

Ladies and Gentlemen! Dear Colleagues! Dear Friends!

I am standing in front of you much affected... no, that's not a good phrase: deeply moved! There is an exceptionally high amount of knowledge, talent, goodwill and love in this Ceremonial Hall of the Hungarian Academy of Sciences today, where the 300 seats became almost fully occupied. Many of you have rearranged meetings and trips or put important things aside just to be able to come to join us today. Let me emphasise that I feel it deep inside that this does not happen because of me. I am only a secondary player in this story. There is something greater than Jonas with us today, there is something greater than Solomon with us today, and there is truly something substantially greater than my inaugural lecture with us today. What (*or more specifically: Who*) I mean under this will become clear (*for many of you*) only at the very end of my lecture.

In the introductory slide of Academy inaugural lectures we can see that the contours of a network unfold in the background. Let me emphasize that I am totally innocent in this, too. The network is part of the inaugural diagram template provided by the Academy. That is: all my academy member colleagues start their inaugural speeches with networks in our Academy whether they like it or not... I might say that these networks have encompassed us... In other words, we have become like Molière's Middle Class Gentleman, who realized after forty years that he had in fact been speaking in prose in all his life. We have to speak of networks even if we do not want to. That is why I am taking the liberty of boring you with networks today.

The scientifically most important message of my lecture will be about the learning and decision-making mechanisms of networks. Besides this there are two more significant pieces of information on the first slide: my research team's homepage (<http://linkgroup.hu>), and my e-mail address ([csermelynet@gmail.com](mailto:csermelynet@gmail.com)). My lecture consists of two parts. The first, longer part summarizes those scientific results that we have reached since my inaugural lecture as a corresponding member of the Academy exactly 6 years ago. The second, shorter part phrases some ideas about wisdom. On one hand, during the second part I would like to ask for the understanding of those who came here only for the sake of a purely scientific lecture today. On the other hand, during the first part I would like to ask for the patience and understanding of those who would like to hear much more than a pure scientific lecture today.

The first important point of the lecture, scientifically, is about what the definition of networks is. We use networks to describe sophisticated, complex systems, and we do it in a way that first we define the network's constituents, the nodes. These nodes are system elements with the same identity. Therefore, if people present here were considered as a social network, we would have to ignore who is old or who is young in the hall, who is a lady and who is a gentleman, who is a secondary school student, who is a member of the Academy and who is a bishop. This huge data loss that comes with such a network simplification is key warning about the application of the network concept to which I will return somewhat later.

For now I finish determining networks stating that it is not enough to define only the nodes in networks. The second important element of the definition is to find out what connections there are among these nodes, i.e. what edges link these nodes together. These edges can be weighted, directed, signed, coloured, and many more. This also applies an enormous simplification. Let me draw your attention to only one detail here: if we would like to interpret an edge as weighted in a network, using the previous example of the social network,

then we have to answer the question how many times the best friends of people sitting here are better friends than their second best friends. And we should be very precise telling that their best friends are only twice or 2.5 times better friends of them than their second best friends are... I think that if we immerse ourselves in this simple example a little, we will feel immediately that how hard it is to be a network scientist. I would like to draw your attention that it makes sense to imply networks describing any complex system at all only, if you have extremely large background knowledge about that complex system. Because when we define this complex system as a network, we throw the 99.99 percent of the available information away at once. However, if you throw the 99,99 percent of the information away, there is a strong possibility that you throw the essence away and you will retain only the rubbish as the remaining 0.01 percent. This is what you will examine very thoroughly and will write a lot of scientific publications about it. This is why a precise definition of networks becomes extremely important.

This is the reason why I would like to begin the content of my scientific lecture with those contributions with which my work team contributed to the systematic data during the past 6 years. We have published two databases fit for this purpose: one of them (<http://comppi.linkgroup.hu>) describes 150,000 proteins' compartmentalized interaction network, out of which the word "compartmentalized" refers to where these proteins are located within the cell: in the nucleus, in the plasma membrane or in the cytoplasm, i.e. in which part of the cell<sup>1</sup>. The reason why it is important and meaningful to deal with such a sheer volume of network information because it shows which proteins were considered to have faulty connections earlier – e.g. from the point of view that those two proteins were supposed to be linked to each other before but one of them is always in the nucleus while the other one always stays in the cytoplasm, so they never ever meet each other within the cell. That's why the earlier hypothesis referring to their connection, with high probability, was false.

However, such a database is good for something else, too: for predicting new functions for different proteins in their new locations and new situations. Let me bring an example that will tell something for the colleagues dealing with molecules, while probably not much for the others. In the mitochondrion, i.e. in the energy generator power plant of the cell, there is a molecule called enoyl coenzyme-A hydratase that is also called crotonase. Crotonase also can be found in the cytoplasm but it has a completely different function there because it takes part in programmed cell death, i.e. the apoptosis. This new function can be suspected or realized when we observe the neighbours of crotonase in the cytoplasm. Birds of a feather flock together, proteins of a neighbourhood... So by its neighbors a role of crotonase in the programmed cell death became revealed, which is not at all obvious, and cannot be found in any handbooks because this protein had been considered to be a single function protein quite clearly before, as we thought that it only took part in the fatty acid metabolism.

The other database we have published (<http://translocatome.linkgroup.hu>) was about translocations<sup>2</sup>. This research inquiry remained at the previous topic of where the proteins are located at different places, compartments, within the cell. We examined now, with the help of

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<sup>1</sup> Veres, D.V., Gyurko, M.D., Thaler, B., Szalay, K., Fazekas, D., Korcsmaros, T. and Csermely, P. (2015) ComPPI: a cellular compartment-specific database for protein-protein interaction network analysis. *Nucleic Acids Res.* 43, D485-D493

<sup>2</sup> Mendik, P., Dobronyi, L., Hári, F., Kerepesi, C., Maia-Moço, L., Buszlai, D., Csermely, P. and Veres, D. (2019) Translocatome: a novel resource for the analysis of protein translocation between cellular organelles. *Nucleic Acid Res.* 47, D495-D505

Péter Mendik and Dániel Veres and others, from where to where proteins get, where the proteins go to when they are moving within the cell. We have determined approximately ten thousand human proteins' translocation probabilities with the help of a modern learning algorithm. Before this, we identified two sets of surely translocatable and not translocatable proteins. (These were the positive and the negative teaching sets). After application the machine learning algorithm we have found that at least one thousand human proteins are likely to go from one place to another within the cell. Moreover, there are another 3 thousand proteins which are likely wandering within the cell. So a cell is much more dynamic than we would think at first sight.

We keep saying about networks that they are very useful, because they make the data visible. – Please note that here I proceed to present one the most important methods that we published with my scientific team in the past 6 years. – Well, it is either so – or not... Now I show you an example of a model network which has 3 different groups. Those who are sitting at the front of this room should have perfect vision to notice zero grouping on this traditional network visualization. In my team, with the leadership of István Kovács, who has recently established an independent research team at the Northwestern University, Chicago, we worked out a network visualization methodology in the past 6 years, where nodes, the components of a network, are interpreted as distributions instead of points<sup>3</sup>. We examined how much these node-distribution functions overlapped when we made the visualization of the network. It is obvious that if we place the two nodes close to each other, its distribution function's overlap will be large, and if we place the two nodes far from each other, the overlap will be nothing or very small. Then we correlate this distribution to the network's edge weights, i.e. the strength of the connections of the adjacent nodes and we optimize this correlation with minimizing a relative entropy function (that's why named the method „EntOpt” available here: <http://apps.cytoscape.org/apps/entoptlayout>)<sup>4</sup>. If we visualize the previous network having 3 originally invisible groups using this new EntOpt method, then it can be seen immediately that the same 3 groups beautifully diverge visually, too.

I would like to draw your attention to that the data loss is higher than one-third in the traditional visualization (37 percent), while in our new presentation method the data loss is only 8 percent, which is not that much. One-third data loss is really painful. The same presentation improvement happens to the networks arising in reality if we apply the EntOpt method developed by us. If we visualize the interaction network of human proteins with a traditional method, those protein complexes that perform protein degradation – this is the proteasome – or those which transmit the effects of different steroid hormones – these are the nuclear hormone receptors –, or those which stabilize the structure of DNA – these are nucleosomes –, and so on... – are not separated from each other, i.e. they overlap each other to a very large extent. On the contrary, if we visualize these complexes with the new EntOpt method developed by us, then these protein complexes beautifully split up visually. Not only these groups can be visually identified but many more groups, too. Using this new EntOpt visualization method, at least ten or fifteen other protein complexes can be distinguished visually within this network, and you may suspect that presumably these other groups also have some functions. Moreover, their functions can be revealed knowing the functions of the proteins. Let me draw your attention to that the data loss here is also 30 percent with

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<sup>3</sup> Kovács, I.A. Mizsei, R. and Csermely P. (2015) A unified data representation theory for network visualization, ordering and coarse-graining. *Scientific Reports*, 5, 13786

<sup>4</sup> B. Ágg, A. Császár, M. Szalay-Bekő, D. V. Veres, R. Mizsei, P. Ferdinandy, P. Csermely and I. A. Kovács (2019): The EntOptLayout Cytoscape plug-in for the efficient visualization of major protein complexes in protein-protein interaction and signalling networks, *Bioinformatics* 35, 4490-4492

traditional visualization and only again 8 percent with our new entropy optimized (EntOpt) presentation.

Now I shall move to the main question of my lecture's scientific part: how to make a good decision? This is already a general issue affecting many researchers; it is more general than those network methodologies I have introduced until now. Let me have three preliminary comments in order to make it clear what I am going to tell you soon.

First comment: networks usually can be divided to cores (few nodes in the center of the network) and periphery (a lot of nodes at the sides of the network). The network core consists of a few nodes. These are linked to each other very strongly and well – that is how we define the network core. The elements of the network periphery are not linked to each other, but they are linked only to the core, so they are only in an indirect connection with each other. The network core mediates these connections. The network core is usually evolutionarily conserved, but the network periphery – and this is very important! – is the source of innovation. The reason why the periphery is the source of innovation is that it is not bound by social conventions (I will keep trying to explain with a social network example what is generally true in the case of networks), so the periphery can accept those pieces of external information that affect this system from outside and can transmit them to the network core or other parts of the network.

In my second comment I would like to draw your attention to two epoch-making discoveries. The first was discovered and published by Stuart Kauffman, who is collaborating with our research team, in 1969, i.e. more than 50 years ago. The essence of the discovery was that the complex systems are converging to a few attractors, i.e. a few stable, often visited states. This is an extremely important finding because it would follow from the basics of mathematics and the structure of the complex systems that many millions (if not billions) of their states can be stable at the same time. But if there would be many millions of states of the complex systems, I could not be sure now whether some members of the audience want to stab me or not because my lecture is boring... So there would not be social conventions, our thoughts would not converge to different thoughts and science would not exist either because not any experiments could be reproduced... So the human world would be existing in a totally different way, if this fundamental rule wasn't there that even the very complicated systems converge into a few attractors. (By "few" I mean 5-6 attractors, i.e. stable states).

John Hopfield, whom a whole information technology field was named after, discovered with his article dated in 1982 that one out of these few attractors, i.e. one of the 5-6 attractors (or one that is not already among them, one that has just arisen) deepens, (i.e. expands, becomes more probable and more stable) if the complicated system learns something. This is a very important finding. It means that those few, 5-6 stable states in the lives of the complex systems are not stable but they are continuously changing depending on what the complex system has just learnt. What it has recently learnt or what the most important for the complex system is will be the most stable state, i.e. that state will be the one in which the complex system stays the most of the times.

The third very important finding was discovered at the same time, independently from each other by Réka Albert, an external member of our Academy collaborating with our research group and Atsushi Mochizuki, a Japanese researcher and his team two-three years ago. Their common finding was that these attractors, i.e. these few very stable privileged states of the complex system are encoded by the network core. It means that those few nodes located in the

middle of the network, which I was mentioned earlier, encode the attractors of the network. So the structure and the operation of the networks are closely linked. That is: as the attractor structure changes, the network core changes, too. The structure and the behaviour of the networks change paralelly. I will detail these changes in the following section.

After reviewing the whole literature, it seems that there are two ways of network decision-making<sup>5</sup>. The first one is decision-making in a usual situation when the influencers of the network core agree with each other, i.e. they have got the same opinion, and they think the same about what should be done in such a situation. This common opinion is quite obvious because this situation is repeated. Moreover, it has been repeated for a lot of times already, so the network knows it very well that there is only one solution that can be done or is worth doing in this situation. Thus this decision is a result of an immediate consensus, so the whole system gives a quick and strong answer to this challenge, i.e. to this environmental change.

It is a completely different situation if a new piece of information reaches the network. In this case the network influencers, the members of the network core (so to say) do not agree. Let me apologise here for anthropomorphizing. This statement is also applicable for those networks, as I soon will present it to you, where there is no consciousness of the individual nodes that is where the nodes are not people but proteins or cells. Proteins and cells may “not agree” as well in case of a new piece of information. How is this made? Proteins e.g. "do not agree" with each other when one of them tries to make a conformation change in vain because its neighbour does not let it happen physically in the space as the neighbour is unable to take a conformation creating space for the "kick" coming from the neighboring protein. This "do not agree" situation may be realized in a lot of different ways in specific, different networks. When the nodes of the network core "do not agree", the problem, the new piece of information spreads in the whole network. This process enables the slow but democratic answer to be born requiring the reconciliation of the whole community. Well, let me add here at the "democratic" attribute that it is not democratic in the sense how we nowadays imagine and practice democracy, as a voting process. Networks occurring in biological systems are "democratic" in the sense that they are contemplative, i.e. their decision is a subject of much consideration, much deliberation, lengthy negotiations and an elaboration of the agreement between the network nodes. All nodes are involved in this reconciliation process, not only the nodes of the central core but the nodes of the network periphery, too. Let me remind everyone here that innovations come from the periphery. So it is very important that the nodes of the periphery should be involved in the decision-making when new pieces of information arrive, otherwise the network will not be innovative, and so the elaboration of the new answer will not be working.

Let me draw your attention to the role of new connections developing during the elaboration process. These new connections link the nodes of the periphery to each other, i.e. those nodes that have not been linked together before by definition. In these cases, when a new answer is needed, exactly the following happens: the nodes of the periphery start to get connected with each other and some of these new connections will be very important when creating the new answer. How does it happen? The answer of the periphery becomes creative and innovative if those nodes get connected to each other that have been very far away in the network earlier. That's why it gives no new solution if the network tries to link its core together again, because the nodes of the network core have been connected to each other very closely already. So

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<sup>5</sup> Csermely, P. (2018) The wisdom of networks: A general adaptation and learning mechanism of complex systems. The network core triggers fast responses to known stimuli; innovations require the slow network periphery and are encoded by core-remodeling. *BioEssays*, 40, 1700150

there is nothing new, nothing innovative if we link the nodes of the network core stronger together since they have already been connected to each other. Innovation can arise only if we link very far nodes together. In what sense this "very far" is very far? These nodes are very far in the sense that they were able to approach each other within the network taking a lot of steps before we connected them. As soon as we connected them, these lots of steps were reduced to only one. Let me emphasize that it takes a lot of courage to make such a distant connection. Regularly these nodes, so to say, cannot communicate with each other because they were very far from each other in the network structure. We must always have this courage in order to let an innovation happen because otherwise there will not be any.

When these distant nodes were connected and it proved to be useful in the new situation of the network, the question would arise in what way was the new connection useful? It proved to be useful because it transmits information, a lot of information, so this connection has to be strengthened to be able to carry the loads of information it transmits. That is those connections proved to be useful have to be strengthened – by the way that's what we call Hebb's learning rule that I will detail in a later section –, and if these new connections have been strengthened well, there is a good chance a new network core forms where – and this is important! – the new core's nodes are not the same as the old ones were. Some of the nodes fell out from the old core and a few new nodes got into the core – i.e. this process may actually be called as a core renewal. E.g. this way a normally functioning election can renew the social environment that used to have a core but a new challenge emerged for the social group and that's why a core renewal was necessary. Let me draw your attention that this reasoning is not new at all. The famous mathematician, Henri Poincare wrote the same in 1913, although not in a network sense, when he wrote a book on the basics of science methodology and he found that linking ideas together that were far away from each other earlier, i.e. for example linking formally remote fields of mathematics to each other, leads to creative solutions. Now let me put it in brackets what I emphasized earlier, too: if these areas were far from each other, and if they have to be interpreted as networks, they need to be identified as the periphery's nodes because only those are far from each other in a network, the core's nodes are not. That is, this decision making form seems to be general.

During the generalization of the above thoughts I would like to first quote the book of Daniel Kahneman, Nobel Laureate in Economics, titled "Thinking, Fast and Slow", also published in Hungarian, in which, based on a lot of model tests and experiments, he wrote the general rule that we, people seem to make decisions in two different ways: either we are in a well-known situation and we realize the solution like a quick, reflexive thought, i.e. we suddenly find the answer: we obviously know what to do. The other case is when we are in an unknown situation and during a contemplative, quite slow, long process, requiring considerations, the solution is forming in us, even without any social consultation, that at last we accept as true, as right, as a good decision.

Neurons work in the same way – in reality of course, they were not examined in humans but in rats or mice, i.e. in experimental animals, but it could be stated that if the experimental animal knows where it is, let's say in a labyrinth, because it was placed into a labyrinth, then only a few neurons are active in its brain because it is obvious for it that it has to turn right as the food is there and it is also obvious that it does not have to turn left as there is a trap there and it gets an electric shock there. But if we put the same mouse or rat in such a labyrinth it did not know earlier, then thousands of neurons or even hundreds of thousands of neurons are activated and start to flash in its brain and throwing bits of thoughts into its brain's central system, like in the hippocampus saying: "don't turn right", "don't turn left", "don't go

forward”, “don’t go backward” etc. and the mouse or the rat realizes after a while from these various considerations that if I turn left now, there is the food and if I turn right, there is the electric shock, so this labyrinth is exactly the other way round than the previous one was – damn those neurobiologist experimenters who keep on annoying me here with this thing...

Proteins work in the exactly same way: the central parts of most proteins are in a well-ordered status. This is what a lot of people have learnt in their basic studies well that a protein in its native state may take only one stable conformation. I was also researching that at least for twenty years. However, it turned out in the recent few decades that the majority of proteins, e.g. precisely 80 percent of proteins taking part in human signal transmission, possess disordered regions, too. These disordered regions are generally positioned at the outer sections, edges of the protein. That means if we imagine the protein as a network, its central ordered part is the core and the disordered regions at its edges act as its periphery. It is true that when a protein has to do a usual thing, e.g. it has to convert some substrates to products via enzymatic activity, then the protein core plays the key role in this process because the core contains those amino acids that encode this function soundly. But if the protein gets into a new and unknown situation, its periphery changes – I’m going to give you an example of this in the next part of my lecture.

But before I show you an example of this new idea-formation, let me detail the idea now that presents Hebb’s learning rule as a general form of learning. Donald Hebb wrote his – actually – popularizing science book in 1949, in which he formulated the basic rule of learning, i.e. when two neurons have an interaction with each other during a learning process the connection between them strengthens during the learning process. So Hebb’s learning rule is in fact a connection strengthening rule between neurons. When not so long ago we looked through the literature and the results published by the colleagues recently, it turned out that Hebb’s learning rule cannot only be interpreted on the level of neurons but within the individual cells, too. Even if this individual cell is not a neuron but a skin cell, a muscle cell or any tissue cell in the body, moreover, even if it is a cell of a unicellular animal. How can the generalization of Hebb’s learning rule be interpreted? When a certain cell answers a signal coming from its environment, it very often causes that two proteins following each other in signal transmission come into physical contact with each other. In such case, if one of the proteins had a disordered part, i.e. a protein periphery-like part, without a structure, bouncing back and forth, this part folds during the forming of the connection. If the signal stops, i.e. the cell is not aware of this new situation any more, these two proteins become dissociated. Let’s observe (and this is very important!) that the disordered region remains folded for a little while. Of course, after a while it will unfold, but it needs time to unfold. So the individual cell has a little time window while it still remembers what happened to it in the previous moment. Here comes an important statement: if the same signal is repeated again, the protein, participating in the process and previously having disordered parts too, does not have to be folded, which needs time, as it is able to connect to the neighbouring protein in signal transmission quickly, because being properly folded it has already been made suitable for that. This results in the property that the cell reacts to the repeated signal much faster and stronger than to the first signal. This property (i.e. faster and stronger reaction to repeated signals) has been proved and verified by a lot of experiments during the past years, in case of a lot of different types of cells, e.g. in case of plant cells, simple monocellular animals, etc. It is interesting that the connection between the two signal transmitting proteins strengthens in exactly the same way during the learning process (as the cell has learnt the new rule what to do in such a situation) like the link between neurons when learning. So actually we can say that Hebb’s learning rule seems to be more general than we thought for almost a hundred

years. Hebb's learning rule is applicable not only for neurons but it can be proved to be valid within the individual cells for individual proteins, too.

Furthermore, we managed to observe and summarize that learning leads to the same signal transmission strengthening not only when two proteins connect with each other but in protein translocation within the cell, in microRNA regulation, or in forming the 3D structure of DNA, in chromatin structure when the cell processes a new signal and it remembers that later. These memories have been recently described by our colleagues in various publications but we were the first to see this as a whole and summarize these observations as the extension of the Hebbian learning rule to the molecular level<sup>6</sup>.

If we examine what the potential learning points could be in the signal transmission network of an epithelial-mesenchymal transition playing a role in cancer metastases, which was extended by my PhD student, Nina Kunsic in the previous years, following Réka Albert's article published in 2014, we can see that several proteins may potentially participate in the learning process. So there are a huge amount of such proteins in our cells that can potentially be parts of a learning process in a signal transmission process. But I would like to draw your attention also to the fact that not all proteins are like that. How these "learning patterns" are exactly formed, what their significance is, which ones are more important and which ones are less important, how learning algorithms can be created out of them, and so on; well, these are the topics my research team is interested in quite intensively nowadays.

As it has been mentioned by the kind introduction of the president of the biology section of our Academy, our results' applications took place in several different ways during the past six years. E.g. our article describing the network paradigm of drug development has become an article recognized as a widely quoted and widely accepted basic article in the literature.

As it was proved by a very young member of our research team, Áron Perez-Lopez, who attended the sophomore year at Apáczai Csere János Secondary School when he wrote his first author article, drug targets work like network cores. Unfortunately this results not only in effects but in side effects, too.

Following the work of Dezső Módos, present in this Ceremonial Hall of the Academy now, and his colleagues, it has also been revealed that not only the network cores but their neighbours can be very important drug targets, too. Let me use a much more understandable analogy for that, i.e. not always the president's telephone number is extremely valuable in one's phone directory but his wife's number is very often much more valuable than that of the president (or in case of a female president then the number of the president's husband...), because a wife (or a husband) knows it much better when and how something, that has to be told very much to the president, has to be told the president, than let's say me, who would call the president in a totally inconvenient time, in a totally inappropriate way, with a completely inadequate message, and that's why my message would be wasted, i.e. it would not have any effect. Proteins behave similarly in networks. The take home message is that not always the most important proteins that have to be attacked by a drug but the ones surrounding them.

As it has been mentioned by the kind introduction of the president of the biology section of our Academy, Turbine, a medium-sized biotech company (<http://turbine.ai>) was founded a few years ago by Kristóf Szalay, Dániel Veres, Iván Fekete, Szabolcs Nagy and me. This

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<sup>6</sup> Csermely, P., Kunsic, N., Mendik, P., Kerestély, M., Faragó, T. Veres, D.V. and Tompa, P. (2020) Learning of signaling networks: molecular mechanisms. *Trends in Biochemical Sciences* 45, 284-294



company was started with five of us and now it has 52 colleagues and is facing a very bright future. (When it goes public, I encourage everyone to buy some of its shares...)

The president of the biology section of our Academy, Prof. László Fésüs summarized the past 6 years' main numbers in his introduction. The number of citations of our articles more than doubled in these six years. It is my great pleasure that 25 scientific students' prizes have been gained by our research team. Let me draw your attention to that networks seem to have become very popular: at the course that I hold network topic at Semmelweis University, which is an optional course where generally there are twenty applicants, there were 430, then 512, and now there are 600 participating students, whom we cannot have seated even at the largest hall of the Semmelweis University...

In the past six years, as it has also been noted in the introduction, my friend Csaba Sóti, who is sitting here in the Hall, has become the Doctor of the Hungarian Academy of Sciences, five of my students have obtained PhD degrees – let me add here that already half of my present PhD students sitting here at this hall are ladies. Moreover, the half of my working team are also ladies, too, so to my great delight the five boys to zero girls ratio in recent PhD students, that is still quite one-sided here, has changed healthily by now.

I passed on the hard job of leading the Hungarian talent support network in 2016 to those of my colleagues who are sitting here in the Hall: to Péter Bajor, László Balogh and Mária Polonkai – thank you for coming here today. The last program in which I took part personally as the inventor and organizer was the Hungarian Templeton Program – a lot of Templeton Fellows are sitting here, thank you very much for coming today. Both the European Council for High Ability and the European Talent Network have been mentioned in the introduction, – let me thank Csilla Fuszek, who is also sitting here with us, for her great help in the international talent support network.

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Now I have arrived to the second part of my lecture which will be shorter; precisely it will be half as long as the first part was. Let me say some words about wisdom. Why is this topic relevant today? My life changed very much three to four years ago. From the joy enjoying before I got to "great joy". I became a university student again. As it was told in the introduction I am a sophomore student of theology/priesthood at the Lutheran Theological University.

A beautiful path has led me here. About four years ago at the Centrál Café my former researcher student friend, Csongor Cserép drew my attention to the book of St. Teresa of Avila, "The Interior Castle". This book describes a wonderful picture about the human soul that can be divided to seven rooms embedded in each other like onion-shells, from which the inmost is Jesus, God Himself. I realized that I had been in the third room quite a lot of times in my life so far. Moreover, I had been on the very threshold of the fourth room, too, but I always fell back into the first one. I had a strong wish to find the path leading inside. St. Ignatian retreats provided me with a lot of inner experiences and evidences. I was given a lot. After a while I felt that have to give this back. This led me back to that Lutheran congregation in Budapest-Angyalföld where once I was baptized and confirmed. I was given a warm welcome there and it is a great pleasure to me that Péter Grendorf, the Lutheran pastor of this congregation, is sitting here right now.

All this was matured in me (*what a coincidence...*) right when, after many decades the Hungarian Lutheran Church has come to the wise decision to open the door and admit late-called pastor students to night classes again. Hereby I would like to thank the Lutheran Church's bishops and leaders sitting in this room for this! The first year class (whose members are also here with us) has become a great team. We have learnt Hebrew and Koine Greek within a semester. We have all passed the first 14 theological courses, including Torah and the Gospels. Almost all of our professors are sitting here in this hall. Let me thank them the incredibly intensive work with which they have given both precious knowledge and spiritual depth to us.

What has changed in me? People often make mistakes in self-evaluation. Therefore let me call four authentic witnesses for that. The first is the late János Balogh, member of the Hungarian Academy of Sciences, who is no longer with us. He said to me in the student research camp in Káptalanfüred more than twenty years ago: "*Peter! You are not teaching science here!*" I stood there devastated in front of János Balogh, I would not have expected this from him, but he seemed to be serious. But the eyes of János Balogh were shining, he started smiling and he continued like this: "*You are not teaching science here – but Humanity!*" Many former student researchers are sitting here today who have taken a distinguished exam of Humanity.

My second witness is one of my former students from Semmelweis University, who said to me in Centrál Café two weeks ago: "*Listen! The pastor profession is not something that bored people in their sixties sitting at home would accidentally choose from the national catalogue of job qualifications just to kill their time... That requires a call!*" My classmates, pastors, priests and bishops sitting here in this hall can witness that pastoral career is really not a pastime activity but a call. Our Lord throws us into the hardest situations of human life. BUT: He does not only throw us into this but sustains us with His firm hands in this drift, too.

My third witness is one of my former PhD students, who leads a working team in Canada now. When I wrote to her that I became a theology student, she reminded me in her answer saying that 15 years ago, being a mentor, I often acted like a pastor already. It felt good to see that the members of my scientific research team (regardless of their worldview) had their fingers crossed for my successful university exams. As we could see on the previous slide, these exams went quite well so far...

Last but not least let me quote my most authentic witness, who is sitting here, István, my son. When I was young I would have never thought that growing old could bring positive changes in my life. It is very nice to experience that it's never too late!

After all, let's think about what wisdom is not all about. First I would bring an example from the English language where the frequency of mentioning the word „wisdom” has very much decreased since the 1800's. I have always been an optimistic person in my whole life, so let me draw your attention to the last little upheaval, i.e. in the past few years it seems like the usage of the word „wisdom” could have risen a bit in the English-speaking world, but we still have room for improvement I think...

We very often mix cleverness with wisdom. We have met a lot of smart little children already. Talent supporting professionals sitting here do not see anything else but smart little children as they have an occupational hazard concerning this... But we usually do not consider a lot of children to be wise. And it has a reason! Scientist colleagues sitting here in this hall have already met a lot of Nobel Laureates and we certainly agree that they are all clever. But not all

of them are definitely wise... So these two terms do not precisely mean the same. I learnt it from my teacher, Károly Bácskai at the Lutheran Theological University that wisdom is not a 180 degrees' turn, so it's not like that so far I "have been drinking" and from now on "I do not drink"... It's not enough for wisdom. Conversion, the real transformation is a 360 degrees' turn when I somehow remain myself but still I have a totally different focus in my life. Denial by itself does not lead to wisdom. Denial alone is not enough.

Following the wiser is not wisdom either. A lot of people very often reduce wisdom to „sure, let's find a wise person and let's follow him”. Well... I'd like to quote an old story from my grandpa's bible (which is a more than 400 years old Károli Bible, with ornamented expressions...): „And when the woman saw that the tree was good for food, and that it was pleasant to the eyes, and a tree to be desired to make one wise, she took of the fruit thereof, and did eat, and gave also unto her husband with her; and he did eat..” (Genesis 3.6) Here, in this story, the wise wanted to listen to an even wiser. But it's not sure (viewed retrospectively) that this was the most effective, the most useful and the best deed of mankind in human destiny...

That is, these examples warn us that wisdom cannot be taken away simply in one step, but it may only be obtained, asked for. The example of Solomon in the Old Testament exhorts us when he asked for wisdom – and he did get it (well, not really in his old age, but for a long time he did...). So wisdom somehow has a different nature than we used to think about it.

Einstein said that wisdom is the reciprocal of the ego. So the smaller is the ego, the bigger is (*can be...*) the wisdom. Well, that may be true... If we revolve only around ourselves and we always stay in our own circles and we never get out of them, our viewpoint does not lead us to a perspective. So we will get lost in life's maze. Because the walls of our life maze are like bushes, which are as tall as a man e.g. in a Japanese tea plantation. So in this maze we never notice the exit – if we are down inside it. But if we are able to fly up to another perspective and we are able to step out of ourselves, we get an immediate understanding and this shows us the way out. Of course, we cannot do this flying up by ourselves.

It is also a part of wisdom when we do something. Usually things are not have to be done when we think that they have to be done. Things have to be done when it is time for them to be done. And the right time is not determined by us but it is given to us from above.

To feel this we need silence. That is, we have to able to eliminate somehow the enormous noise being around us in this century. For this either we are not enough by ourselves, we need God's mercy for this, too.

Let me bring it as a last example that it is not all the same when and how we try to be filled and to give. For being able to give, we have to be filled first. If we want to give without being filled, what we give will be only ourselves and that will not do any good... If we would like to give significantly more than we have been originally, we have to wait for something we can give. This is exactly the same as to find the optimum of the golden mean as the ancient wise men were talking about when they warned us to avoid the extremes. This is the Gospel story of Martha and Mary where Martha was always busy, and she was continuously bustling about, while Mary did nothing more than she sat down and listened to Jesus. After a while Martha got pissed off, freaked out and snapped Mary (and Jesus, too), saying „why do you let her staring at you dumbly, do something, do anything with her”. Jesus answered the furious Martha as follows: „Martha, Martha you are worried and upset about many things, but few

things are needed, or indeed only one. Mary has chosen what is better, and it will not be taken away from her.” (Lk 10, 41-42) That is, to be filled is not only important but also necessary to be able to bustling about. Bustle comes only from charge because bustle without charge is not sure to be fortunate... The whole thing leads to a kind of COMPLETE-ness and integrity, which is already very close to wisdom.

Why is this important? Let me bring the example of yesterday when a hurricane ravaged in Budapest, Hungary. We live in a quite Earth-ruining and innovation-poor age. By innovation-poor I do not mean how many innovations there are around us, well, there are so many of them... The only problem is that only the quantity of these innovations poured on us is high – but their direction is wrong. So we should channel this innovation and creativity into a better direction. We should approach the internal growth instead of the external growth in an innovative way! That is: it is not our environment we have to change but ourselves! That is what we are lazy about, that is what we are unable to do, and that is what we are very retarded for. We do not feel like to do this. We would not like to change. Rather the Earth should be destroyed. But we do not change! So it is necessary to let the thoughts of the periphery, moving us out from our comfort zone, get into the centre of our social thinking. This is the essence of innovation and only from this can internal growth become born.

Finally, let me quote István Széchenyi, who wrote the following in 1826: „*No, we were not born reformers. We must reform ourselves first. We have to attend the school of humility and self-denial.*” Well, this wise saying remained true in the past almost 200 years. Even today we can only observe the wise words of our Academy’s founder.

I would like to thank my recommenders, masters and those who have been my co-authors since 2014. I would like to highlight László Holics with great appreciation among my teachers, who could come here today and who celebrated his 89th birthday yesterday – let’s applaud Mr. Holics! Among my co-authors I am very grateful for the late György Klein. (I also thank the listed 82 other co-authors, and I apologize to all of those whom I cannot mention now due to the lack of time.) Unfortunately György Klein can no longer be with us but all who knew “Gyuri” will preserve the wisdom, the love, the helpfulness and the scientific discernment for a lifetime that György Klein has left to us. I would like to thank my team, which is quite international as you can see, and my family.

Finally, I would like to thank for being born and for my life. Moreover, my appreciation cannot be said in words for the certainty that

- I will be never left alone here or once out there;
- I am connected to everything and
- that what connect us with everyone in this hall
- is love.

And this love is none other than God himself. (1John 4,8b)

And now I tell you the answer to the questions I started my lecture with.

JESUS and His love has been – AND IS – here with us today.

HE IS THE ONE, who is greater than Jonah,

HE IS THE ONE who is greater than Solomon (Matthew 12,41-42) and

HE IS THE ONE who is (*immeasurably much*)

larger than my inaugural lecture today.

Thank you for your kind attention!