HOST–MICROBE INTERACTION

Rules of the game for microbiota

Are the dynamics of our microbial communities unique to us or does everyone's microbiota follow the same rules? The emerging insights into this question could be of relevance to health and disease. SEE LETTER P.259

KAROLINE FAUST & JEROEN RAES

The composition of a body part's microbial community can differ substantially from one person to the next[1–5]. This is due to both host pressures and the dynamic behaviour of the microbes themselves. Understanding whether these interactions are consistent across hosts or whether each individual's microbiota follows its own rules has big implications. If the dynamics of an organ's microbial community are universal, we can use them to predict effective interventions for modulating the microbiota. If, however, microbial dynamics are host-specific, interventions must be designed separately for each person. Bashan *et al.*[6] address this issue using a new approach and report their intriguing observations on page 259.

To find out whether community dynamics are universal, ideally we should study long and densely sampled time series from many individuals with different traits and backgrounds. Models of microbial communities should then be fitted to the varying proportions of microbial species, which may become challenging when going beyond the most dominant groups of species. Such large temporal data sets are currently gravely lacking.

Bashan and colleagues devised an indirect method to address the question of universality. They measured two independent aspects of community similarity: overlap, which compares species assemblies by quantifying the proportion of shared species; and dissimilarity, which assesses the difference in abundance profiles of the shared species between individuals. The dissimilarity is then plotted against the overlap for all sample pairs to create a dissimilarity–overlap curve (DOC). If microbiota dynamics are truly universal (host-independent), then having the same species present should lead to the same relative proportion of those species, because they would dynamically influence each other in the same way. Consequently, a larger proportion of shared species should increase the community similarity and result in the tell-tale negative slope of the DOC (Fig. 1).

The authors tested their method by simulating microbial communities computationally using what is known as the generalized Lotka–Volterra model[7], to generate communities with the same and with different
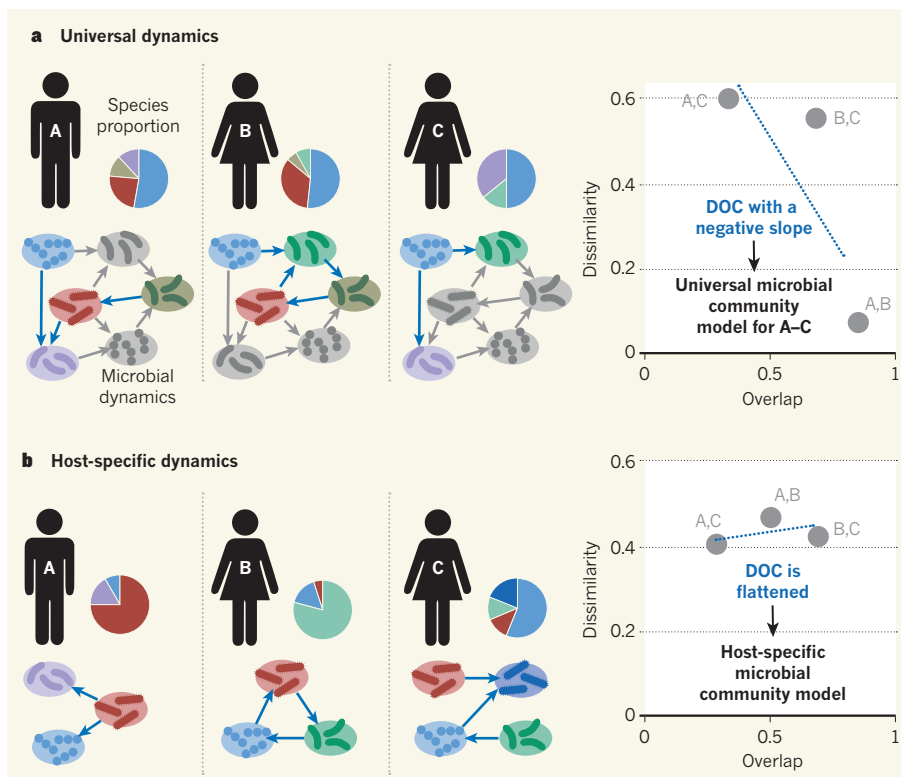

Figure 1 | Learning from similarities and differences in our microbes. To test whether microbial communities within a specific body part have the same underlying dynamics across individuals, Bashan *et al.*[6] used a method known as the dissimilarity–overlap curve (DOC). **a**, If microbial community dynamics are universal between individuals (A–C), the presence of the same species (species represented by coloured nodes; grey nodes represent absent species) should also lead to similar species proportions and a negative DOC slope. Consequently, a single model can be used to predict microbiota behaviour. **b**, If the community dynamics are host-specific, the presence of the same species does not lead to similar proportions and the DOC is flat. This necessitates the development of personalized models.

dynamics as positive and negative controls. In addition, they showed that randomizing data by shuffling microbial species across samples also removes the negative slope. These simulations confirm that the DOC detects universal dynamics and flattens in the absence of such dynamics. The curve even identifies strongly interacting species.

Most notably, the team detected negative slopes for the oral and gut communities in several human-microbiome data sets, including those of the Human Microbiome Project[3] and two human-gut time series[8,9]. However, the skin microbiota displayed weakly negative or flat DOCs in some cases, suggesting that

the microbial dynamics in the skin are host-specific at certain sites. Another interesting finding was that the DOC for the gut microbiota of people recurrently infected with the bacterial pathogen *Clostridium difficile*[10] is flat, but gains a negative slope after faecal transplantation from people who have not been infected.

If the assumptions hold, the consistent negative slopes observed for the healthy cohorts and for people treated after infection with *C. difficile* point to universal gut microbial dynamics. This is good news for all modelling efforts aiming to predict the behaviour of the gut microbiota during interventions or in disease. It means that when parameters such as growth rates and

interactions are determined for the gut microbial community of one healthy human, they are also valid for those of other individuals. Thus, the knowledge of such parameters can be combined across different studies and could, in the long term, allow a detailed, common microbial community model to be developed.

The DOC method has all the hallmarks of a powerful analytical tool. It is easy to implement, addresses a crucial question and may inspire applications beyond its intended use.

But, like all analyses, it makes a couple of assumptions — that the microbiota are in a steady state, and that having the same steady state implies that microbiota are governed by the same dynamics. The second assumption is the more risky: microbiota may end up in similar steady states not because of their intrinsic dynamics, but because of a strong environmental pressure that selects for a particular set of species. The authors rule out obvious host parameters such as diet, weight, age, race and transit time through the gut (measured by stool consistency) that may shape gut microbial communities. However, they do not account for all factors that may conceivably influence the gut microbiota[2], and so cannot provide an entirely conclusive answer regarding the universality of the gut's microbial community dynamics.

The value of this work lies primarily in the importance of the question asked, the originality of the approach and the fact that it could spur a whole range of microbiome research. We expect it to spark fruitful discussions and lead to fresh ideas for analyses and experiments. For instance, it might be plausible to set up an artificial community under controlled conditions within a chemostat and then develop and define a model that describes its dynamics reasonably well. One could then compare the steady states reached by different subsets of the community to directly test the second assumption. If universal dynamics are confirmed, modelling efforts have a better chance of leading to more-effective clinical interventions. Bashan and colleagues' paper gives a glimpse of the deeper insights to be gained once we overcome the hurdles of controlled, high-throughput microbial community cultivation and manipulation. ∎

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GEOCHEMISTRY

Hydrogen and oxygen in the deep Earth

The finding that an unusual iron oxide forms at extremely high pressures suggests that hydrogen and oxygen — two elements that strongly influence Earth's evolution — are generated in the mantle. SEE LETTER P.241

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Hydrogen greatly affects the properties of many materials. It is thought that most of the hydrogen in modern Earth is in water molecules, many of which are found in water-bearing minerals. It is therefore crucial to understand the stability and circulation of such hydrous minerals in Earth's interior, and this need has led to numerous studies of hydrous minerals under high-pressure and high-temperature conditions. In this issue, Hu *et al.*[1] (page 241) cast fresh light on the hydrogen-circulation issue. They report that an oxygen-rich iron oxide, FeO_2, is stabilized at pressures greater than about 76 gigapascals, and that this material might enable previously unknown hydrogen and oxygen cycles to occur in Earth's mantle.

Earth's core is mainly made of metallic iron, whereas the major minerals in the upper mantle contain mostly ferrous iron (Fe^{2+}). The most abundant form of iron on Earth's surface is haematite (Fe_2O_3), which contains ferric iron (Fe^{3+}) and is the main constituent of iron ore. Most of this ferric iron is thought to have formed by the oxidation of ferrous or metallic iron by the modern, oxygen-rich atmosphere.

On the basis of the distribution of ferric, ferrous and metallic iron from the surface to the core, it is thought that Earth's redox state becomes increasingly reducing with depth, so that the amount of ferric iron in the lower mantle would be limited. High-pressure laboratory experiments[2,3] revealed that, when olivine, $(Mg,Fe^{2+})_2SiO_4$ (the most abundant mineral in the upper mantle) is subjected to conditions corresponding to those of the lower mantle, it changes into a mixture of two other minerals, bridgmanite, $(Mg,Fe^{2+})SiO_3$, and ferropericlase, $(Mg,Fe^{2+})O$. However, aluminium ions are also found in the mantle. When these are added,
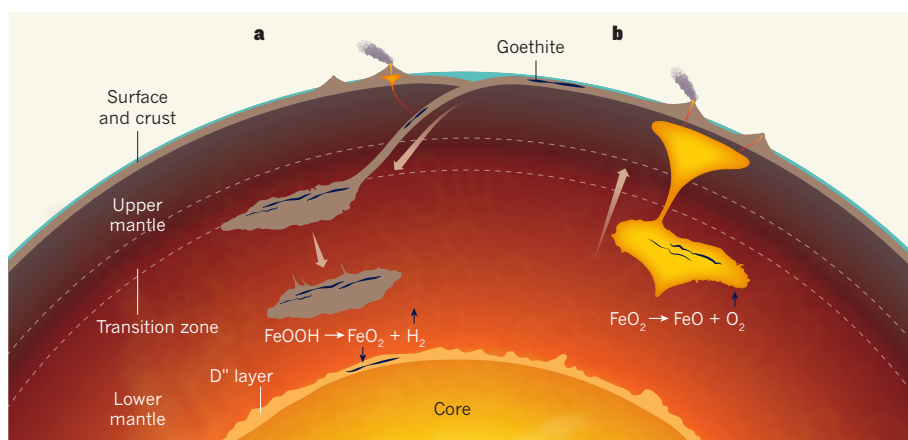

Figure 1 | Proposed source of hydrogen and oxygen in the lower mantle. a, Descending slabs of Earth's crust can be carried to the transition zone between the upper and lower mantle, where they are heated until dense minerals form. The dense material then sinks to the bottom of the lower mantle. Hu *et al.*[1] suggest that when the mineral goethite (FeOOH, commonly formed by the reaction of the mineral haematite and water on Earth's surface) is carried to the mantle by a slab, an oxygen-rich iron oxide (FeO_2) and hydrogen would form at depths greater than 1,800 kilometres. The dense FeO_2 would sink to the bottom of the lower mantle, and might help to explain the structural complexity of the D″ layer, which lies close to the core–mantle boundary. The highly mobile hydrogen would spread upwards. **b**, If the FeO_2-containing material is lifted by motion in the lower mantle, it will break down and release oxygen at depths of less than 1,500 km. (Adapted from a graphic by Jun Tsuchiya.)