

From complexity to simplicity via microbial division of labor inspired by Nature

If someone were to put Nature under a microscope, it would become obvious that microbes are present in all environments on our planet. Microbes are often forced to interact within proximity and share resources as an important key for their survival e.g., natural communities from the oceans to the human intestine. Thus, nutrient availability represents an important key to coordinating the subpopulations of microbial communities also known as microbial consortia and it drives *division of labor* within the ecological network. *Division of labor* reduces the number of tasks and the associated stress for the individual microbe creating a sort of microbial arena in which every single component can contribute with a lower stress load to accomplish the same goal. This may be exemplified by the degradation of complex biological materials by microbial consortia.

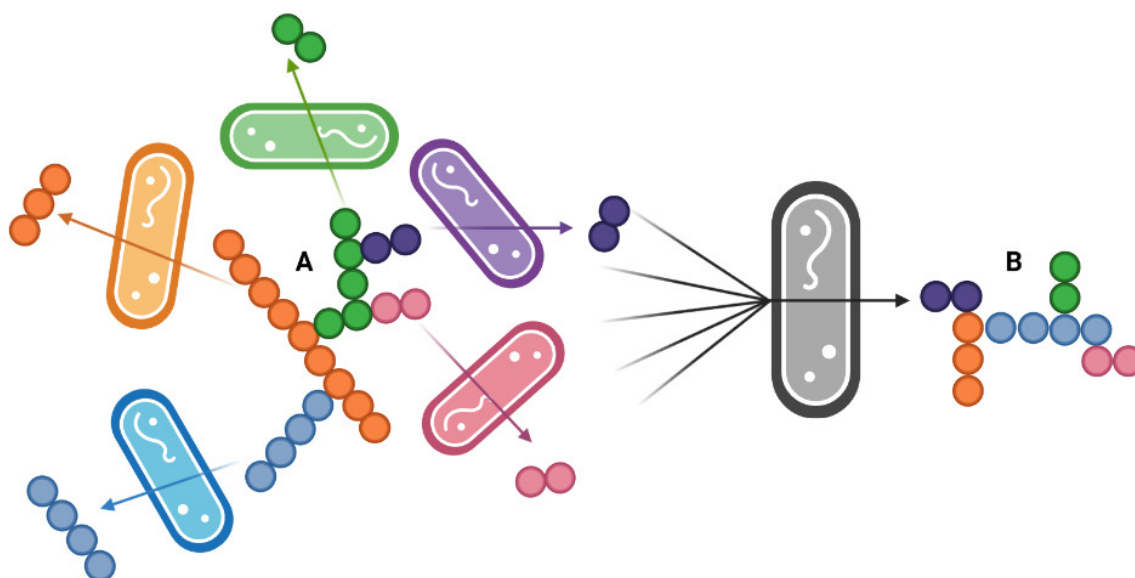


Fig. 1. Microbial consortia to break down a complex substrate (A) into a product (B).

Humankind has used natural communities since millennia e.g., for fermented foods, waste treatment, and agriculture. To achieve a biotechnological process goal such as the conversion of a substrate (A) into a product (B), Nature can be a great inspiration to simplify complex processes by applying “division of labor” as design principle in “synthetic microbial arenas”. As in Nature, commensality and mutualism represent important natural interactions in “microbial synthetic consortia”. Let us consider an example: we want to use a complex raw material A (raw material; substrate), e.g., starch, cellulose, or lignin for the sustainable, environmental-friendly production of a target compound (B), see Figure 1. Different individual microbes cooperate to breakdown A to intermediates that are converted by another microbe to yield B (Fig. 1).

This concept has been applied to the production of the amino acid l-lysine from starch by a synthetic microbial consortium consisting of a starch-degrading, l-lysine auxotrophic *E. coli* strain and a starch-negative, but l-lysine overproducing *C. glutamicum* strain. This interaction is mutualistic since neither microbe can grow with starch in the absence of the other. Since little l-lysine is required to feed the *E. coli* strain the concept could be extended to produce either cadaverine or l-pipecolic acid from the surplus l-lysine (Fig. 2A). A convergent type of interaction describes how two microbes produce two intermediates that are subsequently condensed by the third microbe (Fig. 2B).

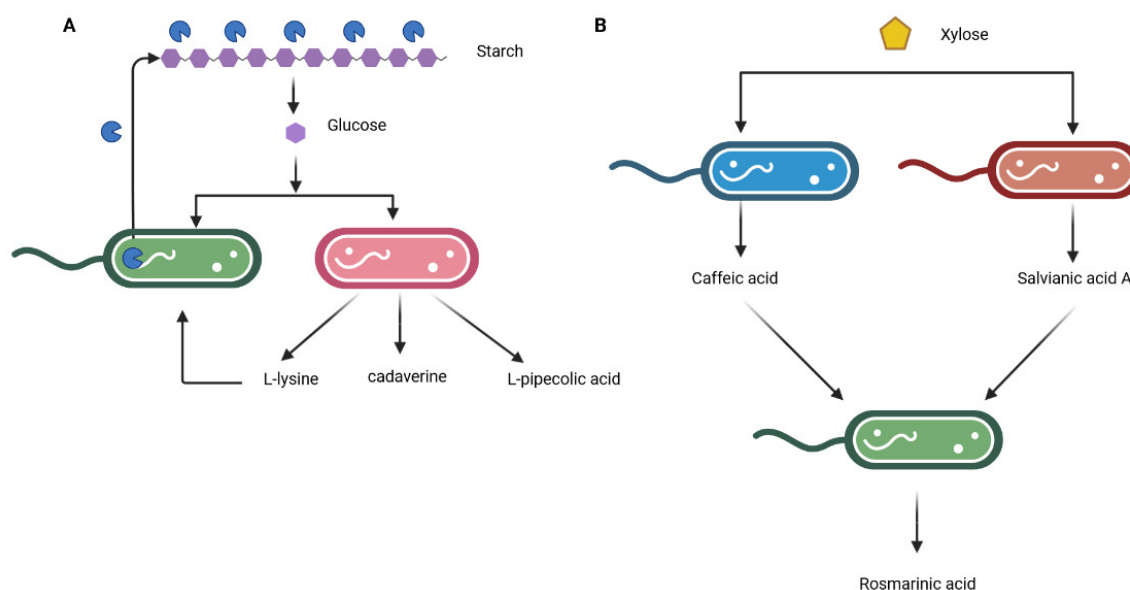


Fig. 2. Examples of a mutualistic microbial consortium for the production of L-lysine, cadaverine, and L-pipecolic acid from starch (A) and production of rosmarinic acid from xylose by a consortium in convergent design mode (B).

Meanwhile, several proofs-of-concept to design and apply synthetic microbial consortia to achieve complex biotechnological tasks by *division of labor* have been achieved. For industrial implementation several technical hurdles have to be overcome. Therefore, in this review, we discuss knowledge gaps that have to be closed to ensure, for example, high titers, yields and productivities of the consortia, their reliable storage or their genetic and compositional stability in bioreactor cultivation during the production phase. Due to the immense potential of the modular design of synthetic consortia, we forecast that sustainable biotechnological production will benefit tremendously from making use of microbial consortia.

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