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“SBLink - Eine webbasierte Software zur Erfassung wissenschaftlicher Tabellendaten”

“SBLink - A web based tool for accessing scientific spreadsheet data”

vorgelegt von
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Zusammenfassung


Abstract

To cope with the data overload that is produced by diverse experiments with ever growing memory consumption is one of the big tasks science has to face. In the past this topic has often been neglected and underestimated. But nowadays many projects and software is trying to address this issue. Though, experimentalists and analysts often lack the enthusiasm to adept certain rules that are supposed to make data usage easier. Part of the problem is that there is not enough powerful and easy to use software. The SBLink project wants to throw in its share to free the users of the tedious task to manually search through spreadsheets in order to extract datasets. These datasets can be curated and saved in a database to gain easy access. It is supposed to be a alternative draft to the common method of introducing standards and only accepting data that corresponds to these standards. This might be another reason for the small participation and the high effort of persuasion that has to be put up to convince users of the advantages. Thus the thesis consists of the description and development of the SBLink tools. It is web-based to enable cross-platform usage and in this way lowering the bar of getting started with the software. Furthermore there is a usage case to address a biological problem. This will be about the question how functional a systems biology model remains when it is used outside of its intended scope.
1 Introduction

As of now there is big demand for data handling and making scientific data publicly accessible\[1\]. A lot of founding and energy is spent to produce databases that try to deal with this issue like the newly emerging “Scientific Data” project of the Nature Publishing Group. Unfortunately similar projects in the past have not been used with a lot of enthusiasm\[2\]. Part of the problem is the difficulty of creating databases that fit the needs of many contributors, is the big variability and complexity in data structures\[3\]. Data that is produced from experiments mostly exists in some form of spreadsheet files. Due to the different environments and operating systems spreadsheet data comes in various formats and structures that are not easily understood without any meta information. The main problem is to extract the data from files in order to process it further. The most common way to address this problem is to establish a certain format or structure that has to be produced by the software used for experiments and in turn can be read by another program. In order to produce these formats there is a demand for standards about what information needs to be included. A project that tries to define these standards for experimental research is the Minimum Information for Biological and Biomedical Investigations (MIBBI) project\[4\]. Its aim is to create checklists for different types of experiments that include the minimal information needed to understand an experiment and to allow reproduction of the results. One prominent example is the Minimum Information about a Microarray Experiment (MIAME) checklis\[5\] that is well established and many times even required of journals to be included in scientific publications that publish microarray-based data. For the MIAME checklist, the two formats MAGE-TAB and MAGE-ML have been evolved\[6\]. Furthermore tools have been developed to assist scientists in producing data that is compliant with the respective standard like RightField\[7\] and ISA-Tools\[8\]. This way of addressing the issue can be called “Top-down”\[9\], because it requires a given and agreed upon structure. This will work well if this is the only kind of experimental data to be worked with and a standard has been developed for this kind of experiment. Especially in Systems Biology scientists who want to find data to validate the results of a modeling approach or create new models are often faced with a different situation. The results of three different types of experiments will most likely be in three different formats and a minimum information standard might not be given. Thus the usual work flow consists of inconvenient manual extraction of datasets with a common spreadsheet editor like Microsoft Excel or an Open Source equivalent. In order to develop a tool that can facilitate this process and leave more time to work on the actual data, the SBLink project has been initiated. In contrast
1.1 Goals

This thesis paper is divided into two main parts. At first the development and functionality of the SBLink tool will be described. In the second part a case study about data validation will be presented to showcase the relevance of the developed tool.
2 Program description

Because SBLink is a web based tool, it uses a web framework in order to be displayed and used from inside a browser. The framework used is web2py [10]. It was chosen since it is programmed in Python, which is familiar to me and also a versatile and powerful programming language. Furthermore it is a well documented and maintained framework.

2.1 Tablib

In order to import, export and handle spreadsheet files a Python library was needed. Tablib by Kenneth Reitz [11] seemed like the best fitting candidate since it already offered exports for various formats like XLS (Excel Binary File Format), XLSX (Excel Workbook), ODS (OpenDocument Spreadsheet), CSV (Comma-separated values) and TSV (Tab-separated values). Additionally it supports the export to JSON (JavaScript Object Notation), which is the native JavaScript data format and therefore crucial since the tool is supposed to be web-based. Unfortunately it lacked the import functionality for most of them. This was implemented by me during a student project. Especially the ODS format posed some challenges, but needed to be included since it is the most common open source spreadsheet format. An ODS file is basically a zipped XML (Extensible Markup Language) document. There are Python packages that can unzip it and parse the XML. To get to the actual data it requires a navigation through the XML nodes to the corresponding cell. (See Figure 2) Based on the ODSReader class by Marco Conti [12] I developed a functional ODS parser that enables Tablib to import ODS files. Furthermore some fixes needed to be done in order to support XLS and XLSX and also the import interface was improved. The original version only included the import of file-like Python objects and I implemented an import function that uses the filename, thus improving usability for inexperienced users.

2.2 Web user interface - the “front end”

The web UI is based on a common HTML (HyperText Markup Language) document which is manipulated with the intensive use of JavaScript. Also the JavaScript library jQuery is used to ease the handling of click events and Ajax (Asynchronous JavaScript and XML) calls.
2.2 Web user interface - the “front end”

Figure 2: XML representation of the first four rows in the spreadsheet on the right.
To get to value of the first cell the parser would traverse like this: **table-row > table-cell > p**. The letters in **text:p** are also single child nodes.

2.2.1 Editor

The first main part of the web user interface that was developed is the spreadsheet editor. It enables the user to view and edit their uploaded spreadsheet files. Like mentioned above it makes heavy use of Ajax [13]. This is a great concept to improve user experience. As the name already suggests it makes asynchronous calls to the server, which implies that when the JavaScript compiler encounters an Ajax call it does not execute it right away, but continues in the code. The call is then started in the background, fetching data and handing them to the browser. This makes it possible to change only parts of the web page and not reloading it each time new information is requested from the server. If the user wants to edit a previously uploaded document, the spreadsheet will be requested from the server and displayed on the web page. In order to get a nice table display a JavaScript plug-in called DataTables [14] is used. If the file is in one of the formats XLS, XSLX or ODS and it has multiple sheets they can be accessed by selecting tabs above the table. In Fig. 3 the sheet “wild type gpd2Δ gpd1Δ” is selected. As a first measure of identifying datasets each spreadsheet is scanned for
2.2 Web user interface - the “front end”

Figure 3: Editor view with various features on display

Strings and numbers. Strings are by default identified as possible headers (red) and numbers are identified as data (green). Afterwards the sheet is scanned again for connected datasets. If a dataset has a string on top it will be attached to the dataset as a header, as can be seen in Fig. 3 with the first dataset having “Measurements” assigned as header. Datasets found in the sheet are then send to the server and database IDs are returned, e.g. the first dataset with the ID 7928. Other features are visible in Fig. 3. In order to keep the user interface as easy and intuitive as possible, most functions where put in a window that pops up when the user clicks on a dataset. It gives the option to change the orientation of datasets in this sheet and displays ID, header and tags of the corresponding dataset. Furthermore it will show if the dataset is grouped with any other dataset. Grouping is possible with the magnet icons displayed on top of the other datasets. If clicked the dataset will also be highlighted and listed as a partner. This selection is explicit and unidirectional. In Fig. 3 the first dataset is grouped with the third dataset (ID 7940), indicated by the highlight and also the remove icon which makes it possible to ungroup this dataset. Another great feature that can be accessed from the pop-up window is the ability to add tags to a dataset. Tags are another mean of identifying datasets besides the header.
and the position. Later on datasets can be filtered on the basis of their tags. The other click icons \( \bullet \) and \( \bullet \) trigger functions for adding and removing cells from a dataset. If a dataset does not contain a string header, there is the possibility to turn the first cell of this dataset into a header.

### 2.2.2 Dataset view

After files have been sufficiently edited the user can switch to the dataset view, although this does not mean that the sheets cannot be edited anymore. In fact, the user can switch back and forth between the dataset view and the editor as many times as needed. To get to a certain dataset it only requires the right selection of the file, sheet and dataset. When selected, grouped datasets are highlighted with a frame. Furthermore informations like the header and tags are displayed. This view also functions as the control center for file management. They can be deleted and the editor can be called. Datasets also have an edit function which shows the editor, scrolls to the right dataset and selects it.

Furthermore the dataset view includes a filter function that searches dataset headers and tag lists and shows the results in order of match quality. To improve the user experience a “fuzzy” search algorithms is implemented that shows results that are similar to the query and does not require the exact term. To determine how “fuzzy” the search is supposed to be, a slider is

![Figure 4: Structure of the dataset view: File → Sheet → Datasets → Data](image)
placed next to the input field which translates to values between 0 and 100 and in this way setting a threshold for the search algorithm. (See Fig. 5) In a later version it is possible to choose whether the filter searches the term in header, tags or both.

Figure 5: A search for the term “gpd” shows datasets with matching header.

2.3 Server - the “back end”

The web2py framework consists of Python scripts on the server side. There is a script to manage the two databases for data files and datasets. The controller script processes all the data sent to the server via Ajax. It inserts information in the according databases and makes them accessible for later use. It also holds functions to return information that is extracted from the database upon certain requests. The search algorithm is implemented here as well and makes use of the “fuzzy wuzzy” library [15].

2.4 Data extraction example

To demonstrate the abilities of the tool I was in the need for sample files and Clemens Kühn was so kind to provide me with data from his last publication [16]. It deals with the reaction of yeast cells to hyper osmotic stress. This will be explained in detail in section 3. The supplement included seven XLS files with most of them having multiple sheets. In addition they are rather large spreadsheets which is also a good way of testing the performance. One file includes all the raw and processed data where datasets need to be extracted. An important condition for the analysis is the concentration of intracellular glycerol which depicts a metabolic reaction to the stress. In order to extract the datasets from the raw data spreadsheet they need to be selected, grouped
with their time courses and tagged. When all the desired sets are curated they can be viewed in the dataset view. Since these are large files which contain a lot of datasets, applying the filter function is very convenient. As can be seen in Fig. 6a the datasets were given a “export_glyc” tag, which makes it easy to filter the results in the dataset view. See Fig. 6b.

Figure 6: Dataset extraction process
2.4 Data extraction example

Afterwards datasets can be selected and exported for further processing or plotting. During the export certain properties like filename, sheet name and tags are preserved and will be visible in the exported file. This file is ready for further processing or plotting. An example export is shown in Fig. 7.

![Figure 7: Export file including three datasets. Above the data are the preserved meta information like filename, tags, units and headers. Next to each dataset are the grouped time courses.](image-url)

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Figure 7: Export file including three datasets. Above the data are the preserved meta information like filename, tags, units and headers. Next to each dataset are the grouped time courses.
3 Data validation of new data versus an older model

In 2010 Zi et al. created a model for studying the Hog1 MAPK response to different forms of osmotic stress[17]. In 2013 Petelenz-Kurdziel and Kühn et al. gathered more scientific data for this process and created another model to fit the data[16]. Part of the data was used in section 2.4. Naturally the question arose whether the new data gathered in [16] would fit the old model from [17]. I used the SBLink tool to extract the relevant data from the supplementary files included in [16] in the same way as described in section 2.4.

3.1 Biological background

The reaction to hyper-osmotic stress in the yeast *S. cerevisiae* is a well studied mechanism and the high-osmolarity glycerol (HOG) mitogen-activated protein kinase (MAPK) signaling pathway is part of the reaction[18]. Upon osmotic stress yeast cells reduce size within seconds. Within less than 1 minute the glycerol export channel Fps1 closes to prevent glycerol leakage[19]. Parallel, the HOG signal transduction system is activated. The initial responses mediated by the active Hog1 include stimulation of ion export, pausing of the cell cycle, reducing of translational capacity and stimulation of glycolysis to enhance production of glycerol. When activated this pathway triggers the accumulation of glycerol to counter the high osmolarity outside of the cell. An additional way of enhancing the glycerol production is the NAD+-dependent glycerol 3-phosphate dehydrogenase encoded by the iso- genes GPD1 and GPD2 whose expression is also stimulated through Hog1[20] resulting in a transcriptional feedback. A diagram of the pathway is visible in Fig. 8.
3.2 Data from Petelenz-Kurdziel et al.

The collected data included measurements for the concentration of phosphorylated Hog1 (Hog1PP), Gpd1 and intracellular glycerol. Besides the wild type different mutant strains were used that were missing some adaptation mechanisms. The single mutations are:

- Hog1∆ and Gpd1∆: Hog1 and gpd1 genes are knocked out, respectively
- Hog1-att: Hog1 is attached to the plasma membrane and therefore...
3.2 Data from Petelenz-Kurdziel et al. Phillipp Schmidt

cannot enter the nucleus, which results in a missing Hog1-dependent gene expression response

- Fps1-Δ1: missing stress dependent closure of Fps1

Figure 9: Time course data. Figure taken from [16]
3.3 Model from Zi et al.

The model has a high resemblance with the one used by Petelenz-Kurdziel et al.[16] and therefore should be able to produce similar results. It does not include Gpd1 as a single species like the other model but rather a function $Yt$ that represents Gpd1 and that cascades over $N = 4$ different additional states $z1 - z4$ in order to resemble an observed time delay $\tau$. It is represented by the following functions.

\[
\frac{dz_1}{dt} = \frac{N \cdot ([Hog1PPn] - [z1])}{\tau} \\
\frac{dz_2}{dt} = \frac{N \cdot ([z1] - [z2])}{\tau} \\
\frac{dz_3}{dt} = \frac{N \cdot ([z2] - [z3])}{\tau} \\
\frac{dz_4}{dt} = \frac{N \cdot ([z2] - [z4])}{\tau} \\
\frac{d[Yt]}{dt} = K_{Yt}^{[z4]} + K_{Yt}^{Yt} \cdot [z4] - K_{Yt}^{Yt} \cdot [Yt]
\]

This state is later used to compare to the data for Gpd1. In the next step the different mutants needed to be included in the model. This was mostly straight forward and intuitive by removing any reactions that involved the knocked out genes. It was especially convenient that the model already contained separate species for Hog1 and Hog1PP inside the nucleus and the cell, respectively. This made it possible to simulate the Hog1-att mutant by removing Hog1 and Hog1PP just inside of the nucleus. A graphical representation of the model is shown in Fig. 10. In the following sections the time course data from Fig. 9 is compared to the data resulting from modeling the different mutants.
3.4 Hog1PP

From the five investigated strains only the wild type, Gpd1Δ and Fps1-Δ1 are suitable for observing the concentration of Hog1PP because in the other two strains it is either completely removed or not present in the nucleus. In Fig. 11 the three simulated Hog1PP concentrations are shown. Only when returning to the steady state after about 20 minutes the curves start to differ much. Prolonged phosphorylation of Hog1 can be observed in the Gpd1Δ strain, what is also visible in the data.
3.4 Hog1PP

When compared to the data the model proves that it is able to predict tendencies very well (See Fig. 12). Apart from slight differences in amplitude the simulations perform satisfactorily. Especially the Gpd1∆ model is able to reach almost exactly the same steady state. To a certain extent this could have been expected of the model since the primary focus was put on reproducing Hog1PP concentration time courses.
Figure 12: The three simulated Hog1PP responses compared to the experimental data.
3.5 Intracellular glycerol

For intracellular glycerol this is a different story. It was not one of the species used for parameter estimation when the model was created and experimental data was only provided for showing how the glycerol changes when exposed to dynamic pulses (e.g., square pulses). Glycerol concentration changes for a constant pulse were not investigated. Furthermore the initial concentration for intracellular glycerol is almost ten times lower in the experimental data. This is due to restrictions during the experiment.

![Figure 13: A closer look at the glycerol concentration time courses. Figure taken from [17]](image)

When comparing the figures 13 and 14 it is obvious that there is only a minor resemblance between some time courses. Apparently the model cannot reproduce the decay of intracellular glycerol. Yet some tendencies are similar. The character of the time course for the hog1Δ and the resulting disadvantage in glycerol accumulation is clearly visible. Also the wild type and the HOG1-att strain show similar positive tendencies which can also be observed in the data. On the other hand it seems like the gpd1Δ and FPS1-Δ1 strains are performing better in the simulation. The comparisons of each strain with its simulated counterpart would not be worthwhile since the progressions are
3.6 Gpd1

For the Gpd1 concentration only two strains are worth looking at since Gpd1Δ, Hog1Δ and Hog1-att all lead to Gpd1 not being expressed. Although in [16] some expression for the Hog1Δ strain was observed. To be in accordance with this observation a partial Hog1-independent increase of Gpd1 mRNA was implemented in the new model approach. In Fig. 15 the two strains that were simulated produced a well fitting time course. The difference in amplitude can be accounted for by the way of implementing the $Yt$ function as a placeholder for Gpd1.
Figure 15: Two simulated Gpd1 responses compared to the experimental data.
4 Discussion

4.1 Modeling results

The results of the data validation show that model created by Zi et al. is able to reproduce some of the new findings. Especially the results for the Hog1PP and Gpd1 concentration time courses fitted nicely. The problems with fitting the model to the glycerol data might have different reason. One aspect is the longer time period. In the original publication most experiments and simulations would not have run longer then 60 to 100 minutes. Unfortunately this is the exact time period were the glycerol levels start to fall. Also the different initial concentration is a problem. Still it is comforting to see that a model created for a specific problem can also be able to reproduce unintended results. While the model was originally created to simulate the effects of fluctuating osmotic stress, it is also manages to simulate strains with knocked out adaption mechanisms. To improve the fits some mechanisms implied in [16] would be worthwhile to incorporate. As mentioned before another function could be added to account for the Gpd1 levels in the HogΔ1 strain. Other suggested methods include osmodependent increase of Gpd2 transcription and the regulation of biomass production to account for other adaption mechanism that are not included in the HOG pathway. A regular parameter estimation step could also solve problems, but it defeat the purpose in a certain way. It is definitely a good example for the possibilities of mathematical modeling when the right tools are used and the right questions are asked.

4.2 SBLink

It could be argued that the functionality of the tool is not very appealing and it could easily be achieved by doing it manually, but that would not be very farsighted. The tool has only been in development for a couple mouth and it should be ensured that certain features work properly before extending functionality and loosing the scope. It is a very simple but different approach to this data assessment problem. For large quantities of data and for regularly used experiments, introducing standards is the method of choice and should always be used if applicable. To be able to choose would be ideal because then the user could decide which approach suits his current problem best. For example an on-line database were the user can choose from any existing standards to include his or her data and if that is not the case have a simple to use data curation tool like SBLInk. Another idea that was obvious during the development was a function to
create templates from an already detected spreadsheet structure that would have to be curated once and then each file of a similar structure could quickly be accessed. Furthermore the original idea to upload models as well and link data to the model species should be the goal.
5 Acknowledgments

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**Technical Abbreviations**

<table>
<thead>
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<th>Description</th>
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<tr>
<td>Ajax</td>
<td>Asynchronous JavaScript and XML</td>
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<tr>
<td>CSV</td>
<td>Comma-separated values</td>
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<tr>
<td>HTML</td>
<td>HyperText Markup Language</td>
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<td>JSON</td>
<td>JavaScript Object Notation</td>
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<td>ODS</td>
<td>OpenDocument Spreadsheet</td>
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<td>TSV</td>
<td>Tab-separated values</td>
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<td>XLS</td>
<td>Excel Binary File Format</td>
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<td>XLSX</td>
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<td>XML</td>
<td>Extensible Markup Language</td>
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Eidesstattliche Erklärung


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