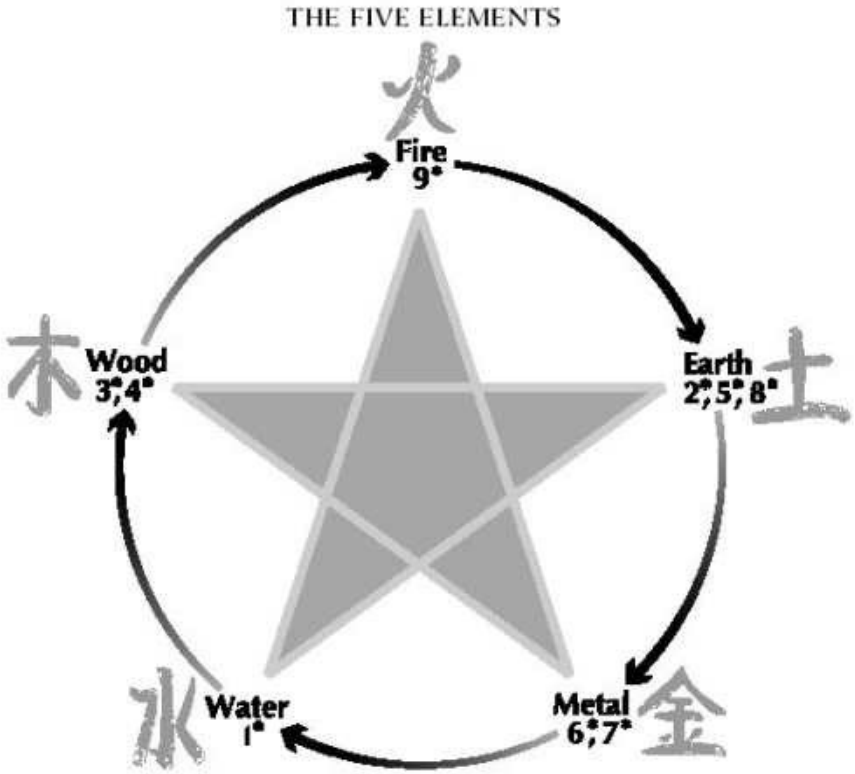
Rethinking causation for complex systems in biomedicine: challenges and new approaches

Sylvia Nagl PhD
Cancer Systems Biology
Oncology

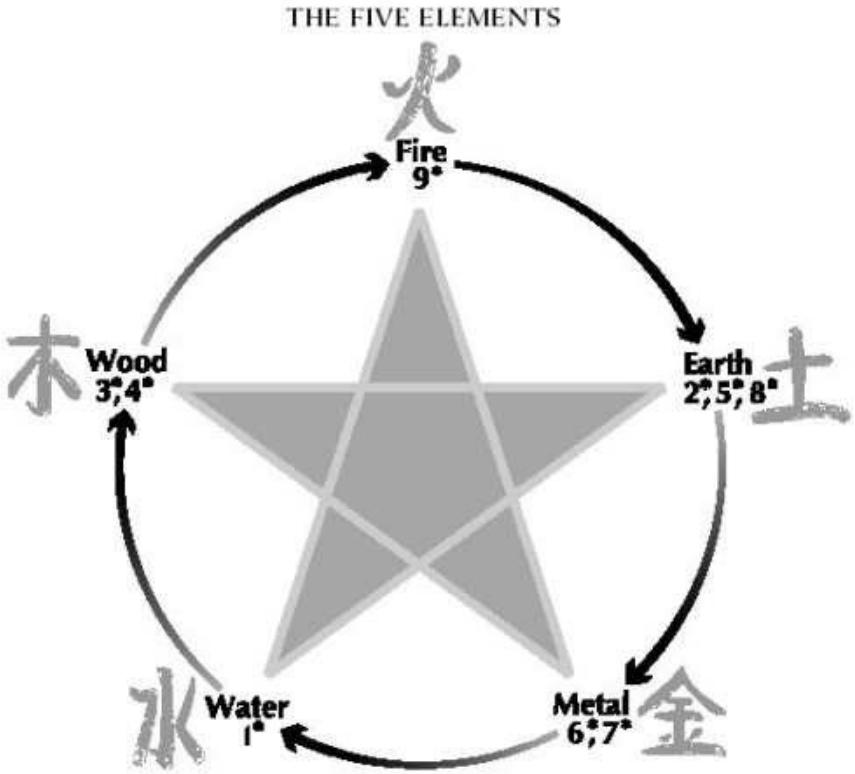
s.nagl@ucl.ac.uk

Ancient systems thinking

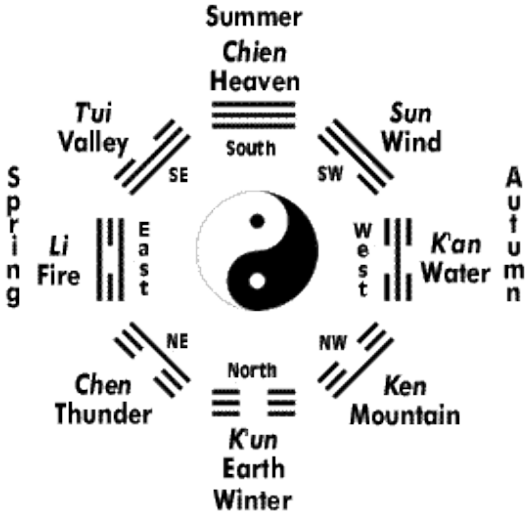


WOOD	Energy which rises upwards, much as a tree grows.
FIRE	Energy which moves outwards, as a fire spreads.
EARTH	Energy which is stabilising and containing, like an earthen bowl.
METAL	Energy which is hardening and moving downwards.
WATER	Energy which flows.

Ancient systems thinking



WOOD	Energy which rises upwards, much as a tree grows.
FIRE	Energy which moves outwards, as a fire spreads.
EARTH	Energy which is stabilising and containing, like an earthen bowl.
METAL	Energy which is hardening and moving downwards.
WATER	Energy which flows.

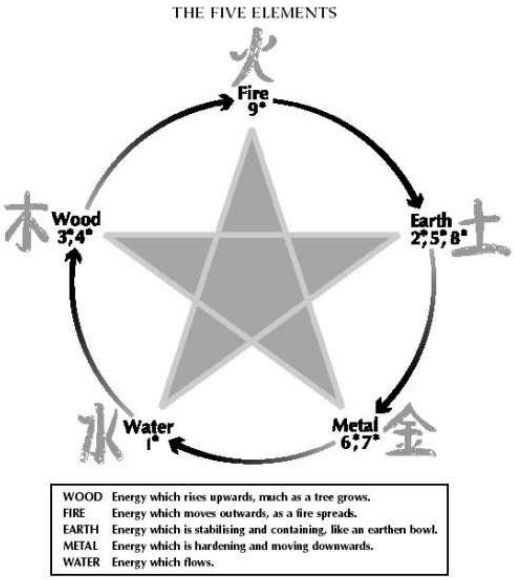


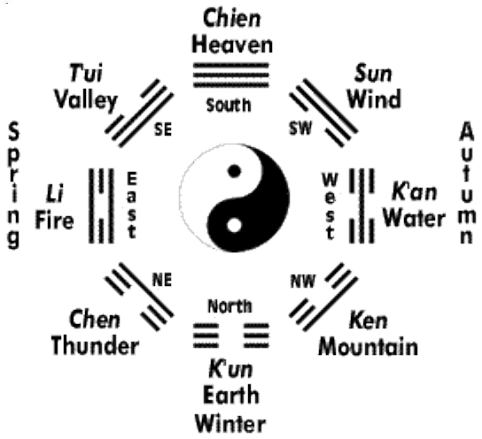
‘cosmological’ –systems thinking

Ancient systems thinking

Season	Element	Yin-Yang Phase	Yin Organ	Yang Organ	Energy Pattern	Color	Emotion	Taste	Voice
Winter	Water	Full yin	Kidney	Urinary bladder	Conserved	Black	Fear	Salty	Groans
Spring	Wood	New yang	Liver	Gallbladder	Expansive	Green	Anger	Sour	Shouts
Summer	Fire	Full yang	Heart	Small Intestine	Culmination, completion	Red	Joy	Bitter	Laughs
Late Summer	Earth	yin-yang balance	Spleen	Stomach	Balance	Yellow	Sympathy	Sweet	Sings
Autumn	Metal	New yin	Lungs	Large Intestine	Contraction and accumulation	White	Grief sadness	Pungent	Weeps

Ancient systems thinking





Shi

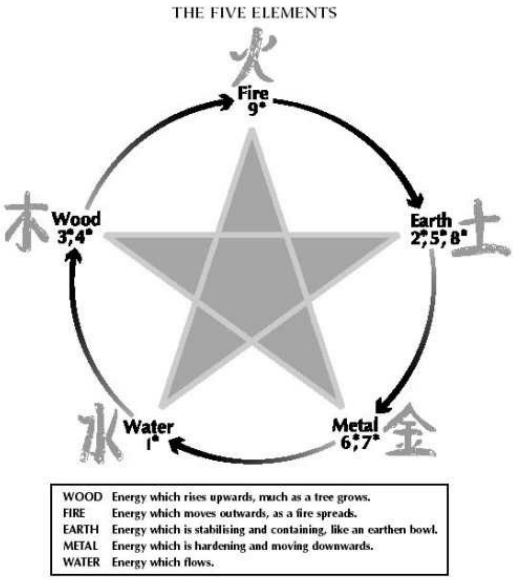
Change

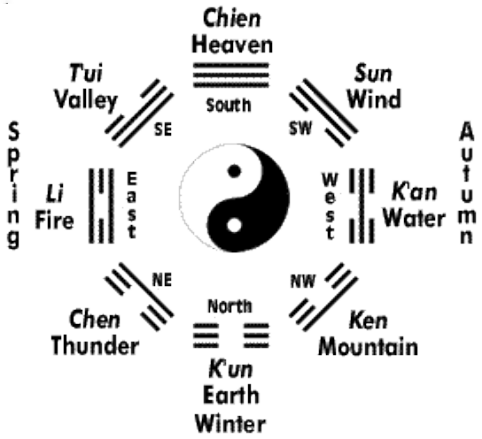
Contextual and relational

Propensity, disposition, circumstance, potential

Conditioning of reality in all its complexity

Ancient systems thinking





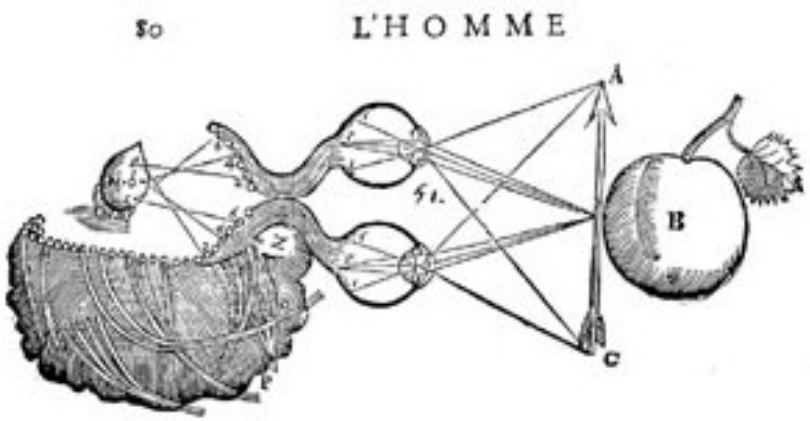
Shi

Non-analytical

Observational

Abstraction and principles

The rise of modern science in the West

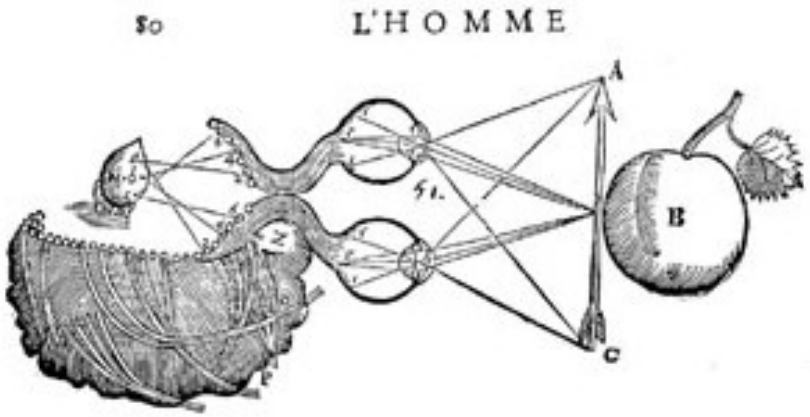


The apple diagram from Descartes' *Traité de l'Homme*,1664

Rene Descartes (1596-1650) stripped the sclera and choroid off the eye of an ox to perform a projection experiment onto a piece of paper. This proved that the retina initially sees an inverted image.

Descartes thought of the brain as a machine with fibres running from the eyes like optical cables. These formed a rudimentary visual pathway. The inner soul within the brain then viewed the image transferred to it along the pathway by vibrational forces.

The rise of modern science in the West



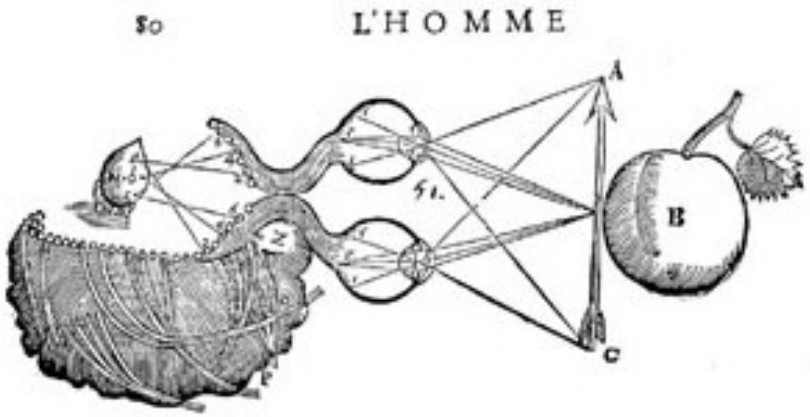
The apple diagram from Descartes'
Traité de l'Homme,1664

Causality

Causation

Analytical

The rise of modern science in the West

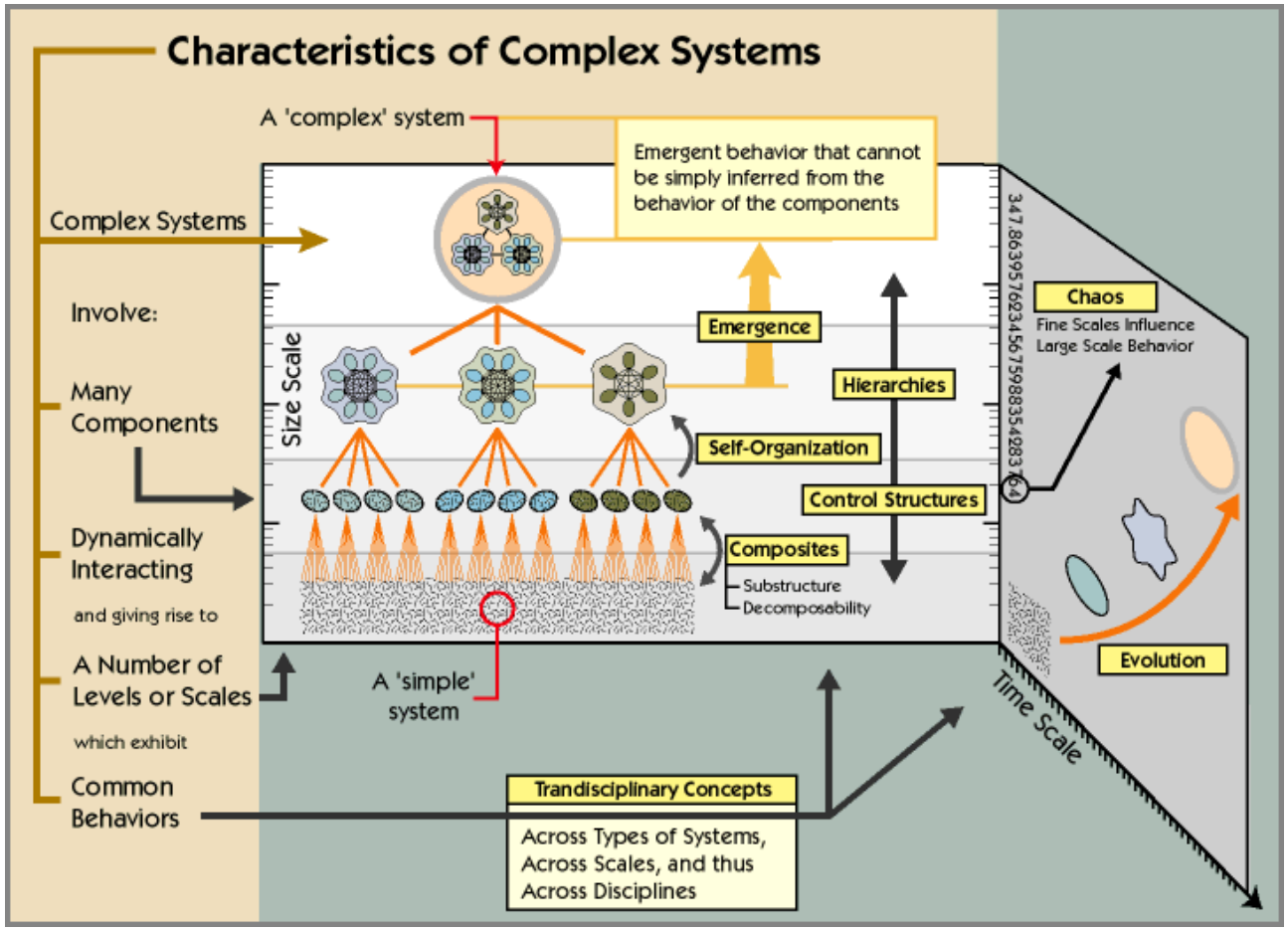


The apple diagram from Descartes'
Traité de l'Homme,1664

What 'causes' the image?

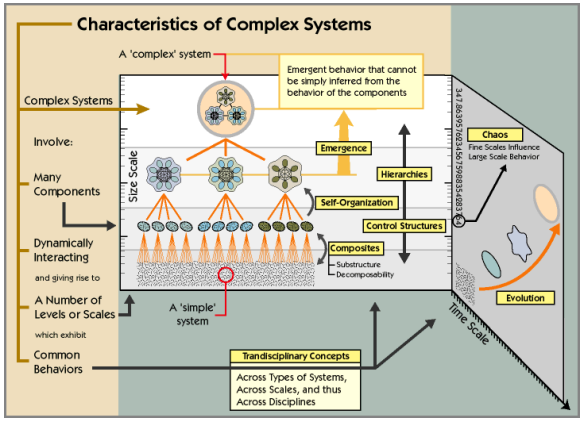
The apple, the eye-machine, the inner soul?

The 21st century: Complexity science



New England Complex Systems Institute - necsi.org

Evolution of thought

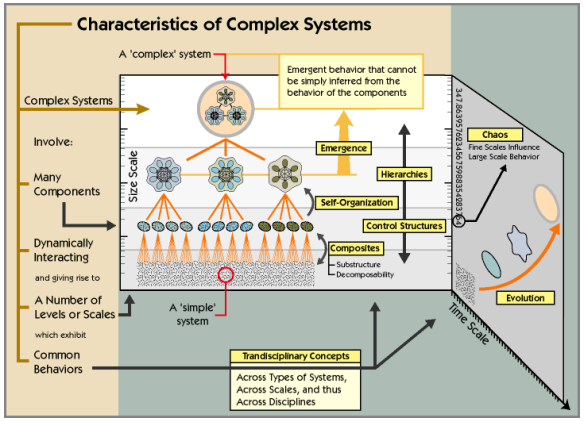


Machine metaphor (mechanistic) with pathways > networks of interactions

Forces > energy (thermodynamics) > information > biological information

Inner soul > genome and genes > distributed networks

Key concepts



Change: Adaptation & evolution

Contextual and relational, built on analytic method and atomism, components:

Emergent structure and behaviour

Simulation

No privileged locus of control – distributed, parallel

Emergence

- Emergent behaviour cannot be strictly inferred from the behaviour of system components.
- Incompletely understood, lacks mature formalisms
- Does not fit comfortably into a framework of mechanistic causation
- Dependencies across scales can be defined probabilistically
- Bayesian nets

Causality in biomedicine

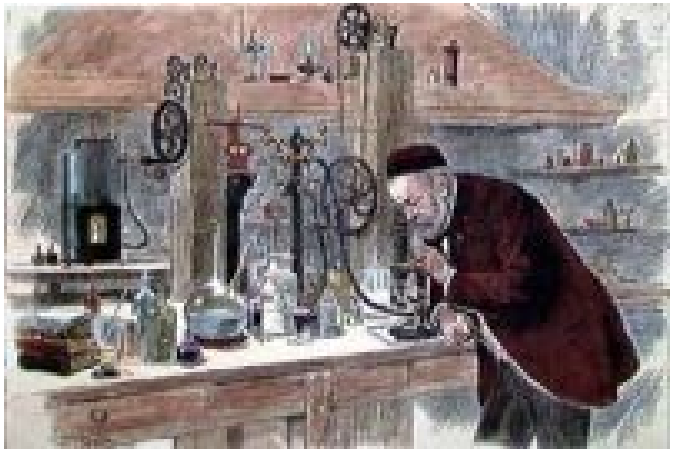
- Symptoms and signs - changes and movements
- Origin of changes?
- Nothing more is observable from events than constant conjunction and perhaps contiguity in space
- David Hume – causation is not in the things we observe even if it is applied to them
- A cause is an epistemological expectation

>> explanatory frameworks, views on causality and motivation?

Explanatory frameworks

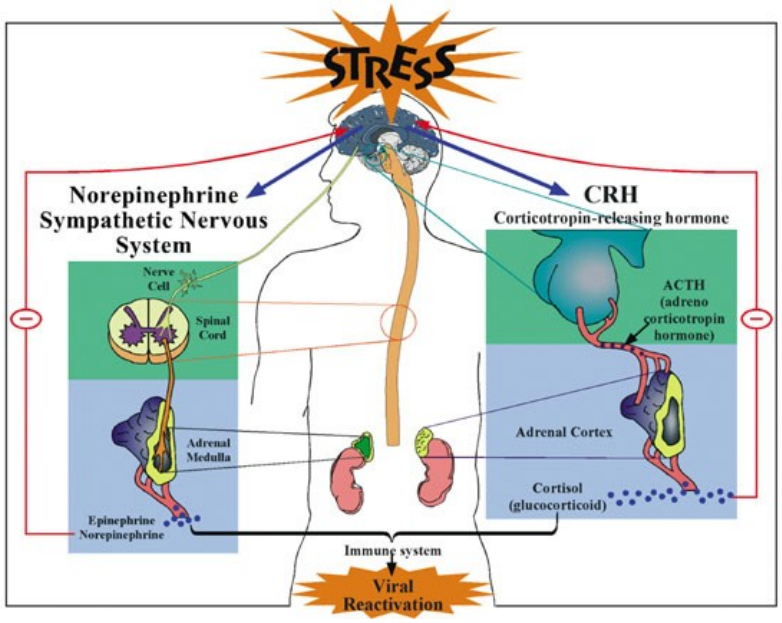
- internal to body, e.g., the four humours of Medieval Medicine

Explanatory frameworks



- external agents, e.g., germ theory of Louis Pasteur

Explanatory frameworks



exploration.nasa.gov

- convergence

viral activation as a result of

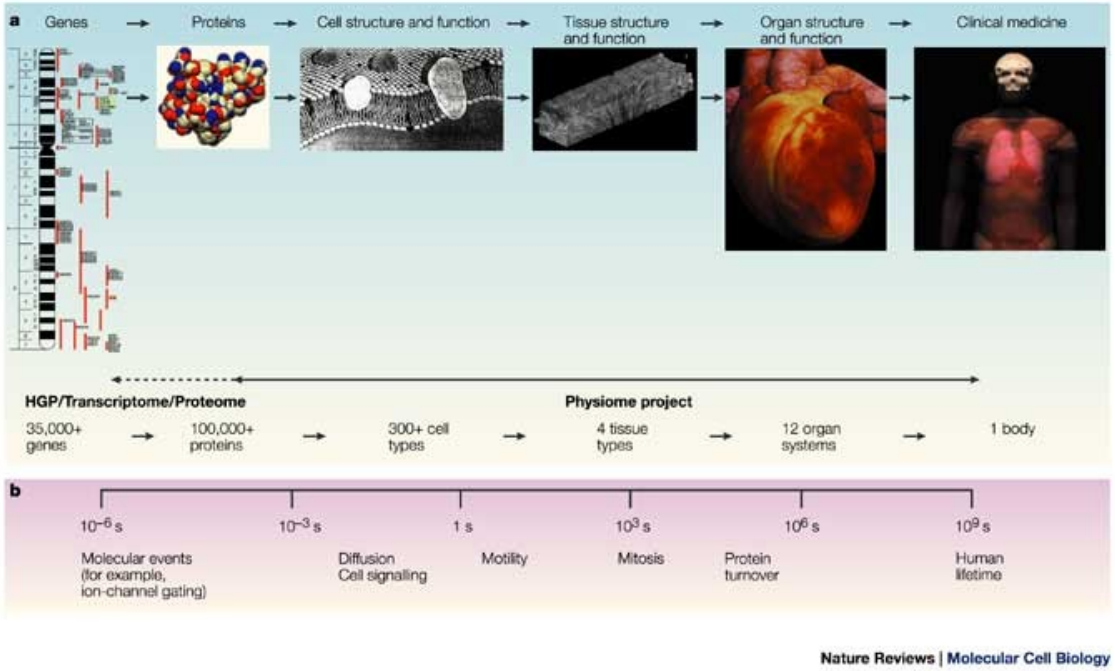
infection plus stress plus compromised immune system

Explanatory frameworks

‘Stress’

- **mind-body**

Explanatory frameworks



Physiome project

- **complex system**
- **semantics of the body**

Motivation in clinical medicine

Seeks causes for

- **Prevention, amelioration, cure, palliation – ‘intervene’**

- **Diagnosis – ‘identify’**
- **Prognosis – ‘predict’**

- **Fundamental differences**

Motivation in biomedical science

- The motivations of medicine and of fundamental biomedical science differ in very significant ways
- Efficacious intervention vs. explanation of mechanism
- Agency-based vs. mechanistic (or probabilistic) causation

Causation and complexity

- How does a complexity framework challenge our established views on causality?
- Both medicine and science are challenged by the distributed, parallel nature of systems, and by emergence
- From single (or few) causes to
  - mutual interdependence of causes
  - distributed networks of causation
  - context-dependence (a factor plus the state of entire system)

Causation and complexity

- **Mutual dependence of physical causes**
- **The biological relevance of any factor, and therefore "the information" it conveys, is jointly determined, frequently in a statistically interactive fashion, by that factor and the system state (Susan Oyama, The Ontogeny of Information, 2000).**
- **The influence of a gene, or a genetic mutation, depends on the context, such as availability of other molecular agents and the state of the biological system, including the rest of the genome.**

Agency-oriented causality in medicine

- **Medicine is particularly focused on an agency-oriented account of causality which seeks to analyse causal relations in terms of the ability of agents to achieve goals by manipulating their 'causes'.**
- **According to this conception of causality, C causes E if and only if bringing about C would be an effective way of bringing about E.**
- **Or, conversely, C is seen as a cause of E if by inhibiting C one can stop E from happening.**
- **The agent may also seek to ground this view of causality in a mechanistic account of physical processes**
    - **mechanistic mode of action of a drug**

Challenge

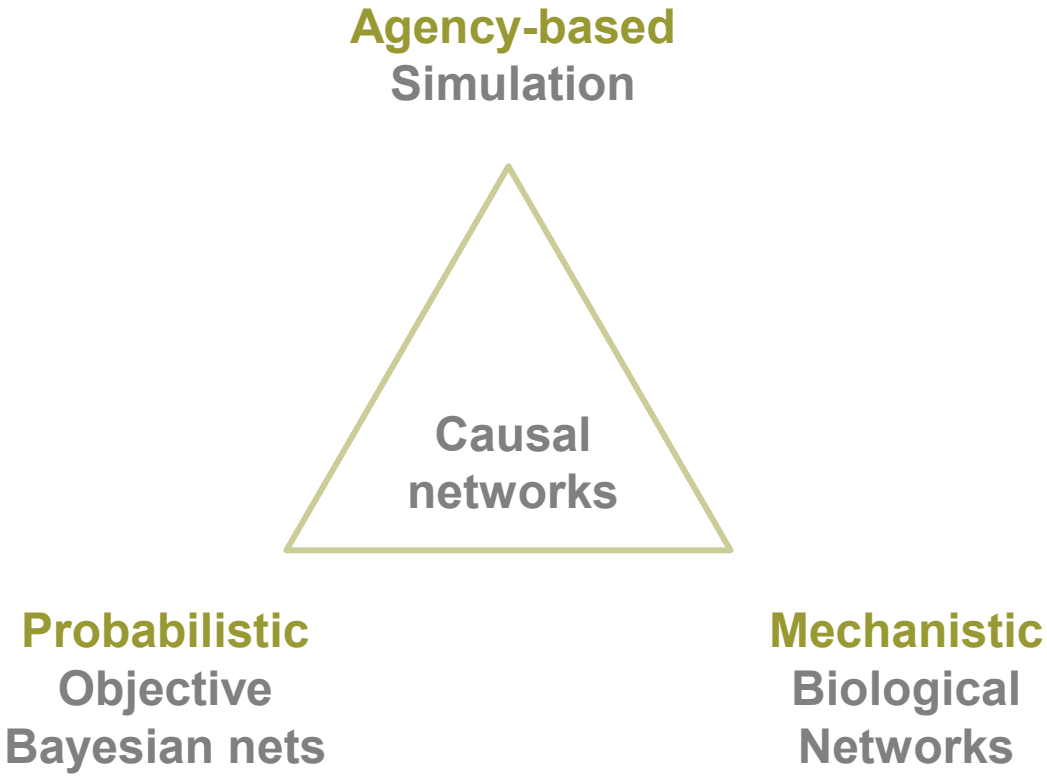
Effective targets for intervention may not be causes in the traditional sense.

In complex systems (and complex diseases) there are multiple targets for intervention to bring about a state change in the system.

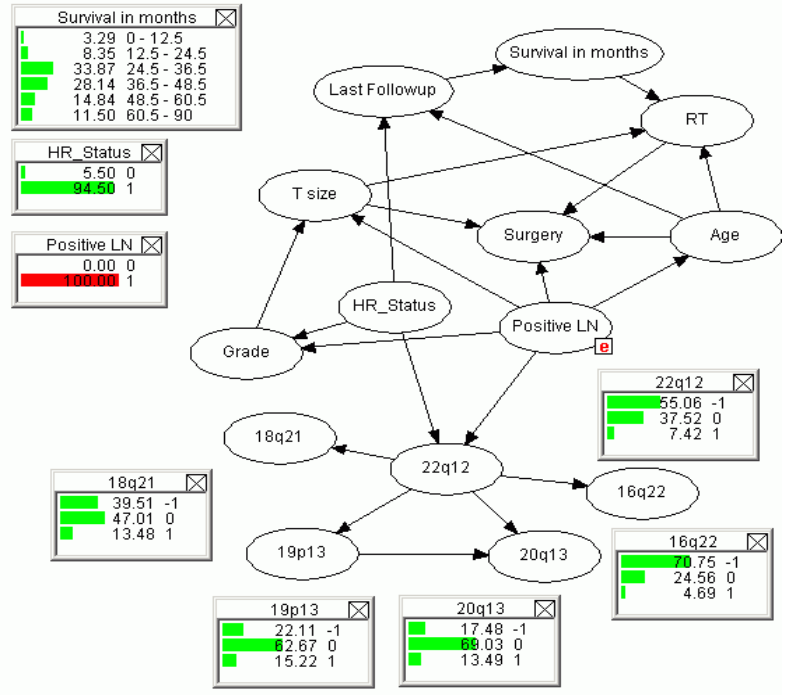
These may be distinct from factors involved in the disease process.

Intervention in such a factor may be ineffective for therapeutic purposes.

Epistemic causation model for complex systems

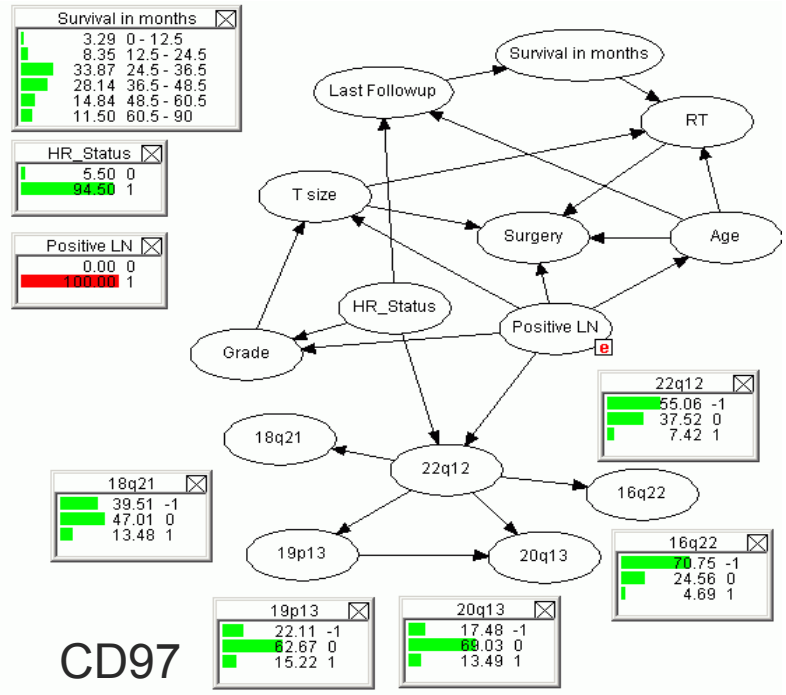


Objective Bayesian net



Chromosomal mutations in breast cancer > metastasis

Objective Bayesian net



KREMEN1

DRG1, TIMP3

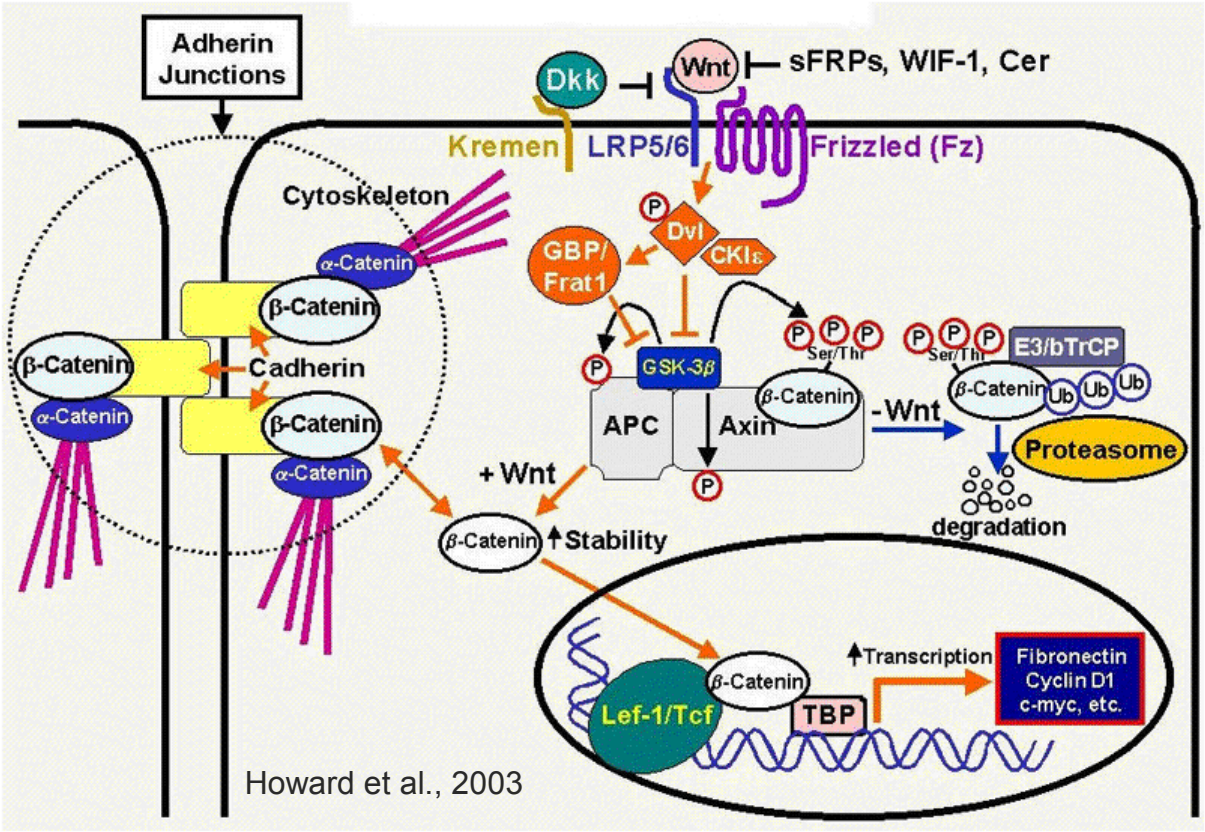
MYH9, CHEK2

cadherin11

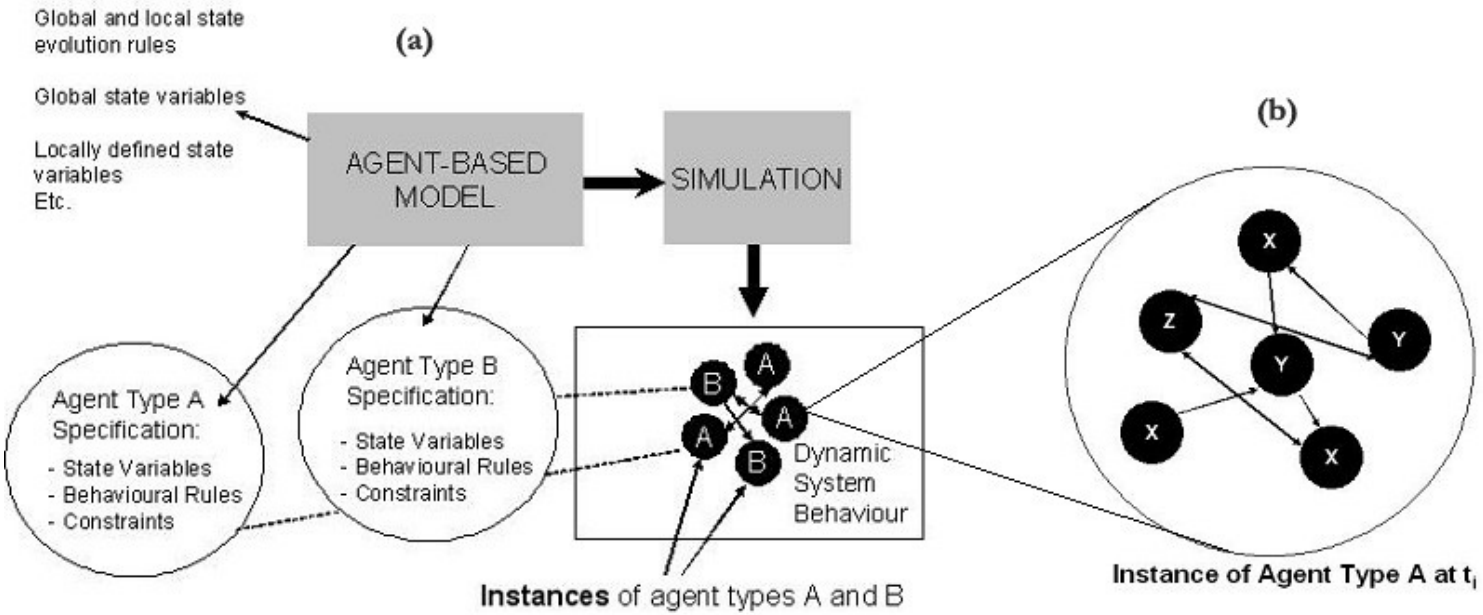
CD97

BMP7,
ELMO2,
BCAS1,
BCAS4,
ZNF217

Biological network



Agent-based simulation



See www.abmsystemsbiology.info for further information.

Molecules

Networks

Cells

Tissues