Decoding Our Inner Universe: The Power of the Microbiome Network Alignment Algorithm

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I am honored to contribute to the program 'Sharing UW-Madison Postdoctoral Scholarly Research with Non-Science Audiences,' sponsored by the Wisconsin Initiative for Science Literacy (WISL). This program, supported by the efforts of the WISL team, including Cayce Osborne, Elizabeth Reynolds, and Professor Bassam Shakhashiri, plays a crucial role in connecting scientific research with the broader public. I joined Dr. Solis-Lemus's lab at the Wisconsin Institute for Discovery two years ago as a postdoctoral researcher and have since worked on several projects. The MiNAA project, which focuses on aligning microbiome networks, has been accepted, and four other projects are currently under review. Recently, I transitioned to the role of scientist in the lab, where I continue to advance computational methods for studying microbiome networks. By analyzing microbial interactions across different health conditions, our research aims to uncover patterns that provide a deeper understanding of how microbiomes contribute to health and disease, potentially guiding new therapeutic strategies.

Introduction:

Did you know that more than half of your body is not human? Human cells make up only 43% of the body's total cell count—the rest are inhabited by trillions of microbes, including bacteria, viruses, and fungi. This vast microbial city within us plays a crucial role in everything from digesting food to influencing our mood. Understanding this hidden half of ourselves, our microbiome, is rapidly transforming our approach to health and disease.

Microbes and Microbiomes:

Microbes are tiny organisms, like bacteria, viruses, and fungi, that live all over (and inside) your body. Imagine your body as a large city filled with countless tiny people—these people are microbes. These tiny citizens live everywhere in and on your body—in your gut, on your skin, in your mouth, inside your nose, and even in places you might not expect, like your lungs and your eyes!

The collection of these microbes in different parts of your body is called your ***microbiome.*** Microbiomes are like the neighborhoods of people in the city. The gut microbiome is like the bustling downtown of this microbial city, where most of the action happens. Meanwhile, the skin microbiome acts like your body's security system, and the oral microbiome keeps your mouth healthy by fighting off harmful invaders. Even your lungs have their own microbiome, quietly working to protect you from respiratory infections. Each part of your body hosts a unique microbiome, just like different neighborhoods in a city.

Figure1: Mapping the Microbial City*:* This visual illustrates the diverse and vibrant microbial communities that populate different parts of the human body, each playing a crucial role in maintaining our health https://geneticliteracyproject.org/2018/04/18/hidden-half-of-us-youre-more-microbe-than-human/.

The Essential Role of Microbes:

Microbes help digest food, fight diseases, and even influence how we feel. While some microbes can cause illness, most are vital to our health. Microbe function reminds me of a line from my favorite song, *Clocks* by Coldplay: 'Am I part of the cure, or am I part of the disease?' Like in the song, the microbes in our body can either keep us healthy or contribute to illness.

Most microbes are part of the "cure," helping your body function smoothly, but a few might be part of the "disease," causing problems when they misbehave. Did you know that your gut microbiome can even affect your mood and influence your depression levels? So, the balance of these microbes can affect how we feel mentally, not just physically!

Just like city workers, microbes work constantly. Some act as chefs, breaking down food, while others serve as security guards, keeping harmful invaders in check. Builders help repair the gut lining, ensuring it stays strong and healthy. **When these microbial workers fail, it's like a city's infrastructure breaking down—leading to illness, allergies, or anxiety.**

Some microbes act as chefs, breaking down complex nutrients into essential components that our bodies can absorb. Others work as security guards, patrolling for harmful invaders and producing substances that keep pathogens in check. There are also builders who repair the gut lining, ensuring it remains a strong barrier. Beyond these roles, some microbes act as waste managers, helping to detoxify harmful substances and remove waste products from the body. Communicators send signals to the immune system, keeping it informed about potential threats or the need for inflammation. Meanwhile, teachers help train the immune system, educating it on which substances are safe and which are dangerous. Together, these microbial 'workers' collaborate to maintain a balanced and healthy environment, much like the diverse roles required to keep a city running smoothly. When these microbial workers fail or their community falls out of balance, it's like a city's infrastructure breaking down—roads crumble, utilities fail, and services grind to a halt—leading to various health issues such as illness, allergies, or anxiety. Just as a well-functioning city requires collaboration among different roles, a healthy microbiome depends on the coordinated efforts of diverse microbial 'workers' to keep everything running smoothly.

Microbiome Networks:

Now, imagine you have a map of the city showing how people in different neighborhoods work together. Some neighborhoods might have close-knit communities where everyone knows each other, while others are more spread out, with people living more independently. In the world of microbes, scientists create similar maps to study how different types of microbes are connected and how they interact with each other in the microbiome. These connections, similar to connections in neighborhoods, form what we call a ***microbiome network*** (See Figure 2).

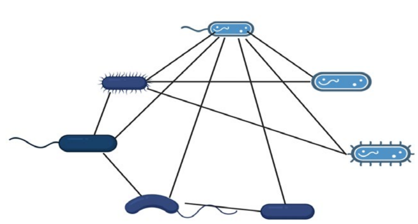


Figure 2: Small Microbiome network. In this image, each shape represents a microbe. The lines between them show how these microbes interact—some may help each other out, some may compete for resources, and others might even hinder each other's growth. Understanding these interactions helps us see how they live together and affect our health.

Just like in a city, where some people are very social—maybe the hub of every gathering or the one organizing events—while others are more isolated and prefer to stay at home, microbes can also play very different roles. Some are the life of the party, connecting many other microbes and coordinating important tasks, while others might act more independently, playing smaller but still essential roles. **Now, do you think all of these people (or microbes) are equally important for keeping the neighborhood (or microbiome) functioning? Not quite!** Just like a community needs a mix of social hubs and quieter residents, your microbiome needs both major players and smaller contributors to maintain balance and health.

Why Aligning Microbiome Networks is Important:

Aligning microbiome networks means comparing two networks—like one healthy and one diseased—to see how their microbes interact. While the same types of microbes exist in both, their interactions can differ. It's like comparing two cities where the people (microbes) are the same, but their relationships vary. By mapping these differences, we can see how similar or distinct the networks are. For example, when comparing the gut microbiome of healthy individuals to those with depression, the networks may look different at first. But after treatment, the interactions begin to resemble those in healthy people, showing that the treatment is working.

For example, when comparing the gut microbiome networks of healthy individuals to those with depression, there may initially be no alignment between the networks, indicating significant differences. However, after treatment (using a meditation app designed to promote relaxation and reduce stress), significant interactions begin to emerge between the two networks, demonstrating that the intervention is having a positive effect.

For example, in our study, we compare the gut microbiome networks of healthy individuals to those with depression. Initially, the networks may show significant differences, indicating no alignment between the groups. However, after participants undergo treatment using a meditation app designed to promote relaxation and reduce stress, we observe that the microbial interactions begin to resemble those in healthy people, demonstrating that the treatment is having a positive effect. In our study, participants' gut microbiomes are measured at baseline and after three months of using the app, allowing us to track the changes in microbiome interactions over time.

MiNAA (Microbiome Network Alignment Algorithm):

At the University of Wisconsin-Madison, under the supervision of Dr. Solis-Lemus and with Reed Nelson as the developer, we created MiNAA (Microbiome Network Alignment Algorithm), a powerful tool for microbiome research. As a postdoctoral researcher in Dr. Solis-Lemus's lab, my primary role in the MiNAA project was to lead the effort in simulating microbiome networks and applying MiNAA to align them. Throughout the project, I worked closely with Dr. Solis-Lemus and Reed Nelson (the developer of MiNAA), contributing to weekly discussions where we brainstormed and identified the appropriate methods to develop MiNAA. I also took charge of testing MiNAA's accuracy and scalability by running simulations of large microbiome networks. My specific contributions include writing the simulation and evaluation codes, developing methods to assess the performance of the algorithm, and ensuring the visualization of the results, with all scripts available on our GitHub. Additionally, Reed and I are guiding a new student in designing a Shiny app (a web-based interface for data visualization and executing MiNAA) to make MiNAA more accessible and user-friendly. And MiNAA acts like a highly intelligent detective, swiftly identifying alignments between large microbiome networks—each containing over 1,000 microbes—in just minutes. Interestingly, 'MiNAA' is also the name of a flower in my native language, Persian, which inspired the logo's design, representing the nodes of the network. MiNAA is both user-friendly and efficient, enabling researchers to gain rapid insights into microbial interactions across different health conditions.

Figure 3: Logo of MINAA. The logo of MINAA, inspired by the 'Minaa' flower, symbolizes the intricate connections within a microbiome network.

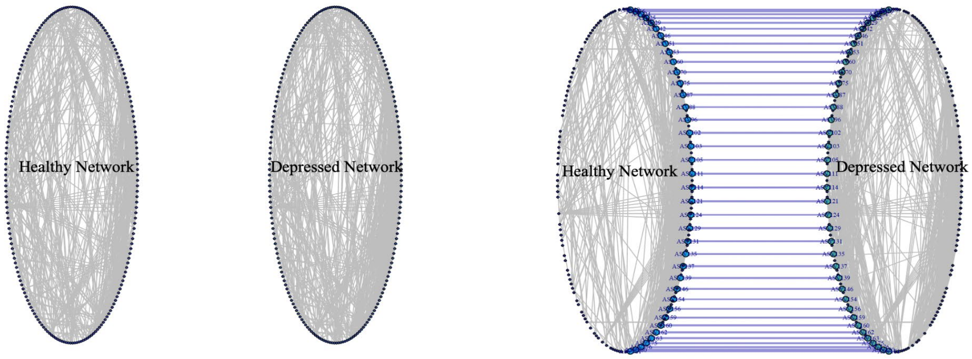
How MiNAA Works:

MiNAA finds the alignment between two networks by identifying nodes (microbes) that have similar neighbors and connections. Imagine you're pairing people in a city based on how similar their neighbors are—those with more connected neighbors get matched. This allows scientists to compare not just individual microbes but also their relationships and roles within their respective networks.

MiNAA aligns two microbiome networks by finding pairs of nodes (microbes) from each network that match based on their similarity in structure and biological characteristics. Imagine you have two different communities, and you need to match people from one community to people in the other based on factors like the distance they need to travel to meet, the number of mutual friends they share, or other common interests. The goal is to find matches that minimize the overall 'cost' of connecting these people.
Similarly, MiNAA constructs an 'overall cost matrix' for the two networks, where each entry represents the alignment cost between a microbe in one network and a microbe in the other. This cost is calculated based on a combination of topological information (such as the number of connections a microbe has with others) and, if provided, biological information (like genetic similarity). The algorithm then uses this cost matrix to align the microbes in a way that minimizes the total alignment cost, effectively finding the best match between the two networks. Just as you would match people from different communities to optimize for minimum travel distance and shared connections, MiNAA aligns microbes to minimize the overall cost based on their network similarities and optional biological characteristics. This approach allows scientists to identify which microbes play similar roles in different environments or health conditions, revealing insights into how microbial communities differ between healthy and diseased states.

Result of MiNAA:

Aligning microbiome networks is a process for looking at two different microbiome networks and comparing them. To illustrate the result of MiNAA, consider the diagram in Figure 4 below.



(a) Before Using Treatment (No Alignment)

(b) After Using Treatment (38 Alignments – Purple lines)

Figure 4: This figure illustrates the results of MiNAA analysis comparing gut microbiome networks between healthy individuals (Healthy Network) and those with depression (Depressed Network). The analysis focused on exact matches between microbes, where only "same-to-same" pairs (e.g., A to A, B to B) were aligned, and mismatches (e.g., A to B) were excluded. Before treatment, no alignments were found among approximately 200 possible "same" microbes. After treatment, 38 exact alignments (purple lines) were identified, indicating increased similarity between the networks.

In Figure 4, two different microbiomes are depicted as parallel circular discs—one gut microbiome network from a healthy person (Healthy Network) and one gut microbiome network from a depressed person (Depressed Network). On each circular disc, the microbes that are part of the microbiome are shown as dots along the circumference of that disc - analogous to the residents of the neighborhood. The nature of a healthy or depressed microbiome network is defined by the interactions which each microbe (dot) has with other microbes in that microbiome network. For both the healthy and depressed microbiome networks, interactions between microbes in each microbiome are shown as light gray lines between the microbes (dots) in Figure 4. Remember, the microbes and their interactions define what a particular gut microbiome network is, as well as how it functions. It turns out that those microbiome networks - the microbes and their interactions with each other - are also important in defining how a healthy gut microbiome network differs from a depressed gut microbiome network.

It turns out that those microbiome networks—the microbes and their interactions with each other— are also important in defining how a healthy gut microbiome network differs from a depressed gut microbiome network. This is because the pattern of microbial interactions can reflect the overall state of the gut environment. In a healthy network, microbes may have more balanced, cooperative interactions, which support essential functions like digestion and immune regulation. In contrast, a depressed network may show disrupted or weaker interactions, indicating an imbalance where some beneficial microbes are less connected or certain harmful microbes have gained influence. These changes in connectivity can affect how the microbiome functions, contributing to symptoms associated with depression.

The alignment of microbiome networks is determined on a microbe by microbe basis. Remember, microbes are the dots in Figure 4 (a) and 4 (b) above. To start the alignment process, the same microbe is considered in the healthy gut microbiome network and the depressed gut microbiome network. If that microbe interacts with the same other microbes in both the healthy and depressed microbiome networks, that microbe is considered to be comparable for those two networks and aligned. To signify the alignment of a microbe in each network, a purple line is drawn between those microbes as illustrated in Figure 4b.

Figures 4(a) and 4(b) show two different degrees of microbiome network alignment.

In Figure 4(a), a healthy gut microbiome network and depressed gut microbiome network are depicted before getting treatment. In this situation, there is no alignment between the two networks because, although the same microbes are in each network, none of those microbes have common interactions with other microbes in their networks.

In Figure 4(b), a different level of alignment is depicted (after Treatment). Here, there are 38 separate microbiome alignments. This represents a situation where the people with the depressed gut microbiome network in Figure 4a have begun medical treatment so that certain characteristics of a healthy gut microbiome network are now replicated in the depressed gut microbiome network.

Conclusion:

Can you see how MiNAA helps scientists assess whether a treatment is working? It shows us that treatments can shift the microbiomes of people with depression to resemble those of healthy individuals. Isn't it incredible how a complex algorithm like MiNAA can lead to better health outcomes?

MiNAA is more than just an algorithm—it's a gateway to understanding how our inner microbial world shapes our health. By mapping the connections between healthy and diseased microbiomes, MiNAA can guide us toward new treatments that restore balance and well-being. As we continue to decode these hidden microbial networks, the potential for personalized healthcare grows. This innovative tool isn't just helping scientists—it's paving the way for better health outcomes for all of us.

In this article, I've focused on the relationship between the gut microbiome and the brain, but MiNAA is versatile and can be applied to any type of disease. By comparing microbiome networks of diseased individuals to those of healthy individuals, MiNAA provides valuable insights that could lead to the development of new treatments for a wide range of human diseases.

If you want to know more please watch our video on youtube:
https://www.youtube.com/watch?v=S9PaA49xyBU&t=48s,
read our paper on JOSS journal: https://joss.theoj.org/papers/10.21105/joss.05448
and see our code and documents on Github: https://github.com/solislemuslab/minaa.