FUNDAÇÃO CALOUSTE GULBENKIAN

CFTC Centro de Física Teórica e Computacional

Disease Dynamics through Coupling of Strain Evolution and Immune Response

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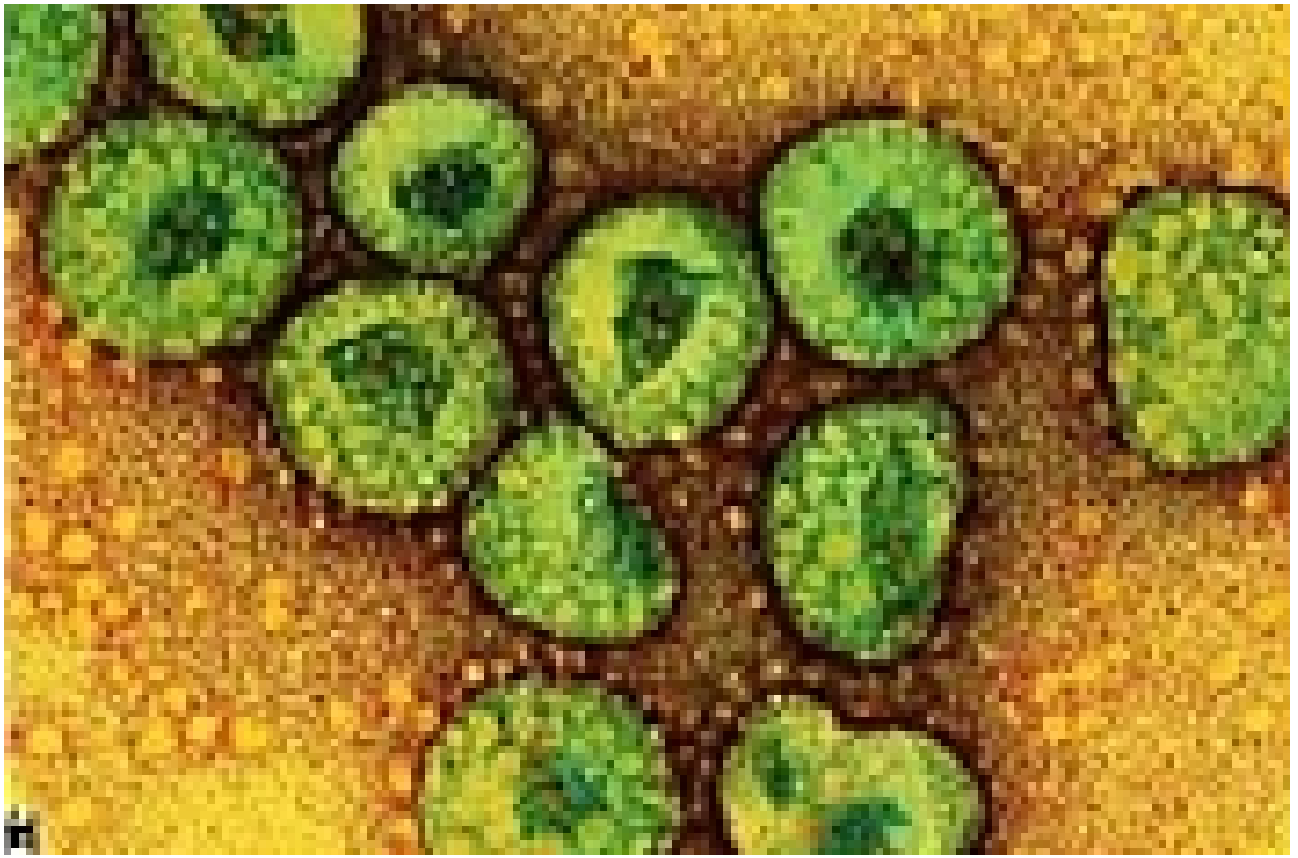
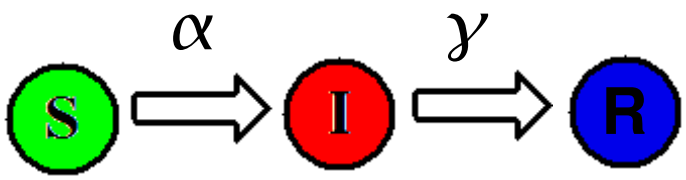


SARS coronavirus, Department Of Public Health, Massachusetts

SIR Model

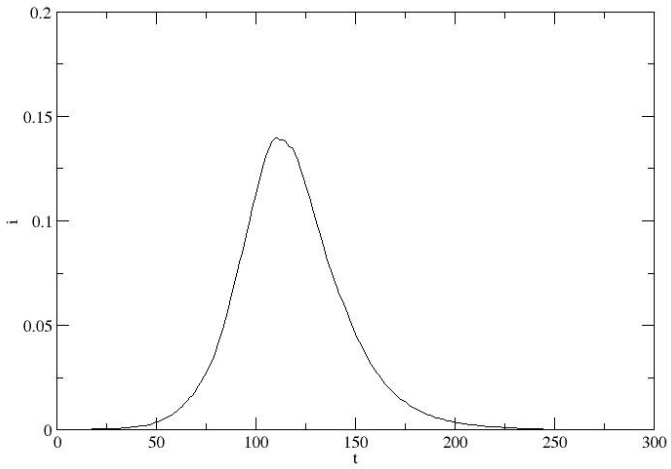


$$\alpha = \beta i$$

$$\frac{ds}{dt} = -\beta i s$$

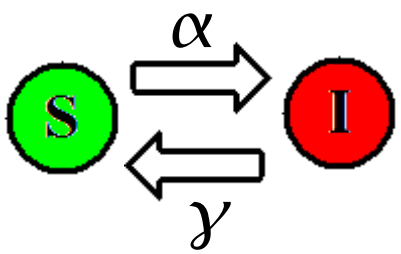
$$\frac{di}{dt} = \beta s i - \gamma i$$

$$s + i + r = 1$$



β=0.02,γ=0.01

SIS Model

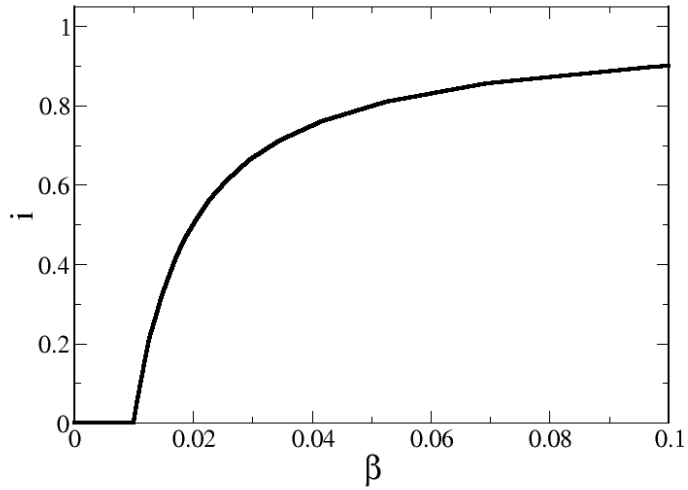


$$\frac{di}{dt} = \beta(1-i)i - ri$$

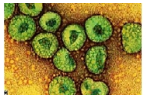
$$s + i = 1$$

epidemic threshold at

$$R_0 := \frac{\beta}{\gamma} = 1$$



γ=0.01

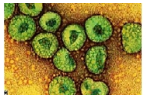


strain-based models capture

- 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

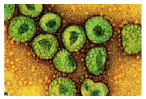
- model strain mutation and immune response (at *within-host level*)
- strain circulation and heterogeneity of immune response (at *population level*)
- couple all that to have a proper flu model



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 μ , replaces original strain immediately during infection

$$\frac{ds}{dt} = -\beta s \sum_{m=1}^{M} i_m$$

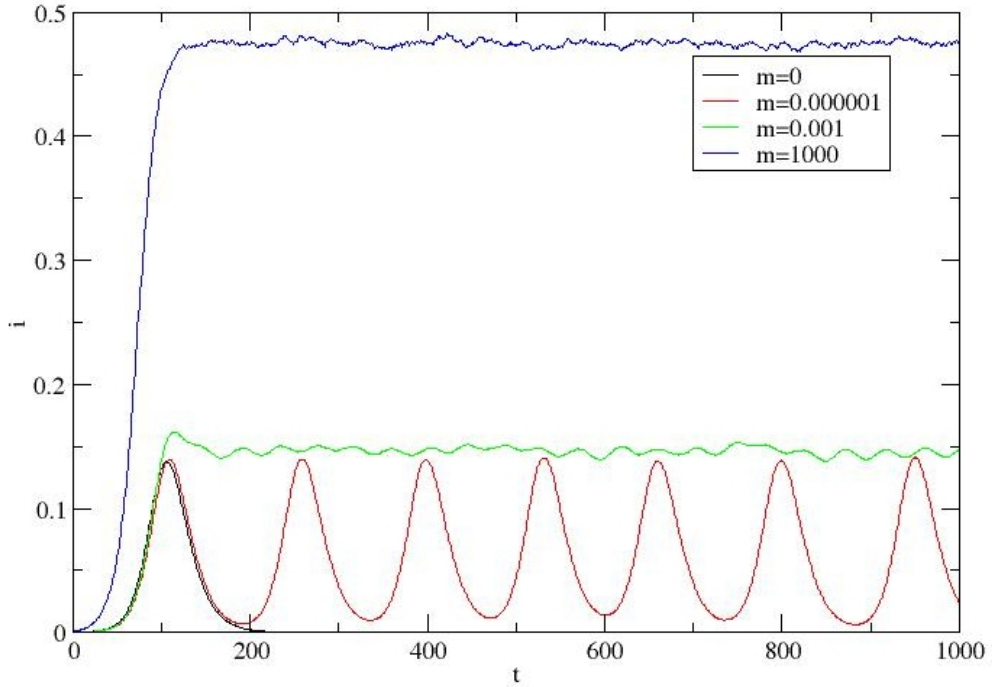
$$\frac{di_1}{dt} = \beta i_1 s - \gamma i_1 - \mu i_1 \qquad \frac{dr_1}{dt} = \gamma i_1 - \beta r_1 \sum_{m=2}^{M} i_m$$

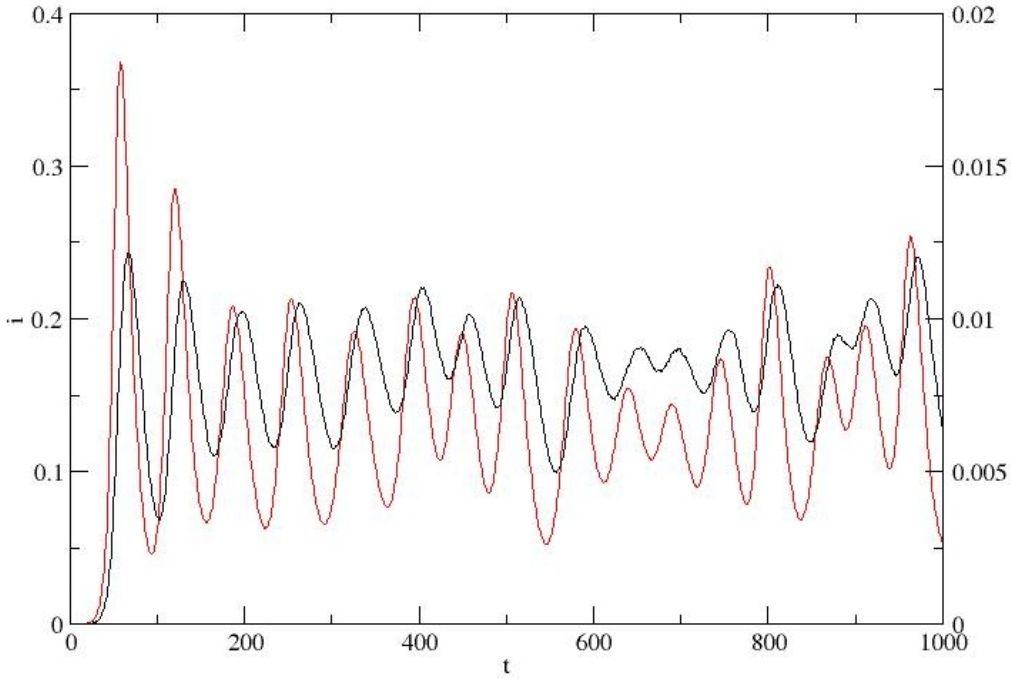
$$\vdots \qquad\qquad \vdots$$

$$\frac{di_k}{dt} = \beta i_k \left(s + \sum_{m=1}^{k-1} r_m \right) - \gamma i_k + \mu \left(i_{k+1} - i_k \right) \qquad \frac{dr_k}{dt} = \gamma i_k - \beta r_k \sum_{m=k+1}^{M} i_m$$

$$\vdots \qquad\qquad \vdots$$

$$\frac{di_M}{dt} = \beta i_N \left(s + \sum_{m=1}^{M-1} r_m \right) - \gamma i_N + \mu i_{M-1} \qquad \frac{dr_M}{dt} = \gamma i_k$$



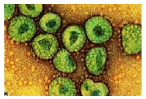


N=10⁶ individuals, I_0=100 initially infected, β=0.02,γ=0.01

3 typical behaviours

- onset of oscillations for $\mu>0$
- steady state from $\mu\sim\beta,\gamma$ on (limiting case $\mu>>\beta,\gamma$ of SIS dynamics with $i \rightarrow 1 - 1/R_0$)
- stochastic extinction for $\mu<<\beta,\gamma$

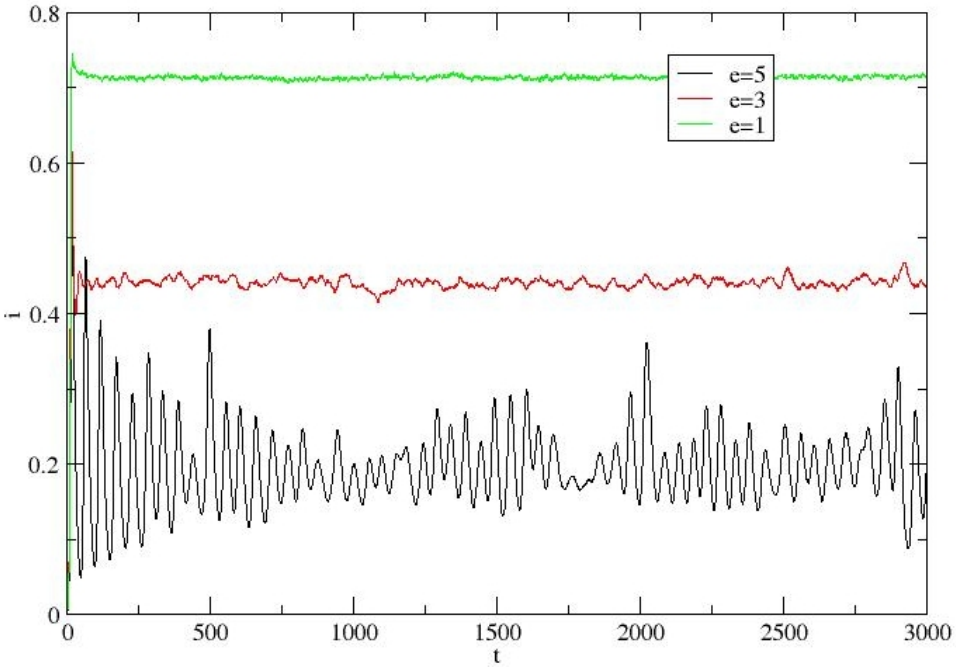
phase shift ρ(γ) between strain density and prevalence in oscillatory regime



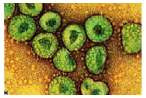
II. Refining Interaction of Virus and Immune Response

cross-immunity of virus through several epitopes

– mutations occur with μ at random epitope
– immune response only evaded if strain has accumulated mutations on *all e* epitopes



N=10⁶ individuals, I_0=100 initially infected,β=1,γ=0.01,μ=0.001



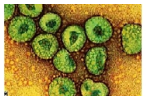
cross-immunity of virus through several epitopes

– the larger *e,* the lower number of strains in equilibrium-> the higher μ 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 μ

- multidimensionality in *e* nontrivial, cannot be offset by changing μ



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)

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

For $\mu=0$:

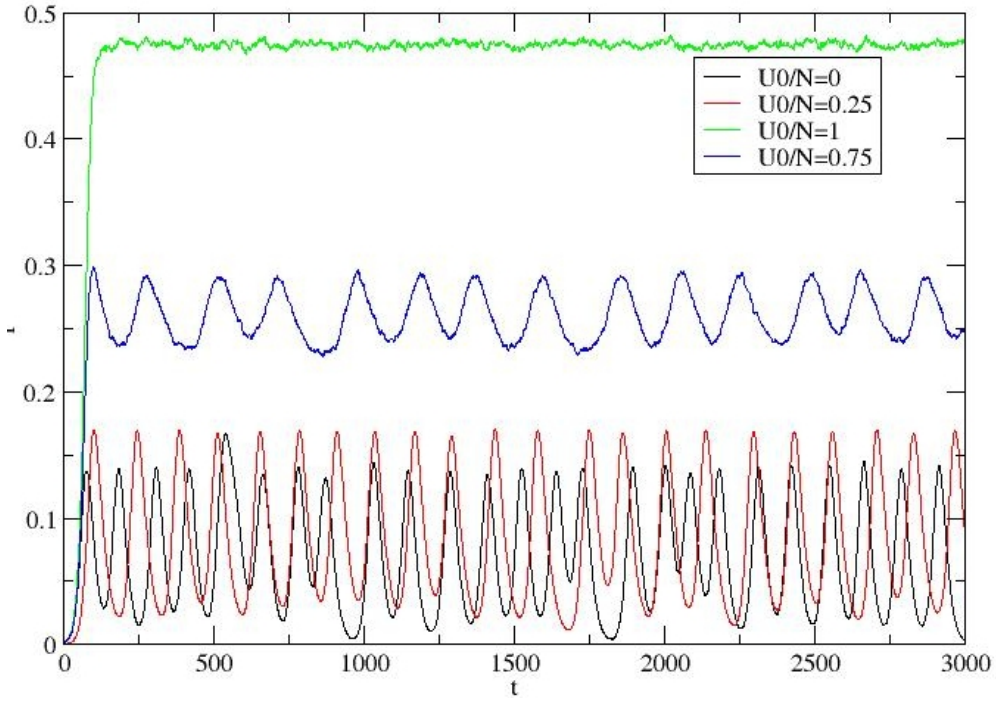
–steady-state prevalence lowered to

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

for all effective $R_0' = R_0 U/N \geq 1$

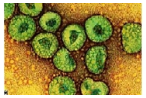
– epidemic threshold increases by *N/U*

For $\mu>0$:



N=10^6 individuals, I_0=100 initially infected,β=1,γ=0.01,μ=0.001, e=1

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



Outlook

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

flu-specific aspects

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