

CS341 SYSTEMS BIOLOGY I

LECTURE 21

SENSITIVITY ANALYSIS

Recall the model we have been examining.

$$(1) \quad \frac{dx}{dt}(t) = f(x(t), p)$$

where p is a vector of parameters (i.e. it is the parameter set).

So far, we have simulated models with fixed parameter sets and have written optimization code to find parameters that allow the model to “work.” To fully understand a model, we want to know how the value of p affects its behavior.¹

Sensitivity analysis explores the effects of parameter values on the model’s behavior. (A system is sensitive to a parameter if the parameter has a large effect on behavior and insensitive to it if it doesn’t.) What do I mean by “model’s behavior”?

- I could mean *the state trajectories over time*. I.e. I could mean that I want to know how each parameter affects the dynamics of all states and at all times.
- I could mean *a particular function of the state trajectories*. E.g. the period of an oscillation or the amplitude of an oscillation, or the difference in peak times between two states.

Depending on the particular project, either of these answers is good. It depends upon the research question we are trying to answer.

We expect the model to reflect the robustness of the biological system. That means we have a set of performance criteria in mind (e.g. the period of oscillation and a minimum amplitude for a circadian clock). And we expect the parameters to have little effect on those criteria. Sort of. Let’s think about this in terms of sensitivity. What does it mean when a model is sensitive to a particular parameter? It could mean one of the following:

- The model does not completely capture the process in question. It could be the case that the biological system is sensitive to that process, but that the process is tightly regulated by other processes. In the real system, the additional regulators

¹Note that even though we don’t write x as a function of p , it must be so – its solution depends on f , which is a function of p .

would prevent the process in question from deviating from its normal speed. This could indicate an area of the model that could use more attention (e.g. further development).

- The process is part of an input pathway that is meant to change the behavior of the system. For example, we expect a circadian clock to be sensitive to the daily light-dark cycle. So we expect processes affected by light to alter the model's behavior. Both the real system and the model should be sensitive to parameters associated with that input path.
- The model is just plain wrong.

How do we compute the sensitivity of a system to a parameter? There are several measures of sensitivity and several approaches to computing it. We will consider the traditional approach. We examine the “local” sensitivities. We do this by looking at the effects of small perturbations on parameters. I.e. we have a nominal (reference) set of parameters, then compare the model's behavior to the behavior of a parameter set with a small change in the value of on parameter (this is called a parametric perturbation).

LOCAL SENSITIVITY ANALYSIS OF A OUTPUT FUNCTION

Given a function $u(p)$ of the solution to Eq. 1 for parameter set p (which is an $N_p \times 1$ vector), we want to know how it changes as the j^{th} parameter changes.

$$(2) \quad \frac{\partial u}{\partial p_j} = \lim_{\Delta p_j \rightarrow 0} \frac{u(p^*) - u(p)}{\Delta p_j}$$

where $p^* = p + e_j \Delta p_j$ and e_j is the j^{th} row of the $N_p \times N_p$ identity matrix.

If we want to compare the sensitivity of u to different parameters, then we should make the sensitivity measure relative to the parameter's value, i.e. we should actually compute $\frac{du}{dp_j} p_j$. How we we compute it?

Use an approximation of the partial derivative:

$$\frac{du}{dp_j} p_j \approx \frac{u(p^*) - u(p)}{\Delta p_j} p_j$$

and choose Δp_j to be a fraction of the size of p_j , e.g.

$$\Delta p_j = 0.01 p_j$$

for all j . Then the computation is

$$\frac{du}{dp_j} p_j \approx \frac{u(p + e_j(0.01 p_j)) - u(p)}{0.01}$$