The Future of Microbiome Research

Organizers: Maureen O’Malley, Paul Griffiths, Derek Skillings, Katarzyna Hooks, Elena Walsh, James Parfrey

Funders: IdEx University of Bordeaux; ARC Laureate Project ‘A Philosophy of Medicine for the 21st Century’, Charles Perkins Centre

Venue: Manly Novotel Hotel, 55 North Steyne, Manly

Artwork: BeautyInSurvival by Bronwyn Bancroft
Organizational support
Elena Walsh (The University of Sydney)

Please email or talk to Elena if you need to work out any organizational details. She will be at the meeting, and available beforehand via email: philosophy.tmb@sydney.edu.au

For other facilitation and speaker support contact James Parfrey (Vancouver).

Twitter hashtag: #FutureMicrobiome2018
Feel free to tweet unless speakers ask you to refrain. Speakers: feel free to say ‘no’. For wifi at the conference, use the free Manly Beach network (3 hours per day)

Monday, November 26

Speakers and abstracts

All main talks in 45-minute slots: 30 minutes for the talk, 15 minutes for discussion (facilitated by session chairs)

9.00am Coffee, registration, socializing (follow signs when at the hotel)

10.00am Introduction and welcome

Paul Griffiths (The University of Sydney)

Paul Griffiths leads the ARC Laureate Project ‘A Philosophy of Medicine for the 21st Century’ and the Theory and Methods in Bioscience group at the Charles Perkins Centre, The University of Sydney.
Theme 1: Human Microbiome Perspectives
Session chair: Derek Skillings

10.15am

Keynote: The future of human microbiome research: hoops, hopes, and hypes

Elisabeth Bik (uBiome)

The past two decades have witnessed an extensive number of microbiome studies, enabled by new sequencing methods and bioinformatics analysis tools. These have led to novel insights into both membership and functionalities of the hitherto invisible worlds associated with the human body and other environments. With this new knowledge come high expectations about the use of the microbiome to diagnose, treat, or prevent human disease. The microbiome is no longer a field studied in academia alone, but now forms a rapidly growing industrial market with applications ranging from pre- and probiotics to cancer therapeutics. As with most fast-growing technologies, there are realistic and false hopes and expectations. There are important considerations to be made in terms of study design and analysis tools, interpretation and extrapolation of results, the definition of "normal", and the roles played by excited media outlets and industry. With these factors in mind, the microbiome is likely to travel through the entire hype cycle and mature into a field with a broad market applicability.

11.00am

 Ancient DNA studies reveal the evolutionary history of the human microbiome

Laura Weyrich (The University of Adelaide)

Examining the evolution of the microorganisms that live within the human body (microbiota) is critical to untangling issues with human health, as well as the biological processes that underlie human evolution. We can now sequence the DNA preserved within calcified dental plaque (calculus) on ancient human and hominin skeletons, which provides an unprecedented opportunity to examine how human microbiota evolve and adapt over geologic time scales. In the study I discuss, we used a shotgun DNA sequencing approach to assess the evolution of ancient oral microbiota in European Neandertals and ancient humans from Europe, the Americas, Asia, and Africa, as well as great apes. Our aim is to understand how these diverse microbial communities have adapted to shifts in lifestyle, diet, and environment over the past 40,000 years. Our study generated the first reconstruction of oral microbiota of an extinct species (Neandertals), and revealed more than 200 bacterial species shared between hominins. We also observed significant changes in the hominin oral microbiota associated with cultural and dietary changes on several different continents. These findings highlight how microbial communities evolve and adapt to alterations in diet and environment around the globe. For example, we observed significant shifts in microbiota that are linked to meat, carbohydrate (sugar), and lactose consumption through time in different environments. Together, these data provide the first record of human microbiota evolution in real-time and provide a better means to understand what makes us human.
11.45am **Morning tea (for everyone)**

---

**Theme 2: Methodological Issues for Microbiomes**

Session chair: John Huss

---

**12.15pm  Metagenomic complications in microbiome analysis**

[Image of speaker]

**Macha Nikolski** (University of Bordeaux)

One of the main goals of microbiome projects is to characterize the microbial communities in terms of the identity and diversity of species present in a given environment. Current next-generation sequencing technologies have provided an opportunity for doing this analysis routinely. Software tools for automated taxonomic assignment for organisms such as bacteria and fungi have since become a mature technology and are now widely used in microbiome studies. However, the abundance of literature on the analysis of metagenomic data has generated a highly variable terminology, which makes navigating the underlying computational concepts a complex task. This talk will first address classical approaches for metagenomic data generation and analysis. I will then focus on the identification of viral sequences in a microbiome sample to pinpoint the experimental and computational difficulties, illustrate them on examples from our own research, and suggest possible avenues to overcome these problems.

---

**1.00pm  Lunch** (boxed lunch for speakers; others on your own: many options nearby)

---

**2.30pm  Re-wilding the lab mouse microbiota**

[Image of speaker]

**Catherine Burke** (University of Technology Sydney), Jenny Kingham (Garvan Institute of Medical Research), Tri Giang Phan (Garvan Institute of Medical Research)

Mouse models of disease are widely used to study disease processes. Increasing evidence suggests that mice bred and raised in clean animal houses are immunologically immature, but that exposure to microbiota from wild mice can reverse this effect. In an effort to produce more realistic animal models of immunological disease, we introduced pet-store mice into an animal facility and co-housed them with laboratory mice. The faecal microbiota of both wild and pet-store mice were characterised to determine if the microbiota was efficiently transferred. Mice before and after co-housing were also examined to determine the effect of co-housing on immunological phenotypes. We discuss the implications of our work for generalizing microbiome findings from laboratory models to humans.
Theme 3: Minds and Microbiomes

Session chair: Paul Griffiths

3.15pm  Advancing translational microbiota-brain research in mental health

Jane Foster (McMaster University)

Researchers in psychiatry and neuroscience are increasingly recognizing the importance of gut-brain communication in mental health. Our relationship with our microbiome begins primarily at birth and matures in the first few years of life. Although the microbiota composition of a healthy adult is relatively stable over time, a variety of factors — sex, age, genetics, developmental and environmental factors — influence microbiota composition and function. In the past decade, we have studied the role of microbiota-brain communication on behaviour in mouse models using germ-free mice (raised in a sterile microisolator and lacking all microbiota), mice exposed to antibiotics, and normal mice. Through our work and that of others, we have seen an amazing increase in our knowledge of how bacteria signal to the brain and the implications this has for psychiatry. There are still many open questions, and a key issue is: how do the results generated in animal models translate to healthy people and to clinical conditions? Evidence is accumulating that the microbiome influences brain function, particularly brain systems related to physical and mental health in people. In addition, the importance of the microbiome to depression and other psychiatric disorders is an active area of clinical research. This presentation will examine the evidence that links microbes to mood and mental health, from mice to humans.

4.00pm  Afternoon tea (for everyone)
**Neuroimmunological concepts in microbiome-gut-brain research**

**Jan Pieter Konsman** (University of Bordeaux)

Any explanation of the effects of gut microbiota on brain, behavior, mood or emotion needs to take into account biological compartments, such as the gut and the brain, and to account for signaling across biological barriers, namely the gut barrier and the blood-brain or blood-nerve barrier. At least two types of explanations have been put forward in microbiome-gut-brain (MGB) research. The first type of explanation can be considered neuroendocrine as it involves the action of mediators produced by gut bacteria, such as acetylcholine, gamma-aminobutyric acid and serotonin, on and in the nervous system. The second type invokes the immune system and the production of cytokines, which, in turn, act on and in the nervous system and can therefore be called neuroimmune. In addition to providing potential biological mechanisms for the effects of gut microbiota on nervous systems, neuroimmune interactions have already been shown by the interdisciplinary field of psychoneuroimmunology to underlie changes in behavior, mood and emotion during systemic inflammation. Hence, neuroimmunological concepts may serve as scaffolds on which MGB research can build. This seems indeed to be the case as several authors in the MGB field refer to neuroimmune interactions or psychoneuroimmunology in titles of reviews and chapters. The aim of the present work is to investigate how neuroimmune concepts have been used in MGB research and to compare this to their employment in psychoneuroimmunology and immunopsychiatry.

---

**Microbiomes and the development of mind**

**Valerie Gray Hardcastle** (Northern Kentucky University)

In their forthcoming article in Behavioral and Brain Sciences, Hooks, Konsman, and O'Malley highlight several methodological limitations in recent and well-cited research into the causal mechanisms that underlie the microbiota-gut-brain (MGB) synergy. Taking infant neurodevelopment as a case study, I shall expand upon their conclusions, arguing that (1) MGB causal interactions are non-linear, complex, and virtually unknown; (2) some of the effects are too short-lived to be neurodevelopmentally relevant; and (3) different research paradigms from the different fields that study the relationship between microbiota and mind inappropriately impact the conclusions drawn. I conclude that the larger pragmatic and conceptual frameworks in which research into the human microbiome are embedded illustrate how socio-historic and other contextual factors constrain how theories function in cross-disciplinary fields.
6.00pm  Microbiome musings: reflections on today’s talks

Jason Scott Robert (Arizona State University)

To conclude today’s programme, Jason will summarize and reflect on the day’s talks and the discussion they generated. Audience input will be invited. The meeting closes at 6.30pm.

7.00pm  Drinks and dinner at Manly Wine Beachfront Restaurant (invitation only)

Tuesday, November 27

Speakers and abstracts

9.00am  Coffee and socializing (everyone)

9.30am  On ‘Stories and Structures’: Curating an exhibition of micrographs and Australian Indigenous art

Jenny Whiting (The University of Sydney)

Microscopy Australia has created an exhibition of imagery that explores connections between electron microscopy and Indigenous artwork. Stories and Structures, the name of that exhibition, focused on very tiny structures, including microbial cells. The aim of the project was to draw out the visual parallels between the representations in Indigenous artworks and the natural structures of the world as revealed by microscopy. As the curator of this exhibition, I will share insights into these images and their overlap, and the common messages they produce. For a preview, visit this site: http://storiesandstructures.micro.org.au/
Theme 3: Microbiome Research Challenges

Session Chair: Alkistis Elliott-Graves (University of Helsinki)

10.00am  How causal are microbiomes?

Kate Lynch (Macquarie University; The University of Sydney)

The microbiome has been claimed to cause a variety of human traits, from disease to behaviour. Often, the whole microbial community — the microbiome — is targeted as causal when making these claims. But is this the right way to think about the causal role of microbiomes? While we know that genes — often many interacting complexes of them — are implicated in human behaviours, no one claims for instance, that ‘the genome’ causes intelligence. So should we be thinking of whole microbiomes as causal, or just certain component parts? In this talk I look at causal claims in microbiome research with a focus on the proportionality of causal explanations.

10.45am  The challenges of clinical microbiome research

Katarzyna Hooks (University of Bordeaux)

Increased scientific interest in microbiota has prompted many studies to link the microbiome (especially that of the gastrointestinal system) to different diseases, from the physiological, such as digestive, autoimmune and circulatory, to the psychiatric. Because microbiota studies rely on metagenomic sequencing, they are highly technology-driven and thus require heavy bioinformatics support. Incorporating patient samples adds another layer of complexity, so clinical microbiomics is best approached through consortia involving multiple specialities, including medical doctors, microbiologists and bioinformaticians. Opportunities to form such interdisciplinary collaborations among scientists and clinicians are becoming more frequent, as funding agencies and research institutions are both actively encouraging them. In this talk, I will discuss the challenges we faced in Bordeaux during collaborative work between researchers and doctors interested in the intestinal microbiota of cystic fibrosis patients. I will introduce the scientific and practical context of the study, the difficulties and the strategies that were adopted to progress the project, and the final results. Upon termination of the study, the benefits and pitfalls of the collaboration were clear, and this has allowed us to generate recommendations for other teams attempting to initiate clinical microbiome projects.

11.30am  Morning tea (for everyone)
12.00pm  Can host-microbiome systems be healthy? Shaping ecosystems vs. curing disease

**Derek Skillings** (University of Pennysylvania; City College NY)

Host-associated microbiomes play a variety of important roles in host health and disease. Attempts to understand and make predictions about complex host-microbiome interactions have led many researchers to talk about microbiomes—especially human-associated ones—in terms of being either healthy or dysbiotic. In this presentation I will look at some alternatives for making sense of “healthy microbiome” talk. I will argue that existing “naturalistic”, or non-evaluative, accounts of human health are not appropriate for microbiomes, and that notions of ecosystem health face similar shortcomings. These problems suggest that “microbiome health” might only be definable in evaluative terms and may never extend beyond a metaphor to organismal health. I will end by looking at some possibilities for understanding overall host health given the importance and ubiquity of microbiomes.

12.45pm  Lunch (boxed lunch for speakers; others on your own: many options nearby)

2.15pm  The microbiome inside and out: Lessons from studying the assembly of surface microbiomes compared to those in the gut

**Laura Parfrey** (University of British Columbia)

Closely related host species often harbor more similar microbiota, a pattern termed phylosymbiosis. In a meta-analysis we show that phylosymbiosis is stronger and more prevalent for microbiota from internal compartments (e.g. animal guts) compared to the surface (e.g. skin). Using simulation we show that simple ecological filtering by phylogenetically correlated host traits generates phylosymbiosis patterns in the absence of co-diversification, but that the signal appears to be stronger than expected for internal compartments. Importantly, microbiota are not cohesive units, but dynamic collections of microbes that are variably acquired from the environment, from neighbours, and occasionally vertically. Sampling strategies that enable disentangling the transmission dynamics and evolutionary history of individual taxa will assist in identifying key members of the microbiota. In a survey of 35 seaweed species and their environment we show that most bacteria are shared across seaweeds and with the environment, while few are characteristic of seaweed species and these are not phylogenetically structured.
Ecological medicine and medical ecology: crosstalk and convergence in microbiome research

John Huss (University of Akron)

In this paper, I analyze case studies of translational research on recovery from perturbation within the intestinal microbiome and within the coral reef microbiome (recovery from coral bleaching episodes). What emerges from an examination of these case studies is a curious convergence. Translational research on microbiome-based, human-assisted ecological restoration (bioremediation) increasingly follows a medical paradigm, whereas research on diagnosing human dysbioses and attempts at cure is moving away from the medical “magic bullet” model toward an ecological restoration paradigm. Both of these take place within a revised evolutionary framework of holobionts and hologenomes. The future of microbiome research will involve translation of our current, incomplete understanding of holobionts and their hologenomes into goal-directed interventions within systems viewed alternately as medical and ecological objects.

Afternoon tea (for everyone)

Use, misuse and abuse of key microbial ecology concepts in microbiome research

Andrew Holmes (The University of Sydney)

The advent of high throughput sequencing has fundamentally changed the way we collect information about ecosystems, especially their microbial components, and has led to what we might term the microbiome era. Unfortunately, the rapid expansion of a disparate biological sampling technology has also created a disjunction between the expertise in collecting and handling these data and their relation to key concepts in biology. How can we more successfully derive biological meaning from these microbiome datasets? Biological systems are highly multidimensional and comprised of units that are intrinsically variable due to propagation of replicative errors via natural selection. They also show scale-dependent patterns in processes and biological organization. Consequently, for both the description of biological systems such as microbiomes, and for predictive explanations of their properties, biologists are utterly dependent on the definition of conceptual terms. For example, conceptual terms such as gene, genome, cell, tissue, species, niche, and community describe biological organization at different scales. All of these are virtually essential for communicating biology yet none of these terms has a universally applicable unambiguous definition. This makes them exceedingly difficult to apply across different ecological, spatial, and temporal scales. I will look at approaches to relate key ecological conceptual terms such as species, niche and community to microbiome sequence datasets.
Theme 5: Making Progress in Microbiome Research

Session Chairs: Jason Robert, Derek Skillings

5.00pm  Wrap-up discussion

Initial summary: Maureen O'Malley (The University of Sydney; University of Bordeaux)

After a short summary of the day’s talks, and their relationship to the previous day’s talks, the floor will be open to speaker and audience input into the future of microbiome research. The meeting ends at 5.30pm sharp.

6.00pm  Barbecue at Shelly Beach (Cabbage Tree Bay, 20 minutes walk; invitation only)