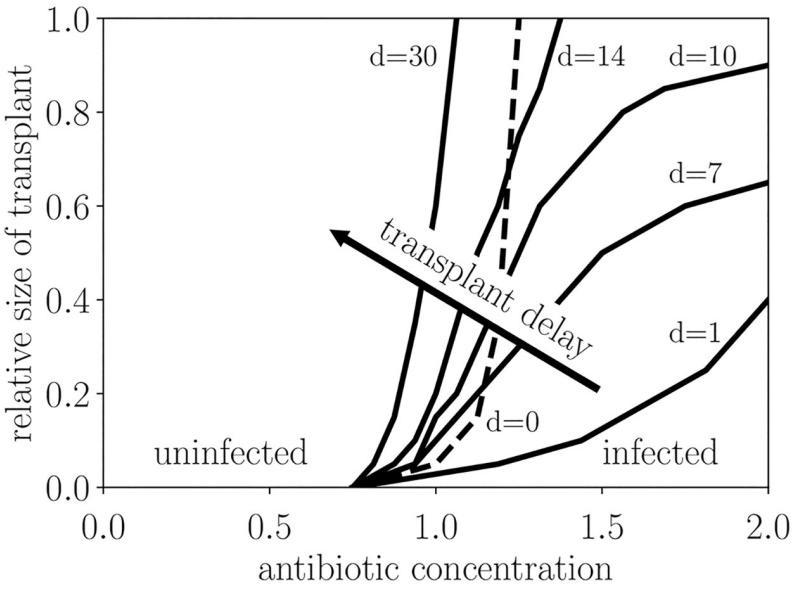
# Mouse Microbiome:

- Start with C Diff fragile state
- Simulate fecal microbial transplants
- Importance of timing!



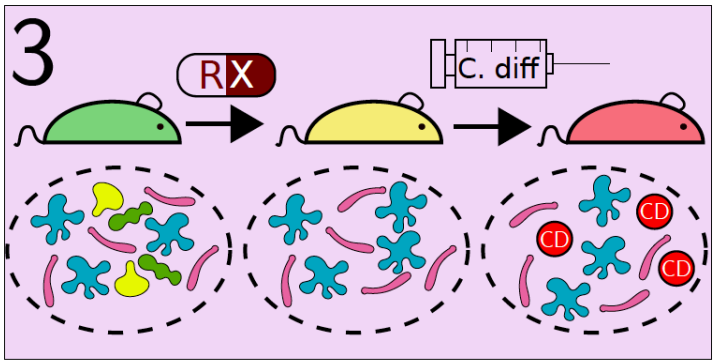

Simulate FMT with varying delays

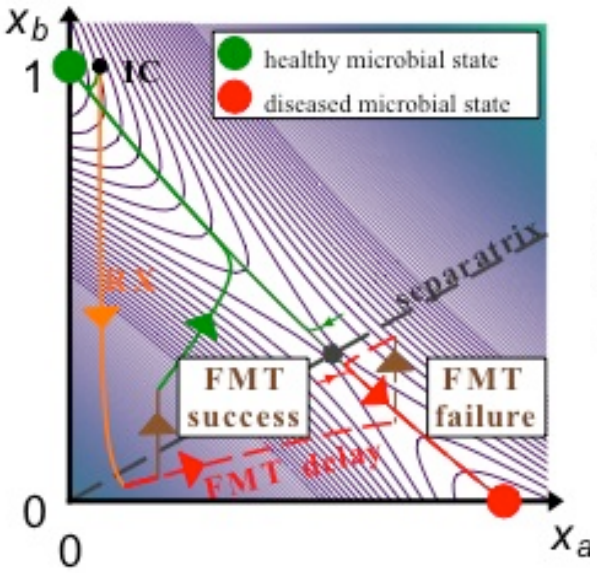



Timing plays a key role in effectiveness of bacteriotherapy

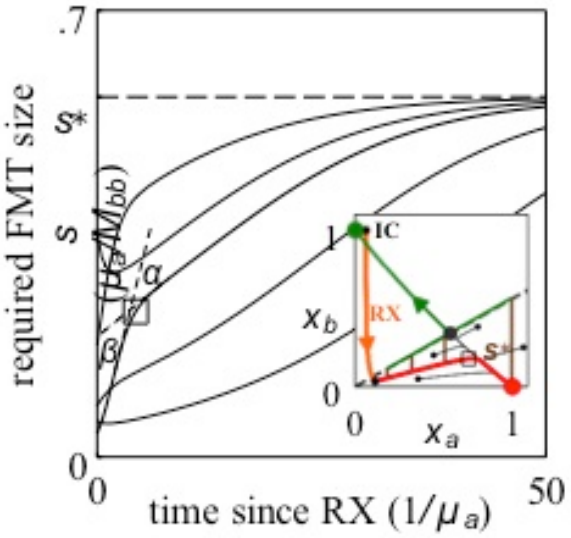
# Mouse Microbiome:

- Results for FMT timing are captured by a low dimensional steady state reduction (SSR)
- Analytically tractable and predictive
- SSR generalizes to other systems

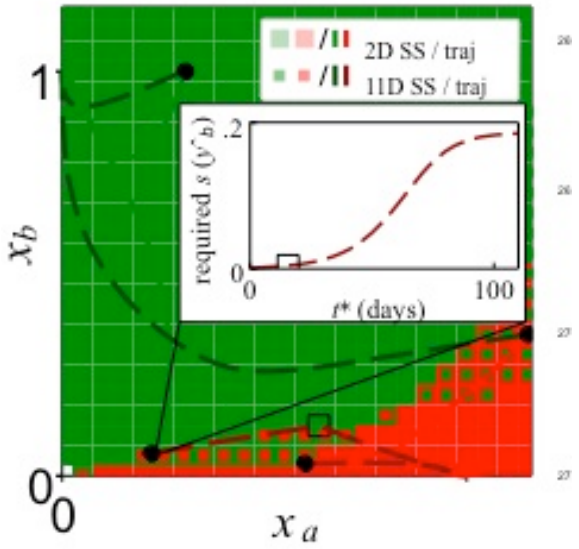



2d dynamical system: healthy and diseased steady states (SS)



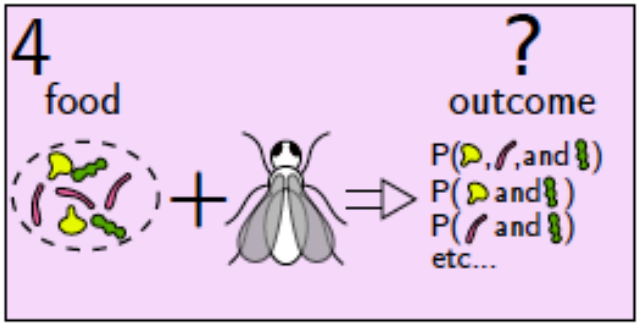

Time trajectories from initiatial condition to SS with FMT shows tradeoffs in size vs. delay

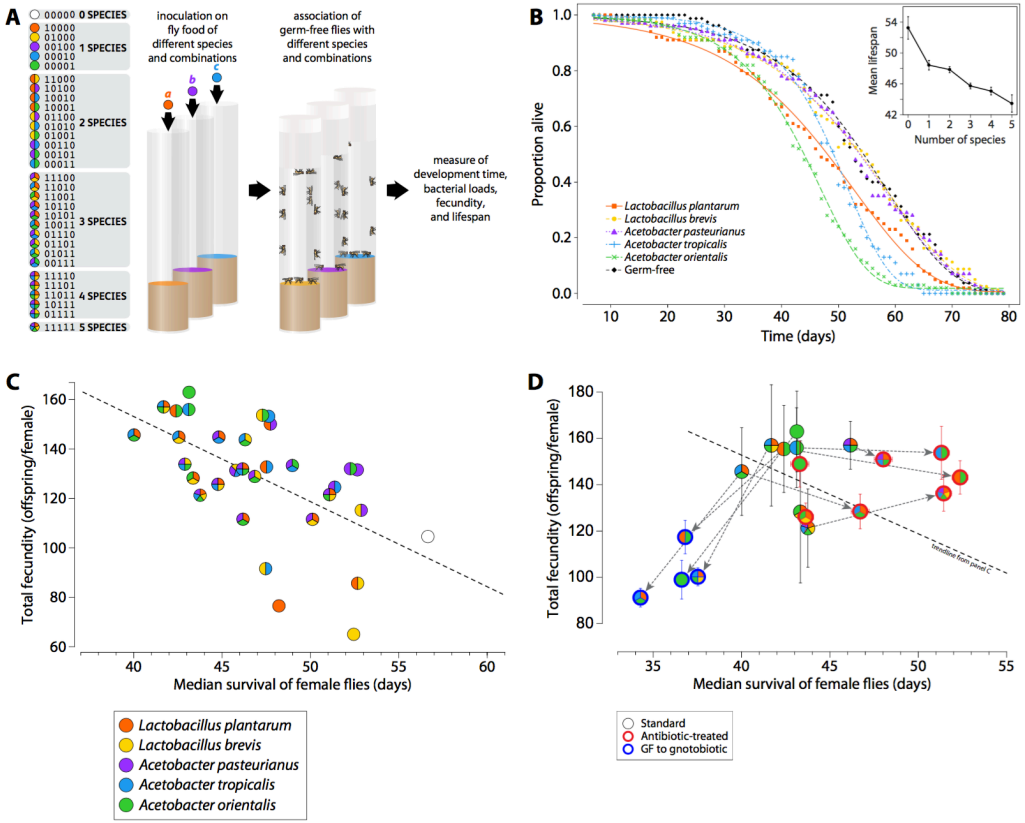



Captures behavior of original model

# Fly Microbiome:

- Experiments correlate all combinations of 5 microbes with host phenotypes
- Microbiome co-evolves with host; interactions shape host fitness
- Microbiome induces a life history tradeoff between lifespan and fecundity

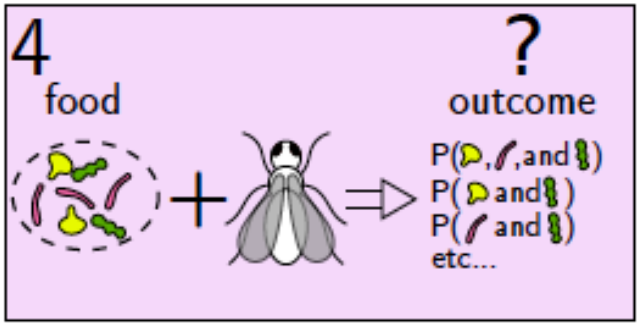


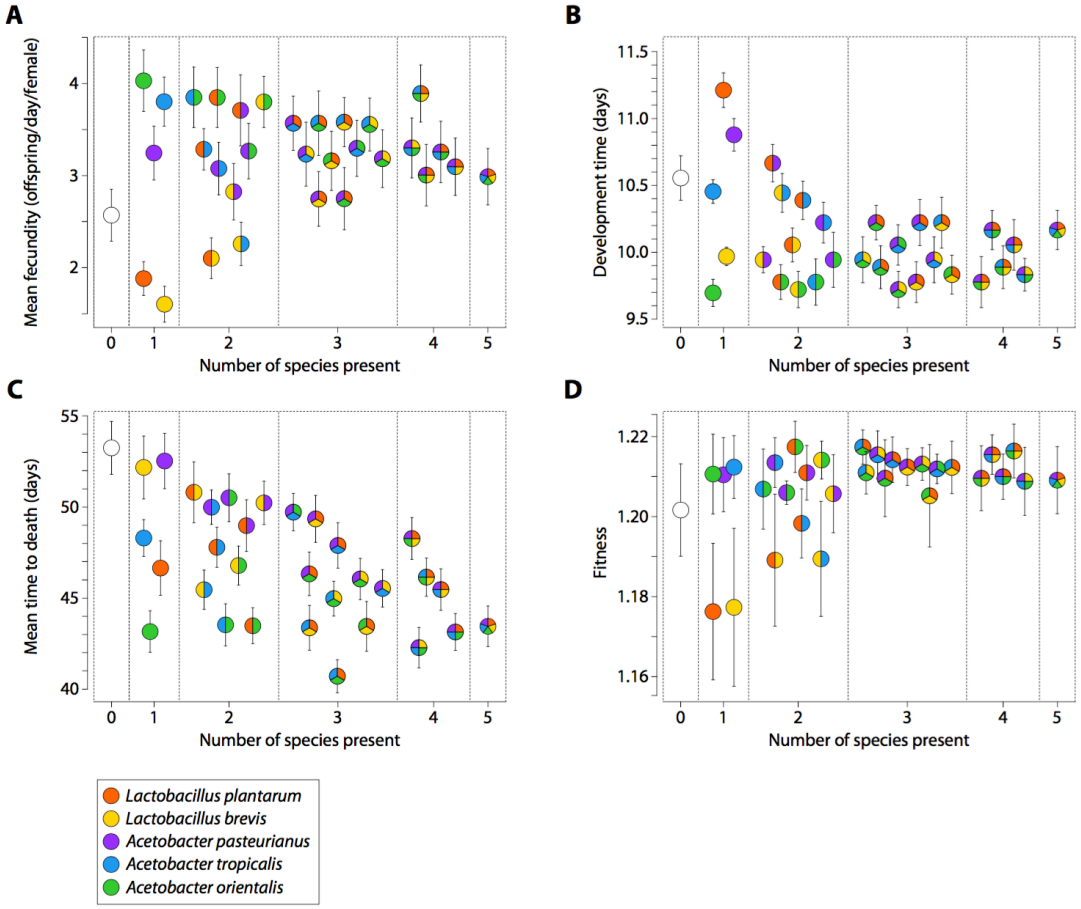




A: Experimental design
B: diversity decreases lifespan
C: High fecundity correlated with shorter lifespan
D: The lifespan-fecundity tradeoff can be broken by putting flies on antibiotics after peak reproduction

# Fly Microbiome:

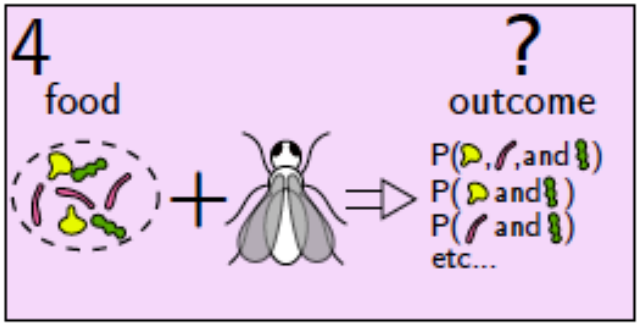
- Microbiome diversity impacts host physiology

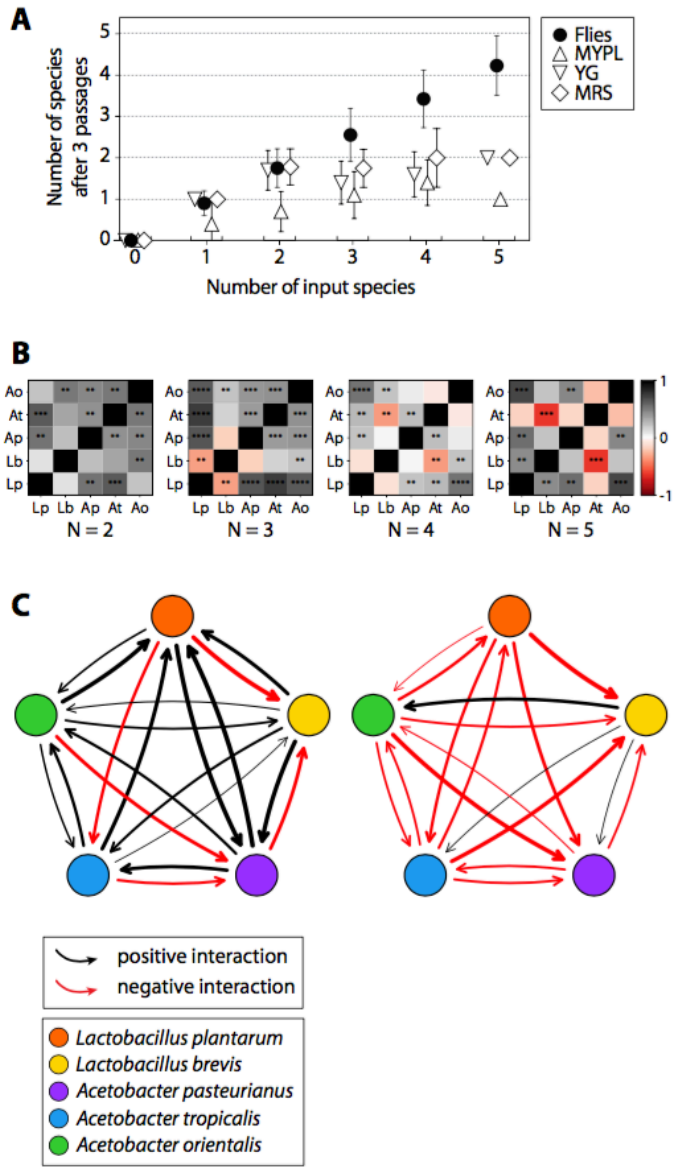



A: Variation in fecundity decreases with diversity
B: Development time decreases with diversity
C: Lifespan decreases with diversity
D: Fitness (Leslie matrix: population growth rate) increases with diversity (combining A-C)

# Fly Microbiome:



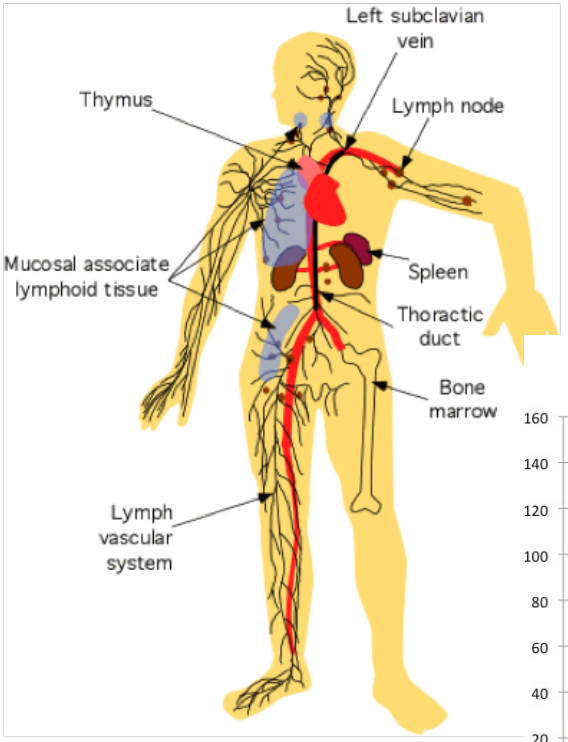



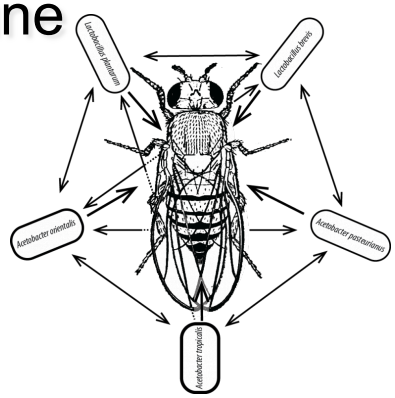

- Microbiome interactions stabilize diversity in the fly gut

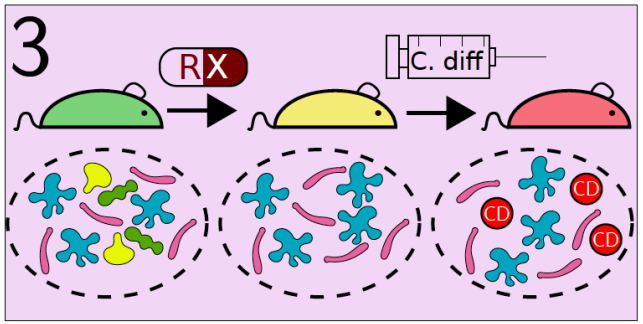
A: Diversity maintained better in fly gut than in liquid coculture
B: Pairwise correlation between species for 2-5 species shows more negative correlation with higher diversity
C: More negative interactions (red) for higher diversity also obtained from a gLV fit (Left: 1-2 species; Right: 3-5 species)

# Interests going forward

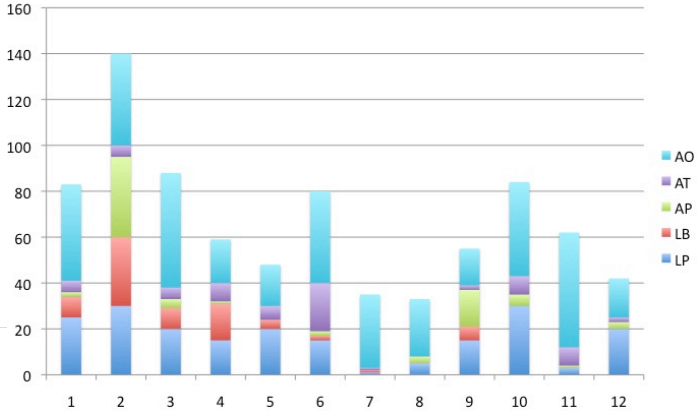
- **Robust yet fragile:** Constraints & tradeoffs lead to vulnerability
- **Diversity of outcomes:** stochasticity, components, history
- **Optimal interventions**: tradeoffs in intensity and timing (SSR)
- **Multiscale/multisystem**: molecular and systems level; microbiome and immune

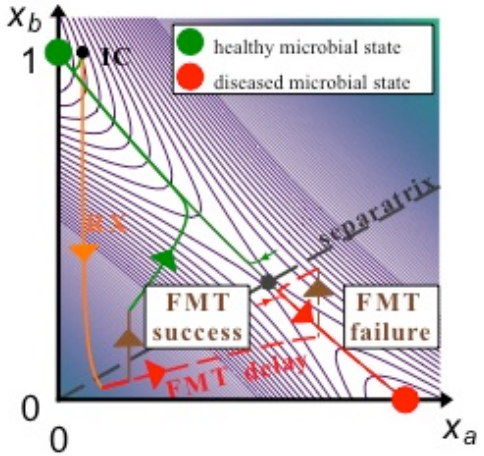





Bacterial load – all five species

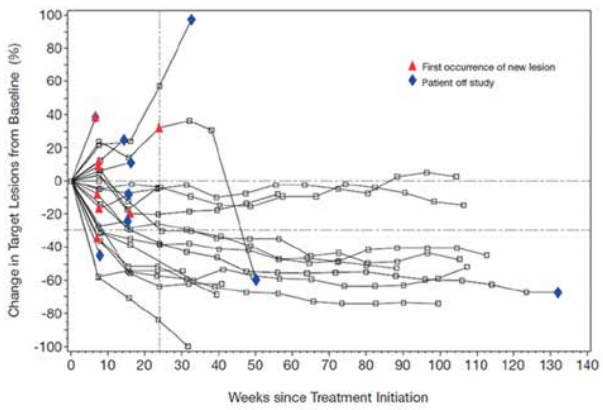


# A few comments on data and individual differences:

*Data is a primary limitation!*

- What are the primary sources of variability in the population?
- What are the relationships between performance and age?
- Are there precursors to fragility?
- Can we predict which individuals/systems will recover and which will collapse?
- Why therapies work on some individuals and fail on others?
- Can we identify ways in which individuals/therapies are malleable?




Cancer Immunotherapy: high variability in individual response *(Lipson, Topalian, 2015).*