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HOW CAN WE CHANGE THE NETWORKS WITHIN AND AROUND OURSELVES?

(Inauguration lecture as a member of the Hungarian Academy, 2014)[1]

Introduction

When preparing for this lecture I received a lot of letters from my friends. They did not wish me good luck, but wrote messages like this: '*Dear Peter, as I know your mother was an actress, actually the best of her time, so I think that it will not be difficult for you to speak to this audience*.'

Ladies and Gentlemen! Dear Mr. President of the Biology Section of the Academy! Dear Mr. Former President of Hungary! Dear Mr. Vice-Presidents of the Academy! Dear Mr. Secretary General of the Academy! Dear Mrs. Deputy Secretary General of the Academy! Dear Mr. Bishop! Dear Classmates in the Biology Section! Dear Friends!

Now, standing in front of You, I realized that the writers of these letters were clearly wrong. Having listed all above, looking at this audience of hundreds of a people it is very difficult to start a lecture. That is why I have decided to tell you three stories before my inaugural lecture on network research. These three stories are all about the beauty of science.

Zinc dipping from the ceiling to the test tube: You should never give up!

My first story started in 1985, when I learnt at Antal Martonosi in the USA how the intracellular concentration of calcium can be measured. Then I brought this quite modern measurement method back home to Hungary. During almost a whole year not a single piece of my results in the USA could not be reproduced in Hungary. In capitalism it was possible to measure calcium concentration, while in socialism it was not possible to measure calcium concentration. I was very disappointed. At that time I believed that this measurement would have been my future, because I would have become the 'calcium measuring Hungarian'. My exasperation lasted until we measured the calcium content of distilled water as a control measurement using plasma emission spectroscopy. As expected, there was no calcium in the distilled water. However, for my BIG surprise it turned out that the distilled water in our laboratory contained micromolar concentrations of zinc, even though no zinc should have been in distilled water at all. After an intensive investigation I found it out that the ceiling of the laboratory was coated with a paint containing zinc oxide. This paint in a form of invisibly small grains fell into the distilled water. Zinc oxide was dissolved in water, and inhibited calcium binding. No wonder that my American results could not be reproduced in Budapest!

A series of targeted tests were followed from this surprising fact, ending up in the finding that zinc ions take part in the signal transduction of T lymphocytes.[2] Recently it was also found that zinc plays a significant role in signal transduction of neurons, i.e. lymphocytes and neurons

[1]The Hungarian version of this text was published by the Hungarian Academy of Sciences in 2014. ISSN: 1419-8959, ISBN: 978-963-508-717-4.

[2]Csermely, P. − Fodor, P. − Somogyi, J. 1987. The tumor promoter tetradecanoylphorbol-13-acetate elicits the redistribution of heavy metals in subcellular fractions of rabbit thymocytes as measured by plasma emission spectroscopy. *Carcinogenesis* 8: 1663−1666.

resemble each other from this point of view, too. As a rather usual situation that happens in case of surprising results, the papers we published at the end of the 1980's on this phenomenon, have reached an increasing citation in the past ten years.

The take home message of my first story is that you must never give up. This saying of the Dalai Lama is hanged on the wall at a central place at our home as the major motto of my family. The saying *'Never give up!'* applies not only to the persistence of scientific research, but human life as a whole, too. Intensive happiness can be reached only, if we do not become disappointed by the failures, if we do not feel self-pity, and make others to feel sorry about us, but if we keep our faith and we never give up.

An unexpected spot in the control test: Achievements should never be badly wanted but have to be accepted

My second story is from the beginning of the 1990's. At that time I was working with C. Ronald Kahn at Harvard University, where my task was to put isolated insulin receptor together with another isolated protein, the 90-kDa heat shock protein (Hsp90) in a test tube, and to examine, whether the heat shock protein was phosphorylated by the insulin receptor.

I isolated the proteins, put them together, and went to my boss, Ron very proudly to report that the test was successful. The heat shock protein was really phosphorylated by the insulin receptor. That was the very moment in my scientific career that I will always remember. Ron answered me the following: '*Peter, this is a nice finding. This test really shows that the heat shock protein was phosphorylated. But what is this spot at the edge of this autoradiograph? This should be the control. This should be the heat shock protein itself. Has it phosphorylated itself as well? Haven't you noticed this, Peter? This is the real surprise! Not what you have just reported!'* This was, how should I say... an extremely memorable message – for life.

Ron's finding prompted me to work hard during the following year. It turned out that the 90-kDa heat shock protein (Hsp90) had an adenosine triphosphate (ATP) binding site, which was able to phosphorylate itself and other proteins. ATP played an important role in the function of this heat shock protein.[3] Later on it also turned out that this was the N-terminal ATP-binding site, and this protein had an other ATP binding site at its C-terminus. The C-terminal binding site was discovered by my former student and friend, *Csaba Sőti*.[4] The discovery of these two binding sites was very important and interesting, because these were ATP-binding sites having totally new structures. Therefore, their existence had to be examined and proved with totally non-conventional tools. Due to the new binding site structure it is not surprising that both of these ATP-binding sites led to the development of new type cancer drugs that already are being used in clinical practice.

The take home message of my second story is that achievements should never be badly wanted, but have to be accepted. This is a message again that goes far beyond what we are doing in scientific research; it applies to our whole life. If we live our lives with a desire to possess everything, which is within our reach, there will be not enough time for us to notice those

[3]Csermely, P. − Kahn, C.R. 1991. The 90-kDa heat shock protein (hsp-90) possesses an ATP binding site and autophosphorylating activity. *J. Biol. Chem.* 266: 4943−4950; Csermely, P. − Kajtár, J. − Hollósi, M. − Jalsovszky, G. − Holly, S. − Kahn. C.R. − Gergely, P. Jr. − Sőti, Cs. − Mihály, K. − Somogyi, J. 1993. ATP induces a conformational change of the 90-kDa heat shock protein (hsp90). *J. Biol. Chem.* 268: 1901−1907.
[4]Sőti, Cs. − Rácz, A. − Csermely, P. 2002). A nucleotide-dependent molecular switch controls ATP binding at the C-terminal domain of Hsp90: N-terminal nucleotide binding unmasks a C-terminal binding pocket. *J. Biol. Chem.* 277: 7066−7075.

miracles that life provides us for free. This is an extremely important message for people living in Western societies and having a dominancy of their left cerebral hemisphere of logical thinking leading to a (too-much) goal-oriented life.

An unexpectedly exciting book: A combination of distant fields is needed for real creativity

By the year of 1998 we were aware of the fact that the 90-kDa heat shock protein (Hsp90) had not only one protein neighbor, e.g. the insulin receptor of my previous story, but at least a thousand ones. In 1998 an article was published that made me thinking a lot. *Susanna Rutherford and Susan Lindquist* published in Nature that 90-kDa heat shock protein (Hsp90) was able to regulate the speed of evolution.[5] Even at that time I was absolutely positive (though it has not happened yet) that for this finding sometimes later they will receive the Nobel Prize. I consider this article a groundbreaking discovery, since it showed the first molecular mechanism of regulating the speed of evolution. We had not have the faintest idea, how this might happen before this paper. However, this publication is groundbreaking for another reason, too. It discovered a fully novel type of regulation that does not work in the usual way of protein 'A' regulates protein 'B', but in a way that hundreds or thousands of proteins regulate one phenomenon together.

From 1998 I was thinking on this problem for months and years. How could those thousand proteins regulate only one effect e.g. the speed of evolution? Which method can be suitable to examine that how a thousand proteins interact with each other and how these millions of interactions result in a single outcome?

Hungary is a very lucky country. We are very lucky, because we are small. As Hungary is such a small country, there are only a very few experts working in the very same professional field as yours. For example there is hardly anyone in this country dealing with heat shock proteins except for the laboratory of my friend, *László Vígh* and ours. That is why if a Hungarian scientist would not like to get bored very soon; he should talk to such colleagues, who apparently have nothing to do with his scientific field. I am very lucky that *Tamás Vicsek* is one of my friends. So I have asked Tamás among a lot of others about what method can describe only one effect of a thousand proteins. Tamás has drawn my attention to the book of *László Barabási*, titled *'Linked'*[6]. (It is my pleasure that Laci could come here today, and he seats in the audience.) The book *'Linked'* opened a new world for me. To say it in another way: Laci linked me forever. His book showed me that network research provides us with a set of tools with which the question of "How a thousand proteins can have one common effect?" can be answered.

It became a very precious, lifelong experience for me that scientists representing very different professional fields can give very substantial ideas to each other. My own network science team (www.linkgroup.hu) is also such a multi-disciplinary group of professionals. I would like to cite Poincaré who wrote in his book on the methodology of mathematics published more than a hundred years ago[7] that real creativity can be borne from a combination of very different disciplines. So the approach that you try to link scientific ideas apparently having nothing in common can be quite fruitful.

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[5]Rutherford, S.L. − Lindquist S. 1998. Hsp90 as a capacitor for morphological evolution. *Nature* 396: 336−342.
[6]Barabási, L. 2002. *Linked*. Perseus Book Group.
[7]Poincare, H. 1908. *The foundations of science*. Science Press, New York.

How similar are the networks inside and around us?

During the past 15 years it became clear that real world networks have a lot of common properties.[8] This statement is shocking because it does not really matters what complex system is described by the network, be it the structure of one protein, protein-protein interactions, inter-cellular networks, like our brain, or the whole human society. These networks are all small-worlds, i.e. their nodes are linked to each other with very short paths. In every network there are hubs, i.e. nodes, which have significantly more edges than other nodes of the network. Similarities help us draw the important conclusion that we should learn from biological networks when thinking about our own life. The reason for this is that biological networks have been learning for three billion years. Humans have not gained such a huge amount of experiences during their limited development (especially, if we consider the million-fold additional difference in the number of generations) that a biological network has already encoded to its structure during the billions of years.

How do networks inside and around us change: what does a yeast cell know that we, humans do not know?

In the next part of my lecture I would like to share three observations with you, which may respond to the question: "How do networks inside and around us change?". The first network adaptation mechanism was found by my friend, *Ágoston Mihalik*.[9] (Ágoston was an undergraduate MD student at the time, when he made this discovery. Currently he does his PhD in the UK.) With Ágoston we examined the protein-protein interaction network of yeast cells at rest and after stress. In case of yeast rest means an extremely high speed of proliferation (it is when yeast runs out of the jar). It is very easy to stress a yeast cell, since it perceives practically every change as stress: if I make it warmer, cooler, if I give more or even if less food to it, etc. The protein-protein interaction network of yeast cells at rest is a protein factory that produces the material of the proliferating yeast cells. In the protein-protein interaction network of quickly proliferating yeast everything is subordinated to this task. Consequently, the middle of the network is occupied by the ribosomal protein complex that is responsible for the synthesis of the new proteins.

How does this protein-protein interaction network change as a result of stress? Ribosome and all related proteins lose their importance. In stress conditions a massive amount of protein synthesis is not necessary anymore, and is not possible either, because the cellular energy becomes very limited. At the same time in stress a lot of functions become very important that help the yeast cell survive. During stress the functions helping survival are arranged in the protein-protein interaction network in a way that those proteins coding survival functions are getting connected very tightly and permanently with each other. In the network language we can say that network modules (i.e. network groups corresponding to protein complexes) become very dense and very cohesive as a response to stress. In non-stressed yeast cells the very same network modules have large overlaps, and are much less distinguishable from each other.

The summary of my first example is that as a result of stress the groups of yeast protein-protein interaction network dissociate, and become more separated from each other. This change is a general response also characterizing our social behavior in crisis conditions. In case of a social

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[8]Csermely P. 2005. *A rejtett hálózatok ereje*. Vince kiadó; Csermely P. 2009. *Weak links*. Springer Verlag, Heidelberg.

[9]Mihalik, Á. − Csermely, P. 2011. Heat shock partially dissociates the overlapping modules of the yeast protein-protein interaction network: a systems level model of adaptation. *PLoS Comput. Biol.* 7: e1002187.

crisis there is a strong intention in the society to 'team up'; a kind of automatic answer of 'let at least our small team join forces'.

However, there is a crucial part of crisis-management that yeast knows, but we humans do not seem know (at least here, in Hungary). Yeast knows that in crisis one of the most important tasks of survival is to keep the connections between distant groups. Moreover, it is in time of crisis, when new links have to be created among the distant groups. In line with this we found with Agoston that in case of stress a lot of proteins become up-regulated in yeast cells that link protein complexes, which are otherwise very far from each other in the protein-protein interaction network. In case of social crisis this solution is (sadly) rare. If we want to survive the crisis situations awaiting us in the 21st century, it is crucial to learn the lesson of biological networks to change our own behavior patterns.

How do networks inside and around us change: alternating network plasticity and rigidity

The second network adaptation mechanism I mention today involves two very different complex system states. One of the complex systems is plastic. This kind of system is so soft, like this coat I am wearing right now. This coat has the characteristic of being able to adapt the shape it is put on. It is adapting to my shape at the moment, but if I dropped it down on the ground (do not worry, I will not do so...) it would adapt to the shape of the floor. It means that such a soft, plastic system is capable of quick adaptation. This advantage is its disadvantage at the same time, because if it is totally plastic, it cannot do anything else except for adaptation.

The other complex system resembles to this academic pulpit in front of me. Such a rigid system cannot adapt itself at all. The academic pulpit fixed its shape at an optimum status. It serves to give an inaugural lecture holding my hand and this computer. The academic pulpit is suitable for performing only these tasks. But the academic pulpit is very good at these limited functions, because it remembers the optimal solution of these tasks during its whole lifetime. The biggest advantage of rigid systems is that they have a very efficient memory, so they preserve the characteristics what they once have learnt. On one hand, rigid systems also have the significant disadvantage that they cannot change their optimal behavior, i.e. they are not capable of adaptation. On the other hand, plastic systems have the advantage of being able to adapt, while having the disadvantage of not having a memory of rigid systems to preserve the results of adaptation.

The duality of rigid and plastic systems was formulated by neuroscientists as the 'stability plasticity dilemma' about ten years ago.[10] When in May, 2012 I spent a month at the Serbelloni Palace in Bellagio as a guest of the Rockefeller Foundation, during writing a review[11] I started to have such thoughts that this plastic/rigid behavior can be applied not only for our brains but for all other complex systems, too. In the last two years we published a number of papers describing this hypothesis.[12] In the meantime it became also increasingly clear that complex systems can

[10]Mermillod, M. − Bugaiska, A. − Bonin P. 2013. The stability-plasticity dilemma: investigating the continuum from catastrophic forgetting to age-limited learning effects. *Front Psychol*. 4: 504.
[11]Gyurkó, D. − Sőti, C. − Steták, A. − Csermely, P. 2014. System level mechanisms of adaptation, learning, memory formation and evolvability: the role of chaperone and other networks. *Curr. Prot. Pept. Sci.* in press, preprint: http://arxiv.org/abs/1206.0094.
[12]Gáspár, E.M. − Csermely, P. 2012. Rigidity and flexibility of biological networks. *Briefings Funct. Genomics* 11: 443−456; Csermely, P. − Korcsmáros, T. − Kiss, H.J.M. − London, G. − Nussinov, R. 2013. Structure and dynamics of biological networks: a novel paradigm of drug discovery. A comprehensive review. *Pharmacol. Therap.* 138: 333−408.

change their rigid/plastic status. During a change from rigidity to plasticity their capacity of learning increases. In the reverse condition turning from plasticity to rigidity, their capacity of selection and encoding the optimal behavior (their memory) increases. A complex system can only adapt to the changes of its environment optimally, if it is able to change itself to both directions. From plastic it turns to rigid, and then from rigid to plastic. Complex systems very often repeat these plasticity/rigidity cycles several times.

In the following part of my lecture I will present three examples of the differences between plastic and rigid systems. The first one is the example of proteins. Protagonists of the example are those molecular chaperones, heat shock proteins that I have already mentioned in my second story. Chaperones help other proteins to fold. How do they help this process? One class of them expands unfolded (or misfolded) proteins. Another class 'sits on' unfolded proteins and extends their peptide backbone. The key action is the same. When chaperones expand or extend unfolded proteins (using the energy of adenosine triphosphate), the unfolded protein becomes more rigid. After the extension step, molecular chaperones release the unfolded protein. During the release-phase the unfolded protein becomes more plastic, and it has a new chance to find its unique native structure from the zillions of possible states. This pull/release (rigidity/plasticity) cycle is repeated many times. If the unfolded protein could not find its native state after the first circle, i.e. it has not succeeded in reaching an optimum network in this single rigid → plastic alternation, the molecular chaperone starts the cycle again.[13] In summary: assisted protein folding can be recognized as a series of plastic → rigid network changes. As a result of this process unfolded proteins have new and new chances to find their globally optimal structure, their native state.

In mathematics the simulated annealing optimization process is generally conducted in a way that the system is warmed up only once (obviously 'warming up' here is only theoretical) and after that it is cooled down only once. If we extend this optimization procedure to multiple cycles, where cooling and warming steps are following each other, the global optimum can be found more effectively than, if we did this thermal cycling only once.[14]

My second example is about cancer stem cells. More and more experimental results prove that the type of cell that is mostly responsible of cancer and metastasis development, called cancer stem cell, has alternating plastic and rigid networks.[15] We have the major problem here that the majority of drugs curing cancer are effective either against the rigid or the plastic network of cancer stem cells. Unfortunately cancer stem cells can easily avoid these anti-cancer therapies, because they can alternate between their rigid and plastic states. These changes are mostly caused by the rigidity and plasticity changes of cancer stem cell networks due to the changes of the environment. A combination or multitarget therapy, where drugs target both plastic and rigid network states may be a very promising way to fight against cancer stem cells.

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[13]Csermely, P. 1999. The "chaperone-percolator" model: a possible molecular mechanism of Anfinsen-cage type chaperone action. *BioEssays* 21: 959−965; Tompa, P. − Csermely, P. 2004. The role of structural disorder in RNA- and protein chaperone function. *FASEB J.* 18: 1169−1175.

[14]Möbius, A. − Neklioudov, A. − Díaz-Sánchez, A. − Hoffmann, K.H. − Fachat, A. − Schreiber, M. 1997. Optimization by thermal cycling. *Phys. Rev. Lett.* 79: 4297−4301.

[15]Csermely, P. − Hódsági, J. − Korcsmáros, T. − Módos, D. − Perez-Lopez, A.R. − Szalay, K. − Veres, D.V. − Lenti, K. − Wu, L.Y. − Zhang, X.S. 2014. Cancer stem cells display extremely large evolvability: alternating plastic and rigid networks as a potential mechanism. Network models, novel therapeutic target strategies and the contributions of hypoxia, inflammation and cellular senescence. Seminars in Cancer Biology, being printed.

My third example for alternating plastic and rigid networks is our brain. In 2011 a very interesting article of Bassett et al[16] was published in PNAS, the proceedings of the National Academy of Sciences of the USA. They measured using the fMRI method how the brains of healthy human volunteers changed during a simple learning process imitating piano play. Results of the measurement were evaluated from the point of view of active neurons and their neighborhood. In this experiment plasticity of the brain was defined as the stability of the membership of active neurons in the groups of other active neurons. If during the learning process an active neuron left the group of active neurons it had been a member of earlier, and became a member of a new group of active neurons, the neuron was defined as plastic. If the active neuron did not leave their original group, the neuron was identified as rigid. During the learning process the number of rigid neurons increased. To make the take home message very simple (and hereby I would like to apologize from those members of the Academy dealing with neuroscience who have honored my lecture with their presence here today), I would say that during learning the brain becomes more rigid. Another exciting result of the same publication (and I am sorry again for the simplification) that people having 'rigid brains', were unable to learn efficiently. This simplified interpretation is obviously almost a commonplace but how great it is to know that this common knowledge (*'if your brain is rigid like a brick, you are unable to learn'*) can be proven from a network point of view.

The second part of my last example is how little birds learn to sing. Those engaged with ornithology (a large number of the biology class members love birds scientifically or as a hobby) know that the importance of learning to sing is especially large in case of male birds. It is because a male bird will hardly have a female partner, if he sings poorly. Thus, it is not a small issue for a young male bird to sing nicely. The article of Derégnaucourt and his colleagues published in Nature in 2005[17] showed that on the first day when the young male bird starts to find his female partner, and learns the very first song of his life, the quality of the song develops very rapidly during the day. By the end of the day the bird sings quite difficult trills. But what happens afterwards? During the night when the bird is sleeping he mostly forgets what he have already learnt. In the next day he has to start the whole process almost at the very beginning. Could be evolution so stupid that it has developed such inefficient birds? No! When the young male bird learns a song 'again', this song will not exactly be the same as the last day's song was, but it will be a better one. Then he forgets parts of this new song, and will learn even a better one again. Seeing this process it cannot be missed that the brains of young male birds most probably become more rigid when learning a new song, and then become more plastic during sleep. Knowledge of singing of a young male bird will be optimal only, if his brain repeats such rigid → plastic cycles at least twenty or thirty times.

The take home message of this example is that learning something once for life is not enough. If today we find the first idea of our lives and we insist to it, we will never have a second idea. If we consider our first idea as our property, and we are afraid of losing it, we will never have a better idea than this very first one was, because we will never be able to let our first idea go. This lesson is again very true not only in case of learning processes but for our whole life.

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[16]Bassett, D.S. − Wymbs, N.F. − Porter, M.A. − Mucha, P.J. − Carlson, J.M. − Grafton, S.T. 2011. Dynamic reconfiguration of human brain networks during learning. *Proc. Natl. Acad. Sci. USA*. 108: 7641−7646.
[17]Derégnaucourt, S. − Mitra, P.P. − Fehér, O. − Pytte, C. − Tchernichovski, O. 2005. How sleep affects the developmental learning of bird song. *Nature* 433: 710−716.

The network concept of creativity

The network concept of creativity is in close correlation with small birds' learning to sing and the rigid → plastic alternation of networks. If I asked someone in the room about what is creativity, he or she would probably say something like creativity is something, which is outstanding, interesting, new and surprising. If somebody is creative, he or she does something unexpected that is really new, extraordinary and original. Creativity very much correlates to playfulness, a plastic status of listening and reacting to lots of things. Farkas Bolyai in his book entitled *'The beginning of Arithmetic'* defined the power of playing as follows: *'Let the child play and grow at the first place: continuous teaching suppresses the power of growing and makes the mind so rocky and dead like a road.'*[18]

In the network concept of creativity a creative network node does not belong to a certain network group, but it changes its group-membership very dynamically.[19] It is impossible to miss that the creative node is exactly that plastic active neuron, which changed its groups of active neurons, and was the premise of learning in the previous example. Let me also refer to the Poincaré quotation mentioned earlier. A creative node collects pieces of knowledge during its wandering across distant network groups that are all coming from very different places, and that have been separated from each other so far. If the creative node now connects and summarizes these formerly distant pieces of knowledge, it will be able to create such solutions that are completely new, i.e. creative.

It is also important to note that not all kinds of creativity are useful. If a fork decides that it will not act like a fork any more, but instead its tines will look like a haystack, it could be a very playful act but I am not sure I would say it is creative because this fork became rather useless for eating. (Unless we use it as a stick at a Chinese restaurant or for scratching our head.) This behavior can rather be called rebellious or nonconformist than creative.

Thus, creativity is not only a plastic, playful behavior, where originality and unexpectedness are important but these features must be completed with quality, usefulness, tradition, so with a kind of rigid behavior to achieve creativity at its full sense. While plastic, playful behavior explores the possible solution methods, rigid behavior selects among the previously found methods and chooses the optimal one.

The dual nature of creativity can be summarized with the take home message that we do well in our lives, if we can be old persons on each even day and young ones on each odd day. This message is as important for the young men and women present here (meaning the 90 percent of the audience because it is the mental age what counts not the biological one) as for the elderly.

How can we change the networks within and around ourselves?

Getting close to the end of my inaugural lecture it is high time I answered the question mentioned in the title of my lecture, namely that *'How can we change the networks within and around ourselves?'*. I summarize my answer in three thoughts.

The main point of the first thought is that it is not at all indifferent when planning an intervention to change our network, that the network is plastic or rigid. We have to approach a plastic or a rigid network in a completely different way. Why? A plastic network, like this coat I

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[18]Bolyai, F. 1830. *Az arithmetika eleje*. Felső Visti Kali József, Marosvásárhely.
[19]Csermely, P. 2008. Creative elements: network-based predictions of active centres in proteins, cellular and social networks. *Trends Biochem. Sci.* 33: 569−576.

am wearing now, dissipates the effect it gets very quickly. On the contrary, in a rigid network effects do not disappear, but are transmitted very efficiently, and can get far away. Let me show you an example: as you can remember, I referred to the academic pulpit in front of me as a rigid network. If I knock on this pulpit, everybody can hear it in this room, because the effect I have had on this pulpit has not disappeared, and was not dissipated, since the pulpit is rigid. If I knock on my coat, nobody can hear it in the room. Believe me, I do not hear it either. The reason why we cannot hear my knocking on the coat is that the plastic network of the coat absorbs the energy of knocking immediately, because the network transforms knocking to heat, and it dissipates the effect.

Thus, if we would like to change a plastic network, we must not aim our action to its periphery. It is totally in vain to shoot the edge of this coat, since nothing on earth happens to the middle of the coat, because the coat is plastic, and the shooting effect does not reach its center. So the only solution for changing a plastic network is to hit its center as strongly and effectively as possible. This central-hit strategy is very important when designing drugs against rapidly proliferating cells.

Naturally, in case of a rigid network it is also perfect to hit its center, because if I manage to do so, it is sure that I can have an effect on the rigid network. There is only one problem with this solution, but that is a very big one. The rigid network will not dissipate my effect. It means that if I hit a rigid network in the very middle of it, I may radically overexcite it, and even destroy it. If the network is a human cell, and my intervention is a drug, when hitting the rigid cell network in the middle, I have to expect side-effects, and even toxicity, i.e. poisoning the patient. In a rigid network is much more adequate not to hit central network nodes but the neighbors of them. It is because by hitting the neighbors of central nodes I can affect these nodes in a way that the effect will be selective.[20] This network influence strategy is very important when designing drugs against the differentiated cells of human tissues.

Antibiotics are very good examples for affecting central nodes of plastic networks. Antibiotics affect those cells that as bacteria or parasites start to proliferate in the human body very aggressively. Networks of a rapidly proliferating cell are plastic, because such networks have to change continuously due to the changes of the cell cycle and the environment of the proliferating cell. The majority of the antibiotics work in a way that they hit a central node of the cellular networks. That is why antibiotics have a profound effect. The effect is so strong sometimes that the infectious bacteria or parasites, which can be characterized with plastic networks, (fortunately) die.

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[20]After my inaugural lecture my friend, Domokos Szász, a member of the Academy, approached me with the question that if hitting the nodes beside the central nodes how could the effect be significantly more selective than if I hit the network's central nodes themselves. The question is absolutely legitimate and at the same time it points at a very significant conceptual difference of approaches. In case of graphs used in mathematics the points of graphs do not have an 'identity', so we consider them completely similar. On the other hand nodes describing complex systems existing in nature (like cells) are not the same at all. This is the only reason why altering (e.g. with a drug) one of the neighbors of a central node (e.g. a protein) will activate only certain effects of the central node, but not all of them. If we hit the central node itself in the middle, we can also achieve some selectivity (because the structure of the node is not homogeneous), but this selectivity is regularly smaller than if we calculate with the complex structure of the neighbor, and the connection between the two nodes during the spread of the effect. Using a graph theory expression, each real network is a colored graph (actually a very much colored one...). This characteristic feature also shows how difficult is to design a good network influence strategy, because for this we need to know the two networks describing the detailed structures of the two interacting neighboring nodes, and we have to connect them. Fortunately the bioinformatics methods enabling these procedures are already available today.

Unlike bacteria, differentiated cells, e.g. the cells of different types of human tissues, are in a persistent environment in which they have learnt to work optimally. Thus, networks of differentiated cells are much more rigid than that of bacteria. No wonder that drugs targeting central nodes of these rigid networks often cause unexpected side-effects. Such drugs like rapamycin or the well-known aspirin, where the latter hits at least fifty targets at the same time, work in a way that they affect not exactly the very protein[21] that is involved in the disease the most, but they bind to a protein besides it.

The number of those drugs is rather low, where we surely know that they affect proteins besides the ones involved in a certain disease. This is due to the fact that the idea of allo-network drugs has been published only in 2011.

In recent years members of my LINK-Group developed a number of methods, which identify influential (but not necessarily always central) network nodes. These methods can be downloaded from our website. Influential nodes can be in the core of network groups, (www.modules.linkgroup.hu, a valuable work of *István Kovács*).[22] Influential nodes can very efficiently build or break network cooperation (in forms of spatial social dilemma games, like the Prisoners' Dilemma game; www.NetworGame.linkgroup.hu, made by *Gábor Simkó*).[23] We also have such a method (www.Turbine.linkgroup.hu, an excellent work of *Kristóf Szalay*)[24] that examines the spread of network signals and noises, altogether called perturbations. I will go into details of this latter method in the rest of my lecture.

Kristóf Szalay has developed the Turbine method package during the past few years. A part of this, called Designer finds such network node groups that if activated (or inhibited) at the same time, the complex system described with a network will be able to alter from its currently specific status to a desired other status. The significance of this method is that the current status can be an illness of a human cell and the desired status can be the healthy cell. It means that the Designer module of the Turbine program package is suitable for finding such drug target groups that, if influenced at the same time, a certain disease can be cured. More and more effective drugs turn out to be such 'multi-target' drugs.[25]

First I would like to present a simple model experiment in order to illustrate the effectiveness of the Turbine Designer program. My friend, Kristóf chose three proteins in the protein-protein

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[21]Nussinov, R. − Tsai, C.-J. − Csermely, P. 2011. Allo-network drugs: harnessing allostery in cellular networks. *Trends Pharmacol. Sci.* 32: 686−693.

[22]Kovács, I.A. − Palotai, R. − Szalay, M.S. − Csermely, P. 2010. Community landscapes: a novel, integrative approach for the determination of overlapping network modules. *PLoS ONE* 7: e12528; Szalay-Bekő, M. − Palotai, R. − Szappanos, B. − Kovács, I.A. − Papp, B. − Csermely, P. 2012. ModuLand plug-in for Cytoscape: determination of hierarchical layers of overlapping network modules and community centrality. *Bioinformatics* 28: 2202−2204.

[23]Simko, G.I. − Csermely, P. (2013) Nodes having a major influence to break cooperation define a novel centrality measure: game centrality. *PLoS ONE* 8: e67159.

[24]Farkas, I.J. − Korcsmáros, T. − Kovács, I.A. − Mihalik, Á. − Palotai, R. − Simkó, G.I. − Szalay, K.Z. − Szalay-Bekő, M. − Vellai, T. − Wang, S. − Csermely, P. 2011. Network-based tools in the identification of novel drug-targets. *Science Signaling* 4: pt3; Szalay, K. Z. − Csermely, P. 2013. Perturbation centrality and Turbine: a novel centrality measure obtained using a versatile network dynamics tool. *PLoS ONE* 8: e78059; Szalay, K. Z. − Csermely, P. 2013. [Method, processor-containing instrument and computer program to design interventions of complex systems] Hungarian patent application No. P1300737.

[25]Csermely, P. − Ágoston, V. − Pongor, S. 2005. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol. Sci.* 26: 178−182; Ágoston, V. − Csermely, P. − Pongor, S. 2005. Multiple, weak hits confuse complex systems: a transcriptional regulatory network as an example. *Phys. Rev. E* 71: 051909.

interaction network of yeast cells. He asked the Turbine Designer program what will be the dynamic status of this network after 15 steps of perturbation propagation. In the test presented here a yeast protein called CDC28 was affected by an impact of hundred thousand units, the GSY2 protein had an impact of fifty thousand units, and the SLT2 protein got an impact of eight thousand units. After having calculated the network status reached after 15 steps Kristóf kept only the information referring to this final status. After that he asked the Turbine Designer program, whether it could figure it out what initial impacts resulted in the exact final status after 15 steps of perturbation propagation. The Turbine Designer program gave the following answer to this question: such a final status occurs in case, if we activate only three proteins out of the total number of 2,444 proteins of the yeast's protein-protein interaction network, namely the CDC28 protein, the GSY2 protein and the SLT2 protein. So the program pinpointed all three activated proteins. Moreover, the program also pinpointed very precisely that how large initial impact has to be given to these proteins in order to reach the required final status. As a summary, the Turbine Designer program predicted with a 99.4 percent accuracy, that what impacts should be given to a complex system to reach a previously specified final status from its starting state.

We got very much excited by this result, which prompted us to examine quite a lot of systems that were closer to medical practice. One of these was a signal transduction network of a T cell leukemia. Not all signaling proteins are in this network, but only the proteins that play a significant role in leukemia development.[26] Our starting question was the following: if the initial network status is the actively proliferating (cancer) status of T lymphocytes after activation with the cytokine, interleukin-7, how can we reach the healthy target status in which lymphocytes will not proliferate rapidly? We asked the Turbine Designer program this question, and it suggested that the following three proteins should be changed: interferon-α1 and CD45 proteins have to be activated, and at the same time phospholipase-C-γ1 has to be inhibited in order to enable T lymphocytes to get from the rapidly proliferating (cancer) status into the inhibited (healthy) status. A very interesting lesson of this simulation was that when we studied the results published in the medical literature it turned out that the same effects of activating interferon-α1 and inhibiting phospholipase-C-γ1 that our simulation resulted in, have already been experimentally confirmed earlier.[27] It was even more exciting that *after* having the simulation results, an article was published describing a similar effect of experimentally activating CD45.[28] A very interesting lesson of our tests is that having the suggested three interventions at the same time, simulation showed that cancer cells did not only stopped proliferation but also the mechanism of their programmed cell death (apoptosis) was activated. As apoptosis 'packs' the dying cells, and unlike other forms of cell death e.g. necrosis, it does not cause inflammation. Thus, the drug intervention designed by Turbine Designer may have one of the most possibly useful effect.

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[26]Zhang, R. − Shah, M.V. − Yang, J. − Nyland, S.B. − Liu, X. − Yun, J.K. − Albert, R. − Loughran, T.P. Jr. 2008. Network model of survival signaling in large granular lymphocyte leukemia. *Proc. Natl. Acad. Sci. USA* 105: 16308−16313.

[27]Goldstein, D. − Laszlo, J. 1988. The role of interferon in cancer therapy: a current perspective. *CA Cancer J. Clin.* 38: 258-277; Sala, G. − Dituri, F. − Raimondi, C. − Previdi, S. − Maffucci, T. − Mazzoletti, M. − Rossi, C. − Iezzi, M. − Lattanzio, R. − Piantelli, M. − Iacobelli, S. − Broggini, M. − Falasca, M. 2008. Phospholipase C-gamma-1 is required for metastasis development and progression. *Cancer Res.* 68: 10187−10196.

[28]Porcu, M. − Kleppe, M. − Gianfelici, V. − Geerdens, E. − De Keersmaecker, K. − Tartaglia, M. − Foà, R. − Soulier, J. − Cauwelier, B. − Uyttebroeck, A. − Macintyre, E. − Vandenberghe, P. − Asnafi, V. − Cools, J. 2012. Mutation of the receptor tyrosine phosphatase PTPRC (CD45) in T-cell acute lymphoblastic leukemia. *Blood* 119: 4476−4479.

Conclusions

The scientific part of my inaugural lecture has three take home messages. The first is that cyclic alterations of network rigidity and plasticity seem to be a very important adaptation mechanism occurring generally in nature. The second key statement is that plastic networks require a hit at their central nodes, while rigid networks should be affected at the neighboring nodes of their central nodes in order to have an intervention, which is effective and gentle at the same time. Finally, it is also an important lesson that network intervention points like drug targets can be well predicted with simulation methods.

In academic inaugural lectures a lot of speakers present numerical data of their own scientific work: impact factors, quotations and things like that. I will present only one numeric description of my work, namely how many letters per year I have written since 2000 when my academic nomination was first arisen. The average number of letters (postal and e-mail) was five thousand per year but there were some years when the number of written letters increased up to fifteen thousand. In these years I participated in the organization of world congresses and the Hungarian Talent Support Network, involving more than 200,000 people in the Carpathian Basin today. In case Mr. President of the Biology Section is still going to hand over to me that green barrel containing my certificate of being a so-called corresponding member of the Hungarian Academy of Sciences that he has put here on the table next to me, I can assure him that with the total of 141,595 letters I have written in the past 14 years, I have surely fulfilled the legitimate requirements towards corresponding members of the Academy at least regarding *correspondence.*

I close my lecture with a quotation of *Khalil Gibran*: *'Work is love made visible'*.[29] This sentence has become my life motto. Up to now four interpretations of this sentence have come to my mind. I would like to share them with You. The first interpretation is a synonym of the flow theory of *Mihály Csíkszentmihályi*[30]. In this respect work makes love visible in a way that the working person feels an immense joy to get united with his work. During this process he discovers new values in himself revealed by his work. According to this first interpretation "work is love made visible" means loving work, loving ourselves and loving all moments of the present. This is a very important and necessary starting point.

The sentence of *'Work is love made visible.'* has a second interpretation, which goes much beyond the first one, and which was given a central role in the original description of Khalil Gibran. During working if we think of not only ourselves but of those many generations that will benefit from our work in the future, and if we love not only the passing moments but those coming generations as well so that we do our best when working wholeheartedly in order to please them with our results, then I believe we have learnt even more of why it is worth living.[31] According to

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[29]Gibran, K. *The prophet.* 2011. Martino Fine Books.

[30]Csíkszentmihályi, M. *Flow: The psychology of optimal experience.* 2008. Harper Perennial Modern Classics.

[31]The story of my friend, *Ágnes Tátrai* highlights a very important part of this thought. Father of Ágnes used to say the following when she was a little girl: '*My dearest daughter, keep on learning because otherwise you will become a street sweeper!*' However, the warning of the father did not end here but it went on like this: *'If you become a street sweeper, my daughter, it is not a problem, but in this case you should clean the street so that if you turn back and look at the work you have accomplished, you should be satisfied with your work.'* The message of this profound wisdom impressed me very deeply, because a nicely swept street will give love for the future pedestrians, whom the street sweeper surely does not know personally. A slice of buttered bread can be prepared in two ways. If you include your love you feel for the person you are preparing the bread for, it turns this simple slice of bread a real miracle. However, if you do not put your love in, the bread and butter can be both very good but it is all in vain, because it will never be a real slice of buttered bread. Let me quote from the short story of István Örkény titled 'Paprika wreath' as the third and last example: *'If we stitch a lot of cherry-paprika on a string they become a paprika wreath. If we do not stitch them on a string they will not be a wreath.*

the second interpretation of the sentence 'love made visible' means the love of others in the future manifested by the results of our today's work. This is a very important point, a way of expanding our Self to the future generations.

Ladies and Gentlemen! I reached this point of thinking about three months ago. These couple of months that have passed since then enlightened two more interpretations of the sentence, *'Work is love made visible.'* According to the third interpretation of the sentence the "love made visible" is the love we have ever been given by others. At the first place by our families, by those, who love us the most, and for whom we live making our lives a beautiful miracle. However, the love given by our closest loving family is also partially coming from a wider group of people. Love that we can make visible during our work is fed not only by the love we have ever been given but by the love that all our ancestors and friends have ever been given and passed to our ancestors, friends and ourselves. So according to the third interpretation of love made visible, it is the love of our loved ones, and love in our own past and in the common human past feeding our past, the ancient and conserved love rooted in our traditions and culture that we can pass over to other people by our work. This is the very important point making the present, future and past a complete circle – or an almost complete one.

However, the *'Work is love made visible.'* sentence has a fourth, and even wider interpretation, too. On the occasion of an academic inaugural lecture such an interpretation can be rarely heard but my thoughts were not complete, if I would not share this fourth interpretation with You. Love around us, flowing on us is not only human love but *Divine love*, too. If we can be united with the Whole World, if we can feel the highest splendor of the Whole World, compared to us being so tiny little, and its Divine love accepting us, then we are really able to pass Love to others through our work or through any moment of our existence. This fourth interpretation help us really understand the deepest sense of the sentence of Khalil Gibran: *'Work is love made visible.'*

Acknowledgements

At the end of my academic inaugural lecture first I would like to express my special thanks to those who have proposed me to be a correspondent member of the Academy since 2003: *László Barabási, Anna Erdei, Gábor Fekete, László Fésüs, Tamás Freund, Péter Friedrich, László Gráf, János Podani, Tamás Pócs, György Székely, Tamás Vicsek* and, last but not least, *László Vígh*. I would like to commemorate the late Péter Friedrich, a former member of the Academy. It is my greatest pleasure that his wife, *Rika* is here with us today.

My teachers and masters deserve special appreciation: *László Holics, János Somogyi, C. Ronald Kahn, Anthony Martonosi and Ernő Varga.* It is a great pleasure to me that László Holics, who was my teacher of physics at the Apáczai Csere János Secondary School, and who celebrated his eighty-third birthday yesterday, could come here today to be with us.

I am very happy about it that I could share the joy of scientific research with a lot of colleagues in the past many decades. Let me name a few of them: *Alper Arslan, Miklós Antal, Adorjan Aszalos, Csaba Böde, Swati Chatterjee, Balázs Dancsó, László Dénes, Tibor Fábián, Péter Gergely Jr., Beatrix Gilányi, Barry Goldstein, Philip Grimley, Judit Hargitai, Jossi Meyerovitch, Ágoston Mihalik, Katalin Mihály, Nguyen Minh-Tu, Gábor Nardai, Robin Palotai, Diána Papp, Eszter Papp, Bálint Pató, Zoltán Pénzes, Ákos Putics,*

Even if the amount of paprika is the same and all are the same red and hot. But still they are not a wreath. Is it only the string that makes a wreath? It is not the string. As we know string is a marginal, third-rate thing. So what makes a wreath? The one who thinks this over and takes care of his thoughts do not wander here and there but stay in track, may find big truths.'

Attila Rácz, Márta Szamel, Sándor Tóth, Mario Saad, Tamás Schnaider, Steve Shoelson, Ken Siddle, Csaba Sőti, Zoltán Spiró, Amere Sreedhar, Attila Steták, Ildikó Szántó, Tibor Vántus, Sándor Varga and Giacomo Zoppini.

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Last but not least I would render my warm thanks to the members of my current work team. It is named 'LINK' (translated to 'fink' in Hungarian; www.linkgroup.hu; where the name does not refer to our work ethic but our rich network connections) counts more than a hundred members. From the hundred I am going to list the names of those 48 people who are participating in our current work the most actively and that is why their names are listed on our website at the time of my lecture: *Gergely Antalfi, Tom Chaturapruek, Lisa Beatrice Caruso, Dávid Fazekas, Iván Fekete, Bánk Fenyves, Merse E.Gáspár, Máté Gulyás, Péter Gyuris, Dávid Gyurkó, János Hódsági, Franck Kalala Mutombo, Huba Kiss, Tamás Korcsmáros, Máté Kormos, István Kovács, Jin-Shan Li, András London, Dezső Módos, Richárd Nagy, Csaba Pál, Balázs Papp, Áron Ricardo Perez-Lopez, Ádám Portschy, Zoé Rimay, Kuljeet Singh Sandhu, Serguei Saavedra, Kornél Schádl, Gábor Simkó, Benjamin Siranosian, Veronika Siska, Jacob Stein, Gábor Szabó, Kristóf Szalay, Máté Szalay-Bekő, Noémi Szendrődi, András Szilágyi, Ádám Szirák, Ákos Szőts, Zsuzsa Szvetelszky, Dénes Türei, Dániel Tüzes, Zsolt Vassy, Dániel Veres, Shijun Wang, Zhen Wang* (Hong Kong), *Zhen Wang* (Dalian) and *Árpád Zahibi Arashk.* As the names show the work team is not only multi-disciplinary but very much international, too, it has members in Basel, Bethesda, Dalian, South Africa, Hong Kong, India, California, Nashville, Beijing, Providence, Rome, San Francisco, Seville and St Paul.

I would like to express my greatest gratitude and appreciation for my Family. It is easy to work with such a wonderful Family and it is easy to achieve results having such a magnificent family background because research becomes as joyful as the whole life.

Thank You very much for Your honorable attention!