EVALUATING THE WITHIN-HOST DYNAMICS OF RANAVIRUS INFECTIONS MECHANISTIC MODELS & EXPERIMENTAL DATA
Growing evidence that infection status is not binary, but quantitative

- Dose-response experiments
- Changes in infectiousness through time
- Variability among individuals
- Virus dynamics are slow relative to time-scale of epidemic dynamics
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**Goal:** develop within-host models to understand the growth of ranaviruses
RESEARCH QUESTIONS

• What are the dynamics of the virus population within the host?

• Does the host’s immune system effectively control the virus population (outside of the Xenopus model system)?

• Does the immune response lead to viral clearance or can persistent infections remain?

• Does the outcome depend on the initial exposure dose?
FEATURES/HYPOTHESES

**Virus growth**
- Exponential (unless controlled)
- Logistic (sigmoidal)

**Removed by immune response**
- Mass action

\[ \phi V \]
\[ \phi V \left(1 - \frac{V}{K}\right) \]
\[ -\beta VZ \]

Carrying capacity \( \approx \) lethal titer in host
**Immune components**

- Michaelis-Menten response to virus
- Michaelis-Menten + homeostatic level
- Homeostatic level + mass-action response to virus

\[
\psi Z \left( \frac{V}{V + \gamma} \right)
\]

- Keeps \( Z \) at baseline-level without virus

\[
(N_z - \delta Z) + \psi Z \left( \frac{V}{V + \gamma} \right)
\]

- \( Z \) grows when contacts \( V \)

\[
(N_z - \delta Z) + \psi Z V
\]

- \( V \) at half maximum
FIT MODELS TO DATA FROM BULLFROGS
TADPOLES EXPOSED TO THREE DOSES & TITERS IN LIVER+KIDNEY MEASURED
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Features we hoped to capture

- Clear rise and fall of viral titers over time (high & low doses)
- Higher peak titer with higher dose of inoculum
- Earlier peak with higher dose of inoculum
- Persistent infections (49 days)
Mass action growth of immune response

\[
\frac{dV}{dt} = \phi V - bVZ \\
\frac{dZ}{dt} = (N_Z - \delta Z) + \psi ZV
\]
Without the homeostatic level of immune response

\[
\frac{dV}{dt} = \phi V - bVZ
\]

\[
\frac{dZ}{dt} = \psi Z \left( \frac{V}{V + \gamma} \right)
\]
Without the homeostatic level of immune response

\[
\frac{dV}{dt} = \phi V - bVZ
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\frac{dZ}{dt} = \psi Z \left( \frac{V}{V + \gamma} \right)
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BEST-FIT MODEL
HITS ALL OF THE RIGHT NOTES

Exponential viral growth
Michaelis-Menten + homeostatic level

\[
\frac{dV}{dt} = \phi V - bVZ
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\frac{dZ}{dt} = (N_Z - \delta Z) + \psi Z \left(\frac{V}{V + \gamma}\right)
\]
BEST-FIT MODEL

HITS ALL OF THE RIGHT NOTES

Exponential viral growth

Michaelis-Menten + homeostatic level

✓ Clear rise and fall of viral titers
✓ Peak titer increases with dose
✓ Earlier peak with higher dose
✓ Persistent infections (49 days)
CONCLUSIONS & PREDICTIONS

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- Virus is (often) controlled by immune response
- Without immune response, virus will grow exponentially
- Higher initial dose makes it harder to control
- Virus reduced to low, but stable dynamic balance
  \[ V^* = \frac{\psi \left( \delta - \frac{\psi}{Z^*} \right)}{1 - \frac{\delta}{\psi} + \frac{N_{Z}}{\psi Z^*}} \]
- Persistence by another means (not PL)
- Demographic stochasticity —> recovery
NEXT STEPS
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Modeling

• Link viral titer with mortality
• Allow stochasticity

Data needs

• repeated samples from same individuals
• paired with immune measures (interferon and ?)