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Research Article

Ab Initio Whole Cell Kinetic Model of *Parabacteroides distasonis* APCS2/PD (pdiMLD26)

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Abstract

Parabacteroids distasonis is a key component of the human gut microbiome, and noted for its ability to produce metabolites that are beneficial for overall gut health. Hence, *P. distasonis* may be a potential target for metabolic engineering, which can benefit from a whole cell kinetic model. Currently, there are no reported kinetic models for the *P. distasonis*. Therefore, this study aims to create a whole cell simulatable kinetic model of *P. distasonis* APCS2/PD using an *ab initio* approach by identifying enzymes from its published genome. The resulting model, pdiMLD26, encompasses of 703 metabolites, 290 enzymes and 752 enzymatic reactions; which acts as a foundational framework for future research.

Keywords: Whole-cell Model; Kinetic Model; Gut Microbiome; Differential Equations; AdvanceSyn Toolkit

Introduction

Parabacteroides distasonis is an essential member of the core gut microbiome [1]. With an average abundance of 1.27% in the gut microbiota, this unassuming microbial agent has been recently identified to play a crucial role in the host wellbeing [2]. A Gram negative, anaerobic bacterium originating from the *Tannerellaceae* family from the *Bacteroides* genus, this specialist fibrolytic bacterium has a rage of degrading enzymes, essential for essential for the breakdown of complex dietary polysaccharides and host-derived glycans within the human gut, facilitating nutrient extraction and microbial cross-feeding [3,4]. There is evidence of *P. distasonis* displaying anti-inflammatory and immunomodulatory properties [5], producing metabolites that are beneficial for overall gut health [6,7], and may even improve recovery of stroke patients [8]. Hence, metabolic engineering of *P. distasonis* has been considered [9].

The process of metabolic engineering often begins with mathematical modelling, which helps prioritise genetic modifications [10,11]. The two dominant approaches [12,13], genome-scale constraint-based models (GSMs) and kinetic models

(KMs), offer different capabilities. While GSMs are effective for estimating metabolic fluxes, their scope is mainly rate-centred. KMs provide predictions of both reaction rates and metabolite yields, giving them a functional edge [14]. They also support in silico gene knock-ins more naturally than GSMs [15]. These advantages make KMs especially valuable for screening engineering ideas computationally before undertaking experiments. As a result, the scientific community has increasingly emphasised the need to develop and expand kinetic model frameworks [16,17].

However, there is no KM of *P. distasonis* to-date. Hence, this study aims to construct a KM of *P. distasonis* APCS2/PD 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 *P. distasonis* APCS2/PD, named as pdiMLD using the nomenclature proposed by Cho and Ling [20], which consists of 703 metabolites, 290 enzymes with corresponding transcriptions and translations, and 752 enzymatic reactions. This model may part of a collation of kinetic models to predict metabolite levels of gut microbiome as recently proposed [21,22].

Materials and Methods

Identification of reactome

The genome of *Parabacteroides distasonis* APCS2/PD (NCBI RefSeq assembly GCF_018279895.1; NCBI GenBank Accession NZ_CP042285.1) was used as source to identify enzymatic genes using the process previously described [15,23,24]. 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 ordinary differential equation (ODE) formats described in Sim., *et al*. [25]. Using BioNumbers-derived parameters, transcription in *E. coli* can be quantitatively approximated. Around 3000 RNA polymerase molecules are present (BioNumbers 106199) [26] but only about a quarter are active (BioNumbers 111676) [27]. Each active enzyme extends RNA at 22 nucleotides per second (BioNumbers 104109) [28], each weighing about 339.5 Da. This yields roughly 5600 kDa of RNA per second (9.3e-18 grams per second). Normalized to the 7e-16 litre volume [29] and distributed across 4225 coding genes (BioNumbers 105443) [30], this corresponds to 2.92 micromolar per gene per second. With an mRNA lifetime of 107.56 seconds (BioNumbers 107666) [31] (0.93% decay/s), the transcriptional rate law becomes d[mRNA]/dt = 0.00292 – 0.0093[mRNA]. Translation proceeds at about 0.278 peptides/s per transcript (BioNumbers 106382) [32], and degradation removes proteins at 2.78e-6 grams per second (BioNumbers 109924) [33]. Thus: d[peptide]/dt = 0.278[mRNA] – 0.00000278[peptide]. The broader metabolic system was represented as ODEs [23,34] with median kinetic constants (kcat = 13.7 per second, Km = 1 mM) [35] and documented following AdvanceSyn guidelines [36].

Model simulation

The constructed model was tested for simulatability using AdvanceSyn Toolkit [36]. 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) C00015 (UDP), (XI) C00025 (L-Glutamate), (XII) C00031 (D-Glucose), (XIII) C00037 (Glycine), (XIV) C00041 (L-Alanine), (XV) C00047 (L-Lysine), (XVI) C00049 (L-Aspartate), (XVII) C00064 (L-Glutamine), (XVIII) C00065 (L-Serine), (XIX) C00073 (L-Methionine), (XX) C00097 (L-Cysteine), (XXI) C00133 (D-Alanine), (XXII) C00148 (L-Proline). The model was simulated using the fourth-order Runge-Kutta method [37,38] 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 *P. distasonis* APCS2/PD consists of 4512 genes, including 4344 protein coding sequences. 290 unique EC numbers consisting of 752 enzymatic reactions involving 703 metabolites were identified and developed into a model based on AdvanceSyn Model Specification [36]. In addition, 580 ODEs acting as placeholder for enzyme transcriptions and translations were added.

The pdiMLD26 model was executed within the AdvanceSyn Toolkit [36], and the presence of valid simulation outputs in Figure 1 confirms that the model is well-formed and free of syntax issues that commonly arise in detailed kinetic models. Although accumulation of ADP and oxaloacetate is observed, this effect stems from the median kinetic parameters applied throughout the model [35], which homogenize reaction behaviours and distort relative fluxes. These outcomes should be regarded only as structural tests as argued in recent model constructions [15,24,39-43]. Nonetheless, this work provides a complete and simulatable whole-cell kinetic model of *P. distasonis* APCS2/PD. It offers a flexible basis for incorporating more refined kinetics, expanding metabolic coverage, or conducting computational experiments on how limited cellular resources are allocated across competing pathways [44-46]. This model may also be incorporated into a collation of kinetic models, to be a meta-model for the predicting metabolite levels produced by various interacting gut microorganisms as recently proposed [21,22].

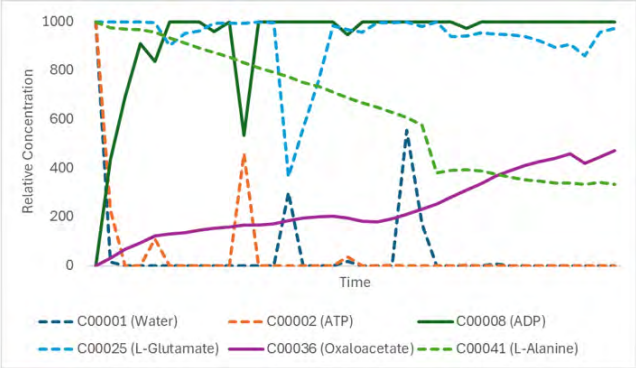

Figure 1: Selection of Simulation Results. A sample of 6 metabolites were shown – 4 of which (in dotted lines – water, ATP, and L-glutamine, and L-alanine) were set at 1000 mM in the model while the other 2 (in solid lines – ADP, and oxaloacetate) were set at 1 mM in the model. The relative concentrations over time shows fluctuations – an advantage of KMs over GSMs. It is important to note that these values only show that the KM is simulatable rather than deriving important insights as median kinetic parameters applied throughout the model.

Conclusion

In this study, we present an *ab initio* whole cell kinetic model of *Parabacteroides distasonis* APCS2/PD. The resulting kinetic model, pdiMLD26; comprising of 703 metabolites, 290 enzymes with corresponding transcriptions and translations, and 752 enzymatic reactions.

Supplementary Materials

Reaction descriptions and model can be download from https://bit.ly/pdiMLD26.

Conflict of Interest

The authors declare no conflict of interest.

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