GOAL SETTING AS A SYSTEM-FORMING FACTOR IN THE MATHEMATICAL MODEL DESIGN: A MODEL OF OXIDATIVE STRESS IN PARKINSON'S DISEASE

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Abstract

Systems Biology aims to understand biological emergence from the interactions of biomolecules, e.g. by integrating the knowledge about these interactions into a computer model and thereby reconstructing biological behavior *in silico*. When building systems biological model we imply, the goal (emergence of useful biological function) as systems forming factor. This allows us to use a model to study design principles of biological system. We review current bioinformatics tools for gene network reconstruction and modeling of dynamic parameters. As a successful example of this systems biological approach, our mechanism-based experimentally validated model enabled us to predict in silico the influence of oxidative stress and various Parkinson's disease conditions (e.g. mutations) on aging. We discuss how this Silicon Human may be used to develop personalized therapies of Parkinson's disease.

Keywords: Theory of functional systems, P.K. Anokhin's Theory, Molecular mechanisms, Gene network, Computer modeling, Parkinson disease, Ageing diseases, Reactive oxygen species.

1. Introduction

Systems biology is holism and reductionism at the same time. Reductionism in the sense that we "calculate" emergent properties from interactions between system components (biomolecules). And holism in the sense that for this we need knowledge about the properties of the components that depend on the state of the entire system. The concept of "useful adaptive result", a key concept in the theory of functional systems by Petr K. Anokhin gave rise to a series of applications in biomedicine and molecular modeling. Recent international meeting Conference "From Functional Systems to a General System Approach" hold in Moscow January 29-30, 2025 at Sechenov University highlighted diverse application of the Functional systems theory to biomedicine (https://congrsysalgbai.ru/).

We consider these approaches using the example of computer modeling of interacting macromolecules [1]. Note that holism is philosophically opposed to reductionism, it does not reduce the complex to the simple. Emergence in systems theory is the appearance of new properties in a system that are not inherent in its components individually. The term was discussed in ancient philosophers' works. Historically, in 1935 P.K. Anokhin introduced the concept of "authorizing afferentation" (since1952 – "reverse afferentation", in cybernetics– "feedback"). At the same time, in the introduction to the collective monography "Problems of Center and Periphery in Physiology of Nervous Activity", P.K. Anokhin gave the first definition of the functional system. The term "feedback" is actively used in foundation of Machine Learning [2,3]. In our example, when a complex is formed between two proteins, the reaction rate will depend not only on the elemental properties of these proteins themselves, reflected in their dissociation constant, but also on the rate of formation and degradation of these proteins, on their intracellular transport, on the work of chaperones, activators or inhibitors, sequestration of any of these proteins. and other intracellular interactions [1,4].

2. Theory of Functional Systems and Molecular Computer Model

Systems biology offers a tool for describing a huge number of such interactions in the form of mathematical equations and solving a system of equations using a computer, which makes it possible to overcome the limitations of the human brain and reconstruct emergent properties in silico.

When creating such system-biological models, a purposeful arrangement of system components is implied in order to achieve some useful emergent properties. It can be said that the interaction of the components is focused on obtaining a useful result. According to P.K. Anokhin's Theory of Functional Systems, it is goal setting that is considered as a system-forming factor [2]. This also fits well with Kant's teaching about the end of all things and his example about the flute: "If Peter carves a flute, then his will (or his movement of his hands in a certain way) causes the flute (O), but his will (his movement of his hands) is determined by Peter's idea of the flute (S)". Such goal-setting in a sense continues Plato's concept of "noema" where the future noema (not yet realized) becomes the current noema in the process of noesis (realization through interaction with the environment). The theory of functional systems does not use the term noema, but in fact implies noesis when discussing reverse afferentation.

The creation of a mathematical model based on the goal-setting of the system and reconstructing the emergence of a useful result makes it possible to study the principles of the design of this system. We offer an example of such a study in this report using the example of step-by-step creation of a model of oxidative stress in Parkinson's disease [4,5,6]. We used computer simulation tool COPASI (Figure 1), graph reconstruction online tools STRING-DB (https://string-db.org/), UniProtKB database, modeling resources of EMBL-EBI Biomodels (https://www.ebi.ac.uk/biomodels/).

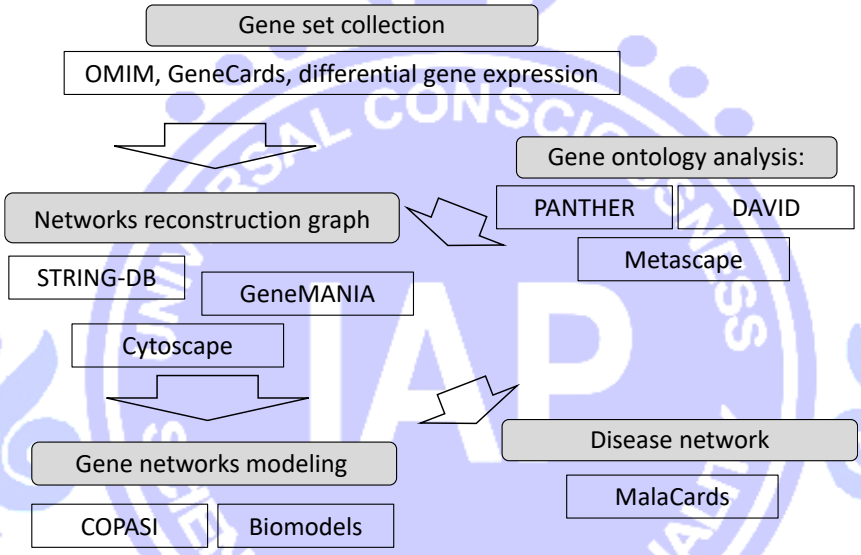

Figure 1: Computer tools used for disease modeling

The central module of our model [4] is the positive feedback between the processes of mitochondrial damage and the production of active radicals; damaged mitochondria produce more active radicals, and this, in turn, further damages the mitochondria. In healthy cells, the concentration of active radicals is controlled, for example, by increasing the synthesis of enzymes and antioxidants that eliminate active radicals and accelerate mitophagy, which eliminates damaged mitochondria (Figure 2).

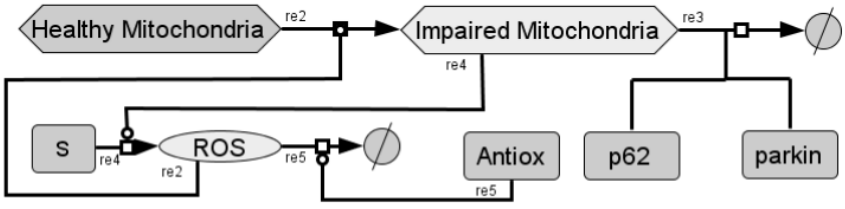

Figure 2: Computer model of Parkinson's disease. Model of healthy and impaired mitochondria in ROS metabolism

Reactive oxygen species (ROS) are produced at various intracellular locations. Transient increases of ROS production play various roles in cell physiology. They enact intracellular signaling that regulates immune responses, cell differentiation, and proliferation downstream of neurotrophic and growth factor signaling. Moderate ROS levels modulate metabolism and activate transcription of detoxifying enzymes such as superoxide dismutase, which, like

the mitophagy mentioned above, may provide resistance against subsequent stronger threats. These mechanisms have been put in the context of the effects of caloric restriction and called “mitochondrial hormesis”, or “mitohormesis”, in which mild stresses leading to ROS production can induce adaptive defense responses and stress tolerance. Paradoxically the ROS thereby appears to extend lifespan and to reduce age-related pathologies such as neurodegenerative disorders and cardiovascular diseases in cellular and animal models.

A balanced setup of such a system is very important. If mitophagy is too active, the cell runs the risk of running out of ATP. If mitophagy is insufficient, the preservation of damaged mitochondria can lead to an excessively high rate of production of active radicals, which can trigger either controlled apoptosis of the entire cell, or, in the worst case, unprogrammed cell death. Fine-tuning the interactions of antioxidant response, mitophagy, and apoptosis involves various signaling pathways, such as NFkB. Deregulation of such interactions can lead either to certain types of cancer when the cell does not die in time, or, conversely, to premature cell death in neurodegenerative diseases.

3. Parkinson’ Disease Model

The ROS management network contributes a disease module56,57 to disease maps such as that of Parkinson’s disease, which show how most features of disease are known to be connected [4]. Affecting 1–3% of the population over 65 years old, Parkinson’s disease is characterized by symptomatic motor dysfunction and alteration of the mood/reward system due to lack of dopamine secretion by dopaminergic neurons.

Figure 3: Characteristic of Parkinson’s disease patients. Tremors.

Parkinson’s disease (PD) is a multifactorial disease; it has been associated with diverse genetic and environmental factors. We have developed computer model of ROS biosynthesis on PD counting key molecular parameters. The model was parameterized using independently obtained experimental data from Maastricht University (MA, Maastricht, the Netherlands) and the University of Milano-Bicocca (Milan, Italy) and adapted to personalized therapy of Parkinson's disease. The mathematical model was described in (Kolodkin et al, 2020) [4] and is freely available on FAIRDOMHub (https://fairdomhub.org/models/571 ?version=1), with more than 2000 downloads and views already.

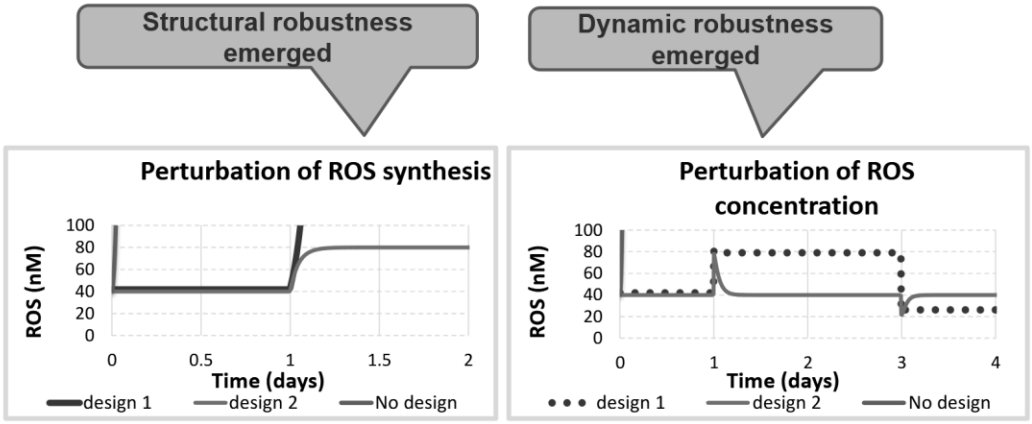

Figure 4: Emergency of structural and dynamic robustness in the Parkinson’s disease mode [4]. The panels show perturbation of ROS biosynthesis and perturbation of ROS concentration by time

The model could be designed and validated using online bioinformatics tool COPASI. Lett's consider test example. There is continued synthesis of Healthy Mitochondria. Healthy Mitochondria get older and are turned into Impaired Mitochondria. Impaired Mitochondria produce ROS. Mitochondrial aging is catalyzed by ROS (positive feed-back). ROS are quenched by antioxidant machinery and Impaired Mitochondria are removed in mitophagy (mitoptosis) with the help of p62 and Parkin proteins. The model will show an increase of ROS synthesis results in a proportional increase of ROS concentration (no homeostatic adaptation). To model homeostasis, we add the nrf2-keap1 system (pink) that is activated by ROS and regulates p62 and antioxidants' concentration (see Figure 2, see also Supplements to [4] for the details).

The created model allows us to "calculate" the aging process in silico and establishes a link between aging and various factors involved in the accelerated death of dopaminergic neurons in the development of Parkinson's disease, such as a lack of DJ-1 protein (encoded by the Park7 gene) and increased polymerization of α-synuclein. Moreover, our model allows us to calculate the coefficient of aging time control to assess the contribution of various molecular processes to the rate of aging, which creates the prerequisites for the development of personalized therapy for Parkinson's disease [5].

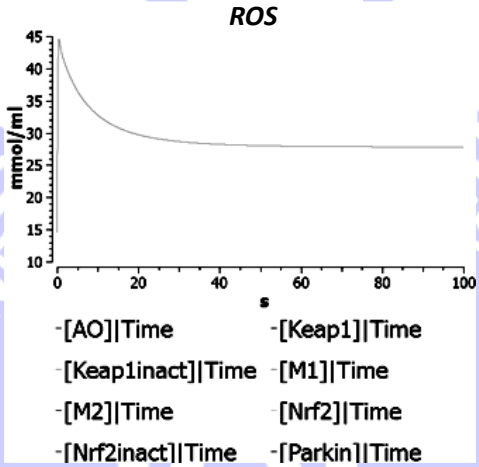

Figure 4: Concentration of transcripts level at PD by the model devoled

The dynamic model represents the development of a gene network of gene interactions in Parkinson's disease [6]. Using the on-line bioinformatics tools OMIM, PANTHER, g:Profiler, GeneMANIA, and STRING-DB, we have analyzed the current array of data related to Parkinson's disease, calculated the categories of gene ontologies for a large list of genes, visualized them, and built gene networks containing the identified key objects and their relationships [6].

Figure 5 presents graph of gene and protein interaction reconstructed for Parkinson's disease genes using GeneMANIA tool. In the center of the reconstructed network structure are genes (proteins) that have a large number of connections with other elements - SNCA, CASP3, GFRA1, HTT, PARK7 (Figure 5).

This trend is supported by current studies of candidate gene associations, in which the most statistically significant signals associated with Parkinson's disease are common variants located close to SNCA, LRRK2 and MAPT, as well as low-frequency coding variants in GBA. SNCA gene encoding α-synuclein is pleiomorphic, and both rare mutations and common variations in this locus change the risk of developing the disease.

Similar modeling approach was applied to other complex diseases such as metabolic syndrome, glioma, schizophrenia [7]. Reconstruction of gene networks underlying molecular mechanisms of gene expression regulation in complex diseases may help find new targets for therapy. Analysis of common genes in the networks for different diseases allows to find connections between different diseases, describe their statistical properties.

To find new gene-targets for diagnostics and therapy we have to reconstruct gene network of the disease, to cluster genes in the network, to reveal key (hub) genes with largest number of interactions in the network. Studying the association of gene function, diseases, and regulatory gene network reconstruction demands data compatibility. Data from different databases follow distinct schemas and are accessible in heterogenic ways [8] demanding database integration. Set of available online bioinformatics tool allow model the disease parameters to search for new targets for therapy.

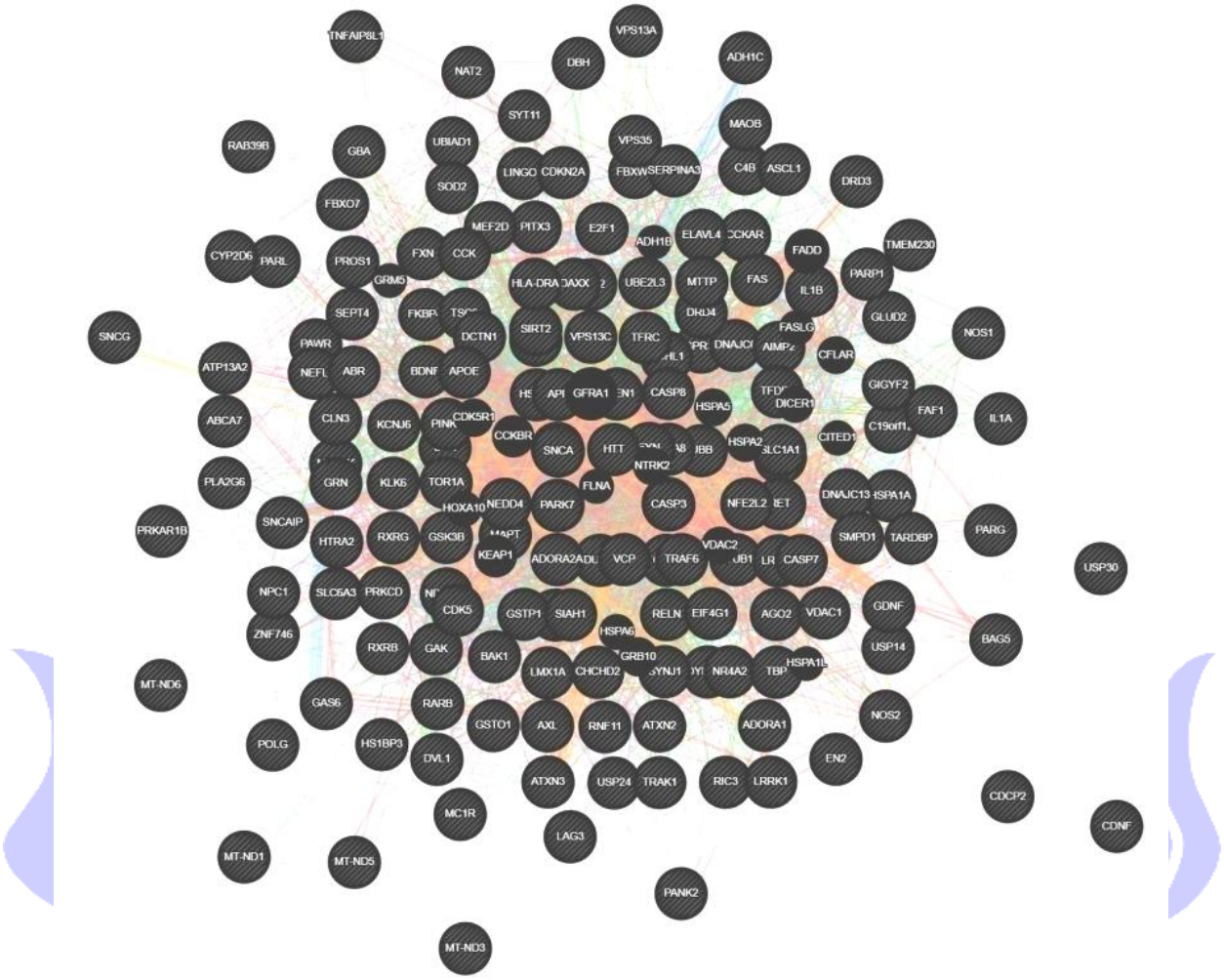

Figure 5: Interaction network for Parkinson's disease genes.
Computer reconstruction was done using GeneMANIA online bioinformatics tool.

In generalization to complex aging diseases problems, note that genetic and epigenetic changes, oxidative stress and inflammation influence the rate of aging, which diseases, lifestyle and environmental factors can further accelerate [9]. Different theories have been proposed to explain the pathogenesis of accelerated aging, including genetic theory, the multi-proteinopathies theory and mitochondrial theory. Genetic theory assumes the accumulation of DNA mutations and/or gene dysregulation. It considers random DNA changes but ignores chromosomal, multifactorial and monogenic alterations. The multi-proteinopathies theory is based on the accumulation/aggregation of misfolded proteins leading to cell dysfunction and causing age-related diseases. The free radical theory considers oxidative damage to DNA and proteins by reactive oxygen species (ROS) as the primary accelerator of aging.

In addition to practical biomedical significance, our mathematical model describing the intracellular control system for the concentration of active radicals clearly demonstrates how the reconstruction of the emergent properties in silico of this system, which is too complex for intuitive understanding by the "naked brain", can help to understand the principles of the design of this system.

4. Conclusion

We may conclude that goal setting as a system-forming factor is important in the mathematical model design. A mere focused medical specialization and standardization, the lack of a holistic, systemic view of the human body, leads to a deadlock in the further development of modern medicine. P.K. Anokhin's functional systems theory

(1935) made a breakthrough in medical science, setting it in a new direction. So far, however, the fundamental aspects of this theory have not been fully applied in practice [3]. Using modern approaches of Artificial Intelligence based on integration of data will extend the application of computer modeling in biomedicine [10].

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