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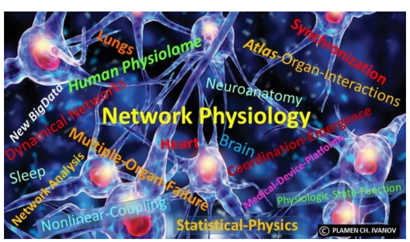
Networks in “Simple” Medicine: Applications to Orthodontic Diagnosis and Treatment

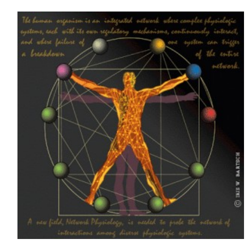
Antonio Scala, PhD
CNR Italy – Institute for Complex Systems

Pietro Auconi MD, Guido Caldarelli PhD,
Lorenzo Franchi MD, A Polimeni MD, J A McNamara MD
G Ierardo MD, Marco Scazzocchio Eng, A Mazza MD



First International Summer Institute on Network Physiology (ISINP)

Lake Como School of Advanced Studies – July 24-29, 2017



ISINP 2017

Overview

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

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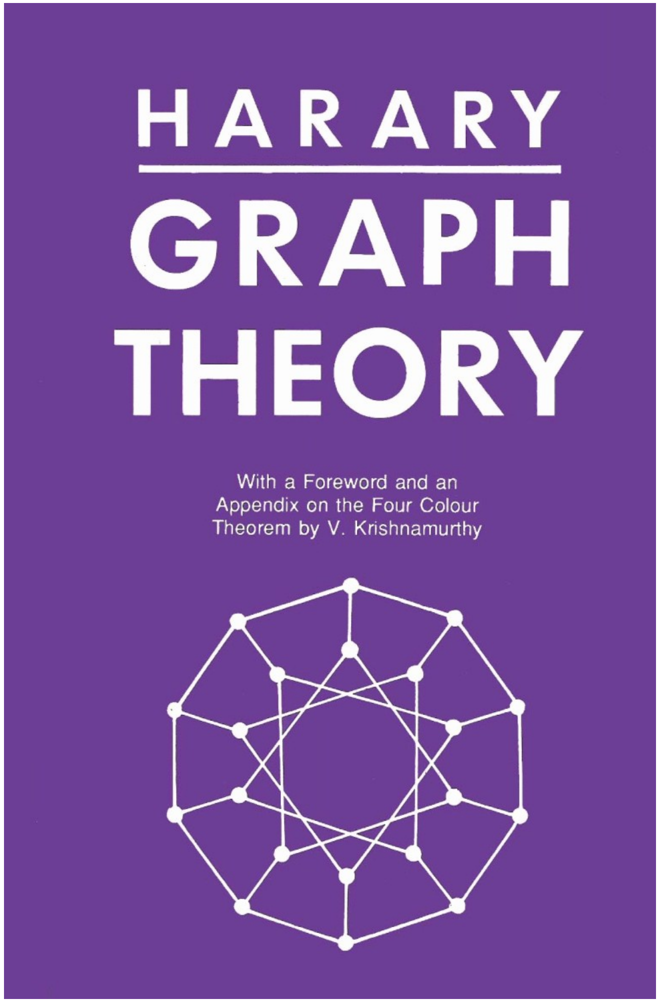
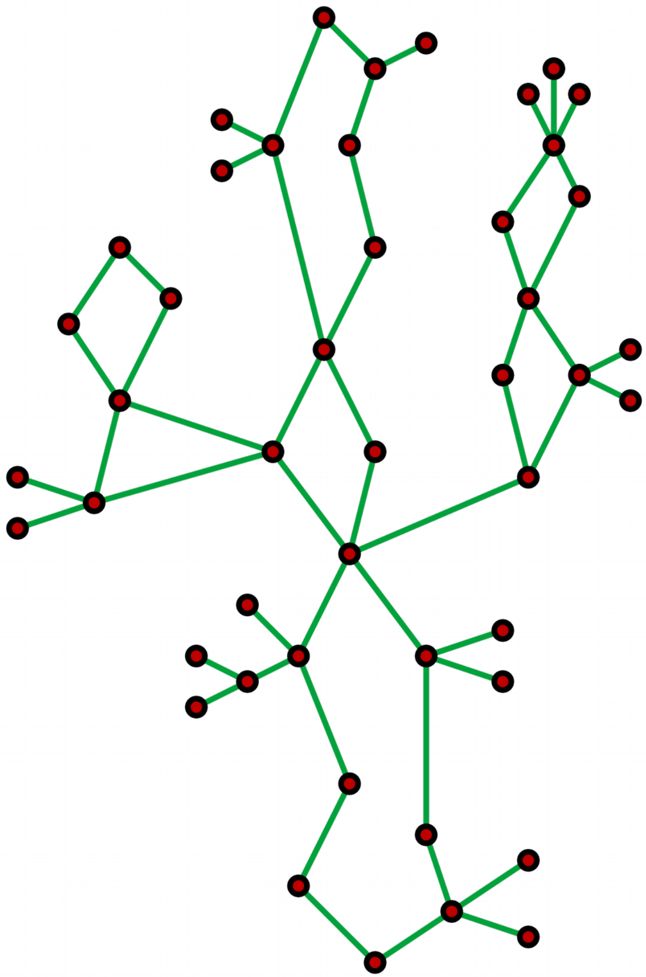
GRAPHS, PHYSICS & NETWORKS





GRAPHS

- Leonhard Euler, 1736: first paper of graph theory

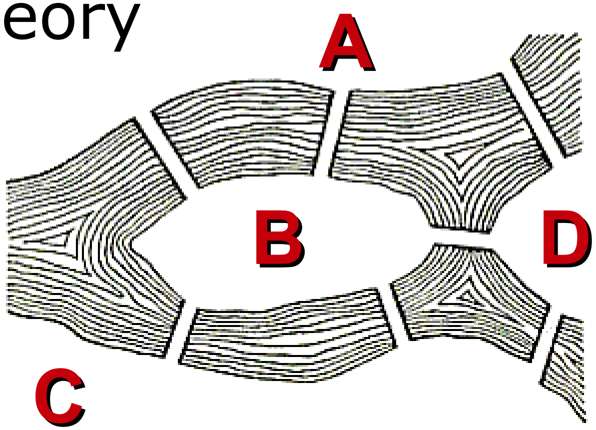


Figure 98. *Geographic Map: The Königsberg Bridges.*

- Dénes Kőnig, 1936: first textbook on graph theory

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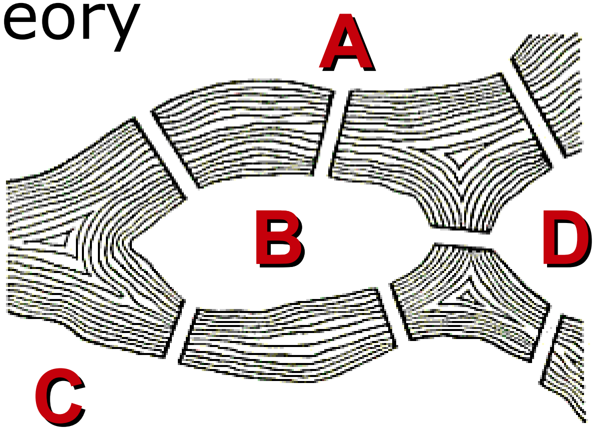

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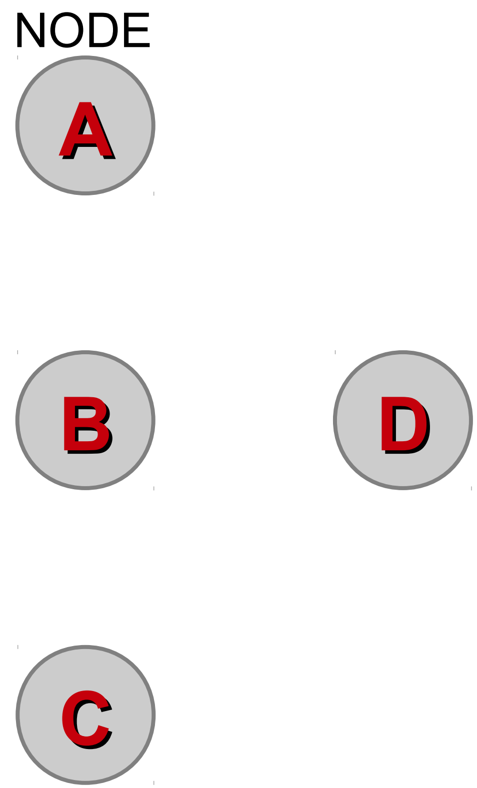

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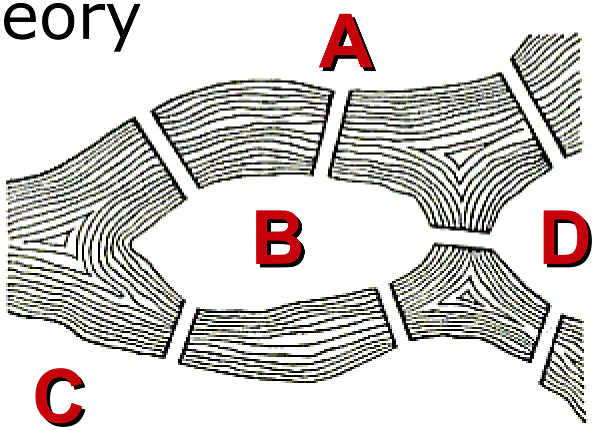

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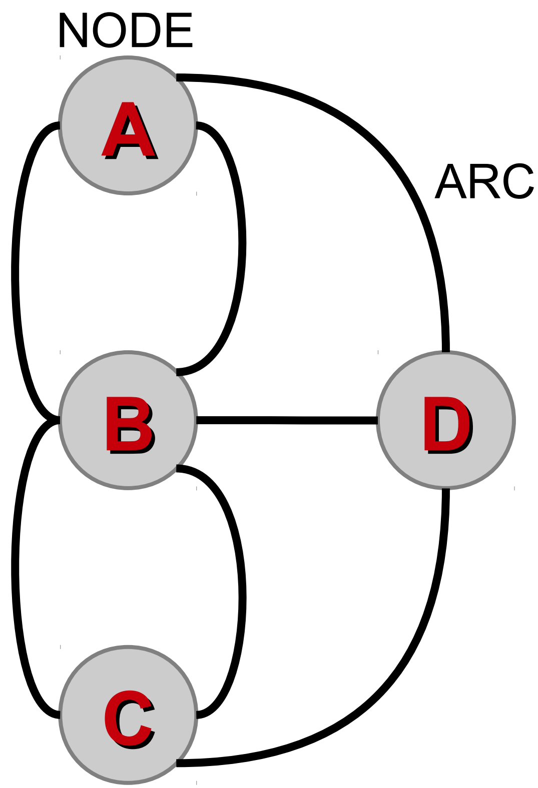
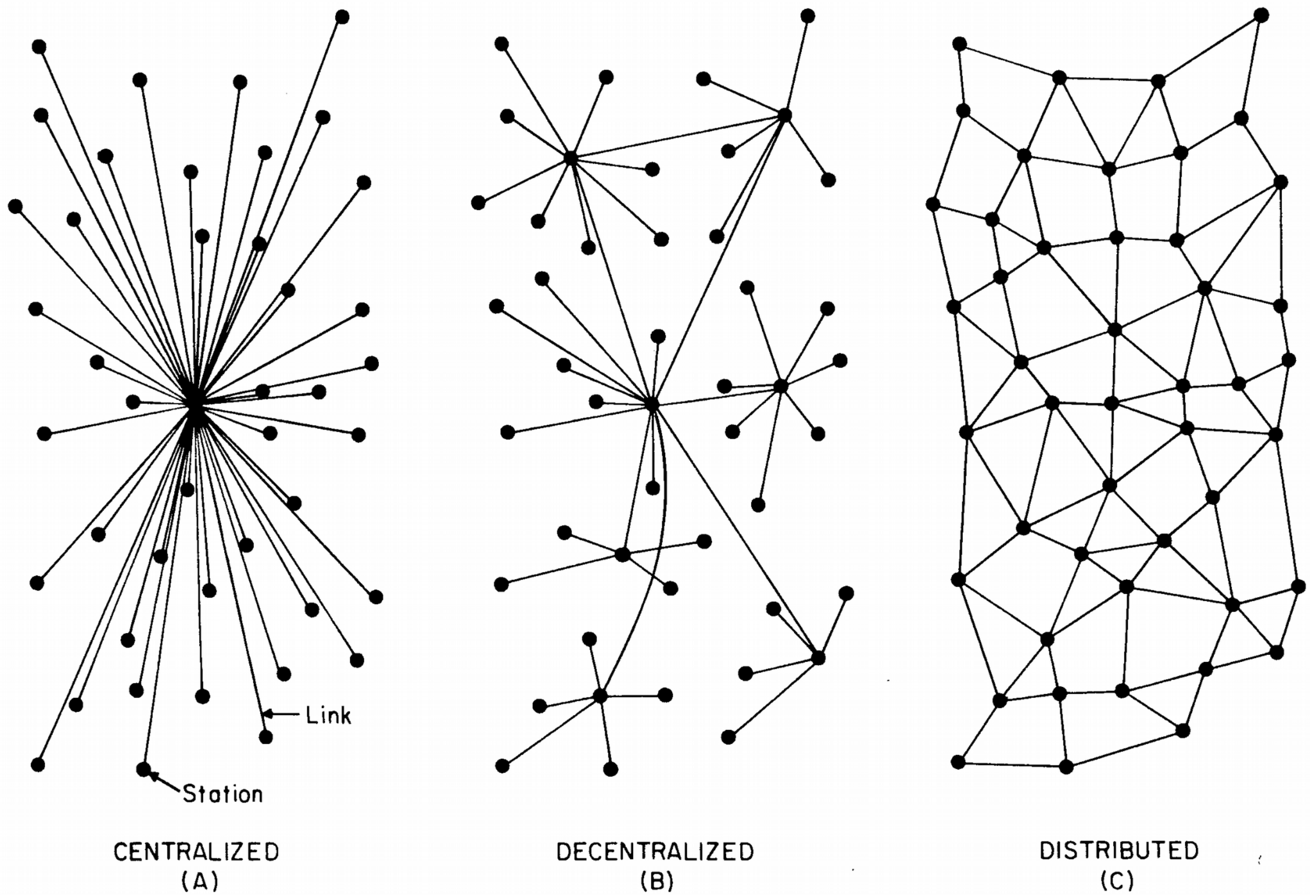


NETWORKS



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

Complex Networks

- Watts & Strogatz: Small World Networks

Small World ("a la Watts & Strogatz")

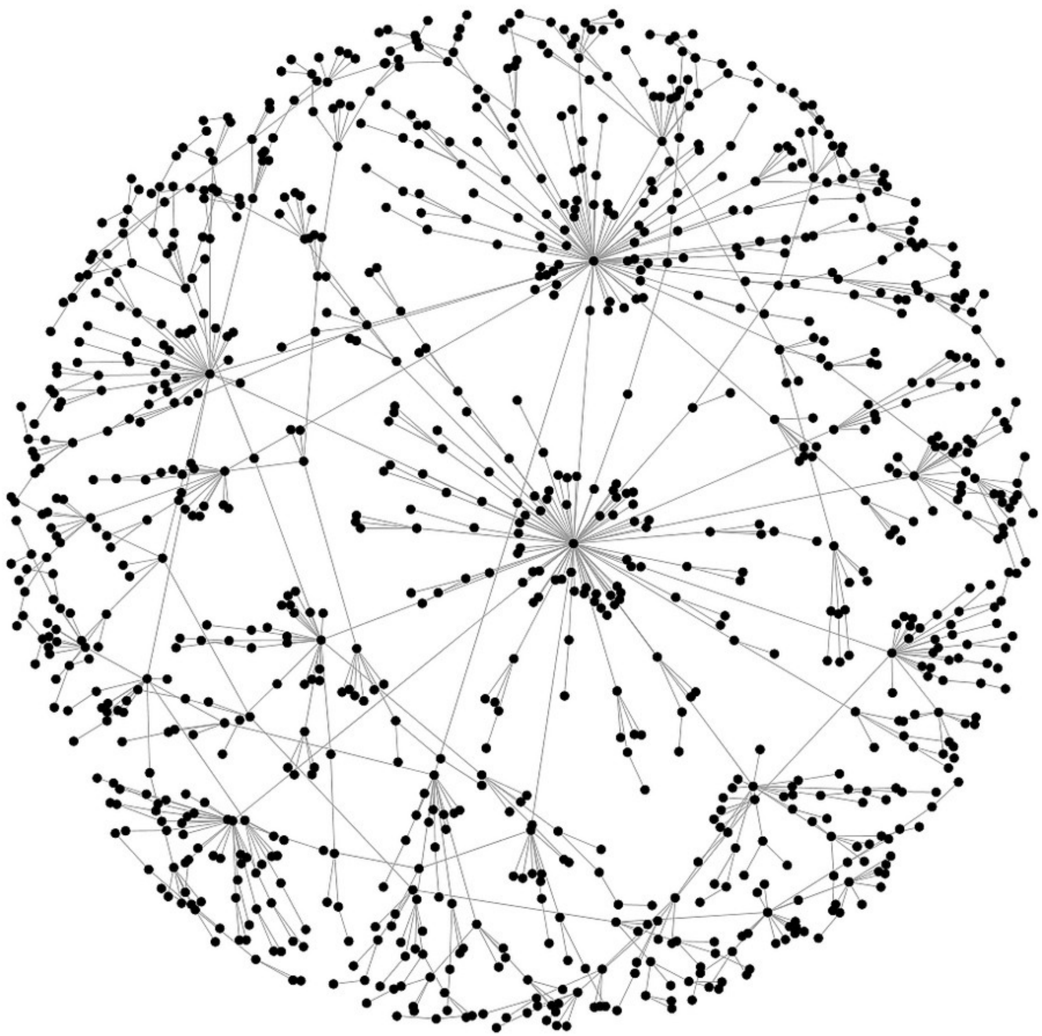
Social Network Analysis

- 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)

Complex Networks

- Watts & Strogatz: Small World Networks
- Barabasi & Albert: Scale Free Networks

Scale Free Network



Complex Networks

- Watts & Strogatz: Small World Networks
- Barabasi & Albert: Scale Free Networks

- Links can be real or virtual
  - Virtual links can be long range
  - Real links are limited

Complex Networks

- Watts & Strogatz: Small World Networks
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- Complex Networks : a Statistical Physics approach
  - Ensembles of networks
  - Collective behaviour (emergence)

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

Network metrics: Centralities

Focused on the importance of the node / edge:

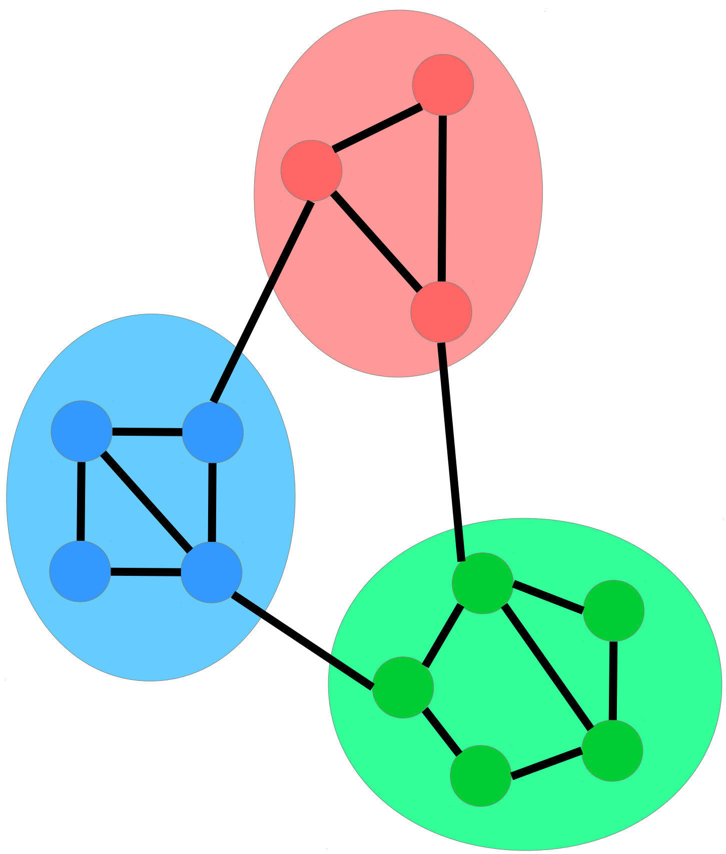
- Degree
- Closeness
- Betweeness
- Eigen/Katz/Page Rank
- Percolation
- Accessibility
- Dynamic influence
- Debt Rank
- ….

Simplifying networks: Communities

- Spin Models
  - find communities like magnetic domains
- Flow trapping
  - define dynamics and observe stagnation
- Minimum-cut methods
  - find communities with minimum inter-linkage
- Hierarchical clustering
  - join recursively less and less connected communities
- Girvan–Newman algorithms
  - remove links among communities
- Modularity maximization
  - maximize target function over communities

Generally speaking, the “Divide and Conquer” approach

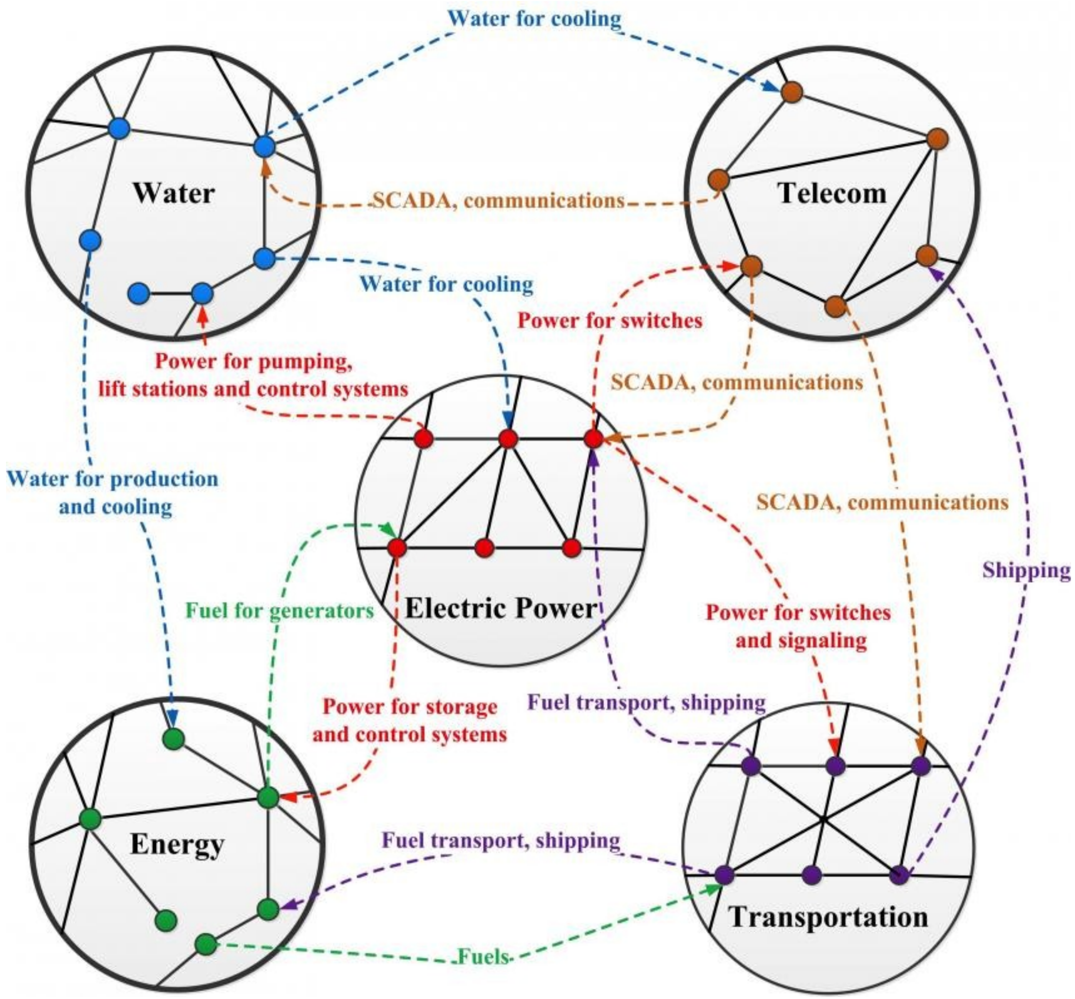
Community Structure



Fundamental open questions even for the most basic models of community detection:

- Are there really clusters or communities? Most algorithms will output some community structure; when are these meaningful or artefacts?
- Can we always extract the communities, fully or partially?
- What is a good benchmark to measure the performance of algorithms, and how good are the current algorithms?

Last fashion: Networks of Networks

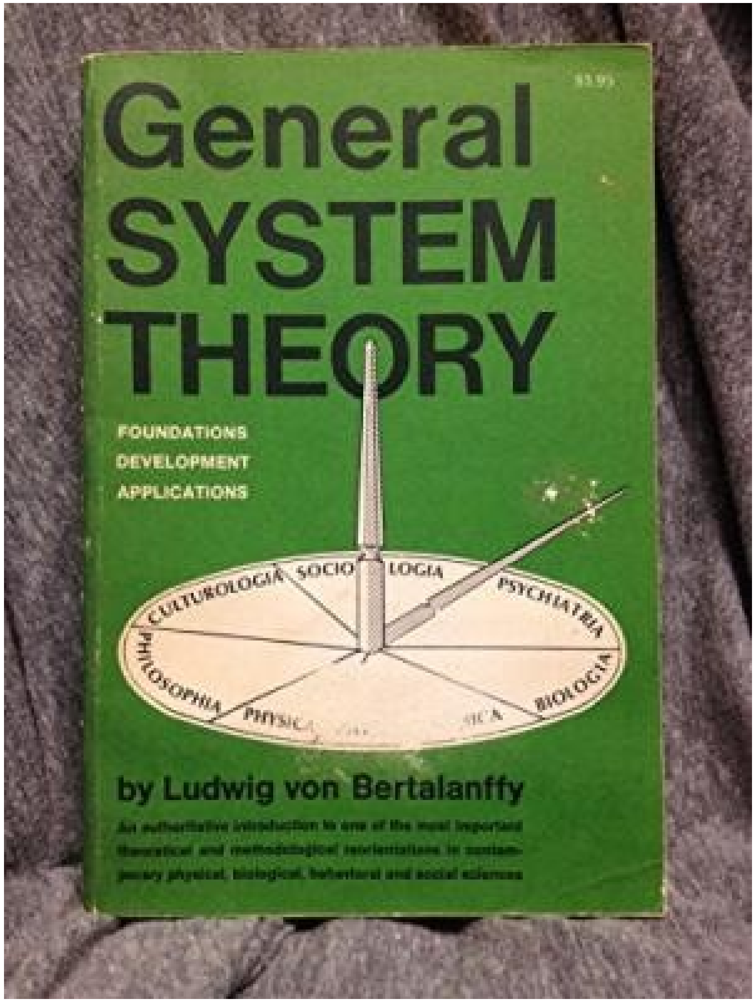


Network Theory: pros & cons

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

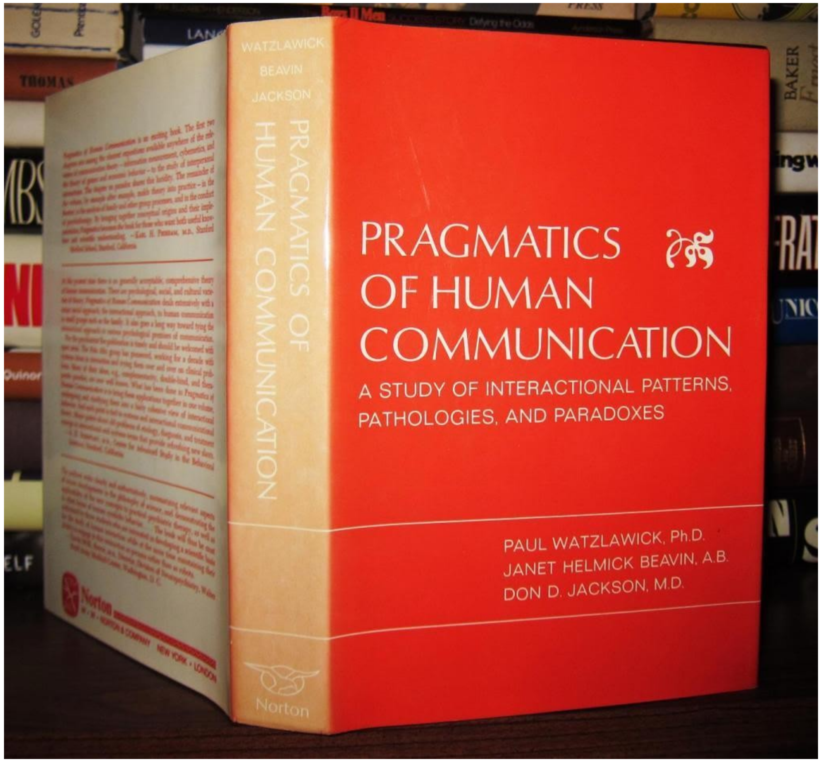
- Networks capture only diadic interactions
- “Danger” of networks motifs
- “Decision dependent” networks: What are the nodes? What are the links? How do I attribute weights?

1968: General System Theory



- GST introduced in 1930 by *Von Bertalanffy*
- System as "a set of elements in interrelation among themselves and the environment"
- Universal principles of organization which hold for all systems, emphasizing holism over reductionism, organism over mechanism and ***equilfinality***

Family therapy & psychotherapy



Watzlavick's "Interactional View" requires a network of communication rules that govern a family homeostasis to maintain the status quo.

Even if the status quo is negative it can still be hard to change.

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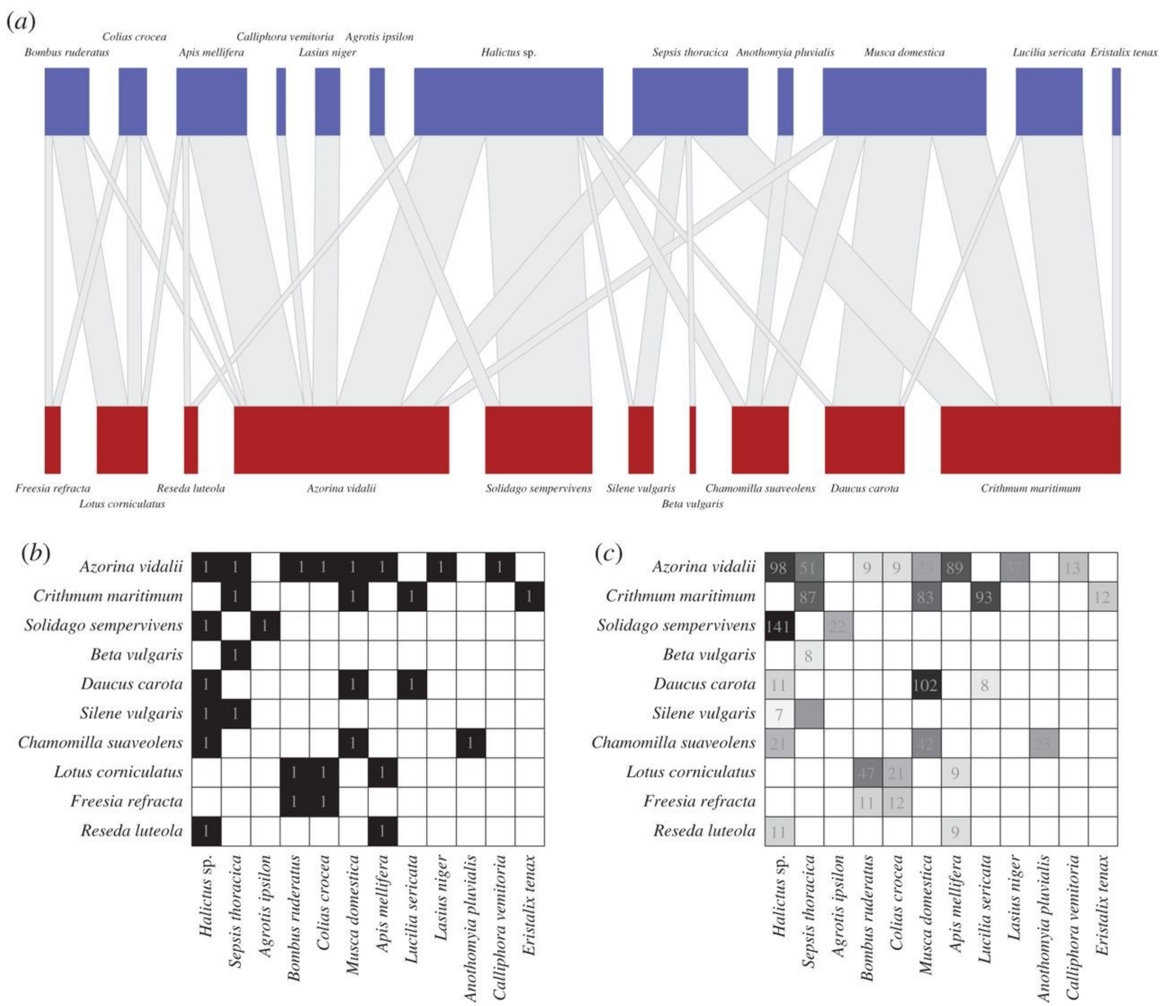
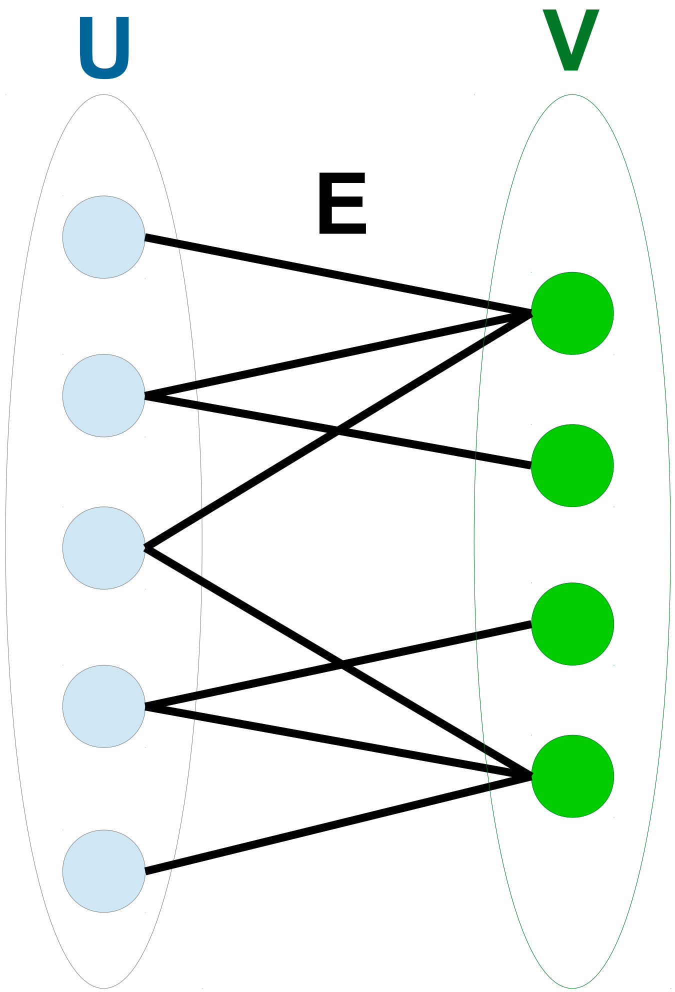
DATA, PROJECTIONS & NETWORKS



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

Bipartite Graphs



Bipartite graph:

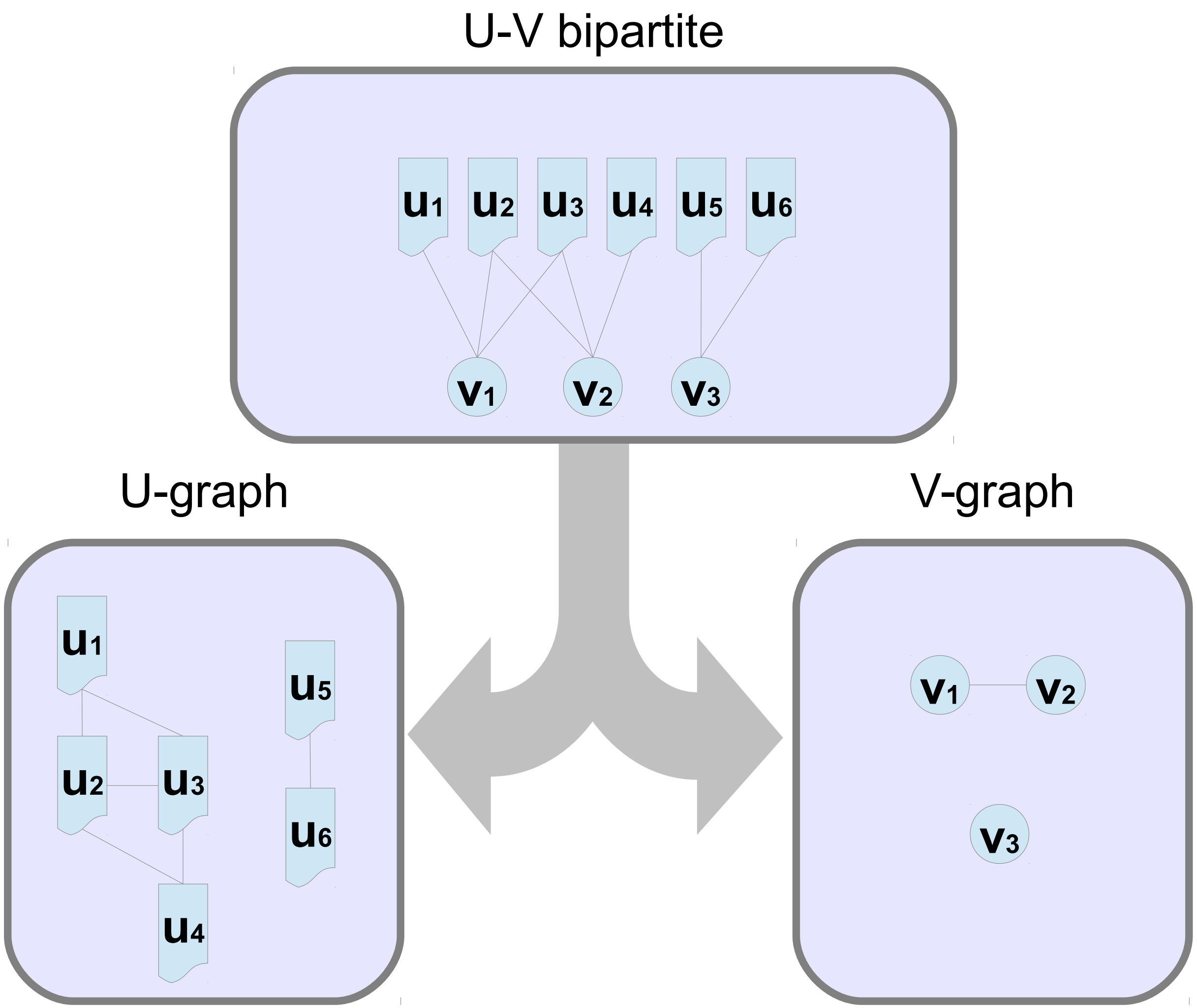
- G = (U, V, E)
- U, V nodes
- E edges among U,V

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

Examples

- Film – Actors
- Papers – Authors
- Nation – Products
- Text – Words
- Birds – Islands
- Plants – Pollinators
- Politician – Votes
- Users – Newsfeeds
- Patients – Sympthoms
- Genes - Individuals

Projections



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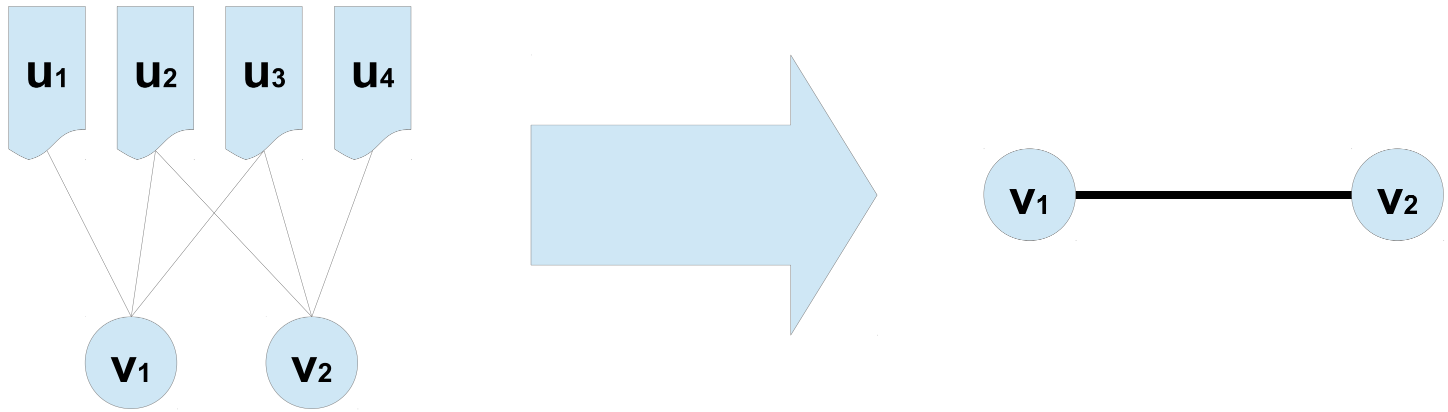
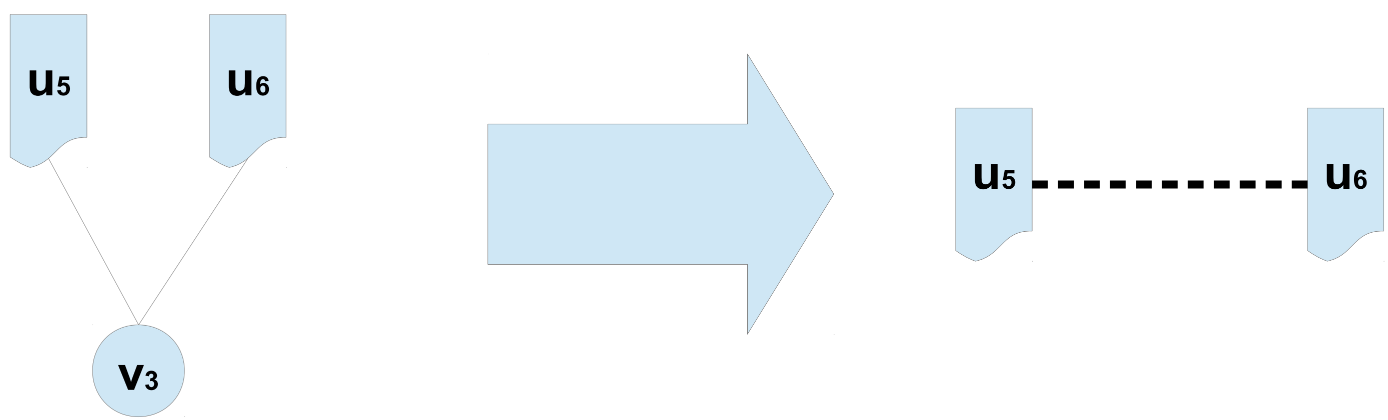


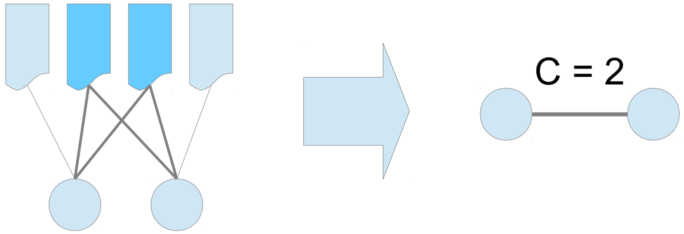


Co-occurrence matrix

- 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

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



- $B B^T \rightarrow$ weighted adjacency matrix of the projection graph on U
- $B^T B \rightarrow$ 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

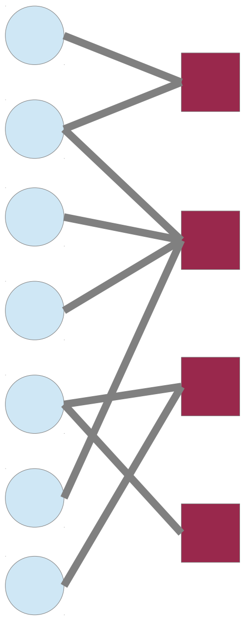
$$S_{uw} = 2\ C_{uw} / (\ C_{uu} + C_{ww}\ )$$

- Correlation matrix

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

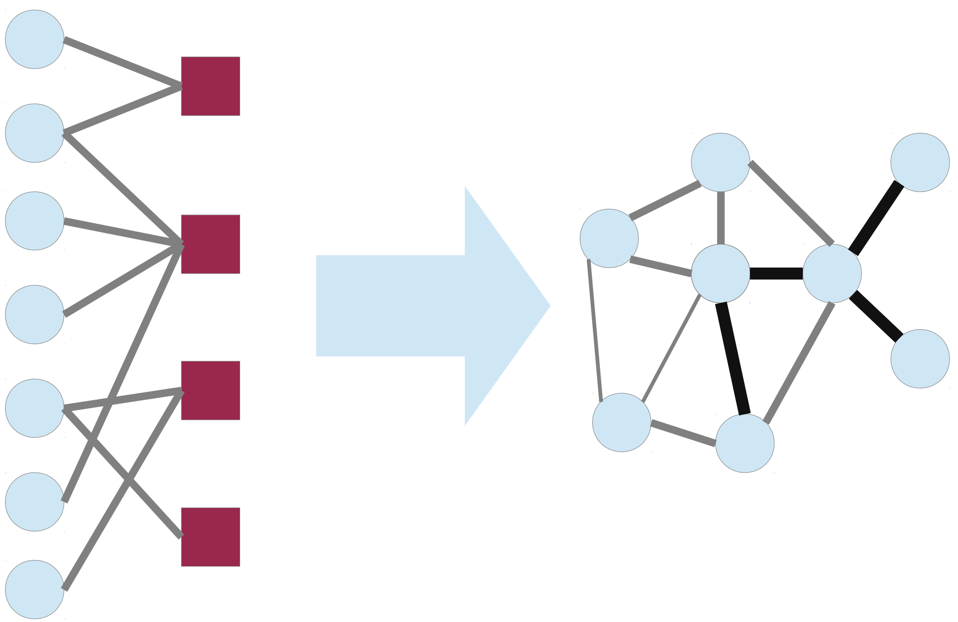
$$\sigma_u^2 = f_u\,(1-f_u\ )$$

Methodology



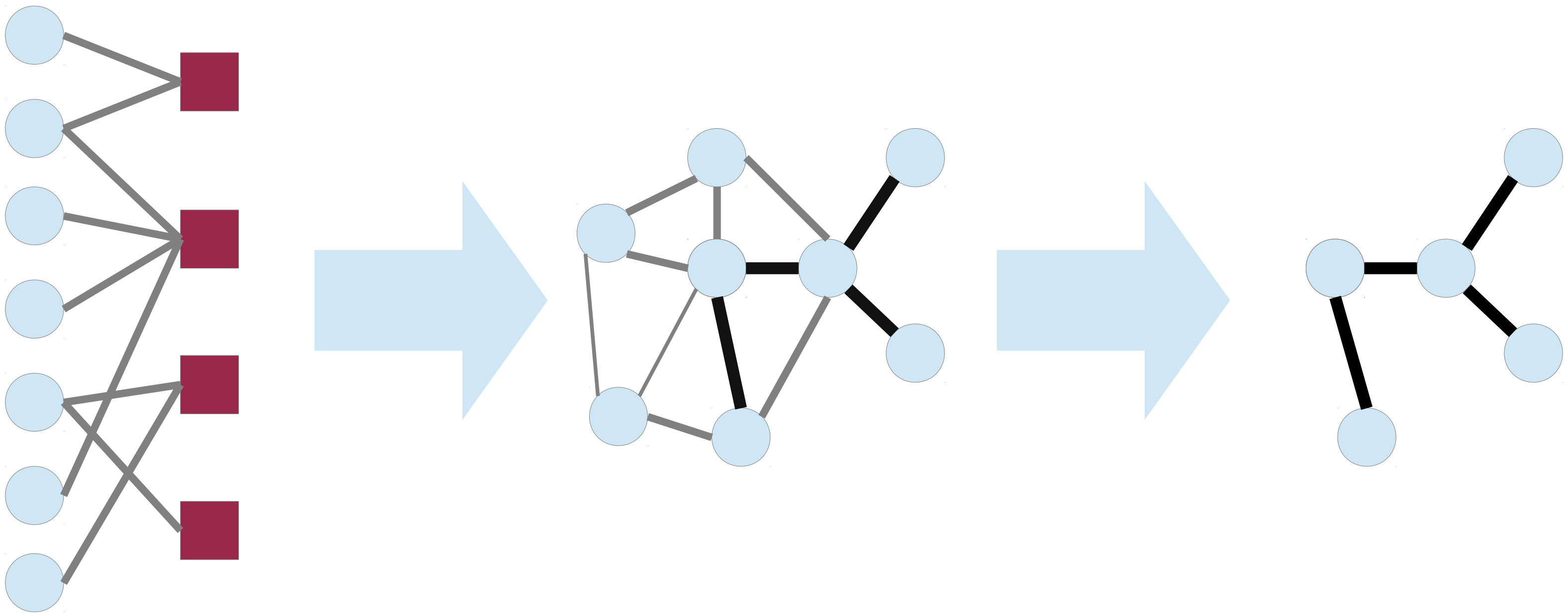
COLLECT

Methodology



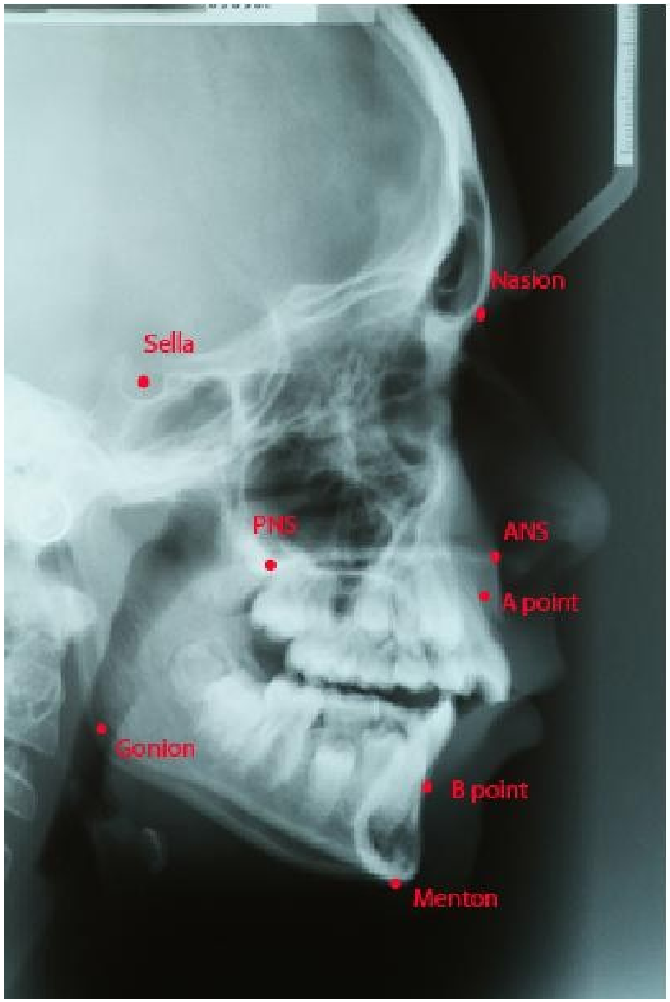
PROJECT

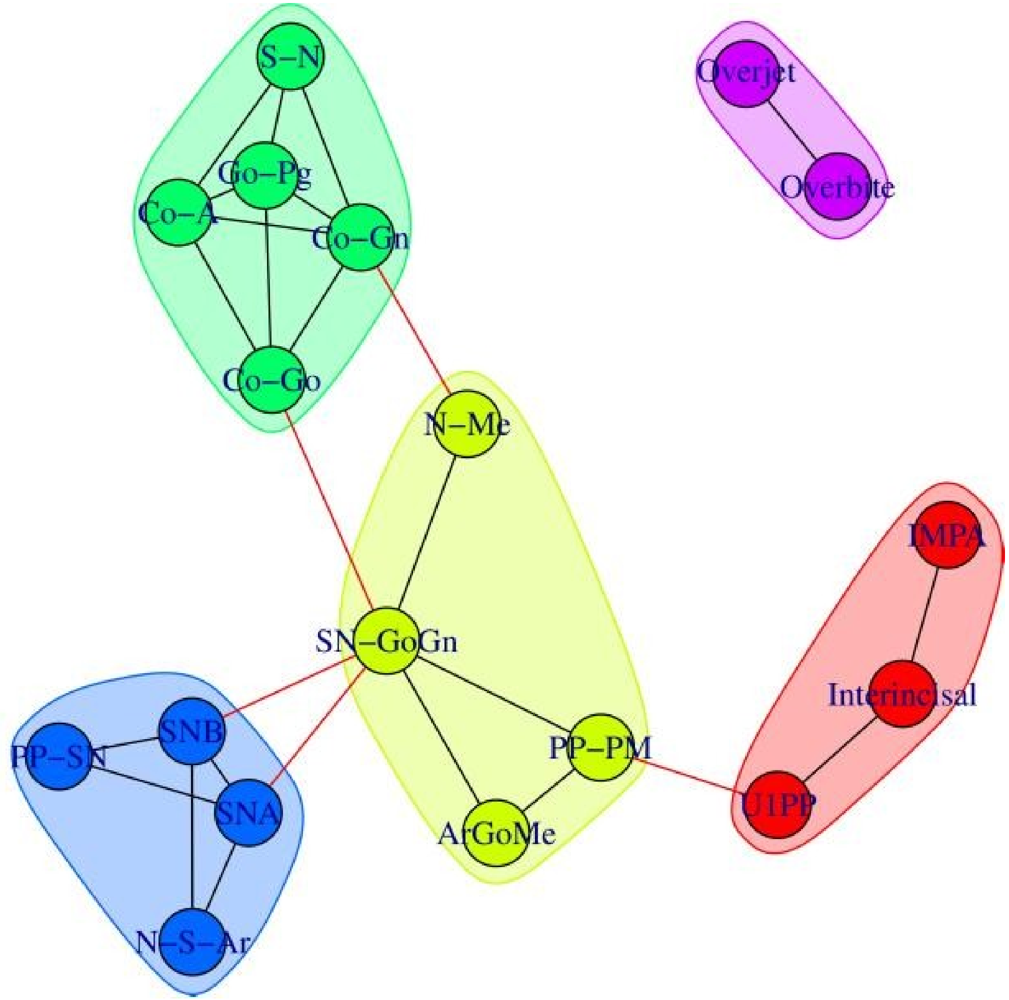
Methodology



SELECT

DENTISTRY, TREATMENTS & NETWORKS

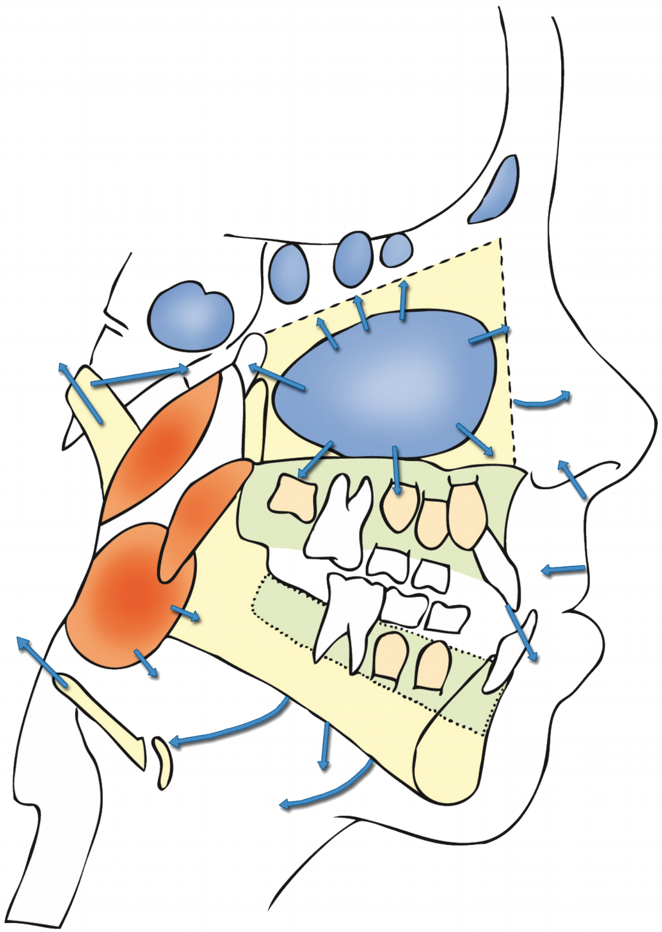




Introduction

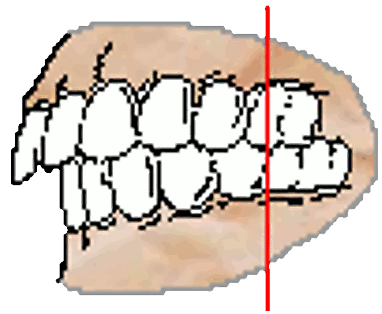
- Motivation: Mining knowledge from Medical Records
- Methods: Network Analysis for Case-Features dataset
- Case-study: Childhood orthodontics

The Complex Oro-Facial System



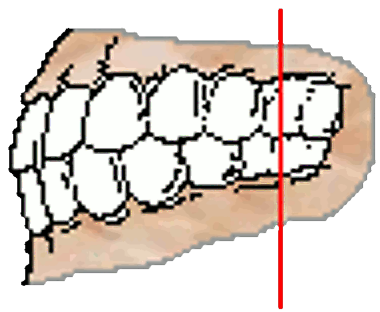
- components
- relations
- interactions
- dynamics

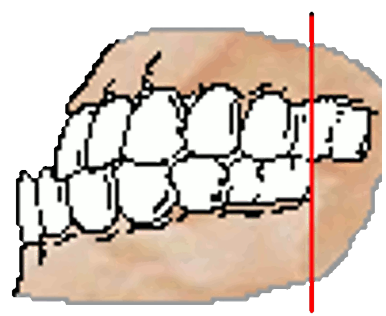
Dental Classes



2nd Class
(bad)

1st Class
(normal)





3rd Class
(worst)

Dataset 1

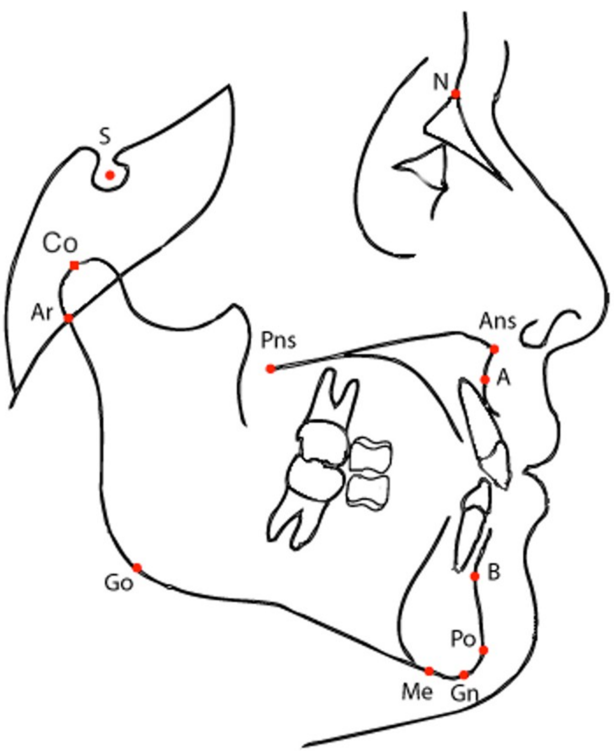
Cases

- 97 subjects (49 males, 48 females)
- age 8-13 (mean 10.2)
- 28 1st class, 44 2nd class, 25 3rd class patients
- Uniform age and gender

Features

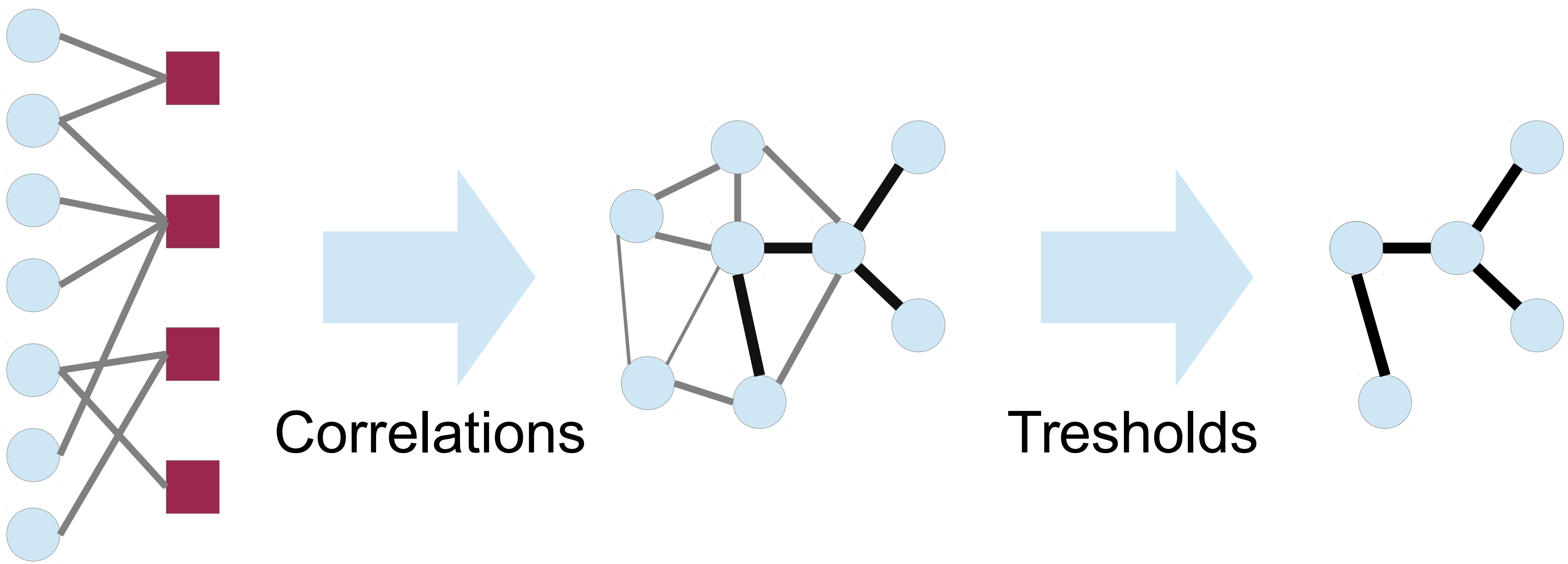
- 33 clinical, anatomic, functional and radiographic features
- 16 landmarks on the cephalograms
- 17 functional and clinical signs or oral habits
- score from -3 to + 3 = standard deviations from the mean

Cephalograms



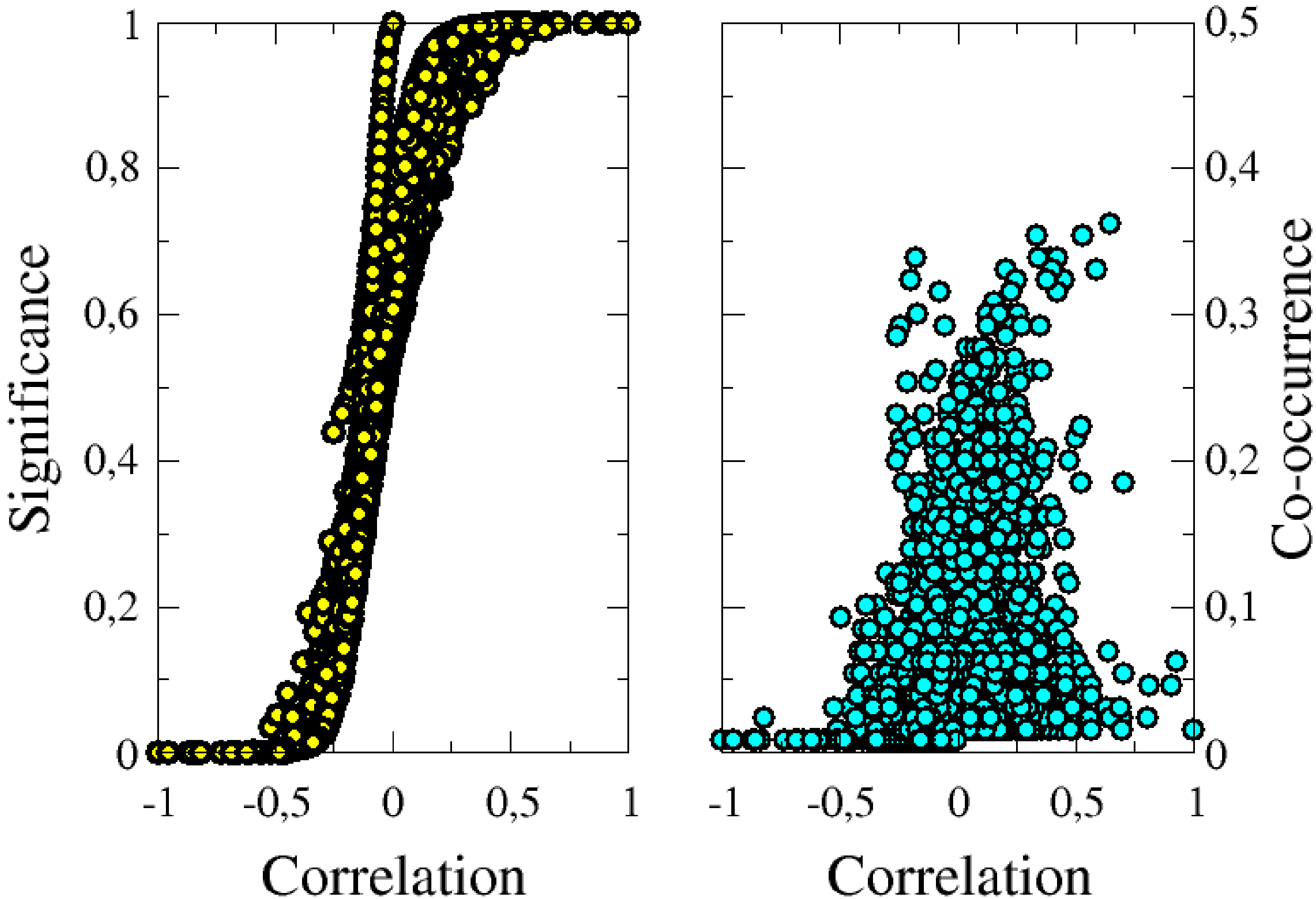
Co-Gn	mandibular length as distance from Co to Gn
Ar-Go	mandibular ramus height
NS-GoGn	divergence of the mandibular plane relative to the anterior cranial base
NS-Ar	saddle angle
….	….

Getting the networks



"PROJECT & SELECT"

Correlation vs Co-occurrence



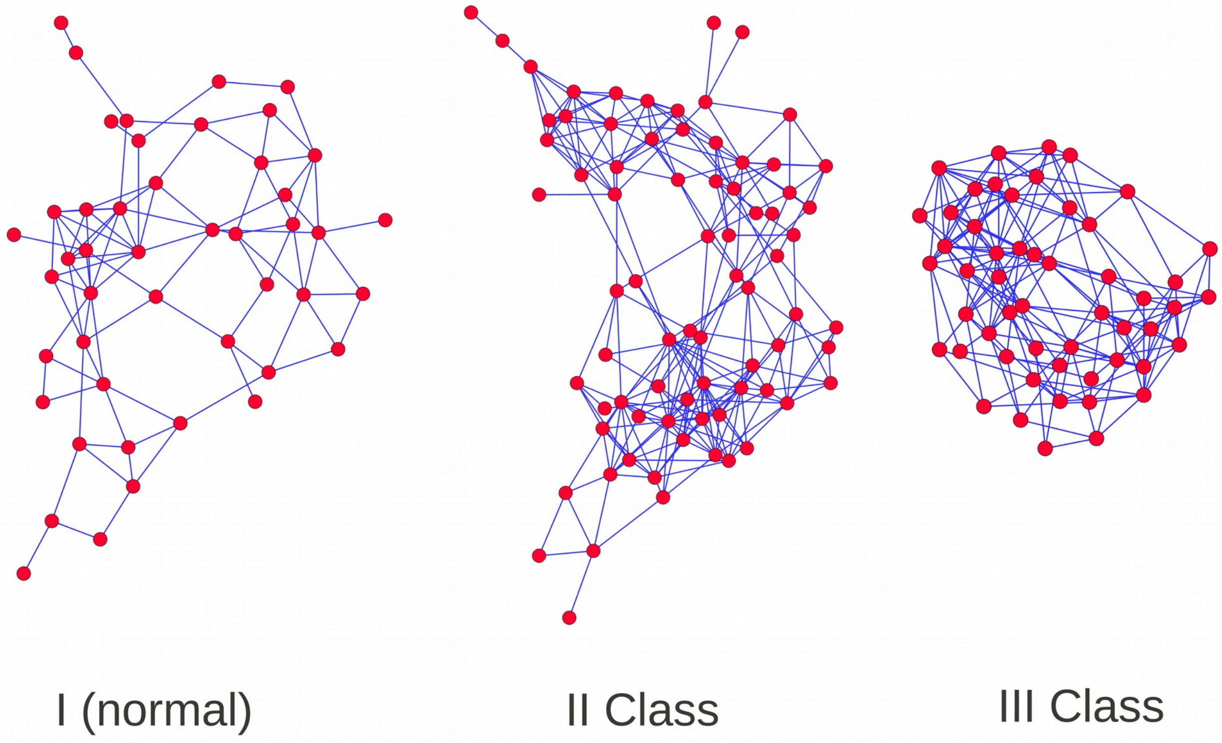
Network metrics

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

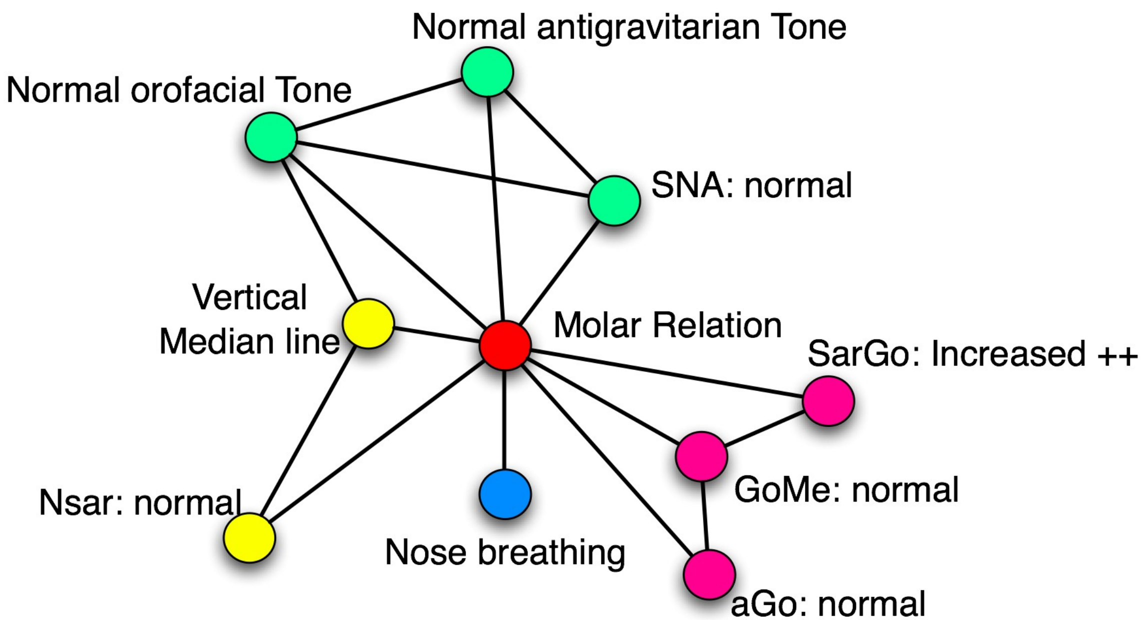
- 2nd and 3rd class features are more connected than those of the control patients.
- 3rd class patients shows a much higher connection and closeness: this topology allows a high transmission of the bite forces and neuromuscular inputs

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*

Dataset 2

- Lateral cephalograms of 70 dentoskeletal Class III patients
  - 7-13 years of age; mean = 9,5 years
  - 40 female, 30 male
  - rapid maxillary expansion and facemask therapy
- Patients re-examined at the end of treatment
  - 11-18 years of age; mean =14,7
- Control group of cohort of 70 untreated Class III
  - for age and sex
  - 11-18 years of age, mean = 14,5

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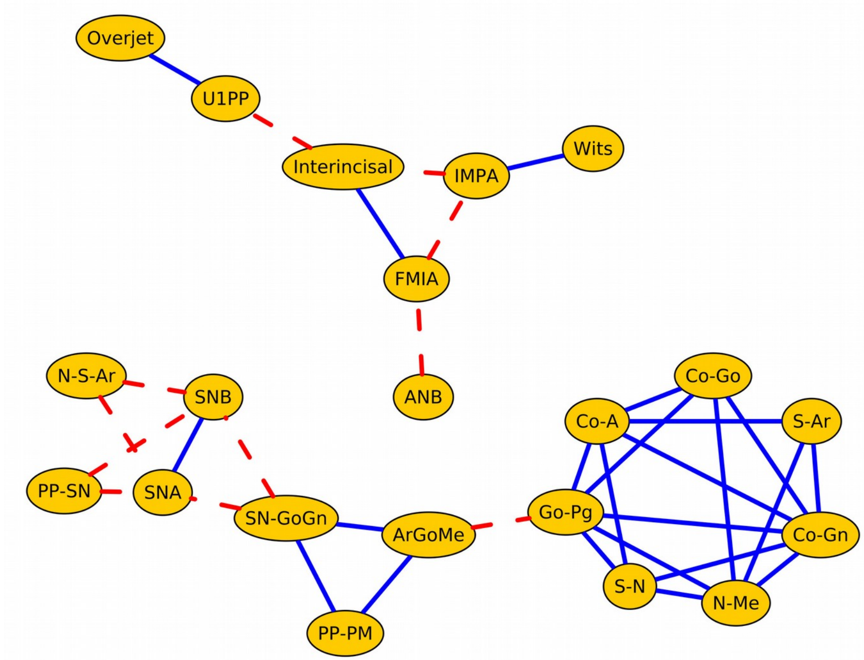
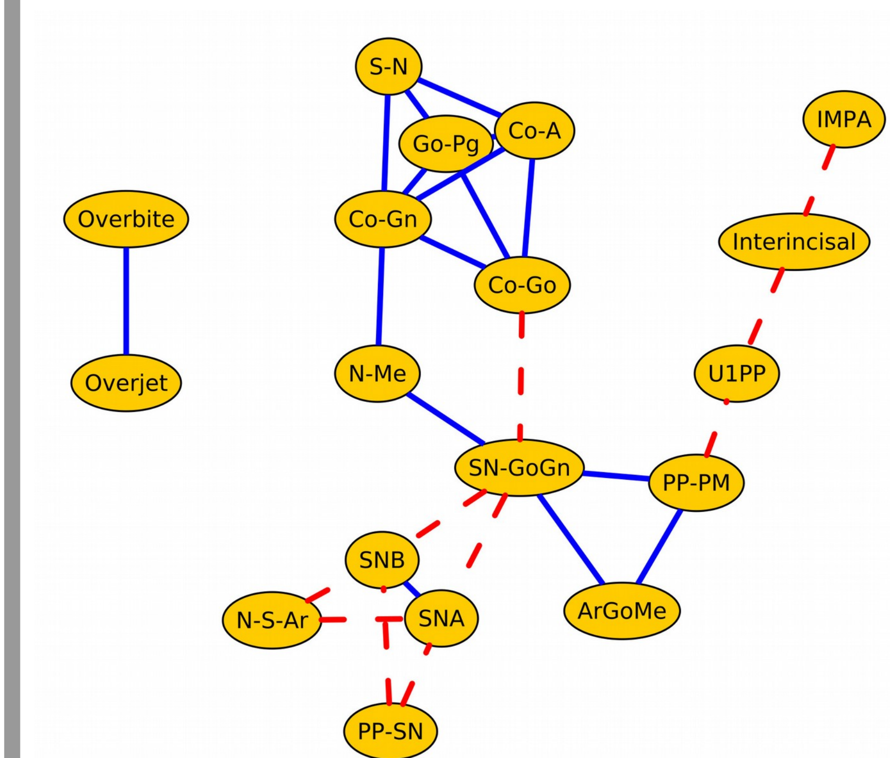
Before treatment *vs* After treatment





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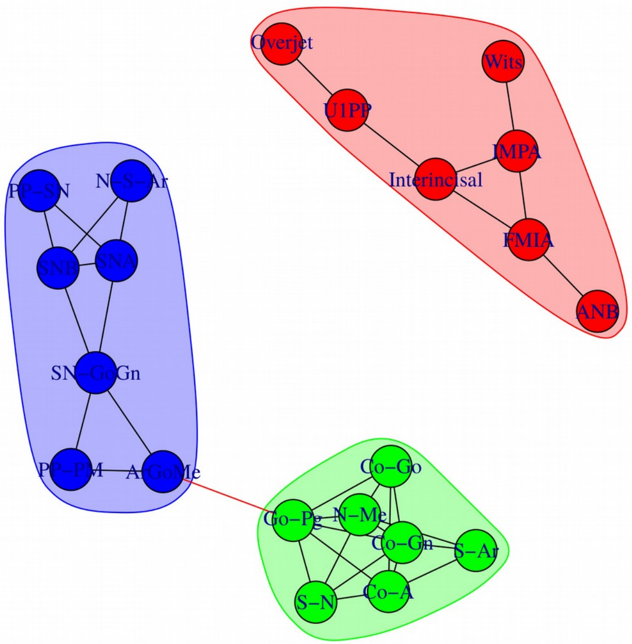

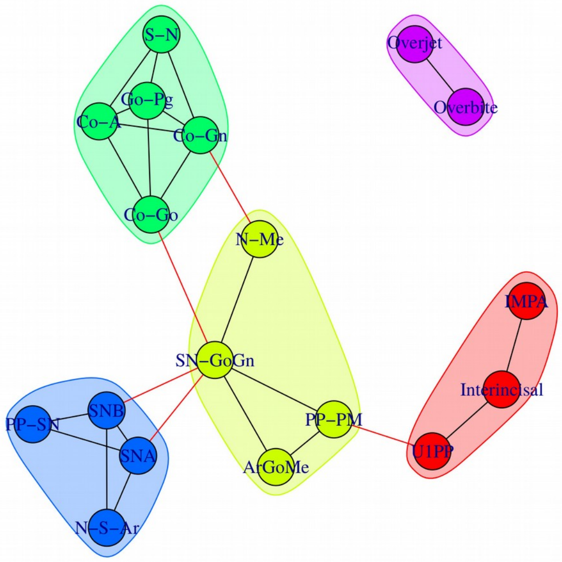

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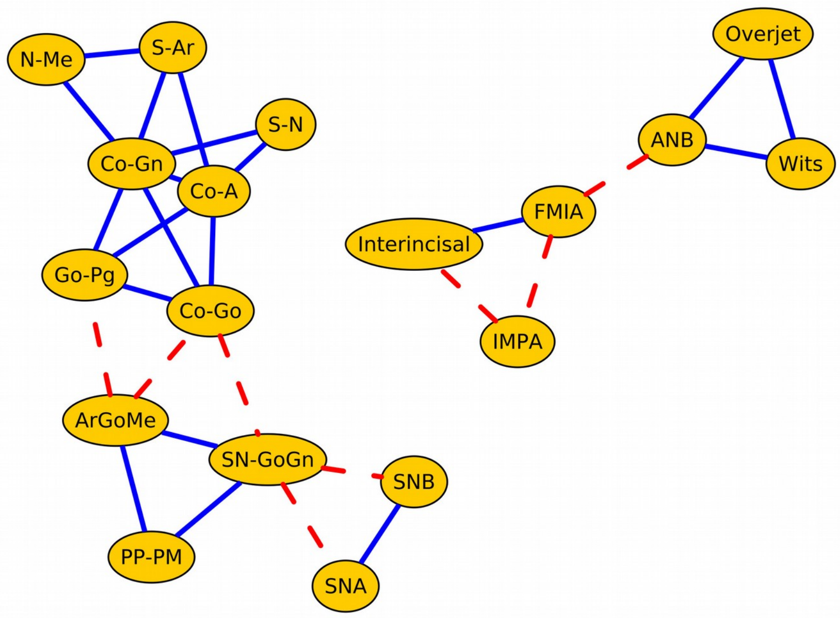
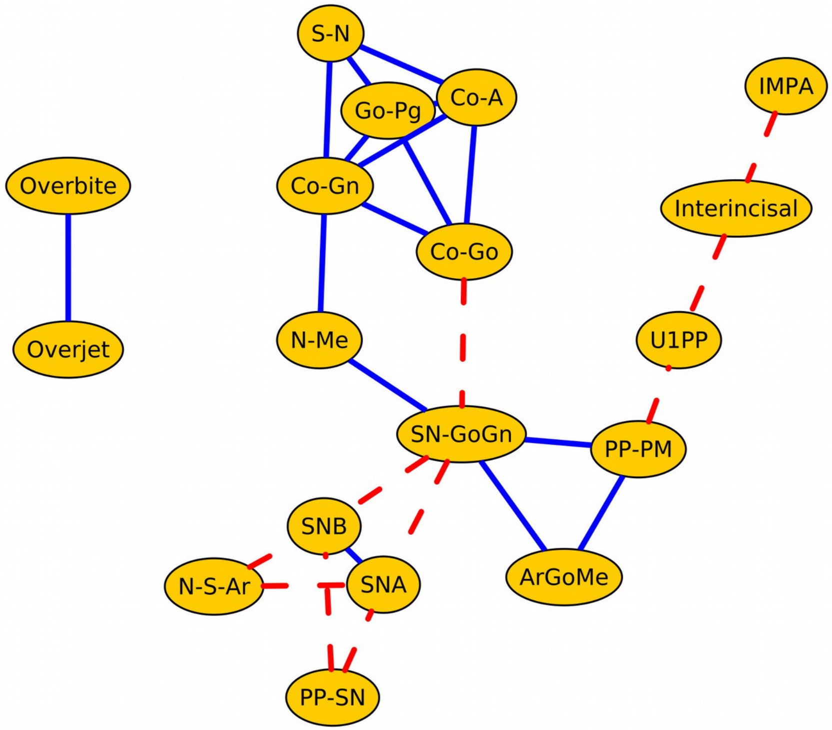
NO treatment *vs* Treatment





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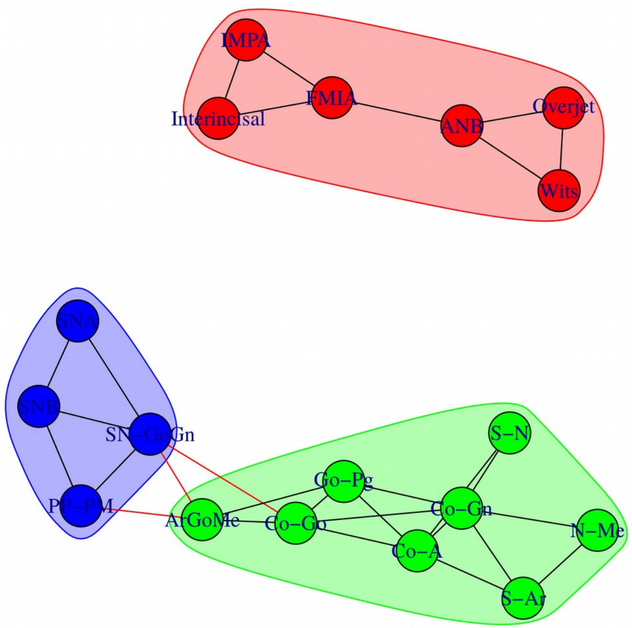
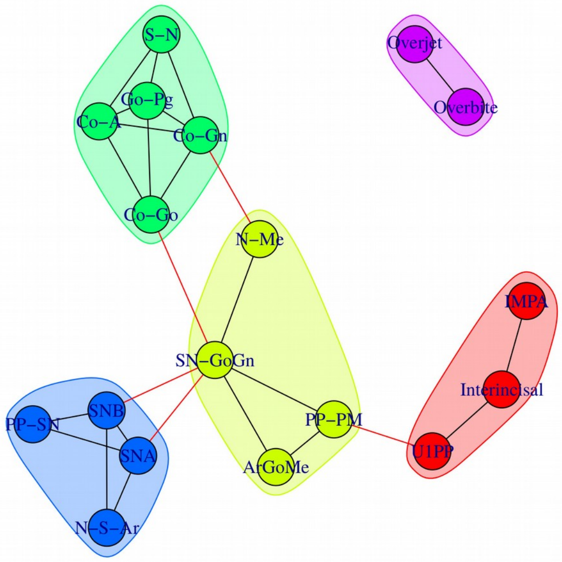
NO treatment *vs* Treatment





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 ?

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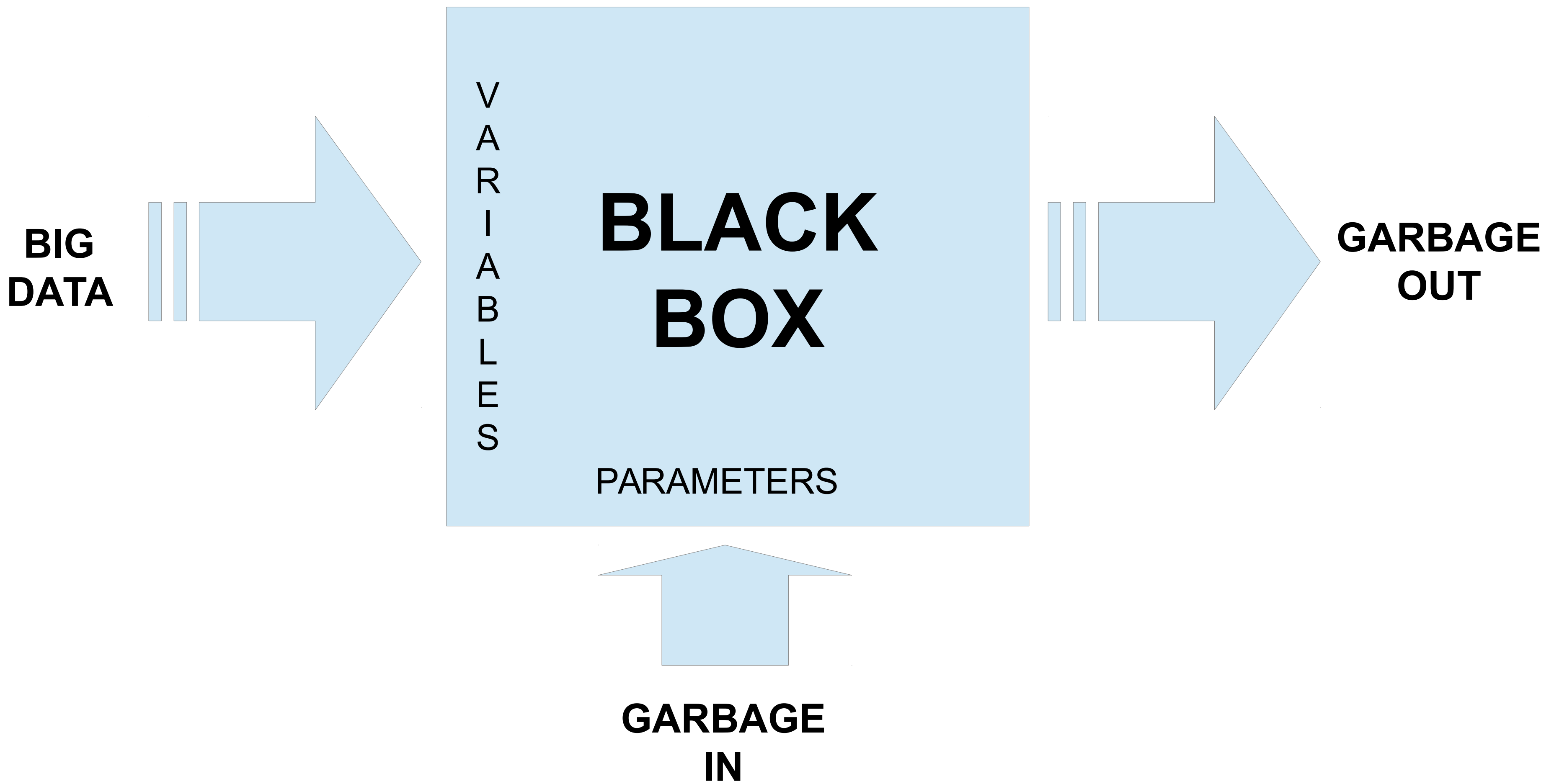
GOAL: infer syndromic phenotypes from clinical data via complex networks methods

BIG DATA, KNOWLEDGE DISCOVERY & NETWORKS

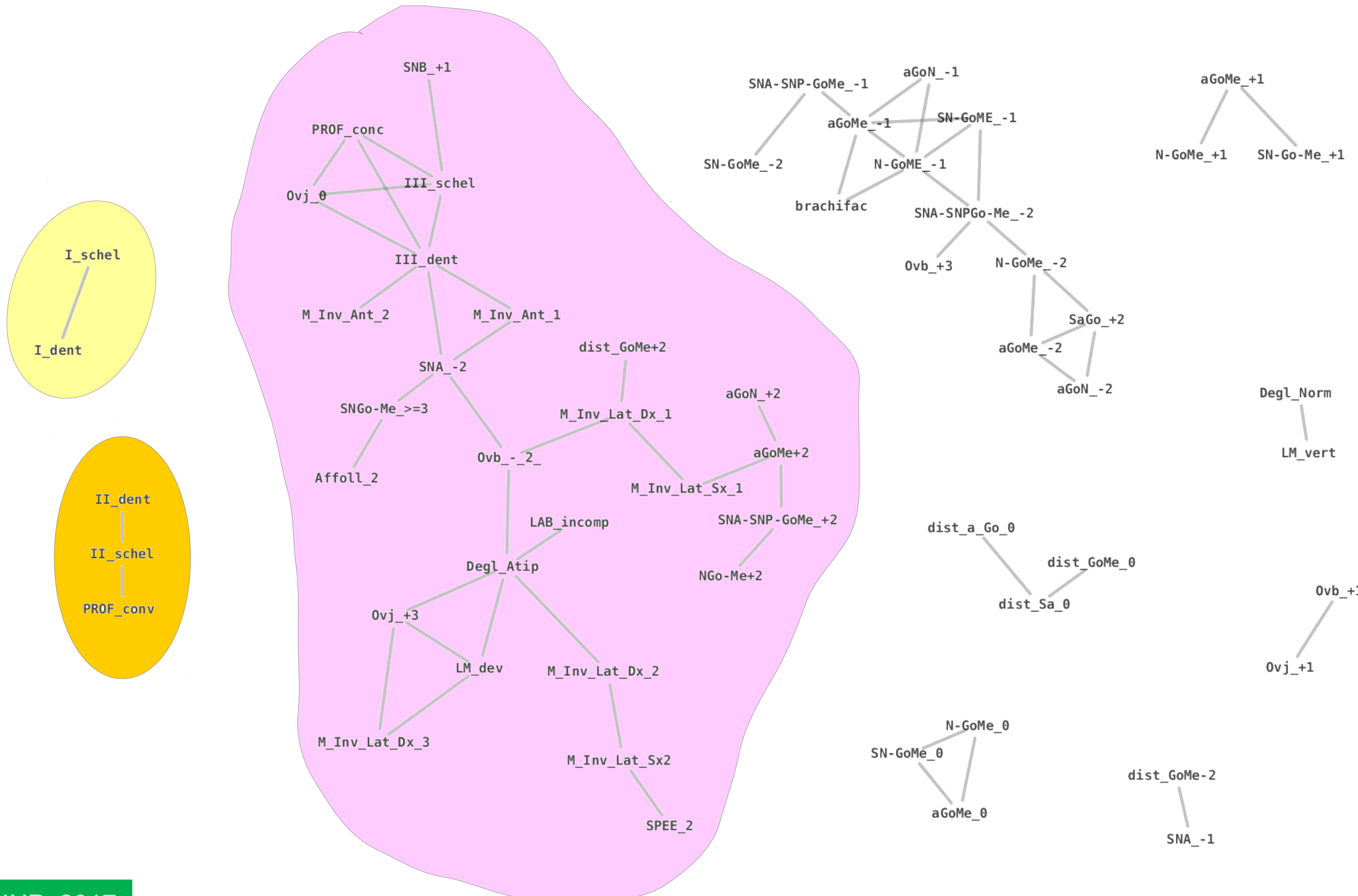


Advertising Complex Networks

- 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

https://sites.google.com/site/antonioscalaphys/

Positive Correlations



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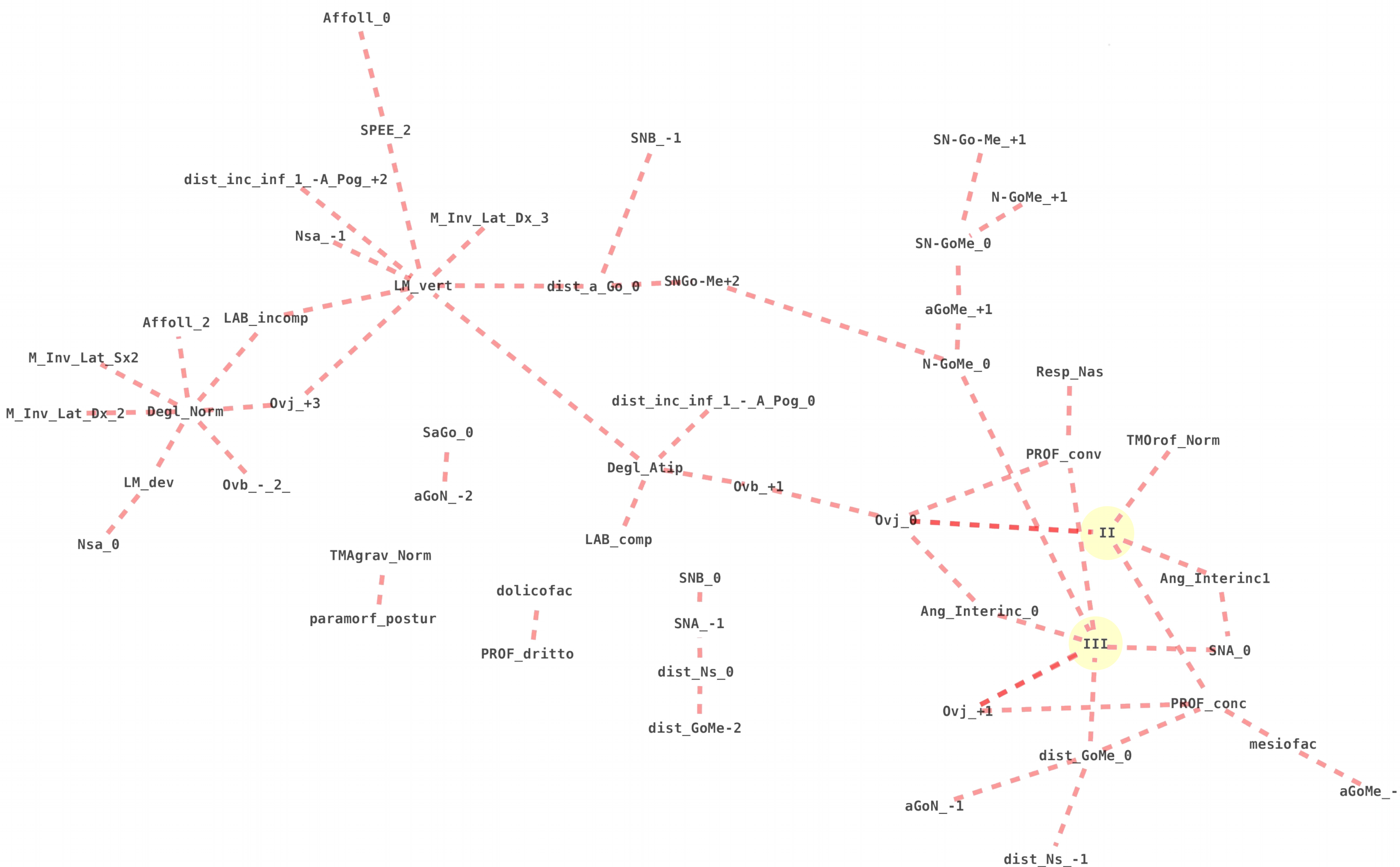
Negative Correlations



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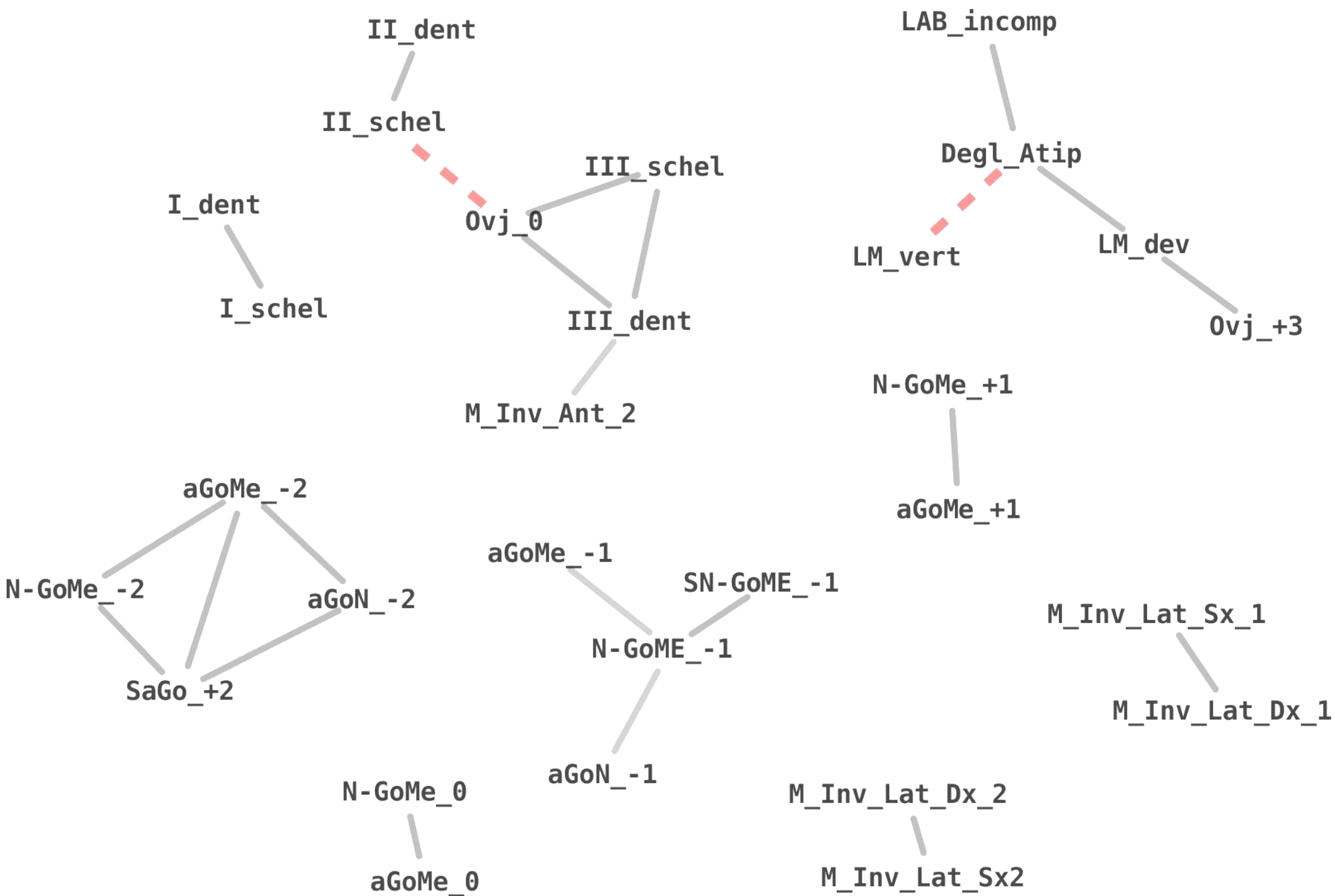
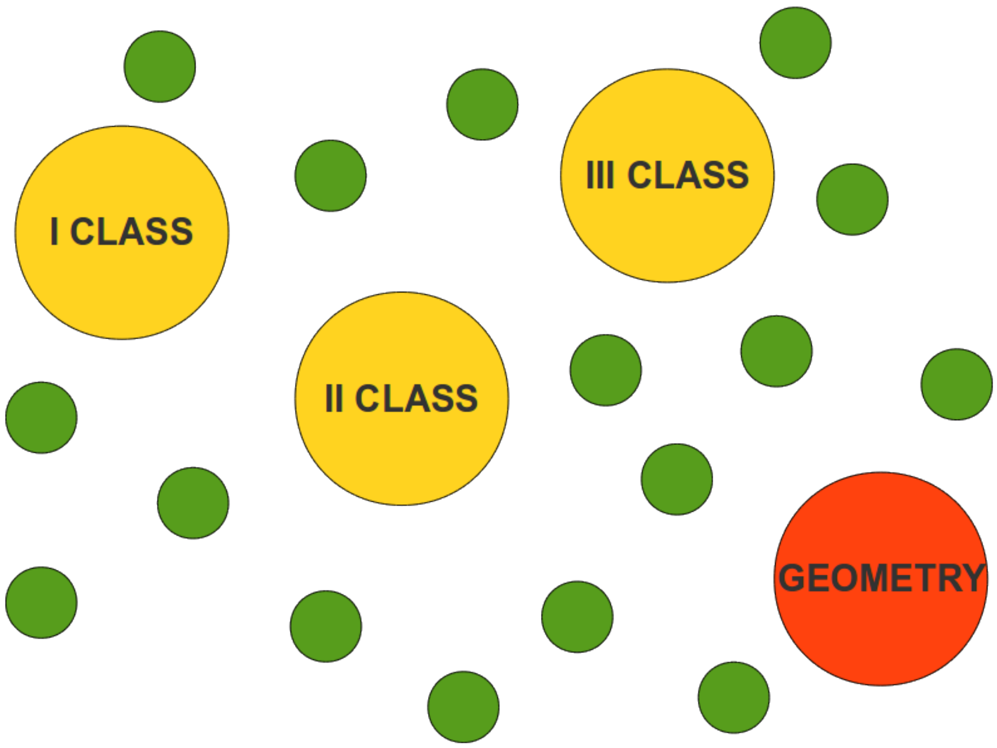
Both Correlations



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 !!!