Mechanisms, Drug Safety and Varied Evidence

Jürgen Landes

Mechanisms in Medicine

Canterbury
5 July 2017

Preface

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- Please ask.
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- On six occasions, the family doctor says: "Paracetamol causes asthma".
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- You get prescriptions for Ibuprofen.

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Me and my Kid

Me and 6 Doctors

- Imagine my kid, which has all sorts of different conditions.
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- On the basis of only this information:
- who is more convinced that “Paracetamol causes asthma” is true?
- You or me?
- Show of hands: Who in this room thinks that s/he is more convinced than me?
- Very good.

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Basic Intuition

- Strong shared intuition that “varied” (“diverse”) evidence confirms more strongly than “narrow” evidence.
- Ceteris paribus.
- In a vacuum.
- Literature agrees, [Hempel, 1966, Horwich, 1982, Earman, 1992, Claveau, 2013] ...
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- Even worse: No convincing Bayesian analysis of the Variety of Evidence Thesis on the market.

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- Model scientific inference within the Bovens & Hartmann approach.
- Explicate notion of varied evidence.
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A Formal Model of Inference

- Hypothesis variable *H*, “Paracetamol causes asthma”.
- Indicator variables *IND*, indicating truth of *H*.
- Evidence variables *E* pertaining to the indicators.
- Bayesian probabilities – Bayesian network.
- [Landes et al., 2017] along Bradford Hill Guidelines.
- We: BN for representing Bayesian belief in *H*.
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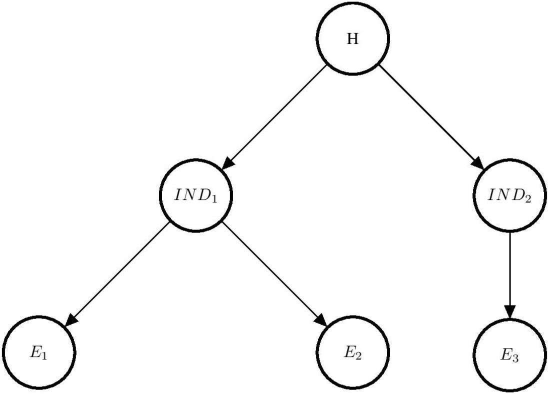

Outline

An Explication of Varied Evidence

- Let $|Ind|$ denote the number of children of variable *IND*.
- Measure for Variety of Evidence

$$Var(\mathcal{E}) := -\sum_{i=1}^{n} |IND_i| \cdot \log(|IND_i|) \quad . \tag{1}$$

- Shannon Entropy of $\langle |IND_1|, |IND_2|, \ldots, |IND_n| \rangle$.
- This captures *one natural* sense of variety.
- Yes, there are other senses, too.

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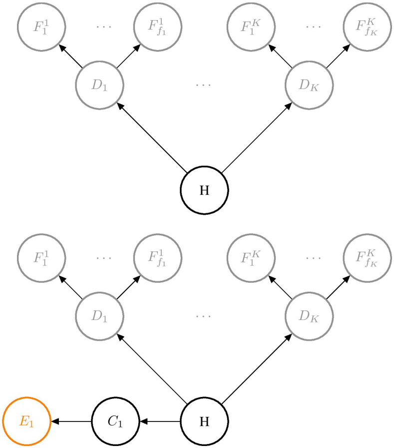
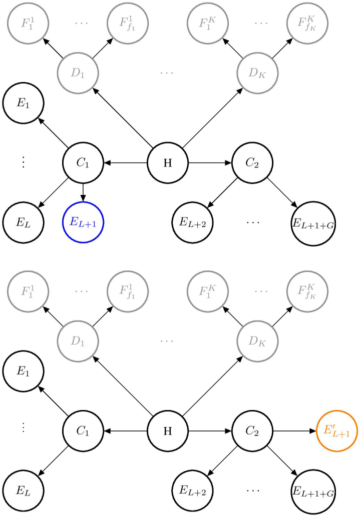


Instance 2 – Adoption



The Bare Minimum

- Other reasonable measures of variety should also declare the bottom situations to be more varied.
- For reasonable priors and ceteris paribus conditions, it should hold that:
  1. $P_{\mathcal{E}}(H) < P_{\mathcal{E}'}(H)$, in Instance 1.
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- Indicators are equally likely, given hypothesis variable: $P(Ind_1|H) = P(Ind_2|H) \approx 1$ and $P(Ind_1|\bar{H}) = P(Ind_2|\bar{H})$.
- For drug induced harms, we rarely have very good RCTs, so evidence for probabilistic dependence and mechanistic evidence become crucial.
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Instances of the Variety of Evidence Thesis

Theorem

$P_{\mathcal{E}}(H) < P_{\mathcal{E}'}(H)$, *in Instance 1.*
$P_{\mathcal{E}}(H) < P_{\mathcal{E}'}(H)$, *in Instance 2.*

Upper Bound for Confirmation

Corollary

There comes a point in life when investigating the exact same consequence yet again cannot provide significant further confirmation for the hypothesis of interest.

If $E_1, \ldots, E_{|Ind|}$ *are the children of Ind, then for all possible measurements* $E_1 = e_1, \ldots, E_{|Ind|} = e_{|Ind|}$

$$P(Hyp|e_1 \ldots e_{|C_1|}\vec{f}) < P(Hyp|c_1\vec{f}) = \frac{1}{1 + \frac{P(\bar{Hyp}) \cdot P(c_1|\bar{Hyp}) \cdot P(\vec{f}|\bar{Hyp})}{P(Hyp) \cdot P(c_1|Hyp) \cdot P(\vec{f}|Hyp)}} < 1.$$

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Variety of Evidence Thesis

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Russo-Williamson Thesis

- According to the RWT: We need evidence for probabilistic dependence and a mechanism in order to establish a causal hypothesis.
- If(!) establishing means large enough Bayesian degree of belief [John agrees, what about Jon?],
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All Roads lead to ...

- Opponents of the RWT may deny – among other things – the ceteris paribus condition on the prior.
- Indicators are equally likely, given hypothesis variable: $P(PD|H) = P(M|H) \approx 1$ and $P(PD|\bar{H}) = P(M|\bar{H})$.
- Problem of the prior.
- If only we could solve the problem of the prior...
- If only there was an epistemology which put forward stronger constraints on rational belief solving the problem of the prior.
- Good thing we are in Kent!

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For the Record

- Models also pronounce on discordant and dis-confirmatory evidence.
- Rightly, I argue.
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Ceteris Paribus Conditions

Network Topology	Condition A
Confirmatory Evidence	$P(e_1\|c_1) > P(e_1\|\bar{c}_1)$

Network Topology	Condition B
Confirmatory Evidence	$P(e_{\|C_1\|}\|c_1) > P(e_{\|C_1\|}\|\bar{c}_1)$ $\prod_{l=\|C_2\|+1}^{\|C_1\|-1} P(e_l\|c_1) > \prod_{l=\|C_2\|+1}^{\|C_1\|-1} P(e_l\|\bar{c}_1)$ $\chi_{11} \cdot \chi_{21} \geq \chi_{10} \cdot \chi_{20}$
Ceteris Paribus	$P(e_{\|C_1\|}\|c_1) = P(e'_{\|C_1\|}\|c_2)$ $P(e_{\|C_1\|}\|\bar{c}_1) = P(e'_{\|C_1\|}\|\bar{c}_2)$ $P(c_1\|h) = P(c_2\|h)$ $P(c_1\|\bar{h}) = P(c_2\|\bar{h})$
Paring Off	$\prod_{n=1}^{\|C_2\|} \frac{P(e_n\|c_1)}{P(e_n\|\bar{c}_1)} = \frac{\chi_{21}}{\chi_{20}}$

$$\chi_{1s} := \prod_{n=1}^{|C_1|-1} P(e_n|c_1^s) \quad \text{and} \quad \chi_{2s} := \prod_{g=1}^{|C_2|} P(e_{|C_1|+g}|c_2^s) \ .$$

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