Asymmetric cell division and its integration with other developmental processes for artificial evolutionary systems

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Abstract

Artificial evolutionary techniques are more and more coupled with mechanisms abstracted from developmental biology. Artificial cells endowed with genetic regulatory networks were used to evolve and develop simulated creatures. This paper reports on the evolution of a simple moving creature using developmental mechanisms such as asymmetric cell division, genetic regulation and cell adhesion and physical interactions between cells. Surprisingly, artificial creatures were evolved able to move using only genetic regulatory networks without the need to employ neural controllers.

Introduction

The last years have seen an increased interest in combining evolutionary algorithm with concepts borrowed from developmental biology. As simple direct encoding schemes, where each primitive of the phenotype is represented by a single parameter (gene), no longer work for complex evolutionary tasks, new concepts have to be found to tackle such tasks successfully. The question arises on which level of abstraction one should start with developmental evolution. In our case the cellular level was chosen: the task to evolve cellular mechanisms is way to complex to be approachable with the current simulation technology. Higher level approaches have also their drawbacks, putting a simulator for the non-trivial task to choose among a plethora of possible structures and mechanisms. As the cell has only a limited set of behaviors (Wolpert, 1998), it is much easier to use those as a guideline to implement an interesting artificial evolutionary system. Still, processes and structures have to be chosen and implemented. The method of investigation to choose among the cellular mechanisms is to analyze the possible value of biological concepts for artificial evolution, to implement the chosen concepts, to investigate the possible advantages of a given concept in simulation and to understand why such a mechanism is useful. In this paper asymmetric cell division (ACD)was combined with other developmental mechanisms in an artificial evolutionary system and their use was investigated by evolving simple behaving creatures.

Although other authors (Kaneko, 1992; Kitano, 1994; Gruau and Whitley, 1993; Cangelosi et al., 1994; Fleischer and Barr, 1992; Vaario and Shimohara, 1997; Kodjabachian and Meyer, 1998) propose to combine developmental processes with evolutionary algorithm, I discuss here only those models that tried to evolve genetic regulatory networks to control the developmental processes. Dellaert and Beer (Dellaert, 1995) proposed a model based on Boolean networks to evolve autonomous agents. Two different models of neurogenesis were developed: one simple and one complex. With the complex model, the authors succeeded in designing an autonomous agent by hand-coding a genome. (Eggenberger, 1997) proposed the use of genetic regulatory networks coupled with developmental processes to use in the field of artificial evolution and was able to evolve simple shapes and simple neural networks. (Bongard, 2002) combined a physical simulator with a genetic regulatory network able to simulate simple organisms such a box pusher. (Eggenberger, 2003b) combined genetic regulatory networks with physical processes during morphogenesis and was able to evolve processes mimicking invagination. (Kumar and Bentley, 2003) also discuss asymmetric cell division.

Methods

Cell fates during development are controlled by two different mechanism: a) cytoplasmic determinants distributed asymmetrically to the cells by ACD and b) inductive signals released from neighboring cells. The exclusive use of either mechanism defines two extremes tactics: mosaic and regulative development. The former development is controlled entirely by cytoplasmic factors. Each cells undergoes autonomous differentiation, so that its fate is determined by lineage independent of its position. Regulative development is controlled entirely by inductive interactions. Each cell is specified conditionally, according to its interactions with other cells. Cell fate is determined by position, irrespective of lineage. Most species use a combination of both mechanisms in their developmental program. ACD allows to control genetically the cell division plane and therefore to control the positioning of the cells individually and precisely. If each cell division is controlled by one gene, this approach is

quite similar to a direct encoding scheme, where a parameter specifies an entity of the phenotype. During cell division cytoplasmic factors are asymmetrically distributed coupling cell division with cell differentiation. This coupling allows artificial evolution to explore mechanisms, which are able to position differentiated cells at precise positions by controlling precisely the cell division. To be useful ACD has to be integrated with other developmental processes. That this is possible, simple moving creatures were evolved in which the shape and the physical interactions among cells are specified by the ACD, the movements were triggered by signalling molecules; all these mechanisms were controlled and integrated by ligand-receptor interactions and genetic regulatory networks.

Gene Regulation

In the current evolutionary simulator the genome consists of two sets of genes: the structural genes encoding cellular functions and the cis-regulators represent switches able to turn on or off a structural gene.

Two classes of structural genes were implemented: in one class artificial substances are produced simulating a simple artificial chemistry in the cells, in the other class a structural gene represents a cellular function such as cell division or cell adhesion. These functions are not evolved but implemented as programs which are called in case the corresponding structural gene was activated. The properties of each structural gene are encoded by seven parameters. The first parameter determines to which class the structural gene belongs and which function this gene will have if it is activated. It is up to the designer to decide how many members the classes of structural genes are made available to the artificial evolutionary system (AES). The second parameter is used to calculate the probability of an interaction with partner molecules. This affinity parameter aff determines which molecule (signalling molecule or axonal receptor) interacts with which partner (regulatory unit or receptor). To each molecule in the simulation a real valued number and a function is assigned, which calculates an artificial binding affinity between the molecules. The third parameter determines the sign of the effect e_{ij}, i.e. inhibitory or excitatory. The fourth parameter specifies the threshold ϑ. This parameter determines how high the sum of the products of all the affinities a_{ij} between the signalling molecules and the regulators times their concentrations has to be in order to turn on or off the associated structural gene. The fifth parameter designates the decay d_i rate for the product. The sixth parameter is used to store the affinity parameter α The seventh parameter is used as the diffusion parameter D_1

$$G_i(c_{sm_0},.,c_{sm_m}) = \frac{1}{2}(1.0 + \tanh(\beta y(c_{sm_0},.,c_{sm_m}))) \quad (1)$$

$$y(x) = 2.0x - 1.0 \quad (2)$$

$$x = \sum_{j=0}(\Theta(a_{ij} * c_{sm_j} - \vartheta_j)) \quad (3)$$

$$\Theta(x) = \begin{cases} 1.0 & : \ if \ x > 0 \\ 0.0 & : \ otherwise \end{cases} \quad (4)$$

Where:

- G_i is the activity of the i-th gene (see equation 1).
- $tanh(x)$ is the hyperbolic tangent.
- a_{ij} affinity to encode the effect between the regulatory unit i and the signalling molecule j (also referred to as transcription factors if they regulate the gene activity).
- $y(x)$ is just a scaling function allowing to have gene activities between 0.0 and 1.0 (see equation 2).
- c_{SM_j} concentration of the signalling molecules j
- ϑ_j is a threshold value controlling the influence of a signalling molecule on a gene (see equation 4).
- $\Theta(x)$ is a normalizing function to make sure that the impact on a structural gene is between 0 and 1.
- β is a parameter affecting the steepness of Θ

One or several regulatory units control a structural gene. Regulatory units are switches that control the activity of the structural gene. Active regulatory units influence the activity of the structural gene, but only an activated structural gene is able to a response such as cell migration or the production of a receptor. Two parameters are assigned to every regulatory unit: an affinity aff_{RU} and a threshold. The affinity aff_{RU} has the same use as the affinity parameter in a structural gene. A signalling molecule is defined by the parameters encoded in the structural gene. Both affinity parameters are used to calculate the probability for an interaction between a regulator and a signalling molecule. Both factors are variables of the affinity function $aff_{Tot} = f_{aff}(aff_T, aff_S)$ and its value will influence the probability of a gene's activation. The threshold defines the limit of the minimal impact able to activate a gene: the product of the affinity aff_{Tot} and the concentration of the signalling molecule has to exceed the threshold's value.

Whether a given gene at position (i,j,k) in a cell on the grid will be activated depends on the affinity and concentration of all the signalling molecules at that position. All these influences are summed up and if this sum exceeds the gene's threshold the gene will be activated or inhibited according to the sign of the effect. All these parameters are varied by the evolutionary strategy and used to explore the interaction space for useful developmental processes able to solve the designer defined tasks. The gene activity of the i-th gene depends on parameters of the structural gene and its regulatory units.

The activation of a gene leads to two types of responses: Either a simulated molecule is produced or a function (implemented as a procedure) is executed. The link between the activation of a gene and its response depends on the first of the seven parameters of a structural gene. The following responses were implemented for the experiments in this paper:

1. Production of chemical substances
   (a) a signalling molecule is produced to communicate between the cells.
   (b) a cell adhesion molecule (CAM) is produced to connect the current cell to another one.
   (c) receptors are produced for signalling molecules.
2. The activation of a gene calls a predefined function of the following types:
   (a) asymmetric cell division (ACD)
   (b) random cell division

Asymmetric Cell Division

Cell differentiation, the process which gives rise to cells with different subsets of active genes, is coupled with cell division. During development there are cells which divide asymmetrically by segregating protein determinants into only one of the daughter cells. ACD is interesting because it provides a mechanism for placing specific cells at precise positions in a developing organism (Horvitz and Herskowitz, 1992). Recently a general concept of how the cell division planes are oriented is emerging: In a first step, an axis of polarity is established in the mother cells and coordinated with the surrounding cells or even the body plan. Along this established axis cell determinants are localized asymmetrically and as the mitotic spindle is oriented along this axis, the cell determinants are also distributed asymmetrically to the two daughter cells(Knoblich, 2001).

There are two types of asymmetric cell division: One is intrinsic (see Figure 1,the other is extrinsic (see Figure 2). ACD allows to control the cell's behavior in detail. It corresponds in many aspects to a direct encoding scheme allowing to specify in detail the cells and it is possible to evolve recursive developmental schemes. Some authors in artificial evolution contrast recursive and developmental approaches, but in fact, developmental processes can also be recursive as shown in (Eggenberger, 2003a). A cell contains asymmetrically distributed cytoplasmic factors, which by the following cell division may be distributed in different amounts to the two daughter cells and therefore influence their fates in two different directions. In order to simulate ACD a new gene class, the asymmetric cell division gene class, was introduced. Two kinds regulate two angles specifying the cell division plane depending on their activities. By regulating these genes, for instance by diluting regulating factors inside the cell, continuous changes of positions can be implemented as illustrated in Figure 3. Additonally, the proposed

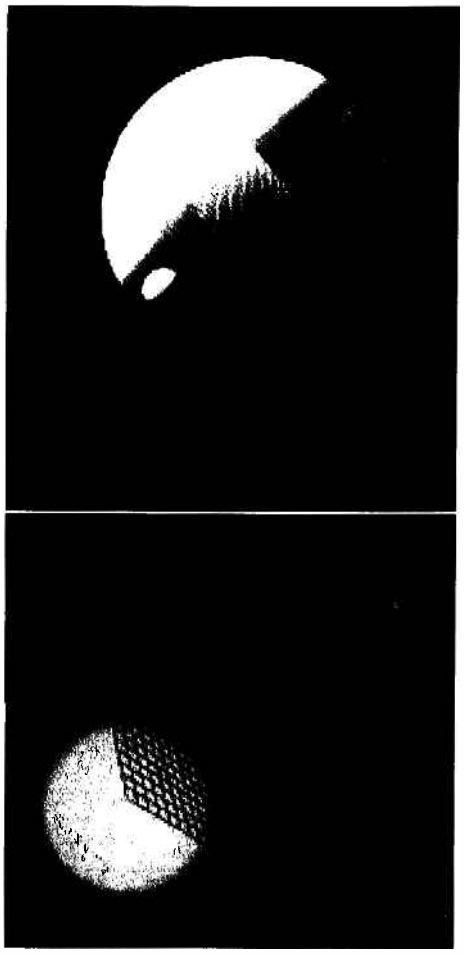

Figure 1: An intrinsic mechanism for asymmetric cell division. Intrinsic determinants are molecules that are expressed in the mother cell (on the left) and then forwarded during mitosis to the two daughter cells. In this example, two different determinants (green and red spheres) are forwarded to the two daughter cells, which will determine two different fates for the two cells.

artificial genome is able to control concurrently its own gene activities, ACD, cell adhesion and physics. This allows the AES to mimic morphogenetic processes in order to create artificial creatures. The idea to include physical processes such as diffusion and cellular interactions into the AES is to exploit these to use the genetic information parsimoniously. The genetic information of shaping or behavior can be reduced, because the intercellular communication allows to change not only single cells, but whole groups of them to perform a given function (reducing the number of parameters means in general a reduction of the search space and an increase in evolvability). If at a given position a morphogen diffuses, it can possibly change the cellular interactions, which will lead to different cellular behaviors and in

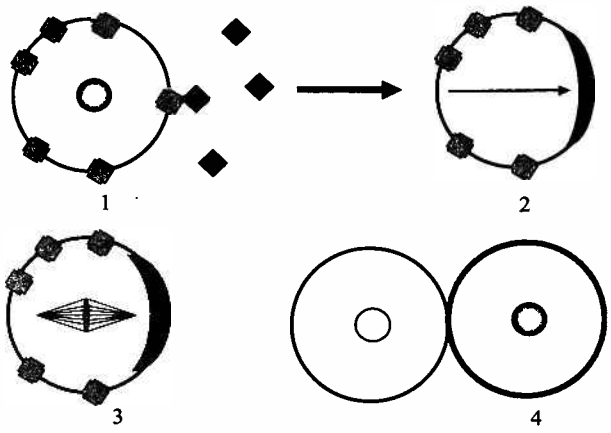

Figure 2: An extrinsic mechanism for asymmetric cell division. An external signal (red blocks) are binding to a membrane bound receptor (1). The excited ligand-receptor complex allows the binding of a protein to the membrane(2). This protein determines in turn the cell division axis (3) and the protein will be only distributed in one cell (4).

the end to different shapes. Another noteworthy property of the proposed approach is that it allows for continuously changing development. The artificial morphogenetic processes can be regulated in such a way that a cell performs a task quite similar, but slightly different than its neighboring cells.

In order to show the possible advantages of this concept, a simple simulator was written allowing to simulate a large number of cells interacting by viscoelastic elements consisting of passive springs and active dashpots. Each cell was connected to its six nearest neighbors. Movements of the cells, the production of pressure etc. will displace the cells in the direction of the applied force, but will also create a contracting force which restricts the movements. The link to the genome was established by assuming that the amount of produced cell adhesion molecules was proportional, for instance, to the spring constant allowing the AES to explore different mechanical interaction patterns between the cells. To each cells a set of differential equation is assigned, which are solved by an ordinary differential equation solver using a fourth-order Runge-Kutta method. Small changes in the genome result in small changes in the shape due to concurrent effects of the cells behavior and their physical properties. The reduction of parameters for the formation of certain shapes (obviously, for random shapes no reduction is possible) is due to the physics taking care of the positioning of cells, which react on tensions and pressures. Again, a physical process takes care of the shaping, but the genes can influence and change the outcome by changing the interaction forces between the cells (for more details see (Eggenberger, 2003b)).

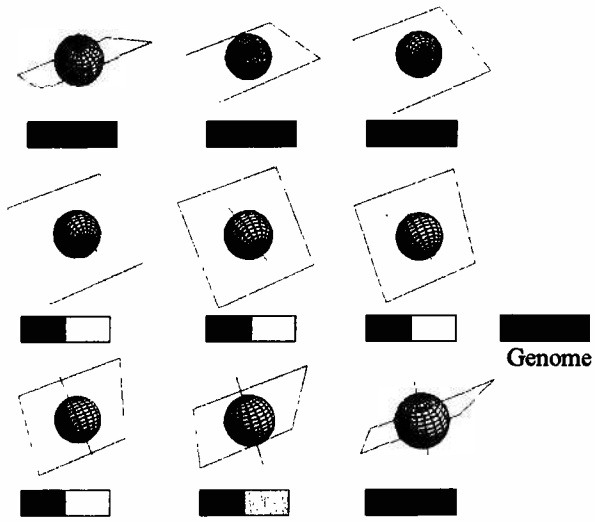

Figure 3: Cell Lineage. The activity of two genes control the cell division plane and will determine the future position of the two daughter cells. Illustrated is an example in which the left gene is inactive and the right gene has an increasing activity (symbolized by colors (blue = no activity, red = highest activity))and the effect of each gene activity pattern on the cell division plane is shown above each genome.

Evolution Strategy

A (2,16)-ES was used to perform the evolutionary runs. Usually a moving solution was found after having tested 100-300 generations. The initial mutation rate Dn was set to 0.3.

Results

The result (illustrated with Figure (5)shows that it is possible to evolve moving creatures based on the above developmental mechanisms. ACD was the mechanism enabling to specify precisely the positions of the cells as well as their physical interactions between the cells where it was necessary. First, ACD determined a T-shaped creature for which a fitness function was defined. The length of the creature was determined by diluting a regulatory factor with each cell division until the impact of the factor on the cell division gene become insufficient and the cell division process in this axis stopped. The cells growing in the perpendicular direction to the first axis used a similar mechanism: A second factor controlled a second cell division gene determining a second cell division plane perpendicular to the first one; this factor was also diluted during cell division which resulted in a cease of cell growth along this second axis.

The final shape was also dependent on the cell adhesion molecules a cell expressed. If two cells had their cell adhesion molecule gene on, they produced a link between each other. The link was weaker or stronger depending on the ac-

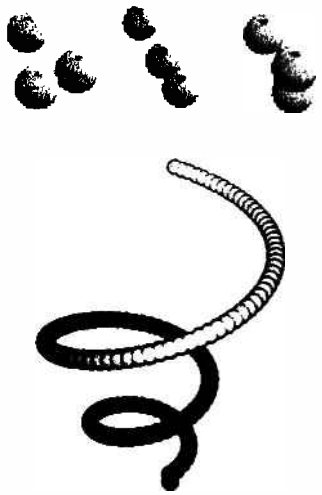

Figure 4: Simulation of asymmetric cell division. In order to simulate asymmetric cell division, a specific type of structural gene was defined representing two parameters determining the cell division plane (upper part of the Figure illustrating the effect of different planes on cell division). In the lower part of the figure an example is illustrated: By diluting regulatory factors controlling the activity of these special structural genes it is possible to change continuously the cell division plane of each cell division allowing to build spirals.

tivation state of the cell adhesion molecule gene. Another cell adhesion molecule was used to get friction on a simulated plane on which the creature was moving. By rhythmically changing the concentration of the adhesion between the cells and the surface the evolutionary system was able to produce a moving creature based on the genetic regulatory network without the need to use a neural controller. Note that ACD specified a T-structure, which due to the physical interactions changed to an arrow-like structure.

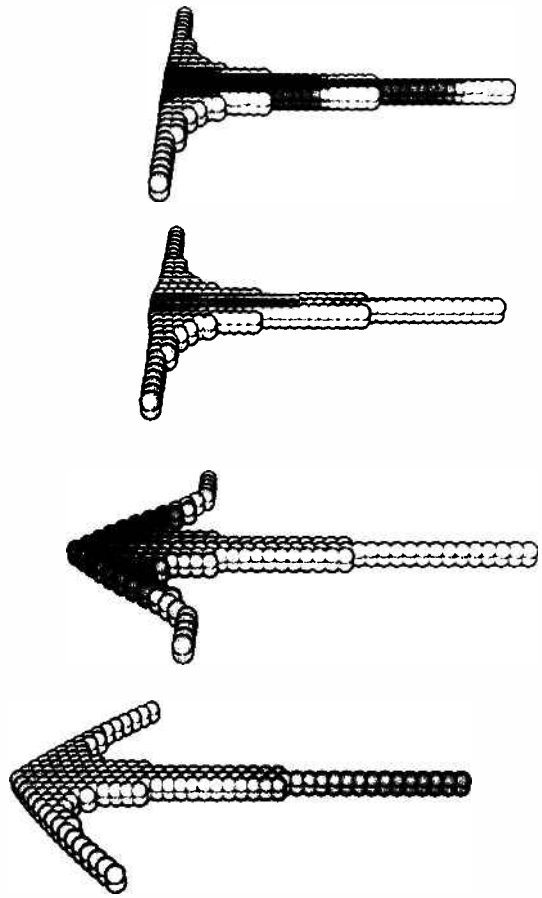

Figure 5: Dynamic shape change during movement. An artificial creature was first specified in a T-Shape, which during the movement of the creature is dynamically reshaped to an arrow-like structure. Note that surprisingly no neural network is needed to control the movement, because the genetic regulatory network is able to control the movements by rhythmically emitting signalling molecules, which change the adhesion properties between the cells as well as the adhesion between the cells and the ground!

Discussion

In order to control precisely the positioning of cells to build functioning structures, ACD implemented as proposed above showed very useful. This paper discusses the mechanisms of internal and external ACD, which allows to distribute artificial cell factors asymmetrically to the cells with concurrent control of the cell division plane allowing to get differentiated cells during the development of a cellular structure. The advantage is that where is no longer a need for symmetry breaking external sources to get the development started and that a evolutionary algorithm endowed with the mechanism of ACD is able to control single cells precisely, if this is needed. In this respect ACD is similar to direct encoding schemes, because factors can control p.e. the positioning of cells very precisely. This leads to the insight that a combination of direct and indirect encodings is probably the best way to go, each having its advantages for differ-

ent problems. As mosaic and regulative development are both used in the developmental program of most organisms, the combination of ACD with developmental processes allowing inductive signalling will expand the power of evolutionary algorithms. In addition, as ACD is also based on a genetic regulatory network, it is easy to combine ACD with other developmental processes such as cell adhesion as was shown with the example of dynamic shaping. Three points are noteworthy: First, movement does not need neural networks to control it, the genetic regulatory networks is able to control movement by rhythmically changing the adhesion to the environment. Second, the genetic specification of a shape may be altered during its use as in biology for instance with bones, where the shape of the bones depends heavily on their use. Third, artificial evolutionary

systems endowed by developmental mechanisms controlled by ligand-receptor interactions and genetic regulatory networks are easy to extend and can solve different problems such as morphogenesis, neurogenesis or learning tasks for robots (see (Eggenberger et al., 2002; Ishiguro et al., 2003; Eggenberger, 2003a)).

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