A brief introduction to multi-scale models

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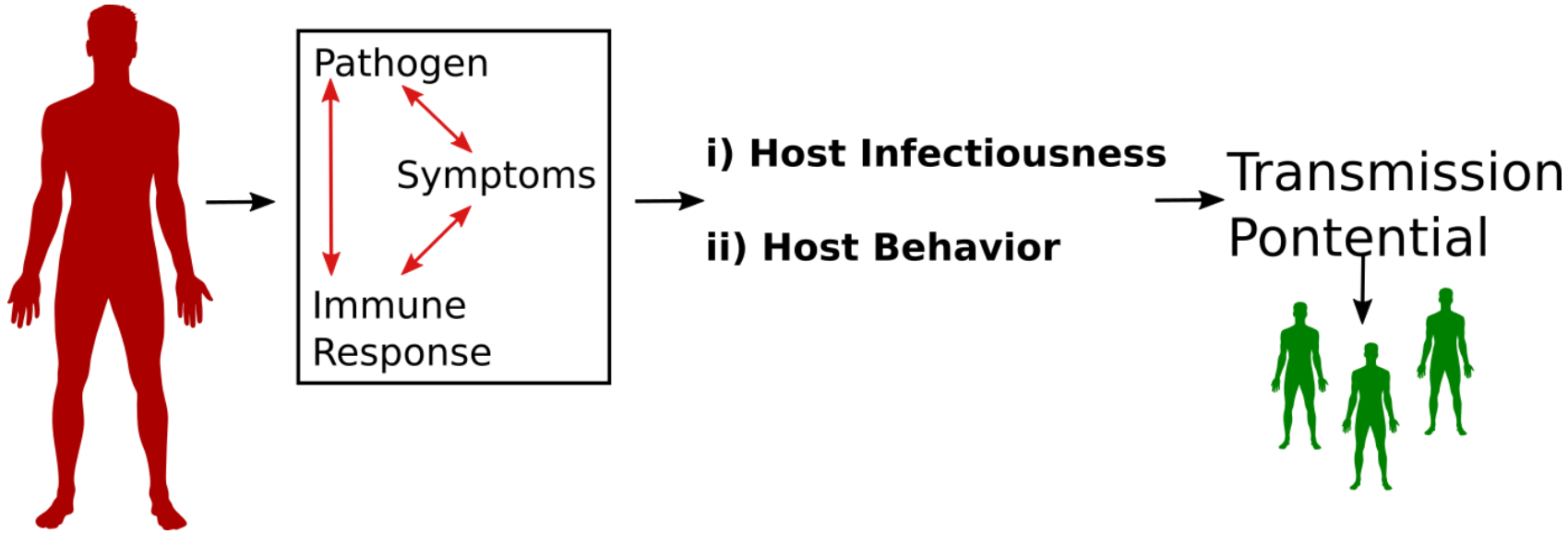
Introduction

- Infectious diseases operate on different temporal and spatial scales.
- Building models that connect scales can allow one to answer new questions.



Ways to model interactions across scales

- Static: A within-host model is analyzed/simulated. Results are being fed into a between-host model, which is subsequently being run.
- Dynamic: A within-host model is being simulated inside a between-host model. Requires an ABM for the between-host model, each agent has its own infection model running.

Simple example model

It is easiest to discuss multi-scale models in the context of an example. Let's consider spread of an acute viral infection (e.g. influenza) at the within-host and the population level.

Within-host model

At the within host level, we can start with the basic virus model.

$$\begin{aligned}\dot{U} &= n - d_U U - bUV \\ \dot{I} &= bUV - d_I I \\ \dot{V} &= pI - d_V V - gbUV\end{aligned}$$

Between-host model

- At the population level, we'll look at the standard SIR model, with compartments being susceptible, infected and infectious, and recovered.
- To avoid confusion, we give all the parameters on the population level model Greek letters.

$$\dot{S} = \nu - \beta SI - \mu S$$
$$\dot{I} = \beta SI - \gamma I - \mu I$$
$$\dot{R} = \gamma I - \mu R$$

Linking models

- Assume transmission rate is linked to virus load, e.g. $\beta = kV$, with k some parameter.

$$\begin{aligned}\dot{S} &= \nu - \mathbf{kV}SI - \mu S \\ \dot{I} &= \mathbf{kV}SI - \gamma I - \mu I \\ \dot{R} &= \gamma I - \mu R\end{aligned}$$

Now the between-host model is connected to the within-host model through the variable V.

Computing virus load

- For a chronic infection model, we can compute V at steady state as function of model parameters.

$$V = \frac{n(p - d_I g)}{d_I d_V} - \frac{d_U}{b}$$

- Changes in the within-host parameters now impact the between-host dynamics.
- A similar model could be made that computes total virus load for an acute infection, and assumes this to be proportional to β (Handel et al. 2013).

Another way to link models

- We could also assume that the duration of the infectious period, $1/\gamma$ is determined by the time V in the within host model drops below a certain level.
- To investigate this:
  - Set within-host model parameters. Run model. Determine time at which $V < 1$ from time-series.
  - Use that time as $1/\gamma$ in the between-host model.
- This approach could be done static (compartmental), or dynamic (ABM).

Using the linked models to answer a question

- We could now answer questions such as: Does increased virus infection (parameter b) lead to more spread on the population level? If we assume link through β and/or γ.
- For a chronic infection, we can see it from the equation:

$$V = \frac{n(p - d_I g)}{d_I d_V} - \frac{d_U}{b}$$

- For an acute infection, we would need to run simulations.

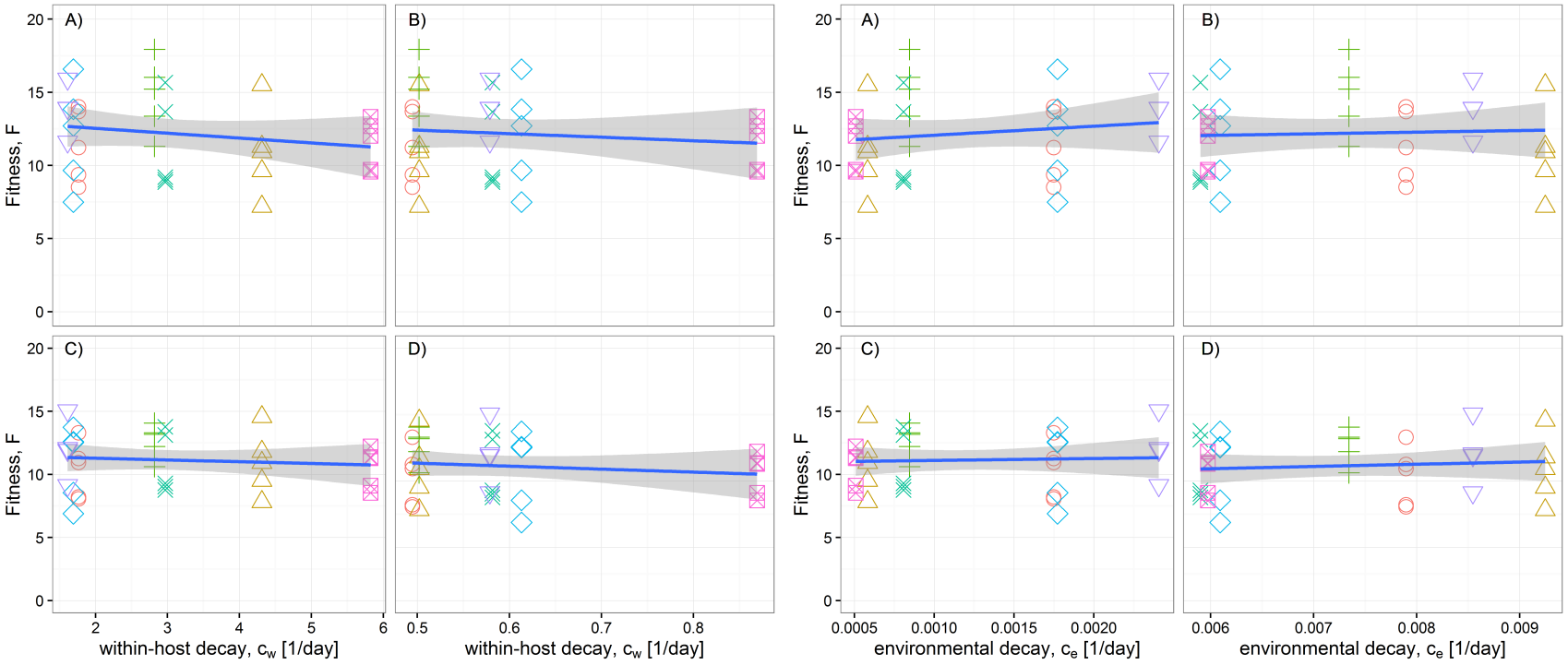
Closing the loop

- So far, we assumed that the lower scale (within-host) affects the higher scale (between-host).
- One could also consider the population level dynamics to impact the within-host level. E.g. if we had a new (flu) strain spreading on the population level which can partially avoid pre-existing immunity, it might impact the within-host dynamics.
- It gets complicated. One either needs to break down the pieces and look at them individually, or put them all in one large simulation.

Example 1

Does low-temperature environmental persistence versus high-temperature within-host persistence pose a potential trade-off for avian influenza (Handel et al. 2013, 2014)?

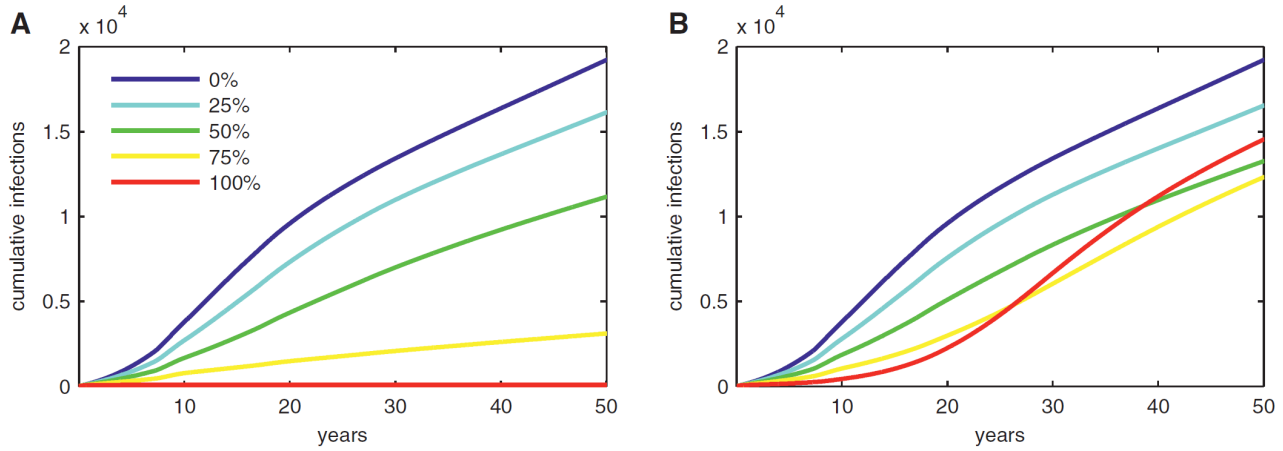
Connect a within-host model and a population level model. Explore how different decay rates at different temperatures affect overall virus fitness.



Example 2

How does drug resistance emergence within an HIV infected individual impact the population level dynamics (Saenz and Bonhoeffer 2013)?

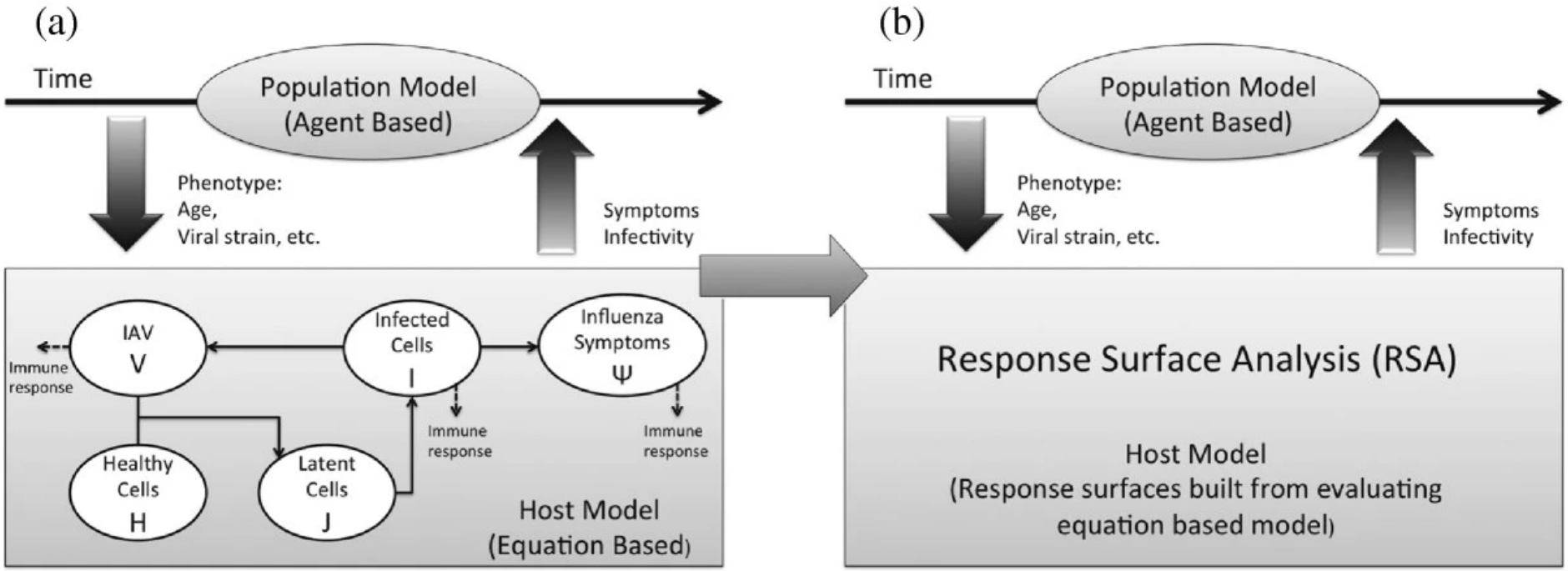
- Virus infection within-host model with drug sensitive and resistant strain and drug treatment.
- The epi model parameters for infection duration and transmission rate are linked to virus load.



Infected cases for different levels of treatment (color) and without (left) and with (right) within-host drug resistance.

Example 3

A fully dynamic multi-scale model for influenza (Lukens et al. 2014).



Further reading

These review papers can provide a good further introduction to the topic: (Childs et al. 2019; Garira 2017; Mideo, Alizon, and Day 2008; Murillo, Murillo, and Perelson 2013; Handel and Rohani 2015)

References

Childs, Lauren M., Fadoua El Moustaid, Zachary Gajewski, Sarah Kadelka, Ryan Nikin-Beers, Jr John W. Smith, Melody Walker, and Leah R. Johnson. 2019. "Linked Within-Host and Between-Host Models and Data for Infectious Diseases: A Systematic Review." *PeerJ* 7 (June): e7057. https://doi.org/10.7717/peerj.7057.

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Saenz, Roberto A., and Sebastian Bonhoeffer. 2013. "Nested Model Reveals Potential Amplification of an HIV Epidemic Due to Drug Resistance." *Epidemics*, Special Issue: Papers from Epidemics3, 5 (1): 34–43. https://doi.org/10.1016/j.epidem.2012.11.002.