

openGUTS v1.0 list of known bugs & issues

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Table 1: Known bugs & issues in the software and desired changes expressed by the test panel that are not currently implemented.

Issue	Technical comments
<p>Important calculation error: IT calculations in calibration and predictions makes use of a shortcut that can lead to errors for time-varying exposure (for scenarios where there is a linear decrease over time). <i>(added 19 May 2020).</i></p>	<p>This error was already part of the openGUTS design and in the prototype. However, it went unnoticed as it only affects calibration/prediction in very specific (and probably uncommon) situations. A separate document on the openGUST web page (linked in the warning texts) explains this issue in more detail.</p>
<p>Calculation: for the dieldrin case study, the IT calibration triggers reprofiling with a “flag_profile[1]: 10000000000”. This is generated in <test_proflik> BLOCK 2.1. The Matlab version does not trigger this for this data set. End result is correct, though.</p>	<p>Response WSC: The condition $\min(\text{coll_tst}(:,\text{parnr})) < \min(\text{parprof}(:,\text{parnr}))$ was true for the data set, triggering the high flag. However, the difference between the minimum of coll_tst and the minimum of parprof was only $\sim 4\text{E-16}$. Thus, the different behaviour between the Matlab version and the C++ version could result from machine precision or varying calculation precision of certain built-in functions.</p>
<p>Calculation: SD calculations are very slow for time-varying exposure. IT calculations and SD-constant run approx. 3x faster in the standalone, compared to the Matlab version, but SD-timevar. is 3x slower. That seems to point at the slowness of the numerical integration of the hazard rate over time.</p>	<p>WSC used rather standard trapezium-rule integration, functionally similar to that built-in in Matlab. We decided to accept the slowness for version 1.0.</p>
<p>Calculation: rounding of LPx to 4 digits seems to take place before calculating survival plots for predictions. In some cases, this can lead to final survival deviating from 90 and 50%. There could be some more intermediate rounding going on. The OGP file saves parameter estimates and the sample in 6 digits, which should be good enough.</p>	
<p>Calculation: for the calculation of the NRMSE and NSE, the values at $t=0$ are excluded. This seemed like a good idea, since the residual will always be zero at $t=0$. However, the response at $t=0$ will</p>	<p>It is likely better to always include the values at $t=0$.</p>

also be used for the mean response in both statistics. Especially for the NSE, this leads to very bad values when the survival response drops rapidly between $t=0$ and the first observation. <i>(added 30 April 2020).</i>	
GUI/general: would be good to have the possibility to drag the output screen (for the output text) to a different height. Now, just a few lines of text are shown, and the user always needs to scroll.	
GUI/general: Number format for small numbers becomes 'scientific' (e.g., 1.875E-5, which is good). However, this is not done for large numbers (becomes a bit messy).	
GUI/general: After pressing the 'Calibrate' button for the first time, the menu item 'Batch' gets an icon, and takes more space in the menu bar.	This seems like a GUI bug.
General: the openGUTS icon (on desktop, File Explorer, etc.) does not scale as other Windows icons do.	
GUI/general: copy data from graph has issues: the model values are correct, but the input data are not (survival as absolute numbers without CI, and exposure scenario is nonsense for time-varying exposure).	
GUI/general: loading an OGP file works. However, if you want to create a report after that, you get the full path of the report made previously, filled in in the file name box. This happens more generally in the software when loading/saving files (and not always the last filepath is shown).	This is unwanted behaviour, though not so problematic.
GUI/general: selecting a new analysis clears everything, but <i>not</i> the results from batch predictions. The previous results always stay in there and cannot be cleared. <i>(added 19 May 2020).</i>	
GUI/input data: if you create a new data matrix and select <No control group>, an error is produced: "Define at least one control group!" This is incorrect in two ways: it should be possible to work without control, and there can only be <i>one</i> control. The workaround is to just select the lowest concentration, and make sure that you fit background hazard hb along with the other parameters in the calibration. <i>(added after v.1.0 release).</i>	
GUI/calibration: it would be nice to have the option to modify time points and effect levels at	This functionality could be built into the Matlab version only. However, since ERA

which LC _{x,t} is calculated. Also for LP _x : option to choose effect level.	usually works with standard values for x and t, there may not be much need for this.
GUI/calibration: in the expert settings, fixing a parameter to a value <i>below</i> the advised range does not work. When the user presses the 'Calibrate' button, the value jumps to the <i>highest</i> value from the advised range. (<i>added 21 April 2020</i>).	Workaround would be to fit the parameter, rather than fixing it, but using a very small range. However, this is unwanted behaviour of the GUI.
Plots/calibration: parameter space plot needs lines for the min-max bounds as in the Matlab version (dark blue lines). Then it is immediately clear how close the parameter cloud is to the bounds.	This is done in the Matlab version, and should not be too hard to implement in the standalone as well. These lines help interpretation of the optimisation.
Plots/calibration: in the LC _x plots, the CIs for LC ₁₀ obscure CIs for LC ₅₀ if they overlap. The best values is however plotted.	This is properly done in the Matlab version already, but requires transparent colours (which could be harder in the standalone).
Plots/calibration/validation/prediction: for survival plots, the time axis is slightly shifted to the right. That is not done for damage and exposure plots in the same picture. All time axes should be the same.	This should be simple to adjust.
Plots/calibration: in the parameter-space plots, the profiles are slightly shifted up (the y-axis does not cross at zero). This is potentially confusing: crossing at zero is best.	This should be simple to adjust.
Calibration: the software ran into problems when only one parameter was fitted. At this moment, the user is therefore forced to fit 2 parameter or more.	This is unlikely to be an issue in practice. Workaround is to set ranges very tight. The Matlab version is able to fit one parameter, if really needed.
Calibration/profiling: in very extreme cases, profiling may find a much better optimum which leaves no points in the cloud (apart from the new best value). This now produces an informative error on screen. However, this may not be necessary. It is unclear whether this occurs in practice, and, in general, such cases would need specialist attention. (<i>reported after v.1.0 release</i>).	The informative error is produced in BLOCK 6.1. This may not be necessary, as long as <coll_ok> contains some good points to continue sampling with. However, <edges_cloud> would then need to be calculated based on <coll_all> AND <coll_ok>. This is already implemented in the BYOM version of the algorithm, but not in openGUTS.
Calibration/profiling/GUI: the optimised profile-likelihood points (that are used for the profile curves in the graphs) are also added to the total sample. However, this is <i>not</i> reflected in the status of the sample size printed on screen, which therefore shows a somewhat smaller sample size than what is actually used (and what is saved in the project file). (<i>reported after v.1.0 release</i>).	This is a small issue in practice, since the reported sample size is of little practical use in most cases.
GUI/predictions: it would be good to have tabs for both GUTS-RED-SD and GUTS-RED-IT on the output tab; same as for calibration and validation	

<p>tabs. If you do an IT run after an SD run, the software still remembers the IT run anyway (the checkboxes for IT and SD act as tab switches). This is counter-intuitive behaviour; I would prefer tabs that are filled when a calculation is performed. I would like to keep the checkboxes for SD or IT, so the user can calculate only one of them.</p>	
<p>GUI/predictions: predictions without CI do not trigger the progress bar. However, for SD, it may take some time. It would be good if the software shows the progress bar for such cases, or displays a text message in the output window (like "calculation running"). Just to let the user know that it is working (and not crashed).</p>	
<p>Report: link to Word seems rather vulnerable. In some cases, error and warning messages appear.</p>	<p>Latest tests look stable. Maybe it is good for users to get some more experience with the software and see if this is still an issue.</p>
<p>Report: the exposure-damage-survival plot is cut up over multiple pages; is it possible to scale it down so that it fits on one page and remains one picture?</p>	
<p>Report: Use Word section headings and create an automated Table of Contents.</p>	
<p>GUI/report: Provide a dialogue for (un-)selecting some parts of the report.</p>	
<p>Report: performing batch calculations after regular LPx estimations leads to problems in the report. The last batch LPx calculation overwrites the regular one, but the plots are still from the regular calculations. Furthermore, plots from previous calculations may appear in the report (even when pressing 'New project').</p>	
<p>Report: calibration algorithm restarts when 'slow kinetics' is indicated. The parameter ranges in the report are the values <i>after</i> the restart. In restarting, the algorithm attempts to decrease the ranges of several parameters, based on the cloud of points found so far. <i>(added 7 May 2020).</i></p>	<p>This is not a bug per se, but it may be unexpected for users to see ranges differ from what they started with (and different ranges for different model runs). Some explanation in the report would be good (also to indicate that a restart occurred).</p>
<p>Report: the selection for what to do with background hazard in the validation stage is not shown in the report. <i>(added 7 May 2020).</i></p>	<p>This is unfortunate, since this information is important to judge the validation output.</p>
<p>Prediction: the calculation of CIs on LPx takes a long time, especially for SD (could be several hours).</p>	<p>This could be eased by using a smaller sub-sample from parameter space, at the expense of underestimating the true width of the CIs. For batch processing, this is implemented as an option in the Matlab version.</p>

<p>Loading OGP: on loading a OGP file, the calibration output is reconstructed on screen. However, the parameter-space plot is lacking the red line for the profile.</p>	<p>If this line is really needed, the data for that line would need to be saved in the OGP file, which implies a change in its format.</p>
<p>Installation: possibility to choose the location for installing the software, rather than forcing C:\Program Files (x86)\openGUTS.</p>	
<p>Installation: issues with admin rights or virus scanners ...</p>	<p>See if this is an issue for users in practice, and what can be done about it.</p>

Table 2: Possible new functionality without requiring major reworking of the code.

On a general note, the choice could be made to restrict updates to the standalone version to bugs/small issues, and to implement new functionality into the Matlab version only. The Matlab version provides identical results to the standalone version, is easier to modify, and the new functionality would mainly be for expert users.

Possible new functionality (not considered for version 1.0)	Technical
Validation: possibility to use more than one data set for validation.	This is already possible in the Matlab version.
Prediction: possibility to use more than one data set for prediction (LPx calculation).	This is already possible in the Matlab version.
Predictions: option to plot CIs on the model curves (survival and damage) for the prediction stage.	This is already possible in the Matlab version, but extremely time consuming. This could be done with a smaller sub-sample.
Predictions: option to save exposure profile from the software, rather than only allowing loading.	
Batch calculations: the batch calculations need the option to calculate LPx with CIs.	This option has been built into the Matlab version already (version 0.8), including the option to use a sub-sample for speed. That could be sufficient.
Input data: other types of exposure scenarios; currently only linear interpolation (with the possibility for instant changes) is used. However, we could also think of an option to use static renewal with exponential decay.	This requires a different input data format, which can easily be confusing. Far simpler would be the possibility to automatically generate stepwise-linear exposure scenarios that approximate a certain exponential decay (this could be a separate tool).
GUI: Possibility to use a conversion factor for prediction scenarios (if they are in different units than the calibration data). Somewhat more elaborate would be an automatic conversion of concentration units. E.g., with drop-down menus to select the relevant units from a list for each data set.	A correction factor for LPx predictions is already possible in the Matlab version.
Plotting: more types of plots. Most interesting would be a single-panel survival plot (with all treatments plotted in the same panel, such that the overall pattern can easily be judged visually).	This could be implemented into the Matlab version only. Note that dose-response plots would be ambiguous when exposure is not constant; these plots are best avoided.
Predictions: specific options for making predictions to aid test design (e.g., calculating pulse height, pulse width, pulse intervals).	Some functionality is already included in the Matlab version (plotting damage and survival for user-entered MFs).
Calibration: option to use data-set-specific background hazard rates in calibration (when calibrating to multiple data sets).	This requires a change in the internal data representation, and would only be a good idea if h_b is fitted to the controls (otherwise too many parameter would need to be fitted simultaneously).
Report: Different functionality/formatting/options for output report(s).	Wait for users to gain experience with the current version.

Report: Also include DRT95 and beta in the report (they are now only shown in the output window of the calibration). <i>(added 21 April 2020)</i>	
Calibration: plot parameter space for two calibrations in such way that it is possible to see if the two calibrations are consistent (whether the clouds overlap).	This could be implemented into the Matlab version only, or even outside of the software in a separate tool, using the saved project files. However, spotting overlap in more than 2 dimensions needs some thought.
GUI/calibration: allow excluding treatments from the data set for calibration (without having to make a new data set).	
Calibration: smarter derivation of initial parameter grid. E.g., including a correlation structure.	This would be complex, and would only improve speed in Round 1 of the optimisation (which is generally very fast anyway).
Batch predictions: currently, the batch mode only produces text output of the LPx values for each profile. This could be augmented with plots (e.g., a multipanel plot with all exposure scenarios and survival).	The Matlab version already creates standard plots for each profile silently (not on screen, but only placed as PDF in the output directory).
Calibration: In cases where parameters are correlated, it may be that a CI for a parameter is affected by another parameter hitting its boundary. For example, for slow kinetics, kd and mw go to zero and bw to infinity, all tightly correlated. One of these three parameters will hit its boundary first, implying that the others cannot continue to more extreme values. Their CIs (at least: one of the bounds) will thus be artificial, and depend on the boundaries of the other parameters.	We can try to identify this behaviour and flag it. However, it would be difficult to do that in a fool-proof manner.
GUI/general: Allow the prototype's mat file to be used by the standalone, and the standalone's output file by the Matlab version.	This could be a separate Matlab tool to translate one file into the other. However, since calibration does not take much time, this is unlikely to be very helpful.
GUI/general: Design a simple Matlab GUI for the Matlab version, to aid use of this version (would still require Matlab to be installed).	Matlab offers options to create GUIs, which can simplify operating the Matlab version (the GUI will make use of the same underlying functions as the current Matlab version).

Table 3: Suggested new functionality that would require major reworking of the code.

In general, it should be considered that BYOM is better suited for these (and several options are already included in the BYOM GUTS package).

New functionality that implies extensive changes in the code.	Technical
Inclusion of GUTS models that separate TK and damage dynamics (the full model). Either allowing the user to provide a TK rate constant, or allow the user to enter body-residue data to be fitted together with survival data.	Even though analytical solutions for damage can be used, this requires very serious modification of the code: inclusion of more functions that calculate model output, more parameters (>4 parameters would require more robustness testing with the optimisation algorithm, with uncertain outcome), serious modification of the LC _{x,t} and LP _x calculations (the analytical solutions and shortcuts will not work anymore), and possibly a different (extended) input data format.
Include TK models that deal with growth dilution or other TK extensions (e.g., saturating kinetics).	This would require serious modification of the LC _{x,t} and LP _x calculations, and likely introduces additional parameters that need to be fitted (so robustness checking of the algorithm). Furthermore, if effects are driven by damage, it is unclear whether growth dilution applies.
Inclusion of GUTS models that use 'GUTS proper', and thus combine SD and IT.	This would require thorough testing of the optimisation algorithm, as it would lead to >4 model parameters. Furthermore, some checking whether the LC _{x,t} and LP _x calculations still apply.
Include sampling error for the CIs on survival probability. This will lead to two types of CIs on model curves: the ones including only parameter uncertainty (which is already available) and wider bounds that account for the differences between individuals (this is where we can expect 95% of new data points to fall). This would allow for better judgement of the validation plots.	This can likely be based on the 'validation profile likelihood', but that needs to be worked out for the multinomial case. This requires theoretical study and testing. However, once the equations are clear, the main change would be to the plotting function.