

Natural selection and evolution in seasonal epidemic models

Viggo Andreasen
Pandemix, Roskilde University

June 13, 2023

Seasonal epidemics

Seasonal epidemics

Onset of epidemic season

If susceptible population exceeds threshold
an epidemic occurs



During epidemic season

SIR-type epidemic – burn-out



Between epidemic seasons

Other processes add to size of susceptible population

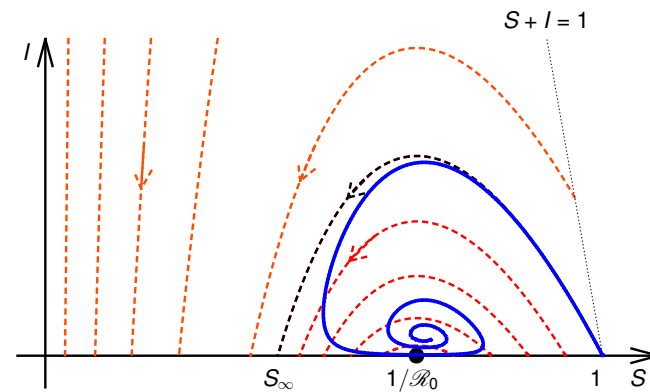
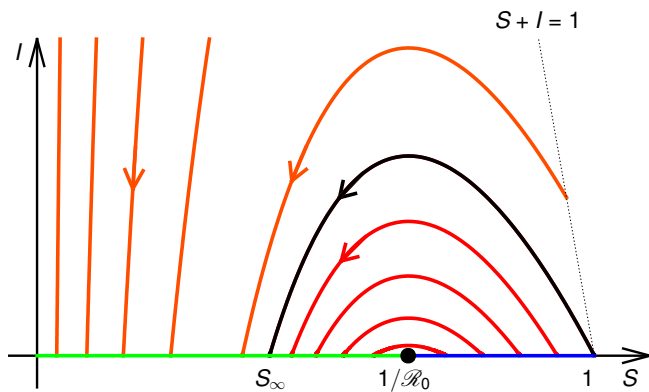


- Strong seasonal component
- Discrete renewal of hosts

Outline

- The single deterministic epidemic in a structured population
- Virus competition in seasonal epidemics
- Seasonal epidemics in the description of influenza epidemiology

Phase Portrait for the SIR -model



SIR -model no demographics

$$\begin{aligned} S'(t) &= -\mathcal{R}_0 SI \\ I'(t) &= \mathcal{R}_0 SI - I \\ dI/dS &= -1 + 1/\mathcal{R}_0 S \end{aligned}$$

SIR -model with demographics

$$\begin{aligned} S'(t) &= -\mathcal{R}_0 SI + \mu(1 - S) \\ I'(t) &= \mathcal{R}_0 SI - I - \mu I \end{aligned}$$

The single epidemic – Structured population

$$\dot{S}_k = -S_k \sum_j b_{kj} I_j$$

$$\dot{I}_k = S_k \sum_j b_{kj} I_j - \nu I_k$$

- Final size in terms of $\phi_k = S_k(\infty)/S_k(0)$ determined by n implicit equations.
- There exists a unique positive root iff $\mathfrak{R}_0 > 1$ (provided B is nonnegative and primitive)

Andreasen(2011) Rass & Radcliffe: *Spatial deterministic epidemics* (2003)

The single epidemic – proportionate mixing

$$\begin{aligned}\dot{S}_k &= -\tau_k \Lambda S_k \\ \dot{I}_k &= \tau_k \Lambda S_k - \nu I_k \\ \Lambda &= \sum \sigma_k I_k \quad k = 1, \dots, n\end{aligned}$$

- Proportionate mixing *in the sense of Barbour (1978)*: $b_{kj} = \tau_k \sigma_j$
- Threshold: $\mathfrak{R}_0 = \frac{1}{\nu} \sum_k \tau_k \sigma_k S_k(0) > 1$
- Final size can be found analytically – as an implicit function in $\phi = S_J(\infty)/S_J(0)$ for index group $J = k$
- The epidemic in the structured population is smaller than that of a homogeneously mixing population with same \mathfrak{R}_0 provided that $\text{Cov}(\sigma, \tau) > 0$

Gart(1968) Andreasen(2011) Katriel (2012) Clancy & Pearce (2012)

Seasonal epidemics - coexistence

- Inspired by the gypsy-moth NPV system
- Gypsy moth is an annual insect - larvae hatch in spring
- Larvae get infected with NPV by eating contaminated leaves
- After ca 2 weeks infected larvae burst and spread new virus
- A few virus particles survive the winter and seed the epidemic next year



Gypsy Moth

(*Lymantria dispar*)

G Dwyer et al, Am. Nat. 156: 105 (2000)



Larvae with Nuclear
Polyhedrosis Virus



Experimental
epidemics

Season-to-season model - Formulation Joint w G Dwyer

Am Nat 201: 639 (2023)

During the season:

$$\begin{aligned}\dot{S} &= -\mathcal{R}_0^I S I \\ \dot{I} &= \mathcal{R}_0^I S I - I\end{aligned}$$

Start of next season:

$$\begin{aligned}S^{n+1}(0) &= 1 - I^{n+1}(0) \\ I^{n+1}(0) &= W_I \int_0^\infty I^n(t) dt = W_I Z^n(\infty)\end{aligned}$$

Final size: $Z^n(\infty) + \frac{1}{\mathcal{R}_0^I} \log(1 - Z^n(\infty)) / (1 - I^n(0)) = 0$

S, I given as fraction of total population at onset.

Z Removed/recovered is given implicitly since $Z = 1 - S - I$.

Time in units of duration of infection.

Theorem: If $\mathcal{R}_0^I > 1$, then there exists a unique stable equilibrium $I^\dagger(0)$.

Invasion condition for a new strain Y

Assume that $I(0) = I^\dagger(0)$ is at equilibrium and $Y(0) \ll I(0)$.
Will $Y(0)$ for next season increase?

$$\dot{S} = -\mathcal{R}_0^I SI - u\mathcal{R}_0^Y SY$$

$$\dot{I} = \mathcal{R}_0^I SI - I$$

$$\dot{Y} = u\mathcal{R}_0^Y SY - uY$$

$Y(0)$ increases if:

$$Y^{\text{next}}(0) = W_Y \int_0^\infty uY(t) dt > Y(0)$$

Linearization

Assume that \mathcal{R}_0^Y is sufficiently small that repeated epidemics does not occur: $\mathcal{R}_0^Y S_\infty^I < 1$.

Since $Y(0) \ll I(0)$, $Y(t) \ll I(t)$ for all t

By linearization, the red term vanishes

$$\dot{S}^\dagger = -\mathcal{R}_0^I S^\dagger I^\dagger - u \mathcal{R}_0^Y S^\dagger Y$$

$$\dot{I}^\dagger = \mathcal{R}_0^I S^\dagger I^\dagger - I^\dagger$$

$$\dot{Y} = u \mathcal{R}_0^Y S^\dagger Y - uY$$

Since the problem is now linear in $Y(0)$ we may assume $Y(0) = 1$

Solving the model

Express dynamics in terms of $x = 1 - S$ $x \in (I_0; x^*)$

$$I'(x) = 1 - \frac{1}{\mathcal{R}_0^I(1-x)} \qquad I(I_0) = I_0$$

$$Y'(x) = u \left(\frac{\mathcal{R}_0^Y(1-x)}{\mathcal{R}_0^I(1-x)I(x)} - \frac{1}{\mathcal{R}_0^I(1-x)I(x)} \right) Y(x) \qquad Y(I_0) = 1$$

where

$$I(x) = x + \frac{1}{\mathcal{R}_0^I} \log(1-x)/(1-I_0)$$

Asymptotic expansion in $W_I \ll 1$

($W_I \ll 1$ corresponds to $I_0 = W_I(1 - S^\dagger(\infty)) \ll 1$)

$$Y'(x) = \frac{u}{\mathcal{R}_0^I I(x)} \left(\mathcal{R}_0^Y - \frac{1}{1-x} \right) Y(x) \quad Y(I_0) = 1$$

where $I(x) = x + \frac{1}{\mathcal{R}_0^I} \log(1-x)/(1-I_0)$

For $I_0 = 0$, $x = 0$ is a *regular singular point* and solutions have the form

$$Y(x) = x^\gamma A(x)$$

where $\gamma = u(\mathcal{R}_0^I - 1)/(\mathcal{R}_0^Y - 1)$ is the *incidental coefficient* and A is an analytical function (Fuchs)

Thus $Y(0) = 0$ for all solutions and we use multiple time scales to find the solution on the short time scale.

Short time scale

Set $\epsilon = I_0/u(\mathcal{R}_0^I - 1)$ and $\tau = x/\epsilon$.

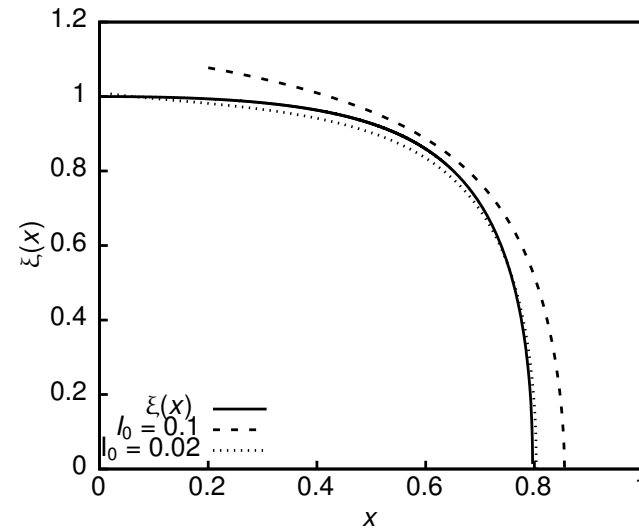
$$Y_b'(\tau) = \frac{Y_b}{1 + \tau/\gamma} \quad Y(I_0) = 1.$$

Matching the solutions

$$Y(x) = \left(\frac{x/\gamma\epsilon + 1}{\mathcal{R}_0^I} \right)^\gamma \xi(x)$$

where ξ solves $\xi(0) = 1$

$$\xi'(x) = \frac{\frac{u}{x-1} - \gamma \frac{x + \log(1-x)}{x^2}}{\mathcal{R}_0^I - 1 + \frac{x + \log(1-x)}{x}} \xi(x)$$



Invasion condition

We set $Y(0) = 1$, so Y can invade if

$$\begin{aligned} 1 < Y^{\text{next}}(0) &= W_Y \int_0^\infty uY(t) dt \\ &= W_Y \int_0^\infty u \left(\frac{x/\gamma\epsilon + 1}{\mathcal{R}_0^I} \right)^\gamma \xi(x) dt \end{aligned}$$

since $\epsilon = I_0/u(\mathcal{R}_0^I - 1)$ and $I_0 = W_I(1 - S^\dagger(\infty))$

$$\approx W_Y W_I^{-\gamma} / D$$

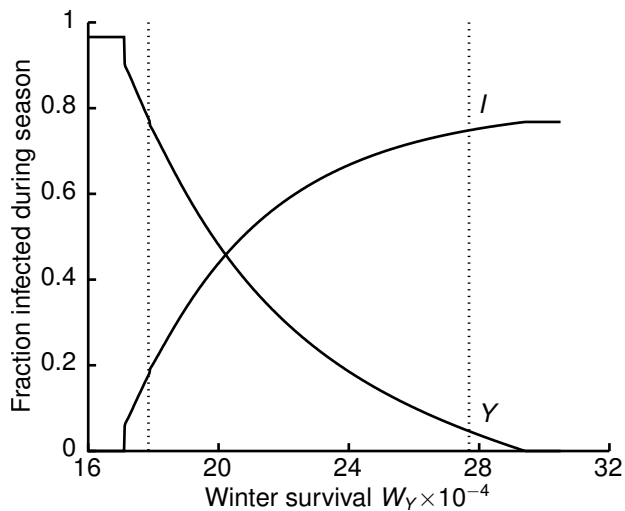
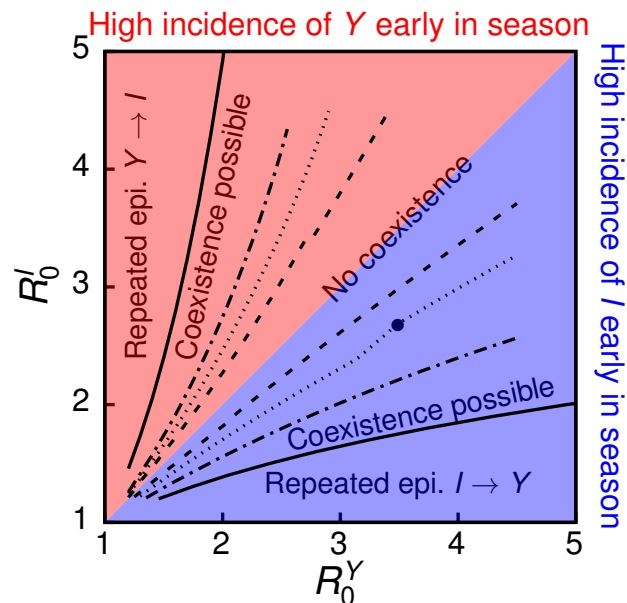
$$DW_I^\gamma < W_Y$$

Mutual invasibility

Repeating the analysis for
 I invades Y

$$D_1 W_I^\gamma < W_Y < D_2 W_I^\gamma$$

There exists a range of
parameter values such that $D_1 < D_2$.



$$u = 1 \quad \mathcal{R}_0^I = 3.5 \quad \mathcal{R}_0^Y = 1.9 \quad W_I = 10^{-7}$$

Coexistence and seasonality

- Pathogen co-existence is possible in a seasonal environment
- Not so in a constant environment Bremermann & Thieme *J Math Biol* **27**: 179 (1989)
- Separation in **timing**. Rogers *Ecology* **66**: 701 (1985)
- Coexistence in continuous environment
- $W_I \ll W_Y$ may be relaxed in heterogeneous environments



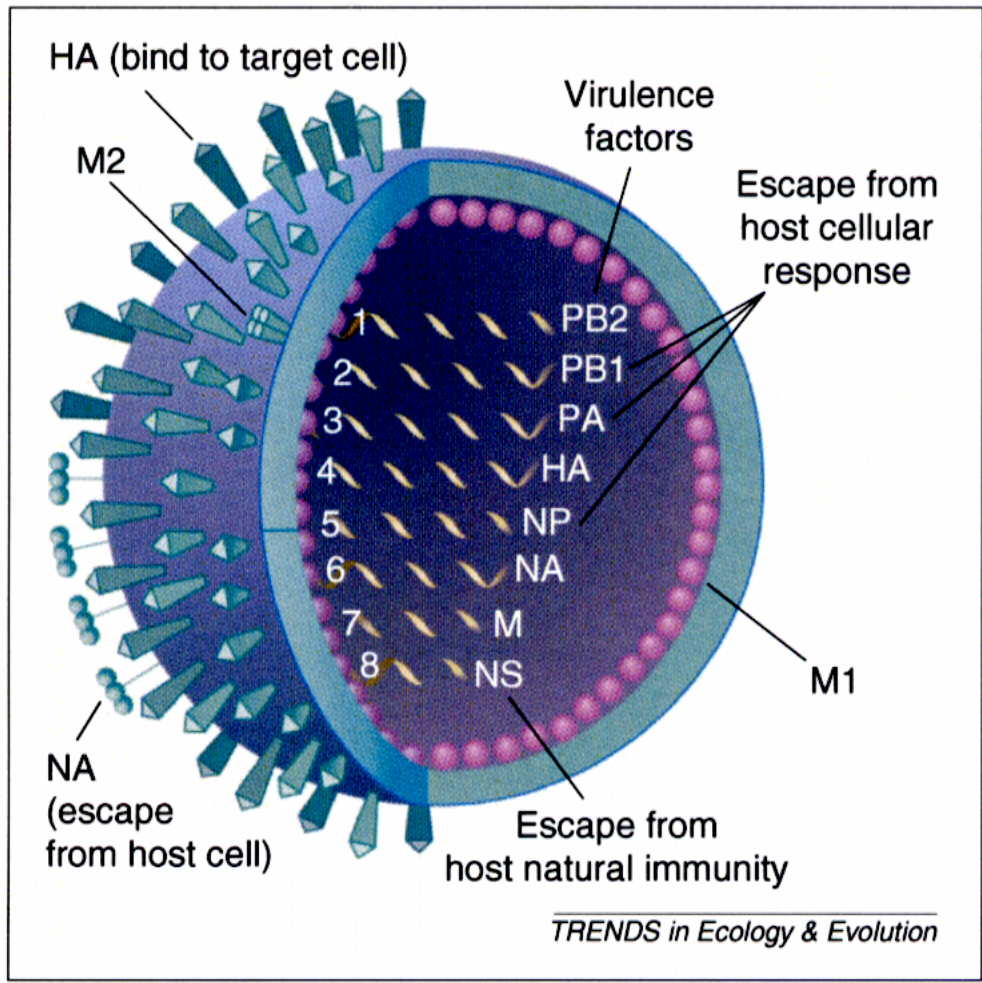
Yellow Adder's tongue
(*Erythronium americanum*)



Five Leaved Ivy
(*Parthenocissus quinquefolia*)

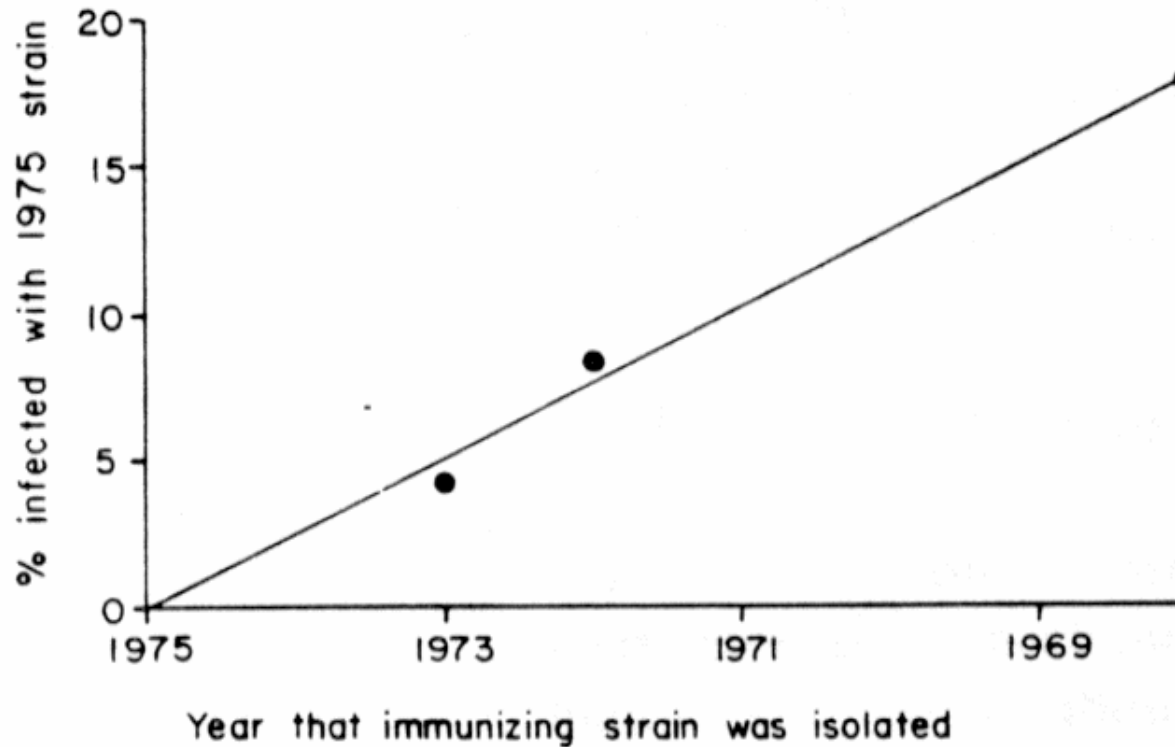
Annual epidemics and influenza epidemiology

- Influenza's natural history
- The epidemiology of a drifting virus
- Pruning of flu phylogeny



Earn et al (2002)

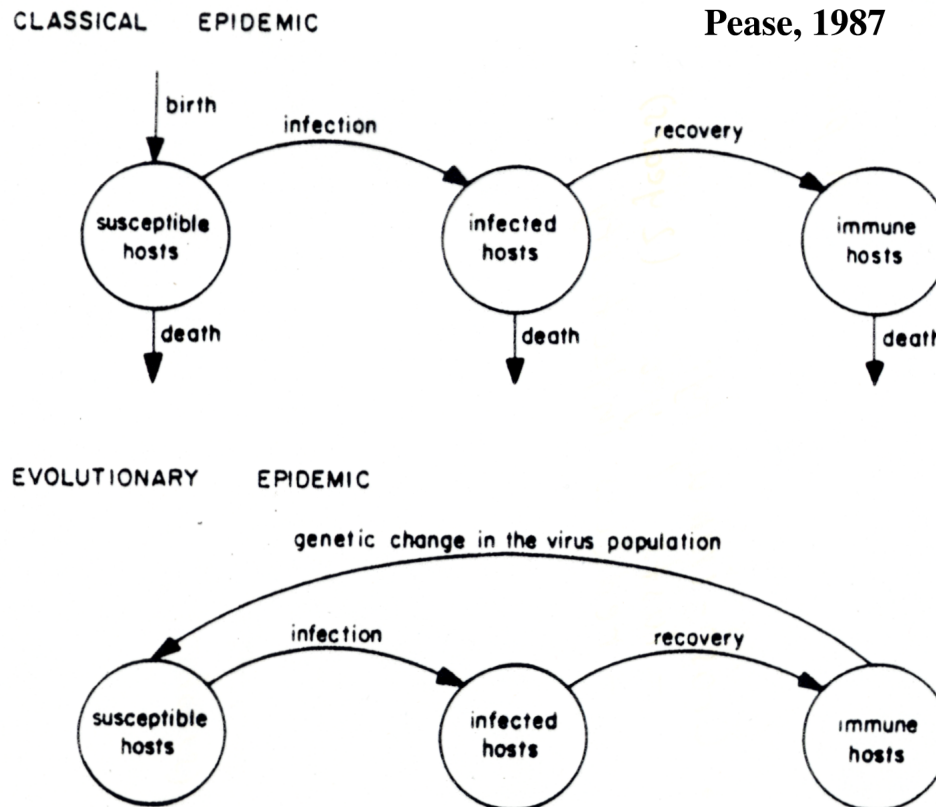
Reinfection of vaccinees



Pease, 1987 after Gill & Murphy 1976

Much more is known now: Koelle et al *Science* (2006) Kucharski et al *PLOS Bio.* (2018)

Evolutionary vs classical epidemiology



Pease(1987)
Inaba(1998, 2002)
Andreasen & Gog
(2020)

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 dynamics

Annual model for flu drift

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

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

S_n, I_n n or more seasons ago

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

Immunity depends on last infection $\sigma_i \leq \sigma_{i+1}, \tau_i \leq \tau_{i+1}$

During epidemic

$$\dot{S}_i = -\tau_i \Lambda S_i$$

$$\dot{I}_i = \tau_i \Lambda S_i - \nu I_i$$

$$\Lambda = \beta \sum \sigma_i I_i$$

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

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

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

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

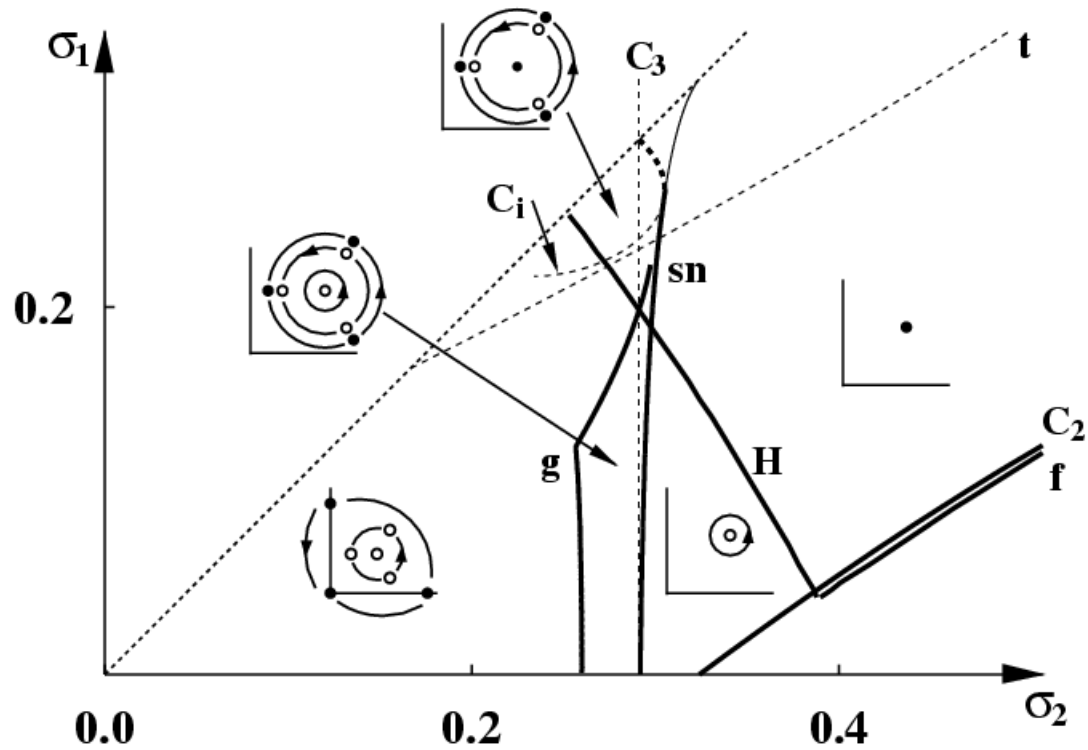
$$\Gamma = \{ S \mid \sum S_i \leq 1, \quad s_i \geq 0 \} \quad F : \Gamma \rightarrow \Gamma$$

Case $n = 3$, $\tau_i = 1$,

i.e. infectivity reduction only; $\Rightarrow \phi$ -eqn simplifies

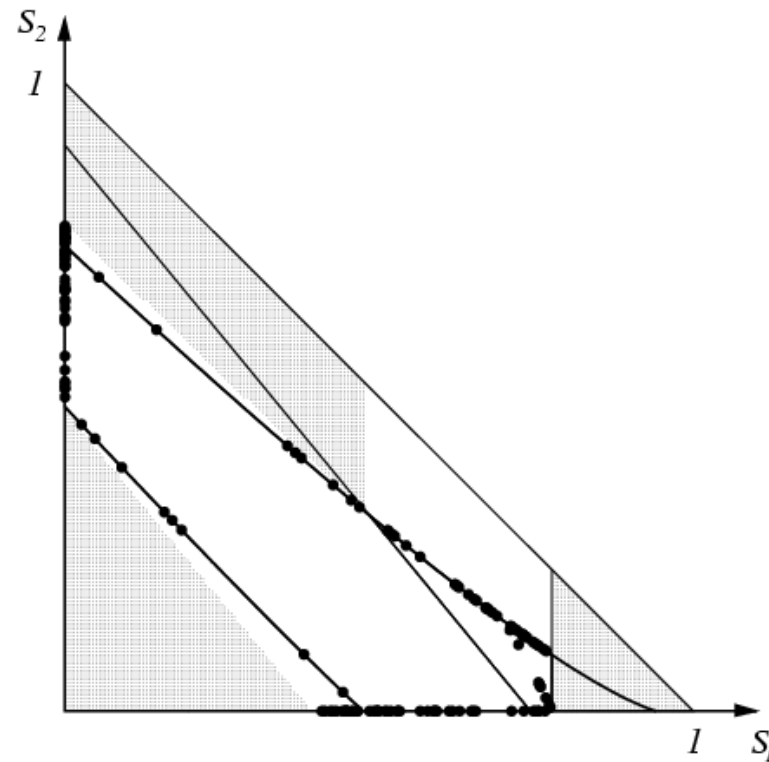
$$0 = \log \phi + q(1 - \phi) \quad q = \mathcal{R}_0 \sum \sigma_i S_i(0)$$

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



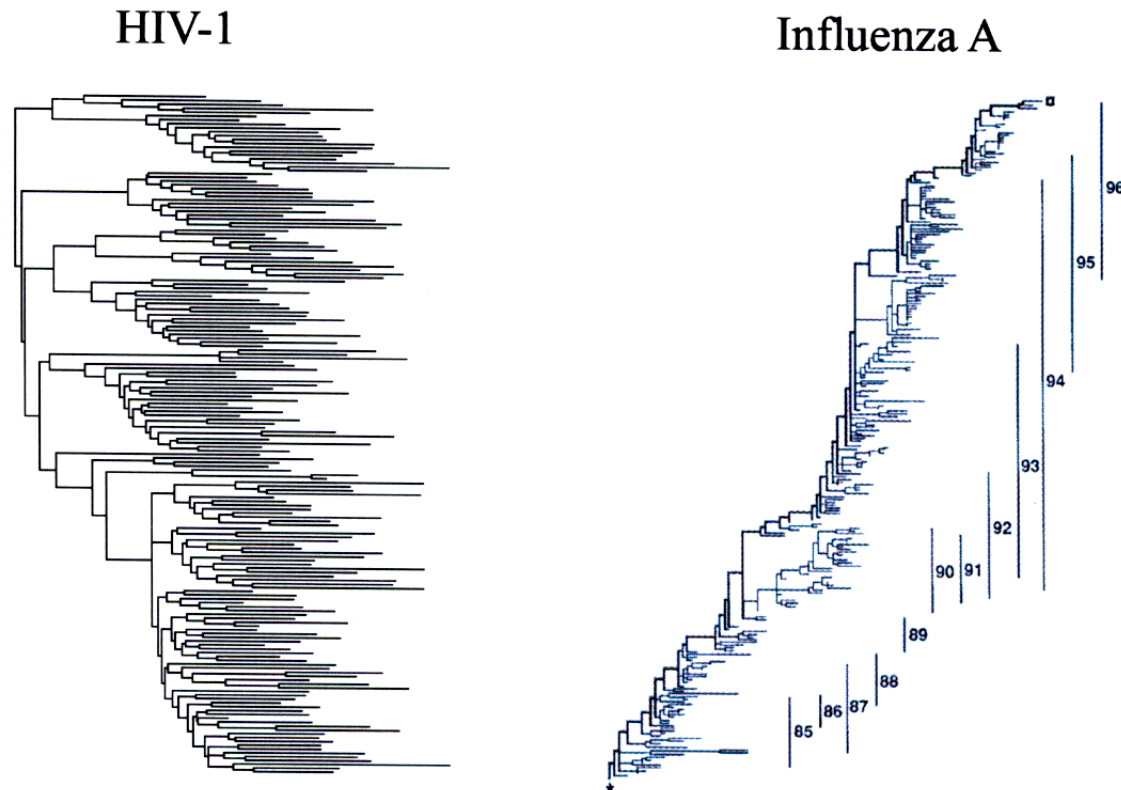
Andreasen 2003

Attractor in annual flu model, $n = 3$



Andreasen *JMB* (2003) Roberts et al *JMB* (2019)

Virus Phylogenies

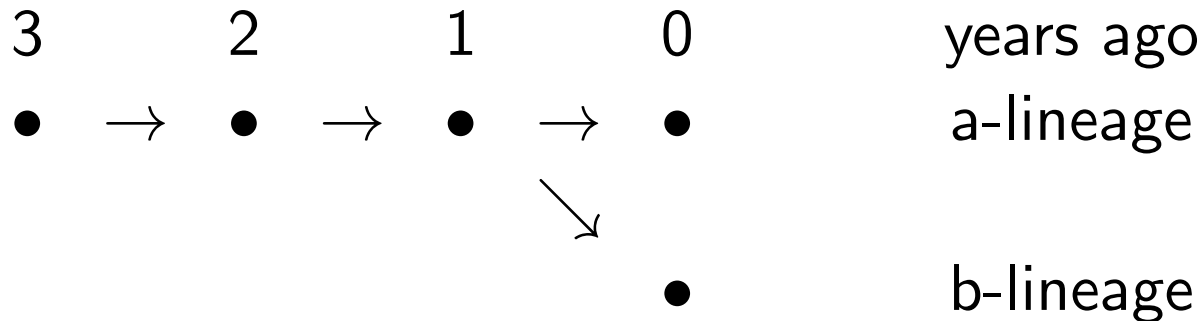


Dushoff et al unpubl, Data from Rambaut et al 2001 and Fitch 1997

Pruning the flu tree

w. A Sasaki, 2006

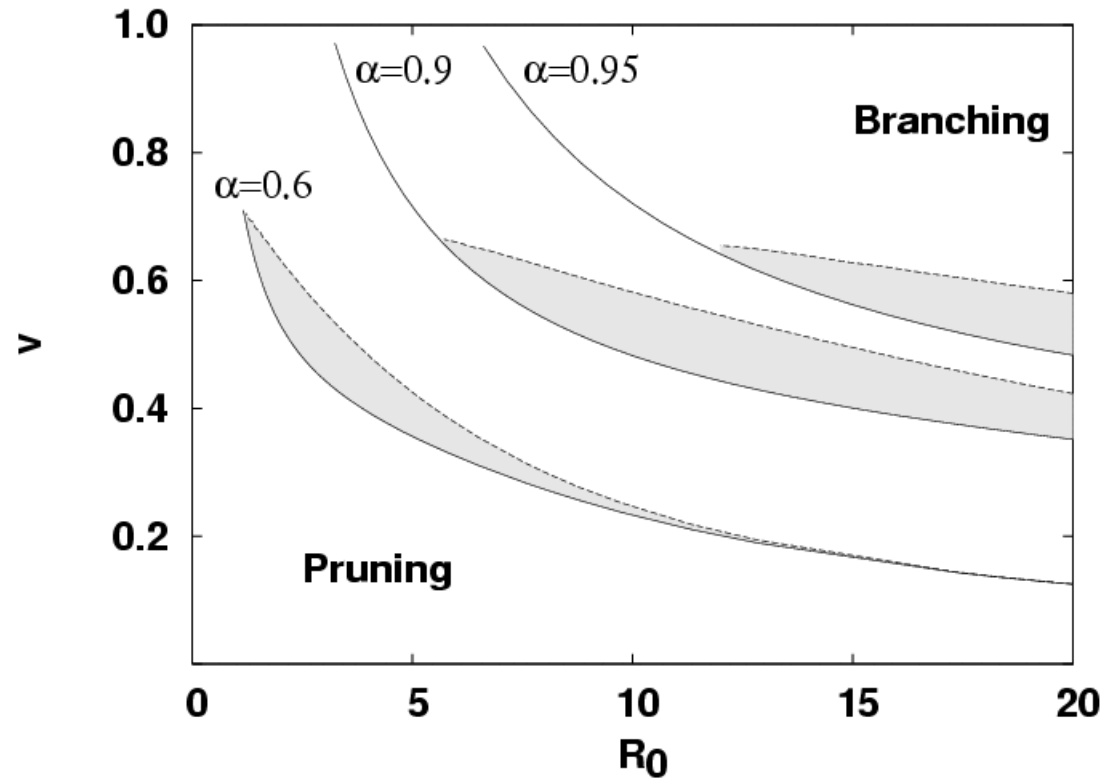
- Strain *a* sweeps through the population
- Strain *b* then enters the population



Cross-immunity (infectivity reduction) to *b*-strain ρ_k
 Only the fraction v of hosts can be reinfected

	S_1	$S_k, k \geq 2$
Infected this season	$\rho_1 = \tau_1$	$\rho_k = \tau_2$
Not infected in season	$\rho_1 = \tau_1$	$\rho_k = \tau_k = 1 - \alpha^k$

Branching conditions



Andreasen & Sasaki, *TPB* (2006)

Agent-based approach: Ferguson et al *Nature* (2003) Tria et al *J Stat Mech: Theor Exp* (2005)

Applications

- Disease-induced selection in diploid hosts (Gillespie, 1975)
- Disease regulation of (insect) hosts (May, 1985; Dwyer et al 2000)
- Disease in life-stock (Roberts & Heesterbeek, 1998)
- Influenza drift (Andreasen, 2003)
- Influenza drift and epidemic size (Boni et al, 2004)
- Age-structured populations (Andreasen & Frommelt, 2005))
- Pruning of influenza phylogeny (Andreasen & Sasaki, 2006)
- Skipping dynamics of childhood diseases (Stone et al, 2007)
- Influenza-immunology: The original anti-genic sin
(Kucharski & Gog, 2012)

Supported by Carlsberg Foundation and Danish Research Council (DFF)