Disease Dynamics through Coupling of Strain Evolution and Immune Response

Stefan Wieland, Instituto Gulbenkian de Ciência, Oeiras, Portugal
SIR Model

\[
\begin{align*}
\frac{ds}{dt} &= -\beta i s \\
\frac{di}{dt} &= \beta s i - \gamma i \\
s + i + r &= 1
\end{align*}
\]

SIS Model

\[
\begin{align*}
\frac{di}{dt} &= \beta(1-i)i - ri \\
s + i &= \backslash
\end{align*}
\]

epidemic threshold at

\[R_0 := \frac{\beta}{\gamma} = 1\]
strain-based models capture

- competition of fixed number of multiple strains
- strain evolution through allowing for variable number of strains via mutation
- intra- and interseason epidemic dynamics

we want to

- model strain mutation and immune response (at within-host level)
- strain circulation and heterogeneity of immune response (at population level)
- couple all that to have a proper flu model
I. Basic Model

II. Refining Interaction of Virus and Immune Response

III. Heterogeneity in Immune Response
Basic SIRS Model

- immunity based on infection history->regain Markov property by introducing strain-specific infection classes
- host's immune response updated by currently hosted strain
- epitope of infecting strain mutates with rate $\mu$, replaces original strain immediately during infection

\[
\frac{d s}{dt} = -\beta s \sum_{m=1}^{M} i_m
\]

\[
\frac{d i_1}{dt} = \beta i_1 s - \gamma i_1 - \mu i_1
\]

\[
\vdots
\]

\[
\frac{d i_k}{dt} = \beta i_k \left( s + \sum_{m=1}^{k-1} r_m \right) - \gamma i_k + \mu (i_{k+1} - i_k)
\]

\[
\vdots
\]

\[
\frac{d i_M}{dt} = \beta i_N \left( s + \sum_{m=1}^{M-1} r_m \right) - \gamma i_N + \mu i_{M-1}
\]

\[
\frac{d r_1}{dt} = \gamma i_1 - \beta r_1 \sum_{m=2}^{M} i_m
\]

\[
\vdots
\]

\[
\frac{d r_k}{dt} = \gamma i_k - \beta r_k \sum_{m=k+1}^{M} i_m
\]

\[
\vdots
\]

\[
\frac{d r_M}{dt} = \gamma i_k
\]
3 typical behaviours
- onset of oscillations for $\mu>0$
- steady state from $\mu \sim \beta, \gamma$ on (limiting case $\mu \gg \beta, \gamma$ of SIS dynamics with $i \rightarrow 1 - 1/\mathcal{R}_0$)
- stochastic extinction for $\mu \ll \beta, \gamma$

phase shift $\rho(\gamma)$ between strain density and prevalence in oscillatory regime

$N=10^6$ individuals, $I_0=100$ initially infected, $\beta=0.02, \gamma=0.01$
II. Refining Interaction of Virus and Immune Response

cross-immunity of virus through several epitopes

- mutations occur with $\mu$ at random epitope
- immune response only evaded if strain has accumulated mutations on all $e$ epitopes

$N=10^6$ individuals, $I_0=100$ initially infected, $\beta=1, \gamma=0.01, \mu=0.001$
cross-immunity of virus through several epitopes

- the larger $e$, the lower number of strains in equilibrium -> the higher $\mu$ has to be to evade immunity

- still triggering oscillations at $m \sim p, r$

- higher epitope numbers $e$ have same effect on mean prevalence as decreased $\mu$

- multidimensionality in $e$ nontrivial, cannot be offset by changing $\mu$
III. Heterogeneity in Immune Response

**young (unprimed) children have**
- no immune memory (quick infection)
- antibody repertoire to just one virus epitope (sole producers of mutants, mutated on respective repertoire epitope)

⇒ coupling SIS dynamics ($U$ kids) with SIRS dynamics ($N$-$U$ adults), mutations just in kids

For $\mu=0$:
- steady-state prevalence lowered to

$$i \rightarrow \frac{U}{N} - \frac{N}{U R_0} < 1 - \frac{1}{R_0} \quad \forall \quad 0 < \frac{U}{N}, R_0 < 1$$

for all effective $R_0' = R_0 U/N \geq 1$
- epidemic threshold increases by $N/U$
For $\mu > 0$:

- small $U/N \Rightarrow$ smaller $\langle i \rangle_t$, than in $U=0$ case (counter-intuitive)
- larger $U/N \Rightarrow$ larger $\langle i \rangle_t$, (significantly weaker overall immune response in population, converging to pure SIS dynamics for $U/N=1$)

$N=10^6$ individuals, $I_0=100$ initially infected, $\beta=1, \gamma=0.01, \mu=0.001, e=1$
Outlook

- mean-field model featuring population's immune response and viruses genetic drift

*flu-specific aspects*

- quantifying $\mu$
- implementing more realistic immune response
- reproducing “cluster jumps”
- predicting next season's dominant strain