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

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Ancient systems thinking

THE FIVE ELEMENTS

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

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‘cosmological’ – systems thinking
### Ancient systems thinking

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

Causality
Causation
Analytical

The apple diagram from Descartes' *Traité de l'Homme*, 1664
The rise of modern science in the West

What ‘causes’ the image?

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

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

viral activation as a result of infection plus stress plus compromised immune system
Explanatory frameworks

‘Stress’

- mind-body
Explanatory frameworks

- complex system
- semantics of the body

Physiome project
Motivation in clinical medicine

Seeks causes for

- Prevention, amelioration, cure, palliation – ‘intervene’
- Diagnosis – ‘identify’
- Prognosis – ‘predict’
- Fundamental differences
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
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)
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
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

- Agency-based Simulation
- Causal networks
- Probabilistic Objective Bayesian nets
- Mechanistic Biological Networks
Chromosomal mutations in breast cancer > metastasis
Objective Bayesian net

KREMEN1, DRG1, TIMP3, MYH9, CHEK2, cdherin11, CD97, BMP7, ELMO2, BCAS1, BCAS4, ZNF217
Biological network

Howard et al., 2003
Agent-based simulation

See www.abmsystemsbiology.info for further information.