MAX PLANCK INSTITUTE
FOR DYNAMICS OF COMPLEX
TECHNICAL SYSTEMS
MAGDEBURG

Mathematical Modeling of Infectious Disease

Compartment and Graph-based Models

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MathCoRe Seminar

Partners:

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Motivation

- Goal: Avoid outbreaks in nusery homes or hospitals.
- Constraint: Tests are expensive and unpleasant.
- Research question: What is a good testing strategie?
  - What is a good model?
  - How to quantify the costs of testing or not testing?

Joint project with Prof. Achim Kaasch[1] from the OVGU Medical Faculty.

[1] `http://www.immb.ovgu.de/`

Outline

1. Compartment Models and Stability Analysis

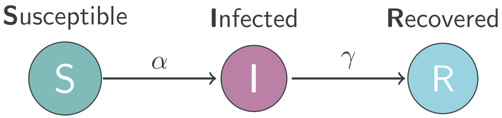
2. The SEIQRT Model and MPC

3. Graph-based Modelling and Simulation

Overview

1. Compartment Models and Stability Analysis
2. The SEIQRT Model and MPC
3. Graph-based Modelling and Simulation

Compartment model SIR



$$N = S + I + R$$

$$\begin{aligned} S' &= -\frac{\alpha}{N} IS \\ I' &= \frac{\alpha}{N} IS - \gamma I \\ R' &= \gamma I \end{aligned}$$

α: infection rate
γ: recovery rate

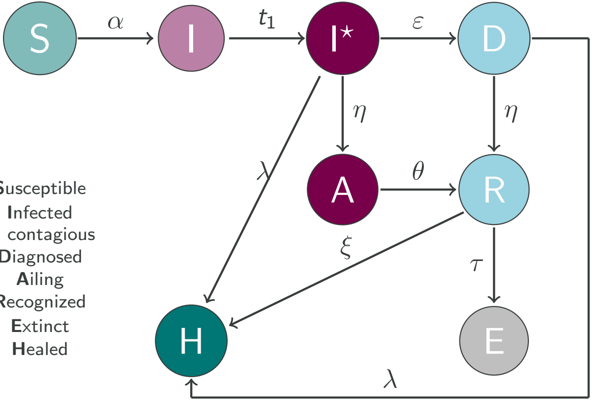
Some basic analysis:

- Conservation of mass: $S' + I' + R' = 0$.
- Positivity: $S(0)$, $I(0)$, $R(0) \geq 0$, then $S(t)$, $I(t)$, $R(t) \geq 0$.
- Set $S(0) + I(0) + R(0) = 1$, then S, I, R represent fractions of the population.

Compartment model

In the spirit of the **S**usceptible-**I**nfected-**R**ecovered approach[1] and the SIDARTHE model[2]

Susceptible
Infected
I* contagious
Diagnosed
Ailing
Recognized
Extinct
Healed



Legend

α	infection rate
t_1	time between infection and becoming contagious
ε	testing frequency of people
η	probability of developing symptoms
θ	testing of symptomatic with time delay of 1 day
λ	probability of being healed
ξ	recovery rate
τ	death rate

[1] W. O. Kermack, A. G. McKendrick. A contribution to the mathematical theory of epidemics. Proceedings of the royal society of london. Series A, Containing papers of a mathematical and physical character, 115(772):700-721, 1927

[2] G. Giordano, F. Blanchini, R. Bruno, P. Colaneri, A. D. Filippo, A. D. Matteo, M. Colaneri. Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy. Nature Medicine, 2020

SIDHARTE model as ODE

$$
\begin{aligned}
\dot{S}(t) &= -S(t)(\alpha I(t) + \beta D(t) + \gamma A(t) + \delta R(t)) \\
\dot{I}(t) &= S(t)(\alpha I(t) + \beta D(t) + \gamma A(t) + \delta R(t)) - (\varepsilon + \zeta + \lambda) I(t) \\
\dot{D}(t) &= \varepsilon I(t) - (\eta + \rho) D(t) \\
\dot{A}(t) &= \zeta I(t) - (\theta + \mu + \kappa) A(t) \\
\dot{R}(t) &= \eta D(t) + \theta A(t) - (\nu + \xi) R(t) \\
\dot{T}(t) &= \mu A(t) + \nu R(t) - (\sigma + \tau) T(t) \\
\dot{H}(t) &= \lambda I(t) + \rho D(t) + \kappa A(t) + \xi R(t) + \sigma T(t) \\
\dot{E}(t) &= \tau T(t)
\end{aligned}
$$

Basic analysis:

- $S' + I' + D' + A' + R' + T' + H' + E' = 0.$
- Positivity, if starting value is positive.
- Consider the states (S, x, H, E), with x collecting all infected.
  - Can show: System has equilibria $(\bar{S}, 0, \bar{H}, \bar{E})$.
  - Can ask: Is some $(\bar{S}, 0, \bar{H}, \bar{E})$ a stable equilibrium.

Stability Analysis

$$
\begin{aligned}
\dot{S}(t) &= -S(t)(\alpha I(t) + \beta D(t) + \gamma A(t) + \delta R(t)) \\
\dot{I}(t) &= S(t)(\alpha I(t) + \beta D(t) + \gamma A(t) + \delta R(t)) - (\varepsilon + \zeta + \lambda) I(t) \\
\dot{D}(t) &= \varepsilon I(t) - (\eta + \rho) D(t) \\
\dot{A}(t) &= \zeta I(t) - (\theta + \mu + \kappa) A(t) \\
\dot{R}(t) &= \eta D(t) + \theta A(t) - (\nu + \xi) R(t) \\
\dot{T}(t) &= \mu A(t) + \nu R(t) - (\sigma + \tau) T(t) \\
\dot{H}(t) &= \lambda I(t) + \rho D(t) + \kappa A(t) + \xi R(t) + \sigma T(t) \\
\dot{E}(t) &= \tau T(t)
\end{aligned}
$$

Consider the states (S, x, H, E), with x collecting all infected.

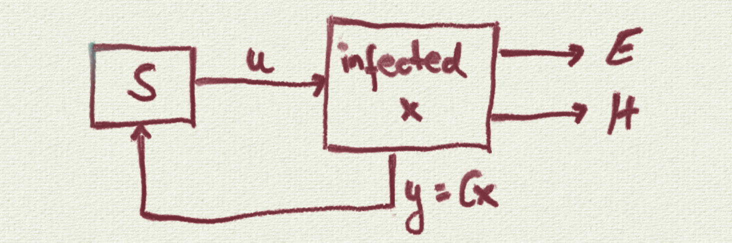
- Nonlinear only in $S(t)Cx(t)$, with $C = \begin{bmatrix} \alpha & \beta & \gamma & \delta & 0 \end{bmatrix}$.
- (H, E) do not contribute to the dynamics.

Rewrite as Feedback Loop

With a matrix $F \in \mathbb{R}^{5,5}$ and $B \in \mathbb{R}^{5,1}$, we rewrite the system as

$$\begin{aligned} \dot{x}(t) &= Fx(t) + Bu(t) \\ \dot{S}(t) &= -S(t)Cx(t) \\ 0 &= u(t) - S(t)Cx(t). \end{aligned}$$

which is a linear system with a nonlinear feedback loop.



Linear Stability Analysis

Linearize about the steady state $\bar{S}$ and substitute $u(t) = \bar{S}Cx(t)$:

$$\begin{bmatrix} \dot{S}(t) \\ \dot{x}(t) \end{bmatrix} = \begin{bmatrix} 0 & -\bar{S}C \\ 0 & F + B\bar{S}C \end{bmatrix} \begin{bmatrix} S(t) \\ x(t) \end{bmatrix}$$

This system is stable in S and asymptotically stable in x

- if, and only if

$$F + B\bar{S}C \text{ is } \textit{Hurwitz},$$

  i.e. all eigenvalues of $F + B\bar{S}C$ have a negative real part,

which, for the SIDHARTE model is the case[2]

- if, and only if,

$$\bar{S} < S^*,$$

  with $S^* =: \frac{1}{R_0}$ being the reciprocal of the *basic reproduction factor*.

[2] Giordano et al. (2020)

Interpretation of the Stability

$$\text{Stability} \quad \leftrightarrow \quad \bar{S} < \frac{1}{R_0} \quad \leftrightarrow \quad R_0 \bar{S} < 1$$

- Given a current stable steady state $\bar{S}$, a (small) number of infections $x(t)$ will simply fade out exponentially.
  - The fraction $\bar{S}$ of unaffected people does not change significantly.

- The reproduction factor R_0 is a function of the model, not of the states.
  - If $\bar{S} = 1$, then $R_0 < 1$ is needed.
  - If $\bar{S} < 1$, then $R_0 > 1$ can be OK.

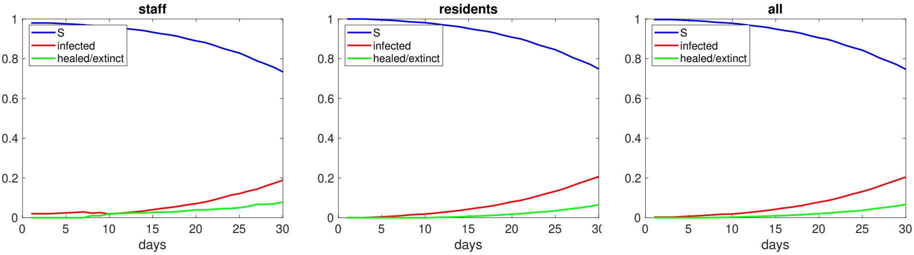
- Starting in an unstable state $\bar{S}$, a pandemics will last at least until $S(t) < \frac{1}{R_0}$.
  - With $R_0 = 3$, this means at least until $S(t) = \frac{1}{3}$ or until 67% of the population has been affected.

Example Computations

Also check of sensitivity

350 people = 300 residents + 50 staff, 1 staff is infected
5 contacts, $\alpha = 0.15$

Test every 7th day



Also check of sensitivity

350 people = 300 residents + 50 staff, 1 staff is infected
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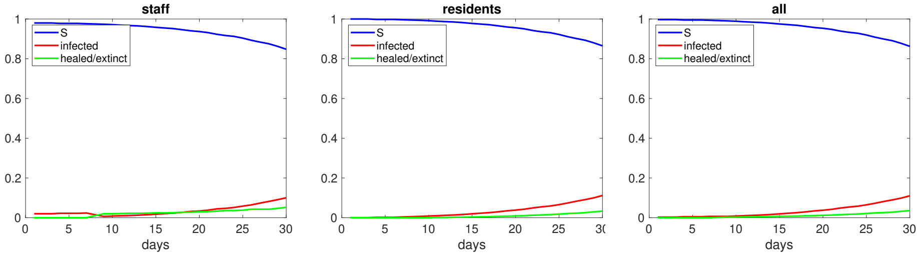
Test every 3rd day

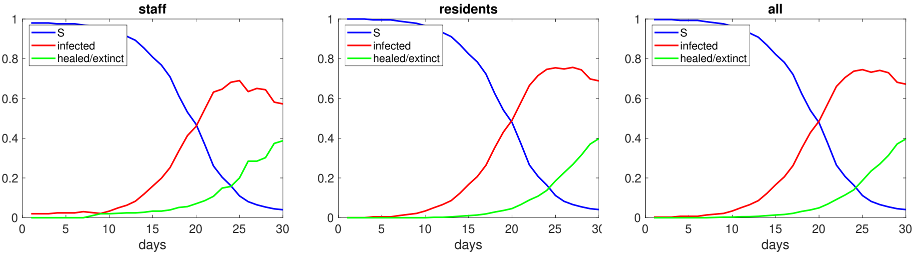


Example Computations

Also check of sensitivity

350 people = 300 residents + 50 staff, 1 staff is infected
5 contacts, $\alpha = 0.3$

Test every 3rd day



Our Current Research Direction

- Applicability to small populations like a nursery home.
  - Consider models with time-delays to account for latencies directly.
- Sensitivity analysis of fitted models
  - Improve the confidence.
  - Find parameters for optimization.

Overview

The SEIQRT Model

Another extension to the classic SIR model[3]

$$\frac{\mathrm{d}}{\mathrm{d}\,t}\, S(t) = -\beta(t)S(t)I(t) + \mu N - \mu S(t)$$

$$\frac{\mathrm{d}}{\mathrm{d}\,t}\, E(t) = \quad \beta(t)S(t)I(t) - (\gamma + \mu)E(t)$$

$$\frac{\mathrm{d}}{\mathrm{d}\,t}\, I(t) = \gamma E(t) - (\eta + \mu + u(t) + \tau)I(t)$$

$$\frac{\mathrm{d}}{\mathrm{d}\,t}\, Q(t) = u(t)I(t) - (\tilde{\eta} + \mu + \tau)Q(t)$$

$$\frac{\mathrm{d}}{\mathrm{d}\,t}\, R(t) = \eta I(t) - \mu R(t)$$

$$\frac{\mathrm{d}}{\mathrm{d}\,t}\, R_Q(t) = \tilde{\eta} Q(t) - \mu R_Q(t)$$

$$\frac{\mathrm{d}}{\mathrm{d}\,t}\, T(t) = \tau I(t) + \tau Q(t) - \mu T(t)$$

[3] Kurt Chudej

The SEIQRT Model

Another extension to the classic SIR model[3]

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}\,t} S(t) &= -\beta(t)S(t)I(t) + \mu N - \mu S(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} E(t) &= \quad \beta(t)S(t)I(t) - (\gamma + \mu)E(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} I(t) &= \gamma E(t) - (\eta + \mu + u(t) + \tau)I(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} Q(t) &= u(t)I(t) - (\tilde{\eta} + \mu + \tau)Q(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} R(t) &= \eta I(t) - \mu R(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} R_Q(t) &= \tilde{\eta} Q(t) - \mu R_Q(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} T(t) &= \tau I(t) + \tau Q(t) - \mu T(t)
\end{aligned}
$$

The research question is how to use the controls we have to achieve what we want!

- quarantine u
- social distancing β
- division of the society by age

[3] Kurt Chudej

SEIQRT model as a flow chart

Blue lines represent linear dynamics, and red lines represent quadratic dynamics.

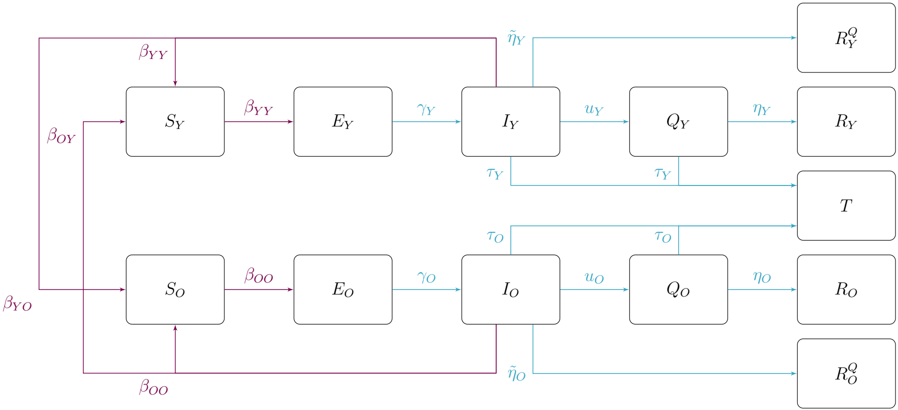


Figure: Schematic representation of the SEIQRT model.

SEIQRT model age compartments I

More Compartments

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}\,t}\, S_Y(t) &= -\beta_{YY}(t)S_Y(t)I_Y(t) - \beta_{YO}(t)S_Y(t)I_O(t) + \mu N - \mu S_Y(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t}\, S_O(t) &= -\beta_{OY}(t)S_O(t)I_Y(t) - \beta_{OO}(t)S_O(t)I_O(t) - \mu S_O(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t}\, E_Y(t) &= \quad \beta_{YY}(t)S_Y(t)I_Y(t) + \beta_{YO}(t)S_Y(t)I_O(t) - (\gamma_Y + \mu)E_Y(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t}\, E_O(t) &= \quad \beta_{OY}(t)S_O(t)I_Y(t) + \beta_{OO}(t)S_O(t)I_O(t) - (\gamma_O + \mu)E_O(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t}\, I_Y(t) &= \gamma_Y E_Y(t) - (\eta_Y + \mu + u_Y(t) + \tau_Y)I_Y(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t}\, I_O(t) &= \gamma_O E_O(t) - (\eta_O + \mu + u_O(t) + \tau_O)I_O(t)
\end{aligned}$$

More Compartments

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}\,t} Q_Y(t) &= u_Y(t) I_Y(t) - (\tilde{\eta}_Y + \mu + \tau_Y) Q_Y(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} Q_O(t) &= u_O(t) I_O(t) - (\tilde{\eta}_O + \mu + \tau_O) Q_O(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} R_Y(t) &= \eta_Y I_Y(t) - \mu R_Y(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} R_O(t) &= \eta_O I_O(t) - \mu R_O(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} R_Y^Q(t) &= \tilde{\eta}_Y Q_Y(t) - \mu R_Y^Q(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} R_O^Q(t) &= \tilde{\eta}_O Q_O(t) - \mu R_O^Q(t) \\
\frac{\mathrm{d}}{\mathrm{d}\,t} T(t) &= \tau_Y I_Y(t) + \tau_O I_O(t) + \tau_Y Q_Y(t) + \tau_O Q_O(t) - \mu T(t)
\end{aligned}
$$

Objective Functions

Priorities: 1) minimize people in quarantine, 2) do not exceed ICU capacity for old people ($\bar{I}_O$), and 3) minimize social distancing ($\beta^0 \sim$ no social distancing).
We assume that $\beta_{OY} = \beta_{YO}$, i.e., old people infect young people as much as young people infect old people.

$$J_1(u, \beta) = \int_{t_k}^{t_k^f} Q_{\mathrm{Y}}(t) + Q_{\mathrm{O}}(t)\,\mathrm{d}t$$

$$J_2(u, \beta) = \int_{t_k}^{t_k^f} \max\{0, I_{\mathrm{O}}(t) - 0.9\bar{I}_{\mathrm{O}}\}^2\,\mathrm{d}t$$

$$J_3(\beta) = \int_{t_k}^{t_k^f} \max\{0, \beta_{YY}(t) - \beta^0\}^2\,\mathrm{d}t$$

$$J_4(\beta) = \int_{t_k}^{t_k^f} \max\{0, \beta_{YO}(t) - \beta^0\}^2\,\mathrm{d}t$$

$$J_5(\beta) = \int_{t_k}^{t_k^f} \max\{0, \beta_{OO}(t) - \beta^0\}^2\,\mathrm{d}t$$

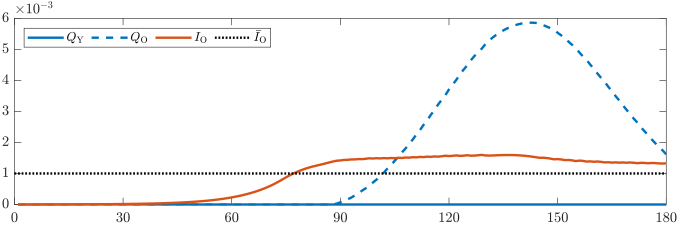
Model predictive control

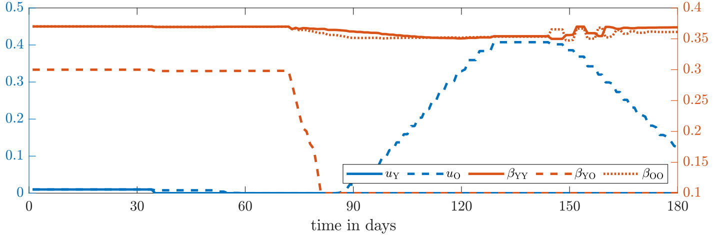
We compute the model predictive control strategy by repeatedly solving the optimal control problem

$$\begin{aligned} \min_{u,\beta} \quad & \mathcal{J}(u,\beta) = \nu_1 J_1(u,\beta) + \nu_2 J_2(u,\beta) \\ & \qquad + \nu_3 J_3(\beta) + \nu_4 J_4(\beta) + \nu_5 J_5(\beta) \\ \text{s.t.} \quad & \dot{x}(t) = f(x(t),u(t),\beta(t)), \quad x(t_k) = x_k^0, \\ & (u(t),\beta(t)) \in [0,1] \times [\underline{\beta},\overline{\beta}]^3 \quad \forall\, t \in [t_k, t_k^f], \end{aligned}$$

Model predictive control – example

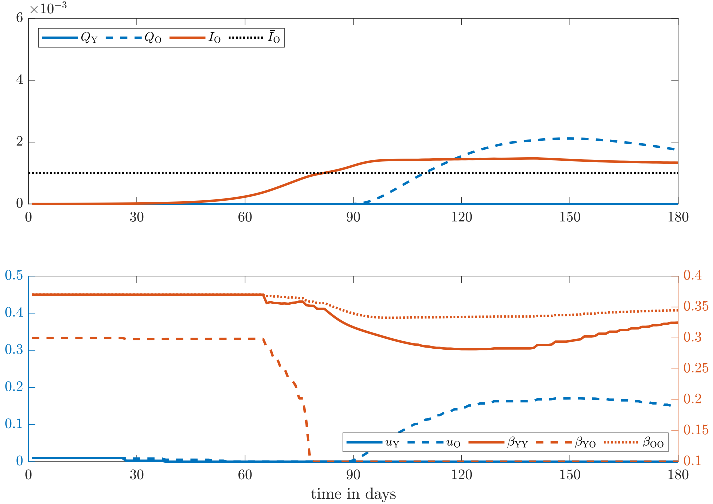
Short horizon – predict 7 days into the future.





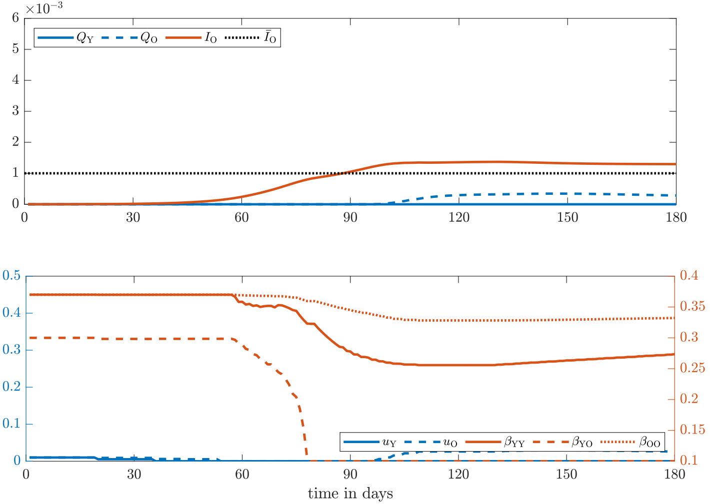
Model predictive control – example

Short horizon – predict 14 days into the future.



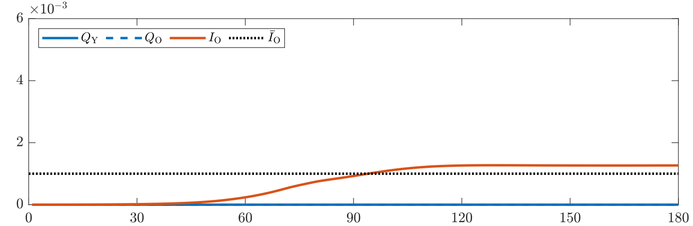
Model predictive control – example

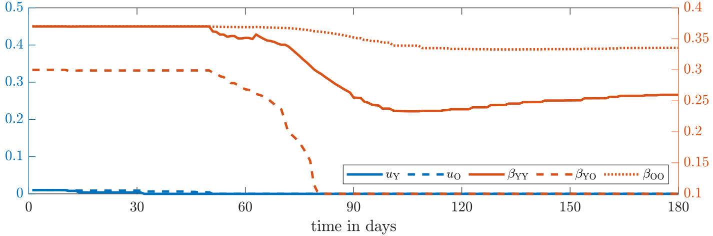
Short horizon – predict 21 days into the future.



Model predictive control – example

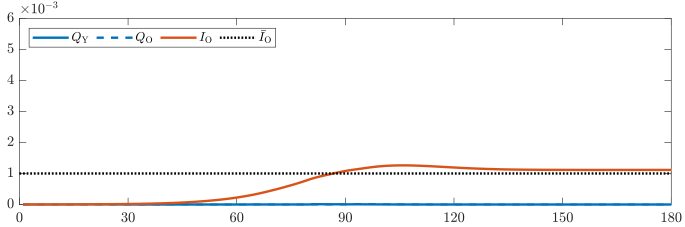
Longer horizon – predict 28 days into the future.

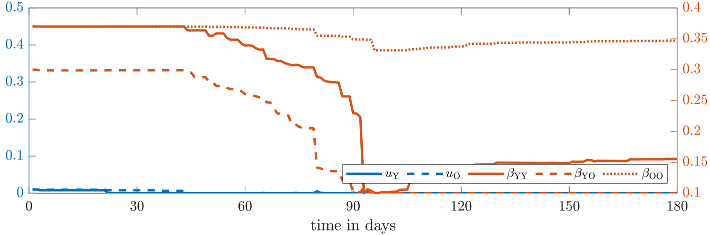




Model predictive control – example

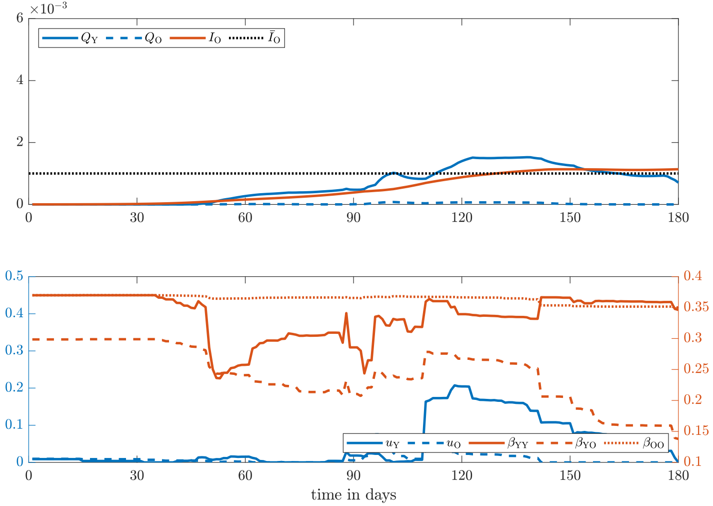
Longer horizon – predict 35 days into the future.





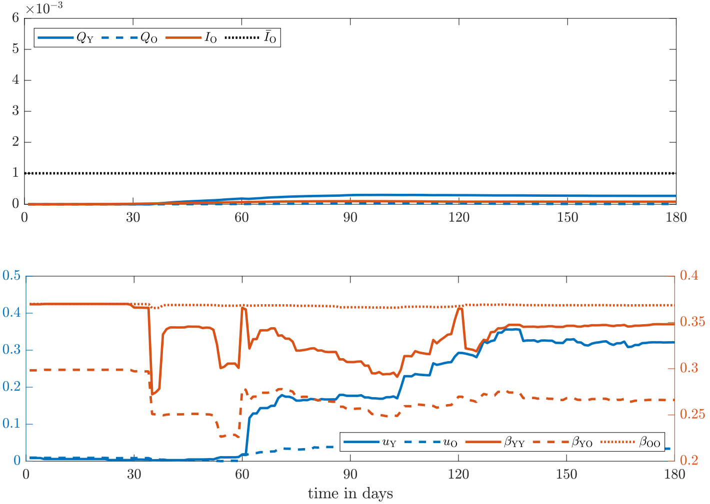
Model predictive control – example

Longer horizon – predict 42 days into the future.



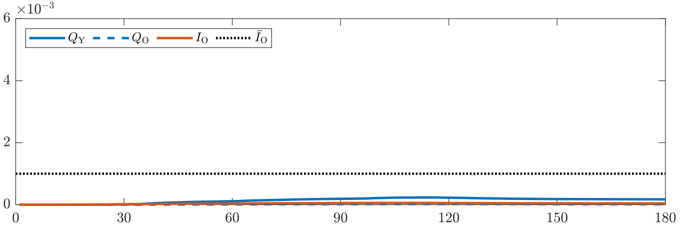
Model predictive control – example

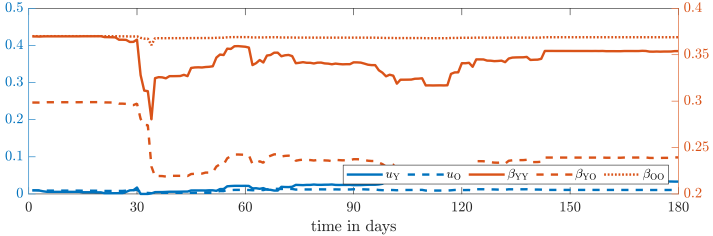
Longer horizon – predict 49 days into the future.



Model predictive control – example

Longer horizon – predict 56 days into the future.



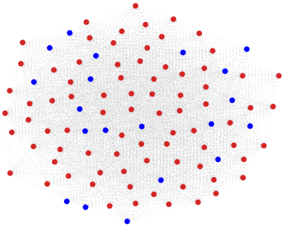


Overview

The Graph Modell

The basis is a weighted graph, where each node represents a person and an edge a probability of meeting each other

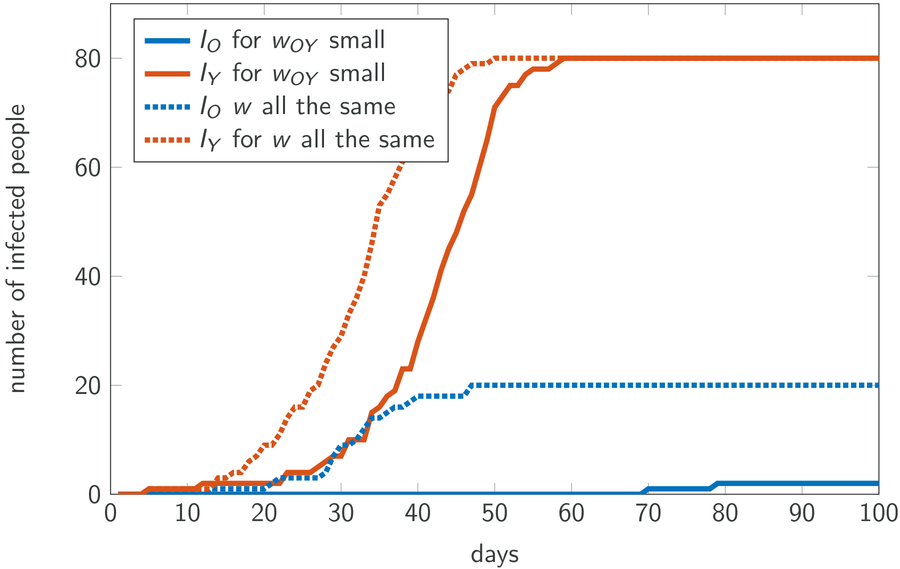
- Forward in time simulation by spreading through the graph
- As in the model above we distinguish nodes that represent old and young people
- from E to I is a matter of time in this model
- quarantine measures can be implemented here as well easily by marking the node quarantine and removing the egdes or changing the edge weights
- same is true for recovery and death rates



A toy example

- 100 Nodes: 20 Old and 80 Young
- Edges on the graph are random in this example
- 3 different transfer probabilies w_{OO}, w_{YY}, w_{YO}
- an infected person becomes infectious after 6 days and no longer infectious after 20
- two simulations
  - all w the same
  - w_{OY} much smaller

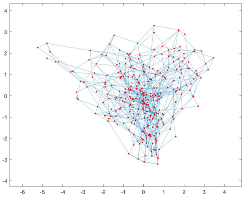
Toy Example Simulation Results



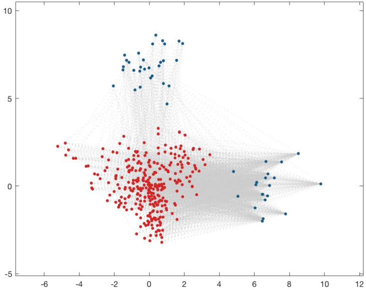
A specific Problem and a more specific graph

An elderly care facility

- 300 residents
- random edges between residents
- with random transfer probabilities between 0 and 0.25.



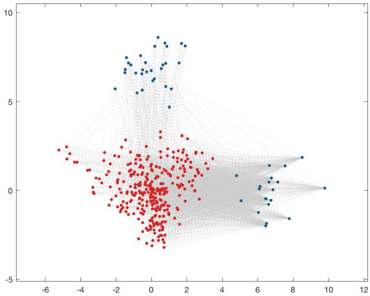
- 30 care taker and 20 other employees
- one care taker for 10 residents with a transfer probability of 0.15
- other caretaker have a transfer probability of 0.05



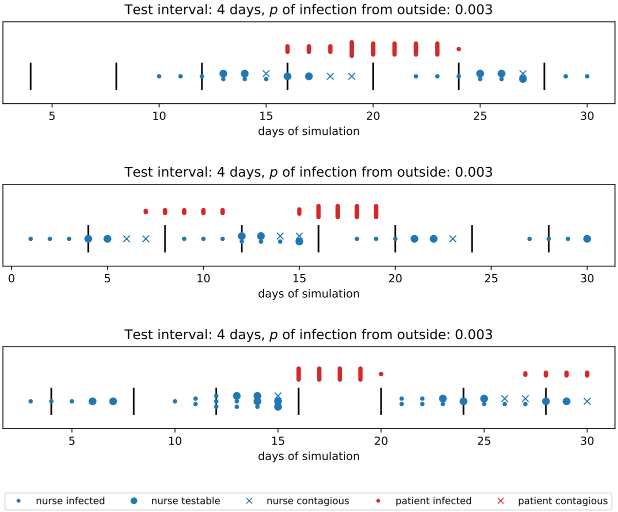
Simulation

Parameters

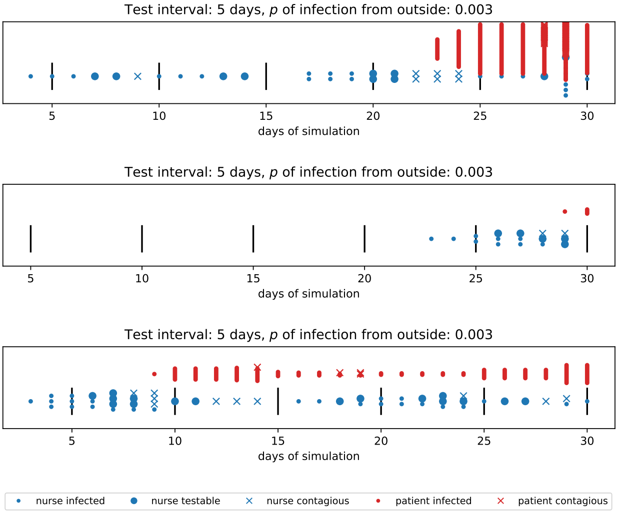
- Infection probability per day from outside 0.003 (only from outside)
- test frequency: every 4,5,6 days
- test show positive result: after 4 days
- infectious after 6 days



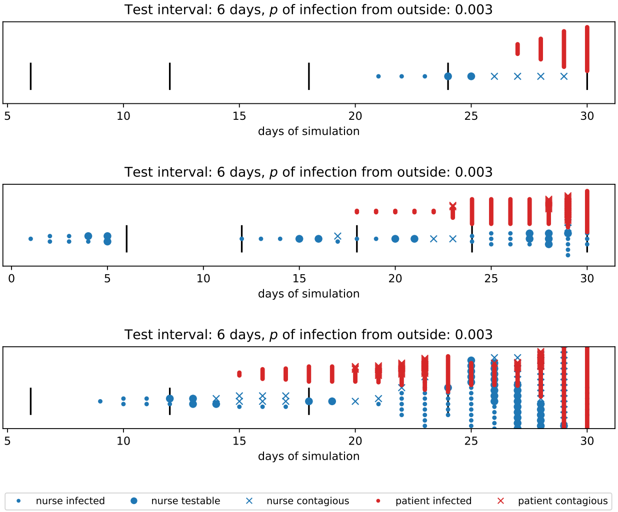
3 realizations for testing every 4 days



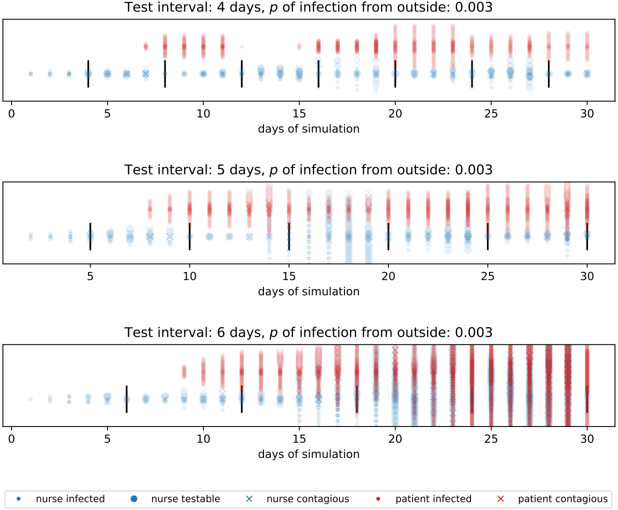
3 realizations for testing every 5 days



3 realizations for testing every 6 days



Overlay of 10 realizations



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GEFÖRDERT VOM

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MAX-PLANCK-INSTITUT FÜR DYNAMIK KOMPLEXER TECHNISCHER SYSTEME MAGDEBURG

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