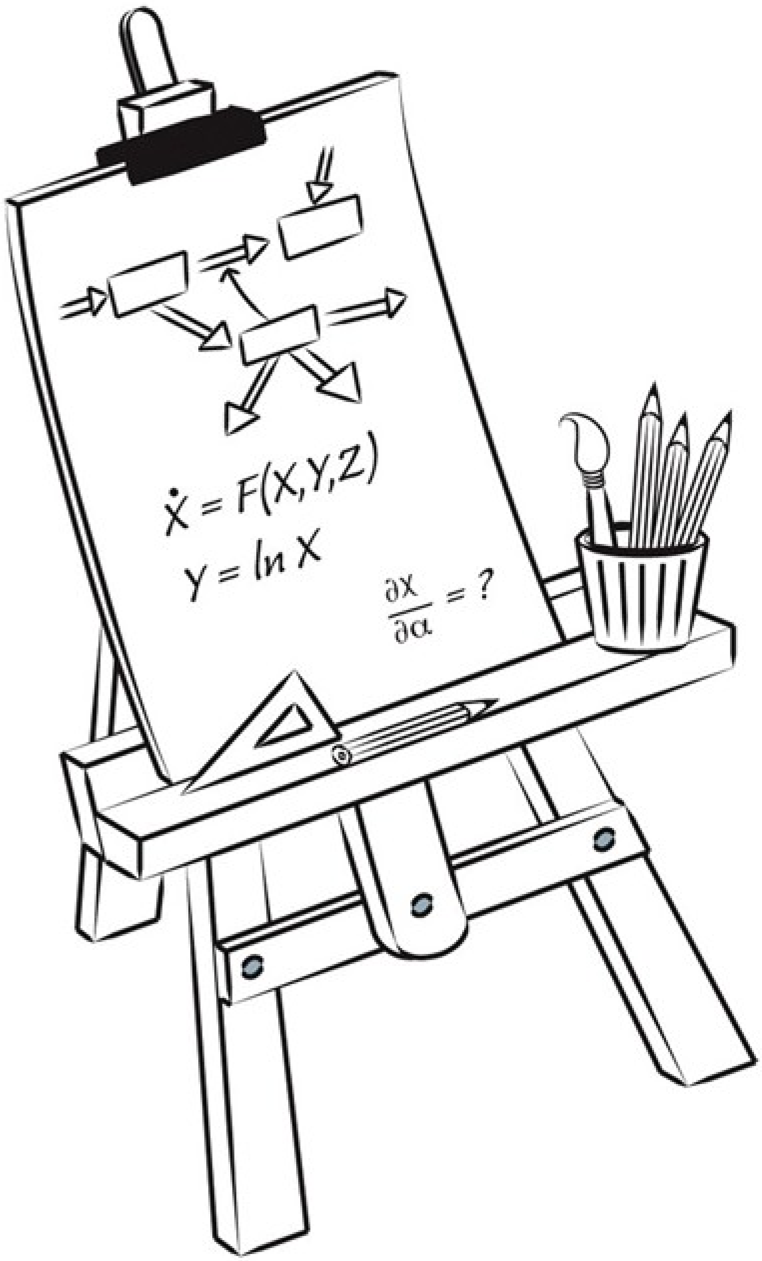
Eberhard O. Voit

A First Course in Systems Biology

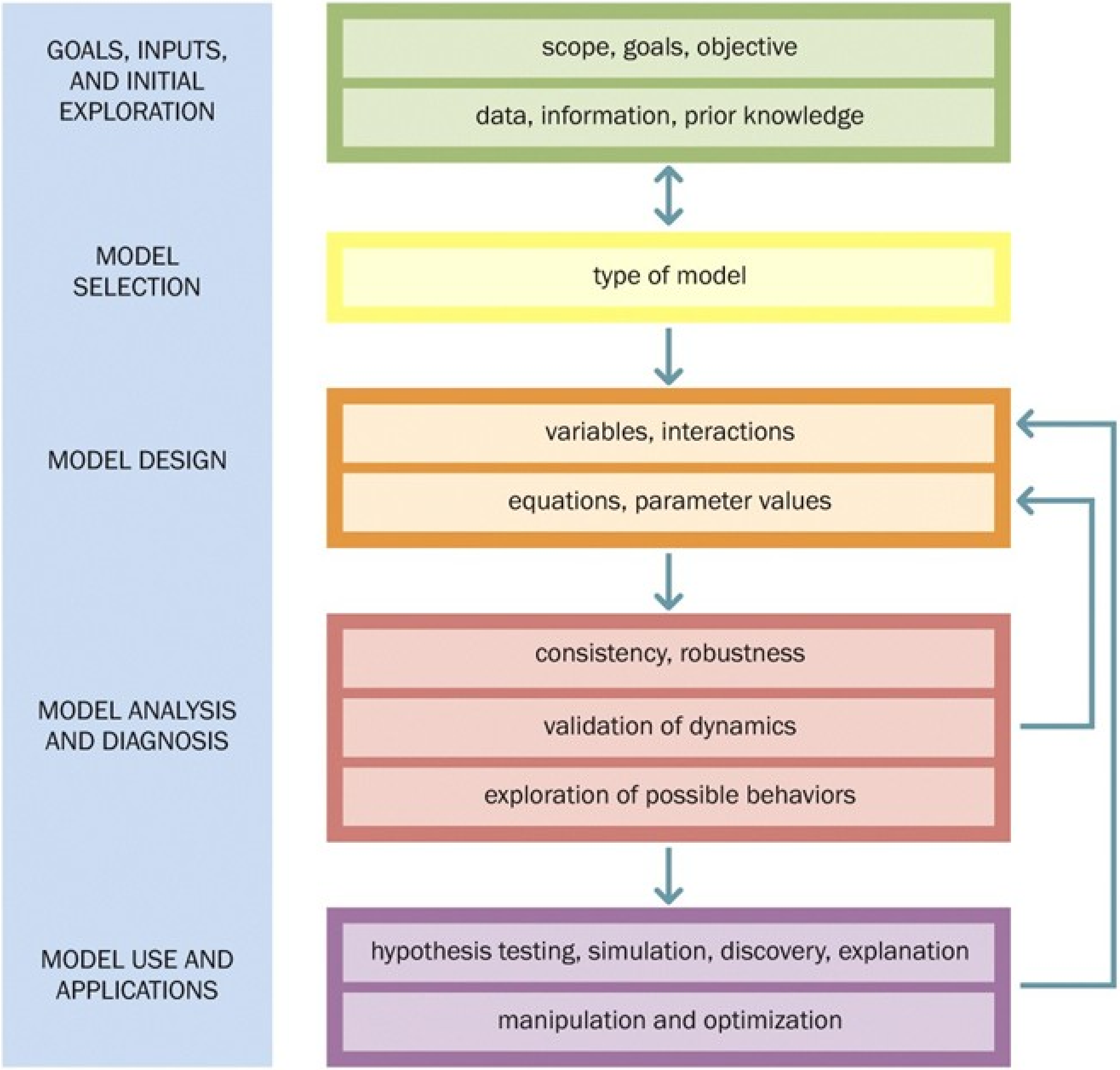
Chapter 2
Introduction to Mathematical Modeling



Model
An artificial construct in the language of Mathematics that represents a process or a phenomenon.

Modeling
The process of creating a *model* to obtain new insights.

It provides explanations, predictions and extrapolations.



GOALS, INPUTS, AND INITIAL EXPLORATION
scope, goals, objective
data, information, prior knowledge
MODEL SELECTION
type of model
MODEL DESIGN
variables, interactions
equations, parameter values
MODEL ANALYSIS AND DIAGNOSIS
consistency, robustness
validation of dynamics
exploration of possible behaviors
MODEL USE AND APPLICATIONS
hypothesis testing, simulation, discovery, explanation
manipulation and optimization

ISSUES TO PONDER DURING THE MODELING PROCESS

Goals, Inputs, and Initial Exploration

- Scope of the model, including goals, objectives, and possible applications
- Data availability or need (types, quantity, quality)
- Other available information (nonquantitative heuristics, qualitative input from experts)
- Expected feasibility of the model
- Relevance and degree of interest within the scientific community

ISSUES TO PONDER DURING THE MODELING PROCESS

Model Selection

- Model structure
  - Explanatory (mechanistic) versus correlative (black box)
  - Static versus dynamic
  - Continuous versus discrete
  - Deterministic versus stochastic
  - Spatially distributed versus spatially homogeneous
  - Open versus closed
  - Most appropriate, feasible approximations

ISSUES TO PONDER DURING THE MODELING PROCESS

Model Design

- Model diagram and lists of components
  - Dependent variables
  - Independent variables
  - Processes and interactions
  - Signals and process modulations
  - Parameters
- Design of symbolic equations
- Parameter estimation
  - Bottom-up
  - Top-down

ISSUES TO PONDER DURING THE MODELING PROCESS

Model Analysis and Diagnosis

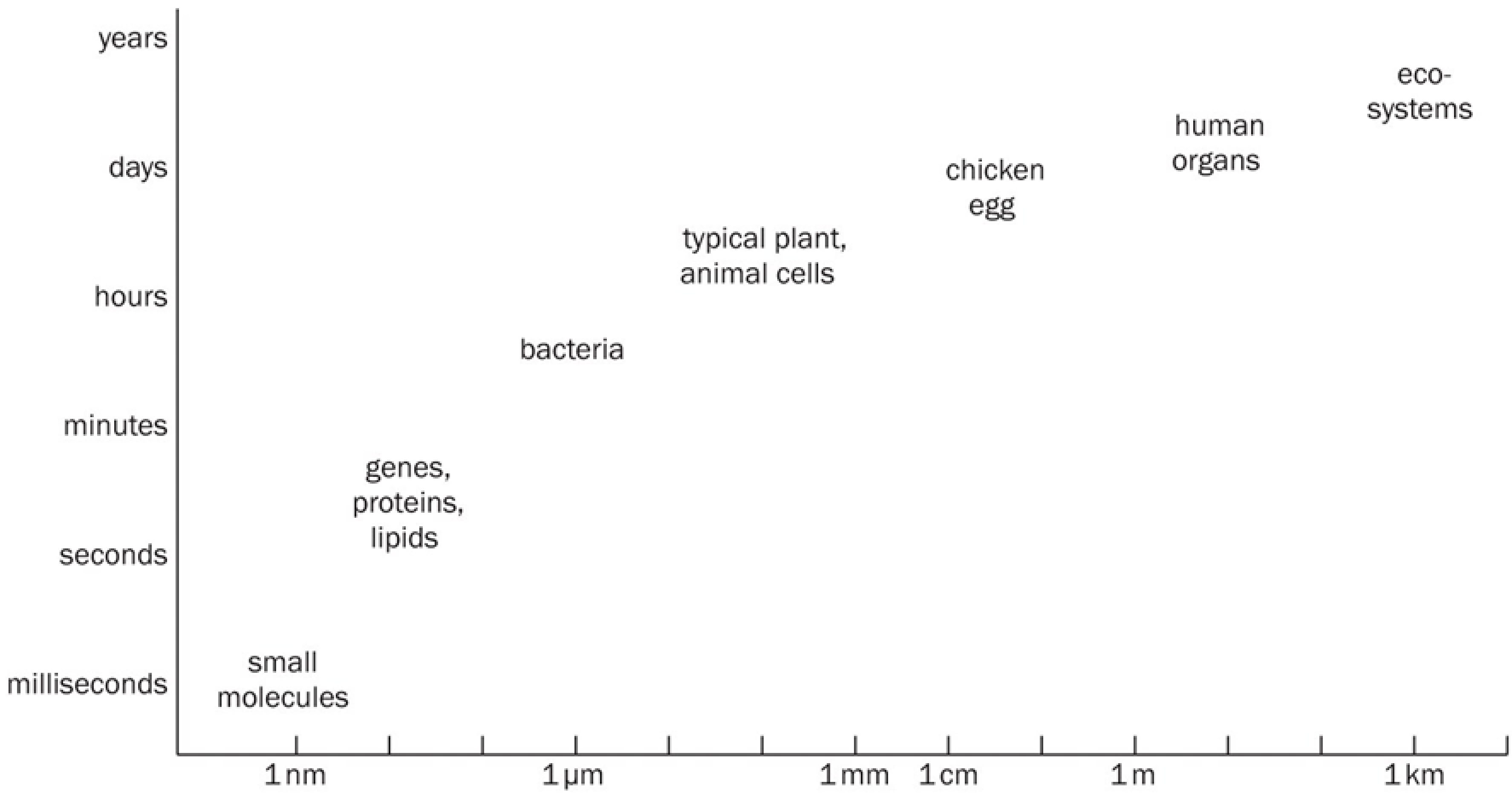
- Internal consistency (conservation of mass)
- External consistency (closeness to data and expert opinion)
- Reasonableness of steady state(s)
- Stability analysis
- Sensitivity and robustness analysis
- Structural and numerical boundaries and limitations
- Range of behaviors that can or cannot be modeled (oscillations, multiple steady states)

ISSUES TO PONDER DURING THE MODELING PROCESS

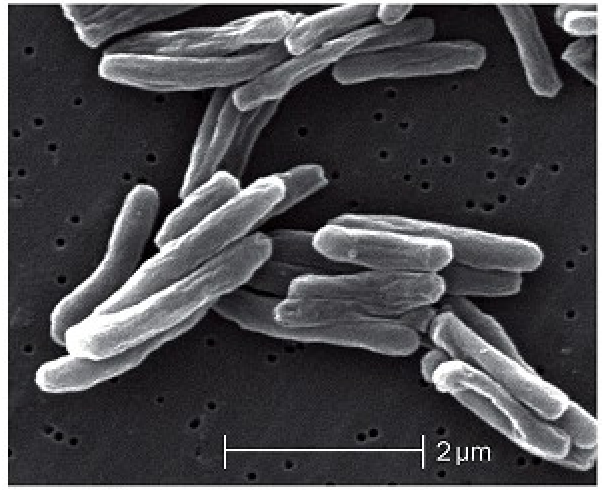
Model Use and Applications

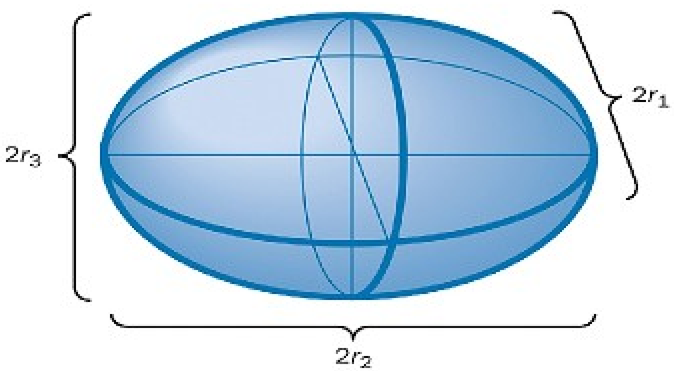
- Confirmation, validation of hypotheses
- Explanation of causes and effects; causes of failure, counterintuitive responses
- Best case, worst case, most likely scenarios
- Manipulation and optimization (treatment of disease; avoidance of undesired states or dynamics; yield optimization in biotechnology)
- Discovery of design principles

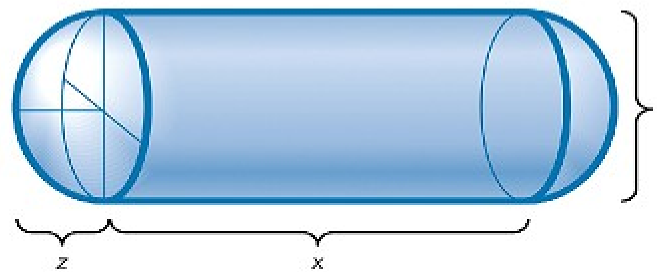
Questions of scale: Size and time



Model Selection and Design





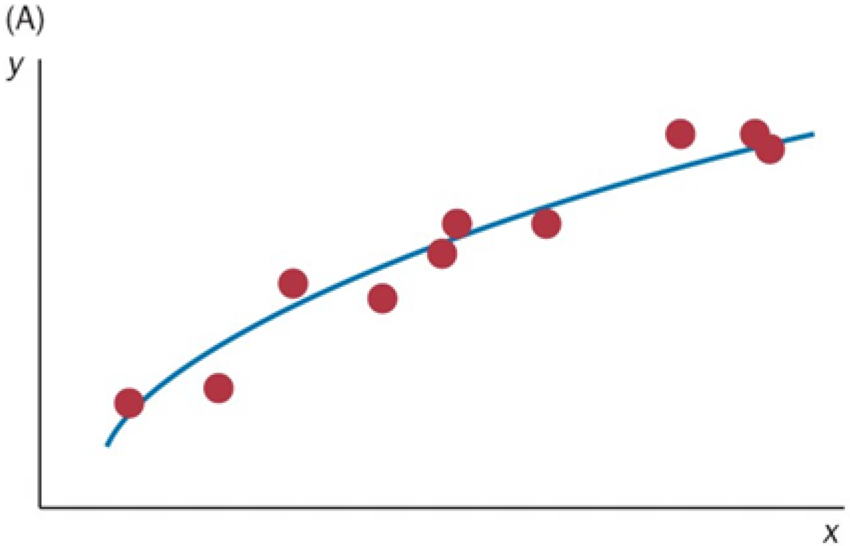


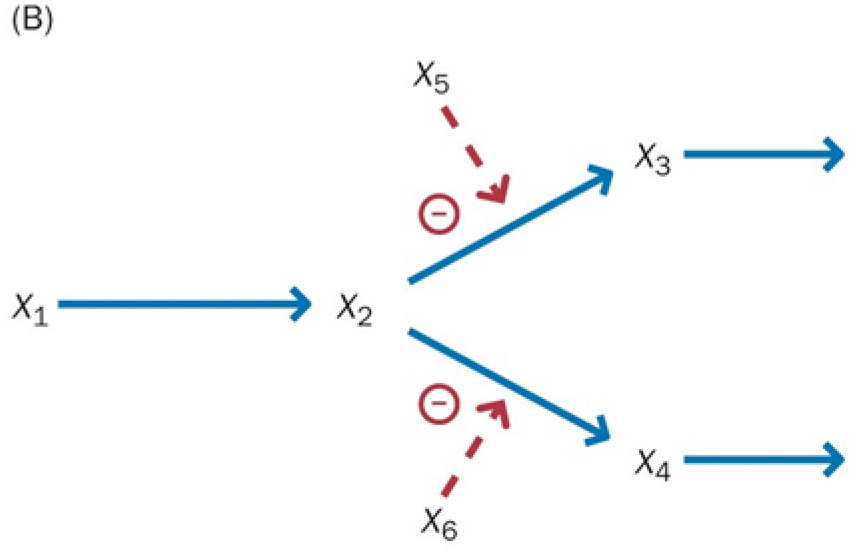
Model Structure

Detail required:

- Correlative
- Explanatory

- Open/closed
- Continuous/discrete





Model Structure

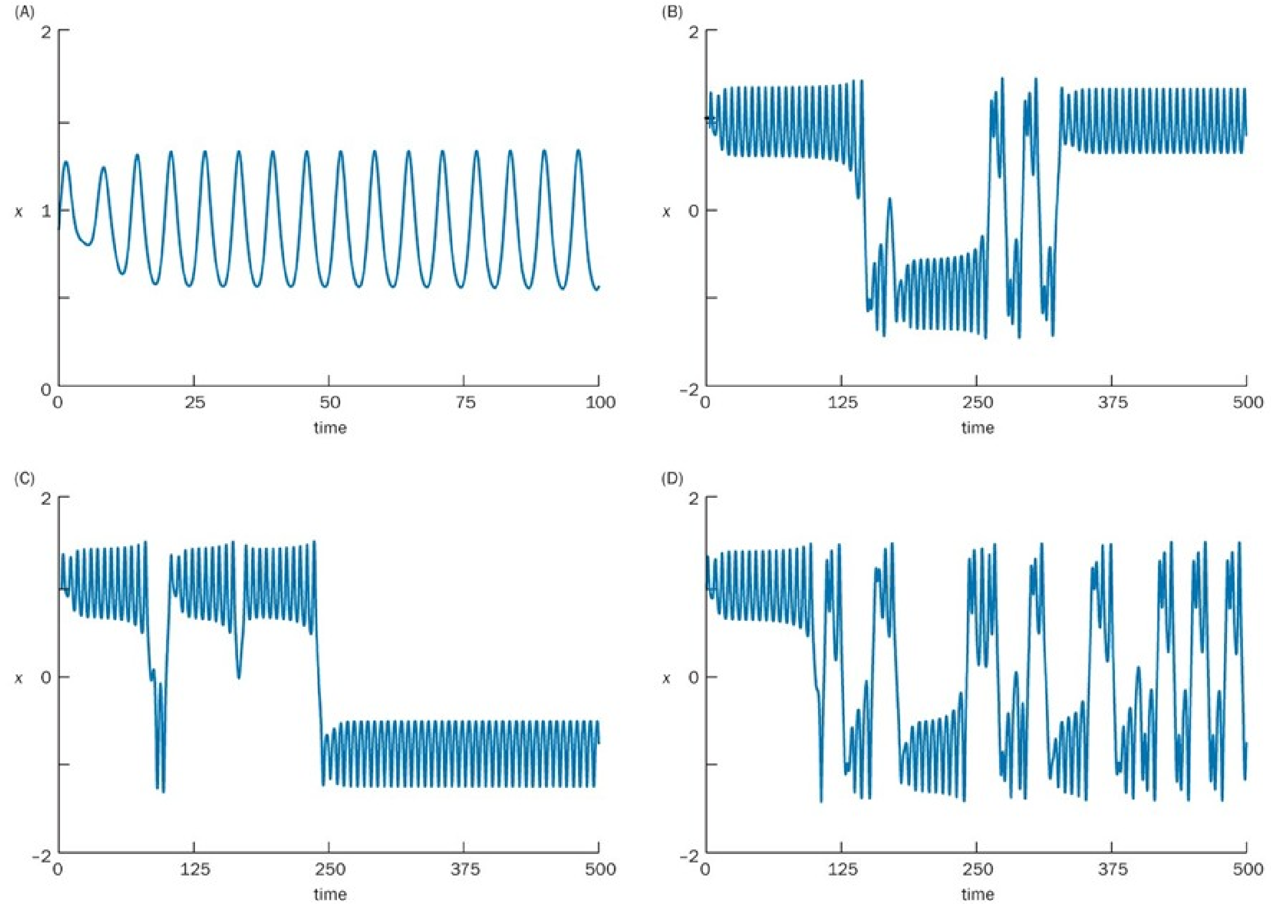
Detail required:

- Deterministic *vs*. stochastic/probabilistic

$$\frac{dx}{dt} = y,$$

$$\frac{dy}{dt} = x - x^3 - 0.25y + A\sin t$$

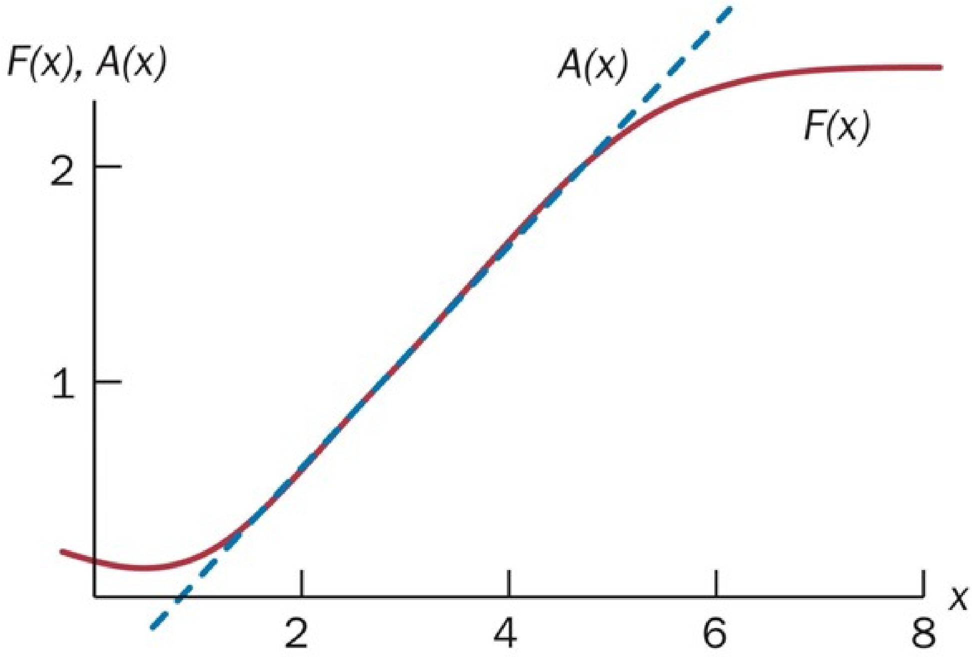
X_0=0.9, y_0=0.4, A=0.26**45**



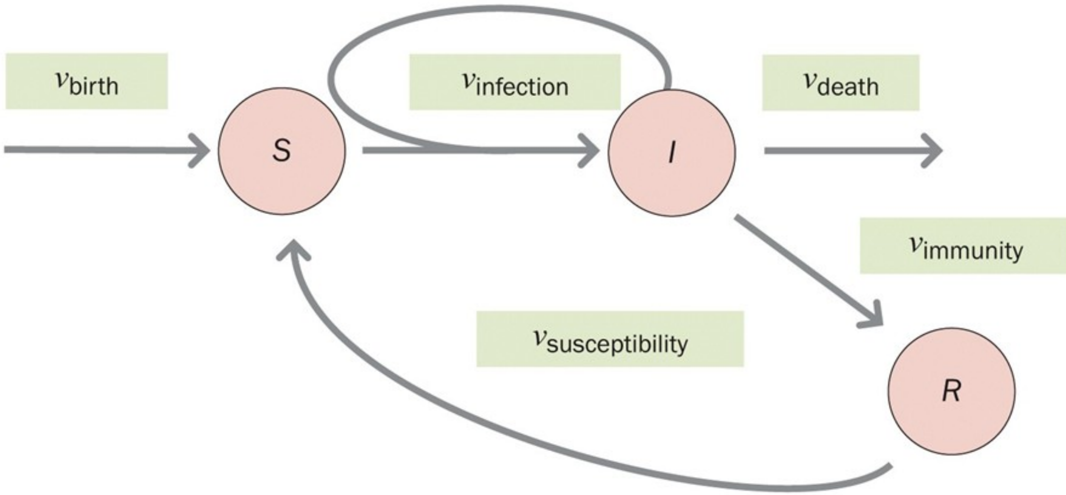
X_0=0.9, y_0=0.4, A=0.26**50**

Model Structure

- Approximations



System Components



Model for disease spread within a population

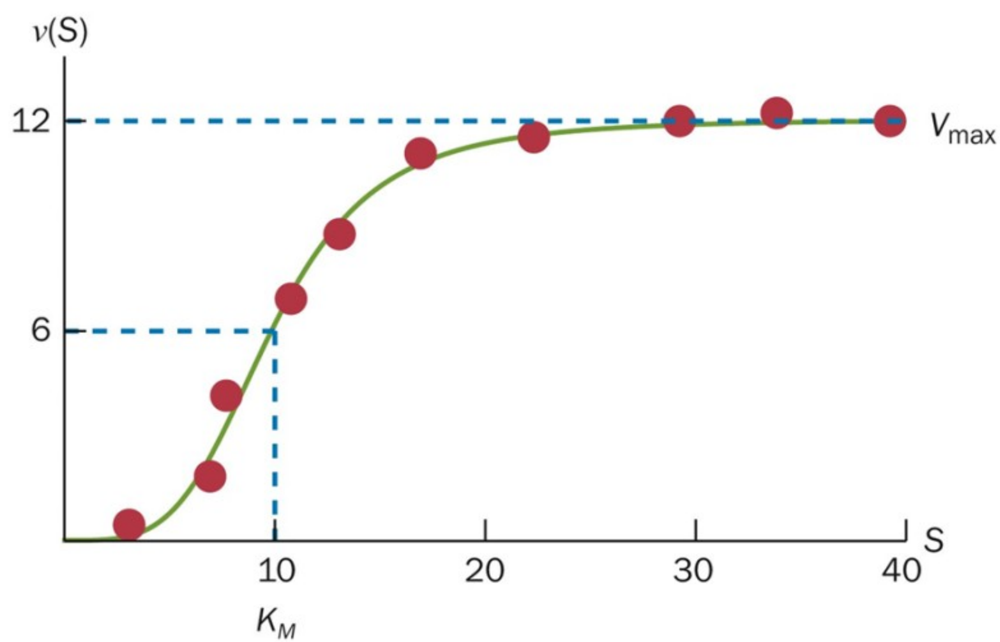
Once model is ready with its components and processes, model equations can be chosen (such as **SIR*** model) resulting in parameter estimation

*SIR: **Susceptible**, **Infected** and **Recovered**

System Components

Parameter estimation

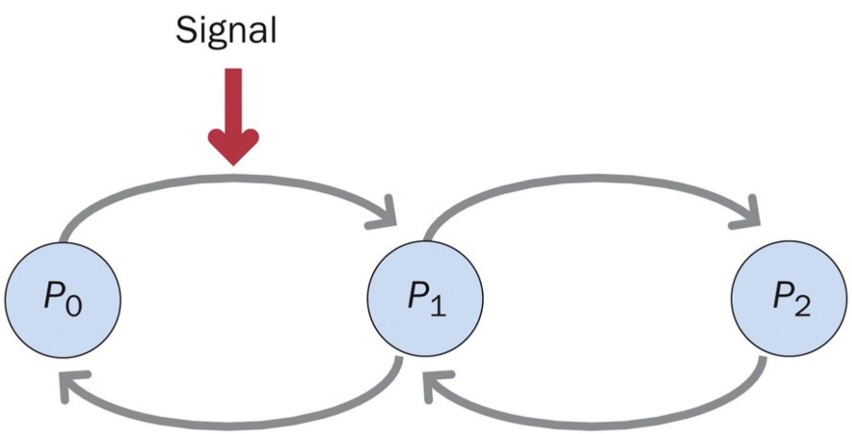
Hill's equation: $$v(S) = \frac{V_{\max} S^n}{K_M^n + S^n}$$



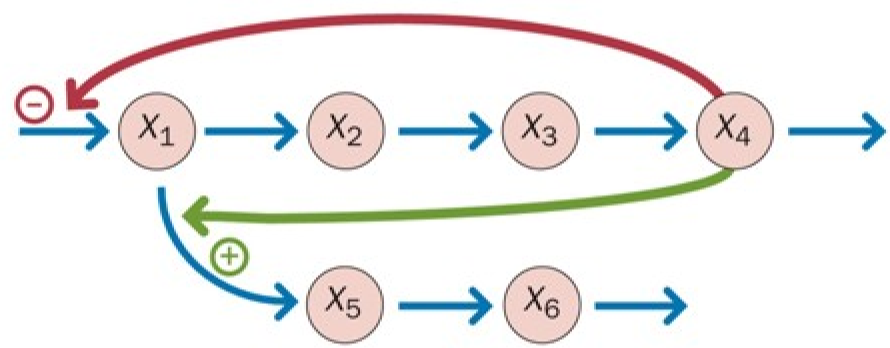
System Components

System Components:

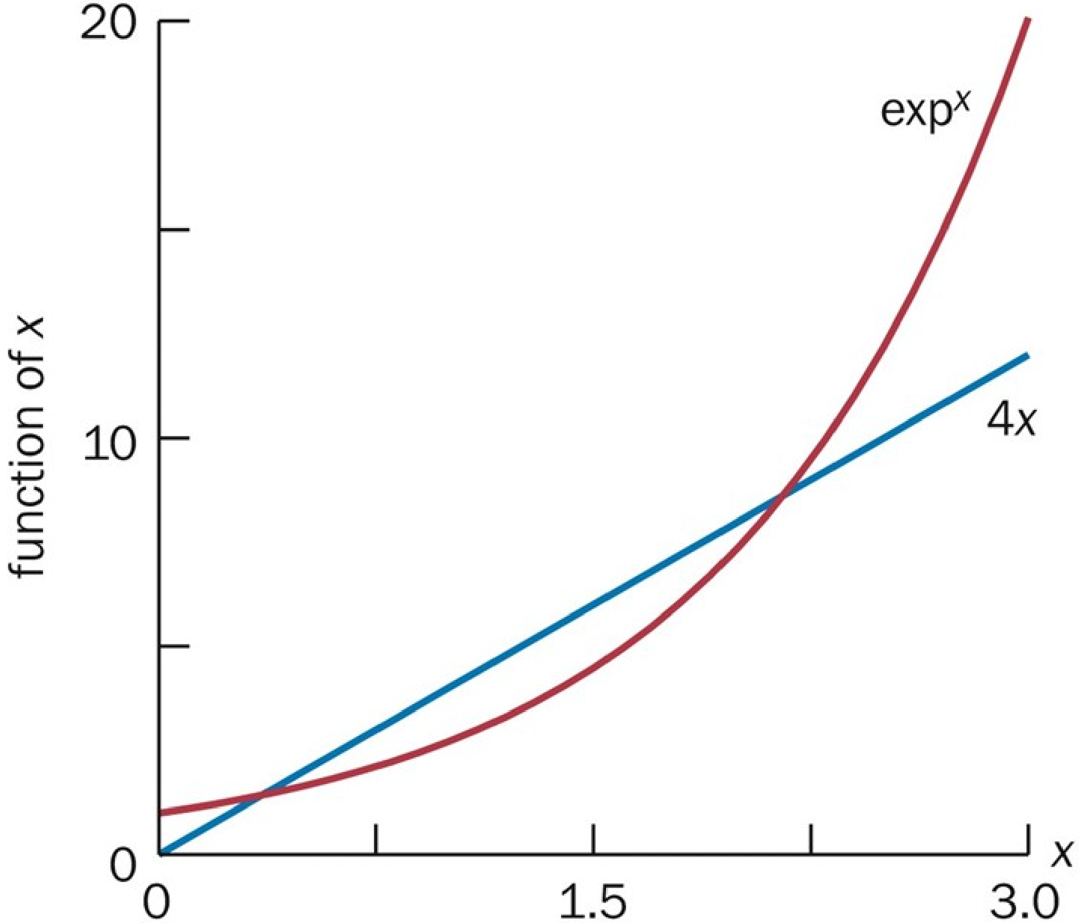
- Multivariate system (*variables* such as genes, cells, individuals, *etc.*)
- Processes and interactions (involve and connect variables)
- Parameters (numerical characteristics *viz*, pH, temperature, turnover rate, *etc.*)
- Universal constants (e, π, *etc.*)



Dependents *vs.* independent variables
Feedback: Inhibition *vs.* activation



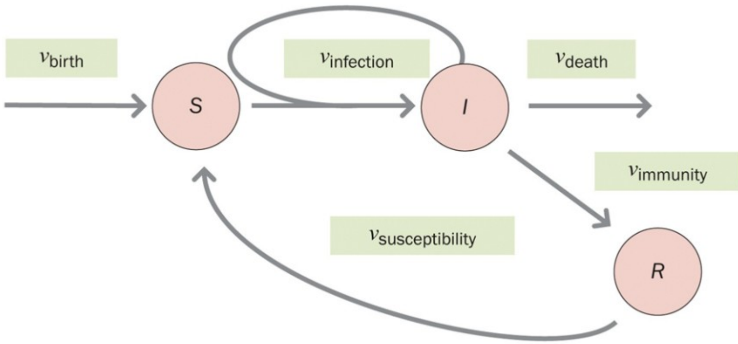
Model Analysis and Diagnosis

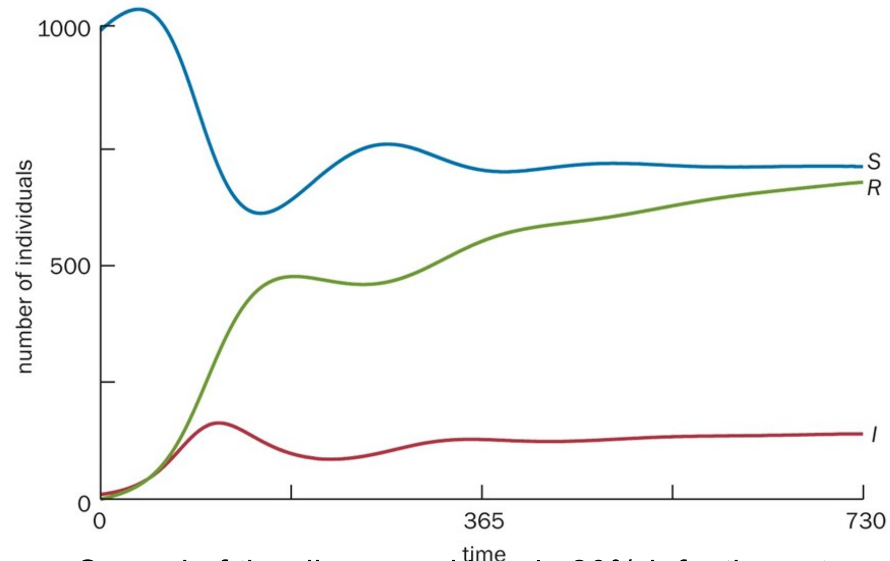


$$e^x - 4x = 0$$

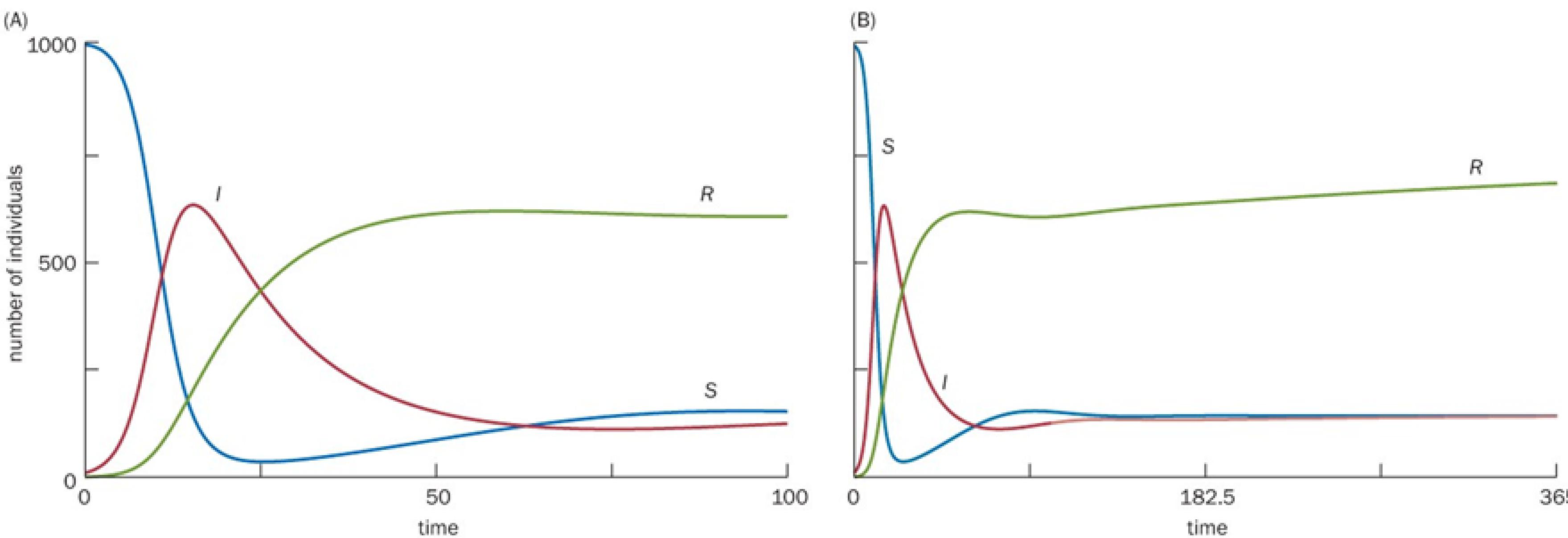
Computer simulations can be used for model evaluation

Model Extensions and Refinements





Spread of the disease with only 20% infection rate

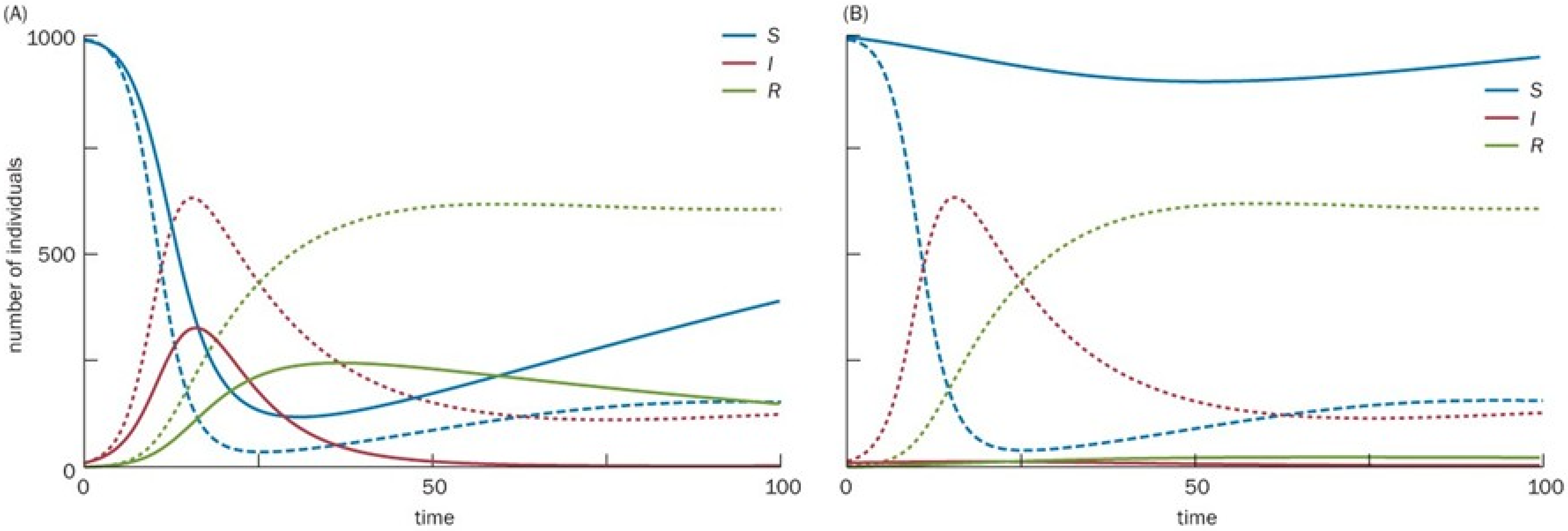


Spread of infectious disease over 100 days and over an year

Exploration and Validation of Dynamical Features

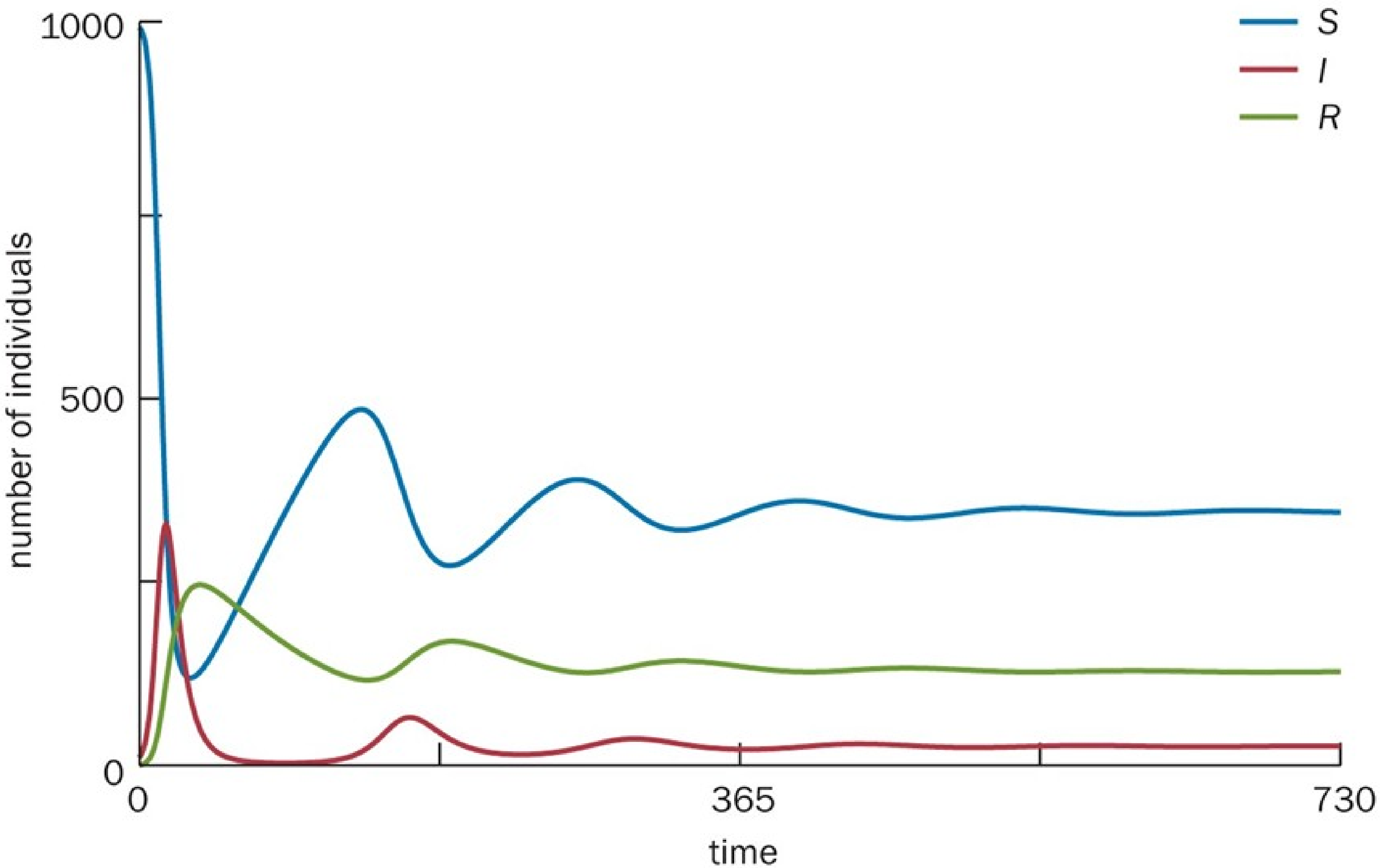
TABLE 1: DECREASE IN THE NUMBER OF INFECTIVES IN THE SYSTEM WHEN THE CONTINUOUS QUARANTINING RATE IS $r_Q = 0.1$; THE DECREASE ROUGHLY CORRESPONDS TO 10% PER TIME UNIT

t	0	1	2	3	4	5	6	7	8	9	10
I	100	90.48	81.87	74.08	67.03	60.65	54.88	49.66	44.93	40.66	36.79

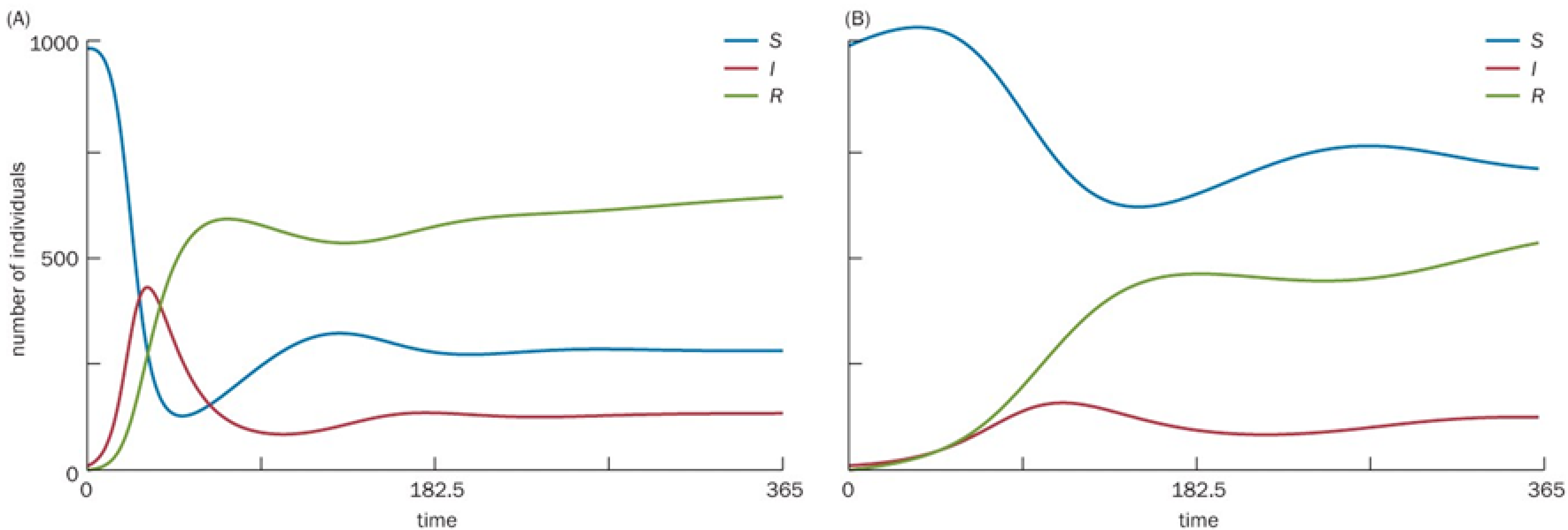


Results of two different quarantine rates (0.1 and 0.4) compared with no quarantine rate (dotted lines)

Model Use and Applications



Quarantine may lead to further outbreaks



Change in infection rates to 50% and 20% of original values give different results *wrt* quarantining