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What's eating your food; a high-throughput model of the human microbiome (MiGut)

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The human body hosts a variety of microbes, called the human microbiota, and these microbes play fundamental roles for food digestion and host physiology. It is estimated that there are the same number of microbial cells in and on our body as human cells; however, with the number of microbial genes outnumbering human genes by 150:1, the genetic potential of our microbiome remains largely undiscovered. Furthermore, the microbiome of each individual is unique, contributing towards the variation in population responses towards nutrition, for example.

One of the most important roles of the human microbiota is in food digestion, where foods, such as fibres, are primarily digested by the gut microbiota. Indeed, our diet is the biggest driver of changes to the microbiome. By producing nutritional metabolic products, microbes provide essential nutrients for the host cells and maintain the homeostasis of many bodily systems, such as the immune system. One example is the microbial metabolism of dietary fibres, such as inulin/starch/pectin, into short-chained fatty acids (SCFA). Microbially-produced SCFAs are a really good example of how important the microbiome-host interactions are, as SCFAs help regulate our immune system and are the primary source of energy for colonocytes. Another example of the interaction between nutrition-microbiome-host, is the influence exerted by the microbiota on our nervous system, known as the gut-brain axis. Here, the microbiota converts aromatic amino acids into neurochemicals, which can act both locally and systemically. However, much of the food-microbiota-host interactions remains unknown.

In vitro models of the human colon have been used extensively in developing understanding of the human gut microbiome and how internal and external factors affect the residing microbial populations. Such models can be highly predictive of in vivo effects of probiotics/prebiotics; indeed, more so than animal models. Models that can replicate the physiochemical conditions found in the human digestive system show good correlation of outcomes compared to human studies. These models consist of multiple compartments to mirror the different environmental conditions as you traverse through the digestive tract. However, the complexity of these models limits the number of models that can be run in parallel. On the other hand, single staged models enable multiple models to be run in parallel but lack the spatial bacterial differentiation present in the colon, making them less clinically reflective. There is often a trade-off between process information/control and throughput, and there are currently no scalable platforms which adequately simulate the colonic environment.

We have engineered the MiGut platform, a miniaturised scalable microbial model of the human colon. The MiGut platform consists of four individual triple-staged reactors with each vessel mirroring the physiochemical conditions of the proximal, medial, and distal colon. This system retains the environmental complexity of the human colon but can be scaled to be able test multiple experimental variables with biological replicates in parallel. We have developed a high-throughput DNA extraction and quantitative PCR analysis system coupled with data visualisation and analysis pipelines capable of measuring microbial populations in real-time. The environmental parameters (pH, temperature, flow rate, oxygen content) were streamed live using the Internet of Things (IoT) and visualised using Microsoft Azure and PowerBI cloud-based software.

Using this system, we examined the effects of banana nutrition on the human gut microbiome. Banana nutrition was chosen due to the high

fibre and tryptophan content, and we measured the production of SCFAs and tryptophan-based neurochemicals. On day 0, a faecal slurry was added to each vessel of each reactor, and a complex nutritional media was continuously infused into each reactor; these microbial populations stabilised after approximately 12 days. Bacterial taxonomic analysis by 16S rRNA sequencing showed that the microbial ecologies within each model were very similar to the microbiota slurry input, with little variation between each model. Once the microbial populations stabilised in the system, we switched our media to include powdered banana to represent eating one banana per day. The banana media caused profound changes to the microbial populations; increases in the Lactobacillus spp., Bifidobacterium spp., and Bacteroides spp. Were observed, whilst Clostridium Leptum group decreased.

We used untargeted metabolite analysis by liquid chromatography mass spectrometry (LC-MS/MS) to search for SCFAs and tryptophan metabolites. The switch to banana media, and the changes in the microbial populations, was associated with an increase in some SCFAs, such as butyric acid, lactic acid, and formic acid. The switch to banana media saw an initial increase in free tryptophan levels that quickly decreased during the remainder of the experiment despite continuous addition of banana tryptophan through the media. This was associated with increased levels of tryptophan metabolites, such as 5-hydroxy-L-tryptophan (which is a precursor to serotonin), and indole-based neurochemicals like indoleacetate and indolepropionic acid.

Here, we have engineered MiGut, a colonic model system that replicates the different environmental complexities as you traverse through the colon whilst retaining the scalability for high-throughput analysis. Each environmental parameter of each vessel, i.e. region of the colon, can be adjusted and accurately controlled to reflect the conditions of different diseased states for example. The increase model throughput needed a molecular approach for microbial analysis, and bioinformatic pipelines to handle the data. Using this system, we show the utility of MiGut to study nutrition-microbiota interactions, using banana consumption as an exemplar, and how diet could drive beneficial metabolites for human health.

Biography

Dr Buckley is a lecturer in Food Microbiology and leads the Microbiome & Nutritional Sciences Group at the University of Leeds, UK. His group's research centres on studying the interactions between xenobiotics and microbe, and to leverage this knowledge to influence disease outcome by manipulating the human microbiota through probiotics and prebiotics. His group develops novel high-throughput models of the human digestive tract, including replicating biofilm communities found on teeth and in the colon, to determine the efficacy of novel drugs, biotherapeutics, and nutrition. He is an author on over 40 primary research articles, review articles, editorials, and book chapters.

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