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Research Article

UniKin2 – A Universal, Pan-Reactome Kinetic Model

Wira Bin Ambel[1,2], Lay Ping Tan[1,2], Dinis Toh[1,2], Divya Thirunavukarasu[1,2], Kowsalya Natarajan[1,2], Maurice HT Ling[2,3,4,3]

[1]*School of Health & Life Sciences, Teesside University, UK*
[2]*Management Development Institute of Singapore, Singapore*
[3]*Newcastle Australia Institute of Higher Education, University of Newcastle, Australia*
[4]*HOHY PTE LTD, Singapore*

Abstract

Whole-cell kinetic models have been used to describe the dynamic response of metabolic pathways under various conditions or analyse the behaviour of enzymes and metabolic networks. Previously, UniKin1 was developed as a foundational and universal whole-cell kinetic model using data from Kyoto Encyclopaedia of Genes and Genomes (KEGG). However, UniKin1 was relatively small and only consists of 306 metabolites, 310 enzymes, and 566 reactions; thereby, restricted its ability to simulate an entire cellular system. In this study, we expanded on UniKin1 by using all the reaction data from KEGG as of 24 January 2025, into UniKin2 which consisted of 30669 metabolites, 9420 enzymes, and 9420 reactions. Hence, UniKin2 can be potentially used for many different purposes such as research in organism-independent simulations, exploration of host-pathogen interactions and metabolic rewiring of diseases.

Introduction

Enzyme kinetics is often mathematically modelled using Michaelis-Menten equation [1], which can be aggregated kinetic models [2]. These kinetic models can be used to describe the dynamic response of metabolic pathways under various conditions in the organisms [3] or to analyse the behaviour of enzymes and metabolic networks [4], and have been shown to contribute significantly to various fields like oncology therapy and pharmacology by providing insights into factors like enzymes regulations, dose optimisation and drug discovery [5].

UniKin1 was developed as a foundational and universal whole-cell kinetic model to simulate enzymatic pathways by utilising rate laws such as Michaelis-Menten equation. It utilises a structure using data extracted from Kyoto Encyclopaedia of Genes and Genomes (KEGG) to generate kinetic models across all species which consists of core reactions linking glucose to 20 amino acids and 5 nucleotides [6]. However, UniKin1 was limited by its relatively narrow reaction datasets as it did not integrate the full reactions available in KEGG which restricted its ability to simulate an entire cellular system [7].

In this study, we expanded on UniKin1 [6] to UniKin2 by using all the reactions available in KEGG [8] as of 24 January 2025.

Materials and Methods

Model Construction

Entire reaction data was extracted from KEGG [8] as of 24 January 2025, and assembled in accordance to AdvanceSyn Model Specification [9]. Each enzymatic reaction was modelled using a standard irreversible Michaelis–Menten rate equation, with a constant turnover number kcat of 13.7 per second and Michaelis–Menten constant km of 1.0 mM, in accordance with the previously established median kinetic values [10]. Each enzyme production was modelled as a pair of default mRNA transcription and peptide translation, using data from *Escherichia coli* as previously explained [7, 11–16].

Corresponding Author: **Maurice HT Ling,** *HOHY PTE LTD, Singapore, Newcastle Australia Institute of Higher Education, University of Newcastle, Australia.*

The resulting mRNA concentration can be expressed as d[mRNA]/dt = 0.00292 – 0.0093[mRNA] mM per second, while the resulting peptide concentration can be expressed by d[peptide]/dt = 0.278[mRNA] – 0.00000278[peptide] uM per second.

Model Simulation

The constructed model was tested for simulatability using AdvanceSyn Toolkit [9]. Initial concentrations of all mRNAs and enzymes were set to 0.0 mM. Metabolite concentrations were uniformly initialised at 1.0 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) C00009 (Orthophosphate), (ix) C00011 (Carbon Dioxide), (x) C00014 (Ammonia), (xi) C00020 (AMP), (xii) C00025 (L-Glutamate), (xiii) C00031 (D-Glucose), (xiv) C00037 (Glycine), (xv) C00041 (L-Alanine), (xvi) C00044 (GTP), (xvii) C00047 (L-Lysine) (xviii) C00049 (L-Aspartate), (xix) C00055 (CMP), (xx) C00062 (L-Arginine), (xxi) C00064 (L-Glutamine), (xxii) C00065 (L-Serine), (xxiii) C00073 (L-Methionine), (xxiv) C00075 (UTP), (xxv) C00078 (L-Tryptophan), (xxvi) C00079 (L-Phenylalanine), (xxvii) C00082 (L-Tyrosine), (xxviii) C00095 (D-Fructose), (xxix) C00097 (L-Cysteine), (xxx) C00105 (UMP), (xxxi) C00123 (L-Leucine), (xxxii) C00124 (D-Galactose), (xxxiii) C00135 (L-Histidine), (xxxiv) C00137 (Dambose), (xxxv) C00144 (GMP), (xxxvi) C00148 (L-Proline), (xxxvii) C00152 (L-Asparagine), (xxxviii) C00159 (D-Mannose), (xxxix) C00183 (L-Valine), (xl) C00188 (L-Threonine), (xli) C00208 (Maltose), (xlii) C00329 (D-Glucosamine), (xliii) C00407 (L-Isoleucine), (xliv) C05688 (L-Selenocysteine). The model was simulated using the fourth-order Runge-Kutta method [17, 18] 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 resulting kinetic model, UniKin2, consists of 30669 metabolites, 9420 enzymes, and 9420 reactions. This is significantly larger than UniKin1 which consists of 306 metabolites, 310 enzymes, and 566 reactions [6, 19]. Our simulation results (Figure 1) suggests that the model is free from syntax error as the presence of simulation results suggests that the constructed model can be simulated – a cornerstone test used in previous studies [7, 11–16].

UniKin2 can be used for large-scale simulation of metabolic dynamics across an organism-independent framework by integrating all pathways from the KEGG database. This model can potentially provide critical insights on how one pathway can influence global metabolic behaviour as seen in diseases that are characterised by widespread metabolic rewiring like cancer and diabetes. Such model can be useful

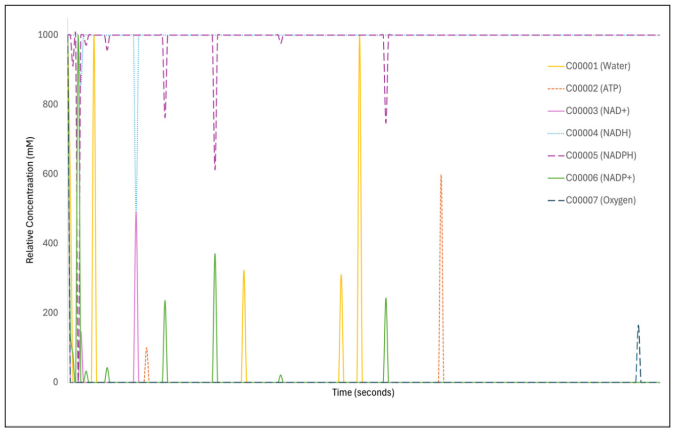

Figure1. *Selection of Simulation Results*

in developing new biomarkers to accurately diagnose different diseases [20, 21]. Additionally, the organism-independent model of UniKin2 enables the simulation of shared metabolic reactions between hosts and pathogens. This facilitates identification of metabolic choke points due to competitive nutrient utilisation during an infection [22]. These insights can allow for an antimicrobial development by identifying metabolic dependencies unique to pathogens while absent in humans[23].

Furthermore, the model facilitates comparative kinetic metabolic studies of different species by tailoring its reactions specific to the individual organisms. This makes UniKin2 a promising tool for metabolic engineering in different organisms and revolutionising pharmacological formulations [24].

However, there are several limitations with UniKin2. It assumes uniform kinetic parameters across all reactions and does not incorporate other factors such

as metabolic compartmentalisation, gene regulations and post-translational modifications. Metabolic compartmentalisation affects metabolic regulations by providing specific chemical environments and protection from reactive metabolites [25]. Additionally, this model does not consider gene regulation and post-translation modifications as they modulate enzymatic activity by adapting to the environment and internal stimulus [26].

Conclusion

By using all available reactions from KEGG as of 24 January 2025, we expanded UniKin1; which consists of 306 metabolites, 310 enzymes, and 566 reactions; to UniKin2; consists of 30669 metabolites, 9420 enzymes, and 9420 reactions.

References

[1] Srinivasan B (2022) A guide to the Michaelis–Menten equation: steady state and beyond. *The FEBS Journal* 289(20):6086–6098. https://doi.org/10.1111/febs.16124

[2] Sim BJH, Tan NTF, Ling MHT (2025) Multilevel Metabolic Modelling Using Ordinary Differential Equations. *Encyclopedia of Bioinformatics and Computational Biology (Second Edition)*, eds Ranganathan S, Cannataro M, Khan AM (Elsevier, Oxford), pp 491–498. https://doi.org/10.1016/B978-0-323-95502-7.00056-7

[3] Tomczak JM, Węglarz-Tomczak E (2019) Estimating kinetic constants in the Michaelis–Menten model from one enzymatic assay using Approximate Bayesian Computation. *FEBS Letters* 593(19):2742–2750. https://doi.org/10.1002/1873-3468.13531

[4] Lorente-Arevalo A, Garcia-Martin A, Ladero M, Bolivar JM (2022) Chemical Reaction Engineering to Understand Applied Kinetics in Free Enzyme Homogeneous Reactors. *Enzyme Engineering*, Methods in Molecular Biology., eds Magnani F, Marabelli C, Paradisi F (Springer US, New York, NY), Vol. 2397, pp 277–320. https://doi.org/10.1007/978-1-0716-1826-4_15

[5] Ma C, Gurkan-Cavusoglu E (2024) A comprehensive review of computational cell cycle models in guiding cancer treatment strategies. *npj Systems Biology and Applications* 10(1):71. https://doi.org/10.1038/s41540-024-00397-7

[6] Murthy MV, Balan D, Kamarudin NJ, Wang VC, Tan XT, Ramesh A, Chew SS, Yablochkin NV, Mathivanan K, Ling MH (2020) UniKin1: A Universal, Non-Species-Specific Whole Cell Kinetic Model. *Acta Scientific Microbiology* 3(10):04–08. https://doi.org/10.31080/ASMI.2020.03.0692

[7] Wong TB, Le MA, Arivazhagan M, Senthilkumar A, Yeo KY, Saisudhanbabu T, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Models of Escherichia coli BL21 (ebeTBSW25) and MG1655 (ecoMAL25). *Scholastic Medical Sciences* 3(2):01–04.

[8] Kanehisa M, Furumichi M, Sato Y, Ishiguro-Watanabe M, Tanabe M (2021) KEGG: Integrating Viruses and Cellular Organisms. *Nucleic Acids Research* 49(D1):D545–D551. https://doi.org/10.1093/nar/gkaa970

[9] Ling MH (2020) AdvanceSyn Toolkit: An Open Source Suite for Model Development and Analysis in Biological Engineering. *MOJ Proteomics & Bioinformatics* 9(4):83–86.

[10] Bar-Even A, Noor E, Savir Y, Liebermeister W, Davidi D, Tawfik DS, Milo R (2011) The Moderately Efficient Enzyme: Evolutionary and Physicochemical Trends Shaping Enzyme Parameters. *Biochemistry* 50(21):4402–4410. https://doi.org/10.1021/bi2002289

[11] Kwan ZJ, Teo W, Lum AK, Ng SM, Ling MH (2024) Ab Initio Whole Cell Kinetic Model of Stutzerimonas balearica DSM 6083 (pbmKZJ23). *Acta Scientific Microbiology* 7(2):28–31.

[12] Saisudhanbabu T, Yeo KY, Arivazhagan M, Senthilkumar A, Le MA, Wong TB, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Limosilactobacillus fermentum EFEL6800 (lfeTS24). *EC Clinical and Medical Case Reports* 8(4):01–04.

[13] Arivazhagan M, Senthilkumar A, Yeo KY, Saisudhanbabu T, Le MA, Wong TB, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Bifidobacterium bifidum BGN4 (bbfMA24). *Acta Scientific Nutritional Health* 9(1):42–45. https://doi.org/10.31080/ASNH.2024.08.1479

[14] Senthilkumar A, Madhunisha A, Yeo KY, Saisudhanbabu T, Le MA, Wong TB, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Lactobacillus acidophilus NCFM (lacAS24). *Journal of Clinical Immunology & Microbiology* 6(1):1–5. https://doi.org/10.46889/JCIM.2025.6103

[15] Maiyappan S, Sim SS, Ramesh G, Low L, Matarage ML, Ling MH (2025) Four Ab Initio Whole Cell Kinetic Models of Bacillus subtilis 168 (bsuLL25) 6051-HGW (bshSM25), N33 (bsuN33SS25), FUA2231 (bsuGR25). *Journal of Clinical Immunology & Microbiology* 6(2):1–6. https://doi.org/10.46889/jcim.2025.6206

[16] Yeo KY, Arivazhagan M, Senthilkumar A, Saisudhanbabu T, Le MA, Wong B, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Yarrowia lipolytica CLIB122 (yliYKY24). *Medicon Medical Sciences* 8(4):01–06.

[17] Yong B (2019) The Comparison of Fourth Order Runge-Kutta and Homotopy Analysis Method for Solving Three Basic Epidemic Models. *Journal of Physics: Conference Series* 1317:012020. https://doi.org/10.1088/1742-6596/1317/1/012020

[18] Ling MH (2016) COPADS IV: Fixed Time-Step ODE Solvers for a System of Equations Implemented as a Set of Python Functions. *Advances in Computer Science: an International Journal* 5(3):5–11.

[19] Cho JL, Ling MH (2021) Adaptation of Whole Cell Kinetic Model Template, UniKin1, to Escherichia coli Whole Cell Kinetic Model, ecoJC20. *EC Microbiology* 17(2):254–260.

[20] Chandel NS (2021) Lipid Metabolism. *Cold Spring Harbor Perspectives in Biology* 13(9):a040576. https://doi.org/10.1101/cshperspect.a040576

[21] Martins Conde P, Pfau T, Pires Pacheco M, Sauter T (2021) A dynamic multi-tissue model to study human metabolism. *npj Systems Biology and Applications* 7(1):5.p\https://doi.org/10.1038/s41540-020-00159-1

[22] Taylor CM, Wang Q, Rosa BA, Huang SC-C, Powell K, Schedl T, Pearce EJ, Abubucker S, Mitreva M (2013) Discovery of Anthelmintic Drug Targets and Drugs Using Chokepoints in Nematode Metabolic Pathways. *PLoS Pathogens* 9(8):e1003505. https://doi.org/10.1371/journal.ppat.1003505

[23] Roemer T, Boone C (2013) Systems-level antimicrobial drug and drug synergy discovery. *Nature Chemical Biology* 9(4):222–231. https://doi.org/10.1038/nchembio.1205

[24] Brunk E, Sahoo S, Zielinski DC, Altunkaya A, Dräger A, Mih N, Gatto F, Nilsson A, Preciat Gonzalez GA, Aurich MK, Prlić A, Sastry A, Danielsdottir AD, Heinken A, Noronha A, Rose PW, Burley SK, Fleming RMT, Nielsen J, Thiele I, Palsson BO (2018) Recon3D Enables a Three-Dimensional View of Gene Variation in Human Metabolism. *Nature Biotechnology* 36(3):272–281. https://doi.org/10.1038/nbt.4072

[25] Bar-Peled L, Kory N (2022) Principles and functions of metabolic compartmentalization. *Nature Metabolism* 4(10):1232–1244. https://doi.org/10.1038/s42255-022-00645-2

[26] Oliveira AP, Sauer U (2012) The importance of post-translational modifications in regulating Saccharomyces cerevisiae metabolism. *FEMS Yeast Research* 12(2):104–117. https://doi.org/10.1111/

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