Mid-Atlantic Microbiome Meet-up meeting on the intersection between academia, government, and industry

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Introduction

The Mid-Atlantic Microbiome Meet-up (M^3) is a community of scientists from the (loosely-defined) Mid-Atlantic region with common interest in the microbiome. The M^3 consortium was started in 2016 and has held annual meetings from 2016-2019. Meetings focused on best practices for microbiome analysis (2016, http://blog.umd.edu/m3/files/2016/12/M3_workshop_November_2016-1iukb26.pdf), metagenomic software validation (2017, https://blog.umd.edu/m3/files/2022/05/M3_CAMI_workshop_May_2017.pdf), biodefense and pathogen detection (2018, https://doi.org/10.1186/s40168-018-0582-5), and predictions (2019, https://doi.org/10.1128/mSystems.00392-19). Following a hiatus in 2020 and 2021, the fifth annual M^3 meeting took place on the campus of the University of Maryland in College Park on April 25, 2022. The event was initially planned for January 2022, but, due to the ongoing impact of the pandemic, had to be rescheduled and reduced in scope. Despite these extenuating circumstances, participation was strong and included 68 registered attendees out of which 24 participated in person and the remaining engaged virtually. A list of institutions represented by the participants is included at the end of the document.

Since the US Food and Drug Administration (FDA)'s decision to regulate human stool as a biologic drug for use in fecal microbiota transplantation (FMT) in 2013,[1] the idea of using bugs-as-drugs has exploded in recent decades alongside interest in studying and characterizing 'microbiome' structure and function using meta-omics methods in the hope of developing new therapeutics and identifying drug targets for various diseases (e.g., obesity, liver disorders,

diabetes, metabolic disorders) (**Figure 1**). Further, in addition to clinical applications, other research fields have been using similar meta-omics methods but in different application spaces to study the microbiome of different environments (e.g., concrete, soil and agriculture, the built environment). In turn, this has led to an increasing number of microbiome-related industries and public-private partnerships, with the Mid-Atlantic region becoming a big player in this field.[2,3] As microbiome-related markets are being projected to grow from USD 269 million in 2023 to USD 1.37 billion by 2029,[2] investment in the study of the microbiome is only expected to increase. To match the growing demands and interest in human microbiome therapeutics development and to sustain these industries, expertise in meta-omics tools is needed. To date, the biggest challenges with using meta-omic approaches include data interpretation, rapid changes in technologies, then need to identify the best methods from the many being developed, and computational/UNIX proficiency within the research community and regional workforce, although the level of programming experience and comfortability with programming languages has been increasing in recent years in certain fields.[4]
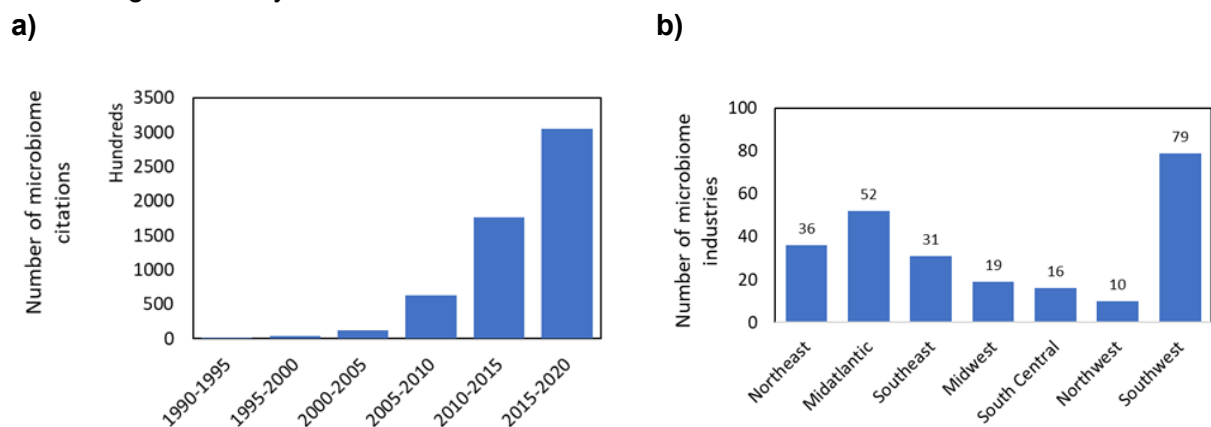
a)   b)

Figure 1. a Growth in the number of citations of 'microbiome'-related work in the academic literature on Google Scholar and **b** regional growth of microbiome industries.[3]

The one-day meeting included several "lightning" presentations on scientific topics contributed by the participants, as well as ample time for personal interactions, and several break-out sessions focused on current challenges in our field. There were 68 registered attendees; 24 in person and 44 virtual. Attendees were from academic (24%), government (53%), industry (16%), and other (7%) scientific institutions (see **Participating institutions** below). The topics presented and discussed during this meeting are outlined below.

Scientific presentations

Brantley Hall (UMD). *Wearable devices for real time measurements of gut microbial metabolites.*

Brantley Hall discussed the necessity to improve functional annotation of the human gut microbiome and to develop devices that can measure corresponding functions. He specifically discussed his group's work on the systematic annotation of cysteine-degrading bacteria in the

human gut microbiome. The metabolic byproduct of this pathway is hydrogen sulfide production. His group found that cysteine-degradation was a ubiquitous function emphasizing the potential for modulating gut microbial hydrogen sulfide production through modulation of cysteine intake. In addition, he discussed the progress made in his lab on developing wearable devices to measure hydrogen sulfide production from humans in real time. Using this new strategy, the efficacy of dietary alterations to modulate gut microbial hydrogen sulfide production can be assessed.

Nadratun Chowdhury (NIST). *Investigating and modeling the regulation of extracellular antibiotic resistance gene bioavailability by naturally occurring nanoparticles*

Nadratun's work examined the role of environmentally relevant nanoparticles (NPs) in regulating extracelllular antibiotic resistance gene (eARG) transfer. eARGs showed the capacity to sorb to model environmental nanoparticles in significant amounts. This sorption also led to increased persistence of eARGs upon exposure to DNase I. Particles decreased bacterial growth and eARG bioavailability in sterile systems without nuclease. When DNase I was present particles increased transformation via chromosomal (but not plasmid-borne) eARGs. Nanoparticles increased transformation more than micron-sized particles, indicating that the nanoscale increases eARG bioavailability.

Carly Muletz-Wolz (Smithsonian National Zoo and Conservation Biology Institute). *Eco-evolutionary processes structure milk microbiomes across the mammalian tree of life*

Carly Muletz-Wolz, molecular ecologist at the Smithsonian National Zoo & Conservation Biology Institute (NZCBI), and co-authors presented 'Eco-evolutionary processes structure milk microbiomes across the mammalian tree of life.' The team used milk samples from the world's largest milk repository at the NZCBI. They sampled 47 species of mammals from all four placental superorders and performed 16S rRNA amplicon sequencing to characterize mammalian milk microbiomes. They used a null-model based approach to quantify deterministic versus stochastic processes impacting mammalian milk microbiomes. They found that microbial species present in milk reflect both stochastic and deterministic processes, and Muletz-Wolz elaborated on the deterministic processes involved, such as host diet and implications for enteromammary trafficking. Muletz-Wolz concluded by highlighting that ecological and evolutionary factors act on milk microbiomes, which set the stage for infant health and development.

Lisa Stabryla (NIST). *Role of bacterial motility in evolutionary mechanisms for acquired antimicrobial resistance.*

Lisa Stabryla discussed methods that combine experimental evolution and whole-genome sequencing to unravel mechanisms of bacterial resistance towards traditional and emerging nano-enabled antimicrobial agents. She specifically highlighted her doctoral research where she focused on silver nanoparticles and determined silver efflux as one potential pathway towards resistance development. She also suggested that bacteria motility may influence the path

towards resistance as various motile strains of E. coli showed differential AMR evolution profiles. Using these methods coupled along with phenotypic motility assays, the role of motility as a non-traditional determinant for AMR will be assessed, which may reveal it to be a promising avenue for development of new therapeutics or AMR monitoring targets.

Breakout sessions

Breakout sessions were conducted as a part of the workshop in order to further the discussion between workshop attendees. For the first session, half of the attendees participated in the data standards and half in the workforce development sessions. All attendees participated in the regional infrastructure session.

Data standards

The data standards session focused on areas the microbiome field needs to address to improve standardization in the field. The questions included:
- What references/standards exist and what need to be created to evaluate microbiome methods?
- What approaches should be taken when there is no "ground truth"?
- What current data sharing practices are effective? Which practices are not effective? What additional practices/tools would help advance the field?
- How do we improve data sharing practices while maintaining data security?
- How do we develop/implement standards for data analytics?

Groups identified available standards from the International Standards Organization (ISO) and the National Institute of Standards and Technology (NIST) as well as past standardization efforts made by the Earth Microbiome Project. The need for methods for well characterized pathogens as well as those for rare taxa was also identified. Standard methods/guidelines are also needed so that new groups can implement appropriate process controls, as well as positive and negative controls. These issues were identified from federal, industry and academic stakeholders and seen as hindering confidence in measurement capabilities and necessary for advancing measurement science and moving the field forward.

Challenges in sequencing complex environmental matrices having 'no ground truth' (e.g., soils) are compounded by the lack of existing databases with adequate coverage of environmental matrices, hindering confidence in measurement capabilities. Data biases can also exist with sample processing methods such as DNA extraction and bioinformatic alignment. Additionally, existing data from the human gut was identified as coming predominantly from high income countries and individuals and therefore is not representative of globally distributed locations. This suggests that existing treatments may be biased for diets in these countries.

Further, a primary challenge in data sharing is the lack of existing metadata in publicly available resources such as NCBI. This, in addition to the lack of sample ID alignment with publication

level data, can make further analysis of data impossible. Data security measures must also be upheld. Are data sharing websites encouraging uploading of human identifiable reads? The lack of standard guidelines for data collection brings up the question of data ethics and is hindering the field from moving forward.

Workforce development

The workforce development session focused on how to recruit, train, and retain microbiome researchers. Questions discussed included:

- What are the training needs for federal or industrial organizations?
- What are the key gaps in expertise in the local region?
- Where would you prioritize training efforts?
    - 2-year undergrad,
    - 4-year undergrad,
    - MS Programs,
    - PhD programs,
    - professional education programs.

Discussions heavily focused on being able to connect data generators with data analysts. Despite strong local universities, in our region there are few PhD-level postdocs and microbiome analysts/associates, making it challenging to find collaborators who can provide deeper data analyses than possible through standardized pipelines. It was noted that it is particularly difficult to find those trained in advanced statistics.

While experts in biology, computer science, and statistics are commonly involved in microbiome research and conferences, researchers from other disciplines, such as math, physics, and chemistry are less common. Promoting involvement from these other disciplines would expand and improve the field, but may require thoughtful connections and advertising, as direct applications of microbiome research in these fields are not always obvious.

One reason due to which we see a dearth of computational scientists in microbiome research at both the federal and industrial level may be that there are large gaps in expected salaries between such scientists and other positions for people with similar qualifications. Another concern is that we are competing with other regions that are strong in biotechnology, including San Diego, San Francisco, Boston, Cleveland and others (**Figure 1b**). In response to COVID-19, remote work has become more common, and may be a way of attracting computational biologists to the area.

It was also noted that it is difficult to recruit lab technicians, associates, and managers at federal and industrial organizations, who have expertise in microbiome sample processing. Many people, including academics and students during their undergraduate and graduate/PhD training, currently rely on sending samples to generalist sequencing cores. This situation is not

optimal, since microbiome samples require specialized processing in order to prevent contamination and to obtain a good representation of the organisms found in the samples.

In terms of prioritizing training efforts, most agreed that we should be introducing people to the microbiome field as young as possible, but there was emphasis on exposing undergraduate computer scientists to problems in computational biology and equipping biology majors with a greater mathematics and computational/programming background to help them obtain interdisciplinary degrees. Many recommended that microbiome researchers do an MS in bioinformatics. Training undergraduate and graduate students in microbiome sample processing was also emphasized.

Regional infrastructure

The regional infrastructure session focused on identifying microbiome resource needs specific to the Mid-Atlantic region. Questions discussed included:

- What structures could support the microbiome ecosystem in the region?
- What needs does your institution have that cannot be fulfilled in house?
- What types of partnerships should be fostered?
- What barriers exist for interactions across "sectors" (academia, industry, government)?

The participants emphasized the need to organize regular meetings in order to foster interactions among members of our community. Also highlighted was the need for regional microbiome-related career fairs that connect academic, government, and industrial employers with potential employees in the region.

While many institutions are developing basic microbiome expertise in-house, specialized expertise frequently requires external collaborations, and a regional microbiome institute could represent a regional clearing-house for such expertise. Some specific examples of "gaps" in expertise reported by participants include immunology and non-DNA measurements (e.g., metabolomics).

Several factors were also identified that limit interactions in our region, particularly across sectors. First, it is difficult to identify people who have relevant expertise or interests, something that is true even within larger organizations, let alone across the Mid-Atlantic region. Participants recommended the establishment of an expertise database or some other mechanism for allowing people to identify potential collaborators. Second, even if researchers connect at local events, many are too busy to commit to further interactions after the event. Seed grants or other incentives can be a valuable resource to promote longer-term interactions within the region.

Other resources/opportunities aimed at fostering collaborative interactions between scientists in the region include events such as hackathons, tutorials, etc. Educational opportunities are

particularly important for helping to develop the regional workforce while also representing an avenue for disseminating the latest scientific discoveries in the field.

Computational resources were also identified as a limitation in this particularly data-intensive field. Many institutions lack centralized high performance computing infrastructures, and cloud solutions tend to be expensive, particularly when necessary to store and transfer large volumes of data. A further barrier to cross-institutional interactions is posed by institutional data security and privacy policies, particularly when dealing with data derived from human subjects. The establishment of a regional computational infrastructure that implements protected "data vaults" to enable collaborative interactions on protected data would, thus, be beneficial for the region.

Conclusions/next steps

This workshop brought together groups from academia, industry and government in order to identify common challenges in microbiome-related areas of research as well as to provide networking opportunities. Participants voiced a desire for collaboration and educational opportunities to learn about emerging analysis techniques. Collaborations across sectors can bring together many stakeholders but participants are worried about ways to fund such collaborative work.

The discussions that occurred during the workshop and immediately afterward identified several avenues for further strengthening the M^3 community. First, we propose the creation of a new seminar series that complements our annual meeting. This series will take place on a quarterly basis and focus on current challenges encountered by members of our community. Thus, we envisage technical tutorials as well as professional development seminars (e.g., navigating intellectual property concerns when collaborating across sectors). As much as possible, this seminar series will be organized in person (with recordings available online after the event) in order to encourage personal interactions within the region. The venue should rotate across our region to enable broader participation. Second, we propose to organize a regional career fair as part of the annual M^3 conference. Students expressed a desire to connect to companies in the region and professionals similarly expressed a need to find talent. Third, we plan to expand engagement within the M^3 community by creating a LinkedIn group, an expertise database, and increasing communication through the M^3 groups.io group.

The combination of these efforts will enable M^3 to further expand to meet the needs of the scientific community in the Mid-Atlantic region. Additionally, they will help expand the M^3 community from clinical microbiome researchers to include researchers who study the complex microbiomes of various environments encountering similar challenges. By fostering an engaged group of government, academic and industrial partners, M^3 helps all member organizations and professionals advance their science as well as their careers.

Special acknowledgments

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The M³ consortium is coordinated by an advisory group that currently includes: Nick Bergman (NBACC), Rita Colwell (U. of Maryland & CosmosID), Jocelyne DiRuggiero (JHU), Elizabeth Grice (UPenn), Jason Kralj (NIST), Hasan Nur (EZ Biome), Mihai Pop (U. of Maryland), Andrea Ottesen (US FDA), Jacques Ravel (U. of Maryland School of Medicine).

Participating institutions

* indicates in-person participants

Academic/non-profit

University of Maryland*
University of Delaware
Immune Tolerance Network
George Washington University
Morgan State University
Raiganj University
Rice University
University of Illinois

Federal

NIH (NIAMS, NLM, NCI, NHGRI)*
NIST*
FDA
NAVSEA*
BNBI/NBACC*
Smithsonian National Zoo & Conservation Biology Institute*

Industry

EZ Biome*
Noble Life Sciences
BioBuzz Media
J. Craig Venter Institute*
ACV Environ*
Integrated Pharma Services

Interim Homes, Inc.
Bloom Science, Inc.
Ardigen

References

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2.   Human Microbiome Market by Product (Prebiotics, Probiotics, Food, Diagnostic Tests, Drugs), Application (Therapeutic, Diagnostic), Disease (Infectious, Metabolic/Endocrine), Research Technology (Genomics, Proteomics, Metabolomics) - Global Forecast to 2029. Markets and Markets Research. 2022. https://www.marketsandmarkets.com/Market-Reports/human-microbiome-market-37621904.html

3.   Microbiome Employers. Biotech Careers. 2022. https://biotech-careers.org/company-core-activity/microbiome

4.   Association of Environmental Engineering and Science Professors Research and Education Conference. June 28-30, 2022. Washington University at St. Louis, Missouri.