Direct and indirect effects of species interactions in disease systems

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Ecological and epidemiological models

• **Consumer-resource** model (Rosenzweig-Macarthur)

\[
\frac{dS}{dt} = ef(A)S - dS \\
\frac{dA}{dt} = r \left(1 - \frac{A}{K}\right)A - f(A)S
\]

• **Susceptible-Infected-Pathogen** model (Cáceres *et al.* 2009)

\[
\frac{dS}{dt} = bS + \rho BI - dS - \beta SZ \\
\frac{dI}{dt} = \beta SZ - (d + \nu)I \\
\frac{dZ}{dt} = \sigma(d + \nu)I - \lambda Z
\]

**Direct effects**: consumers decrease resource density, parasites decrease host densities.
In multi-species systems interactions may be convoluted

“the combination of two interactions involving 3 species can lead to dynamics that cannot be predicted from the analysis of the pairwise interactions alone” (Hatcher et al. 2006)

Examples of such scenarios are abundant:

- Competitors dilute (Nelson et al. 2015, Johnson et al. 2008; toads, frogs and trematodes)
- Competitors amplify (Mastitksy and Veres 2010; mussels and trematodes)
- Predators cause parasites to go extinct (Packer et al. 2003; red grouse and nematodes)
- Predators enhance disease (Duffy et al. 2011; Chaoborus and Daphnia)

**Indirect effects**: “the impact of one species on another is mediated by the action of a third species” (Hatcher et al. 2006)
Focal host of our disease system

_Daphnia dentifera_: very common planktonic crustacean (water flea) inhabiting freshwater lakes and ponds. (Duffy et al. 2005, Duffy et al. 2010, Duffy 2007)

**Why Daphnia?**
- in abundance (Michigan, Indiana, Illinois)
- available field-experimental data (through the Cáceres lab)
- easy to detect infected individuals
- able to link habitat and disease
- well studied organism (ecotoxicology, population genetics, the evolution of sex, phenotypic plasticity, ecophysiology, environmental genomics)
Ecological and epidemiological network

Daphnia

Feed on

Algae
Ecological and epidemiological network

Daphnia

Feed on

Accidentally ingest

Release upon death

Metschnikowia bicuspidata

Algae
Ecological and epidemiological network

- **Daphnia**
  - Feed on **Algae**
  - Accidentally ingest **Dreissena polymorpha**
  - Release upon death

- **Dreissena polymorpha**
  - Feed on **Metschnikowia bicuspidata**

- **Metschnikowia bicuspidata**
  - Feed on **Algae**
Daphnia

Algae

Dreissena polymorpha

Metschnikowia bicuspidata

Ecological and epidemiological network
Ecological and epidemiological network

- **Daphnia**
  - Feed on **Algae**
  - Accidentally ingest **Dreissena polymorpha**

- **Dreissena polymorpha**
  - Release upon death
  - Accidentally ingest, but not a host

- **Metschnikowia bicuspidata**
  - Feed on **Dreissena polymorpha**
  - Feed on **Daphnia**
  - Accidentally ingest
The many faces of virulence

- Disease induced (intrinsic) mortality (Cáceres et al. 2014)
- Reduced fecundity (Ebert 2005)
- Increased predation (extrinsic mortality) (Duffy et al. 2005, Hall et al. 2010)
The many faces of virulence

To understand virulence, we will ignore any competitors and consider a PDE model.

Mathematical model

\[
\frac{dS}{dt} = e_s f^s(A) \left( S + \int_0^{a_0} \rho(a) I(t, a) da \right) - (d + p_s)S - \mu \frac{f^s(A)}{A} SZ
\]

- **growth**
  - conversion efficiency
  - feeding rate

- **loss**
  - predation rate
  - background death rate

- **infection**
  - susceptibility

Ecological Parameters:
- \( f^s(A) = \frac{f_s A}{h_s + A} \)
- Conversion efficiency
- Feeding rate

Ecological Dynamics:
- \( S + A \rightarrow S, \quad \frac{dS}{dt} = e_s \frac{f^s(A)}{A} SA \)
- \( S + Z \rightarrow I, \quad \frac{dI}{dt} = \mu(A)SZ = \mu \frac{f^s(A)}{A} SZ \)
Mathematical model

\[
\frac{dS}{dt} = e_s f^s(A) \left( S + \int_0^{a_0} \rho(a)I(t,a)\,da \right) - (d + p_s)S - \mu \frac{f^s(A)}{A} S
\]

\[
\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -(d + v(a) + \theta(a)p_s)I, \quad I(t,0) = \mu \frac{f^s(A)}{A} S
\]

- disease induced mortality
- predator selectivity parameter
Mathematical model

\[
\frac{dS}{dt} = e_s f^s(A) \left( S + \int_0^{a_0} \rho(a) I(t, a) da \right) - (d + p_s) S - \mu \frac{f^s(A)}{A} SZ
\]

\[
\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -(d + \nu(a) + \theta(a) p_s) I, \quad I(t,0) = \mu \frac{f^s(A)}{A} SZ
\]

\[
\frac{dZ}{dt} = \sigma e_s f^s(A) \left[ (d + \nu(a)) I(t, a) W(a) da - \lambda Z - f^s(A) \left( S + \int_0^{a_0} I(t, a) da \right) \right] \frac{Z}{A}
\]

Overholt et al. 2011
Mathematical model

\[ \frac{dS}{dt} = e_s f^s(A) \left( S + \int_0^{a_0} \rho(a) I(t,a) \, da \right) - (d + p_s) S - \mu \frac{f^s(A)}{A} S Z \]

\[ \frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -(d + v(a) + \theta(a) p_s) I, \quad I(t,0) = \mu \frac{f^s(A)}{A} S Z \]

\[ \frac{dZ}{dt} = \sigma e_s f^s(A) \int_0^{a_0} (d + v(a)) I(t,a) W(a) \, da - \lambda Z - f^s(A) \left( S + \int_0^{a_0} I(t,a) \, da \right) \frac{Z}{A} \]

\[ \frac{dA}{dt} = r \left( 1 - \frac{A}{K} \right) A - f^s(A) \left( S + \int_0^{a_0} I(t,a) \, da \right) \]
Mathematical model

\[
\frac{dS}{dt} = e_s f^S(A) \left( S + \int_0^{a_0} \rho(a) I(t, a) da \right) - (d + p_s) S - \mu \frac{f^S(A)}{A} S Z
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\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -(d + v(a) + \theta(a) p_s) I, \quad I(t, 0) = \mu \frac{f^S(A)}{A} S Z
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\]

\[
\frac{dA}{dt} = r \left( 1 - \frac{A}{K} \right) A - f^S(A) \left( S + \int_0^{a_0} I(t, a) da \right)
\]
Pathogen’s basic reproductive number

\[ R_0 = \frac{\sigma e_s f^s(A_{df}) \int_0^a W(a)(d + \nu(a)) \exp\left(-\int_0^a (d + \nu(\tau) + \theta(\tau)p_s)\,d\tau\right)da}{\lambda + \frac{f^s(A_{df})}{A_{df}} S_{df}} \]

\[ \mu \frac{f^s(A_{df})}{A_{df}} S_{df} \]

spore release

infection transmission

spore loss

Obtained by linear stability analysis around the disease-free steady-state

\[ S_{df} = \frac{e_s r \left(1 - \frac{A_{df}}{K}\right) A_{df}}{d + p_s}, \quad A_{df} = \frac{(d + p_s) h_s}{e_s f_s - (d + p_s)} \]
Pathogen's basic reproductive number

Linearizing the system around the disease-free equilibrium:

\[ S = S_{df} + e^{\Lambda t} s, \quad I = e^{\Lambda t} q, \quad Z = e^{\Lambda t} z, \quad A = A_{df} + e^{\Lambda t} r \]

yields a linear eigenvalue problem that can be rearranged to yield

\[ R(\Lambda) = \frac{\sigma e_S f^S(A_{df}) \int_0^{a_0} W(a)(d + v(a)) e^{-\int_0^a (\Lambda + d + v(\tau) + pS\theta(\tau))d\tau} da}{\Lambda + \lambda + \frac{f^S(A_{df})}{A_{df}} S_{df}} \mu \frac{f^S(A_{df})}{A_{df}} S_{df} = 1. \]

When \( \Lambda = 0 \), it holds \( R(\Lambda) = R_0 \). For real \( \Lambda \), \( R(\Lambda) \) is decreasing. Hence, the above equation has real positive solutions iff \( R_0 = R(0) > 1 \).

Next, let \( \Lambda = x + iy \), with \( x \geq 0 \) and set \( \Lambda_0 = \lambda + \frac{f^S(A_{df})}{A_{df}} S_{df} \) and

\[ g(a) = \sigma e_S f^S(A_{df}) W(a)(d + v(a)) e^{-\int_0^a (d + v(\tau) + pS\theta(\tau))d\tau} \mu \frac{f^S(A_{df})}{A_{df}} S_{df}. \]

Then, \( 1 = |R(\Lambda)| = \left| \int_0^{a_0} g(a)e^{-xa}e^{-iya} da \right| \leq \int_0^{a_0} g(a)e^{-xa} da = R(x) \leq R(0) = R_0 \).

Hence, for \( R_0 < 1 \), stability follows.
Pathogen’s winning strategy: intermediate $h_v$ & higher $h_\theta$.

$v(a) = \frac{v_0}{2}(1 + \tanh(a - h_v))$

$\theta(a) = 1 + \frac{1}{2}(\theta_0 - 1)(1 + \tanh(a - h_\theta))$
Pathogen’s winning strategy: intermediate $h_v$ works for all $v_0$.

$$v(a) = \frac{v_0}{2} \left(1 + \tanh(a - h_v)\right)$$
Pathogen’s winning strategy: above medium $h_\theta$ works for all $\theta_0$.

$$\theta(a) = 1 + \frac{1}{2} (\theta_0 - 1)(1 + \tanh(a - h_\theta))$$
Prevalence: dependence on the timing of intrinsic and extrinsic mortality

\[ P = \frac{\int_{0}^{a_0} I(t, a)da}{S + \int_{0}^{a_0} I(t, a)da} \]

Intermediate \( h_\nu \) is optimal: too soon, not enough spores, too late killed by the fish

Higher \( h_\theta \) is optimal: avoid fish predation at all costs
Predators alone are not enough to “keep the herds healthy”. (Hall et al. 2005, Packer et al. 2003, Rapti and Cáceres 2016)
What did we achieve from this analysis?

Trade-offs exist

The timing of disease life-history events matters

Resources matter
Corresponding ODE model

\[
\frac{dS}{dt} = e_s f^S(A)(S + \rho^{ODE} I) - (d + p_s)S - \mu \frac{f^S(A)}{A} S \theta \\
\frac{dI}{dt} = \mu \frac{f^S(A)}{A} S \theta - (d + v^{ODE} + \theta^{ODE} p_s)I \\
\frac{dZ}{dt} = \sigma e_s f^S(A)(d + v^{ODE})I - \lambda Z - f^S(A)(S + I) \frac{Z}{A} \\
\frac{dA}{dt} = r \left(1 - \frac{A}{K}\right) A - f^S(A)(S + I)
\]

\[
f^S(A) = \frac{f_s A}{h_s + A}
\]

\[
R_0 = \frac{\sigma e_s f^S(A_{df})(d + v^{ODE})}{\left(d + v^{ODE} + \theta^{ODE} p_s\right)\left(\mu f^S(A_{df}) S_{df} + A_{df}\right) S_{df}}
\]
Comparison of basic reproductive numbers

**PDE:**

\[ R_0 = \frac{\sigma e S f^S(A_{df})\int_0^{a_0} W(a)(d+v(a))e^{-\int_0^a (d+v(\tau)+p_s \theta(\tau))d\tau}da}{\lambda + \frac{f^S(A_{df})}{A_{df}} S_{df}} \mu \frac{f^S(A_{df})}{A_{df}} S_{df} \]

**ODE:**

\[ R_0 = \frac{\sigma e S f^S(A_{df})(d+v^{ODE})}{(d+v^{ODE}+\theta^{ODE}p_s)(\lambda + \frac{f^S(A_{df})}{A_{df}} S_{df})} \mu \frac{f^S(A_{df})}{A_{df}} S_{df} \]

The two become equivalent when:

\[ d + v^{ODE} = d \frac{J_1}{J_0} + \frac{J_2}{J_0}, d + v^{ODE} + \theta^{ODE} p_s = \frac{1}{J_0}. \]

\[ J_0 = \int_0^{a_0} e^{-\int_0^a (d+v(\tau)+p_s \theta(\tau))d\tau}da \quad \text{(average life span of infected hosts)} \]

\[ J_1 = \int_0^{a_0} W(a)e^{-\int_0^a (d+v(\tau)+p_s \theta(\tau))d\tau}da \quad \text{(measure of spores within infected hosts)} \]

\[ J_2 = \int_0^{a_0} v(a)W(a)e^{-\int_0^a (d+v(\tau)+p_s \theta(\tau))d\tau}da \]
Identical endemic states when:

\[ \rho^{ODE} = \frac{J_3}{J_0}, \]

where \( J_3 = \int_0^{a_0} \rho(a) e^{-\int_0^a (d + v(\tau) + p_S \theta(\tau)) d\tau} da \)

is the average value of the fecundity reduction parameter over the life-span of the infected host.

Hence, disease prevalence and \( R_0 \) may be matched.
Indirect effects

Density Mediated Indirect Effect
Mussel competition decreases *Daphnia* densities
Indirect effects

Density Mediated Indirect Effect
Mussel competition decreases *Daphnia* densities below the minimum threshold for parasite establishment
Indirect effects

Density Mediated Indirect Effect
Mussels remove spores
Indirect effects

Density Mediated Indirect Effect
Mussels remove spores, thus decreasing infection risk and positively impacting *Daphnia* (Disease dilution, Hall et al. 2009)
Indirect effects

Density Mediated Indirect Effect
Mussel filtration suspends spores
Indirect effects

Density Mediated Indirect Effect
Mussel filtration suspends spores, thus increasing infection risk and negatively impacting *Daphnia*
Indirect effects

Trait Mediated Indirect Effect
Mussel presence reduces *Daphnia* immunity
Indirect effects

Trait Mediated Indirect Effect
Mussel presence reduces *Daphnia* immunity, which positively impacts the pathogen.
Modified mathematical model

\[
\frac{dS}{dt} = e_S f^S(A)(S + \rho I) - (d + p_S)S - \mu \frac{f^S(A)}{A} S Z
\]

\[
\frac{dI}{dt} = \mu \frac{f^S(A)}{A} SZ - (d + v + \theta_I p_S)I
\]

\[
\frac{dZ}{dt} = \sigma e_S f^S(A)(d + v)I - \lambda Z - \lambda_M Z - f^S(A)(S + I) \frac{Z}{A}
\]

\[
\frac{dA}{dt} = rA \left( 1 - \frac{A}{K} \right) - f^S(A)(S + I) - f_M A
\]
Who survives?

just competition: $f_M = 0.16, \lambda_M = 0, \mu = 10$

no mussels: $f_M = 0, \lambda_M = 0, \mu = 10$

competition & resuspension: $f_M = 0.16, \lambda_M = -0.1, \mu = 10$

competition & susceptibility: $f_M = 0.16, \lambda_M = 0, \mu = 15$

Competition, removal & susceptibility: $f_M = 0.16, \lambda_M = 0.1, \mu = 15$
Will there be an epidemic?

\[
R_0 = \frac{\mu \sigma (d + p_S) (d + v)}{d + v + \theta_1 p_S} \times \frac{(r - f_M)K(e_S f_{S0} - (d + p_S)) - rh_S(d + p_S)}{(\lambda + \lambda_M + r - f_M)K(e_S f_{S0} - (d + p_S)) - rh_S(d + p_S)}
\]

\[\lambda_M = 0\]

\[\lambda_M = -0.1\]

\[\lambda_M = 0.1\]
How large is prevalence?

\[ \text{Prev.} = \frac{I_e}{I_e + S_e} = 1 - \frac{S_e}{I_e + S_e} \]

\[ S_{df} = \left( r - f_M - \frac{r A_{df}}{K} \right) \frac{e_s A_{df}}{(d + p_s)} \]

\[ \mu = 15, \lambda_M = 0 \]

How do population densities behave?

\[ A_{df} = \frac{(d + p_s) h_s}{e_s f s_0 - (d + p_s)} \]

\[ A_o = \frac{(r - f_M) K}{r} \]
Is it possible to tease what is happening apart?

<table>
<thead>
<tr>
<th>spore removal</th>
<th>∅</th>
<th>spore resuspension</th>
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<tbody>
<tr>
<td>50% susceptibility increase</td>
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<tr>
<td>25% susceptibility increase</td>
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<tr>
<td>0% susceptibility increase</td>
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Preisser et al. 2005, Werner and Peacor 2003: trait mediated indirect effects are as important as density mediated direct and indirect effects
Indirect-direct effects: what have we learned?

- Trait mediated indirect effects can be as strong as density mediated indirect effects.
- The same species might hurt another one in two different ways simultaneously (resuspend spores = indirect and increase *Daphnia* susceptibility = direct).
- The same species might help another one in two different ways simultaneously (resuspend spores = direct and increase *Daphnia* susceptibility = indirect).
- 2 negative influences (competition and increased susceptibility) + 1 positive influence (spore removal) = no influence (identical *Daphnia* bifurcation diagram).

The algebra of direct and indirect interactions is not straightforward.

What is next?

- Data from ponds
- *Daphnia* immunity
- More info about mussel properties and spore resuspension/removal
- Other systems: bumblebees and trypanosomes, etc.
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THANKS FOR LISTENING!