



# Engineering microbial communities using thermodynamic principles and electrical interfaces

Christian Zerfaß<sup>1,2</sup>, Jing Chen<sup>2</sup> and Orkun S Soyer<sup>1,2</sup>



Microbial communities present the next research frontier. We argue here that understanding and engineering microbial communities requires a holistic view that considers not only species–species, but also species–environment interactions, and feedbacks between ecological and evolutionary dynamics (eco-evo feedbacks). Due this multi-level nature of interactions, we predict that approaches aimed solely at altering specific species populations in a community (through strain enrichment or inhibition), would only have a transient impact, and species–environment and eco-evo feedbacks would eventually drive the microbial community to its original state. We propose a higher-level engineering approach that is based on thermodynamics of microbial growth, and that considers specifically microbial redox biochemistry. Within this approach, the emphasis is on enforcing specific environmental conditions onto the community. These are expected to generate higher-level thermodynamic bounds onto the system, which the community structure and function can then adapt to. We believe that the resulting end-state can be ecologically and evolutionarily stable, mimicking the natural states of complex communities. Toward designing the exact nature of the environmental enforcement, thermodynamics and redox biochemistry can act as coarse-grained principles, while the use of electrodes — as electron providing or accepting redox agents — can provide implementation with spatiotemporal control.

## Addresses

<sup>1</sup> Warwick Integrative Synthetic Biology Center (WISB), University of Warwick, United Kingdom

<sup>2</sup> School of Life Sciences, University of Warwick, United Kingdom

Corresponding author: Soyer, Orkun S ([o.soyer@warwick.ac.uk](mailto:o.soyer@warwick.ac.uk))

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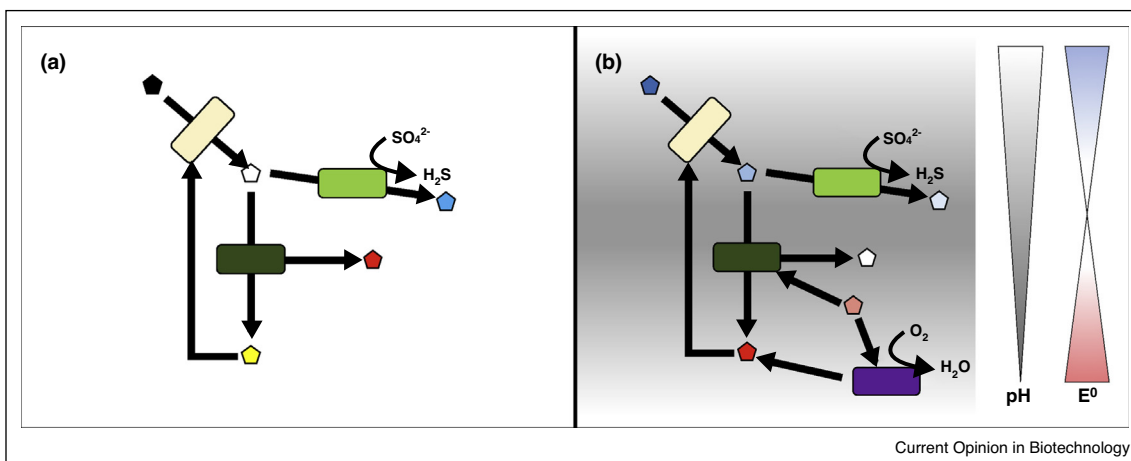
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## Introduction

Microbial communities perform key biochemical transformations of organic and inorganic matter, underpinning the biogeochemical cycles on Earth [1,2] and playing a crucial part in the nutrition and health of higher organisms including humans, animals, and plants [3,4]. Thus, it is not surprising that there is increasing interest in understanding and engineering microbial communities for environmental, medical, and biotechnological applications [5\*,6–9,10\*,11]. Engineering of microbial communities has been proposed both as a top-down approach, controlling metabolic processes for stabilizing complex, natural communities [5\*,6,7] and as a bottom-up approach, for designing defined, synthetic communities with desired functionality [8,9,10\*,11]. In the former direction, most focus has been on gut communities for impacting human and animal health [6,7], and on anaerobic digestion (AD) communities for improving industrial methane production from organic wastes [11]. In the latter direction, early studies focused on implementing defined communities for degradation of organic matter using existing species (e.g. [12–14]), while more recent studies focused on creating synthetic communities with defined (and sometimes synthetically engineered) interactions that give rise to specific biotechnological applications, population dynamics, and community control (e.g. [15–17,18\*,19\*]). In the future, these top-down and bottom-up approaches could merge, with defined, synthetic communities being used to impact and engineer the behavior of complex, natural communities.

Irrespective of their specific aims and level of focus, any engineering approach to microbial communities requires predictive principles for describing community structure and function relationships, and practical tools for shaping these. A simplistic view (that could be considered as a guiding principle in the engineering sense) is to consider complex microbial communities as being composed of different functional groups performing key tasks. This viewpoint suggests that the overall behavior of a complex community can then be modulated in a desired way by including the necessary functional groups or by altering the population fractions of such groups (Figure 1a). We believe that this simplistic view is, however, unlikely to be fruitful as an engineering approach to microbial communities, as it ignores secondary interactions between species and the environment, and the ensuing feedback dynamics.

Figure 1



Microbial communities are affected by species–species and species–environment interactions. **(a)** Classically, microbial communities are thought as functionally distinct groups of microbes (sketched as rectangles) connected through species–species interactions involving metabolite (pentagons) conversions. These can include for example cross-feeding, competition, or auxotrophic interactions (involving the production of metabolites affecting the growth of other species, e.g. yellow pentagon). **(b)** We call for a more holistic view of microbial communities that explicitly takes into account species–environment interactions (indicated with the shaded background), and the feedbacks and intertwined ecological and evolutionary dynamics arising from these. For instance, the impact of metabolic activities of microbes (primarily driven by redox conversions) can directly lead to changes in redox potentials of other reactions (indicated by the standard potential  $E^0$ , bar on the right) and the environmental conditions (such as pH, shown on the right). These changes would then exert a feedback on the whole microbial community, selecting for or against certain groups.

Species–species and species–environment interactions, as well as evolutionary dynamics present significant challenges to complex community engineering. To illustrate the above point, consider for example, increasing the population fraction of a species involved in the fermentation of a particular organic compound. Such an intervention is expected to impact other species in a community directly through creation of substrate-competition (e.g. for carbohydrates), but also indirectly through environmental pH-changes (e.g. acidification through formation of organic acids) [20] and emergence of new cross-feeding interactions (e.g. through organic acids acting as new substrates) [21]. Thus, altering the population of one functional group might present unexpected impacts, or alternatively no impact at all. Indeed, several recent studies find that functional improvements to a community emerge from large-scale community ‘implantation’ or mixing of multiple communities [22,23<sup>\*</sup>], supporting the notion that community function is the result of a community as a whole, inclusive of its myriad species–species and species–environment interactions.

Given the short generation times of some microbes, it is also possible that long-term species–species interactions can result in the evolution of additional genetic interactions. Such evolutionary adaptation is implicated for example by findings of abundant auxotrophic interactions (emerging from the inability of one species to synthesize a compound required for its growth) in communities enriched for degradation of specific compounds [24<sup>\*</sup>].

Evolutionary dynamics can also be driven by species–environment interactions resulting in so-called eco-evo feedbacks [25]. These feedbacks are shown to impact the population dynamics of cooperative traits in a population [26,27,28<sup>\*</sup>], and are proposed as a potential driving force beyond physiological specialization [29,30]. The latter possibility has been demonstrated theoretically in the context of monocultures of *Escherichia coli*, where it is shown that metabolic activities altering the environment can result in a feedback that drives the evolution of different metabolic strategies within this organism [21].

To develop applications of microbial communities, engineering approaches hence need to deal not only with species–species, but also with species–environment interactions and with the ensuing eco-evo feedbacks (Figure 1b).

### Bottom-up engineering needs to consider species–environment and eco-evo feedbacks

For different species to co-exist and achieve a common functional goal, their environment needs to be designed in a way to support (or even enforce) their growth and interactions. This has been achieved for synthetic auxotrophic interactions within one species [17], and cross-feeding and syntrophic interactions among different species [15,16,31]. A key example in the latter direction involves a methanogen and a sulfate reducer, which co-exist in an environment that lacks sulfate (sulfate reducers’ natural choice as an electron acceptor) [31]. This model system is achieved by enforcing a specific environment,

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