Within-host to population-level modeling of mycoplasmal conjunctivitis in wild birds

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1 Background
   • Biological background and research objectives

2 Within-Host Model & Dynamics
   • Model equations and key biological assumptions
   • Host immune response and pathogen dynamics.

3 Variation & Evolution
   • Individual Heterogeneity

4 Movement-Virulence Trade-off
   • Dynamics under a novel “Movement-Virulence” Trade-off

5 Closing Remarks
   • Parting thoughts
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Background

Around 1993, the poultry pathogen *Mycoplasma gallisepticum*, makes the jump to House Finches (*Haemorhous mexicanus*). 
Spatial Spread (Project Feederwatch)
Symptoms Data

Eyescore

![Symptoms Images]
Observed Virulence Dynamics

Epicenter vs. Western Front

Year of Isolate

Virulence Measure

0.0 0.5 1.0 1.5 2.0 2.5 3.0


East

West

**Sources of Variation?**

**Experiment #1**

![Graph A](image)

- **Symptoms (Eyescore)**
  - Severe (N=7)
  - Acute (N=13)

![Graph B](image)

- IgY Antibodies (ΔOD)
  - Severe (N=7)
  - Acute (N=13)

**Experiment #2**

![Graph C](image)

- **Symptoms (Eyescore)**
  - Severe (N=3)
  - Prolonged Acute (N=12)
  - Acute (N=10)

![Graph D](image)

- Pathogen (qPCR Proxy)
  - Severe (N=3)
  - Prolonged Acute (N=12)
  - Acute (N=10)

*Hurtado 2012*
Objectives

1. Which pathogen and host characteristics shape infection outcomes?
2. Which drive observed patterns of individual variation?
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2. Which drive observed patterns of individual variation?

Modeling Challenges
The vertebrate immune response to mycoplasmas is complex!

‘‘...it is likely that almost every component of the host immune system is involved in the response to mycoplasma disease.’’

– Blanchard & Browning, 2005
Model

General Model Equations

\[
\frac{dp}{dt} = k_{pg} p (1 - p) - \frac{k_m p}{\mu_p + p} - K(y) np
\]

\[
\frac{dn}{dt} = \frac{n + k_p p}{x_n + n + k_p p} - \mu_n n
\]

\[
\frac{dy_0}{dt} = \frac{(np)^{\alpha}}{\alpha x^{\alpha}_y + (np)^{\alpha}} - \mu_{y0} y_0
\]

\[
\frac{dy}{dt} = \mu_{y0} y_0 - \mu_y y
\]

where \(K(y)\) is an increasing bounded function of \(y\) with \(K(0) \geq 0\).

Hurtado 2012; Reynolds et al 2006.
Separation of Time Scales

**FAST! Fast Slow**

![Graph showing separation of time scales with different labels and symbols representing different groups of symptoms and pathogen levels over time.](image-url)
Initial Pathogen Dynamics (FAST!)

Without an immune response,

\[
\frac{dp}{dt} = k_{pg} p (1 - p) - \frac{k_m p}{\mu_p + p}
\]

\(\text{Logistic}\)

\(\text{Baseline}\)
Initial Pathogen Dynamics (FAST!)

Without an immune response,

\[
\frac{dp}{dt} = k_{pg}p(1-p) - \frac{k_mp}{\mu_p + p}
\]

Baseline immune defenses \((k_m > 0)\) yield an Allee effect: Bistability between infected and uninfected states.

Depends on the sign of the *intrinsic growth rate*:

\[
r_0 \equiv k_{pg} - k_m/\mu_p
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Fast Time Scale?

**FAST! Fast**  
Slow

### Symptoms (Eyescore)

- **Severe** (N=7)
- **Acute** (N=13)

### Pathogen (qPCR Proxy)

- **Severe** (N=3)
- **Prolonged Acute** (N=12)
- **Acute** (N=10)

### Days

0 20 40 80
Approximate $p-n$ (Fast) Subsystem

Assuming a fast non-specific response $n$ with no positive feedback

\[ \frac{dp}{dt} = k_{pg} p (1 - p) - \frac{k_m p}{\mu_p + p} - K_{ny} n(p) p \]

where,

\[ n(p) = \frac{1}{\mu_n} \left( \frac{p}{\frac{x_n}{k_p} + p} \right) \]
Approximate $p-n$ (Fast) Subsystem

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where,

$$n(p) = \frac{1}{\mu_n} \left( \frac{p}{\frac{x_n}{k_p} + p} \right)$$

Simplified Dynamics

1. Same equilibria as the $p-n$ model without feedback in $n$.
2. $p_* > 0$ stable when $f'_n(p_*) - f'_p(p_*) > 0$ (no cycling).
Simplified Non-specific Immune Response

A. $K_{ny} = 0, k_m = 0$

B. $K_{ny} = 0, k_m > 0$

C. $K_{ny} > 0, k_m = 0$

D. $K_{ny} > 0, k_m > 0$

E. $K_{ny} > 0, k_m > 0; \text{ (rare)}$

F. $K_{ny} > 0, k_m >> 0$
**Slow Time Scale?**

---

**Diagram Description:**

- **FAST! Fast** vs. **Slow**
- **Pathogen (qPCR Proxy):**
  - Severe (N=3)
  - Prolonged Acute (N=12)
  - Acute (N=10)
- **Symptoms (Eyescore):**
  - Severe
  - Acute
  - Prolonged

---

**Graph Details:**

- **Y-axis:** Pathogen (qPCR Proxy) 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
- **X-axis:** Days 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100

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**Legend:**

- ● Severe
- ● Acute
- ▲ Prolonged
Specific Immune Control

The full model can be approximated by

\[ \frac{dp}{dt} = \left( k_p (1 - p) - \frac{k_m}{\mu_p + p} - K(y)n(p) \right) p \]
\[ \frac{dy}{dt} = G(p) - \mu_y y. \]

where \( G(p) = \frac{(n(p)p)^\alpha}{x_y^\alpha + (n(p)p)^\alpha} \), and \( K(y) > 0 \) is increasing on \( \mathbb{R}^+ \).

Stability conditions for \( p_*, y_* > 0 \) can be written using nullclines \( g_p(p) \) and \( g_y(p) \).
Specific Immune Control

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\]

where \( G(p) = \frac{(n(p)p)^{\alpha_x}}{x^{\alpha_x} + (n(p)p)^{\alpha_x}} \), and \( K(y) > 0 \) is increasing on \( \mathbb{R}^+ \).

Stability conditions for \( p_*, y_* > 0 \) can be written using nullclines \( g_p(p) \) and \( g_y(p) \). If \( K, G, n \) are positive and increasing at \( p_* \) then

Case 1 (\( k_m = 0 \))

\( p_*, y_* > 0 \) is always stable.

Case 2 (\( k_m > 0 \))

\( p_*, y_* > 0 \) is stable if

1. \( g'_p(p_*) < g'_y(p_*) \);
2. \( g'_p(p_*) < \frac{\mu_y}{K'(y_*)n(p_*)p_*} \).
Slow Time Scale Dynamics

A

Specific Imm. (y) 1/μ_ya

dy/dt = 0

dp/dt = 0

0 1

B

1/μ_ya

dy/dt = 0

dp/dt = 0

0 1

C

Specific Imm. (y) 1/μ_ya

dy/dt = 0

dp/dt = 0

0 1

D

1/μ_ya

dy/dt = 0

dp/dt = 0

0 1
Persistency \((p_*>0)\) vs. Clearance \((p_* = 0)\)

- **A** \(k_m = 0\): Pathogen \((p_*)\) decreases as specific immunity \((y_*)\) increases.
- **B** \(k_m > 0\): Pathogen \((p_*)\) decreases as specific immunity \((y_*)\) increases, reaching clearance \(y_* = 0\).
- **C** \(k_m = 0\): Pathogen \((p_*)\) decreases as specific immunity \((y_*)\) increases.
- **D** \(k_m > 0\): Pathogen \((p_*)\) decreases as specific immunity \((y_*)\) increases, reaching clearance \(y_* = 0\).
**Individual Variation ⇐⇒ Parameter Variation**

Fig. 1 Data

A

Pathogen (qPCR Proxy)

B

K_{pg} variation

C

μ_{n} variation

D

K_{min} variation
So what have we learned?

**FAST! Fast**

**Slow**

<table>
<thead>
<tr>
<th>Days</th>
<th>Pathogen (qPCR Proxy)</th>
<th>Symptoms (Eyescore)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>Severe (N=7)</td>
</tr>
<tr>
<td>1</td>
<td>0.00</td>
<td>Acute (N=13)</td>
</tr>
<tr>
<td>2</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acute (N=10)
Prolonged Acute (N=12)
Severe (N=3)
Summary #1

1. A (strong) Allee effect is essential for pathogen clearance.
   - Little to no effect on dynamics at higher pathogen loads.
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   - Other sources besides strong baseline immune defenses?
   - What about stochasticity?
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   - What about stochasticity?

2. Three hypotheses why some individuals make better hosts:
   - Suitable “habitat” for the pathogen – high growth rate $k_{pg}$
   - Ineffective baseline immune defenses – low $k_m, K_{min}$
   - Ineffective non-specific response – low $K(\cdot), 1/\mu_n$
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   - Ineffective non-specific response – low $K(\cdot), 1/\mu_n$

3. Other source of variation?
   - Are parameters fixed individual characteristics, or
   - do parameters reflect stochasticity in early interactions with & host cells?
Parameter Variation

A

Fig. 1 Data

Pathogen (qPCR Proxy)

Severe (N=3)
Prolonged, Acute (N=12)
Acute (N=10)

0 1 3 6 20 50 200
0 1 3 7 20 50 200

B

Pathogen

k variation

0 1 3 7 20 50 200
0 1 3 7 20 50 200

C

Pathogen

μn variation

0 1 3 7 20 50 200
0 1 3 7 20 50 200

D

Pathogen

Km variation

0 1 3 7 20 50 200
0 1 3 7 20 50 200

Days

Days

Days

Days
What drives virulence evolution?

1. **Natural selection**: Evolution should maximize fitness.

   \[
   \text{fitness} \approx \frac{\text{"offspring" (\# new infections)}}{\text{"lifetime" (duration of infection)}}
   \]
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2. **Trade-offs**: Fitness components are frequently correlated!

   Ex: The **Transmission-Virulence trade-off** arises from (i) total new infections depending on (ii) duration of infection.
What drives virulence evolution?

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2. **Trade-offs**: Fitness components are frequently correlated!

   Ex: The **Transmission-Virulence trade-off** arises from (i) total new infections depending on (ii) duration of infection.

3. **Immigration/Emigration**: Local gene frequency changes can also occur via movement into and out of a local population.
Emergent Transmission-Virulence Trade-off?

Assume a simple host-mortality model and ask:

Do we see a trade-off in our system?
Emergent Transmission-Virulence Trade-off?

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Do we see a trade-off in our system?

Simulation Assumptions:

1. Survival (Host Fitness) is random, memoryless;
   Model: inhomogeneous Poisson process with rate $\lambda(t)$.

2. Symptoms driven by pathogen load (Parasite Fitness) and
   immune response. $\lambda(t) \propto$ Symptoms.
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   immune response. $\lambda(t) \propto$ Symptoms.

How are mean transmission and virulence related?
Fitness Definitions

**Parasite Fitness:** total pathogen load over the duration of the infection, $T$ (death or recovery time):

$$\pi(T) = \int_0^T p(t)dt$$
Fitness Definitions

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2. **Host Fitness**: Summary statistic $P_s$; Survival to day 40

   $$P_s \equiv 1 - P(T_{death} \leq 40)$$
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2 **Host Fitness**: Summary statistic $P_s$; Survival to day 40

$$P_s \equiv 1 - P(T_{death} \leq 40)$$

defined using the random variable $T_{death}$:

$$P(T_{death} \leq t) = \exp \left(- \int_0^t \lambda(s)ds \right)$$

where *mortality rate* $\lambda(t) \propto U(t) = U(p(t), n(t), y(t))$. 
**Transmission-Virulence Trade-off**

**Part A:**
- \( \lambda \propto K(y)n_p \)
- Graph showing transmission vs. mean total pathogen load with two lines indicating low and high \( k_{pg} \).

**Part B:**
- \( \lambda \propto p \)
- Graph showing transmission vs. mean total pathogen load.

**Part C:**
- \( \lambda \propto n \)
- Graph showing transmission vs. mean total pathogen load.

**Part D:**
- \( \lambda \propto \mu n n + p \)
- Graph showing transmission vs. mean total pathogen load.

**Legend:**
- Transmission: \( E(\pi(T)) \)
- Mean Total Pathogen Load
- Fraction Dead by Day 40
Observed Virulence Evolution

Epicenter vs. Western Front

Osnas, Hurtado, Dobson (submitted)
**Movement-Virulence Trade-off Effects?**

**Observation:** Symptomatic birds move less than healthy birds.

**Multistrain SI model of disease spread:**

\[
\frac{dS}{dt} = D_s \nabla^2 S - \sum_i \beta_i I_i S - dS + \theta
\]

\[
\frac{dl_i}{dt} = D_{li} \nabla^2 l_i + \beta_i I_i S - (d + \alpha)l_i
\]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S = S(x, t))</td>
<td>Susceptible host density at location (x) at time (t)</td>
</tr>
<tr>
<td>(I_i)</td>
<td>Density of hosts infected with strain (i)</td>
</tr>
<tr>
<td>(N)</td>
<td>Total host density ((N = S + I))</td>
</tr>
<tr>
<td>(D_S, D_i)</td>
<td>Movement parameters (diffusion coefficients)</td>
</tr>
<tr>
<td>(\beta_i)</td>
<td>Strain-specific <em>per capita</em> transmission rate</td>
</tr>
<tr>
<td>(\alpha_i)</td>
<td>Strain-specific additional mortality (<em>virulence</em>)</td>
</tr>
</tbody>
</table>

Trade-off Curves

\[ \beta(\alpha) = \tau_0 (1 - \exp(-\tau_1 \alpha)) \]
Trade-off Curves

\[ \beta(\alpha) = \tau_0 \left(1 - \exp\left(-\tau_1 \alpha\right)\right) \]

\[ D(\alpha) = \sigma_0 \exp\left(-\sigma_1 \alpha\right) \]
Mean Virulence Dynamics: Epicenter vs. Wavefront

Lower virulence levels are favored on the front, relative to levels favored in the classical case, and at the epicenter.
Model Approximation: Wavefront

Assume a traveling wave solution (an expanding epidemic) exists.
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On the front, \( I = \sum_i I_i \approx 0 \), and susceptible density is near the disease-free state \( N_0 \equiv \theta / d \). Let \( Q = S / N_0 \) and \( P_i = I_i / N_0 \).
Model Approximation: Wavefront

Assume a traveling wave solution (an expanding epidemic) exists.

On the front, $I = \sum_i I_i \approx 0$, and susceptible density is near the disease-free state $N_0 \equiv \theta/d$. Let $Q = S/N_0$ and $P_i = I_i/N_0$. Then our (1-strain) model is approximately the Skellem Equation:

$$\frac{\partial P_i}{\partial t} = D_i \nabla^2 P_i + r_i P_i$$

where the local fitness of strain $i$ is $r_i = \beta_i S - (d + \alpha_i)$, i.e.,

$$r(\alpha) = \beta(\alpha) S - (d + \alpha)$$

For a single strain, the traveling wave speed is $c_i = 2 \sqrt{r_i D_i}$, i.e.,

$$c(\alpha) = 2 \sqrt{r(\alpha) D(\alpha)}.$$. 
Selection: Max. Wave Speed \((c)\) vs Fitness \((r)\)

Strains that dominate on the front have virulence levels near \(\alpha_*\), satisfying \(c'(\alpha_*) = 0\) and \(c''(\alpha_*) < 0\).

Differentiation yields

\[
c'(\alpha) = \frac{c(\alpha)}{2} \left( \frac{r'(\alpha)}{r(\alpha)} + \frac{D'(\alpha)}{D(\alpha)} \right).
\]

1. With no M-V Trade-off \((D'(\alpha) = 0)\), selection maximizes local fitness \(r_i\).
Simulation Example

Transmission-Virulence Trade-off: \( \beta_i(\alpha) \) a decreasing function.
Movement-Virulence Trade-off: \( D_i(\alpha) \) decreasing.

Max wavespeed prevails: \[ c(\alpha_*) = 2\sqrt{r(\alpha_*)D(\alpha_*)} \]
**Simulation Example**

Transmission-Virulence Trade-off: $\beta_i(\alpha)$ a decreasing function.
Movement-Virulence Trade-off: $D_i(\alpha)$ decreasing.

**Max wavespeed prevails:**

$$c(\alpha_*) = 2\sqrt{r(\alpha_*)D(\alpha_*)}$$
Price Equation Reformulation

What are the *mean trait value* dynamics under our general model?
Price Equation Reformulation

What are the *mean trait value* dynamics under our general model?

Let $z$ represent any of traits $\beta$, $D$ or $\alpha$. Define *local means* by $\bar{z} = \sum_i z_i I_i / I_T$, the *covariance* of traits $y$ and $z$ as $\sigma_{yz} = \bar{yz} - \bar{y}\bar{z}$.

Define average trait values of moving infecteds ($\bar{z}_m$) as follows. The movement rate of strain $i$ individuals is $m_i = D_i \nabla^2 I_i$, with the total movement rate of infecteds $m_T = \sum_i m_i$. Then $\bar{z}_m = \sum_i z_i m_i / m_T$. 
Price Equation Reformulation

*Mean trait* equations, in terms of local means, covariances, and averages among moving individuals:

\[
\frac{\partial}{\partial t} \begin{bmatrix} \bar{\beta} \\ \bar{\alpha} \\ \bar{D} \end{bmatrix} = \begin{bmatrix} \sigma_{\beta \beta} & \sigma_{\beta \alpha} & \sigma_{\beta D} \\ \sigma_{\beta \alpha} & \sigma_{\alpha \alpha} & \sigma_{\alpha D} \\ \sigma_{\beta D} & \sigma_{\alpha D} & \sigma_{DD} \end{bmatrix} \begin{bmatrix} S \\ -1 \\ 0 \end{bmatrix} + \frac{m_T}{l_T} \begin{bmatrix} \bar{\beta}_m - \bar{\beta} \\ \bar{\alpha}_m - \bar{\alpha} \\ \bar{D}_m - \bar{D} \end{bmatrix}
\]

Local Transmission

Movement

A Transmission-Virulence trade-off implies \( \sigma_{\beta \alpha} > 0 \).
Price Equation Results

\[
\frac{\partial}{\partial t} \begin{bmatrix} \bar{\beta} \\ \bar{\alpha} \\ D \end{bmatrix} = \begin{bmatrix} \sigma_{\beta\beta} & \sigma_{\beta\alpha} & \sigma_{\beta D} \\ \sigma_{\beta\alpha} & \sigma_{\alpha\alpha} & \sigma_{\alpha D} \\ \sigma_{\beta D} & \sigma_{\alpha D} & \sigma_{DD} \end{bmatrix} \begin{bmatrix} S \\ -1 \\ 0 \end{bmatrix} + \frac{m_T}{l_T} \begin{bmatrix} \bar{\beta} - \bar{\beta} \\ \bar{\alpha} - \bar{\alpha} \\ \bar{D} - \bar{D} \end{bmatrix}
\]

Local Transmission

Movement

We infer from the first term that selection acts to directly...

1. increase mean local transmission $\bar{\beta}$ with a strength proportional to susceptible population size $S$, and
2. decrease mean local virulence $\bar{\alpha}$.

We also infer (since $\sigma_{\beta\alpha} < 0$) that selection acts indirectly to

3. decrease mean local transmission $\bar{\beta}$, and
4. increase mean local virulence $\bar{\alpha}$.
Data vs Model

**Data**

- **Average Eye Lesion Score**
- **Year of Isolate**

- **East**
- **West**

**Model**

- **Mean Virulence ($\alpha$)**
- **Time**

- **Epicenter**
- **No Movement-Virulence Tradeoff**
- **With Movement-Virulence Tradeoff**
- **Wavefront**
Summary: Movement-Virulence Trade-off

1. Pathogens spread via new infections *and* host movements.
2. Transmission-Virulence & Movement-Virulence trade-offs *both* exists in this system, and probably in many others.
3. Price Equation formulation a nice context for thinking about trade-offs!
4. Are we missing other important trade-offs?
5. What if we complicate host demography or disease progression (e.g., SI vs SIR)?
Parting thoughts on “scaling-up”

1. All models are wrong, some models are useful, multiple models might be more useful.
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4. Host & parasite heterogeneity matters – are we ignoring it?
5. What within-individual information do we need (or not need) to scale up?
6. Are all in-host models host-parasite specific or are there broader categories?
Parting thoughts on “scaling-up”

1. All models are wrong, some models are useful, multiple models might be more useful.
2. How useful (or dangerous) is “coarse-graining” the immune system (cells and molecules vs. functional components)?
3. Within-host stochasticity matters – are we ignoring it?
4. Host & parasite heterogeneity matters – are we ignoring it?
5. What within-individual information do we need (or not need) to scale up?
6. Are all in-host models *host-parasite specific* or are there broader categories?
   **Ex:** Budding vs Bursting viruses, gram± bacteria in different vertebrate tissues, etc.
Questions?
Sources of Variation: Phylogeny...

**Host species variation**
Degree of infectiousness of different bird species

![Graph showing the degree of infectiousness over Days post inoculation of source bird for House sparrow, American goldfinch, and House finch.](image-url)
Discontinuous $p$-nullcline

The specific immune response curve $K(y)$ shapes the $p$-nullcline,

$$g_p(p) = K^{-1}(F(p))$$

$$F(p) = \frac{k_p(1-p) - k_m/(\mu_p + p)}{n(p)}$$
Persistence-Clearance Homoclinic Bifurcation

**A**

\[ \frac{1}{\mu_{\text{y}}} \]

Specific Immune Response \( y \)

Pathogen \( p \)

**B**

\[ \frac{1}{\mu_{\text{y}}} \]

Specific Immune Response \( y \)

Pathogen \( p \)

**C**

\[ \frac{1}{\mu_{\text{y}}} \]

Specific Immune Response \( y \)

Pathogen \( p \)

**D**

\[ \frac{1}{\mu_{\text{y}}} \]

Specific Immune Response \( y \)

Pathogen \( p \)
Model Assumptions

1. 1D spatial domain
2. Susceptible hosts begin at a disease-free equilibrium
3. Infection increases mortality
4. No recovery from disease (SI model)
5. Multiple parasite strains
6. A Transmission-Virulence trade-off exists
7. Hosts move, but sick hosts move less, i.e.,
8. a Movement-Virulence trade-off exists.