Development of a genome-scale metabolic model of *C. thermocellum* assists in strain design for biofuels and chemicals

U.S. DEPARTMENT OF ENERGY | Office of Science

Background

Genome scale modeling is a powerful tool for investigating cellular metabolism, but the current genome scale model (GEM) of *C. thermocellum* is outdated and built for the genetically intractable strain ATCC 27405.

Approach

- A GEM of the more genetically tractable DSM 1313 was constructed and curated for simulation of growth on alternative cellulosic substrates by implementing an adjustable cellulosome.
- The bioenergetic constraints of the GEM were tuned using extensive experimental data leading to accurate phenotypic predictions.

Outcome

- Using the GEM, researchers were able to explore how key redox and bioenergetic reactions change as a function of growth rates and carbon sources in a systematic manner.
- Strain design strategies for the production of ethanol, hydrogen, and isobutanol were also investigated.

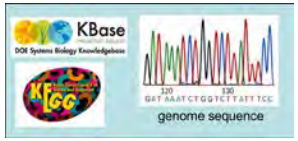
Significance

- Use of the model led to a proposed substrate-dependent regulatory mechanism by which ethanol production is enhanced or limited.
- The model has been added to KBase as a platform for strain design for specialty biofuels and biobased chemicals.

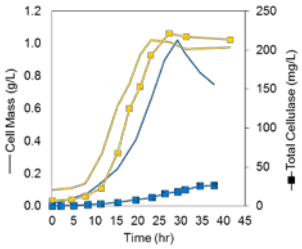
Thompson et al., "Exploring complex cellular phenotypes and model-guided strain design with a novel genome-scale metabolic model of *Clostridium thermocellum* DSM 1313 implementing an adjustable cellulosome", *Biotechnology for Biofuels* 9:194, 2016.
DOI: 10.1186/s13068-016-0607-x

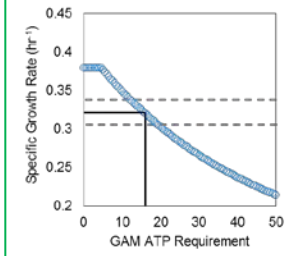
Construction and Curation

Model built from updated genome annotation

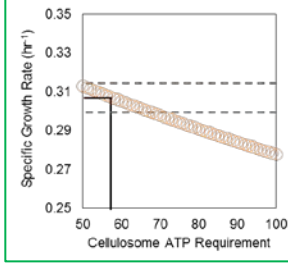


Incorporation of cellulosome synthesis constraints



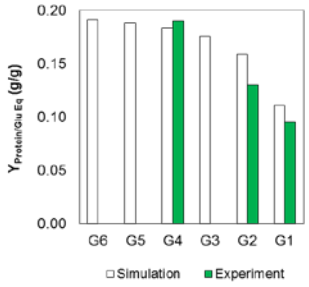


ATP Requirements tuned to Experimental Data



Validation

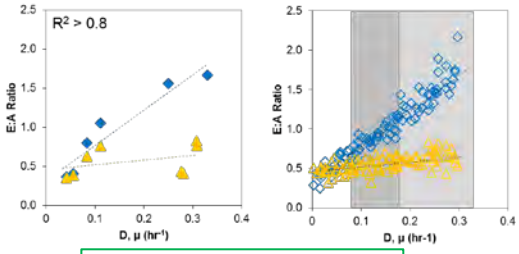
Reproduction of Experimental Observations in silico



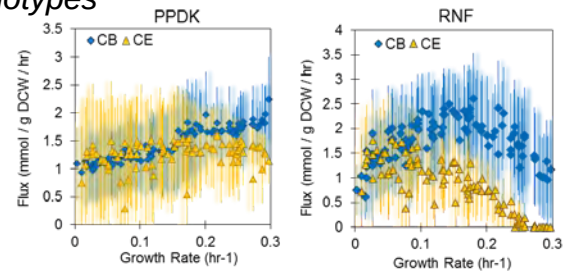
Strain Design via cMCS

Products	Target cut set sizes	# Strain Designs
Ethanol	6	67
	7	185
Hydrogen	4	12
	5	221
	6	1105
	7	4816
Isobutanol	7	28

Exploring Experimentally Observed Phenotypes



Sampling around experimental constraints for phenotypic characterization



GEM allows for reaction level investigation