ROTO Lecture Series

Microbiome foundations and faultlines through the lens of history and philosophy

Aline Potiron

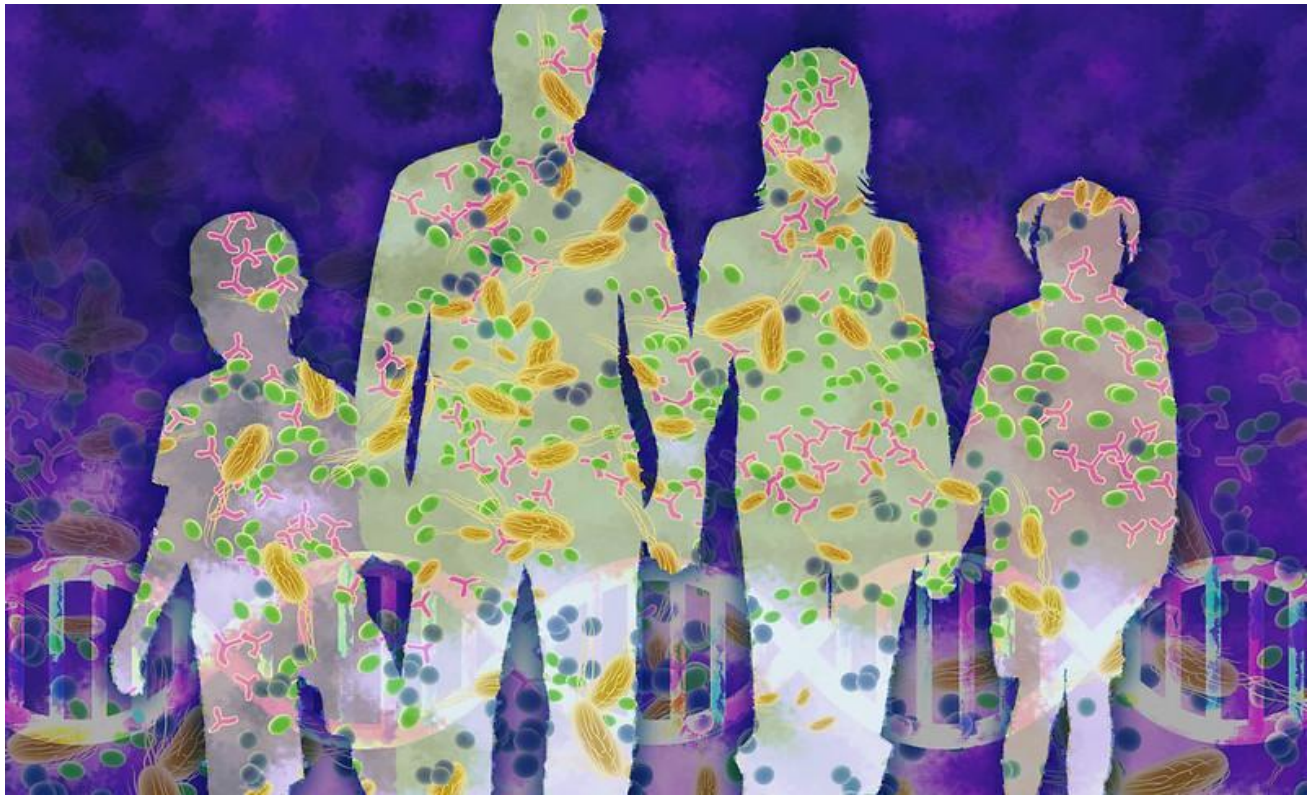
Utrecht University

Microorganisms

Image by Gerd Altmann from Pixabay

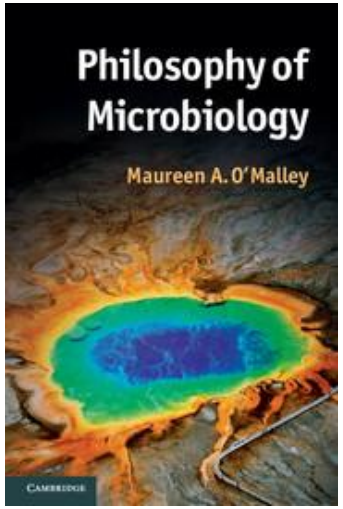
Gilbert and Neufeld 2014

Microbiome



Microbiology And Philosophy

- Philosophy of biology: species definition and delineation, evolutionary theory, the origin of life, etc.
- General philosophy of science: construction and use of models, issues related to causality
- Microbiome Research: Individuality issues, causality issues, ethical issues



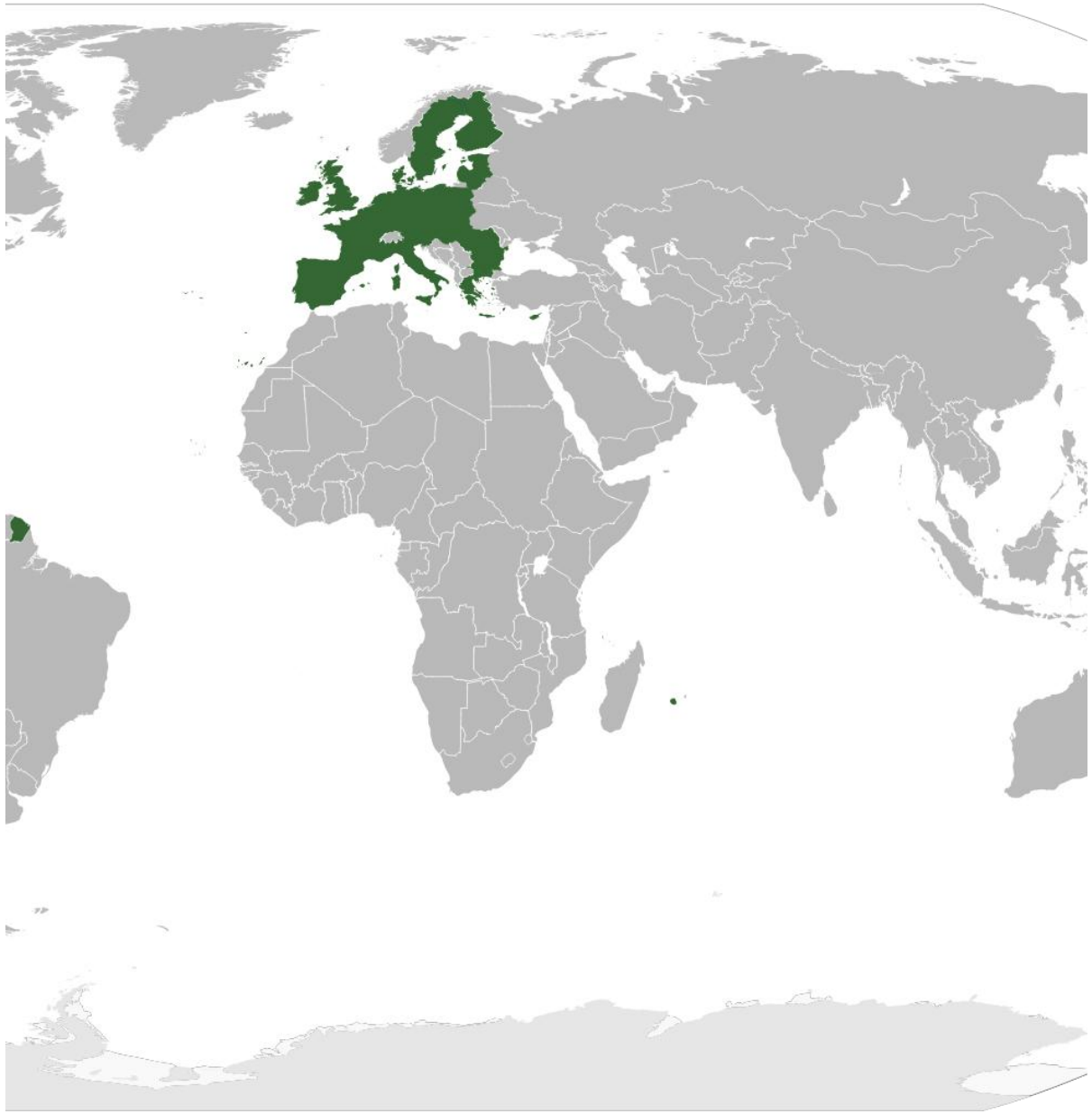
Microbiome foundations and faultlines through the lens of history and philosophy

- Build upon these efforts
- Practice-oriented approach to philosophy
- Rely on my background in microbiology
- *Work in progress*

Table of content

Positionality Statement

- Positionality: an individual's worldview and the stance they take in relation to research and its context (Holmes, 2020).
- White European woman who spent most of her professional life in Europe.
- Biases:
  - The “history” of microbiology I will present is European/Western-centered.
  - My vision and definition of race and my racial experiences are also biased, as I am part of one of the most privileged populations.

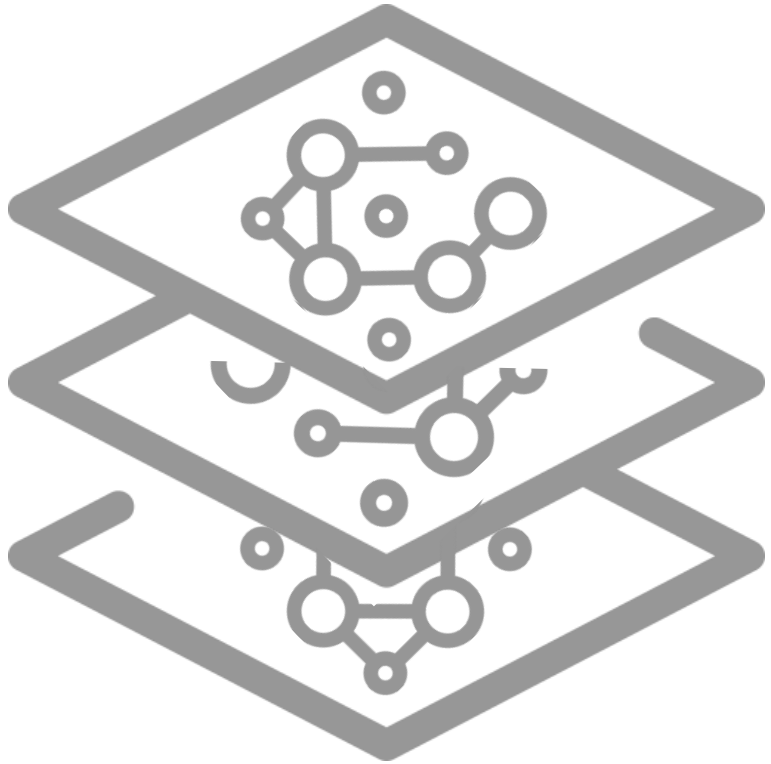


Unearthing the ecological roots of microbiome studies

Causal Inference in Microbiome Research

Tension between the need **for causal explanations** (health and disease phenotype) and the **complexity** of the microbiome.

How to understand causal claims? How to establish them? How to evaluate them?



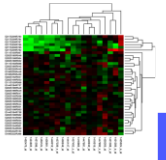
Understanding Causal Claims

Experimental Evidence

- Example: epidemiological studies using dietary interventions, RCTs, animal models called human microbiota-associated

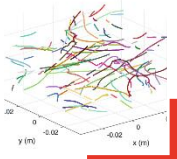
Evidence from Simulations

- Example: Mendelian randomization analysis, mediation analysis, potential-outcomes framework, etc.



Evidence of Mechanisms

- Example: longitudinal and prospective studies, measures of the expressions of host and bacterial genes, measures of the molecules produced by the intestinal tract, etc.



Evidence of Pathways

- Example: the tracking of molecules by using stable isotope probes

Fischbach 2018; Lv et al. 2021; Hanage 2014; Walter et al. 2020; Chaudhari et al. 2021; Maruvada et al. 2017; Hall et al. 2018

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State of the philosophical debate

Difference-making

- Historically grounded in Koch's postulates (Ross and Woodward, 2016, Lynch et al., 2019)
- Interventionism (Woodward, 2003; 2010)
- Well-studied in history, philosophy, and science
- **Normative aspect**: proportionality, stability, and specificity
- **Conclusion**: Causal claims linking the whole microbiome to disease are **weak, often misleading, and sometimes not causal** (Lynch et al., 2019)

"Functionalism(s)"

- Not historically grounded, but related to ecology
- Selected Effect (Klassen, 2020)
- Causal-role function (Schneider, 2020; 2023)
- Unclear as a normative account: it is not clear what will help scientists to get better causal explanations.
- **Conclusion**: Microbiomes are too complex to fully understand their interactions with the hosts.

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My contributions

1. Explain the current status of the discipline and the tensions within it using the history of microbiology
    1. Diverse methods are used to explore causal relationships
    2. Scientists often come from and use two different “perspectives”: medical and ecological
2. Better characterization of the “ecological perspective”
3. Propose an alternative causal framework to understand causal claims

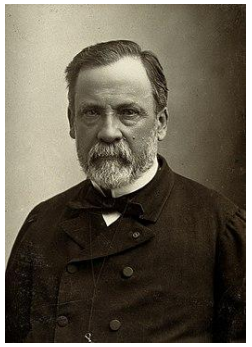
A Brief History of Microbiology

Ecological branch

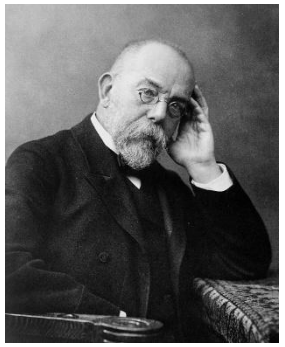
1st Observations 1670s

Ecology
Ernst Haëckel
1866

1870s
Pasteur/Tyndall
Germ theory



1880s
Koch postulates



Beijerinck/Winogradsky
1880s-1950

1930s
Fleming
Antibiotics

1990s
The earliest report of diversity in human gut microbiota using culture-independent methods (Suau et al., 1999)

Human Microbiome Project

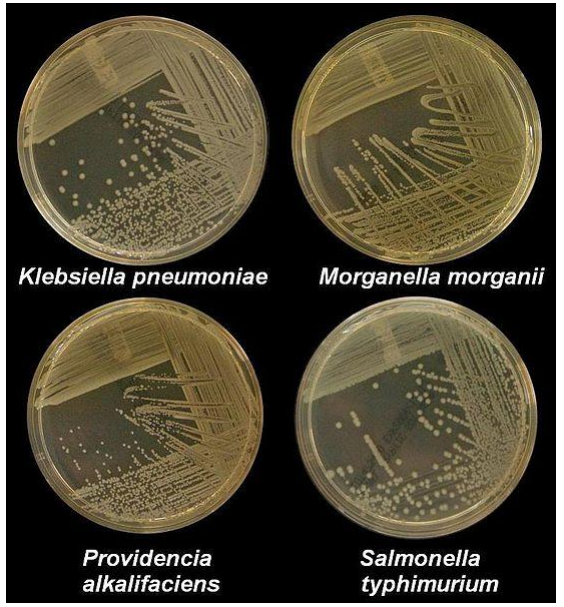
2000s

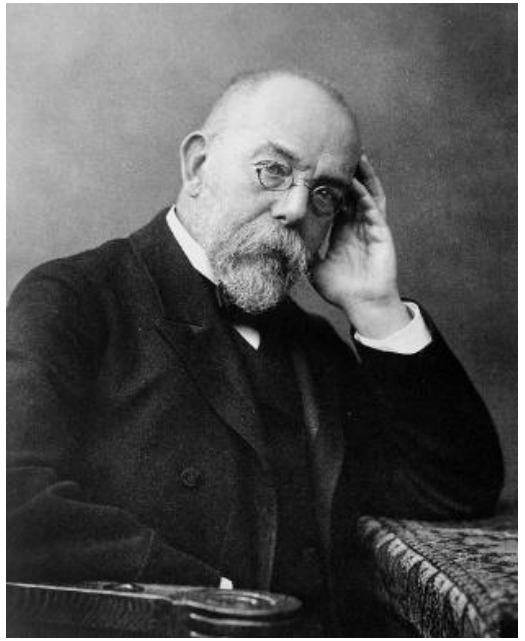
Medical branch

Caumette et al. 2015; Kolter 2021; O'Malley 2014

Medical Microbiology

- A methodological **reductionism** (e.g., pure culture)
- The assumption of **a simple causal architecture** (e.g., the germ theory of diseases)
- A clear separation between different causal elements (e.g., the host and the microorganisms)
- Incarnated by **the germ theory of diseases** and the **Koch's postulates**

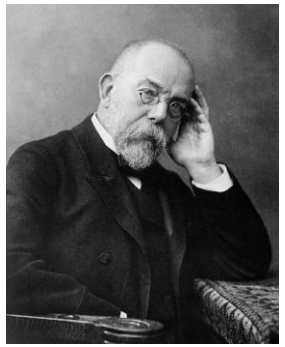




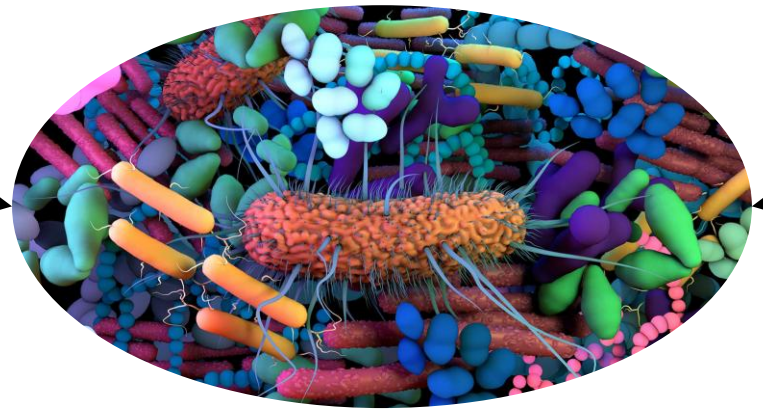
Carter 2003; Ross and Woodward 2016

NB: *Work in progress*
Medical "path", "perspective", or "worldviews"…

A Brief History of Microbiology



Mono-causal
Homogeneous
Interventionism



?

Microbial Ecology

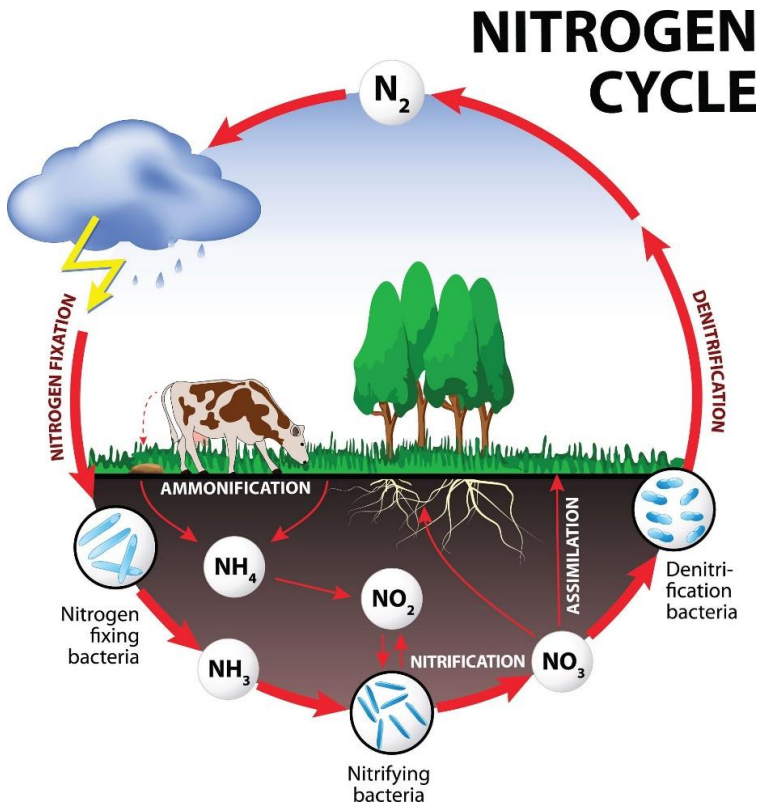
- Sergei Winogradsky: 1856-1953
- A collection of his work published in 1949 entitled Microbiologie du Sol: Problèmes et Méthodes (MS)

Explanans in Microbial Ecology

- What kind of phenomena?

"The search for living agents should always be preceded by knowledge of the phenomena taking place in the natural environment." (MS, 839).

- He is looking for **the flow of material or energy**.



Winogradsky, 1949

Methods in Microbial Ecology

- How to study soil phenomena?

"Studies limited to the physiology and biochemistry of microorganisms could never enlighten us as to the functioning of microflora, which should **not be considered as the sum of individual activities, but as the work of a self-regulating collective**." (MS, 847)

- He want to study **the system as a whole** because he is dubious about the transferability of results obtained in pure cultures

Winogradsky, 1949

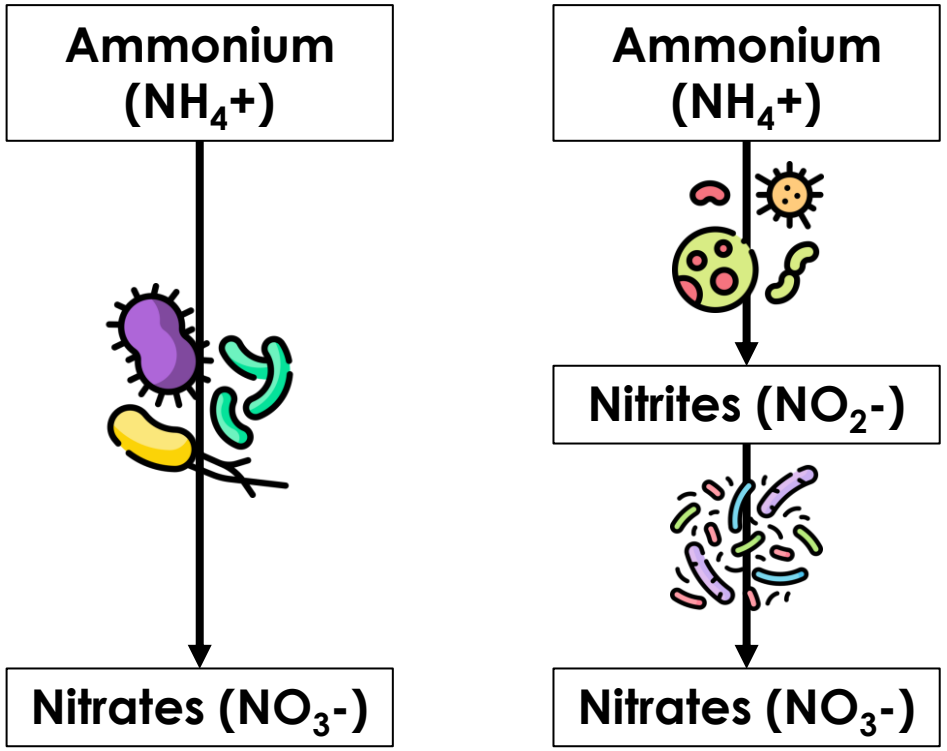
Winogradsky column

Explanandum in Microbial Ecology

- How are those phenomena explained?

"As a result of all the experiments, the conclusion that these are two autonomous functions, each exercised by its own ferment, appears necessary." (MS, 252).

- **Functions** – in a similar sense as Cummins' causal-role function.



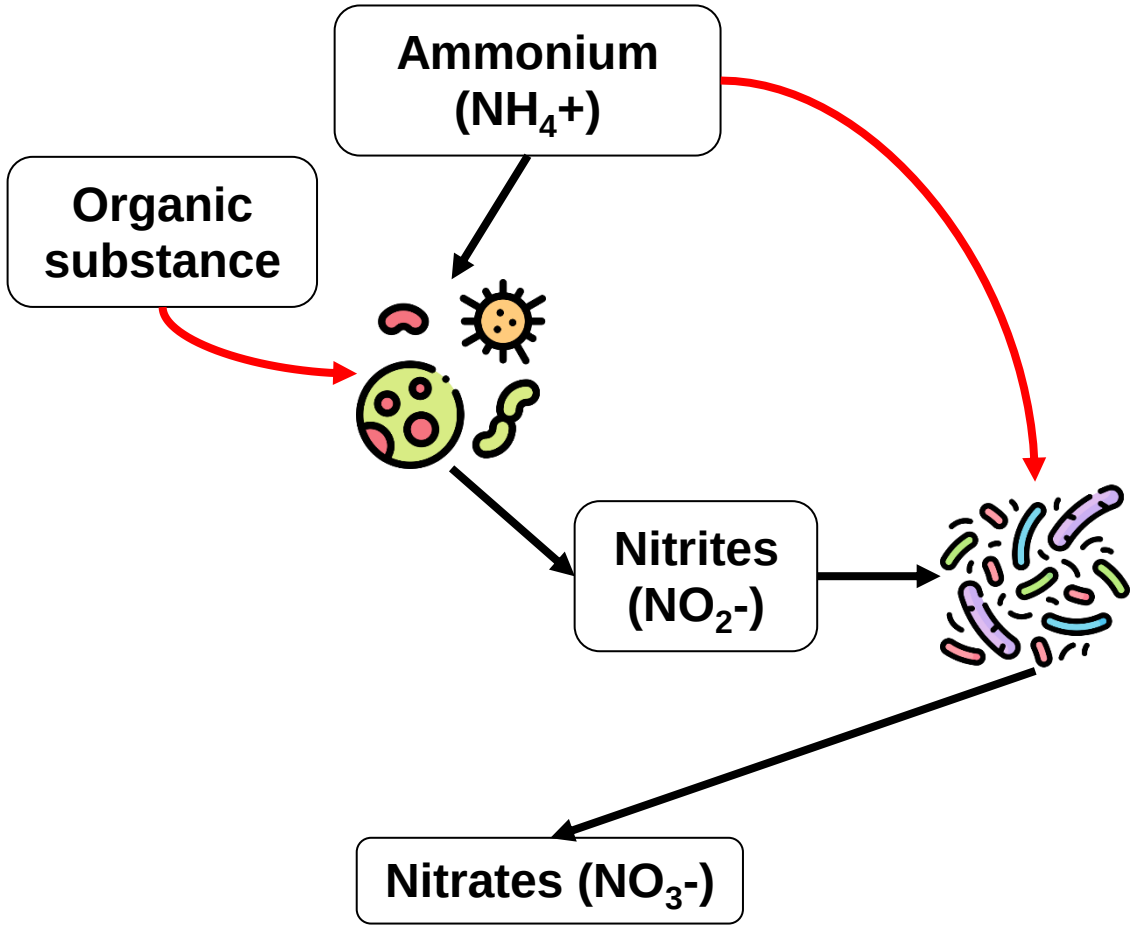
Winogradsky, 1949

Explanandum in Microbial Ecology

- How are those phenomena explained?

"1) the nitrification always leads to the disappearance of all traces of ammonia; 2) it always starts by the production of nitrite that remains stable, as long as the ammonia is present in the soil; 3) it is only when the nitrification stops lacking ammonia, that the nitration starts, leading to the complete oxidation of nitrous ammonium." (MS, 251).

- **Dynamic processes**



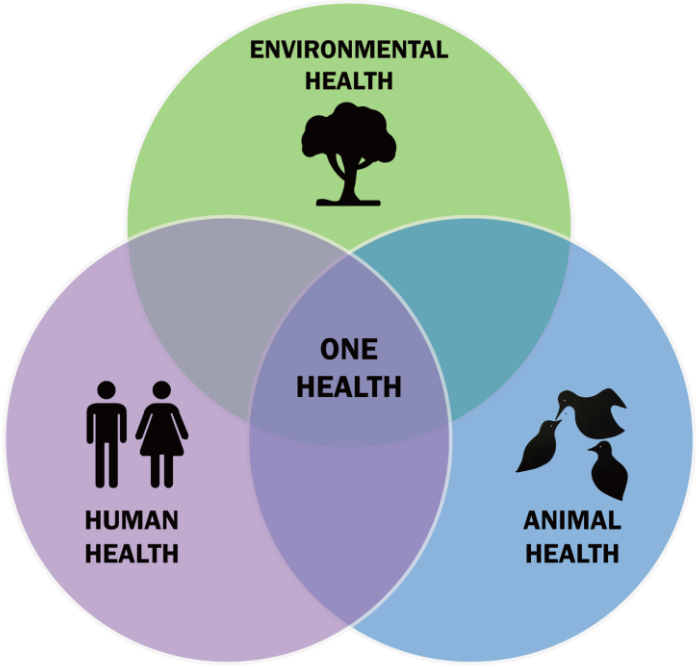
Winogradsky, 1949

My contributions

1. Explain the current status of the discipline and the tensions within it using the history of microbiology
2. Better characterization of the “ecological perspective”
    - Flow of material or energy, dynamic processes, actual vs. possible functions, interactions, system as a whole
    - Recommendations for practitioners
3. Propose an alternative causal framework to understand causal claims

Conclusions for practitioners

- Deeper acknowledgement of the ecological historical background of microbiome studies to solve current challenges.
- More integration
  - **Conceptually**: move from targeting specific pathogens or “silver bullet” microorganisms to managing the entire microorganismal community and studying dynamic interactions
  - **Methodologically**: Complement multiomics approaches with microbial cultures, computational approaches, and simulations.
- **Problems**:
  - How to integrate meaningfully different knowledge?
  - Lack of actionability



Issues with Interventionism and Functionalism(s)

Interventionism

- It is silent on the role of other types of evidence other than interventions.
- It is too stringent for the causal architecture of microbiomes.

- **Consequences:** Lack of available fine-grained interventions in microbiome studies and a lack of empirical justification for the focus on reductionist approaches and proximal causes.

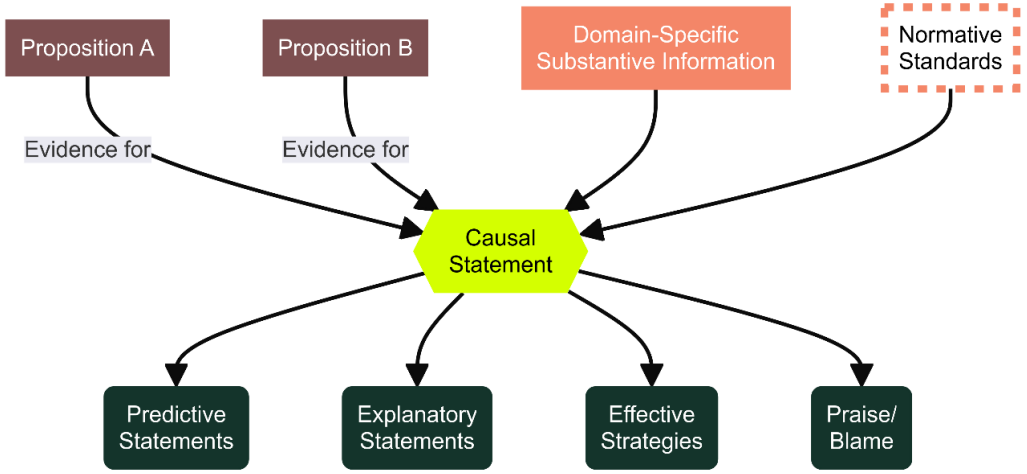
Functionalism(s)

- **Selected-Effect Function** implies second-order causation of the type *"X exists/persists because it causes Y"*

⇒Needs an evolutionary history

- **Causal-Role Function**
- Liberality of what can be a function.
- Teleological
- Might be sufficient in the context of health and disease conceptualized as those of the hosts, but…

Reiss 2015; Steel 2005; Schneider 2023



Reiss 2015; Reiss 2024

Conclusions for philosophy

- An alternative: **Inferentialism**
- *"The microbiome causes obesity"* are to be understood by studying their places within an inferential network available to a scientific community.
- Evidential pluralism: different kinds of evidence can play a role in establishing causal claims
- Causal inferences are licensed only locally in a given inquiry with **specific goals, substantive information, and normative standards.**
- The normative standards for causal claims are those of the **scientific community**.

The myth of ethno-racial categories

Human Categorizations in Microbiomes

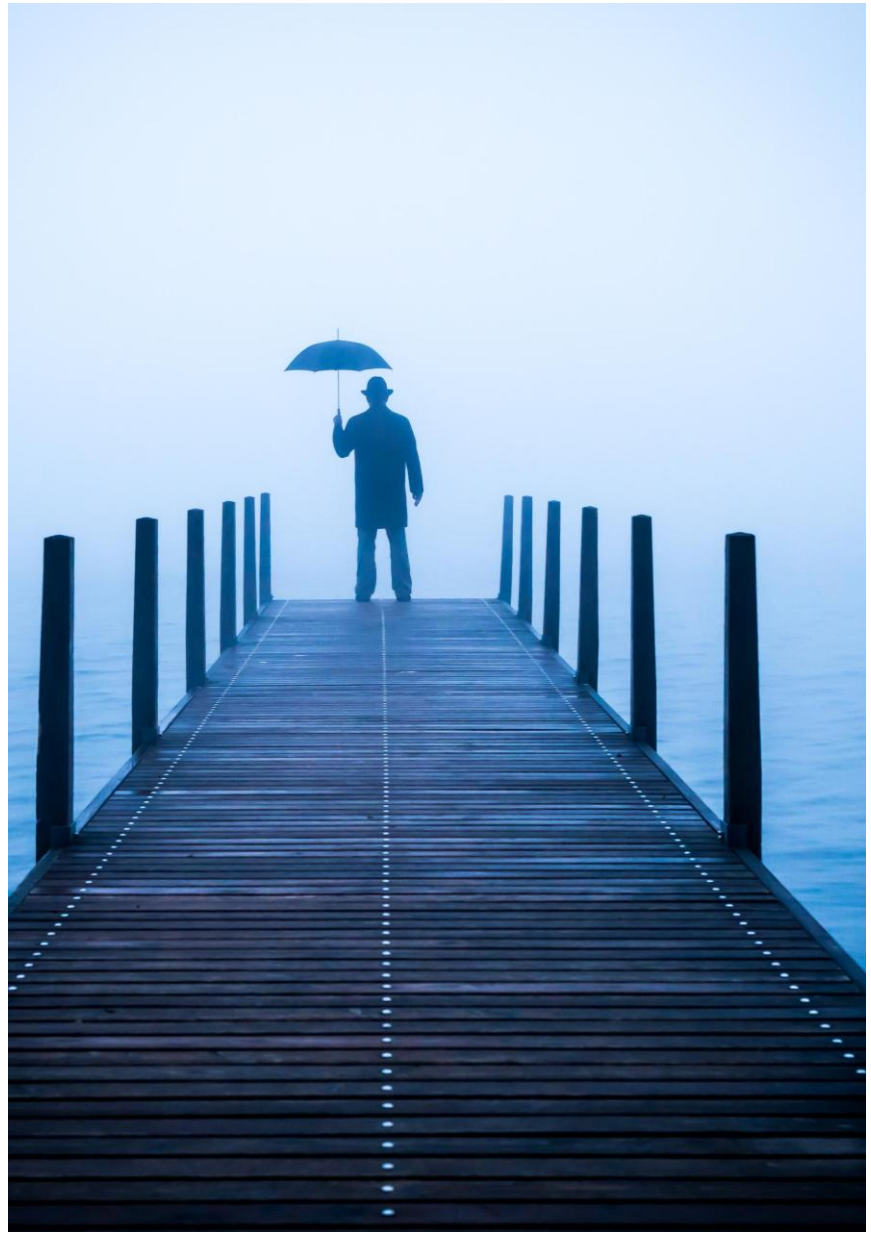
- Microbiome research uses human categorizations, including ethno-racial categories.
- **Civilizational ghosts:** race used as a ghost variable hiding civilizational logics of race with the use of concepts like "Westernized" vs "non-Westernized" and others (Nieves-Delgado and Baedke, 202; for a review, see Rawson 2024).
- **Microbiomization** of biological race reinscribes race as heredity or inheritance, naturalizes socioenvironmental and political dimensions of racial differences (Helmreich 2014).

My contributions

- Studies from 2018, where ethno-racial categories are used to study human health disparities to inform **personalized medicine**.
- I argue that this use is problematic and should be abandoned. I question **the inferential power** of ethno-racial categories in microbiome studies in this context:
    - The definitions of ethno-racial categories are ambiguous and inconsistent, creating **epistemic uncertainty**.
    - These categories **reduce multiple dimensions** into one category, which can result **in stereotyping and essentializing ethno-racial categories through the microbiome.**
    - The **instability of these categories** makes them useless for treating a particular individual.

Conceptual Imprecision

- In medical genetics, ethno-racial categories are ambiguous and inconsistent, creating **epistemic uncertainty** (Malinowska and Serpico, 2023).
- I argue that this **conceptual imprecision also plagues microbiome studies**.
- **Method** (ongoing): non-systematic review in PubMed, EuroPMC, and Web of Science – terms “ethnicity”, “race” in Title and Abstracts associated with “human gut microbiome”



Thomas Leuthard

Conceptual Imprecision

Articles	Terms employed	Define (not explicitly) as
Amato et al. (2021)	Race and ethnicity	“Structurally imposed differences in lifestyle and environmental factors”, often associated with ancestry
Borello et al. (2022)	Race and ethnicity	Proxy for diet
Brooks et al. (2018)	Ethnicity	Self-declared, aspects of human genetic variation, social, economic and cultural variations
Deschasaux et al. (2018)	Ethnicity	HELIUS definition, people with same “diet, lifestyle, or genetics”, Western and non-Western
Gaulke and Sharpton (2018)	Ethnicity	Genetic diversity, geography
Syromyatnikov et al. (2022)	Race and ethnicity	Genetic diversity, living conditions, nationalities and religions

Conceptual Imprecision

01

These studies often **use interchangeably different concepts** such as “race,” “ethnicity,” “geography,” and “nationality.”

02

Few studies **define** these terms before using them, or **do not use them consistently** throughout one paper.

03

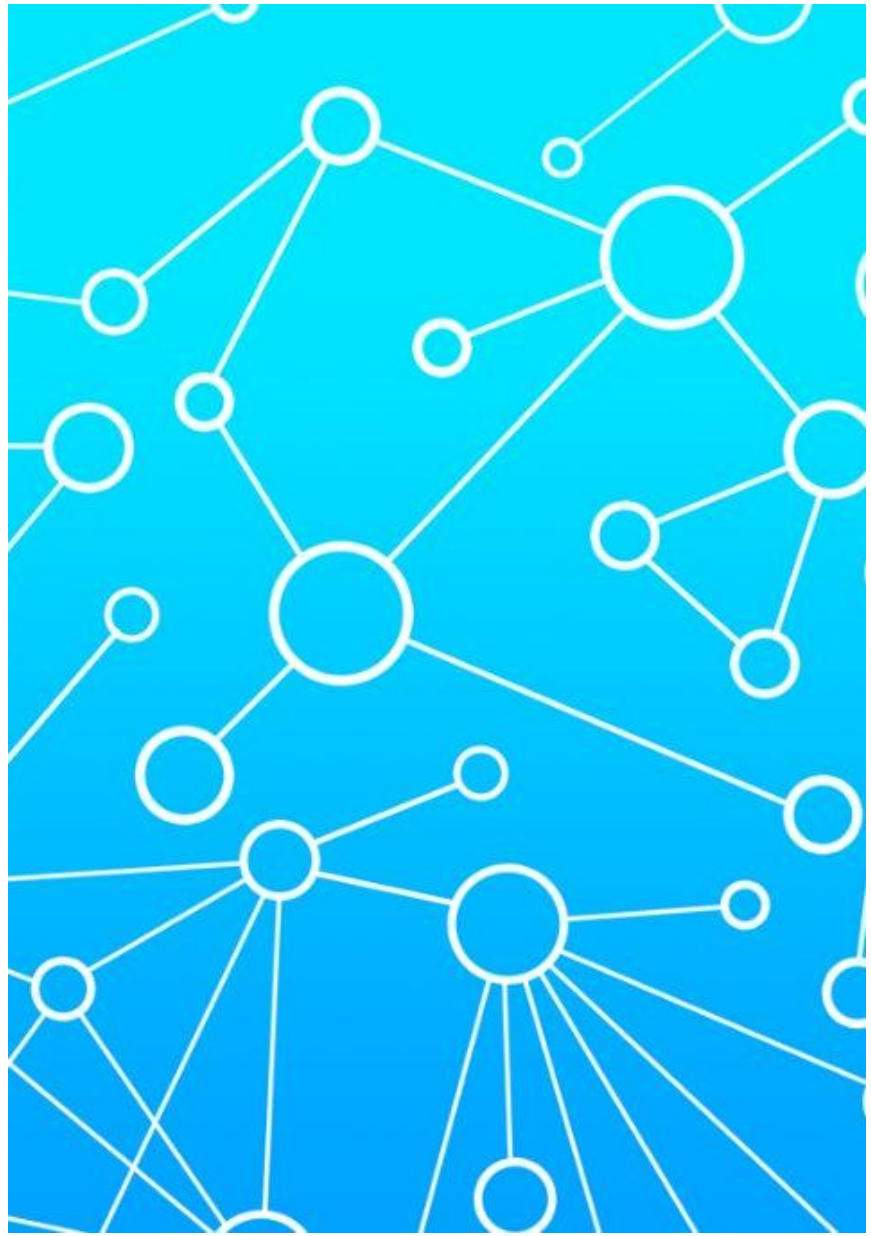
When institutional or more general definitions backed up such papers, those **definitions are not consistent globally and depend mainly on the location of the researchers** (e.g., USA vs Netherlands).

04

This situation prevents **comparative analyses** of different studies and **hinders scientific communication.**

Reduction of Multiple Dimensions

- Ethno-racial categories reduce multiple dimensions, including human genetic diversity, diet, and socio-cultural dimensions, into one category.
- Preliminary results from qualitative studies.
- **Set up**: Three focus groups of scientists based in Germany, specialized in microbiome studies. We ask them, **“According to you, which factors influence the gut microbiome composition?”**
- Causal Network (Fuzzy Cognitive Maps)



Reduction of Multiple Dimension

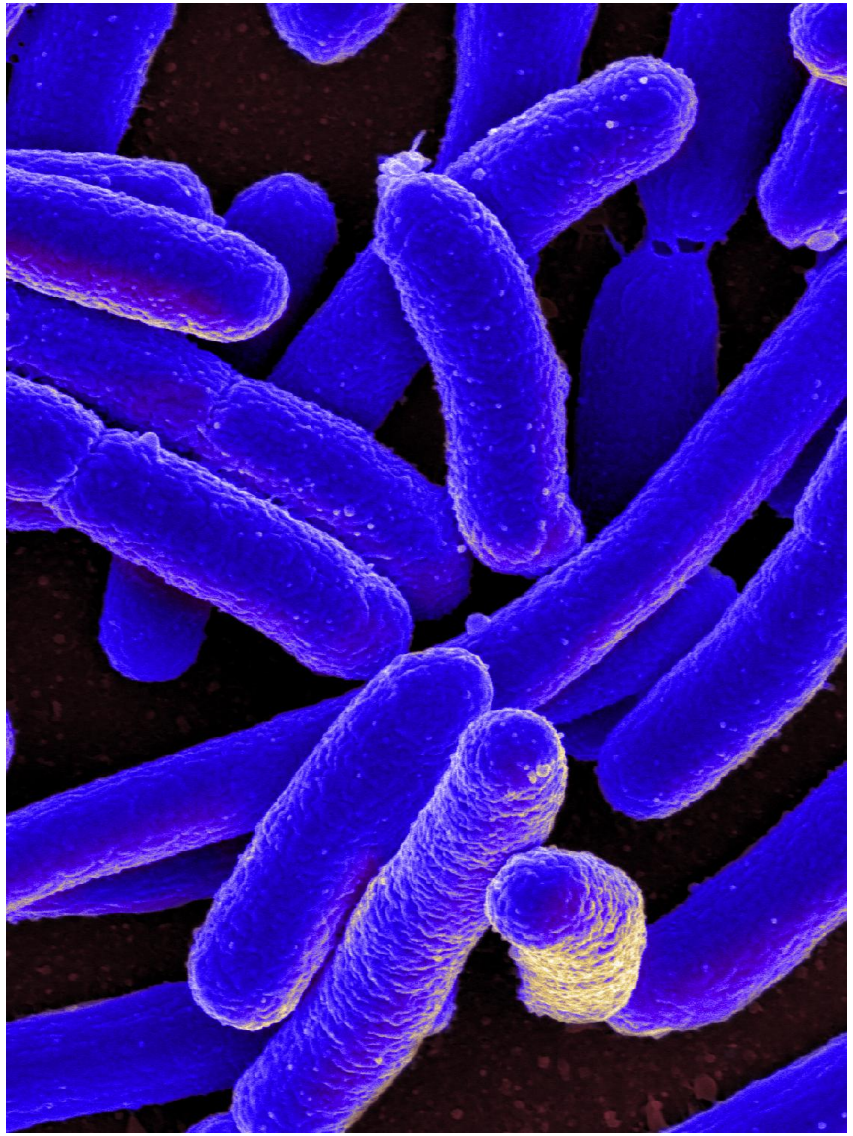
Reduction of Multiple Dimensions

- “Race”: An **umbrella term** for government-decided (social constraint/driver), self-identification, culture, and ethnicity.
- “Race” is exogenous, BUT causally connected to genetic background, which is endogenous.
- **Only “subterms” remain** (that are not specifically clearer): culture is causally connected to diet, and self-identification is causally connected to lifestyle (strongly associated with the notion of choice in this group).

⇒ **Uncertainty about the real causal factor**

- Confusion in cause-effect relationships: It is unclear whether the ethno-racial category is a cause of the microbiome composition or if it is an effect of the diet (or another dimension) mediated by the microbiome.

⇒ **Uncertainty about the causal role (if any) of the racial category**



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Uselessness of ethno-racial categories

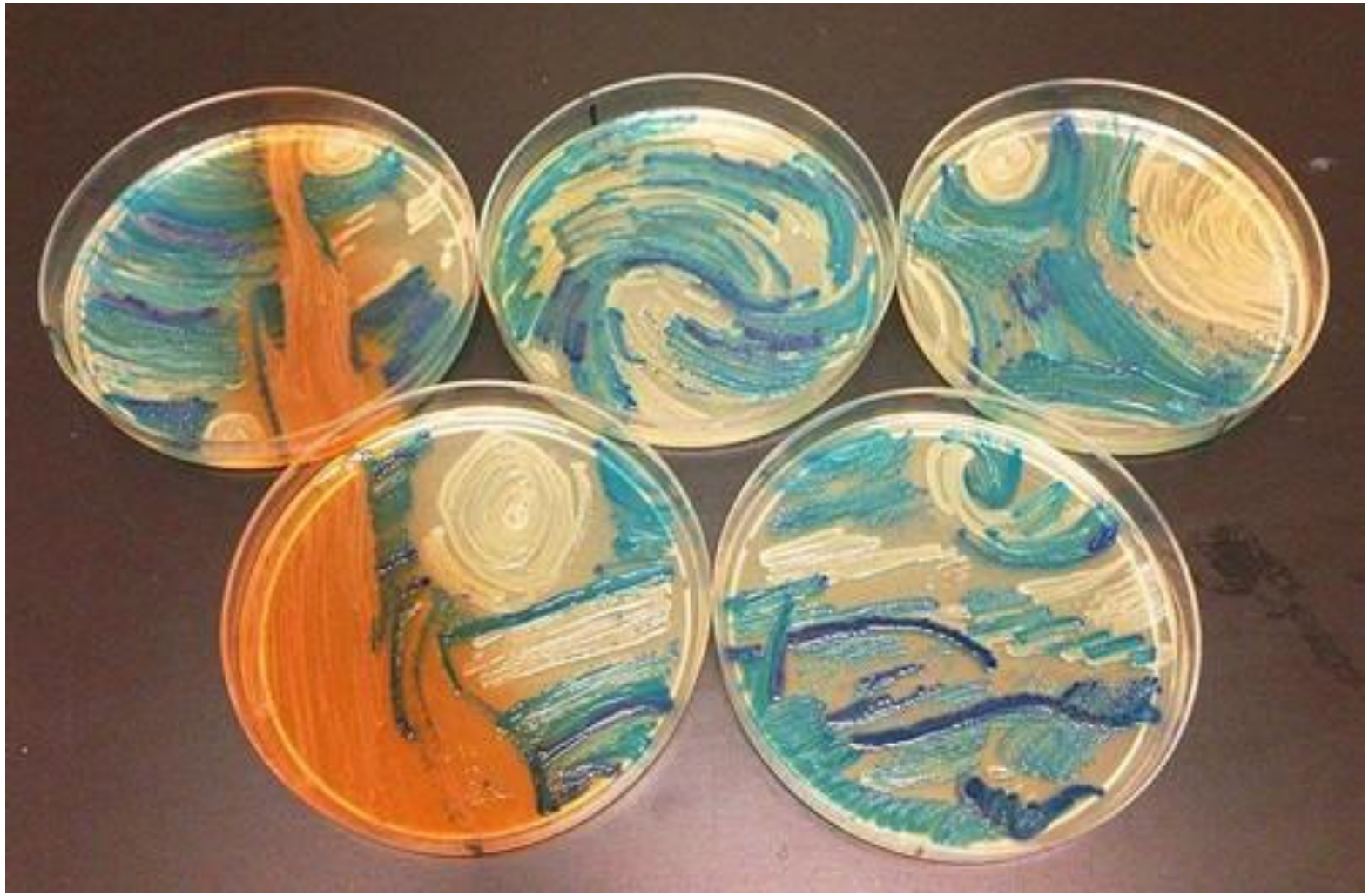
- Few studies have found **consistent, reliable associations between microbial taxa and disease or health phenotypes.** Similarly, no taxa are reliably and consistently associated with a particular **human allele**.
- Even if stable associations were found, these factors could lead **to different classifications of the same human population**, not necessarily consistent with more classical (US-centered) definitions of race, nor consistent between diseases.
- Thus, ethno-racial categories **are useless for treating a particular individual**.

Conclusion

- Ethno-racial categories in microbiome **studies have limited inferential power.**
- The risks of using ethno-racial categories in microbiome studies, including **poor scientific communication**, attributing **a spurious causal role** to these categories, **stereotyping**, and **misplacing individuals** into categories that may not be relevant for treatment or risk-factor assessment, **outweigh any potential benefits**.
- Instead, researchers should focus on the **actual variables** they are interested in, such as diet, to avoid racist descriptions and the microbiomization of ethno-racial categories.

General Conclusion

- **Microbiome foundations: Unearthing the ecological roots of microbiome studies**
  - Explain the **current status** of the discipline and the tensions within it using the history of microbiology
  - Perspective in microbial ecology: **dynamic processes, complex causal systems, interactions**
  - For practitioners: **more integration**
  - Alternative causal framework: **Inferentialism**
- **Microbiome faultlines: The myth of ethno-racial categories**
  - **Limited inferential power** of ethno-racial categories
  - **Abandon** of the use of these categories
  - Focus on the **real variables of interest**



Thank you!

Vincent van Gogh's "The Starry Night" by Melanie Sullivan of Missouri. *American Society of Microbiology.*