Time since infection models and applications to contact tracing and waning immunity

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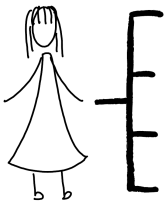
Time since infection (deterministic) models

Probabilities and rates depend on time since infection τ



infectivity $\beta(\tau)$

recovery/isolation rate $\mu(\tau)$

'survival' $\mathcal{F}(\tau)$

incubation $f(\tau)$ …

- can be described by delay equations for $b(t) \in \mathbb{R}$ (population birth rate / incidence)

$$y(t) = \frac{S(t)}{N} \int_0^\infty \beta(\tau)\mathcal{F}(\tau)y(t-\tau)d\tau$$

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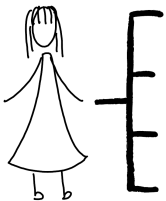

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$$y(t) = \frac{S(t)}{N} \int_0^\infty \beta(\tau)\mathcal{F}(\tau)y(t-\tau)d\tau$$

- or, alternatively, as PDEs
  for $n(t,\cdot) \in L^1$ (population density)

$$\partial_t n(t,\tau) + \partial_\tau n(t,\tau) = -\mu(\tau)n(t,\tau)$$
$$n(t,0) = \frac{S(t)}{N} \int_0^\infty \beta(\tau)n(t,\tau)d\tau$$

- rarely used in applications due to complexity and lack of software
  (ODE compartmental models instead)

Take-home messages

Why should we care? Not just generalisation from Erlang to Gamma!

- more flexibility
- more 'dynamics' $\rightarrow$ waning immunity
- more modelling power $\rightarrow$ contact tracing

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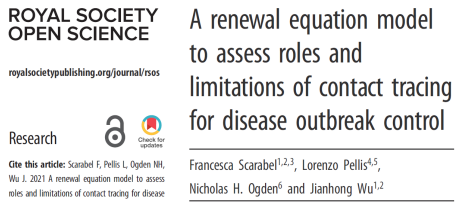


A modelling example: contact tracing

Aims at stopping as many infection chains as possible, as early as possible, by identifying and isolating individuals among the contacts of one confirmed case.
Forward tracing: search for secondary cases of the index case

A model should account for:

- underlying infection spread
- diagnosis/screening program that can initiate contact tracing
- contacts between individuals and infection transmission
  - contacts are distributed in the past
  - infected cases have already progressed through disease stages (and possibly generated infections)

Hard to capture with compartmental ODEs; most often modelled by stochastic agent-based models or branching processes

- time-since-infection approach

A SIR time-since-infection epidemic model (1)

The population is divided into three classes:

- Susceptibles — no immunity, can contract the infection
- Infected — have the disease and can infect others
- Removed — recovered and permanently immune or isolated and not infectious

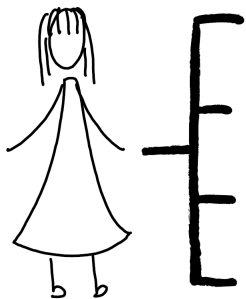
Assuming homogeneous mixing, identical, independent individuals.

Three main processes involved:

1. infection (and recovery)
2. diagnosis from symptoms
3. contact tracing

A SIR time-since-infection epidemic model

Individual parameters defined in terms of time since infection (*TSI*) τ:



infectivity $\beta(\tau)$

incubation period $f_s(\tau)$

diagnosis rate $h_d(\tau)$

tracing rate $h_c(t, \tau)$ (unknown)

A renewal equation for the incidence

The equation for the incidence reads

$$y(t) = \frac{S(t)}{N_0} \int_0^\infty \beta(\tau) y(t-\tau) \underbrace{\mathcal{F}(t,\tau)}_{\substack{\text{prob not yet} \\ \text{isolated}}} \mathrm{d}\tau$$

where

$\mathcal{F}(t,\tau) =$ prob that an individual was not isolated before TSI τ

(defined through the tracing rate h_c, unknown)

Describing forward contact tracing

$$P(\text{individual traced at time } t) \propto P(\text{infector is detected at } t)$$

$$= P(\text{infector is diagnosed or traced at } t)$$

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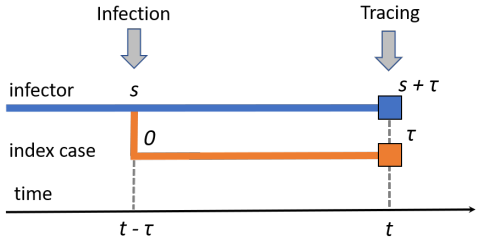
$$P(\text{individual traced at time } t) \propto P(\text{infector is detected at } t)$$

$$= \underbrace{P(\text{infector is diagnosed or traced at } t)}_{\text{break down by time of infection and by infector's TSI}}$$



Integral equation for the contact tracing rate

$$h_c(t, \tau)\,\mathrm{d}t = P(\text{individual traced in } [t, t + \mathrm{d}t] \mid \text{infected at } t - \tau)$$

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$$= \varepsilon_c \int_0^\infty P(\text{infector has ASI in } [s, s+\mathrm{d}s] \text{ at time } t-\tau)$$
$$\times\, P(\text{infector detected in } [t, t+\mathrm{d}t] \mid \text{not detected before } t-\tau, \text{TSI } s)$$

Integral equation for the contact tracing rate

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$$\times P(\text{infector detected in } [t, t+\mathrm{d}t] \mid \text{not detected before } t-\tau, \text{TSI } s)$$

$$= \varepsilon_c \int_0^\infty \left[\frac{\beta(s) y(t-\tau-s) \mathcal{F}(t-\tau, s)\,\mathrm{d}s}{\int_0^\infty \beta(\xi) y(t-\tau-\xi) \mathcal{F}(t-\tau, \xi)\,\mathrm{d}\xi} \right]$$

$$\times \frac{\mathcal{F}(t, \tau+s)(h_d(\tau+s) + h_c(t, \tau+s))}{\mathcal{F}(t-\tau, s)}\,\mathrm{d}t$$

The full model: coupled integral equations

(Scarabel, Pellis, Ogden, Wu, *Royal Society Open Science*, 2021)

Putting everything together we get:

$$h_c(t,\tau) = \frac{\varepsilon_c S(t-\tau)}{N_0 y(t-\tau)} \int_0^\infty \beta(s) y(t-\tau-s)\, \mathcal{F}(t,\tau+s)\, (h_d(\tau+s) + h_c(t,\tau+s))\, \mathrm{d}s$$

$$y(t) = \frac{S(t)}{N_0} \int_0^\infty \beta(s) y(t-s) \mathcal{F}(t,s)\, \mathrm{d}s$$

where:

$$\mathcal{F}(t,\tau) = \mathcal{F}_d(\tau)\mathcal{F}_c(t,\tau) = \mathrm{e}^{-\int_0^\tau [h_d(\sigma)+h_c(t-\tau+\sigma,\sigma)]\,\mathrm{d}\sigma}$$

$$S(t) = N_0 - \int_0^t y(s)\,\mathrm{d}s$$

- delayed in t and advanced in τ
- can be solved using numerical methods

What about measurable quantities?

h_c is hardly measurable in practice

However, we have all the ingredients to compute concrete quantities of interest:

$$\text{nr individuals diagnosed at time } t = \int_0^\infty y(t-s)\mathcal{F}(t,s)h_d(s)\,\mathrm{d}s$$

and

$$\text{nr individuals traced at time } t = \int_0^\infty y(t-s)\mathcal{F}(t,s)h_c(t,s)\,\mathrm{d}s$$

Emerging epidemic

In the approximation $S(t) \approx N_0$ (no depletion of susceptibles), we have $y(t) \approx y_0 \, \mathrm{e}^{rt}$, and the system becomes

$$1 = \int_0^\infty \beta(s)\mathcal{F}(s)\, \mathrm{e}^{-rs}\, \mathrm{d}s$$

$$h_c(\tau) = \varepsilon_c \int_0^\infty \beta(s)\, \mathrm{e}^{-rs}\, \mathcal{F}(\tau + s)\, (h_d(\tau + s) + h_c(\tau + s))\, \mathrm{d}s$$

Note:

- Lotka–Euler type equation for the Malthusian parameter r
- generation time distribution $\beta(s)\mathcal{F}(s)$
- h_c is stationary (independent of t) and satisfies a nonlinear equation

Reproduction numbers

"Average number of secondary infections produced by one typical infected individual in an otherwise susceptible population"

Explicit formulas for the reproduction numbers:

$$R_0 = \int_0^\infty \beta(\tau)\,\mathrm{d}\tau \qquad \text{unconstrained}$$

$$R_d = \int_0^\infty \beta(\tau)\mathcal{F}_d(\tau)\,\mathrm{d}\tau \qquad \text{with diagnosis}$$

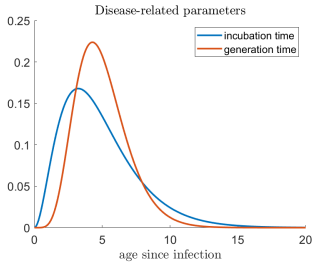
$$R_{d,c} = \int_0^\infty \beta(\tau)\mathcal{F}_d(\tau)\mathcal{F}_c(\tau)\,\mathrm{d}\tau \qquad \text{with diagnosis \& tracing}$$

General insight: the epidemic is under control if the fraction of transmission occurring before isolation is less than $\frac{1}{R_0}$ (regardless of how isolation is achieved)

Analyses for COVID-19

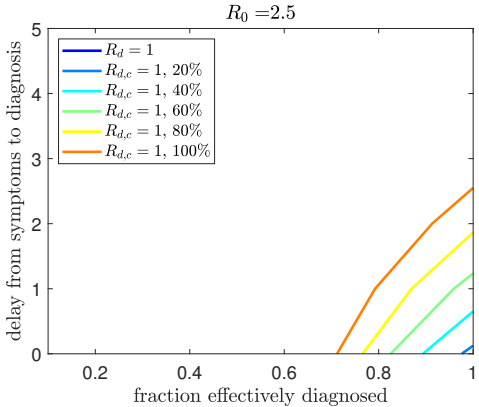
We have investigated the impact of:

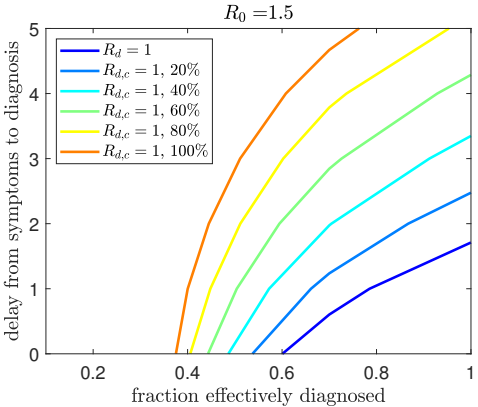
- diagnosis coverage and delay
- tracing coverage (how many contacts effectively traced?)
- tracing window (how many days back from detection to trace?)
- short-term interruption of contact tracing with limited resources



Overton et al. *Inf Dis Mod* (2020)
Ferretti et al. *Science* (2020)

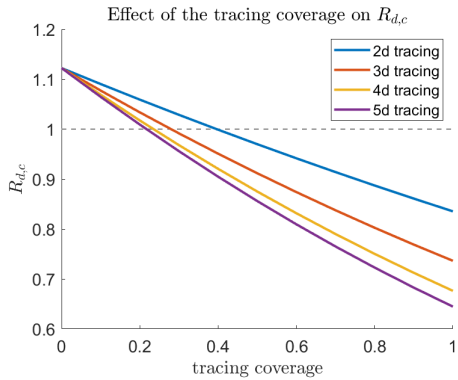
Control of the epidemic with different diagnosis strategies

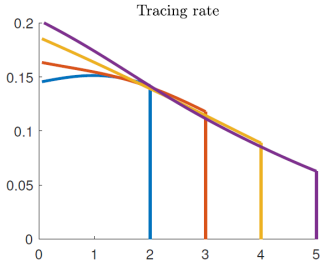




Effect of tracing window ($R_{d,c}$ and computed rate)

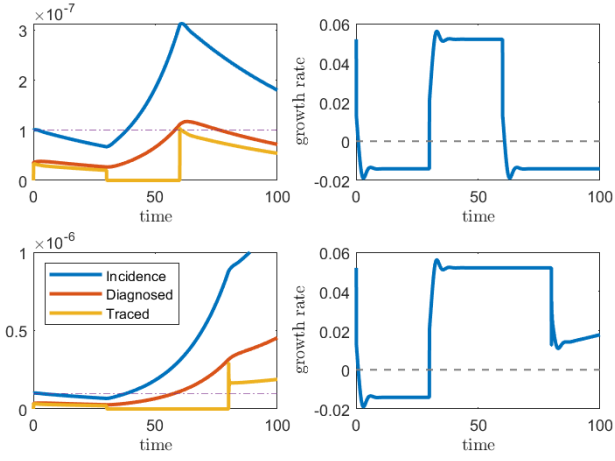
$R_0 = 1.5$, 2-day diagnosis delay, 85% diagnosis





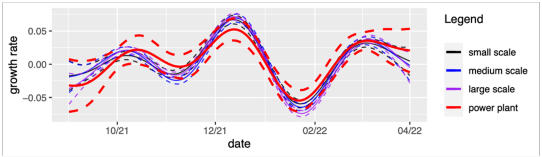
Limit on tracing capacity

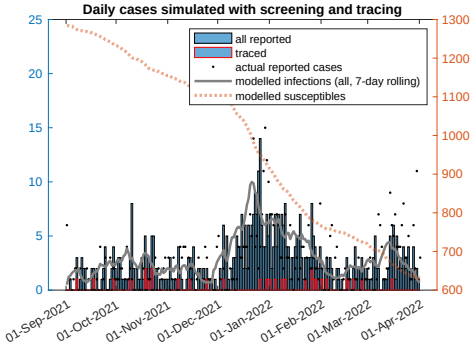
$R_0 = 1.5$, 2-day diagnosis delay, 60% diagnosis



Application to workplace transmission (stochastic model)

PROTECT COVID-19 National Core Study on transmission and environment, 'Deep dive into the UK nuclear energy sector'





- similar trends and larger relative size likely due to better surveillance
- relaxing testing results in more infections but less detected cases

Work with: Ian Hall (Manchester), Protect team

Some remarks on the TSI framework for contact tracing

- deterministic:
  1) relatively easy and fast to simulate
  2) transparent relations between model parameters and output (e.g. R)
- modelling power: first mechanistic model for contact tracing for the full nonlinear epidemic;
  (and first advanced equation in epidemiology)

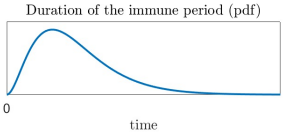
Things I'd like to do

- backward and bidirectional tracing
- correlate infectiousness and incubation period
- comparing with compartmental ODE making simplifying assumptions:
  is the average outcome similar? do we miss something?
- can we extend to simple network structure?

TSI in the context of waning immunity

$$y(t) = \frac{S(t)}{N} \int_0^\infty \beta(\tau) y(t-\tau) \mathcal{F}(\tau)\, \mathrm{d}\tau$$

with $\mathcal{F}(\tau)$ 'survival' to reinfection and boosting of immunity



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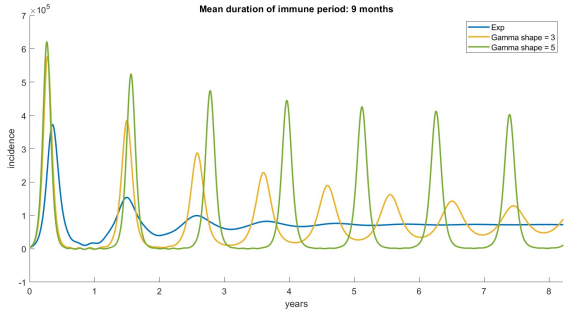
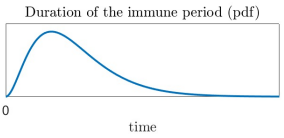
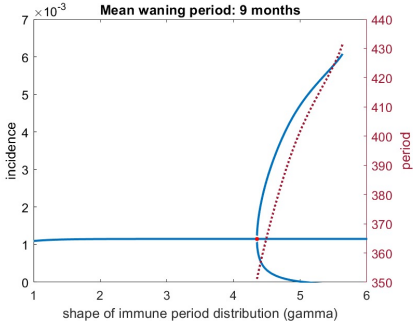


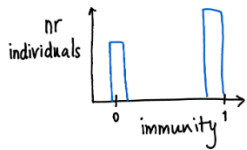




ODEs require a sufficiently large number of compartments (shape of Erlang pdf) to reproduce oscillations

Endemicity, waning immunity and variants

At equilibrium, immunity has a certain stable distribution



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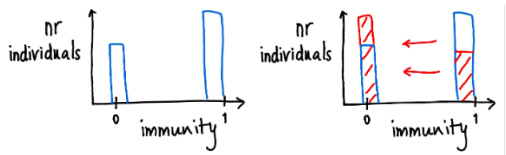
A new variant can:

- escape natural and vaccine-induced immunity (hence “shift” the immunity landscape)



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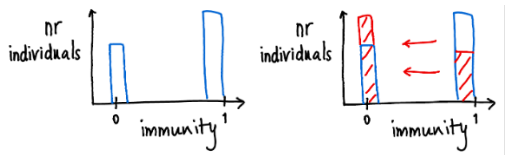
- have different transmissibility (and/or severity…)

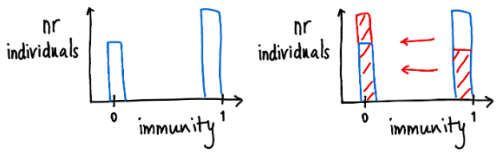


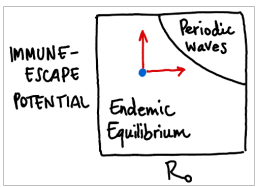
Endemicity, waning immunity and variants

At equilibrium, immunity has a certain stable distribution

A new variant can:

- escape natural and vaccine-induced immunity (hence "shift" the immunity landscape)
- have different transmissibility (and/or severity…)
- affect
  1) the endemic equilibrium state;
  2) its stability;
  3) transient epidemic waves





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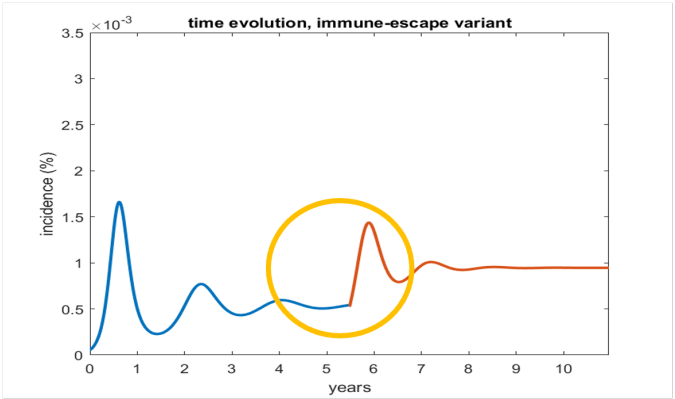
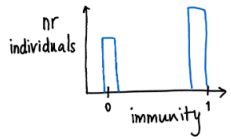
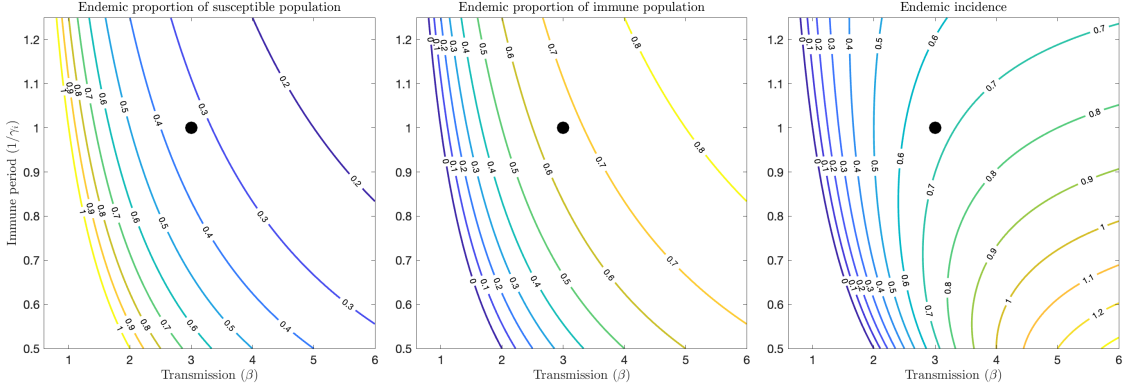
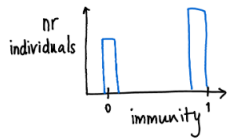


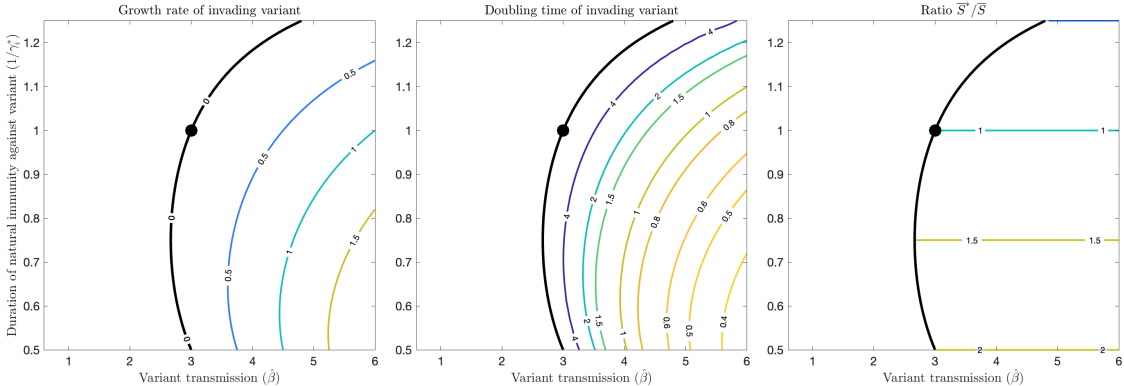
1) Endemic state with waning immunity — SIS





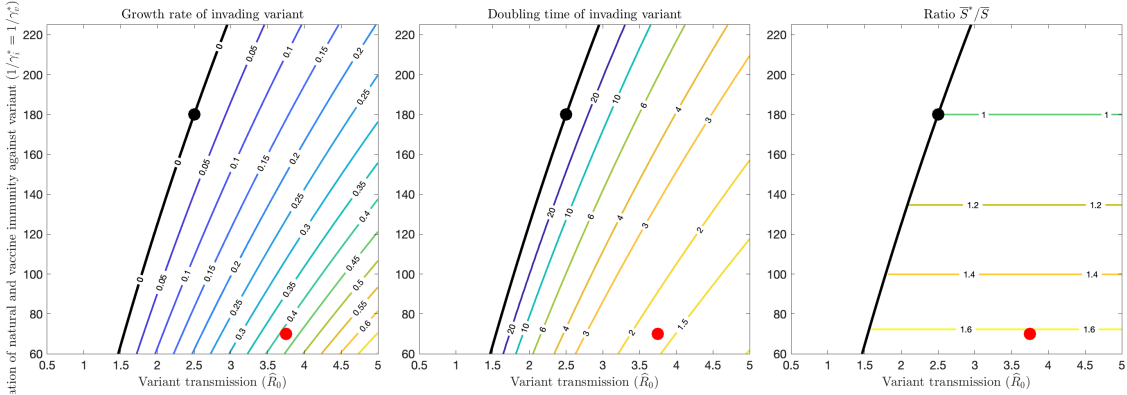
2) Expectations for an invading variant — SIS





In the context of COVID-19: SIRS

in progress



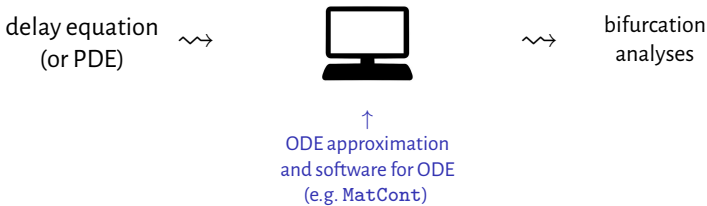
Black: Delta-like; red: Omicron-like

Limitations and things I'd like to do

- preliminary plots are for ODEs
- extend to TSI models (which can account for oscillations)
- can we build 'maps' that help prepare for a next wave in the face of uncertainty?

Numerical methods for delay equations and PSPMs

Work with: Mats Gyllenberg (Helsinki), Odo Diekmann (Utrecht), Rossana Vermiglio, Dimitri Breda & CDLab (Udine)…

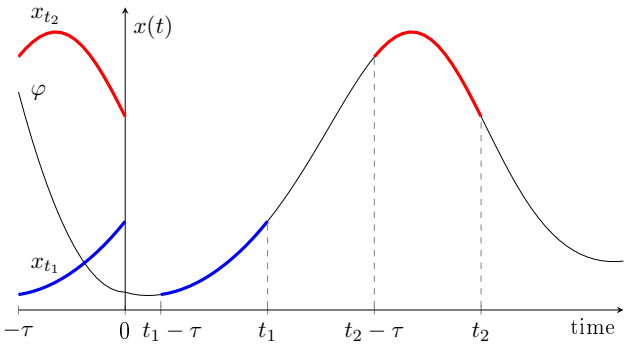


- Simple implementation of the approximating ODE system
- Efficient: low-dimensional approximation of stability of equilibria and periodic orbits
- General: applied to integral, delay differential, partial differential equations

Delay equation: a rule for extending a function given its past

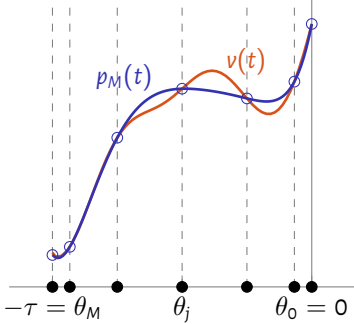
Let $\tau > 0$ be the maximal delay. Given a function x, the history function is

$$x_t \colon [-\tau, 0] \to \mathbb{R}$$
$$x_t(\theta) = x(t+\theta), \quad \theta \in [-\tau, 0]$$



Delay equations and pseudospectral method

$$\dot{v}(t) = \mathcal{A}_0 v(t) + \mathcal{F}(v(t))$$
$$\downarrow$$
$$\dot{V}_M(t) = A_M V_M(t) + F_M(V_M(t))$$



DDEs $\quad \dot{y}(t) = F(y_t) \quad \longrightarrow \quad \begin{cases} \dot{x}_0 = F(p_M) & (x_0 \in \mathbb{R}) \\ \dot{X} = dx_0 + DX & (X \in \mathbb{R}^M) \end{cases}$ with $\quad p_M(t) \approx y_t$

REs $\quad y(t) = F(y_t) \quad \longrightarrow \quad \begin{cases} x_0 = 0 \\ \dot{X} = DX + F(p'_M) & (X \in \mathbb{R}^M) \end{cases}$ with $\quad p_M(t) \approx \int_t^{t+\cdot} y_t(s)ds$

for $D \in \mathbb{R}^{M \times M}$, $d \in \mathbb{R}^M$

Final thoughts

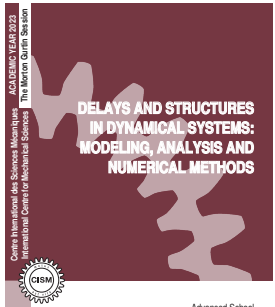
- it's not just a matter of having more general parameters (e.g. Gamma instead of Erlang)
- incorporating more detailed micro-scale (within-host) dynamics may be important; we need to think when it's fair to ignore and when not
- numerical methods should be developed and are being developed

More things I'd like to do

- work towards enabling TSI models in public health through development of numerical methods
- further investigate how the within-host dynamics impacts the population scale
- link more closely within- and between-host models and data

Advertisement

CISM Advanced Course (Udine, Italy)
"Delays and Structures in Dynamical Systems: Modelling, Analysis and Numerical Methods"
November 20–24, 2023



INVITED LECTURERS

Odo Diekmann - Utrecht University, The Netherlands
5 lectures plus discussion on: population dynamics - the notion of state at the individual and at the population level; the notion of environmental condition; the formulation of a size structured model, both in terms of a PDE and in terms of a renewal equation; functional analytic and dynamical systems aspects; density dependence via feedback to the environmental condition; variable maturation delay; biological insights.

Tony Humphries - McGill University, West Montreal, Quebec, Canada
5 lectures plus discussion on: modeling with state-dependent delays; delays defined by threshold conditions; dynamical systems formulation of state-dependent delay equations; linearization and numerical techniques.

Davide Liessi - CDLab, University of Udine, Italy
and **Zachary McCarthy** - LIAM, York University, Toronto, Canada
5 laboratory sessions on: numerical simulation in time of delay equations; computation of equilibria and relevant stability; computation of periodic orbits and relevant stability; numerical continuation; bifurcation analysis from Hopf to chaos - with MATLAB/Octave, Python, MatCont, DDE-Biftool (bring your own laptop).

Stefano Maset - University of Trieste, Italy
and **Rossana Vermiglio** - CDLab, University of Udine, Italy
5 lectures plus discussion on: numerical methods for delay equations; adaptation of continuous methods for ODEs; constrained meshes and superconvergence; functional continuous Runge-Kutta methods; methods for neutral equations; boundary value problems; innovative techniques based on a general abstract formulation; connections to bifurcation analysis.

Shigui Ruan - The University of Miami, Coral Gables, FL, USA
5 lectures plus discussion on: population dynamics models with two structures; relevant semigroup theory and existence of solutions; spectrum theory; eigenvalue problem; stability of steady states; asynchronous exponential growth of solutions (both linear and nonlinear equations will be considered).

Francesca Scarabel - The University of Leeds, UK
5 lectures plus discussion on: examples of mathematical models from ecology and epidemiology; introduction to the dynamical and bifurcation analysis; pseudospectral collocation of nonlinear problems formulated as delay or partial differential equations; stability of equilibria and relevant bifurcations; stability of periodic orbits and relevant bifurcations.

Thank you!

(and questions, comments…?)

Complex behaviour: a model with waning and boosting of immunity

in progress with M.V. Barbarossa, M. Polner and G. Röst

$$\frac{dI}{dt} = \beta SI - (\gamma + d)I$$

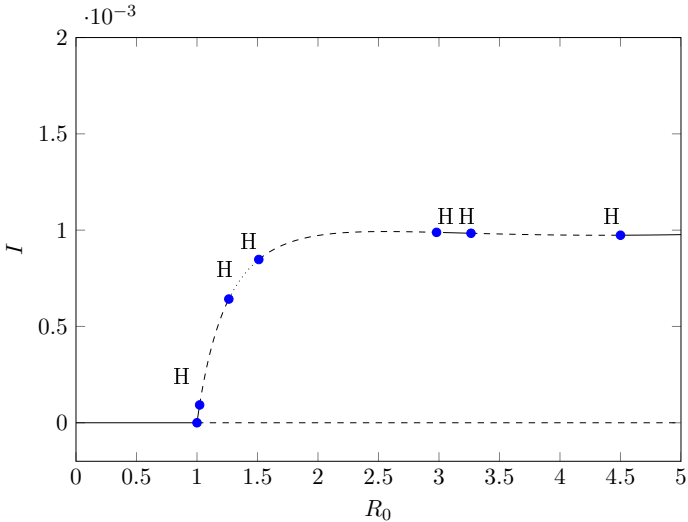
$$\frac{dS}{dt} = d(1 - S) - \beta SI + I(t - \tau) \underbrace{[\gamma + \nu\beta R(t - \tau)]}_{\text{recovered + boosted}} \underbrace{e^{-d\tau - \nu\beta \int_{t-\tau}^{t} I(u)du}}_{\text{“survival” in } R \text{ for time } \tau}$$

- $S + I + R = 1$
- $\beta =$ transmission, $\gamma =$ recovery, $d =$ birth $=$ death
- $\tau =$ maximal duration of immunity unless boosted
- $\nu =$ probability of immunity boosting after contact with infectious individual (boost to the maximal immunity level)

Barbarossa, Polner, Röst, *SIAM. J. Appl. Math.*, 2017

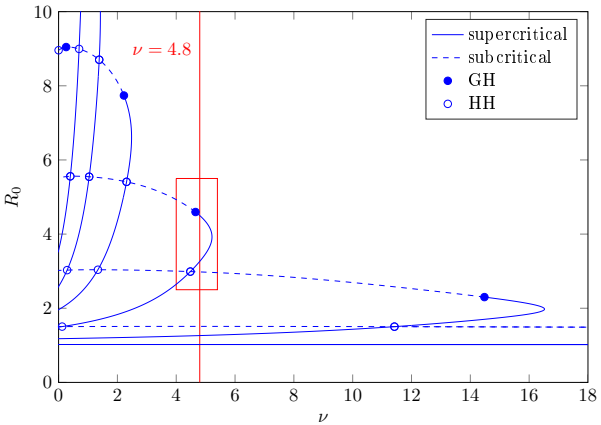
Bifurcations of equilibria

$d = 0.02, \quad \gamma = 17, \quad \nu = 4.8, \quad \tau = 15, \quad R_0 = \frac{\beta}{d+\gamma} \quad (M = 20)$

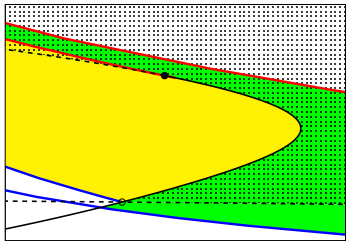


Bifurcations in the plane (ν, R_0)

Hopf bifurcation curves (sub/supercritical)



Zoom



Dotted: stable positive equilibrium
Red: fold bifurcation of cycles
Blue: Neimark-Sacker bifurcations
Green: (at least) one stable periodic solution
Yellow: (at least) two stable coexisting periodic solutions