

COMBACH: A case study to enhance the reproducibility of a dynamic JAK/STAT5 pathway model by creating a fully-featured COMBINE archive

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Abstract

Introduction: The increase of size and complexity of simulation studies in systems biology and systems medicine proposes new challenges to sharing reproducible results. The Computational Modeling in Biology Network (COMBINE) archive improves the coordination of standard formats for several features of simulation studies [1]. On the other side, GitHub has been used as an essential common platform for managing software projects and supporting collaborative development [2]. In this case study, we aimed to develop a fully-featured COMBINE archive of a dynamic pathway model of Janus kinase (JAK)/signal transducer and activator of transcription protein (STAT)5 signaling [3] using agile co-working technologies.

Methods: In this case study, we implemented a GitHub environment to create a publicly traceable progress documentation of a COMBINE archive assembly. Systematic searches for available modeling files (Systems Biology Markup Language (SBML)) and software tools were conducted. The interaction between the tools and the modeling data was assessed and a fitting combination was chosen. Additionally we created the graphical notation files (Systems Biology Graphical Notation Markup Language (SBGN-ML) and Systems Biology Graphical Notation (SBGN)), that are needed to visualize the simulation results. In a next step, we reproduced a substantial part of the original simulation data using both established software tools Complex Pathway Simulator (COPASI) but also the python-based tool Tellurium [4]. Finally, a COMBINE Archive was created using the CombineArchiveWeb application (WebCat) and was made publicly available.

Results: We chose a GitHub repository as collaborative working environment with content versioning, code deposition and development as well as a wiki documentation. This delivered a prompt and sound scaffold for the development of the COMBINE archive. By systematic searches we identified the BACHMANN2011.XML (BIOMD0000000861) as the appropriate model file and were able to add the needed SBGN-ML and SBGN code. To fuse the above simulation components, a Tellurium [4] script was developed to reproduce the numeric and graphical results of the original paper. Finally, we created and validated a COMBINE archive comprehensively assembling all information necessary to reproduce the majority of figures from Bachmann *et al.*[3].

Conclusions: In this case study, we demonstrated the value of agile co-working for the development of a fully-featured COMBINE archive of a dynamic pathway model of JAK/STAT5 signaling [3]. Although we could not reproduce the full extend of the simulations given in the original work due to missing details in the original study, we were able to create a fully functional archive that improves the reproducibility and accessibility of the original research results.

Keywords: FAIR, Systems Biology, Computational Biology, Medical Informatics, Usability, mathematical modeling, negative feedback, suppressor of cytokine (SOCS), COMBINE

Introduction

Scientific background

Reproducibility of results is one of the most fundamental requirements for credibility in scientific research [5]. However, in recent years it became evident that a substantial part of study results are not reproducible. A recent systematic review found that almost 50% of modeling studies could not be reproduced [5]. Especially in systems biology and systems medicine, the increase in size and complexity of models and data-sets proposes new challenges to share reproducible results. Therefore, several initiatives such as the Go FAIR Initiative, FAIDROM or COMBINE were formed aiming to develop and provide standardization efforts and tools to enhance reproducibility in systems biology [6].

One of these tools are so called COMBINE archives, which aim to improve the coordination of standard formats for several features of simulation studies, such as SBML, CellML, SBGN, and Systems Biology Result Markup Language (SBRML). These standards aim to encode, simulate and visualize biological models [1]. Furthermore, COMBINE archives offer the unique opportunity to not only reproduce simulation results but also to access comprehensive metadata such as author information, publication IDs (e.g. Digital Object Identifier (DOI)) and simulation details in one single file. The vast majority of this information is usually stored in different data formats and locations that require a bundle of software tools to handle. COMBINE archives instead bring a single executable file, which is easy to access and comes with proper provenience information. It is obvious that this creates a much higher accessibility to complex systems medicine and systems biology data for researchers and provides a better reproducibility of scientific results.

Rationale for this study

Dynamic Pathway Simulations

Dynamic pathway modeling is needed to describe the complex regulatory system of feedback regulators, to answer this question, Bachmann *et al.* built a dual negative feedback model of JAK2/STAT5 signaling in primary erythroid progenitor cells isolated from mouse fetal livers [3].

Given the background of the only partially reproducible dynamic pathway model of SOCS family members in JAK2/STAT5 signaling from Bachmann *et al.* [3], we were asked to create a fully featured COMBINE archive and reproduce the simulation content, both for educational purposes and for scientific completion of the original work. Furthermore, the created COMBINE Archive could serve as a template to enhance reproducibility of future modelling studies.

Agile working

Agile working has been a major drive for the evolution of working environment especially in information technologies. New definitions on how, where, with whom and when collaboration and the completion of tasks is done are enabled by digital cloud solutions and co-working platforms that integrate the allocation of tasks, versioning of content and the *ad-hoc*-formation of teams. GitHub as a provider of internet-hosted software development and version control tools has been used as an essential common platform for managing software projects and supporting collaborative development. Lately some

educational projects have begun to adopt it for hosting and managing course content to enhance transparency features in the creation, reuse, and remix of materials [2, 7]. In the development of this COMBINE archive we dedicated ourselves to the FAIR-principles and therefore built a completely publicly traceable working environment in GitHub, that can be accessed via the link given in the appendices.

Objectives

Since the number of modeling studies providing both data and meta-data in form of a COMBINE archives are limited, the main objective of this case study was to create a fully featured COMBINE-archive including both scripts to reproduce all simulation figures and easy to access simulation data of the Bachmann model, a dynamic pathway model of JAK/STAT5 signaling [3]. Furthermore, we aimed to create an easy to use guideline on how to compile a COMBINE archive out of an existing simulation model. Besides these aims we were also interested in validating all generated scripts after archive compilation. Finally, we aimed to evaluate the used tools in terms of usability, accessibility and asked if the provided data from the original study was sufficient to reproduce the presented results.

Study design

This case study describes the implementation process of a COMBINE archive using agile co-working and publicly available documentation.

Research questions

The research question was whether there is a comprehensive way of developing a COMBINE archive out of publicly available data sources that allow the public to reproduce all simulation data including the resulting graphs. As secondary question we tested if this task could be performed, documented and archived in an agile working environment and according to the FAIR-principles.

Analysis procedures

To analyze the function of the COMBINE-archive we run several own simulations during the development process and compared the results with existing data from the original publication and with existing graphs *ibidem*.

Validity procedures

To validate the results of our COMBINE archive we conducted a systematic search for available modeling data, tested the content on a metadata level and created SBGN- and Simulation Experiment Description Markup Language (SED-ML)-files that were generated using various tools and that were challenged against the original data in numeric and graphic analyses.

Materials and methods

The tasks of this project were distributed on four teams and split into the sections

- Setup of an agile working environment
- Systematic review of existing materials and comparison of provided models
- Graphical representation
- Supply of one or several model scripts
- Assembly of the COMBINE archive

Setup of an agile working environment

To provide the model from Bachmann *et al.* [3] as a fully featured COMBINE archive, we created the public repository 'Bachmann_Archive' using the open-source platform GitHub, with a Creative Commons (CC)0-1.0-license. We chose GitHub as a data management platform to supervise the course of the project as it provides an intuitive and easily customizable environment, along with features for documentation, and agile project management [2]. This repository contains the proposal directory's structure from Scharm & Waltemath [1] with the following directories:

- Documentation (files describing the model and its characteristics)
- Model (files describing and encoding the biological system, e.g. SBML format)
- Experiment (files describing and encoding the experimental setup, e.g. SED-ML)
- Result (files obtained from running *in silico* experiments, including plots and tables)

Systematic review of existing materials and comparison of provided models

In our systematic search, we found five SBML-Bachmann models in two different repositories, JWS Online and BioModels (see Baseline data). We chose the latest model dating from 14th November 2019 as it provided complementary files for the simulation.

Graphical representation

One of the objectives of our project was to provide a standardized graphical representation of the Bachmann model based on the SBGN. We performed research on the SBGN website providing links to archives and databases, but could not find any existing SBGN of this model. We decided to create an SBGN network *de novo* based on previous works of Le Novère [8] and Touré *et al.* [9]. In this step, we selected the SBGN language, and lastly created the Process Description (PD) map with the web tool Newt Editor (v3.0.3) [10].

To validate the SBGN-ML we, imported it into several software and libraries including LibSBGN from Newt Editor, the open-source software Visualisation and Analysis of Networks containing Experimental Data (VANTED) [11], Krayon for SBGN [12], and SBGNViz [13]. Lastly, we cleaned up the map and colored the relevant features in the model to improve the developed map.

Supply of one or several simulation scripts

The simulation descriptions to reproduce selected experiments from Bachmann *et al.* [3] in combination with the selected model were provided as SED-ML Level 1 Version 3 files. SED-ML files were chosen because they fulfill the recently published Minimum Information about a Simulation Experiment Minimum Information About a Simulation Experiment (MIASE) guidelines (computer-readable exchange format, provision of XML schema).

An overview of existing tools to generate SED-ML files was obtained from the SED-ML website, including a brief description and information on supported model languages. Based on this overview as well as previous experience, we decided to test several different tools in order to create, edit and export SED-ML files for specific experiments using the selected SBML model. Initially, we followed the steps taken by Scharm & Waltemath [1] to generate a default simulation using SED-ML WebTools Version 2.4 and modified this for a specific experiment in COPASI v.4.33.246 [14]. However, given the type of plots to be created, we eventually decided to generate experiment-specific SED-ML files with Tellurium v2.2.0 [4] in order to reproduce the experiments presented by Bachmann *et al.* [3]. We used Google Colaboratory (COLAB), a cloud-based Jupyter notebook service for collaborative Python programming and loaded our scripts to our GitHub repository. Next, the created SED-ML files were validated using SED-ML WebTools. Finally, all acsedml files (including the associated Colab notebooks, output files (plots and tables) and validation results) were integrated into the COMBINE archive.

Assembly of the COMBINE archive

The development of the COMBINE Archive was performed in accordance with a recently published guideline from Schwarm & Waltemath [1].

The final assembly of our fully-featured COMBINE archive of the Bachmann model was executed in the platform WebCat. We used the same structure as described by Schwarm & Waltemath (see 'setup of an agile working environment'), and extended the scaffold by additional sub-folders containing supplementary files. Thus we created a new empty archive with our credentials on the WebCat with the name `::bachmann`. The metadata section of our COMBINE archive includes a brief description of the study and the contact data of the members.

The folder 'documentation' includes the initial paper from Bachmann *et al.* with its additional materials, the paper from Scharm & Waltemath, and the file 'SystemsBiology.bib' with the used literature in our project. 'model' contains files with the latest version of the Bachmann model from 2019 (see 'Model selection') and the sub-folder 'sbgn', it contains pictures, SBGN-ML files, and other supplementary files to visualize the model. The folder 'experiment' provides Python-scripts, SED-ML files, and other additional files to support the simulation. The results of the different simulations and validations are in the folder 'result'. This folder also contains the sub-folders 'Default', 'Fig(3-5)', 'Supp-Fig9', and 'SuppFig9_COPASI' that incorporate comma-separated values (CSV) files with tables, PDF files with reports, and pictures of the performed simulations with different tools. 'result' contains a sub-folder 'validation' including the additional folders 'Test_CO-PASI_2021-06-28' and 'Test_SWT_2021-06-28' with data files of the performed validations from COPASI and SED-ML_Web_Tools (SWT).

The Archive can be accessed via the link in the 'appendices'-section.

Results

Systems Biology Markup Language (SBML) results

In our systematic search we found five available SBML-Bachmann models in two different repositories, JWS Online and BioModels.

We found three models on BioModels. The first model, 'BIOMD0000000347_url.xml', was submitted on 22nd July 2011 and modified on 31st January 2012, this was the first delivered model and support the paper from Bachmann *et al.* [3]. Together with this model were other files in different formats. Most of them were generated by tools to simulate, visualize, validate and document the model, one of them is another SBML model ('BIOMD0000000347_urn.xml'). The third and newest, 'Bachmann2011.xml', was posted on 14th November 2019. This file contained other complementary files for the simulation of this model.

The models provided in JWS Online do not have any date of building or update, so it was not possible to know when these were built. The first model in JWS online, 'bachmann.xml', is from *Mus musculus* and represents the STAT's pathway in a cell simulation *in silico*. The second model, 'bachmann2.xml', was obtained from the BioModels database (BioModels ID: BIOMD0000000347).

Systems Biology Graphical Notation (SBGN) results

Figurative representation of data is a key factor to the rapid perception of information from it. The provision of the graphical representation of a model in a standardized, unambiguous form fosters the reusability and exchangeability of the model. The publication of the Bachmann model contains a process diagram of the model, which not uses a standard graphical notation [3].

Since no off-the-shelf standardised graphical representation could be found, we decided to create our own SBGN map from scratch. Based on the authors' diagram choice in the publication and the suggestions of Le Novère *et al.* [8] and Touré *et al.* [9] we chose the PD language for our COMBINE archive. Following the selection of the SBGN language, we identified several useful tools and ultimately created the PD map with 'Newt Editor'.

To check the validity and integrity of the drafted SBGN, we first used the semantic validation feature of Newt. This feature is based on the LibSBGN javascript library[15]. Furthermore, we imported the SBGN-ML into different tools to ensure the interoperability: VANTED/SBGN-ED, Krayon for SBGN and SBGNViz. Except from some minimal errors not adversely affecting the biological correct representation, our SBGN map was reproducible and editable in three different tools using the SBGN-ML file created.

Next, we beautified the resulting SBGN map in the Newt editor to ensure the network design was in line with the message and the scientific question it aims to communicate [9]. For this, we decided to keep the comprehensive structure of the SBGN map without further reduction of biological components or reactions to enable readers retracing the complex Ordinary Differential Equation (ODE) model. In order to make the SBGN map visually appealing and improve readability, we manually enhanced and decided to highlight the roles of the two transcriptional negative feedback regulators of the suppressor of SOCS family, cytokine-induced SH2-domain containing protein (CIS) and SOCS3, with color (**Figure 1**).

We aimed to provide our SBGN model in a variety of formats to allow recurrence on the

substitute files when the primary files are not applicable in a specific future application. Finally, we were able to provide different SBGN-ML 0.2 codes as well as a GraphML version of our model. The CellDesigner export did not work and also we failed to provide SBGN-ML 0.3 because we were not able to validate this with at least one other tool than Newt editor. Unfortunately, we were not able to further investigate the platform specific problems with exchange formats in detail as we experienced them, but provide a documentation for the community. During the time of our project, the CellDesigner export from Newt editor is already addressed in the discussion to an existing issue on GitHub (<https://github.com/iVis-at-Bilkent/newt/issues/498>). Also, we created a new issue addressing the manual modifications to the provided SBGN-ML version 0.2 main file to make it exchangeable to inform the developers of Newt editor (<https://github.com/iVis-at-Bilkent/newt/issues/679>).

Simulation Experiment Description Markup Language (SED-ML) results

Our goal was to create SED-ML files for our COMBINE archive to reproduce figures containing modeling data. Four figures in the main text (Figures 3 - 6) and one Supplementary Figure (S9) were selected and (partially) reproduced (see **Table 1**).

Initially, we generated a default simulation SED-ML file using SED-ML WebTools and performed an initial simulation. The generated SED-ML file was then used to create a SED-ML file in COPASI v4.33 (as described by Scharm & Waltemath [1]) and reproduced Supplementary Figure 9. The results were stored in our repository. However, COPASI's support for SED-ML files, is limited to simulations using only one model. It is often necessary though to combine different model setups in one simulation, e.g. to compare a wild-type and over-expression condition, which was also the case in our study.

Thus, we generated experiment-specific SED-ML files using Tellurium. The detailed documentation to the scripts are provided on our GitHub-Repository. We generated SED-ML files to reproduce Figure 3A and C, Figure 4, Figure 5A and Supplementary Figure 9. **Figure 2** exemplary shows the output after running the simulation of the SED-ML file to reproduce Figure 4. Notably, to simulate the overexpression of SOCS3 and CIS, two new models were created based on model1, where the parameters SOCS3oe and CISoe were set to 1 to create model2 and model3, respectively. In addition, the initial concentrations for SOCS3 and CIS were roughly set to maximum values for each molecule based on the plots generated. The plots for pJAK2 and pEpoR could not be reproduced since these parameters are not included in the model.

Next, the created SED-ML files were successfully validated in SED-ML WebTools and integrated into the COMBINE archive. COMBINE archive was downloaded and the '.omex' file was executed using Tellurium for testing purposes. The results were added to the final version of the COMBINE archive. Interchangeability between validated SED-ML files was tested by loading individual SED-ML files in COPASI or SED-ML WebTools.

In summary, we were able to reproduce many, but not all experiments. The specific problems encountered while attempting to reproduce the experiments will be addressed in the next section and separate issues in GitHub were opened for future reference.

Unexpected events and observations

Interestingly some required parameters to simulate specific experimental conditions were not included in the model. That way some model outputs are defined by observation functions that were not included as parameters in the model itself.

The plots for phosphorylated Janus kinase (pJAK)2, phosphorylated Erythropoietin receptor (pEpoR) and tSTAT5 (e.g., Fig3, Fig4) could not be generated since these parameters are missing from the model itself. Information on how to derive these observables from existing model parameters is included in the supplementary material of the original study (e.g., Supplementary Information, page 21).

In contrast to CIS and SOCS3, the over-expression of Src homology region 2 (SH-2) domain-containing phosphatase 1 (SHP1) could not be reproduced since the corresponding parameter (SHP1oe) was not included in the model (nor in any other Bachmann model files available online). We did not modify the model in order to simulate different level of Erythropoietin (Epo) as described in the paper. While the corresponding figure legends and supplementary material contain some information on Epo concentrations used for these experiments, it was not clear how to simulate this in the model.

Many figures (e.g. Figure 4) contain experimental data in addition to model simulations. Although this data is referenced as supplementary material in the online version of the paper, we did not include this in our plots. The ranges of the y axes do not correspond to the figures in the paper. Several experiments presented in the paper are based on testing a range of Epo levels. We were not able to reproduce these experiments, because it was not clear how to simulate different Epo concentrations using the model.

Finally, we uploaded all data from our GitHub repository into the platform WebCat, except generated XML file reports since the WebCat interface launches the error: **Unknown Error: Cannot upload file**. Therefore, we created a new ticket-issue in the GitHub repository from the WebCat project.

Reproducibility

As mentioned in the results section there have been some flaws in the reproducibility due to missing data given in the original work [3]. Nevertheless at the end of our project, we could build a fully-featured COMBINE archive and integrate the generated files, reports and pictures of the Bachmann model in the web platform WebCat.

Discussion

Answer to study questions

This study investigated the feasibility to generate a COMBINE archive in a agile working environment and the usability of this format to reproduce a dynamic pathway modeling study of the JAK/STAT5 pathway [3]. We independently built a completely publicly traceable, fully documented and agile working environment in GitHub from scratch. In this environment, our results show that the generation of a fully featured COMBINE archive is feasible and can be performed within two weeks. A broad set of tools to visualize and simulate biological modeling data was evaluated and tested. Furthermore, we could effectively reproduce the vast majority of the results of the original work.

Strengths and weaknesses of the study

Several limitations of our study should be considered. It was conducted for a limited duration of only two weeks due to the educational character. Hence, we could only focus our work on generating a COMBINE archive of a single study. Furthermore, the limited time was one of the reasons why not all data to reproduce the figures could be obtained. In addition, several parameters required to reproduce the full extend of individual plots were not included in the original data itself and therefore could not be reproduced. We will reach out to the authors to ask for the missing parameters. Also some technical issues hindered a barrier-free assembly of the archive. The WebCat interface did not allow the XML reports from the validations to be be uploaded. Due to restricted course duration, another shortcoming of our study is that we were not able to resolve those issues within the project duration.

Results in relation to other studies

Our observations complement the report by Scharm & Waltemath [1] that highlights the feasibility of COMBINE archives to reproduce results from modeling studies [16]. In comparison to this study, we extended not only the amount of generated simulation descriptions and SBGN compliant figures, but also tested and compared different available tools as outlined in the results section. Finally, we fully and comprehensively documented our work in a GitHub Repository under a CC0-1.0 License, enabling and inviting interested colleagues to re-use and share our work.

Meaning and generalizability of the study

The results of this study might be of great importance for future studies in systems medicine and biology by providing the authors with a protocol and guideline to create and validate COMBINE archives on their own. The provision of these archives might serve as a good quality indicator for journals and readers as they meet accepted standards and guidelines in the field such as FAIR [17] and COMBINE. Furthermore, enhancing the accessibility and re-use of published research is beneficial for authors to increase their visibility and citations. Yet, due to the limited number of included studies ($n = 1$), generalizability of this work might be limited and we propose to conduce further research in this area.

Unanswered and new questions

As a result of this project, we built a fully-featured COMBINE archive ('blood, sweat and tears') of the Bachmann model [3] using the web platform WebCat. Yet, some questions remain unsolved at this time:

In case of the provided SBGN files, an interesting field for future projects is definitely the integration of semantic annotations and functional aspects of the model into the SBGN map, with promising publications and reports from the community. As the approach presented by Scharm & Waltemath [1] to automatically create a first draft of SBGN was not suitable for the existing SBML files of the Bachmann model in our project, development of a guideline for modification of the SBML file to improve automated creation of SBGN would be very helpful.

Another interesting aspect for further studies would be to test and improve our generated COMBINE archive in the application Tellurium Notebook, the intuitive Graphical User Interface (GUI) front-end version of Tellurium. It was recently developed and shown to facilitate building and reusing models built with community standards [18]. It enables the user to directly load COMBINE archives, embed them in a human-readable representation and to test models under variety of conditions. In this regard 'tellurium-combine-archive-test-cases', a GitHub repository created by one of the authors contains several COMBINE archives as test cases.

Our finding that several plots could not be reproduced due to lacking parameters is in line with a current study, confirming that lacking parameters is the most common reason for failure to reproduce models [5]. The authors conclude that "*about half of the examined models cannot be reproduced using the information provided in the manuscript*" [5] and propose the use of a "**Reproducibility scorecard**" (see **Table 2** including standards such as COMBINE archives, SED-ML and SBML).

Finally, the co-working environment in a GitHub appeared to be very easy to use and understand throughout the whole project team. We therefore conclude that a publicly available documentation of scientific collaboration and the development of repositories, code and archives can be facilitating Findable, Accessible, Interoperable, Reusable (FAIR) handling of research both in the process of making as well as in the handling of results itself. The authors suggest that, given the easy to access and freely available software tools, more researchers will take the effort to share their work in a traceable and reusable manner. Also in the context of corporate class work our results indicate a high potential to form a precedent for future development of FAIR research output.



Conclusions

It is of evident importance for systems and synthetic biology to create reproducible models. In this case study, we reproduced large parts of a dynamic pathway model of JAK/STAT5 signaling [3] by creating fully-featured COMBINE archive. This study was performed in an agile working environment and made available on GitHub, ensuring a fully publicly traceable documentation of the work process. The provided COMBINE archive might serve as example for future efforts to increase reproducibility of studies in systems, medical and synthetic biology, and educational purposes. However, we were not able to reproduce all results of the investigated model, mostly due to the limited project time and the lack of parameters in the model description. Therefore, further communication with the authors will likely be needed.

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Acronyms

BIDS	Biomedical Informatics and Data Science
CC	Creative Commons
COMBINE	Computational Modeling in Biology Network
CIS	cytokine-induced SH2-domain containing protein
COLAB	Google Colaboratory
COPASI	CComplex Pathway SIMulator
CSV	comma-separated values
DOI	Digital Object Identifier
Epo	Erythropoietin
FAIR	Findable, Accessible, Interoperable, Reusable
GUI	Graphical User Interface
JAK	Janus kinase
MIASE	Minimum Information About a Simulation Experiment
MII	Medical Informatics Initiative
MIRACUM	Medical Informatics for Research and Care in University Medicine
ODE	Ordinary Differential Equation

PD	Process Description
pEpoR	phosphorylated Erythropoietin receptor
pJAK	phosphorylated Janus kinase
SED-ML	Simulation Experiment Description Markup Language
SBGN	Systems Biology Graphical Notation
SBGN-ML	Systems Biology Graphical Notation Markup Language
SBML	Systems Biology Markup Language
SBRML	Systems Biology Result Markup Language
SOCS	suppressor of cytokine
SHP1	Src homology region 2 (SH-2) domain-containing phosphatase 1
STAT	signal transducer and activator of transcription protein
SWT	SED-ML-Web-Tools
VANTED	Visualisation and Analysis of Networks containing Experimental Data
WebCat	CombineArchiveWeb application

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Appendices

GitHub Repository

Our public GitHub repository is available here: https://github.com/ahodelin/Bachmann_Archive [23]. This repository is a collaborative effort of participants of the module "Bioinformatik und Systembiologie" in the Master Program BIDS, organized by the Graduate School Rhein-Neckar in cooperation with the MIRACUM, a consortium of the Medical Informatics Initiative (MII).

COMBINE Archive

The fully featured COMBINE Archive of our project is available here: <https://cat.bio.informatik.uni-rostock.de/rest/share/6b507398-c103-4b92-9c90-d6b105ff1372> under the vignette **::bachmann**. The original publication with the used model (Bachmann *et al.*) is available here: <https://doi.org/https://doi.org/10.1038/msb.2011.50>.

Supplementary materials

1. Table 1: Selection of experiments for reproduction
2. Table 2: Reproducibility Score Card from [5]
3. Figure 1: SBGN map
4. Figure 2: Reproduction of Fig. 4 made by Tellurium