Bio 595

Computers in Biomedical Research

Class notes set 8

Fall 2003

Simulation

A model is a representation of a real system using words, diagrams, mathematical equations

All of science deals with the creation, evaluation, and verification of models of nature

Examples: Bohr model of the atom, Watson-Crick DNA helix, enzyme lock and key model, metabolic pathways

Mathematical Models

Can be simple (with one dependent variable in an explicit equation)

Can be complex, with simultaneous equations and mutually dependent variables ("multi-component" models)

Two ways mathematical models are implemented:

by theoretical derivation and simulation

by empirical derivation through statistical analysis

Mathematical Models

In computer simulation using mathematical models -

1 Simulate data and compare real with calculated results

2 Use graphical rather than tabular output so program results are understandable

Creating a Simulation

Sequence of steps in creating a model

1 analyze the system you want to simulate; determine basic components required for the model (draw a block diagram)

2 Define key variables in the system: express each variable as a function of other system variables and parameters

3 derive the necessary equations either empirically or analytically

4 program the equations into the computer, input the parameters, and run the program

Value of Simulation

Allows quantification of our understanding of a phenomenon, and formulation of hypotheses we can then proceed to confirm (or reject) by using the scientific method.

Developing a math model of a phenomenon allows us to perfect our conceptual model of that phenomenon.

Simulations allow performance of "what if" types of experiments.

Computer simulations are an important teaching tool.

In business, "what if" capabilities are an important part of spreadsheet power, allowing changes to be made in a value to see what happens to the results.

Simple Models

A single explicit equation can serve as an analog or model of a simple process.

Almost any biological process can be described by a response curve relating amplitude of response to stimulus magnitude: a cause-and-effect relation

Multi-component Models

These are grouped sub-models or modules with multiple interdependencies.

Each module can be developed independently and validated

A single component may consist of subcomponents: a hierarchy of structure

Developing Empirical Models

- Get experimental data to see the actual response of the system to a given stimulus
- Get a math formula which responds the same way
- Use this equation to simulate the system’s performance under untested as well as experimentally tested conditions, to validate the model
- Such models don't depend on a theoretical understanding of the processes involved

Developing Empirical Models

To develop a simple empirical model

1. observe or record the actual cause (stimulus) and effect (response) relationship of a real-world system.
2. obtain these data as a y (output) vs. x (input) graph; next, reduce to equation of the form y = fn(x)
3. find appropriate parameters for coefficients and exponents in the model system, either by trial and error, or by curve fitting.

Analytical Models

Use theoretical understanding of phenomenon to develop an equation to predict the system's behavior

Both of these model types can be joined to yield final simulation.

Do a Simulation

To do a simulation you need to

program the computer to simulate data from model equations;

know basic curve shapes fundamental to modeling;

know how to fit curves to data using commercial software like CricketGraph;

know how to perform simple numerical integration

Example of a Simple Model

Population growth (e.g., yeast growth).

Population growth is a function of population density: the more yeast or bacteria, the faster they grow (assuming that there is adequate nutrient):

growth = fn (population density), or

$$G = f(N)$$

Assume that growth is in direct proportionality to the number of cells, then the growth rate equation can take the form

$$G = kN$$

Example

The curve for this equation is a straight line with slope = k. This equation is of limited interest: what we really want is the population size at any time during the growth process, rather than the growth rate. To get this we must rewrite the equation as a differential equation in which growth rate is appropriately expressed as the derivative of population size N as a function of time t, or dN/dt. So the equation now takes the form

$$dN/dt = k\,N$$

Example

Solve this by integrating (that is, we're using the equation for the slope of the growth curve to derive the equation for the growth curve itself). We collect all terms dealing with the dependent variable N on the left side of the equation, and the independent variable and constants on the right side to get

$$\int_{N_0}^{N_t} \frac{dN}{N} = \int_{0}^{t} k\,dt$$

Example

The result of integrating without limits is

$$\ln N = k\,t + c$$

Integrate between limits: take the integral at the upper limit minus the integral at the lower limit, to get

$$\ln N_t - \ln N_o = k * t - k * 0$$

The difference between logs equals the log of a quotient, so we get

$$\ln (N_t/N_o) = k * t$$

Example

Take exponents of both sides of the equation to get

$$Nt/No = e^{k t}$$

or: $$Nt = No * e^{k t}$$

This equation is the classic growth curve: it expresses population Nt at time t as function of initial population No (t = 0) and proportionality constant k (growth rate constant).

To model this on the computer, try values, for example, of k = .02/hour and No = 2/ml; graph N up to t = 50 hours.

Primary Equation Types

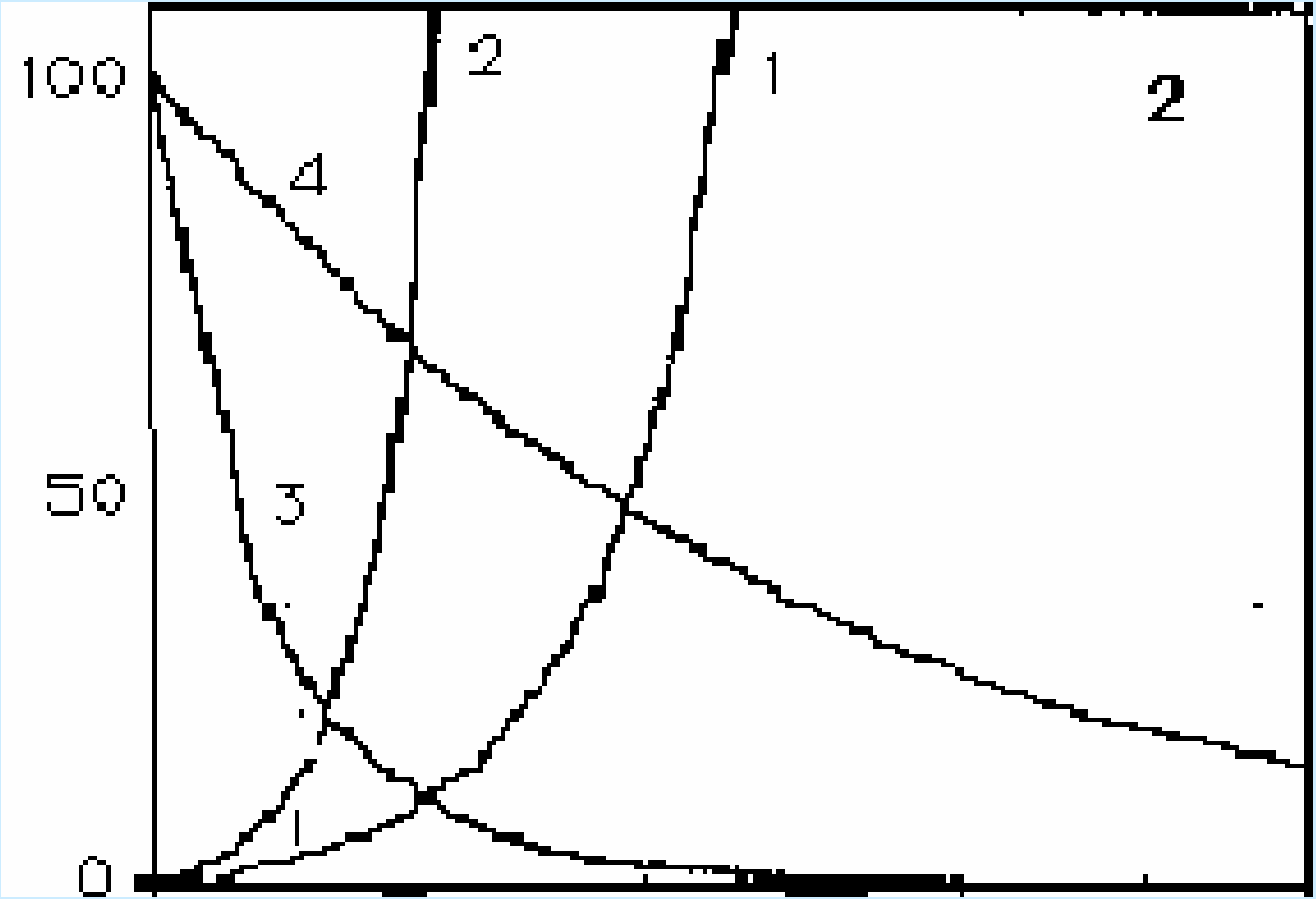
1. Straight line: $y = Ax + B$

2. Exponential: $y = A e^{nx}$

   1: A= 1, n= 0.05 2: A= 1, n= 0.1

   3: A= 100, n= -0.05 4: A= 100, n= -0.01

Exponential



Power, Hyperbola, Saturation

3. Power function: $y = A x^{n}$

1: A=1.5, n=0.7

2: A=100, n=-0.5

3: A=100, n=-0.2

4: A=0.7, n=1.5

4. Hyperbola: $y = A x / (B + x)$

1: A=100, B=50

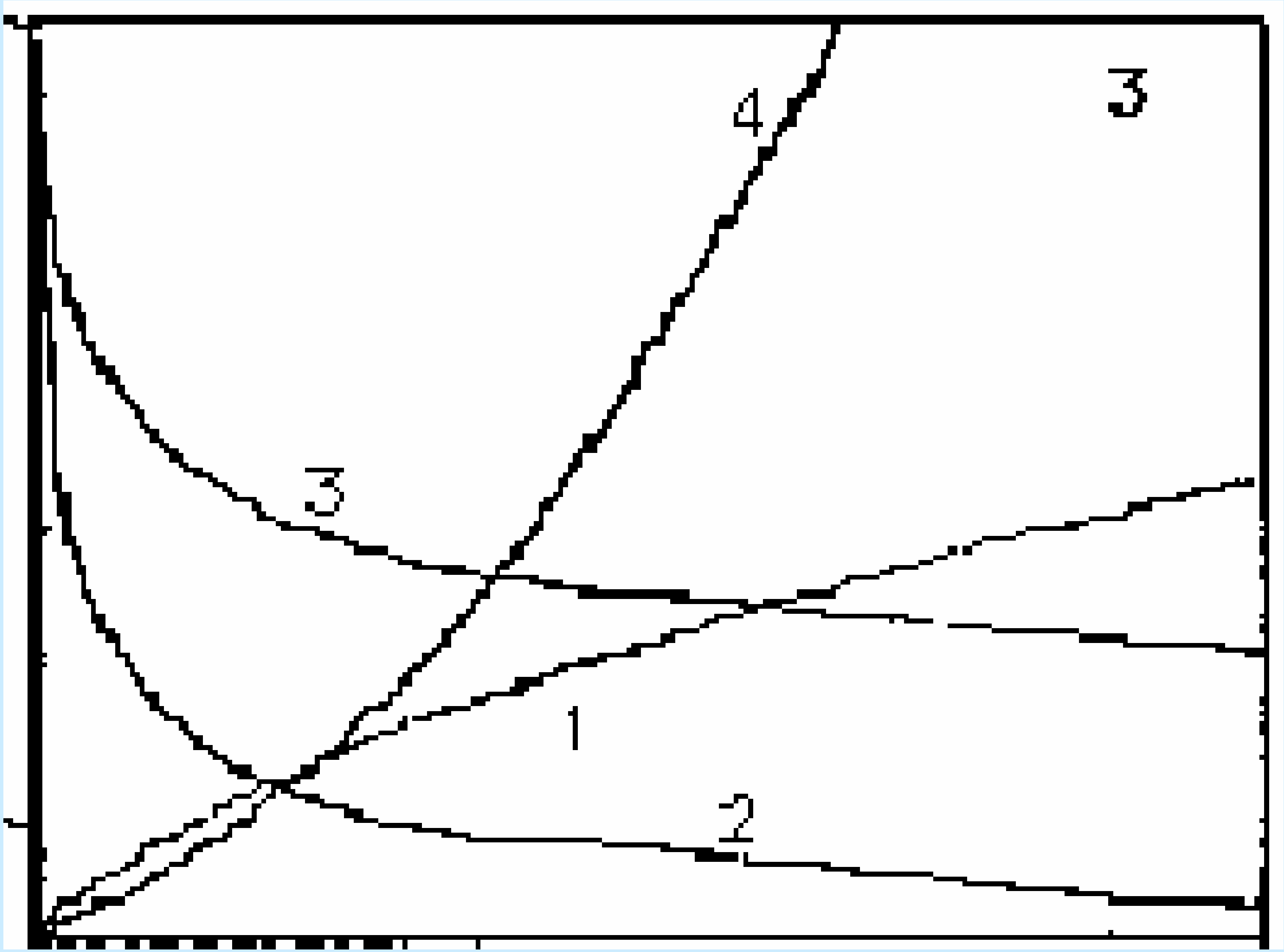
2: A=100, B=20

5. Exponential saturation: y = A (1 - e n x)

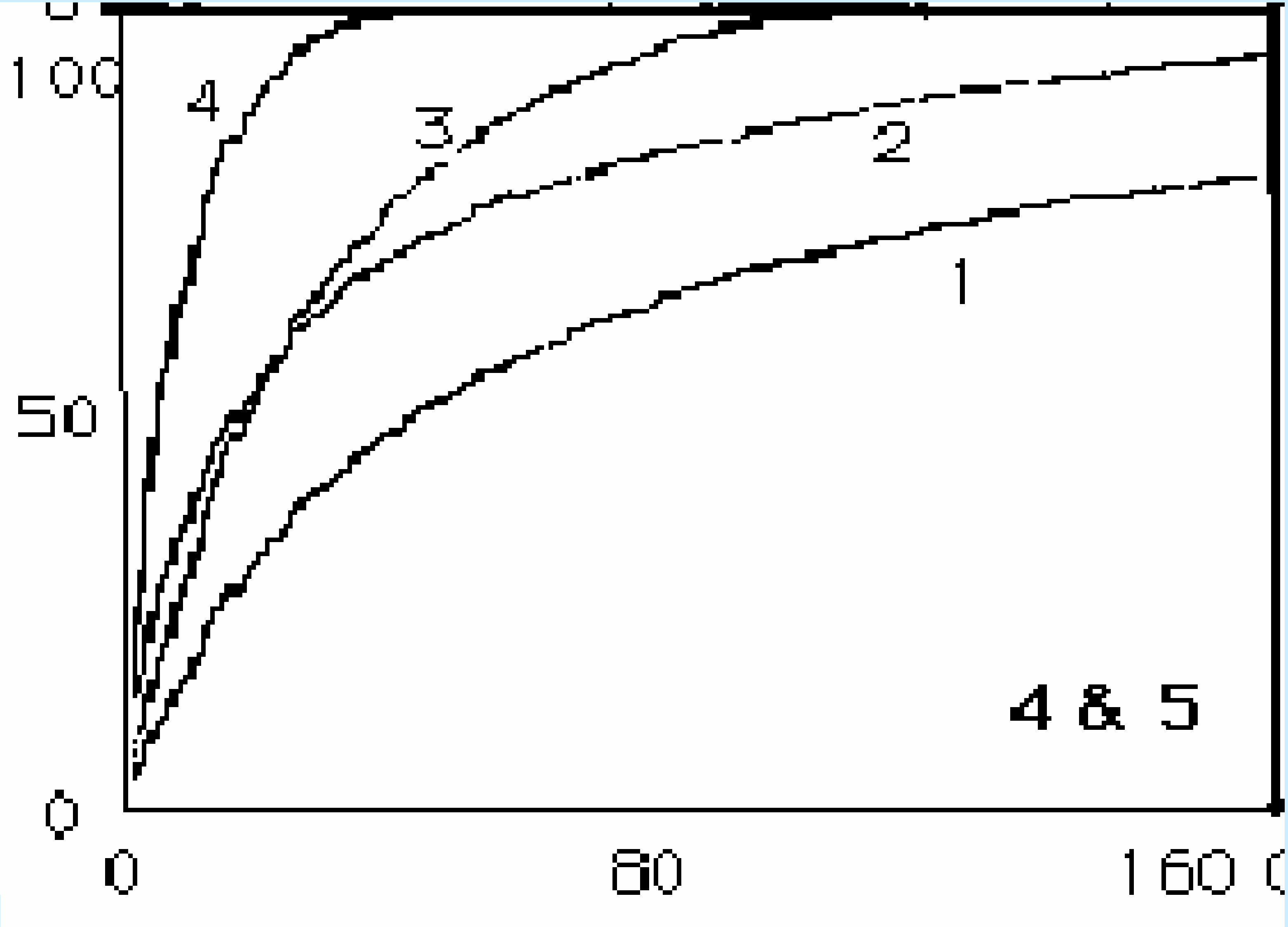
3: A=100, n=-0.1

4: A=100, n=-0.03

Power



Saturation (and Hyperbola)



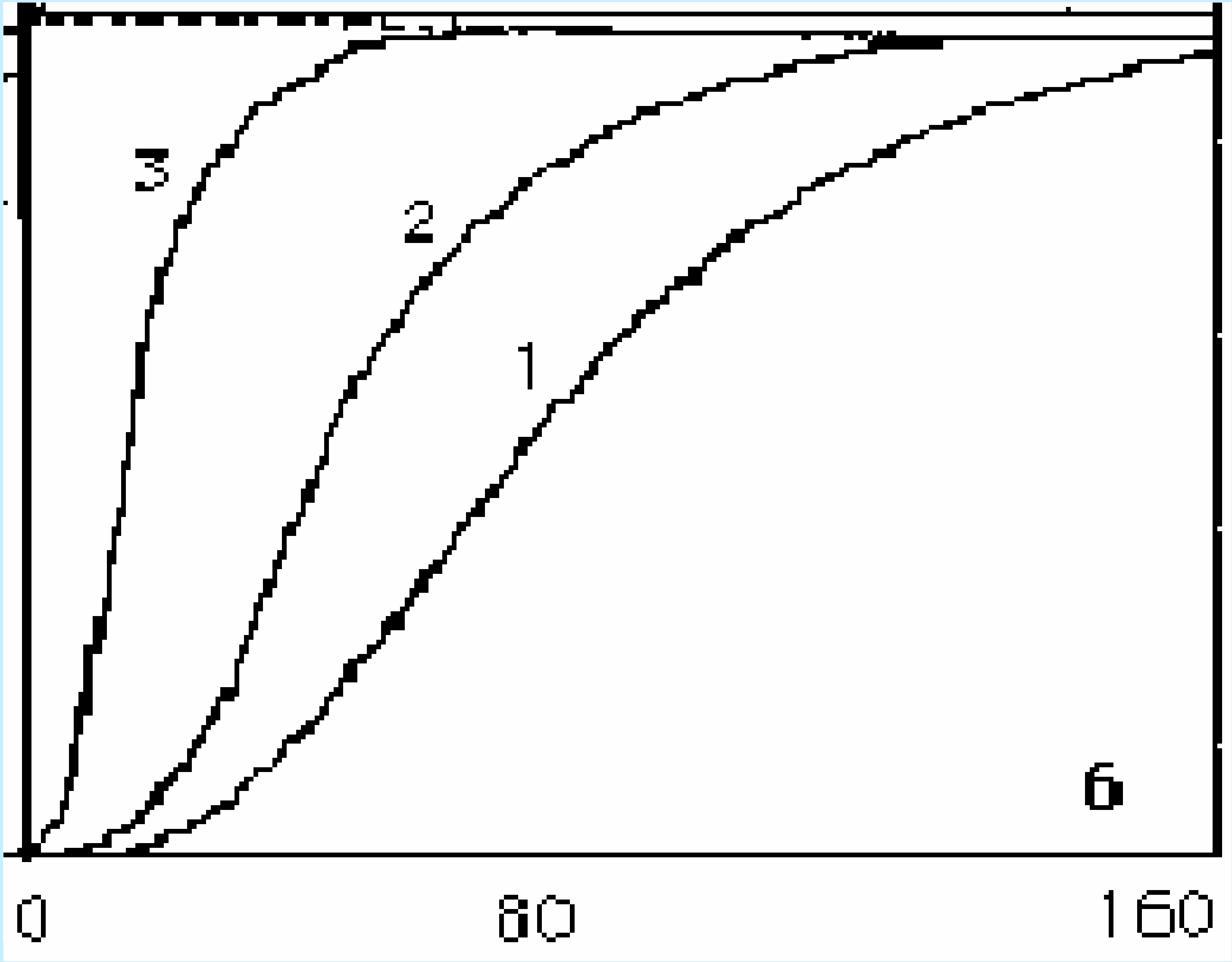
Sigmoid, Inverse

6. Sigmoid: y = A / (1 + B x n)
   1. A=100, n=-3, B=500,000
   2: A=100, n=-3, B=100,000
   3: A=100, n=-3, B=5000

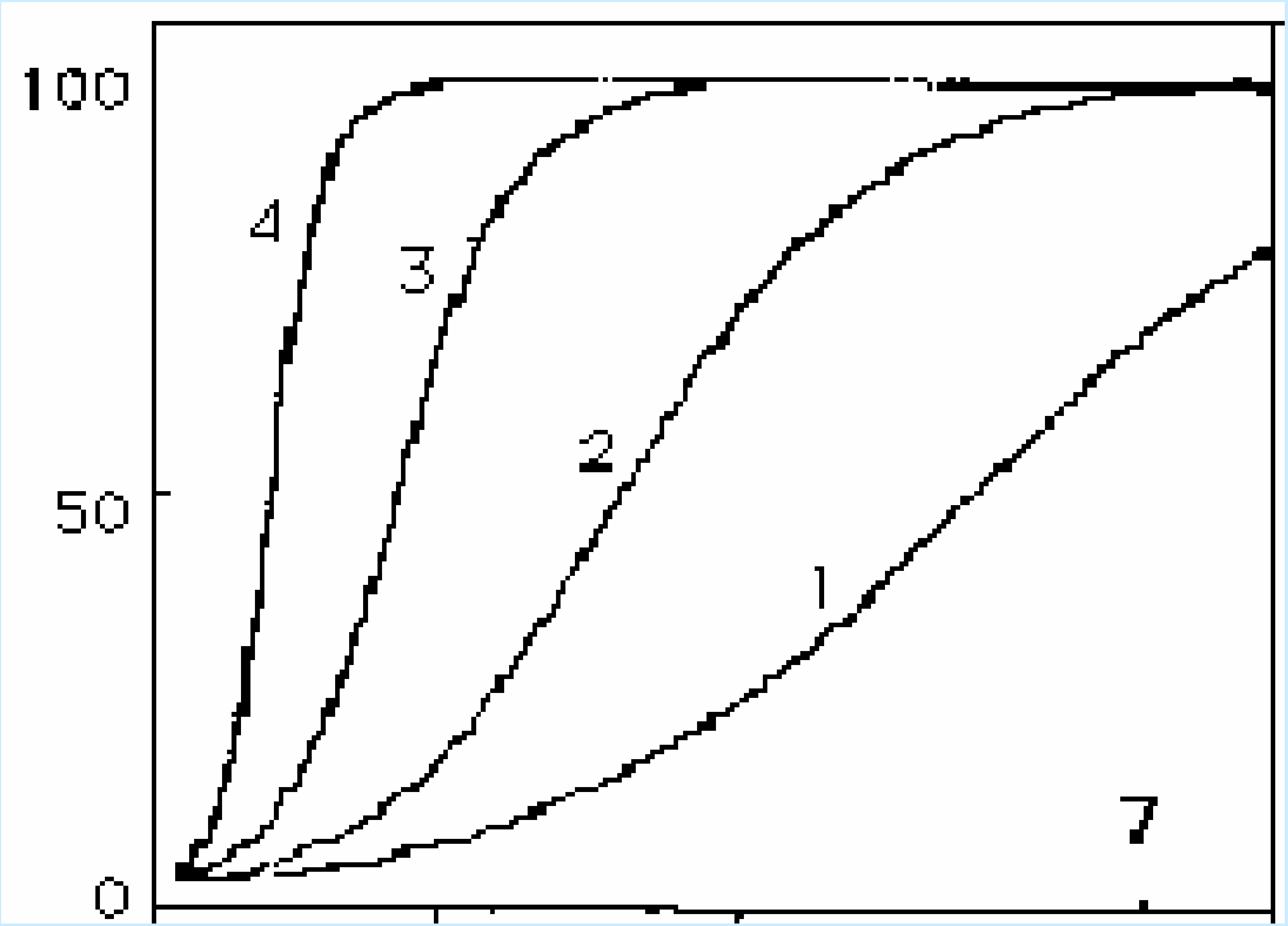
7. Exponential sigmoid: y = A / (1 + B e n x)
   1: A=100, B=50, n=-0.03
   2: A=100, B=50, n=-0.05
   3: A=100, B=50, n=-0.1
   4: A=100, B=50, n=-0.2

8. Modified inverse: y = A / (B + x)
   1: A=2000, B=40 2: A=2000, B=20 3: A=2000, B=0

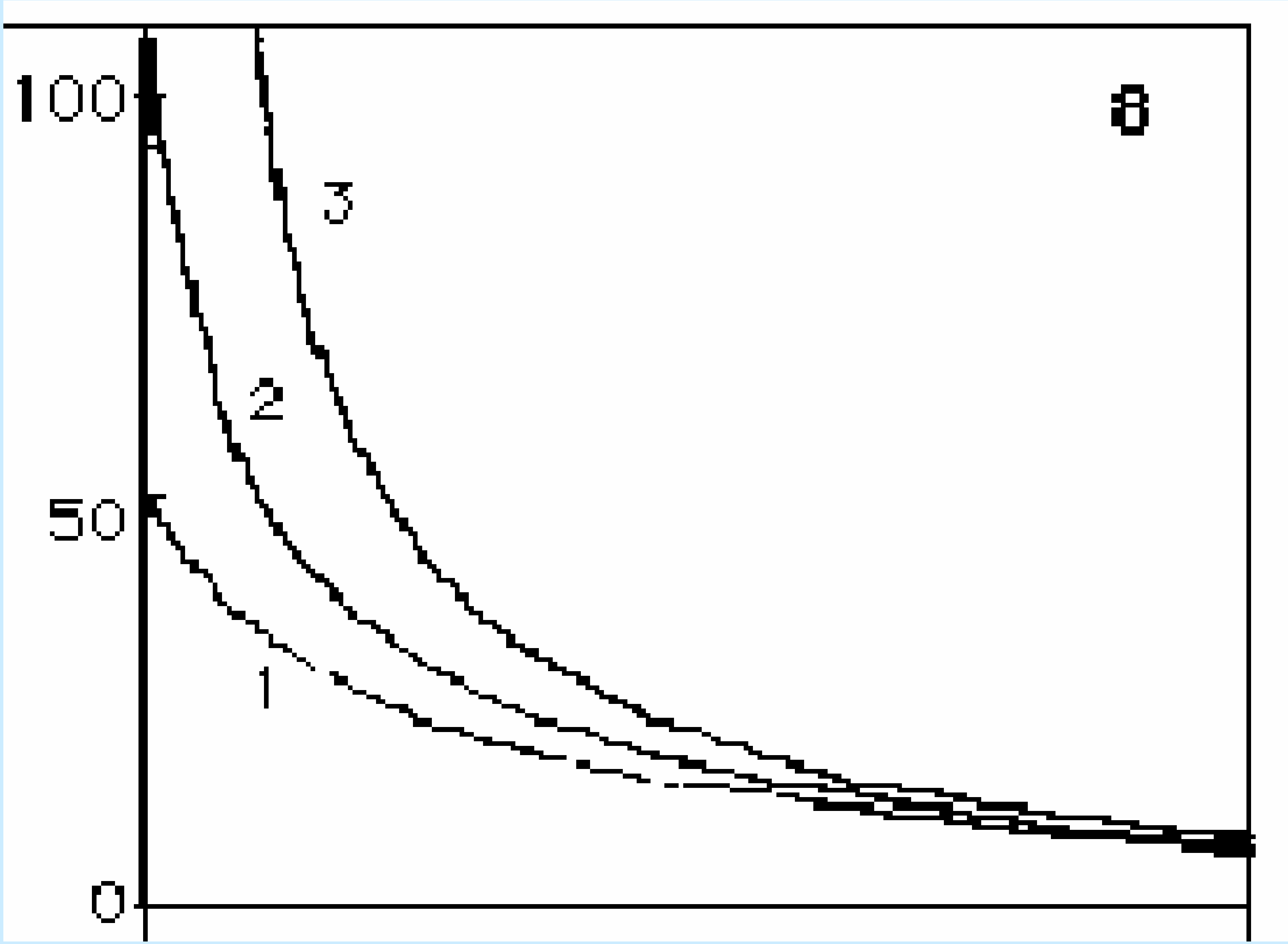
Sigmoid



Exponential Sigmoid



Inverse



Power, Maxima Functions

9. Modified power function: $y = A x^{n} + B$

1: A=0.00001, B=0.25, n=3 2: A=0.001, B=0.25, n=3

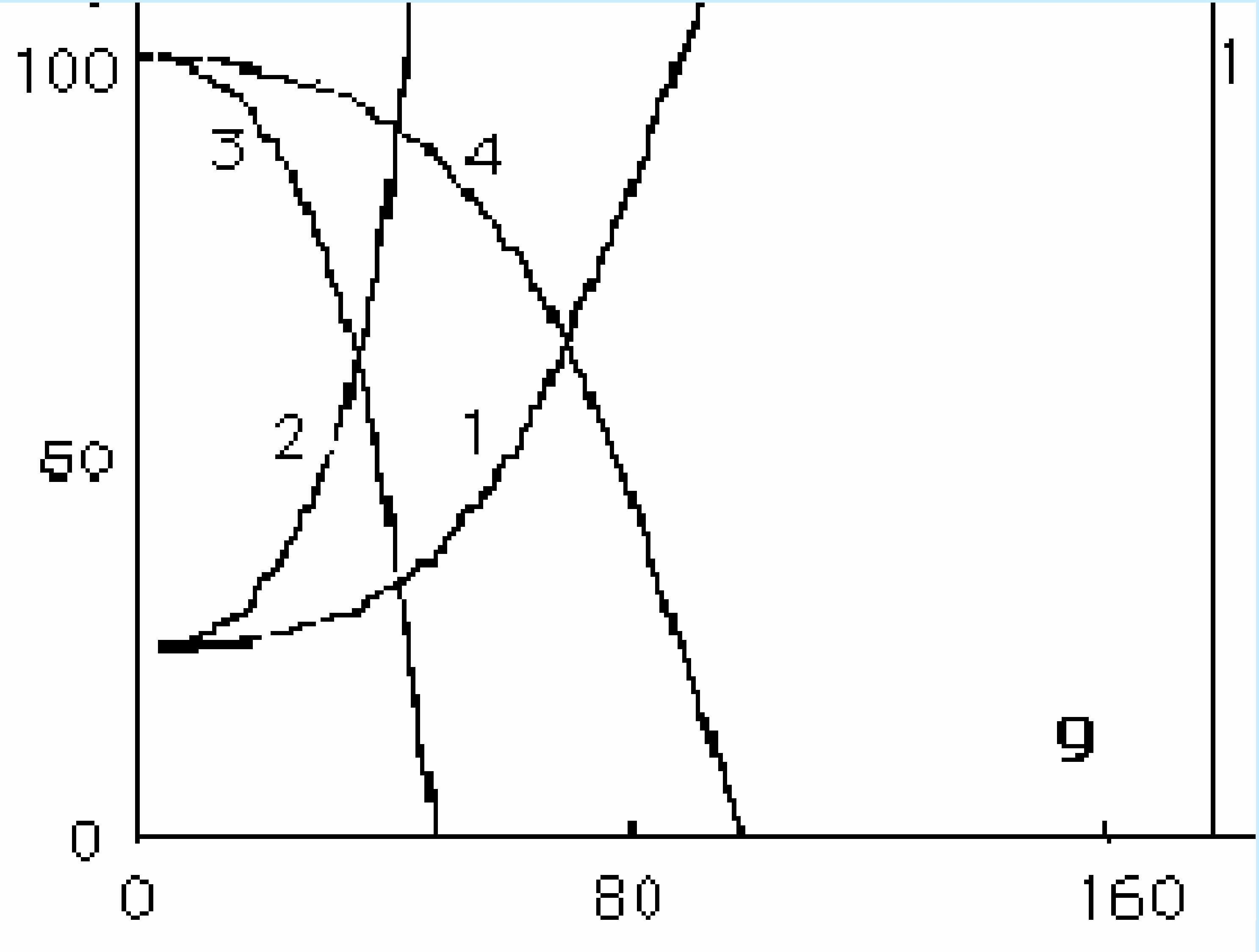
3: A=-0.0001, B=100, n=3 4: A=-0.00001, B=100, n=3

10. Maxima function: $y = A x e^{n x}$

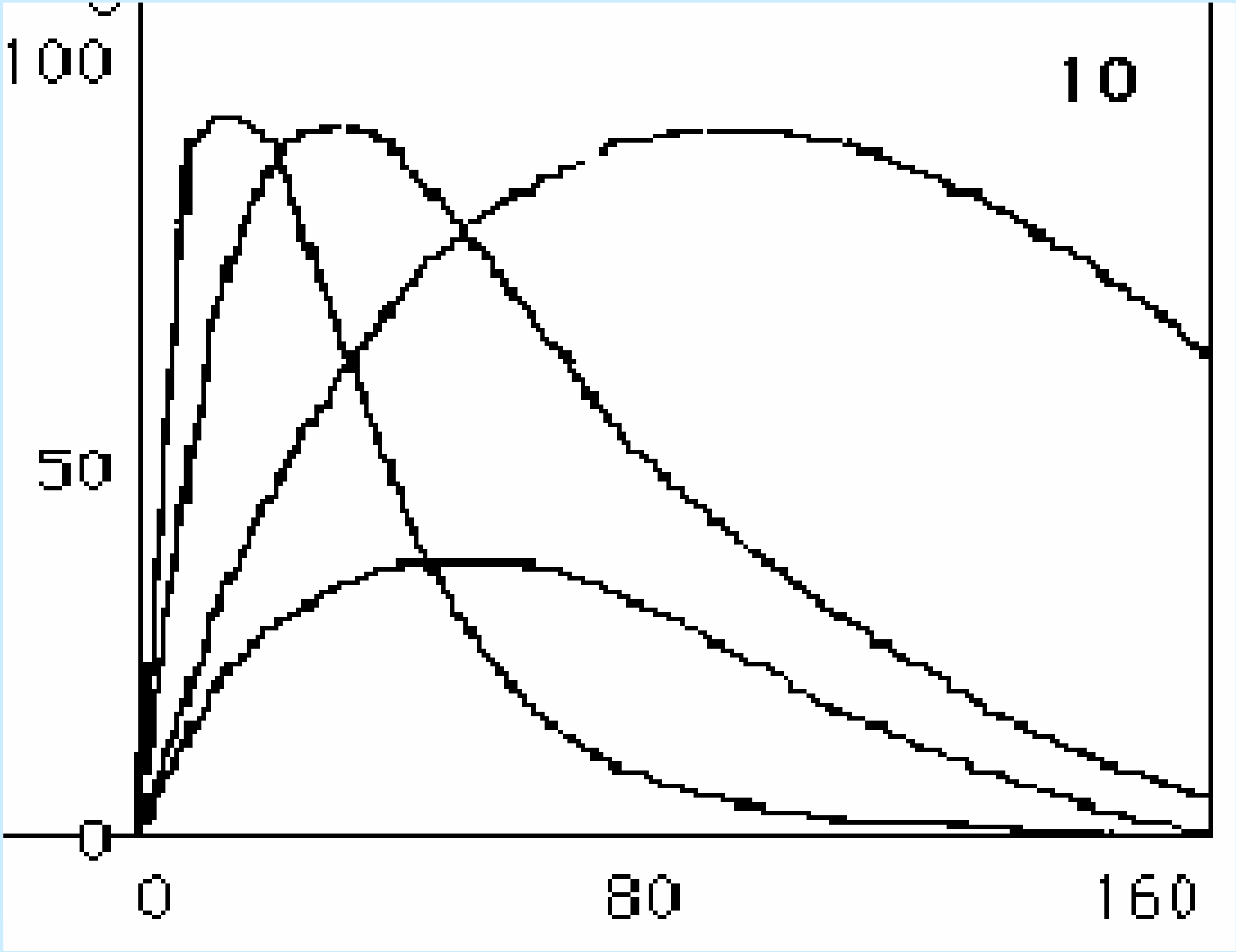
1: A=2, n=-0.02 2: A=2.5, n=-0.01

3: A=7.5, n=-0.03 4: A=15, n=-0.06

Power



Maxima



Compound Equations Curves

Curves showing a maximum or minimum reflect two or more forces competing with each other.

For example, the product of equations (6) and (9) above would yield:

$$y = A/(1+B x^{n}) * (C x^{m} + D)$$

The product of equations (2) and (7) yield:

$$y = e^{nx} * (1 - A e^{mx}) \quad \text{where } m > n$$

To get a minimum, the sum of two equations for exponential growth and exponential decay would yield:

$$y = B e^{-nx} + A e^{mx}$$

Fitting Polynomials to Experimental Data

These functions have little theoretical significance and should be used sparingly.

A commercial program like CricketGraph can fit data to a polynomial, but using this instead of one of the basic curve types may lead to missing an opportunity to begin to understand the underlying basis for a relationship between two variables.