Annual epidemics and natural selection in host-pathogen systems

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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

\[
\begin{align*}
\text{Fitness of uninfected } AA & \quad 1 \\
\text{Fitness of infected } AA & \quad 1 - u \\
\text{Fitness of } AB \text{ and } BB & \quad 1 - \sigma
\end{align*}
\]

\[ p = \text{frequency of } A\text{-allele} \]
\[ q = 1 - p \text{ frequency of } B\text{-allele} \]
The epidemic season

\[
\frac{dS_{AA}}{dt} = -\tau_{AA}\Lambda S_{AA}
\]

\[
\frac{dI_{AA}}{dt} = \tau_{AA}\Lambda S_{AA} - \mu_{AA}I_{AA}
\]

\[
\Lambda = \beta_{AA}I_{AA} + \beta_{AB}I_{AB} + \beta_{BB}I_{BB}
\]

\[
S_{AA}(0) = p^2N \quad I_{AA}(0) \approx \Lambda \ll 1
\]

Fraction infected during the epidemic \( z \)

\[
z = 1 - e^{-zp^2R_0}
\]

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 population size!
Frequency of $A$ at onset of next season:

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

(Stable) equilibrium at

$$z = \frac{\sigma}{u} \quad p = \sqrt{-\log(1 - z)/zR_0}$$
Annual epidemics and influenza epidemiology

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

Annual epidemics and selection
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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. children</th>
<th>No. infected in season</th>
<th>Total No. (%) infected</th>
<th>No. (%) reinfected</th>
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</thead>
<tbody>
<tr>
<td>1975–76</td>
<td>21</td>
<td>8</td>
<td>1</td>
<td>14&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1976–77</td>
<td>19</td>
<td>1</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>1977–78</td>
<td>15</td>
<td>3</td>
<td>6</td>
<td></td>
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<tr>
<td>Total</td>
<td>55</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Frank & Taber, 1983
Reinfection after natural infection H1N1
Houston Family Study

Frank & Taber, 1983

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1975–76</td>
<td>21</td>
<td>5</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td>18(86)</td>
<td>1(5)</td>
</tr>
<tr>
<td>1976–77</td>
<td>19</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>10(53)</td>
<td>0</td>
</tr>
<tr>
<td>1977–78</td>
<td>15</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6(40)</td>
<td>0</td>
</tr>
<tr>
<td>1978–79</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>4(25)</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38(53)</td>
<td>1(1)</td>
</tr>
</tbody>
</table>

Frank & Taber, 1983

Annual epidemics and selection
Reinfection of vaccinees

Pease, 1987 after Gill & Murphy 1976
Cross-immunity in vitro

<table>
<thead>
<tr>
<th>Virus</th>
<th>HK/8/68</th>
<th>E/42/72</th>
<th>PC/1/73</th>
<th>Vic/3/75</th>
<th>Tex/1/77</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Hong Kong/8/68</td>
<td>320</td>
<td>320</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A/England/42/72</td>
<td>80</td>
<td>320</td>
<td>80</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>A/Port Chalmers/1/73</td>
<td>80</td>
<td>160</td>
<td>320</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>A/Victoria/3/75</td>
<td>80</td>
<td>160</td>
<td>320</td>
<td>640</td>
<td>160</td>
</tr>
<tr>
<td>A/Texas/1/77</td>
<td>0</td>
<td>40</td>
<td>160</td>
<td>160</td>
<td>1280</td>
</tr>
<tr>
<td>A/Bangkok/1/79</td>
<td>320</td>
<td>80</td>
<td>320</td>
<td>320</td>
<td>1280</td>
</tr>
<tr>
<td>A/Philippines/2/82</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>A/ Mississippi/1/85</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>40</td>
<td>160</td>
</tr>
<tr>
<td>A/Leningrad/360/86</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>80</td>
</tr>
</tbody>
</table>

Levine, 1992
Pease, 1987

Classical Epidemic

Evolutionary Epidemic

Annual epidemics and selection
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 \( \sum S_i(0) = 1 \)  \( \sum I_i(0) \ll 1 \)
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 \( \phi = \frac{S_n(\infty)}{S_n(0)} \)

\[
R_e = \frac{\beta}{\nu} \sum \sigma_i \tau_i S_i(0)
\]

If \( R_e > 1 \) then \( 0 < \phi < 1 \) solves
\[
0 = \log \phi + \frac{\beta}{\nu} \sum \sigma_i S_i(0)(1 - \phi^{\tau_i})
\]
and \( \phi^{\tau_i} = S_i(\infty)/S_i(0) \)

If \( R_e < 1 \)

No epidemic \( \phi = 1 \)
Year-to-year dynamics (onset → onset)

\[
F : \left( \begin{array}{c}
S_1 \\
S_2 \\
\vdots \\
S_{n-1}
\end{array} \right) \mapsto \left( \begin{array}{c}
\sum (1 - \phi^{\tau_i}) S_i \\
\phi^{\tau_1} S_1 \\
\vdots \\
\phi^{\tau_{n-2}} S_{n-2}
\end{array} \right)
\]

\(S_n = 1 - \sum S_i\) is redundant

\(\Gamma = \{ S \mid \sum S_i \leq 1, \ s_i \geq 0 \}\) \(F : \Gamma \to \Gamma\)

Cases \(n = 2, 3\), \(\tau_i = 1\),
i.e. infectivity reduction only; \(\Rightarrow \phi\)-eqn simplifies
\[
0 = \log \phi + q(1 - \phi) \quad q = R_0 \sum \sigma_i S_i(0)
\]
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 \textbf{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 \( \phi \) prob of not being infected
Dynamics of size-dependent drift

Boniet al ms
Invasion and persistence of drifting virus

\[ \lambda \text{ against } r \text{ for } \kappa = 0.9999 \]

Persistence

One epidemic only

Boni et al ms
Virus selection in annual epidemics

• In haploids competition ≈ selection
• Assume two virus types $I$ and $Y$
• Epidemics within a season

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

• Only the viral type with the highest $R_0$ will produce an epidemic

Saunders, 1981