Altering Communities: From Microbes to Biological Machines

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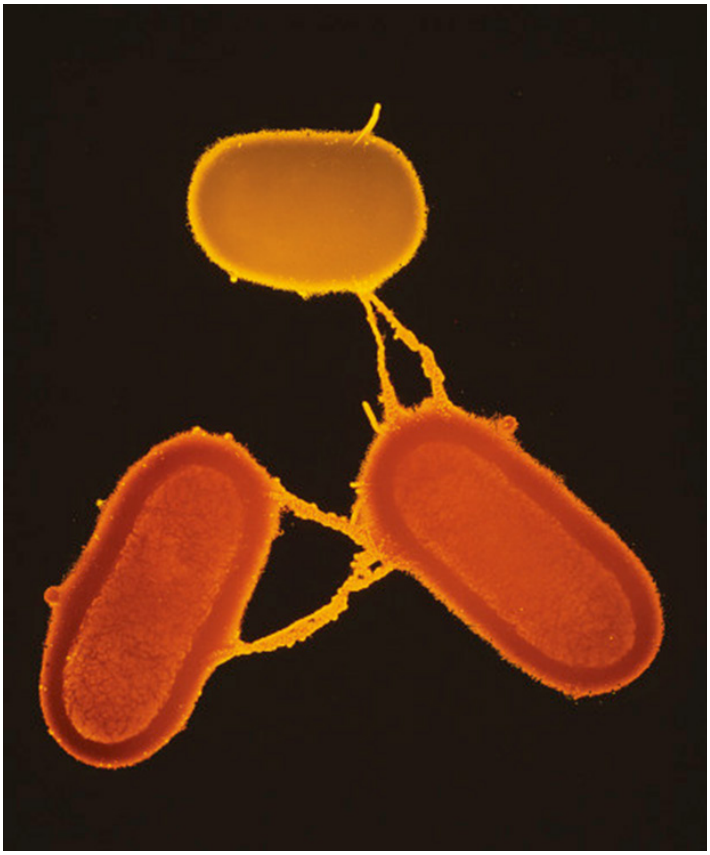
What makes us human: our genes or the microbes that colonize us? Throughout our body the microbes that constitute our microbiome outnumber our human cells, meaning there are more microbes present on us than our own genetically distinct cells (Gallager). Moreover, our microbiome contains more genetic information than our human genome (University of Washington). Does this evidence of a large amount of life colonizing our bodies influence our lives? Indeed, the microbiome has been linked to health outcomes such as the development of autoimmune diseases and contraction of non-communicable diseases (West et al.). Additionally, these microbes distinguish us. Scientists from Harvard University found that the microbiome could be used as an identifying marker of a person in a similar way as authorities use fingerprints and DNA (Dywer). The influence of the microbiota, however, is not uniquely human. In an extreme case, a difference in the microbiome caused speciation. Wasps from the same region developed incompatible microbiomes and lost the ability to reproduce because when attempted it would result in the offspring's death (Yong). Scientists then altered the microbiota of these wasps and found that when they were compatible they were able to produce viable offspring. While there is no such extreme case documented in humans, the microbiome is pivotal to both our health and experiences. There is no doubt that the life that colonizes our bodies has a powerful influence over our lives.

Perhaps, harnessing the potential of the microbiota could lead to the technological revolution science fiction novels envision (Sonneburg). Currently, researchers are seeking to engineer the microbiome to develop novel capabilities. Such capabilities, if achieved, could revolutionize human health in an instant (Lee). Dr. Justin Sonneburg, an assistant professor at Stanford University, can even imagine having individuals alter their microbiome so they are capable of sensing and eliminating biological threats such as the onset of disease (Sonneburg).

Does this mean that scientists must simply find the right genes to paste into the bacteria? In fact, engineering microbiomes has a layer of complexity endowed by the exclusivity and power of the microbial community. Many of the microbes being genetically engineered are model organisms, meaning that they are well studied and protocols for genetic exchange have been standardized. Introducing these microbes into a microbiome, specifically in a mammalian gut, is not entirely feasible and as such scientists must often attempt to alter



non-model bacteria. This is difficult because non-model bacteria have unique ways of regulating their genetic information that can be problematic when attempting to introduce foreign genetic information (Ke, Wang, Yoshikuni).

Upon successful engineering of a non-model organism, scientists must then integrate these microbes into an established microbiome. However, the introduction of these microbes are often short lived as their persistence in the microbiota often only lasts a couple of days. This is problematic because for the person or organism hosting the microbiome, these engineered bacteria must become residents of the microbiome rather than transient travelers.

These two hurdles are a part of the benchmarks scientists hope to overcome in the upcoming years. In a collaborative effort, scientists identified three outcomes for microbiome engineering research in the future: 1) Spatiotemporal Control (understanding the interaction between microbes over time to control/account for these interactions), 2) Func-

tional Biodiversity (being able to apply engineering principles across a wide range of bacteria), and 3) Distributed Metabolism (use of microbes unique metabolism to engender cooperation) (Lee).

Despite these limitations, scientists have still been successful in engineering microbes. Currently, there are two main ways scientists are purposefully altering microbiomes: a top-down approach and a bottom-up approach (Ke, Wang, Yoshikuni). A top down approach introduces genetic information widely across a set of microbes that constitute a microbiome. Much like a person handing out pamphlets hoping that passerbys take the pamphlet home and act on the information, scientists must share the desired genetic information and coax the microbes to take it up. One research project successful at doing this used a new approach called metagenomic alteration of the gut microbiome, nicely coined MAGIC (Ronda et al.). By using a bacterial system of genetic transfer that was accessible to a wide range of bacteria, called RP4 conjugation, they widely distributed the desired genetic information across the community. Then, when the bacteria read the genetic information, the genes told the bacterial cells how to incorporate it into their genome so that the information was no longer transient but more stable. These researchers from Columbia University and Harvard, found that the genetic information they dispersed was accepted by a wide range of bacterial species and actively produced the desired gene. While a vast majority of these bacteria species were able to act as a living therapeutic, the persistence of these microbes only lasted three days.

The second main approach is the bottom-up approach. The bottom-up approach isolates a singular bacterial species from the microbiome and engineers this microbe which will ultimately be re-introduced into the microbial community. One example of this is a group of researchers that modified Escherichia coli, a model bacterial strain, to alleviate the symptoms of Phenylketonuria (PKU) (Isabella et al.). PKU is a genetic disease that makes certain individuals unable to use the molecule phenylalanine (Phe) which is commonly found in proteins. By engineering a strain of bacteria previously used in human clinical trials, researchers were able to introduce a new metabolic pathway that could utilize Phe. This would reduce the harmful effects of Phe build-up such as intellectual disability. The outcome of this research showed a significant reduction of Phe in mice suggesting that this could be a viable therapeutic. Although, the future of this research must address the transience of these probiotics so that this beneficial microbe can provide a long term solution to PKU. Such as understanding microbe-microbe interactions.

The complexity and novelty of the microbiome poses challenges to creating a personalized microbiota. The large amount of resources and expenses are limited when trying to engineer these bacteria into living machines. Despite this, new technologies such as next-generation sequencing and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) have enabled more mobility in synthetic biology research. The potential of the microbiota not only relies upon the accumulation of knowledge but on its application to creating cooperative communities with perceived capabilities.

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