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Engineering insect–microbe symbiosis: synthetic microbial communities for sustainable insect management

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Insect–microbe symbiosis enables innovative modulation of insect biology via gut microbiota engineering. Synthetic microbial communities enhance pathogen resistance, nutrient provisioning, and host fitness. Engineering components of insect microbiomes enables precise manipulation of insect–microbe dynamics, advancing ecofriendly pest control and beneficial insect conservation while addressing biosafety and stability challenges.

Insect–microbe symbiosis: a new frontier for intervention

Insects, as a pivotal taxonomic group, play multifaceted roles in sustaining ecological integrity and human welfare. Beneficial insects, such as bees, serve as indispensable pollinators essential for crop reproduction and global food security. Parasitoid insects function as natural biocontrol agents by regulating agricultural pest populations through host–parasite interactions. Conversely, hematophagous pests like mosquitoes vector various diseases, including malaria and dengue fever, posing substantial public health threats, while phytophagous insects continually cause extensive crop damage, aggravating food security issues. Current pest management heavily relies on chemical insecticides, yet their indiscriminate application promotes resistance and environmental contamination. Simultaneously, beneficial insect populations face drastic declines due to habitat disruption and anthropogenic disturbances, undermining ecosystem integrity. This dichotomy underscores the urgent need for innovative approaches and precision technologies to mitigate pesticide dependence while enhancing ecological balance [1].

There is a rich history of research exploring the symbiotic relationships between insects and microorganisms. Insects and bacteria share a profound evolutionary history, giving rise to diverse symbiotic modalities encompassing intracellular endosymbionts, gut-associated microbiota, and ectosymbionts, which originate through distinct evolutionary trajectories. These symbionts significantly enhance host fitness through nutrient provision, detoxification, reproductive modulation, and pathogen defense [2,3] (Figure 1A). Insect gut symbionts have been explored as tools for interfering with disease transmission and enhancing insect health. For example, administering lipase-producing *Serratia ureilytica* YN1 in mosquitoes can significantly suppress *Plasmodium* development. Acetate-producing microbes restore metabolic homeostasis, and the interplay between *Lactiplantibacillus* and *Acetobacter* enhances pathogen resistance through ecological cooperation in *Drosophila* [4,5]. Given their close association and functional diversity, microbial symbionts represent a promising frontier for insect intervention strategies.

Synthetic gut microbiota as tools for insect manipulation

Although natural gut symbionts have been widely explored for insect interventions, their functional precision and applicability remain limited. Recent studies have focused on using synthetic biology to engineer insect gut microbes. For example, the symbiotic bacterium *Serratia* AS1 was genetically engineered for secretion of anti-*Plasmodium* effector proteins, and the recombinant strains effectively render mosquitoes resistant to malaria parasite infection [6]. Recently, the symbiotic bacterium *Serratia* AS1 has been engineered to simultaneously produce anti-*Plasmodium* and anti-arbovirus effector proteins controlled by a stringent blood-induced promoter. These multifunctional engineered symbiotic strains effectively inhibit *Plasmodium* infection in *Anopheles* mosquitoes and both dengue and Zika virus infections in *Aedes* mosquitoes [7]. Similarly, engineered *Snodgrassella alvi* expressing double-stranded RNA modulates honeybee gene expression and pathogen resistance [8,9].

Natural microbiomes are dynamic and exhibit complex interactions. Insect microbiomes are not only temporally and spatially dynamic, but are also characterized by intricate host specificity shaped through long-term coevolutionary adaptation (Figure 1A). Their composition varies substantially across developmental stages, dietary regimes, and environmental exposures. In eusocial species, this complexity is further compounded by caste-specific microbiota, mediated by trophallaxis, diet sharing, and microhabitat heterogeneity [2,5]. Thus, the microbial communities associated with insects represent some of the most evolutionarily refined and ecologically intricate symbiotic systems in nature, demanding a paradigm shift from single-strain interventions to synthetic consortia engineering.

Synthetic microbial communities (SynComs) are rationally designed microbial consortia that integrate taxa with complementary functions to emulate or enhance natural microbiome dynamics. They achieve functional robustness through modular architectures, where niche partitioning, metabolic cooperation, and redundancy enable dynamic adaptation to environmental and host-derived perturbations. These engineered ecosystems can

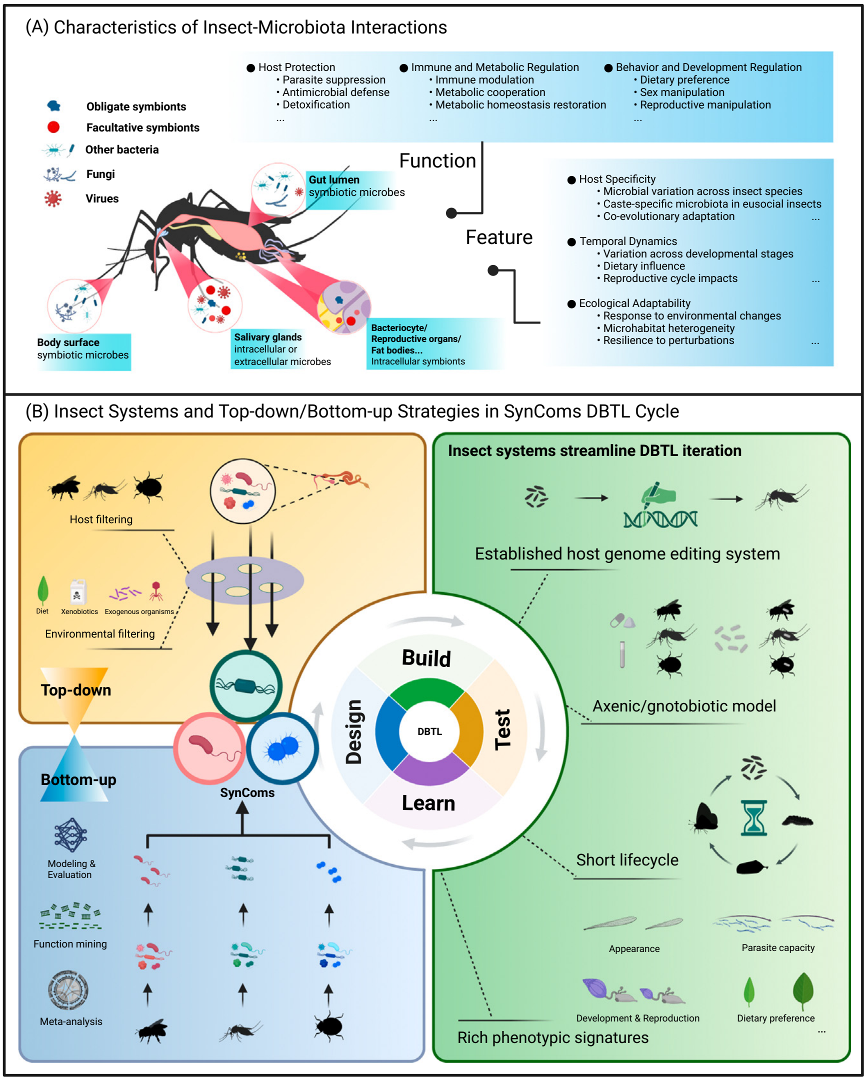

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Figure 1. Insect–microbe interactions and the design–build–test–learn (DBTL) cycle for synthetic microbial community research in insect systems. (A) Symbiotic microbes are closely associated with insects, inhabiting various tissues such as the gut, reproductive organs, salivary glands, body surface, and others, where they play key roles in host protection, immune regulation, and metabolic cooperation. These microbes exhibit host specificity, stage-dependent variation, and adaptability to environmental changes. (B) The DBTL cycle advances synthetic microbial community research through iterative Build, Design, Test, and Learn phases. Top-down insect host and environmental filtering optimizes symbiotic microbe selection. Bottom-up meta-analysis, function mining, modeling, and evaluation enable deliberate selection and synthesis of effective microbes for insect hosts. Insect systems, with mature gene editing, established axenic and gnotobiotic technologies, short life cycles, and rich phenotypes, streamline DBTL iteration. Figure created using BioRender.

simultaneously coordinate multiple tasks – including nutrient processing, pathogen suppression, and immune modulation – within a cohesive framework [10]. In mammal and plant systems, SynComs have been tailored to restore microbial homeostasis and enhance host fitness [10–12]. Although insect-targeted SynCom research remains in its early stages, emerging studies highlight its promising potential to navigate host complexity. In *Drosophila*, simple consortia comprising *Lactiplantibacillus plantarum* and *Acetobacter indonesiensis* exploit host-constructed niches and metabolic cross-feeding to stabilize co-colonization, enhance niche remodeling and host fitness through accelerated development and enhanced pathogen resistance [5]. Similarly, a defined 20-strain SynCom enhances honeybees' resistance to *Hafnia alvei* by activating host immune pathways and antimicrobial peptide production, while maintaining stable colonization across generations despite fluctuations in species-level abundance, demonstrating the feasibility of scalable SynCom design for pathogen control in social insects [13].

Therefore, both strategies based on single bacterial or community assembly are valuable in insect systems. For targeted and straightforward interventions, genetically modifying individual strains offers practical advantages, including technical simplicity, high controllability, and enhanced biosafety, as well as predictable functional outputs [6–9]. In contrast, in cases where multifunctionality, metabolic complementarity, and ecological robustness are desired, SynComs may be more appropriate [10]. However, SynComs' design must account for microbial ecology complexities, requiring advanced tools to ensure stability and efficacy.

Designing SynComs for insect systems: strategies and opportunities

The rational design of SynComs mainly follows two conceptual frameworks: bottom-up assembly and top-down refinement [10]. Bottom-up approaches prioritize the *de novo* construction of microbial consortia from strains with defined and complementary functions [12]. A crucial aspect is the meticulous sourcing and selection of strains with traits critical to host fitness, such as polysaccharide degradation, nutrient biosynthesis, or pathogen inhibition, guided by metagenomic or transcriptomic insights into metabolic pathways and host–microbe interactions. Computational tools, including genome-scale metabolic models and machine learning, further refine design precision by predicting keystone taxa and stabilizing metabolic cross-feeding networks, thereby addressing challenges like community instability in dynamic insect gut environments (Figure 1B).

By contrast, the top-down strategies leverage host- or environment-mediated selective pressures to refine naturally complex microbial communities into functionally optimized consortia [11]. This approach begins by introducing a diverse, naturally derived microbial pool into the insect gut or a simulated gut environment, followed by selective pressure to retain strains that exhibit robust growth, persistence, or host fitness-enhancing traits. For instance, mosquito larvae inoculated with environmental microbiota may yield strains conferring enhanced resistance to arbovirus infection. Community refinement can be further achieved through sequential dropout approaches, iteratively removing non-essential strains to enhance functional stability. By bridging ecological integrity with functional specificity, top-down approaches offer a pragmatic framework for translating natural microbial complexity into targeted insect–microbe symbioses, while providing insights into the evolutionary forces shaping gut community assembly (Figure 1B).

In practice, both approaches are not mutually exclusive, and a hybrid strategy synergistically integrating bottom-up and top-down approaches to construct optimized microbial communities can be adopted. However, scalability requires overcoming hurdles such as host adaptation barriers and spatial heterogeneity in insect gut microhabitats, necessitating iterative design–build–test–learn (DBTL) cycles to optimize functionality and evolutionary compatibility [10]. In insects, the holometabolous development, featuring distinct life stages, provides discrete temporal windows for precise community reconstruction. The short life cycle and prolific reproduction permit rapid iteration of DBTL cycles, allowing for high-throughput testing of microbial consortia configurations. Additionally, the establishment of axenic and gnotobiotic rearing protocols across diverse insect species provides reproducible platforms to systematically design and build the synthetic communities. The test of their functional impacts on insect physiology will further allow iterative learning to refine microbial chassis selection [14]. Furthermore, clustered regularly interspaced short palindromic repeats (CRISPR)-based gene editing platforms across insect models (e.g., fruit fly, silkworm, black soldier fly, mosquitoes) provides opportunities to decode host genetic determinants, such as immune pathways, gut epithelial receptors, and metabolic enzymes governing SynCom dynamics (Figure 1B). Altogether, these advances make insects ideal model systems for refining the development of SynComs, allowing tailored microbiota engineering for specific insect species, life stages, or ecological challenges.

Despite these advances, insect microbiome engineering faces practical challenges, including limited genomic tools for non-model symbionts, unpredictable microbial interaction networks, functional instability of synthetic consortia, and biosafety concerns regarding environmental release (Box 1). Nevertheless, SynComs represent transformative strategy for sustainable ecosystem management, offering dual benefits of pest control and beneficial insect conservation.

Box 1. Challenges and future directions for SynComs in insects

Genetic intractability and host-adapted constraints

Constructing engineered microbial communities for insect systems is constrained by intrinsic limitations in the unculturable and genetically intractable nature of insect-associated symbionts. Unlike model microbial chassis, these symbionts exhibit extreme genomic reduction, host-adapted metabolic dependencies, and lack canonical horizontal gene transfer mechanisms, rendering them recalcitrant to conventional genetic manipulation. Their small genomes often lack well-characterized regulatory elements, such as promoters and ribosomal binding sites, and harbor atypical codon usage patterns. Furthermore, many insect symbionts cannot survive well outside the hosts, complicating *in vitro* cultivation and high-throughput screening. To address these barriers, integrated strategies combining *in situ* gene-editing tools are potentially needed.

Spatiotemporal heterogeneity and interaction complexity

Constructing synthetic community is also challenged by the complexity of insect microbiomes, characterized by intricate interspecies interactions and spatially heterogeneous colonization. Insect microbiota often exhibit niche-specific functional and compositional heterogeneity, driven by physicochemical gradients and host immune modulation. It requires resolving both microbe–microbe interdependencies and host–symbiont coadaptation mechanisms, which remain poorly annotated. Integrated multi-omics approaches, including metagenomics, spatially resolved metabolomics, and single-cell transcriptomics, may be critical for mapping functional networks and niche-specific adaptations. Concurrently, AI-driven genome-scale modeling can predict keystone taxa, infer metabolic bottlenecks, and simulate community dynamics under host physiological constraints. Resolving spatial heterogeneity demands advanced imaging techniques to correlate microbial localization with metabolic activity across gut compartments.

Biosafety and ecological risks

Deploying engineered microbial consortia into open insect populations raises significant concerns regarding biosafety, ecological stability, and functional reliability. In contrast to contained environments, open environments necessitate rigorous safeguards to prevent unintended dissemination or horizontal gene transfer. Furthermore, environmental heterogeneity may alter engineered consortia, leading to functional inconsistency. Engineered auxotrophs that tie bacterial survival to host-derived nutrients can provide niche confinement, while transcriptional silencing systems or toxin–antitoxin modules may enable real-time functional control, deactivating engineered pathways post-mission. Additionally, programmable 'kill-switch' circuits triggered by abiotic factors or quorum sensing depletion may ensure strain self-elimination after environmental release. These approaches potentially balance efficacy, safety, and ecological compatibility in open-system applications.

Insects, with their tractable biology, short generation times, and established gnotobiotic rearing protocols offer robust experimental platforms which serve as ideal systems for deciphering the host–microbe interactions. In conclusion, SynComs beckon a new era in insect–microbe engineering. Investment in insect microbiome engineering promises precision innovations to mitigate vector-borne pandemics, enhance pollination-driven crop productivity, and foster sustainable agroecosystems.

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Declaration of interests

The authors declare no competing interests.

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