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"Love is a microbe too"[1]: Microbiome dialectics

Hub Zwart

Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

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ABSTRACT

Whereas the Human Genome Project was an anthropocentric research endeavour, microbiome research entails a much more interactive and symbiotic view of human existence, seeing human beings as *holobionts*, a term coined by Lynn Margulis to emphasise the interconnectedness and multiplicity of organisms. In this paper, building on previous authors, a dialectical perspective on microbiome research will be adopted, striving to supersede the ontological divide between self and other, humans and microbes, and to incorporate the microbiome as a crucial dimension of human existence, not only corporally, but also in terms of mood and cognition. On the practical level, microbiome insights promise to offer opportunities for self-care and self-management, allowing us to consciously interact with our microbiome to foster wellness and health. How to distinguish realistic scenarios from hype? Here again, an interactive (dialectical) approach is adopted, arguing that practices of the self should result from mutual learning between laboratory research and life-world experience.

Introduction: The Human Genome Project

On June, 26, 2000, President Bill Clinton, together with scientists Francis Collins and Craig Venter, proudly presented a draft version of the human genome sequence to the world, suggesting that humanity had now finally fulfilled its intellectual assignment: *know thyself* (γνῶθι σεαυτόν; Zwart, 2007). Soon, however, it became clear that life is more complex than genetic determinism (i.e., the idea that we basically *are* our genome) suggests (Zwart, 2007). Quoting the words of Alexander Pope's *Essay on Man*, and stating that "the proper study of mankind is man," the speeches presented on that solemn occasion focused exclusively on one favoured species: human beings. The anthropocentric framing obfuscated that our bodies are highly dependent on their ecosystems and actually home to many other genomes besides our own.

A ten-year anniversary series of articles published in *Nature* once again included Francis Collins (2010) and Craig Venter (2010) as human genome pioneers, but all contributing authors now agreed that life proved indeed more complex than was initially expected, while notably Craig Venter explicitly pointed to the 4,000 or so "non-human" genomes which had likewise been sequenced along the way. As a preparatory exercise, the genomes of Caenorhabditis elegans and Drosophila had already been published before taking on the human code, and in the wake of the Human Genome Project (HGP), an exponential number of genomes was added to the list. Paradoxically perhaps, but quite in line with the logic of dialectics, a key result of the HGP was that human existence can only be understood if we no longer single ourselves out from the rest of the living world, from the "non-human" (Dupré & O'Malley, 2007; O'Malley & Dupré, 2007).

Since then, owing to multiple research endeavours, including the Human Microbiome Project (HMP)—a metagenomic initiative to sequence the genomes of all microbiological entities collected from a variety of body sites—we became increasingly aware of the vital role played by the indigenous microbial metagenome in human physiology (Juengst, 2009; Parry & Dupré, 2010a,b). Seen from this perspective, the human body is basically an ecosystem, containing multiple ecological niches and habitats in which a wide variety of cellular species collaborate and compete. Human beings are redefined as superorganisms that incorporate a plethora of symbiotic multiple-species consortia. This challenges traditional views on human identity and individuality. As Rees, Bosch, and Douglas (2018) explained, the three classical biological explanations of the individual self—the immune system, the brain, and the genome—are all challenged by microbiome research. Our resident microbes not only orchestrate the immune system, but they also influence mood and cognition. The realization that humans are not insulated entities, but rather the outcome of multiple interactions with microorganisms, both indigenous and external, has consequences beyond biological disciplines. Our traditional self-image, as autonomous human individuals, is under siege.

E-mail address: zwart@esphil.eur.nl.

[1] Letter from Vincent van Gogh to Wilhelmina van Gogh, Arles, between April 28 and May 2, 1889 [original in French], in: van Gogh (2009), letter 764, translated by the author.

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The question whether we, as organisms, are 'one' or 'many,' and whether we are 'autonomous' or 'dependent,' entails a false dichotomy; for evidently, as hosts to our microbiome, we are both. We are the outcome of a dialectical interplay between autonomy and dependence, singularity and multiplicity, immunisation and receptivity, as moments of a more comprehensive interactive whole. In philosophical terms, what is required is a dialectical understanding of life, advocated in modern biology by authors such as Levins and Lewontin (1985), Gould (2002, pp. 745-757), and Gilbert and Tauber (2016).

Microbiome dialectics

Dialectics is a philosophical approach developed by ancient Greek thinkers such as Heraclitus and Aristotle, but revivified in the early nineteenth century by G. W. F. Hegel. Dialectics sees the world not as a collection of stable entities, but as processes of becoming (Zwart, 2021). For dialectics, being means "being in flux." Heraclitus long ago emphasised that "everything flows" (πάντα ῥεῖ). Dialectically speaking, individuality is not a given, but an outcome. Individuals are the (temporary) result of ongoing processes of individuation.

Hegel understood life as a cycle of cycles, compared to the finitude of inorganic chemical processes. In biology, this line of thinking was adopted by Leo Buss for instance, whose book *The Evolution of Individuality* (Buss,1987) negated the neo-Darwinian idea of individuals as the unit of selection, arguing that individuals are the outcome of cyclical processes. As Buss argues, life cycles are the *sine qua non* of evolution, while evolution is basically the evolution of cycles. In microbiome research, notably Scott Gilbert and Alfred Tauber adopted a dialectical perspective, in their paper, "Rethinking individuality: The dialectics of the Holobiont" (2016).

In the past, Gilbert and Tauber (2016) argued, both in philosophy and in biology, individuals tended to be perceived as insulated entities, as (more or less) uniform organisms, faced with the need to protect themselves against an environment teaming with pathogenic microorganisms and other hostile factors. In dialectics, this is known and the stage of diremption: negating the initial interconnectedness of life. In their "ecological dialectics," however, Gilbert and Tauber emphasise that this duality (between self and other, inside and outside, intimate and foreign) must be superseded, because individuality must be understood as an outcome: a delicate balance, resulting from multiple interactions. Yes, individuals defend themselves (their independence, autonomy, immunity) against challenging environments, but this dialectical moment of negativity and resistance is part of a more comprehensive and integrated process. In the end, the notion of autonomous (self-determining, goal-directed) individuals, struggling with their environments and competing among themselves, not only sounds suspiciously ideological, but it is also scientifically inadequate. Individuality is a balance between rejection and tolerance, and the outcome of multiple complex interactions between organisms and their internal and external environments.

Notably, the recognition of the ubiquity of symbiosis has challenged traditional notions of biological individuality. Although it is often claimed that 'we' are all Darwinians (Acerbi & Mesoudi, 2015; Caporael & Brewer, 1990), microbiome research shows that our view of life is rapidly evolving. Rather than seeing nature in terms of struggle and competition, authors such as Lynn Margulis emphatically acknowledged the importance of collaboration and mutual dependence: seeing individuals as "holobionts" (1991), as collections of closely associated and interacting species, and as components of a web of life (Margulis & Fester, 1991; Margulis & Sagan, 1986, 2002). In various publications, Margulis and her co-authors argued that life on earth depend on a worldwide microbial superorganism, maintaining the conditions that sustain life. Earth is basically a microbial planet. Microbes created the atmosphere. As recyclers, they support the global metabolism. And nearly all metabolic processes were developed by them. They are cyclical beings. Moreover, microbes not only dominate our external environment, they steer our internal environment as well. They are our "forgotten organ," our "collective unconscious" (Dinan, Stilling, Stanton, & Cryan, 2015), affecting human health, mood and cognition. Although initially organisms and their microbial parasites are antagonistic (antithetical), eventually organisms may join forces with their microbes, living better while being hardened by them (Serres, 1982, p. 68).

Thus, increasingly, 'individuals' are understood as symbiotic consortia of hundreds of species: as composite organisms, as 'holobionts' whose physiology entails co-metabolism between host and microbiome (Gilbert & Tauber, 2016, p. 840). Rather than being a mere paradigm shift, this conceptual rethinking of individuality entails an ontological understanding of living beings, displacing the self-centred individual as a governing concept (even on the level of selfish genes) and paying due attention to the beneficial interaction between organisms and their internal and external milieus. Symbiosis is a decisive signature of life on earth.

Biology, Gilbert and Tauber (2016) argue, is a "dialectical discipline," and living nature is a "dialectical world" (p. 842). The initial view (e.g., individuals as insulated organisms threatened by hostile invaders, Smith & Hughes (2013)), must be replaced by an approach which sees organisms as assemblies of hundreds of symbiotic species, e.g., host organisms and their microbiomes. Immunity for instance is not a purely 'negative' (defensive) mechanism, but a comprehensive result: the net balance between rejection and assimilation, reflecting the dynamical interaction between hosts and microbiomes, organisms and ecosystems.

Microbiome research

Recently, a European microbiome research initiative, the *International Human Microbiome Coordination and Support Action* (IHMCSA), was launched. I was invited to join this interdisciplinary endeavour as a philosopher of science, although I prefer to see my field as philosophy *in* science: philosophy as a dialectical (interactive) dialogue, a mutual learning process between various scientific disciplines in combination with other sources of insight (e.g., public intelligence and practical existence, including practices of the self). In such a context, if we want the life sciences – humanities dialogue to work, it is important not to limit philosophical contributions to applied ethics or public engagement in the traditional sense of the term, but to address a broader and more comprehensive spectrum of questions. From a philosophical perspective, a plethora of philosophical issues is at stake in microbiome research, albeit often in an implicit and abstract manner, awaiting further explication. For instance, as indicated above, microbiome research entails a basic view of nature, emphasising collaborative networks and mutual dependencies rather than selfish and competitive entities. And notwithstanding the impact of Darwinism, microbiome research urges us not see nature in terms of struggle and competition, but first and foremost in terms of collaboration and mutual dependence (a web of life). The microbiome is our forgotten, extimate organ, 'extimate' in the sense that it represents both intimacy and otherness. It is internal and embedded, and yet foreign. Such questions help us to make our ethical questions more specific and precise and to add important points of attention to deliberations in the public realm.

What can a dialectical approach add to this? Living in the early-nineteenth century, before the insights of contemporary microbiome research were available to him, Hegel already understood life in terms of interaction: as a cycle of cycles (Hösle, 1987; Zwart, 2021). He emphasised that digestion, for instance, is an interactive process, so that

excrements must be considered as a *product*: they are not mere negativity, mere waste (i.e., useless indigestible matter). Rather, in the course of the digestive process, the organism adds to it and actively expels it. Moreover, as contemporary research reveals, the role of the microbiome should not be reduced to the processes of metabolism taking place inside the gut. Rather, the microbiome is a pervasive and distributed organ. Microbes are everywhere, and the whole human organism is involved in host-microbiome interactions. Finally, microbiome research is itself an interactive field, involving multiple forms of interdisciplinary collaboration. From a dialectical perspective, microbiome research as currently conducted not only *studies* dialectical processes of interaction, but is also itself the result of a dialectical development. The dialectics of nature is studied by a dialectical research field.

Explicating the microbial realm

From a dialectical perspective, a number of stages can be distinguished in microbiological research. The first stage (first 'moment,' dialectically speaking) was represented by pioneers such as Anthony van Leeuwenhoek who, in the 1670s, spotted microbes ("animalculae") with his self-made microscope for the first time, capturing them in unique drawings. It was a moment of revelation, because an unknown realm of microbial life (a terra incognita) was suddenly disclosed. At the same time, the use of the microscope resulted in an ontological divide, between subject (the human observer) and object (the enigmatic novum), between self and otherness. The microscope as a research contrivance materialises both proximity and distance. Although microbes are brought into view, so that we seem to get closer to them, the ontological distance between humans and the microbial realm (between self and other) increases. As Hegel would phrase it, microbes become a "*Gegenstand*": and object, but at the same time an opponent. Until then, we had dwelled in a microbial environment as our natural way of being-in-the-world, co-acting with microbes in a practical manner, in processes such as fermentation. Now, microbes are framed as 'other' and even as a threat. The microbial world is objectified. This is the inevitable stage of diremption which we must past through, but eventually, the dichotomy must be superseded, by realising that microbes are not only 'other' but also 'us' (the third moment).

Microbes were rediscovered in the second half of the nineteenth century by scientists such as Louis Pasteur and Robert Koch, who founded microbiology as a research field. Now, microbes definitely became framed as objects-opponents. Basic dimensions of our environment whose presence had been taken for granted (air, water, domesticated animals, other human beings, etc.) now represented potential threats—we had entered the second dialectical moment. Now, the focus was on negativity, e.g. on the identification of microbes as pathogens: as hostile others, antithetical to human health. Dialectically speaking, vaccination and other forms of immunisation constitute what Hegel refers to as the "negation of the negation" (the third moment). To supersede and overcome the treat, otherness is literally incorporated. A vaccine typically contains a weakened variant that resembles the disease-causing microbial pathogen in such a way that it can be interiorised. Immunisation is achieved by conscious exposure to and partial incorporation of disruptive otherness. Again, immunity is not a given, but a dialectical result.

A letter by Vincent van Gogh

As argued, the third step in the dialectical process is precisely this reconciliation and integration of self and other: the realisation that otherness is something internal. During the fin de siècle, there was already a considerable awareness concerning the importance of microbes for human existence. An interesting illustration of this is a letter written by Vincent van Gogh, at that time a patient in a mental hospital, to his sister Wilhelmina, between late April and early May 1889. He considered when "from time to time I have fits of melancholy, atrocious remorse," that those things "are possibly microbes too, just like love" (van Gogh, 2009, letter 764). Apparently, a physician[2]—"the junior doctor here" who, according to the same letter, was telling the nursing nuns that "love is a microbe too"—had informed him about some recent developments in microbial research and their implications for human self-understanding (van Gogh, 2009, letter 764, as translated in the edition).

This epistolary exchange indicates the awareness that the impact of 'our' microbes exceeds metabolism and digestion. Their impact supersedes the Cartesian mind-body dichotomy (separating the mental from the biological), as the microbiome affects mood, wellness and cognition as well. Thus, microbiome research forces us to reconsider our self-image as autonomous beings.

Again, a dialectical process can be discerned in this. Initially, we see ourselves as autonomous and independent. During the second moment, microbiology reveals the questionability of this self-image. Haunting microbial others can even be spotted inside our body. For haunted individuals, tormented artist such as Van Gogh, however, this may become a consoling idea. The scientific signifier 'microbes' enabled him to reconcile himself with the disruptive experiences that were troubling him.

Building on Freud (1947 [1917]), microbiome research can be envisioned as a 'narcissistic offence.' Scientific breakthroughs, Freud argues, challenge our self-image as human beings. After discovering that we are not the masters of the universe (Copernicus), nor the masters of creation (Darwin), we now discover that we are not even masters in our own house (in German: *Wir sind nicht Herr im eigenen Haus*). This is the second dialectical moment, the moment of 'negation'. Microbes threaten to undermine our sense of agency or self-mastery.

During the third dialectical moment, as we have seen, this dichotomy is superseded, by incorporating otherness as an integral part of the self. Thus, although Van Gogh's bipolar mood swings (allegedly caused by microbes) entailed considerable mental suffering, famously resulting in self-mutilation, there was a more positive and productive outcome as well: his works of arts, with microbes acting a co-creators as it were. On Van Gogh's self-portraits, the skin of his face seems battered, affected, rather than smooth. The very texture of his portraits suggests an awareness that human existence means being-in-a-microbial-world.

This is an intriguing example of how microbiome science extends beyond the life sciences into the humanities, e.g., art history, superseding a divide between the faculties (between the sciences and the arts) which emerged in the eighteenth century (Rees et al., 2018). As Rees and his co-authors argue, the upshot of this is that the stakes of the natural sciences exceed the expertise of the natural sciences as such and reach over into the arts and humanities, necessitating collaboration between research fields which were once framed as incompatible cultures. Thus, the gut-brain axis urges us to supersede the natural sciences—humanities divide, inciting us to build a trans-disciplinary archways between the two.

The gut-brain axis

The gut-brain axis (GBA) refers to the bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centres of the brain with peripheral intestinal functions (Carabotti, Scirocco, Maselli, & Severi, 2015). As indicated, the interaction between microbiota and the GBA is bidirectional, so that it

[2] Probably Felix Rey, portrayed by van Gogh that same year (Martin 2008; 2010). Literally, van Gogh writes (in French) that this physician "s'amuse quelquefois à mystifier les bonnes femmes en leur racontant que l'amour est aussi un microbe" and that he (Vincent) himself doesn't object to that—"Moi, je ne m'y oppose pas [à ce] que l'amour soit un microbe"—because, as he explains in his letter, it is a consolation to know that his mental problems might be caused by microbes too (van Gogh, 2009, letter 764).

involves signalling from gut-microbiota to the brain and back (Zmora, Suez, & Elinav, 2019), thereby confirming the proverbial saying that we are what we eat. Physicians treating cancer patients with cytostatic therapies, resulting in the elimination of gut biota (therefore requiring microbiome transplants), noticed that the latter could give rise to physical and mental changes. Our intestines are more intelligent than we tend to think: they contain huge amounts of neurons and interact with the brain through multiple pathways and two-way contact.

Although the bidirectional communication between gut microbes and the brain occurs via a number of routes (Dinan et al., 2015), the *nervus vagus* (i.e., the vague or wandering nerve) plays a fundamental role in enabling signals to travel from brain to gut and vice versa. Intestinal nerves influence production of neurotransmitters in the brain, but this proves to be a circular process, a cycle of cycles, involving multiple feed-back loops. In their comprehensive analysis Dinan et al. (2015) conclude that gut microbiota play an important role in brain development, cognitive function and fundamental behaviour patterns, such as facilitating social interaction and effectively coping with environmental stressors. Others authors add that the microbiome also plays a major role in psychic ailments, mentioning autism, anxiety disorders and depression as examples, so that microbiome research may necessitate a "paradigm shift" in neuroscience (Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014). Huang et al. (2019) likewise argue in their review article that the gut microbiome plays an important role in the bidirectional communication between the gut and the central nervous system, and that the microbiome may notably have an impact on mood and mood disorders, through the gut-brain microbiota axis. Their focus is clinical, arguing that the gut-brain axis emerges as a promising target for disease diagnosis and therapeutic interventions in the future. Although critics point out that it remains a difficult challenge to separate hype from robust and validated connections between microbes and mental health, a promising program of research is evidently opened up (Faintuch & Faintuch, 2019; Morgan, Romph, Ross, Steward, & Szipszky, 2018; O'Malley, 2014).

Beyond clinical applications, these research findings may also be relevant on a more everyday level, providing opportunities for self-management, giving rise to "practices of the self" (Foucault, 1984; Sloterdijk, 2009), allowing humans to consciously interact with and care for their microbiome via food, diet, exercise, life-style, and so on. Again, this points to opportunities for superseding the divide between the natural and the human sciences. At the same time, as will be argued in the next section, this convergence must be carefully worked out and thought through. Otherwise, this budding research arena may easily become a refuge for unfounded and misguided claims. Here again, the challenge is to distinguish hype from validated insight.

Self-management and promise management: Microbiome research and promisomics

Microbiome research may provide tools for assessing the condition of our microbiome, and for distinguishing between healthy (flourishing) and challenged or unhealthy microbiomes. This may give rise to opportunities for self-tracking and other practices of the self. At the same time, the question emerges how to distinguish realistic scenarios from overpromising, notably in view of the reputation of -omics fields for their tendency towards overpromising or "promisomics" (Chadwick & Zwart, 2013). Will microbiome research indeed allow bio-citizens to become the managers of their own health, via self-monitoring and self-management contrivances, resulting in option for microbiome self-care? To the extent that microbiome research produces a range of medical decision support tools, critical assessment of claims and promises ('expectation management') becomes an urgent task. In current practice, evidence for the reliability and effectivity of self-management tools is often fragile.

This is actually one of the key questions which the IHMCSA consortium mentioned earlier aims to address. What would be needed to develop robust self-management tools for health professionals, clinicians and citizens? How to align lab developments with societal needs to foster translation into daily practice? A note of caution seems called for (Parke, Calcott, & O'Malley, 2018). Yet, some points of attention for responsible microbiome management can nonetheless be outlined.

With the advent of self-tracking and the quantified self, increasingly large numbers of individuals are already using technological tools and wearable sensors to monitor, analyse and improve their daily activities, in order to enhance flourishing, health and wellness (Gimbert & Lapointe, 2015; Swan, 2013; Zwart, 2018). Given the range of companies currently offering gadgets to self-track your microbiome, this market is likely to grow in size. Via smart self-tracking gadgets, the microbiome becomes a window into the metabolism of the body. How to address the promises and pitfalls of microbiome self-tracking? The traditional situation is one in which various types of experts either promote or problematise, either commercialise or criticize the uptake of 'microbiome speak' by citizens. How to integrate robust microbiome insights into decision and advice processes of general practitioners, clinicians, dieticians and other professionals? The focus will often be on regulation and control of ethical issues surrounding self-management tools.

To address such questions, I will once again adopt a dialectical perspective, entailing a triadic scheme. In the initial situation (first moment), self-management is a more or less intuitive practice, taking place in the lifeworld, assisted by low-tech contrivances such as weight scales. Subsequently, more evidence-based options become available, but this creates a diremption between laboratory world (where reliable knowledge is produced) and life world (where practices are based on intuition and practical experience), resulting in self-estrangement perhaps, because we rely on quantifiable indicators rather than bodily experiences. Currently, we are entering the third moment, intent on superseding the divide between laboratory world and life-world. All the world is becoming a living laboratory. We are all research subjects, potentially at least, conducting multiple personal (N = 1) experiments, with the help of a plethora of electronic gadgets. Rather than seeing the extrapolation from laboratory world to life-world as a linear, top-down process, with experts in charge, we should now see it as a dialectical, interactive endeavour. Our bodies and life worlds become field labs or test beds for interactive, participatory trials (giving rise to the quest for new methodologies, e.g., citizens science, crowdsourcing, social labs).

Initially, practices of the self were based on practical experience. Subsequently, laboratories were created for the production of reliable, evidence-based knowledge, resulting in a tension between lifeworld experience (opinion) and laboratory findings (validated knowledge). During this second moment, practical knowledge was negated (challenged, questioned, refuted, rectified) by laboratory science. In the current situation (the third moment), we notice a 'negation of the negation.' Although laboratories remain prolific producers of reliable knowledge claims, these claims now result from interactive research practices. Research performing organisations are facing multiple knowledge deficits, notable concerning the ways in which their knowledge claims and smart devices will function and be adopted in the real world: the messy, complex, socio-cultural environment outside laboratories. To amend this, they must reach out to public knowledge, outside academia and institutionalised research.

Thus, to address these deficits, we must supersede the boundaries between lifeworld and laboratory, as well as between evidence-based findings on the one hand and knowledge generated by N = me experiments in real-life settings on the other (Vegter, Landeweerd, & Zwart, 2020). In the current era of crowdsourcing methodologies, all citizens may become becoming citizen scientists, or participatory research subjects, in principle at least, and this offers opportunities for developing a more interactive and comprehensive view, taking experiences (often meticulously monitored) from self-tracking individuals on board. Bio-citizens are becoming research subjects in their own experimental (technology-based) practices of the self, sharing results and experiences

with multiple others. This offers opportunities for crowdsourcing and participatory research, seeing citizens as life-world experts, using public intelligence as a decisive source of information. The accumulation of observations from single individuals (N = me) may provide insights about the dynamics of the microbiome in particular practices and contexts. And this (participatory research, citizen science) may replace or at least provide a 'complementary' approach to top-down lab inquiries (Gimbert & Lapointe, 2015).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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