# Modeling of evolution of signaling networks in living cells by evolutionary computation

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**Abstract**

This work is an attempt to model the evolution of signaling pathways in living cells with evolutionary computation under different selection criteria and to compare pathways evolved in such a way with those we encounter in nature. It proposes 5-level evolutionary procedure for this purpose, that can be thought as several co-operating genetic algorithms working in parallel on different levels of an abstraction hierarchy corresponding to the conceptual structure of an evolving object. On one hand, this work allows to get some insight into the process of emergence of signaling networks within cells. On the other hand, this is an example of application of genetic algorithm for redesign of a system that was already designed by natural selection. It allows to compare the results produced by computational model of evolution (GA) with the results of natural evolutionary process, which may lead to better understanding of relationship between natural and computational evolution. We can see how close our GAs are to their natural prototype and can get some new understanding of GAs and ideas on their improvement.

## 1 Introduction

The fossil records suggests that unicellular organisms were present on earth 3.5 billions years ago but it required more than another 2.5 billion years for the first multicellular organisms to appear. Why was multicellularity so slow to evolve? Although the answer is not known, it is likely to be connected with the need for elaborate communication mechanism to coordinate behavior of the individual cells for the benefit of the organism as a whole (Alberts, Bray, Lewis, Raff, Roberts, & Watson, 1994).

Exploring an ensemble of alternative networks for a task of designing metabolism (Mittenthal, Yuan, Clarke, & Scheeline, 1998) suggested using a similar procedure for understanding signaling networks. In order to understand the organization of intracellular signaling pathways, we simulate their evolution. We ask, how might mutational processes interact with selection pressures to generate observed features of signaling pathways?

Here we present a new method for representing and mutating signaling pathways, and use it to characterize the signaling pathways that evolve in response to selection for more numerous pathways and for preservation of information in pathways. Section 2 describes our notation and the representation of signaling pathways, section 3 describes the computational procedure, section 4 describes the results and conclusions.

## 2 Representation of signaling pathways

Signaling network on the level of a cell can be compared with neural system on the level of the whole organism. It relays information from the outside world to the nucleus of the cell, so that the cell can make some decisions adequate for its survival. There can be multitude of signals the cell would like to be aware of. Most common type of signal relates to the presence of particular kind of small molecules in the vicinity of the cell. Receptor proteins usually located in the membrane of the cell can sense specific types of molecules, and become activated in their presence.

This information is transferred into the nucleus through the network of signaling pathways. Each pathway has a receptor protein, a sequence of linking proteins, and a target protein. Each of these proteins may contain several domains, which also can be divided into three corresponding classes.

### 2.1 Notation

We will call receptor domains R1, R2, R3, and so on; the target domains T1, T2, T3, etc. Linking domains can be grouped into ordered pairs of pre-domain and post-domain, which we call dyads. We name pre-domains by letters A, B, C, ..., and corresponding post-domains by the same letters with prime A', B', C', etc. The former can bind to the latter, like A - A', B - B', etc. These sets of domains define the following dyads: (A, A'), (B, B'), (C, C'), etc.

### 2.2 Protein structure

As we said, several domains can form a protein, which we describe as a sequence of domains delimited by a dot, e.g. R1.A.B is a receptor protein, which contain one receptor domain R1 and two linking domains A and B.

In our model a protein is not allowed to have both a receptor domain and a target domain. In reality this is possible, and it might be functional for some signaling from the cell surface to cytoplasmic effectors, such as filaments. However, we are concerned with features affecting the length and separation of pathways, and proteins of the form R.T short-circuit investigation of such features.

The following questionable structures of proteins are valid:

**2r**: two receptor domains in the same protein, e.g.

R1.R2.A - A'.B - ...

This is unusual but not impossible. Binding of a ligand to either receptor domain would have the same downstream consequences in our model. However in reality each receptor domain might have a different affinity, and mean binding duration, for its ligand, and produce a different conformational change in cytoplasmic domains, so binding of the two ligands might have different downstream consequences.

**2t**: two target domains in the same protein, e.g.

... - B.C - C'.T1.T2

It is possible, any protein can be multifunctional.

## 2.3 Definition of a pathway

A set of several proteins can form a signaling pathway if

- It has a receptor protein, containing receptor domain.
- It has a target protein, containing target domain.
- There is a directed path from the receptor protein to the target protein, that connects them in such a way, that each two adjacent proteins have complementary linking domains ordered according to the direction of the path.

The task of pathway assembly is a particular case of the task of structural synthesis of information exchange structures. Methods and algorithms for this task were developed in (Kosorukoff, 1995). According to this study the criteria of synthesis can be subdivided into local and global ones. The local ones define the conditions of connectivity of individual elements with each other, while the global ones define the conditions imposed on the generated structure as a whole. The distinction of the current model is the relativity of these concepts across the multiple levels. This makes the local criteria of the upper level be the global criteria of the lower level.

In our definition of a pathway, the first two conditions can be viewed as a part of global criteria: global boundary conditions, and the third one is the local criteria of synthesis based on relation of connectivity.

The main property of pathways that we are concerned with is the length of a pathway. It is defined as the number of proteins in the pathway decreased by one. It is the same of the number of connections between the proteins in the linear pathway.

An example of a pathway is shown below:

R4.C - A'.B.C'.F - B'.E.F.T1

This is a pathway of length two formed by three different proteins. It connects receptor domain R4 to target domain T1. Receptor domain R4 can bind to a particular kind of small molecule, and if this molecule is present in the vicinity of the cell, it will bind to R4 causing activation of pre-domain C. Pre-domain C activates protein A'.B.C'.F through the post-domain C', and pre-domain B activates target protein B'.E.F.T1 through post-domain B'. In such a way the signal about the small molecule is propagated through the pathway to the nucleus, where it can activate or inhibit a gene expression, causing adequate response of the cell.

## 2.4 Pathway structure

Not all combinations of receptor, linking and target proteins satisfying the local criteria of connectivity are valid. A set of global criteria or restrictions should be imposed on the structure of the generated pathways. It is more convenient in this case to represent them as a set of exceptions, which can be called parallel partial pathways (pp). They can be grouped in the following classes:

- post-domain is repeated after pre-domain, e.g.

R1.D - D.D' - D'.T1

- a protein has two or more pre-domains, and two or more of the corresponding post-domains occur in two or more subsequent proteins, e.g.

R3.C'.E.F - A.E.F'.T2 - C'.E'.F'.T4

- futile cycle, e.g.

..A - A'.. - ... - ... - ..A - A'.. -

We generalized these cases into one criterion based on the presence of a post-domain not immediately following its pre-domain. We called it the *non-adjacency criterion*.

The pathways with the following questionable features are valid in our model:

**rr**: two receptor proteins in series, e.g.

R2.D.D' - R3.B.D' - B'.T1

Some EGF receptors can bind ligand, while others bind to an activated receptor. Two different receptors can each homodimerize, or can bind together (heterodimerize) and bind a third kind of ligand.

**tt**: two target proteins in series (note, two target proteins in parallel are an example of parallel pathways, see above), e.g.

R2.D - B.D'.T4 - B'.T1

We can't exclude this possibility, though it is probably rare. E.g. if target domain regulates translation initiation, it may be in a protein that also regulates other target proteins.

**tr**: protein with target domain preceding protein with receptor domain, e.g.

R2.D - D'.B.T4 - R3.B'.C - ...

It can be seen that validity conditions on the level of pathways are very similar to the already-discussed validity conditions on the level of proteins.

## 2.5 Pathways encountered in nature

The signaling pathways that we meet in nature are surprisingly long, given their apparent function. Another characteristic is the significant amount of crosstalk between different pathways, causing them to fork and merge again many times. An example of pathways with crosstalk is shown below:

```
R1.C   -
              A'.B.C'.F - B'.E.F.T1
R4.C   -
```

In this case activation of either receptor R1 or R4 will cause activation of target T1, so the merging of signals take place. Another example is forking:

- B'.E.F.T1

R4.C - A'.B.C'.F

- F'.T2

In this case activation of R4 will cause activation of both targets.

At the beginning of this work we conjectured that longer signaling pathways emerge in the process of evolution with selection for a greater number of pathways. In order to test this hypothesis an evolutionary algorithm was written to simulate the processes of assembling the signaling networks from the proteins that occur inside the cell.

### 2.6 Cell structure

The structure of a cell in our model is determined by the set of proteins that this individual cell contains. This set of proteins together with their local conditions of connectivity determines the signaling network of the cell, which can be constructed and evaluated according to the chosen evaluation criteria.

## 3 Computational procedure

The computation procedure consists of two parts: evolutionary and deterministic. The set of proteins undergo a non-deterministic process of evolution through domain transfer and selection. At the same time the process of signaling network assembly is a deterministic process. It is a part of the cell evaluation and embedded into the evolutionary procedure. In this section we start from the top and describe the evolutionary procedure first and then its deterministic part.

### Genetic algorithm

A genetic algorithm is probably the simplest computational procedure capable of producing evolutionary behavior[1]. It is based on processes of inheritance, selection and crossover, performed on a population of individuals. A simple genetic algorithm uses linear binary representation of individuals (Goldberg, 1989).

Thus conventional representation of a GA specifies a set of procedures to implement three basic processes. Our algorithm used a multi-level representation which reflects the complexity of living cells more adequately. The multi-level representation suggests the multi-layered structure of the algorithm.

Such a multi-level genetic algorithm was described in (Kosorukoff, 2000). This kind of GA can be thought as several co-operating genetic algorithms working in parallel on different levels of an abstraction hierarchy corresponding to the conceptual structure of an evolving object. In our case, there are 5 levels of abstraction in this evolutionary procedure: domain, protein, cell, population, and ensemble. Each upper level embeds a set of objects of the lower level. In this way, each protein contains a set of domains, each cell contains a set of proteins, each population contains a set of cells, and an ensemble contains a set of all populations. On each level we have some evolutionary operators defined: mutation, crossover and selection, although not all of them should necessarily be present at each level. In terms of one particular level, the representation can be thought as linear, so usual GA procedures can be used.

[1]Note, that this definition of genetic algorithm doesn't demand the GA to be an optimization procedure, and this is essential for the application that we are now considering.

Let us see how evolutionary processes are implemented on each level.

## 3.1 Levels

### Domain level

The process of deletion or duplication of a domain is the only process that produces change on this level. Domains are considered elementary.

### Protein level

Domain transfer/deletion is a recombination process on this level. Domain transfer is implemented as duplication of a random domain of one protein and inserting it into another protein chosen also randomly. Domain deletion removes a random domain from random protein. Domain transfer is analogous to crossover, since it involves flow of information across the boundary of individuals (proteins). Domain deletion is analogous to mutation, since in this case the change is internal to each individual.

### Cell level

On the cell level the both domain transfer and deletion are mutations, since no information crosses the cell boundary.

### Cell culture level

On this level selection is implemented according to one of two criteria: the number of pathways, or the information capacity of pathways. Selection affects only the whole cells, the individuals of the adjacent lower level. In each cycle of modeling one random cell in the population reproduces, while the worst cell of the population dies to free space for a new individual, so the population size remains constant. This process can also be called duplication and divergence of the cells, since two initially identical cells will become different in the process of internal changes. No crossover between cells was implemented.

### Ensemble level

The purpose of the ensemble level is to gather statistics over several populations evolving independently in parallel. Thus neither selection nor recombination implemented on this level.

## 3.2 Initialization

Initial conditions consist of initial protein list (for each cell in a population, the list of domains in each protein).

An ensemble contains 10 populations by default, each containing 20 cells, each containing 20 proteins. The number of actual proteins depend on the number of domains, which is an initial condition of an experiment. An initial set of proteins was generated by duplication of domains. A typical example with 16 kinds of domains (2 receptors, 6 linking dyads, and 2 targets) initially contained 68 single-domain proteins (2 copies of each receptor domain and target domain and 5 copies of each linking domain).

## 3.3 Cycle of evolution

In each cycle of evolution, the processes of reproduction, selection and recombination happen. To perform selection we need to evaluate an individual cell. Since we are interested in the properties of a signaling network, we need to construct the network first, then evaluate its parameters.

## 3.4 Recombination

In this particular application, the recombination operator is implemented as a domain transfer process. E.g. a domain transfer on the level of protein is a process in which a domain of one protein is transferred to another protein. This process has the effect similar to the one of crossover, since it provides an exchange of information between individuals (on this level the individuals are proteins).

The example of domain transfer is show below:

$$\begin{matrix} \text{R1.A.B} & & \text{R1.A.B.}\mathbf{C} \\ & \rightarrow & \\ \text{C'.}\mathbf{C}\text{.T1} & & \text{C'.C.T1} \end{matrix}$$

In this case domain C was transferred from protein C'.C.T1 into protein R1.A.B, producing a new pathway between receptor R1 and target T1:

R1.A.B.C - C'.C.T1

Actually, the procedure of domain transfer in our model is just a computational shortcut for a more complex real process. In reality domains are not just transferred from one protein to another. Instead of it, the copy of some part of a genome is inserted into another place in the same genome, that can be caused by a virus or a transposon. Then, the processes of transcription and translation make the result shown in our example.

It is an example of relativity of genetic operators: the domain copying and reinsertion is a mutation of the genome, but at the level of proteins it appears as a recombination transferring domains of one protein into the other. That happens because these are two different level of abstraction hierarchy, and one genome contains genetic codes for multiple proteins.

## 3.5 Fitness evaluation

The criteria of selection may vary, but in each case the signaling network must be assembled for every cell in the population. Two methods of assembling networks were used, using incremental net expansion (Kosorukoff, 1993). In this approach the partially constructed net is expanded incrementally by one element at a time. The first method was based on depth first search (DFS); this was replaced by the Dijkstra shortest path algorithm (Bertsekas & Gallager, 1987) where applicable, for computational efficiency. The difference between the DFS and Dijkstra algorithms is that the former can be used to assemble all pathways, while the latter gives us only the shortest pathways. This limits applicability of Dijkstra algorithm for the purpose of cell evaluation.

The first fitness function was based on reachability of pairs (receptor, target), i.e. the existance of paths between a given receptor and a given target. In the case of the Dijkstra algorithm the fitness is found by counting the pathways that were produced by it.

The second fitness function counts all the pathways, so the Dijkstra algorithm is not applicable, and incremental expansion according to DFS was used, with subsequent counting of pathways.

The third fitness function estimated the informational capacity of signaling net as a communication channel. It was based on modeling of signal propagation through data networks, the same thing that Dijkstra algorithm simulates. All possible combinations of input signals were put at the receptors, and the number of distinct output combinations on the targets was counted. Thus the maximum value of this fitness function is known and equals to $2^r$, where $r$ is the number of receptors.

### 3.6 Organization of the computation

This kind of multi-level algorithm earlier was used in implementing human-based genetic algorithm (HBGA) (Kosorukoff, 2000), that has three level depth. The hierarchy of levels can be represented as a tree, in which nodes of one level form populations. The execution starts at the top level and each cycle of computation involves traversing the tree in depth first walk (DFS) order.

In the process of domain transfer the number of total domains per cell would increase indefinitely. That is why a soft threshold was put on the total number of domains a cell can contain. When the total number of domains in a cell exceeds the limit (in our case 100), random deletions of domains decrease the number of domains in the cell, keeping them close to threshold, reflecting limited size of the cell.

### 3.7 Differences from the usual GA

There are no binary chromosomes of the kind used in the usual GA. The genotype of each domain is its symbolic name. The genotype of each upper level is a set of genotypes of its adjacent lower level. This forms a recursive genotype structure that reflect the recursive nature of the object of modeling.

Building blocks in this case are the objects of one level of the hierarchy, so there is assortment of building blocks of different size (the size is relative to the size of elementary individuals).

The initialization procedure is different from that for a simple GA. The algorithm starts assembling process from a set of the elementary domains. Initially they can also be thought as one domain proteins.

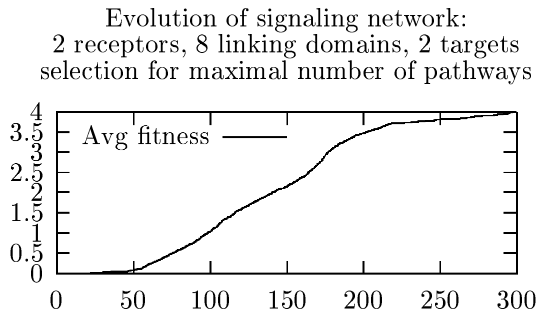
As we have seen, one process has different meaning for different levels, so a crossover process that operates on one level appears from the upper level as a mutation. This is a manifestation of a relativity principle for genetic algorithms. In its general form, it suggests that the observed effect of the same genetic procedure depends on the context in which it happens, including the observer's point of view.

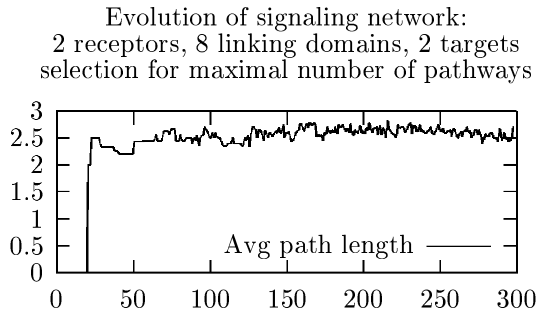
### 3.8 Criteria of selection

Finding appropriate criteria for selection was an important task in this research, because the corresponding criteria in nature are not known. So our approach was to test different criteria and see if the results obtained in the process of evolution are compatible with what is known about signaling networks of living cells. Several criteria were used and two types of them are described here.

#### 3.8.1 Evolution to maximize the number of pathways

Our initial criterion of selection was based on reachability: the number of pairs (receptor, target) such that at least one pathway connects a given receptor and a given target. Obviously in the case of $N$ receptors and $M$ targets this metric of fitness has the ceiling $N * M$. The graphs show the




evolution of ensemble of 20 populations, each containing 20 cells. It can be seen how the average fitness of cells reach its maximum value (in this case 4) when all cells in an ensemble fully develop their signaling pathways in about 300 cycles of evolution. Average pathway contains about 2.5 proteins and this average length didn't change much during the process of evolution.

Later this criteria was modified in hope that the modification would produce longer pathways with more crosstalk. In the modified version, many pathways going between the same pair (receptor, target) were counted, but each additional pathway was counted as half of the previous one in calculating fitness. In this case a cell with any number of pathways connecting the same pair (receptor, target) is still inferior to a cell with only two pathways connecting different pairs (receptor, target). Although this selection criterion was good at producing more crosstalk and longer pathways after some time, shorter pathways still appeared first.

### 3.8.2 Evolution to maximize the capacity of informational channel

During experiments with the preceding selection criteria, it was speculated that maybe longer pathways with heavy crosstalk evolve for some encoding - decoding purposes that would maximize the capacity of informational channels of communication between cells. The set of molecules and proteins that can mediate the communication is limited, and the number of receptors that can be placed on the surface of the cell is also limited, but the effective cooperation of many cells depends on the amount of information they can exchange and interpret despite being in a fairly noisy environment. This suggested that there should be some optimal structure of communication channel between cells.

In this case, the fitness measure was the number of signals which the cell signaling system is capable to transmit from the surface to the nucleus. In our case of $N$ receptors and $M$ targets the maximal fitness will be $\min(2^N, 2^M)$. In this expression, the first part is the number of discrete signals the network is capable to perceive, and the second part is the number of signals it is capable to express.

As we expected the simulation finally produced the pathways with no crosstalk and minimal length. The mechanism by which these pathways were constructed is interestin. Domain transfer is likely to destroy pathways or create crosstalk between them, each leading to reducing informational capacity of the network. In this situation cells developed a mechanism allowing them to maintain the informational pathways effectively. The mechanism employs emergent classification of linking domains into two classes: conductors and insulators. While the former are used actively in forming pathways, the insulators provide a non-conducting substratum in which the pathways are embedded.

The following example shows the set of proteins and pathways in one evolved cell. In this experiment 4 receptor domains, 6 linking dyads, and 4 target domains were used.

| | |
|---|---|
| Cell fitness | 16 |
| Number of domains | 102 |
| Receptor domains | R1, R2, R3, R4 |
| Linking pre-domains | A, B, C, D, E, F |
| Linking post-domains | A', B', C', D', E', F' |
| Target domains | T1, T2, T3, T4 |

Signaling pathways (5)

0: R1.C - C'.T1
1: R2.D.E' - C.D'.T3
2: R3.A'.E - E'.T2
3: R4.F - F'.T4
4: R4.A - A'.F - F'.T4

Proteins taking part in pathways:

| | | | | |
|---|---|---|---|---|
| R1.C | R2.D.E' | R3.A'.E | R4.A | R4.F |
| C'.T1 | E'.T2 | C.D'.T3 | F'.T4 | A'.F |

Proteins not taking part in pathways:

| | | | | | |
|---|---|---|---|---|---|
| 1 | R2 | 2 | R4 | | |
| 3 | A | 3 | A' | 1 | A'.C' |
| 1 | A'.E'.F' | 1 | A.B.E.F | 1 | B' |
| 1 | B'.D' | 1 | B.C' | 1 | B.D |
| 1 | B.D' | 1 | B.D.F | 1 | B.E' |
| 4 | C | 2 | C' | 2 | C'.D' |
| 1 | C'.D'.E'.F' | 1 | C'.F' | 1 | D |
| 1 | D' | 1 | D'.F' | 2 | D.E |
| 1 | D.F | 5 | E | 2 | E' |
| 3 | F | 4 | F' | | |
| 1 | T1 | 2 | T3 | 2 | T4 |

Note, that each pathway uses a different set of dyads. Each pre-protein has no pre-domains in it other than the one that gets used; each post-protein has no post-domains in it other than the one that gets used. This buffers against domain transfer producing cross-talk between pathways. One domain transfer can produce at most one cross-talk. These networks are minimally sensitive to domain transfer perturbing fitness.

# 4 Discussion

The results of this interdisciplinary research project can be grouped into two categories according to the areas that were involved: results for cell biology, and results for genetic algorithms and evolutionary computation.

## 4.1 Results for biology

Software for modeling of signaling net evolution was developed. The experiments with it show how signaling nets emerge as a result of evolution, as well as showing the structure of signaling nets under different criteria of selection, and different initial conditions: the set of available receptor domains, linking domains, and target domains.

Simulations have shown that evolution favors shorter pathways, at least under selection criteria that were used. Shorter pathways evolve first, and have an advantage in comparison with longer pathways, because of their stability: shorter pathways have fewer proteins and so offer fewer host sites for domain transfer and fewer domains that can be deleted. This result was observed in all experiments with different criteria of selection.

## 4.2 Results for GAs

The implementation of multi-level GA used for this research had the same basic idea as the human-based GA (Kosorukoff, 2000), but contained more layers than the previous application. It is another application of multi-level GA, that shows its usefulness in the area of social and living systems, as well as some interesting parallels between the two areas.

In the presence of many layers of evolutionary process, the compensation effect of genetic operators becomes apparent. For example, if a crossover operator is not implemented at some level, the other levels where this process is implemented compensate for the lack of it. The evolution of the whole system continues as a result of this effect, despite the lack of essential operators at many levels, as if they were present. In this biological application the absence of recombination on the level of cells is compensated by recombination on the lower level of proteins, and this effect makes the population of cells evolve by the process of duplication and divergence, as if the absent recombination operator was present. This effect seems to add robustness to the multi-level evolutionary processes in the case where some processes fail to perform their function.

The same effect allows systems including social or biological agents or just acting in a real-world environment to show the evolutionary behavior even without the necessary set of genetic processes, just because they borrow these processes from the other levels of evolution and take them for granted. One of the examples of this is the evolutionary theory of Charles Darwin itself, that was entirely based on the concept of selection. It didn't prevent it to be successful and highly usable, because the processes of inheritance and recombination worked even though the selectionists didn't know their mechanisms.

The recent application of GAs to living systems show a different perspective on the goal and different criteria for evaluation of GAs. The traditional goal of GA, convergence, is not a desired goal in their biological applications, since the biological meaning of convergence during evolution is rigid constancy which is lethal in a changing environment. Both in modeling and applications to the living world our goal seems not to be an optimal solution, but an ongoing process.

## 4.3 Conclusions and future research

This research gave interesting and important results for understanding signaling networks and genetic algorithms. It showed that a multi-level genetic algorithm based on relatively simple computational processes is capable of producing very complex behavior similar to that observed in living systems, and therefore can be used for their modeling.

This research has laid a good background in the form of notation and evolutionary algorithms for better understanding the whole cycle of information metabolism of a living cell.

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