Mathematical modelling of between-pathogen interactions in the human host

Application to influenza viruses and pneumococcus

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Introduction

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$\rightarrow$ **possibilities of interactions during human infection**

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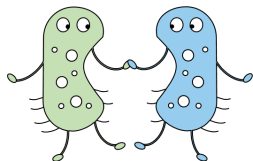
▶ P_2's growth
▶ P_2's severity
▶ P_2's infection duration

Co-circulation of many pathogens in the environnement and inside the human host.

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<div style="text-align:center">

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</div>

increases $\rightarrow$

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- P_2's severity
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Synergistic interaction

increases $\rightarrow$

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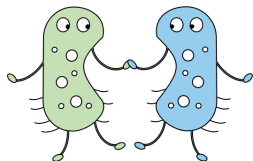
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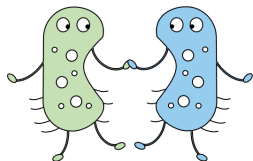- ▶ P_2's infection duration

$\leftarrow$ decreases

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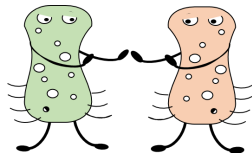
Synergistic interaction

increases $\rightarrow$

Presence of P_1 :

- P_2's growth
- P_2's severity
- P_2's infection duration

Antagonistic interaction

$\leftarrow$ decreases

Often suggested in the literature

Bosch et al. 2013, Mina et al. 2014, Opatowski et al. 2018

First evidence: 1918 influenza pandemic

▶ Majority of deaths caused by secondary bacterial infections

    ▶ *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*

Brundage et al. 2008, Morens et al. 2008, Joseph et al. 2013

▶ Explore, through modelling, the impact of interactions at the individual scale on infection dynamics at the population scale

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▶ Assess, through a simulation study, the ability of several methods to detect an interaction from ecological data

SimFI: Simulator of Flu in Interaction

Objectif Stochastic and realistic simulator of the co-circulation of influenza and another pathogen in a virtual human population.

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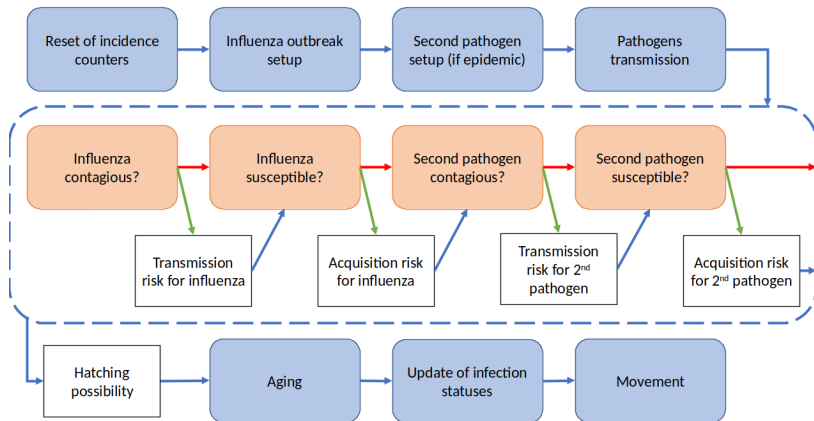
$\rightarrow$ **Agent-based model**

▶ Precise description at the individual scale

▶ Emergence of a global dynamic at the population scale

▶ Study the links between these two scales

Available on the NetLogo platform

Wilensky et al. 1999

Risk	acquisition	transmission	infection
Second pathogen / Influenza	**Susceptible**	**Infected**	**Colonised**
Susceptible	β *no interaction*	β *no interaction*	p *no interaction*
Infected	$\beta \times A$ *acquisition* *mechanism*	$\beta \times \Theta$ *transmission* *mechanism*	$p \times \Pi$ *pathogénicité* *mechanism*

Risk	acquisition	transmission	infection
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Susceptible	β no interaction	β no interaction	p no interaction
Infected	$\beta \times A$ acquisition mechanism	$\beta \times \Theta$ transmission mechanism	$p \times \Pi$ pathogénicité mechanism

Interaction scenario

▶ $A = \Theta = \Pi = 1 \rightarrow$ baseline scenario, no interaction

▶ $A \in [2; 50]$; $\Theta = \Pi = 1$

▶ $\Theta \in [2; 17]$; $A = \Pi = 1$

▶ $\Pi \in [5; 50]$; $A = \Theta = 1$
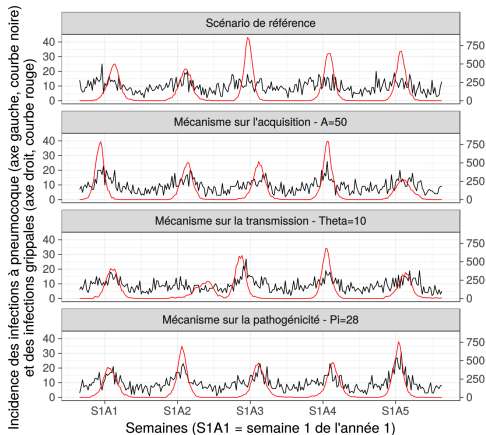
Validation criteria

▶ Influenza *Sentinelles*
  - ▶ Annual number of cases
  - ▶ Epidemic onset
  - ▶ Peak timing
  - ▶ Epidemic duration

▶ Pneumococcal infections
  - ▶ Annual number of cases
    Epibac
  - ▶ Seasonality *Météo France*

Detection of the interaction
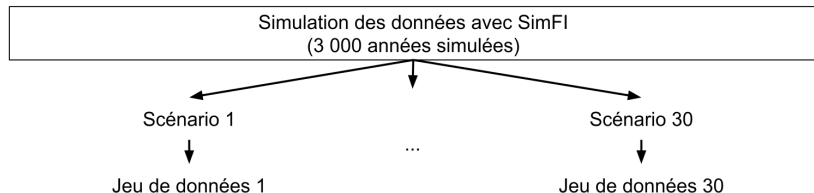
Numerous studies but no gold standard

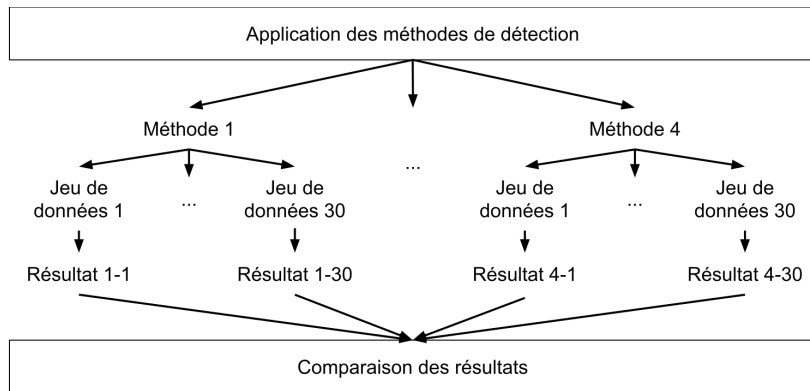1. Regression models

2. Dynamical models

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1. Regression models

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Are these methods adequate to detect such an interaction?

$$F(I_t) \;=\; a + bG_{t+i} + c\cos\frac{2\pi t}{52} + d\sin\frac{2\pi t}{52} + \epsilon_t$$

F	transformation (linear, Poisson, or negative binomiale)
I_t	pneumococcal infections
G_{t+i}	influenza infections
t	week
i	time lag

$$F(I_t) \quad = \quad a + b G_{t+i} + c \cos \frac{2\pi t}{52} + d \sin \frac{2\pi t}{52} + \epsilon_t$$
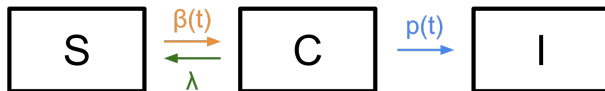
$\rightarrow$ 1 134 000 regressions

Results comparison

Student t-test: $t = \dfrac{\hat{b}}{SE_b}$

Softwares and computing resources

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} &= \lambda C(t) - \beta(t)\dfrac{S(t)C(t)}{N} \\[2mm] \dfrac{\mathrm{d}C}{\mathrm{d}t} &= -\lambda C(t) + \beta(t)\dfrac{S(t)C(t)}{N} \\[2mm] \dfrac{\mathrm{d}I}{\mathrm{d}t} &= p(t)C(t) \end{cases} \qquad \begin{cases} \beta(t) &= \beta_0(1 + \xi \times G(t)) \\[2mm] p(t) &= p_0(1 + \pi \times G(t)) \end{cases}$$

4 parameters to estimate: β_0, ξ, p_0 et π.
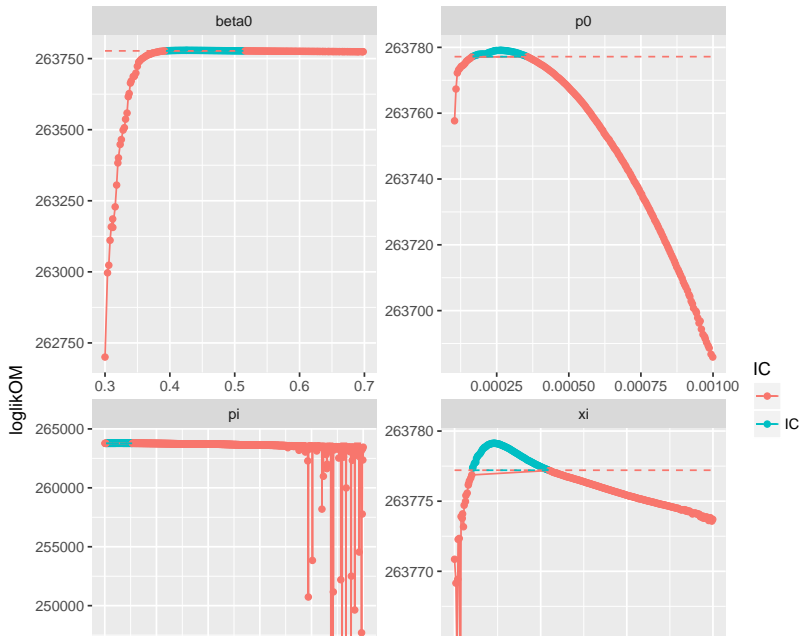
Opatowski et al. 2013

$\rightarrow$ 36 000 estimations and their confidence intervals

Likelihood maximisation

▶ Poisson likelihood

▶ Estimation: NSGA-2 algorithm   *Deb et al. 2002*

▶ Confidence intervals : profiled likelihood on the OpenMOLE platform   *Reuillon et al. 2015*

Softwares and computing resources

🔥 **OpenMOLE**

Conclusion

SimFI model Reconstruction of multi-scales dynmaics, vetter understanding of the impact of interactions

Interaction detection Importance of the method, limits of the analysis of aggregated surveillance data

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Public Health applications

▶ Integrating ecological aspects of interactions

▶ Evaluate the global impact of public health policies
  ▶ optimise drug use
  ▶ fight globally against infectious diseases

Thank you for your attention!