On the Importance of Spatial Structure in Within-Host Viral Dynamics Models

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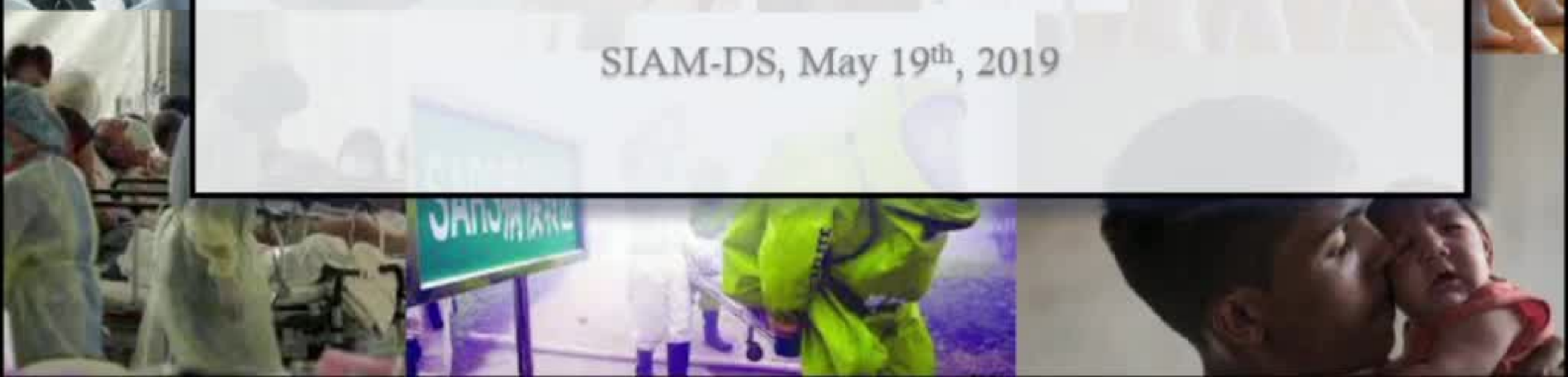
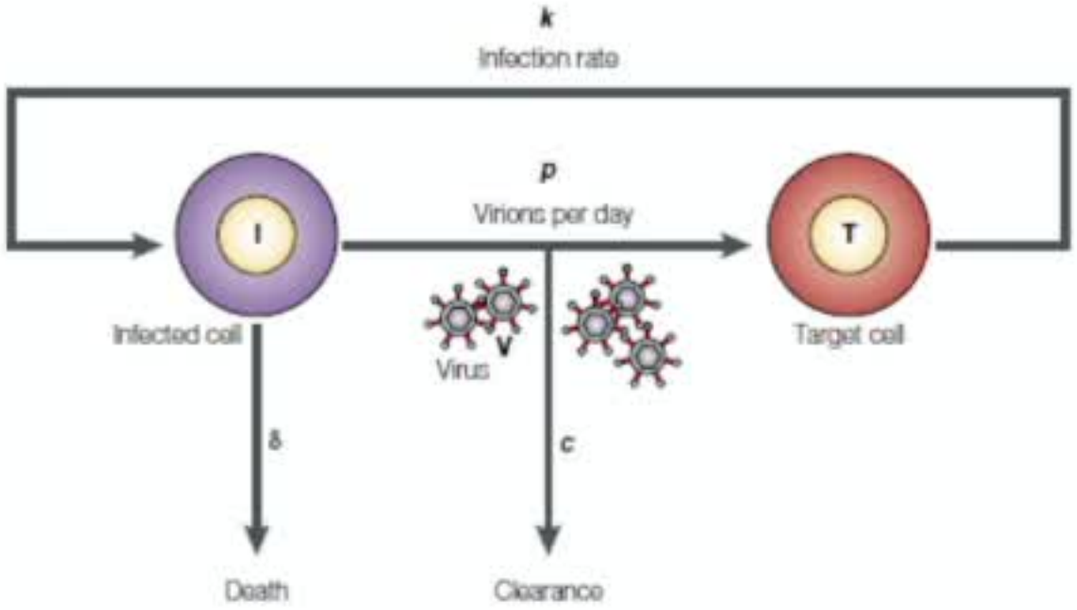
SIAM-DS, May 19th, 2019



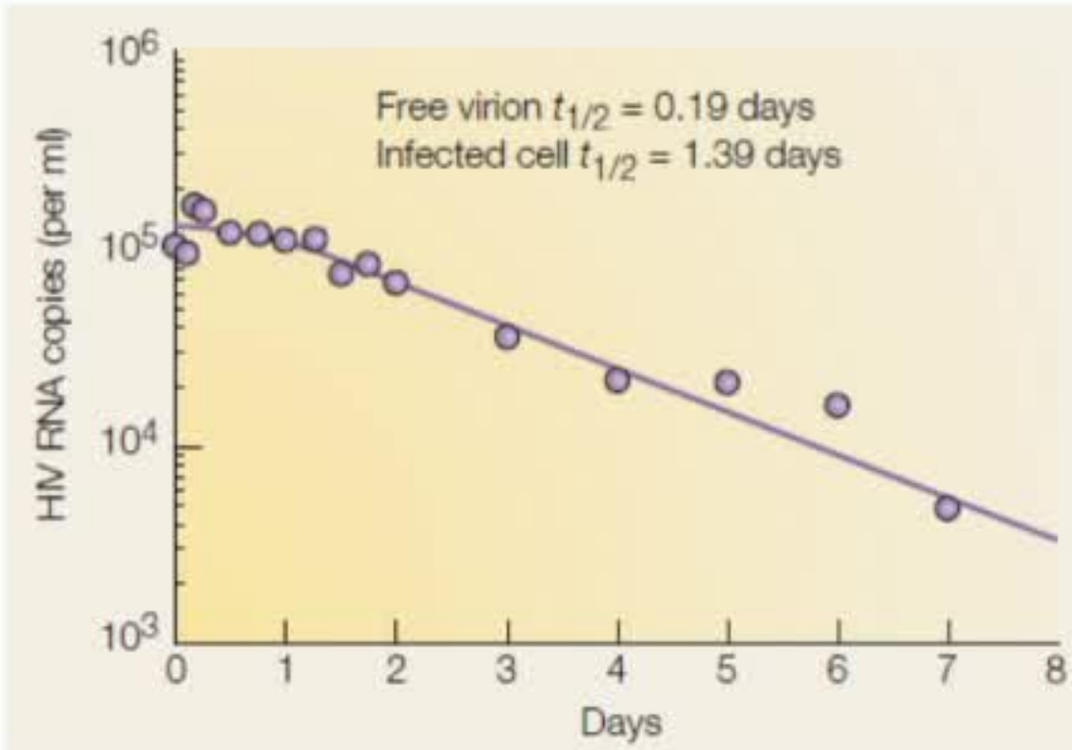
Models with a well-mixed assumption often explain clinical data extremely well

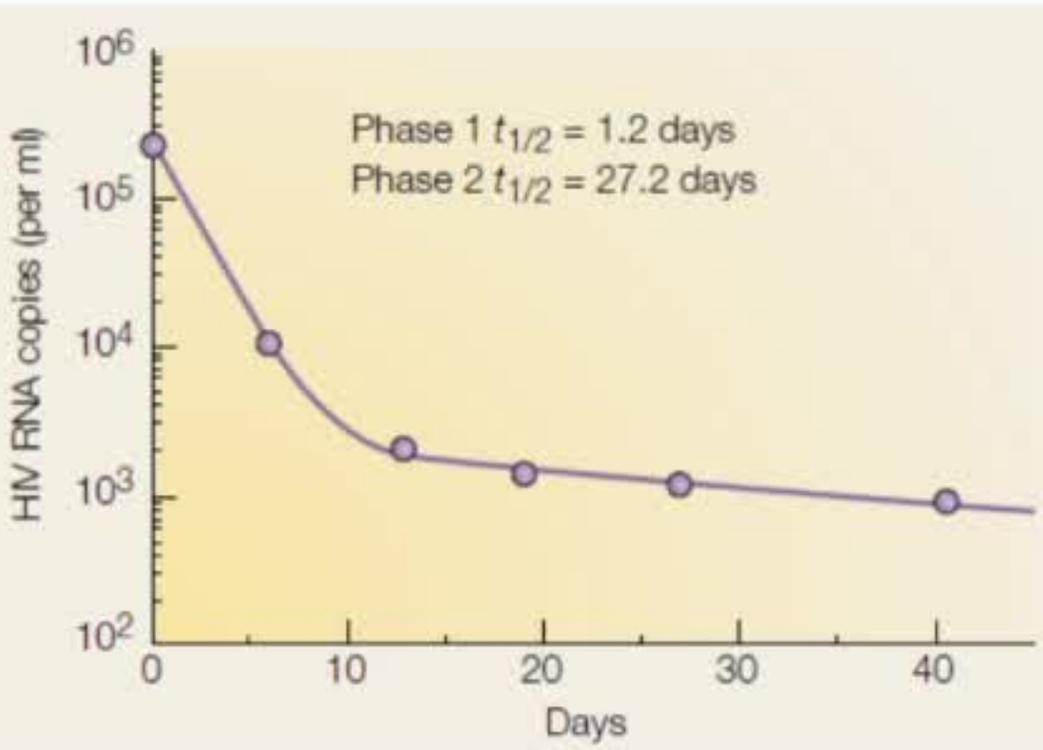


$$dT/dt = \lambda - dT - kVT$$

$$dI/dt = kVT - \delta I$$

$$dV/dt = pI - cV$$





Perelson (2002) Nat. Immuno. Rev.

Considering spatial structure is crucial to the understanding and prediction of the role of many biological processes

1. The frequency of co-infection/ the role of influenza semi-infectious particles.
2. The effectiveness of therapeutics, such as defective interfering particles.
3. The impact of the interferon response to virus infection (especially at the initial period of infection).

Ignoring spatial structure would lead to incorrect conclusions/predictions!

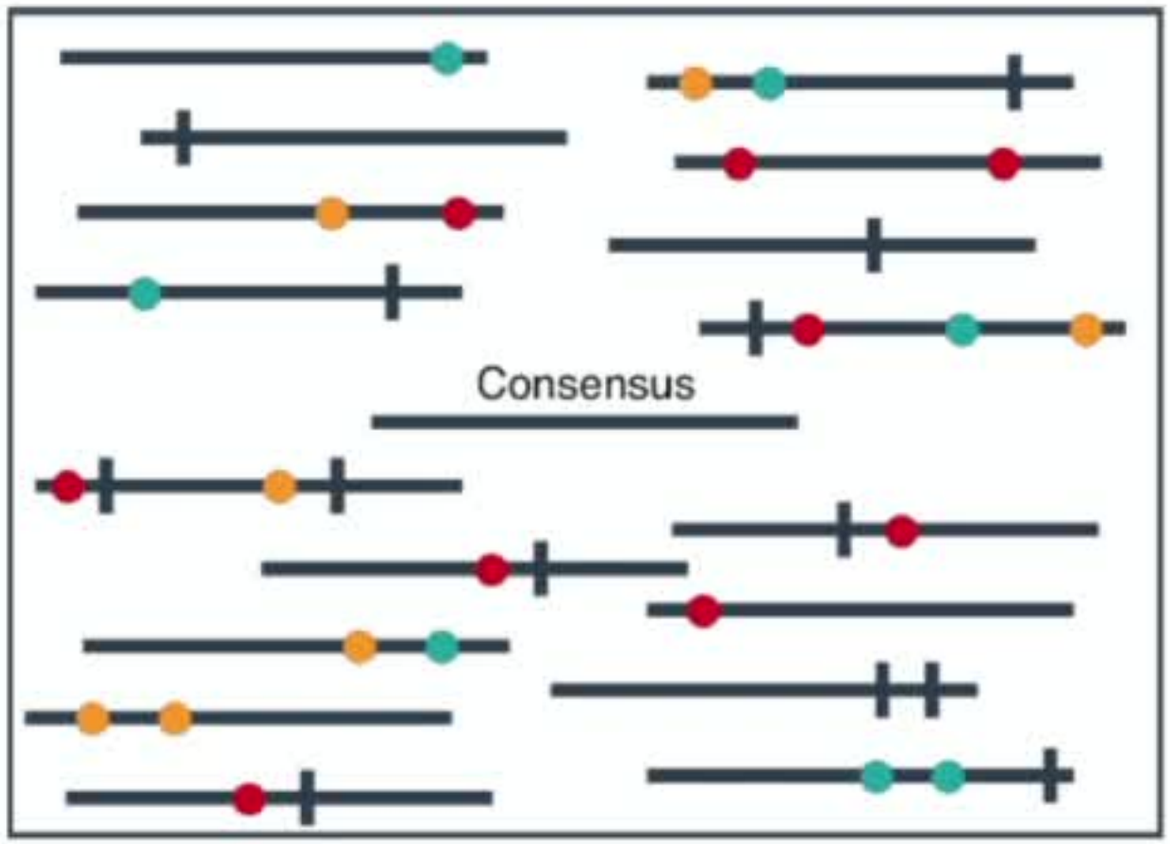
Understanding influenza co-infection dynamics and the role of semi-infectious particles (SIPs) and defective interfering particles (DIPs)

• • •

with Alex Farrell, Chris Brooke and Katia Koelle

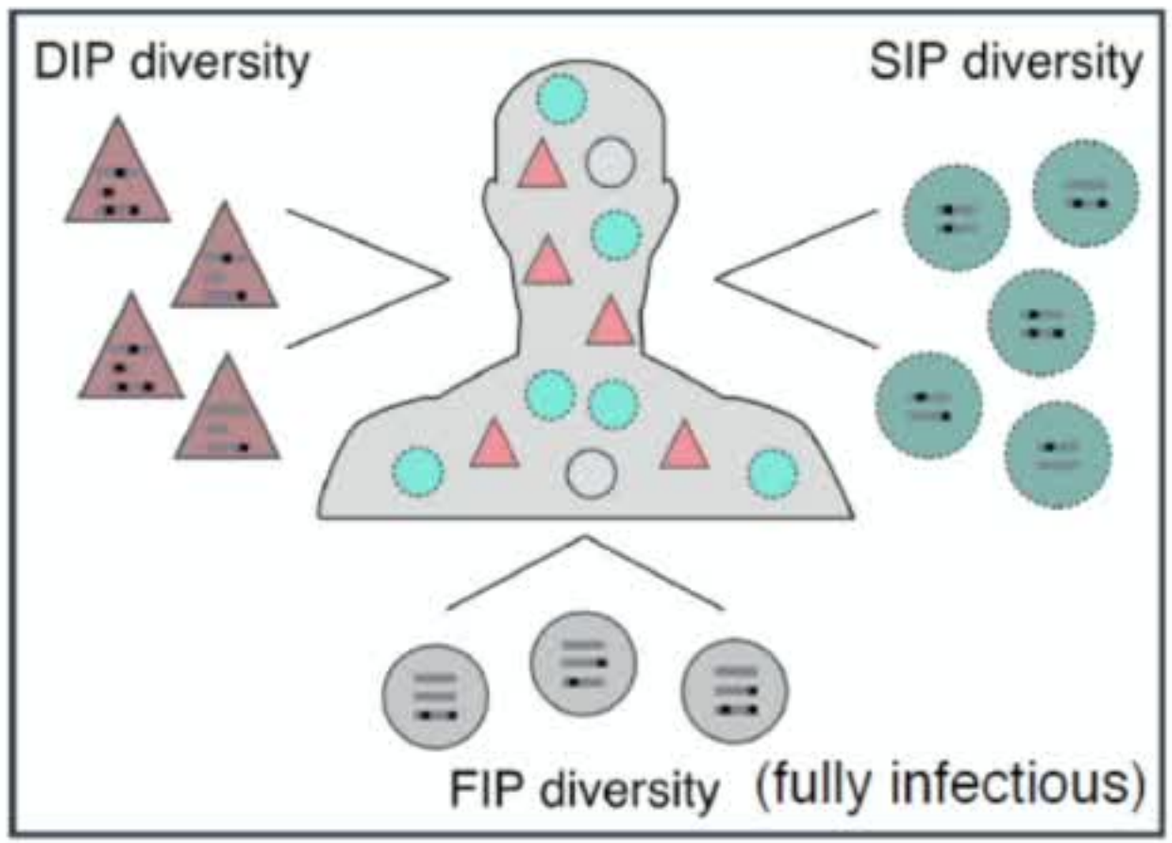
IAV diversity

Genetic Diversity



Sequence variation generated by the high mutation rate of the viral polymerase

Genomic Diversity

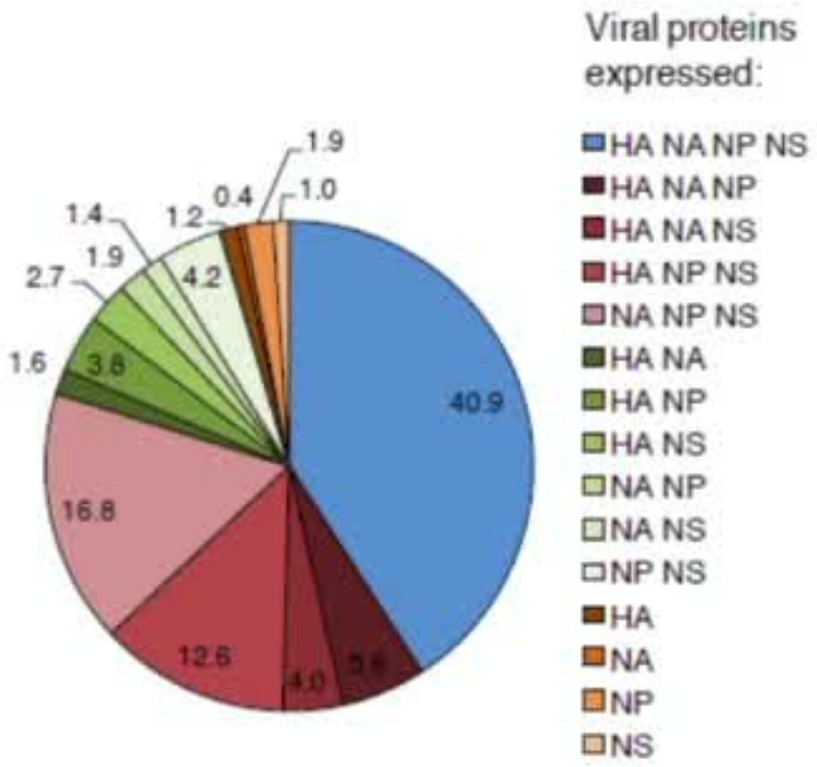


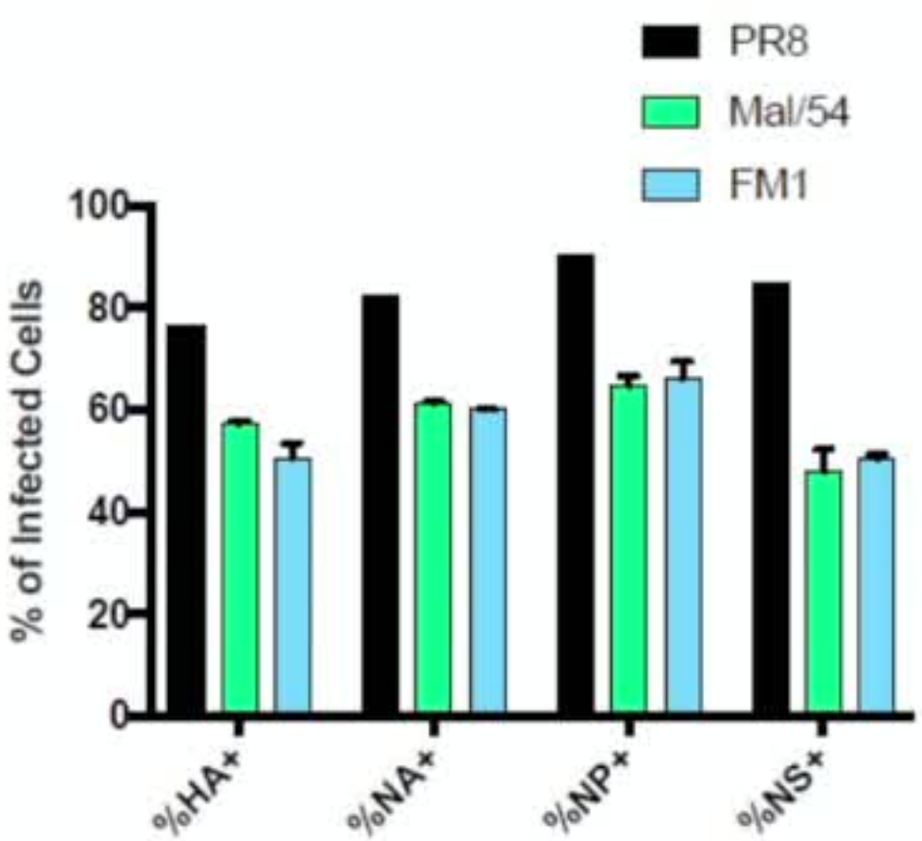
Variation in the genomic content and gene coding capabilities of individual virions

Adapted from Domingo et al. (2012) *MMBR*

Vast majority of IAV particles (70-99%) are "non-infectious"

Semi-infectious particles (SIPs) – virions that express a limited subset of essential viral genes



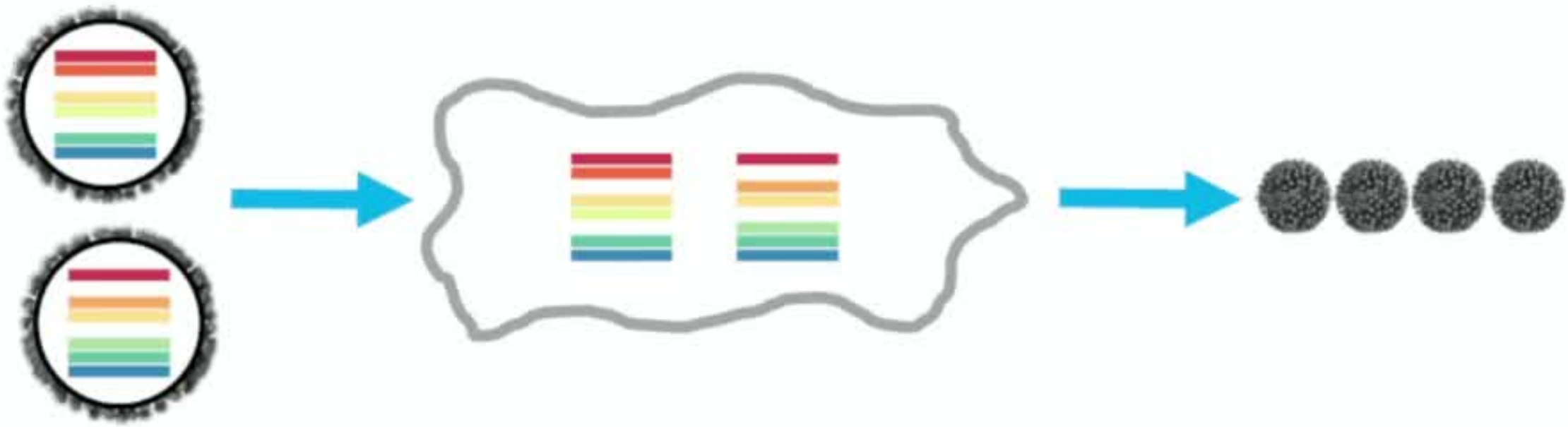


Brooke et al. (2013) *JVI*

Ways of generating a productive infection

I. Infection of a cell with a fully infectious particle (FIP)

II. Infection of a cell with multiple semi-infectious particles (SIPs)



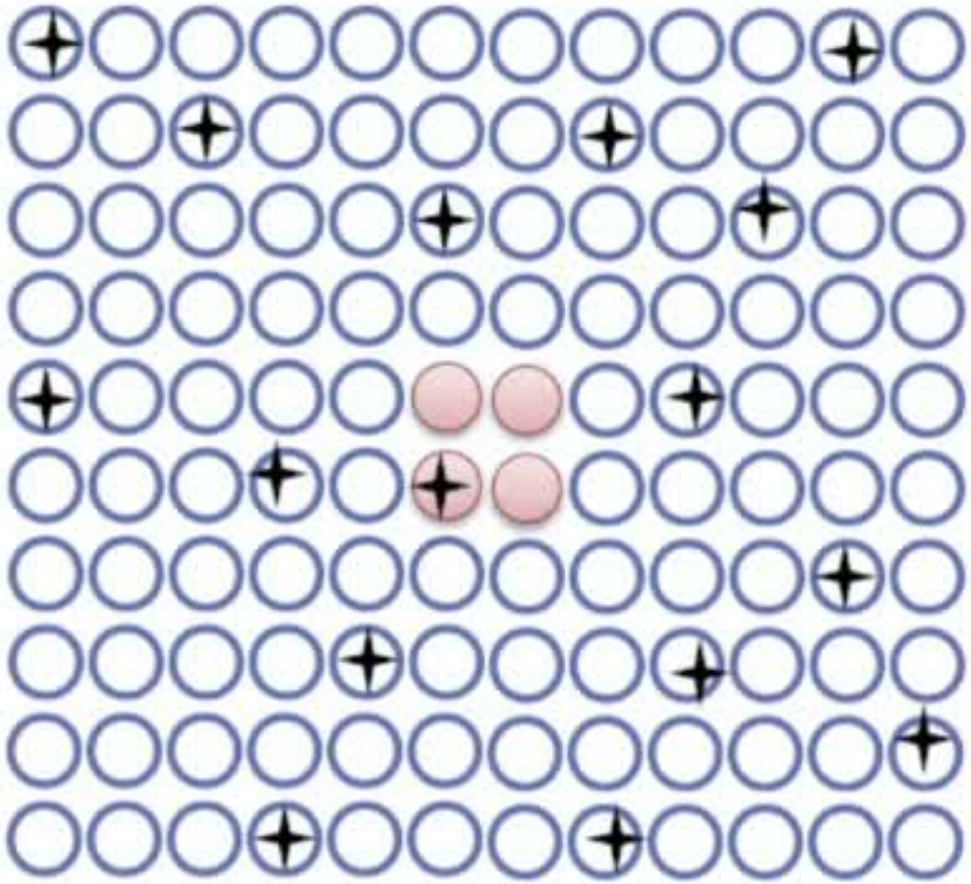
Cellular co-infection and viral complementation are critical for productive IAV infection

Questions

- To what extent SIPs contribute to viral load?
- What is the appropriate model to describe coinfection in a host?
- Is there an advantage/disadvantage in producing large fraction of SIPs?

Model assumptions

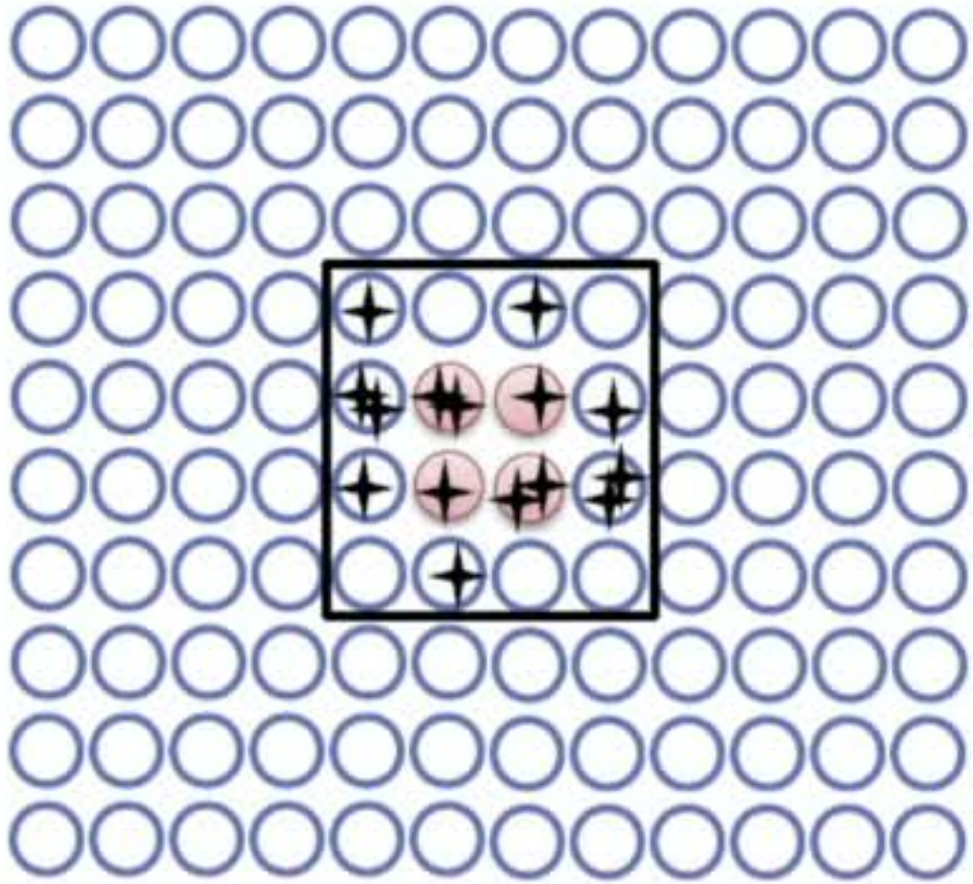
Homogeneous mixing – low frequency of coinfection



Infection in a host

Target cells Infected cells Virus

Target cell saturation – high frequency of coinfection

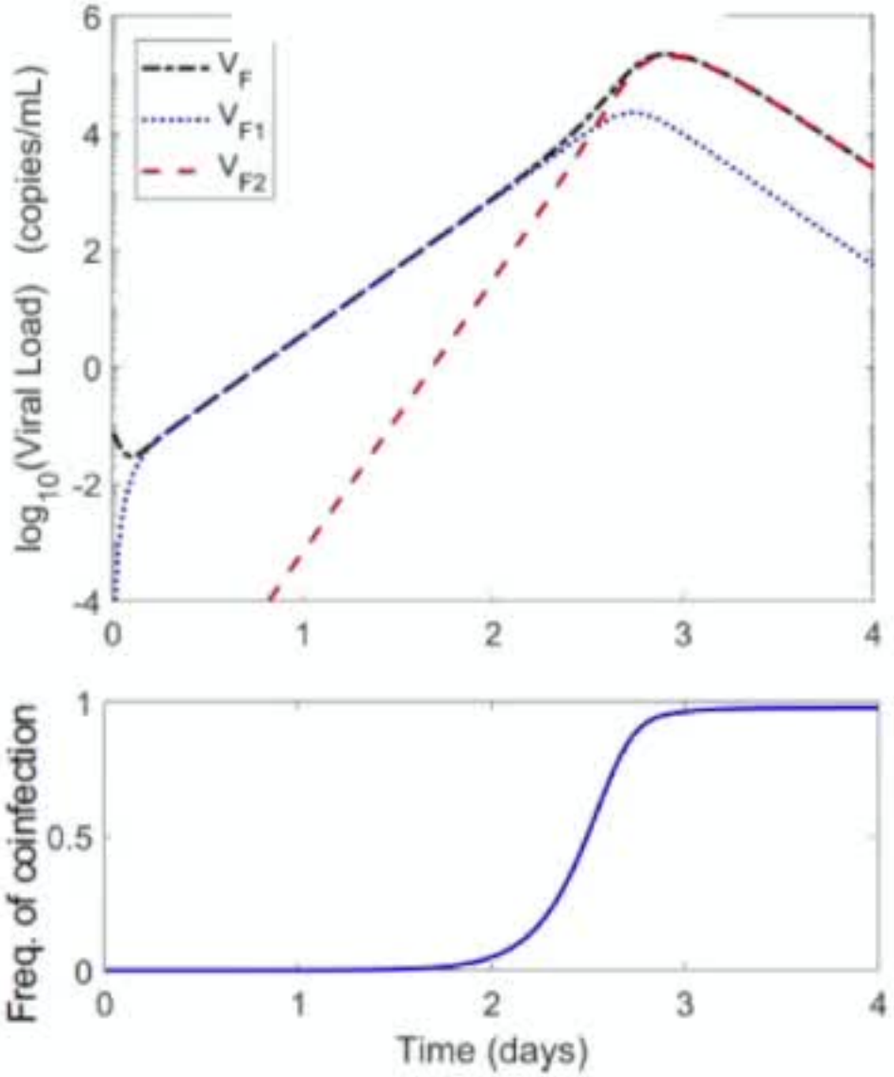


Infection in a host

Range of infection

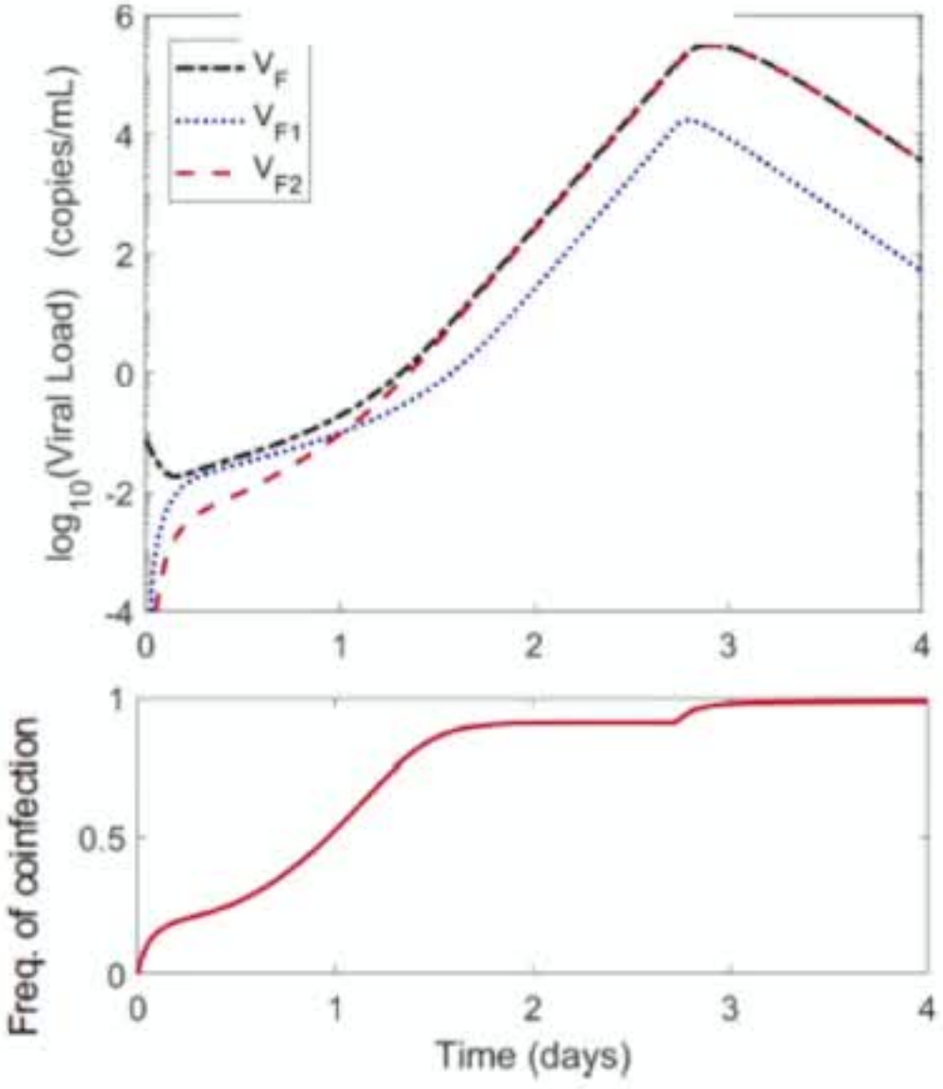
Model results

Homogeneous mixing – low frequency of coinfection



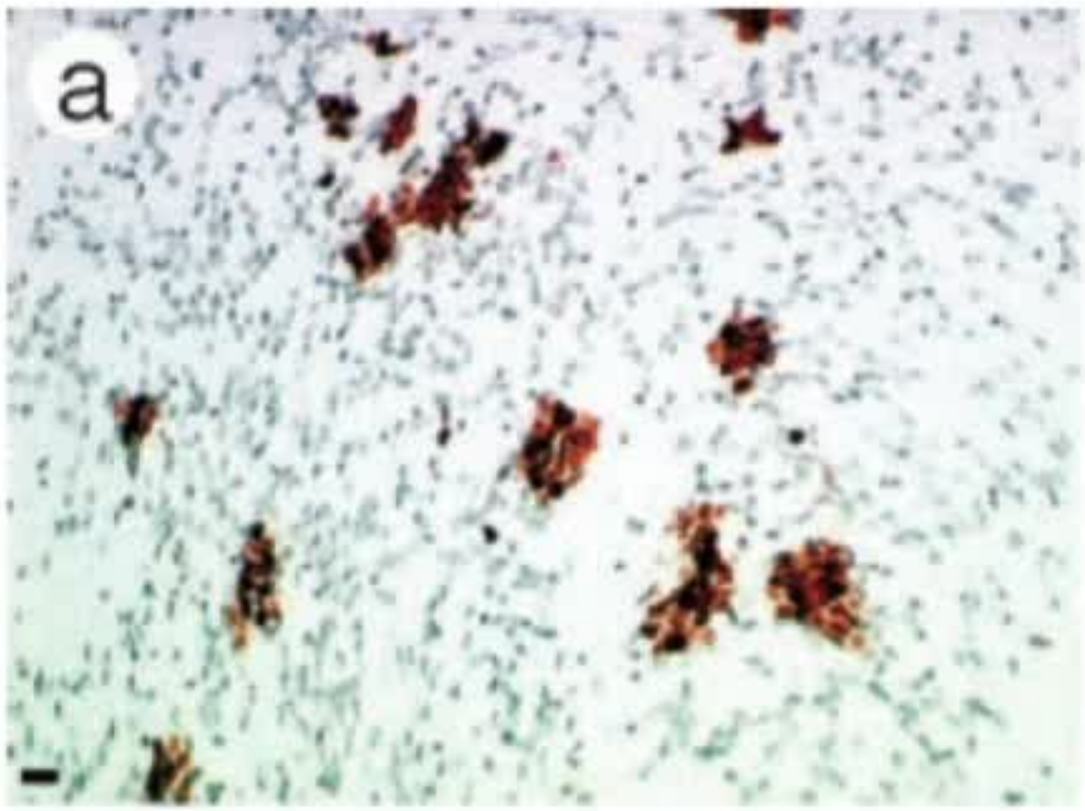
- Freq. of coinfection is low until viral peak
- Viral load is mostly driven by (10-30%) fully-infectious particles (FIPs).

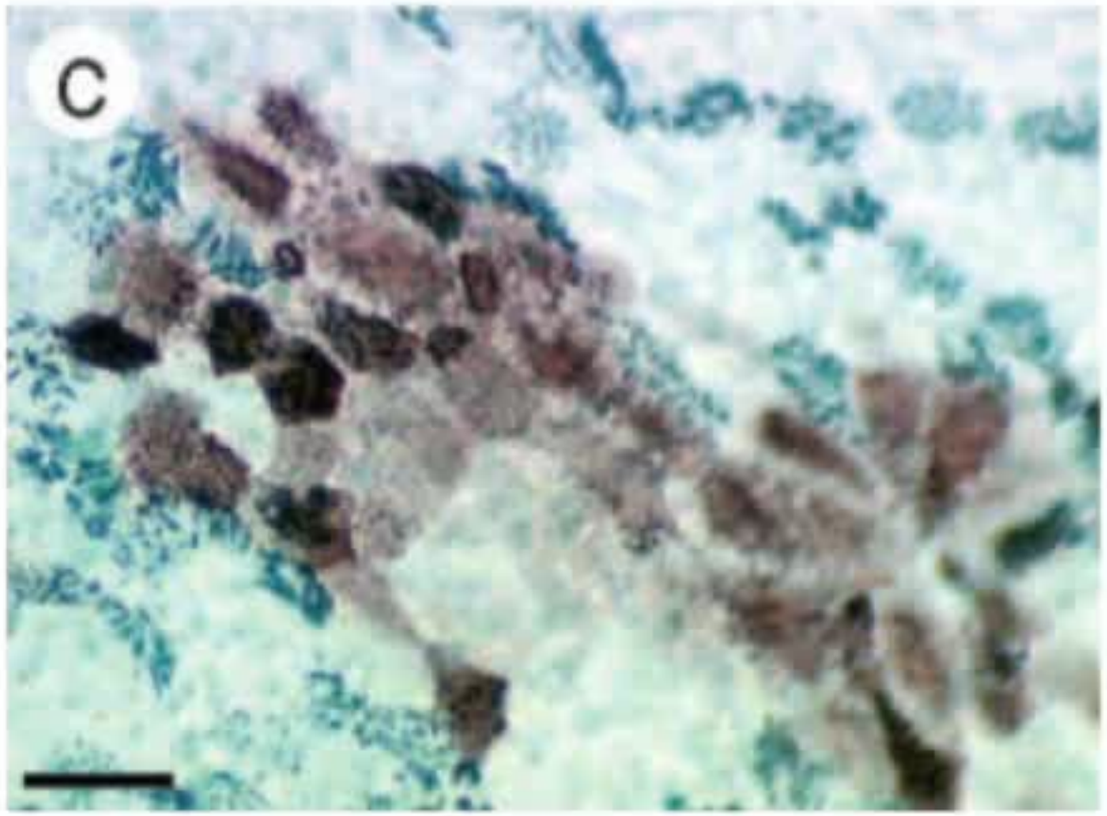
Target cell saturation – high frequency of coinfection



- Freq. of coinfection is high throughout the infection
- Viral load is mostly driven by (70-90%) semi-infectious particles (SIPs).

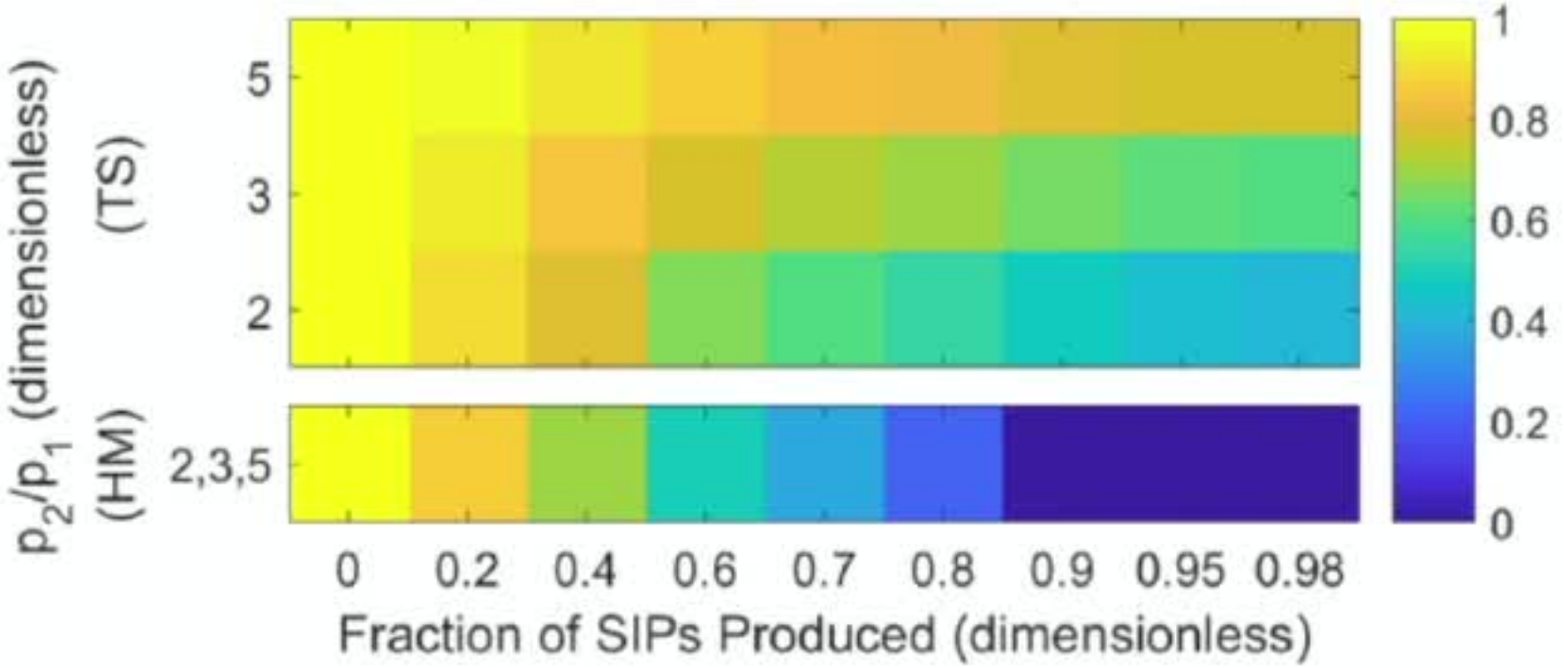
IAV spreads in a spatial manner



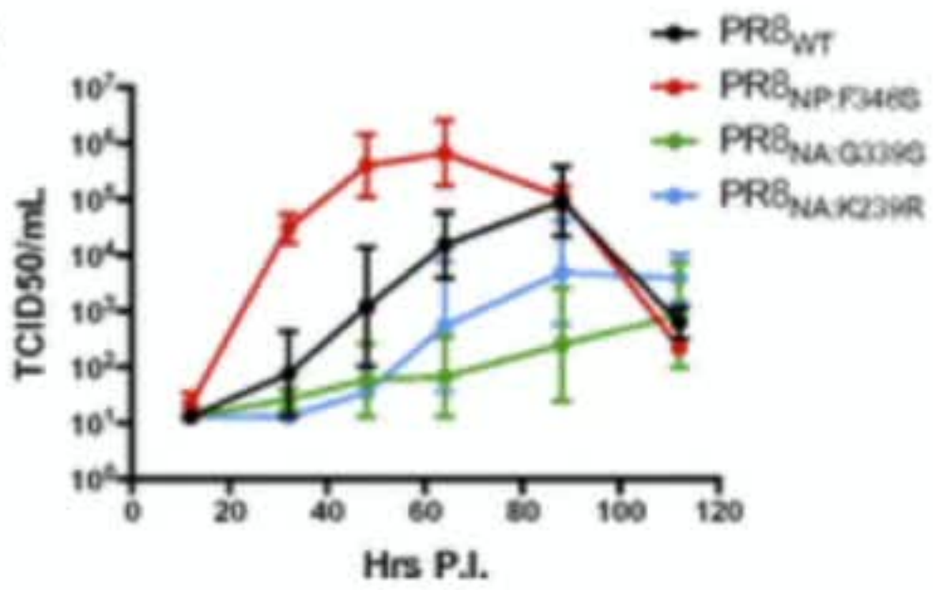


Matrosovich et al. (2004) *PNAS*

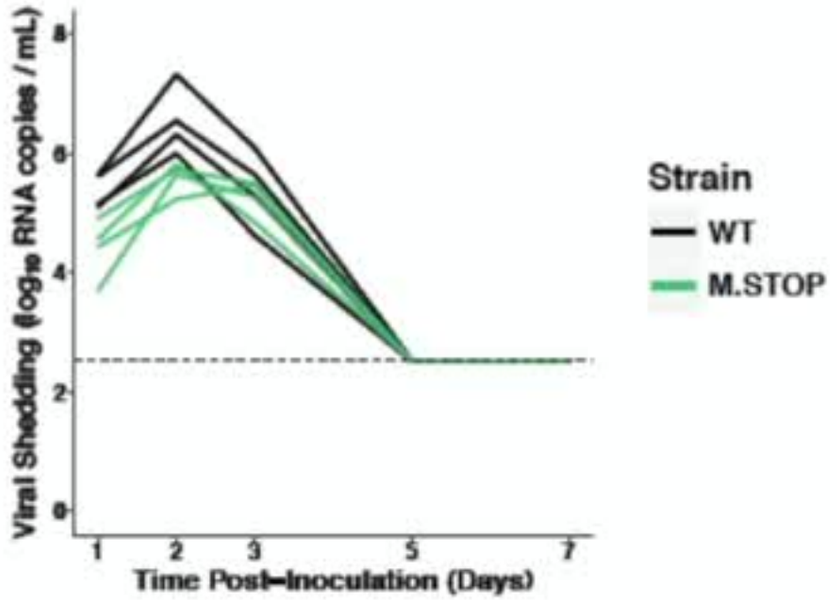
The model with a spatial structure predicts that large SIP production can have a minimal impact on viral fitness



D

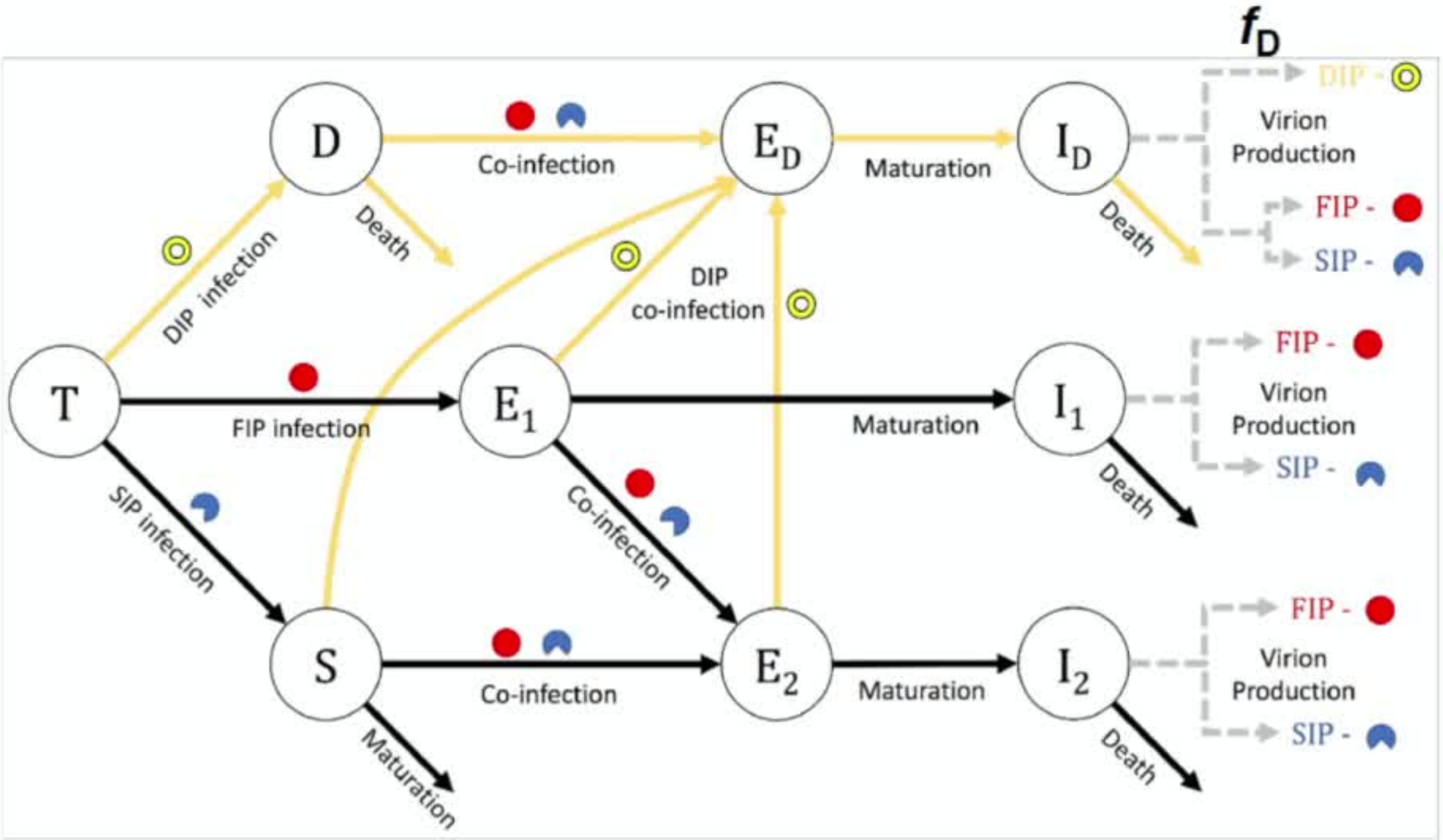


Brooke et al. (2014) PNAS



Jacobs et al. (2019) BioRxiv

A within-host model incorporating FIPs, SIPs and DIPs

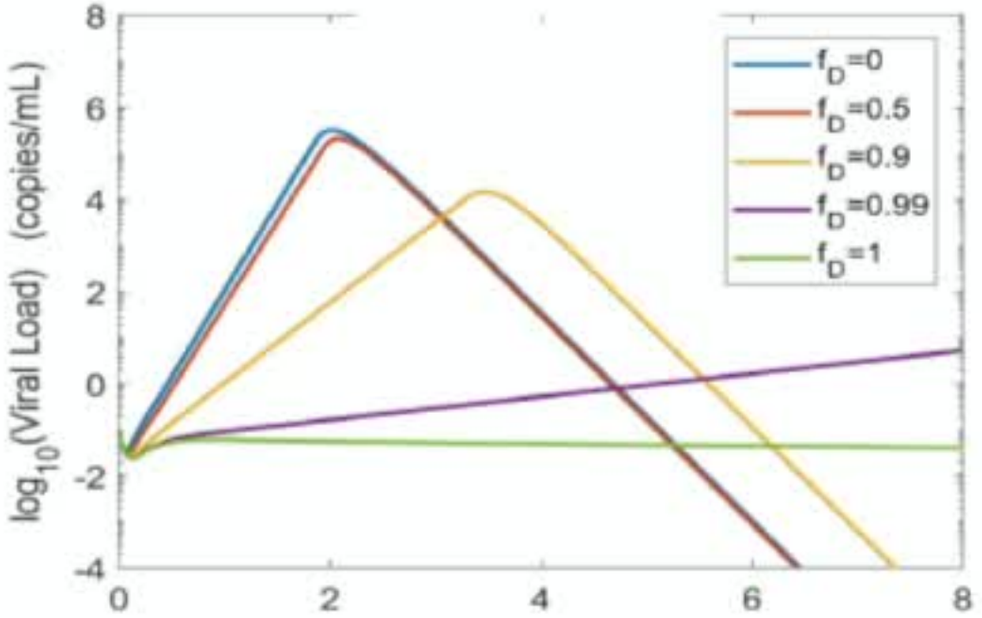


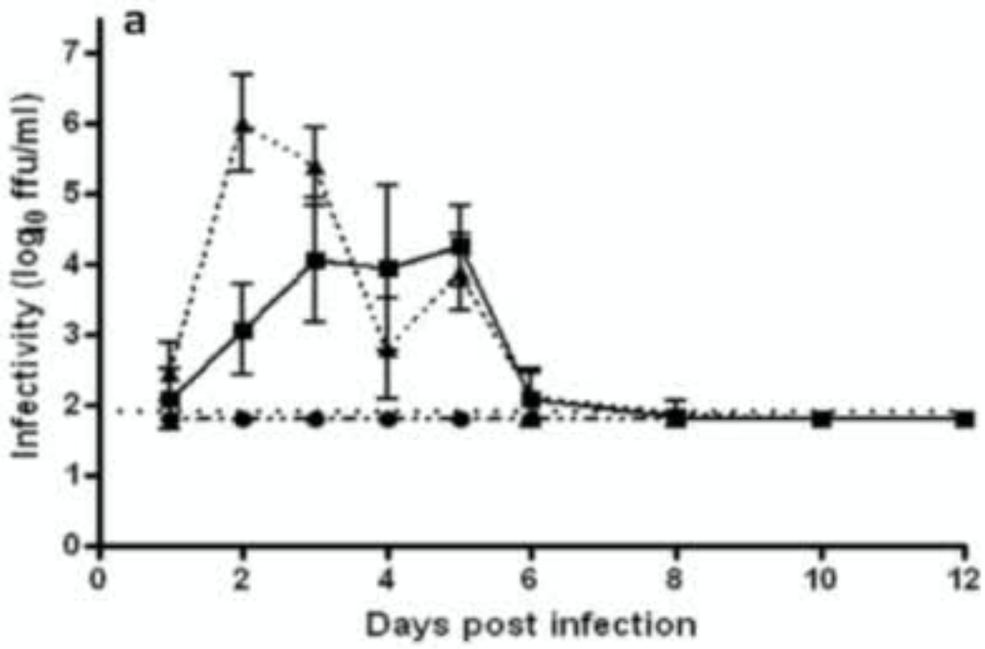
D: DIP infected cells
T: Target cells
S: SIP infected cells

E_D: DIP co-infected cells in the eclipse phase
E_1: FIP infected cells in the eclipse phase
E_2: co-infected cells in the eclipse phase

I_D: productively DIP co-infected cells
I_1: productively FIP infected cells
I_2: productively co-infected cells

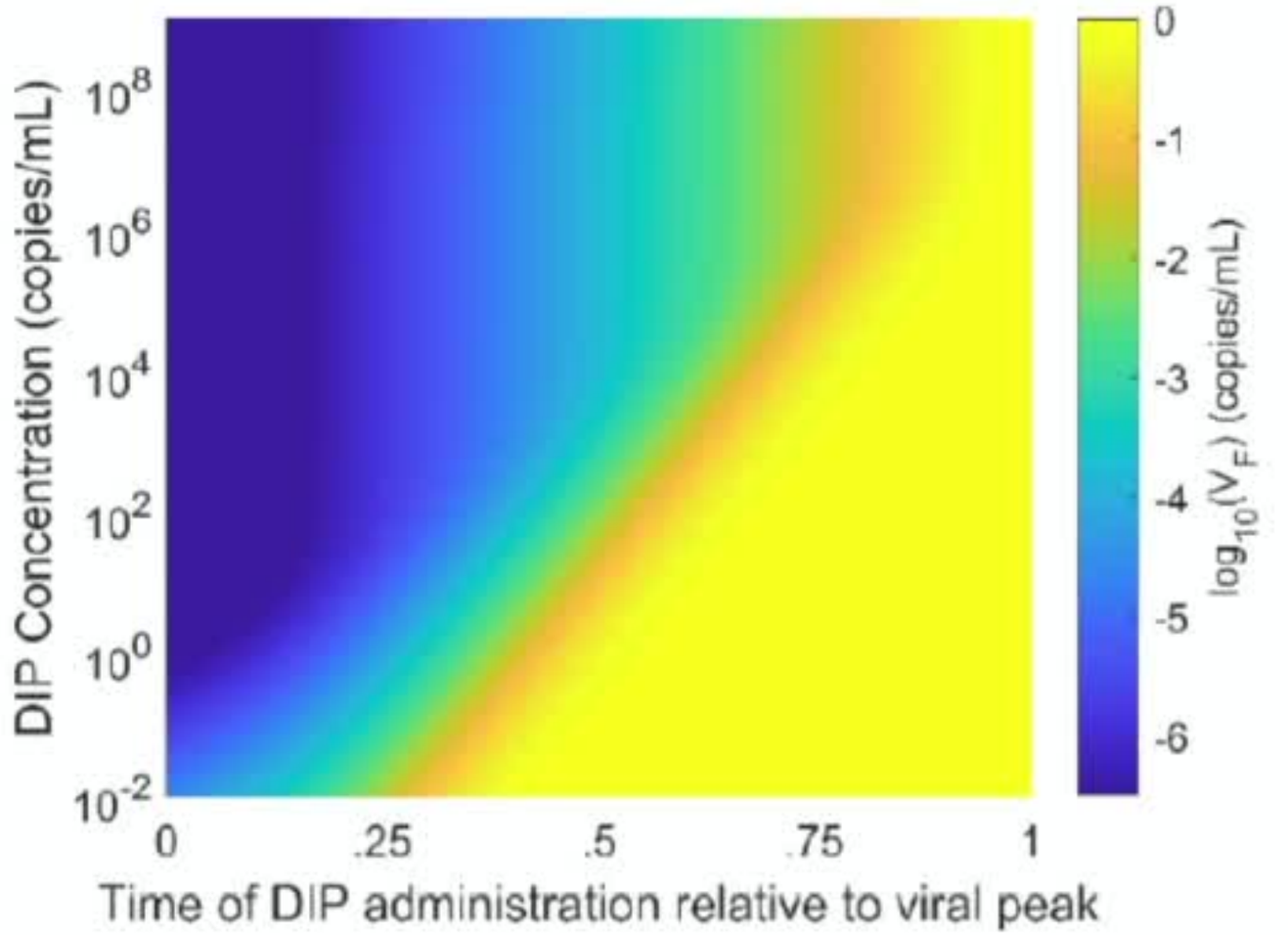
Model predictions consistent with published experiments in ferrets





Dimmock et al. (2012) PLoS One

There exists only a narrow window period before viral peak for effective treatment of acute infections using DIPs.



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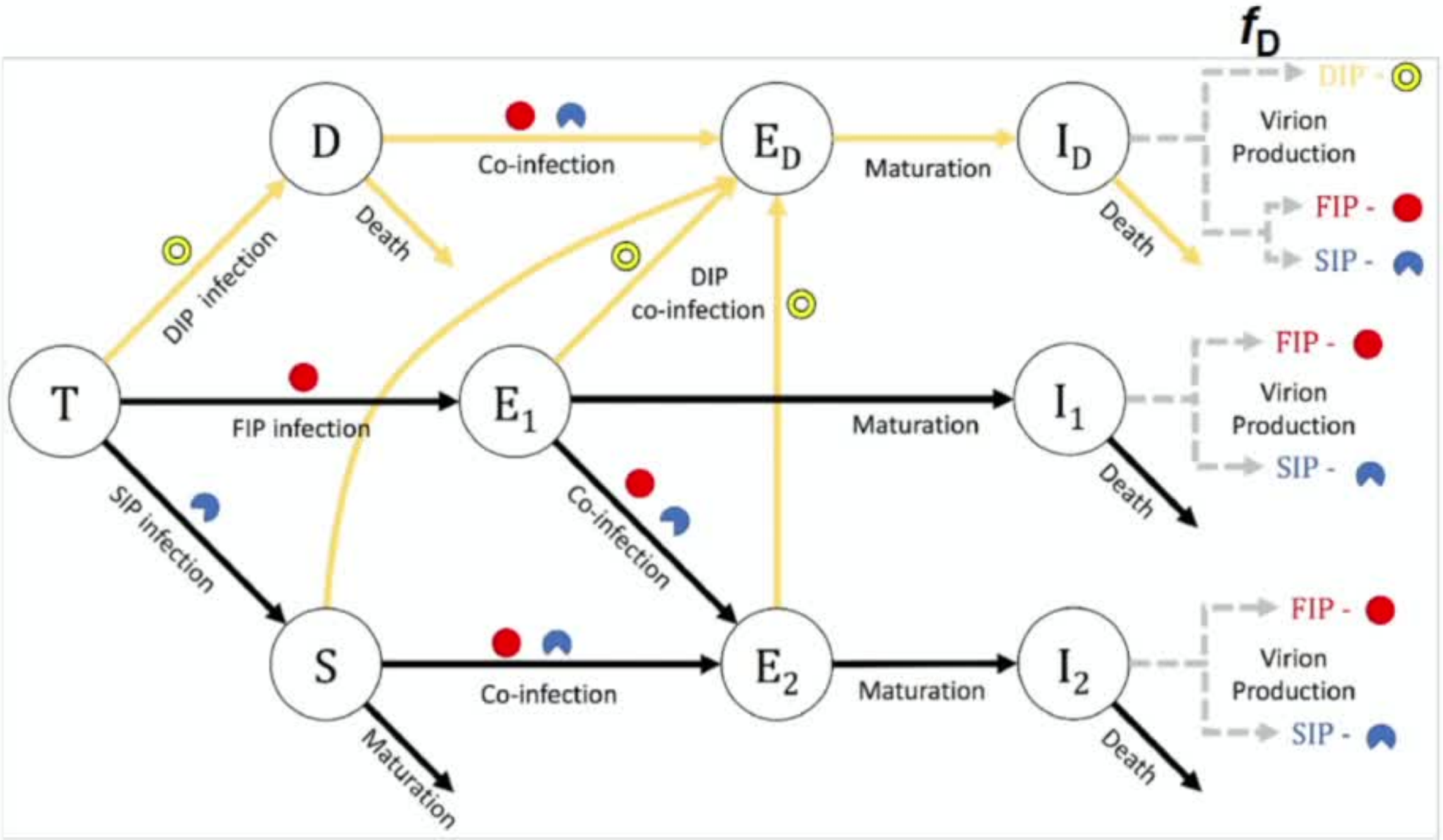

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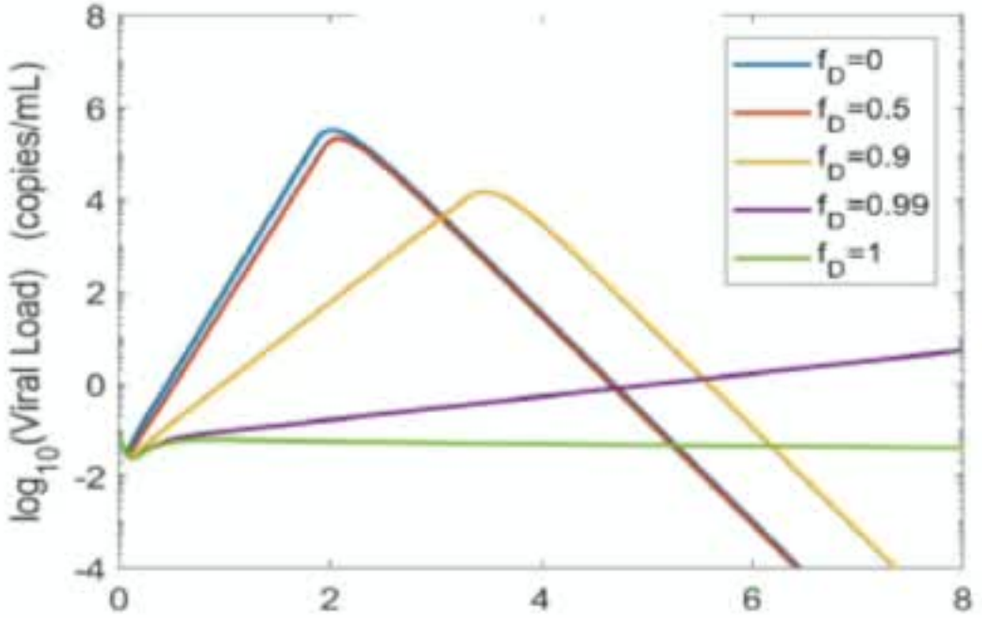

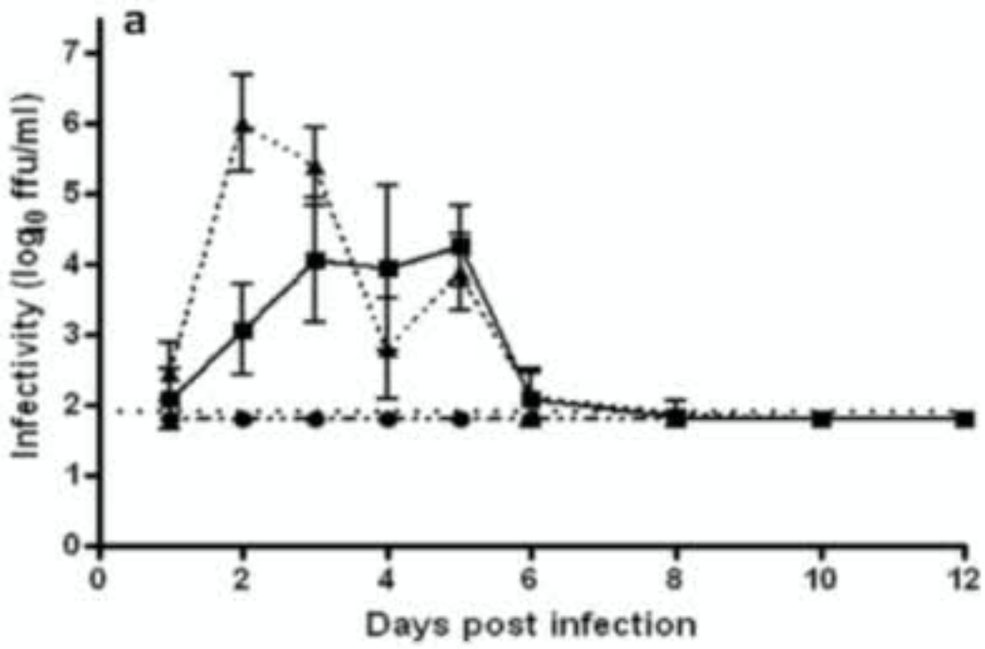

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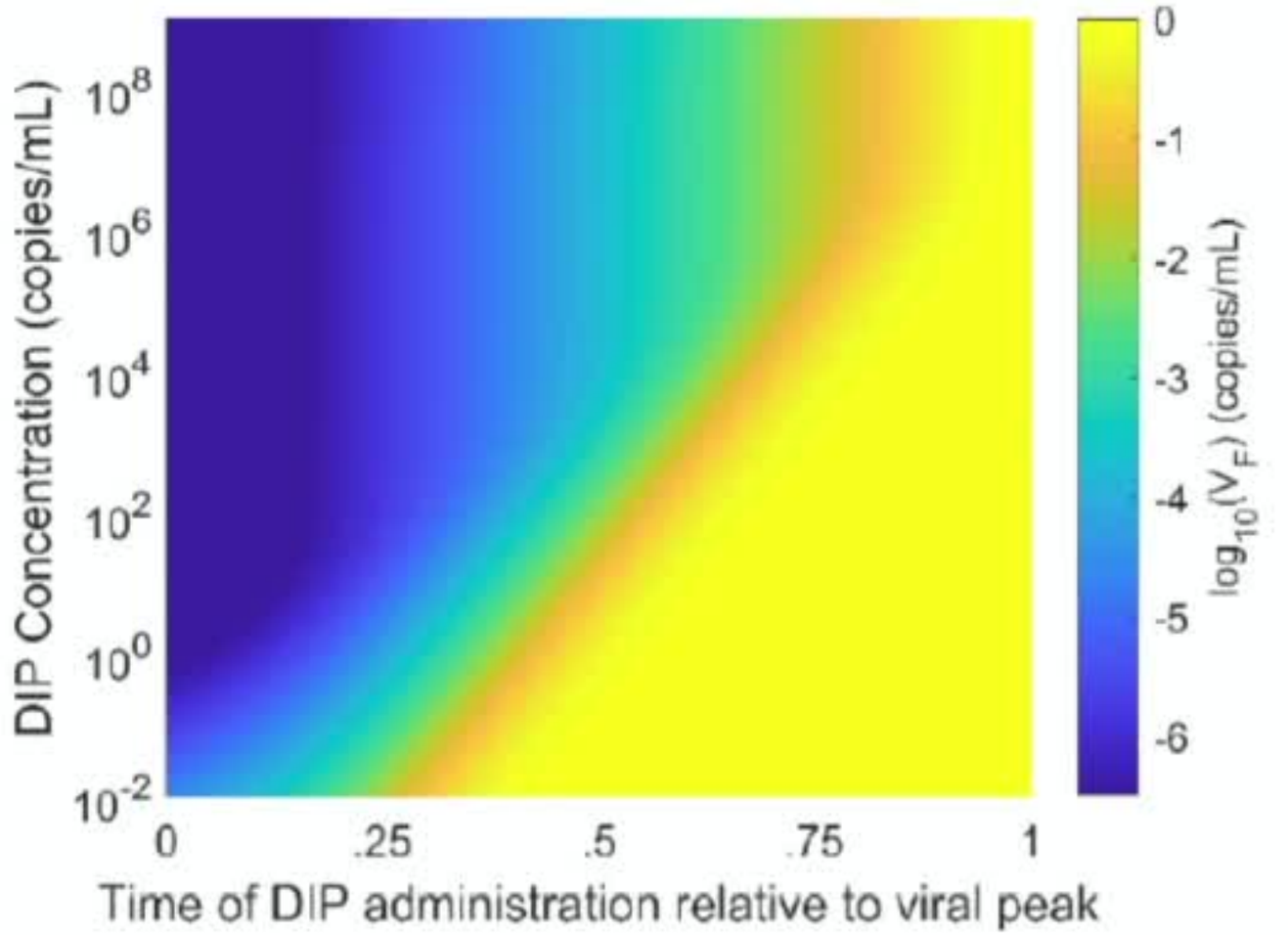

Considering spatial structure is crucial to the understanding and prediction of the role of many biological processes

1. The role of co-infection and semi-infectious particles (SIPs) during IAV infection.
2. The effectiveness of therapeutics, such as DIPs.

viruses

MDPI

Review

Causes and Consequences of Spatial Within-Host Viral Spread

Molly E. Gallagher [1], Christopher B. Brooke [2,3], Ruian Ke [4] and Katia Koelle [1,*]

Acknowledgement

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Infectious diseases infection involves spatial and temporal dynamics of entry, replication, spread and evolution of pathogens. These dynamics occur at spatial and temporal scales and at multiple levels of biological organization, i.e. the cellular level and the in-host level. Mathematical modeling has been critical to quantify the rates at which these processes occur, the role of immune responses and make precise predictions of the efficacy and the impact of therapeutics. This special issue collects recent advances of a broad range of mathematical/statistical modeling studies of infection disease dynamics, immune responses and/or the impact therapeutics.

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