Lecture 3

Disease Ecology and Evolutionary Perspectives

SIR model

Let *S*, *I* and *R* denote the densities of susceptible, infected and recovered hosts, and describe the respective rates of change as

$$\dot{S} = \theta - dS - \lambda S$$
$$\dot{I} = \lambda S - dI - \gamma I - \alpha I$$
$$\dot{R} = \gamma I - dR$$

where θ is a birth rate, *d* is the per capita death rate, λ, the force of infection, is an increasing function of the infective density, γ is the per capita recovery rate, α is the virulence.

Basic reproduction number, R_0

R_0 is the expected number of new infections generated by an infected individual in an otherwise totally susceptible population. If the force of infection takes the linear form $\lambda = \beta I$, then

$$R_0 = \frac{\beta}{d + \gamma + \alpha}$$

If $R_0 < 1$ the pathogen dies out.

Evolution of parasite traits

Antigenic specificities, σ

Virulence, α

Transmission, β

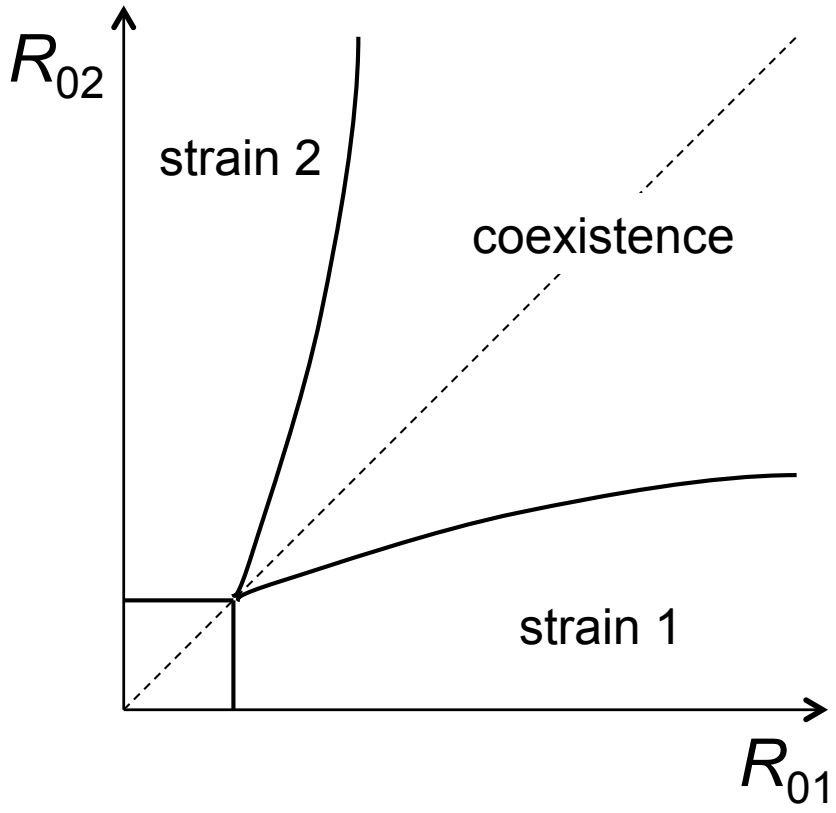
Antigenic diversity

Let S_0, S_1 and S_2 denote the densities of uninfected hosts who have previously experienced no strains, strain 1 and strain 2, respectively, and let I_1 and I_2 denote the densities of hosts infected with strains 1 and 2, respectively. The rates of change are

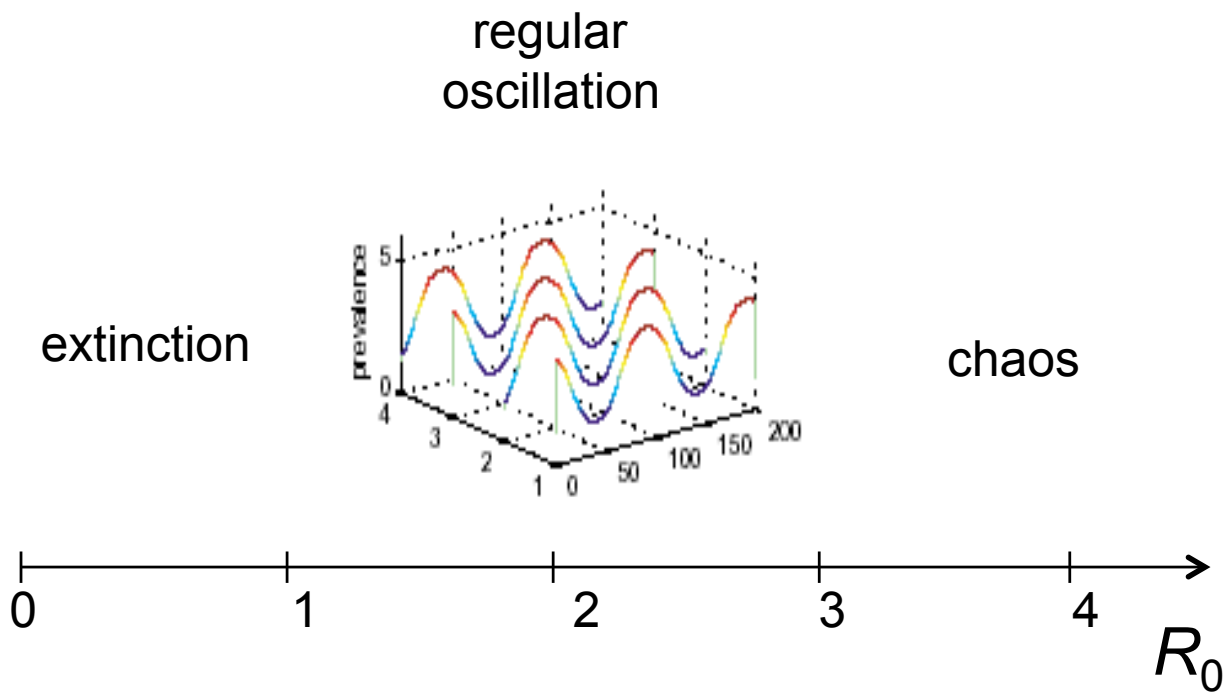
$$\dot{S}_0 = \theta - dS_0 - (\lambda_1 + \lambda_2)S_0$$
$$\dot{S}_1 = \lambda_1 S_0 - dS_1 - \sigma\lambda_2 S_1$$
$$\dot{S}_2 = \lambda_2 S_0 - dS_2 - \sigma\lambda_1 S_2$$
$$\dot{I}_1 = \lambda_1 S_0 + \sigma\lambda_1 S_2 - dI_1 - \gamma I_1 - \alpha I_1$$
$$\dot{I}_2 = \lambda_2 S_0 + \sigma\lambda_2 S_1 - dI_2 - \gamma I_2 - \alpha I_2$$

where λ_1 and λ_2 represent the force of infection for strains 1 and 2, respectively, and σ is the factor reducing susceptibility to reinfection by the heterologous strain due to cross-immunity.

Competitive exclusion



Two loci, two alleles



n strains

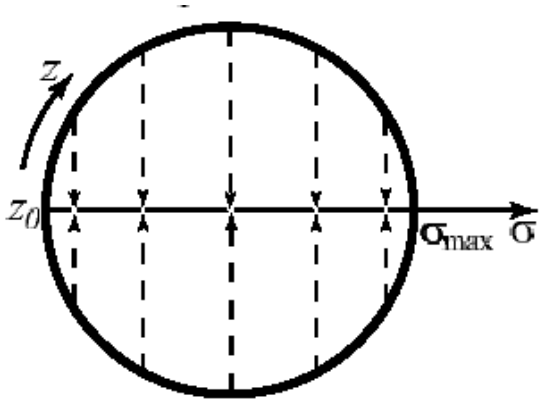
Strains indexed by the set $N = \{1, 2, \ldots, n\}$ and ordered by similarity. Strains compete for hosts and interact through cross-reactive immunity. The dynamics of n strains are described by a system of $2^n + n$ equations.

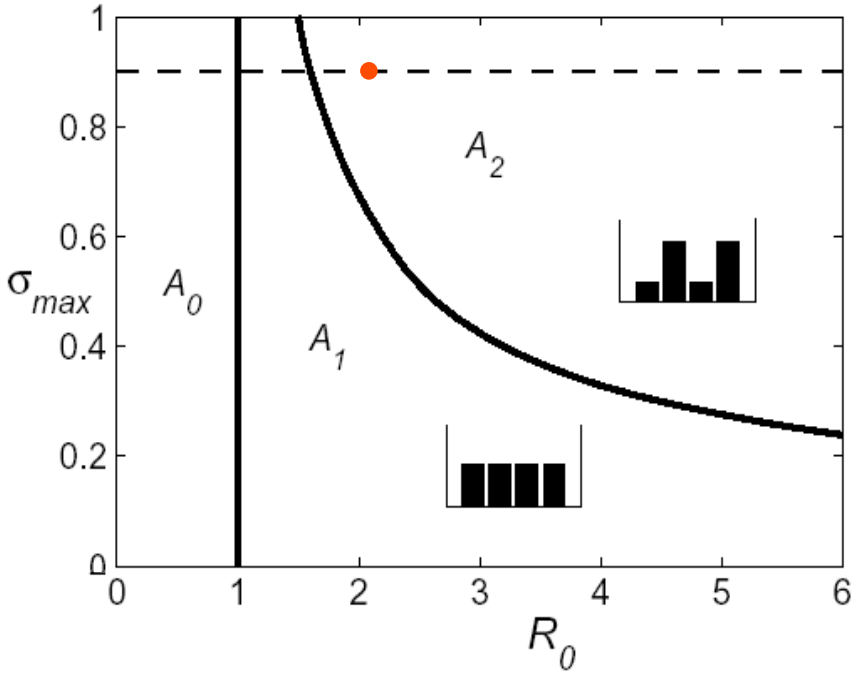
$$\dot{S}_{\varnothing} = e - \sum_{i \in N} \sigma^i_{\varnothing} \Lambda^i S_{\varnothing} - e S_{\varnothing}$$

$$\dot{S}_J = \sum_{i \in J} \sigma^i_{J \setminus i} \Lambda^i S_{J \setminus i} - \sum_{i \notin J} \sigma^i_J \Lambda^i S_J - e S_J$$

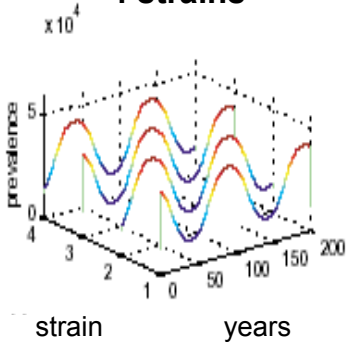
$$\dot{\Lambda}^i = R_0 \sum_{J \subseteq N} \sigma^i_J \Lambda^i S_J - \Lambda^i$$

n strains

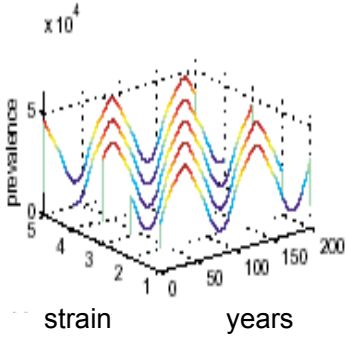




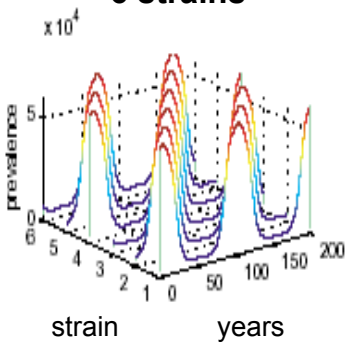
4 strains



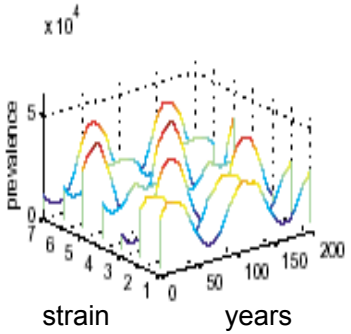
5 strains



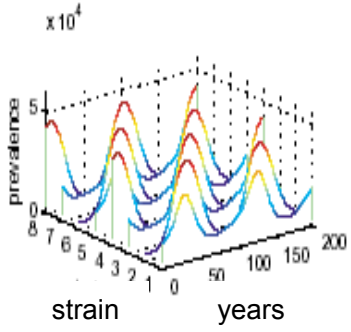
6 strains



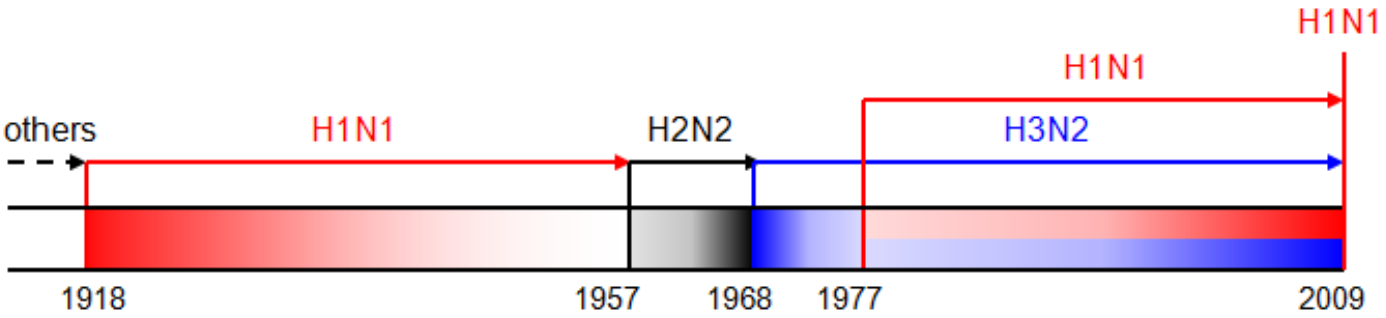
7 strains



8 strains

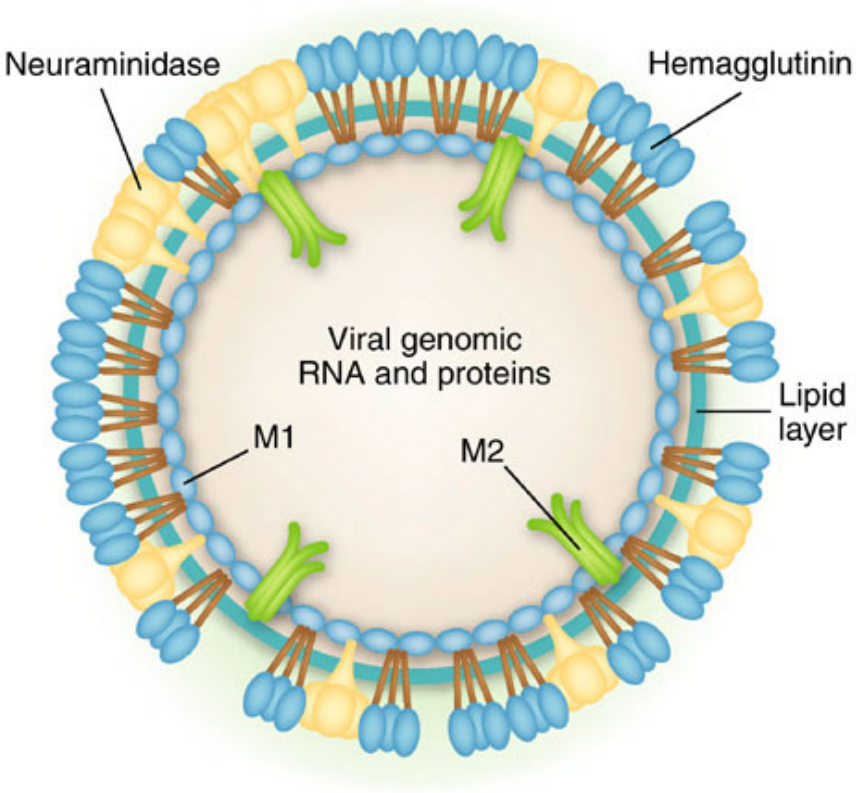


Influenza A antigenic evolution

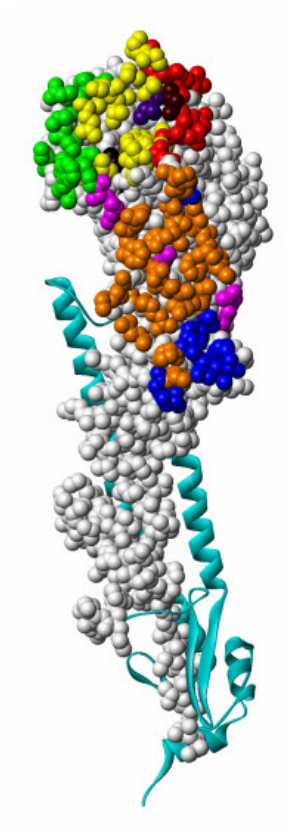


Influenza A antigenic evolution

Influenza virion:

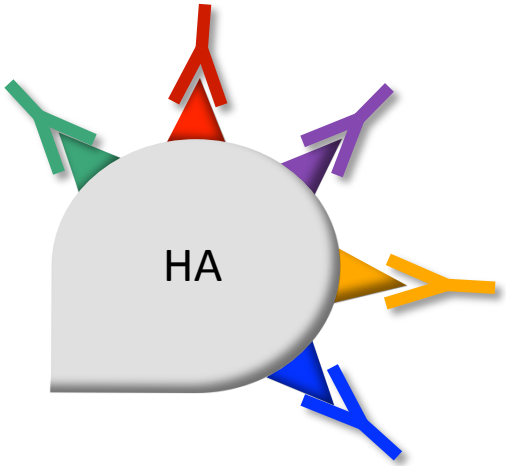


Hemagglutinin (HA):

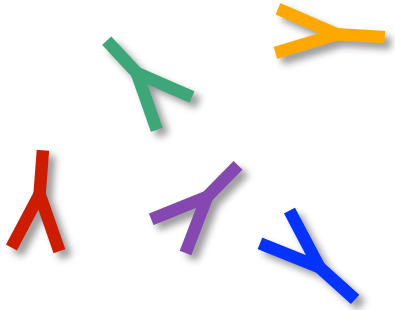


Influenza A antigenic evolution

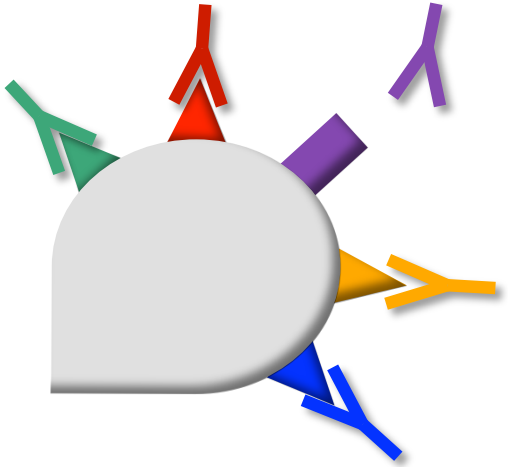
Polyclonal immune response:



Memory:



Mutant:

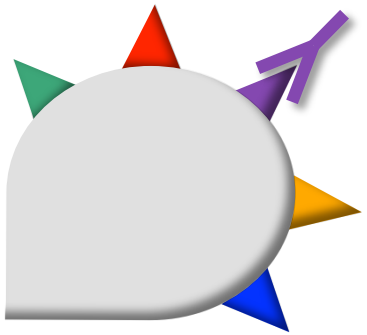


Antigenic changes occur with a frequency of 10^{-6} per infectious dose.

The frequency of variants with multiple mutations is prohibitingly low!

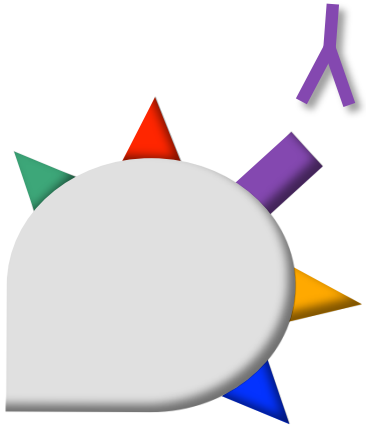
Influenza A antigenic evolution

Monoclonal immune response:



Memory:

Mutant:

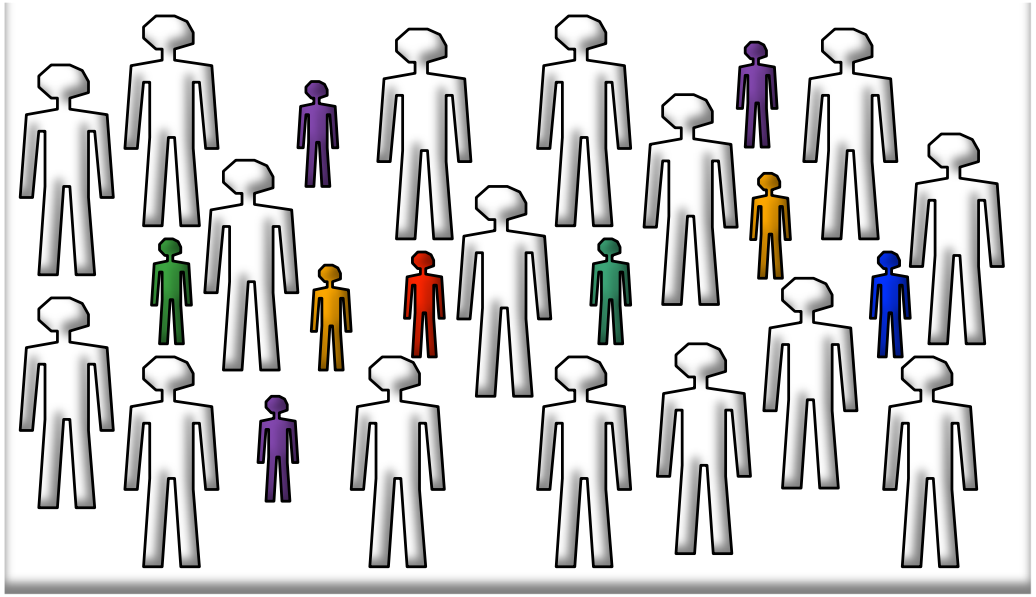


Mutations are serially selected by hosts with different monoclonal responses.

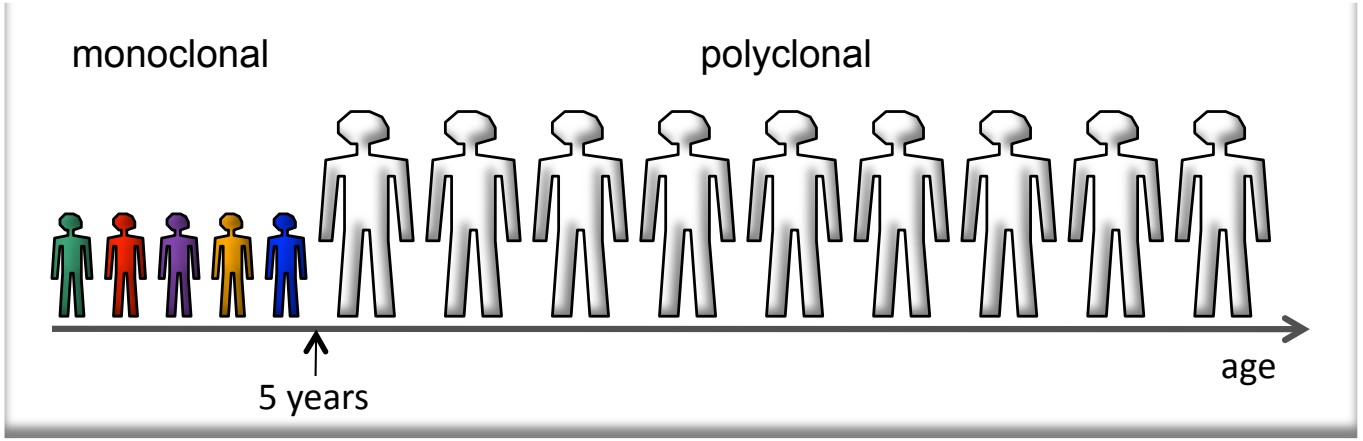
Several passages are required to select a drift variant of epidemiologic significance.

Epidemiology and evolution of influenza A

Individual-based model:

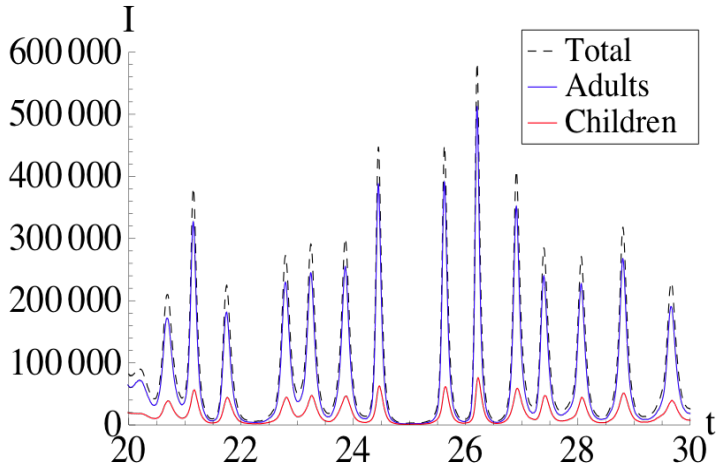


Transition at 5 years of age:

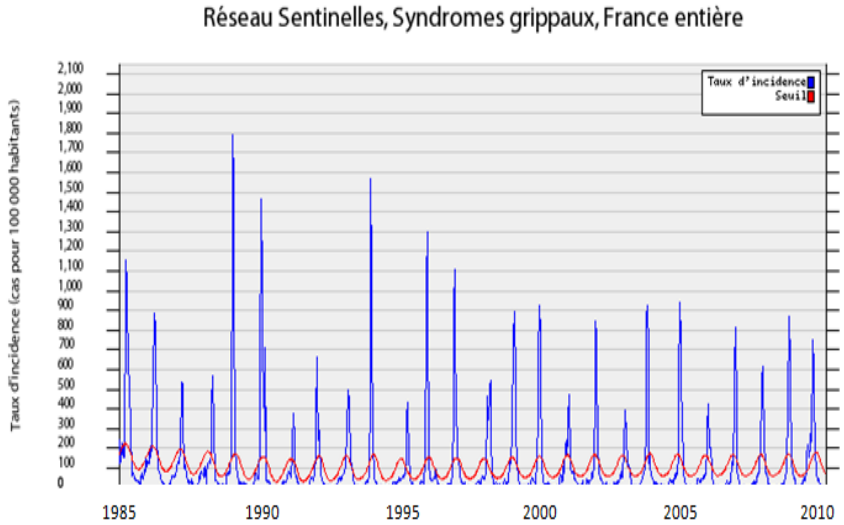


Epidemiology and evolution of influenza A

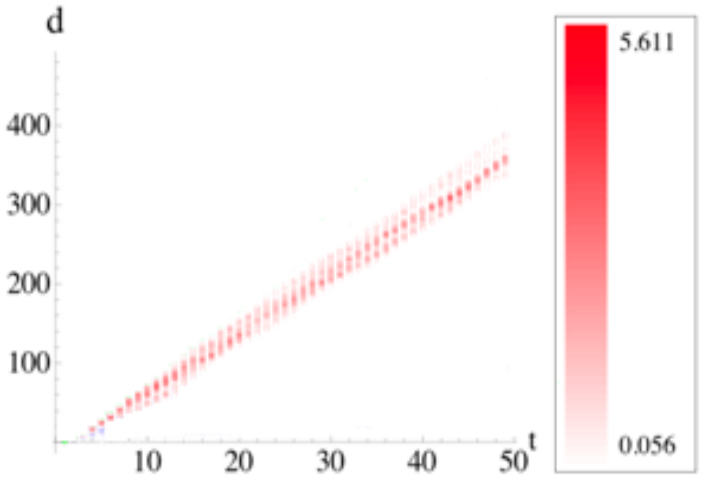
Simulation

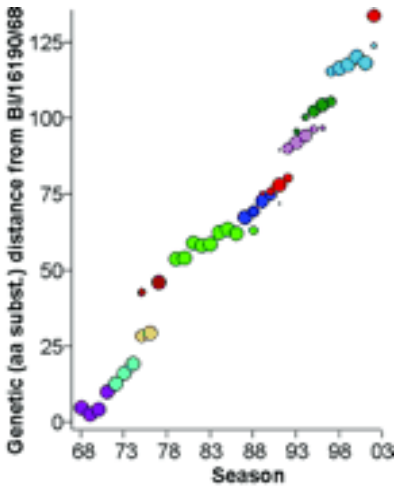


Data



websenti.b3e.jussieu.fr/sentiweb

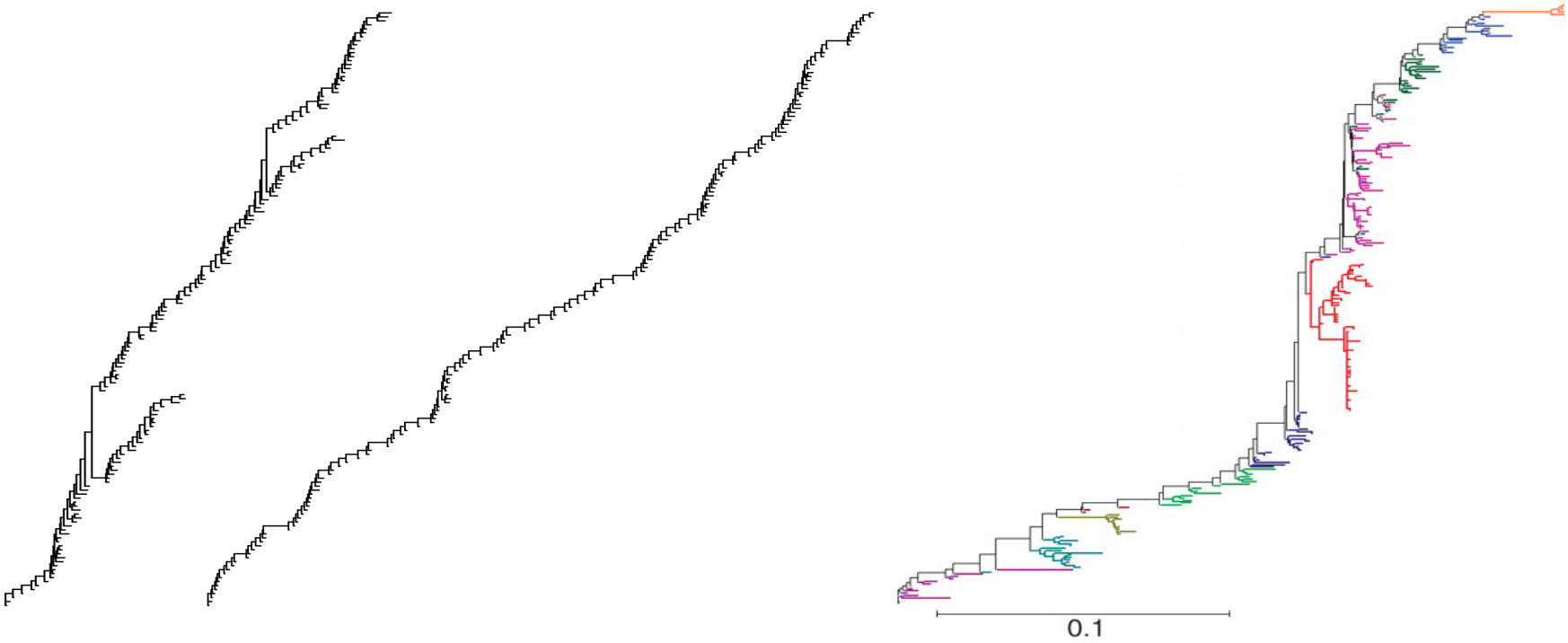




Ladder-like trees

monoclonals enable antigenic escape
polyclonals limit diversity

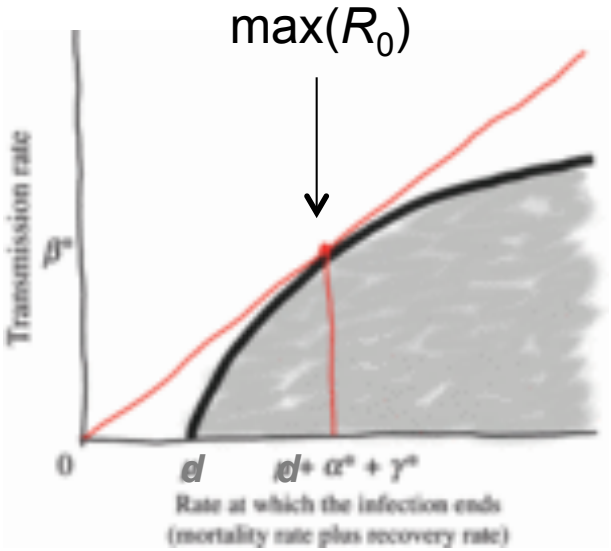
phylodynamics relies on this heterogeneity



Virulence-transmission tradeoff

A 'well-balanced' host-parasite association is not necessarily one in which the parasite does little harm to its hosts. ... Transmission efficiency, and hence reproductive success, is often positively correlated with parasite virulence.

Anderson and May (1982)
Ewald (1983)



However, empirical evidence is conflicting!

Price equation

Let N_i denote the number of asexual individuals of strain i, for $1 \leq i \leq n$, and describe the respective rates of change as

$$\dot{N}_i = r_i N_i - \mu N_i + \mu \sum_{j=1}^{n} m_{ji} N_j$$

where r_i is the per capita rate of change (fitness) of strain i, μ is the mutation rate for all strains, m_{ji} is the probability that a mutation occuring in strain j will result in strain i.

In frequency notation, with q_i denoting the frequency of strain i, we obtain the fundamental equation for the rate of change of strain frequencies

$$\dot{q}_i = q_i (r_i - \bar{r}) - \mu q_i + \mu \sum_{j=1}^{n} m_{ji} q_j$$

where $\bar{r}$ is the average fitness of all strains in the population.

Price equation for the evolution of a specific trait

The rate of evolutionary change in the average value of a trait, *x*, can be derived as

$$\begin{aligned}\dot{\bar{x}} &= \sum_{i=1}^{n} x_i \dot{q}_i \\ &= \left(\sum_{i=1}^{n} q_i x_i r_i - \bar{r}\,\bar{x} \right) - \mu \left(\bar{x} - \sum_{i,j} x_i m_{j\,i} q_j \right) \\ &= \mathrm{cov}(x, r) - \mu\left(\bar{x} - \bar{x}_m\right)\end{aligned}$$

where cov(*x*,*r*) is the covariance between *x* and *r* across all strains, and

$$\bar{x}_m = \sum_{i,j} x_i m_{j\,i} q_j$$

is the average trait value of all mutations that arise.

Applying Price equation to epidemiological models

Take the perspective of the host and interpret q_i as the frequency of all infected hosts that harbour a parasite of strain *i*, m_{ji} the probability that an infection with strain *j* undergoes a transition to an infection with strain *i*, and r_i is the per capita rate of change of hosts infected with strain *i*.

If I_i is the number of hosts infected with strain *i*, and $\lambda_i = \beta_i I_i$ the force of infection with that strain, then we write the *SIR* model as

$$\dot{S} = \theta - dS - S\sum_i \beta_i I_i$$

$$\dot{I}_i = S\beta_i I_i - dI_i - \gamma I_i - \alpha_i I_i$$

$$= r_i I_i$$

where $r_i = S\beta_i - d - \gamma - \alpha_i$ is the per capita rate of change of strain *i*.

Price equation for the evolution of virulence and transmission

Let $\bar{\alpha}$ and $\bar{\beta}$ denote the average virulence and transmission of all strains in the population. The Price equation describes the respective rates of change as

$$\dot{\bar{\alpha}} = S\,\mathrm{cov}(\alpha,\beta) - \mathrm{cov}(\alpha,\alpha) - \mu(\bar{\alpha} - \bar{\alpha}_m)$$
$$\dot{\bar{\beta}} = S\,\mathrm{cov}(\beta,\beta) - \mathrm{cov}(\beta,\alpha) - \mu(\bar{\beta} - \bar{\beta}_m)$$

where $\bar{\alpha}_m$ and $\bar{\beta}_m$ are, respectivelly, the average virulence and transmission of all mutations that arise

$$\bar{\alpha}_m = \sum_{i,j} \alpha_i m_{j\,i} q_j \qquad \text{and} \qquad \bar{\beta}_m = \sum_{i,j} \beta_i m_{j\,i} q_j$$

Price equation for the evolution of virulence and transmission

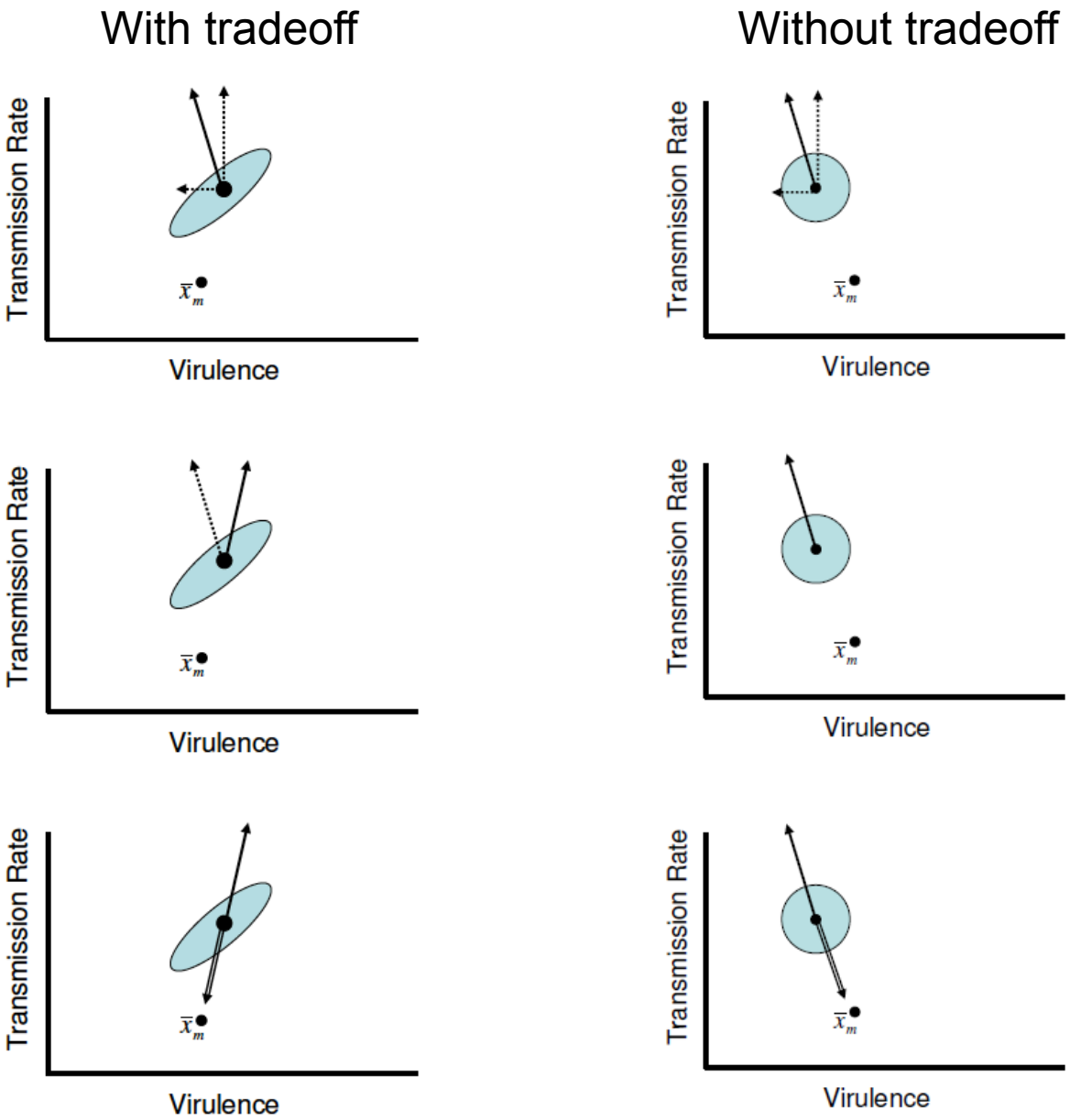
In matrix notation, the evolutionary component becomes

$$\begin{pmatrix} \dot{\overline{\alpha}} \\ \dot{\overline{\beta}} \end{pmatrix} = \mathrm{G}\begin{pmatrix} -1 \\ S \end{pmatrix} - \mu\begin{pmatrix} \overline{\alpha} - \overline{\alpha}_m \\ \overline{\beta} - \overline{\beta}_m \end{pmatrix}$$

where G is the genetic covariance matrix and (-1 S)^T is the selection gradient. This is coupled to the epidemiological system

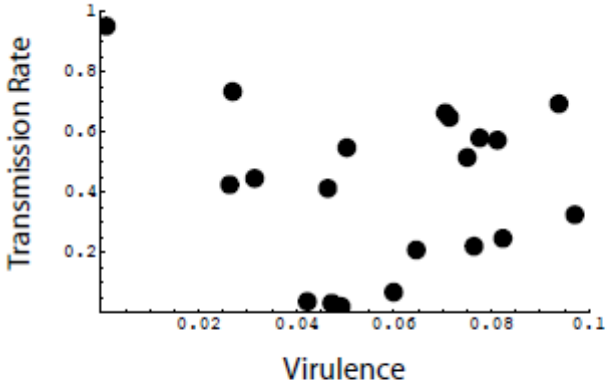
$$\dot{S} = \theta - dS - SI\overline{\beta}$$
$$\dot{I} = SI\overline{\beta} - dI - \gamma I - \overline{\alpha} I$$
$$\dot{R} = \gamma I - dR$$

Intermediate level of virulence and transmission does not require tradeoff

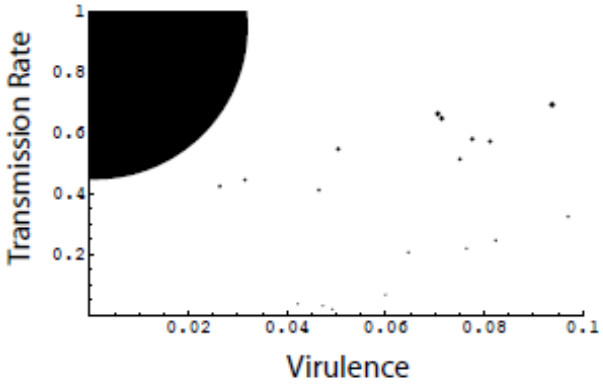


Simulation

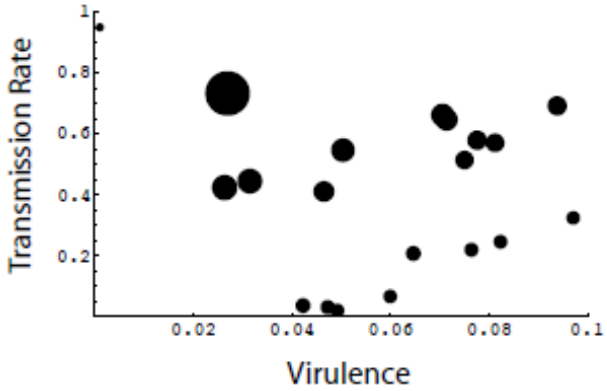
Initial condition:



Simulation (d = 1):



Simulation (d = 0):



Final remarks

1) Essential aspects of the ecology and evolution of pathogen are captured by adequate model structures;

2) Model selection and parameter estimation for complex dynamical systems remains a major challenge.

Bibliography

Gomes MGM, Medley GF, Nokes DJ (2002) On the Determinants of Population Structure in Antigenically Diverse Pathogens. *Proc R Soc Lond*. B 269: 227-233.

Wang TT, Palese P (2009) *Nature Structural & Molecular Biology* 16: 233 -234.

Ponomarenko JV, Bourne PE (2008) *BMC Structural Biology* 7: 64.

Yewdell JW, Webster RG, Gerhard WU (1979) *Nature* 279: 246 -248.

Haaheim LR, Tomasov CC, Barr IG, Hampson AW, Komadina N (2006) *Vaccine* 24: 6708-6711.

Smith DJ, et al (2004) *Science* 305: 371-6.

Parisi A, Parisi JS, Nunes A, Gomes MGM (in press) Heterogeneity in antibody range and the antigenic drift of influenza viruses. *Ecological Complexity.*

Day T, Gandon S (2005) Insights from Price's equation into evolutionary epidemiology. In Disease evolution: models, concepts, and data analyses (eds. Z. Feng, U. Dieckmann, S. Levin). Providence, RI: American Mathematical Society.