Introduction

The workshop was designed to help UKRI-BBSRC's understand the current and future capability needed for microbiome research and enable UKRI-BBSRC to support the continuing development of Integrative Microbiome Research in the UK. The workshop uniquely brought together disciplines from across UKRI-BBSRC's remit and beyond along with Industry, Networks and Learned Societies. Experienced community members provided UKRI-BBSRC with advice around the opportunities for microbiome capability across the breadth of UKRI-BBSRC's microbiome research areas, covering areas including skills, infrastructure, and emerging research approaches. It also enabled a forum to promote the exchange of knowledge across the sector. This document is a summary of the workshop and not a strategy, it is located alongside UKRI-BBSRC's Integrative Microbiome Research priority area as a resource for the microbiome community. Please note the challenges and themes summarised in this document are in no particular order.

Cross-cutting themes throughout the research challenges

- There is plenty that different fields can learn from each other.
- Research on microbes away from the limited variety of model organisms.
- Non-bacterial species.
- Capitalise on all tech advancements.
- Value of synthetic communities to explore complex interactions.
- Integration of data, including multi-omics data.
- Sampling.
- Choosing the right model system.
- Detailed Metadata.
- Data standards.
- A lack of visibility internationally for the UK owing to a more fragmented microbiome research effort.
- Sharing of data, software, tools and methodology within and between communities and fields.

Horizon scanning - what are the potential future innovative and disruptive ways of tackling microbiome function and host interaction?

- Next gen pre-biotic invention (e.g. FMT in a pill, artificial soil).
- Research on microbes away from the limited variety of model organisms.
- Systems level approaches.
- Better controlled standards.
- Strong datasets and metadata.
- Single cell approaches.
- Stable isotope probing – label foods and trace the metabolites.
- Realtime framework for microbiome analysis.
- Functional prediction of proteins using automation.
- Better ways to capture and record enviro- / eco- variables and functional properties.
- Online and searchable encyclopaedia of microbes and global inventory of the 'microbes that matter'.
- Reuse of data and the "FAIR" principles.
- Sample microbiomes repeatably without destroying the habitat.
- Profiling microbiome *in situ* and over time, including high frequency sampling.
- High throughput phenotyping.
- Culturomics studies to develop new methods for unexplored biomes.
- Host depletion/ environmental manipulation.
- Modelling physical space.

Microbiome research challenges

Biomarkers

There is potential for the microbiome to be used as a biomarker in both health and disease, this could be as a signature to predict, stratify and measure including in response to an intervention. This was considered one of the most accessible challenges and a good platform and opportunity for academic industrial relationships. Although the current approaches in this area are fragmented, there is potential for its use across species and fields.

Complexity modelling

Modelling is needed to understand the billions of interactions in a microbiome. There are a significant number of sub-challenges to this including mathematical modelling, function, integrative omics, temporal omics and strain level variation before this can be achieved. Synthetic communities also offer a way to tackle this challenge, but interactions of greater than two or three species is complex. This could unify population, ecology and strain level studies of the microbiome and enable the prediction and design of optimal microbial systems. Unravelling the complexity of microbiome interactions makes this hard to address. However, reaching this challenge is potentially achievable with application of the right methods and techniques including evolution and ecology principles, massively deep sampling of populations and a deep biological understanding to build the complexity of models.

Correlation and causation

The biggest challenge in the microbiome field right now is the need to change from simply showing a correlation of microbiome to a condition to developing a mechanistic understanding of the causation. This move needs to embrace a move from single organism contributions, which are often pathogens, to multi-organism contributions and understanding the mechanism of action and impact of a microbiome on its host and environment. If this challenge was resolved, there is potential to predict the microbiome and enable interventions. Key to this is understanding the underpinning metabolic dialogue between microbes. Currently there is not enough focus across the different kingdoms in research. Studies need to improve the fundamental understanding of all the relevant microbiota, this could be by targeted removal of specific elements and either larger more comprehensive studies to account for the complexity or adding a microbiome element to other projects.

Data analysis and presentation

This is a complex challenge, but with a high potential for impact. Methodology as well as data needs to be effectively shared for openness and simplicity to understand the wide variety of approaches that are currently being taken. The community would also greatly benefit from far more effective illustration of microbial populations that goes beyond bar and pie charts, that limits the investigation of data. In data analysis there is also currently a bias towards answering the easy questions. While there are benefits to standardisation of data analysis, it needs to be weighed against the need for innovation.

Interventions

There is a need to better understand how the commensal microbiome deters colonisation of pathogenic species and how this can reduce dependency on traditional control methods, thereby offering routes to microbial control without the associated risks of resistance. Challenges that need to be addressed included using a dedicated consortium of microbes for microbiota transplant therapies or to be able to modulate the microbiome. There is also the possibility to use the microbiome to understand responses to different treatments, to enhance efficacy and reduce negative side effects. This is a challenge area that is potentially closer to application and commercialisation. However, it is difficult to disentangle the effects of underlying conditions alongside health status and understand the long-term impacts of microbiome interventions. The integration of approaches and concepts between different fields (agricultural, animal and human microbiome etc.) would aid moving forward this challenge.

Functional annotation

The field is held back by the lack of sufficiently rich annotation across the different omics technologies and microbial players. Databases need richer annotation relating to a wider range of microbes across kingdoms (e.g. non-pathogens and non-model organisms) along with a universal aim to have less ‘unknown function’ tags. There is a huge amount of undiscovered microbiology within this challenge as a large proportion of microbes within microbiomes lack knowledge beyond their taxonomic identification. As many microbes are not currently culturable it is difficult to conduct functional studies. Potentials here included high throughput culturing and phenotyping, and openness around the availability of cultures, methodology and data.

Methods

Challenges here included sampling location, defining what is healthy, understanding how the host modulates the microbiome, archiving samples and maintaining sample integrity, reproducibility and modelling. Deciding upon what is a good and relevant model organism stood out as a challenge. Advancement in all these methods could have a large impact, including on the ability to understand function, allowing for more basic evidenced-based science and with new models to understand bacterial and host function. Novel methods are needed to determine causation, identify unknown metabolites and account for strain level differences between microbes, these make it a difficult challenge to address. An emphasis on reproducibility, synthetic communities and standard analysis methods could help start to address this challenge.

Microbial diet and population dynamics

Diet is the main pathway to influence microbiome composition in the gut, with the possibility of targeted dietary and therapeutic interventions at the individual or population level. The safety of introduced microbes needs to be ensured and the non-bacterial microbiome component interactions within diets are not well understood. Highlighted concerns were understanding individual responses and variation, a better understanding of basic microbial science and the two-way food-microbiome interactions. More high-quality systems-based and multidisciplinary studies with data integration are needed.

Microbial ecology and spatial scale

Highlighted in this challenge was the need for micron scale microbial ecology. This includes identifying the community structure of a microbiome, especially in hard to access areas, and absolute quantification of microbe abundance. Addressing this challenge would help enable microbiome modulation and engineering, with a potential for a more comprehensive understanding of the microbiome and move the science beyond correlative studies. As a challenge it is difficult to address due taxonomic and spatial resolutions, genotype to phenotype associations and timescale of different datatypes. Overcoming these issues will require interdisciplinary training across ecology and bioinformatics, and the use of a variety of experimental techniques.

Sampling

This included challenges in longitudinal sampling, rich metadata, *in situ* sampling, minimal manipulation of samples and relevant and representative sampling. Good sampling underpins the whole study and supports reproducibility. There are potentials for this challenge including taking a FAIR[1] approach, having adequate power and confidence in the data. There needs to be more detailed description of sampling methods and minimal standards for funding and publication.

Scales, time series and longitudinal studies

Longitudinal studies are a critical gap in the UK in different fields and is essential for prediction and causal research. Addressing this challenge would enhance the understanding of host-

[1] FAIR Data principles: Findable, Accessible, Interoperable, Re-usable https://www.force11.org/group/fairgroup/fairprinciples

microbe and environment-microbe-host interactions. It would better enable researchers to understand dynamic conditions, variability and responses to interventions and life course effects. The evolution of technology and analysis methods have made standards difficult for longitudinal approaches and compatibility between with samples. In addition, baseline variation makes this challenge hard to address. There is a potential for central capabilities or centres of excellence with collections to enable accessibility and bring about longer-term use and impacts.

What are the current technologies, resources and skills in the field and the UK's capabilities?

Data and computing

The UK has strengths in specific areas within bioinformatics and cloud infrastructure. Additionally, a culture of data sharing exists in the community, although this varies between fields and research areas. Furthermore, the computational resources of a community are not well known to other communities. Metadata standardisation and ontologies are poor, there is a need to incentivise and make it easier to do this at the time of collection and when the data is deposited. Usability, reproducibility and transparency of software, tools and approaches are needed, using sharing tools such as GitHub for code/scripts and Dryad for data, along with opportunities for funding.

Infrastructure

Generally, in the UK, it is easier to sample healthy populations and the NHS gives a joined-up organisation which enhances accessibility. It was felt that the UK had very good expertise in fundamental microbiology and food science and specialised institutions in the UK with specific focusses was also seen as a strength. There are good examples of resources in the UK for research, but many were potentially at capacity. Sequencing was noted as often reliant on in-house capacity, with biobanking and culture collection as a weakness in the UK. Infrastructure for innovation and to support start-ups was noted as a weak point. There are also platforms in the UK that provide the opportunity to improve community building and join up between communities. Opportunities for internal links and partnering with the US and EU were also noted. It highlighted that the EU and US were moving ahead of the UK in terms of microbiome infrastructure.

Multidisciplinary collaboration

Microbiome research requires holistic and interdisciplinary thinking with a consortium of researchers. University structure often allows for easy collaboration and interdisciplinary interaction, along with the NHS providing opportunities and networks. There are also opportunities for international collaboration. There are also opportunities for the commercialisation of microbiome research and a general excitement about the topic, this attracts valuable interest from other disciplines. A national microbiome meeting would bring about opportunities for networking and new interdisciplinary collaborations. There is also a need for more collaborative, multidisciplinary research including between academia and industry. Cross-institutional approaches would be helpful to join up expertise spread throughout the UK. There is also a need for greater networking and visibility of UK microbiome science, particularly globally.

Skills and expertise

The UK is not generating enough or correctly tailored skillsets for microbiome research. Although strengths were noted in a range of fields and skills, training is required for the next generation of microbiome scientist as currently the needed skillsets are scarce. Specific gaps were noted in quantitative skills, big data, machine learning, single cell work and experimental design, alongside the more general skills needed for multidisciplinary science. There are opportunities to improve skills in doctoral training programmes as well as upskilling those at every career stage.

Translation

The UK needs to consider how to better align research excellence with commercial innovation and opportunities. The Knowledge Transfer Network's Microbiome Special Interest Group[2] was considered a strength along with the range of funding schemes that are available to researchers in the UK. There are also many companies interested in microbiome research, although it is difficult for companies navigate the UK's fragmented microbiome communities. Microbiome technologies were noted as generally too early stage to secure venture capital funds. Opportunities were suggested around the transfer of people between academia and industry and to better utilise the existing mechanisms that promote the translation of research. There is also a positive snowball effect with progress in one field of microbiome research improving another area. Threats to translation of research included the changes to the UK political landscape and regulation in area. Microbiome research was noted to still be (relatively) in its infancy and that the expectation maybe a bit high to currently deliver on the promises of microbiome research.

Annex 1: Background and acknowledgements

Registration to attend the workshop was via an expression of interest form on the UKRI-BBSRC website. Applications to participate were invited from across the bioscience research and innovation community. This enabled UKRI-BBSRC to ensure a diverse group of participants, ensuring the breadth of interests and expertise relevant to UKRI-BBSRC were represented at the workshop. In total, 45 individuals attended the workshop, representing a total of 38 research organisations, industry, networks and learned societies from across the UK. In addition, central to the agenda were invited keynote presentations from originators that submitted microbiome focussed big ideas to the Bioscience Big Ideas Pipeline[3]. UKRI-BBSRC gratefully acknowledge the substantial and constructive input from all participants of the workshop.

[2] https://ktn-uk.co.uk/interests/microbiomes
[3] https://bbsrc.ukri.org/news/policy/2019/190611-n-bioscience-big-ideas-pipeline/

Annex 2: UKRI-BBSRC Microbiome Capability Workshop Agenda

Wednesday 4th March 2020

09:30 – 10:00	30mins	*Arrival plus coffee/tea*
10:00 – 10:15	15 mins	**Welcome and Introduction to the Day** *To set the context for the day by providing the rationale for the workshop, how it fits into the wider UKRI-BBSRC strategy, UKRI, etc. followed by Q&A*
10:15 – 10:25	10 mins	**Keynote Presentation 1:** What are the big unanswered questions?
10:25 – 10:35	10 mins	**Keynote Presentation 2:** An Industry perspective on the Microbiome
10:35 – 10:45	10 min	**Introduction to the Morning Session**
10:45 – 11:35	50 mins	**Session 1: What are the biggest research challenges for the microbiome field?** *Looking forward, over the next five years, what are the biggest research challenges for the field and clustering them by their potential to address gaps in our knowledge.*
11:35 – 11:50	*15 mins*	*Coffee break*
11:50 – 12:50	60 mins	**Session 2: Deep dive into the issues from Session 1** *Unpacking and exploring the issues in more detail, including why it is important, what would happen if the challenge could be addressed, what limits our ability to address this challenge and what we need beyond business as usual to overcome these issues.*
12:50 – 13:50	*60 mins*	*Lunch*
13:50 – 14:00	10 mins	**Keynote Presentation 3:** Innovative approaches on the horizon
14:00 – 14:10	10 mins	**Keynote Presentation 4:** Key challenges in technology
14:10 – 14:15	5 mins	**Introduction to Afternoon Session**
14:15 – 15:05	50 mins	**Session 3: What are the potential future innovative and disruptive ways of tackling microbiome function and host interaction?** *Exploring the big knowledge gaps that need to be addressed over the next five years, and what innovative/ distinctive approaches that will be needed.*
15:05 – 15:20	*15 mins*	*Coffee break*
15:20 – 16:20	60 mins	**Session 4: What are the current technologies, resources and skills in the field and the UK's Capabilities?** *Exploring what are the new technologies and ways of analysing data, and how close are these to being available to us? What skills will be needed for this? With this in mind, understanding the UK's strengths and limitations in the field.*
16:20 – 16:30	10 mins	**Wrap up and closing remarks**