Section 1

9:40 – **Kristóf Zsolt Szalay:** *Bringing computational results back to the lab*

10:10 – **Rasoul Rajaei:** *Minimal functional networks: How much network do you need to live?*

10:40 – Herbert Sizek: *Modeling Senescence Through Mitochondrial Shape and Chromosomal Restructuring*

10:55 – David Holland: *Stoichiometric balance in the clathrin-mediated endocytosis protein network regulates functional and nonfunctional dynamics*

Section 2

11:30 – **Bradly Alicea:** *Cybernetic Representations of Suboptimal Regulatory Systems*

12:00 – Vipin Vijayan: *Alignment of dynamic biological networks*

12:15 – Micah Auerbach: *A Boolean Model of Early Stem Cell Fate Decisions*

Section 3

2:00 – **Adilson Motter:** *Control of State Transitions in Biological Networks*

2:30 – **Thomas MacCarthy:** *Robustness and sensitivity in gene regulatory networks under antagonistic coevolution*

3:00 – **Abhijeet Sonawane:** *Constructing Gene Regulatory Networks with Epigenetic data using Message-Passing*

Abstract of talks in the order of presentation:

SECTION 1

Kristóf Zsolt Szalay: *Bringing computational results back to the lab*
(Turbine Ltd.)

Despite recent advances in computational biology, computational and experimental biologists still speak quite different languages and use different measures to validate their hypotheses, which greatly hinders validation of computational methods. In the last years, we've devised a method - using simulations of the underlying signaling network of human cells - that can generate the computational equivalent of one of the most important lab measures in pharma: the LD50 value, the dose required to kill half of the cells in a cell culture. Our results show that computational LD50 values are directly comparable to their lab counterparts, and can be relatively accurate predictors of the experimental LD50 value, thereby giving us a very direct way to assess the validity of different computational methods.

Rasoul Rajaei: *Minimal functional networks: How much network do you need to live?*
(Northeastern University)

How a network's microscopic dynamics translate to behavior of the system as a whole is of fundamental interest to anyone seeking to diagnose, predict, and prevent system-level failures, ranging from genetic diseases to ecosystem collapse. Yet this mapping is generally obscured by the fact that there are many microscopic configurations (e.g. the interconnections between and activities of individual species, banks, or genes) that yield the same macroscopic result (biodiversity, financial health, genetic disease). Here we study this connection between network "genotypes" and network "phenotypes" using as a model system the neuronal network of the nematode C. elegans equipped with integrate-and-fire dynamics. We show that human-recognizable, organism-level behavior such the worm's canonical locomotive response to touch stimuli can be accurately inferred in silico from the microscopic dynamics of the 68 body wall muscles (nodes). This capability allows us to systematically identify the ensemble of network topologies and nodal dynamics consistent with a given macroscopic function, at scales and speeds that would be unattainable through traditional in vivo experiments. We find a good correspondence between the neuronal knockouts we predict to result in a loss of functionality and those predicted by in vivo laser ablation experiments known to disrupt locomotion in the living worm. These findings lend credence to the notion that diagnosing the functionality (or lack thereof) of complex systems can be traced to the detailed features of the system's dynamics.

Herbert Sizek: *Modeling Senescence Through Mitochondrial Shape and Chromosomal Restructuring*
(The College of Wooster)

In aging organisms, senescent cells play a significant role in the degradation of the functionality of tissue. However, a mechanistic understanding of how cells enter into and sustain senescence is unclear and is thought to be multifaceted. Previous computational models of senescence have proposed a singular mechanism to entry into senescence. Here, two previous models of senescence are modeled in a synchronous Boolean model. These two models then were used to develop two modules that focused on mitochondrial structure and membrane potential and senescence associated heterochromatin foci. Integration of these two modules into a larger model by Hamel and Regan (2016) lead to a model that suggested two entry routes into senescence. The activation senescence, as observed in the model, correlates to the experimentally observed features of senescent cells. The model provides an *in silico* demonstration of the differences between developmental senescence, DNA damage induced senescence, and oncogenetic Ras induced senescence. Our results suggest that both mitochondrial structure and chromosomal changes can individually induce senescence, though with differing downstream results. From this model, we can make predictions of cellular behavior in regard to senescence as well as cell cycle and apoptosis that will challenge the current understanding of cell proliferation and arrest.

David Holland: *Stoichiometric balance in the clathrin-mediated endocytosis protein network regulates functional and nonfunctional dynamics*
(Johns Hopkins University)

About 15% of yeast genes decrease cellular fitness when overexpressed. One hypothesis for this "dosage sensitivity" is that protein copy numbers must be balanced relative to their binding partners so as to avoid leftover proteins and incomplete complexes that take up cell space and are prone to misinteractions. We show in toy models that a stoichiometric imbalance in protein copy numbers will lead to more misinteractions due to mass kinetics. By analyzing an interface-resolved protein binding network for the clathrin-mediated endocytosis system in yeast, we found that the real protein copy numbers were significantly more balanced in relation to their binding partners compared to random copy numbers. We were also able to identify proteins that were out of balance. By

studying the time-dependent dynamics of clathrin recruitment to the cell membrane using stochastic simulations, we also found functional pressures for promoting observed stoichiometries. We show how misinteractions could decrease network function, measured via vesicle formation. We show both knockouts and overexpression of various proteins can have significant consequences on the success and speed of vesicle formation.

SECTION 2

Bradly Alicea: *Cybernetic Representations of Suboptimal Regulatory Systems*
(OpenWorm Foundation, Orthogonal Research)

In specific types of regulatory systems (e.g. gene expression), coherent function is directly related to optimal regulation. This often produces structures exhibiting a characteristic function (e.g. biological switches) or pattern of systemic behavior (e.g. mRNA aggregation). Yet such examples are also an artifact of scientific convenience, as complex biological systems more typically exhibit highly complicated, kluge-like, and suboptimal regulatory mechanisms. In this talk, we will revisit cybernetic theory and the assumption of functional optimality to situate this type of regulation in the context of biological variation and complexity. An analytical approach to suboptimality called the Cybernetic Convolutional Architecture (CCA) will exemplify the role of a proposed phenomenon called *biological spaghettification* in enabling regulatory robustness and evolutionary flexibility. Taking into account the Law of Requisite Variety, the Law of Open-Ended Evolution, and the Every Good Regulator Theorem, it will be shown how highly complex generic regulatory mechanisms emerge. Modeling the emergence of regulatory suboptimality is particularly useful in terms of understanding developmental systems, evolutionary origins, and chaotic dynamical behavior.

Vipin Vijayan, Dominic Critchlow, and Tijana Milenkovic: *Alignment of dynamic biological networks*
(University of Notre Dame)

Network alignment (NA), or graph matching, aims to find a node mapping that conserves topologically or functionally similar regions between compared networks [1]. NA is applicable to many fields, such as computer vision, social network science, and ontology matching. Computational biology is no exception. In computational biology, analogous to genomic sequence alignment, NA can aid the transfer of biological knowledge from a molecular (e.g., gene regularity, protein interaction, or metabolic) network of a well-studied species to a network of a poorly-studied species, between the species' conserved (aligned) network regions. Thus, NA can be used to predict new biological knowledge, such as protein function, in poorly-studied species.

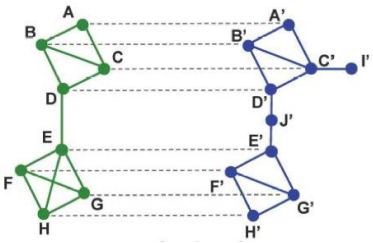

Figure 1: NA finds regions of similarities between networks.

Existing NA methods can only align static networks. However, most complex real-world systems, including the cell and its functioning, evolve over time. Since static networks cannot properly capture the temporal aspect of evolving systems, such systems should be modeled as dynamic networks [2]. We hypothesize that aligning dynamic network representations of evolving systems will produce superior alignments compared to aligning the systems' static network representations, as is currently done.

For this purpose, we introduce the first ever dynamic NA method, DynaMAGNA++ [3]. This proof-of-concept dynamic NA method is an extension of a state-of-the-art static NA method, MAGNA++ [4]. Even though both MAGNA++ and DynaMAGNA++ optimize edge as well as node conservation across the aligned networks, MAGNA++ conserves static edges and similarity between static node neighborhoods, while DynaMAGNA++ conserves dynamic edges (events) and similarity between evolving node neighborhoods. For this purpose, we introduce the first ever measure of dynamic edge conservation and rely on our recent measure of dynamic node

conservation. Importantly, the two dynamic conservation measures can be optimized with any state-of-the-art NA method and not just MAGNA++. We confirm our hypothesis that dynamic NA is superior to static NA, on synthetic and real-world networks, in computational biology (covering molecular gene interaction networks as well as ecological animal proximity networks) and social domains (covering email communications within a company). DynaMAGNA++ is parallelized and has a user-friendly graphical interface.

[1] Faisal, F., Meng, L., Crawford, J., and Milenkovic, T. (2015). The post-genomic era of biological network alignment. EURASIP Journal on Bioinformatics and Systems Biology, 2015(1), 1–19.
[2] Holme, P. (2015). Modern temporal network theory: a colloquium. The European Physical Journal B, 88(9), 1–3
[3] Vijayan, V., Critchlow, D., and Milenkovic, T. (2017). Alignment of dynamic networks. Bioinformatics (*In press*).
[4] Vijayan, V., Saraph, V., and Milenkovic, T. (2015). MAGNA++: Maximizing Accuracy in Global Network Alignment via both node and edge conservation. Bioinformatics, 31(14), 2409–2411.

Micah Auerbach: *A Boolean Model of Early Stem Cell Fate Decisions*
(The College of Wooster)

Stem cell technology promises advancements in medicine and biological research by exploiting cells with the ability to replicate indefinitely before differentiating into any cell type. However, progress is limited by our poor understanding of the regulatory systems that control stem cell identity and lineage choice. We have constructed a Boolean model of a portion of the stem cell regulatory network which is sufficient to describe the first few lineage decisions in early embryonic development, and connected it to a model of cell cycle and apoptosis. Simulation of the model revealed stable states consistent with the naïve and primed embryonic stem cell, as well as the trophectoderm and primitive endoderm. These states are capable of transitioning to other states in response to changing exposure to the environmental inputs LIF, 2i, growth factor, and lineage-specific differentiation signals in ways that are consistent with the developmental program.

SECTION 3

Adilson Motter: *Control of State Transitions in Biological Networks*
(Northwestern University)

Noise is a fundamental part of intracellular processes. While the response of biological systems to noise has been studied extensively, there has been limited understanding of how to exploit it to induce a desired cell state. Here I will present a scalable, quantitative method based on the Freidlin-Wentzell action to predict and control noise-induced switching between different states in genetic networks, which, conveniently, can also control transitions between stable states in the absence of noise. I will discuss applications of this methodology to predict control interventions that can induce lineage changes and to identify new candidate strategies for cancer therapy. This framework offers a systems approach to identifying the key factors for rationally manipulating network dynamics, and should also find use in controlling other classes of complex networks exhibiting multi-stability. (Joint work with D. K. Wells, W. L. Kath).

Thomas MacCarthy: *Robustness and sensitivity in gene regulatory networks under antagonistic coevolution*
(Stony Brook University)

Robustness - defined as tolerance to perturbations such as mutations and environmental fluctuations - is pervasive in biology. Robustness can be observed at many different biological scales ranging from RNA secondary structure all the way up to ecosystems. On an evolutionary timescale, robustness can promote innovation and complexity by increasing the variety of mutations, or genetic variation, which accumulate in a population. But how do robustness and complexity evolve? The magnitude of the evolutionary timescales involved makes it extremely difficult to

address such questions experimentally. Because of this, many studies to date have used computer models that combine simulated evolution with realistic representations of biochemical processes. However, previous studies have been mostly limited to exploring robustness at a single level, usually either protein-protein interaction or gene regulatory networks. This limitation must be overcome in order to explain major changes in biological complexity because the evidence suggests these changes have occurred in parallel at multiple levels. Previous models of gene regulatory network evolution, such as the widely-used Wagner model, have shown that robustness evolves under stabilizing selection, but in more realistic scenarios such as coevolution, it may be advantageous to evolve sensitivity, i.e. for some mutations to change the phenotype. Furthermore, it is unclear how robustness and evolvability will emerge in common coevolutionary scenarios. We have developed a two-population (host, parasite) computational model to investigate how robustness and evolvability become distributed within a network under antagonistic coevolution.

Abhijeet Sonawane: *Constructing Gene Regulatory Networks with Epigenetic data using Message-Passing*
(Harvard Medical School)

The biological processes that drive cellular function can be modeled by a complex network of interactions between regulators (transcription factors) and their targets (genes). One critical influence on these interactions is a cell's "epigenetic state", or whether the regulatory region of a gene is in open chromatin region and physically accessible by a transcription factor in that cell. In our analysis, we used epigenetic information (Dnase-I Seq data) to estimate networks between transcription factors and genes in several different types of cells and benchmarked the accuracy of these networks using independent (ChIP-seq) data. We then applied a message-passing approach to network reconstruction, PANDA (Passing Attributes between Networks for Data Assimilation) to refine these networks. We observed a drastic improvement in network accuracy, including among edges that are uniquely observed in a particular type of cell. Further investigation suggests that the epigenetic state of network interactions can be exploited by PANDA to eliminate spurious links (false-positives) in the networks. Functional enrichment analysis also demonstrates that PANDA is highlighting interactions that are biologically relevant to each cell-type. PANDA works by highlighting common structures across multi-omics networks, a process we are able model using an innovative form of network motifs based on consistency loops.