FROG Analysis Ensures the Reproducibility of Genome Scale Metabolic Models

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Authors

Karthik Raman Miroslav Kratochvíl Brett G. Olivier Matthias König Pratyay Sengupta Dinesh Kumar Kuppa Baskaran Tung V N Nguyen Daniel Lobo St Elmo Wilken Krishna Kumar Tiwari Aswathy K. Raghu Indumathi Palanikumar Lavanya Raajaraam Maziya Ibrahim Sanjaay Balakrishnan Shreyansh Umale Frank Bergmann Tanisha Malpani Venkata P Satagopam **Reinhard Schneider** Moritz E. Beber Sarah Keating Mihail Anton Alina Renz Meiyappan Lakshmanan Dong-Yup Lee Lokanand Koduru Reihaneh Mostolizadeh Oscar Dias Emanuel Cunha Alexandre Oliveira Yi Qing Lee Karsten Zengler Rodrigo Santibáñez-Palominos Manish Kumar Matteo Barberis Bhanwar Lal Puniya Tomáš Helikar Hoang V. Dinh Patrick F. Suthers Costas D. Maranas Isabella Casini Seyed Babak Loghmani Nadine Veith **Nantia Leonidou** Feiran Li Yu Chen Jens Nielsen GaRyoung Lee Sang Mi Lee Gi Bae Kim Pedro T. Monteiro Miguel C. Teixeira Hyun Uk Kim Sang Yup Lee Ulf W. Liebal Lars M. Blank Christian Lieven Chaimaa Tarzi Claudio Angione Manga Enuh Blaise Çelik Pınar Aytar Mikhail Kulyashov Ilya Akberdin Dohyeon Kim Sung Ho Yoon Zhaohui Xu Jyotshana Gautam William T. Scott Peter J. Schaap Jasper J. Koehorst Cristal Zuñiga Gabriela Canto-Encalada Sara Benito-Vaquerizo Ivette Parera Olm Maria Suarez-Diez Qianqian Yuan Hongwu Ma Mohammad Mazharul Islam Jason A. Papin Francisco Zorrilla Kiran Raosaheb Patil Arianna Basile Juan Nogales Granado San León Freddy Castillo-Alfonso Roberto Olivares-Hernández Gabriela Canto-Encalada Gabriel Vigueras-Ramírez **Henning Hermjakob** Andreas Dräger

Abstract

Genome-scale metabolic models (GEMs) and other constraint-based models (CBMs) play a pivotal role in understanding biological phenotypes and advancing research in areas like metabolic engineering, human disease modelling, drug discovery, and personalized medicine. Despite their growing application, a significant challenge remains in ensuring the reproducibility of GEMs, primarily due to inconsistent reporting and inadequate model documentation of model results. Addressing this gap, we introduce FROG analysis, a community-driven initiative aimed at standardizing reproducibility assessments of CBMs and GEMs. The FROG framework encompasses four key analyses—Flux variability, Reaction deletion, Objective function, and Gene deletion—to produce standardized, numerically reproducible FROG reports. These reports serve as reference datasets, enabling model evaluators, curators, and independent researchers to verify the reproducibility of GEMs systematically.

BioModels, a leading repository of systems biology models, has integrated FROG analysis into its curation workflow, enhancing the reproducibility and reusability of submitted GEMs. In our study evaluating 65 GEM submissions from the community, approximately 40% reproduced without intervention, 28% requiring minor adjustments, and 32% needing input from authors. The standardization introduced by FROG analysis facilitated the detection and resolution of issues, ultimately leading to the successful reproduction of all models. By establishing a standardized and comprehensive approach to evaluating GEM reproducibility, FROG analysis significantly contributes to making CBMs and GEMs more transparent, reusable, and reliable for the broader scientific community.