uncertainty increases via a darkening virtual environment and observe these dopamine bumps.

While this theory elegantly accounts for the ramping puzzles, other dopamine puzzles remain. For example, dopamine's encoding of state prediction errors[10,11], dopamine responding to motor actions not yet paired with reward[12], or its role in reverse conditioning[13]. Trying to understand the brain is like continually entering into a deep dark forest where 2 + 2 = 5 and it is not clear which path is the way out. It seems, for now, that if you stick to the reward prediction error path, you'll make it out unscathed.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Microbial communities: The metabolic rate is the trait

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Making sense of the metabolism of microbial communities is a daunting task. Using denitrification as a model metabolism, a new paper shows that the rate of denitrification can often be predicted from genome contents, and dynamical models can be composed to predict denitrification rates of communities of two to five species.

There are rather a lot of microbes. Very many individuals (upwards of 10^{30} globally[1]) and also many species. A recent census estimated $\sim 10^6$ total bacterial and archaeal species, though the exact number depends on how one defines 'species' for asexual organisms[2]. Likewise, natural environments contain a mixed-multitude: a gram of soil might contain 10^7–10^9 individual bacteria[3] representing thousands of taxa[4]. When we inspect natural environments ranging from soils and lakes to animal guts, we find impressive variation between the species found in similar habitats. Consider a human example: our guts hold thousands of species, with only limited correlation between the species in individuals' microbiomes[5]. Is there any order to be found in this chaos?

Recent research has repeatedly highlighted a simple organizing principle for understanding the bewildering species diversity observed in similar habitats. Crudely rendered: the species don't matter, but their metabolism does[6–9]. Environments provide certain resources (for example, plant detritus supplies organic carbon[10]) and lack others (such as the animal gut, which harbors low O_2 concentrations[11]). If sugars and oxygen are available, for example, the environment can support many different sugar-respiring microbes. Further, the observed species composition will be determined by a succession whereby early arrivals degrade the resources available (such as polysaccharides; Figure 1A) and leave behind incompletely

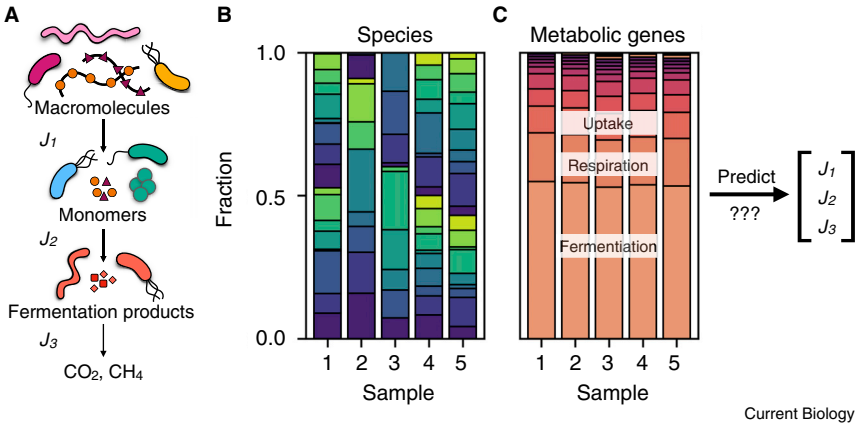

Figure 1. A metabolism-first view of microbial communities.
(A) In any environment, certain resources are renewed by natural processes. Plant detritus, for example, contains macromolecules like proteins and polysaccharides. Various microbes are capable of degrading these polymers to extract energy and make biomass (diagrammed as a pink spirochaete and purple and yellow bacilli). This liberates monomers, creating a niche for specialists that typically partially oxidize ('ferment') monomers to organic acids, creating yet another niche. (B) Because many different microbes are capable of filling each of these niches, similar environments (such as animal guts) or replicate experiments usually vary substantially in species composition. (C) The metabolic gene contents of those same replicates are much more reproducible, suggesting that one might be able to predict the metabolic fluxes (J_1, J_2, J_3 in A) from the gene content of an environment.

metabolized products (like sugars) whose chemical identity determines which other species can join the fray[12,13].

Moreover, species can have overlapping metabolic capabilities, so many distinct stable ecologies can exist[8–10,13] (Figure 1A,B). Indeed, the metabolic gene content of an ecosystem has repeatedly been found to be much more stable than its species composition[6,7,10] (Figure 1B,C). Put another way: there are many more microbial species than metabolic capabilities, so there are many ways of 'packing' species into a stable community that metabolizes available resources[9,13].

The composition of microbial communities is tightly constrained by the availability of nutritional resources. Further, species provide information about community metabolism through their genomes, which express the genes necessary to conserve energy and produce biomass using the resources available. It stands to reason, therefore, that we might be able to predict metabolic rates from the chemistry and gene content of a natural environment (Figure 1C). To do so, we must accept that metabolic rates are the primary trait of interest in microbial communities and measure them quantitatively. In addition to rigorously testing our understanding of metabolism, predictions of metabolic turnover would also be quite useful as many important biogeochemical processes, including the carbon, nitrogen, and sulfur cycles, are substantially catalyzed by microbes[14]. These cycles are perturbed by human activity (for example, CO_2 emissions, fertilizer application) and by global change, so there is pressing interest in predicting the metabolic rates of microbial communities in the wild.

If this optimistic hypothesis — that metabolic rates can be predicted from gene content — is to be true for natural environments like soils, then it must also be true in the lab. A new paper by Karna Gowda, Derek Ping, Madhav Mani, and Seppe Kuehn[15] breaks ground on this proposition in the context of bacterial denitrification. Denitrification is an anaerobic respiration where the oxidation of organic carbon (such as glucose) is coupled to the sequential reduction of nitrate (NO_3^-) to nitrite (NO_2^-), NO, N_2O, and finally N_2 gas (Figure 2A). Here, NO_3^- acts as the terminal electron acceptor, the role O_2 plays in aerobic respiration. As NO_3^- is an excellent electron acceptor ($2\,NO_3^- \leftrightharpoons N_2 + 6\,H_2O$, $E'^\circ \approx +700$ mV), microbes typically prefer it over most alternatives other than dioxygen ($O_2 \leftrightharpoons 2\,H_2O$, $E'^\circ \approx +800$ mV)[16,17]. By isolating and culturing ~80 diverse bacterial denitrifiers (Figure 2A), Gowda *et al.*[15] show that a simple model of denitrification kinetics fits the measured dynamics of NO_3^- and NO_2^- turnover for most isolates. Moreover, the parameters of these models can be predicted from the denitrification genes in each isolate's genome and, in most cases, per-strain models can be composed to predict the denitrification rates of communities comprised of two to five strains.

Some bacteria are capable of complete denitrification, yet others only perform parts of the pathway. Gowda *et al.*[15] isolated bacterial denitrifiers from soil and documented their phenotypes as NO_3^- reducers (Nar, 24 strains), NO_2^- reducers (Nir, 4 strains), and full denitrifiers (Nar/Nir, 52 strains) by incubating each isolate with NO_3^- or NO_2^- and measuring nitrogen oxide concentrations over time. The authors found that nearly every isolate performed all the metabolic activities expected based on its genome, highlighting the profound contribution of the decades of controlled genetic and biochemical experimentation that established the foundational understanding of denitrification upon which this new work is based[16].

Having measured NO_3^- and NO_2^- concentrations over time, Gowda *et al.*[15] proceed to ask if a simple 'consumer resource model' can reproduce the metabolite dynamics measured in pure culture (Figure 2C,D). In their model, each strain is characterized by four parameters: two describing the per-cell rates of NO_3^- and NO_2^- reduction (r_A and r_I, mM/cell/hr units) and two describing the yield of new cells (γ_A and γ_I, cells/mM units). This simplified model accurately reproduces metabolite dynamics and final cell densities for ~80% of isolates across a wide range of culture conditions.

Now you might ask: do all the Nar strains give similar model parameters? What about Nar/Nir and Nir strains? Fit values for r_A, r_I, γ_A, and γ_I vary over ~2 fold, even within these phenotypic designations. What might explain such variation? Multiple distinct enzymes catalyze key steps of denitrification, for example the periplasmic (Nap) and membrane-bound nitrate reductases (Nar) or the copper (NirK) and cytochrome-based (NirS) nitrite reductases[16]. By predicting r_A, r_I, γ_A, and γ_I from the subset of denitrification genes in each genome, Gowda *et al.*[15]

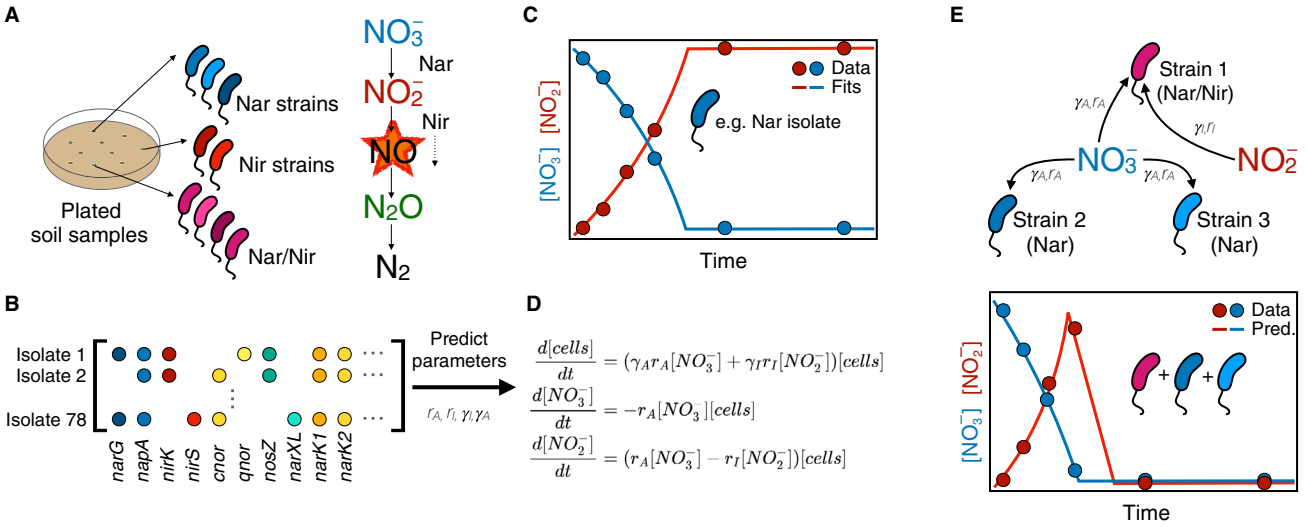

Figure 2. A stepwise approach to 'domesticating' denitrifying microbial communities.
(A) Gowda *et al.* isolated 78 strains and phenotypically characterized them as reducing NO_3^- (Nar strains), NO_2^- (Nir strains) or both (Nar/Nir). As the subsequent pathway intermediates — the toxic NO, the greenhouse gas N_2O, and N_2 — were not measured, Nir and Nar/Nir strains may or may not be able to oxidize NO to N_2. (B) These strains were then sequenced and annotated, verifying that genotypes match phenotypes. (C) Gowda *et al.* then measured the concentrations of NO_3^- and NO_2^- over time in monocultures, demonstrating that the rates of metabolic conversion could be fit to a simple linear differential equation model described in (D). They further show that the four parameters of this single strain denitrification model — r_A, r_I, γ_A, and γ_I — can be predicted with high fidelity from the complement of denitrification genes found in isolate genomes. (E) Consumer resource models assume individual strains interact only by competing for shared metabolic resources, here NO_3^- and NO_2^-. Gowda *et al.* found that such an additive model of communal rates is accurate in most cases.

show that genome contents can accurately predict the dynamics of nitrogen oxide turnover in pure culture. Satisfyingly, their regressions also give interpretable results, with genes related to NO_3^- metabolism being the strongest contributors to r_A and γ_A prediction, and genes of NO_2^- metabolism likewise driving accurate prediction of r_I and γ_I.

Species are rarely found in isolation, so Gowda *et al.*[15] proceeded to investigate whether their consumer resource model can explain metabolite dynamics in co-cultures. To do this, they assumed each strain contributes additively to the rate and yield of NO_3^- and NO_2^- reduction (Figure 2E). This is equivalent to presuming that strains interact only by competing for shared metabolic resources like NO_3^- and NO_2^- [9,13]. However, microbes can interact in many other ways, for example, by secreting antibiotics, altering the pH, or by altering gene expression to adapt their metabolism. We might have expected these unmodeled factors to have cooked their goose. Yet Gowda *et al.*[15] found very strong agreement between their zero-free-parameter predictions and co-culture measurements in nearly all cases.

Nearly all cases, but not all cases. Whenever Nar and Nir strains were cultured together in NO_3^- media, the consumer resource models yielded worse predictions. This observation suggested that Nar+Nir pairs interact in a manner other than resource competition, likely via the toxicity of NO produced by Nir strains. Consistent with this hypothesis, Nar strains were less abundant than predicted in such cultures, and the most-inhibited strain lacked an NO reductase gene. Gowda *et al.*[15] describe a clever 'fix' where they treated Nar+Nir pairs as a single species, which enabled them to use data from pairs to improve predictions of metabolism in communities composed of three to five species.

There is much to learn from the successes of this paper. For example, that Nir strains are apparently rare (4/78 isolates), that genomes can predict metabolite turnover in monoculture, and that the majority of interactions between isolates are quantitatively consistent with resource competition. We note that the quantitative measurement of metabolic rates enabled many of these surprising discoveries, which highlights that rates are the trait of interest when studying metabolism. One hallmark of impactful work is that there is also much to learn from its shortcomings. Microbes commonly secrete toxic molecules, and their toxicity often depends on the chemical environment: for example, pH determines the toxicity of NO[16,18], and O_2 concentration affects the toxicities of NO as well as many antibiotics[16,19]. Further, the chemical environment can vary greatly over short distances — for example, microbes can consume O_2 faster than it diffuses[20]. The challenge of modeling NO toxicity using consumer resource models — a challenge that was only apparent because Gowda *et al.*[15] quantified metabolic rates — suggests that new approaches will be needed to rationalize metabolic turnover in more realistic contexts like soils, guts and water columns, where there is substantial spatiotemporal variation in the chemical microenvironment.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Insect flight: Flies use a throttle to steer

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A new study of flight control in *Drosophila* using neurogenetic methods and a virtual reality flight arena has revealed a group of descending neurons that fully activate the flight motor and steer the fly by independent regulation of the left and right wings.

Animals of all shapes and sizes must maintain stability to move through their environment, but problems of stability and control are particularly salient for small insects. This stems from their small body size and resulting susceptibility to environmental perturbation, as well as the aerodynamics of flapping wings, which produce large torques from small asymmetries in morphology or flapping kinematics. Despite these challenges, fruit flies and other insects maintain flight for hours at a time during dispersal and exhibit remarkable capabilities for recovering from mid-air perturbations[1], aerial tumbles produced in rapid takeoff[2], and even loss of large portions of one wing[3,4]. Although various passive stability mechanisms mediated by aerodynamics and biomechanics do exist[1,5,6], sensory responses are also ubiquitous[7–9], but these are less well understood. In a paper in this issue of *Current Biology*, Namiki, Ros *et al.*[10] report a neurogenetic study that has revealed a group of descending neurons that independently regulates left and right wing flapping amplitude and overall flight motor output in fruit flies (Figure 1). Their findings challenge prior thinking on flight control in flies which supposed steering and motor output were functionally separate, much as steering and acceleration are physically and conceptually separate controls in automobile driving. Their results have implications for many other aspects of flight control in insects and control of movement in general.