



# The puzzle of the evolutionary dynamics of influenza

Luca Peliti

KITP, Santa Barbara and Università “Federico II”, Napoli



# The virus of influenza

## Introduction

### ❖ The virus of influenza

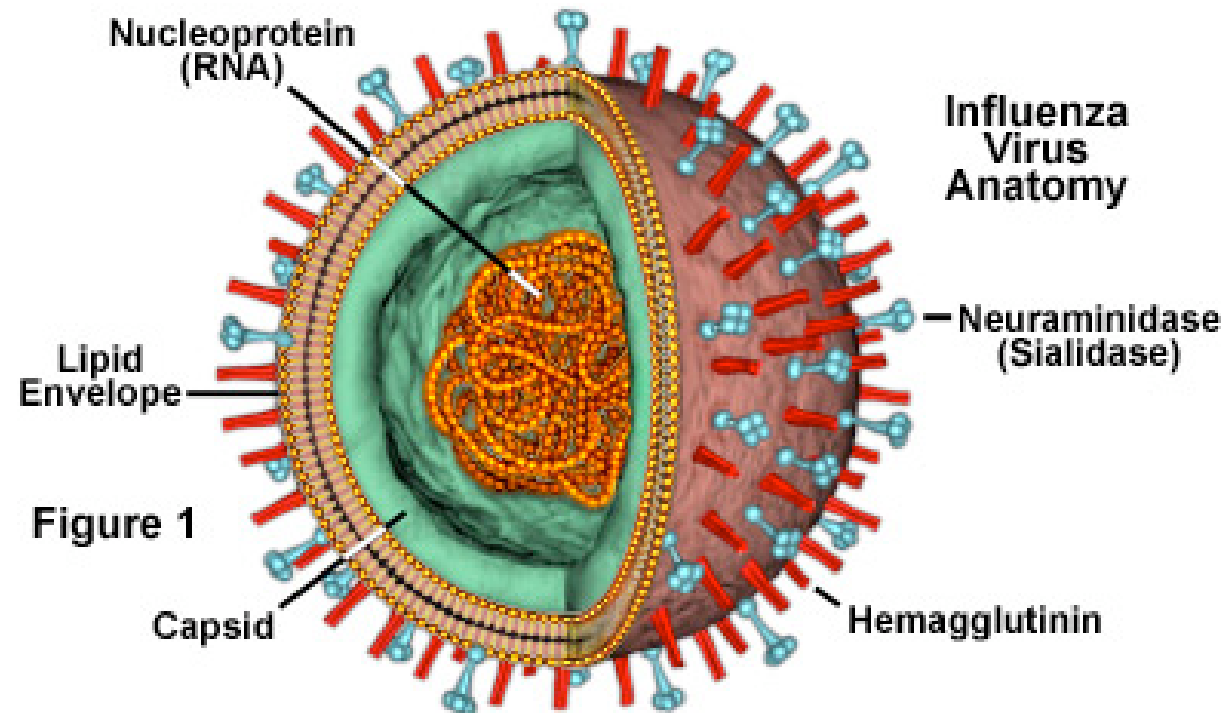
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

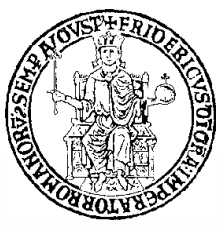
### A minimal model?

## Clusters

## Conclusions



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



# Lifecycle and protein structure

## Introduction

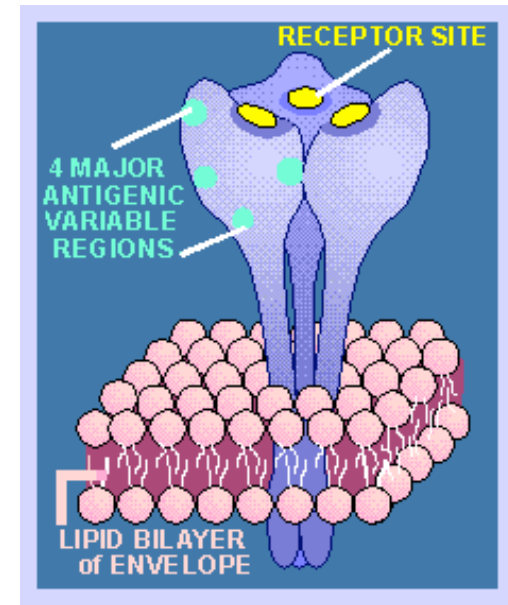
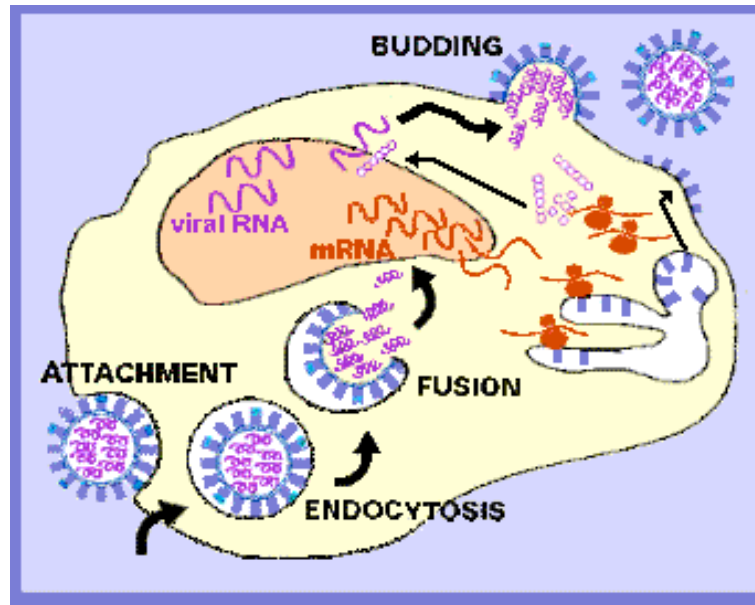
- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

A minimal model?

## Clusters

## Conclusions



Left: Life cycle of the influenza virus

Right: Schematic of the hemagglutinin protein



# Basic facts

## Introduction

---

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure

## ❖ Basic facts

- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

---

## A minimal model?

---

## Clusters

---

## Conclusions

---

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



# Basic facts

## Introduction

---

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure

## ❖ Basic facts

- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

---

## A minimal model?

---

## Clusters

---

## Conclusions

---

- There are three fundamental groups of flu viruses: A, B et C
- Type A originates global epidemics (pandemics)



# Basic facts

## Introduction

---

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure

## Basic facts

- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

---

## A minimal model?

---

## Clusters

---

## Conclusions

---

- There are three fundamental groups of flu viruses: A, B et C
- Type A originates global epidemics (pandemics)
- Type A is classified in subtypes  $H_hN_n$  according to the nature of its HA (Hemoagglutinine) and NA (Neuroaminidase) proteins



# Basic facts

## Introduction

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ **Basic facts**
- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

### A minimal model?

## Clusters

## Conclusions

- There are three fundamental groups of flu viruses: A, B et C
- Type A originates global epidemics (pandemics)
- Type A is classified in subtypes  $H_hN_n$  according to the nature of its HA (Hemoagglutinine) and NA (Neuroaminidase) proteins
- 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

## Introduction

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

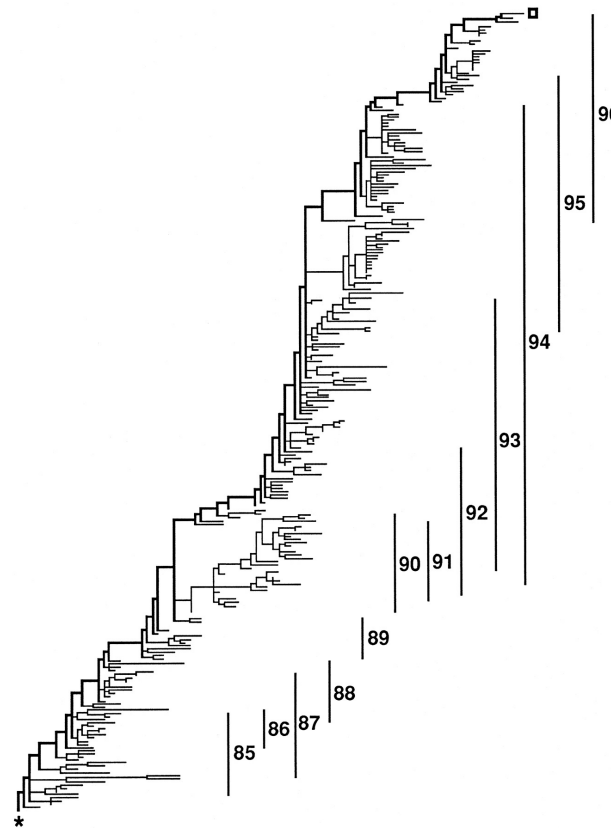
### A minimal model?

## Clusters

## Conclusions

## Flu: type A, subtype H3N2

*Fitch, Bush, Bender and Cox, 1997*







# Properties of the tree

## Introduction

---

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA

## ❖ Properties of the tree

- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

---

### A minimal model?

---

## Clusters

---

## Conclusions

---

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



# Properties of the tree

## Introduction

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA

## ❖ Properties of the tree

- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

## A minimal model?

## Clusters

## Conclusions

- The tree exhibits a well-defined backbone: branches have a median lifetime of 1.45 years
- At any given time, the strain nearest to the backbone can be identified by looking at the number of nonsilent mutations in 18 special codons of the HA gene

*Bush, Bender, Subbarao, Cox and Fitch, 1999*



# Properties of the tree

## Introduction

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA

## ❖ Properties of the tree

- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

## A minimal model?

## Clusters

## Conclusions

- The tree exhibits a well-defined backbone: branches have a median lifetime of 1.45 years
- At any given time, the strain nearest to the backbone can be identified by looking at the number of nonsilent mutations in 18 special codons of the HA gene

*Bush, Bender, Subbarao, Cox and Fitch, 1999*

- The tree does not branch out over long times



# The puzzle

## Introduction

---

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree

## ❖ The puzzle

- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

---

### A minimal model?

---

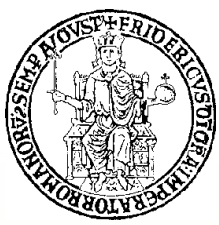
### Clusters

---

### Conclusions

---

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



# Epidemiology and evolutionary dynamics

## Introduction

- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle

## Epidemiology and evolutionary dynamics

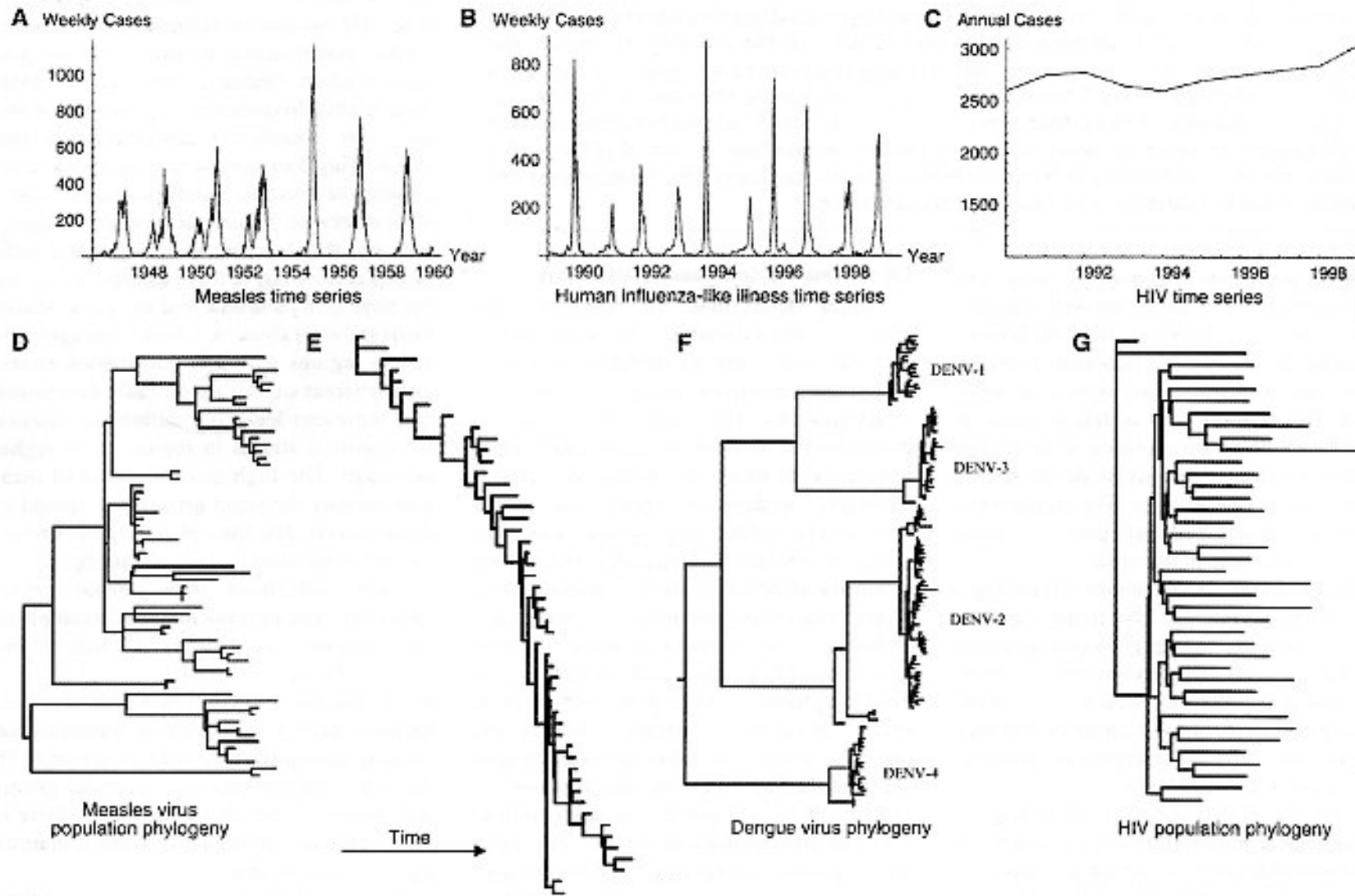
- ❖ Flu vs. in-host HIV evolution

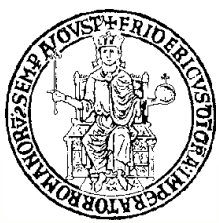
## Models

## A minimal model?

## Clusters

## Conclusions





# Flu vs. in-host HIV evolution

## Introduction

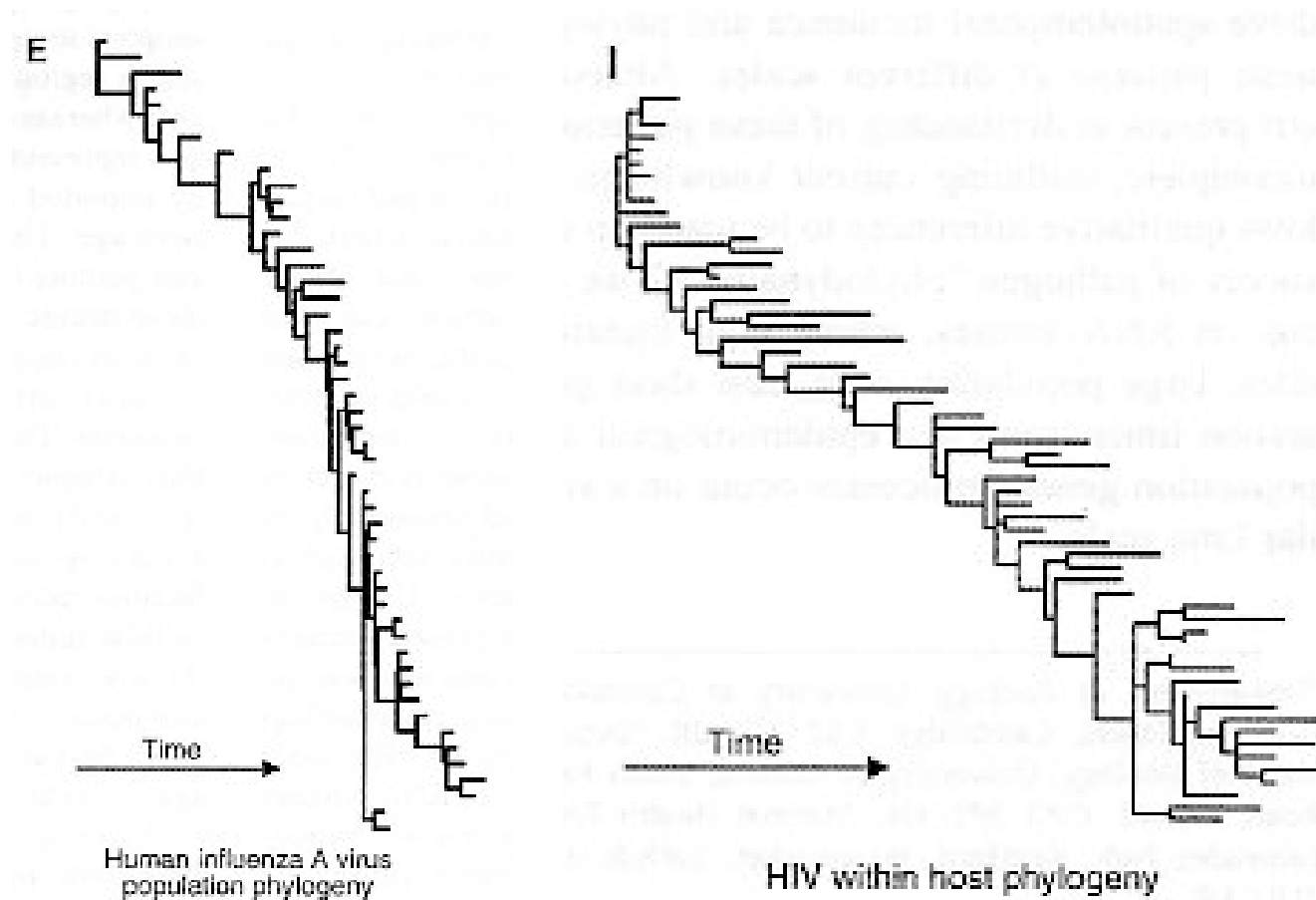
- ❖ The virus of influenza
- ❖ Lifecycle and protein structure
- ❖ Basic facts
- ❖ The phylogenetic tree for HA
- ❖ Properties of the tree
- ❖ The puzzle
- ❖ Epidemiology and evolutionary dynamics
- ❖ Flu vs. in-host HIV evolution

## Models

## A minimal model?

## Clusters

## Conclusions



*Grenfell et al., 2004*



# The classic SIR model: Definition

*Kermack and McKendrick, 1927*

Introduction

Models

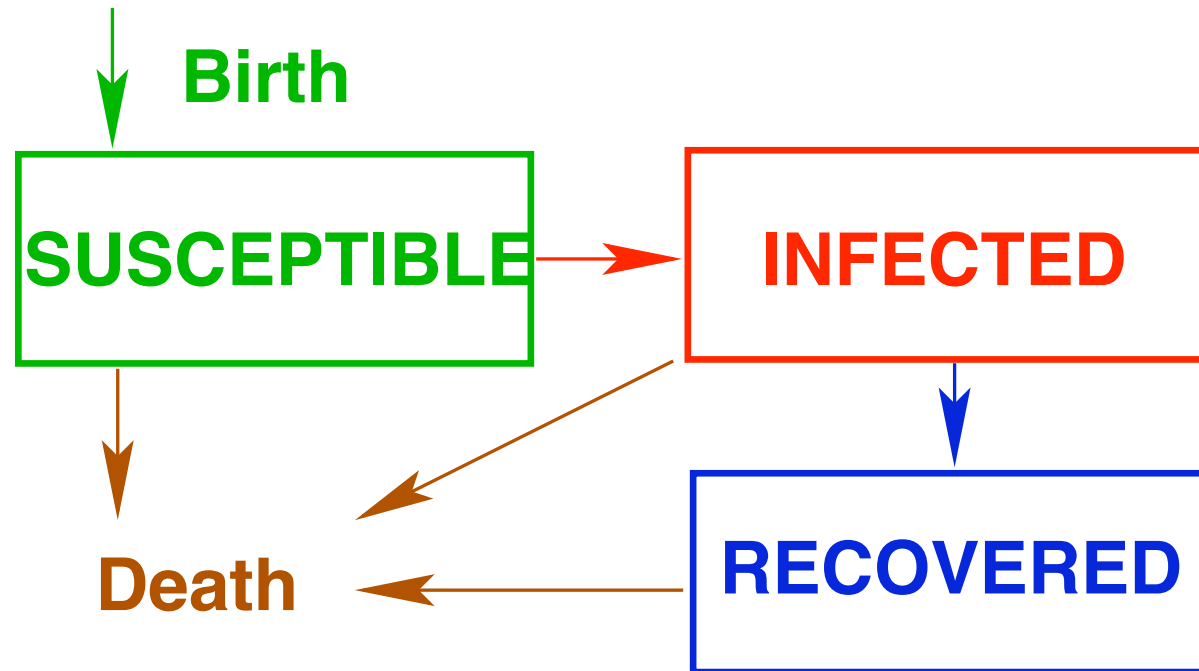
❖ The classic SIR model: Definition

- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

A minimal model?

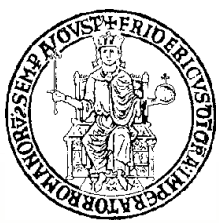
Clusters

Conclusions



$$\frac{dS}{dt} = N\lambda - \frac{\gamma}{N}SI - \lambda S$$

$$\frac{dI}{dt} = \frac{\gamma}{N}SI - (\rho + \lambda)I$$



# The classic SIR model: Behavior

## Introduction

## Models

❖ The classic SIR model: Definition

❖ The classic SIR model: Behavior

❖ Coexisting strains: Modified SIR model

❖ One-dimensional strain space: A travelling wave

❖ Long-lasting disease (HIV)?

❖ Comments

❖ Many strains

❖ The bitstring model

❖ Disease prevalence

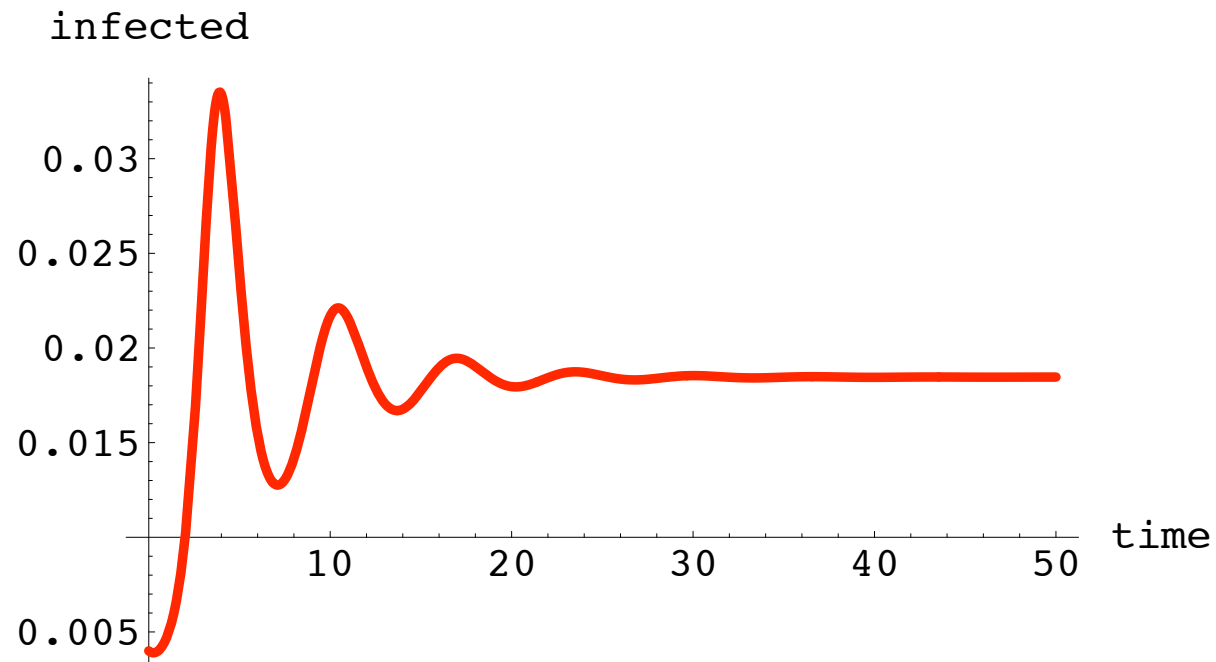
❖ Phase diagram

❖ Comments

A minimal model?

Clusters

Conclusions



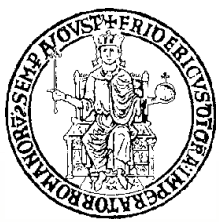
$$S^* = N \frac{\rho + \lambda}{\gamma}$$

$$I^* = \frac{\lambda}{\rho + \lambda} (N - S^*)$$

$$\tau \simeq 2\pi \sqrt{\frac{\rho}{\lambda\gamma}} = 2\pi / \sqrt{\beta\lambda\rho}$$

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





# Coexisting strains: Modified SIR model

Introduction

Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ **Coexisting strains: Modified SIR model**
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

A minimal model?

Clusters

Conclusions

- Viral strain defined by  $k$



# Coexisting strains: Modified SIR model

## Introduction

## Models

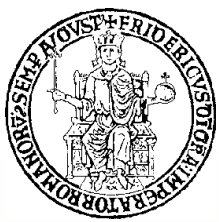
- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ **Coexisting strains: Modified SIR model**
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

## Clusters

## Conclusions

- Viral strain defined by  $k$
- $i_k(t)$ : Population infected by strain  $k$  at time  $t$



# Coexisting strains: Modified SIR model

## Introduction

---

## Models

---

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior

## ❖ Coexisting strains: Modified SIR model

- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

---

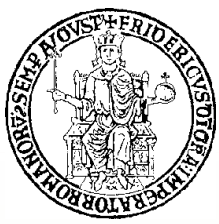
## Clusters

---

## Conclusions

---

- Viral strain defined by  $k$
- $i_k(t)$ : Population infected by strain  $k$  at time  $t$
- $s_k(t)$ : Population susceptible to infection by strain  $k$  at time  $t$



# Coexisting strains: Modified SIR model

## Introduction

---

## Models

---

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior

## ❖ Coexisting strains: Modified SIR model

- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

---

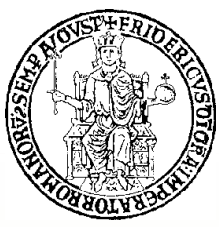
## Clusters

---

## Conclusions

---

- Viral strain defined by  $k$
- $i_k(t)$ : Population infected by strain  $k$  at time  $t$
- $s_k(t)$ : Population susceptible to infection by strain  $k$  at time  $t$
- **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

## Introduction

## Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave

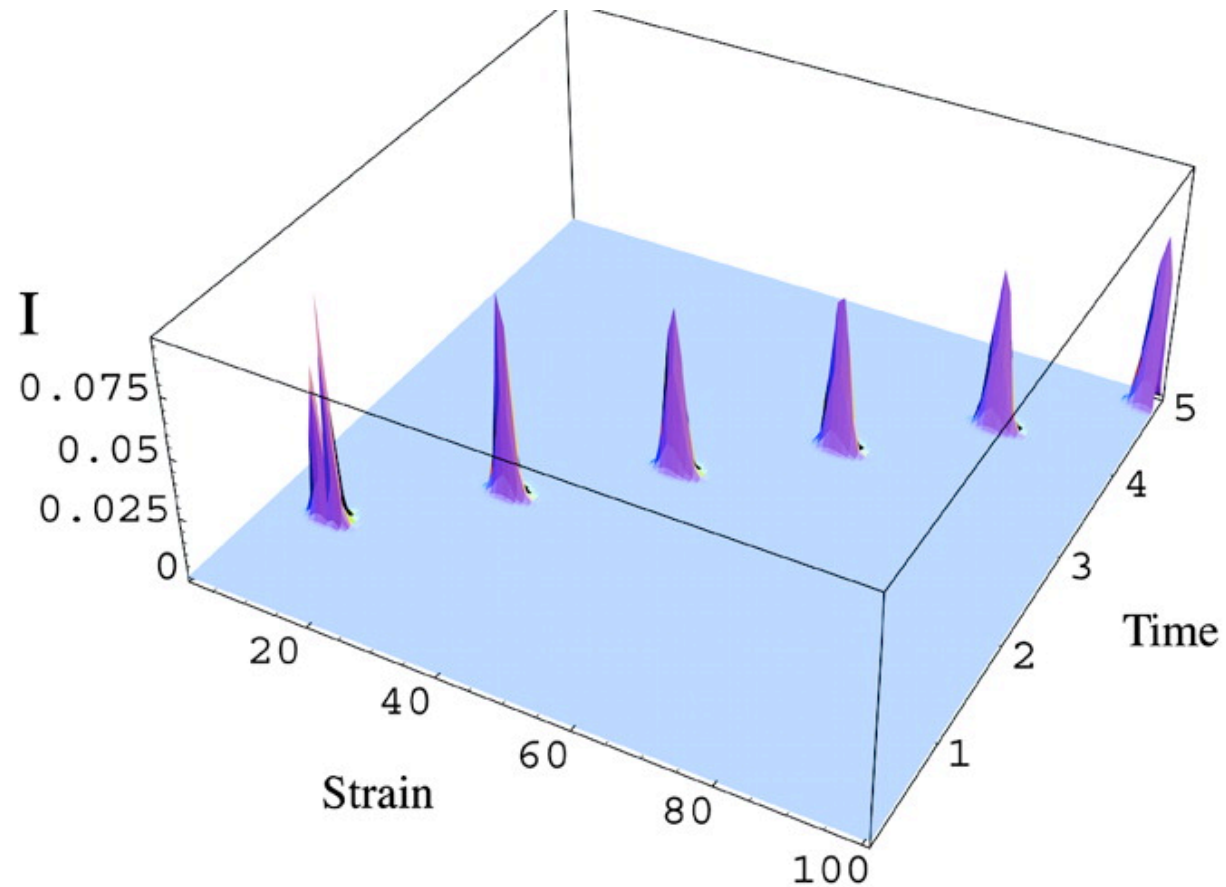
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

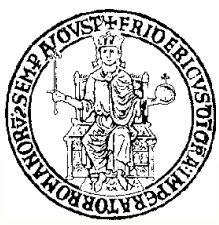
## A minimal model?

## Clusters

## Conclusions

*Andreasen, Lin and Levin, 1997; Gog and Grenfell, 2002*





# Long-lasting disease (HIV)?

## Introduction

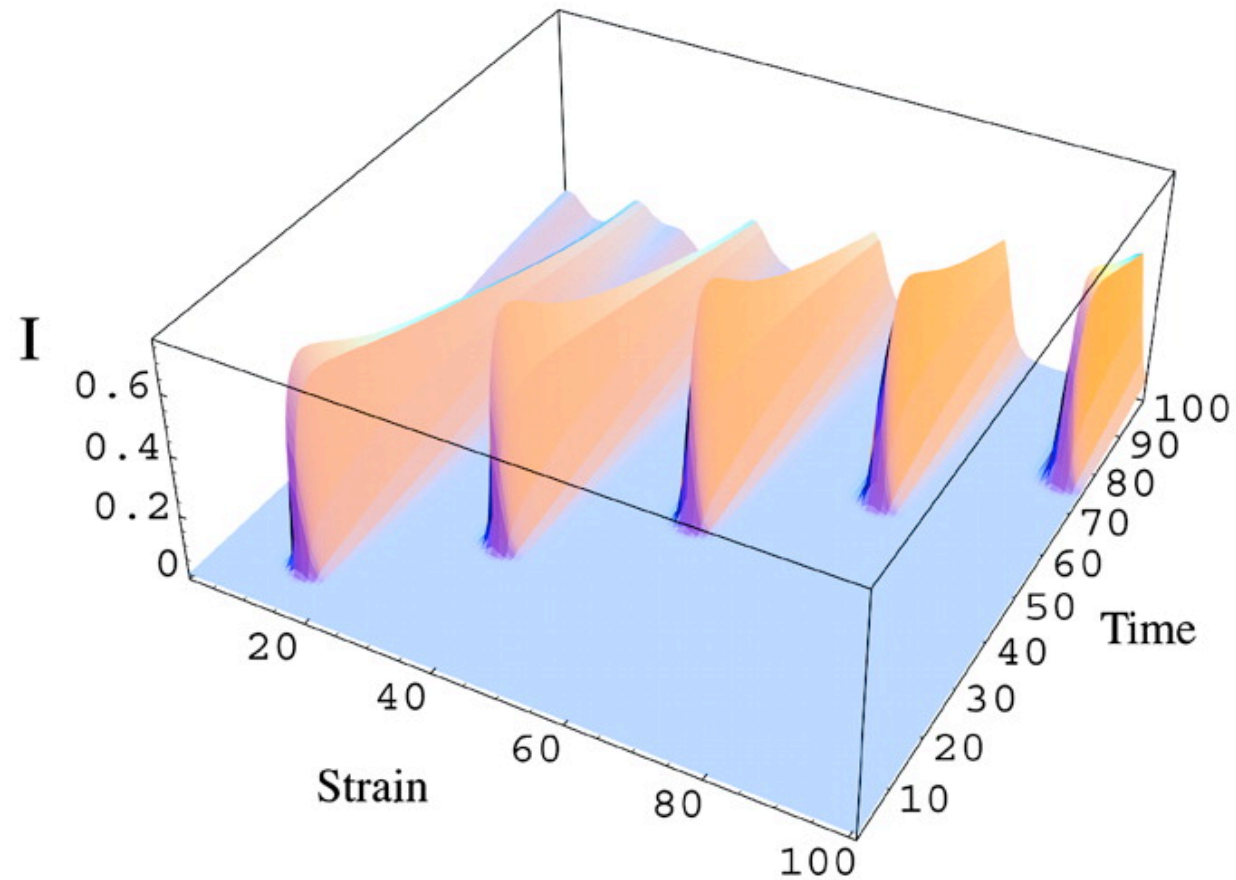
## Models

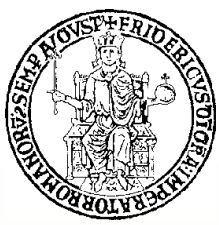
- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

## Clusters

## Conclusions





# Comments

## Introduction

## Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?

## ❖ **Comments**

- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

## Clusters

## Conclusions

- The “speed of evolution”  $dk/dt$  is compatible with the “natural” values of the parameters  $\rho$  (1/one week),  $\lambda$  ( $\sim 1/(50 \div 70 \text{ years})$ ),  $\beta$  (probably  $\sim 4 \div 8$ ) and of the observed substitution rate of the viral strains



# Comments

## Introduction

## Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?

## ❖ Comments

- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

## Clusters

## Conclusions

- The “speed of evolution”  $dk/dt$  is compatible with the “natural” values of the parameters  $\rho$  (1/one week),  $\lambda$  ( $\sim 1/(50 \div 70 \text{ years})$ ),  $\beta$  (probably  $\sim 4 \div 8$ ) and of the observed substitution rate of the viral strains
- The lack of diversification is *assumed* rather than *derived*





# Comments

## Introduction

## Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?

## ❖ Comments

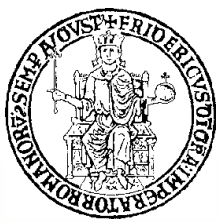
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

## Clusters

## Conclusions

- The “speed of evolution”  $dk/dt$  is compatible with the “natural” values of the parameters  $\rho$  (1/one week),  $\lambda$  ( $\sim 1/(50 \div 70 \text{ years})$ ),  $\beta$  (probably  $\sim 4 \div 8$ ) and of the observed substitution rate of the viral strains
- The lack of diversification is *assumed* rather than *derived*
- Need to consider a more general topology of strain space



# Many strains

## Introduction

---

## Models

---

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ **Many strains**
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

---

## Clusters

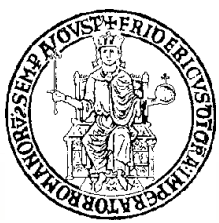
---

## Conclusions

---

## 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*

Introduction

Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ **The bitstring model**
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ Comments

A minimal model?

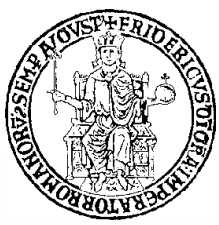
Clusters

Conclusions

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

$$d_H(k, k') = \sum_i (k_i - k'_i)^2$$

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



# Disease prevalence

## Introduction

## Models

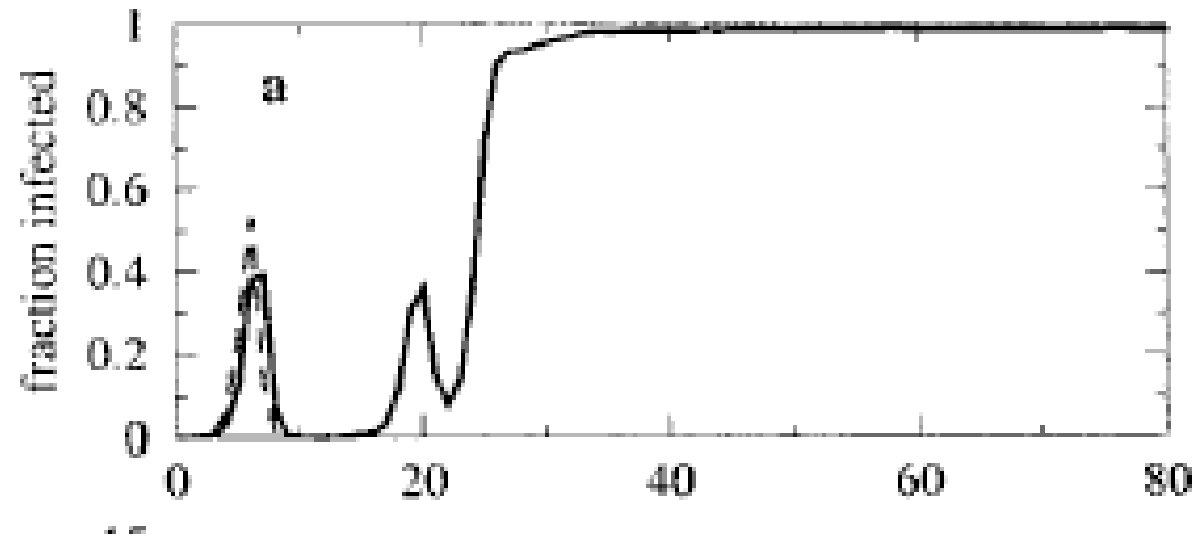
- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence

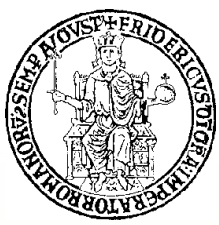
- ❖ Phase diagram
- ❖ Comments

## A minimal model?

## Clusters

## Conclusions





# Phase diagram

## Introduction

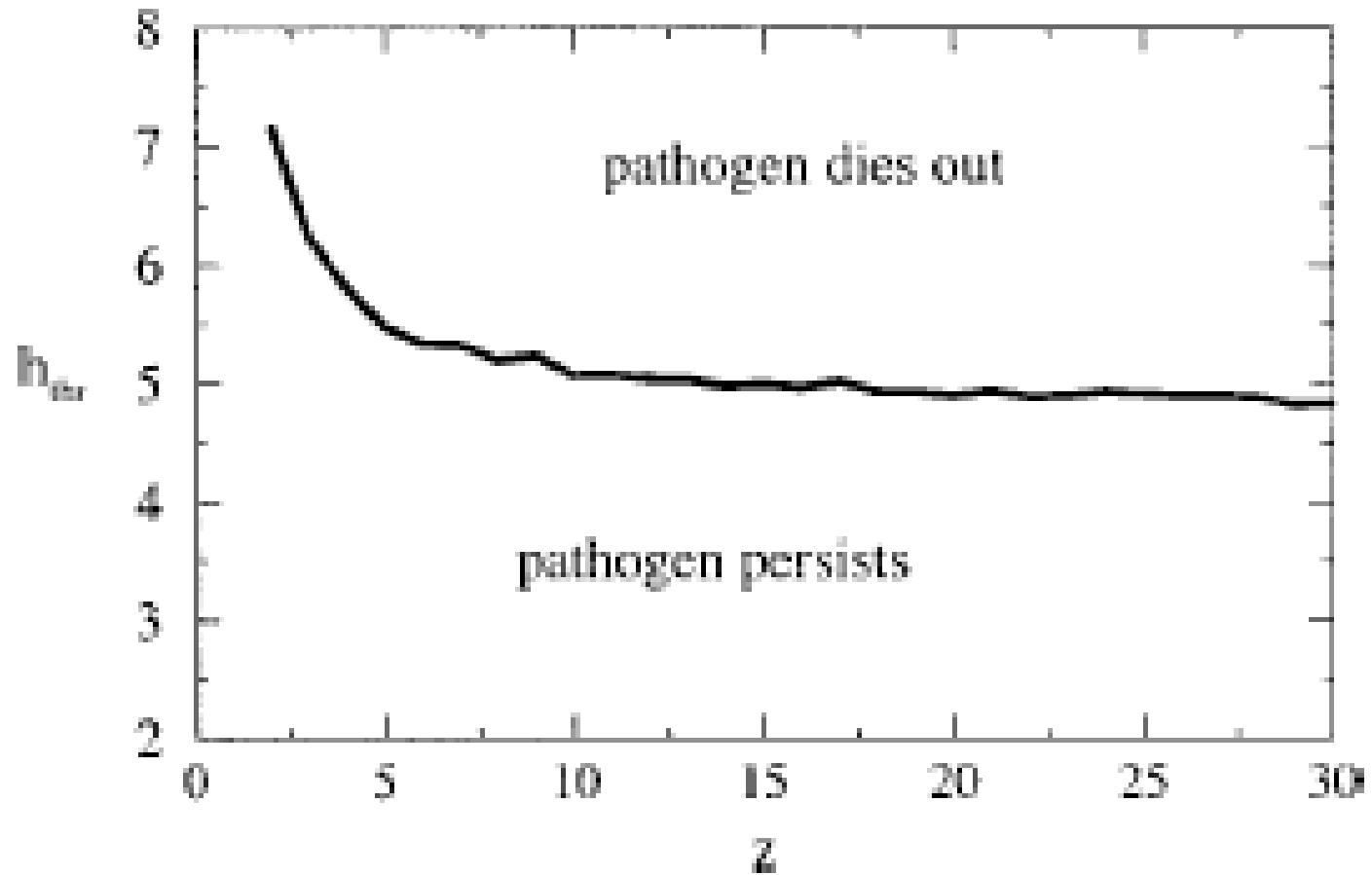
## Models

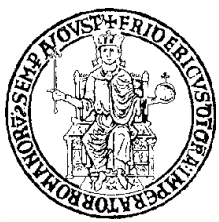
- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ **Phase diagram**
- ❖ Comments

## A minimal model?

## Clusters

## Conclusions





# Comments

Introduction

Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ **Comments**

A minimal model?

Clusters

Conclusions

- Either extinction or boundless proliferation!



# Comments

## Introduction

## Models

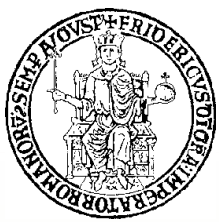
- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ **Comments**

## A minimal model?

## Clusters

## Conclusions

- Either extinction or boundless proliferation!
- 100% of the population is infected in the steady state!



# Comments

## Introduction

## Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ **Comments**

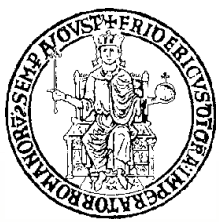
## A minimal model?

## Clusters

## Conclusions

- Either extinction or boundless proliferation!
- 100% of the population is infected in the steady state!
- Cross-immunization is not effective!





# Comments

## Introduction

## Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram
- ❖ **Comments**

## A minimal model?

## Clusters

## Conclusions

- Either extinction or boundless proliferation!
- 100% of the population is infected in the steady state!
- Cross-immunization is not effective!

Branching process:





# Comments

## Introduction

## Models

- ❖ The classic SIR model: Definition
- ❖ The classic SIR model: Behavior
- ❖ Coexisting strains: Modified SIR model
- ❖ One-dimensional strain space: A travelling wave
- ❖ Long-lasting disease (HIV)?
- ❖ Comments
- ❖ Many strains
- ❖ The bitstring model
- ❖ Disease prevalence
- ❖ Phase diagram

## ❖ Comments

## A minimal model?

## Clusters

## Conclusions

- Either extinction or boundless proliferation!
- 100% of the population is infected in the steady state!
- Cross-immunization is not effective!

Branching process:



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



# Short term infinite-range immunity

Introduction

Models

A minimal model?

❖ Short term infinite-range immunity

❖ Modified bitstring model

❖ Observables

❖ Effects of short immunity:  
Prevalence and # strains

❖ Random infectivity and no short immunity

❖ Random infectivity **and** short immunity

❖ Random infectivity **and** short immunity

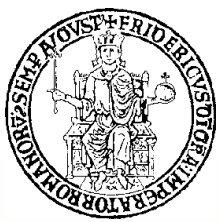
❖ Phylogenetic tree

❖ Comments

Clusters

Conclusions

- Ferguson, Galvani and Bush (2003) conjecture the existence of a short term ( $\sim 6$  months) immunity active against all viral strains, after recovery from an infection



# Short term infinite-range immunity

Introduction

Models

A minimal model?

❖ Short term infinite-range immunity

❖ Modified bitstring model

❖ Observables

❖ Effects of short immunity:  
Prevalence and # strains

❖ Random infectivity and no short immunity

❖ Random infectivity **and** short immunity

❖ Random infectivity **and** short immunity

❖ Phylogenetic tree

❖ Comments

Clusters

Conclusions

- Ferguson, Galvani and Bush (2003) conjecture the existence of a short term ( $\sim 6$  months) immunity active against all viral strains, after recovery from an infection
- This conjecture is contained in a very complex model, with geographical distribution, many parameters, etc.



# Short term infinite-range immunity

Introduction

Models

A minimal model?

❖ Short term infinite-range immunity

❖ Modified bitstring model

❖ Observables

❖ Effects of short immunity:  
Prevalence and # strains

❖ Random infectivity and no short immunity

❖ Random infectivity **and** short immunity

❖ Random infectivity **and** short immunity

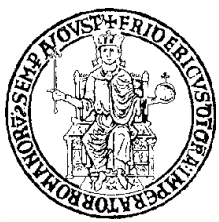
❖ Phylogenetic tree

❖ Comments

Clusters

Conclusions

- Ferguson, Galvani and Bush (2003) conjecture the existence of a short term ( $\sim 6$  months) immunity active against all viral strains, after recovery from an infection
- This conjecture is contained in a very complex model, with geographical distribution, many parameters, etc.
- It has but scanty observational support



# Short term infinite-range immunity

Introduction

Models

A minimal model?

❖ Short term infinite-range immunity

❖ Modified bitstring model

❖ Observables

❖ Effects of short immunity:

Prevalence and # strains

❖ Random infectivity and no short immunity

❖ Random infectivity **and** short immunity

❖ Random infectivity **and** short immunity

❖ Phylogenetic tree

❖ Comments

Clusters

Conclusions

- Ferguson, Galvani and Bush (2003) conjecture the existence of a short term ( $\sim 6$  months) immunity active against all viral strains, after recovery from an infection
- This conjecture is contained in a very complex model, with geographical distribution, many parameters, etc.
- It has but scanty observational support
- Is it sufficient **alone** to describe the observed behavior?



# Modified bitstring model

Tria, Lässig, Peliti and Franz, 2004

Introduction

Models

A minimal model?

❖ Short term  
infinite-range  
immunity

❖ Modified bitstring  
model

❖ Observables

❖ Effects of short  
immunity:  
Prevalence and #  
strains

❖ Random infectivity  
and no short  
immunity

❖ Random infectivity  
and short immunity

❖ Random infectivity  
and short immunity

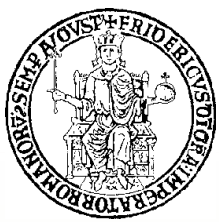
❖ Phylogenetic tree

❖ Comments

Clusters

Conclusions

- 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  $\beta_k$ , extracted at random



# Observables

Introduction

Models

A minimal model?

❖ Short term infinite-range immunity

❖ Modified bitstring model

❖ **Observables**

❖ Effects of short immunity:  
Prevalence and # strains

❖ Random infectivity and no short immunity

❖ Random infectivity **and** short immunity

❖ Random infectivity **and** short immunity

❖ Phylogenetic tree

❖ Comments

Clusters

Conclusions

- # individuals infected by strain  $k$ :  $\nu_k$
- Effective number of strains

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

- Prevalence of the disease

$$I = \sum_k \nu_k$$





# Effects of short immunity: Prevalence and # strains

[Introduction](#)

[Models](#)

[A minimal model?](#)

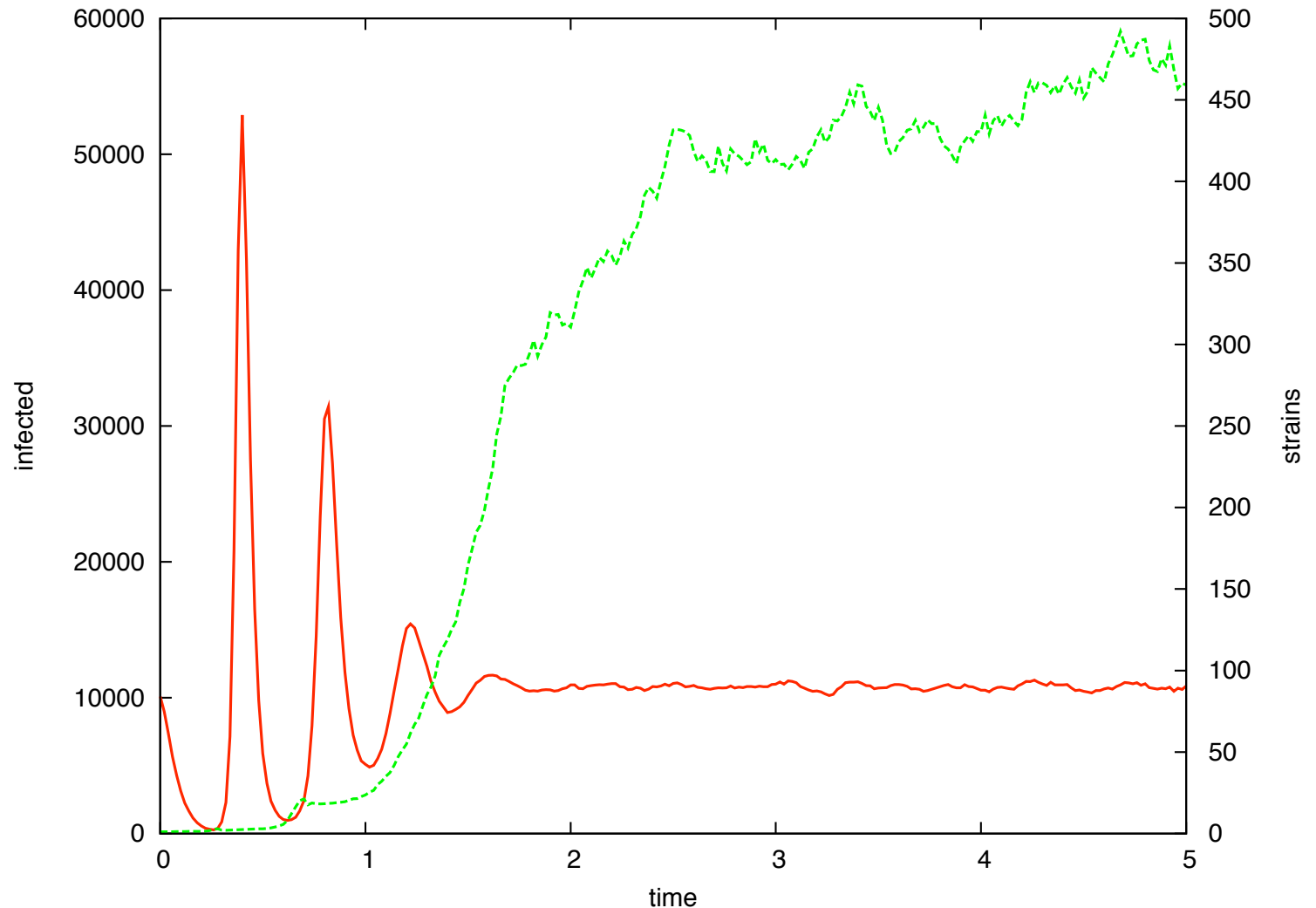
- ❖ Short term infinite-range immunity
- ❖ Modified bitstring model
- ❖ Observables

❖ Effects of short immunity: Prevalence and # strains

- ❖ Random infectivity and no short immunity
- ❖ Random infectivity and short immunity
- ❖ Random infectivity and short immunity
- ❖ Phylogenetic tree
- ❖ Comments

[Clusters](#)

[Conclusions](#)





# Random infectivity and no short immunity

## Introduction

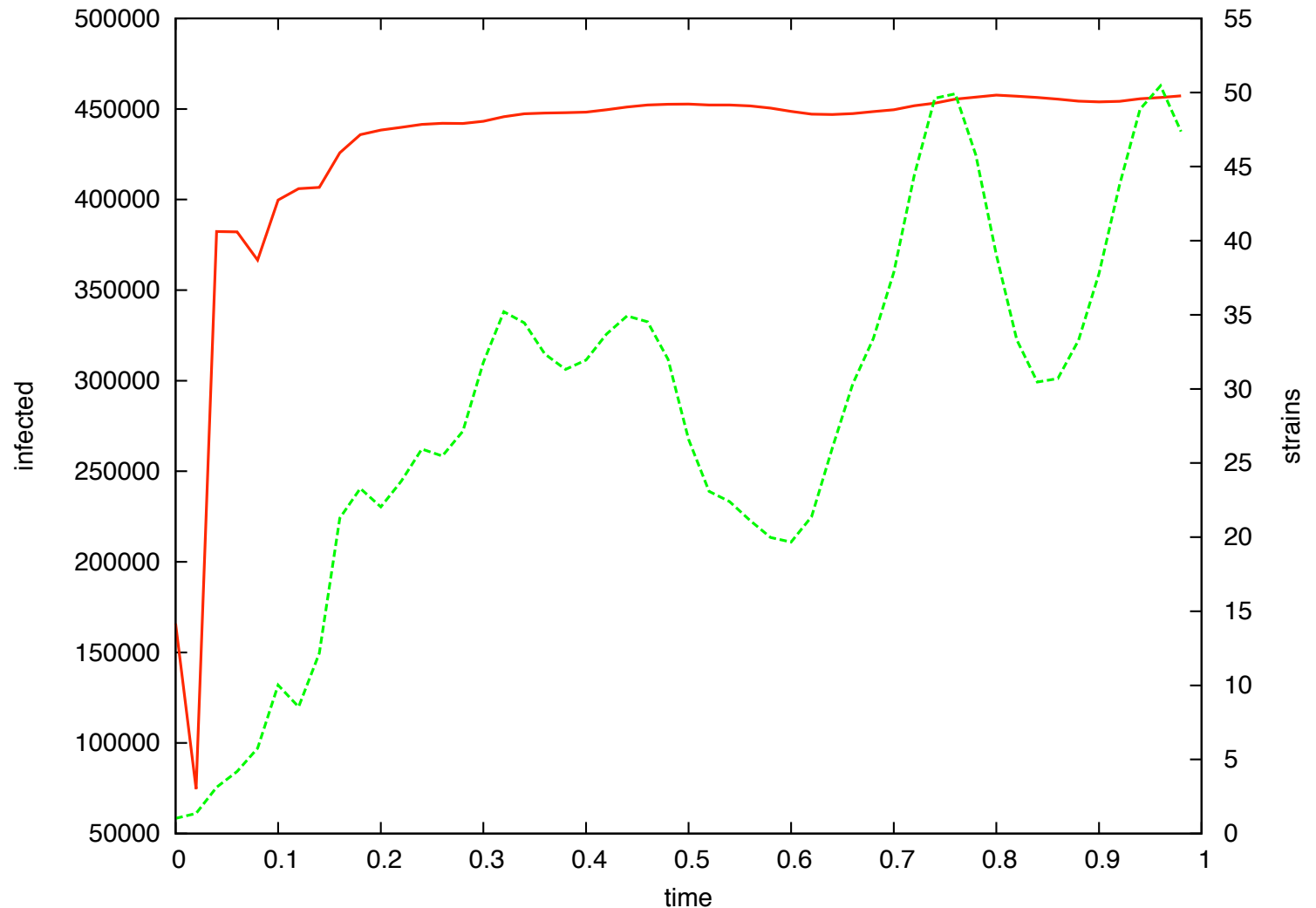
## Models

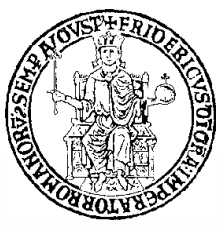
### A minimal model?

- ❖ Short term infinite-range immunity
- ❖ Modified bitstring model
- ❖ Observables
- ❖ Effects of short immunity: Prevalence and # strains
- ❖ **Random infectivity and no short immunity**
- ❖ Random infectivity and short immunity
- ❖ Random infectivity and short immunity
- ❖ Phylogenetic tree
- ❖ Comments

## Clusters

## Conclusions





# Random infectivity and short immunity

[Introduction](#)

[Models](#)

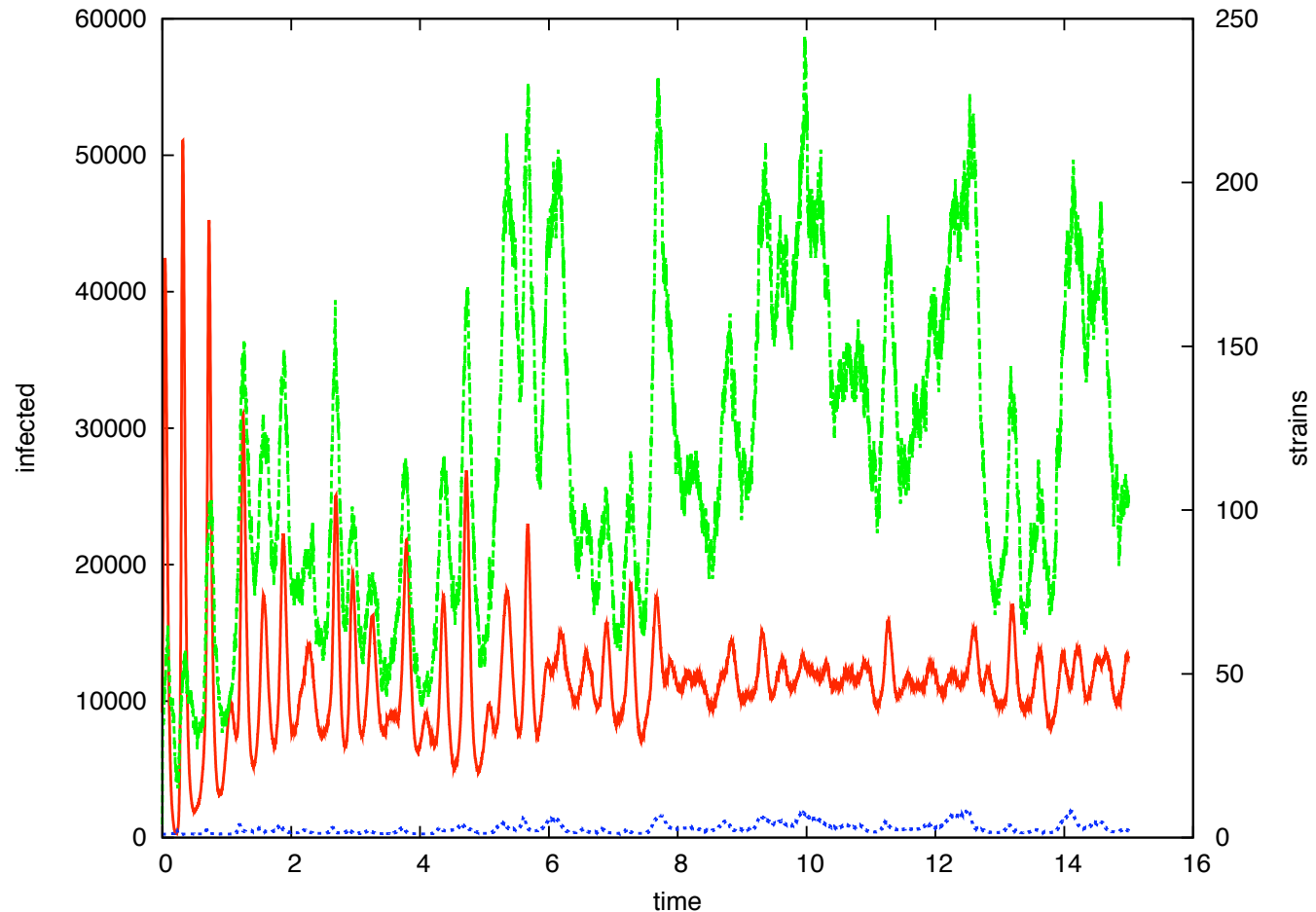
[A minimal model?](#)

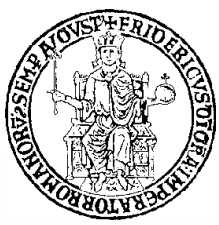
- ❖ Short term infinite-range immunity
- ❖ Modified bitstring model
- ❖ Observables
- ❖ Effects of short immunity: Prevalence and # strains
- ❖ Random infectivity and no short immunity
- ❖ **Random infectivity and short immunity**
- ❖ Random infectivity and short immunity
- ❖ Phylogenetic tree
- ❖ Comments

[Clusters](#)

[Conclusions](#)

## Prevalence and strain number





# Random infectivity *and* short immunity

[Introduction](#)

[Models](#)

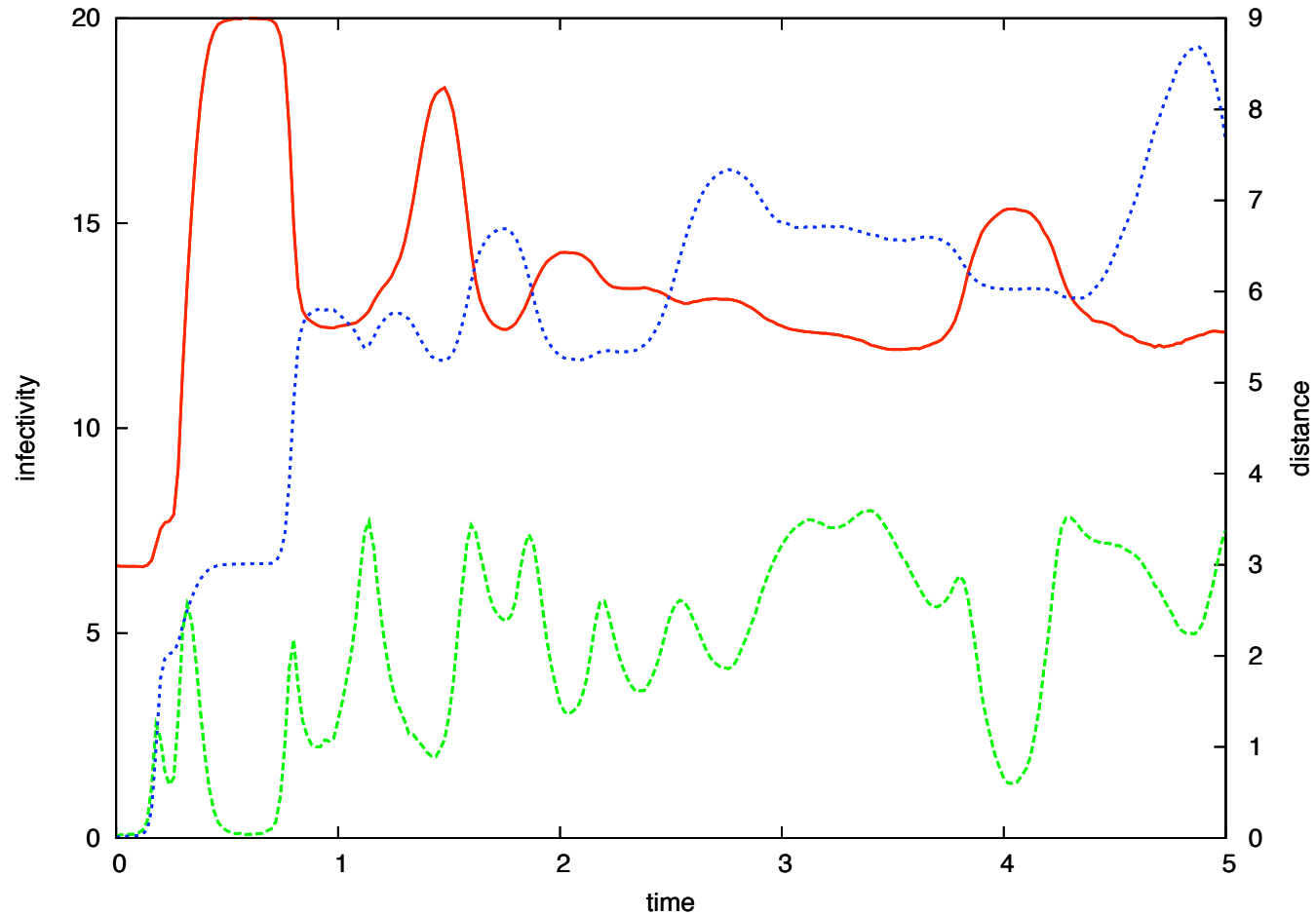
[A minimal model?](#)

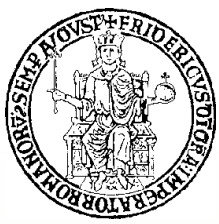
- ❖ Short term infinite-range immunity
- ❖ Modified bitstring model
- ❖ Observables
- ❖ Effects of short immunity: Prevalence and # strains
- ❖ Random infectivity and no short immunity
- ❖ Random infectivity **and** short immunity
- ❖ Random infectivity **and** short immunity
- ❖ Phylogenetic tree
- ❖ Comments

[Clusters](#)

[Conclusions](#)

## Average infectivity and Hamming distance





# Phylogenetic tree

## Introduction

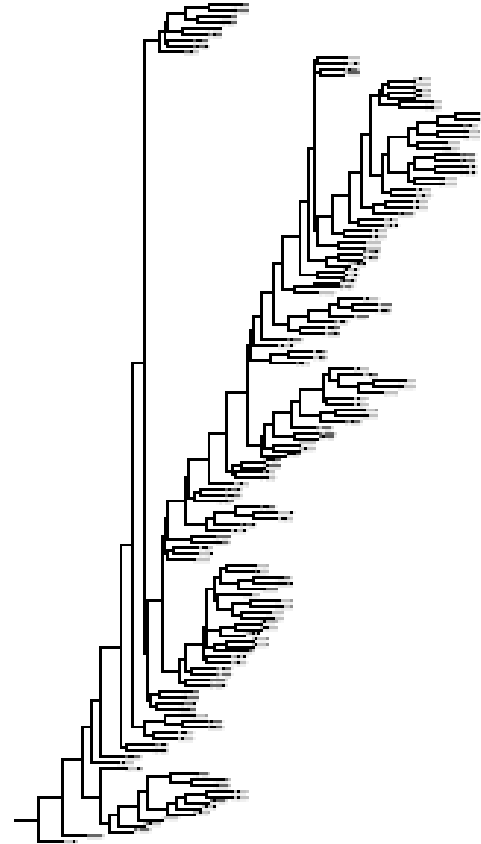
## Models

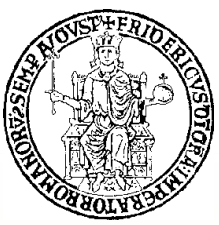
### A minimal model?

- ❖ Short term infinite-range immunity
- ❖ Modified bitstring model
- ❖ Observables
- ❖ Effects of short immunity:  
Prevalence and # strains
- ❖ Random infectivity and no short immunity
- ❖ Random infectivity **and** short immunity
- ❖ Random infectivity **and** short immunity
- ❖ **Phylogenetic tree**
- ❖ Comments

## Clusters

## Conclusions





# Comments

Introduction

Models

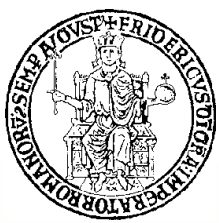
A minimal model?

- ❖ Short term infinite-range immunity
- ❖ Modified bitstring model
- ❖ Observables
- ❖ Effects of short immunity:  
Prevalence and # strains
- ❖ Random infectivity and no short immunity
- ❖ Random infectivity **and** short immunity
- ❖ Random infectivity **and** short immunity
- ❖ Phylogenetic tree
- ❖ **Comments**

Clusters

Conclusions

- 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

Introduction

Models

A minimal model?

Clusters

❖ Clusters

❖ Seasonality

❖ Epochal evolution:  
Cluster transitions

❖ Effects of cluster  
transitions

❖ Clusters trees and  
their relations

❖ Simulations

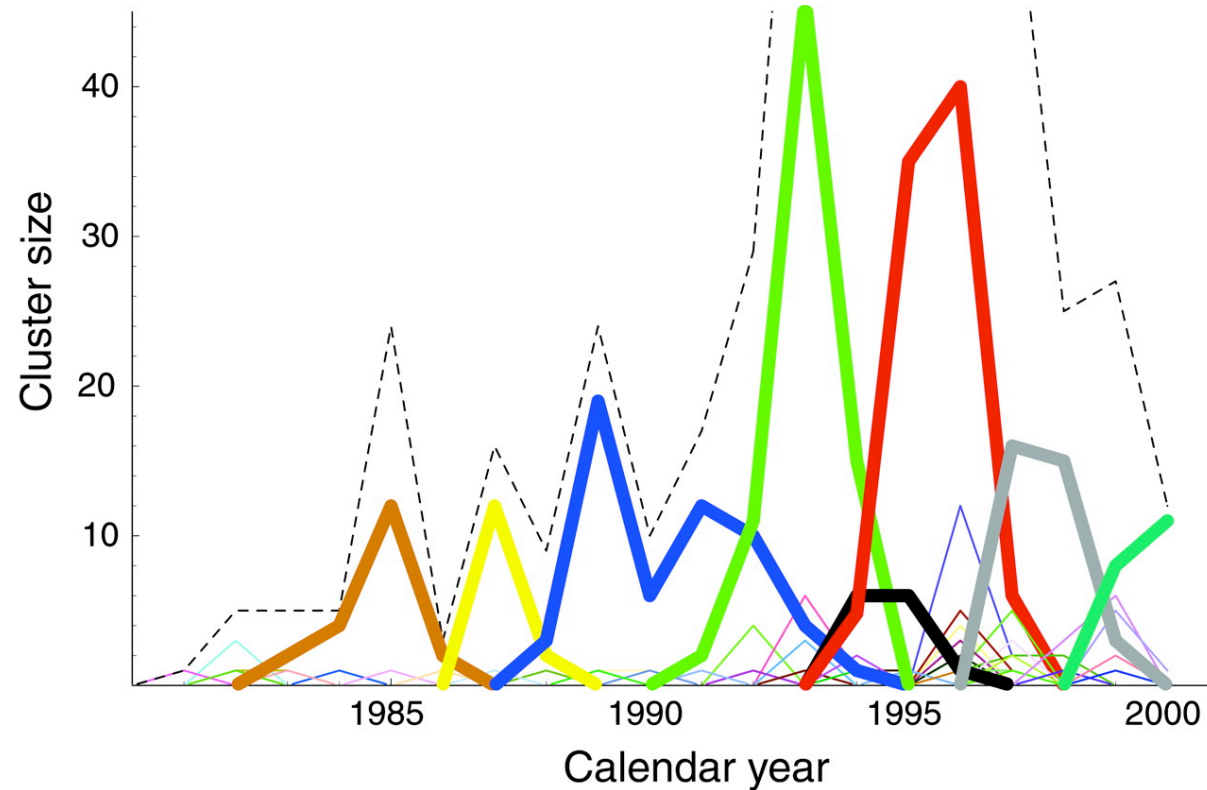
❖ “Influenza  
escapes immunity  
along neutral  
networks”

❖ Antigenic types

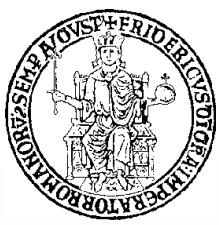
❖ Explanation

Conclusions

*Plotkin, Dushoff and Levin, 2002*



Clusters identified via genetic distance of sequences



# Seasonality

Introduction

Models

A minimal model?

Clusters

❖ Clusters

❖ **Seasonality**

❖ Epochal evolution:

Cluster transitions

❖ Effects of cluster transitions

❖ Clusters trees and their relations

❖ Simulations

❖ "Influenza escapes immunity along neutral networks"

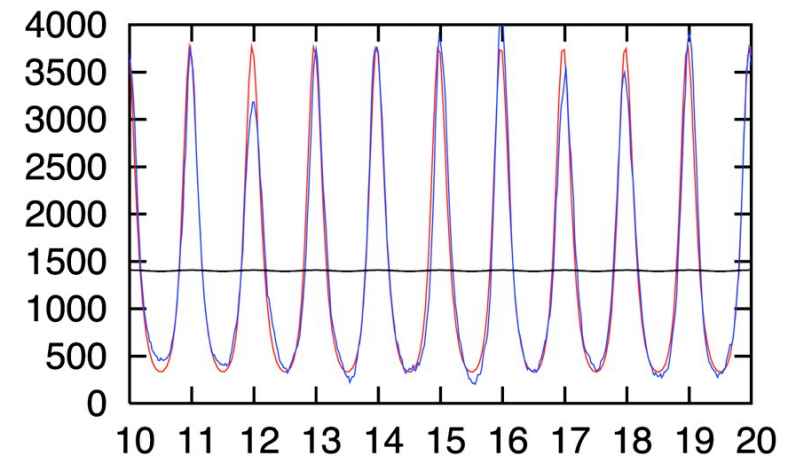
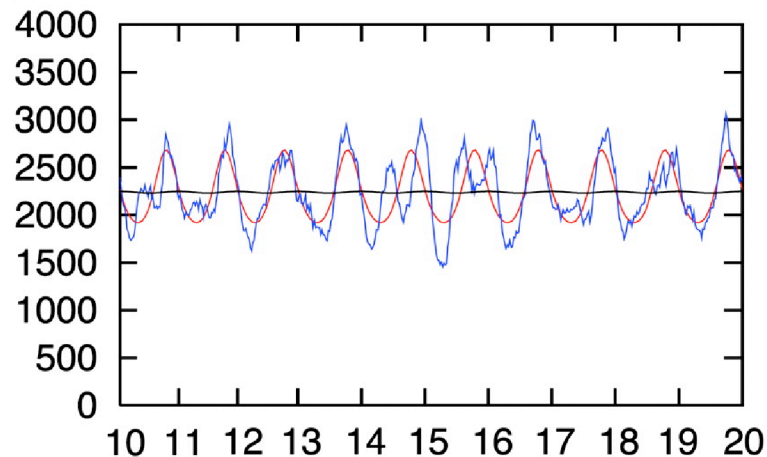
❖ Antigenic types

❖ Explanation

Conclusions

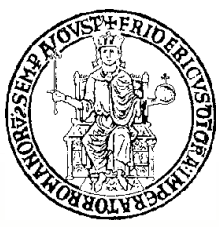
Is the strong seasonality of influenza epidemics linked to the limited duration of immunity due to clusters?

*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

Introduction

Models

A minimal model?

Clusters

❖ Clusters

❖ Seasonality

❖ Epochal evolution:  
Cluster transitions

❖ Effects of cluster  
transitions

❖ Clusters trees and  
their relations

❖ Simulations

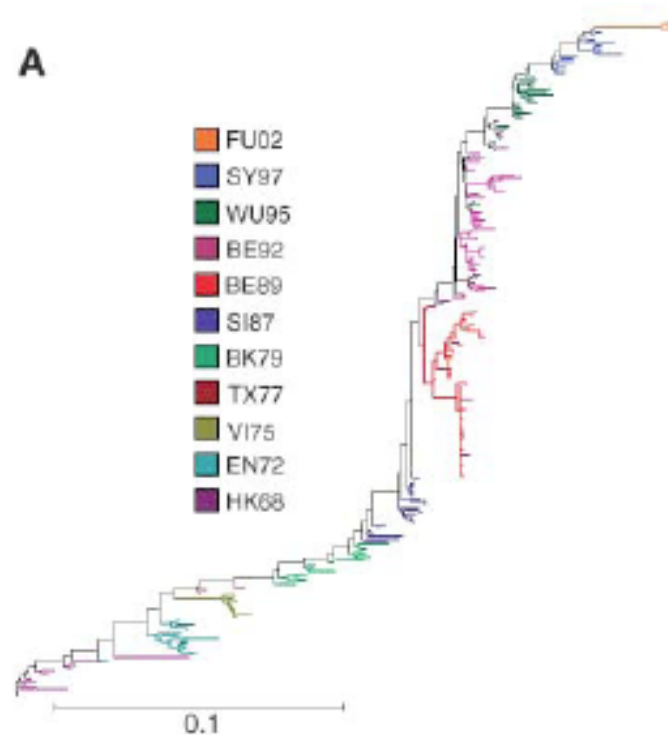
❖ “Influenza  
escapes immunity  
along neutral  
networks”

❖ Antigenic types

❖ Explanation

Conclusions

Koelle, Cobey, Grenfell and Pascual, 2006



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



# Effects of cluster transitions

Introduction

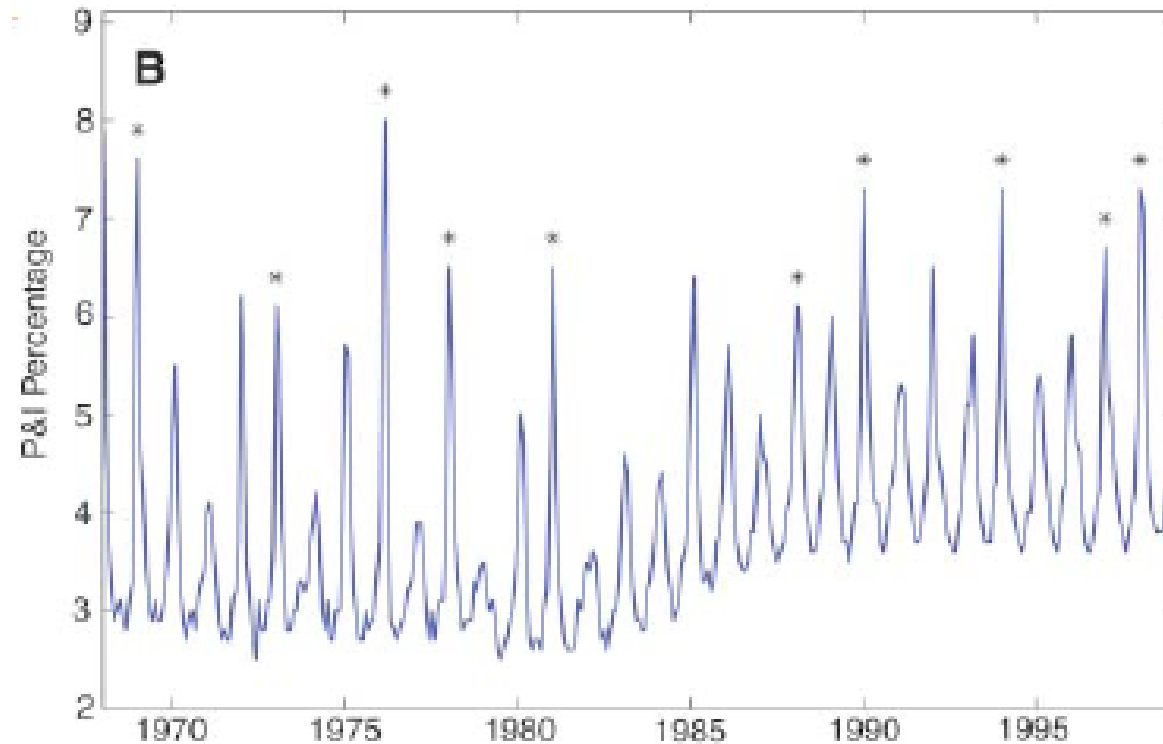
Models

A minimal model?

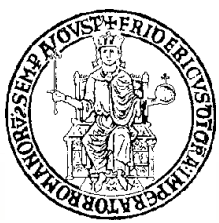
Clusters

- ❖ Clusters
- ❖ Seasonality
- ❖ Epochal evolution:  
Cluster transitions
- ❖ **Effects of cluster transitions**
- ❖ Clusters trees and their relations
- ❖ Simulations
- ❖ “Influenza escapes immunity along neutral networks”
- ❖ Antigenic types
- ❖ Explanation

Conclusions



Death rate series: Stars denote times after a cluster transition



# Clusters trees and their relations

## Introduction

## Models

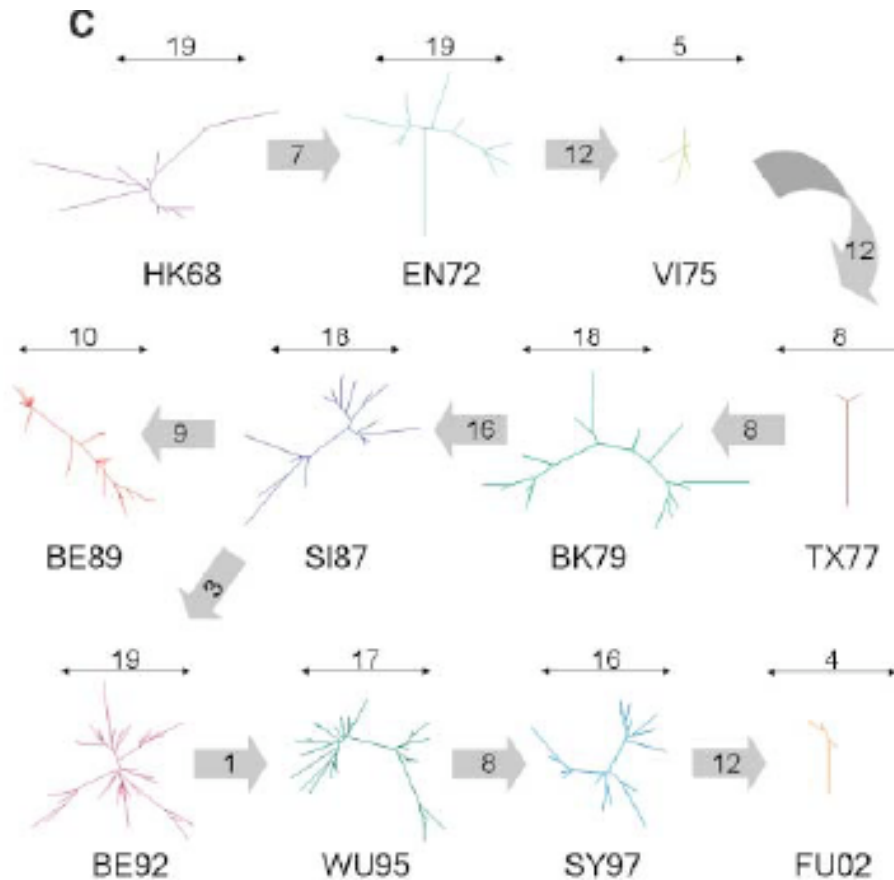
## A minimal model?

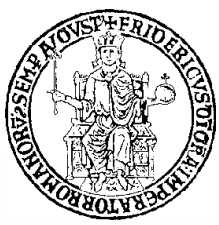
## Clusters

- ❖ Clusters
- ❖ Seasonality
- ❖ Epochal evolution: Cluster transitions
- ❖ Effects of cluster transitions
- ❖ **Clusters trees and their relations**

- ❖ Simulations
- ❖ “Influenza escapes immunity along neutral networks”
- ❖ Antigenic types
- ❖ Explanation

## Conclusions





# Simulations

Introduction

Models

A minimal model?

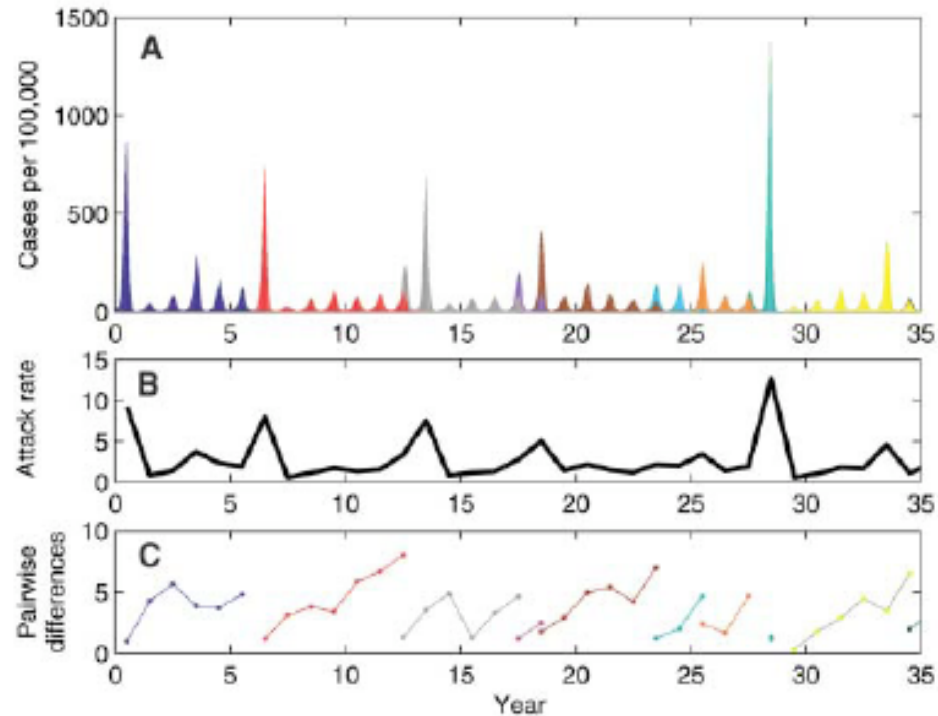
Clusters

- ❖ Clusters
- ❖ Seasonality
- ❖ Epochal evolution:  
Cluster transitions
- ❖ Effects of cluster  
transitions
- ❖ Clusters trees and  
their relations

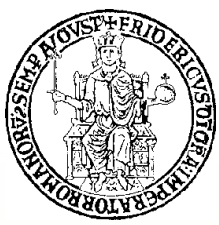
**❖ Simulations**

- ❖ “Influenza  
escapes immunity  
along neutral  
networks”
- ❖ Antigenic types
- ❖ Explanation

Conclusions



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



# “Influenza escapes immunity along neutral networks”

van Nimwegen, 2006

Introduction

Models

A minimal model?

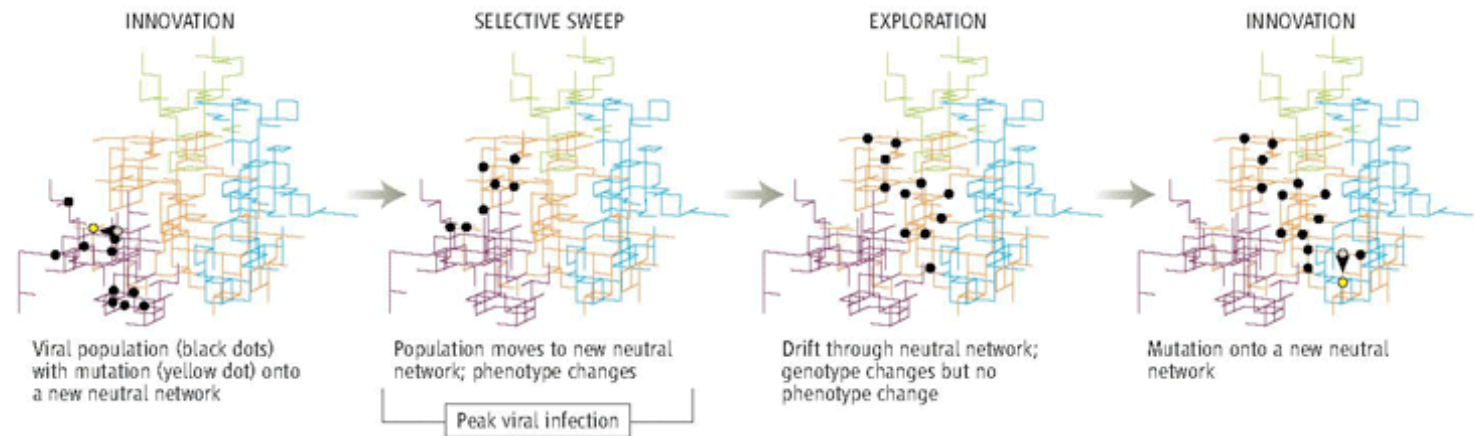
Clusters

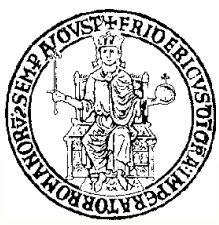
- ❖ Clusters
- ❖ Seasonality
- ❖ Epochal evolution: Cluster transitions
- ❖ Effects of cluster transitions
- ❖ Clusters trees and their relations
- ❖ Simulations

❖ “Influenza escapes immunity along neutral networks”

- ❖ Antigenic types
- ❖ Explanation

Conclusions

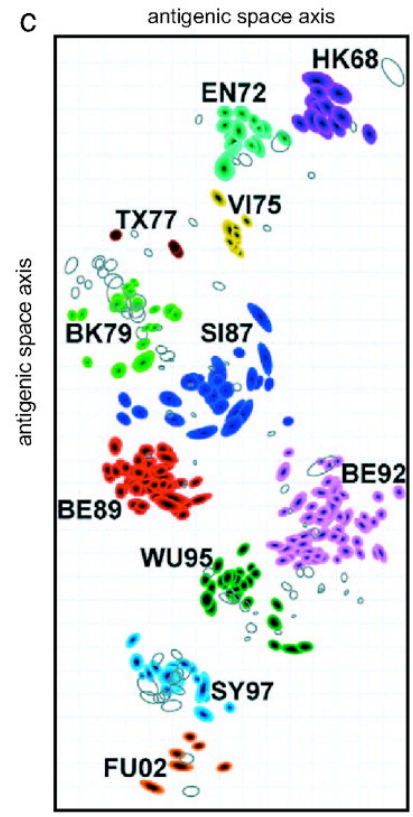
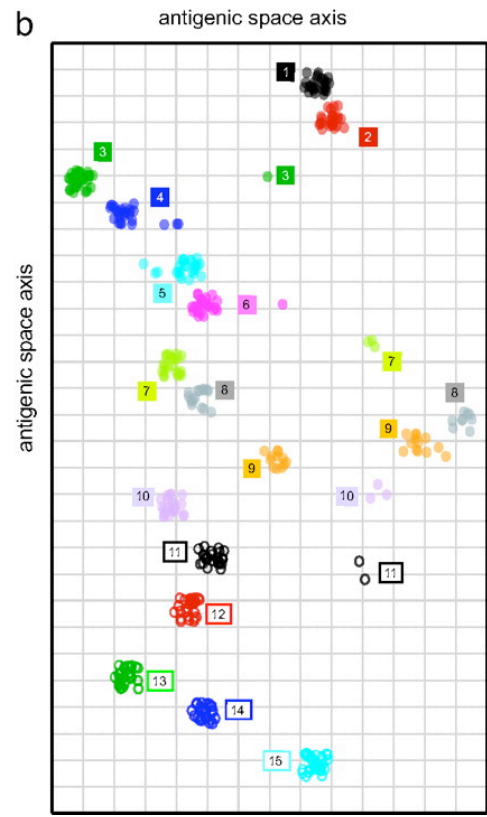




# Antigenic types

Recker, Pybus, Nee and Gupta, 2007

- Introduction
- Models
- A minimal model?
- Clusters
  - ❖ Clusters
  - ❖ Seasonality
  - ❖ Epochal evolution: Cluster transitions
  - ❖ Effects of cluster transitions
  - ❖ Clusters trees and their relations
  - ❖ Simulations
  - ❖ “Influenza escapes immunity along neutral networks”
- ❖ Antigenic types**
- ❖ Explanation
- Conclusions



Left: simulations; Right: data



# Explanation

Introduction

Models

A minimal model?

Clusters

- ❖ Clusters
- ❖ Seasonality
- ❖ Epochal evolution:  
Cluster transitions
- ❖ Effects of cluster  
transitions
- ❖ Clusters trees and  
their relations
- ❖ Simulations
- ❖ “Influenza  
escapes immunity  
along neutral  
networks”
- ❖ Antigenic types
- ❖ **Explanation**

Conclusions

- 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

[Introduction](#)

[Models](#)

[A minimal model?](#)

[Clusters](#)

[Conclusions](#)

❖ [Comments](#)

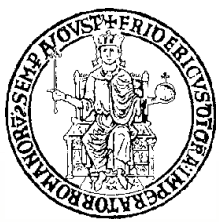
❖ [Conclusions](#)

❖ [Thanks](#)

❖ [Bibliography](#)

- The “antigenic space” has a more complex 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 models do not take into account recombination which is *known* to take place during epidemics





# Conclusions

[Introduction](#)

[Models](#)

[A minimal model?](#)

[Clusters](#)

[Conclusions](#)

❖ [Comments](#)

❖ [Conclusions](#)

❖ [Thanks](#)

❖ [Bibliography](#)

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



# Conclusions

[Introduction](#)

[Models](#)

[A minimal model?](#)

[Clusters](#)

[Conclusions](#)

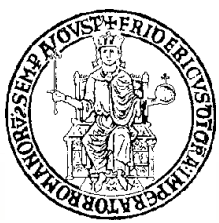
❖ [Comments](#)

❖ [Conclusions](#)

❖ [Thanks](#)

❖ [Bibliography](#)

- 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



# Conclusions

[Introduction](#)

[Models](#)

[A minimal model?](#)

[Clusters](#)

[Conclusions](#)

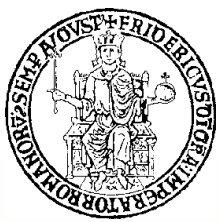
❖ [Comments](#)

❖ [Conclusions](#)

❖ [Thanks](#)

❖ [Bibliography](#)

- 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!



# Thanks

Introduction

Models

A minimal model?

Clusters

Conclusions

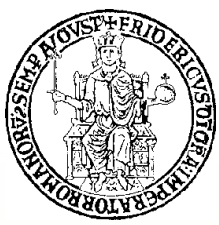
❖ Comments

❖ Conclusions

❖ **Thanks**

❖ Bibliography

- W. Fitch, who introduced me to this problem
- M. Lässig, for long-lasting collaboration and frequent discussions
- S. Franz and F. Tria, for collaboration



# Bibliography

[Introduction](#)

[Models](#)

[A minimal model?](#)

[Clusters](#)

[Conclusions](#)

❖ [Comments](#)

❖ [Conclusions](#)

❖ [Thanks](#)

❖ [Bibliography](#)

D.J. Earn, J. Dushoff, S. Levin, *Trends Ecol. Evol.* **17**, 334 (2002)

W. M. Fitch, R. M. Bush, C. A. Bender, N. J. Cox, *PNAS* **94**, 7712 (1997)

R.M. Bush, C.A. Bender, K. Subbarao, N.J. Cox, W.M. Fitch, *Science* **286**, 1921 (1999)

B.T. Grenfell *et al.*, *Science* **303**, 327 (2004)

W.O. Kermack, A.G. McKendrick, *Proc. Roy. Soc. Lond.* **A 115**, 700 (1927)

V. Andreasen, J. Lin, S.A. Levin, *J. Math. Biol.* **35**, 825 (1997)

J.R. Gog, B.T. Grenfell, *PNAS* **99**, 17209 (2002)

J. Lin, V. Andreasen, R. Casagrandi, S.A. Levin, *J. Theor. Biol.* **222**, 437 (2003)

M.Girvan, D.S. Callaway, M.E.J. Newman, S.H. Strogatz, *Phys. Rev. E* **65**, 031915 (2002)

N.M. Ferguson, A.P. Galvani, R.M. Bush, *Nature* **422**, 428 (2003)

F. Tria, M. Lässig, L. Peliti, S. Franz, *J. Stat. Mech.* **1** P07008 (2005)

J. Plotkin, J. Dushoff, S.A. Levin, *PNAS* **99**, 6263 (2002)

J. Dushoff, J.B. Plotkin, S.A. Levin, D.J.D. Earn, *PNAS* **101**, 16915 (2004)

K. Koelle, S. Cobey, B. Grenfell, M. Pascual, *Science* **314**, 1898 (2006)

D. J. Smith *et al.*, *Science* **305**, 371 (2004)

E. van Nimwegen, *Science* **314**, 1884 (2006)

M. Recker, O.G. Pybus, S. Nee, S. Gupta, *PNAS* **104**, 7711 (2007)