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Network Physiology: a case study in Dental Medicine and an overview of applications to Big Data in Health

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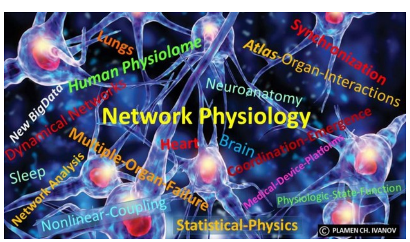
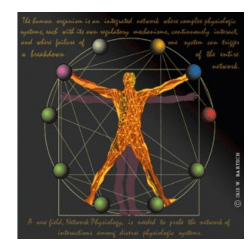


Second International Summer Institute on Network Physiology (ISINP)

Lake Como School of Advanced Studies – July 28 – Aug 2, 2019



ISINP 2019

Overview

- Graphs, Physics & Networks
- Data, Projections & Networks
- Dentistry, Treatments & Networks
- Big Data, Knowledge Discovery & Networks
- Conclusions

GRAPHS

- Leonhard Euler, 1736: first paper of graph theory

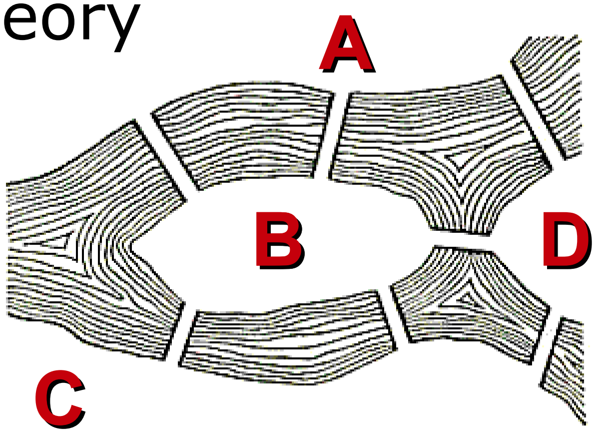


FIGURE 98. *Geographic Map: The Königsberg Bridges.*

- Dénes Kőnig, 1936: first textbook on graph theory

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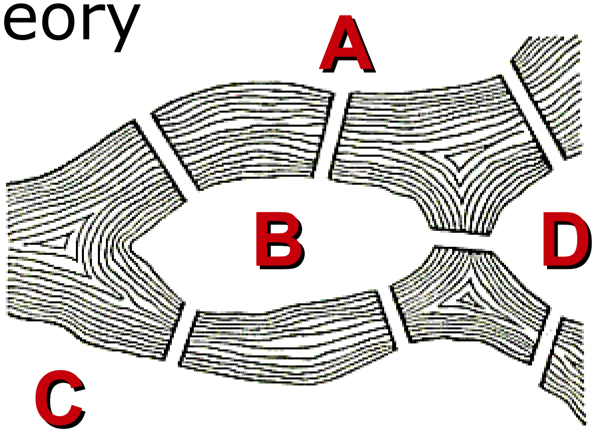

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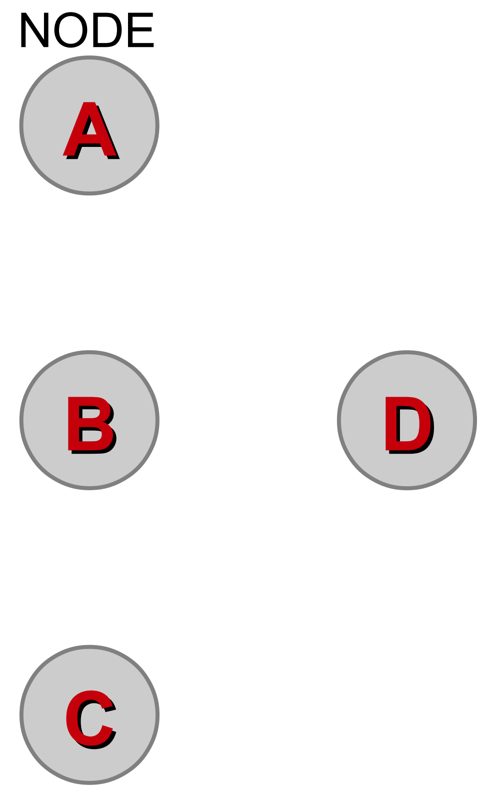

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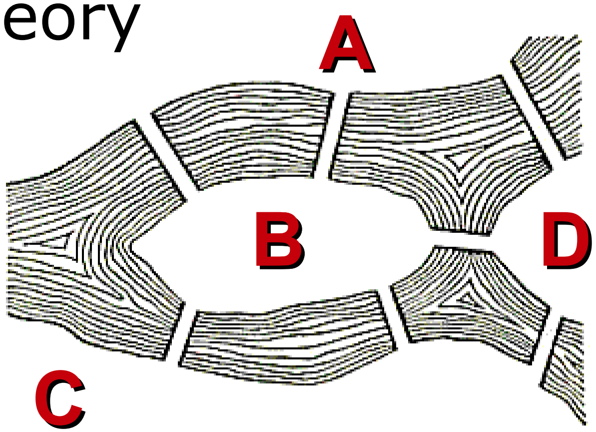

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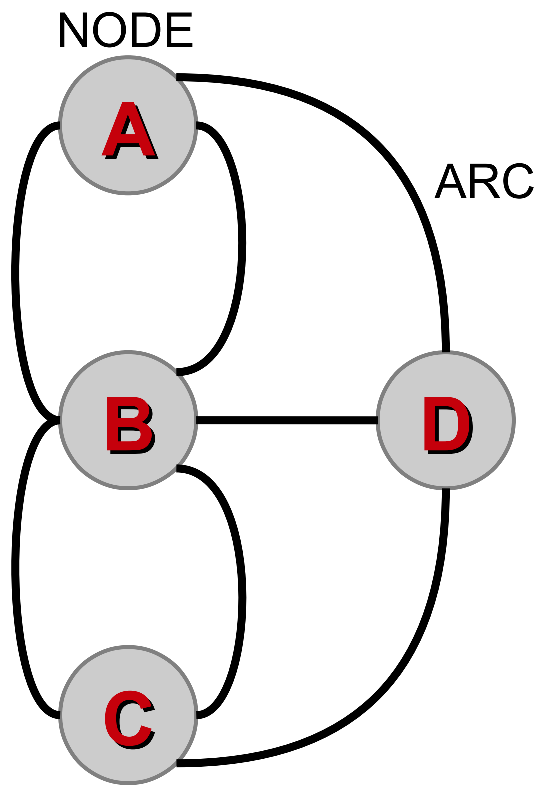
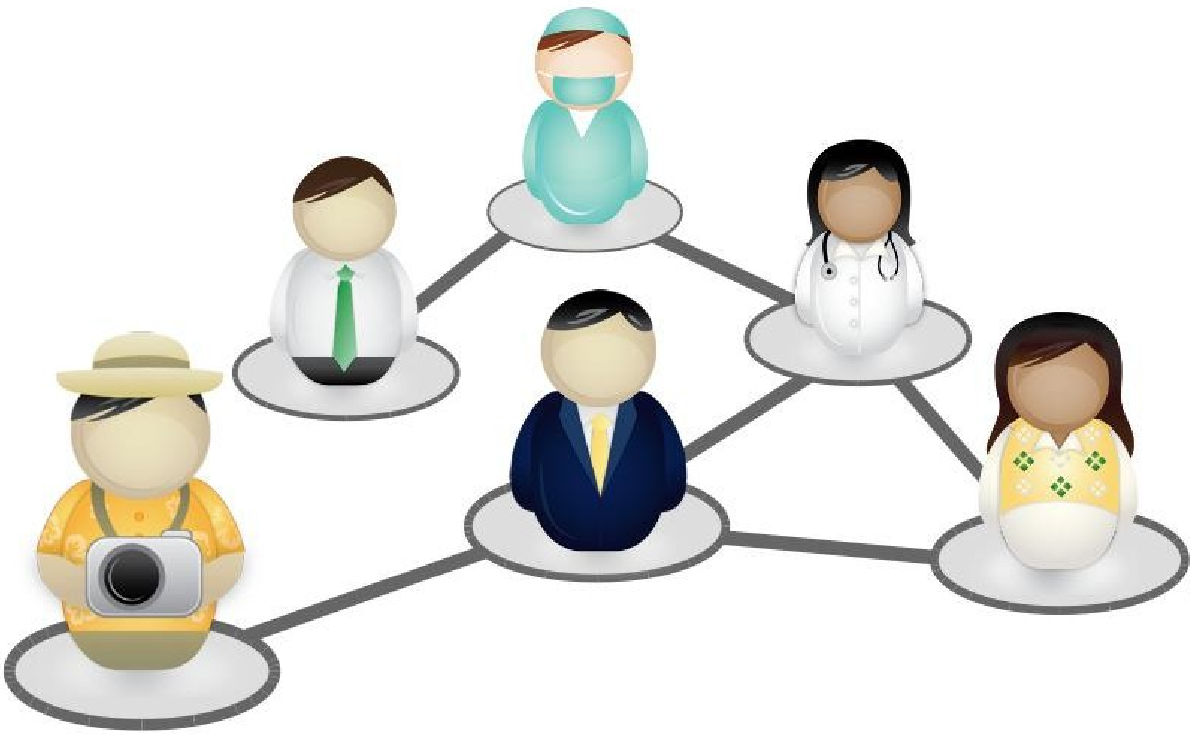
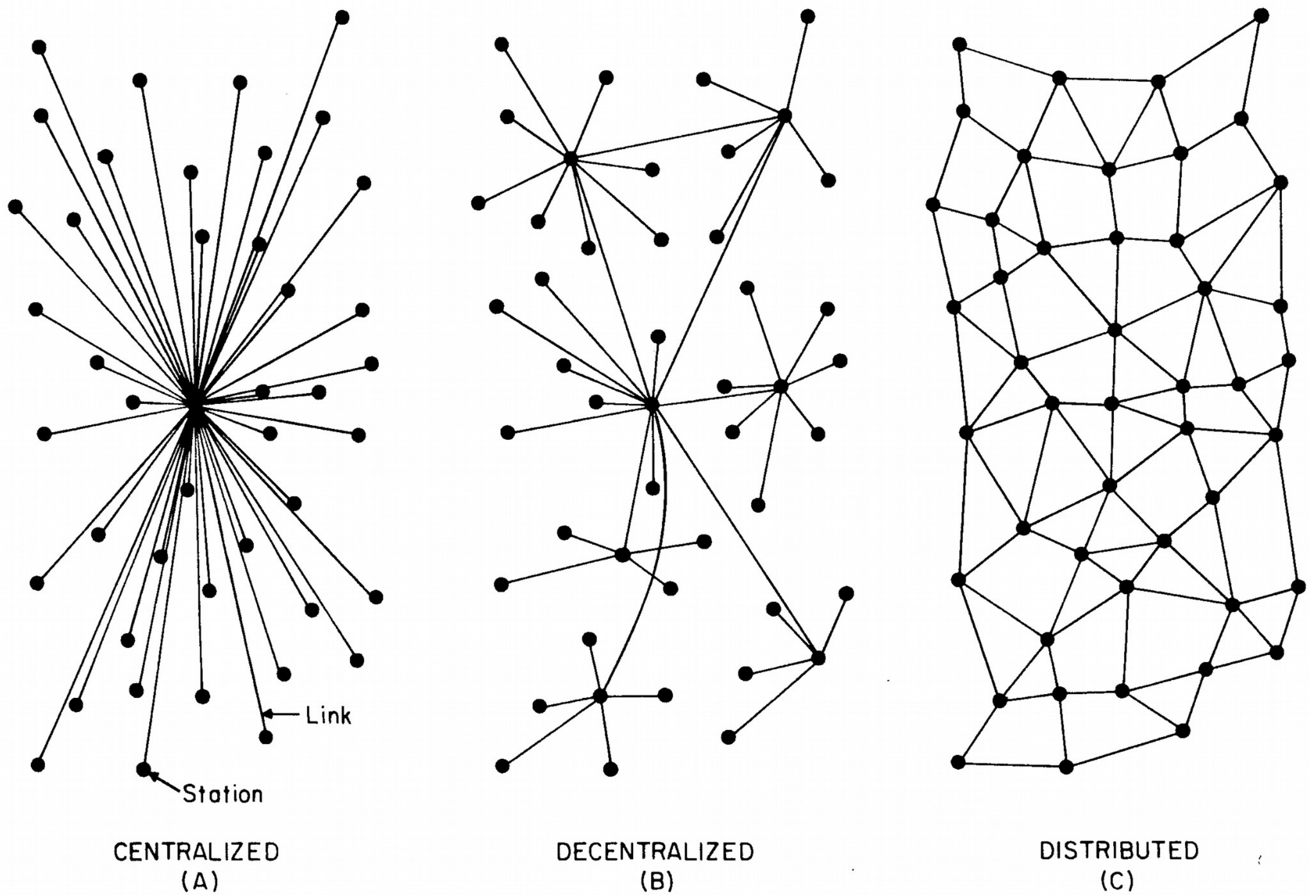


Social Network Analysis



- 1930s : Jacob Moreno and Helen Jennings introduced basic analytical methods.
- 1954: John Arundel Barnes started using the term systematically to denote the patterns of ties defining bounded groups (e.g., tribes, families) and social categories (e.g., gender, ethnicity)

"The" network



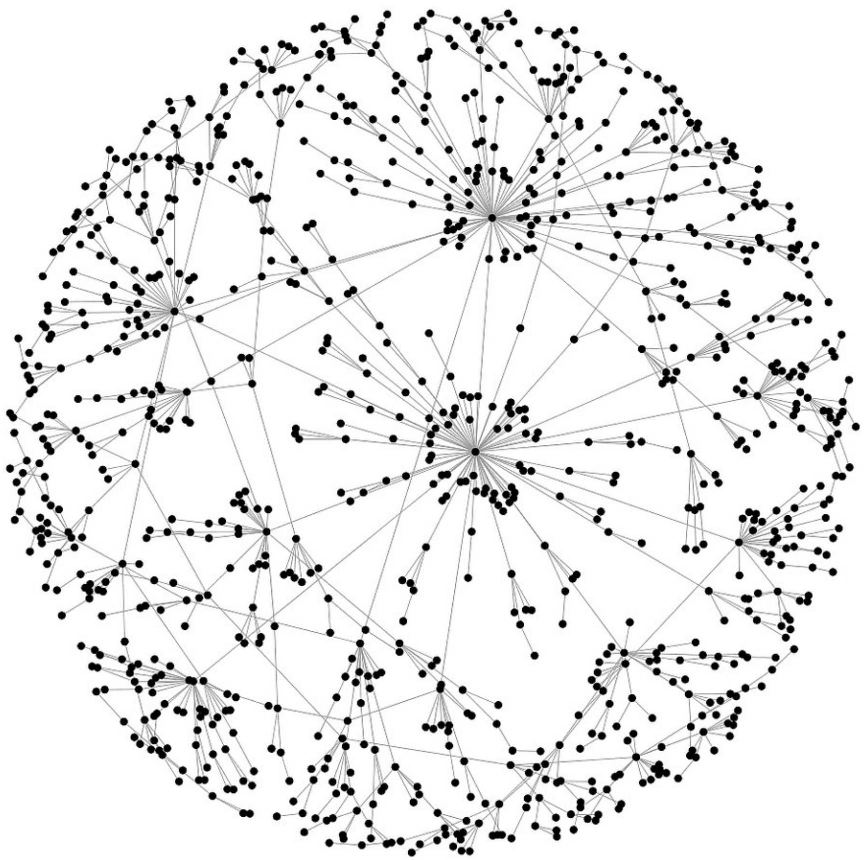
Introduction to Distributed Communications Networks, Paul Baran
Memorandum **RM-3420-PR** August **1964** – RAND corporation

Complex Networks

- Watts & Strogatz: Small World Networks

Complex Networks

- Barabasi & Albert: Scale Free Networks



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1972: More Is Different

4 August 1972, Volume 177, Number 4047 SCIENCE

More Is Different

Broken symmetry and the nature of the hierarchical structure of science.

P. W. Anderson

The reductionist hypothesis may still be a topic for controversy among philosophers, but among the great majority of active scientists I think it is accepted without question. The workings of our minds and bodies, and of all the animate or inanimate matter of which we have any detailed knowledge, are assumed to be controlled by the same set of fundamental laws, which except under certain extreme conditions we feel we know pretty well.

It seems inevitable to go on uncritically to what appears at first sight to be an obvious corollary of reductionism: that if everything obeys the same fundamental laws, then the only scientists who are studying anything really fundamental are those who are working on those laws. In practice, that amounts to some astrophysicists, some elementary particle physicists, some logicians and other mathematicians, and few others. This point of view, which it is the main purpose of this article to oppose, is expressed in a rather well-known passage by Weisskopf (*1*):

> Looking at the development of science in the Twentieth Century one can distinguish two trends, which I will call "intensive" and "extensive" research, lacking a better terminology. In short: intensive research goes for the fundamental laws, extensive research goes for the explanation of phenomena in terms of known fundamental laws. As always, distinctions of this kind are not unambiguous, but they are clear in most cases. Solid state physics, plasma physics, and perhaps also biology are extensive. High energy physics and a good part of nuclear physics are intensive. There is always much less intensive research going on than extensive. Once new fundamental laws are discovered, a large and ever increasing activity begins in order to apply the discoveries to hitherto unexplained phenomena. Thus, there are two dimensions to basic research. The frontier of science extends all along a long line from the newest and most modern intensive research, over the extensive research recently spawned by the intensive research of yesterday, to the broad and well developed web of extensive research activities based on intensive research of past decades.

The effectiveness of this message may be indicated by the fact that I heard it quoted recently by a leader in the field of materials science, who urged the participants at a meeting dedicated to "fundamental problems in condensed matter physics" to accept that there were few or no such problems and that nothing was left but extensive science, which he seemed to equate with device engineering.

The main fallacy in this kind of thinking is that the reductionist hypothesis does not by any means imply a "constructionist" one: The ability to reduce everything to simple fundamental laws does not imply the ability to start from those laws and reconstruct the universe. In fact, the more the elementary particle physicists tell us about the nature of the fundamental laws, the less relevance they seem to have to the very real problems of the rest of science, much less to those of society.

The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity. The behavior of large and complex aggregates of elementary particles, it turns out, is not to be understood in terms of a simple extrapolation of the properties of a few particles. Instead, at each level of complexity entirely new properties appear, and the understanding of the new behaviors requires research which I think is as fundamental in its nature as any other. That is, it seems to me that one may array the sciences roughly linearly in a hierarchy, according to the idea: The elementary entities of science X obey the laws of science Y.

X	Y
solid state or many-body physics	elementary particle physics
chemistry	many-body physics
molecular biology	chemistry
cell biology	molecular biology
·	·
·	·
·	·
psychology	physiology
social sciences	psychology

But this hierarchy does not imply that science X is "just applied Y." At each stage entirely new laws, concepts, and generalizations are necessary, requiring inspiration and creativity to just as great a degree as in the previous one. Psychology is not applied biology, nor is biology applied chemistry.

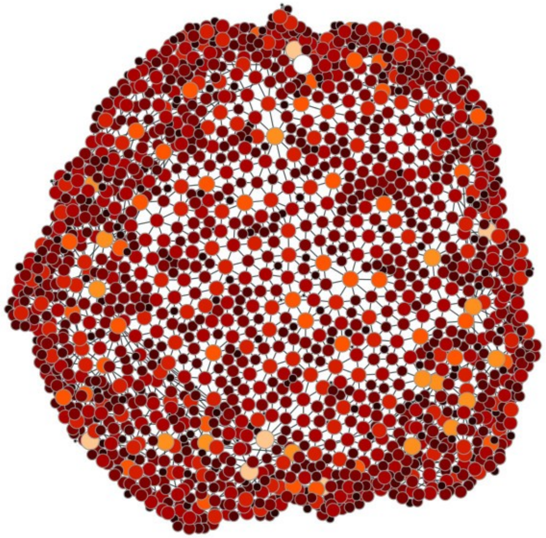
In my own field of many-body physics, we are, perhaps, closer to our fundamental, intensive underpinnings than in any other science in which nontrivial complexities occur, and as a result we have begun to formulate a general theory of just how this shift from quantitative to qualitative differentiation takes place. This formulation, called the theory of "broken symmetry," may be of help in making more generally clear the breakdown of the constructionist converse of reductionism. I will give an elementary and incomplete explanation of these ideas, and then go on to some more general speculative comments about analogies at

The author is a member of the technical staff of the Bell Telephone Laboratories, Murray Hill, New Jersey 07974, and visiting professor of theoretical physics at Cavendish Laboratory, Cambridge, England. This article is an expanded version of a Regents' Lecture given in 1967 at the University of California, La Jolla.

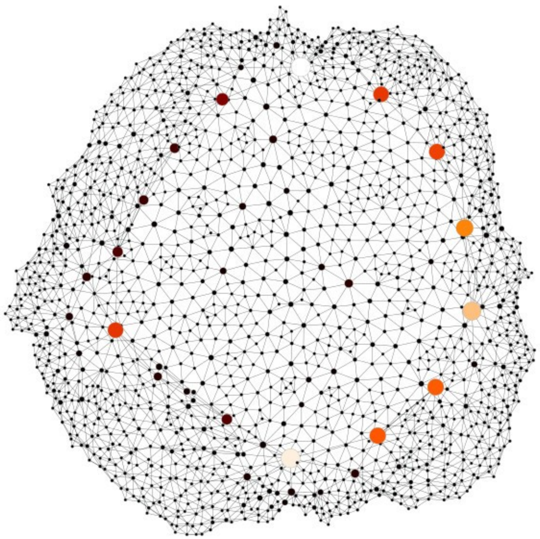
- Knowing better the details does not help
- Interaction creates new "categories" loosely related to the basic components
- From the interaction new (simpler, collective) entities "emerge"
- Universality & Scaling

Simplifying Networks: Centralities

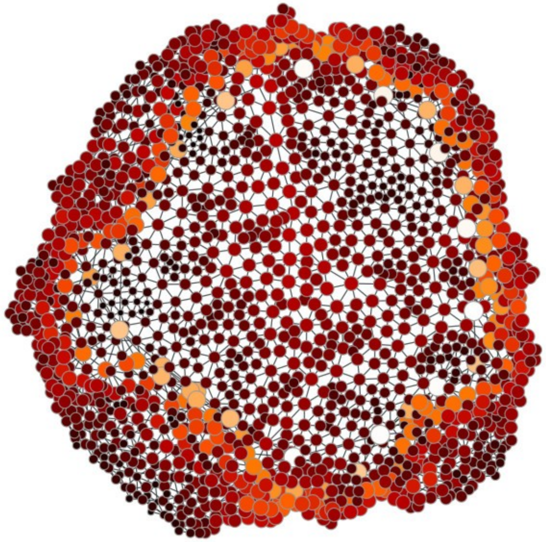
Degree
centrality



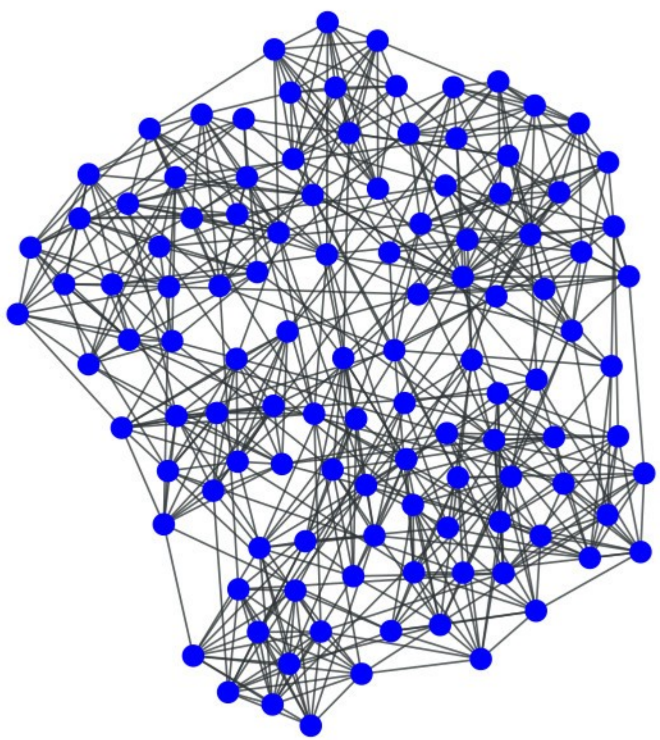
Betweeness
centrality



Closeness
centrality



Simplifying networks: communities



Generally speaking, the “Divide and Conquer” approach

Network Theory: pros & cons

- Descriptions in terms of networks are intrinsically “systemic”
- Emergent phenomena “need” networks
- “Good” communities fight the “dimensional curse”

- Networks capture only diadic interactions
- “Danger” of networks motifs
- “Decision dependent” networks: What are the nodes? What are the links? How do I attribute weights?

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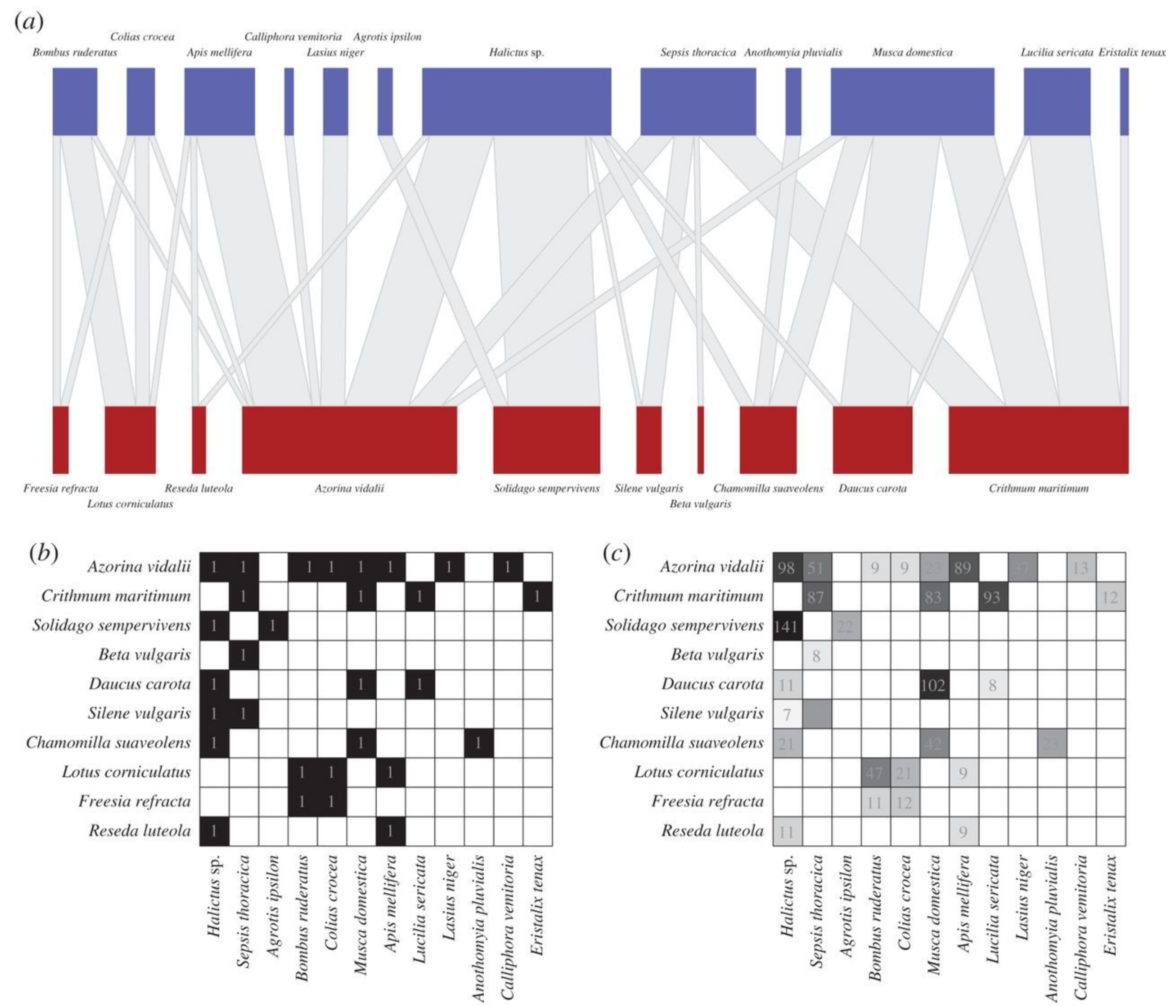
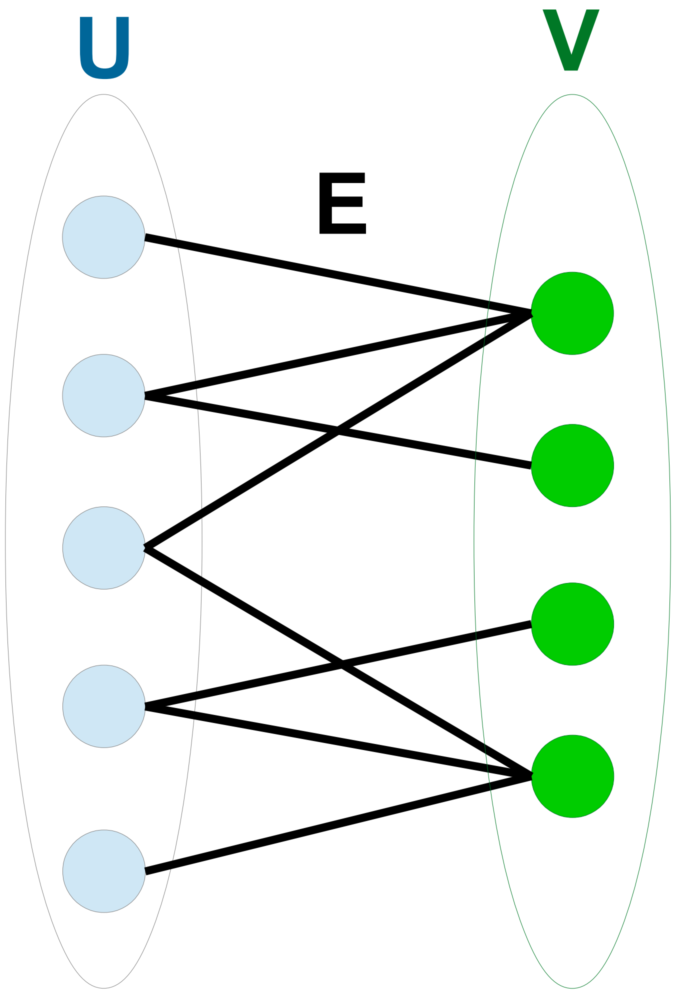
DATA, PROJECTIONS & NETWORKS



Improved community detection in weighted bipartite networks
Stephen J. Beckett 2016
DOI:10.1098/rsos.140536

Bipartite Graphs

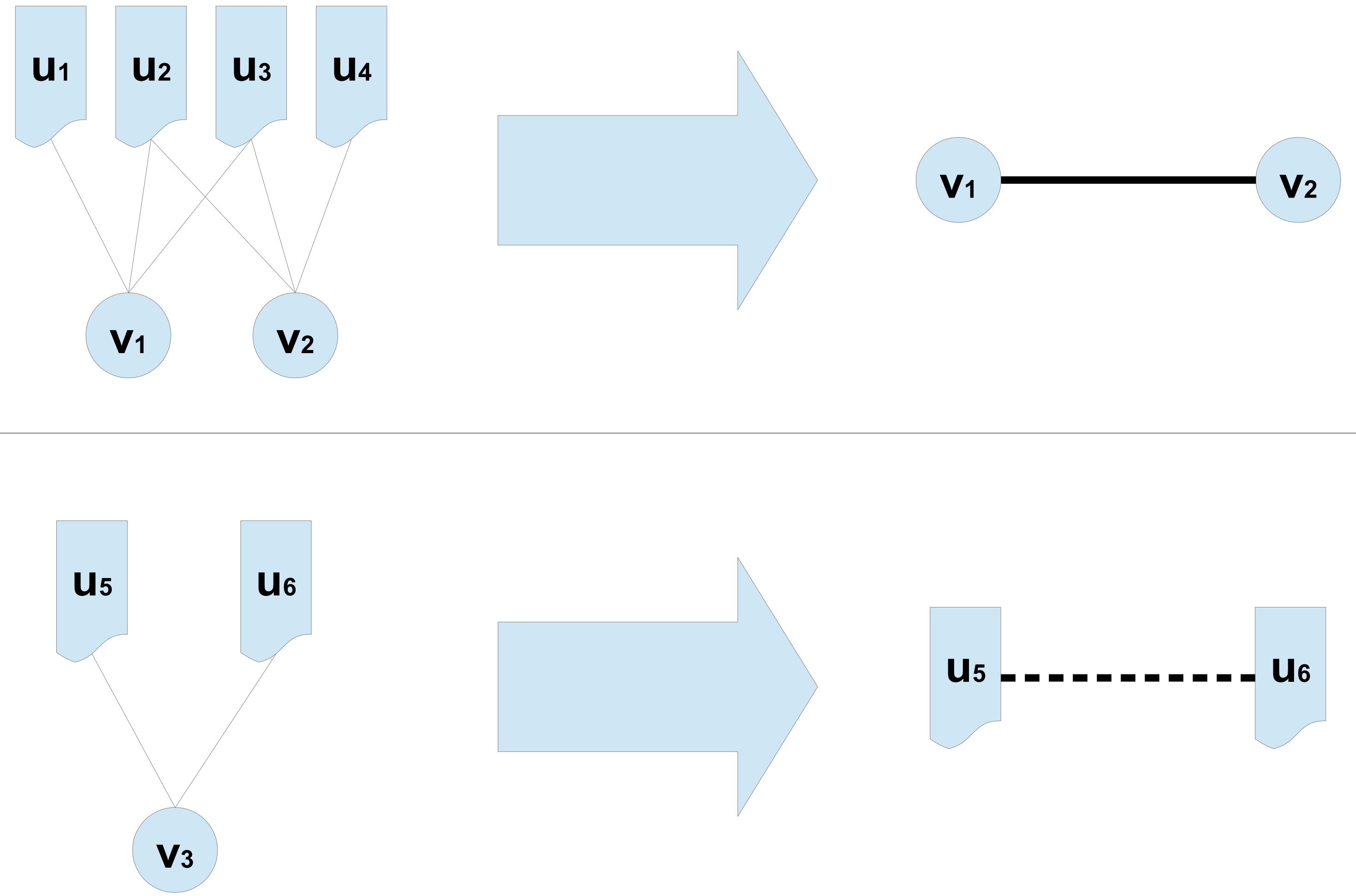


Bipartite graph:

- G = (U, V, E)
- U, V nodes
- E edges among U,V

Bipartite graphs arise naturally when modelling relations between two different classes of entities

Projections

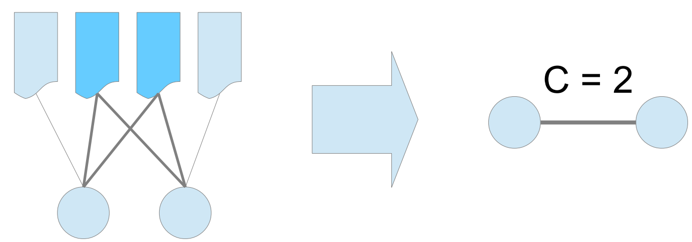


Co-occurrence matrix

- B = adjacency matrix of bipartite graph G = (U,V,E)
- B_{uv} = 1 if v has feature u , B_{uv} = 0 otherwise

The co-occurrence C_{uw} counts the number of times two features u,w occur together

$$C_{uw} = \Sigma_v B_{uv} B_{wv}$$



- $B B^T$ → weighted adjacency matrix of the projection graph on U
- $B^T B$ → weighted adjacency matrix of the projection graph on V

Null model

- C_{uw} = numbers of common neighbors of u,w
- n = maximum possible number of links
- $d_u = C_{uu}$ = degree of u
- $f_u = d_u / n$ fraction of possible links present
- If nodes were chosen at random:

$$f_{uv} = C_{uw} / n \rightarrow f_u f_v$$

$$P_{uw}(C) = \binom{C}{n} (f_u f_v)^{C} (1-f_u f_v)^{n-C}$$

Other Projections

- Similarity Matrix

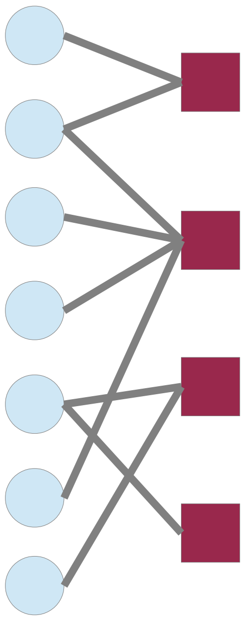
$$S_{uw} = 2\, C_{uw} \,/\, (\, C_{uu} + C_{ww} \,)$$

- Correlation matrix

$$\varphi_{uv} = (\, f_{uv} - f_u\, f_v \,) \,/\, \sigma_u\, \sigma_v$$

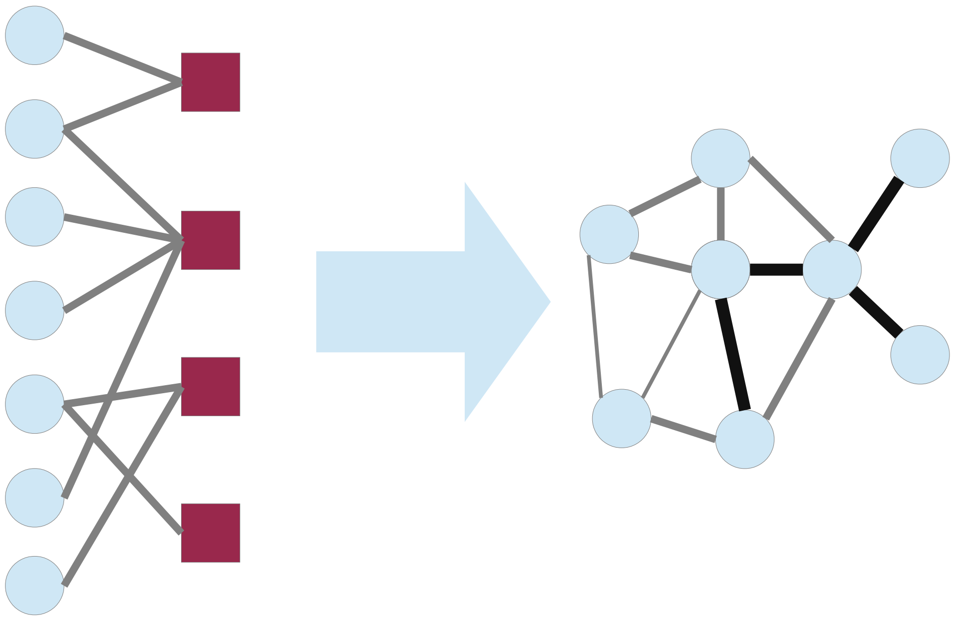
$$\sigma_u^2 = f_u\,(1 - f_u\,)$$

Methodology



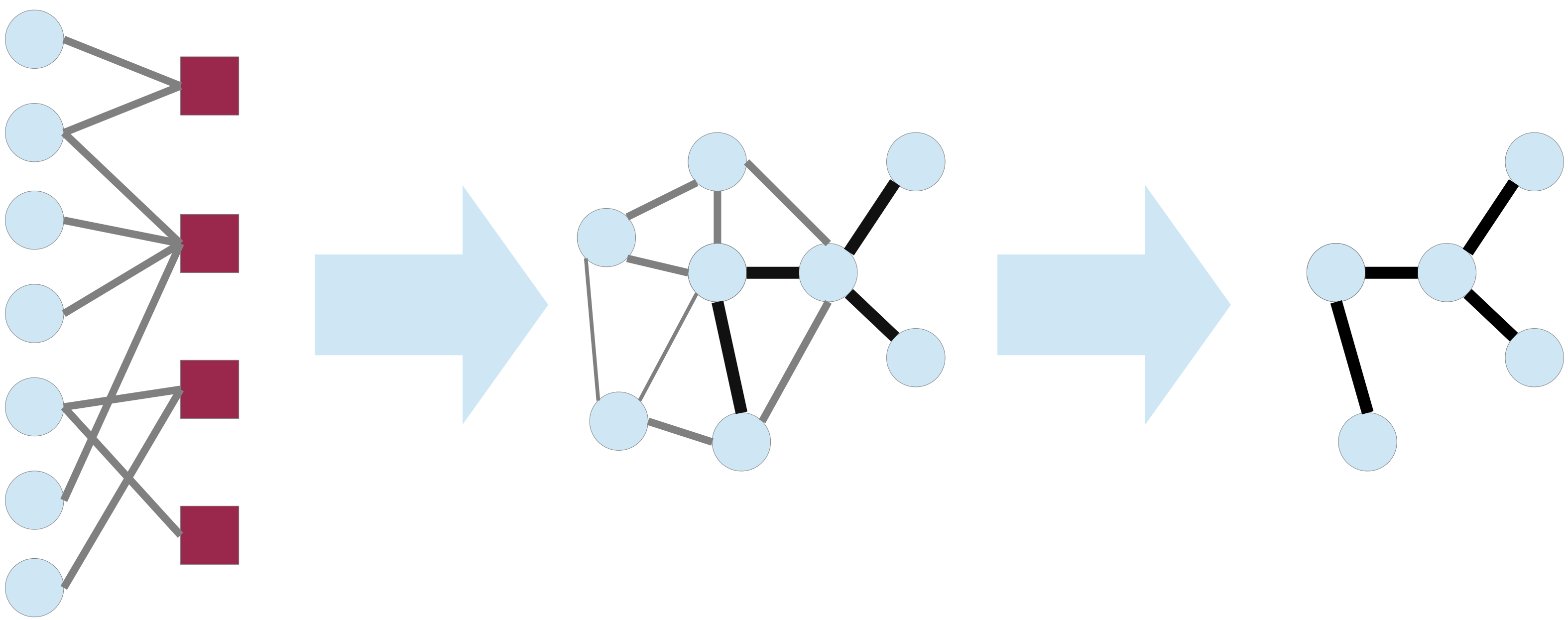
COLLECT

Methodology



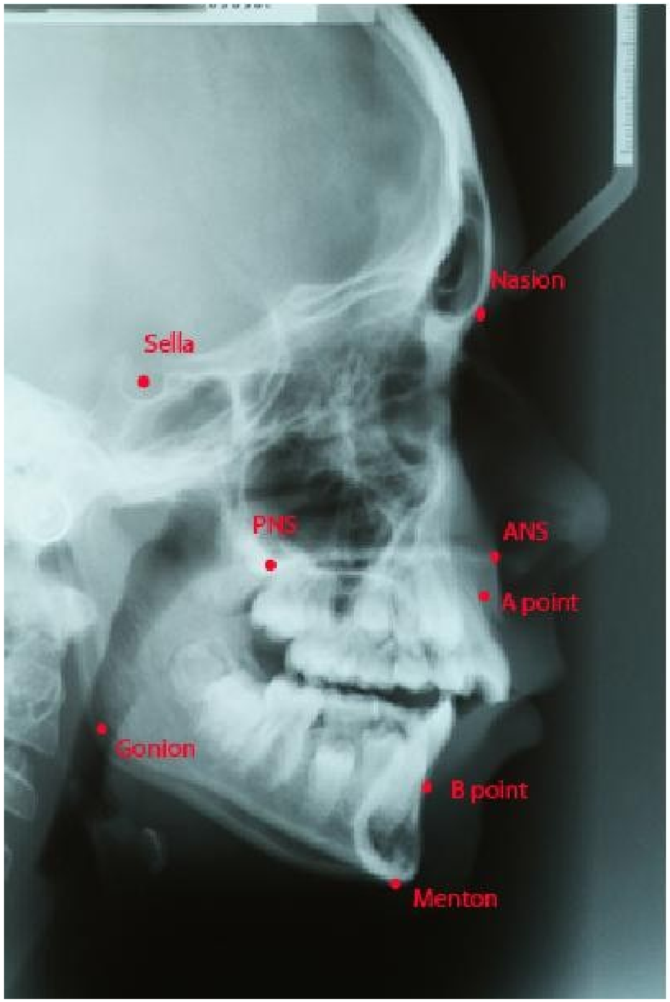
PROJECT

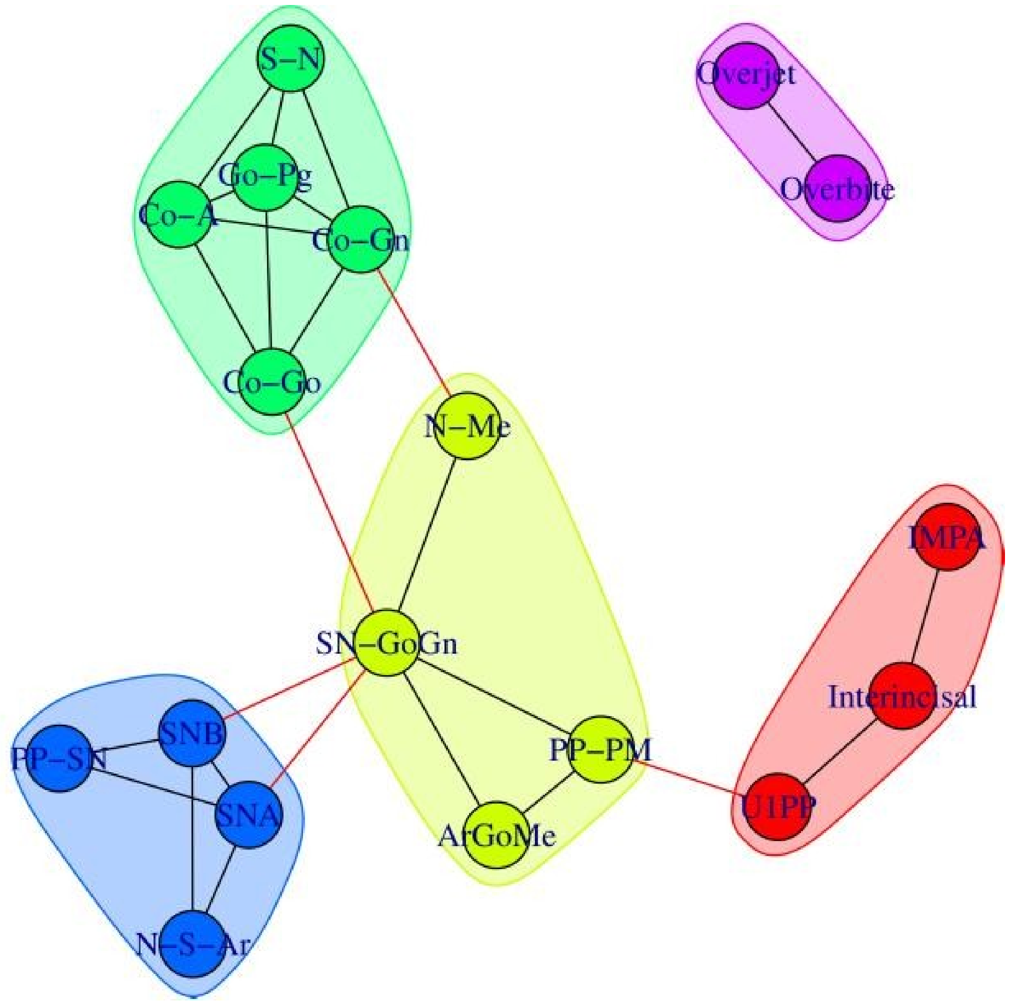
Methodology



SELECT

DENTISTRY, TREATMENTS & NETWORKS

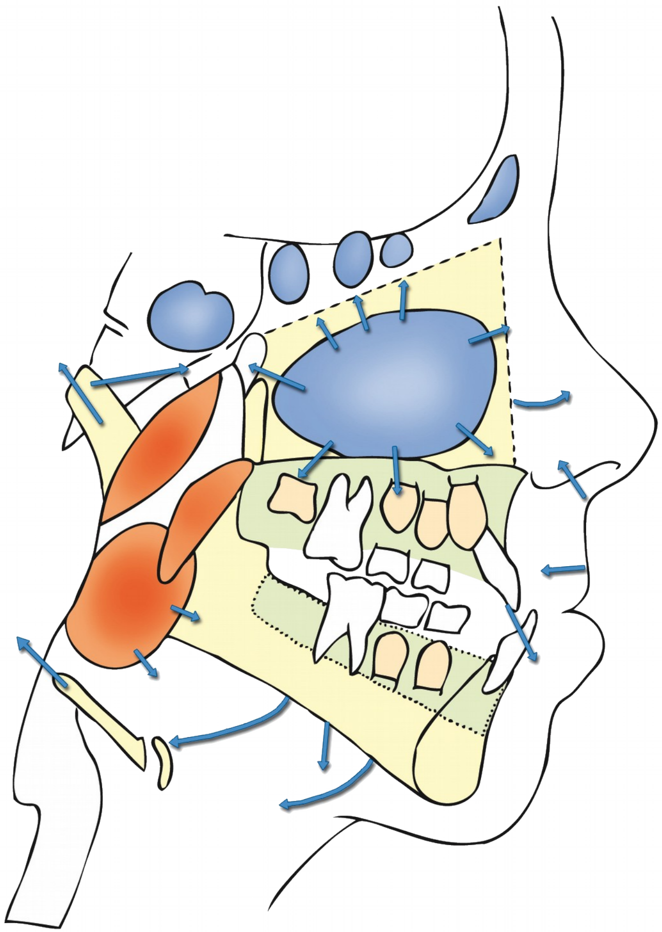




Introduction

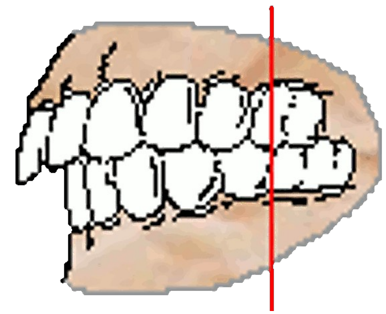
- Motivation: Mining knowledge from Medical Records
- Methods: Network Analysis for Case-Features dataset
- Case-study: Childhood orthodontics

The Complex Oro-Facial System



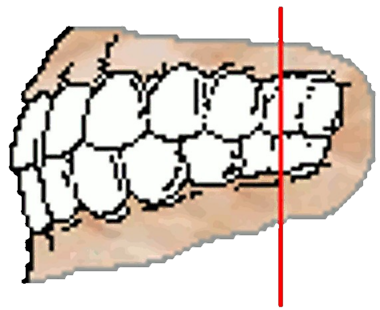
- components
- relations
- interactions
- dynamics

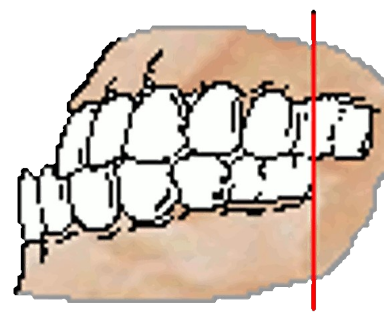
Dental Classes



2nd Class
(bad)

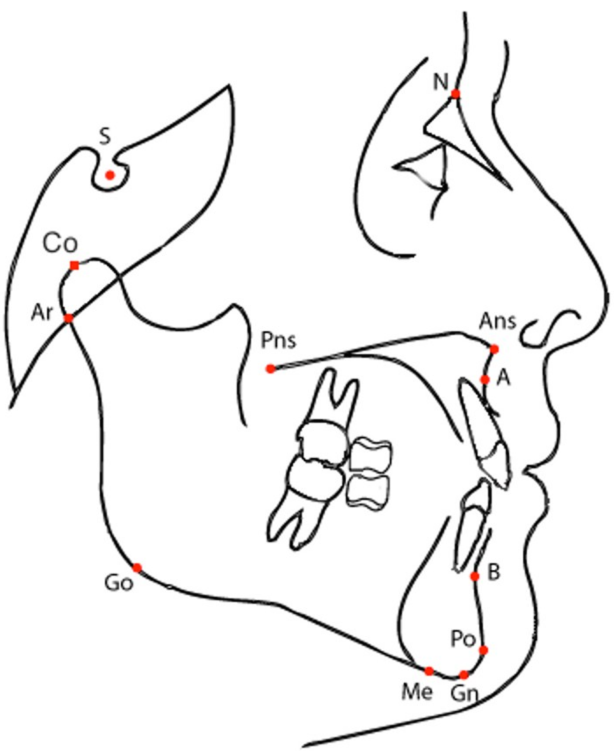
1st Class
(normal)





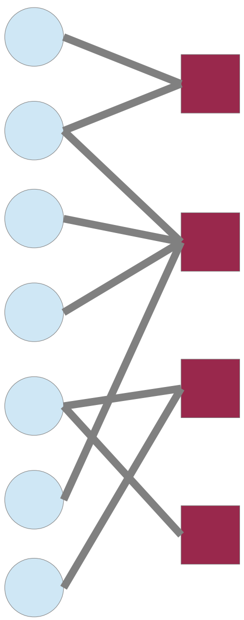
3rd Class
(worst)

Cephalograms

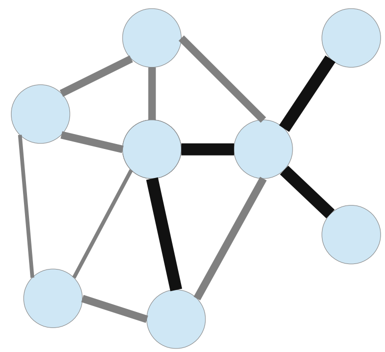


Co-Gn	mandibular length as distance from Co to Gn
Ar-Go	mandibular ramus height
NS-GoGn	divergence of the mandibular plane relative to the anterior cranial base
NS-Ar	saddle angle
….	….

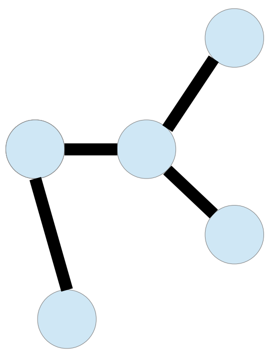
Getting the networks



Correlations

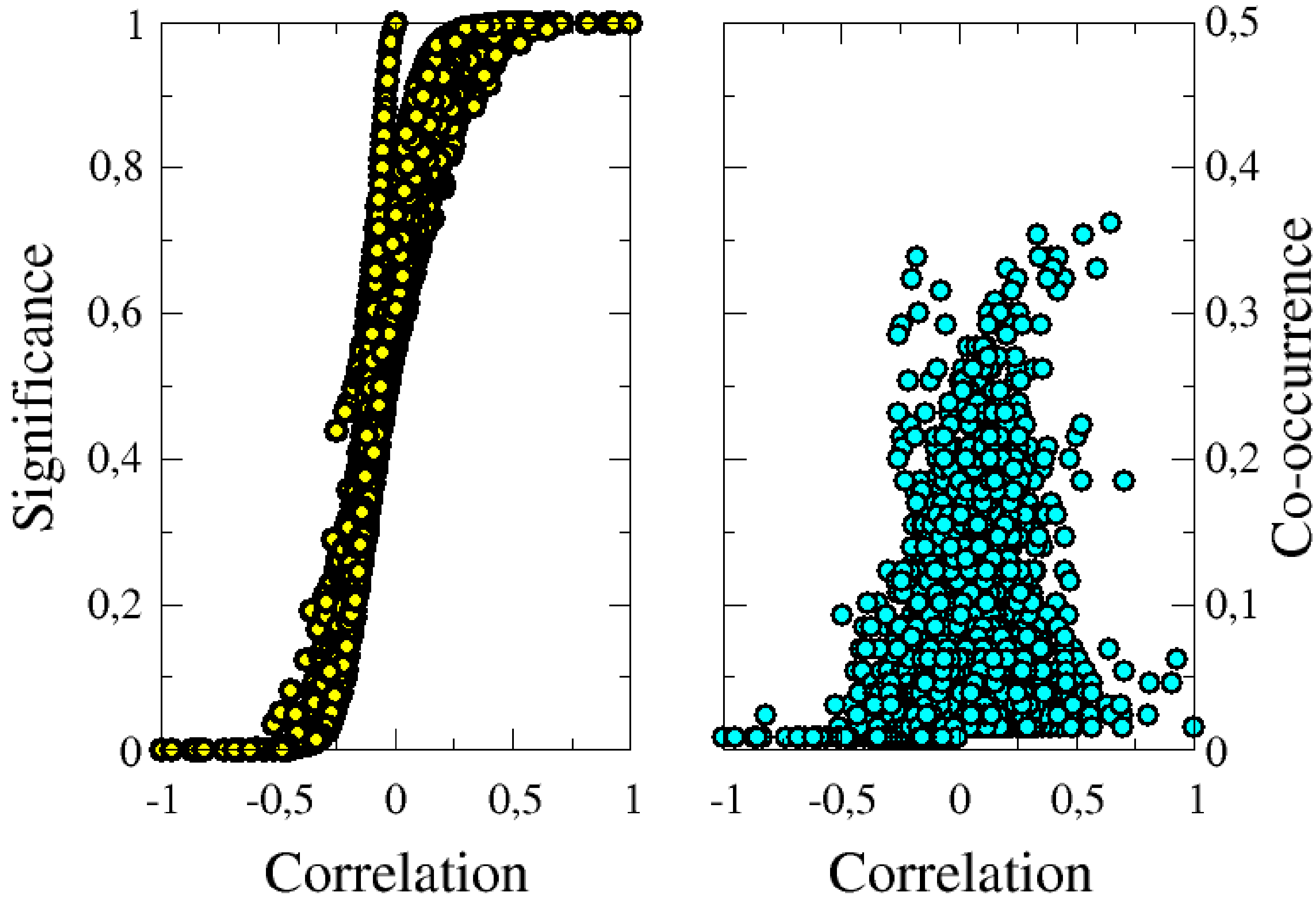


Tresholds



"PROJECT & SELECT"

Correlation vs Co-occurrence



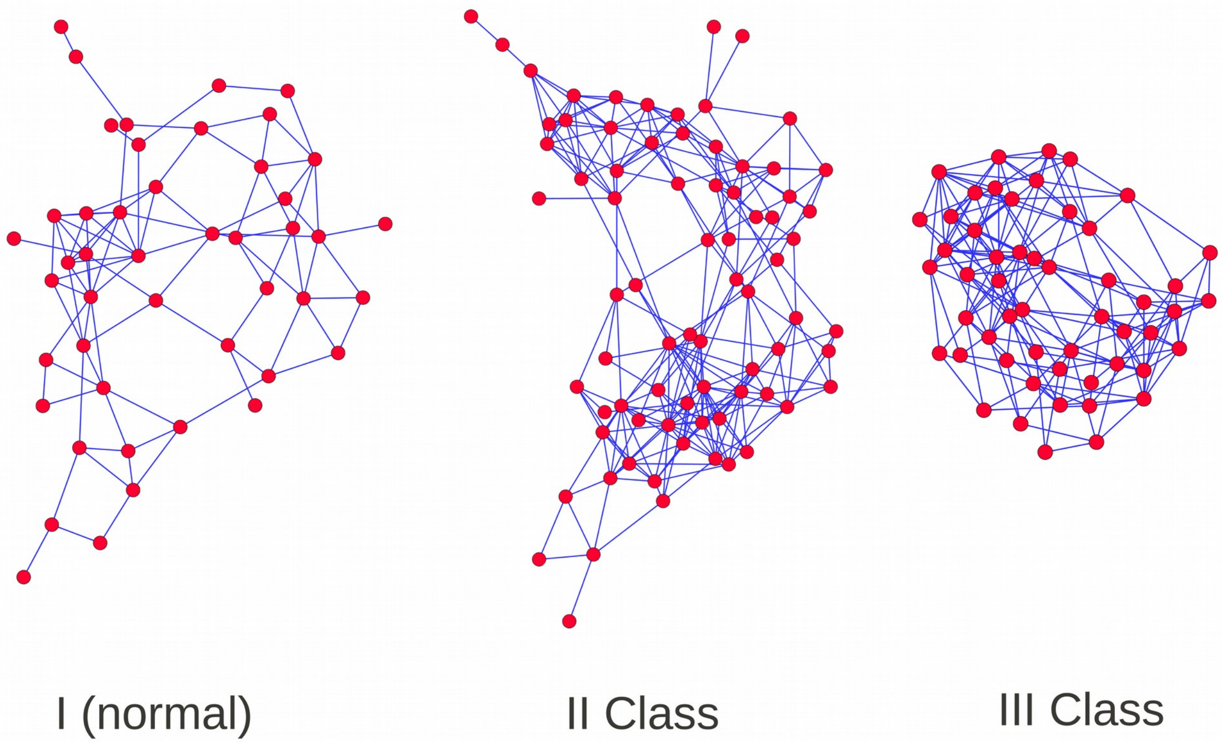
Network metrics

	Average degree	Clustering coefficient	Mean shortest path
1^{st}	4.04	0.28	3.43
2^{nd}	6.45	0.36	3.13
3^{rd}	7.09	0.31	2.39

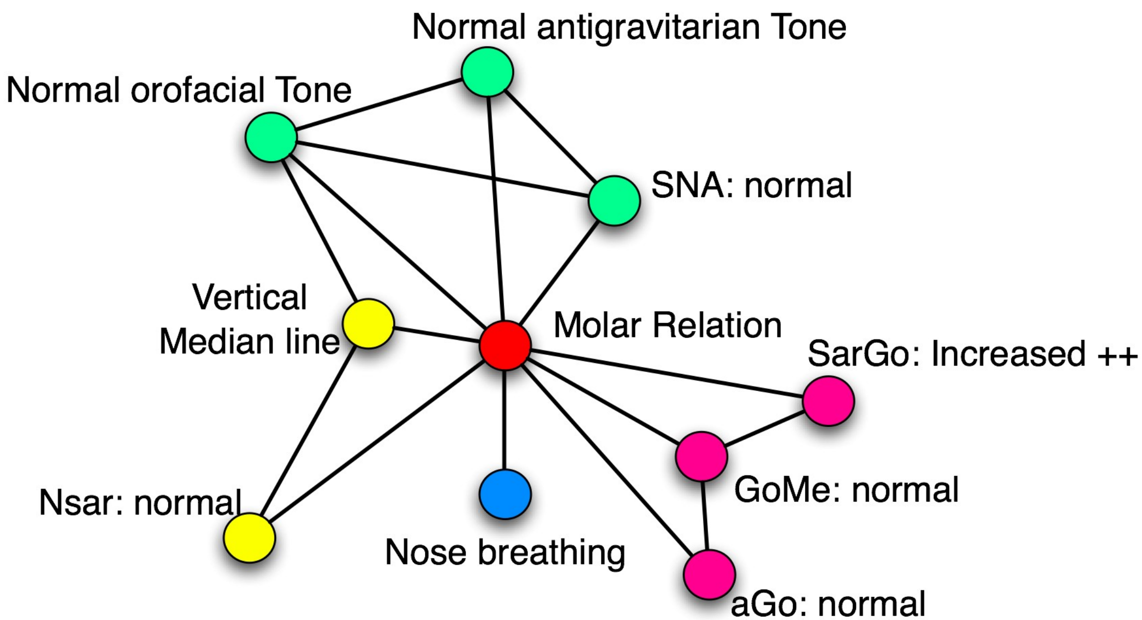
- 2^{nd} and 3^{rd} class features are more connected than those of the control patients.
- 3rd class patients shows a much higher connection and closeness: this topology allows a high transmission of the bite forces and neuromuscular inputs

Classes' network structures

- φ > 30% correlation filtering
- 3rd Class strongly connected but devoid of strong, peculiar hubs



Hubs in 2nd Class



- peculiar hubs as starting point for an orthodontic selective treatment
- hubs do not necessarily correspond to the most evident clinical signs

Results 1

- Features can be considered in the light of the appropriate network specific for that malocclusion

- Represent the system in a visually intuitive way, focus on most important features

- Valuable tool for evidence-based diagnosis in primary orthodontic care

- *Could also be applied to other clinical problems*

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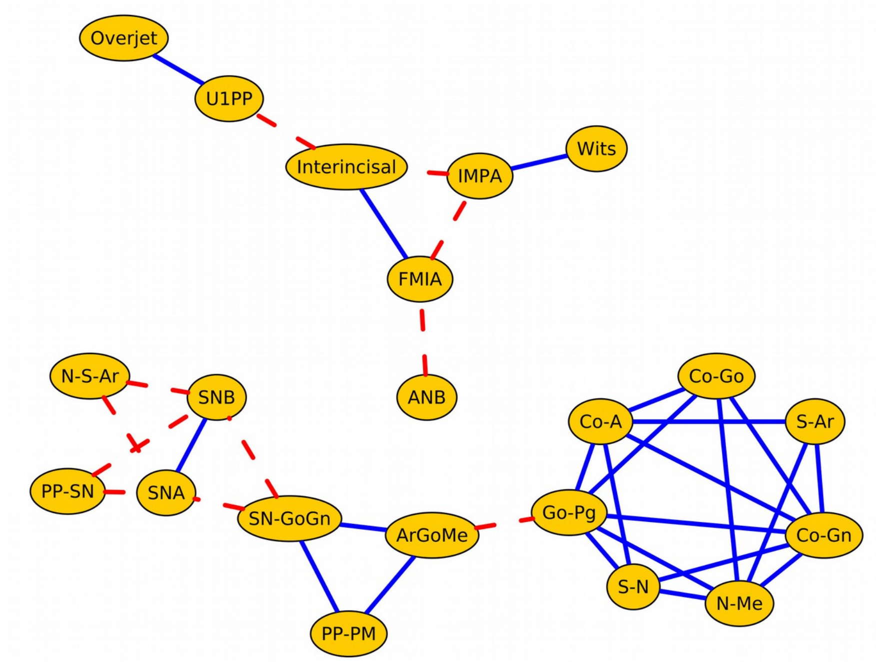
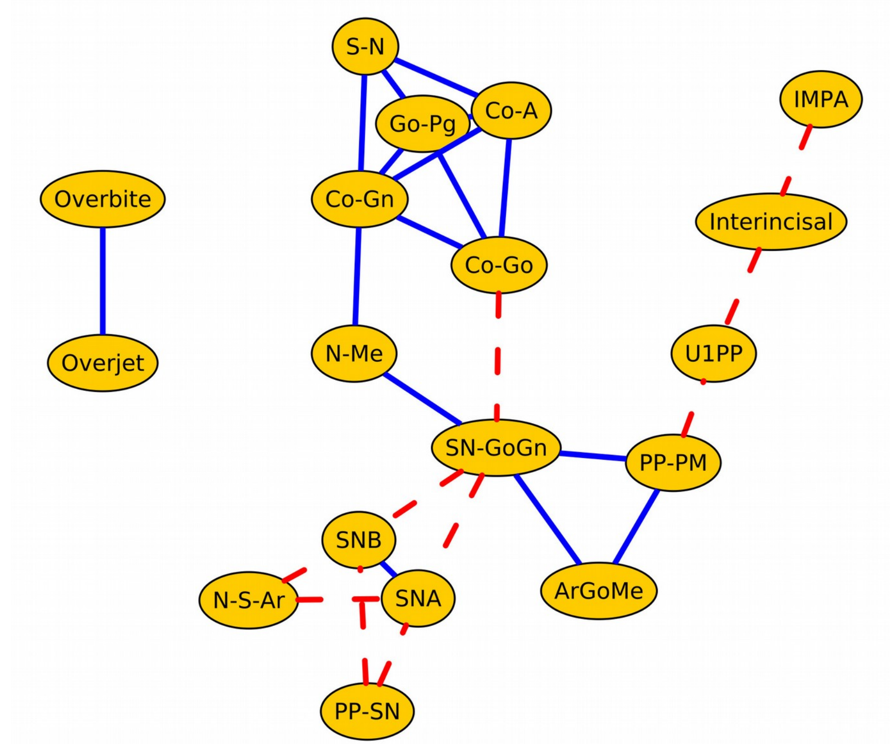
Before treatment *vs* After treatment





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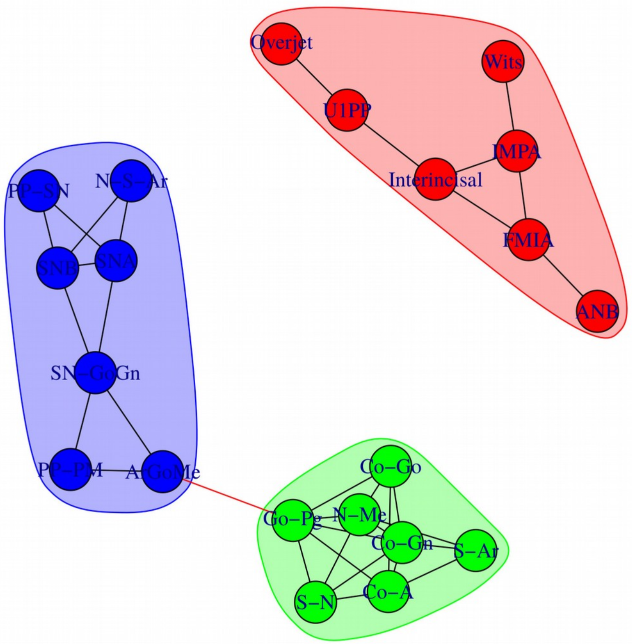

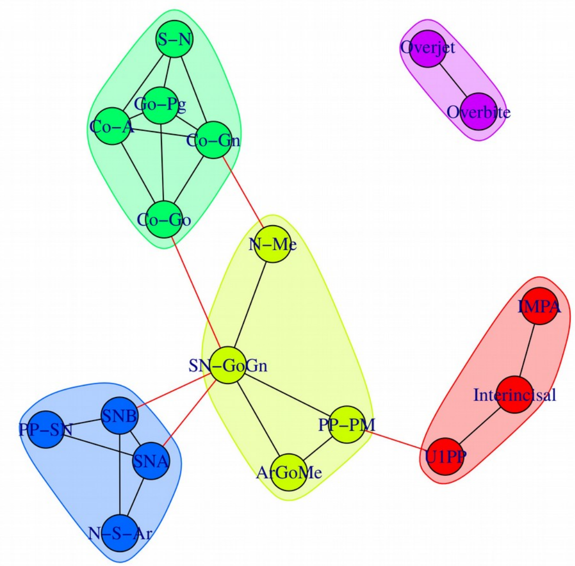

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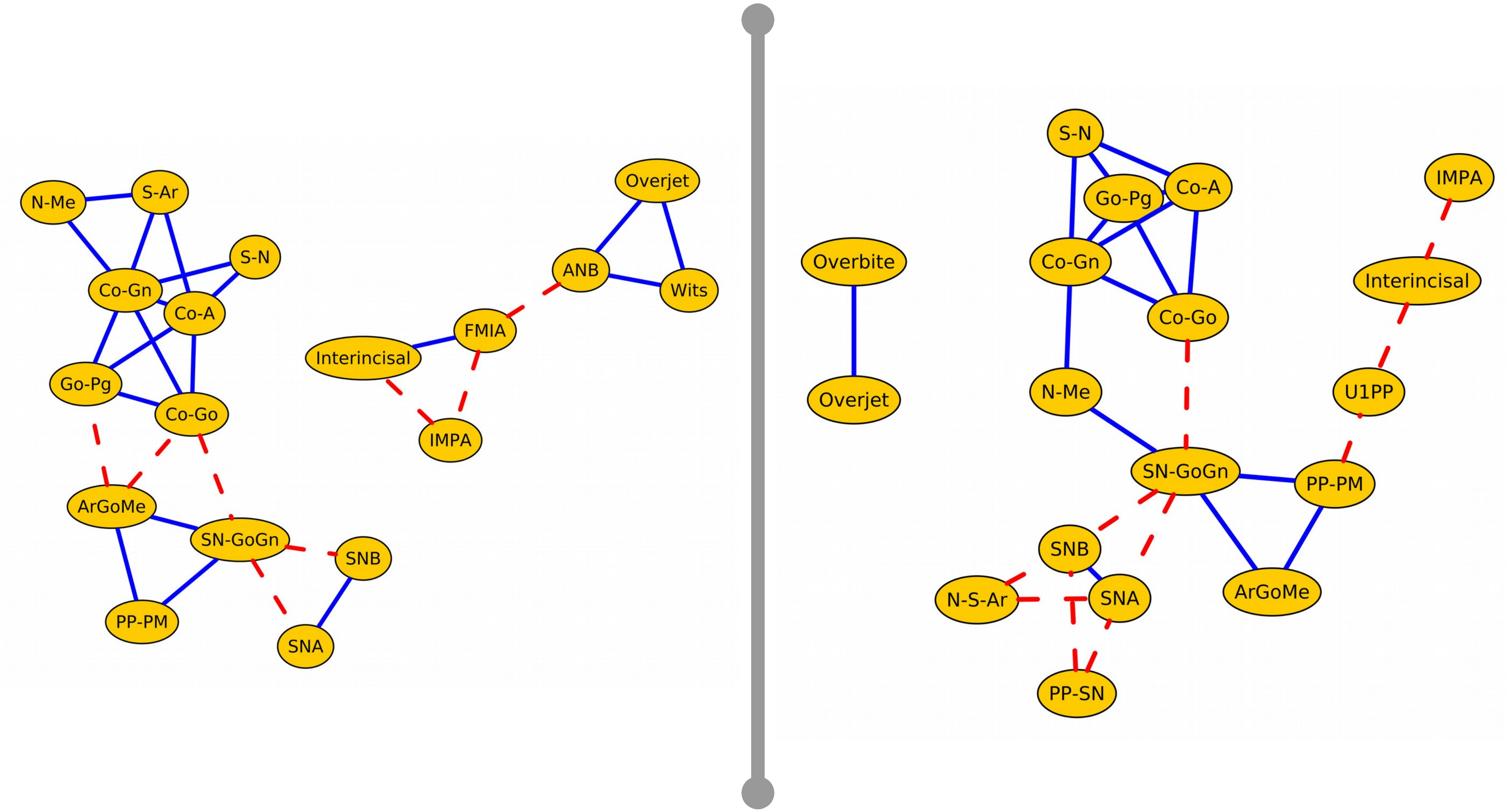
NO treatment *vs* Treatment



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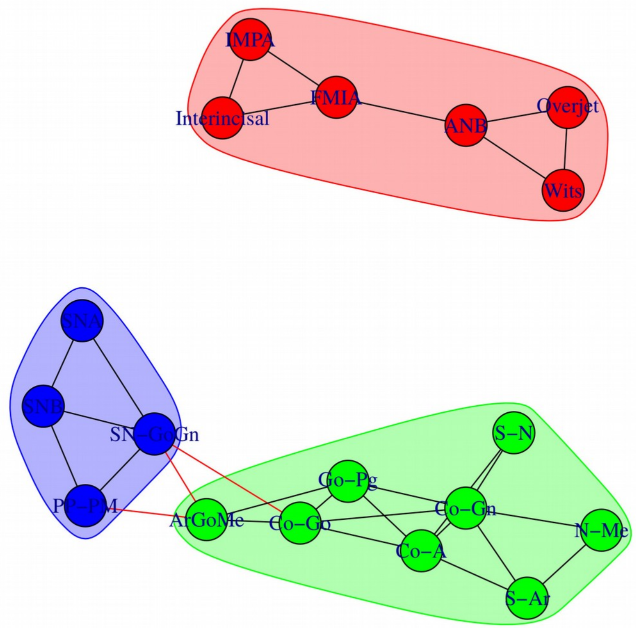
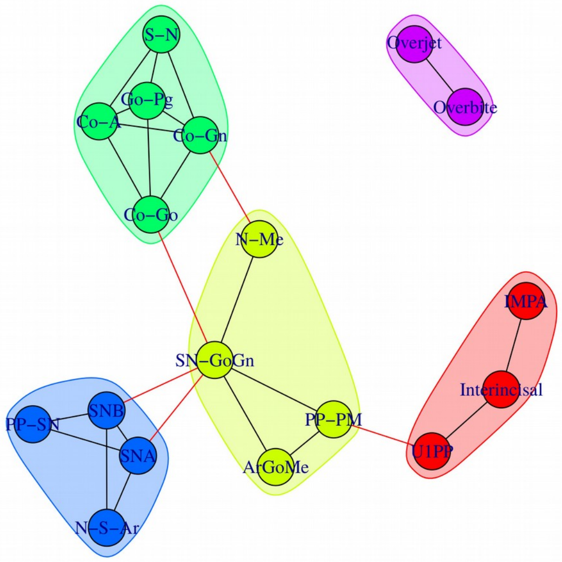
NO treatment *vs* Treatment





Results 2

- Network analysis shows that the progression of Class III dysmorphose arise from the interplay between a number of well-interconnected correlative features
- Features are naturally divided in modules, i.e., groups of densely associated components connected to each other with loose links
- Representative nodes and links can be associated to craniofacial dysmorphoses and to the effects of expansion/facemask protraction therapy

Applications to Medical Diagnostics ?

The classification of human diseases builds on observed correlations between pathological analysis and clinical syndromes (observational skills to define the syndromic phenotype)

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Problem: Classic diagnostic strategy is naturally limited by the lack of sensitivity in identifying preclinical disease and by the lack of specificity in defining disease unequivocally

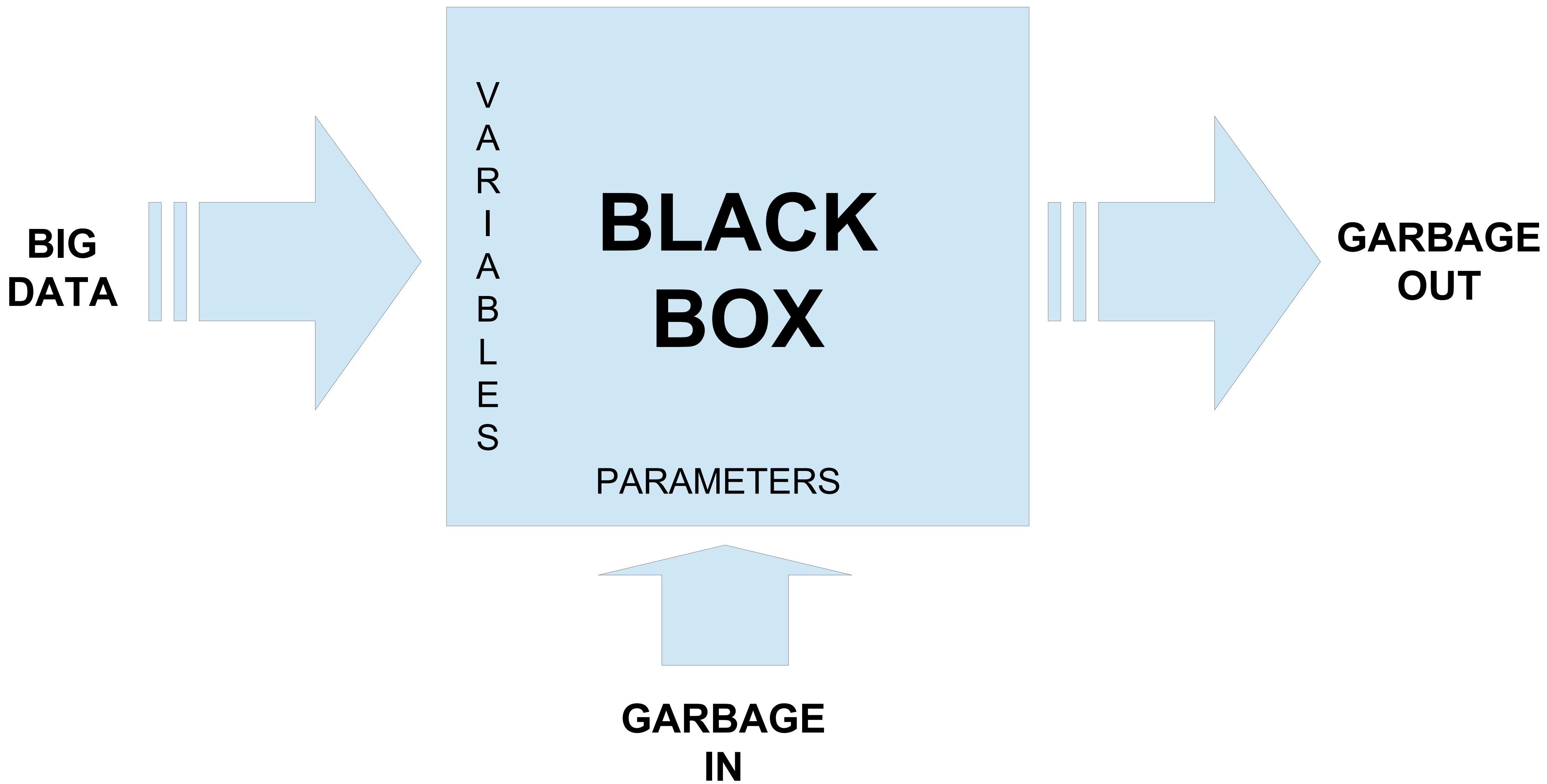
Applications to Medical Diagnostics ?

The classification of human diseases builds on observed correlations between pathological analysis and clinical syndromes (observational skills to define the syndromic phenotype)

Problem: Classic diagnostic strategy is naturally limited by the lack of sensitivity in identifying preclinical disease and by the lack of specificity in defining disease unequivocally

GOAL: infer syndromic phenotypes from clinical data via complex networks methods

BIG DATA, KNOWLEDGE DISCOVERY & NETWORKS



Advertising Complex Networks

- systems cannot be understood in terms of simple atomic components
- data mining can find simple relations and reduce the dimensionality of a problem
- data-mining enriches data with meta-data (classification)
- complex systems ``resist`` data-mining as they could not be easily broken in pieces
- network science looks globally at the relations among the components of a system
- complex network analysis reveals new conceptual classes emerging due to the the interaction among the data

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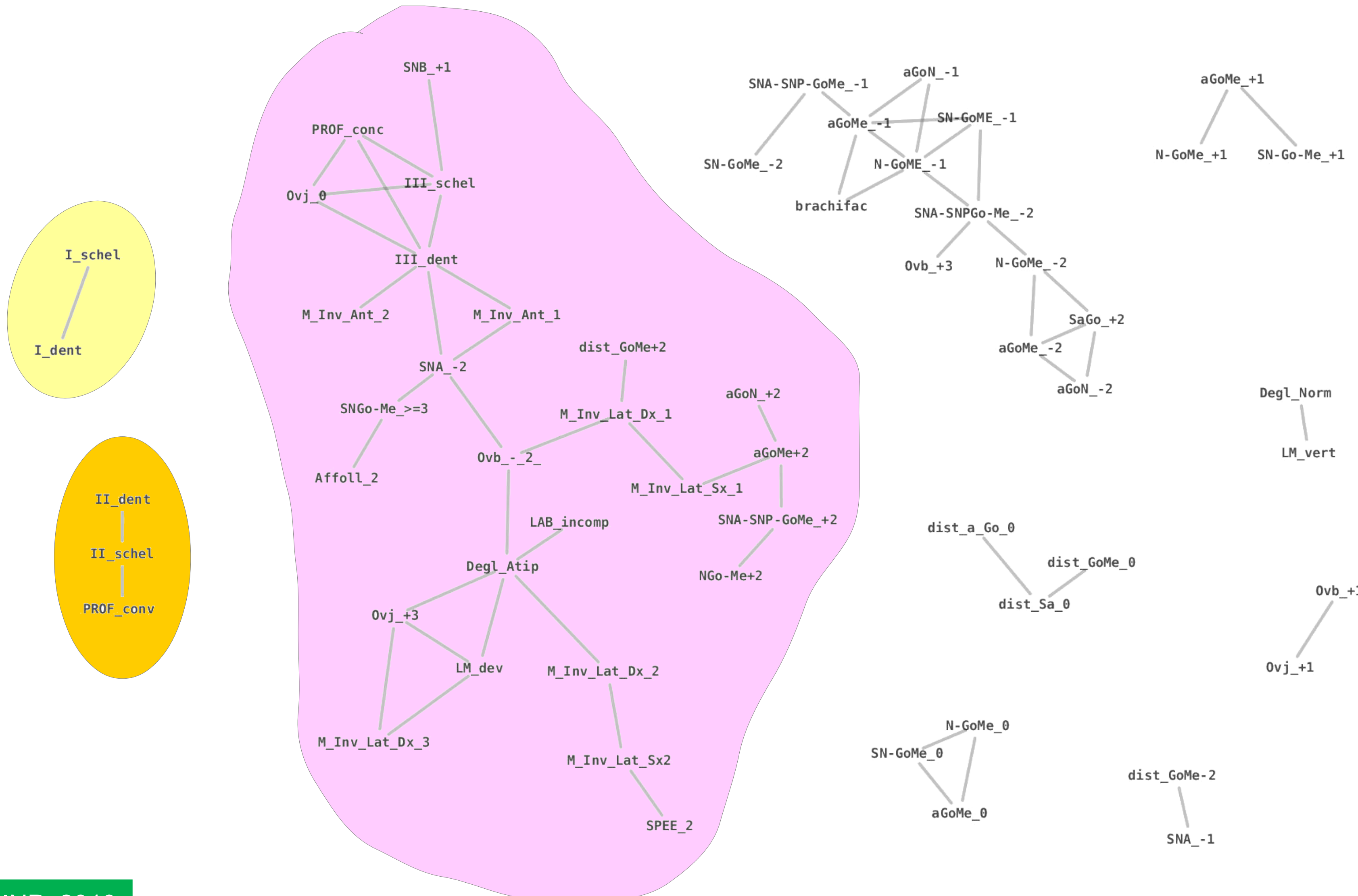
Positive Correlations



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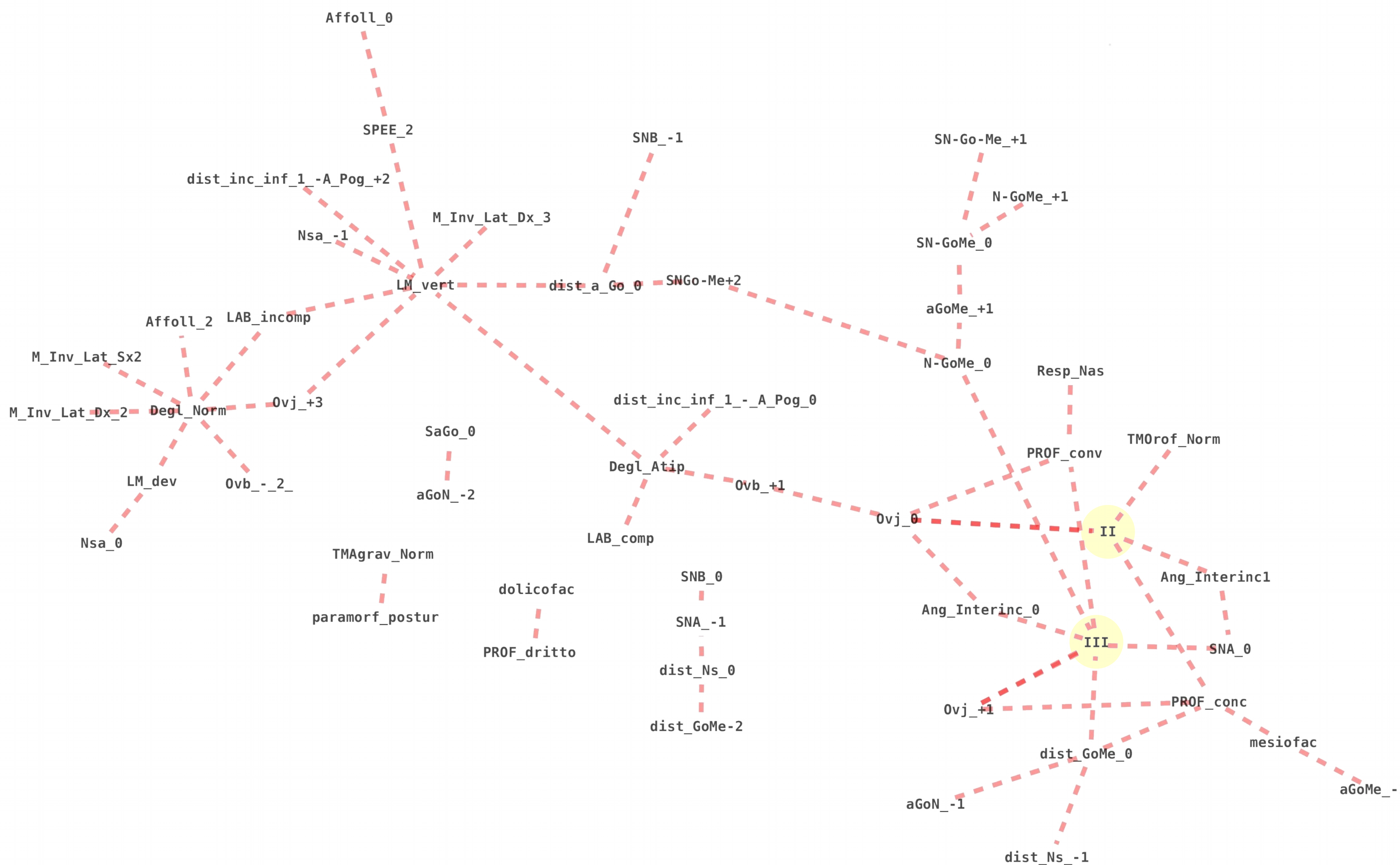
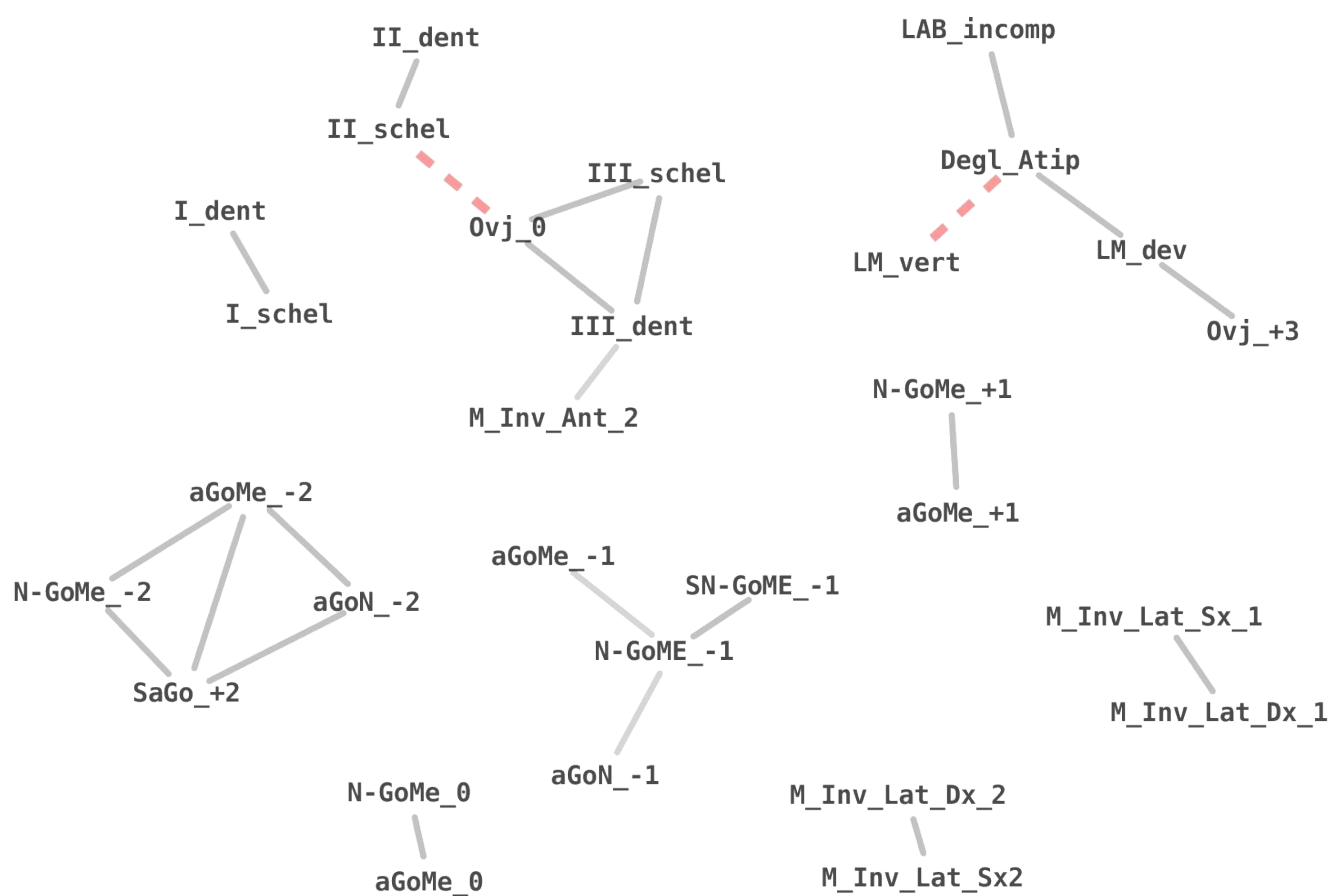
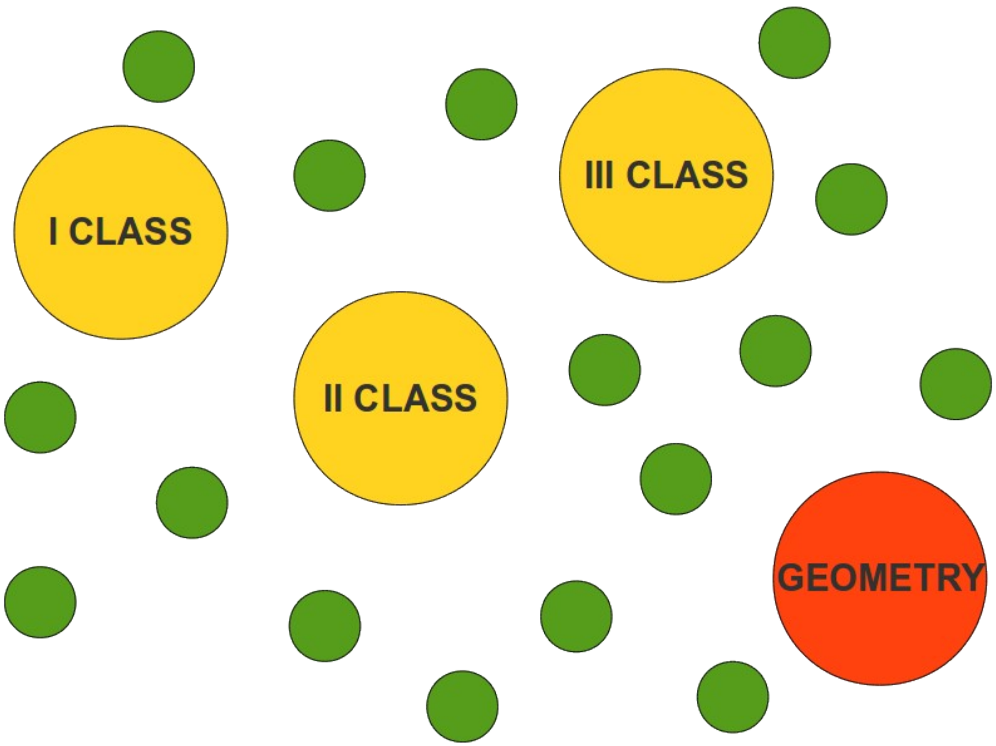
Negative Correlations



Both Correlations



Emergent Classes



Suggestions

- we can extend the reach of computers from analysis to assist hypothesis

- new knowledge simply emerges as plausible patterns from network-based data-mining

Complex Networks can contribute to
mine new knowledge

CONCLUSIONS

- Complex networks represent a powerful tool for implementing a systemic approach (but remember the caveats)
- Massive use of "ordinary" medical data could be a fast source of knowledge before the network physiology revolution is accomplished (and prepare the standardization of the medinfo system)
- Given enough data, heterogeneity can be used to reverse the "design-perform-collect" pattern of scientific experiments

THANKS !!!