Sino-Dutch Centre for Preventive and Personalized Medicine

Diabetes Mellitus en systeem geneeskunde

Voorbeeld van een lopend onderzoek aan het
Sino-Dutch Centre for Preventive and Personalized Medicine

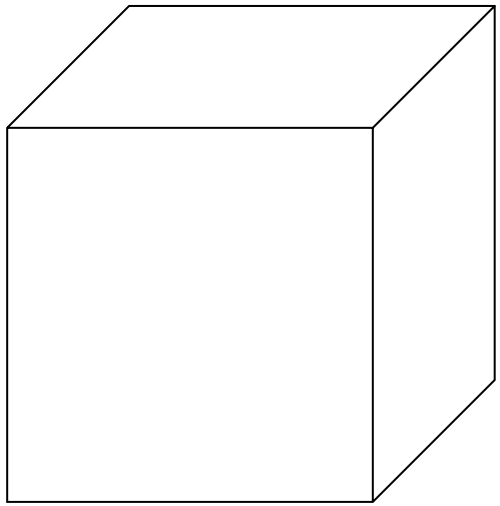
Leiden /Amsterdam Center for Drug Research

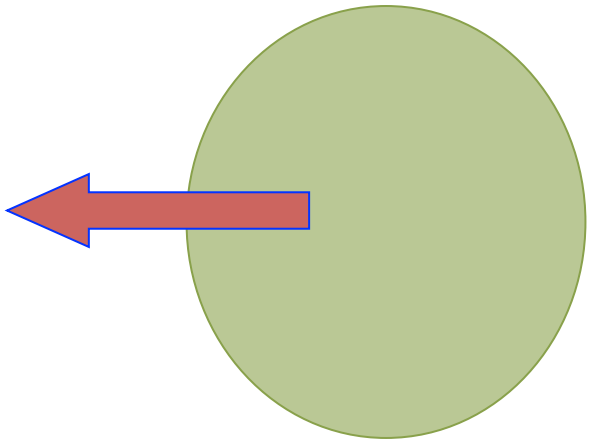
vrije Universiteit amsterdam

DALIAN INSTITUTE OF CHEMICAL PHYSICS, CAS

Netherlands Genomics Initiative

Wat is wetenschap?



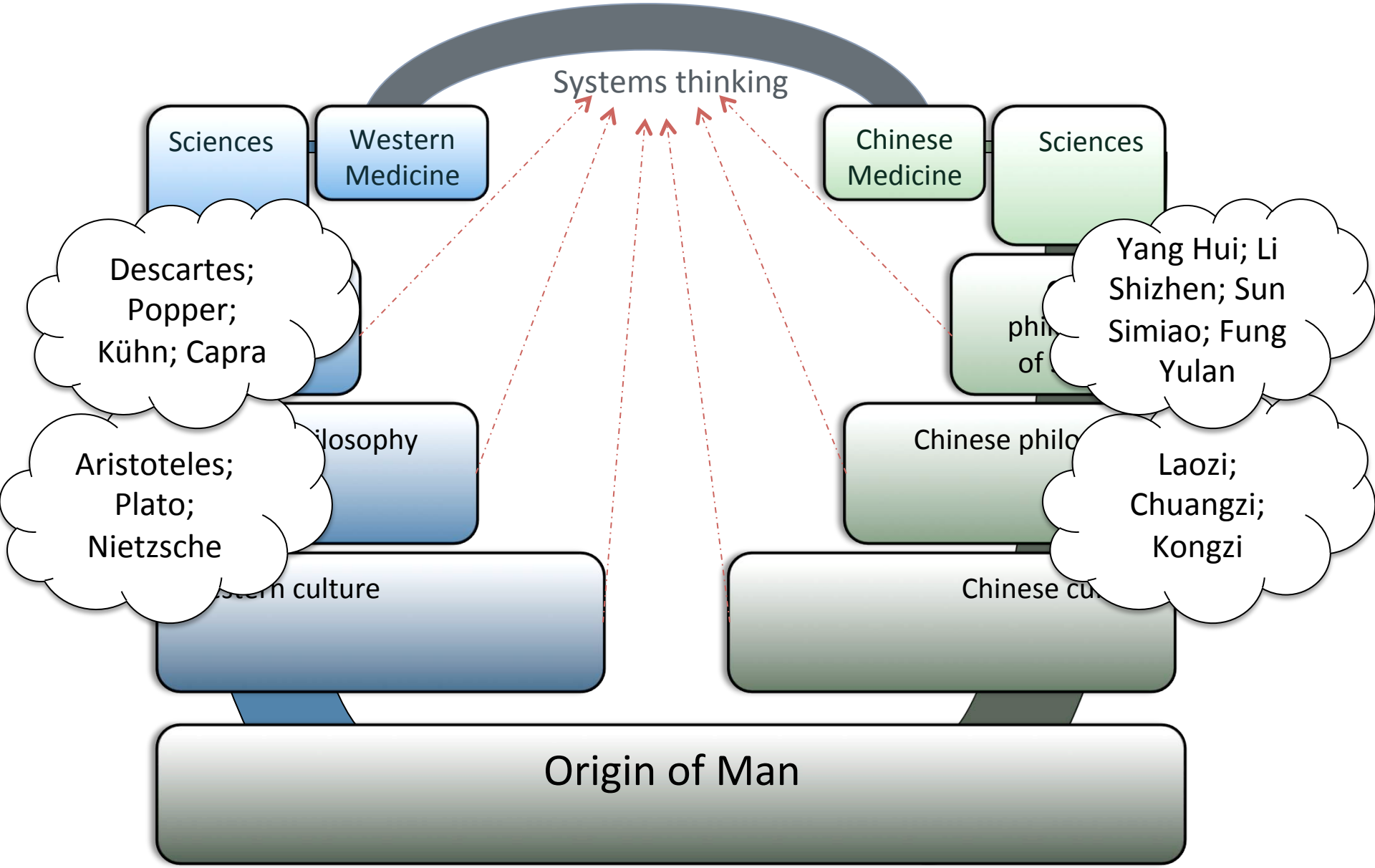


Western science explains, classic Chinese science describes

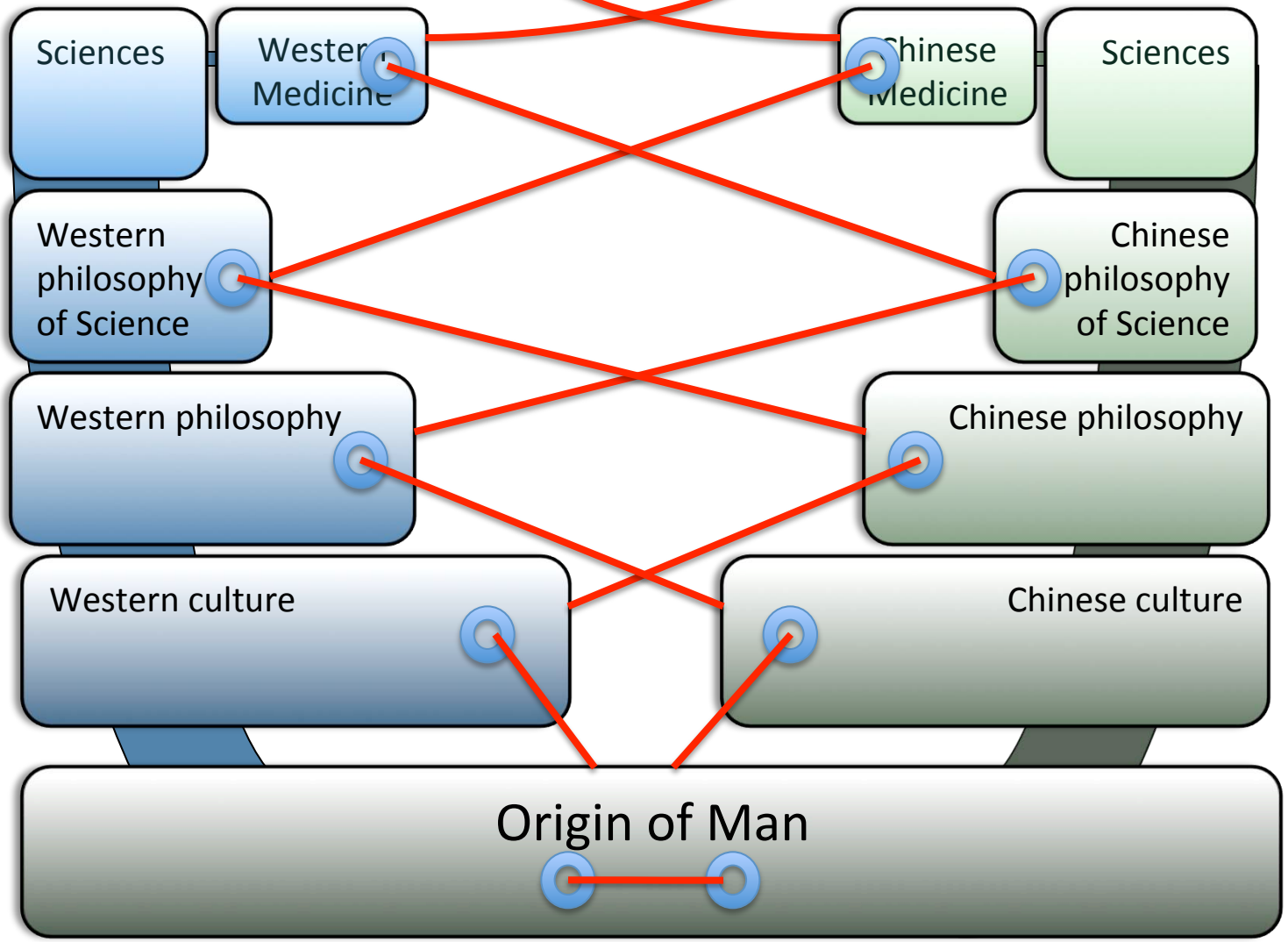
TCM thinking is concept thinking

“If the only tool you have is a hammer, you tend to treat everything as if it were a nail”

Abraham Maslow (1908-1970)


Systems thinking
Sciences
Western Medicine
Chinese Medicine
Sciences
Descartes; Popper; Kühn; Capra
Yang Hui; Li Shizhen; Sun Simiao; Fung Yulan
Aristoteles; Plato; Nietzsche
Laozi; Chuangzi; Kongzi
Origin of Man

New Medicine based on system biology



Waarom systeem theorie?

Systems theory

Systems theory is the interdisciplinary study of systems in general, with the goal of elucidating principles that can be applied to all types of systems at all nesting levels in all fields of research.*The term does not yet have a well-established, precise meaning, but systems theory can reasonably be considered a specialization of systems thinking, a generalization of systems science, a systems approach. The term originates from Bertalanffy's general system theory (GST) and is used in later efforts in other fields, such as the action theory of Talcott Parsons and the social systems theory of Niklas Luhmann.*

In this context the word *systems* is used to refer specifically to self-regulating systems, i.e. that are self-correcting through feedback. Self-regulating systems are found in nature, including the physiological systems of our body, in local and global ecosystems, and in climate—and in human learning processes.

Dynamic Systems Theory

In studying self-organizing systems a shift in focus occurs:

From objects to relationships

From quantity to quality

} Mapping of patterns of relationships

Symptoms

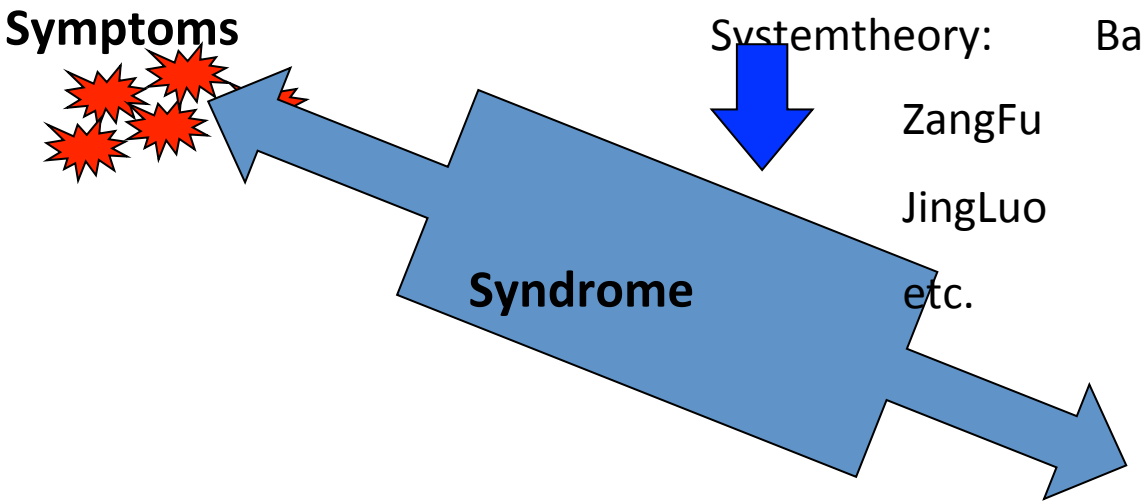
Symptoms

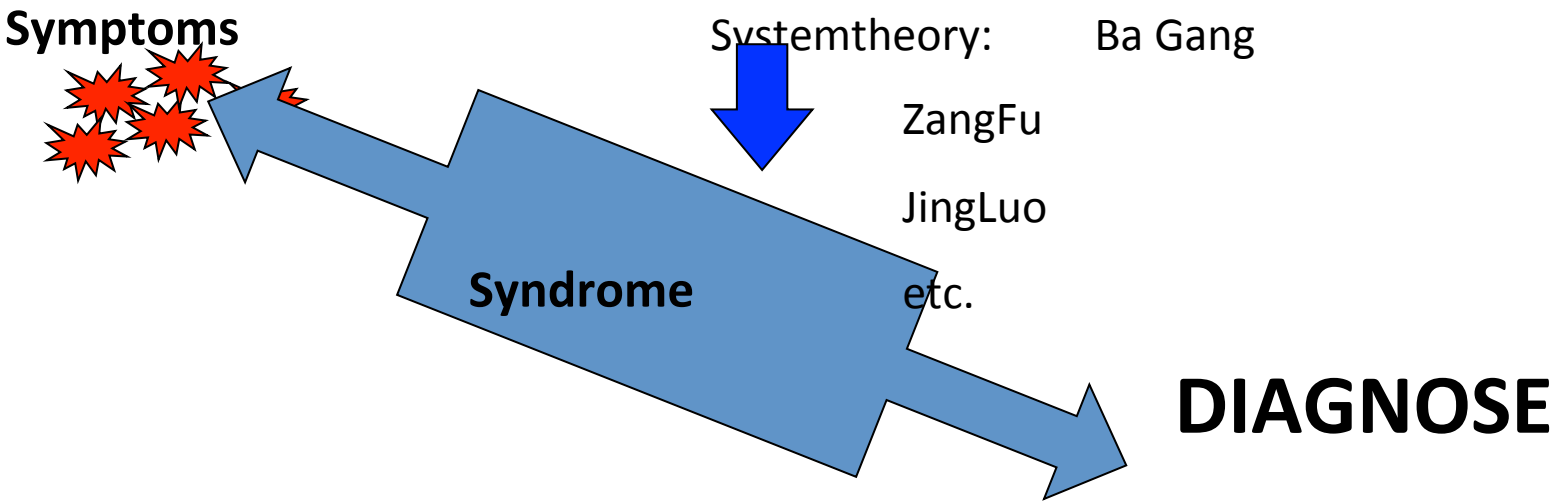
Systemtheory: Ba Gang

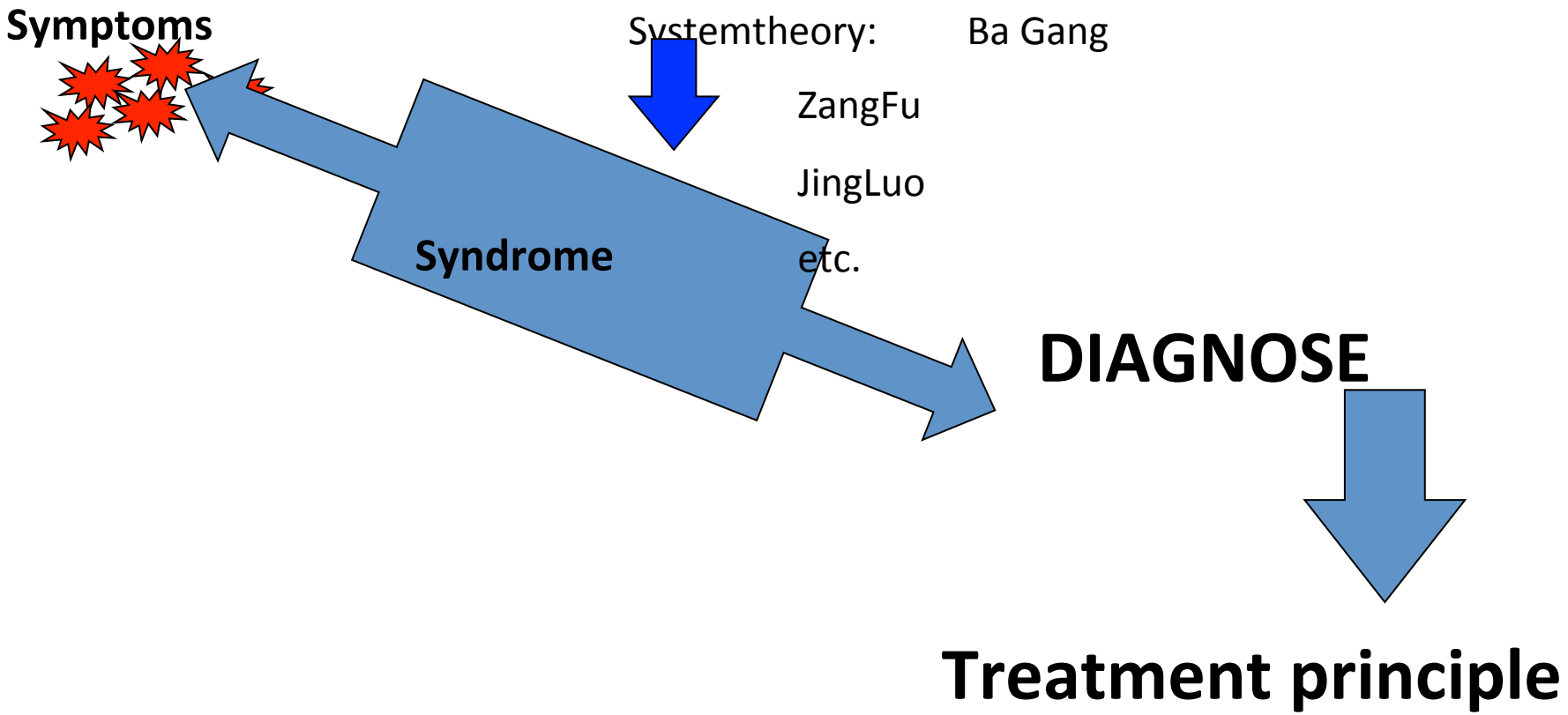
ZangFu

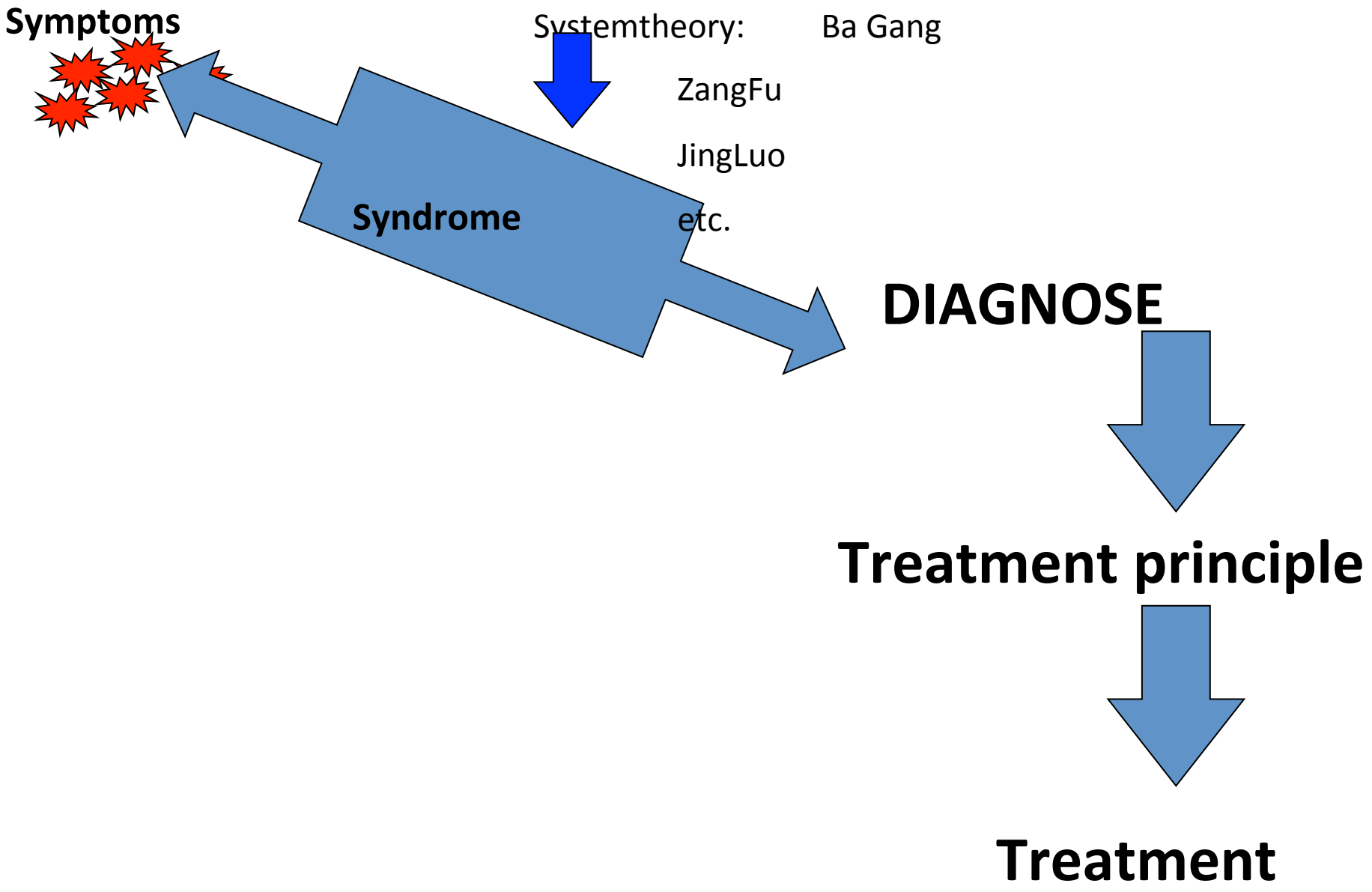
JingLuo

etc.


Symptoms
Systemtheory:
Ba Gang
ZangFu
JingLuo
etc.
Syndrome


Symptoms
Systemtheory:
Ba Gang
ZangFu
JingLuo
etc.
Syndrome
DIAGNOSE


Symptoms
Systemtheory:
Ba Gang
ZangFu
JingLuo
etc.
Syndrome
DIAGNOSE
Treatment principle


Symptoms
Systemtheory:
Ba Gang
ZangFu
JingLuo
etc.
Syndrome
DIAGNOSE
Treatment principle
Treatment

Historical survey of disciplines of Systems Science

* Hungarian biologist **Ludwig von Bertalanffy**: General Systems theory (1945-1955)
* **Norbert Wiener** (1947): Cybernatics, selfregulating systems and feedback
* **Henry M. Paynter** (1961): theory of Bond Grafen, mathematical description of dynamic systems in engineering
* **Benoit Mandelbrot** (1970): chaostheory and fractal mathematics
* **David Ruelle and Floris Takens** (1971): strange attractor, the foundation for chaos theory
* **T.Y. Li and J. Yorke** (1975) introduce the term “chaos” to describe nonlinear systems
* **Ilya Prigogine** (1977): Nobelprice for selforganisation
* **Peter Chechkland** (1981): software development based on hierarchic relations between systems
* **P.M. Senge** (1990) basic system forms as part of a learnig organisation

All kinds of systems thinking:

- Nonlinear dynamics
- Chaos theory
- Dynamic, self-organizing systems
- Fractals

As the 20th century was the century of the revolution of physics, the 21st century will be the century of the revolution of life science

For medicine it will mean a shift from primarely curative to primarely preventive and from general treatments to personalized medicine

Prof. Dr. Jan van der Greef
Leiden University

John N. Warfield

professor Emeritus,
George Mason University, USA

basis for stopping some of the bad practices in systems science community

- Underscoping the Systems Domain
- Unimaginative Workspaces
- Mismatched Media
- Linguistic Pollution
- Premature Quantification
- Insensitivity to Discovered Behavioral Pathologies
- Inadequacy of Comparisons of Alternatives
- Blindness to History
- Monotonous Bifurcation

Source: John N. Warfield; an introduction to systems science (2006)

Blindness to History

Some people thought about systems long ago. There seems to be a strongly entrenched belief that systems thinking originated in the last half of the twentieth century. Virtually every important concept that backs up the key ideas emergent in systems literature are found in ancient literature and in the centuries to follow. It is time to recognize the contributions of these elder scholars and factor them into systems science where their presence is absolutely essential to a mature science.

Source: John N. Warfield; an introduction to systems science (2006)

Data
Information
Knowledge
Wisdom

The Binocular Dilemma

“1 manifests itself in 3”

Yi Jing

3 = Qi

3

1

2

Qi

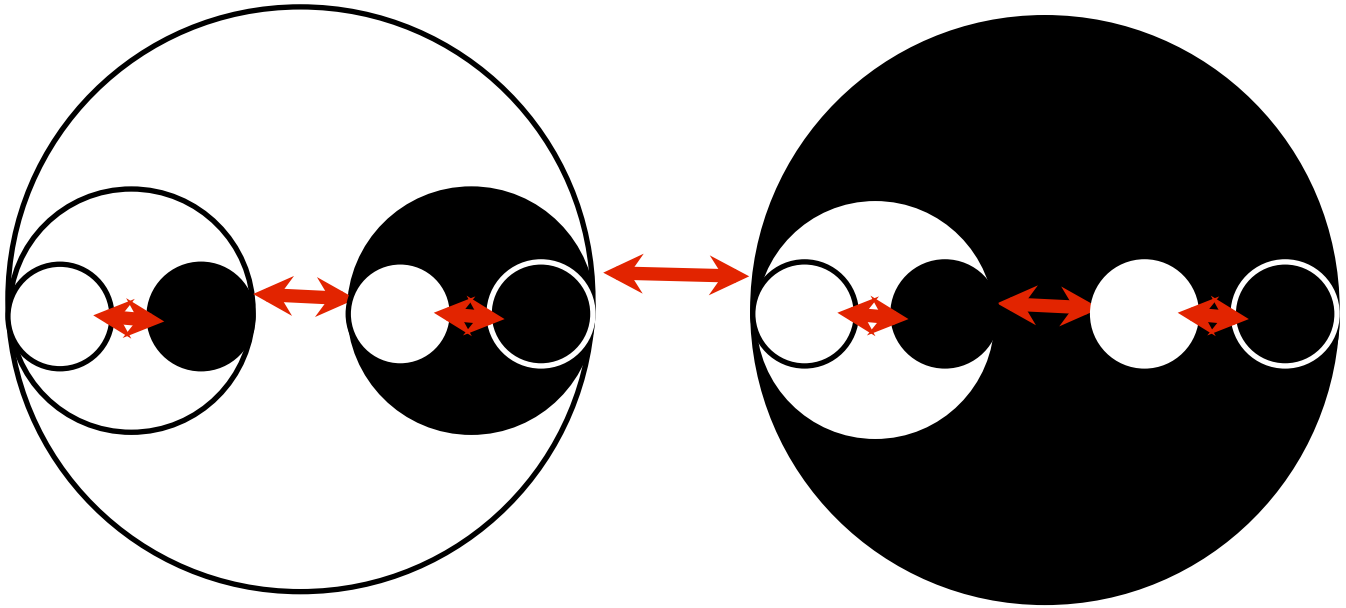
Energy

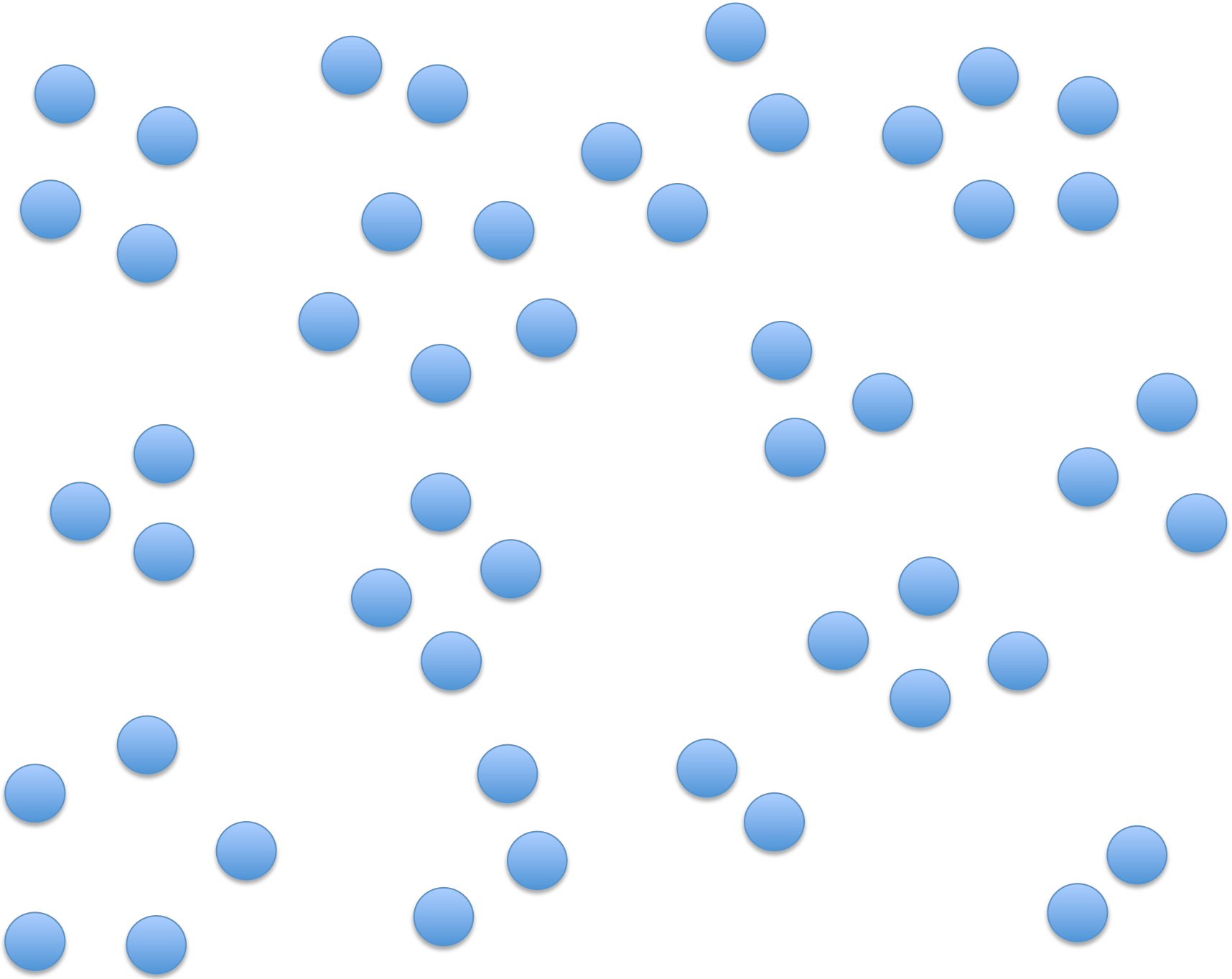
- Connection
- Communication/ Information
- Movement

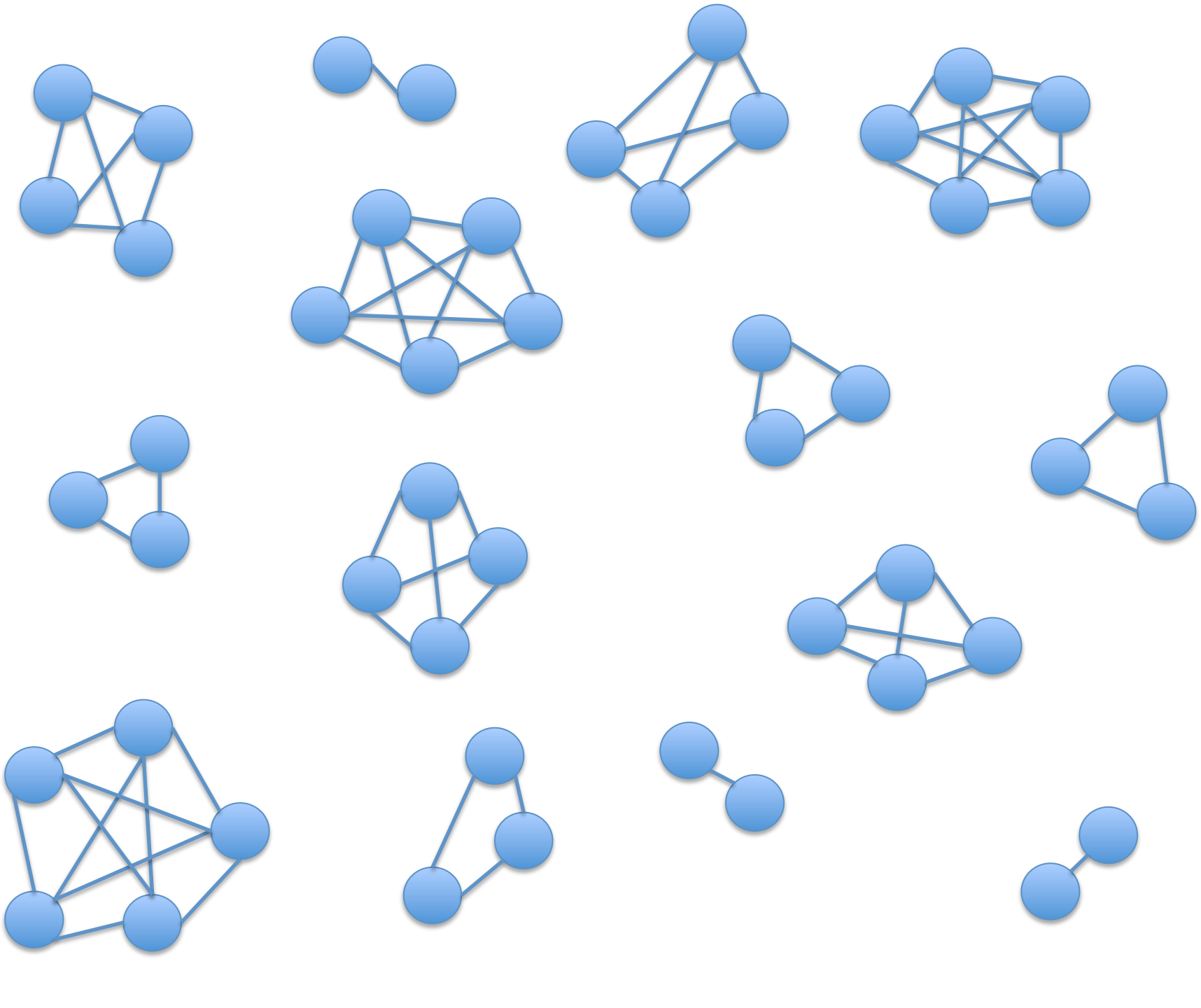
Life

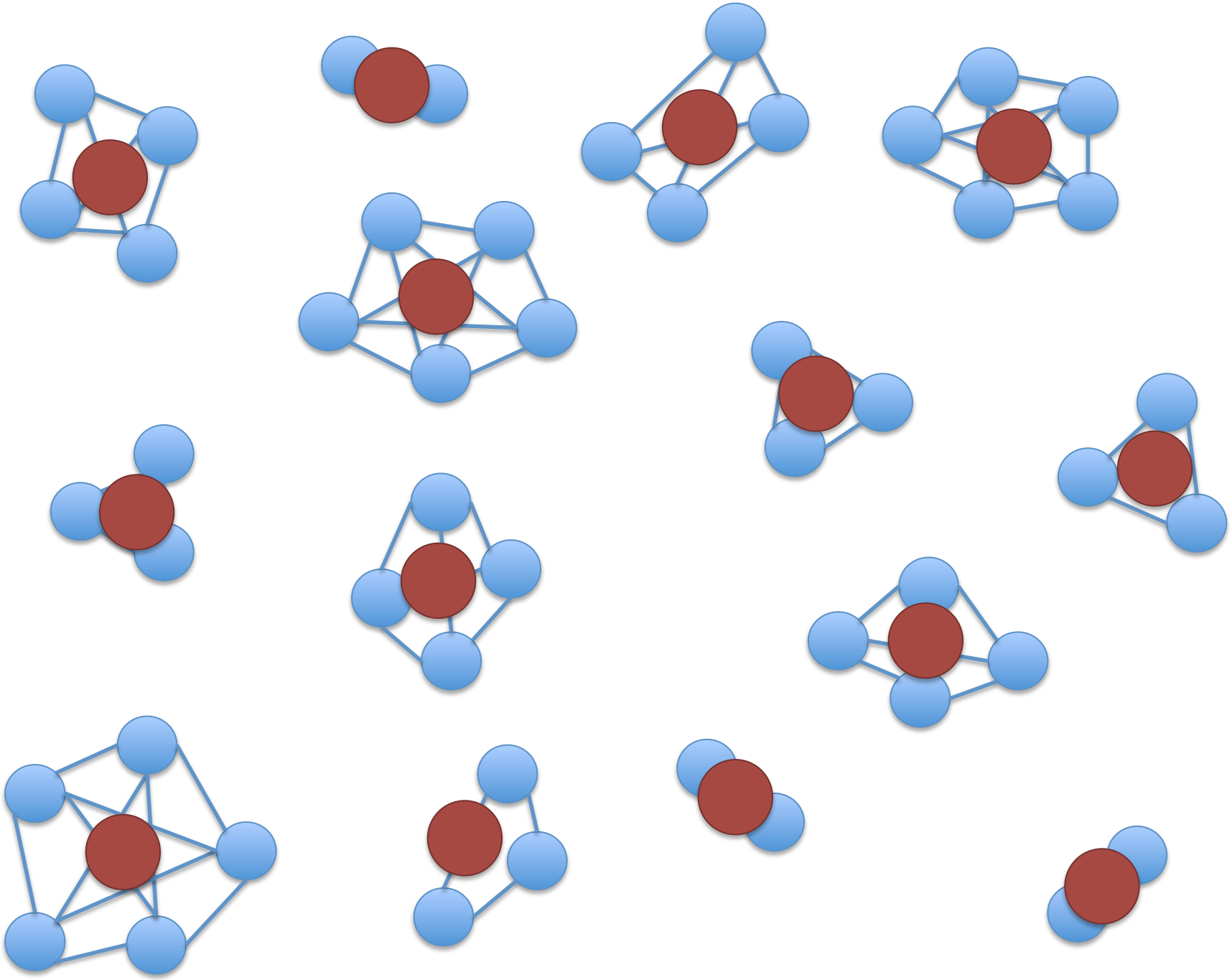
Matter

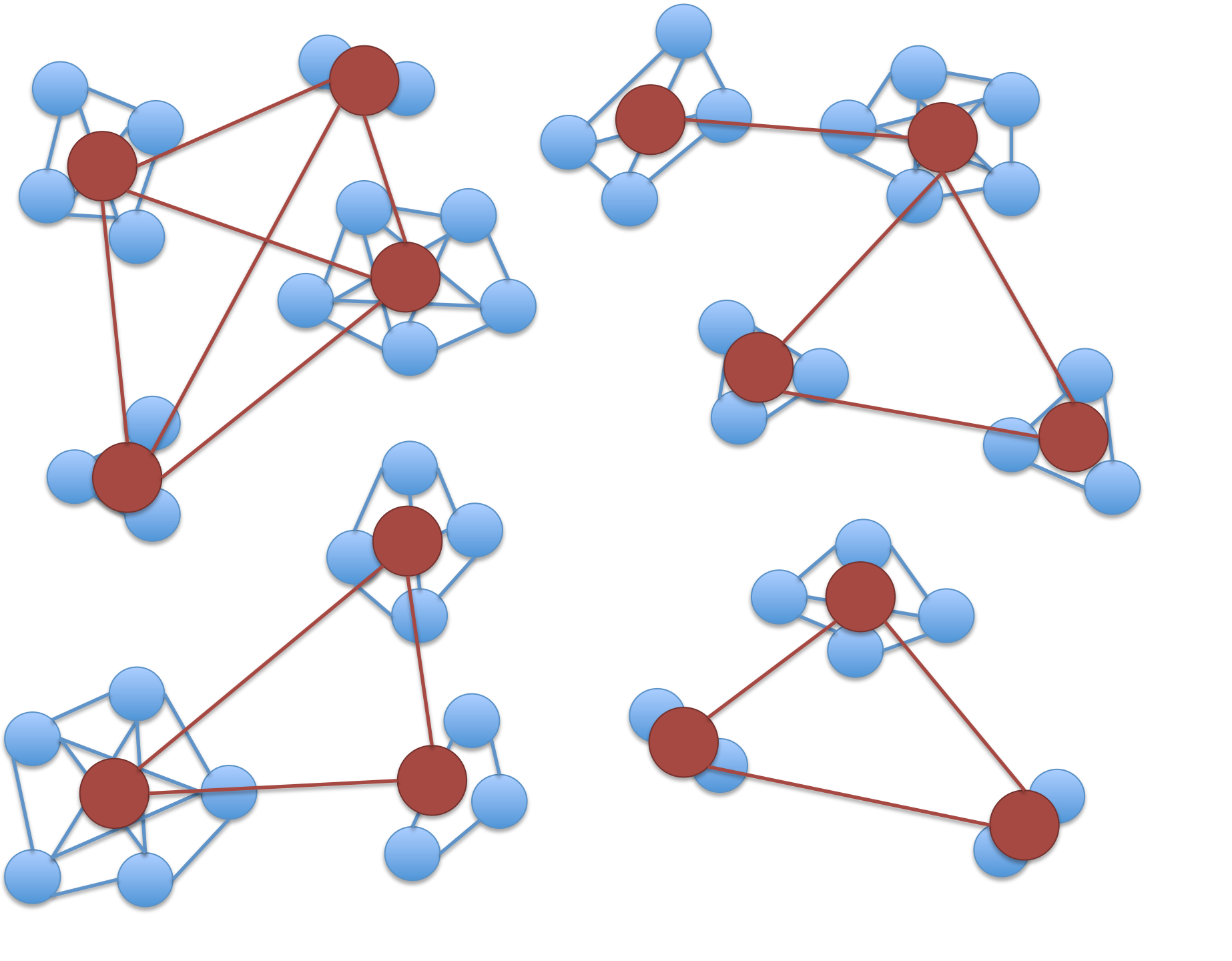
Energy storage under energy flow

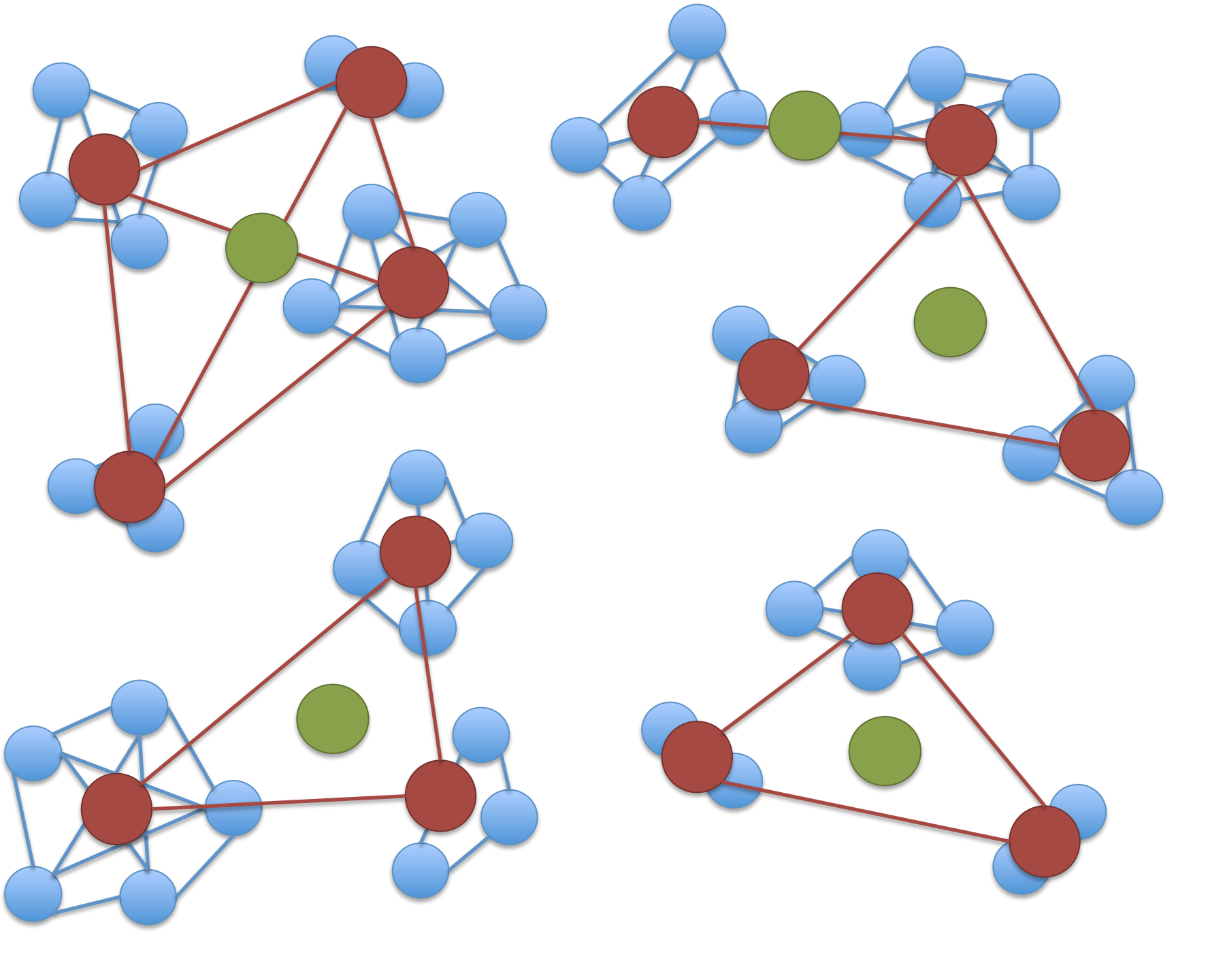


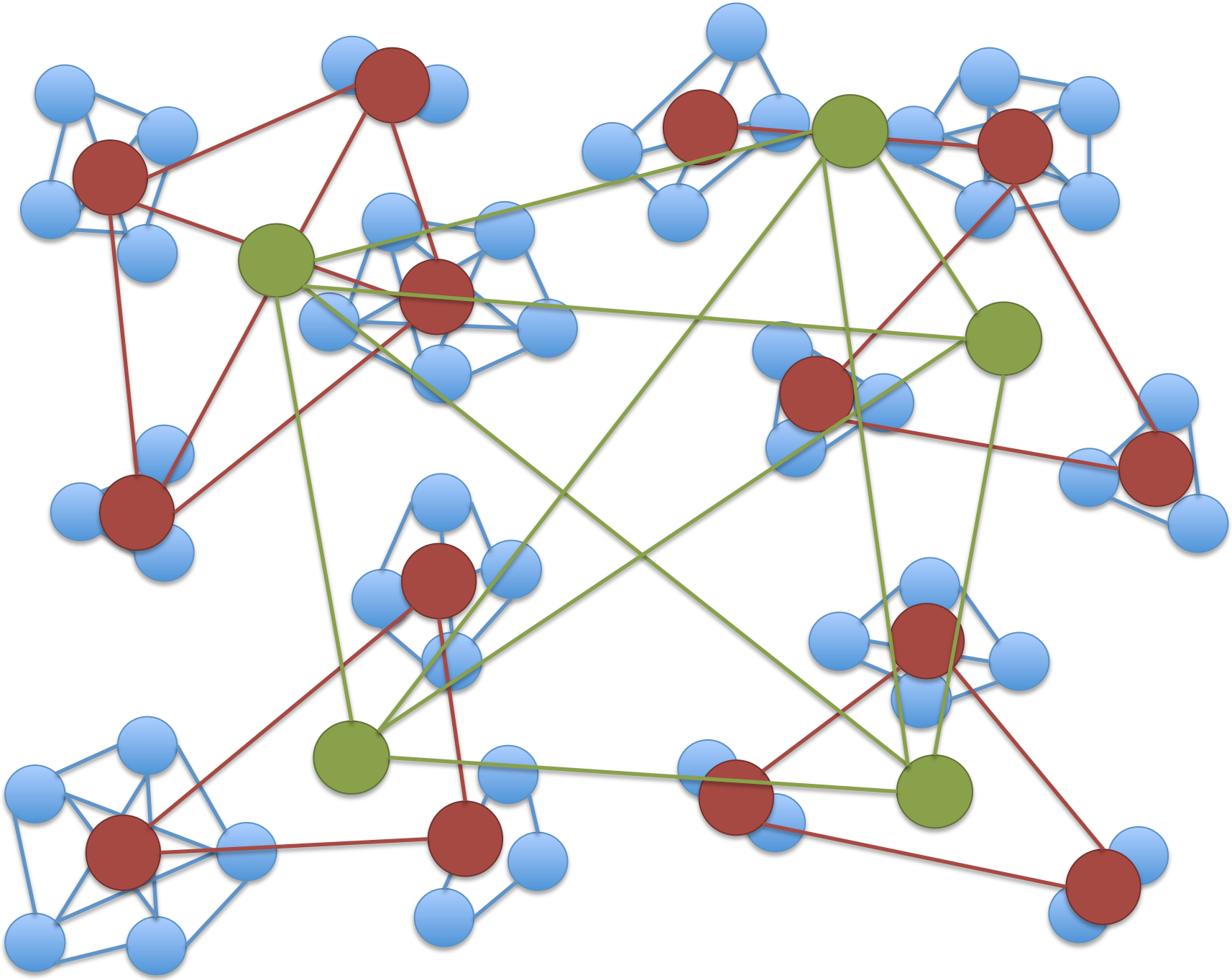


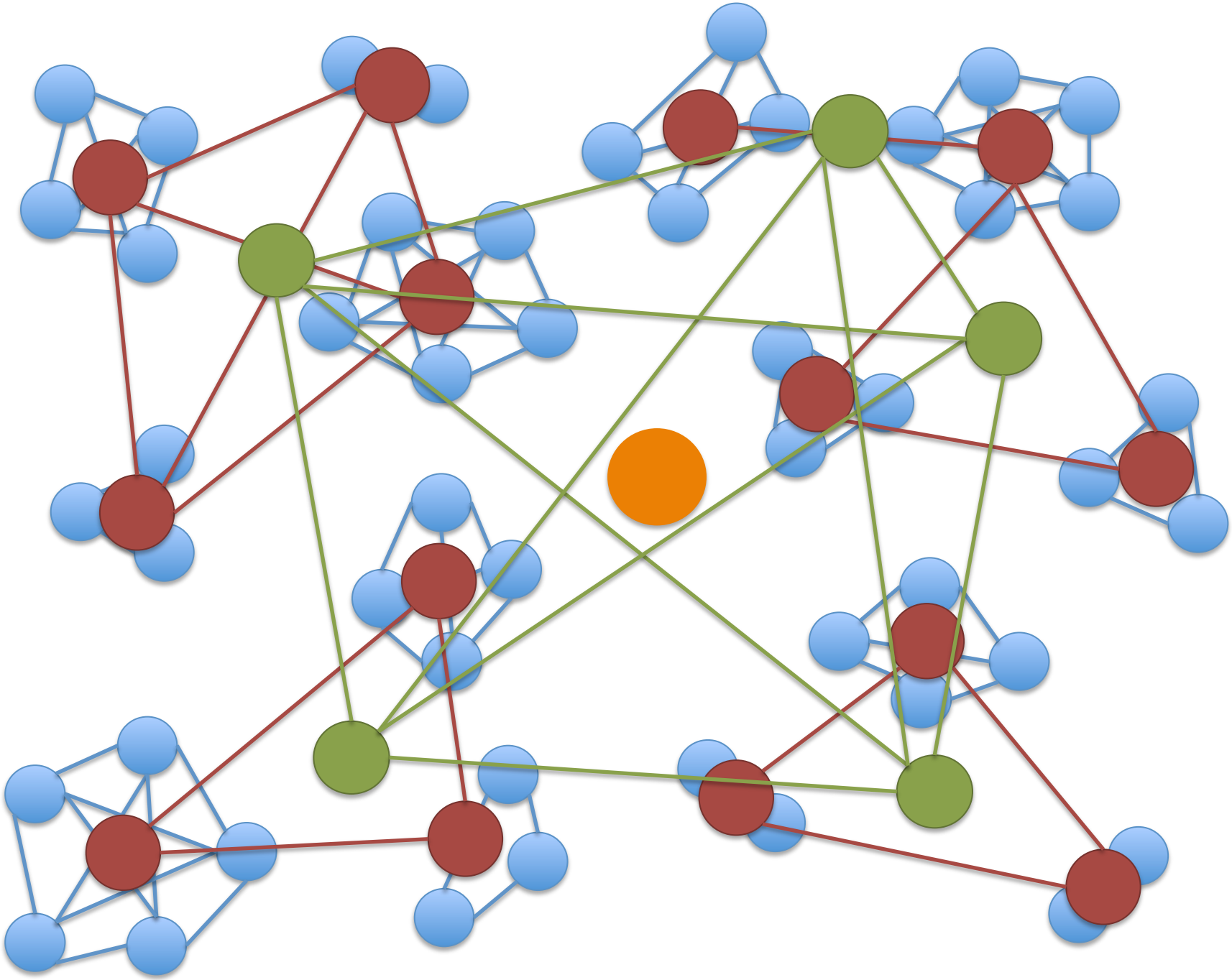


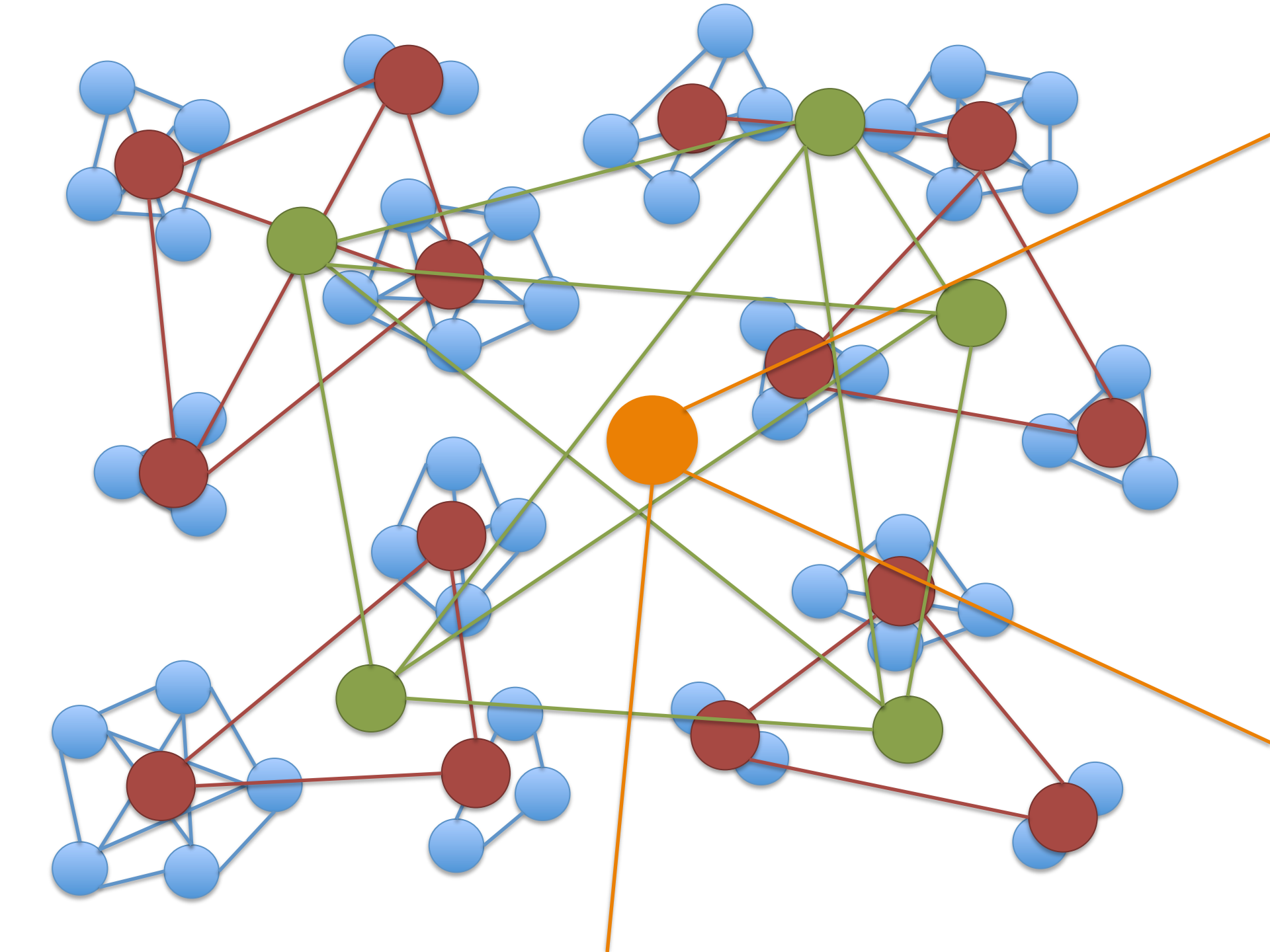


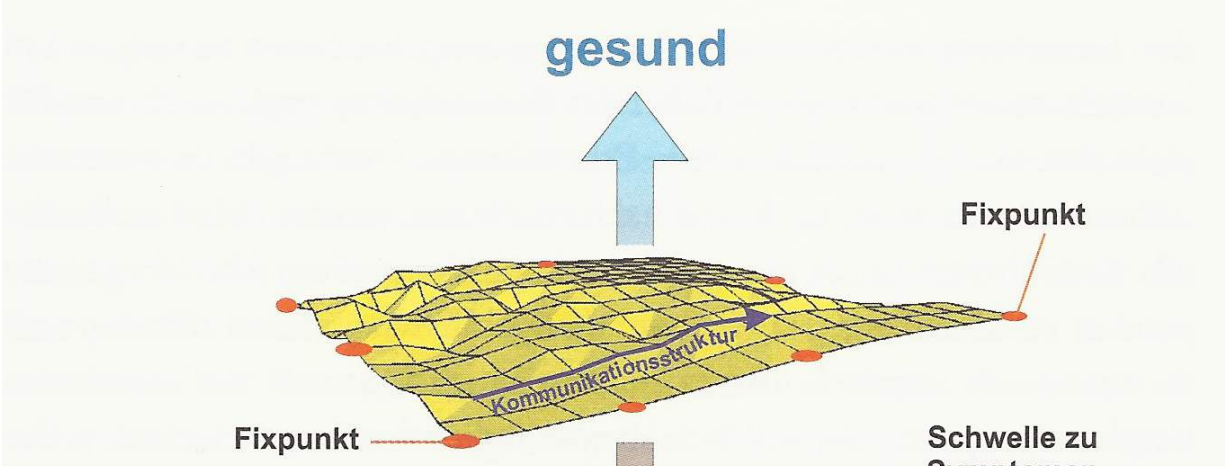




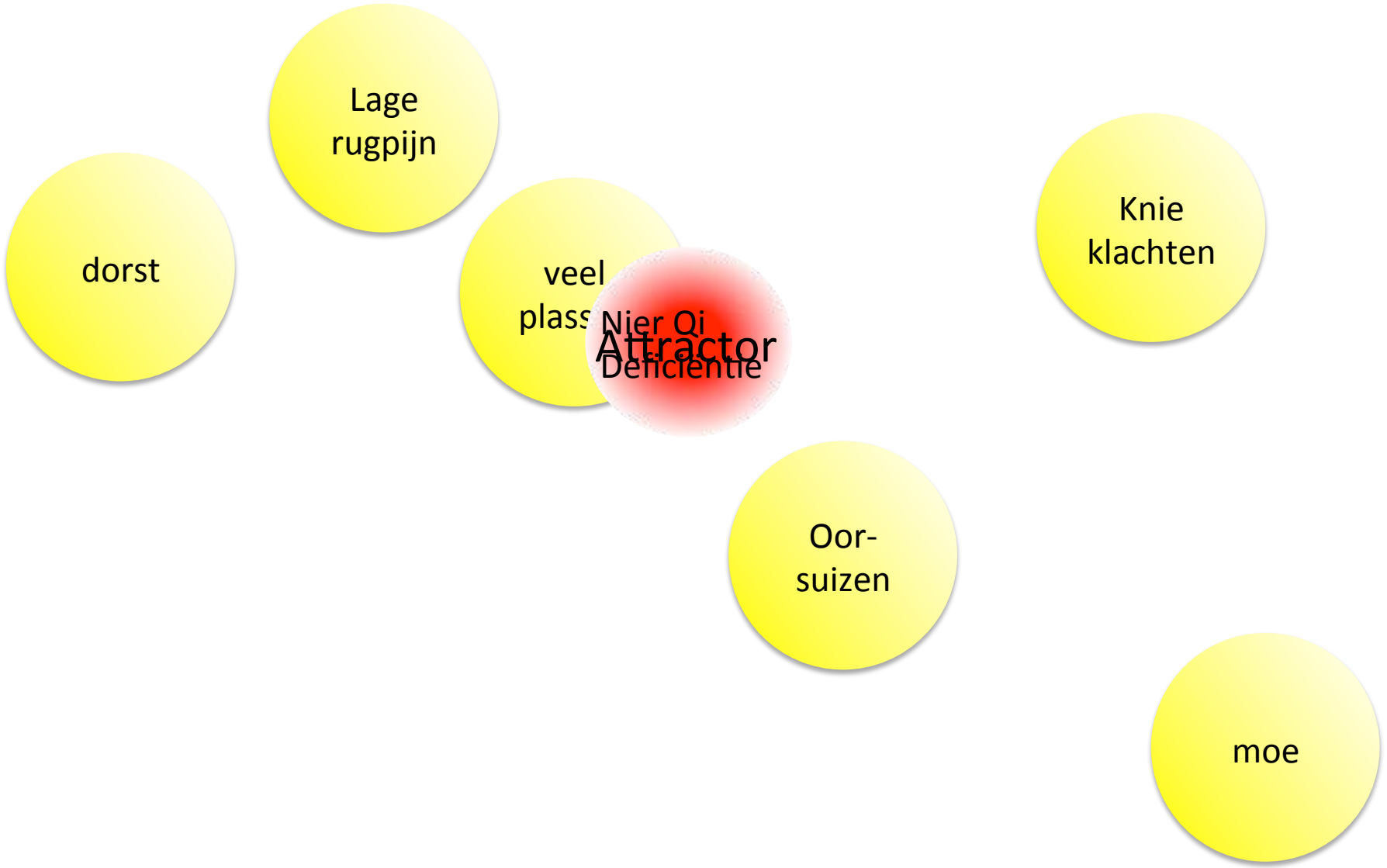


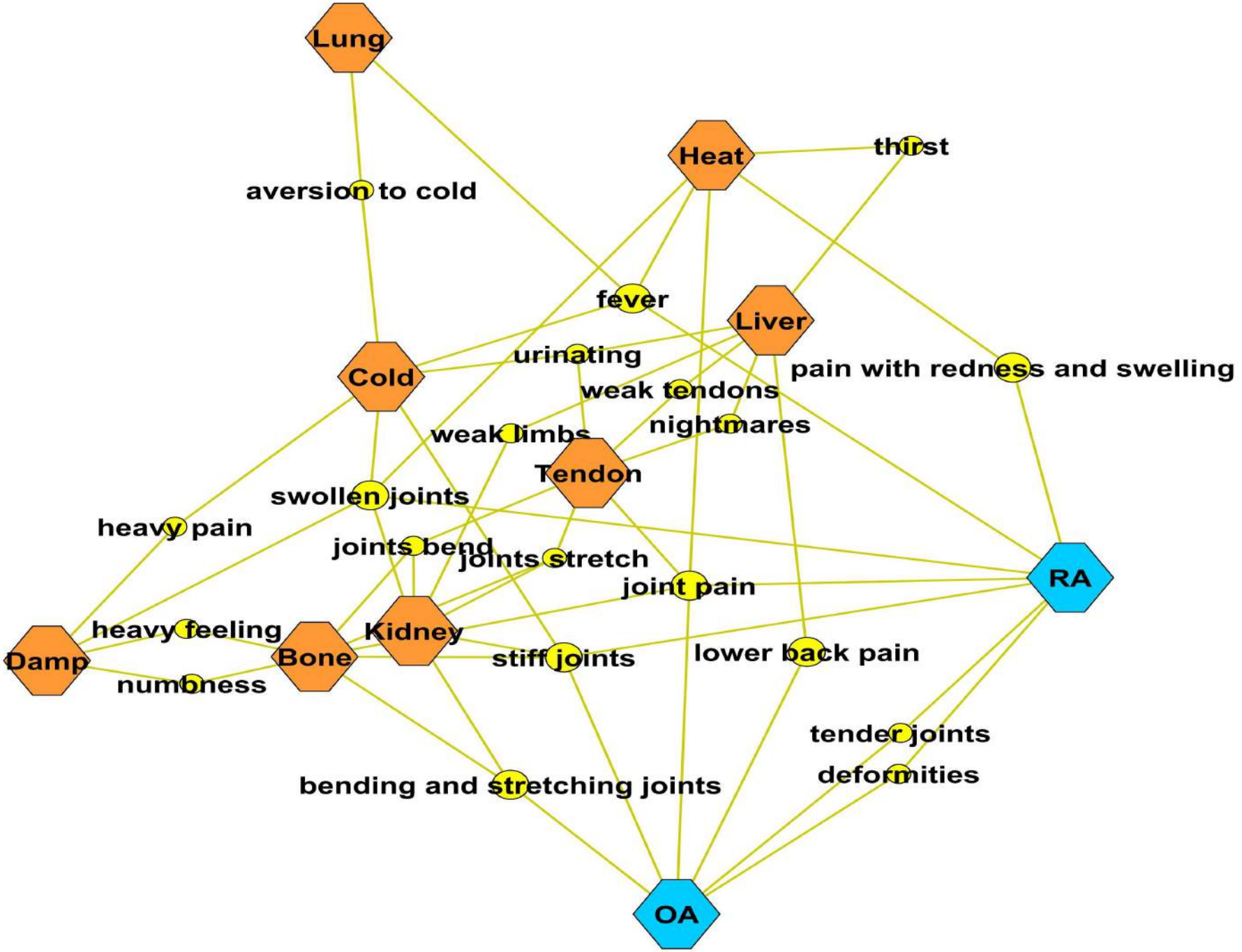


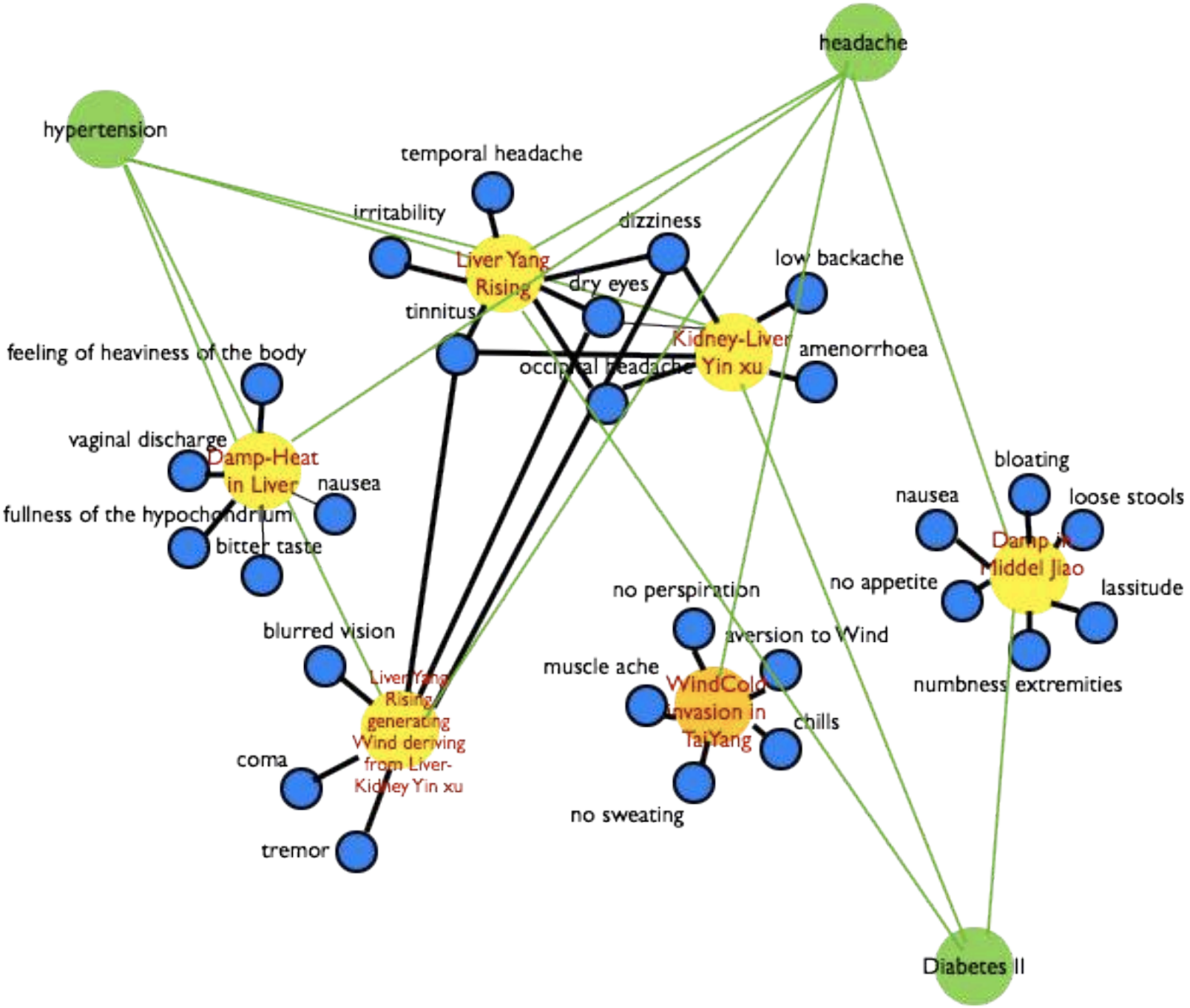


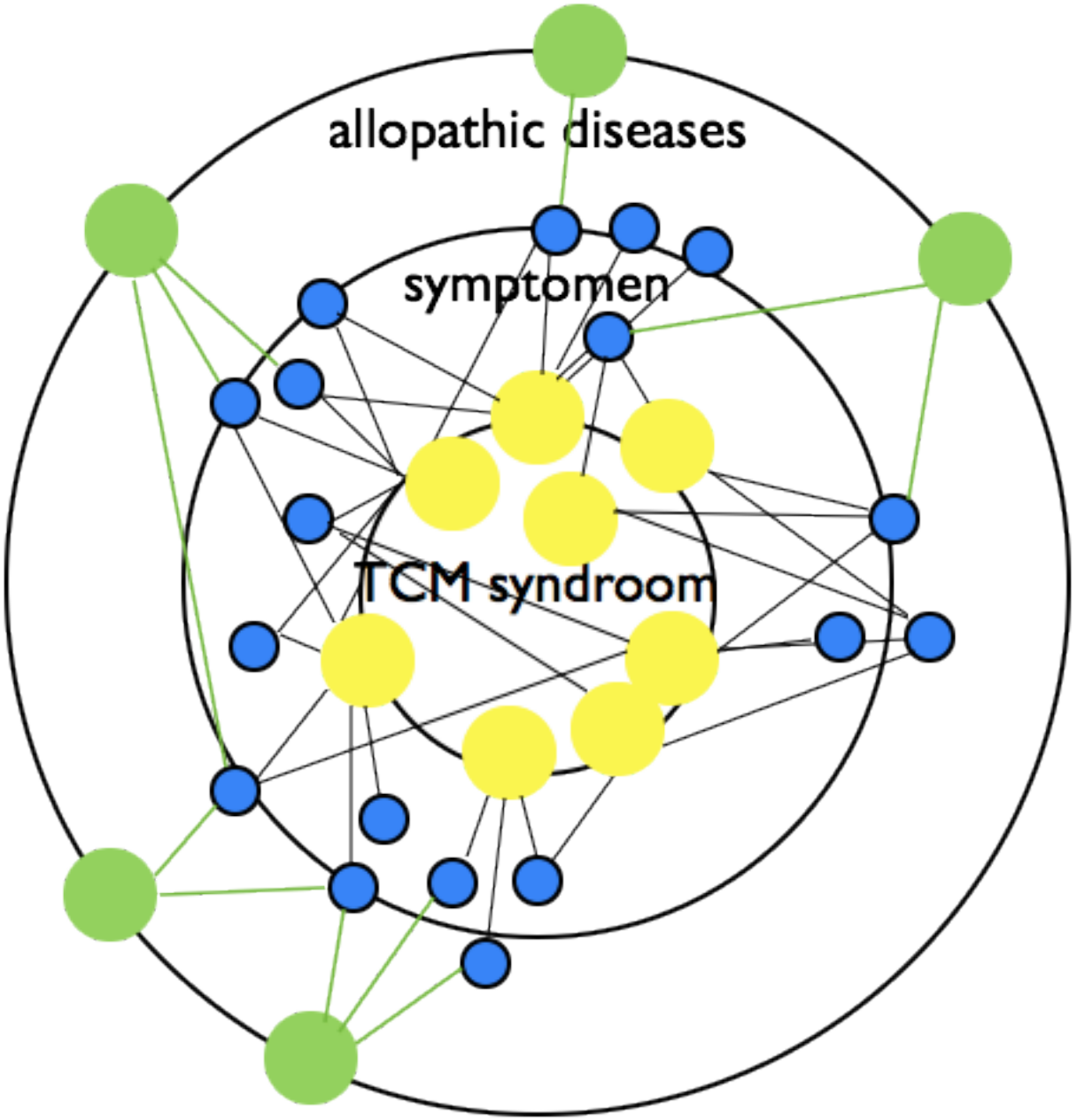


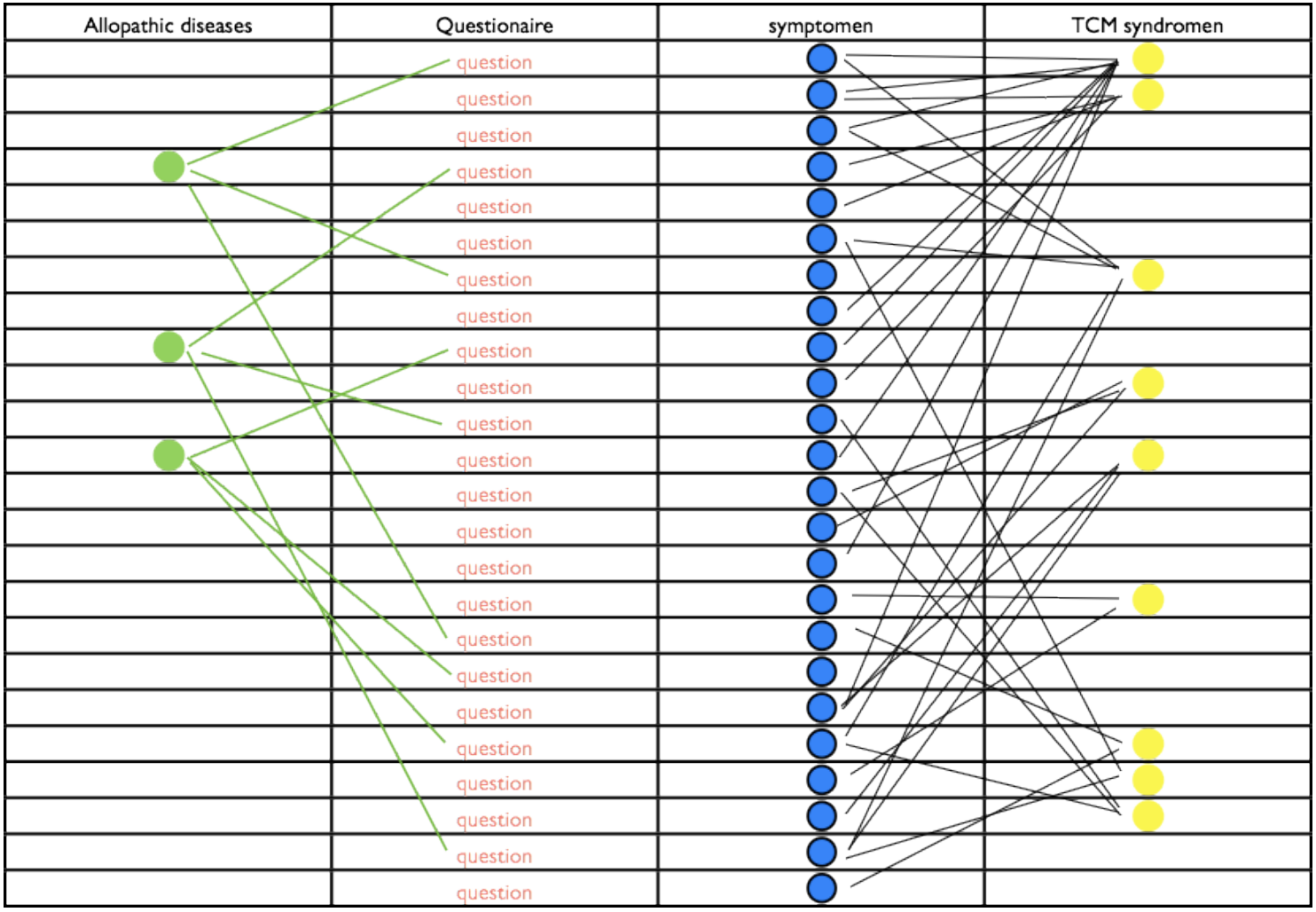
Vernetztes Denken in der biomedizinischen Forschung,
Rainer H. Straub; 2013


Lage rugpijn
dorst
veel plass
Nier Qi Deficientie
Attractor
Knie klachten
Oor-suizen
moe


Lung
Heat
thirst
aversion to cold
fever
Liver
Cold
urinating
pain with redness and swelling
weak tendons
nightmares
weak limbs
Tendon
swollen joints
heavy pain
joints bend
joints stretch
joint pain
RA
heavy feeling
Kidney
Damp
Bone
stiff joints
lower back pain
numbness
tender joints
deformities
bending and stretching joints
OA


headache
hypertension
temporal headache
irritability
dizziness
Liver Yang Rising
low backache
dry eyes
tinnitus
Kidney-Liver Yin xu
amenorrhoea
occipital headache
feeling of heaviness of the body
vaginal discharge
Damp-Heat in Liver
nausea
fullness of the hypochondrium
bitter taste
bloating
nausea
loose stools
Damp in Middel Jiao
no appetite
lassitude
numbness extremities
no perspiration
aversion to Wind
muscle ache
WindCold Invasion in TaiYang
chills
no sweating
blurred vision
Liver Yang Rising generating Wind deriving from Liver-Kidney Yin xu
coma
tremor
Diabetes II


allopathic diseases
symptomen
TCM syndroom


Allopathic diseases
Questionaire
symptomen
TCM syndromen
question
question
question
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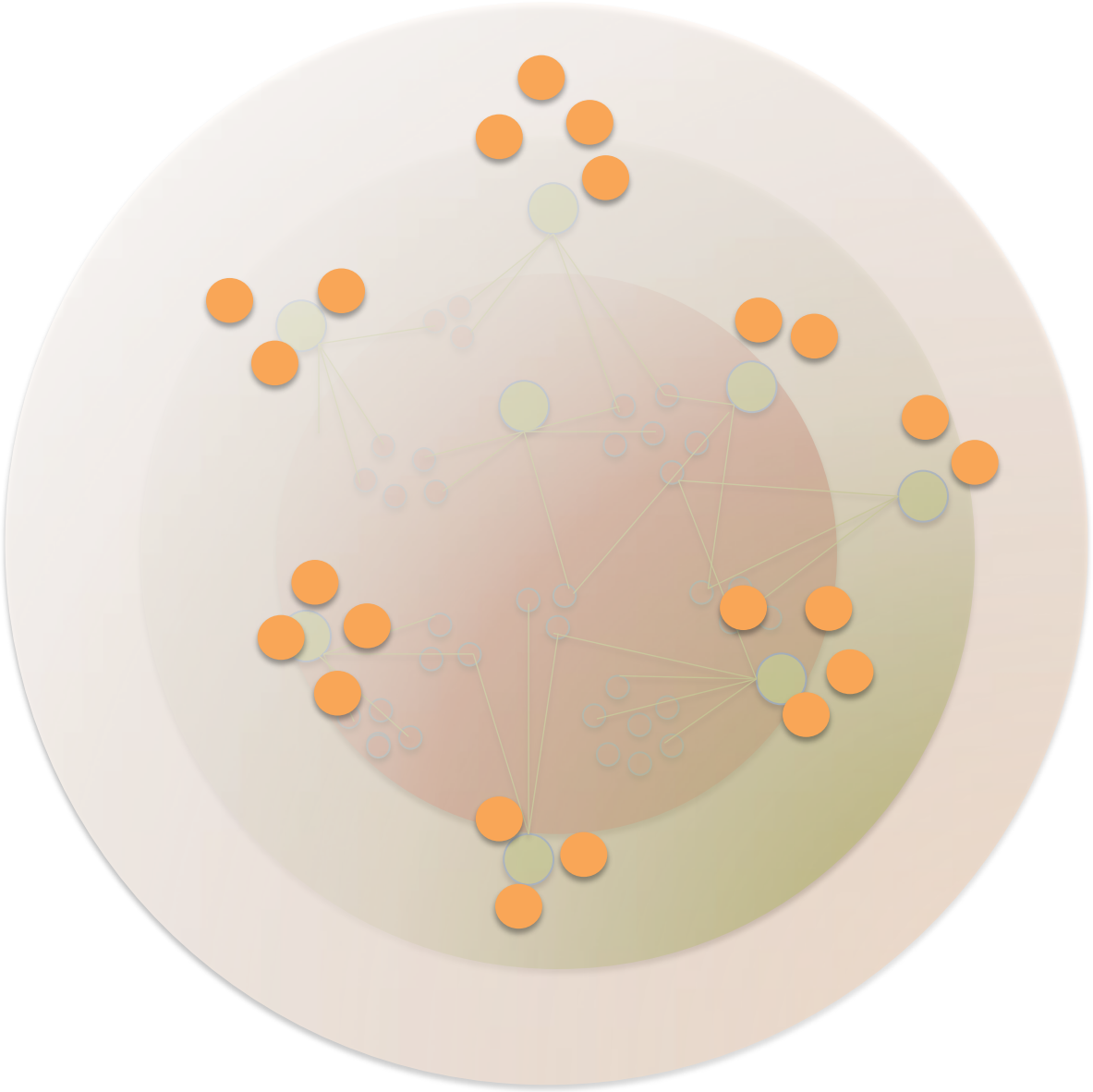
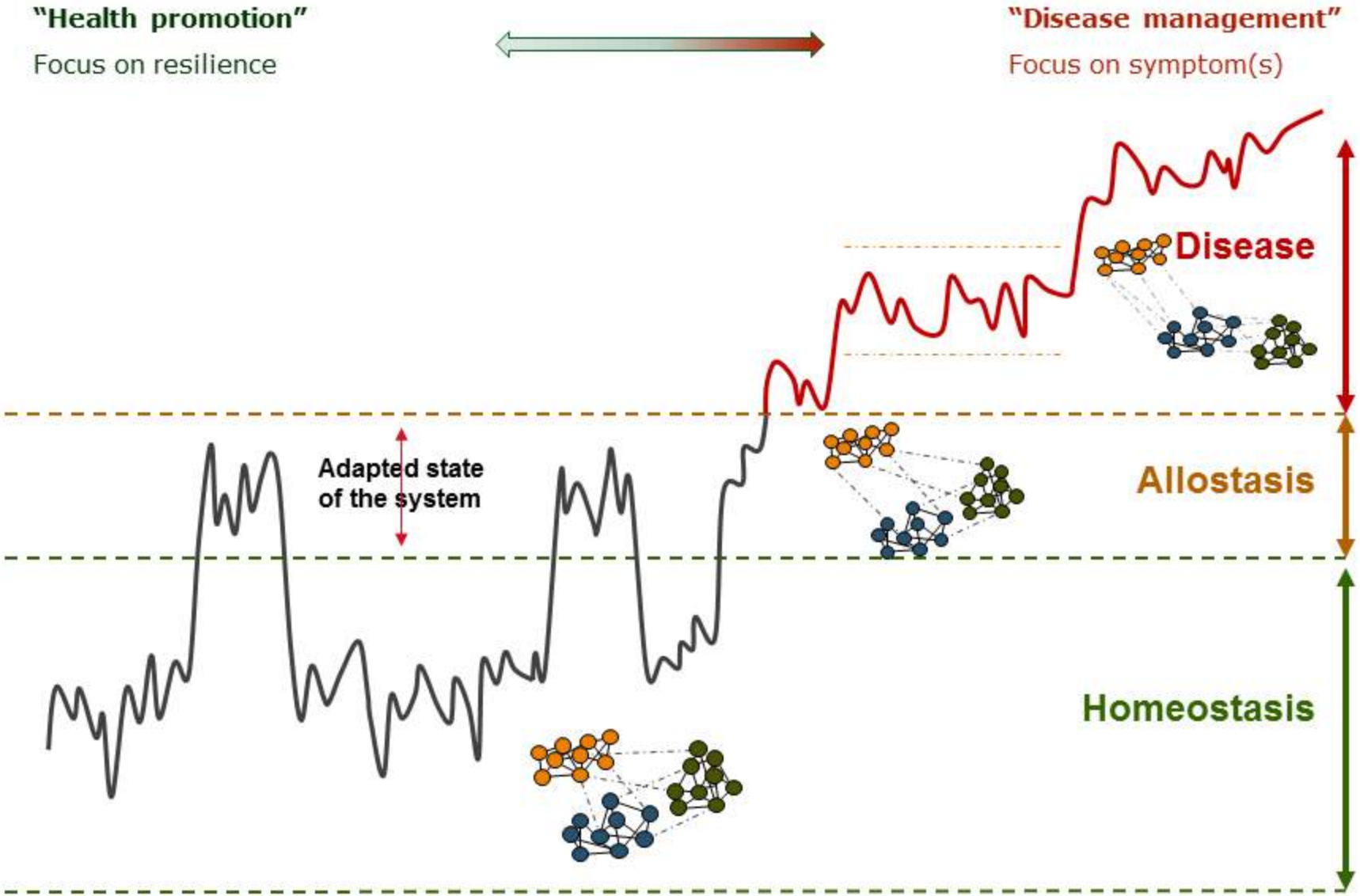
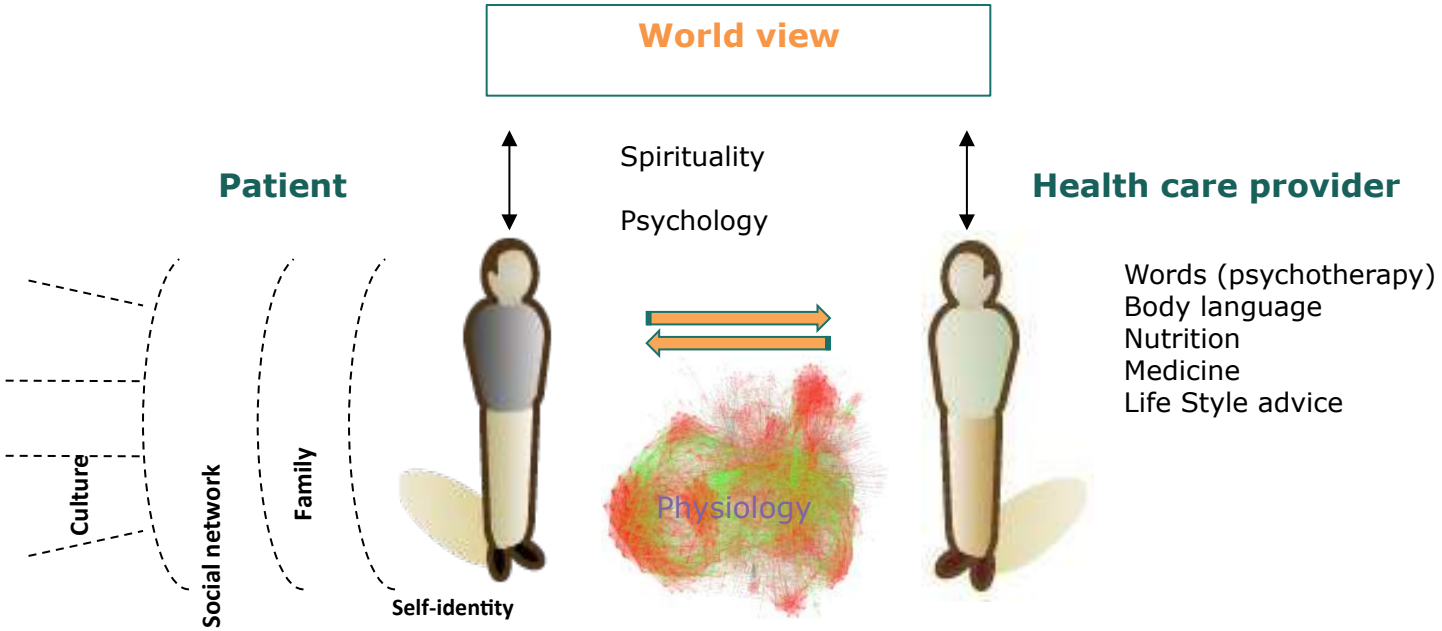



"Health promotion"
Focus on resilience
"Disease management"
Focus on symptom(s)
Disease
Allostasis
Homeostasis
Adapted state
of the system

Wat is gezondheid?

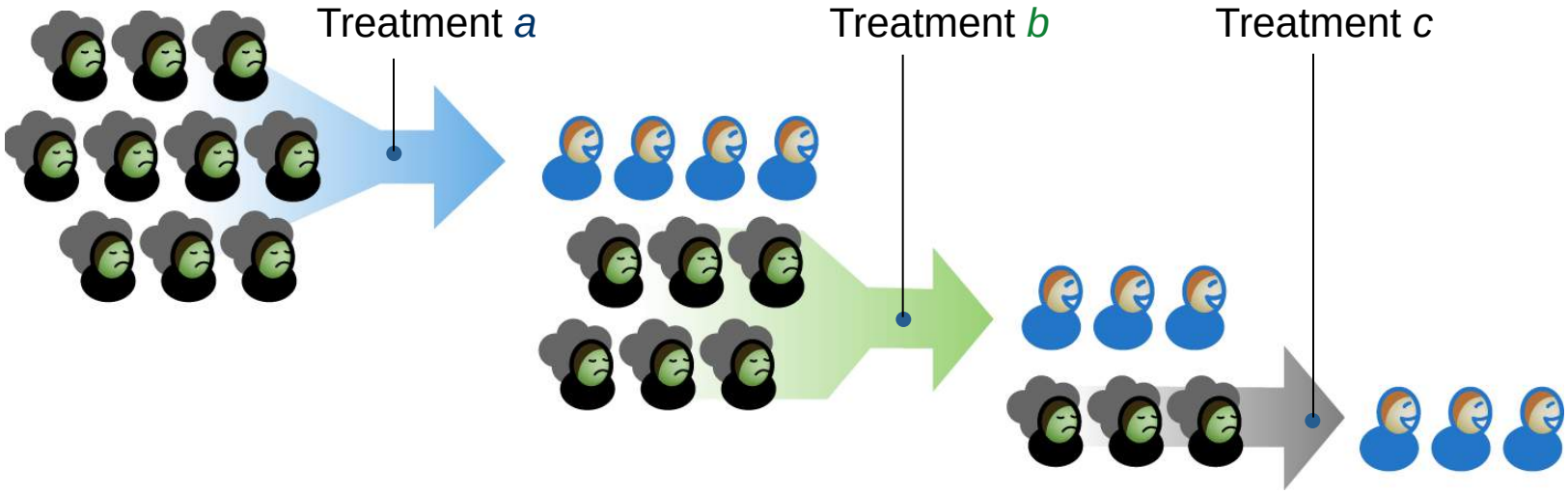
Gezondheid is een dynamische toestand waarbij een systeem een optimale openheid heeft zonder zijn identiteit te verliezen en er een maximale uitwisseling van informatie plaatsvindt tussen het systeem en zijn omgeving


World view
Patient
Spirituality
Psychology
Health care provider
Words (psychotherapy)
Body language
Nutrition
Medicine
Life Style advice
Culture
Social network
Family
Self-identity
Physiology

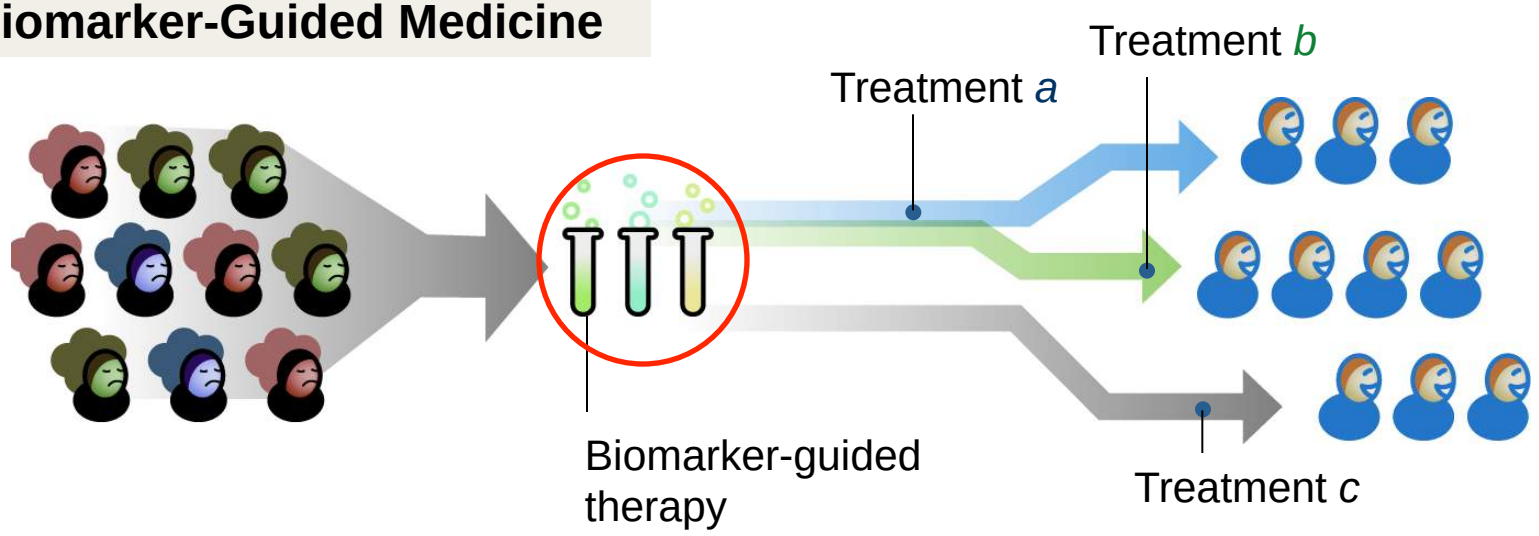
Treating the right patients with the right medicine

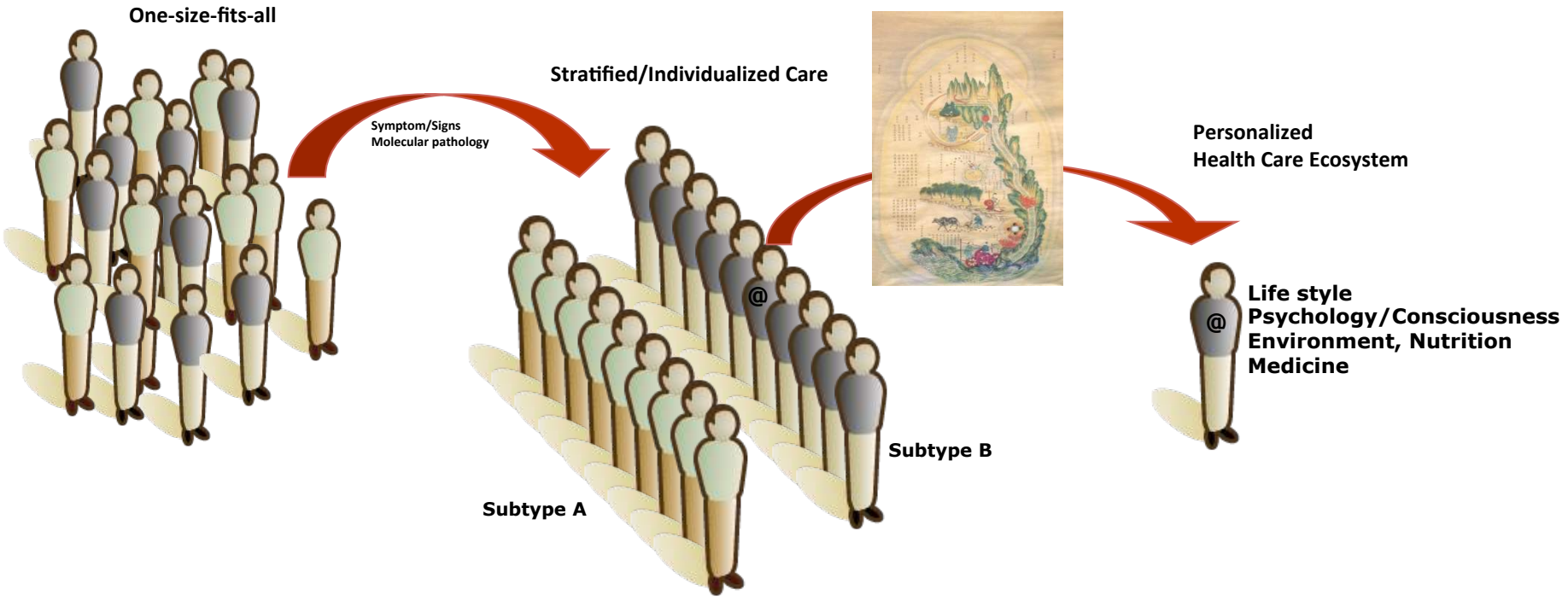
Approach : Current drugs + improved diagnosis

Empirical Medicine



Biomarker-Guided Medicine





Disease - symptom management
1 disease -1 target – 1 (block buster) drug

Targeted care – disease phenotype focus
theranostics related to efficacy and adverse effects

Patient Wellness focus
Integrated systems approach

The ongoing sub-typing of MSX/ Diabetes2 project

- System Biology based development of diagnostic biomarkers for Diabetes type 2

Sino-Dutch Centre for Preventive and Personalized Medicine

A China Dutch joint project of the Sino-Dutch center for Personalized and Preventive Medicine

Koko Wei
PhD student Sino-Dutch Centre, TNO

Leiden /Amsterdam Center for Drug Research

vrije Universiteit amsterdam

DALIAN INSTITUTE OF CHEMICAL PHYSICS,CAS

Netherlands Genomics Initiative

Diabetes Mellitus

diabetes mellitus

Grieks: **diabètès** = door stromen
Latijn: **mellitus** = honingzoet

Chinees: **Xiao Ke** = wasting thirsting

Xiao Ke – etiology & pathogenesis

- **Improper diet:** excessive consumption of greasy, sweet, rich food and alcohol can hinder the function of the Spleen and Stomach. Impaired digestive function leads to food stagnation, which generates heat. Because heat is drying, it injures the Yin and fluid and symptoms of wasting become apparent.

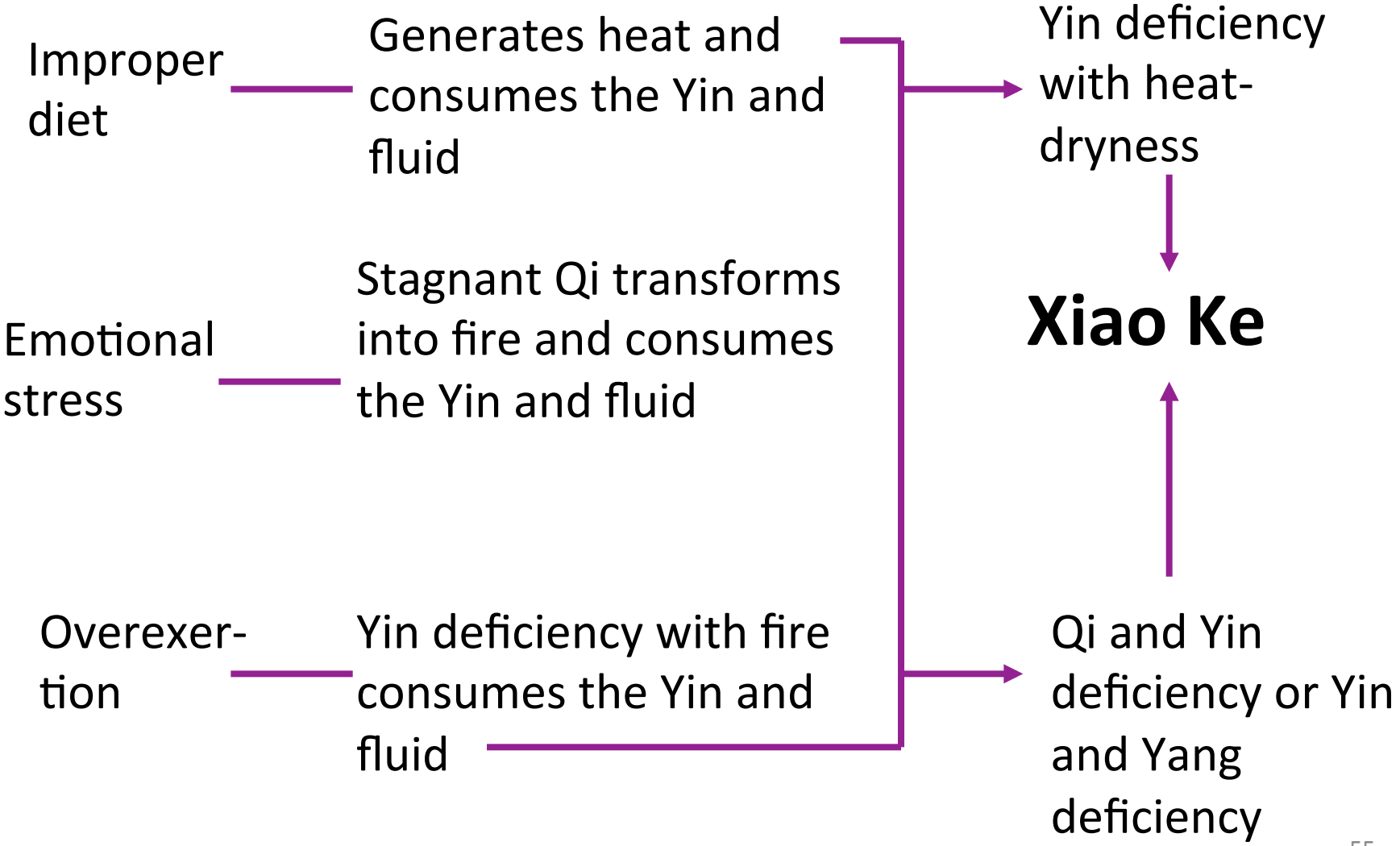
Xiao Ke – etiology & pathogenesis

- **Emotional stress:** caused by longstanding emotional upset may disturb the flow of Qi. Stagnant Qi transforming into fire consumes the Yin and fluid of the Lung and Stomach, inducing wasting and thirsting disorder.

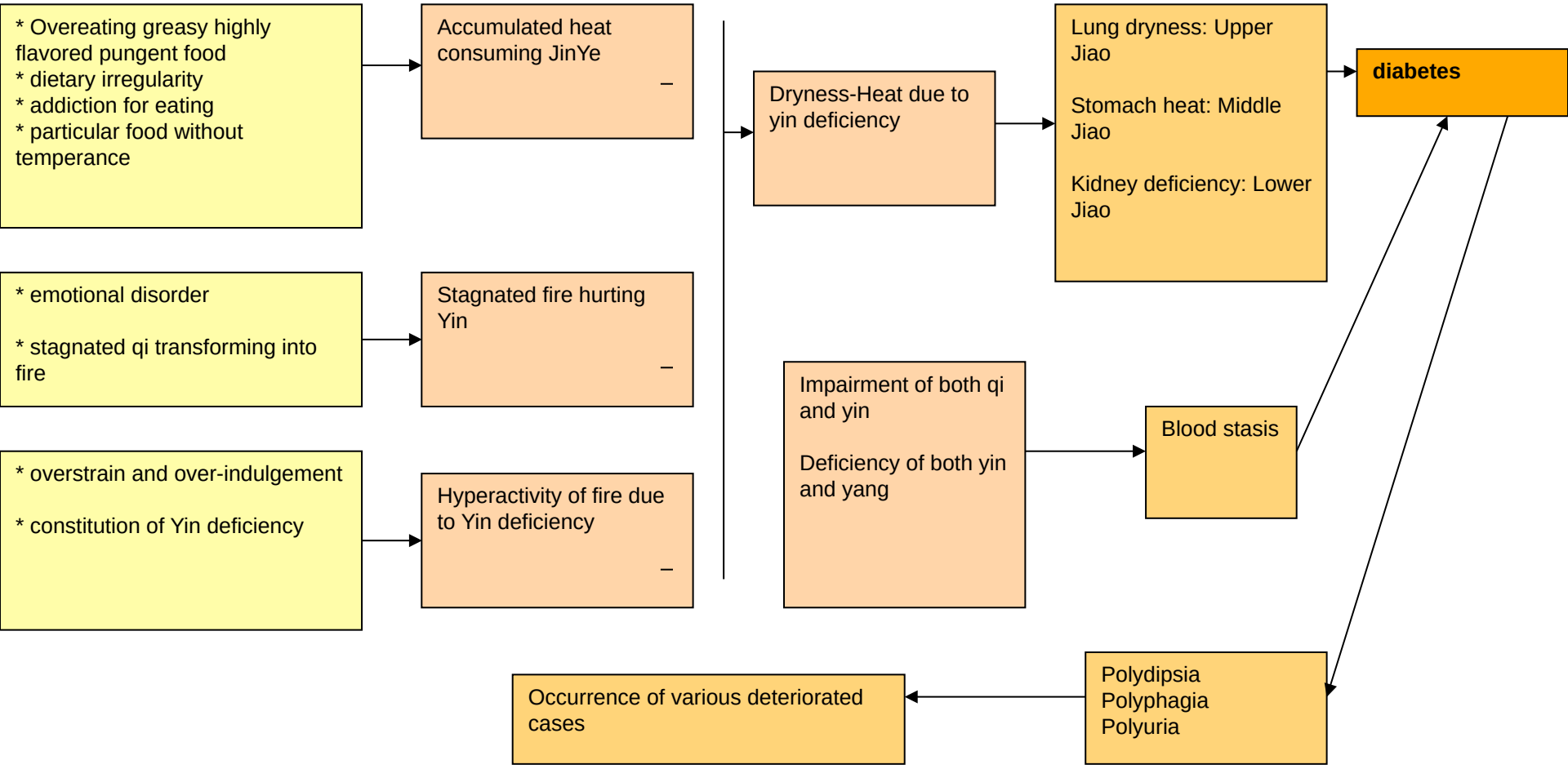
Xiao Ke – etiology & pathogenesis

- **Overexertion:** Yin and Jing can be exhausted when a Yin deficient constitution is further depleted by excessive sexual activity. Yin deficiency with fire flaring upwards will consume Lung and Stomach Yin and fluid. Kidney, Lung and Stomach Yin becomes deficient and cause wasting and thirsting disorder.

Xiao Ke – etiology & pathogenesis



Schematic diagram of etiological factors and morbid mechanism of diabetes



Source:
Zhong Yi Nei Ke (Traditional Chinese Internal Medicine); Long Zhixian; 2000 Academy Press
Practical therapeutics of traditional Chinese medicine; Yan Wu & Warren Fischer; 1997 Paradigm Publications

Xiao Ke

The Classic Diagnosis

Xiao Ke – classic diagnosis

- **Identification of organ involvement:**

  - if intense thirst (polydipsia) and frequent drinking are the primary symptoms, Lung involvement is certain: Upper Jiao

  - if excessive food intake (polyphagia) is the primary symptom, the Stomach is the main organ affected: Middle Jiao

  - if the dominant symptom is excessive urination (polyuria), it indicates that Kidney Yin is deficient: Lower Jiao

Xiao Ke – classic diagnosis
Basic patterns

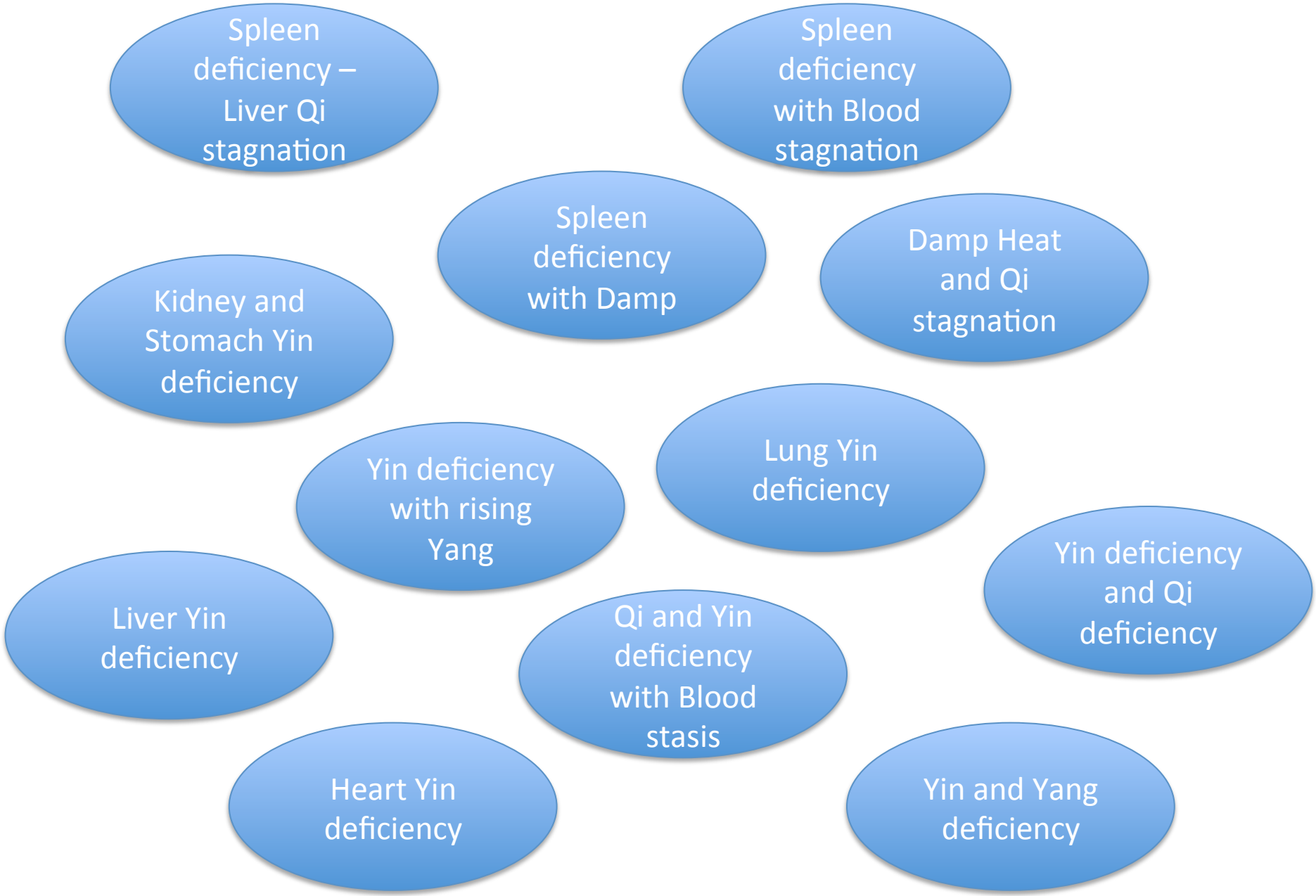
- **Upper Jiao:**
  Lung Heat injuring the fluid

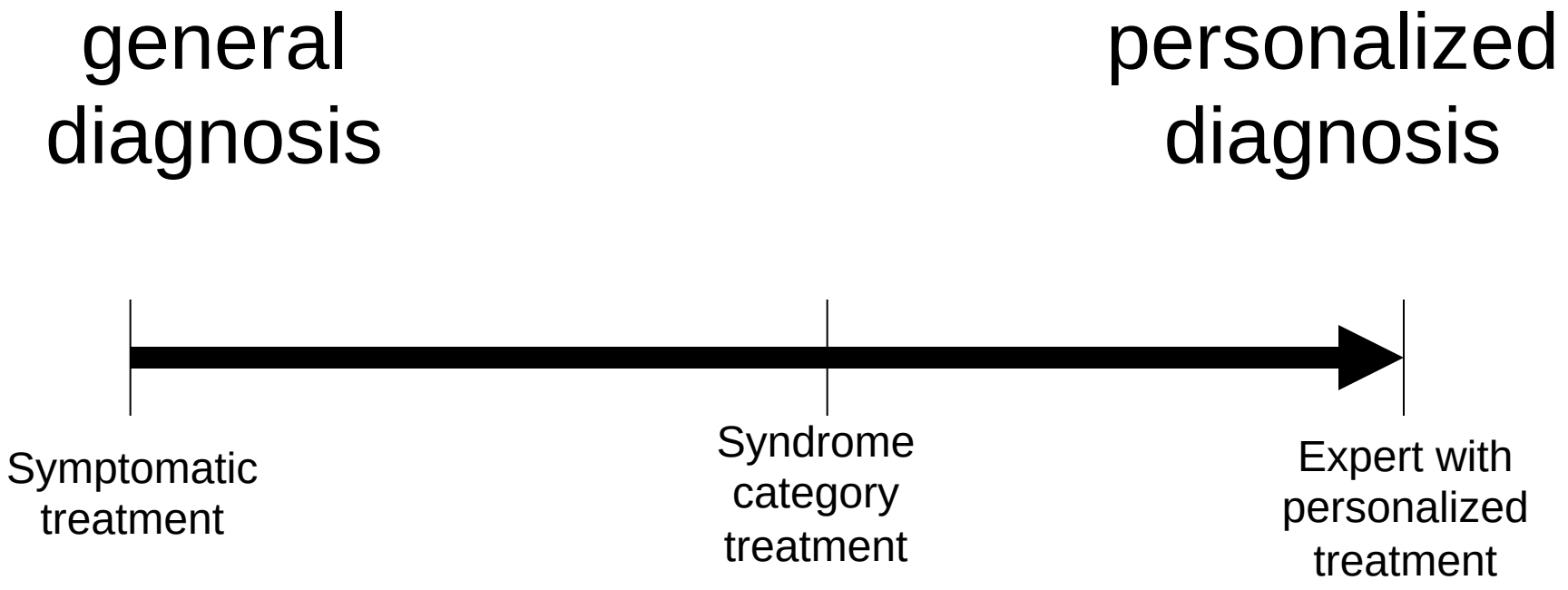
- **Middle Jiao:**
  Excess Stomach Heat

- **Lower Jiao:**
  Kidney Yin deficiency
  Deficiency of both the Yin and Yang

Xiao Ke

The Modern Classic Diagnosis


Spleen deficiency – Liver Qi stagnation
Spleen deficiency with Blood stagnation
Spleen deficiency with Damp
Damp Heat and Qi stagnation
Kidney and Stomach Yin deficiency
Yin deficiency with rising Yang
Lung Yin deficiency
Yin deficiency and Qi deficiency
Liver Yin deficiency
Qi and Yin deficiency with Blood stasis
Heart Yin deficiency
Yin and Yang deficiency


general diagnosis
personalized diagnosis
Symptomatic treatment
Syndrome category treatment
Expert with personalized treatment

Statistical Analysis of the TCM study

TCM CONCEPT DATA:

- Is there agreement between doctors?
- Can we discriminate between subjects, based on the concepts?

DATA:

- Prestudy, Glucose, Blood Lipids
- Biophotons
- Metabolomics

Can we correlate the information in these data sets to the TCM data?

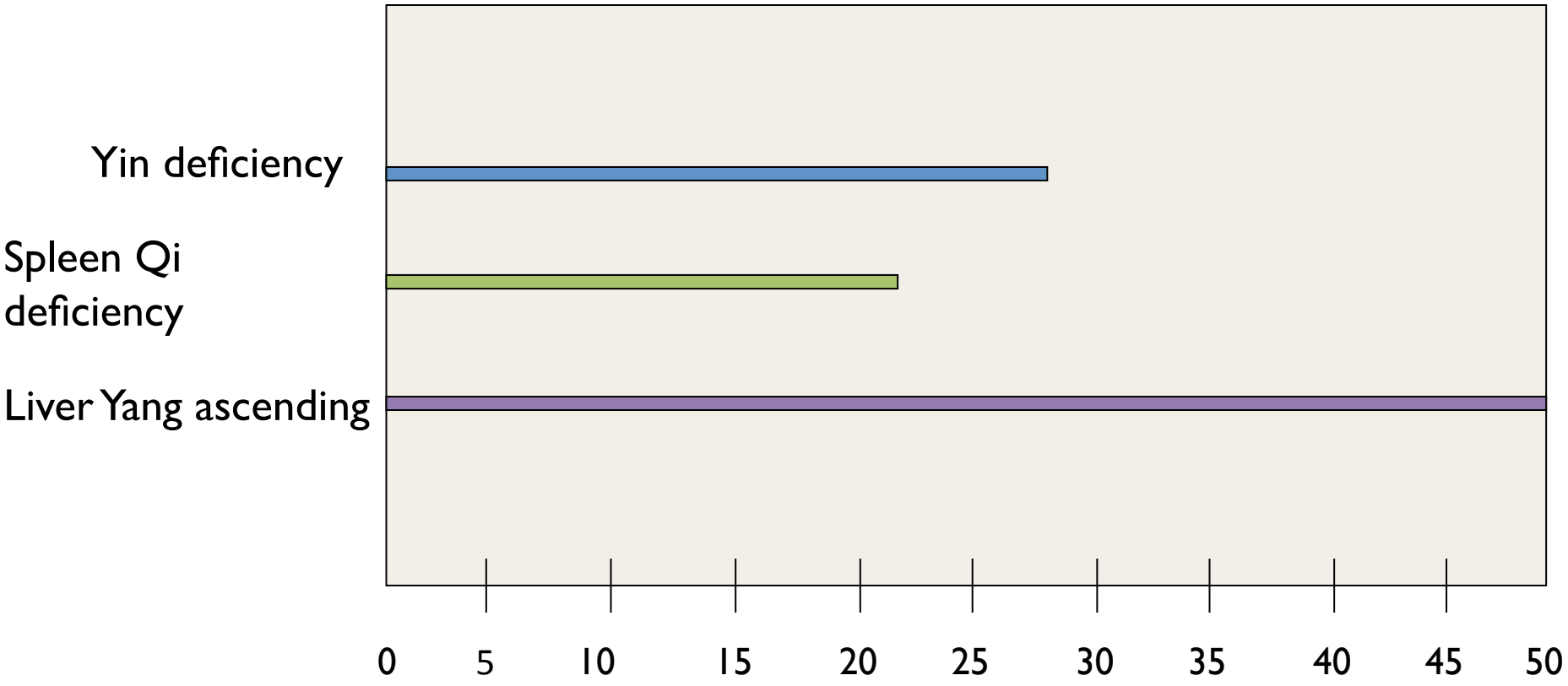
Personalized classification according to the TCM practitioners

Syndrome differentiation and profiling of the syndrome differentiation

TCM diagnosis (3x)

Blood stagnation
Damp-heat in the liver
DampHeat in the Middle Jiao
Damp-heat in the Spleen
Damp-heat in the stomach
DampHeat
Dry Heat consumes Yin
Heart Qi deficiency
Heart Yin deficiency
Heat in the Heart
Kidney Yin deficiency
Liver fire
Liver Qi stagnation
Liver-Yang ascending
Liver-Yin deficiency
Lung Yin deficiency
Lung-Qi deficiency
Qi & Yin deficiency Middle Jiao
Spleen Qi deficiency
Stomach Qi deficiency
Stomach Yin deficiency
Yin deficiency
Yin deficiency in the Middle-Jiao
False heat consumes Yin
Qi deficiency

SUBJECT 33


Yin deficiency
Spleen Qi deficiency
Liver Yang ascending
0
5
10
15
20
25
30
35
40
45
50

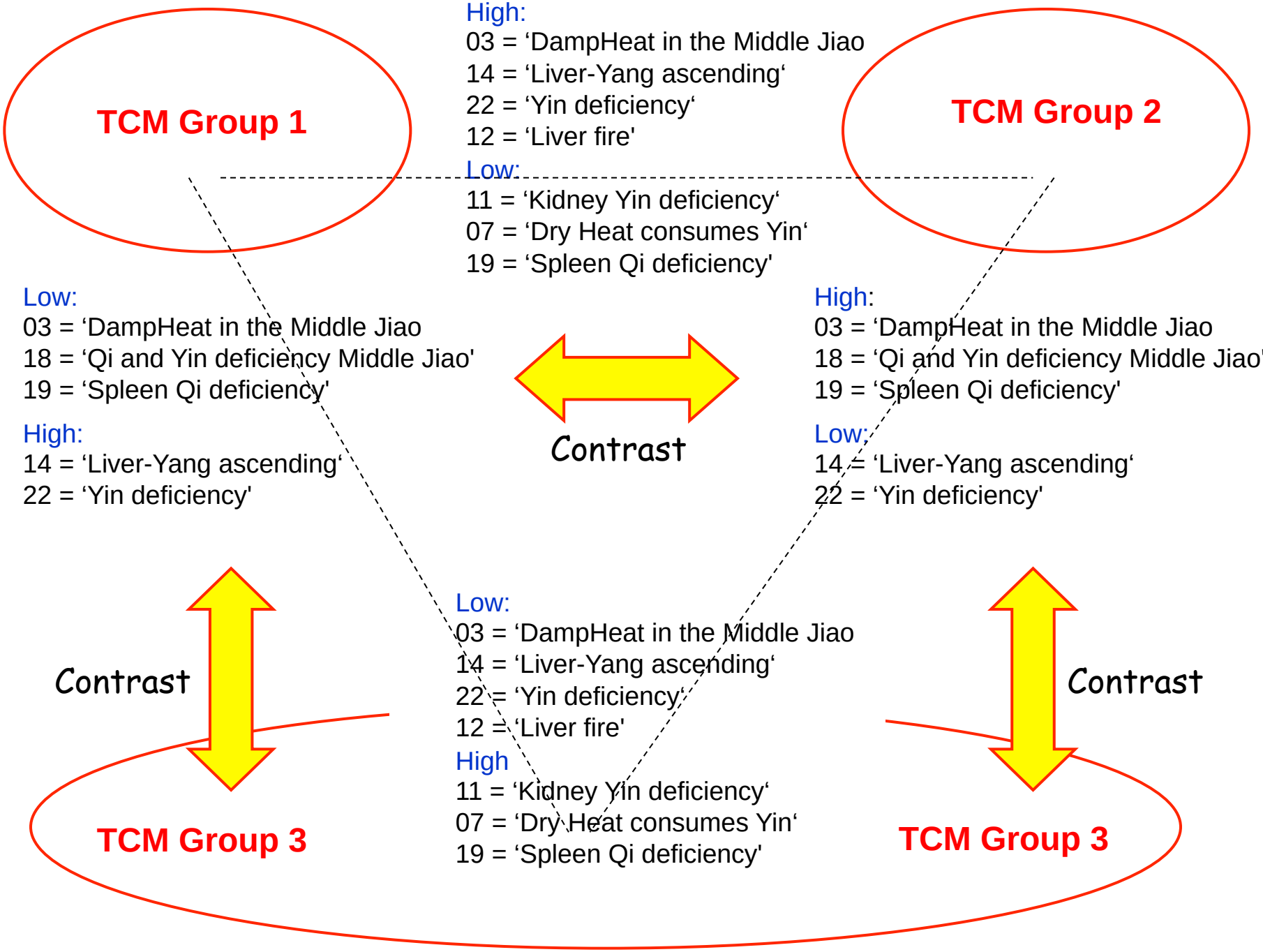
Analysis of Concepts

Is there agreement between doctors?

Yes

Can we quantify the agreement?

85 %


TCM Group 1
High:
03 = ‘DampHeat in the Middle Jiao
14 = ‘Liver-Yang ascending‘
22 = ‘Yin deficiency‘
12 = ‘Liver fire'
Low:
11 = ‘Kidney Yin deficiency‘
07 = ‘Dry Heat consumes Yin‘
19 = ‘Spleen Qi deficiency'
TCM Group 2
Low:
03 = ‘DampHeat in the Middle Jiao
18 = ‘Qi and Yin deficiency Middle Jiao'
19 = ‘Spleen Qi deficiency'
High:
14 = ‘Liver-Yang ascending‘
22 = ‘Yin deficiency'
Contrast
High:
03 = ‘DampHeat in the Middle Jiao
18 = ‘Qi and Yin deficiency Middle Jiao'
19 = ‘Spleen Qi deficiency'
Low:
14 = ‘Liver-Yang ascending‘
22 = ‘Yin deficiency'
Contrast
Contrast
Low:
03 = ‘DampHeat in the Middle Jiao
14 = ‘Liver-Yang ascending‘
22 = ‘Yin deficiency‘
12 = ‘Liver fire'
High
11 = ‘Kidney Yin deficiency‘
07 = ‘Dry Heat consumes Yin‘
19 = ‘Spleen Qi deficiency'
TCM Group 3
TCM Group 3

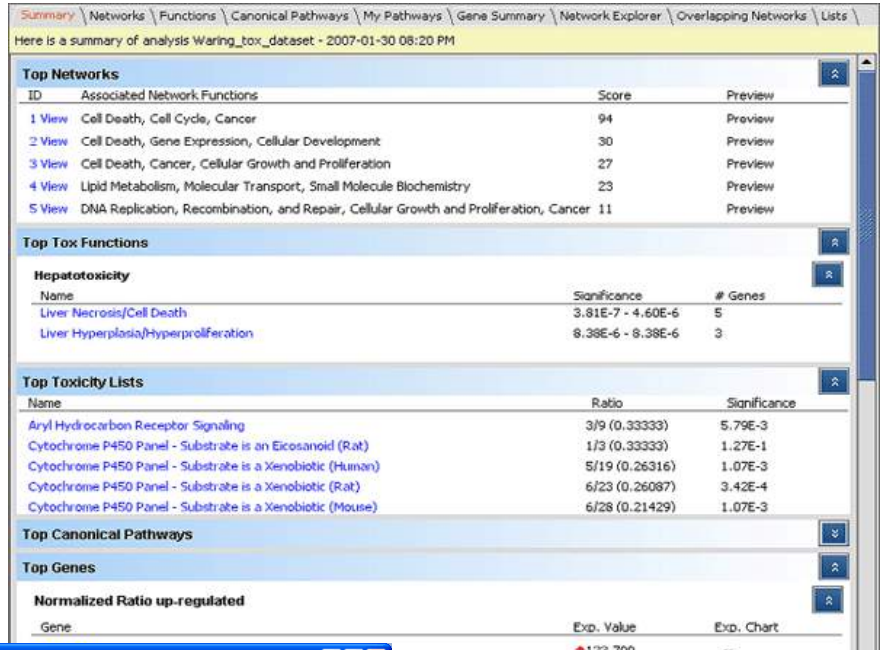
Metabolites

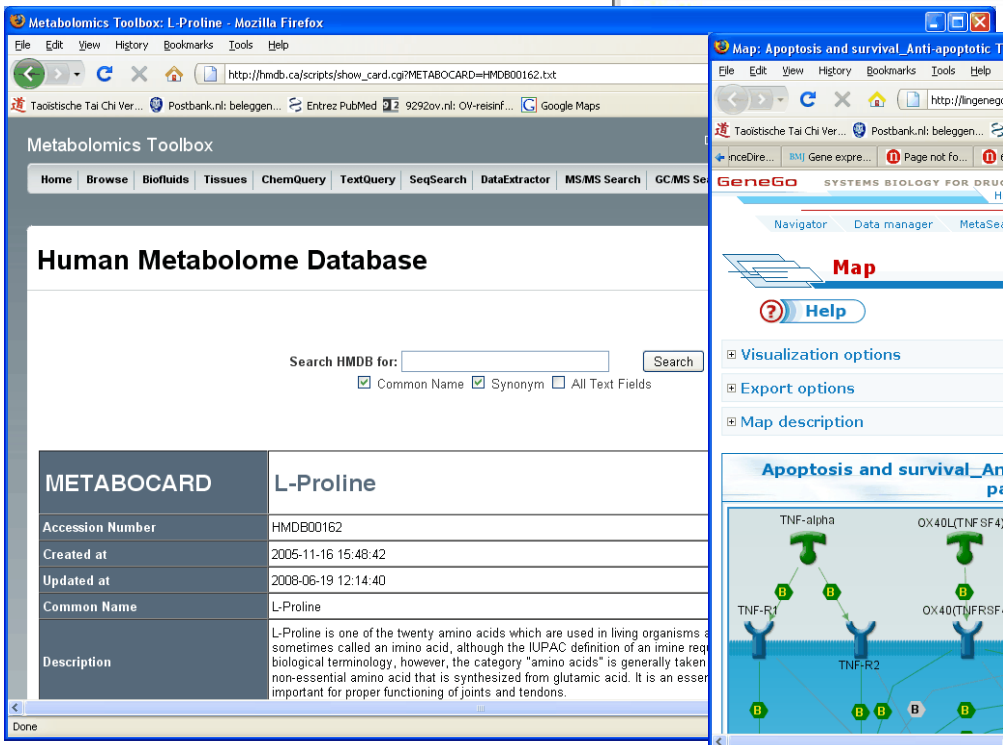
Useful tools to find information about metabolites:

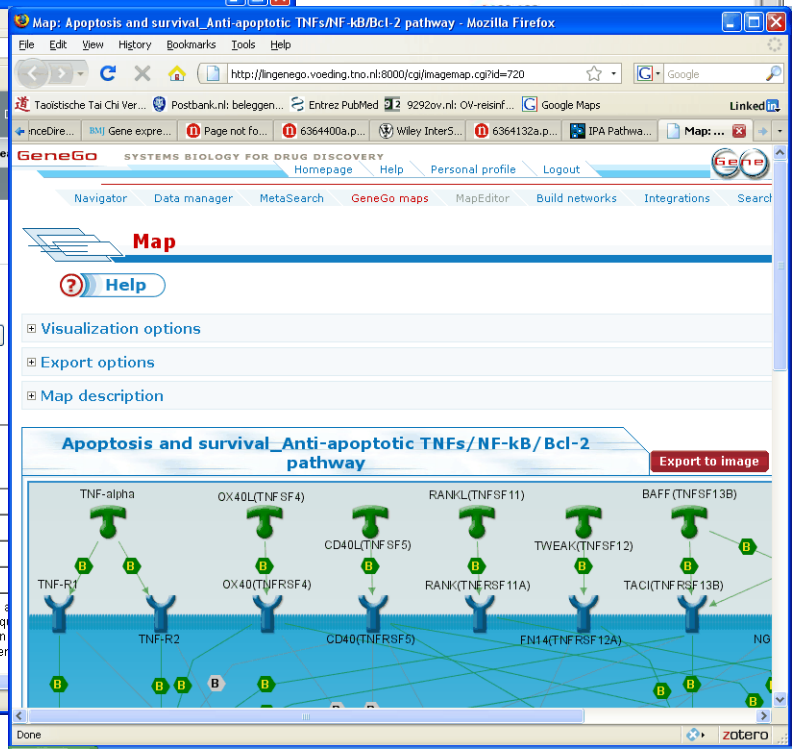
- Metabolomics toolbox
- Ingenuity Pathway Analysis
- MetaCore

Interactions

links to literature







AND NOW?

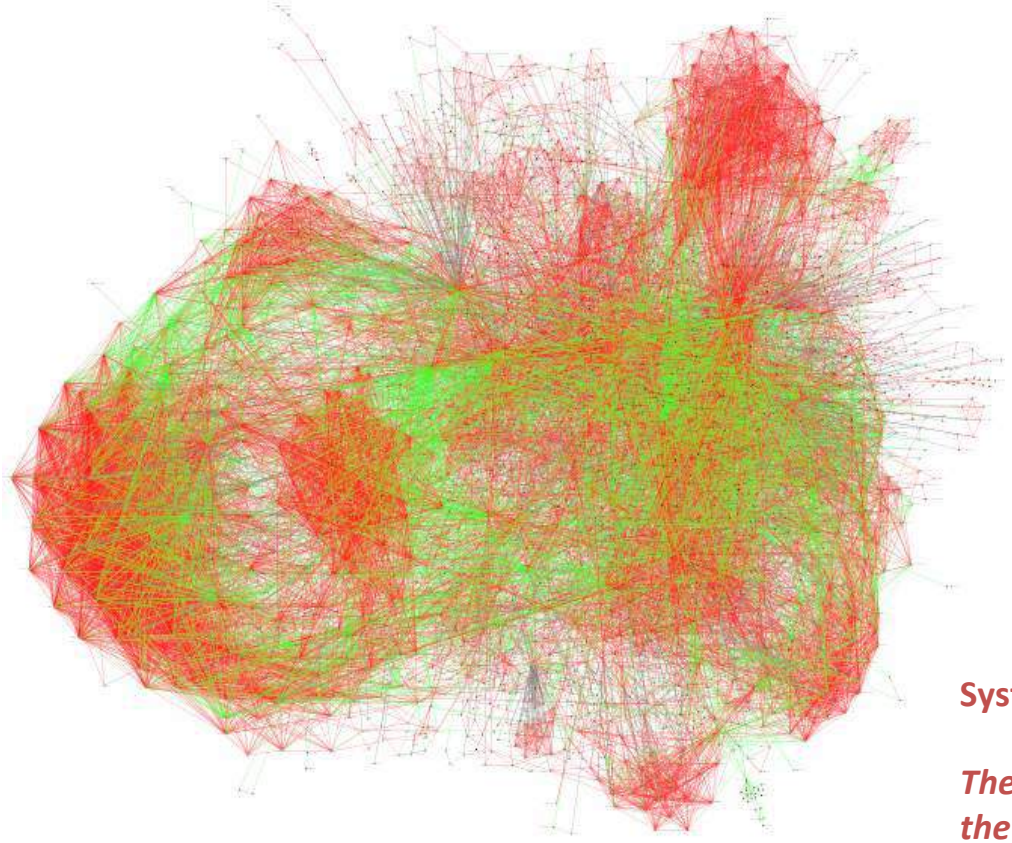
Metabolomics

Fingerprinting

Prediagnosis

Personalized diagnosis

Personalized treatment

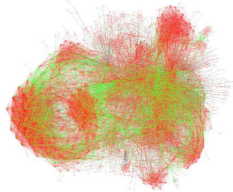


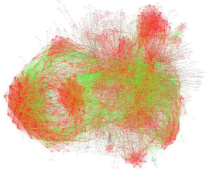
Systems Theory :

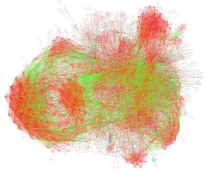
The scale and complexity of
the problem and solution should match

Yaneer Bar-Yam

12 subtypes of Diabetes II: Biomarker fingerprinting


DMII subtype 1


DMII subtype 2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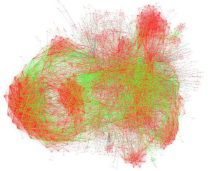
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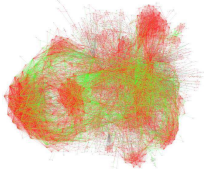
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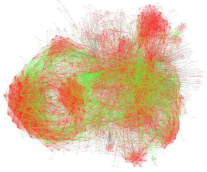
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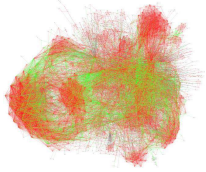
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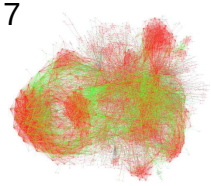
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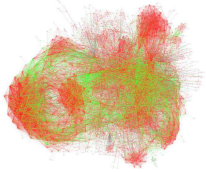
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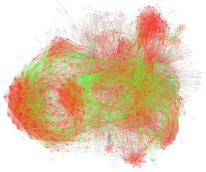
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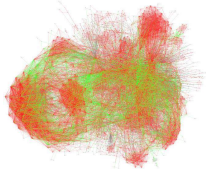
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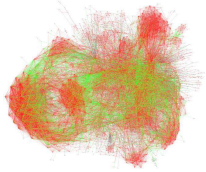
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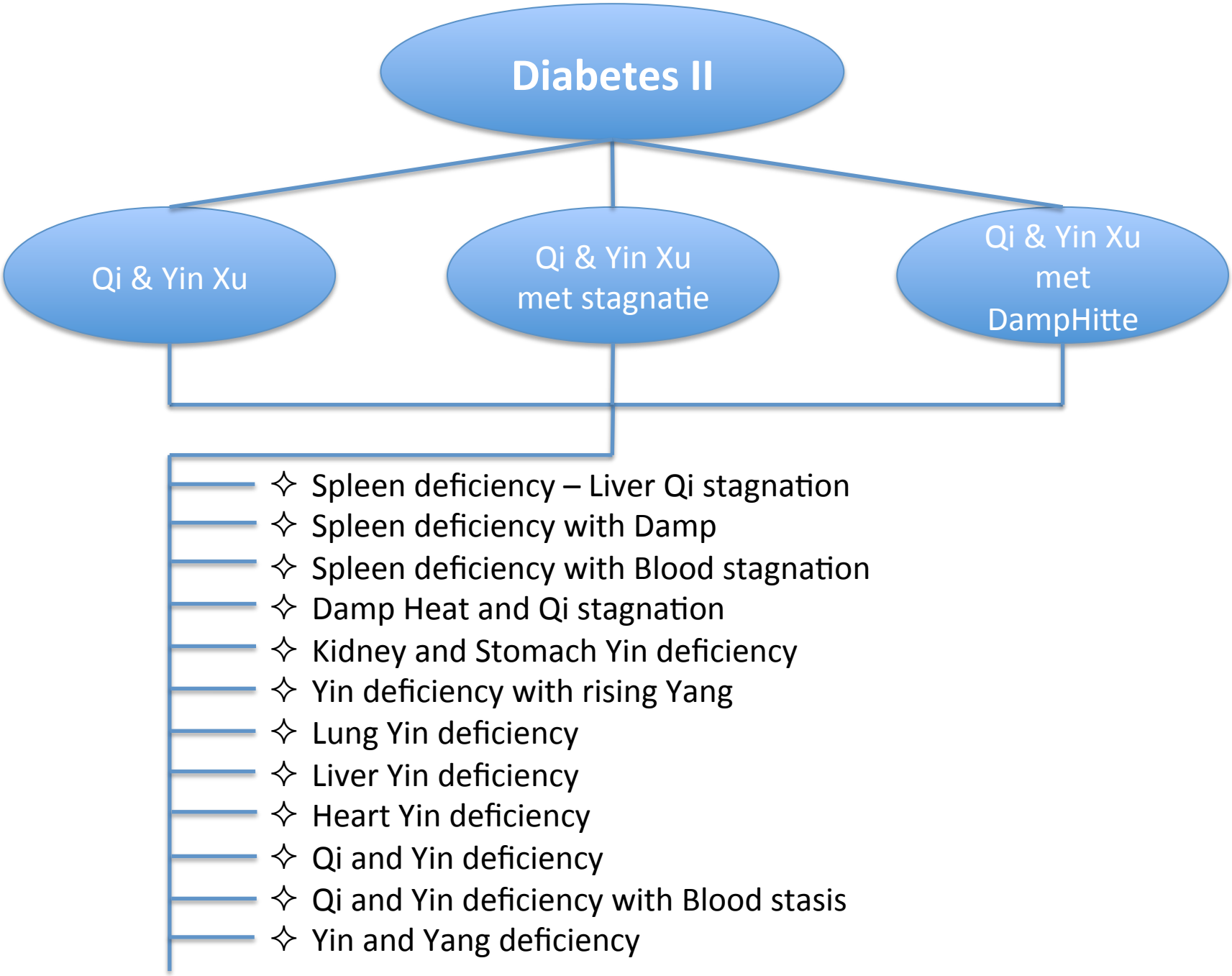
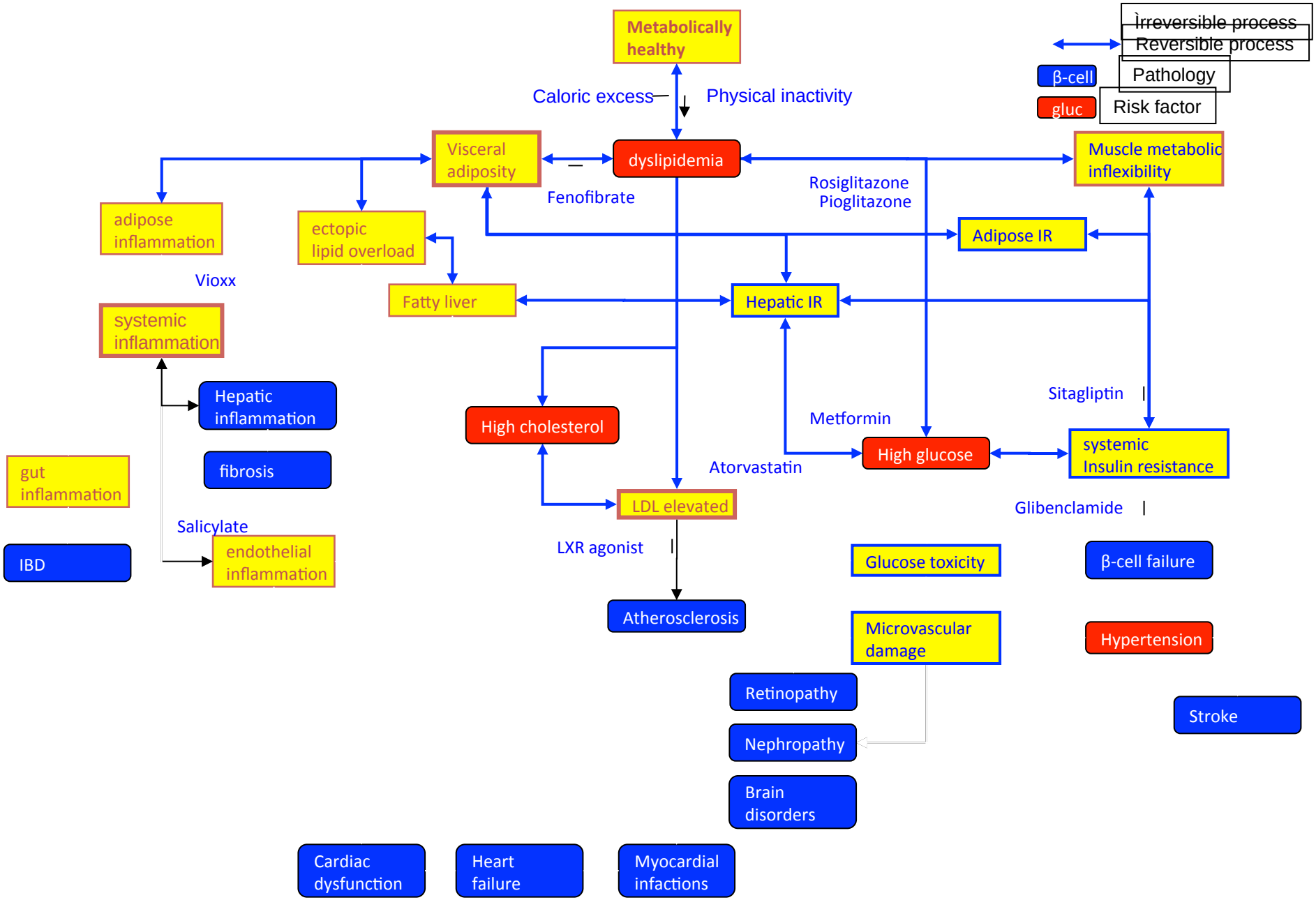

Diabetes II
Qi & Yin Xu
Qi & Yin Xu met stagnatie
Qi & Yin Xu met DampHitte
✧ Spleen deficiency – Liver Qi stagnation
✧ Spleen deficiency with Damp
✧ Spleen deficiency with Blood stagnation
✧ Damp Heat and Qi stagnation
✧ Kidney and Stomach Yin deficiency
✧ Yin deficiency with rising Yang
✧ Lung Yin deficiency
✧ Liver Yin deficiency
✧ Heart Yin deficiency
✧ Qi and Yin deficiency
✧ Qi and Yin deficiency with Blood stasis
✧ Yin and Yang deficiency

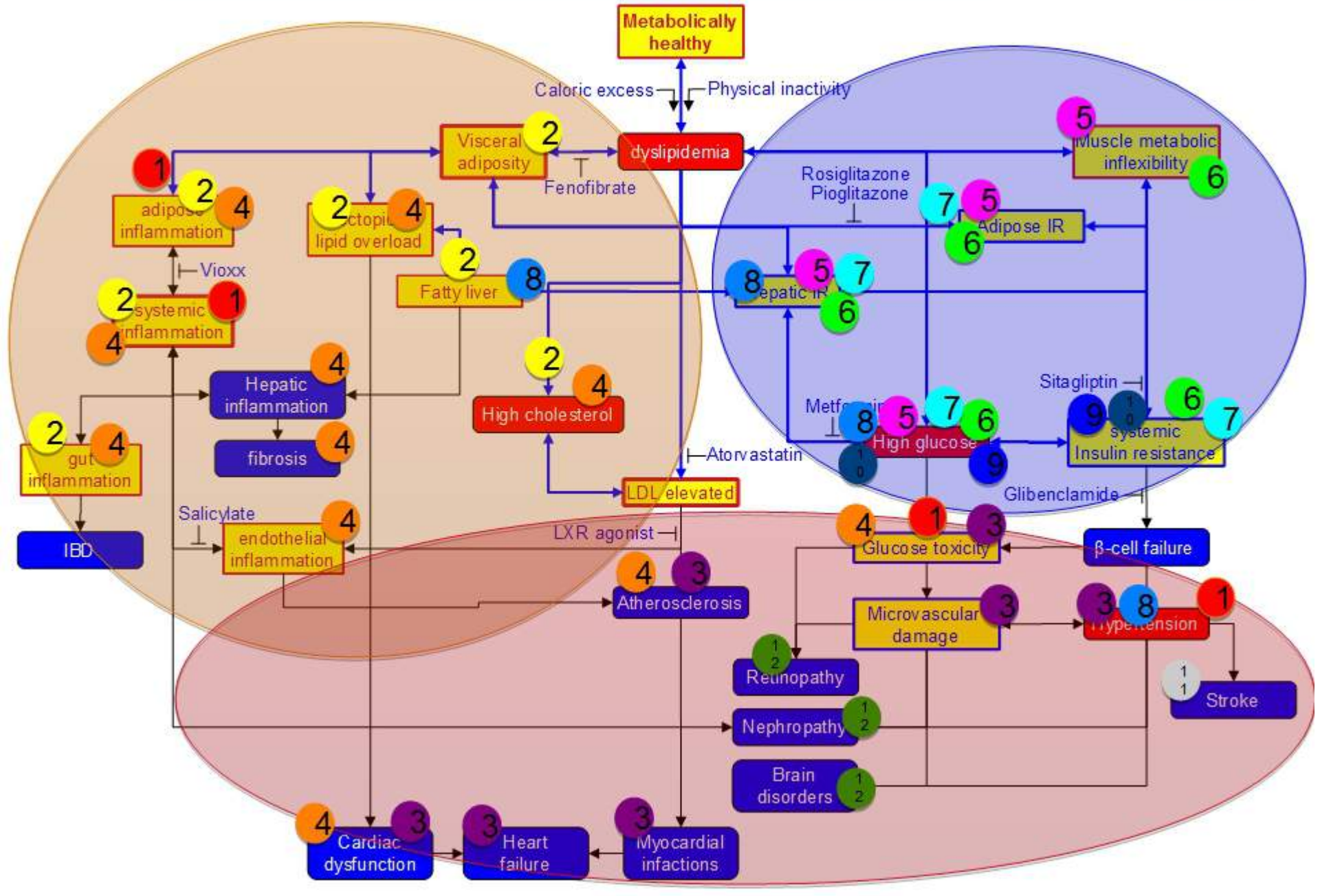

Metabolically healthy
Caloric excess
Physical inactivity
Visceral adiposity
dyslipidemia
Muscle metabolic inflexibility
Fenofibrate
Rosiglitazone
Pioglitazone
adipose inflammation
ectopic lipid overload
Adipose IR
Vioxx
Fatty liver
Hepatic IR
systemic inflammation
Hepatic inflammation
fibrosis
gut inflammation
IBD
Salicylate
endothelial inflammation
High cholesterol
Metformin
Sitagliptin
High glucose
systemic Insulin resistance
Atorvastatin
LDL elevated
Glibenclamide
LXR agonist
Atherosclerosis
Glucose toxicity
β-cell failure
Microvascular damage
Hypertension
Retinopathy
Stroke
Nephropathy
Brain disorders
Cardiac dysfunction
Heart failure
Myocardial infactions
Irreversible process
Reversible process
Pathology
β-cell
gluc
Risk factor

Qi and Yin deficiency with DampHeat

Qi and Yin deficiency with stagnation

Qi and Yin deficiency

TNO innovation for life



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Sino-Dutch Centre for Preventive and Personalized Medicine

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Netherlands Genomics Initiative

Artrose & Reuma Stichting