Biological Systems Modeling

Lecture Notes

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Overview

Preface I

Course Description

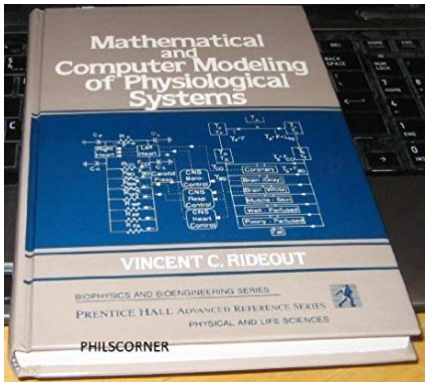
This course introduces students to the art of mathematical modeling for biomedical machine learning applications. It incentivises the use of accurate physical/biological models for boosting the performance of machine learning algorithms. The course introduces the full pipeline of applied mathematical modeling including various model design techniques, model identifiability, parameter identification, model assessment, and model selection. The studied modeling techniques include: analogical, compartmental, ordinary and partial differential equation-based, and agent-based models. These techniques are studied in various biomedical problems and case-studies. This course is homework and project based and it will be presented with an interactive approach using real-world biomedical applications.

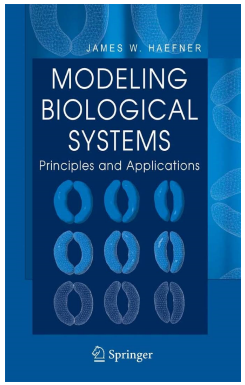
Preface II

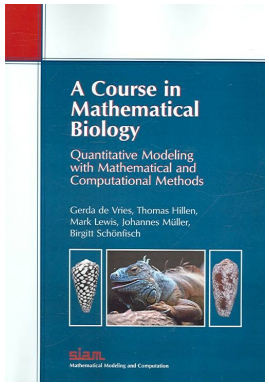
History

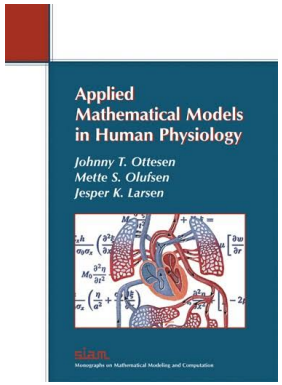
The lecture notes were prepared for a graduate course in *Biological Systems Modeling* presented in the School of Electrical and Computer Engineering of Shiraz University (2009– 2018).

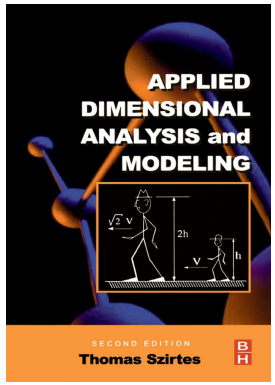
Text Books and Major References

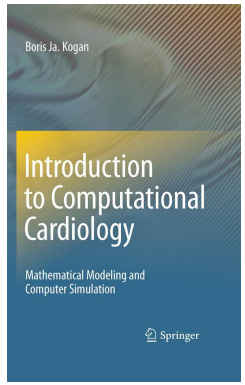


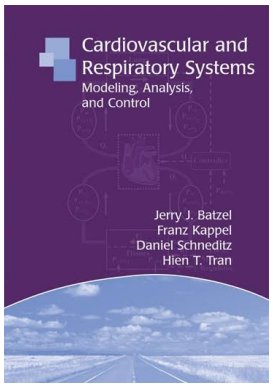


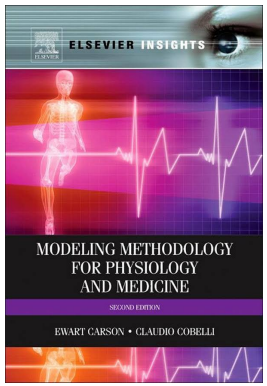


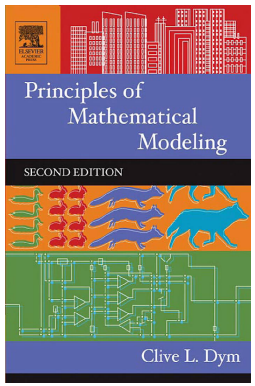


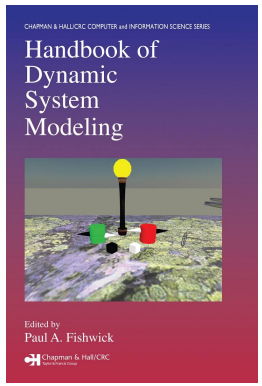


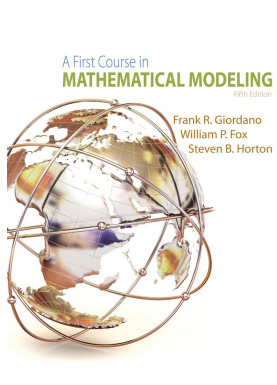


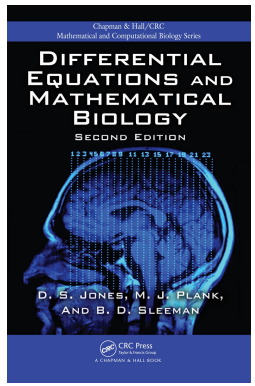


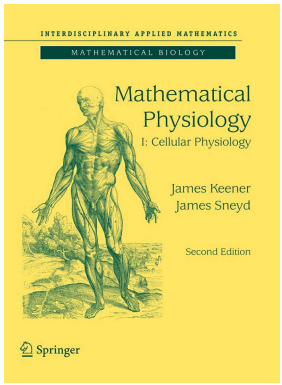


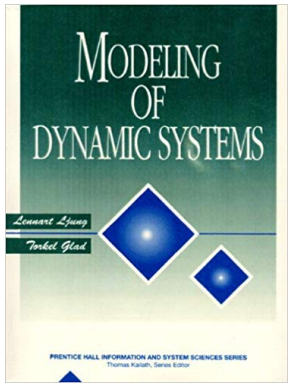


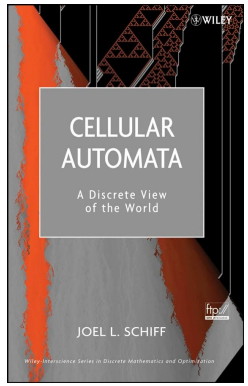


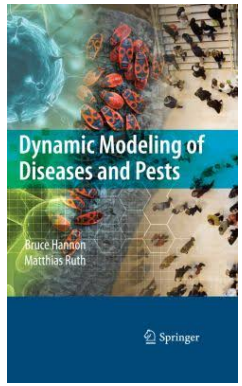












Modeling Methods & Tools

In the first part of the course, we present general definitions, concepts, tools and method used for modeling. The presented examples are mainly for biological systems; but the methods are generic for any modeling problem.

Outline

Introduction to Modeling

What is a model?

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

Introduction to Modeling

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

Where to use a model?

1. Better understanding of systems (system identification)
2. Simulation of a system's behavior (when we know a system we can mimic it and generate synthetic data that is hardly achievable in reality)
3. Prediction of a system's behavior (when we know a system we can predict its future)
4. System control (when we know a system and are able to predict it's behavior, we "might" be able to control it)

From top to bottom the problem becomes more difficult.

Introduction to Modeling

(continued)

Why use a model?

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

1. finding the optimum parameters of an under-construction system by trial and error (too expensive without a model)
2. testing the effect of drugs on human/animal species (crude!)
3. testing a chemical reaction (too dangerous without a model)
4. finding optimum mixtures of an alloy (time taking and costy)
5. studying the formation of galaxies (impossible without a model)

Introduction to Modeling

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How to model?

Is the subject of this course.

Introduction to Modeling

(continued)

Modeling Issues

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

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

Introduction to Modeling

(continued)

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Modeling Doctrine

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

Introduction to Modeling

(continued)

Model Types

- **Mental Model:** Without any formulation, only exists in minds, e.g., predicting your professors' daily mood!
- **Verbal Model:** The relationships can be expressed in terms of verbal (and usually empirical) rules, e.g., economic laws or Fuzzy system rules
- **Physical Model:** Is based on physical laws, e.g., *diffusion law* in physics
- **Mathematical Model:** Have a complete mathematical description, e.g., $E = mc^2$. cf. (Kogan, 2009, Ch. 2)

 From top to bottom the models become more accurate (and somehow more difficult to form)

 Mixtures of these types are possible, e.g., physical laws usually have a mathematical description as well, or some economic laws have been mathematically formulated.

Introduction to Modeling

(continued)

Modeling Approaches

- **Forward Modeling:** From internal (hidden) states to observations
- **Inverse Modeling:** From observations to internal states

These two are not always distinct and in many cases a forward/backward procedure is applied to achieve better models, e.g., modeling head surface electroencephalogram (EEG) signals

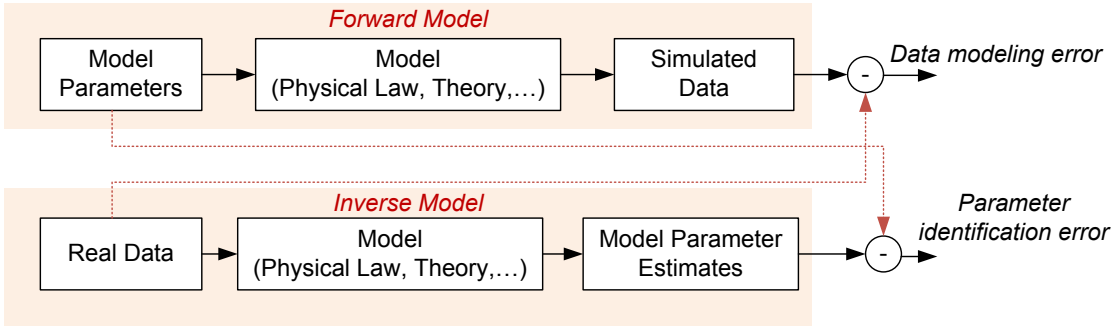

Figure 1: Forward versus Inverse Modeling

Introduction to Modeling

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Forward versus Inverse Modeling

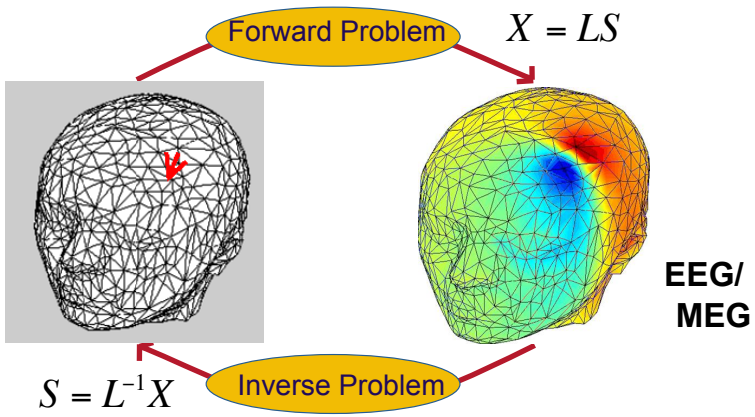

Figure 2: Forward versus Inverse Modeling of the EEG (Adopted from: `http://cfmriweb.ucsd.edu/ttliu/be280a_12/BE280A12_eeg5.pdf`)

✎ Further reading: Low Resolution Brain Electromagnetic Tomography (LORETA) and its extensions, including sLORETA, eLORETA, etc. (Pascual-Marqui et al., 1994, 2002).

Introduction to Modeling

(continued)

Model Types

- **Deterministic:** All parts (equations, rules, signals, etc.) are deterministic, e.g., $x(t) = a\sin(\omega t + \phi)$ with deterministic parameters
- **Stochastic:** Uses stochastic equations, rules, signals, e.g., $x(t) = n(t)$, with $n(t) \sim \mathcal{N}(0, 1)$
- **Hybrid:** Partially deterministic, partially stochastic, e.g., $x(t) = a\sin(\omega t) + n(t)$

Introduction to Modeling

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- **Hybrid:** Partially deterministic, partially stochastic, e.g., $x(t) = a\sin(\omega t) + n(t)$

Depending on the level of abstraction, a complex deterministic model may be approximated by a simple stochastic model, e.g., $x(t) = \sin(\omega t) + 0.01\sin(2\omega t)^2 + 0.03\sqrt{0.2\sin(3\omega t) + 1} + \exp(-100.0t^2)$, depending on the required accuracy, might be approximated by $\tilde{x}(t) = \sin(\omega t) + n(t)$, where $n(t)$ is a noise term with a bounded variance used for modeling the minor terms of $x(t)$

Model Construction

How to Construct a Model

- **Evidence-based:** Using prior (sub-)models based on physical or empirical laws
- **Model fitting:** Fit a model over observed data points
- **Hybrid:** Combination of evidence and data fitting

Introduction to Modeling

(continued)

A Discussion

- "All physical laws are in fact models for physical systems, for which counter examples have not yet been found, within a certain level of abstraction."
  Ex. 1: Kirchhoff voltage and current laws in lumped circuits vs. Maxwell's equations.
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Introduction to Modeling

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Introduction to Modeling

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Introduction to Modeling

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- **Question 1:** Why do the laws of physics obey mathematics?
- **Question 2:** Name a few well-known economic laws. Which types of models are they?
- **Question 3:** Name a few well-known biologic and physiologic laws. Which types of models are they?

Outline

Background

Signal

Any waveform or time-series represented as a function of an independent variable (time, space, samples, etc.).

Example

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

System

- **General 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.

Example

Cardiovascular system, thermal regulation system, glucose control system, etc.

System Properties: Structure

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

Example

$$y = x^2 + 2x + \sqrt{x} \tag{1}$$

- **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 changes in the input

Example

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

System Properties

(continued)

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

Input-Output Mathematical Description

Dynamic systems are of great interest in biological systems modeling. The input-output relationship of these systems can be expressed as follows:

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

Example

$$y(t) = x^2(t) + kt \tag{3}$$

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

Example

$$\ddot{y}(t) + \alpha\dot{y}(t) + b\sqrt{y(t)} = x(t) \tag{4}$$

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. The general form of a linear differential equation is:

$$\sum_{k=0}^{N-1} a_k \frac{d^k y(t)}{dt^k} = \sum_{k=0}^{M-1} b_k \frac{d^k x(t)}{dt^k} \tag{5}$$

- If the coefficients in (5) 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)

The solution of (5) is

$$y(t) = y_h(t) + y_p(t) \tag{6}$$

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

Transfer Functions

For linear time-invariant systems, using Laplace (or Fourier) transform, a transfer function can be assigned to the system:

$$H(s) \triangleq \frac{Y(s)}{X(s)} \tag{7}$$

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

- $H(s)$ 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)

Transfer Functions

(continued)

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Alternative Approach: *State-space analysis*

State Space

States

- 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. States are properties of a system, knowing which make us needless of its past.
- In a physical system, 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.
- State variables are not necessarily unique; but for linear systems their total number (known as the *system's order*) is fixed.
- A system's order can be infinite

State Variables

(continued)

Example

$$\dot{y}(t) + \alpha y(t) = \beta x(t) \tag{8}$$

State Variables

(continued)

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

State Variables

(continued)

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Example

$$y(t) = x(t - t_0) \quad \text{or} \quad H(s) = e^{-t_0 s}$$
$$H(s) = 1 - st_0 + \frac{(st_0)^2}{2} - \ldots = \frac{1}{1 + st_0 + \frac{(st_0)^2}{2} + \ldots} \tag{9}$$

State Variables

(continued)

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This system has infinite number of states. 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

$$\begin{cases} \dot{\boldsymbol{s}}(t) = \boldsymbol{f}(\boldsymbol{s}(t), \boldsymbol{x}(t)) \\ \boldsymbol{y}(t) = \boldsymbol{g}(\boldsymbol{s}(t), \boldsymbol{x}(t)) \end{cases} \tag{10}$$

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

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- State-space representations are not unique; but some *canonical forms* are more common
- 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

$$\begin{cases} \dot{s_1} = f_1(s_1, \ldots, s_n, x_1, \ldots, x_p) \\ \vdots \\ \dot{s_n} = f_n(s_1, \ldots, s_n, x_1, \ldots, x_p) \end{cases} \tag{11}$$

$$\begin{cases} y_1 = g_1(s_1, \ldots, s_n, x_1, \ldots, x_p) \\ \vdots \\ y_m = g_m(s_1, \ldots, s_n, x_1, \ldots, x_p) \end{cases} \tag{12}$$

State Space Representations

(continued)

Linear Case

$$\mathbf{s} = \begin{bmatrix} s_1 \\ \vdots \\ s_n \end{bmatrix}, \mathbf{A} = \begin{bmatrix} a_{11} & \dots & a_{1n} \\ \vdots & & \vdots \\ a_{n1} & \dots & a_{nn} \end{bmatrix}, \mathbf{x} = \begin{bmatrix} x_1 \\ \vdots \\ x_p \end{bmatrix}, \mathbf{y} = \begin{bmatrix} y_1 \\ \vdots \\ y_m \end{bmatrix} \tag{13}$$

$$\begin{cases} \dot{\mathbf{s}}_{n\times 1} = \mathbf{A}_{n\times n}\mathbf{s}_{n\times 1} + \mathbf{B}_{n\times p}\mathbf{x}_{p\times 1} \\ \mathbf{y}_{m\times 1} = \mathbf{C}_{m\times n}\mathbf{s}_{n\times 1} + \mathbf{D}_{m\times p}\mathbf{x}_{p\times 1} \end{cases} \tag{14}$$

Nonlinear Case

$$\begin{cases} \dot{\mathbf{s}}_{n\times 1} = \mathbf{f}_{n\times 1}(\mathbf{s}_{n\times 1}, \mathbf{x}_{p\times 1}) \\ \mathbf{y}_{m\times 1} = \mathbf{g}_{m\times 1}(\mathbf{s}_{n\times 1}, \mathbf{x}_{p\times 1}) \end{cases} \tag{15}$$

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

$$a\frac{d^2y(t)}{dt^2} + b\frac{dy(t)}{dt} + cy(t) = x(t) \tag{16}$$

$$\begin{aligned} s_1 &\overset{\Delta}{=} y(t) & \dot{s}_1 &= s_2 \\ s_2 &\overset{\Delta}{=} \dot{y}(t) \Rightarrow & \dot{s}_2 &= \ddot{y}(t) = \tfrac{1}{a}(x(t) - bs_2 - cs_1) \end{aligned} \tag{17}$$

State-space representation:

$$\begin{bmatrix} \dot{s}_1 \\ \dot{s}_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\frac{c}{a} & -\frac{b}{a} \end{bmatrix} \cdot \begin{bmatrix} s_1 \\ s_2 \end{bmatrix} + \begin{bmatrix} 0 \\ \frac{1}{a} \end{bmatrix} x(t)$$
$$y(t) = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} s_1 \\ s_2 \end{bmatrix} \tag{18}$$

State-Space to Transfer Functions and Differential Equations

Taking the Laplace transform of (14):

$$\mathbf{Y}(s) = \left[\mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B} + \mathbf{D}\right]\mathbf{X}(s) \tag{19}$$

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:

$$\begin{aligned} sY(s) - y(0) &= aY(s) + bX(s) \\ Y(s) &= \frac{y(0)}{s-a} + \frac{bX(s)}{s-a} \Rightarrow \\ y(t) &= y(0)e^{at}u(t) + be^{at}u(t) * x(t) \Rightarrow \\ y(t) &= y(0)e^{at}u(t) + b\int_0^t e^{a(t-\tau)}x(\tau)d\tau \end{aligned} \tag{20}$$

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

Temporal Solutions from State-pace Representation

Vectorial Case

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

$$\begin{aligned} s\mathbf{Y}(s) - \mathbf{y}(0) &= \mathbf{A}\mathbf{Y}(s) + \mathbf{B}\mathbf{X}(s) \\ \mathbf{Y}(s) &= (s\mathbf{I} - \mathbf{A})^{-1}\mathbf{y}(0) + (s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B}\mathbf{X}(s) \\ \mathbf{\Phi}(s) &\stackrel{\Delta}{=} (s\mathbf{I} - \mathbf{A})^{-1} = L\left\{e^{\mathbf{A}t}\right\} = L\left\{\phi(t)\right\} \end{aligned} \tag{21}$$

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

$$\mathbf{y}(t) = \phi(t)\mathbf{y}(0) + \int_0^t \phi(t-\tau)\mathbf{B}\mathbf{x}(\tau)d\tau \tag{22}$$

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

$$\mathbf{y}(t) = \phi(t-t_0)\mathbf{y}(t_0) + \int_{t_0}^t \phi(t-\tau)\mathbf{B}\mathbf{x}(\tau)d\tau \tag{23}$$

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

State Transition Matrix

Example

$$\dot{\mathbf{y}}(t) = \begin{bmatrix} 0 & 1 \\ -2 & -3 \end{bmatrix} \mathbf{y}(t) \tag{24}$$

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

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

$$(s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{s^2 + 3s + 2} \begin{bmatrix} s+3 & 1 \\ -2 & s \end{bmatrix} \Rightarrow \tag{25}$$

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

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 is the subject of *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.

System Discretization

Static system discretization

Since static systems do not evolve in time, the discretization is straightforward: $t \rightarrow nT_s$, 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:

$$\frac{d}{dt}x(t) \rightarrow \frac{x[n+1]-x[n]}{T_s} \tag{26}$$

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 (cf. DSP textbooks)

Discretized models are not unique

Static System Linearization

Consider a static system: $y = f(\mathbf{u})$ $(\mathbf{u} = [u_1, \cdots, u_n]^T)$.

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:

$$\begin{aligned} y &= f(\mathbf{u}_0) + \left.\frac{\partial f(\mathbf{u})}{\partial \mathbf{u}}\right|_{\mathbf{u}=\mathbf{u}_0} (\mathbf{u} - \mathbf{u}_0) + \cdots \\ y &\approx f(\mathbf{u}_0) + \left.\frac{\partial f(\mathbf{u})}{\partial \mathbf{u}}\right|_{\mathbf{u}=\mathbf{u}_0} (\mathbf{u} - \mathbf{u}_0) \end{aligned} \tag{27}$$

$$\frac{\partial f(\mathbf{u})}{\partial \mathbf{u}} = \left[\frac{\partial f(\mathbf{u})}{\partial u_1}, \cdots, \frac{\partial f(\mathbf{u})}{\partial u_n}\right]^T \Bigg|_{\mathbf{u}=u_0} \triangleq \mathbf{g}_0 \tag{28}$$

$$\begin{aligned} & y \approx f(\mathbf{u}_0) + \mathbf{g}_0^T (\mathbf{u} - \mathbf{u}_0) \Rightarrow \\ & y - y_0 \approx \mathbf{g}_0^T (\mathbf{u} - \mathbf{u}_0) \Rightarrow \\ & \delta y \approx \mathbf{g}_0^T \boldsymbol{\delta u} \end{aligned} \tag{29}$$

Static System Linearization

(continued)

Example

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

$$y = u_1^2 u_2^2 + u_2 + 3u_1^2 \tag{30}$$

Static System Linearization

(continued)

Example

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

$$y = u_1^2 u_2^2 + u_2 + 3u_1^2 \tag{30}$$

Approach 1 (Taylor expansion):

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

Static System Linearization

(continued)

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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 (30) 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 $\sqrt{y_0} = u_0$

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

$$\mathbf{A}(t) \triangleq \left.\frac{\partial \mathbf{f}(\mathbf{x},\mathbf{u})}{\partial \mathbf{x}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \quad \mathbf{B}(t) \triangleq \left.\frac{\partial \mathbf{f}(\mathbf{x},\mathbf{u})}{\partial \mathbf{u}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}}$$
$$\mathbf{C}(t) \triangleq \left.\frac{\partial \mathbf{g}(\mathbf{x},\mathbf{u})}{\partial \mathbf{x}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \quad \mathbf{D}(t) \triangleq \left.\frac{\partial \mathbf{g}(\mathbf{x},\mathbf{u})}{\partial \mathbf{u}}\right|_{\substack{\mathbf{x}=\mathbf{x}_0 \\ \mathbf{y}=\mathbf{y}_0}} \tag{31}$$

and considering that

$$\begin{cases} \dot{\mathbf{x}_0} = \mathbf{f}(\mathbf{x}_0,\mathbf{u}_0) \\ \mathbf{y}_0 = \mathbf{g}(\mathbf{x}_0,\mathbf{u}_0) \end{cases} \tag{32}$$

Results in:

$$\begin{cases} \delta\dot{\mathbf{x}}(t) \approx \mathbf{A}(t)\delta\mathbf{x}(t) + \mathbf{B}(t)\delta\mathbf{u}(t) \\ \delta\mathbf{y}(t) \approx \mathbf{C}(t)\delta\mathbf{x}(t) + \mathbf{D}(t)\delta\mathbf{u}(t) \end{cases} \tag{33}$$

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

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).

Chaos in Biological Systems

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Multi-Phasic Fetal Heart Rate

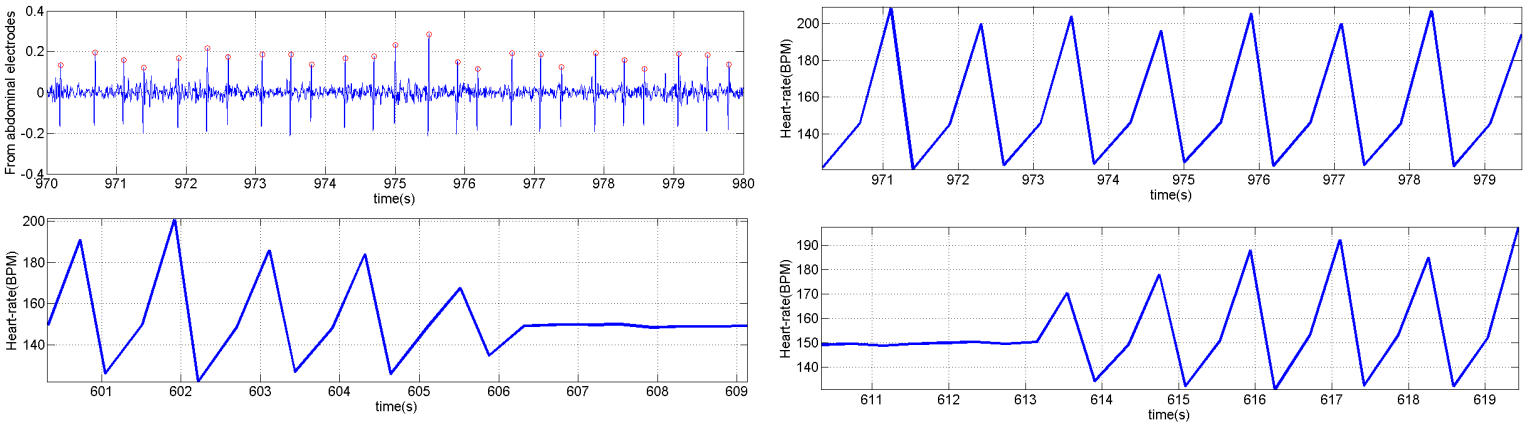


Figure 3: Sample fetal heart rate with temporarily oscillatory characteristics

Nonlinear Dynamical Models & Chaos

(continued)

Some general definitions

- Consider the following dynamical models

$$\text{Continuous Model:} \qquad \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}) \tag{34}$$

$$\text{Discrete Model:} \qquad \mathbf{x}_{n+1} = \mathbf{f}(\mathbf{x}_n) \tag{35}$$

- **Trajectory (Orbit):** Starting from an initial point $\mathbf{x}_0$, is the path of the system over time (or the set of all points that satisfy (34) or (35)
- **Fixed-Point:** Is a point from which the system's trajectory does not exit, once entered! For continuous-time dynamic systems if $\mathbf{f}(\mathbf{x}^*) = 0$, $\mathbf{x}^*$ is a fixed-point. For the discrete-time case $\mathbf{x}^* = \mathbf{f}(\mathbf{x}^*)$ 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.

Chaos in Discrete-Time Systems

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:

$$x_{n+1} = f(x_n) = rx_n(1 - x_n) \tag{36}$$

The fixed-points (which depend on the parameter r) are:

$$x_r^* = rx_r^*(1 - x_r^*) \Rightarrow \begin{cases} x_r^* = 0 \\ x_r^* = 1 - \dfrac{1}{r} \end{cases} \tag{37}$$

Chaos in Discrete-Time Systems

(continued)

The Logistic Map (continued)

Figure 4 shows (36) with respect to the parameter r:

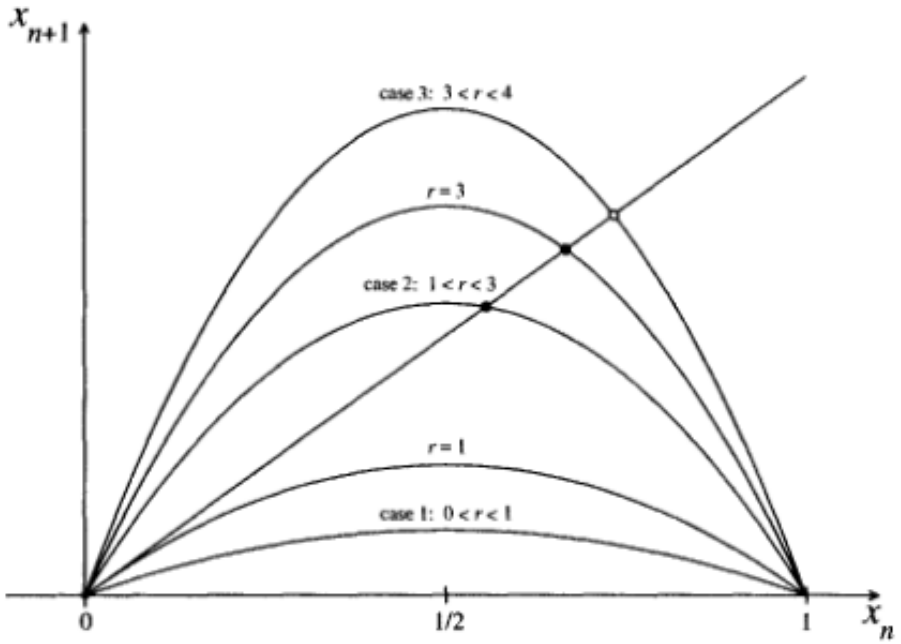


Figure 4: Logistic map fixed-points

Chaos in Discrete-Time Systems

(continued)

The Logistic Map for $0 < r < 1$

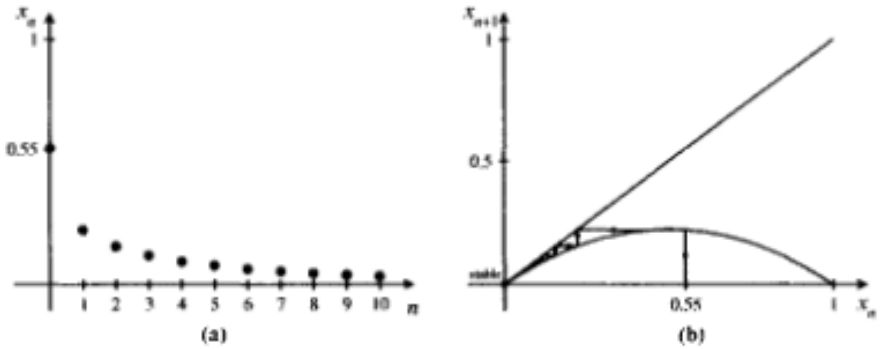


Figure 5: $r = 0.9$

- 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

Chaos in Discrete-Time Systems

(continued)

The Logistic Map for $1 < r < 3$

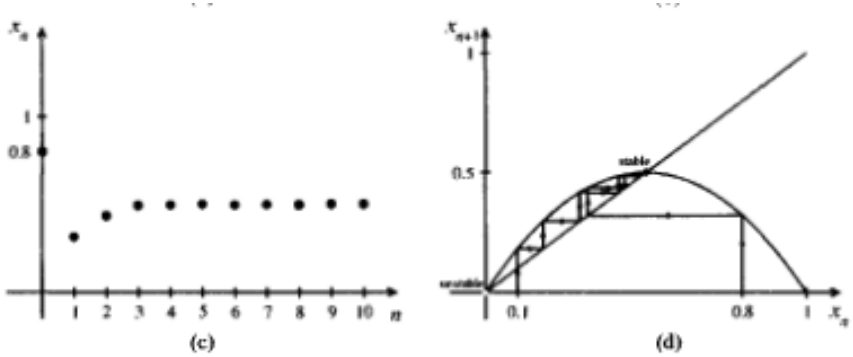


Figure 6: $r = 2$

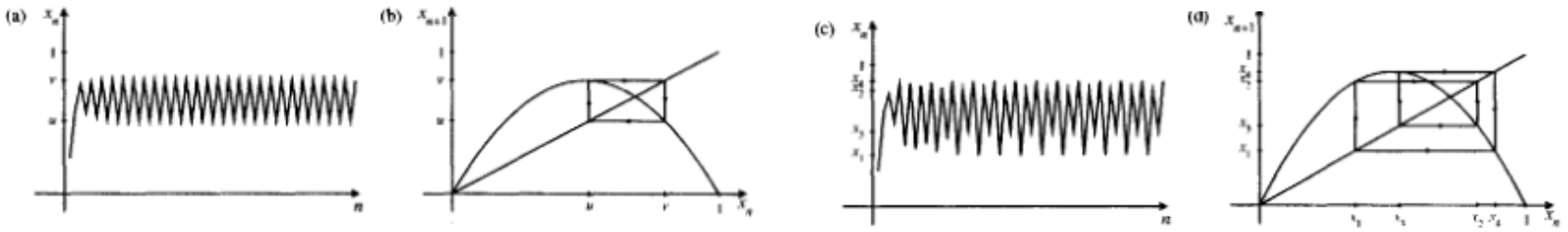
- The fixed-points are $x^* = 0$, which is unstable and $x_r^* = 1 - \frac{1}{r}$, which is stable
- x_r^* is an attractor for all $x \in (0, 1]$, i.e., the population converges x_r^*

Chaos in Discrete-Time Systems

(continued)

The Logistic Map for $3 < r < 4$

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



(a) (b)

Figure 7: (a) $r = 3.2$, (b) $r = 3.45$

- 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

Chaos in Discrete-Time Systems

(continued)

What happens during bifurcation? The fixed-point $x_r^* = 1 - 1/r$ is no longer stable (cf. (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. □

Chaos in Discrete-Time Systems

(continued)

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

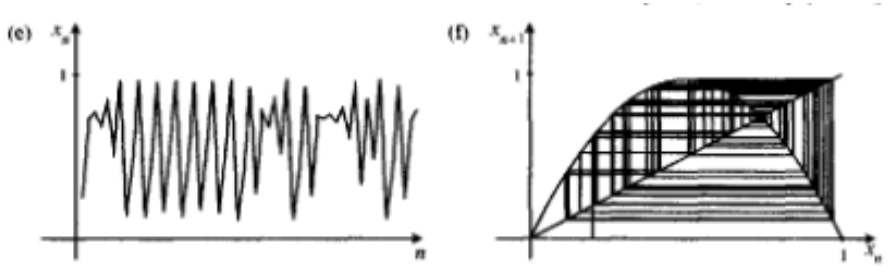


Figure 8: Chaotic case

Chaos in Discrete-Time Systems

(continued)

The Logistic Map Bifurcation Diagram

Figure 9 shows the bifurcation diagram of the discrete logistic map equation

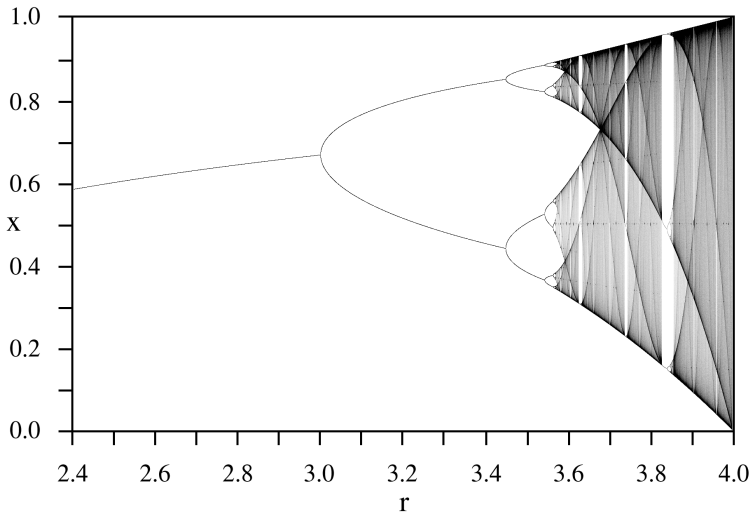


Figure 9: The Logistic Map Bifurcation Diagram

Exercise 1: Find and analyze the first bifurcation points of the logistic map analytically.

Chaos in Continuous-Time Systems

Example: The Lorenz Map

$$\begin{cases} \dot{x} = p(y - x) \\ \dot{y} = -xz + rx - y \\ \dot{z} = xy - bz \end{cases} \quad \mathbf{x} = \begin{bmatrix} x \\ y \\ z \end{bmatrix} \tag{38}$$

In order to find the fixed-points we set $\dot{x} = \dot{y} = \dot{z} = 0$, which gives:

$$\mathbf{x}_1^* = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix} \mathbf{x}_2^* = \begin{bmatrix} -\sqrt{b(r-1)} \\ -\sqrt{b(r-1)} \\ r-1 \end{bmatrix} \quad \mathbf{x}_3^* = \begin{bmatrix} \sqrt{b(r-1)} \\ \sqrt{b(r-1)} \\ r-1 \end{bmatrix} \tag{39}$$

- For $r < 1$ $\mathbf{x}_1^* = 0$ is an attractor for all initial conditions of $\mathbf{x}$
- For $r > 1$ $\mathbf{x}_1^* = 0$ is an unstable fixed-point

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:

$$\delta_n \triangleq \frac{A_n - A_{n-1}}{A_{n+1} - A_n} \to \delta \triangleq \lim_{n\to\infty} \delta_n = 4.66920161\cdots \tag{40}$$

Example

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:

$$\alpha_n \stackrel{\Delta}{=} \frac{d_n}{d_{n+1}} \rightarrow \alpha \stackrel{\Delta}{=} \lim_{n\rightarrow\infty} \alpha_n = 2.5029\cdots \tag{41}$$

Outline

Dimensional Analysis

- Dimensional analysis is a method for finding the relationship between the variables of a model
- Although, dimensional 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)
- Dimensional analysis is also used as a modeling methodology (Szirtes, 2007, Ch. 17)

 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:

$$[x \pm y] = [x] = [y] = X \tag{42}$$

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

$$[x \cdot y] = X \cdot Y \qquad [x/y] = X/Y \tag{43}$$

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 dimensionality; 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).

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 I

(case studies)

Fisher Discrimination Ratio

$$FDR = (x - m_x)(y - m_y)/(\sigma_x \sigma_y) \tag{44}$$

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

Fourier Transform

$$X(f) = \int_{-\infty}^{\infty} x(t) \exp(-j2\pi ft) dt \tag{45}$$

Dimension: $[x] \cdot T = [x] \,/ Hz$: Density per Hz

Dimension Analysis I

(case studies, continued)

The Dirac Delta Function

$$\delta(t), where \int_{-\infty}^{\infty} \delta(t)dt = 1 \tag{46}$$

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

$$R_x[n] = E\{x[n]x^*[n+m]\} = \sum x[n]x^*[n+m] \tag{47}$$

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

Dimension Analysis I

(case studies, continued)

Deterministic Continuous-Time Auto-correlation Function

$$R_x(\tau) = \int x(t)x^*(t+\tau)d\tau \tag{48}$$

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

Power Density Function

$$S_x(f) = \int_{-\infty}^{\infty} R_x(\tau)\exp(-j2\pi f\tau)d\tau \tag{49}$$

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

Dimension Analysis I

(case studies, continued)

Discrete Probability Density Function (pdf)

$$P_X(x), \text{such that } \sum_i P_X(x_i) = 1 \tag{50}$$

Dimension: The discrete pdf is dimensionless

Continuous Probability Density Function

$$f_X(x), \text{such that } \int_{-\infty}^{\infty} f_X(x)dx = 1 \tag{51}$$

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

Dimension Analysis I

(case studies, continued)

Entropy

$$H(X) = -\sum_i P_X(x_i) \log_2(P_X(x_i)) \tag{52}$$

Dimension: $H(X)$ is dimensionless

Continuous Probability Density Function

$$h(X) = -\int_{-\infty}^{\infty} f_X(x) \log(f_X(x)) dx \tag{53}$$

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 dimensional issue by using ratios of probability density functions as the $\log(\cdot)$ argument.

Dimension Analysis

(case studies, continued)

ECG QT Interval Correction Formulas

$$\begin{aligned} \text{Bazett's formula:} \quad & QT_c = \frac{QT}{\sqrt{RR}} \\ \text{Fredericia's formula:} \quad & QT_f = \frac{QT}{\sqrt[3]{RR}} \end{aligned} \tag{54}$$

Both forms are dimensionally inconsistent (they are only valid in certain time scales). For example, 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. In that case, 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*.

- 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.

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

D: particle diameter

g: gravitational acceleration

μ: fluid viscosity

$\rho_1 - \rho_2$: difference between the particle and fluid densities

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

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

l: pendulum length

m: pendulum mass

g: gravitational acceleration

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) 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 prove a model; but it can be used to verify the physical consistency of a model (as a necessary condition).
For a detailed study of dimensional modeling, see (Szirtes, 2007, Ch. 17).

Exercise 2: Propose a model determining the terminal velocity of a raindrop falling from a motionless cloud.

Exercise 3: 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.

Outline

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:

$$\frac{d^2x(t)}{dt^2} + 2\alpha\omega_0\frac{dx(t)}{dt} + \omega_0^2 x(t) = 0, \quad x(t_0) = c_0, x'(t_0) = c_1 \tag{55}$$

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

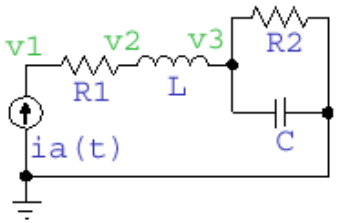
(continued)

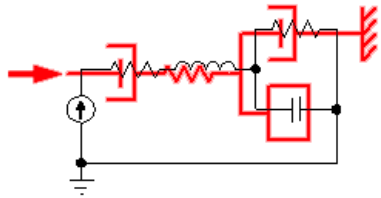
Electrical Equation	Force-Current Analogy	Force-Voltage Analogy
$e = Ri$	$v = \frac{f}{B}$	$f = vB$
$e = L\frac{di}{dt}$	$v = \frac{1}{K}\frac{df}{dt}$	$f = M\frac{dv}{dt} = Ma$
$e = \frac{1}{C}\int idt$	$v = \frac{1}{M}\int fdt$	$f = K\int vdt = Kx$
$Power = e \cdot i$	$Power = v \cdot f$	$Power = f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

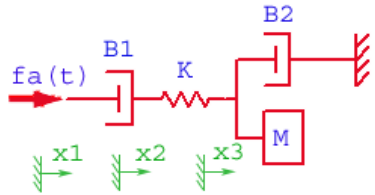
Electro-Mechanical Analogy

(continued)

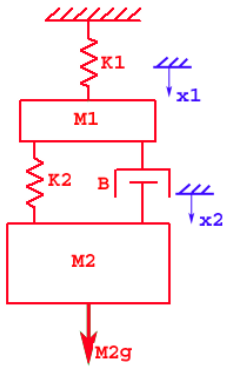
Electrical to Mechanical

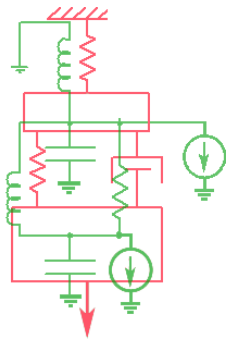


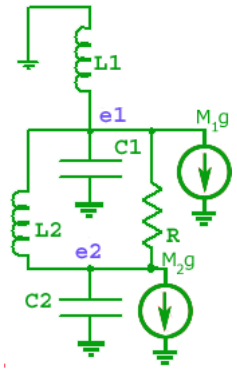




Mechanical to Electrical







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	$f^2 \frac{1}{B} = \frac{v^2}{1/B}$	$\tau^2 \frac{1}{B} = \frac{\omega^2}{1/B}$	$i^2 R = v^2/R$	N/A	$q^2 R = p^2/R$	$v^2 B = f^2/B$	$\omega^2 B_r = \tau^2/B_r$	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	$E = \frac{1}{2} \frac{1}{K} f^2$	$E = \frac{1}{2} \frac{1}{K_r} \tau^2$	$E = \frac{1}{2} L i^2$		$E = \frac{1}{2} I q^2$	$E = \frac{1}{2} M v^2$	$E = \frac{1}{2} J \omega^2$	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	$E = \frac{1}{2} M v^2$	$E = \frac{1}{2} J \omega^2$	$E = \frac{1}{2} C v^2$	$E = CT$ (not analogous)	$E = \frac{1}{2} C p^2$	$E = \frac{1}{2} \frac{1}{K} f^2$	$E = \frac{1}{2} \frac{1}{K_r} \tau^2$	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 10: General analogy between physical systems; adopted from Sullivan (2014)

Analogical Modeling in Biological Systems

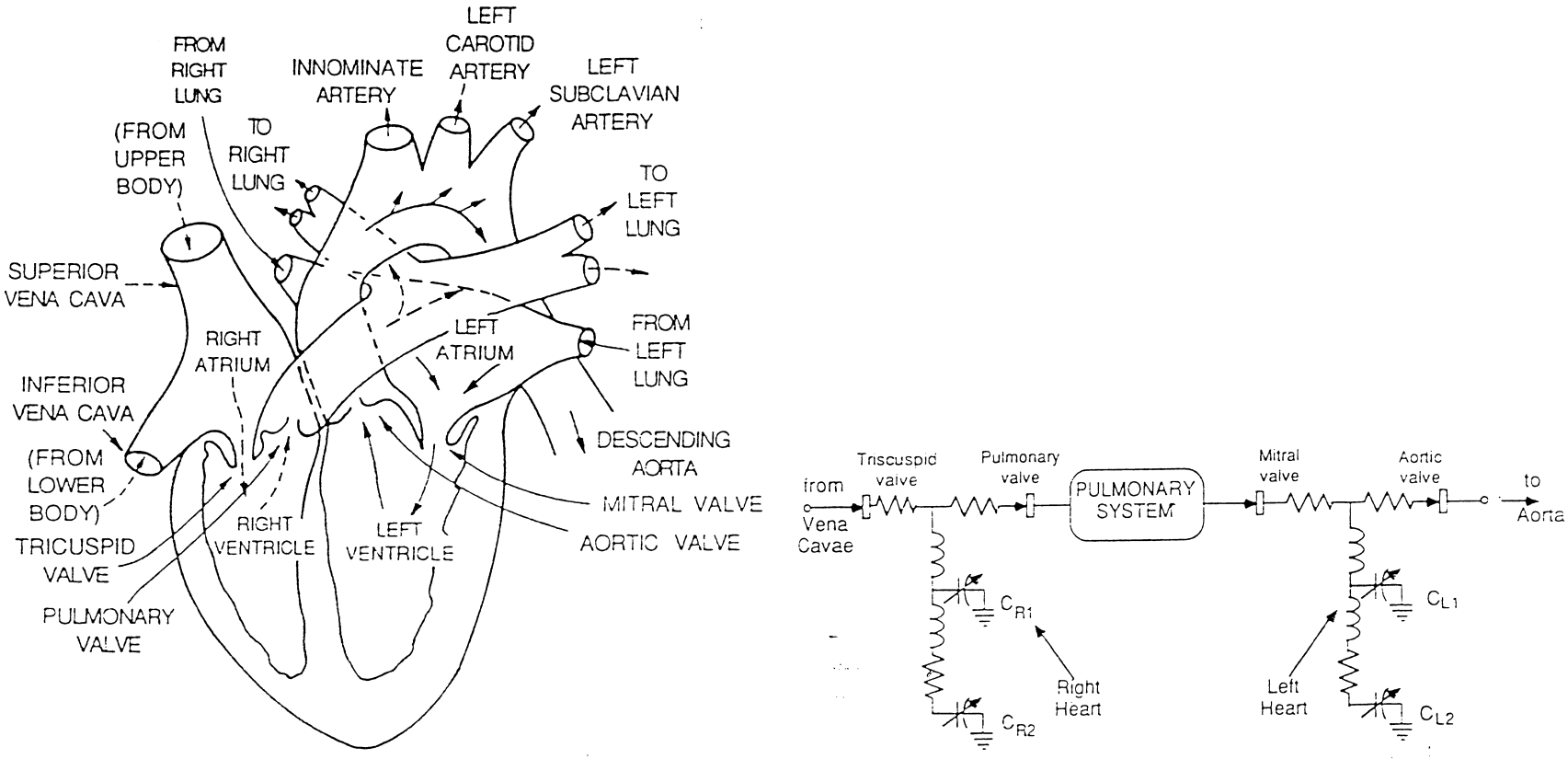


Figure 11: Analogy between cardiac and electrical systems; adopted from Rideout (1991)

Analogical Modeling in Biological Systems

(continued)

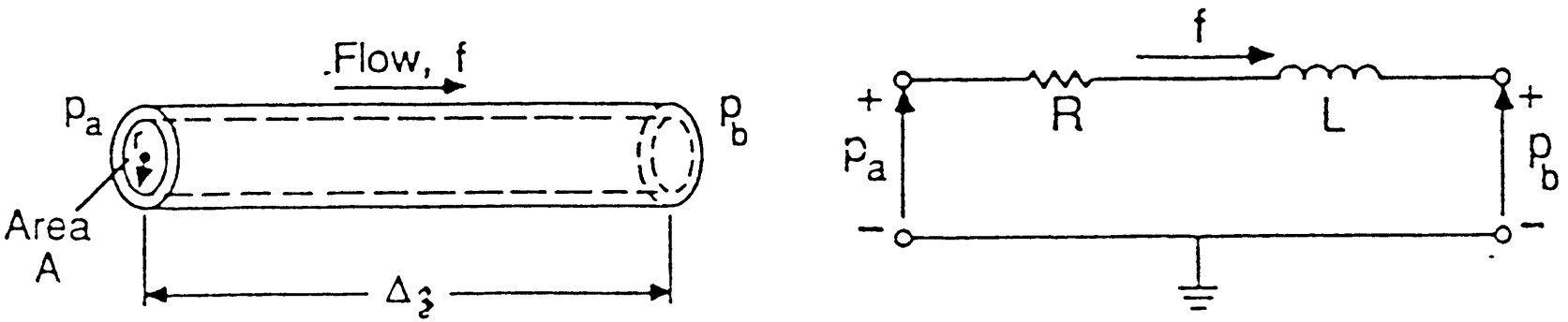


Figure 12: Idealized vein or artery model (vein wall compliance ignored); adopted from (Rideout, 1991, Ch. 4)

Analogical Modeling in Biological Systems

(continued)

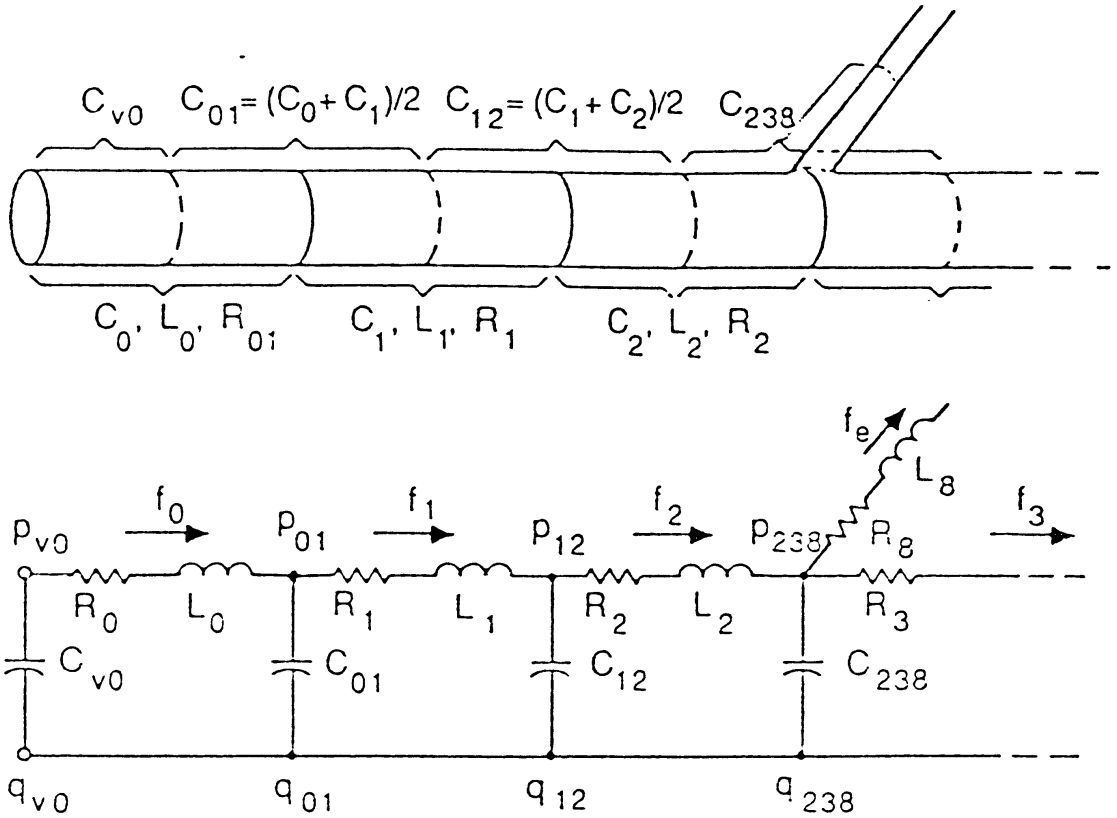


Figure 13: A portion of the aorta (vein wall compliance considered); adopted from (Rideout, 1991, Ch. 4)

Analogical Modeling in Biological Systems

(continued)

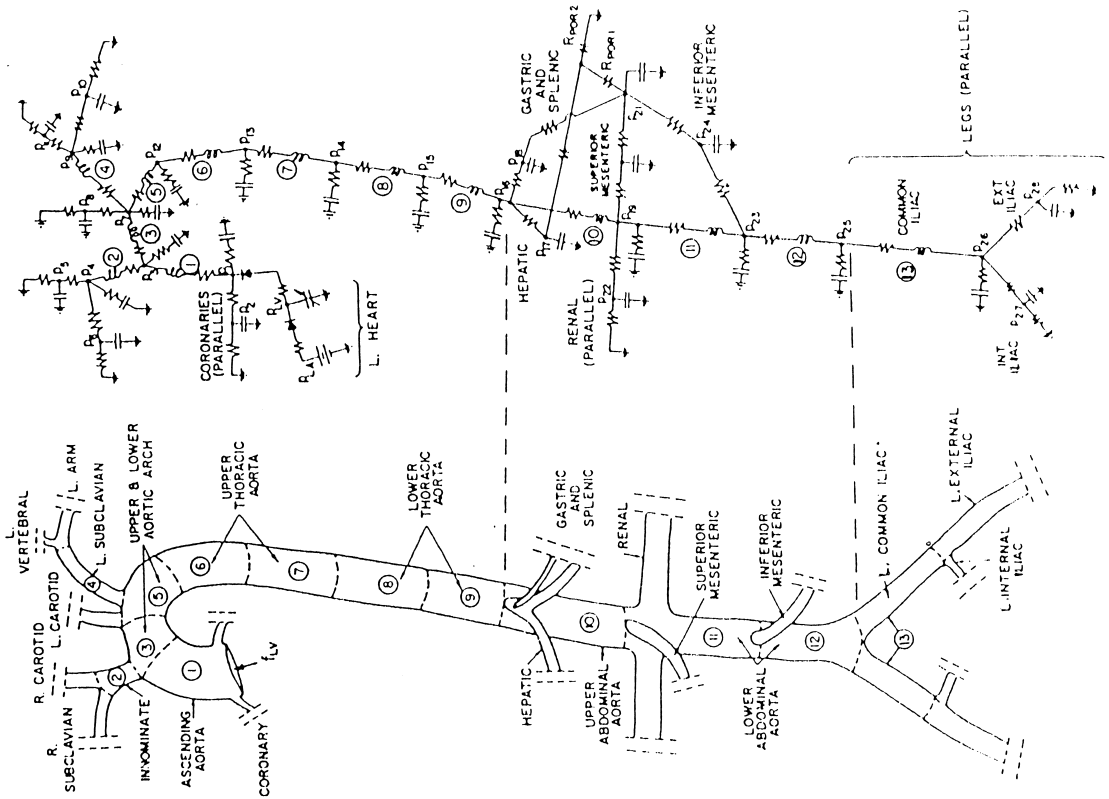
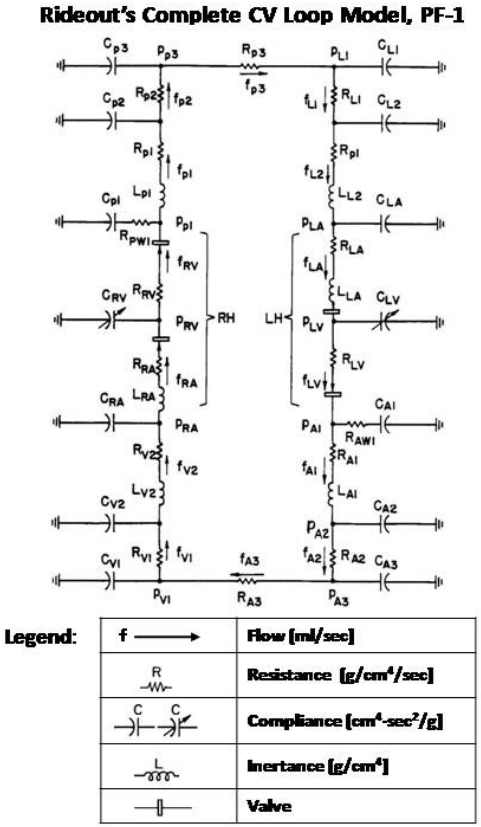


Figure 14: Analogy between cardiovascular and electrical systems; adopted from Rideout (1991)

Analogical Modeling in Biological Systems

(continued)

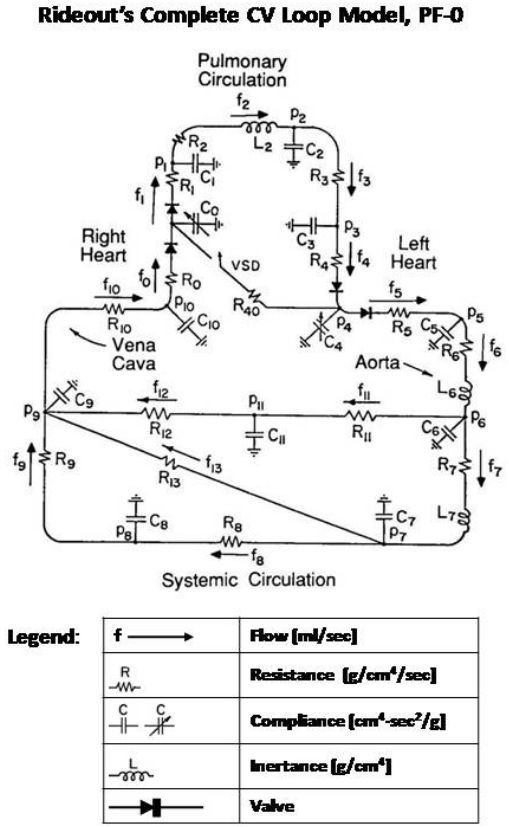


Parameter Values				
Suffix	Anatomy	R	L	C - 10^6
P1	Pulmonary Artery 1	10	1	100
P2	Pulmonary Artery 2	40		300
P3	Pulmonary Artery 3	80		2700
L1	Pulmonary Veins 1	30		1000
L2	Pulmonary Veins 2	10	1	1000
LA	Left Atrium	5	1	11760
LV	Left Ventricle	5	1	Variable
A1	Aorta 1	10	1	180
A2	Aorta 2	160		230
A3	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 15: Rideout's complete non-pulsatile CV pressure-flow loop model 1; adopted from `http://www.physiome.org/`

Analogical Modeling in Biological Systems

(continued)

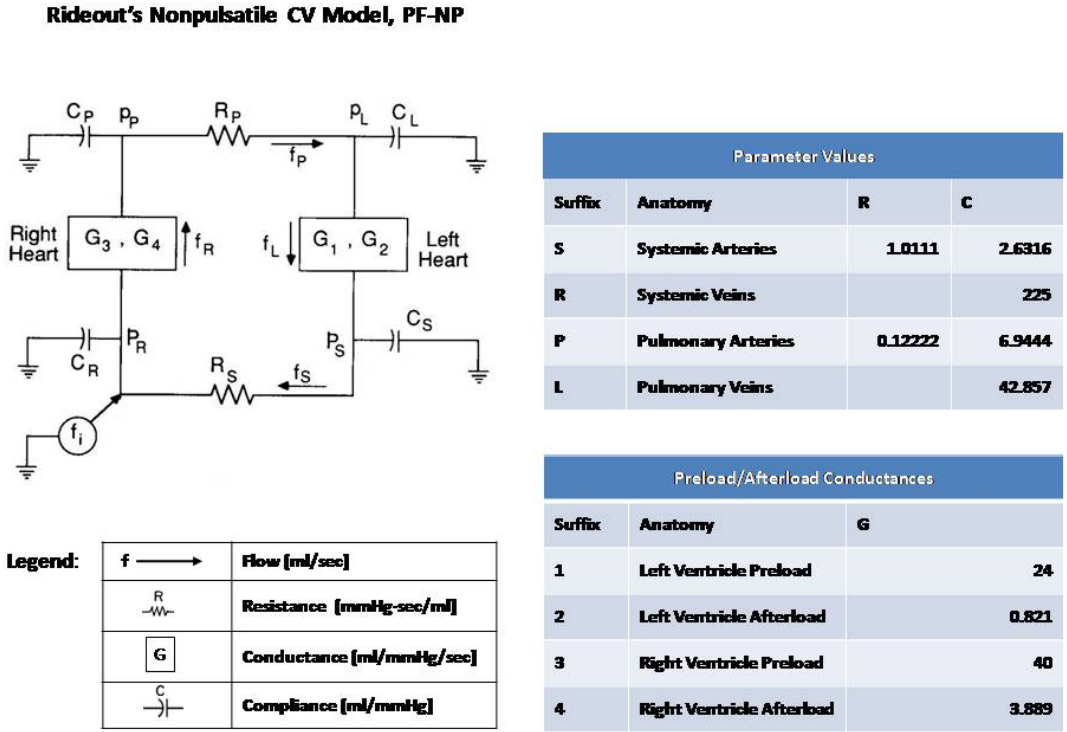


Parameter Values				
	Anatomy	R	L	C - 10^6
0	Right Ventricle	10		Variable
1	Pulmonary Artery	10		1001
2	Pulmonary Artery 2	27	1.332	3003
3	Lung Capillaries	150		5005
4	Left Ventricle	10		Variable
5	Ascending Aorta	13		501
6	Descending Aorta	7	1.332	1001
7	Abdominal Aorta	27	1.332	1336
8	Leg Arteries	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 16: 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 17: Rideout's complete non-pulsatile CV pressure-flow loop model 3; adopted from `http://www.physiome.org/`

Analogical Modeling in Biological Systems

(continued)

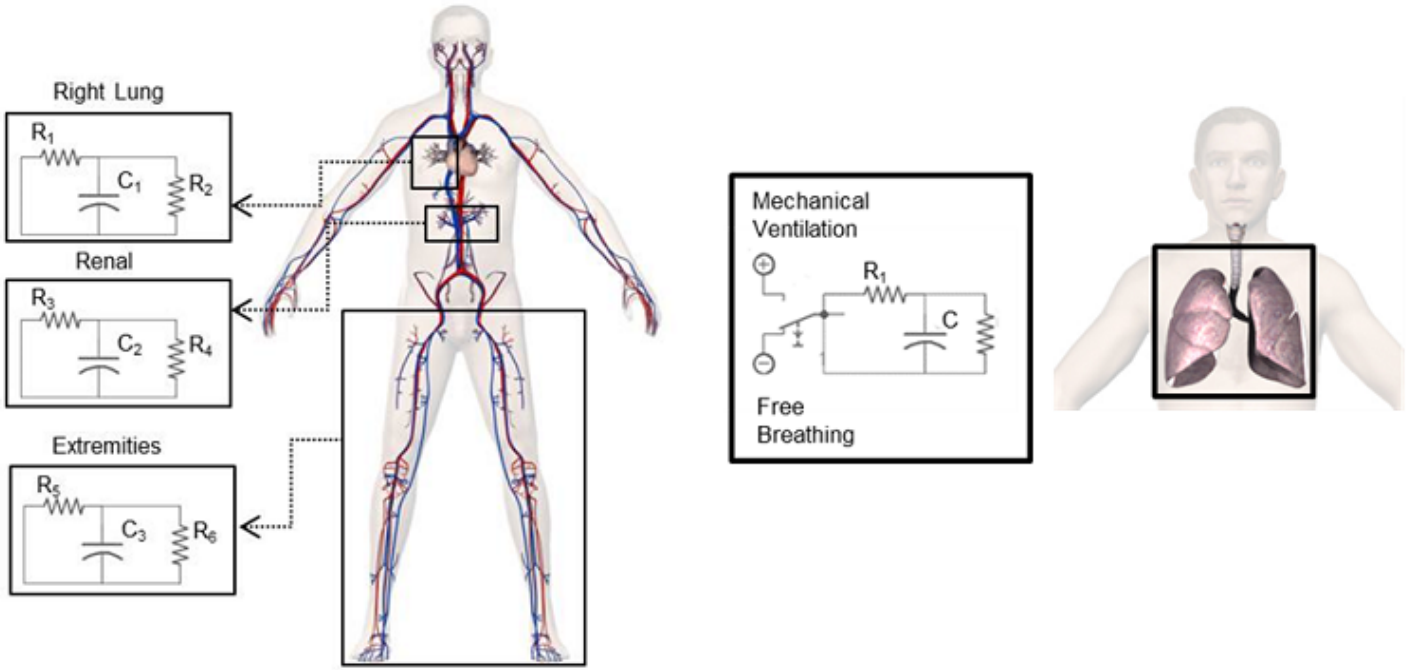


Figure 18: physiology lumped parameter modeling; adopted from `https://physiology.kitware.com/_circuit_methodology.html`

Analogical Modeling in Biological Systems

(continued)

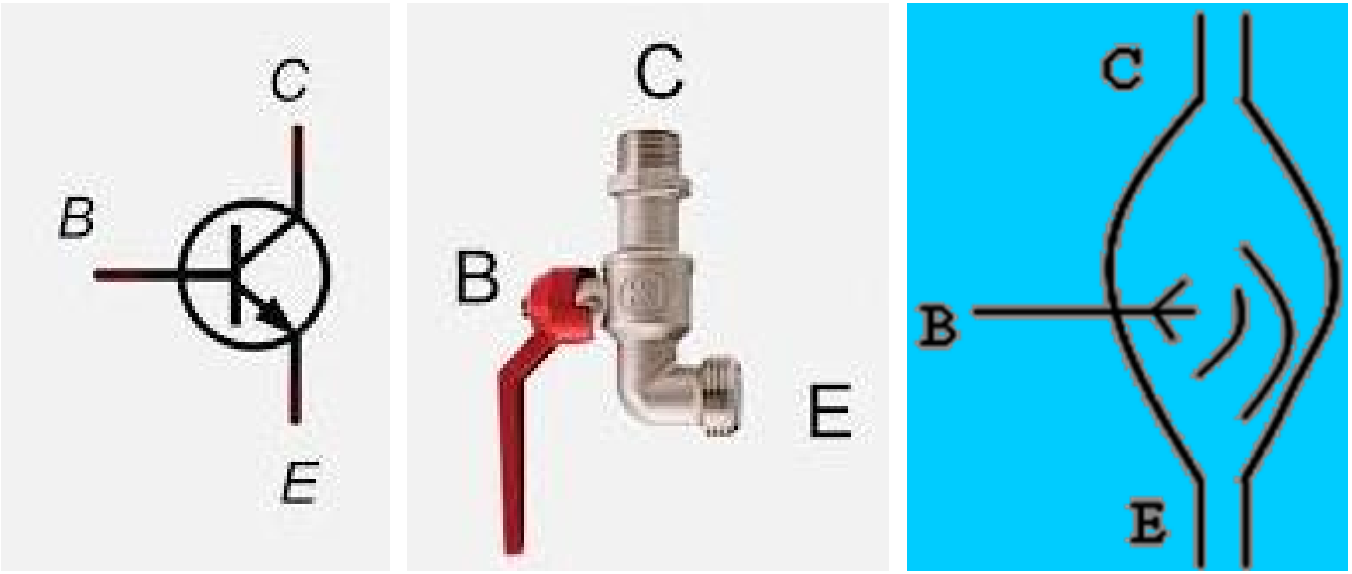


Figure 19: Transistor, Water-tap and muscle analogy

Analogical Modeling in Biological Systems

(continued)

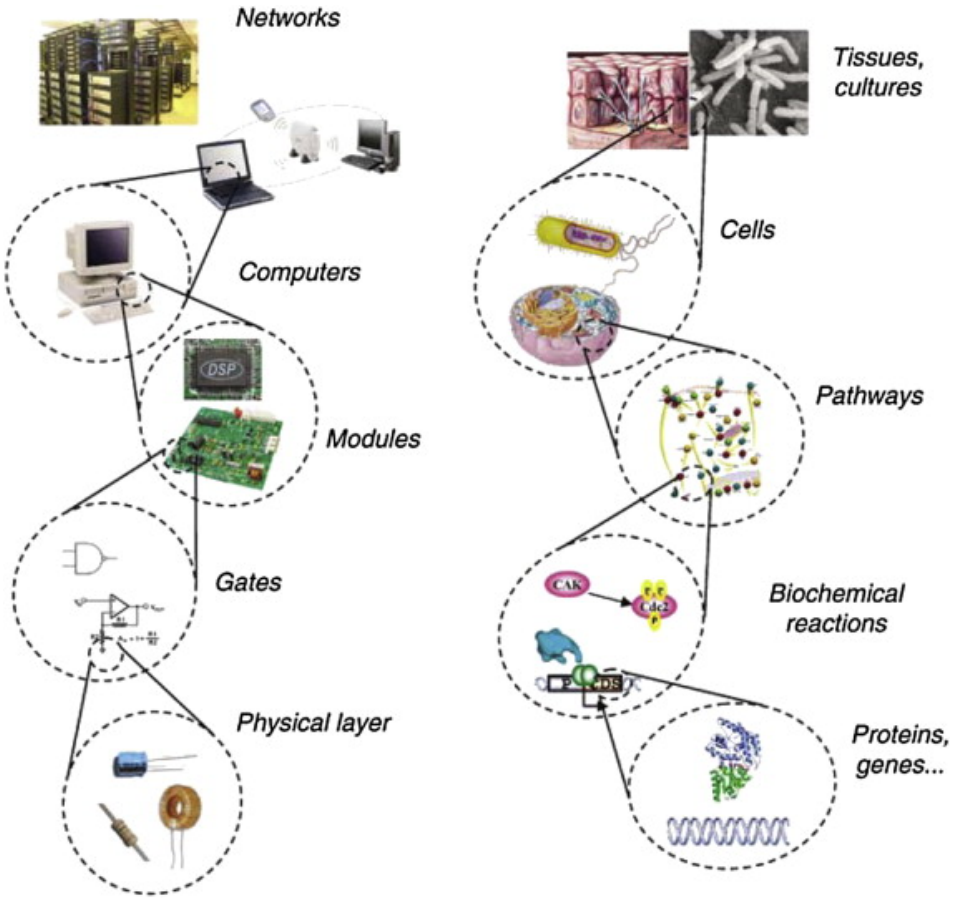


Figure 20: A conceptual analogy between the levels of organization of computing systems and biological systems (Andrianantoandro et al., 2006)

Analogical Modeling in Biological Systems

(continued)

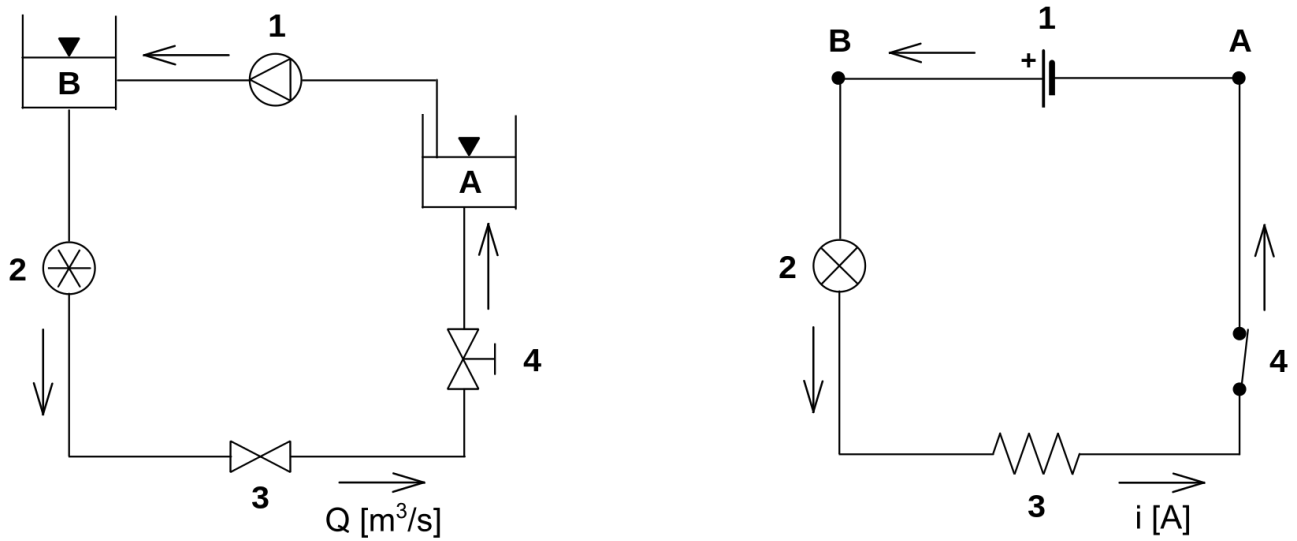


Figure 21: Electro-Hydrolic Analogy

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

Outline

Ordinary vs. Partial Differential Modeling

Introduction

- 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 I

- 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.

Compartmental Modeling II

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 (either analytically or numerically), which is in the form of a first-order state-space model.
6. A compartment model is linear (nonlinear), when its rate flow factors are independent (dependent) of the state variables.
7. A compartment model is time-invariant (time-variant), when its rate flow factors are independent (dependent) of time.
8. 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.

Case Studies

A three-compartment model

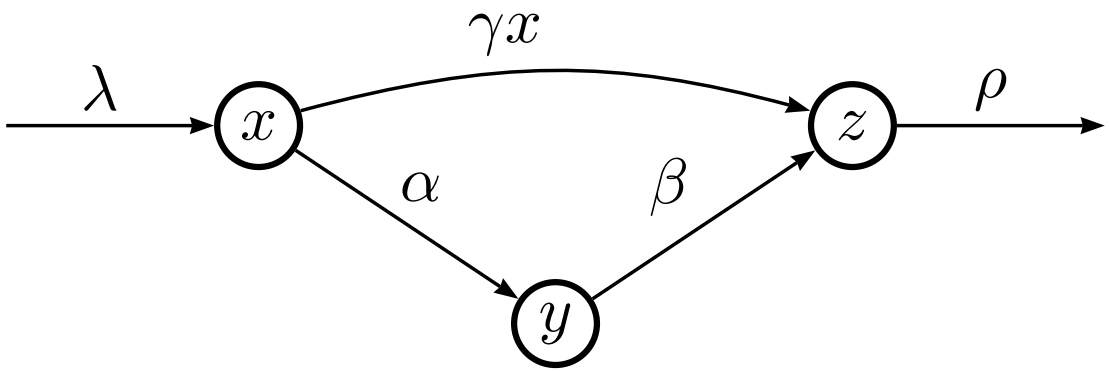


Figure 23: A sample compartmental model

$$\begin{cases} \dot{x}(t) = \lambda - \gamma \cdot x(t)^2 - \alpha x(t) \\ \dot{y}(t) = \alpha x(t) - \beta \cdot y(t) \\ \dot{z}(t) = \gamma \cdot x(t)^2 + \beta \cdot y(t) - \rho z(t) \end{cases} \tag{56}$$

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

Case Studies I

Chemical Reactions (Blomhøj et al., 2014)

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

$$2N_2O_5 \rightarrow 4NO_2 + O_2 \tag{57}$$

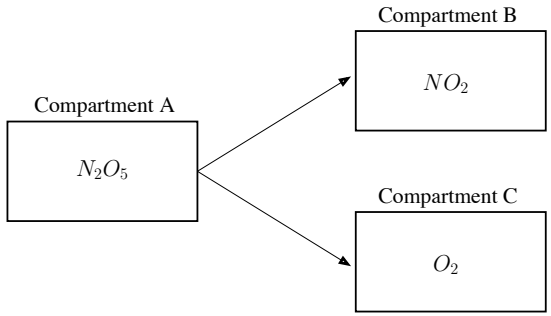


Figure 24: Compartments in chemical reactions; adopted from (Blomhøj et al., 2014)

Case Studies II

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.

$$A \xrightarrow{k} B \qquad \begin{cases} \dot{a}(t) = -ka(t) \\ \dot{b}(t) = ka(t) \end{cases} \tag{58}$$

Reversible Chemical Reaction

In a similar manner, for a reversible chemical reaction

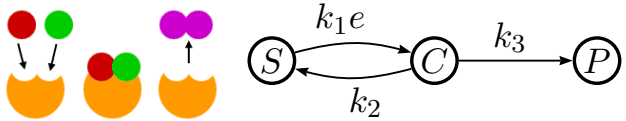
$$A \underset{k_2}{\overset{k_1}{\longleftrightarrow}} B \qquad \begin{cases} \dot{a}(t) = -k_1 a(t) + k_2 b(t) \\ \dot{b}(t) = k_1 a(t) - k_2 b(t) \end{cases} \tag{59}$$

Case Studies III

Enzyme-Catalyzed Reactions: 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.

$$S + E \underset{k_2}{\overset{k_1}{\longleftrightarrow}} C \xrightarrow{k_3} P + E \qquad \begin{cases} \dot{s}(t) = -k_1 s(t)e(t) + k_2 c(t) \\ \dot{e}(t) = -k_1 s(t)e(t) + k_2 c(t) + k_3 c(t) \\ \dot{c}(t) = k_1 s(t)e(t) - k_2 c(t) - k_3 c(t) \\ \dot{p}(t) = k_3 c(t) \end{cases} \tag{60}$$



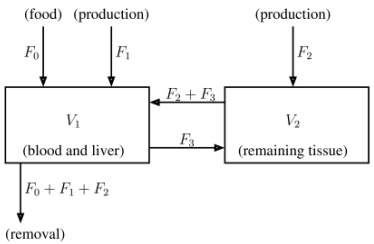
(a) (b)

Figure 25: a) Enzyme-catalyzed reactions; adopted from `http://www.chem4kids.com`. b) The Michaelis-Menten model. Note that $\forall t : \dot{s}(t) + \dot{c(t)} + \dot{p(t)} = 0$.

Case Studies IV

Dynamics of Labeled Cholesterol in the Body (Blomhøj et al. (2014))

- The amount of cholesterol in the body can be modeled by two compartments: 1) blood and liver 2) other body tissues
- In order 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. Here, 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 equations.



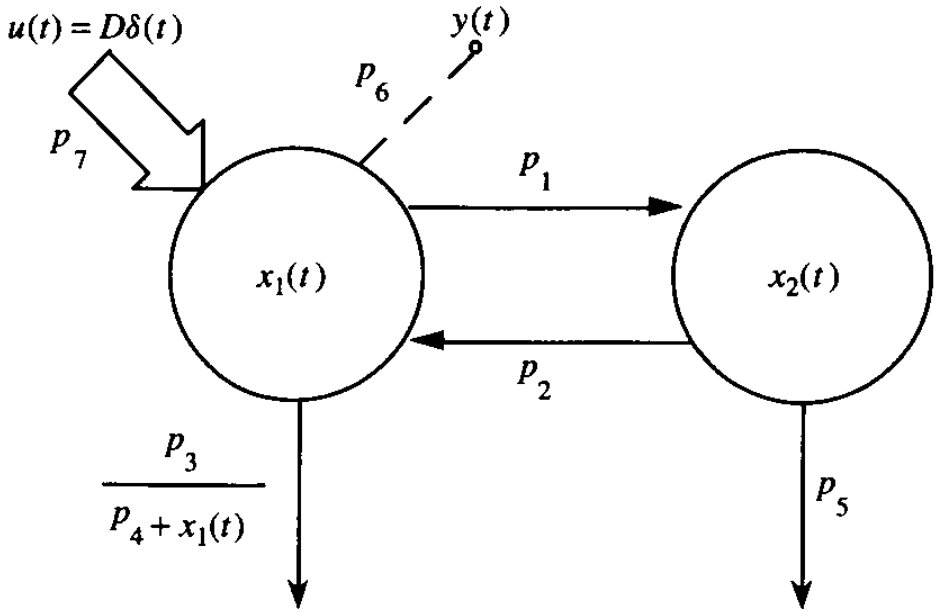
$$\begin{cases} \dot{Q}_1(t) = \dfrac{F_2+F_3}{V_2}Q_2(t) - \dfrac{F_0+F_1+F_2+F_3}{V_1}Q_1(t) \\ \dot{Q}_2(t) = \dfrac{F_3}{V_1}Q_1(t) - \dfrac{F_2+F_3}{V_2}Q_2(t) \end{cases}$$

Case Studies I

(continued)

Drug Kinetics in the Body (Carson and Cobelli, 2001, Ch. 4)

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

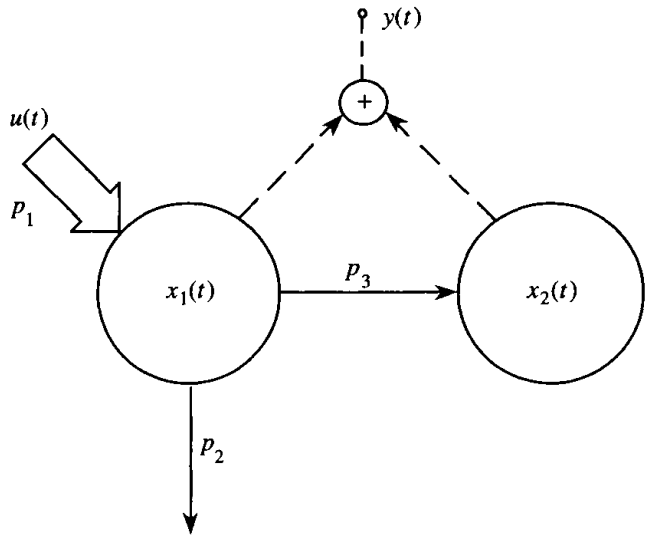


Case Studies II

(continued)

Glucose Metabolism in the Brain (Carson and Cobelli, 2001, Ch. 4)

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



$$p_2(t) = p_2(1 + p_4 e^{-p_5 t}) \quad p_3(t) = p_3(1 + p_4 e^{-p_5 t}) \tag{61}$$

Open Problems

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.

Outline

A Population Growth Model I

Single-Specie Population Growth Model

The objective is to model the population of a single specie 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

A Population Growth Model II

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.

Proposed Model:

Here's a possible model:

$$\frac{dx(t)}{dt} = Ax(t) - Bx^2(t) = Ax(t)(1 - \frac{B}{A}x(t)) \tag{62}$$

A Population Growth Model III

Interpretation:

An exponential growth with a variable rate of growth (the last parenthesis in (62)). The rate of growth is a descending function of $x(t)$.

Dimension Analysis

$$\left[\frac{x}{T}\right] = [A] + [B]\,x^2$$
$$[A] = \frac{X}{T} \qquad [B] = \frac{1}{XT} \tag{63}$$

A Population Growth Model IV

Fixed-points

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

$$Ax(t)(1 - \frac{B}{A}x(t)) = 0 \Rightarrow \begin{cases} x(t) = 0 & \text{(population extinction)} \\ x(t) = \frac{A}{B} & \text{(saturation point)} \end{cases} \tag{64}$$

We next study the stability of the fixed-points using perturbation analysis (cf. 6):

Stability in $x(t) = 0$

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

$$\frac{dx(t)}{dt} = \epsilon(A - B\epsilon) \approx \epsilon A > 0 \Rightarrow \text{The fixed point is unstable} \tag{65}$$

A Population Growth Model V

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

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

$$\begin{cases} \text{if } \epsilon > 0 \Rightarrow \frac{dx(t)}{dt} < 0 \\ \qquad\qquad\qquad\qquad \Rightarrow \text{The fixed point is stable} \\ \text{if } \quad \epsilon < 0 \Rightarrow \frac{dx(t)}{dt} > 0 \end{cases} \tag{66}$$

Competitive Population Growth Model I

Multi-Specie 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 specie model.
2. The increase of each specie influences (decreases) the resources for both species

Proposed Model:

$$\begin{aligned} \dot{x} &= x(t)(\epsilon_1 - \alpha_1 x(t) - \beta_1 y(t)) \\ \dot{y} &= y(t)(\epsilon_2 - \alpha_2 y(t) - \beta_2 x(t)) \end{aligned} \tag{67}$$

Competitive Population Growth Model II

Linearization

$$\begin{cases} x(t) = x_0 + \delta x(t) \\ y(t) = y_0 + \delta y(t) \end{cases} \tag{68}$$

$$\begin{bmatrix} \delta\dot{x} \\ \delta\dot{y} \end{bmatrix} \approx \underbrace{\begin{bmatrix} \epsilon_1 - 2\alpha_1 x_0 - \beta_1 y_0 & -\beta_1 x_0 \\ -\alpha_2 y_0 & \epsilon_2 - 2\beta_2 y_0 - \alpha_2 x_0 \end{bmatrix}}_{A} \begin{bmatrix} \delta x \\ \delta y \end{bmatrix} \tag{69}$$

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

$$\begin{aligned} & x^* = y^* = 0 && x^* = 0, y^* = \frac{\epsilon_2}{\beta_2} \\ & y^* = 0, x^* = \frac{\epsilon_1}{\beta_1} && \begin{cases} \alpha_1 x^* + \beta_1 y^* = \epsilon_1 \\ \alpha_2 x^* + \beta_2 y^* = \epsilon_2 \end{cases} \end{aligned} \tag{70}$$

Competitive Population Growth Model III

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

$$\boldsymbol{A} = \begin{bmatrix} \epsilon_1 & 0 \\ 0 & \epsilon_2 \end{bmatrix} \rightarrow \phi(t) = \begin{bmatrix} e^{\epsilon_1 t} u(t) & 0 \\ 0 & e^{\epsilon_2 t} u(t) \end{bmatrix} \tag{71}$$

$e^{\epsilon_1 t}$ and $e^{\epsilon_2 t}$ are divergent functions 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 and discuss their interpretations in biological systems.

Exercise 5: Study the dynamic properties of the competitive Lotka–Volterra equations.

Epidemiological Modeling I

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 II

Susceptible-Infected (SI) Model:

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

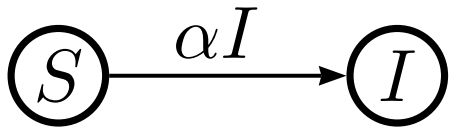


Figure 26: Compartmental description of the SI model

Susceptible-Infected-Susceptible (SIS) Model:

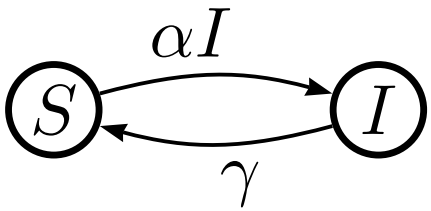


Figure 27: Compartmental description of the SIS model

Epidemiological Modeling III

Susceptible-Infected-Recovered (SIR) Model:

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

$$S(t) + R(t) + I(t) = N \rightarrow \dot{S}(t) + \dot{R}(t) + \dot{I}(t) = 0 \tag{72}$$

The following dynamics is proposed for the population:

$$\begin{cases} \dfrac{dS(t)}{dt} = -\alpha S(t).I(t) \\ \dfrac{dI(t)}{dt} = \alpha S(t) \cdot I(t) - \beta I(t) \\ \dfrac{dR(t)}{dt} = \beta I(t) \end{cases} \tag{73}$$

Epidemiological Modeling IV

SIR Model 1: Life-Time Immunity

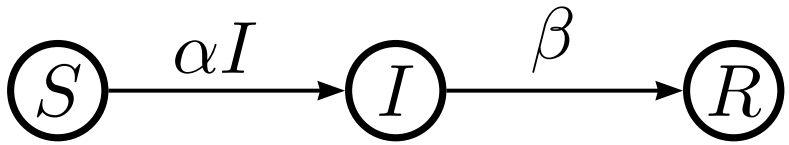


Figure 28: The SIR model providing life-time immunity

SIR Model 2: No Life-Time Immunity

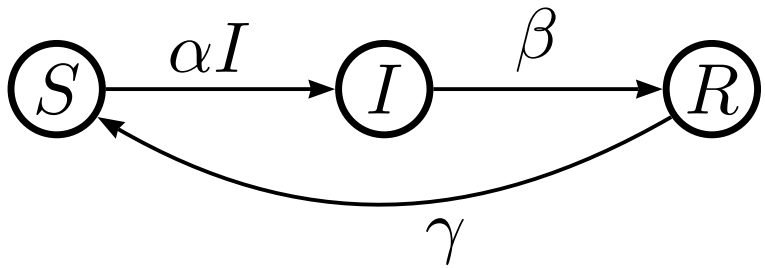


Figure 29: The SIR model without life-time immunity

Epidemiological Modeling V

SIR Model 3: Endemic SIR

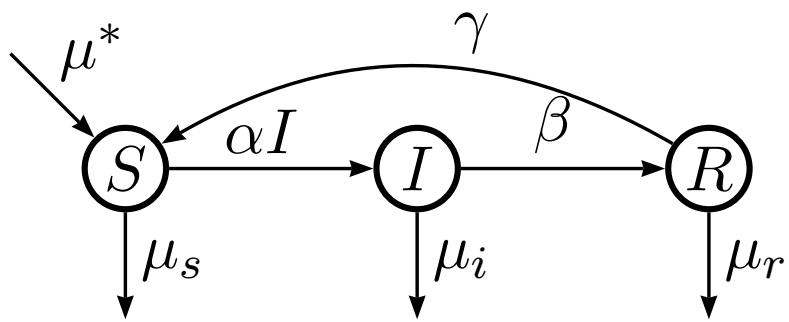


Figure 30: The endemic SIR model without life-time immunity

Epidemiological Modeling VI

A sample SIR Solution

With a given initial condition, (73) can be analytically or numerically solved to find $S(t)$, $I(t)$, and $R(t)$.

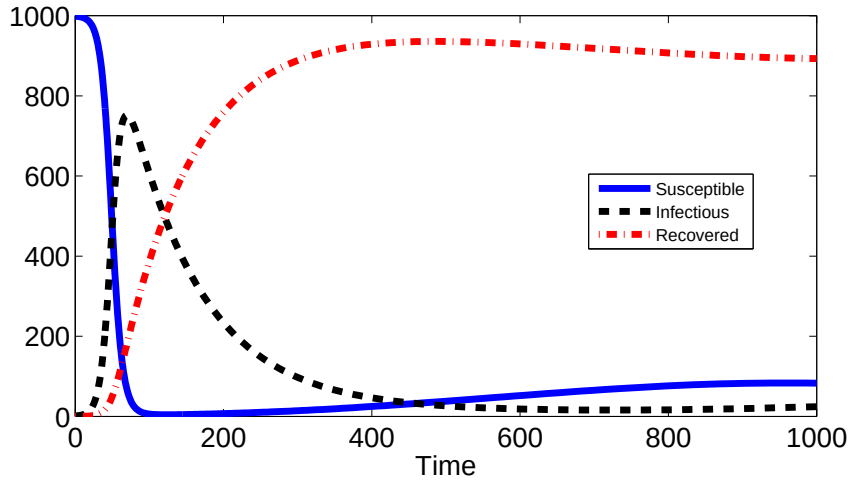


Figure 31: A sample endemic SIR model solution (Chitnis, 2011)

 For widespread epidemic diseases, the slope of $S(t)$, $I(t)$, and $R(t)$ can be more important than the total number of infected individuals. Discuss why?

Epidemiological Modeling VII

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/`

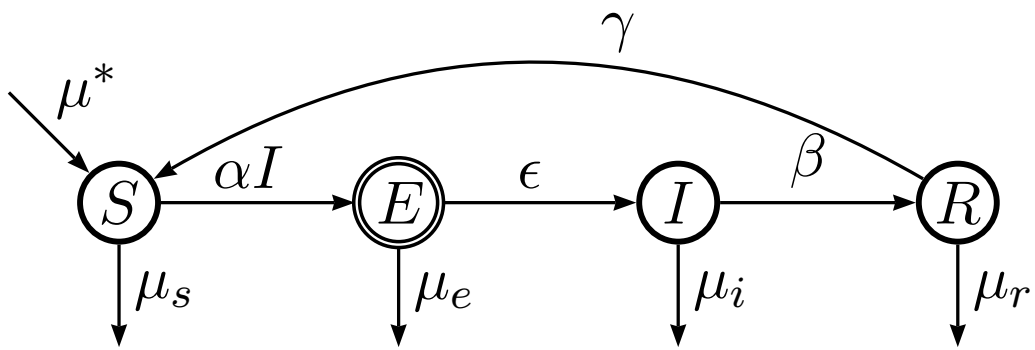


Figure 32: The endemic SEIR model without life-time immunity

Epidemiological Modeling VIII

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 $I(t)$.

Exercise 6: a) Find the fixed-points of the SIR model. b) Simplify the SIR model to a susceptible-infected model. Interpret the model in terms of a competitive growth model.

Exercise 7: Former drug addicts are known to be more prone to addiction even after recovery. Propose a model for drug addiction in a society.

Project Topic 3:

Extend the 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

Epidemiological Modeling IX

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.).

Outline

Partial Differential Modeling

Introduction

Many (biological) models are simultaneously used for the modeling of temporal and spatial variations within a system. For example:

- The spatio-temporal spread of epidemic diseases
- The spatio-temporal diffusion of drugs in the body
- The spatio-temporal propagation of action potentials in the nervous system

For these applications a joint spatio-temporal model is required and the resulting models, which are commonly stated in terms of dynamical equations, 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 1: 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 section.

Age Structured Model I

An Age Structured Model (de Vries et al., 2006, Ch. 4)

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

Assumptions

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

Age Structured Model II

Modeling:

By intuition, we can write

$$u(t, a - \Delta a) - u(t + \Delta t, a) = \mu(a) \times u(t, a) \times \Delta t \tag{74}$$

For example: $u(2013, 59) - u(2014, 60) = \mu(60) \times u(2013, 60) \times 1year$.
Eq. (74) can be rewritten as

$$u(t + \Delta t, a) - u(t, a) = u(t, a - \Delta a) - u(t, a) - \mu(a) \times u(t, a) \times \Delta t \tag{75}$$

Considering $\Delta a = \Delta t$ we have:

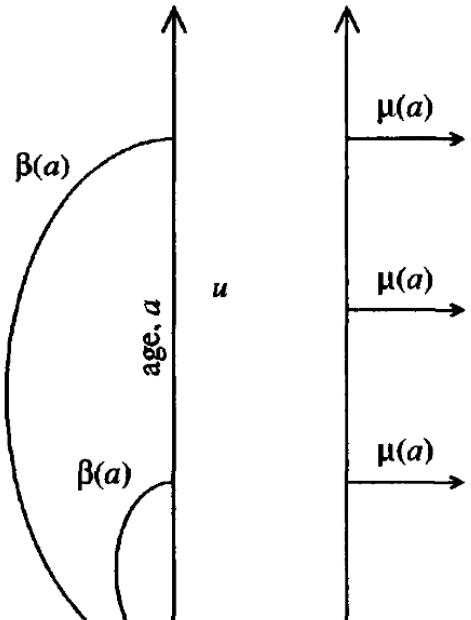
$$\frac{u(t + \Delta t, a) - u(t, a)}{\Delta t} + \frac{u(t, a) - u(t, a - \Delta a)}{\Delta a} = -\mu(a) \times u(t, a) \tag{76}$$

$$\boxed{\frac{\partial u(t, a)}{\partial t} + \frac{\partial u(t, a)}{\partial a} = -\mu(a) \times u(t, a)} \tag{77}$$

Age Structured Model III

Solution:

- In order to solve (77), 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 $\beta(a)$: $u(t,0)=\int_0^\infty \beta(a)u(t,a)da$.



Age Structured Model I

(continued)

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 a modern society. 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 I

Reaction-Diffusion Model (de Vries et al., 2006, Ch. 4)

Reaction Diffusion Equation is a two independent variable PDE equation 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 in Fig. 34.

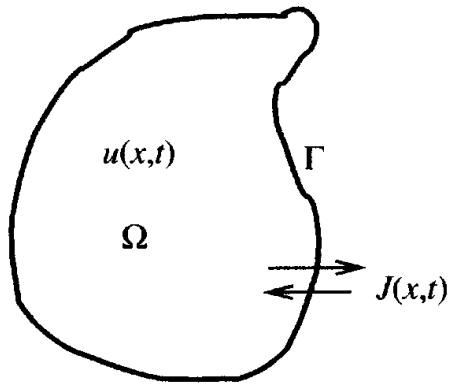


Figure 34: Reaction-Diffusion Model

Reaction-Diffusion Model II

where:

- 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 III

Conservation Principle

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

Mathematically:

$$\frac{d}{dt}\int_{\Omega} u(x,t)dv = -\int_{\Gamma} \mathbf{J}(x,t)\cdot \mathbf{ds} + \int_{\Omega} f[u(x,t)]dv \tag{78}$$

Using the Divergence Theorem:

$$\int_{\Gamma} \mathbf{J}(x,t)\cdot \mathbf{ds} = \int_{\Omega} \nabla\cdot \mathbf{J}(x,t)dv \tag{79}$$

we get:

$$\int_{\Omega} [\frac{\partial}{\partial t}u(x,t) - f(u) + \nabla\cdot \mathbf{J}(x,t)]dv = 0 \tag{80}$$

Reaction-Diffusion Model IV

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

$$\boxed{\frac{\partial}{\partial t}u(x,t) = f(u) - \nabla \cdot \mathbf{J}(x,t)} \tag{81}$$

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.,

$$\mathbf{J}(x,t) = -D\nabla u(x,t) \tag{82}$$

where D is the diffusion coefficient and ∇ is the gradient operator.
Reference: `http://en.wikipedia.org/wiki/Fick's_laws_of_diffusion`

The Fick's law is a macroscopic law, which should be verified for the problem of interest.

Reaction-Diffusion Model V

Using the Fick's Law in (81), we arrive at the reaction-diffusion also known as the heat equation.

$$\boxed{\frac{\partial}{\partial t}u(x,t) = f(u) + D\nabla^2 u(x,t)} \tag{83}$$

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

$$\nabla^2 \triangleq \frac{\partial^2}{\partial x_1^2} + \cdots + \frac{\partial^2}{\partial x_n^2} \tag{84}$$

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

Reaction-Diffusion Model VI

Example: Critical Domain Size

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

$$\frac{\partial}{\partial t}u = D\frac{\partial^2}{\partial x^2}u + \mu u(1-u) \tag{85}$$

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

Reaction-Diffusion Model VII

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 I

Background

In general, spatial propagation in physical systems follow one (or a combination) of the following models:

1. Transportation: particles (in the general sense) are moved from a point to another according to physical laws of motion or diffusion.
2. Wave propagation: no net transportation is made; but only a wave (in the general sense) 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

$$u(x,t) = \phi(x - ct) \tag{86}$$

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

Traveling Wave Model II

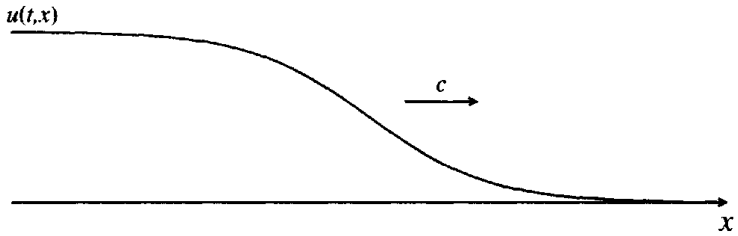


Figure 35: Wave Model

According to (86), we have

$$\frac{\partial}{\partial t}u(x,t) = -c\phi', \quad \frac{\partial^2}{\partial t^2}u(x,t) = c^2\phi'', \quad \frac{\partial^2}{\partial x^2}u(x,t) = \phi'' \tag{87}$$

resulting in

$$\boxed{\frac{\partial^2}{\partial t^2}u(x,t) = c^2\frac{\partial^2}{\partial x^2}u(x,t)} \tag{88}$$

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

Traveling Wave Model III

Wave Model Solutions for the Critical Domain Size Problem

Suppose that we seek wave-like solutions for the critical domain size problem in (85). In this case, the PDE in simplifies to a nonlinear ODE of the wave function $\phi(z)$:

$$D\phi'' + c\phi' + \mu\phi(1-\phi) = 0 \tag{89}$$

which is a second order ODE with a variable natural frequency.

Equation (86) 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.

Exercise 9: Present an interpretation for second order ODE with a variable natural frequency, as in (89), and discuss about its impact on the solution of the critical domain size problem.

Non-classic Wave Models I

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).

Some Useful Interpretations I

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

Gradient of a scalar field

Consider a scalar field $\phi(\mathbf{x})$ in the n-dimensional space $\mathbf{x} = (x_1, \cdots, x_n)$. The gradient of $\phi(\mathbf{x})$ at a point, denoted by $\nabla\phi(\mathbf{x})$, is "a vector indicating the direction of steepest ascent of $\phi(\mathbf{x})$"

Some Useful Interpretations II

Divergence 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 divergence of $\mathbf{F}(\mathbf{x})$ at a point, 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`

Some Useful Interpretations III

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`

Some Useful Interpretations IV

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.

The heat equation without a heat source/sink

Looking again at the heat equation (or diffusion equation) without a heat source/sink: $\frac{\partial}{\partial t}u(x,t) = D\nabla^2 u(x,t)$, one can say that if the points surrounding x in small spheres around it are "on average" hotter than itself, then in the next moment the temperature at x will also increase.

Reference:

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

Some Useful Interpretations V

Further Reading on Differential Equations in Biological & Physical Systems

ODE:

- (de Vries et al., 2006, Ch. 3); specifically see the chapter exercises for combination of ODE and compartmental model examples.
- (Fishwick, 2007, Ch. 17) also has very nice 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.

Outline

Finite State Automata (FSA) I

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.

Elements Of FSA

- 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) II

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) III

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

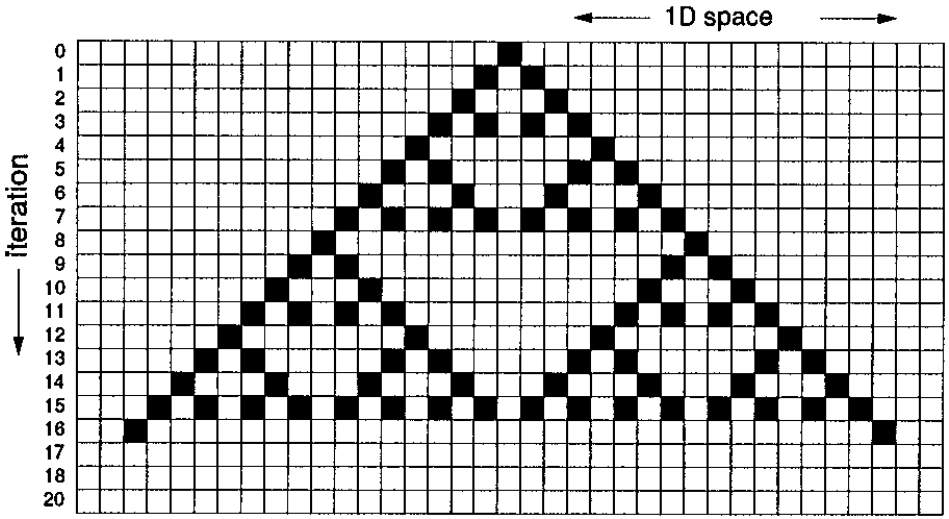
Cellular Automata I

- 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 II

A One-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 III

A Two-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)

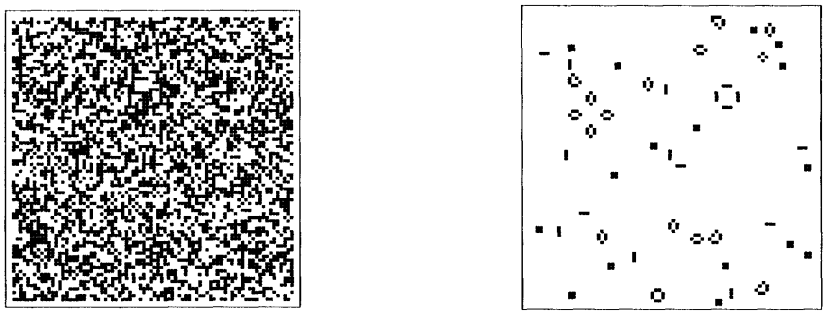


Figure 37: (a) Initial, (b) after 1300 iterations; (de Vries et al., 2006, Ch. 6)

Cellular Automata IV

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

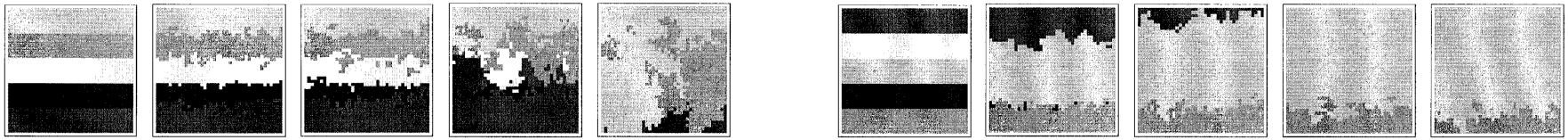


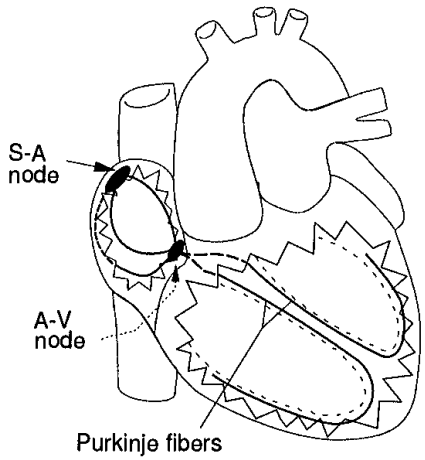
Figure 38: Silvertown's cellular automaton model of plant competition

✎ The same model can be used for (1) modeling fire spread in a jungle or a farm, (2) cross-border race populations in Ethnology.

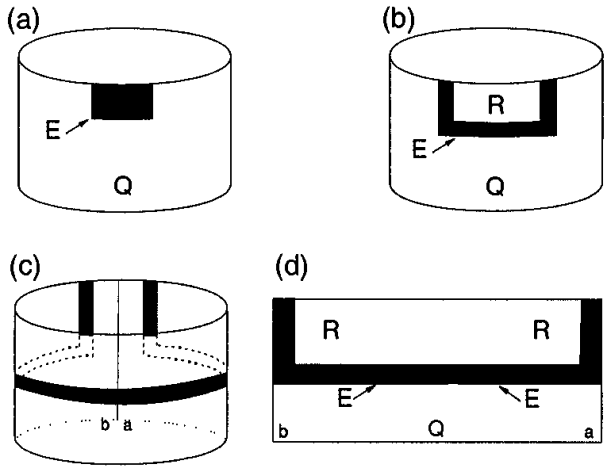
Cellular Automata V

A Three-Dimensional Cellular Automaton: Cardiac Excitable Tissues (Haefner, 2005, Ch. 19)

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



(a) a



(b) b

Figure 39: The (a) myocardium and (b) the 3D ventricular contraction wave front

A Three-Dimensional 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

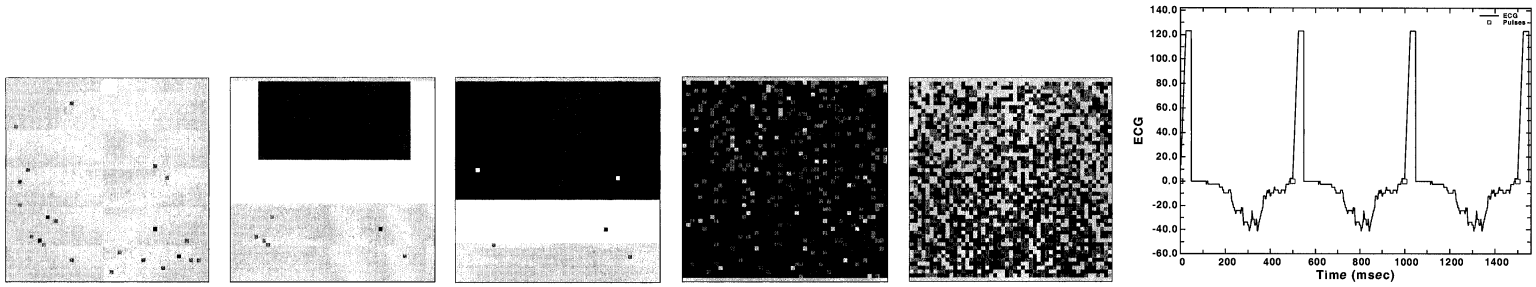


Figure 40: CA output and the generated ECG for a normal heart

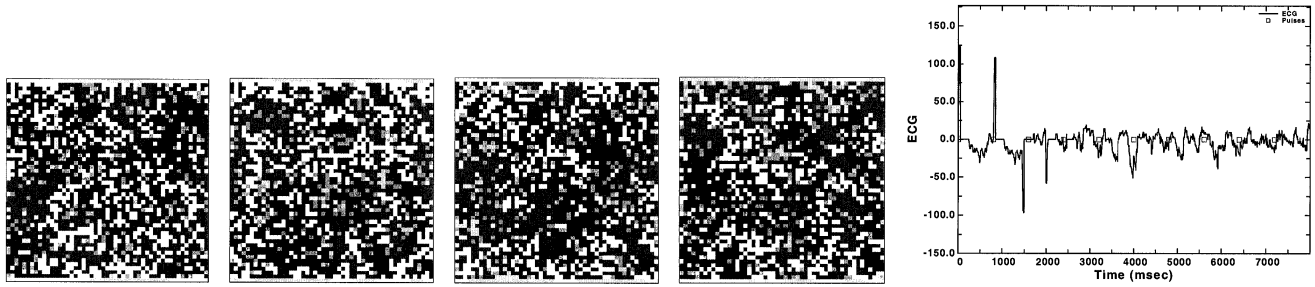


Figure 41: CA output and the generated ECG for a fibrillating heart

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 10: *CA modeling of PDE:* Use the interpretation of the Laplacian operator for the heat equation presented in Section (5) to develop a CA for heat transfer and diffusion models. Simulate the proposed model with various boundary conditions.

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:

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.

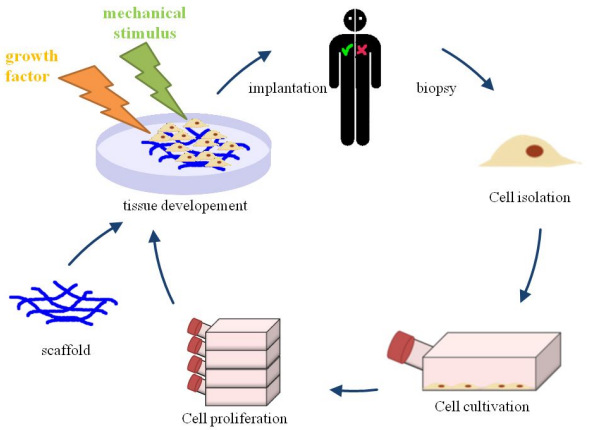


Figure 42: Tissue Engineering Cycle; adopted from
`http://en.wikipedia.org/wiki/Tissue_engineering`

Further Reading and Projects III

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

Outline

Introduction I

Introduction

To this point, various models and modeling techniques were discussed. The presented models were generic, i.e., they all had a set of parameters, 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.

Parameter identification issues

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

Parameter Identifiability I

- 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 (dynamics, etc.)
- Unidentifiable models are not necessarily incorrect; but they have infinite number of possible solutions, which may not be fixed by having 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.

Parameter Identifiability II

Positron Emission Tomography in Non-homogenous Tissues (de Vries et al., 2006, Ch. 7)

Consider the problem of Positron Emission Tomography (PET) in non-homogenous tissues. Each voxel consists of two types of tissues, with relative volumes τ and $1-\tau$, and different absorption rates. The radioactive tracer in the blood vessel has a concentration $B(t)$, and is absorbed by each tissue by diffusion, resulting in tracer concentrations $C(t)$ and $D(t)$ in each tissue (Fig. 43).

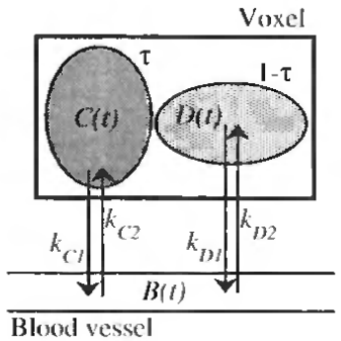


Figure 43: A non-homogenous voxel

Parameter Identifiability III

Positron Emission Tomography in Non-homogenous Tissues (cntd.)

- 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

Parameter Identifiability IV

Solution

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

$$\begin{cases} \dot{C}(t) = -k_{c1}C(t) + k_{c2}B(t) \\ \dot{D}(t) = -k_{d1}D(t) + k_{d2}B(t) \\ s(t) = \tau C(t) + (1-\tau)D(t) \end{cases} \tag{90}$$

Differentiating the third equation in (90) two times and replacing, the problem simplifies to an ODE:

$$\ddot{s}(t) + \theta_a \dot{s}(t) + \theta_b s(t) = \theta_c \dot{B}(t) + \theta_d B(t) \tag{91}$$

where $\theta_a \triangleq k_{d1} + k_{c1}$, $\theta_b \triangleq k_{c1}k_{d1}$, $\theta_c \triangleq \tau k_{c2} + (1-\tau)k_{d2}$ and $\theta_d \triangleq \tau k_{c2}k_{d1} + (1-\tau)k_{c1}k_{d2}$.

The new parameters θ_a, θ_b, θ_c, and θ_d can be found by data fitting over (91). Hence, k_{c1} and k_{d1} are identifiable; but (τ, k_{c2}, k_{d2}), are unidentifiable, unless if additional information is provided. Further reading: (Audoly et al., 2001)

Parameter Estimation I

Introduction

- If a model is identifiable, the next question is how to estimate its parameters.
- Parameter identification is rigorously studied in estimation theory. Herein, we review the following techniques, which are the most common in biological system parameter estimation:
  - 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)
- Although the mentioned techniques are general, we study them from a parameter estimation viewpoint. Refer to classical textbooks on estimation theory for more details (Kay, 1993).

Parameter Estimation II

Background

- Real-world observations are required for fixing model parameters.
- If a model was deterministic and "perfect" and the observations were noiseless, parameter identification would reduce to a set of linear or nonlinear algebraic equations. In that case, depending on the number of unknown parameters and the model's form, a finite number of observations would be necessary and sufficient for finding the parameters. Increasing the number of observations beyond that number would be redundant.
- In practice, models are imperfect and (commonly) stochastic. The observations are also noisy in reality. Therefore, the observations do not exactly fit over the model. Instead, an error cost function is defined and minimized for the model vs. observation errors.
- In this case, increasing the number of observations can typically improve the parameter estimation.

Bayesian Parameter Estimation I

Formulation

- Consider the parametric model

$$\boldsymbol{x} = f(\boldsymbol{\theta}, \boldsymbol{n}) \tag{92}$$

  where $\mathbf{x}$ is the observed output, $\boldsymbol{\theta}$ is the unknown model parameter, and $\boldsymbol{n}$ is 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.
- In what follows, a few of the most common cost functions are studied. See (Kay, 1993, Ch. 11) for a detailed study.

Bayesian Parameter Estimation II

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 III

Non-Symmetric Error Costs

Consider the problem of laser tumor ablation. The problem of targeting a tumor has inevitable modeling, observational and instrumentational errors, which result in a probabilistic scenario with a circular error probability (CEP). Now, if the tumor is at the vicinity of extremely delicate tissues (e.g. inside the brain), the cost of error is no longer symmetric around the desired target point.

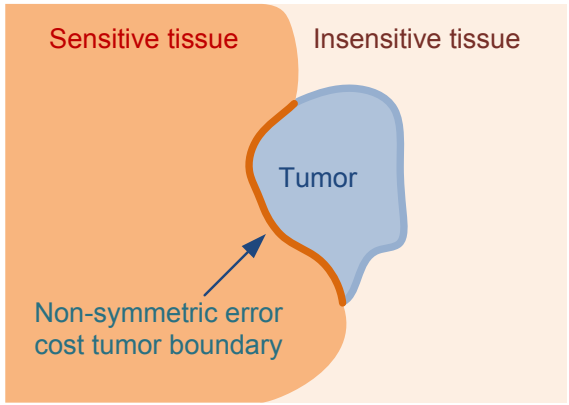


Figure 44: Example of regions with non-symmetric error cost boundaries

Bayesian Parameter Estimation IV

Minimum Mean Square Error (MMSE)

In minimum mean square error (MMSE), the cost function is defined:

$$C_{MMSE}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) = (\boldsymbol{\theta} - \hat{\boldsymbol{\theta}})^2 \tag{93}$$

Hence

$$\hat{\boldsymbol{\theta}}_{MMSE} = \underset{\boldsymbol{\theta}}{\operatorname{argmin}}\, E\{(\boldsymbol{\theta} - \hat{\boldsymbol{\theta}})^2\} \tag{94}$$

The MMSE in (94) is proved to be equal to the mean of the conditional probability density function (pdf) $f_{\boldsymbol{\theta}|\boldsymbol{x}}$

$$\boxed{\hat{\boldsymbol{\theta}}_{MMSE} = E\{\boldsymbol{\theta}|\boldsymbol{x}\}} \tag{95}$$

Bayesian Parameter Estimation V

Minimum Mean Absolute Error (ABS)

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

$$C_{ABS}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) = |\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}| \tag{96}$$

Hence

$$\hat{\boldsymbol{\theta}}_{ABS} = \underset{\boldsymbol{\theta}}{\operatorname{argmin}}\, E\{|\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}|\} \tag{97}$$

The minimum mean absolute error estimator in (97) is proved to be the median of $f_{\boldsymbol{\theta}|\boldsymbol{x}}$, i.e.,

$$\boxed{\int_{-\infty}^{\hat{\boldsymbol{\theta}}_{ABS}} f(\boldsymbol{\theta}|\boldsymbol{x}) d\boldsymbol{\theta} = \int_{\hat{\boldsymbol{\theta}}_{ABS}}^{+\infty} f(\boldsymbol{\theta}|\boldsymbol{x}) d\boldsymbol{\theta}} \tag{98}$$

Bayesian Parameter Estimation VI

Maximum A Posteriori (MAP)

In maximum a posteriori (MAP), the cost function is defined:

$$C_{MAP}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}}) = \begin{cases} 0 & |\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}| \leq \epsilon \\ 1 & |\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}| > \epsilon \end{cases} \tag{99}$$

Hence

$$\hat{\boldsymbol{\theta}}_{MAP} = \underset{\boldsymbol{\theta}}{\text{argmin}}\, E\{C_{MAP}(\boldsymbol{\theta}, \hat{\boldsymbol{\theta}})\} \tag{100}$$

For $\epsilon \to 0$, the MAP estimator in (100) is proved to be the mode (peak point) of $f_{\boldsymbol{\theta}|\boldsymbol{x}}$, i.e.,

$$\boxed{\hat{\boldsymbol{\theta}}_{MAP} = \underset{\boldsymbol{\theta}}{\text{argmax}}\, f(\boldsymbol{\theta}|\boldsymbol{x})} \tag{101}$$

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

Bayesian Parameter Estimation VII

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 11: Interpretations & alternative cost functions

1. Give some interpretations for the MMSE, ABS, and MAP estimators in terms of their cost functions in (93), (96), and (99). How do each of them weight the small versus large errors?
2. Discuss about the possible applications of each of these cost functions. Can you propose other functions?

Project Topic 15:

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 described above, require the posterior probability $f_{\boldsymbol{\theta}|\boldsymbol{x}}$. However,

- While Bayesian estimators assume the parameters $\boldsymbol{\theta}$ to be random variables (RV), in many cases they are not random; they are just unknown model parameters. Therefore, the pdf $f_{\boldsymbol{\theta}|\boldsymbol{x}}$ becomes meaningless (Kay, 1993, Ch. 10).
- Even if the unknown parameters are truly stochastic (or are 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 practice, a more affordable method is to maximize the likelihood function $f_{\boldsymbol{x}|\boldsymbol{\theta}}$:

$$\boxed{\hat{\boldsymbol{\theta}}_{ML} = \underset{\boldsymbol{\theta}}{\operatorname{argmax}}\, f(\boldsymbol{x}|\boldsymbol{\theta})} \tag{102}$$

Maximum Likelihood Parameter Estimation II

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

$$\text{Likelihood} = \frac{\text{Posterior} \times \text{Marginal}}{\text{Prior}} \tag{103}$$

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.
It's intuitively a wise choice, 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.

Estimator Bias

One of the important properties of an estimator is whether or not it is biased.

Unbiased Estimator

The estimation bias is a measure of the average drift of the estimates from their true value:

$$b(\boldsymbol{\theta}) = E\{\hat{\boldsymbol{\theta}}\} - \boldsymbol{\theta} \tag{104}$$

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

$$E\{\hat{\boldsymbol{\theta}}\} = \boldsymbol{\theta} \tag{105}$$

Estimator Variance

The variance of error is another important feature of an estimator, defined as follows

Estimator Variance

An estimator's variance is the mean square error of the estimates from their true values:

$$\text{mse}(\hat{\boldsymbol{\theta}}) = E\{(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta})^2\} \tag{106}$$

Apparently,

$$\text{mse}(\hat{\boldsymbol{\theta}}) = \text{var}(\hat{\boldsymbol{\theta}}) + b(\boldsymbol{\theta})^2 \tag{107}$$

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

✎ The minimum variance unbiased (MVU) estimator is of special interest in estimation theory.

Nonlinear Model Identification I

The problem of 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.

Examples I

Deterministic constant value in noise; single observation

Consider a single noisy observation $y = x + n$, of an unknown DC parameter x embedded in Gaussian noise $n \sim N(0, \sigma_n^2)$. The likelihood equation is

$$f_{Y|X}(y|x) = f_n(y - x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp[-\frac{(y-x)^2}{2\sigma_n^2}] \tag{108}$$

Therefore,

$$\hat{x}_{ML} = \underset{x}{\text{argmax}}\, f_{Y|X}(y|x) = y \tag{109}$$

Examples II

Deterministic constant value in noise; multiple independent observations

Consider multiple noisy observations $y_i = x + n_i$, of an unknown DC 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

$$f_{Y|X} = f_{\mathbf{n}}(y_1 - x, \cdots, y_K - x) = \prod_{i=1}^{K} f_n(y_i - x) = \prod_{i=1}^{K} \frac{1}{\sqrt{2\pi\sigma_n^2}} \exp[-\frac{(y_i - x)^2}{2\sigma_n^2}] \tag{110}$$

The log-likelihood function is

$$ll(x) = \log(f_{Y|X}) = \frac{-K}{2}\log(2\pi\sigma_n^2) - \sum_{i=1}^{K} \frac{(y_i - x)^2}{2\sigma_n^2} \rightarrow \hat{x}_{ML} = \frac{1}{K}\sum_{i=1}^{K} y_i \tag{111}$$

Examples III

Estimating a stochastic variable from multiple noisy observations

$$y_i = x + n_i \quad i = 1, \cdots, K; \quad x \sim N(0, \sigma_x^2); \quad n_i \sim N(0, \sigma_n^2); n_i \text{ are } iid \tag{112}$$

In this case

$$f_{Y|X}(y|x) = \Pi_{i=1}^{K} \frac{1}{\sqrt{2\pi}\sigma_n} \exp[-\frac{(y_i - x)^2}{2\sigma_n^2}], \quad f_X(x) = \frac{1}{\sqrt{2\pi}\sigma_x} \exp[-\frac{x^2}{2\sigma_x^2}] \tag{113}$$

Using $f_{X|Y} = f_{Y|X} f_X / f_Y$ we have

$$\begin{aligned} f(x|y) &= \beta(y) \exp(-\frac{1}{2\sigma_p^2}[x - \frac{\sigma_x^2}{\sigma_x^2 + \frac{\sigma_n^2}{K}}(\frac{1}{K}\sum_{i=0}^{K} y_i)]^2), \quad \sigma_p^2 \triangleq \frac{\sigma_x^2 \sigma_n^2}{K\sigma_x^2 + \sigma_n^2} \\ \rightarrow \hat{x}_{MMSE} &= E\{f(x|y)\} = \frac{\sigma_x^2}{\sigma_x^2 + \frac{\sigma_n^2}{K}}(\frac{1}{K}\sum_{i=1}^{K} y_i) \end{aligned} \tag{114}$$

Examples IV

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 V

Estimation of an unknown variance

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

$$y_i = s_i + n_i; \quad n_i \sim N(0,1); \quad s_i \sim N(0,\theta) \tag{115}$$

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

$$\hat{\theta}_{ML} = \underset{\theta}{\text{argmax}}\, f(\mathbf{y}|\theta) = \underset{\theta}{\text{argmax}} \prod_{i=1}^{K} f(y_i|\theta) = \underset{\theta}{\text{argmax}}[\log f(\mathbf{y}|\theta)] \tag{116}$$

$$\begin{aligned} ll(\theta) &= \sum_{i=1}^{K} \log\left(\frac{1}{\sqrt{2\pi(1+\theta)}} \exp[\frac{-y_i^2}{2(1+\theta)}]\right) \\ \frac{\partial ll(\theta)}{\partial \theta} &= \frac{1}{2}[\frac{K}{1+\theta} - \frac{\sum_{i=1}^{K} y_i^2}{(\theta+1)^2}] = 0 \Rightarrow \qquad \hat{\theta}_{ML} = \max((\frac{1}{K}\sum_{i=1}^{K} y_i^2) - 1, 0) \end{aligned} \tag{117}$$

Examples VI

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)

$$f_A(a) = \mu(a) \exp\left(-\int_0^a \mu(\tau) d\tau\right) \tag{118}$$

which can be simplified as follows if the mortality rate $\mu(a)$ is constant: $f_A(a) = \mu \exp(-\mu a) \quad (a \geq 0)$.
The objective is to find the unknown positive parameter μ, from n mutually independent observations of cells deaths at ages $a_1, \cdots, a_n$. Considering the dimension of μ (inverse time), $\hat{\mu}_1 = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{a_i}$, $\hat{\mu}_2 = 1/\bar{a} = 1/(\frac{1}{n} \sum_{i=1}^{n} a_i)$, $\hat{\mu}_3 = 1/(\prod_{i=1}^{n} a_i)^{1/n}$, etc. Which one is better and Why?

Examples VII

An ML-based solution

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

$$\hat{\mu}_{ML} = \underset{\mu}{\text{argmax}}\, f_A(\mathbf{y}|\mu) \tag{119}$$

Considering the independence of the n observations

$$f_A(\mathbf{y}|\mu) = f_A(a_1, a_2, ..., a_n|\mu) = \prod_{i=1}^{n} f(a_i|\mu) = \mu^n \exp(-\mu \sum_{i=1}^{n} a_i) \tag{120}$$

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

$$\hat{\mu}_{ML} = \frac{1}{\frac{1}{n}\sum_{i=1}^{n} a_i} \tag{121}$$

Examples VIII

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

$$\frac{dp(c)}{dc} = \alpha p(c)(1 - p(c)); \quad \alpha : \text{the mortality rate} \tag{122}$$

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

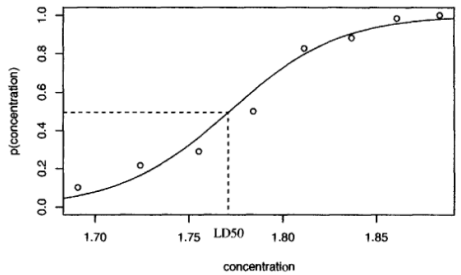


Figure 45: Sample data shown over the optimal curve of $p(c)$

Examples IX

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:

$$p(K(c) = k|\theta) = \binom{n}{k}(p(c))^k(1 - p(c))^{n-k} \tag{123}$$

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:

$$f([k_1, k_2, .., k_n]|\theta) = \prod_{i=1}^{L} p(k(c) = k_i|\theta) = \prod_{i=1}^{L} \binom{n_i}{k_i} p(c_i)^{k_i}(1 - p(c_i))^{n_i - k_i} \tag{124}$$

The ML estimation can be numerically found using real observations.

Examples X

Project Topic 16:

Develop a modeling framework to find the optimal dose for cancer treatment by chemotherapy. The same framework can be extended to radiotherapy.

Further Reading

The expectation maximization (EM) algorithm for solving ML parameter estimation problems (Moon, 1996; Do and Batzoglou, 2008)

Least Squares Error Estimation I

In many (parameter) estimation problems, we only have a data model; but there are no prior assumptions regarding the probability density function of the noise or observations. Therefore, Bayesian and ML estimation frameworks are inapplicable. In these cases, one can simply attempt in finding the set of model parameters, which minimize the average square error between the observations and model, over all the available data points. This method is known as least squares estimation (LSE). The major advantage of LSE is that it cam be solved using a deterministic optimization framework, without requiring any prior stochastic assumptions. It can also be shown that 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

$$x(t) = \hat{x}(t) + e(t), \quad \hat{x}(t) \stackrel{\Delta}{=} \sum_{j=0}^{N-1} a_i t^i \tag{125}$$

a_i: unknown parameters.

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

$$\frac{\partial C}{\partial a_k} = E_t\{2(x(t) - \sum_{i=0}^{N-1} a_i t^i)(-t^k)\} = 0 \Rightarrow E\{t^k x(t)\} = \sum_{i=0}^{N-1} a_i E\{t^k t^i\} \tag{126}$$

$$\boldsymbol{x} = a\boldsymbol{T} \Rightarrow \boldsymbol{a} = \boldsymbol{x}\boldsymbol{T}^{-1}, \qquad \boldsymbol{x} \stackrel{\Delta}{=} [E\{t^k x(t)\}]_k, \quad \boldsymbol{T} \stackrel{\Delta}{=} [E\{t^{k+i}\}]_{k,i} \tag{127}$$

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.

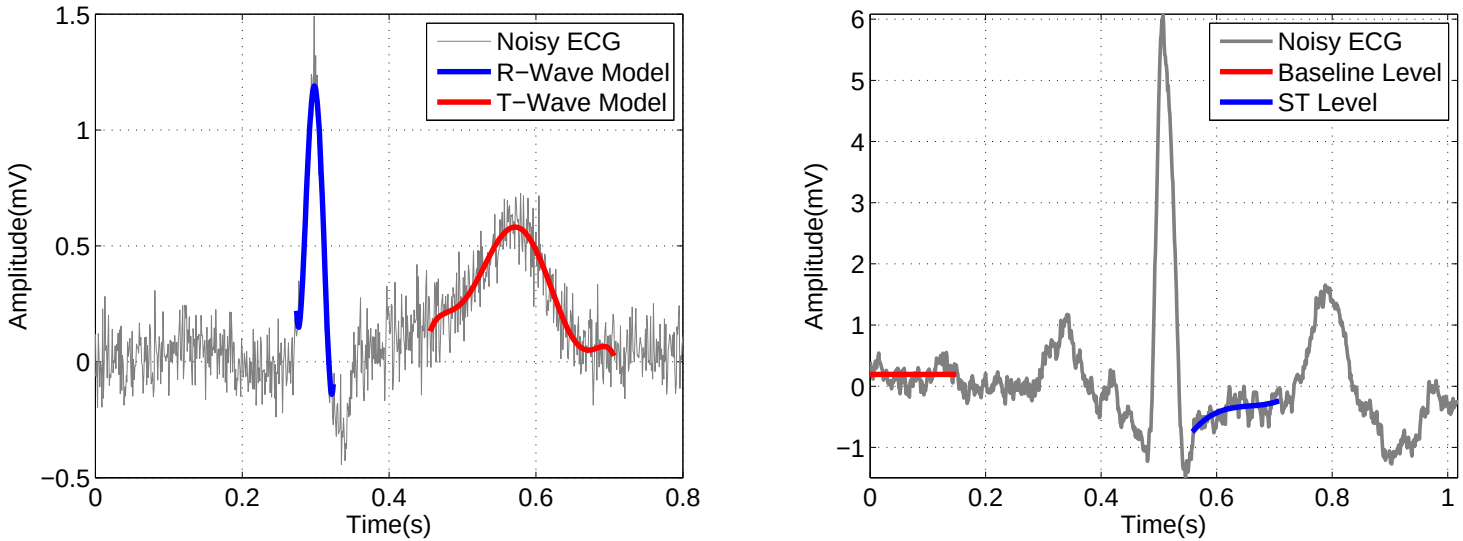


Figure 46: ECG parameter estimation using least square error estimation

Least Squares Error Estimation IV

ECG parameter estimation from noisy signals (continued)

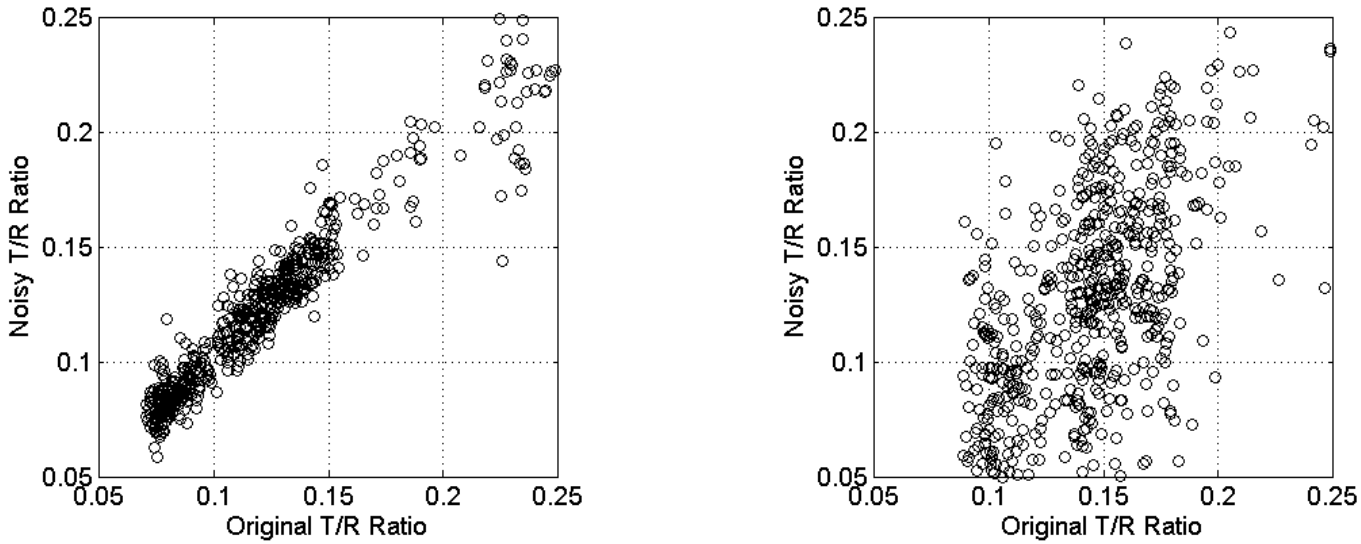


Figure 47: True versus estimated T/R ratio with (left) and without (right) signal modeling from noisy ECG

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

Outline

Model Assessment & 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, one can fit a line over "*any*" pair of data points; but how good is a linear model?
- How to compare various models? Models can be very different in their mathematical structure.
- How to compare models with different number of parameters? Parsimony implies that simple models are preferred over complex ones; but what if the modeling error of a complex model is less than a simple model?

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!*

$$AIC \triangleq 2ll(\hat{p}) - 2n_p, \qquad N > 40 \tag{128}$$

$$AICc \triangleq 2ll(\hat{p}) - 2n_p \frac{N}{N - n_p - 1}, \qquad N \leq 40 \qquad \text{(corrected AIC)} \tag{129}$$

$\hat{p}$: The parameter that maximizes the log-likelihood function $ll(\cdot)$
n_p: number of model parameters
N: number of data points used for estimation

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:

$$\begin{aligned} \mu^{(1)}(c) &= \mu_0 + \mu_1 c \\ \mu^{(2)}(c) &= \nu_0 + \nu_1 \ln(c + \nu_2) \end{aligned} \tag{130}$$

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)
- `http://www.biostat.jhsph.edu/~ririzarr/Teaching/649/section-07.pdf`

Case Studies

In the second part of the course, we focus on specific biological models which have been previously developed, mainly for the human body. In each section, a small overview of the physiology of the problem is presented, followed by the most popular models proposed in the literature. This part is mainly presented from text books and highly cited research articles in this area.

Outline

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. It is the production of insulin and glucagon by the pancreas which ultimately determines if a patient has diabetes, hypoglycemia, or some 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

The overall blood glucose control mechanism is shown in Fig. 48.

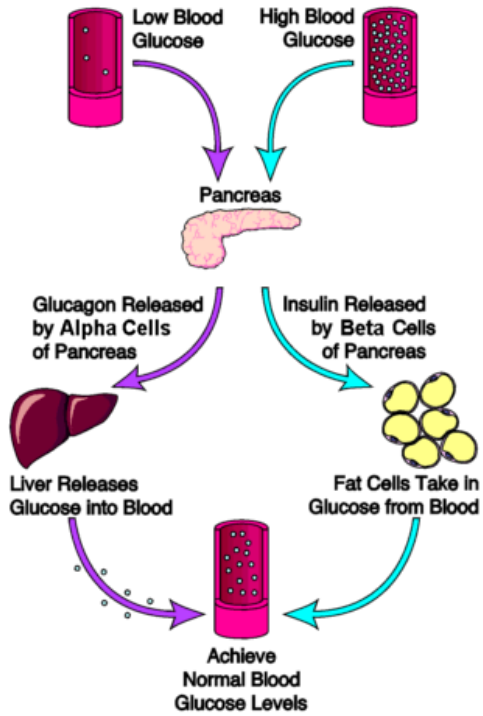


Figure 48: The overall glucose control mechanism (Norman, 2017)

Blood Sugar Regulation Modeling I

Stolwijk-Hardy Glucose Regulation Model (Stolwijk and Hardy, 1974)

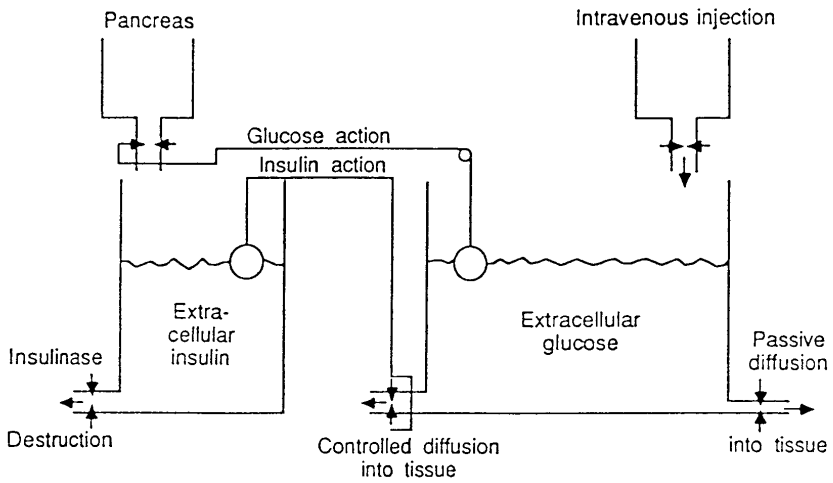


Figure 49: Hydraulic analog of the Stolwijk-Hardy insulin-glucose regulation model (Rideout, 1991, Ch. 8)

Blood Sugar Regulation Modeling II

Bergman's Two-Compartmental Glucose Minimal Model (Bergman et al., 1979; De Gaetano and Arino, 2000; Friis-Jensen, 2007)

$$\begin{aligned}
\frac{dG(t)}{dt} &= -[p_1 + X(t)]G(t) + p_1 G_b, & G(0) &= G_0 \\
\frac{dX(t)}{dt} &= -p_2 X(t) + p_3[I(t) - I_b], & X(0) &= 0 \\
\frac{dI(t)}{dt} &= p_4[G(t) - p_5]^+ t - p_6[I(t) - I_b], & I(0) &= p_7 + I_b
\end{aligned} \tag{131}$$

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

Further Reading on Glucose-Insulin Models

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

Outline

Heat Flow and Thermo-regulation Modeling I

In this chapter, it is shown 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 Flow and Thermo-regulation Modeling II

Heat flow within the body occurs by diffusion in tissues and by blood flow transport in veins and arteries. Heat energy is generated within the body in a number of ways:

- Obligatory:
  - **Gains**: Basal metabolism, muscle action of heart and respiratory system
  - **Losses**: Respiratory (evaporation and heating of air), evaporation of "insensible" perspiration (sweating)
- Involuntary Control:
  - **Gains**: Thermogenesis in muscle due to shivering, increased metabolism in response to cold
  - **Losses**: Evaporation of perspiration released by sudomotor control (stimulation of the sweat glands)
  - **Gains and losses**: Due to conduction, convection, and radiation from the skin; also effects of circulatory changes.
- Voluntary Action:
  - **Gains**: Due to muscle action
  - **Gains or losses**: Due to ingestion of hot or cold liquids

Heat Flow and Thermo-regulation Modeling III

- **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

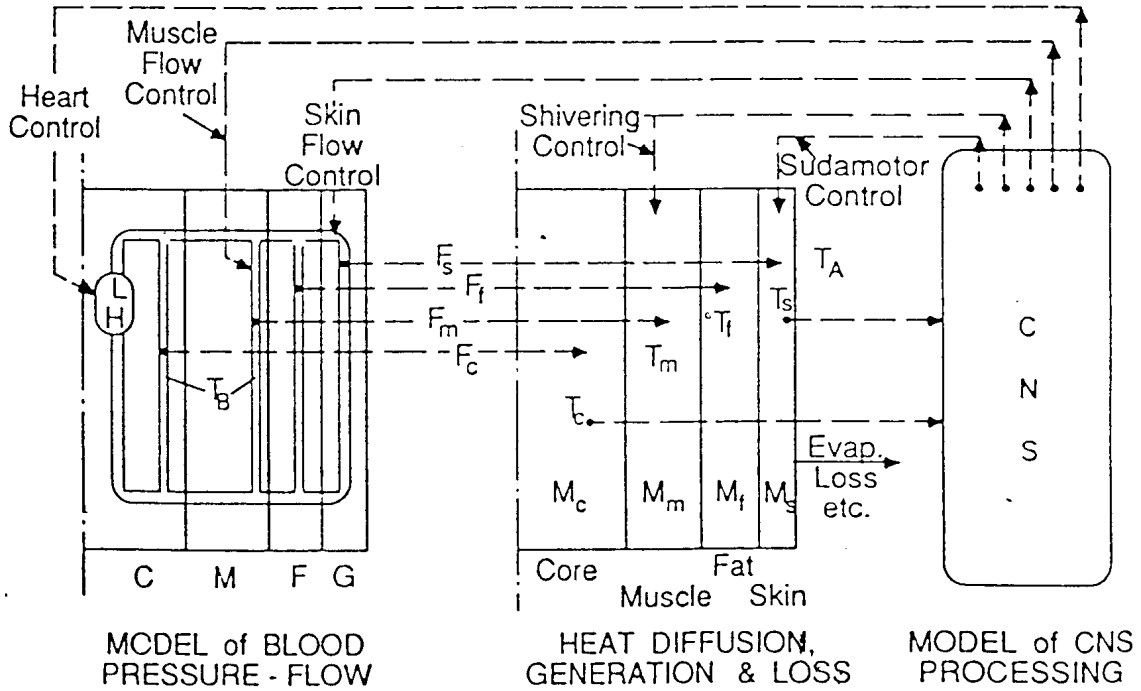


Figure 50: Heat generation and loss in the body (Rideout, 1991, Ch. 7)

Body Heat Flow Model II

Diffusion of heat in the body

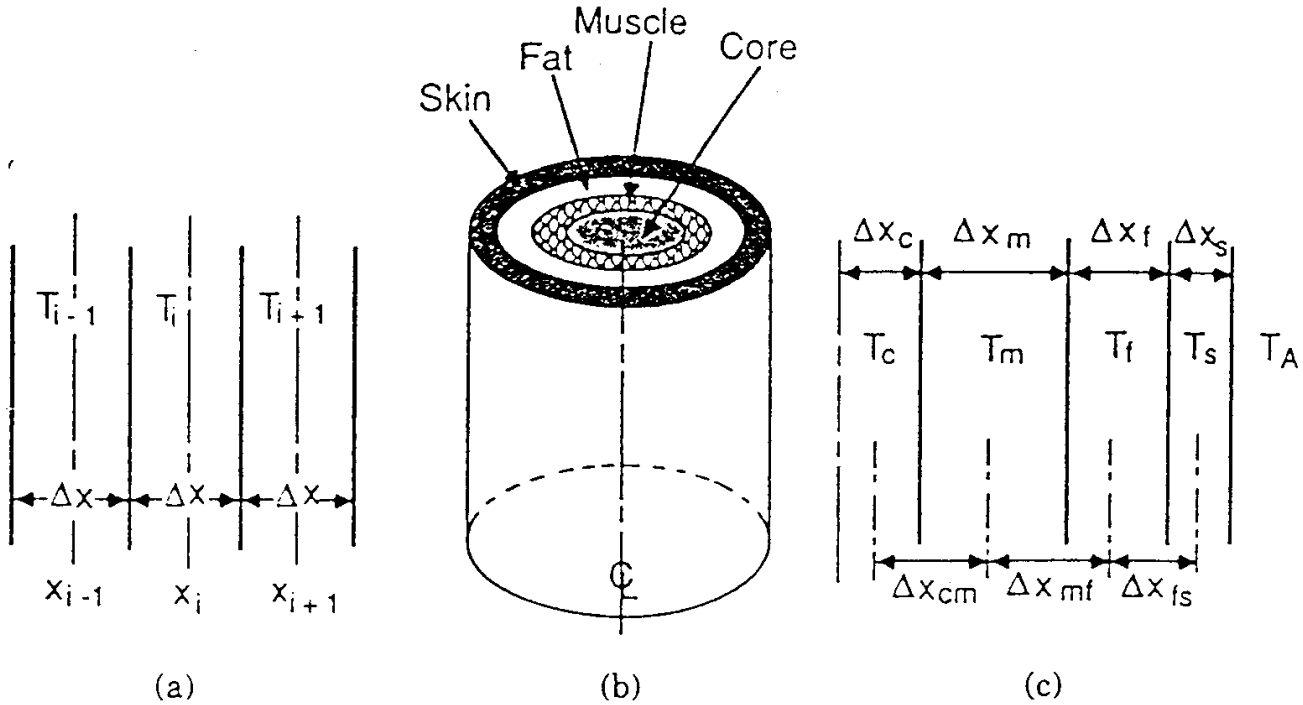


Figure 51: Heat generation and loss in the body (Rideout, 1991, Ch. 7)

Body Heat Flow Model III

Further applications

(a) Proximity Suits

(b) Newborn Incubator

Figure 52: Further applications of thermo-regulation

Body Heat Flow Model IV

Exercise 12: 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).

Outline

Background

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

Cardiovascular System Modeling I

Simplified Cardiovascular System

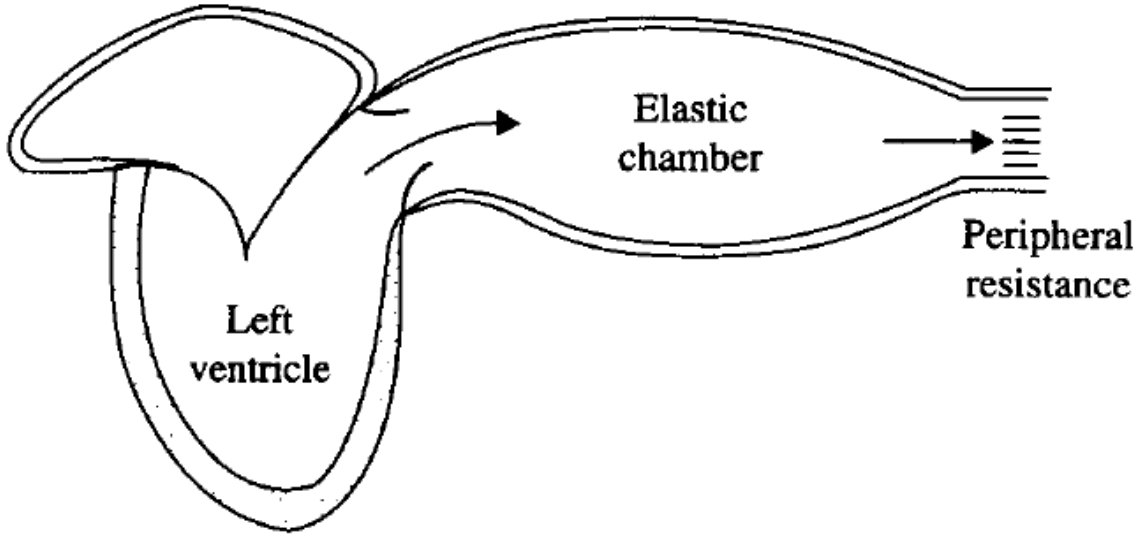
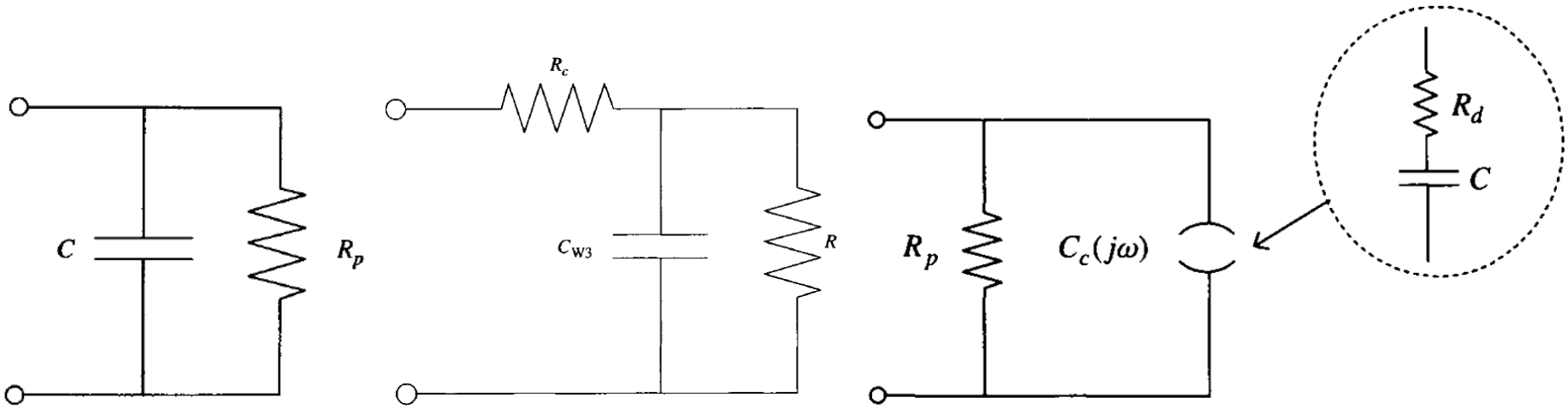


Figure 53: A simplified cardiovascular system (Carson and Cobelli, 2001, Ch. 8)

Cardiovascular System Modeling II

Windkessel models



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

Figure 54: Illustration of different versions of the Windkessel model (Carson and Cobelli, 2001, Ch. 8)

Cardiovascular System Modeling III

Further Cardiovascular System Models

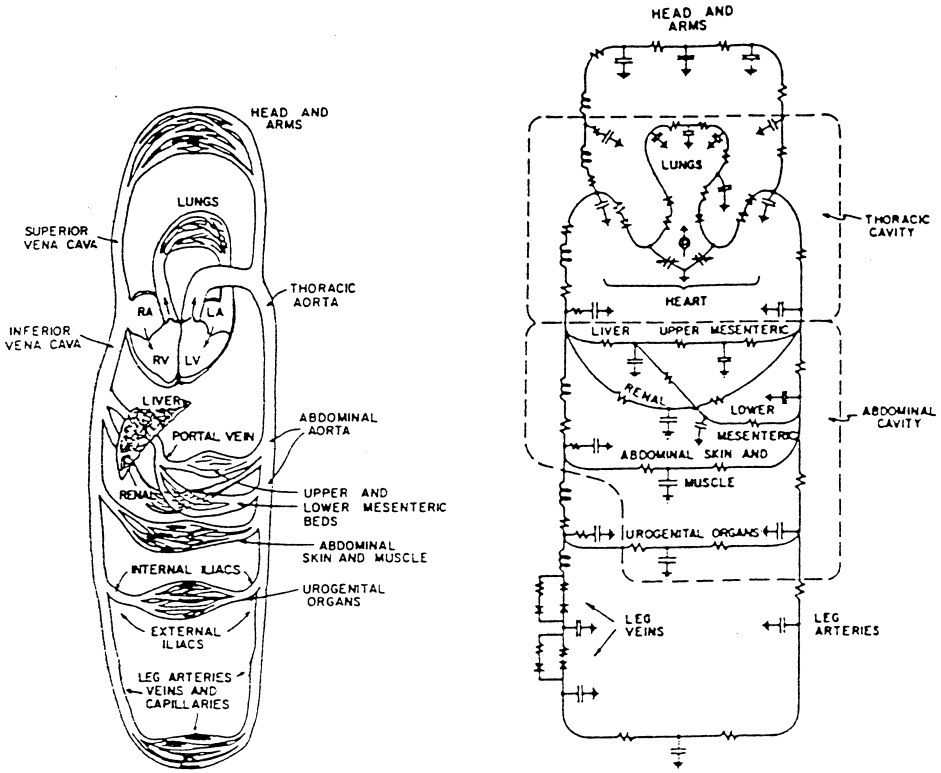


Figure 55: Analogy between cardiovascular and electrical systems; adopted from (Rideout, 1991, Ch. 4)

Outline

Background

Ref: This section is presented from (Carson and Cobelli, 2001, Ch. 9, 10) and Batzel $\mathrm{et\ al.}$ (2007).

Outline

Motivation for Biosignal Modeling

- Biological system modeling and biological signal modeling are deeply related together. In fact, modeling a biological system always results in the modeling of a set of observable signals within the system. On the other hand, biosignal models are always based on physiological aspects of the biological system of interest. Therefore, it is important to have a unified framework, in which both biological signals and systems can be studied at the same time.
- Model-based biosignal processing is another field of research, which is highly dependent on reliable and realistic biosignal models.
- In this section, general methods of biosignal modeling that exist in the literature are studied, together with their relationship with their corresponding biological systems. We study continuous, discrete, deterministic, and stochastic models.
- Herein, our 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:

$$\ddot{x}(t) + 2\alpha\dot{x}(t) + \omega_0^2 x(t) = 0 \tag{132}$$

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

$$x_1 \stackrel{\Delta}{=} x, \qquad x_2 \stackrel{\Delta}{=} \frac{dx}{dt}, \quad \Rightarrow \boldsymbol{x} = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \tag{133}$$

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= -2\alpha x_2 - \omega_0^2 x_1 \\ \dot{\boldsymbol{x}} &= \begin{bmatrix} 0 & 1 \\ -\omega_0^2 & -2\alpha \end{bmatrix} \boldsymbol{x} \end{aligned} \tag{134}$$

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

$$\frac{dx_2}{dx_1} = -\frac{2\alpha x_2 + \omega_0^2 x_1}{x_2} \tag{135}$$

Action Potential Modeling IV

Specifically, for $\alpha = 0$:

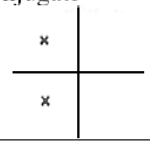
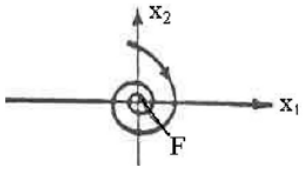
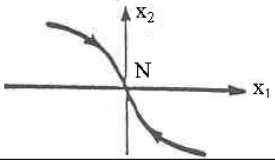
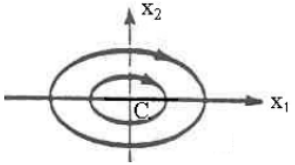
$$\begin{aligned}
&\frac{dx_2}{dx_1} = -\frac{\omega_0^2 x_1}{x_2} \\
&x_2 dx_2 = -\omega_0^2 x_1 dx_1 \Rightarrow \\
&\int_{x_2(0)}^{x_2} x_2 dx_2 = -\int_{x_1(0)}^{x_1} \omega_0^2 x_1 dx_1 \Rightarrow \\
&\frac{1}{2}\left[x_2(t)^2 - x_2(0)^2\right] = \frac{-\omega_0^2}{2}\left[x_1(t)^2 - x_1(0)^2\right] \Rightarrow
\end{aligned} \tag{136}$$

Hence:

$$x_2(t)^2 + \omega_0^2 x_1(t)^2 = x_2(0)^2 + \omega_0^2 x_1(0)^2 = cte \tag{137}$$

Which is an ellipse in the phase-plane.
Typical phase-plane trajectories of this system are shown in Fig. 56.

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

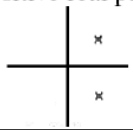
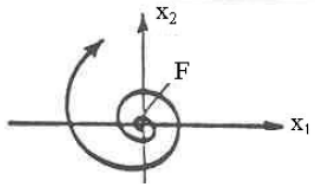
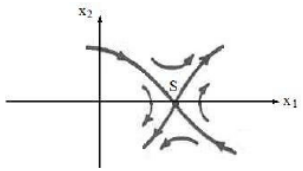
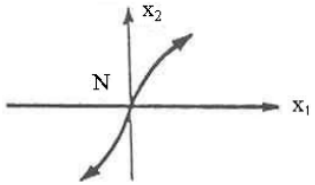
Name	Roots	Sketch
Unstable focus	Complex conjugate with positive real part 	
Saddle point	Unstable equilibrium point 	
Unstable node	Unstable real roots 	Trajectories diverge monotonically from node 

Figure 56: Phase-plane trajectories for linear second-order dynamical systems (Kogan, 2009, Ch. 5)

- Accordingly, $\alpha = 0$ is the threshold between stability and instability.

Action Potential Modeling VII

- Can this model be extended to a self-regulatory oscillator?
- 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

$$\ddot{x}(t) - 2\alpha[1 - x(t)^2]\dot{x}(t) + \omega_0^2 x(t) = 0 \tag{138}$$

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 $x(t)$).

Action Potential Modeling VIII

4. The system has a feedback mechanism, which keeps it at the margin of stability/instability.
5. The temporal shape and period of oscillation depends on the parameters α and ω_0.

The Van der Pol equation (138) 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 $\tau \stackrel{\Delta}{=} 2\alpha t$ and $\phi \stackrel{\Delta}{=} \frac{\omega_0^2}{4\alpha^2}$, simplifies (138) to:

$$\frac{d^2v}{d\tau^2} + (v^2 - 1)\frac{dv}{d\tau} + \phi v = 0 \tag{139}$$

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 $w \triangleq \frac{-dv}{dt} + v - \frac{v^3}{3}$, (139) can be stated in state-space form:

$$\begin{cases} \frac{dw}{d\tau} = \phi v \\ \frac{dv}{d\tau} = v - \frac{v^3}{3} - w \end{cases} \tag{140}$$

$$\frac{\frac{dw}{d\tau}}{\frac{dv}{d\tau}} = \frac{\phi v}{v - \frac{v^3}{3} - \omega} = \zeta = \tan\beta \tag{141}$$

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

$$\text{assume:} v = \epsilon_2 = 0^+ \Rightarrow \begin{cases} v > 0 \text{then: } \tan\beta = \frac{v}{\epsilon_2} \text{and } \beta = 90^o \\ v < 0 \text{then: } \tan\beta = -\frac{v}{\epsilon_2} \text{and } \beta = 270^o \end{cases} \tag{142}$$

Horizontal isocline:

$$\frac{dw}{d\tau} = 0 \Rightarrow \phi v = 0 \tag{143}$$

Action Potential Modeling X

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

$$\text{assume } w = \epsilon_1 = 0^+ \Rightarrow \begin{cases} w > 0, \text{then } \tan\beta = -\frac{\epsilon_1}{w} \text{and } \beta = 180^o \\ w < 0, \text{then } \tan\beta = \frac{\epsilon_1}{w} \text{and } \beta = 0^o \end{cases} \tag{144}$$

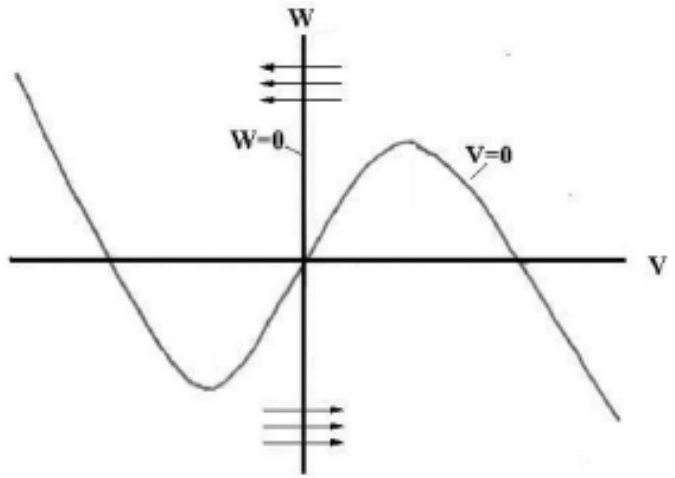


Figure 57: Horizontal isocline of van Der Pol's Model

Action Potential Modeling XI

Vertical isocline:

$$\frac{dv}{d\tau} = 0 \Rightarrow \omega = v - \frac{v^3}{3} \tag{145}$$

The isoclines are shown in fig58

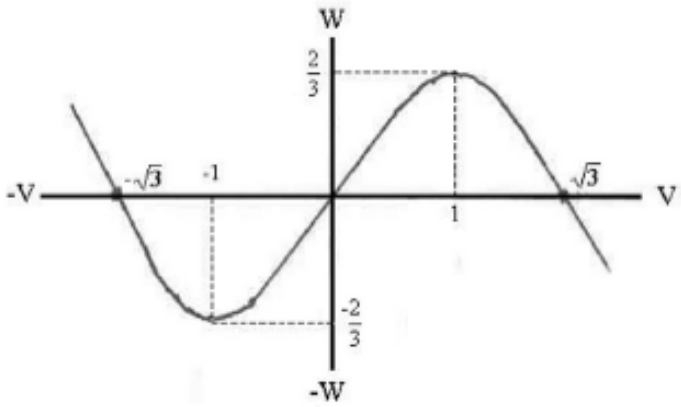


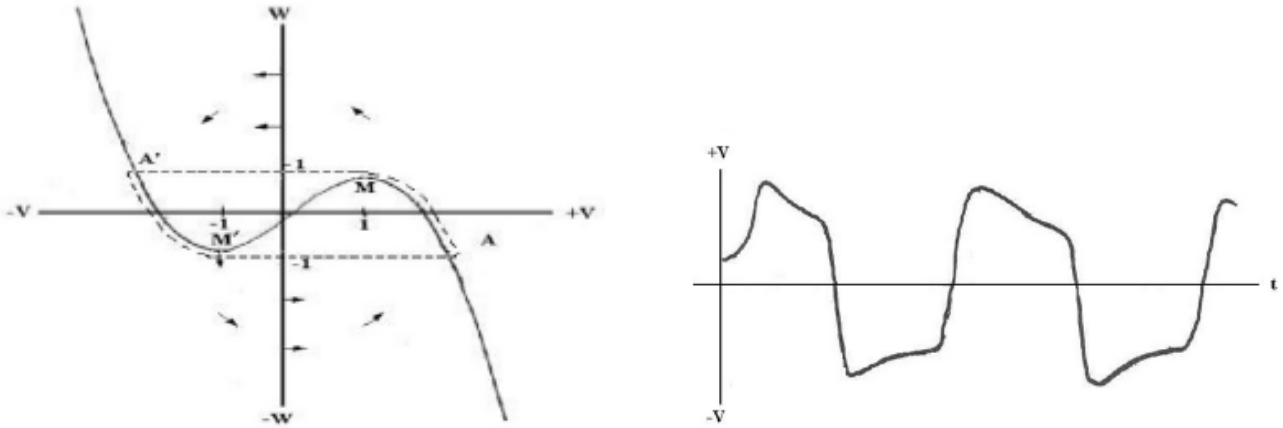
Figure 58: Vertical isocline of van Der Pol's Model

- The fixed-point is at the origin.

Action Potential Modeling XII

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

A typical phase plane graph and its corresponding AP in the time domain are shown in Fig 59.



(a) (b)

Figure 59: 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.

$$\begin{cases} \dfrac{dw}{dt} = \epsilon(v + a - bw) \\ \dfrac{dv}{dt} = v - \dfrac{v^3}{3} - w + I \end{cases} \tag{146}$$

For instance, for $\epsilon = 0.08, a = 0.7, b = 0.8$ the null-isoclines are shown in Fig. 60.

FitzHugh-Nagumo Model of Action Potentials II

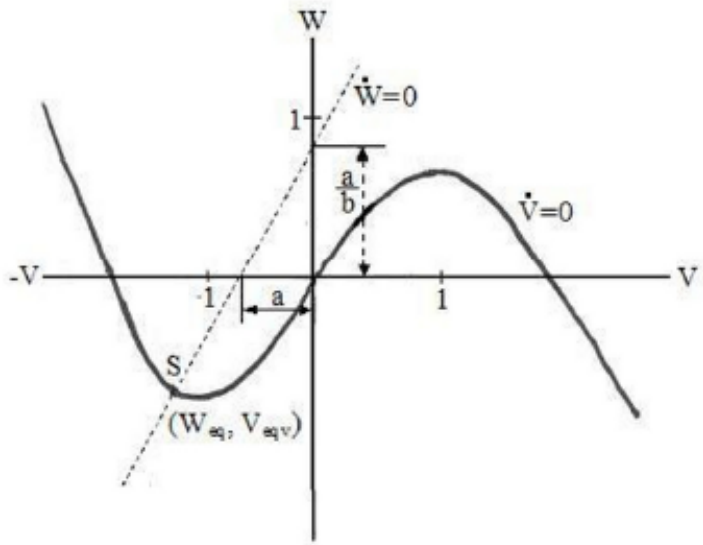
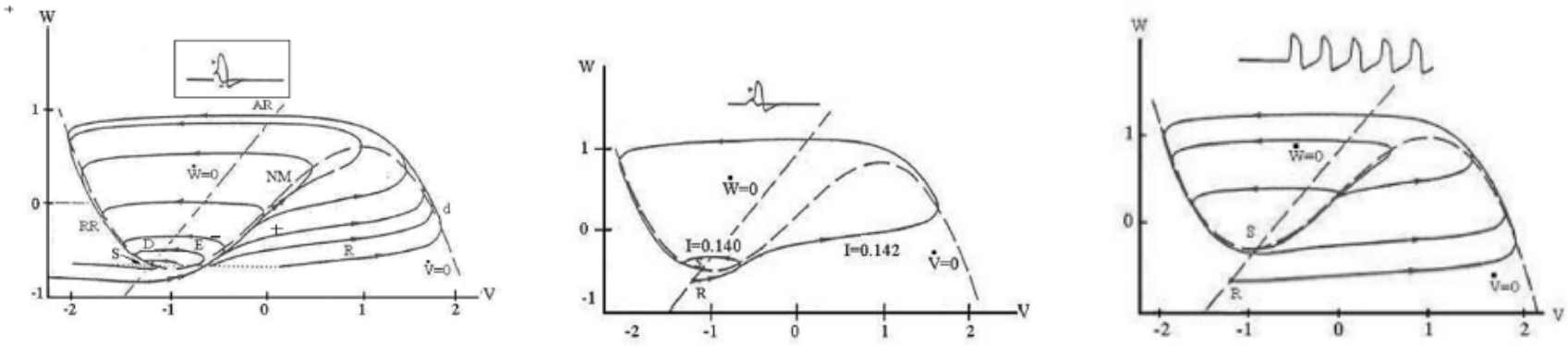


Figure 60: Null-isoclines of FitzHugh-Nagumo's Model

The resulting AP are shown in 61

FitzHugh-Nagumo Model of Action Potentials III



(a) (b) (c)

Figure 61: 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 13: Analyze the fixed-point stability of the FitzHugh-Nagumo model

Exercise (Optional)

1. *Study the Hodgkin-Huxley AP model and compare it with the FitzHugh-Nagumo model from (Keener and Sneyd, 1998, Ch. 4).*
2. *Study the model of Purkinje Fibers, Sinuatrial Node, and Ventricular Cells from (Keener and Sneyd, 1998, Ch. 4).*

Project Topic 17:

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

$$\begin{cases} \dot{x} = \rho x - \omega y \\ \dot{y} = \rho y + \omega x \\ \dot{z} = -\sum_{i \in \{P,Q,R,S,T\}} a_i \Delta\theta_i \exp(-\frac{\Delta\theta_i^2}{2b_i^2}) - (z - z_0) \end{cases} \tag{147}$$

- 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, 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 2: Parameters of the synthetic ECG (147)

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

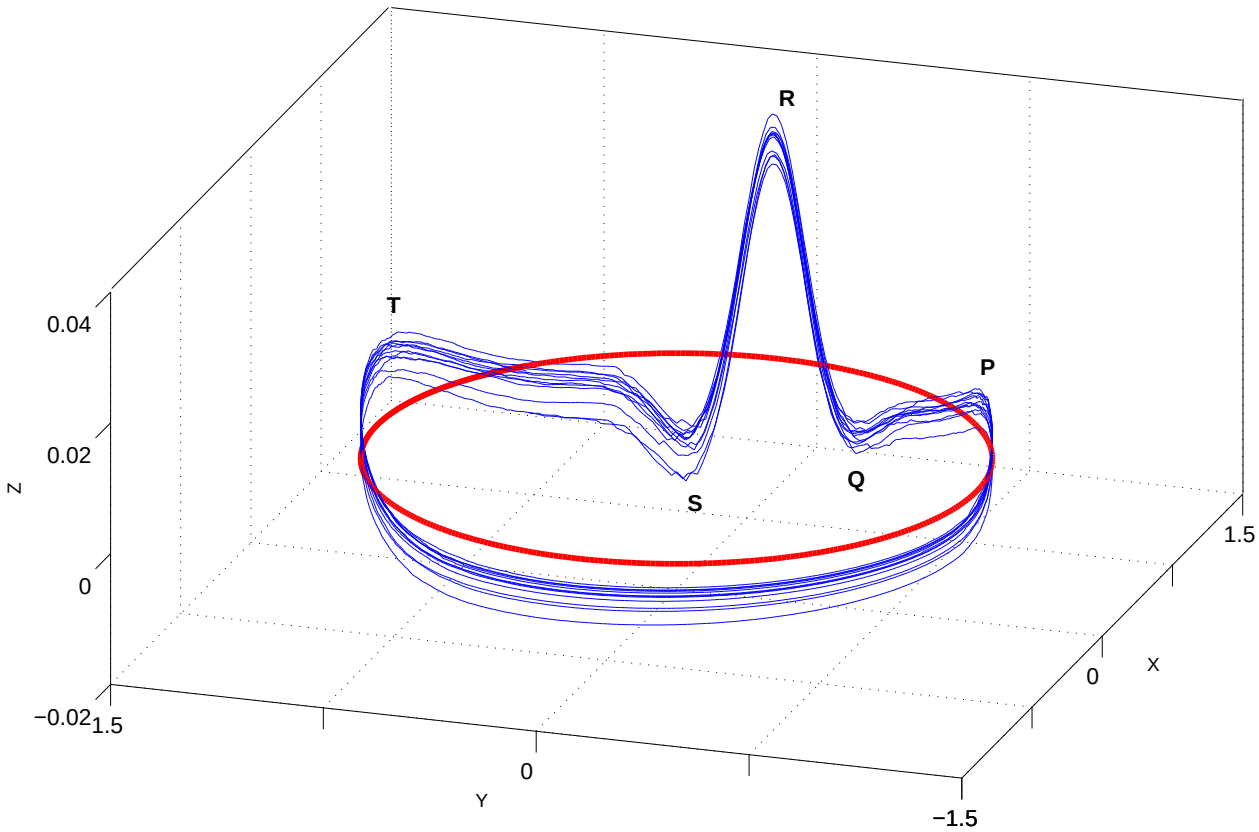


Figure 62: 3D trajectory of (147) McSharry et al. (2003). The red line corresponds with the unit circle in the $x - y$ plane

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

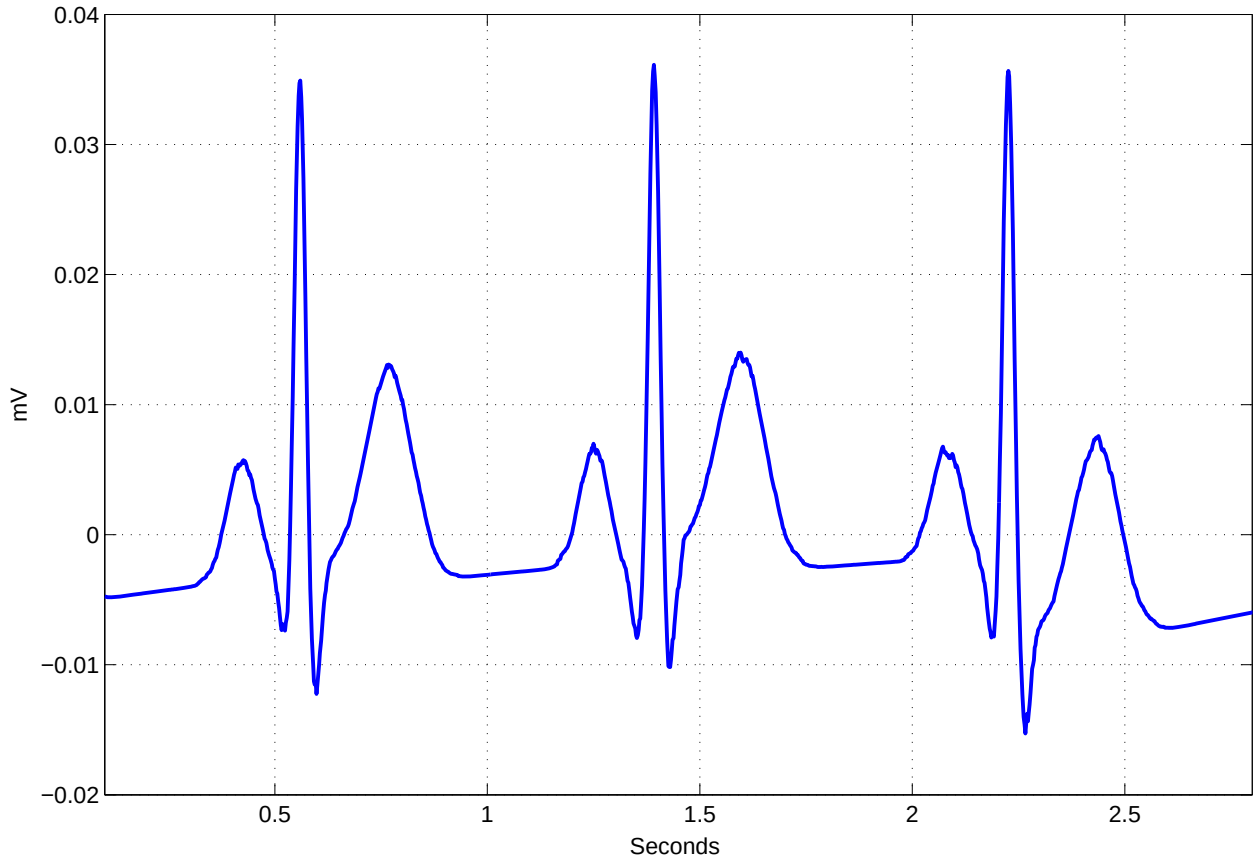


Figure 63: Projection of the 3D trajectory of (147) McSharry et al. (2003) onto the z-axis

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

$$\begin{cases} \dot{r} = r(1-r) \\ \dot{\theta} = \omega \\ \dot{z} = -\sum_{i \in \{P,Q,R,S,T\}} \frac{\alpha_i \omega}{b_i^2} \Delta\theta_i \exp(-\frac{\Delta\theta_i^2}{2b_i^2}) \end{cases} \tag{148}$$

- 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. (2007): I

$$\begin{cases} \theta_{k+1} = (\theta_k + \omega\delta) \mod (2\pi) \\ z_{k+1} = -\sum_i \delta \frac{\alpha_i \omega}{b_i^2} \Delta\theta_i \exp(-\frac{\Delta\theta_i^2}{2b_i^2}) + z_k + \eta \end{cases} \tag{149}$$

- $\Delta\theta_i = (\theta_k - \theta_i) \mod (2\pi)$, 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. (2007): I

$$
\begin{aligned}
\dot{\theta} &= \omega \\
\dot{x} &= -\sum_i \frac{\alpha_i^x \omega}{(b_i^x)^2} \Delta\theta_i^x \exp[-\frac{(\Delta\theta_i^x)^2}{2(b_i^x)^2}] \\
\dot{y} &= -\sum_i \frac{\alpha_i^y \omega}{(b_i^y)^2} \Delta\theta_i^y \exp[-\frac{(\Delta\theta_i^y)^2}{2(b_i^y)^2}] \\
\dot{z} &= -\sum_i \frac{\alpha_i^z \omega}{(b_i^z)^2} \Delta\theta_i^z \exp[-\frac{(\Delta\theta_i^z)^2}{2(b_i^z)^2}]
\end{aligned}
\tag{150}
$$

- $\Delta\theta_i^x = (\theta - \theta_i^x) \mod (2\pi)$, $\Delta\theta_i^y = (\theta - \theta_i^y) \mod (2\pi)$, $\Delta\theta_i^z = (\theta - \theta_i^z) \mod (2\pi)$, and $\omega = 2\pi f$, f is the beat-to-beat heart rate in Hz.
- As before, the first equation in (150) generates a circular trajectory rotating with the frequency of the heart rate.

Vectorcardiogram Modeling Sameni et al. (2007): 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 Form Sameni et al. (2007): I

$$ECG(t) = H \cdot R \cdot \Lambda \cdot s(t) + W(t) \tag{151}$$

- $ECG(t)_{N\times 1}$ 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. (2007): I

$$X(t) = H_m \cdot R_m \cdot \Lambda_m \cdot s_m(t) + H_f \cdot R_f \cdot \Lambda_f \cdot s_f(t) + W(t) \qquad (152)$$

- H_m, H_f, R_m, R_f, Λ_m and, Λ_f have similar definitions as the ones in (151)
- 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. 64). 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. (2007): II

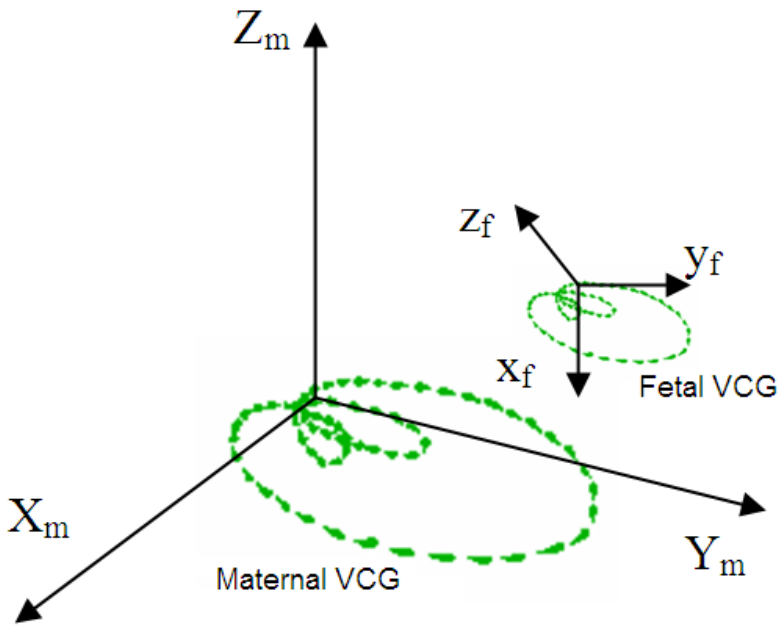


Figure 64: Illustration of the fetal and maternal VCGs vs. their body coordinates

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:

$$h[n] = h_b[n] + h_r[n] + h_p[n] + h_{\text{HRT}}[n] + \dots \tag{153}$$

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 (150). Apparently, any other item that influences the HR can also be considerd in this formulation. A typical example is shown in (65).

Heart Rate Variation Modeling Clifford et al. (2010): III

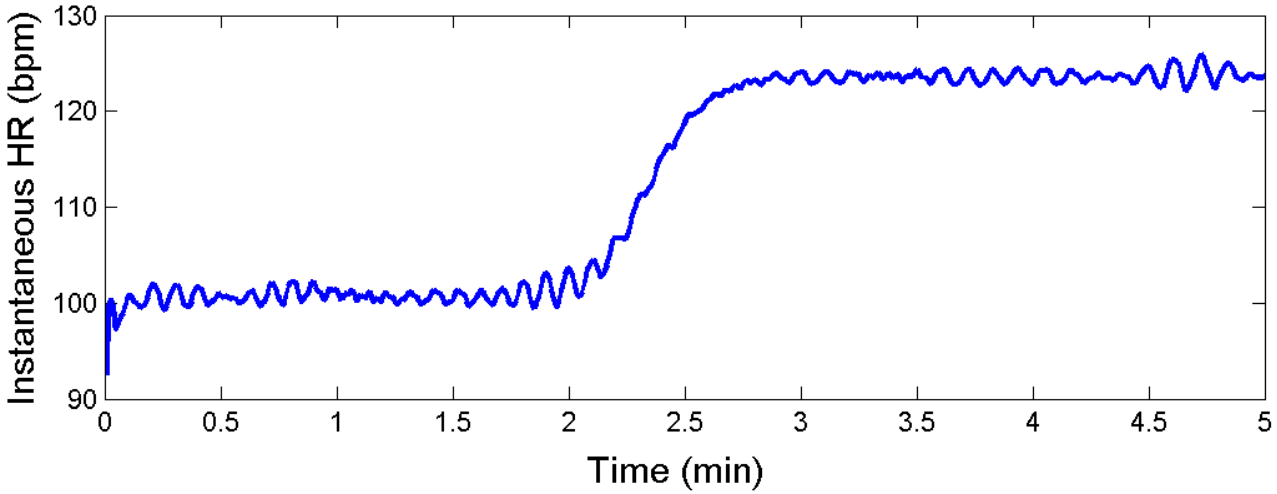


Figure 65: Example of time-varying instantaneous heart rate.

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:

$$\text{STM} = \begin{bmatrix} p_{1,1} & p_{1,2} \\ p_{2,1} & p_{2,2} \end{bmatrix} \tag{154}$$

where, as shown in Fig. 66, 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. 67 and 68).

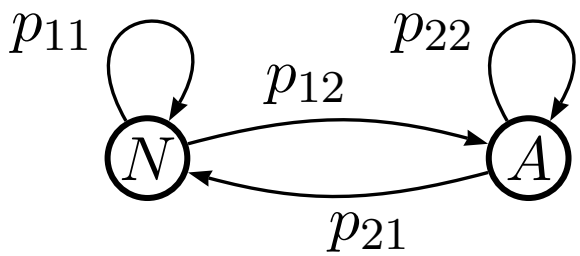


Figure 66: State transition graph between normal (N) and abnormal (A) beats using a first-order Markov chain. The graph can be extended to more abnormal beat types.

Abnormal ECG Modeling Clifford et al. (2010): III

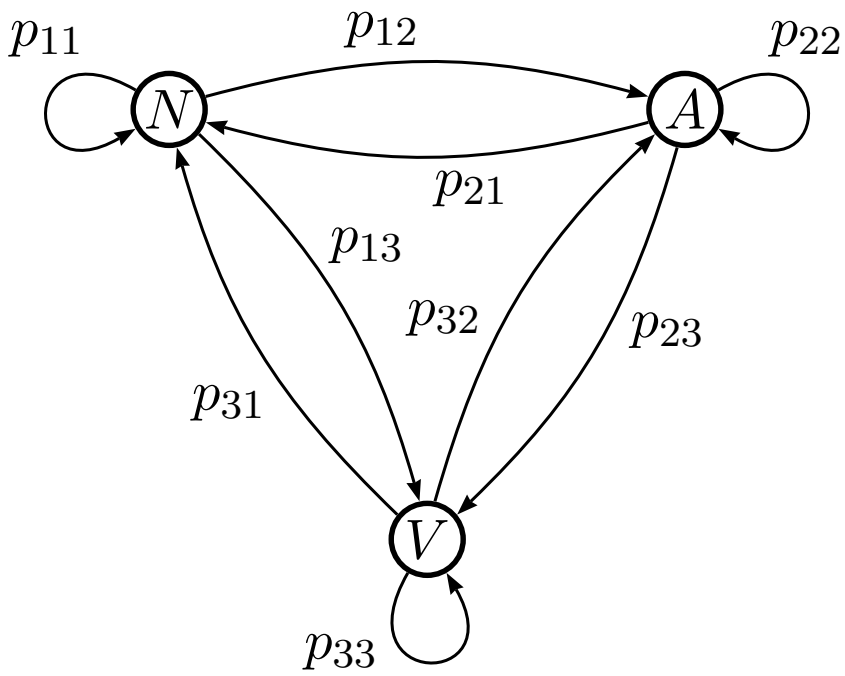


Figure 67: State transition graph between normal (A), abnormal (B), and ectopic (V) beats using a first-order Markov chain.

Abnormal ECG Modeling Clifford et al. (2010): IV

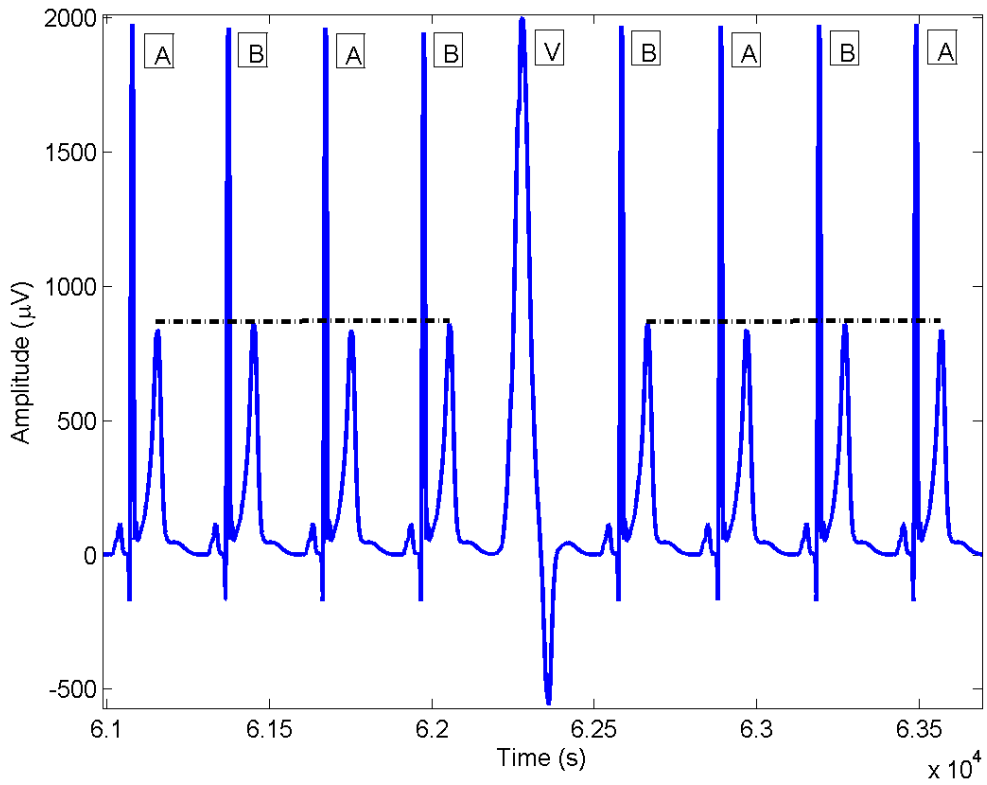


Figure 68: 'ABAB' beat sequence followed by a phase-changing ectopic beat (V). Note that the beats following the ectopic beat will now be of a 'BABA pattern'.

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:

$$p(t) = (\tanh[\vartheta(h(t) - h_{\text{TWA}})] + 1)/2 \tag{155}$$

where $h(t)$ is the instantaneous heart rate defined in Eq. 153, $h_{\text{TWA}} = 95 \pm 5$ 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. 69 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

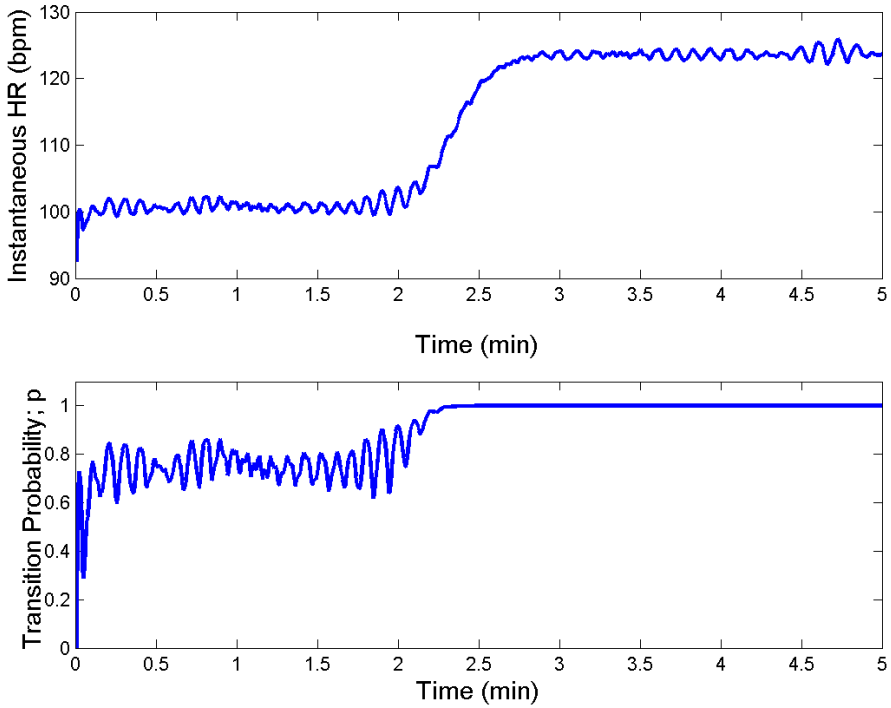


Figure 69: Example of instantaneous heart rate and resultant probability of transition to TWA.

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. 70, 71 and 72

Abnormal ECG Modeling Clifford et al. (2010): VIII

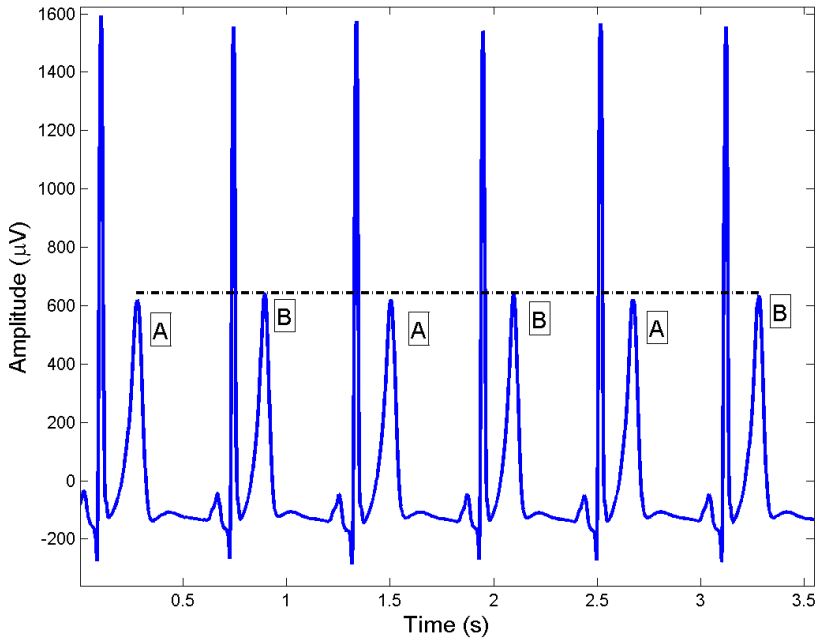


Figure 70: Typical alternating 'ABAB' TWA pattern (with TWA amplitude of 23 μV) generated from our model.

Abnormal ECG Modeling Clifford et al. (2010): IX

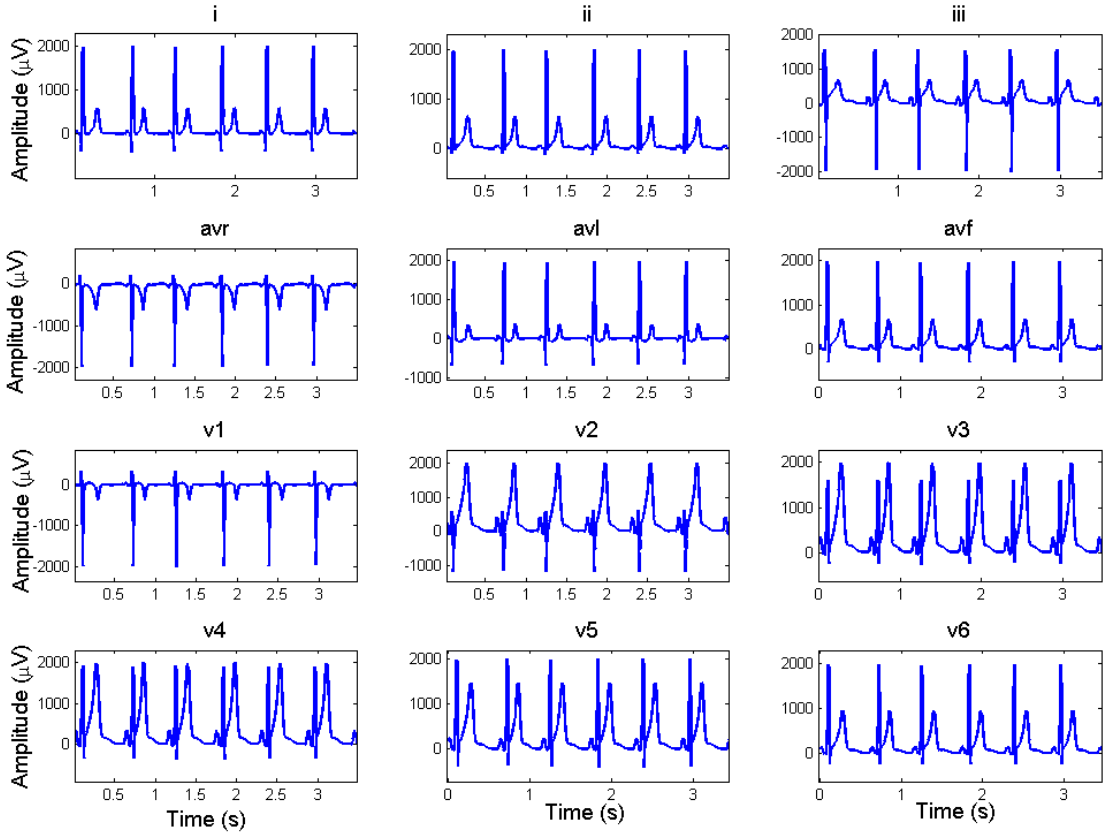


Figure 71: Example of 12 lead ECG after application of IDT.

Abnormal ECG Modeling Clifford et al. (2010): X

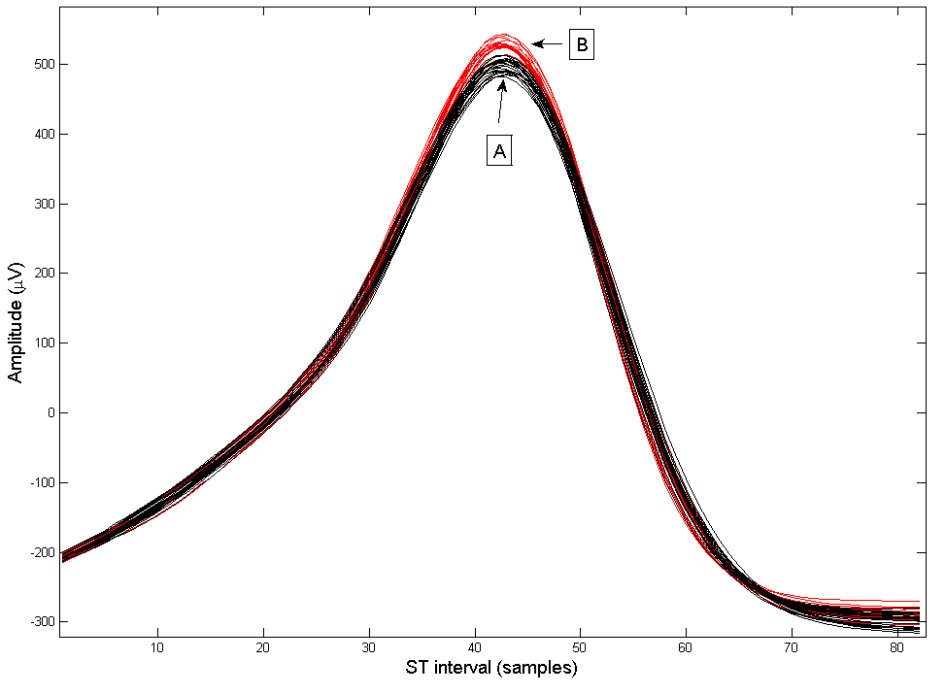


Figure 72: Multiple ST-T segments from two beat classes taken from one of the VCG projections. Class A beats are black and class B beats are red.

[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 I

- 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

Stochastic Biosignal Modeling II

Innovation Process (Papoulis and 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

$$x(t) = \int_0^\infty l(\tau) i(t-\tau) d\tau \tag{156}$$

which has the following spectrum:

$$S_x(f) = \sigma_i^2 |L(f)|^2 \tag{157}$$

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

$$i(t) = \int_0^\infty \gamma(\tau) x(t-\tau) d\tau \tag{158}$$

Stochastic Biosignal Modeling III

Innovation Filter Design

Classical methods for finding the innovation filter impulse response, include:

- Spectral factorization
- Model-based design (AR, MA, ARMA, etc.)

Spectral Factorization I

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 ($j\omega \to s$)

$$S_x(s) = L(s)L(-s) \tag{159}$$

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.

Example

$$\begin{aligned} S_x(\omega) &= \frac{N}{\alpha^2 + \omega^2} \\ S_x(s) &= \frac{N}{(\alpha + s)(\alpha - s)} \\ L(s) &= \frac{\sqrt{N}}{\alpha + s} \Rightarrow l(t) = \sqrt{N} e^{-\alpha t} u(t) \end{aligned} \tag{160}$$

Spectral Factorization II

Example

$$
\begin{aligned}
S_x(\omega) &= \frac{49 + 25\omega^2}{\omega^4 + 10\omega^2 + 9} \\
S_x(s) &= \frac{(7 - 5s)(7 + 5s)}{(1 - s^2)(9 - s^2)} \\
L(s) &= \frac{7 + 5s}{(1 + s)(3 + s)} \Rightarrow l(t) = (e^{-t} + 4e^{-3t})u(t)
\end{aligned}
\tag{161}
$$

Phonocardiogram Modeling I

Almasi et al. (2013) and a few other references + our own method of PCG modeling using bandpass innovation filters....

Outline

Advanced Project Topics: Biologically Inspired Modeling I

Project Topic 18: 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 19: 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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