

Statistical inference for interactions among viruses



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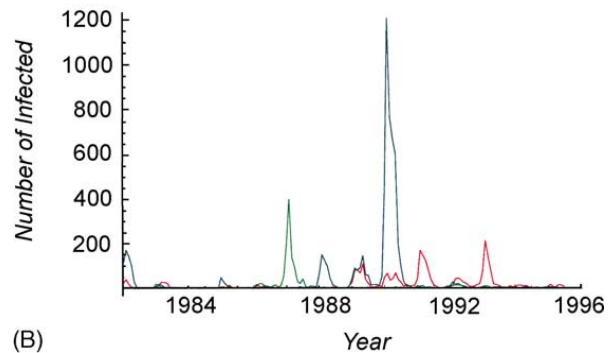
Pathogen interactions

The effect of cross-immunity and seasonal forcing in a multi-strain epidemic model

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Received 26 July 2001; received in revised form 13 February 2002; accepted 18 February 2002
Communicated by Y. Kuramoto

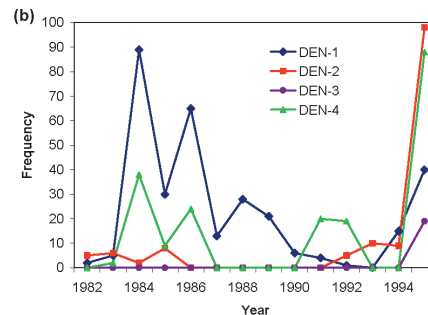


The effect of antibody-dependent enhancement on the transmission dynamics and persistence of multiple-strain pathogens

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Communicated by David Cox, Nuffield College, University of Oxford, Oxford, United Kingdom, October 21, 1998 (received for review February 2, 1998)

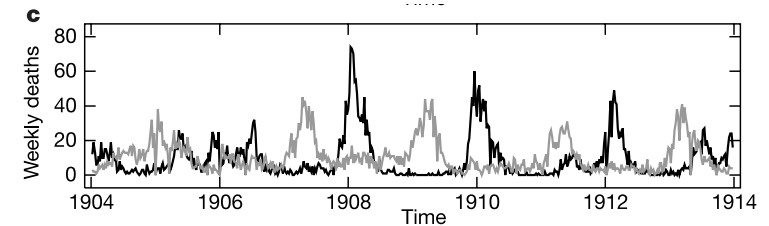


Ecological interference between fatal diseases

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Virus-Virus interactions

Virus-virus interactions grouped into three general categories:

1) Direct interactions

- Nucleic acids/proteins of one virus physically interact with genes/gene products of coinfecting virus
- May involve helper viruses, pseudotype viruses, superinfection exclusion, genomic recombination, embedded viruses, and heterologous transactivation

2) Environmental interactions

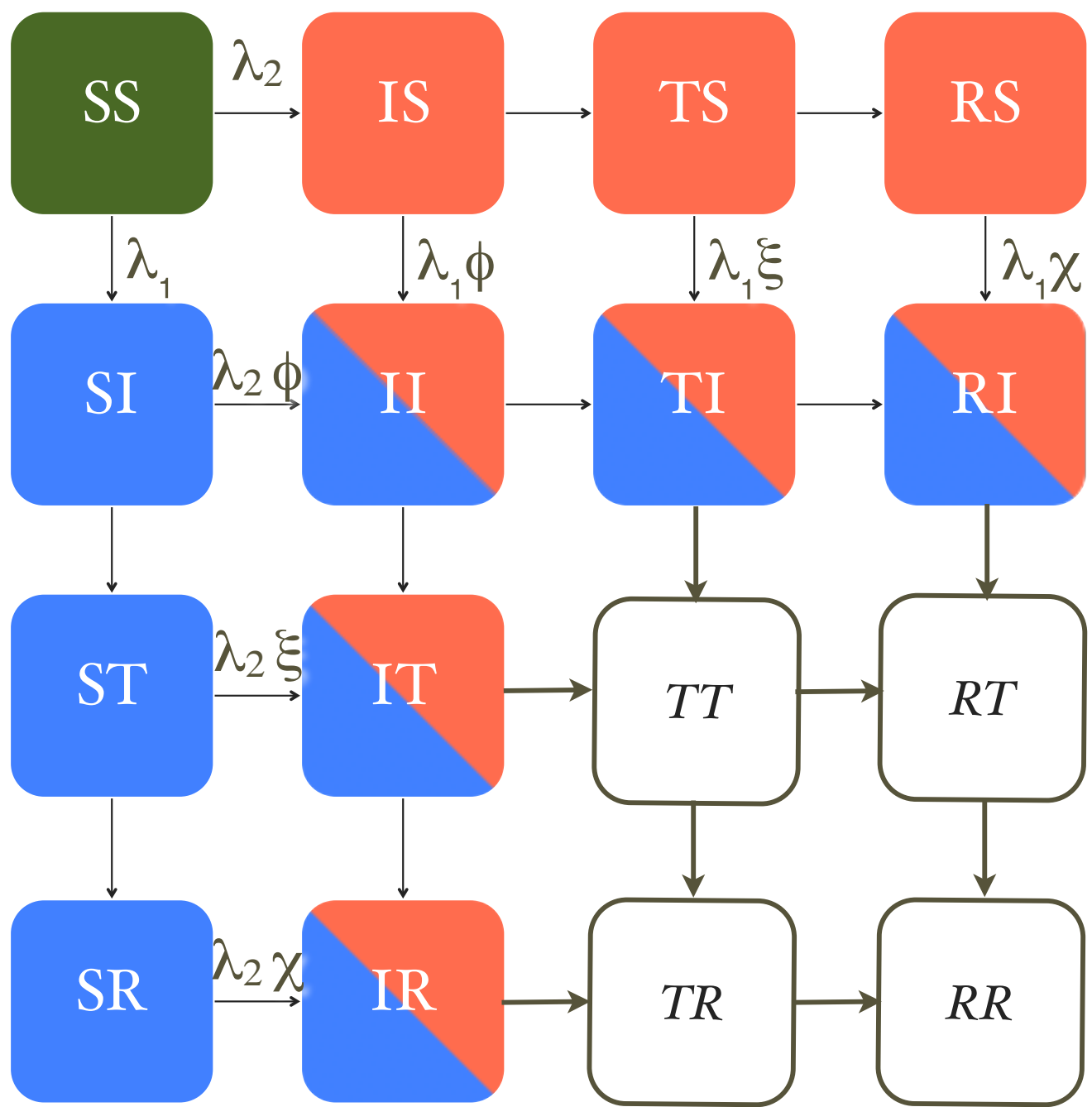
- Viral infection may change pathogenic conditions in host
- May involve indirect transactivation of genes, breakdown of host physical barriers against infection, altered receptor expression, heterologous activation of antiviral pro-drugs, and modification of the interferon-induced antiviral state

3) Immune effects

- only in host species with an adaptive immune system
- altering activation state of cellular components of immune system, induction of autoimmune responses that cross-react with viral antigens, antibody-dependent enhancement of subsequent viral infections, re-shaping T cell memory repertoire. Immunological interactions can occur between viral infections that are completely separated in time

Virus 2

Virus I



ϕ, ξ short-term
 χ permanent

Inference

- Assume $Y(t)$ is observed data for pair of strains:
 - $\{y_1(t), y_2(t), \dots, y_m(t)\}$ for $t = 1, 2, \dots, n$
- System state given by $X(t)$
- Observation model: $f_\theta(Y(t) | X(t))$
- f_θ assumed to be poisson

$$\begin{aligned} L(\theta) &= f(Y(1), Y(2), \dots, Y(n) | \theta) \\ &= \prod_{t=1}^n f_\theta(Y(t) | Y(t-1), Y(t-2), \dots, Y(t)) \\ &= \prod_{t=1}^n L_t(\theta) \end{aligned}$$

$$\log(L(\theta)) = \sum_{j=1}^n \log(L_t(\theta))$$

Our Protocol

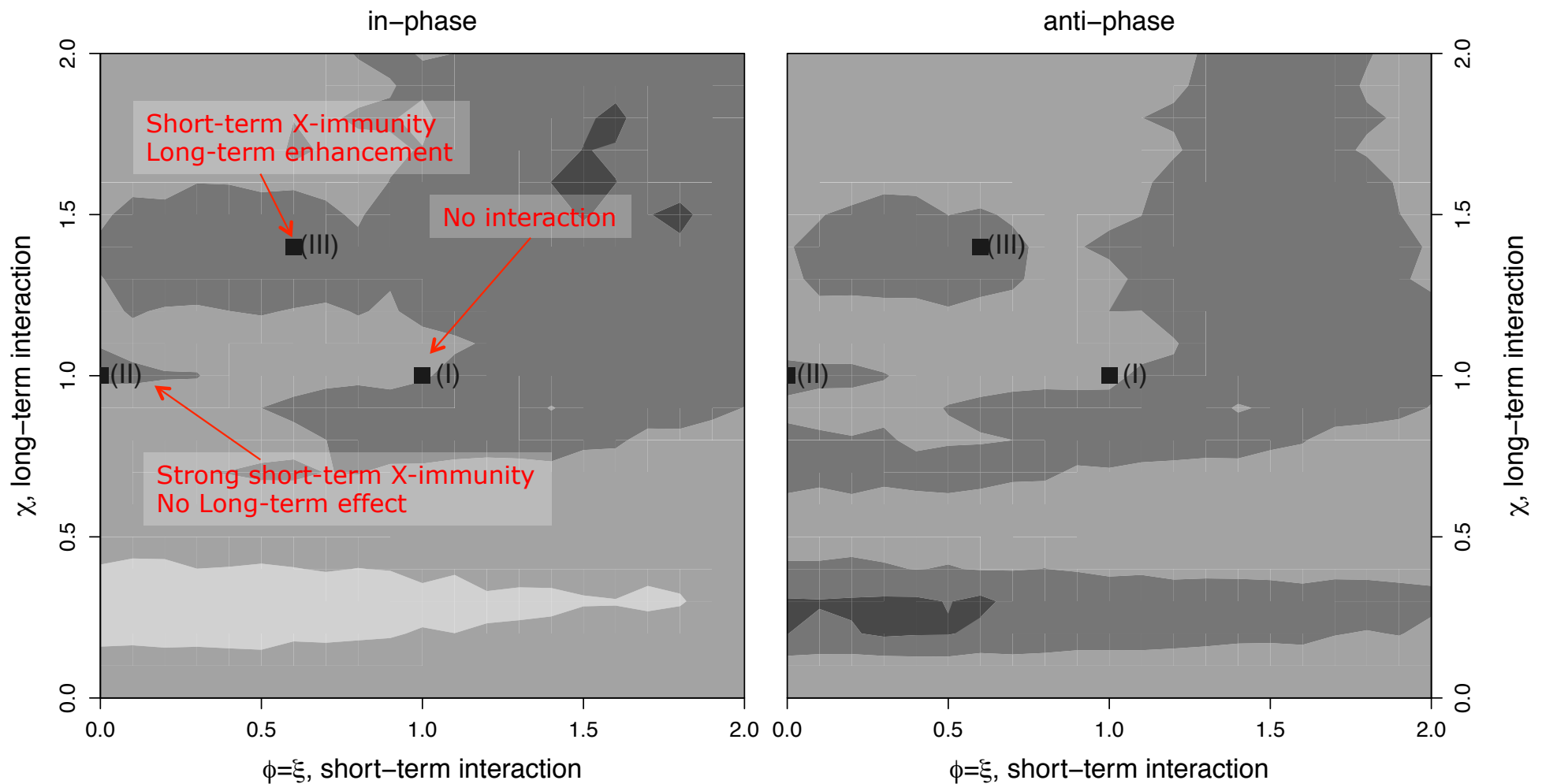
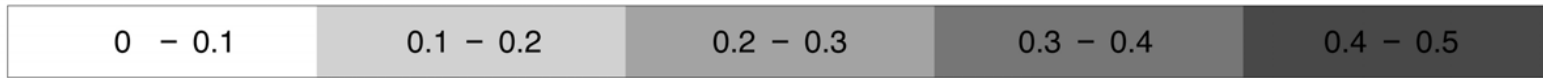
- For any combination of parameters, we generate 40 years of monthly strain-specific incidence data
- True number of new infections are assumed to be sampled according to a Poisson distribution, with reporting fidelity ρ
- For each simulated data set, we compute profile likelihoods over parameters of interest
- Sequential Monte Carlo algorithm to calculate likelihood (using 30,000 particles)
- 5 replicate SMC calculation per parameter combination

Our Protocol

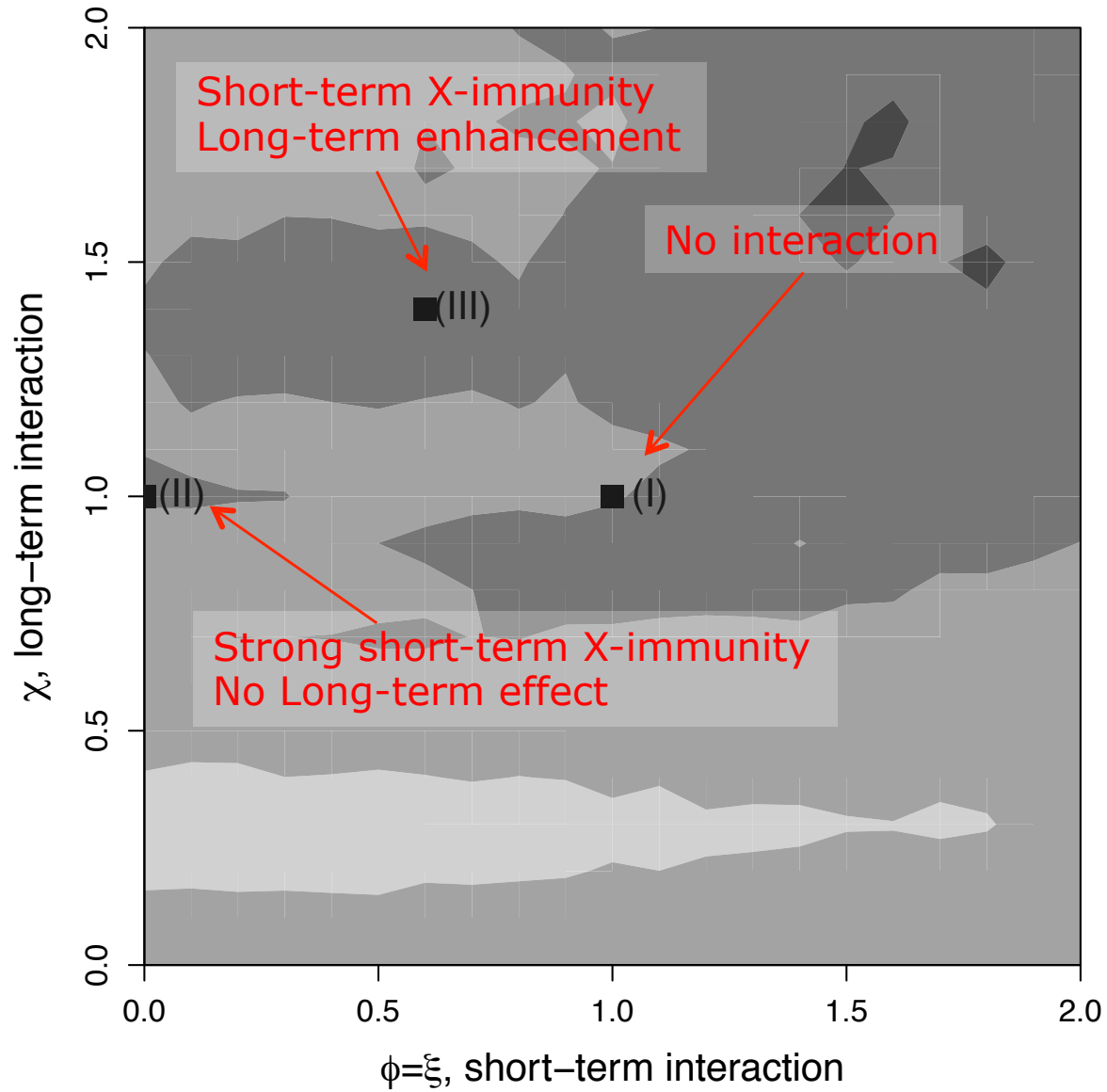
- Assume fix parameter set
- Strain-specific $R_0 \sim 2.7$

Parameter	Description	Range
N	Host population size	10 million
μ	<i>Per capita</i> host birth/mortality rate	0.02 per year
$1/\gamma_i$	Average infectious period	2 weeks
$1/\delta_i$	Average convalescent period	0.1 years
β_i	Transmission rate	70 per year
ϕ_i	Interaction during infectious period	0 – 2
ξ_i	Interaction during convalescent period	0 – 2
χ_i	Interaction during recovered period	0 – 2
ω_i	Force of infection due to immigration	10^{-7}
η	Std. deviation of the gamma-distributed white noise (dW/dt)	$0.01\sqrt{\text{year}}$
ρ	Reporting rate	1

Phase association

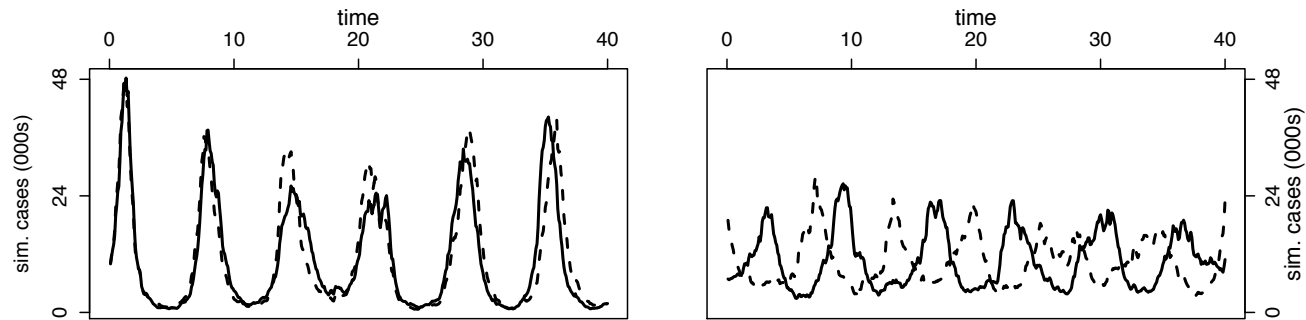


3 Scenarios

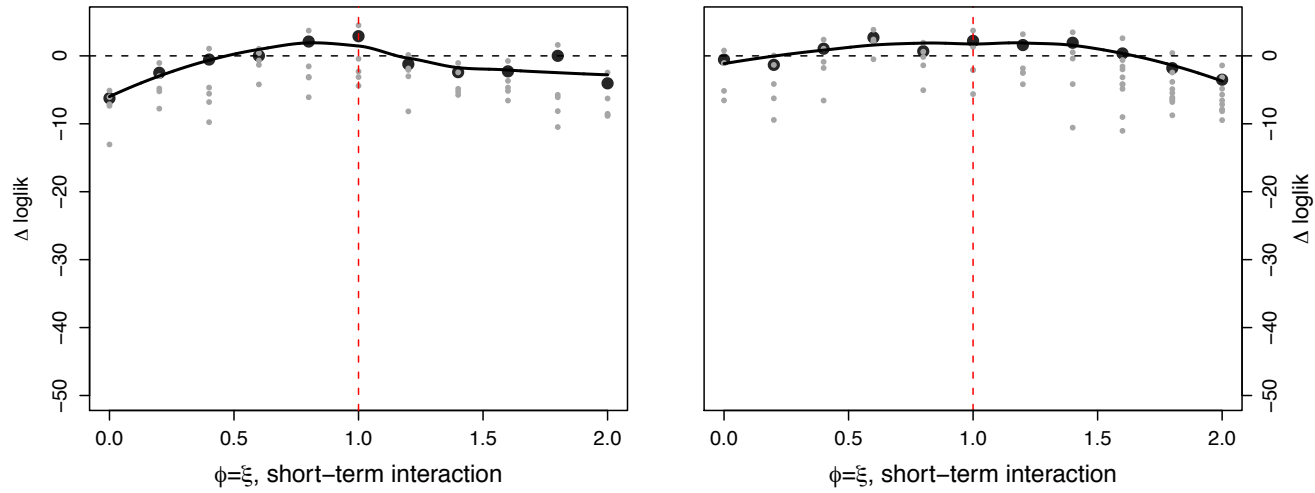


Scenario I

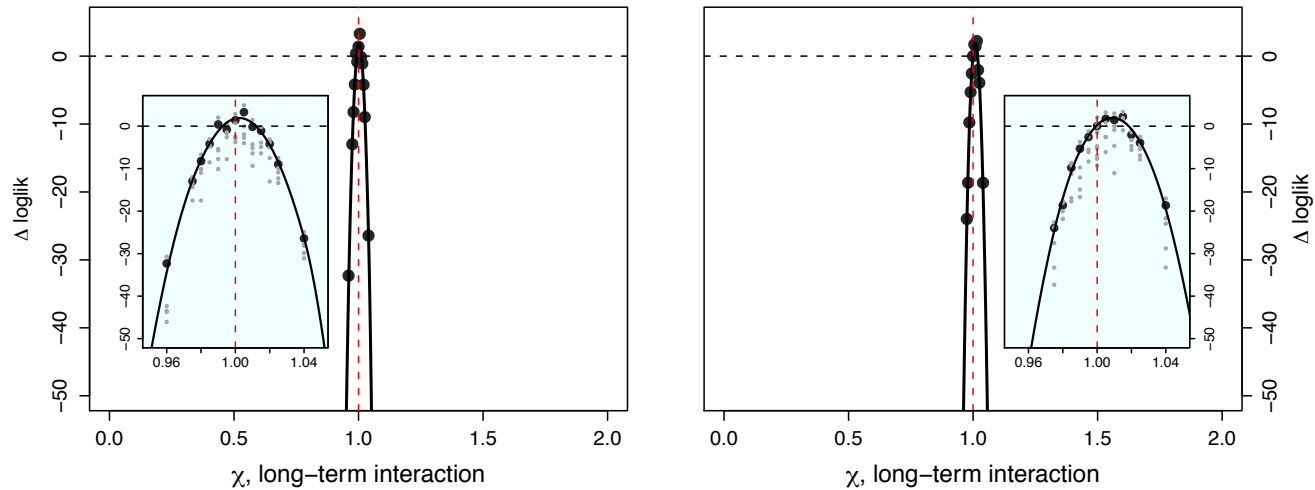
Cases



Short-term

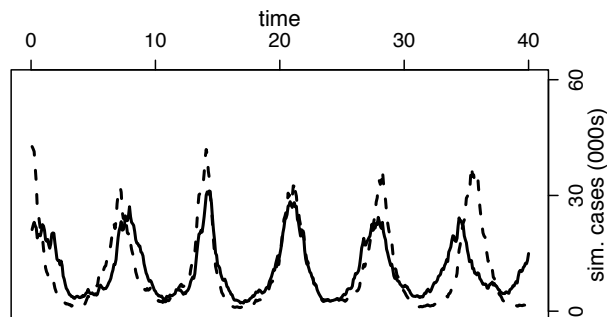
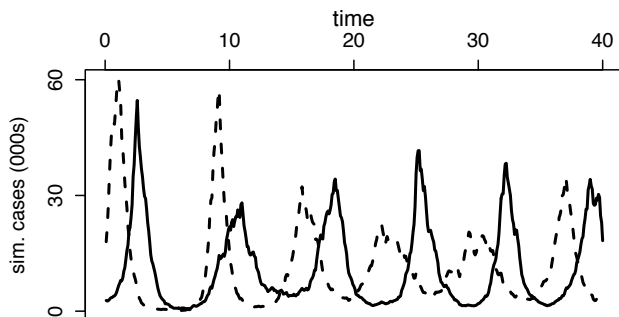


Long-term

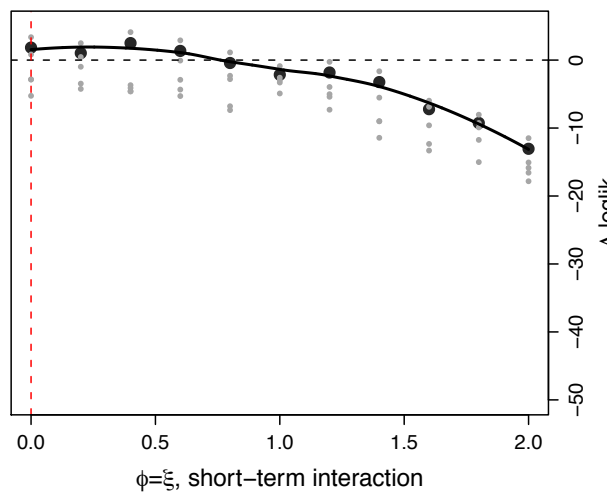
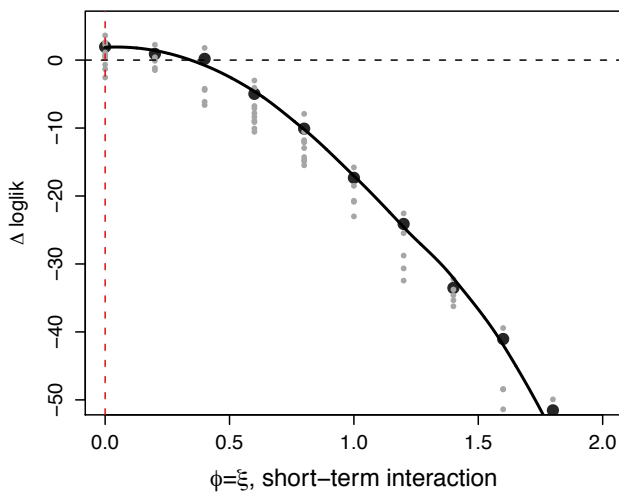


Scenario II

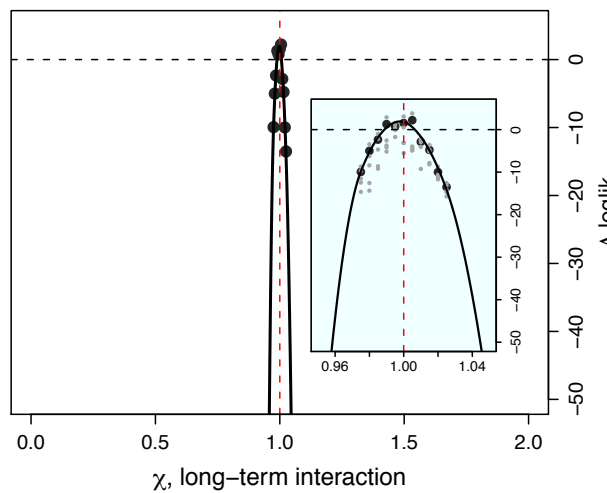
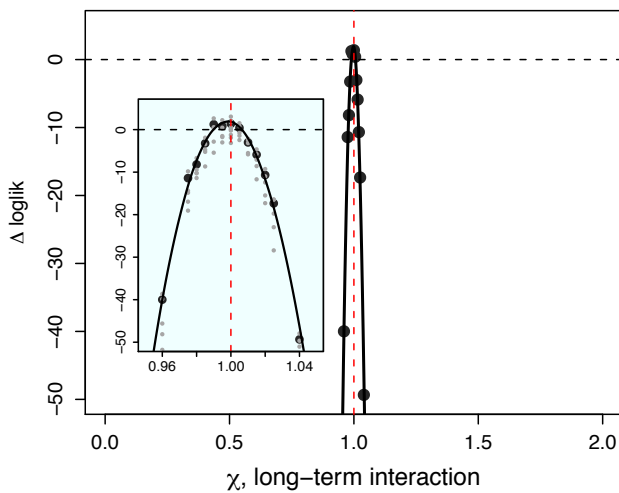
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Short-term

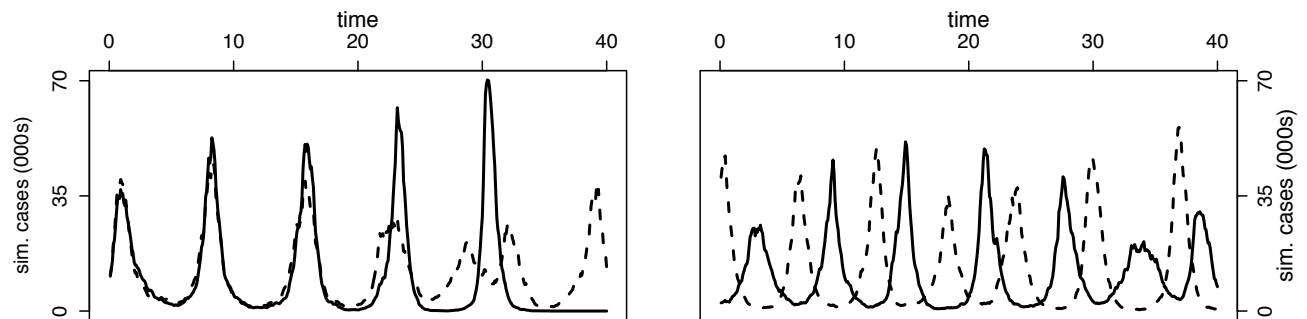


Long-term

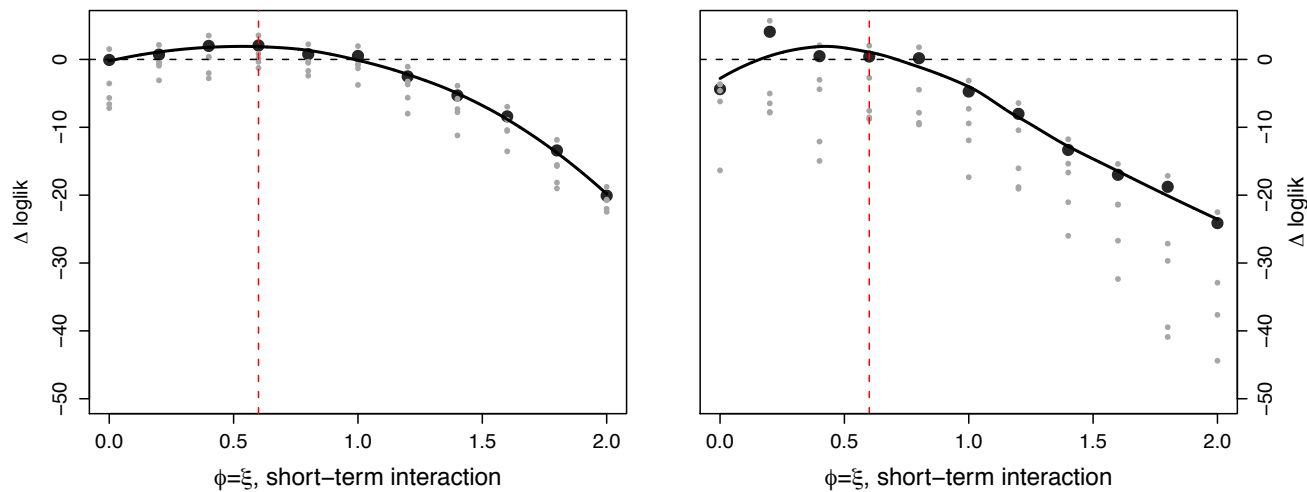


Scenario III

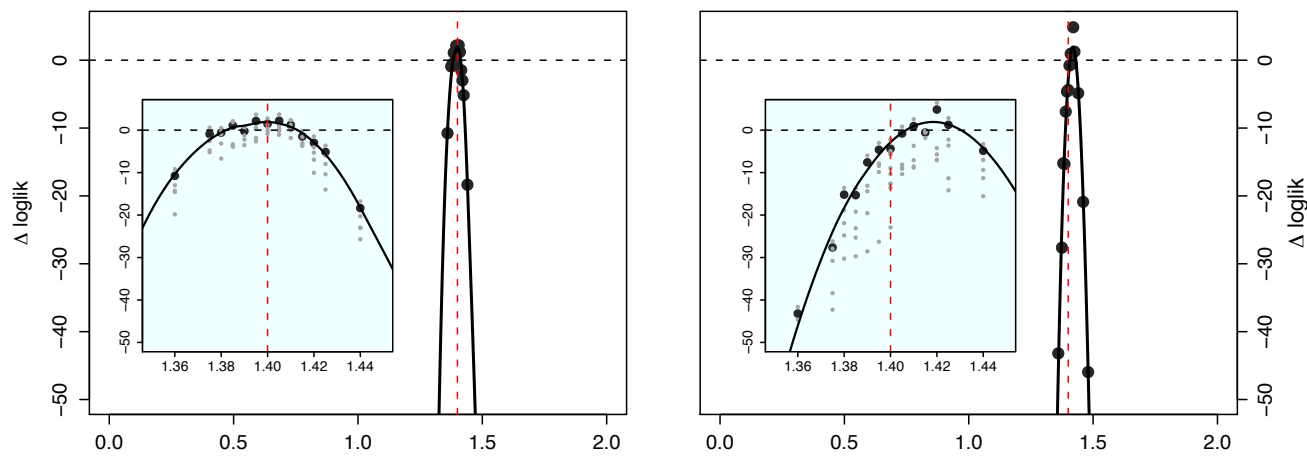
Cases



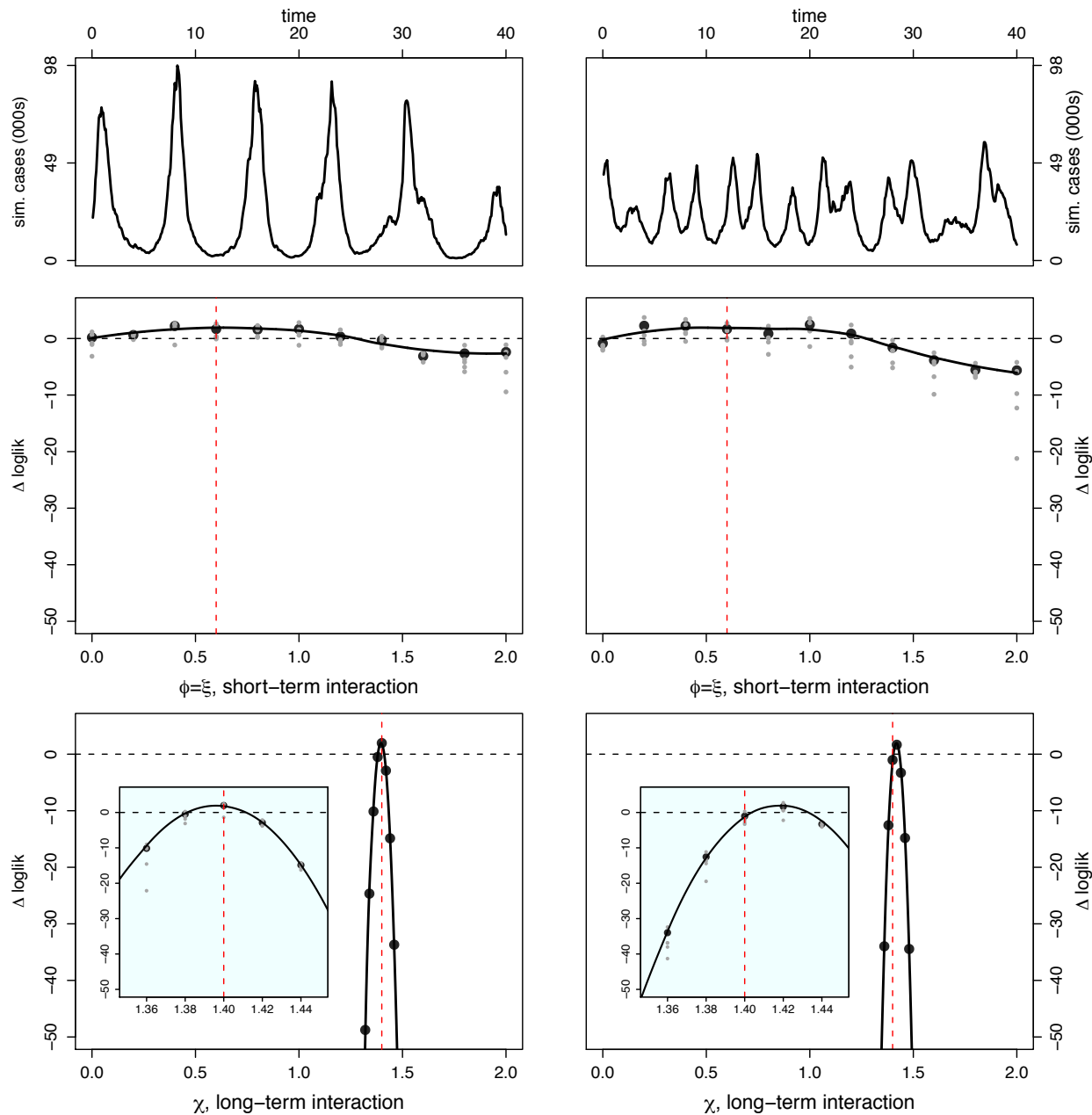
Short-term



Long-term

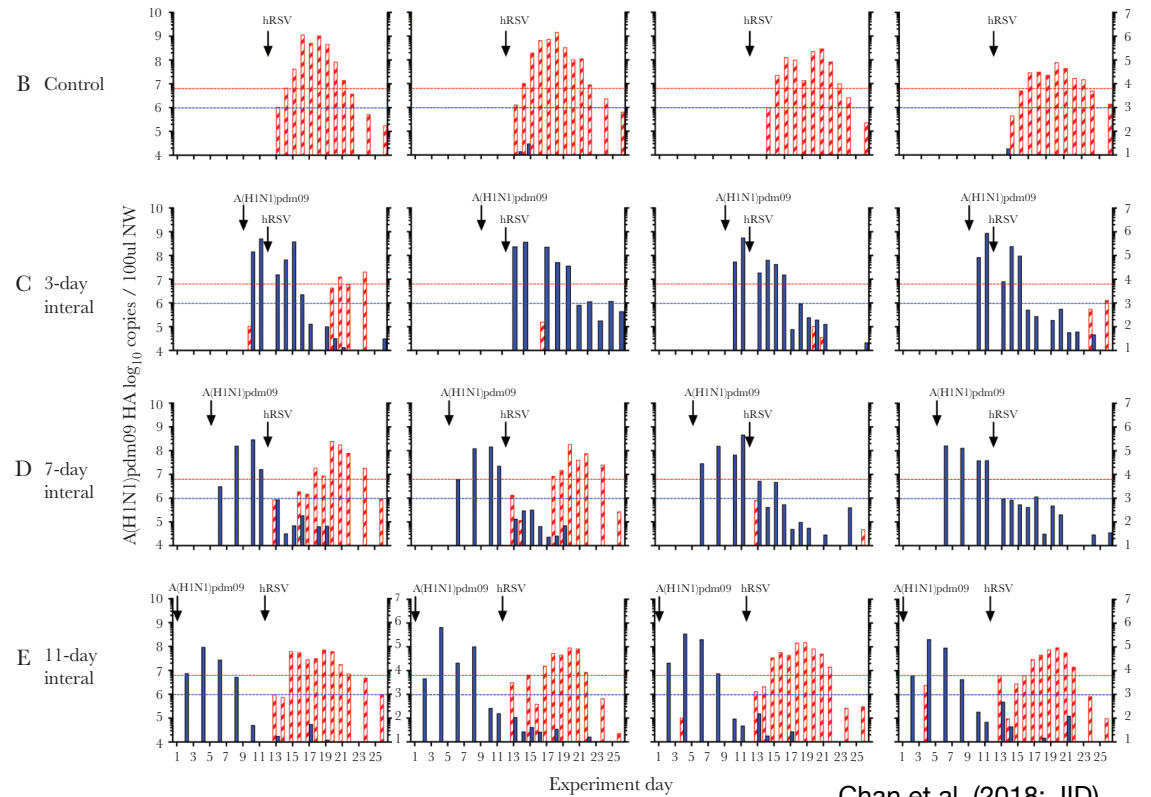


Stress-test IV. Aggregate data



Viral interactions

Antiviral state – influenza-RSV



Preliminary work: influenza A, SARS-CoV-2 and virus-virus interactions

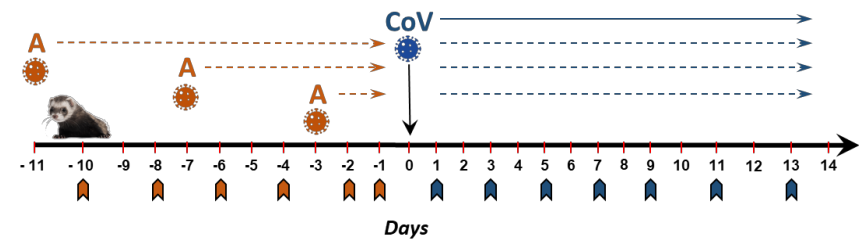
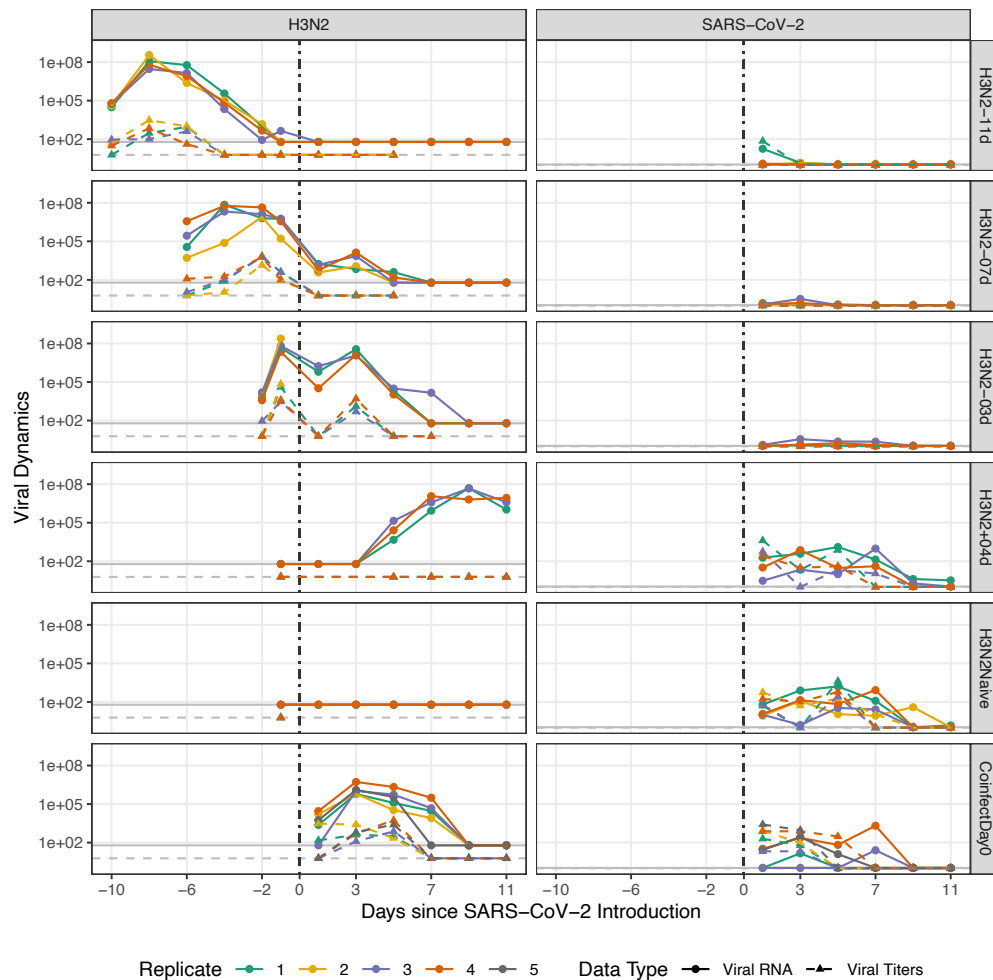
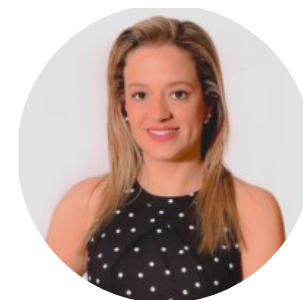


Figure 11: Design of Ferret experiments with Influenza and SARS-CoV-2.

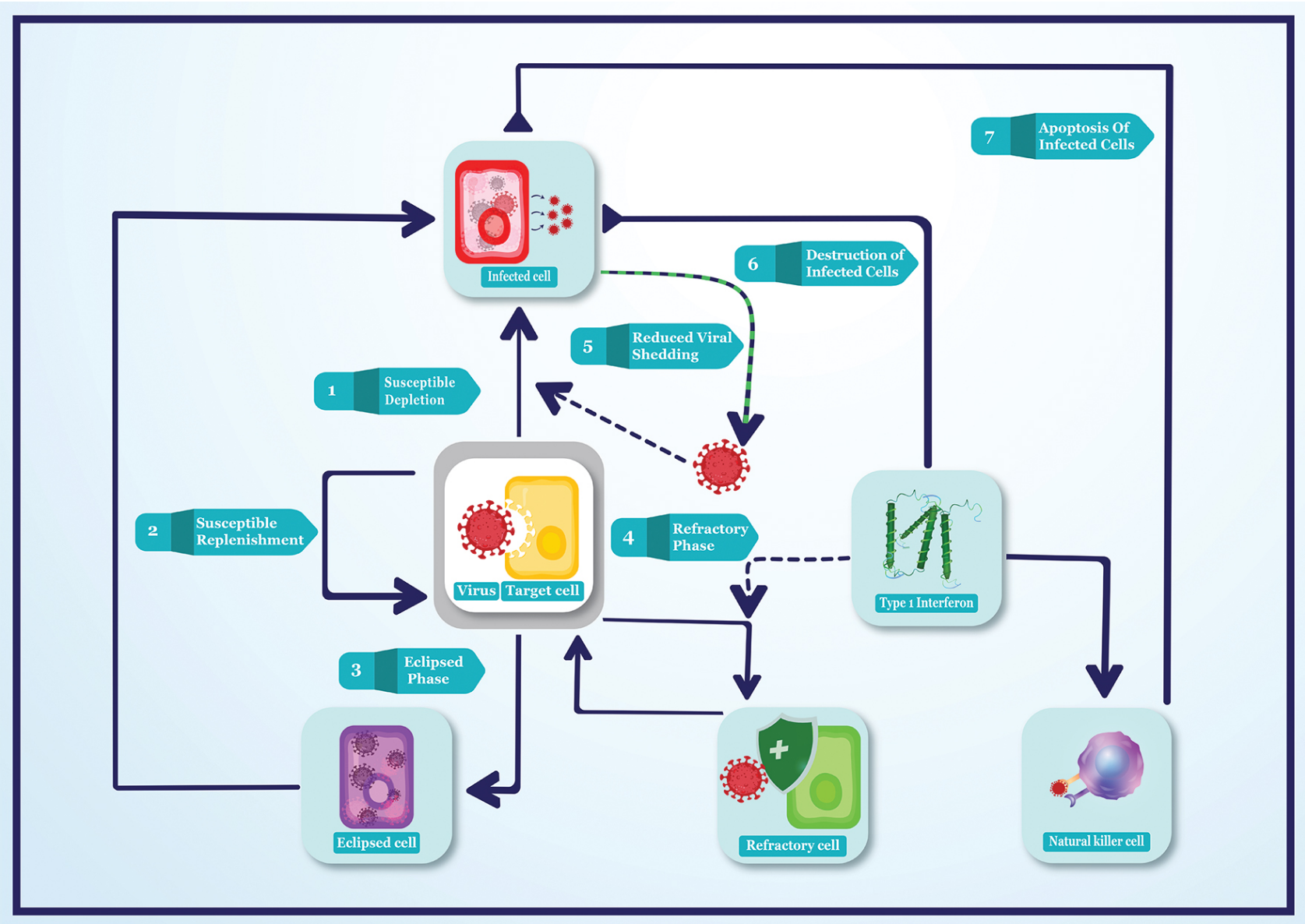
Use within-host models to characterize drivers of virus dynamics and (eventually) determinants of virus interactions



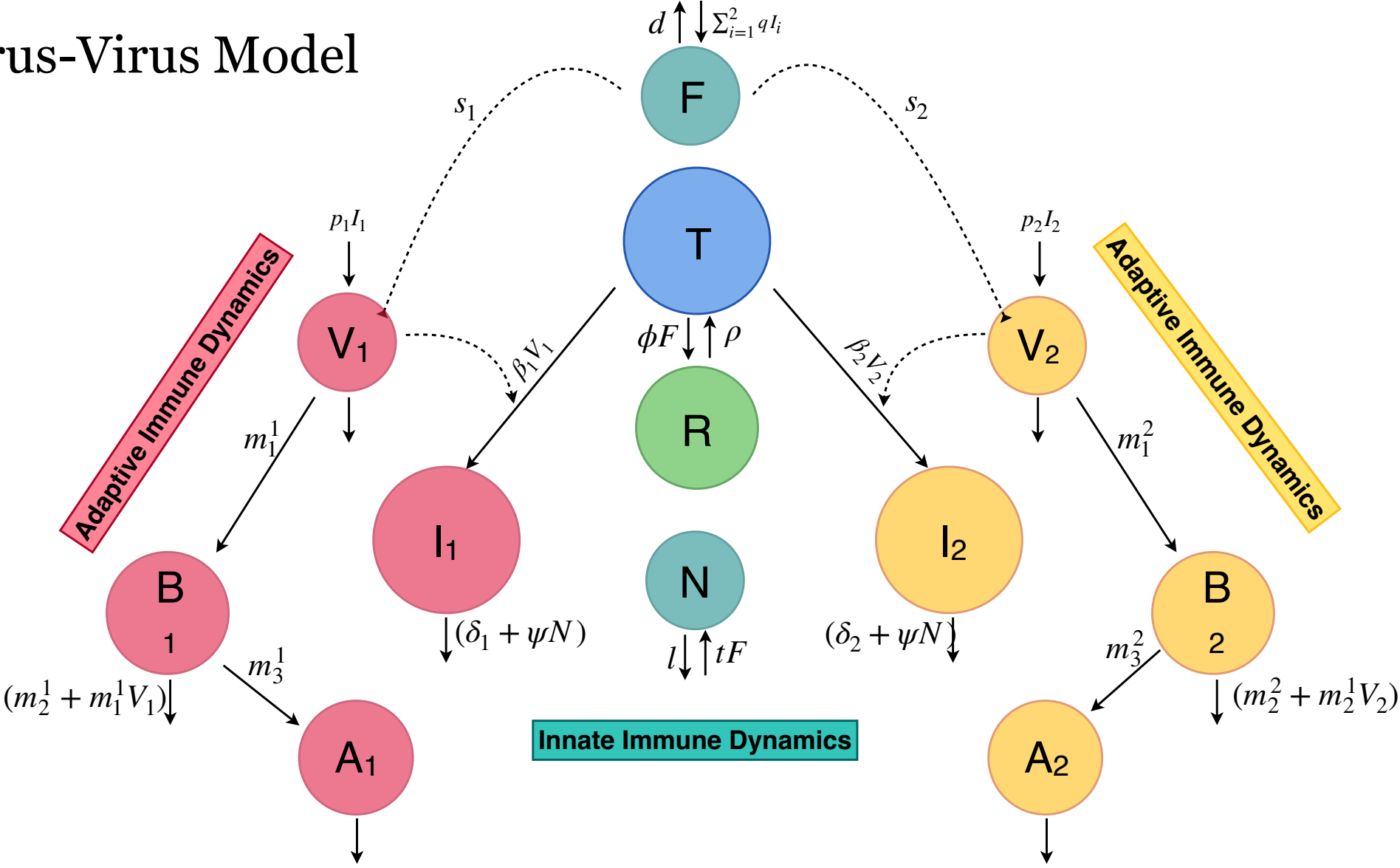
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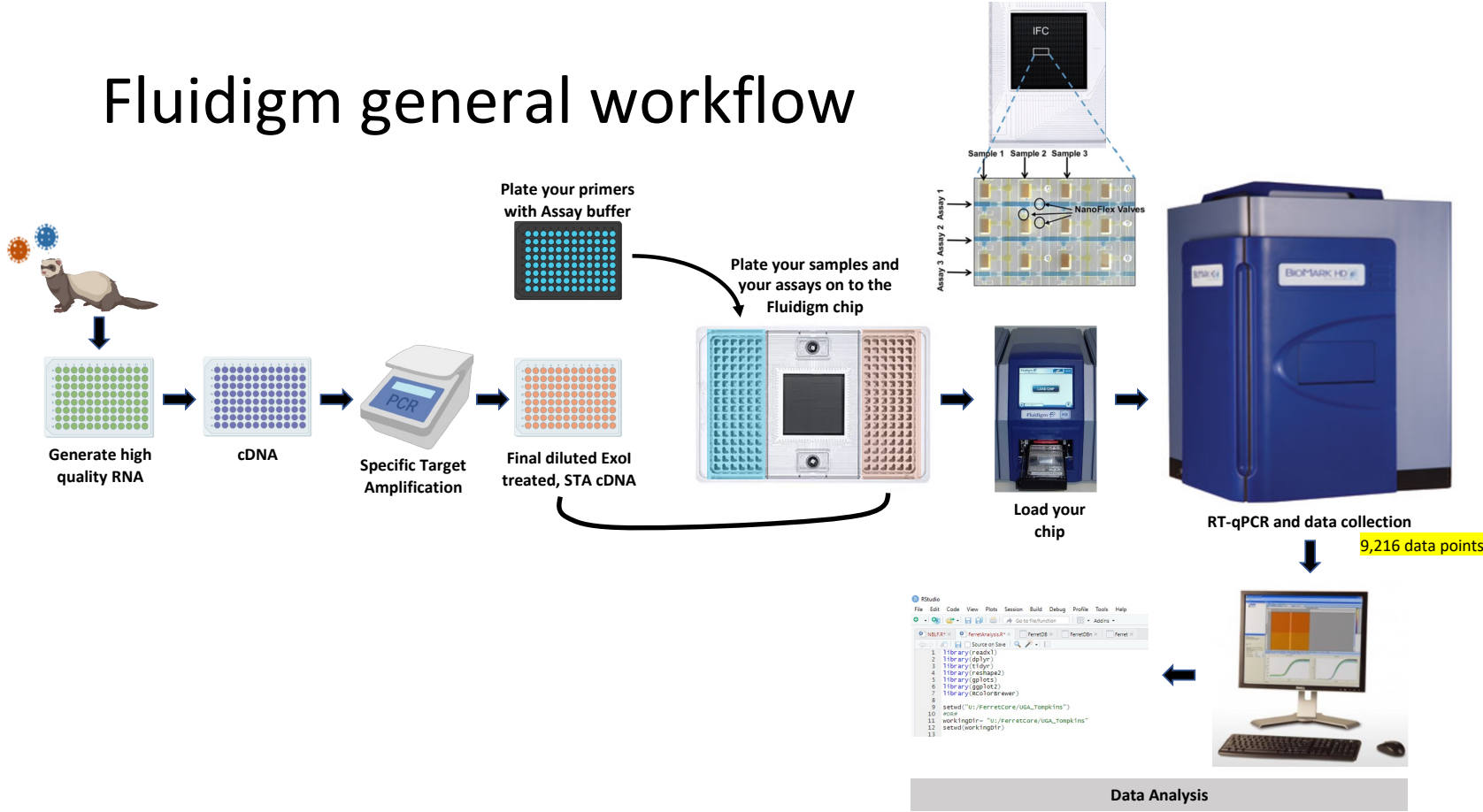


Virus-Virus Model



Immunological transcriptomics data

Fluidigm general workflow



Yes, but ...

- What about
 - Trade-offs in parameters?
 - Length of time series?
 - Under-reporting bias
 - Aggregated data?
 - Unknown initial conditions?

Stress-test the approach!