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Whole-cell modeling for synthetic biology

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Synthetic biology is a relatively new field that brings together scientists from different areas of research such as physics, engineering, mathematics, biochemistry and biology. A major goal of synthetic biology is to design and build synthetic gene networks in order to better understand existing pathways and reprogram organisms with novel functions for a variety of new applications[1-4]. Initial work in synthetic biology has consisted of synthesizing simple gene circuits with predictable behavior such as the toggle switch[5], a stable negative feedback system[6], and a synthetic oscillatory network[7]. These pioneering studies lead to an increased interest in the field, facilitating other synthetic cellular systems such as tunable oscillators[8,9] and mammalian switches[10], bacterial systems capable of detecting light[11], circuits that lead to differential gene expression[12], synthetic logic gates with concomitant DNA-encoded memory storage[13], and networks capable of counting cellular metabolic events[14]. Mathematical modeling has played a critical role in developing these systems; however, a majority of models have been developed using simplified host parameters or in isolation without taking into account the vast number of host cellular processes, which can affect the behavior of the synthetic network[15,16]. This omission of the broader cellular context in models is a likely reason why current models lack predictive power, and multiple rounds of trial-and-error modification of the network are often required to make the network function correctly.

A paper published in the June issue of *Chaos* by Purcell *et al* titled "Towards a whole-cell modeling approach for synthetic biology" raises important questions on using non-isolated models and provides a better understanding toward the interactions between synthetic gene networks and the host cell. The authors used a whole-cell model of *Mycoplasma genitalium*, a species well known in the field of synthetic biology as being the first host of a synthetic genome, to investigate the effect that synthetic gene circuits may have on the host cell dynamics and behavior. The authors also focus on how these effects can vary with circuit size. More specifically, they used varying numbers of *LacI* genes with identical promoters and found an approximately linear relationship between the number of *LacI* genes added and the length of the cell cycle. Similar results were also observed for other common genes used in synthetic biology such as *araC*, *tetR*, and *gfp*. Next, the authors used the JCat online codon optimization tool[17] to re-encode *LacI, araC*, *tetR*, and *gfp* gene sequences for expression in *M. genitalium* in an optimized and unoptimized form to probe into the effects of codon optimization on expression. In agreement with previous work conducted in *E. coli* where it was shown that Codon Adaptation Index has no correlation with gene expression level[18,19], the authors observed no effect of codon optimization on gene expression, but noticed it could have a positive effect on growth rate. Finally, the authors successfully implemented a Goodwin oscillator[8] in the whole-cell model of *M. genitalium* and found qualitatively matched behavior with the *in vivo* dynamics observed in *E. coli*. However, as the authors point out in the

paper, this is a preliminary study that examines the feasibility of using the whole cell model for synthetic biology and further experimental results are necessary to confirm the applicability and accuracy of whole-cell models.

Overall, the authors demonstrate that integrating precise and accurate whole-cell models with synthetic gene circuits may substantially improve the rational design of synthetic biological systems. Robust whole-cell models in synthetic biology have the potential to transform the young field of synthetic biology into a predictive and application-driven engineering discipline.

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