

3rd Workshop and Conference on Modeling Infectious Diseases

Introduction to Stochastic Modelling

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



centre for the
mathematical
modelling of
infectious diseases

The Institute of Mathematical Sciences, Chennai, India

Objectives

- Recall basic concepts of infectious disease modelling.
- Define the structure and formalism of stochastic models.
- Understand the relationship between deterministic and stochastic models.
- Show several examples of applications of stochastic modelling.

Contents

Introduction

Density-Dependent Jump Markov Processes

Some contributions of stochastic modelling to epidemiology

Initial extinction risk

Critical community size

Measles and pertussis in London before/after vaccination

Two-wave flu outbreak in Tristan da Cunha

Diseases considered

- The models are focussed toward the study of *directly transmitted, micro-parasitic infectious diseases*.
- Infectious diseases (such as influenza) can be passed between individuals whereas non-infectious diseases (such as arthritis) develop over an individual's lifespan.
- The infecting pathogen can be either a micro-parasite or a macro-parasite. Micro-parasitic infections develop rapidly so that the intra-host dynamics can be ignored.
- Infectious diseases (both macro- and micro-parasitic) can also be sub-divided into two further categories depending on whether transmission of infection is direct (contact) or indirect (environment).

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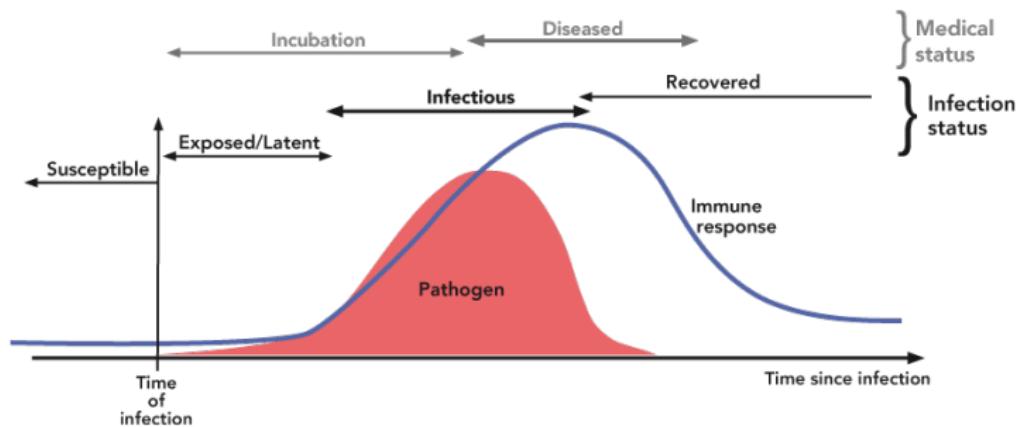
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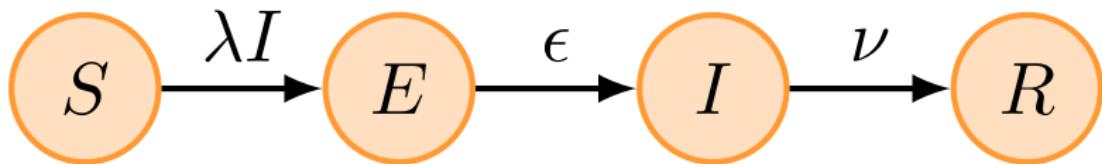
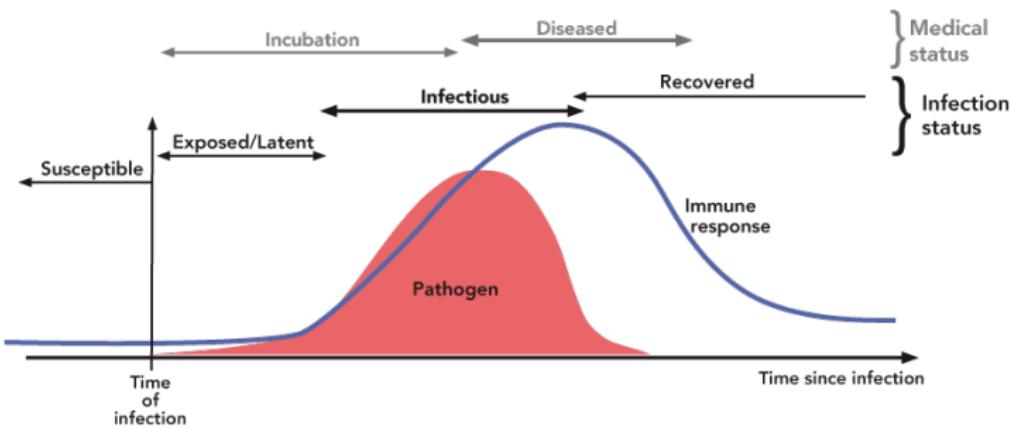
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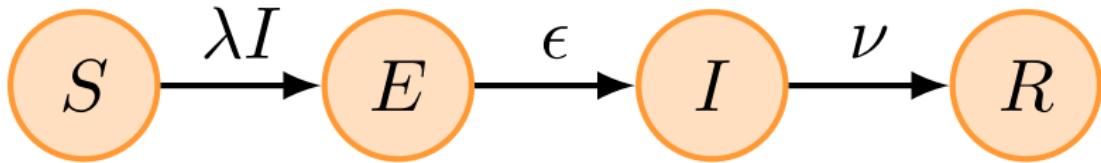
Infection dynamics



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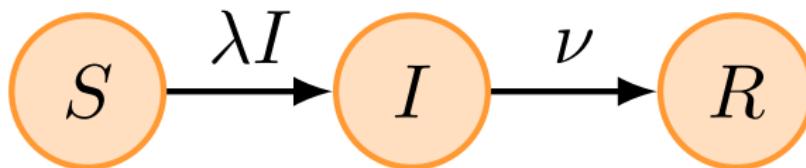


The SEIR model



- λ : rate at which two individuals come into contact.
- λI : per capita force of infection.
- ϵ : inverse of the latent period.
- ν : inverse of the infectious period.

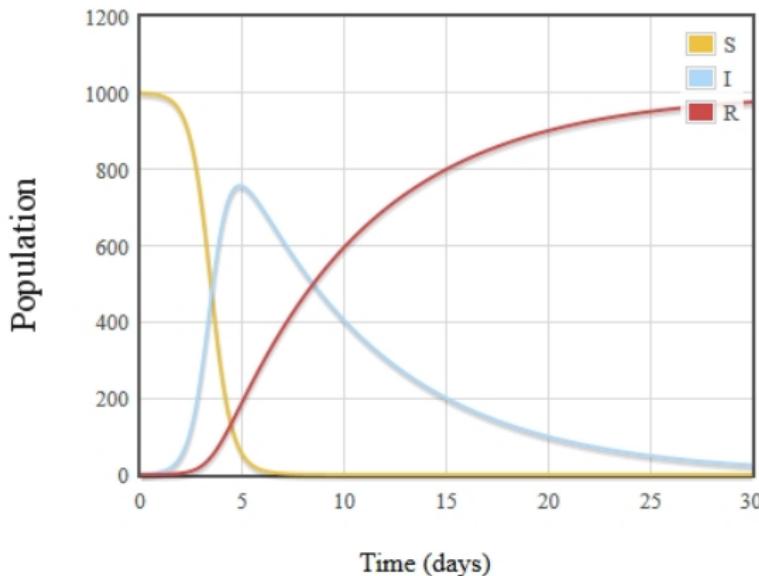
The deterministic SIR model



$$\begin{cases} \frac{dS(t)}{dt} = -\lambda S(t)I(t) \\ \frac{dI(t)}{dt} = \lambda S(t)I(t) - \nu I(t) \\ \frac{dR(t)}{dt} = \nu I(t) \end{cases} \quad (1)$$

With $(S(0), I(0), R(0)) = (S_0, I_0, 0)$
and constant population size $S(t) + I(t) + R(t) = \Omega$.

The deterministic SIR model



Two important results

- An epidemic can occur only if $S_0 > \nu/\lambda$, when the population initially susceptible is above a critical size.
- At the end of the epidemic, it remains S_∞ susceptible individuals, with S_∞ solution of the equation:

$$S_\infty = \Omega + \frac{\nu}{\lambda} \ln\left(\frac{S_\infty}{S_0}\right). \quad (2)$$

- Not all susceptibles will get infected during the epidemic.

Why using stochastic models?

1. It is the natural way to describe how an epidemic disease spreads.
2. Some phenomena are stochastic by nature and cannot be described in a deterministic setting.
3. Take into account the variability of the epidemic process when estimating and forecasting.

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Three sources of stochasticity

1. Demographic (internal).

Depends on the epidemiological process.

2. Environmental (external).

Acts on the epidemiological process.

3. Observation.

Does not change the epidemiological dynamics.

Observation stochasticity

- Diagnostic errors: false positive and false negative.
- Incomplete reporting of cases: 60% for measles.
- Fluctuations of the reporting rate: change in the number of GPs in the surveillance system.
- The reporting rate at time t is $\rho_t \sim \text{Gamma}(1/\phi, \rho\phi)$.
- Conditioning on ρ_t and the incidence in the model (X_t), the observed incidence $Y_t|\rho_t, X_t \sim \text{Poisson}(\rho_t X_t)$.
- Conditioning on X_t , Y_t follows a negative-binomial distribution with:

$$\text{E}[Y_t|X_t] = \rho X_t \text{ and } \text{Var}[Y_t|X_t] = \rho X_t + \phi \rho^2 X_t^2.$$

- This corresponds to an overdispersed observation process.

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Environmental stochasticity

- Stochastic fluctuations of environmental factors (e.g. temperature, humidity) lead to stochastic fluctuations of transmission parameters.

$$\begin{cases} \frac{dS(t)}{dt} = -\lambda(1 + F\xi)S(t)I(t) \\ \frac{dI(t)}{dt} = \lambda(1 + F\xi)S(t)I(t) - \nu I(t) \\ \frac{dR(t)}{dt} = \nu I(t) \end{cases} \quad (3)$$

where ξ is a random variable and F is a forcing constant.

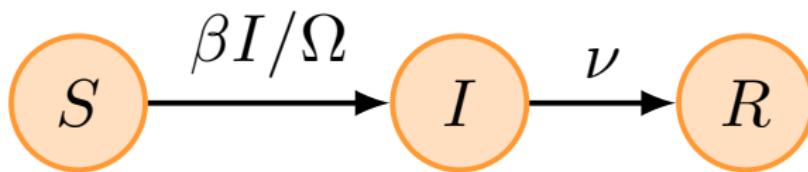
Demographic stochasticity

- Results from the discrete nature of individuals in the population: $(S(t), I(t), R(t)) \in \mathbb{N}^3$.
- Mechanistic modelling of random events at the individual level:
 - Infectious period with mean ν^{-1} and variance σ^2 .
 - Number of contacts \sim Poisson process with intensity β/Ω .
- One can compute the distribution of the final size of the epidemic ($S_0 - S_\infty$).
- To go further, let's assume an exponentially distributed infectious period: $\nu^{-2} = \sigma^2$.
- Memory-less property of the exponential distribution: $\{(S(t), I(t), R(t)) : t \geq 0\}$ becomes a discrete state, continuous time Markov process.

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SIR with demographic stochasticity



Event	Transition	Transition probability within $[t, t + dt]$
Infection	$(s, i, r) \rightarrow (s - 1, i + 1, r)$	$\frac{\beta}{\Omega} s i \, dt + o(dt)$
Recovery	$(s, i, r) \rightarrow (s, i - 1, r + 1)$	$\nu i \, dt + o(dt)$

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Definition

- Let's take a model with d compartments and M transitions.
- We note $\mathbf{X}(t) = (X_1(t) \dots X_d(t))^T \in \mathbb{N}^d$ the vector of the state of the population at time t .
- We define each transition $T_m, m \in \{1, \dots, M\}$, by a vector of state change: $\mathbf{k}_m = (k_{1m} \dots k_{dm})^T \in \mathbb{Z}^d$ and a jump intensity $a_m(\mathbf{x})$, such that:

$$P(\mathbf{X}(t + dt) = \mathbf{x} + \mathbf{k}_m | \mathbf{X}(t) = \mathbf{x}) = a_m(\mathbf{x})dt + o(dt)$$

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- It is density-dependent if $a_m(\mathbf{x}) = \Omega \tilde{a}_m(\Omega^{-1}\mathbf{x})$, where Ω is the population size, assumed constant.

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Remarks

- Almost all Markov models used in epidemiology are DDJMPs (e.g. Bartlett's SIR).
- Natural formalism to model demographic stochasticity.
- Limited analytical results. Mainly on the final size of an outbreak (total number of infected individuals).
- The law of $\mathbf{X}(t)$ at every time t is intractable due to the non-linearity of the contact process.
- In order to study the dynamics of the model, mainly two solutions:
 - Monte-Carlo approach: simulate many realisations of the process to evaluate $\mathbf{X}(t)$ empirically.
 - Analytical approximations: first few moments of $\mathbf{X}(t)$, when population is large.

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Doob-Gillespie algorithm

- Proposed by Joseph L. Doob in 1940s and popularized by Daniel T. Gillespie in 1970s.
- Given a state \mathbf{x} and a time t , simulate the following event:
No transition occurs during the time interval $[t, t + \tau[$ and the transition T_μ occurs at the time $t + \tau$.
- One can show that τ and μ are two random variables with probability density:

$$p(\tau) = a_0(\mathbf{x}) \exp(-a_0(\mathbf{x})\tau), \quad \tau > 0, \quad (5)$$

$$p(\mu) = \frac{a_\mu(\mathbf{x})}{a_0(\mathbf{x})}, \quad \mu = 1, \dots, M, \quad (6)$$

where $a_0(\mathbf{x}) = \sum_{m=1}^M a_m(\mathbf{x})$.

- Slow for large populations because $E[\tau] = 1/a_0(\mathbf{x}) \propto 1/\Omega$.

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Analytical approximations

- Results obtained by Thomas G. Kurtz in the 1970s for the large population limit $\Omega \rightarrow \infty$ of $\mathbf{X}_\Omega = \{\mathbf{X}_\Omega(t) : t \geq 0\}$.
- Two theorems characterise the convergence of the sequences of $\{\Omega^{-1}\mathbf{X}_\Omega\}$.
- Law of large numbers: for large population size and large initial conditions, $\Omega^{-1}\mathbf{X}_\Omega$ can be approximated, over a bounded time interval, by the deterministic solution ϕ :

$$\begin{cases} \frac{d\phi(t)}{dt} = \mathbf{F}(\phi(t)), \\ \phi(0) = \phi_0, \end{cases} \quad (7)$$

where $\mathbf{F}(\mathbf{x}) = \sum_{m=1}^M \mathbf{k}_m \tilde{a}_m(\mathbf{x}), \mathbf{x} \in \mathbb{R}^d$.

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- The next step is to study the deviations of $\Omega^{-1} \mathbf{X}_\Omega$ from ϕ .
- Kurtz's central limit theorem establishes that these deviations are Gaussian and of the order of $1/\sqrt{\Omega}$.
- It follows from these 2 theorems that \mathbf{X}_Ω can be approximated in distribution by:

$$\tilde{\mathbf{X}}_\Omega = \Omega\phi + \sqrt{\Omega}\mathbf{Y}, \quad (8)$$

with $E[\mathbf{Y}(t)] = \Phi(t, 0)\mathbf{Y}_0$ and $\Xi(t) = \text{Cov}[\mathbf{Y}(t), \mathbf{Y}(t)]$
solution of:

$$\frac{d\Xi}{dt} = \partial\mathbf{F}(\phi)\Xi + \Xi(\partial\mathbf{F}(\phi))^T + \mathbf{G}(\phi), \quad (9)$$

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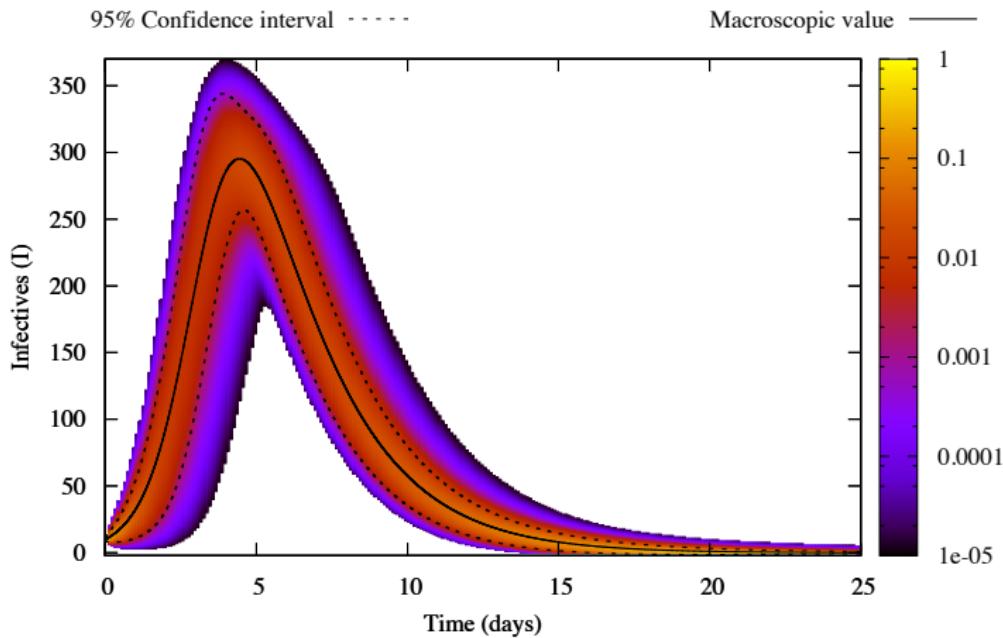
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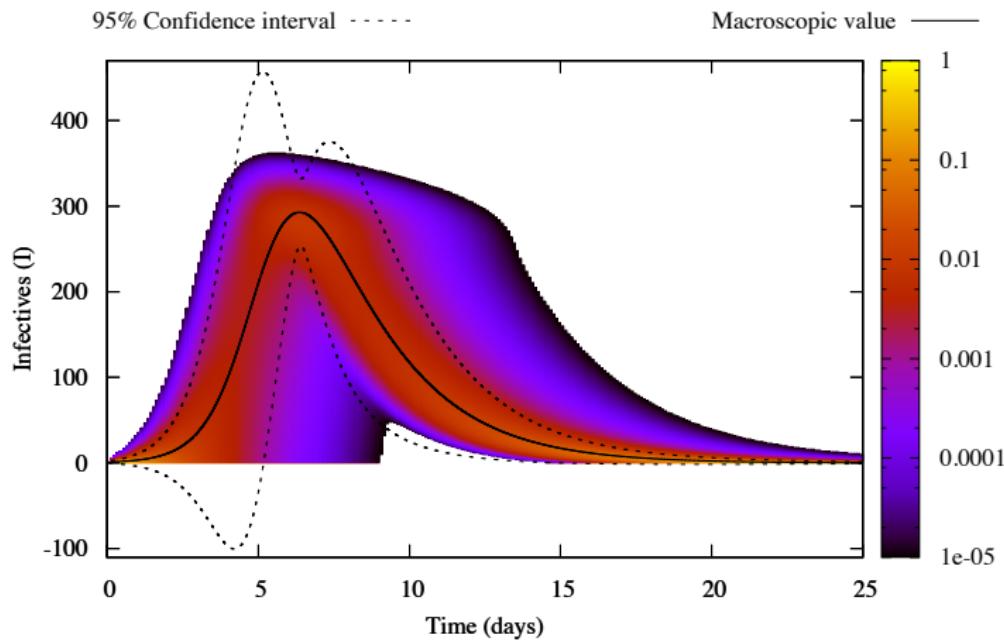
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Monte-Carlo vs Gaussian approximation



Large initial condition I_0

Monte-Carlo vs Gaussian approximation



Small initial condition I_0 .



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- The initial phase of the epidemic can be described by a birth-death process: individuals live for a random duration (infectious period) during which they give birth (infect) according to a Poisson process with intensity β .
- The probability P_{ext} that the birth-death process stops after a *finite* number of generations is q^l_0 , where q is the unique root in $[0, 1[$ of $s = f(s)$, with

$$f(s) = \int_0^\infty e^{-\beta t(1-s)} g_I(t) dt, \quad |s| \leq 1, \quad (10)$$

where g_I is the pdf of the infectious period.

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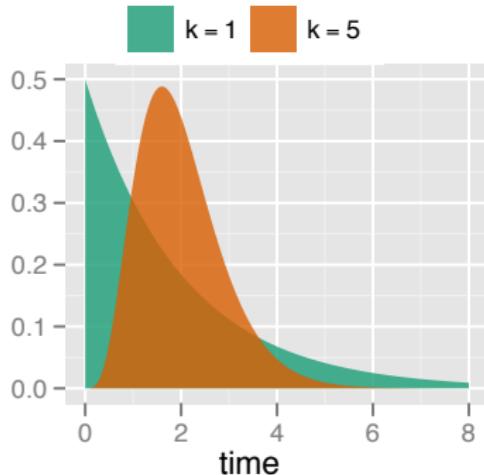
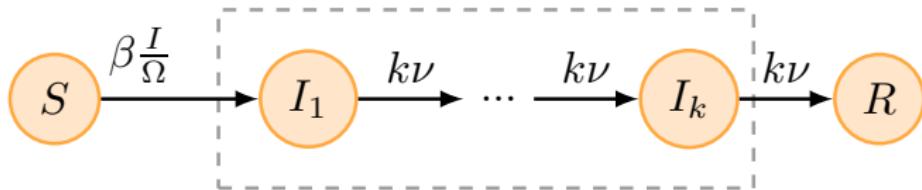
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- The probability P_{ext} that the birth-death process stops after a *finite* number of generations is q^{l_0} , where q is the unique root in $[0, 1[$ of $s = f(s)$, with

$$f(s) = \int_0^{\infty} e^{-\beta t(1-s)} g_I(t) dt, \quad |s| \leq 1, \quad (10)$$

where g_I is the pdf of the infectious period.

- For DDJMPs, we can set $g_I(t; k, \nu) = \Gamma(k, k\nu)$, $k \in \mathbb{N}^*$:

Erlang distribution



$$g_I(t; k, \nu) = \frac{(k\nu)^k t^{k-1} e^{-k\nu t}}{(k-1)!}$$

$$Var_I(t; k, \nu) = \frac{1}{k\nu^2}$$

Initial extinction risk

- $P_{ext} = q_k^{l_0}$
 - For $k = 1$ (exponential distribution), $q_1 = 1/R_0$.
 - For $k = 2$:

and $q_2 < q_1, \forall R_0 > 1$.

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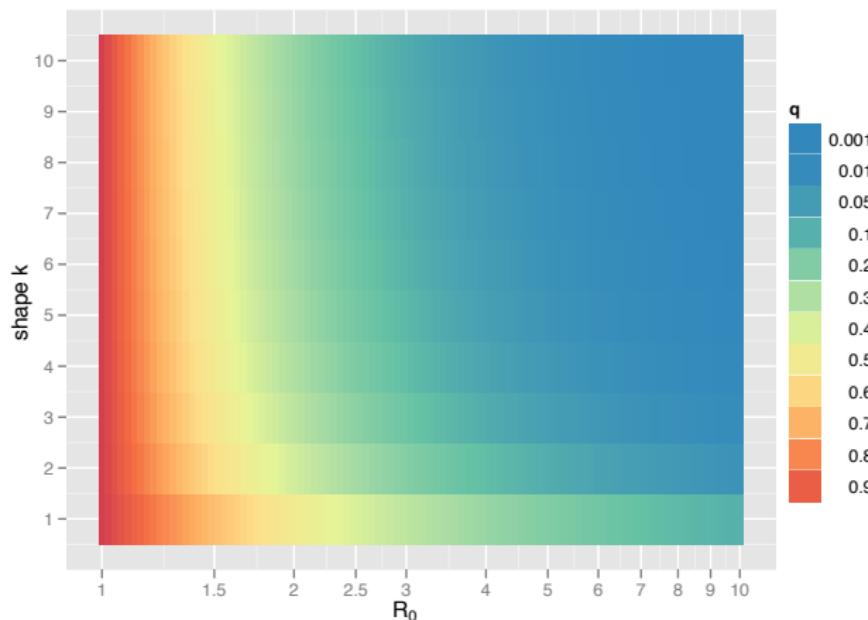
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- For $k \geq 3$, $f(s) = s$ is a $\geq 4^{\text{th}}$ degree polynomial equation and we rely on numerical solutions.

Initial extinction risk



Pathogens with more variable infectious periods have a higher risk of initial extinction.

Critical community size

- Minimum size of a closed human population within which a pathogen can persist indefinitely.
- The value of the CCS depends on the pathogen.
- The CCS of measles is between 100,000 and 200,000 ind.
- There is a lack of such data for other diseases.
- How can we estimate the CCS for these diseases?
- One solution is to use stochastic modelling since the CCS is linked to the concept of risk of extinction.

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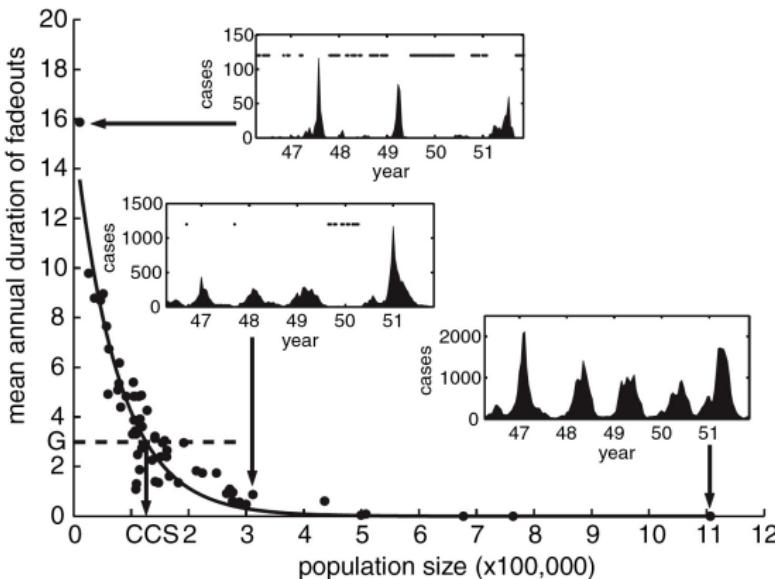
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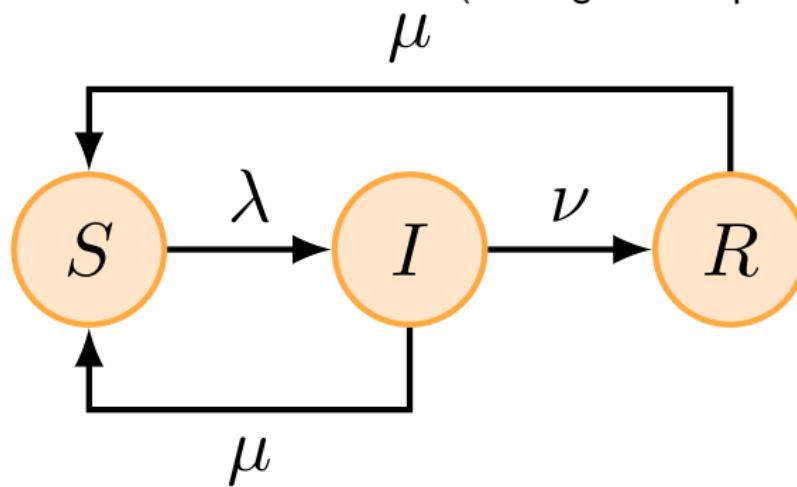
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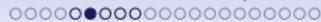
Measure of persistence

- SIR with birth and death (average life expectancy = $1/\mu$)



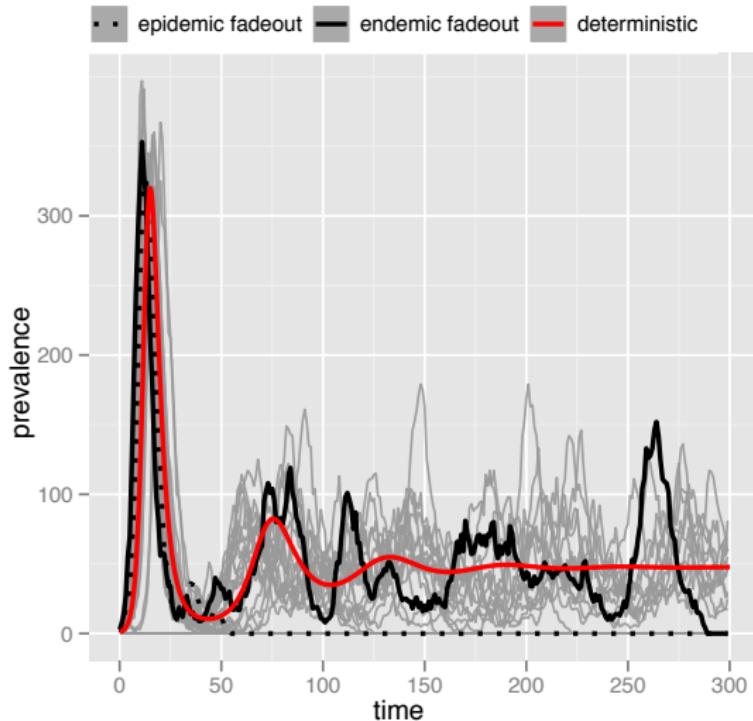
- We consider the expected time to extinction $E[T_\Omega]$ as a measure of persistence: $T_\Omega = \inf\{t \geq 0 : I_\Omega(t) = 0\}$.
- We start from the quasi-stationary distribution, which is the limit of the distribution conditioned on non-extinction:

$$\pi_{\mathbf{x}}^{(\Omega)} = \lim_{t \rightarrow \infty} p(\mathbf{X}_\Omega(t) = \mathbf{x} | \mathbf{X}_\Omega(t) \notin \mathcal{A}). \quad (12)$$



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$$E[T_\Omega] = \frac{1}{(\nu + \mu)\pi_{.,1}^{(\Omega)}}, \quad (13)$$

where $\pi_{.,1}^{(\Omega)} = \sum_{s=0}^{\Omega} \pi_{s,1}^{(\Omega)}$ is the marginal probability of having a single infectious individual at quasi-stationarity.

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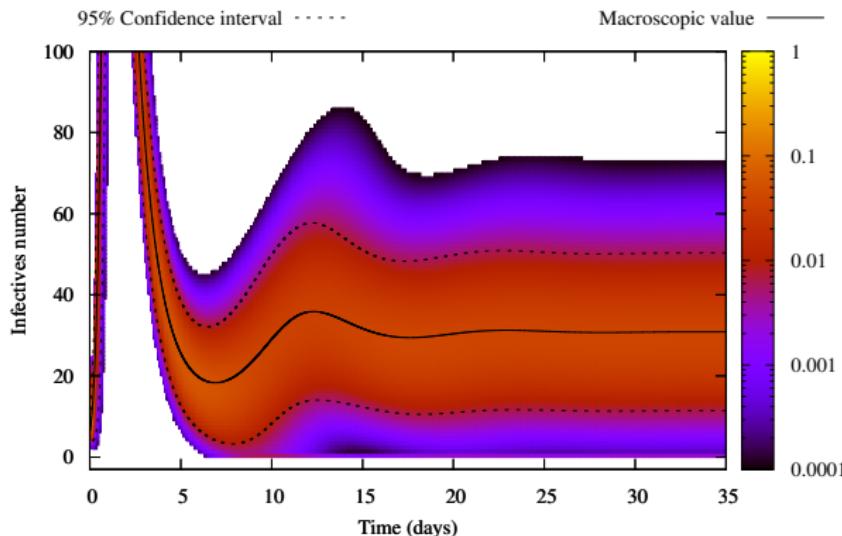
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Quasi-stationary distribution

- In practice, it is not possible to compute $\pi_{s,i}^{(\Omega)}$ analytically.
- Heuristic: use the endemic equilibrium of the Gaussian approximation.



Critical community size

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$$T_0 = E[T_\Omega] \log 2 \quad (14)$$

- For measles ($R_0 = 14$, $\nu^{-1} = 1$ week, $\mu^{-1} = 70$ years) the quasi-period is $\hat{T}_0 = 2.06$ years.
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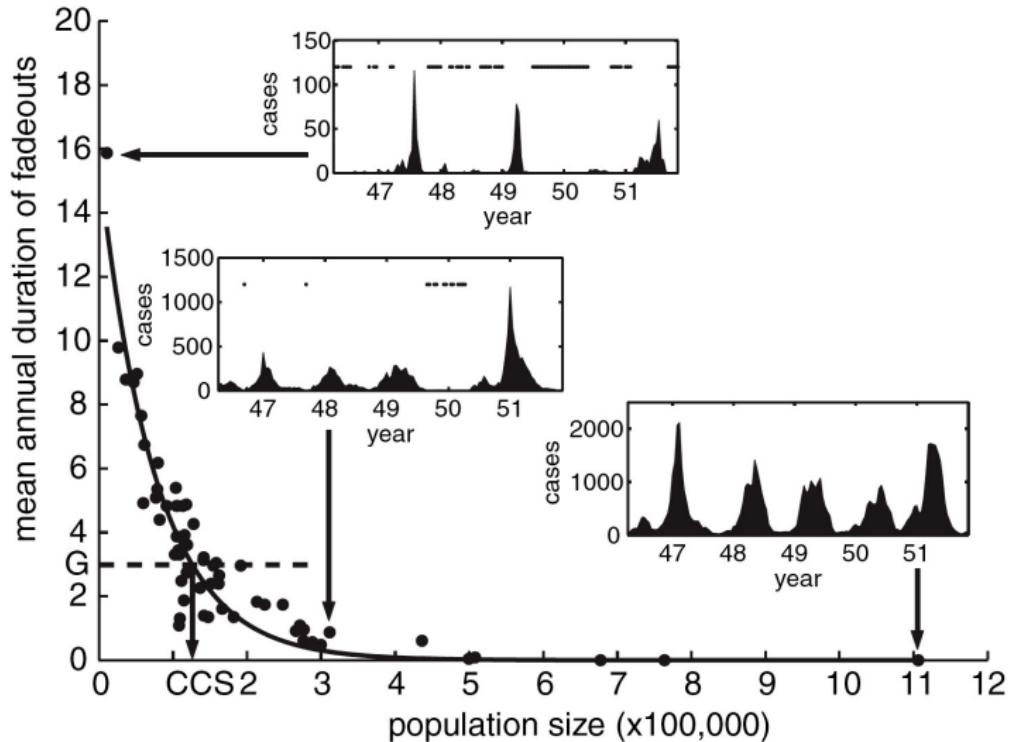
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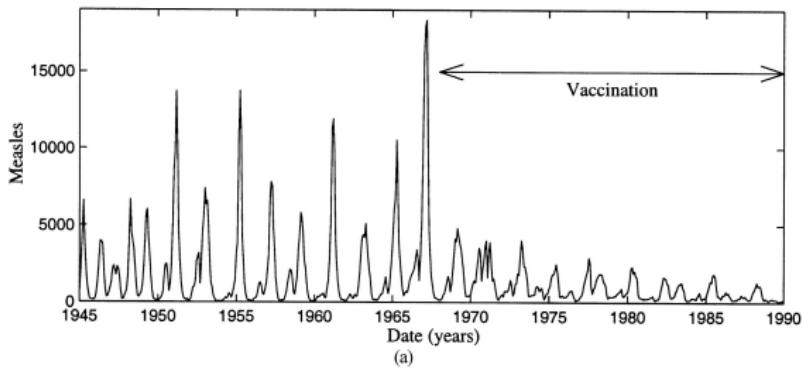
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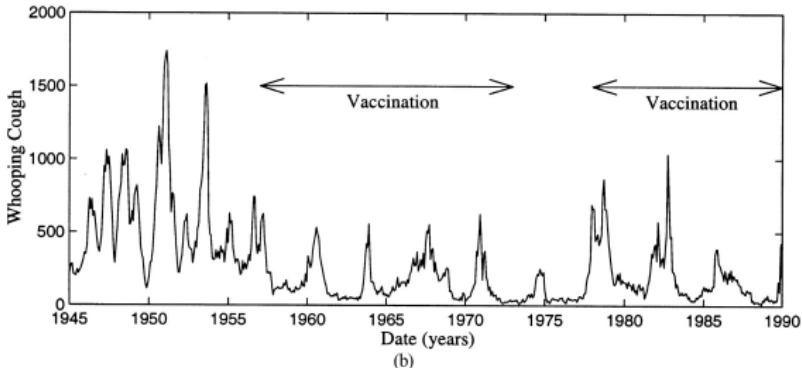
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Measles and pertussis in London before/after vaccination



(a)



(b)

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- The biannual cycle of measles becomes irregular after vaccination.
- The multi-annual cycle of pertussis becomes more regular.
- Although both incidences decrease, the amplitude of pertussis epidemics is similar to that in the pre-vaccine era.
- How pathogens with similar R_0 (≈ 17) and infectious periods (around 2 weeks) can have such different dynamics and transitions following vaccination?

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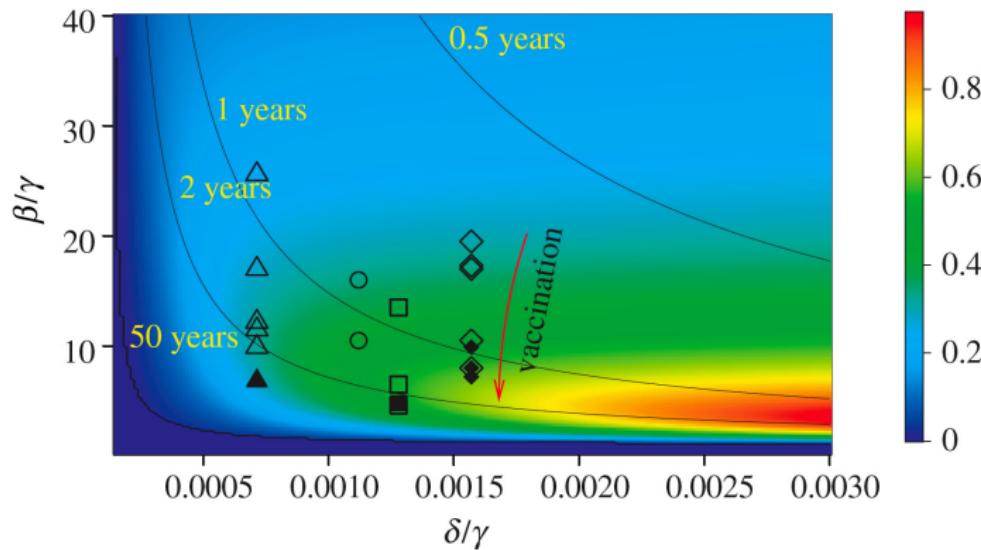
Deterministic vs Stochastic paradigms

- Deterministic paradigm: complex interactions between non-linearity and seasonal forcing lead to amplified oscillations (resonance) and very rich dynamics.
- In this paradigm, stochasticity only plays a passive role: switch between attractors.
- Stochastic paradigm: resonance depends on the capacity of demographic stochasticity to amplify oscillations (active role).
- Gaussian approximation allows us to derive two quantities:
 - Amplification: system's capacity to sustain and amplify the stochastic fluctuations.
 - Coherence: measures the concentration of spectral power around the dominant endogenous frequency.

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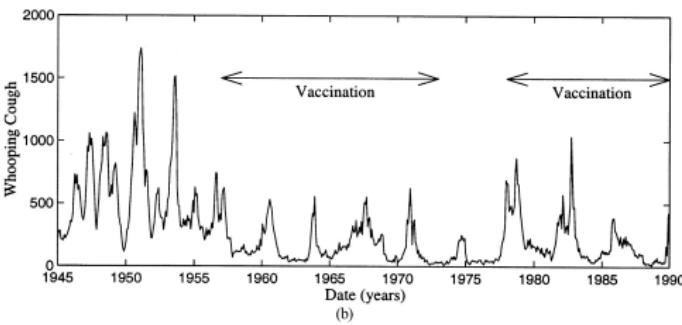
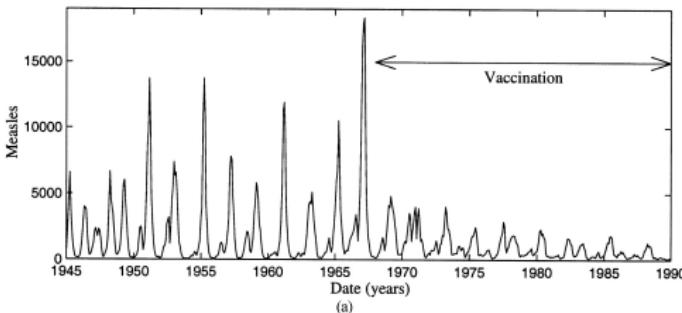
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Amplification of oscillations



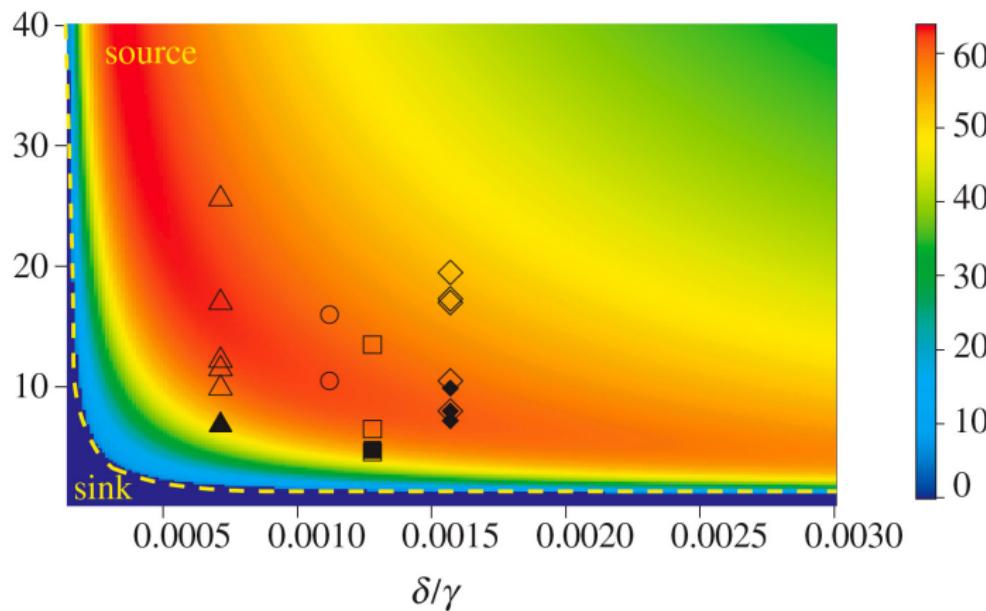
Following vaccination, amplification increases for pertussis (diamonds) but not for measles (triangles).

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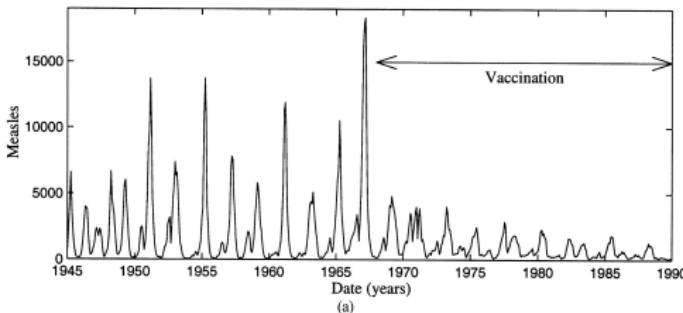
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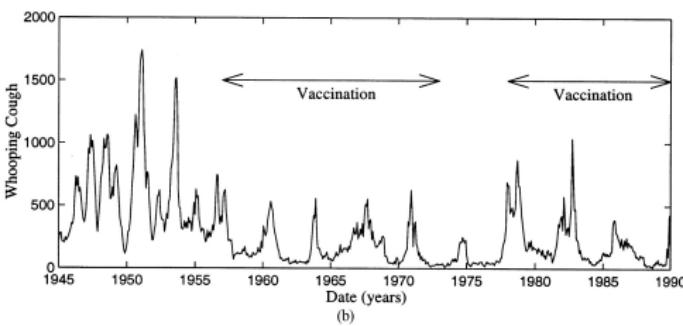


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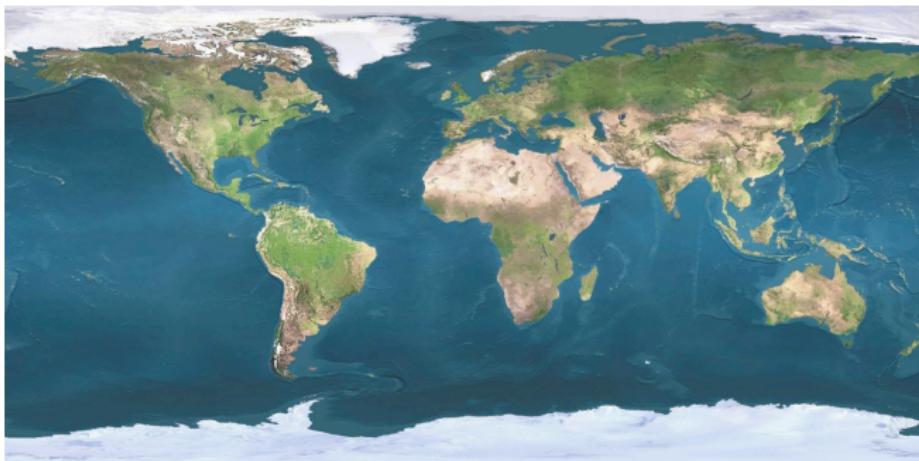
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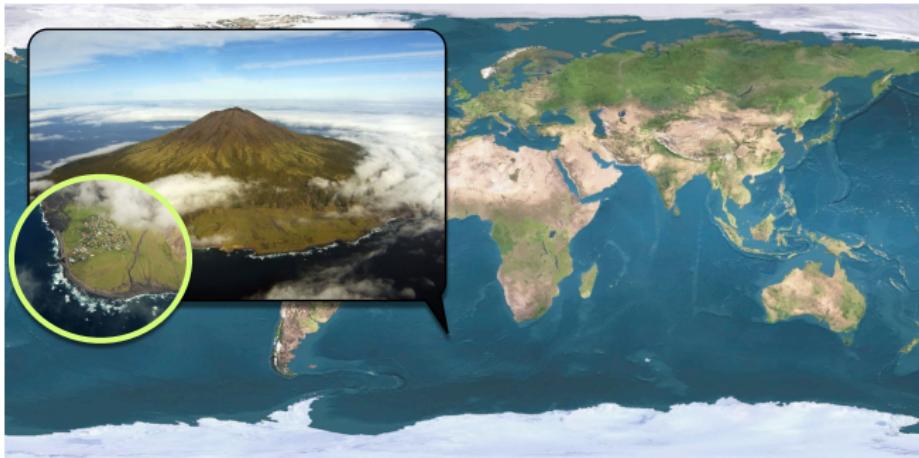
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Two-wave flu outbreak in Tristan da Cunha



The most isolated inhabited place in the world!

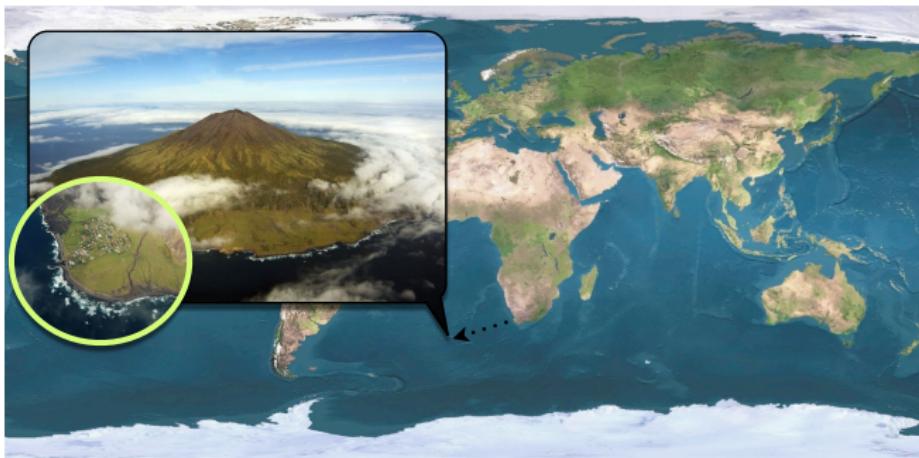
Two-wave flu outbreak in Tristan da Cunha



- Small population ≈ 300 individuals
- Fully isolated
- Free social mixing

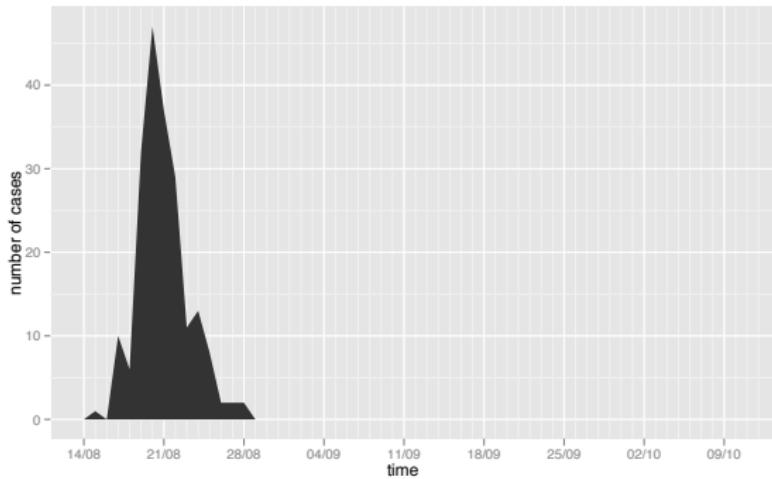
Population almost naive to influenza (Tristan escaped the 1918 Spanish flu!)

Two-wave flu outbreak in Tristan da Cunha



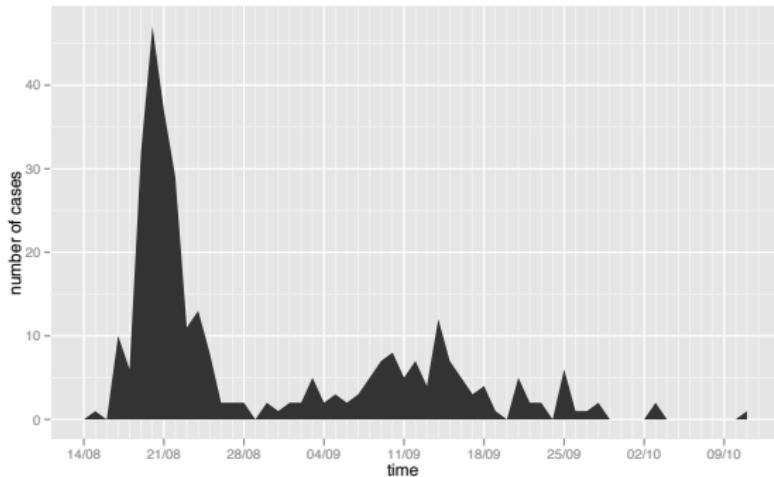
- 1971: a boat returning from Cape-Town landed 2 individuals with flu symptoms
- **A welcome home (homogeneous mixing?) dance was given**

1971 influenza epidemic on Tristan da Cunha



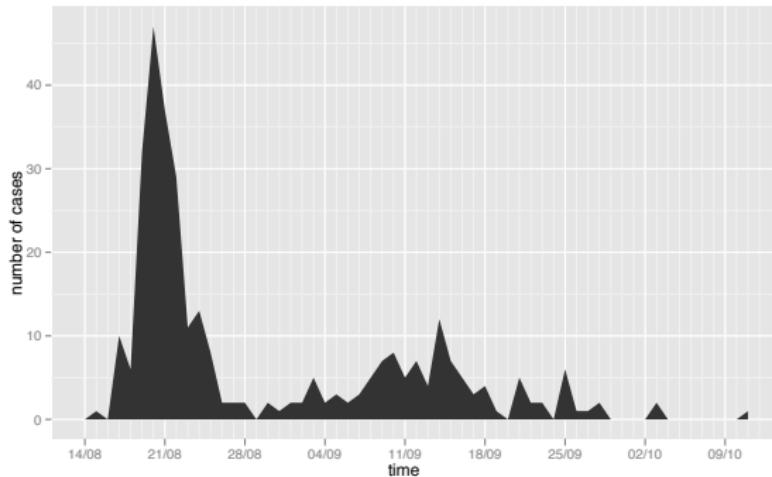
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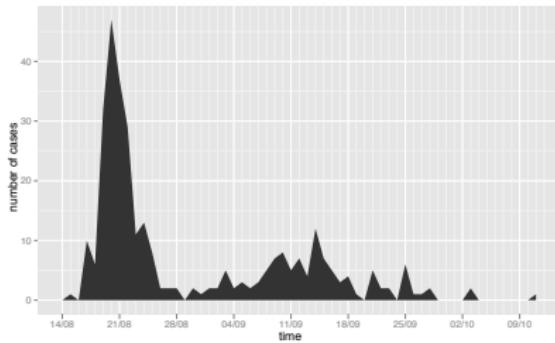
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Mantle and Tyrrell (1973)

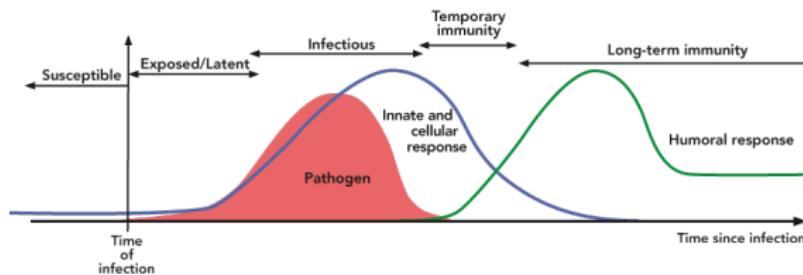
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Objectives

- Disentangling between 5 biological hypotheses that could explain these cases of rapid reinfection
- Accounting for both demographic stochasticity in the epidemic dynamics and under-reporting in the observations

Mechanistic modeling of reinfection hypotheses



Primary immune response to influenza

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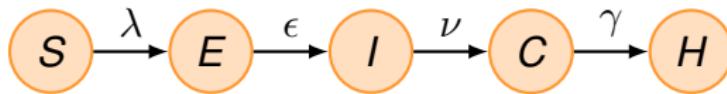
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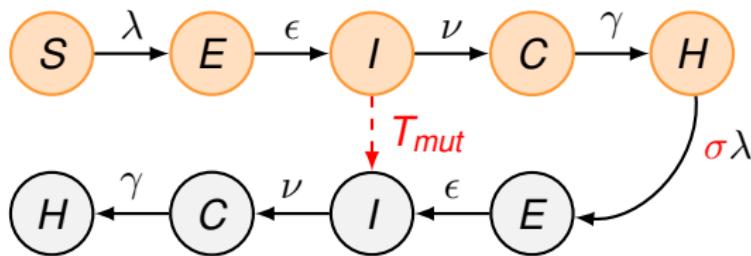
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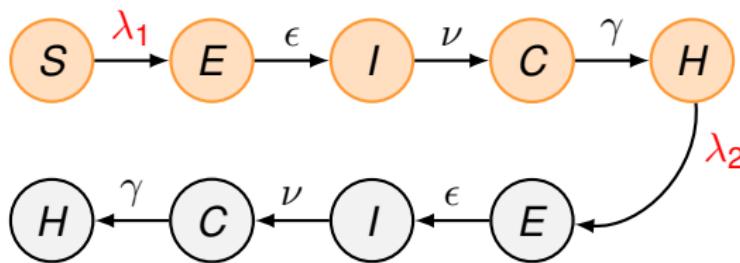
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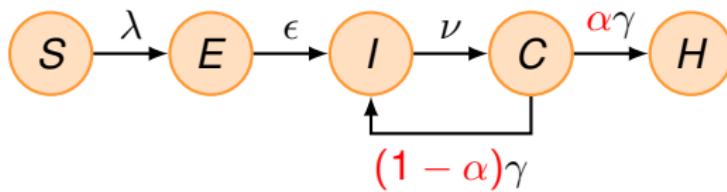
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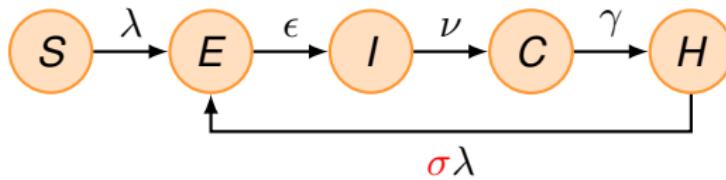
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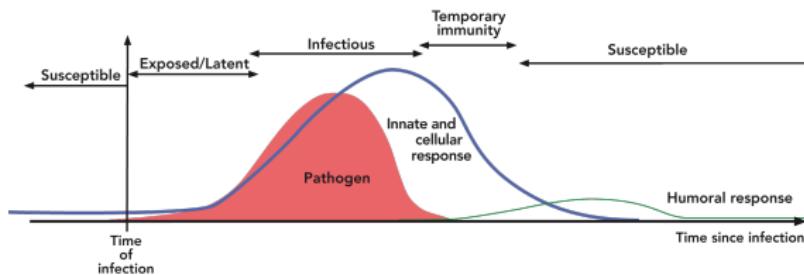
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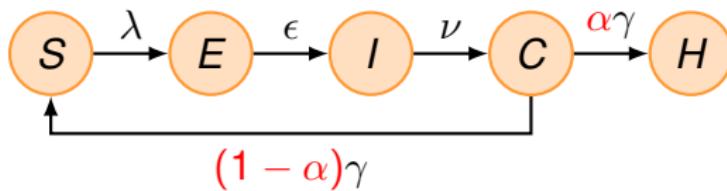
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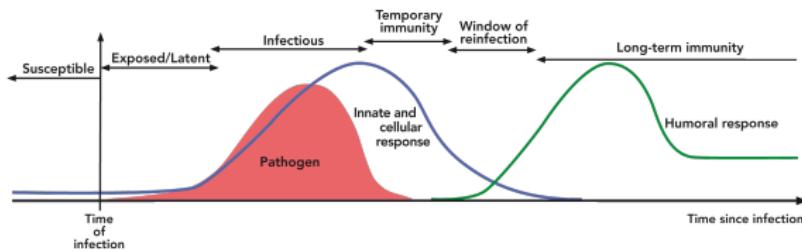
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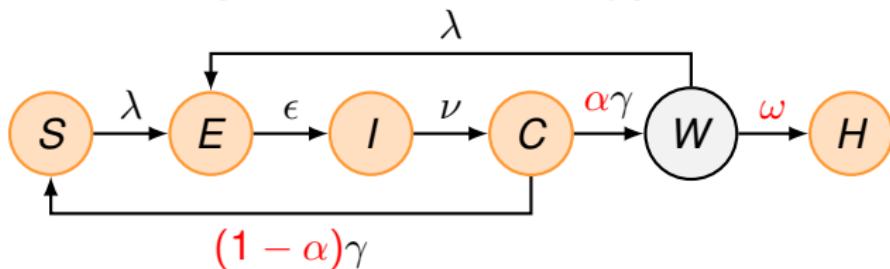
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Confrontation with data

- The unobserved Markov process $\{\mathbf{X}(t) : t \geq 0\}$ depends on an **unknown** parameter vector θ
- Data consist in a collection of $T = 59$ discrete observations $\mathbf{y}_{1:T} = (\mathbf{y}_1, \mathbf{y}_2, \dots, \mathbf{y}_T)$.
- Poisson observation process $h(y_t|x_t, \theta)$ with underreporting $\rho < 1$.
- The likelihood is given by the identity:

$$\mathcal{L}(\mathbf{y}_{1:T}|\theta) = \prod_{t=1}^T \sum_{\mathbf{x}_t \in C} h(\mathbf{y}_t|\mathbf{x}_t, \theta) \sum_{\mathbf{x}_{t-1} \in C} p(\mathbf{x}_t|\mathbf{x}_{t-1}, \theta) P(\mathbf{x}_{t-1}|\mathbf{y}_{1:t-1}, \theta),$$

but is **intractable**

- Sequential Monte-Carlo: only requires to be able to sample from $p(x_t|x_{t-1}, \theta)$ (Doob-Gillespie algo)
- Iterated Filtering (Ionides et al., 2006): find $\hat{\theta}$ which maximizes the likelihood

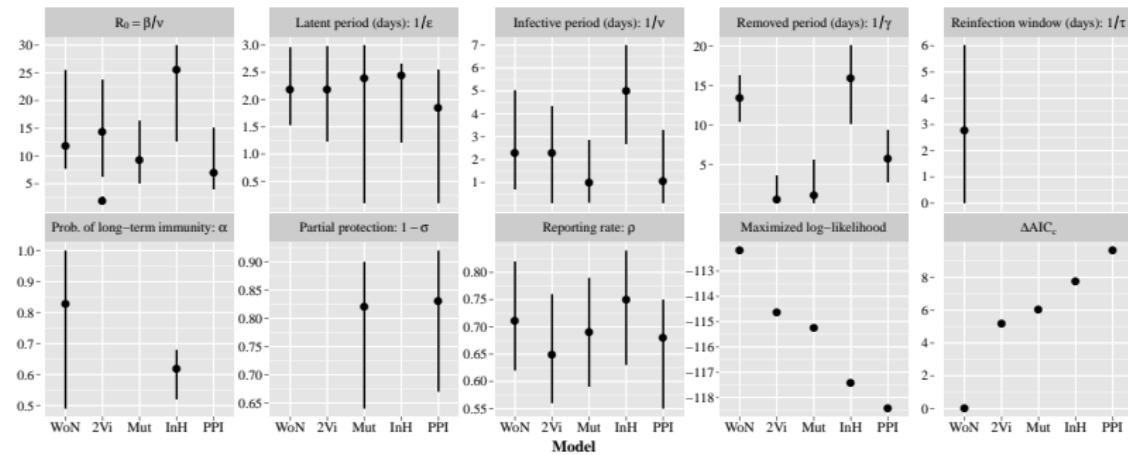
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- Poisson observation process $h(y_t|x_t, \theta)$ with underreporting $\rho < 1$.
- The likelihood is given by the identity:

$$\mathcal{L}(\mathbf{y}_{1:T}|\theta) = \prod_{t=1}^T \sum_{\mathbf{x}_t \in C} h(\mathbf{y}_t|\mathbf{x}_t, \theta) \sum_{\mathbf{x}_{t-1} \in C} p(\mathbf{x}_t|\mathbf{x}_{t-1}, \theta) P(\mathbf{x}_{t-1}|\mathbf{y}_{1:t-1}, \theta),$$

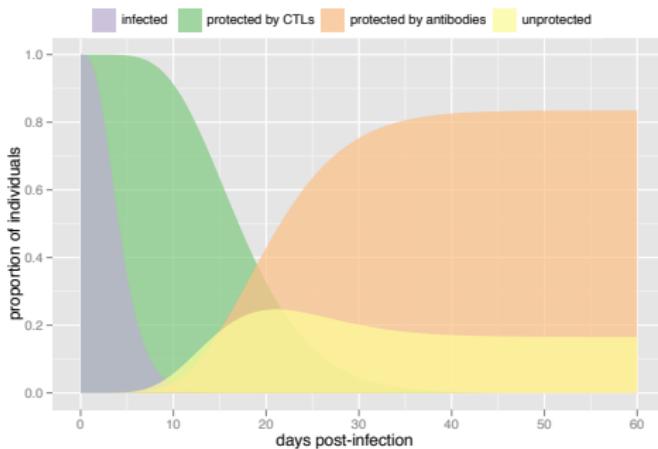
but is **intractable**

- Sequential Monte-Carlo: only requires to be able to sample from $p(x_t|x_{t-1}, \theta)$ (Doob-Gillespie algo)
- Iterated Filtering (Ionides et al., 2006): find $\hat{\theta}$ which maximizes the likelihood



- High estimates for $R_0 \approx 10$
 - We used the corrected Akaike Information Criterion (AIC_c) to select the best model
 - The best model corresponds to the **Window of reinfection or No humoral response** hypothesis

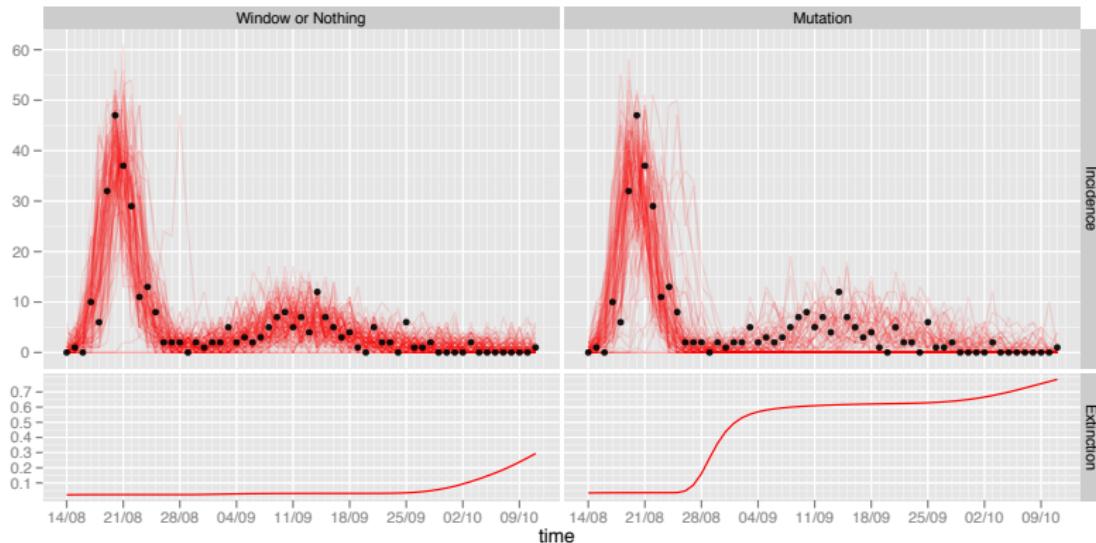
Parameter inference and model selection



Immuno-dynamics

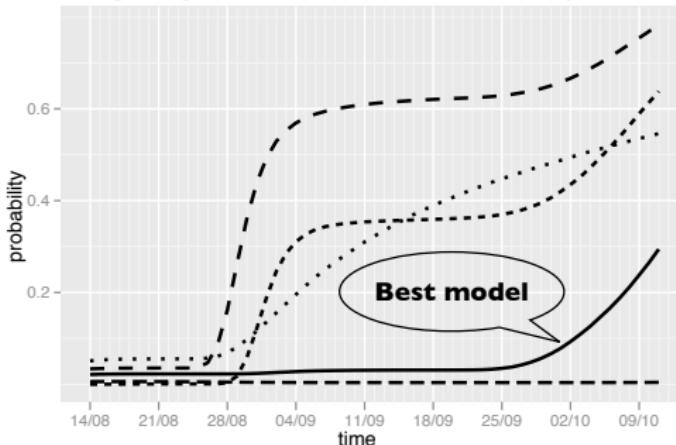
The probability to remain unprotected peaks after 3 weeks due to the window of reinfection and then decreases to $\approx 20\%$ due to the lack of protective antibodies

The role of demographic stochasticity



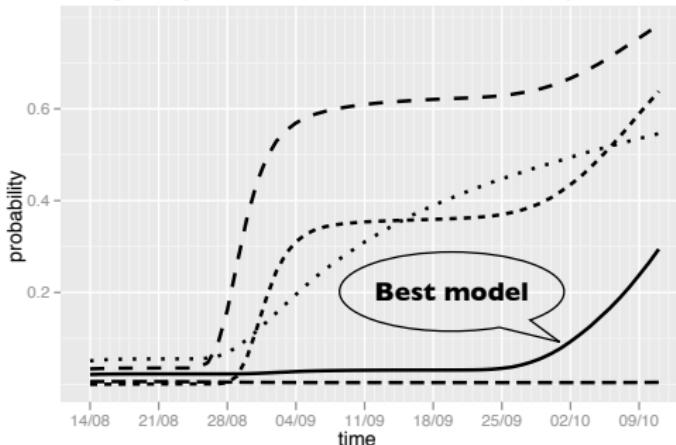
The inter-wave extinction probability varies from one model to another

The role of demographic stochasticity



- The most likely mechanism is robust to inter-wave extinctions
- and prevents a third wave to occur

The role of demographic stochasticity



- The most likely mechanism is robust to inter-wave extinctions
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Conclusion

- Propagation of pathogens in a population is inherently stochastic.
- Stochastic models require Monte-Carlo simulations → intensive as $\Omega \rightarrow \infty$.
- Deterministic models arise as the large population limit ($\Omega \rightarrow \infty$) of the stochastic model.
- One can approximate the stochastic process by a Gaussian process.
- No closed form for the likelihood for stochastic model → numerical methods, Monte-Carlo approach
- With increasing computer resources, more and more stochastic modelling & fitting to data.