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Cellular Automata Modeling of Biomolecular Networks

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1. Introduction

On the eve of the new, 21st century a paradigm shift began in biology and biomedical research. After decades of meticulous studies of individual genes and proteins, and their biological functions, time was ripe for the contours of the forest to start emerging behind the trees. Failures with some new drugs showing unsuspected harmful side effects, along with similar cases in gene engineering, have signaled that the old reductionist approach has its limits. It has been overoptimistic to expect to cure a sickness by curing a single defective gene or a single incapacitated protein, because genes and proteins do not exist and act in isolation; they are part of a system. The new systemic approach in biology and medicine requires to account for the environment in which biomolecules act within the living cell and intercellular space. This environment is organized in complexes, pathways, and networks, containing hundreds and thousands of biomolecules. The essence of the new science of *systems biology* (Kitano, 2002; Ideker, 2004; Alon, 2006; Palsson, 2006; Choi, 2007) and *systems medicine* (Nadeau & Subramanian, 2010) had to be expressed in the language of networks, which are the best means of defining a system as a whole and explaining its features and functions.

Could this postgenomic era start earlier? The answer is: "Yes and No". Yes, because facts for the limitations and pitfalls of the reigning paradigm have been accumulating for a long time, although genomics had still to wait to reach its peak with the advent of the new sequencing technologies and the flood of genetic data that followed. No, because the theoretical foundation and the computational tools were still lacking. Network theory was known for a century and a half since the theory of electrical systems has been proposed by Kirchhoff in 1845. Kirchhoff's work is considered as one of the three pillars of graph theory, along with the Oiler'famous Königsberg bridges problem (1736), and the problem with calculating the number of isomeric compounds in chemistry, investigated first by Cayley in 1874. The second part of the 20th century in graph theory has been marked by the great authority of Erdős (Hoffman, 1998) and Bollobás (2001), which also developed the basics of the theory of random networks. Unfortunately, working within the framework of pure mathematics, these brilliant mathematicians have not been interested in the complex dynamic networks of the real world. There has been a considerable development of theory in social networks (Scott, 1987; Borgatti et al., 2009), however, the point of no return in network theory was reached only at the end of the 1990s (Neuman et al., 2006).

Watts & Strogatz established an important property of complex nonrandom networks - their small diameter - and termed such networks "small-world" ones (Watts & Strogatz, 1998,

Strogatz, 2002, Watts, 1999, 2003). The meaning of this finding is that genes and proteins in the living cell are only few steps away; they are much more strongly intertwined than previously supposed. It was soon confirmed for almost any type of complex networks that they share this property of *smallworldness* (Neuman, 2003). A major contribution of Barabási and coworkers (Barabási & Albert, 1999; Albert et al., 2000; Albert & Barabási, 2000; Barabási, 2002; Barabási & Oltvaj, 2004) summarized other common properties of these networks. It was shown that the node degrees in them are distributed in a specific way characterized with a presence of a few highly connected nodes, whereas the great majority of nodes are of low degree. As a whole the degree distribution is *scale-free*, and follows a *power law* with a negative exponent within the -2.0 to -2.5 range. The highly connected nodes, called *hubs*, were found to play important role in network stability (resilience against random attacks), while on the negative side being also responsible for spreading attacks directed to them through the network in events like epidemics in social networks, vulnerability of ecosystems, etc. The existence of this specific degree distribution in complex networks of different nature was derived from models of network evolution in which new nodes are preferentially attached to nodes with high degrees. Later work (Dorogovtsev et al., 2000; Dorogovtsev & Mendes, 2001) has shown that laws other than the power law could also take place in complex networks, and other patterns of network evolution also play important role.

The specificity of the complex dynamic networks was also extended to their overall *modular structure* (Rives & Galitski, 2003; Neumann & Girwan, 2004; Guimera & Amaral, 2005; Newman, 2006) and their local topology as characterized by high degree of *clustering* (Friedkin, 1984, 1990;) and specific network *motifs* (R. Milo et al., 2002; Wernicke & Rasche, 2006; Alon, 2007). Modularity is also called network's *community structure*. A high degree of modularity implies high degree of connectivity within the modules, while considerably less degree of intermodular connectivity (Reichardt & Bornholdt, 2006). Clustering coefficient measures the degree to which nodes in a network tend to cluster together. In complex dynamic networks, this likelihood tends to be considerably greater than that in random networks of the same size and the same node degree distribution (Watts & Strogatz, 1998; Barrat, 2004; Opsahl, T. & Panzarasa, 2009). Network motifs are subgraphs that occur in real-world networks more frequently than expected in random graphs of comparable size and connectivity. Different types of networks are characterized by their specific motif signature - a preferred small set of subgraphs. The question of whether the motif signature is related to function is still a subject of controversy (Knabe et al., 2008; Konagurthu & Lesk, 2008).

Despite of the young age, the network analysis of complex systems has demonstrated its capacity to produce valuable information in the fields of molecular biology and medicine. Patterns of evolution have been captured studying the evolution of network structure and complexity (Weitz et al., 2007; Hinze & Adami, 2008; Knabe et al., 2008; Mazurie et al., 2010). The detailed characterization of network structure by topological and information-theoretic descriptors provided means for successful phylogenetic reconstruction (Mazurie et al., 2008). The networks of gene, protein and metabolic interactions of model organisms like yeast, fruit fly, and the nematode *C. elegans*, became invaluable resource for modeling human biology, pathology and longevity (Managbanag et al., 2008), and helped in identifying protein markers for cancer and other diseases. The building of the human protein-protein interaction network (the unfinished yet Human Proteome Organization project (HUPO, 2002)) has already help to trace down the effect of drugs on different molecular pathways, raising the hopes for improved drug discovery methods (Butcher et al.,

2004; Hopkins, 2008). All these endeavours have been greatly helped by high level professional software tools (Thomas & Bonchev, 2010) like Ingenuity Pathway Analysis (Ingenuity Systems), Pathway Studio (Ariadne Genomics), Cytoscape (The Cytoscape Software), Fanmod (Wernicke & Rasche), and others, along with publicly available databases for all kinds of biomolecular interactions (KEGG, <http://www.genome.jp/kegg/kegg1.html>; PINA, <http://csbi.ltdk.helsinki.fi/pina/>; Gene Ontology, <http://www.geneontology.org/GO.database.shtml>).

Yet, this explosive development of network theory concerns mainly network structure, rather than network dynamics; networks are static. Many of molecular biology level networks, like protein-protein interactions ones, incorporate all possible interactions, but not only those which are active at a given moment in time. Dynamics of the processes down the numerous network pathways remains largely untouched. The modeling of this dynamics by differential equations (ODE) marked certain success in several specific intracellular processes. The regulation of cell cycle (the sequence of steps by which a cell replicates its genome and distributes the copies between the two daughter cells) received a considerable attention (Tyson, 2001, Csikasz-Nagy et al., 2006). Another series of elaborate models has been focused on regulation in network motifs (the small building blocks of networks, containing several nodes), (Milo et al., 2002) in gene regulatory networks (Mangan & Alon, 2003; Alon, 2006, 2007; Longabaugh & Bolouri, 2006). The high complexity of real-life networks and the lack of experimental kinetic data make constructing of this type of models impractical not only computationally, but even at the stage of defining the very set of equations.

Related to the above mentioned, the aim of this chapter is to show that cellular automata (CA) modeling technique could partially fill the gap in describing the dynamics of biomolecular networks. While not able to provide exact quantitative results, it will be shown that the CA models capture essential dynamic patterns, which can be used to control the dynamics of networks and pathways. CA models of human diseases can help in the fight against cancer and HIV by simulating different strategies of this fight. Another field of application presented is the performance rate of network motifs with different topology, which might have evolutionary and biomedical importance.

2. Cellular automata

2.1 Previous work on CA models of biological systems

The early attempts to model biological systems by cellular automata (CA) have included developmental biology, population biology and neurobiology, along with blast aggregation, neuronal maps, and branching networks, as well as several classical cases of pattern formation (Ermentrout & Edelstein-Keshet, 1993). Quantitative spatial and temporal correlations in sequences of chlorophyll fluorescence images from leaves of *Xanthium strumarium* have been reproduced by cellular automata models with a high statistical significance (Peak et al., 2004). Dynamics of biological networks was investigated by Kauffman who proposed models of random genetic regulatory networks (Kauffman 1969, 1993). These discrete random Boolean networks (RBNs) are named after him as Kauffman (or NK) networks. The models have been used as a basis for the concept of self-organization and emergence of life from randomness, viewing life as a state intermediate between chaos and complete order (Kauffmann, 1993). A step toward more realistic models of Boolean dynamics of biological networks has been to use random networks with scale-free topology

(Aldana, 2003; Kauffman, 2003). The dynamical property of stability or robustness to small perturbations has been found to correlate highly with the relative abundance of specific network motifs in several biological networks (Prill et al., 2005). Such findings support the views for system dynamics strong dependence on network structure.

Networks of biomolecules in the living cell have most frequently elementary steps of enzymatic chemical reactions. The first CA model of an enzymatic reaction has been proposed in 1996 (Kier et al., 1996) and, being prematurely born, remained unnoticed for some time. With the "phase transition" in network theory from random to complex real-life network such a CA approach to "enzymatic reactions networks" was independently proposed in the beginning of the new century (Weimar, 2002). These ideas were developed extensively in the following years in the Center for the Study of Biological Complexity at VCU in Richmond, Virginia (Kier & Witten, 2005; Kier et al., 2005; Bonchev et al., 2006; 2010; Apte et al., 2008, 2010; Taylor et al., 2010).

2.2 The Cellular automata method as applied to network dynamics analysis

Cellular automata (CA) are mathematical machines, which describe the behavior of discrete systems in space, time, and state. CA are a powerful modeling technique with a broad field of applications including mathematics, chemistry, physics, biology, complexity and systems science, computer sciences, social sciences, etc. It has been developed by the mathematical physicist John von Neumann in the mid 1940s, in collaboration with Stanislaw Ulam (von Neumann, 1966). Their pioneering work on self-reproducing automata opened the door to the fascinating area of artificial life. The method became popular in the 1970s with the "Game of Life" of John Conway, popularized by Martin Gardner in Scientific American (Gardner, 1970). A general theory of cellular automata as models of the complex world was proposed by Steven Wolfram, who later advocated cellular automata as an alternative way of making science, an approach that can reproduce not only the known scientific truths, but also open the door to new discoveries (Wolfram, 1986; 2002). A further generalization of the simple CA rules that produce complex behavior was offered by Rucker in his theory of the universal automatism (Rucker, 2005).

Cellular automata have five fundamental features (von Neumann, 1966):

1. They consist of a discrete lattice of cells (1D, 2D or 3D).
2. They evolve in discrete time steps (iterations), beginning with an initial state at time $t = 0$.
3. Each site takes on a finite number of possible values, the simplest being "occupied" and "unoccupied".
4. The value of each site evolves according to the same rules (deterministic or probabilistic ones).
5. The rules for the evolution of a site depend only on the local *neighborhood* of sites around it.

Each cell in the most commonly used square lattice has four neighbor sites (von Neumann neighborhood) and four extended neighbor sites located next to the cell corners (extended von Neumann neighborhood). To avoid "edge effects", the lattice is usually embedded on the surface of a torus. The cell is the basic model of each of the system elements. Its state may change at the next iteration. The contents of a cell may either break away or move to join an occupied neighboring cell. The question which movement will be chosen depends upon the modeled system. The movement of the cells may be simultaneous (synchronous), or the rules may be applied to each cell at random, until all cells have computed their states and trajectories (asynchronous movement). This constitutes one iteration, a unit of time in

the cellular automata simulation. The initial state of the system is random and, thus, does not determine subsequent configurations at any iteration. The same set of rules does not yield the same configurations, except in average. The configurations after many iterations reach a collective organization that possesses relative constancy in appearance and in reportable counts of cells. These are the emergent characteristics of a complex system.

In simulating enzymatic reactions organized in a network it usually suffices to use a 2D-square lattice, with cells partially occupied by molecules and controlled by several simple rules. These are rules describing the probabilities of two adjacent cells to separate, to join, or to change their state after joining. The first rule defines the movement probability, P_m , as a probability that an occupant in an unbound cell will move to one of the four adjacent cells, if that space is unoccupied. If it moves to a cell whose neighbor is an occupied cell, then a bond will form between these cells. The second rule describes the probability for molecule at cell A, to join with a molecule at cell B, when an intermediate cell is vacant. The joined cells can separate again, depending on the breaking probability, P_b . When molecule A is bonded to two molecules, B and C, the simultaneous probability of a breaking away event from both B and C is $P_b(AB)*P_b(AC)$.

In this chapter we follow the general approach used by Kier and Cheng (Kier et al. 1996, 2005a, 2005b) in setting up a CA model of enzyme activity. The mechanism of the enzymatic reaction is assumed to start with an interaction between the substrate S and enzyme E , which form a SE complex. The latter is rearranged to a complex PE between the enzyme E and the product P , which are then separated and the enzyme molecule E is free to take part in another interaction:

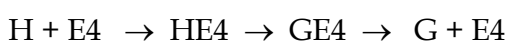
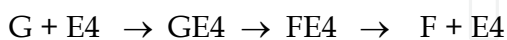
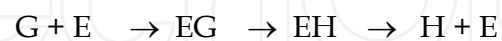
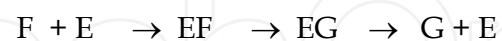
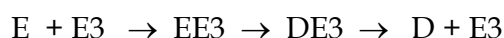
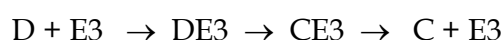
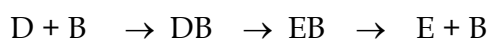
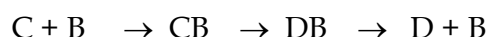
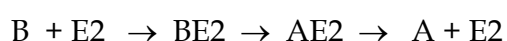
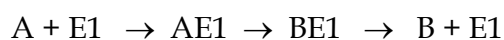


Focusing more on identifying patterns characterizing the (quasi-) steady state reached after many iterations, rather than on the temporal changes, our models are spatial ones. A network to be studied is represented by groups of CA cells, each group including one of the network species: enzymes, substrates, or products. The number of cells in each group is selected so as to reflect the relative concentrations of each network species. Each group of cells moves freely in the grid. The only cell encounters that change the CA configuration are those between a specific substrate and a specific enzyme. When such an encounter occurs, an enzyme-substrate complex is formed. The complex has an assigned probability of changing to a new complex (enzymatic product). Following this, another probability is assigned for the separation of the product from the enzyme. The movement probability, P_m , determines the extent of any movement. Thus, for an enzyme cell, $P_m = 0$ would designate a stationary enzyme. The CA model selected is asynchronous. Cells compute their states one at a time. In our study, all three types of probabilities were assumed equal to unity: $P_m = P_b = P_j = 1$. This means that all cells may interact, join, and break apart with equal probability. Only the cells involved in a specific state change, i.e., enzyme - substrate (ES) or enzyme - product (EP), are endowed with a state-changing probability rule, defined by the transition probability P_c , which describes the probability of an ES pair of cells changing to an EP pair of cells. It may be regarded as a measure for enzyme activity or efficiency. The collection of rules associated with a network species thus represents a profile of the structure of that species and its relationship with other species. By systematically varying the rules, one can arrive at a profile of configurations reflecting the influences of different species.

In modeling the dynamics of a signaling pathway the first goal is to show whether the model reproduces the amplification of the signal through the pathway. The next goal is to examine the pathway sensitivity to a variety of initial conditions, and to reproduce experimentally found patterns of substrate and product variations. Analyzing the findings the ultimate goal is to define the ways to control the pathway dynamics toward a desirable outcome. In what follows we present evidences that the CA method is capable of providing an answer to all these questions.

3. The EGF-induced MAPK signaling pathway as a case study for applying cellular automata to pathways and networks (Kier et al., 2005c)

Mitogen-activated protein kinase (MAPK) pathways are major signaling cascade controlling complex programs such as embryogenesis, differentiation, and cell death, in addition to short-term changes required for homeostasis and hormonal response, gene transcription and cell cycle progression. The molecular mechanism of this pathway has been studied intensively by different numerical methods (differential equations, stochastic approaches, etc.) based on reaction-rate equations (Huang & Ferrell, 1996; Bhalla & Iyengar, 1999; Kholodenko, 2000, McCullagh et al., 2010). Our cellular automata modeling was limited to the major cascade part of the pathway, which has been incorporated in all biochemical models proposed so far. The cascade is shown in Figure 1. The detailed reaction mechanism of the MAPK cascade is shown below in terms of the elementary enzyme reactions:



The 2D-CA models were built from the above reaction mechanisms using a 100 x 100 grid. The probabilities of joining and breaking away cells were assumed to be equal to unity. Each of the models was obtained as the average of 50 runs, each of which included 5000 to 15000 iterations, a number sufficiently large to enable reproducing the steady state (or nearly steady state) of the set of reactions examined. The three substrates MAPKKK, MAPKK, and MAPK, and the four enzymes involved, have some prescribed initial concentrations (a number of CA cells). We have systematically altered the initial concentrations of the above

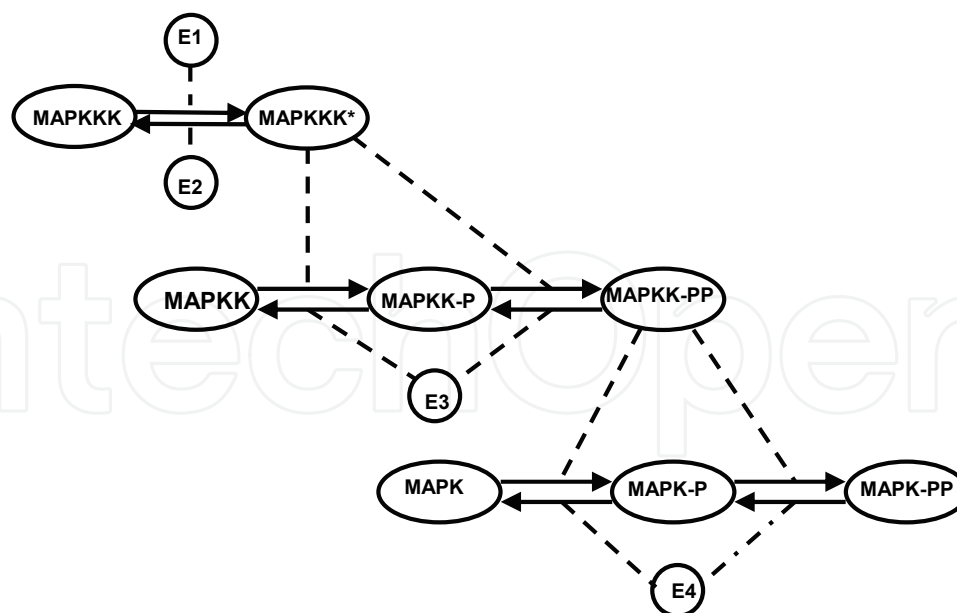


Fig. 1. The MAPK signaling cascade. The catalytic reactions of phosphorylation (*P*) and diphosphorylation (*PP*) are helped by enzymes *E1-E4*, as well as by the activated MAPKKK and MAPK-PP kinases. (Courtesy of “Chemistry and Biodiversity” journal (Kier et al., 2005)).

substrates, as well as the efficiencies of the enzymes. The basic variable was the initial concentration of MAPKKK, which was varied within a 25-fold range from 20 to 500 cells, matching thus the 25-fold range of variation of *E1* used as an initial stimulus in (Huang & Ferrell, 1996). The concentrations of MAPKK and MAPK were kept constant (500 or 250 cells) in most of the models. The four enzymes, denoted by *E1*, *E2*, *E3*, and *E4*, were represented in the CA grid by 50 cells each. In one series of models, we kept the MAPKKK initial concentration equal to 50 cells, and varied the transition probabilities of one of the enzymes within the 0 to 1 range, while keeping constant ($P_c = 0.1$) those of the other three enzymes. In another series, *all* enzyme transition probabilities were kept constant ($P_c = 0.1$), whereas the concentrations of substrates were varied. A third series varied both substrate concentrations and enzyme propensities. The variations in the concentrations of all eight species (the three substrates MAPKKK, MAPKK, and MAPK, and the five products MAPKKK*, MAPKK-P, MAPKK-PP, MAPK-P, and MAPK-PP, denoted in the set of equations as A, C, F, B, D, E, G, and H, respectively) were recorded.

The simulation produced temporal plots, which express the changes in the substrates and products concentrations up to reaching a steady state. The steady-state concentrations of all species were then used to construct spatial models of concentration dependence on the enzyme propensity and other variables of the process. The enzymes activity is controlled by inhibitors, a process that is simulated by cellular automata for the entire probability range of 0 to 1. An example with the concentration profile of the MAPK cascade at variable propensity of enzyme *E3* is shown in Fig. 2.

It was found that the maximum amplification of the cascade signal (the largest production of the doubly phosphorylated MAPK, denoted as species H) occurs at a narrow range of intermediate propensity of enzyme *E3*, due to the reversing of the second row phosphorylation reactions. This result confirms the expectations that the CA models can predict dynamic patterns and help in finding optimum conditions for the input signal amplification.

Better results in the search for optimal ranges of parameters can be obtained by using 3D- or contour plots. Such a plot in Fig. 3 provides optimal ranges of the initial concentration of the

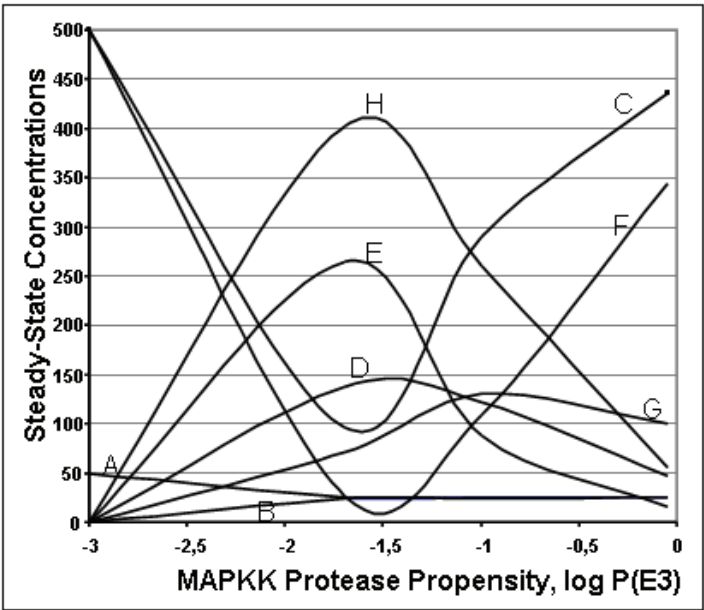


Fig. 2. A spatial model of the concentration dependence of the eight MAPK proteases on the propensity of enzyme E3. A narrow range of the enzyme propensity defines the optimal concentration of the cascade product H and the intermediate E. (Courtesy of “Chemistry and Biodiversity” journal (Kier et al., 2005)).

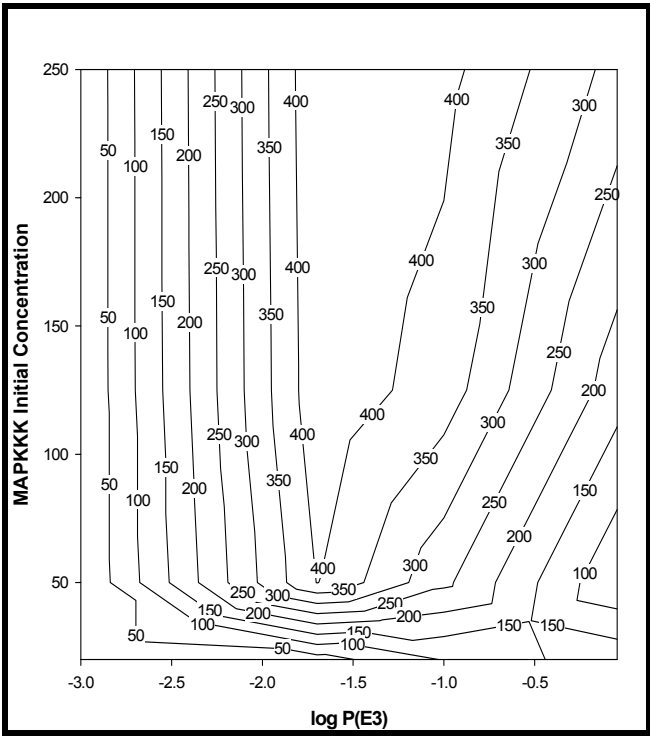


Fig. 3. A contour plot defining the optimal ranges of the MAPKKK initial concentration and the enzyme E3 activity needed to reach the maximum amplification of the cascade outgoing chemical signal MAPK-PP (the contour line of 400 cells). (Courtesy of “Chemistry and Biodiversity” journal (Kier et al., 2005)).

cascade input substrate A (MAPKKK) and the propensity of enzyme E3, needed for reaching a maximal amount of the cascade target product H (MAPK-PP). More specifically, the contour line with MAPK-PP concentration of 400 cells indicates that such optimal conditions can be realized with MAPKKK initial concentration of at least 50 cells and the enzyme E3 activity should be a moderate one (corresponding to the logarithmic range of -1.5 to -1.8).

An important outcome of our CA modeling of the MAPK signaling cascade is the possibility to summarize the patterns of network dynamics in a set of recommendations how to manipulate the network variables in order to achieve a certain result (Table 1). Such a method for pathway control could be of particular importance for the field of drug discovery. Searching to design can also reveal specific mechanistic details of the system studied. Such a conclusion can be drawn from Figs. 4a,b, which show a sigmoid curve of the cascade product *H* dependence on the initial concentration of the source substrate *A*. Such curves deviating from Michaelis-Menten kinetics are a characteristic fingerprint of cooperative effect of cascade enzymes. Our finding confirmed the result obtained in (Huang and Ferrell, 1996) by numerical solutions of the differential rate equations.

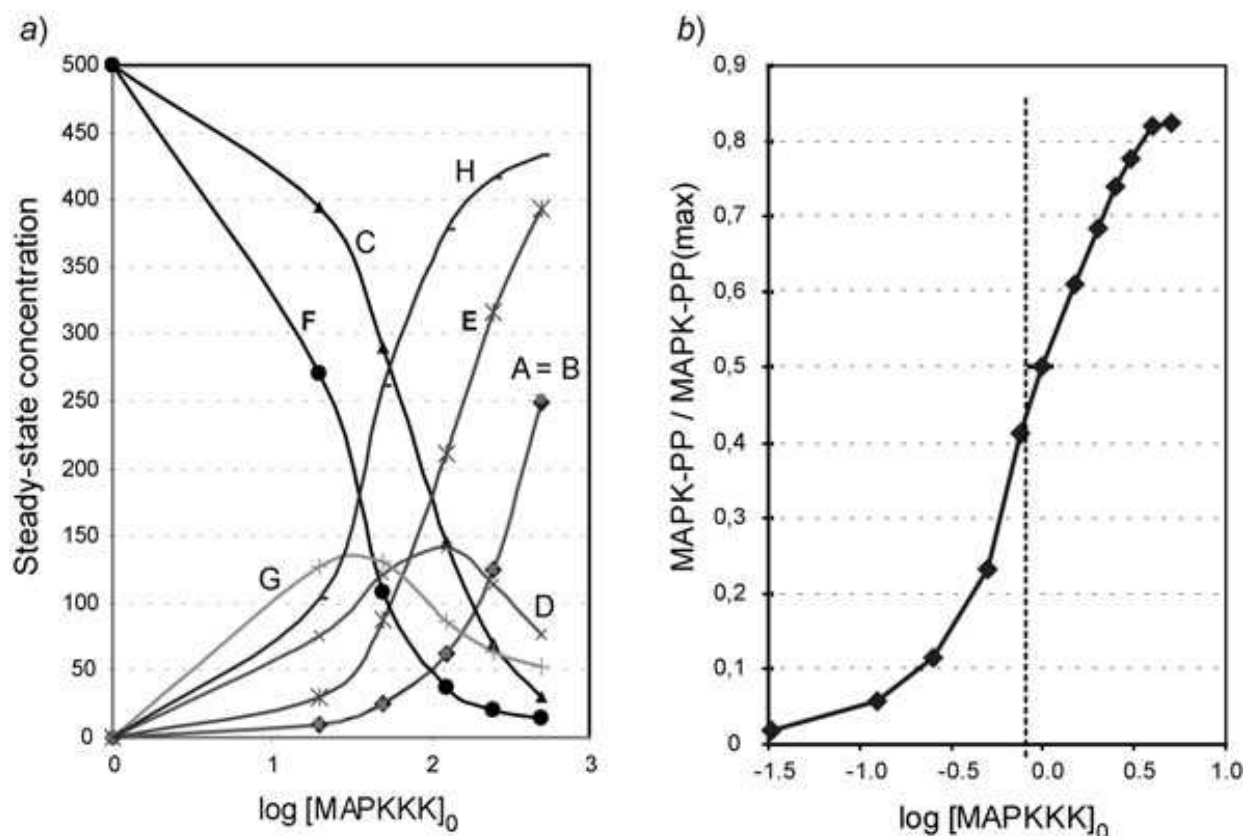


Fig. 4. a) Steady-state concentrations of substrates and products dependence on the initial concentration of MAPKKK. Model parameters used : Enzymes E1-E4 transitional probabilities equal to 0.1; initial concentrations of substrates C and F - 500 cells; b) Relative stimulus/response ($\text{MAPKKK}_0 / \text{MAPK-PP}$) plot with MAPKKK_0 expressed in multiples of EC_{50} . The slope of the H and MAPK-PP curves in the figures evidences for the significant cascade-signal amplification, while the S-shape of the curves confirms the hypothesis for enzymes cooperative action. (Courtesy of "Chemistry and Biodiversity" journal (Kier et al., 2005)).

Objectives		Action needed	Propensity Range
Decrease [MAPK]	→	Inhibit E2, E3, E4	$P = 0.9 \rightarrow P = 0.02$
Increase [MAPK]	→	Inhibit E1	$P = 0.9 \rightarrow P = 0$
Decrease [MAPK-PP]	→	Inhibit E1	$P = 0.9 \rightarrow P = 0$
Increase [MAPK-PP]	→	Inhibit E3, E4	$P = 0.9 \rightarrow P = 0.02$
Decrease [MAPKK]	→	Inhibit E3	$P = 0.9 \rightarrow P = 0.02$
Increase [MAPKK]	→	Inhibit E1	$P = 0.9 \rightarrow P = 0$

Table 1. Inhibiting enzymes E1 to E4 as a tool for controlling the MAPK pathway CA simulations

4. CA models of Apoptosis pathway as a tool for developing strategies to fight cancer

4.1. Cellular automata modeling of the FASL- Activated Apoptosis pathway

Apoptosis is a process of programmed cell death, the most common mechanism by which the body eliminates damaged or unneeded cells such that threaten the organism survival (Wajant, 2002). A number of diseases, including cancer and HIV, are associated with abnormal functioning of apoptosis (Fadeel & Orrenius 2005; Eils et al., 2009). Devising strategies for manipulating apoptosis would have a major impact on drug discovery process, which explains the considerable interest to this topic (Brajušković, 2005; Fulda & Debatin, 2004; Hanahan & Weinberg, 2000; Lowe et al., 2004; Marek et al., 2003; Reed, 2006). Apoptosis can be induced by two types of signaling cascades, *intrinsic* and *extrinsic* ones, the proteins from which are of considerable interest as drug targets. The intrinsic pathways are activated by developmental signals or severe cell stress caused by different environmental factors. The extrinsic signaling is initiated by different chemical signals, such as FAS ligand (FASL). The latter binds to the death receptor FAS (CD95), which induces the formation of the death-inducing signaling complex (DISC) by attracting the FAS-associated death domain protein (FADD) and the *initiator caspases* 8 or 10 (Fig. 1). The recruitment of the two caspases is favored by the formation of a FAS homodimer and a lattice with ordered FAS-FADD pairs. The spatial proximity of CASP8 and CASP10 in the complex triggers their autocatalytic activation and their release into the cytoplasm where they activate CASP3, CASP6, and CASP7 termed *effector caspases*. The activated CASP3 and CASP7 split the heterodimer DFF (DNA Fragmentation Factor), and the released DFF40 starts the DNA fragmentation. CASP6 cleaves the caspase substrates, contributing further to the cell distraction. The pathway is regulated by c-FLIP (FADD-like apoptosis regulator) protein and the IAP (Inhibitor of Apoptosis) protein family, from which XIAP is the most potent inhibitor (Salvesen et al., 2009; Scott et al., 2009).

Using cellular automata we simulated two strategies to fight cancer by modulating the FASL-induced apoptosis. The first strategy builds on recent publications elucidating important details of the role of T-cells in the immune response to fight cancerous and HIV-infected cells (Ferguson & Griffith, 2006). Tumors counterattack the immune system by inducing apoptosis in T-cells using overexpression of FASL, while preventing their own destruction by the same apoptotic mechanism (Igney & Krammer, 2005). In our study (Apte et al., 2010) we simulated a strategy to fight cancer and HIV by blocking the apoptosis in T-cells via maximizing the effect of FLIP and IAP inhibitors (Fig. 5).

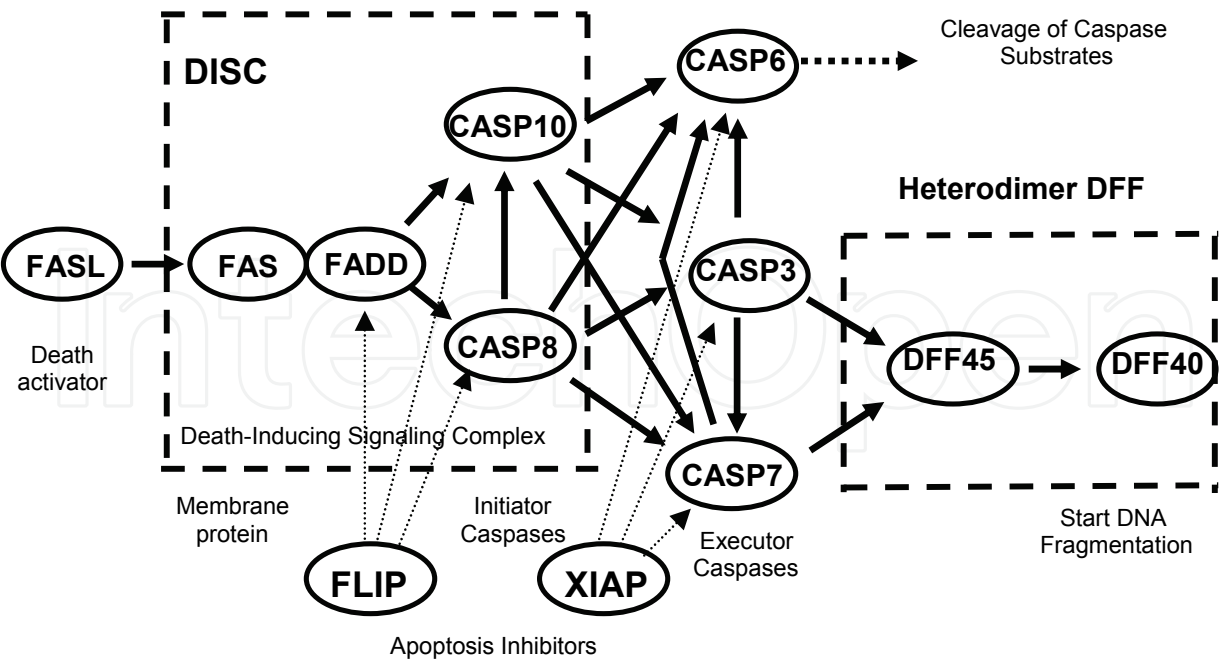
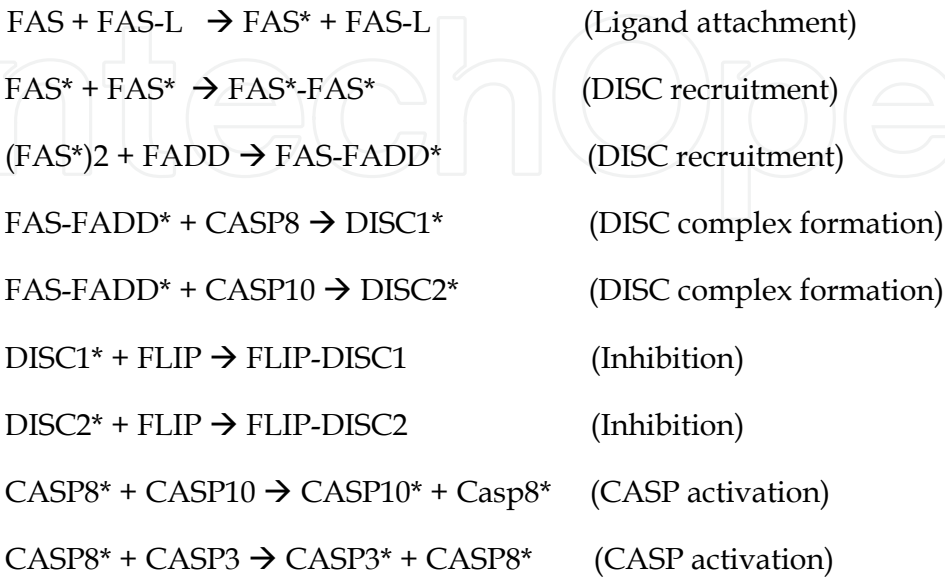


Fig. 5. The apoptosis pathway activated by the FASL protein (Bonchev et al., 2006). A cascade of activations of caspase (CASP) proteases releases the DNA Fragmentation Factor DFF40, which starts the DNA fragmentation, while CASP6 cleaves caspase substrates. The apoptosis performance can be widely modulated using inhibitors FLIP and XIAP (Wilson *et al.*, 2009; Irmeler et al., 2009). (Cellular Automata (CA) Modeling of Biomolecular Networks Dynamics, D. Bonchev, S. Thomas, A. Apte, L. B. Kier, SAR & QSAR in Environmental Research, 2010, reprinted by permission of Taylor & Francis Ltd) <http://www.informaworld.com>).

The detailed set of equations used as an input for the CA simulation is shown below. It matches the mechanistic information on the FASL-triggered apoptosis discussed in the foregoing. The abbreviation used read as follows: An asterisk* stands for "activated"; A-B means complex of A and B; DISC1 and DISC2 stand for the FAS/FADD/CASP8* and FAS/FADD/CASP10* complexes, respectively.



$CASP8^* + CASP6 \rightarrow CASP6^* + CASP8^*$	(CASP activation)
$CASP8^* + CASP7 \rightarrow CASP7^* + CASP8^*$	(CASP activation)
$CASP10 + CASP3 \rightarrow CASP3^* + CASP10^*$	(CASP activation)
$CASP10 + CASP6 \rightarrow CASP6^* + CASP10^*$	(CASP activation)
$CASP10 + CASP7 \rightarrow CASP7^* + CASP10^*$	(CASP activation)
$CASP3^* + CASP6 \rightarrow CASP6^* + CASP3^*$	(CASP activation)
$CASP3^* + CASP7 \rightarrow CASP7^* + CASP3^*$	(CASP activation)
$CASP7^* + CASP6 \rightarrow CASP6^* + CASP7^*$	(CASP activation)
$CASP3^* + DFF \rightarrow DFF45-CASP3^* + DFF40$	(DNA decomposition activation)
$CASP7^* + DFF \rightarrow DFF45-CASP7^* + DFF40$	(DNA decomposition activation)
$CASP3^* + IAP \rightarrow IAP-CASP3$	(Inhibition)
$CASP6^* + IAP \rightarrow IAP-CASP6$	(Inhibition)
$CASP7^* + IAP \rightarrow IAP-CASP7$	(Inhibition)

Our simulation (Apte et al., 2010) has shown neither FLIP, nor XIAP could save the T-cells when acting alone. However, as shown in Fig. 6, when used together these inhibitors act synergistically, and could suppress the apoptosis almost entirely. A similar synergy trend shown to suppress apoptosis in type II colorectal cancer cells (Wilson et al., 2009) may be regarded as an indirect validation of our model.

An alternative, common strategy in fighting cancer is to use apoptosis to directly attack cancer cells. One of the way toward such a goal is to maximize the concentration of the "DNA killer" DFF40 by suppressing the apoptosis inhibitors FLIP and IAP. We simulated such a strategy by varying the transitional probability of the inhibitor suppressors siRNA and SMAC, respectively (Apte et al., 2010). Fig. 7 demonstrates that silencing FLIP, which is stronger inhibitor than IAP, does not suffice since the achieved active concentration of DFF40 does not exceed 60% of the theoretical maximum of 500 cells. The synergistic suppression of FLIP and IAP by siRNA and SMAC, respectively, raises this percentage to 90% and enables a full-scale apoptosis to kill the cancer cells.

We proceeded further from a more complete model of apoptosis by integrating the exogenous pathway of FASL-induced apoptosis with the endogenous pathway of mitochondria-activated apoptosis (Fig. 8). Cells undergoing apoptosis by these two mechanisms are called type I and type II, respectively (Chang et al., 2002; Wilson and al., 2009). The FASL-induced mechanism takes place at high levels of caspase-8, while low levels of this kinase result in expression of the protein BID, which activates the mitochondrial mechanism. The mitochondria releases cytochrome C into the cytoplasm, which in turn activates caspase-9. The cascade is closed with caspase-9 activating caspase-3. In addition, a feedback loop from caspase 3 to caspase 9 to IAP has been hypothesized to deactivate IAP (Creagh & Seamus, 2001; Zhou et al., 2005; Okazaki et al., 2009).

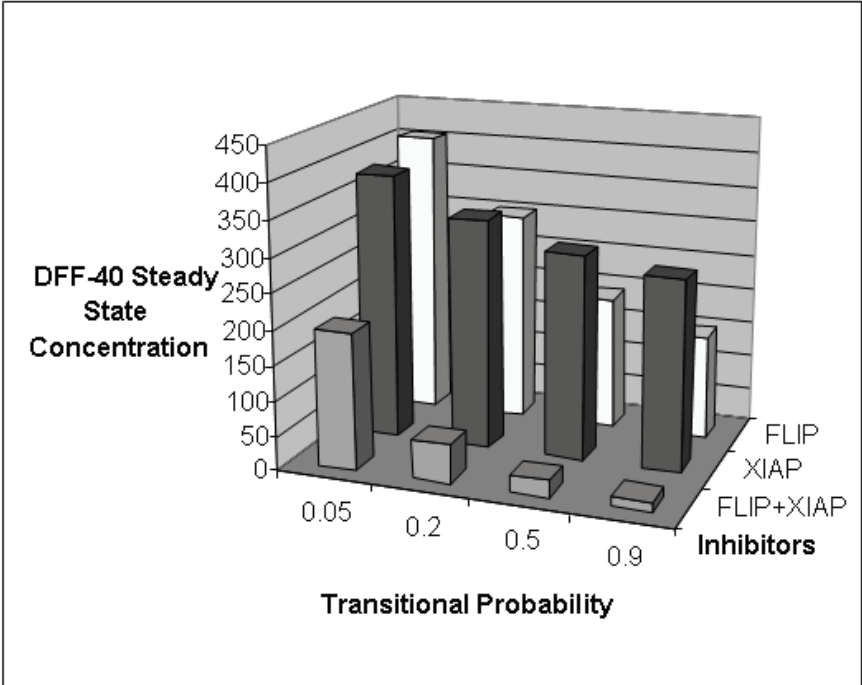


Fig. 6. The concentration of the DNA “killer” DFF-40 reduces with the increase of the inhibitor activity. Acting individually, FLIP and XIAP inhibitors cannot prevent the killing of the immune system T-cells by cancer cells and HIV infection. However, the CA simulation predicts a synergistic effect of the joint use of inhibitors that could save the T-cells, and restore the immune system potency. (Cellular Automata (CA) Modeling of Biomolecular Networks Dynamics, D. Bonchev, S. Thomas, A. Apte, L. B. Kier, SAR & QSAR in Environmental Research, 2010, reprinted by permission of Taylor & Francis Ltd) <http://www.informaworld.com>).

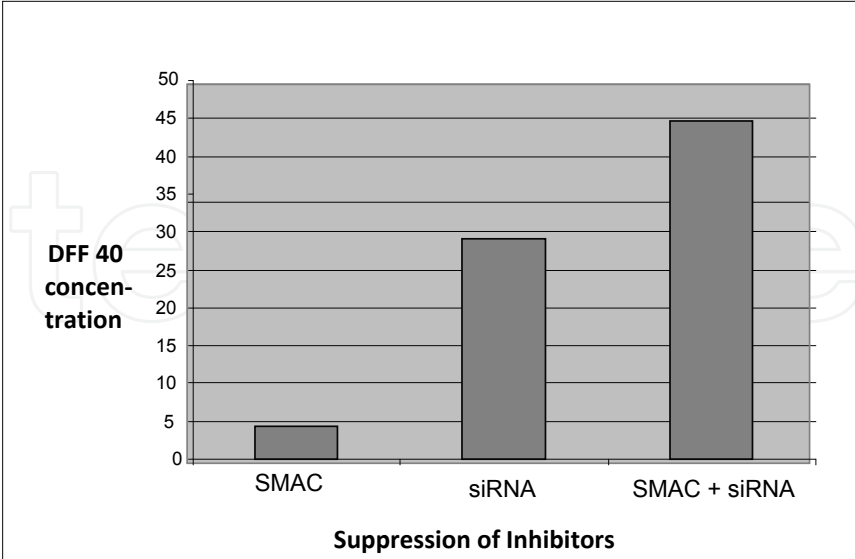


Fig. 7. Suppressing the FLIP and IAP inhibitors by siRNA and SMAC, respectively. The DFF40 steady-state concentration after 25000 cellular automata iterations predicts that a maximal FASL-induced apoptosis is achievable only via joint synergistic suppression of FLIP and IAP inhibitors. (Courtesy of “Chemistry and Biodiversity” journal (Apte et al., 2010-12-31)).

Our simulation showed that adding the feedback loop $CASP3 \rightarrow CASP9 \rightarrow IAP$ to the mitochondria-mediated apoptosis pathway does not affect strongly the concentration of DFF40. However, the enhanced suppression of the IAP inhibitor and the additional activation of CASP9 accelerate considerably the process. We found that under these conditions FASL mechanism is 32 % faster than mitochondrial feed-forward mechanism, and 12 % faster than the mitochondrial feed-forward with a feed-back. (The number of iterations needed for the three mechanisms was 5012 ± 12 vs. 5596 ± 11 vs. 7368 ± 13 , respectively). The interconnectivity of the two apoptosis cascades thus offers a second, redundant mechanism for type-I cell apoptosis in case of failures in the FASL apoptosis pathway, such as no DISC formation or mutated membrane bound FAS, etc. Reducing the CASP8 concentration in such cases switches apoptosis to the mitochondrial pathway with feedback, which is only 12% slower. Complete details of the CA modeling and its parameters are given in (Apte et al., 2010). The data presented in this section demonstrate the great potential of cellular automata technique for biomedical applications.

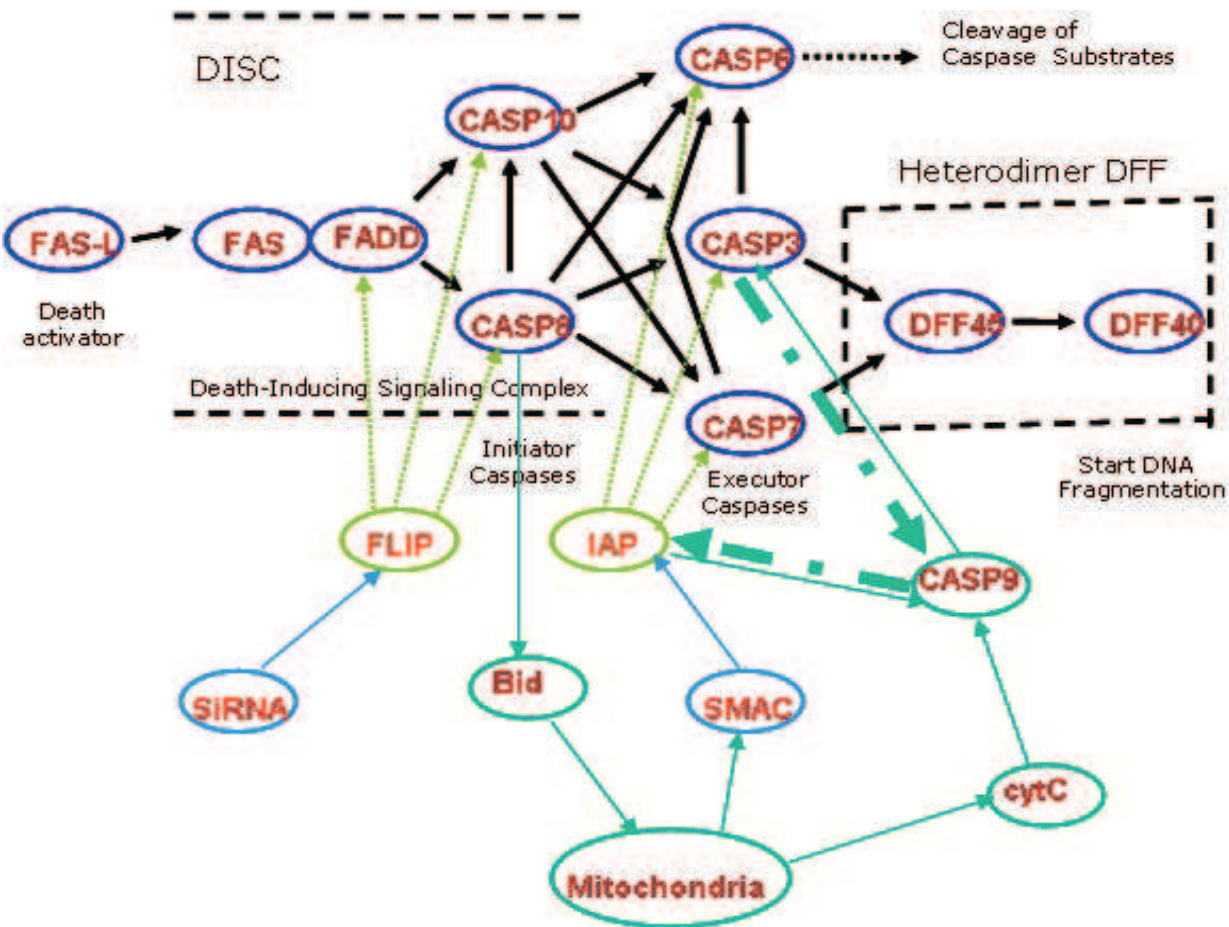


Fig. 8. Integrated scheme of the exogenous FASL-induced apoptosis and the endogenous mitochondrial apoptosis (Apte et al., 2010). At low expression level of CASP8 the mitochondria releases cytochrome C in the cytoplasm, activating thus CASP9, which in turn activates CASP3. A feedback from CASP3 to CASP9 increases the concentration of CASP9 active form, which accelerates apoptosis by suppressing the inhibition from IAP via SMAC protein. A similar suppression of the FAS apoptotic circuit can be achieved by using siRNA. (Courtesy of "Chemistry and Biodiversity" journal (Apte et al., 2010-12-31)).

5. CA modeling of network motifs performance

The cellular automata modeling discussed in the previous sections was directed toward identifying dynamic patterns in networks and pathways, which to provide means for control of their dynamics. A different approach was also pioneered in our Center for the Study of Biological Complexity (Bonchev et al., 2006, Apte et al., 2008, Taylor et al., 2010). It was aimed to search for answers to a fundamental problem: "*How structure affects the dynamics of processes in networks?*". While this question in the general case of networks of arbitrary size is too complex to be answered in a simple manner, a guiding idea was to look for exact answers for the dynamics of network motifs, the smallest structural units of networks (Milo et al., 2002; Alon, 2006, 2007). Such an approach avoids the computational complexity of large systems and, in addition, the CA derived patterns can be verified by ODE simulations (solutions of differential equations).

More specifically, in the search for the best performing structure we compared the same size motifs of different topology, and assessed their *performance* by the overall rate of the processes of conversion of the substrate(s) in the source node(s) into the product(s) of the motif target (or in terms of graph theory of the *subgraph sink*) node(s). In order to extract the topological factor chemical kinetics parameters (concentrations and rate constants) and probabilistic rules (except the transitional probability one), were kept constant. This "freezes" the process stochasticity, making our simulations *de facto* non-stochastic. Different classes of motif topology were defined according to the number of source (S) and target (T) nodes, with major attention being focused on the S1T1 class having a single source and a single target node. Our approach could be of particular interest for *signaling pathways* in biological systems, the overall rate of performance in which measures the effectiveness of converting the incoming chemical signal into an outgoing one. While using the language of biochemical reactions in describing motifs' links, and building on the specific CA approach to network discussed in the previous sections (Kier et al., 2005), the method can be readily applied to networks with different type of node-node relations, including ecological and social networks.

We performed a detailed analysis of the dynamics of different feed-forward (FF) motifs, which have been of considerable interest in biological systems. We extended the concept of FF motif used in the literature, namely "a subgraph that contains a feed-forward link connecting the source and the target nodes", to more general cases the added link in which shortens the distance between the source node and the target one, but not necessarily connects them directly. The *temporal* dynamics of feed-forward motifs in gene regulatory networks has been studied in detail (Mangan & Alon, 2003; Kashtan et al., 2004; Kashtan & Alon, 2005; Alon, 2006, 2007). It was shown that gene evolution depends on the topology of gene regulatory network (Cordero & Hogeweg, 2006). The relation between structural modules and dynamics of cellular networks, has been considered as a basis for cell reprogramming and engineering (Yuan & Hui, 2006). (Chechik et al., 2008) introduced activity and timing motifs, which capture patterns in the dynamic use of a network and reveal principles of transcriptional control of metabolic networks (Naemi, 2008). More generally, relating topology to function lead to a better understanding of dynamic properties of network motifs, e.g., their contribution to network stability (Prill et al., 2005). Our approach is based on CA *spatial* models of the dynamics of generalized feed-forward motifs, which provide information on the concentrations of all substrates and products at the (quasi) steady-state reached after a considerable amount of CA iterations. The overall

reaction rate was assessed in parallel by CA and ODE simulations, as the number of iterations (respectively time in s) needed for 90% conversion of the input signal into the output one. The simulation was performed on a 2D-square lattice, 100 by 100 cells, embedded on the surface of a torus, with a lattice density of 3.6%. Each simulation was run 100 times, which produced a statistics with a sufficiently low standard deviation. Each motif's arc i was assumed to correspond to an enzymatic reaction: $S(i) + E(i) \rightarrow SE(i) \rightarrow PE(i) \rightarrow P(i) + E(i)$, and the probabilistic rules used were the ones for enzymatic reactions (See Section 3). The performance of all directed 4-node feed-forward motifs having a single source and a single target node (S1T1 class) was evaluated and compared to that of the directed linear motif of the same size.

The parallel ODE simulation was carried out in several approximations (Apte et al., 2008). The simplest way to construct an ODE model is to treat each feed-forward link $A \rightarrow B$ without regard to the underlying biochemical processes (e.g., neglecting the formation of substrate-enzyme and enzyme-product complex and the subsequent dissociation of the latter). In doing so, we neglect any nonlinear interactions of various species. The advantage of this linear ODE approach is that with the assumption for constant initial concentrations and rate constants, the linear systems of ODEs can be solved explicitly. Taking into account the formation of the substrate-enzyme complex $SE(i)$, and assuming that the substrate-enzyme complex $SE(i)$ converts with a certain transitional probability into the product $P(i)$ and a release of the enzyme $E(i)$, produced a nonlinear model (NDE), which can be solved only numerically. A second, more detailed nonlinear model (NDE') has taken into account the reversibility of the process of formation of the intermediate $SE(i)$ complex, which is a basic assumption in the theory of enzymatic reactions. The results summarized in Fig. 9 show very good agreement between CA and ODE models.

The ordering of the ten directed 4-node motifs in Fig. 9 was found to follow several topological transformation patterns (Apte et al., 2008). The acceleration of the $S \rightarrow T$ conversion might be predicted in part by conjecturing that every graph transformation that reduces the distance or, alternatively reduces the average path length, between the source and target vertices S and T , accelerates the process. Counting the distance between two neighboring vertices as a unit, one extracts from Fig. 9 a series of topological patterns that improve the motif dynamic performance.

Topodynamic Pattern 1: The shorter the graph distance $d(S \rightarrow T)$ between the source node and the target node in a feed-forward motif, the higher the overall motif dynamic performance:

$$A(d = 3) < B, C(d = 2) < D, E, F, G, H, I(d = 1) \quad (2)$$

Notably, the two bi-parallel motifs **F** and **J** do not obey this pattern.

When considering the average path length one arrives at a more distinctive pattern. It singles out motif **I** to perform with the highest rate, due to the lowest average path length between nodes S and T ($L = (1+2+2)/3 = 5/3$):

Topodynamic Pattern 2: The shorter the average path length $L(S \rightarrow T)$ between the source node and the target node in a feed-forward motif, the higher the overall motif dynamic performance:

$$A(L = 3) < B, C(L = 2.5) < D, E, G, H(L = 2) < I(L = 1.67) \quad (3)$$

Topodynamic Pattern 3: Any ring closure of a linear chain of steps converting a source substrate S into a target product T accelerates the transformation. Acceleration of the process is the strongest when the feed-forward link directly connects the substrate to the target and is the smallest when the link connects the substrate to an intermediate product:

$$A < B < C < D$$

(4)

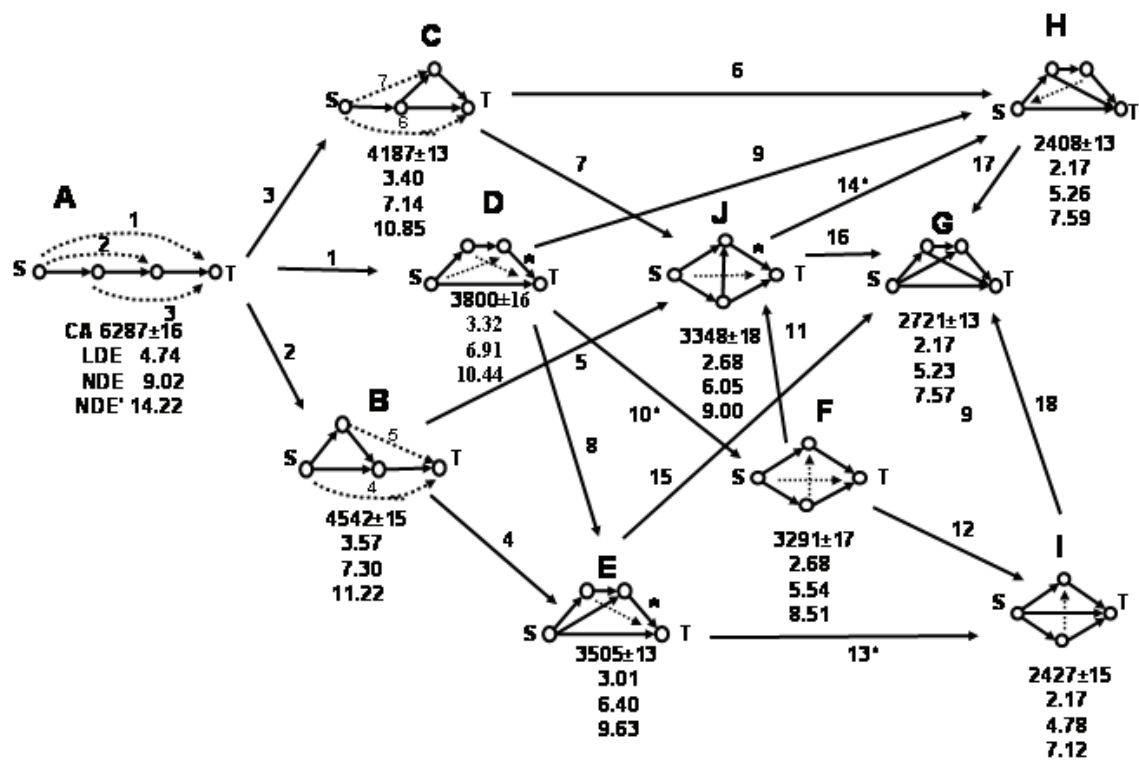


Fig. 9. Performance of 4-node network motifs, evaluated by the rate of converting the source node S substrate into the target node T product, as measured by the number of CA iterations, and by the time in seconds determined from a linear and two nonlinear differential equations models. The motifs from A through J correspond to ID numbers 536, 2118, 2076, 652, 2126, 2182, 2254, 2204, 2190 and 2140, respectively (Milo et al., 2002). The broken lines indicate the manner in which another directed link can be added in a subsequent topological transformation. The asterisks in motifs D, E, and J, stand for the edge, which changes its direction in a subsequent transformation. (Courtesy of Journal of Biological Engineering (Apte et al., 2008)).

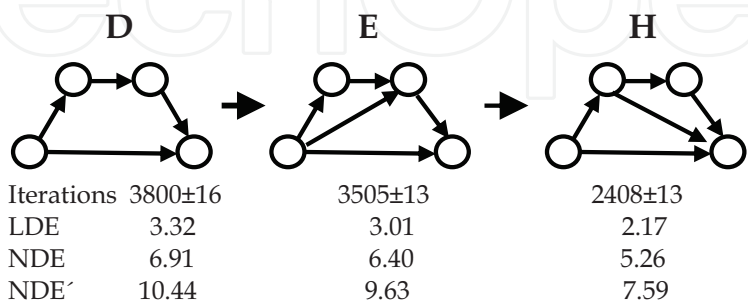


Fig. 10. Adding a second feed-forward edge accelerates the motif performance, particularly when the edge is incident to the target node. (Courtesy of Journal of Biological Engineering (Apte et al., 2008)).

Topodynamic Pattern 4: Adding a second feed-forward edge (*double feed-forward motif*), between a pair of nodes in the longer path of the FF loop, accelerates the conversion of the source substrate into the target product:

$$D < E < H \tag{5}$$

The pattern is illustrated in Fig. 10. Adding a third feed-forward edge does not always have an accelerating effect, as seen from the motifs **H** \rightarrow **G** transformation.

Topodynamic Pattern 5: Reversing the direction of one or more links in a feed-forward motif to turn it into a bi-parallel and tri-parallel one increases the motif performance:

$$\text{Feed-Forward} < \text{Bi-Parallel} < \text{Tri-Parallel} \tag{6}$$

Three such conversions:

$$D < F, E < I, J < H \tag{7}$$

are shown in Fig. 9, where they are denoted by asterisks.

Topodynamic Pattern 6 (Isodynamicity): Some feed-forward motifs with different topology are characterized by the same overall $S \rightarrow T$ conversion rate by the CA and linear ODE models:

$$\text{CA: } H \left(2408 \pm 13 \right) = I \left(2427 \pm 15 \right) \tag{8a}$$

$$\text{ODE: } G = H = I = 2.169053700 \text{ s} \tag{8b}$$

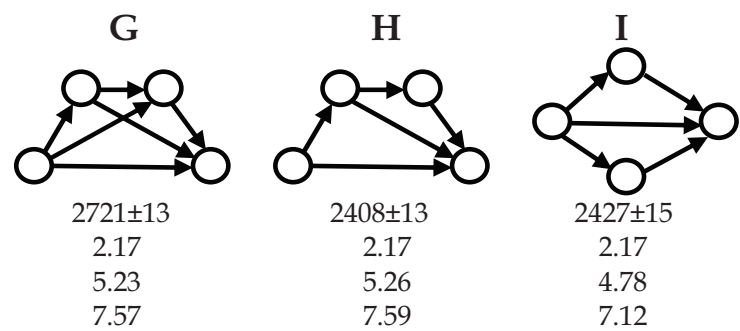


Fig. 11. Motifs **G**, **H**, and **I** are isodynamic according to linear ODE model, whereas CA models confirms the isodynamicity of **H** and **I**. The two nonlinear models show very close isodynamicity of **G** and **H**, while the more detailed NDE' model singles out motif **I** as the best performing one, as also predicted by purely topological arguments in Topodynamic Pattern 2 (see above).

Equality (8a) is valid within the standard deviation ranges of **H** and **I** (2395-2421 vs. 2412-2442). The linear ODE's times also characterize motifs **F** and **J** as isodynamic, whereas their CA estimates diverge slightly (3274-3308 vs. 3330-3366, respectively). The two nonlinear NDE times of motifs **G** and **H** are very close, while the most complex NDE' model classifies motif **I** as best performing:

$$\text{NDE: } G \left(5.23 \right) \approx H \left(5.26 \right) > I \left(4.78 \right) \tag{9a}$$

$$\text{NDE': } G \left(7.57 \right) \approx H \left(7.59 \right) > I \left(7.12 \right) \tag{9b}$$

The concept of motifs isodynchronicity was investigated in more details by linear ODE models. Three theorems were proved (Taylor et al., 2010) for classes of motifs sharing this property. The first such class is motifs containing target vertex with maximal in-degree (Fig. 12a):

Theorem 1. Consider the family of feed-forward motifs on n vertices with a single target vertex. Then all motifs for which the in-degree of the target vertex is $(n-1)$ are isodynamic.

This theorem is easily extended to motifs having many target nodes (Fig. 12b):

Theorem 2. Suppose $1 < k < n$ and consider the family of feed-forward motifs on n vertices with precisely k target vertices. Then all motifs for which the in-degrees of the target vertices are $(n-k)$ are isodynamic.

Theorem 1 expands the isodynchronicity pattern so as to incorporate the class $S(n-1)T1$, while Theorem 2 expands that pattern further to the class of motifs $S(k)T(n-k)$. The third theorem defines isodynchronicity in a class of bi-parallel motifs. This class is also of $S1T1$ type but the single source and single target nodes are connected by two parallel chains of links. Adding in a specific manner links between the two parallel chains does not change the overall motif performance (Fig. 12c).

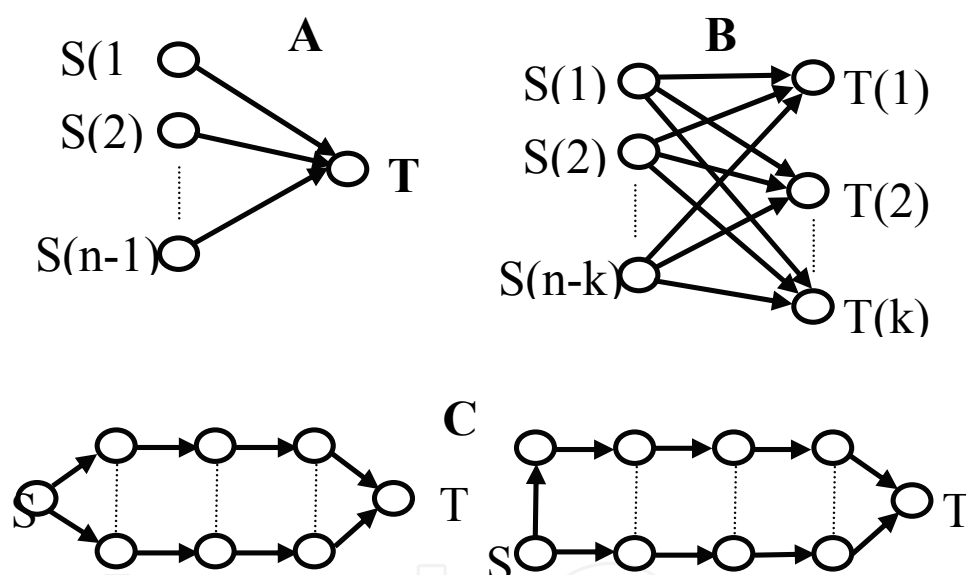


Fig. 12. A, B, C. Illustration of Theorems 1, 2 and 3, respectively.

Theorem 3. Consider the bi-parallel motif on m vertices, with the alternating vertex labeling. Suppose we construct a new motif by adding directed edges between vertices k and $(k+1)$ (regardless of orientation) if k has the same parity as m and $1 < k < (m-1)$. Then this new motif is isodynamic with the bi-parallel motif.

Theorems 1-3 thus identified two large classes of isodynamic feed-forward motifs: such the target vertices of which have maximal in-degree, and bi-parallel motifs with a variable number of redundant edges not changing the performance rate. An idealized case was used, all reactions in which proceed at the same rate, and the formation of intermediate complexes is not taken into account. Nevertheless, numerical simulations with more realistic nonlinear ODE models have shown time estimates close to those produced by the linear models and the CA ones.

6. Conclusion

This chapter summarizes the pioneering work on cellular automata modeling of network dynamics done in our Laboratory. Although obtained at molecular biology level, the findings of our study are easily applicable to complex networks of arbitrary nature. Our approach to such level of complexity is to study in detail small size subnetworks (motifs), reducing strongly computational time, while shedding light on the dynamic patterns of the system as a whole. This approach does not provide exact answers, but rather identifies patterns of behavior. It offers answers to questions like what one has to expect when affecting a network node or node-node interaction (link), providing thus means for network control. The latter could facilitate the search for novel pharmacological targets, as well as for individualized patient treatments. As shown in our work, intimate details of the mechanism of action of diseases can be revealed, such as cooperative action of enzymes, synergetic action or suppression of inhibitors, etc. All this information provides a basis for developing strategies for fighting such diseases like cancer and HIV.

An essential part of such studies is the extraction of useful topological-dynamic (topo-dynamic) patterns describing specific effects of topological structures on network dynamics at constant other conditions. The great advantage of using topology to study network dynamics is in the generality of the patterns found, which do not depend on process specificity or network size. The dynamics of the feed-forward motifs investigated revealed important aspects of networks containing such loops. Any feed-forward link added to a linear cascade of chemical/ biochemical reactions accelerates the process, and the acceleration is further enhanced by adding a second feed-forward link. The acceleration of the overall process in FF motifs increases with the decrease in the distance, and in the average path length, between the input and output nodes. When the distance parameters are kept constant, cellular automata and ODE simulations produce a further finer distinction between the motifs dynamic performance. The concept of isodynamic network motifs revealed important aspects of similarity in dynamic behavior of subnetworks of different topology. The consequence for biological and other systems from this finding is that identical or closely similar rate of performance of processes converting a given input to a desired output can be produced by different network connectivity. It is important to understand whether there is a specific selective advantage to use a certain motif topology among a number of others of similar performance rate.

In the more general case of non-isodynamic network motifs one may expect that evolution might have been using the higher speed of producing a desirable target product from equivalent initial conditions, particularly in signaling pathways. The answer of this question is a subject of our extensive almost completed study, in which the abundance of motifs in metabolic networks, and their higher level of organization termed network of interacting pathways (NIP) (Mazurie et al., 2008, 2010), were analyzed in over 1000 species. Evidence for high statistical support was recovered for the over-representation of certain feed-forward and bi-parallel motifs (subgraphs) with 3 and 4 nodes. The motifs exhibiting considerable enrichment were those having faster performance dynamics and extra null-performance link. The preliminary results favored strongly one of the three fastest motifs found (motif ID # 2204, denoted as **G** in Fig. 9). The high abundance of this motif evidences that evolution conserves this effective topology of maximum cross-talk between the individual metabolic pathways. Motif 2204 exhibits the additional advantage to keep its overall performance almost unchanged even in case of losing one of its links (null-

performance link), in which case it converts to the tri-parallel motif I (ID # 2140), which is also one of the three fastest performing motifs. The lack of statistically significant abundance of such a high speed subgraph may be interpreted as evidence that at equal or close efficacy evolution conserves the structure that provides a higher stability. Having an extra edge which does not contribute to a higher conversion rate is a beneficial redundancy; if this edge is destroyed or incapacitated, the efficacy of performance of the biochemical reactions will remain practically the same. In the context of adaptive significance, these results indicated that the need of higher network resilience against attacks not only compensates the energy price for the extra link formation but also exceeded the potential benefit of a faster performance. Further studies extend this type of motif dynamics analysis on *Drosophila* microRNA-target interaction networks (Woodcock, 2010).

7. Acknowledgments

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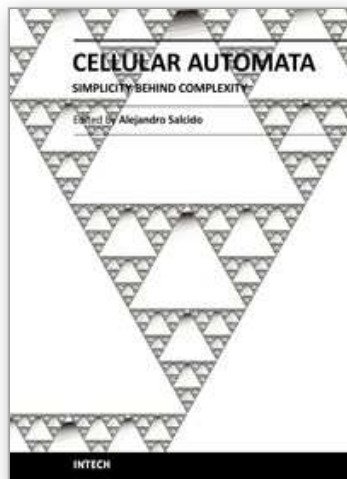
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Cellular automata make up a class of completely discrete dynamical systems, which have become a core subject in the sciences of complexity due to their conceptual simplicity, easiness of implementation for computer simulation, and their ability to exhibit a wide variety of amazingly complex behavior. The feature of simplicity behind complexity of cellular automata has attracted the researchers' attention from a wide range of divergent fields of study of science, which extend from the exact disciplines of mathematical physics up to the social ones, and beyond. Numerous complex systems containing many discrete elements with local interactions have been and are being conveniently modelled as cellular automata. In this book, the versatility of cellular automata as models for a wide diversity of complex systems is underlined through the study of a number of outstanding problems using these innovative techniques for modelling and simulation.

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