Evolving Morphologies of Simulated 3d Organisms Based on Differential Gene Expression

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Abstract

Most simulations of biological evolution depend on a rather restricted set of properties. In this paper a richer model, based on differential gene expression is introduced to control developmental processes in an artificial evolutionary system. Differential gene expression is used to get different cell types and to modulate cell division and cell death. One of the advantages using developmental processes in evolutionary systems is the reduction of the information needed in the genome to encode e.g. shapes or cell types which results in better scaling behavior of the system. My result showed that the shaping of multicellular organisms in 3d is possible with the proposed system.

1 Introduction

In the field of artificial evolution, current research tries to imitate biological concepts of evolution and development to simulate or build artificial organisms. This paper reports on a biologically inspired model that has been used to evolve 3d shapes of simulated, multicellular organisms. The model is based on cell-cell interactions which allow the regulation of gene expression in a specific and concentration dependent way.

As biological organisms are the product of the interplay of genetics, developmental processes and evolution [10, 13], I included several developmental processes, such as cell division, cell death and cell differentiation in the proposed artificial evolutionary system (AES). Even though this makes the whole approach more complex, there are several good reasons to include developmental processes in the AES:

First of all, developmental processes can reduce the information in the genome which is needed to encode a body shape or a neural network. This allows for example to make the length of the genome independent of the number of the cells in an organisms which results in a better scaling behavior, when the number of cells increases. This is especially important in three dimensional system. Second, developmental processes can take advantage of the possibilities of self-organization of a multicomponent system. In our case, the type of the artificial cells is such an emergent property. Cell types are not pre-specified, but a result of intercellular communication. Third, as every cell contains the same genome, an approach with developmental processes is conceptually much closer to the principle of parallel distributed information processing (in this case on the level of genes). This is important, if one wants to distribute the simulation on several computers or processors. Fourth, systems with developmental processes have an inherent stability. An example of this is cell growth: although every cell has the possibility to choose randomly a free place around the six next neighboring places, the emerging shapes are rather similar (see 8). Fifth, from a biological point of view, AES with developmental processes have much more biological appeal and allow therefore a comparison with biological data, which can often be very useful and inspiring.

In the next section I discuss the related work on combining developmental processes with evolutionary computing methods to evolve simulated or real world autonomous agents. In

section three the used biological concepts are explained and in section four the implementation of these concepts are described. Results are presented in section five and in the last section I discuss the advantages and disadvantages of the proposed approach.

2 Related Work

Babloyantz and Hiernaux [1] made a model of gene regulation and cell differentiation which was based on the operon model of gene regulation. They implemented the chemical reactions as ordinary differential equation and chose the parameters of these equations from the biological data of the bacteria Escherichia coli. The model was restricted to one cell. Fleischer and Barr [12] used a genetic encoding (hand coded) to specify the developmental processes by means of ordinary differential equations which were coupled with if-clauses to allow for differential gene expression. While from a biological perspective this approach is highly fruitful it is not suitable for autonomous agents because of the high computational costs. Stork et al. [30] developed a system to evolve artificial networks. They introduced a structured genome which consists of two types of genes, control genes (also called enhancers) and structural genes. The activities of the different genes are directly encoded in an activity table where the state of each gene is determined genetically. In other words, there is no intercellular communication which determines the state of a gene dynamically during development. Belew [2] used a grammar to simulate developmental processes. His scheme is context sensitive, but it is restricted to pre-specified neural network topologies. Gruau and Whitley [14] encoded the developmental process as a grammar tree. In this approach the cells inherit their connections and no context sensitive development is possible. Vaario [31] proposed a grammar-based simulation tool, in which the developmental process is described by a set of rules. A rule-based system bears the danger that certain properties of the system are defined by the designer rather than being emergent from the developmental process. Nolfi [25] and Cangelosi et al. [4] proposed a developmental model for neural networks based on cell division and cell migration. The major flaw of this approach is that the number of the genes in the genome grows with the number of neurons which leads to a bad scaling behavior. Kitano [16] reduced the size of the genome using a graph generation grammar to encode neural network topologies which has a better scaling behavior than direct encoding schemes. Furthermore, he[17, 18] developed a model based on a genetic algorithm to simulate the metabolism of cells, cell division and neurogenesis. The genome encodes metabolic rules which describe chemical reactions in a cell. These rules are linked to ordinary differential equations to calculate the changes of all the possible substances. Also diffusion and active transport of these substances are implemented. In addition a model of neurogenesis is included which is based on special growth factors. Simple cell differentiation of cells were reported (at least two different types of cells), where different substances are marks for the cell's state. Even neural networks were evolved, but to which no function could be assigned. In contrast to our approach, Kitano used no differential gene expression and in his system no forms of cell clusters evolved. Michel and Biondi [23] introduced a developmental model which uses morphogenetic mechanisms to evolve neural control structures for autonomous agents. As this model does not describe any mechanisms about cell differentiation, it is not clear how different cells can result. Sims [29] described a system for the evolution of artificial creatures that compete in a physically realistic simulation of a three-dimensional artificial world. Dellaert and Beer [8, 7, 9] proposed a model based on Boolean networks to evolve autonomous agents in two dimensions. They use a genetic algorithm to specify boolean functions which depend on different cell products which are able to activate a gene. If a gene is activated one or two different substances are produced. Mechanisms of cell differentiation like cell induction and symmetry breaking are included. Their system was able to evolve simple autonomous agents. In this approach the developmental process was not modulated by specific and concentration dependent gene regulation mechanisms.

3 The Used Biological Concepts

The study of developmental biology has led to the identification of many mechanisms for morphogenesis and development. The following mechanisms are generally accepted to be important for development in biological systems:

- cell differentiation (cell lineage and cell-cell interactions)
- cell division [10, 13]
- cell death [10, 13]
- positional information by morphogenetic gradients [35]

These mechanisms will be shortly described in the next section.

3.1 Gene Regulation

In living organisms all somatic cells contain the same genome (with a few exceptions, e.g. as some blood cells (lymphocytes)). The differences between the cells are emergent and due to regulatory mechanisms which can turn genes on or off. Two cells are different, if they have different subsets of active genes. In other words, one can define a cell type as a set of cells with the same gene activity pattern [6, 20, 13].

The activity of a gene is regulated by special regions in the genome, the regulatory units [21, 28]. Two types of regulatory elements affect the activity of a gene. The first group consists of the so-called regulatory units or cis-regulators which represent specific DNA regions. The other group are the transcription factors or trans-regulators which are soluble and affect the activity of a gene by binding on a cis-element of that gene. (See Figure 1).

In prokaryotes (simple unicellular organisms such as bacteria) several genes can be under the control of one single cis regulator. In cells of eukaryotes (more complicated organisms such as plants or vertebrates) typically several cis regulators regulate one single gene.

The activity of a gene depends on the following factors

1. the affinity of the cis- and trans regulators [28]
2. the concentration of trans-regulators at the genome [13]

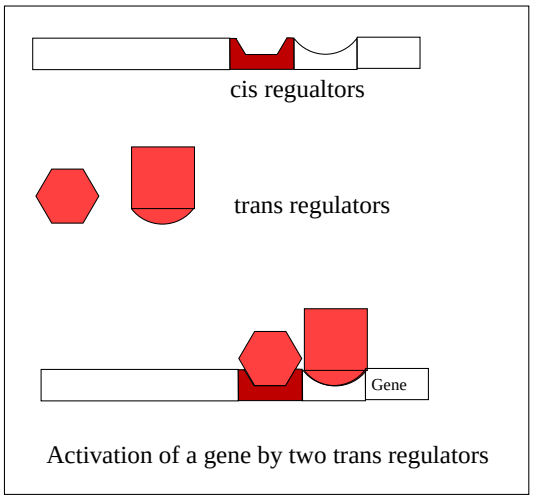

Figure 1: Cis and trans regulatory units are schematically shown. The concentration of the trans regulators (transcription factors) at the cis regulators (regulatory units) and the affinity between the regulators determine the activity of the gene.

3. the interactions of all the proteins which are necessary for the transcription of a gene by polymerases [13][p.380]
4. autocatalytic regulation of the gene once it is activated

3.2 Cell division and Cell Death

The duration of cell division varies among different cell types: Neurons and muscle cells do not divide anymore, whereas gut or blood cells divide all the time. These differences are due to different regulatory mechanisms which control cell division. In cell cultures cells stop to divide, if they have contact with each other (contact inhibition). Another mechanism is the regulation of cell proliferation by growth factors. To these belong several hormones like steroid hormones (such as progesteron which has an effect on nuclear receptors), protein hormones like insuline, nerve growth factors which influence the cell via a surface receptor on the cell membrane or mediators like prostaglandines. An overview on how cells division is regulated, is given in figure 2 [13].

There exist physiological mechanisms in the cell which can cause programmed cell death by activating special genes [10, 13]. It seems that

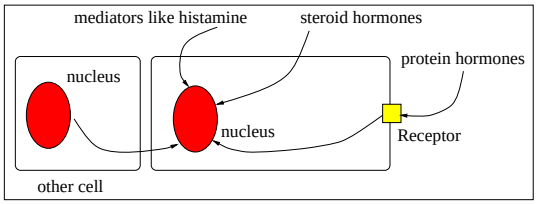

Figure 2: Overview of the possible influences on how cell division by different substances.

primary cell death programs (apoptosis) are conserved in different species throughout evolution [32]. Programmed cell death is seen during many biological processes as development of the neural system [10], the gut, the limb buds, bones or lymphocytes[32]. A well known example is the worm Caenorhabditis elegans in which many cells will die. In vertebrates cell death is used to shape certain body parts. Examples are the limbs in which cell death shapes the joints and separates fingers and toes [13][p.712]. But also in the nervous systems of mammals up to 70 percent of the cells die [10].

3.3 Cell Differentiation

Two cells are different, if they express different subsets of active genes in their genomes. Studies of biological cell differentiation are based on identification and characterization of differentiation markers, which often correspond to certain gene expressions [20].

Cell differentiation is based on two different mechanisms: cell lineage and cell induction. The first is an autonomous mechanism where cell differentiation depends on intracellular factors, which are unequally distributed in different cells [13].

With the second mechanism, cell induction, cells become different because they get different signaling from other cells. Developmental biologists talk of induction, if one embryonic region sends a signal to a a second embryonic region, which determines the fate of this second region [13][p.591].

3.4 Positional Information

Wolpert [33, 34, 35] proposed a mechanism, how cells are informed about their positions during development. An example of such a mechanism is a concentration gradient of a morphogen which every cell is able to read. The effect of a morphogen depends on the type of substance and the affinity between the substance and the cis-regulators. If these effects exceed a certain threshold, genes can be turned on or off. The existence of such morphogens is been established[20, 26]. Developmentally important substances from the mother are placed in the egg at the beginning of the development of the embryo. These substances are used to guide development in the early stages and are often also the base of symmetry breaking mechanisms to determine e.g. the body axis. These so called maternal effects are especially well studied in Drosophila [20]. An example of a morphogen is bicoid RNA, which is used in Drosophila to determine the anterior-posterior axe of the body during the very first stages of development [20, 26].

4 Implementation

4.1 Gene Regulation

To obtain cells which are able to differentiate, I introduced a set of regulatory mechanisms of gene expression in an artificial genome.

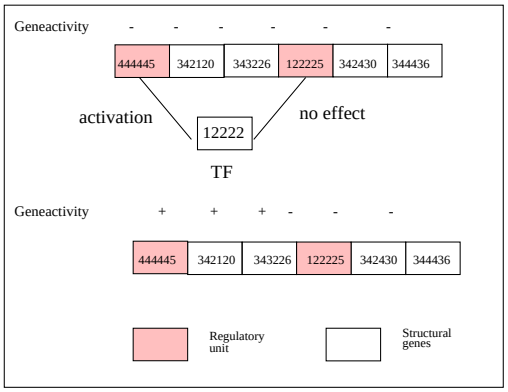

Figure 3: A transcription factor (TF) is compared to two regulatory units and the TF is only able to activate one if the affinity and the concentration are high enough.

In contrast to the usal genetic algorithms, a structured genome was used that contain two classes of genes: regulatory units and structural genes (See figure 1). The regulatory units are some kind of switches to turn on or off the genes they control. Structural genes encode for spe-

cific substances which are used to modulate developmental processes.

Every gene has the same length of n integers of which the last integer (in the following called marker) is used to indicate to which of the two gene classes a specific gene belongs. The possible values of the integers are taken from the set {0,1,2,3,4,5,6}. The first gene of the genome is assumed to be a regulatory unit. The following genes between the first gene and the marker 5 are per definition also regulatory units. All the genes between the marker 5 and the marker 6 are structural genes. The activity of the (these) structural gene(s) depend on the regulatory unit(s) directly adjacent to them. After the marker 6 is encountered the next marker 5 is searched and all genes between them are regulatory units which control the structural genes between the 5 and the next 6. This reading continues until all genes are classified. Several regulatory units can determine the activity of one or several structural genes. Figure 4 illustrates an example of a typical genome which is used in the AES.

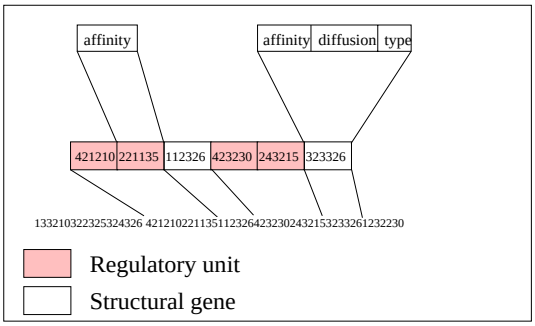

Figure 4: Some integers of the genes are used to encode substance classes and properties like the diffusion coefficient and the region where the affinity is calculated. Type is used to specify to which class a gene product belongs.

The activity of a structural gene is regulated in the following way. Every cell contains a list of transcription factors (TF) which influence its genome. The TF's as well as the regulatory units are implemented as strings of integers. The two strings are then compared: The first n (typically 6-8) integers of the string are used to calculate the affinity. As every string contains numbers out of the set {1,2,3,4 }, the affinity is calculated in base 4. The total difference between the integers of the TF- and the regulator string represents the degree of affinity. As the difference can be negative as well as positive, the sign is used to determine the effect. A negative sign represents an inhibitory effect whereas a positive sign represents an activating effect. In a second step, also the concentration of the TF's is taken into account. A concentration is assigned to every TF. The product of the affinity and the concentration of every TF at a regulatory unit is calculated and the products summed. The same is repeated for every regulatory unit of a gene. The total sum is then put in a sigmoidal function and if a fixed threshold is exceeded, the gene is activated or inhibited (See equations 1,2,3).

$$r_j = \sum_{i=1}^{n} aff_i * conc_i \quad (1)$$

$$a_k = \frac{1}{1 + exp^{-}(\sum_{j=1} r_j)} \quad (2)$$

$$g_k = \begin{cases} -1.0 & : \quad a_k < 0.2 \\ 1.0 & : \quad a_k > 0.8 \\ 0.0 & : \quad otherwise \end{cases} \quad (3)$$

- aff_i = affinity of the ith TF with the jth regulatory unit gene
- $conc_i$ = concentration of the ith TF
- r_j = activity of the jth regulatory unit of a structural gene
- a_k = total sum of the activities of all regulatory units of the kth gene
- g_k = activity of kth gene

4.2 Classes of Gene products

Depending on which structural gene is active, one of the following possibilities can occur:

1. A transcription factor is produced to regulate the gene activities.
2. A cell adhesion molecule (CAM) is produced to connect cells to each other, if on the other cell's surface is a CAM with a high enough affinity

3. A receptor is produced to regulate the communication between the cells.

4. A artificial function like cell division, cell death or searching can occur.

Which of these activities occur is determined by the first three integers of a structural gene (see fig 4).

4.3 Cell Differentiation

To simulate cell differentiation I implemented three different possible pathways to exchange information between cells. First, there are substances which do not leave the cell and which regulate the activity of its own gene. Second, there are substances which penetrate the cell wall and can reach all cells that are nearby. Third, there are specific receptors on the cell surface which can be stimulated by substances. If a transcription factor has a high enough affinity to the receptor, a gene or a group of genes is influenced as if the transcription factor would be at the genome. Only those cells which have a specific receptor on the cell surface will respond to a certain substance (Figure 5).

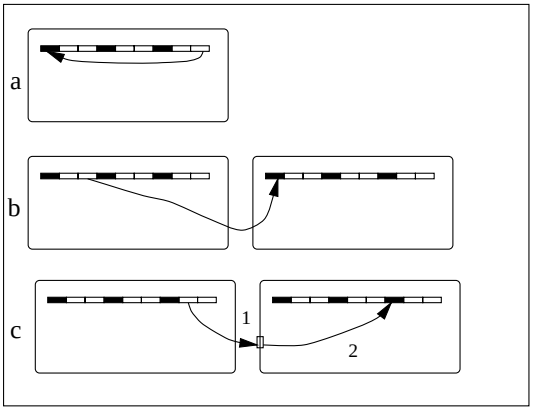

Figure 5: Intercellular gene regulation by activators and repressors.The following regulation scheme is implemented: a. intracellular regulation b. intercellular regulation c. The intercellular communication depends on a receptor (1), which sends an activating signal to a regulatory site (2), if the affinity between the receptor and the transcription factor is high enough.

4.4 Positional Information

The mechanism of positional information is already implemented by the regulatory mechanisms mentioned above. TFs produced by a cell can diffuse to nearby cells. In this case, they could be called morphogens that may induce a change of the state of some genes in cells which can read this message. In my implementation a morphogen is just a kind of TF which is also represented as an integer string with an associated concentration. Note, that this is not a biologically realistic implementation, because TFs can usually not pass the cell membrane. One should note that this mechanism is not just a simple signaling, because the reading mechanism (the cis-regulators) is also controlled by the AES. Therefore the same gradient (same concentrations and the same substance) can have very different effects on different cells (See illustration in figure 7). Some examples of such effects are changes in cell type, cell division rate or motility. These basic developmental processes are in principle implemented the same way.

4.5 Classes of Gene Products and Functions of a Cell

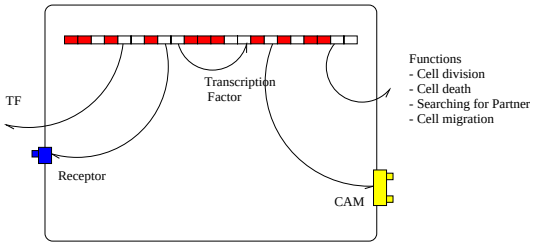

Figure 6: Overview on the products and functions of a cell in the AES.(The functions of the different substances are explained in the text).

The different active genes will determine which substances are produced in a cell. These substances are stored in lists for further use.

At this point of the development the artificial cells have a structured genome, a list which holds the activity of the genes (which can change dynamically) and different lists which represent different substance classes that are contained in the cell.

4.6 Evolution

The base of my AES is a genetic algorithm which changes randomly a population of 120 genomes. In our experiments I used n (usually 8) units which contained 2 regulatory units for 2 structural genes to control the shaping of the multicellular organisms. As genetic operators I used one-point cross over and mutation.

5 Results

5.1 Cell Differentiation

In our AES the concentrations of the morphogens are read by the cells. Depending on which regulatory units are activated, the same morphogen can have different effects. In figure 7 some examples of different effects of the same morphogen are shown. The reading mechanisms (the regulatory units) vary in their affinity, which explains the different effects on the different cells.

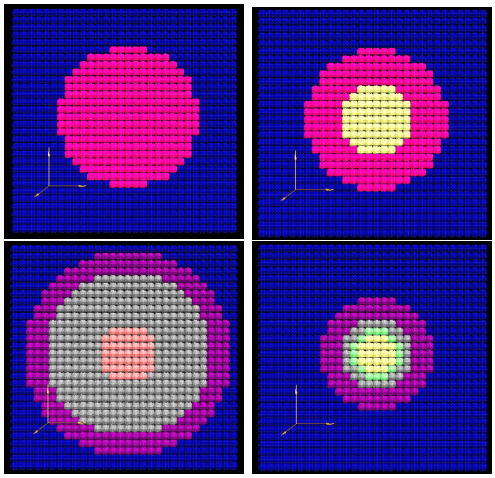

Figure 7: In the middle of a plane of cells a morphogenetic source is put and the cells read the concentration of the morphogen. Different cells have different gene activity patterns. Note that depending on the cell, the same morphogen can have different effects.

5.2 Growth and Forms

In Drosophila the substance bicoid RNA acts as a morphogen to determine the anterior-posterior axis of the body. The genomes are reading the concentration of this morphogen and genes are activated in a specific and concentration dependent way. In analogy to these facts the AES has the possibility to put morphogens at different places in a grid. The different gradients which are possibly built up are a sort of chemical coordinate system which is read by the cells and will inform them of their position by activating different genes. In this way it is possible to guide the growth of cells, because once the concentration of a substance which activates the cell division gene drops below a certain threshold , growth will stop.

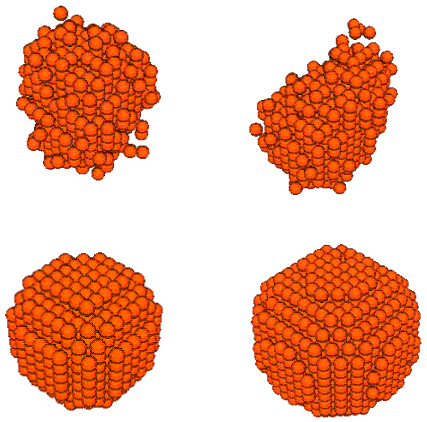

Figure 8: The two upper cell clusters are the result of random cell growth. The two lower cell clusters emerged if in addition one morphogen is allowed to modulate the growth (See text for more details).

In figure 8 the modulating effect of morphogen gradients on a random growth process with contact inhibition is illustrated. During the implemented cell growth, each cell looks for a free place in the next 6 neighbors and chooses one randomly. If there is no empty neighbor hood around a cell, its division is inhibited (contact inhibition). Note that during a random growth process the emergent forms are rather different (See upper part of figure 8). A morphogen producing cell is positioned in the middle of the grid, which activates cell division. If the influence of the concentration of the morphogen and the affinity goes below a threshold, the cells stop to divide. Now, the structure of the cell cluster is smoothed out and becomes independent of the randomness of the

cell division. The size of the balls is the result of the different concentration and the different diffusion properties of the morphogen, as well as the properties of the reading mechanism of the genes (cis-regulators).

5.3 Development of bilateral shapes

First, the program generates the environment and a population of genomes. One cell is positioned in the middle of a 3d grid of typically 30x30x30 sites. This grid represents the environment of the cells and is used to position cells and cell products in the environment. Three sources of different morphogens are positioned on 3 different axes in space with varying distances to the first cell. These sources produce morphogens which diffuse into the environment. The cells are able to read and interprete these gradients with the effect that possibly different genes are expressed. Also cell induction as another mechanism of cell differentiation is used. The cells can synthesize transcription factors, which influence the gene activities of other cells.

The fitness function was depended on the number of cells and their position with respect to the x-axis.

1. $$\text{fitness} = \max - |(\max - n)| \qquad (4)$$
   max = cell number which is assumed optimal
   n = actual cell number after the cell divisions have stopped

2. for every existing cell the fitness was increased, if the cell had a symmeterical counterpart at the other side of the x-axis. After the number of cells stopped to increase, the fitness of the organisms was evaluated. If the number of cells was bigger than a predefined number of cells, the fitness was put to 0.0.

6 Discussion

As the number of genes in the genome is insufficient to specify precisely every cell, epigenetic processes with their combinatorial expression of sets of genes are used in Nature to specify the cells [15]. Therefore, I proposed in this work that biological ideas are useful and applicable to the field of artificial evolution. Implementing

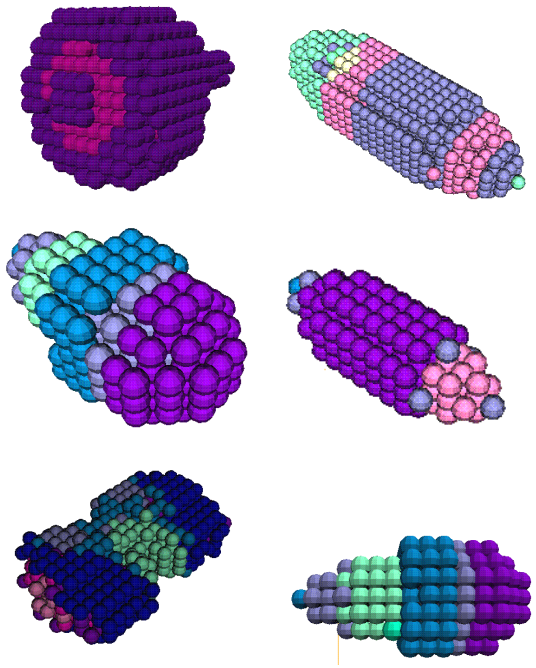

Figure 9: Several examples of evolved forms. The fitness functions only evaluated the number of cells and the bilaterality of the found organisms.

important developmental processes we showed that cell growth, cell differentiation and the development of shapes of simple organisms are in the reach of this AES.

In contrast to less biological approaches the following points are noteworthy:

- as in real cells every artificial cell contains the same genetic information
- differential gene expression allows the modulation of developmental processes such as cell division, cell death and shaping of an organism.
- epigenetic processes allow to reduce the length of the genome. Especially important is the fact that the genome will not necessarily grow, if the number of cells is larger.
- no direct encoding of genetic information for cell types, cell position or links to other cells, because these things are emergent properties of epigenetic processes

The proposed AES was able to evolve three dimensional shapes for simulated, multicellular

organisms. With the proposed AES a step towards the following scientific goals is made:

- the AES evolves plans of three dimensional robots which can be used to produce real world robots
- the investigation of the co-evolution of the morphology (shape) and its neural control structures for 3d, multicellular organisms. It was shown that also neural networks for real world robots can be evolved by the same type of AES [11].
- if one investigates complex systems one tries to understand how simple parts are able to build more complex wholes. In our specific case we ask: What should a singele cell be able to do, if many cells should be able to develop a more complex organism?
- one of the main problems of every artificial evolutionary system is the evolvability. Which capabilities have to be introduced in an AES that systems of increasing complexity can be evolved? (Chaitin[5] gives a definition of complexity).
- analysis of the simulator to explore its limits. We will analyze statistically our AES and test the different results with different initializations of the random generator and the different possibilities of the genetic operators which can be introduced if one uses structured genomes. Interchanging and duplicating genetic material seems very promising to us, especially as these operators change possible interactions between cells.

7 Acknowledgements

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