Delannoy-Bruno *et al*. demonstrate that dietary responses might be mainly determined by the levels of relatively sparse microbiome genes (that become predominant after a dietary intervention), stressing the importance of studying diet–microbiome interactions at the level of genes. Different microbial communities in individuals contributed to these distinct functional capacities, highlighting the possibility that microbiome function (genes), rather than species composition, might correlate with personalized human physiological responses to food.

In some situations, the metabolic and immune-system characteristics of germ-free mice harbouring human microbiomes might affect the validity of using these animals as human surrogates in an experimental context[14,15]. Nevertheless, the fibre-degrading properties of the mice analysed by Delannoy-Bruno *et al*. were strikingly similar to those of humans. This suggests that human microbiome colonization in germ-free mice might be a relevant tool for studying the causal drivers of diet–microbiome interactions and their effect on the mammalian host.

Such studies would greatly benefit from the development of computational-analysis tools that can identify temporal trajectories of microbial genes in response to dietary interventions, in both human donors and mice who receive microbial transplants. In this study, the authors used one such tool, higher-order singular value decomposition, which uncovered a profound microbiome gene response to dietary-fibre supplementation despite the modest sample size. Further refinement of such analytical pipelines, by the expansion of microbiome genome-level databases of gene functions and the incorporation of protein-level features, will probably aid further decoding of the contributions of the dietary–microbiome axis to host physiology.

Delannoy-Bruno and colleagues' findings provide valuable mechanistic insights into the microbial contributions to human dietary responses. This will probably lead to long-term, randomized clinical trials that assess causal links between distinct food ingredients, microbiome modulation and downstream health-related outcomes for humans. Indeed, this research team recently reported[2] that a data-driven dietary intervention targeting the microbiome helped to promote growth in undernourished children. The advances made by Delannoy-Bruno *et al*. bring us closer to the integration of precise microbiome engineering with evidence-based dietary sciences.

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1. Delannoy-Bruno, O. *et al*. *Nature* **595**, 91–95 (2021).
2. Chen, R. Y. *et al*. *N. Engl. J. Med.* **384**, 1517–1528 (2021).
3. Chen, R. Y. *et al*. *N. Engl. J. Med.* **383**, 321–333 (2020).
4. Mostafa, I. *et al*. *BMC Public Health* **20**, 242 (2020).
5. Patnode, M. L. *et al*. *Cell* **179**, 59–73 (2019).
6. Gehrig, J. L. *et al*. *Science* **365**, 139 (2019).
7. Zeevi, D. *et al*. *Cell* **163**, 1079–1094 (2015).
8. Berry, S. E. *et al*. *Nature Med.* **26**, 964–973 (2020).
9. US Department of Health and Human Services and US Department of Agriculture. *2015–2020 Dietary Guidelines for Americans* (HHS/USDA, 2015).
10. Sonnenburg, E. D. *et al*. *Nature* **529**, 212–215 (2016).
11. Eilam, O. *et al*. *mBio* **5**, e01526-14 (2014).
12. Healey, G. *et al*. *Br. J. Nutr.* **119**, 176–189 (2018).
13. Deehan, E. C. *et al*. *Cell Host Microbe* **27**, 389–404 (2020).
14. Al-Asmakh, M. & Zadjali, F. *J. Microbiol. Biotechnol.* **25**, 1583–1588 (2015).
15. Lundberg, R., Toft, M. F., August, B., Hansen, A. K. & Hansen, C. H. F. *Gut Microbes* **7**, 68–74 (2016).

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Ecology

Migratory birds distribute seeds to new climates

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Birds that travel long distances can disperse seeds far and wide. An assessment of the timing and direction of European bird migration reveals how these patterns might affect seed dispersal as the planet warms. **See p.75**

The rapid pace of global warming and its effects on habitats raise the question of whether species are able to keep up so that they remain in suitable living conditions. Some animals can move fast to adjust to a swiftly changing climate. Plants, being less mobile, rely on means such as seed dispersal by animals, wind or water to move to new areas, but this redistribution typically occurs within one kilometre of the original plant[1]. On page 75, González-Varo *et al*.[2] shed light on the potential capacity of migratory birds to aid seed dispersal.

When the climate in a plant's usual range becomes hotter than it can tolerate, it must colonize new, cooler areas that might lie many kilometres away. It is not fully clear how plants distribute their seeds across great distances, let alone how they cross geographical barriers. One explanation for long-distance seed dispersal is through transport by migratory birds. Such birds ingest viable seeds when eating fruit (Fig. 1) and can move them tens or hundreds of kilometres outside the range of a plant species[3]. In this mode of dispersal, the seeds pass through the bird's digestive tract unharmed[4,5] and are deposited in faeces, which provides fertilizer that aids plant growth. In the case of European migratory birds, for example, the direction of seed dispersal will depend on whether the timing of fruit production coincides with a bird's southward trip to warmer regions around the Equator, or northward to cooler regions. Many aspects of this process have been a mystery until now.

González-Varo and colleagues report how plants might be able to keep pace with rapid climate change through the help of migrating birds. The authors analysed the fruiting times of plants, patterns of bird migration and the interactions between fruit-eating birds and fleshy-fruited plants across Europe. Plants with fleshy fruits were chosen for this study because most of their seed transport is by migratory birds[6], and because fleshy-fruited plants are an important component of the woody-plant community in Europe. The common approach until now has been to predict plant dispersal and colonization using models fitted to abiotic factors, such as the current climate. González-Varo *et al*. instead analysed an impressive data set of 949 different seed-dispersal interactions between bird and plant communities, together with data on entire fruiting times and migratory patterns of birds across Europe. The researchers also analysed DNA traces from bird faeces to identify the plants and birds responsible for seed dispersal.

The authors hypothesized that the direction of seed migration depends on how the plants interact with migratory birds, the frequency of these interactions or the number of bird species that might transport seeds from each plant species. González-Varo and colleagues found that 86% of plant species studied might have seeds dispersed by birds during their southward trip towards drier and hotter equatorial regions in autumn, whereas only about one-third of the plant species might be dispersed by birds migrating north in spring. This dispersal trend was more pronounced in

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GETTY

Figure 1 | A young blackcap bird (*Sylvia atricapilla*) eating elderberries.

temperate plants than in the Mediterranean plant communities examined. These results are in general agreement with well-known patterns of fruiting times and bird migrations. For example, the fruit of most fleshy-fruited plants in Europe ripens at a time that coincides with when birds migrate south towards the Equator[7].

Perhaps the most striking feature of these inferred seed movements is the observation that 35% of plant species across European communities, which are closely related on the evolutionary tree (phylogenetically related), might benefit from long-distance dispersal by the northward journey of migratory birds. This particular subset of plants tends to fruit over a long period of time, or has fruits that persist over the winter. This means that the ability of plants to keep up with climate change could be shaped by their evolutionary history — implying that future plant communities in the Northern Hemisphere will probably come from plant species that are phylogenetically closely related and that have migrated from the south. Or, to put it another way, the overwhelming majority of plant species that are dispersed south towards drier and hotter regions at the Equator will probably be less able to keep pace with rapid climate change in their new locations than will the few 'winners' that are instead dispersed north to cooler climates. This has implications for understanding how plants will respond to climate change, and for assessing ecosystem functions and community assembly at higher levels of the food chain. However, for seeds of a given plant species, more evidence is needed to assess whether passing through the guts of birds affects germination success.

To determine which birds might be responsible for the plant redistributions to cooler climates in the north, the authors categorized European bird migrants into Palaearctic (those that fly to southern Europe and northern Africa during their non-breeding season) and Afro-Palaearctic (those that winter in sub-Saharan Africa). Only a few common Palaearctic migrants, such as the blackcap (*Sylvia atricapilla*; Fig. 1) or blackbird (*Turdus merula*), provide most of this crucial dispersal service northwards to cooler regions across Europe. Because migratory birds are able to relocate a small, non-random subset of plants, this could well have a strong influence on the types of plant community that will form under climate-change conditions.

A major problem, however, is that the role of these birds in dispersing seeds over long distances is already at risk from human pressures and environmental changes[8]. Understanding these large-scale seed-dispersal interactions offers a way for targeted conservation actions to protect the areas that are most vulnerable to climate change. This could include boosting protection efforts in and around the wintering grounds of migratory birds — locations that are already experiencing a rise in human pressures, such as illegal bird hunting.

González-Varo and colleagues' focus on seed dispersal across a Northern Hemisphere region means that, as with most ecological analyses, the results are dependent on scale, which can cause issues when interpreting data[9]. Because the Northern Hemisphere has more land area and steeper seasonal temperature gradients than the Southern Hemisphere does, seed-dispersal interactions might have different patterns from those occurring in the Southern Hemisphere or in aquatic systems.

For example, seed-eating birds from the genus *Quelea* migrate from the Southern Hemisphere to spend the dry season in equatorial West Africa, then move southwards again when the rains arrive. Their arrival in southern

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Africa usually coincides with the end of the wet season in this region, when annual grass seeds are in abundance. It will be worth investigating whether migratory birds in the Southern Hemisphere also influence the redistribution of plant communities during global warming. Likewise, exploring the long-distance dispersal of seeds of aquatic plants, such as seagrasses[10] by water birds, is another area for future research that might benefit from González-Varo and colleagues' methods.

This study provides a great example of how migratory birds might assist plant redistribution to new locations that would normally be difficult for them to reach on their own, and which might offer a suitable climate. As the planet warms, understanding how such biological mechanisms reorganize plant communities complements the information available from climate-projection models, which offer predictions of future species distributions.

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1. Jordano, P., García, C., Godoy, J. A. & García-Castaño, J. L. *Proc. Natl Acad. Sci. USA* **104**, 3278–3282 (2007).
2. González-Varo, J. P. *et al. Nature* **595**, 75–79 (2021).
3. Viana, D. S., Santamaría, L. & Figuerola, J. *Trends Ecol. Evol.* **31**, 763–775 (2016).
4. Lehouck, V., Spanhove, T. & Lens, L. *Plant Ecol. Evol.* **144**, 96–100 (2011).
5. Shikang, S., Fuqin, W. & Yuehua, W. *Sci. Rep.* **5**, 11615 (2015).
6. Jordano, P. in *Seeds: The Ecology of Regeneration in Plant Communities 3rd edn* (ed. Gallagher, R. S.) 18–61 (CAB Int., 2014).
7. Dingle, H. *Migration: The Biology of Life on the Move* (Oxford Univ. Press, 2014).
8. Bairlein, F. *Science* **354**, 547–548 (2016).
9. Daru, B. H., Farooq, H., Antonelli, A. & Faurby, S. *Nature Commun.* **11**, 2115 (2020).
10. Rock, B. M. & Daru B. H. *Front. Mar. Sci.* **8**, 608867 (2021).

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Chromosome biology

Base-pair view of gene and enhancer interactions

Anne van Schoonhoven & Ralph Stadhouders

A technique reveals how folded chromosomal DNA interacts in the nucleus, providing information at the level of single base pairs. The achievement offers an unprecedented level of detail about how gene activity is regulated. **See p.125**

How can 2 metres of DNA fit into a nucleus that has an average diameter of only 10 micrometres? Almost all the cells in our body face this storage conundrum, which has intrigued scientists for decades. Moreover, this compaction tour de force folds DNA in the nucleus in a way that is far from random. The pattern of DNA folding is important for many processes that involve our genome, including the regulation of expression of our approximately 20,000 genes. On page 125, Hua *et al.*[1] describe a method they have developed to monitor 3D genome architecture. This information can pinpoint genomic interactions at the level of single base pairs of DNA. It suggests new ways of thinking about how gene expression is controlled, and opens up exciting possibilities for future research.

Humans and other organisms have evolved complex mechanisms to precisely regulate gene expression. Different types of cell express different sets of genes, and these expression patterns might depend on a cell's function, or arise in response to environmental cues, such as viral infection. Central to the control of gene expression are short regulatory sequences of DNA, termed enhancers, which are highly abundant in our genomes. According to current estimates[2], there are up to 810,000 enhancers across the human genome.

Enhancers are bound by the 'bookkeepers' of gene expression: DNA-binding proteins called transcription factors, which bind to short motifs of DNA sequences corresponding to 6–12 base pairs[3]. Enhancers can be located far from the gene(s) that they regulate, and how they stimulate gene expression is a major topic of research[4]. The current leading model is that enhancers and genes are brought into closer spatial proximity by specific patterns of DNA folding, enabling transcription factors to stimulate gene expression despite large intervening genomic distances between an enhancer and a particular gene[5–7].

> **"This level of detail will enable high-resolution dissection of processes involving gene regulation."**

Study of the 3D organization of genomes has been revolutionized by an approach called chromosome conformation capture (3C), which enables researchers to infer the frequencies of interactions between different DNA regions[8]. Such approaches indicate that enhancer–gene interactions occur preferentially in 'insulated' genomic neighbourhoods in the nucleus called topologically associating domains (TADs)[9]. Most TADs are formed by the cooperative action of a DNA-binding protein termed CTCF and a ring-shaped protein complex called cohesin, which is a type of molecular motor that drives a process known as loop extrusion[10]. In this process, cohesin engages DNA and extrudes it, in a similar way to how threading yarn through the eye of a needle forms a loop (Fig. 1). This extrusion continues until cohesin encounters DNA bound to CTCF, which forms a 'roadblock' for loop extrusion, stopping it.

TADs are thought to 'trap' genes and enhancers by thwarting DNA interactions across TAD borders, thereby increasing the probability that matching enhancer–gene pairs find each other. However, until now, 3C technology has been unable to define the nature of the physical contacts between genes and enhancers on the base-pair scale – this would be on a par with the precision with which interactions between DNA and the key transcription factors influencing gene expression have been determined. Hua *et al.* now close this resolution gap by developing a version of 3C that the authors call Micro-Capture-C (MCC).

Building on their previously developed version of 3C methodology[11], the authors made key technical refinements that strikingly improved the resolution of the DNA interactions that could be identified. Like all 3C techniques, MCC captures interactions through chemical crosslinking, which generates bonds between interacting regions of DNA. The crosslinked DNA is then cut into smaller fragments, after which the interactions are captured by gluing together (ligating) interacting DNA strands that are close to each other in the nuclear space.

For the pair of molecular 'scissors' that cuts DNA into small fragments, MCC uses the enzyme micrococcal nuclease (MNase), which fragments DNA in a mainly random fashion, independently of DNA sequences. This enables the generation of much smaller DNA fragments than those obtained using sequence-specific enzymes for DNA digestion. The approach helps to increase the resolution – as previously shown for another version of 3C technology[12]. Crucially, Hua and colleagues show that DNA fragmentation by MNase does not have any major biases in terms of the DNA that is digested, with a minor preference for less-condensed DNA (characteristic of regions containing genes being

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