What mathematics can tell you about cold and flu season:

An introduction to mathematical biology

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12:00PM

Questions about ‘cold and flu’ season

What questions do you have about
infectious disease and **your health**?

Questions about ‘cold and flu’ season

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2. Am I going to get sick?
3. When am I going to get sick?
4. How sick am I going to get?

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infectious disease and **your health**?

1. What is out there to catch?
2. Am I going to get sick?
3. When am I going to get sick?
4. How sick am I going to get?
5. *Should I get sick?*

A global threat

Infectious diseases

- are a part of life.
- affect humans, animals, and plants.
- are continually moving, emerging, and evolving.

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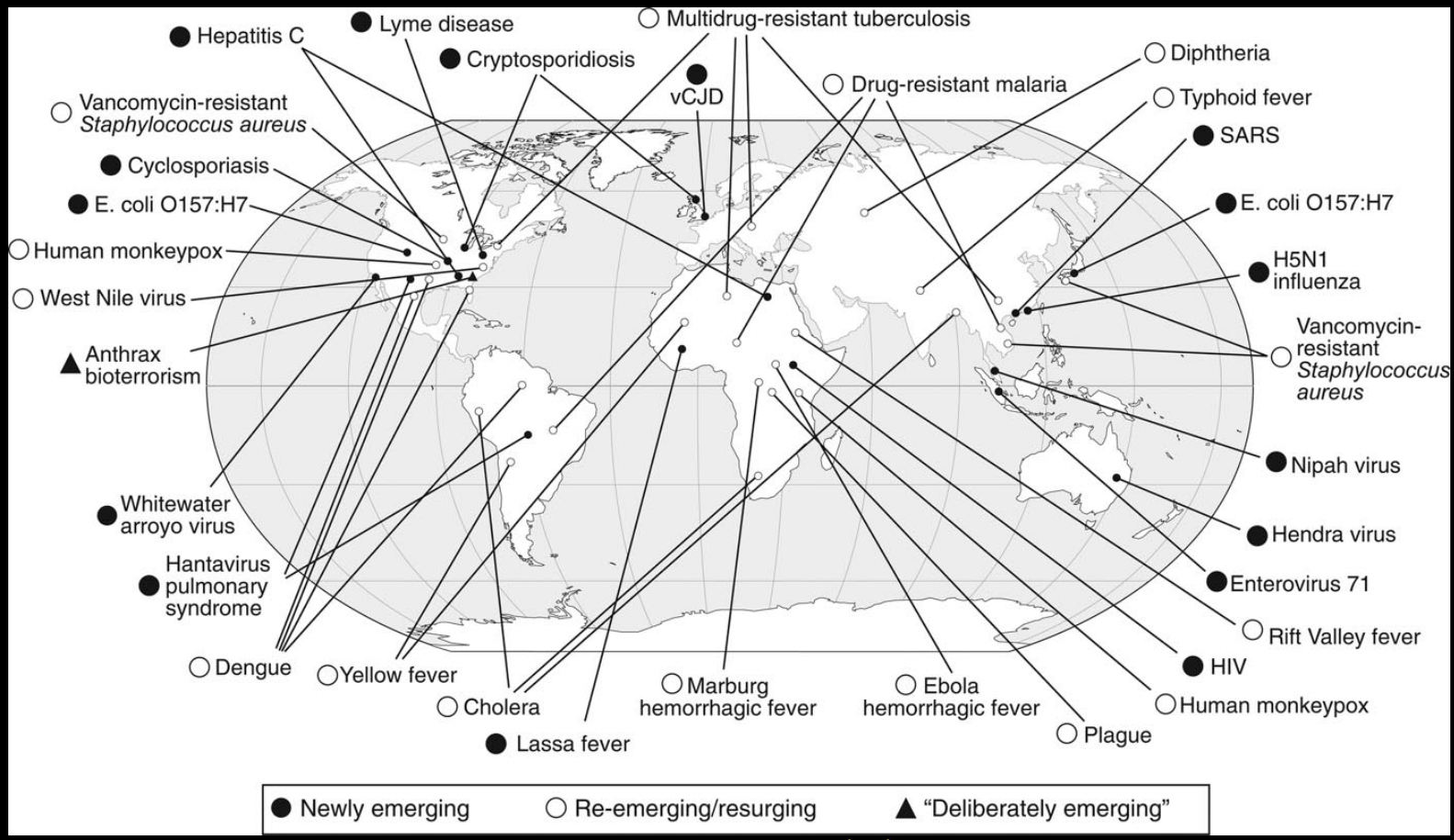
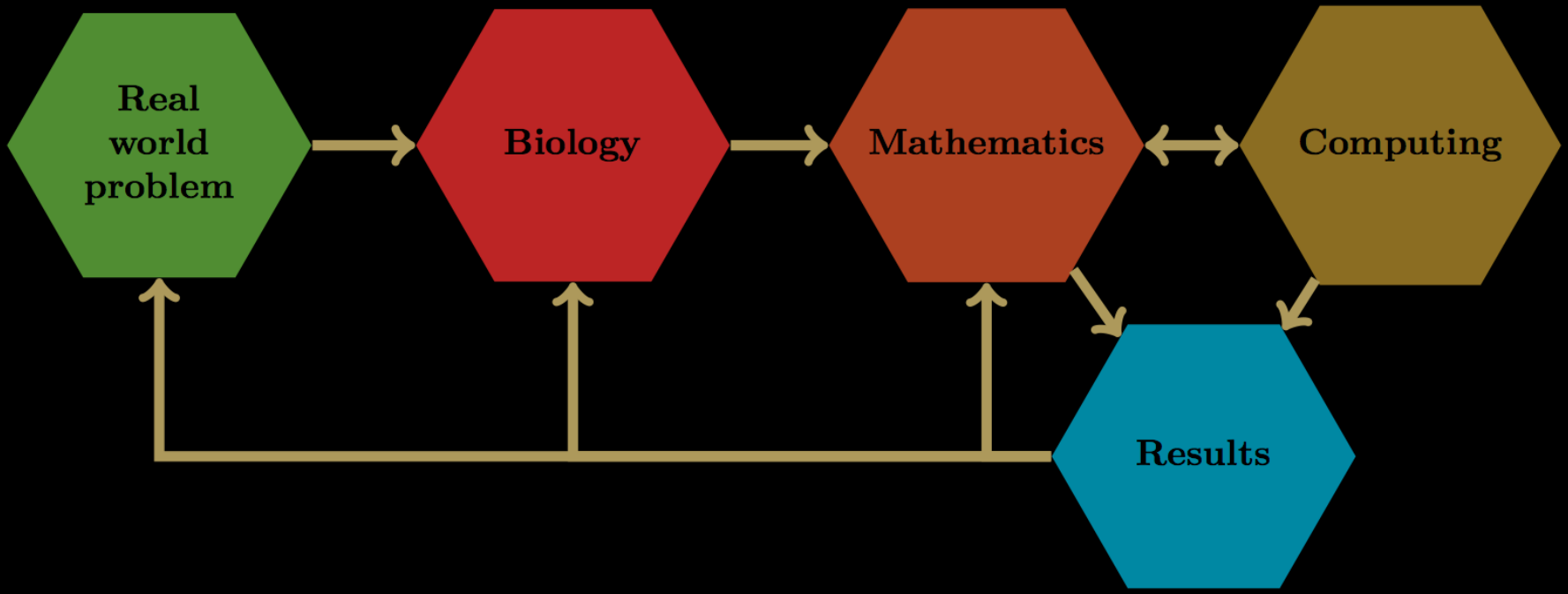


From: A. Fauci, Acad. Med., 80(12) Dec. 2005

Mathematical biology



Everything should be made as simple as possible, but not simpler.

Mathematical modeling: a calculus review

Differential equations are the fundamental tool for describing dynamics.

Derivatives describe how functions change.

Write models about how unknown functions (measurements) change, then study or solve to discover the unknowns.

Building a 'compartment' model

Consider a population of N individuals transitioning between healthy and infectious states, called S for susceptible and I for infectious.

$$\begin{aligned} \text{change in } S &= -\text{ infections} + \text{recoveries} \\ \text{change in } I &= \text{infections} - \text{recoveries} \end{aligned}$$

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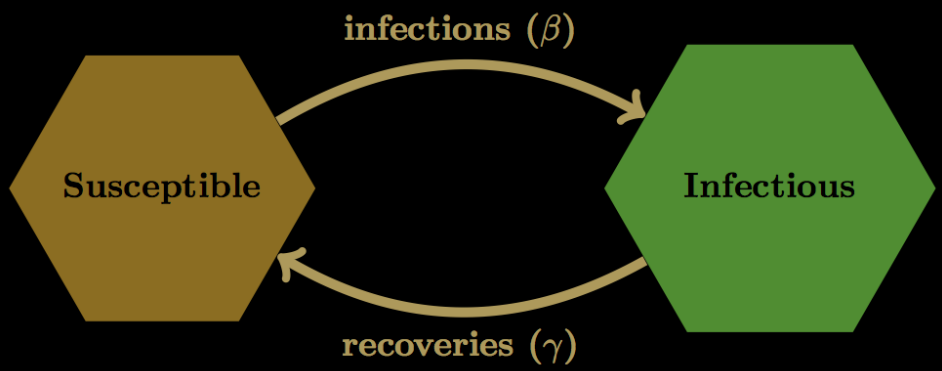

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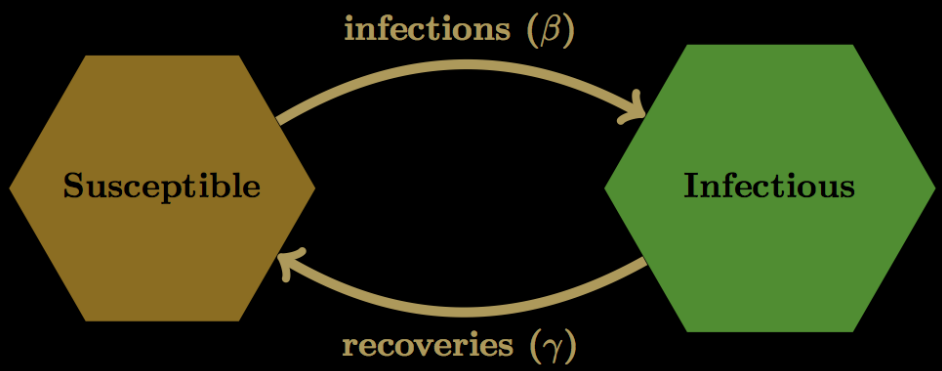

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + \gamma I \\ \frac{dI}{dt} &= \beta SI - \gamma I \end{aligned}$$

History of mathematical epidemiology

- Theory and ideas date back to mid 1700s – Bernoulli on smallpox.
- SIR models applied successfully since early 1900s:
  Malaria, influenza, measles, cholera, HIV/AIDS, rumors, zombies, ...

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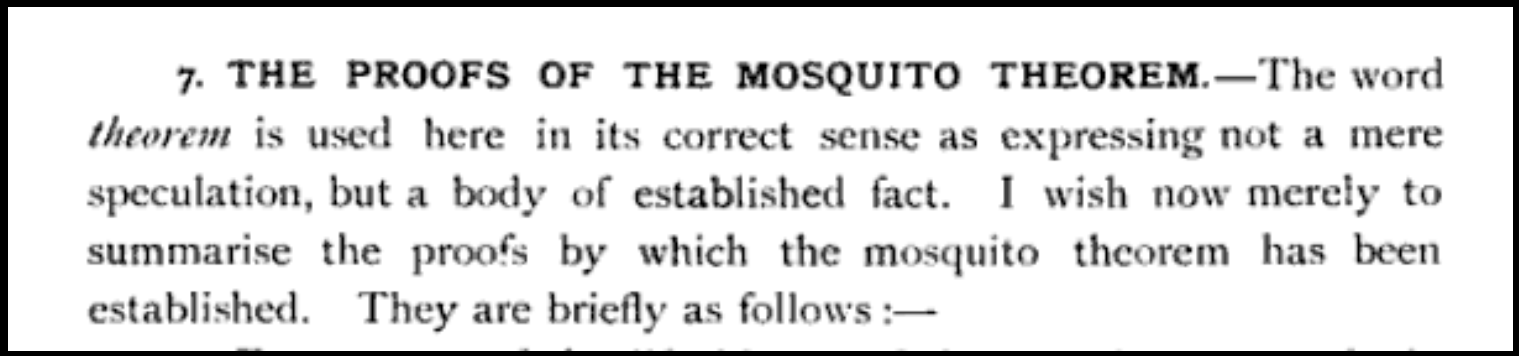

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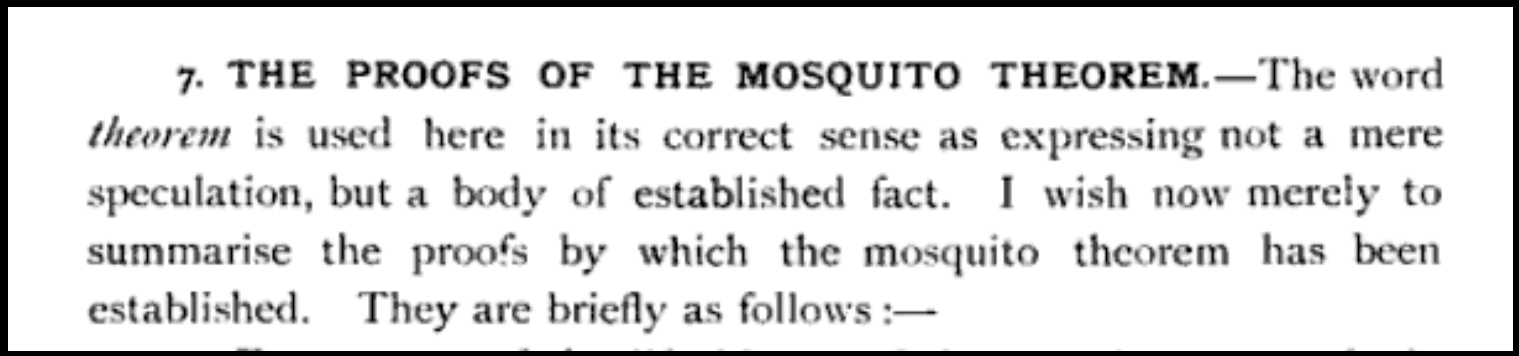

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Potential shortcomings of compartment models:

- no variability between individuals within a compartment
- homogeneous mixing between individuals
- exponentially distributed waiting times
- deterministic

Room for improvement?

What might be missing from the compartment approach?

- individual-level variability
- details, dynamics, or effects of host immunity

With more detailed models, hope to gain understanding of

1. links between immunology (host) and epidemiology (population)
2. ecology of mixed pathogen (multiple virus) communities

Combined effects of these on the evolutionary ecology of pathogens and host public health.

Goals (for today*)

How do infections or exposures that boost immunity affect

- dynamics of an endemic disease*,
- public health planning*,
- ecological interactions between many closely related viruses.

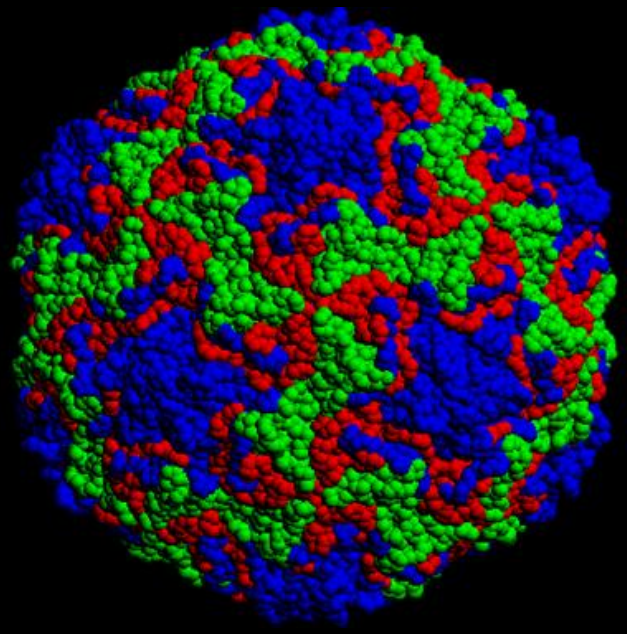
A case study: human rhinoviruses

We each succumb to about 2-3 ‘colds’ per year.

Rhinoviruses cause about half of these colds.

Why study rhinoviruses?

- diverse group - 102 named serotypes
- costly pathogen - $10s of billions per year
- well studied - still poorly understood

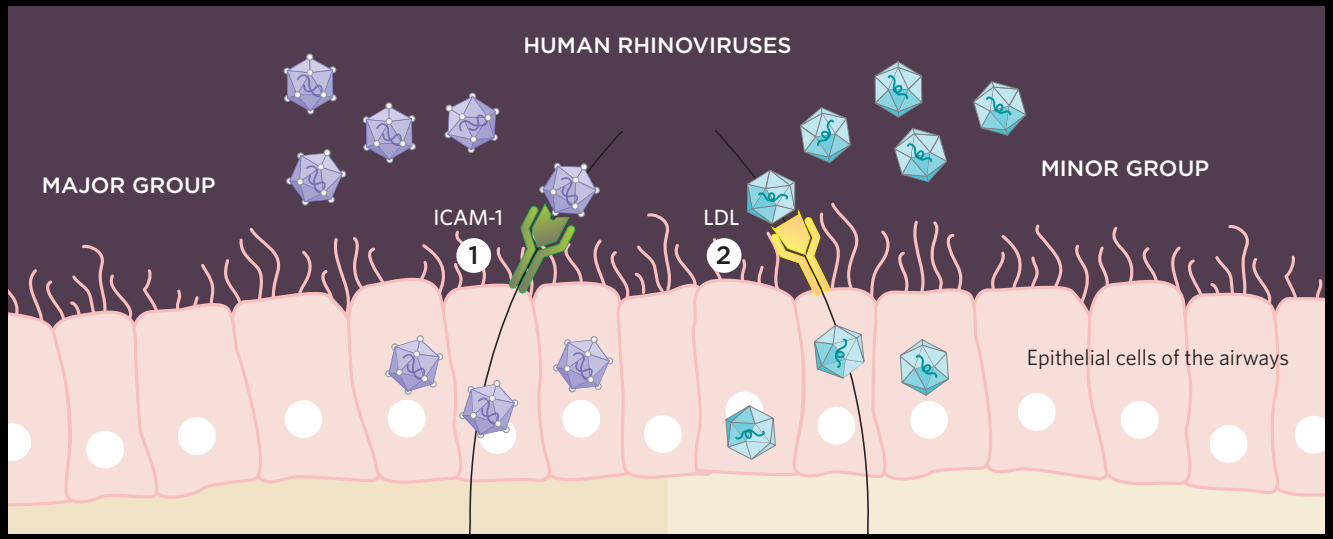


Human rhinovirus 14
Jean-Yves Sgro

Immune response to rhinovirus

Two categories of rhinovirus are the minor group and major group:

- classified based on host cell receptor use



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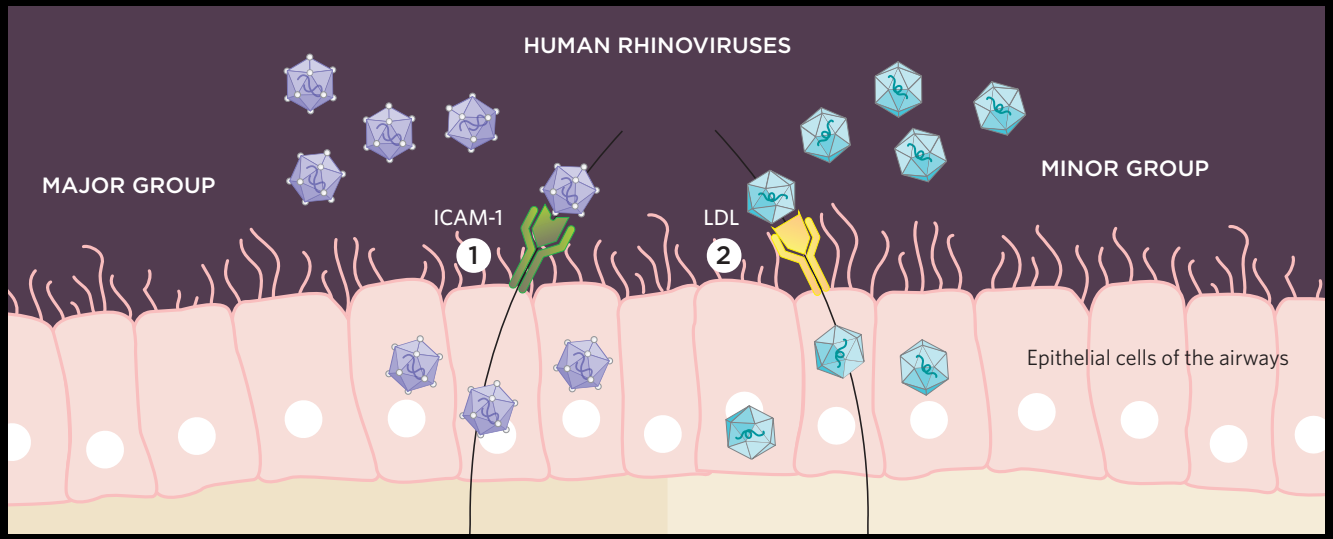

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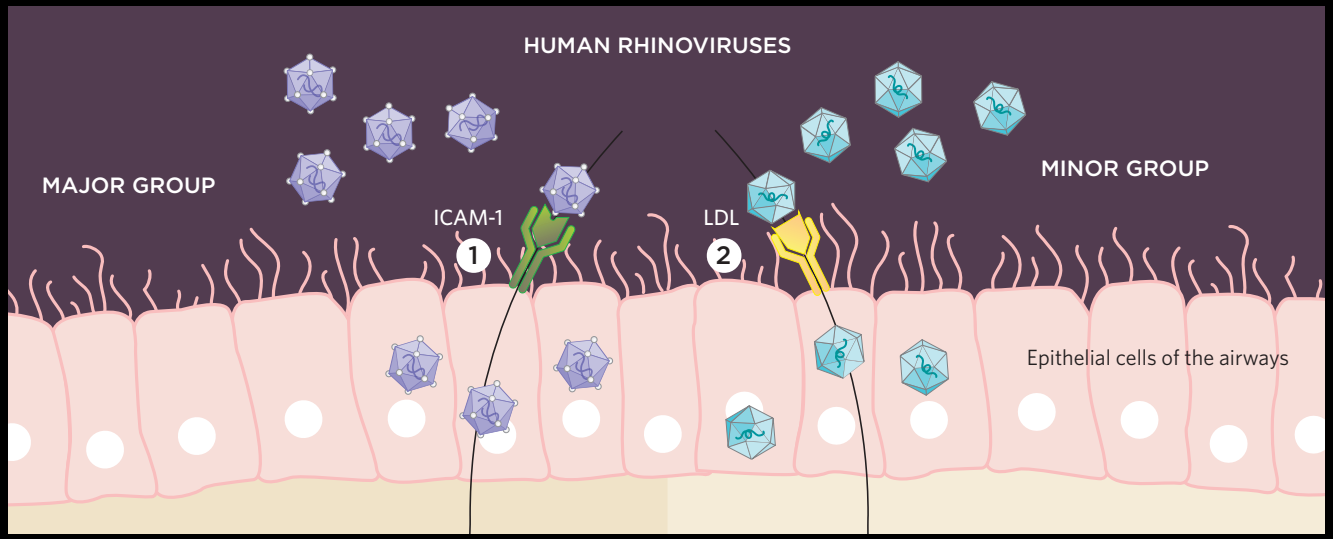

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It was shown in a classic study[1] that

- major group viruses rarely generate immunity
- minor group viruses often generate immunity

[1] Fox, 1985

Persistence of *immunological* memory: British Antarctic Survey

Other respiratory viruses (like influenza) and enteroviruses (like polio) show immunity that

- persists for many years or decades
- blocks or attenuates infection

It was shown[2] that antibody immunity to rhinovirus

- wanes at a rate on the order of many months to a few years
- strongly influences the severity of infection

[2] Holmes *et al.* (1976)

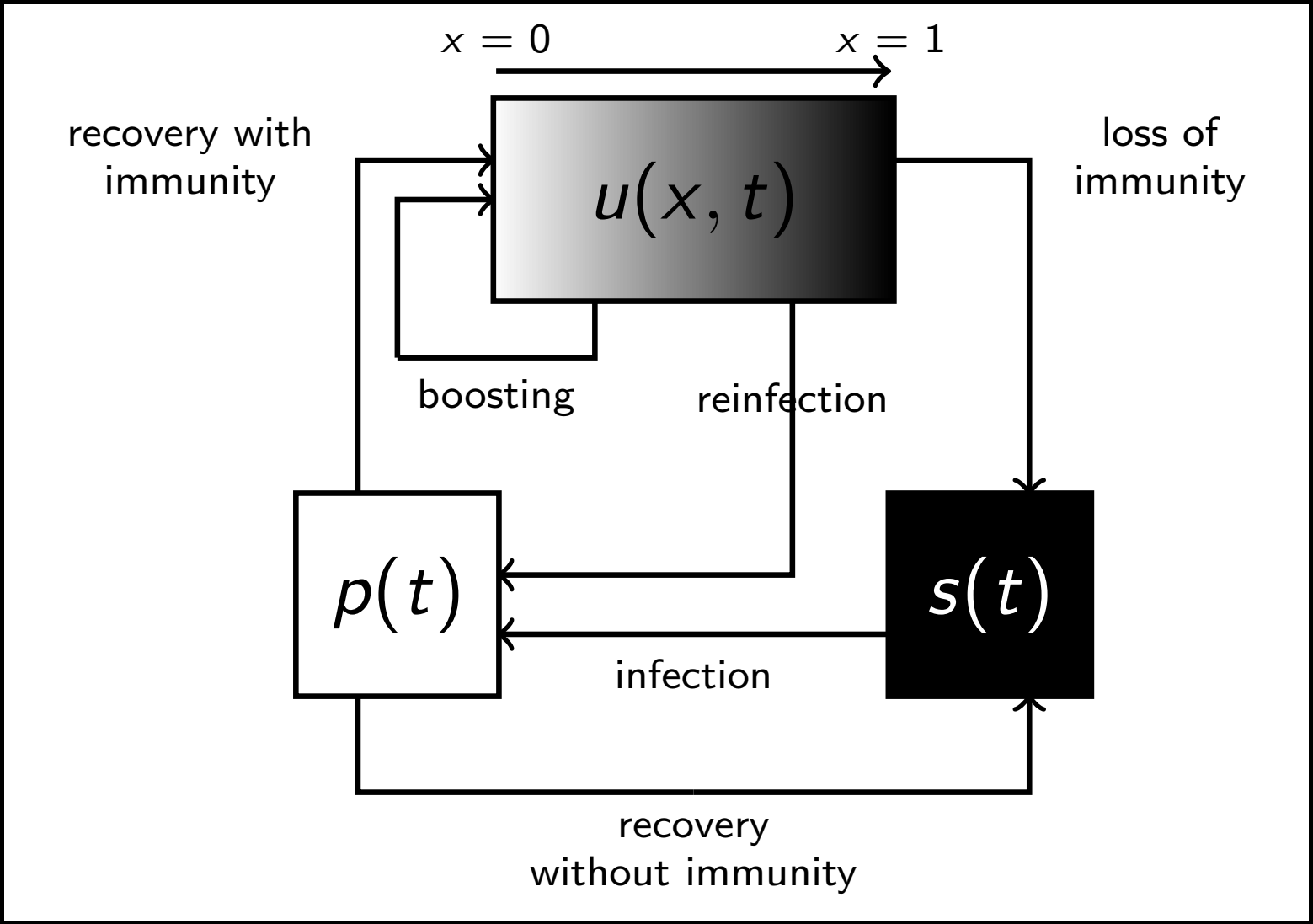
Antiviral immunity

Using a model that characterizes the dynamics of host immunity (here antibodies), we explore the sensitivity of epidemiological dynamics to

- immunogenicity (the amount of immunity)
- waning (the loss of immunity)
- boosting (rise in immunity following reinfection/re-exposure)

Allow strength of immunity to vary in recovered hosts.

Graphical model



Demographic terms not illustrated.

Mathematical model

Let $s(t)$, $p(t)$, and $\overline{u}(t) = \int_0^1 u(x,t)\,dx$, be the susceptible, infectious, and uninfected (immune) fractions of the population.

$$\frac{ds}{dt} = k_u(x)u(x,t)|_{x=1} + (1-\sigma)\gamma p - \lambda_s s p$$

$$\frac{dp}{dt} = \left(\lambda_s s + \int_0^1 (1-q(x'))\lambda_u(x')u(x',t)\,dx' - \gamma\right) p$$

$$\frac{\partial u}{\partial t} + \frac{\partial}{\partial x}\Big(k_u(x)u(x,t)\Big) = -\lambda_u(x)pu(x,t)$$

$$k_u(x)\ u(x,t)|_{x=0} = \left(\sigma\gamma + \int_0^1 q(x')\lambda_u(x')u(x',t)\,dx'\right) p$$

Note: $u(x,t)$ is a density over immune status x.

Parametrization

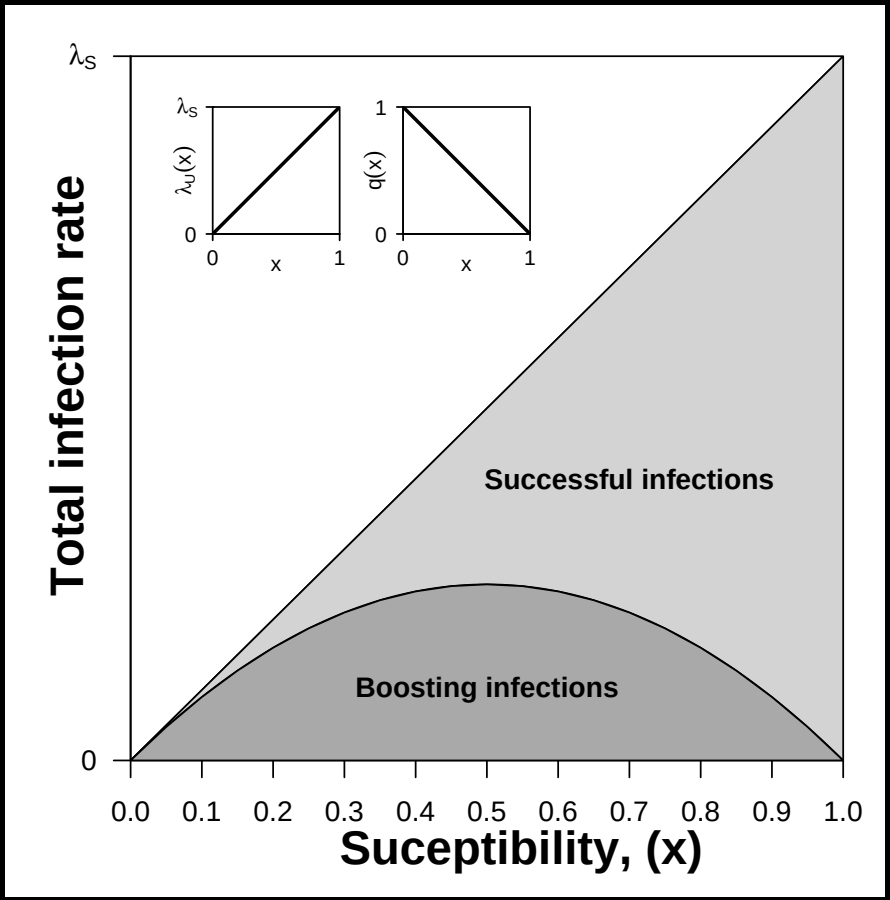
Three functions depend on the immune status, x, of recovered hosts:

- $k_u(x)$: immune waning rate
- $\lambda_u(x)$: total infection rate
- $q(x)$: probability of immune boosting

These parameters (functions) clearly affect

- equilibrium proportions
- stability of endemic equilibria
- equilibrium distribution of $u^*(x)$ with respect to immunity x

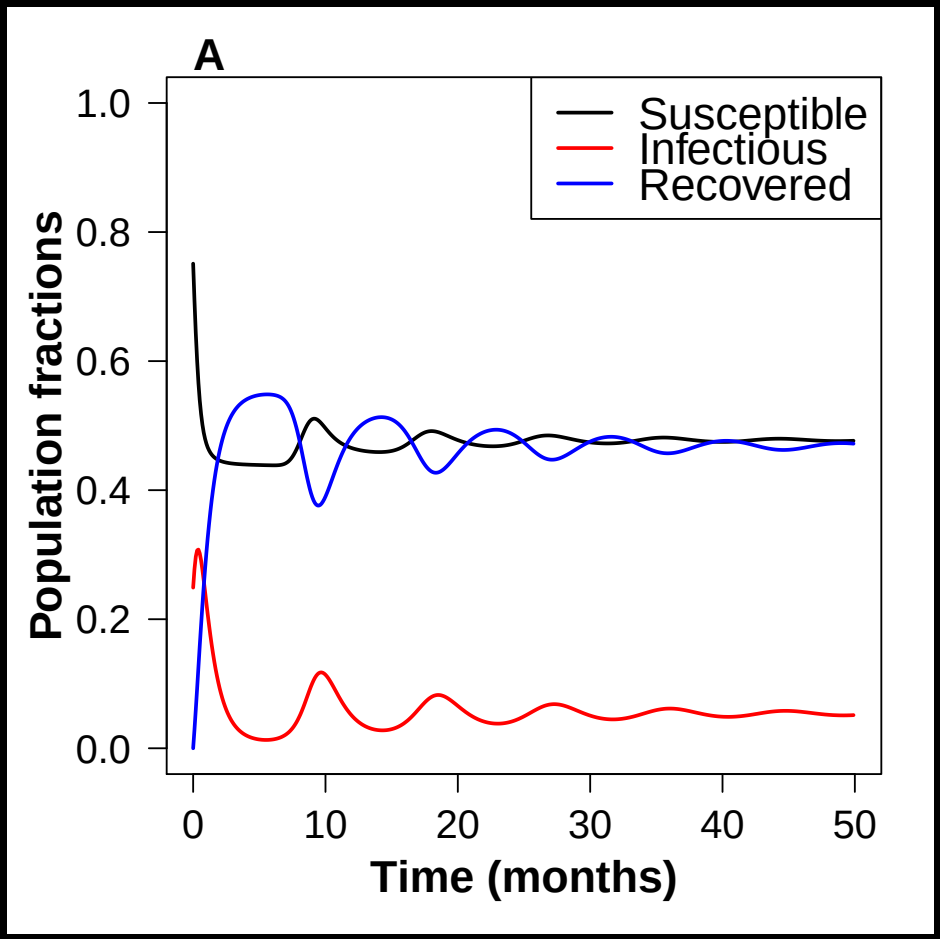
Effects and dynamics of pre-existing immunity



- Total infection rate ($\lambda_u(x)$) increases with susceptibility
- Probability of boosting ($q(x)$) decreases with susceptibility

For today assume that immunity wanes at constant rate, $k_U(x) = K$.

Importance of boosting: Dynamics



- damped oscillations under many parameters

A. Baseline (infections boost strong immunity): $q(x) = 1 - x$

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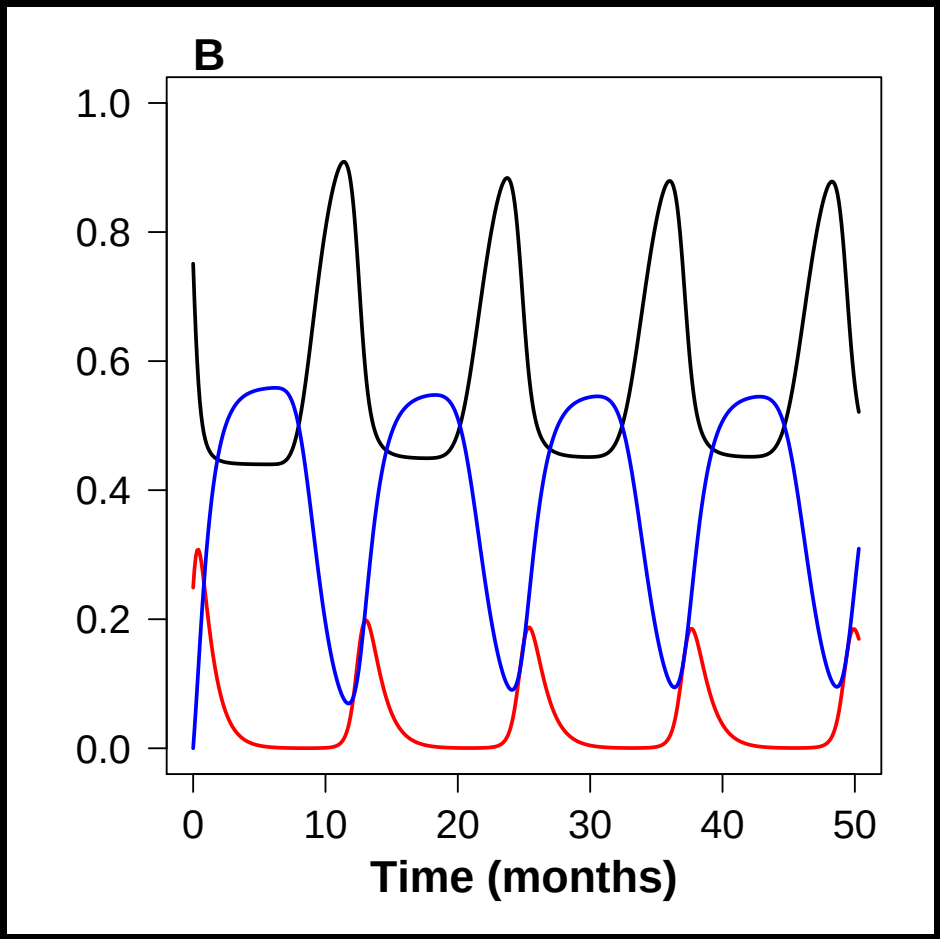

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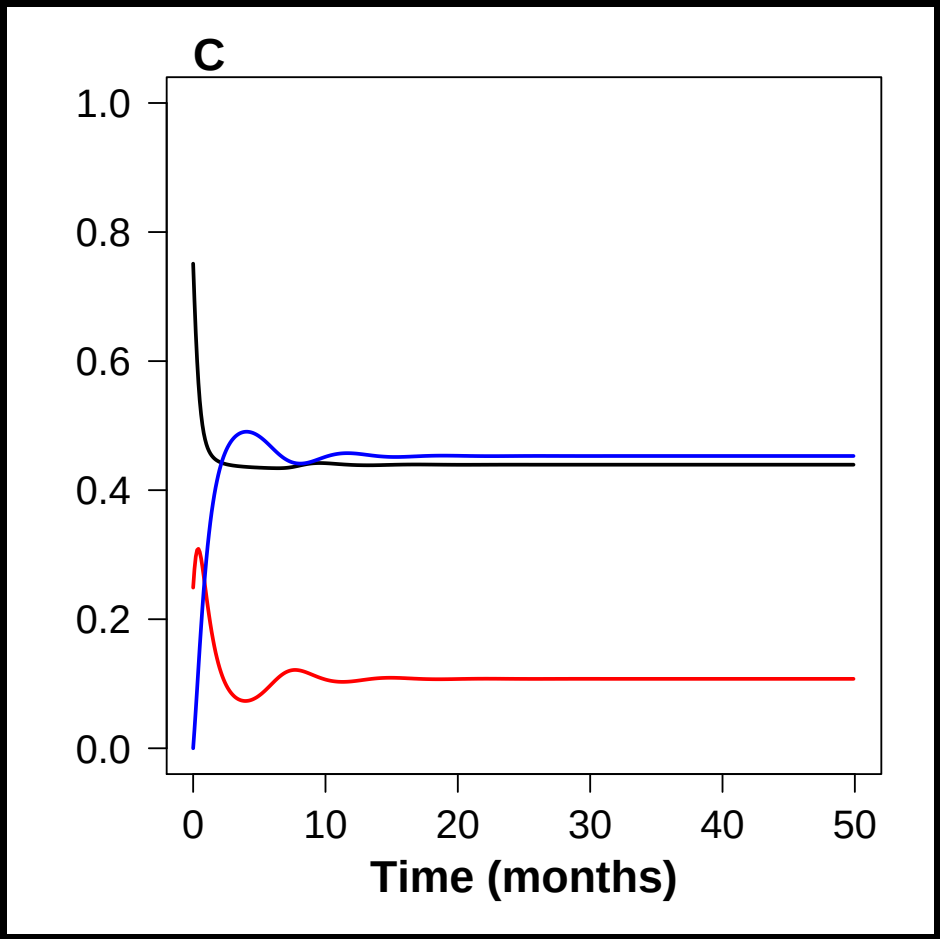
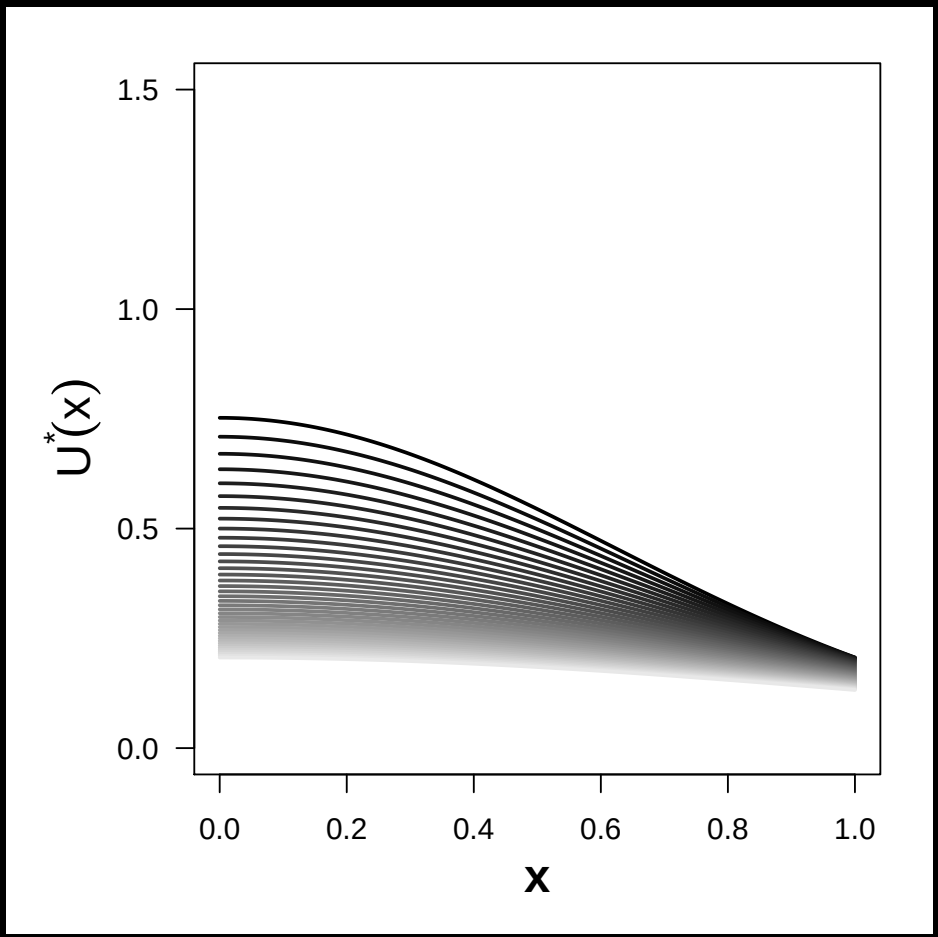


- damped oscillations under many parameters
- sustained oscillations when boosting is probable
- rapidly damped oscillations in the absence of boosting

A. Baseline (infections boost strong immunity): $q(x) = 1 - x$
B. All infections boost immunity: $q(x) = 1$
C. No infections boost immunity: $q(x) = 0$

Equilibrium immune distribution



At equilibrium,

$$u^*(x) \propto G(x)^{p^*} H(x),$$

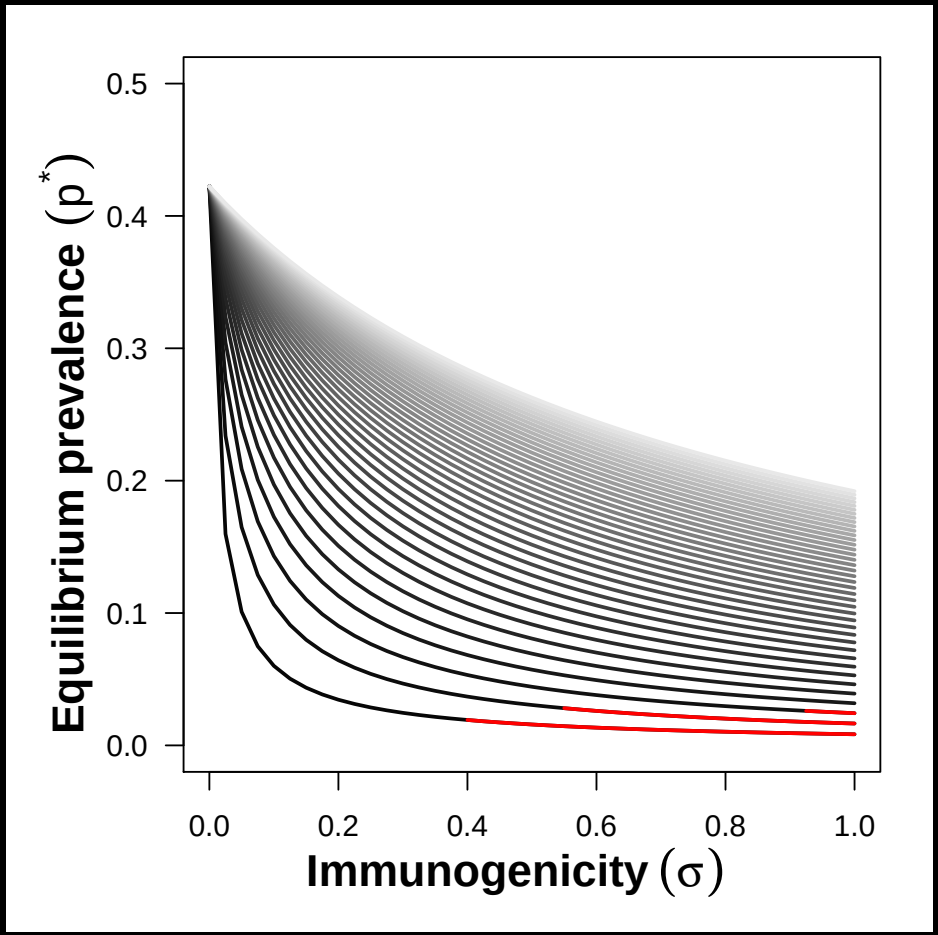
where

$$G(x) = \exp\left(-\int_0^x \frac{\lambda_u(x')}{k_u(x')}\, dx'\right),$$

$$H(x) = \exp\left(-\int_0^x \frac{k_u'(x')+\mu}{k_u(x')}\, dx'\right).$$

Long-lived immunity (black) skewed towards highly immune hosts.
Short-lived immunity (gray) flattens distribution.

Single-serotype prevalence



- Short-lived immunity (high waning or large K, gray) yields high prevalence.
- Strong immunogenicity (large σ) and long-lived immunity (slow waning or small K) drive low prevalence, endemic oscillations (red).

Drivers of oscillation

When reinfections are likely to boost pre-existing immunity,

- bias towards highly immune hosts drastically reduces prevalence
- interepidemic interval increases

Independent of the likelihood of boosting, oscillations arise when highly immunogenic pathogens generate long lasting immunity.

- For the rhinoviruses the 'minor group' viruses are the more immunogenic type.
- Do they tend to oscillate in the real-world?

Summary: Oscillations and public health

Recall, the British Antarctic Survey study found that

- isolated patients were highly susceptible to severe colds
- non-isolated counterparts developed fewer and more mild colds

Thus, multiple mechanisms can drive oscillations in prevalence and average immunity at a population level which might moderate the severity of disease at an individual level.

Complications

Partially immune, reinfected hosts might experience differences in

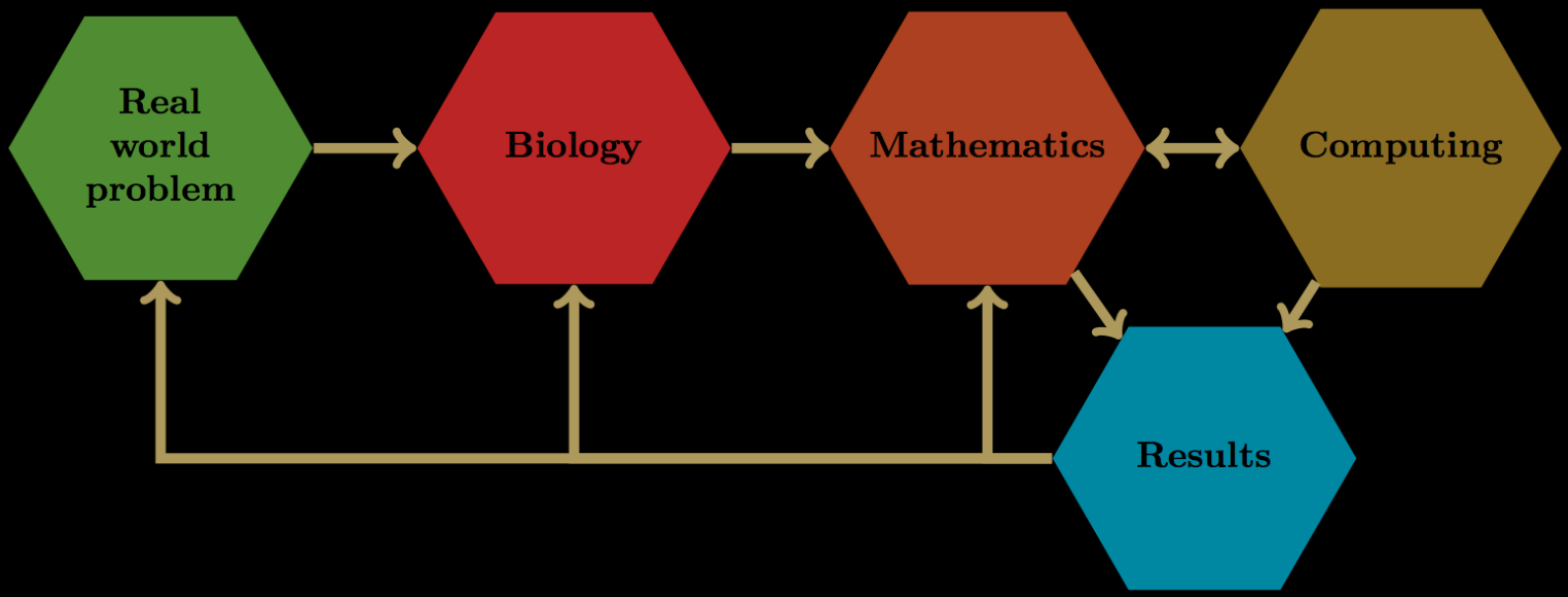
- duration
- infectiousness

of an infection depending on the strength of immunity.

These effects not included in the model, but could be if necessary.

Remember *'as simple as possible, but no simpler.'*

Mathematical biology



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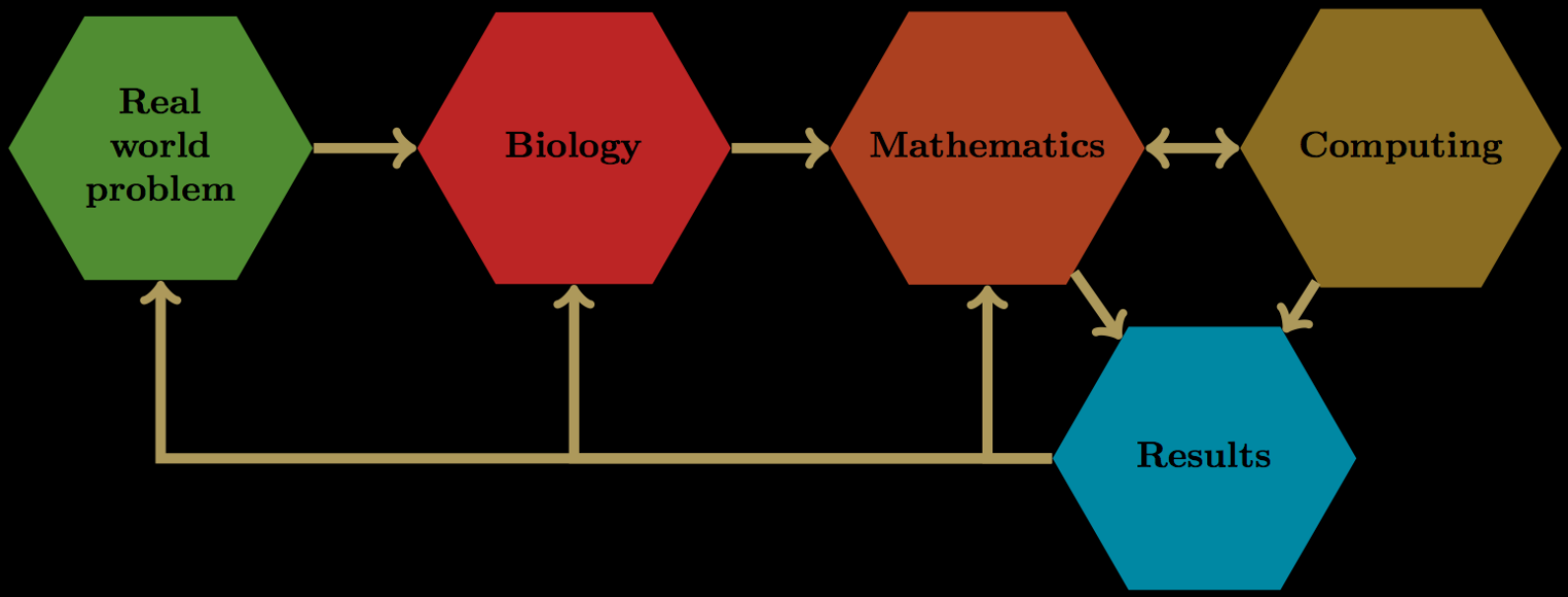

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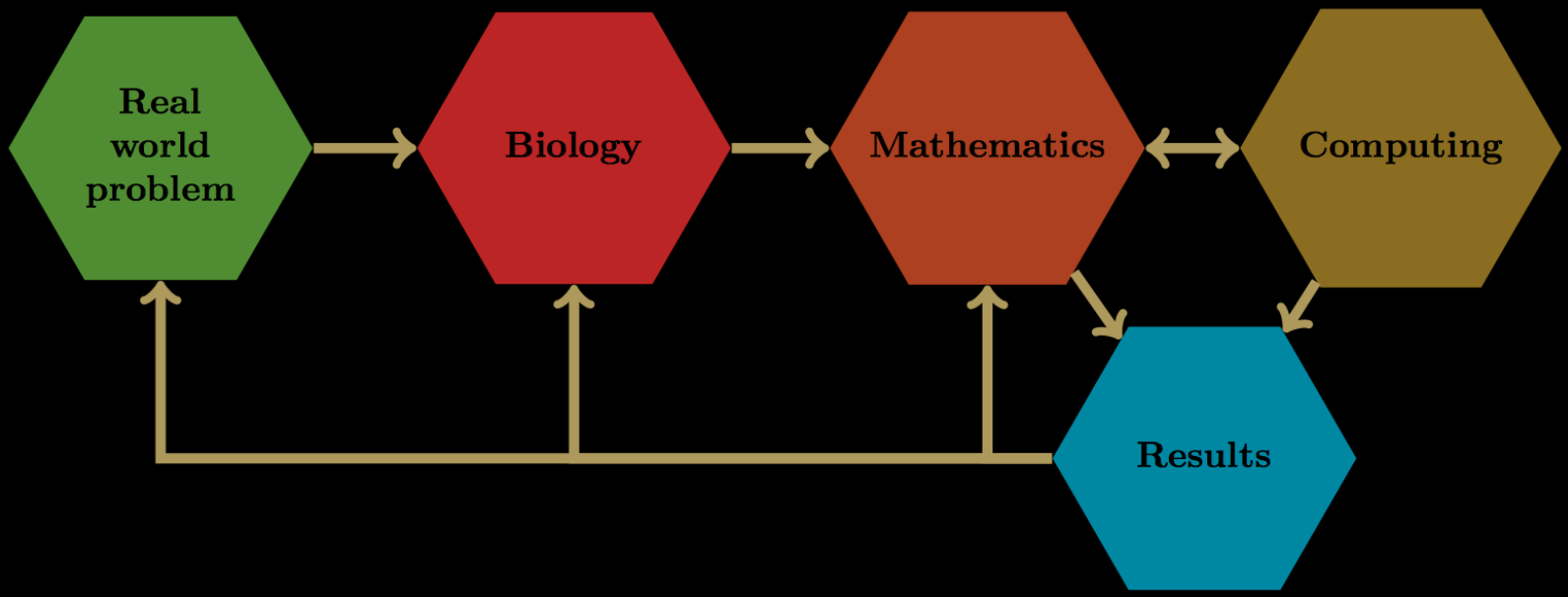

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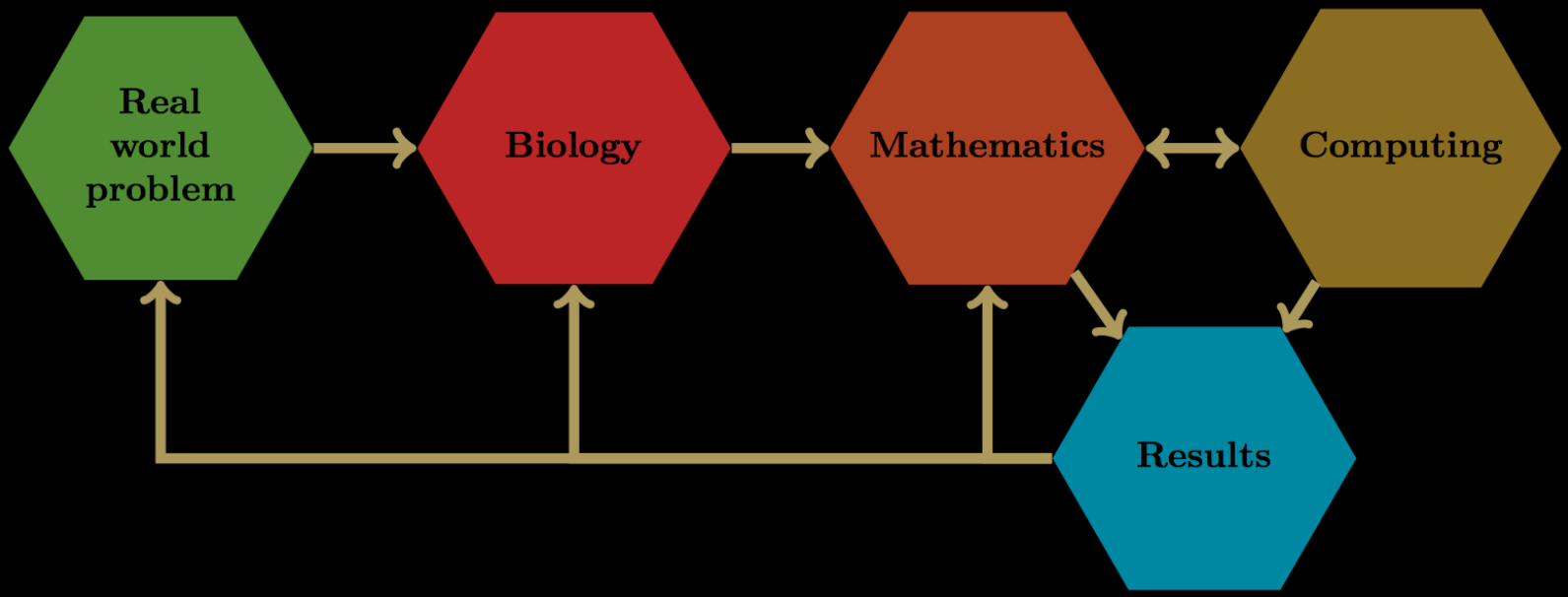

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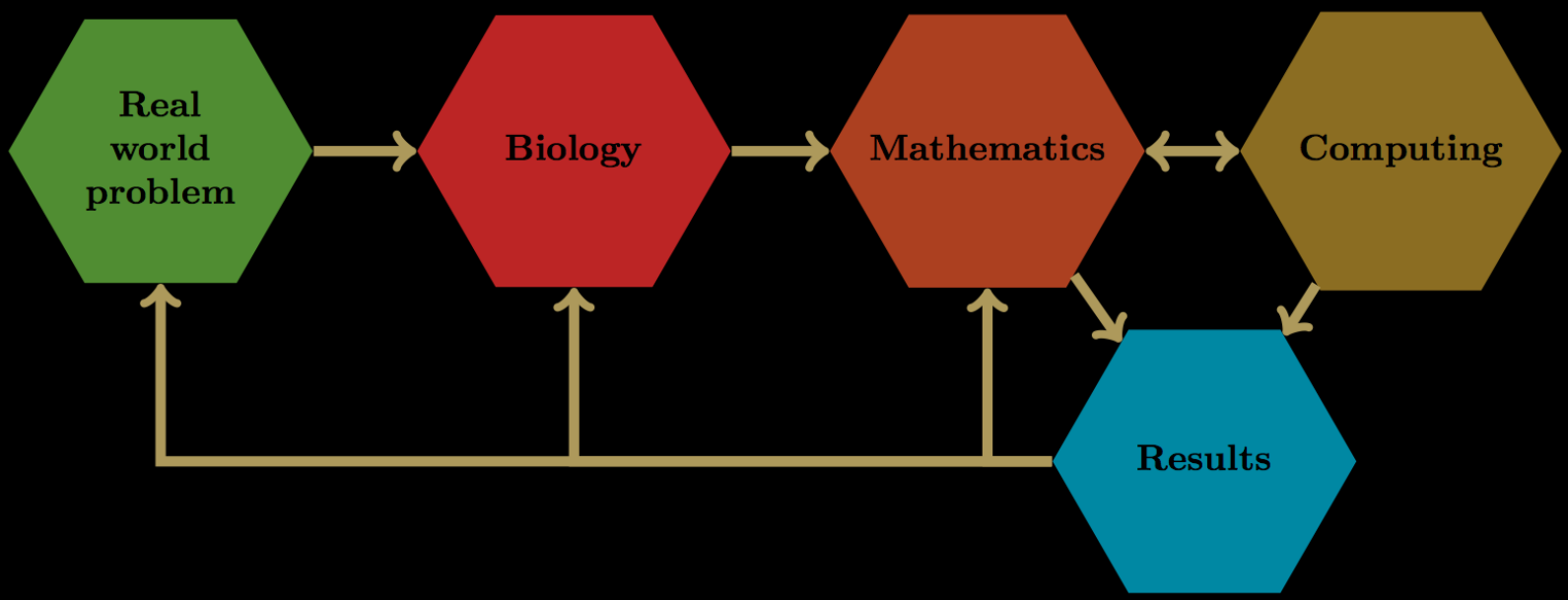

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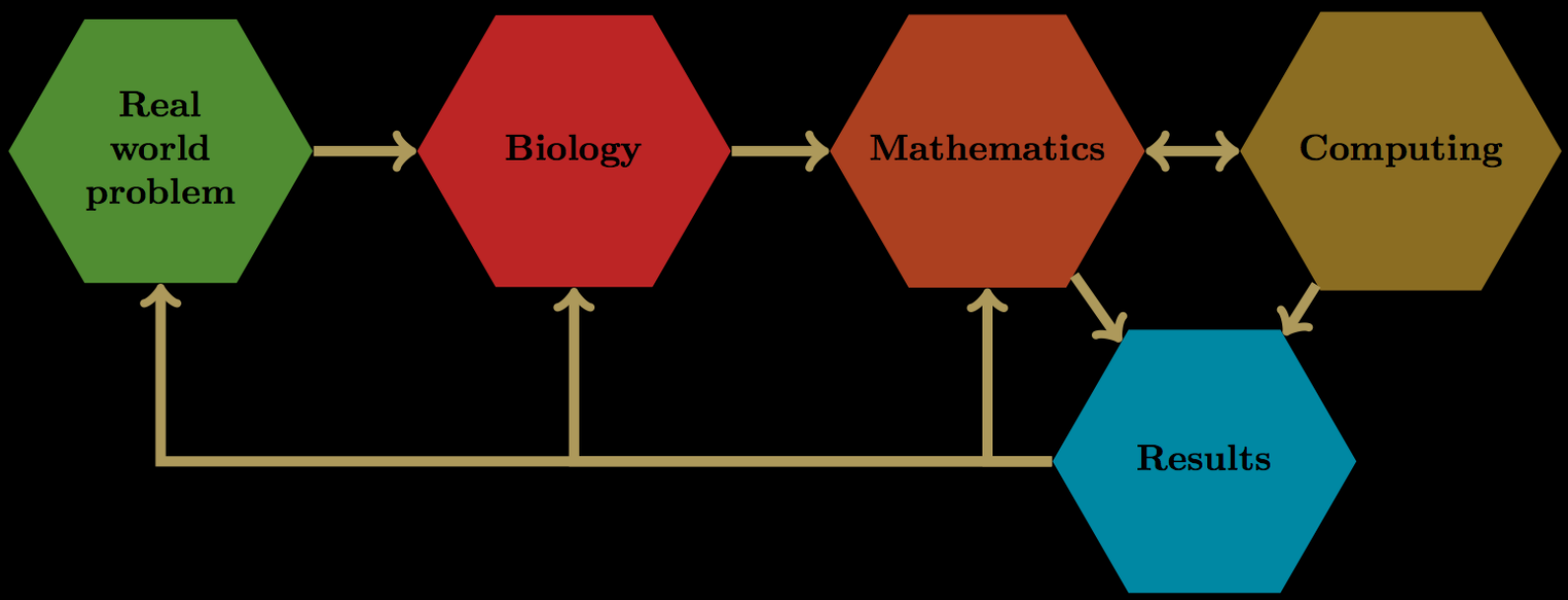

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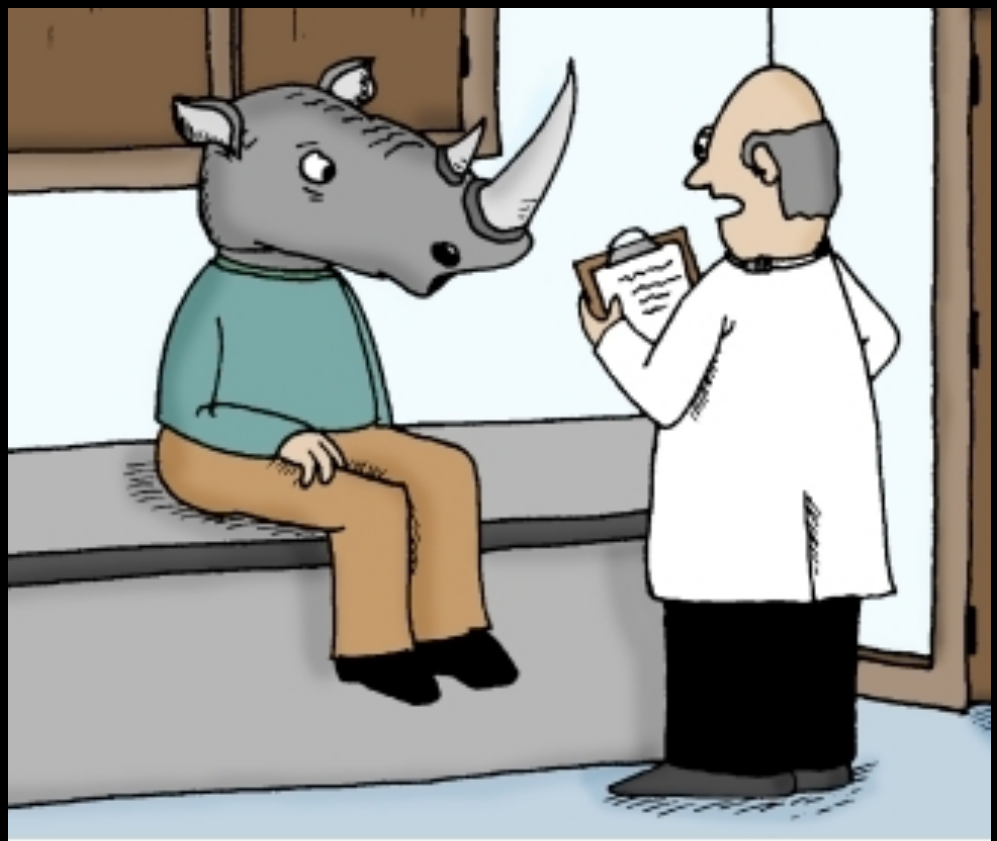
- Facts about host behavior, epidemiology, immunology, and virology.
- Modeling, ODEs, PDEs, analysis, and ....
- Numerical solutions and visualization.
- Drivers of oscillation, health of the population, ecology of pathogens.

The end

Thanks for this opportunity.

Thanks for your attention.

Any questions?



From: Somewhere on the internet.

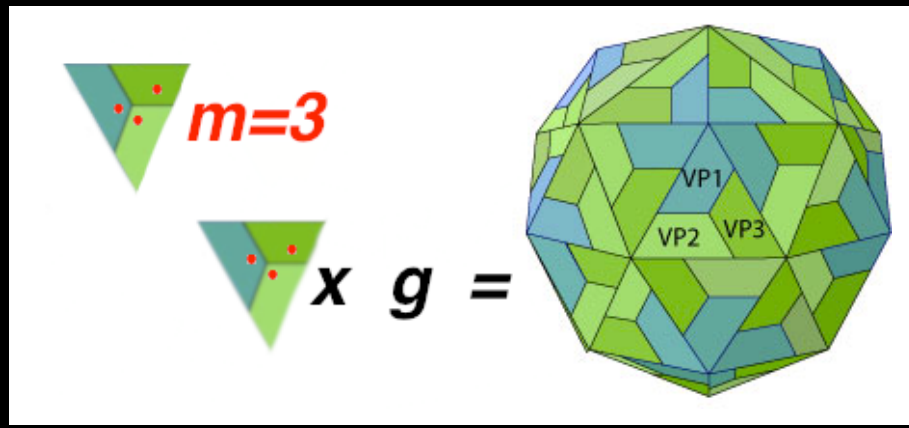
Cross-reactivity relationships

The probability that an antibody against type i neutralizes a virus of type j is given by

$$P_{match,ij} = 1 - (1 - (1 - d_{ij})^m)^g.$$

From binomial distribution with

- probability of match at a m binding locations in an antigenic site is $(1 - d_{ij})^m$ ('success')
- probability of match at one or more of g groups antigenic sites ('trials')



What is the probability that an antibody binds a virus?

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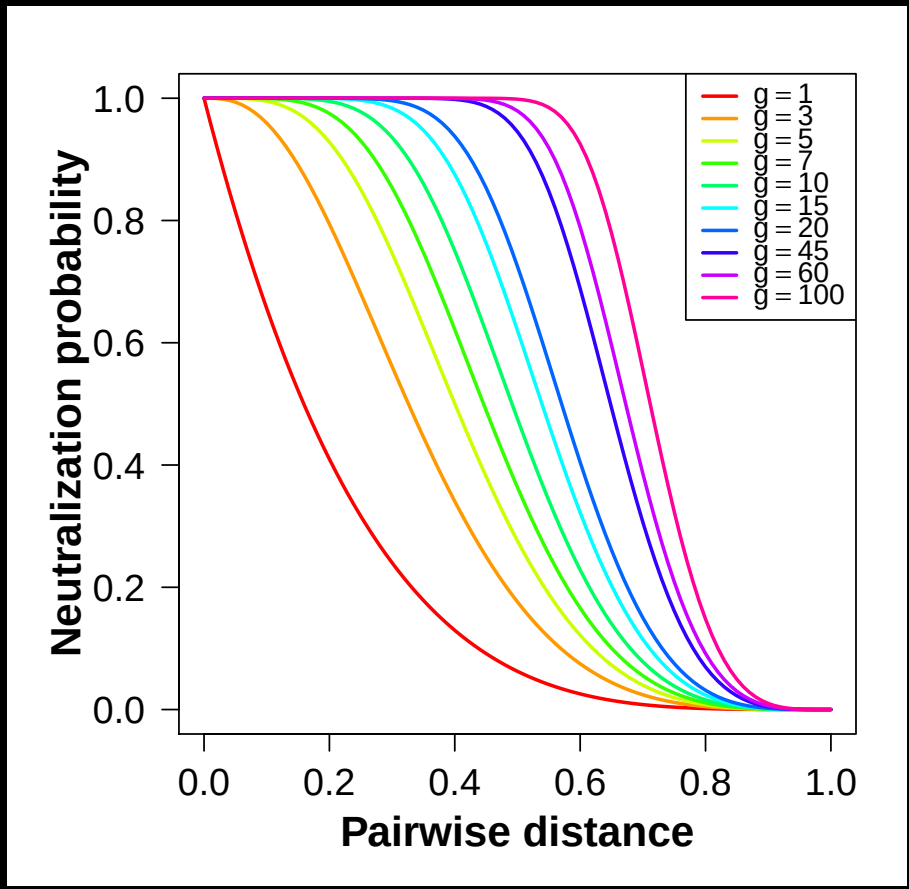


Susceptibility-structured model

Let S be the fraction of susceptible hosts, p_i be the fraction infected by type i, and $U_i(x,t)$ be the density of hosts with susceptibility x to type i.

$$\frac{dS}{dt} = \sum_{j=1}^{n} \Big[k_U(x) U_j(x,t)|_{x=1} + (1-\sigma_j)\gamma p_j - \lambda_S S p_j \Big]$$

then for $i = 1, \ldots, n$

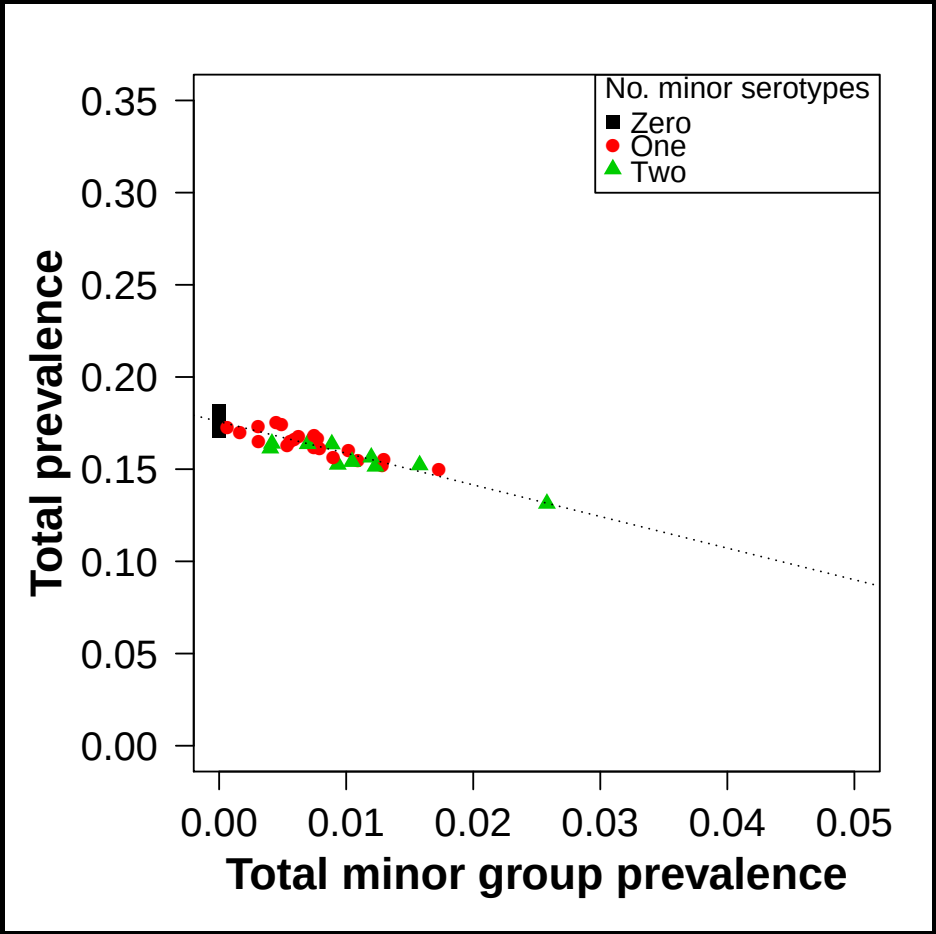
$$\frac{dp_i}{dt} = \lambda_S S p_i + p_i \sum_{j=1}^{n} \Big[\int_0^1 (1 - q(x', d_{ij}))\lambda_U(x', d_{ij}) U_j(x', t)\, dx' \Big] - \gamma p_i$$

$$\frac{\partial U_i}{\partial t} + \frac{\partial}{\partial x}\Big(k_U(x) U_i(x,t) \Big) = -\sum_{j=1}^{n} \Big[\lambda_U(x, d_{ji}) U_i(x,t) p_j \Big]$$

$$k_U(x) U_i(x,t)|_{x=0} = \sigma_i \gamma p_i + \sum_{j=1}^{n} \Big[p_j \int_0^1 q(x', d_{ji}) \lambda_U(x', d_{ji}) U_i(x', t)\, dx' \Big]$$

$d_{ij} = d_{ji}$ is the antigenic distance between a pair (from heat map).

Cost of immunogenicity



Idea: Sample groups of 10 serotypes from the population of 20 available.
Track minor group prevalence.
Track total prevalence.

- Total minor group prevalence predicts total prevalence.
- Immunity to minor group serotypes reduces total prevalence.