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A First Course in Systems Biology

Chapter 4
The Mathematics of Biological Systems

Basic Models

1. Discrete linear
    - Recursive deterministic
    - Recursive stochastic
2. Continuous linear
    - Linear differential equations
    - Linearized models
3. Discrete nonlinear
    - Difference or Ordinary Differential Equations
4. Continuous nonlinear
    - *Ad hoc* models
    - Canonical models
    - Partial Differential Equations and Agent Based Models

1. Discrete linear systems models

Recursive Deterministic Models

$$P_{t+\tau} = 2P_t$$

$$P_{(t+\tau)+\tau} = 2P_{t+\tau} = 2^2 P_{t+\tau}$$

$$P_{t+n\tau} = 2^n P_t$$

GROWTH OF A BACTERIAL POPULATION							
Time (min)	0	30	60	90	120	150	180
Population size	10	20	40	80	160	320	640

Example:

R_n = #RBCs in circulation on day n
M_n = #RBCs produced on day n
f = Fraction of cells removed by spleen
g = Production rate at bone marrow

$$R_{n+1} = (1-f)R_n + M_n$$

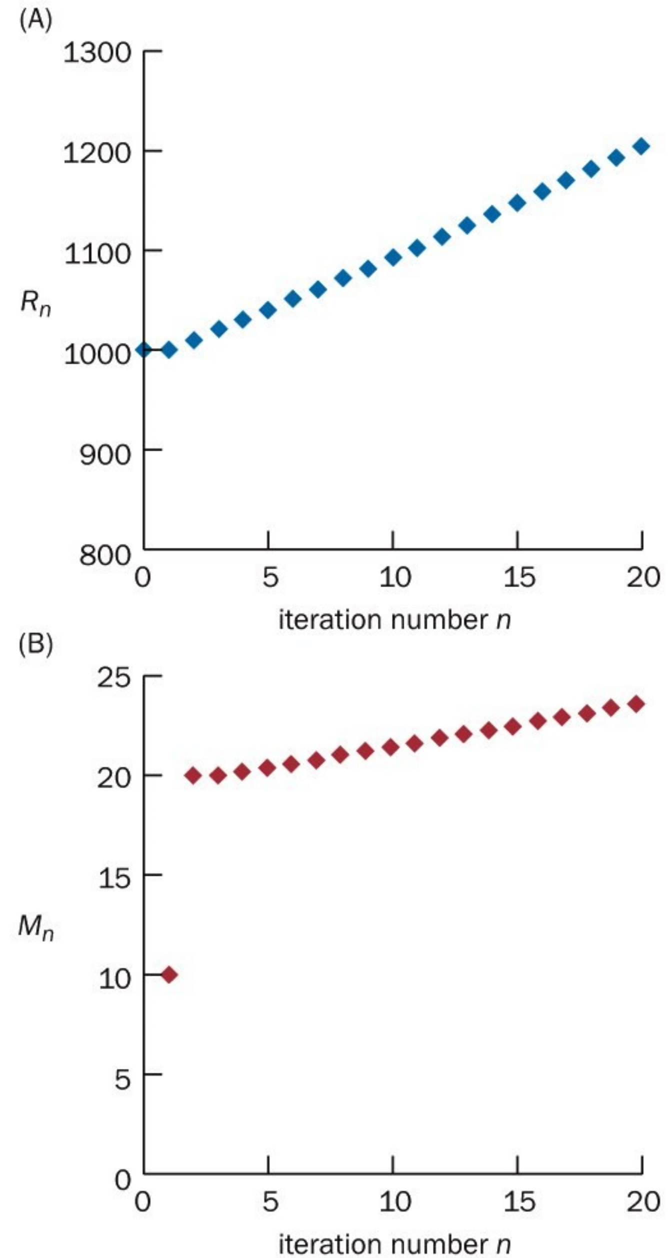
$$M_{n+1} = gfR_n$$

Steady state:

$$R_{n+1} = R_n$$

$$M_{n+1} = M_n$$

$$\begin{pmatrix} R \\ M \end{pmatrix}_{n+k} = \begin{pmatrix} 1-f & 1 \\ gf & 0 \end{pmatrix}^k \begin{pmatrix} R \\ M \end{pmatrix}_n$$



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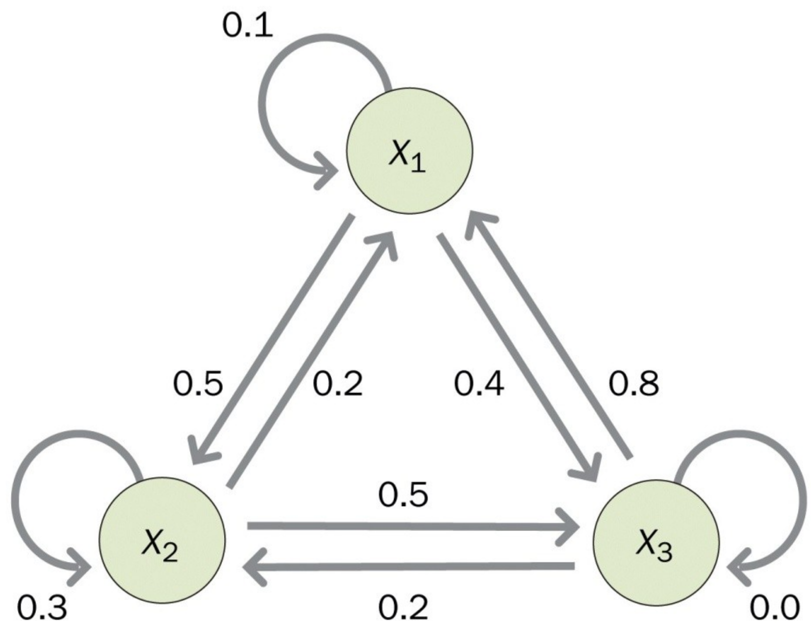
Recursive Stochastic Models

Markov models (Markov chain models):

- Describe a system with *n* states (only)
- At any *discrete* time the system is in one of the *n* states
- Fixed set of probability based transitions between one state to another

$$\mathbf{M} = \begin{pmatrix} 0.1 & 0.5 & 0.4 \\ 0.2 & 0.3 & 0.5 \\ 0.8 & 0.2 & 0.0 \end{pmatrix}$$



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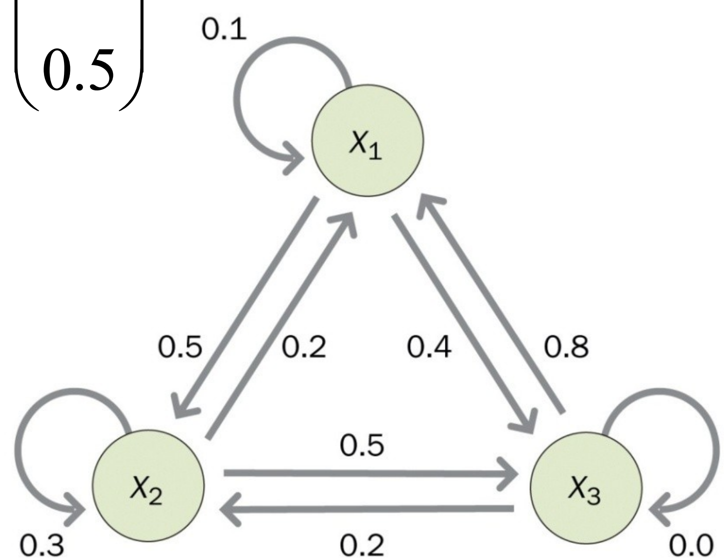
$$\mathbf{M} = \begin{pmatrix} 0.1 & 0.5 & 0.4 \\ 0.2 & 0.3 & 0.5 \\ 0.8 & 0.2 & 0.0 \end{pmatrix} \qquad \mathbf{M}^* = \begin{pmatrix} 0.1 & 0.2 & 0.8 \\ 0.5 & 0.3 & 0.2 \\ 0.4 & 0.5 & 0.0 \end{pmatrix}$$

If the system is in state $\boldsymbol{X_2}$ **at t=0**, probabilities of finding in states X_1, X_2 and X_3 at **t=1** is:

$$\begin{pmatrix} X_1 \\ X_2 \\ X_3 \end{pmatrix}_2 = \mathbf{M}^* \begin{pmatrix} X_1 \\ X_2 \\ X_3 \end{pmatrix}_1 = \begin{pmatrix} 0.1 & 0.2 & 0.8 \\ 0.5 & 0.3 & 0.2 \\ 0.4 & 0.5 & 0.0 \end{pmatrix} \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix} = \begin{pmatrix} 0.2 \\ 0.3 \\ 0.5 \end{pmatrix}$$



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2. Continous linear systems models

DEFINITION: Ordinary Differential Equation

An nth-order ordinary differential equation is an equation that has the general form

$$F(x, y, y', y'', ..., y^{(n)}) = 0 \tag{5}$$

where the primes denote differentiation with respect to x, that is, $y' = dy/dx$, $y'' = d^2y/dx^2$, and so on.

Quite simply, a **differential equation** is an equation that relates the derivatives of an unknown function, the function itself, the variables by which the function is defined, and constants. If the unknown function depends on a single real variable, the differential equation is called an **ordinary differential equation.** The following equations illustrate four well-known ordinary differential equations.

$$\frac{dy}{dx} + y = y^2 \qquad \text{(Bernoulli's equation)} \tag{1a}$$

$$\frac{d^2y}{dx^2} = xy \qquad \text{(Airy's equation)} \tag{1b}$$

$$x^2\frac{d^2y}{dx^2} + x\frac{dy}{dx} + (x^2 - 4)y = 0 \qquad \text{(Bessel's equation)} \tag{1c}$$

$$\frac{d^2y}{dx^2} - (1 - y^2)\frac{dy}{dx} + y = 0 \qquad \text{(Van der Pol's equation)} \tag{1d}$$

In these differential equations the unknown quantity $y = y(x)$ is called the **dependent variable,** and the real variable, x, is called the **independent variable.**

In addition to ordinary differential equations,[†] which contain ordinary derivatives with respect to a single independent variable, a **partial differential equation** is one that contains partial derivatives with respect to more than one independent variable. For example, Eqs. (1a)–(1d) above are ordinary differential equations, whereas Eqs. (3a)–(3d) below are partial differential equations.

$$\frac{\partial u}{\partial x} + \frac{\partial u}{\partial y} = 0 \qquad \text{(flux equation)} \tag{3a}$$

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} \qquad \text{(heat equation)} \tag{3b}$$

$$\frac{\partial^2 u}{\partial t^2} = \frac{\partial^2 u}{\partial x^2} \qquad \text{(wave equation)} \tag{3c}$$

$$\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} = 0 \qquad \text{(Laplace's equation)} \tag{3d}$$

Differential equations are also classified according to their order. The **order** of a differential equation is simply the *order* of the highest derivative that occurs in the equation.

For example,

$$\frac{dy}{dx} - 3y = 2 \qquad \text{(first-order)} \tag{4a}$$

$$\frac{d^2y}{dx^2} + x\frac{dy}{dx} - 3y = 0 \qquad \text{(second-order)} \tag{4b}$$

$$y\left(1 + \left(\frac{dy}{dx}\right)^2\right) = 0 \qquad \text{(first-order)} \tag{4c}$$

$$\frac{d^4y}{dx^4} - y = 0 \qquad \text{(fourth-order)} \tag{4d}$$

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} \qquad \text{(second-order)} \tag{4e}$$

DEFINITION: Linear Differential Equation

An nth-order ordinary differential equation is **linear** when it can be written in the form

$$a_0(x)\frac{d^ny}{dx^n} + a_1(x)\frac{d^{n-1}y}{dx^{n-1}} + \cdots + a_{n-1}(x)\frac{dy}{dx} + a_n(x)\,y = f(x) \quad (a_0(x) \neq 0)$$

The functions $a_0(x), a_1(x), \ldots, a_n(x)$ are called the **coefficients** of the differential equation, and $f(x)$ is called the **nonhomogeneous term.** When the coefficients are constant functions, the differential equation is said to have **constant coefficients.** Unless it is otherwise stated, we shall always assume that the coefficients are continuous functions and that $a_0(x) \neq 0$ in any interval in which the equation is defined. Furthermore, the differential equation is said to be **homogeneous** if $f(x) \equiv 0$ and **nonhomogeneous** if $f(x)$ is *not* identically zero.

Finally, an ordinary differential equation that cannot be written in the above general form is called a **nonlinear ordinary differential equation.**

Some examples of linear and nonlinear differential equations are the following:

$$\frac{dy}{dx} = xy + 1 \qquad \text{(linear)} \tag{6a}$$

$$\frac{d^2y}{dx^2} + x\frac{dy}{dx} + y^2 = 0 \qquad \text{(nonlinear)} \tag{6b}$$

$$a_0(x)\frac{dy}{dx} + a_1(x)\,y = g(x) \qquad \text{(linear)} \tag{6c}$$

$$a_0(x)\frac{d^2y}{dx^2} + a_1(x)\frac{dy}{dx} + a_2(x)\,y = g(x) \qquad \text{(linear)} \tag{6d}$$

$$\frac{dy}{dx} = -\frac{x}{y} \qquad \text{(nonlinear)} \tag{6e}$$

$$yy'' + y' + y = 1 \qquad \text{(nonlinear)} \tag{6f}$$

Simplest example of growth of cells describing exponential growth or decay using a single *linear differential equation (*along with solution shown in the right) is:

$$\frac{dX}{dt} = \dot{X} = aX \qquad\qquad X(t) = X_0 e^{at}$$

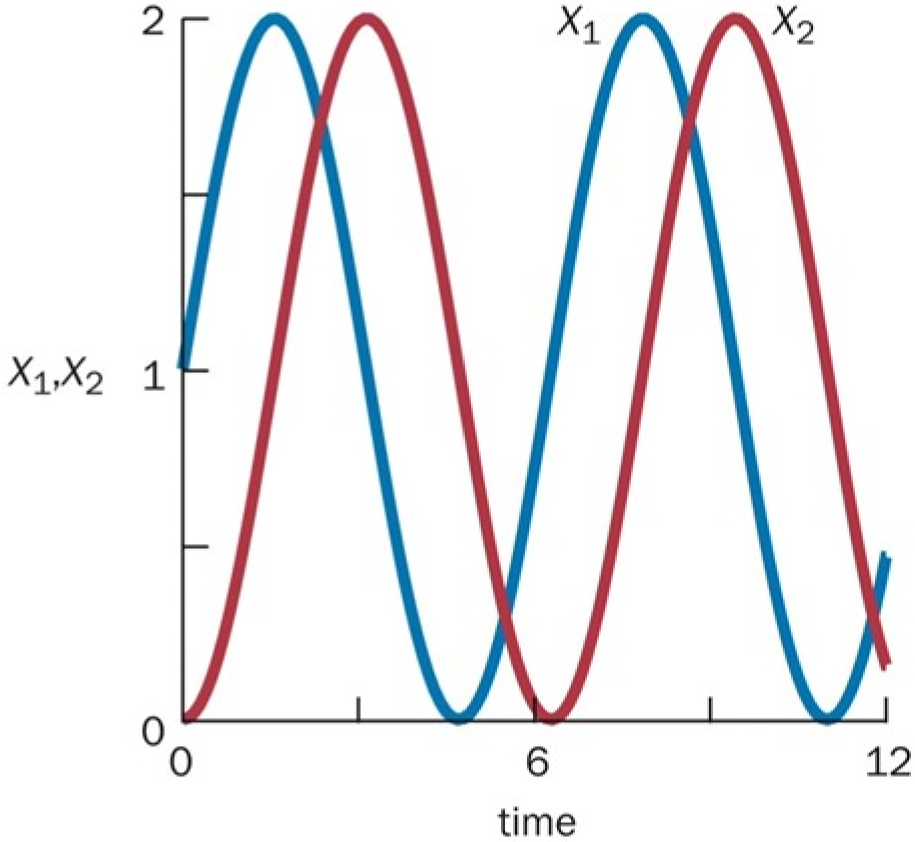
System of linear differential equations with vector **X** and coefficient matrix **A**:

$$\frac{d\mathbf{X}}{dt} = \mathbf{AX}$$

Half life: Time it takes for half of material to be lost.

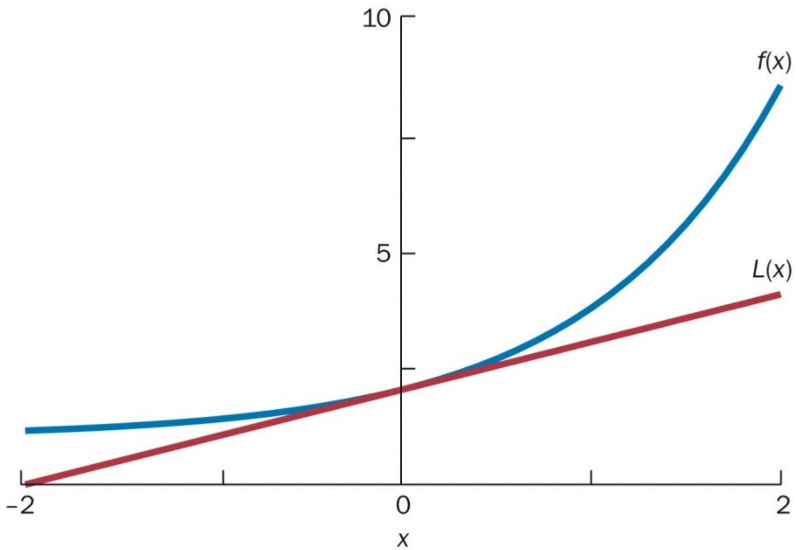
Solutions of the system:

$$\dot{X}_1 = 1 - X_2$$
$$\dot{X}_2 = 1 - X_1$$

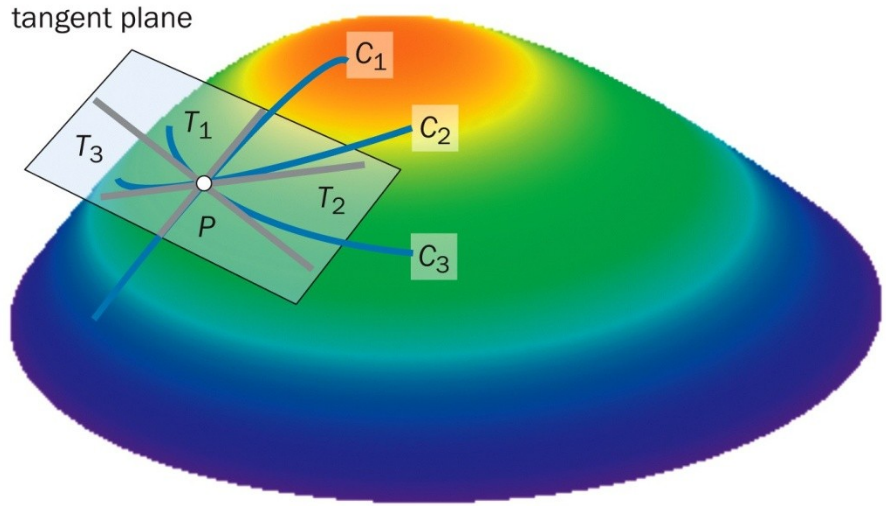


Linearized Models

The approach is to flatten the nonlinear system in a small region around a point of interest called operating point (OP). It is required that the derivatives of the nonlinear system should exist. Analysis can now be done in the tangent plane.



Box 4.1 Figure 1 A First Course in Systems Biology (© Garland Science 2013)



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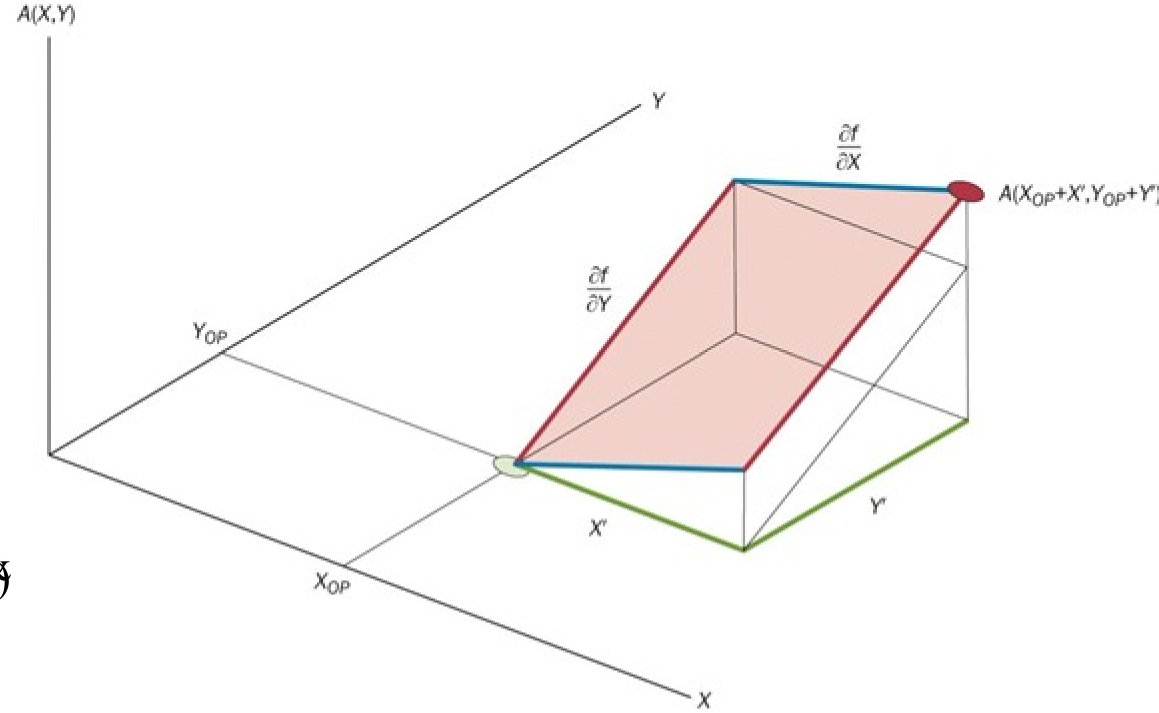
Solutions of the system:



$$\frac{dX}{dt} = f(X,Y)$$

$$\frac{dY}{dt} = g(X,Y)$$

$$\frac{d}{dt}(X_{OP} + \dot{X}) = f(X_{OP} + \dot{X}, Y_{OP} + \dot{Y})$$

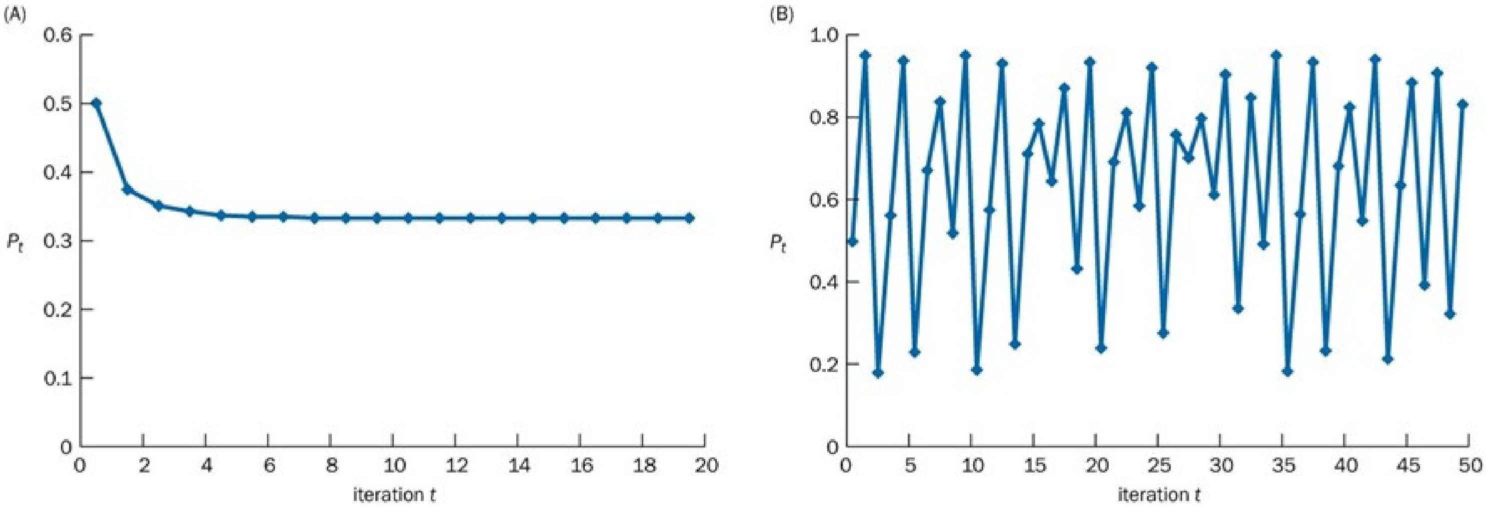
$$\frac{d}{dt}(Y_{OP} + \dot{Y}) = g(X_{OP} + \dot{X}, Y_{OP} + \dot{Y})$$

$$\frac{d}{dt}\begin{pmatrix} X'_1 \\ X'_2 \\ \vdots \\ X'_m \end{pmatrix} = \begin{pmatrix} \frac{\partial f_1}{\partial X'_1} & \frac{\partial f_1}{\partial X'_2} & \cdots & \frac{\partial f_1}{\partial X'_m} \\ \frac{\partial f_2}{\partial X'_1} & \frac{\partial f_2}{\partial X'_2} & \cdots & \frac{\partial f_2}{\partial X'_m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_m}{\partial X'_1} & \frac{\partial f_m}{\partial X'_2} & \cdots & \frac{\partial f_m}{\partial X'_m} \end{pmatrix} \begin{pmatrix} X'_1 \\ X'_2 \\ \vdots \\ X'_m \end{pmatrix}$$

3. Discrete nonlinear systems

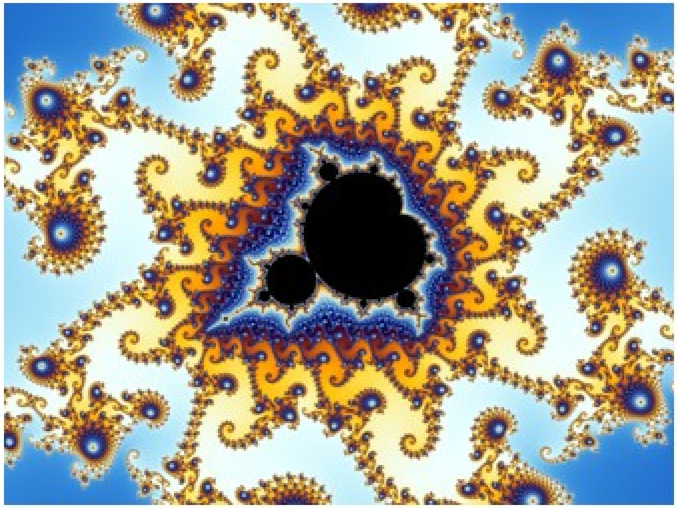
Nonlinear systems can quickly diverge from linear models. Consider **logistic map**. (Logistic map is based on logistic equation (LE) given below):

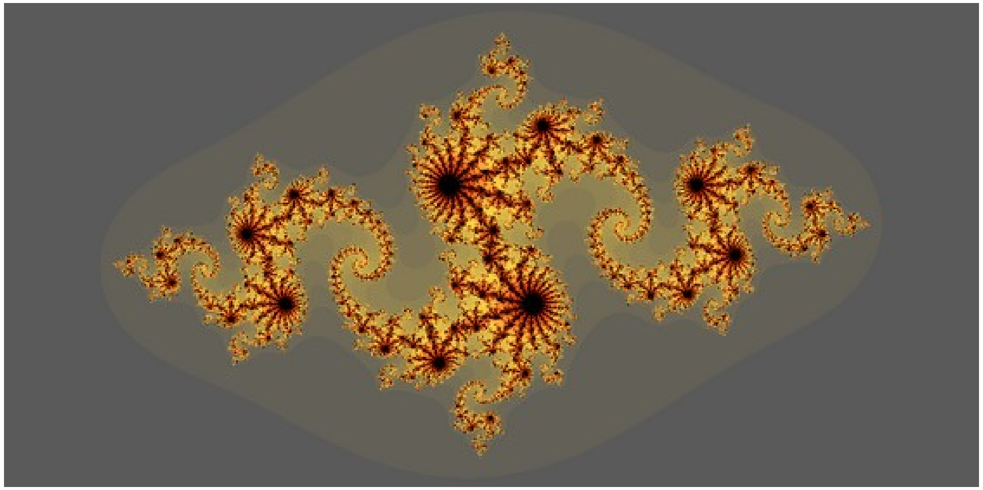
$$P_{t+1} = rP_t(1 - P_t)$$



Two cases: r=1.5 and r=3.8. The second case exhibits chaos.

$$LE: \frac{dN}{dt} = rN(1 - \frac{N}{K})$$

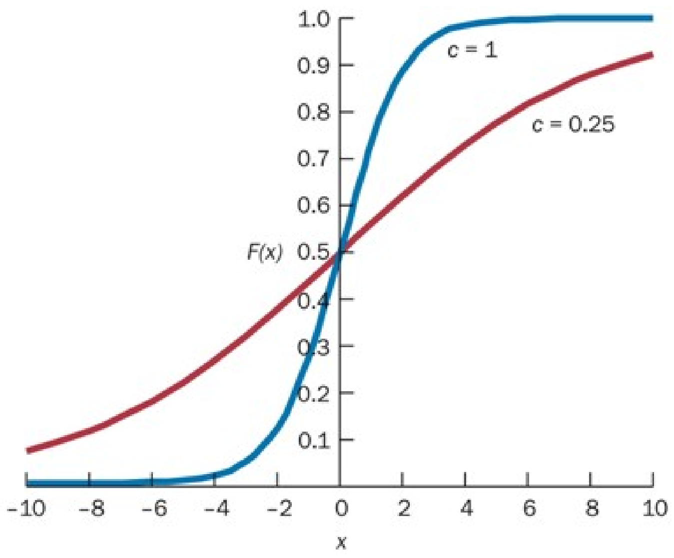



4. Continuous nonlinear systems

***Ad hoc* models**

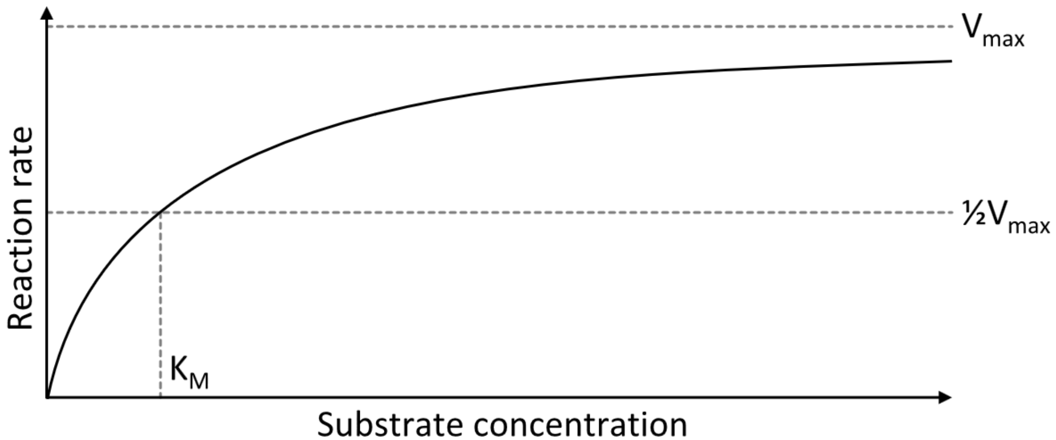
Some models *just* suit a given task!
Consider the logistic equation:

$$F(x) = \frac{a}{b + e^{-cx}}$$



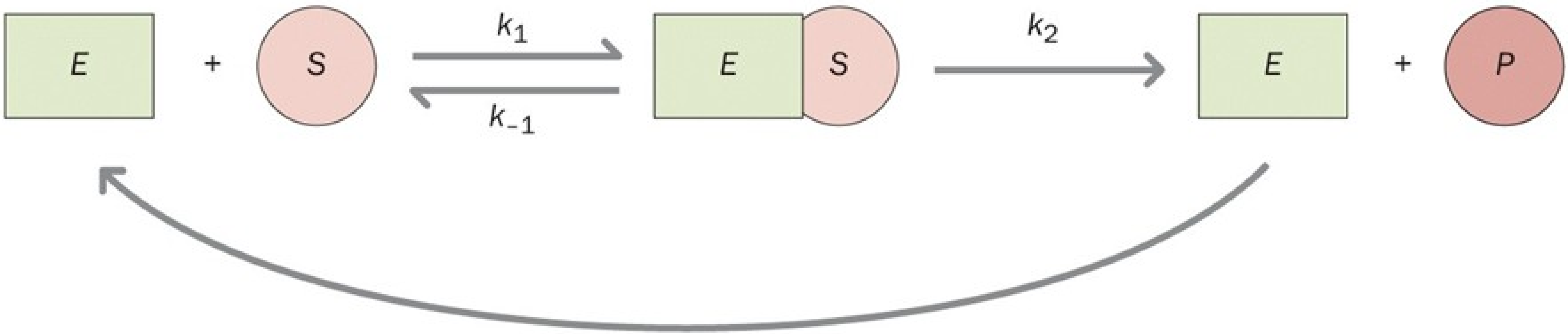
Michaelis-Menten function for enzyme kinetics:

$$v_p = \frac{V_{\max} S}{K_m + S}$$



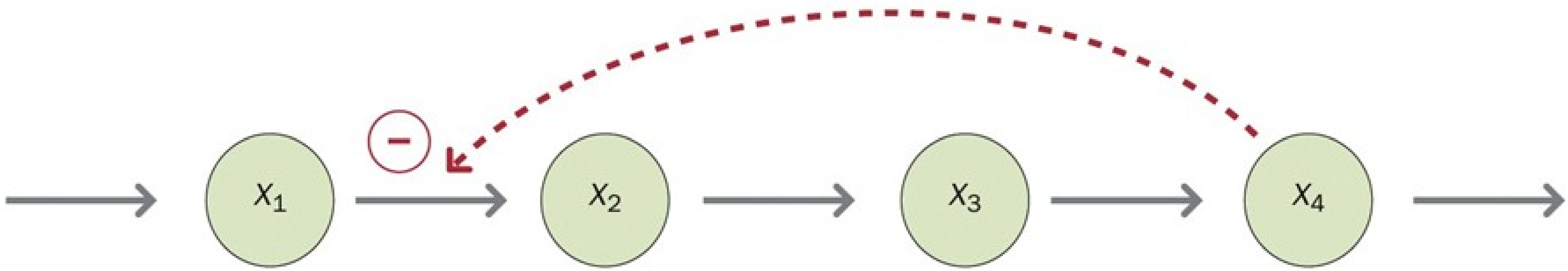
Canonical models

Process of setting up and analyzing models follow strict rules:



Schematic diagram of an enzyme catalyzed reaction

Lokta-Volterra (LV) model: $$\dot{X}_i = \sum_{j=1}^{n} a_{ij} X_i X_j + b_i X_j$$



Linear pathway with feedback

More complicated dynamical systems descriptions

- Ordinary differential equations
- Partial differential equations
- Agent-based modeling

Standard analysis

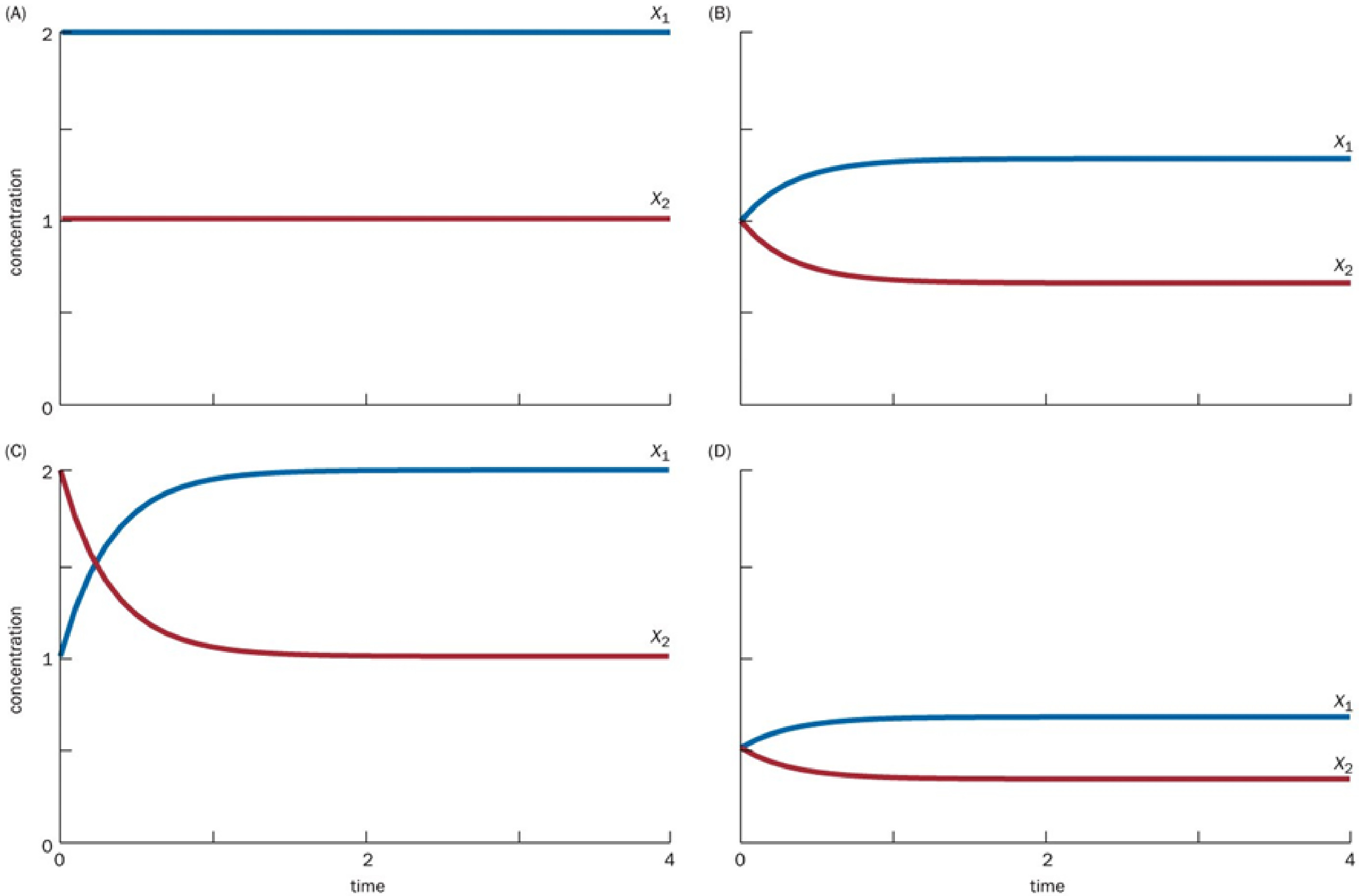
Steady-state analysis

A system is said to be in steady state if there is no change:

- in numbers
- in amount
- in concentration

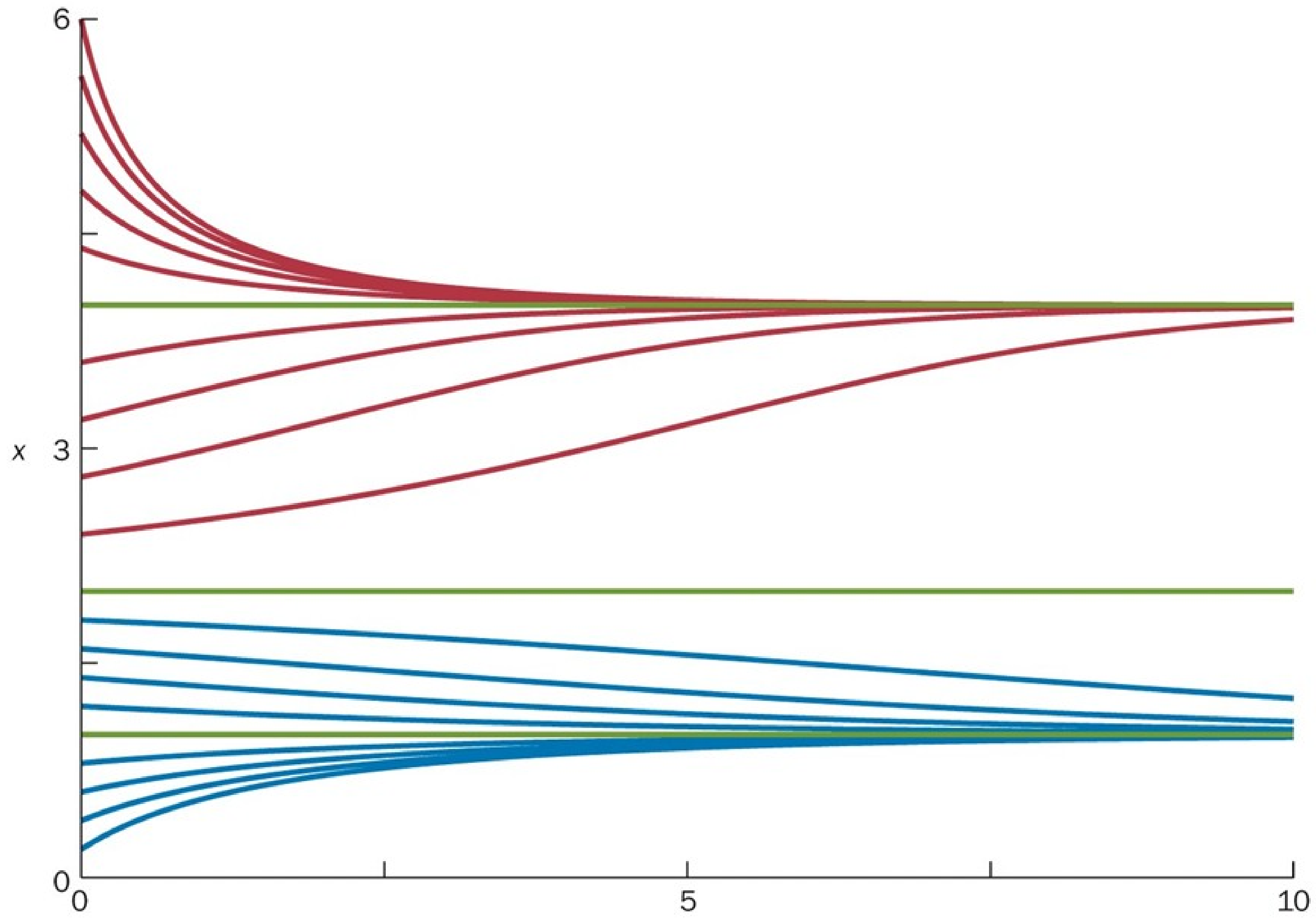
$$\frac{d\mathbf{X}}{dt} = \dot{\mathbf{X}} = \mathbf{AX} + \mathbf{u} = \mathbf{O}$$

$$\dot{\mathbf{X}}_1 = 2\mathbf{X}_2 - \mathbf{X}_1$$
$$\dot{\mathbf{X}}_2 = \mathbf{X}_1 - 2\mathbf{X}_2$$



Example of a non-linear system with isolated steady states:

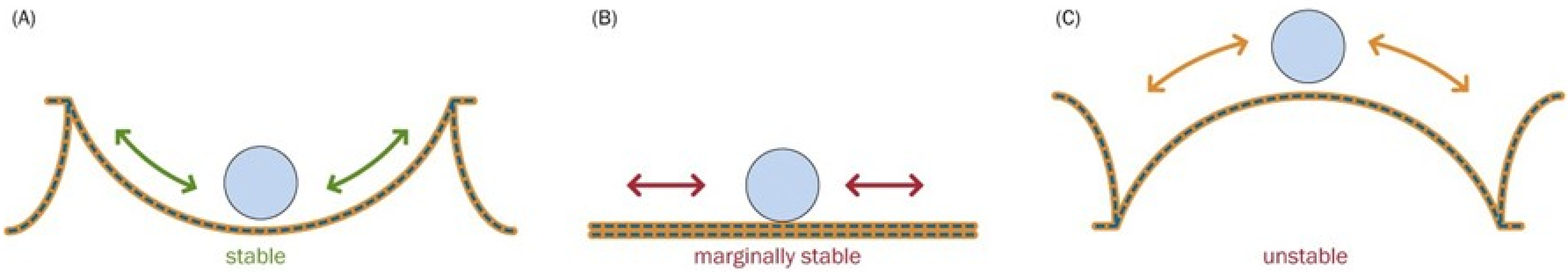
$$\dot{x} = -0.1(x-1)(x-2)(x-4)$$

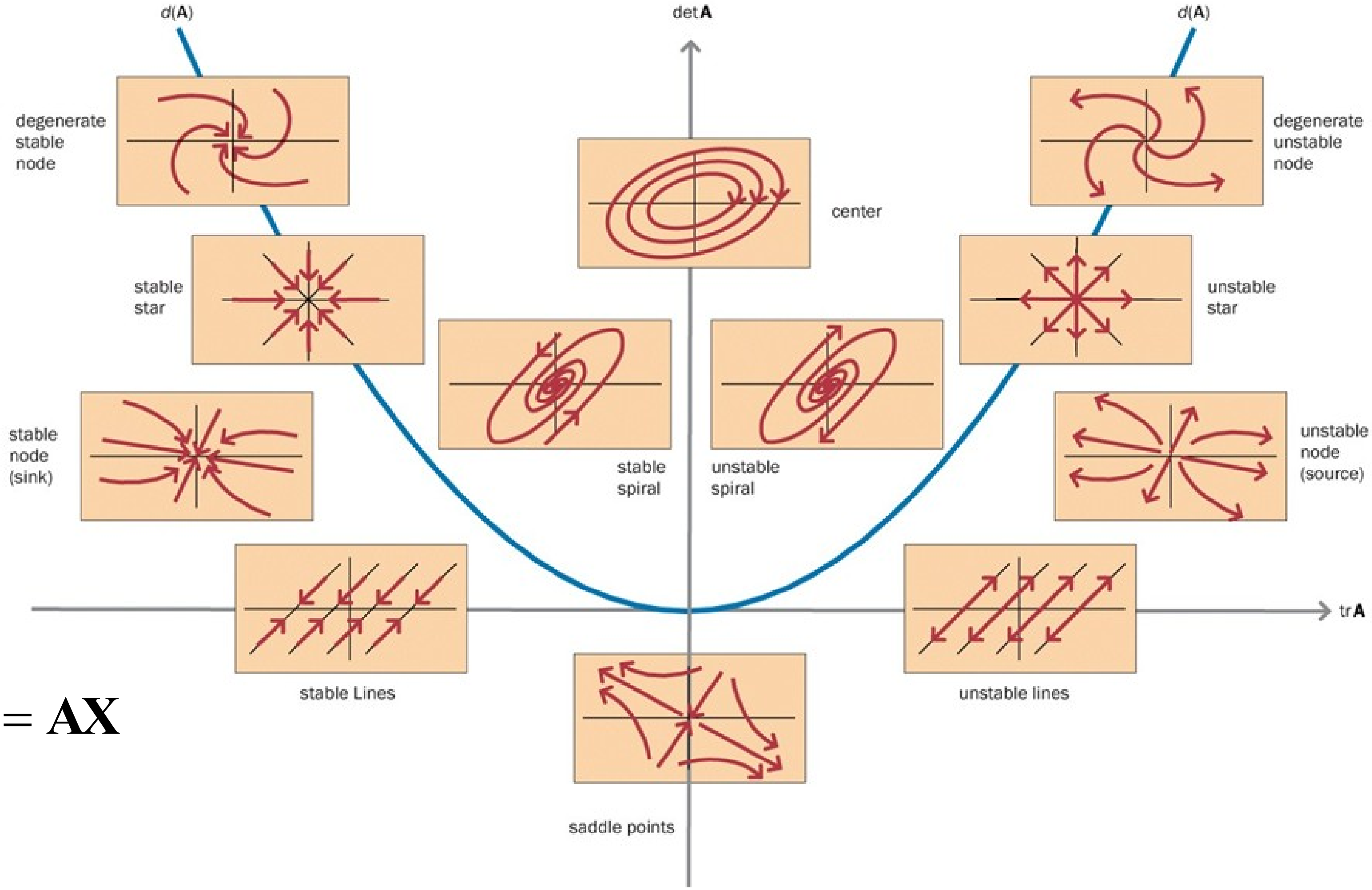


Stability analysis

Assesses the degree to which a system can tolerate perturbations.

- ❑ stable
- ❑ marginally stable
- ❑ unstable





$$\frac{d\mathbf{X}}{dt} = \mathbf{AX}$$

Parameters of interest are trace, determinant and discriminant

$$tr\mathbf{A} = A_{11} + A_{22}$$

$$\det \mathbf{A} = A_{11}A_{22} - A_{12}A_{21}$$

$$d\mathbf{A} = (tr\mathbf{A})^2 - 2\det \mathbf{A}$$

Parameter sensitivity

- Sensitivity tells how much a system is affected by small alterations in parameter values.
- *Sensitivity is not same as stability.* Stability arises despite perturbation in dependent variables. Local stability is based on perturbation of dependent variables.
- Sensitivity/gain analysis relates to parameters/independent variables changing permanently.
- Good, robust systems have *less sensitivity*.

$$F(x;b+\Delta b) \approx F(x;b) + \frac{\partial F(x;b)}{\partial b}\Delta b$$

$$F(x) = \frac{a}{b+e^{-cx}}$$

$$Lt_{x\to\propto}\frac{\partial F(x;b)}{\partial b} = -\frac{a}{b^2}$$

Analysis of systems dynamics

- Bolus experiments
- Persistent changes in structure or input
- Comprehensive screening experiments
- Analysis of critical points where systems behavior changes qualitatively