# Chapter 1

# A Simple Model of Neurogenesis and Cell Differentiation Based on Evolutionary Large Scale Chaos

Based on article by Hiroaky Kitano
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Summary by Amnon Amir
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## 1.1 General

The article deals with creation of multicellular organisms based on metabolic simulation. The purpose is to check if complex multicellular organisms can be created by genetic algorithms running on the metabolic rules in the genome of the cell.

## 1.2 Cell Differentiation

All the cells in a particular multicellular creature contain the same DNA sequence. But it is clearly evident that there are a number of cell types in the creature, which greatly vary in their characteristics. For example both nerve cells and epithelial cells in a human share the exact same DNA sequence, but clearly differ in their shape,function etc.

The process of a cell turning into a specific type, which is usually irreversible, is called *Cell Differentiation. This process is not trivial and raises a few questions, among them:*

- *If the DNA of the all the cells is the same, how do the cells turn into a specific type, and display* Cell Memory which means when this cell divides, the two cells derived are still of the same type as the father.

- *The breaking of symmetry problem: How can a creature with a predefined structure (of various cell types) be created from a symmetrical system. For example in humans, how is the human structure created from a more or less symmetrical ball of a few cells. Where is the breaking of symmetry initiated?.*
- *While containing various cell types, the number of types is still limited and cell types are discrete and different alot from one another. How can this be explained.*
- *This system was originally created by evolution. Does the current understanding of evolution explain for this situation.*

## 1.3 Evolutionary Large scale chaos

*The article tries to create a model for cell differentiation by using a simulation for metabolism of the cells, based on a set of metabolic rules which are coded in the genome of the cells. Even though the set of rules is the same for all the cells in a specific organism, different rules come into expression in different cells because of a different environments of the cells, and therefore different cells are derived. The metabolism of each cell (and therefore the metabolic rules expressed) depend on the status of the cell and of its' neighbors, and hence (as has been shown in other papers) the status of the cells becomes a* Large Scale Chaos, meaning that small differences in current cell metabolism can create a big difference after a few cell cycles. In order to create an interesting set of metabolic rules (i.e. genome), an evolutionary process was applied to organisms, where the genome is the metabolic rules (of all the cells in an organism), and the fitness function (on the organisms) is the number of cells in each organism after a predefined number of cell cycles (for a more exact explanation on metabolism and cell cycle, see next section). Thus we get an *Evolutionary Large Scale Chaos system.*

## 1.4 Metabolism and Cell Cycle

*Each cell in the simulation is composed of a set of metabolites (various substances which the cell contains - like DNA, proteins, etc.). In this paper there were 16 different metabolites.*

*in each turn in the simulation, the concentration of the metabolites in the cell were changed. There are a few ways in which the level of a metabolite can change:*

- *Diffusion from/to near neighboring cells (i.e. if the concentration of the substance in neighboring cells is different, some substance moves from the high concentration to the lower one).*
- *Diffusion from/to the surrounding (i.e. not cells).*

- *Active transport from/to other cells. (by a global set of parameters which define how much from each metabolite the cell moves from/to itself by a process which does not depend on the concentration difference).*

- *Active transport from/to the surrounding.*

- Metabolic rules, which define rules by which one kind of metabolite is turned into another kind. These rules are coded in the Genome of the cell, and are of the form

  'If the level of metabolite $A <$ (or $>$) $n$ then start a reaction that turns metabolite $B$ into $C$ using metabolite $D$ as an enzyme.

  This means that if the condition is met, reduce the concentration of $B$ and increase the concentration of $C$ by the same amount, which is linear in the concentration of $B$ and $D$.

  This is based on the method in which metabolism happens in real cells, where (if looking in a large enough scale) substances are turned to other substances in the cell using enzymes (which are themselves substances in the cell).

*These simulation rules are applied to all the metabolites in each cell of an organism each simulation turn.*

*Cell divide when the level of metabolite A (which represents DNA) is above a specified threshold. Note that when dividing, the metabolites of the parent cell are divided between the daughter cells with a* certain amount of random fluctuation, which gives the small random base of the chaotic process and thus the means for breaking the symmetry.

Cells die when the overall metabolism is too low or too high.

## 1.5 The Simulation

in each evolutionary cycle, organisms were started from the DNA (i.e. metabolic rules) and let to develop for 1200 metabolic turns. after that, the number of cells was counted and the genes of the organisms with the largest number of cells were crossovered to create the next evolutionary cycle organisms.

In the first organisms, no efficient metabolism (i.e. a metabolism which creates substance $A$ which is needed for cell division) was created. Around the 70th evolutionary generation, a simple efficient metabolism was created, which resulted in a huge increase in the number of cells per organism. But this metabolism was simple, and therefore didn't have any rules to stop cell division when the substance level was too low, and therefore after a large increase in cell numbers, alot of cells died due to lack of nutriciants. Around the 100th generation a more complex metabolism was derived. Note that there is alot of place for improvement in the metabolism by creating more control over cell division and metabolism (right use of surrounding nutriciants) and therefore the ideal metabolism is not trivial.

In most individuals of the 100th generation, a pattern of cell differentiation was evident, where cells divided into 2 main types in a coaxial pattern (we define cells types as similar metabolite levels and metabolism rates in same time). The growth of the organism is first in a symmetric manner, and then (after a number of simulation turns), a disparity appears between two sides, where cells of one side divide faster than on the other side. A similar phenomena appears in early embryogenesis and is called the Animal Cap.

The organisms created had these properties even if the various simulation parameters were changed, given that the evolutionary process was run on the new parameters. This means that the whole model is not dependent on a small parameter range.

## 1.6 Neurogenesis

The model was also used for a simulation of neural network growth, using another set of metabolites and metabolic rules to create neural connections between cells, by choosing axon growth directions toward certain metabolite chemical gradients.

The Neural networks received also displayed cell differentiation into short and long distance axons (also in a coaxial manner).

## 1.7 My Opinion

Although the article is called Neurogenesis and Cell Differentiation, I think the more promising direction this article points to is the Cell Differentiation research.

When studying neurogenesis, it takes more than just putting the number of cells and length of axons into the fitness function. It mainly takes the behaviors derived from the neural network, and therefore another level of simulation is needed. On the other hand, simpler models of neural network creation can be used to simulate the cell differentiation in a simpler method (see other articles reviewedin the seminar), which still have enough complexity to give interesting results in behavior evolution.

On the other hand, in studying cell differentiation, the results in this article are very promising. They show basic differentiation in cells sharing the same DNA. There is alot to study using this model, and a large place for improvements in the metabolic simulation used.

Even though this article doesn't fall into the 'classical ALife' category, It seems like an area with alot of importance for biological research.

## 1.8 Remarks about the article

The main problem of the article is that the simulation method is not clear enough and *not reproduce able. A lot of parameters are not explained and the default values of many others are not given. Therefore it is hard to relate to the results of the simulations.*

*other remarks are:*

- *A large attention is given to neurogenesis, which in my opinion doesn't give very interesting results.*
- *There are many arbitrary choices in the simulation methods, which could have been done differently (and more closer to reality in my opinion).*