# Biologically Realistic Primitives for Engineered Morphogenesis

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**Abstract.** Finding ways to engineer morphogenesis in biological systems, to direct the development of a multicellular organism according to desired specifications, will require both high-level understanding of organizing principles in such systems and low-level understanding of how basic tools can be reliably implemented in real cells. Past work has assumed low-level capabilities appropriate to computing agents but not necessarily to biology. Here I discuss potential ways of implementing low-level primitives based on capabilities for which evidence exists in biological systems, with the goal of developing a basis for engineering developmental processes that will be realizable in wetware. I focus on the use of biologically realistic morphogen gradients to produce structures of desired size, provide positional information, and trigger genetic cascades that lead to the growth of more complex structures.

## 1 Introduction

Morphogenesis, the process of development from a single cell to a complex multicellular organism, is one of the great examples of robust collective behavior. The growth and differentiation of genetically identical cells, reliably resulting in a given high-level structure, is the phenomenon that drives the field of developmental biology. Moving from science toward engineering, the field of synthetic biology seeks to find ways to program cells to make them exhibit desired behaviors. While synthetic biology has so far focused on ensembles of unicellular organisms, its ultimate goal will encompass multicellular organisms, enabling us to grow plants and animals of desired morphology by specifying a genetic program.

Achieving this goal will require programming principles for agents with the unique characteristics of biological cells. Existing studies on the engineering of bioinspired structure-forming systems [1–6] draw important ideas from principles known to operate in biological systems, but often make assumptions about the systems they consider that may be unrealistic for living cells or difficult to achieve.

This paper uses an agent-based cell model to consider certain primitives that are known to operate in natural developmental systems and likely to be critical to engineered ones, and seeks to develop principles for their implementation

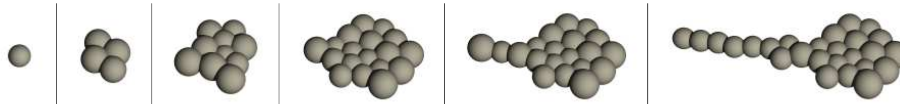

**Fig. 1.** Snapshots during the growth of a rounded structure with a narrow projection, grown using the model and approach for engineered morphogenesis described here.

that may realistically be achievable by synthetic biologists in the near future. These primitives include tissue growth limited to desired dimensions, the establishment of coordinate systems, and the demarcation of well-defined domains of the embryo. In this work I focus on morphogenesis in two-dimensional sheets of cells (Fig. 1), as in epithelial tissues, though the model is intrinsically three-dimensional.

Section 2 discusses related work. Section 3 lays out the assumptions made about cell capabilities. Section 4 describes the agent-based model used to evaluate the approach. Section 5 discusses the primitives addressed here. Section 6 concludes.

## 2 Related Work

Studies of morphogenesis in natural systems have identified key principles that underlie organismal development [7–9]. Substances called morphogens direct cell growth and differentiation, triggering different behaviors depending on their concentration. Some morphogens are produced by cells in genetic cascades as the developmental process unfolds, while others are deposited in the egg by the mother before fertilization. Gradients of morphogen concentration, spatially distributed across an embryo or subregion, are the basic tools used to establish locations and directions. Small concentration differences can be amplified to produce stripes and other sharply demarcated expression regions.

Past work specifically concerned with engineering developmental processes [1–3] has relied on several of these principles. Nagpal [1] describes programming methods for a flat sheet of cells to coordinate folding into any user-specified shape, using axioms from origami. Cells are randomly distributed on the sheet and do not change arrangement or number. Doursat [2,3] demonstrates methods by which a small initial set of cells can grow into a complicated planar structure with controllable shape and differentiation pattern. These studies have abstracted cells into computational units capable of simple calculations, with morphogen gradients implemented using integer counters, and broadcast messages used to signal completion of developmental stages. While such capabilities are eminently suitable for engineered computing systems, they may be problematic for biological cells, and attempts to implement such systems in synthetic biology will have to rely on capabilities available to real cells.

Other studies that have addressed problems of structure formation in engineered distributed systems generally make additional domain-specific assump-

tions that make application to biological cells difficult. Modular robots [4] and collective construction [5] generally require very precise alignment of structural elements, often on a discrete lattice. Programmed self-assembly [6] and collective construction [5] typically use rigid structural units that cannot be rearranged within an assembly once in place. By contrast, cells are variable in size and deformable; they may come together in arbitrary ways, rearrange their configuration at both large and small scales throughout morphogenesis, and produce new units deep within a structure.

An alternative perspective for creating developmental systems with desired characteristics is given by work in evolutionary computation [10, 11]. Such work takes the approach of automated exploration of large search spaces, rather than being concerned with tools and principles for use by human designers.

## 3 Assumptions

I assume that cells possess the following basic capabilities, based on published studies of biological systems:

1. Measure the local concentration of a morphogen, and respond according to whether the concentration falls above or below some threshold [8, 12]. Responses can be to produce a new morphogen and/or to enable cell growth. Multiple thresholds of response may exist for a single morphogen [7, 12, 13] (e.g., through multiple types of receptors with different affinities), so that the same morphogen may, for instance, evoke one response at high concentrations, a different response at low concentrations, and no response in between.
2. Measure and respond to the local *slope* of a morphogen gradient, i.e., the direction of greatest change and the magnitude of that change [8, 14]. Responses can be to produce a new morphogen, to enable cell growth, and/or to affect the orientation of the cleavage plane during division.
3. Determine whether any other cell borders it in a given direction [15, 16].

I further assume that the sources that result in production of some morphogens can be deposited in the egg by the mother, and remain localized as the embryo grows [8]. Finally, I assume that production, diffusion and degradation of morphogens happens quickly compared to growth and movement of cells. This last assumption can be relaxed to some extent, though I do not explore doing so in detail in this work.

## 4 Model

Here I describe the agent-based simulation model used to test the approaches to be described in §5. Cells are modeled as three-dimensional entities normally confined to a two-dimensional sheet, as with epithelial tissue. Future work will consider deformations of the sheet.

The model keeps track of each cell's position (real-valued 3D coordinates) and volume, and the amounts of the various morphogens within that volume. Cells act like deformable, adhesive spheres on an adhesive substrate. Each cell experiences a spring-like force (repulsive at short distances, attractive at longer ones) from each of its neighbors and the substrate, governing its movement in space.

Neighbors can be determined by Voronoi calculation or other methods. For computational efficiency, this model determines which cells border on which others at each time step using a discretized volumetric representation (details omitted for space reasons).

Once neighbors have been identified, forces can be calculated. Pairs of neighboring cells exert opposing forces of magnitude $k(r-r_0)$ on each other along the line connecting their centers, where $k=1$ is a spring constant, $r$ is the distance between the two cell centers, and $r_0$ is the "rest distance" based on the sizes of the two cells (if the cells have volumes $V_1$ and $V_2$, $r_0 = \sqrt[3]{3V_1/4\pi} + \sqrt[3]{3V_2/4\pi}$). Similarly, the substrate exerts a force on cells that neighbor it, acting as a virtual cell with location directly below the other's center. Each cell's position at each time step is updated by an amount proportional to the net force on it, with proportionality constant 1, which gives qualitatively realistic movement without simulating the complete physics of the system. Cell vertical positions are limited to $[0, 0.2]$ to forbid passing through or losing contact with the substrate.

The level $m_{ic}$ of morphogen $i$ in cell $c$ changes according to synthesis, diffusion/transport [17], and degradation:

$$\frac{\Delta m_{ic}}{\Delta t} = \sum_j s_{ij} f_{ij}(m_{jc}) + D_i \sum_{d \in N_c} (\rho_{id} - \rho_{ic}) - \sum_{j \neq i} d_{ij} m_{ic} m_{jc} - d_i m_{ic} \qquad (1)$$

where $s_{ij}$ is the rate at which morphogen $j$ leads to the synthesis of morphogen $i$; $f$ is a function that may be, e.g., linear to reflect a constant rate of synthesis, or sigmoidal to reflect cooperative binding (unless otherwise specified, $f(x) = x$); $D_i$ is the rate of transfer of morphogen between neighboring cells with different concentrations; $N_c$ is the set of neighbors of cell $c$; $\rho_{ic}$ is the concentration of morphogen $i$ in cell $c$ (if $V_c$ is the volume of cell $c$, $\rho_{ic} = m_{ic}/V_c$); $d_{ij}$ is the rate at which morphogen $j$ leads to the degradation of morphogen $i$; and $d_i$ is the intrinsic degradation rate of morphogen $i$.

The gradient of a morphogen at a cell's location is estimated based on the concentration of the morphogen there and at each of the cell's neighbors: $\nabla_{ic} = \sum_{d \in N_c} \frac{\rho_{id} - \rho_{ic}}{|r_{cd}|} \hat{r}_{cd}$, where $r_{cd}$ is the vector from cell $c$ to cell $d$.

The presence of a morphogen may determine cell growth, as described further in §5. If a cell undergoes growth in a given time step, its volume increases by $G = 0.05$ cubic units. If the volume reaches twice its initial value, the cell commits to division: no further growth occurs for $\tau = 30$ time steps, at the end of which division occurs. A new cell is instantaneously created; both daughter cells have half the volume and half the morphogen levels (therefore the same morphogen concentrations) as the mother, and locations equal to that of the

mother plus small opposite offsets along a direction which may be affected by one or more morphogen gradients, as described further in §5.

Simulations are initialized with one cell of volume 1.5 cubic units, with maternally deposited morphogen sources already present as specified in §5. Maternal-effect morphogen sources stay closely localized within an embryo [8], and here are taken to remain entirely with one of the two daughters (the one closer to the edge of the embryo) when a cell divides.

Simulations are written in C and visualized using POV-Ray.

## 5 Primitives

In this section I discuss how tissue growth to limited dimensions can be achieved, using morphogen gradients along one (§5.1) or two (§5.2) axes. I also outline how these gradients can be used to provide position references for cells in an embryo (§5.3), and how genetic cascades can trigger downstream events to produce more complex structures (§5.4).

### 5.1 Constrained growth using morphogen gradients

One critical ability in a developmental system is for a structure to grow out to a given size and then stop growing. Doursat [2, 3] accomplishes this with explicit integer hop counts and broadcast signals. Here I explore how it might be achieved with more realistic consideration of morphogen gradients.

I consider two distinct approaches that involve different spatial concentration profiles, one roughly exponential, the other linear. The primary advantage of the first is that it requires only one morphogen. The primary advantage of the second is that growth to a desired size may be accomplished in logarithmic time rather than linear.

**Exponential gradient** A morphogen with a single source, spreading by diffusion and degrading everywhere, will generate an exponentially decaying concentration profile. The length scale is given by the square root of the ratio of the diffusion constant to the decay constant [9]—here, $\sqrt{D_i/d_i}$.

First consider growth starting from a single cell (growth of structures later in morphogenesis will be considered in §5.4). A maternally deposited morphogen source leads to production of a morphogen gradient. Using *bicoid* in *Drosophila* as a motivating example [8,18], I consider a morphogen $M_1$ whose production is confined to the anterior pole of the embryo and whose product diffuses posteriorward (Fig. 2A). Production of $M_1$ occurs at rate 0.05 in the initial cell, and in the more anterior daughter cell each time a cell producing $M_1$ divides, with no production of $M_1$ elsewhere. (Formally, the mother deposits a morphogen source $M_{-1}$ at level $m_{-1} = 1$, which is neither produced nor degraded by the embryo, which remains confined to the anterior pole, and which results in the production

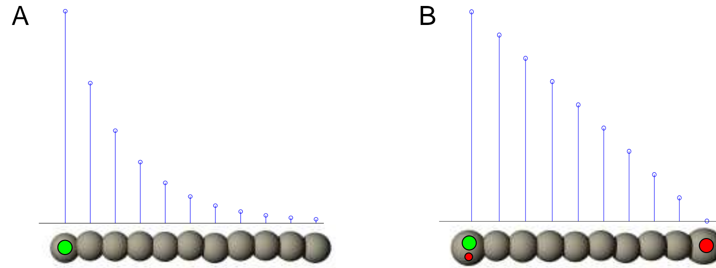


**Fig. 2.** Maternally deposited morphogen sources can lead to the production of a morphogen gradient, which can be used to regulate growth. A: A source $M_{-1}$ (green) at one end, producing a morphogen $M_1$ that degrades at constant rate everywhere, results in an exponentially decreasing $M_1$ concentration profile (stem plot). B: A source $M_{-1}$ (green) at one end producing a diffusible morphogen $M_1$ that does not degrade on its own, and another source $M_{-2}$ (red) at the other end producing a nondiffusible morphogen $M_2$ that degrades $M_1$, results in a linear $M_1$ gradient. With these two sources alone, the slope is independent of distance between the two (so that the concentration at the left end is proportional to that distance); adding a small $M_2$ source to the site of the $M_1$ source limits the $M_1$ concentration there, resulting in a fixed concentration at the left end and a slope inversely proportional to length.

of $M_1$ with rate $s_{1,-1} = 0.05$.) Diffusion of $M_1$ occurs at rate $D_1 = 0.002$, decay at rate $d_1 = 0.001$ everywhere.[1]

A cell can grow if both (1) the concentration $\rho_1$ is high enough and (2) there is no neighboring cell in the "downhill" direction of the concentration gradient. The second condition limits growth to a layer of cells along the posterior edge of the embryo. When division occurs, the cleavage plane is oriented to have its normal vector aligned with the gradient [14].

The final length of the embryo is affected by the concentration threshold at which growth occurs (Fig. 3A) as well as by the diffusion and decay constants $D_1$ and $d_1$. The set of possible final lengths will depend on the ability of cells to resolve differences in concentration levels; in particular, the maximum possible final length will depend on the lowest concentration detectable by a cell. Longer structures will require changing the length scale of the gradient via $D_1$ and $d_1$, and not merely reducing the threshold for growth.

Because growth is confined to a "leading edge" of cell division, the time required to produce a structure of a given length scales linearly with that length (Fig. 3B). The next section considers a mechanism allowing all cells to divide in parallel, resulting in much faster growth.

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[1] These values, and others throughout this paper, are somewhat arbitrarily chosen. Exact parameter choices will affect the exact dimensions of the developing embryo and time course of development, but the qualitative behavior of the developmental process is not sensitive to careful parameter tuning.

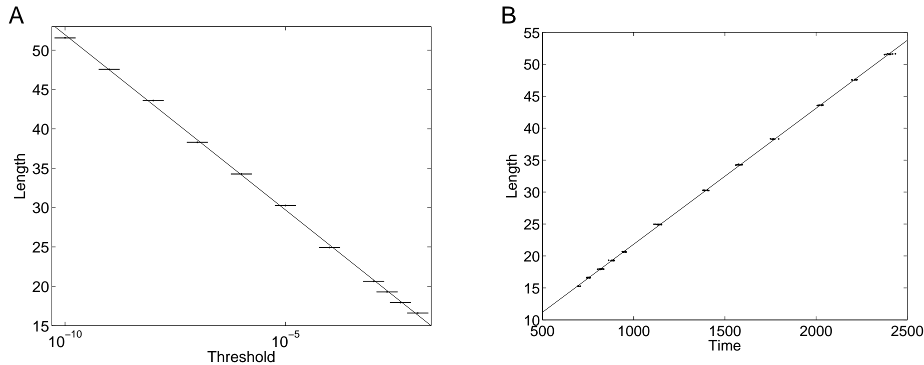


**Fig. 3.** Length control with an exponential morphogen gradient. A: The length of the embryo can be consistently controlled by setting the morphogen concentration threshold at which growth occurs. The relationship is logarithmic (in this example, dividing the threshold by about 1.7 gives an increase in length of one cell). Averages are over 10 independent trials. B: The time required to grow to a given final length is linearly proportional to that length. Each point represents an independent trial.

**Linear gradient** A morphogen produced only at one source and degraded only at one sink will generate a linear concentration profile between the source and sink [7, 9].

A maternally deposited morphogen source $M_{-1}$ confined to the anterior end of the embryo as in the previous section acts as the source for $M_1$, and a second morphogen $M_2$ produced by a maternally deposited morphogen source $M_{-2}$ confined to the posterior end acts as the sink (Fig. 2B). $M_1$ is produced at rate $s_{1,-1} = 0.02$ and $M_2$ at rate $s_{2,-2} = 0.01$. The only effect of $M_2$ is to degrade $M_1$, at rate $d_{12} = 0.05$. $M_1$ does not degrade appreciably on its own ($d_1 = 0$), and $M_2$ is not transferred to cells where it is not produced ($D_2 = 0$). $M_1$ diffuses with rate $D_1 = 0.01$; $M_2$ degrades with rate $d_2 = 0.001$.

With these two maternal deposits $M_{-1}$ and $M_{-2}$, a linear $M_1$ gradient of constant slope will develop between the ends of the embryo; the level $m_1$ at the anterior end will be proportional to the distance between the source and sink. Thus cells at the anterior end can monitor the length of the structure, in a way much like a discrete hop count, and respond in a desired way when the concentration exceeds some threshold. This capability provides a potentially useful tool.

One way to make growth stop when the tissue has reached a desired length, then, is for high levels of $m_1$ to trigger production of an additional, fast-diffusing morphogen that shuts off growth. This approach requires an extra morphogen, however, and potentially a lag while it diffuses during which growth continues asymmetrically at the end away from the source. A more elegant alternative is to add a second deposit of $M_{-2}$ confined to the anterior end, at half the level of that at the posterior end. The level of $M_1$ at the anterior end is then dominated

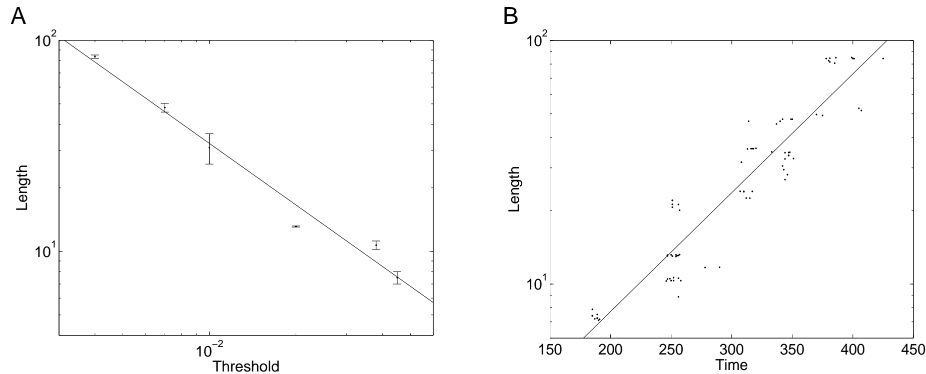


**Fig. 4.** Length control with a linear morphogen gradient. A: The length of the embryo can be controlled by setting the threshold for slope of the morphogen gradient at which growth occurs. The relationship is geometric (halving the threshold doubles the length of the embryo). Averages are over 10 independent trials. B: The time required to grow to a given final length is proportional to the logarithm of that length. Each point represents an independent trial.

by local synthesis and degradation, resulting in a fixed concentration at that site approximately independent of embryo length, and a linear gradient whose slope is inversely proportional to length.

We then specify that a cell can grow if the slope of the $M_1$ gradient exceeds a given threshold; the choice of threshold, and the values of the synthesis and degradation constants, will determine the final length of the structure. All cells in the embryo can simultaneously contribute to its growth, so that the time required to produce a structure of a given length scales logarithmically with that length (Fig. 4B).

**Controlling width via orientation of cell division** When a cell divides, the cell cleavage plane can be influenced by the direction of the gradient [14]. Aligning the plane of division entirely with the gradient leads to growth of the embryo along a straight line; adding a random component to the orientation of the plane results in growth of a wider structure (Fig. 5).

Because the morphogen gradient provides only a local direction reference and not a global one for the developing embryo, stochasticity in the orientation of the cleavage plane can lead to deformation of the overall structure. Fig. 6 shows an example where an embryo has grown in an overall curved shape, using a linear gradient as described above. Although the shape of the embryo can change in this way from trial to trial, its intrinsic size remains reasonably consistent: the length of the embryo was found to vary by less than 15% ($20 \pm 3$) in 9 trials, where length was measured along the shortest cell-to-cell path from source to sink (found using A* search).

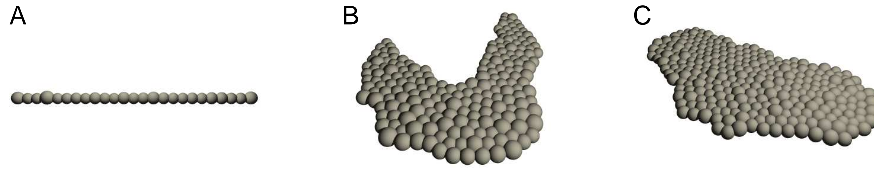


**Fig. 5.** The extent to which the cleavage plane in cell division aligns with a morphogen gradient affects the width of the resulting structure. A: Division aligned completely with gradient. B: Normal vector to plane of division chosen to be 80% aligned with gradient, 20% randomly oriented. Embryo has grown in a curve as in Fig. 6. C: Division randomly oriented. Examples use a linear morphogen gradient with threshold 0.01.

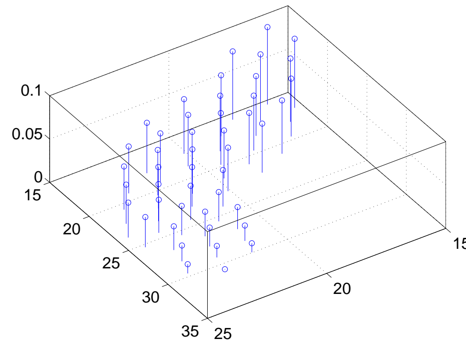


**Fig. 6.** Embryo grown with a linear morphogen gradient, threshold 0.02, and plane of division chosen to be 80% aligned with gradient, 20% randomly aligned. The plot shows the location of each cell in the x-y plane, and the morphogen concentration $\rho_1$ on the z-axis.

### 5.2 Multiple gradients

Multiple independent morphogen gradients can be present in an embryo at the same time, and direct different aspects of its growth. For instance, anteroposterior and dorsoventral axes can be simultaneously established by separate orthogonal gradients, as is the case in *Drosophila* [8]. Two such gradients can allow growth to desired dimensions in both directions.

Fig. 7A shows an example of an embryo grown in this way, using two linear morphogen gradients. A single cell is initialized with four maternal sources: $M_{-1}$ and $M_{-2}$ forming one axis exactly as in the case described above, and an analogous pair $M_{-3}$ and $M_{-4}$ forming another axis. These sources become confined to individual cells as the embryo grows, as in the single-gradient case discussed above. Each cell evaluates the slope of the two gradients independently, and has separate growth thresholds for each, with growth occurring if either threshold is exceeded. When division occurs, the cleavage plane is chosen along one of the two gradients at random, with greater probability for steeper gradients.

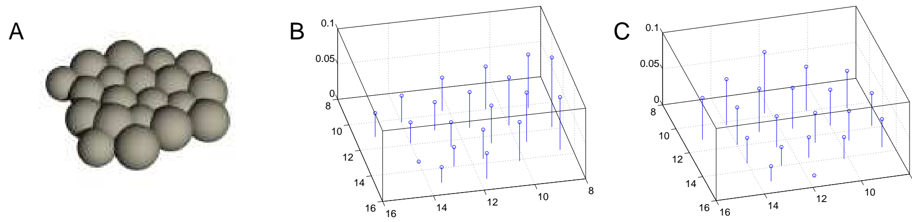


**Fig. 7.** Growth using two independent morphogen gradients. A: An embryo that developed with separate linear gradients as described in the text. B: Concentration $\rho_1$ of one morphogen (source at right, sink at left). C: Concentration $\rho_3$ of the other key morphogen (source at back, sink at front).

### 5.3 Position information

Morphogen gradients provide critical positional information in a developing embryo, allowing cells to undergo differentiation and other key events according to their location [7, 8]. Fig. 7B and C shows how two separate morphogen gradients can serve as cues to establish a two-dimensional coordinate system: the concentration of each gradient carries information about a cell's position along the corresponding axis.

Either exponential or linear gradients can be used in principle for this position information. A cell's ability to localize itself will depend on its ability to resolve differences in concentration, and, when in the presence of noise, on the slope of the morphogen gradient. The profile of an exponential gradient, with its relatively steep drop near the source and shallow slope over most of its length, makes it likely to be less useful than a linear gradient in most situations: with a shallower slope, a given error in estimating the concentration will result in a greater position error.

### 5.4 Cascading effects

With position information available, cells can differentiate by expressing additional morphogens based on their location in an embryo. Fig. 8 shows an example, where cells in the embryo of Fig. 7 can express five additional morphogens $M_5 \cdots M_9$ depending on the concentrations $\rho_1$ and $\rho_3$. Choosing $f_{i1}$ and $f_{i3}$ in Eq. 1 to be sigmoidal functions for $i \in \{5 \cdots 9\}$ allows expression regions to be sharply defined. $M_5$ is expressed where $\rho_3$ is high, $M_6$ where $\rho_3$ is low; $M_7$ is expressed for low $\rho_1$, $M_8$ for intermediate $\rho_1$, and $M_9$ for high $\rho_1$ (details omitted for space constraints).

These morphogens can have additional downstream effects. For instance, we can build on the program that results in the embryo of Fig. 8, adding a morphogen $M_{10}$ produced where expression levels of $M_6$ and $M_9$ are high (purple cells in the figure). Cells for which levels of $M_5$ and $M_7$ are high (red in the figure) respond to $M_{10}$ by growing if $\rho_{10}$ exceeds a given threshold and there is

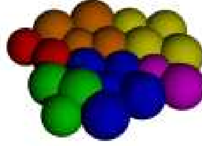

**Fig. 8.** Expression of downstream morphogens in the embryo of Fig. 7. $M_5$ expression is high in the red/orange/yellow regions and low elsewhere; $M_6$ is high in green/blue/purple regions; $M_7$ is high in red/green regions; $M_8$ is high in orange/blue regions; $M_9$ is high in yellow/purple regions.

no neighboring cell in the downhill direction of the $M_{10}$ gradient. In this way we establish a secondary growth process governed by a morphogen with an exponential concentration profile. The morphogen source is produced by the embryo itself rather than maternally deposited factors, and only a subset of cells respond with growth, leading to a narrow "arm" growing out from the main body of the embryo. The resulting structure is the one shown in Fig. 1.

## 6 Conclusion

In this paper I have demonstrated approaches to implementing primitives important for engineered morphogenesis, in ways realistically achievable by real biological systems. While actual realization of these primitives in a synthetic biological system remains far from easy, my hope is that the principles discussed here will help point the way toward engineered morphogenetic systems becoming a reality.

Future work will investigate the control of timing issues in genetic cascades, to explore ways of ensuring that events reliably occur in sequence without using explicit global timing signals; and in a likely related effort, exploring ways of incorporating feedback cycles into genetic cascades rather than using strictly feedforward networks. I also intend to better characterize the mapping between the choice of parameter values and the dimensions of the resulting structure, to allow prediction of structure characteristics from parameters without relying on simulation, and conversely to guide choices of parameter values in order to produce particular desired structures. This last feature will be critical for the eventual goal of global-to-local compilation, the ability to start from a high-level description of a specific user-defined organism and automatically generate a genetic program guaranteed to make a cell develop into that organism. Global-to-local compilation has been achieved in certain related domains [1,5] but remains a challenge for general morphogenetic systems. Another near-term direction for future work is to extend the model to allow three-dimensional deformation of an

epithelial sheet, to begin to incorporate gastrulation and other three-dimensional processes in real morphogenesis into the repertoire of tools available to synthetic systems.

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