FAIR sharing of reproducible and reusable COVID-19 models

Kausthubh Ramachandran[1], Matthias König[2,], Martin Scharm[3], Dagmar Waltemath[4], Henning Hermjakob[1*], Rahuman S Malik Sheriff [1*]

[1] - European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton, Cambridge, UK

[2] - Institute for Theoretical Biology, Humboldt-University Berlin, Berlin, Germany

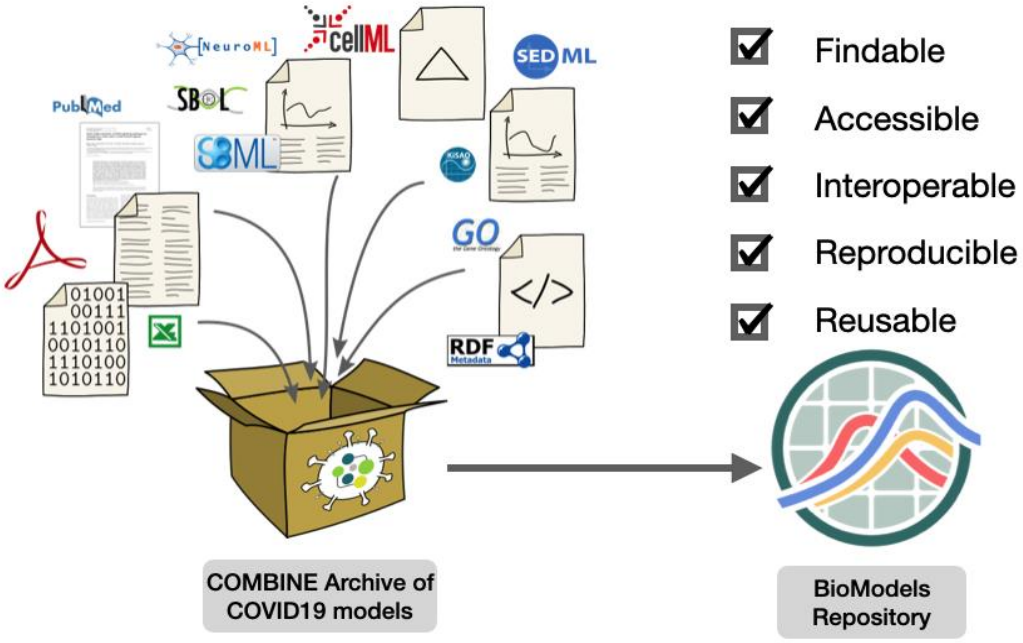
[3] - Department of Systems Biology and Bioinformatics, University of Rostock, 18051 Rostock, Germany

[4] - Department of Medical Informatics, Institute for Community Health, University Medicine Greifswald, Greifswald, Germany

*Corresponding authors:

Rahuman S. Malik Sheriff – sheriff@ebi.ac.uk, Henning Hermjakob – hhe@ebi.ac.uk

Graphical Abstract



Implementing the standards developed by the systems biology community to encode and share COVID-19 epidemiological models can serve as a roadmap to enhance the findability, accessibility, interoperability, reusability of these models. Encoding COVID-19 transmission models using machine readable SBML format, annotating them with cross-references to data resources, packaging up all associated files in COMBINE archives for single-file sharing, and finally curating and disseminating them through a public repository such as BioModels can significantly enhance the reproducibility and repurposing potential.

Introduction

Mathematical modeling of infectious disease transmission using ordinary differential equations (ODEs) has been central to epidemiology for decades. In 1927, Kermack and McKendrick first published the Susceptible-Infected-Recovered (SIR) model to forecast the growth of epidemics[1]. Since then, the SIR model and its derivative versions are used to estimate key parameters, forecast trends in the variation of different variables such as proportion of susceptible population, daily infections, mortality, and test the validity of hypotheses using available data. Disease transmission models for SARS-CoV-2 are used by governments to implement non-pharmaceutical interventions like lockdowns across the globe[2]. More specific transmission models for SARS-CoV-2 variants including the most contagious Delta and Omicron and their transition stages were also developed.

ODEs of epidemiological models representing disease transmission are encoded in a programming language to enable numerical simulation, analysis, and automated visualizations of epidemic forecasts. Since 2020, the number of models simulating transmission dynamics of COVID-19 has increased tremendously. This has prompted several prominent groups to put out calls for transparency in COVID-19 epidemiological research[3–5]. It is normally expected that published models and their results can be reproduced by other scientists with reasonable effort and thus can be trusted. In our recent study[6], we systematically analyzed 455 ordinary differential equation (ODE) models from published research across various fields of biomedical science. We found that the simulation results of nearly half of the published models could not be reproduced with the information provided in the associated publication including supplementary material.

One major issue is that model codes are hard to locate. They are usually spread across different resources like GitHub or personal websites and are not available on a common, publicly accessible repository. The next issue is poor interoperability between different modeling languages and tools. Model codes, when publicly available, are represented in different programming languages and software with diverse coding formats, and they often contain ambiguous annotations, versions, and comments which makes repurposing more difficult. Furthermore, misprints, typographical errors, missing or incomplete information, mismatch between the code and the description in the publication create more obstacles to reproduce, reuse, and repurpose models[6].

Anyone or a combination of the listed roadblocks usually results in the scenario where a modeler is forced to spend a significant amount of time in mining the model code, verifying code reproducibility, repurposing the code to work in the preferred programming environment, and then reusing the model as needed. To reduce costs and effort as well as to respect good scientific practices, it is essential to create and share epidemiological models that are both reliable and reproducible to maximize utility and ensure widespread use. Particularly in an epidemic situation the time needed to reproduce a published result is a critical factor.

Several of these issues were recognized as roadblocks to reproducibility in epidemiological research as early as 2006[7]. Since then, the epidemiology community has taken significant steps to improve the transparency and reproducibility of their studies. A global platform (https://vivli.org/) for sharing clinical data was set up with the expectation that it will be expanded to eventually include non-clinical trial data including epidemiological data[8]. There have also been calls to post the code used to analyze the data publicly along with the data and results obtained from running the code[9]. But these steps are not sufficient to ensure full reproducibility as they do not address the issues of interoperability and ambiguity. Hence, there is a need for more comprehensive measures to increase the reproducibility and ultimately the reliability of epidemiological studies.

The systems biology community faced similar issues and has spent years addressing them. In this article, we outline the measures adopted by the systems biology community to improve model reproducibility and reusability. Furthermore, we demonstrate that these measures can be readily adapted for epidemiological models with minimal effort. We present a proof of concept by rebuilding 24 published COVID-19 transmission models using the systems biology community guidelines and infrastructures. We hope that this effort will be well received by the epidemiological modeling community and can serve as a roadmap to improve reproducibility and reusability in epidemiological modeling.

FAIR sharing of models

Since the SIR model was introduced in 1927, epidemiological models have grown in complexity. The programming tools used to handle these models have also diversified alongside the emergence of programming packages in different languages like R and Python, and very specific software tools such as the Spatiotemporal Epidemiological Modeler (STEM)[10] or the Epidemiological Modeling (EMOD) software[11]. Earlier surveys of the field indicated that 30% of the publications did not detail the steps taken to perform the statistical analyses while 70% specified the use of a specific software package. But, in most cases, the software or packages used were not reported to be available. This has unintentionally led to the accumulation of multiple incompatibilities[7].

Mathematical models in systems biology also have become complex through the rise of interdisciplinary research. Early on the modeling community, therefore, adopted the FAIR principles for data stewardship – Findable, Accessible, Interoperable, and Reusable – to act as a guide to create and share reusable models[12]. The developed best practices, guidelines, and implementations can easily be applied to the epidemiological models (Box1).

Box 1: Steps to share an epidemiological model using FAIR guidelines

- To increase findability, create a permanent and persistent digital identifier (ID) unique to the model by submitting the model to a database such as BioModels[13].

This will facilitate easy identification of the model and its variants and versions.

- To facilitate accessibility, employ standardized protocols which are free and universally implementable to retrieve the model's data or metadata, as available in the BioModels repository. The protocols are also required to employ authorization mechanisms where necessary.

- To ensure interoperability, encode models in a formal, machine-readable format such as the Systems Biology Markup Language (SBML)[14], encode simulation conditions in the Simulation Experiment Description Markup Language (SED-ML)[15], and distribute the codes as COMBINE archives[16].

- To promote reusability, semantically enrich models with standard annotations that specify their different properties and attributes in an unambiguous manner; use suitable ontology terms and cross-references using identifiers.org[17], a perennial URL provider.

Improving model interoperability and reusability

To comply with FAIR principles, at first, the model codes should be encoded in standardized formats to promote interoperability and then semantically enriched with relevant annotations to eliminate ambiguity in the description of model components. Systems biology modelers have formulated and used standard languages like SBML[14] and CellML[18] to encode models and SED-ML[15] to encode simulation conditions. These languages support a wide range of mathematical frameworks and modeling approaches including epidemiological compartmental models. These languages were also developed to handle RDF-based annotations in accordance with the Minimal Information Required to Annotate Model (MIRIAM) guidelines[19] and hence can be used to describe the context of the model.

SBML is a community standard developed under the umbrella of the Computational Modelling in Biology Network (COMBINE) [20] and widely used by modelers to encode, publish and exchange models. Several tools support SBML models including several standalone modeling tools with user-friendly GUIs like COPASI[21], and Cell Designer[22]. SBML can also be imported and interconverted into a human-readable text-based language called Antimony and handled using command-line tool Tellurium in a Python environment[23]. SBML models can be built, manipulated, simulated, analyzed and/or visualized in many of these tools. Other popular simulation platforms like R[24], Mathematica[25] also have dedicated libraries to handle SBML files and run simulations. MatLab SimBiology toolbox also supports SBML. With high interoperability, a SBML model can be readily imported into a wide range of supporting software and further utilized by the modeler, thereby allowing straightforward reproducibility assessment of the model. Epidemiological models of varying structural complexity can be encoded in SBML which

leads to increased interoperability and reusability. However, there are still open opportunities for further development of SBML; one example is the support for contact matrix in epidemiological models, without which multiple equations with individual contact parameters need to be encoded. Parameter estimation can be performed using SBML-supporting tools such as COPASI, MATLAB, D2D, dMOD, parPE, pyABC and pyPESTO[26]. Hence, adapting SBML for epidemiological modeling will provide an added advantage in addition to tackling several of the issues which are impediments to model reproducibility and repurposing.

To enable sharing of models and virtual experiments through a single file, the Open Modelling EXchange (OMEX)[16] format was developed, and it became the basis for the COMBINE archive (Figure 1b). A COMBINE archive is a compressed file that contains all files necessary to reproduce simulation studies. These files may be model files, simulation setups, semantic annotations, descriptions of graphical network layouts, result tables, etc. Since the development of the COMBINE archive, several software tools capable of creating and importing the OMEX file format have been deployed.

Improving model findability and accessibility

While encoding models in standard formats like SBML improves interoperability and reusability, it is also essential to make these models easily findable and accessible. The systems biology community addressed the requirement by setting up several public repositories for model sharing. BioModels is one of the early repositories established 16 years ago and was among the first to endorse and accept submissions in the standard SBML format. It can host submissions from different modeling approaches in any format including the R, C++, Python, MATLAB, Mathematica, SBML, and OMEX formats[27]. By hosting over 2350 models from peer-reviewed literature among which about 1040 are manually curated, BioModels has increased the accessibility, reproducibility, and reusability of models in the systems biology community[28].

One major reason for the enduring and expanding popularity of BioModels is its model curation service. All models submitted to BioModels generate a unique and persistent model identifier. Model submissions are then manually curated by the BioModels team. In the curation process (Figure 1), a curator examines the peer-reviewed publication associated with the model, encodes the model in a standard format like SBML, simulates it using a tool different from the original one used by the authors, reproduces the results, and visualizes the output. At least one of the simulation figures in the publication should be reproduced to consider a model as curated. When the simulation is reproduced, the curator semantically enriches the model by adding annotations to unambiguously indicate all the entities in the model. The curator also creates files in the OMEX and SBML formats and makes all these files publicly available and tags the submission as curated. This rigorous curation pipeline at BioModels ensures the availability of reproducible and reusable model files in the public domain that can be easily accessed using the submission's unique identifier. The semantic annotations further enable sophisticated

mining of models through keyword-based search and facets-based filtering. All the models in BioModels are freely accessible under CC0 license.

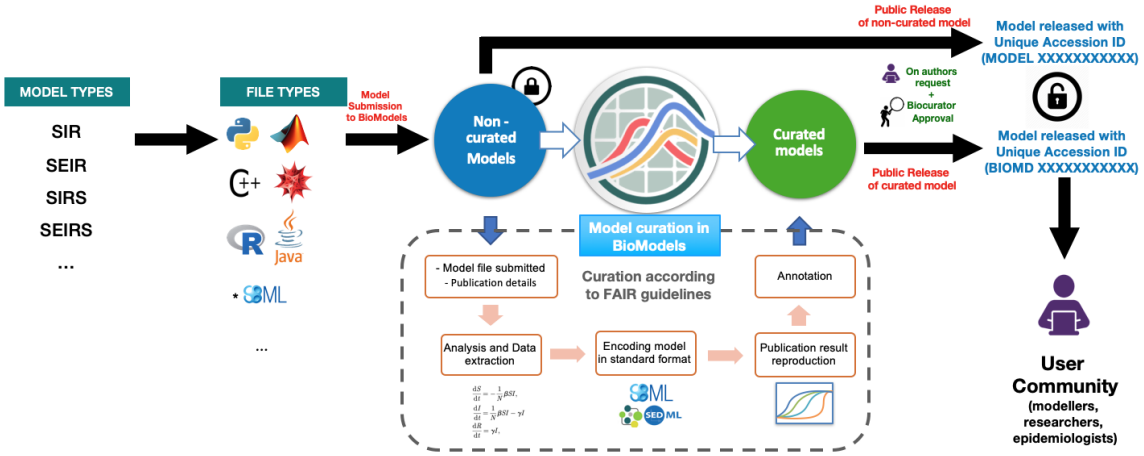


Figure 1: Model submission and FAIR guidelines-compliant curation pipeline in the BioModels: Currently BioModels accepts submissions of SIR models and their derivative versions in any file format. Models submitted can be kept private and released when the associated publication becomes publicly available. The submitted models are manually curated rigorously following FAIR guidelines before the model is released to the public domain. If the submission does not include a standard file format, the model is re-encoded in SBML and SED-ML using tools like COPASI and Tellurium and semantically enriched with controlled vocabularies. At least one simulation figure is reproduced. All model codes and associated files are compressed into a COMBINE archive to enable single file dissemination via the BioModels platform.

FAIR COVID-19 model collection

Epidemiological models of COVID-19 capture the transmission dynamics driven by interactions between individuals of differing disease statuses. Following FAIR principles and the curation pipeline as described earlier, we manually curated 24 COVID-19 transmission models from peer-reviewed, published manuscripts (Table 1). These models were carefully examined, re-encoded in the SBML format, and simulated using COPASI. If at least one of the simulation figures from the model publication is reproduced, the SBML model is semantically enriched with controlled vocabularies. SBML model file, its associated SED-ML files, and other supporting files are then packed as COMBINE archives and published openly in the BioModels with a permanent, unique identifier. Our COVID-19 collection page can be accessed at https://www.ebi.ac.uk/biomodels/covid-19. The verified reproducible SBML code and the COMBINE archives of these models provide higher interoperability thus benefiting a broad scientific community that uses diverse programming environments. The full list of models can be accessed at https://www.ebi.ac.uk/biomodels/search?query=submitter_keywords:COVID-19&domain=biomodels.

The models in our collection provided insights about how disease transmission occurs in the real world and helped to assess the impact of non-pharmaceutical interventions to control disease spread. In such models, the population is usually divided into mutually exclusive compartments and the spread of disease between compartments happens via interaction between them. The simplest model of this kind is the Susceptible-Infected-Recovered (SIR) model with three compartments. For the COVID-19 pandemic, several models have been proposed based on the SIR model with varying degrees of complexity to account for the asymptomatic spreaders, differing social mixing patterns, varying demographics, and government responses. From the models we encoded, three models were simple SIR models, one model was a SIR model with time-dependent transmission parameters. Seven were SEIR models with an additional "Exposed (E)" compartment. "Exposed" compartment was used in the model to account for the time delay in detecting new infections. The remaining models were further modifications of the SIR models taking into account the effect of asymptomatic spread, contact tracing, forecasting hospital capacities, understanding the effect of geographical proximity to transport nodes like airports on transmission, and the scenario of reinfection for a second wave. With further submissions, we hope to rapidly expand our collection of reproducible and reusable COVID-19 models which are already utilized by the community.

Reproducibility scorecard for models

A cornerstone of scientific research is the ability to reproduce results. Reproducibility is the ability to construct the code *de novo* and/or ensure that the mathematical expressions are properly represented and reproduce the simulation results in a software different from the one originally used[29]. Ensuring model reproducibility will help increase reliability and ease of reusability of the model. In our recent study[6] where we highlighted the reproducibility crisis and proposed an 8-point reproducibility scorecard[30] for modelers, reviewers, and journal editors to evaluate models during the peer-review process. We showed that an increase in score increased the chance of model reproducibility and recommended a minimal cut-off of 4. A majority of the COVID-19 models we curated received a score of 3 out of 8 before curation and took significant effort to re-encode and reproduce them.

Conclusion

COVID-19 is the first pandemic of this scale in over a century and its progression was closely studied, monitored, and modeled across the globe. We hope that our effort to implement the standards developed by the systems biology community in COVID-19 epidemiological models can serve as a roadmap to enhance the findability, accessibility, interoperability, and reusability of the models. Following FAIR guidelines to encode in SBML format, annotate the model with cross-references to data resources, packaging up all associated files in COMBINE archives, and publicly disseminating them through standard repository such as BioModels will increase the reproducibility and repurposing of these epidemiological models and help us stay prepared for pandemics. Additionally,

models in the SBML format can benefit from various systems biology modeling tools and algorithms used for model fitting, parameter estimation, sensitivity, and identifiability analysis[14]. Epidemiological modelers can use existing SBML-supporting modeling packages in their work environments to build and analyze models. SBML format specifications and supporting libraries including libSBML and jSBML are openly available and can be used by epidemiological modeling software developers to implement SBML-support in their tools.

A recent funding call from US Defense Advanced Research Projects Agency (DRAPA) titled "Automating Scientific Knowledge Extraction and Modeling (ASKEM)" invited proposals to develop approaches and tools for machine-assisted modeling and simulation through formal representation of epidemiological models of viral pandemics like COVID-19. The representation of COVID-19 models in the machine-readable SBML format would profoundly facilitate such development. By adopting a common format, systems biology and epidemiological modeling communities can greatly benefit from each other's modeling infrastructures. Although we discussed in the context of COVID-19 models, our recommendations are applicable to all epidemiological disease transmission models. Furthermore, we also recommend the use of the reproducibility scorecard that emphasizes model FAIRness to assess models during the peer-review process and thereby improve the reproducibility, reliability, and reusability of the COVID-19 models.

Acknowledgments

MK was supported by the Federal Ministry of Education and Research (BMBF, Germany) within the research network Systems Medicine of the Liver (LiSyM, grant number 031L0054), by the German Research Foundation (DFG) within the Research Unit Programme FOR 5151 "QuaLiPerF (Quantifying Liver Perfusion-Function Relationship in Complex Resection - A Systems Medicine Approach)" by grant number 436883643. KR, HH, and RSMS are supported by EMBL core funding and would like to acknowledge the funding of EMBL member states. The authors received funding for the creation of the COVID-19 model collection from the EOSCsecretariat.eu which received funding from the European Union's Horizon Programme call H2020-INFRAEOSC-05-2018-2019, Grant Agreement number 831644.

Table 1 - List of curated FAIR COVID-19 models. These models can be freely downloaded from BioModels repository, imported into modelling software with SBML support and readily simulated to reproduce simulation studies. (a) number of species (entities) in SBML model, (b) number of global parameters (c) number of reactions in SBML model, (d) reproducibility scorecard based score for each model before curation

Model Publication on BioModels	Model ID	No. of Compartments (a)	No. of Parameters (b)	No. of Transmission steps (c)	Reproducibility Scorecard (d)	Model codes shared publicly?
Giordano2020 - SIDARTHE model of COVID-19 spread in Italy	BIOMD0000000955	8	22	13	4	Yes
Bertozzi2020 - SIR model of scenarios of COVID-19 spread in CA and NY	BIOMD0000000956	3	21	2	4	Yes
Roda2020 - SIR model of COVID-19 spread in Wuhan	BIOMD0000000957	4	3	3	3	No
Ndairou2020 - early-stage transmission dynamics of COVID-19 in Wuhan	BIOMD0000000958	8	14	12	3	No
Paiva2020 - SEIAHRD model of transmission dynamics of COVID-19	BIOMD0000000960	8	133	11	2	No
Zhao2020 - SUQC model of COVID-19 transmission dynamics in Wuhan, Hubei, and China	BIOMD0000000962	5	37	3	3	No
Weitz2020 - SIR model of COVID-19 transmission with shielding	BIOMD0000000963	3	5	2	4	Yes
Mwalili2020 - SEIR model of COVID-19 transmission and environmental pathogen prevalence	BIOMD0000000964	6	15	14	3	No
Cuadros2020 - SIHRD spatiotemporal model of COVID-19 transmission in Ohio	BIOMD0000000969	28	36	32	3	No
Hou2020 - SEIR model of COVID-19 transmission in Wuhan	BIOMD0000000970	5	6	3	3	No
Tang2020 - Estimation of transmission risk of COVID-19 and impact of public health interventions	BIOMD0000000971	8	16	13	3	No
Tang2020 - Estimation of transmission risk of COVID-19 and impact of public health	BIOMD0000000972	8	22	13	3	No

interventions - updated						
Carcione2020 - Deterministic SEIR simulation of a COVID-19 outbreak	BIOMD0000000974	6	6	4	4	Yes
Ghanbari2020 - forecasting the second wave of COVID-19 in Iran	BIOMD0000000976	4	7	5	3	No
Sarkar2020 - SAIR model of COVID-19 transmission with quarantine measures in India	BIOMD0000000977	6	13	15	3	No
Mukandavire2020 - SEIR model of early COVID-19 transmission in South Africa	BIOMD0000000978	4	7	3	3	No
Malkov2020 - SEIRS model of COVID-19 transmission with reinfection	BIOMD0000000979	5	6	4	3	No
Malkov2020 - SEIRS model of COVID-19 transmission with time-varying R values and reinfection	BIOMD0000000980	5	13	4	3	No
Wan2020 - risk estimation and prediction of the transmission of COVID-19 in maninland China excluding Hubei province	BIOMD0000000981	12	17	15	3	No
Law2020 - SIR model of COVID-19 transmission in Malyasia with time-varying parameters	BIOMD0000000982	3	10	2	3	No
Zongo2020 - model of COVID-19 transmission dynamics under containment measures in France	BIOMD0000000983	7	21	10	3	No
Fang2020 - SEIR model of COVID-19 transmission considering government interventions in Wuhan	BIOMD0000000984	5	5	3	3	No
Westerhoff2020 - systems biology model of the coronavirus pandemic 2020	BIOMD0000000988	20	26	18	3	No
Okuonghae2020 - SEAIR model of COVID-19 transmission in Lagos, Nigeria	BIOMD0000000991	9	17	10	3	No

References

1. Kermack WO, McKendrick AG, Walker GT. A contribution to the mathematical theory of epidemics. *Proc R Soc Lond Ser Contain Pap Math Phys Character*. 1927;115(772):700-721. doi:10.1098/rspa.1927.0118

2. Adam D. Special report: The simulations driving the world's response to COVID-19. *Nature*. 2020;580(7802):316-319.
3. Jalali MS, DiGennaro C, Sridhar D. Transparency assessment of COVID-19 models. *Lancet Glob Health*. 2020;8(12):e1459-e1460. doi:10.1016/S2214-109X(20)30447-2
4. Rogers LS, Health JBS of P. Transparency, Reproducibility, and Validation of COVID-19 Projection Models. Johns Hopkins Bloomberg School of Public Health. Accessed July 15, 2021. https://www.jhsph.edu/covid-19/articles/transparency-reproducibility-and-validation-of-covid-19-projection-models.html
5. Becker AD, Grantz KH, Hegde ST, Bérubé S, Cummings DAT, Wesolowski A. Development and dissemination of infectious disease dynamic transmission models during the COVID-19 pandemic: what can we learn from other pathogens and how can we move forward? *Lancet Digit Health*. 2021;3(1):e41-e50. doi:10.1016/S2589-7500(20)30268-5
6. Tiwari K, Kananathan S, Roberts MG, et al. Reproducibility in systems biology modelling. *Mol Syst Biol*. 2021;17(2). doi:10.15252/msb.20209982
7. Peng RD, Dominici F, Zeger SL. Reproducible Epidemiologic Research. *Am J Epidemiol*. 2006;163(9):783-789. doi:10.1093/aje/kwj093
8. Bierer BE, Li R, Barnes M, Sim I. A Global, Neutral Platform for Sharing Trial Data. *N Engl J Med*. 2016;374(25):2411-2413. doi:10.1056/NEJMp1605348
9. Shepherd BE, Blevins Peratikos M, Rebeiro PF, Duda SN, McGowan CC. A Pragmatic Approach for Reproducible Research With Sensitive Data. *Am J Epidemiol*. 2017;186(4):387-392. doi:10.1093/aje/kwx066
10. Douglas JV, Bianco S, Edlund S, et al. STEM: An Open Source Tool for Disease Modeling. *Health Secur*. 2019;17(4):291-306. doi:10.1089/hs.2019.0018
11. Bershteyn A, Gerardin J, Bridenbecker D, et al. Implementation and applications of EMOD, an individual-based multi-disease modeling platform. *Pathog Dis*. 2018;76(5):fty059. doi:10.1093/femspd/fty059
12. Wilkinson MD, Dumontier M, Aalbersberg IjJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data*. 2016;3(1):160018. doi:10.1038/sdata.2016.18
13. Malik-Sheriff RS, Glont M, Nguyen TVN, et al. BioModels—15 years of sharing computational models in life science. *Nucleic Acids Res*. 2019;48(D1):D407-D415. doi:10.1093/nar/gkz1055
14. Keating SM, Waltemath D, König M, et al. SBML Level 3: an extensible format for the exchange and reuse of biological models. *Mol Syst Biol*. 2020;16(8):e9110. doi:10.15252/msb.20199110
15. Waltemath D, Adams R, Bergmann FT, et al. Reproducible computational biology experiments with SED-ML - The Simulation Experiment Description Markup Language. *BMC Syst Biol*. 2011;5(1):198. doi:10.1186/1752-0509-5-198
16. Bergmann FT, Adams R, Moodie S, et al. COMBINE archive and OMEX format: one file to share all information to reproduce a modeling project. *BMC Bioinformatics*. 2014;15(1):369. doi:10.1186/s12859-014-0369-z
17. Juty N, Le Novère N, Laibe C. Identifiers.org and MIRIAM Registry: community resources to provide persistent identification. *Nucleic Acids Res*. 2012;40(Database issue):D580-586. doi:10.1093/nar/gkr1097
18. Lloyd CM, Halstead MDB, Nielsen PF. CellML: its future, present and past. *Prog Biophys Mol Biol*. 2004;85(2-3):433-450. doi:10.1016/j.pbiomolbio.2004.01.004
19. Le Novère N, Finney A, Hucka M, et al. Minimum information requested in the annotation of biochemical models (MIRIAM). *Nat Biotechnol*. 2005;23(12):1509-1515. doi:10.1038/nbt1156

20. Waltemath D, Golebiewski M, Blinov ML, et al. The first 10 years of the international coordination network for standards in systems and synthetic biology (COMBINE). *J Integr Bioinforma*. 2020;17(2-3). doi:10.1515/jib-2020-0005
21. Hoops S, Sahle S, Gauges R, et al. COPASI—a COmplex PAthway SImulator. *Bioinformatics*. 2006;22(24):3067-3074. doi:10.1093/bioinformatics/btl485
22. Funahashi A, Morohashi M, Kitano H, Tanimura N. CellDesigner: a process diagram editor for gene-regulatory and biochemical networks. *BIOSILICO*. 2003;1(5):159-162. doi:10.1016/S1478-5382(03)02370-9
23. Choi K, Medley JK, König M, et al. Tellurium: An Extensible Python-based Modeling Environment for Systems and Synthetic Biology. *Biosystems*. 2018;171:74-79. doi:10.1016/j.biosystems.2018.07.006
24. Radivoyevitch T. A two-way interface between limited Systems Biology Markup Language and R. *BMC Bioinformatics*. 2004;5(1):190. doi:10.1186/1471-2105-5-190
25. Shapiro BE, Hucka M, Finney A, Doyle J. MathSBML: a package for manipulating SBML-based biological models. *Bioinforma Oxf Engl*. 2004;20(16):2829-2831. doi:10.1093/bioinformatics/bth271
26. Schmiester L, Schälte Y, Bergmann FT, et al. PEtab—Interoperable specification of parameter estimation problems in systems biology. Schneidman-Duhovny D, ed. *PLOS Comput Biol*. 2021;17(1):e1008646. doi:10.1371/journal.pcbi.1008646
27. Glont M, Nguyen TVN, Graesslin M, et al. BioModels: expanding horizons to include more modelling approaches and formats. *Nucleic Acids Res*. 2018;46(D1):D1248-D1253. doi:10.1093/nar/gkx1023
28. Mendes P. Reproducible Research Using Biomodels. *Bull Math Biol*. 2018;80(12):3081-3087. doi:10.1007/s11538-018-0498-z
29. Miłkowski M, Hensel WM, Hohol M. Replicability or reproducibility? On the replication crisis in computational neuroscience and sharing only relevant detail. *J Comput Neurosci*. 2018;45(3):163-172. doi:10.1007/s10827-018-0702-z
30. Tiwari K, Waltemath D, Hermjakob H, Malik-Sheriff RS. Reproducibility Scorecard to Assess Systems Biology Models. Published online February 2021. doi:10.5281/zenodo.5786693