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Human gut microbiome research: what are the benefits of the mechanistic causal account?



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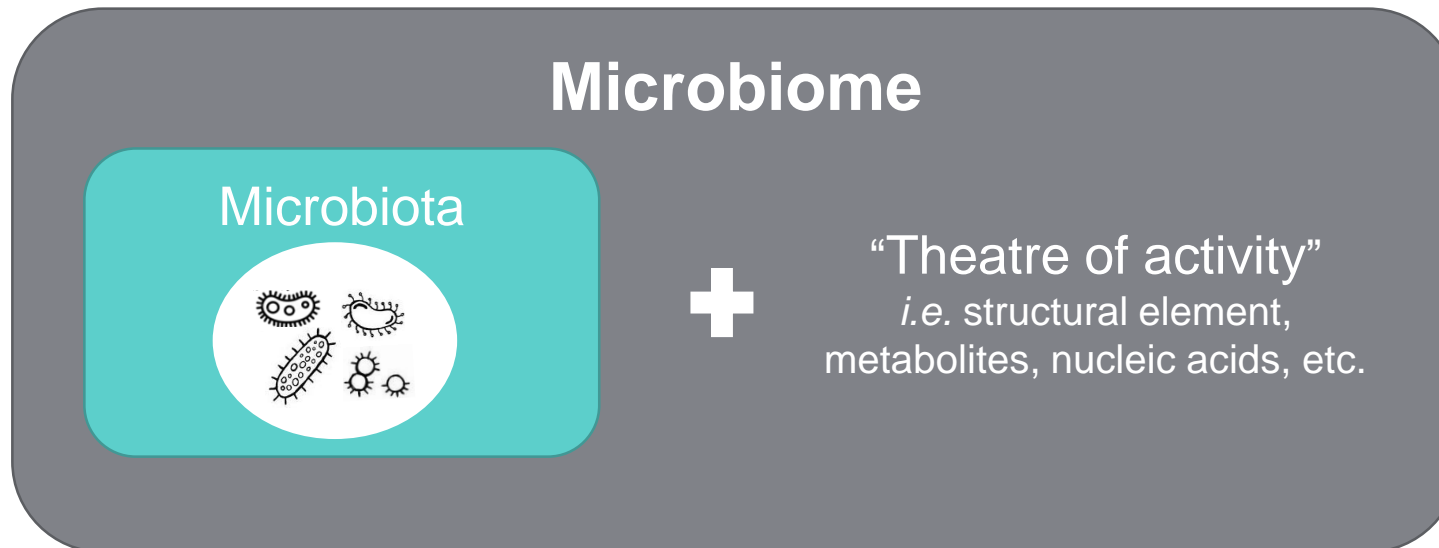
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Aims

1. I argue that the interventionist and mechanistic causal frameworks underlie two distinct historical approaches to microbiology.
2. Human gut microbiome research is at the intersection of this history and mechanisms play a role in the causal explanations in this field.
3. I study the consequences for science and for philosophy of focusing only on the interventionist framework of causal explanation in this domain.

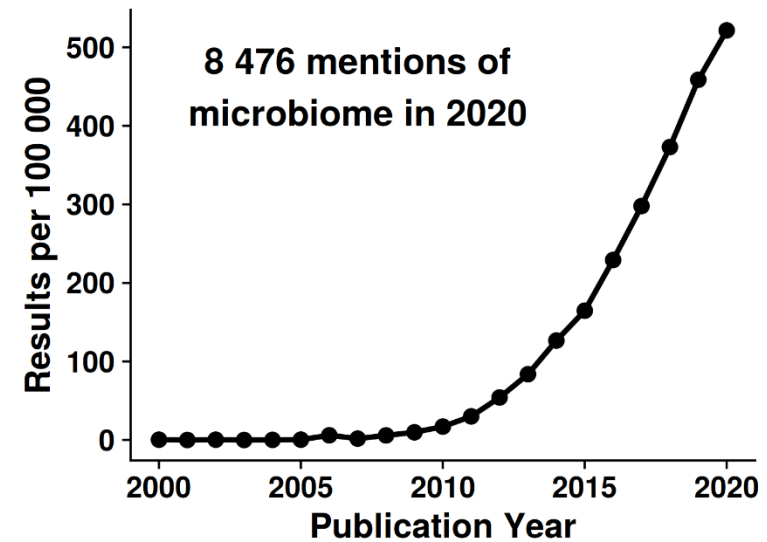
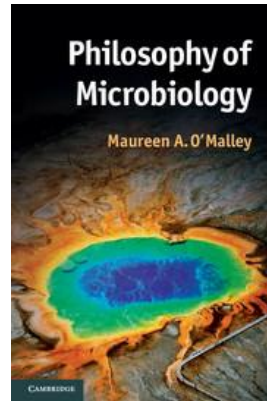
Introduction

- The definition of “microbiome” is difficult, however, a recent attempt for consensus has been published. Here, the microbiome is **the microbiota** – the microorganisms and their “**theatre of activity**” – all their activities and metabolites (Berg et al. 2020).



Introduction

- Microbiomes' studies are a growing research field
 - in science
 - & in philosophy



Based on PubMed titles and abstracts from 2000 to 2020



A recent microbiology topic of growing interest for philosophers is microbiome research, which examines all the microbial communities living in host organisms. In humans, the gut microbiome in particular is associated with many health and disease states experienced by the host, including mental health. There are two foci of philosophical attention given to these heterogeneous microbial consortia in host systems, namely individuality (e.g., Skillings 2016) and causality, specifically the causal role large mixed communities of microbes might play in host health (Lynch et al. 2019).




Introduction

- Human gut microbiomes have been associated with various healthy and diseased human phenotypes.
- This has led philosophers to investigate **causal relationships** within these studies in order to 1) examine whether it occurs and 2) if so, in what form and 3) again if so, what kind of refinement of our philosophical causal theories they may bring.
- In particular, recent philosophical work focuses on **an interventionist causal framework** to investigate 1).
- **Interventionist analysis of Koch's postulates**
⇒ The interventionist causal framework is the only good framework for analysing causal relationships in human gut microbiome research.

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How causal are microbiomes? A comparison with the *Helicobacter pylori* explanation of ulcers

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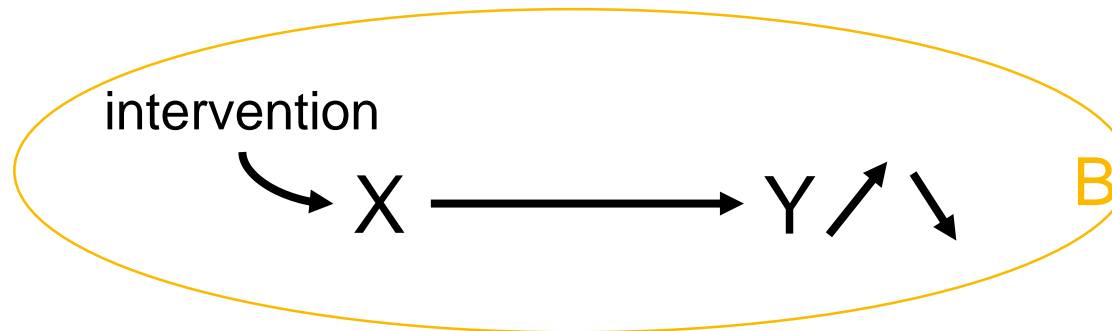
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Two distinct causal frameworks underlying two different historical approaches to microbiology

- I argue, instead, that there are two distinct causal frameworks underlying two different historical approaches to microbiology:
 1. The interventionist framework, based on a reinterpretation of Koch's postulates, was traditionally found in medical microbiology.
 2. The mechanistic or functional framework was traditionally found in ecological microbiology.
 3. Therefore, two distinct causal frameworks can be identified as underlying two distinct approaches of microbiology.

Two distinct causal frameworks underlying two different historical approaches to microbiology

- A causal relationship in the interventionist account is:

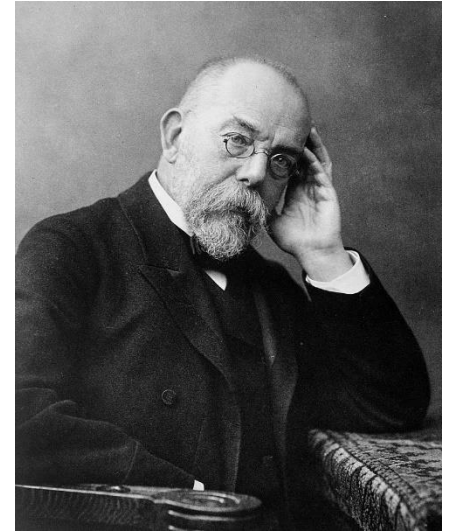


“X causes Y if and only if there are background circumstances B such that if some (single) intervention that changes the value of X (and no other variable) were to occur in B, then Y or the probability distribution of Y would change” (Woodward, 2010, 290).

Woodward, J. (2010). Causation in biology: stability, specificity, and the choice of levels of explanation. *Biology and Philosophy*, 25:287–318. doi:10.1007/s10539-010-9200-z

Two distinct causal frameworks underlying two different historical approaches to microbiology

- **Koch's postulates** (Caumette et al. 2015, 13 and Lynch et al. 2019, 2):
 - i. The microorganism suspected is present in all sick hosts.
 - ii. The microorganism is not present in other diseases or non pathogenically.
 - iii. After being fully isolated in pure culture, the microorganism can infect healthy hosts in producing the classic symptoms of the disease.



⇒ Interventionist flavour

- That does not mean that intervention is all there is in the Koch's postulates but that it is a good approximation of what causality means for this branch of microbiology.
- I will call this branch, **the “medical viewpoint” on microbiology**

Caumette, P., Bertrand, J.-C., & Normand, P. (2015). Some Historical Elements of Microbial Ecology. In *Environmental Microbiology: Fundamentals and Applications* (pp. 9-24).

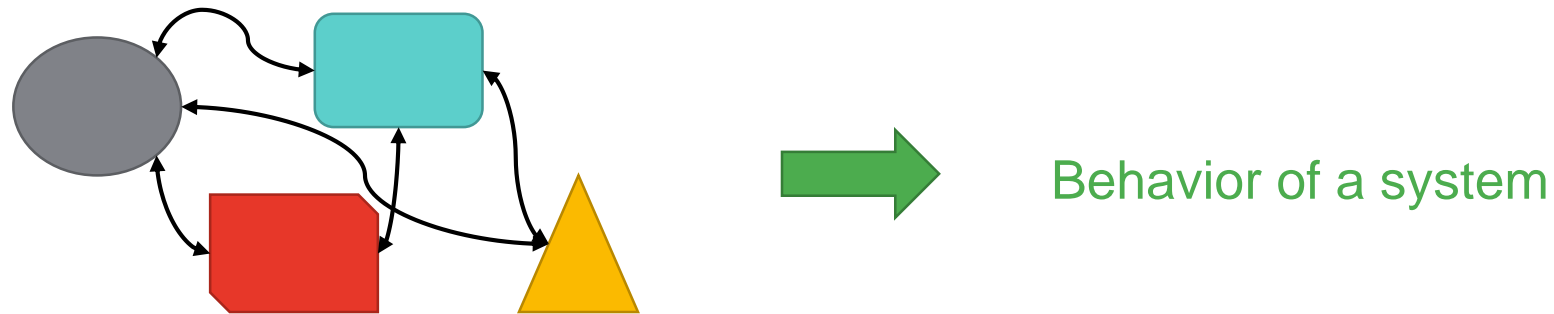
Lynch, K. E., Parke, E. C., & O'Malley, M. A. (2019). How causal are microbiomes? A comparison with the *Helicobacter pylori* explanation of ulcers. *Biology and Philosophy*, 34(62), 1–24. doi:10.1007/s10539-019-9702-2

Two distinct causal frameworks underlying two different historical approaches to microbiology

- A causal relationship in the mechanistic framework is:

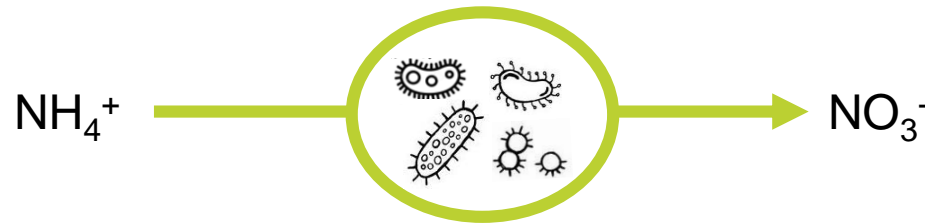
“Two events are causally connected when and only when there is a mechanism connecting them”
(Glennan, 1996, 64)

“A mechanism underlying a behavior is a complex system which produces that behavior by the interaction of a number of parts according to direct causal law” (Glennan, 1996, 52)



Two distinct causal frameworks underlying two different historical approaches to microbiology

- Winogradsky is one of the **founders of microbial ecology** and he studied the capacities of soil **microorganism communities**.
- He made discoveries on **the nitrification cycle** in the soil and in particular on the transformation of ammonia into nitrates.



- The microbiome can be decomposed **into parts** – microorganisms – that **interact** with each other – by transforming chemical compounds into others.

⇒ **Mechanistic flavour** even if scientists in this branch speak about “**functions**”.

⇒ No emphasis on specificity.

- I will call this branch, **the “ecological viewpoint” on microbiology**

Two distinct causal frameworks underlying two different historical approaches to microbiology

- Koch's postulates are the **beginning of microbiology**.
- The history of microbiology is also an **ecological history**: 1) microorganisms are not only pathogens and 2) the whole community is seen as having capacities.
- **Conclusion**: Two distinct causal frameworks – the interventionist and the mechanistic – underlie two different historical approaches to microbiology – one medical and the other ecological.

Mechanisms play a role in the causal explanation of human gut microbiomes

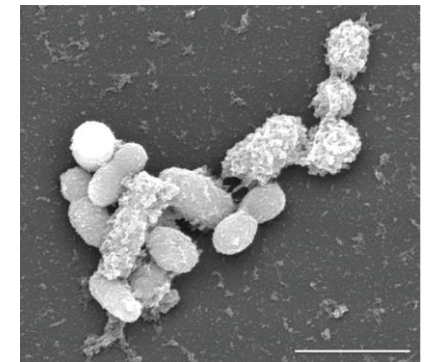
- I argue that scientists value the mechanistic causal explanation.
 1. I identify two main camps in the scientific literature concerning human gut microbiome research, inherited from the history of microbiology.
 2. Therefore, current research on the human gut microbiome is at the crossroads of medical and ecological microbiology.
 3. I show that both camps rely (at least partially) on mechanisms in their causal explanation.
 4. Therefore, the mechanistic causal framework has a place in the analysis of the causal claims of human gut microbiome research.

Mechanisms play a role in the causal explanation of human gut microbiomes.

- The medical viewpoint on microbiology is still present in the first camp of human gut microbiome research.
- **Microorganisms are first isolated** from the human gut microbiome and **their effects** are examined *in vitro* and *in vivo*.
- The main objective is to produce a **probiotic** – a microorganism with interesting properties for human health.
- *In vivo* studies can be seen as **an intervention**, e.g. by feeding the microorganism to mice in order to improve the phenotype of a disease.
- However, the **causal relationship** between the microorganism and the phenotype is **strengthened when a mechanism** is known or at least hypothesized.

Mechanisms play a role in the causal explanation of human gut microbiomes.

- Example: *Akkermansia muciniphila*
- *In vivo* effect (mice and human): reduction of obesity phenotype
- Mechanism: The bacteria decrease the permeability of the gut barrier, which in turn decreases inflammation, which ultimately leads to better control of fat storage, glucose metabolism and energy expenditure.
- A “landmark discovery” is **the mechanism by which the bacteria reduce the permeability of the intestinal barrier**: The bacteria are able to bind the cells of the human intestine.
- Key questions remain, which have both interventionist and mechanistic flavours:
 - “What are the signaling mechanisms by which *A. muciniphila* interacts with human and other hosts?”
 - “Can delivery of *A. muciniphila* alone or in combination with other microbes be used in therapies to increase barrier function, reduce inflammation and cure diseases?”



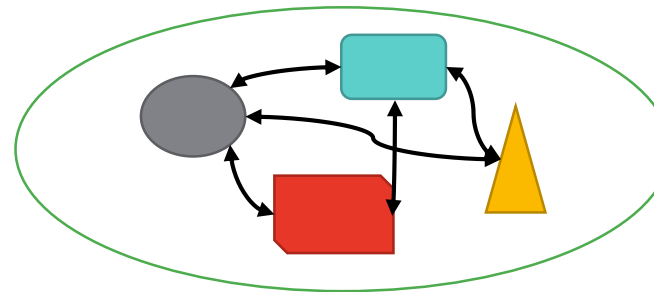
de Vos, W. (2017), Microbe Profile: Akkermansia muciniphila: a conserved intestinal symbiont that acts as the gatekeeper of our mucosa , *Microbiology*, 163:646–648. Doi:10.1099/mic.0.000444

Mechanisms play a role in the causal explanation of human gut microbiomes.

- The ecological viewpoint on microbiology is still present in the second camp of human gut microbiome research.
- It explores the role – understanding **the various capacities** – that **the microbiome**, as a whole, can display in healthy and diseased phenotypes.
- The strategy is then to discover the composition and functions displayed by the components of the microbiome.
- Functions here generally refer to biochemical activities involving several intermediates. The function of the parts (either the microorganisms or the metabolites) is supposed to participate in and **explain the capacity of the microbiome**.
- This camp is based on a **functional analysis of the microbiome**.

Mechanisms play a role in the causal explanation of human gut microbiomes.

- O'Malley has argued that these “functions” could be understood in the “Cummins causal-role sense” (O'Malley, 2014, 147)
- A function of a part of a containing system, is **the capacity displayed by this part that participates in the realisation of the analysed capacity of the containing system** (Cummins, 1975, 762).



Containing System
Display several capacities

- The **mechanistic framework** developed by Glennan is **very close to the functional analysis** proposed by Cummins (Glennan, 1996 and 2002).
- **“function” here can be understood as a mechanism.**

O'Malley, M. (2014), *Philosophy of Microbiology*. Cambridge: Cambridge University Press. doi:10.1017/CBO9781139162524

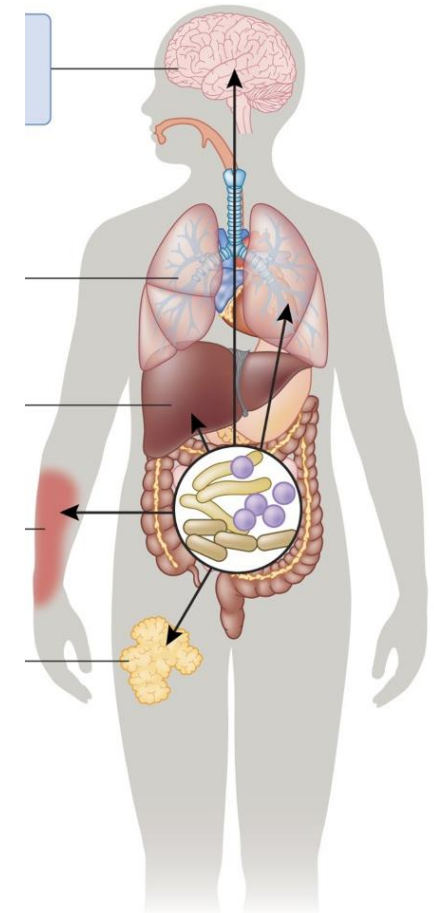
Cummins, R. (1975). Functional Analysis. *The Journal of Philosophy*. 72:741-765. doi:10.2307/2024640

Glennan, S. (1996). Mechanisms and the Nature of Causation. *Erkenntnis*. 44:49-71. doi:10.1007/BF00172853

Glennan, S. (2002). Contextual Unanimity and the Units of Selection Problem. *Philosophy of Science*. 69:118-137. doi:10.1086/338944

Mechanisms play a role in the causal explanation of human gut microbiomes.

- Example: The “host-microbiome” system is a containing system.
 - What are the capacities of this system? E.g. **Health**
 - What are the functions of the parts – or **the mechanism**? E.g. The host ingests food that reaches the microbiome, which takes the energy from the food and delivers it to the host.
 - That does not mean that this mechanism is sufficient for the capacity to appear.
 - **The parts of the containing system may themselves be containing systems that can be decomposed.**
- ⇒ Different levels of analysis can be made.



Debbie Maizels/Nature Publishing Group

Lee, C., Sears, C. & Maruthur, N (2020). Gut microbiome and its role in obesity and insulin resistance. *Ann N Y Acad Sci.* Feb;1461(1):37-52. doi:10.1111/nyas.14107.
Schroeder, B., Bäckhed, F (2016). Signals from the gut microbiota to distant organs in physiology and disease. *Nat Med* 22, 1079–1089. doi:10.1038/nm.4185

Mechanisms play a role in the causal explanation of human gut microbiomes

- **Conclusion:**
 - **The mechanistic analysis is valuable in both camps of scientists**
 - Thus, to assess whether the microbiome is causal in current research, the mechanistic framework can also be used.

Consequences of focusing only on the interventionist framework of causal explanation

- The argument is as follows:
 1. Current philosophical analysis of causality in human gut research focuses on the interventionist causal framework.
 2. I see at least three consequences:
 - i. Methodological and explanatory reductionism
 - ii. Focus on proximal causes
 - iii. Missing the opportunity to learn about causality
 3. I suggest some advantages of considering the mechanistic causal framework.

Consequences of focusing only on the interventionist framework of causal explanation

- Lynch et al. (2019):
 - **Assess whether causal claims about the human gut microbiome are actually causal**
 - The **interventionist causal framework** and in particular the **criteria** developed by Woodward (2010) for a **strong causal relationship within this framework**.
- Three criteria:
 - **Stability**: The extent to which the relationship between X and Y continues to hold under a range of other background circumstances (Woodward, 2010, 292).
 - **Proportionality**: The choice of the right level of explanation (neither too broad nor too narrow) is an empirical question that depends on the causal structure under investigation (Woodward, 2010, 297-8).
 - **Specificity**: The extent to which the relationship between X and Y is close to a one-to-one relationship. The fineness of the influence (Woodward, 2010, 301-8).

Lynch, K. E., Parke, E. C., & O'Malley, M. A. (2019). How causal are microbiomes? A comparison with the *Helicobacter pylori* explanation of ulcers. *Biology and Philosophy*, 34(62), 1–24. doi:10.1007/s10539-019-9702-2

Woodward, J. (2010). Causation in biology: stability, specificity, and the choice of levels of explanation. *Biology and Philosophy*, 25:287–318. doi:10.1007/s10539-010-9200-z

Consequences of focusing only on the interventionist framework of causal explanation

- Research on the human gut microbiome, so far, does not show **stable and specific relationships** between **the whole microbiome and its putative effects**, and **the proportionality of such explanations is often way too wide to be strong** (Lynch et al. 2019).
- ⇒ The **whole microbiome is not causal** in its so-called “effects”
- Advocate a **methodological and explanatory reduction to obtain a stronger causal explanation.**

Consequences of focusing only on the interventionist framework of causal explanation

- **Reduction can strengthen a causal relationship**, but is not advisable in all biological cases (Woodward, 2010, 317).
⇒ Why should it be the case in human gut microbiome research? Some advocates of methodological reduction e.g. Hanage (2014) and Fischbach (2018). But see Berg et al. (2020) advocating a holistic approach in both methods and explanation.
⇒ The choice should be based on **empirical considerations** (Woodward, 2010, 317)
- By reducing the method and explanation in human gut microbiome research, we should achieve more **stable and specific relationships** *i.e.* stronger causal relationships (Lynch et al. 2019).
⇒ It is not clear why such relationships should be **more valuable in this field**.

Berg, G., Rybakova, D., Fischer, D. *et al.* (2020). Microbiome definition re-visited: old concepts and new challenges. *Microbiome* 8, 103. Doi: 10.1186/s40168-020-00875-0

Fischbach, M. (2018). Microbiome: Focus on Causation and Mechanism. *Cell*. 174(4):785-790. doi: 10.1016/j.cell.2018.07.038

Hanage, W. Microbiology: Microbiome science needs a healthy dose of scepticism. *Nature* 512, 247–248 (2014). Doi: 10.1038/512247a

Woodward, J. (2010). Causation in biology: stability, specificity, and the choice of levels of explanation. *Biology and Philosophy*, 25:287–318. doi:10.1007/s10539-010-9200-z

Consequences of focusing only on the interventionist framework of causal explanation

- Focus on **proximal causes** to increase stability and specificity.
 - **Stable and specific relationships are better for intervention and control** (Woodward, 2010, 315).
- ⇒ Looking for proximal causes **doesn't always achieve this goal**: “It may be that specific stable control is achieved through the interaction of a number of different agents which taken individually have a much less stable and specific effect on the outcome of interest.” (Woodward, 2010, note 22, 315).
- We may **lack a more holistic view of the cause**, e.g. the diversity of the whole microbiome is hypothesised to be causal in both healthy and obese phenotypes (Jiao et al. 2018).

Jiao, N., Baker, S. S., Nugent, C. A. et al. (2018). Gut microbiome may contribute to insulin resistance and systemic inflammation in obese rodents: a meta-analysis. *Physiol Genomics*, 50: 244–254. doi: 10.1152/physiolgenomics.00114.2017
Woodward, J. (2010). Causation in biology: stability, specificity, and the choice of levels of explanation. *Biology and Philosophy*, 25:287–318. doi:10.1007/s10539-010-9200-z

Consequences of focusing only on the interventionist framework of causal explanation

- I argue that **in order to be able to focus on proximal causes, it may be useful to start with the more distal causes** to get clues as to where to look for the more proximal causes.
 - Examples:
 - Functional analysis: Looking at the distorted capacities of the microbiome between obese and healthy people. Then look for parts of the microbiome that have or contribute to this capacity.
 - FMT (Fecal Microbiota Transplant): If scientists had not had the idea that “the whole microbiome is causal”, they might never have tried it and would have missed a therapeutic solution (e.g. in the case of *Helicobacter pylori*.)

⇒ **Some therapeutic avenues can be discarded.**

- Amendment by Attah et al. (2020) recognizing that in some cases a coarse-grained, less specified explanation is preferable.

Consequences of focusing only on the interventionist framework of causal explanation

- Missing the opportunity to learn about causality:
- The history of microbiology suggests that **two distinct approaches are underlined by two distinct philosophical frameworks about causality.**
- Philosophers have, until now, emphasise one framework more than the other.
- This is a missed opportunity to learn about causal explanation in human gut microbiome research but also philosophically to learn about causality itself.

Consequences of focusing only on the interventionist framework of causal explanation

- Finally, here are some **advantages** of considering a **mechanistic causal framework**:
- No emphasis on specificity nor on stability, as long as **a mechanism connects the parts, then it is a causal relationship.**
 - Microbiomes have many components that interact with each other, reducing the relative importance of any particular mechanism or causal relationship to the behavior/capacity of the containing system.
- **The whole microbiome can be causal.** Therefore it or its capacities can be directly therapeutically targeted (as it is the case with FMT).
- This framework **does not preclude methodological or explanatory reductionism**: A part of a system may itself be a system to be decomposed and analysed, etc.

Conclusion

- The **mechanistic causal framework** has a place in the analysis of human gut microbiome causality because:
 - It is **consistent with the history of microbiology** even if it is **sometimes difficult to conciliate medical and ecological viewpoints**; interventionist and mechanistic frameworks.
 - It is **consistent with the current trend in human gut microbiome research**, with both camps using mechanistic-like frameworks to strengthen causal relationships.
 - It ensures that **a broader view is maintained, so that therapeutic avenues are not overlooked.**
 - It makes sense **for scientists to talk about the whole microbiome as a causal agent.**

Thank you for your attention

