Generating Turing-like patterns in an off-lattice agent based model: Handout

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1 Background

1.1 Turing's morphogenesis model

From Turing's Chemical Basis of Morphogenesis [6] ,

$$\frac{\partial A}{dt} = f(A,B) + D_A \nabla^2 A, \tag{1}$$
$$\frac{\partial B}{dt} = g(A,B) + D_B \nabla^2 B \tag{2}$$

with no flux boundary conditions: $(\mathbf{n} \cdot \nabla) \begin{pmatrix} A \\ B \end{pmatrix} = 0.$

$f(A,B)$ and $g(A,B)$ are interaction-constitutive relations between A and B, which necessarily include non-linear terms. As specified by Gierer and Meinhardt [2], one field acts as an activator, while the other faster diffusing chemical acts as an inhibitor of the other species.

As an example for the functional form f and g from [5]:

$$f(A,B) = a - A - h(A,B) \tag{3}$$
$$g(A,B) = \alpha(b - B) - h(A,B) \tag{4}$$
$$h(A,B) = \frac{\rho AB}{1 + A + KA^2} \tag{5}$$

which produces the following:

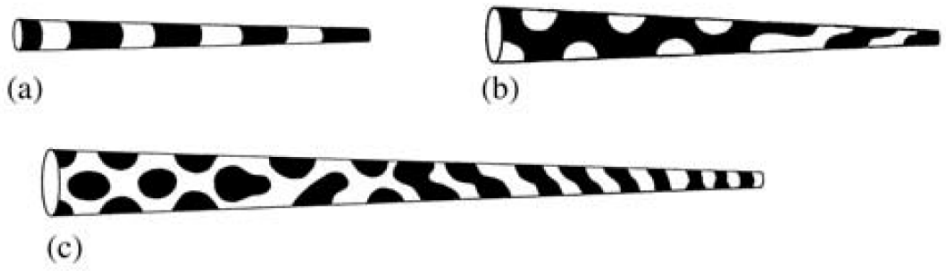

Figure (1) From Murray Volume II, a simulated animal coat pattern [5].

1.2 Turning patterns in cell-based modeling

Using Turing's model of morphogenesis as inspiration, this model attempts to create Turing like patterns but using a discrete, cell-based modeling paradigm. Specifically, our model is implemented in PhysiCell [1]. Other modelers have also created cell-based models of Turing-like patterns, but using fundamentally different rule sets such as differential cell-cell adhesion and stochastic expression of morphogens [3, 4, 7].

To accomplish this, overall we attempt to segregate A and B cells through interactions of inhibition and promotion mitigated through a set of short ranging diffusing chemicals with A cells producing α and B cells producing β. The signaling chemicals affect the base rates of proliferation, apoptosis, and speeds of the opposite cells - increasing rates of apoptosis and cell speed in a saturating logistic form and decreasing proliferation in the opposite fashion ($1 -$ bounded logistic form). These interactions are meant to be parallel to $f(A, B)$ and $g(A, B)$ in Equations 1 and 2 with cell motility acting as the diffusion term in Turing's equations. This casts the signals α and β as almost being a "quorum" like signal, with increasing cellular density increasing the power of the signals promoting death, motility and inhibiting proliferation in the opposing cell species. Additionally, we add a constraint on proliferation based on cell-sensed pressure to a second edition of our model. Finally, in the third iteration of the model, we add self promotion of proliferation, to introduce a more Turing like nonlinearity.

2 Cell Agents

- Cell A - blue
  - These cells act as the 'inhibitors' in a classical Turing Pattern and are affected by B cell's secretion β.
  - Uses PhysiCell's life cycle model and cycles and commits apoptosis with rates dependent on chemical environment (concentration of β as described in Section 5).

  - Motility is enabled with no bias (completely random/diffusive) and speed determined by chemical environment (concentration of β as described in Section 5).
  - A cells secrete α and are affected by β but uptake no chemicals.

- Cell B - yellow
  - These cells act as activators in the typical Turing Pattern equations and are affected by A cell's secretion α.
  - Uses PhysiCell's life cycle model and cycles and commits apoptosis with rates dependent on chemical environment (concentration of α as described in Section 5).
  - Motility is enabled with no bias (completely random/diffusive) and speed determined by chemical environment (concentration of α as described in Section 5).
  - B cells secrete β and are effected by α but uptake no chemicals.

- Wall cells - black
  - These cells line the domain and prevent the A and B cells from leaving the domain.
  - Uses life cycle model and divides and commits apoptosis with transition rates set to zero (never divide or die).
  - Motility is disabled and cells are set to be immovable.
  - Does not secrete or uptake anything.

Note that the default values have the two cell types (A and B) set to the same behaivors (same values for all parameters). Exploring parameters of these cell types to produce different Turing like pattern is one of the fun things about this model! Also, exact ideal values for producing a variety of Turing like patterns are yet to be determined. When additional information becomes available, At the current defaults, cell segregation does occur in simulation lasting 10s of days.

3 Chemical Environment

- **Alpha (α)** is intended to correlate to the inhibitory chemical. It is secreted by A cells and affects B cells. It has a diffusion length scale of 40 μm, decay rate of 62.5 min^{-1} and diffusion coefficient of 100,000 $\frac{\mu m^2}{min}$. α acts more like a quorum signal in this model than an inhibitor in the classic Turing Pattern and the A cell, which secretes α, is what represent the inhibitory "chemical". This deviation from the traditional model allows for additional mechanics interactions to play out.

- **Beta (β)** is intended to correlate to the activator chemical. It is secreted by B cells and affects A cells. It has a diffusion length scale of 40 μm, decay rate of 62.5 min^{-1} and diffusion coefficient of 100,000 $\frac{\mu m^2}{min}$. β also acts more like a quorum signal in this

model than an activator in the classic Turing Pattern and the B cell, which secretes β, is what represent the activator "chemical".

- **Oxygen (O_2)** is turned off in the simulation and thus has no effect on the cells.

Note that the default values have these two chemical fields as equal. Exploring parameters of these two fields that produce a Turing like pattern is one of the fun things about this model! Also, exact ideal values are yet to be determined. When additional information becomes available, the default values will be updated.

4 Simulation Initialization

Cells are initialized randomly at greater than equilibrium spacing. See Section 6.1 for additional information.

Chemical fields are initialized with zero value across the computational domain.

We use no-flux boundary conditions.

5 Models

There are three different model variants which can be selected. The models are called in the update_phenotype() method and are selectable using the *model_number* option in the parameters. The core of each model is the logistic function. It was selected because it is symmetric about the y-axis and provides rapid change around the midpoint with less dramatic change on the extremes (it is sigmoid). The logistic function has the form:

$$l(x) = \frac{L}{1 + e^{-k \cdot (x - x_0)}} \tag{6}$$

We use it as in Equations 7 and 8. Equation 7 is used for promotion of the base parameter (either cell speed or rate of apoptosis), resulting in a value of P of the particular rate. Equation 8 works similarly, but decreases the parameter value as the input increases (base proliferation rate). In both cases, we let x_0 equal 0.5, k equal 10, $\bar{b}_r$ be base rates of proliferation, apoptosis, or speed, and finally x is the local value of α or β as appropriate. This produces a logistic equation bounded between 0 and 1 and set with inflection point at 0.5. See Figure 2 and 3 for a graphical representation of the functions.

$$P = \bar{b}_r \frac{1}{1 + e^{-k(x - x_0)}} \tag{7}$$

$$P = \bar{b}_r \left(1 - \frac{1}{1 + e^{-k(x - x_0)}} \right) \tag{8}$$

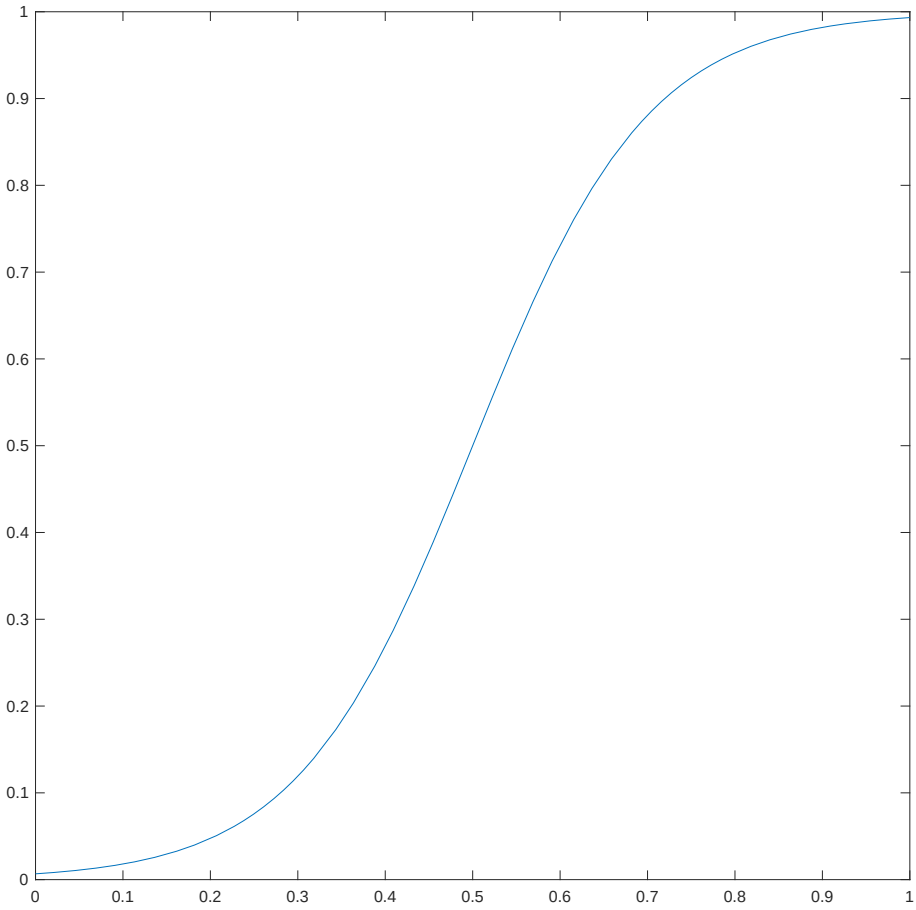

Figure (2) Governing logistic function for promotion.

5.1 Model 1

This was the first model attempted and can be implemented by setting *model_number* to 1. It simply lets $\bar{b}_r$ equal $\bar{b}_{proliferation}$, $\bar{b}_{cellspeed}$, and $\bar{b}_{proliferation}$ with the resulting cross-inhibition

and promotion of A cells by B cells and vice versa. While proliferation is limited somewhat, in this model at the default parameter settings. it is not balanced by apoptosis and the cell count expands without bound.

5.2 Model 2

This model builds on the previous model (Section 5.1) and adds a pressure based control on proliferation. If the cell sensed relative pressure exceeds 0.5, then the rate of proliferation drops to 0. Otherwise, proliferation is governed by Equation 7 with $\bar{b}_r$ set to the base rate of proliferation.

5.3 Model 3

This model builds on the Model 2 (Section 5.2 by retaining the pressure based limit on proliferation and adding another term to the determination of proliferation, based on self-promotion (versus the strict cross-promotion and inhibition of the previous models).

The goal of this model was to make it more Turing-like by having an activator in the function. The motility and apoptosis remain the same as in Models 1 and 2 while adding this activator functionality to proliferation rate updates. This is still symmetric between A and B cells but the bias can be set independently. The equation used for A type cells is

$$\bar{b}_r\left(\frac{1}{1+e^{-k(\alpha-x_0)}}\right)\left(1-\frac{1}{1+e^{-k(\beta-x_0)}}\right)$$

and for B type cells α and β are switched

6 Options

6.1 Cell initialization

There are several cell initializations available, all set by entering integer values into the *placement_pattern* parameter. Using -1 will create a pattern of 7 horizontal strips similar to the initialization in 5.a in Volkening et al. [7]. If you use -2 then it will use the sample pattern as -1 but with the middle chunk of cells cut out, similar to 9.b in Volkening et al.[7]. The space between cells can additionally be changed using *cell_spacing* which is 0.95 by default.

Additionally, integer values any number greater than 1 can be entered into *placement_pattern* which will make the environment saturated with cells, 1, and less saturated as the number

gets bigger. When using this placement pattern you can also set the fraction of cells that will be A type using the *cell_frac_A* which is set to 0.5 by default.

6.2 Model selection

You can select Model 5.1, 5.2 or 5.3 by inserting 1, 2 or 3, respectively, into the *model_number* parameter.

References

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[3] D. Karig, K. M. Martini, T. Lu, N. A. DeLateur, N. Goldenfeld, and R. Weiss. Stochastic Turing patterns in a synthetic bacterial population. *Proceedings of the National Academy of Sciences*, 115(26):6572–6577, June 2018. ISSN 0027-8424, 1091-6490. doi: 10.1073/pnas.1720770115.

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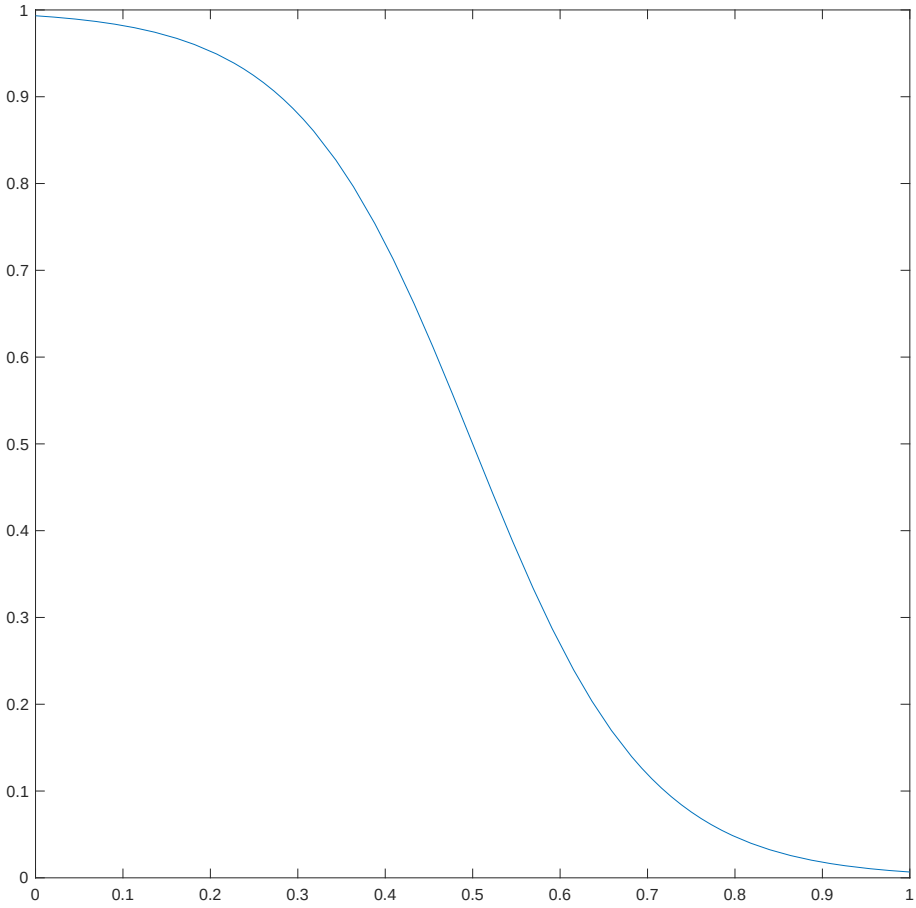

Figure (3) Governing logistic function for inhibition.