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Ab Initio Whole Cell Kinetic Model of Multi-strain *Corynebacterium glutamicum* (cglTY26)

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Abstract

Corynebacterium glutamicum is an industrially important bacterium widely used in amino acid production. In metabolic engineering, metabolic models such as constraint-based genome scale models (GSMs) and kinetic models (KMs) can be useful computational tool guide the rational design of genetic modifications to optimize production of desired compounds in the microbe. Compared to GSMs which 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. A recent whole cell kinetic model of Corynebacterium glutamicum ATCC 13032, cglPS26, has been published. Hence, this study aims to expand cglPS26 into a multi-strain model, cglTY26, contained 1109 metabolites, 511 enzymes and their corresponding transcription and translation processes, and 1195 enzymatic reactions. This model provides a useful toolkit for further refinement, experimental validation, and future applications in metabolic engineering.

Keywords: Whole-cell model, Kinetic model, Differential equations, Multi-strain model, AdvanceSyn Toolkit.

Introduction

Corynebacterium glutamicum is a Gram-positive soil bacterium. It has been a well-established industrial strain since it was discovered in 1957 [1] and was found to be a natural producer of glutamic acid [2]. *C. glutamicum* ATCC 13032 is recognized as "Generally Recognized 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 precursor for monosodium glutamate production, a key flavour enhancer used in the food industry [3]. Other strains of *C. glutamicum* also have important industrial uses. For example, *C. glutamicum* ATCC 21799 for L-lysine production [4], *C. glutamicum* ATCC 13869 for L-valine production [5], and *C. glutamicum* ATCC 13032 has been engineered with argCJBD genes from *C. glutamicum* ATCC 21831 for increased L-ornithine production [6]. This demonstrated versatility in *C. glutamicum*.

Mathematical modelling continues to guide metabolic engineering by revealing how pathways may respond to genetic modifications [7, 8]. Two approaches, genome-scale model (GSM) and kinetic model (KM), account for most modelling efforts [9, 10]. GSMs provide flux-based insights but are limited in predicting yields. KMs are more informative, covering both yields and rates [11], and allow for easier in silico gene knock-ins [12]. These strengths make KMs an attractive tool for assessing competing engineering options before experiments. As a result, the field has seen heightened interest in creating new kinetic models to support more comprehensive and predictive design workflows [13, 14].

Both GSM (iCGB21FR [15]) and whole-cell KM (cglPS26 [16]) of *C. glutamicum* ATCC 13032 have been published, a number of enzymatic reactions were missing in cglPS26 [16]. Hence, this study aims to expand on cglPS26 [16] into a multi-strain whole cell KM by adding missing enzymatic reactions from 30 other strains of *C. glutamicum*. The resulting multi-strain whole cell KM of *C. glutamicum*, named as cglTY26, using the nomenclature proposed by Cho and Ling [17], which consists of 1109 metabolites, 511 enzymes with corresponding transcriptions and translations, and 1195 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 [12, 19, 20]. 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 [21]. 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. This was followed by adding missing enzymatic genes and their corresponding reactions from this following 30 strains; namely, (i) AJ1511 (NZ_AP017557.1), (ii) AR1 (NZ_CP007724.1), (iii) ATCC 13869 (NZ_CP016335.1), (iv) ATCC 14067 (NZ_CP022614.1), (v) ATCC 21573 (NZ_CP068290.1), (vi) ATCC 21799 (NZ_AP022856.1), (vii) ATCC 21831 (NZ_CP007722.1), (viii) B253 (NZ_CP010451.1), (ix) B414 (NZ_CP012297.1), (x) BCA (NZ_CP059382.1), (xi) BE (NZ_CP053188.1), (xii) BIM B-77 (NZ_CM143267.1), (xiii) BIM B-78 (NZ_CM143270.1), (xiv) C1 (NZ_CP017995.1), (xv) Cg21420 (NZ_CP121344.1), (xvi) CGMCC1.15647 (NZ_CP073911.1), (xvii) CICC10064 (NZ_CP012298.1), (xviii) CP (NZ_CP012194.1), (xix) CR101 (NZ_CP080542.1), (xx) JH41 (NZ_CP041729.1), (xxi) MB001 (NC_022040.1), (xxii) R (NC_009342.1), (xxiii) SCgG1 (NC_021351.1), (xxiv) SCgG2 (NC_021352.1),

(xxv) TCCC11822 (NZ_CP020033.1), (xxvi) USDA-ARS-USMARC-56828 (NZ_CP013991.1), (xxvii) WM001 (NZ_CP022394.1), (xxviii) XV (NZ_CP018175.1), (xxix) YI (NZ_CP014984.1), and (xxx) ZL-6 (NZ_CP004062.1).

Model Development. The model was developed using the ordinary differential equation (ODE) formats described in Sim et al. [22]. BioNumbers data suggest that *Escherichia coli* hosts approximately 3000 RNA polymerases (BioNumbers 106199) [23], although only 25% are active at a given time (BioNumbers 111676) [24]. At an elongation rate of 22 nucleotides per second (BioNumbers 104109) [25] and a nucleotide mass of 339.5 Da, this corresponds to around 5600 kDa per second of mRNA (≈9.31e-18 gram per second). With a cell volume of 7e-16 litres [26] and 4225 coding genes (BioNumbers 105443) [27], this translates into roughly 2.92 micromolar per gene per second. If mRNA persists for 107.56 seconds (BioNumbers 107666) [28], degrading at 0.93% per second, then d[mRNA]/dt = 0.00292 – 0.0093[mRNA]. Translation produces about 0.278 peptides per mRNA per second (BioNumbers 106382) [29], while proteins degrade at 2.78e-6 per second (BioNumbers 109924) [30], leading to: d[peptide]/dt = 0.278 [mRNA] – 0.00000278[peptide]. The reactome was modelled via ODEs [19, 31] using median kinetic constants (kcat 13.7 per second, Km 1 mM) [32] and documented in line with the AdvanceSyn Model Specification [33].

Model Simulation. The constructed model was tested for simulatability using AdvanceSyn Toolkit [33]. 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 (CO2), (IX) C00025 (L-Glutamate), (X) C00031 (D-Glucose), (XI) C00037 (Glycine), (XII) C00041 (L-Alanine), (XIII) C00045 (Amino acid), (XIV) C00047 (L-Lysine), (XV) C00064 (L-Glutamine), (XVI) C00065 (L-Serine), (XVII) C00073 (L-Methionine), (XVIII) C00078 (L-Tryptophan), (XIX) C00079 (L-Phenylalanine), (XX) C00097 (L-Cysteine), (XXI) C00123 (L-Leucine), (XXII) C00151 (L-Amino acid), (XXIII) C00155 (L-Homocysteine), (XXIV) C00188 (L-Threonine), (XXV) C00221 (beta-D-Glucose), (XXVI) C00407 (L-Isoleucine), (XXVII) C00638 (Long-chain fatty acid), (XXVIII) C05167 (alpha-Amino acid). The model was simulated using the fourth-order Runge-Kutta method [34, 35] 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

A total of 1109 metabolites, 511 enzymes, and 1195 enzymatic reactions were developed into a model using AdvanceSyn Model Specification [33]. Of which, 468 enzymes were found in *C. glutamicum* ATCC 13032. This is 5.64% higher than the 443 enzymes previously reported [16]. Forty-three enzymes from the other 30 strains were added (Table 1). In addition, 1022 ODEs acting as placeholders for transcription and translation were added.

No.	EC Number	Strain(s)
1.	1.1.1.140	CGMCC1.15647
2.	1.1.1.17	USDA-ARS-USMARC-56828; CGMCC1.15647
3.	1.1.1.30	ATCC 21799; BIM B-78; TCCC11822; BE; Cg21420; AJ1511; B253; CP; YI; ATCC 13869; XV; WM001; R; ZL-6; ATCC 14067
4.	1.1.1.31	B414; ATCC 21573; B253; CGMCC1.15647; CICC10064
5.	1.1.1.336	BIM B-78; B414; TCCC11822; BE; ATCC 21573; Cg21420; AJ1511; B253; CP; YI; ATCC 13869; XV; WM001; R; ZL-6; ATCC 21831; CICC10064; ATCC 14067; JH41
6.	1.1.1.35	SCgG1; SCgG2
7.	1.1.1.47	USDA-ARS-USMARC-56828
8.	1.1.1.93	CGMCC1.15647; SCgG1; SCgG2
9.	1.13.11.15	B414; CICC10064
10.	1.13.11.16	USDA-ARS-USMARC-56828
11.	1.13.11.93	ATCC 21799; BIM B-78; TCCC11822; BE; Cg21420; AJ1511; CP; YI; ATCC 13869; XV; WM001; R; SCgG1; SCgG2; ZL-6; ATCC 14067
12.	1.14.11.33	USDA-ARS-USMARC-56828; ZL-6
13.	1.14.13.149	USDA-ARS-USMARC-56828; R; SCgG1; SCgG2; ATCC 21831; AR1
14.	1.16.1.1	ATCC 21799; BIM B-78; TCCC11822; BE; Cg21420; AJ1511; B253; CP; YI; ATCC 13869; XV; WM001; CGMCC1.15647; R; SCgG1; SCgG2; ZL-6; ATCC 14067
15.	1.2.1.10	USDA-ARS-USMARC-56828
16.	1.3.1.1	ATCC 21573; CGMCC1.15647
17.	1.5.3.2	ATCC 21799; BIM B-78; B414; TCCC11822; BE; ATCC 21573; CR101; Cg21420; AJ1511; B253; CP; USDA-ARS-USMARC-56828; YI; ATCC 13869; XV; WM001; CGMCC1.15647; R; SCgG1; SCgG2; ZL-6; ATCC 21831; AR1; CICC10064; ATCC 14067; JH41
18.	2.1.1.72	BIM B-78; BE; ATCC 21573; USDA-ARS-USMARC-56828; YI; ATCC 14067
19.	2.3.1.39	USDA-ARS-USMARC-56828; CGMCC1.15647; R; SCgG1; SCgG2
20.	2.4.2.52	USDA-ARS-USMARC-56828; CGMCC1.15647; R; SCgG1; SCgG2
21.	2.7.1.197	USDA-ARS-USMARC-56828; CGMCC1.15647
22.	2.7.1.6	YI; ATCC 21831; AR1
23.	2.7.7.49	B414; CICC10064
24.	3.1.12.1	USDA-ARS-USMARC-56828
25.	3.1.21.3	ATCC 21799; BIM B-78; B414; TCCC11822; BE; ATCC 21573; Cg21420; AJ1511; CP; YI; ATCC 13869; XV; WM001; SCgG1; SCgG2; ZL-6; CICC10064; ATCC 14067
26.	3.2.1.18	ATCC 21573; B253; USDA-ARS-USMARC-56828; CGMCC1.15647; R; SCgG1; SCgG2
27.	3.5.1.2	YI
28.	3.5.1.28	BIM B-78; BE; USDA-ARS-USMARC-56828; CGMCC1.15647; R; ATCC 14067
29.	3.5.2.10	ATCC 21799; BIM B-78; TCCC11822; BE; Cg21420; AJ1511; B253; CP; YI; ATCC 13869; XV; WM001; ZL-6; ATCC 21831; AR1; ATCC 14067; JH41
30.	3.5.2.2	ATCC 21573; CGMCC1.15647
31.	3.5.4.5	B253; CGMCC1.15647; R; SCgG1; SCgG2
32.	3.6.1.22	ATCC 21799; BIM B-78; B414; TCCC11822; BE; Cg21420; AJ1511; B253; CP; USDA-ARS-USMARC-56828; ATCC 13869; XV; WM001; R; SCgG1; SCgG2; ZL-6; ATCC 21831; AR1; CICC10064; ATCC 14067; JH41
33.	4.1.1.112	USDA-ARS-USMARC-56828; CGMCC1.15647
34.	4.1.1.88	USDA-ARS-USMARC-56828; CGMCC1.15647; R; SCgG1; SCgG2
35.	4.1.2.14	USDA-ARS-USMARC-56828; CGMCC1.15647; R; SCgG1; SCgG2
36.	4.1.3.16	USDA-ARS-USMARC-56828; CGMCC1.15647; R; SCgG1; SCgG2
37.	4.1.3.17	USDA-ARS-USMARC-56828; CGMCC1.15647
38.	4.1.3.39	USDA-ARS-USMARC-56828
39.	4.2.1.163	B414; USDA-ARS-USMARC-56828; CICC10064
40.	4.2.1.80	USDA-ARS-USMARC-56828
41.	5.1.3.14	ATCC 21799; BIM B-78; B414; TCCC11822; BE; ATCC 21573; Cg21420; AJ1511; B253; CP; YI; ATCC 13869; XV; WM001; CGMCC1.15647; R; ZL-6; ATCC 21831; CICC10064; ATCC 14067; JH41
42.	5.3.2.8	USDA-ARS-USMARC-56828; CGMCC1.15647
43.	6.2.1.16	CGMCC1.15647; R; SCgG1; SCgG2

Table 1: Additional EC Numbers Not Found in *Corynebacterium glutamicum* ATCC 13032.

The cglTY26 model was validated through simulation in AdvanceSyn Toolkit [33], and the trace in Figure 1 confirms that it executes without structural or syntax errors [12, 20, 36–40]. The observation that oscillating coenzyme A should be interpreted cautiously because the simulation employed identical median kinetic constants for all enzymes [32], a simplifying assumption that eliminates enzyme-level variation despite showing substantial predictability [41]. As such, these values serve only to demonstrate structural viability. The main achievement is a multi-strain whole-cell kinetic model of *C. glutamicum*, which future work can refine; for example, by replacing median kinetics with empirical parameters, including regulatory mechanisms, or exploring resource trade-offs under varied conditions [37–39]. This model may also be incorporated into a collation of kinetic models, to be a meta-model for predicting metabolite levels produced by various interacting gut microorganisms as recently proposed [42, 43].

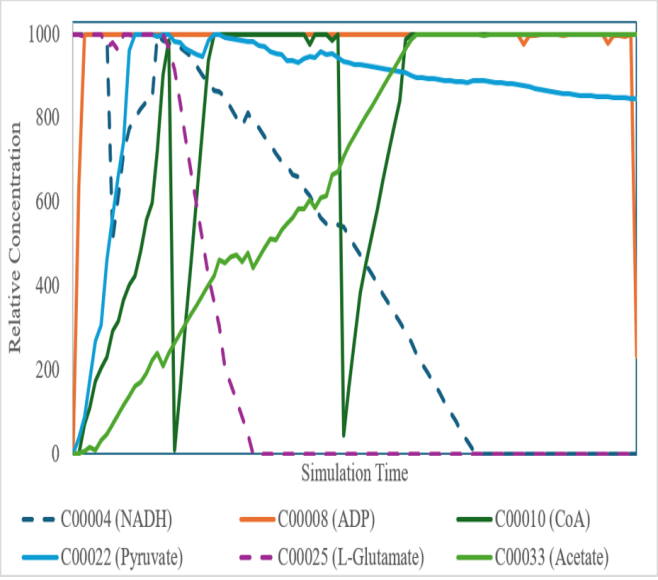

Figure 1. Selection of Simulation Results.

Conclusion

In this study, we present an *ab initio* multi-strain whole cell kinetic model of *C. glutamicum* by taking enzymes from 31 strains. The resulting kinetic model, cglTY26; comprising of 1109 metabolites, 511 enzymes with corresponding transcriptions and translations, and 1195 enzymatic reactions.

Supplementary Materials

Reaction descriptions and model can be download from https://bit.ly/cglTY26.

Conflict of Interest

The authors declare no conflict of interest.

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