VISHN:

Viral Load and Immunity Simulation on a Host Network

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Motivation:

- The COVID-19 pandemic has underscored the significance of factors that occur at the sub-host scale of virus transmission
    - Waning Immunity and reinfections[1]
    - Viral-load dependent transmission[2]
    - Heterogeneous viral load levels between individuals[3] (Ke et al. 2022) [3]

1. X. Ren, J. Zhou, J. Guo, C. Hao, M. Zheng, R. Zhang, Q. Huang, X. Yao, R. Li, and Y. Jin, “Reinfection in patients with covid-19: a systematic review,” Global Health Research and Policy, vol. 7, no. 1, p. 12, 2022.

2. J. A. Hay, L. Kennedy-Shaffer, S. Kanjilal, N. J. Lennon, S. B. Gabriel, M. Lipsitch, and M. J. Mina, “Estimating epidemiologic dynamics from cross-sectional viral load distributions,” Science, vol. 373, no. 6552, p. eabh0635, 2021.

3. R. Ke, P. P. Martinez, R. L. Smith, L. L. Gibson, A. Mirza, M. Conte, N. Gallagher, C. H. Luo, J. Jarrett, R. Zhou et al., “Daily longitudinal sampling of SARS-COV-2 infection reveals substantial heterogeneity in infectiousness,” Nature microbiology, vol. 7, no. 5, pp. 640–652, 2022.

Introduction:

What is VISHN and why is it useful?

- VISHN is an open source customizable simulation framework that links the sub-host scale of virus transmission (virus-to-cell) to the between host scale (person-to-person)
- The framework allows for user-friendly modeling of heterogeneity at both the sub-host and between-host scale for highly customizable simulations
- The framework is flexible and can be used to model the transmission of various infectious diseases

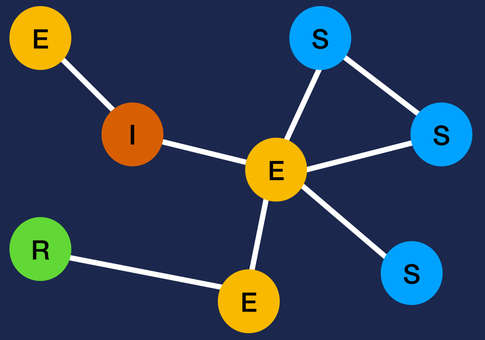
Github Link: https://github.com/jeremynachison/VISHN

A (brief) refresher on epidemiological modeling:

What are some of the most common models?

- Differential Equation Based Models:
  - SIR, SEIR, SIS, etc…
  - Homogeneous mixing
  - Allows for derivation of analytical results without the need for computer simulation
- Network Based Models:
  - Able to account for heterogeneous mixing of individuals

$$\dot{S} = -\beta SI$$
$$\dot{E} = \beta SI - \alpha E$$
$$\dot{I} = \alpha E - \gamma I$$
$$\dot{R} = \gamma I$$



A (brief) refresher on epidemiological modeling:
Metapopulation Models

- Metapopulation Models combine the strengths of differential equation models and network models
    - The population is split into homogeneously mixing subpopulations
    - These subpopulations then mix with each other heterogeneously
    - Example: an SEIR system nested within each node of a network, and the spread along the edges of the network is a function of the Infected population within each node

A (brief) refresher on epidemiological modeling:
Multi-Scale Modeling

- Multi-Scale models are capable of modeling the dynamics at multiple spatial and temporal scales involved in virus transmission
- Metapopulation Models are an example of a Multi-Scale models
    - i.e. linking the within-city scale of virus transmission to the between-city scale
- VISHN is a multi-scale model that links the sub-host scale of virus transmission to the between-host scale

Examples of Multi-Scale Models:

Aguiar et al.[4]

- Uses a multi-scale modeling framework to evaluate lockdown policies and vaccination strategies
- Captures heterogeneity at the sub-host and between-host scales
    - Meta-population model: each node represents a homogeneously mixing subpopulation
    - No incorporation of waning immunity
    - Viral load dependent transmission does not occur between subpopulations

4. M. Aguiar, G. Dosi, D. A. Knopoff, and M. E. Virgillito, “A multiscale network-based model of contagion dynamics: heterogeneity, spatial distancing and vaccination, Mathematical Models and Methods in Applied Sciences, vol. 31, no. 12, pp. 2425–2454, 2021.

Examples of Multi-Scale Models:

Kuylen et al.[5]

- Uses a simple multi-scale model to test the differences between superspreading at the sub-host and between-host scales
    - Assigns a transmission probability (proxy for viral load) and a weighted contact rate (proxy for heterogeneous networks) for each individual
    - No waning immunity, time dependent virus transmission (or any direct modeling of sub-host dynamics), and homogeneously mixing populations
- Found that higher sub-host heterogeneity leads to fewer large outbreaks

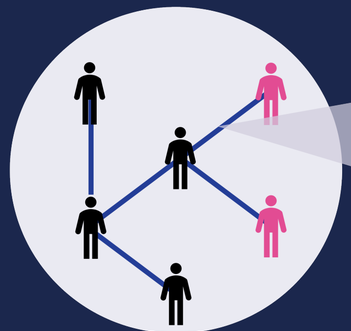
5. E. J. Kuylen, A. Torneri, L. Willem, P. J. Libin, S. Abrams, P. Coletti, N. Franco, F. Verelst, P. Beutels, J. Liesenborgs et al., “Different forms of superspreading lead to different outcomes: Heterogeneity in infectiousness and contact behavior relevant for the case of SARS-COV—2,” PLoS Computational Biology, vol. 18, no. 8, p. e1009980, 2022.

VISHN:

Model Overview

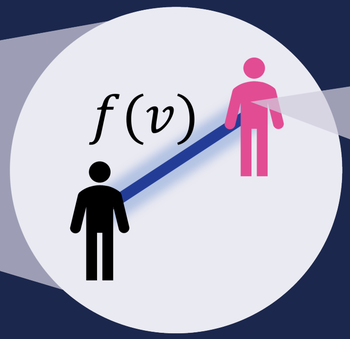
- Sub-host dynamics are modeled via a system of differential equations
- Between-Host transmission is captured via a contact network
- The probability a node becomes infected is calculated by the link function along the edges of the contact network

Between-Host Scale



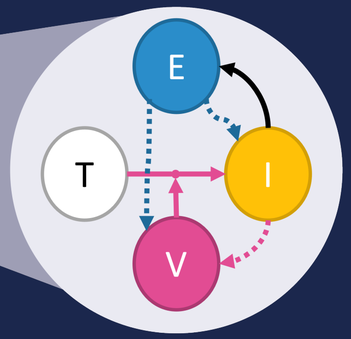
A virus spreads between hosts via the edges of a contact network from infected hosts (pink) to uninfected hosts (black)

Linking the Scales



The probability the virus spreads along an edge from an infected to an uninfected host is a function of the viral load within the infected host

Sub-Host Scale



A system of differential equations is used to model the sub-host dynamics (viral load) of the virus within each host in the network.

VISHN:

The Sub-Host model

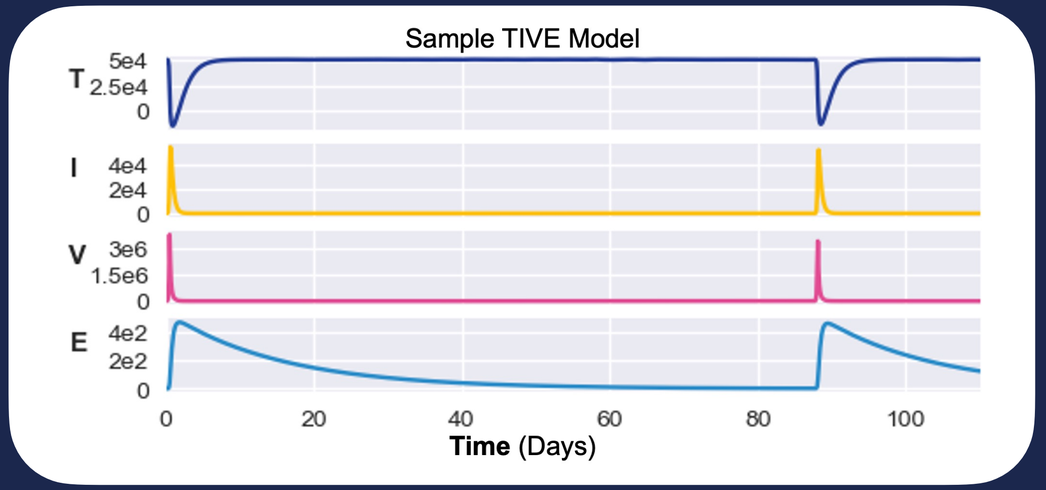
- The TIVE system[6] is a target-cell limited model
    - Target Cells (T), Infected Cells (I), Viral Load (V), Immune Response (E)
- Able to model viral load at the host level to inform transmission between hosts
- Capable of modeling waning immunity and multiple infection cycles

$$\dot{T} = \alpha T(1 - \frac{T+I}{T_{max}}) - \beta VT$$

$$\dot{I} = 1_{V \geq V_{min}}(\beta VT - \delta I - d_X EI)$$

$$\dot{V} = 1_{V \geq V_{min}}(pI - cEV) + 1_{exp}(V_{exp})$$

$$\dot{E} = rI - d_E E$$



6. M. Ciupe, B. Bivort, D. Bortz, and P. Nelson, “Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models,” Mathematical biosciences, vol. 200, no. 1, pp. 1–27, 2006

VISHN:

The Sub-Host model

- The number of infected cells and viral load asymptotically approach zero after an infection
    - Indicator variables are introduced to delineate multiple infection cycles and allow target cells to fully recover.
- A host is exposed to V_{exp} viral load when an infector succeeds in transmitting the virus
    - The probability the infector transmits the virus is a function of their viral load
    - V_{exp} is fixed and does not depend on the viral load of the infector

$$\dot{T} = \alpha T(1 - \frac{T + I}{T_{max}}) - \beta VT$$

$$\dot{I} = 1_{V \geq V_{min}}(\beta VT - \delta I - d_X EI)$$

$$\dot{V} = 1_{V \geq V_{min}}(pI - cEV) + 1_{exp}(V_{exp})$$

$$\dot{E} = rI - d_E E$$

VISHN:

The Sub-Host model

Rate Parameters (day^{-1})	
Parameter	**Description**
α	Target Cell Growth Rate
β	Cell Infectivity Rate
δ	Infective Cell Death Rate
d_x	Infective Cell Clearance Rate
p	Viral Load Growth Rate
c	Viral Load Clearance Rate
r	Immune Cell Growth Rate
d_E	Immune Cell Clearance Rate

Cell Population Parameters	
Parameter	**Description**
T_0	Initial Target Cell Count
I_0	Initial Infected Cell Count
V_0	Initial Viral Load ($TCID_{50}$/mL)
E_0	Initial Immune Cell Count
T_{max}	Target Cell Carrying Capacity
V_{min}	Min Viral Load for an Infection
V_{exp}	Viral Load Exposure

VISHN:

The Between-Host model and Link Function

- The link function, f_{ij}, transforms the viral load within host i into the probability of infecting neighboring host j in the contact network
    - ω_{ij} is the weight along the edge between hosts i and j, c_1, c_2 are the steepness and center of the sigmoid function, respectively, and v_{is} is the viral load within host i at time step s
- The contact network can be any static, undirected graph

$$f_{ij}(v_{is}) = \frac{\omega_{ij}}{1 + e^{(c_1(v_{is} - c_2)}}$$

VISHN:

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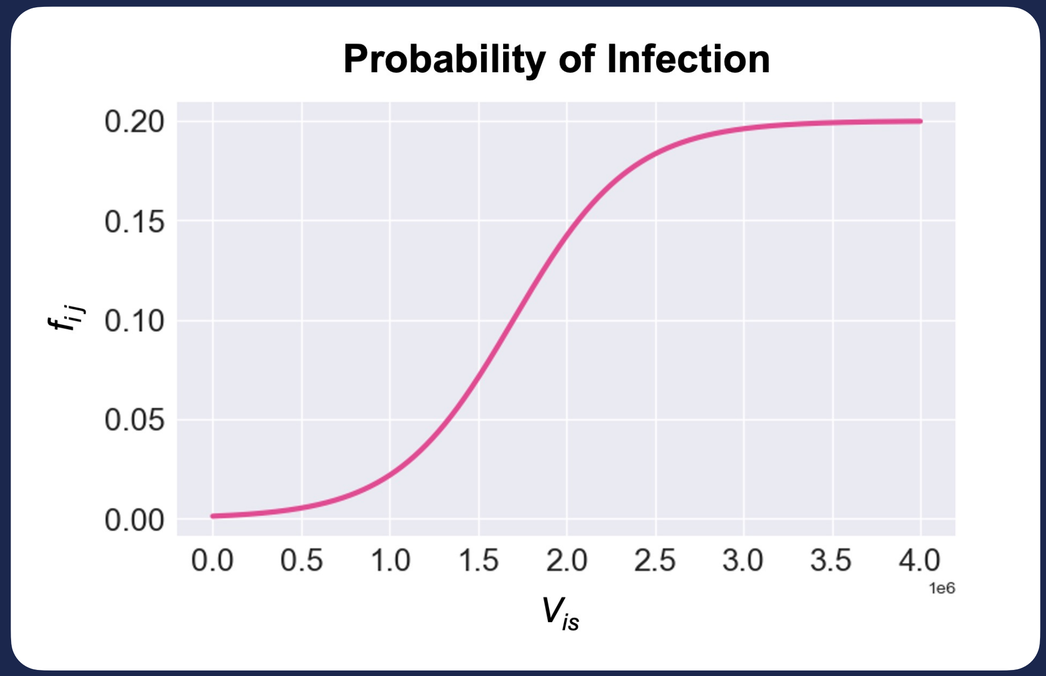
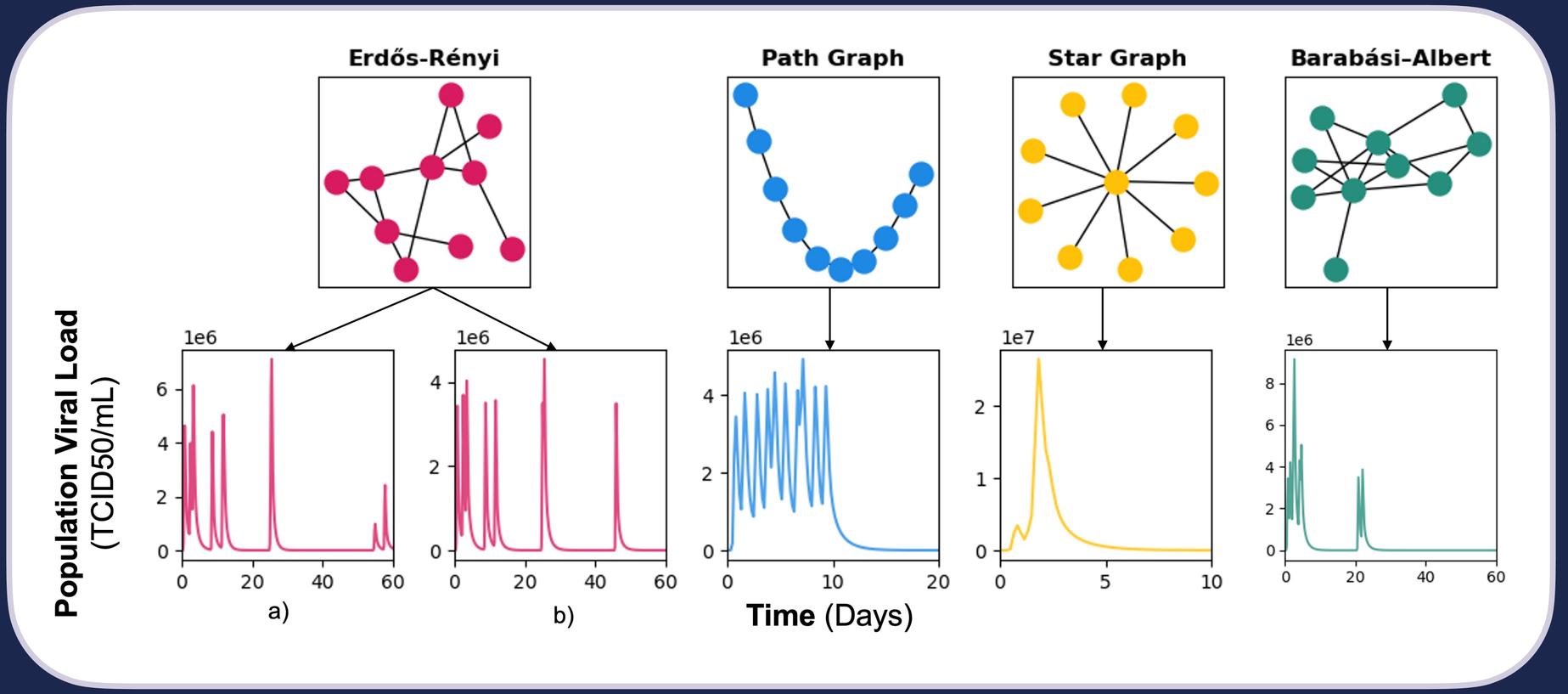


$$c_1 = \frac{-3}{1 \times 10^6}, c_2 = 1.7 \times 10^6, \omega_{ij} = 0.2$$

VISHN:

The Between-Host model and Link Function

- Demonstration of different network structures on population viral load, holding all other parameters constant



VISHN:

Overview of all customizable parameters of a simulation

Network and Link Function Parameters	
Parameter	**Description**
Network File	The static, undirected, weighted contact network
Number Initial infected	The number of initial infected nodes in a simulation
Initial Infected nodes (optional*)	List of specific nodes in the network to initially infect
Link Function Center	Viral load which there is a 50% chance of transmission
Link Function Steepness	The slope of the link function

Sub-Host and Time Parameters	
Parameter	**Description**
Parameter Data	.csv of sub-host parameters to use for each host
Initial Uninfected	The number of initial infected nodes in a simulation
Initial Infected	List of specific nodes in the network to initially infect
Initial Exposure	Allows for modification of the link function for a given virus
Duration, Samples per Day	Total duration of the simulation in days
Samples per Day	Number of simulation steps taken each day

VISHN:

Configuring a simulation

Example.txt

```
NetworkFile=ExampleNetwork.edgelist
NumInitialInfected=2
InitInfectedNodes=[5,10]

InfectionMethod=Individual
Center=1700000
Steepness=-3/1700000
InitialExposure=1e5

Equation=tive
InfectiveIndex=2
ParameterData=ExampleParams.csv
TargetInit=[60000,0,0,0]
InfectedInit=[60000,1,1/6000,0]

Duration=365
SamplesPerDay=6
Seed=0
```

ExampleNetwork.edgelist

```
0 1 {'weight': 0.4}
0 2 {'weight': 0.4}
0 3 {'weight': 0.4}
0 4 {'weight': 0.4}
0 5 {'weight': 0.4}
0 7 {'weight': 0.4}
0 8 {'weight': 0.4}
0 9 {'weight': 0.4}
0 10 {'weight': 0.4}
```

```
[30]: Example_params = pd.read_csv("ExampleParams.csv")
      Example_params.head()
```

[30]:

	delta	p	c	beta	d	dX	r	alpha	N
0	0.8	450.0	0.05	0.00002	0.01	0.0001	0.01	1.2	60000.0
1	0.8	450.0	0.05	0.00002	0.01	0.0001	0.01	1.2	60000.0
2	0.8	450.0	0.05	0.00002	0.01	0.0001	0.01	1.2	60000.0
3	0.8	450.0	0.05	0.00002	0.01	0.0001	0.01	1.2	60000.0
4	0.8	450.0	0.05	0.00002	0.01	0.0001	0.01	1.2	60000.0

```
[5]: result = vn.simulate("Example.txt")
```

VISHN:

Strengths and Weaknesses

Pros:

- Heterogeneity of social mixing
- Viral Load dependent transmission
- Multiple Infection Cycles
- Waning Immunity
- Flexible and highly customizable

Cons:

- Computationally expensive
    - On a MacBook Air, a 100 node network takes ~3.5 minutes, 200 nodes take ~8.5 minutes
- Static network, no external infections
- Validation/Calibration can be difficult
- *No deaths, vaccination

* Planned to be supported in future updates

VISHN Summary:

- VISHN is a multi-scale virus transmission model which links sub-host and between-host viral dynamics
- Both simulation scales are capable of capturing heterogeneity and are customizable
- The modeling framework is highly flexible and has potential for use in many different applications in epidemiological modeling

Demonstration Study:

Consider an outbreak of a virus similar to COVID-19 in a population of 100 individuals, such as a dormitory or a small health care facility.

- Use VISHN to investigate how different contact network structures and host heterogeneity could influence the outbreak

Methods

- Comparing heterogeneous vs. homogeneous contact networks and connectivity:
    - Heterogeneous: run simulations on Barabási-Albert networks with $\gamma \in \{1,2,3\}$
    - Homogeneous: compare to an Erdős–Rényi network with the same mean node degree
- Investigate levels of contact among individuals by adjusting weight on all edges in a simulation for $\omega \in \{0.1,0.2,0.4\}$
- Sub-host heterogeneity:
    - Use TIVE parameters based on Ciupe et al.[6] and Wang et al.[7]
    - Sample parameters from a normal distribution with the standard deviation $\sigma \in \{0,0.05,0.1\}$ percentage of the mean value for a parameter

6. M. Ciupe, B. Bivort, D. Bortz, and P. Nelson, “Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models,” Mathematical biosciences, vol. 200, no. 1, pp. 1–27, 2006

7. S. Wang, Y. Pan, Q. Wang, H. Miao, A. N. Brown, and L. Rong, “Modeling the viral dynamics of SARS-COV-2 infection,” Mathematical biosciences, vol. 328, p.108438, 2020

Methods

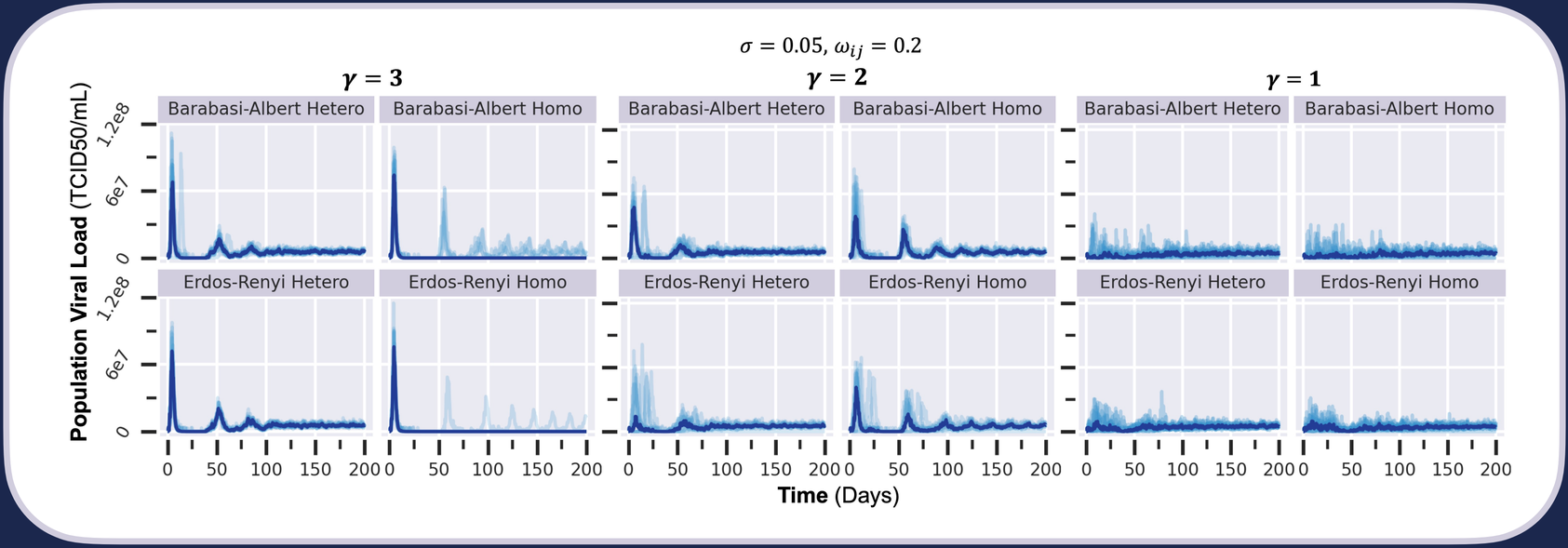
- Run simulations for 365 days, 6 time steps per day
- Each simulation is seeded with one initially infected host
- Adjusting for network mixing (hetero/homogeneous, 2 levels), network connectivity (3 levels), edge weights (3 levels), variance of sub-host heterogeneity (3 levels) results in 54 plausible simulation scenarios
- 10 replicates for each scenario are taken to capture randomness due to the link function

Results

- Networks with higher connectivity have sharper initial infection spikes after which there are fewer subsequent infections

- In the network with moderate connectivity, we can see prominent infection, although subsequent spikes are smaller and resemble damped harmonic oscillations

    - More prominent in homogeneous populations, cycles may be disrupted due to variations in immunity in the heterogeneous setting



Results

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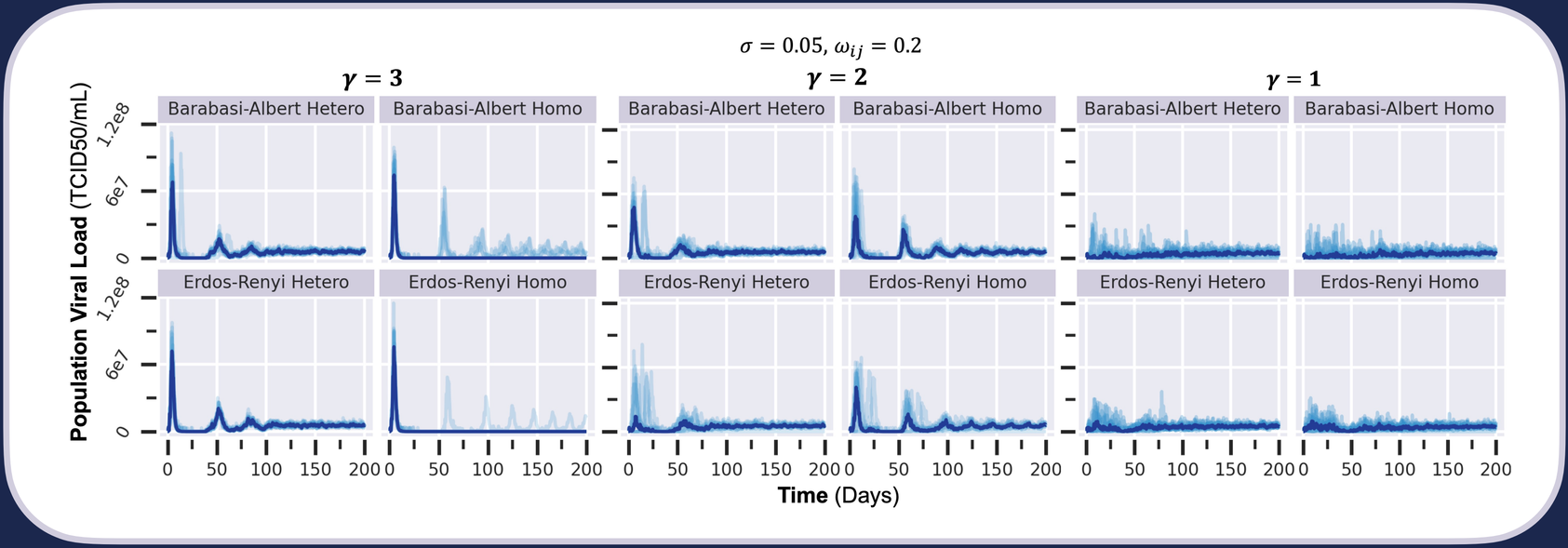
- In the network with moderate connectivity, we can see prominent infection, although subsequent spikes are smaller and resemble damped harmonic oscillations
- For low connectivity, the median viral load shows the virus spreads across the network without large clusters of hosts becoming infected simultaneously



Comparison to Kuylen et al.

- The results of this study align with the simplified model of Kuylen et al.[5]:
    - Higher contact related heterogeneity results in higher and earlier infection spikes
    - Higher infectiousness related heterogeneity lead to large outbreaks less frequently, and slows the spread of the outbreak
    - Higher infectiousness related heterogeneity increases the extinction probability of the epidemic
        - Although extinction probability is not calculated in our study, the more prominent secondary infection cycles in the homogeneous host setting seems to reflect this result

5. E. J. Kuylen, A. Torneri, L. Willem, P. J. Libin, S. Abrams, P. Coletti, N. Franco, F. Verelst, P. Beutels, J. Liesenborgs et al., “Different forms of superspreading lead to different outcomes: Heterogeneity in infectiousness and contact behavior relevant for the case of SARS-COV—2,” PLoS Computational Biology, vol. 18, no. 8, p. e1009980, 2022.

VISHN for future studies

What contributions can be made to the scientific literature?

- Due to its flexibility and support for customization, VISHN can be used to investigate a wide variety of potential case studies in the future:

    1. Fully replicate the experiment of Kuylen et al.[5] using the modeling capabilities of VISHN. Will the results be the same?

    2. Using all of the customizable options, tune a highly realistic model to make public health decisions for a specific congregate setting, like a university dorm, graduation ceremony, or the Olympic Village[8]

    3. Use viral load measurements from wastewater to predict outbreaks/design interventions[9]

5. E. J. Kuylen, A. Torneri, L. Willem, P. J. Libin, S. Abrams, P. Coletti, N. Franco, F. Verelst, P. Beutels, J. Liesenborgs et al., “Different forms of superspreading lead to different outcomes: Heterogeneity in infectiousness and contact behavior relevant for the case of SARS-COV—2,” PLoS Computational Biology, vol. 18, no. 8, p. e1009980, 2022.

8. B. McCloskey, T. Saito, S. Shimada, C. Ikenoue, T. Endericks, L. Mullen, P. Mota, C. K. Kumar, R. Laxminarayan, R. Budgett et al., “The Tokyo 2020 and Beijing 2022 olympic games held during the COVID-19 pandemic: planning, outcomes, and lessons learnt,” The Lancet, vol. 403, no. 10425,pp. 493–502, 2024.

9. D. Proverbio, F. Kemp, S. Magni, L. Ogorzaly, H.-M. Cauchie, J. Gonçalves, A. Skupin, and A. Aalto, “Model-based assessment of COVID-19 epidemic dynamics by wastewater analysis,” Science of the Total Environment, vol. 827, p. 154235, 2022.

References

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