Sumrall L, O'Malley MA. 2024. Conceptual parallels: microbiome research and ancient medicine. *Perspectives in Biology and Medicine*, forthcoming.

Conceptual Parallels: Microbiome Research and Ancient Medicine

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Abstract
The concepts currently operating in much medical microbiome research bear a curious resemblance to an ancient tradition of Western medicine. This tradition, humoral medicine, is concerned with the four humors: yellow and black bile, phlegm, blood. Both humoral medicine and medical microbiome research use notions of imbalance and balance for broad explanations of disease and health. Both traditions also hold that the composition of humors or microbiomes determines bodily as well as mental states. Causality in each system is often conceived teleologically, meaning that humors or microbiomes 'function for' the maintenance of the whole. And ultimately, each framework situates the humors or microbiomes in a multilevel interactionist theory that conceptualizes individual health within a broader environmental context. As well as critically assessing the parallels between these systems, we sketch some explanations of how they may have arisen. Finally, we evaluate the implications of these similarities for the future of medical microbiome research and suggest ways in which the field might move forward.

Introduction

The study of human microbiomes – the microbial communities living in and on human hosts – promises to transform medical insight and its application. Vast bodies of sequence data from these microbes have been linked to every known health and disease state. But although medically oriented microbiome research arose out of ecological approaches to microbiology, the theory and concepts employed to understand microbiomes medically are still a work in progress. The heuristic concepts that have emerged so far in the medical microbiome literature bear a surprising resemblance to one of the most ancient traditions of Western medicine: humoral medicine as promulgated by the medical practitioner and philosopher Galen in the second century CE.

Both humoral medicine and medical microbiome research use notions of imbalance and balance (Olesen and Alm 2016), with undesirable unbalanced states called 'dyskrasia' and 'dysbiosis' respectively. Therapeutically, both systems aim at restoration to a balanced state. Each tradition also holds that the composition of the central entities (humors or microbiomes) determines not just every bodily state but mental ones too. Causality for each is often conceived teleologically, meaning that these focal parts of human bodies 'function for' the maintenance of the whole. And ultimately, each framework asserts that external environments are part of the balance equation, thereby situating the humors or microbiomes in a unified multilevel theory that aims to explain the very nature of health and perhaps even humans.

Usually, humoral medicine is thought to persist in contemporary medicine only in the form of alternative approaches to diagnosis and treatment. Our analysis will show, however, that broad humoral concepts pervade current biomedical research on human microbiomes. As well as describing the parallels between these systems, we outline some broad explanatory sketches: whether these resemblances are due to direct historical continuity, incidental convergence, or a common causal factor. Our key focus, however, is on whether medical microbiome researchers should be concerned that their field currently shares conceptual parallels with humoral medicine, and whether there are positive aspects to these common features. We conclude with reflections on how an interactionist, environment-oriented framework might contribute to modern medical insights.

Medical microbiome research

Microbiome research refers to the large-scale molecular investigation of microorganismal communities, many members of which have yet to be cultured and examined by laboratory-based experimental methods. Although these communities are studied in multiple environmental settings (e.g., oceans, soils, atmospheres, buildings), much of the growth of the science has been based on the microbes that occupy animal hosts, especially humans. Human bodies, particularly the gut, harbor trillions of microorganisms. While traditional microbiology used to focus on single isolated microbes, microbiome research looks at whole microbial communities and their combined effects (Handelsman 2004). The vast majority of human microbiome research is concerned with how microbiomes in the gut, skin, mouth, respiratory system and reproductive organs affect human health, and what these interactions mean for the prevention, diagnosis and treatment of disease in a modern medical context.

There is probably no human disease or illness or condition that has not been linked directly or indirectly to microbiome composition and function. Every system, organ and state of the body has a documented connection of some sort to a microbiome, with the gut microbiome being a key focus of attention due to its size, diversity and systemic connections (Lynch and Pedersen 2016: Vijay and Valdes 2022). Even brain function, mood, mind, personality and behaviour have been connected by study after study to gut microbiomes (Rogers et al. 2016; Butler et al. 2019). While there may be questions about the pathways, generalizability and reproducibility of these connections (e.g., Walter et al. 2020; Lynch et al. 2019; Sze and Schloss 2016), even the most hardened sceptic would not deny that there is *something* important about the associations between human health states and microbiomes.

However, these connections rest on unsteady conceptual foundations that may be undermining deeper scientific understanding. In particular, concepts of disease, health, causation and treatment have been identified as problematic in microbiome interpretations (Olesen and Alm 2016: Hanage 2014; Parke and Plutynski 2023; Inkpen 2019). Although microbiome research has its origins in microbial ecology, ecological theory is employed only to a modest extent (Prosser 2007), and theory-driven human microbial ecology is even less common (for exceptions, see e.g., Foster et al. 2017; Conwill et al. 2022; McDonald et al. 2020). In medically oriented microbiome research, the use of established ecological theory is even rarer. Instead, a particular conceptual vocabulary crops up consistently no matter the disease or health state under investigation.

For example, 'dysbiosis' is a highly favoured term in medical microbiome research (Hooks and O'Malley 2017; Brüssow 2019).[1] Although its meaning is vague, this very vagueness seems to ensure the term's ongoing popularity. Dysbiosis is usually taken to mean a microbiome composition that in at least one study, no matter how small, has been associated with a disease state. The implications are that this is a negative difference that if reversed would lead to better health outcomes. Backing up this loose hypothesis is a cluster of other concepts that are thought to provide the relevant explanatory mechanisms. Dysbiosis, the putative cause of many diseases, is frequently defined as an imbalance in microbiome composition (e.g., Lee et al. 2022). Health, on the other hand, is the outcome of 'eubiosis' (also 'homeostasis'). This term is used for the beneficial state of the microbiome, which is supposedly brought about by a balanced composition.

[1] PubMed catalogues almost 17,850 articles referring to dysbiosis, which is about 9% of the total microbiome/microbiota literature (158,500 articles at the end of 2023).

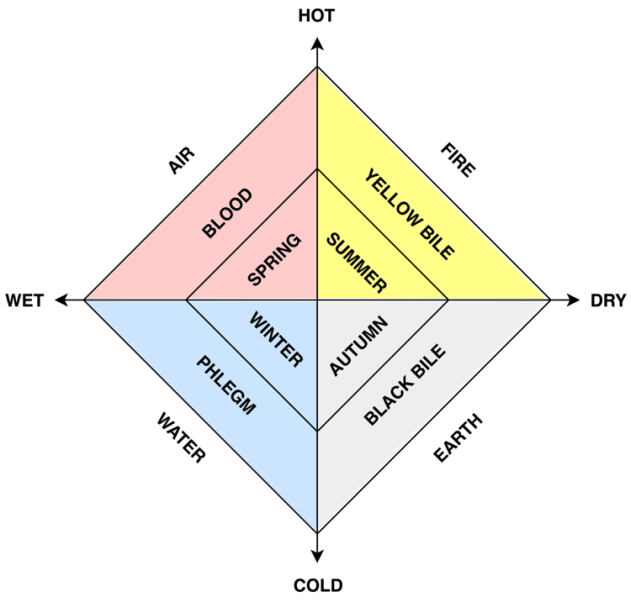
Although 'balance' might seem to be an old-fashioned and scientifically dubious notion, it features prominently as a substitute for theory in a considerable portion of medical microbiome research – especially the more applied literature.[2] That observation is what brings us to a far more ancient tradition of medicine in which balance also played a central conceptual role.

Humoral medicine

Humoral medicine encompasses a broad range of theories and practices that were first described by Hippocratic physicians in the fifth century BCE (Arikha 2007; Porter 1999). In the second century CE, the Roman physician Galen elaborated basic humoral theory into a sophisticated philosophical system of medicine that would shape Western medicine until the nineteenth century. We use 'humoral medicine' to refer to the medical tradition that grew out of Galen's medical philosophy. Despite the complex minutiae of Galen's system and its diverse forms through history, the conceptual foundations of his humoral medical philosophy have an intuitive appeal and are sometimes thought to persist in the background of present-day medicine (Arikha 2007).

Health and disease in humoral medicine are standardly related to the mixture of four humoral fluids (or humors) believed to exist in every human body: phlegm, yellow bile, black bile, and blood (Salas 2020). This humoral system was understood within Aristotle's philosophy of nature, in which the natural world consisted of primary elements (earth, water, air, fire). They formed four combinations of contrary physical qualities (hot and cold, wet and dry). Galen integrated the four humors into his medical philosophy by associating them with these elemental qualities. This theoretical move produced a conceptually satisfying system by granting all features of the natural world their place in a complex network of interdependent parts (Fig 1).

Figure 1: A simple depiction of the oppositions of the four physical qualities in relation to the possible combinations of elements, humors and seasons in humoral medicine. Some of the associations based on shared qualities may still seem intuitive, like the one between phlegm and wintry weather.



[2] In a recent PubMed search for '(microbiome OR microbiota) AND balance' we found almost 5400 published articles using balance in reference to microbiome-host health states, which is 3.4% of the total microbiome/microbiota literature (158,500 articles). We analysed the first 500 of these articles (ranked by relevance) in full-text and found 11 overlapping conceptualizations of balance. Most of these concepts are discussed in this essay.

In humoral medicine, each person was understood to possess their own individualized, natural balance of the four humors in unequal proportions, according to their governing elemental qualities (Kaye 2014). This unique mixture was referred to as their complexion or *krasis*, which was reflected in their physiognomy and behavior. However, the composition of humors in the body fluctuated constantly in response to internal and external influences, which could easily result in humoral imbalance. While the right balance of humors constituted a healthy state in humoral medicine, imbalance constituted a state of disease (Salas 2020; 2019; Kuriyama 2008; Walkden 2022). The goal of medicine was to obtain or maintain the proper balance (*eukrasia*) and to avoid or correct imbalance (*dyskrasia*) through a combination of prophylaxis and therapy.

Purging excess humors was the standard means of countering imbalance (Kuriyama 2008; Walkden 2022). And, since the humors that determined health and illness were connected to change in the world at large, changes in lifestyle and environment were a common preventative and therapeutic focus. Rest, exercise and diet presented crucial opportunities to regulate the qualities that governed the humors. Dietetics became particularly significant, because of the presumption that the four humors were concocted from the contents of the stomach. Food was destined to become humoral fluid, and thus possessed considerable medical relevance in humoral medicine (Grant 2000). Because mental states and emotions were also seen as connected to the motions of the humors in the body, mental and emotional disturbance was often understood in relation to the digestive system (Purnis 2010; Stolberg 2018; Walkden 2022). Only much later were these relations recast in terms of the neurological theories that arose in the eighteenth century (Arikha 2007), and these gut-brain connections have now in turn been made explicitly to contemporary microbiome concepts (e.g., Miller 2018).

Even after humoral explanations were widely discredited and replaced by more modern accounts, the translatability of humoral theory into practice meant that associated medical treatments persisted (e.g., bloodletting). The basics of humoral medicine were commonsensical enough to meet the needs of people who mostly addressed their medical issues at home. An individual's appearance and disposition could be understood through inferences about the four humors and their various mixtures in the body. As part of a world system, the humors helped fit the human body into nature by explaining how health and illness responded to lifestyle and environment. Challenging diseases could be made tractable by humoral physicians, even if cures could be counteracted by further imbalance. All these conceptual and practical features have strong echoes in contemporary microbiome research.

Parallels and their problems

As microbiome research has developed, several features shared with humoral medical philosophy have become increasingly articulated in the scientific literature and its public dissemination. We draw attention to these, not just descriptively, but also to highlight their shared conceptual problems.

Dyskrasia/Dysbiosis vis-à-vis Eukrasia/Eubiosis: One of the most immediate resemblances between humoral medicine and medical microbiome research is the terminology used to refer to healthy and diseased states. Dysbiosis refers to the supposedly imbalanced microbiome that brings about imbalanced states of health, otherwise known as illness or disease. Dyskrasia in humoral medicine similarly refers to abnormal imbalanced states of the humors, which result in abnormal states of body and mind (Arikha 2007; Salas 2020). We find it unlikely that early microbiome research drew directly on the Greek terminology of humoral medicine (see Hooks and O'Malley 2017 for the historical background to 'dysbiosis'), but we do suggest that connections between these terms share some deeper problems.

In the modern medical context, one of the biggest issues for a concept such as dysbiosis is its imprecision and circularity. Anyone diagnosed with a health issue by standard medical means is simply assumed to have an unhealthy (dysbiotic) microbiome (even prior to examining that microbiome). The purportedly dysbiotic microbiome is then assigned a causal role in producing the already diagnosed disease, just as in humoral medicine maladies were automatically attributed to humors. Although efforts are being made in microbiome research to find standardized measures of dysbiotic microbiomes (see Wei et al. 2021), there are considerable doubts as to whether this can be achieved because each human host has a highly individual microbiome at the strain and species level. Even if a 'personalized' dysbiosis metric were viable, there is still fundamental unclarity about whether altered microbiome states are causes or consequences of disease (Levy et al. 2017; Olesen and Alm 2016). It could be argued that 'dysbiosis' is merely a proxy term for unknown microbiome causation, but additional conceptual parallels with dyskrasia suggest there are deeper connections.

Balance and imbalance: Dysbiosis, the putative cause of many diseases, is deemed to be an imbalance in microbiome composition or its 'function'. Health, on the other hand, is conceptualized as 'eubiosis' (also 'homeostasis'). This 'good' state of the microbiome is allegedly brought about by a balanced composition and function (e.g., Winter and Bäumler 2023; Lee et al. 2022; Goyal 2015; Petersen and Round 2014). Despite the fact that balance has also proved immensely difficult to quantify or assess in any non-trivial way (Hooks and O'Malley 2017; Walter et al. 2020; Lynch et al. 2019; O'Malley forthcoming), it underpins many claims about medical microbiome diagnoses and treatments (see Footnote 1) and becomes even more relevant as microbiome findings are discussed outside academia.

A very similar concept of balance also plays a major explanatory role in the framework of the four humors (Arikha 2007; Kaye 2014; Salas 2020). In that system, every species of organism and every individual belonging to that species possessed a natural balance of physical qualities, which manifested in ideal proportions of humoral composition. A pathological imbalance in these humors would produce recognizable diagnostic signs, and the humoral fluids themselves provided a mechanism through which physicians could exercise control over the physical qualities that composed the body and governed its function.

Basically, then, the key idea in each tradition is that there is a natural balance that if disrupted in some way results in imbalance, which is the general cause of all disease and leads to specific illnesses. Both frameworks consider this balance to exist in relative proportions of bodily substances (humors, microbes). Certainly, there are differences in how humoral medicine and microbiome research deploy the concept of balance, especially when it comes to finer-grained details and the historical circumstances of each tradition's development, but echoes of the past in contemporary microbiome literature and its public uptake are hard not to hear.

In ecology, the concept of balance once dominated the field but is now rejected as conceptually unhelpful, especially because it posited a state of nature that was based on non-scientific presuppositions about how the world *should* exist (Egerton 1973; Kaye 2014). When balance is used in medical microbiome research, it focuses medical intervention on the achievement of an undefined ideal state, which is described by terms such as homeostasis. Homeostasis is used in a generic sense of an expectation that there is a microbiome state that maintains health and to which the system must return after perturbations in order to maintain health (e.g., Lee et al. 2022; Dicks et al. 2018). Even though these idealized states of balance may be highly individualized (whether microbes or humors), they are nevertheless thought to offer a general route to diagnosis and treatment.

Therapeutic theory and practice: Diagnosis and treatment of abnormal states of body and mind are understood theoretically and practically in very similar ways in both microbiome and humoral traditions. Both systems describe proportions of focal entities or substances in or on the body that are highly dynamic but capable of being regulated to avoid pathological states of imbalance. Both traditions assume an ideal natural state of health that is determined by these proportions. Indeed, an increasingly popular perspective on human microbiome research asserts that until we restore an ancestral state of microbial balance in the gut we are doomed to be unhealthy (Sonnenburg and Sonnenburg 2019). While claims like this are usually justified in microbiome research by post-Darwinian evolutionary reasoning (despite the essentialist overtones of such claims – see Chellapoo et al. 2023), humoral medicine depended on pre-evolutionary descriptions of natural states that likewise tended towards essentialism (Salas 2020; Arikha 2007). The notion of balance thus describes a hypothetical balancing mechanism that returns organisms to their underlying essential nature.

For both systems, even though each person has a natural individualized balance of microbes or humors, there are nevertheless pathological proportions that affect everyone in predictable ways and this leads to the possibility of standardized treatments. On the practical level of treatment, food and dietary changes are therapeutically central to both humoral and applied microbiome medical philosophies: different types of food are believed to lead to better balance for individuals and improvements in disease conditions (Grant 2000; Valdes et al. 2018). However, the reasoning is somewhat different for each system, as one might expect. Microbiologists consider the impact of food intake on the composition and metabolic output of the gut microbiome (Armet et al. 2022; Zmora et al. 2019), while humoral physicians considered how the elemental qualities of food substances impact the resulting mixture of humoral fluids (Grant 2000). Nevertheless, both microbial and humoral compositions can be influenced by changes in diet, and this becomes an important tool in the therapeutic armory of each tradition and its public uptake.

Although both traditions share a diagnostic focus on excrement, humoral medicine particularly emphasized analysis of urine samples to gain insight into the state of the body as a whole (Wallis 2000). In gut microbiome research, diagnosis is often based on analysis of feces (for microbial content), and treatment too can be based on reintroducing healthy excrement in the form of fecal microbiome transplants. Humoral medicine would also base its diagnoses on different humors being excreted (as sputum, vomit, etc.) but treatments were almost always purgative, rather than focused on introducing healthy humors to replace pathogenic fluids (Kuriyama 2008; Walkden 2022).

More generally, however, the tractable therapies of both these systems enable domestic or 'DIY' medicine. The emphasis on diet in each tradition naturally shifts much of the therapeutic responsibility to the patients themselves. Patients following a regimen based on humoral medicine could also stock medicinal ingredients and make medicines at home; today, microbiome DIY-ers might try off-the-shelf probiotics or non-clinical faecal transplantation (Ekekezie et al. 2020). They might try cosmetics infused with probiotics to rebalance the skin microbiome (e.g., Sfriso et al. 2019). But whatever the treatment, it is done with the idea that there are general but personalized interventions that can be made in humors or microbiomes to cause better states of health.

Causality and function: Causality in microbiome science is problematic, and claims about microbiome causation of disease are currently difficult to justify with bioinformatic analyses and germ-free mouse experimentation (Walter et al. 2020; Hanage 2014). Many causal claims in microbiome research are overblown, inaccurate, or subject to misinterpretation (Lynch et al. 2019; Hooks and O'Malley 2017; Parke and Plutynski 2023; Skillings 2019; Lean 2019). However, the

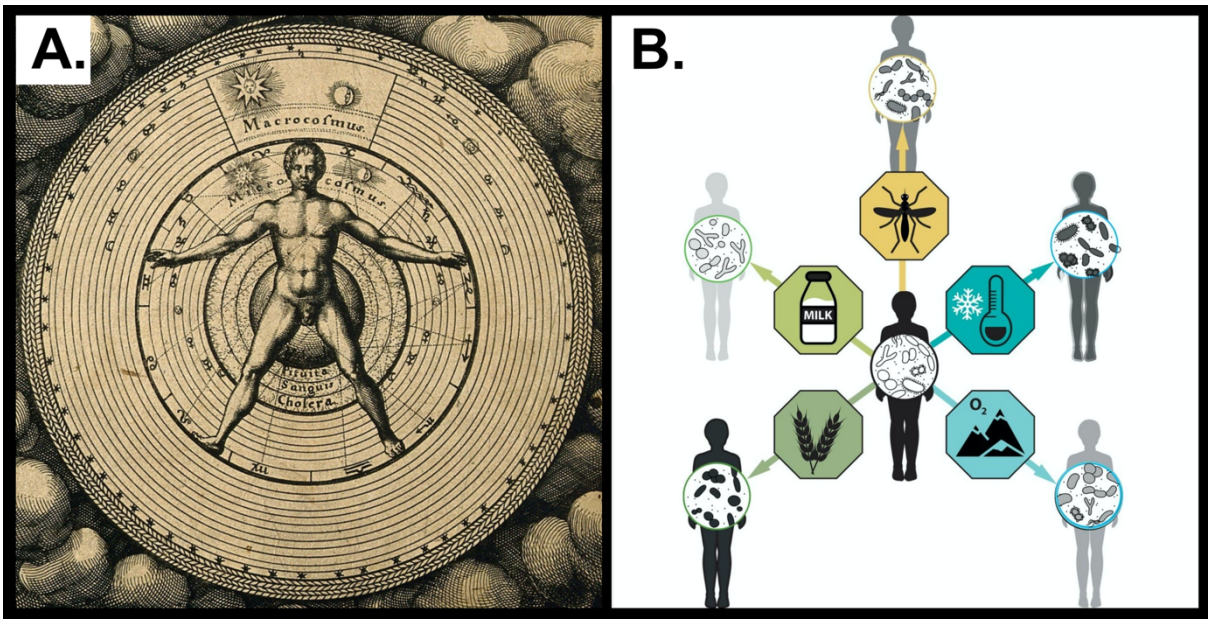
parallel we identify here between humoral medicine and microbiome research goes beyond what we might think of as sequential cause-effect relationships, in which factor A causally produces factor B.

Microbiomes are frequently interpreted as if they function collectively for the health of their human hosts (Klassen 2018; Inkpen 2019). This idea of 'functioning for' is usually understood as teleological, in that activities are carried out for the ongoing maintenance of the whole system, in this case the human and its microbiome. This same notion of function is also hard at work in humoral medicine, which takes Aristotle's notion of 'final cause' (causation that has a goal) and interprets it medically (Salas 2020; Schiefsky 2017). Teleological function is also on display in early ecological views of the balance of nature, such as the reasoning that snakes hibernate in order to provide humans with seasonal freedom from fear of snakes (Browne 1646, in Egerton 1973). Unwarranted as this example may seem to modern ears, it is similarly questionable to interpret microbiomes as 'functioning for' their human hosts in order to make them healthy and 'normal' when microbes are by and large competing fiercely for their own advantage against other microbes and seeking constantly to evade host control and gain advantages for themselves (Foster et al. 2017). These dynamics may lead to host effects that look like evolved benefits (e.g., gut development, immune responses) but are in fact part of the ongoing arms race as hosts such as humans find ways to manage their otherwise invasive occupants.

Evolutionary theory is used to justify a more modern teleological sense of function by drawing on the evolutionary history of organisms to diagnose function as something that has been evolutionarily selected for a certain purpose. But to say that the microbiome has been selected for host function (e.g., health) is running far ahead of any evidential or theoretical support for this claim. It contradicts what is known about the microbiome as a diverse competitive mix of microorganisms, each lineage of which may live only some of their lifecycle in the human body and are thus not committed to the host (Obeng et al. 2021). Even at the least purposeful level of function, that of making a causal contribution to a certain outcome, it is generally not possible to say that the *whole* microbiome plays any such causal role (Lynch et al. 2019). Certain members of the microbiome may carry out particular causal activities that end up providing a net benefit to the host (after all the control costs are calculated), but many so-called benefits may be mere by-products and not part of a dedicated causal interchange between host and microbiome. Saying 'the microbiome functions for the host's health' is thus a problematic claim even when it is taken into account that microbes can be observed and humors (in the subtle fluid sense) could not.

Unified theory: Despite these deep explanatory issues, one outcome of understanding causality in a teleological way is that it contributes to a thoroughgoing unification of different levels of interaction. In humoral medicine, the causal interplay between humors in the body went beyond any skin barrier into the environment itself. That broader environment, while under the influence of bodily humors and human activities, reciprocally shaped the humors determining human health. Many early modern medical treatises posited a cosmology of mutual influence between seasons, celestial bodies and humors, which were all governed by the physical qualities that composed the elements (Arikha 2007; Porter 1999; Siraisi 1990; Hopwood et al. 2021; Fig 1, Fig 2A).

Figure 2: A comparison of how multilevel interactionist approaches work in humoral medicine and medical microbiome research. **A.** A famous early modern example of the 'microcosm/macrocosm' analogy, depicting correspondences between the human body (microcosm) and the cosmos (macrocosm) that it mirrored (de Bry 1617). **B.** Just one example of a depiction of the interactions between microbiomes, hosts and broader environments (Suzuki and Ley 2020). We suggest that microbiome accounts are expanding beyond individual bodies to capture broader environmental phenomena, and that this may be the main positive feature of the alignments with humoral medicine.



As microbiome research extends its popular reach into the humanities literature and public spheres, it has begun to encompass not just the bounded body of single humans, but also the environments that the human body and its microbes inhabit (e.g., Blaser et al. 2016; Formosinho et al. 2022; Fig 2B). It can turn more deeply inwards too, to encompass basic notions of what the self is for a human and its microbiome (Parke 2021). Multilevel interactionist interpretations of microbiomes, humans and their environments can be a direct flow-on effect of teleological explanations in which various parts are conceptualized as functioning for the combined whole. However, it does not require a teleological framework to appreciate a more environmentally oriented view of health. Being able to look beyond individual bodies to their social and natural environments aims ultimately to explain health in relation to populations and how they live. Taking an interactionist stance and bringing broader ecological insights into medicine is increasingly understood as a potential strength of microbiome research (e.g., Suzuki and Ley 2020; O'Toole and Paoli 2023).

This interactionist view of microbiomes is part of the popular appeal of the science. In comparison to modern medicine and its specific accounts of particular illnesses, medical microbiome research and humoral medicine aim to offer a much broader explanatory framework. Usually, scientists are skeptical of unifying theories because they encompass anything and everything. But these unifying powers also give broad theories some of their popular and enduring appeal. While some of the appeal of microbiome research may be due to dubious reasoning (e.g., teleology, balance), it also promotes a view of health that nowadays has many enthusiastic subscribers in public, political and academic spheres. A topic gaining increasing attention is the notion of 'global health' and how it can incorporate microbiome findings and therapeutics (O'Toole and Paoli 2023). We will return to this view after thinking first about how the various similarities between microbiome and humoral medicine may have arisen.

Explanations of the parallels

What might these parallels between microbiome research and an ancient medical philosophy mean? How are they related historically? We see three possible explanations for the existence of these conceptual parallels: convergence, continuity, and commonality.

Convergence is the most obvious explanation. Humoral medicine, with its roots in ancient Greek philosophy and medicine, developed in particular historical contexts in response to existing (and now superseded) needs and priorities. After Galen, its conceptual machinery provided a unified framework that took advantage of existing diagnostic and treatment technology. 1800 years later, microbiome research arose in a different historical and social context, and its medical application is based on modern technological capacities. It is thus more or less coincidence that these two very different historical lines of inquiry share congruent conceptual frameworks. Each tradition, according to a convergence explanation, independently stumbled upon a similar conceptual framework but there is no historical thread connecting them: they merely look the same. In evolutionary terms, the similarities are analogies not homologies.

Continuity is the explanation that is akin to a homology account of similar features: the two traditions share affinities because there is historical continuity between them. While humoral medicine is readily acknowledged as an important part of the history of Western medicine, the continuity thesis goes further in suggesting that humoral medical concepts have managed to persist in underlying medical intuitions (see Porter 1999). Microbiome research would have to be understood as providing the favorable conditions for these outmoded yet persistent medical beliefs to flourish in the scientific mainstream and perhaps even branch into new manifestations of the basic medical philosophy.

Commonality attempts to explain the parallels not by way of a direct continuation (from humoral medicine to microbiome research) or from purely accidental similarities, but instead, as a result of some common factors (or perhaps even a common overarching framework) that have produced comparable medical philosophies despite the vastly different contexts in which these medical systems developed.

One possibility is that the explanatory focus in both systems on teleological causation (in which something functions for the system as a whole) is what has led to the apparently shared conceptual framework. Or, more concretely, it could be the case that something in their sociohistorical contexts is what has shaped the conceptual convergences. One such commonality explanation could be that these systems adopted similar frameworks to make the challenges of medical research tractable and practical. Humoral medicine had a relative paucity of data and yet huge demands to make sense of human illness and find ways of intervening in it. Medical microbiome research, on the other hand, has a dire need to integrate vast amounts of complex data, with insufficient theory and tools to make sense of it. Given the datasets and social pressures that exist in microbiome research, a simple – even simplistic – conceptual framework that could make intuitive sense of overwhelming data would be very attractive.

The three theses are merely explanatory sketches and only much more detailed historiography would enable us to make a detailed case for any one of them. The main point of this essay is not to uncover why two very different medical philosophies share common features, but to evaluate these similarities and tease out their implications.

Implications of humoral parallels in microbiome research

Whatever the explanation for these parallels, the main reason most scientists will be interested in them is to work out what they mean for medical microbiome research. To put it far too simply, do similarities to humoral medical philosophy have negative or positive implications for microbiome research?

One issue that might worry some researchers is that parallels between medical microbiome research and humoral medicine create an unavoidable association with alternative medicine. For the majority of today's biomedical researchers, making this connection is undesirable because of standard views that exclude alternative medicine from mainstream medicine (e.g., Fontanarosa and Lundberg 1998). Consequently, there could easily be interpretations that medical microbiome research is dependent on outdated medical concepts (i.e., humoral ones) that many scientists would describe as self-evidently wrong or 'prescientific' (Olesen and Alm 2016).

Conceptual similarities with humoral medicine are probably most pressing when microbiome research is being translated into medical applications and communicated to the public. For instance, dysbiosis is assumed to be a diagnosable microbiome condition that needs to be restored to a balanced state. Already there are medical and public health interventions available commercially that use this reasoning and are promoted by medics and medical researchers (e.g., Shane 2013; Australian Academy of Science 2017). Although there is limited evidence of negative outcomes for restorative microbiome treatments (for exceptions, see FDA 2023; Kothari et al. 2019), this is largely because of no requirements for such harms to be reported (Bafeta et al. 2018).

Going beyond professional medical contexts, the humoral framing of medical microbiome research is already apparent in mainstream public discourse about health. For instance, dubious commercial 'treatments' are being marketed based on interpretations of microbiome findings that unmistakably recall humoral concepts. Most are based on the goal of restoration to a natural state by interventions such as DIY fecal microbiota transplants, probiotics, and dietary regimes. Diet in particular is touted as an alternative to mainstream medication, including psychotropics (see examples in Hooks et al. 2019), and commercial diagnostics promise customers the achievement of an ideal state of a perfectly balanced microbiome in which illness is merely 'optional' (Viome Life Sciences 2023).

Despite these negative or at least concerning implications, it is also possible to conceive of advantages to adopting a humoral framework. Some researchers draw superficial parallels between microbiome research and humoral medicine, which they construe as a validation of ancient medical insights (e.g., Lyon et al. 2018; Sharma and Agrawal 2022). We think any gains come from broader considerations. For many centuries humoral medicine was *the* major medical paradigm – able to diagnose, explain, and treat disease states within an empirically supported, theoretically unified paradigm. Historically, traditional medical philosophies have proven to be long-lived, easy to communicate to the public, and translatable to domestic medical practices, which modern medicine does not easily achieve. This public relations aptitude might serve one of the broader parallels we have identified. Situating personal health in a broader interactionist framework by relating it to social and environmental conditions – as microbiome discoveries do – may have considerable benefits for modern health delivery (Wilkinson et al. 2021), and this need not be tied to specific concepts such as balance and dysbiosis. This potential advantage, however, will not convince most readers that the parallels listed above are anything but symptoms of a conceptually troubled or at least immature field.

Conclusions

It may feel uncomfortable for some readers that today's medical microbiome research shares some conceptual features with an ancient medical philosophy that is commonly thought of as outmoded and outside contemporary medicine. We suggest that these similarities are best interpreted as raising important questions for the future of microbiome research.

For those who are worried about the parallels and yet wish to retain the positive aspect of an interactionist environment-oriented framework, one option might be to seek an ecological replacement term whenever humoral parallels seem to be at work. So, for instance, humoral concepts such as balance and dysbiosis could be critically compared to established ecological notions such as stability and disturbance. Doing so would generate reflections on whether the ecological concepts are more illuminating, or whether they also have problems.

However, simply importing a slew of ecological concepts without critical attention is not going to be the antidote to any conceptual malaise in microbiome research. Ecological concepts themselves have contested histories and many flaws. For example, balance may have been replaced in ecology by stability, but stability itself has multiple meanings and measures that require careful specification (Grimm and Wissel 1997). The same goes for a concept such as resilience, which sounds self-explanatory and desirable but again covers multiple meanings and interpretations (Angeler and Allen 2016). In short, there are not any off-the-shelf conceptual packages that can simply substitute for microbiome concepts that might be of concern because they are attuned to those of humoral medicine. Sustained critical scrutiny of existing and potential future conceptual frameworks is something in which microbiome research needs to invest.

But if there is any strength to this ancient medical framing, it may well lie in its capacity to connect individual health and disease more effectively to broader environments, by linking minds, bodies and ecologies in a multilevel way so they can be managed for better medical and even environmental outcomes. Anyone wanting to advance the conceptual machinery of microbiome research might want to think about how to sustain a multilevel interactionist perspective while making sure that modern medical needs are met.

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