periodic path imprinted into the clay sphere, simply by rolling as a result of gravity. Much like the case of the globe, closing the path of one of these objects is challenging, even when its 'north pole' is returned to its initial position. However, the authors were (almost always) able to circumvent this problem by creating trajectoids that trace out not one, but two periods of a repeating path as they roll once around.

This approach is surprising, and suggests that there should be a precise mathematical statement saying exactly when a two-period trajectoid exists. The authors provide an example curve that doesn't work, but also show that tiny modifications to that curve make it work. They conjecture that paths that don't work are infinitely rare. It therefore seems likely that any designer wanting to use a trajectoid in a real-world application would not run into problems in constructing one. However, future work developing a more precise mathematical understanding of the issue would help to connect this work to applications, as well as to open up more purely mathematical veins of research.

Even in the absence of a rigorous proof, it seems clear that Sobolev and colleagues' algorithm will find applications in robotics. Sphericon-shaped microrobots that follow simple curving trajectories have already been shown to be stable, and able to move on arbitrary surfaces[4,5]. Deformable robots[6,7] could implement trajectoid geometries to navigate complex landscapes and obstacles.

Beyond robotics, this research has promising applications in fields as far-ranging as quantum computing and medical imaging. In physics, many systems are represented by a point on a sphere. For example, the intrinsic angular momentum (or spin) of an electron can point in any direction, so the curved 'tabletop' trajectory of a trajectoid could represent the orientation of a spin as a function of time[8]. In quantum computing, this representation could be used to control the evolution of a quantum bit[9] — the basic unit of quantum information, which can be encoded in spin.

Similar techniques could be used to help mitigate the effects of unwanted signals in magnetic resonance imaging machines. Trajectoids that have been engineered to control the spin dynamics — and therefore the magnetic fields — in these devices could be used to help separate useful signals from noise[10]. Whether or not these applications materialize, Sobolev and colleagues' algorithm offers an insightful answer to the problem of how to encode an object's trajectory using its shape alone.

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The authors declare no competing interests.

Microbiology

Harnessing a gut bacterial team for human health

Yolanda Sanz

Understanding how our gut bacteria combine forces to co-exist and produce beneficial molecules will be crucial for developing next-generation probiotics. Key progress towards achieving this goal has been made. **See p.381**

The microbial communities in the human gut function as a bioreactor that breaks down nutrients (mainly complex indigestible carbohydrates) and liberates bioactive substances to drive microbe–host interactions and shape host health and disease. Bacteria inhabiting the gut also interact to increase their ability to survive as a team. Disentangling this complex, symbiotic relationship should provide opportunities to promote health. On page 381, Khan *et al.*[1] report efforts to harness a beneficial partnership between species of gut bacteria.

The re-establishment of depleted bacterial species is, theoretically, a straightforward approach to rescuing a perturbed gut ecosystem that has been affected by disease, antibiotics or poor diets that endanger health[2,3]. However, this approach brings specific challenges in terms of growing bacteria for transfer to humans, because most gut-dwelling bacteria live in the absence of oxygen (that is, they are strict anaerobes) and, therefore, require special conditions to grow in the aerobic, *in vitro* world. Also, one species might require others to provide the nutrients for their subsistence inside the gut and for optimal effectiveness in the human host.

> **"Researchers need to learn how to better cultivate and preserve bacteria outside the gut."**

To harness the interactions between collaborating bacteria in the human gut, Khan and colleagues co-isolated strains of two bacterial species that interact through a cross-feeding mechanism involving the exchange of nutrients (Fig. 1a). Specifically, the authors isolated an anaerobic bacterial strain of *Desulfovibrio piger*, together with an anaerobic strain of *Faecalibacterium prausnitzii*, one of the first bacterial species (of a type normally resident in the gut and thus called a commensal species) reported to be depleted in people with Crohn's disease and proposed to act as a driver of health[4].

The two species have complementary nutritional requirements that make them indispensable partners. *Faecalibacterium prausnitzii* consumes the molecule glucose to produce lactate that, in turn, is used by *D. piger* to produce acetate, which is ultimately used by *F. prausnitzii* to produce butyrate. The authors found that *D. piger* enhances carbohydrate fermentation, which is the main metabolic pathway used to obtain energy for many commensal gut bacteria, such as *F. prausnitzii*, by consuming end products such as lactate.

By comparing the metabolite molecules produced in co-culture and monoculture of *F. prausnitzii*, the authors found that the presence of *D. piger* promoted butyrate production by *F. prausnitzii*, enhancing its fermentative capacity. This type of metabolic cooperation is similar to the arrangement that exists for other specialized commensal species such as *Bacteroides uniformis*, which degrades complex carbohydrates and provides substrates for butyrate-producing species such as *Eubacterium rectale*[5]. Such cooperation contributes to the resilience of the gut ecosystem through nutrient exchange[5] and control of the substrates available, which prevents

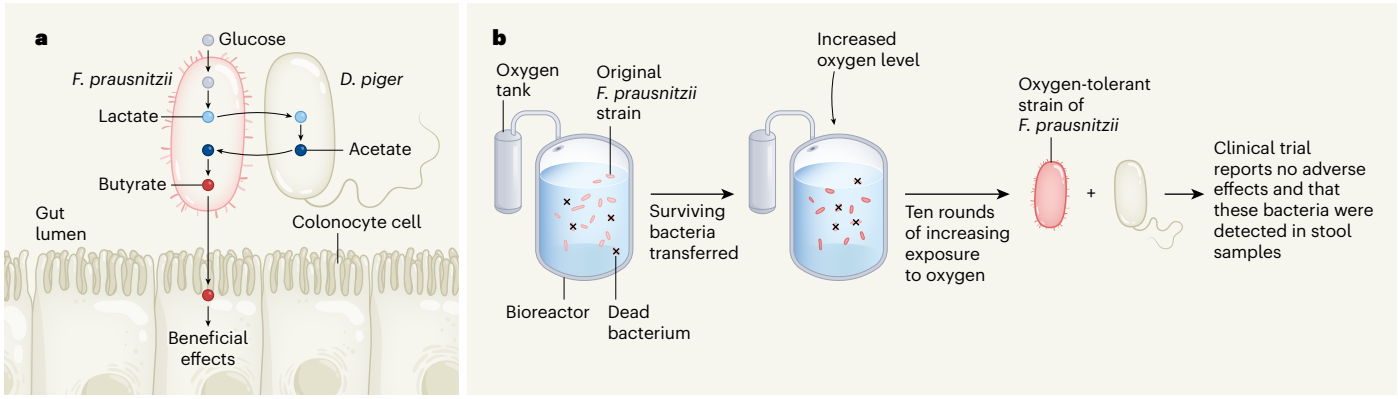

Figure 1 | A path towards harnessing gut bacteria to boost human health. Complex gut bacterial communities interact with one another (and with their human host) through nutrient exchanges that are key to maintaining a healthy system of beneficial interactions. **a**, Khan *et al.*[1] co-cultured two bacterial species (*Faecalibacterium prausnitzii* and *Desulfovibrio piger*) that cross-feed through exchanges of molecules in a pathway that ultimately produces the molecule butyrate. Butyrate benefits the human host through its positive effects on colonocyte cells that line the lumen of the colon and provide a barrier to material entering gut tissue[6]. **b**, The authors improved the tolerance of *F. prausnitzii* to oxygen through successive challenges of populations of the bacterium with increasingly elevated oxygen levels, thereby identifying a strain that survived such conditions while retaining its capacity to make butyrate. The authors also provide a proof-of-concept study of the safety, tolerability and establishment of the bacterial partnership after giving humans an oral dose of the two species.

invasion of the ecological niche of the gut by less-competitive bacteria.

Importantly, the butyrate produced is the main energy source for cells called colonocytes, supporting their function in dampening inflammation and maintaining the integrity of the gut lining, which prevents the contents of the gut lumen from crossing the gut wall and entering the bloodstream[6]. Butyrate might also protect human health beyond its role in the gut, for example, by helping to regulate blood-glucose levels and the balance between energy intake and expenditure that controls body weight[7]. Butyrate can also combat liver inflammation[8].

Once Khan and colleagues had confirmed that the beneficial bacterial interactions occurred outside the gut, they faced the challenge of adapting the more sensitive bacterium of the two, *F. prausnitzii*, to surviving the hardships of the outside world — namely an environment rich in oxygen — with a view to scaling up bacterial production. The authors cultivated *F. prausnitzii* in a bioreactor that simulates a gut environment, then progressively increased oxygen levels and isolated those colonies that survived this treatment (Fig. 1b). Through this process, the authors selected a strain that had evolved a greater oxygen tolerance than the original one, but which nevertheless had the same ability to produce butyrate in co-culture with *D. piger*.

Through genome sequencing, Khan and colleagues identified various mutations in these oxygen-tolerant *F. prausnitzii*, but were unable to relate them to molecular mechanisms underlying oxygen tolerance. The ability to resist certain types of abiotic stress typically confers the ability to resist others, and this helped the authors to scale up *F. prausnitzii* production and downstream manufacturing processes (such as freeze-drying and ensuring storage stability) to formulate a product for clinical trials.

The authors evaluated the safety of the two bacteria in rodents and humans. Classical probiotics belonging to the genera *Lactobacillus* and *Bifidobacterium* have a history of safe use as supplements, and food-safety regulators generally accept them as fit for human consumption. This is clearly not the case for most human-gut bacteria, whose safety as a supplement should be validated even if they are ostensibly commensal species[9,10].

The bacterial combination tested by the authors generated no observable adverse effects when tested in mice. Khan *et al.* then confirmed the tolerability of the combination by testing two doses in 50 healthy human volunteers in a clinical trial (a randomized placebo-controlled study), reporting no adverse events, gut symptoms or alterations in molecular markers of metabolic or immune-system function. The authors detected specific genetic sequences of the bacteria in stool samples from a subset of participants, providing evidence of successful establishment of the bacteria in some of the individuals.

The ability of orally administered bacteria to occupy a niche in the gut will probably depend on the baseline composition of a person's gut-dwelling microbes (the microbiota) and the opportunities that the bacteria have to outcompete rival species. Moreover, efficacy is not dependent on the ability of the bacteria to become permanently established in the new ecological niche, if a transient presence would suffice for beneficial purposes. It is reasonable to expect that probiotics might integrate more easily into a gut ecosystem that has been altered by disease than into a healthy one in which such a bacterial community is sufficiently robust to outgrow foreign invaders.

Repairing the gut ecosystem by reintroducing microbes relevant for human health is a promising strategy for promoting health and managing disease, but major challenges remain. Progress should be made in the identification and recreation of the microbe–microbe interactions that are indispensable in shaping the metabolic fluxes of the ecosystem and conferring benefits to the host. Also, researchers need to learn how to better cultivate and preserve bacteria outside the gut to produce the next generation of beneficial probiotics.

Although the path from the bench to the bedside will be complex, Khan and colleagues' work exemplifies how to overcome some of the inherent challenges of recreating, outside the body, what naturally occurs in the gut. Success on this front is necessary to achieve the promise of harnessing gut microbes for human health.

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The author declares no competing interests.
This article was published online on 2 August 2023.