Hybrid metagenomics and systems biology for understanding host-microbe interactions

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Lab webpage: https://mtms-lab.github.io/

Brief bio

Dr. Nagarajan is Associate Director and Senior Group Leader in the Genome Institute of Singapore, and Associate Professor in the Department of Medicine and Department of Computer Science at the National University of Singapore. His research focuses on developing cutting edge genome analytic tools and using them to study the role of microbial communities in human health. His team conducts research at the interface of genetics, computer science and microbiology, in particular using a systems biology approach to understand host-microbiome-pathogen interactions in various disease conditions. Dr. Nagarajan received a B.A. in Computer Science and Mathematics from Ohio Wesleyan University in 2000, and a Ph.D. in Computer Science from Cornell University in 2006 (Advisor: Prof. Uri Keich). He did his postdoctoral work in the Center for Bioinformatics and Computational Biology at the University of Maryland working on problems in genome assembly and metagenomics (Advisor: Prof. Mihai Pop).
HYBRID METAGENOMICS AND SYSTEMS BIOLOGY FOR UNDERSTANDING HOST-MICROBE INTERACTIONS

Niranjan Nagarajan, PhD
Associate Director, GIS

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Microbiome Research @ GIS – read, reveal and write

We live in a microbial world ... with enormous untapped biodiversity ... and poorly understood function


Challenges

1. Can we do **whole genome analysis** of microbial function for the vast majority of *uncultured organisms*?
2. Can we understand **systems properties of microbiomes** in human health and diseases and move *beyond taxonomic surveys*?
3. Can we develop a **unified framework for rapid identification** of diverse organisms and genes of interest (e.g., antibiotic resistance, multi-kingdom analysis)?

READ: Platinum Gut Metagenomes Project

Rationale: We need references that better capture Asian diversity

109 Singaporean gut microbiomes

<table>
<thead>
<tr>
<th>Race</th>
<th>Chinese</th>
<th>Malay</th>
<th>Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>30</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>26</td>
<td>30</td>
</tr>
</tbody>
</table>

Technology: Hybrid metagenomics (short-reads + long-reads)

High quality genomes w/ 10× contiguity improvement over state-of-the-art

Most strains are unique to Singapore!
Key ethnicity-specific differences in common gut bacterial groups

Gounot et al, *Nature Communications* 2022
Singaporean strains could provide unique therapeutic functions

**Bifidobacterium**
- Early colonizer
- Marker of healthy microbiota
- Breakdown of conjugated bile acids

Gounot et al, *Nature Communications* 2022
READ: Antimicrobial Resistance and Forensics

Rationale: Environmental reservoirs for pathogens and transmission pathways for antibiotic resistance genes remain uncharacterized

Key Result: Enrichment and persistence of multi-drug resistant bacteria and with high similarity to patient isolates

In situ genomic DB + Nanopore Analytics = new spin-off company
READ: Spatial Metagenomics

Rationale: Host-microbe interactions are defined by spatial structure

Key Result: Imaging polymicrobial mixtures at species level

Dr Iain Tan, Dr Shyam Prabhakar, Dr Kok Hao Chen, Dr Isaac Seow

Shi et al., 2020

Highly multiplexed FISH (Chen et al., 2015)
**REVEAL: Microbiome Function in Atopic Dermatitis**

**Rationale:** Atopic dermatitis is a common skin disease where the role of the microbiome remains underexplored

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**Shared signatures and divergence in skin microbiomes of children with atopic dermatitis and their caregivers,** *Journal of Allergy and Clinical Immunology* 2022

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**Key Result:** Distinct microbiome ‘dermotypes’ + sharing between patients and caregivers represent promising therapeutic and clinical intervention points.
**REVEAL:** MDRO colonization of gut microbiome

**Rationale:** Microbiome alterations associated with MDRO colonization could reveal **factors that promote decolonization**

**Key Result:** CPE colonized microbiomes have a loss of diversity and depletion of **species and functions associated with gut inflammation**

Kang et al, *Nature Microbiology* 2022
**WRITE:** Dietary Modulation of Microbiome

**Rationale:** Gut microbial ecosystem relies on cross-feeding interactions established by **key obligate anaerobes**

**Strategy:** **Ecological modeling** of the gut microbiome with additional parameters to capture the influence of diet

Public & Singaporean data

Microbiome modeling software
Li et al, Microbiome 2019; Li et al, PLoS Computational Biology 2021
**WRITE:** Phage modulation of the microbiome

*nature*

>36,000 phages, >3000 are high-quality or complete

*Host range spans gut phyla and genera*

*nature biomedical engineering*

Phage-guided modulation of the gut microbiota of mouse models of colorectal cancer augments their responses to chemotherapy

Sheetal R. Modi, Henry H. Lee, Catherine S. Spina & James J. Collins

Di-Wei Zheng, Xue Dong, Pei Pan, Ke-Wei Chen, Jin-Xuan Fan, Si-Xue Cheng & Xian-Zheng Zhang
# Metagenomics Platform Capabilities

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Traditional Approaches</th>
<th>Our Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-genome analysis for uncultivated organisms</td>
<td>Culture-based or gene-level assembly</td>
<td>Hybrid Assembly: Near-complete genomes from complex metagenomes</td>
</tr>
<tr>
<td>Understanding systems properties of microbiomes</td>
<td>Taxonomic survey, correlation analysis</td>
<td>Microbiome Modelling: Predictive models for microbiome dynamics</td>
</tr>
<tr>
<td>Rapid organism and gene identification</td>
<td>Complex species-specific workflows</td>
<td>Nanopore Analytics: Unified high-resolution workflow</td>
</tr>
</tbody>
</table>

**Applications**

- Quasi-metagenomics for low-biomass samples
- Hybrid Assembly for strain-resolved MAGs
- Microbiome Modelling for predicting perturbation response
- Nanopore Analytics for real-time classification
THANK YOU

www.a-star.edu.sg