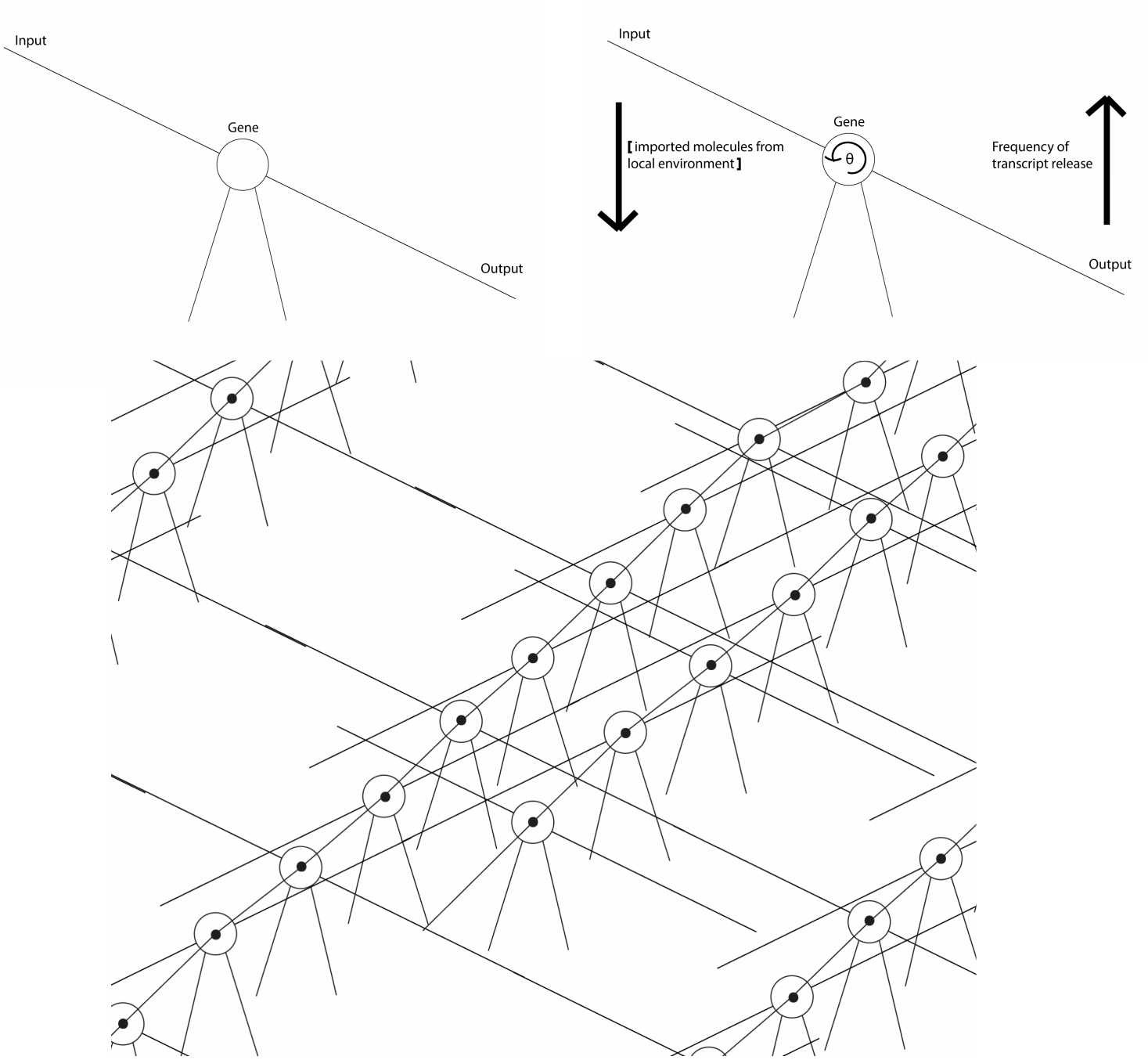
On the human microbiome

The bacterial tendency to chemically tether themselves to nearly any environmental niche on Earth via catalyzing, channeling, shunting and rechanneling flows of evolutionarily- specialized biosynthesis may be at its most striking in and on ourselves. Building upon billions of years of localized molecular relay entanglement promoting the buildup of chemical constraints, bacteria have not only adapted to their varied environments, but seem to have also created their own by sowing (in an almost crop-like manner) increasingly complex layers of niches upon one another. As a result, they now selectively coat many of our tissues with their tiny, rapidly dividing genomes that often act as primary responders in a slew of metabolic and biosensing roles which are only beginning to be understood.

Even if one was to run chronologically backwards across the Earth-webbing spatiotemporal structure of biology, gradually peeling off layer after layer of the tissues and functional components that constitute human-ness, or mammal-ness, or fish-ness, etc., and arrive at a ancient variety of organism such as *C. Elegans*, one would often still find bacteria in similar arrangements and roles, albeit in vastly fewer quantities and functions (**1**). More specifically, if the starting point for this phylogenetic backtracking was indeed a mammal such as *Homo sapiens*, the generalizable pattern of bacteria populating tubes that foster directional nutrient flow would remain relatively static across a great deal of species. The profound impacts of resident bacteria on human health today thus appears to be derived from evolutionarily 'breaking into' a wildly successful nutrient-harvesting design (*channels* of situationally-high, nutrient-metabolizing, bacterially-expressed enzyme concentrations [e.g. intestines]) which permitted an increasing degree of chemical complexity in the form of micro- niches to be perpendicularly sowed over a lengthening, mobile macro-niche. Therefore, the microbiome that has reformed human identity to its now common referral as a "superorganism" (**2**) is founded not only upon the bacterial tendency to biochemically adapt to a variety of niches, but also by their tendency to further enhance their metabolic regeneration capabilities by reforming their environment, sowing their own niches in increasing degrees of chemical complexity and then jettisoning them out into new environments to reassemble said niches.

In this case, niche is defined as a localized region of space where particular patterns of biochemical reactions occur frequently and reliably until a threshold such as a population-cap or other inhibiting factor is reached, primarily including species (DNA sequence)—specific imported energy sources, e.g. enzyme substrates, and exported reaction products. For a niche to become increasingly complex and assemble higher levels of order, exponentially greater numbers of chemical reactions must become 'entangled'. DNA and its capability of storing environmental [chemical] responses (including responses from other genes in the same or separate organisms), lengthening, and adding/modifying reaction-responses will be thought of as the center of this entanglement constituting a biological niche. Each gene will be abstracted as the center of a "mechanical" (electrochemical) relay — a center between the imported and exported molecules of a

reaction-response. As a genome, bacterial or otherwise, grows and/or is modified to be more energetically suited to its surroundings, an increasing number of chemical relays become entangled, trimmed, and 'molded' to the environment (**Figure 1**).



(Figure 1): Entanglement of genetic relays form biochemical niches.

Taking a niche as a set of import-export sustainable, spatially concentrated, constraint-building chemical reactions, the "Input", "Gene", and "Output" sections on the upper left relay will be defined as A, B and C, respectively. "A" will be defined as the concentration of 'transcription-activating molecular micro-systems', with one micro-system defined as one complete set of all molecules required for producing a mRNA transcript from a gene. "B" will be defined as the frequency of gene transcription in nucleotides per second per cumulative concentration of "A" (for a particular period of time). "C" will be defined as the transcript frequency in nucleotides per second, per concentration of "A", per gene size.

Relay centers (genes and genomes) become further entangled with and modified by one another over time through continuous influxes of metabolites. A radically simplified analogy of this environmentally-influenced genetic relay entanglement and 'smoothing out' process might be that it is not entirely unlike the continuous remolding and rearranging of soil particles and pebbles to most energetically suit flows of water in a stream or river. Such streams and rivers consist of continuously fluctuating, but macro-statistically repetitive, volumes — continuously changing, but macro-statistically repetitive, concentrations of water molecules, as would concentrations of metabolites like enzyme substrates and other structural/energetic components be continuously in flux but repeat stabilized patterns over time that could be 'captured' and imprinted into DNA. Furthermore, it may be logically derived that continuously imprinting environmental responses in the form of specific chemical reactions into DNA *decreases* the possibility magnitude and number of potential states of the localized chemical system, in the sense that an increasing number of constraints are imposed onto the DNA molecule and thus its probability of evolving other potential reactions are collapsed and removed (**3**). Paradoxically, when zooming out from the scale of the molecule to that of the organism, such appears to also increase the number of environmental probabilities that the bacterium can adapt to and thus *increases* the possibility magnitude of the number of states the bacterium can exist in. When certain molecules such as various metabolites come within a particular range of a bacterial genome, electrons on said molecules are pulled down a 'channel' of reactions that often pull apart the entire molecule in the process, distributing some of its electrons further through more branching 'canals' of reactions across the cell. These canals are, on the one hand, formed on their 'inside' (e.g. the 'water' in the canal) by oscillations in inter-molecular forces that continuously reform and 'pulse' branching reaction-trees to life, which web through the cell (almost as would blinking Christmas tree lights). Such oscillating inter-molecular forces based on reactant availability allow a bacterium to maintain its form — to hold its structure together. It is therefore the regeneration of these forces, or 'circuits', which in contrast to modern engineering, construct and maintain the form of the circuitboard (the cell, collectively).

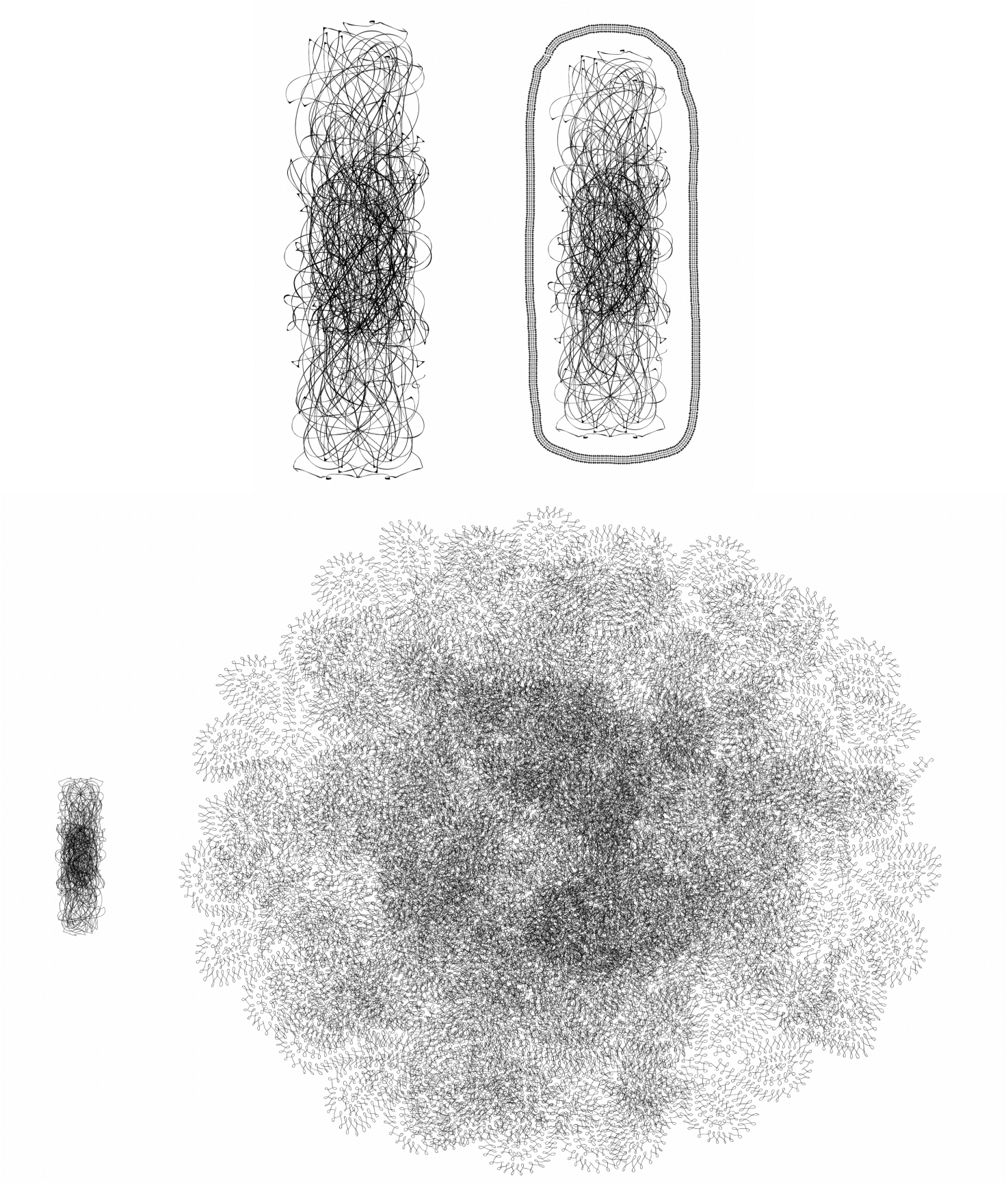
On the other hand, the outside of these canals of reactions could be thought of as 'walled-in' by chemical constraints (**4**). Chemical constraints are simply a local collapse of possibility magnitudes (the 'five-dimensional', logarithmic 'fading out' of 'adjacent molecular possibilities') around a series of reactions which reassemble and redistribute molecules in a manner that regenerates the cell's inter-molecular force reaction-patterns. Additionally, each of these branching canals of reactions is specifically constrained to manipulate or pluck electrons from specific reactants (specific energetic geometries), and therefore only certain types of molecules will fit to 'flow' down a particular canal. As mentioned above, concentrations of molecules such as metabolites that are shuttled down reaction canals oscillate but repeat stabilized patterns over time within upper (saturated) and lower (cell death) form-regeneration- permitting thresholds for the bacterium, ultimately resultant of the chemical constraints accumulated by its genome. With a variety

of species-specific signaling molecules, form- regeneration-permitting thresholds/ constraints for a single bacterium can be 'scaled' across an entire colony, where one of the most striking examples of such can be found in biofilms. Incoming metabolite concentrations are kept within a safe threshold for all members of certain biofilm types by oscillating between outer population growth and inner population starvation (**5**).

An additional and important constraint in bacterial biofilms is also reached at the threshold of a large population with adequate metabolic resources — dispersion. Chemical relays from a small bacterial subpopulation systematically detach themselves from the rest of the biofilm via the activation of genomic environmental-response-reactions that release extracellular matrix degrading enzymes. They subsequently divide and reform a new biofilm and its associated chemical constraints elsewhere by metabolically entangling the canals of chemical reactions of individual bacteria across the entire colony through the partial synchronization of genomic relays. The result is the continual self assembly, release and re-self assembly of a biochemical micro-niche more suited to the resident bacteria (of a biofilm). This process in essence may mark the birth of 'multicellular' birth, and through steadily modifying enough genetic relays and sculpting constraints to maximize the energy that could be harvested from a wide variety of molecules, the micro-niche of a biofilm may have been gradually 'sowed over' — first with epithelial cells/tissues in place of a protective outer layer of bacteria to form a more direct pathway for nutrients, as well as mineral-rich support structures, branching channels to transport metabolites, passageways for intruder-sensing sentinels, and even a biological form of 'GPS'. The result, in jumping from bacteria in a biofilm to those inside the gut of humans, is that said microbial colonizers no longer need to continually reassemble relatively vulnerable micro-niches, but instead simply hop from one eukaryotic transportation complex (billions of years of micro-niche sowing and 'stacking) to another via the birthing process, beginning in the uterus (**6**). In other words, when the 'mobile macro niche' (infant) has self assembled to a degree of complexity sufficient enough for bacterial colonization, instead of being exposed and jettisoned out into the chemical chaos of their surroundings, the bacteria enter their new home avoiding environmental exposure while bathed in a stream of their own nutrients (e.g oligosaccharides for *Bifidobacterium longum* in breast milk) (**7**).

Erwin Schrodinger once took note that "An organism's astonishing gift of concentrating a 'stream of order' on itself... ...of 'drinking orderliness' from a suitable environment — seems to be connected with the presence of the 'aperiodic solids'" [DNA] (**8**). The 'channel' of this "stream of order" can be viewed, collectively (the presence of many entangled 'aperiodic solids' / DNA molecules) in the macro-sense and in higher organisms, as essentially starting with the entirety of the mouth, esophagus, stomach and gut, where the latter three focus almost entirely on breaking down food without absorption. It is instead the intestinal components of this tubular system that may be thought of as the true nexus of intestinally- perpendicular nutrient uptake and of form regeneration initiation in complex multicellular organisms, and one of the key players and primary responders to fluxes of chemical change in this region are massive populations of bacteria. Here, high concentrations of myriad enzyme types are generated by a tubular bacterial mat of localized

and specialized genomes (**Figure 2 - below**) which selectively ‘mine’ incoming, directionally-channeled molecular conglomerates for various energetic and structural components to regenerate their own form and that of their mobile eukaryotic transportation complex.



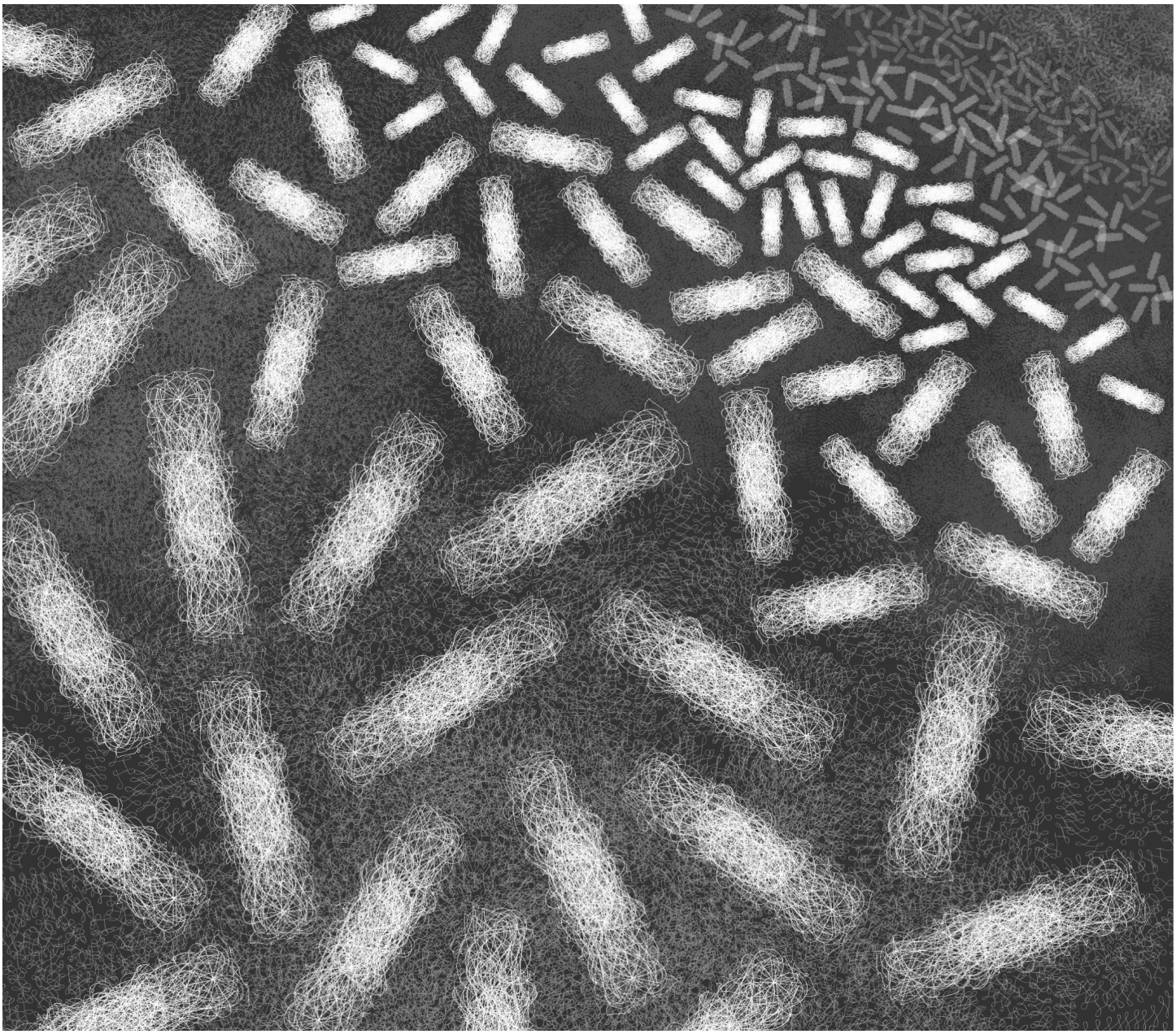


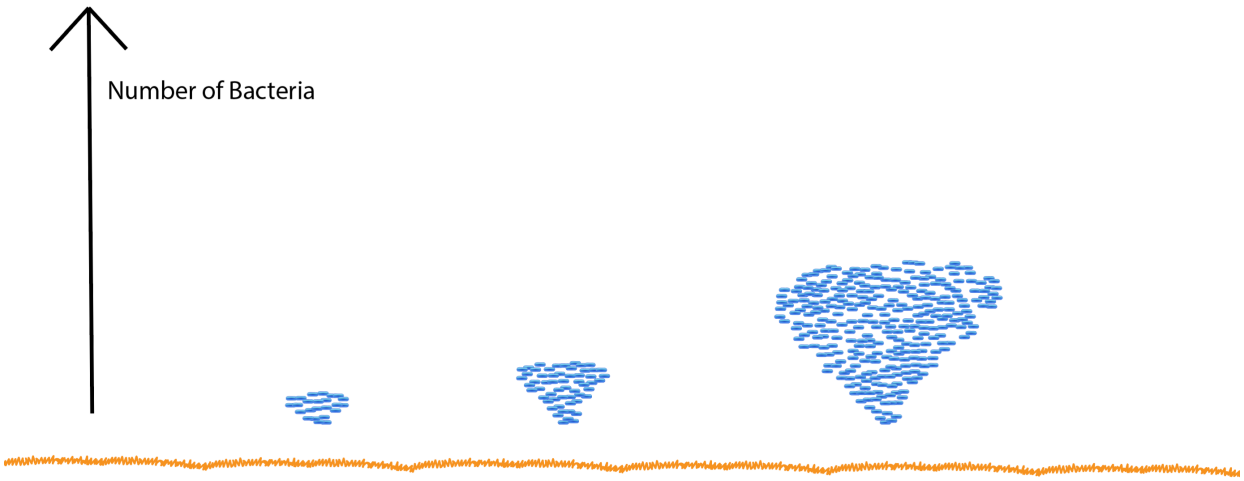
Figure 2: Entangled Genetic Relays in the Intestines form an Interface Between Two Radically Different Types of Genomes.
First from the top, the DNA/genome from a single bacterium is abstractly visualized, initially with a lipid membrane (left) and without (right). Middle: the bacterial genome is placed alongside abstracted, human DNA, not condensed into chromosomes but with the general pattern of nucleosomes maintained, for a hypothetical size comparison. Bottom: Having peeled away all lipids, proteins and other non-nucleotide molecules of which are not direct members of the structure of DNA, and if looking down a region of epithelium in the colon (with other spatial geography/geometry minimized, such as the bacteria-sized pillars formed by microvilli), one would see an outer coating of rapidly dividing, biosensing bacterial genomic relays churning metabolic byproducts downwards via diffusion into ‘swarms’ of human DNA.

“What seems to be going on here... is some kind of gene swarm.” — Terence McKenna

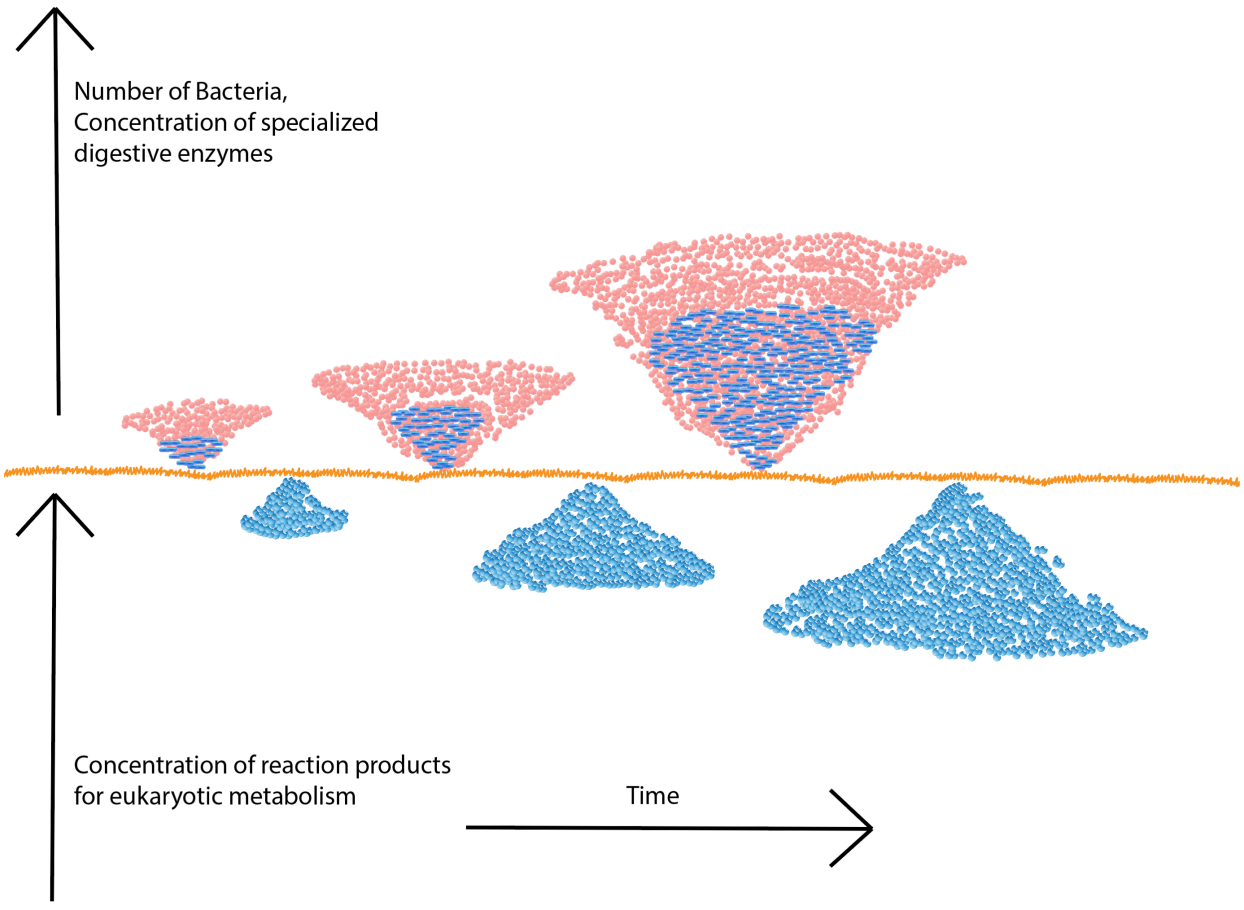
Human intestines — the large intestine in particular — carry a great deal of microbial diversity, and although approximately 40 types of bacteria dominate these regions in terms of abundance, several hundred to 1,000 species can coexist overall (**9**). These rapidly dividing bacterial genomes of great metabolic-pathway-generating variety are capable of enzymatically 'soaking up' a wide range of incoming nutrients on a situational basis, where their leftovers diffuse into the surrounding ocean of eukaryotic microvilli. Although the landscape in our intestines is relatively alien, comparisons could be drawn to that of our Earth's own oceans, where bacteria navigate between microvilli of similar size, resembling fields of sea anemones coating the tops and bottoms of a continuum of hills (villi). If a single bacterium slowly, chemically maneuvering among these microvilli 'anemones' was magnified over 780 times from its original 2-micron length to be barely visible at ~2/3 of a millimeter, and if its intestinal surroundings were also magnified by similar proportions, then said microvilli 'anemones' would also average a similar 2/3 - 1 millimeter in length, while the larger 'hills' (villi) would stand at approximately 2.5 feet tall, and the diameter of the intestine itself (assuming a roughly 7 cm diameter large intestine) would come to be roughly 180 feet wide — or close to the diameter of the circular portion of the Columbia University Business School library (note that comparing the business school to a giant colon is coincidental and out of geometric convenience).

The bacterial inhabitants of this alien landscape stay in constant flux of both population density and species diversity due to the frequently changing metabolic constraints placed on them. Although little experimental evidence has accumulated for directly, visually tracking bacterial population growth rates for individual taxa in the intestines *in vivo* following direct contact with partially digested food after a meal, emerging multidisciplinary techniques such as distributed cell division counting (DCDC) have started to shed light on these dynamics (**10**). Finding in mice that 1) an *E. coli* strain initially divided significantly faster than its removal by defecation and 2) a great deal of these bacteria are lost via cell death, of which both are ultimately functions of gut physiology and diet, it may be logically deduced that initial, direct exposure of bacteria to species-relevant nutrients moving along the fecal stream likely results in initial population growth and subsequent decline as relevant metabolites are locally consumed (**Figure 3**). The variety of bacterial species in the intestines may therefore act as local, oscillating populations of enzyme sponges that, following the biosensing of nutrients, rapidly scale up local concentrations of sensing-gene-enzyme complexes (relays) and subsequently pump metabolic constraints into their surroundings (the rest of the human organism). One of the most well studied examples of such bacterial metabolites are short chain fatty acids which can both locally and systemically trigger a wide range of biochemical reactions (**11**), while a variety of other molecules biochemically upstream of bacterial metabolites cannot be directly accessed by human-genome-produced enzymes. Therefore, even though over many millennia bacteria have gradually ceded more direct control over micro niches in favor of more protective and inclusive macro niches, they are still capable of various forms of enzymatically 'puppeteering' their mobile eukaryotic transportation complex (typically via downstream products of bacterial enzymatic reactions).

Ultimately, the human “super-organism” appears to be at least partially resultant of bacteria biochemically tethering themselves to niches and then creating and tethering new niches together via gradually ‘sowing’ the dispersed and rearranged molecules of biochemical reactions over and through increasingly lengthy and recycled, DNA-centered reaction-relays. Such bacterial niches are therefore products of increasingly entangled metabolic pathways or ‘canals’ among individual and multiple bacteria that place an increasing degree of spatial and chemical/energetic constraints on environmental molecules that diffuse to within a certain range of said niche system. Eventually, instead of small populations of ‘roaming enzyme bags’ hunting substrate ‘prey’ (small, environmentally-exposed bacterial populations), this niche system evolved into a mobile transportation complex for acquiring a wide range of enzyme substrates/metabolites that can prey on and dissolve other mobile transportation complexes. Mostly intriguingly, following billions of years of chemically sowing reactions together perpendicular to streams of directionally channeled concentrations of enzyme substrates (Schrödinger’s “stream of order”), the ‘crop’ that has grown around the ancient tube or worm- like intestinal home of bacteria has reached a degree of chemical complexity which far exceeds the chemotaxing and mechanochemical sensory threshold ranges of a single bacterium. In other words, a population of lifeforms has created a home so comfortable and yet complex that it is utterly unaware of the propagating waves of ion/cation oscillations sitting atop of the transportation complex which self assemble into a series of electrochemical perturbations that spatiotemporally map, inventory and recall environmental energetic transformations to the extent of being able to manipulate them (bacteria included) — e.g., the human brain having developed antibiotics.


Number of Bacteria

Time


Number of Bacteria,
Concentration of specialized
digestive enzymes
Concentration of reaction products
for eukaryotic metabolism
Time

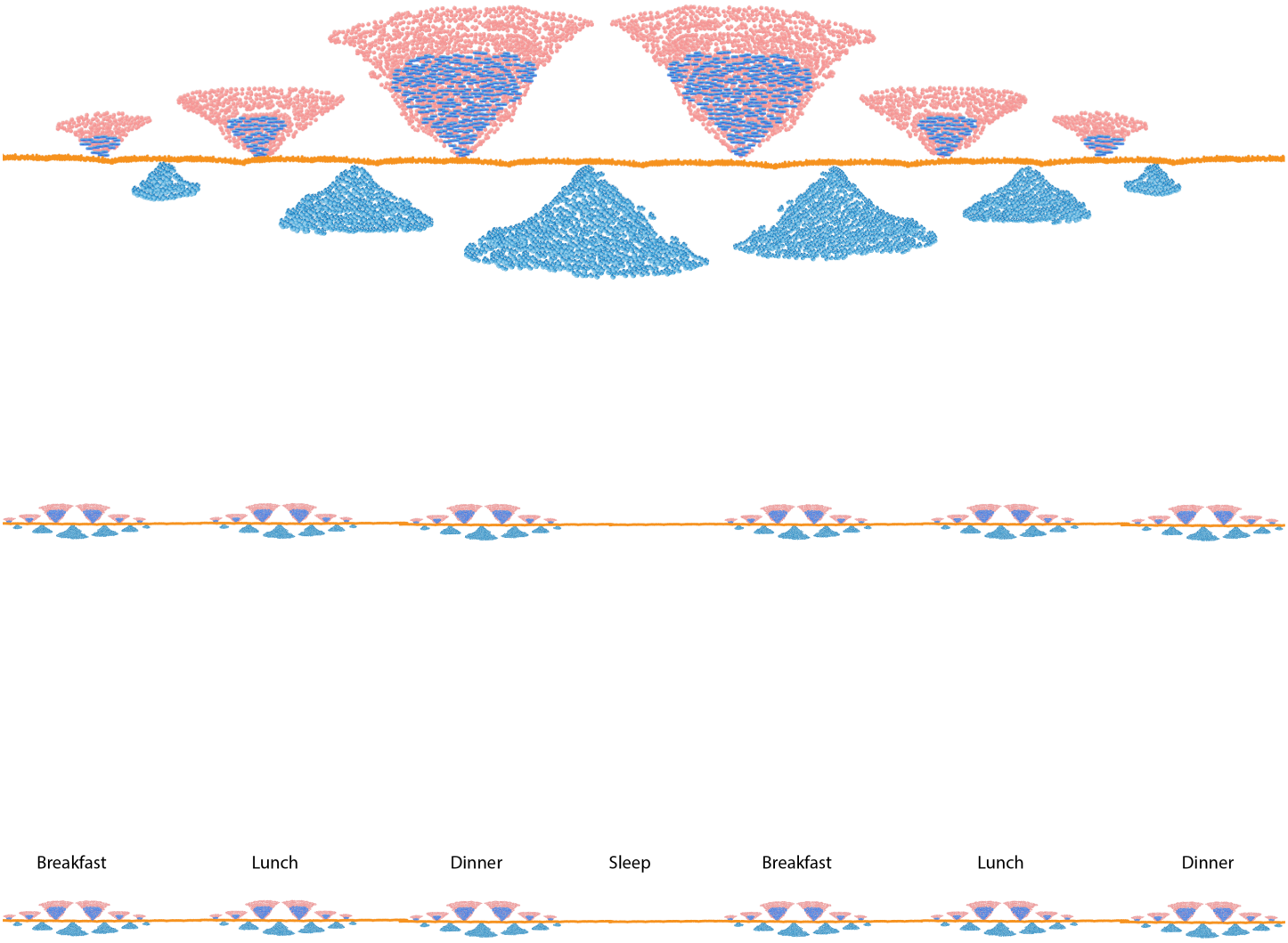


Figure 3: Daily Nutrient (Substrate) Fluxes May Result in Altered, Oscillating Bacterial Populations and Respective Enzyme/Substrate Concentrations.

The first portion of the figure (top) displays a growing population of bacteria in dark blue, abstracted as being on the apical surface/side of the intestinal epithelium. The middle figure incorporates the resultant increase in metabolically-involved enzyme concentrations (red) rising alongside a growing population of bacteria upon contact with a large concentration of nutrients (and thus enzyme substrates). On the opposite side of the intestinal epithelium, the products of said metabolic pathways in light blue can diffuse into and through human cells. The bottom figures abstract these fluxes of bacteria, enzymes and metabolites/metabolic constraints (pumped into the human organism), over time and spiked by direct, periodic contact with nutrients channeled through the intestines (the stream of order).

Citations

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