EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of
Biomedical Informatics

BMI 500: Introduction to Biomedical Informatics

Lecture 11. An Introduction to Model-based Machine Learning

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Overview

Outline

Introduction to modeling

What is a model?

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

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Where to use a model?

1. Identification and better understanding of systems
2. Simulation of a system's behavior; generating synthetic data that are hardly achievable in reality
3. Prediction of a system's future behavior
4. Control is the ultimate goal of modeling; but not always possible

From top to bottom the problem becomes more difficult.

Introduction to modeling
(continued)

Why use a model?

Working with real systems is not always possible, e.g.,

1. Optimizing the parameters of under-construction systems by trial and error (time-taking, expensive and impractical without a model)
2. Testing drugs and new technologies on human/animal species (unethical)
3. Chemical and biological reactions (dangerous without a model)
4. Studying the formation of galaxies or natural species (impossible without a model)

Introduction to modeling
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How to model?

Is the subject of this course.

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✎ Combinations of model types are possible, e.g., physical and economics models can be mathematically formulated.

✎ In quantitative applications, including machine learning, we are interested in mathematical models.

Modeling limitations

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Introduction to modeling
(continued)

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Some models are only valid in certain levels of abstraction. Example: The diffusion law is a macroscopic-level model, not a microscopic one.

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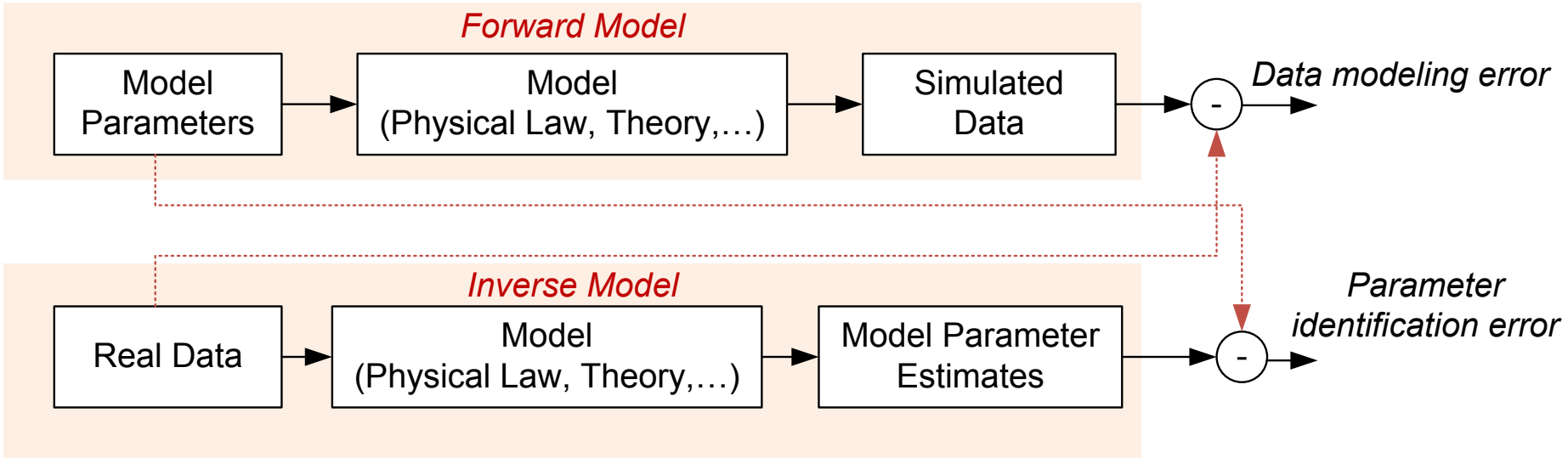
Modeling doctrine

Model should be *as simple as possible, as complex as necessary*.

Modeling approaches

- **Forward:** from modeling to measurements/observations
- **Inverse:** from measurements/observations to model parameters

✎ These approaches are not distinct; we iterate between forward and backward modeling to develop, tune and validate models



Example: Forward versus inverse modeling

Low-resolution brain electromagnetic tomography (LORETA) and its extensions: sLORETA, eLORETA, etc. (Pascual-Marqui et al., 1994, 2002)

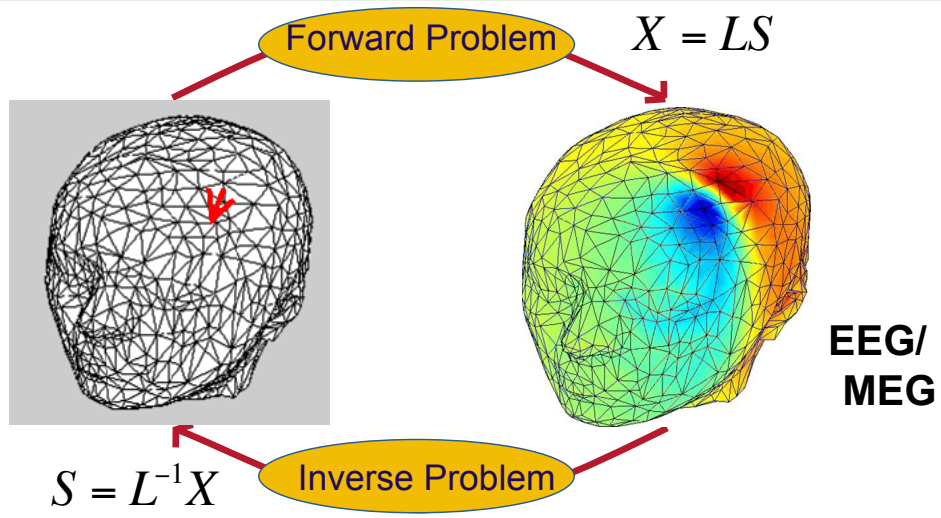


Figure: Adopted from: `http://cfmriweb.ucsd.edu/ttliu/be280a_12/BE280A12_eeg5.pdf`

Model types

- **Deterministic:** all the model elements (rules, equations and parameters) are deterministic, e.g., $x(t) = a\sin(\omega t + \phi)$ with deterministic parameters
- **Stochastic:** have some stochastic elements, e.g., $x(t) \sim \mathcal{N}(0, 1)$
- **Hybrid:** Partially deterministic and stochastic, e.g., $x(t) = a\sin(\omega t) + n(t)$

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✎ Complex deterministic models are sometimes approximated by simple stochastic models

Example

The model
$x(t) = \sin(\omega t) + 0.01\sin(2\omega t)^2 + 0.03\sqrt{0.2\sin(3\omega t) + 1} + \exp\left(-80.0t^2\right)$ can be approximated by $\tilde{x}(t) = \sin(\omega t) + n(t)$, where $n(t)$ is considered a stochastic term with a bounded variance used for modeling the minor terms of $x(t)$

Model construction

How to construct a mathematical model?

- **Evidence-based:** using existing models based on physical, biological or empirical laws
- **Model fitting:** fit a parametric model over observed data points
- **Hybrid:** combination of evidence-based and data fitting

Example: Evidence-based

Intramuscular injection of drugs and its diffusion in the body

Example: Data fitting

Training deep neural networks on biomedical data

Open discussion

- All physical laws are in fact models for physical systems, for which counter examples have not yet been found, within a certain level of abstraction. Examples: 1) Kirchhoff voltage and current laws in lumped circuits vs. Maxwell's equations; 2) Newtonian mechanics vs. relativistic mechanics.

Open discussion

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- Name a few well-known economics laws. Which types of models are they?
- Name a few well-known biologic and physiologic laws. Which types of models are they?

Outline

Model-based machine learning

What is model-based machine learning?

Model-based (also known as physics-informed) machine learning integrates contextual knowledge of a system's properties/behavior (physical, physiological, etc.) in the formation of machine learning models and their training on real-world data (Karniadakis et al., 2021).

Physics-informed machine learning

George Em Karniadakis[1,2]✉, *Ioannis G. Kevrekidis*[3,4], *Lu Lu*[5], *Paris Perdikaris*[6], *Sifan Wang*[7] *and Liu Yang*[1]

Abstract | Despite great progress in simulating multiphysics problems using the numerical discretization of partial differential equations (PDEs), one still cannot seamlessly incorporate noisy data into existing algorithms, mesh generation remains complex, and high-dimensional problems governed by parameterized PDEs cannot be tackled. Moreover, solving inverse problems with hidden physics is often prohibitively expensive and requires different formulations and elaborate computer codes. Machine learning has emerged as a promising alternative, but training deep neural networks requires big data, not always available for scientific problems. Instead, such networks can be trained from additional information obtained by enforcing the physical laws (for example, at

DOI: 10.1038/s42254-021-00314-5

Model-based machine learning
(continued)

Applications of model-based ML

- Ethical AI; acquiring data from living species should be avoided as much as possible

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Model-based machine learning
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- Compensating data imbalance: Generating synthetic data for abnormal and rare border cases that are not available or abundant in real-world datasets

Model-based machine learning
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- Compensating data imbalance: Generating synthetic data for abnormal and rare border cases that are not available or abundant in real-world datasets
- Hybrid physical-ML models: *model what is known with maths, model the unknown (or complex) ones with ML*

Outline

Mathematical modeling of epidemic and pandemic diseases

Pandemic modeling

- **Objective:** To model the outbreak and spread of pandemic diseases and to estimate the effectiveness of pandemic containing policies
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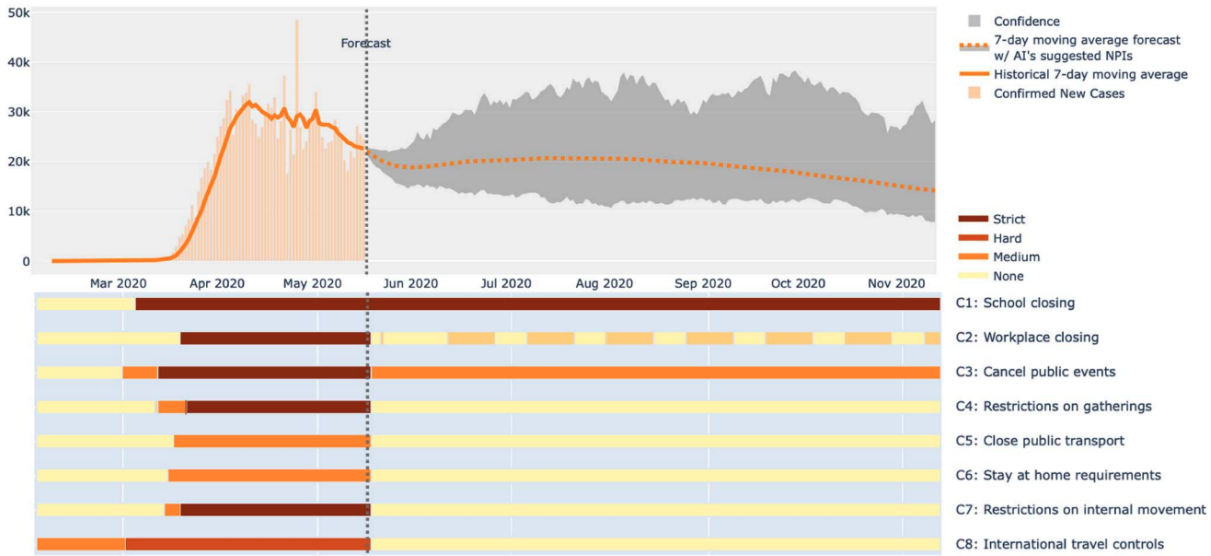

Miikkulainen, et al. (2021). From Prediction to Prescription: Evolutionary Optimization of Nonpharmaceutical Interventions in the COVID-19 Pandemic. IEEE Tran. Evol. Comp. DOI: 10.1109/tevc.2021.3063217

Mathematical modeling of epidemic and pandemic diseases
(continued)

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

Mathematical modeling of epidemic and pandemic diseases (continued)

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- 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

✎ The two methods can be combined in a hybrid model

Outline

Compartmental modeling

Definition

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

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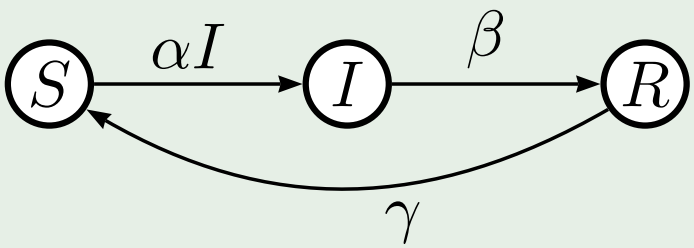
Example: An epidemic without life-time immunity



$$\frac{dS(t)}{dt} = -\alpha S(t)I(t) + \gamma R(t)$$
$$\frac{dI(t)}{dt} = \alpha S(t)I(t) - \beta I(t)$$
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Compartmental modeling of epidemic diseased

Compartmental modeling steps

1. Define the compartments: homogeneous non-overlapping partitions of the population with common properties (up to level of abstraction).
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2. Assign time variables of interest to the compartments
3. Write flow equations between the compartments (how individuals move between compartments)
4. Parameter selection: 1) fact-based, or 2) model fitting on real data

Compartmental modeling of epidemic diseased

Epidemic disease spread in large populations

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

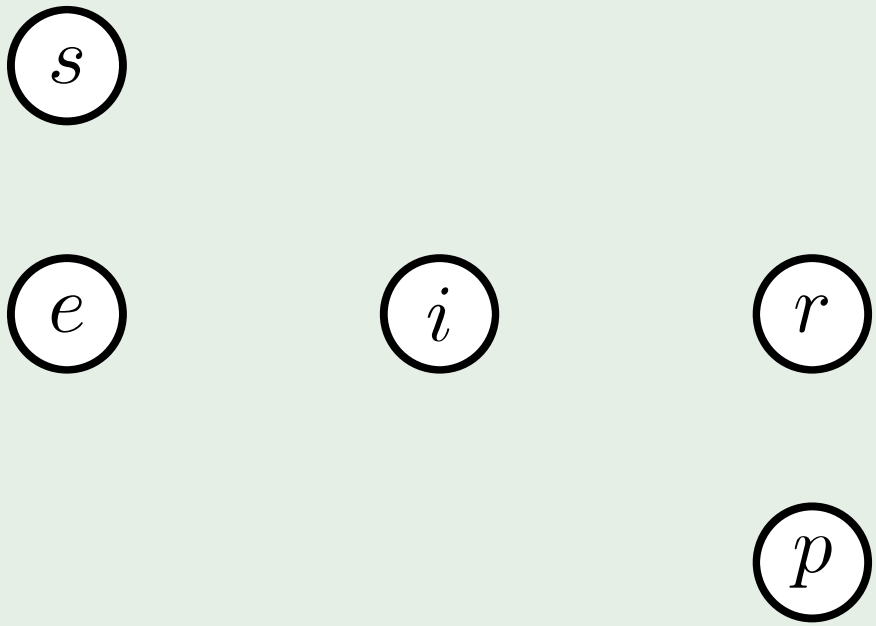
- Susceptibles: $s(t)$
- Exposed (without symptoms): $e(t)$
- Infected (with symptom): $i(t)$
- Recovered: $r(t)$
- Deceased: $p(t)$

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

Compartmental modeling of epidemic diseased
(Continued)

Example: A mortal non-immunizing susceptible-exposed-infected-recovered (SEIR) model

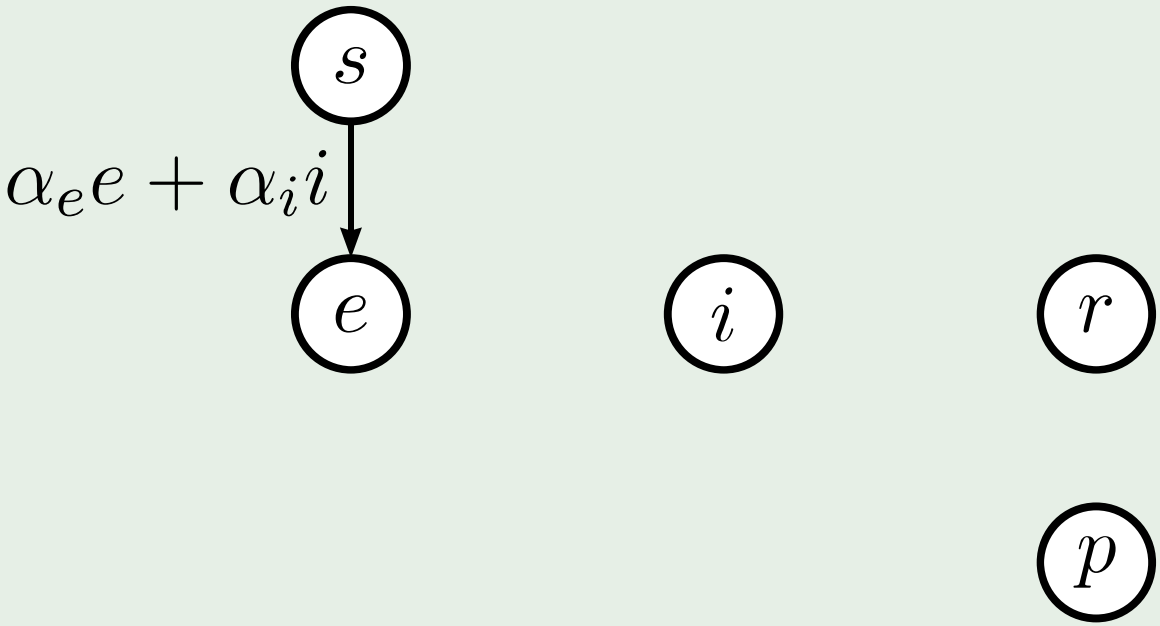
Draw the compartments:



Compartmental modeling of epidemic diseased
(Continued)

Example: A mortal non-immunizing susceptible-exposed-infected-recovered (SEIR) model

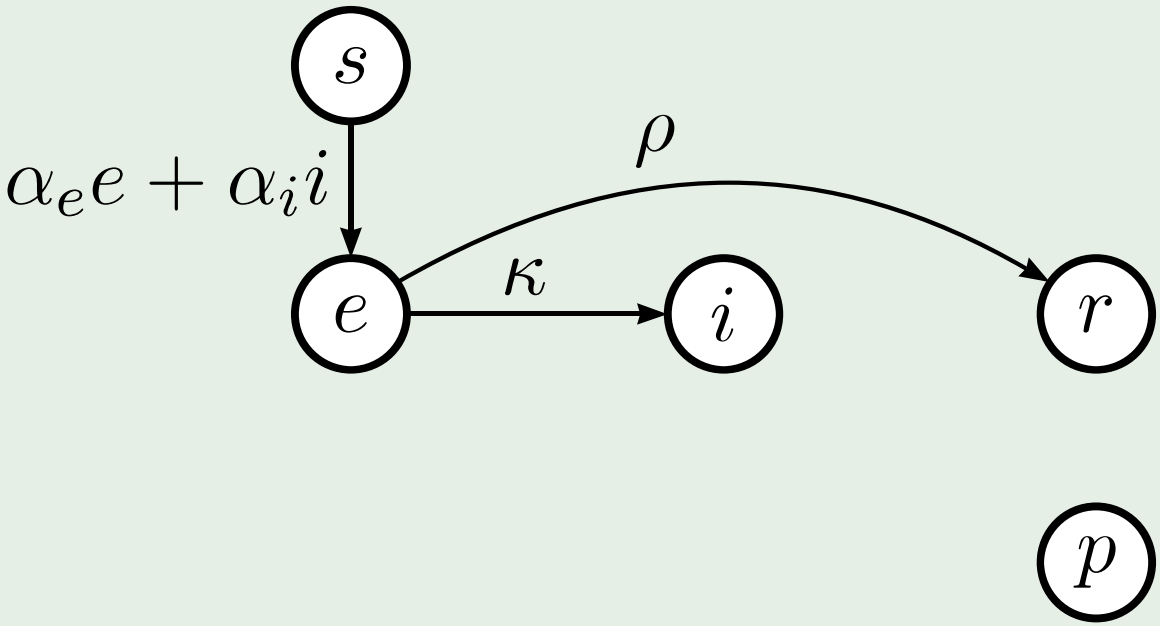
Individuals are infected as they contact infected or exposed subjects.



Compartmental modeling of epidemic diseased
(Continued)

Example: A mortal non-immunizing susceptible-exposed-infected-recovered (SEIR) model

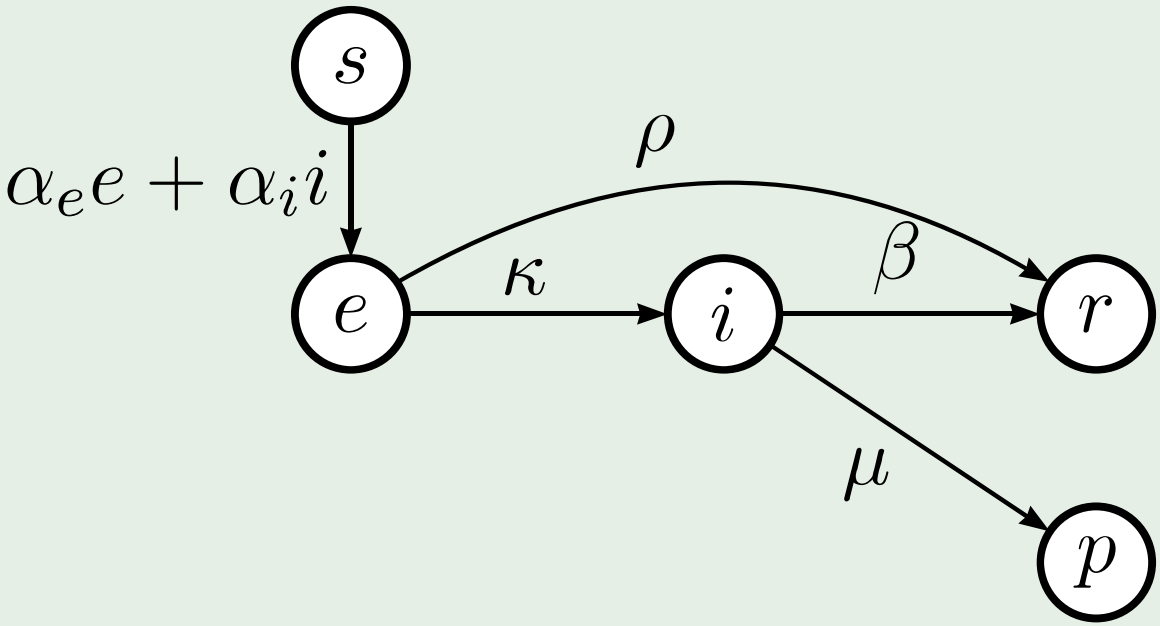
The exposed either recover or become infected with symptoms.



Compartmental modeling of epidemic diseased
(Continued)

Example: A mortal non-immunizing susceptible-exposed-infected-recovered (SEIR) model

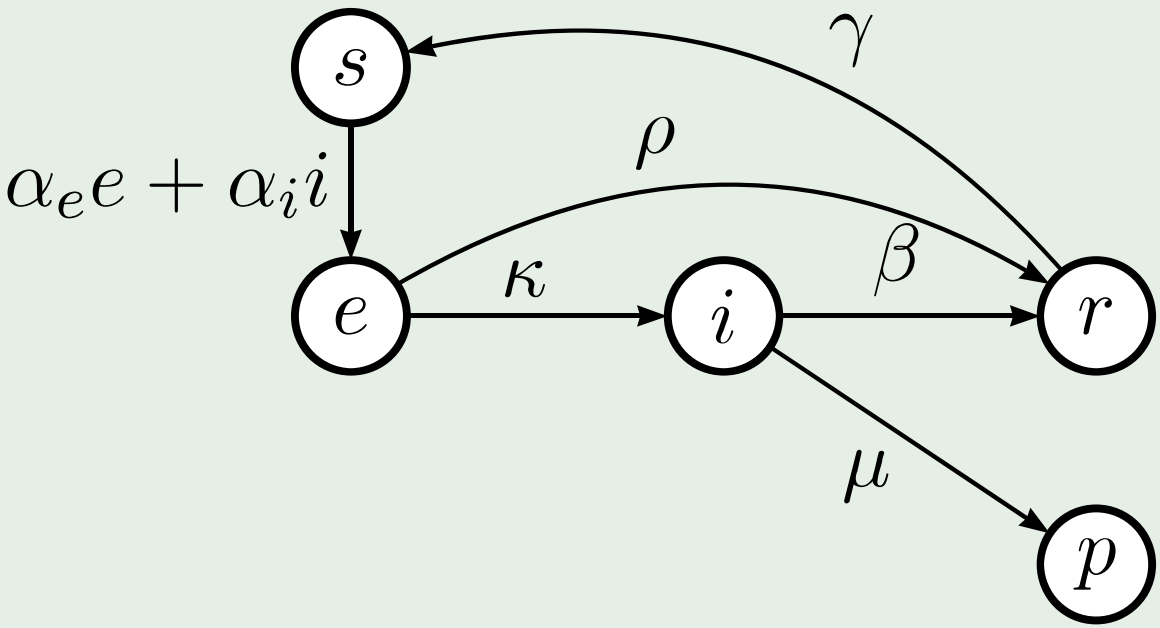
The infected either recover or pass away.



Compartmental modeling of epidemic diseased
(Continued)

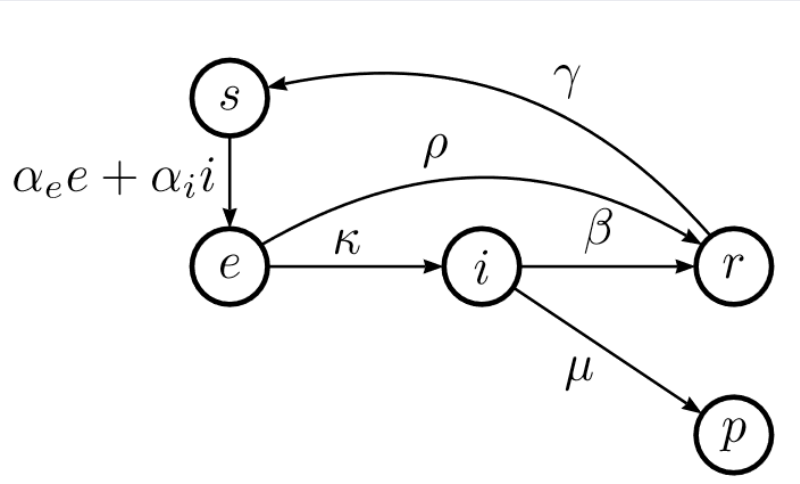
Example: A mortal non-immunizing susceptible-exposed-infected-recovered (SEIR) model

The recovered may again become susceptible.



Example: A mortal non-immunizing susceptible-exposed-infected-recovered (SEIR) model

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



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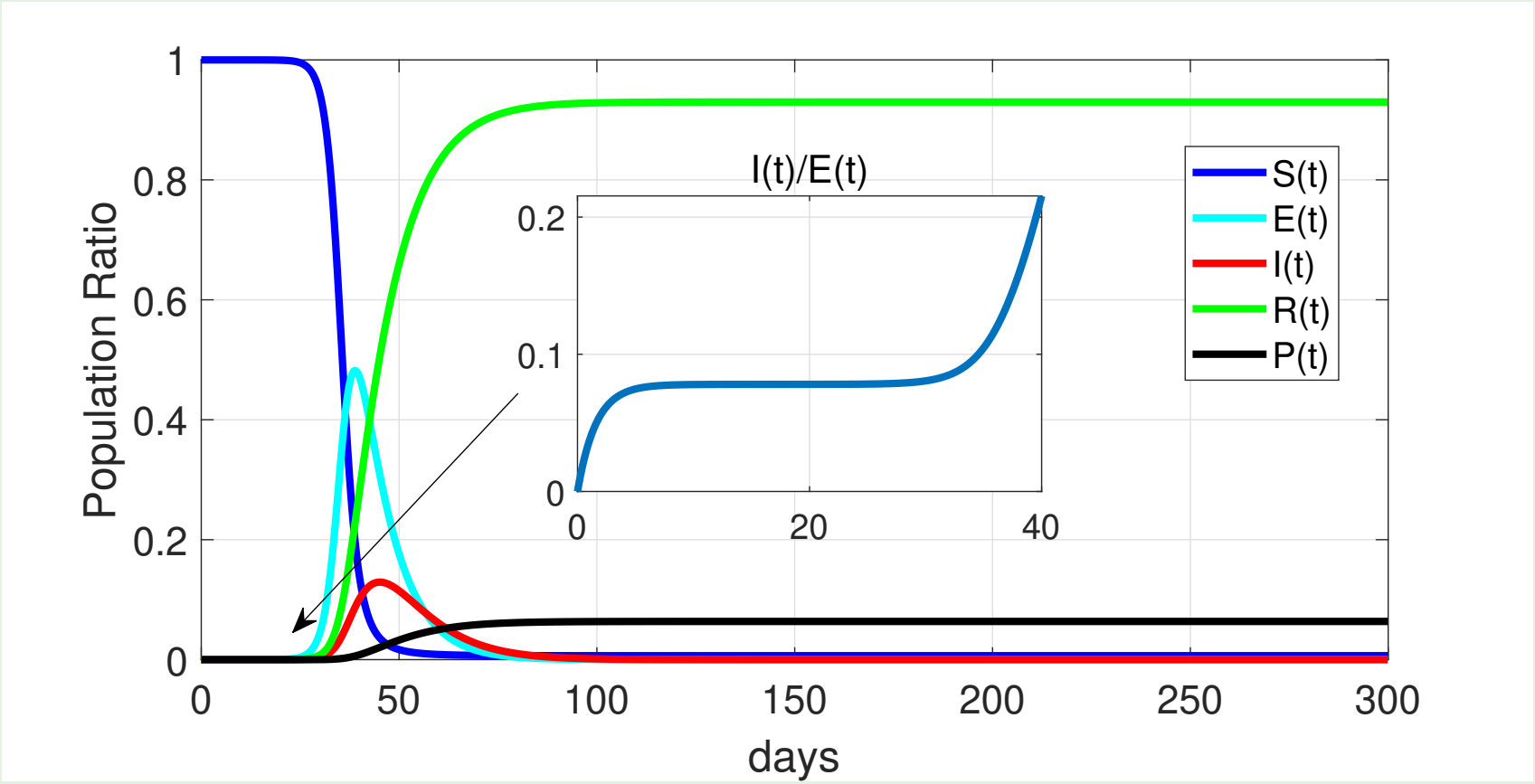
$$\frac{de(t)}{dt} = \alpha_e s(t)e(t) + \alpha_i s(t)i(t) - \kappa e(t) - \rho e(t)$$
$$\frac{di(t)}{dt} = \kappa e(t) - \beta i(t) - \mu i(t)$$
$$\frac{dr(t)}{dt} = \beta i(t) + \rho e(t) - \gamma r(t)$$
$$\frac{dp(t)}{dt} = \mu i(t)$$

Typical solutions

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



Compartmental modeling of epidemic diseased
(Continued)

What can we learn from compartmental models of the pandemic?

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Compartmental modeling of epidemic diseased
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Compartmental modeling of epidemic diseased
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3. Stability of the situation

Compartmental modeling of epidemic diseased
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Compartmental modeling of epidemic diseased
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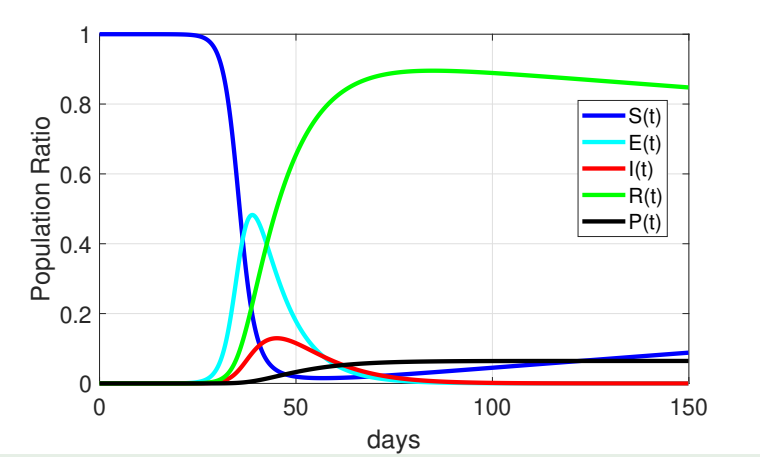
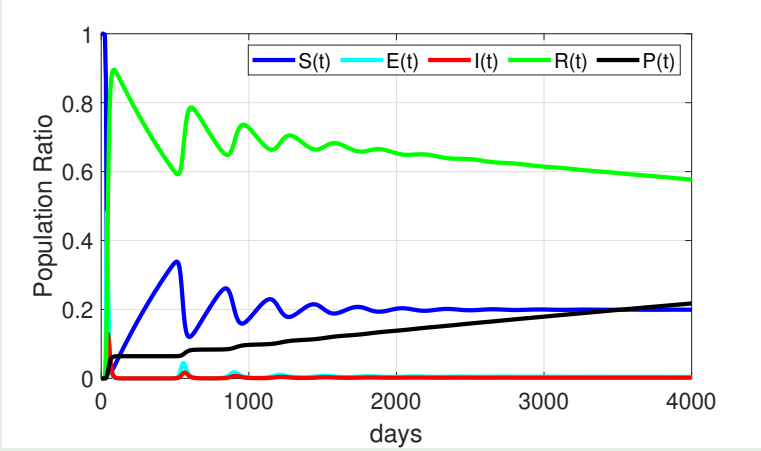
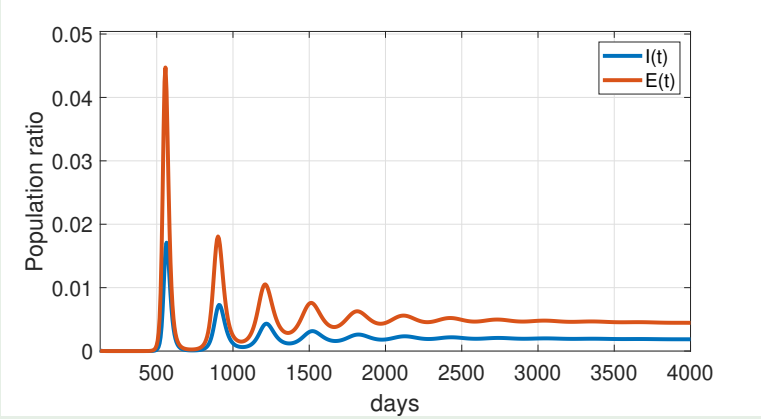
6. The effect of quarantine, social distancing, lockdown, and reopening can be studied
7. Potential future outbreaks of the pandemic
8. The model accuracy and its consistency with real-world data

Typical solutions

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



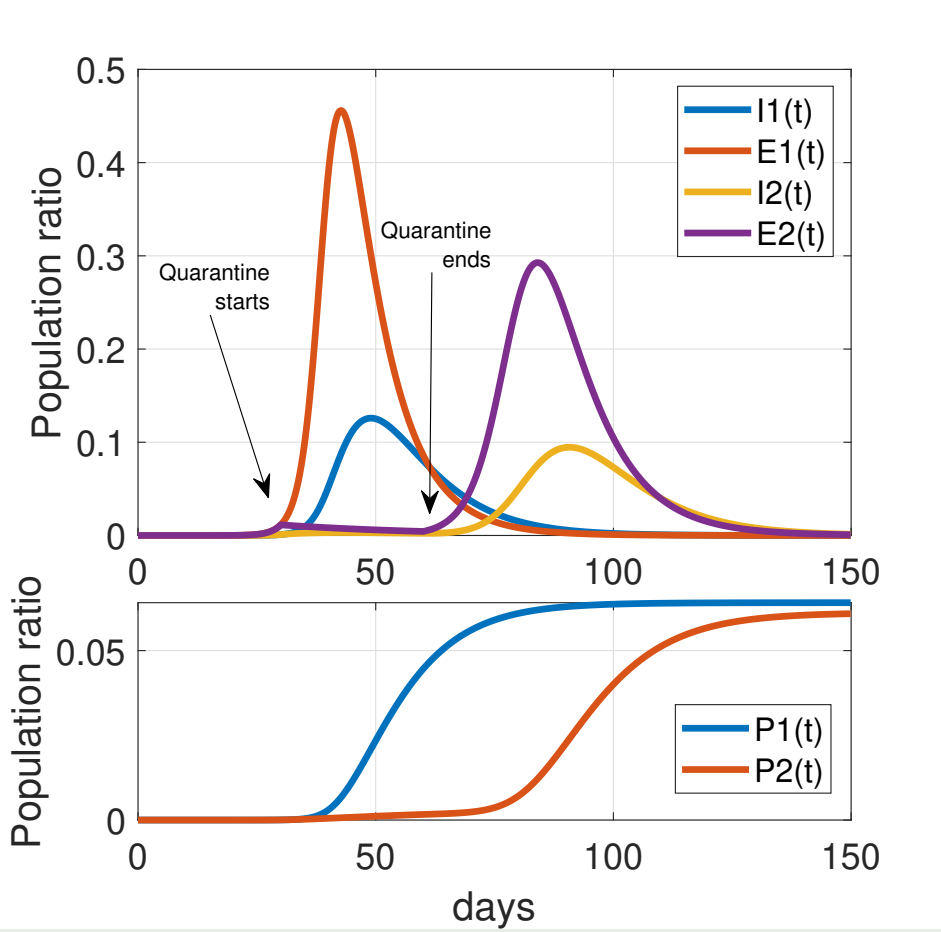




Sameni, R. (2020). Mathematical Modeling of Epidemic Diseases; A Case Study of the COVID-19 Coronavirus (Version 4). DOI: 10.48550/ARXIV.2003.11371

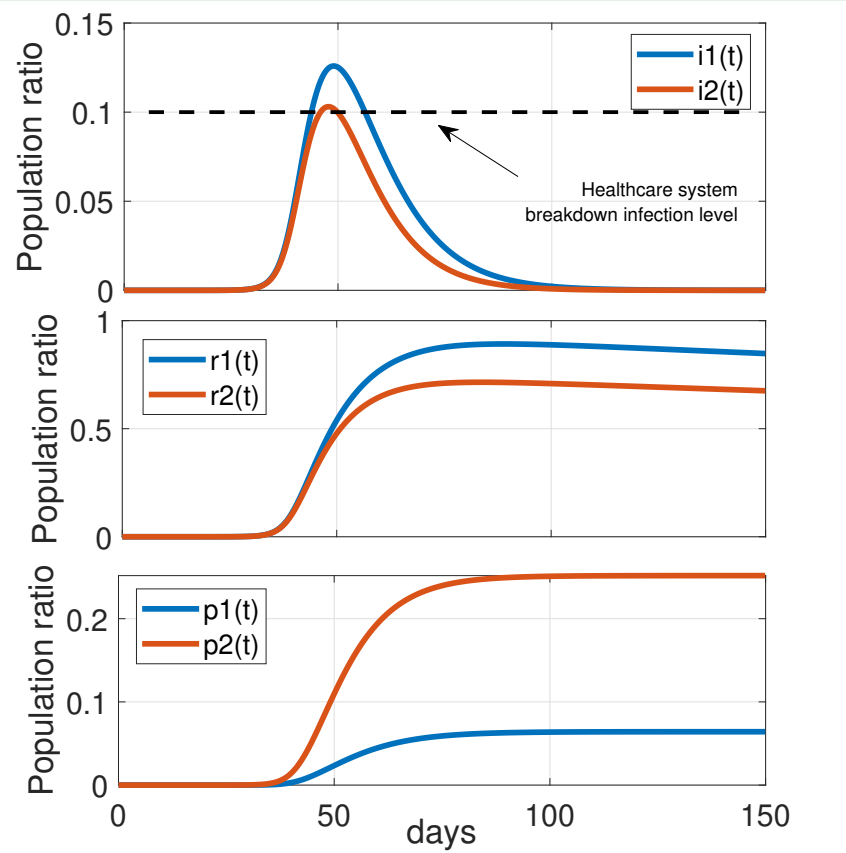
Typical solutions
(continued)

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?

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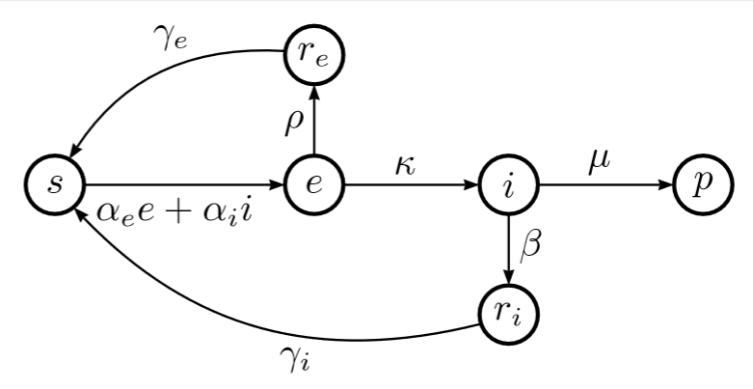
A modified SEIR model

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



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

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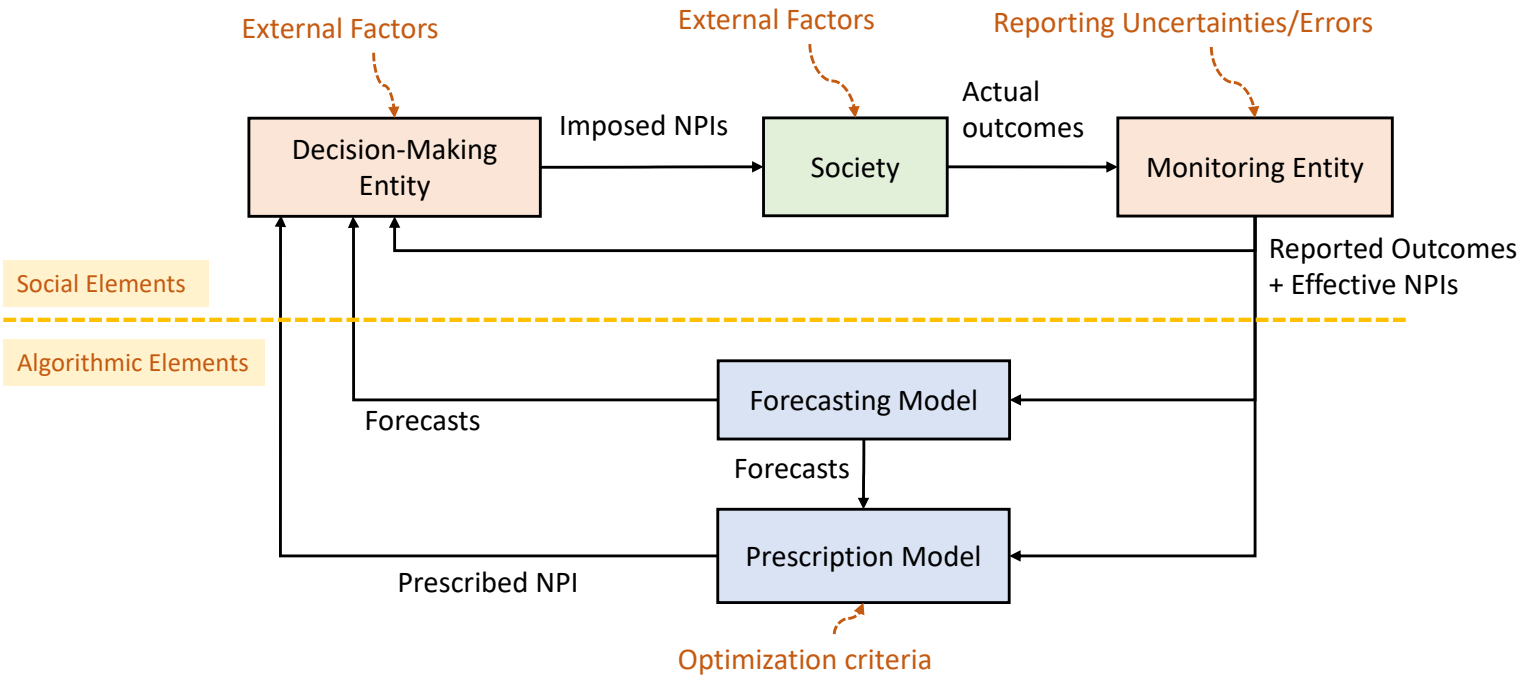
Compartmental modeling of epidemic diseased
(Continued)

Application: Pandemic control by nonpharmaceutical interventions



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Compartmental modeling of epidemic diseased
(Continued)

Shortcomings of macro-level compartmental models

1. Explicit modeling of individual behaviors. For example: "will I get COVID-19 if I go to a party?"

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2. Modeling family-level or community-level behavior

Compartmental modeling of epidemic diseased
(Continued)

Shortcomings of macro-level compartmental models

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2. Modeling family-level or community-level behavior
3. Modeling individual background diseases

Outline

Micro-level modeling of epidemic diseases

Agent-based model steps

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4. Population-wised behavior is estimated through Monte Carlo simulation and the marginalized behavior of the agents (individuals, particles, etc.)
5. Marginal statistics (e.g. the number of exposed, infected, recovered, etc.) are calculated over the entire population

Micro-level modeling of epidemic diseases

Agent-based model elements for pandemic modeling

- Attributes: 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
(continued)

Example: Implementation of agent-based models; an object-oriented approach

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);
```

83 % | No issues found | Ln: 40 | Ch: 1

Micro-level modeling of epidemic diseases
(continued)

Illustration of an agent-based environment

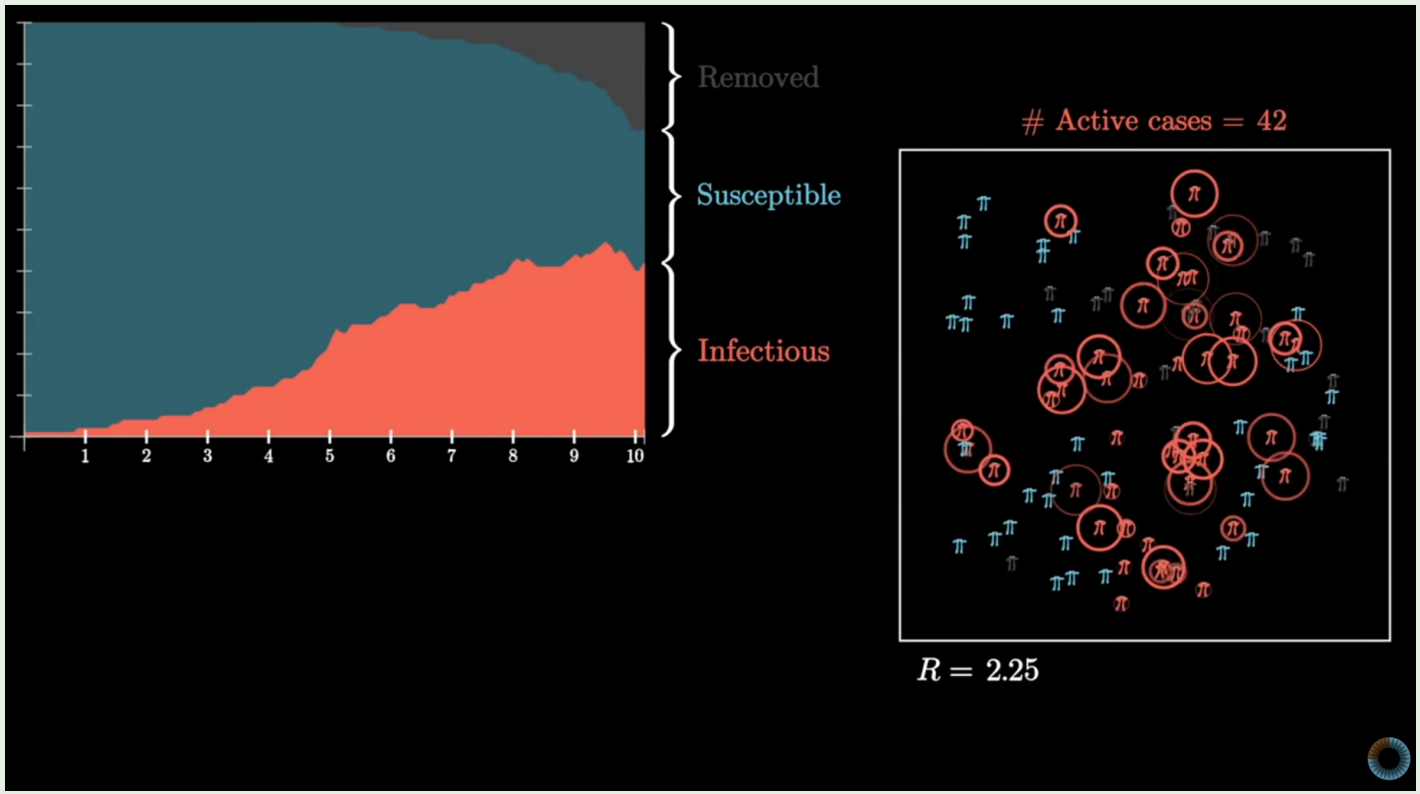

Figure: adopted from `https://youtu.be/gxAaO2rsdIs`

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, ploicymakers, 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, ploicymakers, etc.
3. Is more graphical and more convincing for decision-makers!

Cons

1. There are more parameters; 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 and 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

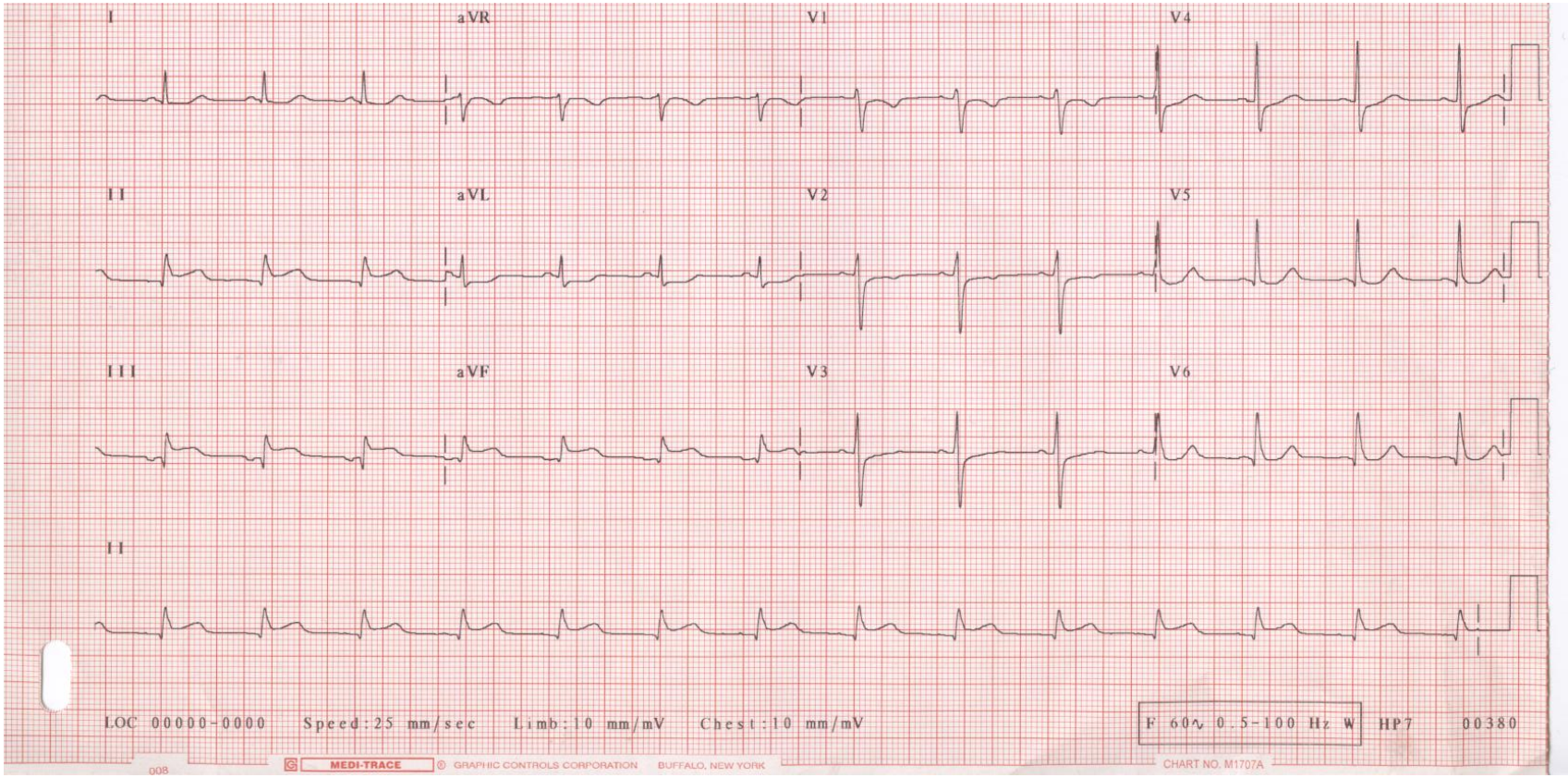
1. Epidemic models: Brauer et al. (2012)
2. Biological systems modeling: Haefner (2005); de Vries et al. (2006)
3. The stochastic aspects of mathematical epidemiology: Britton (2010); Pellis et al. (2012); Brauer et al. (2012); Miller (2019)
4. Optimal estimation and Kalman filtering: Grewal & Andrews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

Outline

Electrocardiogram modeling

Objective

Model the temporal waveform of cardiac signals to produce normal and abnormal electrocardiogram (ECG) data with realistic morphology, heart rates and noises.



Glenlarson, CC BY-SA 3.0

Electrocardiogram modeling

Motivation

- Better understanding of the electrical cardiac function
- Generate synthetic ECG for evaluating biomedical signal processing and machine learning algorithms
- Generating typical and extreme ECG cases for testing ECG devices
- Generating ECG for training data greedy deep learning models
- Dynamic models can be used to develop filtering and forecasting algorithms, e.g. *Kalman filters*

Electrocardiogram modeling
(continued)

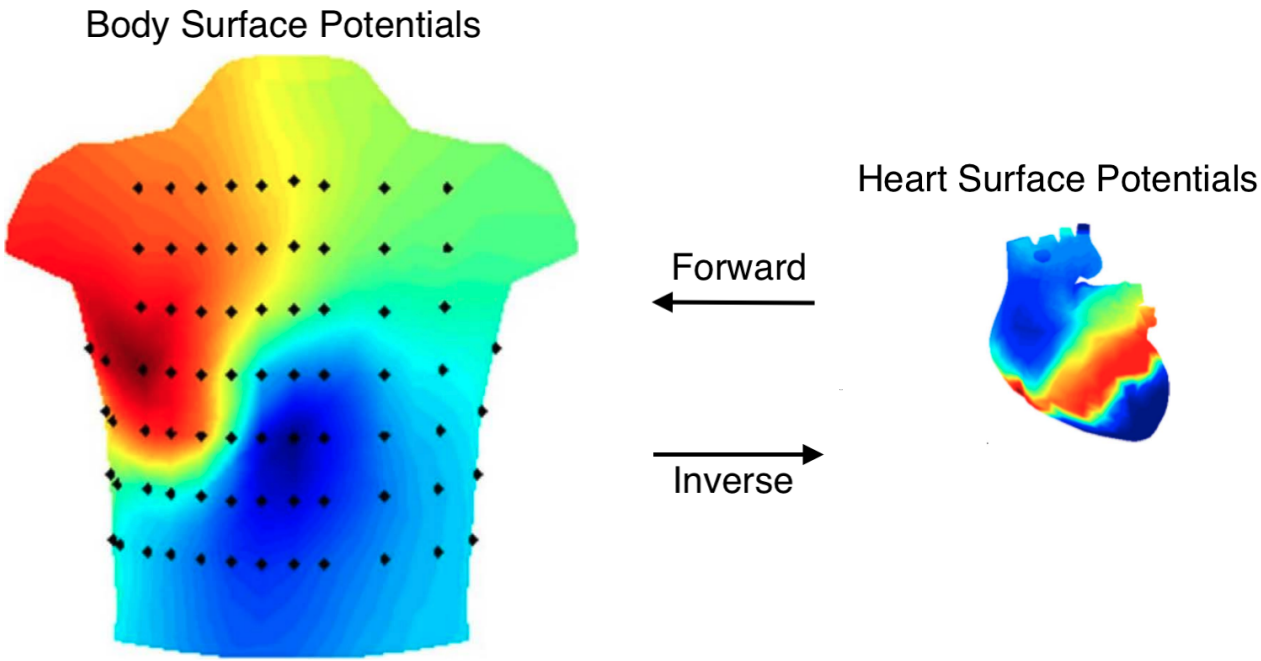
How to model the ECG

1. ECG modeling can be studied in various levels of abstraction, ranging from low-level neural models to high-level body surface potential models.
2. In many applications, macroscopic models that mimic the cardiac signal morphology and heart-rate are required
3. Similar models can be used for adult and fetal ECG and magnetocardiogram (MCG), in normal and abnormal cases
4. The model should also be linked to system-level physiological models of cardiac signals, which consider physiological factors that influence the heart rate and ECG morphology

Forward-backward body potential modeling

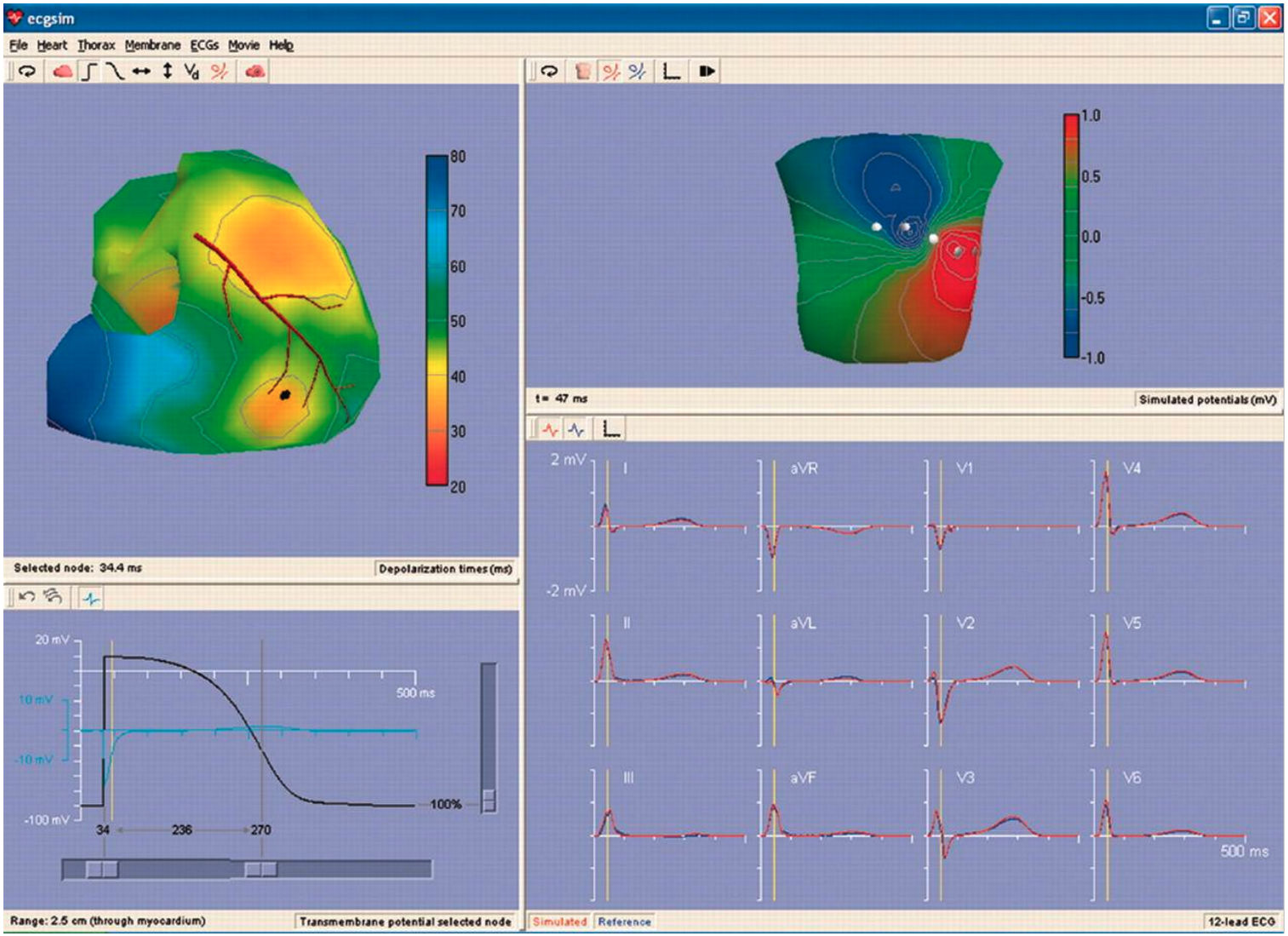
Body/heart surface potential modeling

The forward and inverse problems of body surface and myocardial surface potential estimation is ill-posed, but may be solved by finite and boundary element methods subject to regularity constraints.



Adapted from: Yao, B., & Yang, H. (2016). Physics-driven Spatiotemporal Regularization for High-dimensional Predictive Modeling: A Novel Approach to Solve the Inverse ECG Problem. Scientific Reports. DOI: 10.1038/srep39012

Body surface and myocardial surface potential models



Adopted from: van Oosterom, A. and Oostendorp T.F (2004). ECGSIM: an interactive tool for studying the genesis of QRST waveforms. Heart. BMJ. DOI: 10.1136/hrt.2003.014662

Morphological ECG waveform modeling

Motivation

- Finite and boundary element methods for ECG modeling and simulation are computationally intense and are over-parameterized.
- Alternatively, one may model the body surface ECG as a pseudo-periodic waveform using mathematical functions
- The limited model parameters can be identified by data fitting

A dynamic model for ECG generation

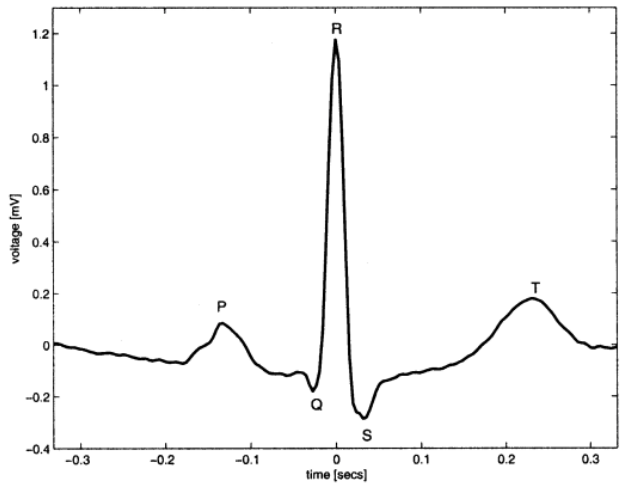
IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 50, NO. 3, MARCH 2003

A Dynamical Model for Generating Synthetic Electrocardiogram Signals

Patrick E. McSharry*, Gari D. Clifford, Lionel Tarassenko, and Leonard A. Smith

***Abstract*—A dynamical model based on three coupled ordinary differential equations is introduced which is capable of generating realistic synthetic electrocardiogram (ECG) signals. The operator can specify the mean and standard deviation of the heart rate, the morphology of the PQRST cycle, and the power spectrum of the RR tachogram. In particular, both respiratory sinus arrhythmia at the high frequencies (HFs) and Mayer waves at the low frequencies (LFs) together with the LF/HF ratio are incorporated in the model. Much of the beat-to-beat variation in morphology and timing of the human ECG, including QT dispersion and R-peak amplitude modulation are shown to result. This model may be employed to assess biomedical signal processing techniques which are used to compute clinical statistics from the ECG.**

***Index Terms*—Dynamical model, heart rate variability (HRV), Mayer waves, QRS morphology, QT-interval, respiratory sinus arrhythmia, RR-interval, RR tachogram, synthetic ECG.**



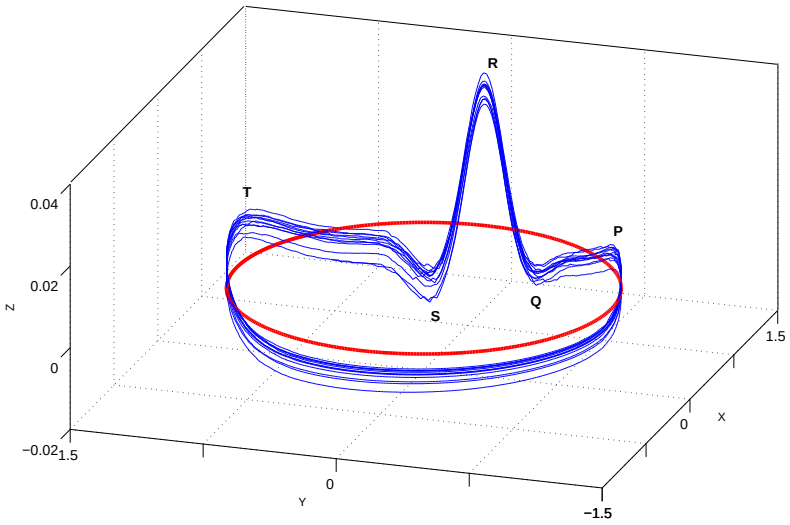
McSharry, P. E., Clifford, G. D., Tarassenko, L., & Smith, L. A. (2003). A dynamical model for generating synthetic electrocardiogram signals. In IEEE Transactions on Biomedical Engineering. DOI: 10.1109/tbme.2003.808805

McSharry-Clifford's model (McSharry et al., 2003)

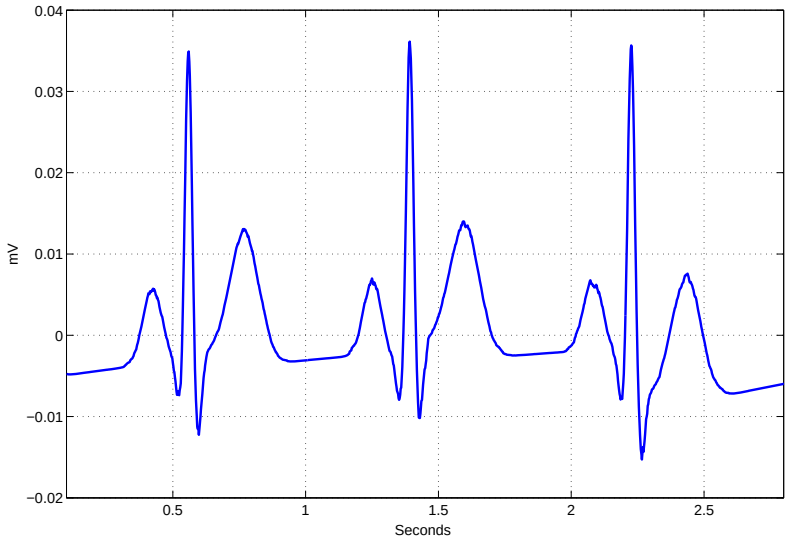
$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = \rho x - \omega y \\ \dfrac{\mathrm{d}y}{\mathrm{d}t} = \rho y + \omega x \\ \dfrac{\mathrm{d}z}{\mathrm{d}t} = -\displaystyle\sum_{i \in \{P,Q,R,S,T\}} a_i \Delta\theta_i \exp\left(-\frac{\Delta\theta_i^2}{2b_i^2}\right) - (z - z_0) \end{cases}$$

- x, y, and z are state variables, $\rho = 1 - \sqrt{x^2 + y^2}$, $\Delta\theta_i = (\theta - \ \theta_i) \mod (2\pi)$, $\theta = \text{atan2}(y, x)$ is the four quadrant arctangent, and ω is the angular velocity of the trajectory as it moves around the limit cycle in the $x - y$ plane.
- a_i, b_i, and θ_i correspond to the amplitude, width, and center parameters of the Gaussian functions.
- The baseline wander of the ECG is modeled with the parameter z_0, considered as a relatively low amplitude sinusoidal component coupled with the respiratory frequency.

McSharry-Clifford's model (McSharry et al., 2003)
(continued)



(a) 3D trajectory of the ECG model. The red line corresponds with the unit circle in the $x - y$ plane



(b) Projection of the 3D trajectory onto the z-axis

Figure: 3D representation and 1D ECG representation of the dynamic modey by McSharry et al. (2003)

The simplified McSharry-Clifford model in polar form (Sameni et al., 2005)

The polar representation of McSharry-Clifford's model is:

$$\begin{cases} \dot{r} = r(1-r) \\ \dot{\theta} = \omega \\ \dot{z} = -\sum_{i \in \{P,Q,R,S,T\}} \frac{\alpha_i \omega}{b_i^2} \Delta\theta_i \exp\left(-\frac{\Delta\theta_i^2}{2b_i^2}\right) \end{cases}$$

The 1st equation converges to $r = 1$ for any $r_0 \in (0, 1]$; the 2nd and 3rd equations do not depend on r. So r can be discarded.

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✎ Dimension analysis and correct coordinate system selection are key techniques in model development.

The simplified McSharry-Clifford's model in discrete form (Sameni et al., 2007b)

$$\begin{cases} \theta_{k+1} = (\theta_k + \omega\delta) \mod (2\pi) \\ z_{k+1} = -\sum_i \delta \frac{\alpha_i \omega}{b_i^2} \Delta\theta_i \exp\left(-\frac{\Delta\theta_i^2}{2b_i^2}\right) + z_k + \eta \end{cases}$$

- $\Delta\theta_i = (\theta_k - \theta_i) \mod (2\pi)$, η is a random additive noise that models the inaccuracies of the dynamic model (including the baseline wander)
- The summation is taken over the number of Gaussian functions used for modeling the shape of a desired ECG.
- Due to the *universal approximation* property of Gaussian functions, any smooth waveform can be approximated by using a sufficient number of Gaussians

McSharry-Clifford's model parameter selection

- Model parameters adopted by McSharry and Clifford to generate their synthetic ECGs:

  Table: Parameters of the synthetic ECG model from (McSharry et al., 2003)

Index(i)	P	Q	R	S	T
$\theta_i(rads.)$	$-\pi/3$	$-\pi/12$	0	$\pi/12$	$\pi/2$
a_i	1.2	-5.0	30	-7.5	0.75
b_i	0.25	0.1	0.1	0.1	0.4

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- Generally, we can fit the sum of Gaussian model over observed ECG records.

Vectorcardiogram modeling (Sameni et al., 2007a) I

$$\dot{\theta} = \omega$$

$$\dot{x} = -\sum_i \frac{\alpha_i^x \omega}{(b_i^x)^2} \Delta\theta_i^x \exp\left[-\frac{(\Delta\theta_i^x)^2}{2(b_i^x)^2}\right]$$

$$\dot{y} = -\sum_i \frac{\alpha_i^y \omega}{(b_i^y)^2} \Delta\theta_i^y \exp\left[-\frac{(\Delta\theta_i^y)^2}{2(b_i^y)^2}\right]$$

$$\dot{z} = -\sum_i \frac{\alpha_i^z \omega}{(b_i^z)^2} \Delta\theta_i^z \exp\left[-\frac{(\Delta\theta_i^z)^2}{2(b_i^z)^2}\right]$$

$\Delta\theta_i^x = (\theta - \theta_i^x) \mod (2\pi)$, $\Delta\theta_i^y = (\theta - \theta_i^y) \mod (2\pi)$, $\Delta\theta_i^z = (\theta - \theta_i^z) \mod (2\pi)$, and $\omega = 2\pi f$, f is the beat-to-beat heart rate in Hz.

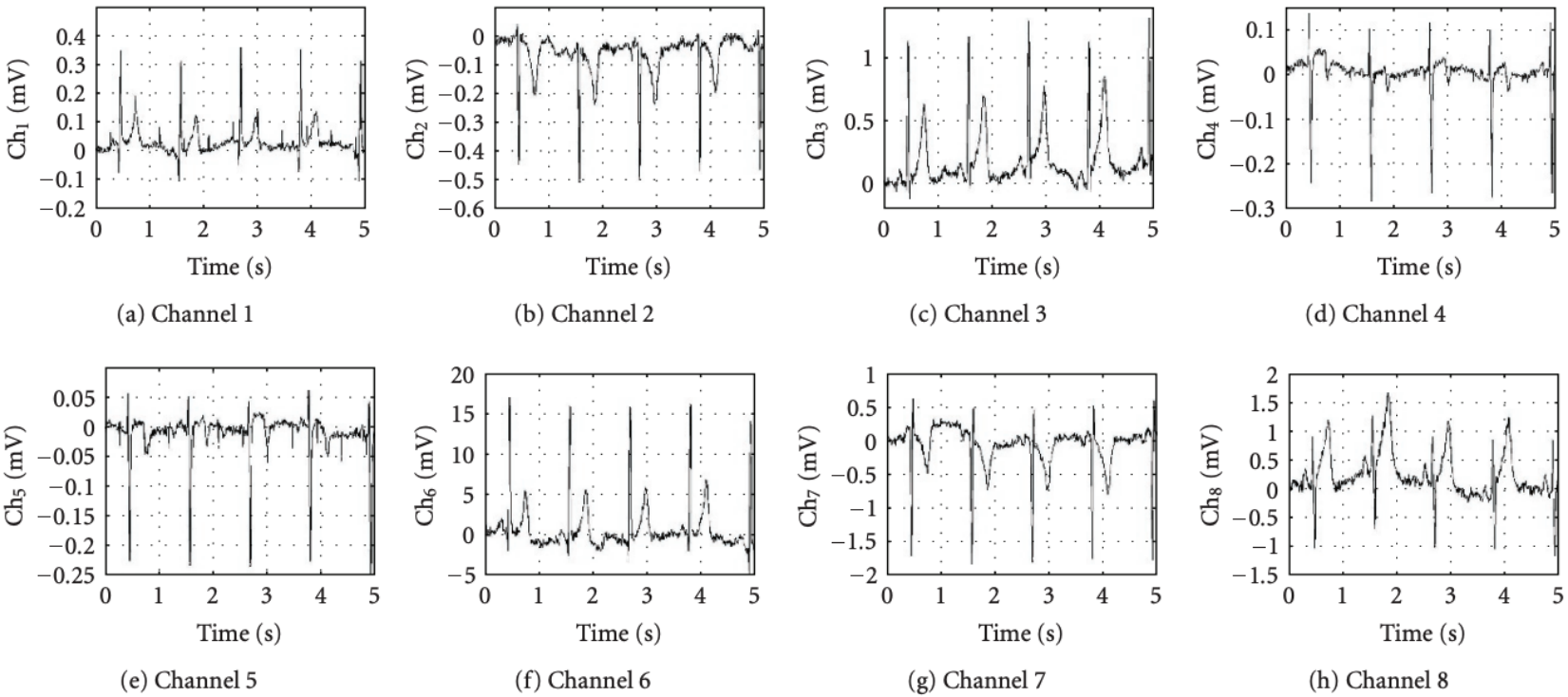
By adding stochastic deviations to the parameters of McSharry-Clifford's model and its extensions, we can generate more realistic cardiac dipoles with inter-beat variations.

Multi-channel ECG generation with realistic noise (Sameni et al., 2007a)

$$ECG(t) = H \cdot R \cdot \Lambda \cdot s(t) + W(t)$$

- $ECG(t)_{N\times 1}$ is a vector of the ECG channels recorded from N leads, $s(t)_{3\times 1} = [x(t), y(t), z(t)]^T$ contains the three components of the dipole vector $\mathbf{d}(t)$, $H_{N\times 3}$ corresponds to the body volume conductor model (as for the Dower transformation matrix), $\Lambda_{3\times 3} = \text{diag}(\lambda_x, \lambda_y, \lambda_z)$ is a diagonal matrix corresponding to the scaling of the dipole in each of the x, y, and z directions, $R_{3\times 3}$ is the rotation matrix for the dipole vector, and $W(t)_{N\times 1}$ is the noise in each of the N ECG channels.
- **Note:** H, R, and Λ are generally functions of time.

Multi-channel ECG generation with realistic noise (Sameni et al., 2007a)
(continued)



Sameni, R., Clifford, G. D., Jutten, C., & Shamsollahi, M. B. (2007). Multichannel ECG and Noise Modeling: Application to Maternal and Fetal ECG Signals. In EURASIP Journal on Advances in Signal Processing. DOI: 10.1155/2007/43407

Joint maternal and fetal ECG model (Sameni et al., 2007a): I

$$X(t) = H_m \cdot R_m \cdot \Lambda_m \cdot s_m(t) + H_f \cdot R_f \cdot \Lambda_f \cdot s_f(t) + W(t)$$

- Subscripts m and f refer to the mother and the fetus, respectively.
- H_m, H_f, R_m, R_f, Λ_m and, Λ_f are body volume conduction, rotation and scaling matrices
- R_f models the relative position of the fetus with respect to the axes of the maternal body, enabeling us to model the fetus in the different typical positions: *vertex* (fetal head-down) or *breech* (fetal head-up).
- $s_f(t) = [x_f(t), y_f(t), z_f(t)]^T$ is a canonical representation of the fetal dipole vector with respect to the fetal body axes.

Joint maternal and fetal ECG model (Sameni et al., 2007a): II

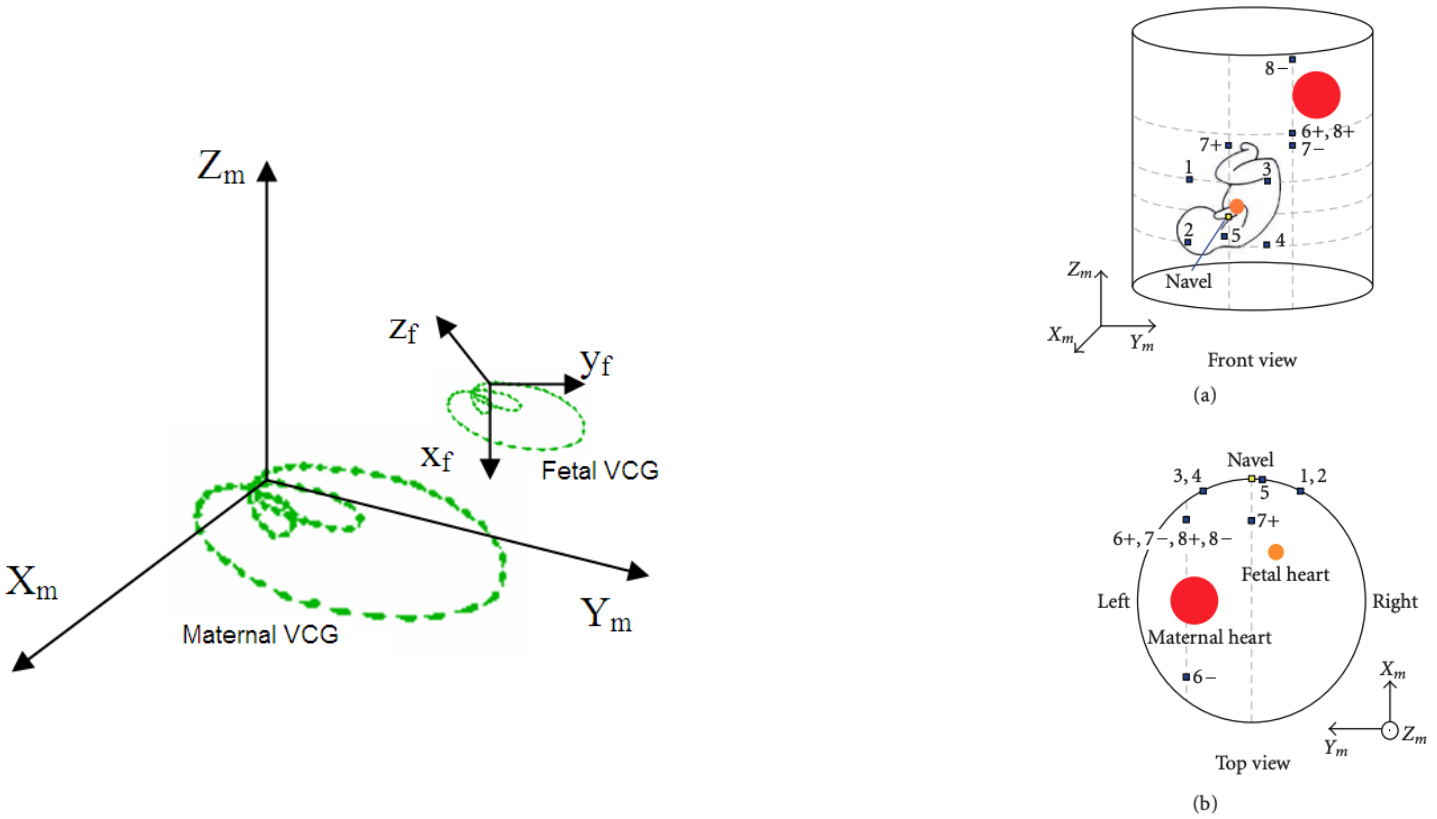


Figure: (left) Illustration of the fetal and maternal VCGs vs. their body coordinates; (right) Model of the maternal torso, with the locations of the maternal and fetal hearts and the simulated electrode configurations

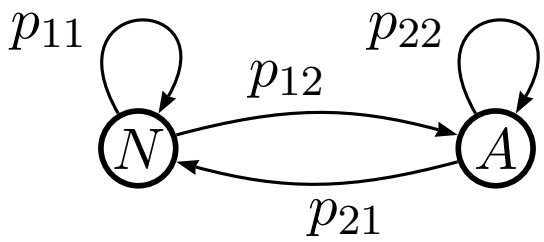
Stochastic ECG models

We can add stochastic aspects to the model:

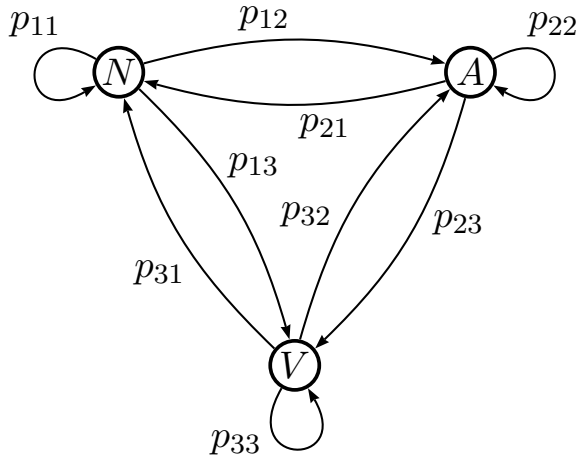
- Beat-to-beat variations of the ECG morphology
- Natural beat-to-beat heart rate variability (HRV)
- Morphological variations due to occasional ectopic beats and arrhythmia
- Heart rate variability due to physical activity and cardiac abnormalities such as Tachycardia and Bradycardia

Markov models are useful tools for modeling beat-wise variation.

Abnormal ECG modeling with Markov models (Clifford et al., 2010): I



(a) State transition graph between normal (N) and abnormal (A) beats using a first-order Markov chain. The graph can be extended to more abnormal beat types.



(b) State transition graph between normal (A), abnormal (B), and ectopic (V) beats using a first-order Markov chain.

Figure: Using Markov chains to model the state transition between a) normal and abnormal, or b) normal, abnormal and ectopic beats

Abnormal ECG modeling with Markov models (Clifford et al., 2010): II

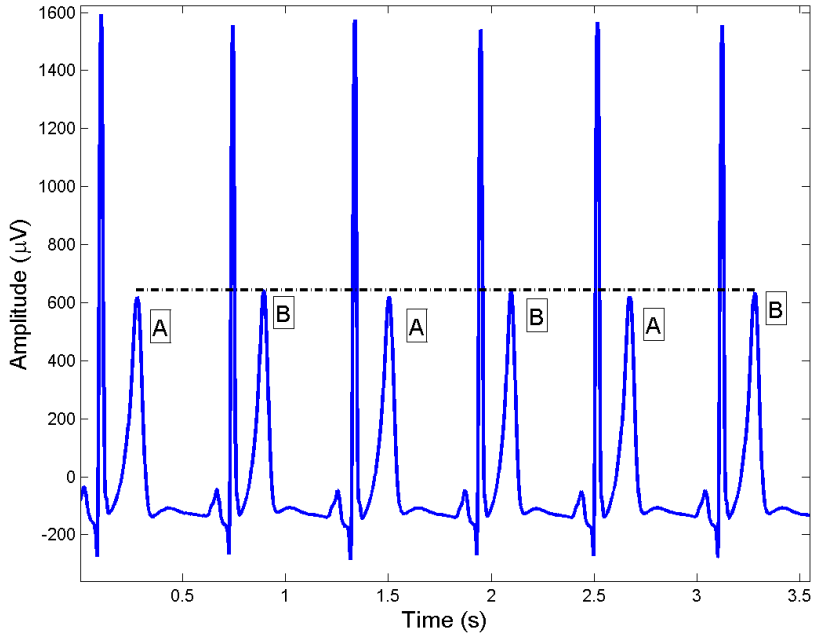
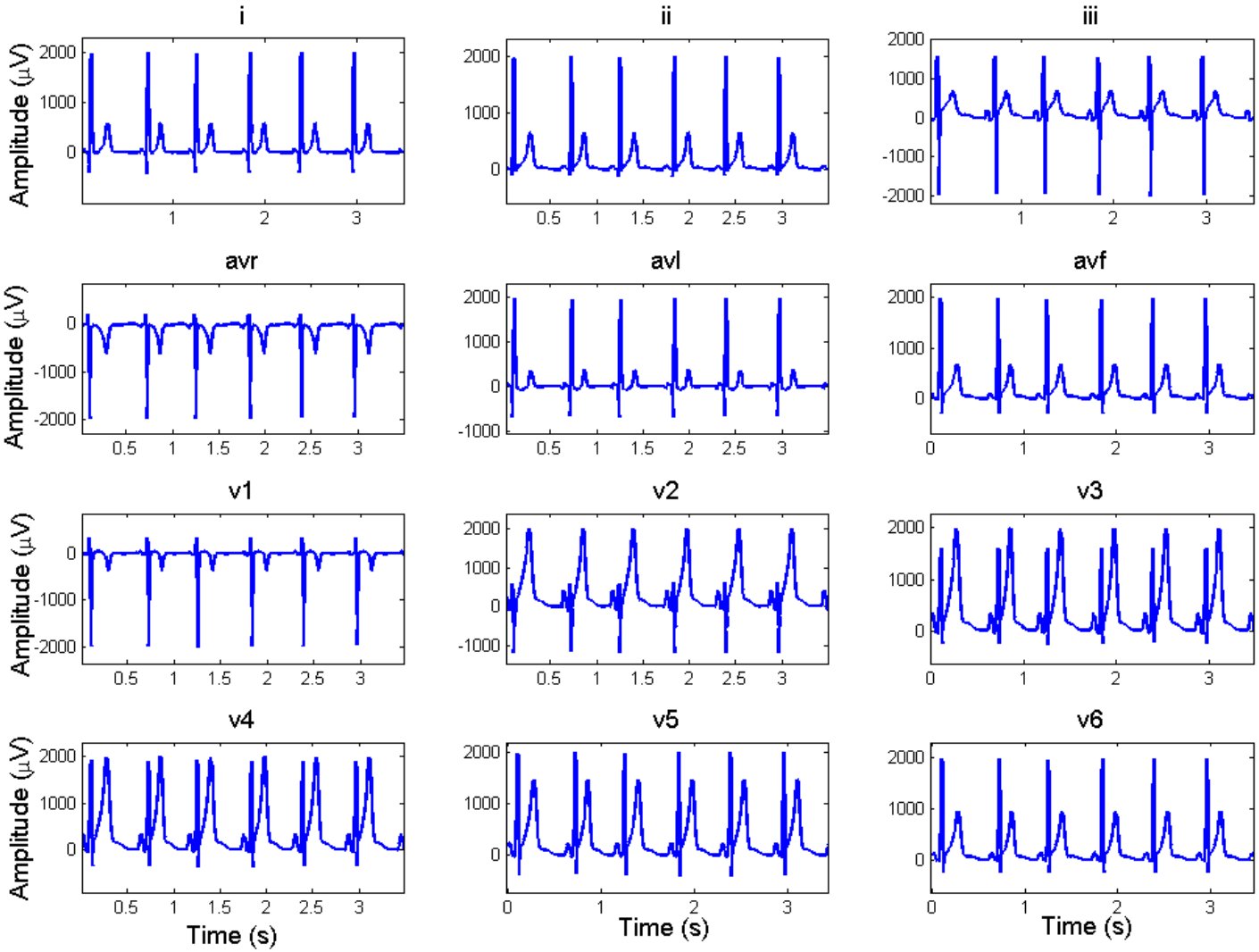
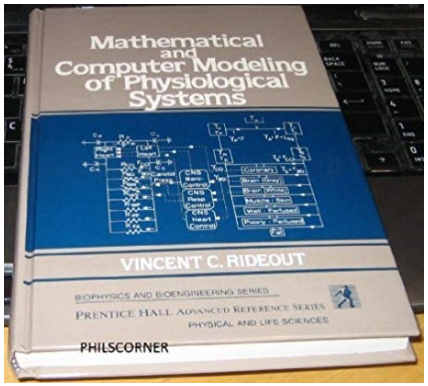


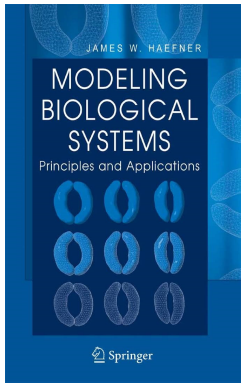
Figure: Typical alternating 'ABAB' TWA pattern generated from our model.

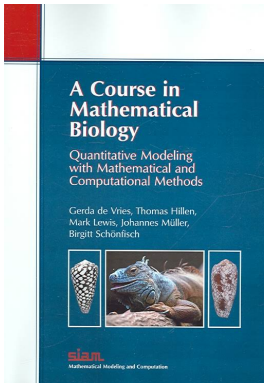
Abnormal ECG modeling with Markov models (Clifford et al., 2010): III

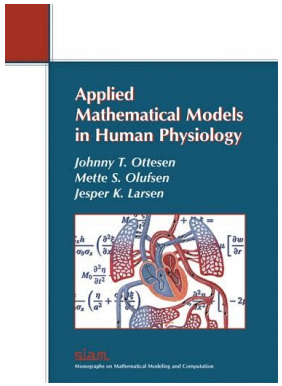


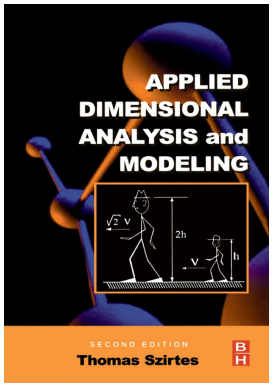
Text books on modeling

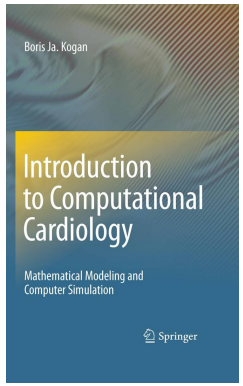


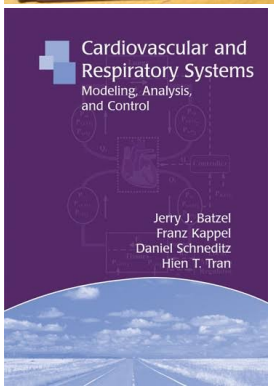


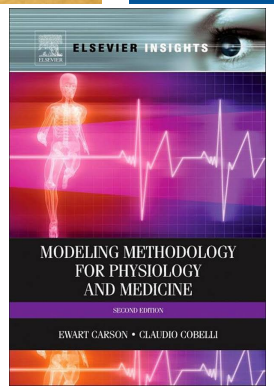


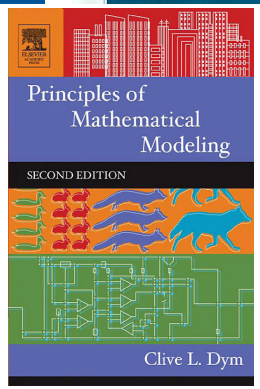


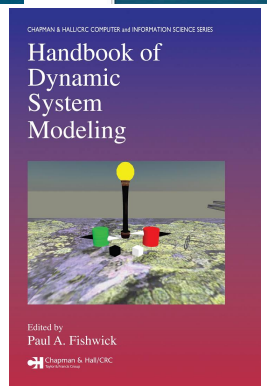


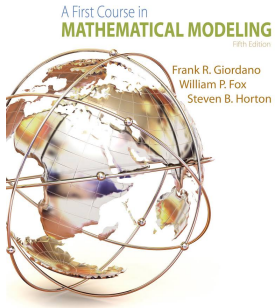


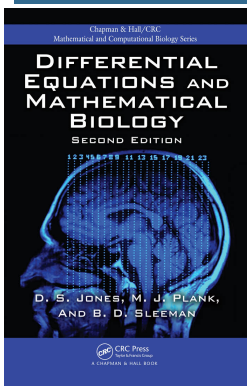


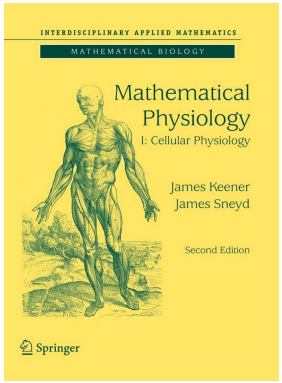


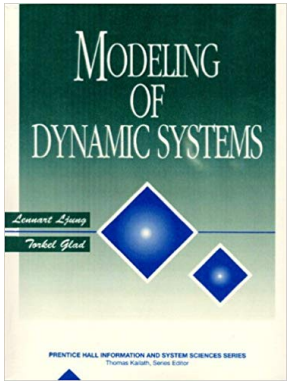


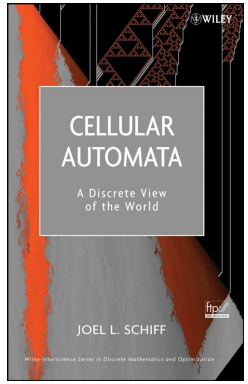


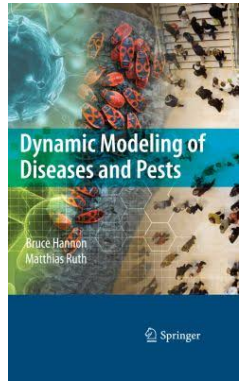












Outline

Lab session source codes

Requirements

- Clone the open-source electrophysiological toolbox (OSET): `https://github.com/alphanumericslab/OSET.git`
- Clone the open-access repository for the mathematical modeling of epidemic diseases: `https://github.com/alphanumericslab/EpidemicModeling`

Sample scripts on modeling with applications

Epidemic spread modeling and data for research

https://youtu.be/gxAaO2rsdIs	A video on agent-based methods (the micro-modeling approach)
https://www.worldometers.info/coronavirus/	COVID-19 real-time data
https://github.com/CSSEGISandData/COVID-19	Johns Hopkins University's CSSE Git repository
testPrescribeXPRIZE02.m	Pandemic optimal control by non-pharmaceutical interventions
https://github.com/alphanumericslab/EpidemicModeling/	Epidemic modeling tools and sample codes

ECG and noise modeling with applications

testECGGenerator1.m	Generates synthetic ECG
testSyntheticMaternalFetalECGGeneration1.m	Generates synthetic mixtures of maternal and fetal ECGs
testAbnormalECGGenerator1.m	Generates synthetic abnormal ECG beats
testNoiseGenerator.m	Generates synthetic biological noises for ECG modeling applications
testKalmanARFilter.m	ECG Baseline wander removal using a first-order AR model for the baseline
testKFNotch.m	Powerline noise cancellation using KF
testECGKalmanFilter.m	ECG Kalman filtering and smoothing

Homework

1. Physics-informed machine learning: write a +500 word summary of the following article with a section on your own comments on the paper: DOI: 10.1038/s42254-021-00314-5
2. Simulate one of the compartmental pandemic models from the following paper in MATLAB or Python (with a Jupyter Notebook containing the results): DOI: 10.48550/arXiv.2003.11371. Please share a Git repository containing the source codes and test scripts.
3. Run and alter the parameters of one of the ECG and noise modeling scripts presented in the lab session (from Slide 69). Write a +250 word summary of the modeling method, with reference to your obtained results. The following papers describe the theory of the ECG modeling scripts:
    - 10.1109/TBME.2003.808805
    - 10.1109/TBME.2007.897817
    - 10.1155/2007/43407
    - 10.1109/AISP.2012.6313817
    - 10.1088/0967-3334/31/5/001

Thank you! Questions?

Part II

Appendixes

6 Pandemic modeling revisited

- Compartmental modeling
- Mathematical epidemiology
- The endemic SEIR model
- Parameter identification
- Future work and further reading

6 Pandemic modeling revisited

- Compartmental modeling
- Mathematical epidemiology
- The endemic SEIR model
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- Future work and further reading

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

Outline

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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Compartmental modeling

Background

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

Example

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

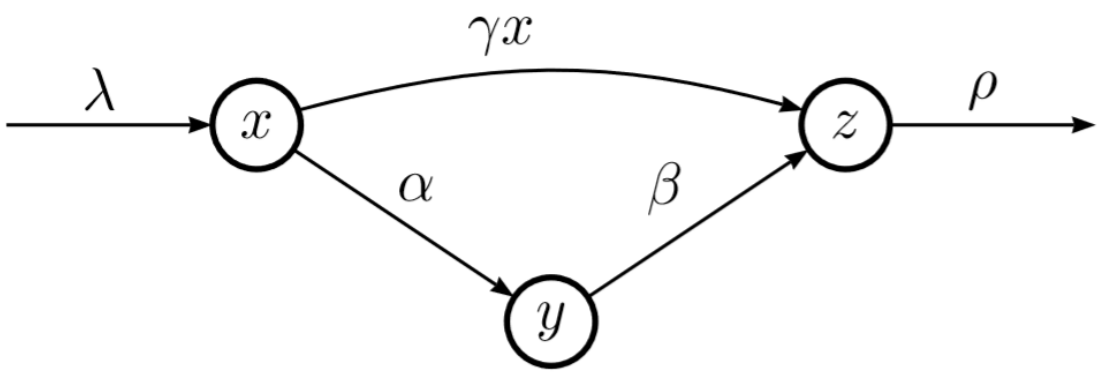


Figure: A sample nonlinear compartmental model

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.

Outline

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.

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 $x_k \overset{\Delta}{=} x(k\Delta)$ is:

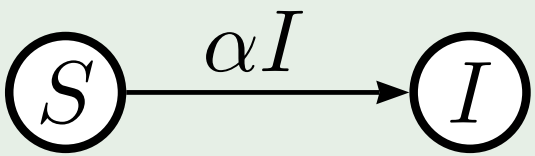
$$x_{k+1} = \underbrace{[1 + \Delta\phi(k\Delta)]}_{\mathcal{R}_0 \text{ (reproduction number)}} x_k$$

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.

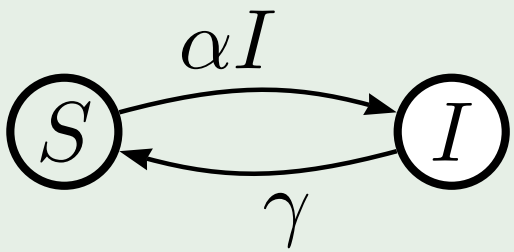
Examples of compartmental models for contagious diseases

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)

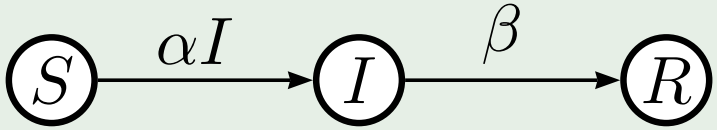
$$\dot{S}(t) = -\alpha S(t)I(t)$$
$$\dot{I}(t) = \alpha S(t)I(t)$$

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

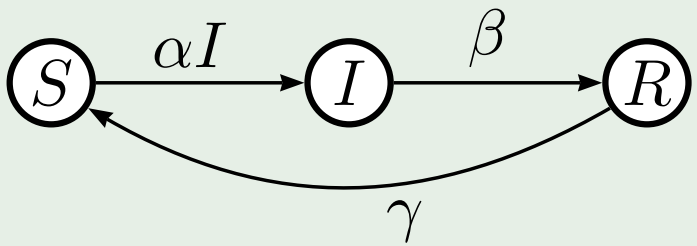
Examples of compartmental models for contagious diseases
(continued)

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

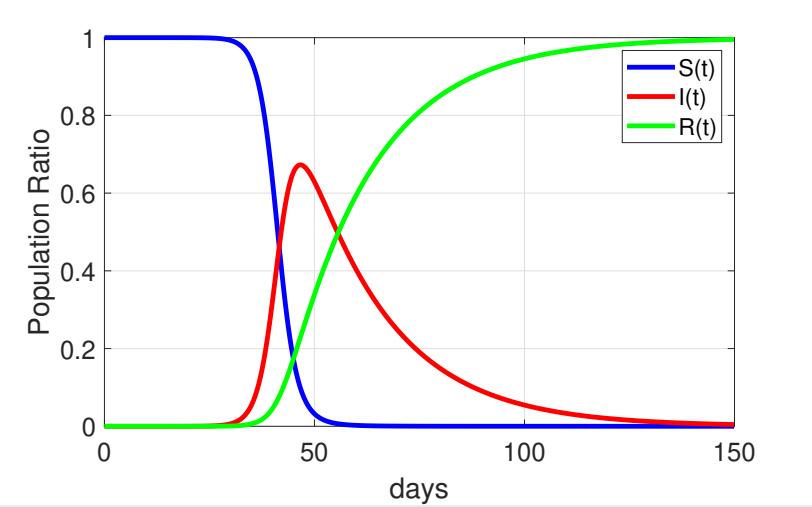
$$\begin{aligned} \dot{S}(t) &= -\alpha S(t)I(t) \\ \dot{I}(t) &= \alpha S(t)I(t) - \beta I(t) \\ \dot{R}(t) &= \beta I(t) \end{aligned} \tag{3}$$

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

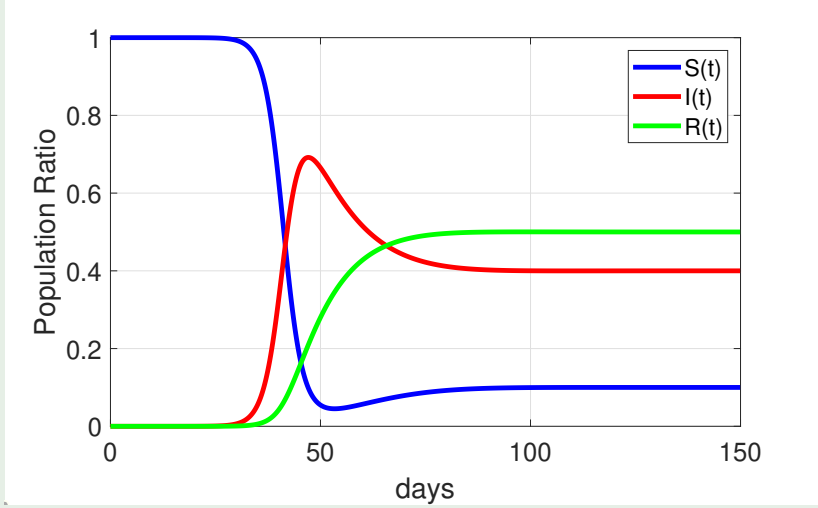
Examples of compartmental models for contagious diseases
(continued)

Typical SIR solutions

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



(a) SIR model with immunity



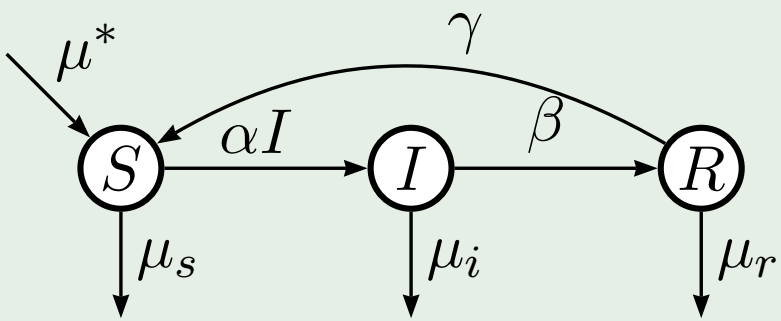
(b) SIR model without immunity

✎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*):



Outline

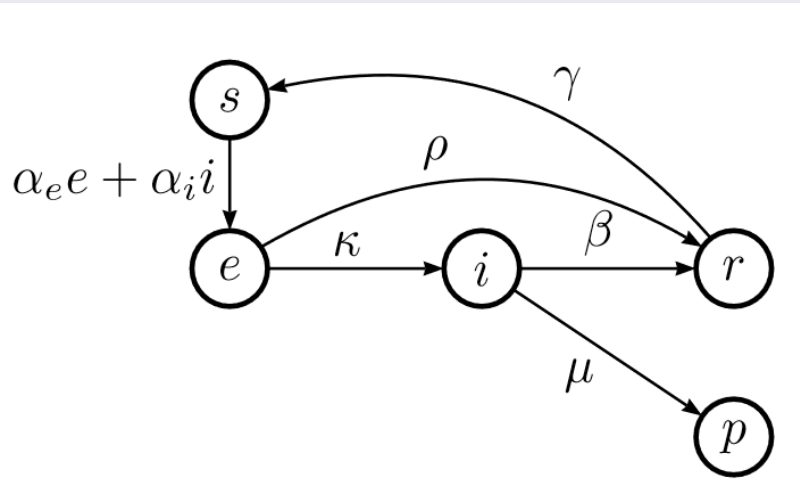
A macro-level model for the COVID-19 coronavirus pandemic

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 $\boldsymbol{g}(\boldsymbol{x}^*) = \boldsymbol{x}^*$.

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The model fixed-points

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

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

Stability of the fixed-point by perturbation analysis

Reminder

The stability of the fixed-point $\boldsymbol{x}^*$ can be checked by perturbation analysis: set $\boldsymbol{x} = \boldsymbol{x}^* + \delta\boldsymbol{x}$ and check the sign of $\boldsymbol{f}(\boldsymbol{x}^* + \delta\boldsymbol{x})$. 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?

Epidemic outbreak behavior

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

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

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

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

Eigen-analysis of the linearized model
(continued)

Properties

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

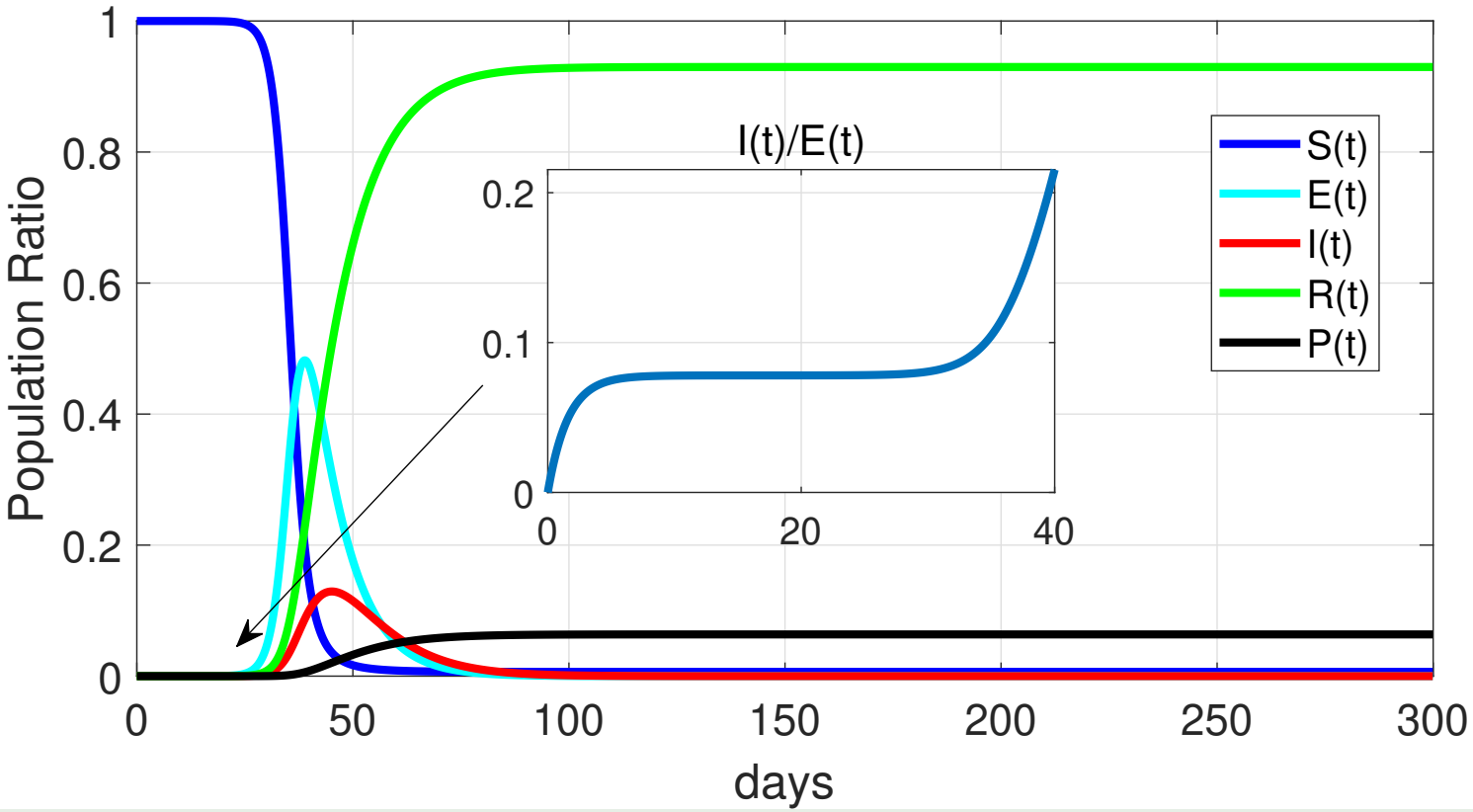
As the infection rate increases, $s(t)$ is no longer close to 1. Taking $s(t) = 1 - e(t) - i(t) - r(t) - p(t)$, the nonlinear model in (4) can be rewritten as:

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

which can be numerically solved from an arbitrary initial condition.

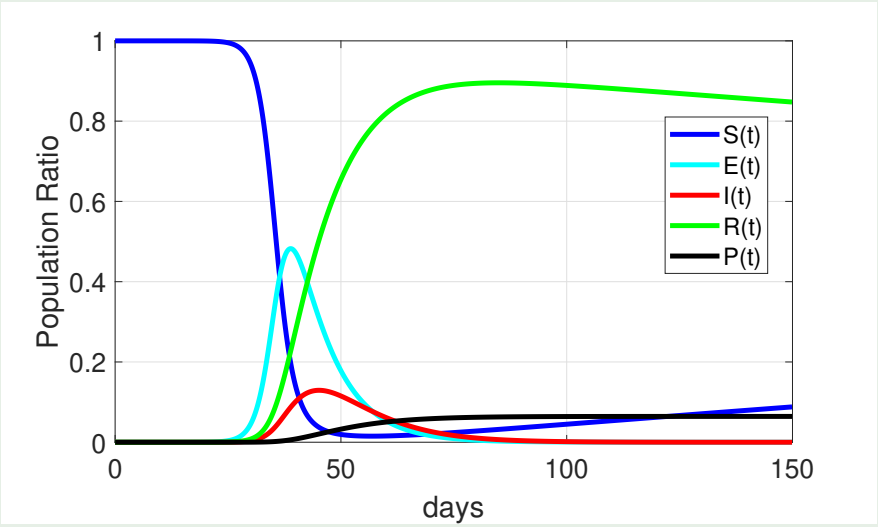
Typical solutions

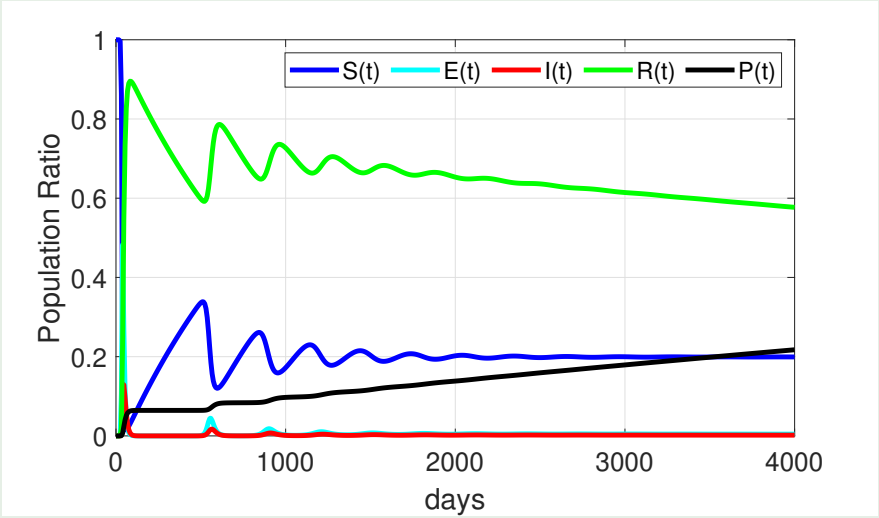
The life-time immune case ($\gamma = 0$)

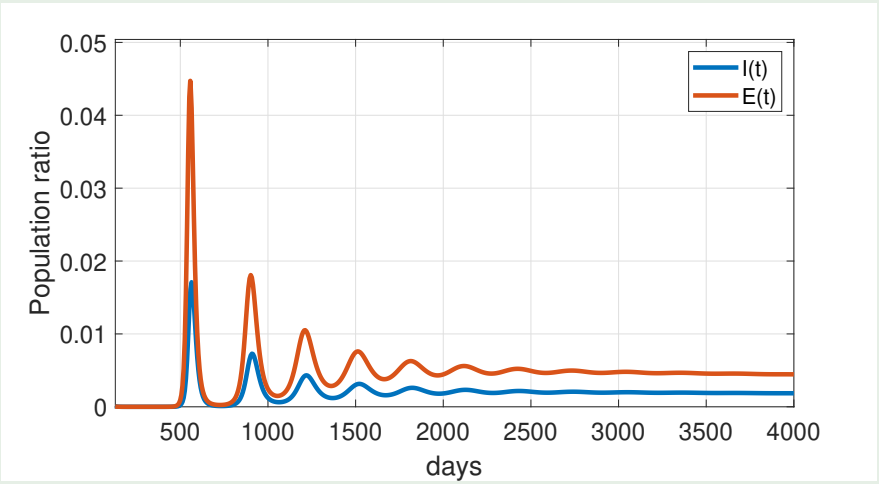


Typical solutions

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)

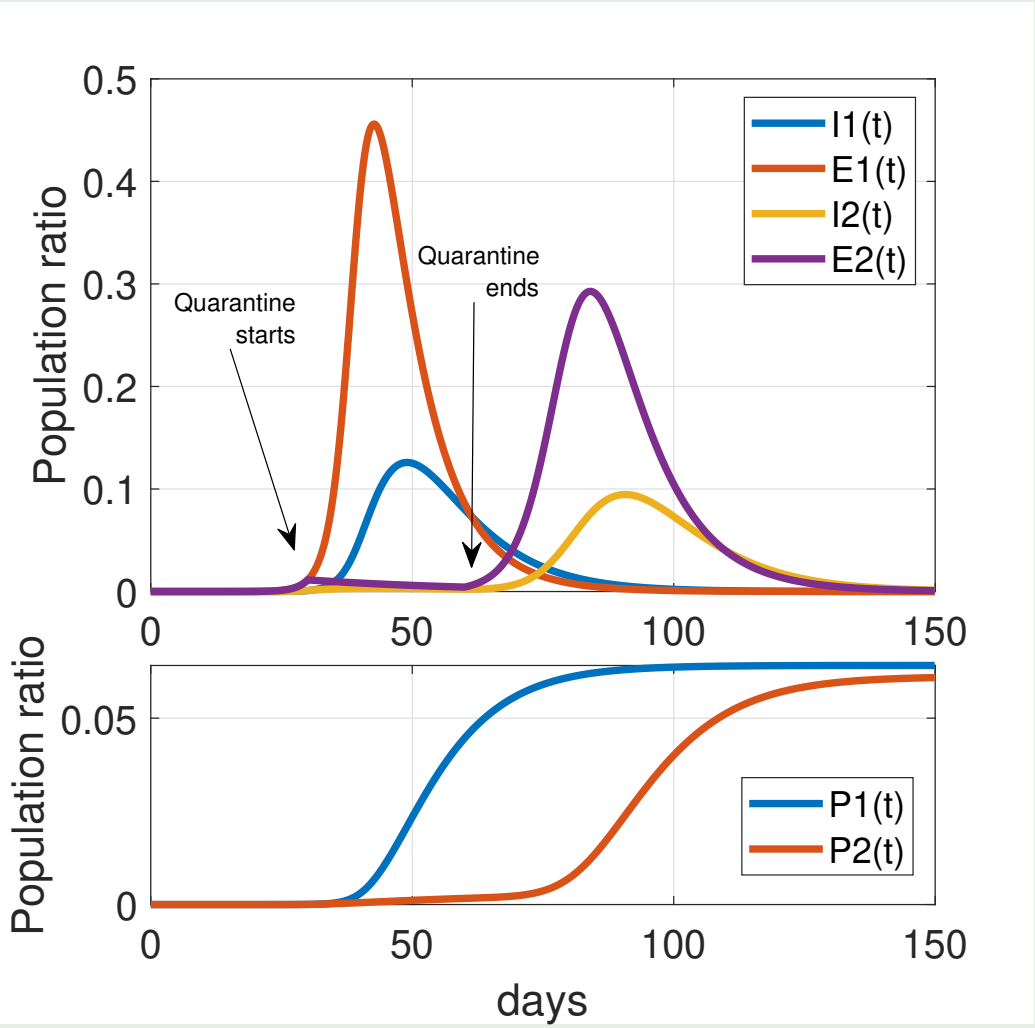
Result: repeated waves of the disease

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`. **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



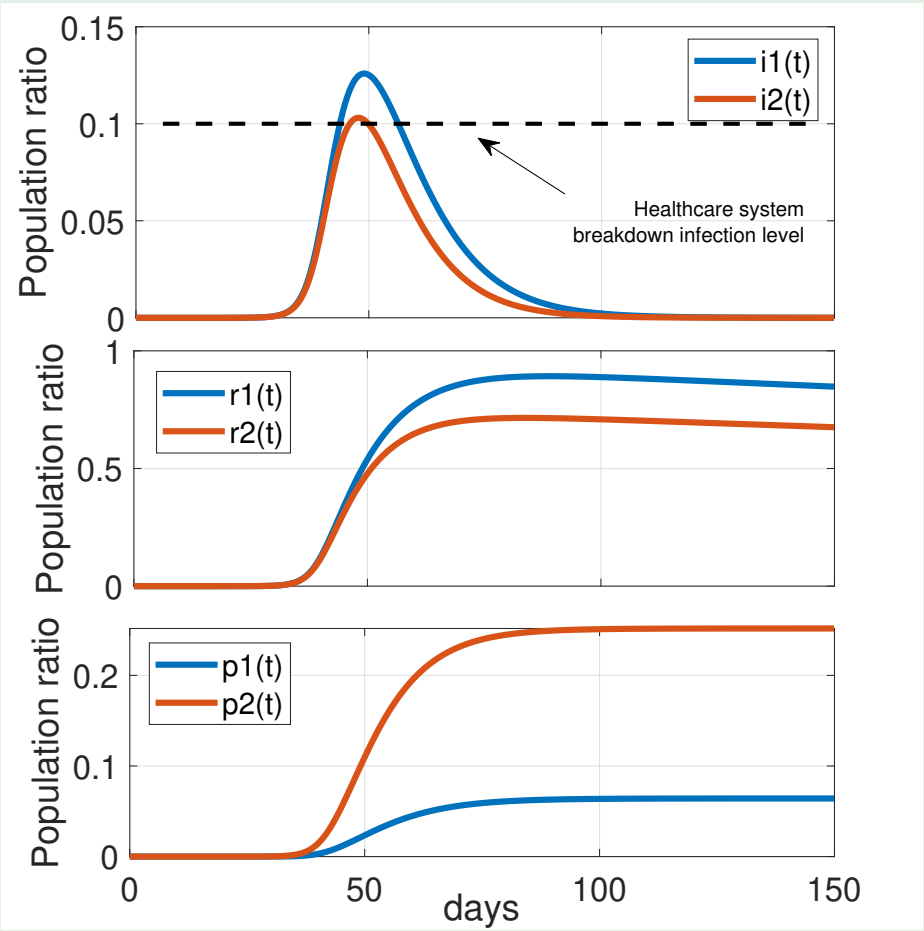
Typical solutions
(continued)

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)

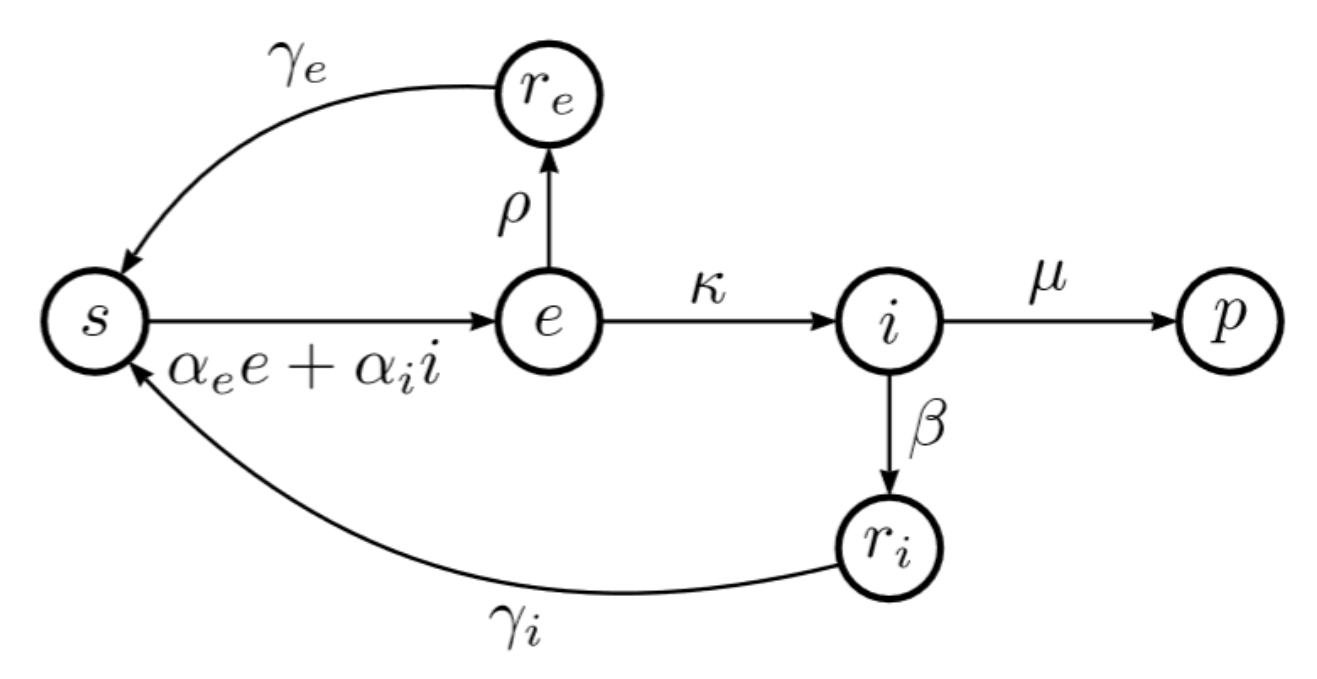
Result: healthcare system breakdown

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:



Outline

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

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

The problem of parameter estimation can be formulated as

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

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)

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

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):

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

where $\boldsymbol{\mathcal{A}}_k$ and $\boldsymbol{\mathcal{C}}_k$ 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

Require: Noisy measurements (regular inaccurate reports) of the epidemic spread y_k
Require: Initial conditions: $\mathbf{Q}$, $\mathbf{R}$, $\hat{x}_0^+$, $\mathbf{P}_0^+$
Ensure: $\hat{x}_k^+$ (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

Outline

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

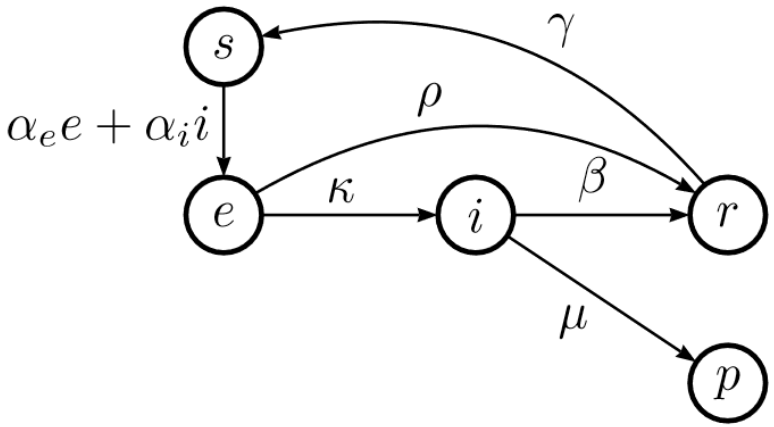
1. The theoretical details of this research: `https://arxiv.org/abs/2003.11371`
2. The source codes of this research: `https://github.com/rsameni/EpidemicModeling.git`
3. COVID-19 real-time data: `https://www.worldometers.info/coronavirus/`
4. Johns Hopkins University's CSSE Git repository: `https://github.com/CSSEGISandData/COVID-19`

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 & Andrews (2001)
5. Linear systems theory: Kailath (1980)
6. 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`

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