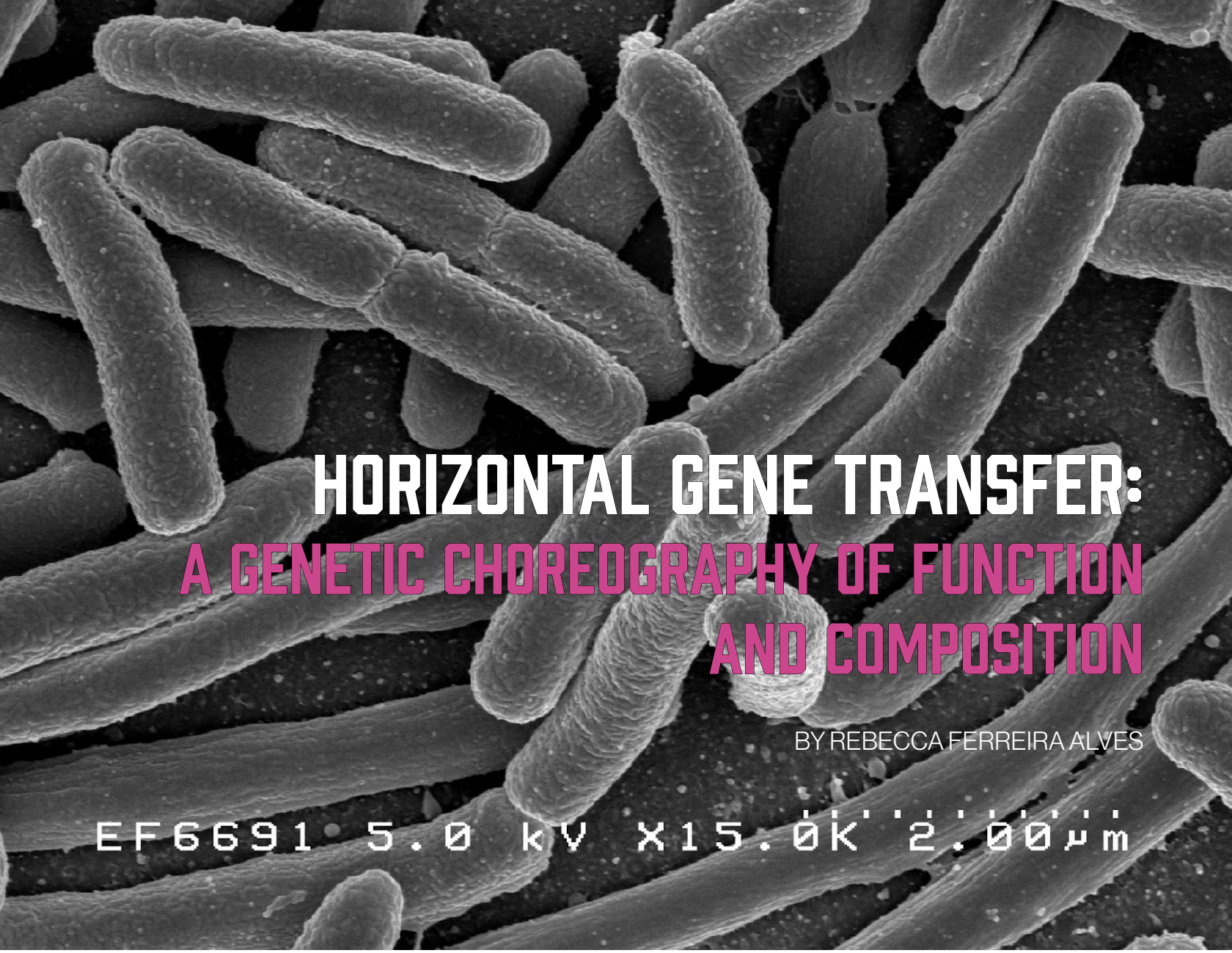

HORIZONTAL GENE TRANSFER: A GENETIC CHOREOGRAPHY OF FUNCTION AND COMPOSITION

BY REBECCA FERREIRA ALVES

Whether you are familiar with it or not, horizontal gene transfer has most likely played a role in your health and well-being. Remember the last time you had to take antibiotics, and how your physician advised you to carefully follow the recommended dosage throughout the whole course of the treatment? What about when shopping for meat at the grocery store, and you found yourself gravitating toward the packages that claimed to be "antibiotic-free"? These seemingly distant events are both concerned primarily with avoiding the establishment of antibiotic resistance, a phenomenon that takes place through horizontal gene transfer.

WHAT IS HORIZONTAL GENE TRANSFER?

A practical way to think about horizontal gene transfer is by contrasting it to a more familiar mechanism of gene transfer. On a family tree, older generations are placed above younger ones—similarly, the sharing of genes from parents to offspring is known as vertical gene transfer, and it is the reason we resemble our parents. Vertical gene transfer is of immeasurable importance to the survival of species, as the reproduction of genetically unique offspring keeps all species in the evolutionary race. Vertical gene transfer is pertinent to all people, biologists and laymen alike. Horizontal gene transfer (HGT), on the other hand, is niche; its role in our everyday lives is not easily evident, which is why most people have never heard of it.

HGT is the process by which organisms share genetic information laterally—that is, outside of the parent-offspring relationship.[1] Imagine a scenario where a friend who is not genetically related to you possesses a certain trait that you desire for yourself. Say they are predisposed to being a morning person, and you envy their effortless ability to be productive early in the day—with the assumption that being a morning person is a genetic trait, HGT would allow you to absorb your friend's genes for yourself. Bacteria are not concerned with morning sluggishness; they use HGT for more fundamental reasons that ultimately affect the health and well-being of all organisms living in Earth's many ecosystems.

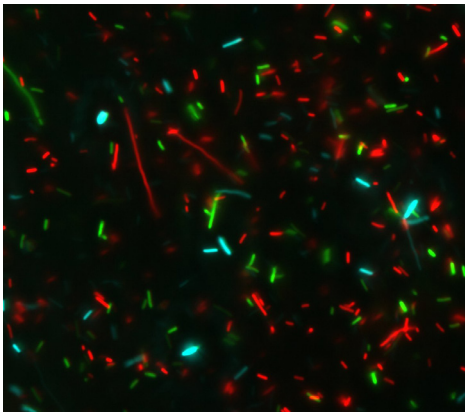

Figure 1: Bacteria Waltz at the Micron Scale. *The presence of the plasmid allows scientists to manipulate genetic makeup by inserting fluorescing genes into the different bacteria—resulting in a colorful genetic dance.*

Horizontal gene transfer is made possible by the unique cellular makeup of prokaryotes—single-celled organisms that can be either bacteria or archaea.[2] On the other hand, eukaryotes, such as humans and other multicellular organisms, are limited to storing genetic information within chromosomal DNA in the nuclei of their cells.[2] As well as chromosomal DNA, bacteria have an additional genetic component that most eukaryotes, with the exception of a few species of yeast,[3] lack: small circular portions of extrachromosomal DNA known as plasmids. Genes stored in the plasmid are mobilizable: they can be shared via HGT and are not restricted to a single organism or even a single species of bacteria.[4] Most commonly, the genes that make certain bacterial infections dangerous to our health are stored in bacterial plasmids, which are then released into the host cells during the process of infection.[4] Since prokaryotes lack a cell nucleus, bacterial chromosomal DNA is coiled into a structure known as the nucleoid; the genes within are coined as "static" due to the inability of the organism to share them via HGT. In contrast, genes in the chromosomal DNA of a bacterium can only be replicated during cellular division.[2]

HGT occurs via three distinct mechanisms: transduction, transformation, and conjugation.[5] With transduction, viruses known as bacteriophages infect the bacterial organism and introduce new DNA in the process.[2] In transformation, bacteria absorb pieces of DNA directly from the environment outside of their cells.[2] Conjugation happens when two bacteria connect via the formation of a cytoplasmic bridge (direct linkage between two cells); DNA is then exchanged from the donor to the recipient through this appendage.[2]

Antibiotic resistance occurs in a community of bacteria when plasmids containing information on how to avoid the detrimental effects of antibiotic drugs are transferred between organisms via HGT. Over time, the population of bacteria will become increasingly resistant to the effects of a drug—and infection will be more successful despite antibiotic treatment.[6] While antibiotic resistance is a fascinating example of the biological reach of HGT, this genetic choreography has far more applications than what meets the eye.

FUNCTION AND COMPOSITION, DECOUPLED

Genes, when expressed, provide the organism with a certain function. In general, the stability of a particular gene's function is proportional to its abundance in the population of a species.[7] Functional stability refers to how prevalent the function associated with a gene is in the given population—stability increases as more organisms of the species begin to express the gene, and it decreases as the number of organisms with that function begins to decline.[8]

Several research initiatives found bacteria in the human gut, marine waters, certain macroalgae, or the foliage of some wildflowers that do not abide by the norms of functional stability.[8] For these microorganisms, the stability can be independent of species. Certain genes and their functions can remain in the genetic pool regardless of the species making up the community—this process is described as function-composition decoupling, where composition refers to the framework of species making up the community of interest.[8] Function-composition decoupling is quantified by how independent from composition the functions of a community become over time, with a larger decoupling representing a smaller (more independent) relationship between the bacterial makeup and function.

The gut microbiome is a fascinating example of how function can be disengaged from composition without sacrificing the efficacy of the tasks being performed by the microorganisms. In the intricate microbiome of the human gut, each person houses a wide variety of species making up their own set of gut bacteria. The composition of bacteria in the gut not only varies between individuals, but a single person can also undergo changes of their bacterial makeup as their habits and environments change.[9] Regardless of this flux in composition, the functions performed by these microorganisms do not vary nearly as much, and every person has their digestion aided in similar ways by their own gut microbiome.[9]

In a recent article published in *Nature Chemical Biology*, researchers from the You Lab and David Lab at Duke University described quantitative and qualitative findings about the relationship between rates of HGT and functional stability in bacterial populations.[8] The study found that the rate at which bacteria share their plasmids through HGT determines the stability of a

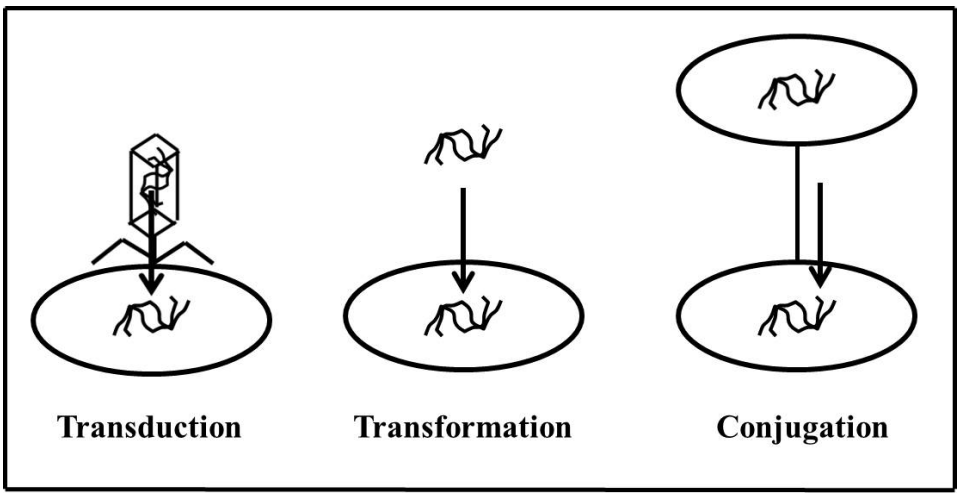

Figure 2: The three mechanisms of HGT: Transduction, Transformation, and Conjugation.

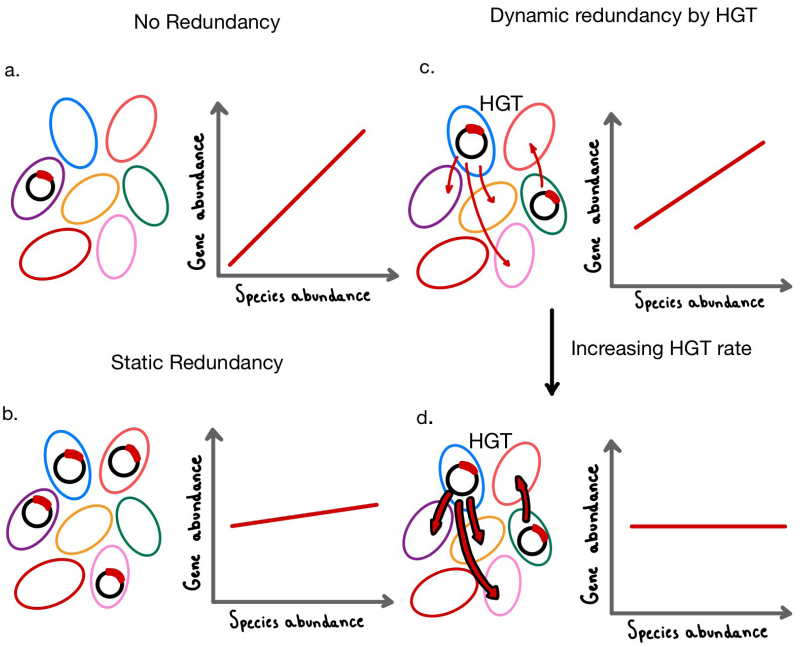

Figure 3: Dynamic redundancy and increased rates of HGT lead to function-composition decoupling. *Each color is representative of a species; the target gene is shown in red within a plasmid. A - No redundancy: The target gene is limited to one species and cannot be mobilized through HGT, resulting in a strong coupling between the gene's function and the species abundance. B - Static Redundancy: The target gene is expressed in several species, but it is not mobilizable and therefore is not in dynamic redundancy. There is some coupling between function and composition, but it is not yet stable and is dependent on several species' abundance. C - Dynamic Redundancy by HGT: HGT introduces dynamic redundancy, but the transfer rate is not fast enough to create a strong decoupling of function and species composition. D - Increased HGT Rate: faster rates of HGT create the strongest decoupling of function and species composition, representing the highest functional stability of the target gene.*

particular gene's functional abundance in a community. If the transfer of a gene among bacteria is fast enough, redundancy is created—several members of the community share the same gene and perform the same function; therefore, the species composition is redundant to that function. Redundancy can be either static or dynamic, as shown in Figure 3. With static redundancy, genetic function is redundant from species because several species already contain that gene to begin with (labeled "b"). Alternatively, dynamic redundancy occurs when a gene initially expressed in only one species can be mobilized via HGT, eventually leading to several species being able to perform the functions associated with it (labeled "c"). The research paper defined that rapid rates of HGT lead to a nearly complete decoupling of function and composition, stabilizing the gene's abundance regardless of the bacterial framework of the community (shown in "d").

This finding is supported both by experimental observations and extensive numerical simulations, further interpreted by statistical analysis. To observe the transfer of genes, the team of researchers simulated artificial complex bacterial communities using computer modeling and held several variables constant through randomization including growth rates, carrying capacity, and plasmid transfer rates. Twenty artificial plasmids were made available to each local population of 50 species; the simulation was allowed to run for 500 hours until it reached stability. The team noted that higher rates of HGT in a simulated population resulted in higher stability of the observed plasmid compared to populations in which the rates of transfer were slower. Further experimental data was obtained from the analysis of synthetic communities of *E. coli*. Twelve total bacterial communities were constructed; six communities were made available with a single target plasmid for transfer, and the remaining six transferred eleven plasmids. Each plasmid contained unique genetic information coding for specific types of antibiotic resistance. These communities underwent several antibiotic dilutions over the course of 15 days. After the course of the experiment, it was determined that the plasmids that were more efficient at conjugating (HGT) demonstrated greater stability in their abundance and that the resistance genes exhibited robustness against composition variation in the communities.

LOOKING AHEAD

The ability of bacterial communities to maintain stable genetic composition regardless of the species makeup is an invaluable tool against external threats such as the introduction of a pathogen or changing environmental conditions. For a company, losing a highly skilled worker can be extremely detrimental to productivity. But if that person were somehow able to share their abilities with other employees, then their departure would not mean a total loss in productivity. Now, the completion of specific tasks is in-

dependent of the presence of an individual, and everyone is just as competent and capable. A bacterial community is capable of having very important functions regardless of what different species make up the pool of "workers," making it robust against external threats and subsequent changes in species composition. In correspondence with *Berkeley Scientific Journal*, Dr. Lingchong You—Professor of Biomedical Engineering at Duke University and investigator on the aforementioned research paper—described this process as a "dynamic division of labor." Rapid rates of HGT allow bacteria to achieve dynamic redundancy, creating a community prepared for fluctuations in composition and still capable of performing its necessary functions for survival.

The beautiful choreography of HGT is a keystone ability of microorganisms—representing an almost infinite source of opportunity and possible applications. As it is tamed and mastered, this genetic dance of microorganisms will continue to open doors in many fields. It has been determined that select specialized microorganisms are capable of degrading plastic[10] or expediting the clean-up of oil spills[11] while others produce molecules used in the synthesis of pharmaceuticals.[12] This novel knowledge about the role of HGT in function-composition decoupling is a stepping stone toward engineering genetically programmed complex microbiota communities to aid in many environmental challenges or expediting the manufacture of life-saving pharmaceutical treatments.

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