3 models: Mechanisms, disease-entities and –omics

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Science is built of facts the way a house is built of bricks: but an accumulation of facts is no more science than a pile of bricks is a house
“It became difficult to find the proper bricks for a task because one had to hunt among so many. It became difficult to find a suitable plot for construction of an edifice because the ground was covered with loose bricks. It became difficult to complete a useful edifice because, as soon as the foundations were discernible, they were buried under an avalanche of random bricks. And, saddest of all, sometimes no effort was made even to maintain the distinction between a pile of bricks and a true edifice.”

(Forscher 1963)
Bricks in medicine are zillions of pieces of knowledge about things, processes, properties. They must be organised (selection) to be tractable (explanation, prediction, therapeutic action). How have practitioners (doctors and medical researchers) organised their knowledge?

• Some say they are organised into practices (Fleck???), models (Schaffner 1986, 1993), theories (review in Lemoine 2014).
Mechanistic motive

The obvious answer is: it is organised in mechanisms (of X, Y, Z)

Yet so many things count as mechanisms that the mechanisms project (as applied to medicine) risks vacuity (diabetes diabetizes is a mechanism)

Besides, in medicine at least, nature is a gigantic mechanism of everything in nature.

And there are inference styles not involving mechanisms in medicine, which should be clearly distinguished.
Introduction: some aims

• To give a positive characterisation of ways of modelling medical knowledge
  – Including some comparative and functional work
• We want to explore and strengthen links to existing scholarship (both philosophical and medical)

• Not about the nature of disease
• Not about “the medical model”
1. Mechanisms

A description of a disease mechanism is a description of the organisation of entities and activities that collectively produce a disease. This must include a description of the pathway linking aetiological factors to symptoms via those entities and activities that describe how these aetiological factors bring about some specified pathology, and in turn how that pathology brings about symptoms.
1a. Mechanisms conference

Fuller: abstractness, incompleteness,
Illari: to avoid vacuity, define which explanations are not mechanistic (from Dupré)
Straif: policy functions of mechanisms
Aronson: mechanisms from/for
Rocca: the airbag example
2. The disease-entity model

The *disease-entity model*: a conceptual model of reasoning about disease, the causes of disease, and the relationship between diseases and symptoms (without worrying too much about causation)
Inferences about disease without good causal knowledge

Inappropriate immune system activation in the eye, leading to protein deposition in anterior chamber of the eye (Flare, cells, keratitic precipitates)

Risk factors: HLA-B27 status
Mechanism: ?? (although ??molecular mimicry)

Treatment: steroid eye-drops, preventing the development of inflammation
2a. Three distinct multifactorial causal narratives

Folk-causal relation
  – No “proper” theory of causation here
  – Causal narratives

3 types of causal narratives
  – CauseA
  – CauseP
  – CauseT
**CauseA:** a (presumptively causal) link between some set of risk factors, and a pathogenic fascicle.

This is the aetiological narrative that describes the development of a specified fascicle from some set of risk factors.
**CauseP:** a (presumptively causal) link between a specified pathogenic fascicle with some set of clinical features.

This is the *pathological* narrative that describes the development of some set of clinical features from a fascicle.
**CauseT**: a link between a specified *treatment* and a fascicle.

This narrative describes how, whatever the exact target of the treatment within the fascicle, it is considered essentially equivalent to any other, as both sever the presumptively causal narrative link from A to S.
**Toy example:** lung cancer

**Risk factors:** smoking, asbestos exposure

**CauseA:** DNA mutations

**Fascicle:** lung cancer

**CauseA** disruption of lung architecture

**Symptoms:** coughing, haemoptysis

**CauseT:** chemotherapy, surgery
Better example: acute anterior uveitis

Risk factors: HLA-B27 status

CauseA: possibly mediated by HPA-B27 (e.g. by molecular mimicry)

Fascicle: Inappropriate immune system activation in the eye

CauseP: Protein deposition in anterior chamber of the eye

Symptoms: Flare, cells, keratitic precipitates develop

CauseT: steroid eye-drops, preventing the development of inflammation
<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Infectious abdominal pain</th>
<th>Neoplastic abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden onset</td>
<td>Diarrhoea and vomiting</td>
<td>Change in bowel habit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gradual onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaemia</td>
</tr>
<tr>
<td>Risk factors</td>
<td>History of travel</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Altered immune status</td>
<td>Age</td>
</tr>
<tr>
<td>Treatment</td>
<td>Rapid response to</td>
<td>Surgical pathology</td>
</tr>
<tr>
<td></td>
<td>antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Response to supportive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>therapy</td>
<td></td>
</tr>
</tbody>
</table>

...
### 2c: DEM vs mechanisms

<table>
<thead>
<tr>
<th>DEM</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>No detailed account of entities and activities</td>
<td>Activities and entities, obvs.</td>
</tr>
<tr>
<td>No real productive continuity</td>
<td>Productive continuity</td>
</tr>
<tr>
<td>Tractable</td>
<td>Exhaustive</td>
</tr>
<tr>
<td>Concentrates on functionally important causes and effects</td>
<td>More holistic</td>
</tr>
<tr>
<td>Impression or abstraction of causal knowledge</td>
<td>(Jonathan Fuller’s talk made this harder)</td>
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3. -omics

A type of model where states are described comparatively by an exhaustive list of biological variables, without any regard to whether they are causes or effects, nor to any chain of causation, nor to any traditional diagnostic class.
3a: signatures

- *omic disease signature*: an exhaustive list of biological variables describing a state of a diseased organism, whether the disease is identified or not, whether the list is common to many organisms or idiosyncratic.

- *omic treatment signature*: an exhaustive list of biological variables describing a state of an organism submitted to a given treatment.
C-map

- phenotype: disease vs control
- drug control
- transcriptome as readouts
- gene expression 'signature' of phenotype
- pattern matching
- gene expression 'signature' of each drug
- 'reverse' signature to disease potential treatment
- Connectivity score
- 'similar' signature to disease potential inducer
### 3c: DEM vs -omics

<table>
<thead>
<tr>
<th>DEM</th>
<th>-omics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear distinction between risk factors, symptoms, and so on</td>
<td>Symmetry between signs, mechanisms, causes – everything is just a biomarker</td>
</tr>
<tr>
<td>Depends on a diagnosis – selecting a fascicle</td>
<td>Theranostic – no diagnosis required</td>
</tr>
<tr>
<td>All about disease entities!</td>
<td>Disease entities not required for confirmation/practice (but might be for discovery)</td>
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### 3c: mechanisms vs -omics

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<tr>
<th><strong>Mechanisms</strong></th>
<th><strong>-omics</strong></th>
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<tr>
<td>Clear distinction between different parts of the mechanism – Ca causes Cb causes Cc...</td>
<td>Symmetry between signs, mechanisms, causes – everything is just a biomarker</td>
</tr>
<tr>
<td>Causation</td>
<td>Association</td>
</tr>
<tr>
<td>Linked to biomedical theories (Elena)</td>
<td>Theoretical neutrality (apparently)</td>
</tr>
<tr>
<td>Depends on a diagnosis – selecting a mechanism, or classifying a new mechanism</td>
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## 4a: DEM vs mechanisms vs -omics

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<tr>
<td>No detailed account of entities and activities</td>
<td>Activities and entities, obvs.</td>
<td>Signatures</td>
</tr>
<tr>
<td>No real productive continuity</td>
<td>Productive continuity</td>
<td>No causation</td>
</tr>
<tr>
<td>Tractable</td>
<td>[crowdsourced]</td>
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</tr>
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<td>Exhaustive</td>
</tr>
<tr>
<td>Impression or abstraction of causal knowledge</td>
<td>(Jonathan Fuller’s talk made this harder)</td>
<td>Not about causes at all</td>
</tr>
<tr>
<td>All about disease entities!</td>
<td>All about disease entities – for refining/changing/challenging existing ideas about disease.</td>
<td>Disease entities not required for confirmation/practice (but might be for discovery)</td>
</tr>
<tr>
<td>Weak links to theory</td>
<td>Explicitly linked to biomedical theories (Elena)</td>
<td>Theoretical neutrality (apparently)</td>
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<tr>
<td>All about diagnosis!</td>
<td>Depends on a diagnosis – selecting a mechanism, or classifying a new mechanism</td>
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4b: broader HPS literature

How/where are the different models used?

• Miriam Solomon’s “untidy pluralism”
• John Pickstone’s (2000) historical “ways of knowing”
• Lara Keuck’s “epistemic hubs”
4c: an open question about ordering

Need to organise stuff (knowledge – facts – whatever) before epistemology happens

Diseases are epistemic meta-entities

Diagnostic kinds are epistemic meta-entities

‘Mechanism of X’ is an epistemic meta-entity

Signatures are epistemic meta-entity
4d: pending research questions

• Are the last two models really not derived from the mechanistic model?
• How and when is any of these models more relevant than any other?
• What happens when the three models do not overlap or contradict one another?
References


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Spare bits for Q&A
Introduction: the nature of disease

“Instead of beginning with diseases as such, we can begin simply with those entities actually of interest to medicine, i.e., the various diagnoses that are made. Our question will then be, to what do these diagnosis names refer and what is the nature of these referents? When a doctor says that a patient has X, where X is lung cancer or cystic fibrosis, etc., what is the nature of that X? The word “disease” does not enter in at all.”

(Simon 2011)
Engel’s 1977 tripartite characterisation:

1. The “old medical model” - disease as deviation from normal, mediated by natural causes
2. The “biomedical model” – a “scientific model; that is, it involved a shared set of assumptions and rules of conduct based on the scientific method and constituted a blueprint for research.”
3. the “biopsychosocial model” (p.132) – Engel’s own (normative) account of a medical model
Introduction: a bit more on the medical model

“We propose that the ‘medical model’ is a process whereby, informed by the best available evidence, doctors advise on, coordinate or deliver interventions for health improvement. It can be summarily stated as ‘does it work?’”

(Shah and Mountain 2007: 375)

Is this just a foil...

Murphy (2013): chimerical and procrustean