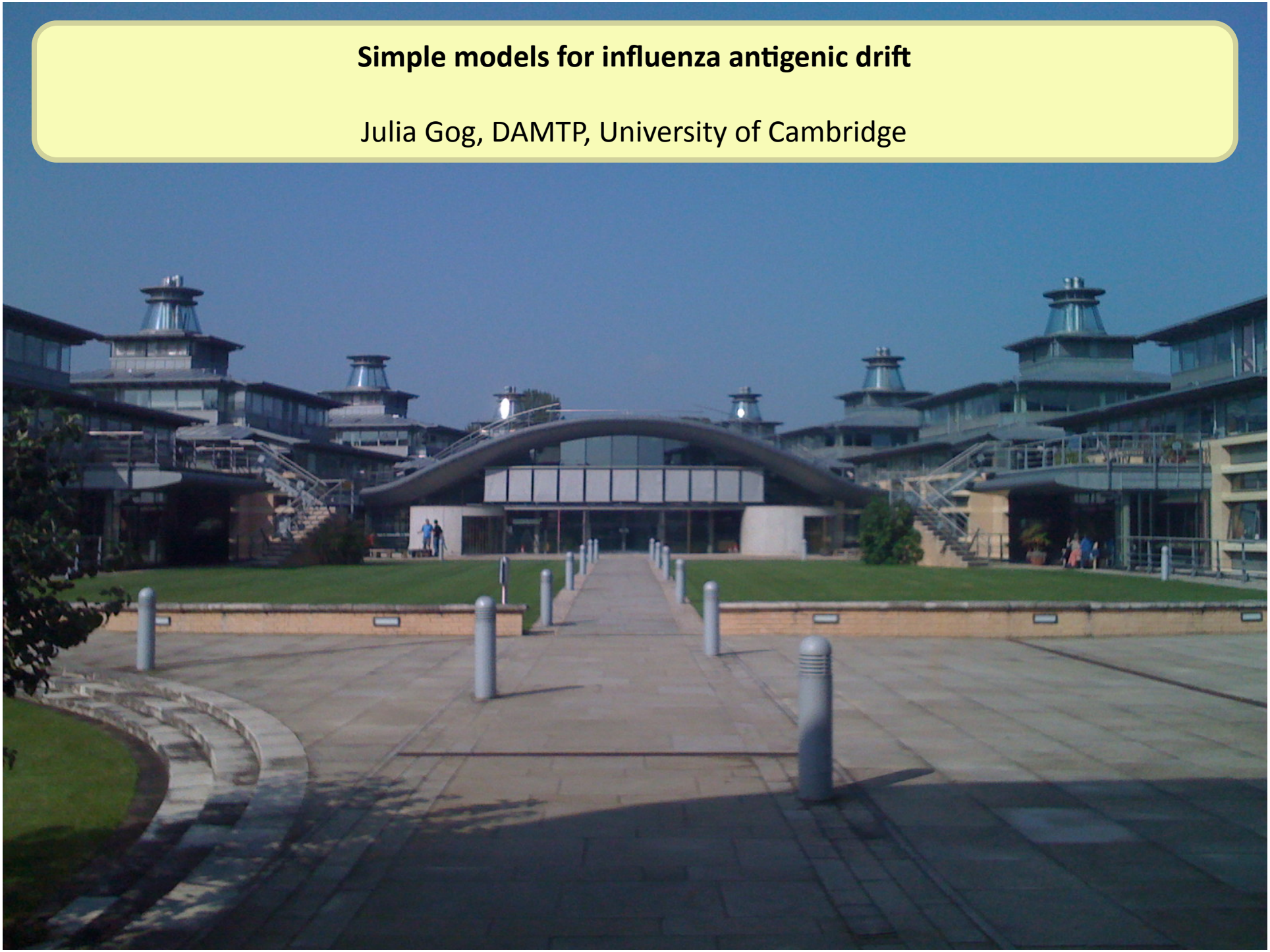
Simple models for influenza antigenic drift

Julia Gog, DAMTP, University of Cambridge



SIR model

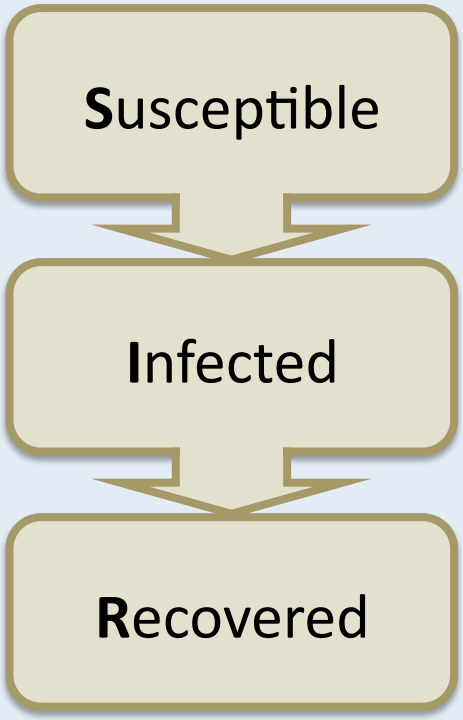
Phylodynamics

Influenza Drift Models

Add evolutionary constraints

Ongoing and other stuff

Classic epidemic model



$$\begin{aligned} \frac{dS}{dt} &= -\beta IS \\ \frac{dI}{dt} &= \beta IS - \nu I \\ \frac{dR}{dt} &= \nu I \end{aligned}$$

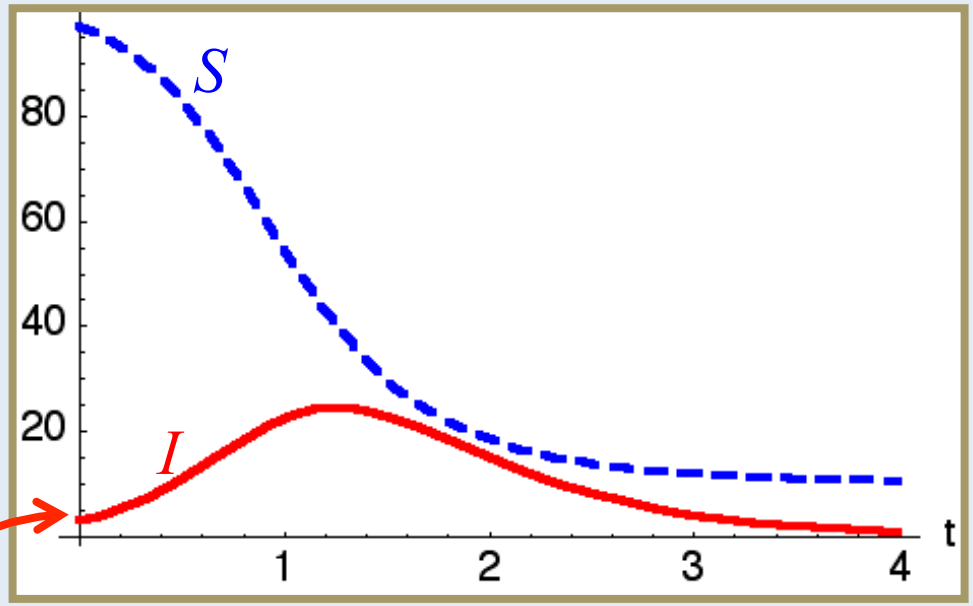
Constant population:

$$S + I + R = N$$

Reproductive ratio:

$$R_0 = \frac{\beta N}{\nu}$$

$$\frac{dS}{dt} = -\beta IS$$
$$\frac{dI}{dt} = \beta IS - \nu I$$



Epidemic threshold:

$$R_0 = \frac{\beta N}{\nu} > 1$$

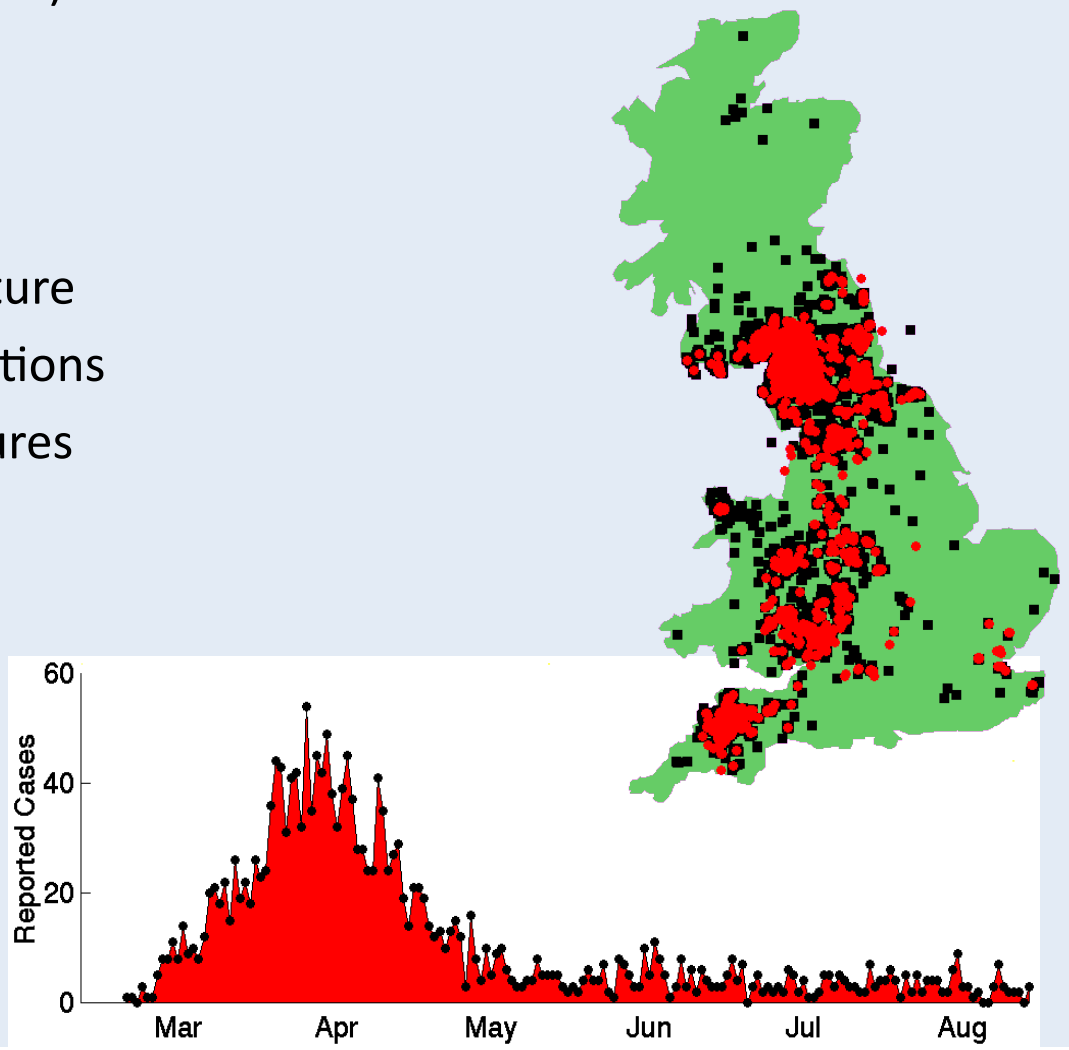
..leads to vaccination threshold:

$$p_c = 1 - 1/R_0$$

The SIR model

Basic model gives many insights, and easy to extend in many ways:

- Host demographics (births/deaths)
- Stochasticity
- Multiple species or host types
- Spatial structure
- Network/metapopulation structure
- Better infectious period distributions
- Effect of different control measures
- Realistic immunity
- Age structure
- Vector-borne
- SEIR and friends



SIR model

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Add evolutionary constraints

Ongoing and other stuff

Grenfell *et al.*, Science 2004

REVIEW

Unifying the Epidemiological and Evolutionary Dynamics of Pathogens

Bryan T. Grenfell,[1]* Oliver G. Pybus,[2] Julia R. Gog,[1] James L. N. Wood,[3] Janet M. Daly,[3] Jenny A. Mumford,[3] Edward C. Holmes[2]

A key priority for infectious disease research is to clarify how pathogen genetic variation, modulated by host immunity, transmission bottlenecks, and epidemic dynamics, determines the wide variety of pathogen phylogenies observed at scales that range from individual host to population. We call the melding of immunodynamics, epidemiology, and evolutionary biology required to achieve this synthesis pathogen "**phylodynamics**."

The population dynamics of many host-pathogen interactions are well characterized (*1*, *2*). However, the link between epidemic processes and pathogen evolution, within and among hosts, is not so well understood. This connection is central to many applied issues, from the evolution of drug resistance and virulence, to vaccine design and the emergence of new diseases. The current revolution in host and pathogen genomics underlines the timeliness of this issue.

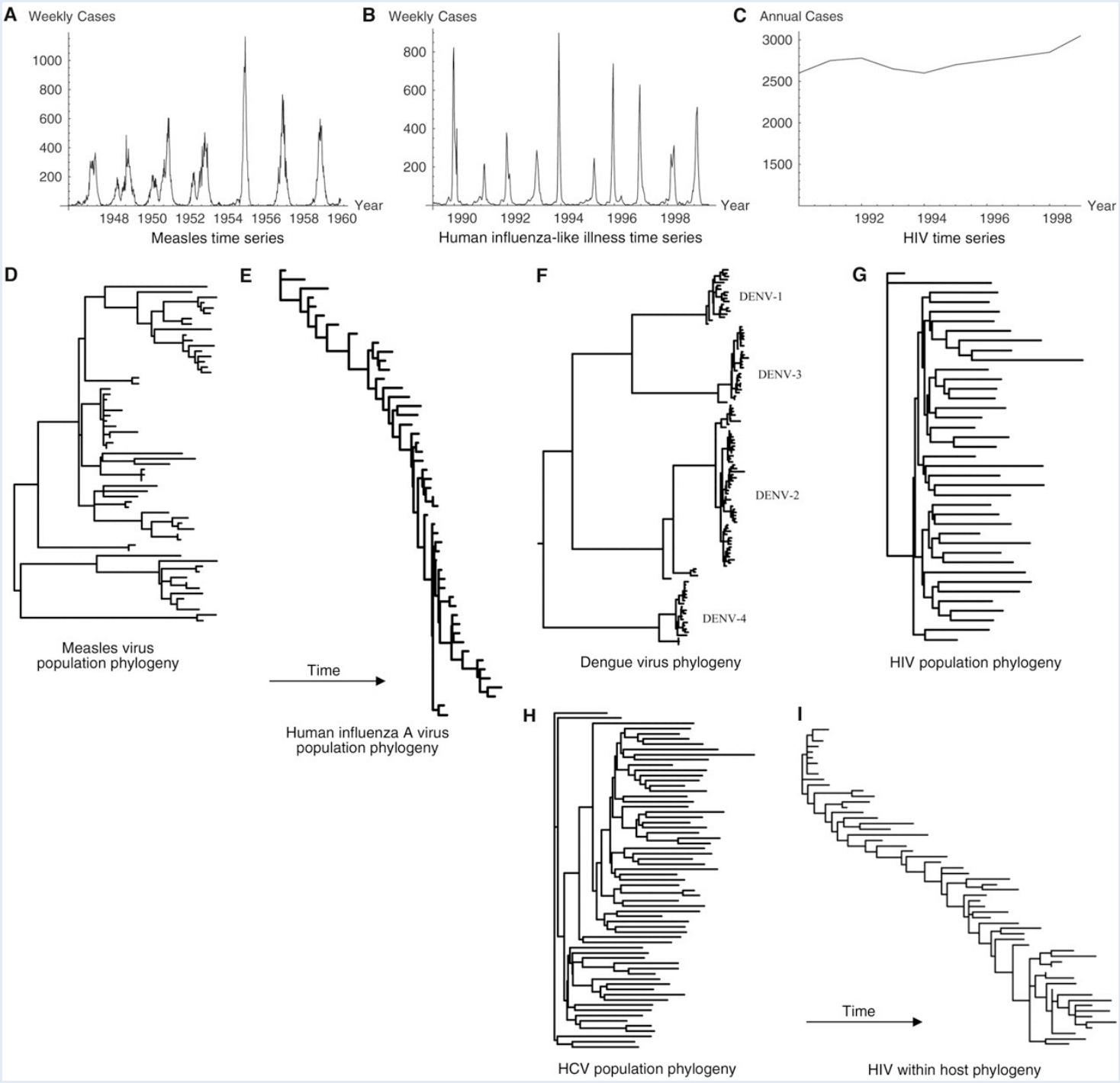
Research on the dynamics of pathogen

Observed Phylodynamic Patterns

A major determinant of epidemic (and therefore phylodynamic) behavior is the relative time scale of infection dynamics and replenishment of susceptible hosts after epidemics (*6*). The main epidemiological distinction is therefore between fast (acute) infections, in which the infectious period is measured in days or weeks, and slower (persistent) infections, which can last years. In contrast, phylogenetic patterns are primarily affected by natural selection that

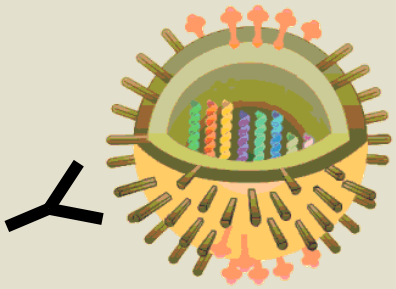
ciently consistently to leave its imprint. Instead, the phylogeny is determined by global spatio-temporal strain dynamics: Some lineages persist in regions with low vaccination coverage, whereas others are globally distributed and represent localized outbreaks initiated by imported strains in regions with higher coverage. The high infectiousness of measles permits the rapid geographic spread of these strains, and their phylogenetic lineages reveal substantial spatial mixing.

Short infections with partial cross-

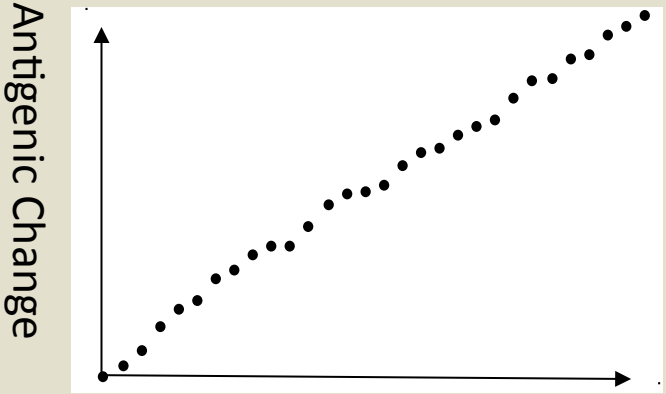

A
Weekly Cases
1000
800
600
400
200
1948 1950 1952 1954 1956 1958 1960
Year
Measles time series
B
Weekly Cases
800
600
400
200
1990 1992 1994 1996 1998
Year
Human influenza-like illness time series
C
Annual Cases
3000
2500
2000
1500
1992 1994 1996 1998
Year
HIV time series
D
Measles virus
population phylogeny
E
Time
Human influenza A virus
population phylogeny
F
DENV-1
DENV-3
DENV-2
DENV-4
Dengue virus phylogeny
G
HIV population phylogeny
H
HCV population phylogeny
I
Time
HIV within host phylogeny

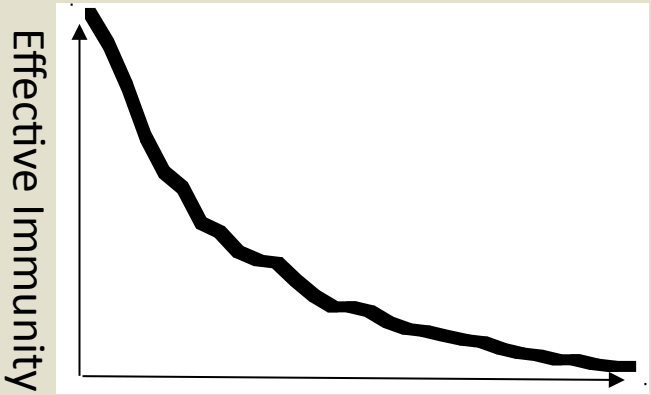
Influenza antigenic drift dogma

Accumulation of mutations in *antigenic sites*



New strains avoid old immunity





SIR model

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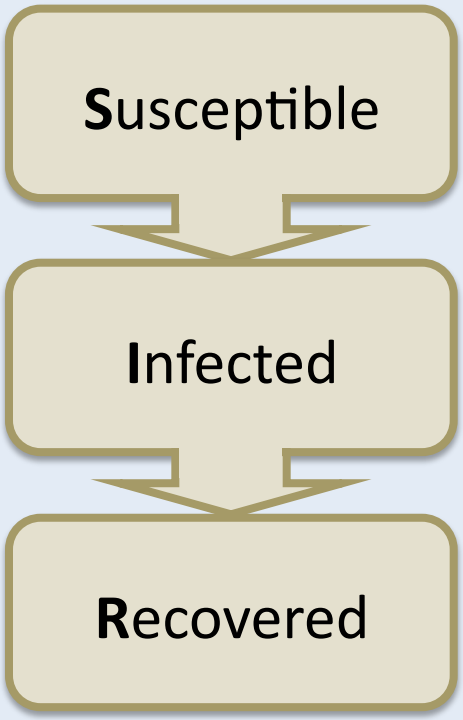
Two ways to extend SIR to model antigenic drift:

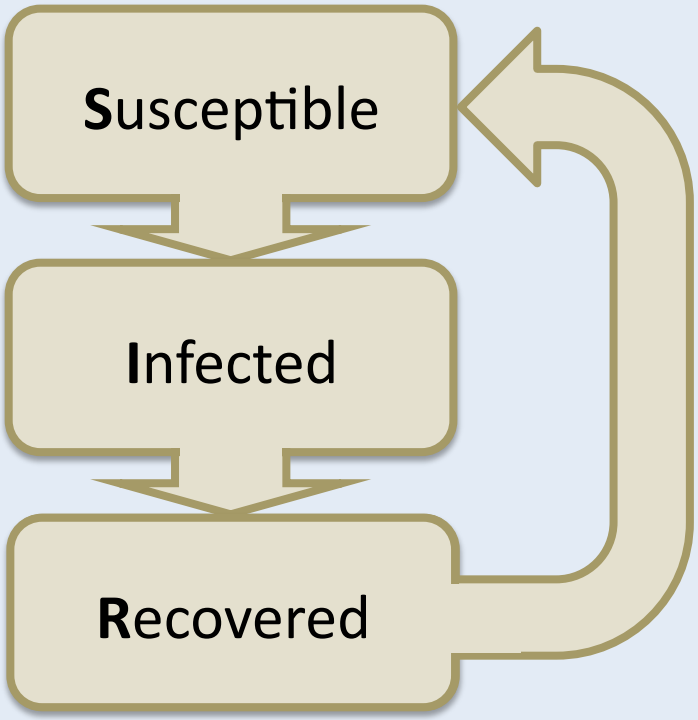
Population variables are updated to reflect antigenic evolution: *In frame of reference that moves with strain*

Population variables account for multiple circulating strains



$$\frac{dS}{dt} = -\beta IS$$
$$\frac{dI}{dt} = \beta IS - \nu I$$
$$\frac{dR}{dt} = \nu I$$

Population variables are updated to reflect antigenic evolution: *In frame of reference that moves with strain*



Not actually a loss of immunity, but a loss of immunity *with respect to the currently circulating strain*

E.g Pease 1987

$$\frac{dS}{dt} = -\beta IS$$
$$\frac{dI}{dt} = \beta IS - \nu I$$
$$\frac{dR}{dt} = \nu I$$

Population variables account for multiple circulating strains

$$\dot{S}_{\mathcal{J}} = \sum_{j \in \mathcal{J}} \nu I^{j}_{\mathcal{J} \setminus j} - \sum_{i \notin \mathcal{J}} \sigma^{i}_{\mathcal{J}} \Lambda^{i} S_{\mathcal{J}} - \mu S_{\mathcal{J}}$$

$\mathcal{J}$

Set of strains those hosts have previously had

Currently infected with strain j

All the cross immunity information

E.g Andreasen 1997

Population variables are updated to reflect antigenic evolution: *In frame of reference that moves with strain*

- Fairly tractable
- Only one strain at a time
- Evolutionary dynamics imposed

Population variables account for multiple circulating strains

- Rapidly intractable
- Strains limited only by tractability
- Evolutionary dynamics emerge

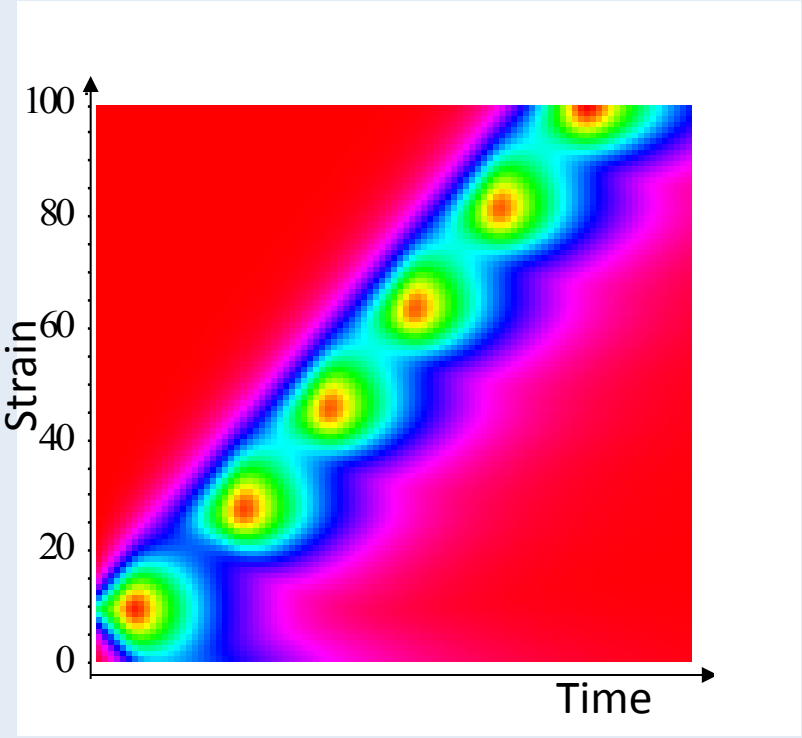
Gog, J.R., Rimmelzwaan, G.F., Osterhaus, A.D.M.E. and Grenfell, B.T. (2003). Population dynamics of rapid fixation in cytotoxic T lymphocyte escape mutants of influenza A. *Proceedings of the National Academy of Sciences, USA* **100** 11143-11147

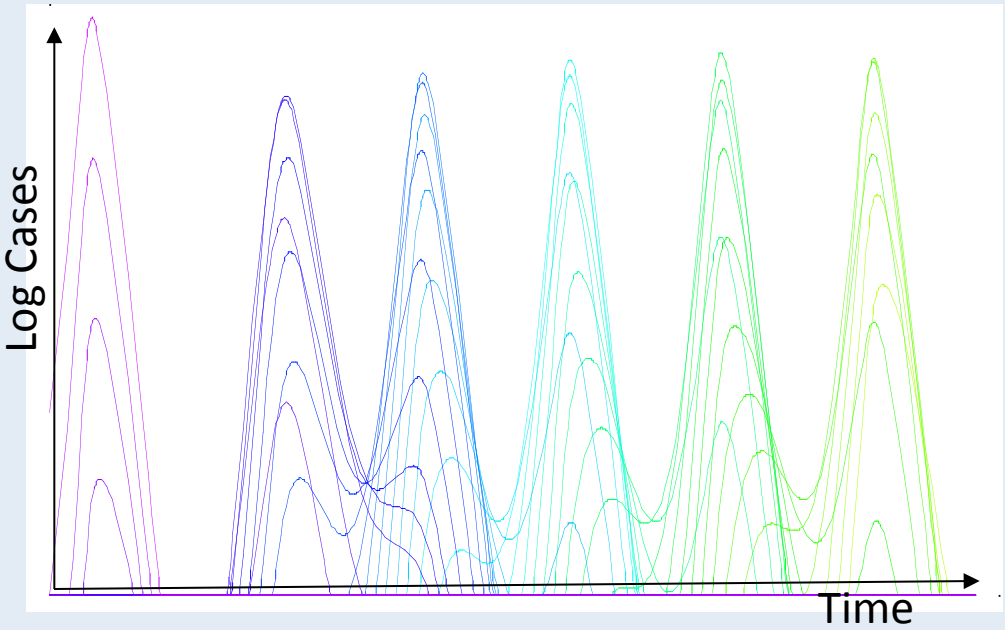
Boni, M.F., Gog, J.R., Andreasen, V., and Christiansen, F.B. (2004) Influenza drift and epidemic size: the race between generating and escaping immunity. *Theoretical Population Biology* **65** 179-191

Gog, J.R. and Swinton, J. (2002). A status-based approach to multiple strain dynamics *Journal of Mathematical Biology* **44** 169-184

Gog, J.R. and Grenfell, B.T. (2002). Dynamics and Selection of Many-Strain Pathogens. *Proceedings of the National Academy of Sciences, USA* **99** 17209-17214

Natural tendency form clusters

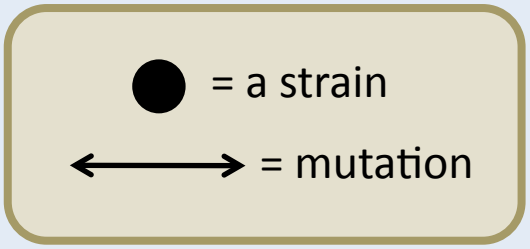


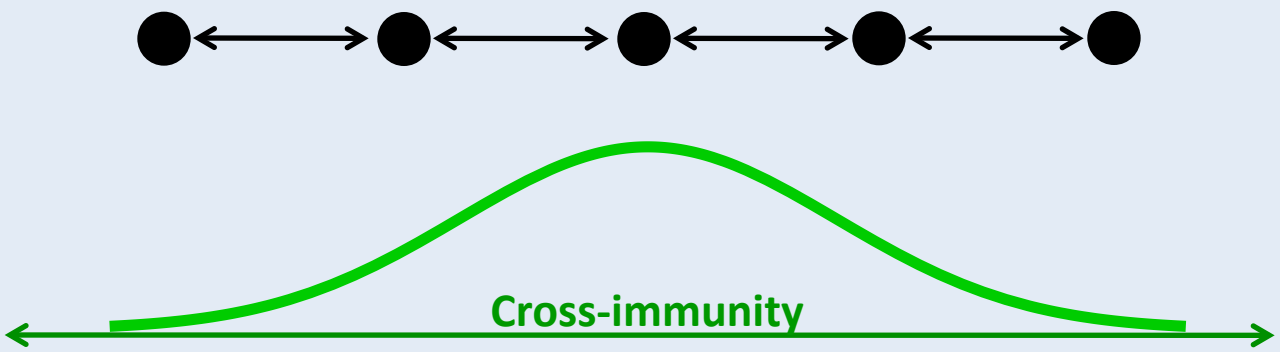


Can make tractable multi-strain models, but need strategic assumptions

Gog & Swinton 2002,
Gog & Grenfell 2002,
Dawes & Gog 2002

Strain space:
Discrete strains on a line: mutation is to immediate neighbours, cross-immunity acts on nearby strains decreasing with distance





All strains have same basic parameters: *intrinsic fitness equal*

However population immunity changes through time: *effective fitness varies*

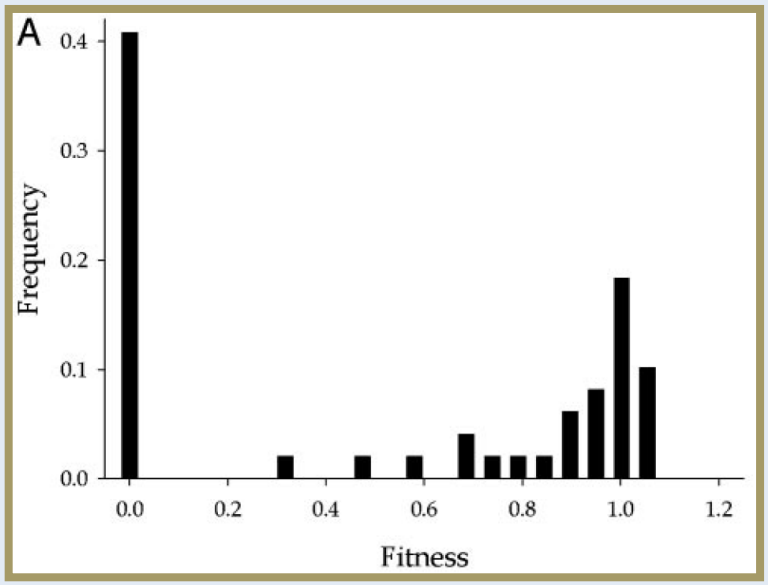
SIR model

Phylodynamics

Influenza Drift Models

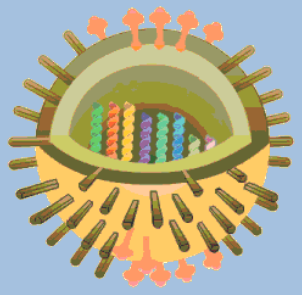
Add evolutionary constraints

Ongoing and other stuff



Sanjuán, Moya, Elena PNAS 2004

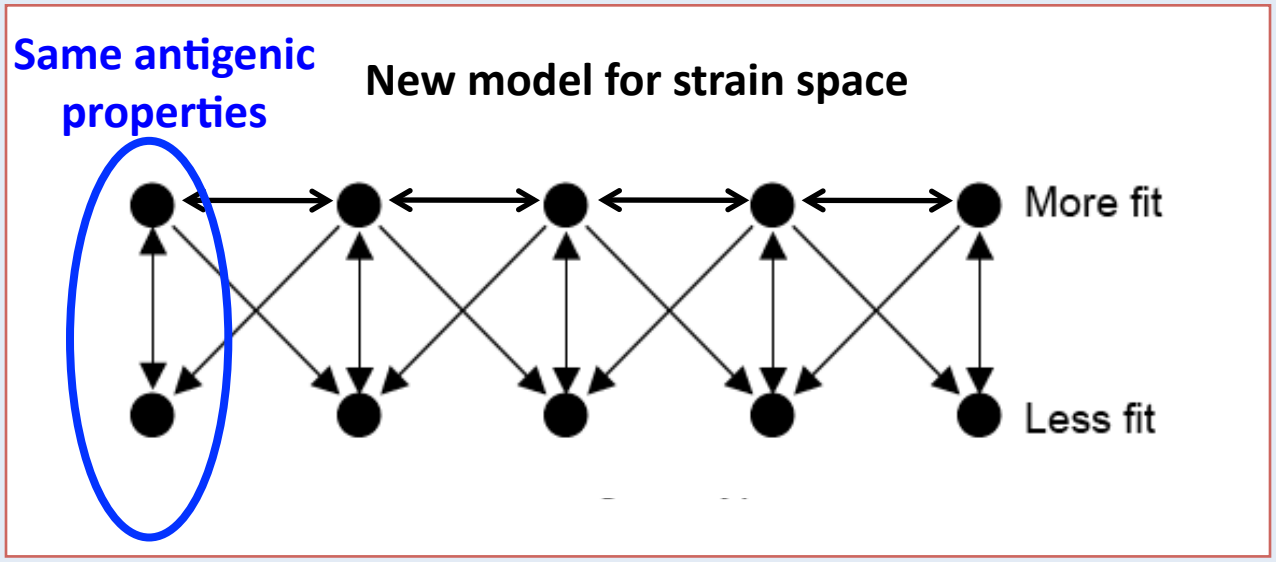
Frequency of fitness values associated with random single-nucleotide substitutions (VSV, in vitro).



For influenza:

Supposing antigenic mutation is associated with a detrimental effect on viral fitness….

…how would this *qualitatively* affect population dynamics of drift?



Horizontal still represents different antigenic types

Force functional constrains: can mutate antigenically but *must* also reduce fitness.

Can later compensate back to full fitness.

Gog, 2008, Vaccine

Discrete time

SEIFR model

Map Equations:

$$\text{new}\,F = F\,e^{-\tau} + (N - F)\frac{\Lambda}{\Lambda + \mu}(1 - e^{-(\Lambda+\mu)})$$

$$\text{new}\,S_a = S_a\,e^{-(\Lambda+\mu)} + N(1 - e^{-\mu}) + \phi_a(1 - e^{-\tau})$$

$$\text{new}\,\phi_a = \phi_a\,e^{-\tau} + S_a\frac{\sum_{\tilde{a},f}(1 - c_{a,\tilde{a}})I_{\tilde{a},f}\beta_f}{\Lambda + \mu}(1 - e^{-(\Lambda+\mu)})$$

$$\text{new}\,E_{a,f} = E_{a,f}\,e^{-\sigma} + S_a\frac{I_{a,f}\beta_f}{\Lambda + \mu}(1 - e^{-(\Lambda+\mu)})$$

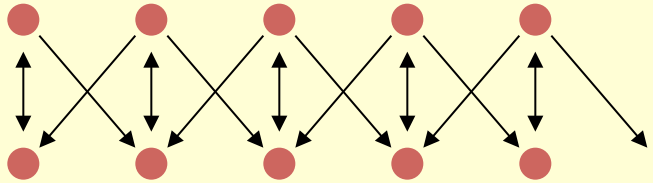
$$\text{new}\,I_{a,f} = I_{a,f}\,e^{-\gamma} + E_{a,f}(1 - e^{-\sigma})$$

$$\text{where}\,\Lambda = \sum_{a,f} I_{a,f}\beta_f$$

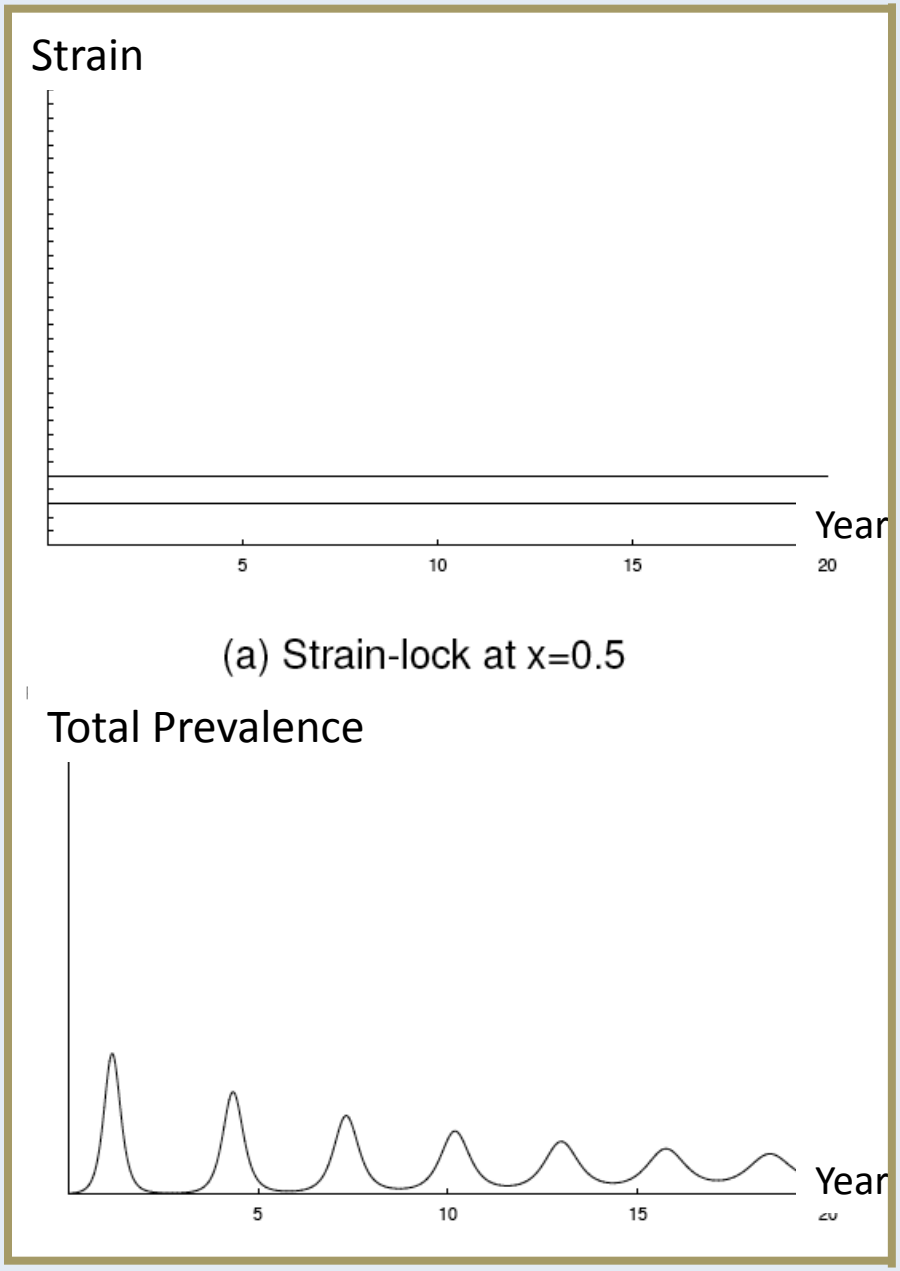
Gog, 2008, Vaccine

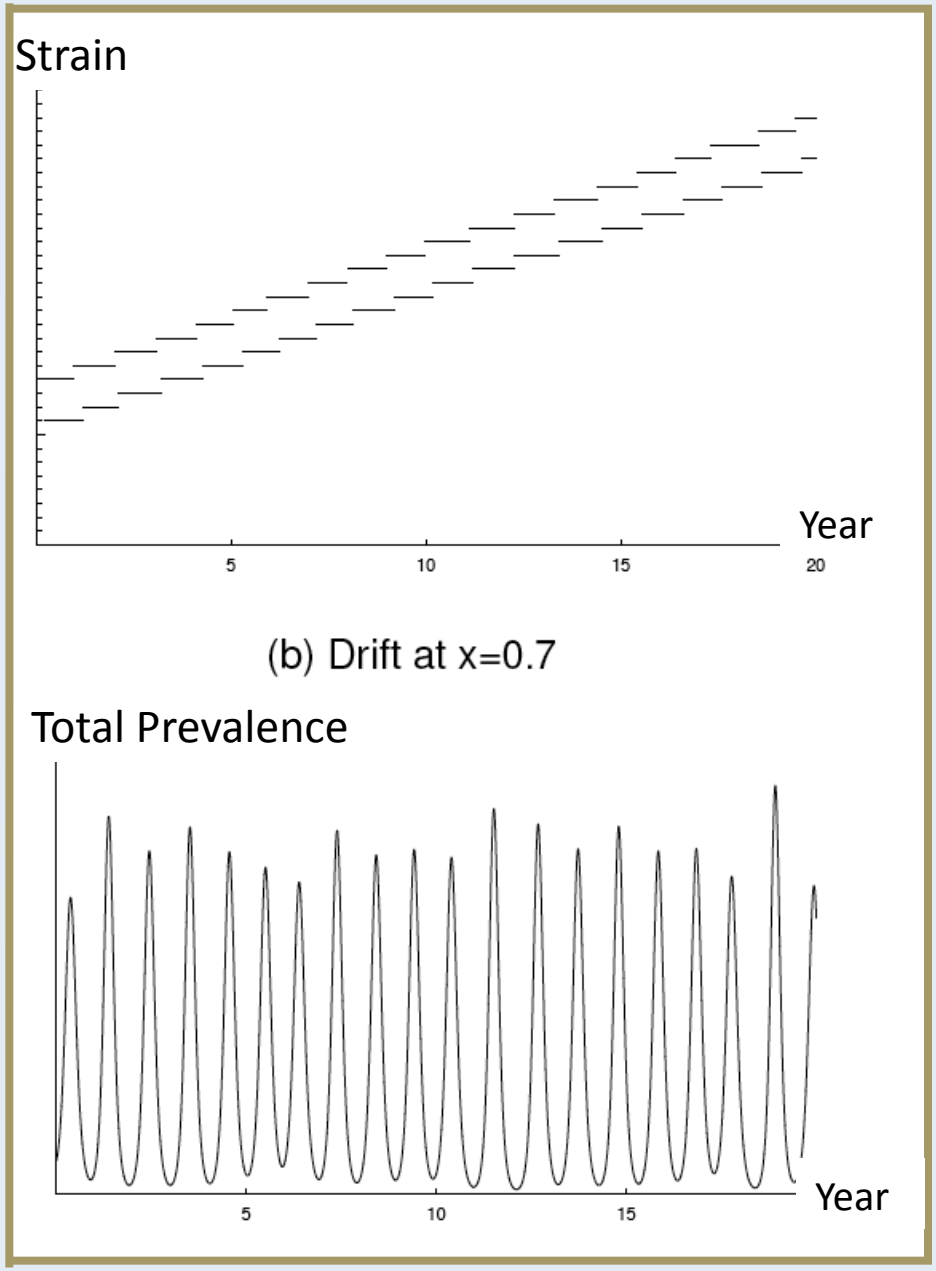
Want to model long-term drift patterns. Will need a lots of strains, but not all the same time. Use **stochastic mutation and extinction**, plus only track current strains:

Active set of strains:



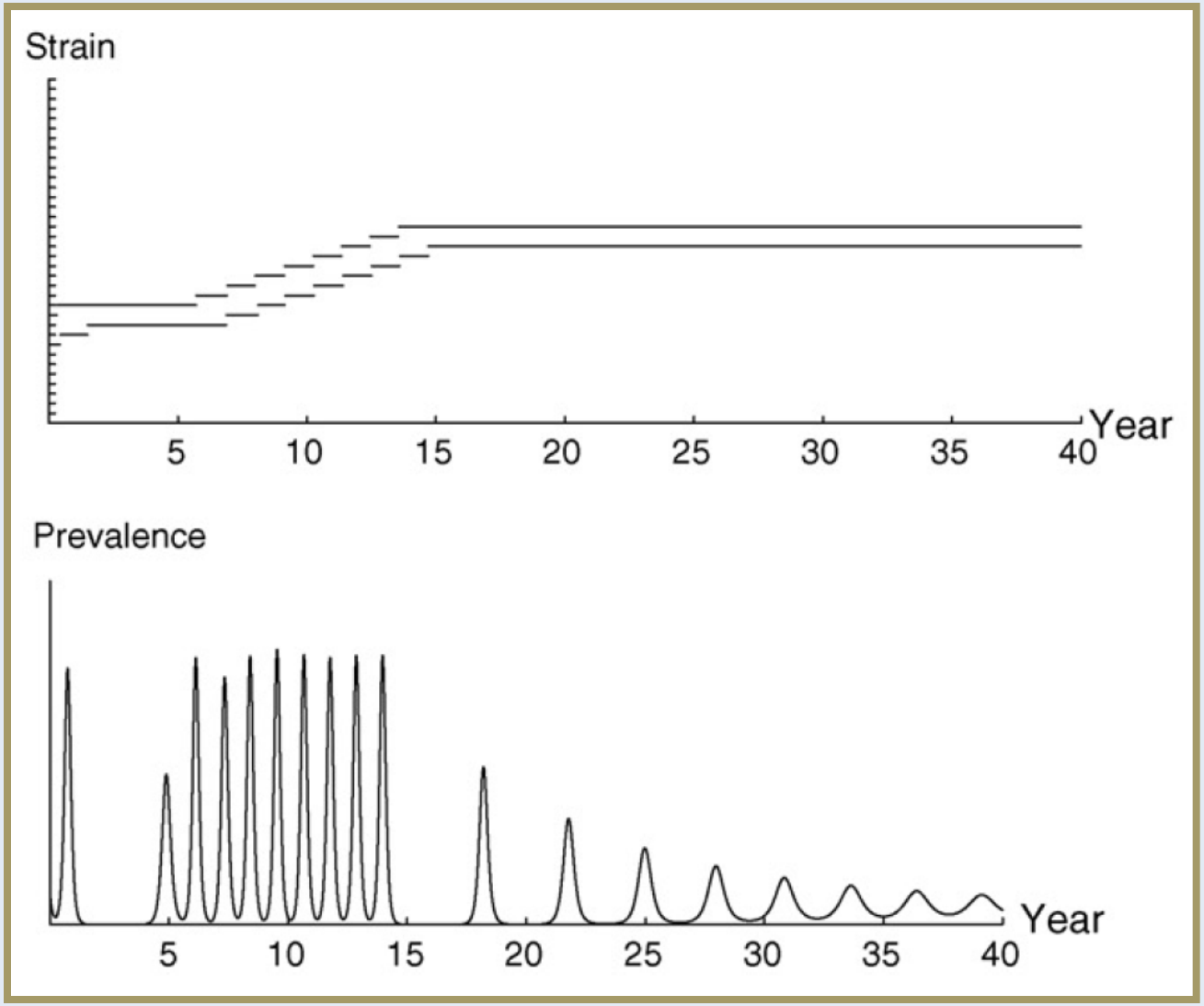
Gog, 2008, Vaccine


Strain
Year
5
10
15
20
(a) Strain-lock at x=0.5
Total Prevalence
Year
5
10
15

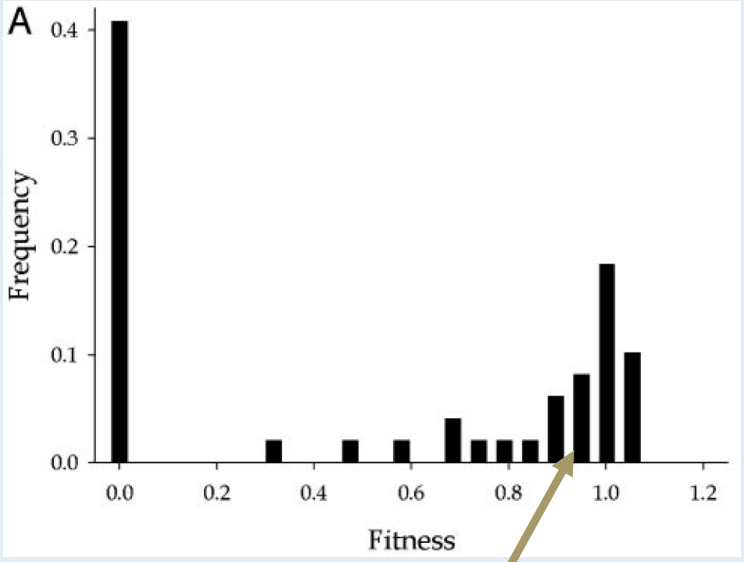

Strain
Year
5
10
15
20
(b) Drift at x=0.7
Total Prevalence
Year
5
10
15

Usually individual run is clearly drifting or clearly locked to a single strain

Sometimes can do both in same run

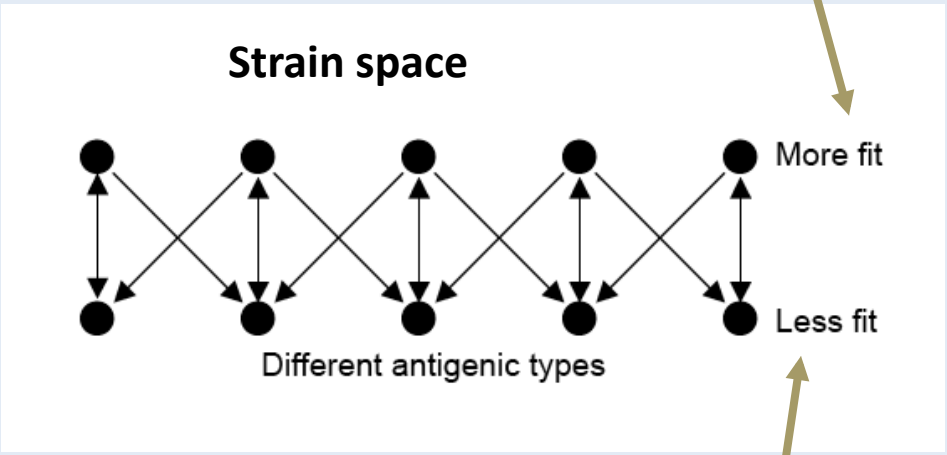


Parameter to explore: **‘Mutant fitness’**
The relative fitness of an antigenic mutation

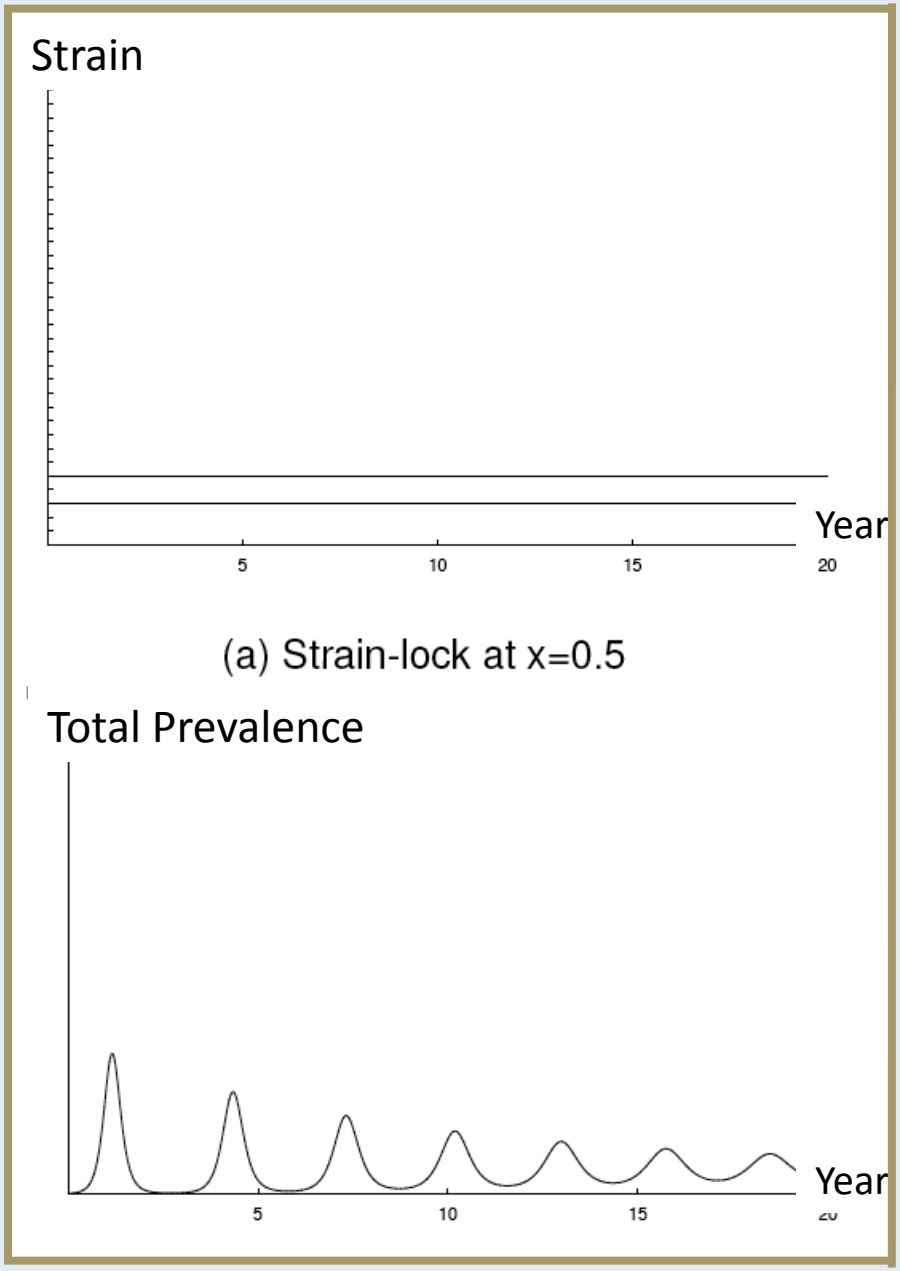


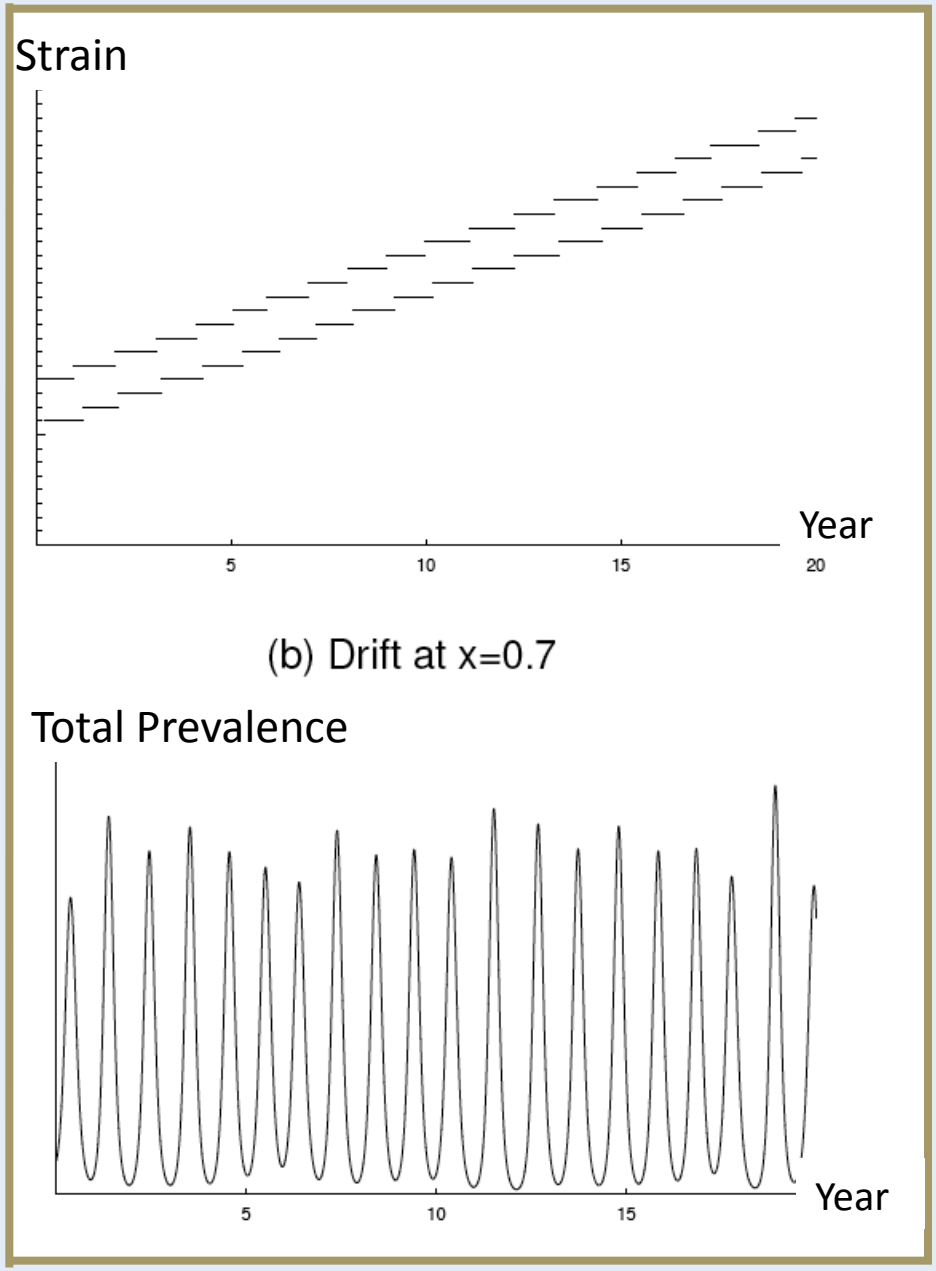
x = Mean mutant fitness

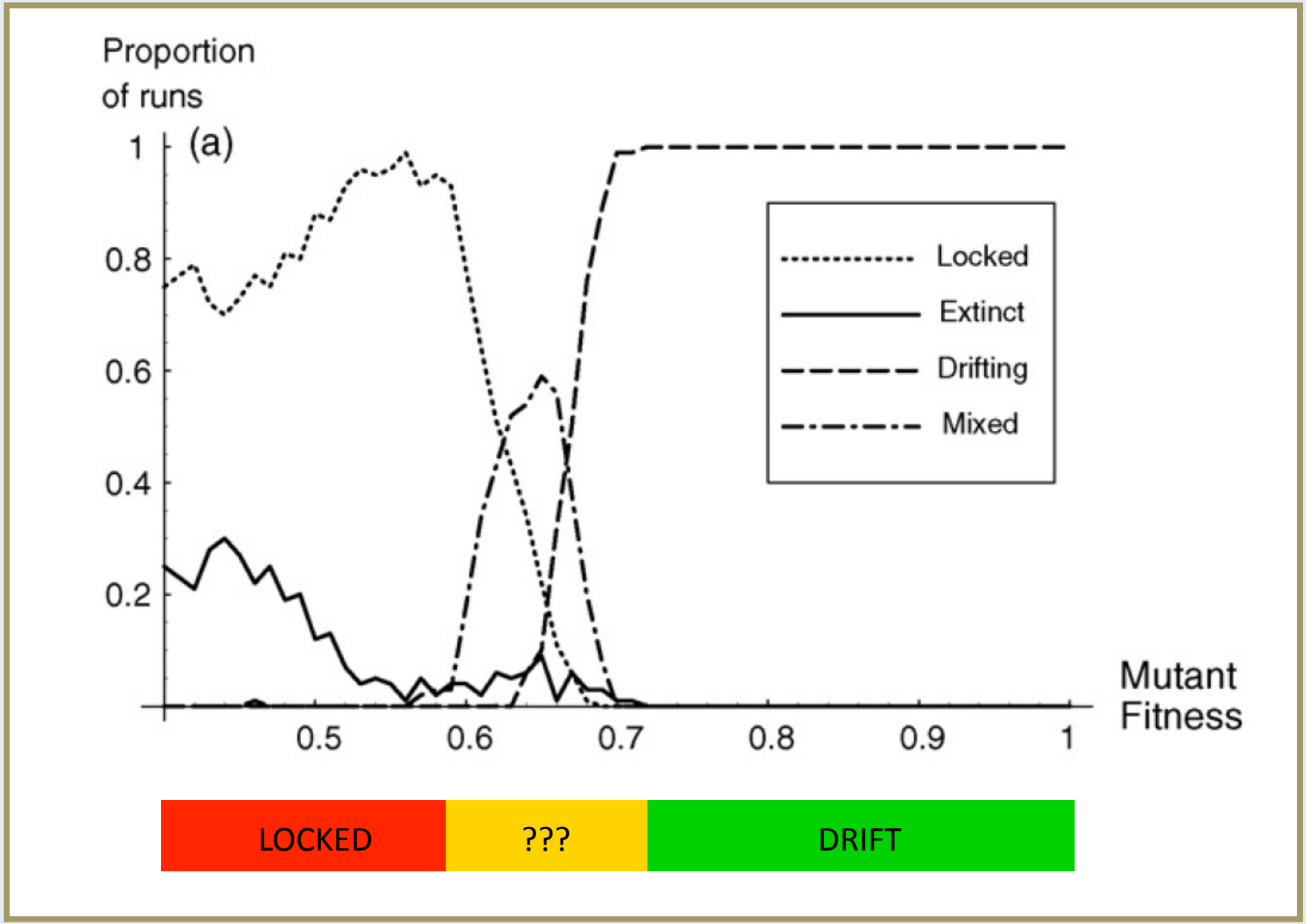
=1

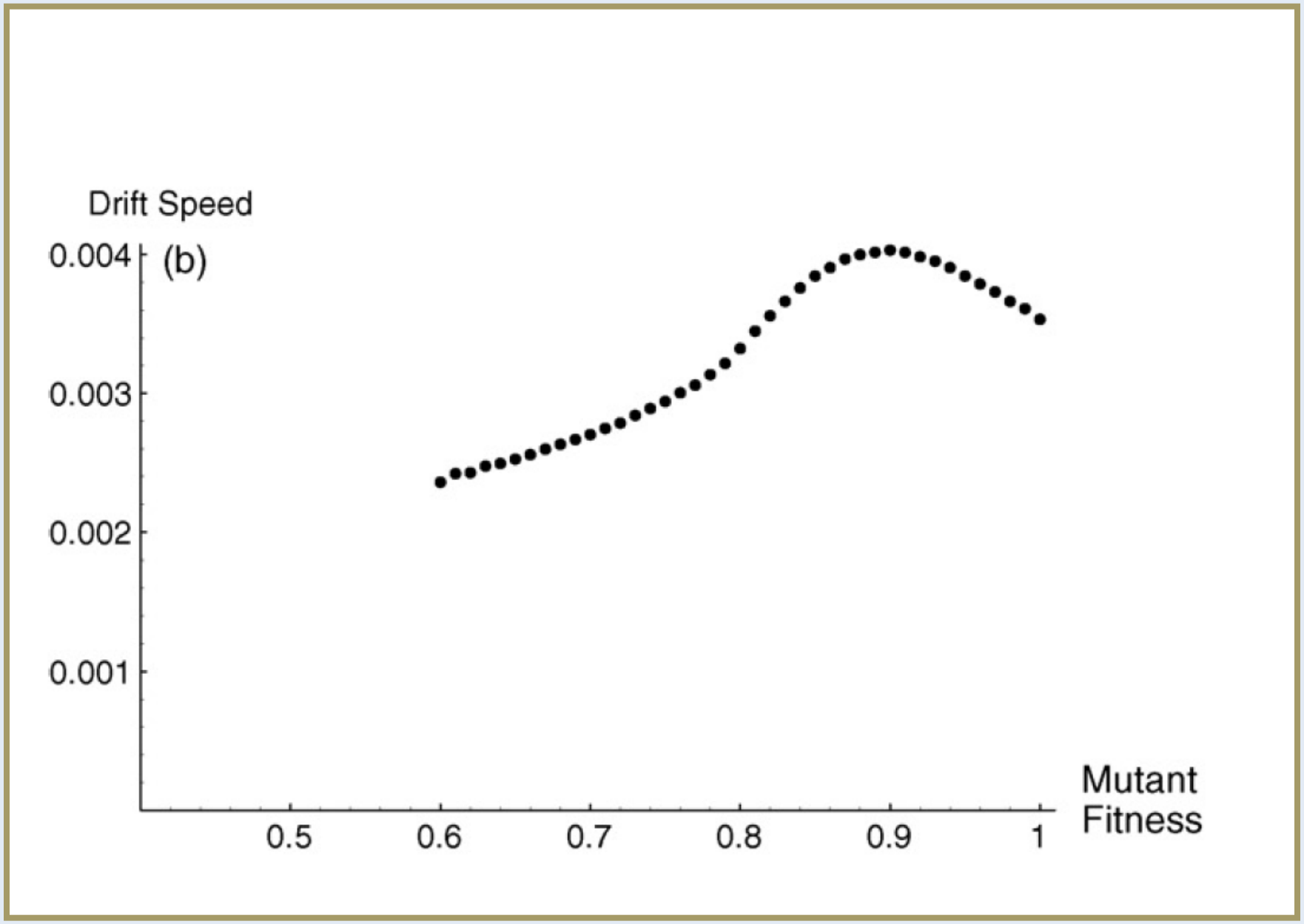


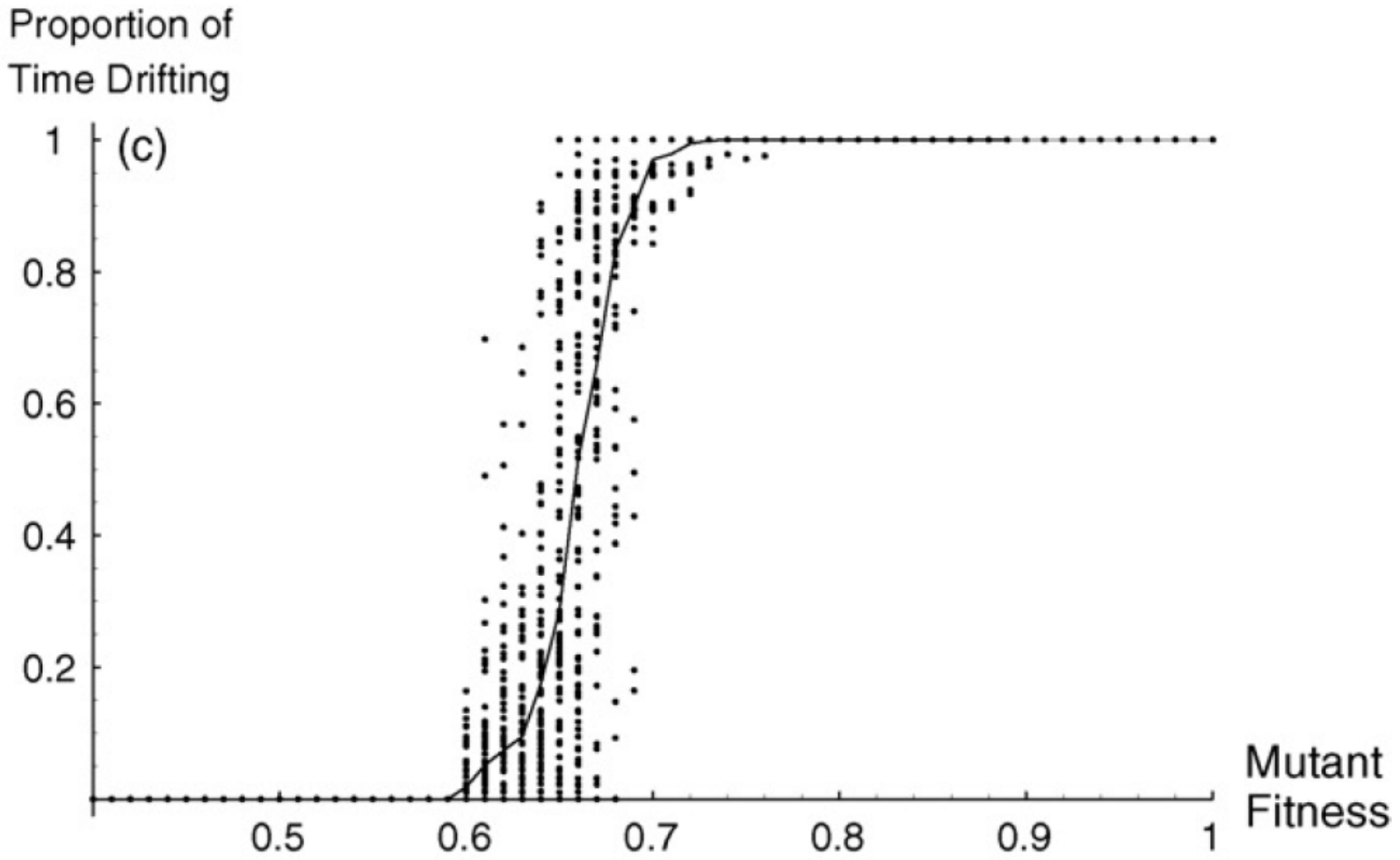
= x


Strain
Year
5
10
15
20
(a) Strain-lock at x=0.5
Total Prevalence
Year
5
10
15

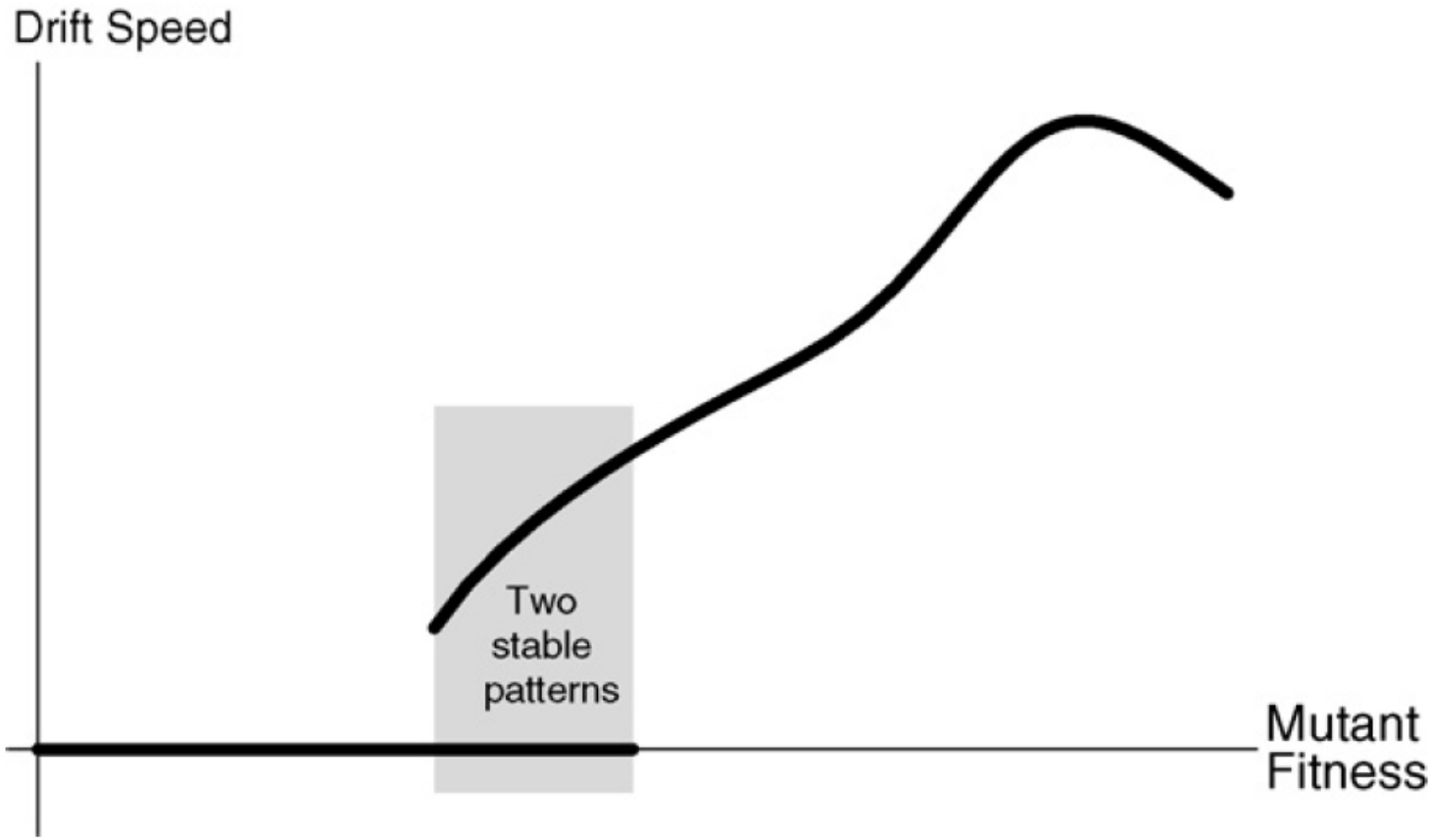

Strain
Year
5
10
15
20
(b) Drift at x=0.7
Total Prevalence
Year
5
10
15


Proportion
of runs
(a)
1
0.8
0.6
0.4
0.2
0.5
0.6
0.7
0.8
0.9
1
Mutant
Fitness
Locked
Extinct
Drifting
Mixed
LOCKED
???
DRIFT


Drift Speed
(b)
0.004
0.003
0.002
0.001
0.5
0.6
0.7
0.8
0.9
1
Mutant
Fitness



(100 runs per parameter value)



Bistable system - **consequences for vaccination**

Conclusions

- Evolutionary constraints could have unexpected and major impact on resultant population dynamics

- This could have important control implications: *stopping or pausing influenza drift would provide a window for further vaccine delivery*

…but caveats…

Some of the caveats

- **Parameters:** illustrative only, or chosen for convenience
- **Model choice**: *Ad hoc* random process, active set approximation, choice of reduced transmission model
- **Initial conditions** (proportions in different behaviors change but speed doesn't)
- Have not considered **heterogeneities** of:
  - Space, seasonality, host structure
  - Antigenic or fitness heterogeneities (used fixed value)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