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Ab Initio Whole Cell Kinetic Model of *Corynebacterium glutamicum* ATCC 13032 (cglPS26)

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Abstract

Corynebacterium glutamicum ATCC 13032 is a Gram-positive facultative anaerobic bacterium, which is a microbial workhorse in industrial biotechnology for the production of amino acids, in particular, glutamic acid. Due to its "GRAS" status, robustness and metabolic versatility, its use has been extended to produce fuels and various value-added products through metabolic engineering. In metabolic engineering, metabolic models such as constraint-based genome scale models (GSMs) and kinetic models (KMs) serve as valuable tools as they provide a mathematical representation of metabolic processes that in turn guide the rational design of genetic modifications to optimize production of desired compounds in the microbe. While GSMs emphasis on steady-state flux distribution, KMs enable a comprehensive dynamic visualization of the metabolic network, by simulating the rate of change of metabolite concentration. Though a GSM of *C. glutamicum* ATCC 13032 exists, there has been no whole cell KM to date. Here, we present a KM of *C. glutamicum* ATCC 13032 constructed using *ab initio* approach by identifying enzymes from its published genome. The resulting kinetic model, cglPS26, comprise of 986 metabolites, 443 enzymes with corresponding transcriptions and translations and 1153 enzymatic reactions. This can be a baseline model for incorporating additional cellular and growth processes, or as a system to examine cellular resource allocations necessary to guide engineering.

Keywords: Whole-cell model; Kinetic model; GRAS; Differential equations; AdvanceSyn Toolkit

Introduction

Corynebacterium glutamicum ATCC 13032 is a Gram-positive, facultative anaerobic bacterium that was first isolated in 1957 and was found to be a natural producer of glutamic acid [1]. Due to its "Generally Accepted as Safe" status by the FDA under GRAS Notice No. AGRN 34, it has been metabolically engineered for large-scale industrial production of glutamic acid, which is neutralized with sodium hydroxide to form monosodium glutamate, a key flavour enhancer used in the food industry [2]. Besides glutamic acid, it has been used for production of arginine [3], lysine [4], homoserine [5], and gamma-hydroxybutyric acid [6]; as well as engineered for the production of biochemicals, biofuels, natural products, proteins, and the biodegradation of environmental pollutants [7, 8].

The workflow of metabolic engineering is often shaped by insights from mathematical models, which help researchers filter and prioritise possible manipulations [9, 10]. Two principal modelling frameworks are used [11, 12]: GSMs and KMs. GSMs, although powerful at predicting metabolic fluxes, are limited mainly to rate-focused outputs. KMs build on this by incorporating yield predictions and by offering more flexible simulation of gene knock-ins [13]. Their ability to provide both quantitative rates and product outcomes makes them well suited for comparing engineering strategies [14]. Because of this utility, many researchers now emphasise the importance of building new kinetic models to expand the modelling toolkit available for metabolic engineering [15, 16].

Although a GSM of *C. glutamicum* ATCC 13032 (iCGB21FR) has been published [17], there is no whole-cell KM of *C. glutamicum* to-date. Hence, this study aims to construct a KM of *C. glutamicum* ATCC 13032 using *ab initio* approach by identifying enzymes from its genome [18], and identifying the corresponding reaction from KEGG [19]. The result is a whole cell KM of *C. glutamicum* ATCC 13032, named as cglPS26, using the nomenclature proposed by Cho and Ling [20], which consists of 986 metabolites, 443 enzymes with corresponding transcriptions and translations, and 1153 enzymatic reactions.

Materials and Methods

Identification of Reactome

The genome of *C. glutamicum* ATCC 13032 (NCBI RefSeq assembly GCF_000011325.1; NCBI GenBank Accession NC_003450.3) [18] was used as source to identify enzymatic genes using the process previously described [13, 21, 22]. Briefly, each enzymatic gene was identified as a presence of complete Enzyme Commission (EC) number in the GenBank record and mapped into reaction IDs via KEGG Ligand Database for Enzyme Nomenclature [19]. For example, EC 1.1.1.23 (https://www.genome.jp/entry/1.1.1.23) catalyses reactions R01158, R01163, and R03012; where the substrates and products of each rection can be identified.

Model Development

The model was developed using methodology in Sim et al. [23]. BioNumbers indicate that *Escherichia coli* contains around 3000 RNA polymerases (BioNumbers 106199) [24], but only about 750 are transcriptionally active (BioNumbers 111676) [25]. Each polymerizes RNA at 22 nucleotides per second (BioNumbers 104109) [26], with each nucleotide weighing 339.5 Da. This gives an approximate mRNA synthesis rate of 5600 kDa/s or 9.3e-18 grams per second. Dividing across the cellular volume (7e-16 litres) [27] and 4225 coding genes (BioNumbers 105443) [28] gives a concentration-based rate of 2.92 micromolar per gene per second. With mRNA lasting about 107.56 seconds (BioNumbers 107666) [29], the degradation constant is 0.0093 per second, giving: d[mRNA]/dt = 0.00292 - 0.0093[mRNA]. Translation produces about 0.278 peptides per transcript per second (BioNumbers 106382) [30], and proteins degrade at 2.78e-6 per second (BioNumbers 109924) [31]. Thus: d[peptide]/dt = 0.278[mRNA] - 0.00000278[peptide]. All metabolite concentrations were handled as ODEs [21, 32] using typical enzyme parameters (kcat = 13.7 per second, Km = 1 mM) [33], with formatting guided by the AdvanceSyn Model Specification [34].

Model Simulation

The constructed model was tested for simulatability using AdvanceSyn Toolkit [34]. Initial concentrations of all mRNA and enzymes were set to 0 mM. Initial concentrations of all metabolites were set to 1 mM except the following which were set to 1000 mM: (I) C00001 (Water), (II) C00002 (ATP), (III) C00003 (NAD+), (IV) C00004 (NADH), (V) C00005 (NADPH), (VI) C00006 (NADP+), (VII)

C00007 (Oxygen), (VIII) C00011 (Carbon Dioxide), (IX) C00014 (Ammonia), (X) C00025 (L-Glutamate), (XI) C00031 (D-Glucose), (XII) C00037 (Glycine), (XIII) C00041 (L-Alanine), (XIV) C00045 (Amino acid), (XV) C00047 (L-Lysine), (XVI) C00049 (L-Aspartate), (XVII) C00064 (L-Glutamine), (XVIII) C00065 (L-Serine), (XIX) C00073 (L-Methionine), (XX) C00078 (L-Tryptophan), (XXI) C00079 (L-Phenylalanine), (XXII) C00082 (L-Tyrosine), (XXIII) C00097 (L-Cysteine), (XXIV) C00099 (beta-Alanine), (XXV) C00123 (L-Leucine), (XXVI) C00133 (D-Alanine), (XXVII) C00148 (L-Proline), (XXVIII) C00151 (L-Amino acid), (XXIX) C00152 (L-Asparagine), (XXX) C00155 (L-Homocysteine), (XXXI) C00183 (L-Valine), (XXXII) C00188 (L-Threonine), (XXXIII) C00221 (beta-D-Glucose), (XXXIV) C00407 (L-Isoleucine), (XXXV) C00638 (Long-chain fatty acid), (XXXVI) C05167 (alpha-Amino acid). The model was simulated using the fourth-order Runge-Kutta method [35, 36] from time zero to 3600 seconds with timestep of 0.1 second, and the concentrations of metabolites were bounded between 0 millimolar and 1000 millimolar. The simulation results were sampled every 2 seconds.

Results and Discussion

The annotated genome of *C. glutamicum* ATCC 13032 consists of 3079 genes, including 2948 protein coding sequences. 443 unique EC numbers consisting of 1153 enzymatic reactions involving 986 metabolites were identified and developed into a model based on AdvanceSyn Model Specification [34]. In addition, 886 ODEs acting as placeholder for enzyme transcriptions and translations were added. This is comparable to the published GSM of *C. glutamicum*, iCGB21FR [17], consisting of 1042 metabolites.

We executed the cglPS26 model in the AdvanceSyn Toolkit [34]. The simulation output (illustrated in Figure 1) shows that the model runs without syntax or structural errors as argued in recent model constructions [13, 22, 37-41], which is a critical baseline test for any whole-cell kinetic model. The observation that CDP (C00112) and GDP (C00035) accumulates at the same rate and the the steady decline of L-glutamate (C00025) must be interpreted cautiously as this behaviour may stem from using uniform median values for all enzyme kinetic parameters (turnover numbers and Michaelis-Menten constants) as per the dataset in Bar-Even et al. [33], rather than empirically measured, strain-specific parameters. As such, the current output serves as a proof-of-concept: a fully workable kinetic model of *C. glutamicum* ATCC 13032 which can act as a scaffold for further refinement; whether that means adding growth regulation, metabolic branching, or resource allocation modules [42-44].

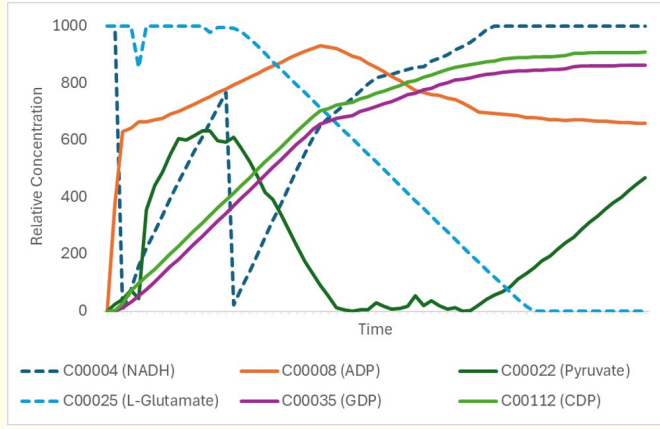

Figure 1: Selection of Simulation Results.

Conclusion

Here, we present an *ab initio* whole cell kinetic model of *C. glutamicum* ATCC 13032, cglPS26; comprising of 986 metabolites, 443 enzymes with corresponding transcriptions and translations, and 1153 enzymatic reactions.

Supplementary Materials

Reaction descriptions and model can be download from https://bit.ly/cglPS26.

Conflict of Interest

The authors declare no conflict of interest.

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