

# **Synthesis and decomposition approach for rational design of a biochemical network**

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The goals of synthetic and systems biology are to understand the mechanisms of how biochemical networks generate particular cellular functions in response to environmental stresses or genetic changes and to rationally design these molecular processes to meet an engineering purpose. It is difficult to understand the entire biochemical network within a cell because it is too large and complicated. An alternative method would be to decompose the whole network into subnetworks in terms of topology or regulatory architecture and to build their associated mathematical models. Analogous to engineering systems, biochemical networks can be decomposed into hierarchical modules consisting of biomolecules, elementary networks/modes, and their combined networks. Biomolecules are assembled to form elementary networks, which are called network motifs or building blocks, with basic functions such as ultrasensitivity, adaptation, oscillation, and bistability. Elementary networks are further assembled to form functional combined networks to generate a variety of biological functions. Combined networks can produce additional, synergistic, or emergent functions. This synthetic approach is analogous to the standard strategy of engineering systems with a scalable, hierarchical modular structure, where a set of off-the-shelf parts with operation specifications can be combined.

In this report, such decomposition and synthesis approach is applied to a central metabolic system with gene regulatory networks. We found the intrinsic elementary modes out of a huge number of them and that the TCA cycle is coupled with glycolysis for complete digestion of carbon sources. To take intermediate metabolites from the TCA cycle as materials required for synthesis of some compounds, the pathway from PEP to OAA is essentially required. The glucose PTS and ammonia assimilation module responsible for uptaking environmental carbon and nitrogen sources are regulated in a more complex manner and using more genes than any other metabolic reactions, suggesting that the uptake systems are critically important for metabolic systems. In addition, we show that the complicated ammonia assimilation system consists of just three elementary networks and they are rationally assembled