Incorporating Infected Cell Phenotypes Into Models of Within-Host Viral Dynamics

Katia Koelle
Department of Biology, Emory University

SIAM 2019, Snowbird, UT
May 19, 2019

Collaborators

Chris Brooke - UIUC

Ruian Ke – LANL

DARPA Intercept program: Focused on the development of defective interfering viruses as potential anti-viral therapeutics

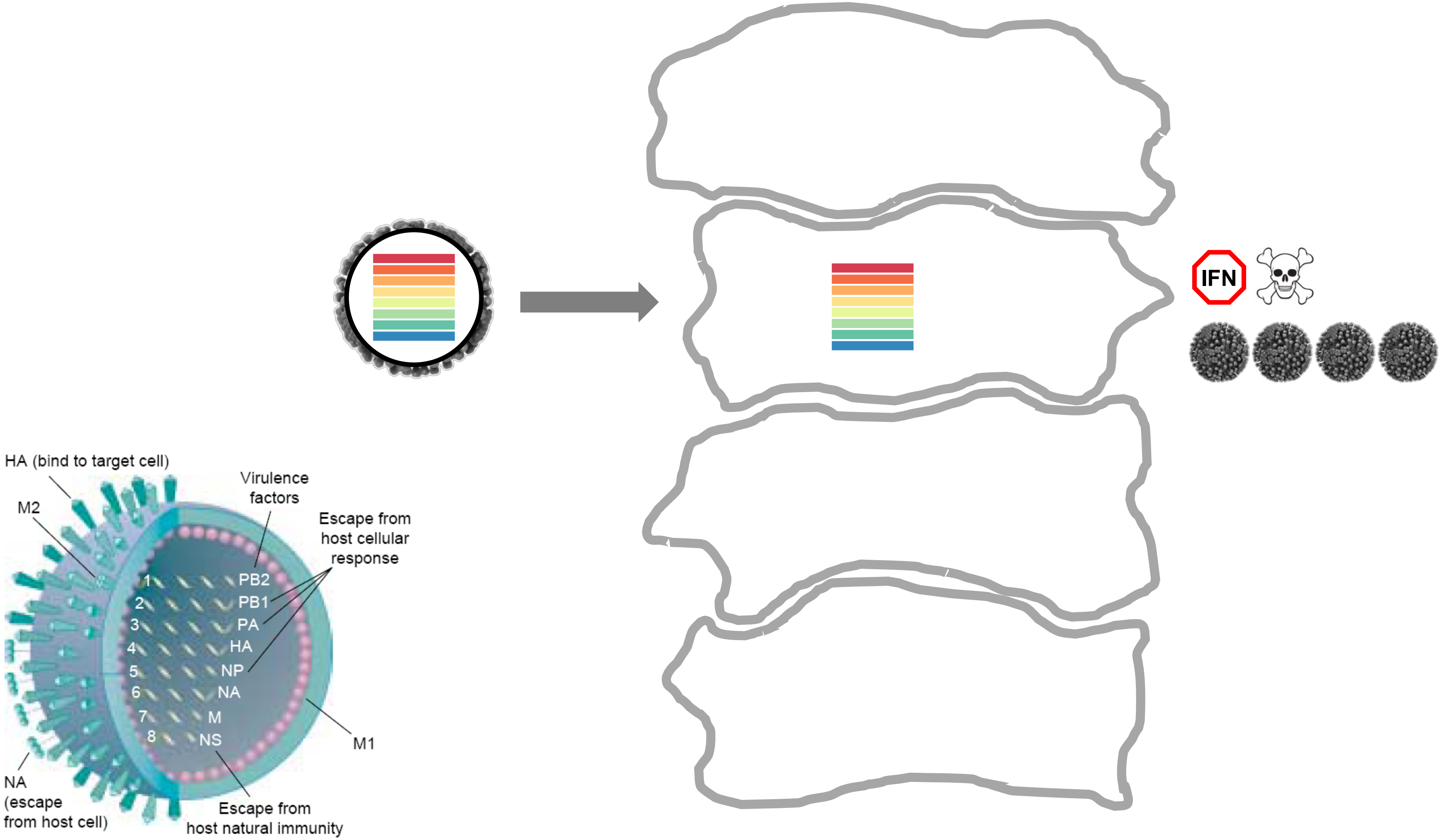
Molly Gallagher
Emory

Jeremy Harris
Emory

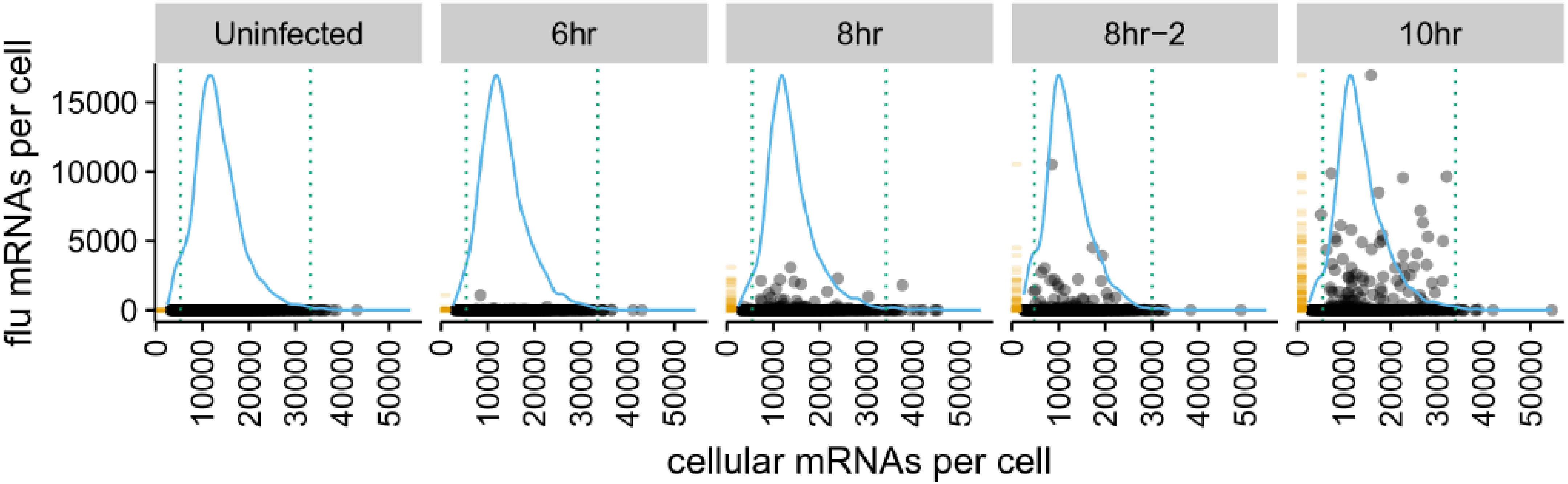
Brigitte Martin
UIUC

Alex Farrell
NCSU

Viral entry and change in behavior (phenotype) of infected cell

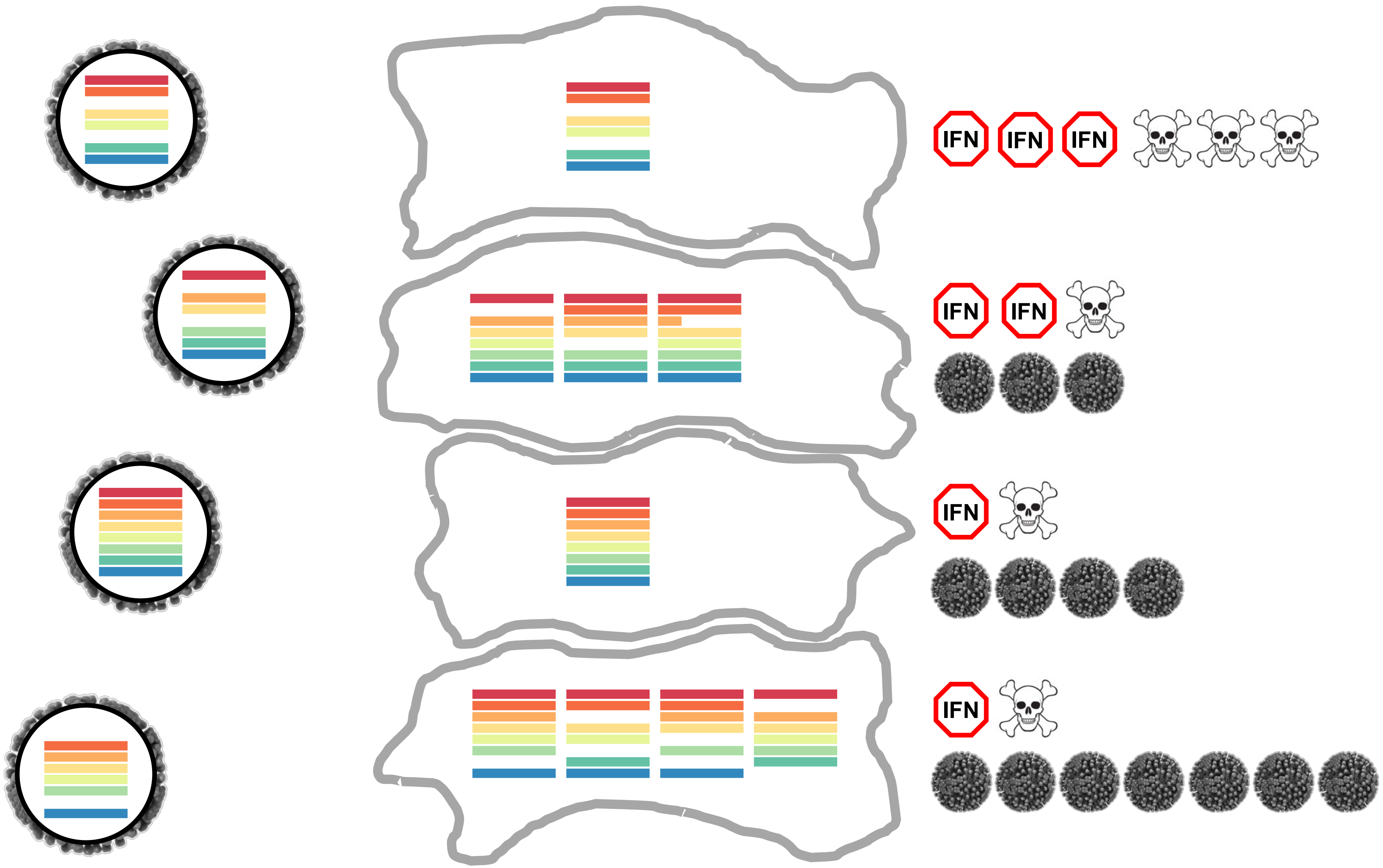


Singly infected cells exhibit extreme heterogeneity in their phenotypes

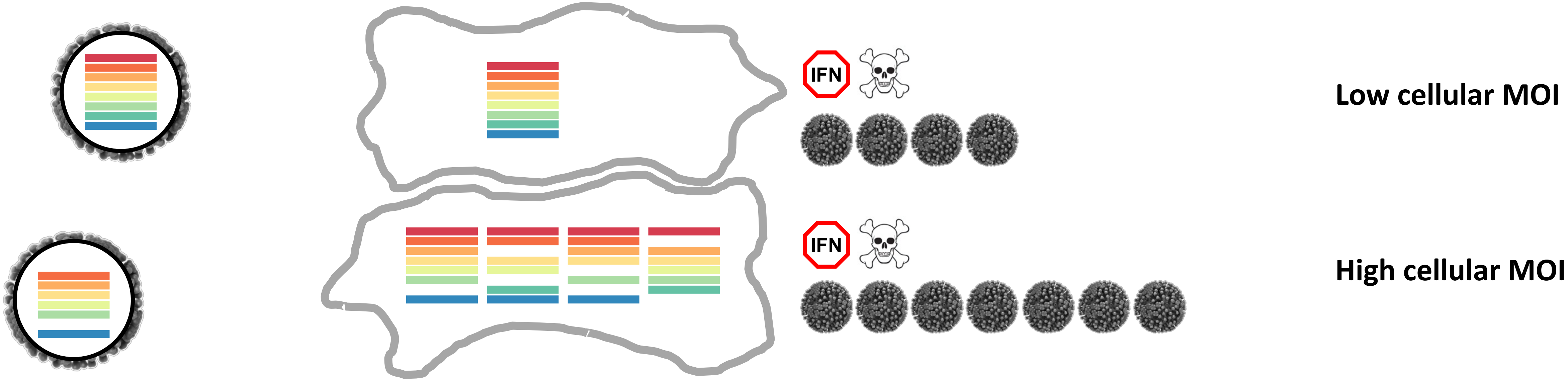


Russell et al. (2018) *eLife*

Infected cells more generally exhibit extreme heterogeneity in their phenotypes

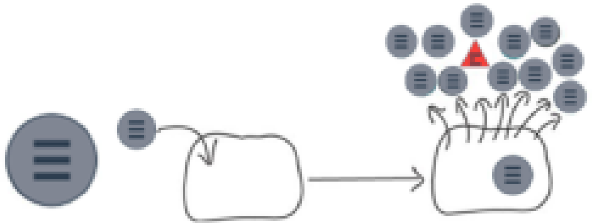


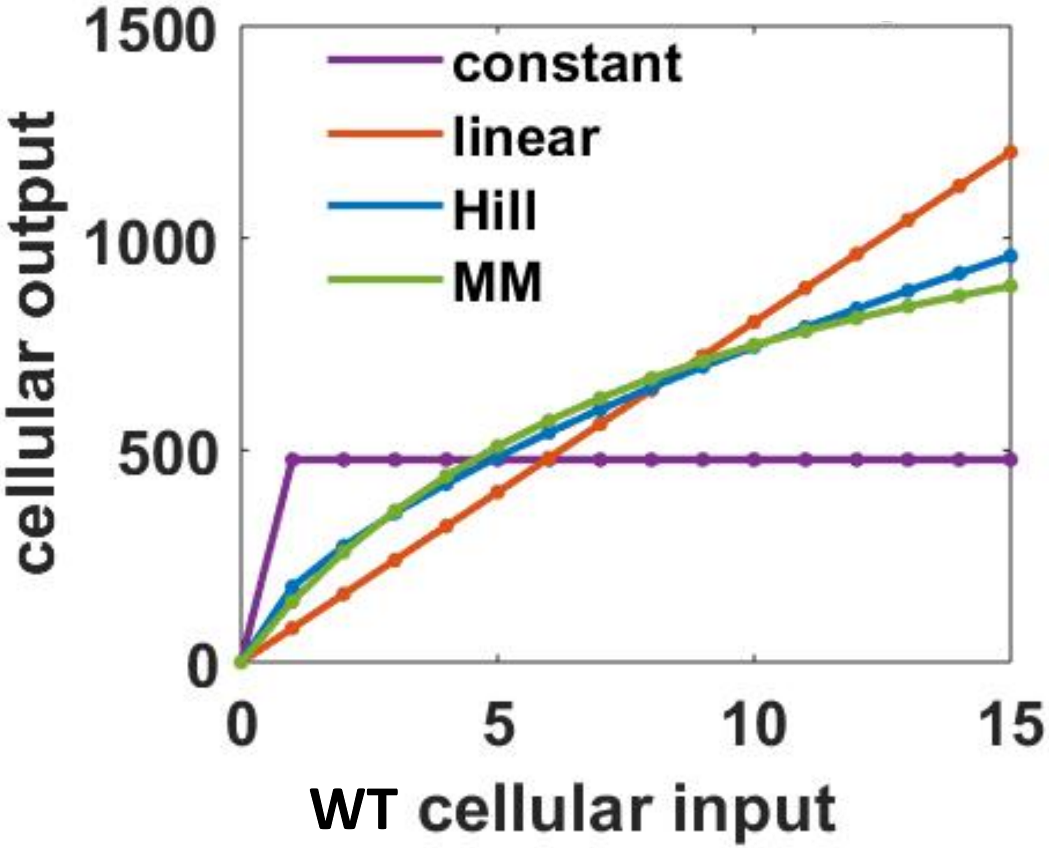
Some infected cell phenotypes scale with cellular MOI

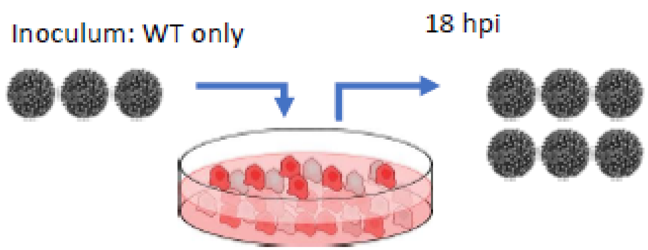


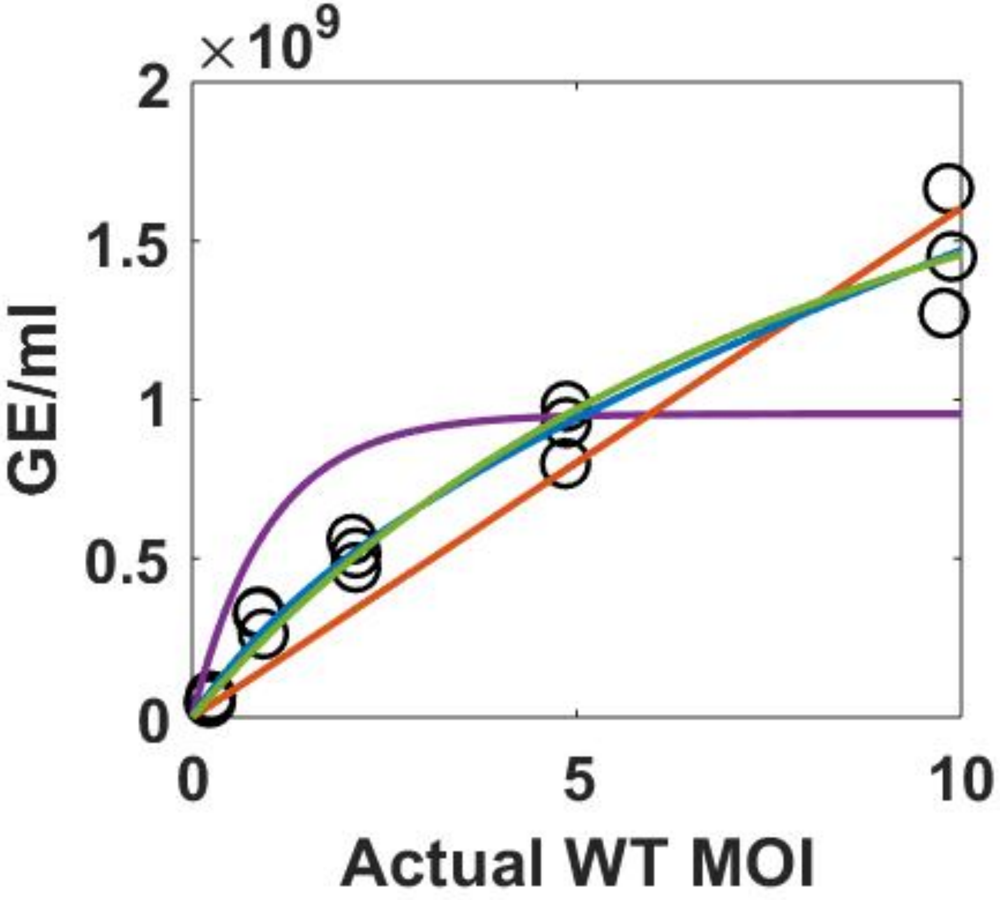
- Viral yield
- Cellular death rate
- Superinfection exclusion
- Interferon induction

Experiments show that viral yield scales with cellular input





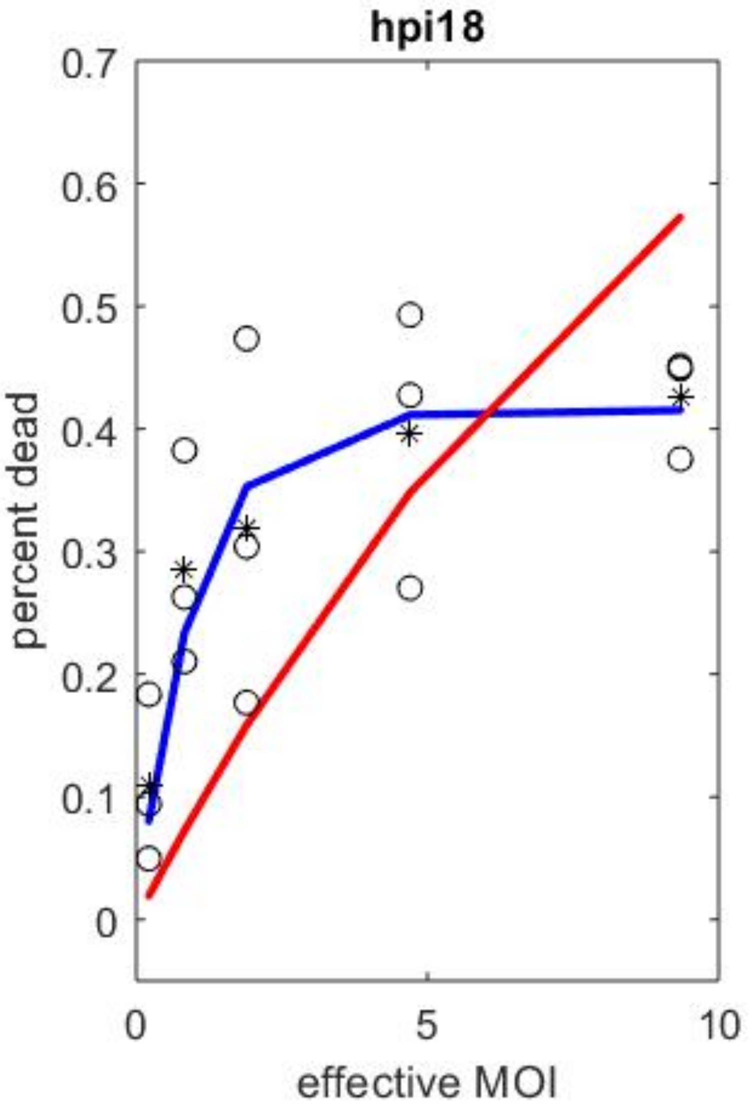




Experiments show that cellular death rate is similar across infected cells

▬ Infected cells have same death rates

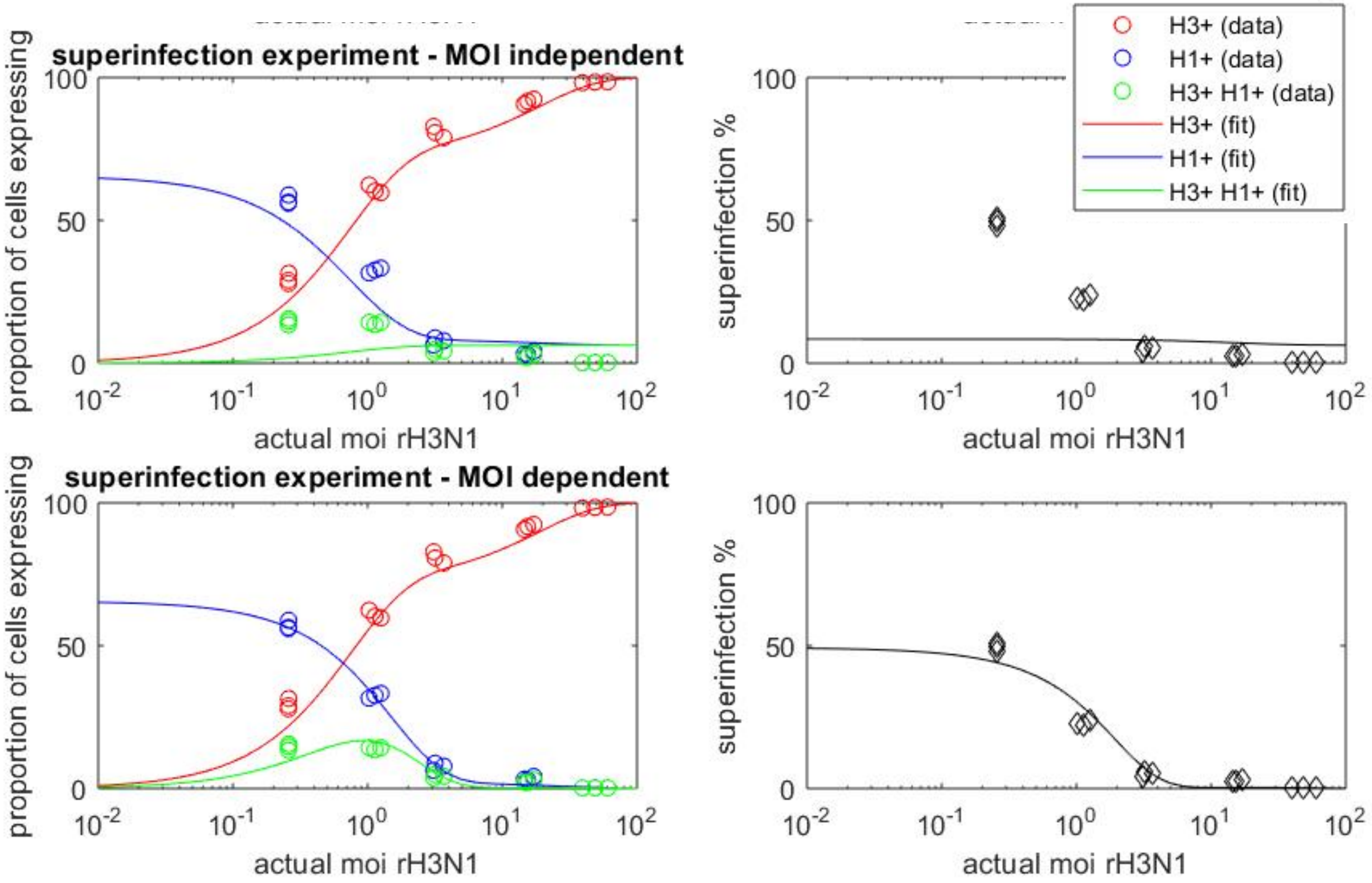
▬ Infected cell death rates increase linearly with cellular MOI



Experiments show that rate of superinfection exclusion scales with cellular MOI

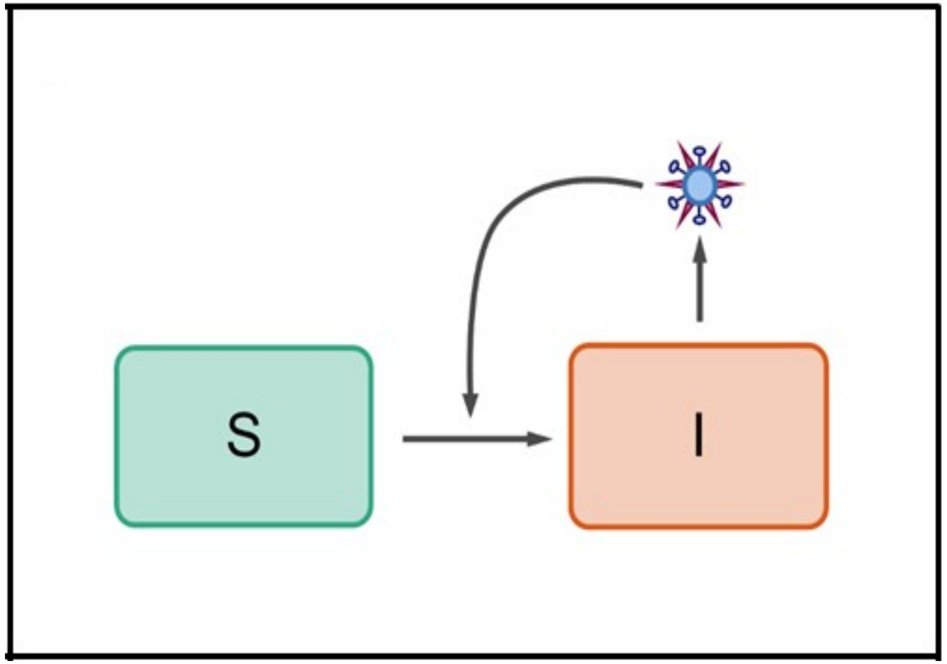
- Add H3 virus into cells (at various MOIs)
- Wait 6 hours
- Add H1 virus into cells (at single MOI)
- Quantify: - proportion of cells that are H3+
  - proportion of cells that are H1+
  - proportion of cells that are both H3+ and H1+

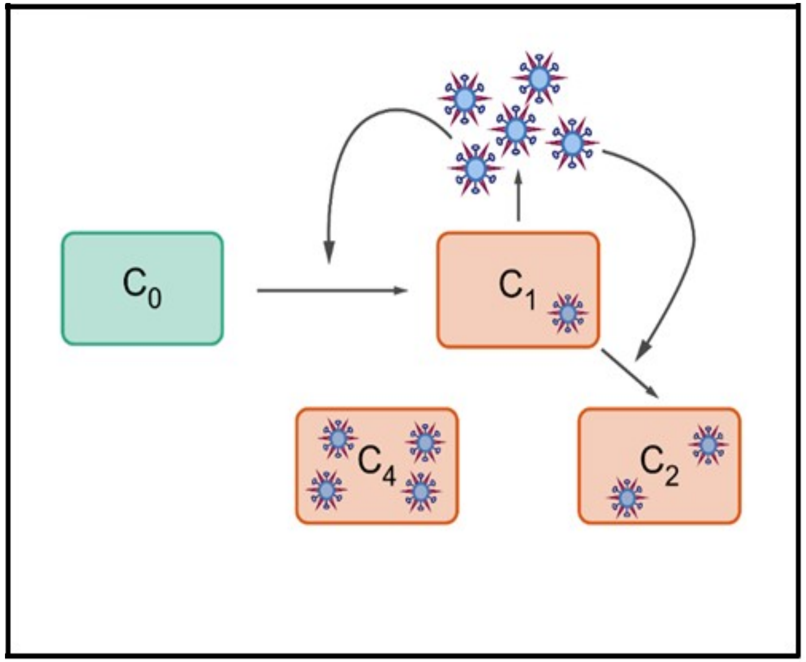
% of cells that are superinfected
(H3+ plus H1+)/(H3+)



Superinfection exclusion happens more quickly at higher cellular MOI

Modeling within-host dynamics



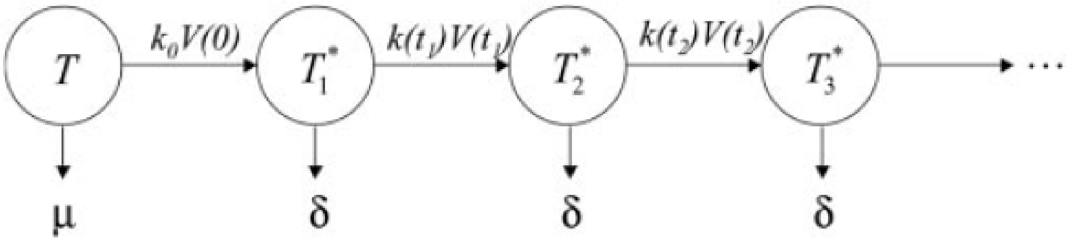


Baccam et al. (2006) *JVI*
Saenz et al. (2010) *JVI*
Pawelek et al. (2012) *PLOS CB*

Dixit & Perelson (2005) *PNAS*
Dixit & Perelson (2004) *JVI*

Cummings et al. (2012) *Biology Direct*
Phan & Wodarz (2015) *Mathematical Biosciences*
Wodarz & Levy (2011) *JRS Interface*
Wodarz et al. (2018) *BioRxiv*

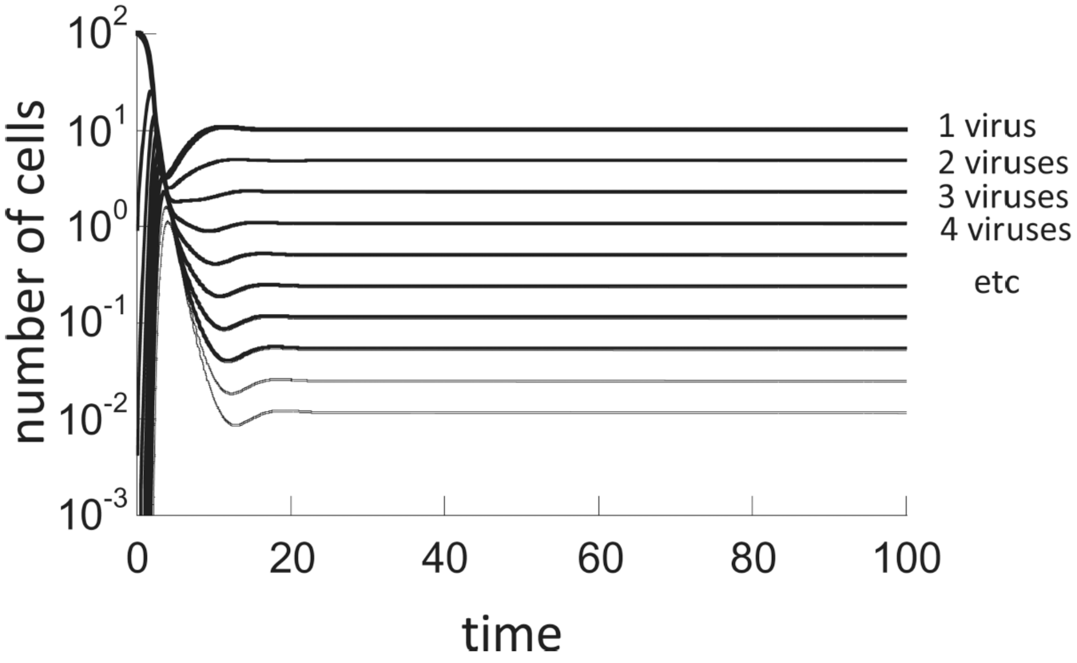
Models that allow for multiply-infected cells



Dixit & Perelson (2005) *PNAS*

Viral dynamics of this model are the same as within-host SIR-type models, as long as the viral production from infected cells and cellular death rates are independent of cellular MOI.

Scalable under limited assumptions (folds into within-host SIR model)



Phan & Wodarz (2015) *Mathematical Biosciences*

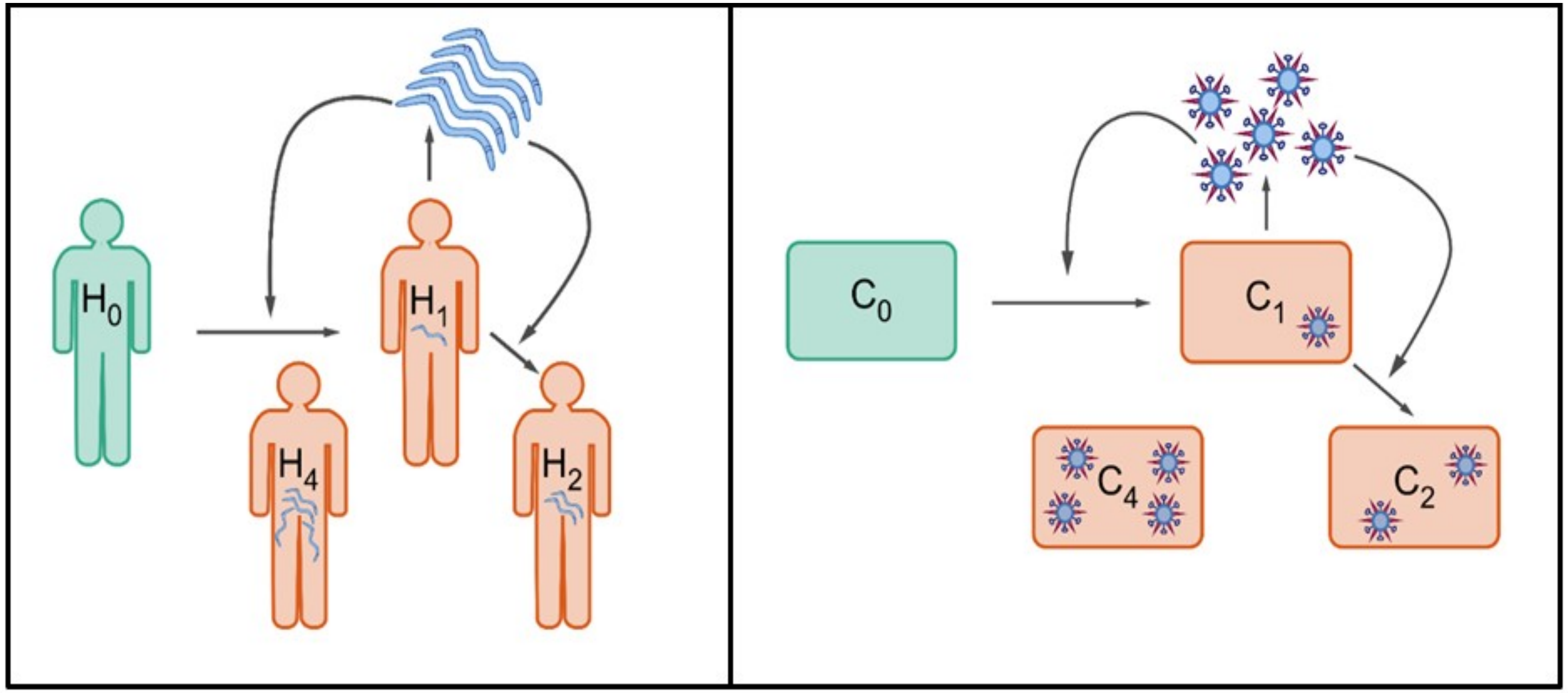
Not scalable

Goal:

To develop a within-host modeling framework that allows for the incorporation of cellular-MOI dependent infected cell phenotypes

in a scalable manner

Modeling the dynamics of multiply-infected cells



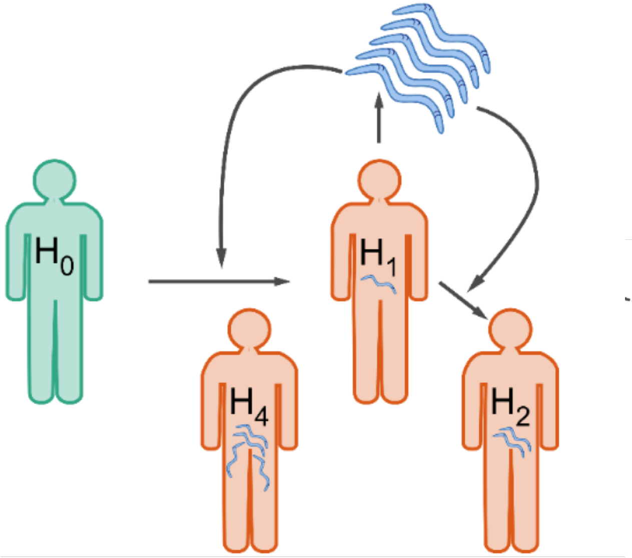
Epidemiological macroparasite model

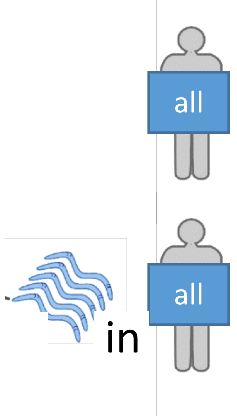
- Host death rate depends on host’s nematode burden
- Nematode production rate depends on host’s nematode burden

Within-host “macroparasite” model

- Cell death rate can depend on cellular input
- Viral production rate can depend on cellular input

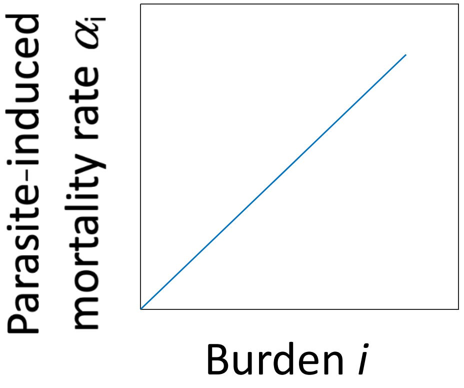
Low-dimensional nature of population-level "macroparasite" models

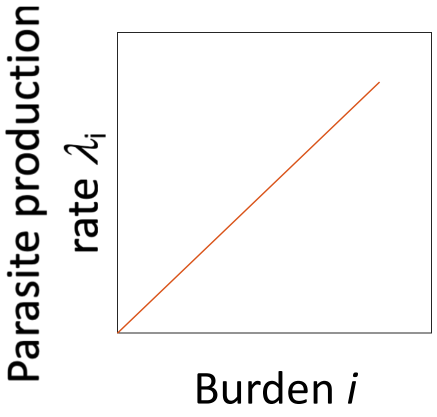




$$\frac{dH}{dt} = aH - bH - H\sum_{i=0}^{\infty} \alpha_i p_i$$

$$\frac{dP}{dt} = \left[H\sum_{i=0}^{\infty} \lambda_i p_i\right]\frac{H}{H_0 + H} - H\sum_{i=0}^{\infty} \alpha_i p_i i$$





$$\frac{dH}{dt} = aH - bH - \alpha P$$

$$\frac{dP}{dt} = \lambda P\frac{H}{H_0 + H} - \alpha H E(i^2)$$

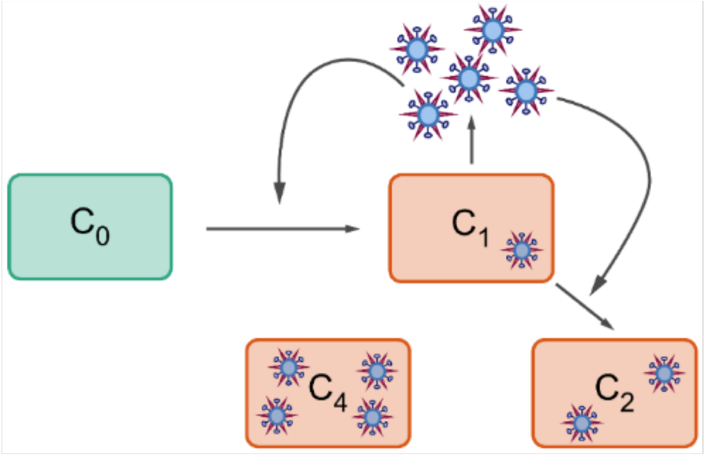
NB distn of parasite burden

$$\frac{dH}{dt} = aH - bH - \alpha P$$

$$\frac{dP}{dt} = \lambda P\frac{H}{H_0 + H} - \alpha\left(\frac{1 + k}{k}\right)\left(\frac{P^2}{H}\right)$$

k = NB dispersion parameter

Low-dimensional nature of within-host “macroparasite” models

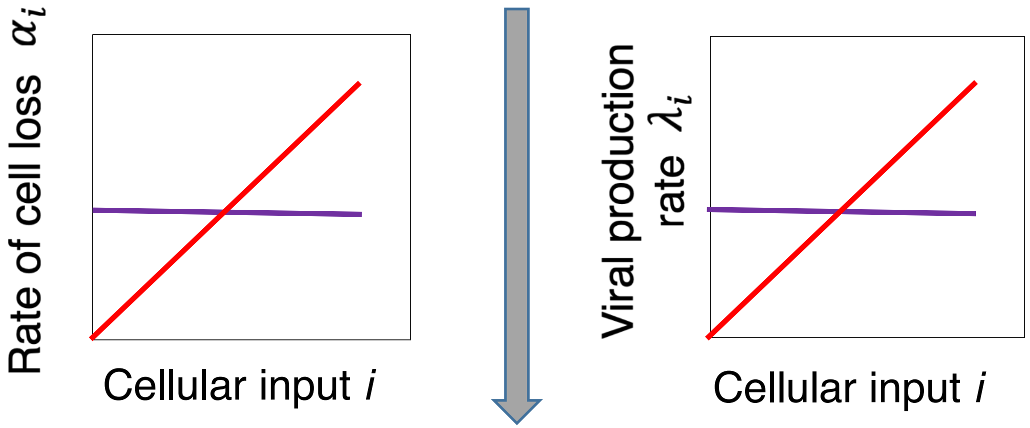


$$\frac{dC}{dt} = -C \sum_{i=0}^{\infty} \alpha_i p_i$$

$$\frac{dP}{dt} = \beta CV - C \sum_{i=0}^{\infty} i \alpha_i p_i$$

$$\frac{dV}{dt} = \left(C \sum_{i=0}^{\infty} \lambda_i p_i \right) - \eta V - \beta CV$$

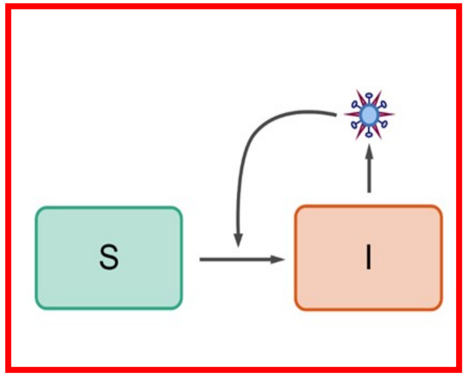
NB distribution of viral particles *P* across host cells +

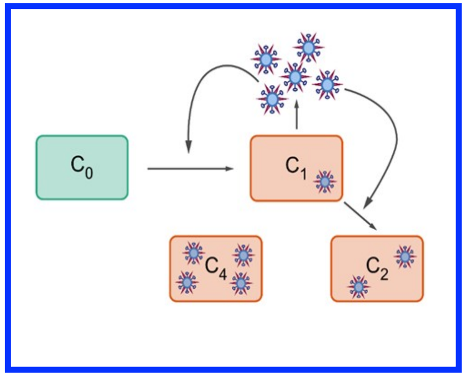


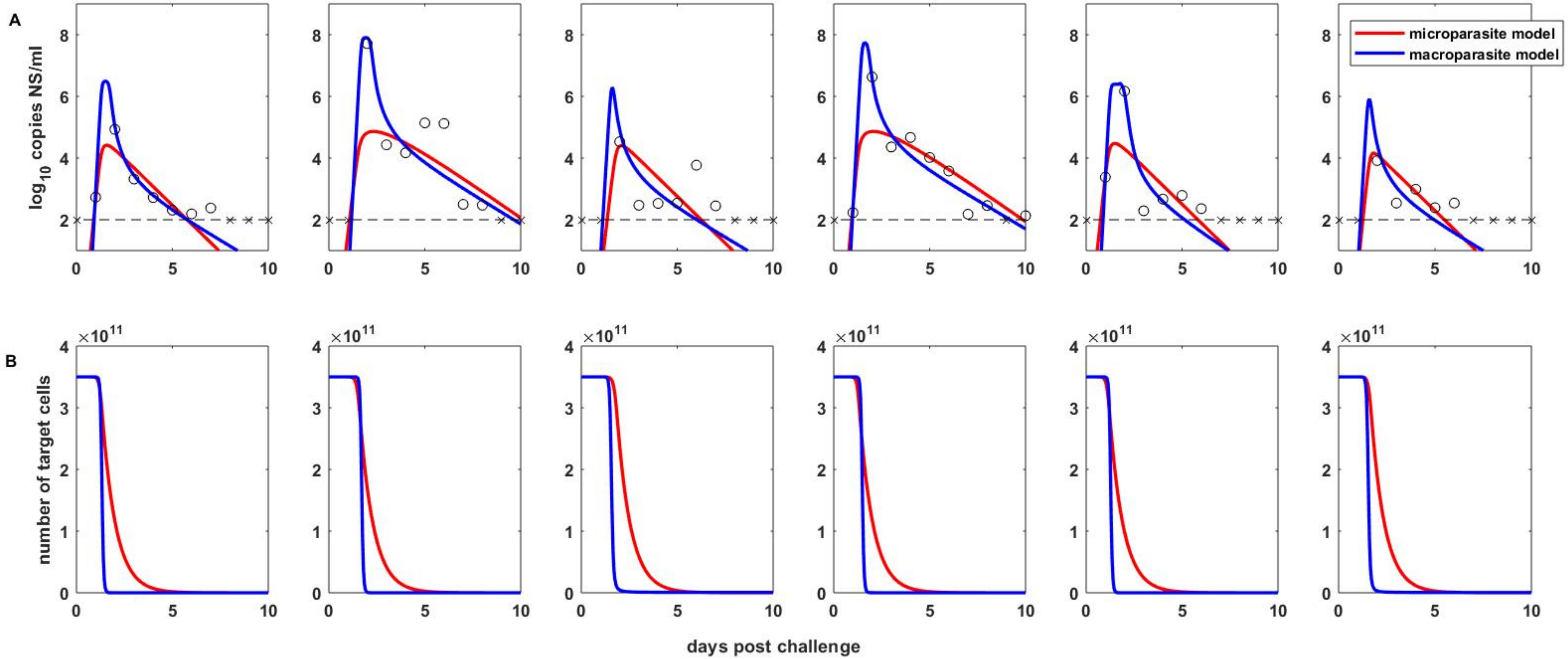
Low dimensional (3D) set of equations

Koelle, Farrell, Brooke, Ke (in revision) *Virus Evolution*. bioRXiv (doi: 10.1101/359067)

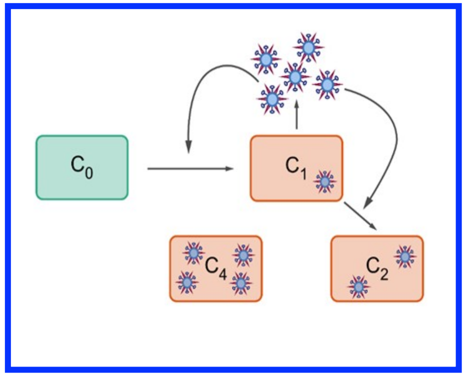
Model dynamics

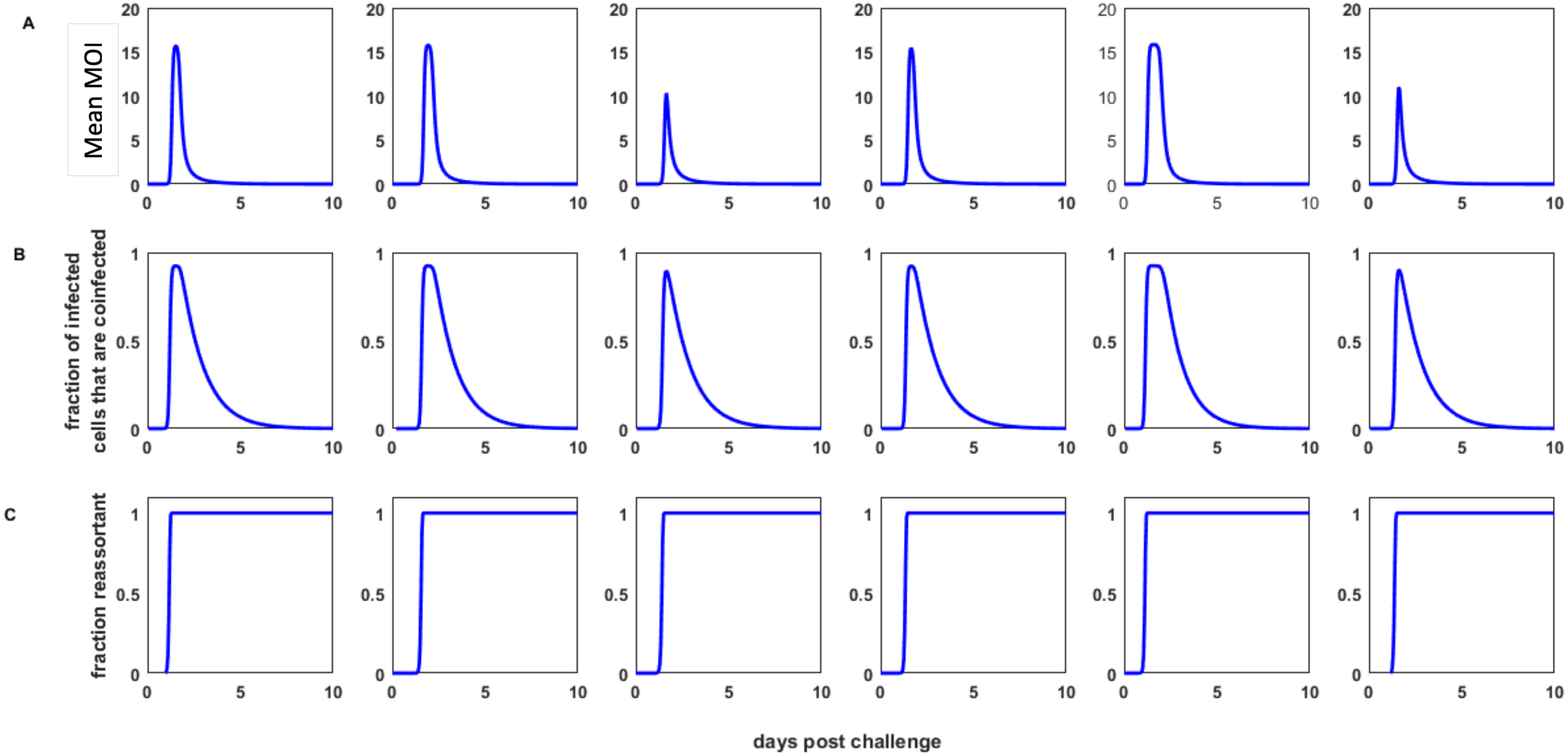




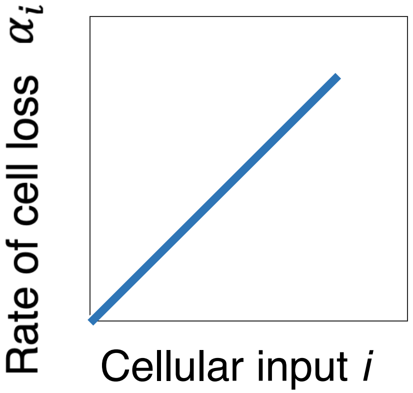


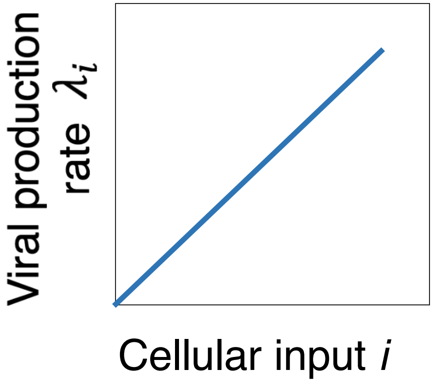
Model dynamics



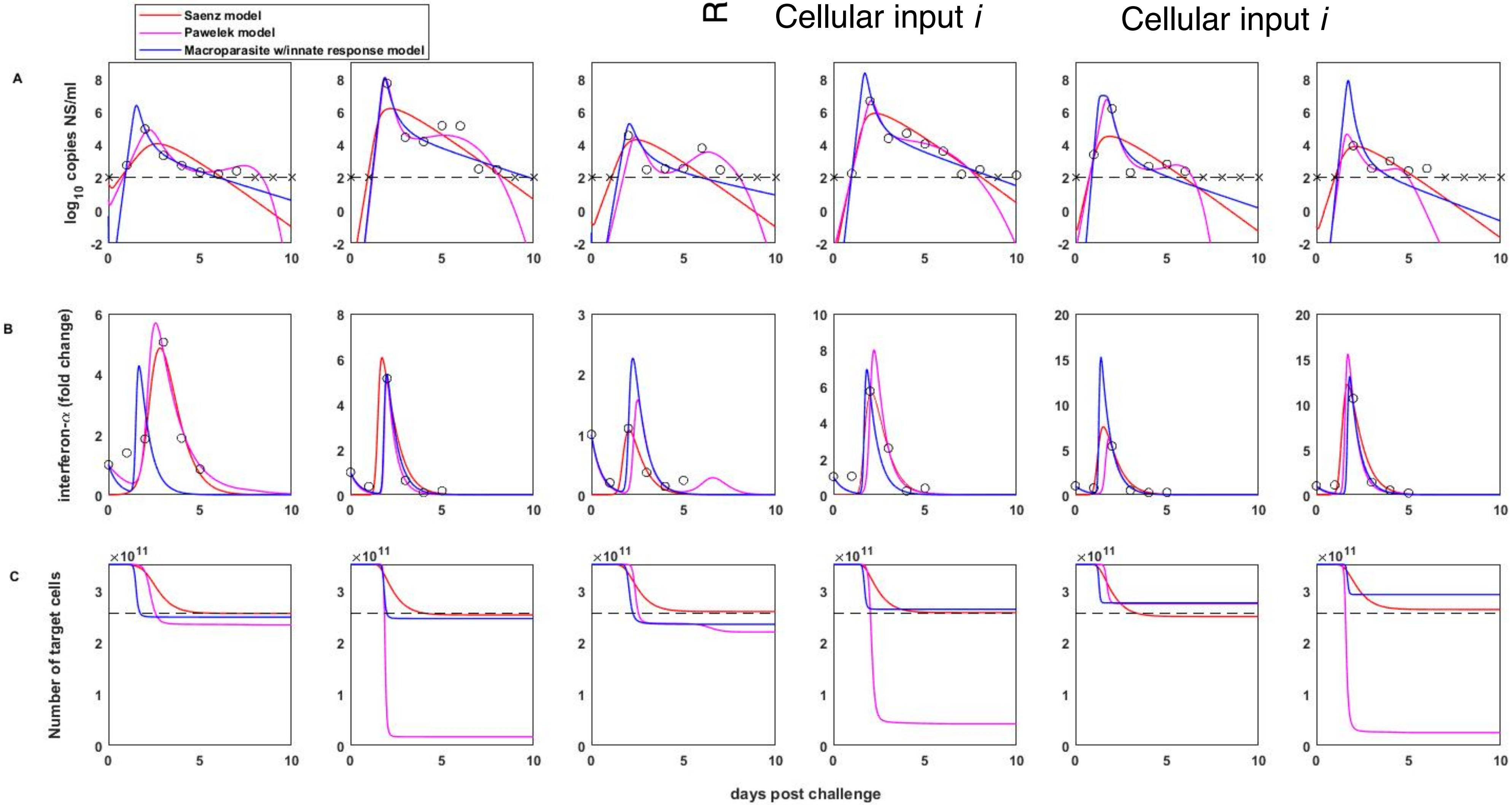


Model dynamics with innate immune response



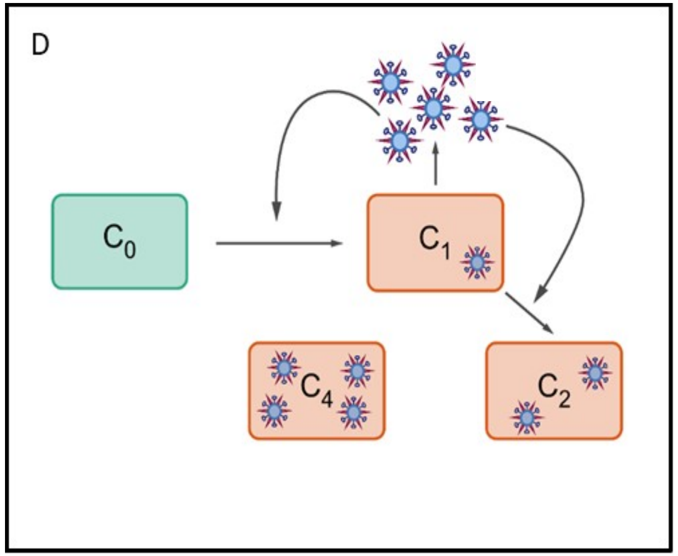


+ innate immune response



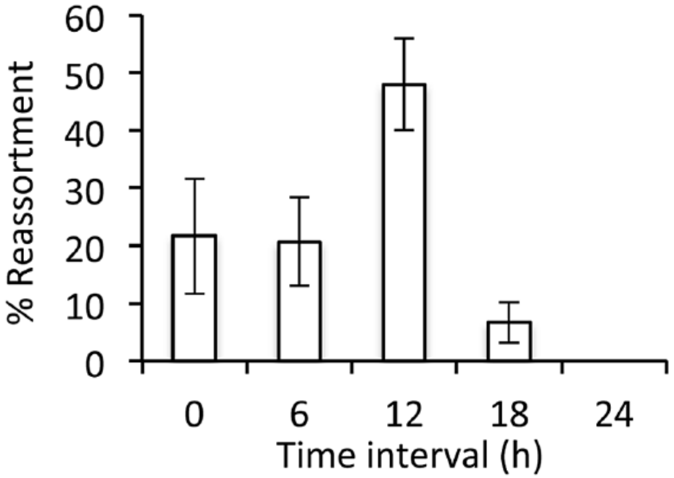
Current extensions to within-host macroparasite model framework

- Adoption of experimentally-derived functional forms
- Alternative, implicit incorporation of space
- Fitting to data involving multiple strains of virus where coinfection is critical

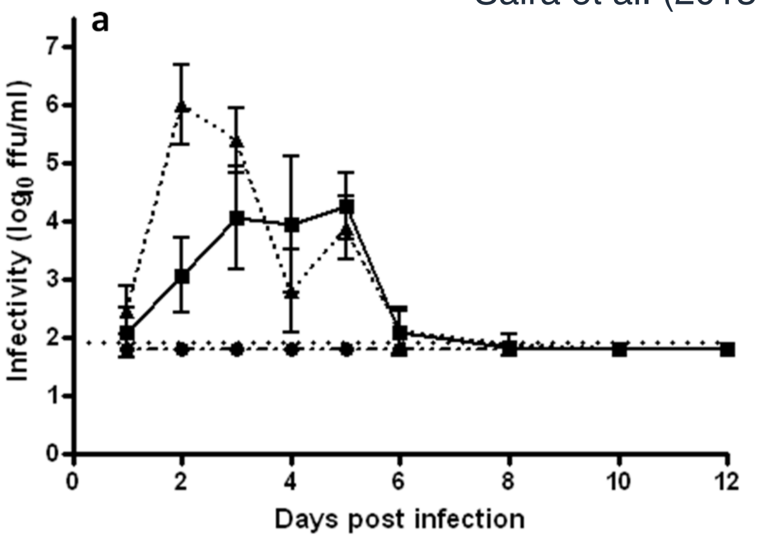


Molly Gallagher
Emory

Saira et al. (2013) *JVI*



Marshall et al. (2013) *PLoS Pathogens*



Dimmock et al. (2012) *PLoS One*

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