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Ab Initio Whole Cell Kinetic Model of *Streptococcus salivarius* JIM8777 (stjDNV26)

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ABSTRACT

Streptococcus salivarius is one of the earliest bacterial colonies of the human host which is established itself in the oral cavity within the first day after birth. It has been considered for probiotic applications due to its low virulence factor, including its potential benefits in children's health. Mathematical kinetic models generate time-dependent profiles of simulated metabolites, which can be used to guide metabolic engineering approaches. However, there is no kinetic model of S. salivarius to-date. In this study, we present a whole cell simulatable kinetic model of S. salivarius JIM8777, stjDNV26, constructed using enzymatic reactions identified via enzymes from its published genome. The resulting model consists of 842 metabolites, 364 enzymes with corresponding transcriptions and translations, and 778 enzymatic reactions; which can be a baseline model for incorporating other cellular and growth processes, or as a system to examine cellular resource allocations necessary for engineering.

Keywords

Whole-cell model, Kinetic model, Differential equations, Oral commensal, Probiotic, Human Infant, AdvanceSyn Toolkit.

Introduction

Streptococcus salivarius is one of the earliest bacterial colonizers of the human host, establishing itself in the oral cavity within the first days after birth and persisting as a dominant and stable component of the oral and upper respiratory tract microbiota throughout life [1]. *S. salivarius* exhibits immunomodulatory properties [2,3], and is generally regarded as a commensal organism with low virulence [4]. Hence, it has been considered for probiotic applications [5-7], including its potential benefits in children's health and prophylaxis [8]. As a results, various strains of engineered *S. salivarius* has been evaluated for tolerance and probiotic potential [9-11].

Mathematical modelling is a useful tool in metabolic engineering. Two broad modelling traditions dominate this space [12,13]: GSMs and KMs. GSMs, being constraint-based, are powerful but limited largely to predicting reaction rates. KMs, however, can forecast both fluxes and product yields [14], giving them an added layer of utility. They also handle in silico gene knock-ins with greater flexibility than GSMs [15]. These strengths collectively make KMs an appealing choice for early-stage assessment of engineering alternatives. In recent years, this has led to an increasing call across the field to create more robust and readily accessible kinetic models [16,17].

However, there is no whole cell kinetic models of *S. salivarius* to date. Hence, this study aims to construct a KM of *S. salivarius* JIM8777, originally was isolated from the oral cavity of a healthy human infant, using *ab initio* approach by identifying enzymes from its published genome [18], and identifying the corresponding reaction from KEGG [19]. The result is a whole cell KM of *S. salivarius* JIM8777, named as stjDNV26, using the nomenclature proposed by Cho and Ling [20], which consists of 842 metabolites,

364 enzymes with corresponding transcriptions and translations, and 778 enzymatic reactions.

Materials and Methods

Identification of Reactome

The annotated genome of *Streptococcus salivarius* JIM8777 [18] (NCBI RefSeq assembly GCF_000253315.1; NCBI GenBank Accession NC_017595.1) was used as source to identify enzymatic genes using the process previously described [15,21,22]. 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 the principles described in Sim et al. [23]. Using BioNumbers as a foundation, transcription in *Escherichia coli* can be quantified with reasonable confidence. Approximately 3000 RNA polymerases exist per cell (BioNumbers 106199) [24], though only one-quarter participate in active elongation (BioNumbers 111676) [25]. Their polymerization speed (22 nucleotides per second) (BioNumbers 104109) [26] and the average nucleotide mass (339.5 Da) correspond to an output of about 5600 kDa/s (≈9.3e-18 g/s). When normalized to a cellular volume of 7e-16 L [27] and 4225 coding genes (BioNumbers 105443) [28], this results in about 2.92 micromolar per gene per second. With mean mRNA stability of 107.56 seconds (BioNumbers 107666) [29] (0.93% decay/s) (BioNumbers 109924) [30], we obtain: d[mRNA]/dt = 0.00292 – 0.0093[mRNA]. Protein production proceeds at 0.278 peptides/s per transcript (BioNumbers 106382) [31], while *E. coli* proteins degrade at about 2.78e-6 per second. Hence: d[peptide]/dt = 0.278[mRNA] – 0.00000278[peptide]. The overall model was implemented as ODEs [21,32] using representative kinetic constants (kcat = 13.7/s, Km = 1 mM) [33], structured per AdvanceSyn specifications [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) C00008 (ADP), (IX) C00009 (Orthophosphate), (X) C00010 (CoA), (XI) C00011 (Carbon Dioxide), (XII) C00013 (Diphosphate), (XIII) C00014 (Ammonia), (XIV) C00015 (UDP), (XV) C00016 (FAD), (XVI) C00019 (S-Adenosyl-L-methionine), (XVII) C00020 (AMP), (XVIII) C00021 (S-Adenosyl-L-homocysteine), (XIX) C00022 (Pyruvate), (XX) C00024 (Acetyl-CoA), (XXI) C00025 (L-Glutamate), (XXII) C00029 (UDP-glucose), (XXIII) C00031 (D-Glucose), (XXIV) C00035 (GDP), (XXV) C00037 (Glycine), (XXVI) C00041 (L-Alanine), (XXVII) C00047 (L-Lysine), (XXVIII) C00049 (L-Aspartate), (XXIX) C00062 (L-Arginine), (XXX) C00064 (L-Glutamine), (XXXI) C00065 (L-Serine), (XXXII) C00078 (L-Tryptophan), (XXXIII) C00079 (L-Phenylalanine), (XXXIV) C00080 (H+), (XXXV) C00082 (L-Tyrosine), (XXXVI) C00097 (L-Cysteine), (XXXVII) C00147 (Adenine), (XXXVIII) C00148 (L-Proline), (XXXIX) C00183 (L-Valine). 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 *Streptococcus salivarius* JIM8777 [18] consists of 2055 genes, including 1936 protein coding sequences. 364 unique EC numbers consisting of 778 enzymatic reactions involving 842 metabolites were identified and developed into a model based on AdvanceSyn Model Specification [34]. In addition, 728 ODEs acting as placeholder for enzyme transcriptions and translations were added.

The stjDNV26 model was run using the AdvanceSyn Toolkit [34], and the resulting simulation curves in Figure 1 confirm that the model is free from syntax errors and structurally consistent as previously argued [15,22,37-41]. Achieving such a clean run is an important indicator of correctness given the complexity of whole-cell kinetic systems. The apparent increased rate of acetate production over glyoxylate may arises due to the universal use of median kinetic parameters [42], which ignore enzyme-specific behaviour and should not be interpreted biologically. The key contribution here is a simulatable and extensible whole-cell kinetic model for *S. salivarius* JIM8777. It can serve as a platform for integrating more biological realism, additional processes such as growth coupling, or comparative studies of resource allocation patterns under various metabolic scenarios [43-45].

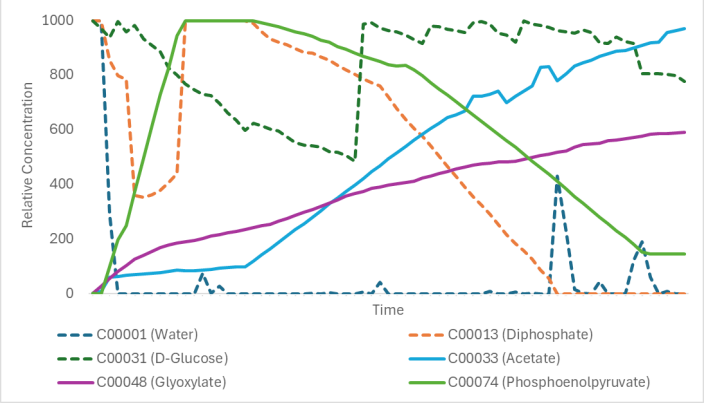

Figure 1: Selection of Simulation Results.

Conclusion

We present an *ab initio* whole cell kinetic model of *Streptococcus salivarius* JIM8777, stjDNV26; comprising of 842 metabolites,

364 enzymes with corresponding transcriptions and translations, and 778 enzymatic reactions.

Supplementary Materials

Reaction descriptions and model can be download from https://bit.ly/stjDNV26.

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