Bioinformatics: Network Analysis

Analyses of Biological Systems Models

COMP 572 (BIOS 572 / BIOE 564) - Fall 2013
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- Steady-state analysis
- Stability analysis
- Parameter sensitivity

Steady-state Analysis

- A steady state is a condition of a system in which none of the variables change in number, amount, or concentration.
- This does not mean that nothing is happening in the system (a condition referred to as thermodynamic equilibrium).

Steady-state Analysis

- Steady-state analyses address three basic questions:
  - Q1: Does the system has one, many, or no steady states, and can we compute them?
  - Q2: Is the system stable at a given steady state?
  - Q3: How sensitive to perturbations is the system at a given steady state?

Steady-state Analysis

- In a linear system, the steady state is relatively easy to assess, because the derivates are zero, by definition of a steady state.

Steady-state Analysis

$$\frac{d\mathbf{X}}{dt} = \mathbf{AX} + \mathbf{u} = \mathbf{0}$$

no steady-state solution

or

exactly one solution

or

whole lines, planes, etc., satisfy the equations

Steady-state Analysis

$$\begin{aligned} dX_1/dt &= 2X_2 - 2X_1 \\ dX_2/dt &= X_1 - 2X_2 \end{aligned}$$

Unique, attainable, trivial steady-state: (0,0)

Steady-state Analysis

$$\begin{aligned} dX_1/dt &= 2X_2 - 0.5X_1 \\ dX_2/dt &= X_1 - 2X_2 \end{aligned}$$

Unique, trivial steady-state: (0,0)

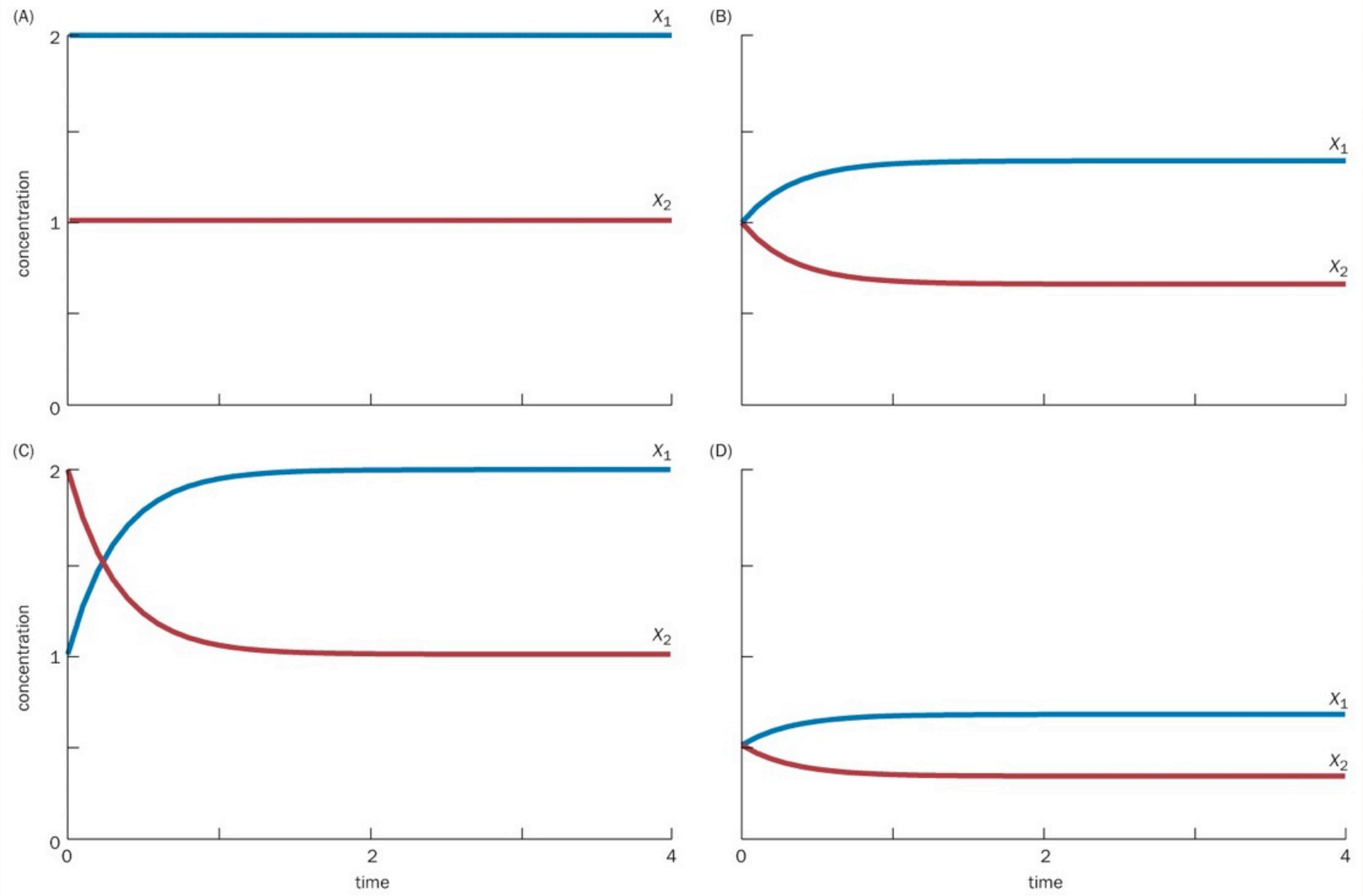
Starting a simulation anywhere other than (0,0) leads to unbounded growth.

Steady-state Analysis

$$\begin{aligned} dX_1/dt &= 2X_2 - X_1 \\ dX_2/dt &= X_1 - 2X_2 \end{aligned}$$

Infinitely many solutions, including (0,0)

$$\begin{aligned} dX_1/dt &= 2X_2 - X_1 \\ dX_2/dt &= X_1 - 2X_2 \end{aligned}$$



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Steady-state Analysis

$$\begin{aligned} dX_1/dt &= 2X_2 - X_1 + 1 \\ dX_2/dt &= X_1 - 2X_2 \end{aligned}$$

no steady-state!

Steady-state Analysis

- The computation of steady states in nonlinear systems is in general much harder.
- One strategy is to do a simulation and check where the solutions stabilizes, but this has drawbacks:
  - if the steady state is unstable, the simulation will avoid it
  - a nonlinear system may possess different, isolated steady states.

$$dx/dt = -0.1(x-1)(x-2)(x-4)$$

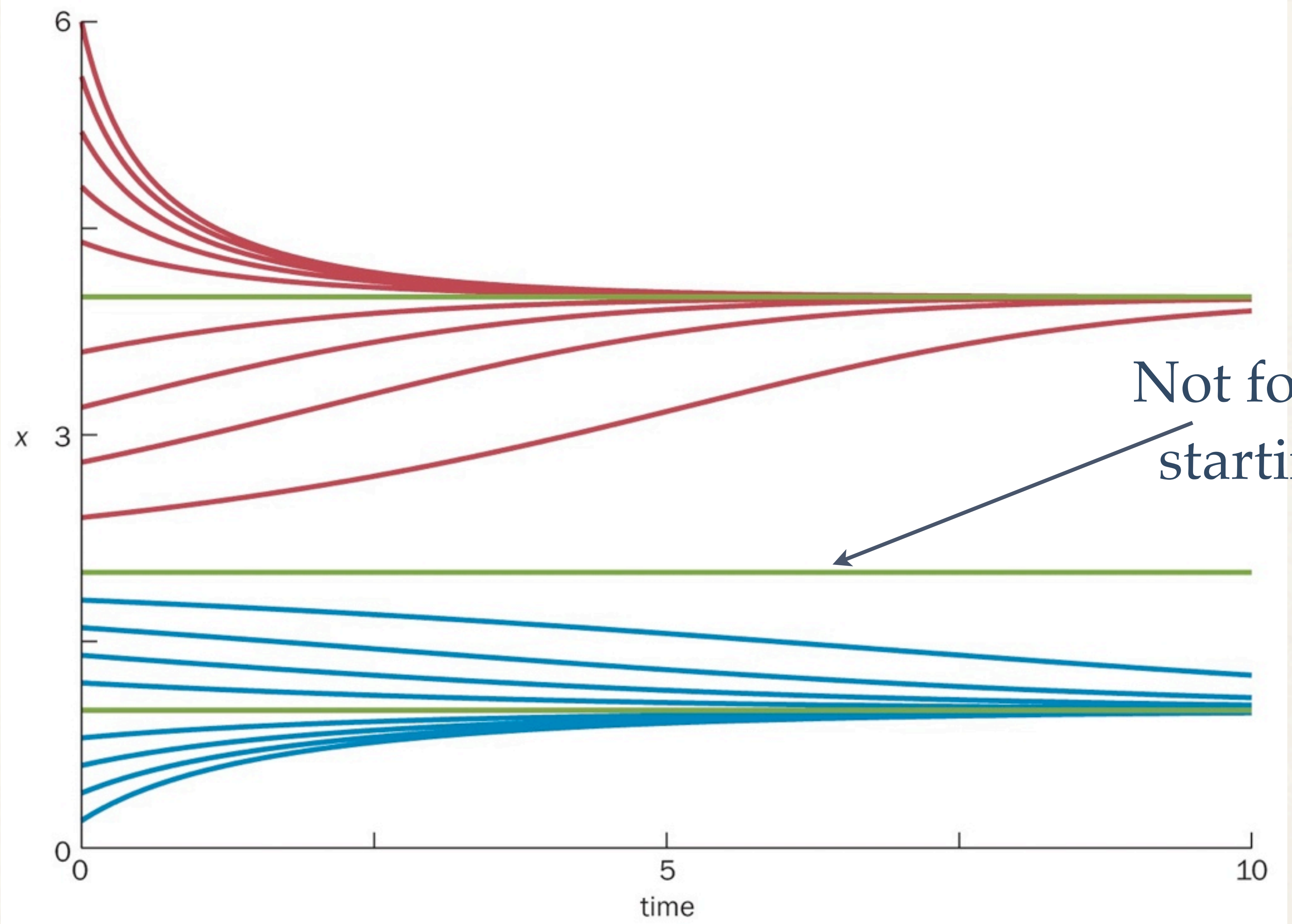


Figure 4.14 A First Course in Systems Biology (© Garland Science 2013)

Not found unless starting from 2.

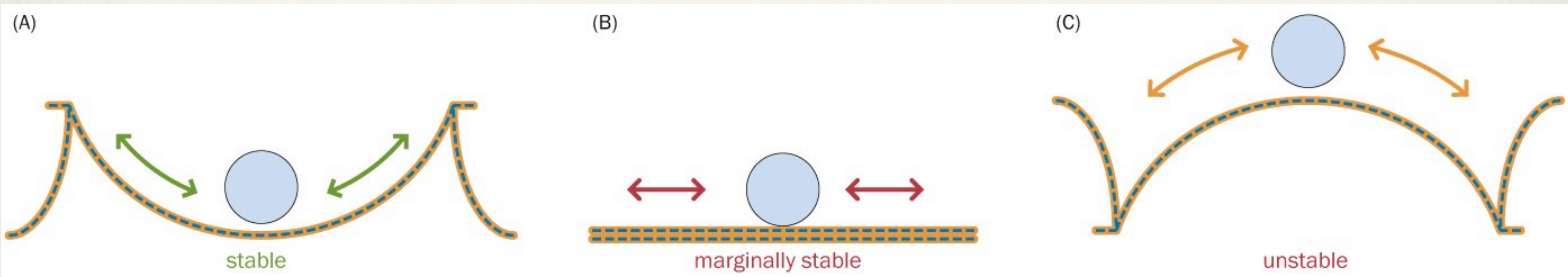
Steady-state Analysis

- A second strategy uses search algorithms (gradient search):
  - Start with a guess
  - Compute how good the guess by evaluating the steady-state equations and computing how different they are from zero
  - Check “neighbors” of the guess and go in the direction of improvement

- Once we have computed the steady state(s), we can use it as an operating point to analyze important features such as stability and parameter sensitivities.

Stability Analysis

- Stability analysis assesses the degree to which a system can tolerate perturbations.
- In the simplest case of local stability analysis, one asks whether the system will return to a steady state after a small perturbation.



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Important: We're talking about relatively <u>small</u> perturbations!

Stability Analysis

- Whether the steady state of a dynamical system is table or not is not a trivial question.
- However, it can be answered computationally in two ways.
- One way is to start a simulation with the system at steady state, perturb it slightly, and observe whether it goes back to the steady state.

Stability Analysis

- The second way is to study the system matrix.
- In the case of a linear system, the matrix is given directly.
- In the case of nonlinear systems, the system is first linearized, so that the matrix of interest is he Jacobian, which contains partial derivatives of the system.
- In either case, the decision on stability rests with the eigenvalues of the matrix.

$$\mathbf{A}\mathbf{v} = \lambda\mathbf{v}$$

eigenvector of A
(nonzero vector)

eigenvalue of A
(corresponding to v)

Stability Analysis

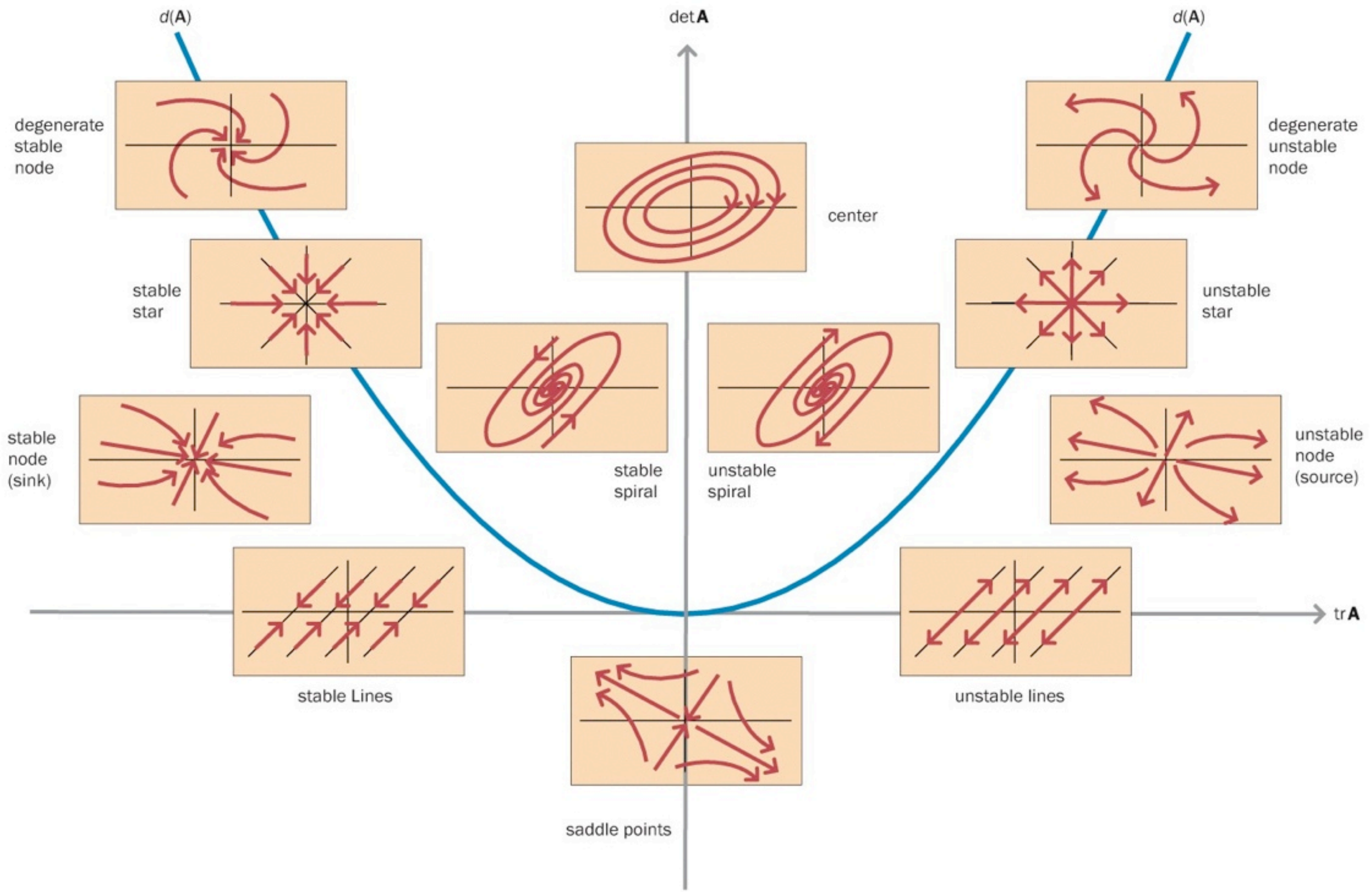
- If any of the eigenvalues has a positive real part, the system is locally unstable.
- For stability, all real parts have to be negative.
- Cases with real parts equal to zero are complicated and require additional analysis or simulation studies.

Stability Analysis

- In the case of a two-variable linear system without input ($d\mathbf{X}/dt=\mathbf{A}\mathbf{X}$), the stability analysis is particularly instructive, because one can distinguish all different behaviors of the system close to its steady state (0,0).

Stability Analysis

- The stability of (0,0) can be determined by three features of **A**:
  - Its trace: tr **A** $= A_{11} + A_{22}$
  - Its determinant: det **A** $= A_{11}A_{22} - A_{12}A_{21}$
  - Its discriminant: d(**A**) = (tr **A**)^2 - 4 det **A**



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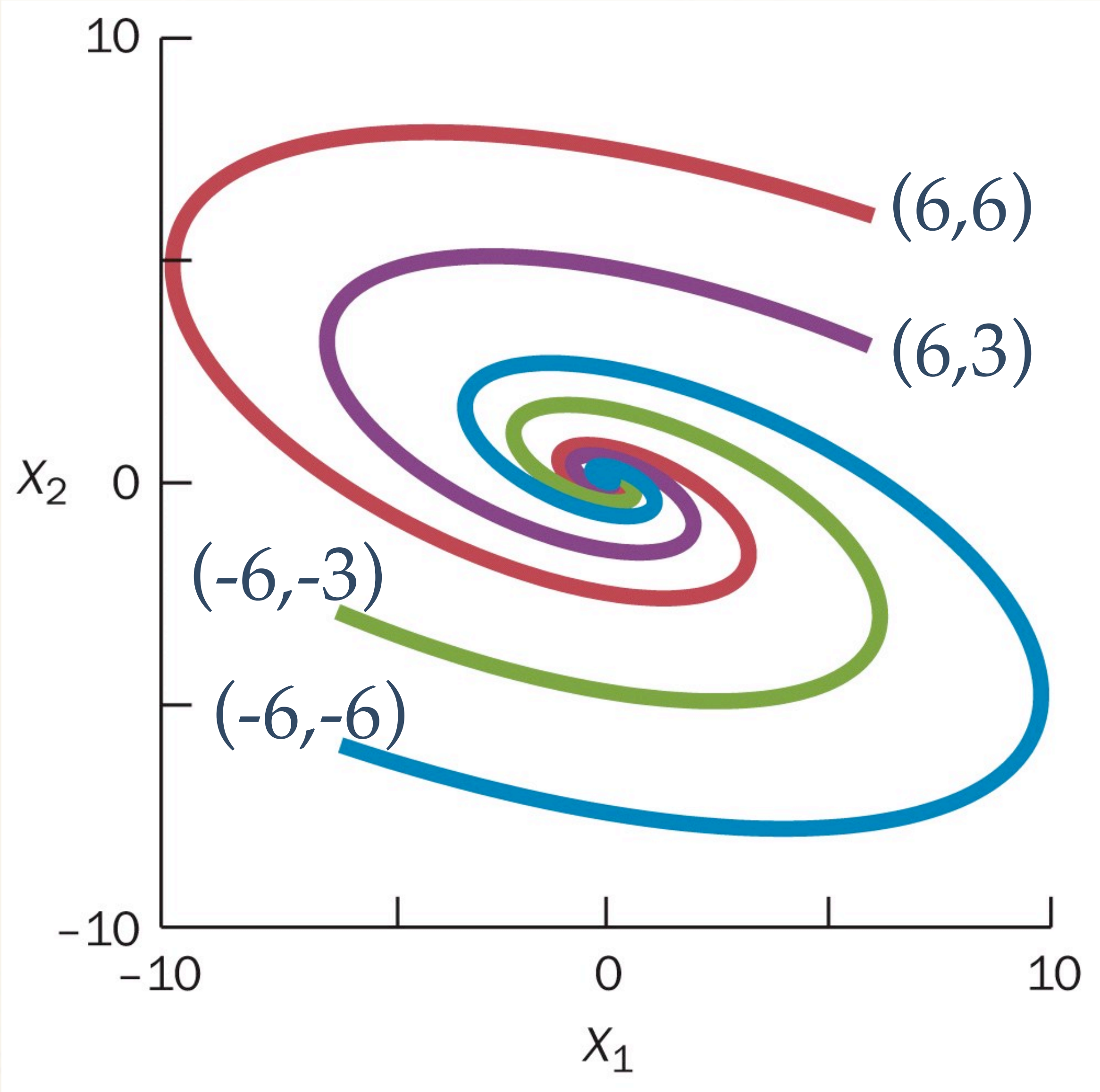

Figure 4.17 A First Course in Systems Biology (© Garland Science 2013)

$$
\begin{aligned}
dX_1/dt &= -3X_1 - 6X_2 \\
dX_2/dt &= 2X_1 + X_2
\end{aligned}
$$

Parameter Sensitivity

- Sensitivity analysis is concerned with the generic question of how much a system is affected by small alterations in parameter values.
- In stability analysis, variables are perturbed, and one studies the system's response to the perturbation.
- In sensitivity analysis, parameters are permanently changed and one studies, for example, how different the new steady state is from the one under the original parameter values.

Parameter Sensitivity

- Sensitivity analysis is a crucial component of any systems analysis, because it can quickly show if a model is wrong.
- Good, robust models usually have low sensitivities, which means that they are quite tolerant to small, persistent alterations, in which a parameter remains altered.
- However, there are exceptions, for instance in signal transduction systems, where even small changes in signal intensity are greatly amplified.

Parameter Sensitivity

- Typical sensitivity analyses are again executed with the system matrix or a linear system or the Jacobian of a linearized nonlinear system.
- While steady-state sensitivities are the most prevalent, it is also possible to compute sensitivities of other features, such as trajectories or amplitudes of stable oscillations.

Acknowledgment

- Voit, "A First Course in Systems Biology," 2013.