Proceedings of the Nutrition Society

cambridge.org/pns

The Nutrition Society Congress 2026 was held at The Royal Society, London on 20th-21st January 2026

Winter Conference 2026: Pushing the Boundaries of Nutritional Science

Gowland Hopkins Medal Lecture

Review Article

Cite this article: Flint HJ (2026). Combining sequence-based approaches with anaerobic microbiology and modelling to understand gut microbial communities. *Proceedings of the Nutrition Society*, page 1 of 9. doi: 10.1017/S0029665126105072

Received: 4 March 2026 UTC
Revised: 2 June 2026 UTC
Accepted: 23 June 2026 UTC

Keywords:
Gut microbiota; Dietary fibre; Butyrate production; Lactate utilisation; Colonic pH

Email: harryjflint@outlook.com

© The Author(s), 2026. Published by Cambridge University Press on behalf of The Nutrition Society. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

Combining sequence-based approaches with anaerobic microbiology and modelling to understand gut microbial communities

Harry J. Flint

University of Aberdeen Rowett Institute of Nutrition and Health, UK

Abstract

Gut micro-organisms possess biochemical capabilities that far exceed those of their mammalian hosts, particularly in the ability to gain energy from the breakdown of diet-derived plant material (fibre). This article reviews investigations into gut microbial communities conducted by Harry Flint and his research group. First, extracellular cellulosome and amylosome enzyme complexes were found to mediate the breakdown of plant cell walls and resistant starch by specialised Firmicutes bacteria, both in the human colon and in the rumen. In contrast, Bacteroidetes (*Bacteroides, Prevotella* spp.) rely on their ability to capture soluble carbohydrates. Human dietary studies examining the impact of fibre sources upon microbiota composition and metabolism identified 'diet-responsive' species. In addition, dominant species of butyrate-producing bacteria, including a subset able to convert lactate to butyrate, were isolated from healthy human volunteers. Most produce butyrate from carbohydrates via butyryl-CoA:acetate CoA-transferase, with uptake of external acetate, while lactate conversion is associated with a highly inducible gene cluster (*lct*). In pH-controlled chemostat studies, mildly acid pH depressed growth of propionate-producing Bacteroidetes, but favoured butyrate production by Firmicutes. This may explain why % butyrate among SCFA increases with total faecal SCFA concentration in human studies. Although lactate is normally consumed by lactate-utilising bacteria, destabilisation of the microbial community associated with lactate accumulation can result in radically altered microbiota and metabolite profiles. A theoretical model based on microbial functional groups (MFG) was developed to better understand community dynamics. Consequences for nutritional research of our expanding knowledge of the microbial ecology of the human gut are considered.

Background: learning the ropes

A degree in Biological Sciences at Edinburgh University led me to a PhD in the Genetics department, supervised by Henrik Kacser, who is remembered for his influential theories on the control of metabolic flux and for being a pioneer of Systems Biology[1,2]. My project, using the fungus *Neurospora,* explored flux control in amino acid pathways[3]. My first jobs were lectureships at Nottingham University and the University of the West Indies (Barbados). I then secured an MRC grant that took me back to Edinburgh as I suddenly realised how quickly things were changing in my field – by this time (the early '80s) the recombinant DNA revolution was in full swing. Taking advantage of expertise in my old department, I was able to clone a *Neurospora* gene (ornithine transcarbamylase) and study the phenomenon of general amino acid control at the level of transcription and protein expression.

Contrasting systems for microbial carbohydrate utilisation by gut bacteria

In 1985, I became a full-time research scientist at the Rowett Institute in Aberdeen, with the brief of applying recombinant DNA techniques to improve productivity in ruminant animals (I was regarded as a 'genetic engineer'). At the start I knew nothing of the remarkable diversity of rumen micro-organisms or their extreme sensitivity to oxygen, but I soon became fascinated by the ability of native rumen organisms to degrade the plant material on which the animals depend for nearly all their dietary energy. Gene libraries were constructed from the gram-positive cellulose-degrader *Ruminococcus flavefaciens* and screened for activity against cellulose, xylan and beta-glucan. This yielded some of the first polysaccharidase gene sequences from rumen bacteria, revealing that polypeptides could carry more than one catalytic domain[4]. Also present were short, non-catalytic, regions (dockerins) that we recognised as indicative of an enzyme complex. We went on to establish that *R. flavefaciens* produced the most sophisticated cellulosome complex known (and the first in a gut bacterium) incorporating some 220 gene products[5,6]. This work owed much to the dedication of Marco Rincon in my lab, also to our collaboration with Ed Bayer's lab in Israel, and a genome sequence made available by Bryan White in Illinois.

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

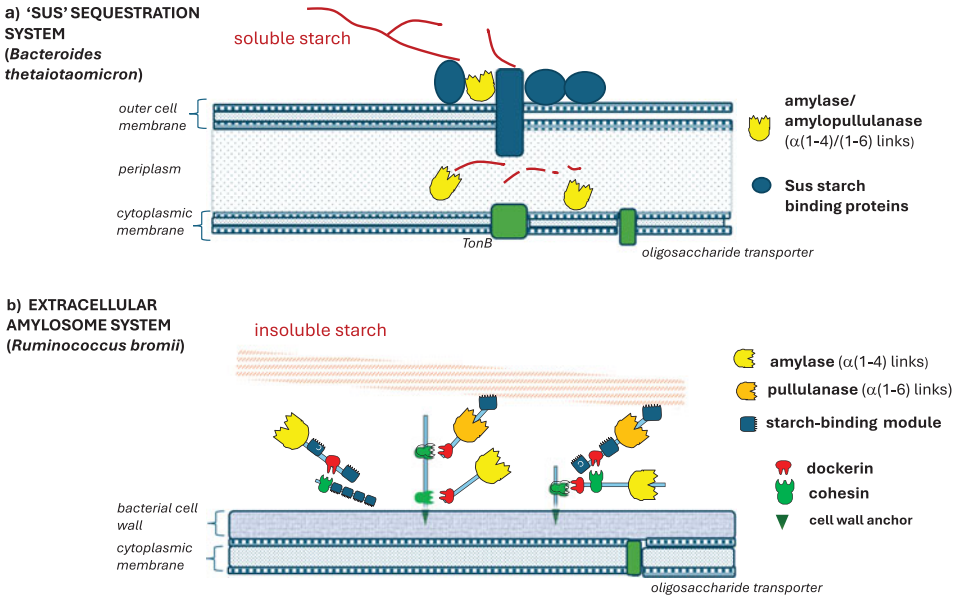


Figure 1. Contrasting enzyme systems involved in the utilisation of dietary starches by gut bacteria. (a) The Starch Utilization System (Sus) first described by Abigail Salyers in the human colonic bacterium *Bacteroides thetaiotaomicron*[9,10]. This system allows binding of soluble starch fragments that are largely broken down by enzymes in the periplasmic space; there is no evidence that it can act on insoluble resistant starches. (b) The extracellular 'amylosome' system of the gram-positive anaerobe, *Ruminococcus bromii*[60,61]. The enzymes, which carry their own starch-binding modules, are organised into complexes via dockerin:cohesin interactions and held onto the bacterial cell surface via sortase-mediated attachment. *R. bromii* is a highly effective degrader of insoluble resistant starches.

In parallel, my lab cloned DNA fragments coding for xylanases from the gram-negative anaerobe *Prevotella bryantii*, identifying a gene cluster that also encoded an unusual two-component regulator[7]. Genome sequencing in the USA completed the picture, showing that this cluster was in fact a Polysaccharide Utilization Locus (or PUL)[8], resembling those in human colonic *Bacteroides*. *Bacteroides* PUL encode surface proteins that trap soluble carbohydrates which are then hydrolysed within the gram-negative periplasmic space[9,10] (Fig. 1). The contrast between this organisation (referred to as a 'sequestration' system by its discoverer, Abigail Salyers) and the extracellular enzyme complex of *R. flavefaciens* was highlighted in an invited review[11]. The '*Sus* (starch utilization system)-type' systems of gram-negative Bacteroidetes appear geared to the utilisation of soluble polysaccharides; whereas the elaborate cell-attached systems found in certain specialised Firmicutes evolved to degrade insoluble fibre (Fig. 1).

Understanding the microbial community of the human large intestine

Identifying resident human colonic bacteria that help to maintain health

In the late 1990's my research switched to the anaerobic microbial community of the human large intestine. Our initial target was to define the bacteria responsible for producing butyrate which, surprisingly, were little known despite the well-documented role of butyrate in maintaining colonic health[12]. Our approach was to isolate bacteria from faecal samples using strictly anaerobic techniques developed for the rumen, accompanied by 16S rRNA gene sequencing, which revealed that many isolates were not closely related to known species[13]. We also selectively isolated human colonic bacteria that could utilise lactate for growth, recovering new species that convert lactate and acetate to butyrate[14,15]. Interest in the human gut microbiota was growing rapidly at this time, but with frequent claims that most gut bacteria were 'unculturable'. For this reason, we examined bacterial diversity by direct PCR amplification and sequencing of 16S rRNA genes in DNA recovered from colon samples, proving that the butyrate-producing bacteria we had cultured were highly abundant within the colonic microbiota[16]. This was the first time that sequencing of directly amplified 16S rRNA genes had been used to analyse the microbiota of human colon samples (as opposed to faecal samples[17]) although a subsequent paper from David Relman's lab in California, using the same primers, performed vastly more sequencing[18]. The use of anaerobic rumen fluid-based media appears to have been the key to our success in isolating 'novel' species[19], but for convenience we designed a rumen fluid-free medium containing a mixture of SCFA (YCFA medium) that supports growth of most of our isolates[20]. *Faecalibacterium prausnitzii* requires acetate[21], but, along with related species of Ruminococcaceae, also has complex vitamin requirements[22,23]. Oxygen sensitivity is also a major factor; whereas the better-studied colonic *Bacteroides* strains can survive in air for several hours, many of our new Firmicutes isolates could not survive longer than a few minutes[24]. Surprisingly, *F. prausntzii,* although an obligate anaerobe, proved able to exploit very low oxygen concentrations, a capability that may help it survive in proximity to the gut wall[25].

DNA sequencing methods were being improved at a bewildering pace during this period. Soon they allowed draft bacterial genomes to be completed within days, and metagenomic analyses to be performed through mass sequencing of DNA from mixed samples, followed by sophisticated bio-informatic analysis, as shown by a landmark paper from the EU MetaHit study[26]. Reference genomes from cultured organisms proved critical in assigning these metagenome sequences, however, and we can note that 14 out of the 56 most abundant cultured species detected in the MetaHit analysis came from our isolates. Many of these butyrate-producing species have since been reported to show reduced abundance in a wide range of disease states[12,27–29]. indicating that they represent important components of a healthy gut microbiota.

New insights into butyrate and propionate formation and lactate utilisation

Many colonic butyrate-producing bacteria, including those related to *Roseburia* and *Faecalibacterium*, consume acetate when grown in pure culture[13]. These bacteria were shown to depend on butyryl-CoA:acetate CoA-transferase rather than butyrate kinase for the final step in butyrate formation. The *butCoAT* gene from a

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

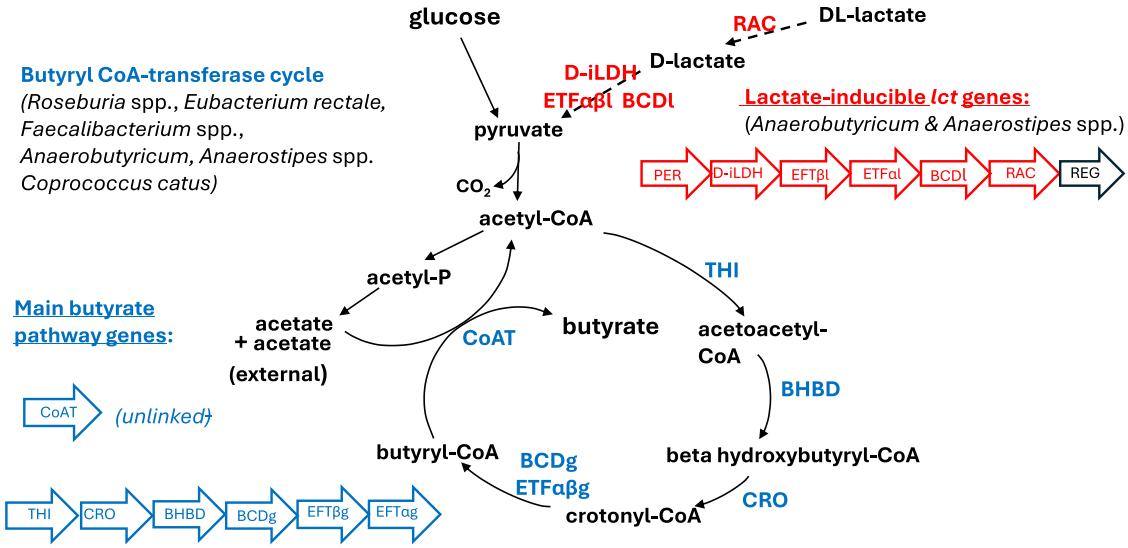


Figure 2. Butyrate formation from carbohydrates and from lactate in dominant human colonic anaerobes. Many Firmicutes bacteria employ butyryl-CoA:acetate CoA-transferase to produce butyrate. Genes and enzymes involved in the main pathway from acetyl-CoA are shown here in blue, with five clustered genes and the unlinked gene that encodes the CoA-transferase indicated. The ability of *Anaerobutyricum* and *Anaerostipes* spp. to produce butyrate from lactate depends on a second, highly inducible, gene cluster (*lct*), indicated in red. The cluster encodes a second butyryl-CoA dehydrogenase (BCDl) enzyme that appears to replace the function of the 'normal' enzyme (BCDg) during growth on lactate[40]. The alternative butyrate kinase pathway (not shown here) is used to produce butyrate in some *Coprococcus* and *Clostridium* species. *Key:* THI thiolase; BHBD beta-hydroxybutyrate dehyrogenase; CRO crotonase; BCD butyryl-CoA dehydrogenase; ETFβg, ETFαg electron-transferring flavoprotein (growth on carbohydrate); CoAT butyryl-CoA: acetate CoA-transferase; PER lactate permease; D-iLDH D-lactate dehydrogenase; ETFβl, ETFαl electron-transferring flavoprotein (lactate inducible); RAC lactate racemase; REG *lct* regulatory protein. Gene orders shown are for *A. soehngenii* L2-7[35,40]. *Anaerostipes hadrus* lacks the racemase gene and can only utilise D-lactate.

R. hominis strain was overexpressed to determine the enzyme's specificity[30] and the diversity of human gut bacteria carrying this gene explored using degenerate PCR primers[31]. Net acetate uptake varied with growth conditions, especially the initial culture pH. We were able to explain this by proposing that variable amounts of external acetate could lead to the formation of acetyl-CoA and butyrate via the CoA-transferase reaction[32]. Based on recent work in Germany[33,34], the reduction of crotonate by butyryl-CoA dehydrogenase (BCD) together with electron-transferring flavoprotein (ETF) produces reduced ferrodoxin that in turn drives additional energy gain via ion gradients[35]. We predicted that greater net acetate uptake per mol of glucose fermented should be linked to an increase in energy yield and butyrate formation[32]. Evidence consistent with this shift in stoichiometry also came from incubations of mixed faecal bacteria with different carbohydrate energy sources in which % butyrate among the SCFA products was higher with an initial pH of 5.5 than one of 6.5 for any given % of butyrate producers within the mix[36].

The formation of lactate from butyrate was assumed to require lactate oxidation to pyruvate, an energetically unfavourable reaction under anaerobic conditions[37]. With the advent of RNAseq technology, we were able to study gene expression during growth on lactate compared with glucose. This revealed a massive ($\log2 > 14$) up-regulation of six clustered genes (*lct*) concerned with lactate utilisation in our isolate (L2-7) of *Anaerobutyricum soehngenii* (formerly *Eubacterium hallii*)[38,39] during growth on lactate[40]. Unexpectedly, these include an acyl-CoA dehydrogenase that is an alternative to the BCD enzyme normally expressed during growth on glucose (Fig. 2). The down-regulation of the main butyrate pathway BCD and ETF genes strongly suggests that on lactate, it is the *lct*-encoded BCD and ETF that function together with the D-iLDH to ensure close linkage of lactate oxidation with the reduction of crotonate. In the rumen, lactate is mainly converted via the acrylate or succinate pathways to propionate. We also discovered the acrylate pathway in the human gut anaerobe *Coprococcus catus*, although this organism produces butyrate when growing on carbohydrates[40].

After surveying the distribution of fermentation pathways in human gut anaerobes, based on available metagenome sequences and amplification of diagnostic genes, we concluded that propionate and butyrate are generally produced from carbohydrates by different bacterial species in the human colon. At least one butyrate-producing Firmicutes possesses the propanediol pathway that converts fucose or rhamnose to propionate[41], and, as noted above, *C. catus* can produce propionate via the acrylate pathway, but the bulk of propionate production comes from the Bacteroidetes, via succinate[42].

Changes in gut microbiota and metabolites in obese volunteers on weight loss diets

We collaborated in several studies run by Alex Johnstone, through the Human Nutrition Unit at the Rowett Institute, looking at the impact of weight loss diets in overweight subjects. These studies benefitted from complete control over food intake, with all meals prepared by the HNU kitchen. At first our microbiota analysis was limited to enumeration by FISH (fluorescent in situ hybridisation) microscopy using a panel of probes targeting 16S rRNA genes. FISH analysis had some advantages, being free of uncertainties around sample storage and DNA extraction that dogged some early sequence-based studies. This method delivers absolute cell counts, rather than relative abundance, and revealed that the numbers of *Roseburia/E.rectale* cells[19] correlated very well with butyrate concentrations in faecal samples[43]. A second study reported more extensive data on faecal metabolite concentrations, revealing a major impact of weight loss diets low in carbohydrate and fibre on phytochemicals; this, together with the decrease in butyrate, suggested

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

such diets may pose risks for colonic health if maintained in the long term[44].

We found no evidence in these studies for a deficiency in Bacteroidetes in obese individuals[45]. This contrasted with results from an earlier sequence-based study[46] which reported a major phylum-level change in the ratio of Firmicutes to Bacteroidetes in obese compared with lean individuals. Our findings agreed with another FISH-based study[47], and with subsequent reports from sequence-based or metagenomic analysis[48]. Nevertheless, there is some evidence that a few species within the microbiota may influence fat deposition, either promoting it[49] or decreasing it[50].

It was also suggested that the gut microbiota should promote weight gain because they supply additional calories to the host via the SCFA produced by the fermentation of fibre[51,52]. The net contribution of gut micro-organisms to 'energy harvest' is not quite so clearcut, however, based on further analysis and experimental findings[53]. In particular, we know that the same amount of sugar consumed as fibre yields substantially fewer calories via the absorption of fermentation products by comparison with sugar absorbed directly. Thus, replacing digestible starch with the same amount of resistant starch (RS), for example, will increase microbial fermentation in the colon, but it delivers fewer net calories and may also contribute to satiety[54].

Evidence for diet-responsive species within the human gut microbiota

It soon became obvious that FISH microscopy was too slow and laborious compared to newer sequence-based methods. Our next human study, that compared weight maintenance diets incorporating different types of fibre (RS or wheat bran), employed 16S rRNA targeted qPCR techniques developed by my colleague Petra Louis, 16S rRNA gene sequencing with Alan Walker (at the Sanger Institute) and microarray analysis through a collaboration with Willem De Vos in the Netherlands[55,56]. We were still concerned to avoid artefacts, however, and all samples were processed rapidly before freezing. Only later did we settle on a glycerol storage procedure to allow freezing without the risk of losing DNA from certain bacterial groups. This proved to be our most significant human study for understanding of the gut microbiota. Up to this point, there was a view that a healthy adult individual's microbiota composition was stable through time. Our study however revealed significant microbiota changes with the different dietary regimens, providing evidence of 'diet-responsive' species, especially in the case of diets high in RS[55]. The two greatest responders (in relative abundance) were the Firmicutes *Ruminococcus bromii* and *Eubacterium rectale* – except that two of our 14 individuals harboured no *R. bromii* on any diet. Extraordinarily, these were the only two individuals who showed significant residual starch in their faecal samples. The clear implication was that *R. bromii* was uniquely well equipped to degrade this substrate, making it a 'keystone species' for the release of energy from this substrate[57,58]. *R. bromii* produces acetate, ethanol and formate as products in pure culture but co-culture with an acetogen consumes the formate[23], suggesting that acetate will be its main product in the colon. A subsequent human study of similar design that contrasted extreme plant-based and animal-based diets demonstrated still more wide-ranging shifts in species composition[59].

Understanding how Ruminococcus bromii degrades resistant starch

Work on cultured strains established the superiority of *R. bromii* over *Bacteroides thetaiotaomicron* (in which the classic 'Sus' starch utilisation system was first described[9]) in degrading RS in pure culture, with the latter only able to use soluble starches efficiently. Cross-feeding of breakdown products between *R. bromii* and other species was also demonstrated[57]. A genome sequence for our *R. bromii* strain enabled us to establish its amylase complement. A real surprise was that five large extracellular amylases carried dockerin sequences, suggesting that they must be part of an enzyme complex, and protein:protein interactions were quickly established with the help of our Israeli cellulosome collaborators. We decided to call these new complexes (the first involving starch-degrading enzymes) 'amylosomes[60]' (Fig. 1). But how widespread was this system? We compared the genome sequences of the very few extant strains of *R. bromii* (one from the USA, two from Scotland, one from South America and a rumen strain from Australia), establishing that the major amylosome components were very highly conserved[61]. Around this time, we also uncovered a cellulosome system in a human colonic bacterium (*Ruminococcus champanellensis*) that can degrade crystalline cellulose[62,63]. This closely resembles the system previously documented in its rumen relative, *R. flavefaciens*. These cases show that the nutritional niche, rather than the mammalian host species, is the key determinant of the enzyme system. The *R. bromii* genomes also revealed a full set of sporulation genes, and sporulation was confirmed experimentally[61]. Sporulation is likely to be more common than previously assumed among 'non-sporing' anaerobes[64], helping to explain how such highly oxygen-sensitive species can colonise new hosts.

Microbial fermentation of soluble v. insoluble fibres

When genome sequences first became available for human gut anaerobes, by far the largest number and diversity of genes for carbohydrate active enzymes (notably glycosyl hydrolases) was evident among *Bacteroides* species[65]. It was widely assumed that this group must therefore be largely responsible for fibre degradation in the large intestine. As we have seen, however, *Bacteroides* are poorly equipped to utilise insoluble fibre and were not prevalent among the 'diet-responsive' species detected in our human studies, most of which were Firmicutes[56]. A small subset of Firmicutes were the primary colonisers of wheat bran detected using an *in vitro* model system[66]. The remarkable GH gene diversity in *Bacteroides* is however likely to confer great versality in the utilisation of soluble carbohydrates of dietary and host origin[10]. In a subsequent human dietary study[67], we found that another group of Bacteroidetes (*Prevotella spp.* especially *P. copri*), responded strongly to soluble xylan derivatives (AXOS). 8 of the 21 volunteers harboured *Prevotella* before the intervention, with bifidobacteria showing the greatest response in the 13 individuals who lacked *Prevotella*. The reasons for this striking variation in the occurrence of *Prevotella*, indicating apparent mutual exclusion between *Prevotella* and *Bacteroides*, are still unknown, although dietary fibre intake may be a contributing factor[68,69].

Studying the impact of soluble fibres and pH change in chemostat communities

Continuous cultures can be run *in vitro* under anaerobic conditions with a constant inflow of nutrient medium (and matching outflow) at a controlled pH (chemostats)[70]. This provides an excellent opportunity to study the behaviour of microbial communities established from a faecal inoculum and supplied with soluble polysaccharide fibres. We used a single stage system to examine the impact of alternative substrates (apple pectin or

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

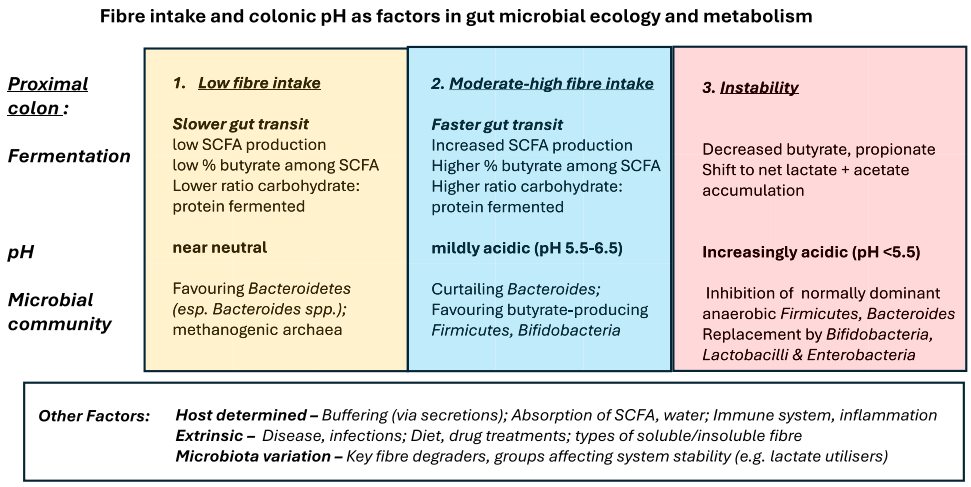


Figure 3. Fibre intake and pH as factors determining microbial ecology and metabolism in the human colon: a simplified picture. Typically, pH is mildly acidic in the proximal colon, then increases along the transverse and distal colon. Three conditions for the proximal colon are distinguished here. **1.** At low fibre intakes (highlighted in **beige**), concentrations of SCFA resulting from fermentation are low and colonic pH close to neutrality. Gut transit may be slow and protein fermentation (signalled by production of BCFA) may be significant compared to fermentation of carbohydrate fibre. **2.** At moderate or high (including recommended) intakes of fermentable fibre (highlighted in **blue**), colonic pH becomes mildly acidic due to the SCFA formed by fermentation. % butyrate among SCFA increases, and % BCFA decreases (reflecting increased fermentation of carbohydrate relative to protein). **3.** (highlighted in **mauve**), a variety of factors (disease, infection, pH too low) can cause highly unbalanced patterns of fermentation, with accumulation of lactate and acetate (acidosis). In each case, the likely shifts in the microbial community are indicated, based on evidence from chemostat communities[71,73,75], human dietary studies[43,44,83] and theoretical modelling[79,81]. The second condition (**blue**) is considered optimal for gut and systemic health. It should be stressed that a great many factors combine to influence gut metabolism and microbial populations, contributing to inter-individual and temporal variation. These are listed in the bottom panel. Also, faecal SCFA concentrations measured in human volunteer studies reflect fermentation along the colon, especially in the distal colon, where pH is higher and propionate-producing *Bacteroides* are likely to proliferate. Our modelling used available information to predict the situation in the proximal colon *in vivo*.

inulin) over a stepped pH range from 5.5 to 6.9 (and in reverse) on the composition of separate microbial communities derived from three healthy donors[71]. A striking conclusion was the extreme specificity of responses to the substrate, with different species of *Bacteroides* being promoted by inulin and by pectin. Another chemostat study explored the impact of substrate diversity upon microbiota diversity. The community established with a simple homopolymer (inulin) gave rise to a less diverse community than a highly complex substrate such as apple pectin, or mixtures of up to six different soluble fibre sources[72]. A more diverse gut microbiota is suggested to offer health benefits[48].

It was notable that *Bacteroides* became less dominant at lower pH values[71]. We had observed this phenomenon previously in chemostats supplied with a mixture of polysaccharides (mainly soluble starch), with pH 5.5 promoting butyrate production[73]. *Bacteroides* are evidently more sensitive to slightly acidic pH than are the butyrate-producing Firmicutes, which become able to compete for the substrates at the lower pH. This hypothesis was supported by measuring the growth rates of pure cultures at different initial pH values[74]. Significantly, the inhibition of *B. thetaiotaomicron* growth at pH 5.5 was increased by concentrations of SCFA normally found in the colon (Fig. 3). These findings suggest that *Bacteroides* will compete more successfully in the less acidic distal regions of the colon *in vivo*.

In another set of chemostat experiments, we asked how constant infusion of lactate (coming either from the intestinal microbiota, or from host tissues) might affect a colonic microbial community. Infusion of 20mM DL lactate had no discernible effect on microbiota composition or metabolite concentrations if the pH was maintained at 6.5, indicating efficient consumption by lactate-utilising bacteria (LUB)[75]. At pH 5.5, however, the community readily tipped into a state in which lactate and acetate were the major products and the normally dominant anaerobes (Bacteroides and Firmicutes) were replaced by Actinobacteria, Lactobacilli and Enterobacteria[75,76] (Fig. 3). As the pH was held constant, this points to differential inhibition of growth of the various bacterial groups by lactate. The potential for using LUB such as *A. soehngenii* as therapeutic probiotics[15] is now being actively explored[77]. The ability of pathogenic enterobacteria such as *Salmonella* to benefit from lactate availability[78] is a significant health concern.

Theoretical modelling of the human colonic microbiota

Steady state systems are amenable to mathematical modelling. With expert colleagues from Biomathematics and Statistics Scotland (BioSS), we developed a model based on 10 Microbial Functional Groups, chosen to align approximately with phylogenetic groups of bacteria and archaea (methanogens) and to represent the range of metabolic activities considered above. Detailed assumptions on pathways, substrate preferences, metabolic outputs, growth rates and pH responses were built into the model, based on our experimental observations on representative isolates. The resulting simulations came remarkably close to our chemostat data for butyrate concentration[73] with a good approximation to the pH-driven switch from Firmicutes to Bacteroidetes[79,80]. Simulation of the lactate infusion experiments required modifying our 10 microbial functional groups (MFG) model by assuming different Ki's for different MFG[75]. This reproduced the phenomena of perturbation and recovery observed with 10mM lactate infusions at pH 5.5. Furthermore, the outcome was predicted to depend critically on the assumed populations within the microbial inoculum of the two MFG groups representing LUB.

Helen Kettle took on the still more challenging task of translating our 10 MFG model into the context of the human intestine, with the additional complexities of periodic intake, gut compartments, variations in gut transit and the absorption of SCFA and water[81]. This was the first attempt to consider detailed microbial community dynamics in the context of the human colon in an exact, quantitative

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

manner (an earlier treatment had considered only two microbial groups[82]). While some of the assumptions may require subsequent modification in the light of new information, the model allows such adjustments to be quickly tested *in silico*.

Explanations for, and significance of, the 'butyrate shift' seen in human studies

Analysis of available data from 10 human studies conducted at the Rowett Institute over a 10-year period confirmed some highly significant relationships. Looking at baseline samples from 163 volunteers, there was a positive correlation between total SCFA concentration in faecal samples and the % butyrate among total SCFA[83]. Faecal pH measurements, available from half of these studies, confirmed that lower pH correlated with higher total SCFA concentration. The question then is, why should mildly acidic pH favour butyrate production? One explanation is the stoichiometric shift associated with the CoA-transferase pathway, that can result in more butyrate per mol of glucose fermented at slightly acidic pH[32]. A second is our evidence that some butyrate-producers become more able to compete for soluble carbohydrate substrates as *Bacteroides* growth is suppressed by slightly acidic pH[71,73]. A third is that bifidobacteria and other lactate-producers are also stimulated at acidic pH, with much of the lactate being routed to butyrate by LUB. While this butyrate shift might perhaps be preventable by better buffering of the pH in the proximal colon, evidence that an enhanced butyrate supply is beneficial for the colonic mucosa[84] suggests that the pH drop (due to the rapid fermentation of fibre) is likely to be host-controlled[85]. Thus, a pH environment in the proximal colon that favours butyrate production can be seen as a mechanism for ensuring an adequate supply of butyrate as the major energy source for the colonic epithelium, with consequent health benefits. Earlier indications of this phenomenon, based on much smaller numbers of volunteers, have suggested that reduced butyrate production occurs in individuals exhibiting methanogenesis and/or slow gut transit[86,87].

The other significant change we observed with increasing total [SCFA] was a decrease in % of branched-chain fatty acids (BCFA)[83]. Since BCFA derive exclusively from branched-chain amino acids, this can be explained simply if the increase in total [SCFA] reflects increased fermentation of carbohydrate fibre relative to protein (Fig. 3).

Conclusions – where next for research on the gut microbiota in relation to nutrition?

Can DNA sequencing tell us everything about the microbiota?

The past 25 years have seen an explosion of interest in the human gut microbiota and its role in human health, driven primarily by the vastly improved speed and throughput of nucleic acid sequencing technologies that bypass the need for microbial culturing. This has transformed our knowledge of diversity within the human gut microbiota across the globe, and for different age groups, dietary habits and disease states[88–92]. Most information on gut microbiota profiles has come from single 'snapshot' faecal samples however and there is scope for more controlled intervention studies that address defined questions.

Sequence information, by itself, has limitations. While metagenomes can yield functionally relevant information, this depends critically on accurate gene annotation. Work involving cultured micro-organisms, including isolation of new taxa, plays an essential role in advancing fundamental scientific knowledge and informing gene annotation. Importantly, culturing can also give rise to novel therapeutic probiotics and prebiotic strategies. Another promising area is the investigation of secondary metabolites produced by gut anaerobes, some of which act as antimicrobial agents or signal molecules[93,94].

The relative proportions of microbial taxa, or genes, estimated from metagenomes are hard to relate to physiology and human metabolism in any truly quantitative manner. For this we need to deal in absolute cell counts, rates of substrate degradation and metabolite flows, while also considering mucosal absorption and gut transit. Only then is it possible to develop deterministic theoretical models that simulate microbial fermentation in the gut[82]. Our own mathematical modelling, based on 10 MFG, relied on cultured isolates for assumptions about growth rates, pH sensitivity, substrate preferences and biochemical pathways[75,79,81]. While our model was designed to predict the major products of carbohydrate fermentation, similar approaches could be used for other important metabolites (e.g. vitamins, phytochemicals and bile acids) given enough information to define the relevant functional groups.

Inter-individual variation in the gut microbiota

Gut microbiota composition changes throughout life from infancy to adulthood to old age, and with dietary change, disease and medication[29,55,59,88,89]. Nevertheless, microbiota composition in adults shows individuality and stability over time. An early proposal to subdivide adult human microbiota profiles into three discrete 'enterotypes' proved controversial[95], although the difference between individuals for whom *Prevotella* or *Bacteroides* is the predominant genus of gram-negative anaerobe has been found repeatedly[68,69]. It is still unclear whether dietary differences, some form of mutual exclusion, or a combination of these factors, are responsible. Furthermore, evidence that the human genotype influences gut microbiota composition is growing rapidly[96]. For example, genetic variation in the production of digestive enzymes and in genes specifying components of the immune system[97] can influence the microbiota.

There is a strong argument that we should be aiming at individual, rather than universal, dietary recommendations. Some people suffering from irritable bowel syndrome (IBS) are intolerant of fibre and their health can improve with diets that lack fermentable material[98]. Exclusions also apply to those suffering from coeliac disease or food allergies, while adult lactose-intolerance affects much of the world's population[99].

Prebiotics v. complex fibre sources from food?

In vitro chemostat studies reveal that microbial community responses to single types of soluble fibre can be highly species-specific[71]. Nevertheless, different species can be promoted depending on the initial inoculum, and *in vivo* dietary supplementation studies with prebiotics show that different species may be promoted in different individuals[67]. This means that impacts on health will not be uniform. On the other hand, any increase in fermentable fibre tends to decrease the pH of the proximal colon, altering the competition between different groups of gut bacteria (Fig. 3). This probably explains why low pH-tolerant bifidobacteria are promoted by a such wide range of 'prebiotic' fibres. An important benefit from 'natural' fibre sources is that potentially beneficial phytochemicals intrinsic to plant cell walls are released and further transformed during microbial breakdown[44,66]. Furthermore, they contain mainly insoluble fibre that is likely to be more slowly fermented within the colon. Also, a varied intake of

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

natural fibre sources is more likely to increase microbiota diversity by comparison with intake of a single prebiotic fibre.

Microbiota diversity

There is evidence that individuals with higher microbiota diversity show better biomarkers for metabolic health than those with lower diversity, while in low diversity groups both microbiota diversity and health scores can be improved with dietary change[48,100]. It has also been shown that gut microbiota diversity is greater in 'hunter-gatherer' communities than in urban populations[101]. 'Western' style diets, early use of antibiotics and caesarian birth, are all considered factors that tend to decrease microbiota diversity[102–104]. Increasing and diversifying dietary fibre intake should help to increase microbiota diversity. On the other hand, it has been argued that in many individuals from industrialised countries, key microbial species (or functional groups) have been irreversibly lost, or never acquired at birth[102]. We know surprisingly little about the ability of gut anaerobes to recolonise the adult gut, either naturally or by deliberate introduction, and this seems a topic worthy of more research. It would be particularly relevant to know whether new species can be acquired in humans following a diet shift, or a change in drug (including antibiotic) treatment, that creates new niches. More generally, a broader evolutionary perspective would be valuable[105].

The success of Faecal Microbiota Transfer (FMT) in restoring a healthy microbiota in patients suffering from *Clostridium difficile* infection[106] has encouraged interest in using 'health-promoting' bacteria as therapeutics, and this is an increasingly active area. Candidates can now include obligate anaerobes, some of which are known to produce spores, while others can be delivered in ways that protect them against oxygen. In addition to single organisms[77], the use of 'cocktails' of isolated gut bacteria has also been examined[107]. Genome sequencing can help to ensure safety by confirming the absence of genes connected with pathogenicity or antibiotic resistance.

Bottom line

Can we define a healthy microbiota, other than to say it is that found in a healthy person? The extent of redundancy and diversity within the microbial community means this cannot be done in detail at the species level, but the presence of key functional groups and keystone species offers a better approach. The supply of health-protective nutrients, roles in fibre degradation, anti-inflammatory action and activities such as lactate utilisation that help to stabilise the community, can all be considered. The most obvious feature of a 'healthy' gut microbiota, however, must be the near absence of infectious pathogens, together with the protective barrier provided against them by the resident microbial community[108]. We know that the prevalence of different pathogens varies widely with geography. So far, most detailed work on gut microbial ecology has been pursued in Europe, North America and Japan, but there is a clear need for more intensive study of the dominant representatives of the gut microbiota worldwide, including their interactions, their relationship to diet and their role in preserving health[69,109].

Acknowledgements. I would like to thank my colleagues at the Rowett Institute who contributed over the past 40 years to the work described here including Sylvia Duncan, Jennifer Martin, Petra Louis, Alan Walker, Karen Scott, Wendy Russell, Alex Johnstone, Susan Pryde, Georgina Hold, Carol Leitch, Nicole Reichardt, Jenny Laverde, Indrani Mukhopadhya, Alvaro Belenguer, Rustam Aminov, Colin Stewart, Gerald Lobley, Macro Rincon, Adela Barcenilla, Xiaolei Ze, Faith Chung and Paul Sheridan. Indeed, I am grateful to all the talented PhD students, postdoctoral researchers, visiting scientists and co-workers who contributed so much to our research over the years. Thanks also to Helen Kettle, Grietje Holtrop and Graham Horgan of BioSS (Biomathematics and Statistics Scotland) for their amazing contributions on mathematical modelling and statistical analysis. Finally, I must acknowledge the immense value of our many collaborations with laboratories across Europe (UK, Spain, France, Netherlands, Germany, Finland and Italy) and in Israel, USA, China and Japan.

Financial support. No financial support was involved in the preparation of this manuscript. Sources of support for the research described here are given in the individual papers cited.

Author contributions. The author had sole responsibility for all aspects of the preparation of this manuscript.

Competing interests. None.

References

1. Kacser H & Burns JA (1973) The control of flux. *Symp Soc Exp Biol* **27**, 65–104.
2. Martinoga B (2018) *Molecular tinkering: the Edinburgh scientists who changed the face of modern biology*. CPI Group (UK) Ltd, Croydon.
3. Flint HJ, Tateson RW, Barthelmess IB, *et al.* (1981) Control of the flux in the arginine pathway of *Neurospora crassa*: modulations of enzyme activity and concentration. *Biochem J* **200**, 231–246.
4. Flint HJ, Martin J, McPherson CA, *et al.* (1993) A bifunctional enzyme having separate xylanase and ß(1,3-1,4) glucanase domains, encoded by the *xynD* gene of *Ruminococcus flavefaciens*. *J Bacteriol* **175**, 2943–2951.
5. Rincon MT, Ding S-Y, McCrae SI, *et al.* (2003) Novel organisation and divergent dockerin specificities in the cellulosome system of *Ruminococcus flavefaciens*. *J Bacteriol* **185**, 713–713.
6. Rincon MT, Dassa B, Flint HJ, *et al.* (2010) Abundance and diversity of dockerin- containing proteins in the fiber-degrading rumen bacterium *Ruminococcus flavefaciens* FD-1. *PLoS One* **5**, 8, art e12476.
7. Miyamoto H, Hirase T, Mercer DK, *et al.* (2003) Involvement of the two component regulatory protein XynR in positive control of xylanase gene expression in the ruminal anaerobe *Prevotella bryantii* $B_1$4. *J Bacteriol* **185**, 2219–2226.
8. Dodd D, Moon YH, Swaminathan K, *et al.* (2010) Transcriptomic analysis of xylan degradation by *Prevotella bryantii* and insights into energy acquisition by xylanoytic Bacteroidetes. *J Biol Chem* **285**, 30261–30273.
9. Reeves AR, Wang GR & Salyers AA (1997) Characterisation of four outer membrane proteins that play a role in utilization of starch by *Bacteroides thetaiotaomicron*. *J Bacteriol* **179**, 643–649.
10. Martens EC, Koropatkin NM, Smith TJ, *et al.* (2009) Complex glycan catabolism by the human gut microbiota: the bacteroides Sus-like paradigm. *J Biol Chem* **284**, 24673–24577.
11. Flint HJ, Bayer, EA, Rincon MT, *et al.* (2008) Polysaccharide utilization by gut bacteria: potential for new insights from genomic analysis. *Nat Microb Rev* **8**, 121–131.
12. Hamer HM, Jonkers D, Venema K, *et al.* (2008) Review article: the role of butyrate on colonic function. *Alim Pharmacol Therap* **27**, 104–119.
13. Barcenilla A, Pryde SE, Martin J, *et al.* (2000) Phylogenetic relationships of dominant butyrate producing bacteria from the human gut. *Appl Environ Microbiol* **66**, 1654–1661.
14. Duncan SH, Louis P &Flint HJ (2004) Lactate-utilising bacteria from human feces that produce butyrate as a major fermentation product. *Appl Environ Microbiol* **70**, 5810–5817.
15. Duncan SH, Flint HJ (2004) "Lactic acid utilising bacteria and their therapeutic use". Patent.
16. Hold GL, Pryde SE, Russell VJ, *et al.* (2002) Assessment of microbial diversity in human colonic samples by 16S rDNA sequence analysis. *FEMS Microbiol Ecol* **39**, 33–39.
17. Suau A, Bonnet R, Sutren M, *et al.* (1999) Direct analysis of genes encoding 16S rRNA from complex communities reveals many novel

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

molecular species within the human gut. *Appl Environ Microbiol* **65**, 4799–4807.
18. Eckberg PB, Bik EM, Bernstein CN, *et al.* (2005) Diversity of the human intestinal microbial flora. *Science* **308**, 1635–1638.
19. Aminov RI, Walker AW, Duncan SH, *et al.* (2006) Molecular detection, cultivation and improved FISH detection of a dominant group of human gut bacteria related to *Roseburia* and *Eubacterium rectale*. *Appl Environ Microbiol* **72**, 6371–6376.
20. Lopez-Siles M, Khan T, Duncan SH, *et al.* (2012) Cultured representatives of two major groups of human colonic *Faecalibacterium prausnitzii* can utilize pectin, uronic acids, and host derived substrates for growth. *Appl Environ Microbiol* **78**, 420–428.
21. Barcenilla A (1999) Diversity of the butyrate-producing microflora of the human gut. PhD thesis. Robert Gordon University, Aberdeen, UK.
22. Soto-Martin EC, Warnke J, Farquharson FM, *et al.* (2020) Vitamin biosynthesis by human gut butyrate-producing bacteria and cross-feeding in synthetic microbial communities. *MBio* **11**, e00886–20.
23. Laverde Gomez JA, Mukhopadhya I, Duncan SH, *et al.* (2019) Formate cross-feeding and cooperative metabolic interactions revealed by transcriptomics in co-cultures of acetogenic and amylolytic human colonic bacteria. *Environ Microbiol* **21**, 259–271.
24. Flint HJ, Duncan SH, Scott KP, *et al.* (2007) Interactions and competition within the microbial community of the human large intestine: key links between diet and health. *Environ Microbiol* **9**, 1101–1111.
25. Khan MT, Duncan SH, Stams AJM, *et al.* (2012) The gut anaerobe *Faecalibacterium prausnitzii* uses an extracellular electron shuttle to grow at oxic-anoxic interphases. *ISME J* **6**, 1578–1585.
26. Qin J, Li R, Raes J, *et al.* (2010) A human gene catalogue established by metagenome sequencing. *Nature* **464**, 59–65.
27. Sokol H, Pigneur B, Watterlot L, *et al.* (2008) *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis in Crohn's disease patients. *Proc Natl Acad Sci USA* **105**, 16731–16736.
28. Louis P, Hold GL & Flint HJ (2014) The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microb* **12**, 661–672.
29. Forslund K, Hildebrand F, Nielsen T, *et al*, (2015) Disentangling type 2 diabetes and metformin signatures in the human gut microbiota. *Nature* **528**, 262–266.
30. Charrier C, Duncan SH, Reid MD, *et al.* (2006) A new class of CoA-transferase involved in short chain fatty acid metabolism in butyrate-producing human colonic bacteria. *Microbiology* **152**, 179–185.
31. Louis P, Young P, Holtrop G, *et al.* (2010) Diversity of human colonic butyrate-producing bacteria revealed by analysis of the butyryl CoA: acetate CoA-transferase gene. *Environ Microbiol* **12**, 303–314.
32. Louis P, Flint HJ (2017). Formation of propionate and butyrate by the human colonic microbiota. *Environ Microbiol* **19**, 29–41.
33. Li F, Hinderberger J, Seedorf N, *et al.* (2008) Coupled ferrodoxin and crotonyl coenzyme A (CoA) reduction with NADH catalyzed by the butyryl-CoA/Etf complex from *Clostridium kluyveri*. *J Bacteriol* **190**, 843–850.
34. Buckel W, Thauer RK (2013) Energy conservation via electron bifurcating ferrodoxin oxidation and proton/Na^+ translocating ferrodoxin reduction. *BBA-Bioenergetics* **1827**, 94–113.
35. Louis P, Flint HJ (2009). Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. *FEMS Microbiol Letts* **294**, 1–8.
36. Reichardt N, Vollmer M, Holtrop G, *et al.* (2018) Specific substrate-driven changes in human faecal microbiota compostion contrasts with functional redundancy in short chain fatty acid production. *ISME J* **12**, 610–622.
37. Weghoff M, Bertsch J &Muller V (2015) A novel mode of lactate metabolism in strictly anaerobic bacteria. *Env Microbiol* **17**, 670–677.
38. Shetty SA, Zuffy S, Bui TPN, *et al.* (2018) Reclassification of *Eubacterium hallii* as *Anaerobutyricum hallii gen. nov. comb. nov*. and description of *Anaerobutyricum soehngenii* sp. nov., a butyrate and propionate producing bacterium from infant faeces. *Int J Syst Evol Microbiol* **68**, 3741–3746.
39. Shetty SA, Boeren S, Bui TPN, *et al.* (2020) Unravelling lactate-acetate and sugar conversion into butyrate by intestinal *Anaerobutyricum* and *Anaerostipes* by comparative proteogenomics. *Env Microbiol* **22**, 4863–4875.
40. Sheridan PO, Louis P, Tsompanidou E, *et al.* (2022) Distribution, organization, and expression of genes concerned with anaerobic lactate-utilization in human intestinal bacteria. *Microb Genom* **8**, 000739.
41. Scott KP, Martin JC, Campbell G, *et al.* (2006). Whole genome transcription profiling reveals genes upregulated by growth on fucose in the human gut bacterium *Roseburia inulinivorans*. *J Bacteriol* **188**, 4340–4349.
42. Reichardt N, Duncan SH, Young P, *et al.* (2014). Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. *ISME J* **8**, 1323–1335.
43. Duncan SH, Belenguer A, Holtrop G, *et al.* (2007) Reduced dietary intake of carbohydrate by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl Environ Microbiol* **73**, 1073–1078.
44. Russell WR, Gratz S, Duncan SH, *et al* (2011). High protein, reduced carbohydrate diets promote metabolite profiles likely to be detrimental to colonic health. *Am J Clin Nutrition* **93**, 1062–1072.
45. Duncan SH, Lobley GE, Holtrop G, *et al.* (2008) Human colonic microbiota associated with diet obesity and weight loss. *Int J Obesity* **32**, 1729–1724.
46. Ley RE, Turnbaugh PJ, Klein S, *et al.* (2006) Microbial ecology: human gut microbes associated with obesity. *Nature* **444**, 1022–1023.
47. Schwiertz AD, Tars D, Schafer K, *et al.* (2010) Microbiota and SCFA in lean and overweight healthy subjects. *Obesity* **18**, 190–195.
48. Le Chatelier E, Nielsen T, Qin J, *et al.* (2013) Richness of human gut microbiome correlates with metabolic markers. *Nature* **500**, 541–546.
49. Woting A, Pfeiffer N, Loh G, *et al.* (2014) *Clostridium ramosum* promotes high fat diet-induced obesity in gnotobiotic mouse models. *MBio* **5**, 1530–1514.
50. Goodrich JK, Waters JL, Poole AC, *et al.* (2014). Human genetics shape the gut microbiome. *Cell* **159**, 789–799.
51. Backhed F, Ding H, Wang T, *et al.* (2004) The gut microbiota as an environmental factor that regulates fat storage. *Proc Nat Acad Sci USA* **101**, 15718–15723.
52. Turnbaugh PJ, Ley RE, Mahowald MA, *et al.* (2006) An obesity associated microbiome with an increased capacity for energy harvest. *Nature* **444**, 1027–1031.
53. Fleissner CK, Huebel N, El-Bary MMA, *et al.* (2010) Absence of intestinal microbiota does not protect mice from diet-induced obesity. *Br J Nutr* **104**, 919–929.
54. Flint HJ (2020) Do my microbes make me fat? Potential for the gut microbiota to influence energy balance, obesity and metabolic health in humans. In '*Why Gut Microbes Matter: understanding our microbiome*, pp. 97–108. Switzerland: Springer-Nature. *Fascinating Life Sciences Series*.
55. Walker AW, Ince J, Duncan SH, *et al.* (2011) Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J* **5**, 220–230.
56. Salonen A, Lahti L, Salojärvi J, *et al.* (2014). Impact of diet and individual variation on intestinal microbiota composition and fermentation products in obese men. *ISME J* **8**, 2218–2230.
57. Ze X, Duncan SH, Louis P, *et al.* (2012) *Ruminococcus bromii* is a keystone species for the degradation of resistant starch in the human colon. *ISME J* **6**, 1535–1543.
58. Ze X, Le Mougen F, Duncan SH, *et al.* (2013) Some are more equal than others: the role of keystone species in the degradation of recalcitrant substrates. *Gut Microbes* **4**, 236–240.
59. David LA, Maurice CF, Carmody RN, *et al.* (2014) Diet rapidly and reproducibly alters the human gut microbiome. *Nature* **505**, 559–563.
60. Ze X, Ben David Y, Laverde-Gomez J, *et al.* (2015) Exceptional starch-degrading activity in the human colonic anaerobe *Ruminococcus bromii* coincides with unique organization of its extracellular enzymes into 'amylosomes'. *MBio* **6**, e01058–15.
61. Mukhopadhya I, Morais S, Laverde-Gomez J, *et al.* (2018) Sporulation capability and amylosome conservation among diverse human colonic and rumen isolates of the keystone starch-degrader *Ruminococcus bromii*. *Environ Microbiol* **20**, 324–336.
62. Ben David Y, Dassa B, Borovok I, *et al.* (2015) Ruminococcal cellulosome systems from rumen to human. *Environ Microbiol* **17**, 3407–3426.

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072

63. Chassard C, Delmas E, Robert C, *et al.* (2010) *Ruminococcus champanellensis sp. nov*., a cellulose-degrading bacterium from human gut microbiota. *Int J Syst Microbiol* **62**, 138–143.
64. Browne HP, Forster SC, Anonye BO, *et al.* (2016) Culturing the 'unculturable' human microbiota reveals novel taxa and extensive sporulation. *Nature* **533**, 543–546.
65. El Kaouturi AE, Armougam F, Gordon JI, *et al.* (2013) The abundance and variety of carbohydrate-active enzymes in the human gut microflora. *Nat Rev Microbiol* **11**, 497–504.
66. Duncan SH, Russell WR, Quartieri A, *et al.* (2016) Wheat bran promotes enrichment within the human colonic microbiota of butyrate-producing bacteria that release ferulic acid. *Environ Microbiol* **18**, 2214–2225.
67. Chung WSF, Walker AW, Bosscher D, *et al.* (2020) Relative abundance of the *Prevotella* genus within the human gut microbiota of elderly volunteers determines the inter-individual responses to dietary supplementation with wheatbran arabinoxylan oligosaccharides. *BMC Microbiology* **20**, 283.
68. Wu GD, Chen J, Hoffmann C, *et al.* (2011) Linking long-term dietary patterns with gut microbial enterotypes. *Science* **334**, 105–108.
69. De Filippo C, Cavalieri D, Di Paolo M, *et al.* (2010) Impact of diet in shaping gut microbiota revealed by a comparative study of children from Europe and rural Africa. *Proc Natl Acad Sci USA* **107**, 14691–14696.
70. Macfarlane GT, Hay S, Gibson GR (1989) Influence of mucin on glycosidase, protease and arylamidase activities of human gut bacteria grown in a 3-stage continuous culture system. *J Appl Bacteriol* **66**, 407–417.
71. Chung WCF, Walker AW, Louis P, *et al.* (2016) Modulation of the human gut microbiota by dietary fibres occurs at the species level. *BMC Biology* **14**, art 3.
72. Chung WSF, Walker AW, Vermeiren J, *et al.* (2019) Impact of carbohydrate substrate complexity on the diversity of the human colonic microbiota. *FEMS Microbiol Ecol* **95** (1), fiy201.
73. Walker AW, Duncan SH, MacWilliam Leitch EC, *et al.* (2005) pH and peptide supply can radically alter bacterial populations and short chain fatty acid ratios within human colonic microbial communities. *Appl Environ Microbiol* **71**, 3692–3700.
74. Duncan SH, Louis P, Thomson JM, *et al.* (2009) The role of pH in determining the species composition of the human colonic microbiota. *Environ Microbiol* **11**, 2112–2122.
75. Wang SP, Rubio LA, Duncan SH, *et al.* (2020) Pivotal roles for pH, lactate, and lactate-utilizing bacteria in the stability of a human colonic microbial ecosystem. *mSystems* **5** (5). https://doi.org/10.1128/msystems.00645-20.
76. Louis P, Duncan SH, Sheridan PO, *et al.* (2022) Microbial lactate utilisation and the stability of the gut microbiome. *Gut Microbiome* **3**, e3 1–16.
77. Gilijamse DW, Hartstra AV, Levin E, *et al.* (2020) Treatment with *Anaerobutyricum soehngenii*: a pilot study of safety and dose response effects on glucose metabolism in human subjects with metabolic syndrome. *NPJ Biofilms Microbiome* **6**, 6.
78. Gillis CC, Hughes ER, Spiga L, *et al.* (2018) Dysbiosis-associated change in host metabolism generates lactate to support *salmonella* growth. *Cell Host Microbe* **23**, 54–64.
79. Kettle H, Louis P, Holtrop G, *et al.* (2015) Modelling the emergent dynamics and major metabolites of the human colonic microbiota. *Environ Microbiol* **17**, 1615–1630.
80. Widder S, Allen RJ, Pfeiffer T, *et al.* (2016) Challenges in microbial ecology: building predictive understanding of community function and dynamics. *ISME J* **10**, 2557–2568.
81. Kettle H, Louis P &Flint HJ (2022) Process-based modelling of microbial community dynamics in the human colon. *J Royal Society Interface* **19**, 20220489.
82. Cremer J, Arnoldini M, Hwa T, *et al.* (2017) Effect of water flow and chemical environment on microbiota growth and composition in the human colon. *Proc Natl Acad Sci USA* **114**, 6438–6443.
83. LaBouyer M, Holtrop G, Horgan G, *et al.* (2022) Higher total faecal short chain fatty concentrations correlate with increasing proportions of butyrate and decreasing proportions of branched chain fatty acids across multiple human studies. *Gut Microbiome* **3**, e2 1–14.
84. Roediger WEW (1980) The colonic epithelium in ulcerative colitis: an energy deficiency disease? *Lancet* **116**, 712–715.
85. Flint HJ, Louis P & Duncan SH (2024) Why does increased microbial fermentation in the human colon shift toward butyrate? *AIMS Microbiol* **10**, 311–319.
86. Lewis SJ, Heaton KW (1997) Increasing butyrate concentration in the distal colon by accelerating intestinal transit. *Gut* **41**, 245–251.
87. Abell GCJ, Conlon MA, McOrist AL (2006) Methanogenic archaea in adult human faecal samples are inversely related to butyrate concentration. *Mic Ecol Health Dis* **18**, 154–160.
88. Dominguez-Bello MG, Costello EK, Conteras M, *et al.* (2010) Delivery mode shapes the acquisition and structure of initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA* **107**, 11971–11975.
89. Claesson MJ, Jeffery IB, Conde S, *et al.* (2012) Gut microbiota composition correlates with diet and health in the elderly. *Nature* **488**, 178–184.
90. Falony G, Joossens M, Vieira-Silva S, *et al.* (2016) Population-level analysis of gut microbiota variation. *Science* **352**, 560–564.
91. Zhernakova A, Kurishilov A, Bonder ML, *et al.* (2016) Population-based metagenomics analysis reveals markers for gut microbiota composition and diversity. *Science* **352**, 565–569.
92. Yatsunenko T, Rey FE, Manary MJ, *et al.* (2012) Human gut microbiota viewed across age and geography. *Nature* **486**, 222–227.
93. Donia MS, Cimermancic P, Schulze CJ, *et al.* (2014) A systematic analysis of biosynthetic gene clusters in the human microbiome reveals a common family of antibiotics. *Cell* **158**, 1402–1414.
94. Hatziioanou D, Gherghisan-Filip C, Saalbach N, *et al.* (2017) Discovery of a novel lantibiotic from *Blautia obeum* A2-162, isolated from the human gastrointestinal tract. *Microbiology* **163**, 1292–1305.
95. Arumugam M, Raes J, Pelletier E, *et al.* (2011) Enterotypes of the human gut microbiome. *Nature* **473**, 174–180.
96. Turpin W, Espin-Garcia O, Xu W, *et al.* (2016) Association of host genome with intestinal microbial composition in a large healthy cohort. *Nat Genet* **48**, 1413–1417.
97. Sidiq T, Yoshihama S & Downs I (2016) Nod2, a critical regulator of ileal microbiota and Crohn's disease. *Front Immunol* **7**, 367.
98. Simren M, Barbara G, Flint HJ, *et al.* (2013) Intestinal microbiota in functional bowel disease: a ROME foundation working team report. *Gut* **61**, 159–176.
99. Udigos-Rodriguez S, Matallana-Gonzalez MC, Sanchez-Mata MC. (2018) Lactose malabsorption and intolerance: a review. *Food Funct* **9**, 4156–4168.
100. Cotillard A, Kennedy SP, Kong LC, *et al.* (2013) Dietary intervention impact on gut microbial richness. *Nature* **500**, 585–588.
101. Schnorr SL, Candela M, Rampelli S, *et al.* (2014) Gut microbiome of the Hadza hunter gatherers. *Nature Commun* **5**, 3654.
102. Blaser MJ (2017) The theory of disappearing microbiota and the epidemic of chronic diseases. *Nat Rev Immunol* **17**, 461–463.
103. Sonnenberg ED, Sonnenberg JL (2019) The ancestral and industrialised gut microbiota and implications for human health. *Nat Rev Microbiol* **19**, 383–390.
104. Sonnenberg ED, Smits SA, Tikhonov M, *et al.* (2016) Diet-induced extinctions in the gut microbiota compound over generations. *Nature* **529**, 212–215.
105. Tannock GW (2023) Understanding of the gut microbiota by considering human evolution: a story of fire, cereals, cooking, molecular ingenuity and functional cooperation. *Mic Mol Biol Rev* **88**, 200127–200122.
106. Konig J, Siebenhaar A, Hogenauer C, *et al.* (2017) Consensus report: faecal microbiota transfer – clinical applications and procedures. *Alim Pharmacol Therap* **45**, 222–239.
107. Petrof EO, Gloor GB, Vanner SJ, *et al.* (2013) Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome* **1**, 3.
108. Lawley TD, Clare S, Walker AW, *et al.* (2012) Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. *PLoS Pathogens* **8**, e1002995.
109. O'Keefe SJD, Li JV, Lahti L, *et al.* (2015) Fat, fibre and cancer risk in African Americans and rural Africans. *Nat Commun* **6**, 6342.

Downloaded from https://www.cambridge.org/core. UNIVERSIDAD AUTONOMA METROPOLITANA, on 17 Nov 2026 at 01:49:10, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/S0029665126105072