Annual epidemics and natural selection in host-pathogen systems

Viggo Andreasen
Roskilde University

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Annual epidemics

Onset of epidemic season

If susceptible population exceeds threshold

an epidemic occurs

↓

During epidemic season

SIR-type epidemic

↓

Between epidemic seasons

Other processes add to size of susceptible population

↓

Applications:

- Disease-induced selection (Gillespie, 1975)
- Disease regulation of hosts (May, 1985; Dwyer et al 2000)
- Influenza drift (Andreasen,2003)
- Influenza drift and epidemic size (Boni et al, submitted)
- Pruning of influenza phylogeny (Andreasen & Sasaki,in prep)

Outline

- Annual epidemics
- Annual epidemics as a way to model disease-induced selection in diploids
- Annual epidemics in the description of influenza epidemiology
- Virus competition in annual epidemics

Disease-induced selection in diploids
Challenges for the modeller:

- Host lifespan $\gg$ infection period
- Good genetic models for:
  - generation-to-generation
  - slow selection
- Good epidemic models for:
  - transmission dynamics during an epidemic
  - endemic diseases with constant pop size

Idea: assume one epidemic in each host generation

The Gillespie model

- One autosomal locus with two alleles and random mating

Example: resistance is dominant

- AA susceptible to disease
- AB and BB resistant

Fitness of uninfected AA	1
Fitness of infected AA	$1-u$
Fitness of AB and BB	$1-\sigma$

$p =$ frequency af A-allele
$q = 1-p$ frequency of B-allele

The epidemic season

$$
\begin{aligned}
\frac{dS_{AA}}{dt} &= -\tau_{AA}\Lambda S_{AA} \\
\frac{dI_{AA}}{dt} &= \tau_{AA}\Lambda S_{AA} - \mu_{AA} I_{AA} \\
\Lambda &= \beta_{AA} I_{AA} + \beta_{AB} I_{AB} + \beta_{BB} I_{BB} \\
S_{AA}(0) &= p^2 N \quad I_{AA}(0) \approx \Lambda \ll 1
\end{aligned}
$$

Fraction infected during the epidemic z

$$z = 1 - e^{-zp^2\mathcal{R}_0}$$

Effect of disease on fitness of AA: $W_{AA} = 1 - z + (1-u)z = 1 - uz$.

Long term dynamics

At onset of epidemic season frequency of A is p.
After
- epidemic
- other selective factors
- perfect regulation of populatrion size !

Frequency of A at onset of next season:

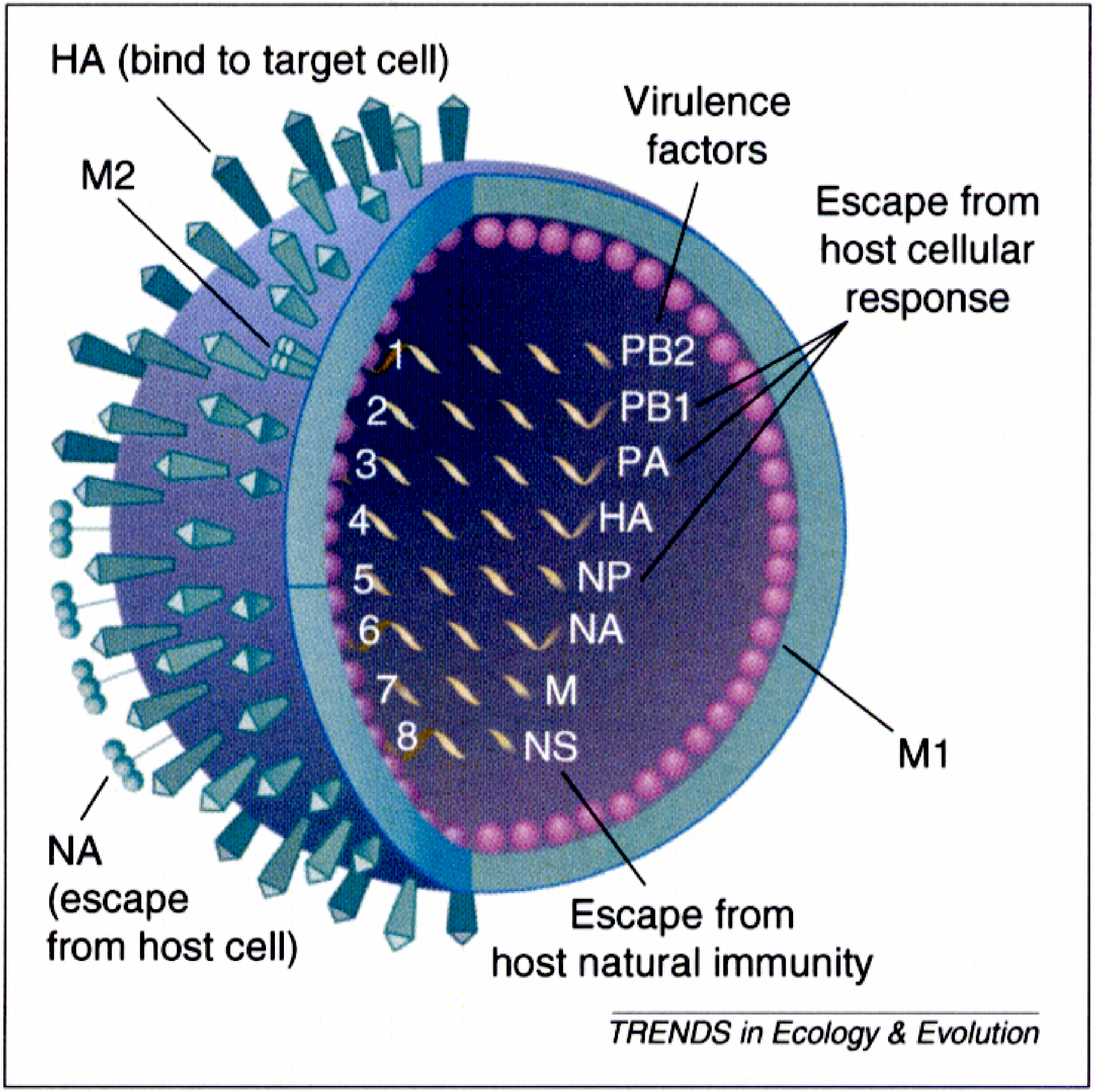
$$p' = \frac{p^2 W_{AA} + pq W_{AB}}{\bar{W}} = \frac{(1-uz)p^2 + (1-\sigma)pq}{(1-uz)p^2 + (1-\sigma)q(1+p)}$$

(Stable) equilibrium at

$$z = \sigma/u \qquad p = \sqrt{-\log(1-z)/z\mathcal{R}_0}$$

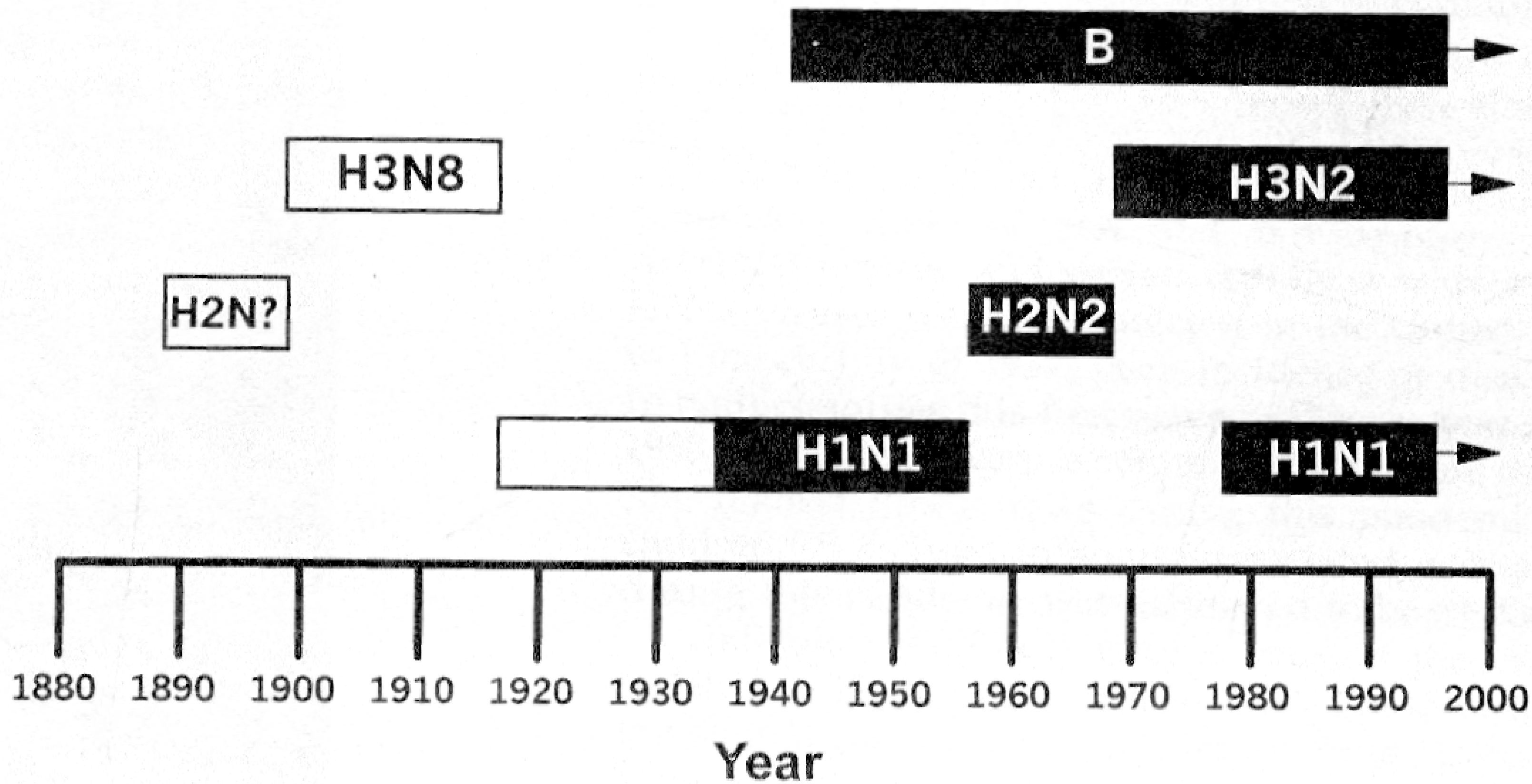
Annual epidemics and influenza epidemiology

- Influenza's natural history
- The epidemiology of a drifting virus
- Drift length and epidemic size
- Pruning of flu phylogeny



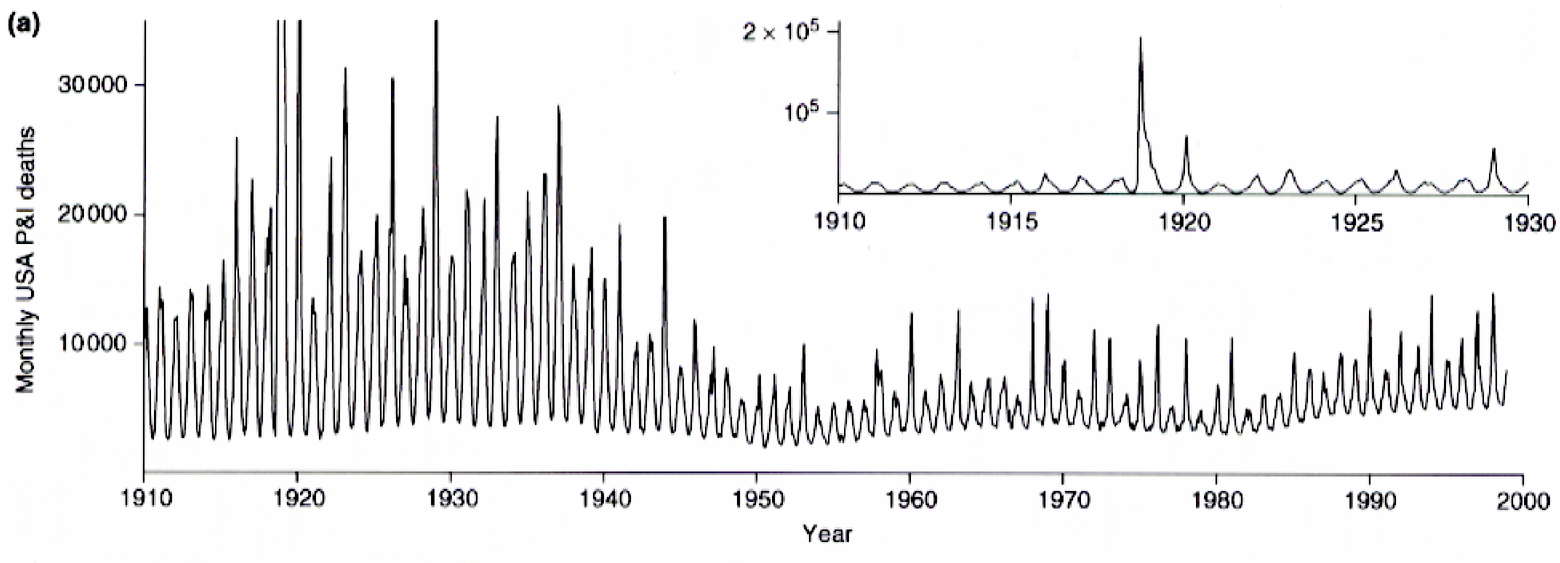
Earn et al (2002)

Influenza A subtypes



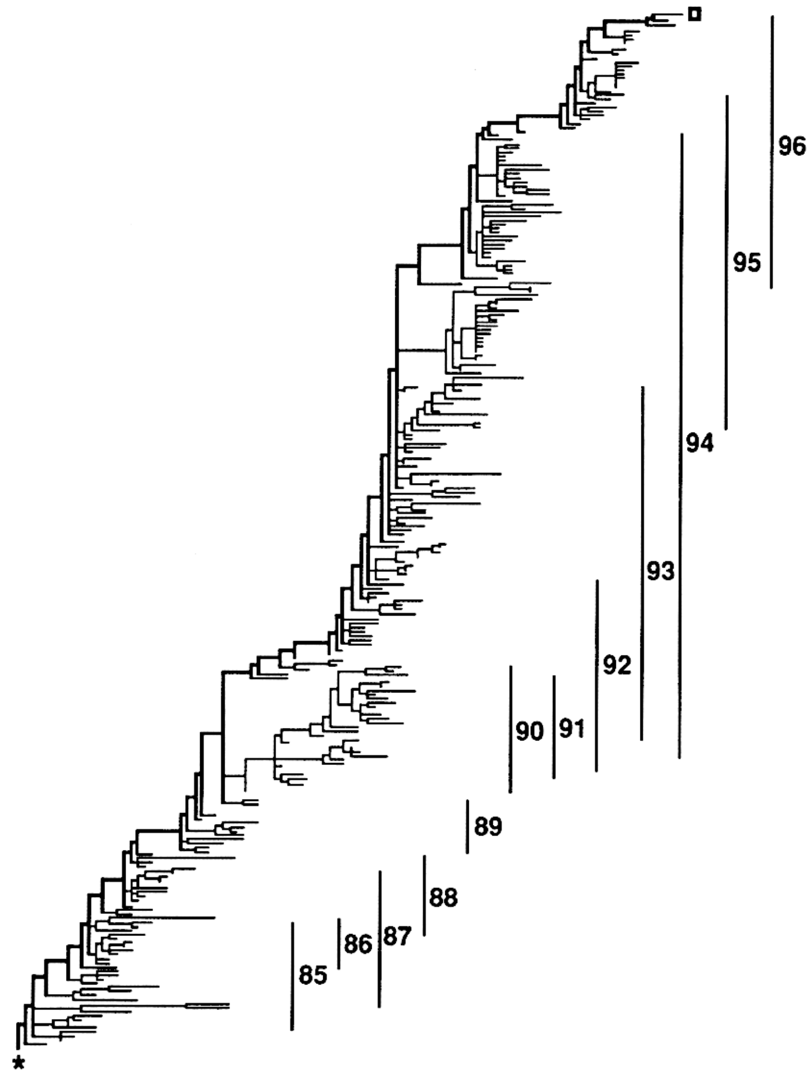
Cox & Fukuda, 1998

Deaths caused by P&I in USA



Ferguson et al 2003

Phylogeny of Influenza A



Fitch et al, 1997

Reinfection after natural infection H3N2 Houston Family Study

TABLE I. Influenza A (H3N2) Infection* in Children Observed From Birth† in the Houston Family Study, 1975–81

Cohort[a]	No. children	No. infected in season[b]				Total No. (%) infected	No. (%) reinfected	
		1975–76	1976–77	1977–78	1980–81		Once	Twice
1975–76	21	8	1	14[c]	6	20(95)	7(33)[c]	1(5)
1976–77	19		1	9	7	16(84)	1(5)[d]	0
1977–78	15			3	6	9(60)	0[d]	0
Total	55					45(82)	8(15)	1(2)

Frank & Taber, 1983

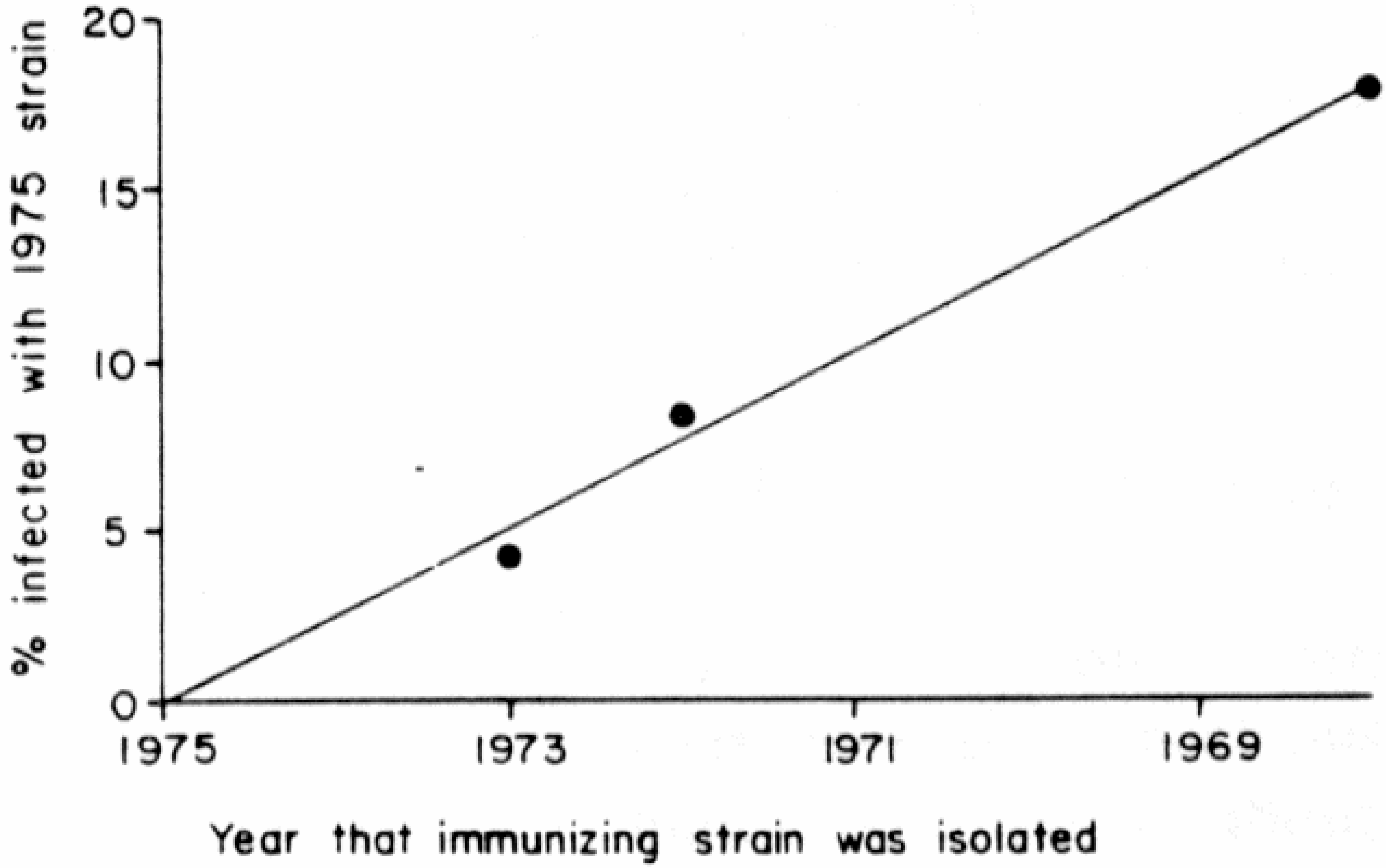
Reinfection after natural infection H1N1
Houston Family Study

TABLE V. Influenza A (H1N1) Infection[*] in Children Observed From Birth[†] in the Houston Family Study, 1975–81

Cohort[a,b]	No. children	No. infected 1977–78	1978–79	1979–80	1980–81	Total No. (%) infected	No. (%) reinfected
1975–76	21	5	8[c]	0	6	18(86)	1(5)
1976–77	19	2	2	1	5	10(53)	0
1977–78	15	3	0	0	3	6(40)	0
1978–79	16		1	0	3	4(25)	0
All	71					38(53)	1(1)

Frank & Taber, 1983

Reinfection of vaccinees



Pease, 1987 after Gill & Murphy 1976

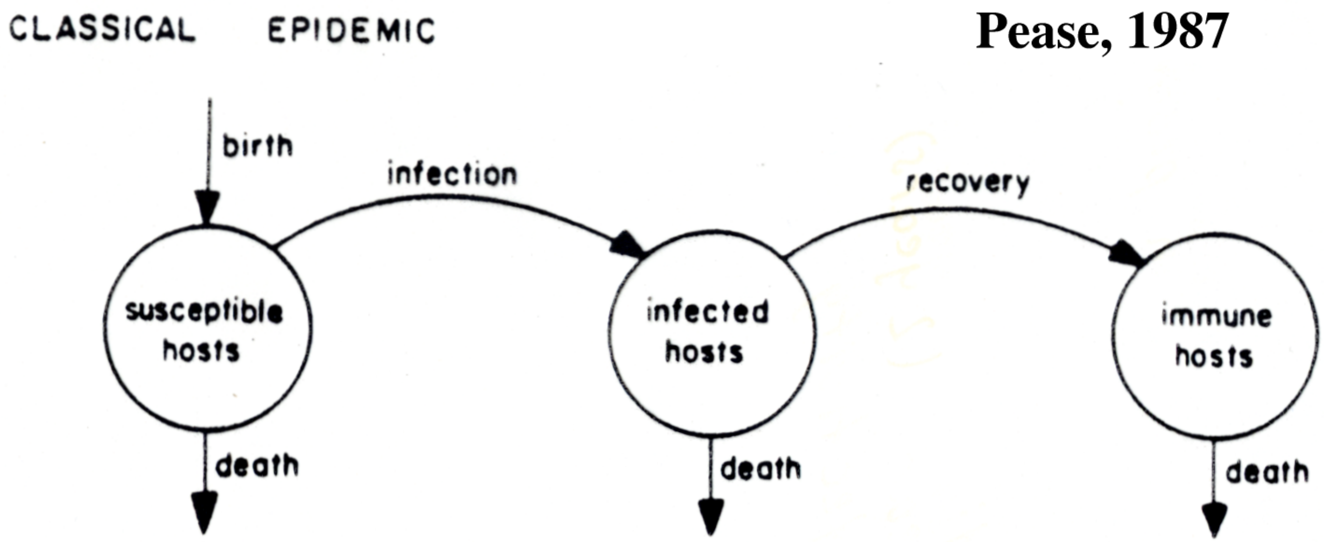
Cross-immunity in vitro

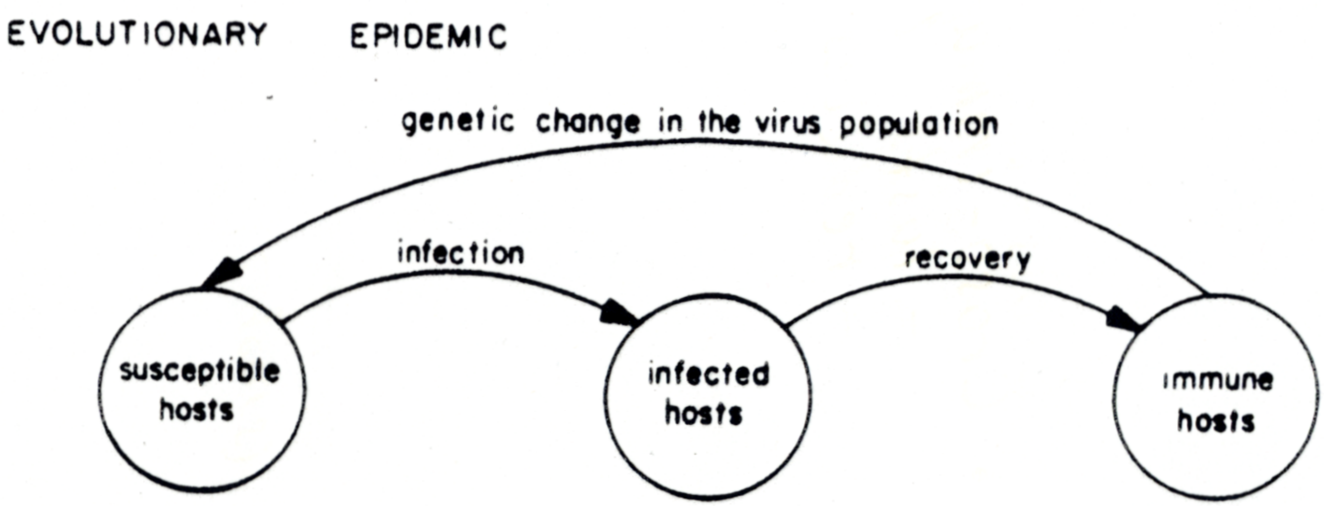
Hemagglutination Inhibition of H3N2 Influenza A Viruses Isolated Between 1968 and 1986

	Antibody units that inhibit hemagglutination				
Virus	**HK/8/68**	**E/42/72**	**PC/1/73**	**Vic/3/75**	**Tex/1/77**
A/Hong Kong/8/68	320	320	0	0	0
A/England/42/72	80	320	80	40	0
A/Port Chalmers/1/73	80	160	320	80	40
A/Victoria/3/75	80	160	320	640	160
A/Texas/1/77	0	40	160	160	1280
A/Bangkok/1/79	320	80	320	320	1280
A/Philippines/2/82	0	0	0	0	80
A/Mississippi/1/85	0	0	80	40	160
A/Leningrad/360/86	0	0	0	0	80

Levine, 1992

Pease, 1987


CLASSICAL EPIDEMIC
birth
infection
recovery
susceptible hosts
infected hosts
immune hosts
death
death
death


EVOLUTIONARY EPIDEMIC
genetic change in the virus population
infection
recovery
susceptible hosts
infected hosts
immune hosts

Epidemiology of a drifting virus
discrete version of model by Pease 1987

- In each season one new strain appears
- Prior to each season the strain drifts a fixed amount
- If possible an epidemic occurs
- Epidemic burns out before season is over
- Susceptibility and infectivity depends of number of seasons since last infection
- SIR-type dynamics
- No vital dymanics

Annual model for flu drift

S_i : # of hosts who have not been infected in this season and whoes most recent infection occurred i seasons ago

I_i : # of hosts who are currently infected and whoes most recent infection occurred i seasons ago

S_n, I_n n or more seasons ago

At start of season $\sum S_i(0) = 1 \qquad \sum I_i(0) \ll 1$

During epidemic

$$\begin{aligned}\dot{S}_i &= -\tau_i \Lambda S_i \\ \dot{I}_i &= \tau_i \Lambda S_i - \nu I_i \\ \Lambda &= \beta \sum \sigma_i I_i\end{aligned}$$

Outcome of epidemic $\phi = \frac{S_n(\infty)}{S_n(0)}$

$$\mathcal{R}_e = \frac{\beta}{\nu} \sum \sigma_i \tau_i S_i(0)$$

If $\mathcal{R}_e > 1$ then $0 < \phi < 1$ solves

$0 = \log \phi + \beta/\nu \sum \sigma_i S_i(0)(1 - \phi^{\tau_i})$

and $\phi^{\tau_i} = S_i(\infty)/S_i(0)$

If $\mathcal{R}_e < 1$

No epidemic $\phi = 1$

Year-to-year dynamics (onset $\rightarrow$ onset)

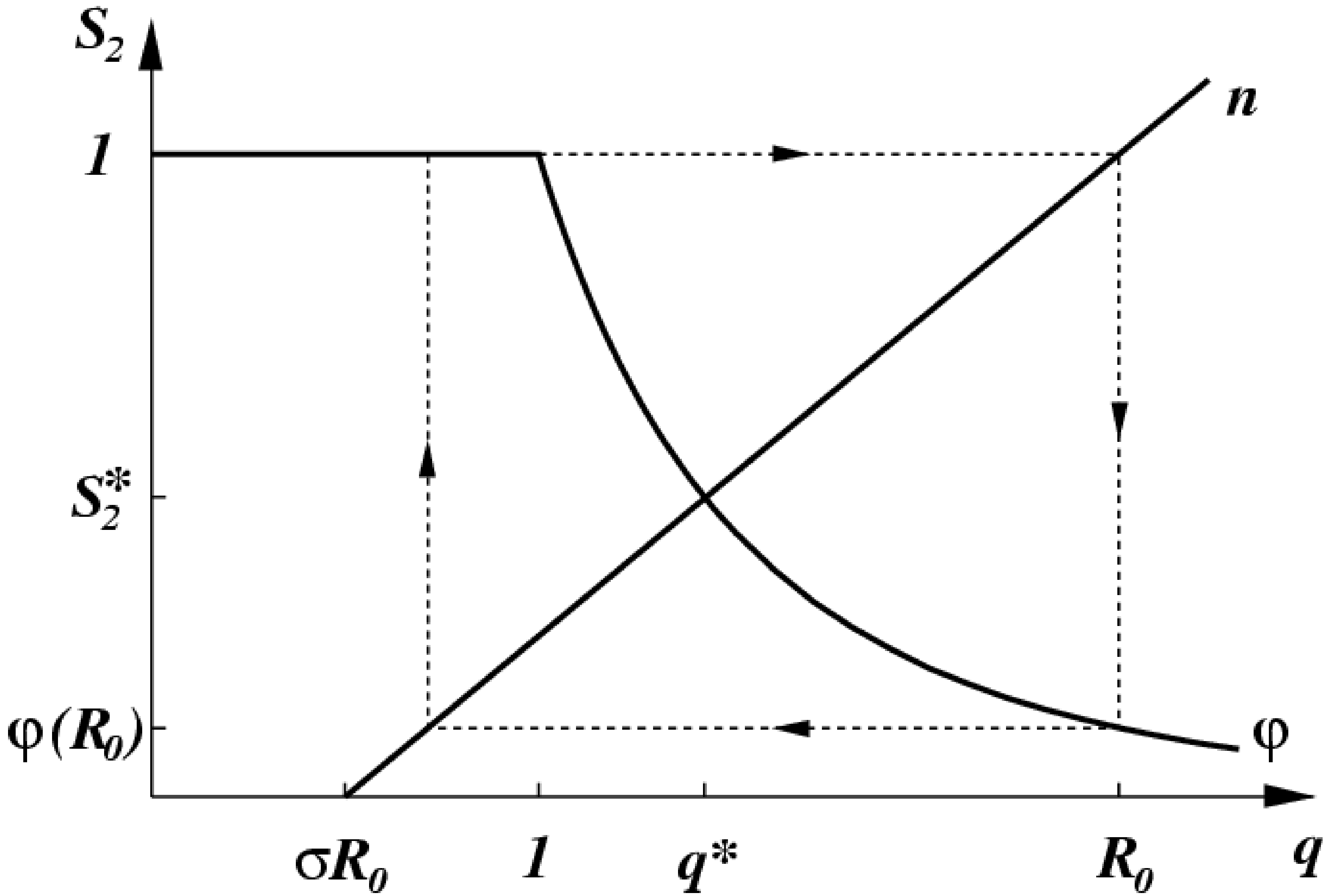
$$F : \begin{pmatrix} S_1 \\ S_2 \\ \vdots \\ S_{n-1} \end{pmatrix} \mapsto \begin{pmatrix} \sum(1-\phi^{\tau_i})S_i \\ \phi^{\tau_1}S_1 \\ \vdots \\ \phi^{\tau_{n-2}}S_{n-2} \end{pmatrix}$$

$S_n = 1 - \sum S_i$ is redundant

$\Gamma = \{ S \mid \sum S_i \leq 1, \quad s_i \geq 0 \}$ $\qquad F : \Gamma \rightarrow \Gamma$

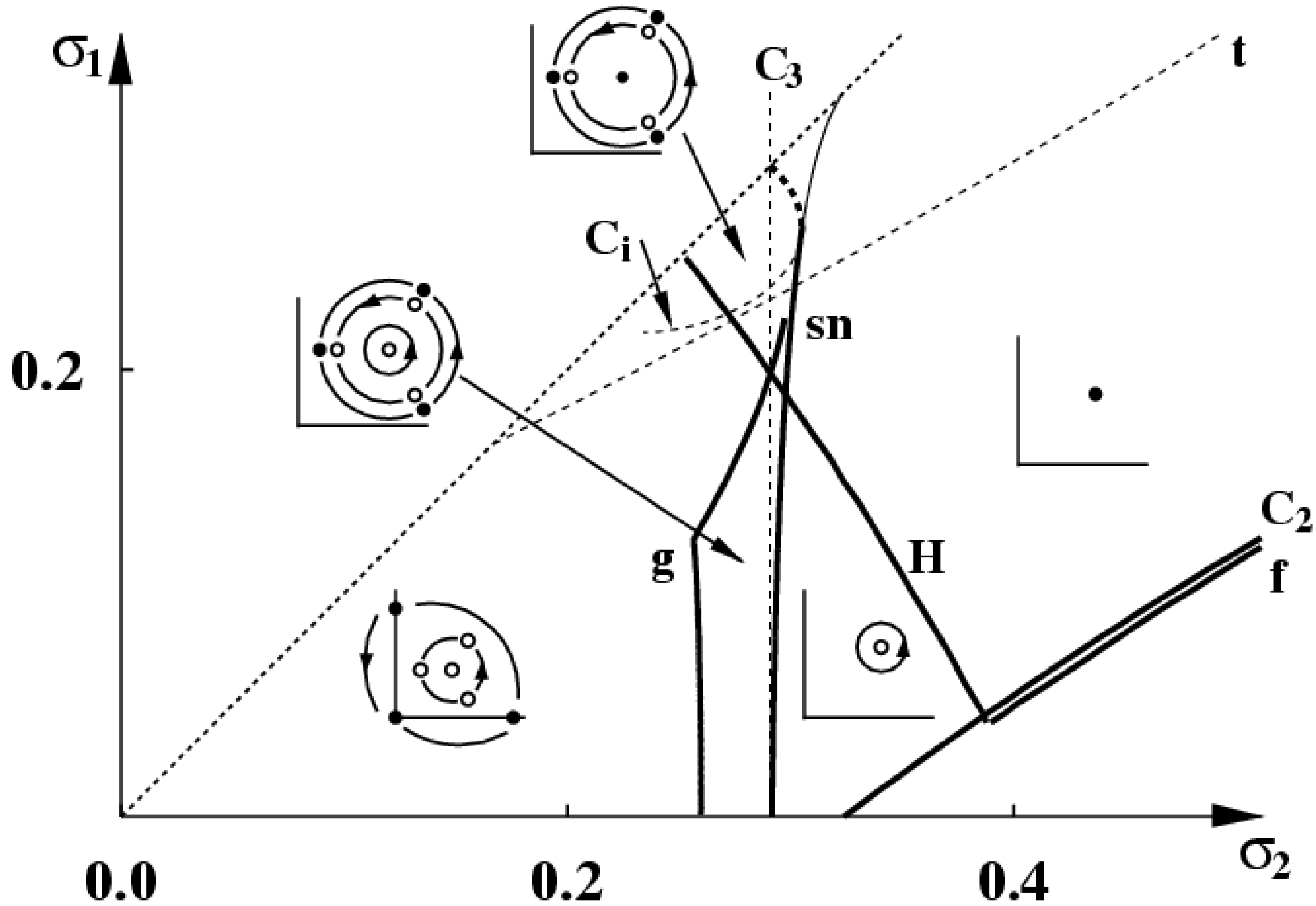
Cases $n = 2, 3, \quad \tau_i = 1,$
i.e. infectivity reduction only; $\Rightarrow$ ϕ-eqn simplifies
$0 = \log\phi + q(1-\phi) \qquad q = \mathcal{R}_0 \sum \sigma_i S_i(0)$

Dynamics for Annual flu epidemics, $n = 2$



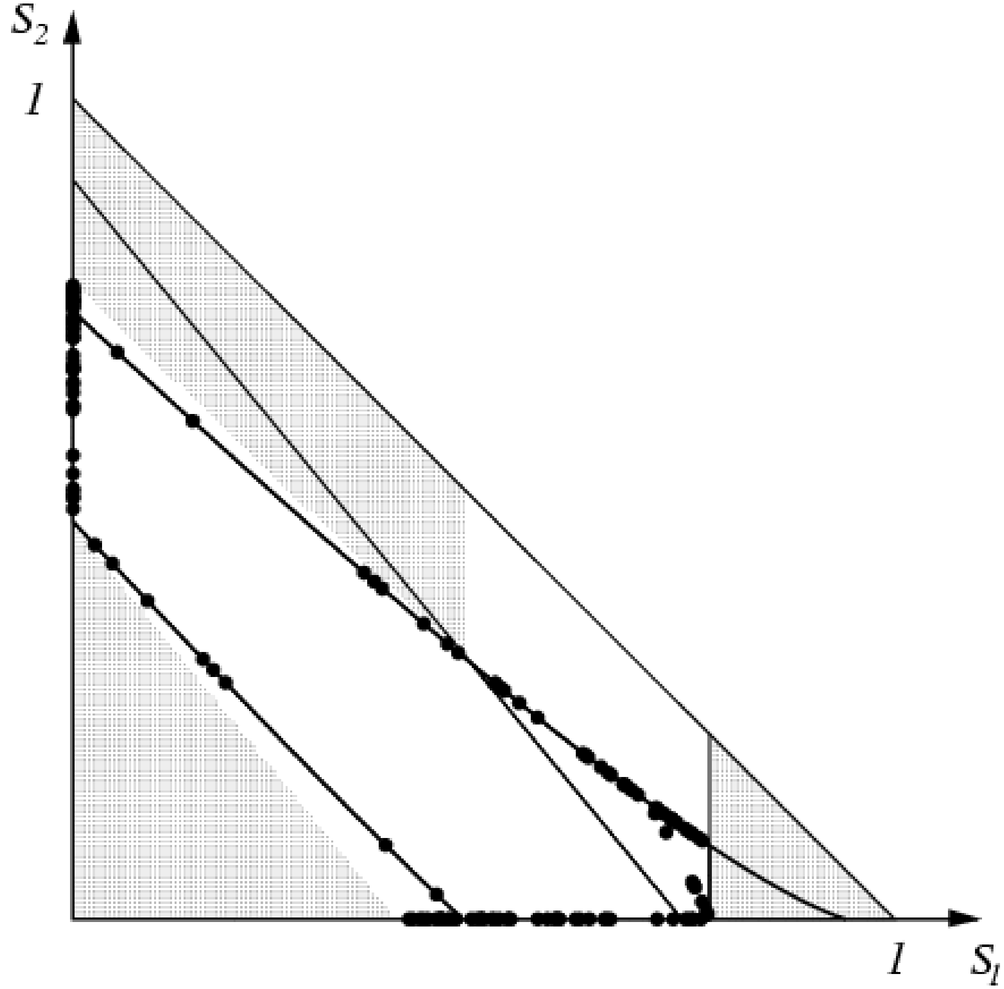
Andreasen 2003

Bifurcation diagram for annual flu epidemics, $n = 3$



Andreasen 2003

Attractor in annual flu model, $n = 3$

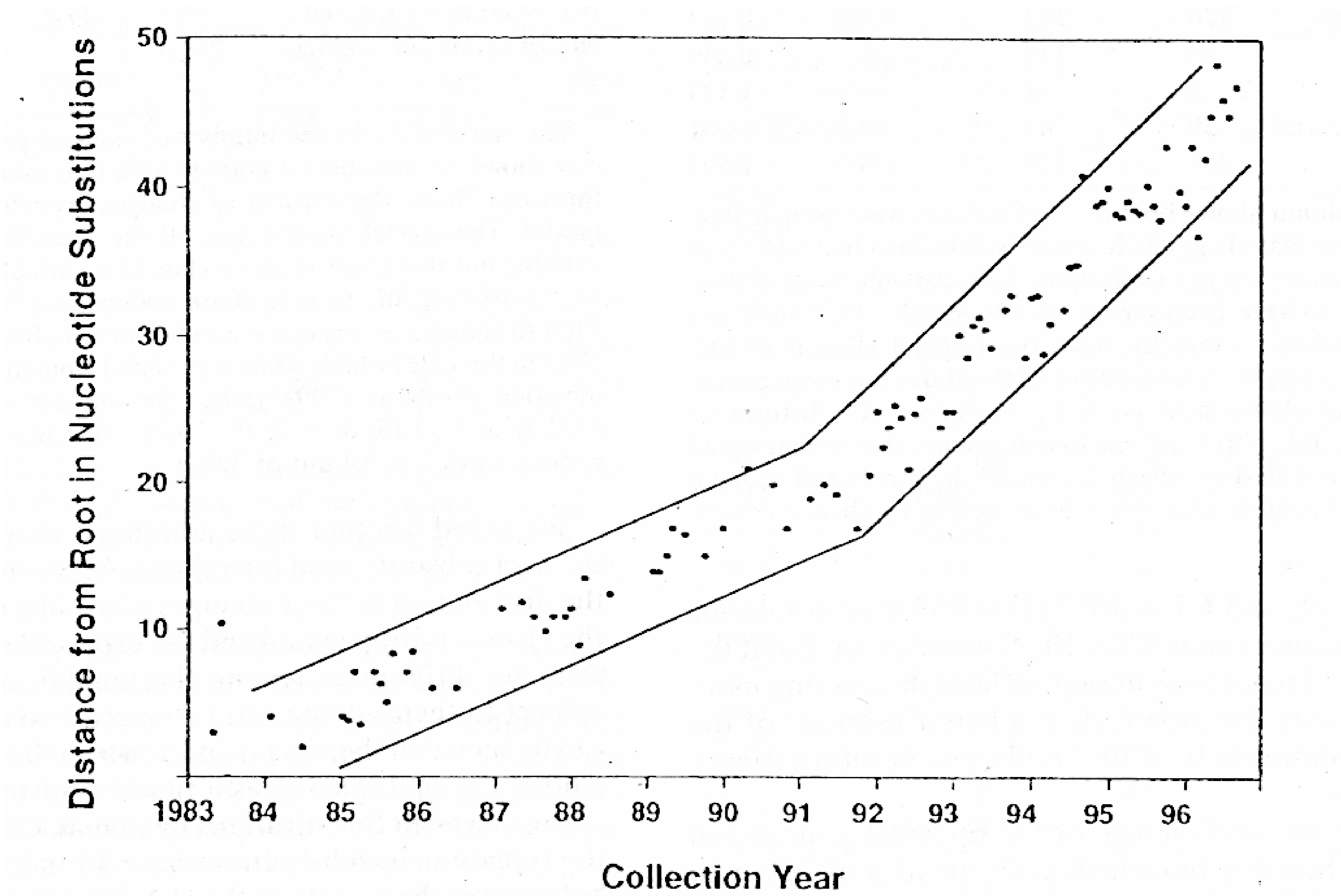


Andreasen 2003

Conclusions flu-drift model

- Focus on host immune structure
- Explicit rule for introduction of susceptible
- Recognizes seasonality and pronounced epidemics
- Epidemic levels as observed in nature
- Not a word on time within season
- Not a word about persistence or causes of drift

Aminoacid substitutions in HA1 (H3N2)
Fitch et al, 1997

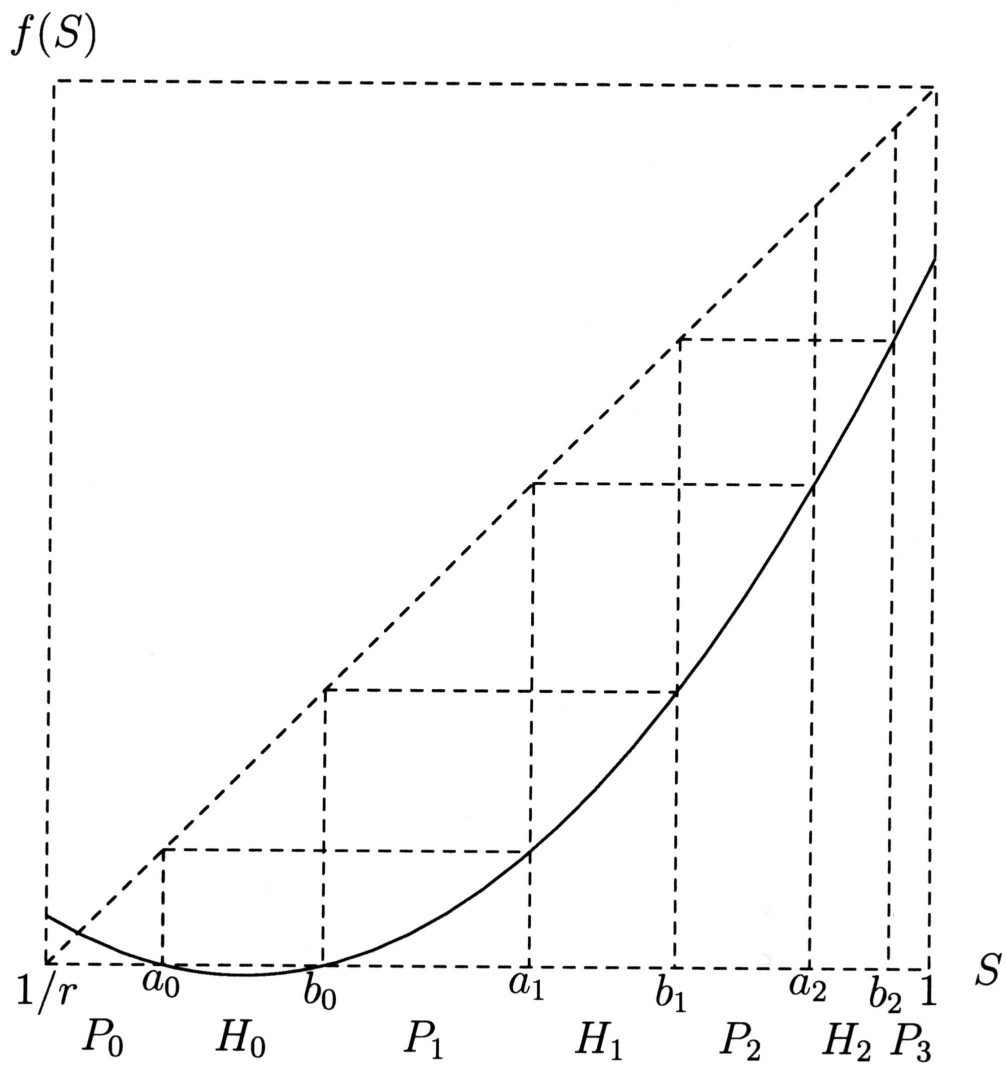


Drift speed and epidemic size Boni et al submitted

- Seasonal dynamics as before; infectivity reduction
- X-immunity decays with "distance"
  $\sigma = 1 - \exp(-d)$
- Distance is additive over years
- Distance grows linearly with size of epidemic I, $d = \kappa + \lambda I$

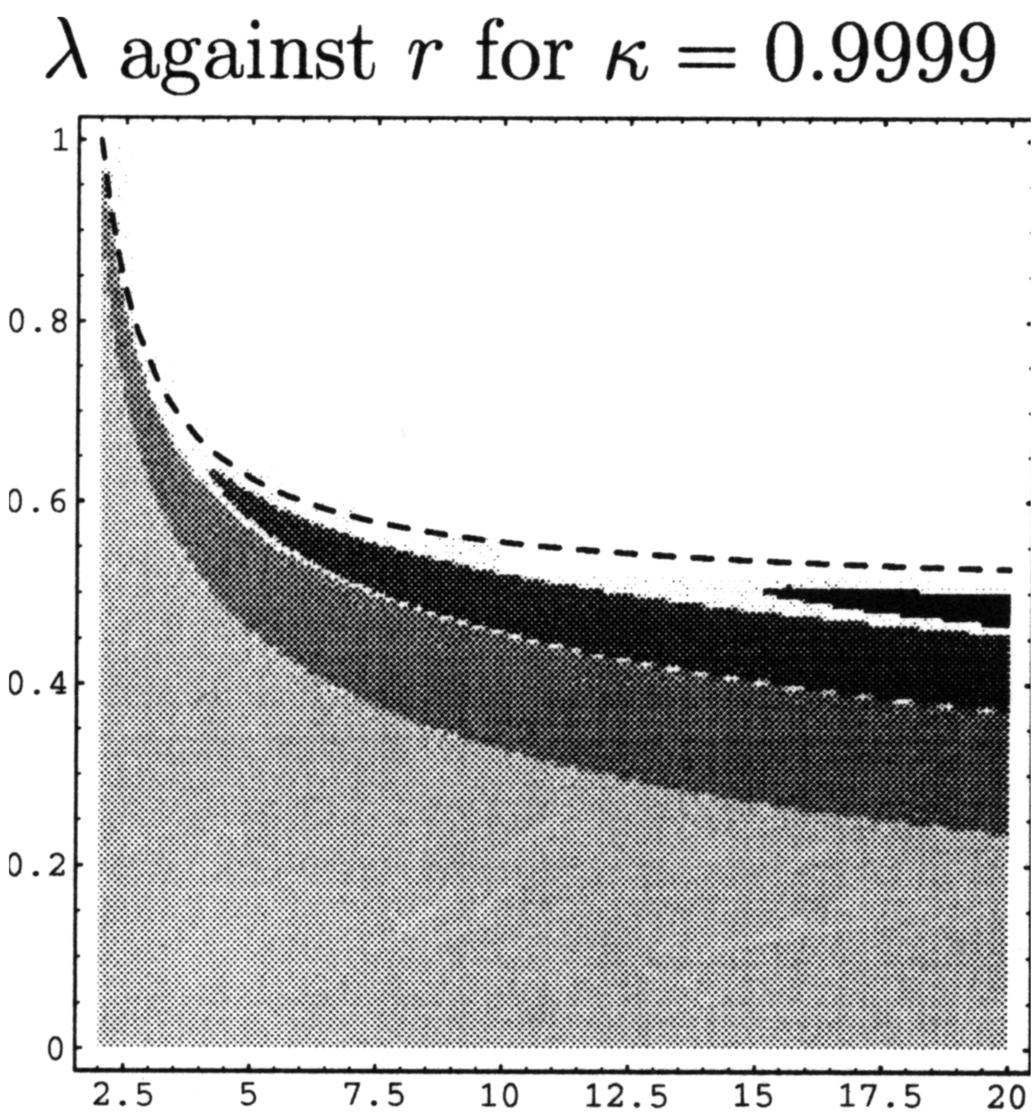
- $S = \sum \sigma_i S_i$ weighted susceptibility
- Outcome of epidemic in terms of S
  $f(S) = 1 - \kappa\phi^{\lambda}(1 - \phi S)$
  where ϕ prob of not being infected

Dynamics of size-dependent drift



Boni et al ms

Invasion and persistence of drifting virus



Persistence

One epidemic only

Boni et al ms

Virus selection in annual epidemics

- In haploids competition $\approx$ selection
- Assume two virus types I and Y
- Epidemics within a season

$$\begin{aligned}\dot{S} &= -\beta_I I S - \beta_Y Y S \\ \dot{I} &= \beta_I I S - \nu_I I \\ \dot{Y} &= \beta_Y Y S - \nu_Y Y\end{aligned}$$

- Only the viral type with the highest $\mathcal{R}_0$ will produce an epidemic

Saunders, 1981