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

\[ \frac{dX}{dt} = AX + u = 0 \]

no steady-state solution

or

exactly one solution

or

whole lines, planes, etc., satisfy the equations
Steady-state Analysis

\[ \begin{align*}
    \frac{dX_1}{dt} &= 2X_2 - 2X_1 \\
    \frac{dX_2}{dt} &= X_1 - 2X_2 
\end{align*} \]

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

\[
\begin{align*}
    \frac{dX_1}{dt} &= 2X_2 - 0.5X_1 \\
    \frac{dX_2}{dt} &= X_1 - 2X_2
\end{align*}
\]

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

Starting a simulation anywhere other than (0,0) leads to unbounded growth.
Steady-state Analysis

\[
\begin{align*}
\frac{dX_1}{dt} &= 2X_2 - X_1 \\
\frac{dX_2}{dt} &= X_1 - 2X_2
\end{align*}
\]

Infinitely many solutions, including (0,0)
\[
\frac{dX_1}{dt} = 2X_2 - X_1 \\
\frac{dX_2}{dt} = X_1 - 2X_2
\]
Steady-state Analysis

\[
\begin{align*}
\frac{dX_1}{dt} & = 2X_2 - X_1 + 1 \\
\frac{dX_2}{dt} & = X_1 - 2X_2
\end{align*}
\]

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.
\[ \frac{dx}{dt} = -0.1(x - 1)(x - 2)(x - 4) \]

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.
Important: We’re talking about relatively small 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.
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 the Jacobian, which contains partial derivatives of the system.

In either case, the decision on stability rests with the eigenvalues of the matrix.
$Av = \lambda v$

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.
In the case of a two-variable linear system without input (dX/ dt=AX), 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: \( \text{tr } A = A_{11} + A_{22} \)
  - Its determinant: \( \text{det } A = A_{11}A_{22} - A_{12}A_{21} \)
  - Its discriminant: \( d(A) = (\text{tr } A)^2 - 4 \text{ det } A \)
\[ \frac{dX_1}{dt} = -3X_1 - 6X_2 \]
\[ \frac{dX_2}{dt} = 2X_1 + X_2 \]
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