Rule Based Diffusion Modeling of Neural Development

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Abstract

The present paper demonstrates the developmental potential rendered by reaction-diffusion based mechanics in cellular organization and their significance in neural development. Experiments show that under minimal but sufficient parametric conditions reaction-diffusion mechanics which induce genetic regulation can account for fundamental stages of neural development such as cellular maintenance, motility and axon growth for neural structures.

Introduction

Many approaches to science and engineering that attempt to better understand and exploit the fundamental principles of complex behaviour are still today largely reminiscent of a classic centralist perspective. By attributing the responsibility of complex morphological phenomena such as cellular growth, differentiation, migration, self-maintenance to a central genetic code, but also, sensory-motor control, knowledge acquisition, problem solving etc. to a central cognitive operational code, these approaches may fail to appreciate the significance and impact of the material conditions in which such phenomena take place. Stent's thought experiment makes a good point of this: a super-civilization of aliens on another planet that would receive complete cat DNA would not succeed in reconstructing a feline without knowing anything about the environment in which the genome operates (Stent 1977). In his seminal work on morphogenesis Turing laid the formal foundation for a deeper understanding of the development of complex form, such as the formation of tissue from cells (Turing 1952). The scientific merit in gaining a better understanding for how this cellular development takes place is not the only appealing aspect of this field, but discovering

methods to implement such mechanisms in artificial milieu as opposed to simulations using indirect formal descriptions should also be of great interest for engineering purposes and may exhibit situation dependent features ignored by more abstract models. This paper will elaborate these two parts. After introducing the context of the present topic, I will demonstrate that local rule based modeling of chemicals following Turing's reaction-diffusion principle can exhibit accurate dynamics in a simple french flag experiment, and argue that this may be a good approach for the implementation for real-time developing systems. I will then illustrate how genetic inspired regulation of chemical reactions can give rise to neural like growth formations via diffusion and attraction dynamics.

Guided Development from Local Information

Near the end of the XIX^{th} century, forefathers of developmental biology such as Driesch and later Spemann, have emphasized the importance of the context in which cells are situated for the development of an organism. For instance, by artificially separating a sea urchin blastomere into two, Driesch demonstrated that each early cell gives rise to a complete larva, thus disproving the conception that each part of the early fertilized cell is predetermined for a specific function. Later Spemann and Mangold illustrated how the transplanted tissue from an early gastrula onto another gastrula of a newt would undergo cellular differentiation according to their new position, unless these originating tissues came from the region of the dorsal lip (Spemann 1938). By transplanting dorsal lip tissue onto a host gastrula, they showed that a number of unexpected tissues would begin to form in this host at the location of the grafts, such as a neural tube, notochord, somites etc. These results were the first to indicate that some group of cells in the early stages of development specialize at earlier stages than others and play an 'organizing' role in the differentiation of cells for various tissues in the embryo. This process is known as induction. The difficulty in succeeding work to identify the underlying principles guiding certain cells to specialize at earlier stages than others, has often lead to the disbelief that an inherent organizing mechanism is responsible for induction. As Purves and Lichtman describe, Spemann has been accused of advocating such a principle when no real simple 'organizer' seems to exist (Purves and Lichtman 1985). Interestingly, it appears that the search for an organizer could actually be completely misguided. Again, the search for a central mechanism of specialization responsible for induction seems to be sought in this view, but an alternate view of morphogenesis has risen through subsequent experiments. Experi-

ments which detected the importance of the surrounding tissue in the determination of these specialized parts. In 1947, Harrison showed that ablation of a section of the neural plate was compensated for in later stages of development (Harrison 1947). Hence the entirety of the specialized region is not required for proper development. To account for this sort of regulation it has been suggested that a morphogenetic field is present for the proper control of each particular tissue: a cellular region that can give rise to the rest of the tissue. The neural plate for example, is considered to be the morphogenic field of the nervous system. Two possible scenarios seem plausible to account for this, either the cells of the tissue have the potential to differentiate into other cells of that tissue at an early enough stage, or each cell in the area disposes of individual information which taken together are responsible for regulating a cell or group of cells at a particular loci. Although the later possibility cannot be ruled out, the former seems to constitute a simpler explanation. A more refined conception of morphogenetic fields stems from the observations that the phenotypic expression of cells may be deeply correlated to their location with respect to neighbouring cells. A number of theorists supported by experiments have introduced the potential of position dependent information in cell differentiation (Locke 1959, Schaller et al 1979). In particular Lewis Wolpert was amongts the first to account for these observations with his positional information theory (Wolpert 1969, 2002). This theory states that cells posses the ability to differentiate and express individual phenotypic traits in virtue of internal mechanisms that are sensitive to threshold concentrations of local chemical gradients. When a specific local chemical threshold is present in the cell's milieu or communicated to it via other neighbouring cells, it may trigger the regulation of specific genes and the production of corresponding proteins. Therefor stimulating or inhibiting particular phenotypes. With this theory it becomes possible to explain a number of experimental results, such as the lack of eyespot expression on a butterfly's wing after a number of cells located at the presumed center of the spot are removed in early development (Nijhout 1980). In this scenario, the removed cells located at the center would normally distribute chemicals radially to the neighbouring cells so to regulate the expression of pigment chemicals. Hence the positional information theory can account for both regulative and inductive phenomema, since from these localized principles it seems possible for cells to chemically regulate and possibly even trigger the differentiation of neighbouring cells. These regulating or inducing cells should not be seen as 'special' in any way however, or the causal account of regulation may regress indefinitely. To complete the picture it is important to see how all tissue cells are subject to regulation by their environment, but that the determination of some may occur at earlier stages than others. Determination 'locks' some of the cell's genetic regulative

capability prior to differentiation. These cells may thus play a guiding or amplifying role in the coordination of others without being exclusive to this role.

The Chemical Foundation of Positional Information

At the basis of this position information theory lies the requirement for a proper mechanism of chemical dynamics. Alan Turing's work in the early 50's on chemical diffusion and reaction counts as the foundation for any modern description of these dynamics (Turing 1952). Because Turing's development was geared to the elaboration of chemical models of morphogenesis his work was already adapted to the later requirements of positional information theory. In his work he argues that the basis for all organic dynamics is driven by the diffusion of some chemicals. In situ, it may help to think of some chemical located in an aqueous like environment. In a simple condition, if this chemical is uniformly distributed throughout the space then little motion or at most brownian motion will take place. However, diffusion can take place most simply in conditions where chemical concentration is not uniform. Although it is possible as Turing argues, that self amplification of motion takes place from natural oscillation of brownian motion, it is useful for modeling purposes to consider the existence of a chemical source. At this source point, chemical concentration will be higher. Because the increase of chemical concentration at that the source point eventually surpasses the density of the milieu these chemicals will repulse each other towards the area of least density; this is the diffusive characteristic of chemical propagation. By placing a sink at some other point in space, a continuous chemical gradient may form. A space rich in chemical alone though, cannot account for any interesting tissue formation. Hence, the other important aspect of this approach is to consider the reactive properties of these morphogens as Turing calls them. Although a number of reaction schemes are possible, three basic patterns are most prominent. In the first scenario, the presence of a single morphogen in sufficient concentration provokes the production of another morphogen, e.g. $A + A \rightarrow B$. In the second scenario, two morphogens react to produce a third, e.g. $A+C \rightarrow B$. In the third scenario, a morphogen is transformed into another by a second morphogen while this second does not itself transform, e.g. $A+C \rightarrow B+C$. In this latter form, C is said to catalyze A to produce B. This third process is crucial to the chemical dynamics of cell interaction and genesis of form. As Turing suggests himself, cell genes appear to precisely fill this catalytic role. Indeed his original proposal is still compatible with the contemporary view regarding gene transcription into specific proteins.

Although multiple stages of reactions are involved in the transcription from mRNA to chains of amino acids for protein formation, the notion of catalysis may still serve as a useful short hand for these underlying phenomena. Because morphogen reaction gives rise to new morphogens, the concentration of this product is bound to increase at the reaction site. This advances a fundamental insight made explicit by Turing's work: the effect of chemical diffusion leading to reaction at particular sites triggers novel diffusive patterns, which under appropriate conditions may self maintain. Although most modern takes on this insight have mainly emphasized Turing's idea that chemical regulation of functional proteins can be achieved in virtue of genetic regulation, some, as I also intend to illustrate here, have extended these principles to structural morphogens as well. Varela et al. for instance introduced a reaction-diffusion based model for cell membrane self-repair (Varela et al. 1974, Zeleny 1977, Ikegami and Suzuki 2008).

Before investigating the potential of chemical dynamics for the account of organismic formation and behaviour, it is important not only to formally describe the dynamics of diffusion, but also see how some forms of modeling should allow for a mechanistic level of simulation which, in my opinion, may give rise to novel insights as to the alternate manners in which ontogenetic phenomena may take place in situ. This should in turn be useful for the scientific and engineering prospect of hardware implementation.

Rule Based Simulation for Developmental Models

As mentioned above, Turing's formulation for chemical reaction and diffusion was primarily concerned with inter cell propagation of morphogens. In its most basic form two morphogens concentrations, say X and Y, are employed to demonstrate how a group of cells configured in ring pattern, can communicate. In this model, the change in concentrations of X and Y for a particular cell r is computed with the following differential equations,

$$\frac{\partial X_r}{\partial t} = f(X_r, Y_r) + \mu(X_{r+1} - 2X_r + X_{r-1})$$
$$\frac{\partial Y_r}{\partial t} = g(X_r, Y_r) + \upsilon(Y_{r+1} - 2Y_r + Y_{r-1})$$

where $r \in \{1, ..., N\}$ indicates a cell, f the reaction rate leading to an increase of X, μ the diffusion constant of X, g the increase rate of Y, and υ the diffusion constant of Y. In this scenario the reactions f and g apply to both morphogens and increase one or the other respectively. Moreover, the concentration of the chemical gradient is propagated to a

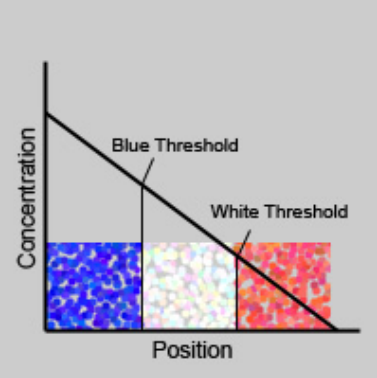

Figure 1: Wolpert's french flag problem. Illustration of chemical threshold for differential cell phenotype expression.

cell with respect to both its neighbours. In cases where cell tissues constitute of an agglomeration of similar cells, it is necessary to consider the entire neighbourhood. For instance, to illustrate the applicability of the position information theory Wolpert introduced a toy problem known as the 'french flag problem'. This problem is designed to indicate how the presence of a chemical gradient in a two dimensional plane can serve as basis for the cellular detection of local chemical concentration and differentiate accordingly to form a simple but organized tissue. In this case three types of phenotypes can be expressed with respect to local gradient: a blue cell pigment, a white pigment, and a red pigment. If the local chemical concentration decreases continuously with respect to space, cells may detect these concentrations under a specific threshold and express a pigment accordingly so as to form a french flag like tissue (see figure 1). In this experiment a single morphogen is required because in the simplest case no extra chemical is required for cell differentiation with respect to position along the gradient. It is important to note that more than a single solution exist to this problem. The simplest, would assume that non differentiated cells are already in place; cells would then express different colours according to the chemical threshold. Another possibility is to have pre-differentiated cells (independent of the local chemical threshold) in equal numbers which migrate to their positions according to their differential density with respect to the chemical concentration. Yet, because in both cases the number of cells for each colour will ultimately be fixed, any disruption to the formed tissue will prevent restoration of a french flag pattern. To exhibit the potential of positional information theory to effectively regulate tissue lesion as seen in Harrison's experiments, it is necessary to adopt a slightly more sophisticated model. Interestingly modern

takes on this simple problem have often employed significantly more sophisticated models of cell dynamics. Miller and Banzhaf for instance propose a sophisticated model of cell regulation for differentiation and positioning by endowing each cell with what they describe as a Cartesian Genetic Program under the control of boolean circuits (Miller and Banzhaf 2003). In this model each cell stores four data elements to be used by the program: two input connections from antecedent cells, a function which computes an output from the input signals, and a position. By evolving the genetic programs Miller and Banzhaf obtain artificial stem cells which differentiate according to local chemical gradients. Their experiments are successful in demonstrating the ability of their model to not only generate a french flag tissue from a single cell, but also to recover from cell ablation, as well as generate other desired evolved patterns via evolutionary fitness conditions. Although their aim is to elaborate powerful internal genetic mechanisms, which they effectively succeed in doing, accounting for the generation and regulation of a french flag like tissue is possible in much simpler terms. The model I introduce here, seeks to illustrate that via a combination of both differentiation and migration as used by the two first solutions introduced, and with the additional ability of artificial cell mitosis, it is possible to obtain a french flag like tissue from a single cell that is resilient to disruption.

Experiment 1

The model employed to resolve the french flag problem with regulation, makes three assumptions: cells can move like morphogens according to diffusive dynamics, cells of the same type have a tendency to attract each other, and cell division occurs at a random uniform rate. The first assumption can be made because of observed chemotactic behaviours in cells, hence cell motility can be dependent on local chemical concentrations. The second assumption regarding attraction may be supported by known principles of cell adhesion with the use of chemicals such as cadherins, but also communication via chemical diffusion, direct contact, or gap junctions (Wolpert 2002, Alberts et al. 2002). The final assumption regarding divisibility rate is made to minimize the complexity of the proposed model, and should not prevent the validation of the point I wish to make.

Method

For this problem it is sufficient to consider a two-dimensional euclidian space with 90 x 30 units that are wrapped at each end. A substrate source is placed at (15, 15), and a sink at (75, 15). Each substrate chemical occupies its own unit of space. A substrate S is released from

the source within the moore neighbourhood (the 8 adjacent units) at the rate $R_{source} = \frac{1}{3}t$, were t is a time step. Similarly the substrate sink removes any substrate chemical S within its moore neighbourhood but at the rate $R_{sink} = t$. Because each substrate particle is a discreet element in the environment, a discreet method based on the counting of local substrate quantities is employed. An attempt to express the motion of an individual particle (its diffusion) in the space may result in the following expressions,

$$S_{x_{t+1}} = \begin{cases} S_{x_t} - sign(\phi(S_x, S, r_S)) & \text{if P}(\parallel \phi(S_x, S, r_S) \parallel) \geq \mu_S \\ 0 & \text{otherwise} \end{cases}$$

$$S_{y_{t+1}} = \begin{cases} S_{y_t} - sign(\phi(S_y, S, r_S)) & \text{if P}(\parallel \phi(S_y, S, r_S) \parallel) \geq \mu_S \\ 0 & \text{otherwise} \end{cases}$$

$$\text{with,} \quad \phi(p, C, r) = \delta_C(N_c(p + r) - N_c(p - r))$$

where S_x and S_y are the coordinates of a particle S in the euclidian space, $N_c(area)$ the number of particles C within the area $r_S * r_S$ on either side of the input position (here we set $r_S = 2$ indicates the radius of sensitivity), δ_C the density coefficient for the particle type C, $sign(a)$ returns -1 if a is negative and +1 otherwise, μ_S the diffusion coefficient for chemical S (here $\mu_S = 3$), and $P(\phi)$ a random integer value with uniform probability in the range [0, ϕ]. The underlying intuition being that each particle is repulsed by only a single position from the neighbouring particles with respect to their quantity within a specific range. This repulsion occurs with a greater probability as this local density increases.

Three cell types are used in the experiment, red, white and blue. The differentiation threshold is fixed - beyond a concentration of 3 or more substrate chemicals in a radius of 2 units red cells differentiate into white cells; when this concentration augments to 8 or more cells become blue. All cells follow the same behavioural principles:
- A cell occupies a single unit of space.
- A cell is repulsed from other cells and substrate particles following an equivalent diffusion process as seen with substrates S.
- A cell is attracted to cells of the same type with respect to their quantity within a local radius. To do this the new position is obtained by adding (rather than subtracting) the sign of the neighbourhood density difference ϕ, resulting in a sort of inverse diffusion.
- A cell may only enter a space if it is empty. Note that the cell space is superimposed to the substrate space. Although cell motion is affected by the local density of the substrate, their position can overlap.
- A cell cannot change position if cells of other types are in its moore

neighbourhood. Hence cells of other types are strongly bound to each other.
- A cell can differentiate into any other cell type with respect to their threshold to local substrate concentration.
- A cell can divided with a probability $P_{div} = 1/50t$ after a minimal number of 1000 time steps have occurred, if at least one empty space is located in the moore neighbourhood to place the daughter cell.

For each cell type $\mu = 2$, and $r = 3$, however because the experiment begins with a single red cell we may set, $\delta_R = 5$, $\delta_W = 3$, $\delta_B = 2$, so to stimulate the aversion of white and blue cells in the proximity of red cells. Although cells occupy as much space as a chemicals, the ability to adjust density coefficients, radius of sensitivity and diffusion coefficients, provides for cell specific characteristics to the areas of the space that they occupy.

A single red cell is placed at the center of the space. After 1000 time steps any cell may start to divide. This was meant to allow the morphogen S to diffuse sufficiently in the space before pattern formation occurs. To ease computation and prevent bias due to sequential particle updating of the simulation, the substrate and cells are updated in an interlaced fashion over three separate passes. A single pass updates 1/3 of the particles in a temporary space matrix, which after three passes updates to the main space. This is necessary because chemical and cell motion are not fully determined over time, but are subject to probabilistic conditions.

Results

After conducting a number of runs the set of parameters, as specified above, were deemed adequate to illustrate the potential of the model to demonstrate principles of positional information theory. Figure 2 shows 10 separate stages of development of a french flag according to this model. From the first few frames we notice how substrate chemicals disperse from the source into the space (the black particles). In frames 1 and 2 we notice how the initial red cell and some daughters have divided. Interestingly frame 2 shows the early formation of a vertical 'band' of cells after 1200 time steps. This is due to the repulsion from substrate chemicals that approach from the left. At $t = 1800$ (frame 3) the concentration of chemical S in the underlying space is sufficiently present in the border region of the red cell strip to trigger differentiation of red cells into white cells. By $t = 2500$ (frame 4) we notice that the tissue has started to shift towards the right moving away from the area of greater chemical density. At this stage cells in the highest density region begin to differentiate into blue cells. This growth continues in subsequent steps as seen in frame 5. At this stage a reasonably shaped french flag is formed. To verify that this model can

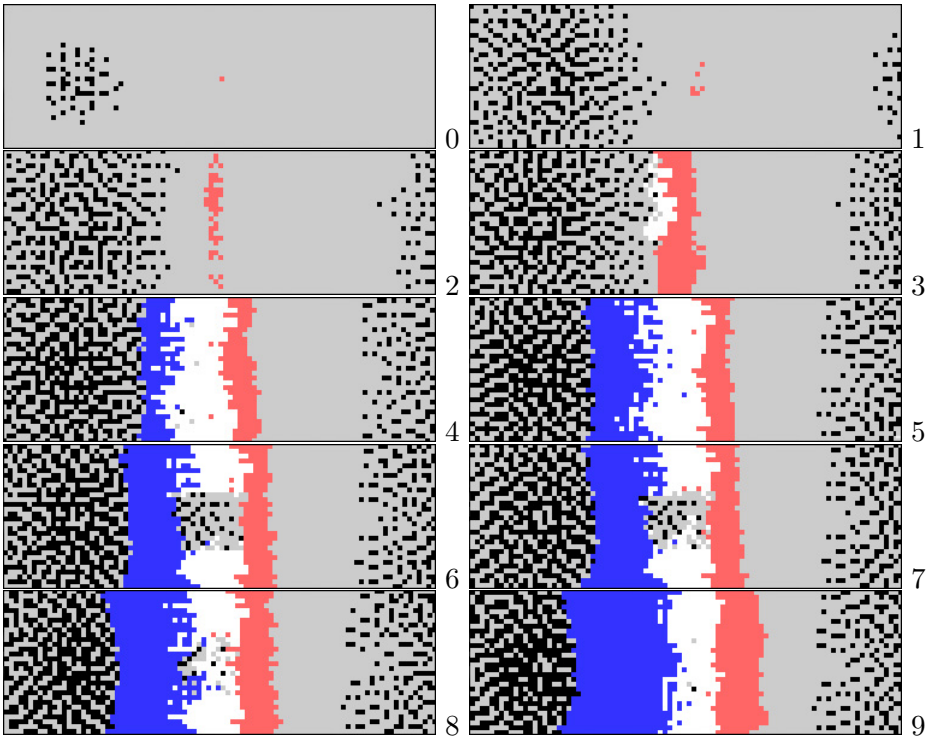

Figure 2: The simulated growth of a 'french flag'. Black particles are the substrate, coloured ones are cells. Frame 0 was taken at time step t = 100, frame 1 at t = 1010, frame 2 at t = 1200, frame 3 at t = 1800, frame 4 at t= 2500, frame 5 at t = 3000, frame 6 at t = 3010 at which point a large portion at the center of the flag was removed, frame 7 at t = 3200, frame 8 at t = 3400, and frame 9 at t = 4000.

account for the principle of tissue regulation as observed by Harrison but also experimented with by Miller and Banzhaf, the growth process was paused at $t = 3010$ during which a large central portion of the flag was removed as can be seen in frame 6. As soon as the growth process is resumed, dividing cells quickly begin to populate the empty patch, this occurs because a statistical number of cells on the inside border of the lesion begin to replicate and invest the area (see frame 7 and 8). Within approximately 1000 time steps the flag although continuously growing, is mostly restored (frame 9). At this stage the cell duplication is halted and diffusion stopped which stabilizes the flag.

These results support the claim that fairly simple diffusive and attractive dynamics between cells and a single type of substrate can give

rise to self-regulating tissue constituted of differentiated cells. This model may present some draw backs however. By allowing substrate chemicals to occupy the same amount of space as an entire cell provides for a rather coarse chemical gradient throughout the space, which may result in greater malformations of the flag. Although a more refined gradient could be obtained by allocating a much smaller fraction of space to substrate chemicals, the characteristics of the model itself don't need to change. Another limitation stems from the lack of a cell division regulation process. Such a process would allow stricter boundary conditions to be imposed on tissue formation. Although it may be reasonable to assume that cells cease to divide after a number of times which could easily be implemented with a cell internal counter, this would add unnecessary artificiality to the model and would not easily account for sharp boundary conditions. The ability for cell to regulate their division is one of the strong features of Miller ad Banzhaf, which they achieve with their internal Catersian genetic programs, their model however also requires that cell record their position explicitly. I believe however that given the presence and diffusion of additional chemicals in the space, proper boundary conditions may be obtained implicitly. This notion of implicit 'knowledge' of some position in space is the key value of Wolpert's theory.

In a similar sense the conditions of operation of particle dynamics (cells and substrate) are also implicit in this model, this brings additional value. Each particle abides by *local* rules, much like in von Neuman's cellular automata (von Neuman 1966). Because of this the environment is simulated without the requirement for global descriptions of the dynamics. Since particles in this model are causally subjected to the effects of their environment no dangerous oversimplification or abstraction is made, i.e. the model is explicit as to the necessary and sufficient conditions for its application in a physical milieu. Not only this, but the values and operations are discreet. This represents a significant advantage for construction purposes. A scientist or engineer could in principle succeed in building a system exhibiting biological like dynamics in hardware sufficiently complex to satisfy the model's criteria without the requirement for a global or central operator.

Additionally by taking advantage of local diffusive and attraction properties, it becomes possible within this approach to investigate in greater detail different aspects of cellular dynamics. In particular, protein regulation, membrane maintenance, and cell specialization. In the following I present experimental results which look precisely at membrane formation and maintenance, neural cell motility, and axon growth. I do not claim to do justice to each topic in the following, since their complexity and variety are vast. I propose instead, that interesting observations and novel insights may stem from minimal modeling of these joint cellular activities.

Growing a Neuron via Chemical Regulation

A cell's membrane counts as one of its most basic properties (Alberts et al. 2002). As emphasized by the autopoietic criteria for life, a living organism must be organizationally closed (Maturana and Valera 1980). For the cell, the membrane fulfills this criteria of closure. Various models of autopoietic structures aimed at demonstrating how reaction-diffusion chemical dynamics can enable cells to maintain this membrane closure in a strict fashion (Varela et al. 1974, Ikegami and Suzuki 2008). Ikegami and Suzuki have borrowed aspects of Varela's SCL (Substrate Catalyst Link) model to illustrate potential mechanisms of membrane maintenance and a form of chemotaxis from the motility of cells up a chemical stream. Modeling the physics of membrane motion in two-dimensions requires a complex set of rules that I do not consider in the present exploration. The SCL model however, proposes that a catalyst C transforms two substrate chemicals S into a link chemical L. This link can then attach to other link chemicals so to form a membrane. The notion of chemical catalysis for the production of other essential chemicals to the cell is quite useful. As mentioned earlier, a catalyst may be though of as a simplified mechanism of genetic regulation. The model assumes that the catalyst can detect the kind and quantity of chemicals in its neighbourhood so to perform a particular reaction. Hence the produced chemical, alike a protein, can then abide by diffusive mechanics to serve a variety of functions; in this case the maintenance of the cell membrane.

The migration of nervous cells is a key aspect of development in vertebrates and invertebrates. At the embryonic stage neural cells will migrate over large distances. After mitosis at the ventricular lining, neural precursor cells will migrate to higher layers (Purves and Lichtman 1985). Typically an 'inside out' development pattern takes place where earlier neural cells end up in the lowest layers of the cortex, whereas latter cells traverse these layers towards the most superficial positions. Some evidence has supported the claim that radial glial cells assists cortical neurons in their migration (Rakic and Sidman 1973), but others have disputed these results (Goldowitz and Mullen 1982). The matter of fact is that neural cell migration must also have a means to determine the correct position of fixation. This may be accounted for by the positional information theory. By remaining sensitive to the local chemical gradient a migrating neuron should fixate under appropriate environmental conditions. After neural cells undergo their final differentiation, axonal growth is triggered. A fascinating aspect of this process is that neural axons after crossing large distances, will ultimately find a developmentally coherent target neuron. This growth process consists of the propagation of growth cone filopodia via a continued extension and retraction of the actin cytoskeleton (Wolpert 2002). A

number of mechanisms have been considered to account for this outgrowth. Letourneau proposed that adhesive properties of the surface may play an important part (Letourneau 1975). Another possibility is known as galvanotropism, whereby electrical stimulation guides the direction of the axon migration (Jaffe 1979). The leading contender to explain this however, is the dual action of chemical repulsion and attraction on the growth cone (Gundersen and Barrett 1979, Wolpert 2002).

Experiment 2

The following model attempts to illustrate three principles at the single cell level that are founded on reaction-diffusion mechanisms: membrane formation and maintenance via regulated protein diffusion, chemotactic migration and fixation of the same neural cell with respect to local gradient which triggers the outgrowth of an axon via a chemical repulsion mechanism.

Method

For this experiment the space was enlarged to 45 x 120 units. A substrate S is diffused in the same fashion as in experiment 1 with the exception that a lower diffusion factor $\mu_S = 2$ is used. The source is placed at (22, 100) with release rate $R_{source} = t$ and the sink at (22, 15) with rate $R_{sink} = t$. A single catalyst is placed a the center of the space (22, 60). This catalyst is slightly attracted to the regions of higher density, under the same conditions are mentioned in experiment 1, but with parameters $\mu_C = 6$, $\delta_C = 4$, $r_C = 3$. Similarly to Ikegami and Suzuki's model, if two substrate chemicals S are in the moore neighbourhood of the catalyst, a protein P is produced under the reaction: $C + 2S \rightarrow C + P$. This morphogen is set to be highly volatile by repositioning according to its attraction to other proteins P. Rather than updating the position by a single unit with increasing probability as the local chemical density increases, the new position is update by the difference $\phi(P_x, P, r_P)$ and $\phi(P_y, P, r_P)$ precisely; with parameters $\mu_P = 3$, $\delta_P = 3$, $r_P = 3$. This particle can be eliminated with probability $P_{reduce} = 1/50t$ if there are less than 2, or more than 6 P's in its moore neighbourhood, corresponding to conditions of instability. Under similar assumption as in the SCL model, a membrane chemical M can be produced within a certain radius of the catalyst ($r = 5$). This production occurs if 2 or more chemicals P are in its moore neighbourhood resulting in the reaction: $nP \rightarrow M + (n-1)P$ for $n > 1$. Membrane morphogens behave in a special way so as to favour their agglomeration around the catalyst.

Typical biological membranes are composed of fatty acids arranged

in a bi-layer. Because water is the principle inert substance in the cell's environment, the hydrophobic tails of two fatty acids meet and join to other pairs, the hydrophilic head of each remains therefor exposed to either the outside environment or the inside of the cell. Interestingly mixing fatty acids in water will typically give rise to the self organization of a cell like membrane. Although it would be interesting to exploit such self organizing principles, the present model only borrows some aspects of chemical interaction typically ignored in reaction-diffusion models: a mechanism for polarity. This is accomplished by assigning the value -1 or +1 to each side of the chemical at a particular spatial location. Since diffusion is computed with respect to the number of chemicals in the neighbouring area, attraction can be applied in a specific direction by flipping the charge on the side of the particle corresponding to that direction. Although possibly a number of phenomena may be exploited from such a setup, only one is exploited here: a polar chemical changes its polar directions so that it matches that of its neighbours. This results in the an active reformation of the membrane particles in space, and favours their agglomeration. On top of being subjected to standard attraction dynamics with parameters $\mu_M = 4$, $\delta_M = 2$, $r_M = 4$, the polarity of each particle is determined by randomly assigned a negative pole to one of the particle's surfaces with probability $P_{Mpolarity} = 1/4t$ (all other surfaces being positive) if no neighbour membrane particles are present, in which case the polarities are coordinated. Membrane chemicals may also reduce if their positions move beyond a certain distance of the catalyst C, $r > 7$ with probability $M_{reduce} = 1/20t$.

Finally, when the the catalyst is completely surrounded by membrane particles, it cannot change position any further. Hence the cell becomes fixed. At this stage an axon particle is created under the reaction $C + 8M \rightarrow C + 7M + A$. Although for a more accurate treatment of neural dynamics, axonal growth should be a product of the cytoskeleton actin. This outgrowth though, may also follow a diffusive behaviour. Thus, to simplify the model a single chemical A which leaves a trace it implemented. This chemical is highly repulsed by high concentrations of substrate chemicals using standard diffusion rules. Chemical A parameters are, $\mu_A = 3$, $r_A = 10$ (no density is required since a chemical A has no diffusive impact on other chemicals).

Results

Although all biological cells are the product of cell division from the fertilized egg, the current experiment investigates a more radical scenario: the way in which a cell membrane could generate from a single catalyst. This approach is taken, because the basic dynamic principles of the model rely on reaction-diffusion. Hence the point of getting a

catalyst to react with the environment substrate can be made more clear by starting with a small number of chemicals. Figure 3 shows the different stages of the neuron growth experiment. Frame 0 displays the initial diffusion of substrate S, and the catalyst C located in the middle of the space. At this stage the catalyst tends to move downwards towards a region of greater concentration of S. After a few hundred time steps, the concentration is sufficient for C to catalyze proteins P (frame 1). Due to the high diffusive but self attracting nature of P, highly mobile groups begin to form quickly. When these chemical clusters are positioned at 5 units away from C, membrane particles are generated as seen in frame 2. Hence the substrate which is released at the source, regulates the catalysis of proteins P which in turn trigger the formation of the membrane chemicals. Because membrane particles are polarized, they tend to form clusters around the catalyst. Yet since this membrane is maintained only if an adequate amount of protein is available in the area, it is possible for the membrane to decay almost entirely at times. This presents a weakness in the current model. However, because the catalyst tends to travel towards areas of high substrate concentrations, the amount of protein catalyzed tends to remain high. This ensures a better maintenance of the membrane. Yet this membrane is still not exactly moving with the catalyst, but instead decays and regenerates if the catalyst moves. A better approach would be to implement membrane motion via reconfiguration in space, much like Ikegami and Suzuki's model. Once the membrane encloses the catalyst entirely a reaction with the catalyst induces the production of an axon chemical A (see frame 4 and 5). Because this chemical is highly diffusive, it tends to propagate quickly towards an area where the substrate is in least concentration, namely the sink. Thus axonal growth is implemented here as an entirely diffusive mechanism. This makes a significantly simplified case in comparison to biological observations. Yet, as observed in real cells, axonal growth is guided entirely locally via chemical repulsion without any global guidance. Hence, this approach still represents a more physically realistic implementation of neural cell development. Because of this, the setup of the experiment could easily be extended so to illustrate target neuron attraction. One would simply have to place another catalyst in the space, which under appropriate conditions would regulate the release of an additional chemical. This chemical could then attract the first neuron's axon. By adopting this method, it is suggested that artificial neural networks may be modeled at a level sufficiently detailed to expose novel dynamics using similar network development schemes.

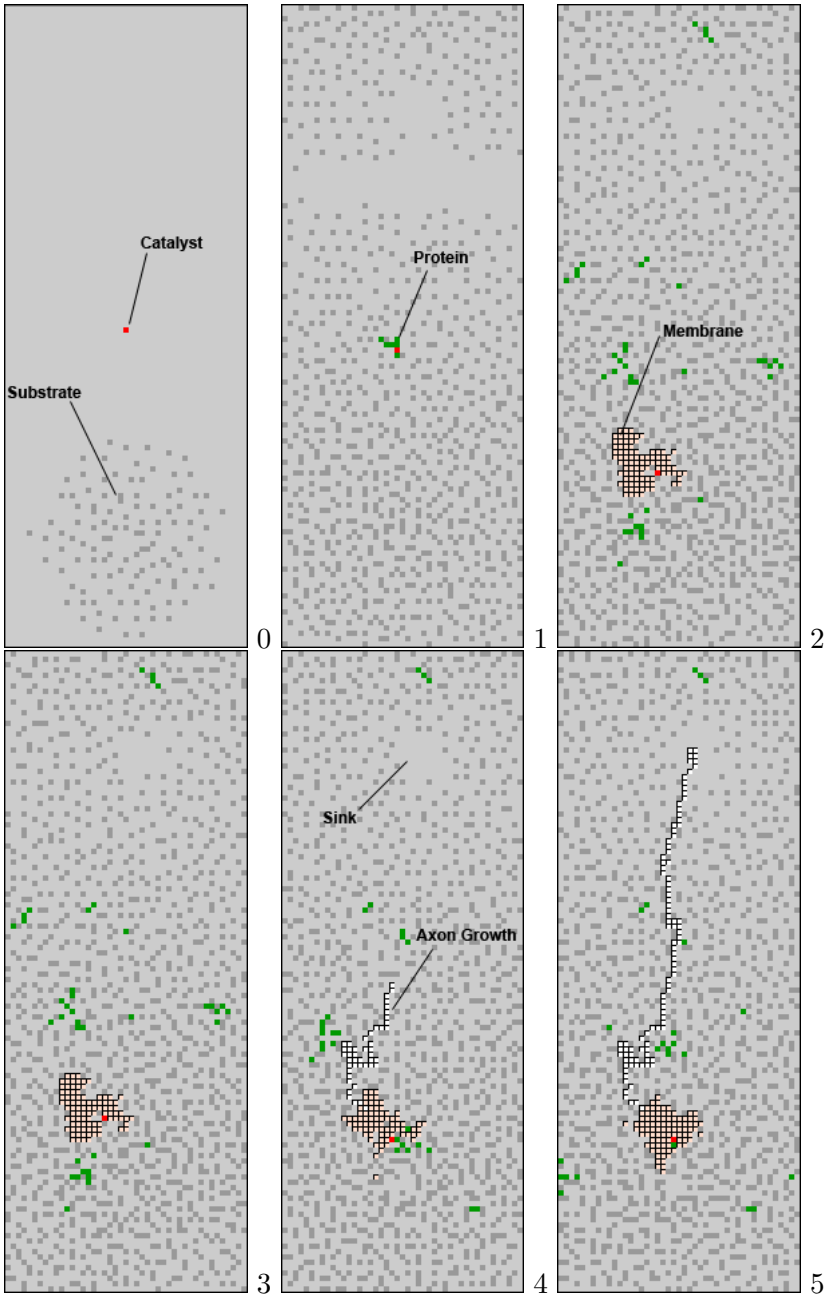

Figure 3: The developmental stages of an artificial neuron. Frame 0 at $t = 200$, frame 1 at $t = 900$, frame 2 at $t = 1400$, frame 3 at $t = 1600$, frame 4 at $t = 1700$, frame 5 at $t = 1750$.

Final Remarks

Although a number of efforts have developed sophisticated models of neural genetic regulation for scientific exploration or control systems design, very few investigate the potential of implicit dynamics such as those defended by the positional information theory (Nolfi and Parisi 1991, Jacobi 1995, Delaert 1995, Michel 2001). The aims of the present paper is to motivate the notion that a better understanding of complex behaviour may be achieved by raising attention to developmental dynamics of co-dependent constituent parts, such as cells. In the first experiment, a mechanism of cell division and positioning via diffusion demonstrates that elementary tissue formation is possible without the requirement of elaborate cellular internal programs. Instead, the environmental chemicals are sufficient to turn on or off the expression of certain traits. Furthermore, the coordinated activity of these cells gave rise to mechanisms of self-repair without any central operator. Extending this, the second experiment further supports the claim, that complex local behaviour can arise from the effect of environmental conditions on the regulation of catalytic processes. Processes which in turn give rise to new chemicals and behaviours. According to this approach, becomes possible to implement detailed models of cellular processes such as neural growth. Interesting extensions to this work would investigate ways in which to model functional synaptic potentiation. This would allow for actual neural computation to occur. Finally, the results obtained from these experiments underscore the potential dynamics achieved with a single base chemical: the substrate. The availability of this chemical marks the origin and requirement of any sophisticated chemical and cellular behaviour based on reaction-diffusion. The availability of energy from the surrounding environment must therefor constitute the prime condition for complex phenomena.

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