CEDARS-SINAI MEDICAL CENTER

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Research Statement

I am passionate about leveraging computational approaches to advance human health and wellbeing. By designing scalable, rigorous, and innovative computational models, I aim to address complex biological questions and translate data-driven insights into actionable solutions for improving health outcomes. My research focuses on developing and applying cutting-edge algorithms, machine learning, and data science techniques to analyze diverse biological data types, with the goal of uncovering novel biomarkers, understanding disease mechanisms, and enabling personalized interventions. While my past work has extensively explored microbial communities as a key aspect of animal and human health, I am equally committed to interdisciplinary collaborations that address pressing challenges in areas such as precision medicine, population health, and health informatics.

Past and current research: My research has focused on developing computational approaches to study microbiome-host interactions under diverse physiological and environmental conditions. By integrating multi-omics data types—genomics, metagenomics, transcriptomics (bulk, single-cell and spatial), and metabolomics—I have explored how factors such as diet, lifestyle, host genetics, and health status shape microbial composition, function, and interkingdom interactions. This work has spanned human and animal models, unraveling dynamic relationships that govern gut microbial ecology and its profound impact on host health. In developing a research statement, I seek to expand the depth of knowledge, breadth of collaboration, and importantly tackle pressing questions without losing track of my primary research interest – "explore microbiome-host interactions using advance Omics and computational strategies" to improve health and wellbeing.

One of the most striking findings in my research emerged from studying traditional human populations in the Central African Republic. By comparing their gut microbiome to that of African Old-World monkeys, I demonstrated how subsistence strategies and dietary habits profoundly influence microbial composition. This work revealed parallels in functional adaptations of the gut microbiome in response to dietary stimuli, shedding light on the role of interkingdom interactions in regulating host metabolism and physiology (Published in **mSphere 2019**; **mSystems 2021 and in npj Biofilms and Microbiome 2022**). Similarly, I extended these insights to animal models, examining how variations in diet and feed types alter microbiome composition and function in horses and beef cattle (published in **Journal of Equine Veterinary Science 2020** and **Animal Microbiome 2022**). These studies

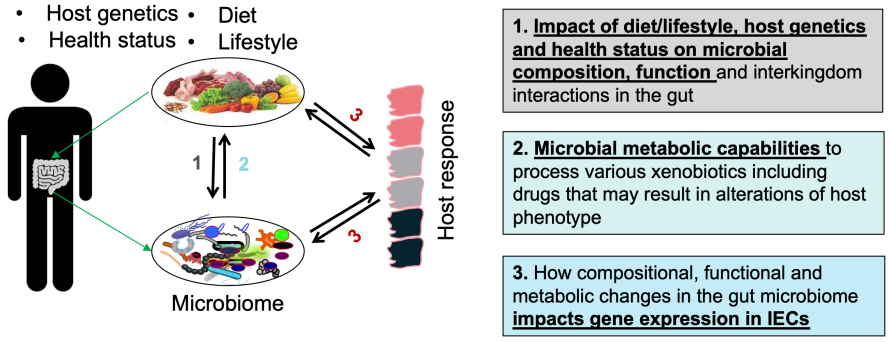

Figure 1. Interplay of Diet, Host Genetics, and Microbiome in Shaping Gut Health and Disease. *The figure highlights how diet, lifestyle, and host genetics influence microbial composition, function, and xenobiotic metabolism, which in turn modulate intestinal epithelial cell (IEC) gene expression and host phenotype.*

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emphasized the critical role of the microbiome in animal health and nutrition. Beyond composition, I have delved into the metabolic capabilities of the microbiome, particularly its role in processing xenobiotics such as drugs (published in **Scientific Reports 2017 and in Gut Microbiome 2025**). My research identified a novel microbial species, Flavonifractor plautii, a flavonoid-degrading bacterium implicated in colorectal cancer progression (published in **mSystems 2019**). This discovery not only highlighted the potential of the microbiome to modulate host phenotype but also underscored its relevance in therapeutic development. Building on these findings, I am actively exploring microbial enzymes involved in xenobiotic metabolism and their variations across health and disease states (published in **Cancer Prevention Research 2020**). To deepen the understanding of how these compositional and metabolic shifts influence host physiology, I developed computational pipelines for analyzing microbiome-host interactions using meta-transcriptomics. This approach allowed me to profile gene expression patterns in intestinal epithelial cells (IECs) and link them to microbial community dynamics. For instance, in populations with distinct dietary lifestyles, I uncovered alterations in genes governing intestinal barrier integrity, immune response, and nutrient sensing (**Under preparation**). These results provided a mechanistic framework for understanding how microbial communities influence host health at the molecular level. My work has also contributed to the identification of microbial biomarkers in various diseases, including colorectal cancer, head and neck cancer, Wilson's disease, dental carries, and oral cancer (published in **Frontiers in Cellular and Infection Microbiology 2022**, **Journal of Oral Microbiology 2022**, **and Hepatology Communications *2023***). By profiling microbial communities in smokers with and without head and neck cancer, I identified key microbial biomarkers associated with DNA damage. Additionally, I have participated in large-scale metagenomic studies to construct gut microbial gene catalogs and elucidate unique microbial functions in the Indian population (published in **GigaScience 2019**). These efforts highlight the translational potential of microbiome research in biomarker discovery and therapeutic innovation.

My current research leverages cutting-edge technologies, including **imaging mass cytometry (data presented in DDW 2022)**, **single-nuclei RNA sequencing**, and **multi-omics integration**, to investigate microbial regulation of immune responses in Crohn's disease. By analyzing high-dimensional datasets, I aim to uncover how host-microbiome interactions, particularly with C. innocuum, influence disease progression and immune modulation. I develop and optimize scalable computational pipelines to integrate multi-modal data, enabling the discovery of disease mechanisms and potential biomarkers. This work advances our understanding of gastrointestinal inflammation and provides insights into host-pathogen dynamics in Crohn's disease.

Future Plans: I will keep applying AI/machine learning and other data-driven approaches for targets and biomarkers identification and to better understand the factors contributing to various disease with main emphasis can be on gastrointestinal diseases. One of my main interests is to dissect the mechanisms by which microbial members regulate the immune responses and regulates the host metabolism and physiology under diverse physiological conditions. I aim to utilize novel microbial measures and computational approaches to analyze and integrate multi modal (ranging from sequencing to imaging) data datasets to understand microbiome community structuring and how it influences host nutrition, intestinal health, and overall well-being of animals and humans.

Example Project: Predicting Impact of Microbiome on Host Physiology

It is essential to dissect the mechanisms by which microbial communities interact with the host to identify microbial markers associated with animal and human health. I am highly interested in the development and implementation of novel computational methods/tools to analyze and interpret large, heterogeneous multi-omics datasets. So, I would like to implement multi-omics data integration pipelines (genomics, transcriptomics, proteomics, metabolomics and microbial genomics libraries) to identify pathogenic (causative) factors associated with gastrointestinal health. I will utilize these approaches to identify and

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validate microbial species, genes, metabolites, and their interactive partners in host intestinal epithelial cells under diverse physiological conditions.

My research will be divided in the following components:

1. **Microbial Quantification Approaches:** A major challenge lies in the methods used for microbial quantification (e.g., relative abundances/proportions). Apart from technical and biological variations across studies, relative abundance often introduces significant biases that limit global biomarker identification. For instance, comparative microbiome studies frequently identify certain microbes associated with feed habits or diseases, but the patterns are often inconsistent across studies. The relative proportion of microbial members in a community can drastically shift when one or two bacterial species bloom, leading to false positives. Researchers are advancing and adopting new computational strategies to overcome these limitations. Although no perfect solution exists, promising alternatives allow the direct quantification of bacterial activity instead of relying on relative proportions. A notable recent advancement is the development of methods to compute bacterial replication rates (PTRs) from metagenomic datasets, which can measure absolute changes in bacterial activities. I have applied bacterial activity measures (PTRs) and compared them with relative abundances using machine-learning-based tools on a longitudinal IBD cohort. Preliminary results suggest that alternative approaches, such as bacterial replication rates, may yield more robust and meaningful associations in microbiome studies. Moving forward, I will continue applying such measures and advanced computational methods to analyze and integrate multi-omics datasets to answer critical questions related to microbial associations with gastrointestinal physiology, intestinal health, immune responses, and animal/human growth and well-being.

2. **Exploring Mechanistic Roles of Identified Microbes**: Most microbiome studies identify microbial markers associated with health or disease but often fail to explore how these microbes contribute to disease progression. While association-based studies provide valuable insights, they typically lack an understanding of the mechanisms by which microbes drive disease phenotypes. I aim to address this gap by identifying microbial genes, peptides, proteins, and metabolites that may be involved in disease progression. To achieve this, I plan to use **shotgun metagenomics**, incorporating both long-read and short-read sequencing, to reconstruct complete genomes and identify relevant genes and proteins. I will also employ approaches such as **genome-scale metabolic modeling** to predict the metabolic potential of microbial communities of interest. Additionally, I will utilize **metabolomics pipelines** to identify functional microbial molecules. If necessary, specific disease or animal models will be incorporated to validate these findings experimentally. Recent studies have successfully combined computational and experimental models to identify microbial-derived toxins that promote colorectal cancer metastasis (Cell Host & Microbe, Dec 2024). However, more comprehensive and integrative studies are needed to fully elucidate the role of microbes in health and disease.

3. **Investigating Host Responses at a Finer Level**: Another critical limitation in microbiome research is the insufficient exploration of host responses to microbial metabolites or molecules. I aim to develop computational approaches to screen host genes or receptors that may directly interact with microbial-derived molecules. Such studies will require validation at multiple levels, including experimental confirmation. Leveraging my drug discovery expertise, I plan to develop receptor-specific models based on target bioactivity analysis (e.g., a preliminary model I developed for one target: TargetBioactivityAnalysis). To achieve this, I will compile potential host receptors—such as **G-protein coupled receptors (GPCRs)**—using literature reports and fundamental biological knowledge to identify candidates that may interact directly or indirectly with microbial

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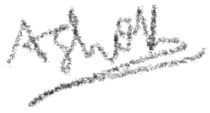
metabolites. Known bioactive and inactive molecules for each receptor will be obtained from repositories like **DrugBank**, and their molecular features will be used to develop receptor-specific computational models. These models will enable screening of the entire metabolite pool to quickly identify potential bioactive metabolites for specific receptors. Additional approaches, such as **network-based analyses** and **molecular docking**, will also be explored to further characterize microbiome-host interactions. Findings from these computational screenings will require thorough validation using **in vitro assays**, **transcriptomics**, or **receptor-binding studies** to confirm predictions and provide robust insights. These kinds of approaches can provide a solid framework to identify microbial regulated therapeutic targets for drug discovery.

By integrating: **1)** advance quantification measures and computational approaches; **2)** characterization of microbially derived molecules and **3)** exploring the direct associations between microbial-derived molecules and host genes or receptors. Well-designed studies that incorporate these three components will enable a more comprehensive understanding of disease mechanisms and establish microbiomes as potential therapeutic targets. I aim to dedicate my research career to developing and utilizing computational approaches that integrate multi-omics datasets to achieve these goals.

In the past, I have co-written an R03 grant as a Co-PI and assisted with various R01 grants during my tenure at UMN and Cedars. Additionally, I have actively worked as a teaching and research mentor, guiding students in conducting microbiome analysis using data from already published projects. One of my responsibilities was/is to develop and implement computational pipelines/workflows and machine learning algorithms to process multi-omics datasets, thereby facilitating the research of other lab members and departmental researchers. In the past, I have developed various tutorial for best practices and processing of **16S rRNA**, **shotgun metagenomics**, **scRNA-seq**, **spatial transcriptomics** datasets. I will continue to write grants to secure funding, develop tutorials and teach the various computational aspects to deal with multi-modal dataset to better understand the host health. I strongly believe that my research experience and goals align seamlessly with the department's mission, and I am eager to contribute to advancing this vision through innovative and integrative approaches.

Thank you,
Ashok Kumar Sharma



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