Single Differential Equations: Application to Embryonic Cell Development

MATH 469, Texas A&M University

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Overview

This application of single first-order autonomous ODE is adapted from the article "Thresholds in Development," by J. Lewis, J. M. W. Slack, and L. Wolpert in J. Theoretical Biology **65** (1977) 579-590.

During the early stages of development, an embryo's cells (such as stem cells) all appear to be the same, so the question arises: how do these cells ultimately differentiate to become blood cells, skin cells, neurons, etc.?

Laboratory studies suggest that signaling molecules called morphogens diffuse through the embryo at some stage of development, and cell type is determined by the concentration of morphogens at the cell location during this stage.

Overview

In the referenced article, the authors focus on two primary questions associated with this process:

1. **The selection question.** How can small changes in morphogen concentration lead to large changes in cell development? E.g., how can a small change in morphogen communicate to a cell that it should become a skin cell rather than a neuron?

2. **The memory question.** Once the morphogens have run their course, how do the cells remember, during subsequent development, what they're supposed to become?

In order to answer these questions, the authors focus on the activation of a particular gene G by a morphogen S (S for *signaling* molecule). They let $g(t)$ denote the "gene product," by which they mean a variable that measures the level of activation induced in the gene G by the morphogen S at time t. I.e., the larger $g(t)$ is, the more likely it is that gene G will be activated.

The Model

As a model for the dynamics of $g(t)$, the authors use

$$\frac{dg}{dt} = k_1 S + \frac{k_2 g^2}{k_3 + g^2} - k_4 g.$$

Here, S denotes the concentration of morphogens at the cell location, and the constants k_1, k_2, k_3, and k_4 are all positive. This model is based on the following phenomenological assumptions:

1. The gene product increases at a rate proportional to the concentration of morphogens S.

2. In the absence of morphogens, the gene product declines if it is either below a lower threshold or above an upper threshold. In the intermediate region, it increases.

The Model

To better understand Item 2, notice that we can express the latter two terms in the model as

$$g\left(\frac{k_2 g}{k_3 + g^2} - k_4\right).$$

Since $k_4 > 0$, we see that this quantity is negative for g sufficiently small or for g sufficiently large. (We'll be explicit about this in our stability analysis).

Using this model, the authors were able to address their questions by considering the nature of equilibrium points.

Equilibrium Points and Stability

Recall that the model is

$$\frac{dg}{dt} = k_1 S + \frac{k_2 g^2}{k_3 + g^2} - k_4 g,$$

For notational convenience, let's set

$$f(g; S) := k_1 S + \frac{k_2 g^2}{k_3 + g^2} - k_4 g.$$

Since $k_3 + g^2 > 0$, the function

$$F(g; S) = (k_3 + g^2) f(g; S)$$

will have precisely the same zeros and signs as $f(g; S)$. This means that we can use $F(g; S)$ (rather than $f(g; S)$) both to determine our equilibrium points and to analyze their stability.

Equilibrium Points and Stability

For the equilibrium points, we set

$$0 = F(\hat{g}; S) = (k_3 + \hat{g}^2)k_1 S + k_2\hat{g}^2 - (k_3 + \hat{g}^2)k_4\hat{g}.$$

This is a cubic equation for $\hat{g}$,

$$-k_4\hat{g}^3 + (k_1 S + k_2)\hat{g}^2 - k_3 k_4\hat{g} + k_1 k_3 S = 0.$$

We particularly want to understand what happens as S varies. Let's start with $S = 0$, in which case we have

$$-k_4\hat{g}^3 + k_2\hat{g}^2 - k_3 k_4\hat{g} = 0 \implies -\hat{g}(k_4\hat{g}^2 - k_2\hat{g} + k_3 k_4) = 0.$$

We see that $\hat{g} = 0$ is a fixed point, and there are two more fixed points

$$\hat{g}_\pm = \frac{k_2 \pm \sqrt{k_2^2 - 4k_3 k_4^2}}{2k_4}.$$

Equilibrium Points and Stability

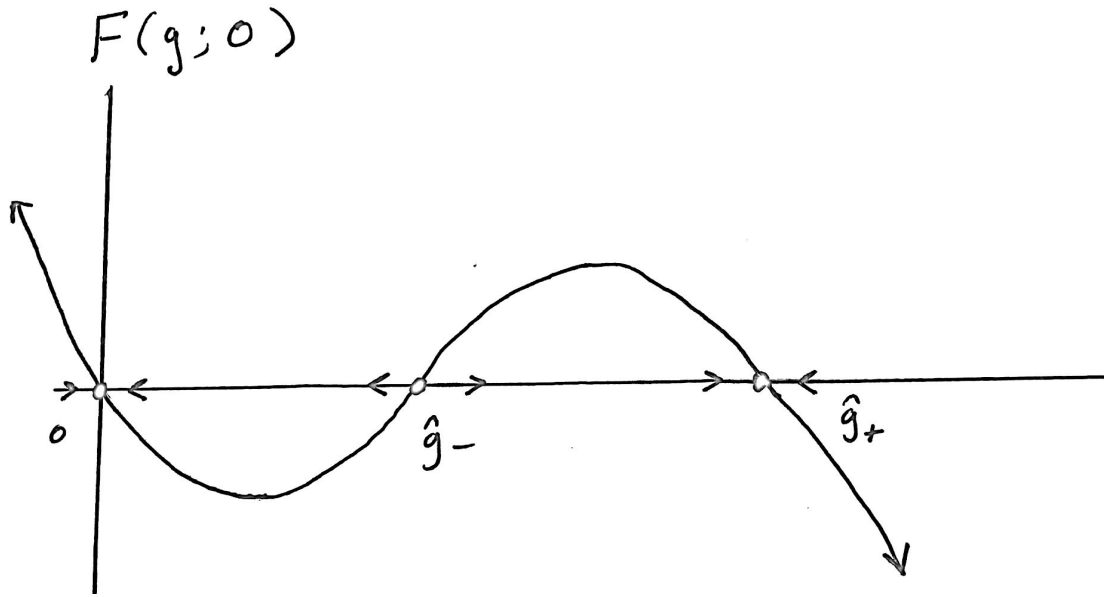
The interesting case is when the discriminant $k_2^2 - 4k_3k_4^2$ is positive, so that there are three fixed points. Since

$$k_2 > \sqrt{k_2^2 - 4k_3k_4^2},$$

we can order these as

$$0 < \hat{g}_- < \hat{g}_+.$$

We can sketch this as follows:



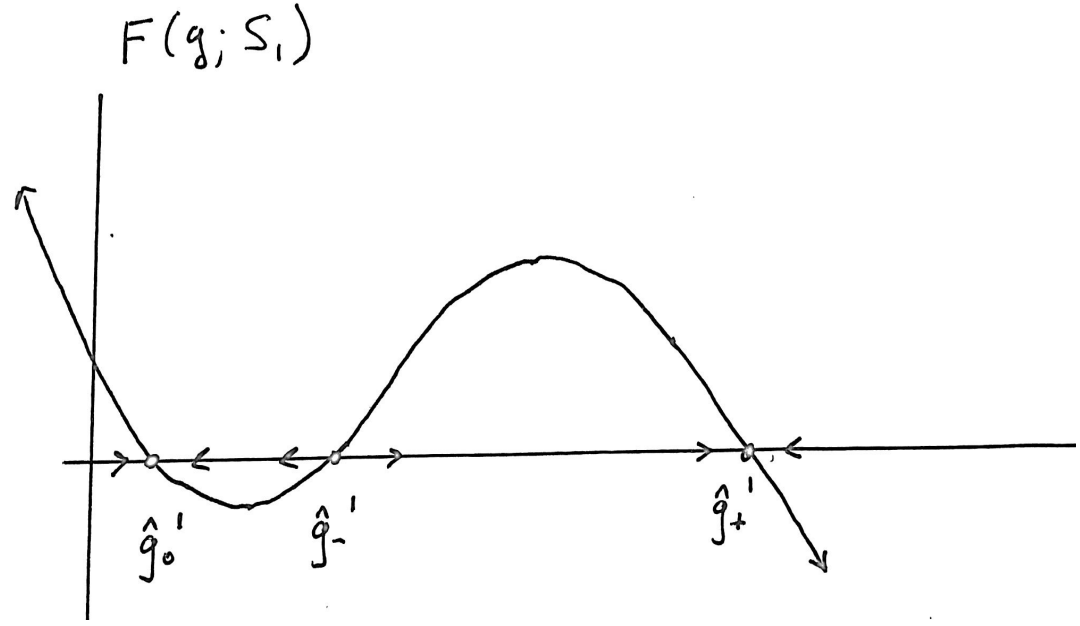
Equilibrium Points and Stability

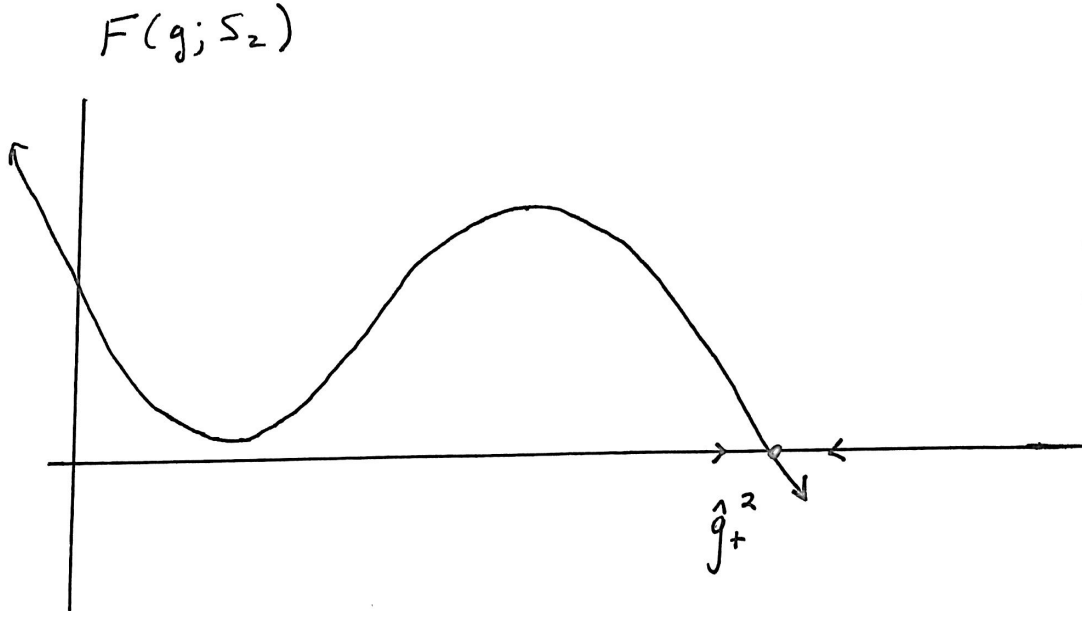
As S increases, this graph lifts upward. On the next slide, plots are given for $S_1 > 0$ and $S_2 > S_1$, with S_2 taken large enough so that there is only one fixed point.

The gene product $g(t)$ is initially small, and since $\hat{g}_0^1$ is asymptotically stable, we expect that if S is small, then $g(t)$ will remain small.

But once S gets large enough so that the lower two equilibrium points are no longer there (e.g., for $S = S_2$), then since $\hat{g}_+^2$ is asymptotically stable, we expect that $g(t)$ will increase to this significantly larger value. In this case, the gene will express itself. This answers the expression question.

Now suppose $g(t)$ is near $\hat{g}_+^2$, and the value of S decreases back near 0. Since $\hat{g}_+$ is asymptotically stable, we expect $g(t)$ to remain near $\hat{g}_+$, in which case the gene will continue being expressed. This answers the memory question.


$F(q; S_1)$
$\hat{q}_0^{\,1}$
$\hat{q}_-^{\,1}$
$\hat{q}_+^{\,1}$


$F(q; S_2)$
$\hat{q}_+^{\,2}$