Molecular Coordination of Hierarchical Self-Assembly

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Abstract

A serious challenge to nanotechnology is the problem of assembling complex physical systems that are structured from the nanoscale up through the macroscale, but embryological morphogenesis provides a good model of how it can be accomplished. Morphogenesis (whether natural or artificial) is an example of *embodied computation*, which exploits physical processes for computational ends, or performs computations for their physical effects. Examples of embodied computation in natural morphogenesis are found at many levels, from allosteric proteins, which perform simple embodied computations, up through cells, which act to create tissues with specific patterns, compositions, and forms. The fundamental developmental processes, or approximations to them, are feasible in artificial morphogenetic systems, but there are also differences between natural and artificial systems, which future research must address. We present a notation for describing morphogenetic programs and illustrate its use with three examples: simple diffusion, path routing, and the clock-and-wavefront model of segmentation. Much research remains to be done, but we show how

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to implement the fundamental processes of morphogenesis and thereby coordinate very large numbers of agents to self-assemble into multiscale complex hierarchical systems.

Keywords: algorithmic assembly, embodied computation, embodiment, embryological development, metamorphosis, molecular communication, morphogenesis, nano communication, nanofabrication, nanotechnology, Moore's Law, self-assembly, self-organization.

1   Introduction

1.1   Hierarchical Self-Assembly

There has been rapid progress in nanotechnology, but much of it is still at the level of producing novel materials, which must be assembled into macroscopic systems by conventional manufacturing techniques. The value of this approach cannot be denied, because it permits new materials to be integrated into a well-developed manufacturing technology. Complex natural systems are quite different, however, for they grow and develop through self-organization, at many scales from the nanoscale (nanometers) up through the macroscale (meters). Even conventional computer systems exhibit many hierarchical levels, from submicron features, up through devices and circuits, to millimeter-scale cores and chips, to boards and manufactured products. How can we produce artificial systems exhibiting complex structure at many size scales, from nanometers to meters?

1.2   Embryological Morphogenesis as a Model

Embryological development provides an inspiring example of how an extremely complex, hierarchically structured system can organize itself from the nanoscale up to the macroscale. From the nanoscale structures within cells, up through the assembly of cells and other materials into tissues, and tissues into organs, to constitute a living organism. Especially inspiring is the self-organization of the nervous system, which assembles some dozens of neurons into cortical minicolumns, dozens of minicolumns into macrocolumns, tens of thousands of macrocolumns into functional regions (such as the 52 Brodmann areas), and connects these regions into a functional brain with perhaps 100 billion neurons and tens of thousands of connections per neuron.

Although there is much that we do not know about embryological development, it is a clear that it is a process that is primarily self-organized but also conditioned by interaction with the environment [Ede88]. Mechanochemical processes are the principle agents of *morphogenesis* (creation of three-dimensional physical form), for molecules mediate both communication and the bonds that transmit mechanical force.

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Therefore, aside from its practical applications in nanotechnology, morphogenesis can teach us how molecular communication and control can coordinate nanoscale assembly.

1.3 Self-assembly of Robots

While there will be many applications of multiscale hierarchical self-organization in nanotechnology, one of the most compelling is the assembly of future robots and their components. Advanced robotic systems will require sensors, effectors, and control systems with a complexity approaching or even exceeding corresponding natural systems.

For example, we would like to have an artificial retina with capabilities comparable to the human retina, which comprises some 100 million sensors and intraretinal neural processing that compresses the data into about a million optic nerve fibers. To construct an artificial retina of comparable complexity, we will need to assemble hundreds of millions of components into a functional organization, and self-organization seems the most promising approach.

Artificial robot skin is another good candidate for artificial morphogenesis. Our ability to grasp objects securely but delicately, and to manipulate them flexibly, depends on detailed haptic and cutaneous input from millions of sensors in our skin, underlying flesh, joints, etc. How can these sensors be incorporated into a flexible but tough artificial skin and be appropriately connected to the robot's central control and coordination system? Artificial morphogenesis is a promising possibility.

Likewise, effectors capable of delicate, highly coordinated movement may require artificial muscles with a complex micro- or nanostructure. In humans and other vertebrates, millions of neurons control individual muscle fibers in order to achieve fluent motion.

Recent decades have demonstrated the value of neural networks for implementing adaptive cognitive and control systems. But brain-scale artificial neural networks will require new approaches to creating artificial neurons and assembling them into functional circuits. The best example of how to do this is the embryological development of the vertebrate brain. Likewise, the "nerves" of such robots will have to be wired in a self-directing fashion. In addition to the difficulty of routing them, their inputs and outputs will be into dense sensor, actuator, and neural arrays comprising large numbers of microscopic elements.

However, accomplishing artificial morphogenesis at this scale requires computing to be conceptualized in less abstract terms than we usually do.

2 Embodied Computation

2.1 Embodied Intelligence

In recent decades there has been growing recognition of the importance of embodiment as a foundation for intelligence [Bro91, Cla97, CC98, Dre79, IPSK04, JR07, Men10, PB07, PLI07, PS99]. Whereas it had been traditional in artificial intelligence and cognitive science to suppose that intelligence requires complex internal models of the body and the world in order to behave competently, it has been found that embodied agents can function competently without these complex models by exploiting their bodies and their physical environments as their own models. Embodied agents do not require a complex analytical model of their world in order to behave competently in it. Information structures emerge from an agent's purposeful interaction with its physical environment.

Furthermore, the embodied perspective recognizes that often the goal of intelligence is not to obtain some abstract *answer*, but to have some *physical effect* in the physical world. This could be moving from one place to another, capturing prey, avoiding predators, eating, mating, etc. This is especially the case in morphogenesis, for the information processing, communication, coordination, and self-organization of the cells is directed toward the creation of a specific physical object — the newborn organism. Likewise in artificial morphogenesis, the goal is less information processing than physical effect; communication and computation are a means to this end.

2.2 Definition of Embodied Computation

We may extend the ideas of embodied intelligence to computing in general [Mac08, Mac09a, Macss]. *Embodied computation* may be defined as computation in which the physical realization of the computation or the physical effects of the computation are essential to the computation. In terms of its essential dependence on its realization, embodied computation is similar to *material computation* and the *in materio computer* [Ste04, Ste08], but the centrality of physical effect to its definition allies it to embodied cognition. Embodied computation will be increasingly important in our pursuit of post-Moore's Law computing technologies [Mac08, Mac09a, Macss, Mac09c].

2.3 Embodiment and Nanocomputation

Nanocomputation forces a convergence of the informational and the physical that requires an embodied approach. First, nanocomputation is closer to the physical processes that realize it. Hitherto computers have been built on many levels of abstraction. For example, real numbers and operations on them are implemented in

terms of many bits and sequential circuits that process them. Individual bits and circuits, in turn, are composed of many individual transistors and other circuit elements. Even here there are levels of abstraction; for example, flip-flops use continuous physical laws to implement discrete devices by operating transistors in saturation. As we push towards higher densities and higher speeds, we will not have the luxury of these levels of abstraction, and our computational models will have to become more like fundamental physical processes [Mac09c].

Another reason that embodiment is essential to nanocomputation is that the physical effects that we are accustomed to ignore in contemporary computing are proportionately larger and cannot be abstracted away. For example, noise (e.g., thermal noise), quantum uncertainty, faults, defects, randomness and other deviations from an idealized perfection are all unavoidable. Rather than viewing these effects as undesirable intrusions on computation, it is better to reconceptualize computation in terms of these inevitable characteristics of nanoscale systems, and so make productive use of them. For example, noise, uncertainty, faults, etc. can be exploited as sources of useful *free variability* (as used for example in stochastic optimization).

Furthermore, and especially relevant to nanoscale self-assembly, the physical realizations of computation are often at the same scale as their intended physical effects. Therefore, there is no need for actuators to translate low-level control signals into large-scale physical effects; the same physical processes that realize the computation may constitute its physical effect. At the nanoscale, computation may be truly embodied in that input and output transduction is unnecessary [Mac08]. (As will be explained in Sec. 3.1, allosteric proteins are excellent examples of this coincidence of the physical and the computational.)

3 Embodied Computation in Morphogenesis

3.1 Proteins as Computational Elements

Proteins are fundamental agents of embodied computation, because they are the nexus of informational and physical processes in living things. The function of a protein, of course, depends primarily on its shape, on the chemical groups that are thus hidden or exposed, and on its resulting affinities, but also on the protein's dynamical properties.

A protein's physical structure is determined by its amino acid sequence, which is encoded in DNA and transcribed into RNA. The resulting polypeptide sequence folds up into a complex three-dimensional shape with characteristic mechanical, chemical, and other physical properties relevant to its function in the organism. In this case we have a fairly direct relationship between an information structure, as encoded in the DNA, and a functional physical structure (the protein molecule). The DNA is

not some abstract blueprint for the protein's physical structure, but by its translation into a polypeptide sequence it self-organizes into a physical structure.

Fundamental to embodied computation at the cellular level are *allosteric proteins*, which have multiple conformations with different functions, and can be switched between these conformations by binding regulatory molecules [Bra09, pp. 63–5, 78–9]. In these cases the information processing function — the decision to function in different ways depending on the regulatory input — is realized directly by the change in protein shape cause by the regulatory molecule. Some allosteric proteins have nine regulatory sites and can respond to various combinations of regulators, implementing hierarchical regulation, making these proteins more complex than simple switches [Bra09, pp. 63–5, 78–9].

3.2 Tissues

During embryological morphogenesis cells interact primarily in two kinds of tissue, *mesenchyme* and *epithelium*, which often interact in pairs [Ede88, pp. 16, 21].

Mesenchyme is a tissue in which largely unattached cells are suspended or migrate through a three-dimensional *extracellular matrix* composed of proteins, polysaccharides, and other nonliving substances. It is viscoelastic "soft matter" through which cells can move and morphogens can diffuse [FN05, p. 3].

In contrast to mesenchyme, cells may be tightly bound into sheets, called *epithelia*. Typically the cells are arranged in a polarized orientation, bound side to side, with their apical ends forming a tight seal on one side of the sheet, and their basal ends, on the other side, contacting an extracellular matrix, often in the form of a *basement membrane* [Ede88, p. 68]. Although the cells are bound together, they are still able to move relatively to each other, which is an important morphogenetic mechanism [Ede88, pp. 71–8].

Epithelia are essential vehicles for morphogenesis, for as they fold, stretch, and deform in other ways, they bring different cells and tissues in contact with each other, triggering further morphogenetic processes [Ede88, pp. 71–8]. Among other functions, epithelia confine cell migration and morphogen diffusion, thus altering the progress of morphogenesis.

Also essential to morphogenesis are *epithelial-mesenchymal transformations*, in which mesenchyme may condense into an epithelium, or an epithelium "dissolves" and disperses into mesenchyme [Ede88, pp. 67–71].

3.3 Fundamental Morphogenetic Processes

What are the fundamental mechanisms of embryological morphogenesis? Edelman has categorized the primary processes of morphogenesis into *driving forces* and *regu-*

latory processes [Ede88, p. 17]. The driving forces are cell division, cell death, and cell movement, and the regulatory processes are cell adhesion and cell differentiation. Some of these processes have obvious analogs in artificial systems, but others do not, an issue we address later (Sec. 4.2).

More specifically, biologists have identified a dozen or so processes that seem to be sufficient for natural morphogenesis, summarized into a convenient taxonomy by I. Salazar-Ciudad, J. Jemvall, and S. A. Newman [SCJN03]. First, they distinguish (1) *cell autonomous* mechanisms, in which cells do not interact, (2) *inductive* mechanisms, in which cells signal each other, resulting in a change of cell state, and (3) *morphogenetic* mechanisms (in the narrow sense), in which cells interact, resulting in pattern changes but not state changes.

There are three cell autonomous mechanisms: *division of a heterogeneous egg*, in which a heterogeneous distribution of proteins and other materials in the egg leads to a heterogeneous distribution in the daughter cells, *asymmetric mitosis*, in which gene products are differentially transported to the daughters during cell division, and *internal temporal dynamics coupled to mitosis*, in which cyclic expression of genes is uncoupled with the cell cycle, so that daughter cells acquire different states. Since artificial morphogenesis is unlikely to use self-reproduction as a means of tissue growth (see Sec. 4.2), we expect cell autonomous mechanisms to take a smaller role in artificial morphogenesis than in its natural inspiration; their role in complex pattern creation is in any case limited [SCJN03]. Rather, in artificial morphogenesis newly arriving agents will have their states determined by agents already present, primarily by inductive mechanisms, to which we now turn.

Inductive mechanisms may be classified as *hierarchical* or *emergent*, both of which involve cell signaling by means of secretion of diffusible chemicals, by membrane-bound chemicals, or by direct signaling through cell-to-cell junctions. Hierarchical induction refers to mechanisms by which one group of cells influences another, but in which any backward signaling does not affect the first group's signaling. This is not the case for emergent (or self-organizing) induction, in which there are reciprocal effects between signaling regions. Examples include reaction-diffusion processes, which are basic to embryological pattern formation [Mei82, Tur52]. In general, emergent mechanisms seem more capable of producing a variety of complex patterns than hierarchic ones [SCJN03].

This is also the case for morphogenetic mechanisms (in the narrow sense of processes that rearrange cells without altering their states), but which depend on the mechanical properties of cells and the extracellular matrices, including their viscosity, elasticity, and cohesiveness [SCJN03]. One of these morphogenetic mechanisms is *directed mitosis*, which causes daughter cells to be located at specific positions relative to an oriented mother cell; although artificial morphogenesis might not use mitosis, a similar effect can be achieved by having newly arriving agents assume an orientation

with respect to existing agents. A mechanism more appropriate to artificial morphogenesis is *differential growth*, in which regions growing at different rates can affect the developing form. *Apoptosis* (programmed cell death) can lead to a change of form through the consequent rearrangement of the surrounding regions; although artificial agents do not literally die, the effect of apoptosis can be achieved by having agents leave the system or by having them disassemble themselves (see also Sec. 4.2).

Migration is a fundamental morphogenetic mechanism, in artificial systems as well as natural. Movement may be guided by a chemical gradient (*chemotaxis*) or by an adhesive gradient in an insoluble substrate (*haptotaxis*), and non-directed movement may be speeded or slowed by an ambient chemical signal (*chemokinesis*). This is the heart of molecular communication in morphogenesis, and it is here where we see most clearly the role of molecular coordination in self-assembly. However, full exploitation of these processes will require the development of artificial agents able to respond to molecular signals and to control their molecular interaction with other active agents and with inactive structures.

Differential adhesion is a morphogenetic mechanism by which cells can sort themselves into distinct populations [BFG00, Hog00]; combined with cell anisotropy and non-uniformly distributed adhesive molecules, differential adhesion can lead to the formation of lumens (cavities), invaginations, evaginations, and other functional forms [FN05, ch. 4]. Differential adhesion is also fundamental to epithelial-mesenchymal transformations (Sec. 3.2). We expect differential adhesion to play an important role in artificial morphogenesis, since there are variety of ways to control adhesion between artificial agents (Sec. 4.2).

Contraction is a morphogenetic process resulting from individual cell contraction, which can change the shape of tissues, either by direct cell-to-cell connection in epithelium or by mechanical transmission through an extracellular matrix in mesenchyme. Therefore it will be useful if artificial morphogenetic agents also have some ability to change their shape.

The last class of morphogenetic processes affects the viscoelastic extracellular matrix, leading to a change of tissue shape. For example, cells may add to or degrade the matrix material, or through hydration cause existing matrix material to swell. We expect that artificial morphogenesis will also make use of *matrix deposition and loss*, perhaps in preference to mitosis and apoptosis, by having artificial agents secrete, absorb, or otherwise manipulate inert materials and inactive components.

Finally, Salazar-Ciudad et al. [SCJN03] observe that inductive and morphogenetic mechanisms can interact in two fundamentally different ways. Simplest is *morphostatic* interaction, in which inductive mechanisms establish "genetic territories" (or "morphogenetic fields") on which, afterwards, morphogenetic mechanisms operate. That is, induction establishes a spatial pattern of cell states, which then govern the morphogenetic reshaping of three-dimensional form. In contrast, induction and mor-

phogenesis are simultaneous in *morphodynamic* interaction, which is therefore much more complicated to understand, but also more capable of producing complex patterns and forms. The challenge for artificial morphogenesis is to understand both morpho-static and morphodynamic interactions in order to self-assemble complex, functional hierarchical structures.

4 Artificial Morphogenesis

4.1 Morphogenesis as Embodied Computation

Embryological development uses molecular interactions to regulate and coordinate morphogenesis in order to generate complex hierarchical systems, organized from the nanoscale up through the macroscale. Our goal is to understand this process as embodied computation, so that we can identify which physical relationships are essential to it, in order to realize them in different, artificial self-assembling systems. In particular, this will help us to understand how to exploit molecular coordination at the nanoscale in order to realize complex embodied computation.

For example, we know that diffusion is an important means of signaling and co-ordination in development, for it can broadcast information through a region, or establish gradients that create patterns. In many cases the particular molecules that diffuse are not so important as more abstract properties: that they can be produced and detected by the agents, and that they have certain relative diffusion and degra-dation rates relative to other processes. Nevertheless, physical diffusion is a process that can be profitably exploited at the nanoscale, and so we should learn how to use it.

A closely related process occurs when a sufficiently stimulated cell produces a signal that stimulates nearby cells. This causes a wave of activity to propagate through the medium. Examples of such *excitable media* are found in the propa-gation of neural action potentials [GK02], the aggregation of the slime mold *Dic-tyostelium discoideum* [Kes01, PC96], and the clock-and-wavefront model of somito-genesis [CZ76, DP08, GOW$^+$08], among others. Excitable media can be implemented in many different ways, and so they can be implemented in many systems for the pur-poses of morphogenesis.

As discussed in Sec. 3.3, chemotaxis is an important morphogenetic mechanism, but it can be implemented by a variety of means. All that is required is the estab-lishment of a gradient — perhaps by diffusion of a signal molecule — and an agent capable of moving up or down the gradient. Whether the gradient is of molecular concentration, of adhesion, of electrical charge, or of something else matters only insofar as the agent can follow it on the intended length scale.

In general terms our approach is to take natural morphogenetic processes, express them mathematically (if not already done in the literature), and understand them in general physical terms (e.g., diffusion, adhesion, attraction, stress, pressure). This abstract description is the essence of the embodied computation, which can then be realized by other physical systems conforming to the mathematical description (which constitutes, in effect, a morphogenetic "program"). Even models that have been rejected as explanations of morphogenesis in embryos may be useful in artificial systems, if they have the correct dynamical behavior.

In general, artificial morphogenesis can be considered a species of *amorphous computing* [AAC+00], but — especially after the morphogenetic process has progressed — it is anything but amorphous. Indeed, it is prior forms that create the conditions that govern the creation of later forms. There has, of course, been much work in the computational modeling of natural morphogenesis, some of which is applicable to our project, but our goal is nanotechnological. Other researchers have addressed similar goals, for example in the context of reconfigurable robotics, and sometimes inspired by morphogenesis [GCM05, MK07, NKC03], but in our opinion they have not taken full advantage of developmental science nor faced up to the problem of very large numbers of agents (hundreds of thousands to hundreds of millions).

4.2   Natural vs. Artificial Morphogenesis

Depending on the realization medium, there may be significant differences between natural and artificial morphogenesis. Of course, if genetically-engineered organisms are used for artificial morphogenesis, then the differences from natural morphogenesis might not be great, but in this paper we will focus on artificial agents that may use biological materials but are not living organisms (see Fig. 1). Therefore we must consider the way that morphogenetic processes need to be adapted for artificial agents.

Among the primary processes of morphogenesis, Edelman lists three *driving forces*. The first is *cell proliferation*, which results from cell division, and is the principal means by which tissues increase in size. However, at this time we do not have a feasible means of making self-reproducing artificial agents, and so proliferation must be accomplished by different means in artificial morphogenesis.

One approach is to provide a supply of new (or recycled) agents, but they will need a path to proliferation sites, which creates additional problems. It is difficult to tell at this time whether this problem will be a minor difference between natural and artificial morphogenesis, or whether it will dictate wholly new approaches in artificial systems. Fortunately, simulations will be useful in determining alternative approaches to cell division.

Another driving force is programmed cell death (*apoptosis*), that is, *cell elimination*, which is one of the most important processes for sculpting tissues and for
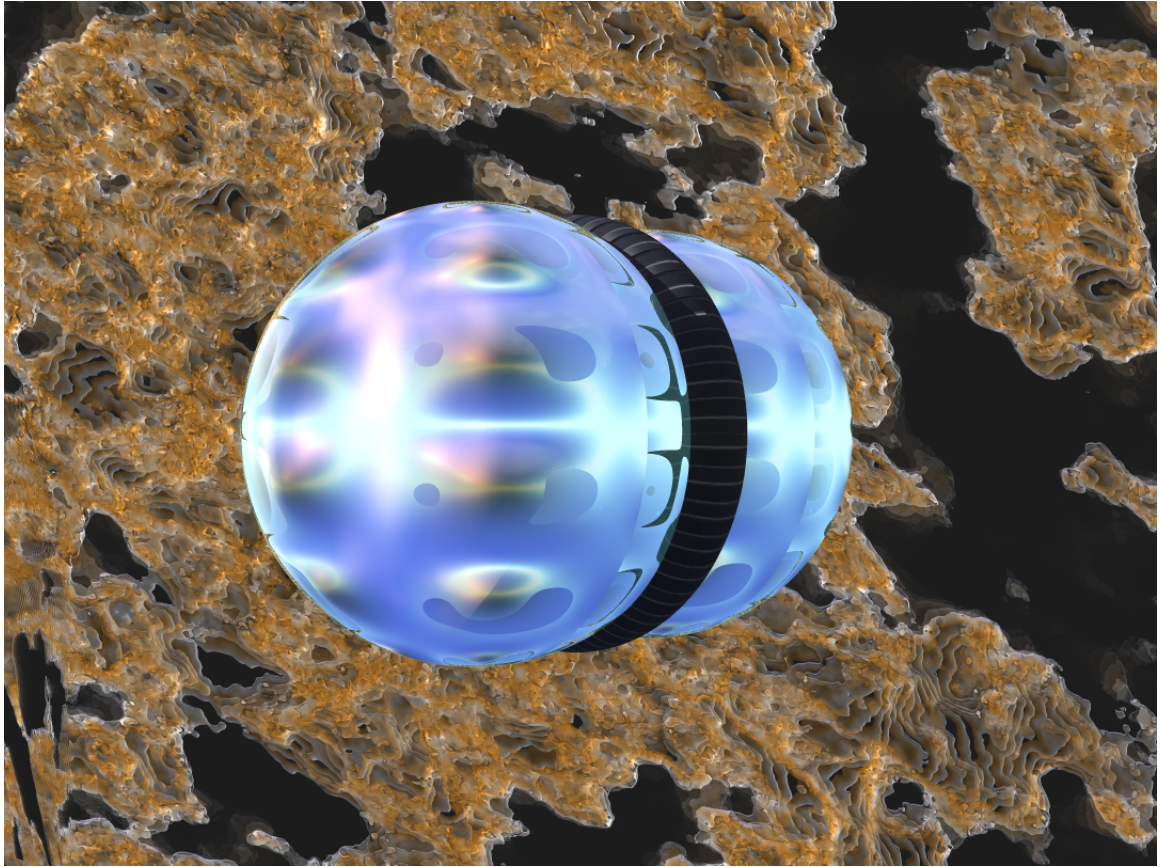
Figure 1: Artistic depiction of microrobot. Such a robot might have molecular sensors and actuators to allow temporary or permanent attachment to other robots or to inactive structures. At least limited ability to change shape would be useful for artificial morphogenesis.

fine-tuning structure (as in the nervous system). Artificial analogues are much more feasible than for cell division, since it is easy to imagine mechanisms by which artificial agents inactivate and even disassemble themselves. However, the end products may be less amenable to reabsorption or recycling than natural substances, but this does not seem to be an insurmountable problem. Again, simulations will allow alternative approaches to be explored.

The third driving force is *cell migration*, and the principal means by which cells move during morphogenesis is by changing shape (e.g., by extending lamellipodia) and controlling their adhesion to other cells and to the extracellular matrix. Adhesion is implemented by a variety of *cell adhesion molecules* (CAMs) and *substrate adhesion molecules* (SAMs), which are deployed on the cell membrane in an orchestrated but stochastic manner [Ede88, ch. 7].

It seems unlikely that artificial agents will have a comparable flexible shape, or the variety of CAMs and SAMs or flexibility in deploying them. However it is plausible that migration of artificial agents will be primarily be means of control of local adhesion. But we may have to adapt some morphogenetic processes to accommodate artificial agents with more limited locomotive abilities than their natural counterparts. Electrostatic adhesion is another possibility [GCM05], but it does not have the specificity of molecular adhesion, which may be crucial for morphogenesis.

In addition to the driving forces, Edelman includes two regulatory processes among the primary morphogenetic processes. The first regulatory process is *differentiation*, by which a cell changes its genetic expression and thereby becomes more specialized in its function. There are several ways that artificial morphogenetic agents can accomplish the same purpose. Obviously, any computational system can have multiple internal control states that regulate its operation, and this is the direct analogue of cell differentiation. Protein and genetic regulatory circuits in cells correspond in many ways to electrical circuits [Bra09, Bra95]. However, internal states occupy physical resources, and artificial microscopic agents might have limited internal state spaces.

Natural morphogenesis operates with genetically identical cells descended from a single cell. (An exception would be the quasi-morphogenetic assembly of genetically diverse slime mold amoebae into an organized "slug.") However, artificial morphogenetic processes are not constrained in this way. Since proliferation cannot be implemented through self-reproduction, but requires an external source of new agents, therefore differentiation can be handled by providing agents of different kinds. However, this does require a change in morphogenetic processes, since instead of agents differentiating in situ, already specialized agents will have to find their way to their destinations from outside the tissue. In practice, we expect that artificial morphogenesis will make use of both processes, with specialized agents further differentiating by change of internal state.

The second regulatory process is adhesion, both cell to cell and cell to substrate.
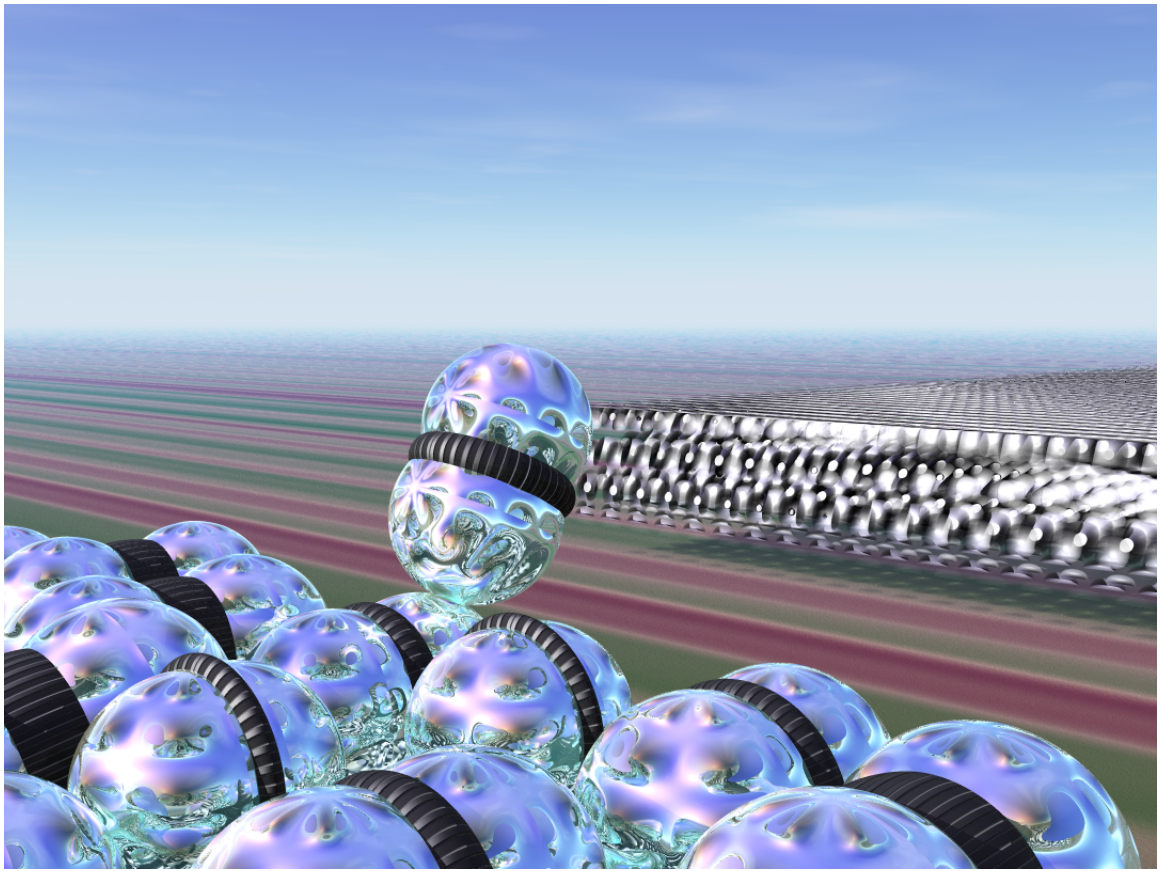
Figure 2: Artistic depiction of microrobots self-assembling to form artificial tissues. Microrobots might use molecular or electrostatic means of adhering to each other or to other, inactive structures or components.

Adhesion has mechanical functions, as a basis of cell motion and of both elastic and rigid tissues, but adhesive molecules also provide signals regulating differentiation, epithelial-mesenchymal transformations, etc. Therefore we must consider how analogous functions can be accomplished with artificial agents (see Fig. 2). For example, temporary adhesion, especially for purposes of migration, might be implemented by electrostatic or magnetic actuators [GCM05]. The same would apply to epithelial-mesenchymal transformations. More permanent adhesion could be implemented by mechanical latching [RV00].

As discussed in Sec. 3.3, extracellular matrix depletion and loss are fundamental morphogenetic processes. The extracellular matrix is the medium through which mesenchymal cells move, it is a medium through which morphogens diffuse, and it provides a substrate to which cells adhere — all important functions in artificial morphogenesis as well. Furthermore, although active agents (cells or microrobots) are often the medium of morphogenetic self-assembly (see, e.g., Fig. 2), agents may also arrange inactive components and substances as part of the final structure. Non-living agents may be less capable of producing these substances than living cells, and so in some applications we will have to find alternative solutions. For example, rather than having agents produce materials in situ, they may have to go and transport them from an external supply, or bring them along when they are arriving externally in lieu of in situ reproduction. Which solution is most appropriate will depend on the details of the morphogenetic process, including the relative quantities of material involved. Similar considerations apply to matrix elimination.

Cells have flexible membranes and, by controlling their cytoskeletons, are able to change shape in a variety of ways; they are also able to redistribute the adhesive molecules on their membranes. These capabilities are important for contraction, differential adhesion, and other morphogenetic processes (Sec. 3.3). Although artificial agents may have similar capabilities, we expect them to be less extensive and less flexible. It is difficult to evaluate the effect of these differences without the capabilities of a specific microrobot in mind, although some of the possibilities may be explored through simulation.

As explained in Sec. 1.3, future robotic systems will require artificial morphogenesis for their assembly. In particular, we expect that intermediate and long distance connections will be required, for example, to implement the robotic "nervous system." During embryological development, neurons send out long projections (*neurites*), which find their way to their destinations, primarily by following chemical signposts. It seems unlikely that foreseeable microrobots will be able to change their shape and grow to this extent, so artificial morphogenesis may have to find alternative approaches to creating long distance connections. For example, a microrobot (analogous to a neural *growth cone*) can follow the signposts, creating a path from the origin to the destination by depositing some substance in its wake. (See Sec. 5.2,

below, for a simulation of an artificial morphogenetic program for generating such connections.)

4.3   Levels of Description

Biologists use a variety of means to describe morphogenetic processes, including mathematical equations, agent-based models, and qualitative descriptions, such as *influence diagrams* [Bon97, TA07]. To enable the development of artificial morphogenesis, we have been developing and evaluating a formal notation, which can be thought of as a kind of programming language, oriented toward artificial morphogenesis [Mac09b, Mac10a, Mac, Mac10b] (see Sec. 5 for examples).

Morphogenetic agents are discrete (e.g., cells or microrobots), but — especially in the context of complex, hierarchically structured systems — the numbers of agents are so large that it is generally convenient to treat them as a continuum. Biologists often make use of partial differential equations and continuum mechanics to describe these processes [FN05, Mei82, BFG00, Tab04], and we have found this to be a useful mathematical framework.

One advantage of a continuum approach over more agent-based models is that it ensures that our morphogenetic processes scale up to very large numbers of very small agents, for in the continuum limit we have an infinite number of infinitesimal agents. We take this to be an advantage over some other approaches to self-assembly, programmable matter, etc. that have been demonstrated (generally in simulation) for modest numbers of agents (generally, at most hundreds), but do not obviously scale up to very large numbers (tens of thousands to millions or more).

Nevertheless, it is sometimes more convenient to treat tissues as collectives of discrete agents. One reason is that there may be small-sample effects when the density of agents is low, and in these cases it may be better to treat the agents from the perspective of statistical mechanics. Another reason is that it is sometimes more intuitive to describe behavior from an agent-oriented perspective, that is, a cell- or robot-eye view [Bon97]. Our approach to this issue is to use a *material* (Lagrangian) reference frame, as opposed to a *spatial* (Eulerian) frame [Mac09b, Mac10a, Mac, Mac10b]. We are also developing formal tools to help us negotiate the borderlands where the continuum approximation is not appropriate [Mac09b, Mac]. In general, in our development of techniques and notation, we are attempting to maintain complementary perspectives, so that continuum methods also apply to large numbers of spatially organized discrete elements.

More specifically, the requirements of complementarity have dictated a different spatial scale from some other approaches to describing morphogenesis. For example, COMPUCELL3D models morphogenetic processes at a level below individual cells in order to be able to address changes in cell shape [CHC⁺05]. We, however,

describe morphogenesis at a higher level, at which differential volume elements represent ensembles of agents. This requires some special approaches, described elsewhere [Mac09b, Mac10a, Mac, Mac10b], for dealing with ensembles whose constituent agents might not all have the same values for their properties, and for dealing with properties such as shape and orientation.

4.4   Change Equations

As have most biologists, we have found it most convenient to describe morphogenetic processes by means of differential equations. However, sometimes it is convenient to treat them as discrete-time processes, for example, when they are simulated on a digital computer.

Therefore, we have been experimenting with formal *change equations*, which have complementary interpretations as differential equations and finite difference equations. For example, the change equation

$$Đ X = F(X, Y, \ldots)$$

can be interpreted as a differential equation, $\partial X/\partial t = F(X, Y, \ldots)$, or as a finite difference equation, $\Delta X/\Delta t = F(X, Y, \ldots)$, where the time step Δt is implicit in the notation. The formal rules for manipulating change equations respects their complementary continuous-time and discrete-time interpretations.

4.5   More and Less Specific Implementations

Embodied computational processes can be more or less specific to particular physical realizations; they may depend on physical properties and processes that are more or less common. Therefore, in developing an embodied computational process we must decide how specific to particular class of physical realizations we want it to be. For example, in morphogenesis, we do not want to tie ourselves to accomplishing things the same way as an embryo does. A more abstract description of the natural process may have alternative realizations that are just as effective but more suitable to artificial morphogenesis.

For example, in embryological somitogenesis cell proliferation causes the embryo's tail bud to recede from its head end because the new cells push them apart (see Sec. 5.3 below). However, for the purposes of somitogenesis all that matters is that the distance between the head region and tail bud increases while maintaining a constant cell density between them. One way to accomplish this is the way the embryo does, with cell division increasing the tissue volume and pushing the head and tail apart. But for artificial morphogenesis is might be more feasible to accomplish the same

effect in a different way. For example, the tail bud agents could migrate away from the head, which would tend to decrease the agent density between the head and tail. The decrease in density could recruit agents from an external supply to join the intermediate tissue and restore the density to its nominal value. Here we have two more-specific realizations of one more-abstract embodied computational process.

Analogous to the class and subclass structure in object-oriented programming languages, we can see that embodied computational processes, in morphogenesis and other applications, can be arranged in hierarchies of more or less specific physical behavior. As will be shown in the following examples, our morphogenetic programming notation defines substances in a similar class hierarchy.

5 Examples

5.1 Simple Diffusion

To illustrate our experimental notation for artificial morphogenesis, we begin with a simple, familiar example, diffusion. The fundamental concept is a *substance*, which is a class of materials with common properties and behavior (analogous to a *class* in an object-oriented programming language). A morphogenetic program comprises a number of *bodies* or *tissues*, each an instance of a substance. (Bodies are analogous to the objects of object-oriented programming.) As in continuum mechanics, a body or tissue is treated as a continuum of *material points*, which undergoes deformation as a result of its dynamical laws [FN05, Tab04]. A fundamental property of every material point in a body is $\mathbf{p}$, its position in three-dimensional space. Therefore, in the simplest case diffusion is defined by a stochastic differential equation governing the position of each point:

$$\mathrm{D}\mathbf{p} = \boldsymbol{\mu} + \boldsymbol{\sigma}\,\mathrm{D}\mathbf{W}.$$

Here $\boldsymbol{\mu}$ is a vector field defining a drift velocity (perhaps caused externally) at each point in space; the Wiener derivative $\mathrm{D}\mathbf{W}$ is an n-dimensional random vector (normally distributed with zero mean and unit variance in each dimension), which is the source of n degrees of random variability (Brownian motion) for the particle; and $\boldsymbol{\sigma}$ is an $3 \times n$ tensor field, which — at each point in space — describes three-dimensional diffusibility resulting from the sources of randomness. (Consistent complementary discrete and continuous interpretations of the above stochastic differential equation require that it be interpreted according to the Itō calculus, as explained elsewhere [Mac09b, Mac, Mac10b].)

Our notation declares the fundamental variables (without specifying their values) and defines the behavior of the substance (here called *morphogen*):

substance morphogen:

  vector field $\boldsymbol{\mu}$ $\parallel$ drift velocity
  order-2 **field**$(3 \times n)$ $\boldsymbol{\sigma}$ $\parallel$ diffusion tensor
  order-1 **random**(n) $\mathbf{W}$ $\parallel$ random motion

  behavior:

$$\text{Đ}\mathbf{p} \;=\; \boldsymbol{\mu} + \boldsymbol{\sigma}\,\text{Đ}\mathbf{W}$$

The above is a particle-oriented (or agent-oriented) description of diffusion, but often we want a higher level description that addresses the probability density of particles and how it evolves in time. This is provided by Fokker-Planck equation for the probability density ϕ:

$$\text{Đ}\phi = \nabla \cdot [-\boldsymbol{\mu}\phi + \nabla \cdot (\boldsymbol{\sigma}\boldsymbol{\sigma}^{\mathrm{T}}\,\phi)/2].$$

We describe this in our notation, where for convenience we define the 3×3 diffusion tensor field $\mathbf{D} = \boldsymbol{\sigma}\boldsymbol{\sigma}^{\mathrm{T}}/2$ and express the equation in terms of the particle flux $\mathbf{j}$:

  substance morphogen:

    scalar field ϕ $\parallel$ concentration
    vector fields:
        $\mathbf{j}$ $\parallel$ flux
        $\boldsymbol{\mu}$ $\parallel$ drift velocity
    order-2 **field** $\mathbf{D}$ $\parallel$ diffusion tensor

  behavior:

$$\begin{aligned}
\mathbf{j} &\;=\; \boldsymbol{\mu}\phi - \nabla \cdot (\mathbf{D}\phi) && \parallel \text{ flux from drift and diffusion} \\
\text{Đ}\phi &\;=\; -\nabla \cdot \mathbf{j} && \parallel \text{ change in concentration}
\end{aligned}$$

The preceding notation defines the substance *morphogen*, but it does not define any bodies of this substance. This is accomplished by a definition such as the following, where for simplicity we define a body called *Volume*, whose initial state has a small concentration of particles around the origin:

  body Volume **of** morphogen:
      for $X^2 + Y^2 + Z^2 \leq 1$:
          $\mathbf{j} = 0$ $\parallel$ initial 0 flux
          $\boldsymbol{\mu} = 0$ $\parallel$ drift vector
          $\mathbf{D} = 0.1\mathbf{I}$ $\parallel$ isotropic diffusion
      for $X^2 + Y^2 + Z^2 \leq 0.001$: $\phi = 1$ $\parallel$ initial density inside sphere
      for $X^2 + Y^2 + Z^2 > 0.001$: $\phi = 0$ $\parallel$ zero density outside sphere

5.2 Path Routing

To illustrate one mechanism by which long range connections might be established, as for an artificial neural cortex, we present a path-routing process inspired by neuron growth. The goal is to make paths through a three-dimensional medium from specific origins to corresponding destinations without colliding with (or coming too close to) existing paths.

The destination secretes an *attractant A*, which diffuses through the medium and degrades (or leaves the system) at certain rates. Existing paths clamp the attractant concentration to 0. A body of agents (which, by analogy with neurogenesis, we call a *growth cone*) follows the gradient of the attractant at a constant velocity, which leads it to the destination while avoiding collisions with existing paths. As the growth cone moves through the medium, it creates the path in its wake.

We begin with a definition of the medium through which the attractant diffuses. The principal variable is A, attractant concentration, but there is also G, which represents the concentration of goal (or destination) markers, and P, which represents the concentration of markers for new or existing paths. Various constants govern diffusion and degradation.

substance medium:
scalar fields:

A	‖ attractant concentration
G	‖ goal concentration
P	‖ path concentration

order-2 **field** $\mathbf{D}_A$ ‖ attractant diff. tensor
scalars:

τ_A	‖ attractant decay constant
γ	‖ attractant deposition accel. rate
τ_P	‖ path clamping constant

behavior:

$$\text{‖ diffusion - decay + goal signaling - path clamping:}$$
$$\text{Đ}A \;=\; \mathbf{D}_A \triangle A - A/\tau_A + \gamma G A - P/\tau_P$$

The behavioral equation describes the change in attractant concentration. The first two terms are diffusion and degradation (in which we use $\triangle = \nabla \cdot \nabla$ for the Laplacian operator on tensor fields); the third term defines accelerating generation of attractant in the goal region; and the fourth term represents the elimination of attractant in existing and new paths (assuming $\tau_P \ll \tau_A$).

The growth cone is a body composed of a substance that we call *neurite*, which is defined:

substance neurite:
  scalar field C ‖ neurite concentration
  vector field v   ‖ velocity field
  order-2 **field** σ ‖ neurite diffusion tensor
  order-1 **random W**   ‖ random motion
  scalars:
        α ‖ cone migration rate
        β ‖ path deposition rate

  behavior:

$$
\begin{aligned}
\mathbf{v} &= \alpha(\nabla A/\|\nabla A\| + \sigma\mathbf{W}) &&\text{‖ go approximately in gradient direction}\\
Ð\mathbf{p} &= \mathbf{v} \\
ÐC &= -\nabla \cdot (C\mathbf{v}) + \mathbf{v} \cdot \nabla C &&\text{‖ concentration change in material frame}\\
ÐP &= \beta C &&\text{‖ deposit path}
\end{aligned}
$$

The equation for **v** causes neurites to move at a constant rate in the direction of the attractant gradient, but with a random perturbation $\sigma\mathbf{W}$ (to ensure paths do not get stuck). For simplicity, all points of a growth cone (neurite body) move with identical velocity (i.e., the stochastic element affects all points identically). The change equation for **p** causes the neurite body to deform in accord with the velocity field. The change equation for C describes the change in concentration (which constitutes the motion of the growth cone) in the material frame. Finally, the change equation for P describes the deposition of path substance in the wake of the growth cone.

Finally, having defined the substances and their behaviors, it remains to specify the bodies and their initial states. In this simple example, there are two bodies, the growth cone in its original location and the goal (destination) marker. The goal body is initialized:

  body Goal **of** attractant:
    for $\|\mathbf{p} - \mathbf{g}\| \leq 0.001$:
      $A = 1$
      $G = 1$
    for $\|\mathbf{p} - \mathbf{g}\| > 0.001$:
      $A = 0$
      $G = 0$

For the sake of the example, we have defined Goal to be a body of neurite within a radius of 0.001 (arbitrary units) of **g**, the location of the goal. Initialization of the other parameters $(\mathbf{D}_A, \tau_A, \gamma, \tau_P)$ is omitted for clarity. We have also omitted initialization of P to allow for the possibility of already formed paths.

The growth cone is initialized to a small region around **s**, the source or origin of the path:
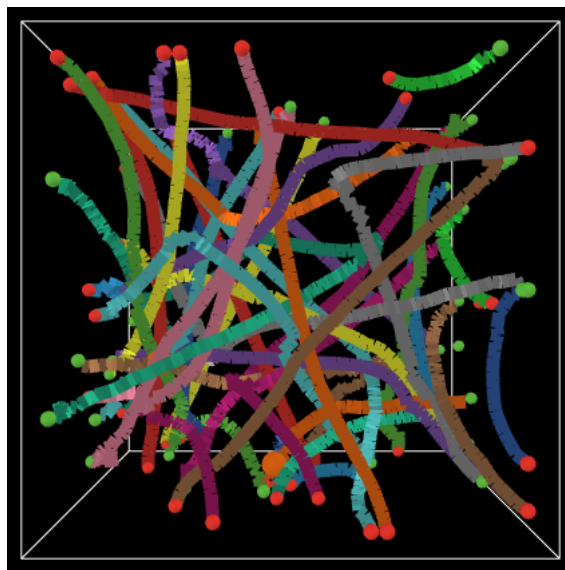
Figure 3: Simulation of path growth process. In this example 40 paths, occupying approximately 5% of the medium, were produced. In each case random origin and destination points were chosen on the four surrounding surfaces of a cube of the medium, and the algorithm was allowed to create a path.

> **body** GrowthCone **of** neurite:
> $\mathbf{v} = 0$
> **for** $\|\mathbf{p} - \mathbf{s}\| \leq 0.001$: $C = 1$
> **for** $\|\mathbf{p} - \mathbf{s}\| > 0.001$: $C = 0$

This morphogenetic program defines the routing of a path from a specified source to a specified destination, avoiding existing paths in the process. In the usual case many such paths would be needed. This can be accomplished by having different attractant substances and neurite substances attracted to them, or by creating the paths sequentially. We have simulated the latter process.

Figure 3 shows the results of a simulation of a sequential multiple path routing process. In this example 40 paths, occupying approximately 5% of the medium, were produced. In each case random origin and destination points were chosen on four surrounding surfaces of a cube of the medium, and the algorithm was allowed to create a path. After each path was complete, a time delay permitted the attractant to diffuse and degrade to background levels before picking the next origin and destination. This decreased the likelihood of one path interfering with the routing of the next, which still occurs in a few cases (where a path make a sharp, unnecessary turn).

5.3 Clock-and-Wavefront

An important problems for morphogenesis is how to count things; for example, how does an embryo count the correct number of vertebrae for its species? Several models have been proposed [CZ76, DP08, GOW$^+$08, BSM03, BSM06b, BSM06a], all of which may be relevant for artificial morphogenesis. We have investigated a variant of the *clock-and-wavefront model* originally proposed by Cooke and Zeeman in the mid 1970s [CZ76].

The process can be described briefly as follows (see simulation in Fig. 4). The individual segments or somites are formed sequentially from the anterior end of the embryo to its posterior end as the embryo grows posteriorly. Each new segment is formed in a "sensitive region" of low concentration of two morphogens, a *rostral* or *anterior morphogen* diffusing from already differentiated segments and a *caudal* or *posterior morphogen* diffusing from the tail bud. There is a pacemaker in the tail bud that periodically produces a pulse of a signaling chemical, the *segmentation signal*. This signal propagates anteriorly and when it passes through the sensitive region it causes the cells in that region to differentiate into a new segment. Therefore the segment length is determined jointly by the growth rate and the clock period (see the example in an earlier paper [Mac10b]); the number of segments is determined by the duration of the extension process.

The clock-and-wavefront process is easy to translate into a morphogenetic program (we omit the programming notation for brevity). Thus, the posterior (caudal) morphogen concentration $C \in [0, 1]$ is maintained at its maximum concentration in the tail bud ($C = 1$ where $T \gg 0$), and otherwise diffuses and degrades at specified rates:

$$\mathrm{Đ}C = D_C \triangle C - C/\tau_C + \kappa_C T(1 - C).$$

We choose κ_C to be large enough to cause rapid saturation of C in the tail bud.

The anterior (rostral) morphogen concentration $R \in [0, 1]$ is maintained at its maximum concentration in the somites (i.e., $R = 1$ where $S \gg 0$), and otherwise diffuses and degrades at specified rates:

$$\mathrm{Đ}R = D_R \triangle R - R/\tau_R + \kappa_R S(1 - R).$$

κ_R is chosen to cause rapid saturation of R in the somites.

Growth continues so long as a variable $G > \vartheta_G$, which decays at a rate $\mathrm{Đ}G = -G/\tau_G$. Typically we set $\vartheta_G = 1/e$ and $G_0 = 1$ so that the time constant τ_G is the duration of the growth period.

The tail bud has a clock signal K, with frequency ω, which can be described as a simple sinusoidal oscillator, $\mathrm{Đ}^2 K = -\omega^2 K$. So long as growth continues, whenever the clock is above a threshold ϑ_K, the tail bud emits a pulse of the segmentation
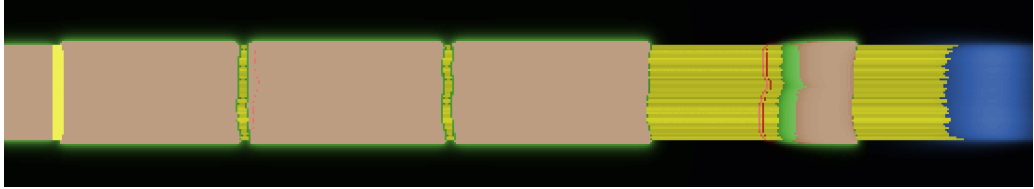
Figure 4: Simulation of somitogenesis by clock-and-wavefront process. In this figure the colors indicate the dominant signal in a region. Brown color indicates differentiated somite tissue ($S \approx 1$). From left to right there is a short rostral (head) segment, which is initialized in a differentiated state, three completed segments, and a fourth segment in the process of differentiation. Green color bordering differentiated tissue represents the rostral or anterior morphogen (R), which diffuses throughout the tissue, but is visible in this figure only in undifferentiated areas. The yellow color represent cell mass M growing to the right. The blue region on the far right represents a high concentration of the caudal or posterior morphogen (C) diffusing from the tail bud or caudal segment (invisible in the blue region). The red line represents a wave of the segmentation signal α propagating through the cell mass toward the head. When a wave of the segmentation signal passes from the tail bud to the left, a segment will differentiate only where the concentrations of both the anterior R and posterior C morphogens are sufficiently small. In this case we can see the differentiation of the fourth segment beginning in the wake of the α wave; the green color represents R morphogen that is already diffusing from this newly differentiated tissue. The very faint red line at the left end of the second full segment is the previous α wave, still propagating toward the head. R morphogen diffusing from the most recently completed segment prevents a new segment from fusing with it, leaving the small bands of (yellow) undifferentiated tissue visible between the segments. (The following parameters, in arbitrary but consistent units, were used in the simulation: $D_R = D_C = 0.007$, $\tau_R = \tau_C = 1$, $\kappa_R = \kappa_C = 10$, $R_{\mathrm{upb}} = C_{\mathrm{upb}} = 0.1$, $\kappa_S = 5$, $D_\alpha = 0.01$, $\tau_\alpha = 0.6$, $\alpha_{\mathrm{lwb}} = 0.1$, $\vartheta_\alpha = 0.2$, $\vartheta_K = 0.9$, $\vartheta_\varrho = 0.05$, $\tau_\varrho = 1$, $\omega = 1$, $r = 0.7$, $\lambda = 1$, $G_0 = 1$, $\vartheta_G = 1/e$, and $\tau_G = 30$. The step sizes for the simulation were $\Delta x = \Delta y = 0.04$ and $\Delta t = 0.04$.)

signal α, which diffuses at rate D_α and degrades with time constant τ_α. These are represented by the terms $+Tu(G - \vartheta_G)u(K - \vartheta_K) + D_\alpha \triangle\alpha - \alpha/\tau_\alpha$ (where u is a unit step or Heaviside function[1]), which together contribute to Đα.

If the α morphogen is above a threshold ϑ_α and the medium (regions with $1 \geq M \gg 0$) is not in its refractory period, then the medium "fires," generating a pulse of α and entering a refractory period represented by a nonnegative recovery variable ϱ (with time constant τ_ϱ and threshold ϑ_ϱ). (The refractory period assures that the wave propagates in one direction.) Thus the medium fires if $\phi \approx 1$, where

$$\phi = Mu(\alpha - \vartheta_\alpha)u(\vartheta_\varrho - \varrho).$$

Hence we can state the change equations for the segmentation signal and its recovery variable:

$$\begin{aligned} Đ\alpha &= \phi + Tu(G - \vartheta_G)u(K - \vartheta_K) + D_\alpha\triangle\alpha - \alpha/\tau_\alpha, \\ Đ\varrho &= \phi - \varrho/\tau_\varrho. \end{aligned}$$

Somitogenesis then takes place when a sufficiently strong $(> \alpha_{\mathrm{lwb}})$ segmentation wave passes through unsegmented tissue $(S = 0)$ in which both the anterior and posterior morphogen concentrations are below their thresholds $(R_{\mathrm{upb}}, C_{\mathrm{upb}})$:

$$Đ S = \kappa_S S(1 - S) + u(\alpha - \alpha_{\mathrm{lwb}})u(R_{\mathrm{upb}} - R)u(C_{\mathrm{upb}} - C).$$

The tail bud is a separate body, which is characterized by $T = 1$ in a small region ($T = 0$ outside it); this body is moving at a constant velocity (to the right in Fig. 4), leaving undifferentiated tissue ($M = 1, S = 0$) in its wake. In an embryo this movement is caused by cell proliferation in the caudal region, but in artificial morphogenesis, it could be caused by the entry of new agents into the caudal region, or by any other process that caused the tail bud to move away from rostral region (recall Sec. 4.4). Therefore, we may take the tail agents to be moving with a velocity $r\mathbf{u}$, where $\mathbf{u}$ is a unit vector in the direction of tail movement. The tail agent flux is then $rT\mathbf{u}$, and the change in tail agent concentration is given by the negative divergence of the flux:

$$Đ T = -\nabla(rT\mathbf{u}) = -r(\mathbf{u} \cdot \nabla T + T\nabla \cdot \mathbf{u}).$$

Production of undifferentiated tissue is given by $Đ M = rT/\lambda$, where λ is the length of the tail bud.

---

[1]That is, $u(x) = 0$ for $x \leq 0$ and $u(x) = 1$ for $x > 0$.

6 Conclusions

We have discussed the problem of assembling complex physical systems that are structured from the nanoscale up through the macroscale, such as future robots, and have argued that embryological morphogenesis provides a good model of how this can be accomplished. Morphogenesis (whether natural or artificial) is an example of embodied computation, which exploits physical processes for computational ends, or performs computations for their physical effects. Examples of embodied computation in natural morphogenesis can be found at many levels, from allosteric proteins, which perform simple embodied computations, up through cells, which act to create tissues with specific patterns, compositions, and forms. We reviewed the fundamental developmental processes and argued that these processes, or approximations to them, will be feasible in artificial morphogenetic systems. Nevertheless, there will likely be differences, which future research must address. We outlined a notation for describing morphogenetic programs and illustrated its use with three examples: simple diffusion, path routing, and the clock-and-wavefront model of segmentation. While much research remains to be done — at the simulation level before we attempt physical implementations — our results to date show how we may implement the fundamental processes of morphogenesis and thereby coordinate very large numbers of agents to self-assemble into multiscale complex hierarchical systems.

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