

THE PARADOX OF THE SHIP OF THESEUS AND THE GUT MICROBIOME



Bryan Hanley*

* ACTA -The joint Dental Faculty of the University of Amsterdam and the VU Amsterdam
a.b.hanley@acta.nl



Josephine Hunt

THE PARADOX

The human gut microbiome has been associated both in the scientific and popular press with a number of health conditions. These include “your risk of developing obesity, heart disease, Type 2 diabetes and a wide range of other conditions”¹. In addition, “Higher levels of gut microbiome diversity are generally thought to be a good thing.”¹ although such statements are often made with little proof being offered. In addition, colonies comprising single species can be highly biologically active while having zero diversity.

There are over 1,000 different microbial species colonising the human gut. These are grouped into families, genera and strains so the numbers detected depends on the granularity of the level of inspection. Their interaction with the human host is responsible for a range of physiological effects such as enhancing immunity and aiding digestion. Because of advances in DNA sequencing

technologies, the identification of which species are present is now much more complete however this does little to differentiate a ‘healthy’ from an ‘unhealthy’ gut microbiome². Different microbes can be affected by diet and linking this to clinical outcomes is emerging. In addition, sequencing of the gut microbiome is highly biased towards the identification of bacterial species. Other organisms (e.g. fungi, viruses, yeasts) which are known to be present are much less completely catalogued. Moreover, sequencing gives composition only and nothing on functionality of the microbes or the potential interaction between microbes.

This leads to two challenges:

1. How can we derive a more complete and more comprehensive map of the microbial species present in the gut microbiome?
2. How can we determine what functional benefit derives from each different

microbial entity - or combination thereof - and how does this impact upon the health of the host?

One approach to the second of these challenges makes use of the concept of replacing one microbial species with another one and determining health outcomes that result. The principle is embedded in the metaphor of the Ship of Theseus. The Ship of Theseus is a paradox which was perhaps most notably included in *The Life of Theseus* by Plutarch. The paradox revolves around the idea of whether a ship that had been restored by replacing every single wooden part remained the same ship. Can two microbiomes that are biologically different (at whatever level of hierarchy we choose as relevant) but functionally identical, actually exist? If so then the further paradox about there being a number of ‘healthy’ states of the human gut microbiome can be explained. In order to investigate this idea further, we need to define the microbiome itself.

THE BIOLOGICAL PARADOX

A common theme when considering biological systems (including microbiomes) is the search for homeostasis. A homeostatic living system is one that is in equilibrium and is therefore resistant to perturbation.

Within a microbiome, different phyla, genera, species and strains exist and comprise the microbiome. A number of terms are used to define the properties of a microbiome and these give an indication both of how microbiomes are defined and what is considered important.

Species Richness

This is defined as the number of species that are found during a specific measurement however, do the numbers of each species that are present reveal anything useful regarding the functional properties of the microbiome?

Species Diversity

Species diversity is a measure of the proportion of each species that are present.

There are a number of other terms which are used to describe the properties of the species present in a microbiome including Dominance, Evenness, Rarity and Abundance.

Knowledge of species richness and diversity is not particularly useful as it does not provide information about the dynamics of a microbiome, its functional properties or its effect upon the system (including the host). These are far more crucial questions than merely defining composition in a non quantified manner.

One of the drivers for the measurement of types of bacteria present in microbiomes has been advances in nucleic acid sequencing. Particularly noteworthy in this context is the growth in the analysis of 16SrRNA from bacteria³. The

sequences obtained are then compared to microbial genomic databases to identify and profile the bacteria. The identification is only as comprehensive as the constraints of the sampling of the population allow.

A map of the functional attributes of the microbiome will be much more useful. The ecosystem as a whole impacts markedly upon health (and is amenable to change). It is insufficient to merely know what is there and in what relative numbers – we must know what they are doing and how they are interacting with each other and with the host.

THE MICROBIOME AND THE SHIP OF THESEUS

If we apply the 'Ship of Theseus' paradox to the microbiome, we can think of components of the microbiome as the timbers and other components of the ship. If we replace one microbe with another that is genetically different but functionally identical then repeat this for each microbial component then we should, eventually, end up with a microbiome that is completely different in terms of its component species but is functionally identical to that which we started with. Perhaps the most contentious part of this exercise relates to the question – what does functionally identical mean? We can consider the answer to this in several ways:

- Internally the microbe has the same cellular machinery and functions in the same way as that which it is replacing.
- Its relationship with the other microbial components is the same as that which it is replacing. This means that, for example, it produces (and responds) to microbial mediators such as quorum sensing molecules (small molecular signals produced by microbes in mixed

communities) in an identical way as the original microbe.

- It impacts upon and responds to the host in precisely the same way as the original microbe. This means that, for example, it provokes an identical immune response as the original.

While this may seem an esoteric argument, it is crucial to a number of aspects of the microbiome and therefore the host⁴. For example, the human gut microbiome is constantly changing and, in order to prevent harmful dysbiosis, it must act collectively to repress uncontrolled growth of pathogens. Not all healthy microbiomes are identical however at a 'prevention of pathogen growth' functional level, it is reasonable to assume that they share certain characteristics. If we can identify the functional characteristics of this property and how the microbiome organises this in different cases, then we will be closer to having a metabolic map of the microbiome. One way of probing this might be to examine the routes by which different microbiomes become dysbiotic. While they are 'healthy' we assume that they share certain functional characteristics but, depending on their nature, their progression to dysbiosis may occur by a number of routes. This has been described as the 'Anna Karenina Principle'^{5,6} based upon the opening line of Leo Tolstoy's *Anna Karenina*, "all happy families are all alike; each unhappy family is unhappy in its own way". This suggests that "healthy" microbiomes are alike and each disease-associated microbiome is "sick" in its own way. The application of this principle suggests that all health microbiomes share certain characteristics but the principle, as amended by the Ship of Theseus paradox, suggests that the functional result (prevention of dysbiosis) may be the same

even if the means to achieve that aim is different.

CONCLUSION

The Ship of Theseus Paradox combined with the Anna Karenina Principle provides a way of looking at microbiomes which may have consequences on how we can most effectively manipulate it maximum benefit. This is critically important as we know that the microbiome (unlike our genetics) can be altered functionally and therefore has major capacity to straightforwardly improve human health. It should be noted, however, that there is no exact way of describing biological systems (or, indeed any other system) in terms of metaphors. If they were exact then they would not be metaphors⁷. Determining which functional characteristics contribute to different states of the microbiome is a massive step on the way to developing methods (dietary) to maximise the benefits of a healthy microbiome.

References

1. <https://www.nytimes.com/interactive/2021/10/07/well/live/microbiome-gut-health.html>
2. Nature 577, S6-S8 (2020)doi: <https://doi.org/10.1038/d41586-020-00193-3>
3. Li K, Bihan M, Yooseph S, Methé BA (2012) Analyses of the Microbial Diversity across the Human Microbiome. PLoS ONE 7(6): e32118. <https://doi.org/10.1371/journal.pone.0032118>
4. Klassen, J.L. Defining microbiome function. Nat Microbiol 3, 864–869 (2018).
5. A B Hanley, W Crielaard – Presentation to the Mars Inc. Science Leadership Team, 2010.
6. Ma ZS. Testing the Anna Karenina Principle in Human Microbiome-Associated Diseases. iScience. 2020 Apr 24;23(4):101007. doi: 10.1016/j.isci.2020.101007. Epub 2020 Mar 25. PMID: 32305861; PMCID: PMC7163324.
7. S Hossenfelder. Existential Physics, Chapter 5. Atlantic Books, London, 2022.