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Research Article

Ab initio Whole Cell Kinetic Model of *Desulfovibrio desulfuricans* L4 (ddsAAR26)

Atoshi Abirami RajKumar[1,2], Cheryl Kai Ning Kang[1,2], Sragvi Verma[1,2], Diya Nanthakumarvani[1,2], Shafeeqa Abul-Hasan[1,2], Leesha Haarshiny Perumal[1,2], Maurice HT Ling[2,3,4*]

[1]Department of Applied Sciences, Northumbria University, United Kingdom
[2]Management Development Institute of Singapore, Singapore
[3]Newcastle Australia Institute of Higher Education, University of Newcastle, Australia
[4]HOHY PTE LTD, Singapore

***Correspondence author:** Maurice HT Ling, Management Development Institute of Singapore, Singapore and Newcastle Australia Institute of Higher Education, University of Newcastle, Australia and HOHY PTE LTD, Singapore; Email: mauriceling@acm.org

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Abstract

Desulfovibrio desulfuricans is a Gram-negative, anaerobic sulfate-reducing bacterium with applications in bioremediation and is likely to involve metabolic engineering and synthetic biology. Metabolic engineering and synthetic biology approaches are often guided by mathematical models. To date, no whole-cell kinetic model has been reported for this organism. In this study, we present an *Ab initio* whole-cell kinetic model of *D. desulfuricans* L4, ddsAAR26, comprising of 701 metabolites, 275 enzymes with associated transcription and translation processes and 573 enzymatic reactions, formulated as a system of ordinary differential equations. Enzymatic reactions are represented using Michaelis-Menten kinetics with median kinetic values. This establishes computational framework for future model refinement and extension.

Keywords: Whole-Cell Model; Kinetic Model; Differential Equations; AdvanceSyn Toolkit

Introduction

Sulfur is a highly dynamic element that cycles continuously between soil, water, microorganisms and living organisms. In oxygen-limited environments; such as wetlands, sediments and rice paddies; much of this cycling is driven by anaerobic microorganisms that use sulfate as a terminal electron acceptor and release hydrogen sulfide as a metabolic by-product [1]. Sulfate-Reducing Bacteria (SRB), including members of the genus *Desulfovibrio* are abundant in these environments and play a major role in shaping sulfur availability and redox conditions; thereby, linking environmental sulfur cycling to human exposure through soil, water and sulfur-rich foods [2,3]. *Desulfovibrio desulfuricans* is a Gram-negative, anaerobic, sulfate-reducing bacterium [4]. The anaerobic and nutrient-rich conditions of the human gastrointestinal tract closely resemble sedimentary environments, making it a suitable habitat for SRB. In the gut, *Desulfovibrio* species can reduce sulfate to hydrogen sulfide which may disrupt epithelial barrier integrity; thus, making sulfur metabolism a key determinant of gut homeostasis [2,5,6]. Hydrogen sulfide may influence the gut-brain axis through modulation of vagal signalling, mitochondrial function and neuroinflammatory pathways [3]. Elevated levels of *Desulfovibrio* species have been reported in neurodegenerative disorders such as Parkinson's disease [7]. Besides human health, SRB including *D. desulfuricans* are also used in the industry, including wastewater treatment systems and bioremediation of sulfate-rich effluents and these efforts is likely to involve metabolic engineering and synthetic biology in the foreseeable future [8-19].

Metabolic engineering frequently relies on mathematical modelling to evaluate potential genetic interventions [20,21]. Good Statistical Monitorings (GSMs) and Knowledge Graphs (KGs) are the prevailing modelling styles in the field [22,23]. GSMs are useful for rate-based analyses but are not ideal for predicting yields or handling complex gene knock-ins [24]. KMs address these gaps: they can forecast yields and rates and make simulated knock-ins much easier to conduct [25]. This combination of capabilities positions KMs as a strong candidate for pre-experimental evaluation of engineering concepts. Consequently, there has been an increasing call in recent years to accelerate the development of new kinetic models [26,27].

However, there is no whole cell KM of *D. desulfuricans* to-date. As such, this study aims to construct a KM of *D. desulfuricans* L4 using *Ab initio* approach by identifying enzymes from its annotated genome and identifying the corresponding reaction from KEGG [28]. The result is a whole cell KM of *D. desulfuricans* L4, named as ddsAAR26 using the nomenclature proposed by Cho and Ling which consists of 701 metabolites, 275 enzymes with corresponding transcriptions and translations and 573 enzymatic reactions [29].

Materials and Methods

Identification of Reactome

The genome of *Desulfovibrio desulfuricans* L4 (NCBI RefSeq assembly GCF_017815575.1; NCBI GenBank Accession NZ_CP072608.1) was used as source to identify enzymatic genes using the process previously described [24,30,31]. 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 [28]. 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 the Ordinary Differential Equation (ODE) formats described in Sim, et al. [32]. Estimating transcriptional activity in E. coli can be done directly using BioNumbers. The cell contains roughly 3000 RNA polymerases (BioNumbers 106199) and only about 25% are actively polymerizing (BioNumbers 111676) at 22 nt/s (BioNumbers 104109) [33-35]. With each nucleotide weighing 339.5 Da, the total output is ~5600 kDa/s (9.3×10^{-18} g/s). When this synthesis is expressed relative to a 7×10^{-16} L cell volume and 4225 genes (BioNumbers 105443), it yields 2.92 micromolar per gene per second [36]. Coupling this with an average transcript stability of 107.56 seconds (BioNumbers 107666) (0.93% decay per second), the resulting ODE is d[mRNA]/dt = 0.00292 - 0.0093[mRNA] [36-38]. Protein synthesis occurs at ~0.278 peptides/mRNA/s (BioNumbers 106382) while degradation is slow (2.78×10^{-6}/s) (BioNumbers 109924) [39,40]. Thus, d[peptide]/dt = 0.278[mRNA]-0.00000278[peptide]. The whole biochemical network was encoded as ODEs using typical enzyme constants (kcat = 13.7 s^{-1}; Km = 1 mM) and aligned with the AdvanceSyn modelling framework [30,41-43].

Model Simulation

The constructed model was tested for simulatability using AdvanceSyn Toolkit [43]. 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) C00016 (FAD), (X) C00024 (Acetyl-CoA), (XI) C00025 (L-Glutamate), (XII) C00026 (2-Oxoglutarate), (XIII) C00029 (UDP-glucose), (XIV) C00033 (Acetate), (XV) C00039 (DNA), (XVI) C00043 (UDP-N-Acetyl-Alpha-D-Glucosamine), (XVII) C00045 (Amino Acid), (XVIII) C00048 (Glyoxylate), (XIX) C00051 (Glutathione), (XX) C00063 (CTP), (XXI) C00065 (L-Serine), (XXII) C00066 (tRNA), (XXIII) C00074 (Phosphoenolpyruvate), (XXIV) C00079 (L-Phenylalanine), (XXV) C00080 (H+), (XXVI) C00084 (Acetaldehyde), (XXVII) C00093 (sn-Glycerol 3-Phosphate), (XXVIII) C00125 (Ferricytochrome c), (XXIX) C00149 ((S)-Malate), (XXX) C00188 (L-Threonine). The model was simulated using the fourth-order Runge-Kutta method 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 [44,45].

Results and Discussion

As of 29 April 2024, the annotated genome of *D. desulfuricans* L4 consists of 3030 genes, including 2943 protein coding sequences. 275 unique EC numbers consisting of 573 enzymatic reactions involving 701 metabolites were identified and developed into a

model based on AdvanceSyn Model Specification [43]. In addition, 550 ODEs acting as placeholder for enzyme transcriptions and translations were added.

Using the AdvanceSyn Toolkit [43], we executed the ddsAAR26 system and verified successful simulation through the trajectories displayed in Fig. 1. This validation confirms that the model is syntactically clean and structurally coherent as argued by previous studies constructions [24,31,46-48], which is a necessary foundation for future biological refinement. Although the relative concentrations of Adenosine Diphosphate (ADP) and coenzyme A appears elevated, this may reflect the imposed uniformity of median kinetic constants, which were chosen to allow structural validation before detailed parameterization [42]. Therefore, such results should therefore not be viewed as physiologically meaningful outputs. Instead, this model establishes a working whole-cell kinetic framework for *D. desulfuricans* L4 that is ready for enrichment with additional pathways, regulatory circuits or organism-specific kinetic datasets to support more realistic simulations [49-51].

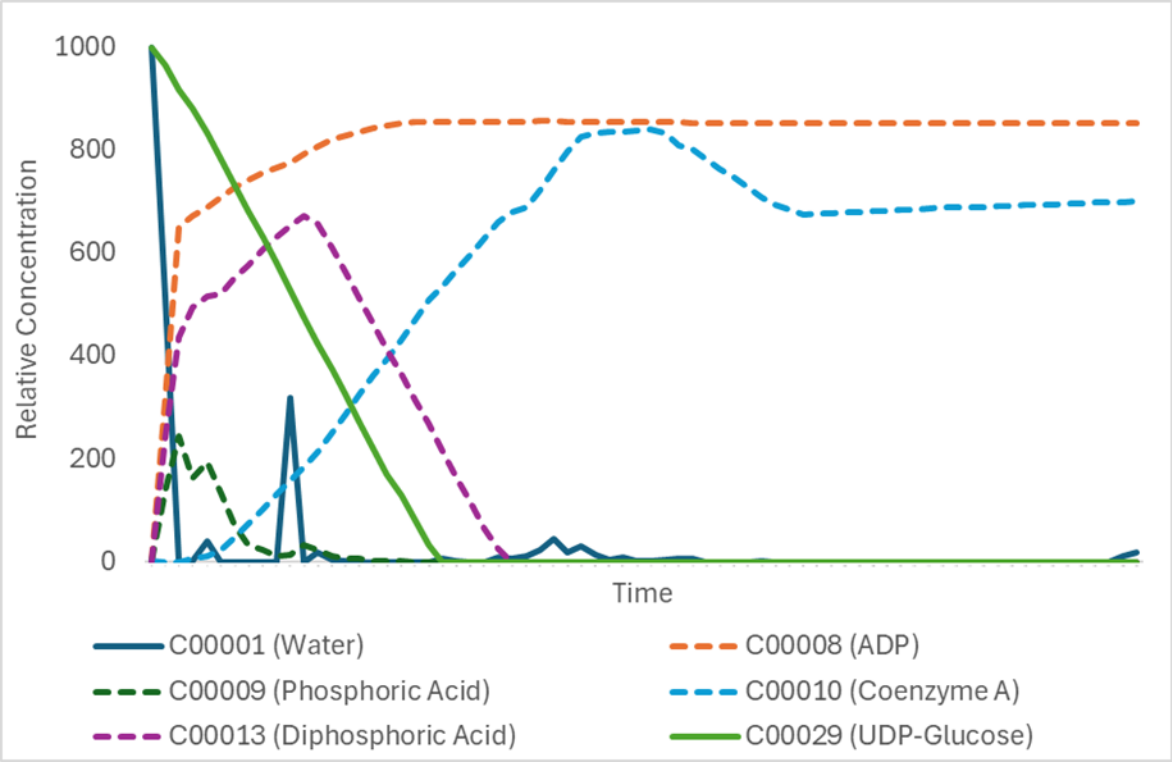

Figure 1. Selection of simulation results.

Conclusion

In this study, we present an *Ab initio* whole cell kinetic model of *Desulfovibrio desulfuricans* L4, ddsAAR26; comprising of 701 metabolites, 275 enzymes with corresponding transcriptions and translations and 573 enzymatic reactions.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding details

None.

Ethical Approval

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

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Supplementary Materials

Reaction descriptions and model can be download from https://bit.ly/ddsAAR26.

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