

Applying the design-build-test paradigm in microbiome engineering

Hoang Long Pham^{1,2,*}, Chun Loong Ho^{1,2,*}, Adison Wong^{1,2,*},
 Yung Seng Lee^{2,3} and Matthew Wook Chang^{1,2}



The recently discovered roles of human microbiome in health and diseases have inspired research efforts across many disciplines to engineer microbiome for health benefits. In this review, we highlight recent progress in human microbiome research and how modifications to the microbiome could result in implications to human health. Furthermore, we discuss the application of a 'design-build-test' framework to expedite microbiome engineering efforts by reviewing current literature on three key aspects: design principles to engineer the human microbiome, methods to engineer microbiome with desired functions, and analytical techniques to examine complex microbiome samples.

Addresses

¹ Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, 117596, Singapore

² NUS Synthetic Biology for Clinical and Technological Innovation (SynCTI), Life Sciences Institute, National University of Singapore, 117456, Singapore

³ Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, 119074, Singapore

Corresponding author: Chang, Matthew Wook (bchcmw@nus.edu.sg)

* These authors contributed equally to this work.

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Introduction

Recent discoveries on the roles of the human gut microbiome in health and diseases have inspired novel means for prophylactic and therapeutic intervention against disease onset and progression. The engineering of human microbiome for health benefits and related applications could be observed across many disciplines in nanotechnology, chemistry, and biology. Nanoscale instruments are being fabricated to interface with human microbiome for real-time monitoring of health status, or for on-site protection against early disease onset [1]. Chemical microbiome modifiers, such as prebiotics, probiotics,

and antibiotics, have long been prescribed by doctors for disease treatment [2]. With the advent of DNA sequencing and metabolomics tools allowing data analysis at higher resolution and throughput, interests to develop biological modifiers for *in situ* precision engineering of the human microbiome are increasingly gaining momentum [3,4*,5]. Synthetic biology envisages microbiome engineering as one of the grand frontiers of precision medicine. Genetic programs have been installed into single-species microbial communities to perform diagnostic and therapeutic operations, such as regulating glucose level in the blood, or detecting liver metastasis in urine [6,7]. Alongside these developments, there is emerging global interest to expand the said conceptual frameworks for the development of synthetic cellular consortia that could enable targeted engineering of the human microbiome and deliver the corresponding health benefits [5]. The 'design-build-test' (DBT) cycle is an engineering paradigm that is widely practiced among engineering disciplines for the design of experiments and the rational optimization of technology. In this review, we aim to demonstrate how the DBT cycle can be strategically applied to expedite microbiome engineering efforts. To support this proposition, we herein assess the status of human gut microbiome engineering with a focus on three key aspects: design principles to engineer the human microbiome, methods to reassemble microbiome with desired functions, and analytical techniques to examine complex microbiome samples.

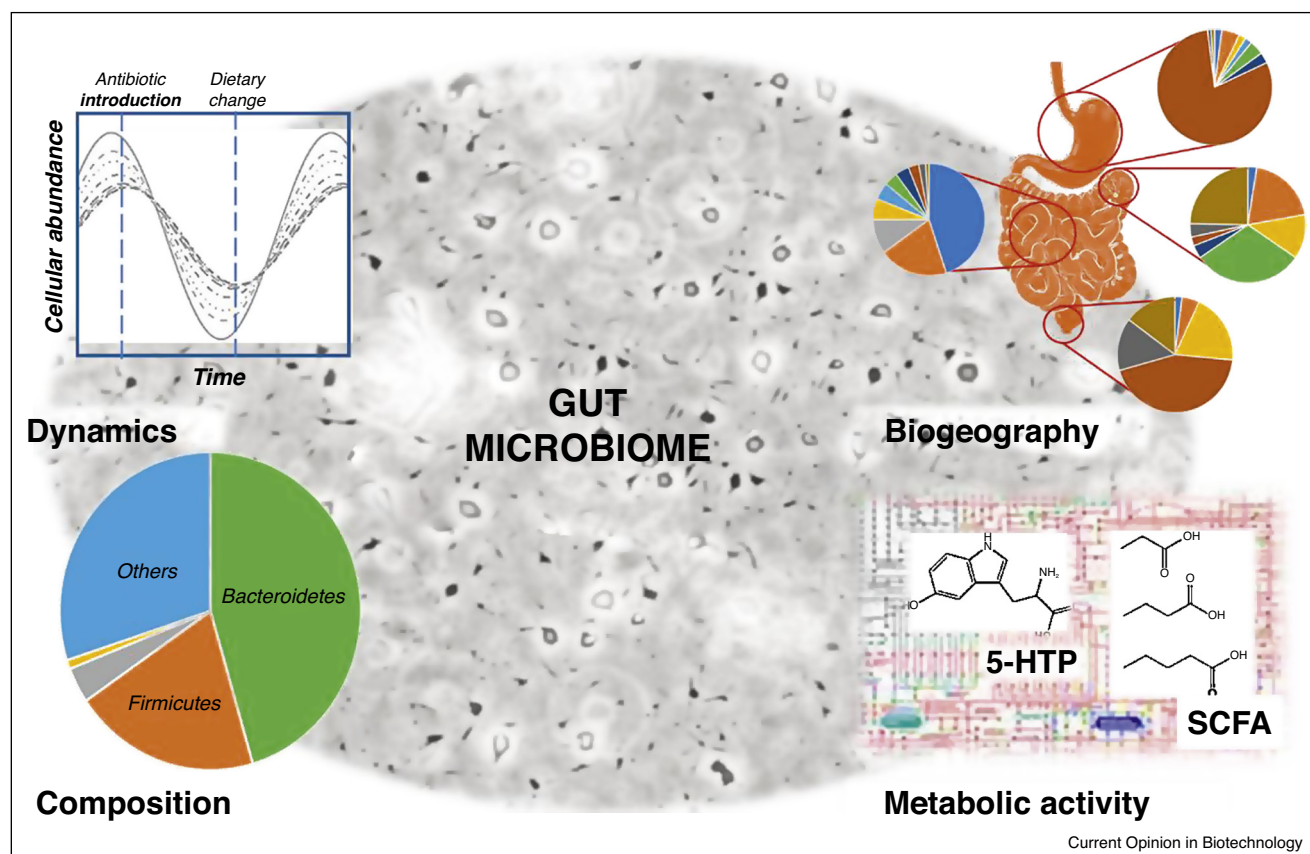
Design

Harnessing the design principles of natural microbiome represents a pioneering step for rational microbiome engineering. In this section, we review the current knowledge on fundamental design features of natural human gut microbiome, including the composition and dynamics, biogeography, and metabolic activity (Figure 1). Examples illustrating the application of these understanding to modify microbiome are presented.

Composition and dynamics

The analysis of gut microbiome composition and dynamics at various stages of life has continued to shed lights on their regulatory roles in health and diseases, leading to potential therapeutic strategies. In newborns, the founding gut microbial community is volatile and profoundly influenced by delivery modes, host genetics, diet transitions, and antibiotic usage [8–10]. On the contrary, in

Figure 1



The design principles of human microbiome.

The complex biology of human gut microbiome has been investigated in various aspects, including composition and dynamics, biogeography, and metabolic activity. Taxonomic composition of gut microbiota is volatile in newborns [8–10], but longitudinally stable in adult for up to 5 years [12**]. Microbial signatures of diseases could be inferred by comparing microbiota composition of healthy and unhealthy individuals [14–19]. Environment factors, such as antimicrobial level, nutrient availability, pH, and oxygen, affect the distribution of dominant species across the human gastrointestinal tract, leading to unique regulation of host biology at specific niches [20,22,23,24**]. Metabolic activity of gut microbes also exerts cross-kingdom communication with human host, such as signaling cascades involved in gut–brain interactions [25,26,27**].

healthy adults, large-scale analyses have revealed remarkable intrapersonal stability of gut microbiota compositions despite their large interpersonal variation [11**]. A study involving long-term tracking of human fecal contents reported a ~60% conservation of microbiota members in a diet-controlled cohort over 5 years [12**]. By analyzing the discordance of taxonomic composition between unhealthy individuals and healthy controls, microbial signatures of disease manifestation (dysbiosis) could be inferred. In an early study, Turnbaugh *et al.* demonstrated the association between a major shift in relative abundance of *Bacteroidetes* and *Firmicutes* and the increased capacity of obese phenotypes to harvest energy from diet, implying the critical roles of these bacterial divisions in obesity pathophysiology [13]. In immunology, correlation was drawn between the low abundance of specific genera (*Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*) and high risk factor in childhood asthma, possibly due to enterohepatic

metabolites dysregulation [14]. More recent studies reported the protective effects of *Clostridia* species against food allergen sensitization, or the contribution of *Lactobacillus* and *Bifidobacterium* abundance in resistance against *Plasmodium*-induced malaria infection [15,16]. Notably, Pedersent *et al.* integrated human phenotypes, serum metabolome, and gut microbiome datasets to identify and validate *Prevotella copri* as the driving species that induce insulin resistance in human host via branched-chain amino acids biosynthesis regulation [17]. Carcinogenesis amplification or mitigation effects of specific ‘oncomicrobes’ have been extensively reported and reviewed [18]. Studies on the influence of gut microbiome in aging are ongoing. For instance, a recent phylogenetic analysis comparing microbiota composition between various age groups (adults, elderly, centenarians, and semi-supercentenarians) revealed the enrichment of a health-associated symbiotic cocktail uniquely present in long-living human subjects [19].

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