Curating models from BioModels: Developing a workflow for creating OMEX files

Jin Xu[1*], Lucian Smith[1]

1 Department of Bioengineering, University of Washington, Seattle, WA, USA

* jin.xu.phys@gmail.com

Abstract

The reproducibility of computational biology models can be greatly facilitated by widely adopted standards and public repositories. We examined 50 models from the BioModels Database and attempted to validate the original curation and correct some of them if necessary. For each model, we reproduced these published results using Tellurium. Once reproduced we manually created a new set of files, with the model information stored by the Systems Biology Markup Language (SBML), and simulation instructions stored by the Simulation Experiment Description Markup Language (SED-ML), and everything included in an Open Modeling EXchange (OMEX) file, which could be used with a variety of simulators to reproduce the same results. On the one hand, the validation procedure of 50 models developed a manual workflow that we would use to build an automatic platform to help users more easily curate and verify models in the future. On the other hand, these exercises allowed us to find the limitations and possible enhancement of the current curation and tooling to verify and curate models.

Author summary

Public repositories with models deposited using standard formats are an important activity in computational systems biology, which allows scientists to easily find, access, and reuse them to rerun simulations or derive new ones using compatible software or tools. Common standards and public repositories can facilitate the reuse and regeneration of computational biology models beyond the software originally used to perform the simulations. As an exercise to validate and correct the current curation, we examined a selection of models in the BioModels Database. For each model, we reproduced some published results in the corresponding papers by a certain software. Once reproduced we manually created a standard file package using the model and its simulation information stored in the standard formats. These exercises not only allowed us to develop a workflow that we would use to develop an automatic online platform to help users more easily curate models for existing or future databases and repositories but also allowed us to find the limitations and possible enhancement of the current curation and tooling to verify and curate models.

Introduction

Because discoveries are almost always dependent on previous results, methodologies, and theories, reproducibility has become a fundamental part of the scientific process [1]. Therefore, the deposition of models in public repositories using standard formats like

the Systems Biology Markup Language (SBML) [2] or CellML [3] has been an important activity in computational systems biology. The repositories allow scientists to easily find and access models, use them to run simulations, and derive new models and simulations using compatible software applications. During the last couple of decades, many classic models have been added to model repositories. Public standards and repositories can facilitate the reuse and regeneration of computational biology models that will outlive the original used specific software [4].

The BioModels Database (https://www.ebi.ac.uk/biomodels/) [5,6] is one of the largest public open-source databases for quantitative biological models, where the models are manually curated and enriched. However, there are some limitations of the current curation efforts for the BioModels Database. For instance, some curated plots are not the same as those found in the published papers, and the description of how the plots were created is usually limited to a text file listing the simulation software used. Storing this information using the Simulation Experiment Description Markup Language (SED-ML) [7] has the potential to encode these experiments and to be extended to cover more results from the paper. SED-ML files are present in about a third of the BioModels Database (373 of 1058 entries), but have not been validated nor verified against multiple simulators.

To validate and correct the curated models, we examined 50 models in the BioModels Database, and successfully reproduced published results using Tellurium [8,9]. Once reproduced we updated the existing SED-ML file or created a new SED-ML file from scratch which repeated this experiment, and stored this with the original Systems Biology Markup Language (SBML) model in an Open Modeling EXchange (OMEX) [10] file.

The successful reproduction of the 50 models suggested a certain manual workflow to generate OMEX files. During the reproducing process, some curated results were corrected and extended. Therefore, the procedure identified issues in reproducing models from the perspective of tooling and papers. We found some limitations in the tooling and papers to achieve reproducibility and suggested some possible enhancements for curation and tooling in the future.

Materials and Methods

To demonstrate how to validate, correct, and extend the current curation of BioModels entries, we examined a selection of models to develop a manual workflow to generate OMEX files. Here, we present a systematic analysis of model reproducibility by attempting to independently reproduce published modeling results. In total, we investigated 50 models selected from the BioModels Database. These 50 models looked promising and seemed easy to fix and extend. For each model, we reproduced the published results using Tellurium version 2.2.5.2 that uses RoadRunner version 2.3.1 [11,12]. Once reproduced, we manually created a standard OMEX file using SBML and SED-ML following the manual workflow steps as below.

Read and modify the SBML file

To reproduce figures other than the one initially curated, values in the model itself can often be changed. This can be accomplished manually using tools such as Antimony [13] and libSBML [14]. We can also modify SBML files manually and directly.

For example, the curation for BIOMD0000000720 [15] (`https://www.ebi.ac.uk/biomodels/BIOMD0000000720#Curation`) only provides the reproduced figure Fig 7a. We were able to extend this to reproduce Figures 6, 7, and 9 by adjusting the appropriate parameters and initial values, as listed in Table 1. In Fig 1,

we have shown the successfully reproduced Fig 7a and extended Fig 7b and Fig 9 as representations.

Table 1. The 50 reproduced models from BioModels Database.

BioModel ID	Paper	Figure	Improvement	BioModel ID	Paper	Figure	Improvement
BIOMD0000000003	[16]	Fig 3	validated	BIOMD0000000850	[17]	Fig 3-1, 3-2	extended
BIOMD0000000005	[18]	Fig 3a	validated	BIOMD0000000877	[19]	Fig 1, 2	extended
BIOMD0000000010	[20]	Fig 2A	corrected	BIOMD0000000894	[21]	Fig 3a	validated
BIOMD0000000079	[22]	Fig 3, 4, 6	extended	BIOMD0000000909	[23]	Fig 10	extended
BIOMD0000000548	[24]	Fig 3	validated	BIOMD0000000911	[25]	Fig 1	validated
BIOMD0000000552	[26]	Fig 1	validated	BIOMD0000000916	[27]	Fig 2, 3	corrected
BIOMD0000000555	[28]	Fig 1	validated	BIOMD0000000930	[29]	Fig 1	extended
BIOMD0000000618	[30]	Fig 4	validated	BIOMD0000000932	[31]	Fig 4	validated
BIOMD0000000642	[32]	Fig 1	validated	BIOMD0000000933	[33]	Fig 3	validated
BIOMD0000000667	[34]	Fig 2	validated	BIOMD0000000939	[35]	Fig 2-7	extended
BIOMD0000000671	[36]	Fig 3	validated	BIOMD0000000947	[37]	Fig 6	validated
BIOMD0000000704	[38]	Fig 8, 9	extended	BIOMD0000000948	[39]	Fig 3	validated
BIOMD0000000712	[40]	Fig 2	extended	BIOMD0000000949	[41]	Fig 2	validated
BIOMD0000000720	[15]	Fig 6, 7, 9	extended	BIOMD0000000953	[42]	Fig 7B	extended
BIOMD0000000745	[43]	Fig 6 up	extended	BIOMD0000000964	[44]	Fig 2	corrected
BIOMD0000000757	[45]	Fig 1	validated	BIOMD0000000967	[46]	Fig 2	validated
BIOMD0000000780	[47]	Fig 6	validated	BIOMD0000000970	[48]	Fig 2	corrected
BIOMD0000000781	[47]	Fig 4	validated	BIOMD0000000984	[49]	Fig 3	validated
BIOMD0000000782	[47]	Fig 1-3	validated	BIOMD0000000986	[50]	Fig 2	validated
BIOMD0000000785	[51]	Fig 3b	validated	BIOMD0000001004	[52]	Fig 3	validated
BIOMD0000000793	[53]	Fig 2, 3	validated	BIOMD0000001006	[54]	Fig 2	corrected
BIOMD0000000795	[53]	Fig 4	validated	BIOMD0000001023	[55]	Fig 5	validated
BIOMD0000000799	[56]	Fig 8-10	extended	BIOMD0000001026	[57]	Fig 7	extended
BIOMD0000000815	[58]	Fig 5-7	extended	BIOMD0000001037	[59]	Fig 10	validated
BIOMD0000000839	[60]	Fig 2, 3	corrected	BIOMD0000001038	[59]	Fig 11	validated

The BioModel ID, Paper, Figure, and Improvement columns are for the model IDs in the BioModels Database, the published journal articles where the models were originally from, the reproduced figure indices in the paper correspondingly, and our contribution to improve the original curation. "Validated" means that the original curated figure is correct, and we successfully reproduced the curated result and did not reproduce additional results from the original article. "Corrected" means that the original curated figure is incorrect, but we successfully corrected the results to be the same as in the original article. "Extended" means that the original curated figure is correct, but we reproduced more results beyond the original curation.

Read and modify the SED-ML file

SED-ML is a representation format based on XML for the encoding and exchange of simulation descriptions on computational models of biological systems. It stores all the simulation information of a certain biology model. We first read the simulation information of the model from the SED-ML file. The model simulation information includes but is not limited to the model to simulate, time courses, and output formats. Some curation might not be correct, then we needed to correct the curation by adjusting the SED-ML files. We used phraSED-ML [61] and libSEDML [62] to achieve the modification.

For example, the curation of Figure 3 for BIOMD0000000916 (`https://www.ebi.ac.uk/biomodels/BIOMD0000000916#Curation`) is incorrect, with saturation around 0.8 instead of 1. We noticed that the original curation only

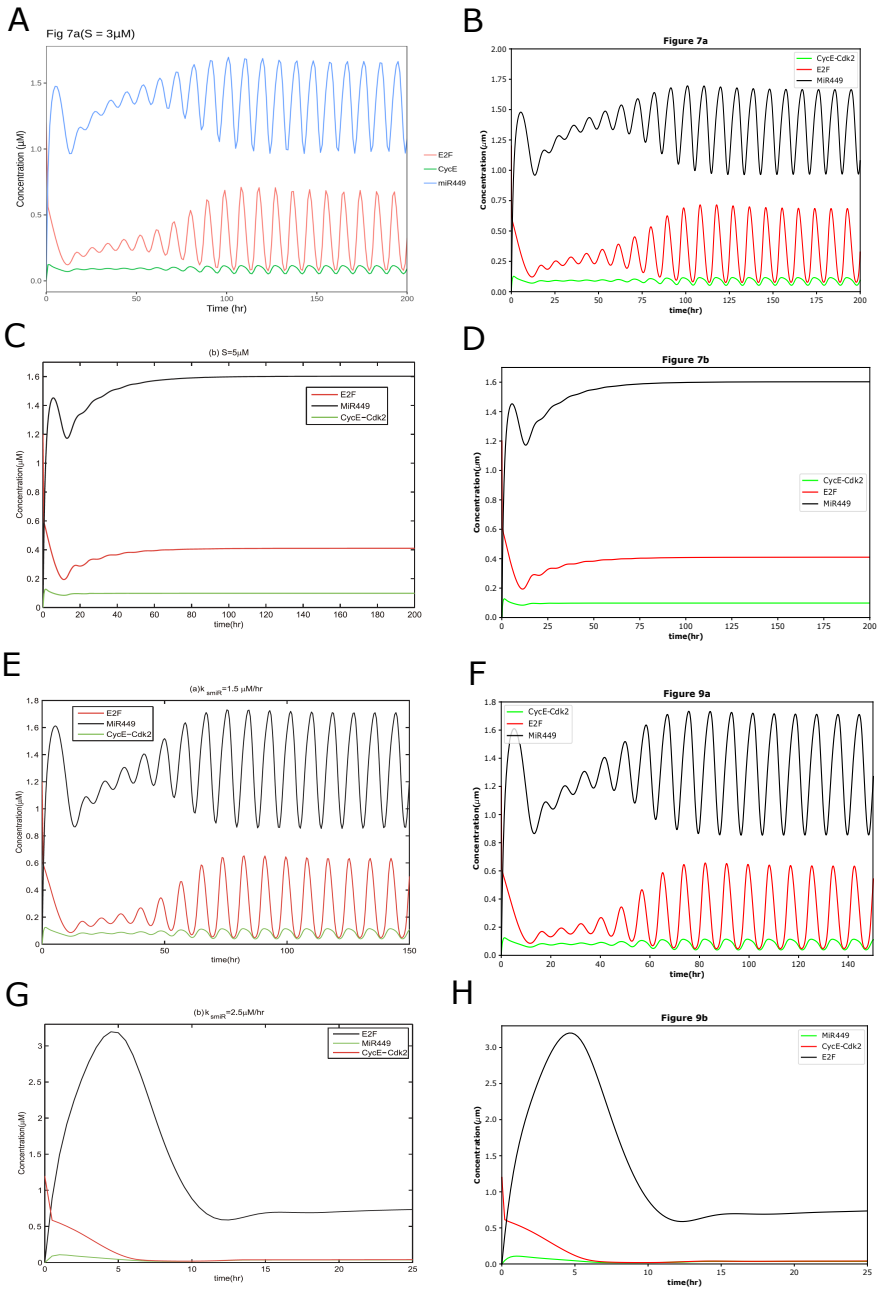

Fig 1. The reproduced results based on BIOMD0000000720. BIOMD0000000720 describes the dynamical behaviors of Rb-E2F pathway including negative feedback loops involving miR449. (A) is the original curation from the BioModels Database which is comparable with Fig 7a in the original paper [15] except line styles. (C), (E), and (G) are the original results published in the paper as Fig 7b and Fig 9. The figures illustrate the time courses of [E2F], [CycE-Cdk2] and [MiR449] with different values of k_{smiR} and S. (B), (D), (F), and (H) indicated the comparable results reproduced by Tellurium.

considered the contribution from X_2 to make the saturation value smaller than in the paper. Therefore, we adjusted the contribution from both X_2 and X_3, and successfully

corrected the original curation of Fig 3. In Fig 2, we have shown the corrected figure (Fig 2B) compared with the figure in the paper (Fig 2A) and the original curation (Fig 2C). It is also listed in Table 1.

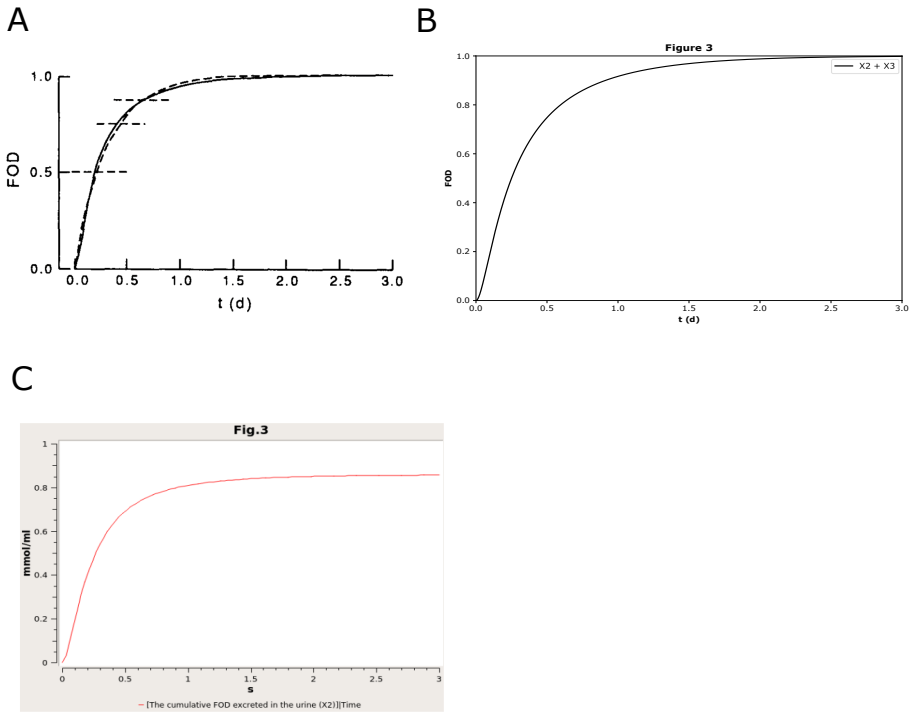

Fig 2. The reproduced results based on BIOMD00000000916. BIOMD0000000916 describes a hypothetic model about the kinetics of control metabolism and excretion. (A) is the original results published in the paper [27] as Fig 3. The figures illustrate the total excretion of the [^{3}H]F metabolites from the body as the time goes. (B) indicated the comparable results reproduced by Tellurium. (C) is the original curation from the BioModels Database which is not the same as in the corresponding paper.

Here, our workflow just assumed that there were SED-ML files that existed and might need modifications. However, some models in BioModels do not provide SED-ML files but only provide SBML model files. Of the 50 models we selected for curation, nine had no existing SED-ML. For five of these models, a COPASI save file was present which allowed COPASI to export a new SED-ML file. For four of them, we created new SED-ML files from scratch.

Generate figures by libSEDML and create OMEX files

The final steps were to generate comparable plots by Tellurium as the plots shown in the original articles. To make the visualizations vivid, article authors usually use different colors and line styles to represent their results. libSEDML can modify and store the styles of the plots in the SED-ML files.

For example, Fig 3 in the curation for BIOMD0000000003 (`https://www.ebi.ac.uk/biomodels/BIOMD0000000003#Curation`) had different line styles from the original published article. Then, we adjusted the line style of cyclin protease (X) to dashed lines from solid line style and added some colors to distinguish cdc2 kinase (M) and cyclin concentration (C). In Fig 3, we have shown our reproduced

figure with dashed lines (Fig 3B) compared with the figure in the paper (Fig 3A) and the original curation (Fig 3C) without dashed lines. It is also listed in Table 1.

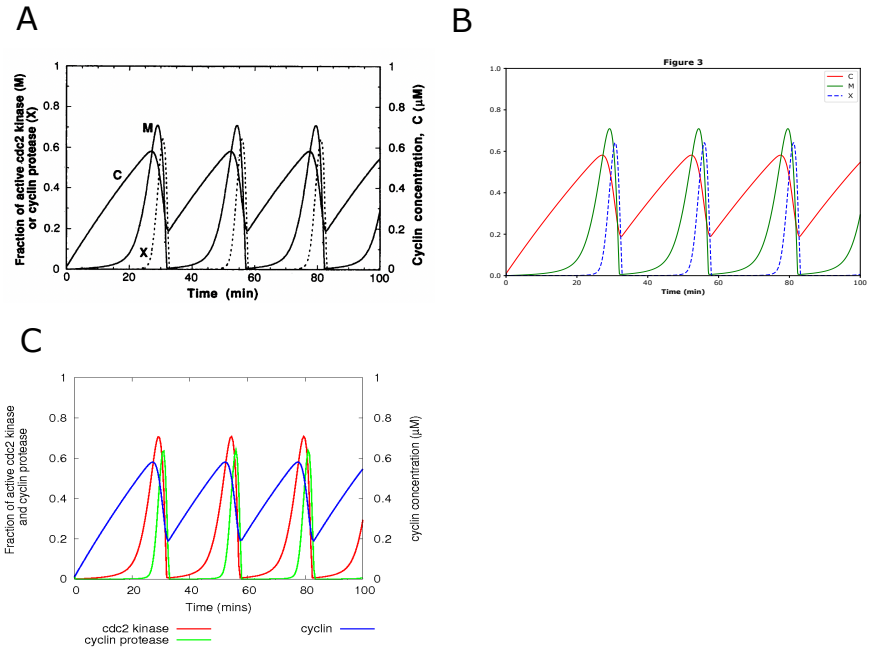

Fig 3. The reproduced results based on BIOMD0000000003. BIOMD0000000003 describes a minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase. (A) is the original result published in the paper [16] as Fig 3. The figure shows how the fraction of active cdc2 kinase (M), cyclin protease (X), and cyclin concentration (C) go with time in minutes. (B) indicated the comparable result reproduced by Tellurium. (C) is the original curation from the BioModels Database with comparable results except line styles.

Once we had all the information of the model and the simulation information with its output styles stored in SBML and SED-ML files, we manually created the OMEX files in the end.

The three steps mentioned above allowed us to achieve a manual workflow to generate OMEX files programming by Tellurium in Python. There are two sample scripts about the generation of OMEX files available on GitHub (`https://github.com/sys-bio/Developing-a-workflow-for-creating-OMEX-files`) under the folder of `script_examples`. The generation process of BIOMD0000000010 was based on the phraSED-ML string, while the generation process of BIOMD0000000003 was based on the SED-ML file.

Results

Successful reproduction with the workflow

We successfully validated, corrected, and extended 50 models in the BioModels Database following the workflow stated in the section Materials and Methods. Table 1 indicates all the reproduced models and their corresponding papers and figures. Among all the 50 models, we validated 30 models, corrected six models, and extended 14 models. "Validated" means that the original curated figure is correct, and we successfully reproduced the curated result and did not reproduce additional results from

the original article. "Corrected" means that the original curated figure is incorrect, but we successfully corrected the results to be the same as in the original article. "Extended" means that the original curated figure is correct, but we reproduced more results beyond the original curation. The "Corrected" also included the cases with both correction and extension. We also adjusted the line colors and styles according to the original papers, which were not indicated in Table 1. Among the 50 reproduced models, we adjusted eight models with their line colors and styles to be comparable with the original articles. Here we selected some interesting models as representations to illustrate the current curated BioModels status corresponding to their original published articles.

The first example is a model of "Validated". There is usually one plot in one paper corresponding to a certain BioModel curation. For example, BIOMD0000001023 (`https://www.ebi.ac.uk/biomodels/BIOMD0000001023#Curation`) curates the Fig 5 in the corresponding paper [55], which is correct. Here we validated the curation in Tellurium as shown in Fig 4, as an example to illustrate that the manual workflow worked.

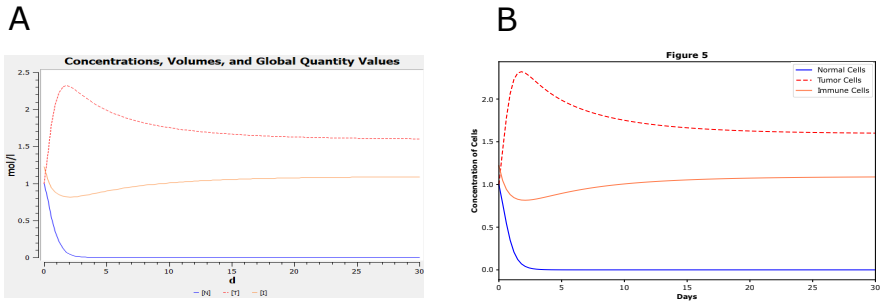

Fig 4. The reproduced results based on BIOMD0000001023. BIOMD0000001023 describes a new ODE-based model for tumor cells and immune system competition. (A) is the original curation from the BioModels Database which is comparable with Fig 5 in the corresponding paper [55]. The figure shows how the concentration of normal, tumor, and immune cells go with time in days. (B) indicated the comparable result validated by Tellurium.

The second example is a model of "Extended". The model in a BioModels entry can correspond to multiple reproducible plots. In many cases, some plots were reproduced during curation, such as BIOMD0000000939 (`https://www.ebi.ac.uk/biomodels/BIOMD0000000939#Curation`). In this BioModels entry, the plots from Figures 2, 3, 4, and 6 were reproduced. However, we were able to additionally reproduce more plots from Figures 5 and 7 by adjusting the parameters. Fig 5 provided the validation of the curation of Fig 4 and Fig 6 in the paper [35] and represented the extra results of Fig 5 and Fig 7 as an extension of the curation.

In some cases, there are multiple BioModels corresponding to one single paper. Therefore, a possible extension to the current curation regarding a certain model should be made after a cross-check with all the BioModels regarding the same paper. As shown in Table 1, there are three papers covering multiple BioModels. In details, BIOMD0000000780, BIOMD0000000781, and BIOMD0000000782 correspond to one paper [47]; BIOMD0000000793 and BIOMD0000000795 correspond to one paper [53]; and BIOMD0000001037 and BIOMD0000001038 correspond to one paper [59].

The third example is a model of "Corrected". Some entries contained extra information in their plots than were present in the published figures, making visual comparison difficult. For example, the entry BIOMD0000000839 (`https://www.ebi.ac.uk/biomodels/BIOMD0000000839#Curation`) contains the

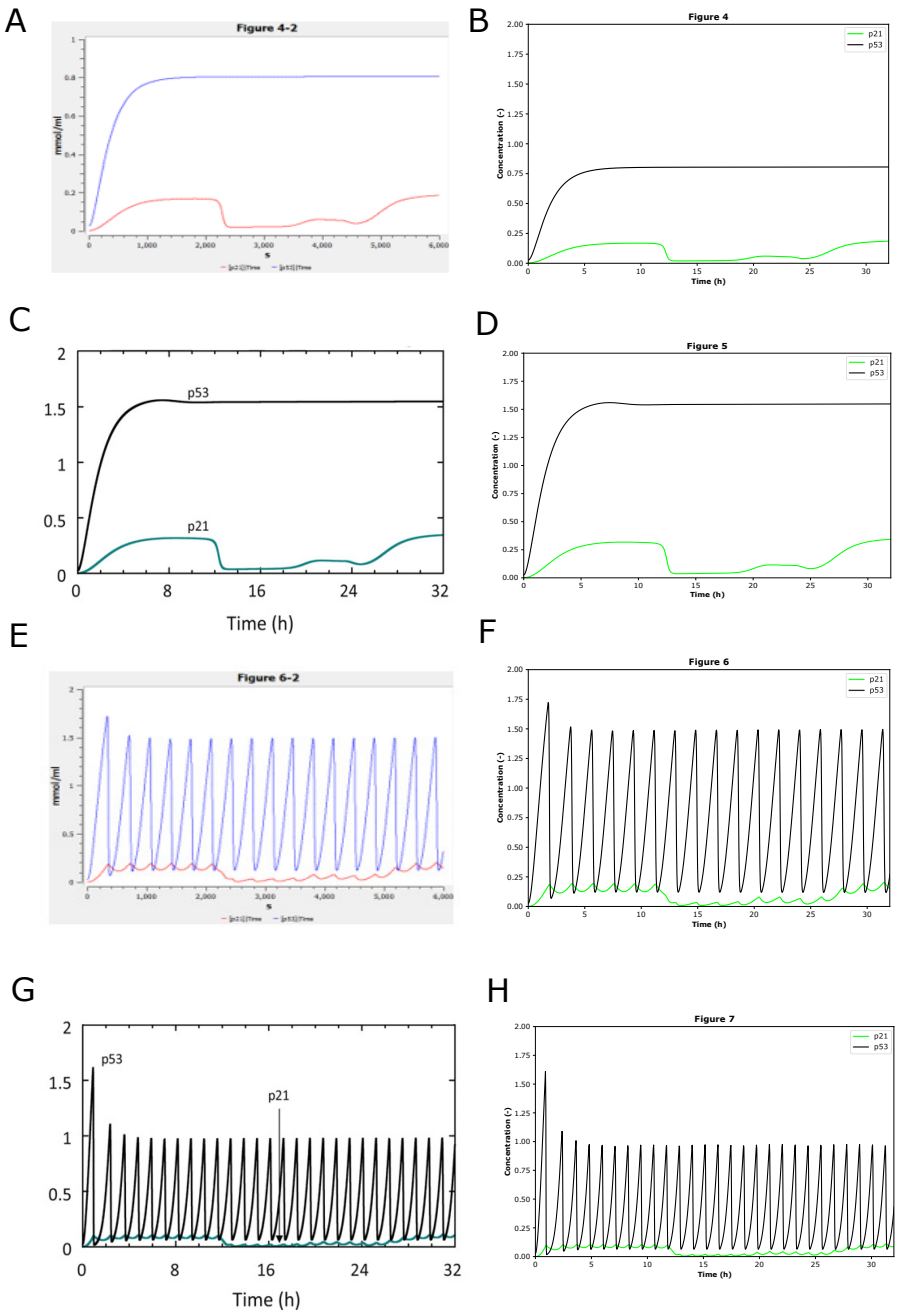

Fig 5. The reproduced results based on BIOMD0000000939. BIOMD0000000939 describes the mathematical modeling of cell cycle regulation in response to DNA damage. (A) and (E) are the original curation which is comparable with Figs 4 and 6 in the paper [35] except the line styles and axis scales. (C) and (G) are the original results published in Figs 5 and 7 in the paper. Figs (A), (C), (E), and (G) illustrate how the concentrations of p53 and p21 go with time in hours with the DNA damage signal (DDS) as 0.002, 0.004, 0.008, 0.016. (B), (D), (F), and (H) indicated the comparable results reproduced by Tellurium.

entire simulation from time zero to time 250, while the paper only displays the plot

between time points 150 to 250. There is also a time shift in the curated plot compared with the original article. We corrected these plots as shown in Fig 6.

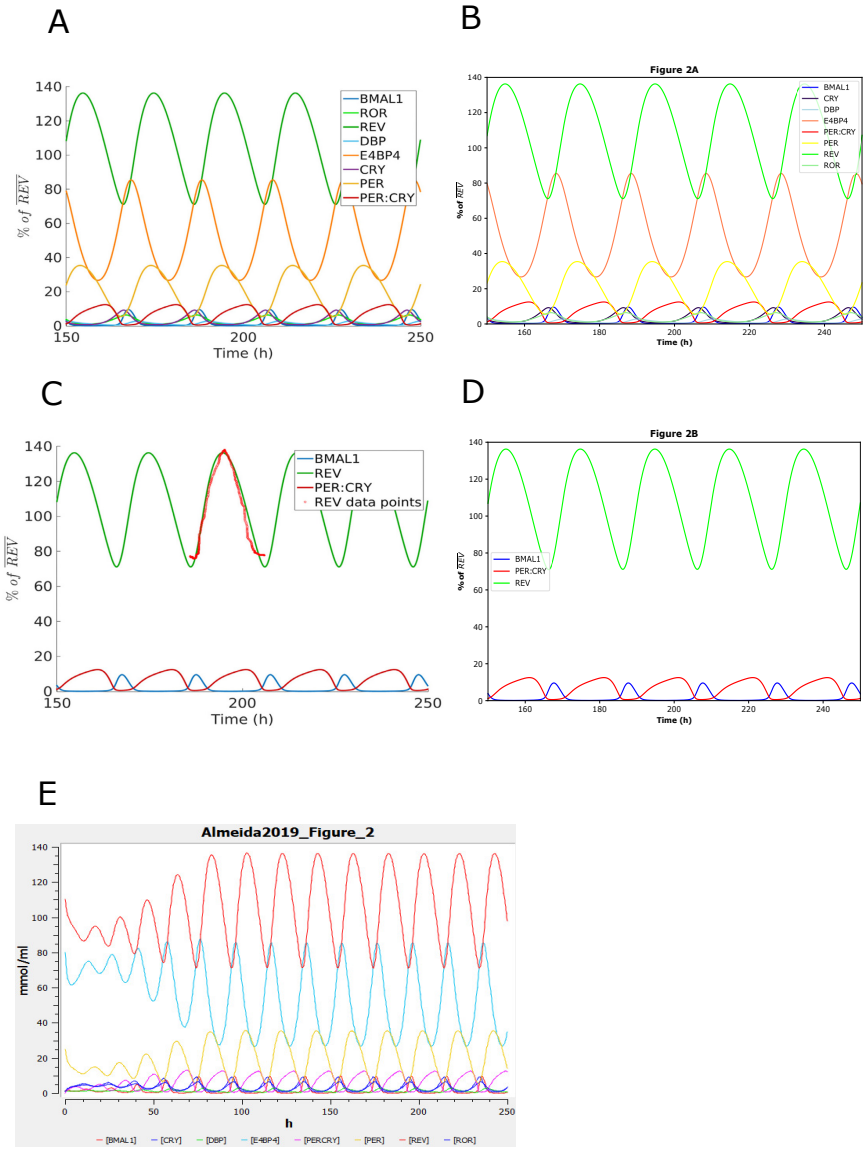

Fig 6. The reproduced results based on BIOMD0000000839. BIOMD0000000839 describes the transcription-based circadian mechanism that controls the duration of molecular clock states in response to signaling inputs. (A) and (C) are the original results published in the paper [60] as Fig 2. The figures illustrate the mammalian circadian clock described by a model focused on transcriptional regulation. (B) and (D) indicate the comparable results reproduced by Tellurium. (E) is the original curation which is not exactly the same as the original paper.

Following the validated, extended, and corrected examples in the three BioModels BIOMD0000001023, BIOMD0000000939, and BIOMD0000000839, readers could also go to GitHub (`https://github.com/sys-bio/Developing-a-workflow-for-creating-OMEX-files`) to cross-check all our successfully reproduced models by comparing the reproduced plots with their original results in the corresponding papers. The original curation from

BioModels Database was stored under the folder `original_curation` inside each BioModel folder, i.e., BIOMD000000XXXX, as a comparison to illustrate our improvement. Figures available on GitHub could also get re-generated via the OMEX files provided on GitHub by a simple type in the Tellurium command line: `te.executeCombineArchive("path to/BIOMD000000XXXX.omex")`

The 50 successfully validated and corrected BioModels curation on GitHub illustrated that our manual workflow described in the section Materials and Methods worked somehow with the current curation and tooling. However, there were still some limitations.

Non-reproduction due to tooling

The tooling we used were Tellurium, RoadRunner, libSBML, libSEDML, and phraSED-ML. The successful 50 reproduced models illustrated the advantages of these tools, however, the current tooling also had some limitations. The figures that we successfully reproduced were mostly simulations based on time courses. While more complex figures were not able to be reproduced due to the software and standards used, i.e., figures of bifurcation, 3D plots, etc. For example, we were not able to create an OMEX file following our manual workflow for the phase portraits of Fig 1 and Fig 2 nor the 3D plots of Fig 4 and Fig 5 in the Alharbi paper [59], because the current version of SED-ML does not support it. Therefore, the tooling needs to be improved and advanced in the future for curation.

In addition, it would be good for SED-ML to combine two plots into one in the future, but the current tooling does not make use of this capability. For instance, BIOMD0000000815 has an interesting procedure of cell density change at the beginning, elimination, after the change, and escape. We have extended the curation to cover Fig 7 in the paper [58]. However, the current tooling could only display the procedure in two separate figures as shown in Fig 7.

Furthermore, SED-ML does not support the capacity to insert subplots into one plot nor support bar plots. For instance, in MODEL2002110001 corresponding to the paper [63], Fig 2a has a bar subplot as shown in Fig 8. This can be expressed in SED-ML, but few interpreters yet support these features. However, it is possible that SED-ML can store all the simulations regarding subplots and bar plots in the future, as we successfully reproduced this model by Tellurium and curated the simulation by Python scripts in BioModels Database (`https://www.ebi.ac.uk/biomodels/MODEL2002110001#Overview`) and GitHub (`https://github.com/SunnyXu/Unlimited_multistability`) several years ago.

Non-reproduction due to paper information

In addition, not all the figures in one paper were reproducible due to errors or a lack of information from the corresponding papers. For instance, some parameters were given incorrectly or even not given. Some figures needed experimental data to fit, while some formulas or functions were not given to reproduce the dynamical behaviors. There are some examples shown in Table 2.

Therefore, it would be good to provide the data to plot or fit in the paper. For instance, Fig2B in the BIOMD0000000839 corresponding to the paper [60] shows data that is unavailable, and therefore cannot be added to the plot. See Fig 6C and Fig 6D.

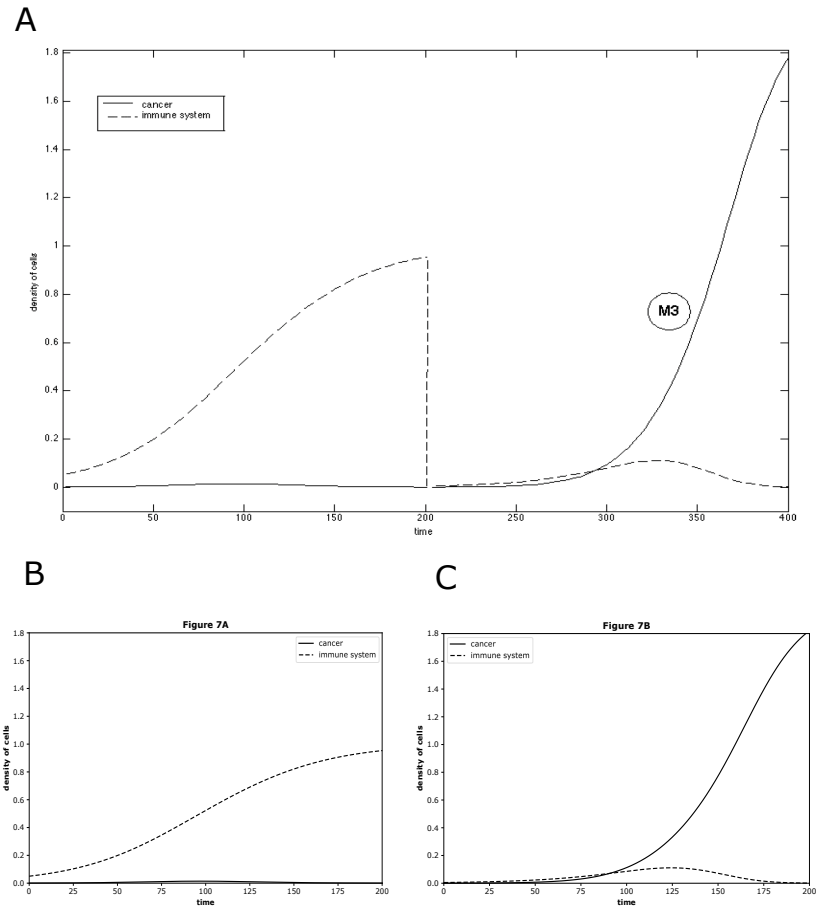

Fig 7. The reproduced results based on BIOMD0000000815. BIOMD0000000815 describes a mathematical model of induced cancer-adaptive immune system competition. (A) is the original result published in the paper [58] as Fig 7. The figure illustrates the evolution of the area of the sarcoma for mice M3, from the beginning, elimination, to the treatment, escape. (B) and (C) indicated the comparable results reproduced by Tellurium.

Table 2. Non-reproduction examples with certain limitations from papers.

Limitations	Examples
non-reproduction due to given parameters	548, 642, 757, 780, 877, 949, and 984
non-reproduction due to lack of formulae	005
non-reproduction due to lack of data	745 and 909
non-reproduction due to lack of related instructions	953

The numbers in the Examples column are the last three digits of the ID from the certain related BioModel.

Discussion

In the BioModels Database, the SED-ML, is not often present, and even when it is, is not always able to reproduce the figures shown in the corresponding papers. In addition, there is a potential to extend the curation with more results, which means some of the current entries could be extended. Our work cross-checked 50 BioModels and corrected/extended some of them if necessary. The exercises of the 50 models allowed us to develop a manual workflow that would help us achieve a possible automatic workflow

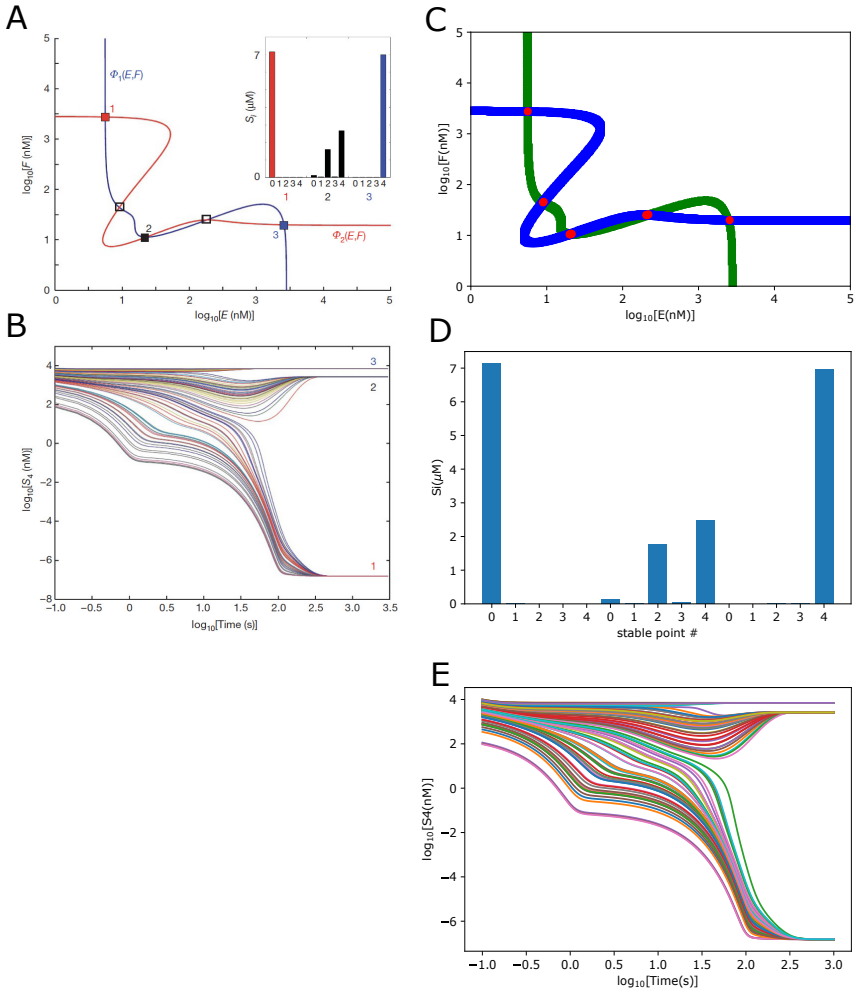

Fig 8. The reproduced results based on MODEL2002110001. MODEL2002110001 describes the unlimited multistability in multisite phosphorylation systems. (A) and (B) are the original results published in the paper [63] as Fig 2. The figure illustrates the Multistability of an $n = 4$ distributive sequential system. (C), (D), and (E) indicated the comparable results reproduced by Tellurium.

to generate a possible automatically on-line platform in the future, i.e., `https://biosimulations.org` and `www.reproducibilityportal.org`, and eventually to help users more easily curate models.

The tooling we used were Tellurium, RoadRunner, libSBML, libSEDML, and phraSED-ML. The successful 50 reproduced models illustrated the advantages of these tools, however, the current tooling had some limitations. The figures that we successfully reproduced were mostly simulations based on time courses, while more complex figures were not able to be curated as OMEX files, i.e., figures of bifurcation, 3D plots, or bar graphs. Therefore, the tooling needs to be improved in the future. It would also be good for more interpreters to implement certain advanced SED-ML features such as combined subplots.

In addition, not all the figures in one paper were reproducible due to a lack of information provided in the paper. For instance, some parameters were given incorrectly or not given. Some figures needed experimental data to fit, while some formulas or

functions were not given to reproduce the dynamical behaviors. Therefore, it would be good for the authors to publish papers with corresponding data. It would also be good for authors and/or curators to store all the information regarding the publications, i.e., models by SBML files, simulation by SED-ML files, related experimental data, code in repertoire, and possible attachment of the corresponding article.

Acknowledgments

J.X. appreciates John H. Gennari and Herbert M. Sauro's comments on the early stage of the manuscript. J.X. also thanks Frank T. Bergmann for his assistance in using libSEDML.

Data Availability Statement

The reproduced models and code for this project are available on GitHub (`https://github.com/sys-bio/Developing-a-workflow-for-creating-OMEX-files`).

Funding

Funding for this work is provided by P41EB023912.

Author Contributions

Conceptualization: Jin Xu, Lucian Smith; Data curation: Jin Xu; Formal analysis: Jin Xu; Investigation: Jin Xu; Methodology: Jin Xu, Lucian Smith; Project administration: Jin Xu; Resources: Jin Xu; Software: Jin Xu; Supervision: Jin Xu, Lucian Smith Validation: Jin Xu; Visualization: Jin Xu; Writing – original draft: Jin Xu; Writing – review & editing: Lucian Smith.

References

1. Popper K. The Logic of Scientific Discovery. Routledge; 2005.
2. Hucka M, Bergmann FT, Chaouiya C, Dräger A, Hoops S, Keating SM, et al. The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core Release 2. Journal of Integrative Bioinformatics. 2019;16(2):20190021. doi:10.1515/jib-2019-0021.
3. Hedley W, Nelson M, Bullivant D, Nielsen P. A short introduction to CellML. Philosophical Transactions of the Royal Society A. 2001;359:1073–1089. doi:10.1098/rsta.2001.0817.
4. Mendes P. Reproducibility and FAIR principles: the case of a segment polarity network model. Frontiers in Cell and Developmental Biology. 2023;11. doi:10.3389/fcell.2023.1201673.
5. Le Novere N, Bornstein B, Broicher A, Courtot M, Donizelli M, Dharuri H, et al. BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems. Nucleic acids research. 2006;34(suppl_1):D689–D691.

6. Malik-Sheriff RS, Glont M, Nguyen TV, Tiwari K, Roberts MG, Xavier A, et al. BioModels—15 years of sharing computational models in life science. Nucleic acids research. 2020;48(D1):D407–D415.

7. Bergmann FT, Cooper J, König M, Moraru I, Nickerson D, Novère NL, et al. Simulation Experiment Description Markup Language (SED-ML) Level 1 Version 3 (L1V3). Journal of Integrative Bioinformatics. 2018;15(1):20170086. doi:doi:10.1515/jib-2017-0086.

8. Choi K, Medley J, König M, Stocking K, Smith L, Gu S, et al. Tellurium: An extensible python-based modeling environment for systems and synthetic biology. Biosystems. 2018;171. doi:10.1016/j.biosystems.2018.07.006.

9. Medley J, Choi K, König M, Smith L, Gu S, Hellerstein J, et al. Tellurium notebooks—An environment for reproducible dynamical modeling in systems biology. PLOS Computational Biology. 2018;14:e1006220. doi:10.1371/journal.pcbi.1006220.

10. Neal M, Gennari J, Waltemath D, Nickerson D, König M. Open modeling and exchange (OMEX) metadata specification version 1.0. Journal of integrative bioinformatics. 2020;-1. doi:10.1515/jib-2020-0020.

11. Somogyi E, Bouteiller JM, Glazier J, König M, Medley K, Swat M, et al. libRoadRunner: A High Performance SBML Simulation and Analysis Library. Bioinformatics. 2015;31. doi:10.1093/bioinformatics/btv363.

12. Welsh C, Xu J, Smith L, König M, Choi K, Sauro H. libRoadRunner 2.0: A High Performance SBML Simulation and Analysis Library. Bioinformatics. 2022;39. doi:10.1093/bioinformatics/btac770.

13. Smith LP, Bergmann FT, Chandran D, Sauro HM. Antimony: a modular model definition language. Bioinformatics. 2009;25(18):2452–2454. doi:10.1093/bioinformatics/btp401.

14. Bornstein BJ, Keating SM, Jouraku A, Hucka M. LibSBML: an API library for SBML. Bioinformatics. 2008;24(6):880–881.

15. Yan F, Liu H, Hao J, Liu Z. Dynamical Behaviors of Rb-E2F Pathway Including Negative Feedback Loops Involving miR449. PLOS ONE. 2012;7(9):1–13. doi:10.1371/journal.pone.0043908.

16. Goldbeter A. A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase. Proceedings of the National Academy of Sciences. 1991;88(20):9107–9111. doi:10.1073/pnas.88.20.9107.

17. Jenner AL, Kim PS, Frascoli F. Oncolytic virotherapy for tumours following a Gompertz growth law. Journal of Theoretical Biology. 2019;480:129–140. doi:https://doi.org/10.1016/j.jtbi.2019.08.002.

18. Tyson JJ. Modeling the cell division cycle: cdc2 and cyclin interactions. Proceedings of the National Academy of Sciences. 1991;88(16):7328–7332. doi:10.1073/pnas.88.16.7328.

19. Ontah G, Trisilowati T, Darti I. Dynamic Analysis of a Tumor Treatment Model Using Oncolytic Virus and Chemotherapy with Saturated Infection Rate. IOP Conference Series: Materials Science and Engineering. 2019;546:032025. doi:10.1088/1757-899X/546/3/032025.

20. Kholodenko B. Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. European Journal of Biochemistry. 2000;267:1583 – 1588. doi:10.1046/j.1432-1327.2000.01197.x.

21. Bose T, Trimper S. Noise-assisted interactions of tumor and immune cells. Phys Rev E. 2011;84:021927. doi:10.1103/PhysRevE.84.021927.

22. Goldbeter A. A model for the dynamics of human weight cycling. Journal of biosciences. 2006;31:129–36. doi:10.1007/BF02705242.

23. De Pillis LG, Radunskaya A. The dynamics of an optimally controlled tumor model: A case study. Mathematical and Computer Modelling. 2003;37(11):1221–1244. doi:https://doi.org/10.1016/S0895-7177(03)00133-X.

24. Sneppen K, Lizana L, Jensen M, Pigolotti S, Otzen D. Modeling proteasome dynamics in Parkinson's disease. Physical biology. 2009;6:036005. doi:10.1088/1478-3975/6/3/036005.

25. Merola A, Cosentino C, Amato F. An insight into tumor dormancy equilibrium via the analysis of its domain of attraction. Biomedical Signal Processing and Control. 2008;3(3):212–219. doi:https://doi.org/10.1016/j.bspc.2008.02.001.

26. EHRENSTEIN G, GALDZICKI Z, LANGE GD. A Positive-Feedback Model for the Loss of Acetylcholine in Alzheimer's Disease. Annals of the New York Academy of Sciences. 2000;899(1):283–291. doi:https://doi.org/10.1111/j.1749-6632.2000.tb06194.x.

27. Kraan GPB, Drayer NM, de Bruin R. Kinetics of cortisol metabolism and excretion. A hypothetic model based on the cumulative urinary radioactivity in eight multiple pituitary deficient patients. The Journal of Steroid Biochemistry and Molecular Biology. 1992;42(2):169–177. doi:https://doi.org/10.1016/0960-0760(92)90025-E.

28. Auer S, Kashchiev D. Insight into the correlation between lag time and aggregation rate in the kinetics of protein aggregation. Proteins: Structure, Function, and Bioinformatics. 2010;78(11):2412–2416. doi:https://doi.org/10.1002/prot.22762.

29. Liu P, Liu X. Dynamics of a tumor-immune model considering targeted chemotherapy. Chaos, Solitons and Fractals. 2017;98:7–13. doi:https://doi.org/10.1016/j.chaos.2017.03.002.

30. Krohn M, Lange C, Hofrichter J, Scheffler K, Stenzel J, Steffen J, et al. Cerebral amyloid-β proteostasis is regulated by the membrane transport protein ABCC1 in mice. The Journal of clinical investigation. 2011;121:3924–31. doi:10.1172/JCI57867.

31. Garde R, Ibrahim B, Kovacs A, Schuster S. Differential equation-based minimal model describing metabolic oscillations in Bacillus subtilis biofilms. Royal Society Open Science. 2020;7:190810. doi:10.1098/rsos.190810.

32. Zidana C, Sorofa W, Chiyaka E. Assessing the Effects of Estrogen on the Dynamics of Breast Cancer. Computational and mathematical methods in medicine. 2012;2012:473572. doi:10.1155/2012/473572.

33. Kosiuk I, Szmolyan P. Geometric analysis of the Goldbeter minimal model for the embryonic cell cycle. Journal of mathematical biology. 2015;72. doi:10.1007/s00285-015-0905-0.

34. Hornberg J, Binder B, Bruggeman F, Schoeberl B, Heinrich R, Westerhoff H. Control of MAPK signalling: From complexity to what really matters. Oncogene. 2005;24:5533–42. doi:10.1038/sj.onc.1208817.

35. Iwamoto K, Hamada H, Eguchi Y, Okamoto M. Mathematical modeling of cell cycle regulation in response to DNA damage: Exploring mechanisms of cell-fate determination. Biosystems. 2011;103(3):384–391. doi:https://doi.org/10.1016/j.biosystems.2010.11.011.

36. Murphy H, Jaafari H, Dobrovolny H. Differences in predictions of ODE models of tumor growth: A cautionary example. BMC cancer. 2016;16:163. doi:10.1186/s12885-016-2164-x.

37. Lee DW, Ha SK, Choi I, Sung JH. 3D gut-liver chip with a PK model for prediction of first-pass metabolism. Biomedical microdevices. 2017;19(4):100. doi:10.1007/s10544-017-0242-8.

38. Aguda BD. A quantitative analysis of the kinetics of the G_2 DNA damage checkpoint system. Proceedings of the National Academy of Sciences. 1999;96(20):11352–11357. doi:10.1073/pnas.96.20.11352.

39. Landberg R, Åman P, Friberg LE, Vessby B, Adlercreutz H, Kamal-Eldin A. Dose response of whole-grain biomarkers: alkylresorcinols in human plasma and their metabolites in urine in relation to intake. The American Journal of Clinical Nutrition. 2009;89(1):290–296. doi:https://doi.org/10.3945/ajcn.2008.26709.

40. Manchanda H, Seidel N, Krumbholz A, Sauerbrei A, Schmidtke M, Guthke R. Within-host influenza dynamics: A small-scale mathematical modeling approach. Biosystems. 2014;118:51–59. doi:https://doi.org/10.1016/j.biosystems.2014.02.004.

41. Chitnis N, Hyman J, Cushing J. Determining Important Parameters in the Spread of Malaria Through the Sensitivity Analysis of a Mathematical Model. Bulletin of mathematical biology. 2008;70:1272–96. doi:10.1007/s11538-008-9299-0.

42. Queralt E, Lehane C, Novak B, Uhlmann F. Downregulation of PP2ACdc55 Phosphatase by Separase Initiates Mitotic Exit in Budding Yeast. Cell. 2006;125(4):719–732. doi:10.1016/j.cell.2006.03.038.

43. Jarrett A, Bloom M, Godfrey W, Syed A, Ekrut D, Ehrlich L, et al. Mathematical modelling of trastuzumab-induced immune response in an in vivo murine model of HER2+ breast cancer. Mathematical Medicine and Biology: A Journal of the IMA. 2018;36. doi:10.1093/imammb/dqy014.

44. Mwalili S, Kimathi M, Ojiambo V, Gathungu D, Mbogo R. SEIR model for COVID-19 dynamics incorporating the environment and social distancing. BMC Research Notes. 2020;13. doi:10.1186/s13104-020-05192-1.

45. Abernathy K, Burke J. Modeling the Treatment of Glioblastoma Multiforme and Cancer Stem Cells with Ordinary Differential Equations. Computational and Mathematical Methods in Medicine. 2016;2016:1–11. doi:10.1155/2016/1239861.

46. McLean AR, Emery VC, Webster A, Griffiths PD. Population dynamics of HIV within an individual after treatment with zidovudine. AIDS. 1991;5:485–490.

47. Wang Z, Guo Z, Peng H. A mathematical model verifying potent oncolytic efficacy of M1 virus. Mathematical Biosciences. 2016;276:19–27. doi:https://doi.org/10.1016/j.mbs.2016.03.001.

48. Hou C, Chen J, Zhou Y, Hua L, Yuan J, He S, et al. The effectiveness of quarantine of Wuhan city against the Corona Virus Disease 2019 (COVID-19): A well-mixed SEIR model analysis. Journal of Medical Virology. 2020;92(7):841–848. doi:https://doi.org/10.1002/jmv.25827.

49. Fang Y, Nie Y, Penny M. Transmission dynamics of the COVID-19 outbreak and effectiveness of government interventions: A data-driven analysis. Journal of Medical Virology. 2020;92(6):645–659. doi:https://doi.org/10.1002/jmv.25750.

50. Aubry L, Klein G, Martiel JL, Satre M. Modelling of fluid-phase endocytosis kinetics in the amoebae of the cellular slime mouldDictyostelium discoideum. A multicompartmental approach. Acta Biotheoretica. 1995;43(4):319–333. doi:10.1007/BF00713556.

51. Sotolongo-Costa O, Morales Molina L, Rodríguez Perez D, Antoranz JC, Chacón Reyes M. Behavior of tumors under nonstationary therapy. Physica D: Nonlinear Phenomena. 2003;178(3):242–253. doi:https://doi.org/10.1016/S0167-2789(03)00005-8.

52. Intosalmi J, Ahlfors H, Rautio S, Mannerström H, Chen ZJ, Lahesmaa R, et al. Analyzing Th17 cell differentiation dynamics using a novel integrative modeling framework for time-course RNA sequencing data. BMC Systems Biology. 2015;9.

53. Chen K, Pienta KJ. Modeling invasion of metastasizing cancer cells to bone marrow utilizing ecological principles. Theoretical Biology & Medical Modelling. 2011;8:36 – 36.

54. Andrea Ciliberto BN, Tyson JJ. Steady States and Oscillations in the p53/Mdm2 Network. Cell Cycle. 2005;4(3):488–493. doi:10.4161/cc.4.3.1548.

55. Alharbi SA, Rambely AS. A New ODE-Based Model for Tumor Cells and Immune System Competition. Mathematics. 2020;8(8). doi:10.3390/math8081285.

56. Cucuianu A, Precup R. A Hypothetical-Mathematical Model of Acute Myeloid Leukaemia Pathogenesis. Computational and Mathematical Methods in Medicine. 2010;2010. doi:10.1080/17486700902973751.

57. Kurlovics J, Zake D, Zaharenko L, Berzins K, Klovins J, Stalidzans E. Metformin Transport Rates Between Plasma and Red Blood Cells in Humans. Clinical Pharmacokinetics. 2021;61. doi:10.1007/s40262-021-01058-2.

58. CHROBAK JM, HERRERO H. A MATHEMATICAL MODEL OF INDUCED CANCER-ADAPTIVE IMMUNE SYSTEM COMPETITION. Journal of Biological Systems. 2011;19(03):521–532. doi:10.1142/S0218339011004111.

59. Alharbi S, Rambely A. Dynamic Simulation for Analyzing the Effects of the Intervention of Vitamins on Delaying the Growth of Tumor Cells. IEEE Access. 2019;PP:1–1. doi:10.1109/ACCESS.2019.2940060.

60. Almeida S, Chaves M, Delaunay F. Transcription-based circadian mechanism controls the duration of molecular clock states in response to signaling inputs. Journal of Theoretical Biology. 2020;484:110015. doi:https://doi.org/10.1016/j.jtbi.2019.110015.

61. Choi K, Smith LP, Medley JK, Sauro HM. phraSED-ML: A paraphrased, human-readable adaptation of SED-ML. Journal of Bioinformatics and Computational Biology. 2016;14(06):1650035. doi:10.1142/S0219720016500359.

62. Bergmann FT, Nickerson D, Waltemath D, Scharm M. SED-ML web tools: generate, modify and export standard-compliant simulation studies. Bioinformatics. 2017;33(8):1253–1254. doi:10.1093/bioinformatics/btw812.

63. Thomson M, Gunawardena J. Unlimited multistability in multisite phosphorylation systems. Nature. 2009;460:274–7. doi:10.1038/nature08102.