The Concept of Balance in Microbiome Research

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Abstract

Microbiome research is changing how ecosystems, including animal bodies, are understood. In the case of humans, microbiome knowledge is transforming medical approaches and applications. However, the field is still young, and many conceptual and explanatory issues need resolving. These include how microbiome causality is understood, and how to conceptualize the role microbiomes have in the health status of their hosts and other ecosystems. A key concept that crops up in the medical microbiome literature is 'balance'. A balanced microbiome is thought to produce health and an imbalanced one disease. Based on a quantitative and qualitative analysis of how balance is used in the microbiome literature, this 'think again' essay critically analyses each of the several sub-conceptions of balance. As well as identifying problems with these uses, the essay suggests some starting points for filling this conceptual gap in microbiome research.

Introduction

As human microbiome research matures, it continues to develop the conceptual legacies of its earliest years. Especially in medical microbiome research, a number of loose descriptive concepts continue to be used even though some researchers feel such terms have outlived their usefulness. One of these persisting earlier terms is dysbiosis (aka an unhealthy microbiome) – a concept that has been thoroughly analysed, critiqued and found wanting (see, e.g., [1, 2, 3]). But a cognate concept that is often associated with dysbiosis has received far less attention, and its use may be at least as problematic. This term is balance, which is another ill-defined but intuitively plausible description of microbiome states and how they impact their hosts. This 'think again' essay will argue that most uses of balance in microbiome research are not only loose and slippery but also quite probably harmful for the ongoing development of microbiome interpretations and applications.

But first, it is necessary to establish just how widespread this use of balance is. If it is rare, or used only outside the academic literature, then whatever inherent problems it has will not matter to the field. And even if it is common, there may be good uses of balance that outweigh the deficient ones. To provide a snapshot of the field, it makes sense to start with a basic bibliometric overview of balance and how it is deployed in microbiome research.

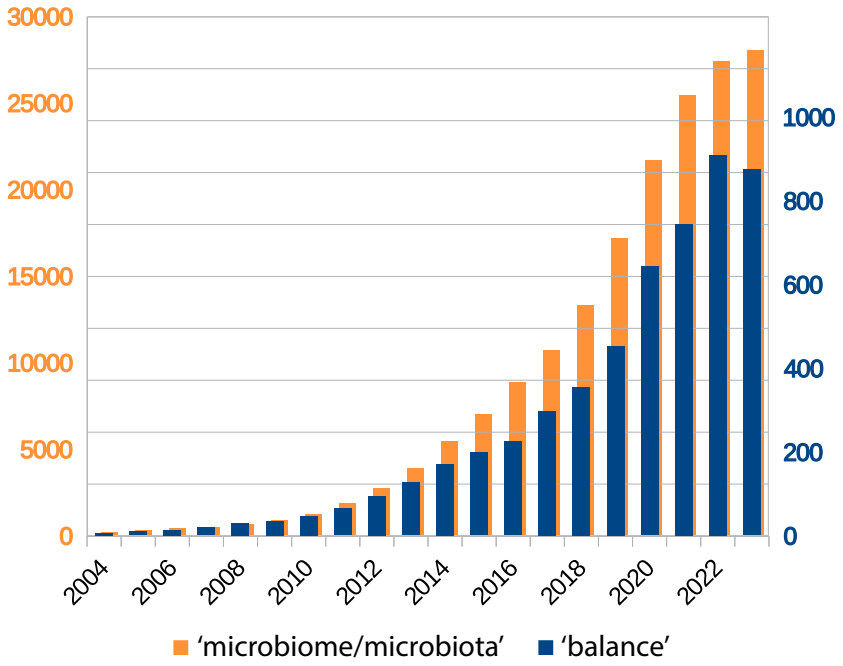
Balance and its occurrence in the microbiome literature

A rudimentary PubMed search looking for papers with '(microbiome OR microbiota) AND balance' in the full text (including abstract and title) finds 5400 scientific articles (see Supporting Information). The total microbiome literature consists of around 160,000 published papers, so balance features in more than 3% of *all* the articles on microbiome research. This is quite a large number of papers when the total literature covers numerous ecosystems and

non-human organisms from algae to pigs. If the search is restricted to '(microbiome OR microbiota) AND human AND balance', then balance is found in nearly 4% of the literature. This percentage is less than the term 'dysbiosis', which is mentioned in almost 18,000 microbiome articles (about 9% of the total literature and 14% of the human literature). However, balance might be even more conceptually important than dysbiosis, because – as we will see below – it helps explain what dysbiosis is, and might even be the hypothetical mechanism that allows dysbiosis to prevail in the literature despite its many conceptual flaws. [1]

Is it possible that all these uses of balance are old and now recognized as obsolete? That is not the case, because only 12% of the total microbiome literature using balance was published earlier than 2015 (see SI). Microbiome research is thought to be 'maturing' after its earlier years (pre-2015) in which it focused mostly on composition and *any* association. [4] If the field is indeed maturing, that maturation seems to include steadily accumulating mentions of balance (Figure 1).

Figure 1: Numbers of papers using balance in the total microbiome/microbiota literature. This graph captures the number of times each year that 'balance' is used in conjunction with microbiome or microbiota, and then depicts that against the total number of microbiome/microbiota papers. Balance shows a steady upward trend in use each year. Some false positives are included in these numbers (e.g., 'flux balance'). Numbers were negligible before 2005. 2023 shows a slight dip most likely due to incomplete data for the year. Figure credits: Michel Durinx.



Another objection might be that all these uses of balance are found only in low-quality research outlets. While it is the case that the 5400 'balance' papers came from a wide range of journals

and may not be cutting-edge research articles (reviews and opinions were included), some very illuminating discussions of balance have been published in high-profile journals.

For example, in 2015 *Cell Host & Microbe*, a premier outlet for microbiome studies, published an entire special issue under the theme of the 'overarching concept of host-microbiota balance'. [5] The editorial argued that: 'it is the balance between a host and its microbiome that determines health' and that there is 'a scientific basis to the concept of balance, as alluded to in the practice of Eastern medicine'. [5] This connection to traditional medicine is a conceptual issue that will get further attention below.

There are many more recent examples of serious attention being paid to microbiome balance in esteemed journals. Just one of these is a 2023 article in *Proceedings of the National Academy of Sciences USA*, where Winter and Bäumler reflect on the opposite of microbiome balance:

> 'Few recent advances in human medicine have been as influential as the finding that an imbalance (dysbiosis) of our resident microbial communities in the colon is linked to many chronic human illnesses'. [6]

It is not just high-profile publications that attest to the role of balance in the field. The term also features in the name and mission of a major scientific research consortium, the DFG 'Balance of the Microverse Cluster of Excellence' in Jena, Germany. [7] The consortium describes itself as concerned with not only understanding balance in a wide range of microbially inhabited ecosystems, but also its opposite, imbalance, and how balance is restored.

> 'Anthropogenic impact or infectious microorganisms can cause a dramatic imbalance in microbial communities, resulting in the deterioration of ecosystems, weather extremes, severe crop loss or diseases … The vision of the Microverse Cluster is to investigate the dynamic balance of complex microbial communities from the molecular to the ecosystem level. This should enable us to develop new technologies to maintain the balance or restore it'. [7]

Although these publication counts and quotes give an indication of balance as a live and potentially important concept in microbiome research, they do not show the actual conceptual role of this term in the literature. What scientists are using balance to mean is more important than numbers of times the term is used, or the status of journals or scientific institutions where microbiome balance is mentioned.

Conceptualizing balance

A preliminary sense of how balance is used was gained from a full-text analysis of the first 500 of the 5400 papers identified as discussing microbiome/microbiota balance. These 500 papers were ranked by PubMed as 'best match' for the search, and most were very recent publications. Interpretive analysis of each paper produced 11 ways in which loose conceptualizations of balance were applied to microbiomes (Table 1).

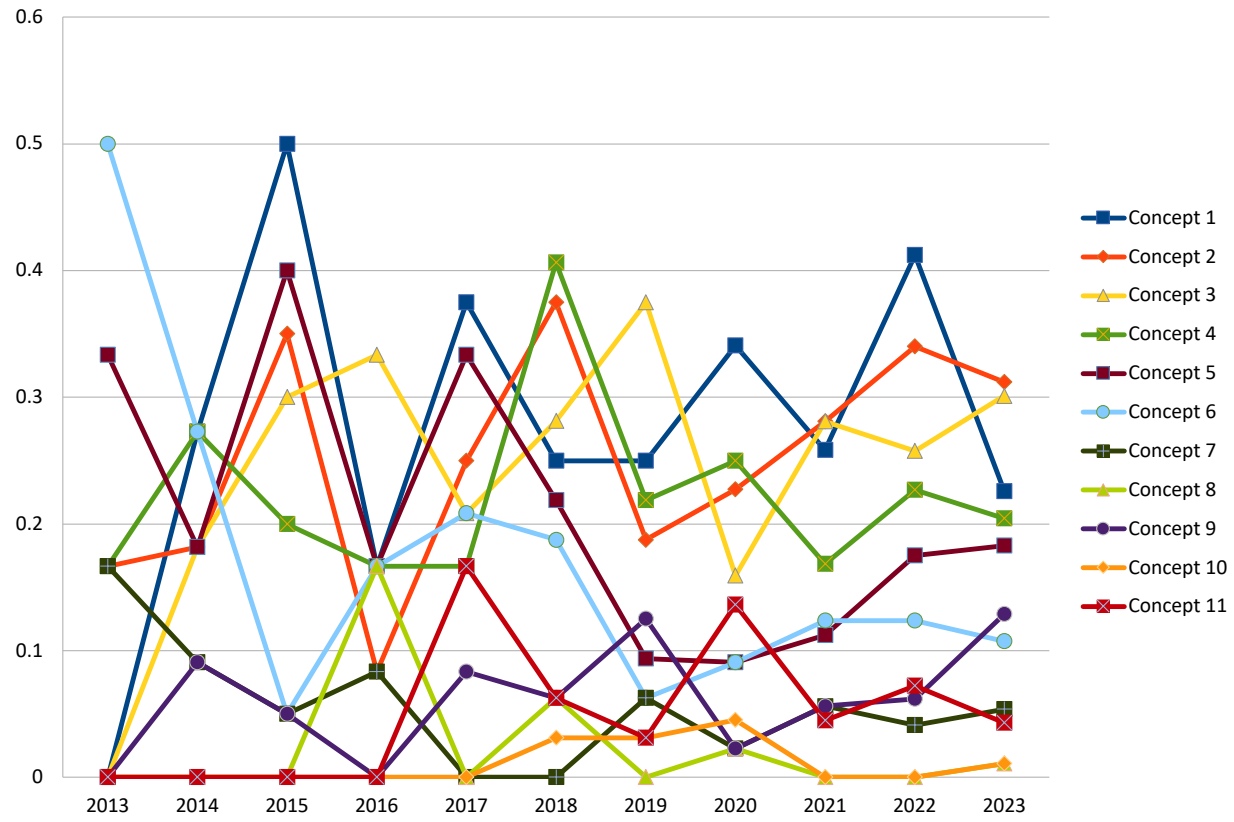
Most papers in the sample of 500 used a combination of interpretations of balance (see SI). Sometimes these meanings were explicit, and other times they could only be inferred from the

context of use. After just over 120 papers, no new conceptualizations were found. The interpretations are listed in Table 1 in order of appearance and how common they were in the sample (see Figure 2 for more details of sub-concept occurrence). In addition, this order of concepts becomes increasingly explanatory about what balance is and does. Each of these concepts requires some discussion to make their meaning clear.

Table 1: Concepts of balance. The analysis excluded a small number of publications using balance in a non-relevant sense (e.g., 'flux balance') as well as those in texts that were not fully available (see SI). A single publication might use multiple concepts of balance. See Figure 2 for relative uses of each concept of balance per year.

Sub-concept of balance	**Interpretation**
Concept 1	State with positive relationship to health (and normality)
Concept 2	Opposite of state requiring re-balancing for health
Concept 3	State that becomes imbalanced due to changes in composition and/or function of microbiome (specified and unspecified)
Concept 4	Opposite of dysbiosis
Concept 5	Opposite of imbalance between pathogens and commensals or harmful vs beneficial
Concept 6	Homeostasis/equilibrium
Concept 7	Eubiosis and/or symbiosis
Concept 8	Coevolved coexistence
Concept 9	Ecological balance
Concept 10	Problems of conceptualizing balance
Concept 11	Unspecified meaning

Figure 2: Numbers per year of 11 balance concepts in 500 full-text microbiome/microbiota publications. Some publications may use multiple conceptualizations of balance. Each counts as one use of balance. The y-axis is the relative frequency of each concept per year. The x-axis starts at 2013 due to the PubMed sample of 500 'best matches' going back only that far. False positives (e.g., 'flux balance', 'electrolyte balance') are excluded from this sample. Figure credits: Michel Durinx.



Concepts 1 and 2: Balance as health, balance as opposite of non-health
These two concepts state very simply that balance and health have a positive relationship, and that imbalance and illness do too. But although a causal connection is often implied (i.e., a balanced microbiome causes host health, and an imbalanced microbiome causes host illness), causal claims are not always part of these two conceptualizations. A lot of the literature leaves the actual relationship vague (see Table 2). And although the majority of the literature using balance in these two senses is about human health, a small proportion of it concerns plants, other animals, and ecosystems in general.

Concepts 1 and 2 provide a very descriptive account of balance that assumes a balanced microbiome and health go together. Although balance is itself meant to explain illness, this concept leaves the explanation open or takes it as so self-evident it needs no further details.

Table 2: Representative quotes for Concepts 1-7

Concept	Representative quotes
Concepts 1 & 2: Balance as health; balance as the opposite of non-health	'As is known to all, a balanced microecosystem of the nasal cavity and intestines is essential to biological health'. [8] 'This microbiota normally has a balanced composition that confers health, and disruption of this balance (dysbiosis) confers disease susceptibility.' [9]

Concepts 3 & 5: Balance as a state that is lost due to taxa change or proportions of harmful/beneficial microbes	'Diversity refers to the number of different taxa within a sample and evenness in the distribution of these taxa; these properties of the microbiota promote "resilience," which refers to the maintenance of balance despite disturbances.' [10] 'A disrupted microbiome balance, rather than an altered single microorganism, is related to the pathogenesis of depression.' [11] 'It is important to maintain the microbial balance of beneficial, neutral and harmful bacteria for the sake of the system's stability and health'. [12]
Concept 4: Balance as the opposite of dysbiosis	'A shift in the balance of microbiota composition such that it may become deleterious to host health is termed "dysbiosis".' [13] 'Dysbiosis, a loss of balance in the microbiota'. [14] 'Dysbiosis, i.e., microbial imbalance, especially of the gut microbiota, has been associated with the development of several diseases'. [15]
Concept 6: Balance as homeostasis	'Homeostasis: a balanced relationship between host tissues and the resident microbiota that prevents destructive inflammation or disease'. [16] 'A balanced gut microbiota is important for human health, but the mechanisms that maintain homeostasis are incompletely understood … an imbalance in the microbial community (dysbiosis) is an underlying cause of sickness'. [17]
Concept 7: Balance as eubiosis/symbiosis	'The gut microbiome has highly balanced symbiotic interactions with the host.' [18] 'A balanced gut microbiota with high stability has symbiotic interactions with the immune system of the host.' [19] 'Man's co-evolution with microbiota over time has led to a finely balanced relationship which is referred to as host–bacterial mutualism.' [20] 'This balance can nevertheless, undergo distortions that may lead to a shift from a healthy, symbiotic, relationship to a pathological, dysbiotic one.' [21]

Concepts 3 and 5: Balance as a state that is lost due either to particular taxa changing, or to alterations in proportions of harmful versus beneficial microbes.

These two concepts are also closely related and only separated in the list due to another frequently invoked concept sliding between and applying to both of them (Concept 4, see below). Concept 3 is more concerned with named taxa, regardless of taxon level, and is agnostic about whether these are harmful taxa or not. Concept 5, however, assumes that

changes in composition that are associated with illness must be due to fluctuations in pathogen proportions that change the relationship of the microbiome to the host (see Table 2).

Although often used quite descriptively, these two concepts are hinting more strongly at mechanistic explanations involving balance. In Concept 3, changes in taxa are taken to have some sort of effect on the host, and Concept 5 pushes this further by positing that a change in the negative-positive balance between host and microbiome is why illness comes about. However, because both these concepts are usually applied only after an illness is diagnosed by other means in the host, it remains doubtful how explanatory such concepts really are. Imbalance is just another synonym for illness in this sort of reasoning, and it leaves unexplored the question of whether imbalance and health can co-exist.

Concept 4: Balance as the opposite of dysbiosis

Dysbiosis is another hugely popular term in the microbiome literature. Around 9% of the total microbiome literature uses dysbiosis, and over 14% of the human microbiome literature mentions it. It can mean merely an altered microbiome, but most commonly, dysbiosis is conceptualized as the imbalanced state of the microbiome when the host is ill (see Table 2). In other words, many uses of dysbiosis are interchangeable with imbalance, with each undefined term the definition of the other term. In some of its uses, imbalance-as-dysbiosis is meant to be explanatory (see Table 2), which involves accounts of why imbalance is a problem and how it brings about illness. But in attempting these elaborations, Concept 4 can get itself into an explanatory tangle.

There already exist a number of critiques of dysbiosis. [1, 2, 3] These papers are critical of that fact that dysbiosis is not usually a measured state, but a state that is assumed because of the ill-health of the host. If a host is unwell, the reasoning is that they must have a dysbiotic microbiome whatever its composition, and that the dysbiotic microbiome must be the cause of the illness. This sort of circular reasoning, and the lack of operational precision of dysbiosis, means that at least some microbiome scientists caution against using the term (e.g., [2]). If we now find dysbiosis operating as a synonym for 'imbalance', it might mean that the concept of balance is in similar trouble and that a new circularity has been imposed (i.e., dysbiosis is the loss of microbiome balance; balance is the opposite of dysbiosis).

Concept 6: Balance as homeostasis

Homeostasis is often contrasted to dysbiosis, and also invoked as the proper meaning of balance (see Table 2). The term homeostasis is central to much physiology, where it describes the capacity of a system to return to a 'set point' by means of signals and correction mechanisms that form a negative feedback loop. [22] In many respects, homeostasis is a description of an evolutionarily selected system state for which at least some mechanisms are known to exist. Phenomena such as body temperature and blood sugar and salt levels are considered homeostatic, which means they stay within a certain range that may be adjusted in different circumstances. [22] Immune systems are also claimed to be homeostatic, because after responding to an immunological challenge they return to a resting state. [23] Suggestions are sometimes made that body size/adiposity is controlled by homeostatic regulation, but this may be more of an idealization than a physiological reality. [24] Many social and psychological phenomena are also supposedly homeostatic (e.g., [25]) but these uses may be quite loose

even though abstract accounts of homeostasis do not preclude any phenomena. Most generally, diseases of all kinds are conceptualized as 'failures of homeostasis' [26] and this is the broad attitude taken in the medical microbiome literature.

Famed microbiologist René Dubos (1901-1982) introduced the concept of homeostasis to the medical study of mammalian microbiota, and he interpreted it evolutionarily and symbiotically. [27] Dubos saw humans and their microbes as adaptively balanced in a homeostatic relationship that determined host health status. This idea, reinvigorated by microbiome research, conceptualizes host-microbiome homeostasis as a system selected to have a certain health-producing state. [28] Feedback mechanisms keep reproducing the health-giving balanced state until modern conditions overwhelm this evolved homeostasis. Dysbiosis is frequently defined as the failure of microbiome homeostasis (e.g., [29]).

Why is this conceptualization a problem? As psychologist-philosopher John Maze (1923-2008) pointed out with regard to the copious deployment of homeostasis in post-WW2 psychology, 'a vaguely conceived and therefore very accommodating force named homeostasis' may hinder inquiry by conceptualizing mere by-products as the goals of systems, thus preventing closer attention to actual underlying mechanisms. [30] Microbiome research papers tend to do something similar, with homeostasis taken as a blanket explanation of the role microbes play in health and disease (e.g., [31, 18]). Even when it is not known how homeostasis works, it is still seen as explaining host states. For instance, a composite interpretation that has elements of Concepts 1, 2, 4, and 6 attempts to link them all explanatorily:

> 'A balanced gut microbiota is important for human health, but the mechanisms that maintain homeostasis are incompletely understood … an imbalance in the microbial community (dysbiosis) is an underlying cause of sickness'. [17]

However, because it is not clear that host-microbiome relationships are homeostatic, and because 'homeostasis' is more likely to be an expectation than a finding, it becomes important to add additional layers of explanation about why there would be homeostasis and what biological processes would bring it about.

Concept 7: Balance as eubiosis and/or symbiosis

Eubiosis is a positive term, coined when dysbiosis was first used (see [1]). While eubiosis is simply defined as the opposite of dysbiosis, its use is increasingly supplemented or even replaced by the notion of symbiosis. In this expanded concept of balance, symbiosis is taken to have positive connotations for the host (see Table 2). Mutual benefit is assumed between host and microbes, and the microbiome as a whole is often conceptualized as functioning *for* the host. While not all microbiome research makes this conceptual move, it is more likely in the medical microbiome literature and this is especially the case when balance is invoked.

Traditionally, symbiosis has meant merely the intimate living together of different species. [32] This intimacy can have positive, negative and indifferent outcomes for the partners, but there is a trend in popular interpretations and even some of the evolutionary literature to take symbiosis to mean exclusively mutualism. [33] For symbiosis-as-mutualism interpretations of balance, it is assumed that the majority of the microbiome works for the host and controls any aberrantly pathogenic members of the community (e.g., [34, 20]). Evolution is supposed to have

brought about this health-producing relationship, with host health being good for the microbiome and vice-versa (e.g., [35, 36, 21]).

Concept 7 is thus invoking evolutionary theory to explain the relationship between host and microbes, which becomes necessarily mutualistic, and this mutualism is packaged up mechanistically as balance. The key question to raise here, however, is whether it is justified to assume mutualism and whether the long history of human occupation by microbes means the symbiosis functions *for* healthy hosts. Many standard evolutionary interpretations of microbiome-host relationships depict a very different situation, with a great deal of conflict and control, and very accidental benefits that are sometimes merely evolved dependencies. [37, 38, 39, 40] One reason these conflict-control dynamics might be better interpretations than mutualism is because of the limited coevolution of microbiomes and human hosts.

Concept 8: Balance as coevolved coexistence

This concept invokes evolutionary views that are often connected to those of Concept 7. The host-microbiome symbiosis is taken to be so intimate that despite microbiomes consisting of hundreds or thousands of lineages, those lineages are believed to be coevolving with the host lineage (Table 3). Claims of coevolution, however, require clear evidence of reciprocal selection, and the majority of claims do not provide it at either a phenotypic or genetic level. Many of these instances nevertheless go on to argue that not only has coevolution occurred but that it is so comprehensive that host and microbiome should be regarded as a single functional and evolutionary unit, called by some a 'holobiont' (e.g., [41]). In addition, some of these claims suggest that coevolution has perfectly balanced the host-microbiome relationship, and that the best form of balance evolved in the ancestral hunter-gatherer past of the human species (see Table 3). Now that our environments, activities and selective forces have changed, this balance is deemed to have been upset, and recovering it is the focus of microbiome therapeutics (e.g., [42]).

There is a lot of debate about what 'holobiont' can legitimately mean. [43] It is not clear how much mutual adaptation and functional integration there is between a host and all its microbes. Most evolutionary-theoretic views would suggest that the host imposes tight control on its microbial occupants, and the microbial occupants compete intensively among themselves for advantage (e.g., [37]). This is not mutualism. And while there may be some signatures of coevolution between host and individual microbial lineages, mostly that is not the case. Even in classic pairwise cases of coevolution, such as pollinator-flower relationships, there can be considerable doubts about the coevolution of, for example, plants with extremely deep nectaries and pollinators with a matchingly long probobscis. [44] Despite appearing to be 'obviously' coevolutionary, this relationship can potentially be 'one-sided', which is to say it is *not* coevolutionary in the standard sense. [44]

In the microbiome situation, things are even less clear. There are large numbers of species involved, not a single pair of species. Microbiome compositions at the level of species and strains differ from one host to another. Microbes can come and go, and many are not stuck with the host for the entire microbial lifecycle. [45] Any contributions to hosts can be made by many different combinations of microbes, which means there is unlikely to be much reciprocal selection. That means coevolution is probably not happening (except in occasional pairwise

relationships), and that this explanatory interpretation of balance is on shaky theoretical ground. In particular, claims about coevolution cannot be used to justify particular approaches to treatment that depend on notions of an ancestral coevolved microbiome and how its balancing effects produce health.

Table 3: Representative quotes for Concepts 8-11

Concept	Representative quotes
Concept 8: Balance as coevolved coexistence	'It is conceivable that coevolution over millions of years resulted in a harmonious balance between the human host and the oral microbiome, like that found in all wild-living animal species. Probably, the first dramatic challenge to this coexistence was the dietary shifts that occurred as a result of the transition of the human population from a hunter-gatherer lifestyle to a farming lifestyle.' [41] 'We might expect that loss of these coevolved microbes and associated functions would have a negative health impact … with the shift in the composition of the industrialized microbiota, certain services may be lost or out of balance, resulting in suboptimal states of host physiology or disease'. [42]
Concept 9: Ecological balance	'Changes in the appropriate ecological balance … identify the health of microbial community balance'. [46] 'A balanced gut microbiota with high stability has symbiotic interactions with the immune system of the host'. [19] 'In ecological systems, species can keep themselves in balanced numbers by negative feedback mechanisms, which can allow long-term stability.' [47]
Concept 10: Balance as a problematic concept	'Dysbiosis suggests that (1) a "balanced" skin microbiome has been defined; (2) a "balanced" skin microbiome is equivalent to skin health; and (3) an "imbalance" is causal of disease. Demonstrating causality of dysbiotic states presents [methodological] challenges.' [48] 'This balanced microbial community functions as a microbial organ … Comparison of the gut microbiota composition between different individuals reveals very little overlap on the species level, thus making it problematic to define what a "balanced microbial community" or a functional microbial organ should look like.' [49]

	'As cataloguing microbial species and their genes does not reveal what represents a balanced microbial community, some go as far as to suggest that the balance concept is a holdover from prescientific thought, as it cannot be measured and is, therefore, not useful for microbiome research.' 'Our inability to define balance, in turn, makes it problematic to specify what constitutes an imbalance in the microbiota, commonly referred to as dysbiosis, a major organizing concept in microbiome research.' [50]
Concept 11: Unspecified	'Metagenomic analyses are very useful for microbial classification aimed at unveiling key players driving microbiota balances'. [51] 'Their co-occurrence network revealed the existence of a complex and delicate balance among microbial communities.' [52] 'The balance between optimal and dysregulated host-microbiota interactions has completely changed our understanding of immunity and inflammation'. [53]

Concept 9: Ecological balance

If evolutionary theory is currently not adding explanatory depth to balance concepts, it makes sense to turn to ecology, which has a long history of referring to balance. [54] Claims about 'ecological balance' in microbiome research often occur without any specifications of what it entails (e.g., [46]; see Table 3). However, in a small number of ecological interpretations, hints are made that stability lies at the heart of ecological balance (e.g., [19]). But stability tends not to be elaborated in microbiome-balance papers either, although whenever it is expanded upon (e.g., as some sort of environmental homeostasis), it is deemed to be positively related to health (e.g., [47]). Microbiome stability is often seen as synonymous with resilience, the capacity to return to a pre-existing state (e.g., [10]), and this is sometimes conceptualized as an equilibrium, which is also discussed in terms of balance and homeostasis (e.g., [55]).

All these uses are problematic. Although balance has a 300-year history in ecological writing, the many conceptual issues that accompanied the term led to its abandonment by most ecologists in the mid-twentieth century. [54] The basic drawback was that this venerable concept of balance assumed some sort of ideal state that nature strove to achieve and maintain. [56, 54] Balance, like homeostasis, implies mechanisms that bring systems back to a balanced state after perturbations, and such mechanisms could only be speculated on by earlier ecologists. Balance had to remain imprecise in order to persist conceptually in ecology, and in the end the imprecision overwhelmed the concept's usefulness.

Stability might seem the obvious replacement concept, and it has both an empirical and mathematical pedigree. But just like balance in microbiome research, stability in ecology consists of multiple overlapping and distinct conceptions, some of which require very different

bodies of evidence and mathematical theory. Stability is thus multivalent, because it covers a variety of different meanings that range from 'unchanged' to 'resilient' and 'persistent'. [57] Rather than a generic concept of stability that might apply to an ecosystem, fine-grained conceptualizations and applications of specific models turn out to be the only way to counter confusion and unclarity. [57] Notably, however, even when specific models of stability are applied, there can still be confusion between what empirical ecologists mean by stability and what mathematical modellers mean (e.g., the famous debates in the 1970s about stability and its relationship to diversity and complexity – see [58]).

These general conundrums about stability are exacerbated in medical microbiome studies of hosts and health because of different so-called stable states being associated with health and disease. An ill host can have a very stable 'bad' microbiome – so stable, in fact, that the state of ill-health persists despite therapeutic interventions. [59, 55] And as ecologists worked out some decades ago, unstable systems can be very resilient, [60] which means using stability as a synonym for resilience is likely to lead to additional confusion.

So although 'stability' sounds like a promising synonym for 'balance', especially because it comes with a proper scientific background and a mathematical apparatus, it is currently not contributing insight into how microbiomes might cause ill-health or health. And if terms such as 'equilibrium' are thrown into the mix without any modelling or measurement (e.g., [55]) then we are back to our conceptual starting point. Just like balance, when used in some generic sense, stability (or equilibrium or homeostasis) fails to explain much or even anything at all apart from researcher expectations. It is only when microbiome stability is modelled more precisely without invoking 'balance' that we see how these conceptual ambiguities can be overcome and the circularity severed (e.g., [61, 62]).

Concept 10: Balance as a problematic concept

A small minority of the full-text articles mentioning microbiome balance do so to examine the problems of balance (see Table 3). Although most of these articles are looking for ways in which to justify and continue using balance (often connecting it to justifications for dysbiosis), these papers do not shy away from the fundamental issues that obscure conceptions and measurements of balance. The most-noted issues are those of defining and measuring balance then establishing causality between imbalance and ill-health (e.g., [48, 49]).

A few of the papers that address the problems of balance are concerned with the historical resonance of balance with ancient medical philosophies (e.g., [50, 2]). There are indeed some remarkable similarities in how microbiome findings are framed and how the ancient substances of the four humours are theorized. [63] These parallels are celebrated in a small number of unabashedly speculative pieces on the potential connections between microbiome balance and the mystic substances of ancient or traditional medicine (e.g., [64, 65, 66, 67, 5] A growing body of other literature focuses on possible therapeutic connections between Chinese traditional medicine and microbiome research, with the notion of balance (often as Concept 6) featuring prominently in such pieces (see, e.g., [68, 69, 70]). These traditionally oriented publications are obviously not problematizing the connections, but for many microbiome researchers such links are likely to indicate yet more clearly how loose and open the concept of balance is, and how it can be made to serve a wide range of research agendas.

Concept 11: Unspecified concepts of balance

A small portion of the microbiome-balance literature neither states nor even implies what balance actually means (Table 3). Even though balance is a key term in these passages, it is apparently taken to be a self-evident notion. In some of these cases, 'balance' is elaborated by additional terms that are also unspecified, such as 'delicate' and 'complex', or with unexplained terms (e.g., 'optimal') specifying the difference between balanced and imbalanced microbiome states (see Table 3). Although authors of these papers could be criticized for using an unspecified term, it is not clear from the nine articulated concepts that conceptual specification would lead to greater clarity.

Is an unspecified notion of balance acceptable if it is a placeholder for a concept that will eventually be better specified? The problem with this view is that the broad notion of balance is already framing data interpretation and applications. 'Rebalancing', for example, is the main therapeutic aim of much applied microbiome research. Even if balance is meant only loosely, it sets out a certain structure that implies both explanation ('the illness is caused by disturbed balance') and appropriate intervention ('balance and thus health can be restored by going back to the original state'), despite the lack of both theoretical justification and evidence.

Another conceivable reason to retain an unspecified notion of balance is that not all scientific language is for scientists. Terms may be serving public communication purposes, with balance possibly getting across in a simplified form some of the potential of microbiome research for public health uptake. The problems on the scientific side of balance, however, become even more pernicious when balance is used commercially in the public sphere. Microbiome balance is evoked copiously in the marketing of probiotics, dietary supplements, cosmetics and lifestyle enhancements (e.g., exercise regimes) as the mechanism by which these purchases will lead to better health. For the science to echo the slipshod language of marketing seems a misstep.

A balanced verdict

Intuitively appealing and persistent but problematic concepts have a long history in science. Some are problematic because of their looseness (e.g., life, disease, holism), whereas others are problematic because of their multivalence (e.g., stability, species, gene, drug, emotion). Balance can be both loose (Concepts 1, 2, 11) and have multiple meanings (Concepts 3, 4, 5, 6, 7, 8, 9) as well as recognized problems (see Concept 10). It is sometimes the case that vague concepts actually allow flexibility and accommodate new findings (e.g., chemistry terms in [71]; 'resilience' in [72]), thus leading to scientific development, but this is an observation that can only be made retrospectively. Such instances do not suggest that present-day sciences *should* employ loose concepts if they want to make progress.

As shown above, several conceptualizations of balance actually misinterpret or mislead by using established theory either without justification or incorrectly (e.g., Concepts 6 and 8). Even if researchers are willing to accept a plurality of concepts to be applied in different contexts, that does not mean every one of the conceptualizations available is good and helpful. And if there are inconsistencies between concepts of balance (e.g., Concepts 1 and 9), then the appropriate circumstances of usage have to be thought about quite carefully. Worryingly,

although a majority of the human-based uses of balance concern the gut microbiome, the same concepts and all their implications are used for microbiomes in other parts of the body. This broad use is problematic because it is well-known that microbiomes in different parts of the body have different dynamics and potentially very different relationships with the host. [73, 74]

Box 1 suggests some constructive options in relation to all these problems. One way of proceeding is to work out the positive concept (balance) before assuming there is a negative one (imbalance), or even that the negative state is the clear opposite of the positive one. A concept such as balance should ideally explain mechanistically why certain states exist and why changes in those states can result in disease. Drawing from evolutionary and ecological theory makes considerable sense, even in a medical context, because without theoretical predictions any measures of balance are likely to be descriptive and post-hoc. But in deploying these theoretical frameworks, a whole raft of questions have to be addressed. For instance, what sorts of stability produces health? Are there general measures of health-producing microbiomes, or will it come to down to individualized patterns? How does selection operate on such variable relationships, and is selection even relevant to health? Is illness really a 'breakdown' of homeostasis or does it require very different ways of thinking about the relevant regulatory processes? These and many more questions cannot be answered without carefully designed studies based on longitudinal and site-specific data to understand what the pathways might be from healthy to unhealthy states and back again (e.g., [75]).

Box 1: Getting meaning out of balance in microbiome research

The range of ways in which 'balance' is used in microbiome research has positive and negative accounts that may not be simple opposites. Each of these positive-negative pairs plays different roles in the research process. Some are purely descriptive, whereas others make causal hints, and yet others invoke evolutionary and ecological theory to explain why balanced or imbalanced microbiomes bring about healthy or diseased states of the host. The most promising roles balance plays in microbiome research are explanatory, in which ecological and evolutionary theory are invoked to explain host-microbiome relationships via theoretical mechanisms (see text for discussion), even if some of the current terminology is problematic (in quote marks). These are the most likely candidates for the development of appropriate metrics, but considerable work remains to be done.

ROLE IN RESEARCH	Balance (positive concept)	Imbalance (negative concept)
Descriptive	Microbiome state that underlies health	Microbiome state that underlies illness
Descriptive with causal implications	Composition or function that produces health: known by association	Composition or function that produces illness: known by association
Descriptive with causal implications	Beneficial microbiome: 'good microbiomes cause health' in various ways	Harmful microbiome: 'bad microbiomes cause illness' in various ways

Descriptive with explanatory implications	'Eubiosis': a microbiome state that is associated with health and assumed to explain that healthy condition mechanistically	'Dysbiosis': a microbiome state that is associated with illness and assumed to explain that illness condition mechanistically
Explanatory	Symbiosis, 'coevolution': An eco-evolutionary account of why health and not illness results from a relationship between host and microbiome	Pathogenesis, evolutionary mismatch: An eco-evolutionary account of why illness and not health results from a relationship between host and microbiome
Explanatory	'Homeostasis', 'stability': a state regulated by specified mechanisms to maintain a beneficial eco-evolutionary relationship between microbes and host	'Non-homeostasis', 'instability': a state no longer regulated by specified mechanisms to maintain a beneficial eco-evolutionary relationship between microbes and host

Conclusions

By breaking down the ways in which a concept is used, we gain a better understanding of how effectively that concept is working in the field. Understanding concepts can lead to appreciation of the full ramifications of particular terms. Even if they look innocuous, they can have all sorts of tricky undercurrents. Not many microbiome researchers, for example, will want to buy into terminology that echoes forms of medicine that most of them consider outdated or at least obscure from modern medical perspectives.

The analysis above suggests that balance is currently a loose, unhelpful term that is forming the conceptual cement of a growing body of medical microbiome research. Contradictions and circularity mark many of its uses. Although balance is mostly untheorized, when theoretical statements are made (e.g., 'balance is homeostasis', 'evolution has fused host and microbiome into a balanced symbiosis'), these end up being inaccurate, misleading, and obfuscating. However, thinking more carefully about these theoretical justifications and the metrics they require is potentially a way forward for the concept of balance. Box 1 shows how there are some explanatory uses of balance that could be worked out better theoretically and empirically to illuminate microbiome causality and how it contributes to host health and disease.

The other option, of course, is to try and eliminate the notion of balance altogether. If microbiome research were to take a strict lesson from the history of balance in ecology, that might be a reasonable outcome to emulate. But without some sort of replacement, the conceptual gap in microbiome research is likely to continue to attract loose uses of balance. The field needs a positive effort to plug that gap. Even the most medical applications of

microbiome research may need to think more about how evolutionary and ecological theories can be used to develop sounder notions of balance.

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