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Opinion Article

Orthogonal Biological Systems Transforming Synthetic Biology

Lucas Palmer*

Department of Orthogonal Circuit Design in Synthetic Biology, University Hospital Berlin, Germany,

DESCRIPTION

The primary motivation behind orthogonal biological systems is precision and reliability. Traditional genetic engineering relies on manipulating an organism's native pathways, which often leads to unpredictable interactions, metabolic burden, or unintended side effects. Orthogonal systems, in contrast, are designed to minimize such crosstalk by employing components that do not naturally exist in the host or operate through synthetic pathways that are isolated from endogenous processes orthogonal ribosomes, transcription factors, and metabolic pathways can be constructed so that synthetic genes are expressed exclusively through these artificial components, leaving native cellular functions largely unaffected.

Synthetic biology applications, especially those involving engineered microorganisms, often raise concerns about ecological risks and biosafety. Orthogonal systems can act as a safeguard by limiting the ability of engineered genetic material to interact with wild type organisms. For instance, orthogonal genetic codes or synthetic nucleotides can ensure that engineered genes cannot be read or expressed by natural organisms, reducing the risk of horizontal gene transfer. This built in containment adds a new layer of security, complementing traditional biocontainment strategies such as auxotrophy or kill switches.

Orthogonal Systems offer tremendous opportunities for innovation in biotechnology and medicine. In metabolic engineering, synthetic pathways designed to operate orthogonally can produce high value chemicals, biofuels, or pharmaceuticals without perturbing the host's essential metabolism. By insulating engineered pathways from the host's regulatory networks, researchers can achieve more consistent yields and reduce metabolic stress, which often limits the efficiency of traditional engineered microbes. Orthogonal systems also allow for parallel execution of multiple synthetic processes within the same organism, creating a modular platform for highly complex biochemical production.

In the scope of therapeutics, orthogonal systems hold promise for precision medicine. Cells engineered with orthogonal signaling circuits could sense specific disease states and respond by producing therapeutic molecules only under defined conditions. Such systems could minimize side effects by limiting drug release to the target environment. Additionally, orthogonal synthetic circuits can be designed to function in human cells or immune cells without disrupting their natural functions, enabling safer and more predictable interventions in gene therapy, immunotherapy, or tissue engineering.

Despite their potential, designing orthogonal biological systems remains a formidable challenge. Achieving true orthogonality requires a deep understanding of the host's cellular machinery and careful engineering of synthetic components that are compatible with cellular environments but do not interfere with native functions. This often involves designing new genetic codes, synthetic ribosomes, or novel metabolic enzymes, which requires advanced computational tools, experimental validation, and iterative optimization. Evolutionary pressures within living cells can also compromise orthogonality over time, as synthetic systems may mutate or adapt in ways that reintroduce crosstalk with the host. Therefore, robust orthogonal designs must account for both functionality and long term stability.

Another limitation is the current scope of orthogonal systems, which is mostly confined to model organisms such as Escherichia coli or Saccharomyces cerevisiae. Expanding these approaches to non model organisms, multicellular systems, or mammalian cells introduces additional complexity due to differences in regulatory networks, cellular compartments and genome organization. Overcoming these challenges will require continued innovation in synthetic biology tools, genome engineering, and systems biology modeling.

Orthogonal biological systems represent a paradigm shift in synthetic biology. By decoupling engineered functions from native cellular machinery, these systems offer enhanced precision, safety, and versatility. They hold transformative potential for biotechnology, medicine, environmental applications, and fundamental research. However, realizing this potential requires careful design, rigorous testing, and long term considerations for stability and evolutionary resilience. As synthetic biology continues to advance, orthogonal systems are likely to become foundational tools for building more sophisticated, reliable and controllable living technologies.

Correspondence to: Lucas Palmer, Department of Orthogonal Circuit Design in Synthetic Biology, University Hospital Berlin, Germany, E-mail: lucas.palmer@gmil.com

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