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Networks elective course

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Network medicine in uncovering networks of diseases

The world population continues aging as we go further. The number of people over 60 years is expected to double by 2050, and the number of people over 80 years old is expected to triple in that same time. (United Nations, Department of Economic and Social Affairs, Population Division 2017. World population Ageing 2017- Highlights ST/ESA/SER.A397). As the population grows older, medicine confronts new challenges of treating diseases becoming more common and growing as major socio-economic burden. At the same time younger and younger people are suffering from obesity and metabolic syndrome, which are connected to various diseases like diabetes mellitus.

Network medicine is a science that makes it possible to explore and identify disease modules and pathways, and the relationships between different disease phenotypes. It is also a useful tool in pharmacology. Most of the current drugs in use do not cure, but only alleviate the symptoms of a disease. With the help of network medicine in drug development, by understanding the whole disease network and it's connections, it could be possible to develop drugs that may cure a particular disease. (Barabási, Gulbahce, Loscalzo: Network Medicine: A network-based Approach to Human Disease. Nat Rev Genet. 2011.)

The human disease network is a bipartite network that has two sets of nodes; one representing all known genetic disorders and one representing all known disease genes in the human genome. Disease and a gene are linked if a mutation in that gene is detected in the

disease. In this human disease network it can be seen that the same genes play a role in the development in most of the diseases. (Goh, Cusick, Valle, Childs, Vidal, Barabasi. The human disease networks. PNAS, 2007.)

However we know there is more to disease development than genes and molecular networks. Cardiovascular diseases and diabetes mellitus type 2 are strongly linked to obesity and lifestyle. Since this aspect of the disease cannot be investigated based on the genetic or molecular networks, it is useful to take a look at social networks.

A child born to obese parents has an elevated risk for obesity and related diseases in the future. This can be explained by genetic components, but research shows that it is not only the genetics that matter. It was observed in a study by N. A. Christakis and J. H. Fowler, that if one of two friends became obese, the chances that the other friend would become obese as well was 171%. The chance that friends in the same social network of an obese person would become obese as well, was 20% higher than in an random network. (A.-L. Barabasi. From Obesity to the "Diseasome". NEJM. 357;4.2007)

Since social network is a weighted network, where the strengths of all the links are not equal, it is possible to be more influenced by some connections in the network than others. I would like to raise an example of another social network, Instagram. Instagram is a popular social networking system owned by Facebook, where users share pictures and videos. With an hashtag #fitnessmotivation there can be found 41.4 million results. The hashtag #healthyfood gives 44.7 million results. So it is relatively safe to say that these are trending topics on Instagram. To start a trending topic, there has to be an influencer, a node, which acquires many links and becomes a hub. These hubs acquire more and more links due to preferential attachment, and by this way reach more and more users of Instagram, and influence many

people. One of these hubs is a fitness influencer Kayla Itsines. She is an Australian personal trainer, who is followed by 9,6 million people on Instagram. As social media grows to play a bigger part in our lives, it might be possible that the links to social media hubs will become more influential than the links inside our social network of friends, and by this way would be a motivating factor for young people to attain more healthy life-style habits.

Moving forward from the young to the old, and from life-style choices to disease processes that are inevitable with aging. (Even though many of these disease processes are also influenced by life-style choices). Aging is a complex process, and it seems to be a sum of multiple factors, like accumulation of mutations, and oxidative stress to cells. Aging is not only characteristic for human networks, but for most of the real systems. During the life of the network it meets perturbations, which create noise in the network. Noise is important for the stability of the network. Weak links are essential to dissipate the noise into the network, which leads to relaxation and achievement of a new equilibrium and retaining integrity of the network. If however the noise is excess or accumulating (like mutations in the human DNA), it cannot be dissipated and leads to development of tension in the network. Slower recovery from perturbations is one of the early warning signals of critical phase transitions, which leads to death of the organism.

Aging causes disorganization of the network, which leads to changes in the network topology, where the small-worldness may be lost and hub structure reorganized. Aging networks become more rigid.

Protein aggregation creates noise increase in neurons and might be a factor in development of neurodegenerative diseases like Alzheimer's disease and Parkinson's. Alzheimer's disease pathogenesis is believed to result from accumulation of amyloid-β peptides.

They cause dysfunction in GABAergic neurons, which in turn increases excitation in principal cells and lead to destabilization of neuronal networks. The abnormal synaptic activity causes network instability and can evoke epileptiform activity. (J.J. Palop & L. Mucke: Amyloid-β-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nature Neuroscience. Vol13.No.7.2010)

Progressive loss of neurons with age is also in the focus of Alzheimer's disease research. The amount of neurons that a brain can lose before it has an impact on the integrity of the neural network, can be measured by robustness. Brain networks can be studied as structural connectivity networks, where links are the anatomical connections between brain regions, or as a functional connectivity network, where links are dependencies between separate neurophysiological events. (H. Aerts, W. Fias, K. Caeyenberghs, D. Marinazzo: Brain networks under attack: robustness properties and the impact of lesions. Brain 2016: 139; 3063-3083.) As we know the brain is highly robust against attacks. This is evident when looking into statistics of patients with strokes, brain injuries or brain tumors, and how many of these patients survive the attack and can function again. Scale-free networks attain high robustness against attacks against random nodes. This is because in a scale-free networks there are more small degree nodes than hubs, so the probability or removing a small node is much higher than removing a highly connected hub. However, if the attack targets hubs, the network becomes highly vulnerable to these attacks.

The functional connectivity network can be studied by functional magnetic resonance imaging (fMRI). With this method it was found that the human brain network shows a neocortex of highly connected hubs and an exponentially truncated power law degree distribution. This kind of network architecture was found to be more robust to targeted attacks on its hubs than a

scale-free network. (S. Achard, R. Salvador, B. Whitcher, J. Suckling, E. Bullmore: A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J Neurosci. 2006. Jan 4;26 (1): 63-72).) Hubs in the brain can be described according to their roles in the brain structure. The 'provincial hubs' link mostly to other nodes in the same module, while 'connector hubs' are connecting across multiple different modules. Lesions affecting the connector hubs caused more widespread disturbances in the functional connectivity of the brain network, due to the increased path length of the remaining network. In Alzheimer's disease the brain atrophy affects primarily the hubs, even to the point where they lose their hub status. This leads to alterations in the anatomical and functional network topology. So why is it, that the attacks against hubs seem to have such a big impact after all, even though the brain network architecture seemed to have a high attack tolerance against it hubs? The answer can be that the disease doesn't just affect one small part of the brain, but spreads through the network, and this way can attack the central regions vulnerable to pathological processes. (A. Hannelore, W. Fias, K. Caeyenberghs, D. Marinazzo: Brain 2016.)

The treatment of Alzheimer's disease is a work in progress. There are many drugs available to alleviate the symptoms of the disease, but there are no disease modifying agents. (Dunkel et al. 2012. Clinical utility of neuroprotective agents in neurodegenerative diseases: current status of drug development for Alzheimer's, Parkinson's and Huntington's diseases, and amyotrophic lateral sclerosis.) To create these kind of drugs, it is necessary to know the disease associated genes and other disease-associated networks.

In neurodegenerative diseases cellular proteins undergo reconfigurations, and this is why protein-protein interaction networks are important for the drug design. Protein-protein interaction networks are called interactomes. They can be further refined into domain networks, which are

networks of the interacting protein domains. These domains can act as drug targets trough activation or inhibition. Mapping these domains and their edges it is possible to create drugs that can lead to disconnecting the network by inhibition of a certain domain. This gives higher specificity for the drug action than targeting the whole protein.

Mutations occurring in the protein networks in particular diseases occur often at a central position in the interactome, bridging two or more modules. These disease associated proteins do not act as hubs, and by targeting these non-hubs, it is possible to avoid unwanted side-effects.

Drugs targeting protein-protein interactions are called edgetic drugs, which work mostly by inhibiting interactions, and the benefit in these is high specificity. There are other kinds of metabolic-related drugs that are also edgetic drugs, and target the edges between the metabolites. At the moment the development of edgetic drugs are concentrated on protein-protein interactions. There are however still aspects in the development of these drugs that needs to be solved, like the edge-weights, which define the binding affinity of the drug.

The process of disease is often associated with multiple-genes, causing changes in protein networks, metabolic networks and expression of microRNAs in the networks. Also not only genes are behind the development of diseases, but also life-style choices affected by social networks. The complexity of diseases brings challenges for the drug development, which is why new drug development strategies are needed. With the help of network medicine it is possible to map the different aspects connected to the development of the disease, and create drugs targeting these specific points, and this way find disease curing drugs with minimal side-effects. This may offer solutions to treating millions of patients suffering from chronic diseases not currently treatable.

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