Introduction to Modeling Methodology

- Modeling theory and practice in relation to physiology and medicine.
- Modeling methodology
- How models used in the areas of physiology and medicine
- Fundamentals of modeling process = a mapping or transforming of a physiological system into a model (Carson, Fig. 1.1.)

I. The Need for Models

i) Physiological Complexity

- Complexity characterizes much of physiology
- Physiological system
  (1) Elements and their connectivity in terms of hierarchy: the levels of molecule, cell, organ, and organism.
  (2) Complex process:
    - Nonlinear, stochastic, and time-varying effects
    - Regulation and control
    - Feedback in chemical reactions, hormonal control mechanism, metabolic processes
  (3) Complexity exists at each level of the hierarchy and across levels within the physiological system
  (4) No direct measurement possible. Only indirect measures are feasible -> Some models are needed to infer the value of the quantity of real interest. Ex) only blood values of a metabolite is readable, but the real interest lines in its value in body tissue.
- Adopt models to aid our understanding

ii) Models and Their Purposes

- What do we mean by the term *model*?
  - It is a representation of reality involving some degree of approximation.
  - Models can take many forms: conceptual, mental, verbal, physical, statistical, mathematical, logical, or graphical in forms
  - This class is mostly about mathematical modeling and its realization in computer programs
- What is the purpose of modeling activity?
  - Modeling can be used to describe, interpret, predict, or explain.

- Ex) A mathematical expression, a single exponential decay can provide a compact description of data that approximates to a first-order process.
- Ex) A mathematical model can be used to interpret data collected as part of a lung function test.
- Ex) A model of glucose and insulin can be used to gain additional insight into and explanation of the complex endocrine dynamics in the diabetic patient.
- Aiding understanding
- Testing hypothesis
- Measuring inferences, simulating and examining experimental design
- Teaching and learning. By means of simulation, the student can be exposed to a richer range of physiological and pathophysiological situations
- A tool for experimental design. If the number of blood samples that can be withdrawn from a patient is limited in a given period of time, models can be used to determine the times at which blood samples should be withdrawn to obtain the maximum information from the experiment in relation to pharmacokinetics or pharmacodynamics effects

– Next steps: model formulation, determination of degree to which the model is an approximation of reality, model identification, parameter estimation, model validation.

iii) Modeling Approaches

In developing a mathematical model, two fundamental approaches

1. Based on experimental data; A data-driven approach
2. Based on a fundamental understanding of the physical and chemical processes that give rise to the resultant experimental data

- Modeling the Data
    - Data driven or black box models
    - Find quantitative description of physiological systems based o n input-output (I/O) descriptions derived from experimental data collected on the system.
    - Why data models? They are appropriate where there is a lack of knowledge of the underlying physiology and where an overall I/O representation of the system’s dynamics is needed.
    - Fig. 1.3
    - Techniques: time series analysis, transfer function analysis, convolution-

deconvolution techniques, mostly restricted to linear systems.

- Modeling the System
  - Model the system based on a priori knowledge and the nature of the assumptions that can be made.
  - Fig. 1.4
  - Kinds of models
    - Static vs. dynamic models
    - Deterministic vs. stochastic
    - Time-invariant vs. time-varying
    - Lumped vs. distributed
    - Linear vs. nonlinear
    - Continuous vs. discrete
  - Static models: restricted to steady-state conditions and do not attempt to capture the richness of a system's dynamics
  - Ex) In the circulatory or respiratory context, static models can provide useful relationships between mean pressure, flow, and impedance
  - Dynamic models have been employed in fields such as cellular dynamics and metabolic compartmental descriptions
  - Nonlinear models reflect the fact that all physiological phenomena are truly nonlinear. In some situations, linearity is assumed.
  - Time-invariant: this means that system parameters are assumed not to vary with time. May not be true for some cases

iv) Simulation

- Simulation is the process of the solving the model to examine its output behavior
- This process involves examining the time course of one or more of the variables
- Perform computer experiments on the model
- When is simulation required?
  - Perform simulation during the process of model building or once the model is completed
  - During model building, simulation can be performed to clarify aspects of system behavior to determine whether a proposed model representation is appropriate. This is done by comparison of the model response with experimental data from the same situation.
  - When simulation is carried out on a complete, validated model, simulation yields output responses that provides information on system behavior

- Depending on the modeling purpose, this information assists in describing the system, predicting behavior, or yielding additional insights.

- Why use simulation?
  - Simulation offers a way forward in situations in which it might not be appropriate, convenient, or desirable to perform particular experiments on the system.
  - Such situations could include those in which experiments cannot be done at all, are too difficult, are too dangerous, are not ethical, or would take too long to obtain results.
  - Simulation offers an alternative that can overcome the preceding limitations.
- How to perform simulations?
  - First, we need a mathematical model that is complete; all its parameters are specified and initial conditions are defined for all the variables
  - Implement the model on the computer using Fortran, C, or Matlab
  - Solve the model on the computer
  - The solution yields the time course of the system variables

v) Model Identification

- Identification
  - To complete the transformation from system to model, we must have a model structure and fully determined parameters.
  - Fig. 1.5 for model identification process
  - The solution requires data
  - The I/O data from the experiment must contain that part of the model with the unknown parameter values.
  - In the model identification process, data are mapped into parameters values by the model where errors can occur in both the data and the model
  - Error in data: a consequence of measurement errors
  - Error in model: errors in model structure
  - Other types of errors: noise on the test signals and disturbances
  - Two types of models: parametric models and nonparametric models
- Identification of Parametric Models
  - Identifiability: is it possible to make unique estimates of all the unknown parameters assuming that the experimental data were complete and noise-free.
  - Two factors in model identifiability: experimental data is rich enough to estimate all the unknown parameters and the complexity of the model
  - Techniques for parameter estimation: there are many mostly based on linear least

squares. This means minimize the error between the measured data and computed data.

- Identification of Nonparametric Models
  - Nonparametric models when a data modeling approach has been adopted
  - Three elements: input, output, and impulse response
  - Techniques: deconvolution etc.

vi) Model Validation

- Validating a model is essentially examining whether it is good enough in relation to its intended purpose
- No model is perfect.
- If one is working with a set of competing candidate models, the validation process involves determining which of them is best in relation to its intended purpose.
- A valid model is one that has successfully passed through the validation process
- Fig. 1.6
- A successful outcome to the modeling process is critically dependent on both the quality of the model and the quality of experimental data (Fig. 1.7)