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1 *uFREASI: user-FRIENDly Elemental dAta procesSIng*

2 **A FREE and EASY-to-use tool for elemental data treatment.**

3
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11 **Abstract**

12 Inductively Coupled Plasma – Mass Spectrometry (ICP-MS) allows the quantification of trace
13 and ultra-trace elements (mg/kg to fg/kg) by separating elements as a function of their mass-
14 to-charge ratios (m/z) after ionisation into an argon plasma. In spite of being rigorous and
15 accurate, the “Results” modules provided by many manufacturers are often uneasy to use and
16 operators have little control on the calculation. Moreover, the large amount of raw data
17 generated makes the manual treatment very long and not reliable using a “home-made”
18 spreadsheet. The user-FRIENDly Elemental dAta procesSIng (uFREASI) software presented in
19 this paper follows a configurable step-by-step procedure allowing a quick and reliable data
20 treatment plus an automatic uncertainty propagation. The concentration calculation is
21 performed using the ordinary least square method after an external calibration. The software
22 proposes many options to correct and to monitor the signal, to warrant both quality and
23 understanding of data treatment. uFREASI is supported by Windows, Mac OS X and Linux

24 operating system, is open and extensible, and is freely downloadable at
25 <http://www.ipgp.fr/~tharaud/uFREASI>.

26

27 **KeyWords**

28 Inductively Coupled plasma – Mass Spectrometry, multi-elementary analysis, automated
29 calculation of concentrations, uncertainty propagation.

30

31 **Abbreviations**

<i>uFREASI</i>	user-FRiendly Elemental dAta procesSIng
<i>Q-ICP-MS</i>	Quadripole – Inductively Coupled Plasma – Mass Spectrometry
<i>HR-ICP-MS</i>	High Resolution – Inductively Coupled Plasma – Mass Spectrometry
<i>ICP-OES</i>	Inductively Coupled Plasma – Optical Emission Spectrometry
<i>GUI</i>	Graphical User Interface
<i>LGPL</i>	Lesser General Public License
<i>STD_</i>	Standard (use for the external calibration)
<i>BLK_</i>	Blank (use for the external calibration)
<i>QC_</i>	Quality Control
<i>VS_</i>	Verification Sample
<i>IS_</i>	Internal Standard
<i>SD</i>	Standard Deviation
<i>RSD</i>	Relative Standard Deviation
<i>STD_i</i>	Known concentration of an element in a standard
\overline{STD}	Average of concentrations of an element in all standards
<i>INT_i</i>	Measured intensity of an element in a standard
\overline{INT}	Average of measured intensities of an element in all standards

BLK_i	Measured intensity of an element in a blank
\overline{BLK}	Average of measured intensities in all blanks
δBLK	Uncertainty on the measured intensity of a blank
n	Number of measurements
S	Slope
δS	Uncertainty on the slope
Y	Y-intercept
δY	Uncertainty on the Y-intercept
R^2	Coefficient of determination
$(I.S.)_0$	Reference intensity of the Internal Standard
$\delta(I.S.)_0$	Uncertainty on the reference intensity of the Internal Standard intensity
$(I.S.)_t$	Measured intensity of the Internal Standard
$\delta(I.S.)_t$	Uncertainty on the measured intensity of the Internal Standard
α	Correction factor of Internal Standard variations
I_m	Measured intensity
I_c	Corrected intensity
LOD	Limit Of Detection
LOQ	Limit Of Quantification

32

33 **1. Introduction.**

34 Inductively Coupled Plasma Mass Spectrometry (ICP-MS) [1] is a powerful tool allowing the
35 detection and quantification of multiple chemical elements in a large variety of man made
36 products, geological, environmental and biological samples [2]. For example, it is currently
37 applied to the multi-elementary analysis in surface waters [3], soils and sediments [4] as well
38 as petroleum [5] or biological fluids [6].

39 The principle of ICP-MS techniques is the introduction of aerosol samples into an argon
40 plasma. The plasma dries the aerosol, dissociates the molecules, and then form singly charged
41 ions by removing an electron from the components. These ions are directed into a mass
42 filtering device known as the mass spectrometer, which allows the components separation
43 depending on the mass-to-charge ratio (m/z) [7]. Thus, ICP-MS allows the analysis, in the
44 same sequence, of (almost) the entire periodic table and of many isotopes of a given chemical
45 element.

46 The most commonly used mass filter is a radio frequency (RF) quadrupole field which
47 separates ions passing through oscillating electrical fields created between 4 parallel rods [1].
48 This kind of mass spectrometer called Quadrupole – ICP-MS allows the routine analysis of
49 major, minor and trace level elements using if needed a collision/reaction cell to reduce
50 interferences. However, the continuous development of ICP-MS techniques over the last 30
51 years has led to machines more and more powerful in terms of sensitivity, accuracy,
52 resolution and detection limit of ultra-trace elements [8]. This is particularly true for High-
53 Resolution - ICP-MS [9], which specificity consists in the addition of an electrostatic filter to
54 a magnetic one. This allows a better discrimination between elements of interest and
55 interferences (analytical resolution), without suffering an important loss of sensitivity [10].
56 Moreover, three different resolution modes (low, medium and high) may be used in the case
57 of HR-ICP-MS [11]. Although this analytical technique can produce robust results, the large
58 amount of data produced in one single sequence is challenging regarding the data treatment.
59 For instance, it is possible to analyse in the same sequence more than 50 elements on more
60 than 300 samples (i.e. 15000 raw data per day).

61 “Results” modules are systematically included in the software displayed by ICP-MS
62 manufacturer. Nevertheless, users get very few information on the equations and corrections
63 applied for the data treatment and thus often consider these tools as “black boxes”.

64 Consequently, most ICP-MS users have developed their own customised data treatment
65 spreadsheet with or without automation. A survey performed in 2012 during an annual French
66 workshop (CNRS “Isotrace” Conference on traces and isotopes measurements in earth
67 sciences, n = 27 users) revealed that 56% of users obtained their final results through “home-
68 made” spreadsheets, whereas the others use the manufacturer software, often as a duplicate of
69 their customised spreadsheet. Currently, it appears to be little standardization of the data
70 treatment procedure with respect to how ICP-MS results are treated among research groups.
71 Additionally, due to the large amount of data generated, the manual treatment is too long and
72 subject to errors, whereas uncertainties propagation are often disregarded.

73 Our aim is to provide an accessible and reliable data treatment to ICP-MS users. Thus, we
74 developed an integrated software system to process, analyze, and assess the quality of ICP-
75 MS data: uFREASI, for "user-FRiendly Elemental dAta procesSIng". The system is open,
76 extensible and freely available ([http://www.ipgp.fr/~tharaud/ uFREASI](http://www.ipgp.fr/~tharaud/uFREASI)). It is supported by
77 Windows, Mac OS X and Linux operating systems. On the basis of the raw signal measured
78 for each chemical element, uFREASI will calculate the elemental concentrations in both a
79 rigorous (*i.e.* with trustable error calculation) and easy-to-use ways. The present paper focuses
80 on the description of data treatment concerning 2 commonly used ICP-MS *i.e.* an HR-ICP-
81 MS (Element II from ThermoScientific) and a Q-ICP-MS (Agilent 7500 from Agilent
82 Technologies). However, the uFREASI software can easily be adapted to read other ICP-MS
83 files.

84 **2. System Design.**

85 uFREASI authors philosophy is to provide an open source, free license and friendly software
86 to treat data from ICP-MS. In this matter, uFREASI source code and binaries are distributed
87 under the terms of the Lesser General Public License version 3 (LGPL) [12] and this software
88 offers an intuitive Graphical User Interface (GUI) [13] designed with the Qt [14] and Qwt

89 [15] free license development frameworks. These latter were chosen due to their many
90 graphical widgets available and to their portability into any operating systems. As its
91 framework, uFREASI is implemented in C++ programming language [16]. Moreover, all the
92 necessary tools for uFREASI modification (i.e. C++ compilers and integrated development
93 environments) are free license and available on Windows, Mac OS X and Linux operating
94 systems.

95 uFREASI is a standalone software and its architecture implements the Model-View-
96 Controller software design pattern [17]. This latter is commonly used to design software
97 architecture into components. Thus, the uFREASI architecture is constituted by three
98 components: the GUI, the data structures and the algorithm (Figure 1).

99 The GUI controls the algorithm, displays data and draws plots. The algorithm component
100 initializes the data structures and uses them to calculate the output data. Finally, the data
101 structures part designs the ICP-MS data and stores the output data.

102 **2.1 The Graphical User Interface.**

103 The uFREASI GUI is designed as simple and friendly as possible using Qt Designer (Digia,
104 Helsinki, Finland). This latter is a powerful free license tool which helps designing rapidly
105 GUI layout by using on-screen forms. It generates the GUI C++ code, which is connected to
106 the other components of the code. The GUI is divided into two sections: the *control buttons*
107 panel and the *display* panel as shown in Video 1. The primary features of the system (i.e.
108 loading input data, saving output data and plots, and starting the data processing) are accessed
109 through the *control buttons* panel. The *display panel* is composed of multiple tabs where the
110 data *input* and *output* tables, the *configuration* panel and the plots (*calibration*, *internal*
111 *standard* and *signal evolution*) are displayed. The panel features will be detailed in later
112 sections and shown in Video 1.

113 **2.2 The data structures**

114 Two fundamental data structures are used in uFREASI: the *element* and *sample* data
115 structures. *Element* data structure contains all information for a given chemical element: its
116 name, mass and corresponding ICP-MS resolution. *Sample* data structure contains all results
117 of an ICP-MS analysis for a given sample: its name, nature (*e.g.* unknown sample, blank,
118 standard or quality control) and signal intensities with associated Relative Standard Deviation
119 (RSD), of each element measured in the sample. This data structure also contains a field
120 dedicated to the final concentrations calculated for each mass with its RSD. Both data
121 structures are indexed and stored into specific arrays available for the uFREASI algorithm.

122 **2.3.Algorithm**

123 Basically, elemental concentrations in samples are calculated by external calibration, using
124 intensities measured by ICP-MS for each mass, and a linear regression on standard
125 concentrations.

126 Data treatment consists in a configurable processing displayed in Figure 2. Depending on
127 processing options selected by the user, some steps are either compulsory, optional or
128 preferred over others. The treatment starts by the *input data processing* step, which consists in
129 selecting the instrument used for the data acquisition in the *ICP-MS selection* section and then
130 loading the “handmade” *Standards and Quality Control concentrations* and the formatted
131 *ICP-MS raw intensities* CSV files. Afterwards, the *internal standard normalization* step could
132 be executed or not, preliminarily to the *linear regression* step, which is compulsory. This step
133 may be performed either i) by subtracting blank to all samples (*blank subtraction* path) or ii)
134 by adding blank value, as a standard equals to zero (*y-intercept* path) or iii) without any blank
135 correction. Afterwards, concentrations and associated uncertainties are calculated for each
136 element, before the optional *quality control validation* step, which helps the user to certify the
137 analysis. Limits of Detection and Quantification (*i.e.* LOD and LOQ, respectively) are

138 compulsorily calculated for each element, before the construction of a final table containing,
139 for each sample, the elemental concentrations, the uncertainties, the LOD and LOQ.

140 **3. Processing steps**

141 The Video 1 shows an example of the data treatment as a tutorial. It can be downloaded at
142 <http://www.ipgp.fr/~tharaud/uFREASI>.

143 **3.1 Data input**

144 On the one hand, the system needs the report file containing raw intensities of samples
145 measured by ICP-MS and, on the other hand, the theoretical concentrations of standards and
146 quality controls. These data are displayed in files specifically formatted for uFREASI data
147 loading.

148 **Standards and Quality controls file.** This is a Comma-Separated Values (CSV) format file
149 containing all the theoretical concentrations for each standard and quality control used. It is
150 filled by the user following a downloadable predefined template
151 (<http://www.ipgp.fr/~tharaud/uFREASI>). The associated RSDs are optional. This file is
152 serviceable for given STD and QC samples.

153 **ICP-MS report file.** At the moment, this report must be a CSV file specifically formatted to
154 be compatible with uFREASI (see the template at: <http://www.ipgp.fr/~tharaud/uFREASI>).
155 Indeed, this format fit with the output CSV file of an HR-ICP-MS and a Q-ICP-MS, but the
156 modular architecture of the system would allows in the future the addition of new file readers,
157 in order to read any others ICP-MS (or ICP-OES) report files.

158 ICP-MS report file provides, for every element in all samples analysed, the average signal
159 intensity and its RSD (respectively in counts per second and in percent) ordered in tabular
160 form. For the HR-ICP-MS and the Q-ICP-MS files, the respective corresponding ICP-MS
161 resolution (i.e. high, medium or low resolution) and mode (i.e. collision/reaction cell or not)
162 are also specified for each element when necessary.

163 The software deduces the nature of the sample, *i.e.* unknown sample, standard, blank or
164 quality control, from the sample's name: the samples must be specifically named using a
165 particular set of prefixes, each one referring to a specific nature. BLK_, STD_, QC_ and VS_,
166 are used to characterise a blank, a standard, a quality control and a verification sample,
167 respectively. uFREASI considers a sample whose name does not contain any of the above
168 prefixes, as an unknown sample. Consequently, it is recommended that users name each
169 sample accordingly to this nomenclature in the instrument sequence editor *before* the ICP-MS
170 analysis, to prevent any renaming or manual changes on the data report.

171 **ICP-MS selection.** The user must select the correct instrument used to acquire the data. At
172 the moment, two models are available i) HR-ICP-MS and ii) Q-ICP-MS.

173 **Data loading.** Input data are in tabular format. uFREASI reading is performed cell by cell.
174 Every cell contents is assigned to a corresponding specific field in the system's data structures
175 (*element* or *sample* data structures), which is determined by the cell's content (numeric or
176 character string) and its location in the table. Next, the system determines the sample's nature
177 thanks to the prefix and fetches the corresponding element concentrations for STD and QC
178 from the standards and quality controls files.

179 **3.2 External calibration**

180 Many calibration methods exist to determine concentration by ICP-MS [1]. The most widely
181 applied is the external calibration method, used here by uFREASI to perform the
182 determination of elemental concentrations in unknown samples. Moreover, the user may
183 configure the calculation process.

184 **Linear regression.** Known concentrations of elements in a standard (STD_i) are plotted as a
185 function of corresponding measured intensities (INT_i). The linear regression coefficients are
186 then calculated with a least squares analysis [18], in order to convert, for each element, the
187 intensity measured in the unknown sample into a concentration.

188 A simple matrix sample (often called “blank”, BLK) is usually analyzed to determine the
189 analytical background. The linear regression may be performed either i) by adding blank
190 value, as a standard equals to zero (tick-box “y-intercept”); ii) by subtracting blank intensity
191 to all samples (tick-box “blank subtraction”) or iii) without any blank correction (Figure 3).
192 Details are given in annexe A.

193 **Internal Standard normalization.** Additionally, an Internal Standard (IS; a chemical
194 element different from analytes) can be added to samples at constant concentration and
195 measured during the whole ICP-MS sequence in order to correct for matrix effects [19]. The
196 basic principle is to correct the measured intensity (I_m) by a factor defined for each sample,
197 relatively to a reference value. This factor is defined as the ratio of the IS reference intensity
198 over the IS intensity in the sample (see annexe A). This normalization is enabled in the tab
199 *configuration* (Figure 3). The sample of reference is selected in the first drop-down menu and
200 the reference element is defined separately for each resolution (tick-boxes).

201 **Quality Controls validation.** Certified reference materials [20] are analysed to control the
202 validity of the external calibration. These samples of known and certified concentrations are
203 labelled as Quality Controls (QC). The program validates the external calibration if the
204 measured value associated to its SD meets the certified one.

205 **3.3 Determination of uncertainties after error propagation.**

206 uFREASI takes into account uncertainties associated to each computation step for the
207 calculation of final error on concentrations. Uncertainties on the slope (δS) and Y-intercept
208 (δY) are first determined. Then, according to the computation options, the different
209 uncertainties are spread. The equations used for error propagation are given in this section and
210 detailed in annexe B.

211 When the concentration is simply calculated with linear regression coefficients using Y-
212 intercept option, the uncertainty propagation equation is:

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{((\delta I_m)^2 + (\delta Y)^2)}{(I_m - Y)^2}\right) + \left(\frac{\delta S}{S}\right)^2}$$

213 If the blank subtraction option is selected, this equation becomes:

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{((\delta I)^2 + (\delta BLK)^2 + (\delta Y)^2)}{(I - BLK - Y)^2}\right) + \left(\frac{\delta S}{S}\right)^2}$$

214 Then, when the concentration is determined with linear regression coefficients using the Y-
215 intercept option and the Internal Standard normalization, the uncertainty propagation equation
216 is:

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{\left(\left(\frac{\delta I_m}{I_m}\right)^2 + \left(\frac{\delta(I.S.)_0}{(I.S.)_0}\right)^2 + \left(\frac{\delta(I.S.)_t}{(I.S.)_t}\right)^2\right) * \left(\frac{I_m * (I.S.)_0}{(I.S.)_t}\right)^2 + (\delta Y)^2}{\left(\frac{I_m * (I.S.)_0}{(I.S.)_t} - Y\right)^2}\right) + \left(\frac{\delta S}{S}\right)^2}$$

217 Lastly, if the user chooses to subtract blank and to normalize the signal to the internal
218 standard variation, the uncertainty propagation equation becomes:

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{\left(\frac{(\delta I_m)^2 + (\delta BLK)^2}{(I_m - BLK)^2} + \left(\frac{\delta(I.S.)_0}{(I.S.)_0}\right)^2 + \left(\frac{\delta(I.S.)_t}{(I.S.)_t}\right)^2\right) * \left(\frac{(I_m - BLK) * (I.S.)_0}{(I.S.)_t}\right)^2 + (\delta Y)^2}{\left(\frac{(I_m - BLK) * (I.S.)_0}{(I.S.)_t} - Y\right)^2}\right) + \left(\frac{\delta S}{S}\right)^2}$$

219 3.4 LOD and LOQ calculation

220 Limit Of Detection (LOD) and Limit Of Quantification (LOQ) calculations are based on the
221 standard deviation (SD_{BLK}) of a BLK sequence analysis (more details on the LOD and LOQ
222 calculation are given in annexe C). This sequence of blank measurements ($n_{BLK} > 3$) should
223 be ideally analysed at the beginning of the analytical procedure to determine the overall
224 background signal.

225 **Limit Of Detection.** The Limit Of Detection (LOD) is the “minimum detectable value” [21].

226 A value higher than the LOD means that the signal is significantly different from the
227 background noise of the analytical procedure. This LOD (in counts per second) is defined as
228 three times the standard deviation of the blank signal (SD_{BLK}) [21]. This intensity is then

229 converted in concentration thanks to linear regression coefficients and then the LOD is
230 displayed as a concentration in the output file. Nevertheless a value higher than the LOD is
231 not necessary quantifiable.

232 **Limit Of Quantification.** The Limit Of Quantification (LOQ) is the “minimum quantifiable
233 value”, i.e. the smallest signal value significantly higher than the background noise to make it
234 reasonably quantifiable. It is defined as 10 times the standard deviation of the blank signal
235 (SD_{BLK}) [21]. In the same way as the LOD, the LOQ of the signal (intensity) is converted in
236 concentration units and then displayed in the output file.

237 **3.5 Outputs report generation**

238 The output data file is saved as CSV format to make it easy to modify in any spreadsheet or
239 text editors. Each column represents an element with the measured isotope and the
240 measurement resolution and each line represents a sample. The table also contains LOD and
241 LOQ for each element. Calculated elemental concentration with standard deviation and
242 relative standard deviation (in per cent) are given for each sample. Standard deviations are
243 calculated according to uncertainty propagation equations (see section 3.3). The character
244 string “<LOQ” replaces concentration values below the limit of quantification.

245 **4. Monitoring**

246 In order to control the external calibration validity, the stability and the cleanliness of the
247 analytical procedure, uFREASI automatically provides a monitoring of the most important
248 parameters detailed hereafter.

249 **4.1. External calibration and Quality Controls**

250 The tab *calibration* (Figure 4) presents the calibration curve (intensity measured versus
251 standard concentration) for each element and quality indicators. For instance, black square
252 points represent calibration standard with their associated uncertainties, the blue line is the
253 linear regression curve and red square points represent Quality Controls with their associated

254 uncertainties. The QC x-axis and y-axis values are the certified concentration and the
255 measured intensity, respectively (corrected by blank and IS signals if selected). The linear
256 regression equation, the coefficient of determination and limits of detection and quantification
257 are displayed just below the graph. In addition, it is possible to zoom on any part of the curve
258 in this tab.

259 **4.2. Internal Standard.**

260 The tab *Internal Standard* shows the evolution of the Internal Standard signal with time. In
261 case of HR-ICP-MS measurement, the IS signal evolution can be followed for each resolution
262 (High, Medium or Low) thanks to the drop-down menu by selection on the top left side.
263 Moreover, both the IS average intensity and IS standard deviation (in counts per second) are
264 indicated below the graph.

265 **4.3. Evolutions**

266 To control cross contamination between samples or standards, uFREASI displays the signal
267 of periodically analysed blank for each element. In the tab *evolutions*, the variation of the
268 blank signal is plotted versus the sample running order and element of interest is selected in
269 the column on the left.

270 Moreover, the ICPMS sensitivity may evolve during the sequence, which would induce a bias
271 in the calculated sample concentrations. To control this evolution, verification samples (also
272 called “VS”) with similar matrix than unknown samples are periodically analysed. Intensities
273 measured in the Verification Sample as a function of the samples running order are available
274 in the tab *evolutions* for each element. VS evolution is currently a control parameter without
275 any signal correction related to VS variation. However, this could be an improvement for a
276 future work.

277 **5. Conclusion**

278 ICP-MS is a powerful technique used in many fields (geochemistry, biomedical research,
279 semiconductor analysis, etc.). It provides an accurate and multi-elemental analysis on a large
280 variety and number of samples. For the calculation of concentrations, the commercial
281 software displayed with these devices are often assimilated to “black boxes” by most users,
282 because of their lack of control on each step of the data treatment. Moreover, the large amount
283 of raw data produced by ICP-MS makes their manual treatment and validation long, and
284 difficult when using "home-made" spreadsheets.

285 In order to solve these problems, we developed an easy-to-use, efficient and free software:
286 uFREASI (user-FRriendly Elemental dAta proceSsIng). The step-by-step procedure used
287 minimizes the data treatment time and also improves its reliability comparatively to "home-
288 made" spreadsheets. A post-analysis control on the validity of the external calibration, the
289 cleanliness and the stability of the device is available through monitoring displays. In
290 addition, uFREASI provides accurate and reliable errors on concentrations, calculated after
291 uncertainty propagation through the whole treatment process.

292 The frameworks (Qt, and Qwt) used for this software development are free license and the
293 source code and binaries are distributed under the terms of the Lesser General Public License
294 version 3 (LGPL). Hence, uFREASI is freely downloadable online
295 (<http://www.ipgp.fr/~tharaud/uFREASI>) and the source code may be directly requested to the
296 corresponding author.

297 **6. Future work**

298 uFREASI is still in progress and many improvements may be performed at short notice:

299 - the uFREASI software is able to read data file from ThermoScientific HR-ICP-MS Element
300 II and from Agilent Technologies Agilent 7500 Q-ICP-MS, which are among the most
301 commonly used ICP-MS. Otherwise, user has to manually format ICP-MS raw data file to fit
302 to one of these predefined template. Additional readers are currently developed to fit to others

303 common ICP-MS raw data files and would be included in the software, to improve again the
304 easiness of the treatment;

305 - the coefficient of determination (R^2) is not necessary a guarantee of linearity. The latter
306 could be checked more rigorously. For instance, assessing the well close fitting of the external
307 calibration should be performed by uFREASI with a Fisher-Snedecor test based on the ISO
308 11095 norm [22]: this statistical method tests the assumption of non-linearity of the linear
309 dynamic range;

310 - the ordinary least square method is used in uFREASI for elemental concentrations
311 calculation. However, Mermet [18] determined that offering the possibility of reprocessing is
312 the most beneficial procedure to take complete advantages of the external calibration.
313 Consequently, depending on each analyte concentration, uFREASI should provide the
314 possibility to select the most appropriate standards;

315 - the verification sample (VS) evolution is currently a control parameter without any signal
316 correction related to its variation. A signal correction of each analyte thanks to the VS
317 evolution could be optionally applied;

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372 **Annexes**

373 **Annexe A. Calculation of concentrations.**

374 In uFREASI, external calibration is used to determine elemental concentrations. Linear
375 regression coefficients are calculated with the ordinary least-square analysis [18].

376 First the slope (S) is determine by:

377 **Equation 1**

$$S = \frac{\sum((STD_i - \overline{STD}) * (INT_i - \overline{INT}))}{\sum(STD_i - \overline{STD})^2}$$

378 Then the Y-intercept (Y) by:

379 **Equation 2**

$$Y = \overline{INT} - S * \overline{STD}$$

380 Finally, the coefficient of determination (R^2) is calculated to confirm the linearity of the
381 regression as follows:

382 **Equation 3**

$$R^2 = 1 - \frac{\sum(INT_i - (S * STD_i + Y))^2}{\sum(INT_i - \overline{INT})^2}$$

383 These linear regression coefficients are used to convert the intensity of the unknown sample
384 as a concentration. Due to the different configurations available in uFREASI (Figure 2 and
385 Figure 3), it exists different possibilities to calculate a concentration. Each possibility is
386 described below.

387 **Y-intercept option.** With this configuration, the blank is used to calculate the slope and the
388 Y-intercept as a standard at a concentration equal to zero. Thus, for the determination of the
389 unknown sample concentration from the measured intensity (I_m) the equation is:

390 **Equation 4**

$$Concentration = \frac{(I_m - Y)}{S}$$

391 **Blank correction.** In this case, the blank intensity (BLK) is directly subtracted to sample
392 intensities. Thus, to calculate the unknown sample concentration the equation used is:

393 **Equation 5**

$$\text{Concentration} = \frac{(I_m - BLK - Y)}{S}$$

394 **Internal Standard normalization.** A factor alpha (α) is calculated for each Internal Standard
395 measurement ((I.S.)_t) with the selected reference sample ((I.S.)_o), as:

396 **Equation 6**

$$\alpha = \frac{(I.S.)_o}{(I.S.)_t}$$

397 In order to correct matrix effect, measured intensity (I_m)_t is multiplied by α to give corrected
398 intensity (I_c)_t as:

399 **Equation 7**

$$I_c = I_m * \alpha$$

400 Hence, in the case of the Y-intercept choice the following equation is used to determine the
401 unknown sample concentration.

402 **Equation 8**

$$\text{Concentration} = \frac{[(I_m * \alpha) - Y]}{S}$$

403 If the blank subtraction is chosen, the Equation 6 is integrated to the Equation 5 and the
404 concentration is determined by:

405 **Equation 9**

$$\text{Concentration} = \frac{[((I_m - BLK) * \alpha) - Y]}{S}$$

406 **Annexe B. Uncertainty propagation.**

407 uFREASI calculate uncertainties on the slope (δS) and the Y-intercept (δY) with the
408 following equations [18]:

409 **Équation 10**

$$\delta S = \sqrt{\frac{\sum (INT_i - \overline{INT})^2 - S^2 \sum (STD_i - \overline{STD})^2}{(n-2) \sum (STD_i - \overline{STD})^2}}$$

410 **Équation 11**

$$\delta Y = \sqrt{\left(\frac{\sum (INT_i - \overline{INT})^2 - S^2 \sum (STD_i - \overline{STD})^2}{(n-2)} \right) \left(\frac{1}{n} + \frac{\overline{STD}^2}{\sum (STD_i - \overline{STD})^2} \right)}$$

411 Then these equations are used to determine equations for the uncertainty propagation in each
412 possible configuration.

413 **Linear regression with Y-intercept option.** If the user chooses to calculate linear regression
414 coefficients with the Y-intercept option, the Equation 4 is obtained:

$$Concentration = \frac{(I_m - Y)}{S}$$

415 Thus, this equation can be split up into:

$$416 \quad Concentration = A/S \quad \text{with} \quad A = I_m - B - Y$$

417 Consequently, error for each equation is given by:

$$\frac{\delta Concentration}{Concentration} = \sqrt{\left(\frac{\delta A}{A} \right)^2 + \left(\frac{\delta S}{S} \right)^2}$$

418 and

$$\delta A = \sqrt{(\delta I_m)^2 + (\delta Y)^2}$$

419 Finally, in this case the uncertainty propagation equation is:

420 **Équation 12**

$$\frac{\delta Concentration}{Concentration} = \sqrt{\left(\frac{((\delta I_m)^2 + (\delta Y)^2)}{(I_m - Y)^2} \right) + \left(\frac{\delta S}{S} \right)^2}$$

421 **Linear regression with blank correction.** In order to correct intensities with the background
422 signal, the user can subtract blank signal (BLK) to standards and samples. Thus, the Equation
423 5 for the concentration computation is:

$$\text{Concentration} = \frac{(I_m - BLK - Y)}{S}$$

424 The equation split up gives:

$$425 \quad \text{Concentration} = A/S \quad \text{with} \quad A = I_m - BLK - Y$$

426 And errors on each equation are:

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{\delta A}{A}\right)^2 + \left(\frac{\delta S}{S}\right)^2}$$

427 and

$$\delta A = \sqrt{(\delta I_m)^2 + (\delta BLK)^2 + (\delta Y)^2}$$

428 Finally, the uncertainty propagation equation becomes:

429 **Équation 13**

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{((\delta I)^2 + (\delta BLK)^2 + (\delta Y)^2)}{(I - B - Y)^2}\right) + \left(\frac{\delta S}{S}\right)^2}$$

430 **Linear regression with Y-intercept option and Internal Standard normalization.** In order
 431 to correct matrix effect, uFREASI allows Internal Standard normalization. In the case where
 432 the linear regression is calculated with a standard at a concentration equal to zero, the
 433 correction is done from the Equation 6 and Equation 8:

$$\text{Concentration} = \frac{\left[\left(I_m * \frac{(I.S.)_0}{(I.S.)_t} \right) - Y \right]}{S}$$

434 Hence, if the equation is split we obtain:

$$435 \quad \text{Concentration} = A/S \quad \text{with} \quad A = C - Y$$

$$436 \quad \text{and} \quad C = (I_m * (I.S.)_0) / (I.S.)_t$$

437 Then, error on each equation is given by:

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{\delta A}{A}\right)^2 + \left(\frac{\delta S}{S}\right)^2}$$

$$\delta A = \sqrt{(\delta C)^2 + (\delta Y)^2}$$

438 and

$$\frac{\delta C}{C} = \sqrt{\left(\frac{\delta I_m}{I_m}\right)^2 + \left(\frac{\delta(I.S.)_0}{(I.S.)_0}\right)^2 + \left(\frac{\delta(I.S.)_t}{(I.S.)_t}\right)^2}$$

439 Finally, the following propagation equation allows the calculation of the final uncertainty:

440 **Equation 14**

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{\left(\left(\frac{\delta I_m}{I_m}\right)^2 + \left(\frac{\delta(I.S.)_0}{(I.S.)_0}\right)^2 + \left(\frac{\delta(I.S.)_t}{(I.S.)_t}\right)^2\right) * \left(\frac{I_m * (I.S.)_0}{(I.S.)_t}\right)^2 + (\delta Y)^2}{\left(\frac{I_m * (I.S.)_0}{(I.S.)_t} - Y\right)^2}\right) + \left(\frac{\delta S}{S}\right)^2}$$

441 **Linear regression with blank and Internal Standard correction.** If the user chooses to
 442 subtract blank and also to correct the signal from the internal standard variation before the
 443 external calibration, the Equation 6 and Equation 9 give the concentration computation as:

$$\text{Concentration} = \frac{\left[\left(I_m - BLK\right) * \left(\frac{(I.S.)_0}{(I.S.)_t}\right)\right] - Y}{S}$$

444 So, the splitted equation is:

445 $\text{Concentration} = A/S$ with $A = C - Y$

446 $C = E * F$

447 $E = I_m - BLK$

448 $F = (I.S.)_0 / (I.S.)_t$

449 Then, error on each equation is given by:

$$\delta A = \sqrt{(\delta C)^2 + (\delta Y)^2}$$

$$\frac{\delta C}{C} = \sqrt{\left(\frac{\delta E}{E}\right)^2 + \left(\frac{\delta F}{F}\right)^2}$$

$$\delta E = \sqrt{(\delta I_m)^2 + (\delta BLK)^2}$$

450 and

$$\frac{\delta F}{F} = \sqrt{\left(\frac{\delta(I.S.)_0}{(I.S.)_0}\right)^2 + \left(\frac{\delta(I.S.)_t}{(I.S.)_t}\right)^2}$$

451 Finally, we obtain the uncertainty propagation equation as:

452 **Équation 15**

$$\frac{\delta \text{Concentration}}{\text{Concentration}} = \sqrt{\left(\frac{\left(\frac{(\delta I_m)^2 + (\delta BLK)^2}{(I_m - BLK)^2} + \left(\frac{\delta(I.S.)_0}{(I.S.)_0}\right)^2 + \left(\frac{\delta(I.S.)_t}{(I.S.)_t}\right)^2\right) * \left(\frac{(I_m - BLK) * (I.S.)_0}{(I.S.)_t}\right)^2 + (\delta Y)^2}{\left(\frac{(I_m - BLK) * (I.S.)_0}{(I.S.)_t} - Y\right)^2}\right) + \left(\frac{\delta S}{S}\right)^2}$$

453 **Annexe C. Limit Of Detection & Limit Of Quantification.**

454 Before establishing Limit Of Detection (LOD) and Limit Of Quantification (LOQ), it is
 455 necessary to calculate blank average intensity (\overline{BLK}) and standard deviation (SD_{BLK}).
 456 uFREASI takes the first BLK sequence and calculate \overline{BLK} (or “BLK_Avg_First_Seq” in the
 457 software) with the expression:

458 **Equation 16**

$$\overline{BLK} = \frac{\sum BLK_i}{n}$$

459 This average is transformed in concentration with the linear regression and made available for
 460 blank correction or Y-intercept. The standard deviation of the BLK is then calculated with
 461 uFREASI by:

462 **Equation 17**

$$SD_{BLK} = \sqrt{\frac{\sum (BLK_i - \overline{BLK})^2}{n}}$$

463 **Limit Of Detection.**

464 **Equation 18**

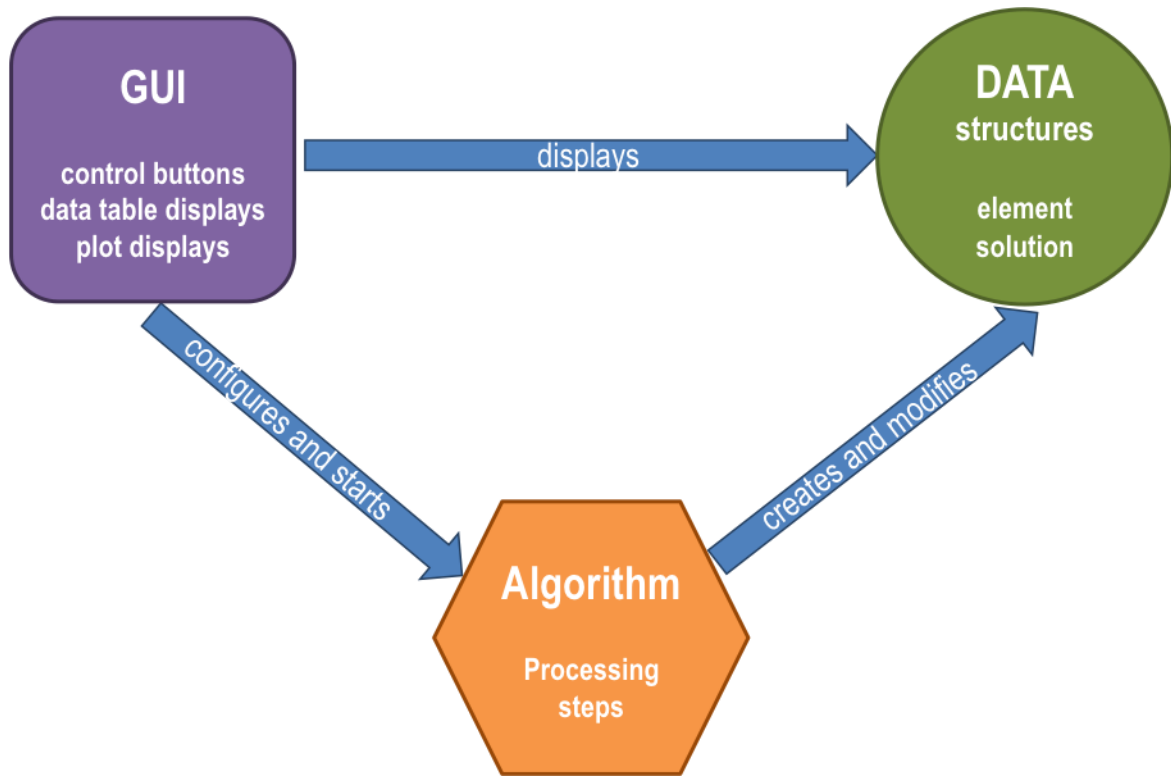
$$LOD = 3 * SD_{BLK}$$

465 **Limit Of Quantification.**

466 **Equation 19**

$$LOQ = 10 * SD_{BLK}$$

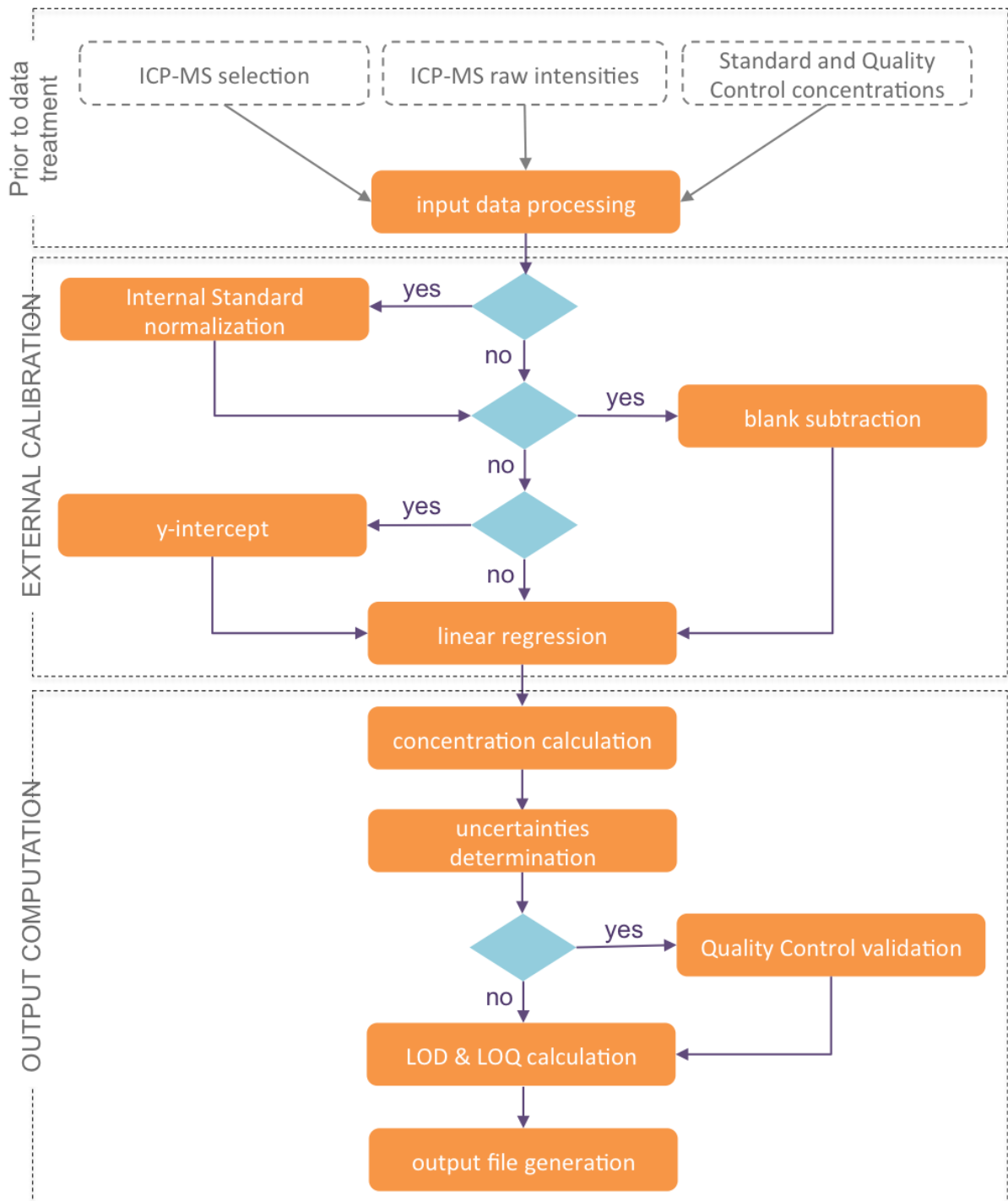
467 **Figure captions**



468

469 Figure 1- uFREASI architecture

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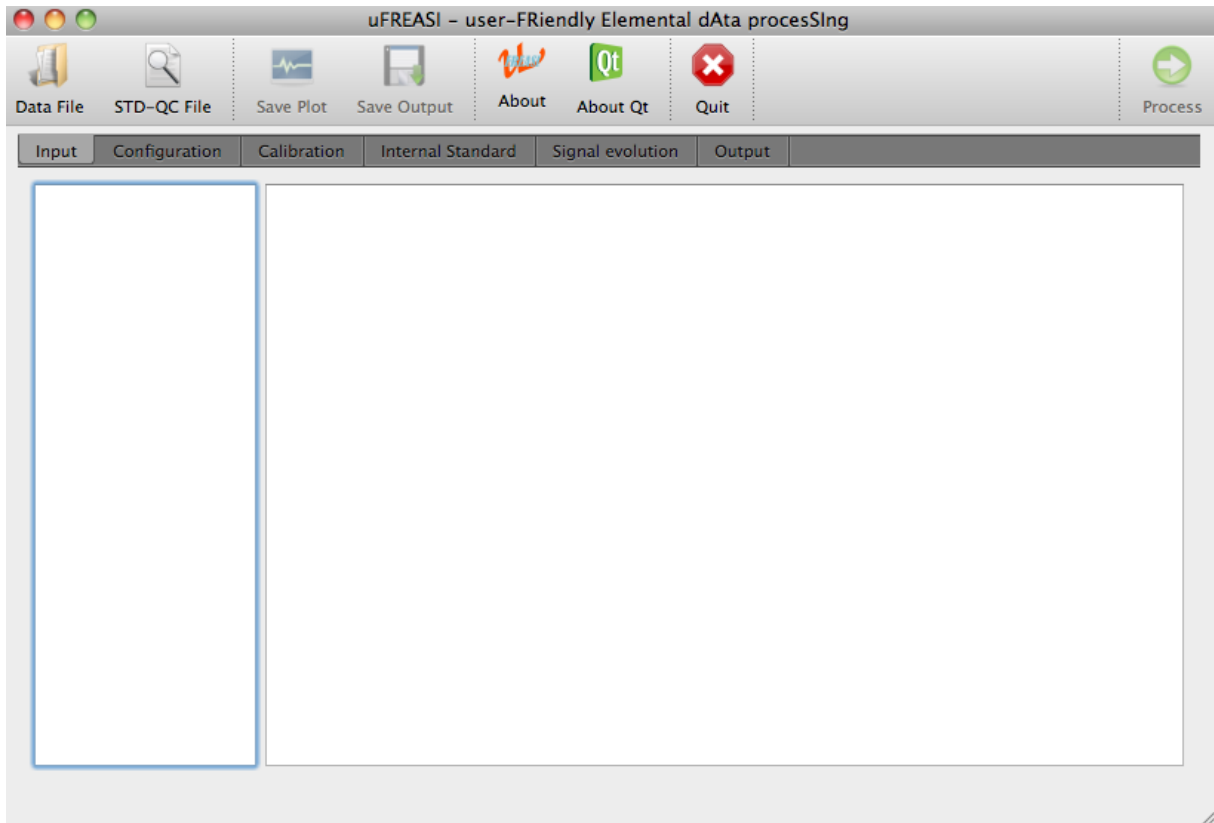


471

472 Figure 2- Flowchart of the uFREASI algorithm. Rounded rectangles represent processing step and diamonds are

473 decisions

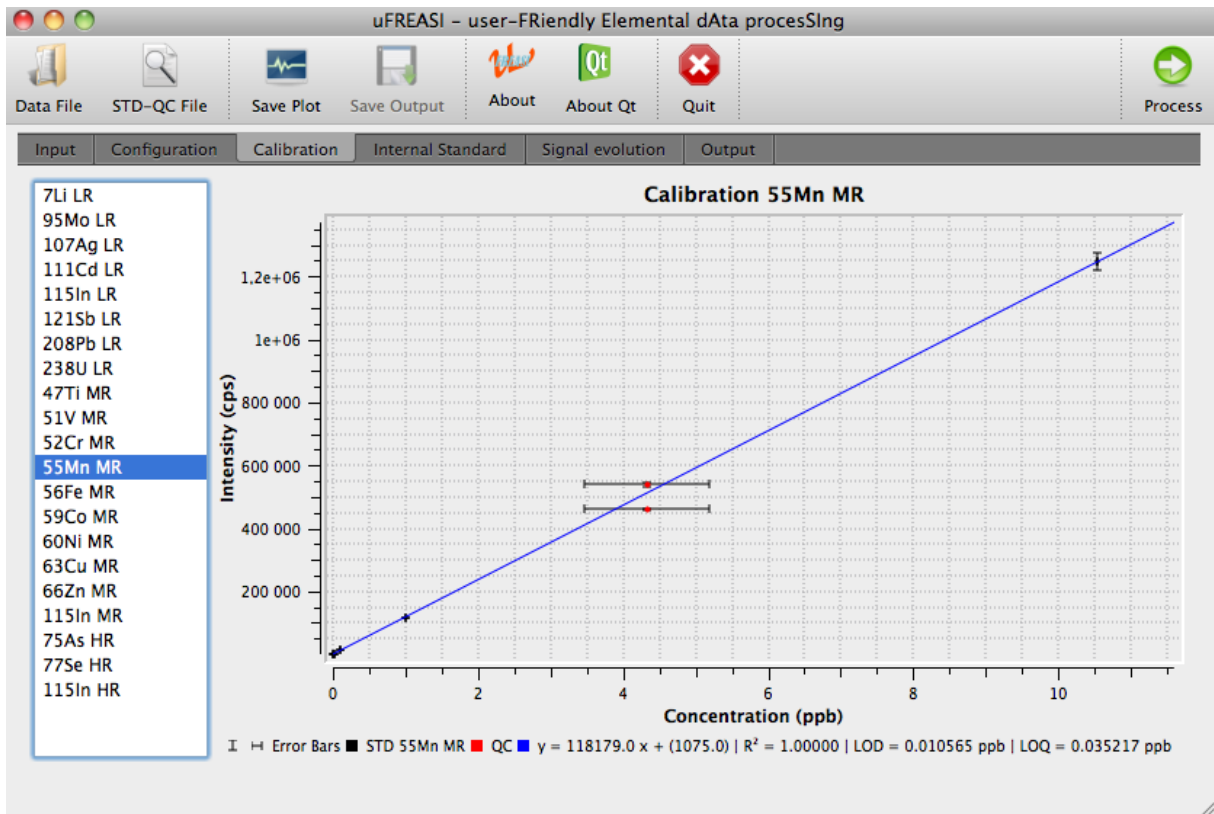
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476 Figure 3- Tab Configuration in uFREASI

477



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479 Figure 4- Tab calibration in uFREASI. Overview of the external calibration.