University of Nebraska Omaha

Innovative Population-based Approaches for Analyzing Mobility Data in Continuous Health Applications

NexTech 2019

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September 2019

Population Analysis in Biomedical Informatics

- Background and general introduction
- The Health Informatics Angle – connecting mobility and health
- The Bioinformatics Angle – Systems Biology and Network Models
- The Computing Angle – How to implement the proposed models

Background and General Introduction

IT and Future Opportunities

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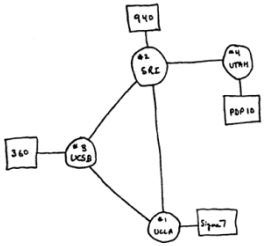
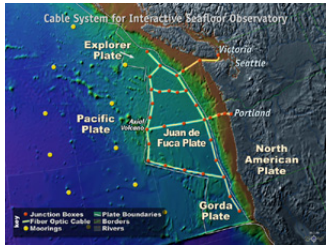
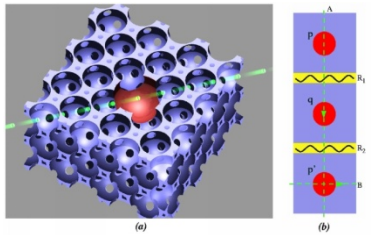
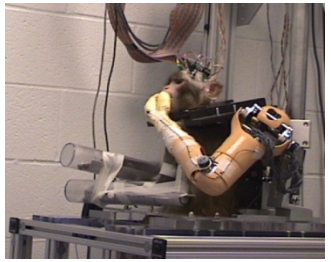
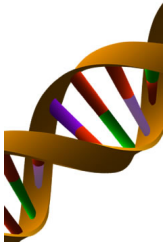
- Creating the future of networking
- Driving advances in all fields of science and engineering
- Revolutionizing transportation
- Personalized education
- The smart grid
- Predictive, preventive, personal medicine
- Quantum computing
- Empowerment for the developing world
- Personalized health monitoring => quality of life
- Harnessing parallelism
- Neurobotics
- Synthetic biology

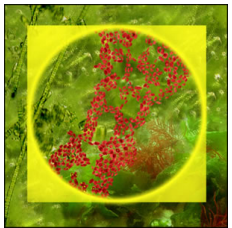












Biomedical Informatics: The new major revolution in Sciences!

- Each generation, a scientific discipline emerges with a bang and promises to change the way we do things – a game changer.
- The last major new discipline was Computer Science over 50 years ago.
- Is it Biomedical Informatics (BMI) for this generation?
- The connection to Human Health add another layer of significance to BMI

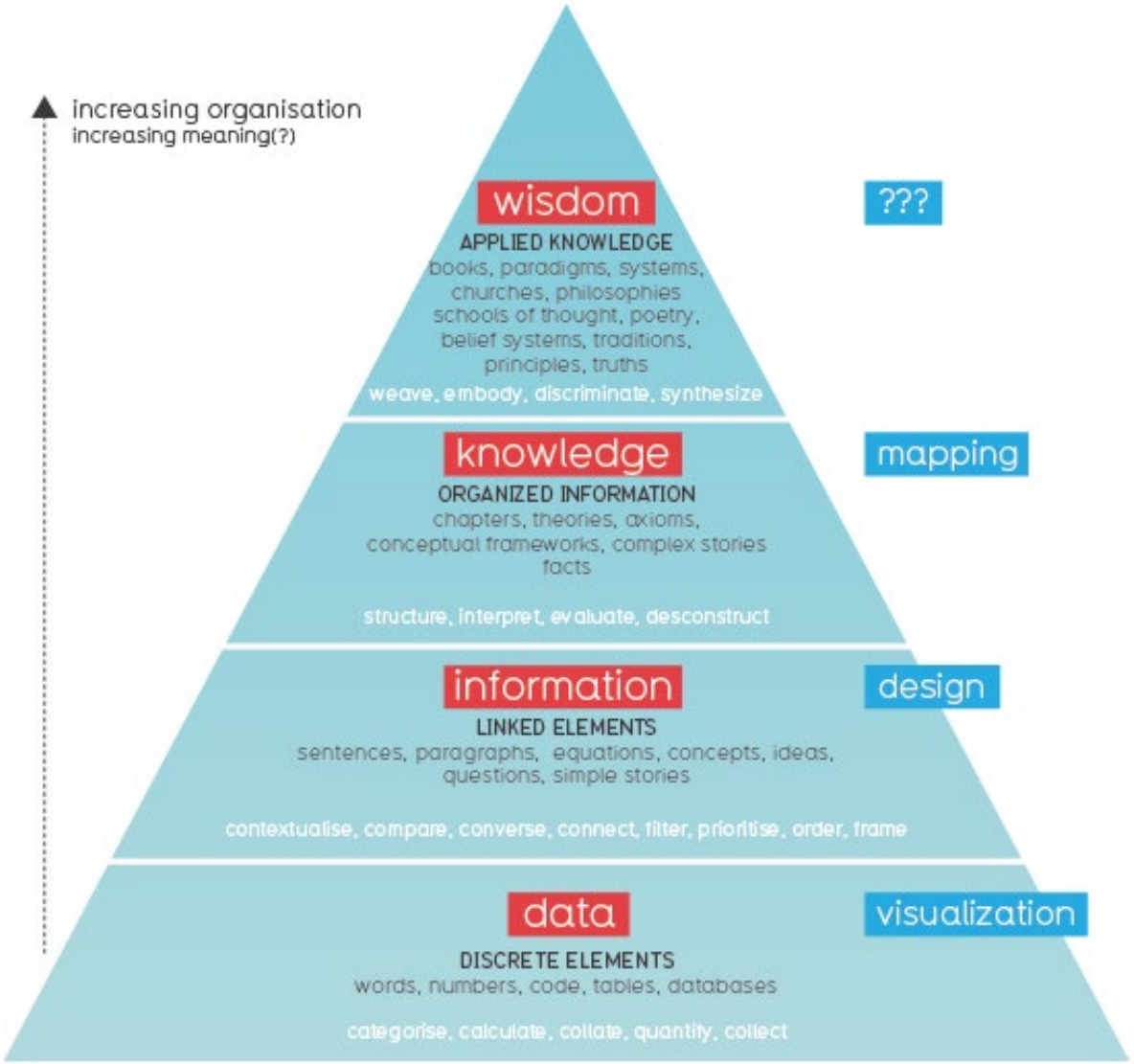
Revolution in Healthcare and Biomedical Research

- Revolutionize Biomedical Research and change healthcare models
- So much relevant data is currently available:
  - Remove the guessing aspect in conducting scientific research and practicing medicine
  - Proactive treatment and personalized medicine
- The availability of data shifted biomedical sciences sciences from pure experimental disciplines to hybrid knowledge-experimental based disciplines
- Incorporating Computational Sciences and Biosciences remains challenging - Interdisciplinary Research? Translational Research? Big Data Analytics?

It's all about the Data!

- How it all began:
  - Advances in medical instruments and computational technologies led to new new research directions
  - Massive accumulation of Biomedical data led to investigating new potential discoveries
  - The availability of enormous various types of public/private Biomedical data
  - How to take advantage of the available data
- Bioinformatics - Health Informatics - Biomedical Imaging - Public Health Informatics Biomedical Devices
- A new direction is now possible

Data-Information-Knowledge-Wisdom



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Smart Data Data-Driven Decisions

- Data: Physical entities at lowest abstraction level; contain little/no meaning – Measured data
- Information: Derived from data via interpretation – Processed data
- Knowledge: Obtained by inductive reasoning, typically through automated analysis and iterative collaboration – data + relationships
- Decision Support

Biomedical Informatics in 2019

- Bioinformatics/BMI is well recognized by researchers and practitioners
- Many believe that Bioinformatics or BMI to be that special discipline for this generation
- Back at mid nineties, one would have expected Bioinformatics to be further along after over 20 years.

Current Barriers in BMI

- On the biomedical side:
  - Too much focus on data collection
  - Competition to own the latest technology
  - Excitement associated with New technologies – which leads to more raw data
  - The black box syndrome
- On the computational side:
  - Certain level of casualness remain a major concern – just another application domain
  - Inconsistent results – lack of robustness and reproducibility
  - Heuristics and thresholds
  - Lack of Biomedical-rich integration

Data Generation vs. Analysis/Integration

- New technologies lead to new data:
  - Competition to have the latest technology
  - Focus on storage needs to store yet more data
- Biomedical community needs to move from a total focus on data generation to a blended focus of measured data generation and data analysis/interpretation/visualization
- How do we leverage data? Integratable? Scalable?
- From Data to Information to Knowledge to Advanced Decision Making

Biomedical Informatics and Big Data

- All the features of Big Data are represented:
  - Volume: New levels of massive data
  - Variety: Only one type of data is not enough
  - Veracity: Not always fully compete or fully trusted
  - Velocity: Data is collected continuously

- Multiple levels of Big Data analysis:
  - Populations
  - Individuals
  - Many granularities in between

Network Modeling and Population Analysis

- It is difficult to provide useful analysis or assessment elements in isolation
- Almost all analysis-related studies are conducted by comparing elements to its population or a group of similar features
- We approach big data analytics by building networks (graphs) of elements under study using different types of inter-relationships among the elements – such as correlations
- We then use graph theoretic properties of constructed networks to mine useful knowledge associated with big data

Examples of Population Analysis

- Biological Networks in Bioinformatics
  - Correlations among genes or interactions among proteins
  - Analysis of microbiomes in soil, water, human guts
- Correlation between mobility and health level
  - Monitoring mobility levels
  - Aging of cells and aging of systems
- Similarity networks and population analysis to study safety issues in bridges
  - Identify bridges that are not safe
  - Propose different maintenance schedules of bridges based on their sufficiency rating
- Analysis of financial markets using behavior networks
  - Analysis of stocks
  - Analysis of financial sectors

Population Analysis

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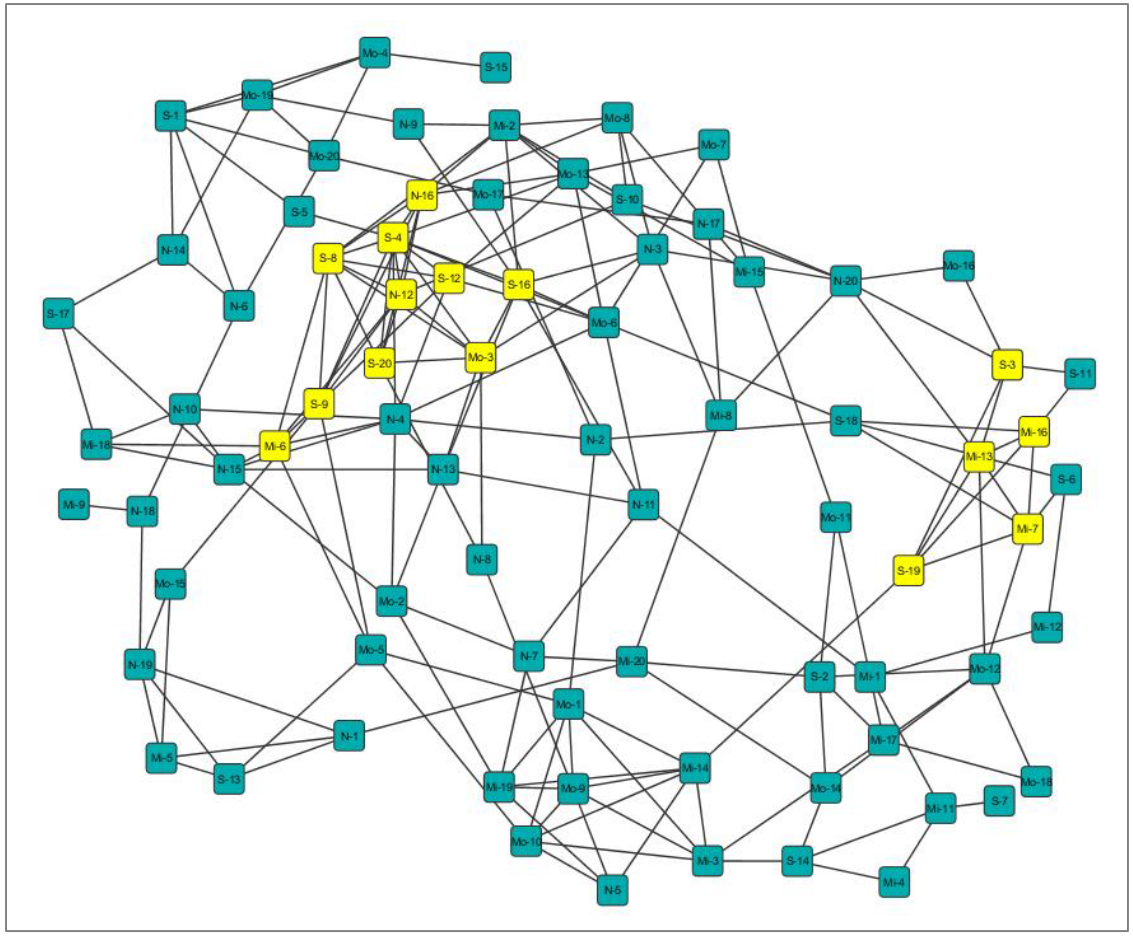
- Correlation graph using mobility parameters



Data Analysis: Systems

- Integrated Approach:
  - Networks model relationships, not just elements
  - Discover groups of relationships between genes

- Discovery
  - Examine changes in systems
    - Control Group vs. Patient Group
    - Young vs. old
    - Stage x versus Stage y in disease progression

The Health Informatics Angle Connecting Mobility and Health

Wireless Networks in Aging

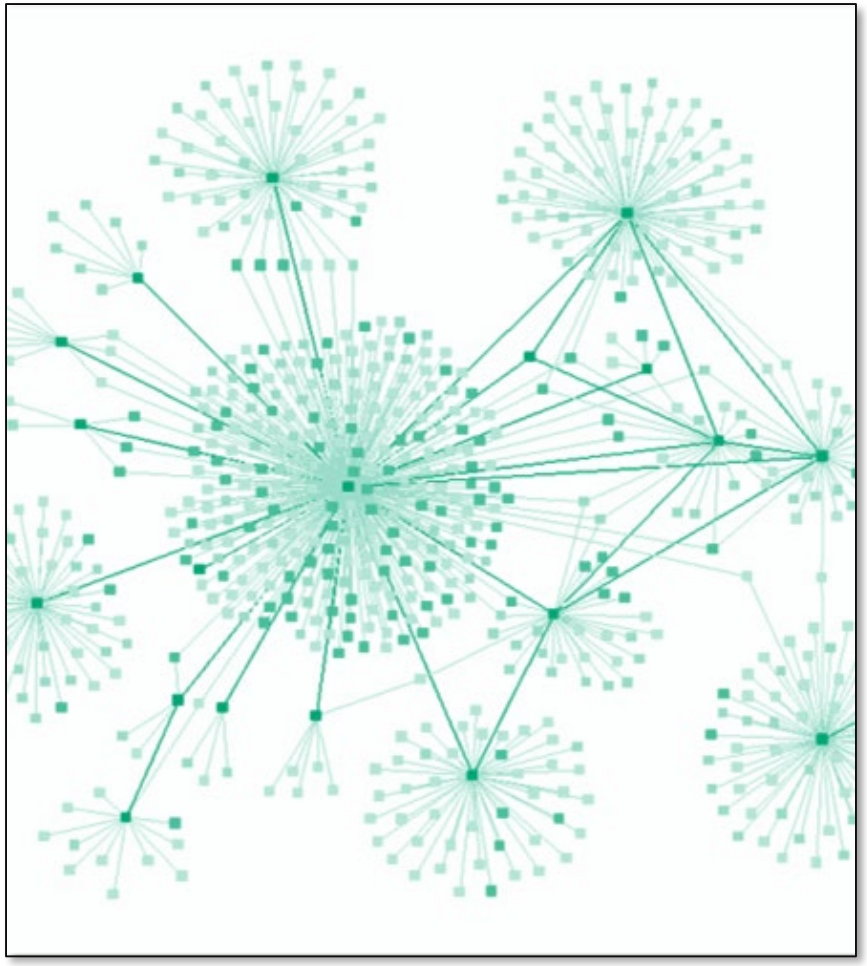
- Correlation between mobility and health level
- Monitoring mobility levels
- Aging of cells and aging of systems
- Collaboration between Bioinformatics group, Wireless Networks group and Decision Support Systems group

BMI Networks

- A BMI network represents elements and their interactions

- Nodes → elements
- Edges → relationships

- Can represent multiple types of elements and relationships



Correlation and Co-occurance Network Applications

- "Versus" analysis
  - Normal vs. disease
  - Times/environments
- Model for high-throughput data
  - Especially useful in microarrays
- Identification of groups of causative genes
  - Ability to rank based on graph structure
  - Identify sets of co-regulated, co-expressed genes

Power of Correlation Analysis

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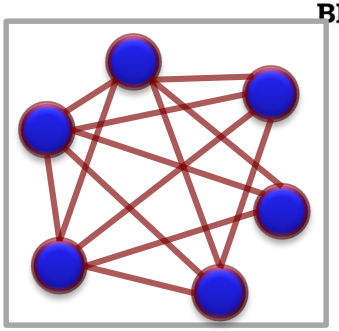
- Correlation versus Causation
- Correlation networks
- Casting the net wide – signal and noise
- The use of enrichment before obtaining information and after for validation

Local Structures

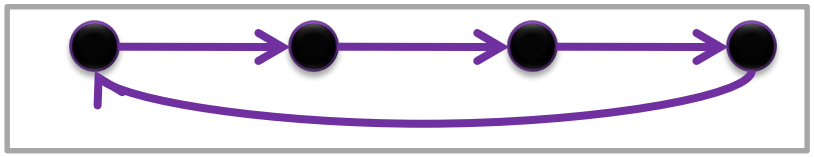
- **Cliques**

  Protein complexes, regulatory modules



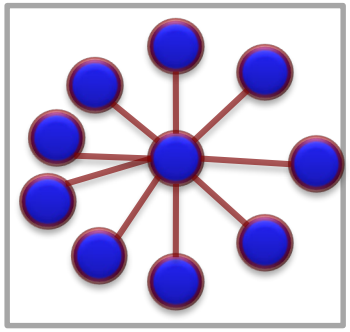
- **Pathways**

  Signaling cascades

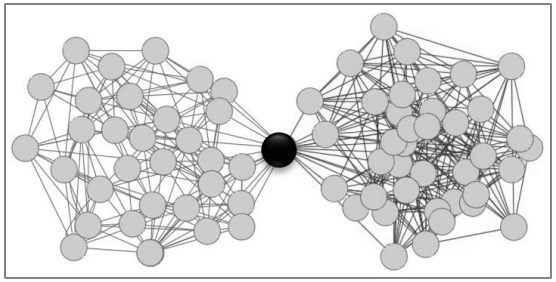


- **Hubs**

  Regulators, TFs, active proteins



- **Articulation points – Gateways**



Hypothesis

Correlation networks are an excellent tool for mining relationship rich knowledge from high-throughput data

Using systems biology approach, CN can help identify:

- *Critical Genes* that are essential for survival
- *Subsets of genes* that are responsible for biological functions

Measures of centrality to identify key elements:

Proves existence of structure/function relationship in correlation networks

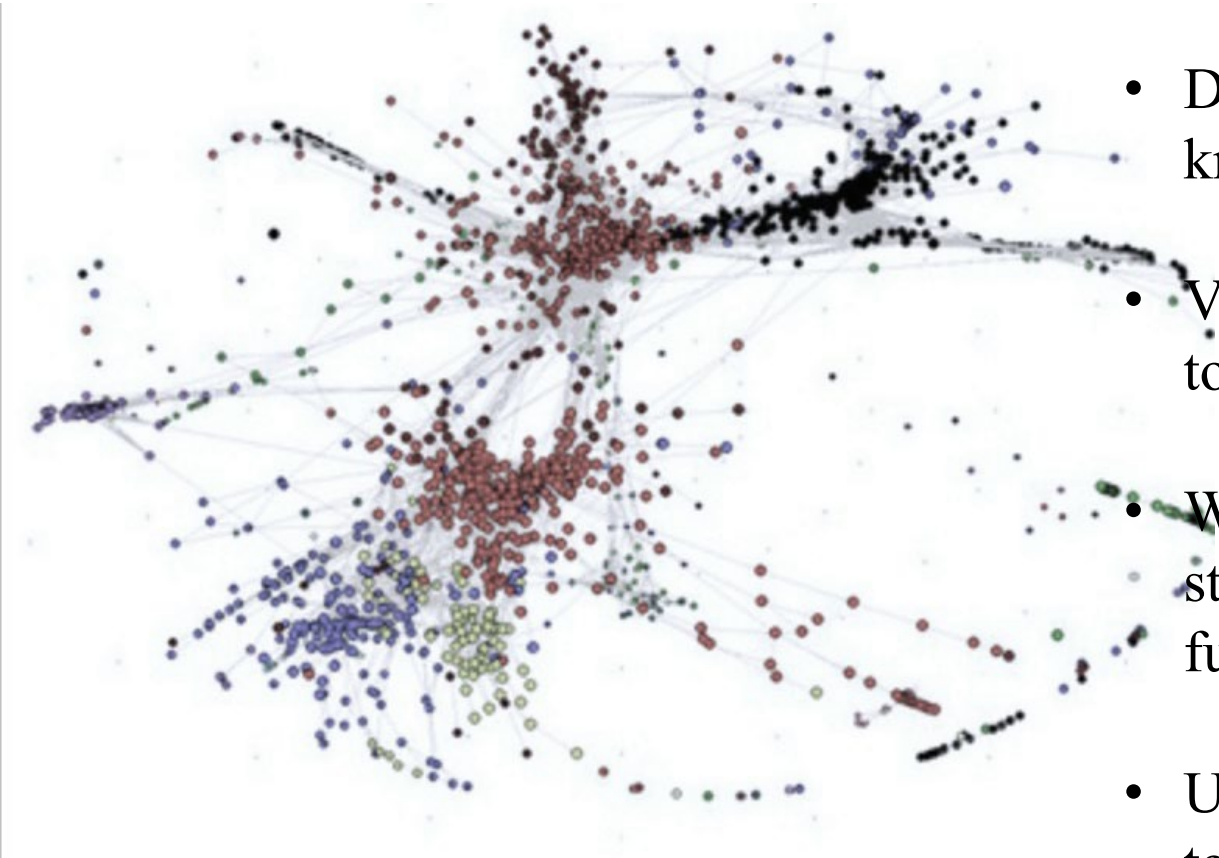
Health Monitoring

- Availability of many large useful devices – focus on collecting relevant data
- Availability of numerous helpful software packages
- Lack of data integration and trendiness of the discipline
- Fragmented efforts by computational scientists and biomedical scientists
- Lack of translational work – from the research domain to health care applications
- Increasing interest among researchers, industry and educators

How to collect mobility data?

- Laboratory setting
- Real-world setting
- Self-reported data collection method
- Using monitoring devices, sensors and accelerometers or using Internet of Things (IoT) devices

Correlation Networks and Population Analysis



- Able to handle ‘big’ data
- Draws from centuries of knowledge in graph theory
- Visually appealing and easy to understand
- When built correctly, structures can be tied to function
- Used in social, biological, technical applications

Goals of the Project

- Mobility Profile
  - Patient wearing a 3D-accelerometer will be monitored 24/7.
  - A complete mobility profile will be available for patients and care providers.
- Health hazards Prediction using Mobility Profiles
  - The system will identify anomalous movement and patterns that usually result in a fall or injury,
  - We would be able to take preemptive measures when such a pattern is detected, in order to reduce the occurrence of falls and prevent fall-related injuries.
  - We will develop an index that enables health care providers to determine how likely people are to fall.

Earlier Mobility Models

Experimental Studies

- Simulation Study
  - Mobility of nurses in a hospital – 8 hour shifts versus 12 hour shifts
  - Monitoring mobility pattern changes at different times during the shift
- Experimental Study
  - Mobility of mice in a cage
  - Identifying/classification of various groups based on mobility characteristics

Nursing Study

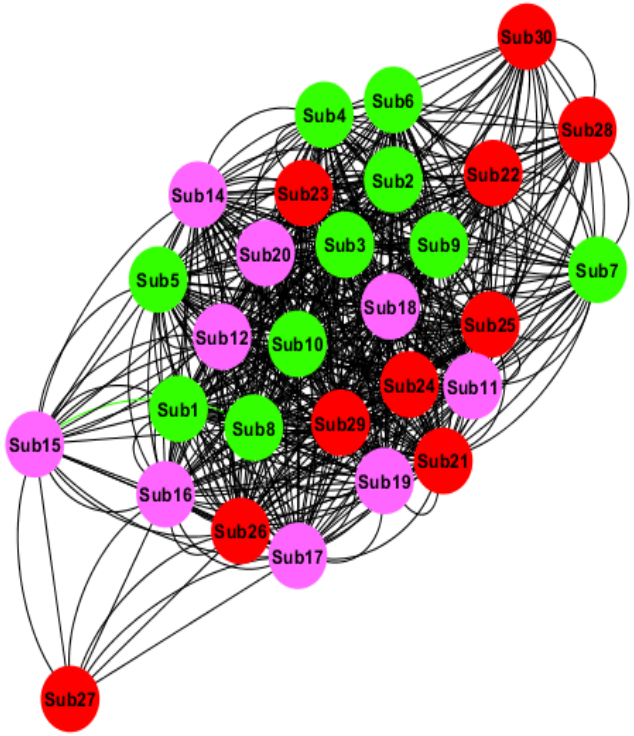
- Sample Generation Setting
  - Weighted activity level value
  - Each group has different mobility decline rate per hour
  - Group1 - 10%/hour, group2 - 20%/hour and group 3 – 30%/hour (shown in different colors)

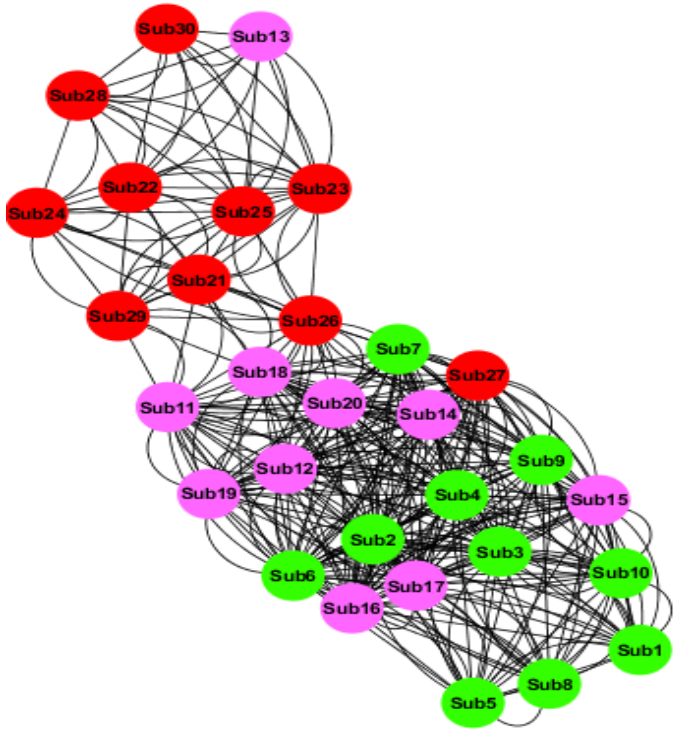
	Sub1	-	-	Sub30
Work start	553.78	-	-	384.85
2nd hours	498.40	-	-	269.40
4th hours	448.56	-	-	188.58
6th hours	403.71	-	-	132.01
Work end	363.34	-	-	92.40

Scenario Description

- Analyzing clusters from correlation networks
- Networks are constructed for every mobility samples captured from nurses at 4 different times as the day progresses.
- Magnitude based analysis applied
- Different levels of mobility decline in nurses identified from networks.

Networks Formed



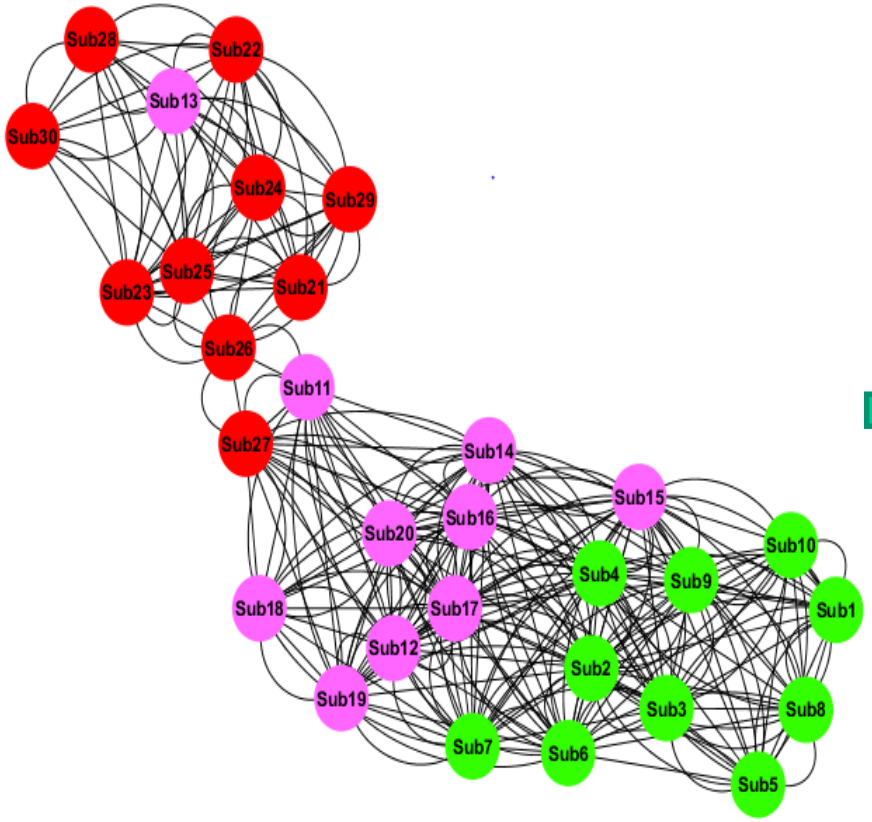


Sample 1

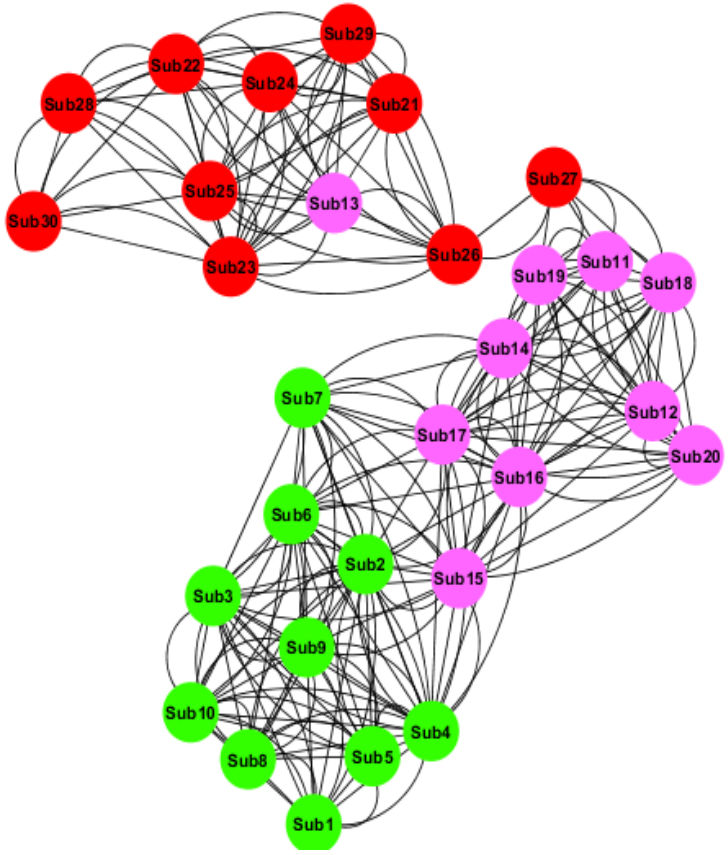
Sample 2

Green nodes – Group 1
Pink nodes – Group 2
Red nodes – Group 3

Networks Formed



Sample 3



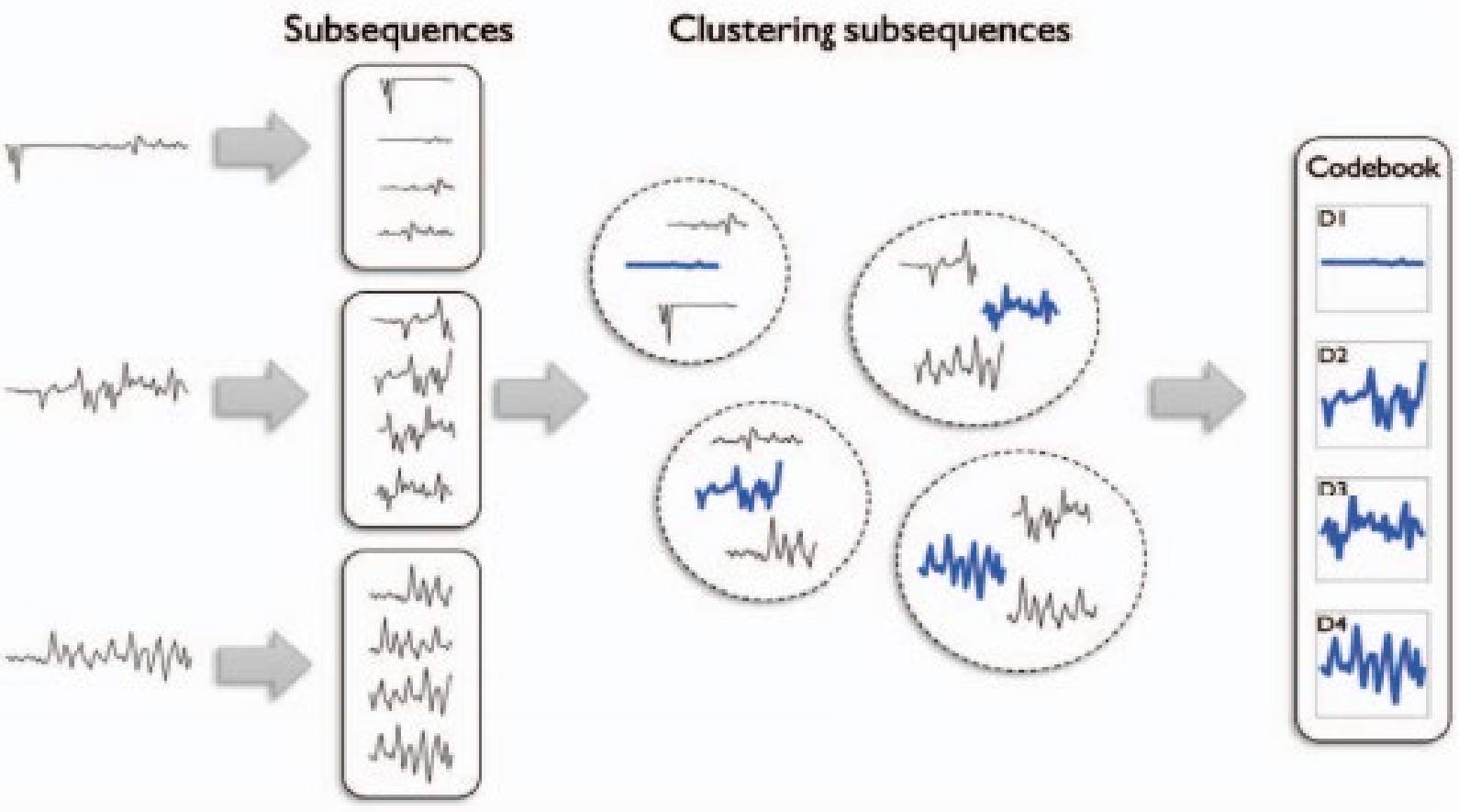
Sample 4

Green nodes – Group 1
Pink nodes – Group 2
Red nodes – Group 3

Results

- In the beginning of working days, clusters have mixed groups
- As the time progressed in the day, the same colored nodes (nurses) formed a separate clusters according to their raw mobility meausres.
- This network shows different clusters each of low (red), medium (pink) and high (green) mobilities.
- Application to predict medical hazards
- Practical to free-living environment

Feature Engineering- Movement Words Coding Scheme



Dataset: Participants and Protocol (Ankle Data)

- Protocol:
  - 40 Meter Walking (10-meter walkway back and forth)
  - Sampling frequency:100
  - Mild PD

	Control	PD	Geriatrics
Number of subjects	10	10	10
Gender (M/F)	5:5	6:4	5:5
Age	64 ± 8.4	63.8 ± 9.3	81 ± 4.1
UPDRS III		12.7 ± 6.0	
H & Y		1.7 ± 0.9	

Dataset: Participants and Protocol (Ankle Data)

- Protocol:
  - 4 minute Walking (around the hospital)
  - Sampling frequency:100
  - Moderate PD

	Control	PD	Geriatrics
Number of subjects	5	5	5
Gender (M/F)	3:2	3:2	2:3
Age	64 ± 10	72 ± 6.3	81 ± 5.9
UPDRS III		20.8 ± 6.1	
H & Y		2.6 ± 0.5	

Dataset: Participants and Protocol (Wrist Data)
First Phase

- Three phases of data collection (6-months period between each two phases)- One week of data per individual-
- Sampling frequency:100
- Mild, moderate, and sever PD (overall mild PD)

	Healthy young	Healthy elderlies	PD
Number of subjects	24	32	25
Gender (M/F)	14/10	10/22	20/5
Age	24 ± 3.6	64.2 ± 7	71 ± 6.2
UPDRS III		------	
H & Y			1.73 ± 0.83

Modeling: Machine Learning

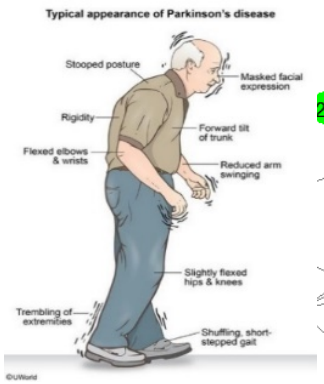
- **Standard Features:**
  - All features (32)
  - First reduced set of features (22)
    - Using Information Gain and Ranker methods
  - Second reduced set of features (8)
    - Using Pearson Correlation coefficient and ANOVA table
  - Third reduced set of features (7)
    - feature sets with one feature less than the optimal number of features
- **Document-of-Words Features:**
  - 10 Features for wrist data and 4 features for ankle data
- **Various Machine Learning Techniques:**
  - SVM, Random Forest, Naïve Bayes, AdaBoost, and bagging
- **Validation:**
  - K-Fold Cross validation
- **Accuracy measures:**
  - F-measure, Precision, Recall

Population Analysis and Similarity Network Models

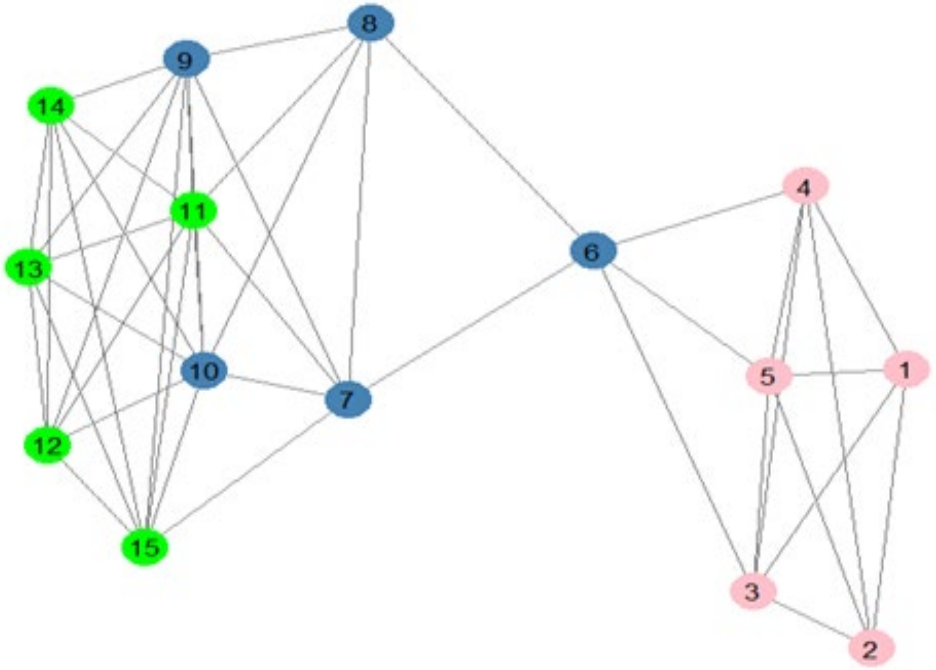
- Pairwise Correlation
  - A pairwise Pearson correlation analysis between subjects, using gait parameters
  - Threshold → 90%
  - Significance → 0.05

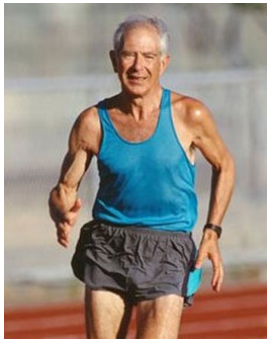
- Creating Network Model
  - Vertices represent subjects
  - If two subjects are highly correlated, there is an edge

Similarity Network Model – Wrist Data-Word Features

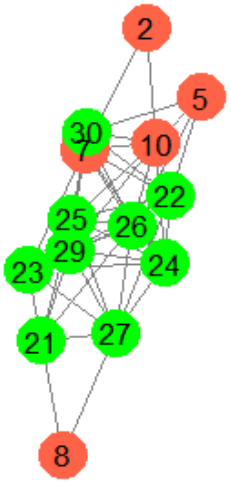


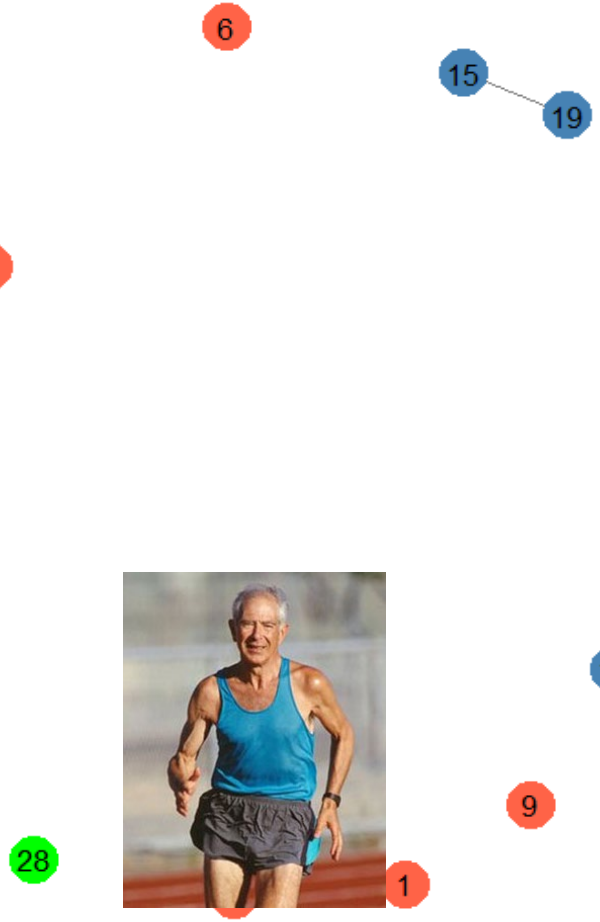
Similarity Network Model- Ankle Data (Moderate PD)-All Features



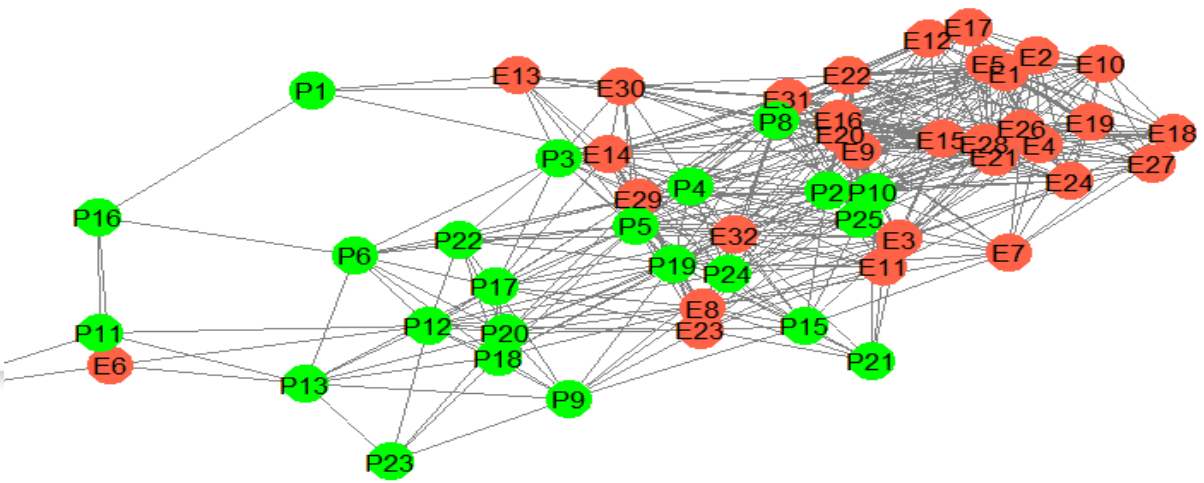


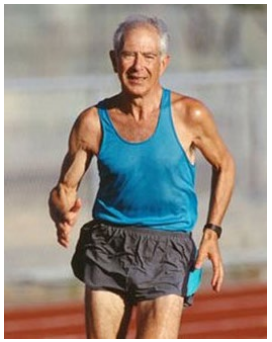
Similarity Network Model- Ankle Data (Mild PD) All Features





Similarity Network Model for the data from the first phase of wrist dataset- Threshold at **90%-** PD and HE





Subject	Gender	Age	MoCA	FoG	FAB	TUG	GDS	H&Y	MFES	Lawton
PD8	Male	69	28	2	39	6.7	0	1	10	8
PD10	Male	71	28	1	39	6.7	1	1	9.3	8
PD1	Male	83	26	8	39	11.2	0	1	8.6	8
PD21	Male	54	25	0	39	9.0	0	1	10	8

Summary of Case Study

- Correlation Network model worked beautifully when we applied it to both dataset.
- MIGMC provided us with the best set of features
- Accelerometers at ankles and Wrist can capture gait parameters that are useful in early diagnosis of disease.
- The performance of Bag-of-Words model is ,if not higher than, equal to the Standard Model
- Ankle data are more precise in identification of patients with PD compared to Wrist Data
- Still wrist could be argued as a better body location (87.5% accuracy is good enough)

Applications in hospital: Post-operative Nursing Care

- A *post-operative* assessment is very important to a full and speedy *recovery from* any type of *surgery*.
  - a full assessment and an individualized treatment plan based upon the patient's needs and level of function, coupled with clinician expectations

Applications for health subject: Physical therapy / Rehabilitation

- help a patient perform rehabilitation exercises to improve their balance and mobility, and
- find exercises that meet patient's specific needs and abilities.

The Bioinformatics Angle
Systems Biology and Network Models

Data Analysis: Systems Biology

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- Integrated Approach:
  - Networks model relationships, not just elements
  - Discover groups of relationships between genes

- Discovery
  - Examine changes in systems
    - Normal vs. diseased
    - Young vs. old
    - Stage x versus Stage y

Case Study in Aging

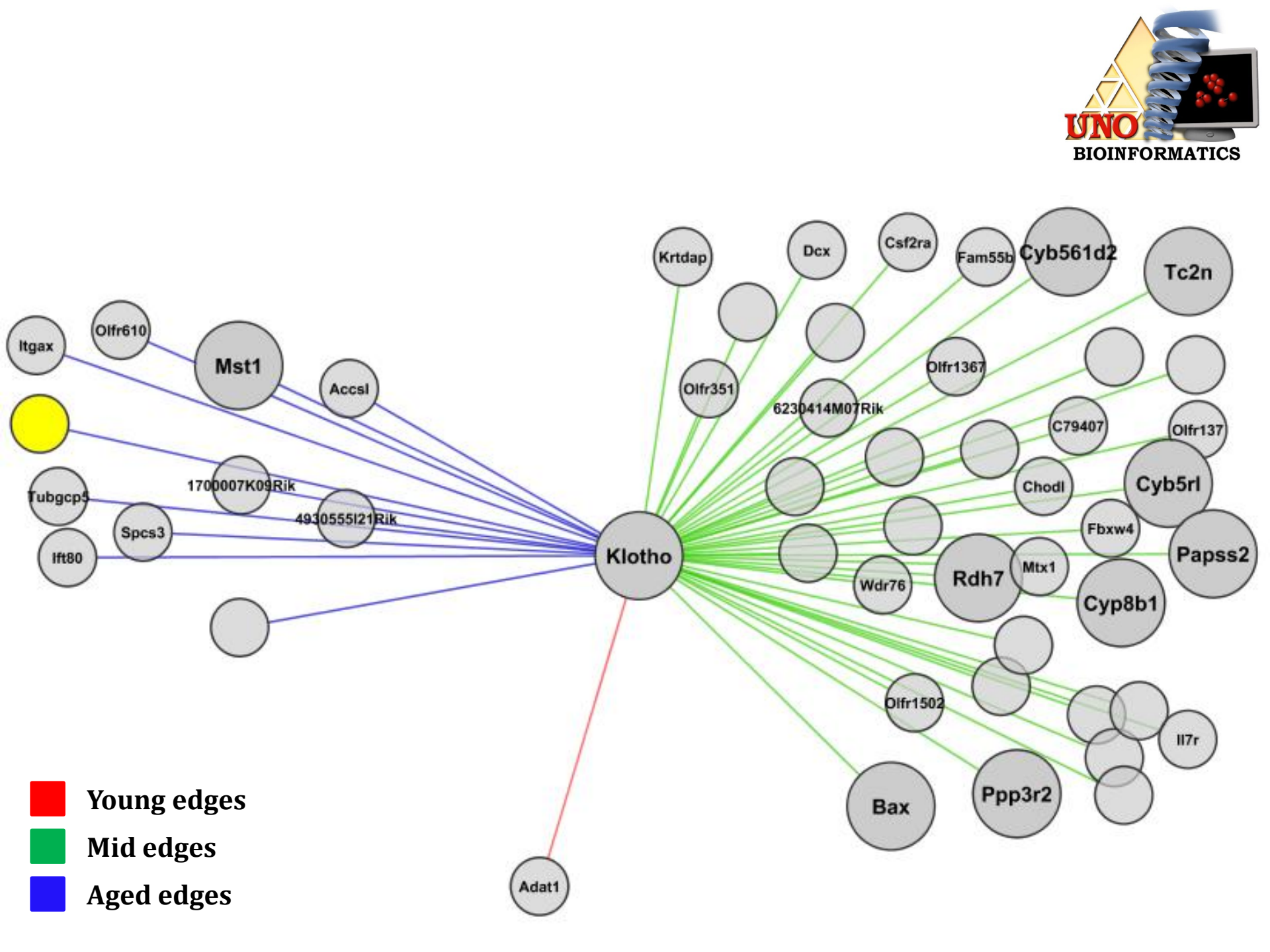
- 5 sets of temporal gene expression data

Strain	Gender	Tissue Type	Ages
BalbC	Male	Hypothalamus	Young, mid-age, aged
CBA	Male	Hypothalamus	Young, mid-age, aged
C57_J20	Male	Hypothalamus	Young, aged
BalbC	Female	Hypothalamus	Young, aged
BalbC	Female	Frontal cortex	Young, aged

Hub Lethality

- Young Male BalbC Mouse
  - 12/20 hubs tested for *in vivo* knockout
    - 8/12 lethal phenotype pre-/peri-natally
    - 4/12 non-lethal but system-affecting
    - 0/12 no observed phenotype

- Aged Male BalbC Mouse
  - 11/20 hubs tested for *in vivo* knockout
    - 7/11 lethal phenotype pre-/peri-natally
    - 3/11 non-lethal but system-affecting
    - 1/11 no observed phenotype (Aldh3a1)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Fbxw4
Ift80
Klotho
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Rdh7
Mtx1
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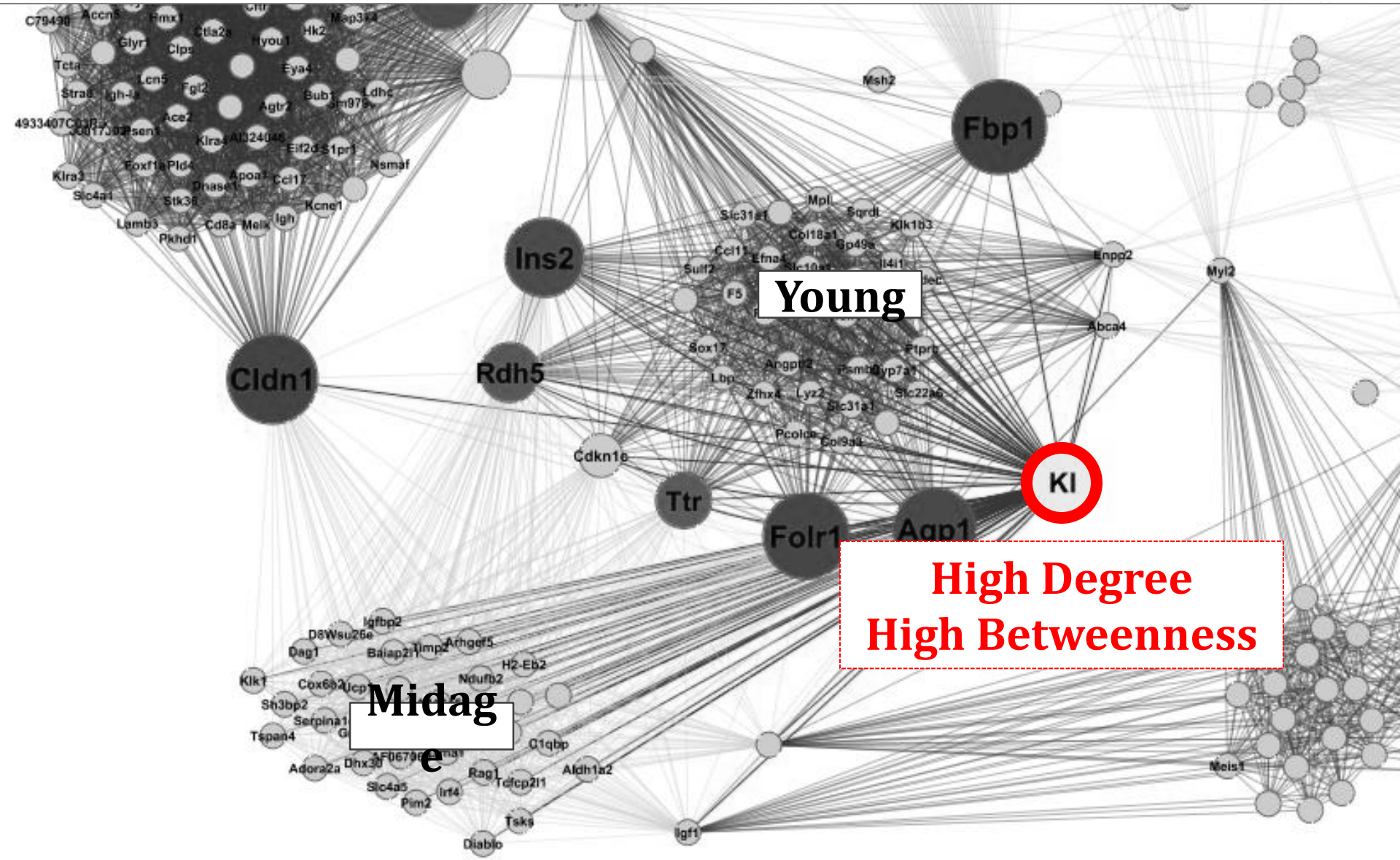
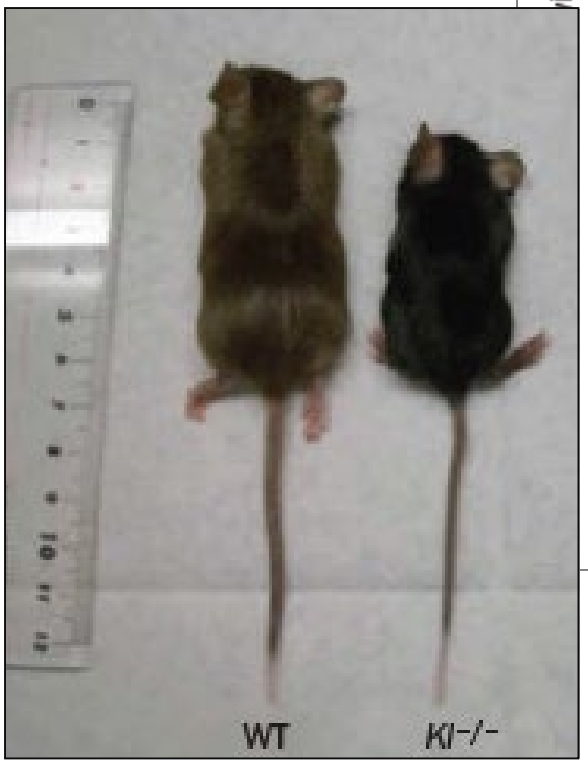
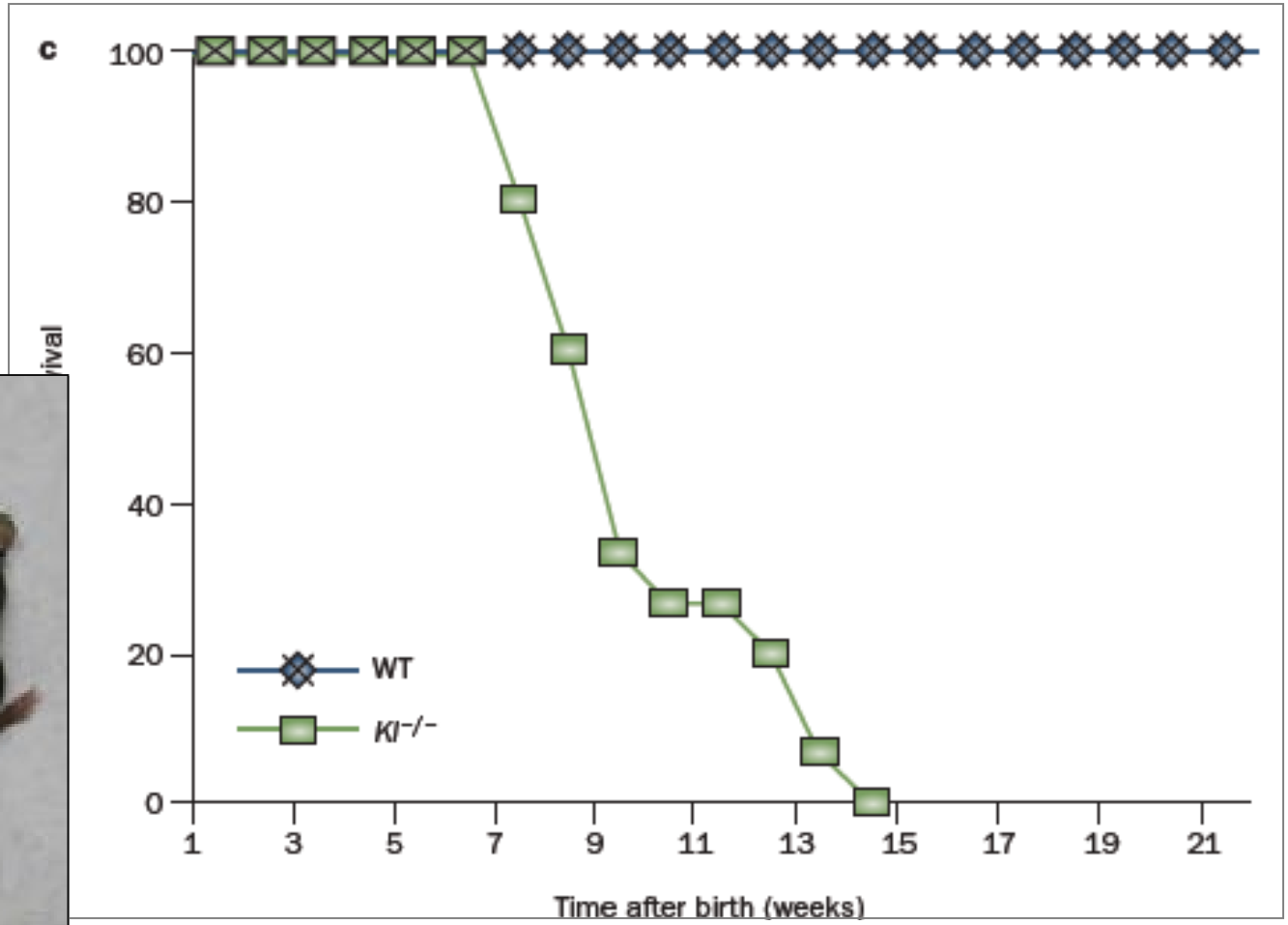
Olfr1502
Il7r
Bax
Ppp3r2
Adat1
Young edges
Mid edges
Aged edges

Critical Node: Klotho



Validation





Razzaque,2009. Nat. Rev. Endocrin. 5:611-619

HIV and Drug Addiction

- Methamphetamine is a major drug of abuse with reported high use by HIV-infected groups
- Methamphetamine users have higher risk of getting HIV infection
- Impact on nervous system is higher when Methamphetamine is used by HIV infected individual (neuronal injury)

Role of Methamphetamine

Infected	Not Infected
Infected + Combinatorial Drugs	Not Infected + Combinatorial Drugs
Infected + Meth	Not Infected + Meth
Infected + Meth + Combinatorial Drugs	Not Infected + Meth + Combinatorial Drugs

Clusters Enriched in Specific Functions

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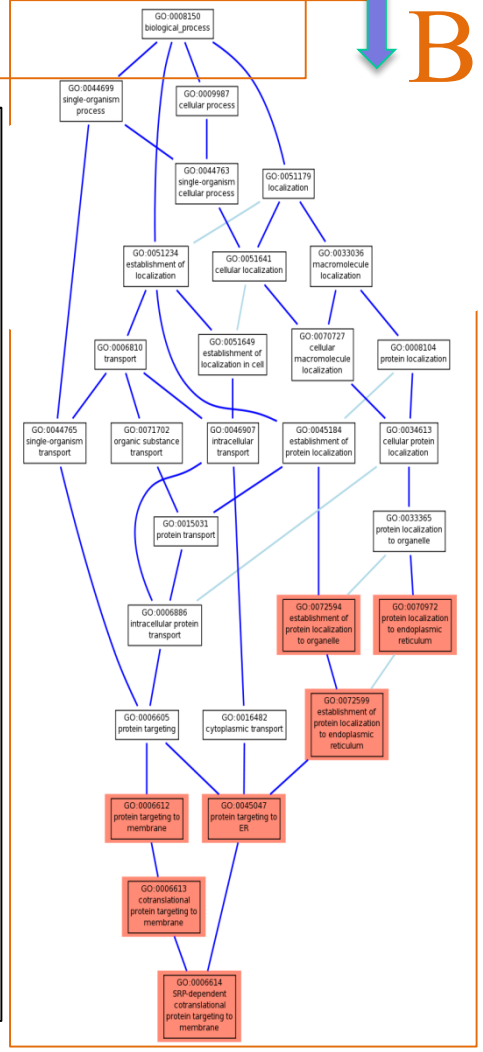
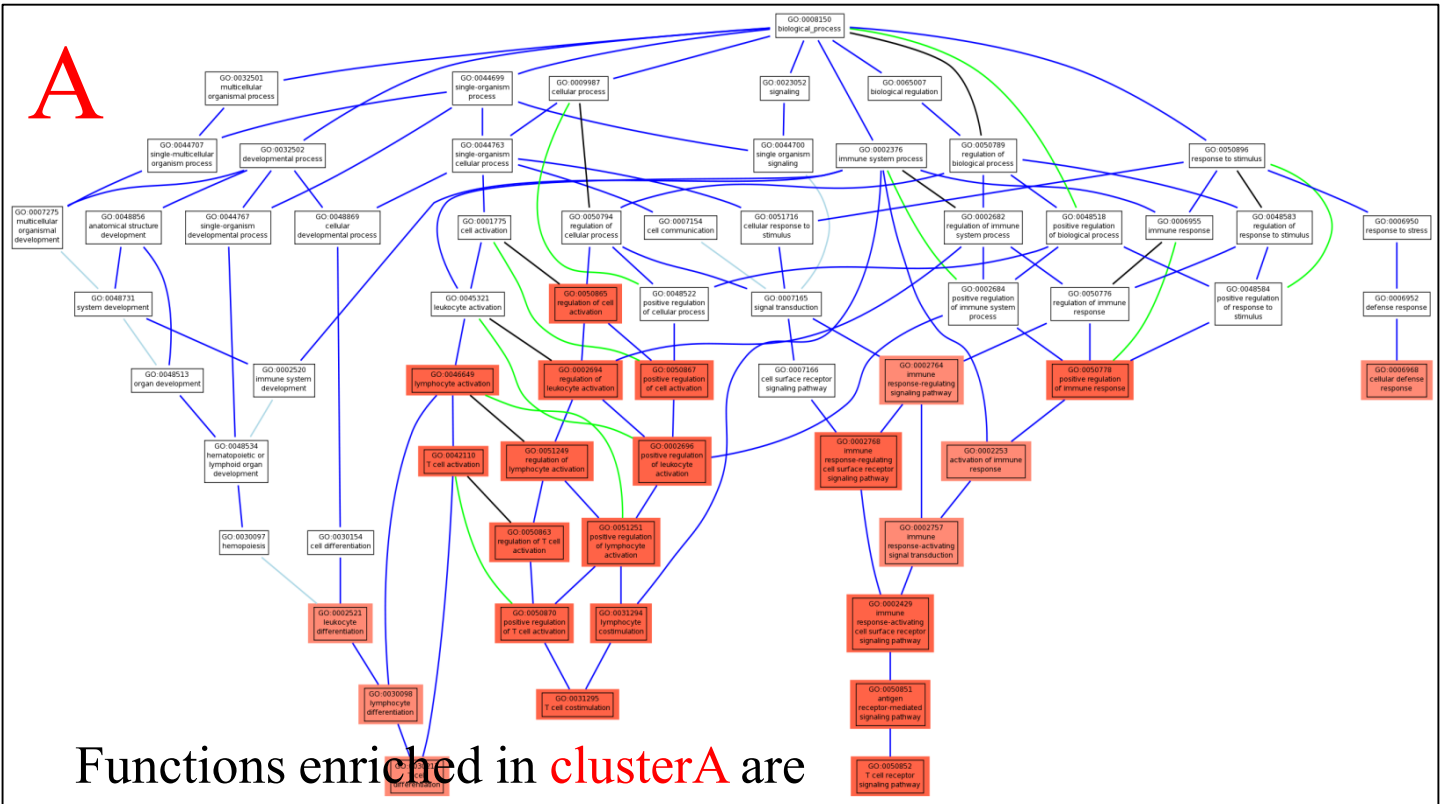
Functions enriched in clusterB are protein targeting and localization.

B

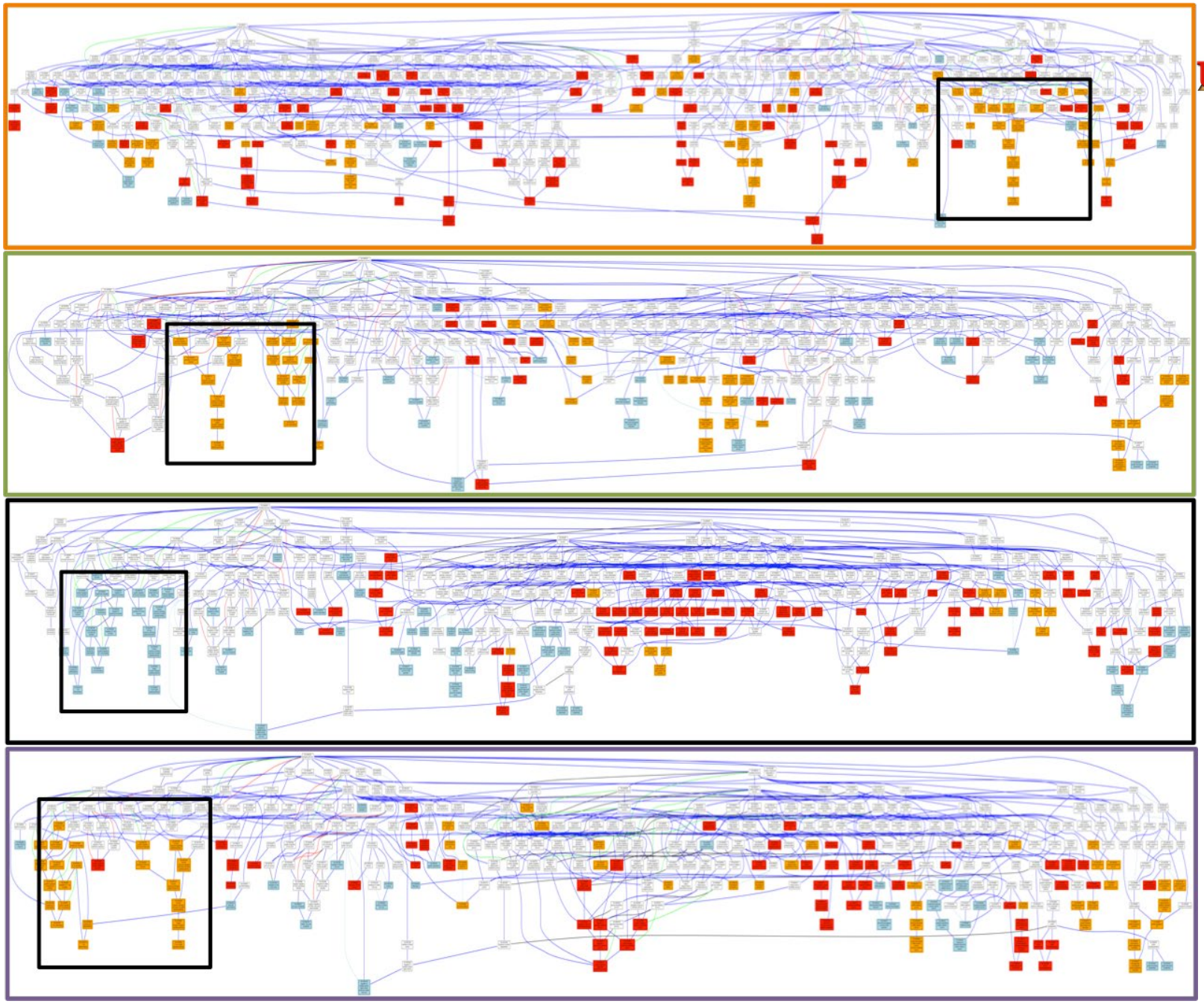


A



Functions enriched in clusterA are all immune response specific.

Orange nodes = enriched in both sets; Blue nodes = enriched only in Uninfected



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Infected vs. Uninfected

HIV treatment vs. Uninfected

Infected + Meth vs. Uninfected

Infected + Meth+ Treatment vs. Uninfected

Obtained Results

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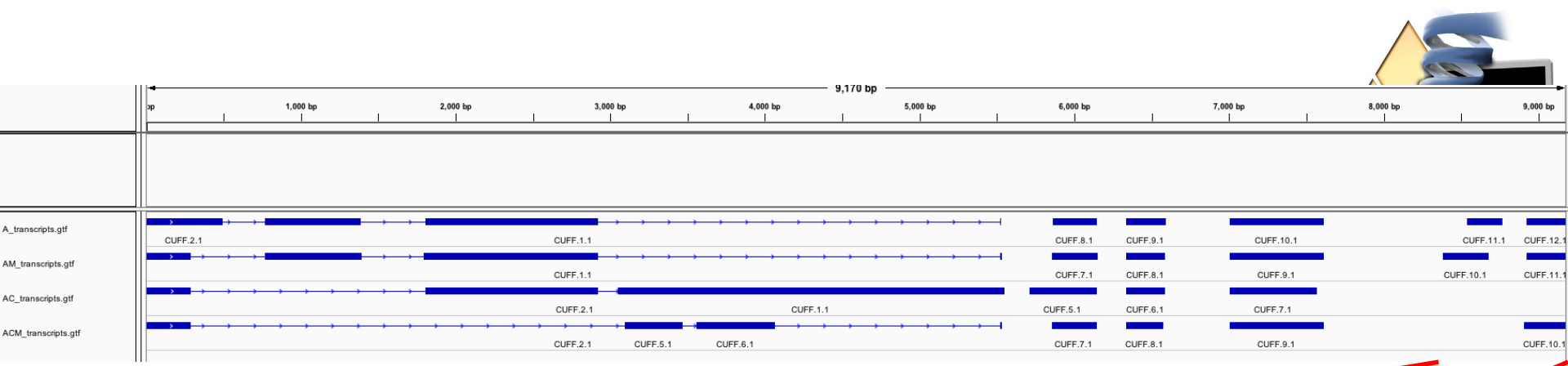
- Large number of nodes are enriched in only one network in Infected + Meth network.
  - Many functions enriched in other conditions have been dropped out in Infected + Meth network.
- Most of the lost functions reappear in Infected + Treated
- Some of these lost functions reappear in Infected + Meth + Treatment

Validation: *nef* gene (GenBank)

- viral accessory protein
- important for virus replication in vivo
- determinant of HIV-1 pathogenesis
- down-regulates cell surface CD4 and MHC class I molecules; enhances virus infectivity through interactions with multiple cellular signaling proteins



Region of *nef* gene

A

AM

AC: disappeared

ACM: comes back

The Computing Angle
How to implement the proposed models

How to implement this stuff? Computational Issues

- Graph/Network Modeling
- Graph Algorithms
- High Performance Computing
  - Beyond surface-level adaptation of known algorithms
- Wireless Networks
- Statistical Analysis
- Storage/processing models - Security and Privacy

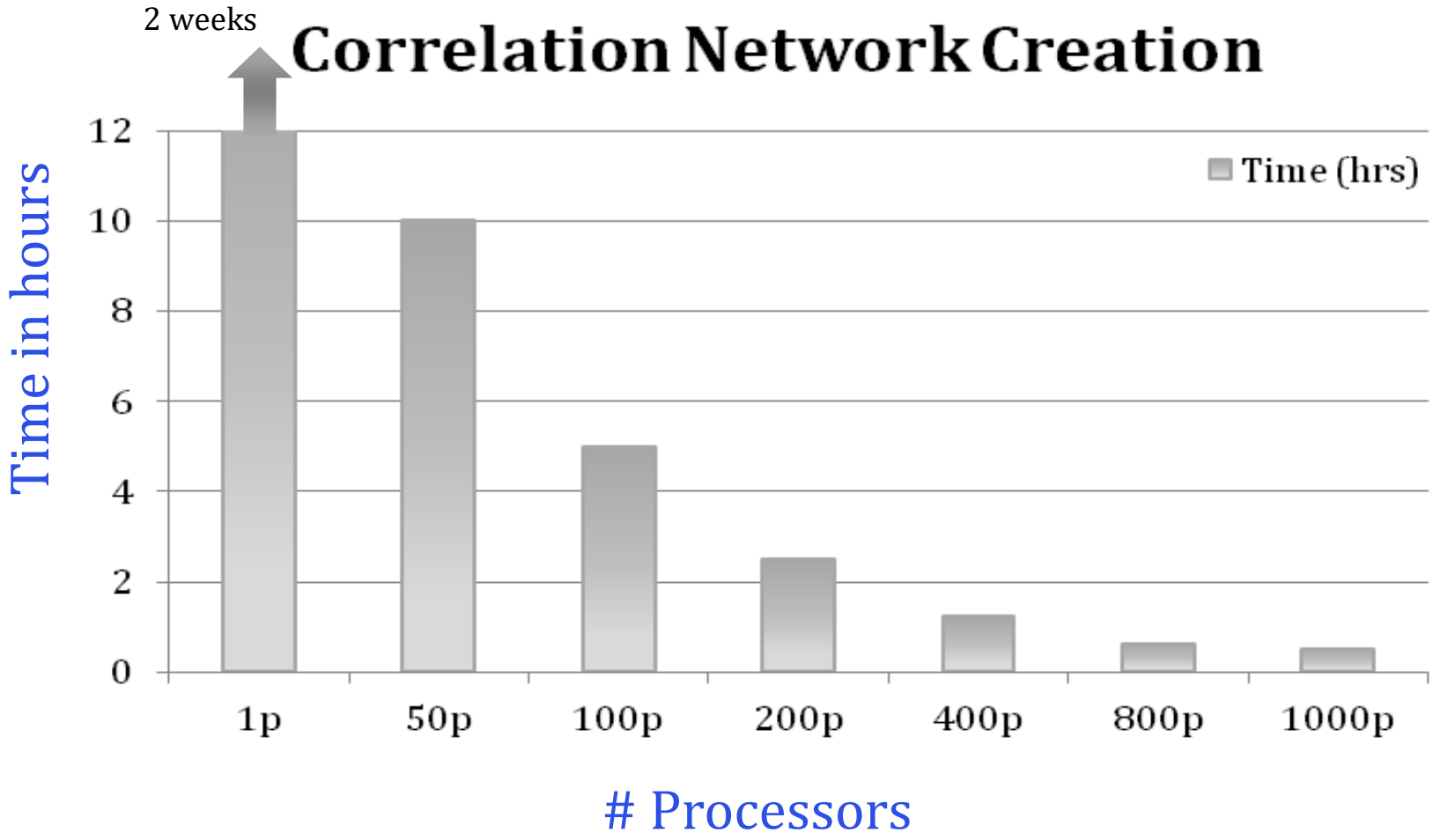
HPC and Big Data

- Network creation: 2 weeks on PC
  - 10 hours in parallel, 50 nodes
  - 40,000 nodes = 800 million edges (pairwise)
  - 40,000 ! Potential relationships
  - Big data or big relationship domain

- Network analysis: Best in parallel
  - Only 3% of entire genome forms complexes

- Holland Computing Center: Firefly 1150 8-core cluster – from weeks to hours/minutes

The Need for HPC



Technical/Innovative Solutions

- Smarter input data: better user level utilization plus integrated domain knowledge with computational tools
- New data reduction models to deal with large data sizes and allow for better and faster data mining
- Better application specific parallelization – custom solutions lead to better performance
- Better scheduling model: multi-layer dynamic scheduling solution

Network Filters

Design a network filter and obtain a sub-network of the original network such that:

- It maintains the important stuff – signal
- Remove unimportant stuff – noise
- Maintain network elements of biological relevance
- Uncover new ones

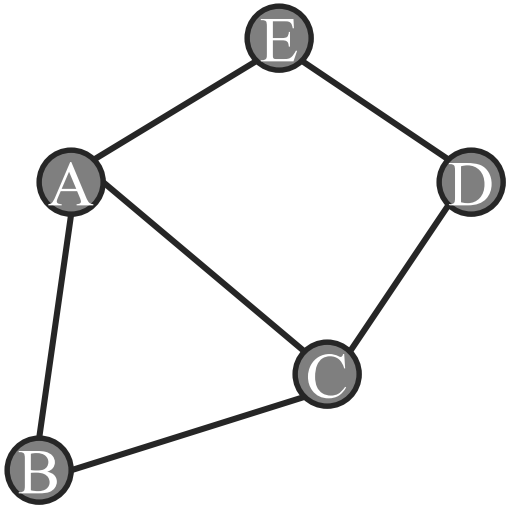
Chordal Graph Sampling

Goal: Develop a parallel network sampling technique that *filters noise*, while *preserving the important characteristics of the network*.

- ✓Maximal Chordal Subgraph
  - ➢Spanning subgraph of the network w
    - ➢No cycles of length larger than three
- ✓Properties of Chordal Graph
  - ➢Preserves most cliques and highly connected regions of the network
  - ➢Most NP hard problems can be solved in polynomial time
  - ➢Complexity of finding maximal chordal subgraphs: **O(|E|*max_deg)**

Why chordal graphs?

- Chordal graphs are triangulated
  - We want to preserve K_3 subgraphs (triangle)
  - K_3 graphs/motifs are known to represent co-regulated genes
  - Use chordal graphs as a filter for finding co-regulated structures



Subgraph formed by A,B,C is more likely to be biologically relevant.

If gene A and gene B are co-regulated, and if gene A and gene C are co-regulated, then genes B and C will be co-regulated.

Biosciences at Crossroads

- Many Scientific disciplines are now at crossroads
- The proper penetration of IT represent tremendous challenges and great opportunities
- The importance of interdisciplinary approach and knowledge integration to problem solving
- The need for in-depth analysis and problem solving rather than the surface-level approaches
- This may lead to scientific revolution

Acknowledgments

- UNO Bioinformatics Group

  Kiran Bastola

  Sanjukta Bhoomwick
  Kate Cooper
  Dario Ghersi
  Ishwor Thapa
  Ling Zhang

  Sean West
  Vi Dam
  Suyeon Kim
  Donovan Orn
  Elham Rastegari

- Biomedical Researchers

  Richard Hallworth
  Vivian Marmalat

- Funding Sources

  NIH
  NSF

  Nebraska Research Initiative

- Former Group Members

  Alexander Churbanov
  Xutao Deng
  Huiming Geng
  Xiaolu Huang
  Daniel Quest
  Julia Warnke-Sommer