EVOLUTION OF ALTERNATIVE CONTROL LOOPS OF BIOLOGICAL SYSTEMS

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Abstract: *Biological systems are complex, difficult, open, nonlinear and self-regulated, self-organized living systems. Such systems are known to be considerably robust to environmental changes and genetic perturbations. It is possible due observed property called robustness. Robustness is a fundamental feature of complex systems that allows them to maintain its functions despite external and internal perturbations. The main mechanism that ensures the robustness of a system is a system control that consists of negative and positive feedback. Presence of feedback is the important party of control in biological systems. The deviations of object from the target state by the means of feedback loops form the control action which brings the system back to the target state. A complete understanding of network robustness and their evolution requires that the biochemical network topological singularities, functional and dynamic changes that are caused by perturbations, are explored. For achievement this issue computational modeling is required. In this manuscript we explore scientific literature with a goal to characterize the robustness and the prime system control mechanism (feedback mechanism) that ensure it, to indicate and analyze existing network growth models of their evolution.*

Keywords: biological systems, robustness, feedback, biochemical network, network structure, network growth models, Boolean network model, modeling of evolution, systems biology.

Introduction

Biological systems are complex, difficult, open, nonlinear and, in some cases, independent living systems such as cell, animal and human. They have requirements, purposes and aspiration to satisfy them, and facilities to choose and change the behaviour depending on circumstances or conditions (see Fig.1.). Since long time many researchers aim to find the methods how to control biological system. In most cases the main goal of control is to cope with the illnesses and complex diseases or industrial biotechnology tasks (for example, reception of the maximum quantity of ethanol).

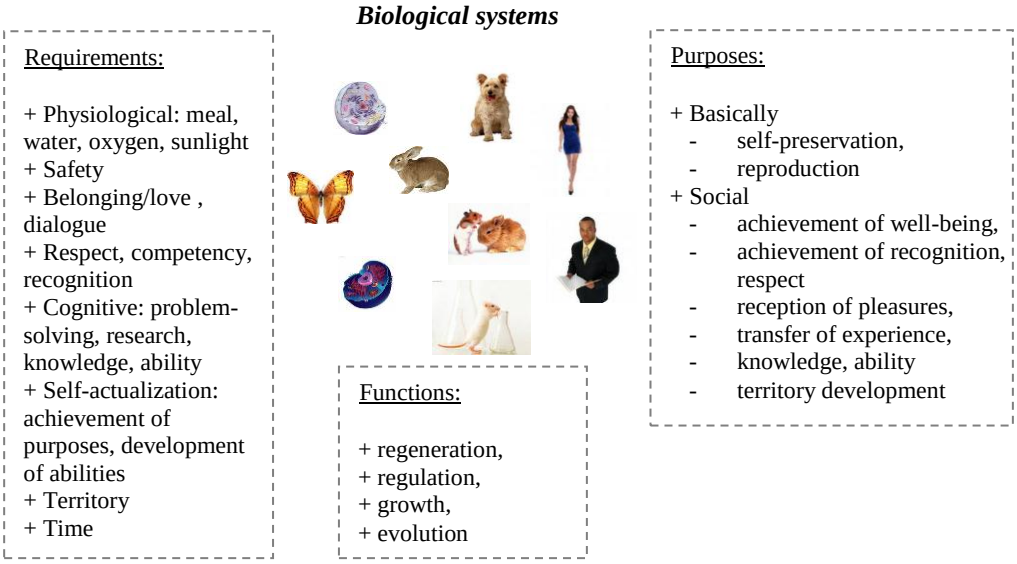

Fig.1. **Requirements of biological systems.**

Defining all possible requirements of biological systems that are mentioned on figure, in attention Maslow's hierarchy of human needs (Maslow, 1943) has been accepted.

From the social viewpoint it is much easier to induce on action the biological system by influence on behaviour and consciousness. For example, the main task in this case is not to admit the disease and to carry out preventive actions. Le Chatelier's principle (Kay, 2000) means that if to have possibility to change internal and external environment of the biological system these actions will provoke its some behavior directed on elimination of undesirable influence or on preservation if the influence is desirable.

From the biological viewpoint it is much more difficult while the biological systems have a set of many states, are self-organized and are known to be considerably robust (Kwon et al., 2007, Kitano, 2004, Barabasi et al., 2004) to environmental changes. In this case the main task of control is first, to understand the basically building, underlying and existence principles of biological system, and second, to learn to "switch" and maintain the system in necessary state.

Biological systems are self-organized systems as operating factors of such system arise in her. Therefore control in biological systems is self-control, regulation processes – self-regulation processes.

Control is process of system streamlining according to changes in the external and internal environment for the purpose of counteraction to disorganization factors. This process is carried out by means of the elements which are a part of the system. Control is function of the organized systems, providing performance of following tasks:

- preservation of certain system structure;
- maintenance of a mode of system activity;
- realization of the purpose of system activity by a certain rule (algorithm).

These control tasks dare by means of regulation. Regulation is directed on maintenance homeostasis, caused by ability of biological systems to develop reactions in reply to changes of environment parameters which exclude or reduce to a minimum the consequences of these changes. Regulation is function of the operating systems, providing performance of following tasks:

- maintenance of a constancy of adjustable size at some certain level;
- change of adjustable variable under the set law (program regulation);
- change of adjustable size according to a course of some external process (watching regulation) (USTUA, 2002).

The important party of control in biological systems is presence of feedback. Without feedback self-control and self-regulation processes are impossible (USTUA, 2002). Feedback and biological regulation are two sides of the same coin, reflecting the need of the biological system - particularly living cell - to deal with changing environments, to generate cell to cell heterogeneity and to optimize cellular metabolism to a given external condition (Krishna et al., 2007).

Robustness and feedback

Many complex systems are known to be considerably robust to environmental changes (Kwon et al., 2007, Kitano, 2004, Barabasi et al., 2004). It is a key feature of system, which refers to the system's ability to respond to changes in the external conditions or internal organization while maintaining relatively normal behavior (Barabasi et al., 2004).

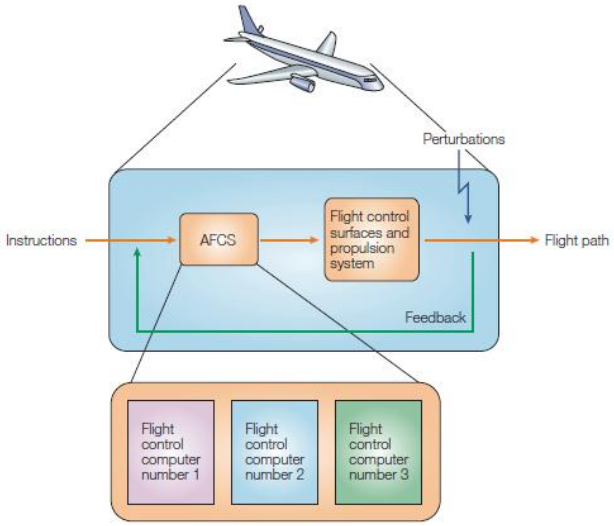

Fig.2. **Airplane as robustness explanation example.**
(Kitano, 2004)

The commercial passenger airplane (see Fig.2.) is one of the best examples that describe the concept of robustness. Many modern airplanes have an automatic flight control system (AFCS) that maintains a flight path (direction, altitude and velocity of flight) against perturbations in atmospheric conditions. This can be accomplished by a feedback control in which deviations from the defined flight path are automatically corrected. AFCS is the crucial component that allows the robust maintenance of the flight path by controlling the airplane's flight-control surfaces (rudder, elevator, flaps, aileron, etc) and the propulsion system (engines). AFCS is generally composed of three modules with the same functions, thereby creating redundancy, although each is designed differently (heterogeneity) to avoid a common mode failure. Three computers are modular, so that

failure in one module does not affect the functions of other parts of the system. This type of mechanism is implemented using digital technologies that decouple low-level voltages from digital signal (ON/OFF of pulses), thereby preventing noise from influencing its functions. Although this is a simplified explanation of the actual system, the concept applies to details of the basic system as much as it does to the more complex systems. Although there are differences between man-made systems and biological systems, the similarities are overwhelming. Fundamentally, robustness is the basic organizational principle of evolving dynamic systems, be it through evolution, competition, a market niche or society (Kitano, 2004).

As argue Kitano, robustness is a ubiquitously observed property of biological systems and fundamental feature of complex systems that allows a system to maintain its functions despite external and internal perturbations, to be evolvable against environmental and genetic perturbations. This is a phenomenon that cannot be understood by looking at the individual components (Kitano, 2004). Robustness is attained by several underlying principles that are universal to both biological organisms and sophisticated engineering systems. There are trades-offs between robustness, fragility, resources demands and performance which explain system behavior, including patterns of failure, and provide a possible framework for how biological systems have evolved and been organized (Kitano, 2004). Kitano note, that in some cases, such as cancer, disease state establishes its own robustness against therapeutic interventions. Understanding robustness and its intrinsic properties will provide a more profound understanding of biological systems, their anomalies, complex diseases, countermeasures and a guiding's principles for therapy design (Kitano, 2004).

The mechanisms that ensure the robustness of a system are: *system control, alternative (or fail-safe) mechanisms, modularity* and *decoupling*, but these mechanisms need to be organized into coherent architecture to be effective at the level of the organism. The prime mechanism for coping with environmental perturbations is the *system control* that consists of *negative* and *positive feedback* to attain a robust dynamic response and many biological subsystems use the combinations of these systems control (Kitano, 2004).

The principle of feedback is one of main principles of self-control and self-organizing of biological systems. By means of feedback deviations of object from the set condition (state) form operating influences which result an object condition (state) in the set. Feedback is a return influence of process results on its course (USTUA, 2002).

From the viewpoint of network structure feedback is organized on *feedback loops*. Feedback loop is closed simple cycle (Kwon et al., 2007, Barabasi et al, 2004) of any length (Hallinan et al., 2006) with the set of nodes where the nodes are not revisited except the starting and ending nodes (see Fig.3.).

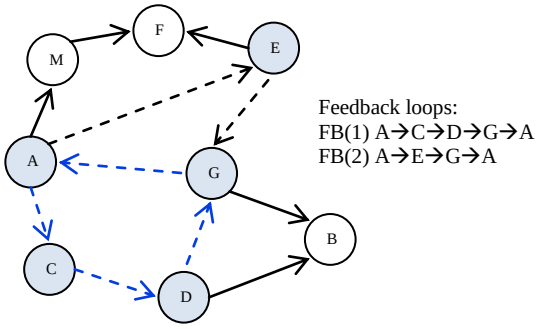

Fig.3. **Feedback loop.**
(Rubina et al., 2010)

Negative feedback. Negative feedback promotes restoration of an initial condition of system. They provide stability of system functions, their stability to external influences and are the basic mechanism of energetic and metabolic balance in biological systems, control of population's number, self-control of evolutionary process (USTUA, 2002). Systems involving negative feedback loops tend to settle to a steady state, which may be stable or unstable (Hallinan et al., 2005).

Positive feedback. Positive feedback by means of process results strengthens it. Positive feedback with draws system all further from an initial condition and strengthen the processes of ability to live. They play a special role for growth and development. On the basis of positive feedback mechanisms self-organizing at all levels begins. In a consequence on positive feedback mechanisms then imposes restrictions of negative feedback (USTUA, 2002). Positive feedback loops promote multistationarity. It is the existence of a number of different stable states. For example, multistationarity is fundamental to the development of bistable switches in regulatory networks, in which there are two stable states, between which the system can be moved by an external stimulus. Bistable switches are essentially a memory for the cell, since the state in which it finds itself is dependent upon the history of the system (Hallinan et al., 2005).

Positive feedback contributes to robustness by amplifying the stimuli, often producing bistability, so that the activation level of a downstream pathway can be clearly distinguished from non-stimulated states, and so that these states can be maintained (Kitano, 2004).

The most studied examples of robust adaptation is the bacterial chemotaxis. It uses negative feedback to attain the perfect adaptation that allows chemotaxis to occur in response to a wide range of stimuli even if network topologies are not the same. Krishna with colleagues indicates that a key part of overall system of molecular regulation is the interface between the genetic and the metabolic network. A motif that occurs very often at this interface is a negative feedback loop used to regulate the level of the signal molecules (Krishna et al., 2007).
Feedback controls sometimes compensate for changes in rate constants of interactions within the network and changes in the initial state of the network. A computational study of the cell cycle demonstrated that removing some genes does not necessarily block the cell cycle; it might only make it more fragile against perturbations (Kitano, 2004).

Robustness and alternative control loops

Kwon and colleagues have verified hypothesis on the relationship between feedback loops and the robustness of a network by employing Boolean network models. They have examined robustness with respect to the initial state mutations, update rule mutations, and the number of coupled feedback loops (see Fig.4.) of a network during evolution. They found that there is a strong positive correlation between the number of coupled feedback loops and the robustness of a network. Their simulations showed that the networks involved by preferential attachment (by preferential attachment a node is more likely to connect to a node with a high degree) are more robust and produce more coupled feedback loops (Kim et al., 2008) than the random networks. For example, it was found that three distinct feedback loops responsible for genetic regulation, mRNA attenuation, and enzyme inhibition that regulate tryptophan concentrations in Escherichia coli. The complex regulatory network formed by the feedback loops induces a rapid and stable response, while being robust against uncertainties (Venkatesh et al, 2004, Kwon et al., 2007).

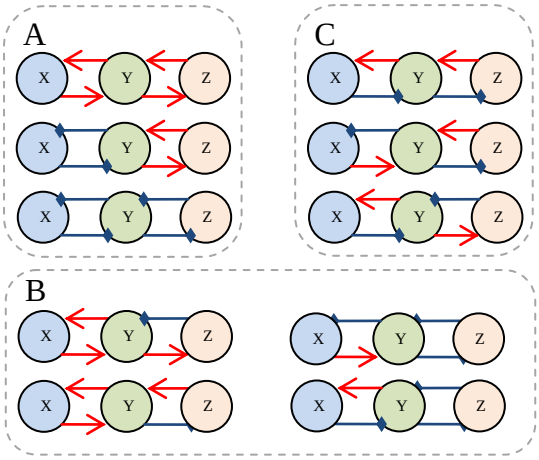

Fig.4. **Network motifs of coupled feedback loops.**
(*A*) Positive-Positive structures. (*B*) Positive-Negative structures. (*C*) Negative-Negative structures.
(Kim et al., 2008).

Robustness can be enhanced if there are multiple means to achieve a specific function, because failure of one of them can be rescued by others by *alternative (or fail-safe) mechanisms*. The existence of alternative mechanisms at the system-component level allows regulatory feedback to remain intact despite mutations. It is usually attained by having multiple heterogeneous components and modules with overlapping functions. This concept encompasses redundancy, overlapping function and diversity, as the differing degrees of similarity between the various alternative means that are available. Redundancy generally refers to a situation in which several identical, or similar, components (or modules) can replace each other when another component fails. Diversity, or heterogeneity, represents the other extreme, whereby a specific function can be attained by different means available in a population of heterogeneous components (Kitano 2004).
A complete understanding of network robustness requires that the functional and dynamic changes that are caused by perturbations are explored. In a cellular network, each node has a slightly different cellular function and therefore the effect of a perturbation cannot depend on the node's degree only. The activity of the various metabolic reactions or regulatory interactions differs widely; some are highly active under most growth conditions, other switch on only under environmental circumstances. Therefore, an ultimate description of cellular networks requires that both the intensity (strength) and the temporal aspects of the interactions are considered. As Barabasi with colleagues have note and indicate that there are hot links in metabolic and genetic networks, in many non-biological networks to, and their activity following a wide distribution. For example, the biochemical activity in both the metabolic and genetic networks is dominated by several "hot links" that represent high activity interactions that are embedded into web of less active interactions (Barabasi et al., 2004).

To explore biochemical networks computational network models, these modeling, simulation and analysis are needed.

Alternatives in networks and evolution

Biological systems components and their interaction can be present in network form. From the viewpoint of biochemical network architecture, main ingredients of biological system are molecules, interactions, pathways and networks. A biological system can be viewed to be formed conceptually from individual molecules, to pairwaise interactions, to local structures (including network motifs, molecules, pathways, subnetworks) and eventually to global biomolecular networks (Zhang, 2009). Biomolecular networks allow visualizing and describing of intracellular molecular interactions of cellular system by using available metabolic and gene regulation experimental data (Zhang, 2009), as well as representation of many biochemical processes such as metabolism, gene regulation, signal transduction (Zhenjun et al, 2005).

There is a growing interest in understanding the principles of biochemical network evolution, such as protein-protein interaction, signaling, metabolic, gene regulatory networks, and many network growth models have been proposed to investigate this issue (Kwon et al., 2007). Meanwhile, there have been various studies on the topological properties of biochemical networks, and one prominent result is about the scale-free property (Barabasi et al., 2004, Kwon et al., 2007). The main singularity of scale-free networks is that most number of their nodes has only a few links, but few nodes called hubs have a very large number of links. In this regard, finding a network growth model that can produce a scale-free network has become an issue (Kwon et al., 2007).

Network of different types can be distinguished by their degree distributions. Scale-free network has a power-law degree distribution, $P(k) \sim k^{-y}$, indicating that a few hubs (highly connected nodes) bind numerous small nodes, while they are playing a significant role in the network. The structure and dynamics of these networks are independent of the network size as measured by the number of nodes. For example, protein-protein interaction networks have the features of a scale-free network, while most proteins participate in only a few interactions, while a small set of hubs participate in dozens of interactions. This type of network has a characteristic property known as the "small-world effect", which states that any two nodes can be connected via short path of a few links. Although the small-world effect is a property of random networks such as internet, scientific collaboration networks, metabolic networks, the path length in scale-free networks is much shorter than that predicted by the small-world effect. Therefore, scale-free networks are "ultra-small" (Zhang, 2009).

At most cases, biochemical networks are scale-free. Barabasi with colleagues (Barabasi et al., 2004) exploring scale-free networks have indicated two types of network robustness: topological robustness and functional and dynamical (Alon et al., 1999) robustness. Similar to both robustness types are selective: whereas some important parameters remain unchanged under perturbations, others vary widely. For example, scale-free networks do not have a critical threshold for disintegration – they are amazingly robust against accidental failure (Albert et al., 2000, Vázquez et al., 2003): even if 80% of randomly selected nodes fail, the remaining 20% still form a compact cluster with a past connecting any two nodes. This is because random failure affects mainly the numerous small degree nodes, the absence of which doesn't disrupt the network integrity (Albert et al., 2000).

The second example is the adaptation time or steady-state behavior in chemotaxis show strong variations in response to changes in protein concentrations (Barabasi et al., 2004, Alon et al., 1999).

For the last century and years have been created many network growth models such as random growing models, duplication-mutation models, random static network models, aging vertex network models, small-world network models, random Boolean network models, mathematical models by using differential equations. We can call them of network evolution models or network evolutionary models. All this called network models are related to the scale-free networks, except small-world network model and tie basic algorithms of network growth to a real biological basis, naturally reproducing the scale-free network architecture. Such network is more robust to random failure. This is because random failure affects mainly the numerous small degree nodes, the absence of which doesn't disrupt the network integrity (Albert et al., 2000).

All this network models are created to reconstruct and explore biochemical networks *in silico* on theoretical underground with a goal to establish and identify different network properties and singularities, to interpret the received results concerning real systems and if it is possible to test and convinced *in vivo*.

The duplication-mutation models suggest that network growth occurs through the duplication of an existing node and mutation of links by deleting an existing link or adding a new link running the growth procedure many times (Vāzquez et al., 2003, Sole et al., 2002, Kwon et al., 2007). This model leaves aside many finer details of the genetic evolution that lies behind the duplication and divergence process (Vāzquez et al., 2003).

Vāzquez et al. have translated the evolution of the Protein Interaction Networks into a growing network model. The model aims only to capture the most basic factors affecting the topological evolution of the network. It can be consider each node of the network as the protein expressed by a gene. After gene duplication, both expressed proteins will have the same interactions. This corresponds to the addition of a new node in the network with links pointing to the neighbors of its ancestor. Eventually, some of the common links will be removed because of the divergence process. Vāzquez et al. have formalized this process by defining an evolving network in which, at each time step, a node is added according to the duplication and divergence rules by using parameters p and q. In

this model, each node in the network represents a protein that is expressed by a gene, and the network grows as follows. At each time step, one selects a random node – call it node *i* – and carries out two steps in sequence. First step includes duplication. In association with node *i*, a new node *i'* enters the network and is linked to the same nodes to which *i* is linked. This reflects the idea that the new protein, the result of duplication, is identical to the old protein; hence, it interacts with other proteins in the very same way. Also, with some probability p, a link is added between *i* and *i'* to account for the possibility that these two (identical) proteins also interact. At the next step comes divergence. Mutations in the genes associated with *i* and *i'* will gradually produce differences in these proteins, altering their interactions. The model accounts for this divergence by considering in turn all the proteins j to which *i* and *i'* are linked, selecting one of these at random, and removing it with probability q (Vāzquez et al., 2003).

In the random growing models network growth occurs through the adding of new node and random *k* links to it where *k* is the initial number of neighbors of incoming node. In a random static network models a new node is added and new undirected link is randomly added with probability δ between two uniformly at random chosen vertices (Callaway et al., 2001, Kwon et al., 2007). This process is repeated by many time steps. Callaway et al. have concluded that grown graphs, however randomly they are constructed, are fundamentally different from their static random graph counterparts. These dramatic differences between grown and static random graphs stem from a positive correlation between the degrees of connected vertices in the grown graph - older vertices tend to have higher degree, and to link with other high-degree vertices, merely by virtue of their age (Callaway et al., 2001).

Aging vertex network model based on a finite memory of the nodes (Klemm et al., 2002). In aging vertex network models the probability of producing new edges decrease with the age of network node (Kwon et al., 2007).

The small-world network models based on an interpretation between regular ring lattices and randomly connected graphs (Watts et al., 1998, Kwon et al., 2007). In this model each edge with probability *q* is deleted and a new edge is added for a random node.

Boolean network model (Kaufmann,1969, Shmulevich et al., 2002, Shmulevich et al., 2002, Chaves et al., 2005, Steggles et al., 2006, Paszek, 2007, Morris et al., 2010) is a popular type of network models. They consist $G(V,F)$ of a set of nodes $V=(x_1, x_2, ..., x_n)$, directed links between them and of a list of Boolean functions $F=(f_1, f_2, ..., f_n)$. In boolean models each variable $x_i \in \{0,1\}$, $i=1,2...n$ can only attain two values (0/1 or on/off). For example, these values represent whether a gene is being expressed, or the concentration of a protein is above a certain threshold, at time t (Sontag et al., 2007). The nodes are assumed to have binary activation, being either on or off at any given time step (Hallinan et al., 2005). Each directed edge can be characterized as either an inhibition or an activation (Sontag et al., 2007). The behavior of each network node x_i is described by Boolean function f_i based on its inputs.

Above mentioned models for a network growth basis take only two types of mutations – gene duplication (whole genome duplication, locally confined gene duplication, retrotransposition) and loss (Yamada et al., 2009), which are the most important drivers of network evolution. Gene duplication implies the addition of a network node and also the addition of links. With the loss of a gene not only the node but also all associated links are lost. But there are many other types of genetic mutations that can influence the process of network evolution. They do not modify a gene as whole, but modify a gene or its regulation in a way that results in link addition or loss. These genetic changes can be point mutations, insertions or deletions, or mutations that affect the regulation of the gene (Yamada et al, 2009). As Yamada with colleague note by investigating metabolic and protein interaction networks the evolution of network nodes and links is coupled to the genetic material of a cell, but the links can change over time even if nodes are unaffected, the rewiring of links can occurs without gene duplication and link changes might occur more frequently than node changes. There are plenty of genetic mechanisms that can easily lead to the link addition or deletion. Apart from point of mutations, alternative splicing and domain accretion, inversion, shuffling and duplication are other means for the fast acquisition or loss of links. But the quantification of link changes remains difficult, while requires sufficient network data in several species, which are slowly emerging, whereas network nodes can be studied just by genome comparison. Combinations of these can even occur, whereby forming the link is under positive selection (Yamada et al., 2009).

Conclusion

The prime singularity and phenomena of biological systems is their robustness that allows a system to maintain its functions despite external and internal perturbations, to be evolvable against environmental and genetic perturbations.

The prime mechanism for coping with environmental perturbations is the *system control* that consists of *negative* and *positive feedback* to attain a robust dynamic response and many biological subsystems use the combinations of these systems control (Kitano, 2004). Negative feedback promote restoration of an initial condition of system, but positive - withdraws system all further from an initial condition and strengthen the processes of ability to live (USTUA, 2002). Positive feedback loops promote multistationarity; that is the existence of a number of different

stable states. Several authors believe that the analysis of network feedback loops is not just the best but the only way in which complex networks can be analyzed (Hallinan et al., 2005).
There exist many different models, which researchers can use for modeling and exploring of biochemical networks. The popular type of network growth models is Boolean network model.
The basis of every model is the structure of examined biochemical network. It means that every model first of all is structural model. Structural model characterize and provide information of the connectivity (topology) of the interactions involved in a cellular process that described biochemical network. Identifying topological features in networks such as node degree, degree distribution, feedback loops is an important part of understanding the relationship between network structure and functions of their subunits.
Structural analysis of biochemical networks contributes to a deeper understanding of network-wide interdependencies, causal relationships, and basic functional capabilities. Some insights into the dynamic properties can nevertheless often be obtained, because fundamental properties of the dynamic behavior are often governed by the network structure (Klamt et al, 2006).
Development of alternative control loops during evolution of biological networks is one of the necessary preconditions of robustness of biological systems.

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