EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of
Biomedical Informatics

Model-Based Machine Learning

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Overview

1. The art of modeling
2. Modeling methodologies
3. Mathematical modeling tools
4. Nonlinear dynamical models & chaos
5. Biological growth & epidemiology
6. Compartmental modeling
7. Dimensional modeling & analysis
8. Analogical modeling
9. Partial differential modeling
10. Cellular automata
11. Model identifiability & parameter identification
12. Model assessment & selection
13. Model-based ML for bias removal & ethical AI
14. Synthetic data modeling & generation
15. *Case studies & advanced modeling topics

Evaluation

Grading:

- Exercises and homework (40%): should be delivered on time
- Semester project (40%): project topics should be selected and delivered as a single-page proposal, by Jan 25th, 2023. Final report delivered as a complete technical/conference/journal preprint.
- Punctuality, attendance and class participation (20%)

Please read the class syllabus and policies from Canvas. The slides are updated after each session with answers to the questions and discussions from the class.

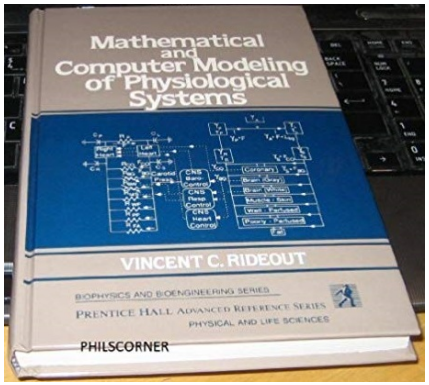
The semester project

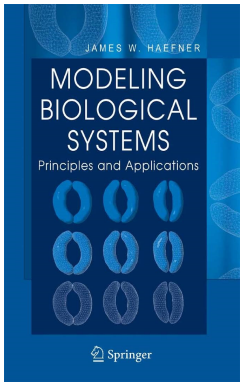
Can be one of the following:

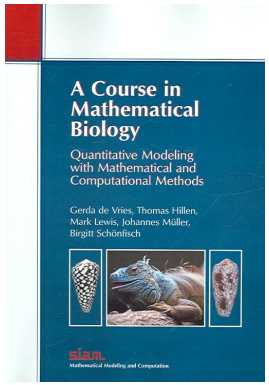
1. Implementing the full pipeline of a real-world modeling problem with machine-learning applications.
2. Using fact-based and physics-informed modeling to design or improve the performance of a given machine learning problem.

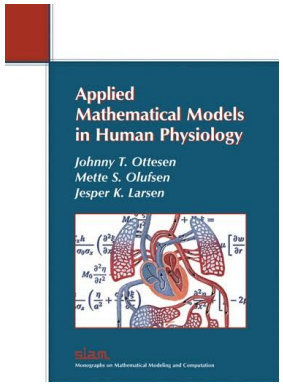
The projects should be ideally aligned with your thesis research.

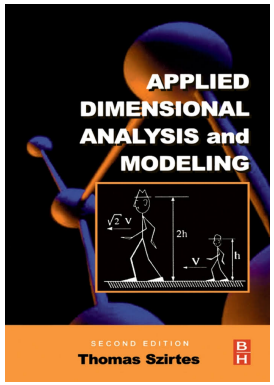
Text Books and Major References

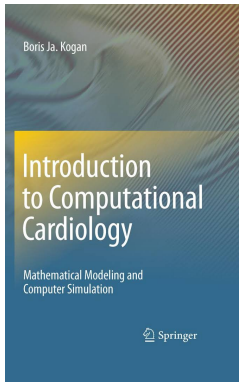


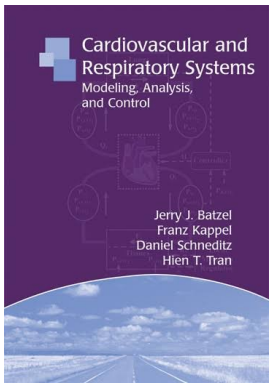


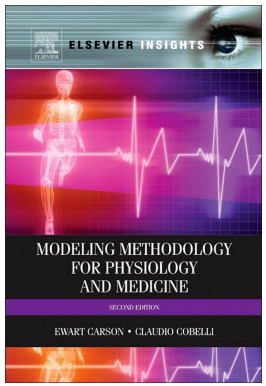


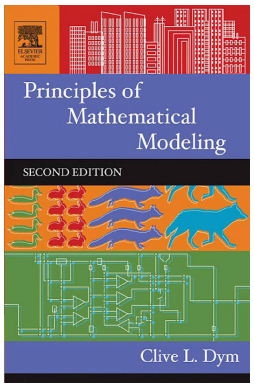


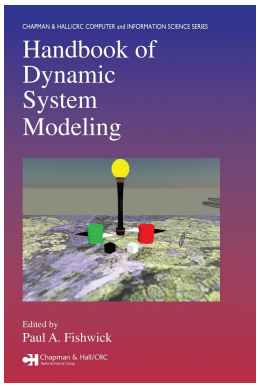


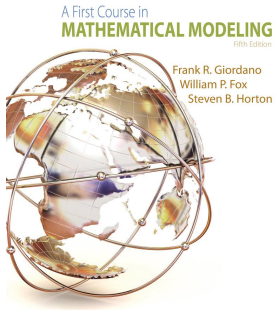


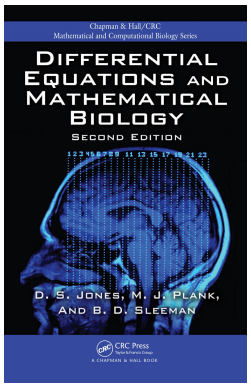


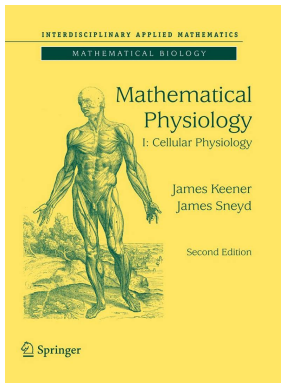


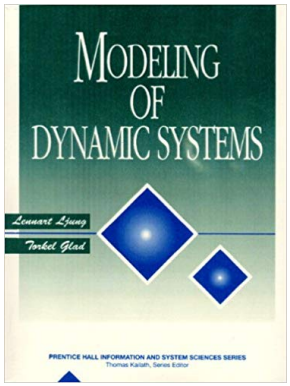


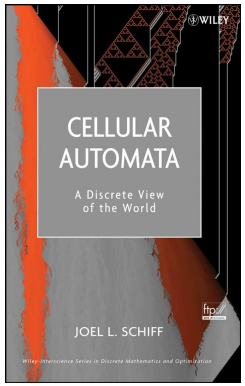


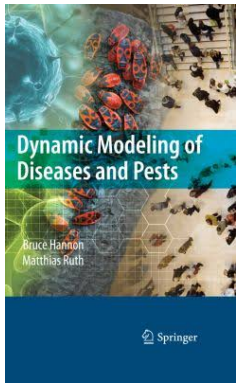












What is a model?

Model

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

Forms of models

- Mathematical equations
- Software
- Synthetic time series
- A firmware or hardware
- Another physical system
- etc. or a combination of multiple forms.

Where to use models?

Modeling applications

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.


"All models are wrong; some are useful!"
— George Box

Why use a model?

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

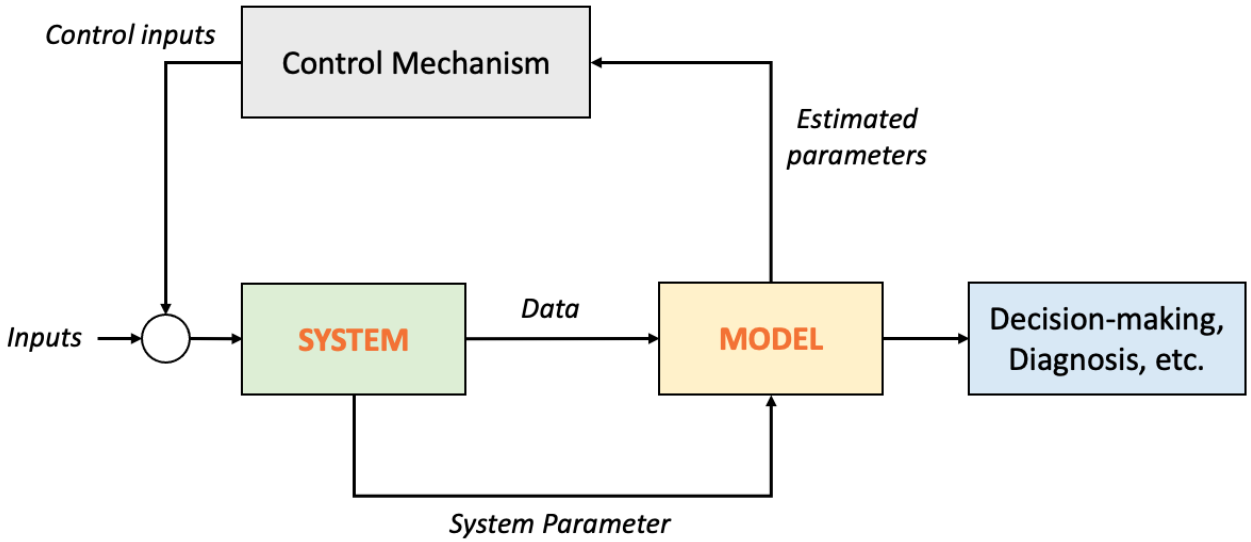
1. Optimizing the parameters of under-construction systems by trial and error (time-taking, expensive and impractical without a model)
2. Testing drugs and new technologies on human/animal species (unethical)
3. Chemical and biological reactions (dangerous without a model)
4. Studying the formation of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

How to model?

Is the subject of this course.

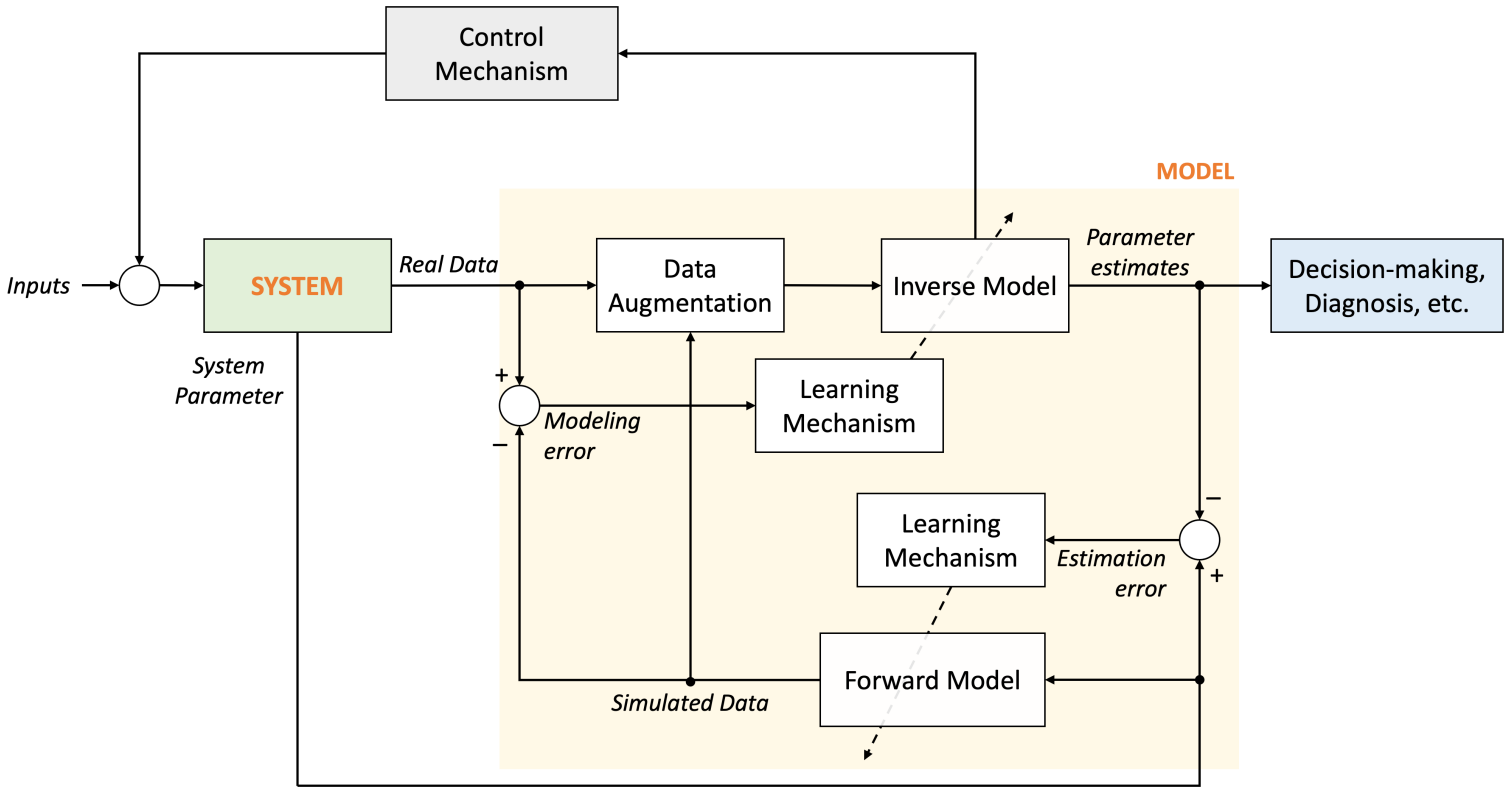
Modeling in machine learning

The big picture



Modeling in machine learning

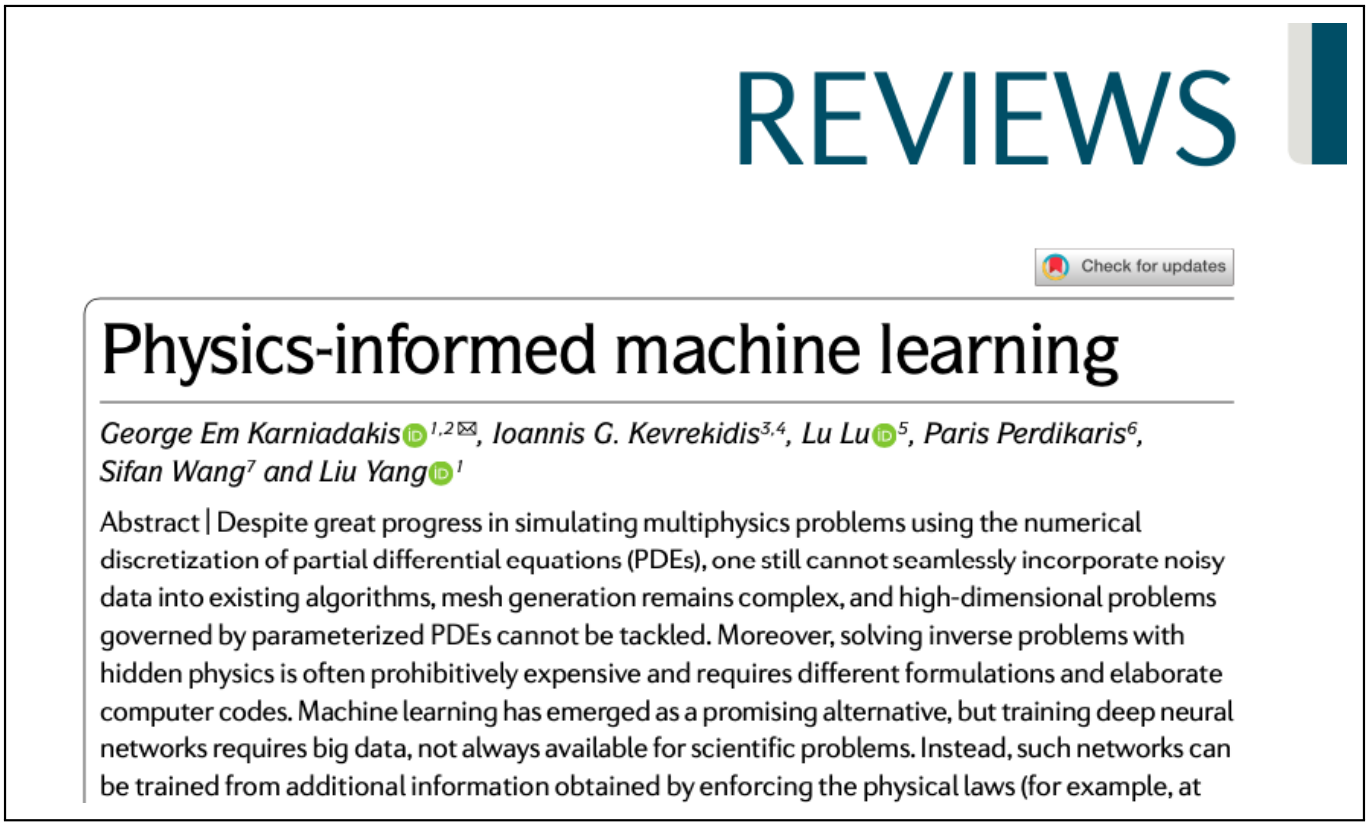
Inside a model



Model-based machine learning

What is model-based machine learning?

Model-based (a.k.a **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.



REVIEWS

Check for updates

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

(Karniadakis et al., 2021) DOI: 10.1038/s42254-021-00314-5

Model-based machine learning

(continued)

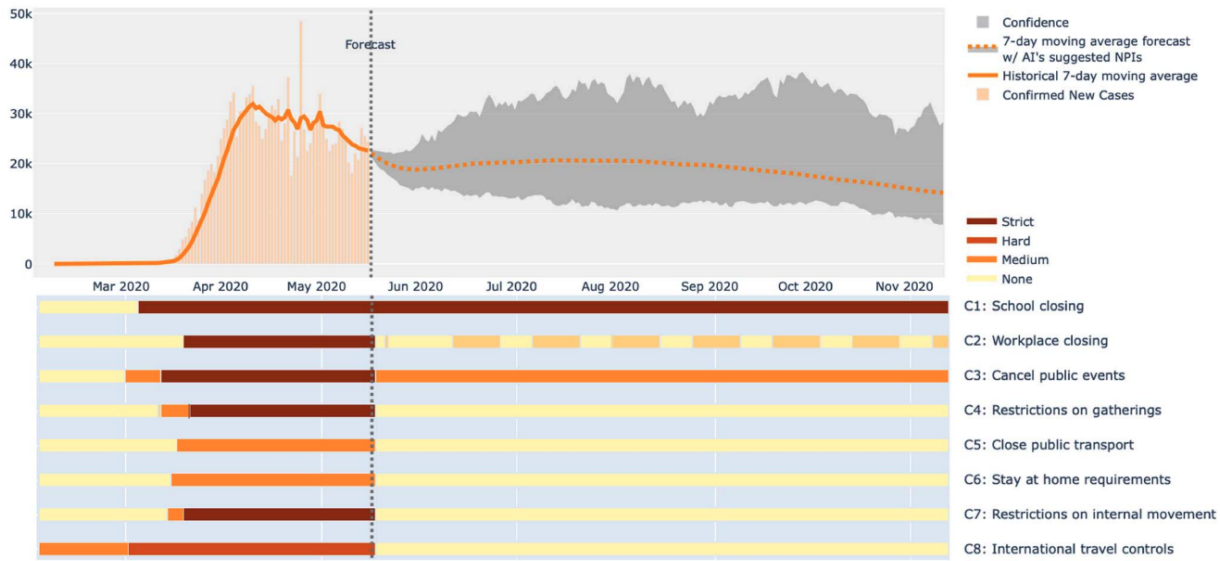
Applications of model-based machine learning

- **Ethical AI**; we should avoid acquiring data from living species as much as possible
- **Artificial patients** and personal health information protection
- Enforcing physical constraints on ML models
- Developing models for generating synthetic (yet accurate) data for data-greedy **deep learning** models, similar to **generative adversarial networks** (GANs)
- 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*

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
- **Context:** Mathematical epidemiology; biological systems modeling; applied mathematics; computer simulation; optimal control theory



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

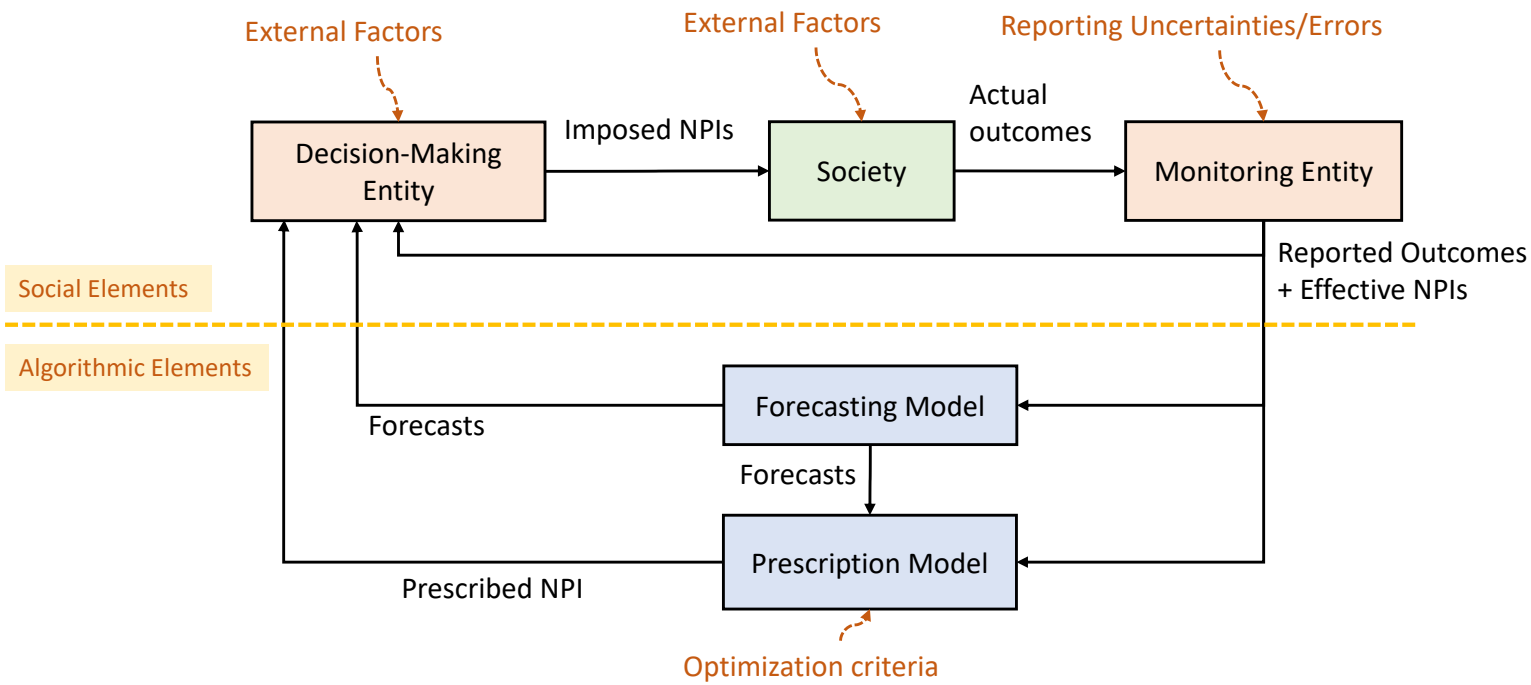
- Top-down (macro-level modeling): **compartmental models** and **spatio-temporal compartmental models**
  - **Tools:** ordinary differential equations, partial differential equations, dynamic systems, estimation theory
- Bottom-up (micro-level modeling): **modeling the activity of a population of individuals**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

✎ The two methods can be combined in a **hybrid model**

Compartmental modeling of epidemic diseased

(Continued)

Application: Pandemic control by nonpharmaceutical interventions



Sameni, R. (2022). Model-Based Prediction and Optimal Control of Pandemics by Non-Pharmaceutical Interventions. In IEEE Journal of Selected Topics in Signal Processing. DOI: 10.1109/jstsp.2021.3129118

Compartmental modeling of epidemic diseased

An overview of a typical compartmental model for epidemic diseases:

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**: $p(t)$

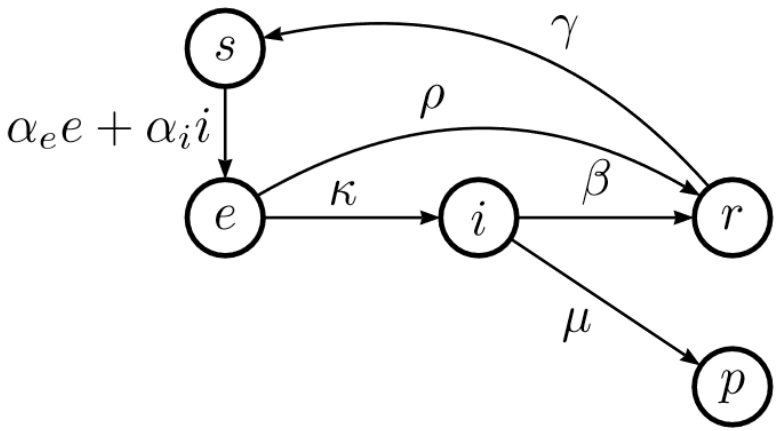
subject to $s(t) + e(t) + i(t) + r(t) + p(t) = 1$

Compartmental modeling of epidemic diseased

(Continued)

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

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



$$\frac{\mathrm{d}s(t)}{\mathrm{d}t} = -\alpha_e s(t)e(t) - \alpha_i s(t)i(t) + \gamma r(t)$$

$$\frac{\mathrm{d}e(t)}{\mathrm{d}t} = \alpha_e s(t)e(t) + \alpha_i s(t)i(t) - \kappa e(t) - \rho e(t)$$

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = \kappa e(t) - \beta i(t) - \mu i(t)$$

$$\frac{\mathrm{d}r(t)}{\mathrm{d}t} = \beta i(t) + \rho e(t) - \gamma r(t)$$

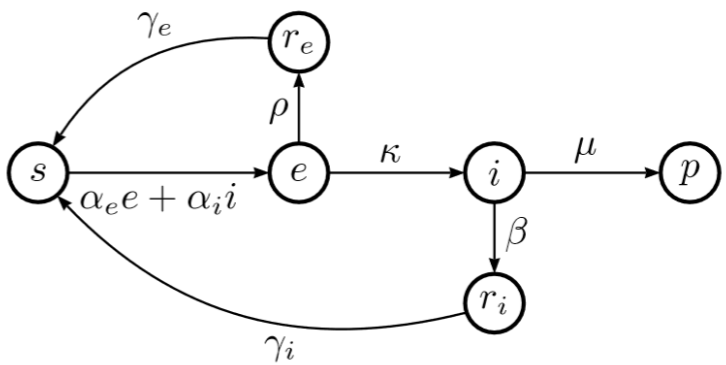
$$\frac{\mathrm{d}p(t)}{\mathrm{d}t} = \mu i(t)$$

Model extensions

Is the model unique? **No!**

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.)

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

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);
```

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Micro-level modeling of epidemic diseases

(continued)

Illustration of an agent-based simulation environment

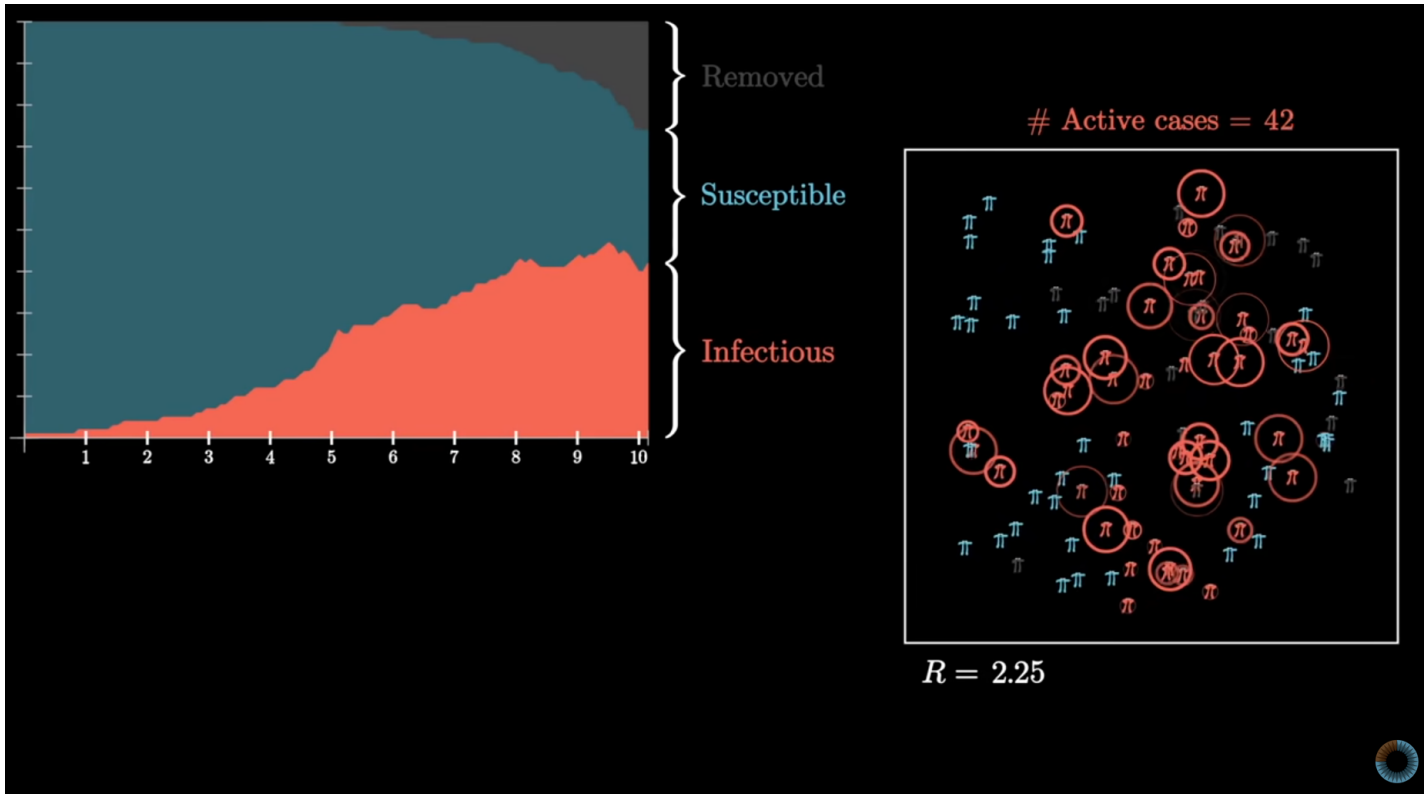
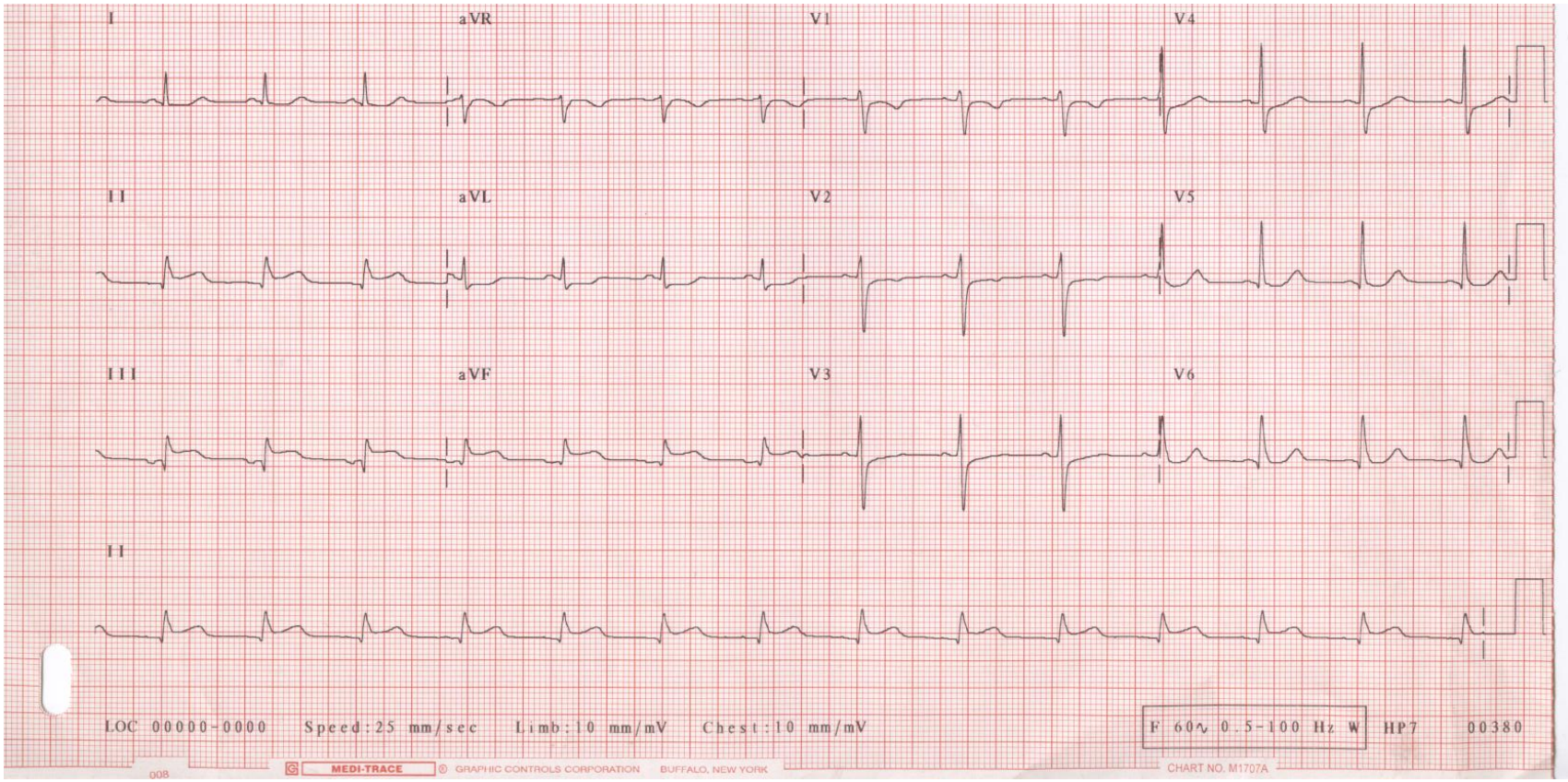


Figure: adopted from `https://youtu.be/gxAaO2rsdIs`

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.

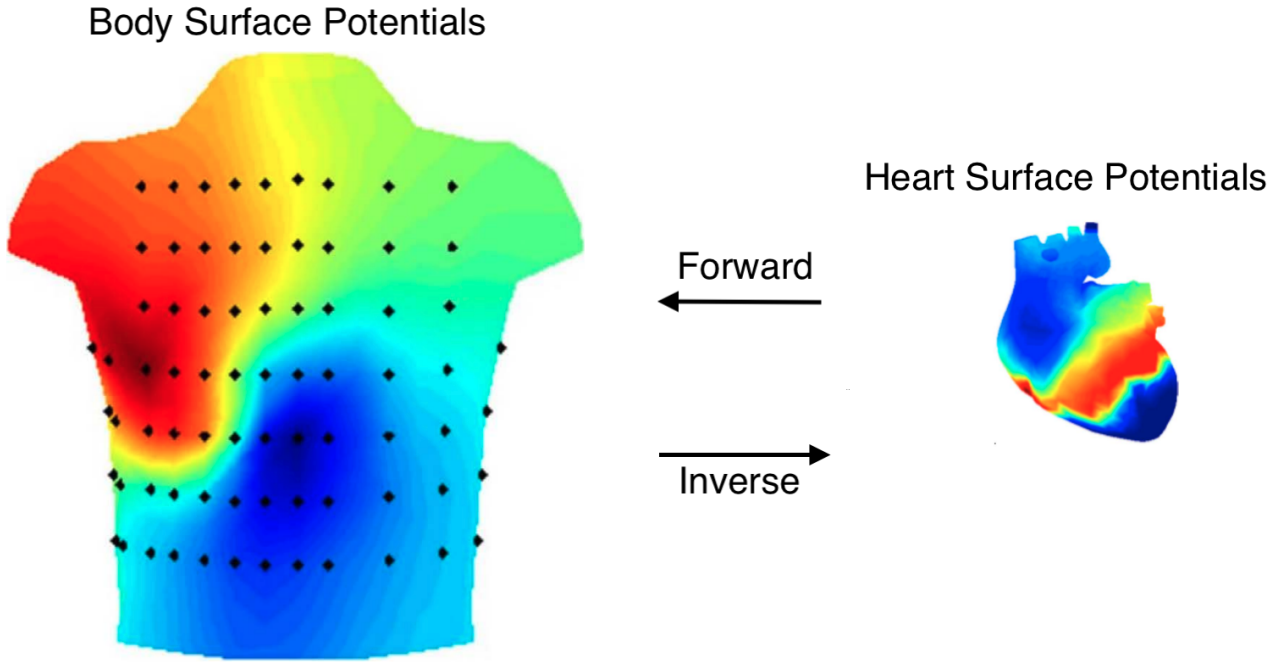


Glenlarson, CC BY-SA 3.0

Forward-backward body potential modeling

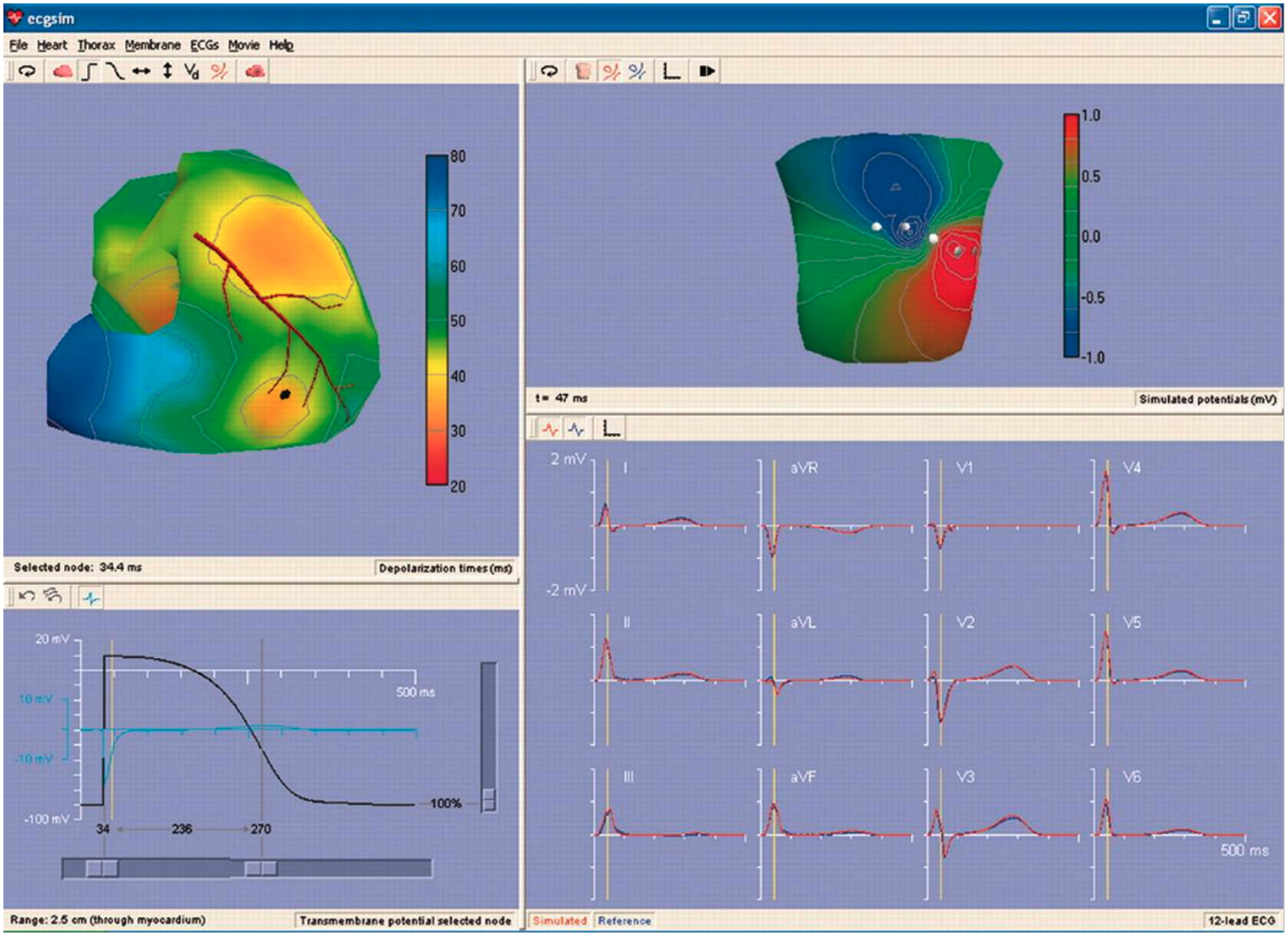
Body/heart surface potential modeling

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

A dynamic model for ECG generation

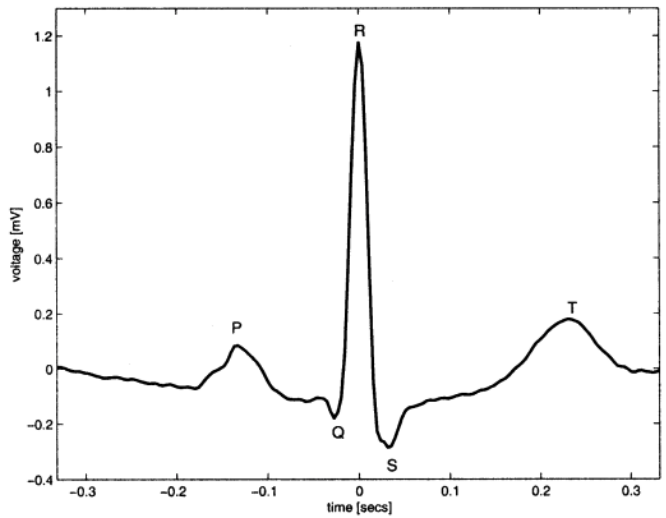
IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 50, NO. 3, MARCH 2003 289

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.**



DOI: 10.1109/tbme.2003.808805

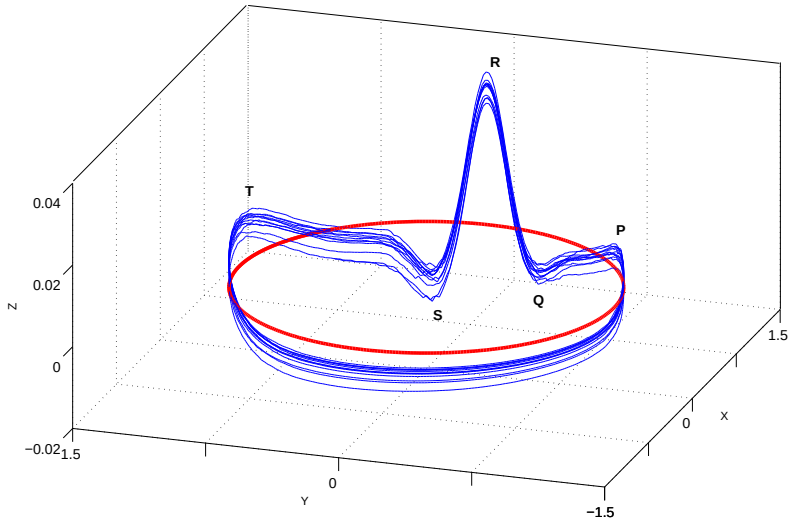
McSharry-Clifford's model (McSharry et al., 2003)

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

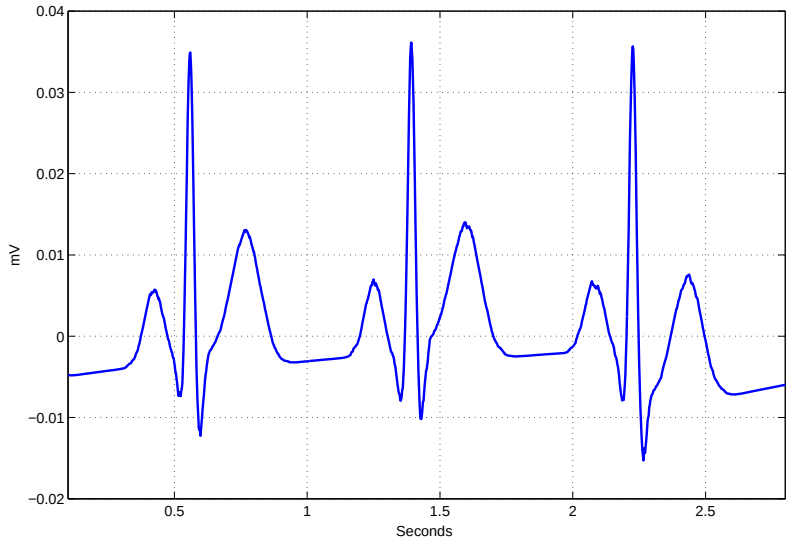
- x, y, and z are state variables, $\rho = 1 - \sqrt{x^2 + y^2}$, $\Delta\theta_i = (\theta - \ \theta_i) \mod (2\pi)$, $\theta = \text{atan2}(y, x)$ is the four quadrant arctangent, and ω is the angular velocity of the trajectory as it moves around the limit cycle in the $x - y$ plane.
- a_i, b_i, and 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 model by McSharry et al. (2003)

Modeling methodology

Model types

- **Mental:** no formulation; only exists in the mind, e.g., categorizing people's personality and temperament from their behaviors (in psychology)
- **Verbal:** can be expressed in verbal form, e.g., supply and demand (in microeconomics)
- **Mathematical:** have a rigorous mathematical description, e.g., laws of physics (Kogan, 2009, Ch. 2)


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 methodology

(continued)

Modeling limitations

- Models are **not unique**; different models can co-exist for a single system. *Modeling is "an art"!*
- Model are only **slices of reality**
- All models have **scopes**, outside of which they are invalid.
- Modeling can be done at different **levels of abstraction**

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

Modeling doctrine

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

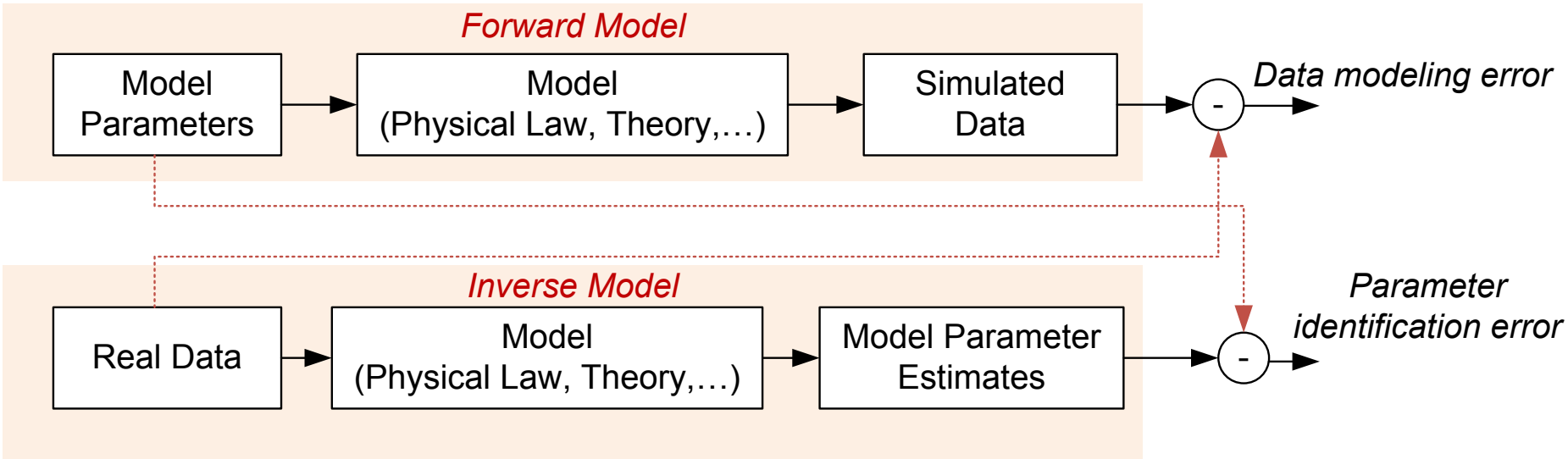
Modeling methodology

(continued)

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



Modeling methodology

(continued)

Example: Forward versus inverse modeling

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

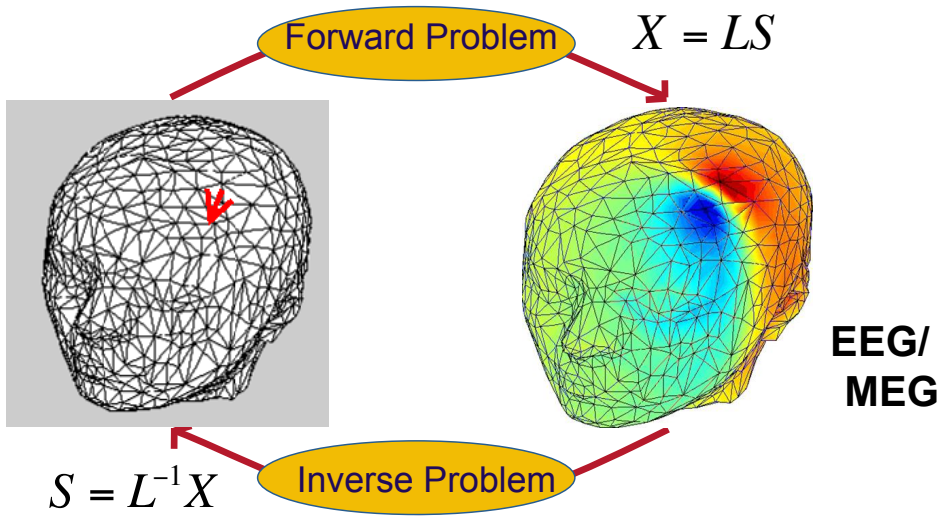


Figure: Adopted from: `http://cfmriweb.ucsd.edu/ttliu/be280a_12/BE280A12_eeg5.pdf`

Modeling methodology

(continued)

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., $x(t) = a\sin(\omega t) + n(t)$

✎ 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

Overview

In this lecture we review some of the mathematical prerequisites of the course on dynamic systems, signal and system discretization and linearinzation.

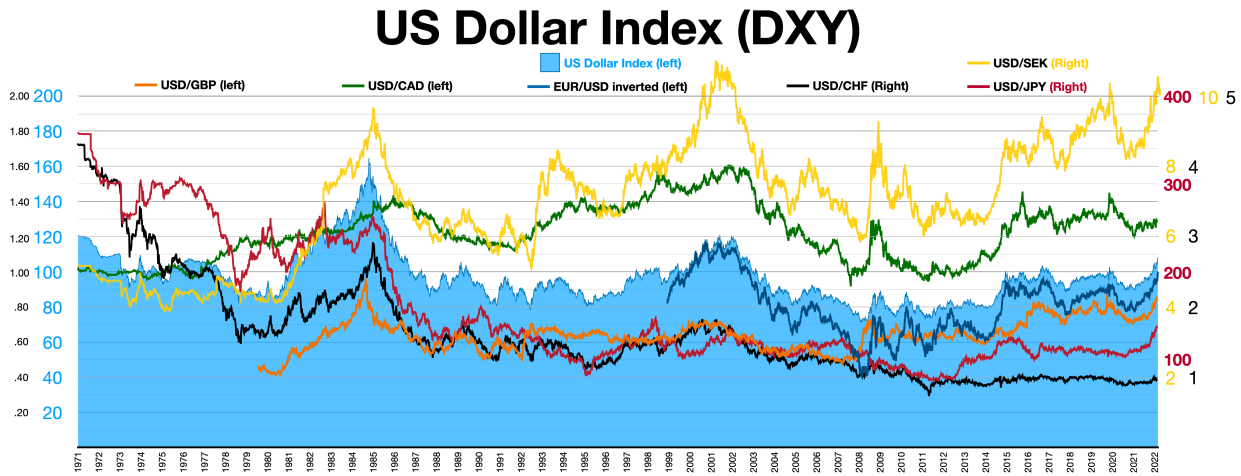
Signal or time-series

Definitions

- **Signal:** A waveform or time-series represented as a function of an independent variable (time, space, samples, etc.).
- Signals can be continuous or discrete functions of the independent variable (usually time in our context): $x(t)$, $x[k]$ or x_n.

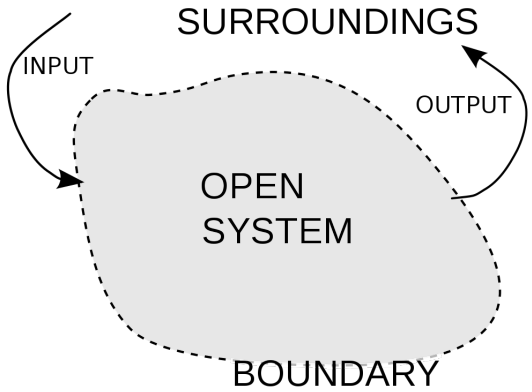
Example

Blood pressure variations in time, change of pressure vs altitude, stock market daily charts, electrocardiogram and electroencephalogram waveforms, etc.



System

- **Broad definition:** a set of entities interacting together as parts of a mechanism forming a *complex whole*.
- **In our context:** a mathematical/algorithmic process that maps an input to an output.
- **Examples:** Cardiovascular system, thermal regulation system, a machine learning model, etc.



https://en.wikipedia.org/wiki/System. Peter de Padua Krauss; CC BY-SA 4.0

System input-output mathematical description

The input-output relationship of systems may be explicit or implicit:

- **Explicit:** The output can be directly calculated from the input

Example

$$y(t) = x^2(t) + kt$$

- **Implicit:** Only an implicit relation between the input and output are available

Example

$$\ddot{y}(t) + \alpha\dot{y}(t) + b\sqrt{y(t)} = x(t)$$

System types

- **Static:** No temporal evolution in the system or its output

Example

$$y = x^2 + 2x + \sqrt{x}$$

- **Dynamic:** The system evolves in time, i.e., the input-output process is not point-wise; besides the instantaneous input, the output also depends on the **rate of changes** in the input and/or output

Example

$$\ddot{y}(t) + 2\alpha\dot{y}(t) + \omega_0^2 y(t) = x(t)$$

System properties

Linearity

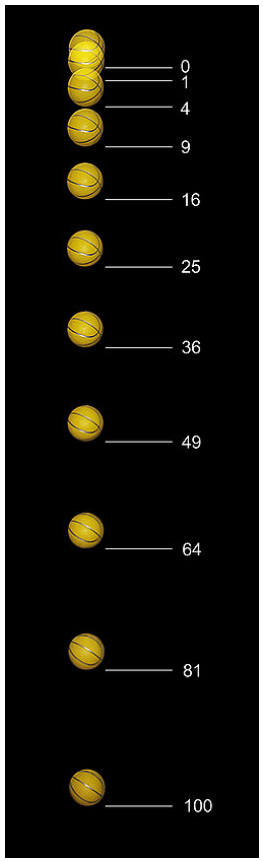
- **Linear:** The input-output relationship is linear: **additivity** and **homogeneity** hold
- **Nonlinear:** The input-output relationship is nonlinear (the system is either **non-additive** or **non-homogeneous**)

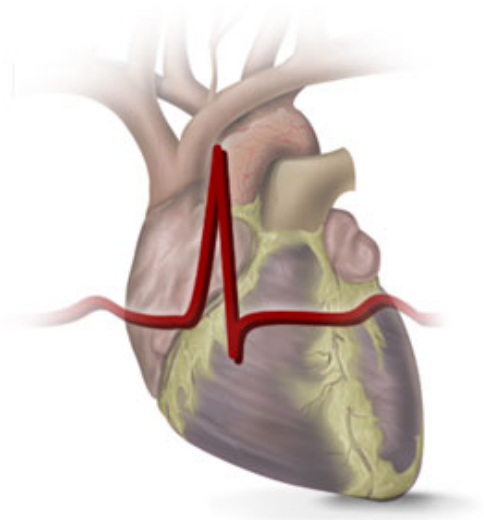
Time dependence

- **Time-variant:** The input-output mapping depends on the time origin
- **Time-invariant:** The input-output mapping *does not* depend on the time origin

Dynamics

Dynamics: Evolution of a signal/system in time. Any movement/change comprises a dynamics.





Dynamic equations

Differential/difference equations are used to formulate dynamic systems, e.g.,

Constant acceleration motion (linear-continuous)

$$a\ddot{y}(t) + b\dot{y}(t) + cy(t) = 0$$

The Van der Pol model for action potentials (nonlinear-continuous)

$$\ddot{y}(t) - 2\alpha[1 - y(t)^2]\dot{y}(t) + \omega_0^2 y(t) = 0$$

First-order lowpass filter or an autoregressive model (linear-discrete)

$$y_{n+1} = \alpha y_n + x_n$$

The Logistic Map in biological growth (nonlinear-discrete)

$$y_{n+1} = r y_n (1 - y_n)$$

Differential equations

- In many systems, the *rate* of output and input of a system are related (instead of the input or outputs themselves). This relationship can be modeled by **differential equations**:

$$\frac{dy(t)}{dt} = f\left(x(t)\right)$$

- The general form of a linear differential equation is:

$$\sum_{k=0}^{N-1} a_k \frac{d^k y(t)}{dt^k} = \sum_{k=0}^{M-1} b_k \frac{d^k x(t)}{dt^k} \qquad (*)$$

- If the coefficients are constant, the system is **time-invariant**
- If the initial states are zero, the system is **linear**; otherwise it is **incrementally linear (affine)**

Differential equations

(continued)

Reminder: solution of linear differential equations

The solution of equation (*) is

$$y(t) = y_h(t) + y_p(t)$$

where

- $y_h(t)$: the homogeneous response to initial states
- $y_p(t)$: the particular response to the system input

The system is only linear when $y_h(t) = 0$, i.e., initial states are zero

Transformations and transfer functions

- Sometimes, it is easier to study signals/systems in **transform domains**.
- For linear time-invariant systems, using Laplace (or Fourier) transform, a **transfer function** can be assigned to the system:

$$H(s) \triangleq \frac{Y(s)}{X(s)}$$

where $X(s)$ and $Y(s)$ are Laplace transforms of $x(t)$ and $y(t)$.

Further notes

- $H(s)$ is used for *steady-state* analysis but not (explicitly) for *transient analysis*. For *stable* systems, the response to initial states converge to zero. Hence, in steady-state, the output can be exactly determined using $H(s)$
- The system is stable if the poles are in the left half plane.
- The farther the poles are from the origin, the faster the effect of initial states vanish

Transfer functions

(continued)

Transfer function limitations

- It is restricted to LTI systems (or systems which can be approximated by LTI systems)
- It can only be used for steady-state analysis and and not for transient analysis (although the transfer function has indirect implications on the transient properties of a system)

Alternative approach: *State-space analysis*

State variables

- **States** are properties of a system (usually represented as a vector), through which the system's response to a given input can be uniquely found.
- In physical/biological systems, storage of the 'past information' requires energy saving elements (capacitors, inductors, neurons, cells, etc.). In digital systems memory elements (registers) are required to preserve states.

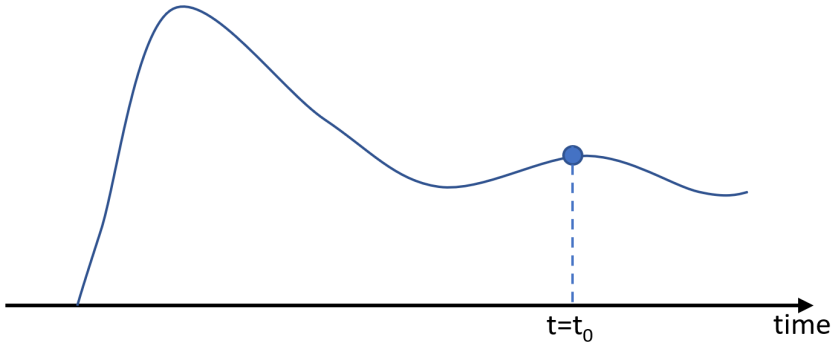


Figure: State trajectory

- Knowledge of a system's dynamics, its **states** at time t_0 and the future inputs make us needless of its past ($t < t_0$), i.e. it is not important how the system reached that state.

State variables

(continued)

Example: First-order system

$$\dot{y}(t) + \alpha y(t) = \beta x(t)$$

This system has one state; knowledge of $y(t_0)$ and $x(t)$ is sufficient to determine $y(t)$ for all $t \in [t_0, \infty)$.

Example: continuous-time delay

$$y(t) = x(t - t_0)$$

This system has infinite number of states.

State Variables

(continued)

The continuous delay

The continuous-time delay has infinite number of states, but it may be approximated with low-order state-space models when the input is *low frequency* ($|f_{\max} t_0|$ is small)

$$y(t) = x(t - t_0) \quad \text{or} \quad H(s) = e^{-t_0 s}$$

$$H(s) = 1 - st_0 + \frac{(st_0)^2}{2} - \ldots = \frac{1}{1 + st_0 + \frac{(st_0)^2}{2} + \ldots}$$

For $|st_0| \ll 1$, the system can be approximated with lower order systems. A small value of st_0 implies a *narrow-band* system working at a relatively *low frequency*.

State-space representations

State-space equations

Set of first-order differential (difference) equations relating the system inputs, outputs, and states

$$\begin{cases} \dot{\boldsymbol{s}}(t) = \boldsymbol{f}(\boldsymbol{s}(t), \boldsymbol{x}(t)) \\ \boldsymbol{y}(t) = \boldsymbol{g}(\boldsymbol{s}(t), \boldsymbol{x}(t)) \end{cases}$$

where $\boldsymbol{x}(t)$, $\boldsymbol{y}(t)$, and $\boldsymbol{s}(t)$ are the input, output and state vectors.

- State-space representations are not unique; but some *canonical forms* are of especial interest
- For LTI systems, differential and state-space equations can be converted to one another
- Scalar differential equations of order n, are converted into n first order state-space differential equations (if the system is **irreducible**)

State-space representations

(continued)

State-space equations for multi-input multi-output (MIMO) systems

$$\begin{cases} \dot{s_1} = f_1(s_1, \ldots, s_n, x_1, \ldots, x_p) \\ \vdots \\ \dot{s_n} = f_n(s_1, \ldots, s_n, x_1, \ldots, x_p) \end{cases}$$

$$\begin{cases} y_1 = g_1(s_1, \ldots, s_n, x_1, \ldots, x_p) \\ \vdots \\ y_m = g_m(s_1, \ldots, s_n, x_1, \ldots, x_p) \end{cases}$$

State-space representations

(continued)

Linear case

$$\mathbf{s} = \begin{bmatrix} s_1 \\ \vdots \\ s_n \end{bmatrix}, \mathbf{A} = \begin{bmatrix} a_{11} & \dots & a_{1n} \\ \vdots & & \vdots \\ a_{n1} & \dots & a_{nn} \end{bmatrix}, \mathbf{x} = \begin{bmatrix} x_1 \\ \vdots \\ x_p \end{bmatrix}, \mathbf{y} = \begin{bmatrix} y_1 \\ \vdots \\ y_m \end{bmatrix}$$

$$\begin{cases} \dot{\mathbf{s}}_{n\times 1} = \mathbf{A}_{n\times n}\mathbf{s}_{n\times 1} + \mathbf{B}_{n\times p}\mathbf{x}_{p\times 1} \\ \mathbf{y}_{m\times 1} = \mathbf{C}_{m\times n}\mathbf{s}_{n\times 1} + \mathbf{D}_{m\times p}\mathbf{x}_{p\times 1} \end{cases} \quad (\triangle)$$

Nonlinear case

$$\begin{cases} \dot{\mathbf{s}}_{n\times 1} = \mathbf{f}_{n\times 1}(\mathbf{s}_{n\times 1}, \mathbf{x}_{p\times 1}) \\ \mathbf{y}_{m\times 1} = \mathbf{g}_{m\times 1}(\mathbf{s}_{n\times 1}, \mathbf{x}_{p\times 1}) \end{cases}$$

Canonical state-space representations

Controllable state-space forms

Controllability is the ability to drive the system states to arbitrary values through the input signal or noise in finite time (Kailath, 1980; Tsakalis, 2001)

Example

Controlling blood pressure through drug intake.

Observable state-space forms

Observability describes the ability to infer the system states given output measurements (Kailath, 1980; Tsakalis, 2001)

Example

Output demonstration of internal body infections as fever.

Question: Are physiological systems necessarily controllable and/or observable?

State-space representations

(continued)

Example

$$a\frac{d^2y(t)}{dt^2} + b\frac{dy(t)}{dt} + cy(t) = x(t)$$

$$\begin{cases} s_1 \overset{\Delta}{=} y(t) & \dot{s}_1 = s_2 \\ s_2 \overset{\Delta}{=} \dot{y}(t) \Rightarrow & \dot{s}_2 = \ddot{y}(t) = \frac{1}{a}(x(t) - bs_2 - cs_1) \end{cases}$$

State-space representation:

$$\begin{bmatrix} \dot{s}_1 \\ \dot{s}_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\frac{c}{a} & -\frac{b}{a} \end{bmatrix} \cdot \begin{bmatrix} s_1 \\ s_2 \end{bmatrix} + \begin{bmatrix} 0 \\ \frac{1}{a} \end{bmatrix} x(t)$$

$$y(t) = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} s_1 \\ s_2 \end{bmatrix}$$

State-space to transfer functions and differential equations

Transfer functions of linear state-space representations

Taking the Laplace transform of ($\triangle$):

$$\mathbf{Y}(s) = \left[\mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B} + \mathbf{D}\right] \mathbf{X}(s)$$

Transfer matrix: $\mathbf{H}(s) \triangleq \mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B} + \mathbf{D}$

- In contrast to state-space equations, $\mathbf{H}(s)$ is unique.
- Taking the inverse Laplace transform, takes the system back to the time domain (in differential equation or impulse response form)

Temporal solutions from state-space representation

Scalar Case

Example

Consider the system $\dot{y}(t) = ay(t) + bx(t)$, with initial condition $y(0)$. Taking the Laplace transform, we find:

$$sY(s) - y(0) = aY(s) + bX(s)$$

$$Y(s) = \frac{y(0)}{s-a} + \frac{bX(s)}{s-a} \Rightarrow$$

$$y(t) = y(0)e^{at}u(t) + be^{at}u(t) * x(t) \Rightarrow$$

$$y(t) = y(0)e^{at}u(t) + b\int_0^t e^{a(t-\tau)}x(\tau)d\tau$$

When $a < 0$, the effect of initial conditions vanish in time

Temporal solutions from state-space representation

Vectorial Case

The vectorial differential equation $\dot{\mathbf{y}}(t) = \mathbf{A}\mathbf{y}(t) + \mathbf{B}\mathbf{x}(t)$ yields:

$$s\mathbf{Y}(s) - \mathbf{y}(0) = \mathbf{A}\mathbf{Y}(s) + \mathbf{B}\mathbf{X}(s)$$
$$\mathbf{Y}(s) = (s\mathbf{I} - \mathbf{A})^{-1}\mathbf{y}(0) + (s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B}\mathbf{X}(s)$$
$$\mathbf{\Phi}(s) \stackrel{\Delta}{=} (s\mathbf{I} - \mathbf{A})^{-1} = L\left\{e^{\mathbf{A}t}\right\} = L\left\{\phi(t)\right\}$$

where $\phi(t) = e^{\mathbf{A}t}u(t)$ is the **state transition matrix**.
Hence:

$$\mathbf{y}(t) = \phi(t)\mathbf{y}(0) + \int_0^t \phi(t-\tau)\mathbf{B}\mathbf{x}(\tau)d\tau$$

Or, if the initial states are given at $t = t_0$:

$$\mathbf{y}(t) = \phi(t-t_0)\mathbf{y}(t_0) + \int_{t_0}^t \phi(t-\tau)\mathbf{B}\mathbf{x}(\tau)d\tau$$

Whenever $\mathbf{x}(t) = \mathbf{0}$ we have: $\mathbf{y}(t) = \phi(t-t_0)\mathbf{y}(t_0)$

State transition matrix

Example

$$\dot{\mathbf{y}}(t) = \begin{bmatrix} 0 & 1 \\ -2 & -3 \end{bmatrix} \mathbf{y}(t)$$

with $\mathbf{y}(0) = \mathbf{0}$.
Solution:

$$(s\mathbf{I} - \mathbf{A}) = \begin{bmatrix} s & -1 \\ 2 & s+3 \end{bmatrix}$$

$$(s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{s^2 + 3s + 2} \begin{bmatrix} s+3 & 1 \\ -2 & s \end{bmatrix} \Rightarrow$$

$$\phi(t) = L^{-1}\{\mathbf{\Phi}(s)\} = \begin{bmatrix} -e^{-2t} + 2e^{-t} & e^{-t} - e^{-2t} \\ -2e^{-t} + 2e^{-2t} & -e^{-t} + 2e^{-2t} \end{bmatrix} u(t)$$

This matrix indicates variation of each state over time with respect to the specific initial condition.

State transition matrix

(continued)

Properties

- $\phi(0) = \mathbf{I}$: No state transition without time elapse (state transition requires time)
- $\phi^{-1}(\tau) = \phi(-\tau) \Rightarrow \mathbf{x}(t_0) = \phi^{-1}(t - t_0)\mathbf{x}(t)$: Time is reversible using the inverse transition matrix
- $\phi(t_1 + t_2) = \phi(t_1)\phi(t_2) = \phi(t_2)\phi(t_1)$: Time epochs can be split into smaller segments (special case: $[\phi(\Delta)]^k = \phi(k\Delta)$)
- $\phi(t_2 - t_0) = \phi(t_2 - t_1)\phi(t_1 - t_0)$: State transition is independent of the time path (like the **work** done in a **conservative system**)

Continuous vs. discrete models

- Models can be continuous or discrete in time.
- With current digital simulation and modeling systems, models are either discrete by definition or are discretized during the modeling and simulation procedure.
- Discretization in time consists of converting a continuous-time signal/system to a discrete-time signal/system.

Continuous vs. discrete models

(continued)

Examples of signal discretization and discrete signals

- **Discretized signal:** An ECG signal sampled and stored in a computer
- **Intrinsically discrete signal:** The heart rate time-series is discrete by definition

Examples of system discretization vs discrete systems

- **Discretized system:** Simulation of the respiratory system or cell-growth in a computer
- **Discrete systems:** Digital cardiac pacemakers, biofeedback systems, etc.

Signal discretization

Signal discretization

- Signal discretization and discrete signals are studied *digital signal processing*
- The question is how to go from a continuous-time signal $x(t)$ to a discrete-time signal $x[n]$
- In the real world, discrete signals are achieved by sampling a continuous-time signal in a *uniform* or *non-uniform* manner.
- **Uniform Sampling:** $x[n] = x(nT_s)$ with fixed sampling frequency T_s
- **Nonuniform Sampling:** $x[n] = x(t_n)$ with variable (irregular) sampling times

System discretization

Static system discretization

Since static systems do not evolve in time, the discretization is straightforward: $t \to nT_s$, where T_s is the sampling time.

Dynamic system discretization

- Differential forms are approximated with difference equations of the appropriate order.
- **First-order discretization:** For small Δ, $\frac{d}{dt}x(t) \approx \frac{x(t+\Delta)-x(t)}{\Delta}$.
- If T_s is small 'enough' (an order of magnitude smaller than the Nyquist frequency is typically fine), Δ can be replaced by T_s. Hence:

$$\frac{d}{dt}x(t) \to \frac{x[n+1]-x[n]}{T_s}$$

System discretization

(continued)

- The same procedure can be used for state-space representations of models.
- For higher-order discretizations, the first-order can be extended or one may use an appropriate approximation of the desired order.

The discretization error increases if T_s is not small enough.

System discretization

(continued)

Discrete systems can be obtained from continuous ones using various approaches:

- Time-domain: The system is discretized from the *implicit* or *explicit* forms of its input/output equation
- Frequency-domain: $H(s)$ is transfered to $H(z)$ using a conformal mapping (Oppenheim et al., 1999)

Discretized models are not unique

Static system linearization

Consider a static system: $y = f(\mathbf{u})$ $(\mathbf{u} = [u_1, \cdots, u_n]^T)$. A first-order Taylor expansion around $y_0 = f(\mathbf{u}_0)$ results in:

$$y = f(\mathbf{u}_0) + \left.\frac{\partial f(\mathbf{u})}{\partial \mathbf{u}}\right|_{\mathbf{u}=\mathbf{u}_0} (\mathbf{u} - \mathbf{u}_0) + \cdots$$

$$y \approx f(\mathbf{u}_0) + \left.\frac{\partial f(\mathbf{u})}{\partial \mathbf{u}}\right|_{\mathbf{u}=\mathbf{u}_0} (\mathbf{u} - \mathbf{u}_0)$$

$$\frac{\partial f(\mathbf{u})}{\partial \mathbf{u}} = \left[\frac{\partial f(\mathbf{u})}{\partial u_1}, \cdots, \frac{\partial f(\mathbf{u})}{\partial u_n}\right]^T \Bigg|_{\mathbf{u}=u_0} \triangleq \mathbf{g}_0$$

$$y \approx f(\mathbf{u}_0) + \mathbf{g}_0^T(\mathbf{u} - \mathbf{u}_0) \Rightarrow$$
$$y - y_0 \approx \mathbf{g}_0^T(\mathbf{u} - \mathbf{u}_0) \Rightarrow$$
$$\delta y \approx \mathbf{g}_0^T \boldsymbol{\delta u}$$

Static system linearization

(continued)

Example

Linearize the following static system around $\bar{u}_1 = \bar{u}_2 = 0, \bar{y} = 0$:

$$y = u_1^2 u_2^2 + u_2 + 3u_1^2$$

Approach 1 (Taylor expansion):

$$g^T = \begin{bmatrix} 2u_1 u_2^2 + 6u_1 & 2u_2 u_1^2 + 1 \end{bmatrix} |_{u_1=u_2=0} = \begin{bmatrix} 0 & 1 \end{bmatrix} \Rightarrow \delta y \approx \begin{bmatrix} 0 & 1 \end{bmatrix} \begin{bmatrix} \delta u_1 \\ \delta u_1 \end{bmatrix} = \delta u_2$$

Approach 2 (Perturbation theory): Insert $u_1 = \bar{u}_1 + \delta u_1$, $u_2 = \bar{u}_2 + \delta u_2$, and $y = \bar{y} + \delta y$ in (11) and discard the second and higher-order terms:

$$(\bar{y} + \delta y) = (\bar{u}_1 + \delta u_1)^2 (\bar{u}_2 + \delta u_2)^2 + (\bar{u}_2 + \delta u_2) + 3(\bar{u}_1 + \delta u_1)^2$$

which results in $\delta y \approx \delta u_2$ (*Note: this is only valid at* $\bar{u}_1 = \bar{u}_2 = 0$).

Dynamic system linearization

The **perturbation** approach can also be used for linearizing dynamic systems:

Example

Linearize $y\frac{d^2y}{dt^2} + u^2\frac{dy}{dt} + \sqrt{y} = u$ around $\sqrt{y_0} = u_0$

Solution: Replacing $u(t) = u_0 + \delta u(t)$ and $y(t) = y_0 + \delta y(t)$ gives:

$$(y_0 + \delta y)\frac{d^2}{dt^2}(y_0 + \delta y) + (u_0 + \delta u)^2\frac{d}{dt}(y_0 + \delta y) + \sqrt{y_0 + \delta y} = u_0 + \delta u$$

Replacing $\sqrt{y_0 + \delta y}$ with its Taylor expansion:

$$\sqrt{y_0 + \delta y} = (y_0 + \delta y)^{\frac{1}{2}} = y_0^{\frac{1}{2}} + \frac{1}{2\sqrt{y_0}}\delta y + \textit{(second and higher-order terms)}$$

Dynamic system linearization

(continued)

Example (continued)

By discarding the second and higher-order terms, we find

$$y_0 \frac{d^2}{dt^2}(\delta y) + u_0^2 \frac{d}{dt}(\delta y) + \sqrt{y_0} + \frac{1}{2\sqrt{y_0}}\delta y \approx u_0 + \delta u$$

$$y_0 \ddot{\delta y} + u_0^2 \dot{\delta y} + \frac{1}{2\sqrt{y_0}}\delta y \approx \delta u$$

 This approximation is only valid around (u_0, y_0). The transfer function *at this point* is:

$$H(s) = \frac{\Delta Y(s)}{\Delta U(s)} \approx \frac{1}{y_0 s^2 + u_0^2 s + \frac{1}{2\sqrt{y_0}}}$$

Depending on the application, $\delta u(t)$ and $\delta y(t)$ should be small enough to ensure the validity of these approximations.

Nonlinear state-space system linearization

Linearize the following system around $(\mathbf{u}_0, \mathbf{x}_0, \mathbf{y}_0)$:

$$\begin{cases} \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}) \\ \mathbf{y} = \mathbf{g}(\mathbf{x}, \mathbf{u}) \end{cases}$$

The overall approach is similar:

$$\begin{cases} \mathbf{u}(t) = \mathbf{u}_0 + \boldsymbol{\delta}\mathbf{u}(t) \\ \mathbf{y}(t) = \mathbf{y}_0 + \boldsymbol{\delta}\mathbf{y}(t) \\ \mathbf{x}(t) = \mathbf{x}_0 + \boldsymbol{\delta}\mathbf{x}(t) \end{cases}$$

$$\begin{aligned} \dot{\mathbf{x}}_0 + \boldsymbol{\delta}\dot{\mathbf{x}}(t) = \quad & \mathbf{f}(\mathbf{x}_0 + \boldsymbol{\delta}\mathbf{x}(t), \mathbf{u}_0 + \boldsymbol{\delta}\mathbf{u}(t)) \\ & = \mathbf{f}(\mathbf{x}_0, \mathbf{u}_0) + \left.\frac{\partial \mathbf{f}(\mathbf{x}, \mathbf{u})}{\partial \mathbf{x}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \boldsymbol{\delta}\mathbf{x}(t) + \left.\frac{\partial \mathbf{f}(\mathbf{x}, \mathbf{u})}{\partial \mathbf{u}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \boldsymbol{\delta}\mathbf{u}(t) \\ & + \cdots \\ \mathbf{y}_0 + \boldsymbol{\delta}\mathbf{y}(t) = \quad & \mathbf{g}(\mathbf{x}_0 + \boldsymbol{\delta}\mathbf{x}(t), \mathbf{u}_0 + \boldsymbol{\delta}\mathbf{u}(t)) \\ & = \mathbf{g}(\mathbf{x}_0, \mathbf{u}_0) + \left.\frac{\partial \mathbf{g}(\mathbf{x}, \mathbf{u})}{\partial \mathbf{x}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \boldsymbol{\delta}\mathbf{x}(t) + \left.\frac{\partial \mathbf{g}(\mathbf{x}, \mathbf{u})}{\partial \mathbf{u}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \boldsymbol{\delta}\mathbf{u}(t) \\ & + \cdots \end{aligned}$$

Nonlinear state-space system linearization

(continued)

Defining

$$\mathbf{A}(t) \triangleq \left.\frac{\partial \mathbf{f}(\mathbf{x},\mathbf{u})}{\partial \mathbf{x}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \qquad \mathbf{B}(t) \triangleq \left.\frac{\partial \mathbf{f}(\mathbf{x},\mathbf{u})}{\partial \mathbf{u}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}}$$

$$\mathbf{C}(t) \triangleq \left.\frac{\partial \mathbf{g}(\mathbf{x},\mathbf{u})}{\partial \mathbf{x}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \qquad \mathbf{D}(t) \triangleq \left.\frac{\partial \mathbf{g}(\mathbf{x},\mathbf{u})}{\partial \mathbf{u}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}}$$

and considering that

$$\begin{cases} \dot{\mathbf{x}_0} = \mathbf{f}(\mathbf{x}_0,\mathbf{u}_0) \\ \mathbf{y}_0 = \mathbf{g}(\mathbf{x}_0,\mathbf{u}_0) \end{cases}$$

Results in:

$$\begin{cases} \delta\dot{\mathbf{x}}(t) \approx \mathbf{A}(t)\delta\mathbf{x}(t) + \mathbf{B}(t)\delta\mathbf{u}(t) \\ \delta\mathbf{y}(t) \approx \mathbf{C}(t)\delta\mathbf{x}(t) + \mathbf{D}(t)\delta\mathbf{u}(t) \end{cases}$$

which is a linear approximation of the original nonlinear state-space equations around $(\mathbf{u}_0, \mathbf{x}_0, \mathbf{y}_0)$.

Stability analysis of nonlinear systems

In linear systems

All the system poles should be in the left half plane

In nonlinear systems

1. The system is first linearized around the desired point
2. The state transition matrix is calculated for the linearized system: $\phi(s) = (s\boldsymbol{I} - \boldsymbol{A})^{-1}$ $(\phi(t) = L^{-1}\{\phi(s)\})$
3. In order to have a stable system, the poles of $\phi(s)$ should be in the left half plane (or $\lim_{t\to\infty} \phi(t) = 0$), around the point of interest

Further reading

- Kailath, T. (1980). *Linear Systems*.
  Prentice Hall
- Dorf, R. C. & Bishop, R. H. (2021). *Modern Control Systems*.
  Pearson Prentice Hall, 13th edition
- Ogata, K. (2010). *Modern control engineering*.
  Prentice hall, 5th edition
- Oppenheim, A., Schafer, R., & Buck, J. (1999). *Discrete-time signal processing*.
  Prentice-Hall signal processing series. Prentice Hall
- Tsakalis, K. S. (2001). Stability, controllability, observability.
  Lecture Notes

Nonlinear dynamics & chaos

- Many real-world systems have nonlinear dynamics
- Nonlinear dynamical systems are prone to **chaos**
- Chaos is a **stochastic-like** phenomena in nonlinear dynamical systems
- Although deterministic, **chaotic** systems' states are very susceptible to initial conditions and perturbations (noise)
- The period of repetition approaches infinity in chaos. Therefore, the system's state may not be identified if the initial condition is unknown

Chaos in biological systems

Population growth

The population oscillation of a community between successive generations due to their life styles and resources (Hilborn, 2000, Ch. 1).

Multi-phasic fetal heart rate

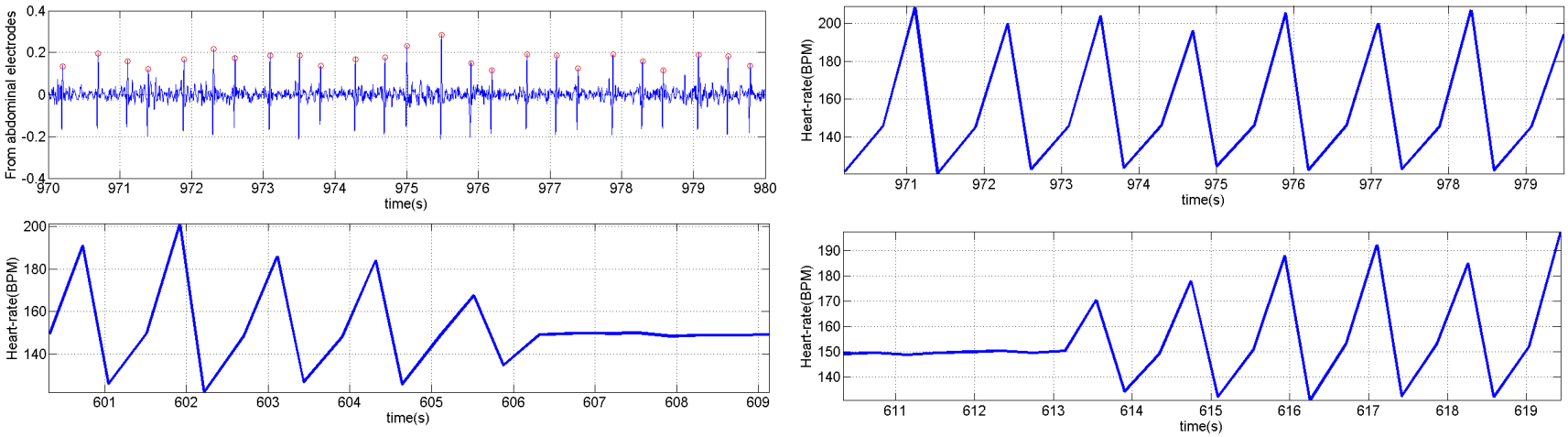


Figure: Sample fetal heart rate with temporarily oscillatory characteristics

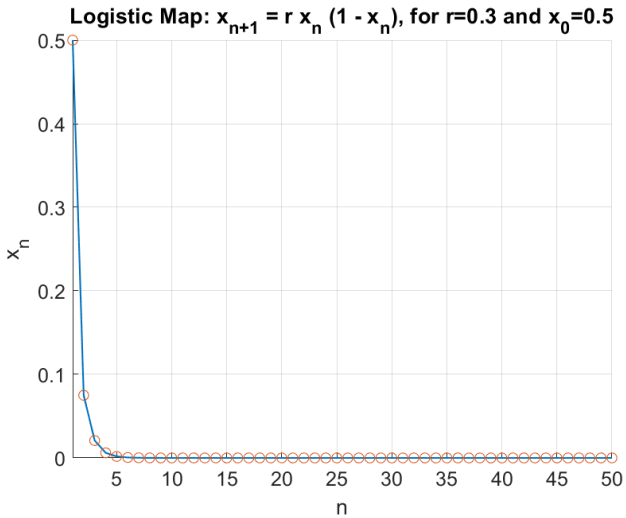
Chaos in discrete-time systems

The Logistic Map

Example: The Logistic Map

The following discrete-time model, known as the *Logistic Map*, appears in many discrete (or discretized) biological models such as growth of species or cells:

$$x_{n+1} = f(x_n) = rx_n(1 - x_n)$$



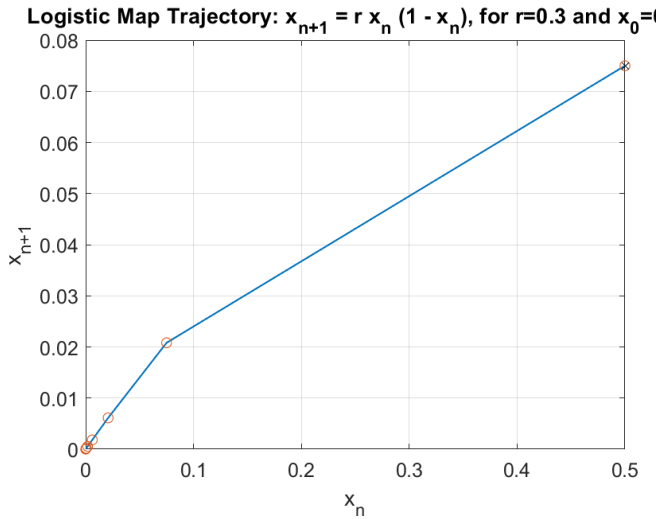
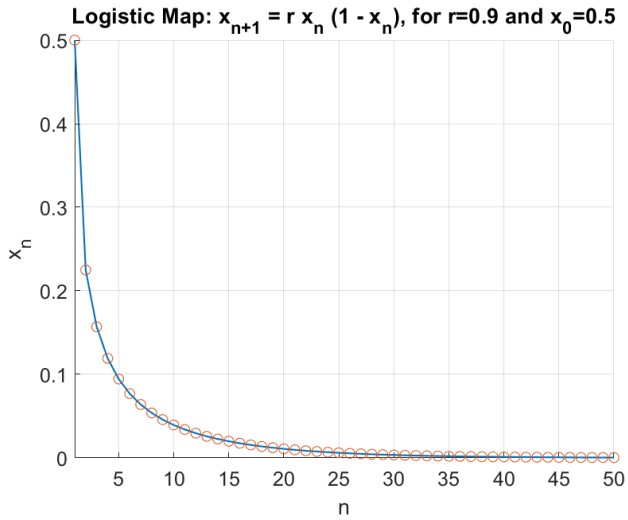
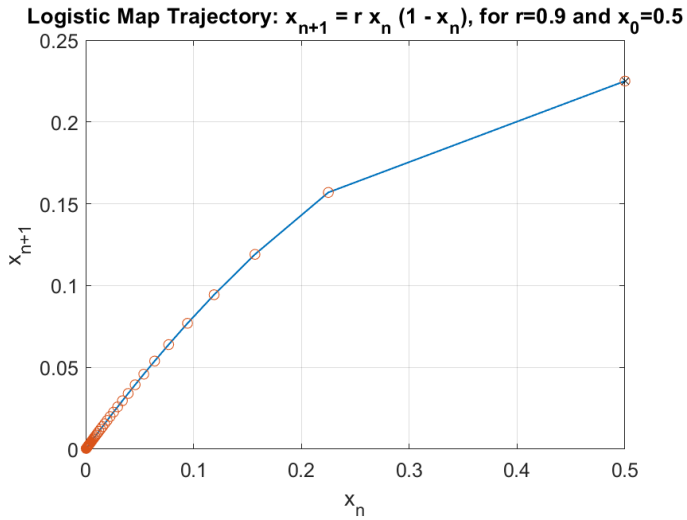


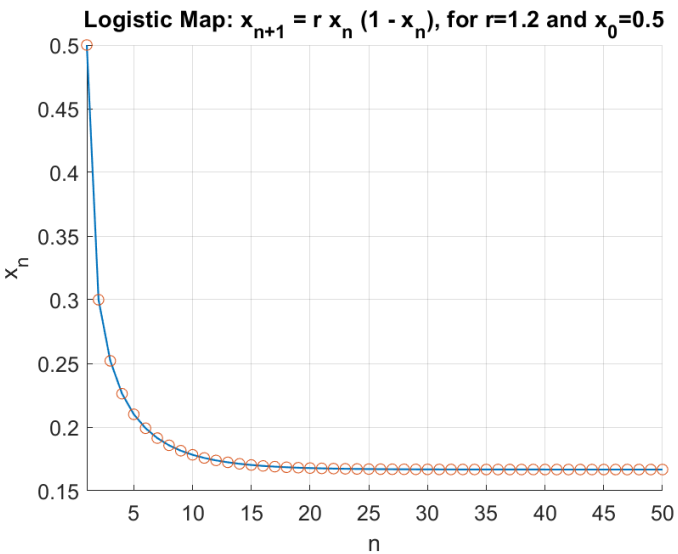
Figure: Logistic Map for r =0.3 and x_0 =0.5

Chaos in discrete-time systems

The Logistic Map (continued)







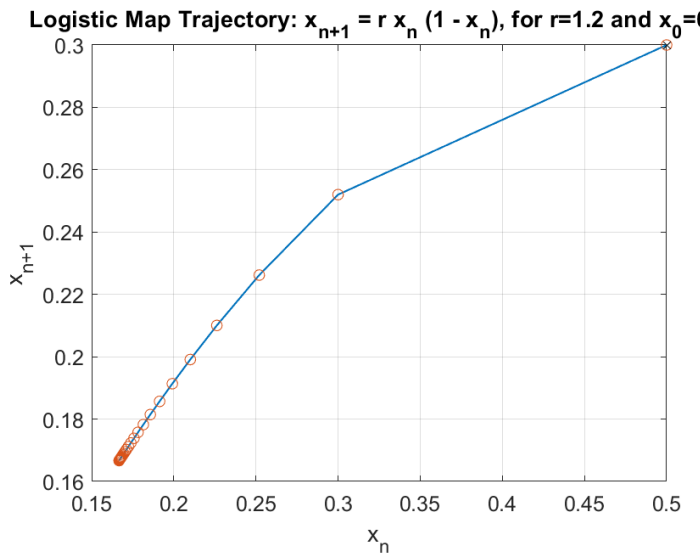
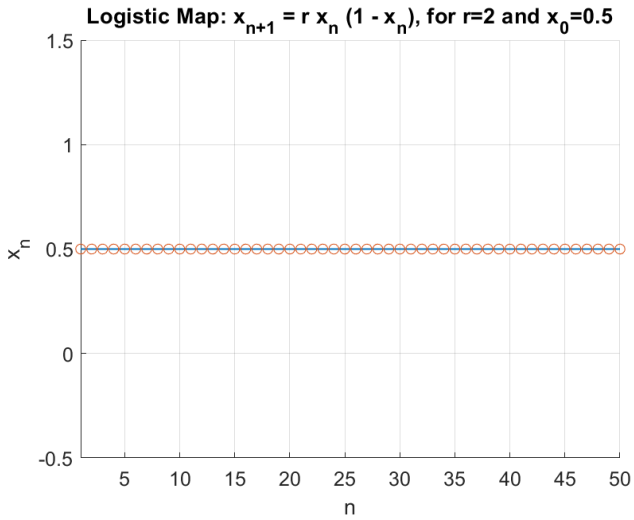
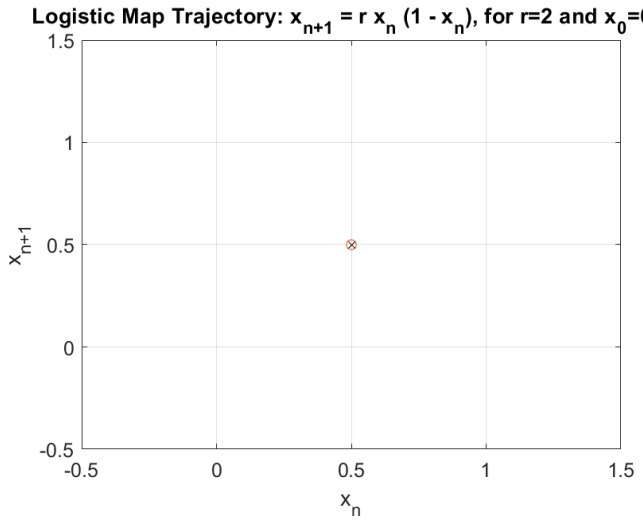


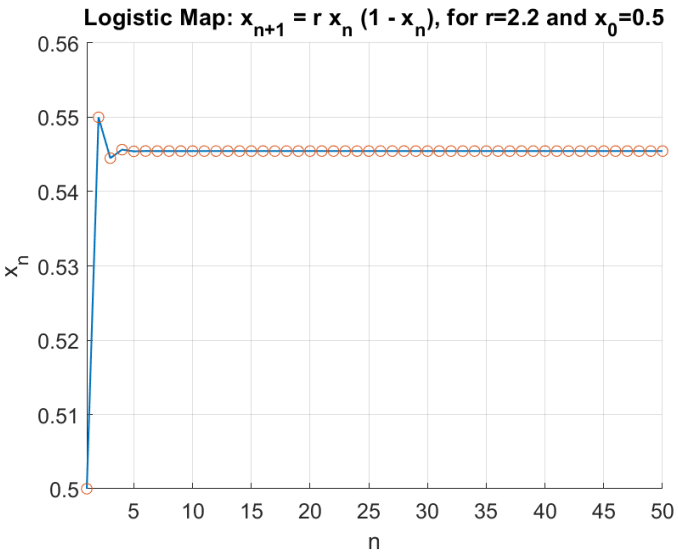
Figure: Logistic Map for r =0.9 and 1.2, and x_0 =0.5

Chaos in discrete-time systems

The Logistic Map (continued)







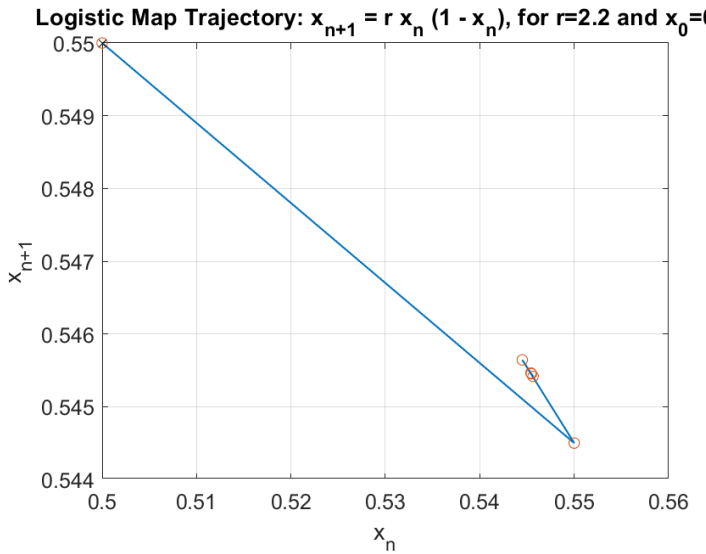
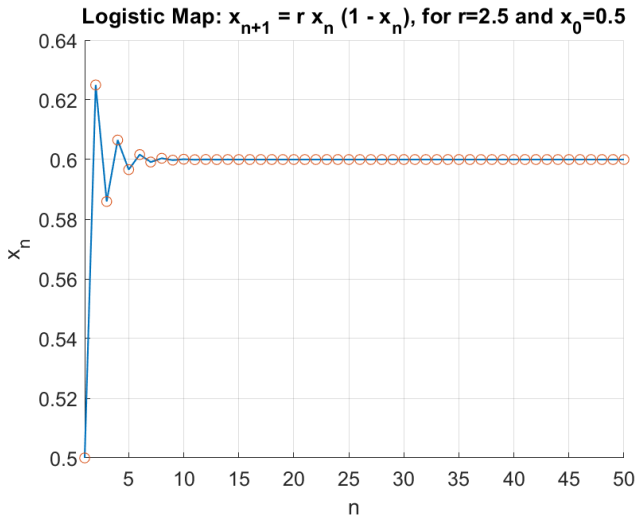
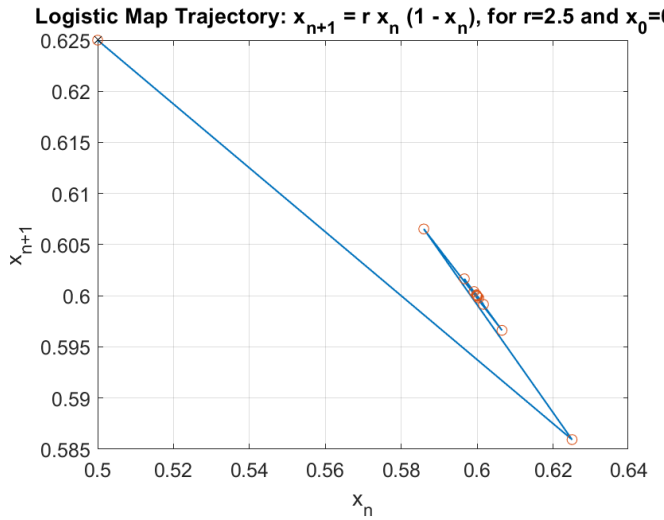


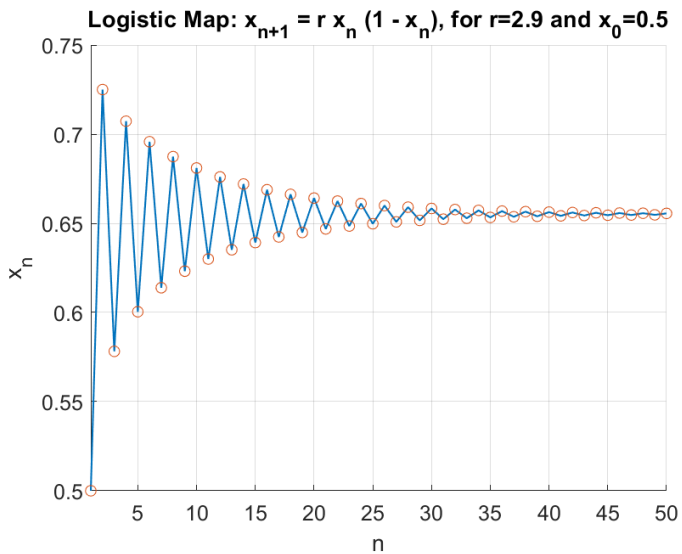
Figure: Logistic Map for r =2.0 and 2.2, and x_0 =0.5

Chaos in discrete-time systems

The Logistic Map (continued)







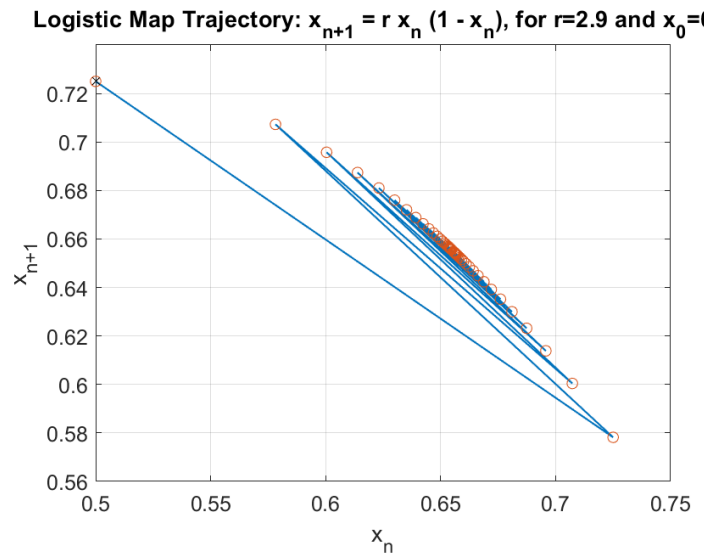
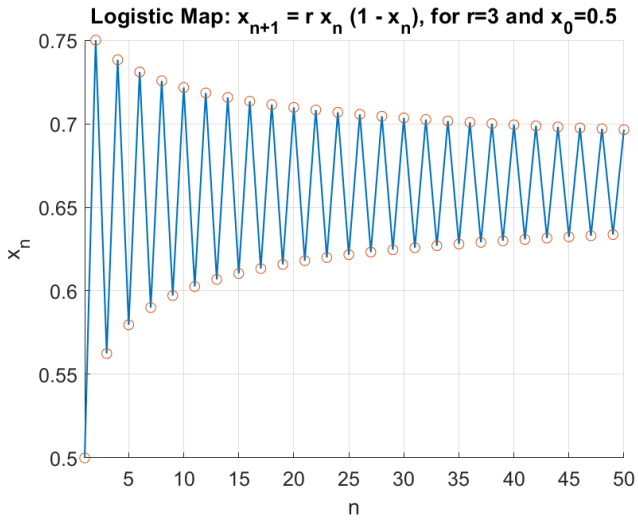
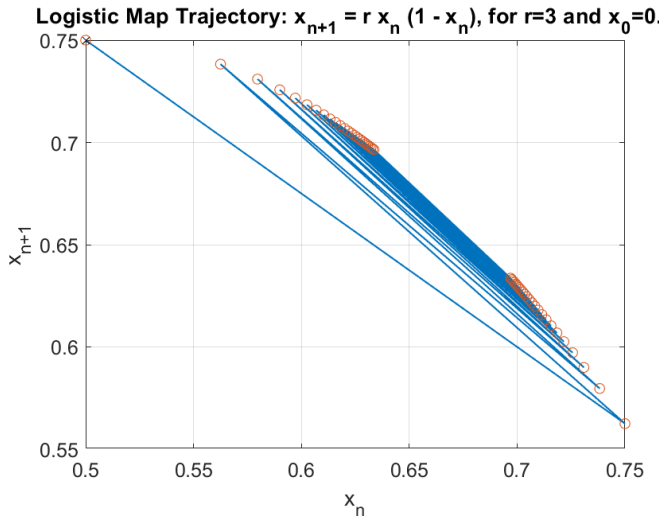


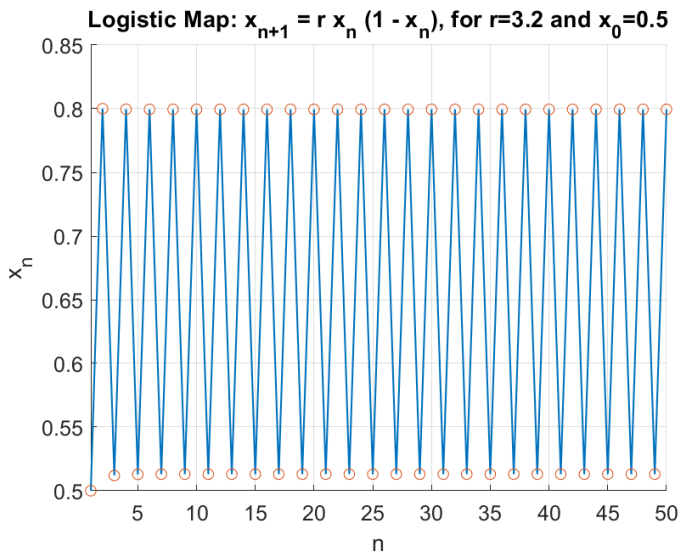
Figure: Logistic Map for r =2.5 and 2.9, and x_0 =0.5

Chaos in discrete-time systems

The Logistic Map (continued)







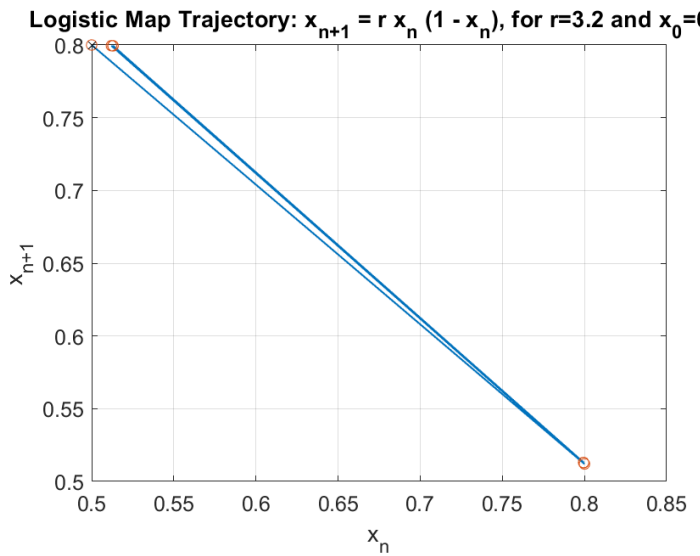
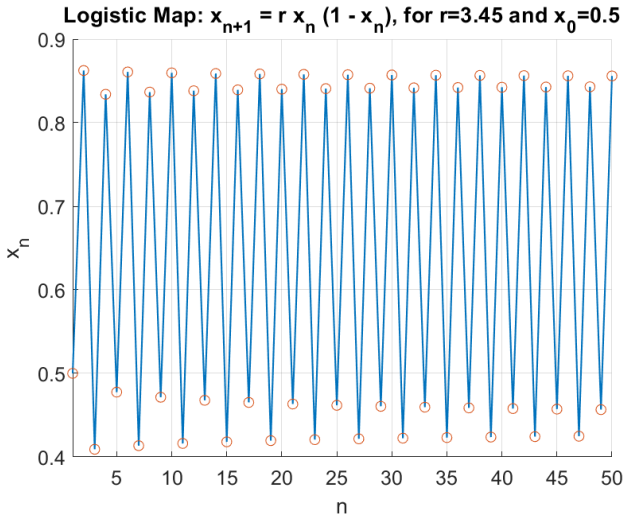
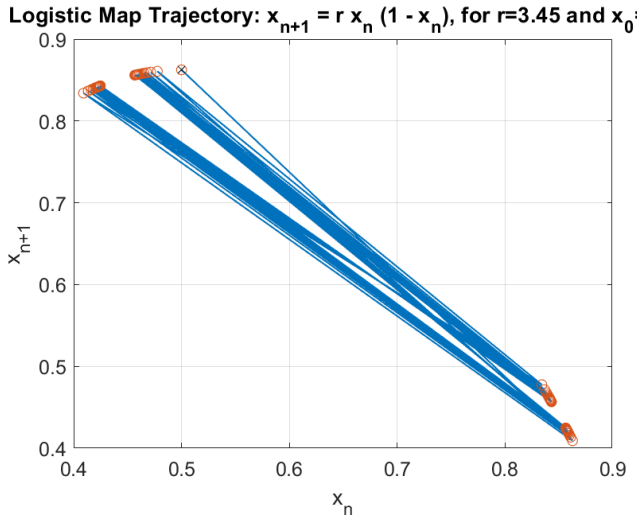


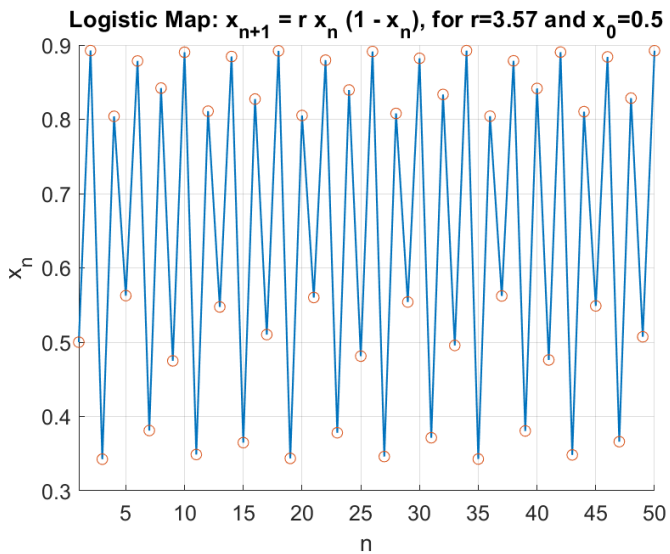
Figure: Logistic Map for r =3.0 and 3.2, and x_0 =0.5

Chaos in discrete-time systems

The Logistic Map (continued)







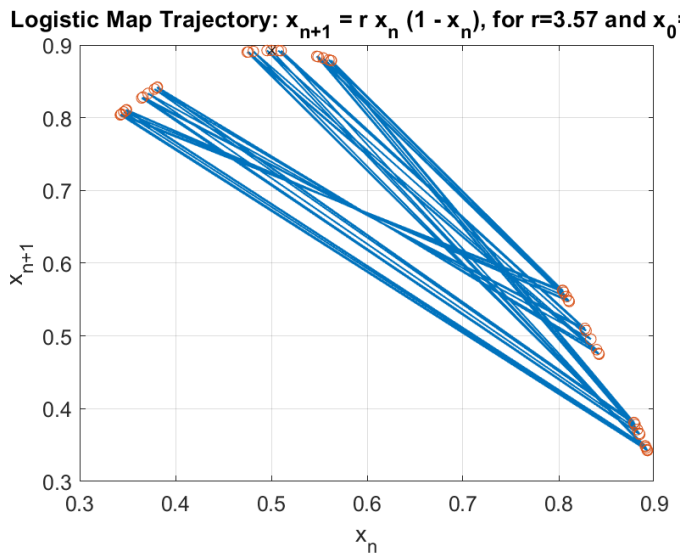
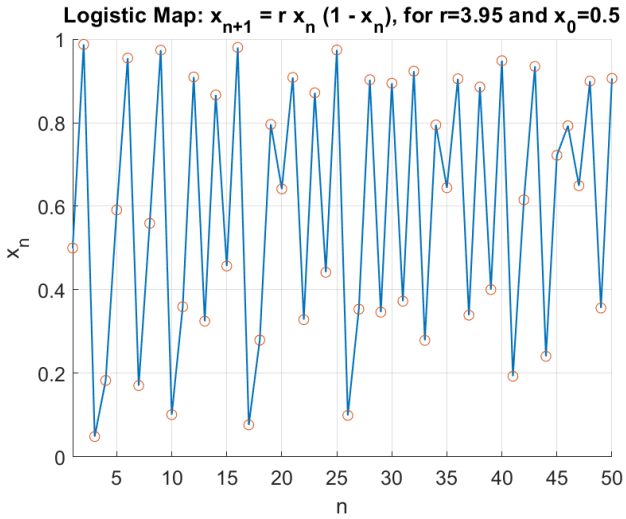
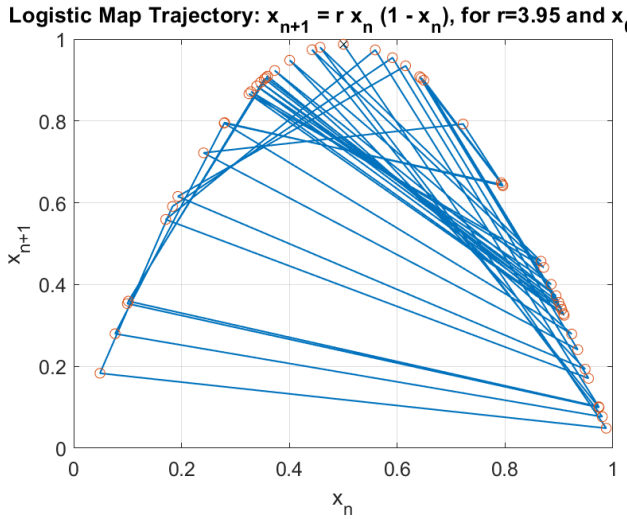


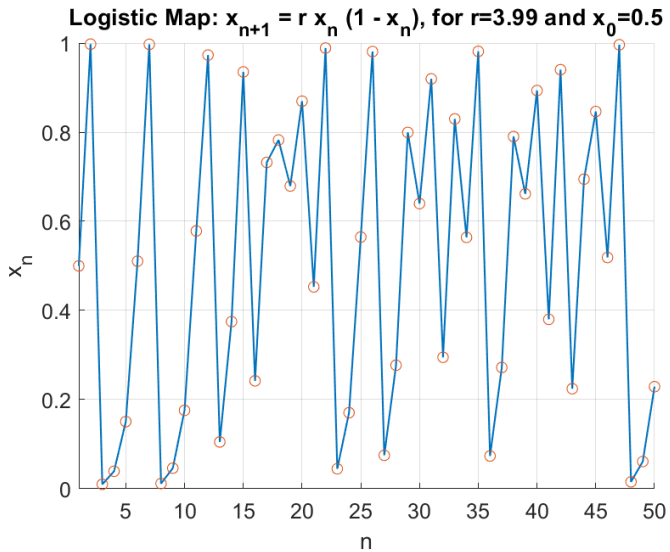
Figure: Logistic Map for r =3.45 and 3.57, and x_0 =0.5

Chaos in discrete-time systems

The Logistic Map (continued)







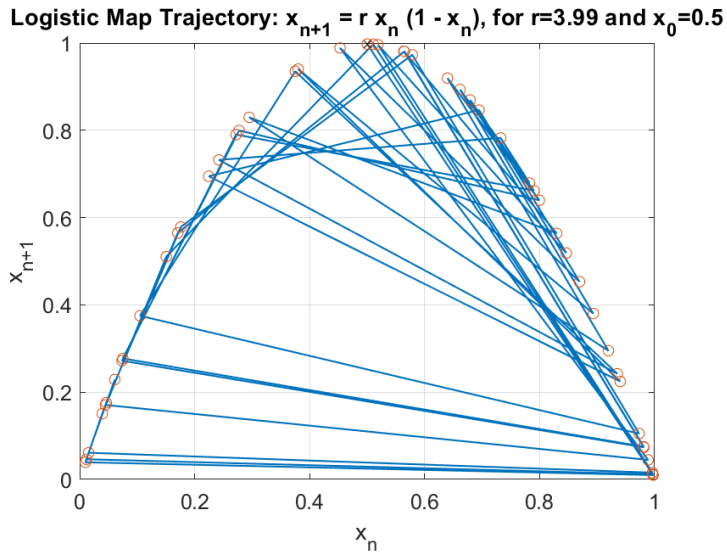


Figure: Logistic Map for r =3.95 and 3.99, and x_0 =0.5

Nonlinear dynamical models & chaos

Fixed-points and trajectories

Consider the following **dynamical models**

$$\text{Continuous Model:} \qquad \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}) \qquad (*)$$

$$\text{Discrete Model:} \qquad \mathbf{x}_{n+1} = \mathbf{g}(\mathbf{x}_n) \qquad (**)$$

Trajectory (orbit):

Is the path of the system over time, i.e., the set of all points that satisfy (*) or (**), starting from an initial point $\mathbf{x}_0$.

Fixed-point:

Is a point from which the system's trajectory does not exit, once reached. For continuous-time dynamic systems if $\mathbf{f}(\mathbf{x}^*) = 0$, $\mathbf{x}^*$ is a fixed-point. For the discrete-time case $\mathbf{x}^* = \mathbf{g}(\mathbf{x}^*)$ is a fixed-point.

Stability of fixed-points

Fixed-point stability assessment

- **Rigorous:** Lyapunov stability analysis techniques
- **Empirical:** Perturb the fixed-point with small (positive and negative) values and check if the system's dynamics brings it back to the fixed-point (adopted from **Perturbation Theory**)

See (Hilborn, 2000, Ch. 5) for details.

Fixed-point analysis by perturbation

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.

Explaining the Logistic Map behavior

Fixed-point analysis of the Logistic Map

The fixed-points or the Logistic Map are:

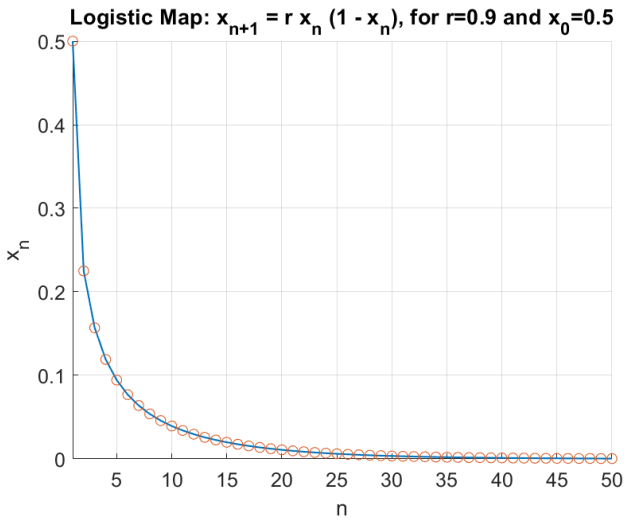
$$x_r^* = r x_r^* (1 - x_r^*) \Rightarrow \begin{cases} x_r^* = 0 \\ x_r^* = 1 - \dfrac{1}{r} \end{cases}$$

which depend on the parameter r.

Explaining the Logistic Map behavior

(continued)

The Logistic Map for $0 < r < 1$



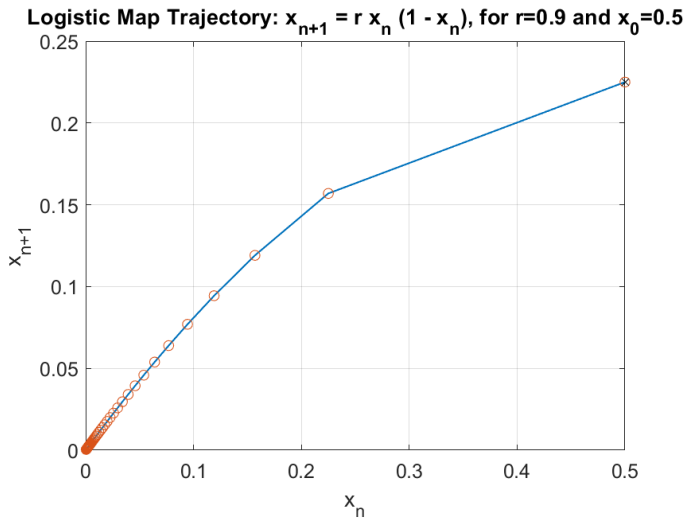


Figure: Logistic Map for r =0.9 and x_0 =0.5

- The only fixed-point is $x^* = 0$, which is **stable**
- $x^* = 0$ is an **attractor** for all initial conditions $x \in [0, 1]$ (called the **basin of attraction**), i.e., the population vanishes

Explaining the Logistic Map behavior

(continued)

The Logistic Map for $1 < r < 3$

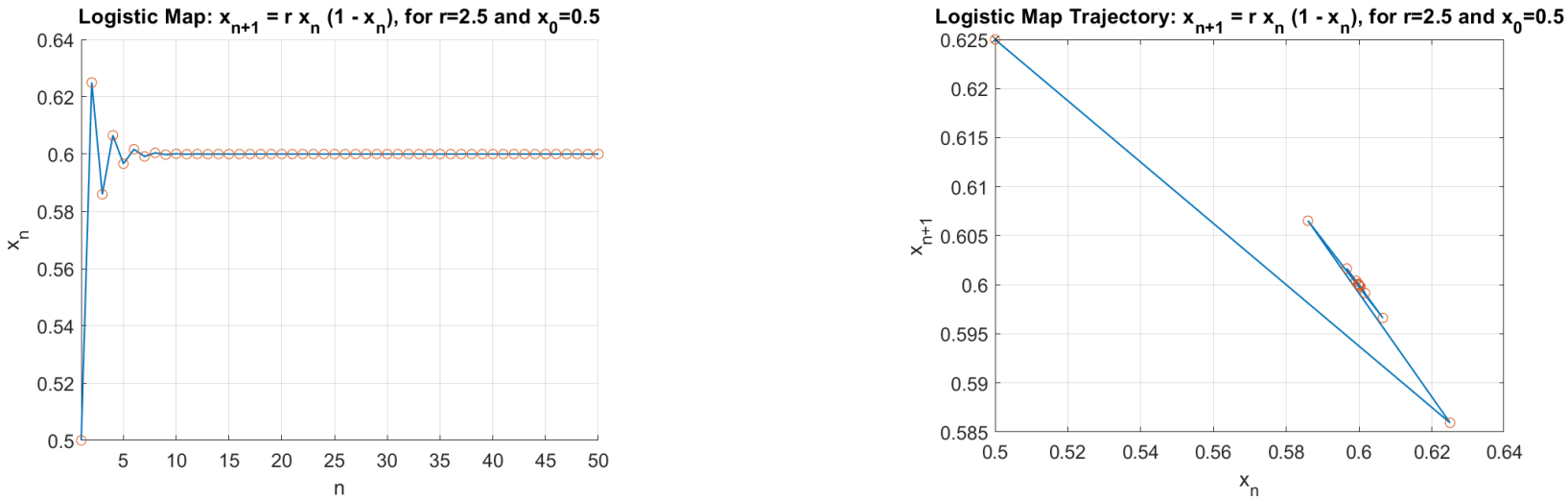


Figure: Logistic Map for r =2.5 and x_0 =0.5

- The fixed-points are $x^* = 0$, which is **unstable** and $x_r^* = 1 - \frac{1}{r}$, which is **stable**
- x_r^* is an **attractor** for all $x \in (0, 1]$, i.e., the population converges x_r^*

Explaining the Logistic Map behavior

(continued)

The Logistic Map for $3 < r < 4$

The first **bifurcation** (splitting of fixed points) occurs at $r > 3$

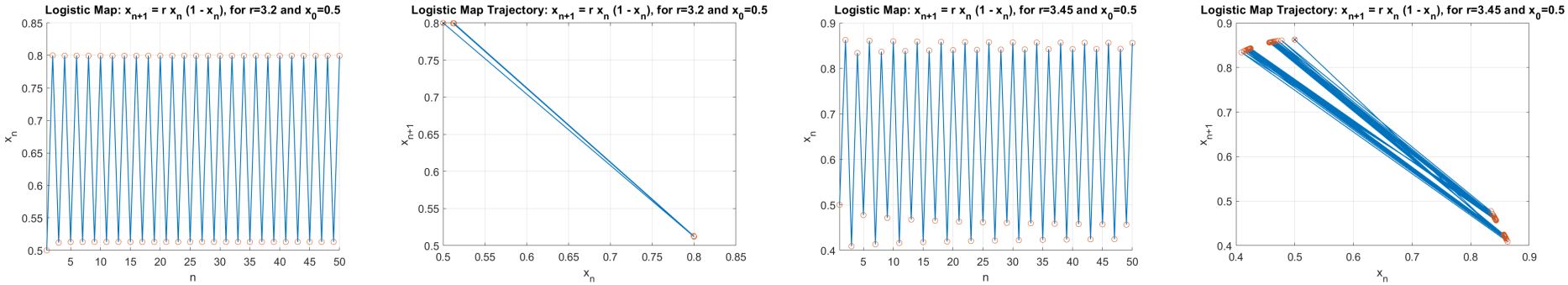


Figure: Logistic Map for r =3.2 and 3.45, and x_0 =0.5

- For $r = 3.2$, the population oscillates between two values. In this case as $n \to \infty$, $x_{n+2} = x_n$. In order to find the fixed-points, the following equations should be solved simultaneously: $y^* = rx^*(1 - x^*), \quad x^* = ry^*(1 - y^*)$.
- For $r = 3.45$, the population oscillates between four values

Explaining the Logistic Map behavior

(continued)

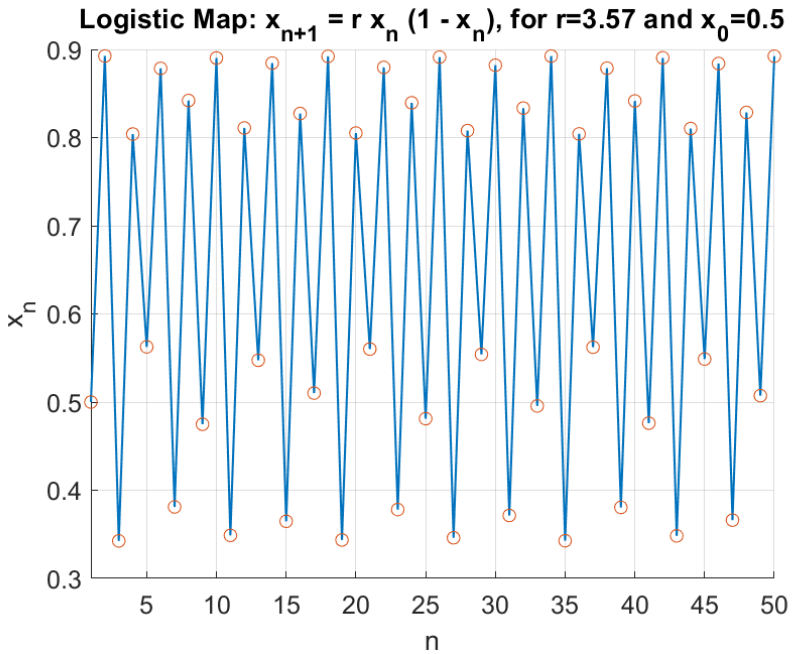
What happens during bifurcation?

- The fixed-point $x_r^* = 1 - 1/r$ is no longer stable (Hilborn, 2000, Ch. 1).
- **Proof:** Perturb the fixed-point with small positive and negative values: $x_n = x_r^* \pm \epsilon$, and analyze the effect on the stability of the fixed-point.

Explaining the Logistic Map behavior

(continued)

The Logistic Map in chaos ($r > 3.5699\cdots$)



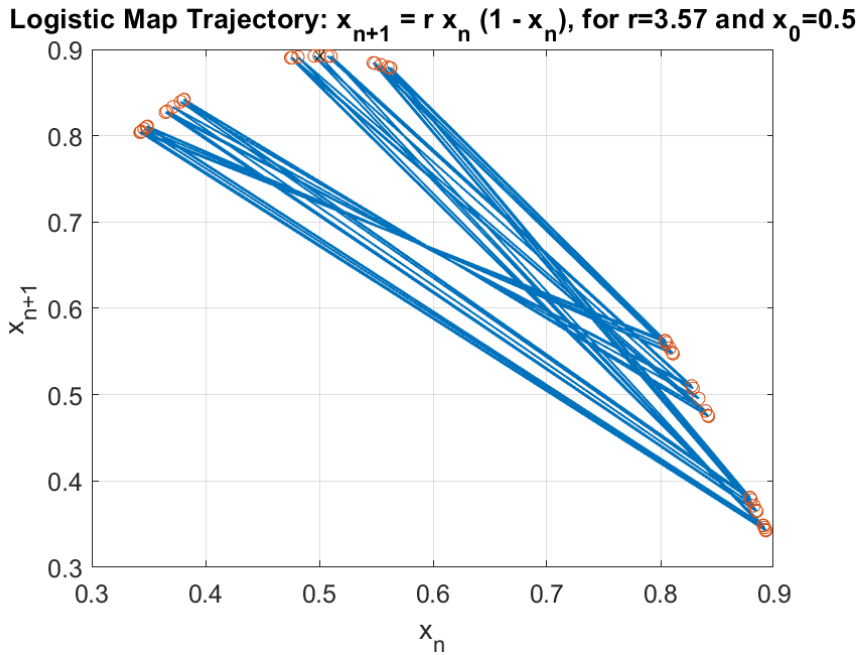
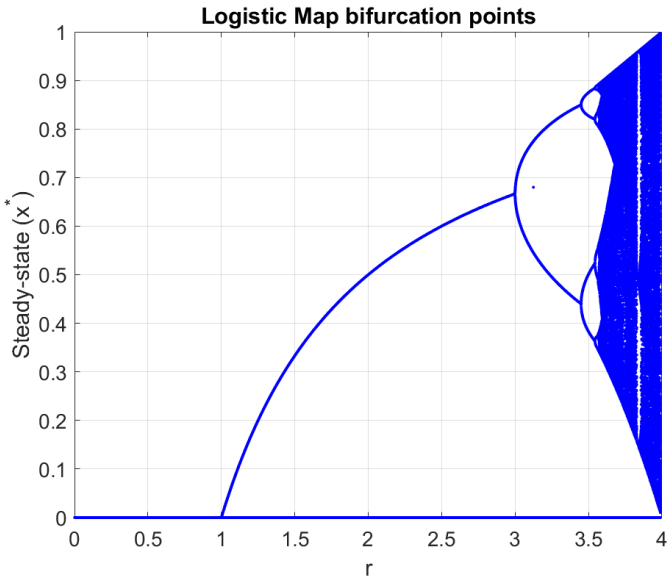


Figure: Logistic Map for r =3.57 and x_0 =0.5

Explaining the Logistic Map behavior

(continued)

The Logistic Map bifurcation diagram



Exercise 1:

1. Write a function `x = LogisticMap(r, x0, N)` and a test program to simulate the Logistic Map with arbitrary initial conditions `x0`, rate parameter `r` and length `N`.
2. Find and analyze the first bifurcation points of the logistic map analytically.

Chaos in continuous-time systems

Example: the Lorenz Map

The Lorenz Map is a simplified mathematical model for atmospheric convection:

$$\begin{cases} \dot{x} = p(y - x) \\ \dot{y} = -xz + rx - y \\ \dot{z} = xy - bz \end{cases}, \quad \text{State vector: } \mathbf{s} \stackrel{\Delta}{=} \begin{bmatrix} x \\ y \\ z \end{bmatrix}$$

Exercise 2:

1. Calculate the fixed-points of the Lorenz Map
2. Are the fixed-points stable?

Chaos in continuous-time systems

Example: an epidemiological dynamic model

The susceptible-infected-recovered (SIR) model is a continuous dynamic model used to study the spread of epidemic/pandemic diseases:

$$\dot{s}(t) = -\alpha s(t) i(t) + \gamma r(t)$$
$$\dot{i}(t) = \alpha s(t) i(t) - \beta i(t)$$
$$\dot{r}(t) = \beta i(t) - \gamma r(t)$$

Exercise 3:

1. Calculate the fixed-points of the SIR model
2. Are the fixed-points stable?

General properties of chaotic models

- Chaos may occur in continuous-time systems (of order higher than 1) or discrete-time systems (of any order)
- Without having the initial conditions, the systems' states are unpredictable
- Chaotic systems are very susceptible to errors in calculations or initial states

Universal properties of chaotic systems

Question: Can we find any common and universal properties, which hold for all (or a class of) chaotic systems? (similar to e, π, etc.)

Feigenbaum Delta

- Consider $A_1, A_2, \cdots, A_n$ as the bifurcation points of a chaotic system. It has been shown that for a broad class of chaotic systems we have:

$$\delta_n \triangleq \frac{A_n - A_{n-1}}{A_{n+1} - A_n} \rightarrow \delta \triangleq \lim_{n\rightarrow\infty} \delta_n = 4.66920161\cdots$$

- The Logistic Map: $x_{n+1} = r x_n(1 - x_n)$, and the Sine Map: $x_{n+1} = B\sin(\pi x_n)$, both follow this property.

Universal properties of chaotic systems

(continued)

Feigenbaum Time Scaling

- Consider $d_1, d_2, \cdots, d_n$ as the gap between the oscillating amplitudes at bifurcation points.
- It has been shown that for a broad class of chaotic systems we have:

$$\alpha_n \stackrel{\Delta}{=} \frac{d_n}{d_{n+1}} \rightarrow \alpha \stackrel{\Delta}{=} \lim_{n\rightarrow\infty} \alpha_n = 2.5029\cdots$$

A population growth model

Single-species population growth model

The objective is to model the population of a single species living in finite resource conditions. For example, bacterial growth in laboratory.

Observations:

1. When the population is small, the rate of growth is proportional to the population
2. The population saturates as the population reaches a certain number

Modeling:

Restate the observations in a formal manner:

- $x(t) \stackrel{\Delta}{=}$ population at time t
- if $|x(t)| \ll 1 \Longrightarrow |\frac{dx(t)}{dt}| \propto |x(t)|$
- if $|x(t)| \gg 1 \Longrightarrow |\frac{dx(t)}{dt}| \to 0$

Question: Propose a simple model that satisfies the observations.

A population growth model

(continued)

A model that satisfies the observations:

$$\frac{dx(t)}{dt} = Ax(t) - Bx^2(t) = Ax(t)[1 - \frac{B}{A}x(t)] \qquad (*)$$

Interpretation:

An **exponential growth** with a variable **rate of growth** (the bracket term in *). The rate of growth is a descending function of $x(t)$.

Dimension Analysis

$$\left[\frac{x}{T}\right] = [A] + [B]\,x^2$$

$$[A] = \frac{X}{T} \qquad [B] = \frac{1}{XT}$$

A population growth model

Fixed-point analysis

Fixed-points of (*)

$$\frac{dx(t)}{dt} = 0 \Rightarrow$$

$$Ax(t)\left[1 - \frac{B}{A}x(t)\right] = 0 \Rightarrow \begin{cases} x(t) = 0 & \text{(population extinction)} \\ x(t) = \dfrac{A}{B} & \text{(saturation point)} \end{cases}$$

A population growth model

Fixed-point stability by perturbation analysis

Stability at $x(t) = 0$

$$x(t) = \epsilon > 0$$

$$\frac{dx(t)}{dt} = \epsilon(A - B\epsilon) \approx \epsilon A > 0$$

$\therefore$ The fixed point is unstable

Stability at $x(t) = \frac{A}{B}$

$$x(t) = \frac{A}{B} + \epsilon \Rightarrow \frac{dx(t)}{dt} = (\frac{A}{B} + \epsilon)(-B\epsilon)$$

$$\begin{cases} \text{if } \epsilon > 0 \Rightarrow \frac{dx(t)}{dt} < 0 \\ \text{if } \quad \epsilon < 0 \Rightarrow \frac{dx(t)}{dt} > 0 \end{cases}$$

$\therefore$ The fixed point is stable

Competitive population growth model

Multi-species competitive population growth model

The objective is to model the population of two competing species in finite resource conditions. For example, two species of a fish in a pond, or the number of white cells versus body infections.

Observations:

1. In the marginal case, when one of the species is missing, the model follows a single-species model.
2. The increase of each species influences (decreases) the resources for both species

Proposed Model:

$$\dot{x} = x(t)[\epsilon_1 - \alpha_1 x(t) - \beta_1 y(t)]$$
$$\dot{y} = y(t)[\epsilon_2 - \alpha_2 y(t) - \beta_2 x(t)]$$

Competitive population growth model

Fixed-point analysis

Linearization

$$\begin{cases} x(t) = x_0 + \delta x(t) \\ y(t) = y_0 + \delta y(t) \end{cases}$$

$$\begin{bmatrix} \delta\dot{x} \\ \delta\dot{y} \end{bmatrix} \approx \underbrace{\begin{bmatrix} \epsilon_1 - 2\alpha_1 x_0 - \beta_1 y_0 & -\beta_1 x_0 \\ -\alpha_2 y_0 & \epsilon_2 - 2\beta_2 y_0 - \alpha_2 x_0 \end{bmatrix}}_{A} \begin{bmatrix} \delta x \\ \delta y \end{bmatrix}$$

Fixed-points ($\dot{x} = \dot{y} = 0$):

$$x^* = y^* = 0 \qquad x^* = 0, y^* = \frac{\epsilon_2}{\beta_2}$$

$$y^* = 0, x^* = \frac{\epsilon_1}{\beta_1} \qquad \begin{cases} \alpha_1 x^* + \beta_1 y^* = \epsilon_1 \\ \alpha_2 x^* + \beta_2 y^* = \epsilon_2 \end{cases}$$

Competitive population growth model

Fixed-point stability analysis

Stability at $x^* = y^* = 0$:

$$\boldsymbol{A} = \begin{bmatrix} \epsilon_1 & 0 \\ 0 & \epsilon_2 \end{bmatrix} \rightarrow \phi(t) = \begin{bmatrix} e^{\epsilon_1 t} u(t) & 0 \\ 0 & e^{\epsilon_2 t} u(t) \end{bmatrix}$$

$e^{\epsilon_1 t}$ and $e^{\epsilon_2 t}$ are exponentially growing functions of time for $\epsilon_1, \epsilon_2 > 0$. Therefore, $x^* = y^* = 0$ is an unstable fixed-point.

Exercise 4:

Study the stability of the other fixed-points of the competitive population growth model and discuss their interpretations in biological systems.

Predator–prey models

The Lotka–Volterra equations

$$\begin{cases} \dot{x}(t) = \alpha x(t) - \beta x(t) y(t) \\ \dot{y}(t) = \delta x(t) y(t) - \gamma y(t) \end{cases}$$

Question: Interpret the model

Exercise 5:

Study the dynamic properties of the competitive **Lotka–Volterra** predator–prey model.

Ordinary vs. partial differential modeling

- Differential (difference) equations arise in many modeling problems
- The incentive for the vast application of these equations is that in many real world applications, the rate of changes of a variable is related to other variables.
- Two common forms of differential equations are
  - *Ordinary differential equations* (ODE)
  - *Partial differential equations* (PDE)
- In ODE modeling, the variations of a variable is studied versus another variable, such as time, space, etc.
- In PDE modeling, the variations are modeled versus more than one variable
- In the following sections, various real-world biological models in which ODE and PDE arise are studied. Compartmental models are the first example.

Compartmental modeling

- Compartmental modeling is used as a (visual) means of representing dynamic equations
- A compartment is an abstract entity representing the quantity of interest (volume, number, density, etc.). It is visually represented by a box, with the variable of interest indicated inside
- Depending on the level of abstraction, each of the variables of interest (equivalent to system states) are represented by a single compartment
- Each compartment is assumed to be **homogeneous**.
- Compartments interact with one-another through a set of rate equations, indicated by flashes between the compartments
- Compartmental models can be converted to a set of first order linear or nonlinear equations (and vice versa), by writing the net flow into a compartment
- Compartmental modeling is also known as **mass transport** (Rideout, 1991), or **mass action** (Ingalls, 2012), in the literature.

Basics of compartmental modeling

1. Identify the quantities of interest as distinct compartments.
2. Select a variable for each compartment quantity (as a function of time). These variables are the **state vaiables** of the resulting **state-space equations**.
3. Link the compartments with arrows indicating the **rate** of quantity flow from each compartment to another, written over the arrows.
4. Write the corresponding first-order differential equations of the model
5. Solve/analyze the system of equation (analytically or numerically)

Notes

- A compartment model is **linear** (**nonlinear**), when its rate flow factors are independent (dependent) of the state variables.
- A compartment model is **time-invariant** (**time-variant**), when its rate flow factors are independent (dependent) of time.
- 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.

Compartmental model construction

A three-compartment model

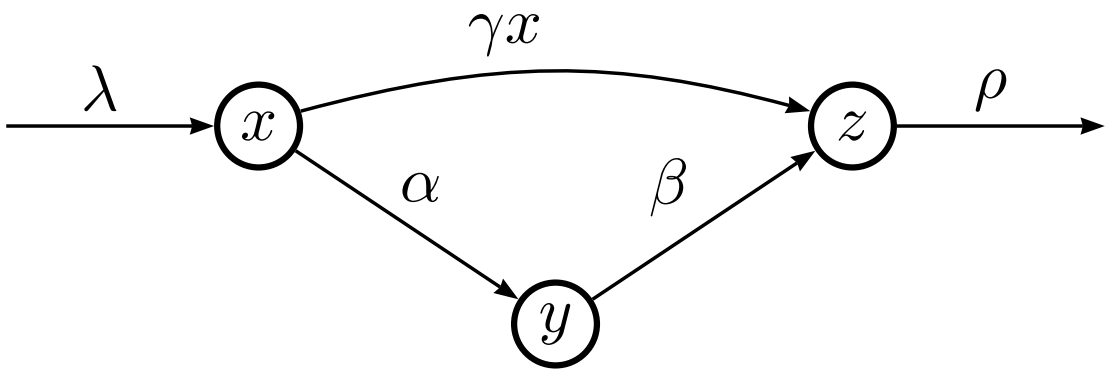


Figure: A sample compartmental model

$$\begin{cases} \dot{x}(t) = \lambda - \gamma \cdot x(t)^2 - \alpha x(t) \\ \dot{y}(t) = \alpha x(t) - \beta \cdot y(t) \\ \dot{z}(t) = \gamma \cdot x(t)^2 + \beta \cdot y(t) - \rho z(t) \end{cases}$$

The model is nonlinear, due to the state-dependency of the rate flow between x and z.

Chemical reactions

Chemical reactions (Blomhøj et al., 2014)

- Chemical reactions are good examples of compartmental models.
- Each substance is considered as a separate compartment.

$$2N_2O_5 \rightarrow 4NO_2 + O_2$$

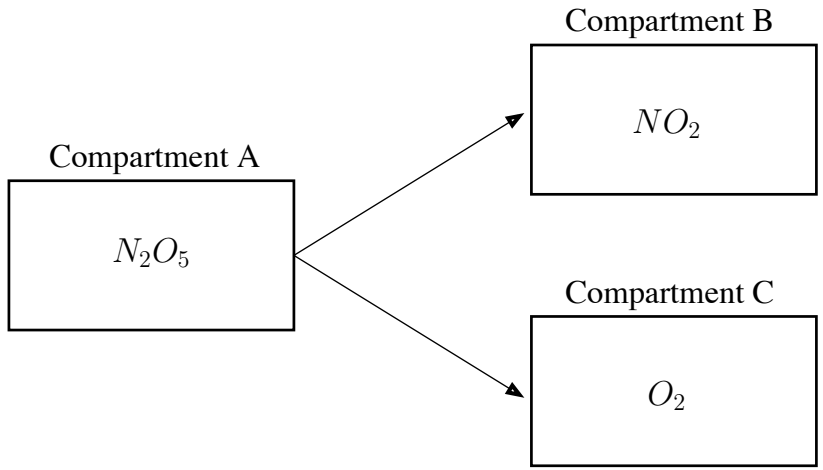


Figure: Compartments in chemical reactions; adopted from (Blomhøj et al., 2014)

Chemical reactions

(continued)

Irreversible chemical reaction

Considering $a(t)$ and $b(t)$ as the concentration of molecules of type A and B (each considered as a compartment) in an irreversible chemical reaction at time t.

$$A \xrightarrow{k} B \qquad \begin{cases} \dot{a}(t) = -ka(t) \\ \dot{b}(t) = ka(t) \end{cases}$$

Reversible chemical reaction

In a similar manner, for a reversible chemical reaction

$$A \underset{k_2}{\overset{k_1}{\longleftrightarrow}} B \qquad \begin{cases} \dot{a}(t) = -k_1 a(t) + k_2 b(t) \\ \dot{b}(t) = k_1 a(t) - k_2 b(t) \end{cases}$$

Enzyme-catalyzed reactions

The Michaelis-Menten kinetics (Ingalls, 2012, Ch. 2, 3)

Consider $s(t)$, $e(t)$, $c(t)$, and $p(t)$, as the concentrations of substrate, enzyme, substrate complex and product, in an enzyme-catalyzed reaction.

$$S + E \underset{k_2}{\overset{k_1}{\longleftrightarrow}} C \xrightarrow{k_3} P + E$$

$$\begin{cases} \dot{s}(t) = -k_1 s(t)e(t) + k_2 c(t) \\ \dot{e}(t) = -k_1 s(t)e(t) + k_2 c(t) + k_3 c(t) \\ \dot{c}(t) = k_1 s(t)e(t) - k_2 c(t) - k_3 c(t) \\ \dot{p}(t) = k_3 c(t) \end{cases}$$

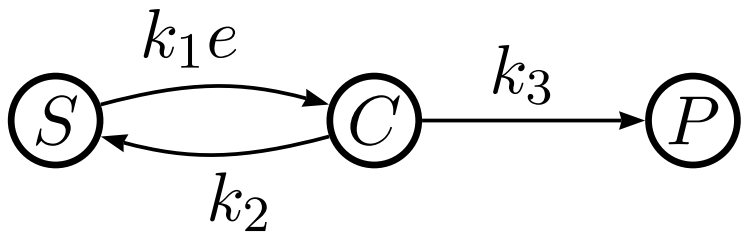
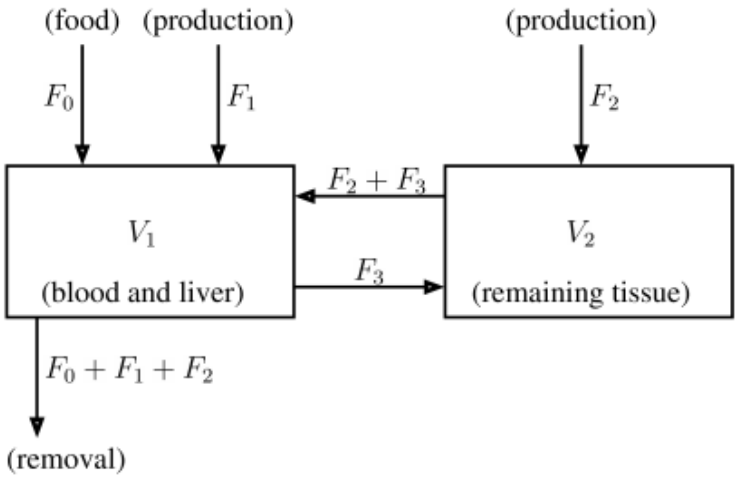


Figure: a) Enzyme-catalyzed reactions; adopted from `http://www.chem4kids.com`. b) The Michaelis-Menten model. Note that $\forall t : \dot{s}(t) + \dot{c}(t) + \dot{p}(t) = 0$.

Dynamics of labeled cholesterol in the body (Blomhøj et al., 2014)

- **Procedure:** To trace the cholesterol, a small amount of the radioactive substance C^{14} is injected in the blood stream and the circulation of the labeled cholesterol is tracked by radio imaging. The objective is to model the dynamics of the radioactive cholesterol and not the cholesterol in the blood and food. Hence the inflow of food and blood is ignored in the model.
- The problem can be modeled by two compartments: 1) blood and liver 2) other body tissues

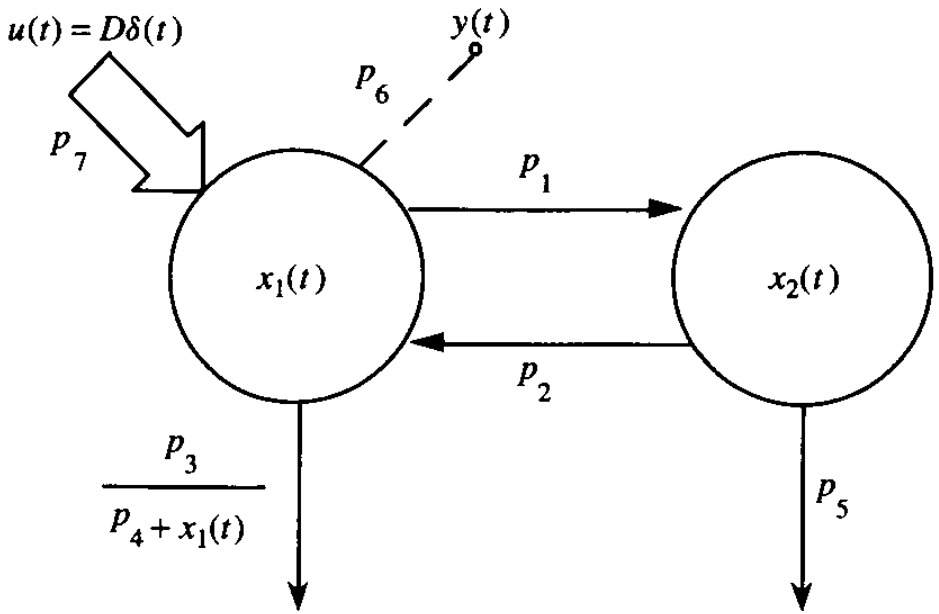


$$\begin{cases} \dot{Q}_1(t) = \dfrac{F_2 + F_3}{V_2} Q_2(t) - \dfrac{F_0 + F_1 + F_2 + F_3}{V_1} Q_1(t) \\ \dot{Q}_2(t) = \dfrac{F_3}{V_1} Q_1(t) - \dfrac{F_2 + F_3}{V_2} Q_2(t) \end{cases}$$

Drug kinetics modeling

Drug kinetics in the body (Carson & Cobelli, 2001, Ch. 4)

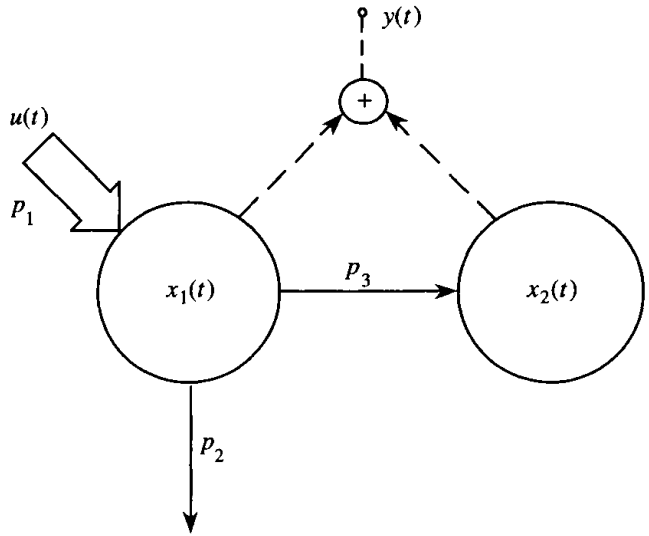
- Consider a nonlinear model with two compartments corresponding to the **blood** and **tissues**



Glucose metabolism

Glucose metabolism in the brain (Carson & Cobelli, 2001, Ch. 4)

- Consider a time-varying model with two compartments corresponding to **fluorodeoxyglucose (FDG)** and **FDG-6-phosphate** concentrations in the brain
- The model parameters are time-varying



$$p_2(t) = p_2(1 + p_4 e^{-p_5 t}) \quad p_3(t) = p_3(1 + p_4 e^{-p_5 t})$$

Epidemiological modeling

Modeling Epidemic Diseases

The objective is to model the propagation of epidemic diseases among a population.

Assumptions:

- The disease transfers via contact
- The disease may or may not be mortal
- There may or may not be births during the period of study
- Immunity:
  1. Case 1: Recovered patients are susceptible to the disease (the disease does not cause immunity)
  2. Case 2: Recovered patients are no longer susceptible to the disease (the disease causes immunity)

Depending on these assumptions, different models may be proposed.

Epidemiological modeling

Susceptible-Infected (SI) Model:

The population is divided to two groups: Susceptible $S(t)$, and Infected $I(t)$

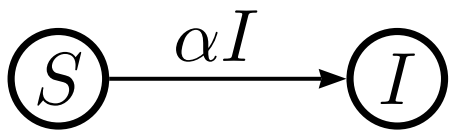


Figure: Compartmental description of the SI model

Susceptible-Infected-Susceptible (SIS) Model:

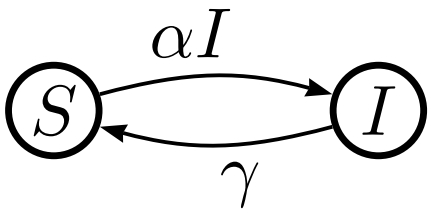


Figure: Compartmental description of the SIS model

Epidemiological modeling

(continued)

Susceptible-Infected-Recovered (SIR) Model:

The population is divided to three groups: $S(t)$: Susceptible, $I(t)$: Infected, $R(t)$: Recovered

$$S(t) + R(t) + I(t) = N \rightarrow \dot{S}(t) + \dot{R}(t) + \dot{I}(t) = 0$$

The following dynamics is proposed for the population:

$$\begin{cases} \dfrac{dS(t)}{dt} = -\alpha S(t).I(t) \\ \dfrac{dI(t)}{dt} = \alpha S(t) \cdot I(t) - \beta I(t) \\ \dfrac{dR(t)}{dt} = \beta I(t) \end{cases} \qquad (\dagger)$$

Epidemiological modeling

(continued)

SIR Model 1: Life-Time Immunity

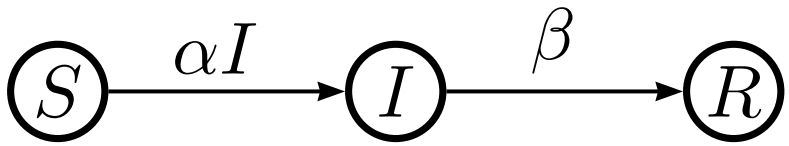


Figure: The SIR model providing life-time immunity

SIR Model 2: No Life-Time Immunity

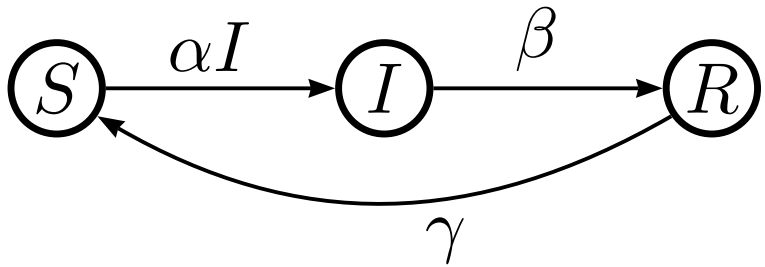


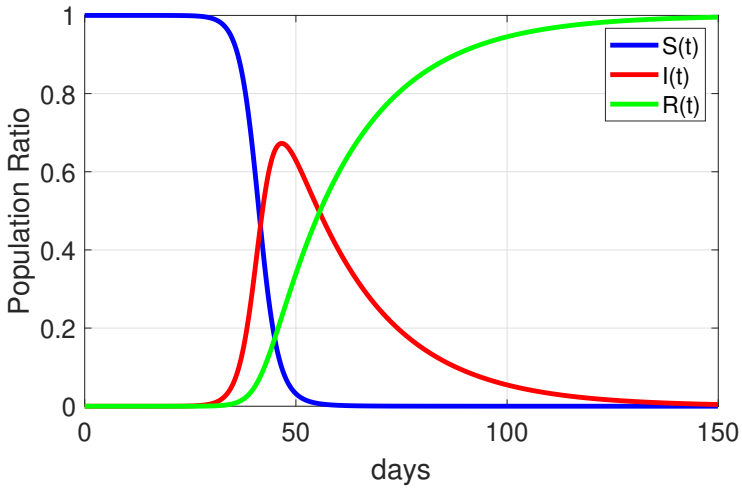
Figure: The SIR model without life-time immunity

Examples of compartmental models for contagious diseases

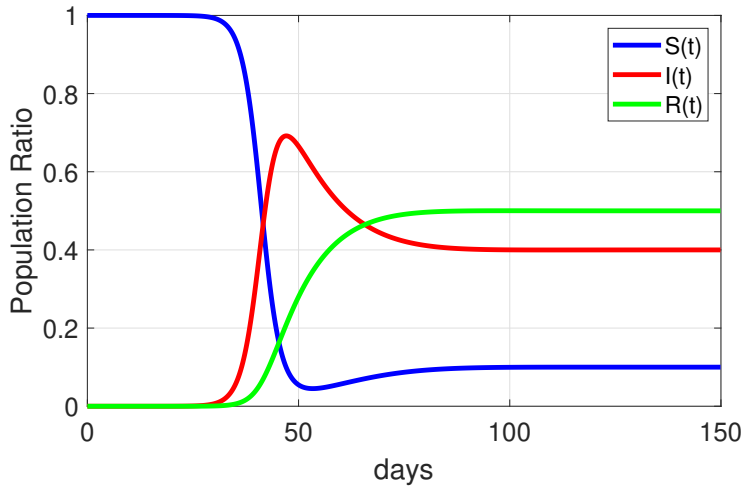
(continued)

Typical SIR solutions

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



(a) SIR model with immunity



(b) SIR model without immunity

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

Epidemiological modeling

(continued)

SIR Model 3: Endemic SIR

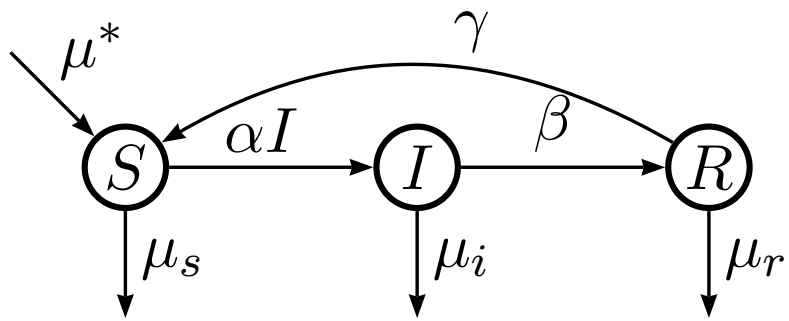


Figure: The endemic SIR model without life-time immunity

Epidemiological modeling

(continued)

Susceptible-Exposed-Infected-Recovered (SEIR)

Many infectious diseases are characterized by an incubation period between **exposure** to **clinical symptoms**. Subjects exposed to the infection are much more dangerous for the public as compared to the subjects showing clinical symptoms. For example, the HIV virus in its **clinical latency** stage. Cf. `https://www.aids.gov/hiv-aids-basics/`

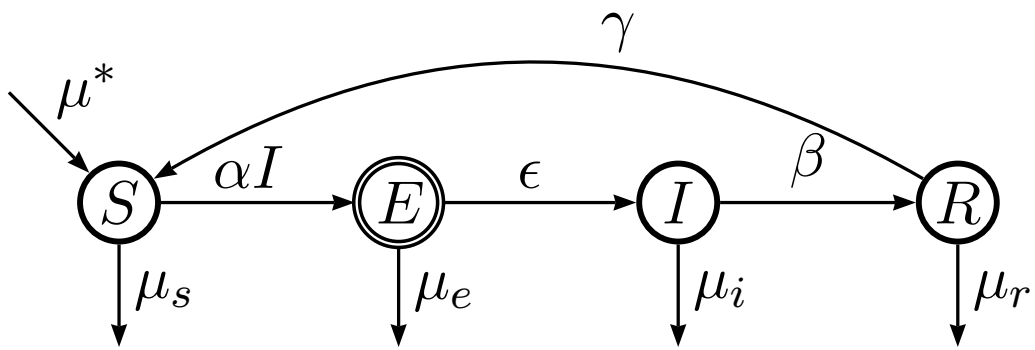


Figure: The endemic SEIR model without life-time immunity

Question: The prediction and control of the slope of $I(t)$ is a critical parameter of interest. Why? Discuss and simulate the impact of the model parameters on the slope of $I(t)$.

A macro-level model for the COVID-19 pandemic

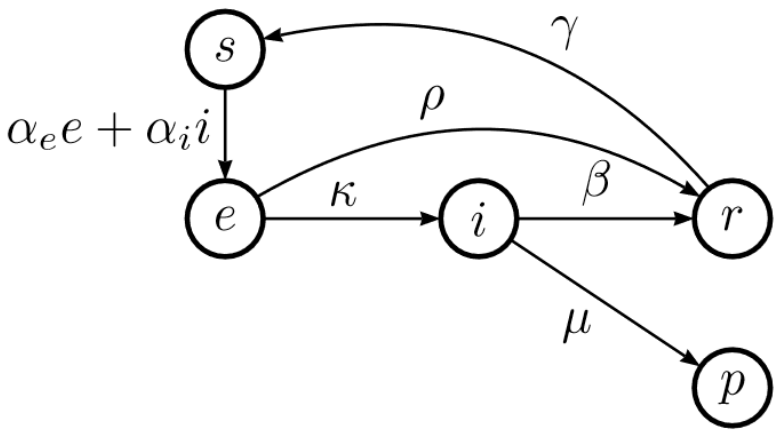
Assumptions and level of abstraction

- 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.)

A macro-level model for the COVID-19 pandemic

(continued)

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



$$\frac{ds(t)}{dt} = -\alpha_e s(t)e(t) - \alpha_i s(t)i(t) + \gamma r(t)$$

$$\frac{de(t)}{dt} = \alpha_e s(t)e(t) + \alpha_i s(t)i(t) - \kappa e(t) - \rho e(t)$$

$$\frac{di(t)}{dt} = \kappa e(t) - \beta i(t) - \mu i(t)$$

$$\frac{dr(t)}{dt} = \beta i(t) + \rho e(t) - \gamma r(t)$$

$$\frac{dp(t)}{dt} = \mu i(t)$$

A macro-level model for the COVID-19 pandemic

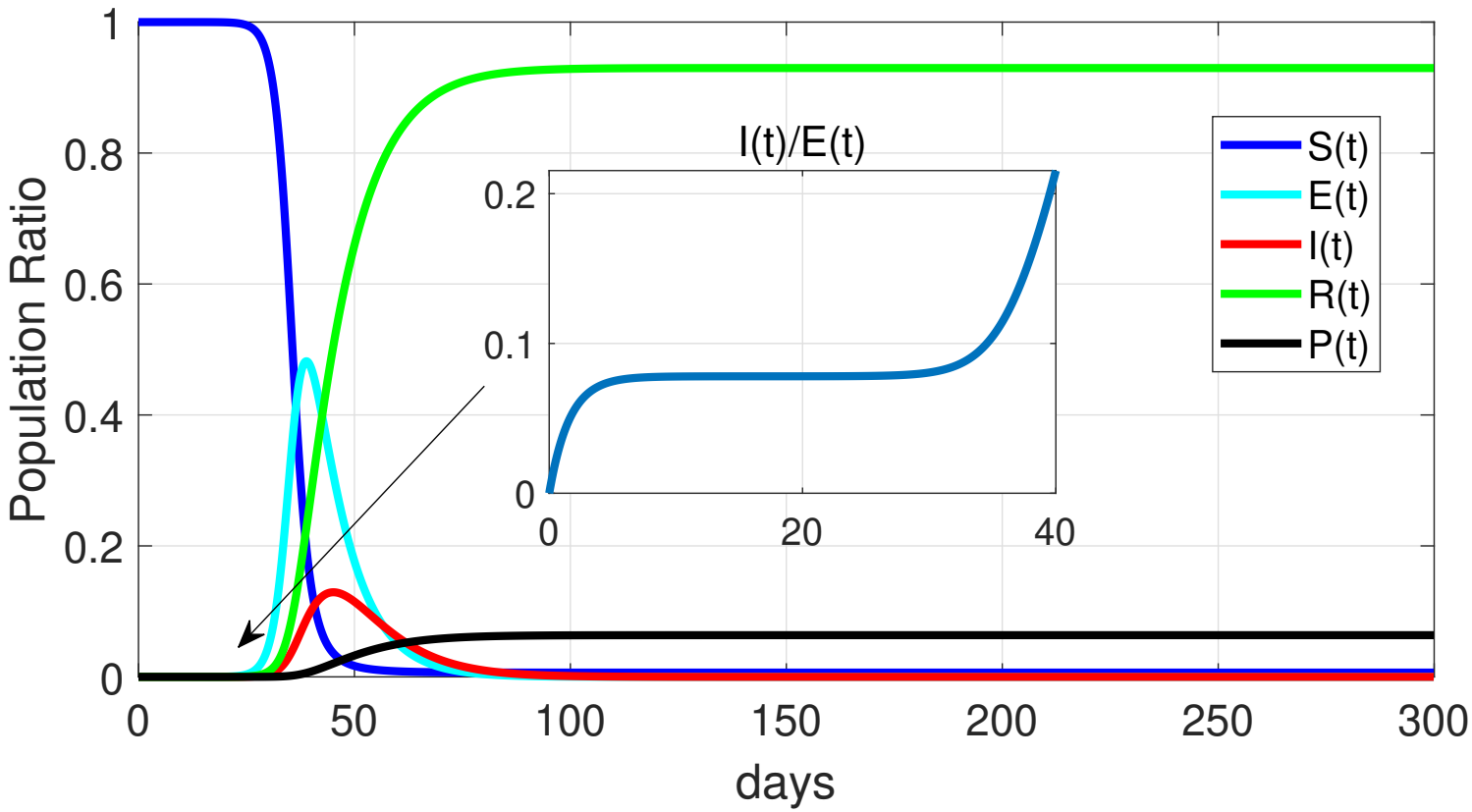
(continued)

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).

Typical solutions

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



Repeated pandemic waves

(continued)

Repeated waves of the disease

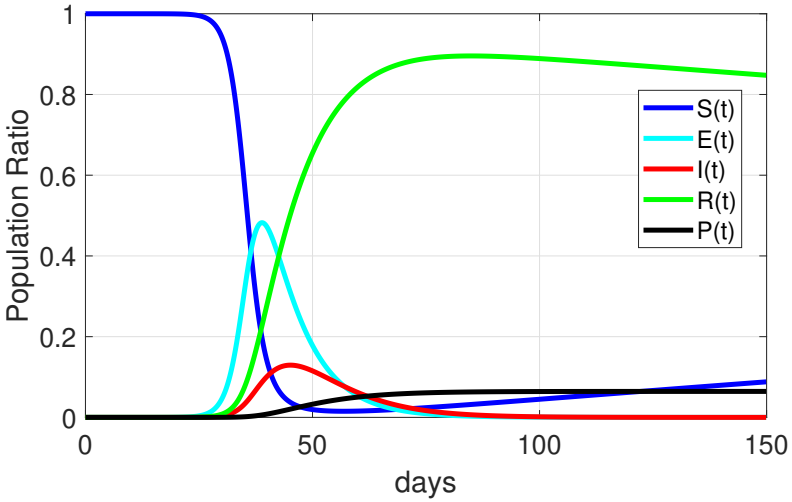
- The epidemic disease can repeat pseudo-periodically over time (in later seasons or years) and turn into a persistent disease in the long term. The amplitude and time gap of the infection peaks depends on the model parameters.
- **Example:** The 1918 Spanish flu, which had three pandemic waves.

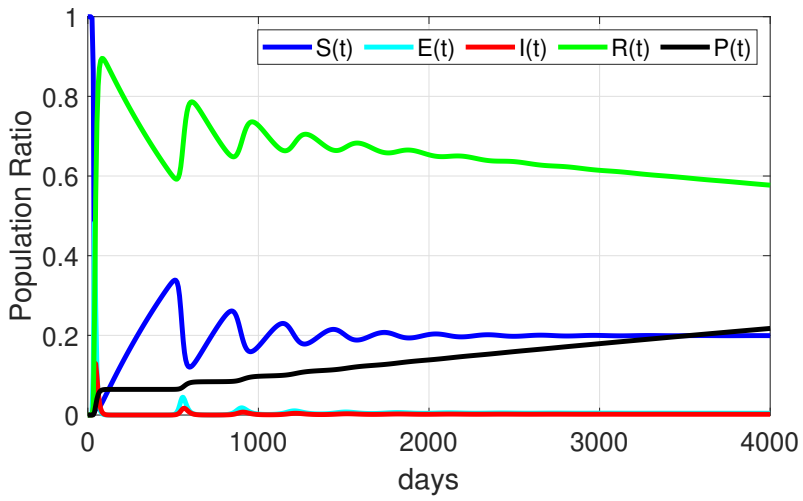
Note: In our model, the peaks can be found by finding the solutions of the model when $\frac{di(t)}{dt} = 0$ (the local infection peaks).

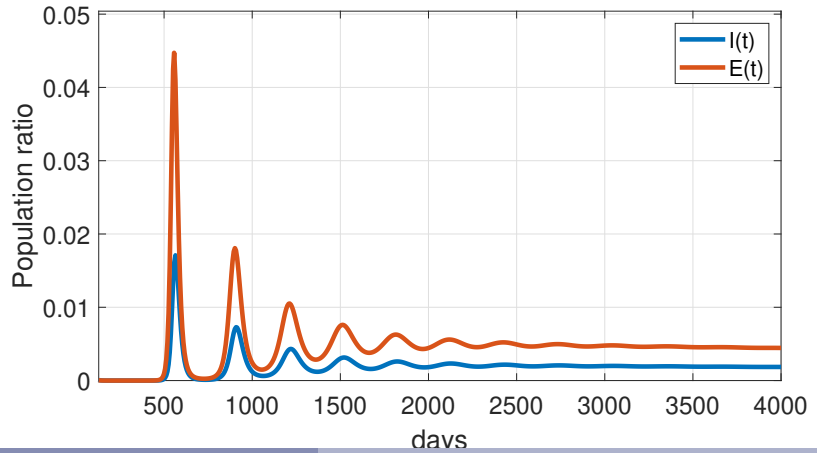
Repeated pandemic waves

(continued)

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

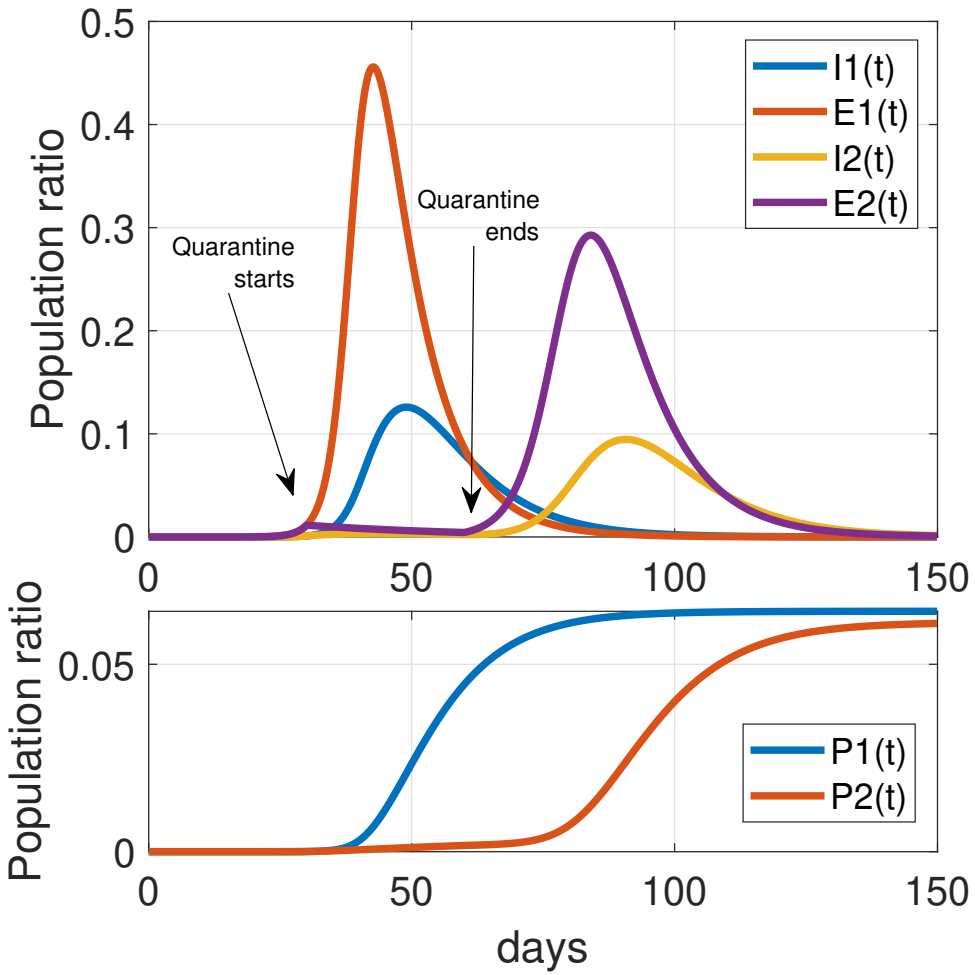






Impact of short quarantine periods

Short quarantine periods



Impact of short quarantine periods

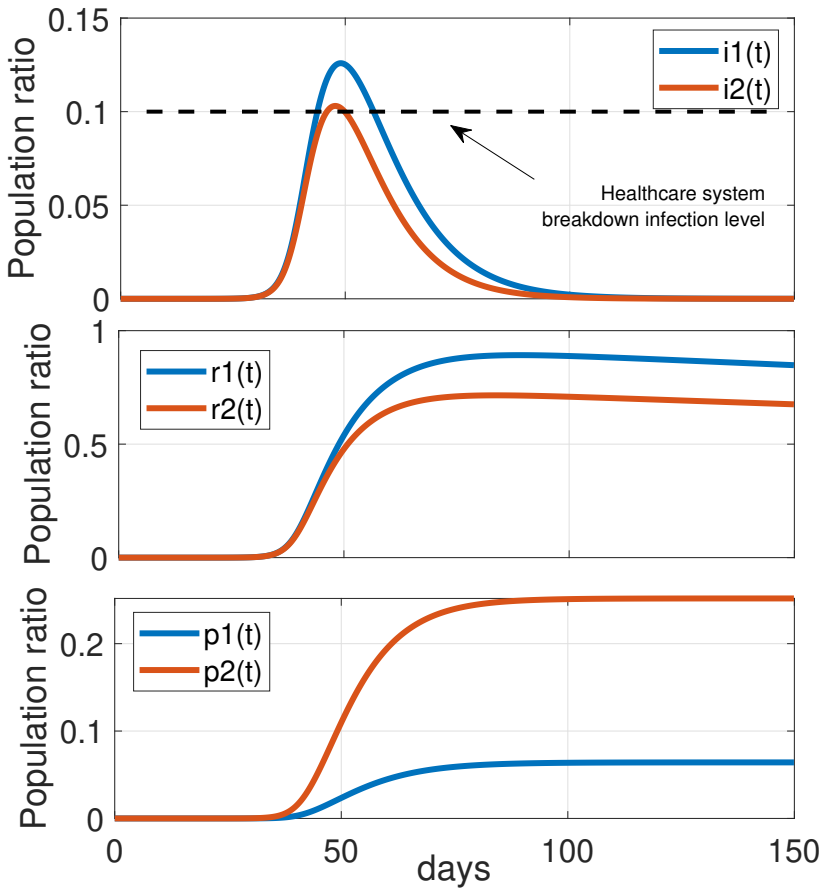
(continued)

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."

Healthcare system saturation

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

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

Healthcare system saturation

(continued)

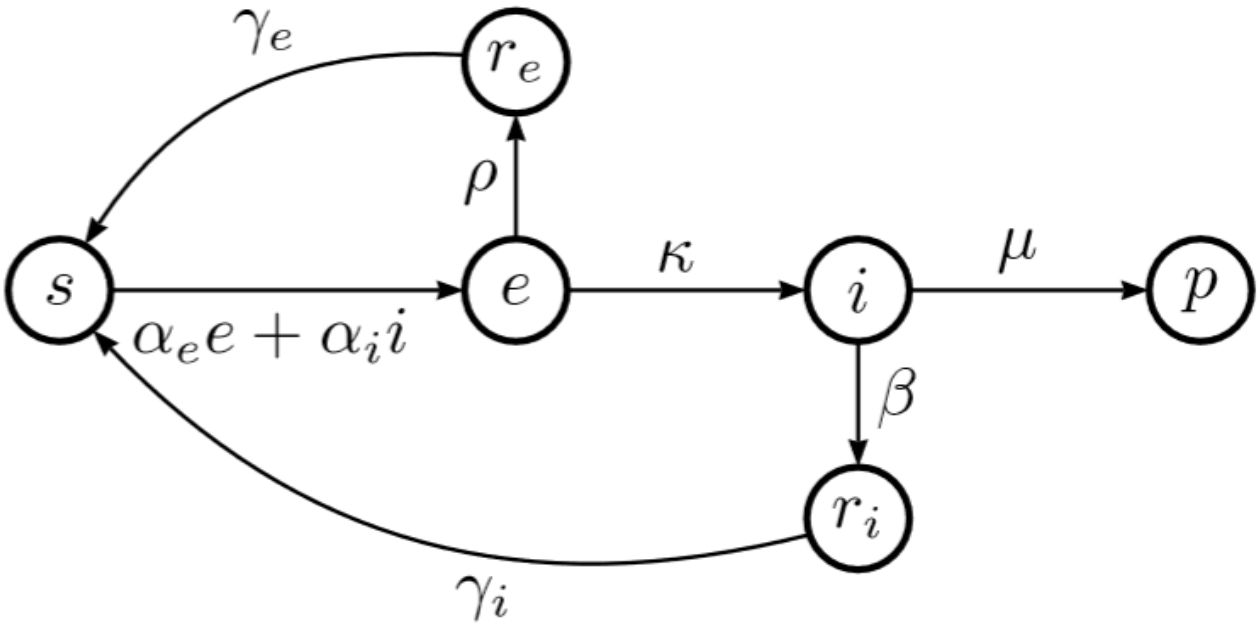
Result: healthcare system breakdown

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:



Epidemiological modeling

(continued)

Exercise 6:

1. a) Find the fixed-points of the SIR model (†) on Slide 120.
   b) Simplify the SIR model to a susceptible-infected model.
   c) Interpret the model in terms of a competitive growth model.
2. Former drug addicts are known to be more prone to addiction even after recovery. Propose a model for drug addiction in a community.

Further reading

Compartmental models specifically designed for COVID-19:

- Sameni, R. (2020). Mathematical modeling of epidemic diseases; a case study of the COVID-19 coronavirus.
  arXiv preprint
- Sameni, R. (2022). Model-based prediction and optimal control of pandemics by non-pharmaceutical interventions.
  IEEE Journal of Selected Topics in Signal Processing, 16(2), 307–317
- A lecture on mathematical modeling of epidemic diseases:
  `https://youtu.be/pasyQympFGE`

Research project ideas

(compartmental models)

Project Topic 1:

Propose a compartmental model for the life cycle of toxic material in nature.

Project Topic 2:

Propose a macroscopic compartmental model of the human body based on **ancient Iranian medicine**.

Research project ideas

(epidemic models)

Project Topic 3:

Extend the SIR epidemic model to the following cases (Chitnis, 2011):

- Mortal diseases plus natural birth/death conditions
- Diseases with different target groups (infants/adults/elderly, gender, etc.)
- SEIR model with stochastic uncertainties

Project Topic 4:

Using the SIR models, develop an **Extended Kalman Filter** for predicting epidemic disease propagation

Project Topic 5:

Use the SEIR prototype to develop a model for AIDS in a community with different target groups (infants/adults/elderly, gender, etc.).

Dimensional analysis

- Dimension analysis is a method for finding the relationship between the variables of a model
- Although, dimension analysis alone does not give the exact form of a model, but it can help with the construction, modification and reduction of the number of model variables
- It is based on three assumptions:
  1. Physical quantities always have dimensions, e.g., mass (M), length (L), time (T), etc.
  2. Any physical model (including biological systems) should be consistent in dimensions (**dimension consistency**)
  3. Physical laws (biological models in our context) should not alter when changing the units measuring the dimensions (**dimensional homogeneity**)

In some domains of science and engineering, dimensionless models are used, which is beyond the scope of the current course; cf. Szirtes (2007)

Basic rules of dimension analysis I

1. The dimension of the physical quantity x is denoted $[x] = X$
2. Addition $(+)$, subtraction $(-)$, and equality $(=)$ operators are only applicable to quantities of the same dimension:

$$[x \pm y] = [x] = [y] = X$$

3. In multiplication $(\times)$ and division $(/)$, we have:

$$[x \cdot y] = X \cdot Y \qquad [x/y] = X/Y$$

4. Depending on the context, any physical quantity has a dimension that is a product of powers of a set of **fundamental dimensions**, such as M, L, T, etc.
5. A system's input and output may differ in dimensions.

Basic rules of dimension analysis II

6. Although theoretically, the order of cascade LTI systems may be interchanged, dimension mismatch may not permit this interchange in reality. For example, two LTI systems that map pressure to voltage, and voltage to displacement may not be interchanged.
7. Time-domain sampling does not alter a signals dimensions; but special care must be taken in discretizing continuous-time systems.
8. Both arguments and values of mathematical functions such as $\sin(\cdot)$, $\cos(\cdot)$, $\exp(\cdot)$, $\log(\cdot)$, etc. are dimensionless.

Dimension analysis

(continued)

Example (Vas, 2014)

The equation $t = \sqrt{2d/g}$ that describes the time a body falls from a distance d under gravity (g) holds in all systems, whereas the equation $t = \sqrt{d/16.1}$ is not dimensionally homogeneous because it depends on a particular systems (units of g are neglected so the units of the left and the right side of the equation do not match).

Sinusoidal voltages, currents, motion, etc.

In $x(t) = 2\sin(\omega t)$, '2' is not just a scalar. It has the same dimension as x.

Dimension analysis

(continued)

Some basic physical dimensions

Mass	M	Angular acceleration	T^{-2}
Length	L	Momentum	MLT^{-1}
Time	T	Angular momentum	ML^2T^{-1}
Velocity	LT^{-1}	Density	ML^{-3}
Acceleration	LT^{-2}	Viscosity	$ML^{-1}T^{-1}$
Force	MLT^{-2}	Pressure	$ML^{-1}T^{-2}$
Energy, work, heat, torque, entropy	ML^2T^{-2}	Surface tension	MT^{-2}
Frequency, angular velocity	T^{-1}	Power	ML^2T^{-3}

Dimension analysis in mathematical modeling and physical equations

Case studies

Fisher discrimination ratio (FDR)

$$FDR = (x - m_x)(y - m_y)/(\sigma_x \sigma_y)$$

Dimension: $[x] \cdot [y] \,/\, [x] \cdot [y] \Rightarrow$ is dimensionless

The Fourier transform

$$X(f) = \int_{-\infty}^{\infty} x(t) \exp(-j2\pi ft) dt$$

dimension: $[x] \cdot T = [x] \,/ Hz$: density per Hz

Dimension analysis in mathematical modeling and physical equations
(case studies, continued)

The Dirac delta function

$$\delta(t), where \int_{-\infty}^{\infty} \delta(t)dt = 1$$

Dimension: $[\delta(t)] \cdot T = 1 \Rightarrow [\delta(t)] = 1/T = Hz$

The Kronecker delta function $\delta[n]$ is dimensionless

Deterministic discrete-time auto-correlation function

$$R_x[n] = E\{x[n]x^*[n+m]\} = \sum x[n]x^*[n+m]$$

Dimension: $[R_x[n]] = [x]^2$

Dimension analysis in mathematical modeling and physical equations
(case studies, continued)

Deterministic continuous-time auto-correlation function

$$R_x(\tau) = \int x(t)x^*(t+\tau)d\tau$$

Dimension: $[R_x(\tau)] = [x]^2 \cdot T$

Power density function

$$S_x(f) = \int_{-\infty}^{\infty} R_x(\tau)\exp(-j2\pi f\tau)d\tau$$

Dimension: $[S_x(f)] = [x]^2 . T^2 = [x]^2 \cdot T/Hz \Rightarrow$ power density per Hz

Dimension analysis in mathematical modeling and physical equations
(case studies, continued)

Discrete probability density function (pdf)

$$P_X(x), \text{such that } \sum_i P_X(x_i) = 1$$

Dimension: The discrete pdf is dimensionless

Continuous pdf

$$f_X(x), \text{such that } \int_{-\infty}^{\infty} f_X(x)dx = 1$$

Dimension: The continuous pdf has a density of $1/[x]$ or $1/X$

Dimension analysis in mathematical modeling and physical equations
(case studies, continued)

Entropy

$$H(X) = -\sum_i P_X(x_i) \log_2(P_X(x_i))$$

Dimension: $H(X)$ is dimensionless

Differential Entropy (continuous probability density function)

$$h(X) = -\int_{-\infty}^{\infty} f_X(x) \log(f_X(x)) dx$$

Dimension: $h(X)$ is dimensionally inconsistent and problematic in practice (we can't take the logarithm of $f_X(x)$ for variables with dimensions). The **Kullback–Leibler** divergence is an alternative, which can solve the dimension issue by using ratios of probability density functions as the $\log(\cdot)$ argument.

Dimension analysis in mathematical modeling and physical equations

Corrected QT interval formulas (QTc)

$$\text{Bazett's formula:} \quad QT_c = \frac{QT}{\sqrt{RR}}$$

$$\text{Fredericia's formula:} \quad QT_f = \frac{QT}{\sqrt[3]{RR}}$$

- Both forms are dimensionally inconsistent (they are only valid in certain time scales)
- In Bazett's formula, when the QT and RR-intervals are in millimeters (on standard ECG paper), the ECG must be recorded at a speed of 25mm/sec.
- Normal values of QT_c have been reported to be between 300 and 450. At longer QT-intervals, the patient is at risk for *torsade de pointes*.

Refs:

- Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920; 7: 353-370.
- Jackman WM, Friday KJ, Anderson JL, et al. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis.* 1988; 31: 115-172.

Further examples

Exercise (Optional): Study the dimensions of the following physical laws:

- Ohm's law: $V_r = RI_r$
- Linear capacitor's current-voltage relationship: $i_c(t) = C\frac{dv_c(t)}{dt}$
- Linear coil's current-voltage relationship: $v_l(t) = L\frac{di_l(t)}{dt}$
- Mass–energy equivalence: $E = mc^2$
- Newton's law of motion: $F = ma$
- Fick's first law of diffusion: $J = -D\frac{d\varphi}{dx}$ (J is diffusion flux; D is the diffusion coefficient; φ is concentration; x is position)
- Coulomb's law: $\mathbf{F} = k_e\frac{|q_1 q_2|}{r^2}$
- Newton's law of universal gravitation: $F = G\frac{m_1 m_2}{r^2}$
- Time dilation (General Relativity): $\Delta t' = \dfrac{\Delta t}{\sqrt{1 - \frac{v^2}{c^2}}}$

Model construction by dimension analysis

Dimensionality as a modeling tool

- Dimension analysis is also used as a modeling methodology (Szirtes, 2007, Ch. 17)
- Dimension analysis can be used to reject/correct models with inconsistent dimensions
- It can also be used to guess "potentially correct" models
- **Note:** Dimension analysis does not independently prove the correctness of models. Data/measurements are required to validate models.

Dimensionality as a modeling tool

Example: falling particle velocity (Vas, 2014)

Objective: propose a model to describe the terminal velocity of a particle that falls under gravity through a viscous fluid.

Relevant variables:

v: particle velocity (LT^{-1})

D: particle diameter (L)

g: gravitational acceleration (LT^{-2})

μ: fluid viscosity $(ML^{-1}T^{-1})$

$\rho_1 - \rho_2$: difference between the particle and fluid densities (ML^{-3})

Generic model: $v = kD^a\mu^b g^c(\rho_1 - \rho_2)$ (k is a dimentionless scalar)

Equating the exponents of M, L and T on both sides:

$$\begin{aligned} 0 &= b + 1 \\ 1 &= a - b + c - 3 \\ -1 &= -b - 2c \end{aligned}$$

which gives $a = 2$, $b = -1$, and $c = 1$. Hence $v = \dfrac{kD^2 g(\rho_1 - \rho_2)}{\mu}$

Dimensionality as a modeling tool

(continued)

Example: period of a swinging pendulum (Vas, 2014)

Objective: propose a model for describing the period of a swinging pendulum.

Relevant variables:

- t: swing period (T)
- l: pendulum length (L)
- m: pendulum mass (M)
- g: gravitational acceleration (LT^{-2})
- θ: swing angle (dimensionless)

Generic model: $t = kl^a m^b g^c \theta^d$ (k is a dimentionless const.)

Equating the exponents of M, L and T on both sides gives: $t = kl^{1/2} g^{-1/2} \theta^d$

Further information (e.g. by measurement) is required to to fix d and k.

Question: How good is this model? Measurements will judge!

Dimensionality as a modeling tool

(continued)

Example: Period of a swinging pendulum with air resistance (Vas, 2014)

Objective: Modify the previous model by incorporating the air resistance R (MLT^{-2}) effect

Generic model: $t = kl^a m^b g^c \theta^d R^e$ (k is a dimentionless const.)

Equating the exponents of M, L and T on both sides, yields: $b + e = 0$, $a + c + e = 0$, and $-2c - 2e = 1$. This time we only have three equations and five variables. The model can be solved, leaving two *degrees of freedom* (DoF).

- Setting b and d as the DoF: $t = k \left(\frac{l}{g}\right)^{1/2} \left(\frac{mg}{R}\right)^b \theta^d$
- Setting c and d as the DoF: $t = k \left(\frac{lm}{R}\right)^{1/2} \left(\frac{mg}{R}\right)^c \theta^d$

which are both dimensionally correct. Further information (e.g. measurements) are needed to select the true model.

Dimensionality as a modeling tool

(continued)

Dimensional analysis does not necessarily approve a model; but it can be used to verify the physical consistency of a model (as a necessary condition), and propose "potentially correct" models.
For a detailed study of dimensional modeling, see (Szirtes, 2007, Ch. 17).

Exercise 7:

1. Propose a model determining the terminal velocity of a raindrop falling from a stationary cloud.
2. Propose a model for the volume flow rate $\frac{dV}{dt}$ of blood flowing in an artery as a function of the pressure P drop per unit length of artery, the radius r, the blood density ρ and the blood viscosity μ.

System analogy I

(continued)

- The mathematical laws of real-world systems are highly analogical
- These analogies result in rather similar dynamical equations among these systems
- The analogy between two systems can be used to model a given system with its **dual system**. For example, mechanical, physiological or chemical systems may be modeled by their electrical dual systems

System analogy II

(continued)

Electrical vs. mechanical analogy

The generic second order differential equation:

$$\frac{d^2x(t)}{dt^2} + 2\alpha\omega_0\frac{dx(t)}{dt} + \omega_0^2 x(t) = 0, \quad x(t_0) = c_0, \dot{x}(t_0) = c_1$$

can be used for both electrical and mechanical systems. The generic solution of this equation appears in both domains. These solutions can be mapped to one another by selecting a proper scaling factor, which converts electrical variables and parameters to mechanical and vice versa.

System analogy III

(continued)

Method:

1. Write the governing mathematical equations of the original and its dual systems
2. Equate the dual variables and parameters of the two systems
3. Analyze/solve the dual system and extend its results to the original system by analogy (using proper scaling factors)

Electro-mechanical analogy

Analogous quantities

Electrical quantity	Force-current analogy	Force-voltage analogy
Voltage, e	Velocity, v	Force, f
Current, i	Force, f	Velocity, v
Resistance, R	Lubricity, $1/B$	Friction, B
Capacitance, C	Mass, M	Compliance (Inverse spring constant), $1/K$
Inductance, L	Compliance, $1/K$	Mass, M
Transformer, $N_1 : N_2$	Lever, $L_1 : L_2$	Lever, $L_1 : L_2$

Electro-mechanical analogy

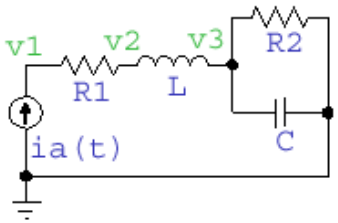
(continued)

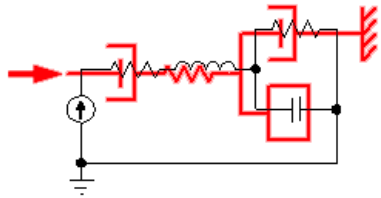
Electrical equation	Force-current analogy	Force-voltage analogy
$e = Ri$	$v = \frac{f}{B}$	$f = vB$
$e = L\frac{di}{dt}$	$v = \frac{1}{K}\frac{df}{dt}$	$f = M\frac{dv}{dt} = Ma$
$e = \frac{1}{C}\int idt$	$v = \frac{1}{M}\int fdt$	$f = K\int vdt = Kx$
$Power = e \cdot i$	$Power = v \cdot f$	$Power = f \cdot v$
$\frac{e_1}{e_2} = \frac{i_2}{i_1} = \frac{N_1}{N_2}$	$\frac{v_1}{v_2} = \frac{f_2}{f_1} = \frac{L_1}{L_2}$	$\frac{f_1}{f_2} = \frac{v_2}{v_1} = \frac{L_2}{L_1}$
$E_{capacitor} = \frac{1}{2}Ce^2$	$E_{mass} = \frac{1}{2}Mv^2$	$E_{spring} = \frac{1}{2}Kx^2$
$E_{inductor} = \frac{1}{2}Li^2$	$E_{spring} = \frac{1}{2}Kx^2$	$E_{mass} = \frac{1}{2}Mv^2$
$\sum_{node} Currents = 0$	$\sum_{object} Forces = 0$	$\sum_{loop} Velocities = 0$
$\sum_{loop} Voltages = 0$	$\sum_{loop} Velocities = 0$	$\sum_{object} Forces = 0$

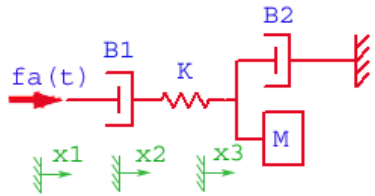
Electro-mechanical analogy

(continued)

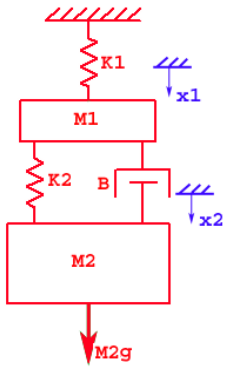
Electrical to mechanical

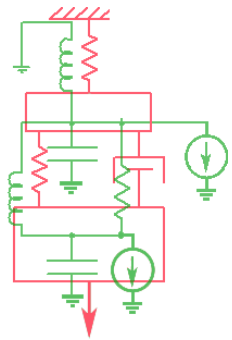


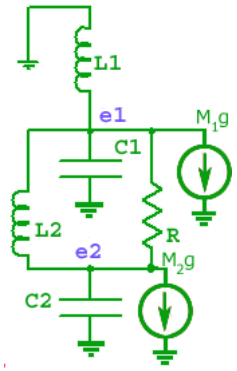




Mechanical to electrical







Adopted from: `lpsa.swarthmore.edu/Analogs/ElectricalMechanicalAnalogs.html`

Physical system analogy

Topology-Preserving Set (book's analogy)					Intuitive Analogy Set			
	⇔ intuitive stretch				⇔ topology change			
Description	Trans Mech	Rot Mech	Electrical	Thermal	Fluid	Trans Mech	Rot Mech	Description
"through" variable	f (force)	τ (torque)	i (current)	ϕ (heat flux)	q (flow)	v (velocity)	ω (angular velocity)	Motion
"across" variable	v (velocity)	ω (angular velocity)	v (voltage)	T, θ (temperature)	p (pressure)	f (force)	τ (torque)	Push (force)
Dissipative element	$v = \frac{1}{B} f$	$\omega = \frac{1}{B_r} \tau$	$v = iR$	$\theta = \phi R$	$p = qR$	$f = vB$	$\tau = \omega B_r$	Dissipative element
Dissipation	$f^2 \frac{1}{B} = \frac{v^2}{1/B}$	$\tau^2 \frac{1}{B} = \frac{\omega^2}{1/B}$	$i^2R = v^2/R$	N/A	$q^2R = p^2/R$	$v^2B = f^2/B$	$\omega^2 B_r = \tau^2/B_r$	Dissipation
Through-variable storage element	$v = \frac{1}{K} \frac{df}{dt}$ or $\int v dt = \frac{1}{K} f$	$\omega = \frac{1}{K_r} \frac{d\tau}{dt}$ or $\int \omega dt = \frac{1}{K_r} \tau$	$v = L \frac{di}{dt}$	N/A	$p = I \frac{dq}{dt}$	$f = M \frac{dv}{dt}$ (one end must be "grounded")	$\tau = J \frac{d\omega}{dt}$ (one end must be "grounded")	Motion storage element
Energy	$E = \frac{1}{2} \frac{1}{K} f^2$	$E = \frac{1}{2} \frac{1}{K_r} \tau^2$	$E = ½Li^2$		$E = ½Iq^2$	$E = ½Mv^2$	$E = ½J\omega^2$	Energy
Impedance	Standard definition is at right		$V(s)=I(s)Ls$		$P(s) = Q(s)Is$	$F(s) = V(s)Ms$	$T(s) = \Omega(s)Js$	Impedance
Across-variable storage element	$f = M \frac{dv}{dt}$ (one end must be "grounded")	$\tau = J \frac{d\omega}{dt}$	$i = C \frac{dv}{dt}$	$\phi = C \frac{d\theta}{dt}$ (one end must be "grounded")	$q = C \frac{dp}{dt}$ (one end usually "grounded")	$v = \frac{1}{K} \frac{df}{dt}$ or $\int v dt = \frac{1}{K} f$	$\omega = \frac{1}{K_r} \frac{d\tau}{dt}$ or $\int \omega dt = \frac{1}{K_r} \tau$	Push (force) storage element
Energy	$E = ½Mv^2$	$E = ½J\omega^2$	$E = ½Cv^2$	$E = CT$ (not analogous)	$E = ½C p^2$	$E = \frac{1}{2} \frac{1}{K} f^2$	$E = \frac{1}{2} \frac{1}{K_r} \tau^2$	Energy
Impedance	The standard definition of mechanical impedance is the one on the right, based on the intuitive analogy.		$V(s) = I(s) \frac{1}{sC}$	$\Theta(s) = \Phi(s) \frac{1}{sC}$	$P(s) = Q(s) \frac{1}{sC}$	$F(s) = V(s) \frac{K}{s}$	$T(s) = \Omega(s) \frac{K_r}{s}$	Impedance

Note: None of the across variables are written as, for example, $(\theta_1 - \theta_2) = \phi R$. That is because the variable *for a particular element* is implicitly the difference across it for any across variable.

Figure: General analogy between physical systems; adopted from Sullivan (2014)

Analogical modeling in biological systems

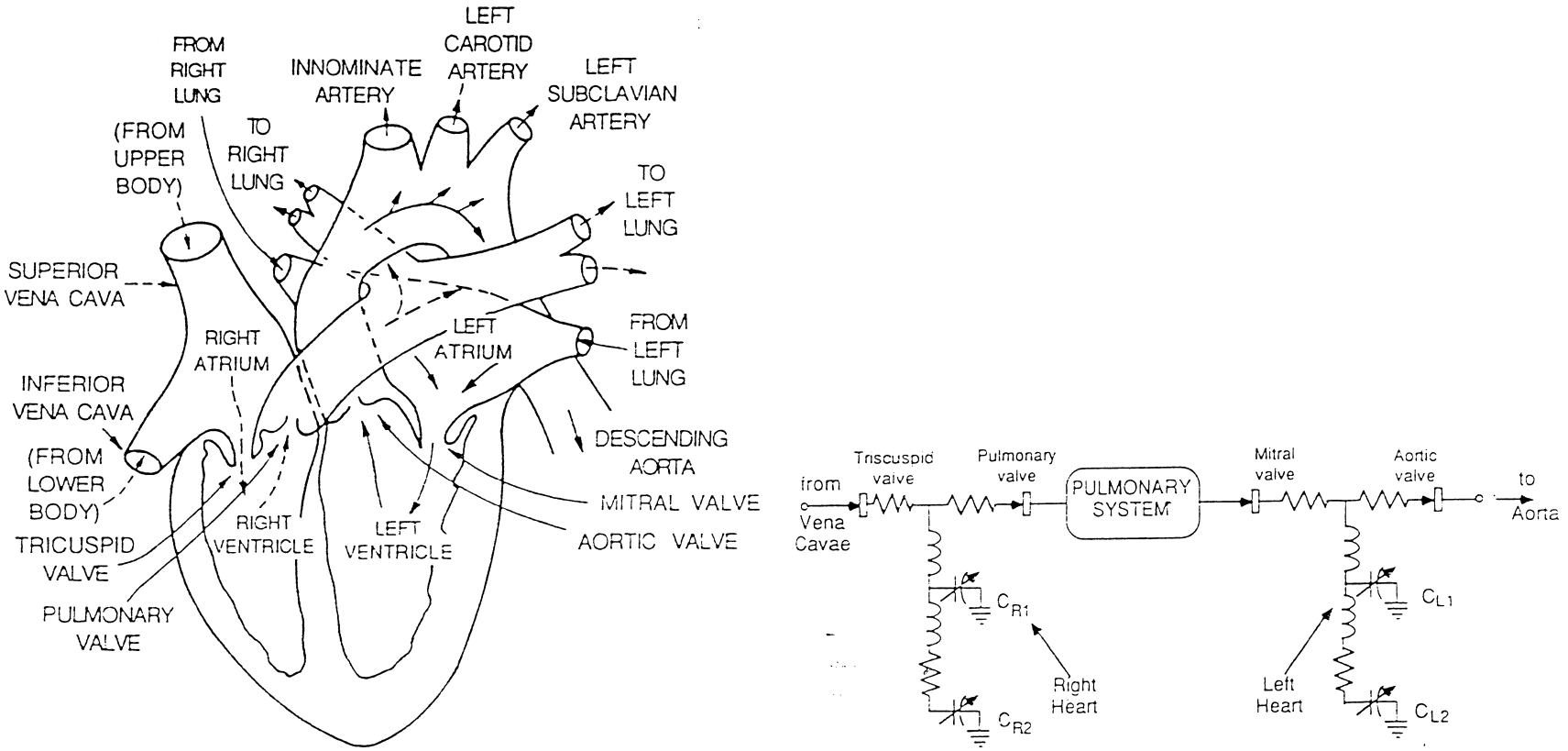


Figure: Analogy between cardiac and electrical systems; adopted from Rideout (1991)

Analogical modeling in biological systems

(continued)

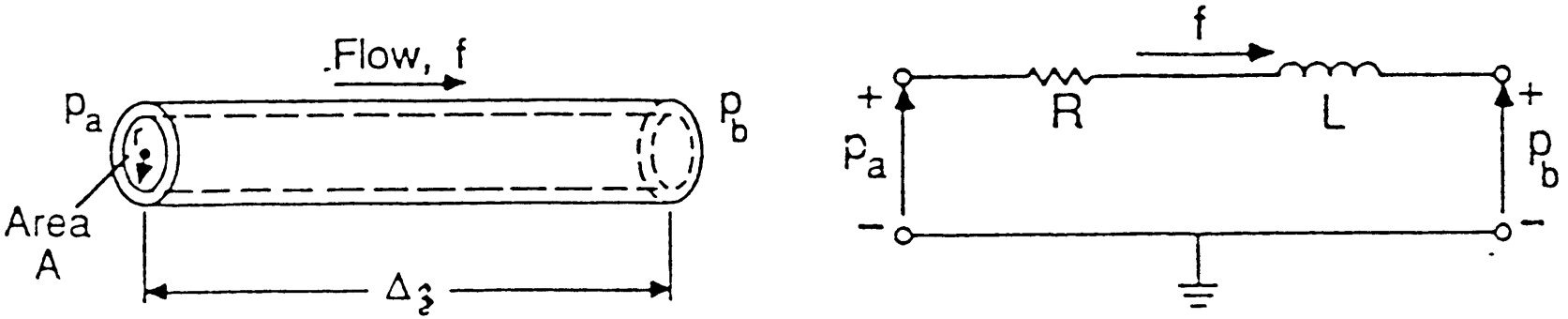


Figure: Idealized vein or artery model (vein wall compliance ignored); adopted from (Rideout, 1991, Ch. 4)

Analogical modeling in biological systems

(continued)

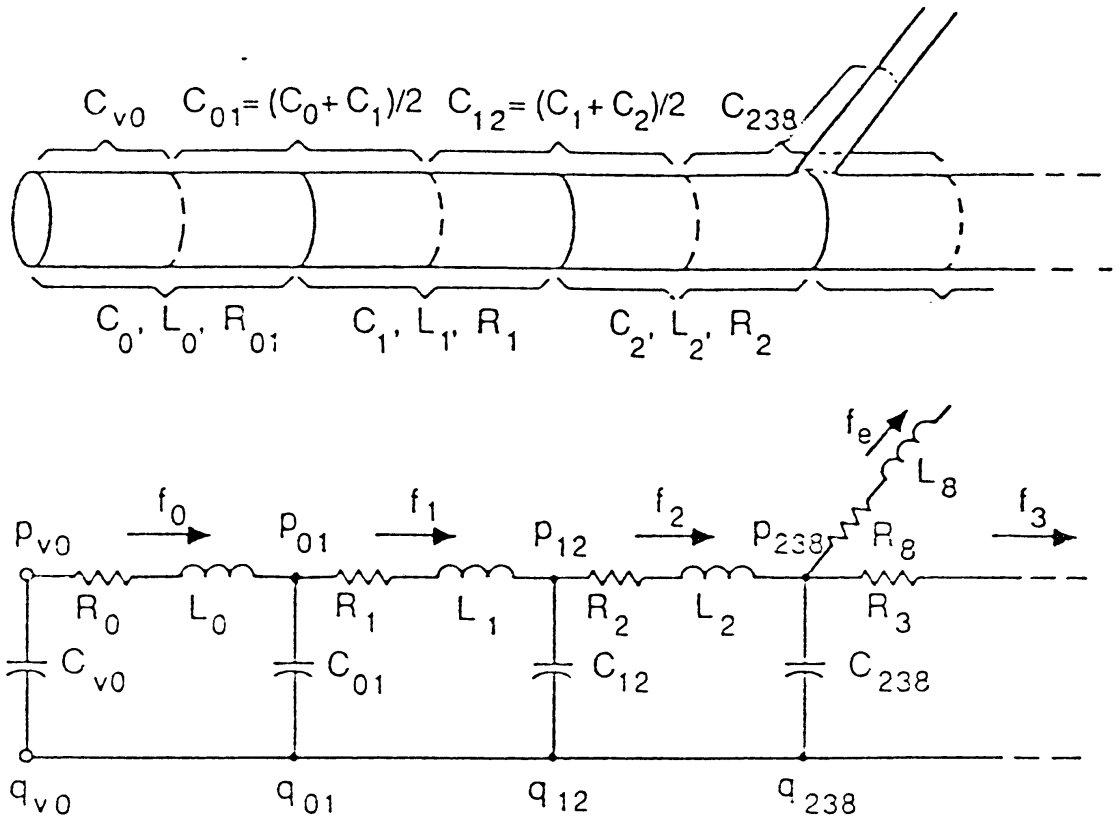


Figure: A portion of the aorta (vein wall compliance considered); adopted from (Rideout, 1991, Ch. 4)

Analogical modeling in biological systems

(continued)

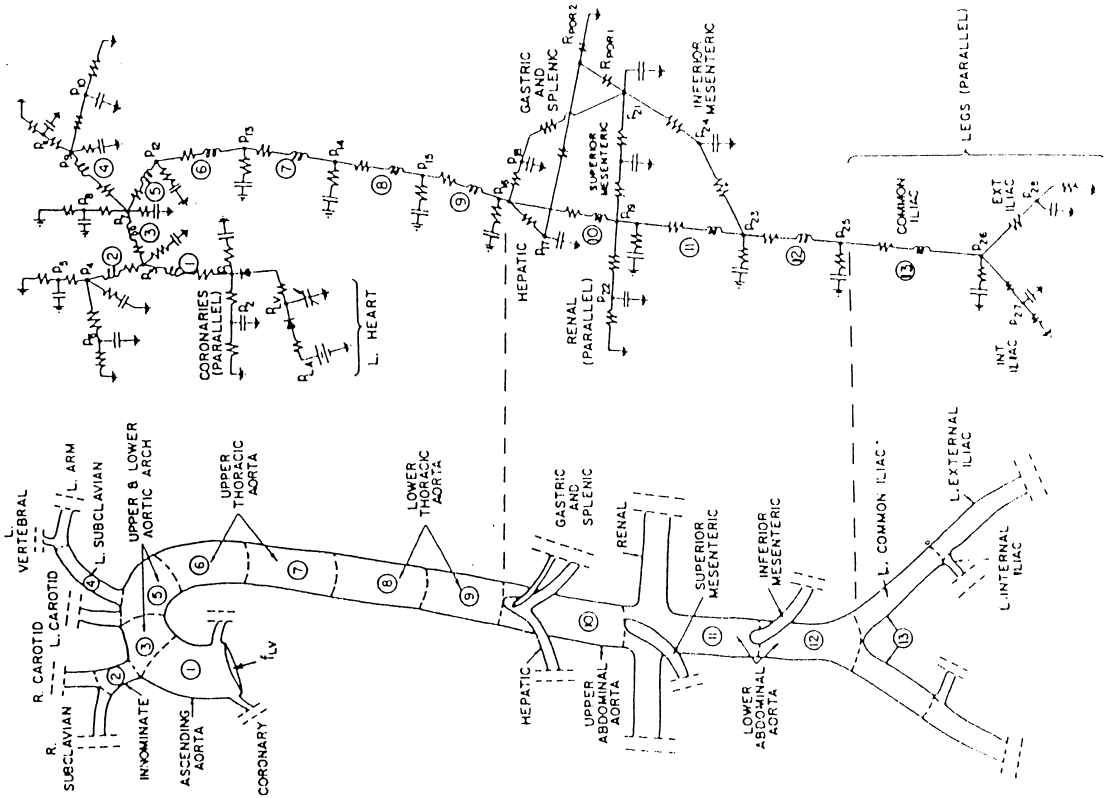
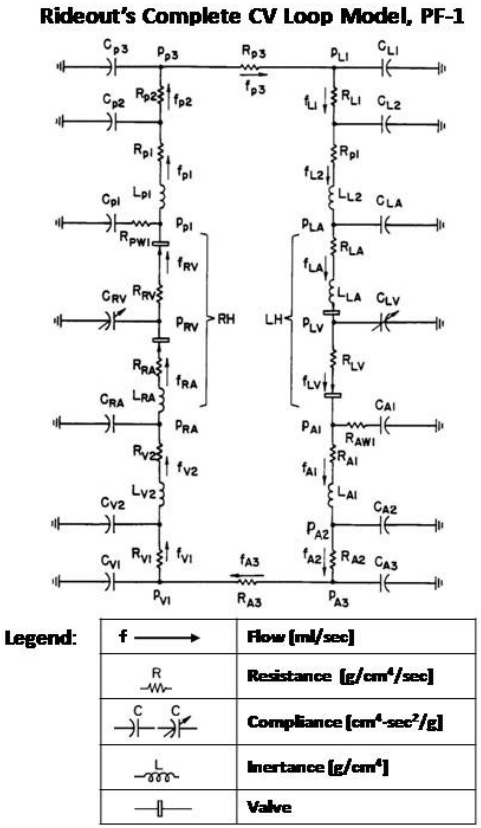


Figure: Analogy between cardiovascular and electrical systems; adopted from Rideout (1991)

Analogical modeling in biological systems

(continued)

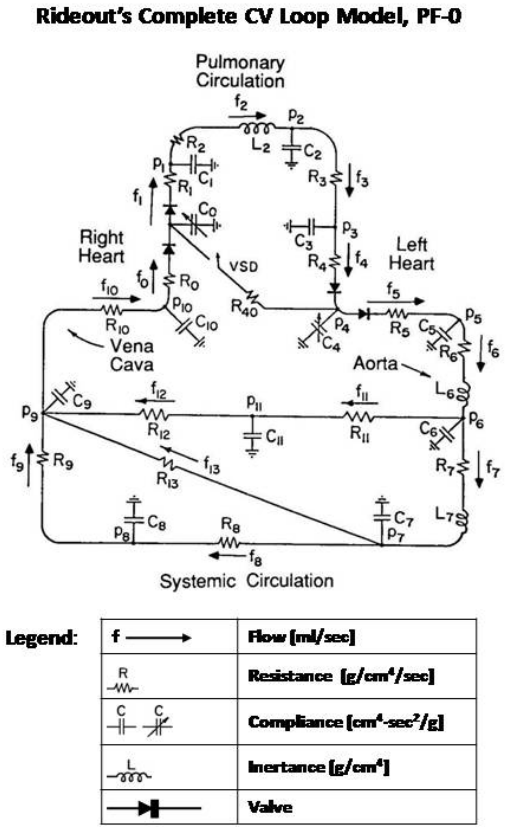


Parameter Values				
Suffix	Anatomy	R	L	C - 10^6
P1	Pulmonary Artery 1	10	1	100
P2	Pulmonary Artery 2	40		300
P3	Pulmonary Artery 3	80		2700
L1	Pulmonary Veins 1	30		1000
L2	Pulmonary Veins 2	10	1	1000
LA	Left Atrium	5	1	11760
LV	Left Ventricle	5	1	Variable
A1	Aorta 1	10	1	180
A2	Aorta 2	160		230
A3	Aorta 3	1000		1820
V1	Systemic Veins 1	90		21000
V2	Systemic Veins 2	10	1	45000
RA	Right Atrium	5	1	45000
RV	Right Ventricle	5	1	Variable

Figure: Rideout's complete non-pulsatile CV pressure-flow loop model 1; adopted from `http://www.physiome.org/`

Analogical modeling in biological systems

(continued)

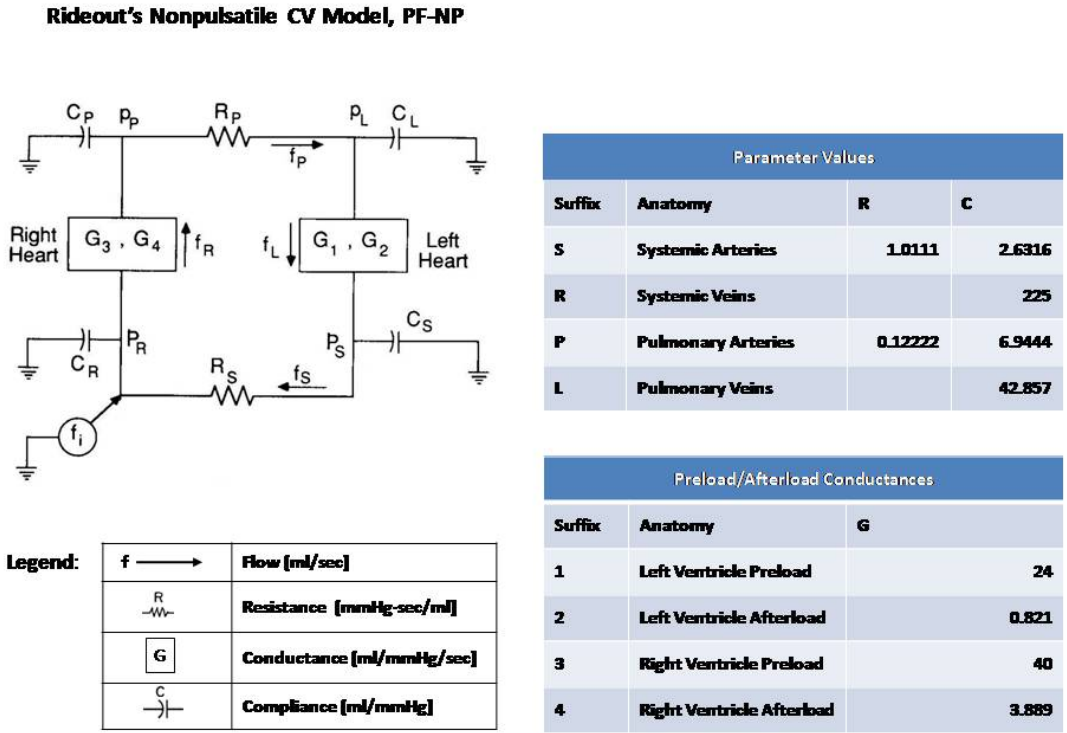


Parameter Values				
	Anatomy	R	L	C - 10^6
0	Right Ventricle	10		Variable
1	Pulmonary Artery	10		1001
2	Pulmonary Artery 2	27	1.332	3003
3	Lung Capillaries	150		5005
4	Left Ventricle	10		Variable
5	Ascending Aorta	13		501
6	Descending Aorta	7	1.332	1001
7	Abdominal Aorta	27	1.332	1336
8	Leg Arteries	5328		8314
9	Leg Veins	13		1001
10	Vena Cava	13		5005
11	Upper Body Arteries	1332		2002
12	Upper Body Veins	1332		
13	Internal Organ Veins	5328		
40	VSD	250		

Figure: Rideout's complete non-pulsatile CV pressure-flow loop model 2; adopted from `http://www.physiome.org/`

Analogical modeling in biological systems

(continued)



Parameter Values			
Suffix	Anatomy	R	C
S	Systemic Arteries	1.0111	2.6316
R	Systemic Veins		225
P	Pulmonary Arteries	0.12222	6.9444
L	Pulmonary Veins		42.857

Preload/Afterload Conductances		
Suffix	Anatomy	G
1	Left Ventricle Preload	24
2	Left Ventricle Afterload	0.821
3	Right Ventricle Preload	40
4	Right Ventricle Afterload	3.889

Figure: Rideout's complete non-pulsatile CV pressure-flow loop model 3; adopted from `http://www.physiome.org/`

Analogical modeling in biological systems

(continued)

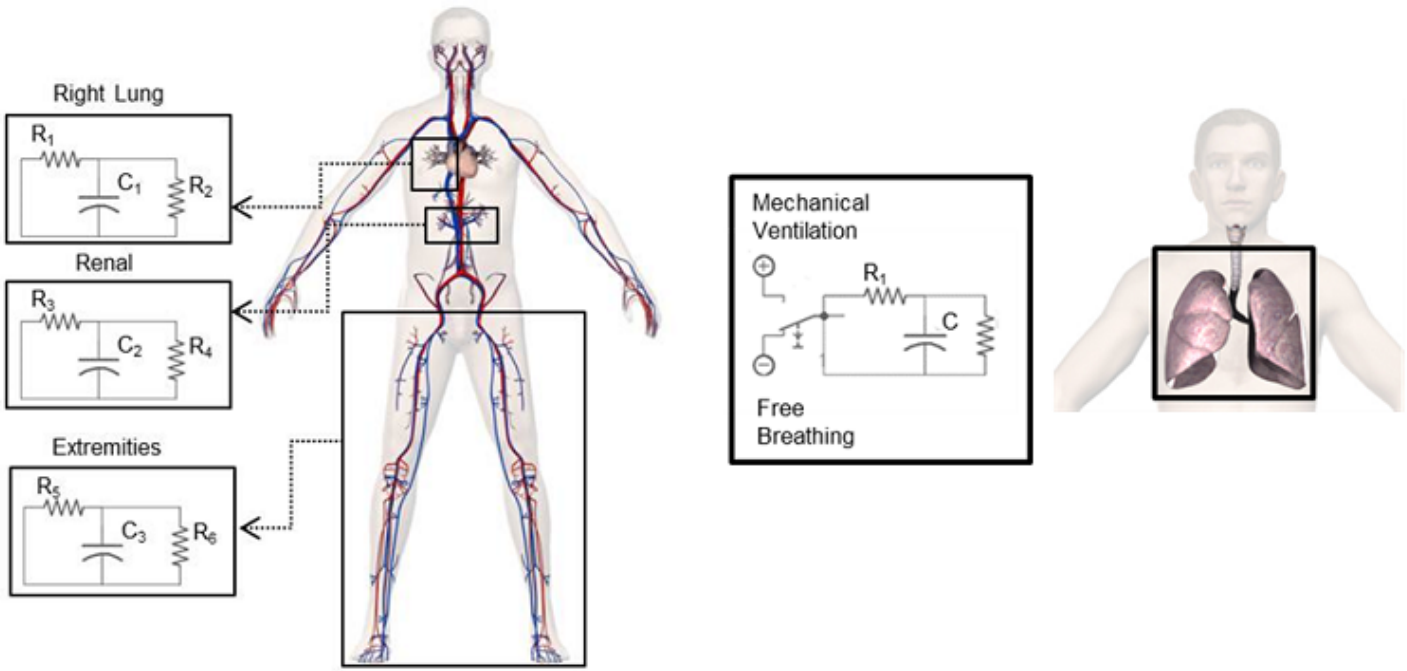


Figure: physiology lumped parameter modeling; adopted from `https://physiology.kitware.com/_circuit_methodology.html`

Analogical modeling in biological systems

(continued)

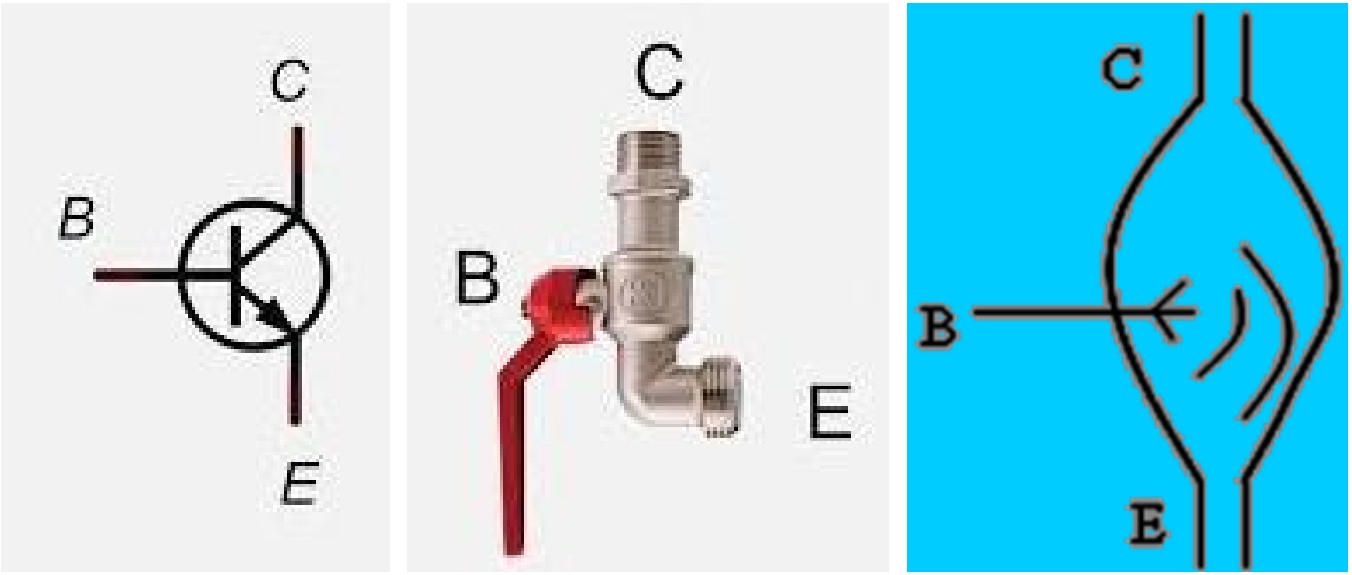


Figure: Transistor, Water-tap and muscle analogy

Analogical modeling in biological systems

(continued)

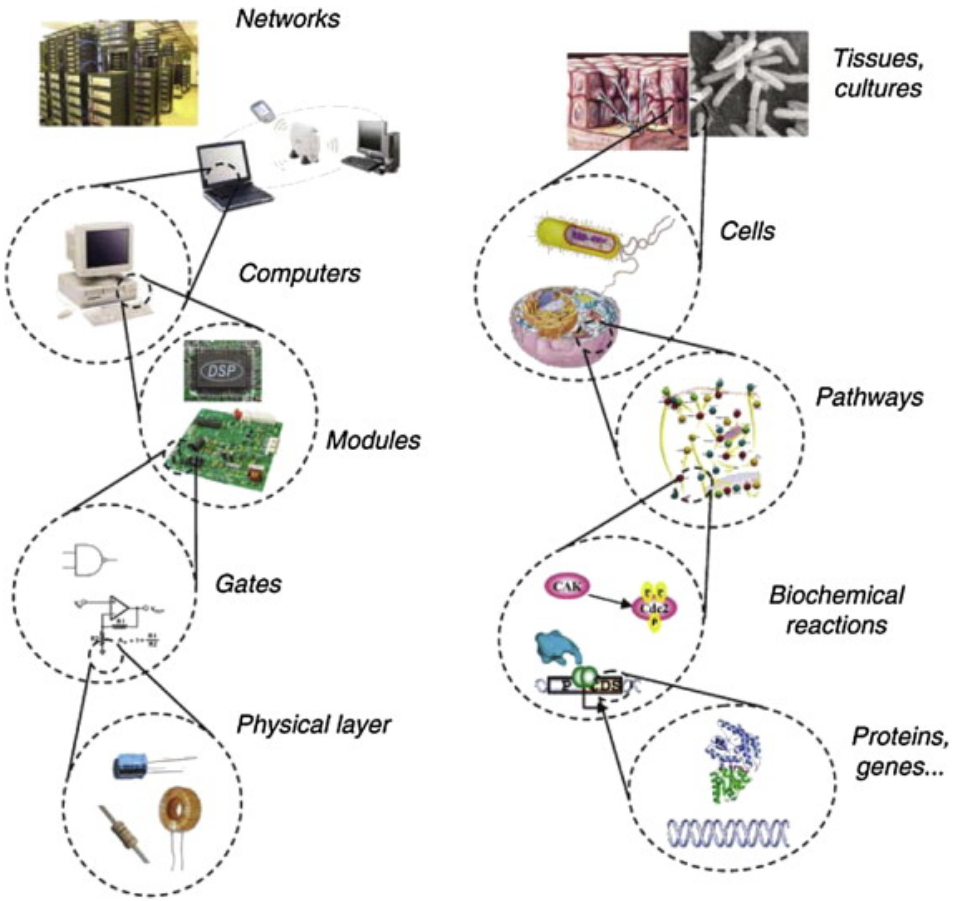


Figure: A conceptual analogy between the levels of organization of computing systems and biological systems (Andrianantoandro et al., 2006)

Analogical modeling in biological systems

(continued)

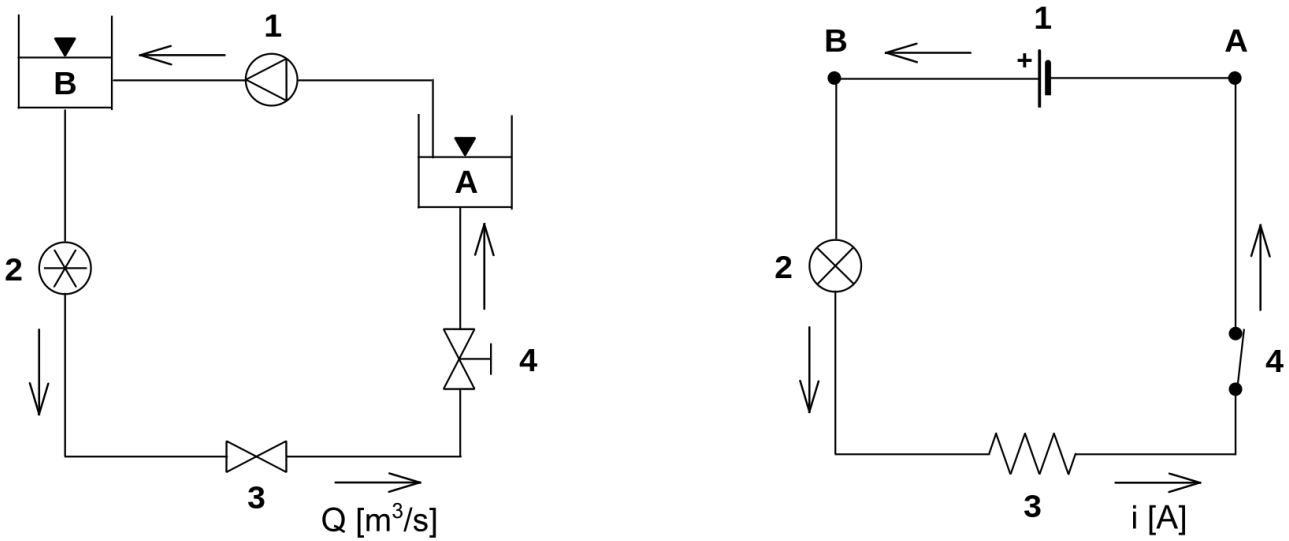


Figure: Electro-hydrolic analogy

Analogical modeling in biological systems

(continued)

		Description	BioGears Included				Other Possible Extensions		
			Generic	Electrical	Fluid	Thermal	Translational	Rotational	Concentrational
Variables	Primary	Across	Potential	Voltage	Pressure	Temperature	Velocity	Angular Velocity	Concentration
		Through	Flux	Current	Flow	Heat Flow	Force	Torque	Flow
	Integrated	∫(Across)·dt	------	Magnetic Flux	Pressure Momentum	------	Displacement	Angular Displacement	------
		∫(Through)·dt	Quantity	Charge	Volume	Heat	Momentum	Angular Momentum	Quantity
Elements	Passive	Resistor	Resistance	Resistance	Resistance	Resistance	Damping	Damping	Clearance
		Capacitor	Capacitance	Capacitance	Compliance	Capacitance	Mass	Inertia	Capacitance
		Inductor	Inductance	Inductance	Inertance	Inductance	Stiffness	Torsional Stiffness	------
	Source	Across Source	Potential Source	Voltage Source	Pressure Source	Temperature Source	Velocity Source	Angular Velocity Source	Concentration Source
		Through Source	Flux Source	Current Source	Flow Source	Heat Flow Source	Force Source	Torque Source	Flow source

Key: In the CDM

Figure: Other types of analogies; adopted from `https://physiology.kitware.com/_circuit_methodology.html`

Analogical modeling

Concluding remarks

- Before digital computers became popular, analogical models were used for simulating/solving differential equations and dynamic systems with analog systems; read more [here].
- Currently numerical analysis and computer simulations have replaced most analog computers.
- Analogical modeling is still used for model conception and illustration.

Partial differential modeling

Introduction

Many (biological) models are simultaneously used to model variations of a system over multiple variables. For example:

- Spatio-temporal spread of epidemic diseases
- Spatio-temporal diffusion of drugs in the body
- Spatio-temporal propagation of action potentials in the nervous system
- Aging of a society over time

For these applications, joint spatio-temporal or bitemporal models are required.

The resulting (dynamic) models are in the form of **partial differential equations (PDE)**.

Partial differential modeling

(continued)

Background

Consider $U(a, b)$, a function of two independent variables. Denoting $U_a \triangleq \partial U/\partial a$ and $U_{ab} \triangleq \partial^2 U/\partial a \partial b$, the most common PDE in physical and biological models are:

Table: Common partial differential equations

Model	Functional	Variables	Equation
Time-Age Equation	$U(t, a)$	time-age	$U_t + U_a = f(t, a)$
Heat (Diffusion) Equation	$U(x, t)$	position-time	$U_t = \alpha U_{xx}$
Wave Equation	$U(x, t)$	position-time	$U_{tt} = c^2 U_{xx}$
Laplace Equation	$U(x, y)$	position-position	$U_{xx} + U_{yy} = 0$

The application and derivation of these models for biological systems are presented in this lecture.

Age structured model

An age structured model (de Vries et al., 2006, Ch. 4)

The female population is considered as an indicator of a community's fertilization capacity. In this example, we seek a two-variable model for the population of females as a function of age and time.

Assumptions

- $u(t, a)$ is the percentage of people with age a at time t
- $\mu(a)$ is an age dependent death rate
- Age and time have the same propagation rate

Age structured model

(continued)

By intuition, we can write

$$u(t, a - \Delta a) - u(t + \Delta t, a) = \mu(a) \times u(t, a) \times \Delta t \qquad (*)$$

Example: $u(2022, 59) - u(2023, 60) = \mu(60) \times u(2022, 60) \times 1year$.
Eq. (*) can be rewritten as

$$u(t + \Delta t, a) - u(t, a) = u(t, a - \Delta a) - u(t, a) - \mu(a) \times u(t, a) \times \Delta t$$

Considering $\Delta a = \Delta t$, we find:

$$\frac{u(t + \Delta t, a) - u(t, a)}{\Delta t} + \frac{u(t, a) - u(t, a - \Delta a)}{\Delta a} = -\mu(a) \times u(t, a)$$

$$\boxed{\frac{\partial u(t, a)}{\partial t} + \frac{\partial u(t, a)}{\partial a} = -\mu(a) \times u(t, a)} \qquad (**)$$

Age structured model

(continued)

- To solve (**), we require boundary conditions for $u(t, a)$ at $t = 0$ and $a = 0$.
- $u_0(a) = u(0, a)$ is the initial non-negative female age distribution. $N_0 = \int u_0(a)da$ is the initial population size.
- $u(t, 0)$ is the newborn density at time t, which is related to the age-dependent **reproduction rate** $\beta(a)$: $u(t, 0) = \int_0^\infty \beta(a)u(t, a)da$.

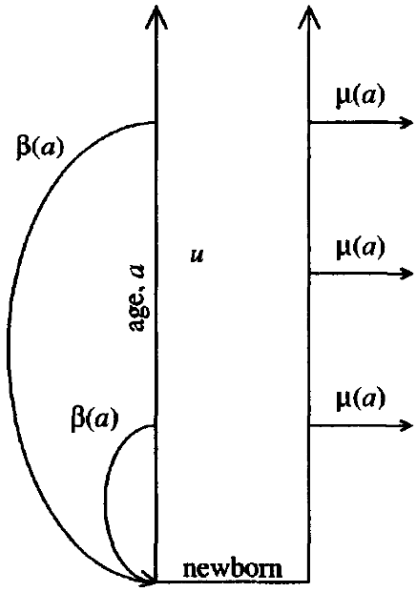


Figure: Arrow diagram of an aging model; adopted from (de Vries et al., 2006, P. 99)

Age structured model

Topics for research

Project Topic 6:

Use the age-time model to form a model for **life expectancy** of a population.

Project Topic 7:

Propose a model for studying the **working population** in modern societies. Use this model to estimate the proper retirement age for an aging society with low/high birth rates.

Project Topic 8:

Propose a continuous-in-time discrete-in-space model for the spread of epidemic diseases between neighboring towns. Study the **West Nile virus** as a case study.

Reaction-diffusion model

(de Vries et al., 2006, Ch. 4)

The **reaction-diffusion** model is a bivariate PDE for modeling the spatial transport (spread) of mass, population, substance, heat, etc. over time.

Consider a virtual volume containing an arbitrary population (or substance) $u(x, t)$, as shown below.

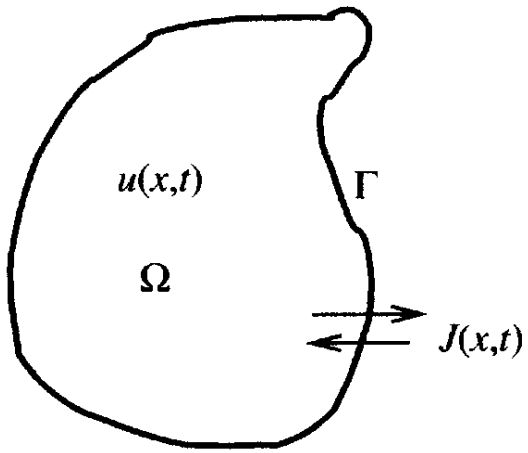


Figure: Reaction-diffusion model

- Ω: an arbitrary volume containing the population
- Γ: the volume boundary
- x: position
- $u(x, t)$: population density under study (a **scalar**)
- $\mathbf{J}(x, t)$: flux of $u(x, t)$ exiting the boundary (a **vector** passing the volume boundaries)
- $f[u(x, t)]$: birth/death, creation/vanishing, or production/destruction rate (time-space dependent)

Reaction-diffusion model

(continued)

Conservation principle

Change of population in Ω = Population flux out of Γ + Population change due to birth/death

Mathematically:

$$\frac{d}{dt}\int_{\Omega} u(x,t)dv = -\int_{\Gamma} \mathbf{J}(x,t)\cdot \mathbf{ds} + \int_{\Omega} f[u(x,t)]dv$$

Reminder: divergence theorem

The divergence theorem related volume and volume-boundary surface integrals

$$\int_{\Gamma} \mathbf{J}(x,t)\cdot \mathbf{ds} = \int_{\Omega} \nabla\cdot \mathbf{J}(x,t)dv$$

Reaction-diffusion

(continued)

Using the **Divergence Theorem**:

$$\int_{\Gamma} \mathbf{J}(x,t) \cdot \mathbf{ds} = \int_{\Omega} \nabla \cdot \mathbf{J}(x,t) dv$$

we get:

$$\int_{\Omega} [\frac{\partial}{\partial t} u(x,t) - f(u) + \nabla \cdot \mathbf{J}(x,t)] dv = 0$$

which is satisfied for any **arbitrary** Ω. Hence, we have:

$$\boxed{\frac{\partial}{\partial t} u(x,t) = f(u) - \nabla \cdot \mathbf{J}(x,t)} \qquad (\dagger)$$

Reaction diffusion mode

A special case

The Fick's law

The flux goes from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the concentration gradient (**spatial derivative**), i.e.,

$$\mathbf{J}(x,t) = -D\nabla u(x,t)$$

where D is the **diffusion coefficient** and ∇ is the gradient operator.

Reaction diffusion mode

The Fick's law (continued)

 The Fick's law is a macroscopic law, which should be verified for the problem of interest. Using the Fick's Law in (†), we arrive at the **reaction-diffusion** also known as the **heat** equation.

$$\boxed{\frac{\partial}{\partial t}u(x,t) = f(u) + D\nabla^2 u(x,t)}$$

where ∇^2 is the **Laplacian operator**, defined as:

$$\nabla^2 \triangleq \frac{\partial^2}{\partial x_1^2} + \cdots + \frac{\partial^2}{\partial x_n^2}$$

and $x = (x_1, \cdots, x_n)$ are the spatial dimensions of $u(x,t)$.

Reaction diffusion mode

The Fick's law (continued)

Example: Critical Domain Size

Fisher's equation for a population $u(x,t)$ density in a saturating region is as follows:

$$\frac{\partial}{\partial t}u = D\frac{\partial^2}{\partial x^2}u + \mu u(1-u) \qquad (\S)$$

The model has been originally proposed for the spread of an advantageous gene in a population (de Vries et al., 2006, Ch. 4). It has both spatial and temporal spread. While the population spreads in space by diffusion, the population saturates due to finite resources (cf. Section 6).

Exercise (Optional)

How large must a region be to support a given population? See de Vries et al. (2006, Section 4.3.3)

Reaction diffusion mode

(continued)

Project Topic 9:

Consider the problem of epidemiological modeling with spatial propagation. The classical SIR model with homogeneous compartments may no longer be used for this problem. Propose a PDE for modeling the joint spatial and temporal propagation of a disease.

Traveling wave model

Background

Spatial propagation in physical systems follows one (or a combination) of these models:

1. Transportation: **particles** move from one point to another according to physical laws of motion or diffusion.
2. Wave propagation: no net transportation is made; but only a **wave** carries energy (information) from one point to another.

In wave models, for a given density function $u(x, t)$ we seek solutions of the form

$$u(x, t) = \phi(x - ct) \qquad (\ddagger)$$

where c is the **wave speed** and $\phi(z)$ is the **wave function** (a function of space).

Traveling wave model

(continued)

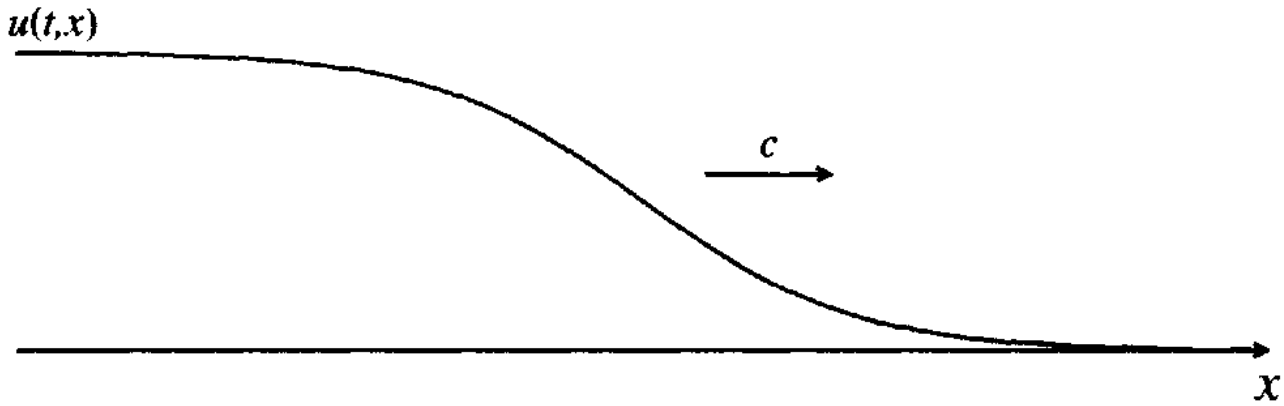


Figure: Wave model

- The wave model has numerous biological applications including: group displacement (migration) of species, propagation of AP in the nervous system, propagation of acoustic signals in the body, propagation of a blood pulse through the veins, etc.
- Equation (‡) is the basic assumption in wave models, which linearly relates the time and space variables using the wave function. In biological models, one can think of alternative (and possibly nonlinear) space-time relations.

Traveling wave model

(continued)

According to the wave equation (‡), we have

$$\frac{\partial}{\partial t}u(x,t) = -c\dot{\phi}, \quad \frac{\partial^2}{\partial t^2}u(x,t) = c^2\ddot{\phi}, \quad \frac{\partial^2}{\partial x^2}u(x,t) = \ddot{\phi}$$

resulting in

$$\boxed{\frac{\partial^2}{\partial t^2}u(x,t) = c^2\frac{\partial^2}{\partial x^2}u(x,t)}$$

which is known as the **traveling wave model**. As before, boundary conditions are needed to solve this equation.

 Wave model solutions for the critical domain size problem:

We can find wave-like solutions for the critical domain size problem in (§). In this case, the PDE simplifies to a nonlinear ODE of the wave function $\phi(z)$:

$$D\ddot{\phi} + c\dot{\phi} + \mu\phi(1-\phi) = 0 \qquad (¶)$$

which is a 2nd-order ODE with a variable **natural frequency**.

Traveling wave model

(continued)

Exercise (Optional)

Provide an interpretation for a 2nd-order ODE with a variable natural frequency as in (¶), and discuss its impact on the solution of the critical domain size problem.

Non-classic wave models

Motivation

Wave-like propagation models are applicable to problems with non-physical and non-uniform media with preferred path ways or even along a graph. For example:

- Propagation of action potentials through the nervous system.
- Spread of news or rumors in a society or a social network.

In each case, suitable wave-like models can be proposed for the propagation of information. It is clear that vicinities are not uniform in these examples.

Project Topic 10:

Propose and verify a wave-based model across a graph for action potentials in the body, or news spread in a social network. This idea can later be combined with **Cellular Automata** modeling (cf. later lectures).

Interpretation of mathematical operators

There are interesting physical interpretations for many of the common elements of differential equations, which are rather helpful for model construction:

- Gradient
- Divergence
- Curl
- Laplacian

Interpretation of mathematical operators

Gradient

Gradient of a scalar field

For a scalar field $\phi(\mathbf{x})$ in the n-dimensional space $\mathbf{x} = (x_1, \cdots, x_n)$, the gradient of $\phi(\mathbf{x})$, denoted by $\nabla\phi(\mathbf{x})$, is *a vector towards the steepest ascent of* $\phi(\mathbf{x})$

Interpretation of mathematical operators

Divergence

Divergence of a vector field

For a vector field $\mathbf{F}(\mathbf{x})$ in the n-dimensional space $\mathbf{x} = (x_1, \cdots, x_n)$, the divergence of $\mathbf{F}(\mathbf{x})$, denoted by $\nabla \cdot \mathbf{F}$, "is equal to the infinitesimal flux of the field per unit volume through a sphere centered at that point. This is why we say the divergence measures the tendency of the vector field to **diverge** from a point." Loosely speaking, the divergence is the amount of stuff created at (or exiting from) a point.

Reference: `http://www.math.uwaterloo.ca/~karigian/teaching/multivariable-calculus/curldiv.pdf`

Interpretation of mathematical operators

Curl

Curl of a vector field

Consider a vector field $\mathbf{F}(\mathbf{x})$ in the n-dimensional space $\mathbf{x} = (x_1, \cdots, x_n)$. The components of the curl of a vector field at a point in a given direction denoted by $\nabla \times \mathbf{F}$, is equal to "the infinitesimal circulation of the field per unit area around a circular path centered at that point, in a plane whose normal vector points in the given direction, with orientation given by the right hand rule. Hence the curl measures the tendency of the vector field to **curl** around a given point in a direction given by the right hand rule."

Reference: `http://www.math.uwaterloo.ca/~karigian/teaching/multivariable-calculus/curldiv.pdf`

Interpretation of mathematical operators

Laplacian

Laplacian of a scalar field

Consider a scalar field $\phi(\mathbf{x})$ in the n-dimensional space $\mathbf{x} = (x_1, \cdots, x_n)$. The Laplacian of $\phi(\mathbf{x})$ (or the divergence of its gradient) at a point $\mathbf{x}$, denoted by $\nabla^2\phi(\mathbf{x})$, is "essentially" (i.e., up to a scaling factor) equal to the average difference of $\phi(\mathbf{x})$ and its neighboring points. The proof is based on the Taylor expansion of ϕ around zero.

Interpreting the **heat** (**diffusion**) equation without a source/sink:

In $\frac{\partial}{\partial t}u(x,t) = D\nabla^2 u(x,t)$, if the surrounding points of x are warmer than x (*on average*), then the temperature at x will also increase at the next moment.

Reference:

`http://math.stackexchange.com/questions/50274/intuitive-interpretation-of-the-laplacian`

Solving ODE and PDE

- ODE and PDE can be solved by their initial and boundary conditions.
- ODE and PDE can be solved analytically or numerically.
- Analytical solutions are not always possible (especially for nonlinear OSE/PDE)
- Numerical solutions are most common. They require discretization of ODEs and PDEs.

Numerical solution of ODE

Example: Solve $\dot{x}(t) = \alpha x(t)$ with the initial condition $x(0) = x_0$

- $\dot{x}(t) \approx [x(t) - x(t - \Delta)]/\Delta$ for "relatively small" Δ (compared to the speed of variations of $x(t)$)
- Hence $x(t) \approx (1 - \Delta\alpha)^{-1} x(t - \Delta)$, or with a time shift:

$$x(t + \Delta) \approx (1 - \Delta\alpha)^{-1} x(t) \qquad (\S\S)$$

  which can be solved iteratively from the initial condition x_0.
- Alternatively, using $\dot{x}(t) \approx [x(t + \Delta) - x(t)]/\Delta$ we find

$$x(t + \Delta) \approx (1 + \Delta\alpha) x(t) \qquad (\P\P)$$

Question: Do (§§) and (¶¶) contradict? *Hint:* Δ is small!

Numerical solution of ODE

(continued)

Example: Solve $\ddot{x}(t) + \alpha\dot{x}(t) + \beta x(t) = 0$ with the initial condition $x(0) = x_0$, $\dot{x}(0) = x_1$

- For small Δ, $\dot{x}(t) \approx [x(t) - x(t-\Delta)]/\Delta$ and $\ddot{x}(t) = \frac{d}{dt}\dot{x}(t) \approx \{[x(t) - x(t-\Delta)] - [x(t-\Delta) - x(t-2\Delta)]\}/\Delta^2$
- Hence:

$$(1 + \alpha\Delta + \beta\Delta^2)x(t) \approx (2 + \alpha\Delta)x(t-\Delta) - x(t-2\Delta)]$$

or:

$$x(t+2\Delta) \approx (1 + \alpha\Delta + \beta\Delta^2)^{-1}[(2 + \alpha\Delta)x(t+\Delta) - x(t)]$$

which can be solved iteratively from the initial condition x_0 and x_1.

Numerical solution of PDE

Example: Solve the wave equation $\frac{\partial^2}{\partial t^2}u(x,t) = c^2\frac{\partial^2}{\partial x^2}u(x,t)$

For small Δ_t and Δ_x:

- $\frac{\partial}{\partial t}u(x,t) \approx \frac{u(x,t) - u(x,t-\Delta_t)}{\Delta_t}$
- $\frac{\partial^2}{\partial t^2}u(x,t) = \frac{\partial}{\partial t}[\frac{\partial}{\partial t}u(x,t)] \approx \frac{u(x,t) - 2u(x,t-\Delta_t) + u(x,t-2\Delta_t)}{\Delta_t^2}$
- $\frac{\partial}{\partial x}u(x,t) \approx \frac{u(x,t) - u(x-\Delta_x,t)}{\Delta_x}$
- $\frac{\partial^2}{\partial x^2}u(x,t) = \frac{\partial}{\partial x}[\frac{\partial}{\partial x}u(x,t)] \approx \frac{u(x,t) - 2u(x-\Delta_x,t) + u(x-2\Delta_x,t)}{\Delta_x^2}$

Exercise 8:

Write a code to solve the wave equations, given the initial and boundary conditions.

Further reading

Further reading on differential equations in biological & physical systems

ODE:

- de Vries et al. (2006, Ch. 3). See the chapter exercises for examples on combination of ODE and compartmental models.
- Fishwick (2007, Ch. 17) has very interesting and practical examples.

PDE:

- de Vries et al. (2006, Ch. 4, 5)
- *"Modelling with Partial Differential Equations,"* By: Peter Bastian, Online Available: `http://conan.iwr.uni-heidelberg.de/teaching/numerik2_ws2010/chapter01_27.10.2010.pdf`
- Haberman (1998), for theory and applications.

Finite-state automata (FSA)

Background

- Finite-state automata (FSA) is a mathematical construct for describing systems with finite number of **states**.
- FSA can be used as a modeling tool for describing the temporal evolution of many biological systems.
- As shown in the following examples, it is also possible to integrate and combine FSA with previous modeling techniques.

Finite-state automata (FSA)

(continued)

Elements of Finite-state automata

- A finite number of states
- An output alphabet (numerical/non-numeric data stream)
- State transition rules

The state relationships are commonly shown by a graph.

Finite-state automata (FSA)

(continued)

FSA Types 1

- **Determinant**: Only one output from each state
- **Indeterminant**: There is at least one state with more than one possible output

FSA Types 2

- **Deterministic**: All the FSA elements are deterministic
- **Stochastic**: At least one of the FSA elements is random (the state transitions, the rules, the output, etc.)

For example, in an indeterminant FSA the **next state** can be chosen according to some statistical rule.

Finite-state automata (FSA)

(continued)

State Transition Rules

The transition from one state to another can be due to:

- An input signal (or an event)
- Current (or sequence of previous) states

Example

Figure: (a) Determinant and (b) Indeterminant Finite State Machines; adopted from (Haefner, 2005)

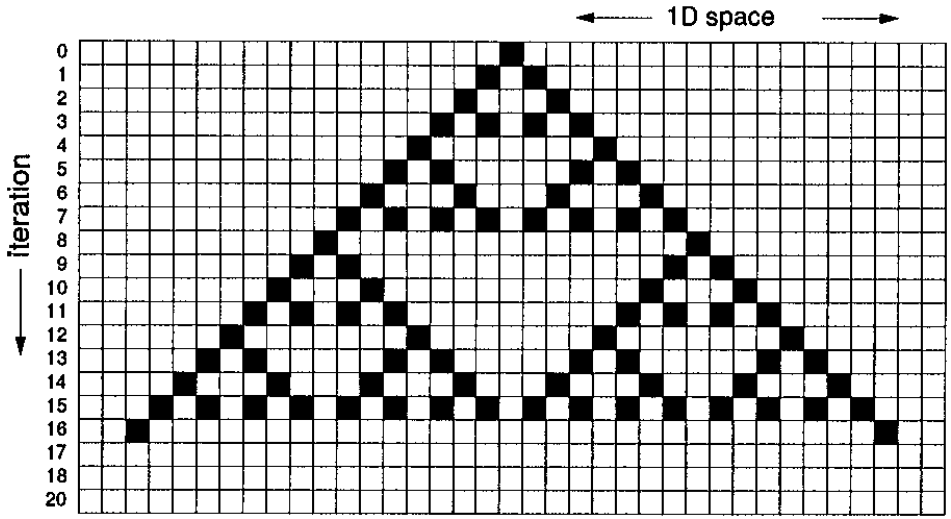
Cellular automata

- Cellular Automaton (CA) is a spatial realization of Finite-state automata (FSA)
- First, a set of cells are defined in space. Each cell is a FSA with an arbitrary output.
- The state transition rules of each cell are defined according to the current (and previous) states of that cell and its spatial neighbors.

Cellular automata

A 1-dimensional cellular Automaton (Haefner, 2005, Ch. 19)

- Consider N adjacent pixels. Each pixel can take binary (output) values 0 or 1. In this example, the cell output and cell states are selected to be identical.
- Define the following state transition rule: *"if a middle cell is in state 0 and has exactly one neighbor in state 1, the middle cell state changes to 1. Otherwise, the state becomes (or remains) 0. "*



Cellular automata

(continued)

A 2-dimensional cellular automaton: Conway's Game of Life (de Vries et al., 2006, Ch. 6)

- Consider a two-dimensional grid. Each cell can be 0 (dead) or 1 (alive).
- Define the following state transition rules:
  - A living cell stays alive if it has two or three living neighbors; otherwise it dies (analogical to under-crowded and over-crowded colonies)
  - A dead cell becomes alive if exactly three neighbors are living (analogical to reproduction)

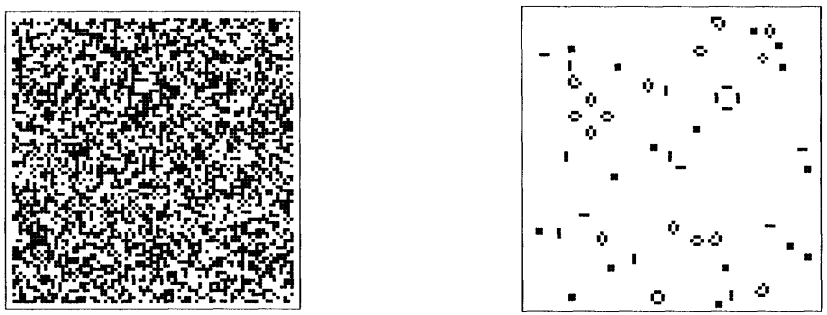


Figure: (a) Initial, (b) after 1300 iterations; (de Vries et al., 2006, Ch. 6)

Cellular automata

(continued)

Plant competition: Silvertown's CA model (Haefner, 2005, Ch. 19)

Consider the problem of grass growth in a farm. The practical issues include:

- Farmers partition their lands and cultivate different crops in each partition
- Grasses and weeds spread across the partitioned randomly (with a diffusion-like model) or by wind (with a advection-like model)
- The tendency of spatial spread is variable among different plants and pests

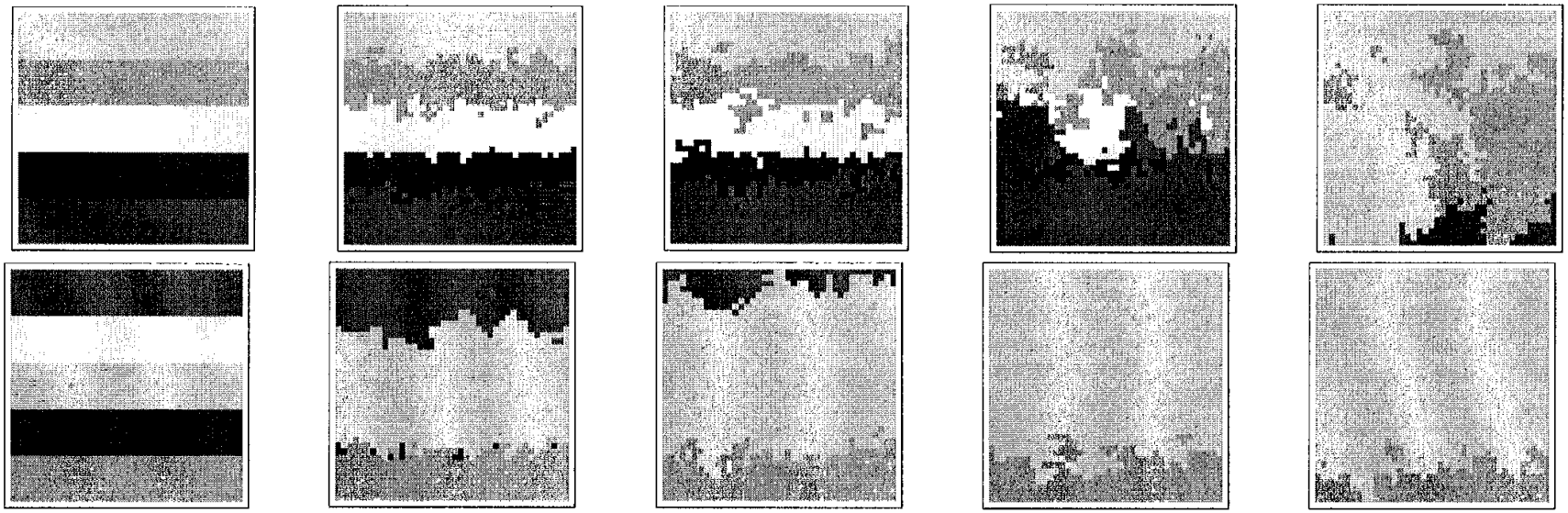


Figure: Silvertown's cellular automaton model of plant competition

Cellular automata

(continued)

A 3D cellular automaton: cardiac excitable tissues (Haefner, 2005, Ch. 19)

The excitation of the myocardium can be modeled with a three-dimensional CA

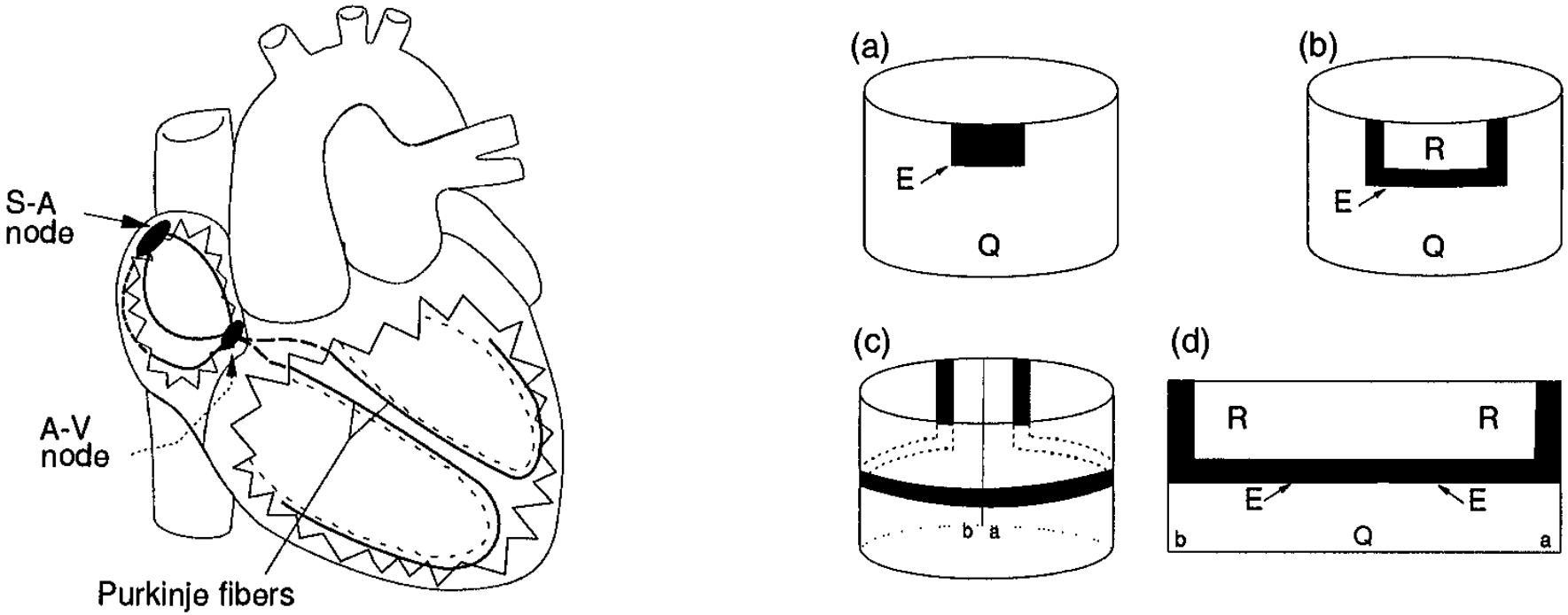


Figure: The (a) myocardium and (b) the 3D ventricular contraction wave front

Cellular automata

(continued)

A 3D cellular automaton (continued)

By modeling the cardiac excitable cells with a 3D CA, the outputs of the cardiac CA for a normal and fibrillating heart are as follows

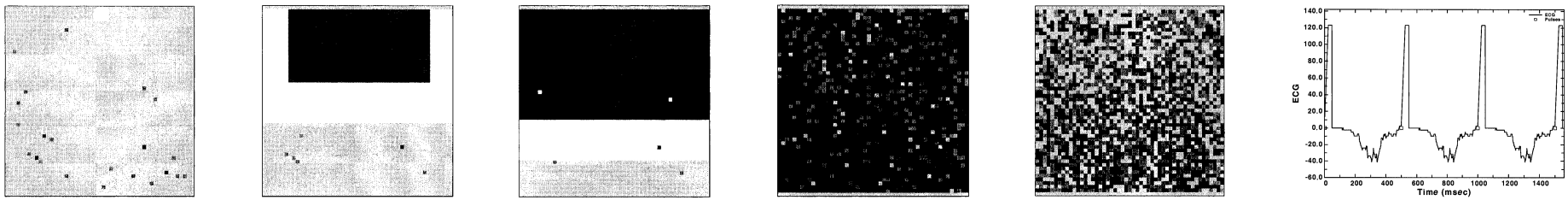


Figure: CA output and the generated ECG for a normal heart

Figure: CA output and the generated ECG for a fibrillating heart

Cellular automata Issues I

Boundary Conditions

In finite dimension CA, the boundary cells of the region can be handled with the following approaches:

- Adding a virtual boundary with fixed states
- Defining special rules for the boundary cells
- Connecting the boundary edges to form a closed loop (in 1D) or surface (in 2D)

Cellular automata's Level of Abstraction

While many previous models, such as diffusion equation in Section 1, are based on **macroscopic** approximations of a system, cellular automata provides a means of **microscopic** modeling of these systems. If the CA rules be well-defined, the overall (big-picture) of CA will resemble its macroscopic model. See the following exercise to verify this fact.

Cellular automata Issues II

Exercise 9: Cellular automata

Select between the following exercises:

1. Use the interpretation of the Laplacian operator for the heat equation presented in the PDE lecture to develop a cellular automata for heat transfer and diffusion models. Simulate the proposed model with various boundary conditions.
2. Use cellular automata to model the propagation of cardiac contraction waves within the myocardium. You may use a rectangular grid as shown in the case studies of this section, or a graph structure consisting of the SA node, the AV node, bundle of His, left and right bundle branches, and the Purkinje fibers

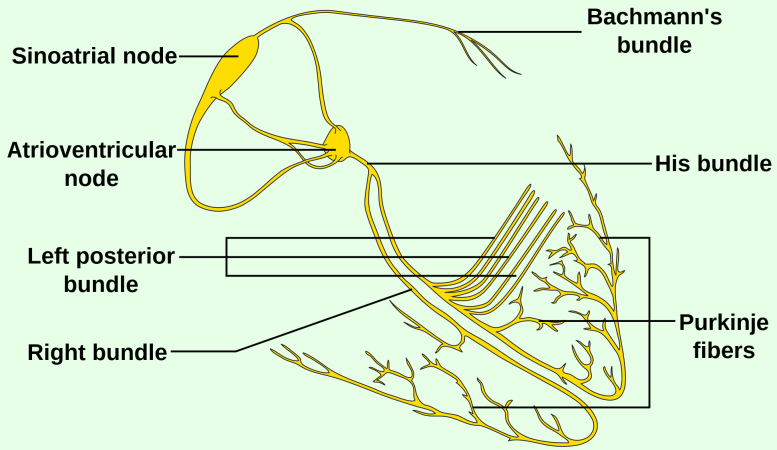


Figure: Electrical conduction system of the heart; `https://en.wikipedia.org/wiki/Purkinje_fibers` (CC BY-SA 3.0)

Further reading and projects I

Further reading

- See (Haefner, 2005, Ch. 19) and (de Vries et al., 2006, Ch. 6) for further examples and sample projects.
- See (Schiff, 2008) for an in-depth study of cellular automata.

Project Topic 11:

Develop a complete CA-based model for modeling various cardiac defects using real physiological and anatomical models of the heart.

Project Topic 12:

Consider the problem of epidemiological modeling with spatial propagation. The classical SIR model with homogeneous compartments may no longer be used for this problem. Propose a CA model for this problem by combining spatial and temporal propagation of a disease.

Further reading and projects II

Project Topic 13:

Implementing cellular automata on **graph signals**

Project Topic 14:

CA can be applied to regions with irregular spatial neighborhoods. Develop a CA for the following applications

- Biological: Propagation of action potentials throughout the nervous system (in the brain, the sensory/motor system, the cardiac tissue, etc.)
- Social: Connectivity graphs in various **social networks**

Further reading and projects III

Project Topic 15:

Tissue Engineering is an emerging technology in biology and medicine. The principles and tools of biological modeling discussed so far, can be used to model the development of tissues in the lab. Based on the literature of **cell culture**, propose a model for *in vitro* tissue development.

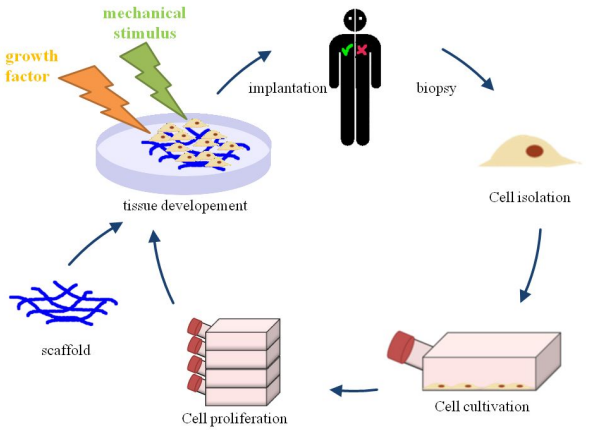


Figure: Tissue Engineering Cycle; adopted from
`http://en.wikipedia.org/wiki/Tissue_engineering`

Model identifiability and parameter identification

Introduction

- To this point, various models and modeling techniques were discussed.
- The models were generic and parametric, which enabled them to be tuned for different applications and to fit real data.
- The identification of the tunable parameters of a model are the subject of this section.
- We will study identifiability and parameter identification with two approaches:
  1. Classical parameter estimation (using estimation theory)
  2. Using machine learning and deep learning

Model identification questions

- Are the model parameters **identifiable**?
- How to identify the model parameters?

Parameter identifiability

- Mathematically, not all models are **identifiable** (regardless of the accuracy or size of available observations used for tuning the model parameters)
- **Identifiability** of a model depends on its mathematical form
- **Unidentifiable** models are not necessarily incorrect models; they have infinite number of solutions, which may not be fixed given real-world observations.
- Many biological systems have unidentifiable parameters.
- In dynamical systems, the concept of identifiability is closely related to the notion of model **observability**.

Nonlinear model identification

- Parameter identification of linear models (linear-in-parameter) is well addressed in the literature (Kay, 1993). However, nonlinear models are commonly challenging to tackle using estimation theoretical frameworks.
- One possible approach is to apply a **transformation** or **factorization** on the model to make the model linear in parameters (or at least a subset of parameters). Besides the main text, see (Kay, 1993, P. 255) for some nice examples.

Unidentifiable models

(case-study)

Example: **positron emission tomography (PET)** in non-homogenous tissues (de Vries et al., 2006, Ch. 7)

- Each **voxel** consists of two types of tissues, with relative volumes τ and $1-\tau$, and different absorption rates.
- Radioactive tracer in blood vessels has a concentration $B(t)$ and is absorbed by tissues by **diffusion**, resulting in tracer concentrations $C(t)$ and $D(t)$ in each tissue.

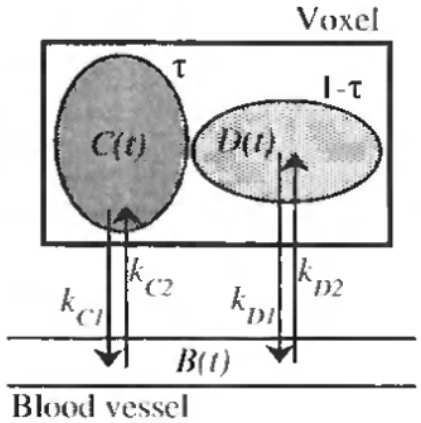


Figure: A non-homogenous voxel

Unidentifiable models

(case-study continued)

Positron Emission Tomography in Non-homogenous Tissues (continued)

- The concentration $B(t)$ is the system's input (known)
- The PET system measures the per-voxel radioactive concentration: $s(t) = \tau C(t) + (1 - \tau)D(t)$
- The tunable (unknown) model parameters are $(\tau, k_{c1}, k_{c2}, k_{d1}, k_{d2})$, which are also the set of tissue-dependent parameters used to form a PET image

Unidentifiable models

(case-study continued)

Solution

- The problem may be formulated as a compartmental model with equations:

$$\begin{cases} \dot{C}(t) = -k_{c1}C(t) + k_{c2}B(t) \\ \dot{D}(t) = -k_{d1}D(t) + k_{d2}B(t) \\ s(t) = \tau C(t) + (1-\tau)D(t) \end{cases} \qquad (\S)$$

Defining $\theta_a \overset{\Delta}{=} k_{d1} + k_{c1}$, $\theta_b \overset{\Delta}{=} k_{c1}k_{d1}$, $\theta_c \overset{\Delta}{=} \tau k_{c2} + (1-\tau)k_{d2}$, $\theta_d \overset{\Delta}{=} \tau k_{c2}k_{d1} + (1-\tau)k_{c1}k_{d2}$ and differentiating the last equation in (§) twice, the problem simplifies to an ODE:

$$\ddot{s}(t) + \theta_a \dot{s}(t) + \theta_b s(t) = \theta_c \dot{B}(t) + \theta_d B(t) \qquad (\S\S)$$

- The parameters θ_a, θ_b, θ_c, and θ_d can be found by data fitting over (§§). Hence, k_{c1} and k_{d1} are **identifiable** from pairs of $s(t)$ and $B(t)$; but (τ, k_{c2}, k_{d2}) are **unidentifiable**, unless additional information is provided; cf. Audoly et al. (2001)

Parameter estimation

Introduction

- If a model is identifiable, the next question is how to estimate its parameters.
- Real-world observations are required for fixing model parameters.
- For deterministic and identifiable models (with "perfect" noiseless observations) parameter identification reduces to a set of linear or nonlinear algebraic equations, which can be solved with a finite number of observation.
- In practice, models are imperfect and (commonly) stochastic, the observations are noisy and do not exactly fit the model. So, an **error cost function** is defined and minimized to fit the model on the observation.
- In this case, increasing the number of observations can typically improve the parameter estimation.
- We will study parameter estimation with two approaches:
  - **Machine-learning** and **deep learning based** methods
  - **Estimation theoretical** approaches

Machine learning approach to parameter estimation

Approach

Consider the parametric forward model:

$$\boldsymbol{x} = \boldsymbol{h}(\boldsymbol{u}, \boldsymbol{n}; \boldsymbol{\theta})$$

where $\boldsymbol{u}$ is the model input, $\boldsymbol{x}$ is the observed output, $\boldsymbol{\theta}$ is the unknown model parameter, and $\boldsymbol{n}$ is the model noise.

1. Use the forward model to generate 'many' synthetic random data $\boldsymbol{u}$, $\boldsymbol{x}$ and $\boldsymbol{n}$.
2. Train the machine learning model Γ (e.g., a shallow or deep neural network) by using the combined $[\boldsymbol{u}, \boldsymbol{x}]$ as input and $\hat{\boldsymbol{\theta}}$ as output (use the standard training and validation approach in ML).
3. Assuming that the training converges and Γ is trained, Γ can be provided with real input-output pairs from real data and used to estimate the unknown parameters.

Machine learning approach to parameter estimation

(continued)

Estimation theoretical approach to parameter estimation

Estimation theoretical methods for parameter estimation

Parameter identification is rigorously studied in **estimation theory**, with different approaches (Kay, 1993):

- Bayesian estimators: Minimum mean square error (MMSE), Maximum a posteriori (MAP), etc. **(for stochastic parameters with known priors)**
- Maximum likelihood (ML) and Expectation maximization (EM) **(for deterministic unknown parameters or stochastic parameters with unknown priors)**
- Least Squares (LS) Error **(no stochastic assumptions available)**

Bayesian parameter estimation

Formulation

- Consider the parametric model

$$\boldsymbol{x} = \boldsymbol{h}(\boldsymbol{u}, \boldsymbol{n}; \boldsymbol{\theta})$$

  where $\boldsymbol{u}$ is the model input, $\boldsymbol{x}$ is the observed output, $\boldsymbol{\theta}$ is the unknown model parameter, and $\boldsymbol{n}$ is the model noise.
- The objective is to find the parameter estimate $\hat{\boldsymbol{\theta}}$, which minimizes the average **cost of error** between the observations and the model.
- The **cost of error**, denoted by $C(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}})$ is rather subjective and application dependent.
- We will study some of the most common cost functions. See (Kay, 1993, Ch. 11) for a detailed study.

Bayesian parameter estimation

(continued)

Cost function properties

Desired properties of an error cost function include:

- $C(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) \geq 0$, with equality obtained at $\boldsymbol{\theta} = \hat{\boldsymbol{\theta}}$
- $C(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) = L(|\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}|)$ which implies that the cost is symmetric for positive/negative errors

Error costs are not always symmetric in practice.

Bayesian parameter estimation

Minimum mean square error

Minimum mean square error (MMSE)

In MMSE, the cost function is defined:

$$C_{MMSE}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) = (\boldsymbol{\theta} - \hat{\boldsymbol{\theta}})^2$$

Hence

$$\hat{\boldsymbol{\theta}}_{MMSE} = \arg\min_{\boldsymbol{\theta}} E\{(\boldsymbol{\theta} - \hat{\boldsymbol{\theta}})^2\}$$

The MMSE solution is proved to be equal to the **mean** of the conditional probability density function (pdf) $f_{\boldsymbol{\theta}|\boldsymbol{x}}$:

$$\boxed{\hat{\boldsymbol{\theta}}_{MMSE} = E\{\boldsymbol{\theta}|\boldsymbol{x}\}}$$

Bayesian parameter estimation

(continued)

Minimum mean absolute error (ABS)

In minimum mean absolute error, the cost function is defined:

$$C_{ABS}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) = |\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}|$$

Hence

$$\hat{\boldsymbol{\theta}}_{ABS} = \arg\min_{\boldsymbol{\theta}} E\{|\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}|\} \qquad (\star)$$

The minimum mean absolute error estimator in $(\star)$ is proved to be the **median** of $f_{\boldsymbol{\theta}|\boldsymbol{x}}$, i.e.,

$$\boxed{\int_{-\infty}^{\hat{\boldsymbol{\theta}}_{ABS}} f(\boldsymbol{\theta}|\boldsymbol{x}) d\boldsymbol{\theta} = \int_{\hat{\boldsymbol{\theta}}_{ABS}}^{+\infty} f(\boldsymbol{\theta}|\boldsymbol{x}) d\boldsymbol{\theta}}$$

Bayesian parameter estimation

Maximum a posteriori

Maximum a posteriori (MAP)

In MAP, the cost function is defined:

$$C_{MAP}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) = \begin{cases} 0 & |\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}| \leq \epsilon \\ 1 & |\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}| > \epsilon \end{cases}$$

Hence

$$\hat{\boldsymbol{\theta}}_{MAP} = \arg\min_{\boldsymbol{\theta}} E\{C_{MAP}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}})\} \qquad (\star\star)$$

For $\epsilon \to 0$, the MAP estimator in $(\star\star)$ is proved to be the **mode** (peak point) of $f_{\boldsymbol{\theta}|\boldsymbol{x}}$, i.e.,

$$\boxed{\hat{\boldsymbol{\theta}}_{MAP} = \arg\max_{\boldsymbol{\theta}} f(\boldsymbol{\theta}|\boldsymbol{x})}$$

which given an observation $\boldsymbol{x}$ is the most-probable value for the parameter $\boldsymbol{\theta}$.

Bayesian parameter estimation

(continued)

In general, $\hat{\boldsymbol{\theta}}_{MMSE} \neq \hat{\boldsymbol{\theta}}_{ABS} \neq \hat{\boldsymbol{\theta}}_{MAP}$; but they can be equal depending on the form of $f_{\boldsymbol{\theta}|\boldsymbol{x}}$ (Kay, 1993, P. 345).

Exercise (optional): Interpretations & alternative cost functions

1. Give interpretations for the MMSE, ABS, and MAP estimators in terms of their cost functions. How does each model weigh small vs large errors?
2. Discuss the possible applications of each of these cost functions. Can you propose other functions?

Asymmetric error cost functions

Example: Laser tumor ablation

- Laser ablation has inevitable modeling, observational and instrumentational errors, which result in a probabilistic scenario (cf. *circular error probability (CEP)*).
- If the tumor is at the vicinity of extremely delicate tissues, e.g. inside the brain, the cost of error should not be symmetric around the desired target point.

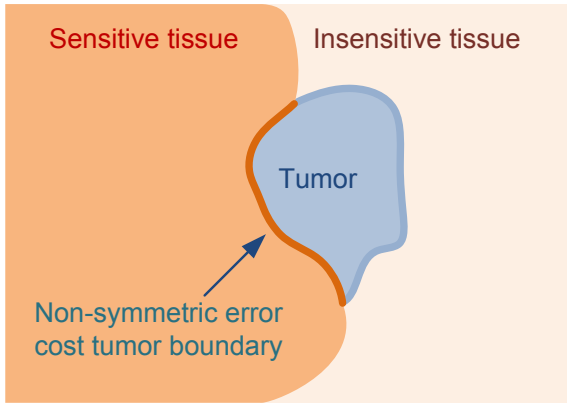


Figure: Example of regions with non-symmetric error cost boundaries

Bayesian parameter estimation

(continued)

Project Topic 16:

Develop an estimation theoretical framework for regions with non-symmetric boundaries (applicable to the problem of laser tumor ablation). The boundary shape can be considered as a known parametric curve. This shape should be considered in the targeting error cost function.

Maximum likelihood parameter estimation I

- All the different flavors of the Bayesian estimator require the posterior probability $f_{\boldsymbol{\theta}|\boldsymbol{x}}$.
- While Bayesian estimators assume the model parameters $\boldsymbol{\theta}$ **random variables (RV)**, in many cases they are not random; they are just **unknown**. Therefore, the pdf $f_{\boldsymbol{\theta}|\boldsymbol{x}}$ becomes meaningless (Kay, 1993, Ch. 10).
- Even if the unknown parameters are truly stochastic (or assumed to be "zero-variance RV", as a work around), the posterior probability $f_{\boldsymbol{\theta}|\boldsymbol{x}}$ is not always available.
- In fact, the assumption of having $f_{\boldsymbol{\theta}|\boldsymbol{x}}$ reads: *"for any given observation $\boldsymbol{x}$, the pdf (i.e., all the statistical properties) of the parameter $\boldsymbol{\theta}$ is known"*. This is a big assumption.
- In these case, we may maximize the **likelihood function** $f_{\boldsymbol{x}|\boldsymbol{\theta}}$:

$$\boxed{\hat{\boldsymbol{\theta}}_{ML} = \arg\max_{\boldsymbol{\theta}} f(\boldsymbol{x}|\boldsymbol{\theta})}$$

Maximum likelihood parameter estimation II

- The **maximum likelihood (ML)** estimator does not suffer from the noted Bayesian estimation issues; but is more intuitive (less rigorous) as compared to the Bayesian estimators (it is not always clear what cost function is minimized by the ML estimator).
- $f_{\boldsymbol{x}|\boldsymbol{\theta}}$ reads: *"the distribution of the observations $\boldsymbol{x}$, for a given parameter $\boldsymbol{\theta}$."*
- **Question:** why should one choose the maximum of $f_{\boldsymbol{x}|\boldsymbol{\theta}}$ as the best choice of a model's unknown parameter?
- **Hint:** according to the **Bayes' rule** $f_{\boldsymbol{x}|\boldsymbol{\theta}} = \dfrac{f_{\boldsymbol{\theta}|\boldsymbol{x}} f_{\boldsymbol{x}}}{f_{\boldsymbol{\theta}}}$, i.e.,

$$\text{Likelihood} = \frac{\text{Posterior} \times \text{Marginal}}{\text{Prior}}$$

Therefore, maximizing the likelihood with respect to $\boldsymbol{\theta}$, means....

Maximum likelihood parameter estimation III

ML interpretation

- Considering the fact that the area under the pdf is equal to 1, for **uni-modal** distributions, the pdf becomes more "spiky", when it has a smaller scatter (variance) around its mean.
- So, loosely speaking, the ML estimator chooses the optimal model parameter as the one that leads to the least scattered (most concentrated) observations.
- So the ML objective is reasonable, when we only have a model and a set of observations with little information about the unknown parameters. See (Kay, 1993, Section 7.4) for further details.

Quality of estimation

The quality of an estimator is assessed by its **bias** and **variance**.

Estimation bias

- **Bias** is a measure of the average drift of the estimates from their true value:

$$b(\boldsymbol{\theta}) = E\{\hat{\boldsymbol{\theta}}\} - \boldsymbol{\theta}$$

- An **unbiased** estimator is one that provides the true value of the parameter *on average*, i.e.,

$$E\{\hat{\boldsymbol{\theta}}\} = \boldsymbol{\theta}$$

Estimation variance

- The **variance** of error is another important property of an estimator.
- An estimator's **variance** is the mean square error of the estimates from their true values:

$$\text{mse}(\hat{\boldsymbol{\theta}}) = E\{(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta})^2\}$$

The **minimum variance unbiased (MVU)** estimator is of special interest.

Geometric interpretation of estimation errors

Apparently:

$$\text{mse}(\hat{\boldsymbol{\theta}}) = \text{var}(\hat{\boldsymbol{\theta}}) + b(\boldsymbol{\theta})^2$$

which shows that an estimator's error is composed of two errors: variance of the estimator plus the squared bias.

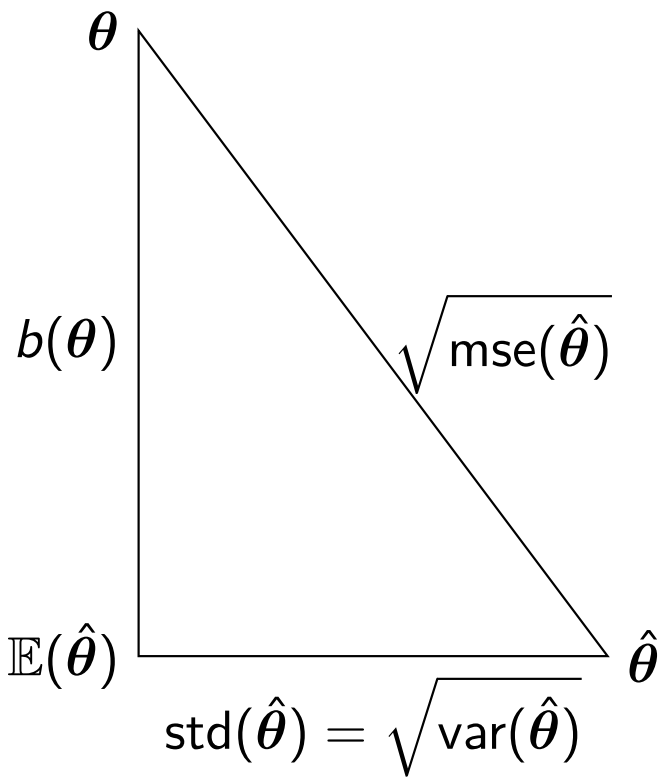


Figure: An illustration of estimation error elements; adapted from Kahneman et al. (2021)

Examples

Deterministic constant value in noise from single observation

Data Model: a single noisy observation $y = x + n$, of an unknown constant parameter x embedded in Gaussian noise $n \sim N(0, \sigma_n^2)$.

- **Question:** What is the appropriate estimation framework for estimating x?
- The likelihood equation is

$$f_{Y|X}(y|x) = f_n(y - x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[-\frac{(y-x)^2}{2\sigma_n^2}\right]$$

Therefore,

$$\hat{x}_{ML} = \arg\max_x f_{Y|X}(y|x) = y$$

Question: How can we solve the same problem with a neural network?

Examples

continued

Deterministic constant value in noise from multiple independent observations

Data model: multiple noisy observations $y_i = x + n_i$ of an unknown constant parameter x embedded in *iid* Gaussian noise $n_i \sim N(0, \sigma_n^2)$. Defining $\mathbf{n} = (n_1, \cdots, n_K)$, the likelihood equation is

$$f_{Y|X} = f_{\mathbf{n}}(y_1 - x, \cdots, y_K - x) = \prod_{i=1}^{K} f_n(y_i - x) = \prod_{i=1}^{K} \frac{1}{\sqrt{2\pi\sigma_n^2}} \exp\left[-\frac{(y_i - x)^2}{2\sigma_n^2}\right]$$

The log-likelihood function is

$$ll(x) = \log\left(f_{Y|X}\right) = \frac{-K}{2}\log\left(2\pi\sigma_n^2\right) - \sum_{i=1}^{K} \frac{(y_i - x)^2}{2\sigma_n^2} \rightarrow \hat{x}_{ML} = \frac{1}{K}\sum_{i=1}^{K} y_i$$

Examples

continued

Estimating a stochastic variable from multiple noisy observations

$$y_i = x + n_i \quad i = 1, \cdots, K; \quad x \sim N(0, \sigma_x^2); \quad n_i \sim N(0, \sigma_n^2); n_i \text{ are } iid$$

In this case a **Bayesian estimation** framework can be used:

$$f_{Y|X}(y|x) = \prod_{i=1}^{K} \frac{1}{\sqrt{2\pi}\sigma_n} \exp\left[-\frac{(y_i - x)^2}{2\sigma_n^2}\right], \quad f_X(x) = \frac{1}{\sqrt{2\pi}\sigma_x} \exp\left[-\frac{x^2}{2\sigma_x^2}\right]$$

Using $f_{X|Y} = f_{Y|X} f_X / f_Y$, we find:

$$f_{X|Y}(x|y) = \beta(y) \exp\left(-\frac{1}{2\sigma_p^2}[x - \frac{\sigma_x^2}{\sigma_x^2 + \frac{\sigma_n^2}{K}}(\frac{1}{K}\sum_{i=0}^{K} y_i)]^2\right), \quad \sigma_p^2 \triangleq \frac{\sigma_x^2 \sigma_n^2}{K\sigma_x^2 + \sigma_n^2}$$

$$\rightarrow \hat{x}_{MMSE} = E\left\{f_{X|Y}(x|y)\right\} = \frac{\sigma_x^2}{\sigma_x^2 + \frac{\sigma_n^2}{K}}(\frac{1}{K}\sum_{i=1}^{K} y_i)$$

Examples

continued

Discussion

In the previous example it can be shown that

1. $\hat{\boldsymbol{\theta}}_{MMSE} = \hat{\boldsymbol{\theta}}_{ABS} = \hat{\boldsymbol{\theta}}_{MAP}$
2. $E\{(x - \hat{x})^2\} = \sigma_p^2$, i.e., the **estimation quality** depends on the number of observations, not the observations themselves.
3. If the prior information is very bad, $\sigma_x^2 \to \infty$ and $\hat{x} \to \frac{1}{K}\sum_{i=1}^{K} y_i$
4. If the prior information is very good, $\sigma_x^2 \to 0$ and $\hat{x} \to 0$, which is the mean of the prior information
5. The estimate of x only depends on the mean of observations, not the individual observations. In this case the mean of observations is the **sufficient statistics**.
6. The inverse of estimation covariance is a measure of **information**. In this example $\frac{1}{\sigma_p^2} = \frac{1}{\sigma_x^2} + \frac{K}{\sigma_n^2}$, which means that our information of the random variable x is increased by $\frac{K}{\sigma_n^2}$ after observing $\{y_i\}_{i=1}^{K}$.

Examples

continued

Estimation of an unknown variance

We want to estimate the signal variance θ from K independent observations:

$$y_i = s_i + n_i; \quad n_i \sim N(0,1); \quad s_i \sim N(0,\theta)$$

Accordingly, we have $y_i \sim N(0, \theta + 1)$. Hence,

$$\hat{\theta}_{ML} = \arg\max_{\theta} f(\mathbf{y}|\theta) = \arg\max_{\theta} \prod_{i=1}^{K} f(y_i|\theta) = \arg\max_{\theta} [\log f(\mathbf{y}|\theta)]$$

$$ll(\theta) = \sum_{i=1}^{K} \log\left(\frac{1}{\sqrt{2\pi(1+\theta)}} \exp\left[\frac{-y_i^2}{2(1+\theta)}\right]\right)$$

$$\frac{\partial ll(\theta)}{\partial \theta} = \frac{1}{2}\left[\frac{K}{1+\theta} - \frac{\sum_{i=1}^{K} y_i^2}{(\theta+1)^2}\right] = 0 \Rightarrow \qquad \hat{\theta}_{ML} = \max\left(\left(\frac{1}{K}\sum_{i=1}^{K} y_i^2\right) - 1, 0\right)$$

Examples I

continued

Time to cell death for *in vitro* cell culture (de Vries et al., 2006, Ch. 7)

During cell culture, the pdf of cell death at age 'a' can be modeled as follows (de Vries et al., 2006, Sec. 5.3.1):

$$f_A(a) = \mu(a) \exp\left(-\int_0^a \mu(\tau) d\tau\right)$$

which, if the **mortality rate** $\mu(a)$ is constant, simplifies to: $f_A(a) = \mu \exp(-\mu a)$.
The objective is to find the positive parameter μ, from n mutually independent observations of cells deaths at ages $a_1, \cdots, a_n$.
Some ideas: Considering the dimension of μ (inverse time):

$$\hat{\mu}_1 = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{a_i}, \quad \hat{\mu}_2 = 1/\bar{a} = 1/(\frac{1}{n}\sum_{i=1}^{n} a_i), \quad \hat{\mu}_3 = 1/(\prod_{i=1}^{n} a_i)^{1/n}, \text{ etc.}$$

Which one is better and Why?

Examples II

continued

An ML-based solution

Defining the observation vector $\mathbf{y} = [a_1, a_2, ...a_n]$ we have

$$\hat{\mu}_{ML} = \arg\max_{\mu} f_A(\mathbf{y}|\mu)$$

Considering the independence of the n observations

$$f_A(\mathbf{y}|\mu) = f_A(a_1, a_2, ..., a_n|\mu) = \prod_{i=1}^{n} f(a_i|\mu) = \mu^n \exp\left(-\mu \sum_{i=1}^{n} a_i\right)$$

Differentiating the log-likelihood function $\log f(\mathbf{y}|\mu)$ we find

$$\hat{\mu}_{ML} = \frac{1}{\frac{1}{n}\sum_{i=1}^{n} a_i}$$

Examples III

continued

The amount of dose required to kill beetles (LD50 dose) (de Vries et al., 2006, Sec. 7.2.1)

$p(c)$: The probability of beetles' death using a chemical substance of dose c

$$\frac{dp(c)}{dc} = \alpha p(c)(1 - p(c)); \quad \alpha : \text{the mortality rate}$$

for simplicity we define β such that $p(\frac{\beta}{\alpha}) = \frac{1}{2}$, resulting in $p(c) = \frac{1}{1+e^{\beta - \alpha c}}$

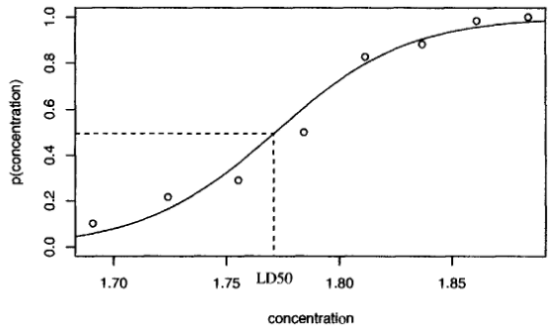


Figure: Sample data shown over the optimal curve of $p(c)$

Examples IV

continued

LD50 dose (continued)

The unknown parameter set is $\theta = (\alpha, \beta)$. As the observations, we count the number of killed insects $K(c)$ having applied the dose c to n insects. The probability of having $K(c)$ insects killed is:

$$p(K(c) = k|\theta) = \binom{n}{k}(p(c))^k(1 - p(c))^{n-k}$$

Repeating the experiment in $c_1, \cdots, c_L$ doses for $n_1, \cdots, n_L$ number of insects and observing $k_1, \cdots, k_L$ killed insects, and assuming the beetle deaths to be independent, we have:

$$f([k_1, k_2, .., k_n]|\theta) = \prod_{i=1}^{L} p(k(c) = k_i|\theta) = \prod_{i=1}^{L} \binom{n_i}{k_i} p(c_i)^{k_i}(1 - p(c_i))^{n_i - k_i}$$

The ML estimation can be numerically found using real observations.

Least Squares Error Estimation I

Introduction

- In many parameter estimation problems, we only have a **data model** and a set of observations; without any prior assumptions on the pdf of the noise or observations.
- Hence, Bayesian and ML estimation frameworks are inapplicable.
- So one can simply find the set of model parameters that minimize the average square error between the observations and model, over all available data points.
- This method is known as **least squares estimation (LSE)**.
- LSE can be solved using a deterministic optimization framework, without any prior stochastic assumptions.
- Interestingly, LSE provides the same solution as the MAP and ML estimators for a broad class of parameter estimation problems.

Least Squares Error Estimation II

LSE for Polynomial Models

Consider the noisy observations $x(t)$ $(t = 1, \cdots, T)$ and the polynomial data model

$$x(t) = \hat{x}(t) + e(t), \quad \hat{x}(t) \stackrel{\Delta}{=} \sum_{j=0}^{N-1} a_i t^i$$

a_i: unknown parameters.

We seek to minimize the cost function: $C = E\{e^2(t)\} = E_t\{\left(x(t) - \sum_{i=0}^{N-1} a_i t^i\right)^2\}$

$$\frac{\partial C}{\partial a_k} = E_t\{2(x(t) - \sum_{i=0}^{N-1} a_i t^i)(-t^k)\} = 0 \Rightarrow E\{t^k x(t)\} = \sum_{i=0}^{N-1} a_i E\{t^k t^i\}$$

$$\boldsymbol{x} = a\boldsymbol{T} \Rightarrow \boldsymbol{a} = \boldsymbol{x}\boldsymbol{T}^{-1}, \qquad \boldsymbol{x} \stackrel{\Delta}{=} [E\{t^k x(t)\}]_k, \quad \boldsymbol{T} \stackrel{\Delta}{=} [E\{t^{k+i}\}]_{k,i}$$

Least Squares Error Estimation III

ECG parameter estimation from noisy signals

The problem of estimating diagnostic parameters from ECG segments such as the QRS, T, or ST-segment, is of interest. Using prior models (e.g. polynomial models of given orders), we would like to estimate the model coefficients.

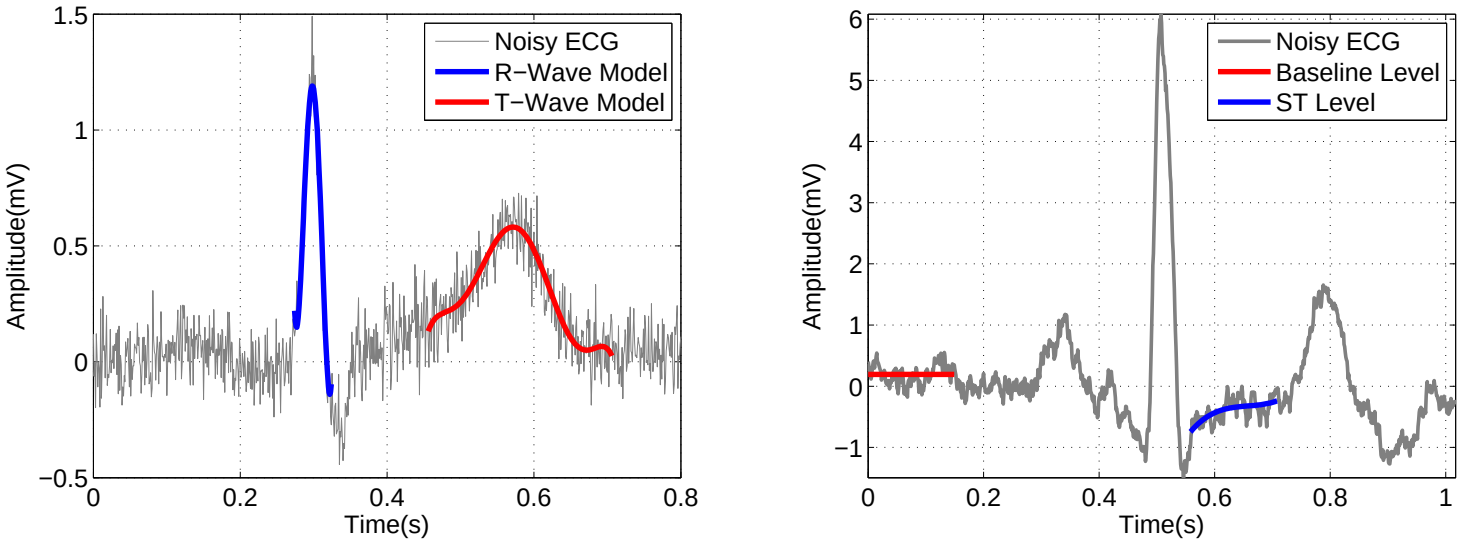


Figure: ECG parameter estimation using least square error estimation

Least Squares Error Estimation IV

ECG parameter estimation from noisy signals (continued)

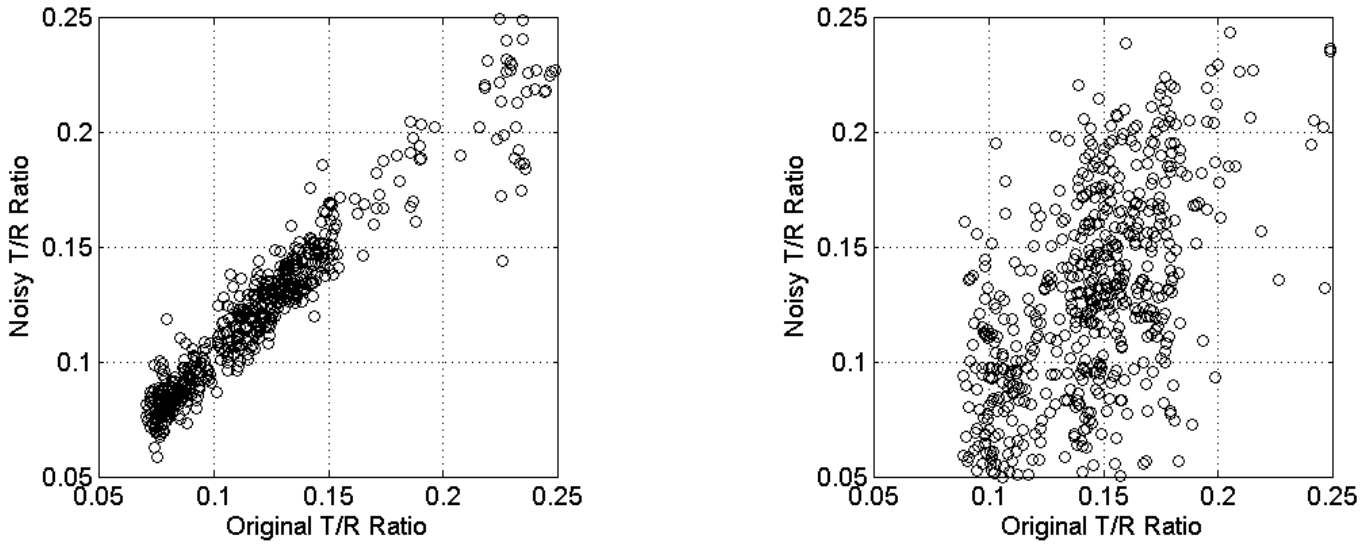


Figure: True versus estimated T/R ratio with (left) and without (right) signal modeling from noisy ECG

Further Topics

Further topics discussed in this section (Haefner, 2005, Ch. 7):

- Examples of various biological parameter estimation problems solved by LSE
- The advantages of having models, which are **linear in parameters**
- Model transformation and how to transform models into a **linear in parameters** model?
- Reservations regarding model transformation
  ✎ Model transformation is good for illustration and model verification (to show how good a model is); but nonlinear LSE parameter estimation methods are preferred in practice for parameter estimation. Cf. **nlinfit** and **lsqnonlin** functions in Matlab.
- Weighted least square error (WLSE) parameter estimation

Model assessment and selection

Suppose that a set of models have been proposed for a given problem. We need to see:

- **How good is a model?** For example, we can fit a line over "*any*" set of data points; but how good is a linear model?
- **How to compare models?** Models have different mathematical structure.
- **How to compare models with different number of parameters?** Parsimony implies that simple models are preferred over complex ones; but which one should we choose when a complicated model is more accurate than a simple one?

Akaike information criteria I

Akaike information criteria (AIC): A criteria for comparing various parameter estimation approaches having different levels of complexity and error. *The higher the AIC, the better!*

$$AIC \triangleq 2ll(\hat{\boldsymbol{p}}|\boldsymbol{x}) - 2n_p, \qquad N > 40$$
$$AICc \triangleq 2ll(\hat{\boldsymbol{p}}|\boldsymbol{x}) - 2n_p \frac{N}{N-n_p-1}, \qquad N \leq 40 \qquad \text{(Corrected AIC)}$$

- N: number of data points used for estimation
- $\boldsymbol{x}$: measurements with N data-points
- $\hat{\boldsymbol{p}}$: the parameter that maximizes the **log-likelihood** function $ll(\hat{\boldsymbol{p}}|\boldsymbol{x})$
- n_p: number of model parameters

Akaike information criteria II

Salmonella population mean estimation (de Vries et al., 2006, Sec. 7.3)

The population of Salmonella subject to a dose c of **Quinoline** is assumed to follow a Poisson distribution with an unknown mean parameter μ. Two models have been proposed for this problem:

$$\mu^{(1)}(c) = \mu_0 + \mu_1 c$$
$$\mu^{(2)}(c) = \nu_0 + \nu_1 \ln(c + \nu_2)$$

By calculating the log-likelihood and AIC for both models, we find: $\text{AIC}^{(1)} = -53.4$ and $\text{AIC}^{(2)} = -38.1$, which suggests that the second model is better (despite its complexity).

Akaike information criteria III

Further Reading

- de Vries et al. (2006, Sec. 7.3)
- Rafael A. Irizarry, Statistical Learning: Algorithmic and Nonparametric Approaches, Ch. 7: Model Assessment and SelectionJohns Hopkins University.

Bias in machine learning and AI

Research questions

- Do certain algorithms perform differently by age/sex/race?
- Do these biases differ by algorithm/model design metric?
- Can we mitigate algorithm biases?

Approaches

1. Data imbalance correction techniques: resampling, class weighting, ensemble methods, cost-sensitive learning, etc.
2. Optimizing ML models subject to health equity and reduced bias objective functions
3. Data augmentation: generating new synthetic samples for the minority class

Case study

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journal homepage: www.jecgonline.com

Age, sex and race bias in automated arrhythmia detectors

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ARTICLE INFO

Keywords:
Bias
Race
Age
Sex
Machine learning
Healthcare

ABSTRACT

Despite the recent explosion of machine learning applied to medical data, very few studies have examined algorithmic bias in any meaningful manner, comparing across algorithms, databases, and assessment metrics. In this study, we compared the biases in sex, age, and race of 56 algorithms on over 130,000 electrocardiograms (ECGs) using several metrics and propose a machine learning model design to reduce bias. Participants of the 2021 PhysioNet Challenge designed and implemented working, open-source algorithms to identify clinical diagnosis from 2- lead ECG recordings. We grouped the data from the training, validation, and test datasets by sex (male vs female), age (binned by decade), and race (Asian, Black, White, and Other) whenever possible. We computed recording-wise accuracy, area under the receiver operating characteristic curve (AUROC), area under the precision recall curve (AUPRC), F-measure, and the Challenge Score for each of the 56 algorithms. The Mann-Whitney U and the Kruskal-Wallis tests assessed the performance differences of algorithms across these demographic groups. Group trends revealed similar values for the AUROC, AUPRC, and F-measure for both male and female groups across the training, validation, and test sets. However, recording-wise accuracies were 20% higher ($p < 0.01$) and the Challenge Score 12% lower ($p = 0.02$) for female subjects on the test set. AUPRC, F-measure, and the Challenge Score increased with age, while recording-wise accuracy and AUROC decreased with age. The results were similar for the training and test sets, but only recording-wise accuracy (12% decrease per decade, $p < 0.01$), Challenge Score (1% increase per decade, $p < 0.01$), and AUROC (1% decrease per decade, $p < 0.01$) were statistically different on the test set. We observed similar AUROC, AUPRC, Challenge Score, and F-

DOI: 10.1038/s42254-021-00314-5

Case study

(continued)

PhysioNet Challenge 2021

- Academic and industrial participants of the 2021 PhysioNet Challenge designed and implemented working, open-source algorithms to identify 26 clinical diagnoses from 2-lead ECG recordings
- **Data:** 131,155 recordings from 9 databases, 4 countries, and 3 continents.
- 88,253 public for training, 6,630 hidden for validation, and 36,272 hidden for test

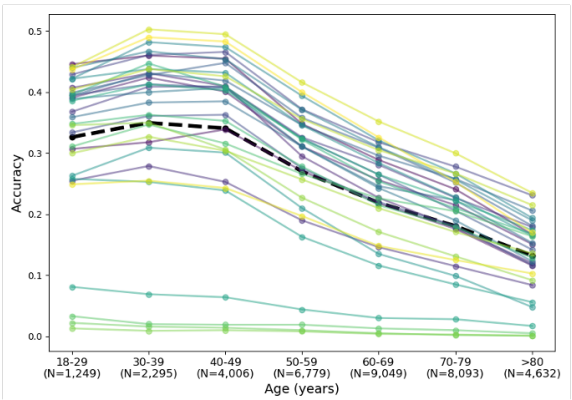
Method

- Grouped the training, validation, and test datasets by sex (male vs female), age (binned by decade), and race (Asian, Black, White, and Other) whenever possible
- Computed "per-recording accuracy", area under the receiver operating characteristic curve (AUROC), area under the precision recall curve (AUPRC), F-measure, and the Challenge Score (a metric designed for the 2021 Challenge which considered diagnosis severity)
- The Mann-Whitney U and the Kruskal-Wallis tests assessed the performance differences of algorithms across these demographic groups

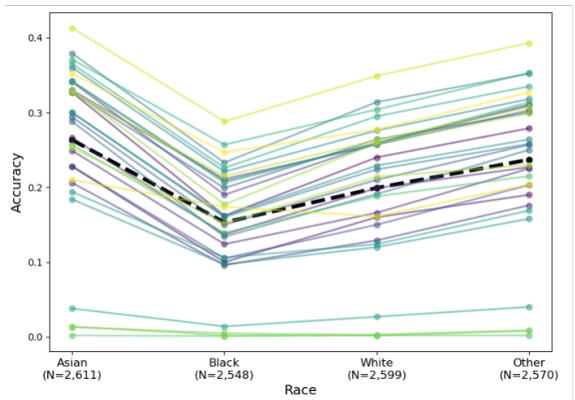
Case study

(continued)

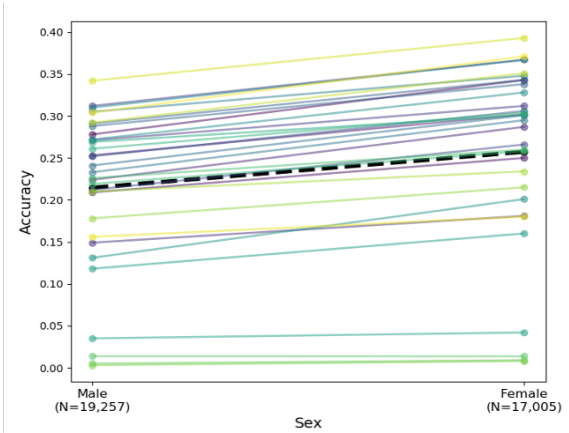
Results



(a) Age; ∼12% decrease/decade, $p<0.01$



(b) Race; 39% difference, $p<0.01$



(c) Sex, 20% difference, $p<0.01$

Figure: Performance biases in the 2021 PhysioNet Challenge algorithms

Proposed solution

Optimal classifier design; a multi-objective landscape

- Optimal classifier design is a multiobjective problem Common optimization criteria:
  - ML metrics (Objective): accuracy, AUROC, AUPRC, F-measure, etc.
  - Cost-based (Subjective): ad hoc cost functions that take into account real-world costs of false positives and false negatives per application

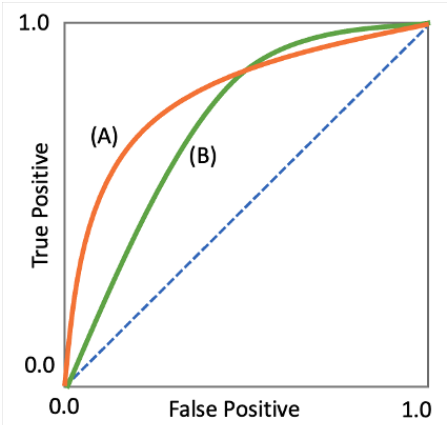


Figure: Typical ROC showing no optimal model (each model outperforms the other for certain criteria)

Why not optimize for better health equity and less bias?

Reduced-bias ML model design

Proposed scheme: For a parametric model/algorithm θ, we propose a regularized (or "bias-penalized") optimization loss function:

$$C(\theta) = f(\theta) + \lambda\phi(\theta)$$

- $C(\theta)$: loss function
- $f(\theta)$: conventional machine-learning loss functions
- $\phi(\theta)$: bias metric
- λ: regularization (penalization) factor

For example:

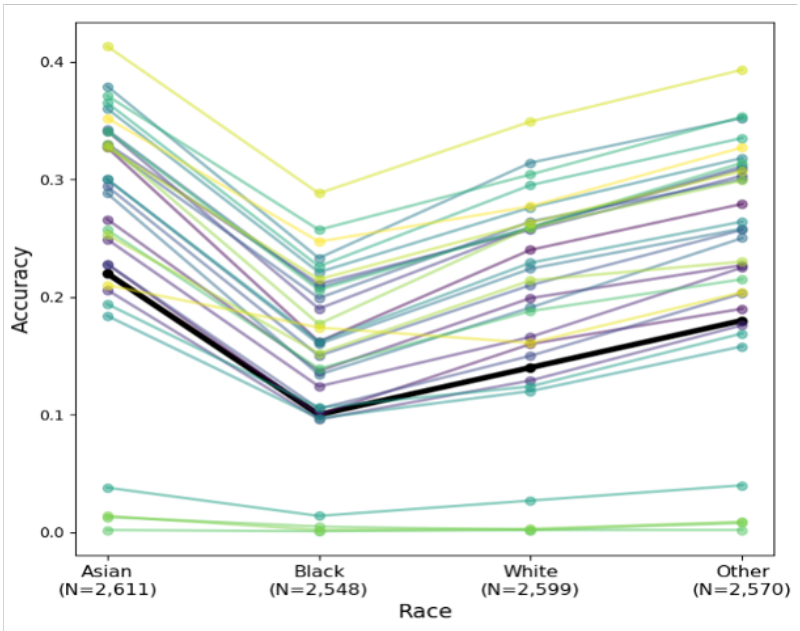
$$C = \text{Accuracy} + \lambda|\text{difference in accuracy between Black \& Asian subjects}|$$

Note: Constrained optimization generally degrades the optimization cost in favor of satisfying the additional constraint (a **reduced-bias** in this study)

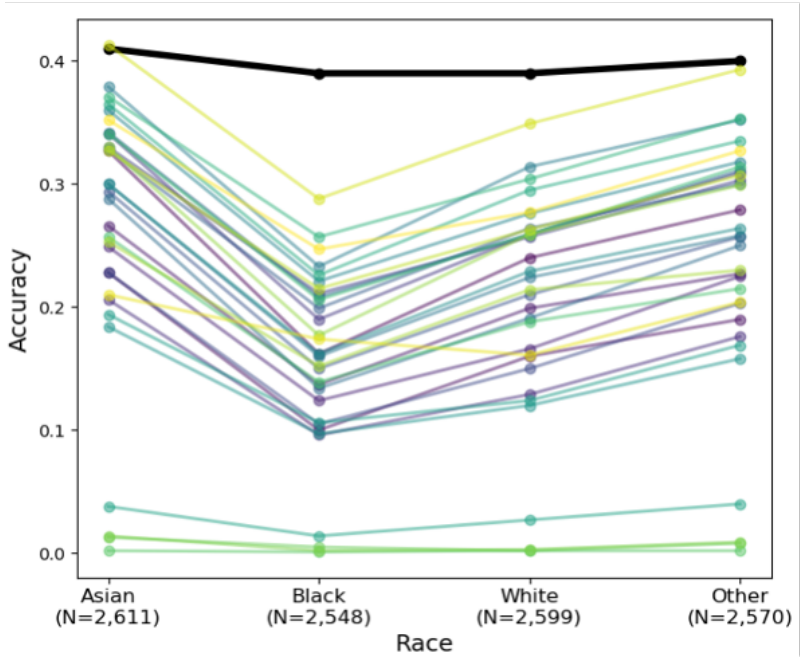
Reduced-bias ML model design

(continued)

Results after bias reduction



(a) Before bias correction



(b) After bias correction

Figure: Performance biases of an ensemble model from the 2021 PhysioNet Challenge algorithms before (left) and after (right) bias correction

Bias-reduction by data augmentation

The bipedal-spring mass human walk dynamics model

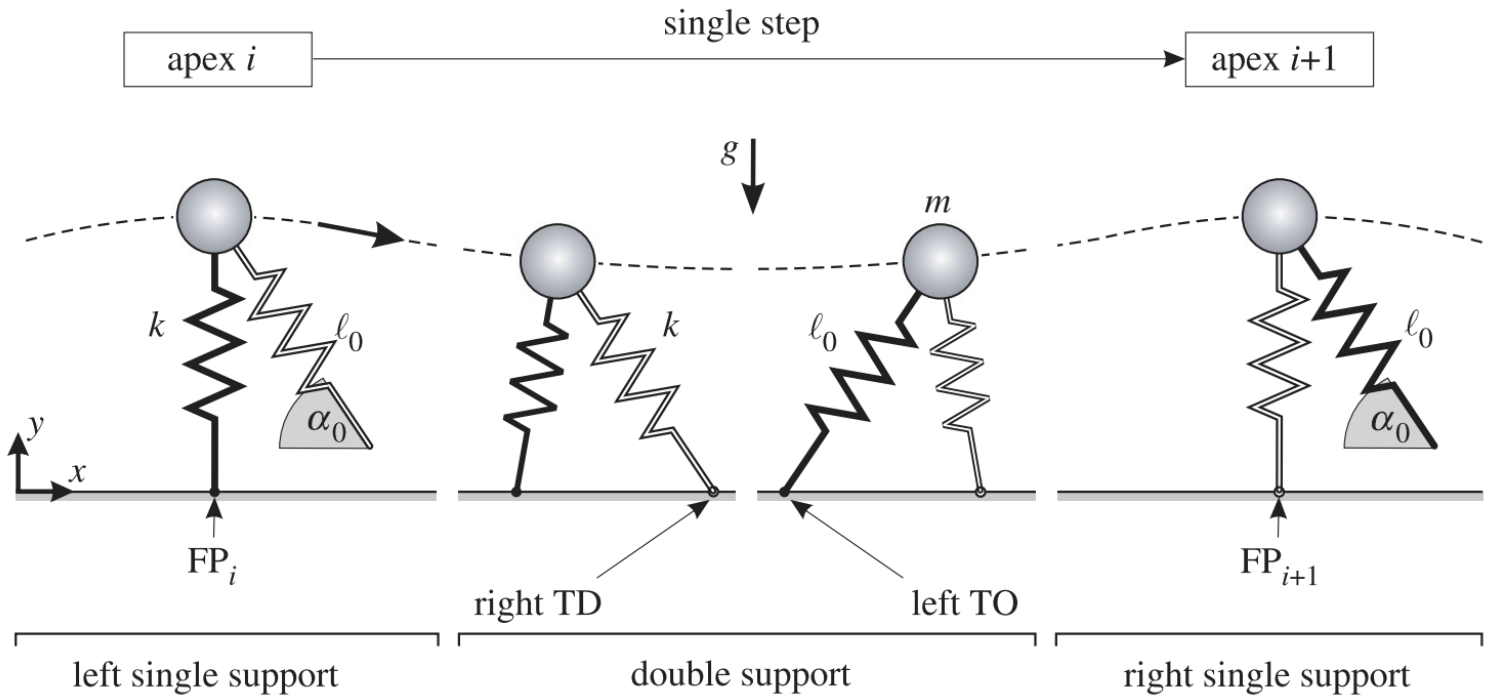


Figure: Geyer et al (2006). Compliant leg behaviour explains basic dynamics of walking and running. Proc. Royal Soc. B: Biol. Sci., 273 (1603). DOI: 10.1098/rspb.2006.3637

Bias-reduction by data augmentation

(continued)

The center of mass dynamics of the bipedal-spring mass human walking model:

For a single step from apex i to $i+1$:

- initial left leg single support: $m\ddot{x} = Px$, $m\ddot{y} = Py - mg$
- intermittent double support: $m\ddot{x} = Px - Q(d-x)$, $m\ddot{y} = Py + Qy - mg$
- final right leg single support: $m\ddot{x} = -Q(d-x)$, $m\ddot{y} = Qy - mg$

where $P = k(l_0/\sqrt{x^2+y^2} - 1)$, $Q = k(l_0/\sqrt{(d-x)^2+y^2} - 1)$, $d = \mathrm{FP}_{i+1,x} - \mathrm{FP}_{i,x}$, and FP denotes the foot point of a stance spring.

Question

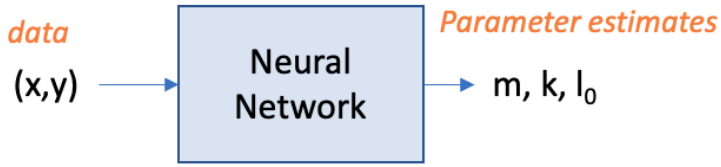
- Can we fit this model onto real data and train a neural network to estimate the model parameters m, k and l from real measurements?
- **Application:** extract physics-based features from motion sensors attached to patients, to study/classify their walking patterns

Bias-reduction by data augmentation

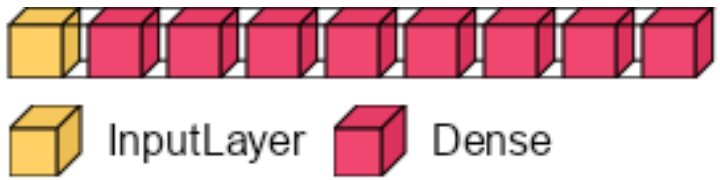
(continued)

Data augmentation

- We can use Page 263 equations as the forward model to generate synthetic data required for training a neural network for parameter identification from real data.



- **Parameter sweep range:** N = 1,000,000, g = 10 m/s^2, dt=0.1s, $m \sim U[60, 75]$ kg, $k \sim U[8000, 10000]$ N/m, $l_0 \sim U[0.6, 0.8]$ m, $x_0 \sim U[0, 0.1]$ m, $y_0 \sim U[0, 0.1]$ m.
- **Training/validation setup:** 80% training, 10% validation, 10% testing
- **Neural network architecture:**



Bias-reduction by data augmentation

(continued)

Results

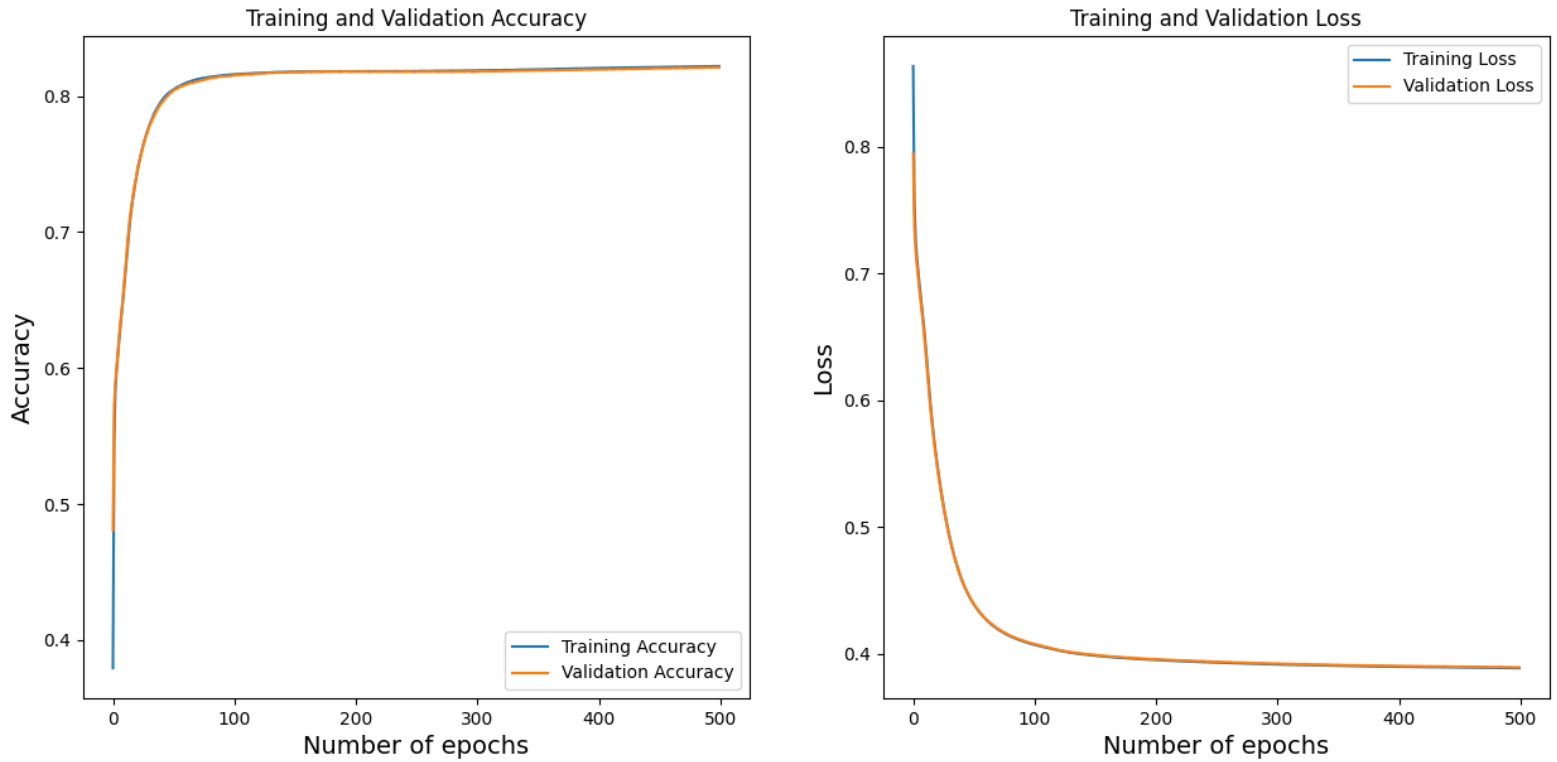
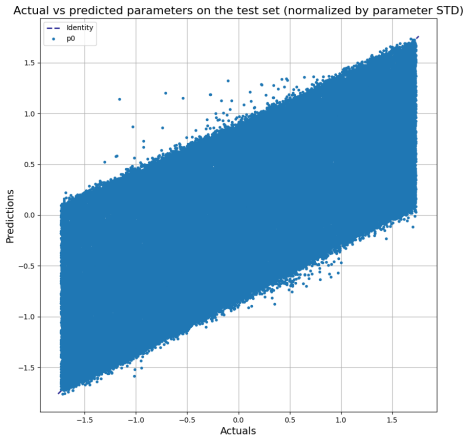


Figure: Training and validation set accuracy and loss

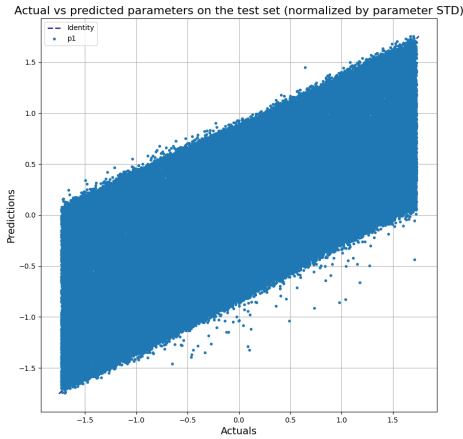
Bias-reduction by data augmentation

(continued)

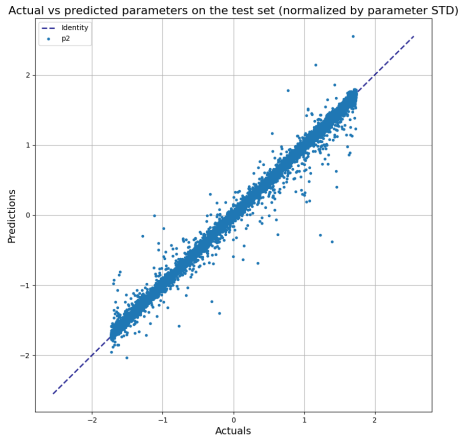
Results



(a) m



(b) k



(c) l_0

Figure: Model performances on the unseen test set for the three parameters m, k and l_0

Interpretation: Parameters m and k are unidentifiable (can not be learned uniquely), but l_0 is identifiable from the observation data (x, y)

Bias-reduction by data augmentation

(continued)

Results

The bipedal-spring mass model (Page 263) is identifiable in terms of the parameters l_0 and m/k:

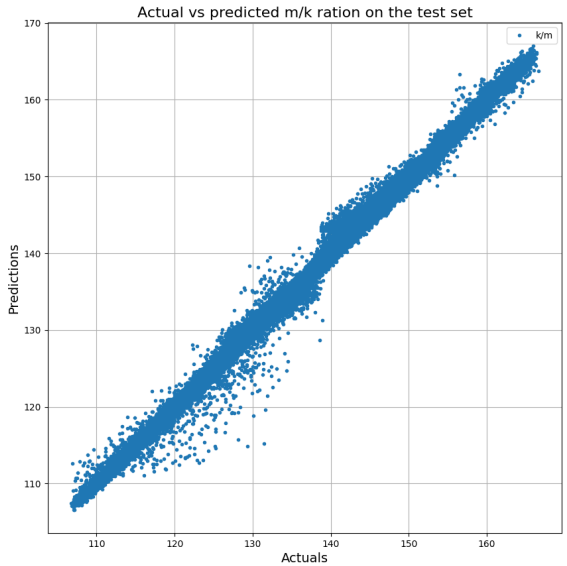


Figure: Model performance in estimating the ratio $\rho = m/k$ (instead of the individual parameters m and k)

Data augmentation with generative models and ethical AI

Background

- Synthetic data used for training ML models can be generated with arbitrary distributions
- The performance boosting due to synthetic data augmentation is more realistic and generalizable, when the distributions matches real populations

Question

1. How to choose the distributions of synthetic data model parameters to obtain ML/AI models with improved health equity?
2. For example, for a biomarker that has a Normal distribution in real world data (including the outliers), is it better to train ML models on synthetic biomarker that follow the actual population-wide distributions, or should we sweep the model parameters uniformly to cover the corner cases of the population?
3. Which is the best choice, performance-wise?
4. Which is the most ethical?

Using artificial intelligence chatbots for model development

Large language models (LLMs) are changing our perspective to modeling.

Exercise 10: Use ChatGPT or other LLM-based chatbots to explore ideas for the pre-selected semester projects.

1. Articulate the project definition in the chatbot. Based on the responses, modify and refine the problem.
2. Ask for a mathematical/algorithmic formulation of the project
3. Study the proposed solutions of the chatbot critically (explore the proposed algorithm, validate the dimensions of the mathematical model, etc.)
4. When the model seems accurate, ask the chatbot to provide you with the source code for implementing the model
5. Test and debug the model interactively. Avoid manual debugging. If the code fails, communicate the error with the chatbot and ask for model/code corrections.

Deliverables: 1) The log of the interactions with the chatbot; 2) A critical discussion regarding the accuracy of the model/codes and the performance of the chatbot's model as compared to your previously developed and tested models for the project.

Synthetic data generation

Introduction

Synthetic realistic data generated by physics-informed (knowledge-based) models can be leveraged to boost the performance of machine learning models for:

- Developing high-order models such as deep neural networks for small datasets
- Addressing data imbalance and improving performance for underrepresented classes
- Stress-testing models in corner cases
- Privacy preserving and avoiding protected health information (PHI) leakage

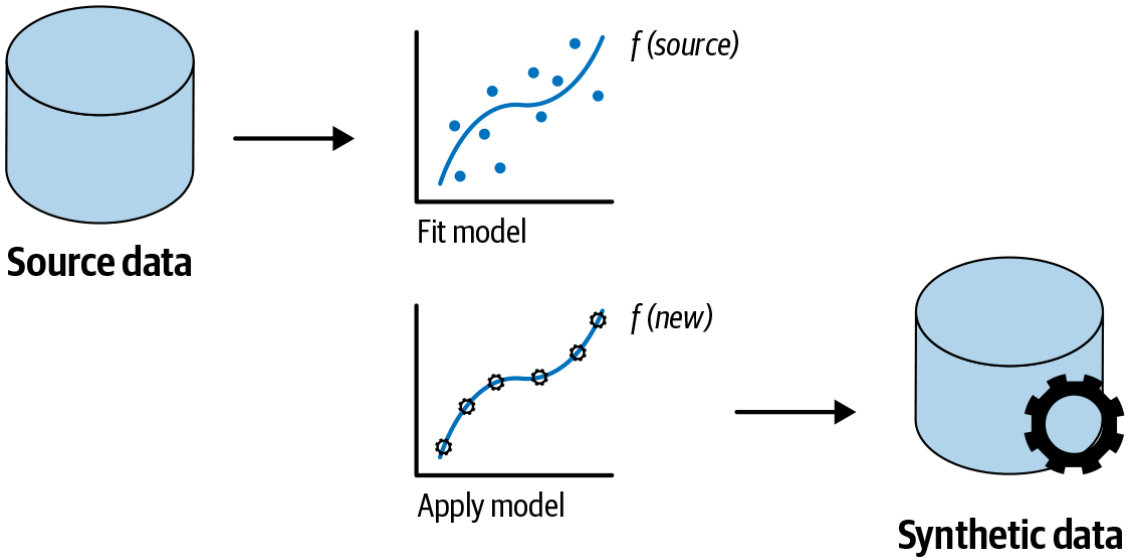


Figure: Conceptual process of data generation, adopted from: Emam, Khaled. Practical Synthetic Data Generation. O'Reilly Media, Inc, 2020.

Synthetic data generation methods

How to generate synthetic data

- Stochastic distribution fitting
- Model-based data generation
- Hybrid models

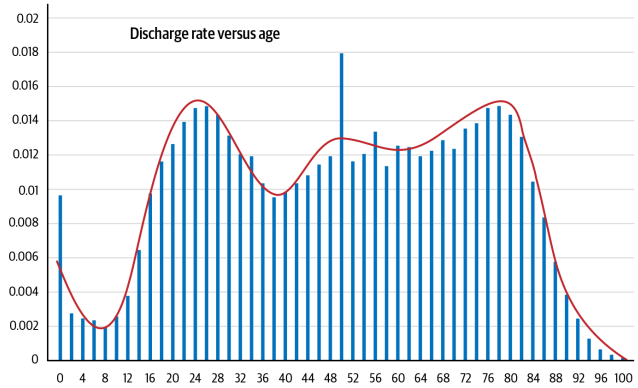
Stochastic distribution fitting

Approach

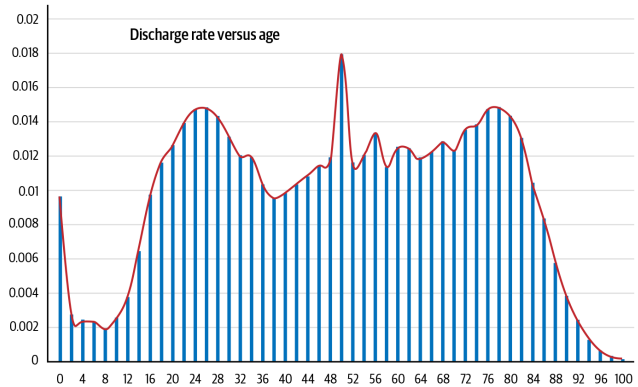
1. Fit a parametric or non-parametric distribution on the training dataset
2. Generate random samples from the fitted distribution

Challenges

1. Multimodal distributions
2. Multivariate and time-series data
3. Small training datasets and inaccuracy of the fitted models
4. Measuring 'goodness of fit' is subjective
5. Dealing with outliers



(a) Model I



(b) Model II

Figure: Hospital discharge rate vs age with two models, adopted from (Khaled, 2020)

Stochastic distribution goodness of fit

The Kolmogorov-Smirnov (KS) test

Measures the difference between the empirical distribution function of the data and the cumulative distribution function of the reference (here, 'the fitted') distribution.

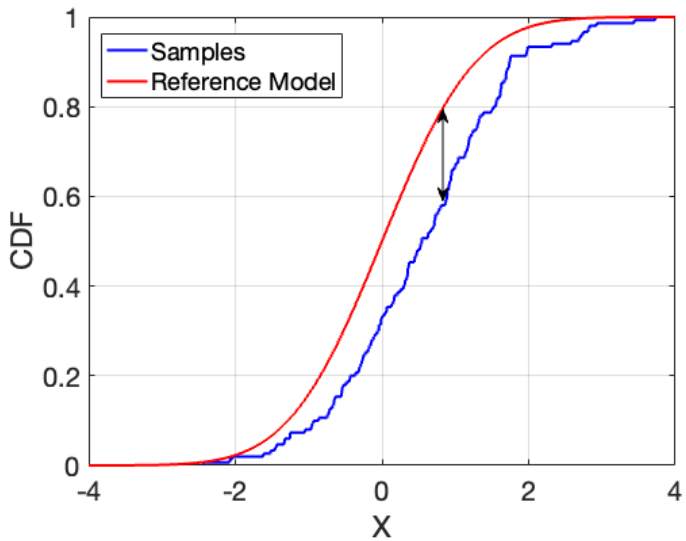


Figure: Kolmogorov-Smirnov (KS) test

Arbitrary stochastic distribution generation

Generating random variables (RVs) of arbitrary distribution

Lemma: To generate RVs X with a probability density function (pdf) $f_X(x)$:

1. Generate uniform random variables $u \sim U[0, 1]$
2. Calculate $x = F_X^{-1}(u)$ where $F_X(\cdot)$ is the cumulative distribution function (CDF)

Proof: (Papoulis & Pillai, 2002)

Notes:

- Conversely, passing the ensembles of a RV through its CDF results in a uniformly distributed RV: $u \sim U[0, 1]$
- The technique is generalizable to multivariate data

Synthetic stochastic time-series data generation

Innovation filter design

Common methods for generating synthetic time-series data:

- Stationary time-series:
  - Spectral domain approach: spectral factorization and innovations filter design
  - Time-domain approach: AR, MA, ARMA, etc.
- Nonstationary time-series:
  - Time-varying AR, MA, ARMA, etc.
  - Dynamic modeling

Stationary synthetic data generation using innovations filter

Innovation process (Papoulis & Pillai, 2002, Ch. 11)

Consider a causal LTI system with the impulse response $l(t)$. The output of this system to a white noise input $i(t)$ with variance σ_i^2 is

$$x(t) = \int_0^\infty l(\tau) i(t-\tau) d\tau$$

which has the following spectrum:

$$S_x(f) = \sigma_i^2 |L(f)|^2$$

If $l(t)$ is *minimum phase*, the inverse of $l(t)$, known as the *whitening filter* and denoted by $\gamma(t)$, exists and

$$i(t) = \int_0^\infty \gamma(\tau) x(t-\tau) d\tau$$

Stationary synthetic data generation using innovations filter
(continued)

Spectral factorization (Papoulis & Pillai, 2002, Ch. 11)

If the desired signal spectrum has the form $S_x(\omega) = \frac{A(\omega^2)}{B(\omega^2)}$, it is easy to show that $S_x(s)$ can be factorized as follows ($j\omega \to s$)

$$S_x(s) = L(s)L(-s)$$

where $L(s)$ (the innovation filter) is arranged such that it contains all the zeros and poles of $S_x(s)$ in the left side of the s-plane, i.e., $L(s)$ is minimum phase. This guarantees that $L(s)$ and $\Gamma(s) = \frac{1}{L(s)}$ (the whitening filter) are both stable.

Stationary synthetic data generation using innovations filter
(continued)

Example

Suppose we are interested in generating synthetic data with the spectrum $S_x(\omega) = \frac{N}{\alpha^2+\omega^2}$. Then $L(s)L(-s) = \frac{N}{(\alpha+s)(\alpha-s)}$, or

$$L(s) = \frac{\sqrt{N}}{\alpha + s} \Rightarrow l(t) = \sqrt{N}e^{-\alpha t}u(t): \quad \text{innovations filter}$$

Example

Suppose we want to generate synthetic data with the spectrum $S_x(\omega) = \frac{49+25\omega^2}{\omega^4+10\omega^2+9}$, or $L(s)L(-s) = \frac{(7-5s)(7+5s)}{(1-s^2)(9-s^2)}$. Hence:

$$L(s) = \frac{7 + 5s}{(1 + s)(3 + s)} \Rightarrow l(t) = (e^{-t} + 4e^{-3t})u(t)$$

Stationary synthetic data generation using linear time-invariant models

There are several models used to model time-series data:

- **Autoregressive (AR)**

$$y_t = \phi_1 y_{t-1} + \phi_2 y_{t-2} + \cdots + \phi_p y_{t-p} + \epsilon_t$$

- **Moving average (MA)**

$$y_t = \epsilon_t + \theta_1 \epsilon_{t-1} + \theta_2 \epsilon_{t-2} + \cdots + \theta_q \epsilon_{t-q}$$

- **Autoregressive moving average (ARMA)**

$$y_t = \phi_1 y_{t-1} + \phi_2 y_{t-2} + \cdots + \phi_p y_{t-p} + \epsilon_t + \theta_1 \epsilon_{t-1} + \theta_2 \epsilon_{t-2} + \cdots + \theta_q \epsilon_{t-q}$$

where y_t is the value of the time-series variable at time t, $\phi_1, \phi_2, \ldots, \phi_p$ are the autoregressive coefficients, p is the AR model order, $\epsilon_t, \epsilon_{t-1}, \ldots, \epsilon_{t-q}$ are the error terms at time t and the previous q time points, and $\theta_1, \theta_2, \ldots, \theta_q$ are the MA coefficients. ARMA is the most general.

Stationary synthetic data generation using innovations filter via autoregressive modeling

- Autoregressive modeling is a method used to model time-series data
- It assumes that the value of a variable at a given time point depends linearly on its previous values
- The order of the model is the number of previous values used to predict the current value.
- The coefficients of the autoregressive model can be estimated using several methods, including the Yule-Walker equations.

Autoregressive model fitting using the Yule-Walker equations

The general form of an autoregressive (AR) model of order p is:

$$y_t = \phi_1 y_{t-1} + \phi_2 y_{t-2} + \cdots + \phi_p y_{t-p} + \epsilon_t$$

where:

- y_t is the value of the time series variable at time t.
- $\phi_1, \phi_2, \ldots, \phi_p$ are the autoregressive coefficients.
- $y_{t-1}, y_{t-2}, \ldots, y_{t-p}$ are the previous values of the model output.
- ϵ_t is the error term at time t (the model input) with variance σ^2

This equation states that the value of y_t depends linearly on its past values $y_{t-1}, y_{t-2}, \ldots, y_{t-p}$ and a random error term ϵ_t. The order of the AR model is given by p, which is the number of past values used to predict the current value. The autoregressive coefficients $\phi_1, \phi_2, \ldots, \phi_p$ represent the weights given to the previous values in the prediction of the current value.

Autoregressive model fitting using the Yule-Walker equations I
(continued)

- The Yule-Walker equations are a set of linear equations that can be used to estimate the coefficients of an autoregressive model.
- For an AR(p) model, the Yule-Walker equations are given by:

$$
\begin{aligned}
r_0 &= \sum_{k=1}^{p} \phi_k r_k + \sigma^2 \\
r_1 &= \phi_1 r_0 + \sum_{k=2}^{p} \phi_k r_k \\
&\vdots \\
r_p &= \phi_p r_0 + \phi_{p-1} r_1 + \cdots + \phi_1 r_{p-1}
\end{aligned}
$$

where $r_k = E_m\{y_{m+k} y_m\}$ is the output autocovariance at lag k, $\phi_1, \phi_2, \ldots, \phi_p$ are the autoregressive coefficients, and σ^2 is the variance of the error term.

The Yule-Walker equations in matrix form

The Yule-Walker equations relate the autocorrelation function to the autoregressive coefficients of an AR(p) model:

$$\begin{pmatrix} r_0 & r_1 & \cdots & r_{p-1} \\ r_1 & r_0 & \cdots & r_{p-2} \\ \vdots & \vdots & \ddots & \vdots \\ r_{p-1} & r_{p-2} & \cdots & r_0 \end{pmatrix} \begin{pmatrix} \phi_1 \\ \phi_2 \\ \vdots \\ \phi_p \end{pmatrix} = \begin{pmatrix} r_1 \\ r_2 \\ \vdots \\ r_p \end{pmatrix}$$

We can solve for ϕ by inverting the autocorrelation matrix:

$$\boldsymbol{\phi} = \begin{pmatrix} \phi_1 \\ \phi_2 \\ \vdots \\ \phi_p \end{pmatrix} = \begin{pmatrix} r_0 & r_1 & \cdots & r_{p-1} \\ r_1 & r_0 & \cdots & r_{p-2} \\ \vdots & \vdots & \ddots & \vdots \\ r_{p-1} & r_{p-2} & \cdots & r_0 \end{pmatrix}^{-1} \begin{pmatrix} r_1 \\ r_2 \\ \vdots \\ r_p \end{pmatrix}$$

Further notes

- The Yule-Walker is not the only method for AR model fitting
- There are also algorithms for fitting MA and ARMA models, which are more complicated than the AR equations.
- It can be shown that $ARMA(p, q)$ models can be approximated with an AR model of higher models.
- Therefore, AR models are the most popular.
- AR, MA and ARMA models can be used to model nonstationary time-series by making the model coefficients a function of time (commonly with slow fluctuations)

Time-series generation using dynamic models

Nonlinear dynamic models

- Using context knowledge, Linear or nonlinear dynamic models can be used to model time-series data

$$\begin{cases} \dot{\mathbf{s}} = \mathbf{f}(\mathbf{s}, \mathbf{x}, \mathbf{w}) \\ \mathbf{y} = \mathbf{g}(\mathbf{s}, \mathbf{x}) + \mathbf{v} \end{cases}$$

  where $\boldsymbol{x}(t) \in \mathbb{R}^{p\times 1}$, $\boldsymbol{y}(t) \in \mathbb{R}^{m\times 1}$, and $\boldsymbol{s}(t) \in \mathbb{R}^{n\times 1}$ are the input, output and state vectors. The vectors $\mathbf{w} \in \mathbb{R}^{q\times 1}$ and $\mathbf{v} \in \mathbb{R}^{m\times 1}$ are the process and measurement noises, respectively.
- After model fitting, synthetic data can be generated in arbitrary quantities using random process and measurement noises and inputs.

Blood sugar regulation & diabetes I

Background

- "The human body maintains the blood glucose (sugar) in a very narrow range. **Insulin** and **glucagon** are the hormones which make this happen, but in opposite manners. Both insulin and glucagon (**pancreatic endocrine hormones**) are secreted from the pancreas. The production of insulin and glucagon by the pancreas ultimately determine if a patient has diabetes, hypoglycemia, or other sugar problem." (Norman, 2017)
- **Diabetes**: The condition in which the body's ability to produce or respond to the insulin hormone is impaired. The three common diabetes types are:
  - **Type 1**: "The body's immune system destroys the cells that release insulin, eventually eliminating insulin production from the body."
  - **Type 2**: "The body isn't able to use insulin the right way (called **insulin resistance**). As type 2 diabetes gets worse, the pancreas may make less and less insulin (called **insulin deficiency**)."

Ref: `http://www.webmd.com/diabetes/tc/diabetes-differences-between-type-1-and-2-topic-overview`

Blood sugar regulation & diabetes II

Glucose Control Mechanism

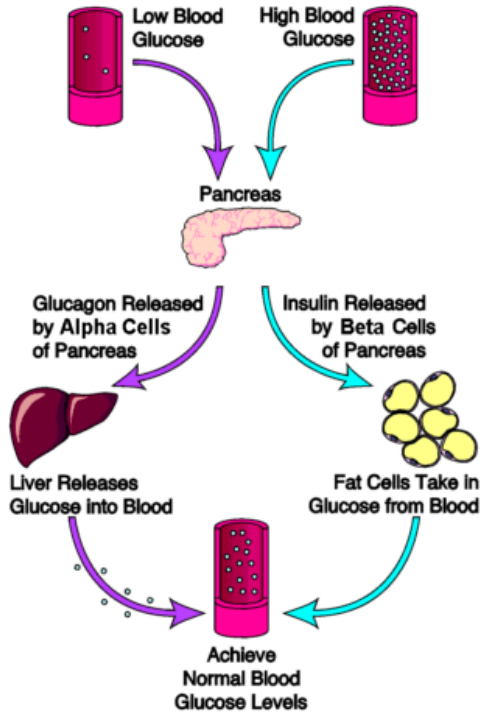


Figure: The overall glucose control mechanism (Norman, 2017)

Blood sugar regulation modeling I

Stolwijk-Hardy glucose regulation model (Stolwijk & Hardy, 1974)

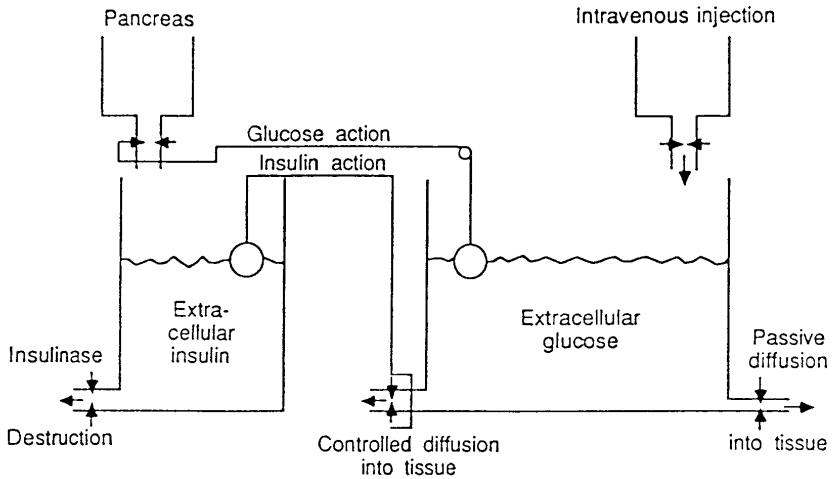


Figure: Hydraulic analog of the Stolwijk-Hardy insulin-glucose regulation model (Rideout, 1991, Ch. 8)

Blood sugar regulation modeling II

Bergman's multi-compartmental glucose minimal model (Bergman et al., 1979; De Gaetano & Arino, 2000; Friis-Jensen, 2007)

$$\begin{aligned}
\frac{dG(t)}{dt} &= -[p_1 + X(t)]G(t) + p_1 G_b, & G(0) &= G_0 \\
\frac{dX(t)}{dt} &= -p_2 X(t) + p_3[I(t) - I_b], & X(0) &= 0 \\
\frac{dI(t)}{dt} &= p_4[G(t) - p_5]^+ t - p_6[I(t) - I_b], & I(0) &= p_7 + I_b
\end{aligned}$$

- $G(t)$: blood glucose concentration
- $X(t)$: effect of active insulin
- $I(t)$: blood insulin concentration

Blood sugar regulation modeling III

Further reading on glucose-insulin models

- Carson & Cobelli (2001, Ch. 11)
- Friis-Jensen (2007)
- Steil et al. (2005)
- De Gaetano & Arino (2000)
- Bergman et al. (1979)

Heat flow and thermo-regulation modeling

We will study the problem of thermo-regulation from a modeling perspective and show how a model based on the heat equation takes the form of a compartmental model for heat flow within the body. Major reference: (Rideout, 1991, Ch. 7)

Background

- In higher forms of life (such as the human body), the internal body temperature is maintained at a rather constant level, despite changes in the external environment, to provide blood and tissue metabolic processes and cellular life. In addition,
- **Hypothermia** is used as an aid in anesthesia and muscle relaxation
- **Hyperthermia** is used for cancer ablation
- **Thermo-regulation** has notable applications in **newborn incubators** and **protective clothing** design

Heat propagation model in the human body

Heat flow occurs by diffusion in tissues and by blood flow transportation in veins and arteries. Heat is generated in a number of ways:

- **Obligatory**:
  - **Gain**: basal metabolism, muscle action of heart and respiratory system
  - **Loss**: respiratory (evaporation and air heating), evaporation of "insensible" perspiration (sweating)
- **Involuntary Control**:
  - **Gain**: muscular thermogenesis by shivering, increased metabolism in response to cold
  - **Loss**: evaporation of perspiration released by sudomotor control (stimulation of the sweat glands)
  - **Gain and loss**: due to conduction, convection, and radiation from the skin; also effects of circulatory changes.
- **Voluntary Action**:
  - **Gain**: due to muscle action
  - **Gain or loss**: due to ingestion of hot or cold liquids
  - **System parameter changes**: by adding or removing clothing, changing of heat or air movement in environment

Body heat flow model I

Multiple modeling of body heat flow

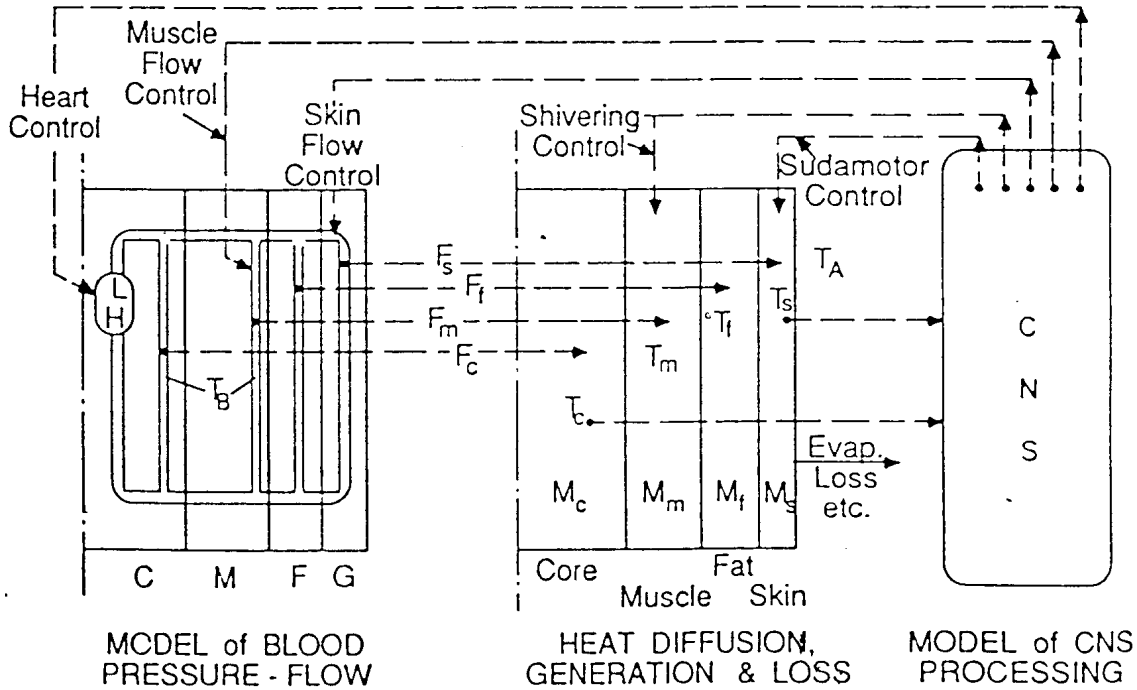


Figure: Heat generation and loss in the body (Rideout, 1991, Ch. 7)

Body heat flow model II

Diffusion of heat in the body

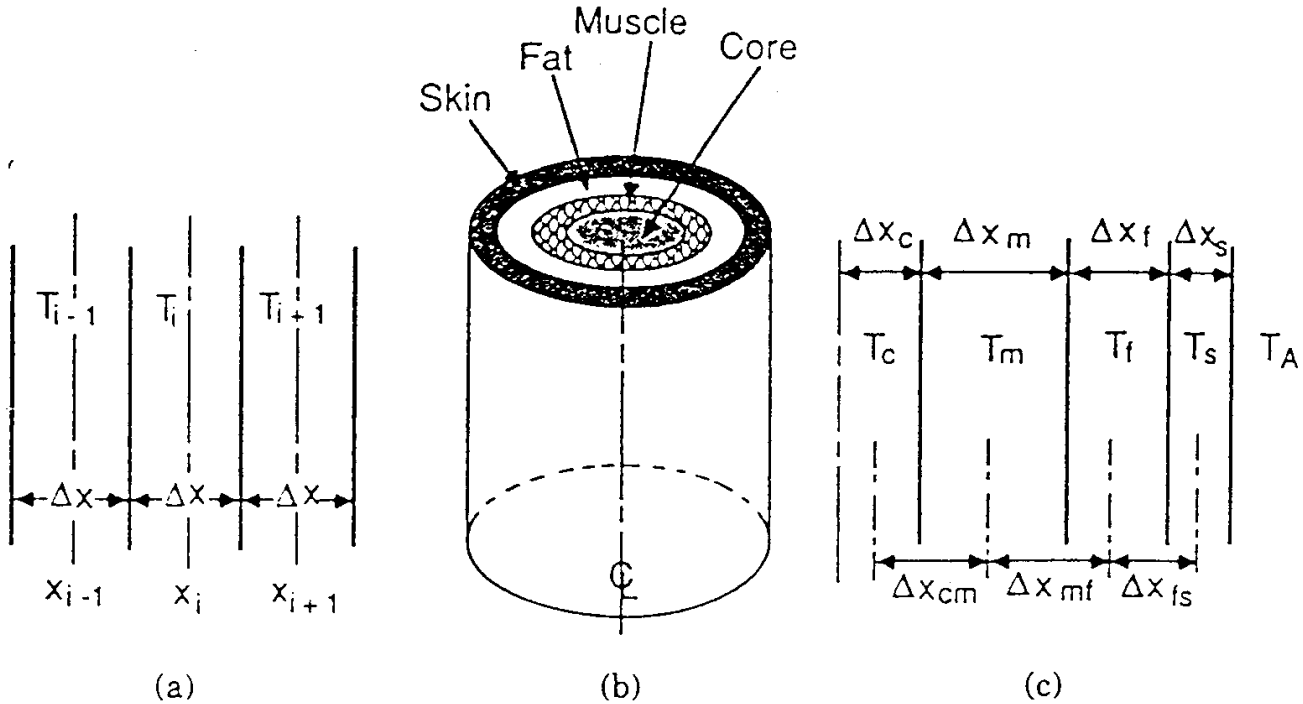


Figure: Heat generation and loss in the body (Rideout, 1991, Ch. 7)

Body heat flow model III

Further applications

(a) Proximity Suits

(b) Newborn Incubator

Figure: Further applications of thermo-regulation

Body heat flow model IV

Exercise (optional): Heat flow in the human body

1. Derive a four compartment model consisting of the body core, muscle, fat and skin to illustrate the heat flow and thermoregulatory system within the human body.
2. Write the diffusion equations for the developed model. The required equations and parameters may be adopted from (Rideout, 1991, Ch. 7).

Cardiovascular system modeling I

Simplified cardiovascular system

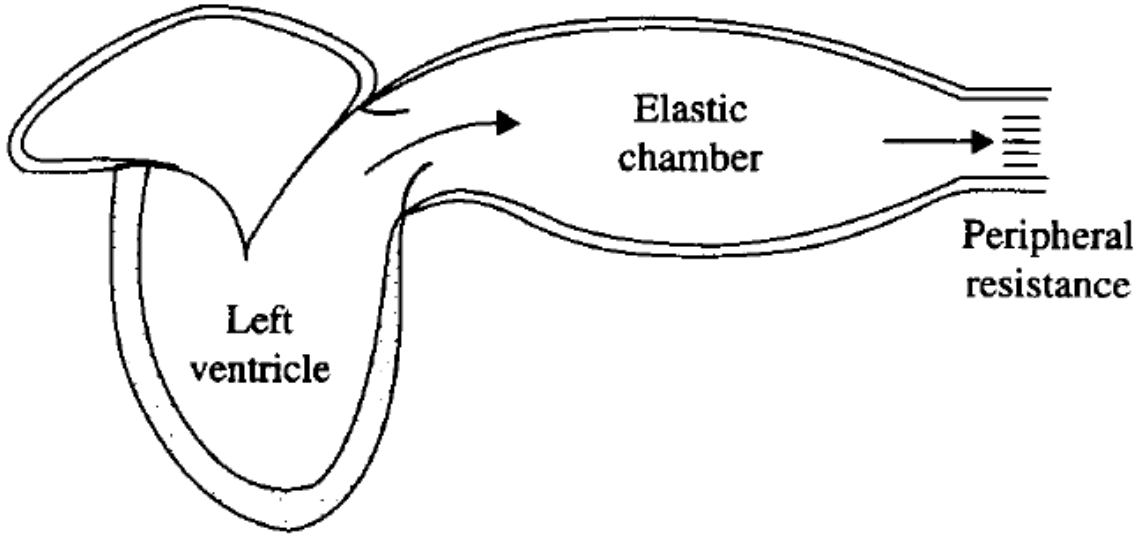
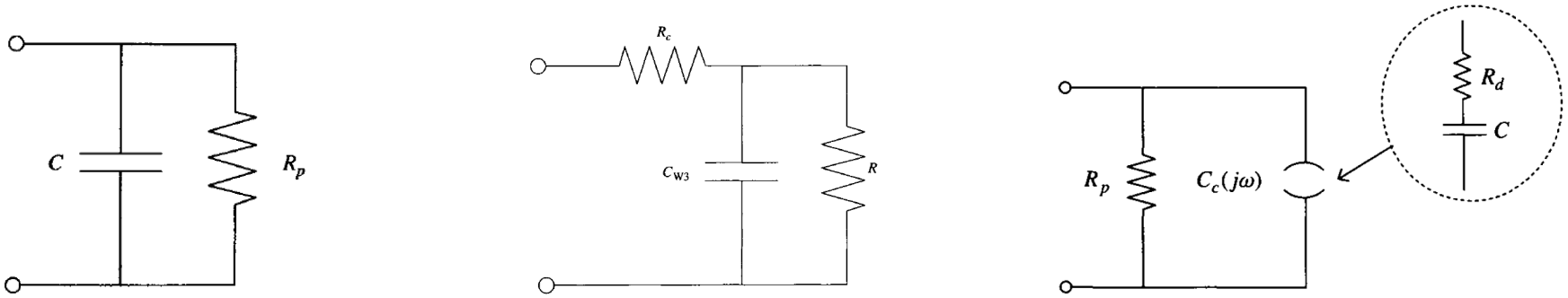


Figure: A simplified cardiovascular system (Carson & Cobelli, 2001, Ch. 8)

Ref: An introduction on cardiovascular system modeling from (Rideout, 1991, Ch. 4) and (Carson & Cobelli, 2001, Ch. 8)

Cardiovascular system modeling II

Windkessel models



(a) 2-element (b) 3-element (c) Viscoelastic

Figure: Illustration of different versions of the Windkessel model (Carson & Cobelli, 2001, Ch. 8)

Cardiovascular system modeling III

Further cardiovascular system models

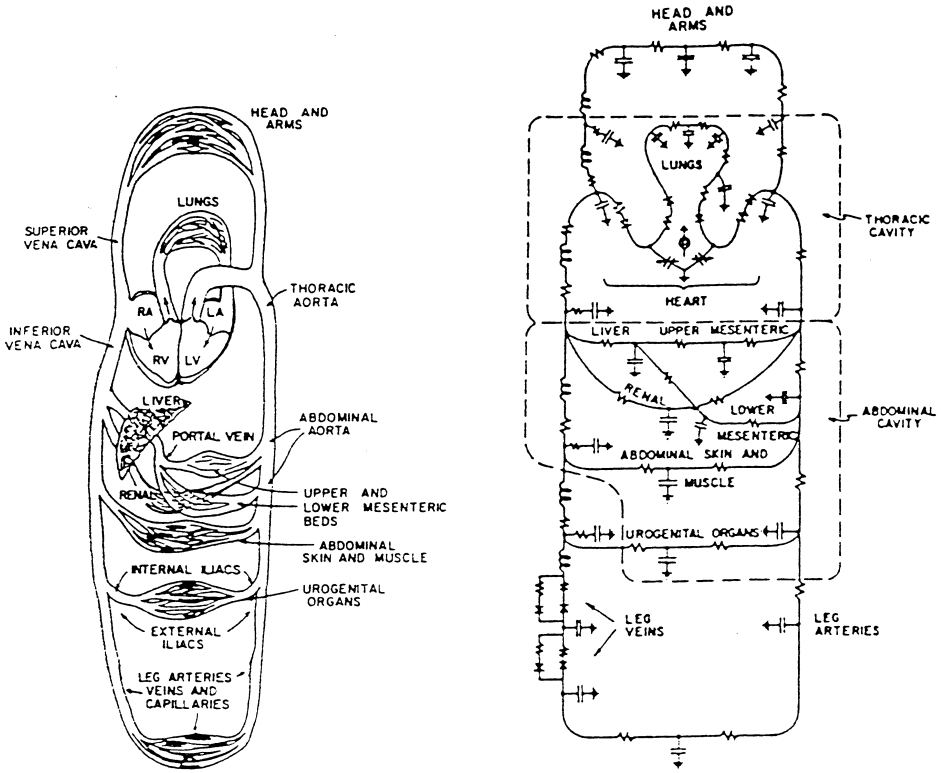


Figure: Analogy between cardiovascular and electrical systems; adopted from (Rideout, 1991, Ch. 4)

Motivation for biosignal modeling

- Biological systems and signals modeling are deeply entangled.
- Modeling a biological system always results in the modeling of a set of observable signals. On the other hand, biosignal models are always based on physiological aspects of the biological system of interest. Hence, a unified framework is needed to study biological signals and systems at the same time.
- Model-based biosignal processing highly depends on reliable and realistic biosignal models.
- In this section, we study general methods of biosignal modeling with their relationship with the corresponding biological systems.
- The ultimate modeling perspective is to obtain a general framework for **hierarchic modeling** of biological signals and systems (including both signal-level and system-level aspects of biological systems), with applications in **artificial patient** modeling.

Action potential modeling I

Objective: To model the temporal waveform of spontaneous action potentials (AP) in cardiac pacemaker tissues

Background:

1. The regular cardiac contraction (the *sinus rhythm*) is initiated by a group of neurons located in the right atrium of the heart, known as the pacemaker or sino-atrial (SA)-node
2. The SA-node is triggered spontaneously in a self-excitatory manner
3. The temporal pattern and period of trigger is influenced by various physiological systems

Modeling:

1. This problem can be modeled in various forms. In this section, we focus on a dynamic model solution. Alternative models of the AP are studied in other sections.
2. For this problem, we need to have a self-regulatory dynamic model.

Action potential modeling II

The simplest dynamic model, which can generate oscillations is the classical second-order differential equation:

$$\ddot{x}(t) + 2\alpha\dot{x}(t) + \omega_0^2 x(t) = 0 \qquad (*)$$

with the following properties:

	$\alpha > 0$	$\alpha < 0$	$\alpha = 0$
$\alpha^2 < \omega_0^2$	damped oscillations	unstable oscillations	oscillatory
$\alpha^2 > \omega_0^2$	exponential decay	exponential divergence	–

Action potential modeling III

State-space form: This system can also be stated in state-space form

$$x_1 \stackrel{\Delta}{=} x, \qquad x_2 \stackrel{\Delta}{=} \frac{dx}{dt}, \quad \Rightarrow \boldsymbol{x} = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

$$\dot{x}_1 = x_2$$
$$\dot{x}_2 = -2\alpha x_2 - \omega_0^2 x_1$$
$$\dot{\boldsymbol{x}} = \begin{bmatrix} 0 & 1 \\ -\omega_0^2 & -2\alpha \end{bmatrix} \boldsymbol{x}$$

Phase-plane: To construct a trajectory in the phase-plane the time dependence is omitted from the state-space equations:

$$\frac{dx_2}{dx_1} = -\frac{2\alpha x_2 + \omega_0^2 x_1}{x_2}$$

Action potential modeling IV

Specifically, for $\alpha = 0$:

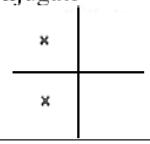
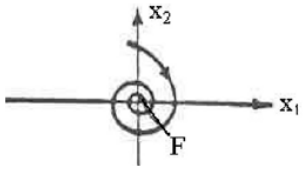
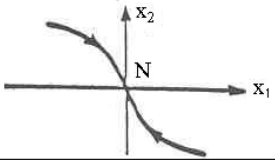
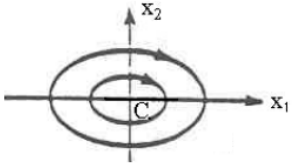
$$\frac{dx_2}{dx_1} = -\frac{\omega_0^2 x_1}{x_2}$$
$$x_2 dx_2 = -\omega_0^2 x_1 dx_1 \Rightarrow$$
$$\int_{x_2(0)}^{x_2} x_2 dx_2 = -\int_{x_1(0)}^{x_1} \omega_0^2 x_1 dx_1 \Rightarrow$$
$$\frac{1}{2}\left[x_2(t)^2 - x_2(0)^2\right] = \frac{-\omega_0^2}{2}\left[x_1(t)^2 - x_1(0)^2\right] \Rightarrow$$

Hence:

$$x_2(t)^2 + \omega_0^2 x_1(t)^2 = x_2(0)^2 + \omega_0^2 x_1(0)^2 = cte$$

Which is an ellipse in the phase-plane.
Typical phase-plane trajectories of this system are shown in Fig. 79.

Action potential modeling V

Name	Roots	Sketch
Stable focus or spiral	Damped complex conjugate 	Trajectories spiral asymptotically to focus 
Stable node	Stable real roots 	Trajectories approach node monotonically 
Vertex or center (Structurally unstable)	Imaginary roots 	Conservative system or oscillator 

Action potential modeling VI

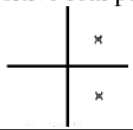
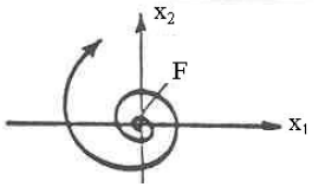
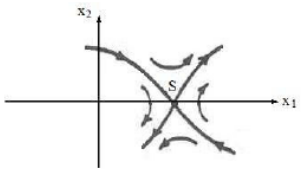
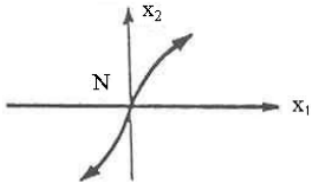
Name	Roots	Sketch
Unstable focus	Complex conjugate with positive real part 	
Saddle point	Unstable equilibrium point 	
Unstable node	Unstable real roots 	Trajectories diverge monotonically from node 

Figure: Phase-plane trajectories for linear second-order dynamical systems (Kogan, 2009, Ch. 5)

- Accordingly, $\alpha = 0$ is the threshold between stability and instability.
- Can this model be extended to a self-regulatory oscillator?

Action potential modeling VII

- We seek a time-invariant model that is independent of the time origin (relies only on the system's internal states).

Idea: Making α a function of the signal amplitude $x(t)$, through a sort of feedback mechanism.

The Van der Pol Model

$$\ddot{x}(t) - 2\alpha[1 - x(t)^2]\dot{x}(t) + \omega_0^2 x(t) = 0 \qquad (\dagger)$$

Interpretation:

1. Starting from $x(t_0) = \epsilon$, the system is unstable and tends to increase the amplitude of $x(t)$.
2. As the amplitude increases $2\alpha[1 - x(t)^2]$ approaches zero.
3. Thereafter, $-2\alpha[1 - x(t)^2]$ becomes positive and the system stabilizes itself (reduces the amplitude of $x(t)$).
4. The system has a feedback mechanism, which keeps it at the margin of stability/instability.

Action potential modeling VIII

5. The temporal shape and period of oscillation depends on the parameters α and ω_0.

The Van der Pol equation (†) is the basic model used for modeling self-excitatory cells (Kogan, 2009, Ch. 5). In order to simplify the analysis and interpretation of this model, the number of parameters of the model can be reduced as follows: Suppose that $v(t)$ represents an AP, which follows the Van der Pol model. Defining $\tau \triangleq 2\alpha t$ and $\phi \triangleq \frac{\omega_0^2}{4\alpha^2}$, simplifies (†) to:

$$\frac{d^2v}{d\tau^2} + (v^2 - 1)\frac{dv}{d\tau} + \phi v = 0 \qquad (\ddagger)$$

which only depends on ϕ, the square quality factor (**Q-factor**) of the second-order damped oscillation [1].

Action potential modeling IX

Defining a new variable $w \triangleq \frac{-dv}{dt} + v - \frac{v^3}{3}$, $(\ddagger)$ can be stated in state-space form:

$$\begin{cases} \frac{dw}{d\tau} = \phi v \\ \frac{dv}{d\tau} = v - \frac{v^3}{3} - w \end{cases}$$

$$\frac{\frac{dw}{d\tau}}{\frac{dv}{d\tau}} = \frac{\phi v}{v - \frac{v^3}{3} - \omega} = \zeta = \tan\beta$$

$$\frac{dv}{d\tau} = 0 \Rightarrow \tan\beta = \infty \Rightarrow$$

$$\text{assume: } v = \epsilon_2 = 0^+ \Rightarrow \begin{cases} v > 0 \text{then: } \tan\beta = \frac{v}{\epsilon_2} \text{and } \beta = 90^o \\ v < 0 \text{then: } \tan\beta = -\frac{v}{\epsilon_2} \text{and } \beta = 270^o \end{cases}$$

Horizontal isocline:

$$\frac{dw}{d\tau} = 0 \Rightarrow \phi v = 0$$

Action potential modeling X

$$\frac{dw}{d\tau} = \Phi v = 0 \Rightarrow \tan\beta = 0 \Rightarrow$$

$$\text{assume } w = \epsilon_1 = 0^+ \Rightarrow \begin{cases} w > 0, \text{then } \tan\beta = -\frac{\epsilon_1}{w} \text{and } \beta = 180^o \\ w < 0, \text{then } \tan\beta = \frac{\epsilon_1}{w} \text{and } \beta = 0^o \end{cases}$$

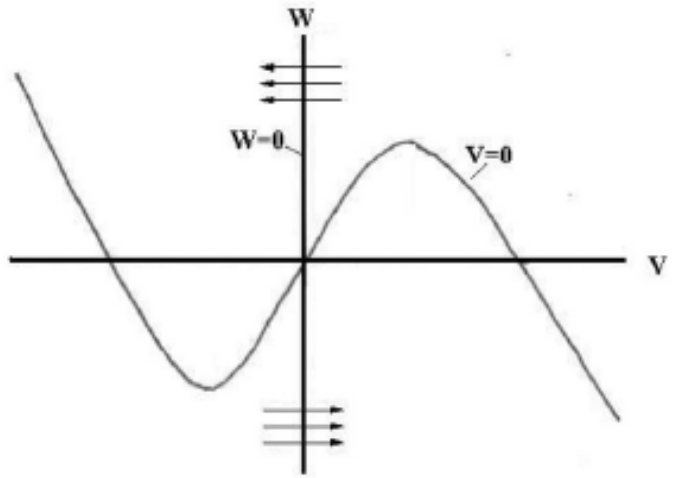


Figure: Horizontal isocline of van Der Pol's model

Action potential modeling XI

Vertical isocline:

$$\frac{dv}{d\tau} = 0 \Rightarrow \omega = v - \frac{v^3}{3}$$

The isoclines are shown in Fig. 81

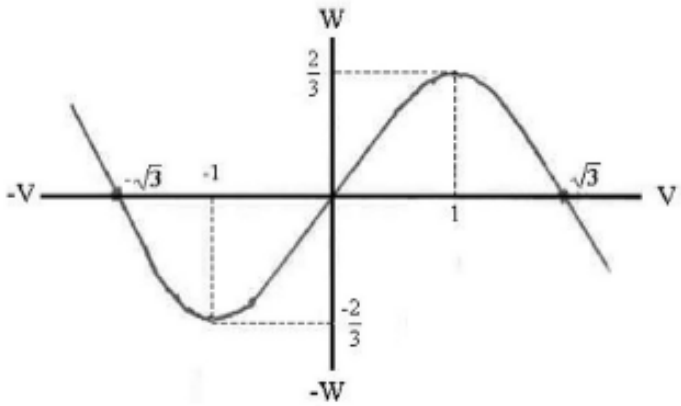
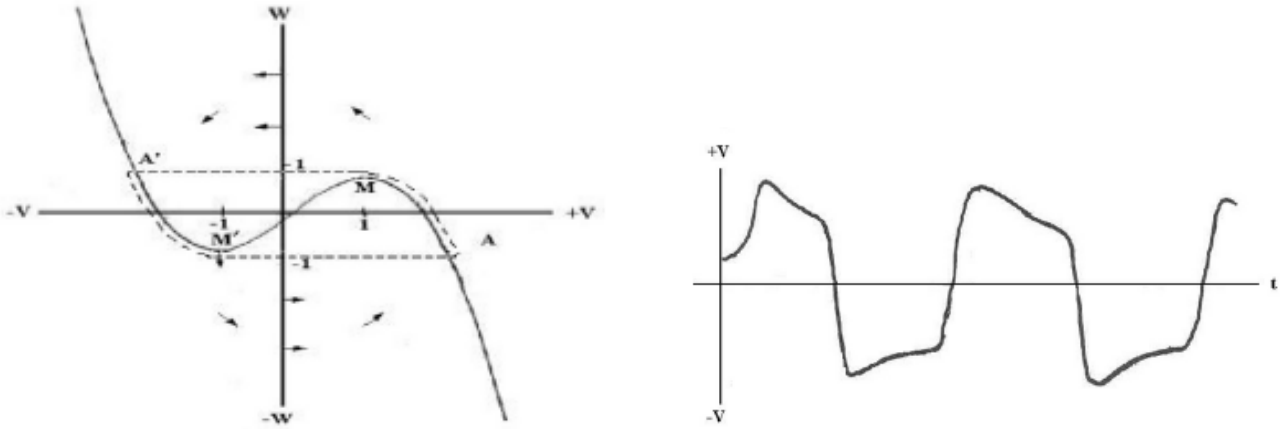


Figure: Vertical isocline of van Der Pol's Model

- The fixed-point is at the origin.
- By adding a small perturbation at the origin we notice that this fixed-point is unstable.

Action potential modeling XII

A typical phase plane graph and its corresponding AP in the time domain are shown in Fig. 82.



(a) (b)

Figure: A typical phase plane graph and its corresponding AP generated by the Van der Pol equation

[1] The Q-factor is in terms proportional to the ration of the energy stored to the energy lost per cycle of oscillation

FitzHugh-Nagumo model of action potentials I

The FitzHugh-Nagumo model of action potentials is basically a modification of the VP equation, which changes the horizontal isocline from vertical axis to a sloped line and elevates the third order function of $\frac{dv}{dt}$ by I.

$$\begin{cases} \dfrac{dw}{dt} = \epsilon(v + a - bw) \\ \dfrac{dv}{dt} = v - \dfrac{v^3}{3} - w + I \end{cases}$$

For instance, for $\epsilon = 0.08, a = 0.7, b = 0.8$ the null-isoclines are shown in Fig. 83.

FitzHugh-Nagumo model of action potentials II

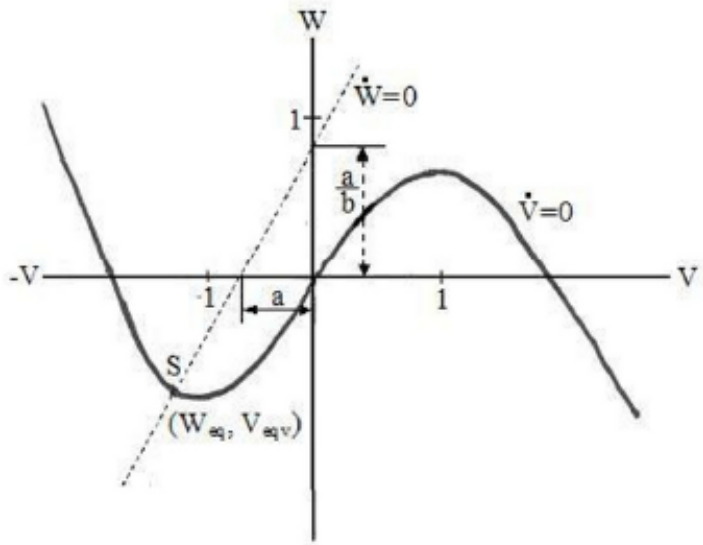


Figure: Null-isoclines of FitzHugh-Nagumo's model

The resulting AP are shown in Fig. 84

FitzHugh-Nagumo model of action potentials III

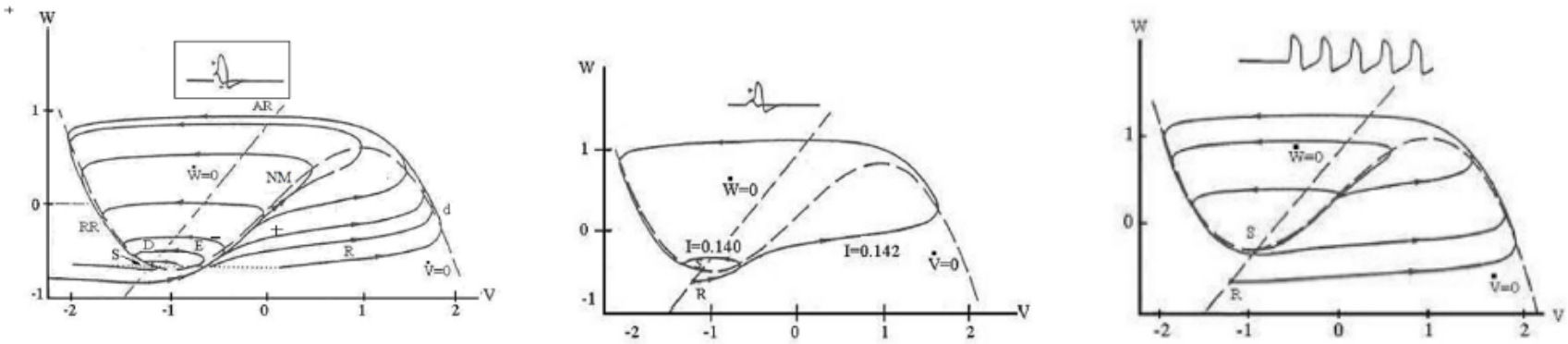


Figure: AP resulting from FitzHugh-Nagumo's model

FitzHugh-Nagumo model of action potentials IV

An alternative approach for deriving AP models, is to analyze simplified cell-level ionic reactions within the neurons.

Exercise (optional)

1. Analyze the fixed-point stability of the FitzHugh-Nagumo model
2. Study the Hodgkin-Huxley AP model and compare it with the FitzHugh-Nagumo model from (Keener & Sneyd, 1998, Ch. 4).
3. Study the model of Purkinje fibers, sinuatrial node, and ventricular cells from (Keener & Sneyd, 1998, Ch. 4).

Project Topic 18:

Develop a GUI for illustration of the phase-plane and time-domain of AP generated by the FitzHugh-Nagumo model

Electrocardiogram modeling

Objective: To model the temporal waveform of cardiac signals, which are able to produce normal (and abnormal) ECG (or MCG) morphology and heart rates
Modeling:

1. The problem of cardiac signal modeling can be studied in various levels of abstraction, ranging from low-level neural models to high-level body surface potential models.
2. For a vast range of application, macroscopic models, which mimic the cardiac signal morphology and heart-rate are required
3. Due to the similarity of the ECG and MCG temporal morphology, the same modeling framework can be used for both signals
4. We expect the model to be applicable for both adult and fetal cardiac signals, in normal and abnormal cases
5. 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

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

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

- x, y, and z are state variables, $\rho = 1 - \sqrt{x^2 + y^2}$, $\Delta\theta_i = (\theta - \ \theta_i)$ mod (2π), $\theta = \text{atan2}(y, x)$ 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, listed in Table 2.
- 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) II

Table: Parameters of the synthetic ECG (•)

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

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

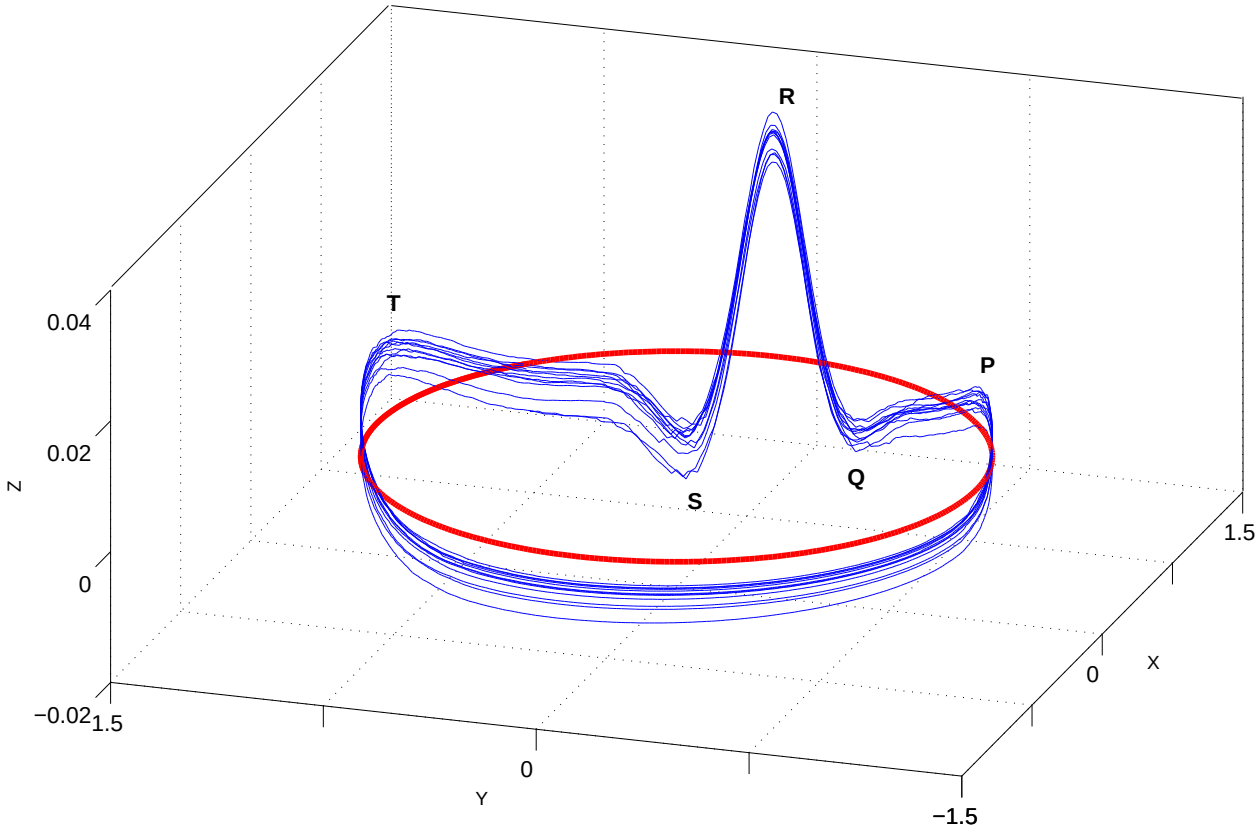


Figure: 3D trajectory of (•) McSharry et al. (2003). The red line corresponds with the unit circle in the $x - y$ plane

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

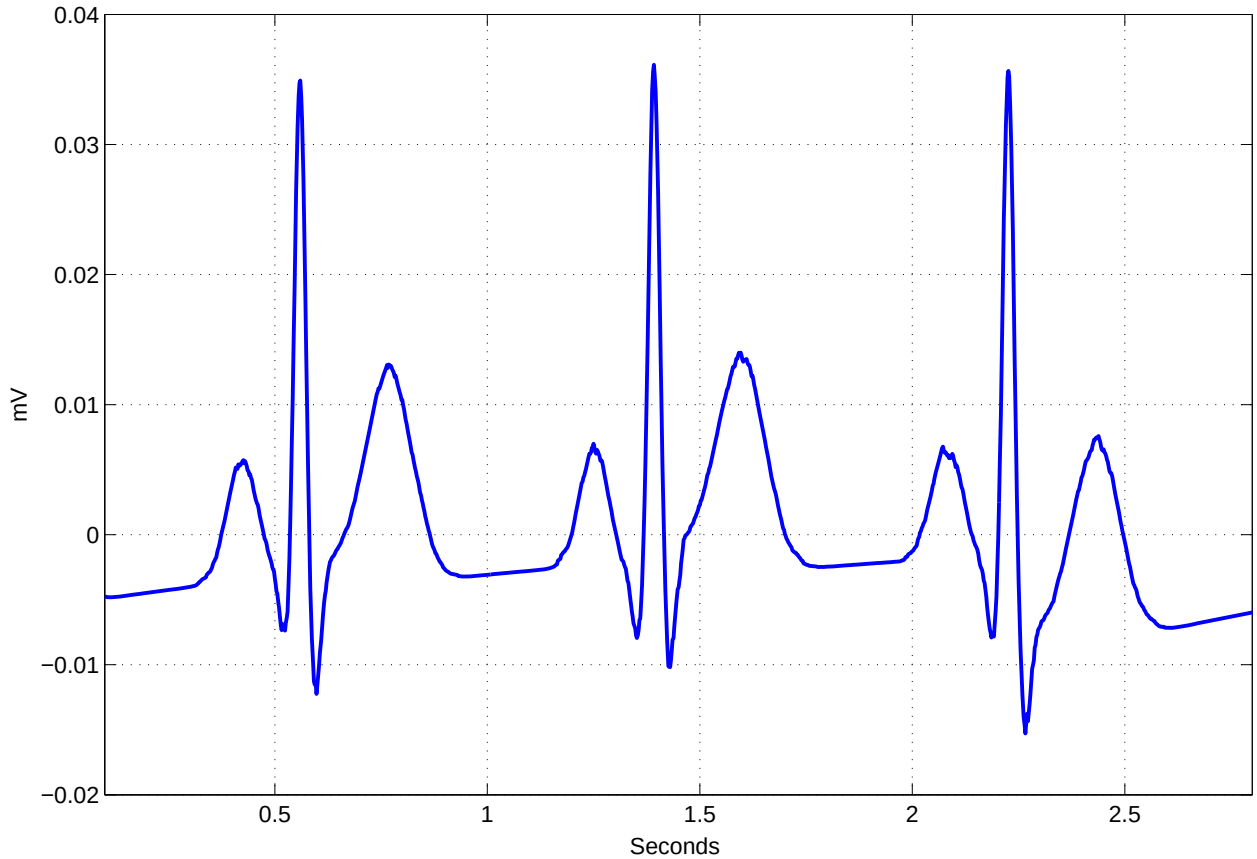


Figure: Projection of the 3D trajectory of (•) McSharry et al. (2003) onto the z-axis

Polar form of the ECG model with simplifications (Sameni et al., 2005):

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

- The term $(z - z_0)$ in the original equations causes dimensional mismatch and is removed in the modified equations (baseline wander and other noises can be modeled with more general formulations, discussed later)
- The first equation converges to $r = 1$ for any initial value in the range $r_0 \in (0, 1]$
- The second and third equations do not depend on r. We can therefore discard the first equation

Simplified form in discrete form (Sameni et al., 2007b): I

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

- $\Delta\theta_i = (\theta_k - \theta_i) \mod (2\pi)$, 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

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

$$
\begin{aligned}
\dot{\theta} &= \omega \\
\dot{x} &= -\sum_i \frac{\alpha_i^x \omega}{(b_i^x)^2} \Delta\theta_i^x \exp\left[-\frac{(\Delta\theta_i^x)^2}{2(b_i^x)^2}\right] \\
\dot{y} &= -\sum_i \frac{\alpha_i^y \omega}{(b_i^y)^2} \Delta\theta_i^y \exp\left[-\frac{(\Delta\theta_i^y)^2}{2(b_i^y)^2}\right] \\
\dot{z} &= -\sum_i \frac{\alpha_i^z \omega}{(b_i^z)^2} \Delta\theta_i^z \exp\left[-\frac{(\Delta\theta_i^z)^2}{2(b_i^z)^2}\right]
\end{aligned}
\tag{+}
$$

- $\Delta\theta_i^x = (\theta - \theta_i^x) \mod (2\pi)$, $\Delta\theta_i^y = (\theta - \theta_i^y) \mod (2\pi)$, $\Delta\theta_i^z = (\theta - \theta_i^z) \mod (2\pi)$, and $\omega = 2\pi f$, f is the beat-to-beat heart rate in Hz.
- As before, the first equation in $(+)$ generates a circular trajectory rotating with the frequency of the heart rate.

Vectorcardiogram modeling (Sameni et al., 2007a): II

- Each of the three coordinates of the dipole vector $\mathbf{d}(t) = [x(t), y(t), z(t)]^T$, is modeled by a summation of Gaussian functions with amplitudes α_i^x, α_i^y, and α_i^z; widths b_i^x, b_i^y, and b_i^z; and located at rotational angles θ_i^x, θ_i^y, and θ_i^z.
- Intuitively, the baseline of each of the dipole coordinates is pushed up and down, as the trajectory approaches the centers of the Gaussian functions, generating a moving and variable length vector in the (x, y, z) space.

By adding stochastic deviations to the parameters of McSharry-Clifford's model and its extensions, i.e. considering them as random variables rather than deterministic constants, it is possible to generate more realistic cardiac dipoles with inter-beat variations.

Multichannel ECG model (Sameni et al., 2007a): I

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

- $ECG(t)_{N\times 1}$ 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.

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

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

- H_m, H_f, R_m, R_f, Λ_m and, Λ_f have similar definitions as the ones in ($\circ$)
- Subscripts m and f refer to the mother and the fetus, respectively.
- R_f has the additional interpretation that its mean value ($E_t\{R_f\} = R_0$) is not an identity matrix, considered as the relative position of the fetus with respect to the axes of the maternal body. This feature enables modeling the fetus in the different typical positions such as *vertex* (fetal head-down) or *breech* (fetal head-up) WebMD (2005).
- $s_f(t) = [x_f(t), y_f(t), z_f(t)]^T$ is a canonical representation of the fetal dipole vector, defined with respect to the fetal body axes (Fig. 87). To calculate this vector with respect to the maternal body axes, $s_f(t)$ is rotated by the 3-dimensional rotation matrix of R_0:

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

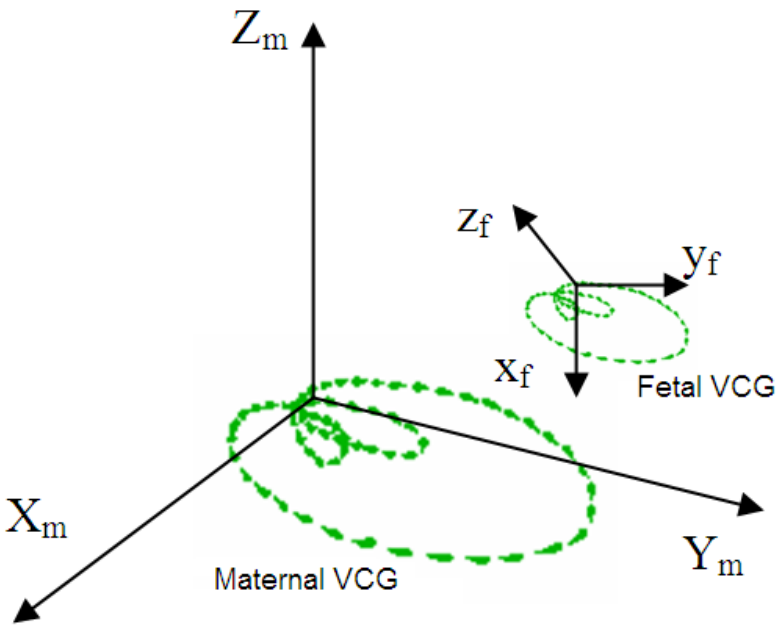


Figure: Illustration of the fetal and maternal VCGs vs. their body coordinates

Stochastic ECG models I

The ECG modeling framework described in previous sections is fully deterministic and the generated ECG are periodic. This framework can be made more realistic by considering stochastic aspects of real ECG, including:

- Minor beat-to-beat variations of the ECG morphology
- Natural beat-to-beat **heart rate variability** (HRV)
- Casual morphological variations caused by cardiac arrhythmia
- Heart rate variability caused by physical activity and cardiac abnormalities such as Tachycardia and Bradycardia

Within the stated framework, it is straightforward to model the fist two items, by adding stochastic deviations to the parameters of the ECG model. For beat-wise variations (of the hear-rate or ECG morphology), a discrete stochastic model is required. The Markov model is a useful tool for this purpose.

Heart rate variation modeling (Clifford et al., 2010): I

- A normal heart rate is known to have beat-to-beat variations known as *heart rate variability* (HRV). Besides the natural HRV, the base heart rate can vary by physical activity and cardiac abnormalities such as Tachycardia and Bradycardia.
- All these variations can be considered in previously stated ECG models, by replacing the constant ω by $\omega[n] = 2\pi h[n]/(60\sqrt[\varsigma]{h_{av}})$, where $h[n]$ is the beat-to-beat heart rate per minute (RPM), h_{av} is the mean of the last p heart rates (typically with $p = 6$) normalized by 60BPM, and $\sqrt[\varsigma]{h_{av}}$ accounts for Bazett or Fredericia-like corrections for ς=2 and 3, respectively (Hodges, 1997).

Heart rate variation modeling (Clifford et al., 2010): II

- $h[n]$ may itself be modeled as follows:

$$h[n] = h_b[n] + h_r[n] + h_p[n] + h_{\text{HRT}}[n] + \dots \qquad (\diamond)$$

where n is the beat number, $h_b[n]$ is the baseline heart-rate, $h_r[n]$ models the long-term variations of the RR interval, $h_p[n]$ is due to physical activity, $h_{\text{HRT}}(t)$ models the heart rate turbulence (HRT) phenomenon, and $h[n]$ is the resulting time-varying RR interval time series, which forms the input for ω in $(+)$. Apparently, any other item that influences the HR can also be considerd in this formulation. A typical example is shown in Fig. (88).

Heart rate variation modeling (Clifford et al., 2010): III

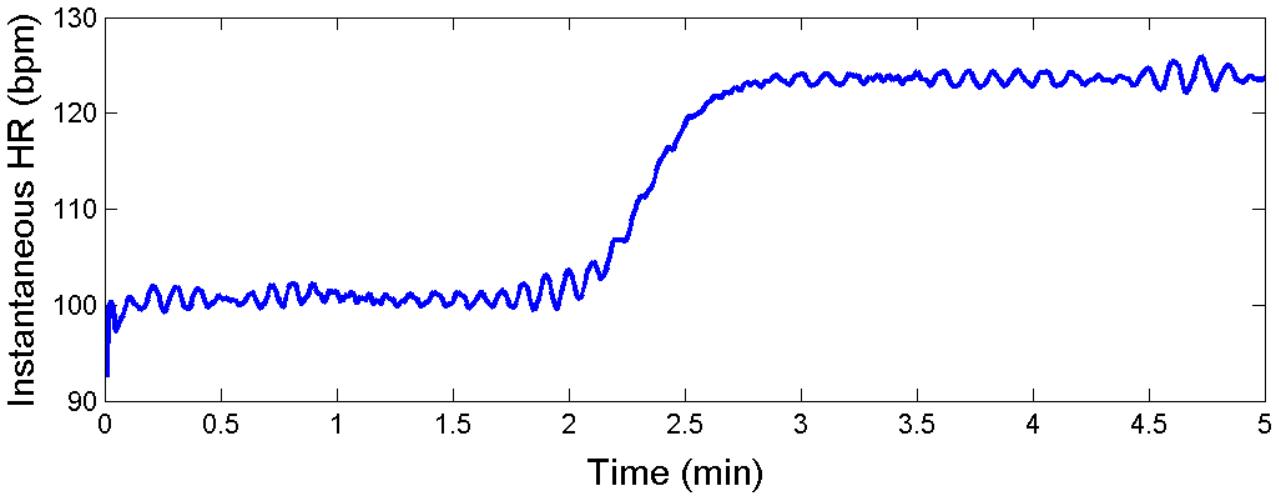


Figure: Example of time-varying instantaneous heart rate.

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

Beat-to-beat morphological variations of the ECG can be incorporated in previous models, using a *finite state machine* (FSM). In (Clifford et al., 2010), a general framework was presented for modeling *T-wave alternans* (TWA), as a typical example.
Accordingly, the transition from one beat type to another can be modeled using a first-order Markov chain[2]. Considering each beat (normal or abnormal) as a state, the state transition matrix (STM) is defined as follows:

$$\text{STM} = \begin{bmatrix} p_{1,1} & p_{1,2} \\ p_{2,1} & p_{2,2} \end{bmatrix}$$

where, as shown in Fig. 89, the $p_{i,j}$ $(0 \leq p_{i,j} \leq 1)$ are the transition probabilities from normal (N) to abnormal (A) beats, and vice versa.
For TWA modeling one can choose a symmetric formulation:
$\text{STM} = [\ 1-p \ \ p\ ;\ p \ \ 1-p\ ]$, i.e., the probability of transition of normal to abnormal beats is the same as the probability of transition from abnormal to

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

normal. For TWA we have two extremes; *stationary continuous TWA* and *normal sinus rhythms*, which are achieved by setting $p = 1$ and $p = 0$, respectively. Generally, the STM has the same number of rows (and columns) as the number of beat types and a similar probabilistic framework may be used for generating more than two beat types (see Figs. 90 and 91).

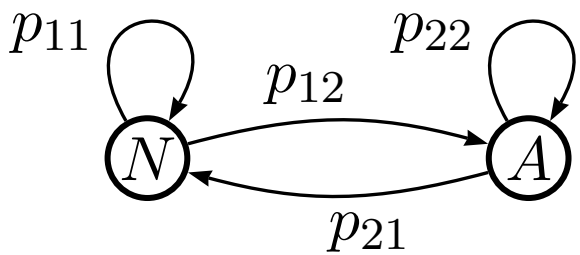


Figure: State transition graph between normal (N) and abnormal (A) beats using a first-order Markov chain. The graph can be extended to more abnormal beat types.

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

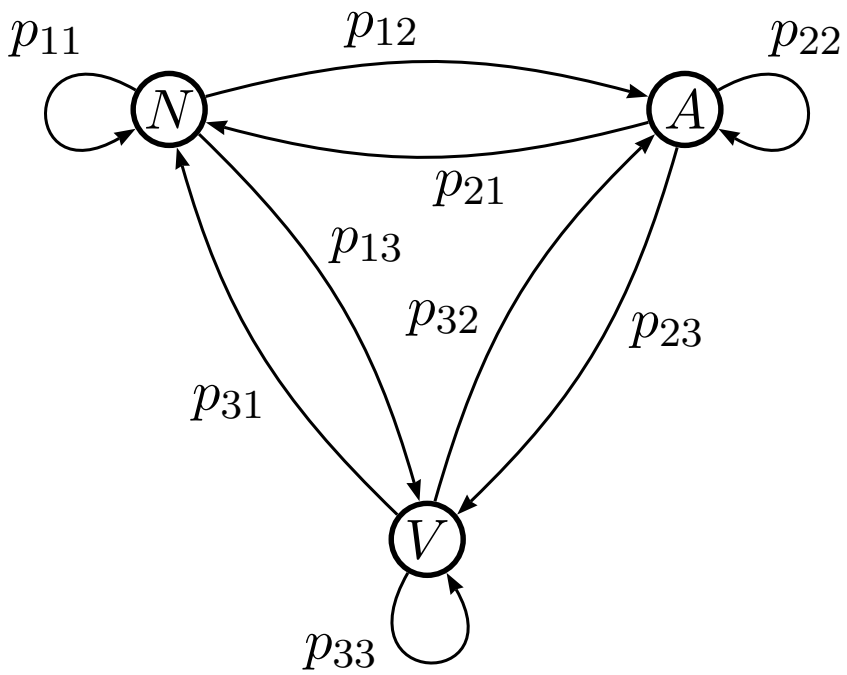


Figure: State transition graph between normal (A), abnormal (B), and ectopic (V) beats using a first-order Markov chain.

Abnormal ECG modeling (Clifford et al., 2010): IV

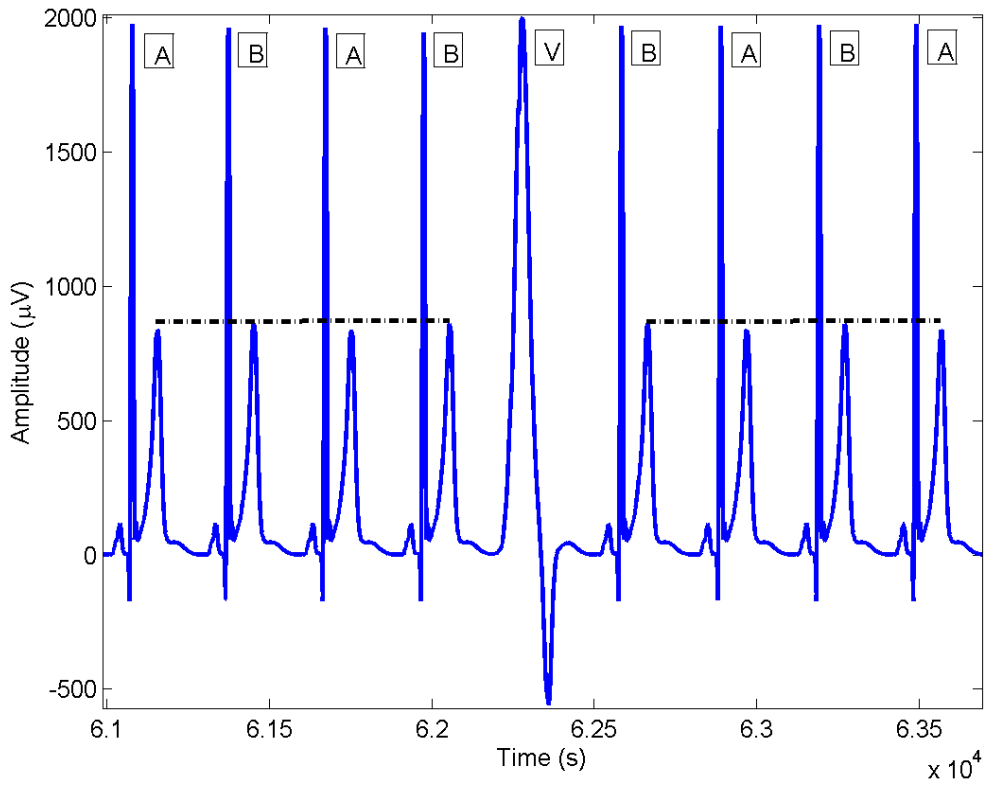


Figure: 'ABAB' beat sequence followed by a phase-changing ectopic beat (V). Note that the beats following the ectopic beat will now be of a 'BABA pattern'.

Abnormal ECG modeling (Clifford et al., 2010): V

Heart-rate dependent probabilistic models: The proposed probabilistic framework can be extended to model heart-rate dependent abnormalities. As an example, it is known that cardiac abnormalities such as the TWA are more probable in higher heart rates (Narayan, 2006). Therefore, to simulate the dependence on HR of the TWA effect, we can modify p to:

$$p(t) = (\tanh[\vartheta(h(t) - h_{\text{TWA}})] + 1)/2$$

where $h(t)$ is the instantaneous heart rate defined in $(\diamond)$, $h_{\text{TWA}} = 95 \pm 5$ BPM is the typical HR range at which the TWA effect manifests, and ϑ=0.2 BPM^{-1} controls the typical slope of transition. Furthermore, we require $0 \leq p(t) \leq 1$ to satisfy the requirements of a probability function.
Fig. 92 illustrates an example of instantaneous heart rate and the resultant probability of transition to TWA derived from such a procedure.

Abnormal ECG modeling (Clifford et al., 2010): VI

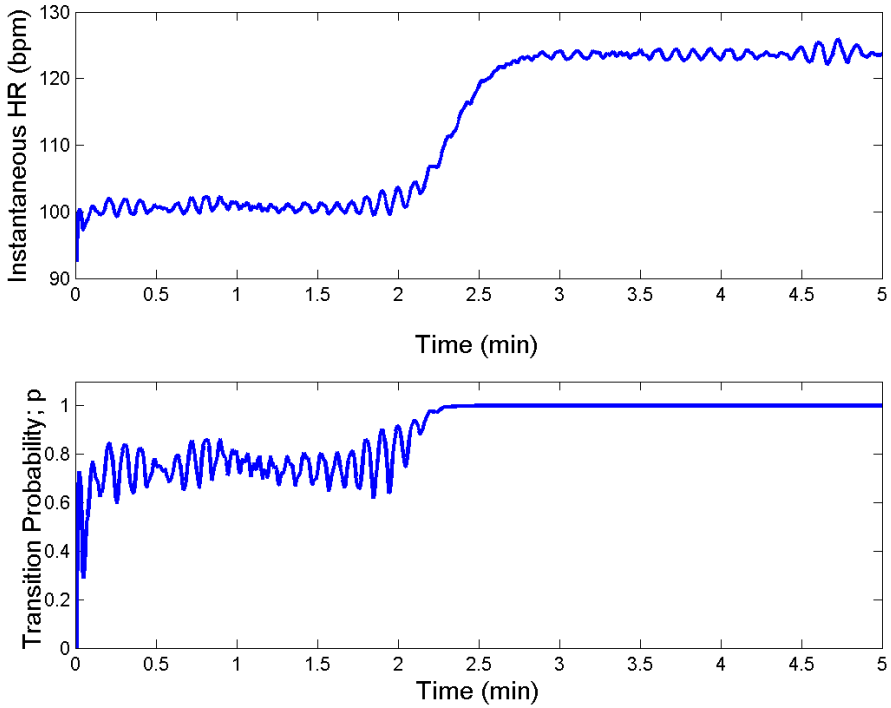


Figure: Example of instantaneous heart rate and resultant probability of transition to TWA.

Abnormal ECG modeling (Clifford et al., 2010): VII

Incorporating the STM in the ECG generator model: The STM is used to generate random states for switching between different beat types. Following the ECG and VCG model presented in previous sections, to generate synthetic ECG, the state transition (or the choice of beat type) is made at the point of phase wrapping, where the cardiac phase θ jumps from π to $-\pi$. Typical outputs of the model are shown in Figs. 93, 94 and 95

Abnormal ECG modeling (Clifford et al., 2010): VIII

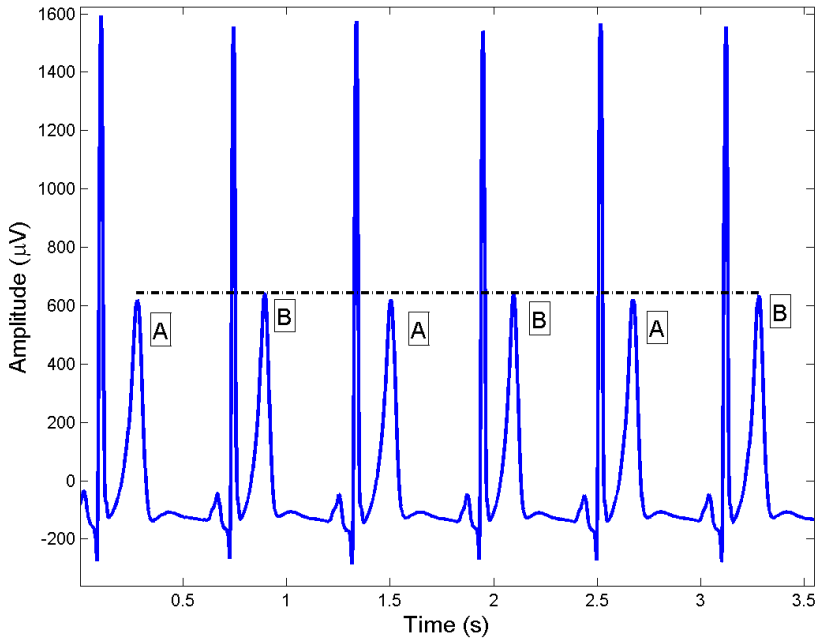


Figure: Typical alternating 'ABAB' TWA pattern (with TWA amplitude of 23 μV) generated from our model.

Abnormal ECG modeling (Clifford et al., 2010): IX

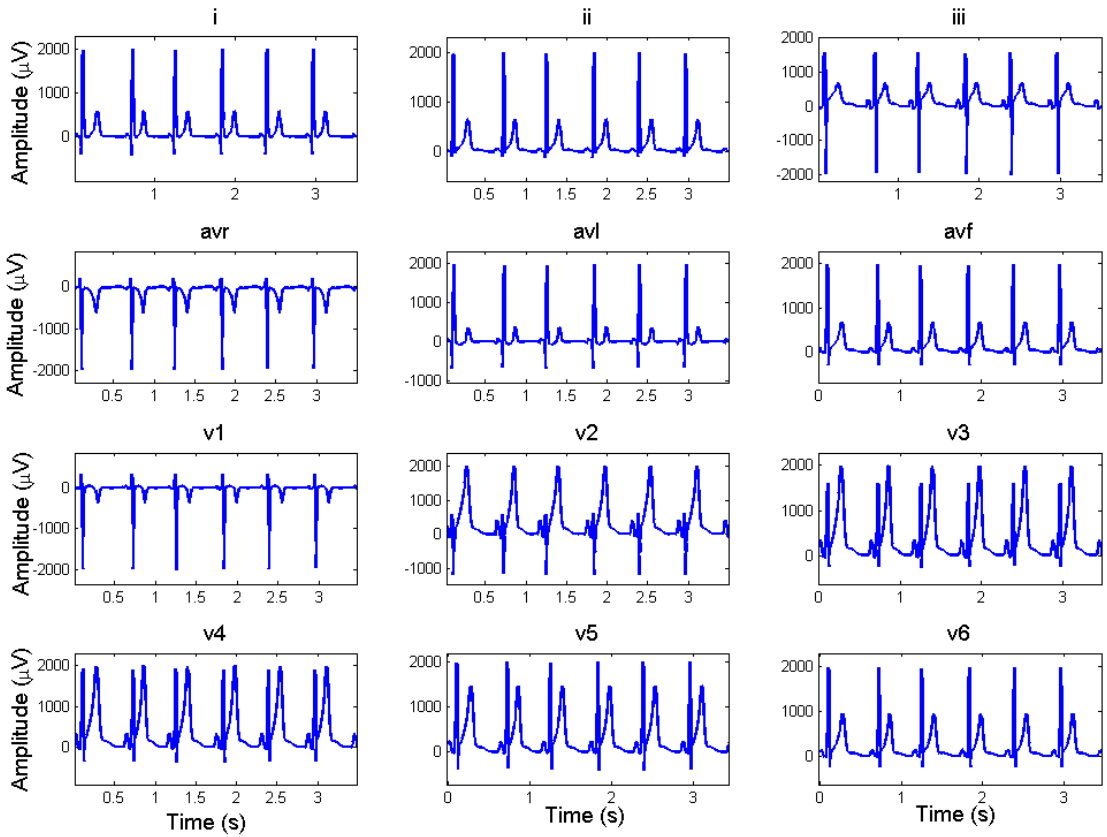


Figure: Example of 12 lead ECG after application of IDT.

Abnormal ECG modeling (Clifford et al., 2010): X

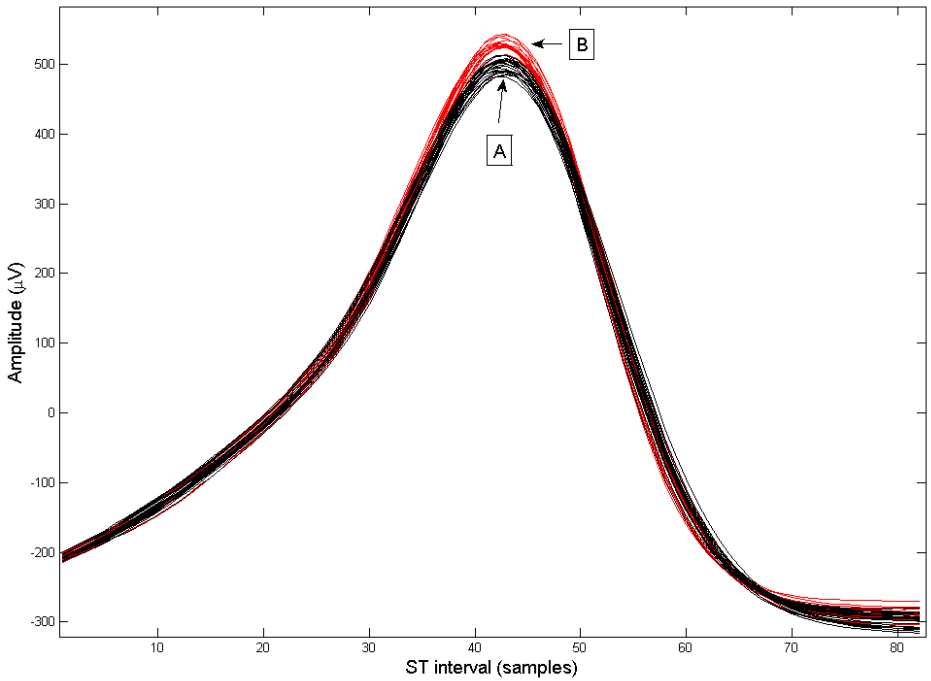


Figure: Multiple ST-T segments from two beat classes taken from one of the VCG projections. Class A beats are black and class B beats are red.

[2] The assumption of a first-order Markov chain is only to simplify the training of the model parameters from relatively short data sets. Generalization to higher-order Markov chains is straightforward.

Stochastic biosignal modeling

- In some applications, including EEG modeling, the desired signals are highly stochastic and the modeling objective is to generate signals with specific spectral form.
- For these applications, the temporal structure of the signal is of less interest, as compared to its spectral contents.
- The **innovation process** can be used to model such signals

Further reading

Phonocardiogram modeling

- Almasi et al. (2013): Almasi, A., Shamsollahi, M.B, and Senhadji, L. (2013). Bayesian denoising framework of phonocardiogram based on a new dynamical model. In IRBM (Vol. 34, Issue 3, pp. 214–225). Elsevier BV. DOI:10.1016/j.irbm.2013.01.017

Advanced project topics: Biologically Inspired Modeling I

Project Topic 19: Traffic modeling

The objective of this project is the modeling of metropolitan traffic using ideas from mathematical modeling and biological systems. This model has interesting applications in traffic monitoring and control (using **event-based control**).

Advanced project topics: Biologically Inspired Modeling II

Project Topic 20: Enterprise evolution

The objective of this project is to model the emerging and bankrupt of companies and firms using ideas from nature and biology, to find models for the most successful companies and the long lasting ones. From many aspects the life cycle of companies can be compared with biological communities. The questions and issues, which can be studied within this framework include:

- What happens for large companies versus small ones?
- What is the most efficient size for a surviving company?
- How is it that huge companies can fail while small ones may succeed, or vice versa (under certain social or economical events). This is similar to what happens for large versus small animals under specific environmental events.
- In nature, small species coexist with large ones; just like companies: it isn't beneficial for large companies to spend time and resources on small projects.
- How to define the "efficiency" of a company inspired from nature's efficiency? Energy, age, size, productivity, versatility, geographical spread?

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