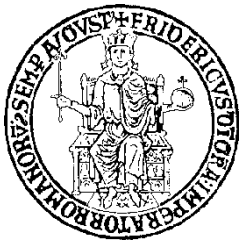


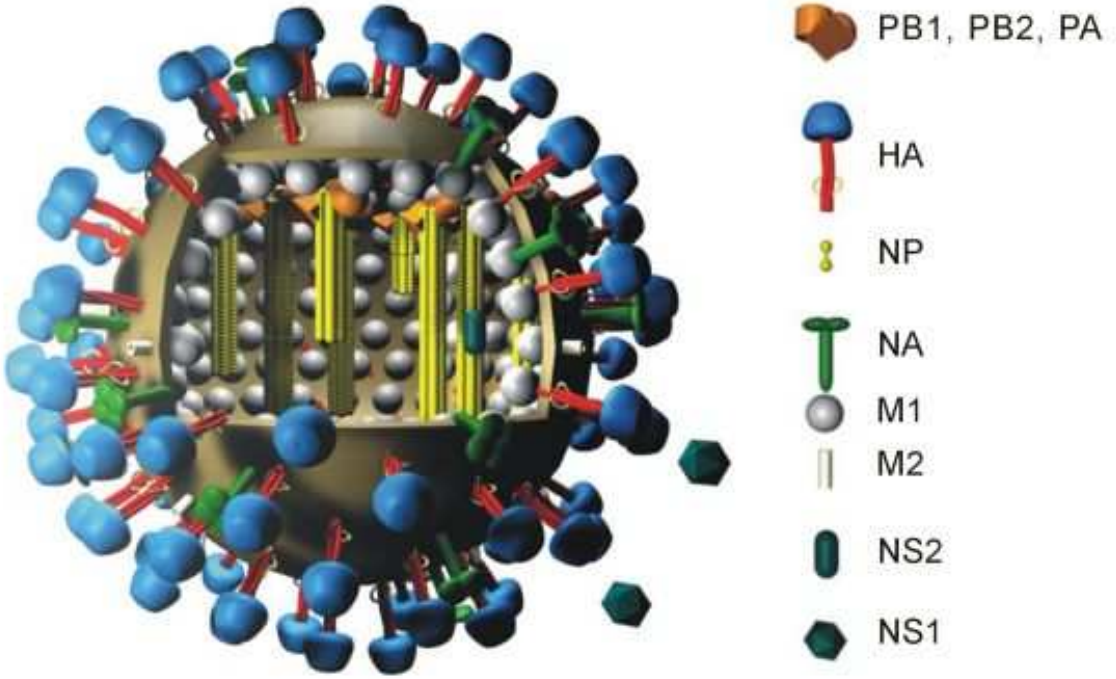
The puzzle of the evolutionary dynamics of influenza

Luca Peliti

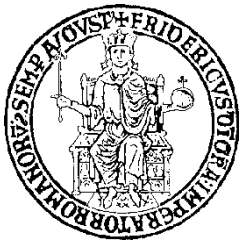
Dipartimento di Scienze Fisiche, Unità CNISM and Sezione INFN

Università “Federico II”, Napoli (Italy)

The virus of influenza

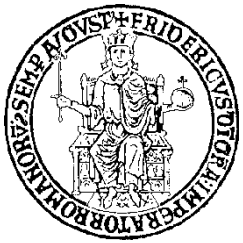


The virus of the flu evolves so fast that it can reinfect the same individual several times even from one year to the next



Basic facts

- There are three fundamental groups of flu viruses: A, B et C



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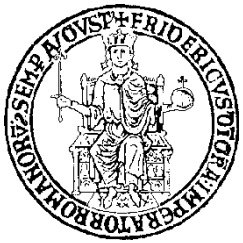

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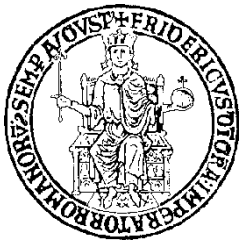

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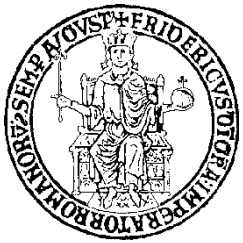
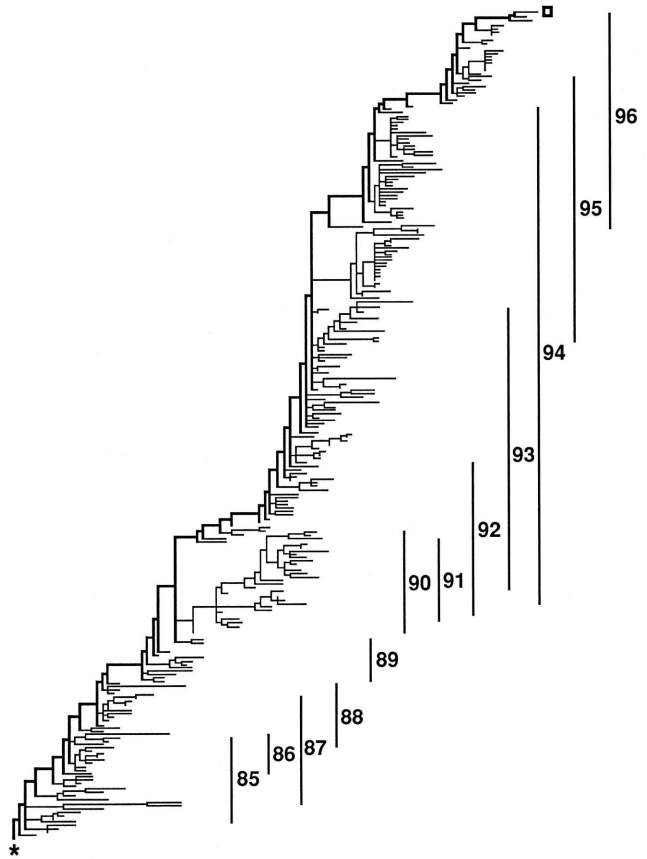
- Today's dominant subtype is H3N2, but subtype H1N1 (which had disappeared at the beginning of the '60s) is also present (maybe due to a laboratory accident)

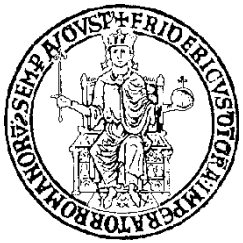


The phylogenetic tree for HA

Flu: type A, subtype H3N2, gene HA1

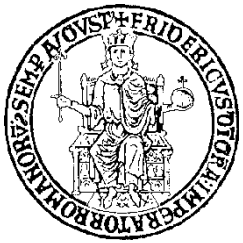
Fitch, Bush, Bender and Cox, 1997





Properties of the tree

- The tree exhibits a well-defined backbone: branches have a median lifetime of 1.45 years



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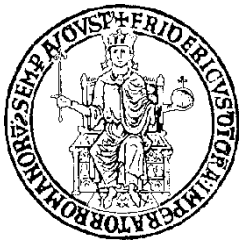

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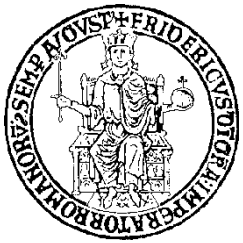

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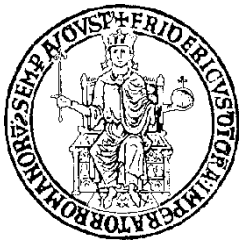
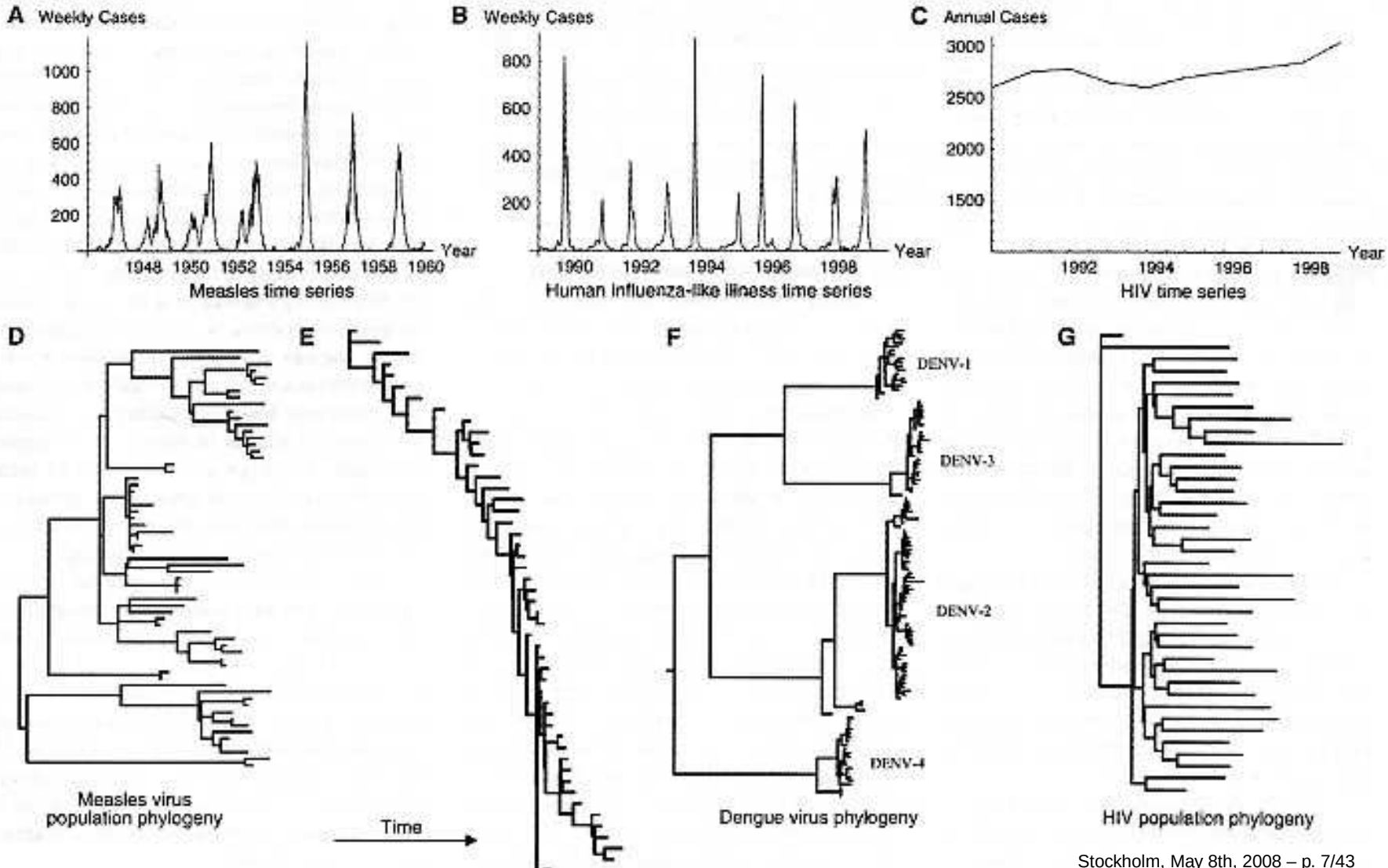
- The tree does not branch out over long times

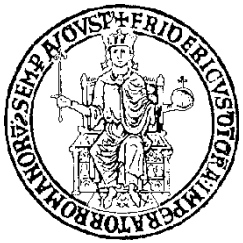


The puzzle

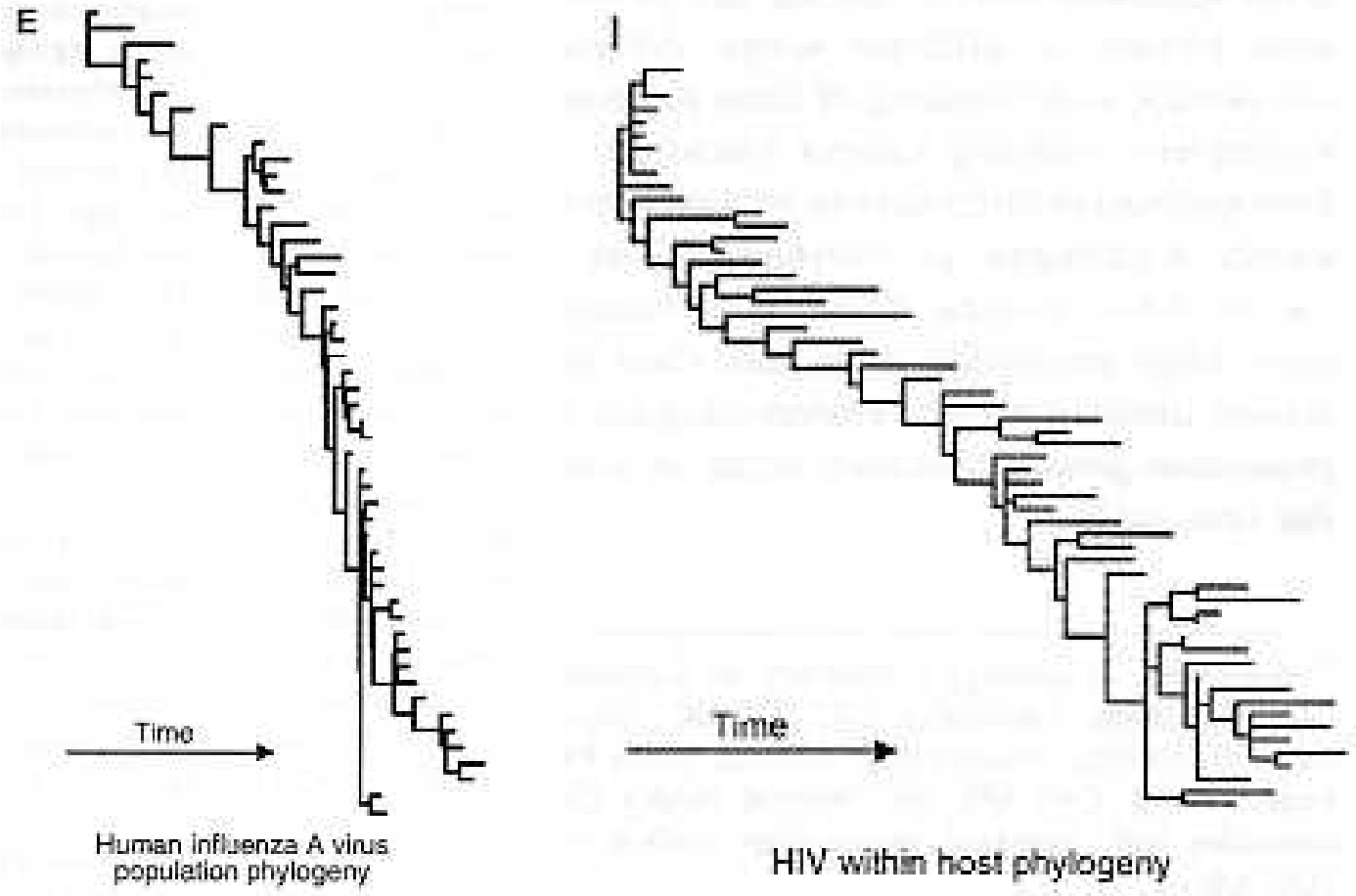
Why does the dominant strain change fast, but the virus does not diversify?

Epidemiology and evolutionary dynamics

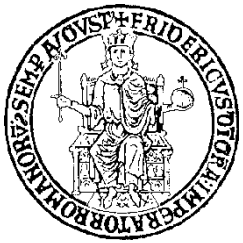




Flu vs. in-host HIV evolution

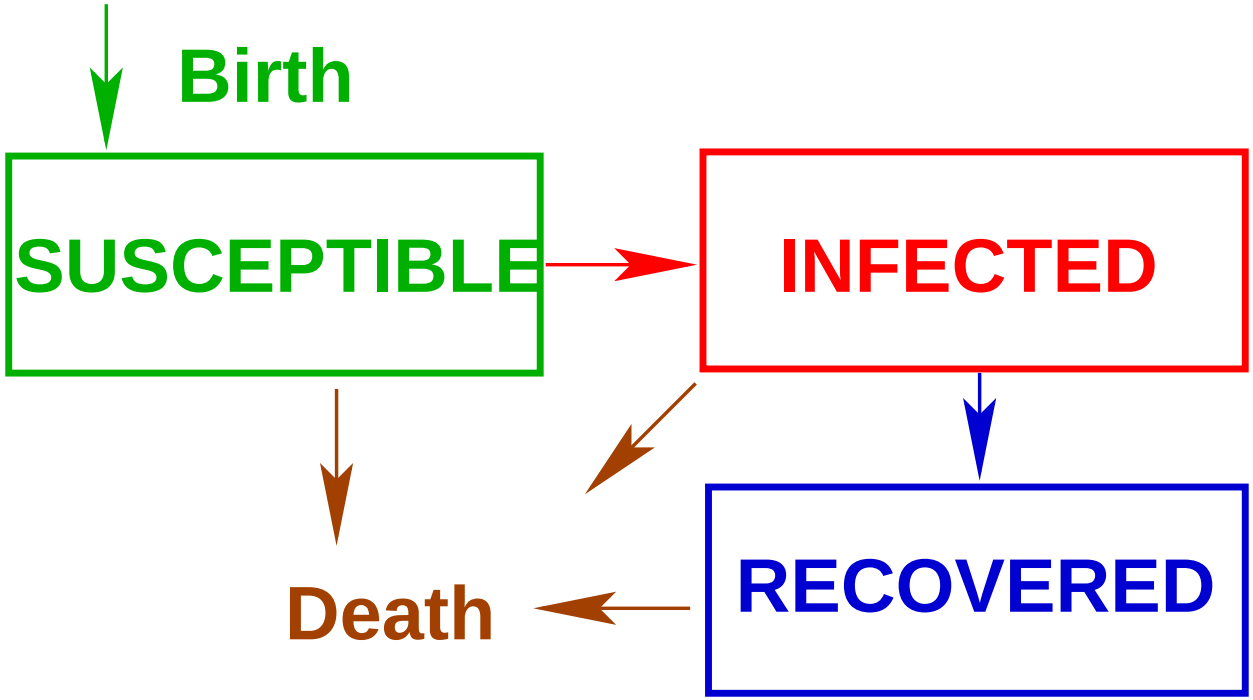


Grenfell et al., 2004

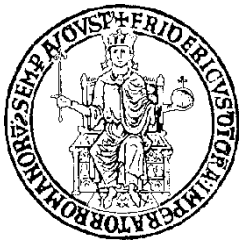


The classic SIR model: Definition

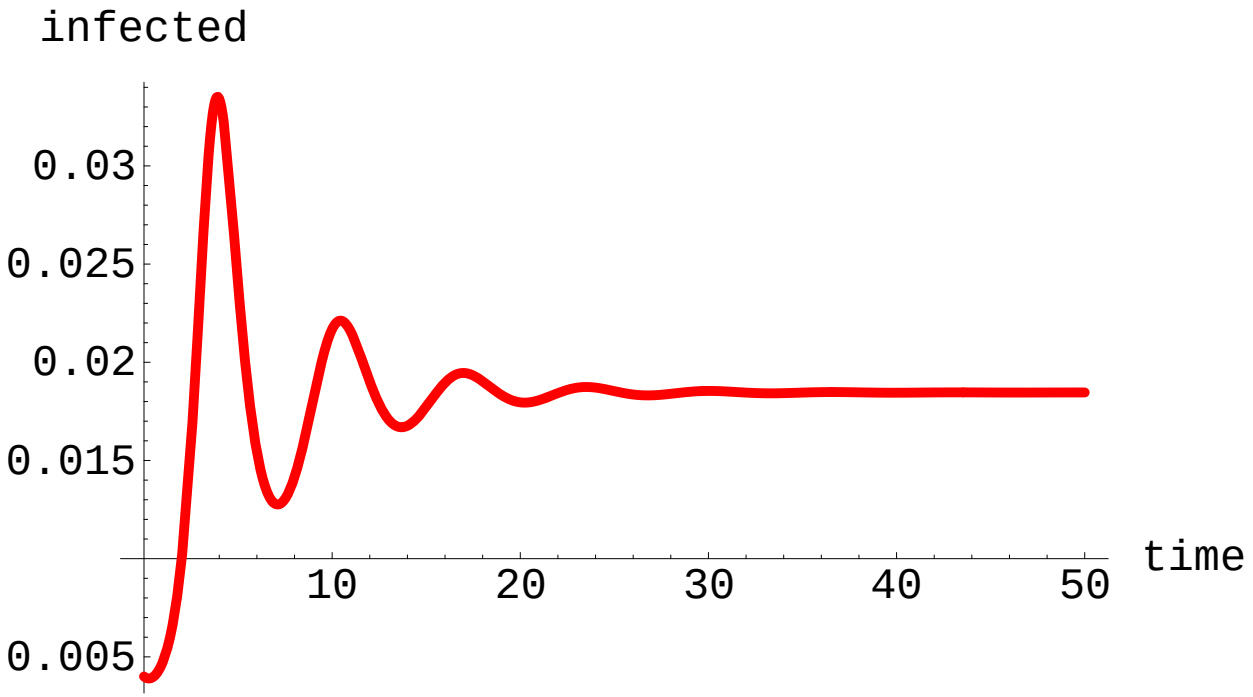
Kermack and McKendrick, 1927



$$\frac{\mathrm{d}S}{\mathrm{d}t} = N\lambda - \frac{\gamma}{N}SI - \lambda S \qquad \frac{\mathrm{d}I}{\mathrm{d}t} = \frac{\gamma}{N}SI - (\rho + \lambda)I$$

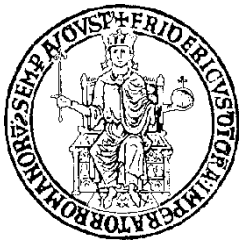


The classic SIR model: Behavior



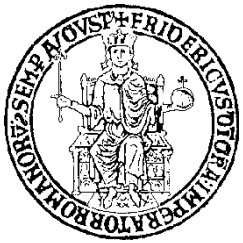
$$S^* = N\,\frac{\rho+\lambda}{\gamma} \qquad I^* = \frac{\lambda}{\rho+\lambda}(N-S^*) \qquad \tau \simeq 2\pi\sqrt{\frac{\rho}{\lambda\gamma}} = 2\pi/\sqrt{\beta\lambda\rho}$$

$$\beta = \gamma/\rho$$



Coexisting strains: Modified SIR model

- Viral strain defined by k



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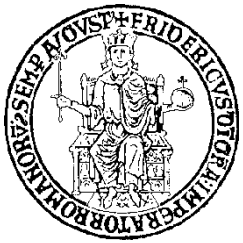

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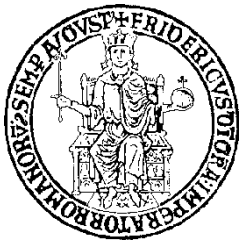

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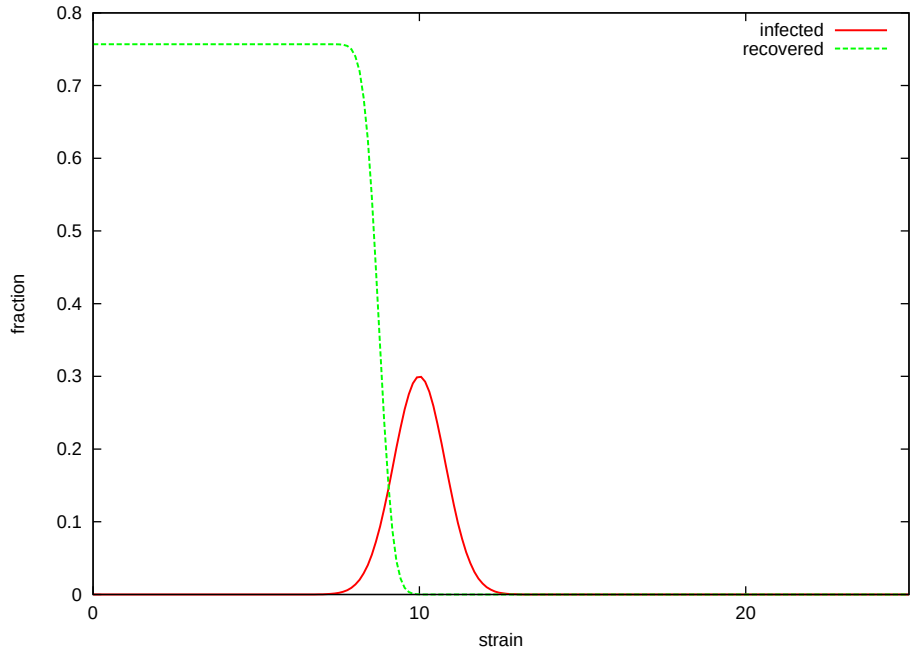
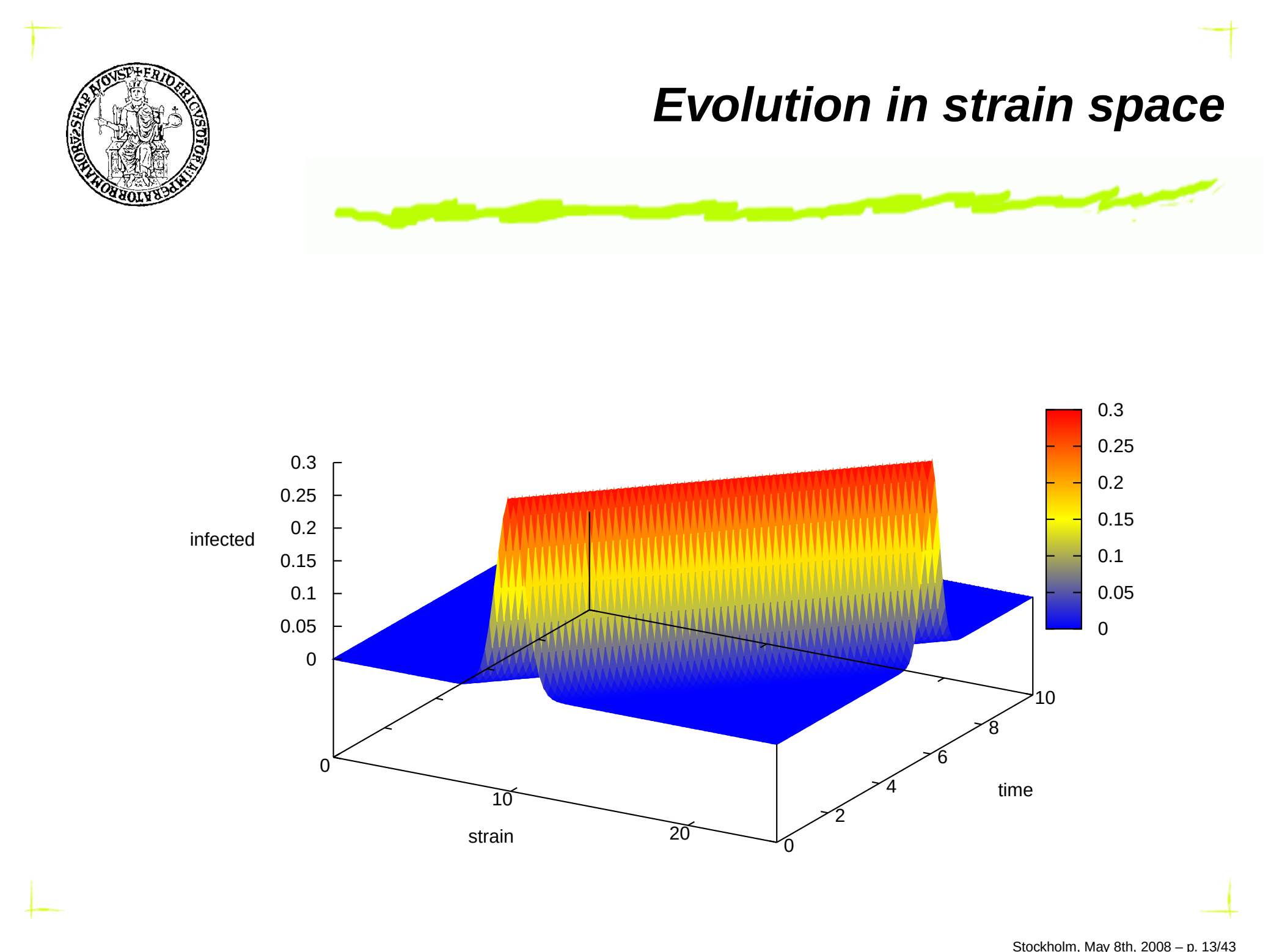
- **Cross-immunization:** With probability $K_{kk'}$ an individual with antibodies against strain k is also immune against strain k

One-dimensional strain space: A travelling wave

Andreasen, Lin and Levin, 1997

Mutations generate new strains
Cross-immunity is short-ranged in $|k - k'|$
Akin to spatial propagation of epidemics

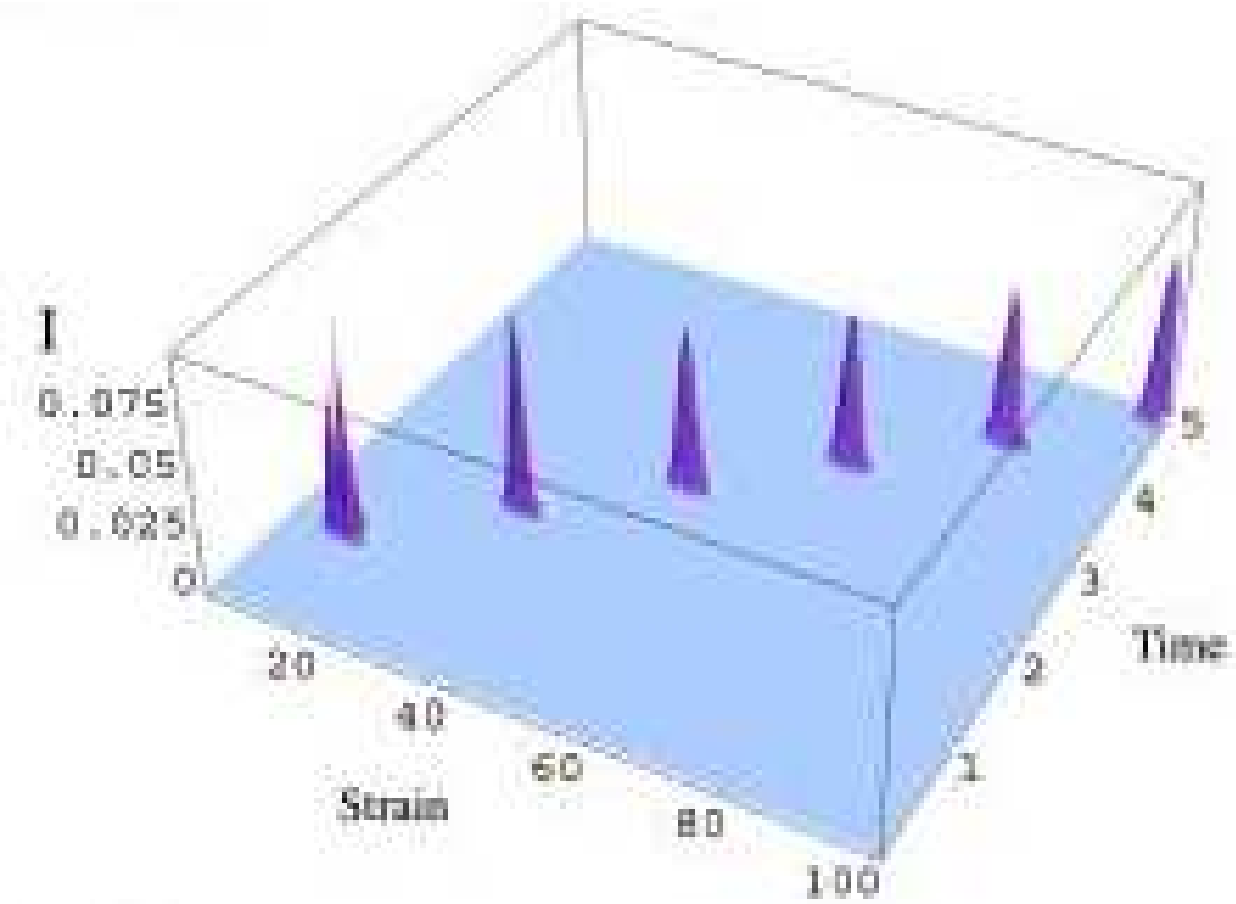




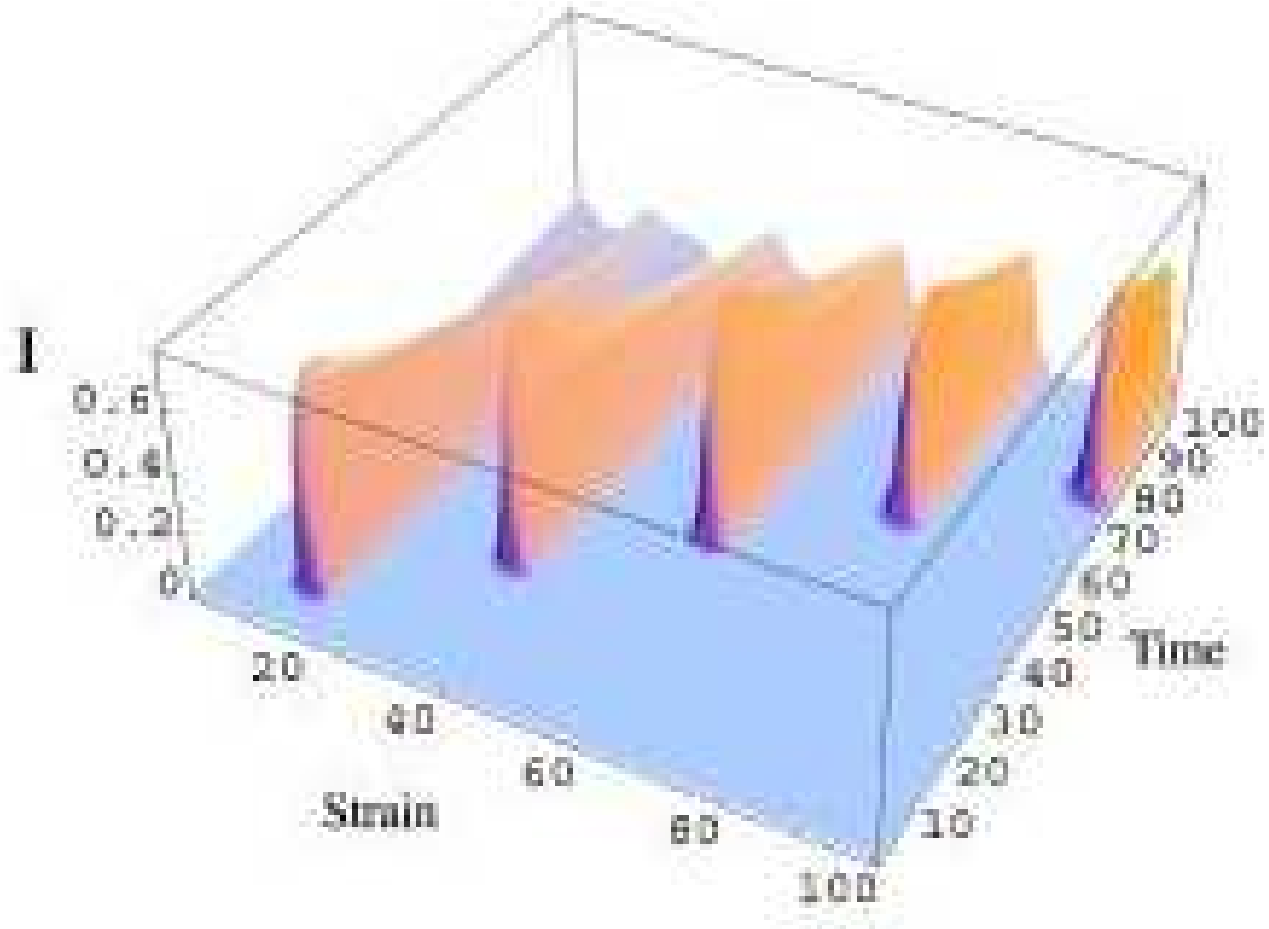
Evolution in strain space

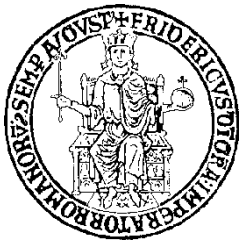
Peak oscillations

Gog and Grenfell, 2002; Lin, Andreasen, Casagrandi and Levin, 2003



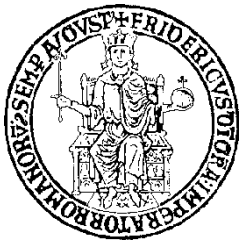
Long-lasting disease (HIV)?





Comments

- The "speed of evolution" $\mathrm{d}k/\mathrm{d}t$ is compatible with the "natural" values of the parameters ρ ($1/$one week), λ ($\sim 1/(50 \div 70$ years), β (probably $\sim 6 \div 10$) and of the observed substitution rate of the viral strains



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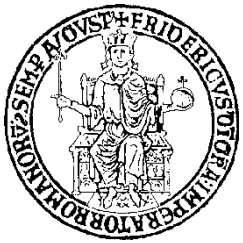

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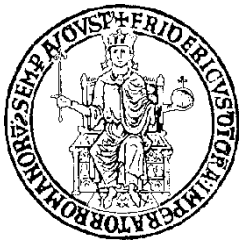
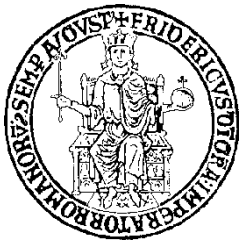
- Need to consider a more general topology of strain space



Many strains

SIR model difficult to generalize:

- Cross-immunization with n strains requires at least 2^n states
- Need to keep past data indefinitely
- Finite population size constraint hard to implement



The bitstring model

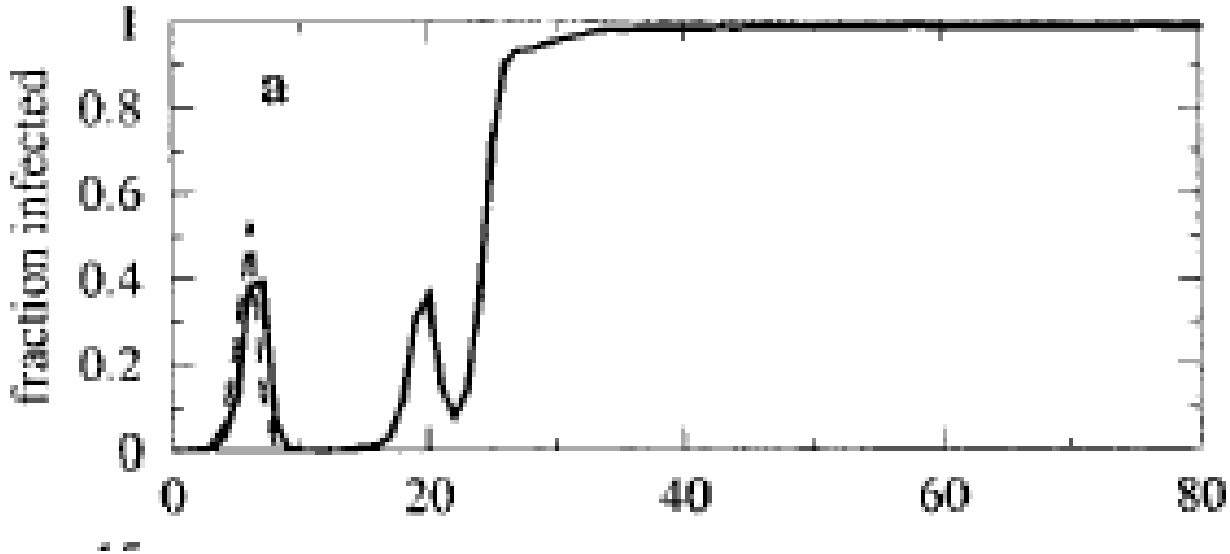
Girvan, Callaway, Newman and Strogatz, 2002

- Viral strain k identified by a Boolean string $(1, 1, 0, \ldots)$
- Cross-immunization effectiveness function of the Hamming distance

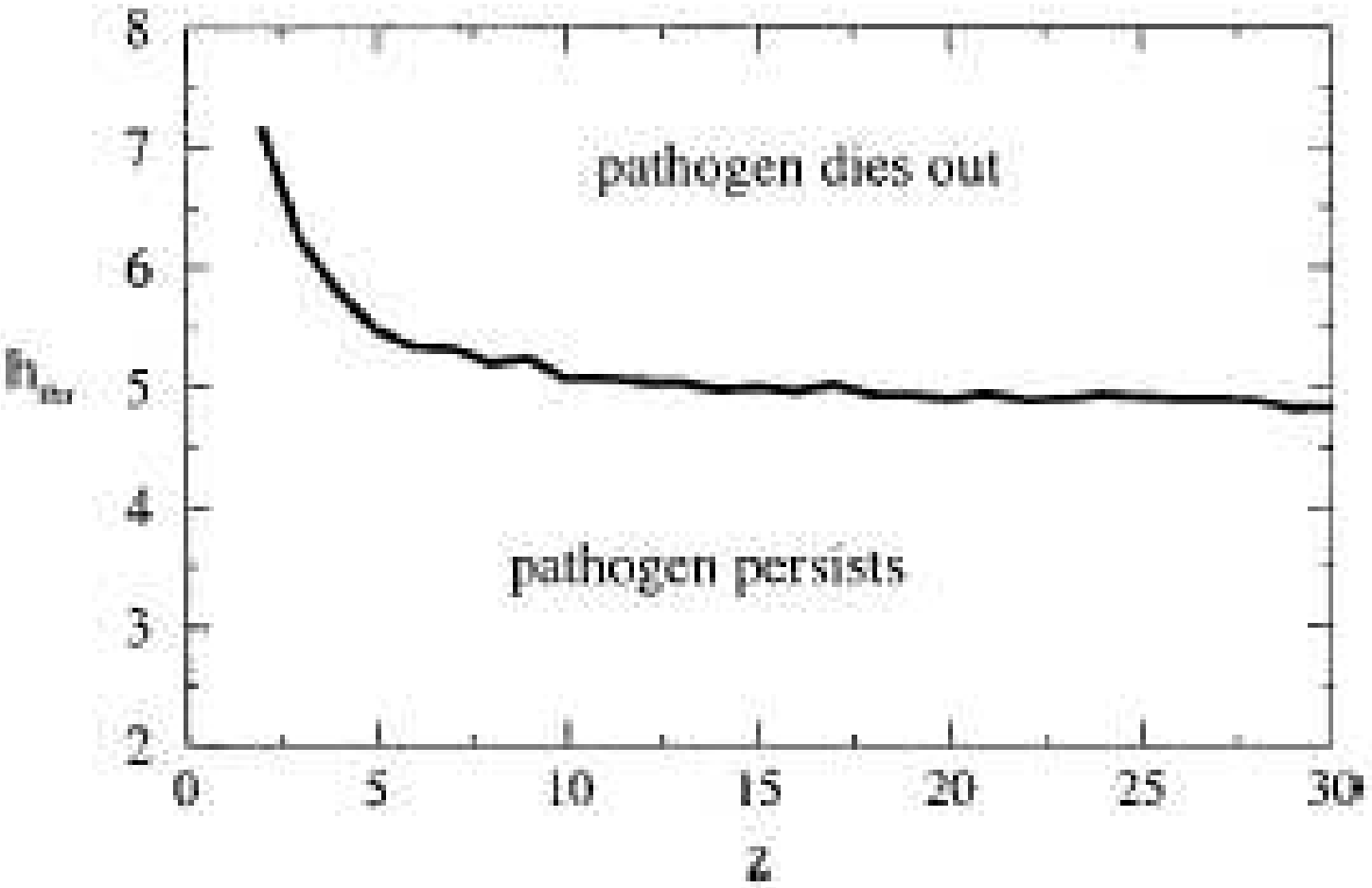
$$d_{\mathrm{H}}(k, k') = \sum_i (k_i - k'_i)^2$$

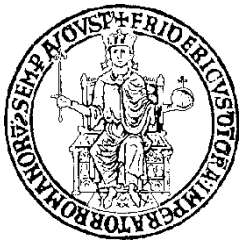
- Analysis via an individual-based model: Specific (life long) immunity embedded in individual infection history $\Sigma_\alpha = \{k^{(1)}, \ldots, k^{(t)}\}$, $\alpha = 1, \ldots, N$

Disease incidence



Phase diagram





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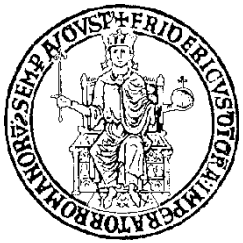

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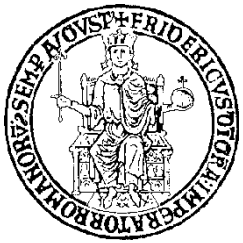

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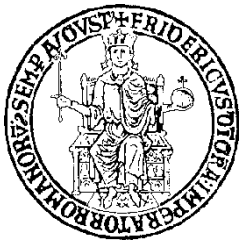

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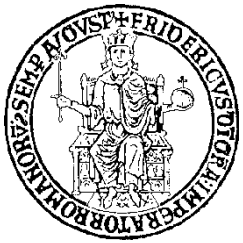
$$\emptyset \xleftarrow{\delta} X \xrightarrow{r} 2X$$



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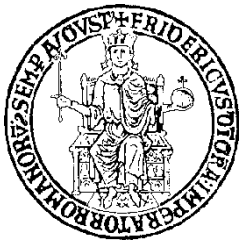
$$\emptyset \xleftarrow{\delta} X \xrightarrow{r} 2X$$

- $\delta \geq r$: Extinction
- $\delta < r$: Boundless proliferation



Short term infinite-range immunity

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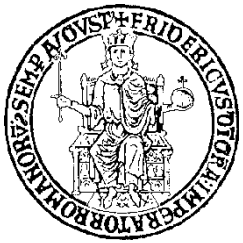

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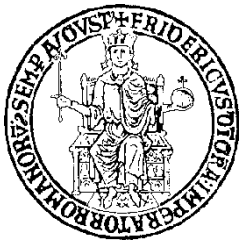
- This conjecture is contained in a very complex model, with geographical distribution, many parameters, etc.



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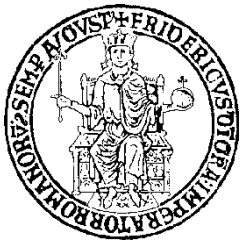
- This conjecture is contained in a very complex model, with geographical distribution, many parameters, etc.
- It has but scanty observational support



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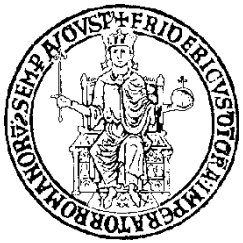
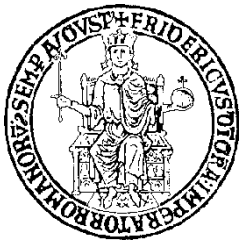
- It has but scanty observational support
- Is it sufficient alone to describe the observed behavior?



Modified bitstring model

Tria, Lässig, Peliti and Franz, 2004

- Individual-based models with bitstring strains
- Short-range persistent cross-immunity
- Short-term *infinite-range* cross-immunity
- Each viral strain k is characterized by its "bare" infectivity β_k, extracted at random



Observables

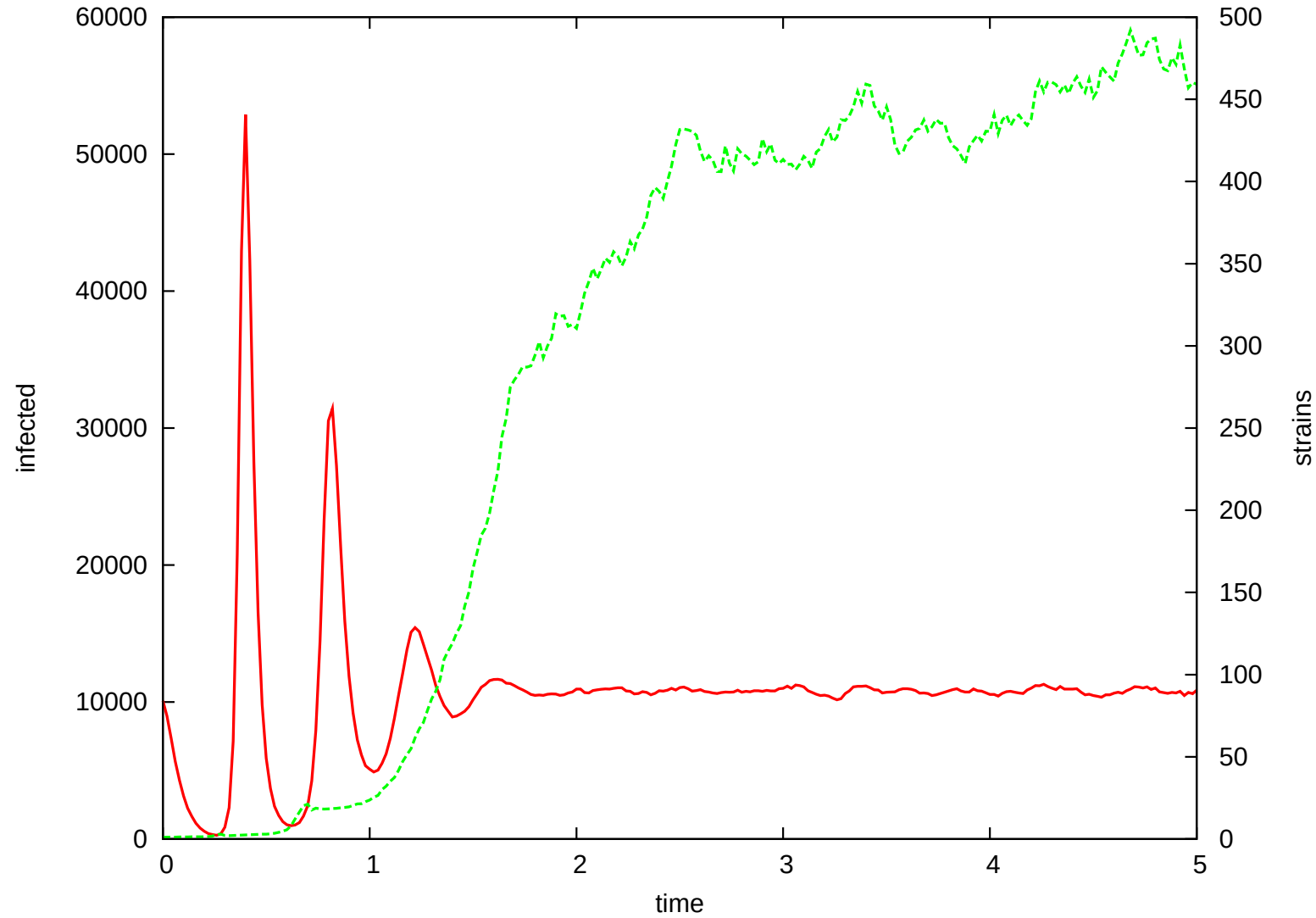
- # individuals infected by strain k: ν_k
- Effective number of strains

$$n = \left(\sum_k \nu_k \right)^2 \Big/ \left(\sum_k \nu_k^2 \right)$$

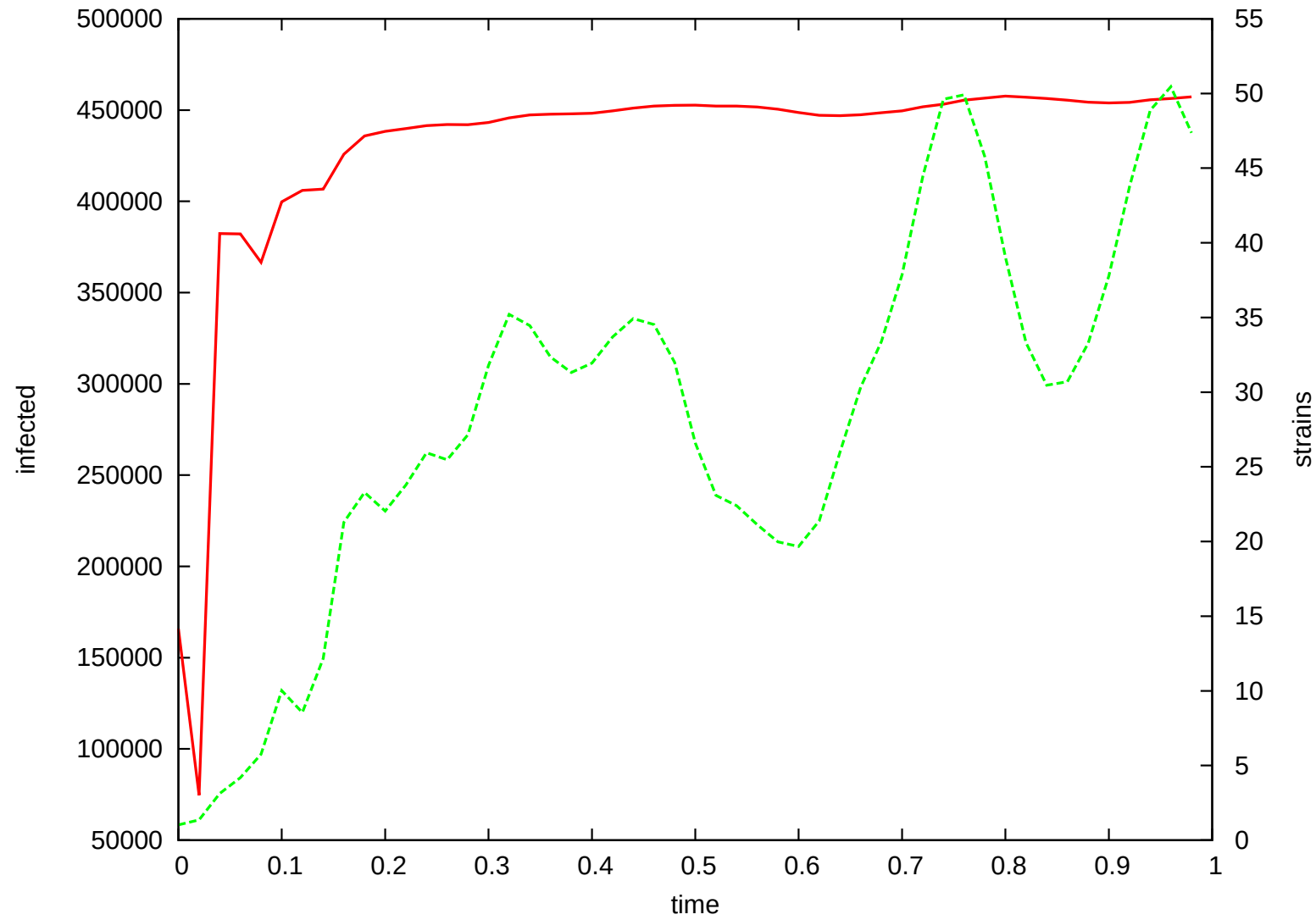
- Incidence of the disease

$$I = \sum_k \nu_k$$

Effects of short immunity: Incidence and # strains

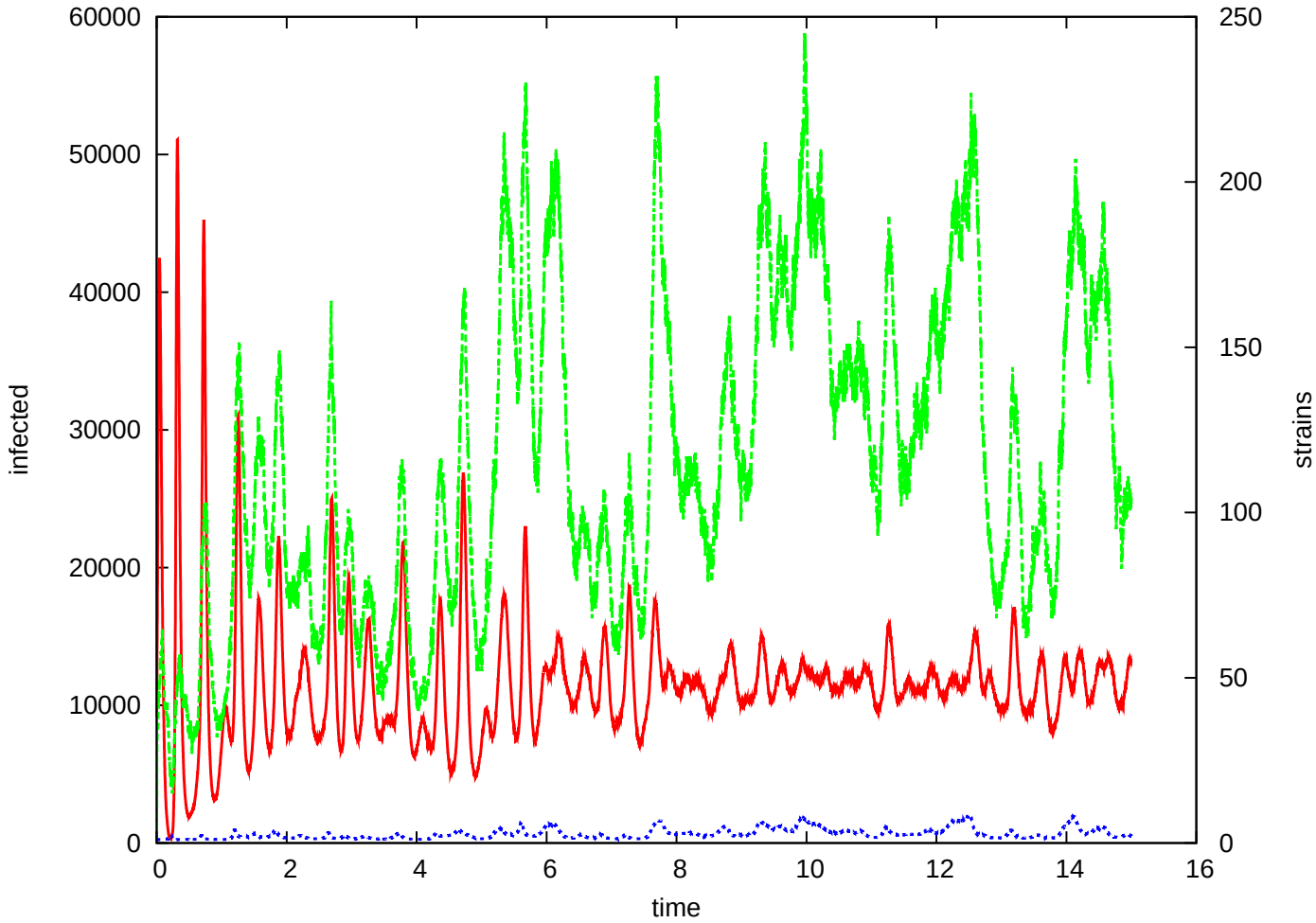


Random infectivity and no short immunity



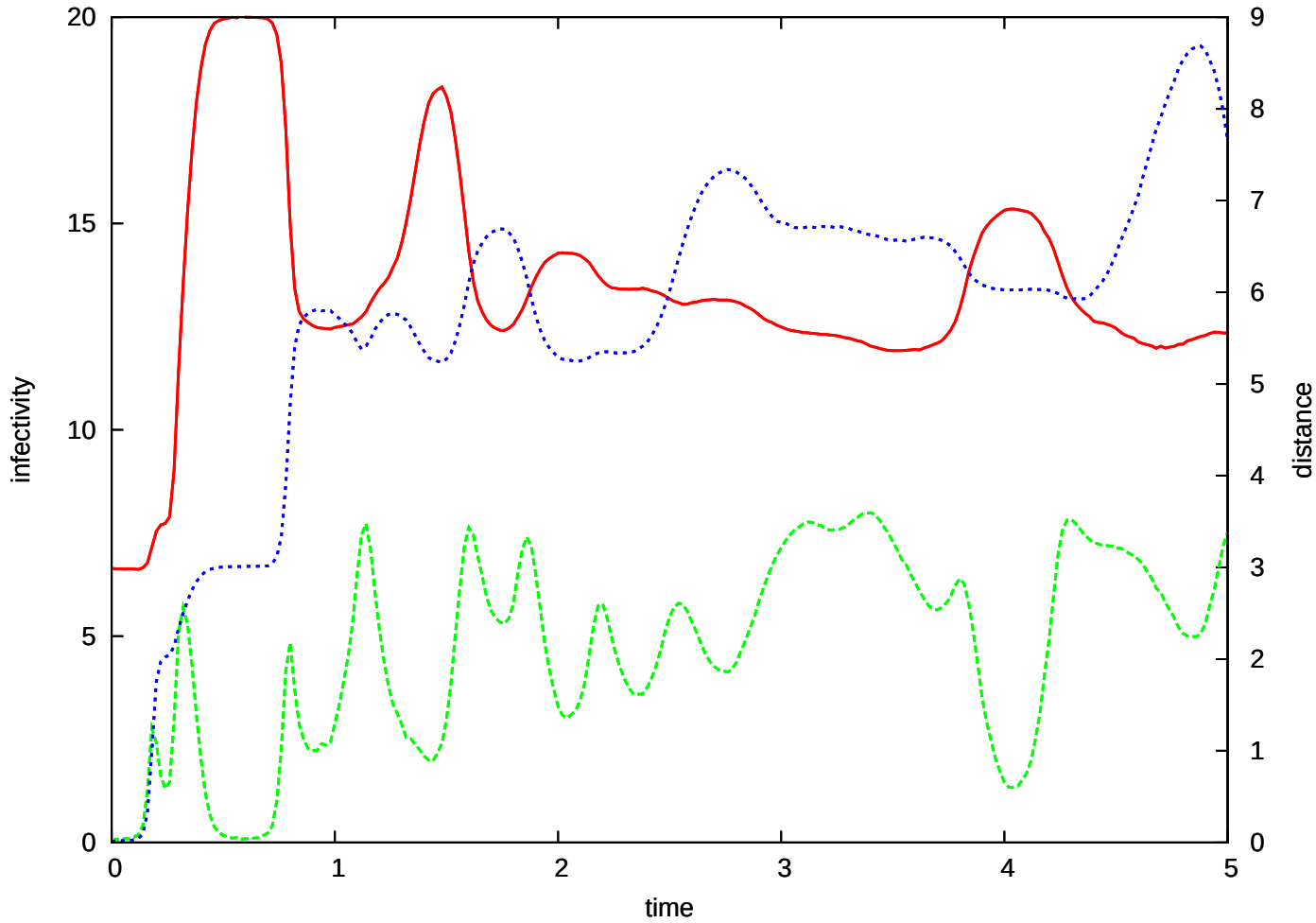
Random infectivity and short immunity

Incidence and strain number

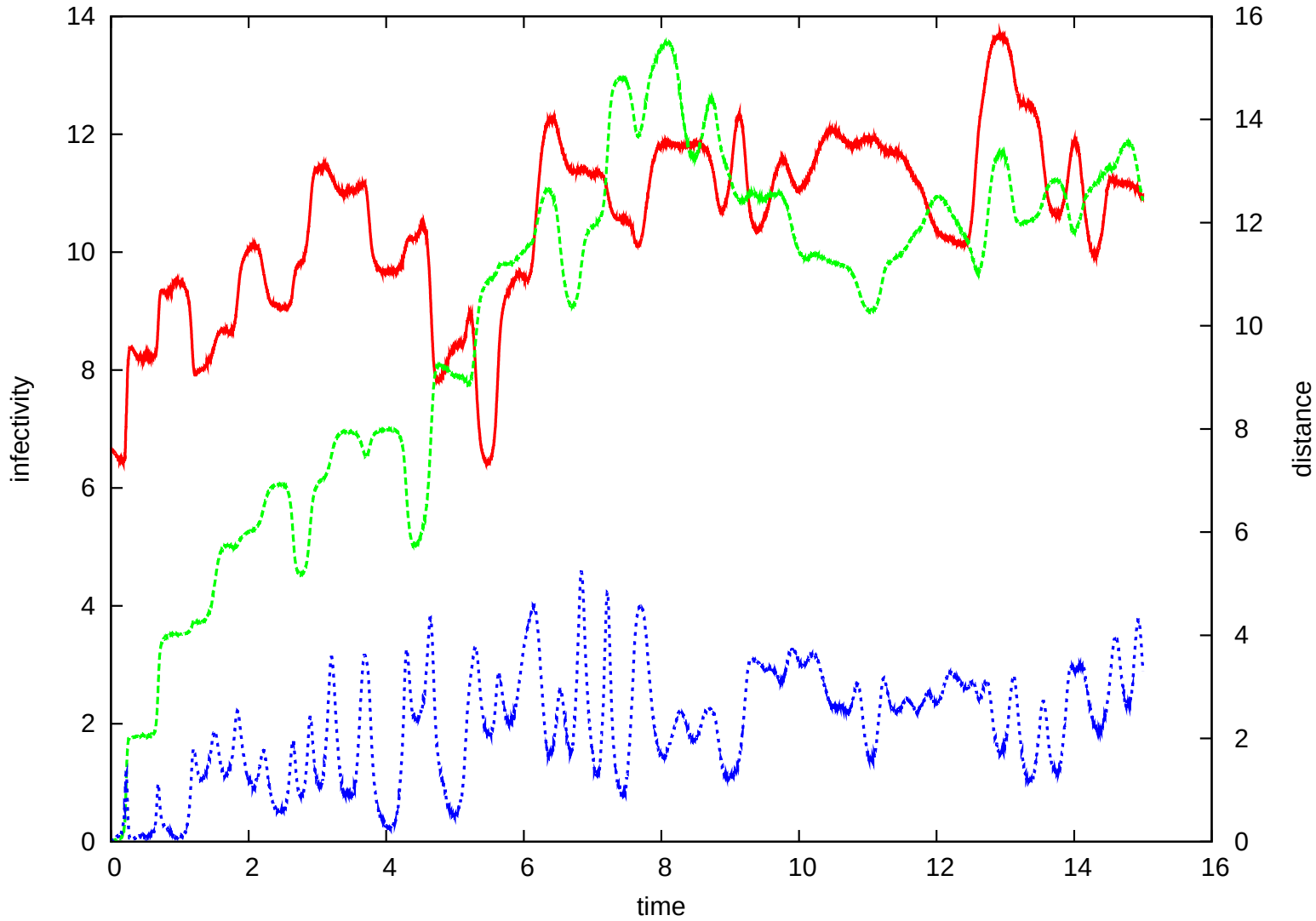


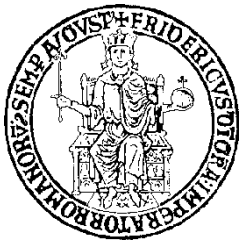
Random infectivity and short immunity

Average infectivity and Hamming distance

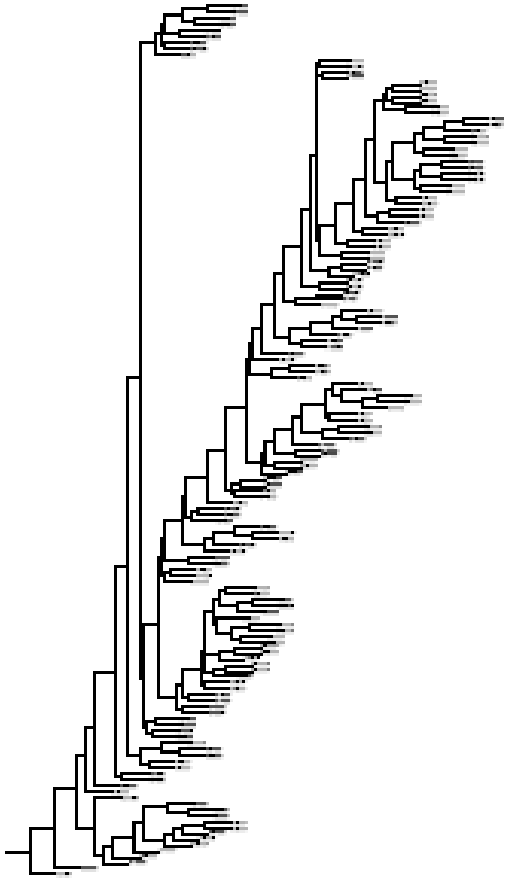


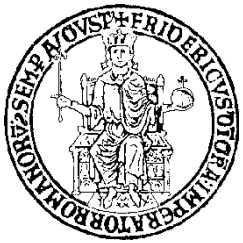
With higher time resolution





Phylogenetic tree



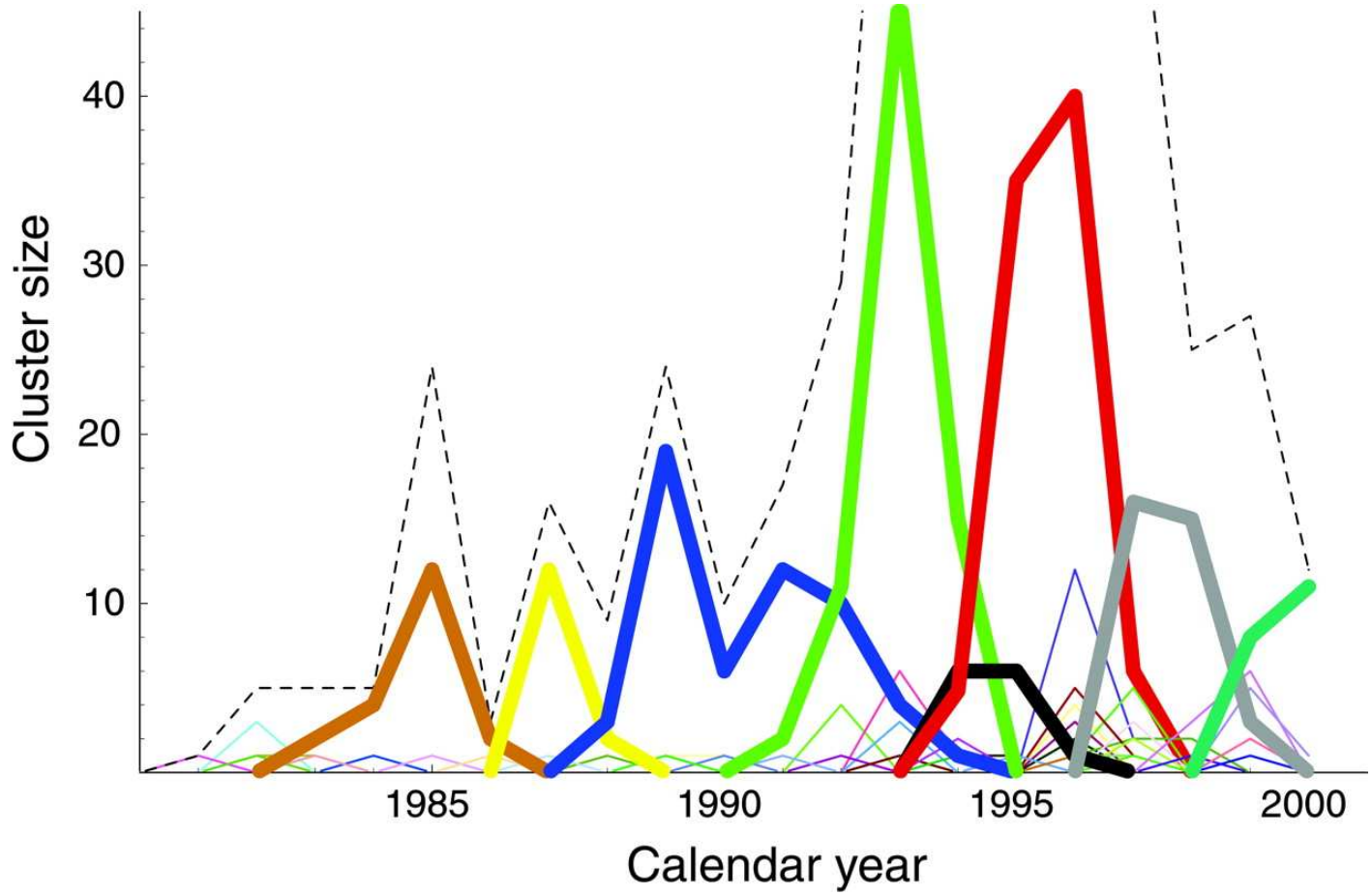


Comments

- The randomness in the infectivity parameter is difficult to check but not unreasonable
- The short-term wide-range immunity has little evidence in its favor
- Some properties of the epidemiological dynamics are lacking: e.g., seasonality
- The topology of the antigenic space can be more complex

Clusters

Plotkin, Dushoff and Levin, 2002

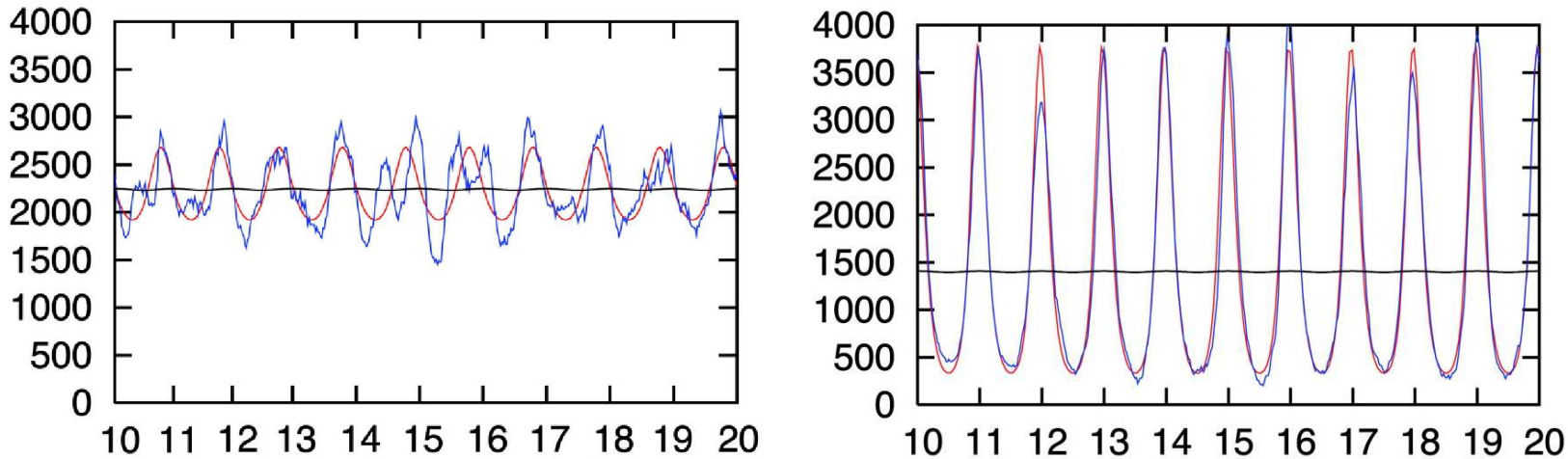


Clusters identified via genomic distance

Seasonality

Is the strong seasonality of influenza epidemics linked to the limited duration of immunity due to clusters?

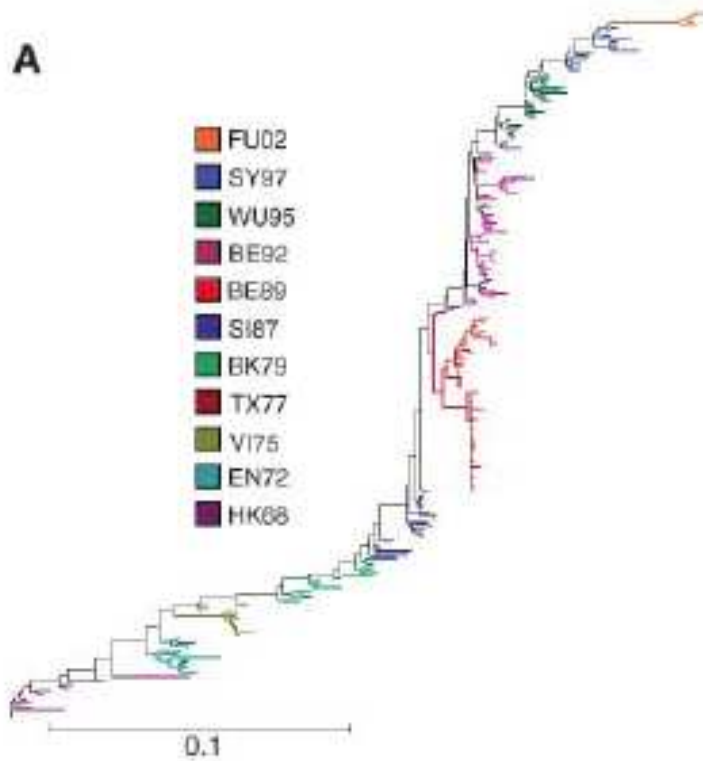
Plotkin, Dushoff, Levin and Earn, 2004



Left: Immunity duration 4 yr; Right: Immunity duration 8 yr; Small sinusoidal perturbations in infectivity

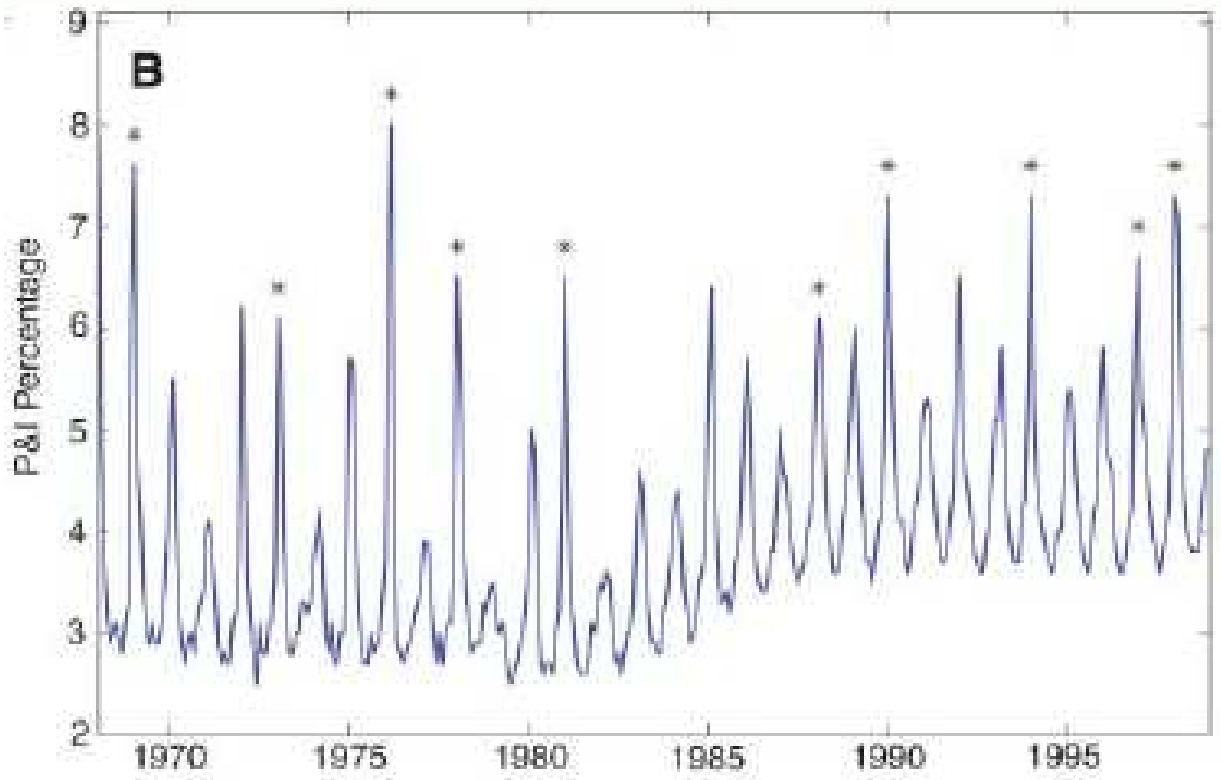
Epochal evolution: Cluster transitions

Koelle, Cobey, Grenfell and Pascual, 2006



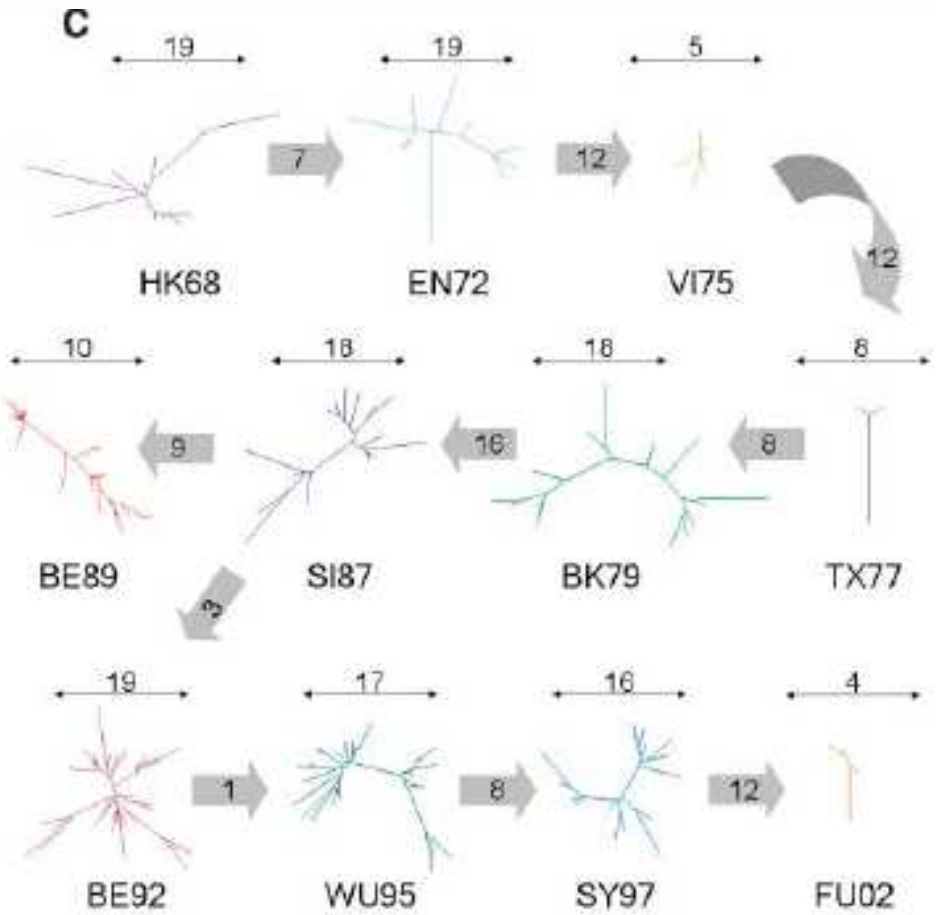
Phylogenetic tree of the HA1 gene, color-coded according to the *antigenic* clusters

Effects of cluster transitions

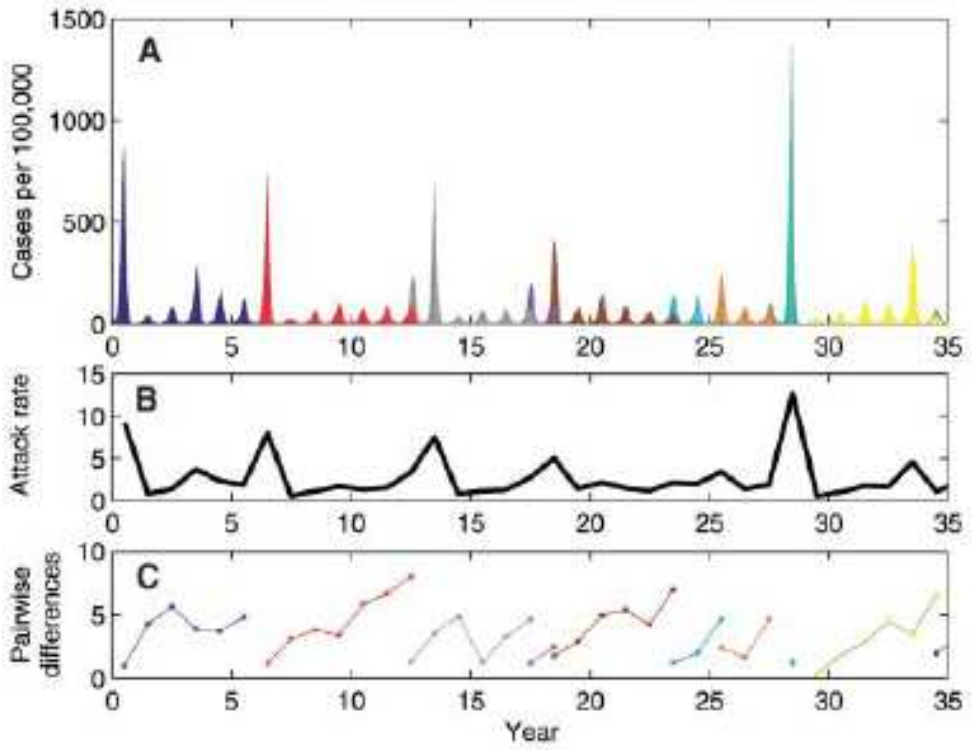


Death rate series: Stars denote times after a cluster transition

Clusters trees and their relations



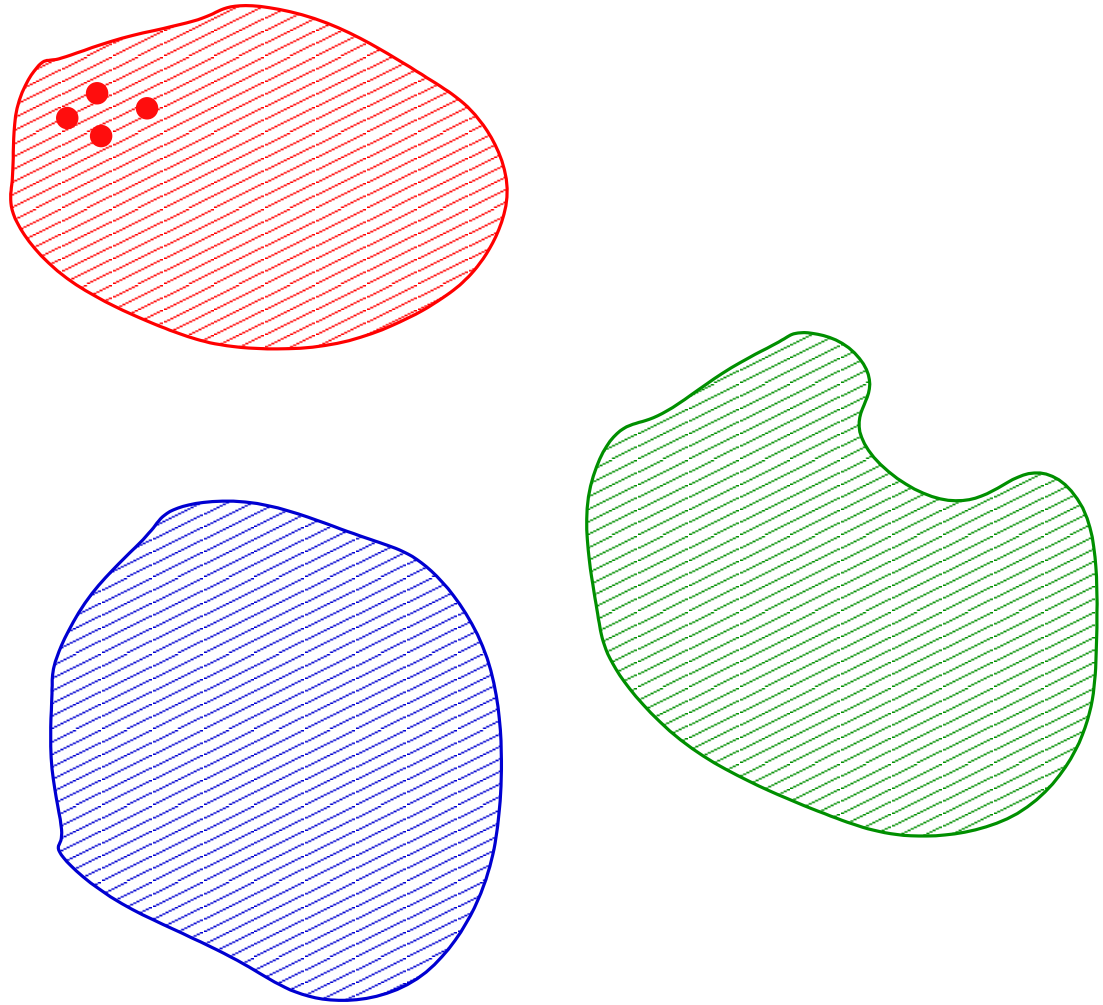
Simulations



Based on a “spin-glass” model of genotype $\longrightarrow$ phenotype mapping

“Influenza escapes immunity along neutral networks”

van Nimwegen, 2006



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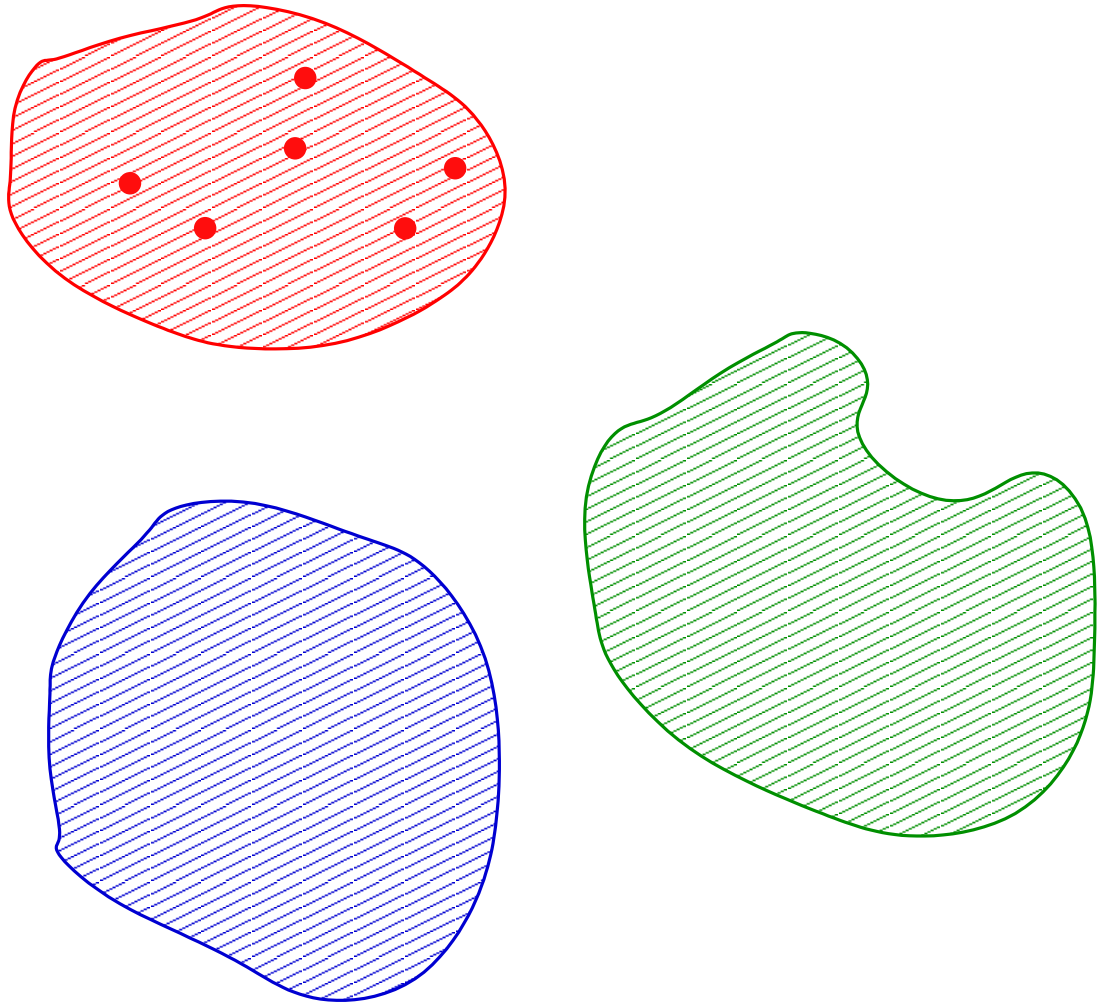

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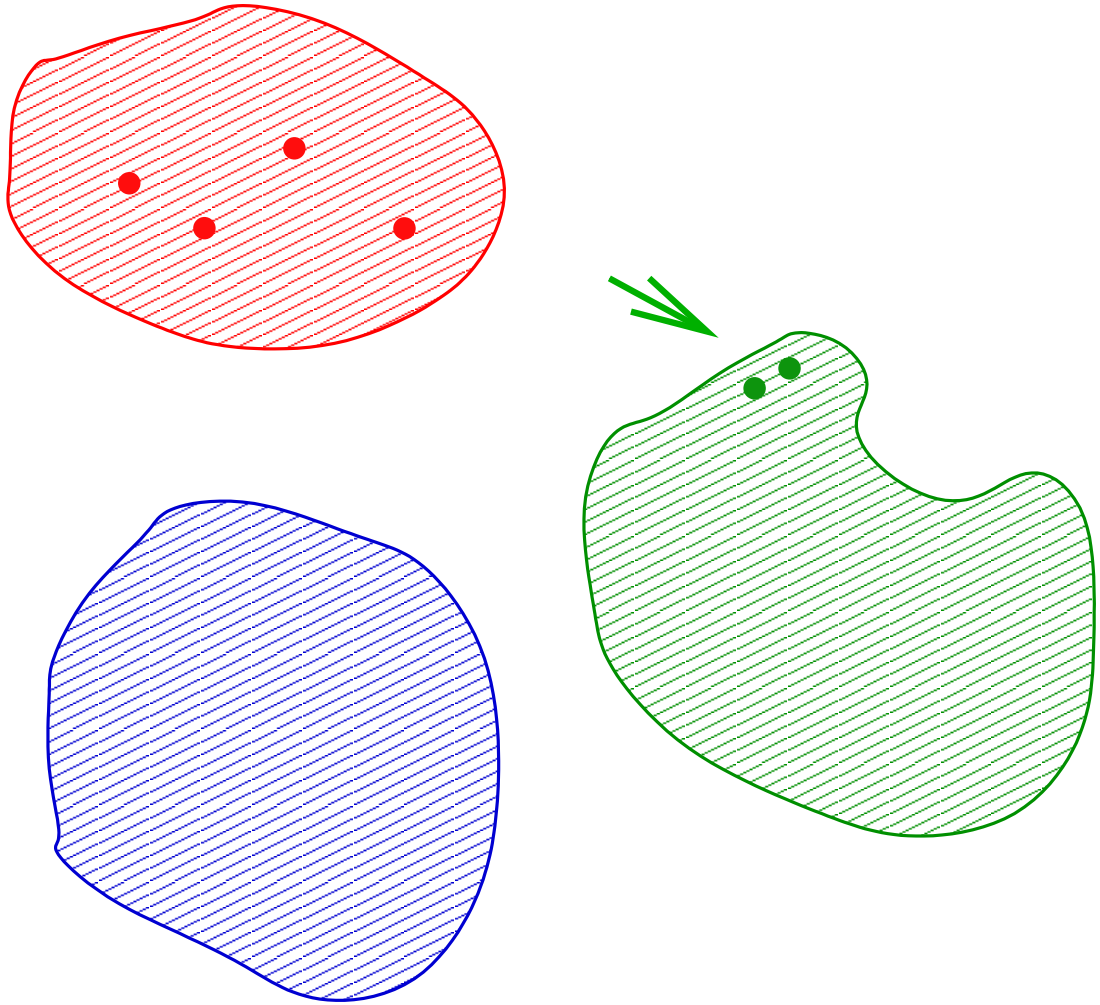

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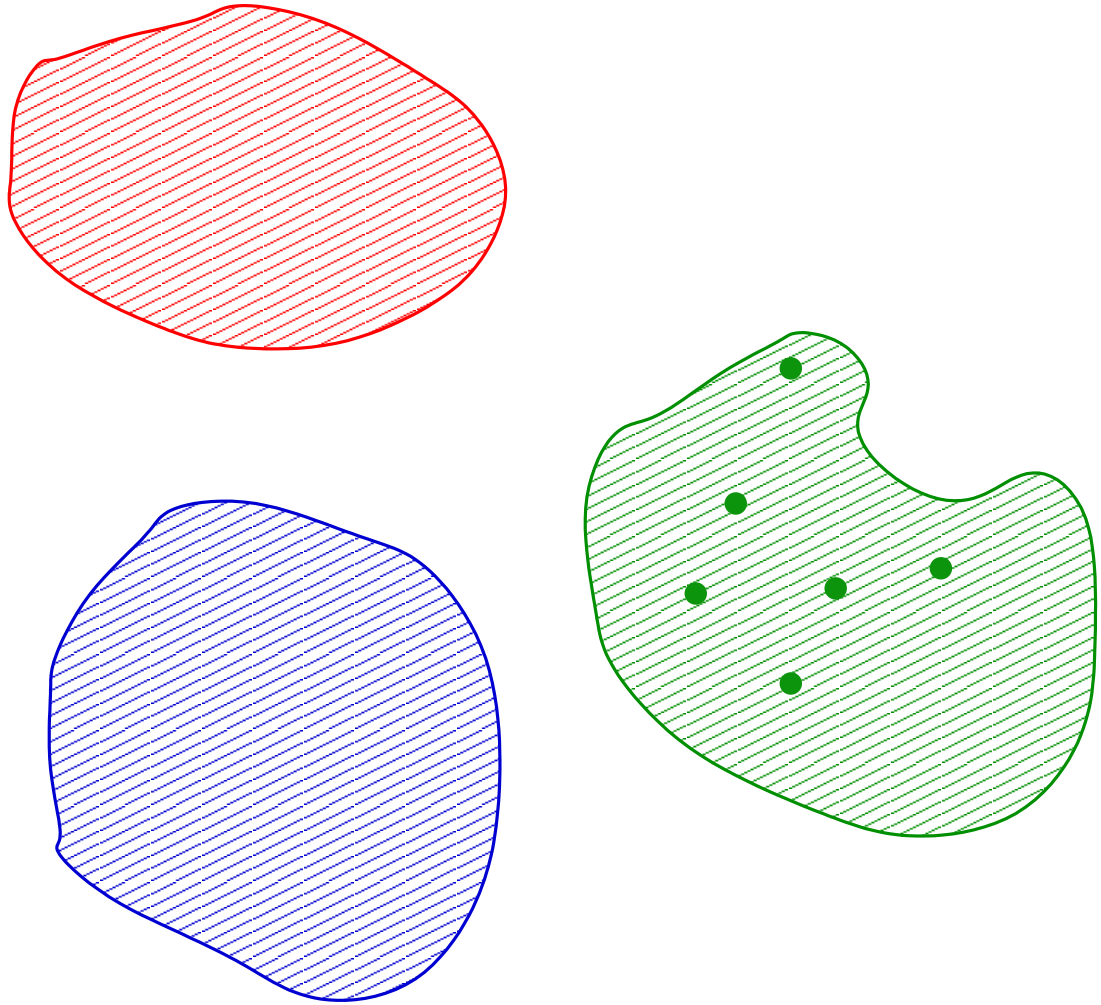

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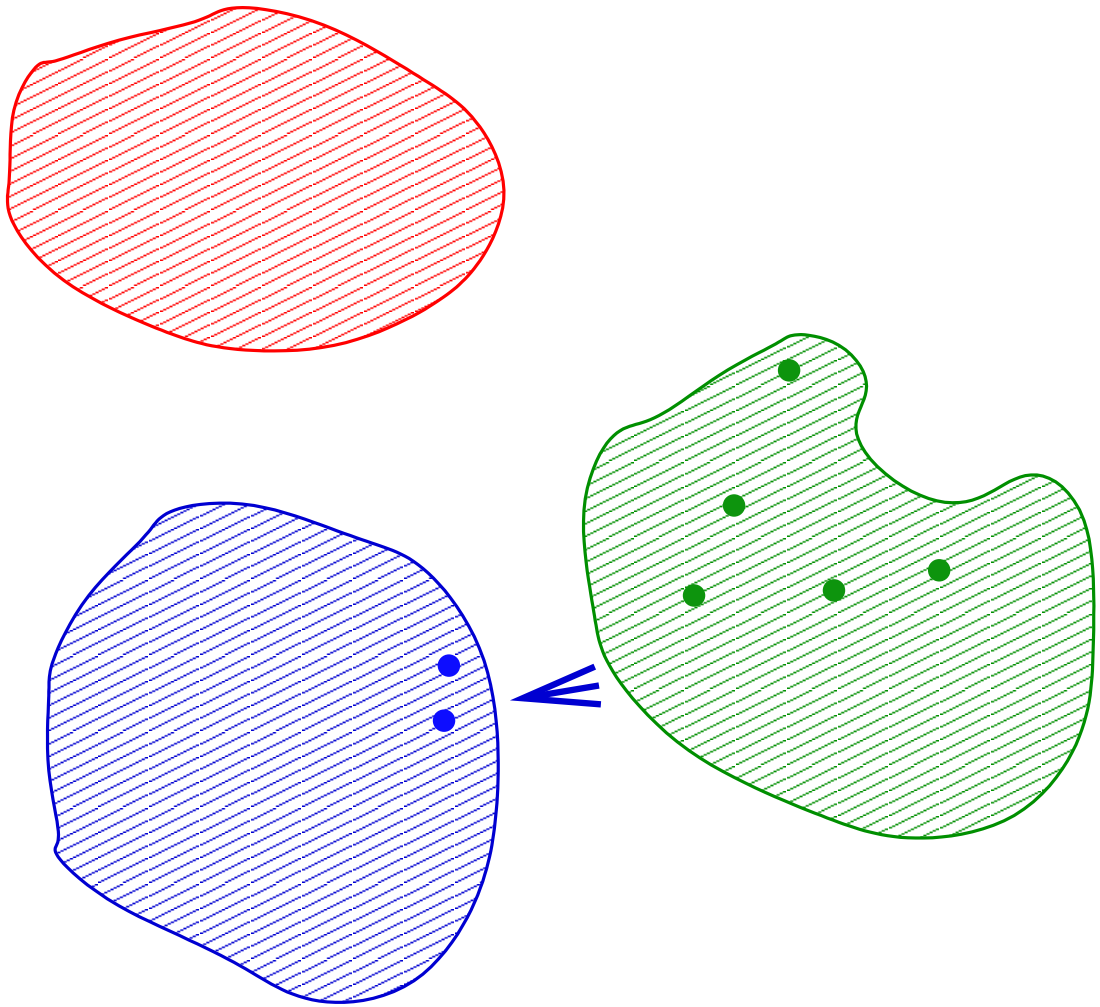

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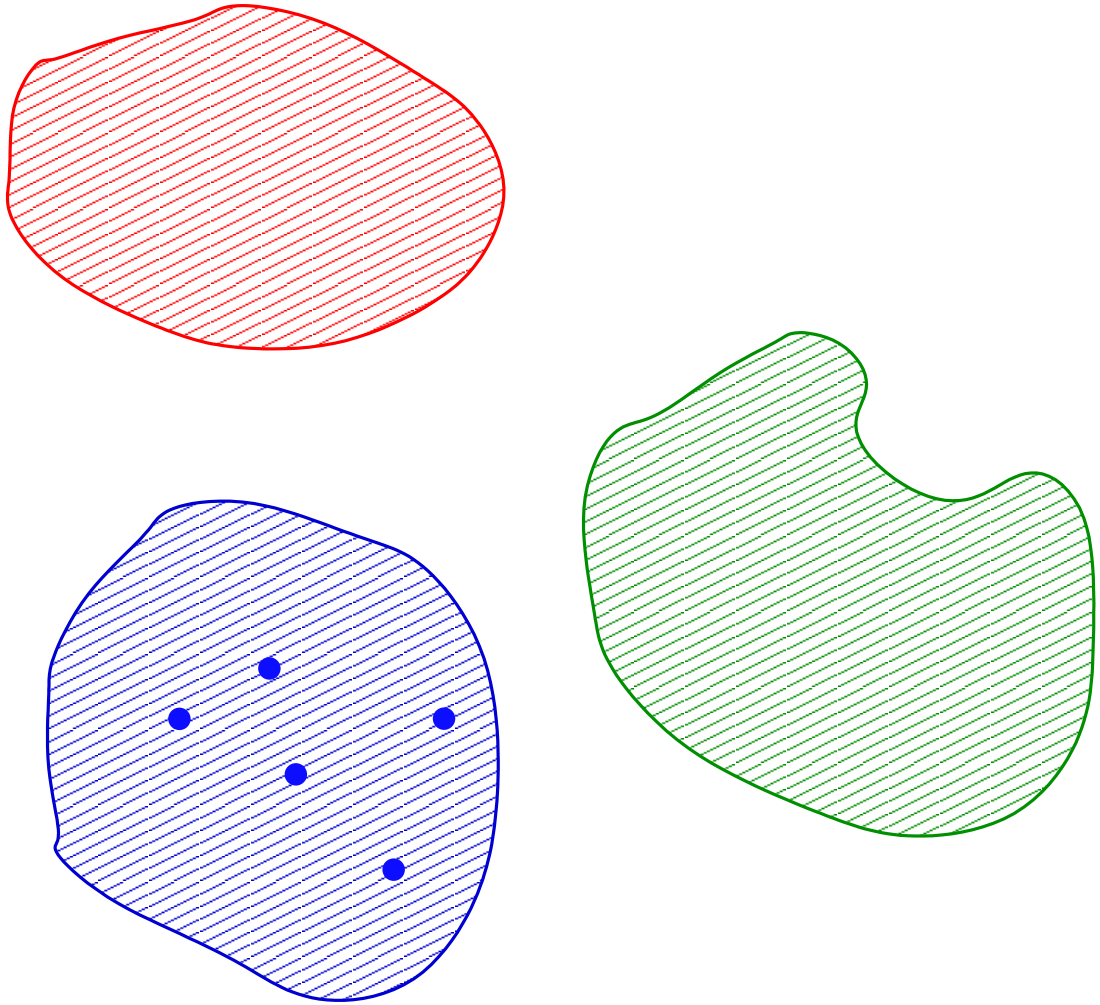
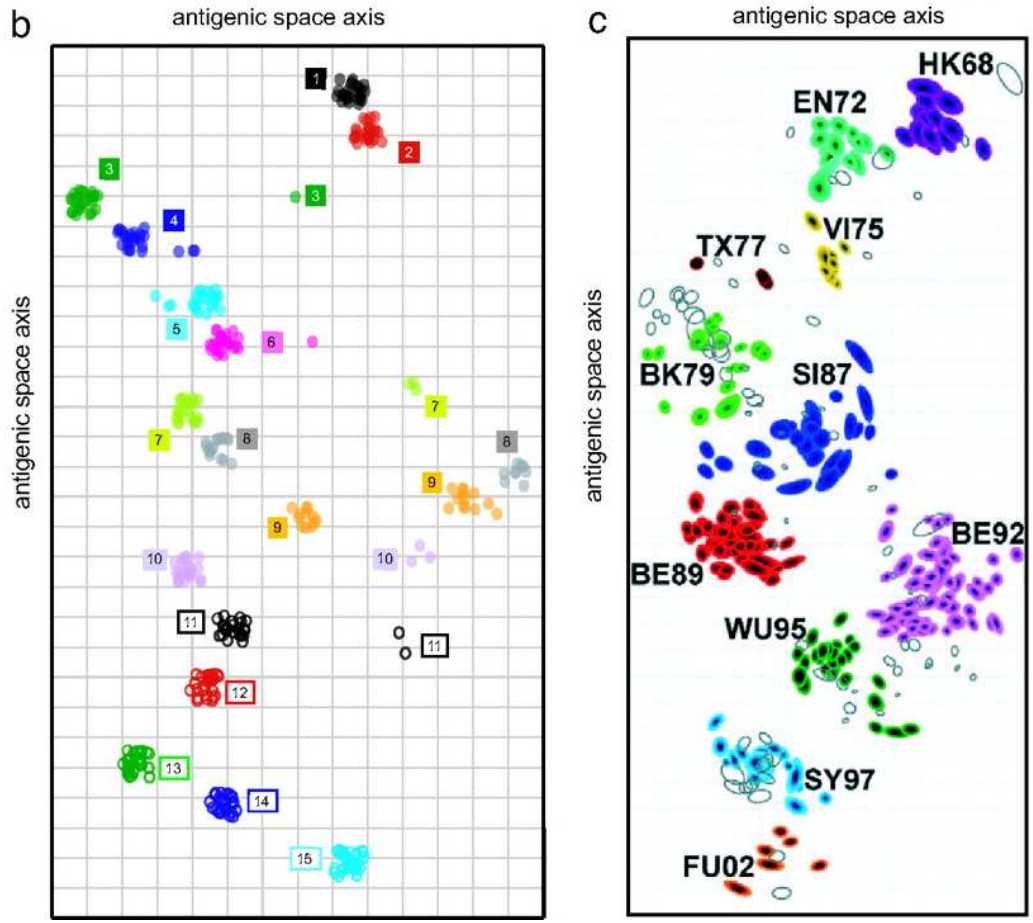
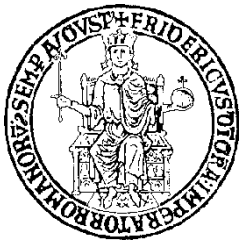


Antigenic types

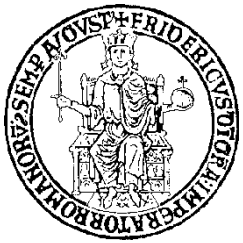
Recker, Pybus, Nee and Gupta, 2007





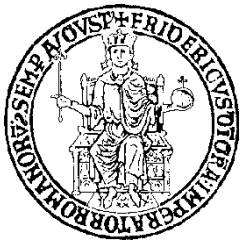
Explanation

- The plot is a projection on the plane of the two principal factors
- The path followed in this plane looks more like a zig-zag than a diffusion
- Antigenic types seem to reappear over and over again
- This happens in spite of an ongoing change at the whole-genome level



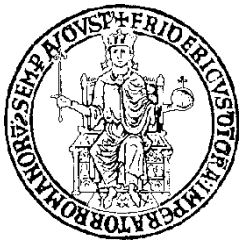
Comments

- The “antigenic space” has a stranger structure than suspected
- The lack of diversification is not *directly* explained by the neutral network model
- Antigenic transition is NOT equivalent to shorter host lifetime
- These model to not take into account recombination which is *known* to take place during epidemics



Conclusions

- In the dynamics of influenza the epidemiological and the evolutionary levels are intertwined



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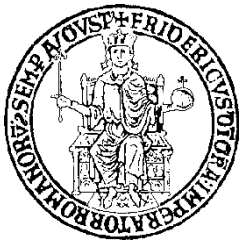
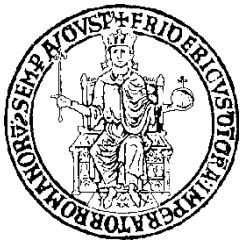
- Answering the puzzle of influenza might also shed light on the behavior of the HIV infection



Conclusions

- In the dynamics of influenza the epidemiological and the evolutionary levels are intertwined
- Answering the puzzle of influenza might also shed light on the behavior of the HIV infection
- But there is still quite some way to go!



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