

# Can Mechanism plus Statistical Relevance add up to “Good Enough” Causation?

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# Aims

- To expand upon Russo and Williamson's account of causality in medicine
  - Mechanisms
  - Statistics
  - Interaction between mechanism and statistics
- To study an example of causal discovery in medicine using the RWT

# The Russo-Williamson Thesis

[Russo and Williamson, 2007]

- Causation is monistic and epistemic
- But the evidence for this causation is pluralistic
  - Mechanistic (dependency)
  - Statistical (difference-making)
- Theoretical, rather than historical

# Filling out the RWT

- Mechanisms
  - The ‘New Mechanistic Philosophy’
  - Consensus features of mechanisms
  - Mechanisms for medicine
- Statistics
  - Statistical relevance
  - Epistemic homogeneity
- Interaction between mechanism and statistics

# The 'New Mechanistic Philosophy'

- Machamer, Darden and Craver, 2000
- Glennan, 2002
- Bechtel and Abrahamsen, 2005
- Woodward, 2002

# The ‘New Mechanistic Philosophy’

- Machamer, Darden and Craver, 2000
  - “Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions”
- Glennan, 2002
- Bechtel and Abrahamsen, 2005
- Woodward, 2002

# The 'New Mechanistic Philosophy'

- Machamer, Darden and Craver, 2000
- Glennan, 2002
  - “...a mechanism for a behaviour is a complex system that produces that behaviour by the interaction of a number of parts, where the interactions between parts can be characterized by direct, invariant, change-relating generalization.”
- Bechtel and Abrahamsen, 2005
- Woodward, 2002

# The ‘New Mechanistic Philosophy’

- Machamer, Darden and Craver, 2000
- Glennan, 2002
- Bechtel and Abrahamsen, 2005
  - “A mechanism is a structure performing a function in virtue of its component parts, component operations, and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena.”
- Woodward, 2002



# The ‘New Mechanistic Philosophy’

- Machamer, Darden and Craver, 2000
- Glennan, 2002
- Bechtel and Abrahamsen, 2005
- Woodward, 2002
  - “...a necessary condition for a representation to be an acceptable model of a mechanism is that the representation (i) describe an organized or structured set of parts or components, where (ii) the behaviour of each component is described by a generalization that is invariant under intervention, and where (iii) the generalizations governing each component are also independently changeable, and where (iv) the representation allows us to see how, in virtue of (i), (ii) and (iii), the overall output of the mechanism will vary under manipulation of the input to each component and changes in the components themselves.”

## Consensus features of mechanisms

- Organisation of elements
- Interaction of upstream effects with downstream elements
- Regular output-input relationship

# Mechanisms for medicine

- Philosophical mechanisms often don't capture the richness and complexity of medical mechanisms
- I'd suggest that a degree of extension, along the following lines, is required
  - Ability to innately encompass probabilistic information
  - Ability to describe and explain type/token causal problems
  - Ability to differentiate important causal factors from background conditions

# Salmon's Statistical Relevance and statistical evidence

[Salmon, 1971: 42]

- For an event  $x$  where we wish to find the probability it has attribute  $B$ :
  - Assign  $x$  to a reference class  $A$
  - Partition  $A$  by property  $C$
  - $C$  is statistically relevant to  $B$  in  $A$  iff:  
$$P(A.C,B) \neq P(A.B)$$

# The Reference Class Rule

[Salmon, 1971: 43]

“Choose the broadest homogeneous reference class to which the single event belongs”

# Homogeneity and Statistical Relevance

[Salmon, 1971: 43]

“A reference class is homogeneous if there is no way, even in principle, to effect a statistically relevant partition without already knowing which elements have the attributes in question, and which do not”

# Epistemic Homogeneity

[Salmon, 1971: 44]

“When we know or suspect that a reference class is not homogeneous, but we do not know how to make any statistically relevant partition, we may say that the reference class is epistemically homogeneous.”

# Interaction between mechanism and statistics

- Bidirectional
- Reflected in nature of research programmes



## Interaction: From mechanism to statistics

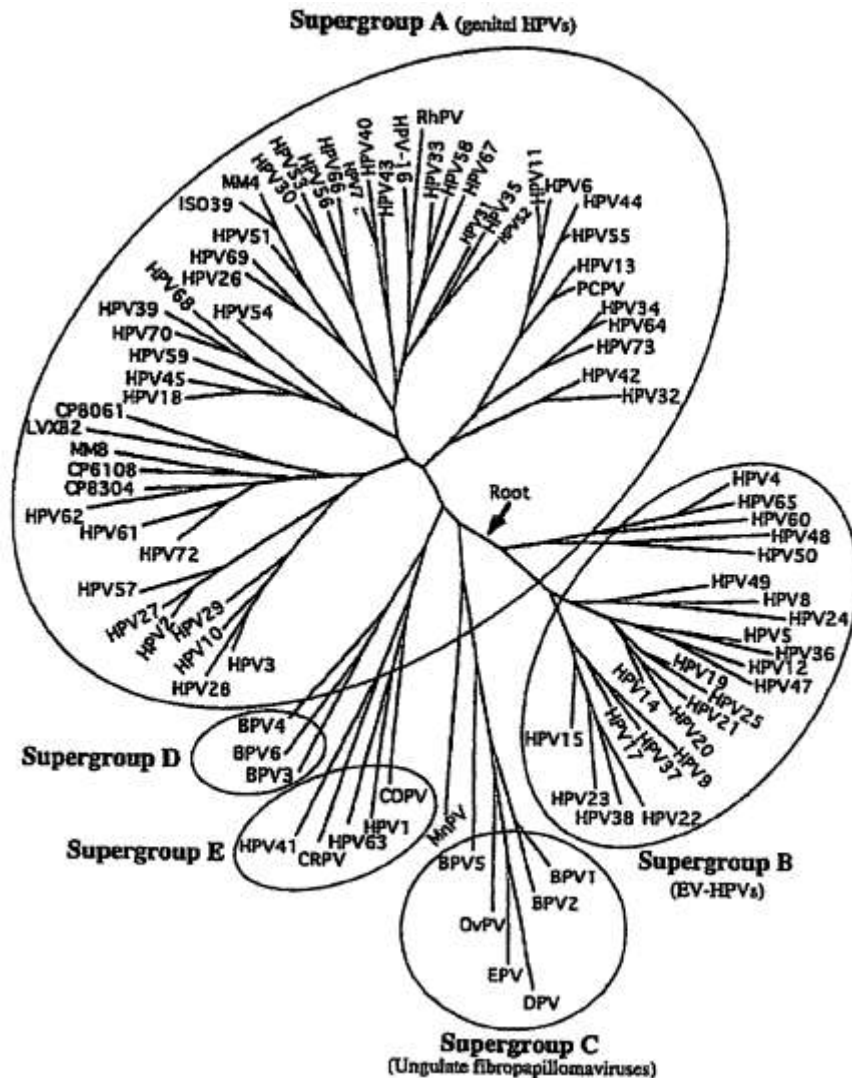
- Mechanisms give us grounds to epistemically partition our data
- Thus, features arising from mechanistic inquiry suggest the direction that statistical work should take
- Help with confounding

## Interaction: From statistics to mechanism

- In turn, statistical results inform us of the applicability of our mechanisms
- For instance, is a (mechanistically discovered) aetiological pathway clinically significant for disease causation?

# Example - Causation of cervical cancer

# HPV and cervical cancer [Lowy and Howley, 2001: 2232]



- Caused by infection with the human papillomavirus (HPV)
- Complex biology:
  - More than 110 types identified with varying propensity to cause cervical cancer
  - High-risk types
    - **16, 18, 31, 45**

# The history of cervical cancer causation: 3 phases

- Phase 1 (up to 1966)
  - Largely epidemiological identification of risk factors
- Phase 2 (1966—83)
  - Causation by herpes simplex virus (HSV)
- Phase 3 (1987 onward)
  - Causation by HPV

## Phase 1: Epidemiological risk factors

- Non-specific, complex, interrelated sociobiological modifiers of cervical cancer risk
- No consensus about causation or correlation
- Causal claims often characterised by reliance on plausibility

## Phase 2: Causation by HSV

- Identification of a possibly viral aetiology of cervical cancer
- Suggestion that the causal virus is HSV, largely by analogy with properties of other herpesviridae
- Alteration of research methodology
- Generation of evidence linking HSV and cervical cancer

## Phase 2: Evidence for herpes simplex virus as cause of cervical cancer

[Alexander, 1973: 1486]

1. HSV is a commensal organism
2. HSV is transmitted venerally
3. HSV is compatible with known risk factors, including:
  1. First coitus at early age
  2. Multiple sexual partners or promiscuity
  3. Low socioeconomic status
4. Herpes viruses are implicated in similar disease states
5. HSV is recoverable from some tumour cells



## Phase 2: Herpesviridae cause many tumours

Name	Disease
Epstein-Barr virus (HHV-4)	Burkitt's lymphoma
	Nasopharyngeal carcinoma
	Various leukaemias and lymphomas
Kaposi's sarcoma virus (HHV-8)	Kaposi's sarcoma
	Abdominal cavity B-cell lymphoma / Primary effusion lymphoma
	Multicentric Castleman's disease
Gallid herpesvirus 2 (GaHV-2)	Marek's disease (chickens)
Saimiriine herpesvirus type 2 (HVS-2)	Transmissible tumours in new world monkeys
Herpesvirus ateles type 1 (HVA-1)	T-cell lymphomas in new world monkeys
Ranid herpesvirus 1 (RaHV-1)	Lucké renal adenocarcinoma (Northern leopard frog)

## Phase 2: So what's the problem?

- Apparently strong evidence connecting HSV and cervical cancer
- But HSV is not now considered the cause of cervical cancer. Why was this research on HSV faulty?
  - Reliance on plausibility, especially linking HSV-oncogenesis with other herpesviridae
  - Result: problematic parts of mechanism remained uninvestigated statistically, leading to unreliable mechanism of pathogenesis
  - No integration between types of evidence

## From phase 2 to phase 3

[Dürst et al, 1983; Vonka et al, 1987]

- Development of molecular techniques for detecting DNA changed the understanding of mechanism dramatically
  - Failure of detection of HSV DNA in cervical cancer
  - Improvements in detecting multiple strains of HPV
- This mechanistic development lead to study of the oncogenic potential of papillomaviruses in populations
  - Detection of HPV DNA in some cervical cancers
- This in turn lead to mechanistic investigation of the role of co-factors, confounders, risk factors and so on

## Getting back to causation...

- Development of a conjoint research programme
- Trigger: search for a specific aetiology and consequent interpretive framework
- Integration of laboratory and epidemiological investigation
- Recursive process:
  - laboratory work guides epidemiology
  - epidemiology guides laboratory work
- Production of interdependent mechanistic and statistical evidence
  - Russo and Williamson [2007] and extensions...

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