The abstract describes work under

"Numerical Optimization Algorithms and Software for Systems Biology" 2009-2012, Michael Saunders (Stanford University) et. al. in response to DOE program DE-PS02-08ER08-01

to be continued under our recent award for:

"Multiscale Molecular Systems Biology: Reconstruction and Model Optimization" 2012-2016 Michael Saunders (Stanford University) et. al., in response to Predictive Multiscale Models for Biomedical, Biological, Behavioral, Environmental and Clinical Research (Interagency U01)

Abstract:

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Biological systems are inherently hierarchal and multiscale in time and space. A major challenge of systems biology is to describe biological systems as a computational model, which can be used to derive novel hypothesis and drive experiments leading to new knowledge. The constraint-based reconstruction and analysis approach has been successfully applied to metabolism and to the macromolecular synthesis machinery assembly. Here, we present the first integrated stoichiometric multiscale model of metabolism and macromolecular synthesis for Escherichia coli K12 MG1655, which describes the sequence-specific synthesis and function of almost 2000 gene products at molecular detail. We added linear constraints, which couple enzyme synthesis and catalysis reactions. Comparison with experimental data showed improvement of growth phenotype prediction with the multiscale model over E. coli's metabolic model alone. Many of the genes covered by this integrated model are well conserved across enterobacters and other less related bacteria. We addressed the question whether the bias in synonymous codon usage could affect the growth phenotype and environmental niches that an organism can occupy. We created two classes of in silico strains, one with more biased codon usage and one with more equilibrated codon usage than the wildtype. The reduced growth phenotype in biased strains was caused by tRNA supply shortage, indicating that expansion of tRNA gene content or tRNA codon recognition allow E. coli to respond to changes in codon usage bias. Our analysis suggests that in order to maximize growth and to adapt to new environmental niches, codon usage and tRNA content must co-evolve. These results provide further evidence for the mutation-selection-drift balance theory of codon usage bias. This integrated multiscale reconstruction successfully demonstrates that the constraint- based modeling approach is well suited to whole cell modeling endeavors.

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