Challenges calculatoires et de modélisation posés par l'épidémiologie des maladies infectieuses

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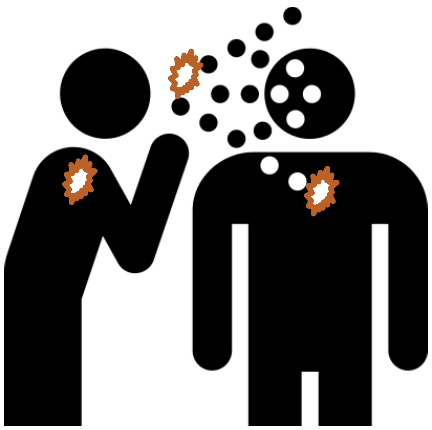
Forum Teratec, 28 juin 2017

Infectious disease epidemiology

INFECTIOUS DISEASES



- Transmissible disease +
  Introduction of a microbe in the body

- Microbes
  - Bacteria, virus, parasite, …

- Examples
  - Virus: VIH, flu, Ebola, Varicella, …
  - Bacteria: Meningococcus, *S. aureus, C Trachomatis* …
  - Parasite: Malaria, …

Transmission

- Direct
  - Airborne
  - Skin (hand carriage)
  - Blood *(HIV, hepatitis C…)*
  - Sexually *(HIV)*
  - At birth

- Indirect (intermediate vector) :
  - Inanimate (*water, food, soil, objects*)
  - Animate, *insect bits (malaria, zika), animal (rabies)*

EPIDEMIOLOGY

Study of diseases in populations

Study of the factors at the origin of diseases

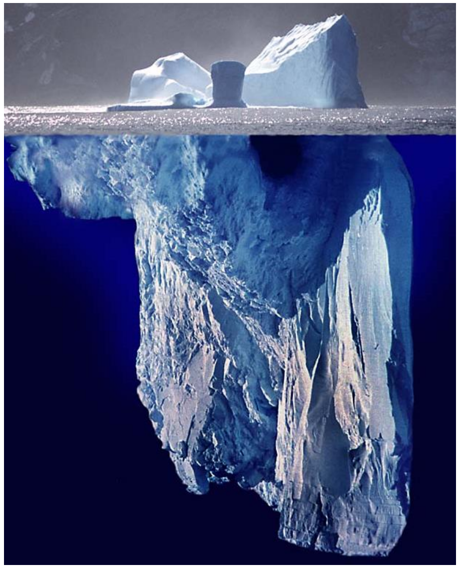
$\Rightarrow$ Populations $\neq$ Individuals

PUBLIC HEALTH: ACTIONS TO FIGHT AN EPIDEMICS

- **Medical actions :**
  - Vaccination
  - Disinfection
  - Antibiotics
  - Isolation, quarantine

- **Other actions**
  - Hygiene
  - School closure, transport limitation
  - Masks

Motivation for modelling



wikipedia

- **Disease transmission** is a dynamic and mechanistic process
- Collected data is partial

  Need to take into account unobserved phenomenon (eg. transmission)

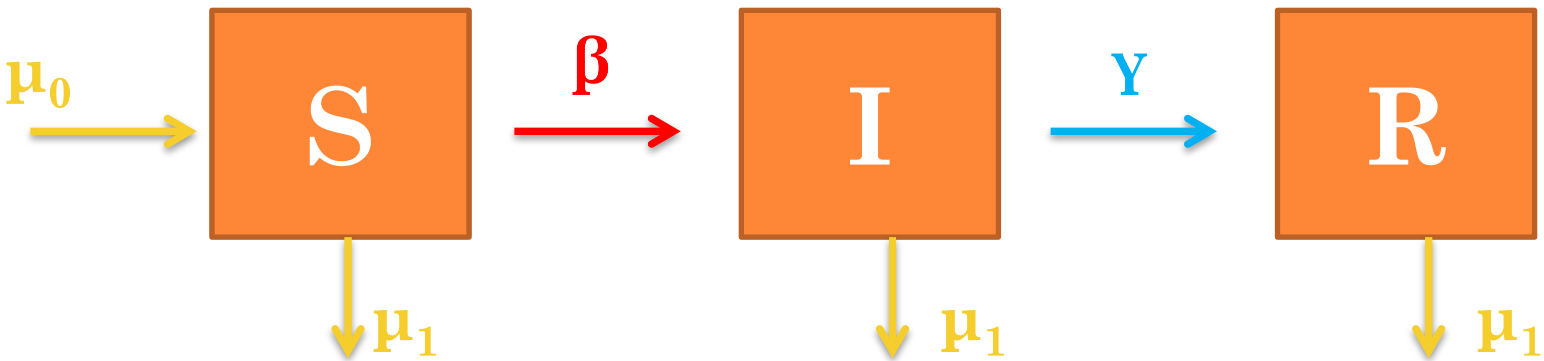
  => Consider the problem as whole
- Experiments: carrying out studies in populations
  - Expensive
  - Sometimes not feasible (ethics)

  => *in silico* experiments

Modelling the transmission of infectious diseases

Référence: the SIR model

- **Disease with lifelong immunity**



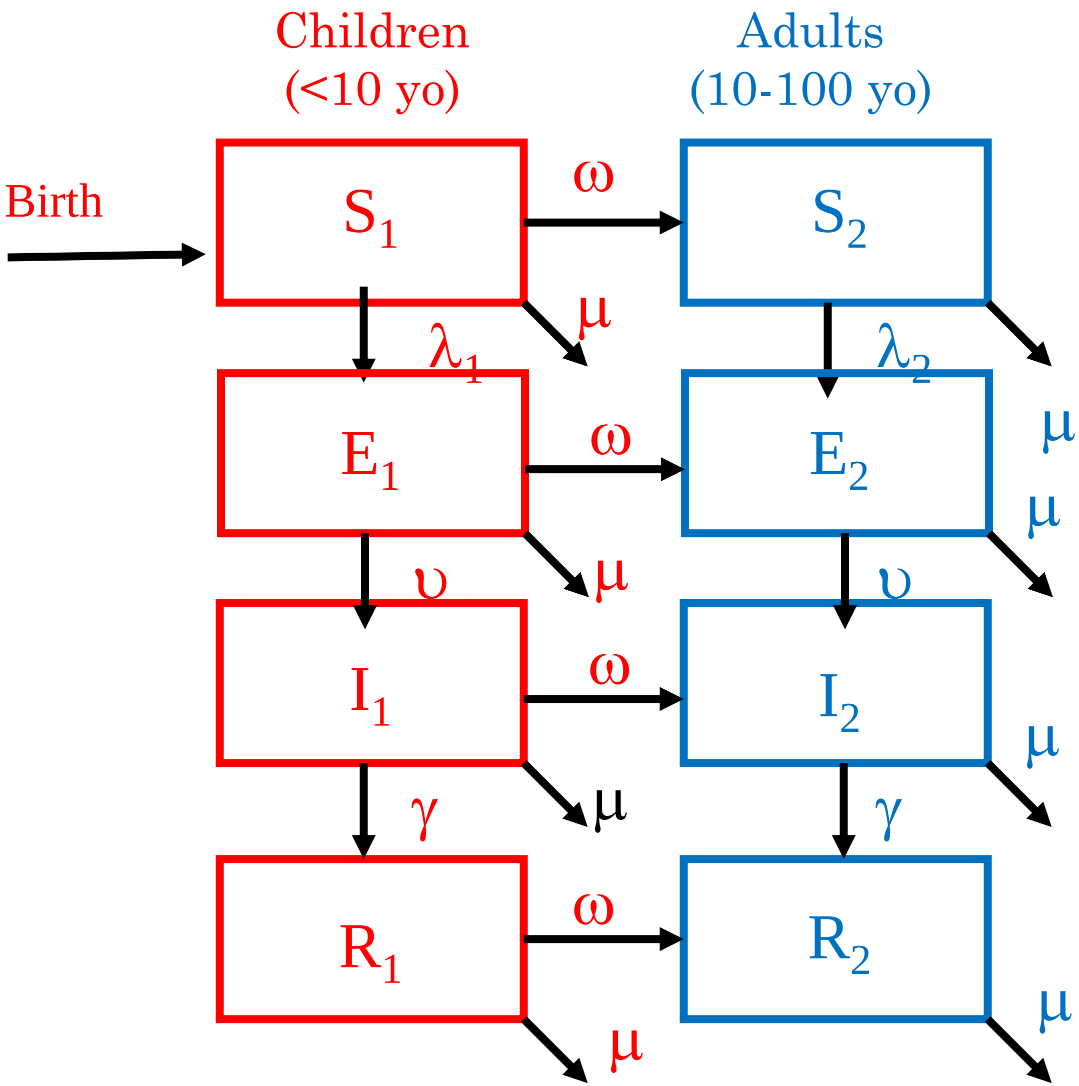
S : susceptible
I : infected
R : recovered

$$\begin{cases} \dfrac{dS}{dt} = \mu_0(S+I+R) - \beta S\dfrac{I}{N} - \mu_1 S \\ \dfrac{dI}{dt} = \beta S\dfrac{I}{N} - \gamma I - \mu_1 I \\ \dfrac{dR}{dt} = \gamma I - \mu_1 R \\ N = S+I+R \end{cases}$$

μ_0 : natality
μ_1 : death
β : transmission
γ : recovery rate

Extension – measle

- Structured on age + « incubation » state



$$\frac{dS_1}{dt} = birth - S_1(\beta_{11}I_1 + \beta_{12}I_2) - (\mu + \omega)S_1$$

$$\frac{dS_2}{dt} = \omega S_1 - S_2(\beta_{21}I_1 + \beta_{22}I_2) - \mu S_2$$

$$\frac{dE_1}{dt} = S_1(\beta_{11}I_1 + \beta_{12}I_2) - (\mu + \omega + \upsilon)E_1$$

$$\frac{dE_2}{dt} = S_2(\beta_{21}I_1 + \beta_{22}I_2) - (\mu + \upsilon)E_2$$

$$\frac{dI_1}{dt} = \upsilon I_1 - (\mu + \omega + \gamma)I_1$$

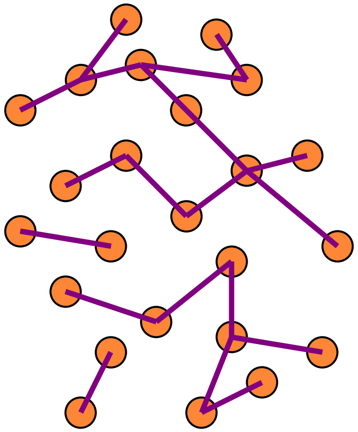
$$\frac{dI_2}{dt} = \upsilon I_2 - (\mu + \gamma)I_2$$

$$\frac{dR_1}{dt} = \gamma I_1 - \mu R_1 - \omega R_1$$

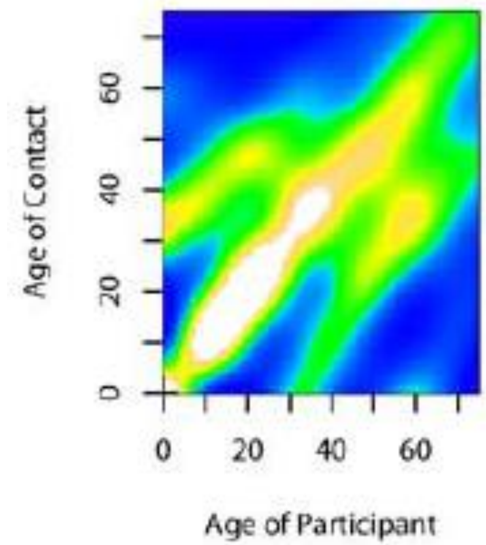
$$\frac{dR_2}{dt} = \gamma I_2 - \mu R_2 - \omega R_1$$

Homogeneous mixing … an unrealistic hypothesis

Sexual network

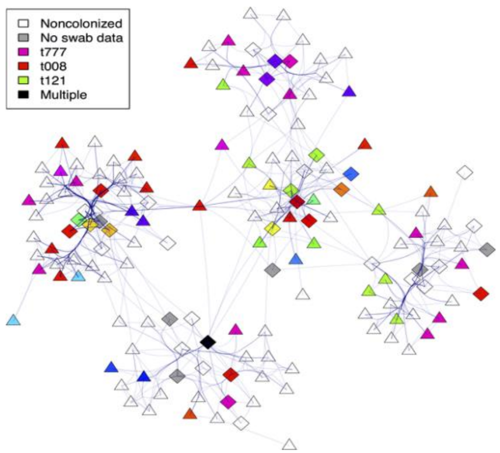


Air borne transmission



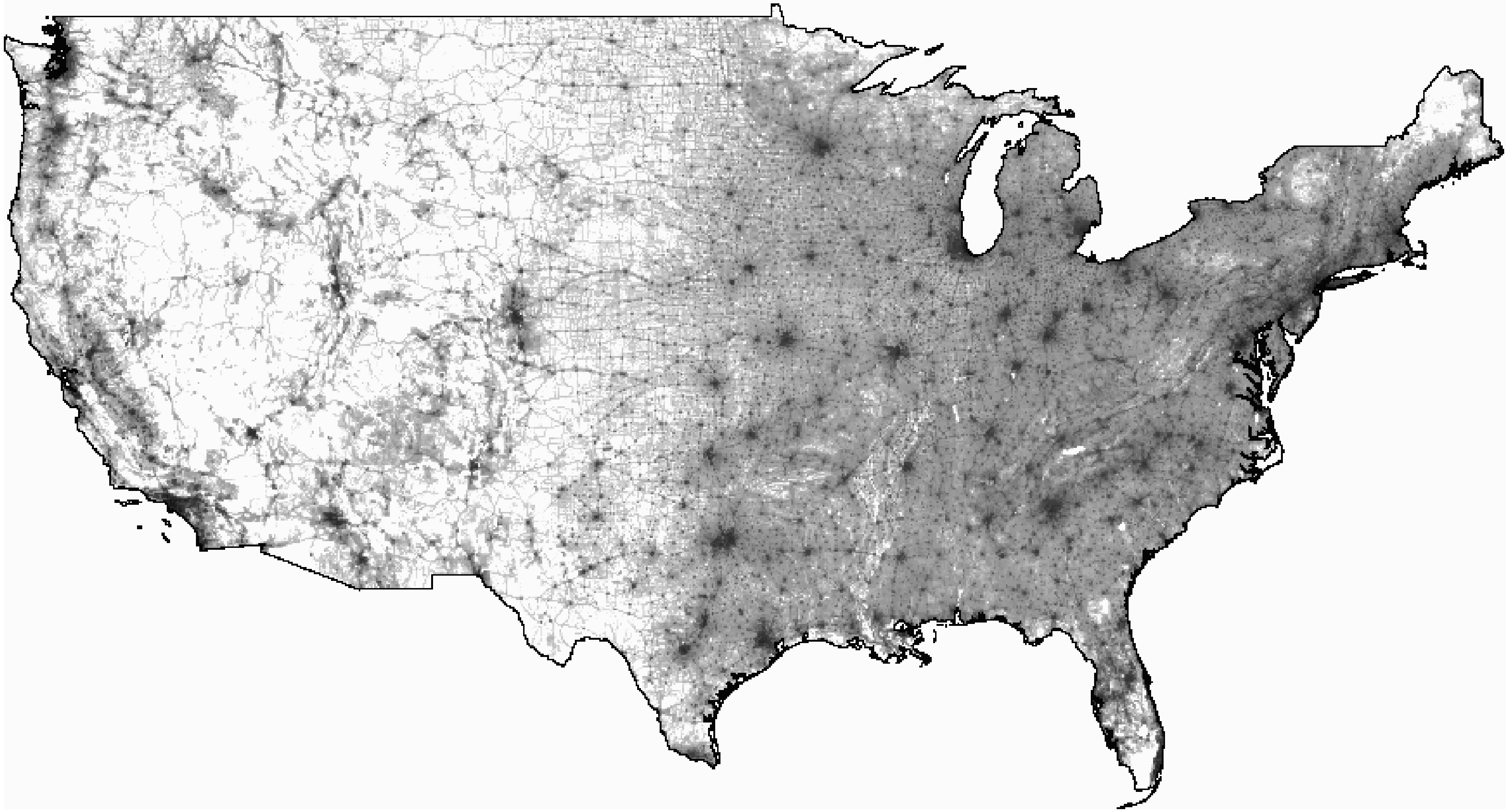
[Mossong et al PLoS Med (2008)]

Hospital network



ALTERNATIVE APPROACH – AGENT BASED MODELLING

Individuals are specifically modelled. The global dynamics is then studied.



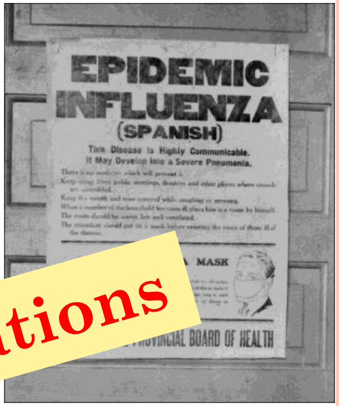
Ferguson et al, Nature 2006

OBJECTIVES OF MODELLING

- **Better understand phenomenon at stake**
  - Transmission routes, at risk behaviors, natural history of disease

Statistical inference

- **Anticipate the impact of interventions, optimization**
  - *Eg*. Influenza pandemics
    - School closure?
    - Transport limitation?
    - If vaccine available, who should be vaccinated in priority? Babies? Elderly? Health care workers?



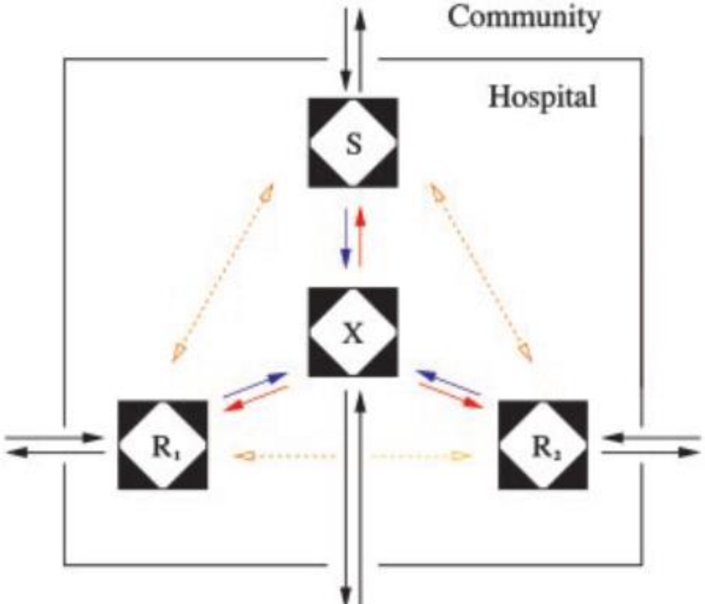
Simulations

- **Support for decision making** (in real time)
  - Public health
  - Prescription

Modelling and computational challenges

1) Population vs individuals, a matter of size

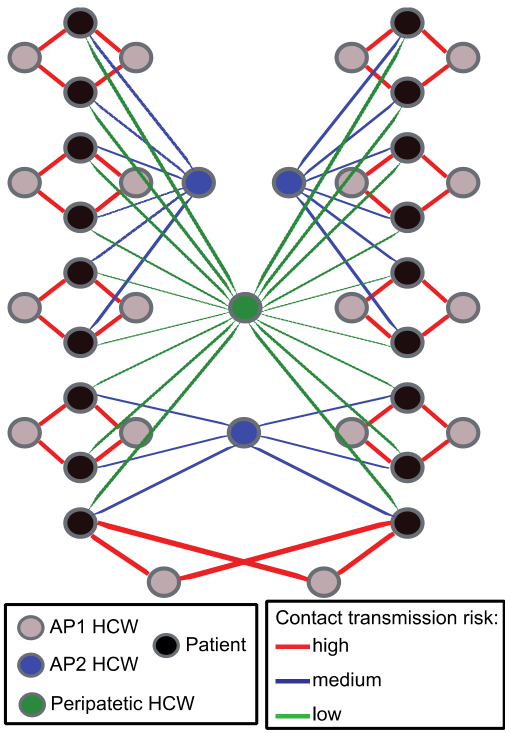
- Example hospital model



(Bonhoeffer et al, PNAS 1997)
(Bergstrom et al, PNAS 2004)

4 differential equations, ~10 parameters

Network of contact in the ICU



Peripatetic health-care workers as potential superspreaders

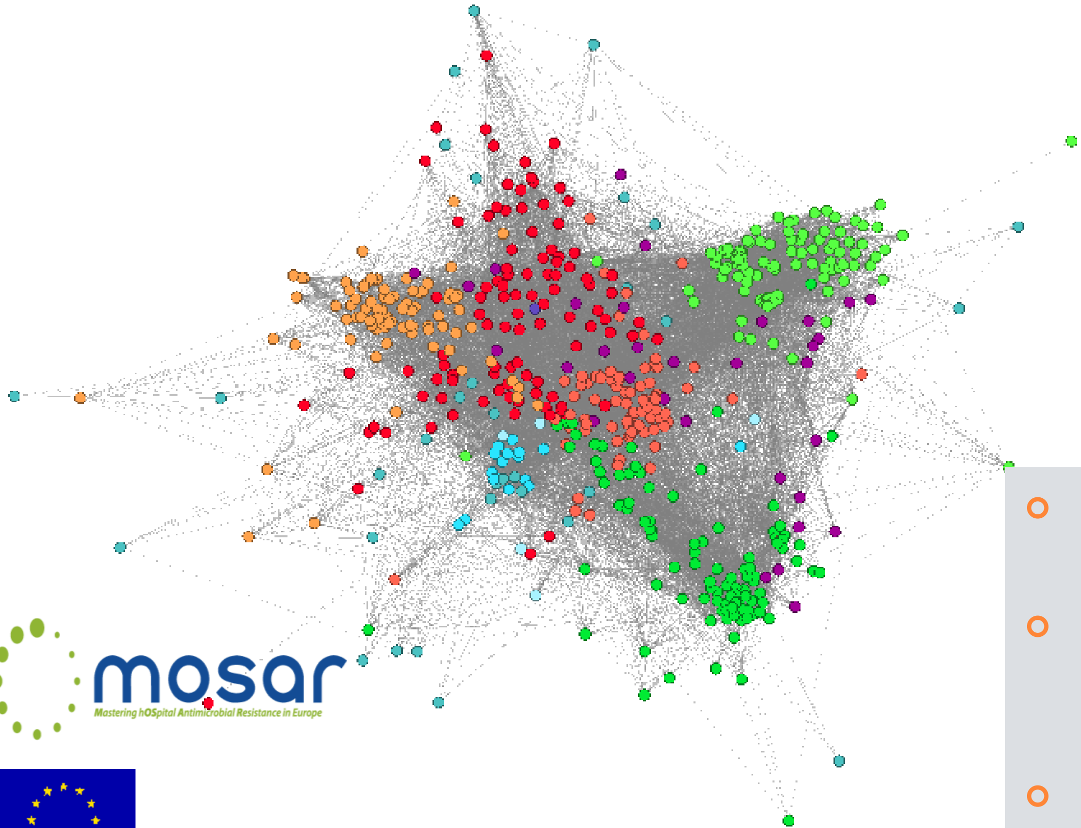
Laura Temime, Lulla Opatowski, Yohan Pannet, Christian Brun-Buisson, Pierre Yves Boelle and Didier Guillemot

18420–18428 | PNAS | October 27, 2009 | vol. 106 | no. 43 www.pnas.org/cgi/doi/10.1073/pnas.0900974106

~25 agents, 4 different types, >30 parameters, time step: 1 min

… And a matter of available data! Hospital: real networks

- Ibird study : log-censors carried by all health care workers and patients in Berck hospital for 4 months



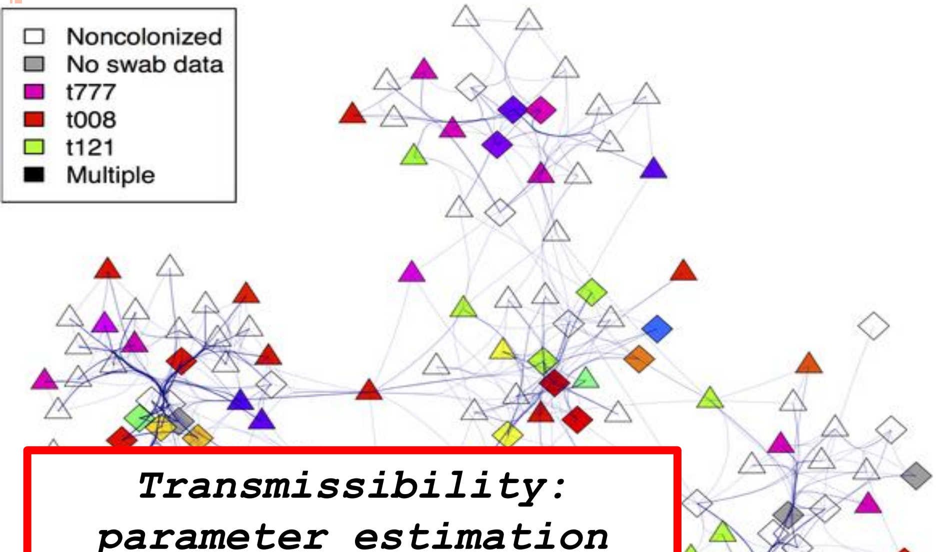
Guillemot et al.

- 800 individuals followed up for 4 months
- Nasal and rectal swabs collected every week => 6623 nasal swabs and 2497 stool samples
- >1,350,104 proximity signals of 30 sec eq. to 167,107 days of contacts between participants.

mosar
Mastering hOSpital Antimicrobial Resistance in Europe

Sixth Framework Programme

Data analysis



PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Detailed Contact Data and the Dissemination of *Staphylococcus aureus* in Hospitals

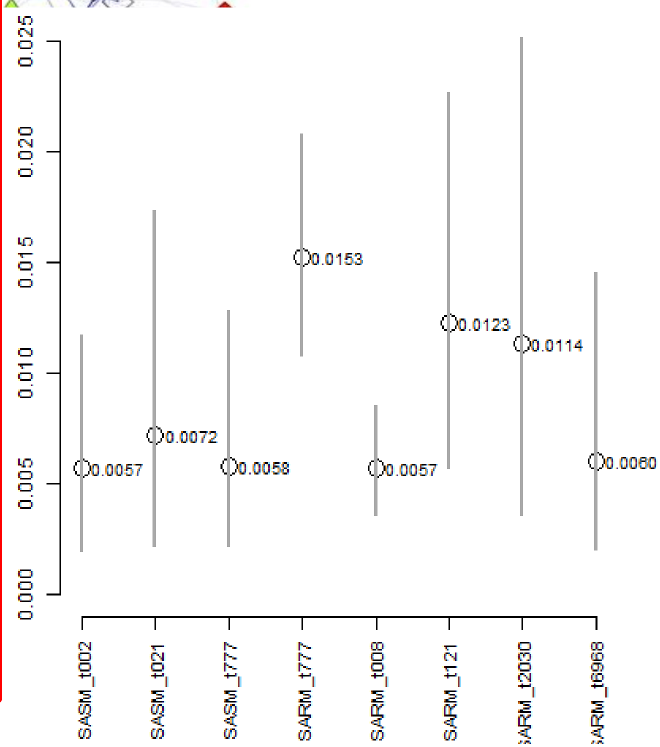
Thomas Obadia[1,2]*, Romain Silhol[3], Lulla Opatowski[4,5,6], Laura Temime[7], Judith Legrand[8], Anne C. M. Thiébaut[4,5,6], Jean-Louis Herrmann[9,10], Éric Fleury[11,12], Didier Guillemot[4,5,6,13], Pierre-Yves Boëlle[1,2,14]*, on behalf of the I-Bird Study Group[¶]

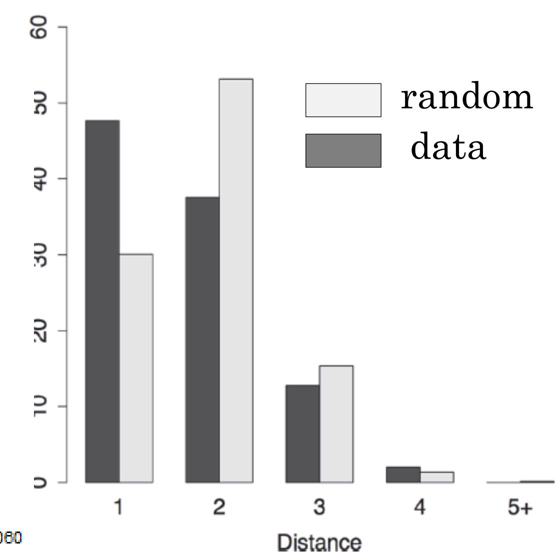
Transmissibility: parameter estimation using MCMC

8 unknown parameters
>50 augmented data
Time step: 1 day
MCMC: 1.10^6 steps
Execution time ~ 1 week on cluster

Challenges

Additional parameters
Augmentation data on the network





2) Individual based simulation of HPV transmission to assess the impact of vaccination

- Human papillomavirus, sexual transmission
- Vaccine available (protects against HPV16 & HPV18)
- Model :
  - Sexually active heterosexual population between 15 and 30 years
  - Introduction of vaccination scenarios in 13 year-old girls

Sexual behavior characteristics

- Virgin
- Single
- In couple

Infectious state characteristics (V & NV)

- Susceptible
- Infected
- Immunized following infection
- Vaccinated

HPV MODEL

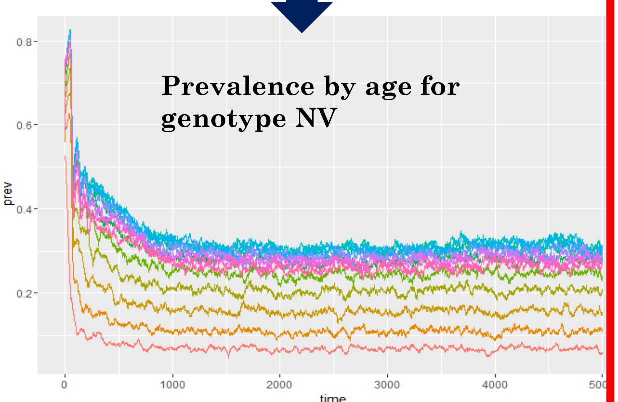
Parameterization

HPV Natural history

Data from sociological studies: **Sexual behaviors**

Calibration: Prevalence as a function of age (pre-vaccine era)

Individual data infectious state, age, gender …



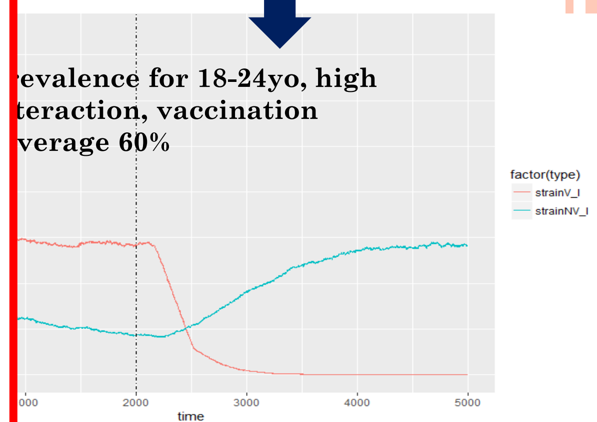
Simulation

~30 parameters
80,000 individuals
5000 weeks
Execution time: 10 min on computer
>100 simulations

Challenge

- Population size
- 2 genotypes included only, 100 identified!

Simulation of scenarios

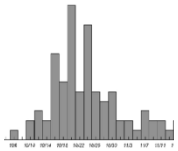


3) Major challenge: multi-scale process

Population

Between-host transmission (heterogeneous)

Public health policies



Individuals

Colonization/infection of ecosystems
(gut, skin, naso-, oro-pharynx)

Infection

Immunity

Drug exposure (vaccine, antibiotics)

Cell, microorganism

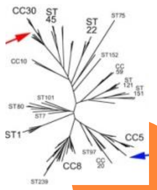
Genetic evolution :

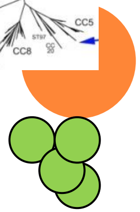
Mutations, genes transfer

Ecology of pathogens:

Colonies, cellular organization

Interactions, competition and synergy

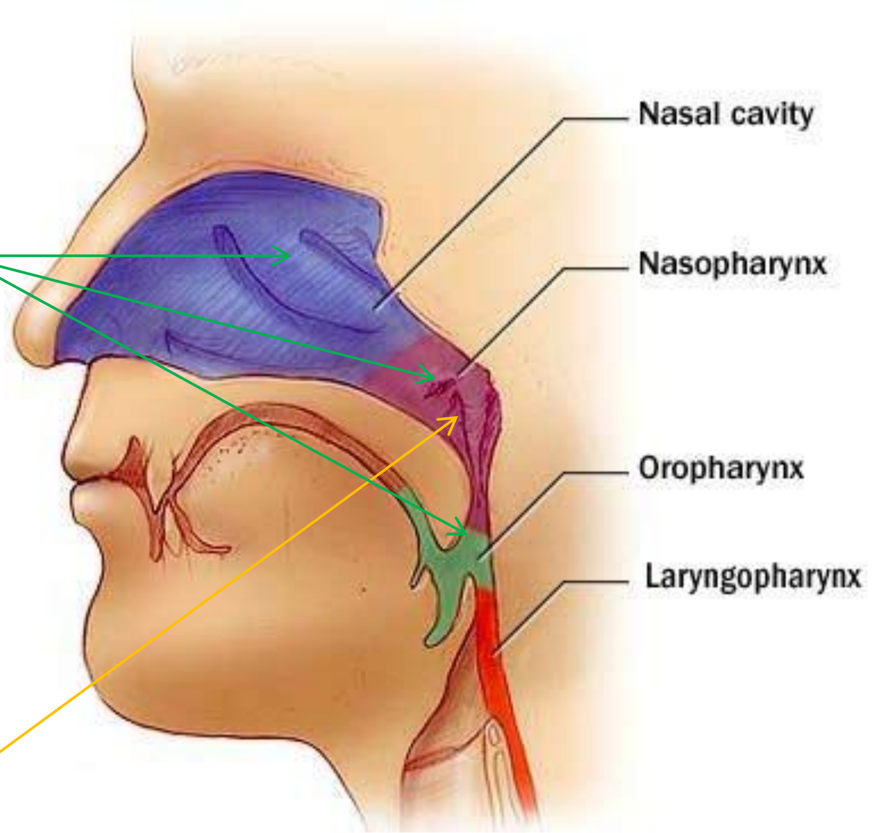




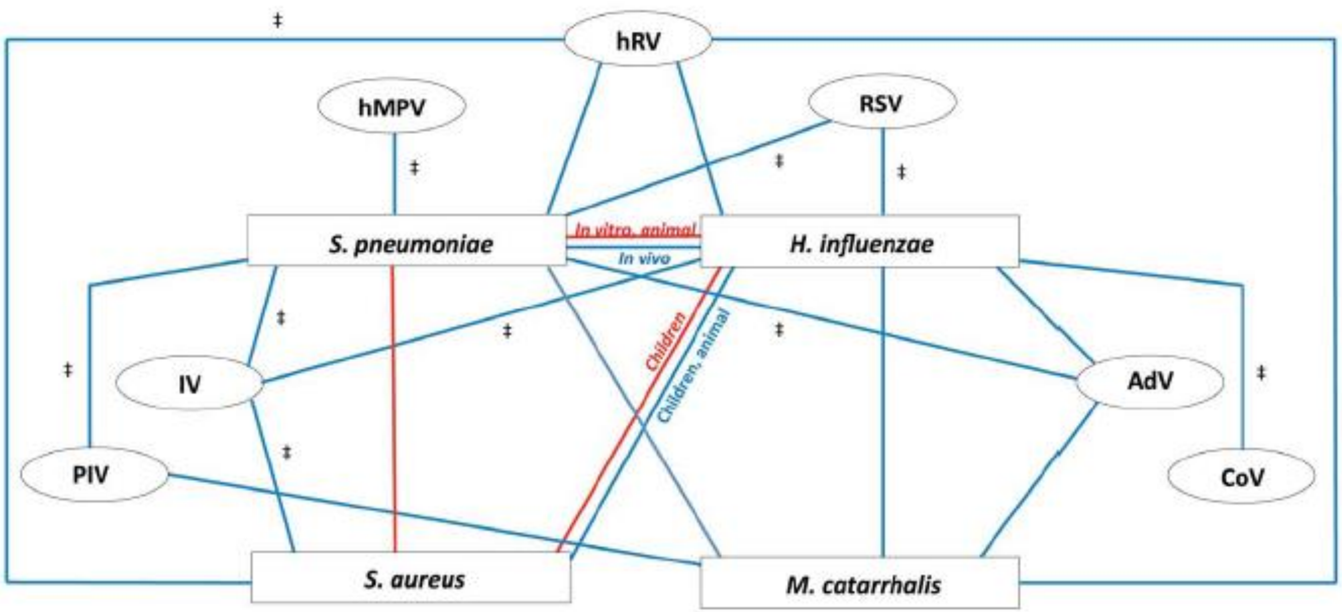
Ecological complexity
Co-inhabitants in the respiratory tract

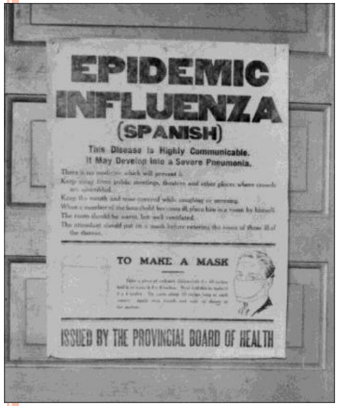
- Commensal bacteria
  - *S. pneumoniae (~100 serotypes)*
  - *S. aureus*
  - *H. Influenzae*
  - *N. meningitidis*
  - *M. Catarrhalis …*

- Respiratory viruses
  - Respiratory Syncytial virus
  - Influenza A, B
  - Rhinoviruses
  - Adenoviruses
  - Coronaviruses
  - Parainfluenza viruses …



BACTERIAL AND VIRAL INTERACTIONS INT HE RESPIRATORY TRACT





In pandemics most fatalities were due to a secondary bacterial infection : *S. pneumoniae*, *S. aureus, H Influenzae or N meningitidis*

Bosch et al, PLoS Pathogens 2013

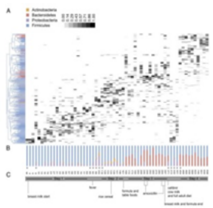
Include More individual risk factors: microbiota?

Multi-dimensional data

16S rDNA

Clinical and epidemiological data for all individuals

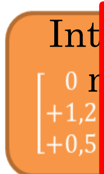
CHARLI PROJECT

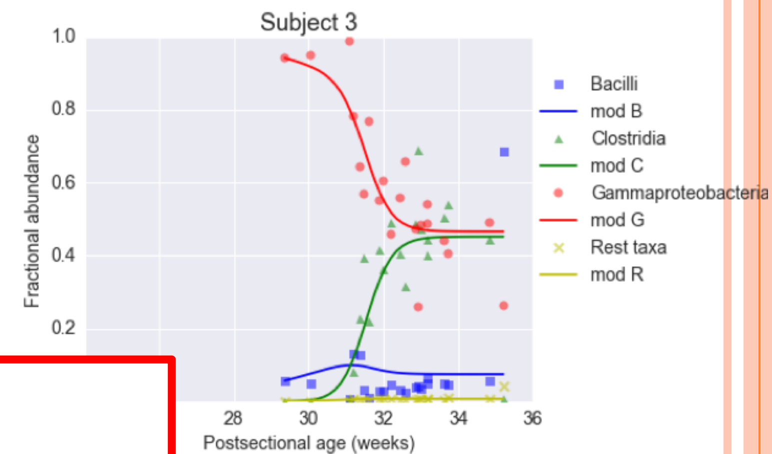


Mathematical model

$$\frac{dX_i}{dt} = A(X_i) + B(X_1, \ldots, X_N) + C(E_1, \ldots, E_K)$$
$$\forall i = 1, \ldots, N$$

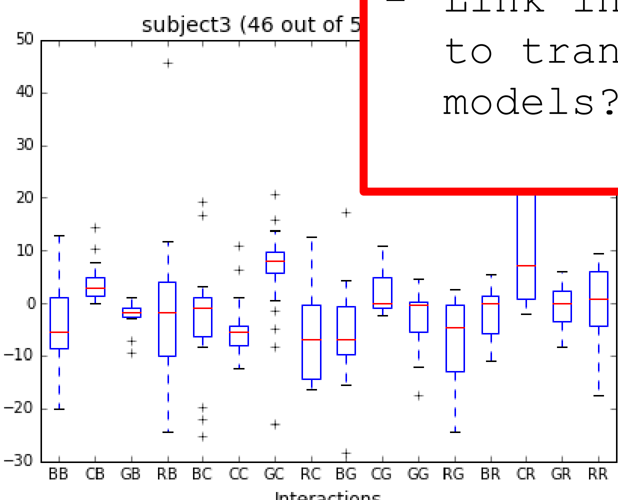
Statistical inference

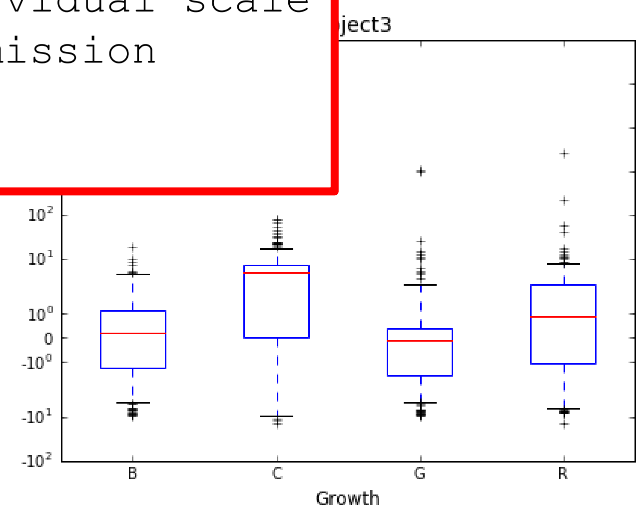




Challenge

- Add more species
- Link individual scale to transmission models?





[Gao et al, work in progress]

CHALLENGES

Population

Between-host transmission (heterogeneous)

>6

1) Formalizing different complexity levels

- Microbiology
- Host / pathogen interaction
- Between-host transmission

Individ

Immunity

Drug exposure (vaccine

Multiple ecosystems

2) Data integration and model parameter estimation

- Biological experiments
- Epidemiological investigations

Cell, microorganism

Genetic evolution :

Mutations, genes transf

Ecology of pathogens:

isation

n and synergy

3) Intensive simulations

10 bacteria in the gut

Collaborators

B2PHI
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Bich Tram Huynh
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Benoit Garin

Merci !