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Submitted on 26 Mar 2015

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**To link to this article**

DOI: [10.7551/978-0-262-32621-6-ch087](http://dx.doi.org/10.7551/978-0-262-32621-6-ch087)

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Self-organization of Symbiotic Multicellular Structures

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Abstract

This paper presents a new model for the development of artificial creatures from a single cell. The model aims at providing a more biologically plausible abstraction of the morphogenesis and the specialization process, which the organogenesis follows. It is built upon three main elements: a cellular physics system that simulates division and intercellular adhesion dynamics, a simplified cell cycle offering to the cells the possibility to select actions such as division, quiescence, differentiation or apoptosis and, finally, a cell specialization mechanism quantifying the ability to perform different functions. An evolved artificial gene regulatory network is employed as a cell controller. As a proof-of-concept, we present two experiments where the morphology of a multicellular organism is guided by cell weaknesses and efficiency at performing different functions under environmental stress.

Introduction

In nature, the cellular specialization (or differentiation) process allowing a single celled organism to grow organs of various shapes and functions is a key mechanism in the development of complex morphologies, behaviors and developmental strategies. Over the past few years, many developmental models have been designed to simulate the growth of virtual multicellular organisms. They have been dealing with different levels of biological realism that directly impact on the complexity and the computational cost of the model. From the cellular automata in the 1960s (Von Neumann et al., 1966) and its offspring (Gardner, 1970; De Garis et al., 1999; Chavoya and Duthen, 2008) to today’s models (Hotz, 2004; Joachimczak and Wróbel, 2008; Doursat, 2009; Cussat-Blanc et al., 2012a), this field of research evolved by getting closer to the biological reality. However, though cell differentiation was frequently explored (e.g. French flag problem), the models used evolutionary algorithms guided by an exogenous engineered fitness function describing a predefined morphology.

In the last decades, some cell development models also explored the creation of multicellular organisms which would be evaluated not directly in regard with their morphology but in terms of capability to fulfill a certain function. Co-evolution of morphology and control system showed interesting results, using global control methods such as neural networks in order to, for example, push a block (Bongard and Pfeifer, 2003), or using an artificial gene regulatory network to locally contract cells and swim, such as what Joachimczak et al. did, using a two phase development and explicitly forcing animats to stop growing through fitness function (Joachimczak and Wróbel, 2012) or such as what Schramm did with, however, a subobjective of the evolution being an explicit shape description (Schramm et al., 2011).

The work presented in this paper offers to investigate the emergence of morphologies, developmental capabilities and behaviors of a multicellular simulation. Contrary to many other models (previously cited), this system does not rely on any global controller nor has to enforce any particular differentiation pattern or morphology through a fitness function, but has to find developmental strategies to adapt to and to compose with a hostile environment as well as a more biologically plausible specialization process.

We present a developmental model (named SOMAS, for Self-Organizing Multicellular Artificial Systems) in which cells embed a simplified simulation of a cell cycle regulated by an artificial gene regulatory network. Thus, cells are given the possibility to divide, to specialize, to stay in a quiescent state or to commit apoptosis. Moreover, a mass-spring-damper system simulates the cell mechanics with intercellular collisions and adhesions, and a simplified artificial chemistry is used for both nutrient transformation into energy and morphogen diffusion. The organisms develop from one stem cell and an evolutionary algorithm is used in order to select the ones that succeed in developing in a hostile environment. One of the main goals of the model is to present a simple but efficient way to bring biological plausibility to the specialization process. Our work is based on the idea that the specialization process of biological cells selects characteristics to develop while other domains are abandoned. The interesting side effect of such process is the need for cellular cooperation through the creation of interdependent functional organs. In our model, we quantify specialization states in terms of weaknesses and ef-
SOMAS is designed to provide some bio-inspired capabilities to the cells. In particular, we focused on the following three main components: an artificial chemistry providing the cells with the ability to interact and to produce energy, a cell physics model that simulates the collision and adhesion mechanisms and a cell cycle abstraction with the possibility to specialize into different cellular states, controlled by a gene regulatory network.

Artificial chemistry

The chemistry is here aimed toward two main goals. First, the diffusion of morphogens in the environment is used by the cells in order to communicate and gain, for example, positional informations. Secondly, it provides the cells with the basics for energy management. Both aspects are detailed in the following paragraphs.

Morphogens

Morphogens are signaling molecules produced by cells. They play an essential role in embryogenesis. Often produced from a localized source, the morphogen concentration gradient helps cells to localize themselves and trigger cell specialization. We use a simplified morphogen diffusion system based on a grid in which cells inject and sense morphogens concentrations level. An artificial gene regulatory network described hereafter and embedded in each cell governs the morphogen production rate.

A morphogen is characterized by its attenuation speed (from which can be deduced its range) and its evaporation rate. At each time step, morphogen levels are updated on the morphogen grid: their concentration are first decreased according to their evaporation rate, before being diffused to the neighboring grid cells. When a grid’s cell diffuses its concentration to its surrounding, the neighbors receive its morphogen concentration multiplied by the attenuation speed of the morphogen. The morphogen concentration $C_i$ received by a grid cell $i$ from a neighboring source of morphogen with a concentration of $C_S$ is thus equals to:

$$C_i = C_S \times (1 - R_m \ast d(i, S))$$

with $R_m \in [0, 1]$ the attenuation speed of morphogen $m$ and $d(i, S)$ the distance between the centers of cells $i$ and $S$.

A morphogen grid cell concentration always keeps the maximum concentration value offered (which either directly comes from a cell placed on it or from the diffusion of its neighbors grid cells). When a cell senses the morphogen concentration for its position, the morphogen grid computes and returns the average concentration of the 9 nearest grid’s cells centers weighted by their distance to said position. The same interpolation process is used when the cell diffuses its morphogens into the grid cells. With grid cells in the same order of size as the cells, this system allows for “smooth enough” morphogens gradient (as can be seen in figure 3) formation without the algorithmic complexity of a purely continuous model. Morphogen concentration $C_m$ at position $m$ is thus equals to:

$$C_m = \frac{\sum_{i=0}^{8} C_i}{\sum_{i=0}^{8} \frac{1}{d(i, m)}}$$

with $C_i$ the morphogen concentration in grid cell $i$ and $d(i, m)$ the distance between $m$ and cell $i$ center’s position. Figure 1 depicts this morphogen concentration computation.

In figures 2 and 3, three morphogens are produced by different cells. Their concentrations are mapped to the cyan,
Cell actions

Cells are able to perform four main actions, designed after the possible actions and transformations a real living cell can undergo: division, apoptosis, quiescence and specialization. The division is a cellular action of prime importance, as it is the main mechanism behind organ growth. If the exact replication of the mitosis process is not necessary, it is however important to be able to reproduce the external manifestations of division. In this model, a cell can only begin division if it has enough energy and if the membrane pressure is not too high. The cell then grows to double its size (the collision-spring triggering distance increases). The division axis is chosen according to the compression forces the
cell experiences: it will divide perpendicularly to the most compressed axis. When actual division occurs, a clone cell of initial size is created, and energy and nutrients are split in two equal parts.

The apoptosis is the programmed “clean” death of a cell. All of its nutrients are diffused to the neighbors and the cell is deleted from the environment.

When a cell enters quiescence, it cannot choose to begin another cellular action for a certain number of decision steps and its energy consumption is reduced.

Cell specialization is one of the key mechanisms behind the formation of organs in living organisms and is also at the heart of this work. Specializing cells progressively modify their properties in order to better fulfill certain functions, thus becoming differentiated cells. This specialization process is here represented by the walk through a tree structure in which every node contains a set of values to be assigned to the cell’s properties. Once a cell reaches a certain node, which we call specialization state, it cannot go back to a previous state and the cell’s attributes values are replaced with the ones described by the new specialization state. Such a state contains information about three main aspects: (1) the physical properties (biomass, size, global stiffness and adhesion) of the cell; (2) the controller (the subpart of the artificial gene regulatory network to be used, this mechanism being meant to mimic the way a differentiated cell would only express a subpart of its genome); (3) the skill values of the cells that describe its efficiency in performing various tasks, such as using a certain type of nutrients to produce energy or being able to withstand the impact of harmful particles from the environment. This final concept is crucial to the experiments presented hereafter and will be described with more details later on.

As in nature, these actions, among other internal regulations, are regulated according to an artificial gene regulatory network.

Specialization tree

At the heart of the experiments presented in the next section is the concept of “skills design”, or the quantification of efficiency for cells from different specialization states to fulfill certain functions. The general idea, inspired by the observation of living multicellular organisms, is that cells cannot be omnipotent, i.e. they cannot do everything with “full” efficiency. Cell specialization is thus always a matter of getting better at doing something and letting other important functions aside. To survive in a complex environment, the cells then have to cooperate and organize so that they optimally use their capacities.

In our model, we implemented this idea with the repartition of a fixed number of skill “points” to distribute between various functions. In the particular case of the experiment presented in the paper, they are the ambrosia production, which is the ability to retrieve nutrients from the environment and turn them into ambrosia, the diffusion efficiency, which quantifies the ability to diffuse ambrosia to nearby cells, the energy efficiency (the more developed this competence, the less energy the cell consumes at each time step), the ambrosia capacity, which quantifies the ability to store a large amount of ambrosia and the stress resistance, which is the ability to withstand aggression from the environment (in the experiments presented hereafter, environmental aggressions are represented by particles of various intensities).

Specialization states are thus crafted by distributing skill points into characteristics. Once the balance in the influence of those skill points is carefully established, specialization trees can be described in both their topology and in the skill points distribution for each of their specialization state. In this work, the trees are hand-crafted but they are ultimately meant to be part of the virtual creature’s DNA, subjected to evolution.

Gene regulation

In nature, a gene regulatory network is a network of proteins. The cascading interactions between these proteins control genome expression by the use of external signals collected from protein sensors localized on the membrane (Davidson, 2006). These signals activate or inhibit the transcription of the genes, which then determines the cell’s behavior. Here, we use an artificial gene regulatory network which is a simplified computational model inspired by its biological counterpart. This kind of controller has been used in many developmental models of the literature (Bongard and Pfeifer, 2003; Hotz, 2004; Flann et al., 2005; Knabe et al., 2008; Joachimczak and Wróbel, 2008; Doursat, 2009; Cussat-Blanc et al., 2012a) and to control virtual and real robots (Nicolau et al., 2010; Joachimczak and Wróbel, 2010; Cussat-Blanc et al., 2012b).

Dynamics

The artificial Gene Regulatory Network (GRN) used in this model is based on Cussat-Blanc’s model (Cussat-Blanc et al., 2012b). It is however modified in order to allow for a better precision by using continuous tags. Moreover, all the protein concentrations are clamped between 0 and 1, allowing their absolute concentration values to be directly used without need of comparing them to each other. A gene regulatory network is therefore defined as a set of interacting proteins defined by three tags, coded as floating-point numbers between 0 and 1, and a type. The protein tag describes the proteins themselves. The enhancer tag is compared to the protein tags of other proteins to compute the enhancing matching factor between two proteins. The inhibitor tag is used as the enhancer tag to calculate the inhibiting matching factor between two proteins. Finally, the protein type determines if the protein is an input protein, whose concentration is given by the environment of the GRN and which regulates other proteins but is not regulated, an output protein, whose concentration is used as an output
of the network and which is regulated but does not regulate other proteins, or a regulatory protein, an internal protein that regulates and is regulated by other proteins.

The dynamics of the GRN are calculated as follows. First, the affinity of a protein $a$ with another protein $b$ is given by the enhancing factor $u_{ab}^+ = |enha - ida|$ and the inhibiting $u_{ab}^- = |inhb - idb|$ (where $ida$ is the protein tag, $enha$ is the enhancer tag and $inhb$ is the inhibitor tag of protein $x$).

Then, the proteins are compared two by two using the enhancing and the inhibiting matching factors. For each protein of the network, the global enhancing and inhibiting values are given by the following equations:

$$g_i = \frac{1}{N} \sum_{j=1}^{N} c_j e^{\beta(u_{ij}^+ - u_{max}^+)} ; h_i = \frac{1}{N} \sum_{j=1}^{N} c_j e^{\beta(u_{ij}^- - u_{max}^-)}$$

where $g_i$ (resp. $h_i$) is the enhancing (resp. inhibiting) value for a protein $i$, $N$ is the number of proteins in the network, $c_j$ is the concentration of protein $j$ and $u_{max}^+$ (resp. $u_{max}^-$) is the maximum enhancing (resp. inhibiting) matching factor observed. $\beta$ is a control parameter that set up the “usable” distance between the proteins.

The final modification of protein $i$’s concentration is given by the following differential equation:

$$\frac{dc_i}{dt} = \delta(g_i - h_i)$$

Where $\delta$ sets up the speed of reaction of the regulatory network: the higher, the more sudden the transitions in the GRN; the lower, the smoother the transitions.

Cell behavior regulation The inputs proteins are connected to both the surrounding of the cell and its internal state. In order to allow behavior to change according to the specialization state, each of these inputs are duplicated for each possible state but only one set per differentiation state is activated at a time, the GRN thus being fed with the same input data but from different input proteins. These data are the concentration in each morphogen, the membrane pressure, the energy level of the cell, the ambrosia quantity divided by the maximum ambrosia storage capacity of the cell and the nutrients concentration in the environment.

The outputs of the GRN are the following: one protein per cell action (quiescence, apoptosis, division or specialization): the action with the highest output protein concentration is chosen and, in case of specialization, the protein with the highest concentration among all the “specialization” output proteins will determine the state the cell must specialize into; one protein for each morphogen, which concentration level directly gives the cells morphogen production; one protein to decide the proportion of ambrosia to be transformed into energy, and therefore allows the cell to choose between storing ambrosia or refilling its energy level; one protein that gives the proportion of ambrosia to be diffused to nearby cells; another protein giving the amount of nutrients a cell should transform into ambrosia, relatively to the maximum consumption capabilities of the cell (defined by its current type) and limited by the environment resources.

When an action is triggered, the GRN powered decision system is locked until the end of the action (e.g. cells cannot trigger apoptosis while they are dividing). However, all other systems (morphogen production, ambrosia transformation and diffusion, etc.) are maintained and the GRN still controls the corresponding outputs.

Genetic algorithm This model is meant to be optimized by a genetic algorithm. A standard genetic algorithm is used with a crossover that crosses two GRN protein sets and a mutation operator that can equiprobably randomly modify a tag, add a new regulatory protein or delete a regulatory protein.

As we stated in the introduction of this paper, the aim of this work is also to avoid designing a fitness function that would directly guide the organogenesis process. We want morphological complexity to emerge from the differences in specialization states and the need for cells to survive as long as possible in a hostile environment. Each growing organism is thus only evaluated by its survival time, in simulation steps, the longer the better.

Experiments As a proof-of-concept and as a first step toward more complex experiments on organogenesis, we developed two environments with two different kinds of constraints. The aim is to show the capacity of the model to produce organized developmental strategies without explicit morphology specification hard-coded in the fitness function. The first experiment presented in this paper consists in studying the specialization and auto-organization capacity of cells attacked by harmful particles. The second one adds complexity by constraining the energy of the environment.

First experiment: surviving aggressions The first of these two experiments takes place in a hostile environment where dangerous particles are aimed toward the center, which is where the first cell appears. We can draw an analogy between this scenario and radiations that would destroy unprepared cells. In a more general way, these particles are a metaphor of any punctual stress that living multicellular organisms need to face while developing.

Initial conditions For this first experiment, we manually set up a specialization tree with only two states: the nutritive state and the defensive state. Specialization can only occur from the nutritive state to the defensive state and the first cell of the organism is nutritive. The nutritive state is characterized by its ability to produce energy and ambrosia together with a lack of defense against particles. In direct
opposition (and thus complementarity) to the nutritive state is the defensive state, which offers a good defense against particles but a very low nutritive efficiency. Table 1 shows skill points distributions for the relevant skills set.

<table>
<thead>
<tr>
<th>Property</th>
<th>N</th>
<th>D</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrosia Production</td>
<td></td>
<td>3</td>
<td>Nutrients units a cell can turn into ambrosia at each time step</td>
</tr>
<tr>
<td>Ambrosia Storage</td>
<td>10</td>
<td></td>
<td>Maximum amount of ambrosia that can be stored</td>
</tr>
<tr>
<td>Resistance</td>
<td></td>
<td>10</td>
<td>Amount of energy that can be absorbed from particles before the cell dies</td>
</tr>
<tr>
<td>(here, a particle has 1 energy)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Skill points repartition for the two specialization states N (nutritive) and D (defensive).

Results The results show a global increase in the creatures’ life time (the fitness function, expressed in number of frame) over the generations. By observing the best individuals and by looking at the evolution of the selected genome, generations after generations, we can identify three key developmental strategy elements (depicted on figure 5):

1. Clusters: After a few generations, cells start to organize themselves in fuzzy clusters where a few nutritive cells are surrounded by protective cells. This strategy seems to be an effective way to use the specialization states: energy providing cells, which are vulnerable, stay protected from the particles by feeding a shell of protective cells. More notably, the formation of these clusters relies extensively on the use of apoptosis, and thus present interesting similarities with the experimental evolution of multicellular “snowflakes clusters” with yeast (Ratchiff et al., 2012).

2. Constant renewing: later in the evolution, cells inside the clusters tend to constantly divide and specialize into defensive cells. This makes up for the defensive cells dying because of the aggression of the particles but also because they receive less ambrosia when they are far from the nutritive cells. It is also to be noted that cellular clusters tend to be stable, maintaining an average number of cells throughout their life.

3. Shifting from the center. We observe that, over the dozen different evolution runs we made, a special behavior tends to emerge near the “end” of the evolution runs: movement (at cluster level). Organisms tend to avoid the center of the environment which is way more dangerous than the outskirts because of the concentric pattern formed by the particles. They do so by using an unbalanced division ratio and apoptosis: division rate is more intensive on one side of the cluster than on the other side. We verified that this behavior was not just a consequence of the particles being denser in the middle of the environment: the same organisms put in a particle free environment demonstrated the same behavior (depicted by figure 6).
**Second experiment: adding an energy constraint**

For this second experiment, the cells have to survive under harder constraints. They now not only have to survive aggression from harmful particles, but they also have to compose with a stronger energy constraint. Nutrients are indeed placed on a square centered in the environment where particle density is maximum. Moreover, they are cyclically appearing and disappearing, with an increasing amount of time between every two appearances. Therefore, the organism will have to face episodes of starvation. Moving too soon toward the exterior of the circle in order to escape highly dense particles might thus not be a viable option anymore.

In addition to this constraint, nutritive cells can no longer store large amount of ambrosia. In order for an organism to be able to store it, a third specialization type is introduced: the storage state. The analogy could be made with lipid cells which are storing energetic molecules in living beings. The characteristics of this new specialization state are almost no resistance to particles (0.1 points), no nutrients extraction capabilities (ambrosia production rate is null), a high ambrosia storage capacity (10 points) and a perfect ambrosia diffusion efficiency. The other two specialization states (nutritive and defensive) are kept identical to experiment 1, except for their ambrosia storage capacity which is now set to 0.5. The first cell is nutritive and can specialize into either defensive or storage.

**Results**

The results show a strong convergence in the development strategies over the 6 evolutionary runs (120 generations of 400 individuals each) launched for this experiment. Figure 7 shows a timelapse of one of the best individuals. The best strategy seems to be the following scheme. First, lots of nutritive cells are created from the initial cell (they can easily survive as the nutrients only disappear for short periods of time at the beginning of the simulation and particles are still far away). Secondly, a shield of protective cells starts to appear. At this stage of the simulation, nutrients are still abundant and the main concern for the organism is to protect them against particles. The organisms that fail in this task in the early generations try to compensate with quick proliferation but eventually die quite early in the simulation due to the particle damages. Then, as nutrient availability starts to become a problem, most organisms start specializing some of their nutritive cells into storage ones. Here, the only difference between organisms that end up with an average fitness and the ones that have the best fitnesses is the localization of these storage cells. The best organisms place the storage cells away from the center of the circle of particles, but with still a network of nutritive cells surrounded by defensives near the center, where nutrients still appear. We can see this behavior between frame 750 and 1000 of figure 7: nutritive cells that were waiting on the extremity of the organism specialize into storage cells in anticipation of starvation. Finally, with the simulation moving forward, appearances of nutrients become extremely rare, and the organisms shrink to a tiny cluster composed of a few storage cells diffusing the ambrosia they collected to a shield of defensive cells. Figure 8 gives an overview of these steps by showing the cell population through time.

The organism was able to find a strategy to adapt to periodical starvation by using the storage state in a suitable way. This illustrates the capacity of the model to step up in complexity in order to manage a new specialization state and harder environmental constraints, as well as how the model can give birth to interesting development strategies.
Conclusion and discussion

This article detailed a model (SOMAS) which aims to provide a base for the organogenesis of virtual organisms. The focus of SOMAS has been made on three main layers: the cellular physics, the simplified cell cycle and the specialization mechanism. The experiments gave encouraging initial results as cells successfully specialized into different available types to better fulfill certain function and adopted a particular morphology and cooperation-based strategy, demonstrating the ability for the model to produce complex developmental plans without any complex fitness design. Morphology and strategy emerged from both the environmental constraints and the intrinsic weaknesses and efficiency the cells had to compose with. The first results showed the formation of clusters and collection of cells that could easily be compared to some of the early living multicellular organisms, which were often barely more than aggregated clusters of specialized monocellular organisms living in symbiosis.

This model aims to bring tools to the artificial life researches for a better abstraction of the consequences and manifestations of living cell specialization. It avoids the design of an omnipotent multipurpose cell as well as the use of complex fitness functions which would explicitly enforce the desired phenotype of the creatures. Our model tries to abstract the underlying complex realities of the cellular specialization process by capturing some of its essential observable implications. One of the idea behind this model is therefore that organogenesis, and thus complexity and diversity in the shape and functions of multicellular organisms, is a direct consequence of the incapacity for a cellular type at being efficient on every front at the same time.

A certain number of enhancements will be at the heart of our future work. First, we presented here experiments where specialization types were manually designed. The next step is to integrate this design directly into the creature's DNA. Optimum cell specialization trees structure as well as skill points distribution will have to be found through an evolutionary process. This means a meticulous balancing work has to be done. We also want to increase the number of attributes specialization states can be formed with.

Another important research path we want to explore is co-evolution. Here, we presented experiments where the fitness was kept as simple as possible: it just is the amount of time organisms can survive. Therefore, the model seems well suited for a coevolution approach where all organisms could, for example, compete for their survival in a limited nutrient environment. Using the potentiality of the physical engine by adding physical constraints would also be another way to encourage organisms in finding innovating morphologies.

References


Cussat-Blane, S., Sanchez, S., and Duthen, Y. (2012b). Controlling cooperative and conflicting continuous actions with a gene regulatory network. In *Conference on Computational Intelligence in Games (CIG '12)*. IEEE.


