MISI Calculator Guide.
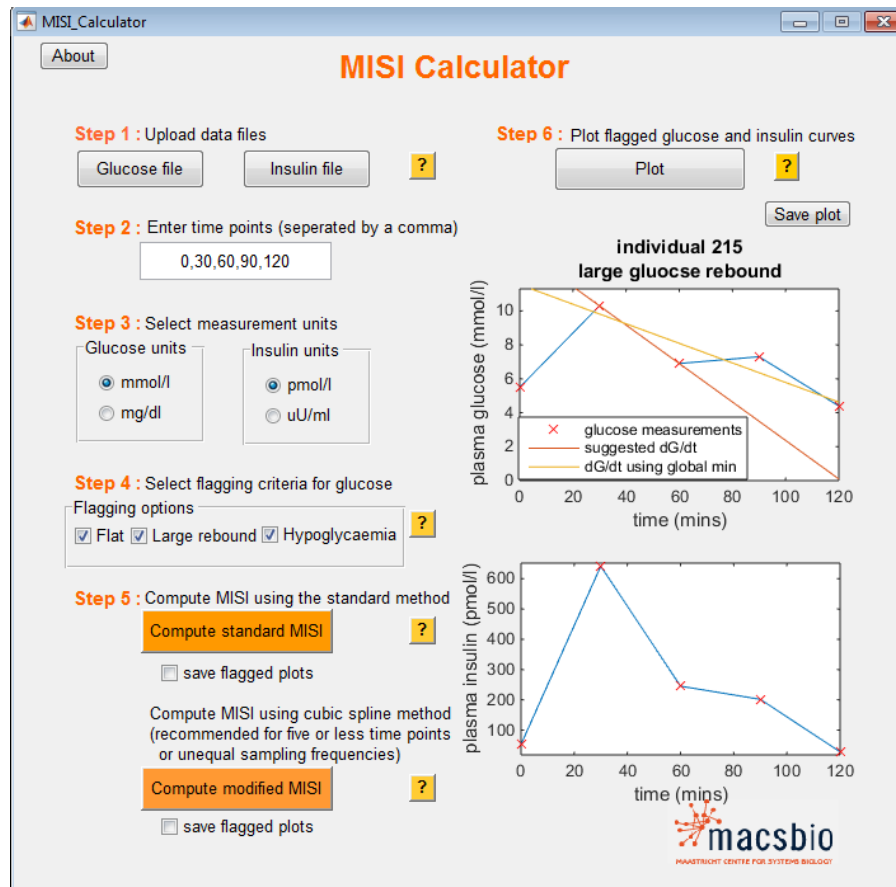
The MISI Calculator allows for the calculation of the muscle insulin sensitivity index (MISI) on oral glucose tolerance test (OGTT) data using both the original method proposed by Abdul-Ghani et al. (2007) and also the modified cubic spline method proposed by O'Donovan et al. (in preparation).

The Muscle Insulin Sensitivity Index:
The Muscle Insulin Sensitivity Index (MISI) was proposed by Abdul Ghani et al. (2007). MISI aims to quantify muscle specific insulin sensitivity using OGTT data and has been validated against comparison with the hyperinsulinemic euglycaemic clamp combined with a glucose tracer infusion. MISI is calculated as $\frac{dG}{dt}\Big/\bar{I}$, where $\frac{dG}{dt}$ is the line of best fit from the peak of the glucose curve to the nadir and $\bar{I}$ is the mean insulin over the duration of the OGTT. MISI is built on the assumption that the decay in the glucose curve during an OGTT ($\frac{dG}{dt}$) is primarily due to the uptake of ingested glucose by the skeletal muscle as the raised insulin concentration will have inhibited endogenous glucose production.

A modified Muscle Insulin Sensitivity Index (modified MISI) was proposed by O'Donovan et al. (in preparation). It makes use of cubic splining to infer the full OGTT glucose and insulin curve from them measured data thereby improving prediction of the glucose peak and nadir

while also accounting for unequal sampling schedules. MISI is then computed on the inferred glucose and insulin curves.

Installation of the MISI Calculator:

The MISI calculator can be installed by downloading and unzipping the MISI Calculator folder which can be found at www.maastrichtuniversity.nl/misi. Selecting the MISI_Calculator_Installer application will being the installation procedure. Please note that Matlab Runtime will be installed on your machine as part of the installation procedure if it is not already present. It is not advised to install the MISI Calculator on tablets, or other smaller devices, as Matlab runtime is 410 MB. The installation of the MISI Calculator may take some minutes if Matlab Runtime is not already installed on the machine. Sample glucose and insulin .xlsx files are also included in the MISI Calculator folder

Using the MISI Calculator:

Step 1: Uploading glucose and insulin data

Glucose and insulin OGTT data should be uploaded in separate .xlsx format files (excel work books). Each file should have the following layout (example file below);
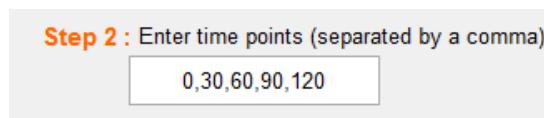
- Row one may contain variable names. This row will not be used in calculation so should be left blank if no variable names are entered. Note: do not use text/strings as these will be interpreted as missing values.
- Each subsequent row should contain the OGTT data for each individual test.
- The first column of each row should contain an identifier or ID number for each test. Note: do not use text/strings as these will be interpreted as missing values.
- Remaining columns should contain the glucose/insulin measurements at each time point over the OGTT.

	A	B	C	D	E	F	G
1	ID	0	30	60	90	120	
2	1001	92.15027	126.9038	118.1854	92.3385	79.63209	
3	1002	76.60285		120.5116	123.6065	116.5771	
4	1003	76.0533	123.9557	127.0093	102.0423	81.06324	
5	1004	96.96584	150.6754	176.0265	186.1207	186.9347	

- Glucose/insulin file may contain missing values (empty cells or cells containg text in the excel file). MISI will not be calculated for these rows, the output file will state "missing value(s)" in column three if either glucose or insulin OGTT data contained one or more missing values.
- Uploaded glucose data may be measured in mmol/L or mg/dL, insulin data may be measured in pmol/L or µU/ml. All units will be converted to SI units in step 3.

Step 2 : Entering time points.

Measurement time points during OGTT should be entered directly into the calculator. Time points should be entered in minutes in ascending order into the window seperated by a comma. Press enter key once all time points have been entered.
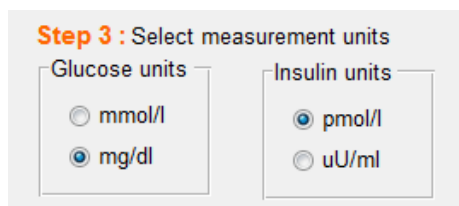

For the calculation of MISI the 120 minute time point is required regardless of the OGTT sampling schedule. The 120 minute time point should be the final time point used the the calculation of MISI.

Note: If you receive an error *"Please enter time points"* ensure you have pressed the enter key after entering the time points.

Step 3 : Specifying measurement units.

Select measurement units of uploaded glucose and insulin data by selecting the button in respective measurement unit panels on the calculator. Default units are SI units of mmol/L for glucose and pmol/L for insulin. Units will be converted to µmol/L and pmol/L for glucose and insulin respctively for the calculation of MISI. (µmol/L of gluocse is used rather than mmol/L to normalise the resulting MISI values.)

**Step 4 :** Criteia for flagging glucose curve for manual inspection.

Allows user to select criteria for which glucose curves will be flagged for manual inspection of the computed/suggested MISI values. By default all three boxes are checked. Glucose curves may be flagged for;

- Flat glucose curves; glucose curves with a peak less than 0.5 mmol/L greater than the fasting value. Such curves yield potentially erroneous low MISI values when computed on OGTT data with five time points or less as data has failed to capture a very early glucose peak. The calculator will suggest a MISI value in the output file and provide a graphical representation of this suggested value in the plot.

- Hypoglycaemia; OGTT curves where glucose concentration falls below 3.5 mmol/L. The MISI Calculator will suggest a MISI value, but the curve will be flagged for manual inspection.
- Large glucose rebounds; rebound in glucose curve following nadir is greater than 0.5 mmol/L. Particularly an issue in more frequently sampled OGTT data (seven or more time points) as fluctions in glucose data due to measurement/assay erros may introduce a false nadir. Calculator will suggest MISI values computed using global minimum as well as nadir in output file.

Please refer to O'Donovan et al. (in preperation) for more information on flagging of glucose curves for computation of MISI.

Step 4 : Select flagging criteria for glucose curves
Flagging options
☑ Flat ☑ Large rebound ☑ Hypoglycaemia
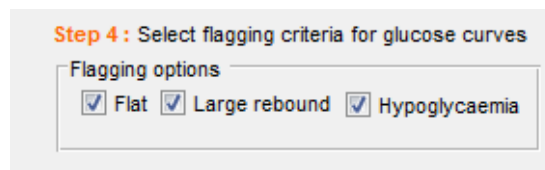
Note: Peak at 120; as there is no unique solution for $\frac{dG}{dt}$ when the glucose peak occurs at the final sampled time point it is not possible to compute MISI. All such glucose curves will be flagged.

Order of filtering for flagging; Firstly curves will be screened for having a peak a 120 minutes, followed by flat curves, curves which display hypoglycaemia, and then those with large glucose rebounds.

Step 5: Compute MISI :

Compute standard MISI: Selecting this button will compute MISI for the uploaded OGTT glucose and insulin data using the original method as proposed by Abdul-Ghani et al. (2007). The user will be asked to specify a directory in which the output file and any output figures will be written.

Compute modified MISI: Selecting this button will compute MISI for the uploaded OGTT glucose and insulin data using the modified cubic spline method as proposed by O'Donovan et al. (in preperation). This method is recommended for OGTT data with five or less sampling points or with unequal sampling intervals. The user will be asked to specify a directory in which the output file and any output figures will be written.

Step 5 : Compute MISI using the standard method

Compute standard MISI   ?

☑ save flagged plots

Compute MISI using cubic spline method
(recommended for five or less time points
or unequal sampling frequencies)

Compute modified MISI   ?

☑ save flagged plots

Save flagged plots: Checking the *save flagged plots* box below either Compute MISI button before calculation of MISI will save a figure of glucose and insulin curves along with a graphical representations of the suggested MISI value (line described by $\frac{dG}{dt}$) for each flagged glucose curve. Figures will be saved to the directory specified by the user for the output files. **Caution:** Saving all flagged plots may take some time for larger data sets.

Output File: The output file will be written to the user specified directory. In the case of the standard method the file will be entitled "standard_MISI_score(1).xslx" and for the modified method "modified_MISI_score(1).xlsx", where the number in parentheses indicated the version of the file, to avoid overwriting files. The output file will have the following format;

|	A	B	C	D	E	F	G
1	ID number	MISI	Reason for exclusion	suggested value	Using global minimum		
2	1001	0.144842					
3	1002		missing value(s)				
4	1003	0.198615					
5	1004		hypoglycaemia	0.467121048			
6	1005		peak at 120 minutes				
7	1006	0.02699					
8	1007	0.02247					
9	1008	0.026604					
10	1009		large gluocse rebound	0.006663165	0.022967		
11	1010		flat glucose curve	0.169629118			
12	1011	0.055315					
13	1012	0.065785					

- Column one will contain the user specified identifers/ID numbers for each individual.
- Column two will contain the computed MISI value. This entry will be blank if the input data contained missing values or the MISI value was flagged.
- Column three will contain a statement providing the reason for excluding this individual from computing MISI.
- Column four will contain a suggested MISI value with $\frac{dG}{dt}$ computed from glucose peak to nadir where this is numercally possible. (green line in below figure)
- Column five will contain a suggested MISI value with $\frac{dG}{dt}$ computed from glucose peak to global minimum in the case of a gluocse curve flagged for a large glucose rebound. (blue line in below figure)

The user may then manually evaluate which suggested value should be selected.
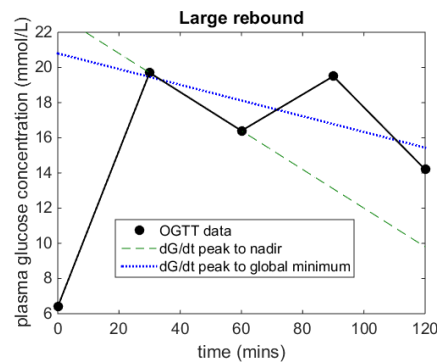
Step 6 : Visualising flagged glucose curves.

It is possible to visualise all flagged glucose curves within the MISI calculator. Selecting the *Plot* button will plot the glucose and insulin curves for each flagged individual along with a graphical representation of the suggested MISI value for the **most recent calculation of MISI(** in the case of glucose curves flagged due to a large rebound the suggested $\frac{dG}{dt}$ computed using both the nadir and the global minimum will be displayed). The title of each plot will contain the user supplied identifer/ID number for the flagged individual and the reason for flagging the glucose curve. It is also possible to save an individual flagged glucose and insulin figure from the calculator by selecting the *save plot* button located to the lower left of the *Plot* button. Plots will be saved as a .png file to the same directory as specified for the output of the calculation of MISI. Selecting the *Plot* button again will display the glucose and insulin curves for the next flagged individual.
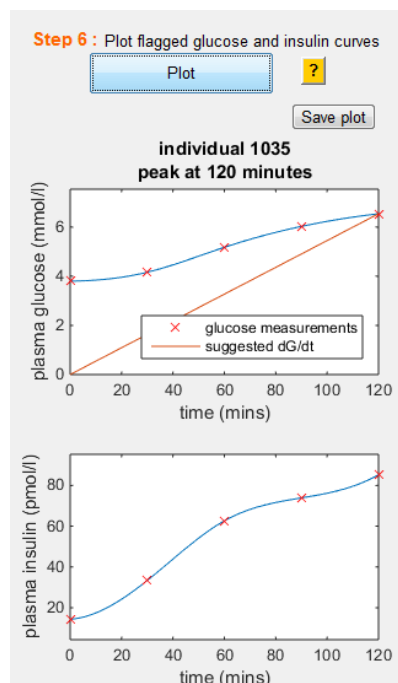
At each step of the MISI calculator it is possbile to select the help button for additional nformation and help regarding the step.