Modeling Mechanical Effects on Cell Differentiation

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1 Background

It is generally understood that chemical signaling plays a major role in embryonic stem cell differentiation, but what is less clear is the role of mechanics in guiding the process. Previous experiments [1] have determined that mechanical stresses help govern the process of *in vitro* neural induction, in which a circular cell layer forms into a core of specialized neural plate (NP) cells, surrounded by a ring of neural plate boundary (NPB) cells. This was followed by a phenomenological model [2], which treats the growing cell colony as a continuum and models the formation of the two cell domains by a partial differential equation. This model predicts that for a given set of external parameters, there is only one allowed position of the domain wall. However, it also neglects the fact that cells are discrete entities and that the size of individual cells is not insignificant relative to the total width of the colony. Here, we analyze a discretized version of this continuum model, and examine the differences in pattern formation under the two models.

2 Model

In our discrete model, we assume a regular one-dimensional lattice of N cells with positions $x_1, x_2, ..., x_N$. We treat the type of each cell by the scalar w_i, and take a value near 0 to indicate an NP cell and a value near 1 to indicate an NPB cell. We then expect to see step function-like patterns of w_i in which the first several cells are near 0, followed by an abrupt step up to near 1. We model the time evolution of the w_i by the system of ordinary differential equations

$$\dot{w}_i = w(1-w)(w-w_{\mathrm{mid}}) + g\sum_{j=1}^{N}[s_j(x_i)w_j] - \alpha\sigma^* \quad (1)$$

where the cubic term encodes the "preference" of a cell to settle at one of two states (the first and last roots of the cubic) and the sum represents feedback from all cells (note that since the sum is over all j, self-feedback is present) with feedback strength g, and the last term is a constant shift applied to all cells, which allows us to tune the position of the domain wall. The functions $s_j(x)$ represent the (non-dimensionalized) mechanical stress due to interactions of cell j with the substrate, which decay with some characteristic dimensionless length scale λ. w_{mid} is a free parameter that biases the system toward the NP or NPB state.
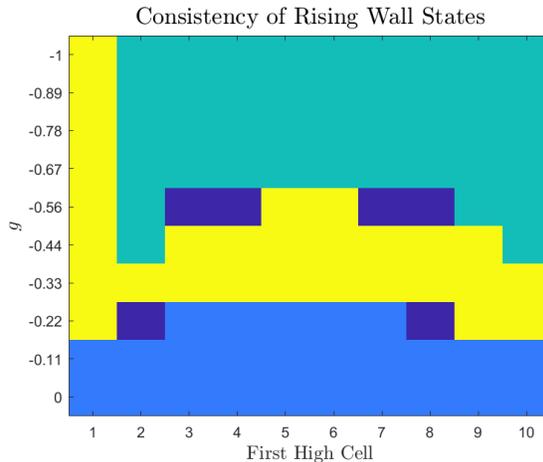

Figure 1: Color plot of consistency for different test states and coupling constants. Each pixel represents a state with a given wall position (given by the first high cell) and feedback strength g. Teal and light blue indicate low- and high-inconsistent states, blue indicates consistent states where root-finding fails, and yellow indicates consistent states. Parameter values: $\alpha\sigma^* = 0.2$, $\lambda = 0.13$, $w_{\mathrm{mid}} = 0.5$.
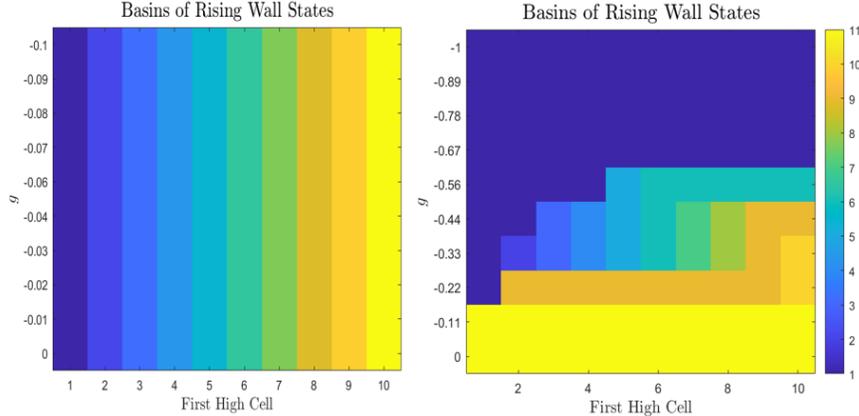
Figure 2: Basins of attraction. Coloration indicates the domain wall position (first high cell) for the final state of the system with initial conditions from figure 2. Right: Parameter values from previous figure. Left: Continuum model parameters, $\alpha\sigma^* = 0.03$, $\lambda = 0.13$, $w_{\text{mid}} = 0.5$.

3 Analysis & Results

An important result of the continuum model is that for any set of parameters, there is one stable position of the domain wall. We must then examine the question of existence and stability of domain wall states. A helpful tool in this analysis is the idea of *consistency*. Consider the curve described by $\dot{w}_i(w_i)$, holding the w values of all other cells constant. Depending on stress due to other cells and the constant stress, which shift this cubic curve up or down, there are either one or three possible roots. Suppose that in some domain wall state $\mathbf{w}$, in which all cells are either low or high, there exists a cell $w_k \approx 1$ (high), but the curve $\dot{w}_k(w_k)$ only has the low root due to a large negative shift. This state is then not an allowable equilibrium state of the model ($\dot{\mathbf{w}} = \mathbf{0}$) and we say the state is *high-inconsistent*. We define a state to be *low-inconsistent* similarly, and if a state is neither high- nor low- inconsistent then we say it is consistent.

To examine the degree to which consistency affects our model, we first construct a set of test domain wall states $\mathbf{w}^j$:

$$w_i^j = \begin{cases} 0 & i < j \\ 1 & i \geq j \end{cases} \tag{2}$$

We then construct the time-derivative curve $\dot{w}_i^j(w_i^j)$ for each cell and determine whether the state is consistent. We repeat this procedure for each of several values of the coupling strength g. Finally, if a state is consistent, we perform Newton's method for root-finding on equation (1) using the test state as an initial guess, to confirm that a state with that domain wall position is an allowed equilibrium state. In some cases this root-finding failed, likely due to the fact that our tests of consistency neglects certain indirect effects on the shift of the curves. The results are shown in figure 2. Note that at low coupling, the only shift is $-\alpha\sigma^*$, so the high root is unavailable. At high coupling, the shift is large and positive, so the low root is unavailable. Note that for certain values of g, there is more than consistent domain wall state. This stands in contrast to the continuum model, in which all initial conditions are attracted to the same domain wall state.

It is possible that while multiple equilibruim states exist, only one is stable to small perturbations. We determine the stability of an equilibrium state by the eigenvalues of the Jacobian of equation (1):

$$J_{ij} = \frac{\partial \dot{w}_i}{\partial w_j} = \frac{\mathrm{d}f}{\mathrm{d}w_j}\delta_{ij} + gs_j(x_i) \tag{3}$$

Where f is the cubic contribution to equation (1). The eigenvalues of J were determined for all equilibrium states found earlier, and they were determined to in every case be negative, indicating that the state was stable.

2

A final check on the behavior of our model is to simply solve the system of differential equations numerically. We integrate equation (1) using MATLAB's `ode45` command for the values of g and initial conditions given in Figure (2) until $\dot{\mathbf{w}} = \mathbf{0}$ and determine the position of the domain wall in the final state. The results are shown in Figure (3). As we can see, every state that was found to be inconsistent or for which root-finding failed, when used as an initial condition, "transitioned" into a different state, while the states that were found to be consistent were relatively unchanged. This verifies that there truly can be multiple allowed domain wall positions for the same set of parameter values.
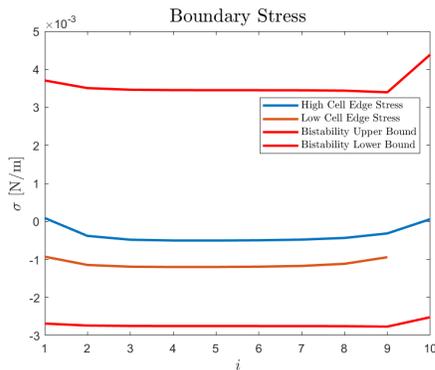

Figure 3: Stress on the right (blue) and left (orange) side of the domain wall as a function of domain wall position. Red curves show the maximum stress for which the low root exists and minimum stress for which the high root exists. Parameter values from Figure (2), left.

To determine what might cause there to be so many allowed equilibrium states, we must look at how the domain wall position affects stress levels. Taking a fixed value of g, we determine the total stress at the domain wall position x_j for the wall state $\mathbf{w}^j$, as shown in in Figure (3). We can then compare this to the largest positive and negative stresses for which the low and high roots exist, respectively, and find that for the parameter values used in [2], the stresses are simply too small in magnitude to create inconsistency, likely due to the small value of g and the fact that in the discrete model, cells are far enough apart that they are receiving feedback from relatively few sources, whereas in the continuum model, the stresses are higher.

4   Conclusion

The continuum model presented in [2] is a potentially powerful tool for analyzing the role of mechanical effects in tissue development. This summer, I have worked to verify one of the key underlying assumptions of this model, that a discrete lattice of cells is well-approximated by a continuum. Unfortunately, for the continuum parameter values, the discrete model does not perform as expected, but it does share the same qualitative behavior in a different parameter regime. Given more time, it would be helpful to more closely examine the reasons for the small stresses seen here and to expand the model from one to two dimensions, which is the situation modeled by [2]. These additional studies will provide new insights into the effects of discretization on the model's behavior.

References

[1] Xufeng Xue et al. Mechanics-guided embryonic patterning of neuroectoderm tissue from human pluripotent stem cells. *Nature Materials*, 2018.

[2] Hayden Nunley et al. Generation of fate patterns via intercellular forces. *Preprint*, 2020.