Reconstructing functional networks in the human intestinal tract using synthetic microbiomes
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The human intestinal tract harbors one of the most densely populated and open microbial ecosystems. The application of multi-omics approaches has provided insight into a wide array of complex interactions between the various groups of mainly anaerobic colonic microbes as well as the host–microbe dialogue. Integration of multi-omics techniques in cultivation based experiments that vary in complexity from monocultures to synthetic microbial communities identified key metabolic players in the trophic interactions as well as their ecological dynamics. A synergy between these approaches will be of utmost importance to reconstruct the functional interaction networks at the ecosystem level within the human intestinal microbiome. The improved understanding of microbiome functioning at ecosystem level will further aid in developing better predictive models and design of effective microbiome modulation strategies for health benefits.

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Introduction
The microbes in the colon are in a continuous state of dynamic interactions with the host as well as other microbes. Consequently, microbes play a major role in balancing human health while the human host also has an impact on the survival of microbes [1–3]. The trophic interactions in the intestinal tract facilitate coexistence of complementory species that share the resources derived from consumed food and products generated by the host [4⁴]. Studying the metabolic interactions as well as identifying emergent biosynthetic pathways resulting from multiple interacting species is challenging due to the complexity of the intestinal microbiome that includes over 1000 species of mainly anaerobic bacteria, archaea, and fungi [5].

The colon is the most densely populated site in the human intestinal tract, and an anaerobic fermentative lifestyle is the major physiological characteristic of the high numbers of bacteria and archaea that reside there. These convert the substrates originating from host-associated glycans or dietary fibers and proteins that have not been taken up by the host. Fermentation end products such as short-chain fatty acids (SCFAs), including acetate, propionate and butyrate, as well as medium chain fatty acids (MCFAs), like caproate, and branched chain fatty acids (BCFAs), such as iso-butyrate and isovalerate, play a crucial role in normal host physiology [1,6–9]. This central metabolism in the colon results in a thriving ecosystem giving rise to highly complex and dynamic interactions between the microbes themselves and between the host and microbes. Consequently, diet is considered as a promising avenue for modulating the microbiome for achieving health benefits by supporting the growth of known beneficial microbes [10,11]. However, our understanding of the complex metabolic interactions resulting from different dietary fibers is limited. Finally, understanding the ecological principles governing the assembly, structure, and function of the microbiome under the influence of diet and consequent metabolic interactions have not been studied in detail. Therefore, integrating the ecological information obtained through population level microbiome studies and the physiological information obtained through in-citro and in-vivo studies is vital for reconstructing the functional interaction networks at the community level to design better microbiome modulation strategies.

Reconstructing functional networks using fecal samples
It is important to acknowledge that intestinal microorganisms are not independently growing free-living entities. Information obtained from investigation of a given bacterium in isolation may not represent its natural lifestyle. Therefore, it will be crucial to study bacterial populations as communities by growing multiple bacterial species together in well-controlled settings that mimic the natural ecosystem. Integration of multi-disciplinary approaches will be crucial for improving our knowledge regarding the physiology, interaction networks and role of intestinal microorganisms in human health (Figure 1).
Fecal samples have been widely used in batch and continuous fermentation systems to investigate the fate of dietary fibers and resulting microbial interaction networks. Resistant carbohydrates, which include resistant starch, non-starch polysaccharides (NSP) and oligosaccharides (including pre-biotics, e.g. fructo-oligosaccharides, galacto-oligosaccharides), are important determinants of microbial composition and function [6,10,12,13]. Mucus-derived glycans are another important growth and energy source, and their utilization has major implications for host health as mucus acts as a barrier against pathogen invasion [14,15,16]. Most of our understanding of the microbial metabolic interactions has been derived from investigating faecal samples by metagenomic and to some extent by metatranscriptomic and metaproteomic approaches. These have been used for both in-vivo and in-vitro anaerobic fermentation systems. Inoculation of in vitro anaerobic fermentation systems containing different carbohydrates has revealed a predominance of Bacteroides species [17]. Several Bacteroides species are capable of utilizing diverse carbohydrates and thus are considered to be one of the most metabolically versatile groups in the human intestinal tract. Dietary interventions in humans and subsequent molecular analysis of fecal samples have revealed phylotypes related to Ruminococccae as dominant groups in resistant starch utilization, whereas phylotypes related to Lachnospiraceae were dominant in NSP degradation [18]. A recent dietary intervention study investigating the effect of resistant starch 2 (RS2) in human subjects included metagenomics and observed that Ruminococcus bromii contributed the majority of the key genes for RS2 degradation, further validating its role as a key degrader of resistant starch [19,20]. A major challenge in reconstructing microbial interaction networks using fecal samples is the presence of a large number of unknown functions that have not been annotated well. In natural samples, the unknown contribution of bacteriophages, and the high variability across different inocula pose major challenges in deciphering the microbial interactions. Moreover, the role of uncultured microorganisms in governing ecological outcomes via hitherto unknown interactions makes predictive modelling a challenging activity. Finally, most currently employed sequencing-based molecular...
Reconstructing functional networks using cultured microorganisms from the human intestinal tract

Specialist bacteria capable of degrading complex dietary fibers and mucus are key players in the community as they provide simple carbohydrates for other microbes in the community. Known examples of such bacteria are *R. bromii*, *Eubacterium rectale* and *Bacteroides thetaiotaomicron* capable of degrading complex polysaccharides, and *Akkermansia muciniphila*, *Barnesiella intestinalis* and *Bacteroides caccae* that are capable of degrading mucus [20, 25, 26, 27, 28]. An experimentally verified metabolic interaction network is the one between *A. muciniphila* and butyrate producers *Anaerostipes haliotis* and *Eubacterium hallii*, and *Faecalibacterium prausnitzii* [14]. The butyrate producers benefitted from simple sugars released from mucus by *A. muciniphila*, and in turn *A. muciniphila* benefitted from the *E. hallii*-mediated production of vitamin B12, an important co-factor in the propionate biosynthesis pathway.

In-vitro growth assays have identified polysaccharide-degrading bacteria that utilize the dietary carbohydrates reaching the colon undigested. For example, resistant starch can be utilized by *R. bromii* and *E. rectale*, sylan can be utilized by *Bacteroides intestinalis*, *Bacteroides ovatus*, *Bacteroides dorei*, *Bacteroides cellulosolyticus*, *Bacteroides xylanisolvens* and *Roseburia intestinalis*, whereas pectin can be used by *B. ovatus*, *B. thetaiotaomicron*, some strains of *F. prausnitzii*, *Eubacterium eligens* and *Lachnospira pectinoschiza* [6, 20, 29–31]. Co-culture experiments combining degraders and non-degraders have revealed interesting cross-feeding pathways, such as utilization of lactate to produce butyrate or propionate [32]. This has allowed reconstructing the dominant metabolic pathway starting from degradation of dietary carbohydrates to production of dominant SCFAs detected in feces *viz.* acetate, butyrate, and propionate. Formate and lactate are known intermediates of microbial fermentation but are detected in low amounts in feces. Conversion of formate produced by amylolytic bacteria (*R. bromii*) to acetate by an acetogen (*Blautia hydrogenotropha*) has been recently shown to be a contributing factor for high amounts of acetate [33]. Potential emergent properties that are related to biosynthetic pathways for amino acid, vitamin and co-factor metabolism and other non-central metabolic pathways have been identified using RNA-sequencing in both *in vivo* and *in vitro* co-culture experiments [33–37]. However, the influence of regulation of secondary biosynthesis pathways in the presence of interacting partners and subsequent impact on the overall community level functional interaction network is largely unknown. Therefore, there is a need to incorporate high complexity in terms of phylogenetic and functional diversity in experiments aimed at reconstructing the functional interaction network in the human intestinal tract.

Leveraging the concept of minimal microbiomes for reconstructing functional networks of the human intestinal microbiome

One approach to better understand the microbial interaction networks and develop predictive modelling tools is to grow microorganisms in combinations as co-, tri- or even more complex cultures, building up to create a consortium of microorganisms that could be representative of a functioning minimal microbial community of the human intestinal tract. The first attempt at developing a defined microbial community in a host was done in 1965 by Russell W. Schaedler et al., who composed the ‘Schaedler flora’ comprising five dominant bacterial isolates in mice [38]. The ‘Schaedler flora’ was further modified to include three more isolates. This Altered Schaedler flora (ASF) has been widely used to study the relationship between the murine host and intestinal microbiota [39, 40]. A proof of concept study showed the applicability of the ASF in therapeutically modulating the murine host metabolism as to decrease intestinal ammonia levels as the eight bacteria that make up the ASF have a minimal urease gene content [41].

A number of other defined microbial communities have been designed to investigate microbial interactions, develop predictive models and study specific hypotheses such as conferring colonization resistance (CR) against pathogens in a host (Table 1). The complexity of these defined microbial communities ranges from 2 to 33 bacterial isolates while the selection is often based on characteristics such as dominance and prevalence. These defined microbial communities can be considered as a minimal microbiome, a term coined previously to describe the smallest set of microbes and/or microbial functions needed to develop a stable community [42]. These minimal microbiomes allow researchers to gain mechanistic insights regarding several aspects of host-microbiome and within microbiome interactions [26, 43, 44, 45]. The recently developed Minimal
### Table 1

<table>
<thead>
<tr>
<th>Original host of bacterial isolates</th>
<th>Defined intestinal microbial communities</th>
<th>No. of isolates</th>
<th>Selection approach</th>
<th>Application(s)</th>
<th>Ref(s)</th>
</tr>
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<tbody>
<tr>
<td>Human</td>
<td>Microbial Ecosystem Therapeutic (MET)</td>
<td>33</td>
<td>Cultivation of bacteria from donor feces. Screened for antibiotic resistance. Susceptible isolates chosen representing Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria.</td>
<td>Proposed alternative to fecal transplant by repopulating the intestinal tract with defined bacterial communities representative of the normal microbiota.</td>
<td>[52**]</td>
</tr>
<tr>
<td>Synthetic Gut Community (SGC-1)</td>
<td></td>
<td>3</td>
<td>Isolated from human feces, abundant with genome sequence available. Faecalibacterium prausnitzii and Roseburia intestinalis were chosen for ability to produce butyrate, while Blautia hydrogenotrophica was chosen for its ability to utilize CO\textsubscript{2} and H\textsubscript{2} apart from its ability to produce acetate. All belong to Firmicutes.</td>
<td>A minimal model to investigate interactions between the intestinal bacteria as well to develop predictive models for community dynamics.</td>
<td>[50**]</td>
</tr>
<tr>
<td>Synthetic Human Gut Microbiome Communities</td>
<td></td>
<td>12</td>
<td>Isolated from human feces and chosen to cover major functions and phylogenetic diversity present in the human intestinal tract. The community has representatives from phyla Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria.</td>
<td>Useful for developing predictive models for microbial community dynamics as well as investigate microbial interactions involved in community assembly.</td>
<td>[51**]</td>
</tr>
<tr>
<td>Model 15-member human gut microbiota</td>
<td>Synthetic Microbiota (SM)</td>
<td>14</td>
<td>Genome sequenced human intestinal isolates representing the five dominant phyla Bacteroidetes, Firmicutes, Actinobacteria, Verrucomicrobia, and Proteobacteria and ability to carry out important core metabolic functions such as mucus and dietary fiber degradation as well as short chain fatty acid production.</td>
<td>Used for investigating the spatial organization of the key intestinal tract bacteria at different scales. Effect of dietary fiber deprivation was investigated along with its effect on mucus layer.</td>
<td>[53] [28**]</td>
</tr>
<tr>
<td>Mice</td>
<td>Oligo-Mouse-Microbiota (Oligo-MM\textsuperscript{12}) plus Facultative anaerobes (FA\textsuperscript{3})</td>
<td>15</td>
<td>Bacterial isolates cultivated from the specified pathogen-free (SPF) mice. Isolates representative of most prevalent and abundant phyla Bacteroidetes, Firmicutes, Actinobacteria, Verrucomicrobia, and Proteobacteria.</td>
<td>The Oligo-MM\textsuperscript{12} was tested for its ability to confer colonization resistance against Salmonella enterica serovar Typhimurium. Incorporating three isolates of FA\textsuperscript{3} provided colonization resistance similar to the conventional complex mice microbiota initially used to create gnotobiotic mouse.</td>
<td>[43**] [38]</td>
</tr>
<tr>
<td>Schaedler flora (SF)</td>
<td></td>
<td>5</td>
<td>Dominant bacteria isolated from mice. Aerobic and aerotolerant anaerobic bacteria.</td>
<td>Widely used for investigating mechanisms host-microbiota relationship as well as microbe–microbe interactions.</td>
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<td>Altered Schaedler flora (ASF)</td>
<td></td>
<td>8</td>
<td>Modified version which included ASF356 (Clostridium sp.), ASF360 (Lactobacillus intestinalis), ASF361 (Lactobacillus murinus), ASF457 (Mucispirillum schaedleri), ASF492 (Eubacterium plexicaudatum), ASF500 (Pseudoflavonifractor sp.), ASF502 (Clostridium sp.) and ASF519 (Parabacteroides goldsteinii)</td>
<td></td>
<td></td>
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<td>[39,54,**,55]</td>
<td></td>
<td>7 out of 8 original strains</td>
<td>Parabacteroides goldsteinii (ASF519) ASF356 (Clostridium sp.), ASF361 (Lactobacillus murinus), ASF457 (Mucispirillum schaedleri), ASF492 (Eubacterium plexicaudatum), ASF500 (Pseudoflavonifractor sp.), ASF502 (Clostridium sp.) Missing strain was ASF360 Bacteroidetes, Firmicutes, Verrucomicrobia, Proteobacteria, Actinobacteria representative of strains enriched in mouse.</td>
<td>Original ASF strains were maintained in laboratory mice. Proportional abundances varied in the host and had minimal urease activity. This ASF was demonstrated to treat hyperammonemia in mouse model and hyperammonemia in the Altered Schaedler flora model. Update to the Altered Schaedler flora. Highly representative of mouse gut microbiome and can be used for studying microbe-microbe and host–microbe interactions.</td>
<td>[41**] [46**]</td>
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Bacteriome (MIBAC-1) consisting of 18 mouse-derived bacterial strains is an example of one such minimal microbiome and may replace the ASF in future studies of the mouse microbiome. From the extensive culture collection of mouse intestinal microorganisms, a minimal bacterial consortium (Oligo-MM1²) was designed to investigate CR against Salmonella enterica serovar Typhimurium [43**,46**]. In-vivo experiments with Oligo-MM1² revealed the importance of facultative anaerobes in improving CR. These two studies demonstrated the importance of combining large scale culturing approaches and multi-omics to investigate mechanisms of host–microbe interactions.

When designing a minimal microbiome, it is important to consider the major factors influencing the intestinal microbiome. For example, diet is a major source of carbon and energy and other nutrients required for growth for intestinal bacteria, alongside host-derived compounds such as mucus. Diet, especially components that cannot be digested by the host, influence the composition and metabolic (fermentation) activity of the microbiome [2,18,47]. For instance breakdown of starch and fructooligosaccharides results in cross-feeding not only via the partial breakdown products of complex substrates but also due to the fermentation end products (lactate and acetate) produced by primary degraders and consumed by butyrate-producing bacteria [48]. High functional redundancy, especially with regards to the butyrate producers using monosaccharides leads to competition for resources in the intestinal microbiome [49]. Recently, two studies used synthetic communities to model community dynamics and metabolic interactions between dominant and prevalent human intestinal bacteria [50**,51**]. Investigation of pair-wise interactions and community dynamics of a consortium of 12 human intestinal bacterial strains was used to build predictive models of community assembly and co-existence [51**]. Using a combination of mathematical modelling, culturing, metabolite measurements, and transcriptomics of a three species synthetic community, an emergent metabolic behavior was identified in F. prausnitzii, which downregulated the B12 production pathway due to its availability from partners in the tri-culture [50**]. The design of the three species synthetic community incorporated both potential cross-feeding as well as competitive interactions thereby allowing the investigation and predictive modelling of metabolic interactions driving such ecological interactions [50**].

**Conceptual understanding for the design of minimal microbiomes**

Complex ecological processes determine the successful assembly of microbial communities, and thermodynamic constraints, metabolic pathways, and regulatory circuits play a major role in successful survival and propagation at the level of individual microbial cells [56,57]. Therefore, integrating these features in top-down and bottom-up approaches for the design of minimal microbiomes is essential. The latter approach would involve understanding the metabolic roles played by each of the bacteria identified in the human intestinal microbiome. The size and complexity of a minimal microbiome can be tuned to address two main broadly defined aims, that is, 1) unravelling metabolic interactions, 2) investigating key ecological concepts. For example, lactate and acetate are produced as a result of fermentation and breakdown of polysaccharides by bacteria such as E. rectale, R. bromii or Bifidobacterium spp. and they can be subsequently used by E. hallii and related species to produce butyrate [58,59*]. Two-species systems have been used in order to understand trophic metabolic interactions addressing polysaccharide degradation and butyrate production [60,61*]. Similarly, trophic metabolic interactions between mucus degraders and butyrate producers have been studied using two-species systems [14*]. The two-species systems can be upgraded to incorporate ecosystem processes of competition, by including two competing polysaccharide degraders, and two butyrate producers that compete for polysaccharide breakdown products. Such four-species cultures can be used to investigate pairwise species competition and complementarity as well as metabolic inter-dependencies. To address specific ecological concepts, the design should aim at higher complexity to more comprehensively mimic the human intestinal microbiome. For example, to investigate the effect of functional redundancy on community assembly, selection of bacterial species that have functional overlap at different trophic levels will be crucial. Ecophysiology guided approaches that incorporate the knowledge of physiology, metabolic potential of each species with their ecological roles, and properties such as prevalence, dominance and rarity will be important in the rational design of minimal microbiomes that mimic natural ecosystems.

**Challenges, opportunities, and future prospects**

**Several bacteria remain uncharacterized**

There exists a major lacuna in our understanding of the metabolic roles of individual species, especially of some core species such as Subdoligranulum variable, Coprococcus eutactus, Lachnospira pectinoschiza and members of Dialister and Collinsella, to just name a few. In addition to these, bacteria related to the genus Oscillibacter, uncharacterized Lachnospiraceae and uncharacterized Ruminococcaceae have been cultured and sequenced as part of the human microbiome project, MetaHIT reference genomes, Cultural Genome Reference (CGR) and Human Gastrointestinal Bacteria Culture Collection (HBC) and are consistently identified in molecular profiling studies of the microbiome [62–65]. However, due to a lack of metabolic characterization, their roles in the community remain elusive. In addition to the cultured bacterial species, there remain a few key bacterial groups that
have not yet been grown as pure cultures, one example being *Oscillospira* and related bacteria [66,67]. While high-throughput cultivation strategies, also termed culturomics, have achieved success in cultivating a claimed >70% of the human intestinal bacteria, isolation of some key species will require more targeted approaches [68]. These approaches will require integrating the knowledge of their ecology and predicted nutrient requirements based on metagenome-assembled genomes.

Using *in-silico* approaches to model and predict microbial community level interactions and dynamics has received considerable interest [69–71,72]. However, a major challenge with the currently available bioinformatics tools is the accuracy of functional annotations for genomes and metagenomes. Improvements in the accuracy of genome annotation tools will be crucial for metabolic modelling approaches that are used to simulate and predict microbial interactions in defined as well as natural communities. Recently, a large number of semi-curated constraint-based metabolic models of human intestinal bacteria were created [73]. These models are now being used to investigate microbial interactions in communities as well as in pairs of microorganisms [74]. A graph theory-based approach employing metabolic networks to identify species complementarity and competition is also available [75]. Results and observation of both constraint-based metabolic models and graph theory-based metabolic networks are only as good as the functional gene annotation that the current bioinformatics tools provide. A major challenge is to annotate transporter genes, which encode key functions that influence the accuracy of *in-silico* prediction of microbial interactions [73,76]. By integrating multi-omics data and physiological studies, metabolic models have been developed for *A. muciniphila* (iAkK-Muc_588), *F. prausnitzii* (iFPraus_c1l.0), *Bacteroides thetaiotaomicron* (iBth1201), *Eubacterium rectale* (iErc400), and the methanogen *Methanobrevibacter smithii* (iMsii385) [77–79]. Focus on developing improved metabolic models for these and other core microorganisms will be crucial for improving the accuracy of our understanding of the metabolic interaction networks and predictive modelling, involving the designing of minimal microbiomes with known ecophysiological properties.

**Minimal microbiome(s) to understand the intricacies of the intestinal microbiome**

Minimal microbiomes will be crucial for unravelling active metabolic networks and potential interactions which may be hidden due to the extensive technical noise and several unknowns in the studies based on natural communities (for e.g. feces). Minimal microbiomes allow for studying emergent metabolic behaviors that could explain the evolution of co-operation and competition between the microbial members [26,45,50,51]. There still remains a wide-open field for similar studies investigating several combinations of core and non-core species to address diverse research questions. Multi-species interactions, which incorporate competition for mucus or dietary fiber breakdown products and other nutrients, and potential emergent properties of these interactions have not been investigated. Importantly, the effect of diet and mucus degrading key stone species on the overall community dynamics remains understudied. We propose that future development of minimal microbiomes should address these questions by designing-specific minimal microbiomes. For instance, to investigate the ecological and metabolic interaction dynamics in the mucus layer, a mucus-based minimal microbiome which could include mucin degraders and other co-occurring bacteria can be designed.

The understanding of ecophysiological features of natural microbiomes using minimal microbiomes can have far reaching implications in the design and development of therapeutics. More than two decades ago, a mixture of ten different facultative aerobic and anaerobic bacterial strains was shown to inhibit *Clostridioides difficile* in five patients suffering from chronic relapsing diarrhoea [80]. Years later, a defined consortium of 33 bacterial strains (MET-1) has shown potential in treatment of *C. difficile* infections [52]. However, the mechanism of action of these live therapeutics is unknown. Therefore, investigation of host–microbe interaction dynamics will be crucial for unravelling the mechanism of action of such minimal microbiomes. Development of predictive models for *in-situ* behavior of minimal microbiomes will be necessary for achieving effective therapeutic success in humans. Designing minimal microbiomes with defined functional outputs, such as the production of butyrate, sequestering of ammonia, or synthesis of vitamin B12, holds a promise for targeted intervention strategies. In addition to these live microbial therapeutics, cell-free supernatants with bioactive metabolites can be produced in industrial scale fermenters using minimal microbiomes to mimic the natural extracellular components in the human intestinal tract.

**Conclusions/outlook**

The last few years have seen a rise in studies that move forward from mere associations to identifying mechanisms of how microbes influence host health. One of the major focus areas has been the understanding of metabolic interactions and ecological dynamics. Moving forward from co-cultures and tri-cultures, the studies employing minimal microbiomes are expected to provide deep insights that are relevant at the ecosystem level. Synergy between culture independent and dependent experimental approaches driven by specific hypotheses is expected to play a crucial role in advancing our knowledge of microbial communities associated with human and animal hosts and for developing effective microbiome modulation strategies.
Conflict of interest statement
Nothing declared.

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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

● of special interest
●● of outstanding interest


This work elegantly describes the active microbial members involved in starch fermentation using RNA-based stable isotope probing.


On the basis of known co-occurrence relationships from molecular surveys, this study reconstructs the functional interactions between key mucus degraders and butyrate producers.


Using multi-omics approach, this study describes the key role of *R. bromii* in resistant starch degradation and the subsequent cross-feeding by butyrate producers as well as *H2* scavenging bacteria.


This study uses a human derive minimal microbial community to study the effect of dietary fiber deprivation on the host health using a mouse model. A good example of application of defined microbial community to study host-microbe interactions.


A proof of concept study which demonstrated the applicability of defined bacterial consortia to treat hyperammonemia in mice.


This study elegantly demonstrates the design of a mice minimal microbiome that confers colonization resistance comparable to that of a conventional mice microbiota. It also shows the importance of facultative anaerobes in the intestinal tract as their inclusion was vital for improved colonization resistance.


An extensive collection of microbes isolated from mice which may be used to replace altered Schaedler Flora. Report a wide array of growth conditions for capturing large bacterial diversity in culture. Additionally, one minimal consortia of mice-enriched bacterial strains are designed.


The authors used a simplified three-species bacterial community and tested the influence of partners on growth. The authors developed a mathematical model which could predict the tri-culture community dynamics using data obtained from bi-culture growth experiments. Integration of transcriptomics allowed the authors for identifying emergent behavior in F. prausnitzii which downregulated the B12 production pathway due to its availability from partners in tri-culture.


Using a defined microbial community of 12 species, the authors decipher microbial interactions and build predictive models which demonstrate the importance of pairwise interactions as drivers of multi-species community dynamics.


This study elegantly demonstrates the potential for using defined bacterial communities as alternative to fecal microbiota transplant in curing antibiotic-resistant Clostridium difficile infection.


The authors employ a systems level approach to elucidate the metabolic interactions between the members of the altered Schaedler flora (ASF). The authors make well-designed use of in vitro mono-culture and co-culture growth assays, constraint based genome scale metabolic models and metabolomics to developed a Constant Yield Expectation Model. This is a promising approach for elucidating interspecies interactions and developing predictive modeling for microbial communities.


First study to demonstrate the role of lactate as a key cross-feeding metabolite between a starch-degrading species and butyrate producers in human intestinal tract.


This study elegantly shows which of the key intestinal tract bacteria can utilize which of the common complex polysaccharide as well as the effect of chain length on the ability of bacteria to degrade these fibers.


Creation of first systems-based community level microbe–microbe and microbe–host metabolic interaction network.


Largest collection of semi-curated genome scale metabolic models (GEMs). These GEMs provide a starting point for modelling metabolic interaction networks at different scale from two species to community-level.


An *in-silico* toolbox for simulating pairwise microbe–microbe and host-microbe interactions using constrained-based metabolic models. This toolbox allows for integrating metagenomics data to reconstruct community level microbial interactions.


Earliest report of treating chronic relapsing *Clostridium difficile* diarrhea using a defined consortia of bacterial strains.