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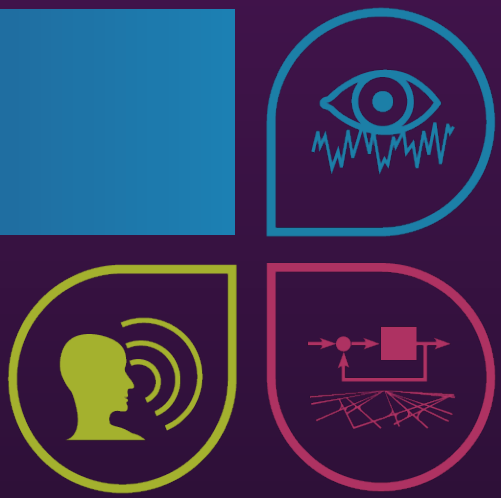
Mathematical Modeling of Epidemic Diseases



A case study of the COVID-19 coronavirus

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Part I

Short Lecture

An introduction to biological systems modeling

Compartmental modeling of a pandemic

Agent-based modeling of a pandemic



What is a model?

An entity that resembles a system or object in certain aspects, but is easier to work with as compared to the original system.

Introduction to modeling

What is a model?

An entity that resembles a system or object in certain aspects, but is easier to work with as compared to the original system.

Models are used for:

1. System identification
2. Simulation
3. Prediction
4. Control (the ultimate objective; but not always achievable)

Introduction to modeling
(continued)

Is it possible to model a complex biological and social phenomena such as a global pandemic?

Introduction to modeling
(continued)

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Yes! But subject to some conditions:

Introduction to modeling
(continued)

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1. Defining the model scope and level of abstraction

Introduction to modeling
(continued)

Is it possible to model a complex biological and social phenomena such as a global pandemic?

Yes! But subject to some conditions:

1. Defining the model scope and level of abstraction
2. Knowledge of the sources of modeling and observation errors

Introduction to modeling
(continued)

Is it possible to model a complex biological and social phenomena such as a global pandemic?

Yes! But subject to some conditions:

1. Defining the model scope and level of abstraction
2. Knowledge of the sources of modeling and observation errors
3. Access to reliable data

Mathematical modeling of epidemic and pandemic diseases

Context

Mathematical epidemiology; Biological systems modeling; Applied mathematics; Computer simulation

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Major approaches

- Top-down (macro-level modeling): compartmental models and spatio-temporal compartmental models
  - **Tools:** ordinary differential equations, partial differential equations, dynamic systems, estimation theory

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Major approaches

- Top-down (macro-level modeling): compartmental models and spatio-temporal compartmental models
  - **Tools:** ordinary differential equations, partial differential equations, dynamic systems, estimation theory
- Bottom-up (micro-level modeling): modeling the activity of a population of individuals
  - **Tools:** agent-based methods, cellular automata and computerized simulations

✎ These methods can be combined in a hybrid model



Compartmental modeling

Definition

A compartmental model is a weighted directed graph representation of a linear or nonlinear dynamic system

Compartmental modeling

Definition

A compartmental model is a weighted directed graph representation of a linear or nonlinear dynamic system

Steps

1. Partition the population into homogeneous groups of individuals (known as compartments)
2. Assign time-variables to the compartments
3. Write flow equations between the compartments
4. Model analysis, simulation, parameter estimation, and prediction

Compartmental modeling of epidemic diseased

Epidemic disease spread in large populations

A population of N individuals can be partitioned into population fractions:

- Susceptibles: $s(t)$
- Exposed (without symptoms): $e(t)$
- Infected (with symptom): $i(t)$
- Recovered: $r(t)$
- Deceased: $p(t)$

subject to $s(t) + e(t) + i(t) + r(t) + p(t) = 1$

Compartmental modeling of epidemic diseased

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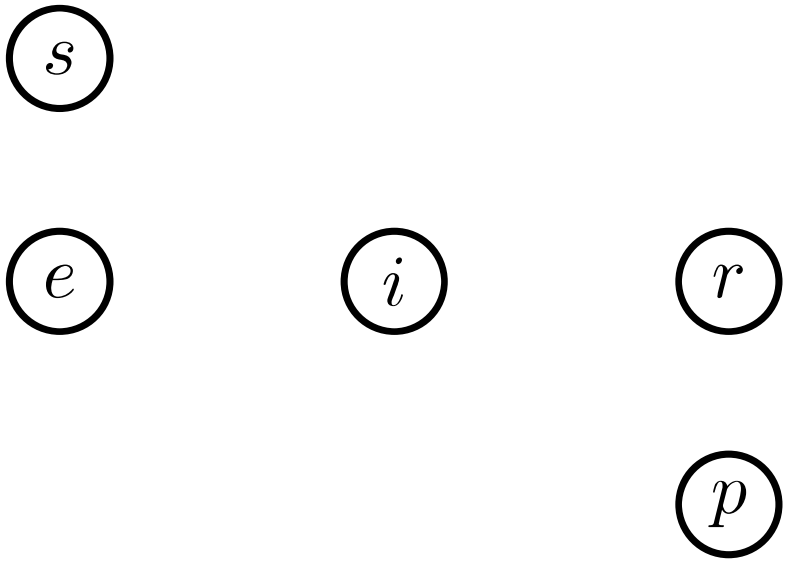
✎ In the sequel we study a:
mortal non-immunizing susceptible-exposed-infected-recovered (SEIR) model

Compartmental modeling of epidemic diseased
(Continued)

A mortal SEIR model without lifetime immunity

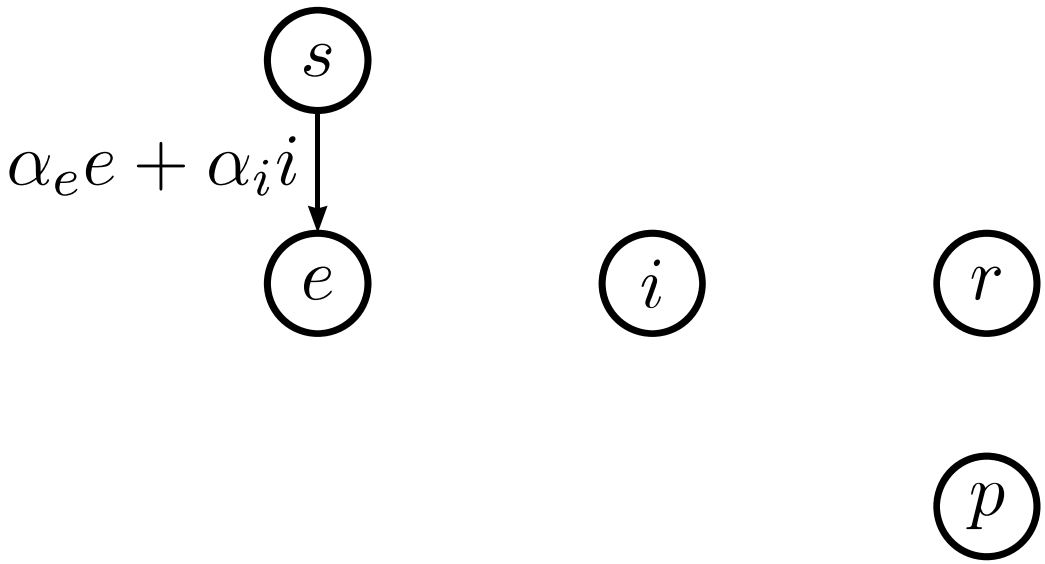
Start with the compartments.



Compartmental modeling of epidemic diseased
(Continued)

A mortal SEIR model without lifetime immunity

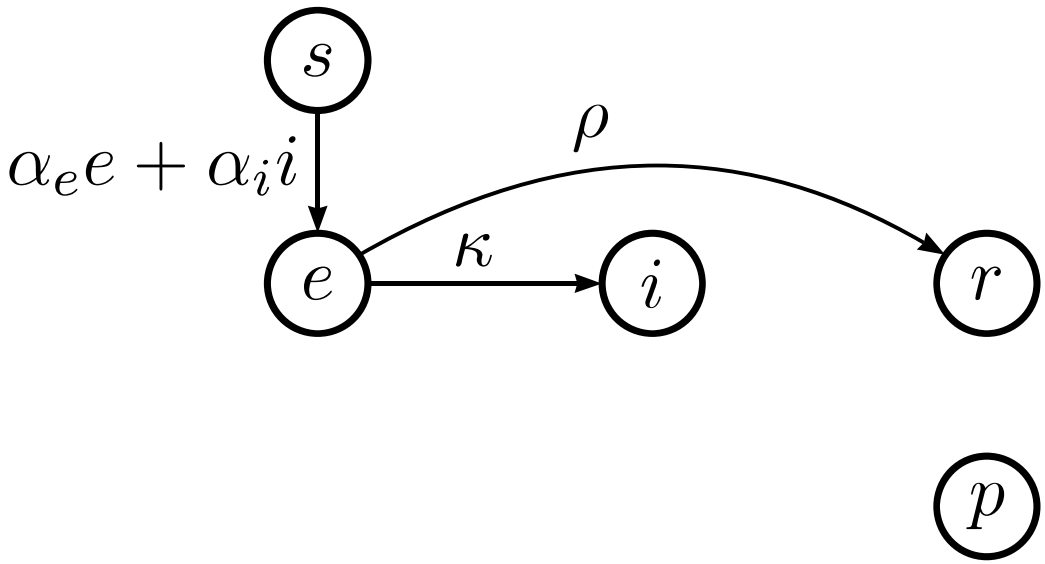
Individuals are infected as they contact infected or exposed subjects.



Compartmental modeling of epidemic diseased
(Continued)

A mortal SEIR model without lifetime immunity

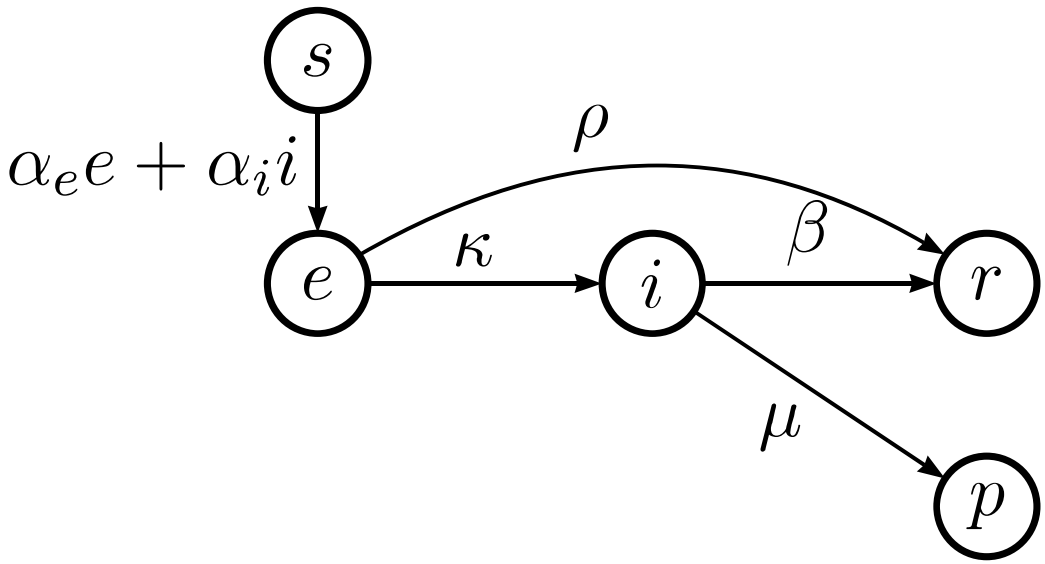
The exposed either recover or become infected with symptoms.



Compartmental modeling of epidemic diseased
(Continued)

A mortal SEIR model without lifetime immunity

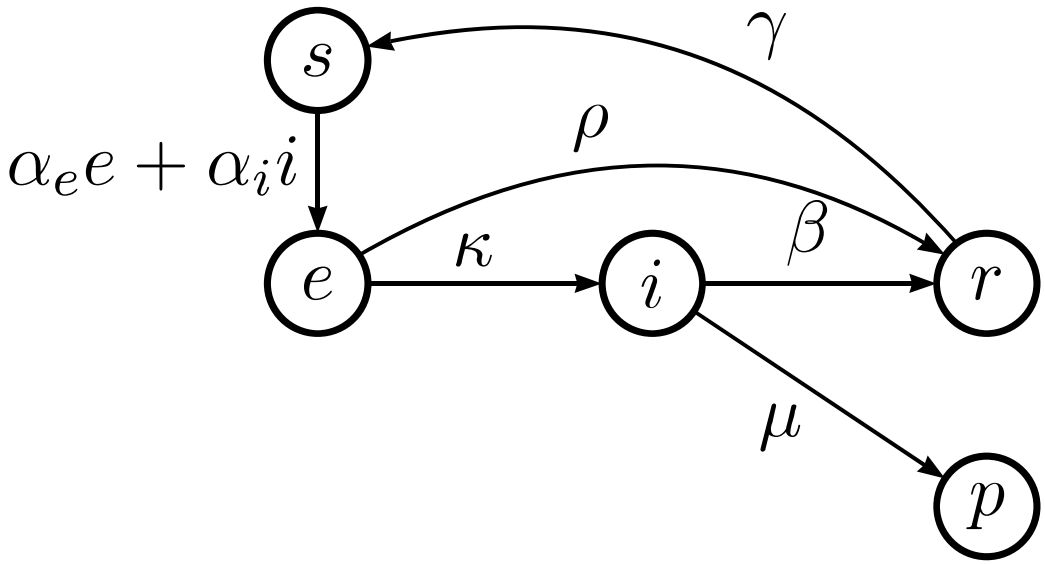
The infected either recover or pass away.



Compartmental modeling of epidemic diseased
(Continued)

A mortal SEIR model without lifetime immunity

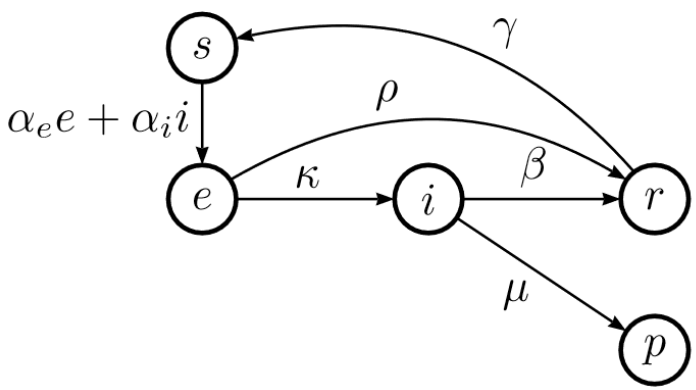
The recovered may again become susceptible.



Compartmental modeling of epidemic diseased
(Continued)

A non-immunizing fatal susceptible-exposed-infected-recovered (SEIR) model

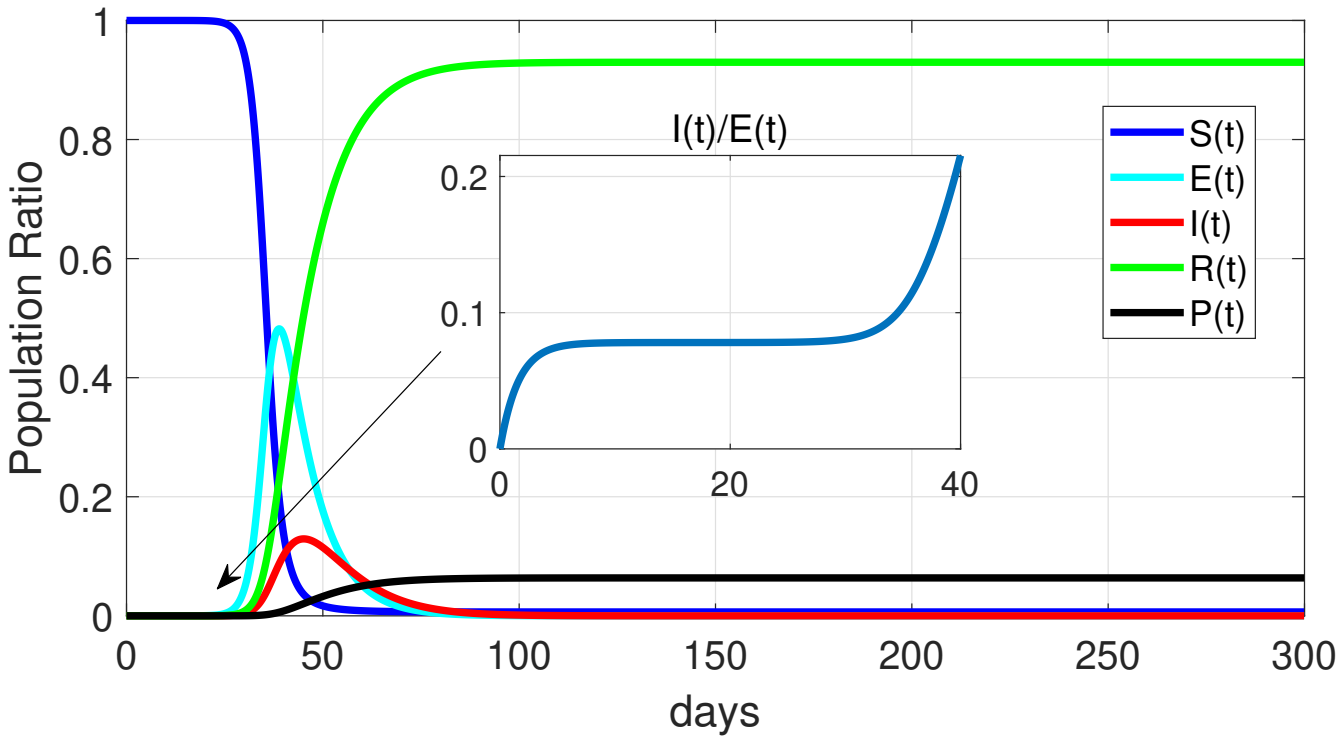
The full model and its corresponding dynamic equations, which can be numerically solved from initial conditions $[s(t_0), e(t_0), i(t_0), r(t_0), p(t_0)]$:



$$\frac{ds(t)}{dt} = -\alpha_e s(t)e(t) - \alpha_i s(t)i(t) + \gamma r(t)$$
$$\frac{de(t)}{dt} = \alpha_e s(t)e(t) + \alpha_i s(t)i(t) - \kappa e(t) - \rho e(t)$$
$$\frac{di(t)}{dt} = \kappa e(t) - \beta i(t) - \mu i(t)$$
$$\frac{dr(t)}{dt} = \beta i(t) + \rho e(t) - \gamma r(t)$$
$$\frac{dp(t)}{dt} = \mu i(t)$$

Typical solutions

The life-time immune case ($\gamma = 0$)



Compartmental modeling of epidemic diseased
(Continued)

What can we learn from the macro-level SEIR model?

Compartmental modeling of epidemic diseased
(Continued)

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Compartmental modeling of epidemic diseased
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Compartmental modeling of epidemic diseased
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Compartmental modeling of epidemic diseased
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Compartmental modeling of epidemic diseased
(Continued)

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Compartmental modeling of epidemic diseased
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Compartmental modeling of epidemic diseased
(Continued)

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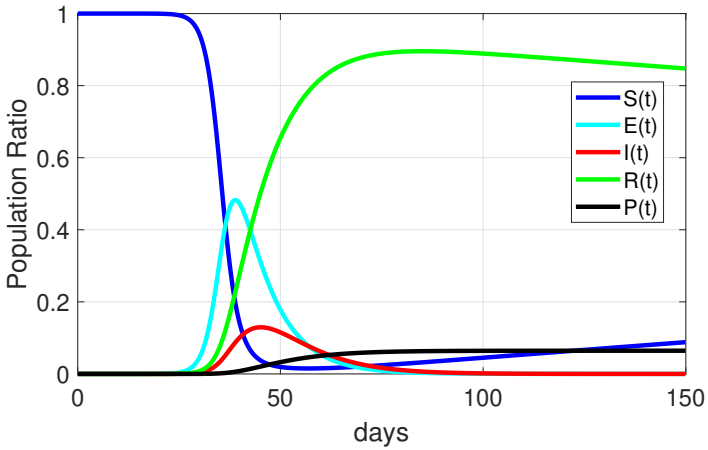
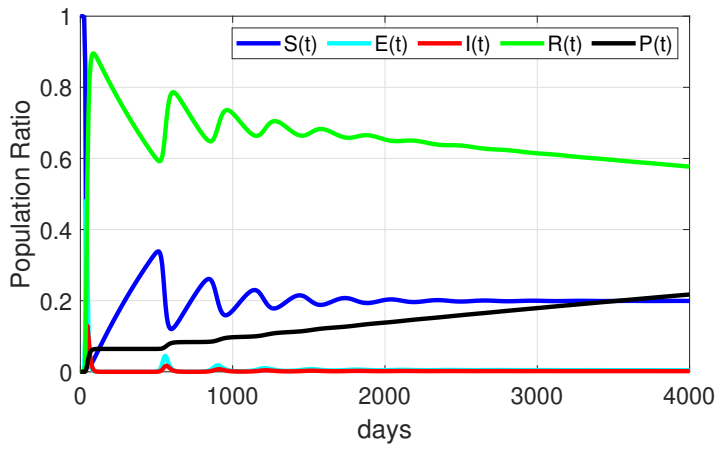
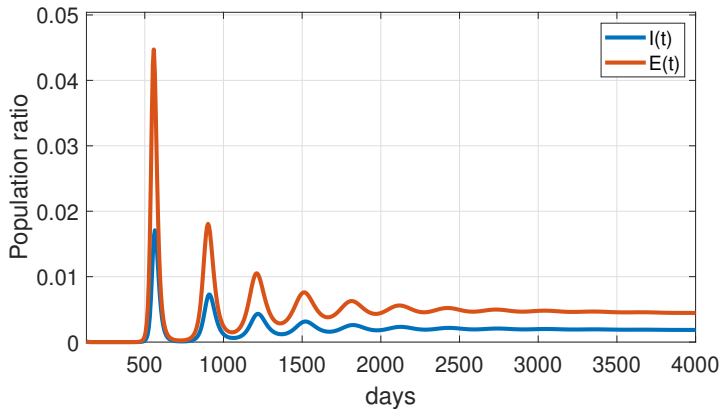
6. Potential future outbreaks
7. The model accuracy and the consistency of the reported data

Typical solutions
(Continued)

The non-immunizing case ($\gamma \neq 0$) in short- and long-term

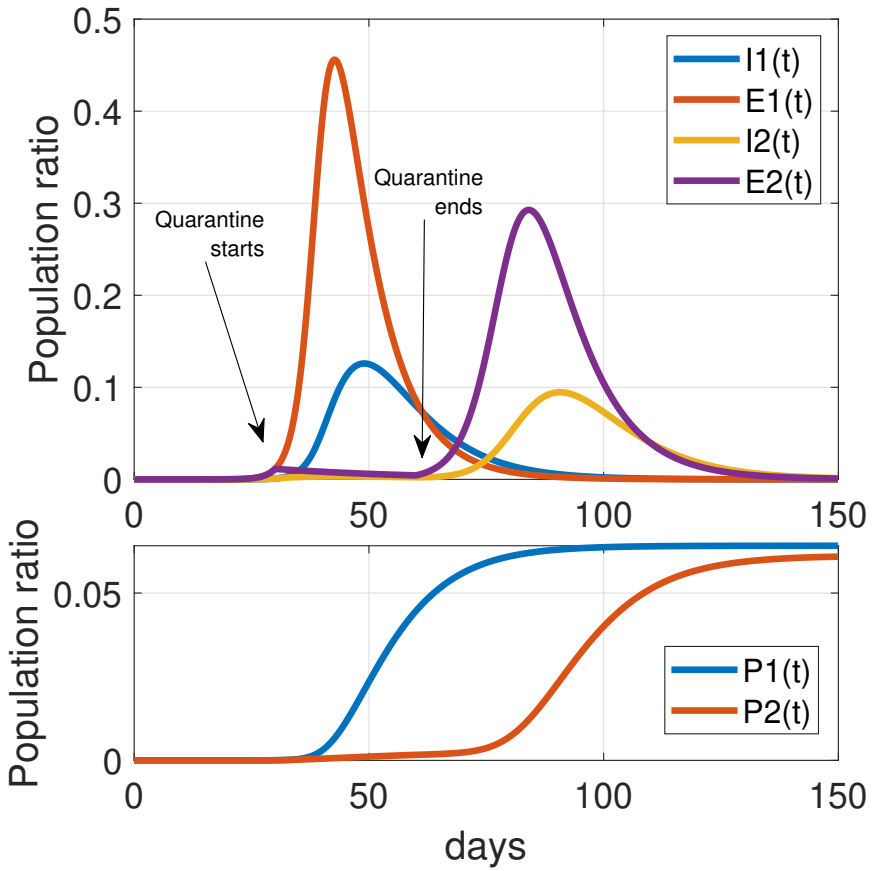






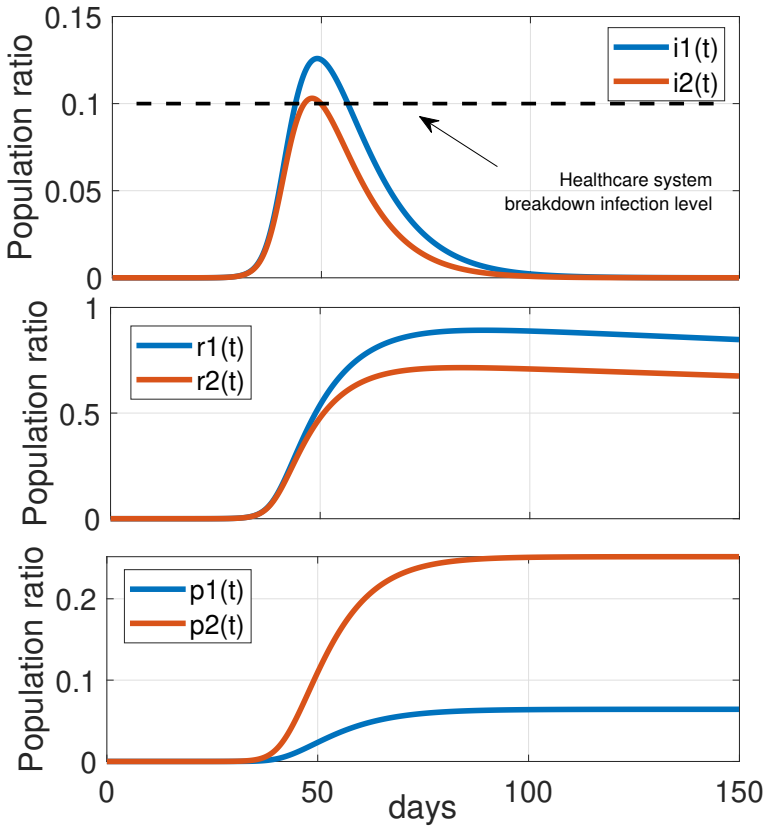
Typical solutions
(continued)

Insufficient lockdown periods



Typical solutions
(continued)

Healthcare system saturation and breakdown



Time-variant model parameters:

$$\beta(t) = (\beta_s - \beta_0)h(i(t)) + \beta_0$$
$$\mu(t) = (\mu_s - \mu_0)h(i(t)) + \mu_0$$

where

$$h(i) = \frac{1}{2}[1 + \tanh(\frac{i - i_0}{\sigma})]$$

Model extensions

Is the model unique?

Model extensions

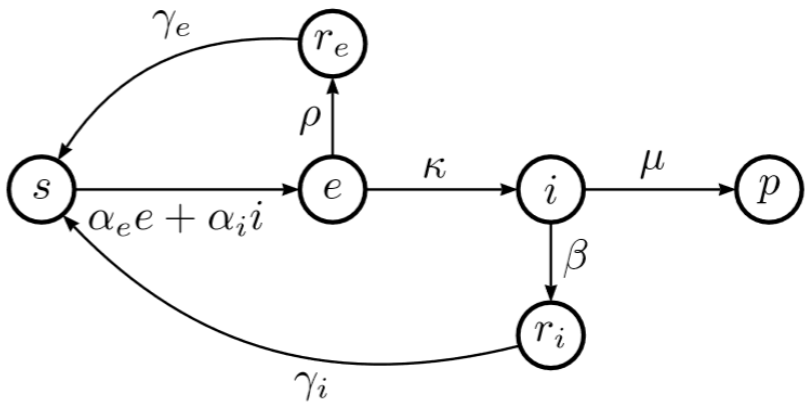
Is the model unique? No!

Model extensions

Is the model unique? No!

A modified SEIR model

- An extension of the fatal SEIR model for Coronavirus modeling is to assume that the recoveries from exposure and infection are separate compartments r_e and r_i:



- Other possible extensions: consider age groups, gender, seasons, geopolitical factors (hemispheres, cities, countries, continents, etc.)

Compartmental modeling of epidemic diseased
(Continued)

What we can't do with macro-level models?

Compartmental modeling of epidemic diseased
(Continued)

What we can't do with macro-level models?

1. Explicit modeling of individual behaviors

Compartmental modeling of epidemic diseased
(Continued)

What we can't do with macro-level models?

1. Explicit modeling of individual behaviors
2. Modeling family-level or community-level behavior

Compartmental modeling of epidemic diseased
(Continued)

What we can't do with macro-level models?

1. Explicit modeling of individual behaviors
2. Modeling family-level or community-level behavior
3. Modeling background individual diseases

An introduction to biological systems modeling

Compartmental modeling of a pandemic

Agent-based modeling of a pandemic

Micro-level modeling of epidemic diseases

Agent-based models

1. Individuals are modeled as abstract entities with certain properties and behaviors in an environment

Micro-level modeling of epidemic diseases

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1. Individuals are modeled as abstract entities with certain properties and behaviors in an environment
   - Properties: age, gender, nationality, infection status, background illness, social group, environment density, chance of illness, etc.
   - Behaviors: going to work/school, shaking hands, traveling with public transport, going to markets, etc.
   - Environment: school, office, market, bus, train, etc.

Micro-level modeling of epidemic diseases

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2. A large population of individuals are simulated, as they randomly interact with one another in the environment and their health condition switches (statistically)

Micro-level modeling of epidemic diseases

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3. Marginal statistics (e.g. the number of exposed, infected, recovered, etc.) are calculated over the entire population

Micro-level modeling of epidemic diseases

(continued)

Illustration of the individual entity

Environment.h | Individual.h | Epidemiology.cpp

Epidemiology | (Global Scope)

```
class Individual
{
    friend class Environment;
private:
    Gender gender;
    double age;
    double height;
    double weight;

    Nationality nationality;
    Country country;
    Location location_initial;
    Location location;
    DisplacementMatrix displacement_matrix;

    HealthRecord healthrecord;
    InfectionStatus healthstatus;
    InfectionLevels healthlevel;
public:

    int Move();
    friend int InteractBilateral(Individual indv1, Individual indv2);
    friend int ImpactUnilateral(Individual indv_source, Individual indv_destination);
    int ImpactEnvironment(Environment env);
    int GetImpactedByEnvironment(Environment env);
```

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Micro-level modeling of epidemic diseases
(continued)

Illustration of an agent-based environment

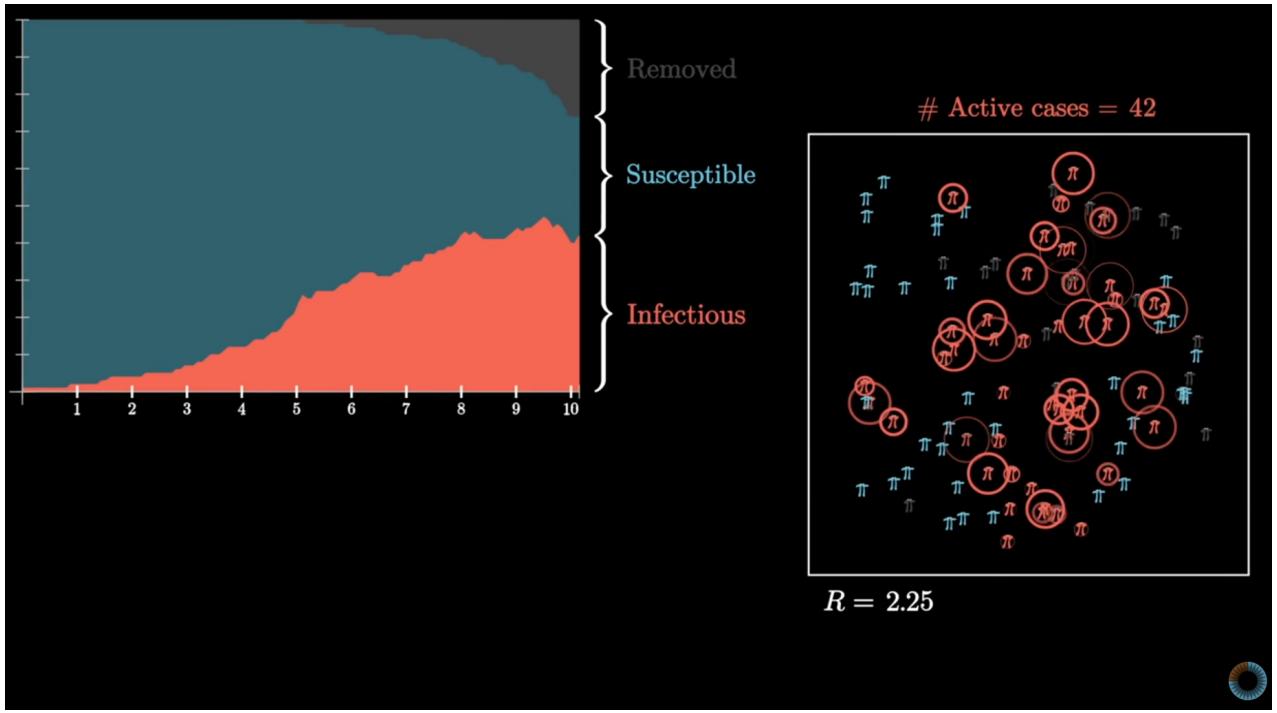

Figure: adopted from https://youtu.be/gxAaO2rsdIs

Micro-level modeling of epidemic diseases
(continued)

Pros

1. The provided information is low-level and higher in resolution (at individual, family, and community-level)
2. Can result in guidelines for individuals, families, syndicates, etc.
3. Is more graphical and more convincing for decision makers!

Micro-level modeling of epidemic diseases
(continued)

Pros

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2. Can result in guidelines for individuals, families, syndicates, etc.
3. Is more graphical and more convincing for decision makers!

Cons

1. Selection and tuning of individual parameters is more difficult than in macro-level models
2. Mathematical proofs for identifiability, stability, and confidence intervals are no longer achievable
3. The simulations can be very susceptible to initial conditions (simulation seeds)

Resources and further reading

Resources

1. The theoretical details of this research: https://arxiv.org/abs/2003.11371
2. The source codes of this research: https://github.com/rsameni/EpidemicModeling.git
3. COVID-19 real-time data: https://www.worldometers.info/coronavirus/
4. Johns Hopkins University's CSSE Git repository: https://github.com/CSSEGISandData/COVID-19

Further reading

1. Epidemic models: Brauer et al. (2012)
2. Biological systems modeling: Haefner (2005); de Vries et al. (2006)
3. The stochastic aspects of mathematical epidemiology: Britton (2010); Pellis et al. (2012); Brauer et al. (2012); Miller (2019)
4. Optimal estimation and Kalman filtering: Grewal and Andrews (2001)
5. Linear systems theory: Kailath (1980)
6. Bill Gates' 2015 TED talk on pandemic outbreak: https://www.ted.com/talks/bill_gates_the_next_outbreak_we_re_not_ready
7. An interesting video on agent-based methods (the micro-modeling approach): https://youtu.be/gxAaO2rsdIs

Part II

Detailed Lecture



What is a model?

An entity that resembles a system or object in certain aspects; but is easier to work with as compared to the original system.

Introduction to modeling

What is a model?

An entity that resembles a system or object in certain aspects; but is easier to work with as compared to the original system.

Why to model a system?

1. System identification
2. Simulation
3. Prediction
4. Control (the ultimate objective; but not always achievable)

✎ From top to bottom the problem becomes more difficult.

Introduction to modeling
(continued)

Context and limitations

- Models are not unique (different models can co-exist for a single system)
- A model is only "a slice of reality"
- All models have a scope, outside of which they are invalid
- Modeling can be done in different levels of abstraction

Example: The diffusion law is a macroscopic-level model, not a microscopic one.

Introduction to modeling
(continued)

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Modeling doctrine

"A model should be as simple as possible, as complex as necessary"

Mathematical modeling of epidemic & pandemic diseases

Major modeling approaches

- Top-down (macro modeling):
  - Compartmental models: ordinary differential equations and dynamic systems
  - Spatio-temporal models: partial differential equations
- Bottom-up (micro modeling):
  - Individual activity modeling: cellular automata

✎ These methods can be combined in a hybrid model

✎ The herein presented method for epidemic modeling is based on compartmental modeling



Compartmental modeling

Background

- A Compartmental model (also known as mass transport or mass action) is a weighted directed graph representation of a dynamic system

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- A Compartment is an abstract entity representing the quantity of interest at the desired level of abstraction (volume, number, density, etc.).
- Each compartment is assumed to be internally homogeneous (no distinction between its elements)
- Compartments interact together through a set of rate equations

Compartmental modeling
(continued)

Example

$$\begin{aligned}\dot{x}(t) &= \lambda - \gamma x(t)^2 - \alpha x(t)\\ \dot{y}(t) &= \alpha x(t) - \beta y(t)\\ \dot{z}(t) &= \gamma x(t)^2 + \beta y(t) - \rho z(t)\end{aligned} \tag{1}$$

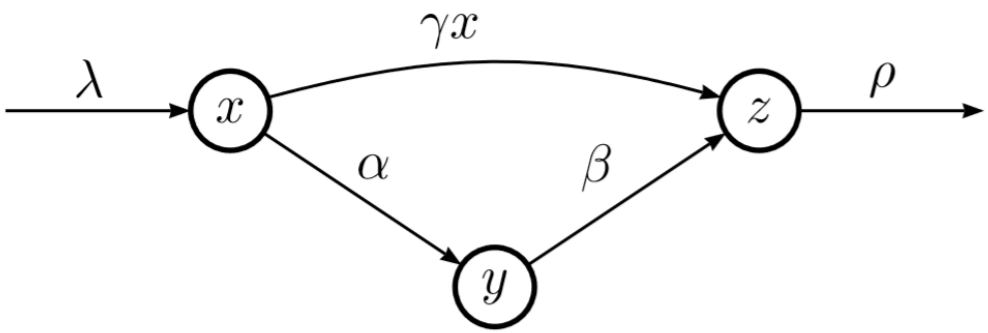


Figure: A sample nonlinear compartmental model

Compartmental modeling
(continued)

Notes

1. Compartmental models can be converted to a set of first order linear or nonlinear equations (and vice versa), by writing the net flow into the compartments.
2. A compartmental model is linear (nonlinear), when its rate flow factors are independent (dependent) of the state variables.
3. A compartmental model is time-invariant (time-variant), when its rate flow factors are independent (dependent) of time.
4. Compartmental models may be open or closed. In closed systems, the quantities are only passed between the compartments, while in open systems the quantities may flow into or out of the whole system.



Modeling the propagation of epidemic diseases

Assumptions:

- Contagious diseases transfer via contact with reproduction number $\mathcal{R}_0$
- The disease may or may not be fatal
- There may or may not be births during the period of study
- The disease may or may not result in lifetime or partial immunity
- Vaccination may or may not exist

Depending on the assumptions, different models may be proposed.

Modeling the propagation of epidemic diseases
(continued)

Reminder: exponential outbreak of diseases

Disease propagation by contact implies that for a number of $x(t)$ infected individuals:

$$\frac{dx(t)}{dt} \approx \frac{x(t+\Delta) - x(t)}{\Delta} = x(t)\phi(t) \tag{2}$$

where $\phi(t)$ is the reproduction function. In the discrete case, the kth generation of the infection spread $x_k \stackrel{\Delta}{=} x(k\Delta)$ is:

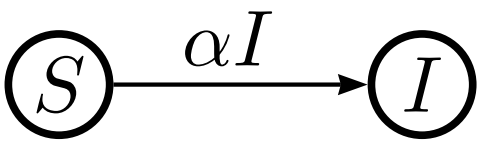
$$x_{k+1} = \underbrace{[1 + \Delta\phi(k\Delta)]}_{\mathcal{R}_0 \text{ (reproduction number)}} x_k$$

If for all k, $\mathcal{R}_0 < 1$ (or $\phi(\cdot) < 0$), the infection vanishes; otherwise if $\mathcal{R}_0 > 1$ (or $\phi(\cdot) > 0$) it spreads.

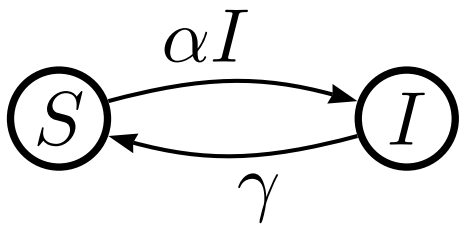
Examples of compartmental models for contagious diseases

The susceptible-infected models with and without immunity

The population is split to susceptibles $S(t)$ and infected $I(t)$ individuals, subject to $S(t) + I(t) = N$



(a) Susceptible-infected (SI)



(b) Susceptible-infected-susceptible (SIS)

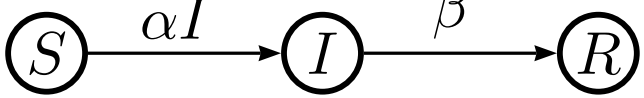
$$\dot{S}(t) = -\alpha S(t)I(t)$$
$$\dot{I}(t) = \alpha S(t)I(t)$$

$$\dot{S}(t) = -\alpha S(t)I(t) + \gamma I(t)$$
$$\dot{I}(t) = \alpha S(t)I(t) - \gamma I(t)$$

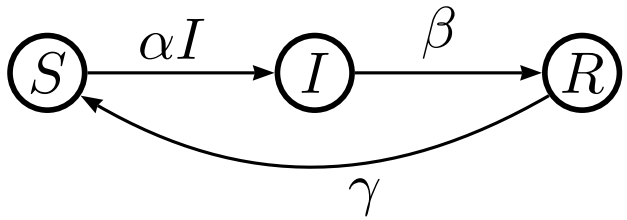
Examples of compartmental models for contagious diseases (continued)

The susceptible-infected-recovered (SIR) model

The population is divided to three groups: $S(t)$: susceptibles, $I(t)$: infected, $R(t)$: recovered, subject to $S(t) + R(t) + I(t) = N$.



(a) SIR with life-time immunity



(b) SIR without life-time immunity

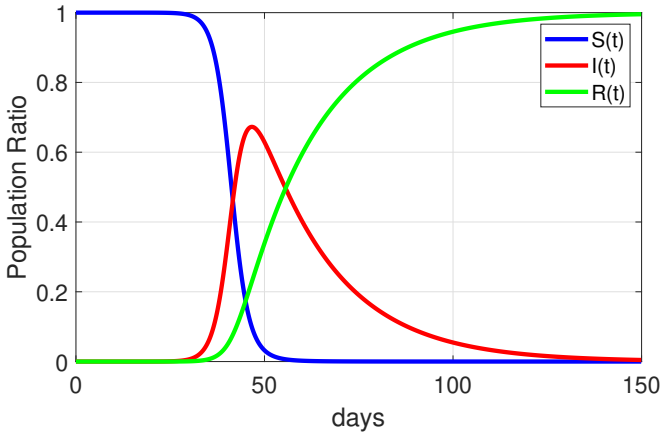
$$\begin{aligned} \dot{S}(t) &= -\alpha S(t)I(t) \\ \dot{I}(t) &= \alpha S(t)I(t) - \beta I(t) \\ \dot{R}(t) &= \beta I(t) \end{aligned} \qquad (3)$$

$$\begin{aligned} \dot{S}(t) &= -\alpha S(t)I(t) + \gamma R(t) \\ \dot{I}(t) &= \alpha S(t)I(t) - \beta I(t) \\ \dot{R}(t) &= \beta I(t) - \gamma R(t) \end{aligned}$$

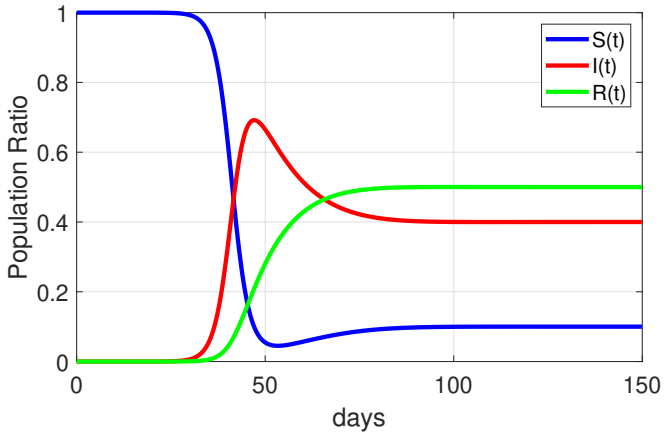
Examples of compartmental models for contagious diseases (continued)

Typical SIR solutions

With a given initial condition SIR models can be numerically solved.



(a) SIR model with immunity



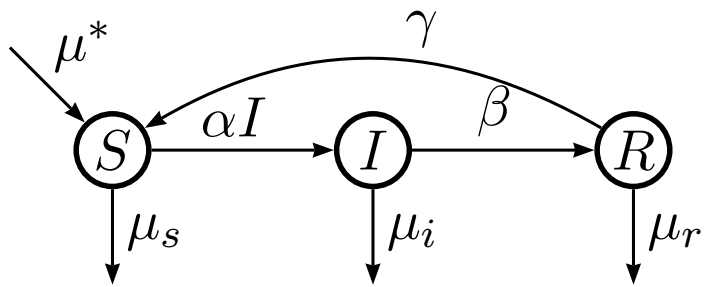
(b) SIR model without immunity

✎ For epidemic diseases, the peak and slope of $I(t)$ is more important than the total number of infected individuals. Why?

Examples of compartmental models for contagious diseases (continued)

A fatal SIR model without life-time immunity

The family of SIR models may also have birth and death rates (making the system *open*):





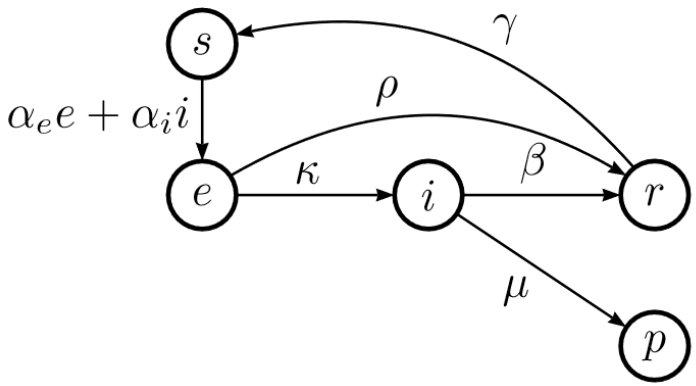
A macro-level model for the COVID-19 coronavirus pandemic

Assumptions and level of abstraction

- The compartments are the population fractions (subject to $s(t) + e(t) + i(t) + r(t) + p(t) = 1$):
  - $s(t)$: susceptible
  - $e(t)$: exposed (symptom-less)
  - $i(t)$: infected (with symptom)
  - $r(t)$: recovered
  - $p(t)$: deceased
- Birth and natural deaths have been neglected
- No distinction between male and female subjects
- No age groups have not been considered (no population pyramid)
- No vaccinations
- No geopolitical factors (country borders, regional quarantines, etc.)

The proposed model

A non-immunizing fatal susceptible-exposed-infected-recovered (SEIR) model



$$
\begin{aligned}
\frac{ds(t)}{dt} &= -\alpha_e s(t)e(t) - \alpha_i s(t)i(t) + \gamma r(t) \\
\frac{de(t)}{dt} &= \alpha_e s(t)e(t) + \alpha_i s(t)i(t) - \kappa e(t) - \rho e(t) \\
\frac{di(t)}{dt} &= \kappa e(t) - \beta i(t) - \mu i(t) \\
\frac{dr(t)}{dt} &= \beta i(t) + \rho e(t) - \gamma r(t) \\
\frac{dp(t)}{dt} &= \mu i(t)
\end{aligned}
\tag{4}
$$

The proposed model
(continued)

The model parameters

- α_i: contagion factor between the infected and susceptibles
- α_e: contagion factor between the exposed and susceptibles
- κ: rate of symptom appearance in exposed subjects
- γ: reinfection rate
- β: recovery rate of the infected
- ρ: recovery rate of the exposed (recovery without symptoms)
- μ: mortality rate of the infected
- e_0: initial exposed population (seed).

Fixed-point analysis

Reminder

The fixed-points of continuous dynamic systems (flows) of the form $\dot{\boldsymbol{x}}(t) = \boldsymbol{f}(\boldsymbol{x})$ are the solutions of $\boldsymbol{f}(\boldsymbol{x}^*) = \boldsymbol{0}$, and the fixed-points of discrete-time dynamic systems (maps) of the form $\boldsymbol{x}_{k+1} = \boldsymbol{g}(\boldsymbol{x}_k)$ are the solutions of $\boldsymbol{g}(\boldsymbol{x}^*) = \boldsymbol{x}^*$.

Fixed-point analysis

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The model fixed-points

The studied model has only one fixed-point, which is the no-disease case $i(t) = e(t) = r(t) = 0$:

$$(s^*(t), e^*(t), i^*(t), r^*(t), p^*(t)) = (1 - p_0, 0, 0, 0, p_0) \qquad (5)$$

Stability of the fixed-point by perturbation analysis

Reminder

The stability of the fixed-point $\boldsymbol{x}^*$ can be checked by perturbation analysis: set $\boldsymbol{x} = \boldsymbol{x}^* + \boldsymbol{\delta x}$ and check the sign of $\boldsymbol{f}(\boldsymbol{x}^* + \boldsymbol{\delta x})$. If the system's dynamics drives it back to the fixed-point, the fixed-point is stable.

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Stability of the model fixed-point

Letting $(s(t), e(t), i(t), r(t), p(t)) = (1 - p_0 - \epsilon, \epsilon, 0, 0, p_0)$ for some $0 < \epsilon \ll 1$, we find:

$$\begin{aligned} \frac{ds(t)}{dt} &= -\alpha_e(1 - p_0 - \epsilon)\epsilon \approx -\alpha_e(1 - p_0)\epsilon < 0 \\ \frac{de(t)}{dt} &= \alpha_e(1 - p_0 - \epsilon)\epsilon - \kappa\epsilon - \rho\epsilon \approx (\alpha_e - \alpha_e p_0 - \kappa - \rho)\epsilon \\ \frac{di(t)}{dt} &= \kappa\epsilon > 0 \quad \frac{dr(t)}{dt} = \rho\epsilon > 0 \quad \frac{dp(t)}{dt} = 0 \end{aligned} \tag{6}$$

Stability of the fixed-point by perturbation analysis
(continued)

Result

The fixed-point is unstable, which implies that the outbreak of pandemics are inevitable and potentially mortal.

Stability of the fixed-point by perturbation analysis
(continued)

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What happens after the outbreak and how can we control it?

Stability of the fixed-point by perturbation analysis
(continued)

Result

The fixed-point is unstable, which implies that the outbreak of pandemics are inevitable and potentially mortal.

What happens after the outbreak and how can we control it?

Fact

The system does not have any external inputs to be used for control. We can only change the parameters of the system (by quarantine, social distancing, hygiene, etc.), such that it becomes internally stable.

Studied aspects

The aspects studied in the sequel:

1. The linear approximation during its initial outbreak
2. The general nonlinear case when a large fraction of the population has been infected
3. Parameter identification

Epidemic outbreak behavior

Large population approximation

During the primary stages of an epidemic outbreak (when a small fraction of a large population are infected), we can assume $s(t) \approx 1$. What does this imply?

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Interpretation

1. The propagation behavior during outbreak does not depend on the total population, but rather depends on hygiene and contact patterns.

Epidemic outbreak behavior

Large population approximation

During the primary stages of an epidemic outbreak (when a small fraction of a large population are infected), we can assume $s(t) \approx 1$. What does this imply?

Interpretation

1. The propagation behavior during outbreak does not depend on the total population, but rather depends on hygiene and contact patterns.
2. During the primary stages of an epidemic outbreak, it has the same properties and takes the same number of victims in countries with 10 million, 100 million or 1 billion population.

Epidemic outbreak behavior
(continued)

Linear approximation ($s(t) \approx 1$):

$$\begin{bmatrix} \frac{de(t)}{dt} \\ \frac{di(t)}{dt} \\ \frac{dr(t)}{dt} \\ \frac{dp(t)}{dt} \end{bmatrix} \approx \underbrace{\begin{bmatrix} (\alpha_e - \kappa - \rho) & \alpha_i & 0 & 0 \\ \kappa & -(\beta + \mu) & 0 & 0 \\ \rho & \beta & -\gamma & 0 \\ 0 & \mu & 0 & 0 \end{bmatrix}}_{\mathbf{A}} \begin{bmatrix} e(t) \\ i(t) \\ r(t) \\ p(t) \end{bmatrix} \quad (7)$$

Defining $\boldsymbol{x}(t) = (e(t), i(t), r(t), p(t))^T$, (7) can be written in matrix form: $\frac{d}{dt}\boldsymbol{x}(t) = \mathbf{A}\boldsymbol{x}(t)$, $\boldsymbol{x}(0) = (e_0, 0, 0, 0)$

Eigen-analysis of the linearized model

Eigenvalues (defining $\delta \triangleq \alpha_e - \kappa - \rho$):

$$\begin{aligned}
\lambda_1 &= 0, \quad \lambda_2 = -\gamma \\
\lambda_3 &= \frac{\delta - \beta - \mu + \sqrt{(\delta + \beta + \mu)^2 + 4\kappa\alpha_i}}{2} \\
\lambda_4 &= \frac{\delta - \beta - \mu - \sqrt{(\delta + \beta + \mu)^2 + 4\kappa\alpha_i}}{2}
\end{aligned} \tag{8}$$

Eigenvectors:

$$\begin{aligned}
\mathbf{v}_1 &= (0, 0, 0, k_1)^T, \quad \mathbf{v}_2 = (0, 0, k_2, 0)^T \\
\mathbf{v}_3 &= k_3(1, \frac{\lambda_3 - \delta}{\alpha_i}, \frac{\rho\alpha_i + \beta(\lambda_3 - \delta)}{\alpha_i(\lambda_3 + \gamma)}, \frac{\mu(\lambda_3 - \delta)}{\alpha_i\lambda_3}) \\
\mathbf{v}_4 &= k_4(1, \frac{\lambda_4 - \delta}{\alpha_i}, \frac{\rho\alpha_i + \beta(\lambda_4 - \delta)}{\alpha_i(\lambda_4 + \gamma)}, \frac{\mu(\lambda_4 - \delta)}{\alpha_i\lambda_4})
\end{aligned} \tag{9}$$

Eigen-analysis of the linearized model
(continued)

Reminder

- The dynamic system $\dot{\boldsymbol{x}}(t) = \mathbf{A}\boldsymbol{x}(t)$ is stable if all the eigenvalues of $\mathbf{A}$ have negative real parts.
- The solution of the system is:

$$\boldsymbol{x}(t) = \sum_{k=1}^{m} a_k e^{\lambda_k t} \mathbf{v}_k \tag{10}$$

subject to $\boldsymbol{x}(0) = \boldsymbol{x}_0$.

Eigen-analysis of the linearized model
(continued)

Properties

1. $\lambda_3 > \delta > \lambda_4$; hence λ_3 is the dominant eigenvalue.

Eigen-analysis of the linearized model
(continued)

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$$\boxed{\kappa\alpha_i < (\kappa + \rho - \alpha_e)(\beta + \mu)}$$

Eigen-analysis of the linearized model
(continued)

Properties

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2. The necessary and sufficient condition for the system stability is $\lambda_3 < 0$, or:

$$\boxed{\kappa\alpha_i < (\kappa + \rho - \alpha_e)(\beta + \mu)}$$

3. During the outbreak, the infected and exposed populations are:

$$\begin{aligned} i(t) &= \frac{e_0(\lambda_3 - \delta)(\delta - \lambda_4)}{\alpha_i(\lambda_3 - \lambda_4)}[\exp(\lambda_3 t) - \exp(\lambda_4 t)] \\ e(t) &= \frac{e_0}{\lambda_3 - \lambda_4}[(\lambda_3 - \delta)\exp(\lambda_4 t) + (\delta - \lambda_4)\exp(\lambda_3 t)] \end{aligned} \tag{11}$$

Model properties during outbreak

Result: exponential outbreak

If $\lambda_3 > 0$, the system is unstable, the epidemic outbreaks exponentially and without enforcing lockdown, social distancing and quarantine of the infected cases (resulting in a change of the eigenvalues), the exponential increase in the number of infected subjects continues to a point where a significant percentage of the population is infected (and deceased).

Model properties during outbreak

(continued)

Result: reproduction number

Under countermeasures, the model eigenvalues change and λ_3 (the dominant eigenvalue), or equivalently the reproduction number $\mathcal{R}_0 = e^{\Delta\lambda_3}$, is the parameter that can be tracked as a score for evaluating how good countermeasures such as social distancing and quarantine perform. The system is stabilized when $\mathcal{R}_0 < 1$.

Model properties during outbreak

(continued)

Result: initial infection size

The initial infected seed size e_0 is not the most critical parameter for epidemic management. Regions with smaller initial seeds of infection may end up with a higher infection and death toll, depending on factors such as human-contact patterns and personal hygiene.

The general nonlinear case

The system model revisited

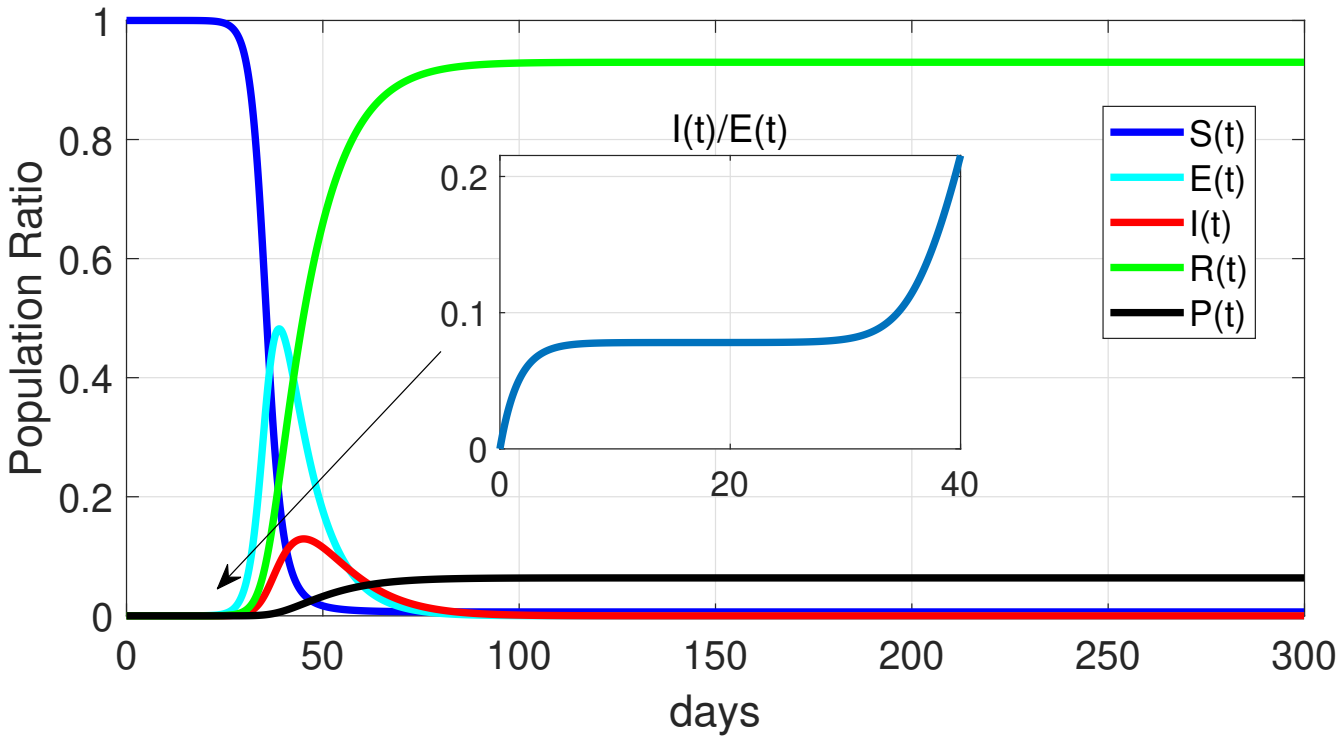
As the infection rate increases, $s(t)$ is no longer close to 1. Taking $s(t) = 1 - e(t) - i(t) - r(t) - p(t)$, the nonlinear model in (4) can be rewritten as:

$$\begin{aligned}
\frac{de(t)}{dt} &= [1 - e(t) - i(t) - r(t) - p(t)][\alpha_e e(t) + \alpha_i i(t)] - \kappa e(t) - \rho e(t) \\
\frac{di(t)}{dt} &= \kappa e(t) - \beta i(t) - \mu i(t) \\
\frac{dr(t)}{dt} &= \beta i(t) + \rho e(t) - \gamma r(t) \\
\frac{dp(t)}{dt} &= \mu i(t)
\end{aligned} \tag{12}$$

which can be numerically solved from an arbitrary initial condition.

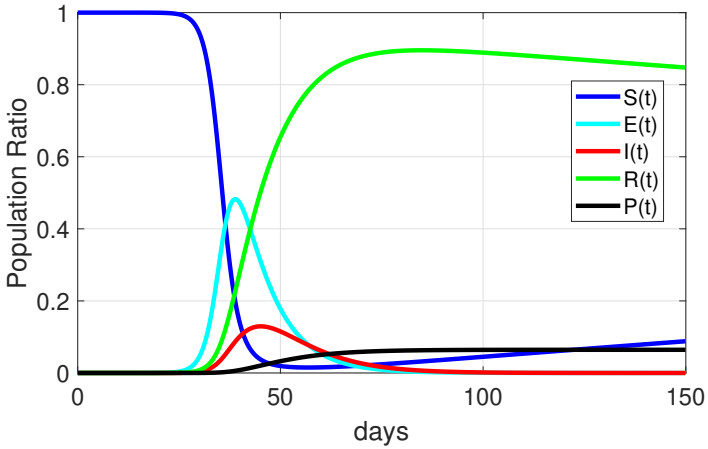
Typical solutions

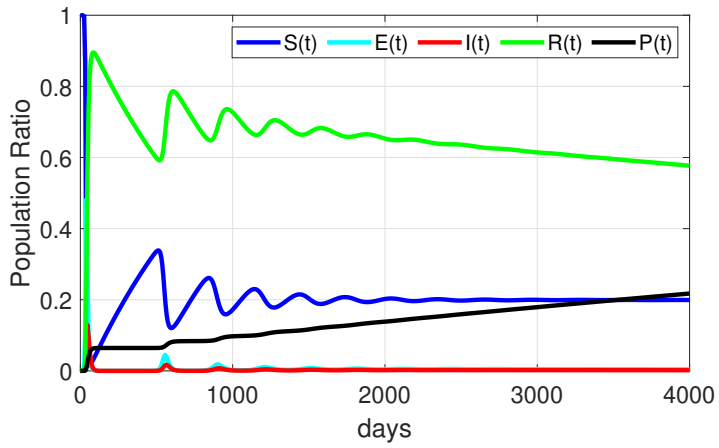
The life-time immune case ($\gamma = 0$)

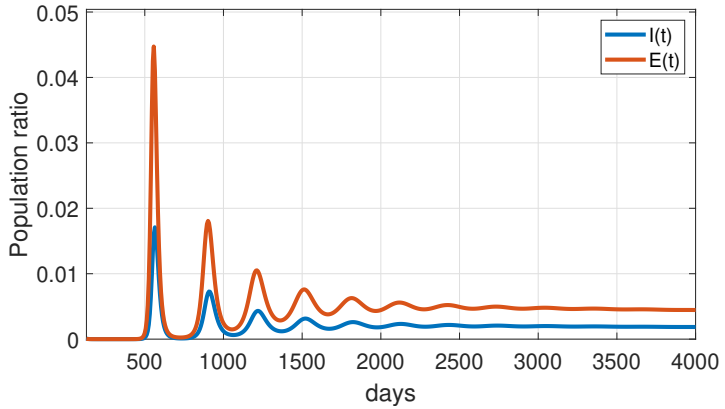


Typical solutions

The non-immunizing case ($\gamma \neq 0$) in short- and long-term







Typical solutions
(continued)

Result: repeated waves of the disease

The epidemic disease can repeat pseudo-periodically over time (in later seasons or years) and turn into a persistent disease in the long term. The amplitude and time gap of the infection peaks depends on the model parameters.

Example: The 1918 Spanish flu, which had three pandemic waves.
See: https://en.wikipedia.org/wiki/Spanish_flu.

Typical solutions
(continued)

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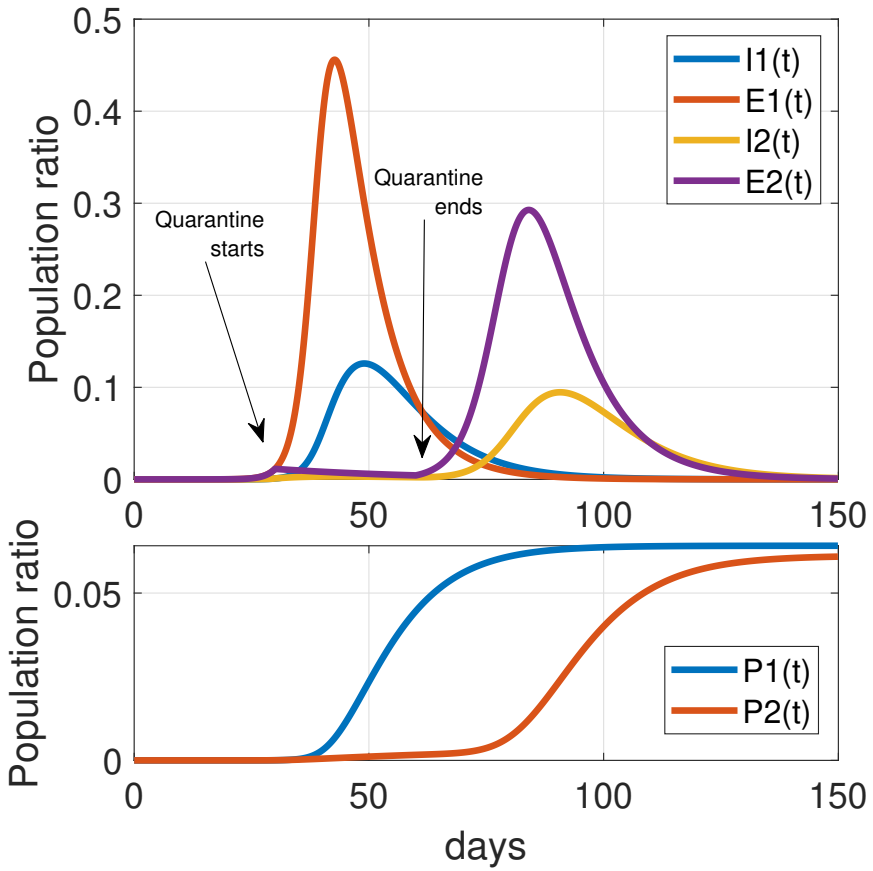
Example: The 1918 Spanish flu, which had three pandemic waves. See: https://en.wikipedia.org/wiki/Spanish_flu. **Note:** In our model, the peaks can be found by finding the solutions of the model when $\frac{di(t)}{dt} = 0$ (the local infection peaks).

Typical solutions
(continued)

Short quarantine periods



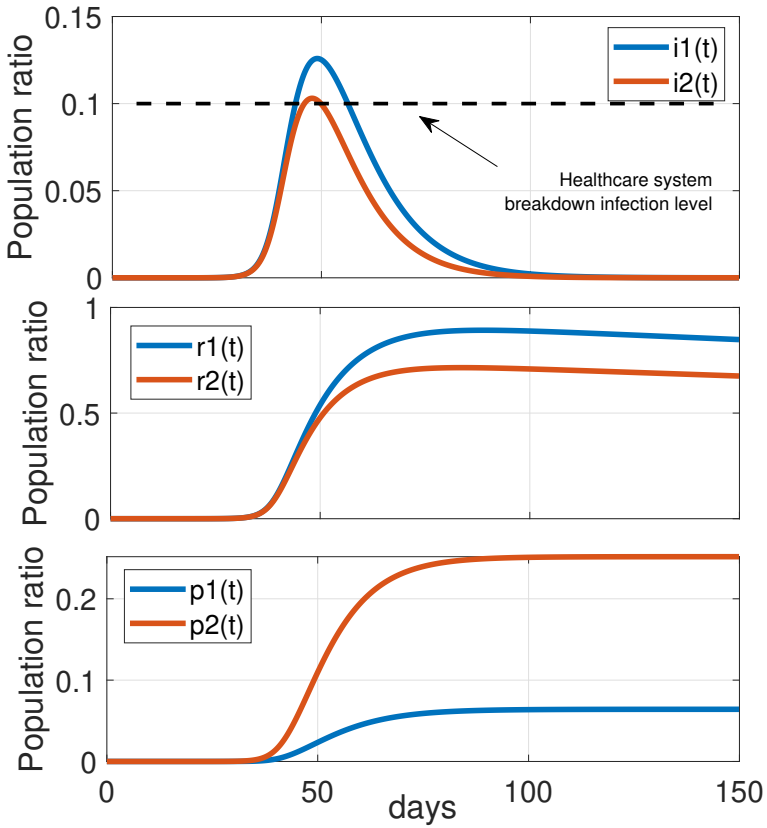
Typical solutions
(continued)

Result: inadequate lockdown

Imposing quarantines is effective in delaying and reducing the infection population peaks; but is insufficient in the long term. Social distancing and other measures should remain for a long period after the initial quarantine, to make the number of contaminated subjects equal to "zero."

Typical solutions
(continued)

Healthcare system saturation and breakdown



Time-variant model parameters:

$$\beta(t) = (\beta_s - \beta_0)h(i(t)) + \beta_0$$
$$\mu(t) = (\mu_s - \mu_0)h(i(t)) + \mu_0$$

where

$$h(i) = \frac{1}{2}[1 + \tanh(\frac{i - i_0}{\sigma})]$$

Typical solutions
(continued)

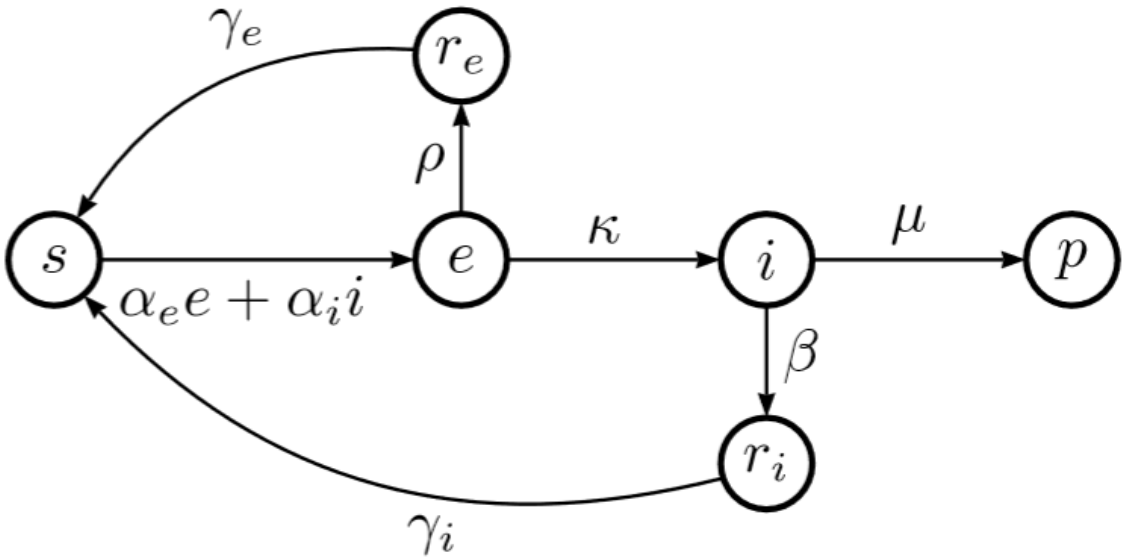
Result: healthcare system breakdown

The death toll increases significantly as the system approaches the break-point of its healthcare resources.

Model extensions

Unobservable exposed recoveries

An extension of the fatal SEIR model for Coronavirus modeling, assuming that the recoveries from exposure and infection are separate compartments r_e and r_i:



Parameter identification

Methods for identifying the model parameters

1. Offline: Using constrained nonlinear least squares parameter estimation
2. Online: Using extended Kalman filter for joint parameter and variable estimation

Constrained nonlinear least squares parameter estimation

Problem Formulation

Consider the general form of the state-space model:

$$\begin{aligned} \dot{\boldsymbol{x}}(t) &= \mathbf{f}(\boldsymbol{x}(t), \boldsymbol{w}(t); \boldsymbol{\theta}(t), t) \\ \boldsymbol{y}(t) &= \mathbf{g}(\boldsymbol{x}(t); \boldsymbol{\theta}(t), t) + \boldsymbol{v}(t) \end{aligned} \tag{13}$$

Define the modeling error function

$$\boldsymbol{e}(t) \triangleq \boldsymbol{y}(t) - \mathbf{g}(\boldsymbol{x}(t); \boldsymbol{\theta}(t), t) \tag{14}$$

The problem of parameter estimation can be formulated as

$$\hat{\boldsymbol{\theta}} = \arg\min_{\boldsymbol{\theta}} \operatorname{tr} \mathbb{E}[\boldsymbol{e}(t) \mathbf{W} \boldsymbol{e}(t)^T] \tag{15}$$

subject to: $\boldsymbol{\theta}_{\min} \leq \boldsymbol{\theta} \leq \boldsymbol{\theta}_{\max}$, $\dot{\boldsymbol{x}}(t) = \mathbf{f}(\boldsymbol{x}(t), \boldsymbol{w}(t); \boldsymbol{\theta}, t)$, $\boldsymbol{x}(0) = \boldsymbol{x}_0$

An extended Kalman filter for joint parameter and variable estimation

Problem Formulation

Suppose that we consider the parameters as state variables with a Wiener process dynamics:

$$
\begin{aligned}
\frac{de(t)}{dt} &= [1 - e(t) - i(t) - r(t) - p(t)][\alpha_e(t)e(t) + \alpha_i(t)i(t)] \\
&\quad -\kappa(t)e(t) - \rho(t)e(t) \\
\frac{di(t)}{dt} &= \kappa(t)e(t) - \beta(t)i(t) - \mu(t)i(t) \\
\frac{dr(t)}{dt} &= \beta(t)i(t) + \rho(t)e(t) - \gamma(t)r(t) \\
\frac{dp(t)}{dt} &= \mu(t)i(t) \\
\frac{d\alpha_i(t)}{dt} &= \frac{du_i}{dt}(t) + w_i(t) \qquad \frac{d\alpha_e(t)}{dt} = \frac{du_e}{dt}(t) + w_e(t) \\
\frac{d\kappa(t)}{dt} &= w_\kappa(t) \qquad \frac{d\beta(t)}{dt} = w_\beta(t) \qquad \frac{d\rho(t)}{dt} = w_\rho(t) \\
\frac{d\mu(t)}{dt} &= w_\mu(t) \qquad \frac{d\gamma(t)}{dt} = w_\gamma(t)
\end{aligned}
\tag{16}
$$

An extended Kalman filter for joint parameter and variable estimation
(continued)

Measurements

The regular reports of the infected, recovered and death tolls can be considered as (noisy) measurements of the state variables:

$$\begin{bmatrix} I(t) \\ R(t) \\ P(t) \end{bmatrix} = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} e(t) \\ i(t) \\ r(t) \\ p(t) \end{bmatrix} + \begin{bmatrix} v_e(t) \\ v_i(t) \\ v_r(t) \\ v_p(t) \end{bmatrix} \tag{17}$$

where $I(t)$, $R(t)$, and $P(t)$ are the reported values (potentially inaccurate).

Origin of measurement noise

Inexact population information, intentional and unintentional misreports, mis-classified death reasons (e.g. for the elderly or the subjects suffering from multiple health issues).

An extended Kalman filter for joint parameter and variable estimation
(continued)

Question: Can we estimate the model parameters and the unmeasurable variable $e(t)$ from the regular inaccurate reports?

An extended Kalman filter for joint parameter and variable estimation
(continued)

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Reminder: observability

The state-space model:

$$\begin{aligned} \dot{\boldsymbol{x}}(t) &= \mathbf{f}(\boldsymbol{x}(t), \boldsymbol{w}(t); \boldsymbol{\theta}(t), t) \\ \boldsymbol{y}(t) &= \mathbf{g}(\boldsymbol{x}(t); \boldsymbol{\theta}(t), t) + \boldsymbol{v}(t) \end{aligned} \tag{18}$$

is observable from its outputs, if the state variables can be estimated from the observations in finite time (Kailath, 1980).

Reminder: observability rank-test

The dynamic system (18) is observable if the following matrix (known as the observability matrix) is rank n (the number of state variables):

$$\mathcal{O}_k = \begin{bmatrix} \mathcal{C}_k \\ \mathcal{C}_k \mathcal{A}_k \\ \dots \\ \mathcal{C}_k \mathcal{A}_k^{n-1} \end{bmatrix} \tag{19}$$

where $\mathcal{A}_k$ and $\mathcal{C}_k$ are the Jacobians of $\boldsymbol{f}(\cdot)$ and $\boldsymbol{g}(\cdot)$, with respect to the state vector.

An extended Kalman filter for joint parameter and variable estimation
(continued)

Algorithm 1 An extended Kalman filter for simultaneous compartment variables and model parameters tracking

Input: Noisy measurements (regular inaccurate reports) of the epidemic spread y_k
Input: Initial conditions: $\mathbf{Q}$, $\mathbf{R}$, $\hat{x}_0^+$, $\mathbf{P}_0^+$
Output: $\hat{x}_k^+$ (vector of state and model parameter estimates)

for $k = 0 \cdots T$ **do**
  State prediction:
  $\hat{x}_{k+1}^- = \mathbf{f}(\hat{x}_k^+, \bar{w}; \hat{\theta}_k^+, k\Delta)$
  $\mathbf{P}_{k+1}^- = \mathcal{A}_k^+ \mathbf{P}_k^+ \mathcal{A}_k^{+T} + \mathbf{Q}$
  Measurement update:
  $\mathbf{K}_k = \mathbf{P}_k^- \mathcal{C}_k^{-T} [\mathcal{C}_k^- \mathbf{P}_k^- \mathcal{C}_k^{-T} + \mathbf{R}]^{-1}$
  $\hat{y}_k^- = \mathbf{g}(\hat{x}_k^-; \hat{\theta}_k^-, k\Delta)$
  $i_k = y_k - \hat{y}_k^-$
  $\hat{\sigma}_k^+ = \hat{\sigma}_k^- + \mathbf{K}_k i_k$
  $\mathbf{P}_k^+ = [\mathbf{I} - \mathbf{K}_k \mathcal{C}_k^-] \mathbf{P}_k^-$
  Check and enforce variable and parameter ranges using hard-constraints
  Performance monitoring
end for



Exercises and future work

Model extensions

The model can be extended from various aspects, including:

- Considering birth and natural death
- Differentiating between various groups (infants, adults, elderly, gender, prior illness, etc.)
- Parameter estimation from real data
- Finding the repetition periods of the pandemic wave

Resources and further reading

Resources

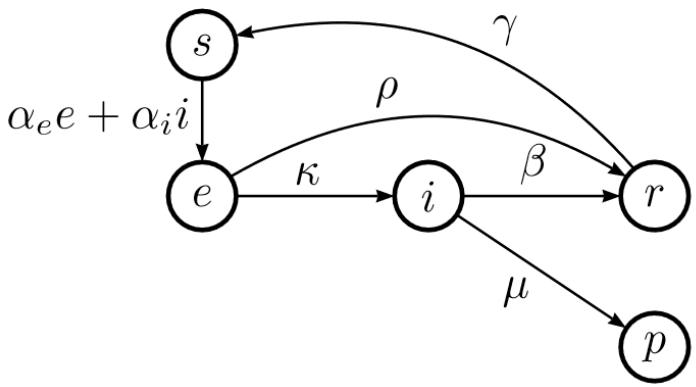
1. The theoretical details of this research: https://arxiv.org/abs/2003.11371
2. The source codes of this research: https://github.com/rsameni/EpidemicModeling.git
3. COVID-19 real-time data: https://www.worldometers.info/coronavirus/
4. Johns Hopkins University's CSSE Git repository: https://github.com/CSSEGISandData/COVID-19

Further reading

1. Epidemic models: Brauer et al. (2012)
2. Biological systems modeling: Haefner (2005); de Vries et al. (2006)
3. The stochastic aspects of mathematical epidemiology: Britton (2010); Pellis et al. (2012); Brauer et al. (2012); Miller (2019)
4. Optimal estimation and Kalman filtering: Grewal and Andrews (2001)
5. Linear systems theory: Kailath (1980)
6. Bill Gates' 2015 TED talk on pandemic outbreak: https://www.ted.com/talks/bill_gates_the_next_outbreak_we_re_not_ready
7. An interesting video on agent-based methods (the micro-modeling approach): https://youtu.be/gxAaO2rsdIs

The proposed model in a glance

A non-immunizing fatal model with five compartments: susceptibles $s(t)$, exposed $e(t)$, infected $i(t)$, recovered $r(t)$ and deceased $p(t)$:



$$\frac{ds(t)}{dt} = -\alpha_e s(t)e(t) - \alpha_i s(t)i(t) + \gamma r(t)$$
$$\frac{de(t)}{dt} = \alpha_e s(t)e(t) + \alpha_i s(t)i(t) - \kappa e(t) - \rho e(t)$$
$$\frac{di(t)}{dt} = \kappa e(t) - \beta i(t) - \mu i(t)$$
$$\frac{dr(t)}{dt} = \beta i(t) + \rho e(t) - \gamma r(t)$$
$$\frac{dp(t)}{dt} = \mu i(t)$$

The mathematical properties of this model has been studied both analytically and by simulation in our technical report:
https://arxiv.org/abs/2003.11371

References I

Fred Brauer, Carlos Castillo-Chavez, and Carlos Castillo-Chavez. *Mathematical models in population biology and epidemiology*, volume 2. Springer, 2012.

Tom Britton. Stochastic epidemic models: a survey. *Mathematical biosciences*, 225(1):24–35, 2010.

G. de Vries, T. Hillen, M. Lewis, B. Schõnfisch, and J. Muller. *A Course in Mathematical Biology: Quantitative Modeling with Mathematical and Computational Methods*. Monographs on Mathematical Modeling and Computation. Society for Industrial and Applied Mathematics, 2006. ISBN 9780898716122.

M. S. Grewal and A. P. Andrews. *Kalman Filtering: Theory and Practice Using Matlab*. John Wiley & Sons, Inc., 2nd edition, 2001.

References II

J.W. Haefner. *Modeling Biological Systems: Principles and Applications*. Springer, 2005. ISBN 9780387250113.

Thomas Kailath. *Linear Systems*. Prentice Hall, 1980.

Joel C Miller. Distribution of outbreak sizes for sir disease in finite populations. *arXiv preprint arXiv:1907.05138*, 2019.

Lorenzo Pellis, Frank Ball, and Pieter Trapman. Reproduction numbers for epidemic models with households and other social structures. I. Definition and calculation of R0. *Mathematical biosciences*, 235(1):85–97, 2012.