

YogurtDesign: using systems biology to predict functional interactions in microbial communities

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Yogurt: a practical problem with exciting scientific challenges

Many industrial biotechnological processes are carried out by consortia of bacteria, rather than single strains. To improve performances of such processes, the biotech industry currently relies mostly on screening-based selection of isolated strains with desired properties. However, these properties are very often influenced by other consortium members in unknown ways. Screening consortia is challenging, because only a tiny subset of all the many possible combinations can ever be tested. There is therefore a need to develop methods that can predict performance of strains in consortia, on the basis of the genome and selected phenotypic traits. This project aims to develop an integrative bioinformatics and modeling approach to predict microbial community functioning from the properties of the constituent isolates.

We will do this through a real industrial use case: the design of microbial cultures for the production of yogurt. Industrial-scale yogurt production is carried out with a broad range of cultures consisting mainly of *Streptococcus thermophilus* and *Lactobacillus delbrueckii ssp. bulgaricus* strains. Different cultures (a blend of typically 2 to 5 different strains) are formulated to obtain desirable characteristics in the final product, such as fast acidification to a desired acidity, optimal texture, reduced fat levels, proper sweetness or desired flavor profile. Understanding the genetic determinants of variability between strains related to such functionalities is a key question in the industry. However, the overall function of milk-fermenting strains can largely be modulated by the metabolic interactions between the individual strains. Yogurt fermentation therefore is an excellent test case to develop rational community designer methods, as it consists of relatively few species and its interactions and industrially-relevant properties are based on metabolism – an area amenable to rigorous experimental and computational analyses.

Our approach is twofold: A data-driven approach can identify which features (genes, sequence variations, metabolic network attributes, protein expression) predict functionality in the consortium. This will include growth, as well as key parameters for functionality such as flavour and acidification profiles, for hundreds of combinations of strains in different media. The resultant statistical models can be directly to prioritise combinations of strains based on features of the individual strains.

However, to explore the space of possibilities beyond what was screened for, mechanistic insight into community function will be required. Therefore, in parallel the project will develop mechanistic models that quantitatively and comprehensively describe the metabolic performance of representative *S. thermophilus* and *L. bulgaricus* strains alone and in co-culture, first in chemically defined media, later in milk. Knowledge on strain interactions will be learned from state-of-the-art omics data acquisition in combination with a suite of (genome-scale) modeling approaches. Through structural and parameter sensitivity analysis we will subsequently identify the key interactions and parameters that determine community function, and link those to strain diversity and culture design. This should enable to explore the full potential of various *S. thermophilus* - *L. bulgaricus* combinations for the targeted production of yogurt with desirable properties, in this case acidity and flavour. In this way, this project sets an example how the improvement of industrial fermentations by microbial communities can be achieved through systems biology.