

Exactive Plus EMR QuickStart Guide

About this Guide

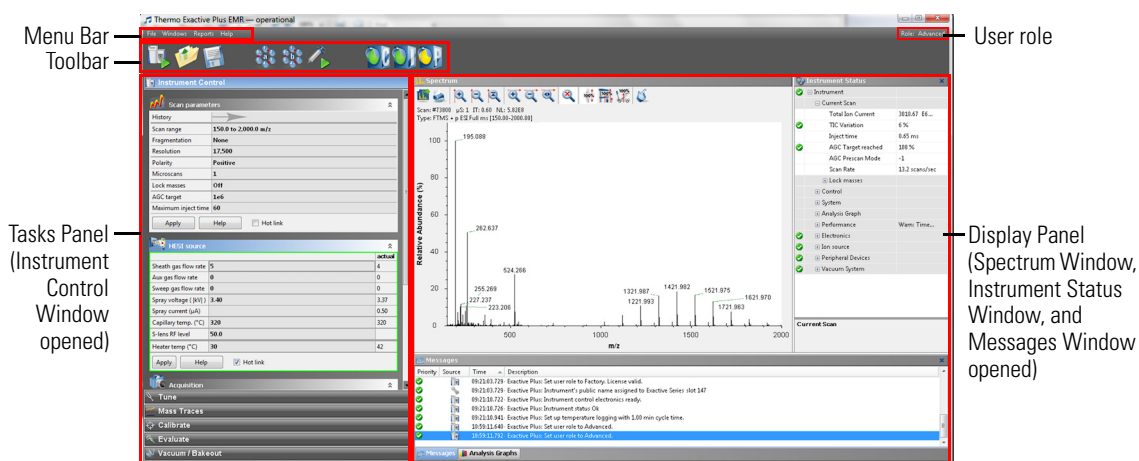
This *Exactive Plus EMR QuickStart Guide* gives an introduction on setting up and using the Thermo Scientific™ Exactive™ Plus EMR mass spectrometer. This guide is intended for all personnel who operate the Exactive Plus EMR mass spectrometer.

Please note that this guide does not contain any safety notices and precautionary statements. Thus, it is mandatory to read also the *Exactive Series Operating Manual* and the *Ion Max and Ion Max-S API Source Hardware Manual*.

Exactive Plus EMR Tune

Use Exactive Plus EMR Tune to operate the Exactive Plus EMR mass spectrometer via the data system computer. It has the following components:

- The *menu bar* provides drop-down menus with commands for operating the program. On its right side it shows the active user role.
- The *toolbar* provides symbol shortcuts for frequently used commands.
- The *tasks panel* provides six windows: Instrument Control, Tune, Mass Traces, Calibrate, Evaluate, and Vacuum/Bakeout. The *instrument control window* is divided into three additional windows for defining scan parameters, setting API source parameters, and acquiring and storing measurement data.
- The *display panel* provides various windows for showing real-time information about the current measurement and the instrument status.



❖ To display the Exactive Plus EMR Tune program

Choose **Start > Programs > Thermo Exactive Series > Tune**.

Before going on, check that the following preconditions are fulfilled:

- The main power circuit breaker switch is in the On (I) position and the electronics service switch is in the Operating Mode position, the gas pressure is within the operational limit, and the vacuum levels are sufficient for operating the instrument.
- The Ion Max API source with H-ESI probe is installed on the mass spectrometer. You have checked the proper position of the H-ESI probe in the Ion Max API source housing.
- Power supply and communication between syringe pump and mass spectrometer are established. A clean, 500 µL Unimetrics syringe with 450 µL of calibration solution for positive ion mode is placed into the syringe pump. An infusion line is installed between the syringe pump and the grounding union that is held by the grounding bar of the Ion Max API source.

Refer to the *Exactive Series Operating Manual* for instructions about preparing the positive ion mode calibration solution or buying the ready-to-use solution from Thermo Fisher Scientific (refer to www.fishersci.com, catalog number PI88323).

Preparation





Getting Ions from Infusion Experiments

Setting up Exactive Plus EMR Tune



- The data system computer with the Exactive Plus EMR Tune software is switched on and the mass spectrometer is placed in Standby mode.

For information about performing these tasks, refer to the *Exactive Series Operating Manual*, the *Exactive Plus EMR Software Manual* or the Exactive Plus EMR Tune Help, and the *Ion Max and Ion Max-S API Source Hardware Manual*.

This topic describes how to test the instrument before you can tune and calibrate your Exactive Plus EMR mass spectrometer automatically.

❖ To set up the mass spectrometer in the Exactive Plus EMR Tune software for tuning and calibrating in the H-ESI/MS mode

- If you have not already done so, choose **Start > Programs > Thermo Exactive Series> Tune** to start the Exactive Plus EMR Tune program.
- In the Exactive Plus EMR Tune window, on the toolbar, click the **On/Off/Standby** button to take the mass spectrometer out of the Standby mode or Off mode and turn it On. When you turn the mass spectrometer to On, you initiate the following events:
 - The mass spectrometer begins scanning.
 - Nitrogen flows into the H-ESI probe.
 - The Exactive Plus EMR mass spectrometer applies high voltage to the H-ESI probe.
 - The spectrum window of Exactive Plus EMR Tune shows a real-time display of the mass spectrum.
- If necessary, open an existing tune file:
 - Choose **File > Load Tune File** to display the Open dialog box.
 - Browse for the folder C:\Xcalibur\methods\. Select a tune file, for example *default.mstune*.
 - Click **Open** to open the file. Exactive Plus EMR Tune downloads the Tune Method parameters to the mass spectrometer.
- Examine the pre-tune H-ESI source settings:
 - From the Instrument Control panel, open the H-ESI source window. See figure right.
 - Set the *sheath gas flow rate* to 12.
 - Leave the auxiliary gas flow rate at 0.
 - Leave the sweep gas flow rate at 0.
 - Set the *spray voltage* to 4 kV.
 - Set the *capillary temperature* to 320 °C.
 - Leave the *S-lens RF level* at 50.
 - Set the *auxiliary gas heater temperature* to 0 °C.
 - If you have made any changes in the window, click **Apply**.

NOTICE Select the Hot link check box to apply all changes in real time. A green frame around the parameter box indicates an active hot link. ▲

HESI source		actual
Sheath gas flow rate	12	
Aux gas flow rate	0	
Sweep gas flow rate	0	
Spray voltage ([kV])	4.00	
Spray current (µA)		
Capillary temp. (°C)	320	
S-lens RF level	50.0	
Aux gas heater temp (°C)	0	
Source Auto-Defaults...		
Apply Help ☐ Hot link		

Testing the Mass Spectrometer



5. Set the scan parameters for tuning and calibration:
 - a. From the Instrument Control panel, open the Scan parameters window. See figure right.
 - b. Enter a *scan range* between *m/z* 150 and 2000.
 - c. Set *Fragmentation* to *None* to specify that the ion source fragmentation option is turned off.
 - d. Select 17500 for *Resolution*.
 - e. Set the *ion polarity mode* to *Positive*.
 - f. Set the total number of *microscans* to 1.
 - g. Set *Lock masses* to *Off*.
 - h. Select 1e6 for *AGC target*.
 - i. Specify a *maximum injection time* of 50 ms.
 - j. If you have made any changes in the window, click **Apply** or select the Hot link check box.

Scan parameters	
History	
Scan range	150.0 to 2,000.0 m/z
Fragmentation	None
Resolution	17,500
Polarity	Positive
Microscans	1
Lock masses	Off
AGC target	1e6
Maximum inject time	50
Apply Help ☒ Hot link	

The mass spectrometer is now properly set up for tuning and calibration in the H-ESI/MS mode.

In this section, you can test whether the mass spectrometer is operating properly. Infuse a low concentration calibration solution for positive ion mode—containing n-butylamine, caffeine, MRFA, and Ultramark 1621—into the H-ESI source using the syringe pump. Monitor the real-time display of the mass spectrum to ensure that a stable spray of solution enters the mass spectrometer.

Refer to the *Exactive Series Operating Manual* for instructions about preparing the positive ion mode calibration solution or buying the ready-to-use solution from Thermo Fisher Scientific (refer to www.fishersci.com, catalog number PI88323).

❖ To test the operation of the mass spectrometer in H-ESI/MS mode

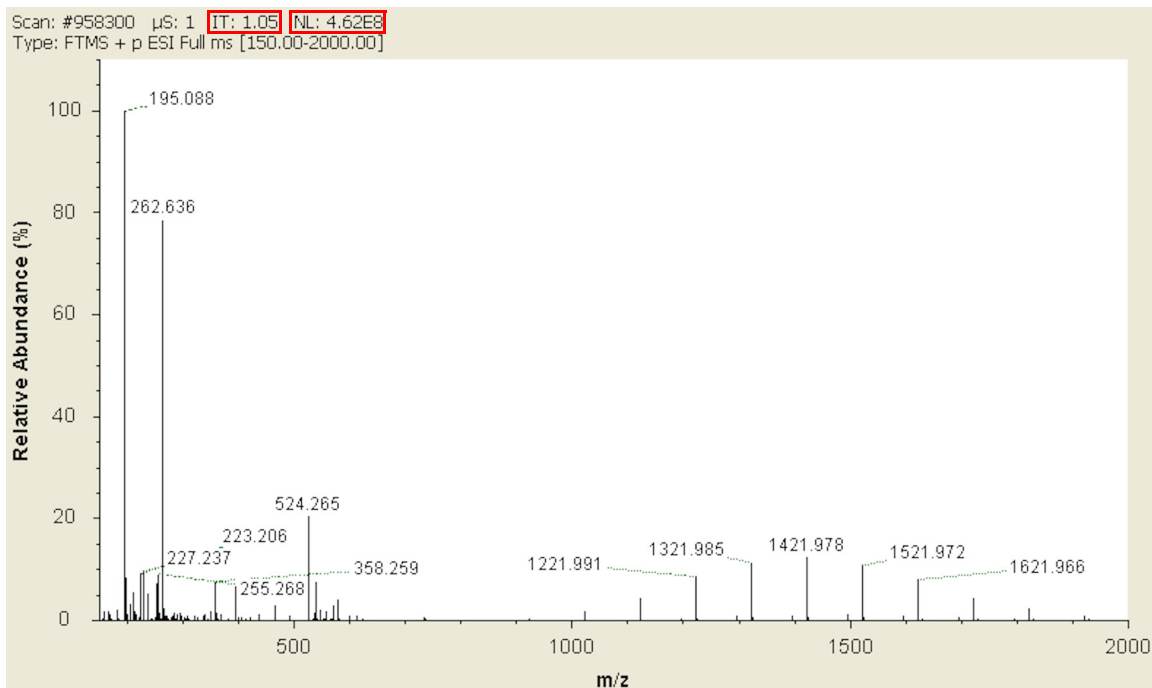
1. Click the arrow of the **Syringe Pump** button to display the Syringe Pump dialog box. See figure right.
2. Turn on the syringe pump and set an infusion flow rate of 5 $\mu\text{L}/\text{min}$, as follows:
 - a. Select *Unimetrics* to specify the proper *syringe type*.
 - b. Select 500 in the *Volume* list box to set the proper syringe volume. Note that the Exactive Plus EMR mass spectrometer automatically sets the syringe ID to its proper value of 3.257 mm.
 - c. Specify a *flow rate* of 5 $\mu\text{L}/\text{min}$.
 - d. Click **Apply** to apply the syringe parameters.
 - e. Click **Start** to start the syringe pump.

Syringe type	Unimetrics
Volume (μL)	500
Syringe inner diameter (mm)	3.257
Flow rate ($\mu\text{L} / \text{min}$)	5.000
Apply Help	
Manual control Start Stop	

NOTICE Once you have set the syringe parameters, just click the **Syringe Pump** button to switch on or off the syringe pump. ▲

3. Test the efficiency and stability of the spray of calibration solution into the mass spectrometer. Monitor the data for the calibration solution, as follows:
 - a. In the spectrum window of Exactive Plus EMR Tune, observe the mass spectra of the singly-charged ions of the positive ion mode calibration solution. See figure on the next page. The ions are as follows:
 - Caffeine: *m/z* 195
 - MRFA: *m/z* 262.6 (doubly charged), *m/z* 524
 - Ultramark 1621: *m/z* 1122, 1222, 1322, 1422, 1522, 1622, 1722, 1822

- b. At the top of the spectrum window, notice the values for the inject time (IT) and normalized target level (NL). See figure below.



- c. Observe the values for NL and IT in the spectrum window. As calibration solution infuses, and the readback values fluctuate, check the status of the ion current signal:
- Is the signal present?
 - Is the signal stable? Check in the instrument status window that the TIC variation has stabilized at about 15% or less from scan to scan (green check mark). See figure right.

Instrument status	
Instrument	
Current Scan	
Total Ion Current	53.64 E6 ions/sec
TIC Variation	7 %
Inject time	9.55 ms
AGC Target reached	100 %
AGC Prescan Mode	1
Scan Rate	2.3 scans/sec
Lock masses	
Current Scan	

If the answer to both questions in [step 3c](#) is “Yes,” then your mass spectrometer is operating properly.

If the answer to one of these questions is “No,” then try the following troubleshooting measures:

- Make sure that the H-ESI probe is properly assembled and that the needle position is correct.
- Make sure that the entrance to the ion transfer capillary is clean.
- Make sure that the solution entering the probe is free of air bubbles and that the tubing and connectors are free of leaks and that they are not clogged.
- Make sure that spray voltage is appropriate.
- Make sure that discharge does not take place.

Your mass spectrometer is operating properly in the H-ESI mode. You are now ready to tune and calibrate the mass spectrometer.

Tuning

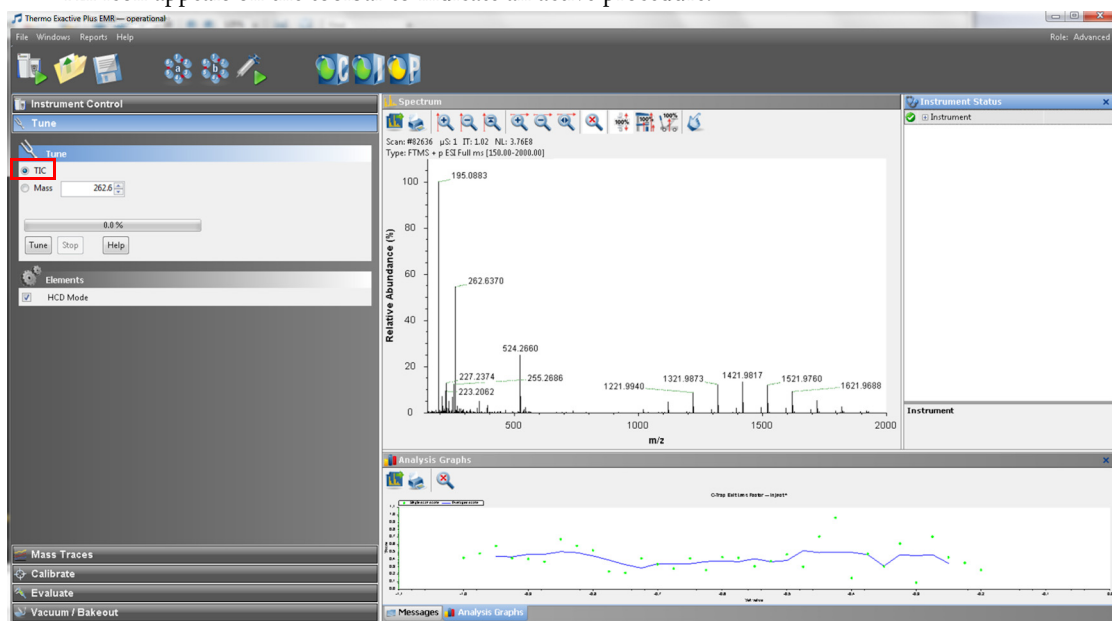
After having established that your Exactive Plus EMR mass spectrometer is working properly in the H-ESI mode, you can now tune the mass spectrometer automatically. Automatically tuning is only available for the HCD mode. It optimizes voltage settings for ion transfer optics to ensure highest sensitivity in HCD mode. Note that tuning is compound and technique dependent.

❖ To tune the Exactive Plus EMR mass spectrometer HCD mode

1. Click the **On/Off/Standby** button to take the mass spectrometer out of the Standby mode or Off mode and turn it On.
2. Click the **Syringe Pump** button to start the syringe pump.



3. In the Tune window, select the TIC option button to specify that the Exactive Plus EMR mass spectrometer optimizes on the total ion current (TIC) intensity. See figure below.
4. CE fragmentation is always automatically activated in the Fragmentation dialog box. (See [page 8](#).) The tuning procedure comprises only HCD relevant parameters.
5. Click **Tune** to start the automatic tuning procedure:
 - The Tune window indicates the completed percentage of the tuning process by a progress bar.
 - A message box informs you about the active tuning procedure and the currently tuned parameter.
 - The analysis graphs window displays a graphic representation of the tuning process for the currently tuned parameter.
 - The messages window shows a record of the tuning steps.
 - An icon appears on the toolbar to indicate an active procedure.



6. A message box informs you that the tuning procedure is completed. The message box also contains information about the factor by which the signal was increased. Click **OK** to close the message box.
7. Choose **File > Save Tune File as** to save the adjusted parameters in a Tune Method:
 - a. In the displayed dialog box, enter a name for the new tune file.
 - b. Click on **Save** to save the new tune parameters and to close the dialog box.

The new tune file is specific to your particular analyte and solvent flow rate. (In this example, you save settings obtained using calibration solution.) You can call the Tune Method again and use it as a starting point for optimization of the mass spectrometer for a different analyte of interest or with a different flow rate.

After having tuned the Exactive Plus EMR mass spectrometer, it should be calibrated to ensure the mass accuracy of the results. Usually, it is sufficient to perform a mass calibration only. Before you start the calibration, check again that you have a stable spray: Focus on the injection time (IT) and on the normalized level (NL) in the header information on the spectrum window.

NOTICE If the system was in Off mode before, put the instrument into On mode for at least 90 minutes before you perform a mass calibration. ▲

❖ **To calibrate the Exactive Plus EMR mass spectrometer for positive ion mode**

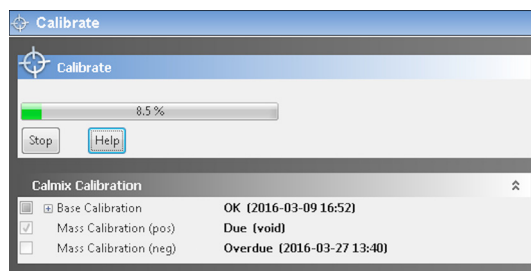
1. Place a clean, 500 μ L Unimetrics syringe with 450 μ L of calibration solution for the positive ion mode into the syringe pump.
2. Click the **On/Off/Standby** button to take the mass spectrometer out of the Standby mode or Off mode and turn it On.
3. Click the **Syringe Pump** button to start the syringe pump.

Mass Calibration

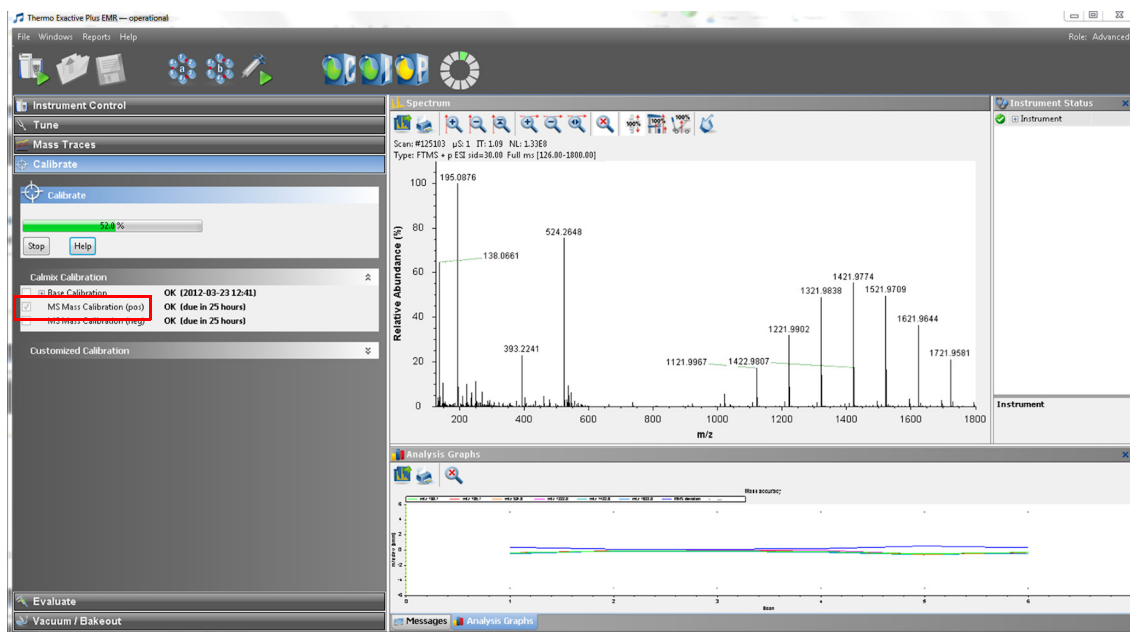
Positive Ion Mode Calibration



- Click the title bar of the Calibrate window to display it.
- In the Calmix Calibration sub-window, select the Mass Calibration (pos) check box to specify a mass calibration for the positive ion mode. See figure right.
- In the Calibrate window, click **Calibrate** to start the automatic calibration procedure:



- The Calibrate window indicates the completed percentage of the calibration process by a progress bar.
 - Exactive Plus EMR Tune displays a message box that informs about the active calibration procedure and the currently calibrated parameter.
 - The analysis graphs window displays a graphic representation of the calibration process for the currently tuned parameter.
 - The messages window shows a record of the calibration.
- An icon appears on the toolbar to indicate an active procedure.



- A message box appears when the calibration procedure is completed. The message box also informs you that Exactive Plus EMR Tune has automatically saved the calibration results. Click **OK** to close the message box.

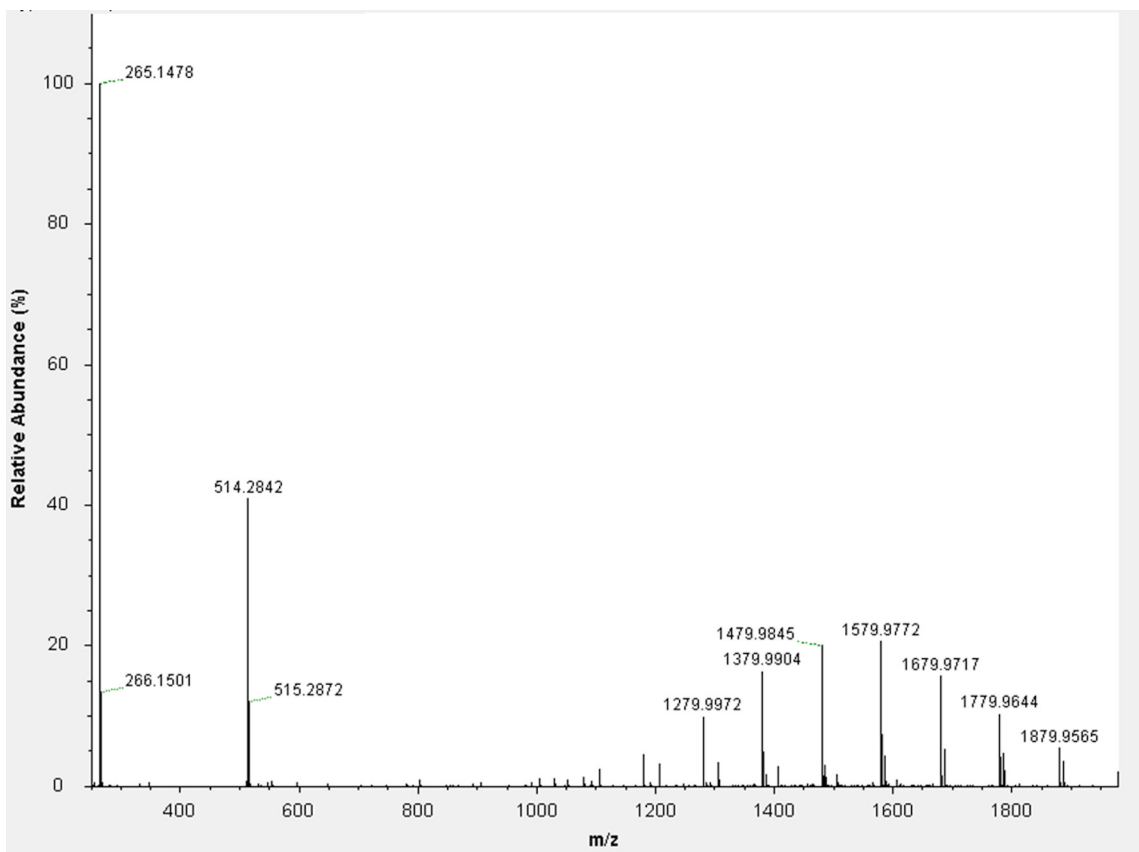
Negative Ion Mode Calibration

Before you perform measurements in the negative ion mode, the mass spectrometer must be calibrated with a calibration solution containing sodium dodecyl sulfate, sodium taurocholate, and Ultramark 1621. Refer to the *Exactive Series Operating Manual* for instructions about preparing the negative ion mode calibration solution or buying the ready-to-use solution from Thermo Fisher Scientific (refer to www.fishersci.com, catalog number PI88324).

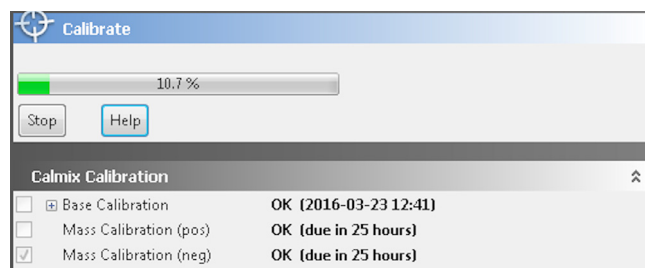
❖ To calibrate the Exactive Plus EMR mass spectrometer for negative ion mode

- Place a clean, 500 μ L Unimetrics syringe with 450 μ L of calibration solution for the negative ion mode into the syringe pump.
- Click the **On/Off/Standby** button to take the mass spectrometer out of the Standby mode or Off mode and turn it On.
- Click the **Syringe Pump** button to start the syringe pump.
- In the spectrum window of Exactive Plus EMR Tune, observe the mass spectra of the singly-charged ions of the negative ion mode calibration solution. See the figure on the next page. The ions are as follows:
 - Sodium dodecyl sulfate: m/z 265
 - Sodium taurocholate: m/z 514
 - Ultramark 1621: m/z 1280, 1380, 1480, 1580, 1680, 1780





- Click the title bar of the Calibrate window to display it.
- In the Calmix Calibration sub-window, select the Mass Calibration (neg) check box to specify a mass calibration for the negative ion mode. See figure right.
- In the Calibrate window, click **Calibrate** to start the automatic calibration procedure.
- The Calibrate window indicates the completed percentage of the calibration process by a progress bar.
- A message box informs you when the calibration procedure is completed. Click **OK** to close the message box.



Evaluation

Evaluation of Positive Mass Calibration



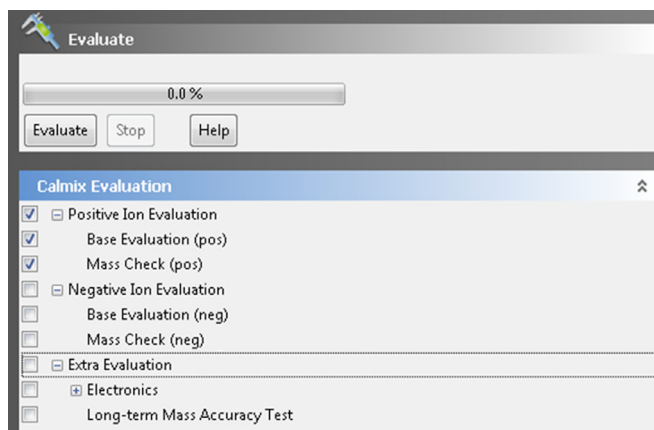
Use the Evaluate window of the Tasks panel to perform an automatic check of the instrument calibration.

The following example describes an evaluation of the positive mass calibration.

❖ To evaluate the mass calibration for positive ion mode

- Place a clean, 500 μ L Unimetrics syringe with 450 μ L of calibration solution for the positive ion mode into the syringe pump.
- Click the **On/Off/Standby** button to take the mass spectrometer out of the Standby mode or Off mode and turn it On.
- Click the **Syringe Pump** button to start the syringe pump.

4. Click the title bar of the Evaluate window to display it.
5. In the Calmix Evaluation sub-window, select the Mass Check (pos) check box to evaluate the mass calibration for the positive ion mode. See figure right.
6. In the Evaluate window, click **Evaluate** to start the automatic evaluation procedure.
7. The Evaluate window indicates the completed percentage of the evaluation process by a progress bar.



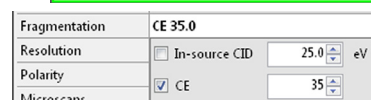
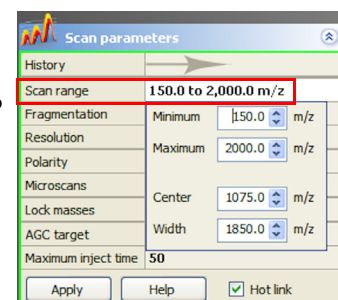
8. A message box informs you when the evaluation procedure is completed. Click **OK** to close the message box.
- If this evaluation fails, calibrate the Exactive Plus EMR mass spectrometer as described on [page 5](#).

In the previous examples, the Exactive Plus EMR mass spectrometer operates in the full scan mode. The following examples show the mass spectrometer operating in other scan modes.

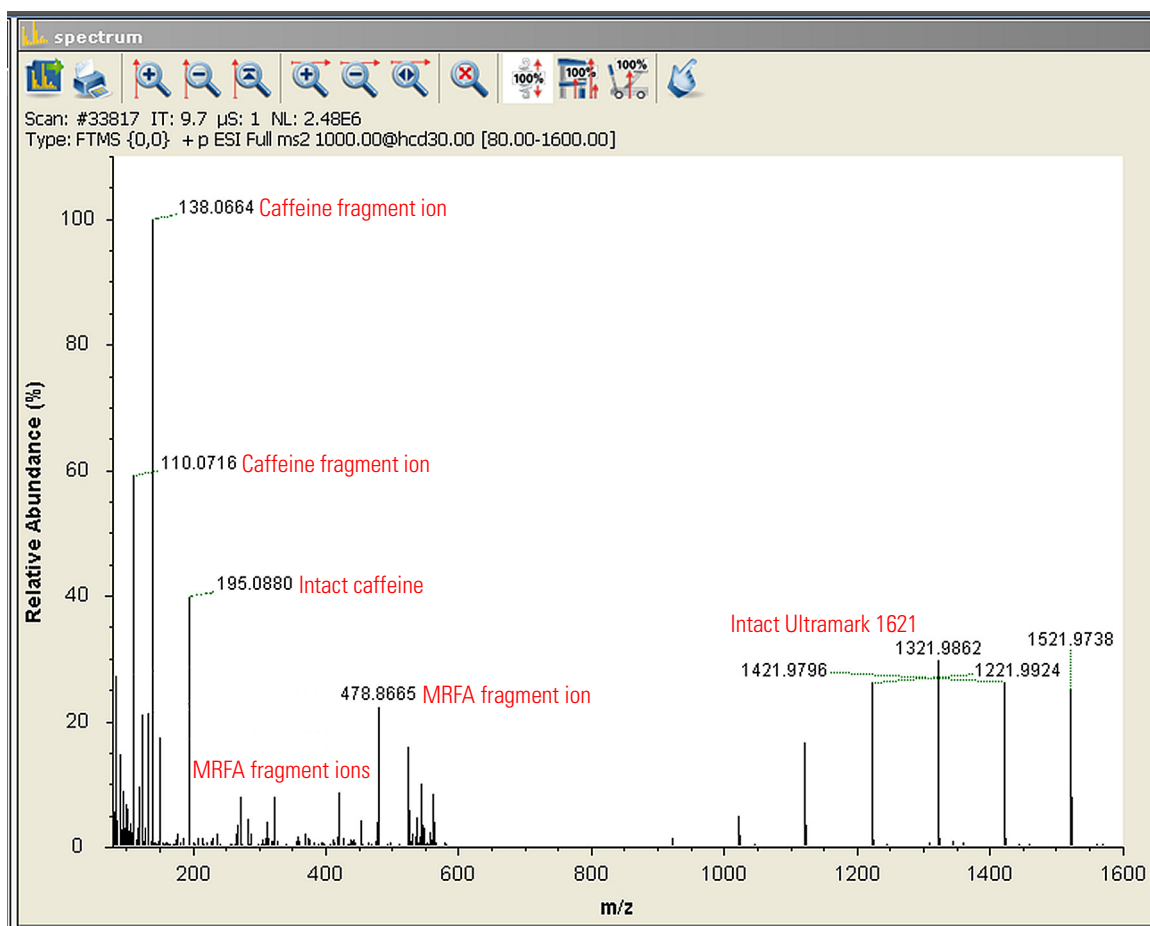
The Exactive Plus EMR mass spectrometer allows performing All Ion Fragmentation (AIF) measurements. The following example describes an AIF fragmentation experiment.

❖ **To set the scan parameters for an AIF fragmentation experiment with CE**

1. If necessary, tune and calibrate your Exactive Plus EMR mass spectrometer as described above.
2. Set the scan parameters in the Scan parameters window:
 - a. Click into the Scan Range field to display the Scan Range dialog box.
 - b. Adjust the scan range according to your requirements (from m/z 150 to m/z 2000, for example). See figure right.
3. Perform the data acquisition as described on [page 11](#).



The figure below shows a typical spectrum of an AIF fragmentation experiment with HCD.

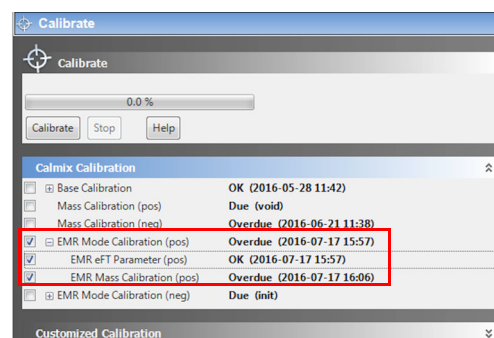


Performing Experiments in the EMR Mode

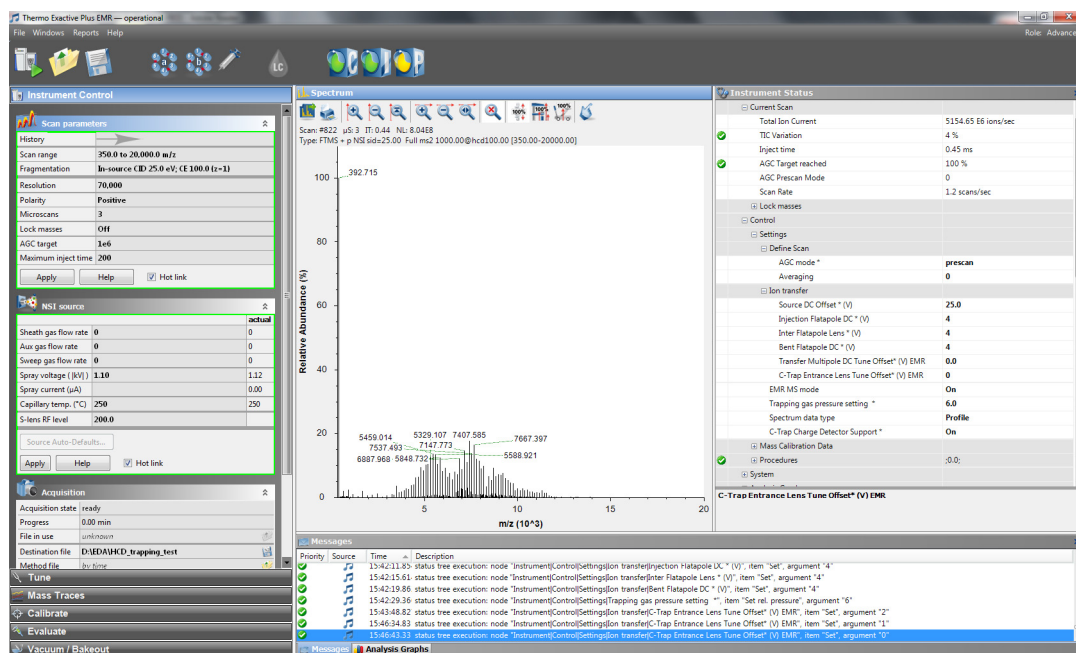
This mode of operation enables the analysis of molecules especially in Native condition, including monoclonal Antibodies (mAb), monitoring of antibody-antigen binding, analysis of antibody-drug conjugates and large protein complexes. We recommend that you use direct infusion using the TriVersa NanoMate™ (TVNM) from Advion, Inc. or the Thermo Scientific Nanospray Flex source with an emitter. The samples prepared in 5–10 mmole ammonium acetate solution in pH 7 provide a stable spray.

❖ To perform an experiment in the EMR mode

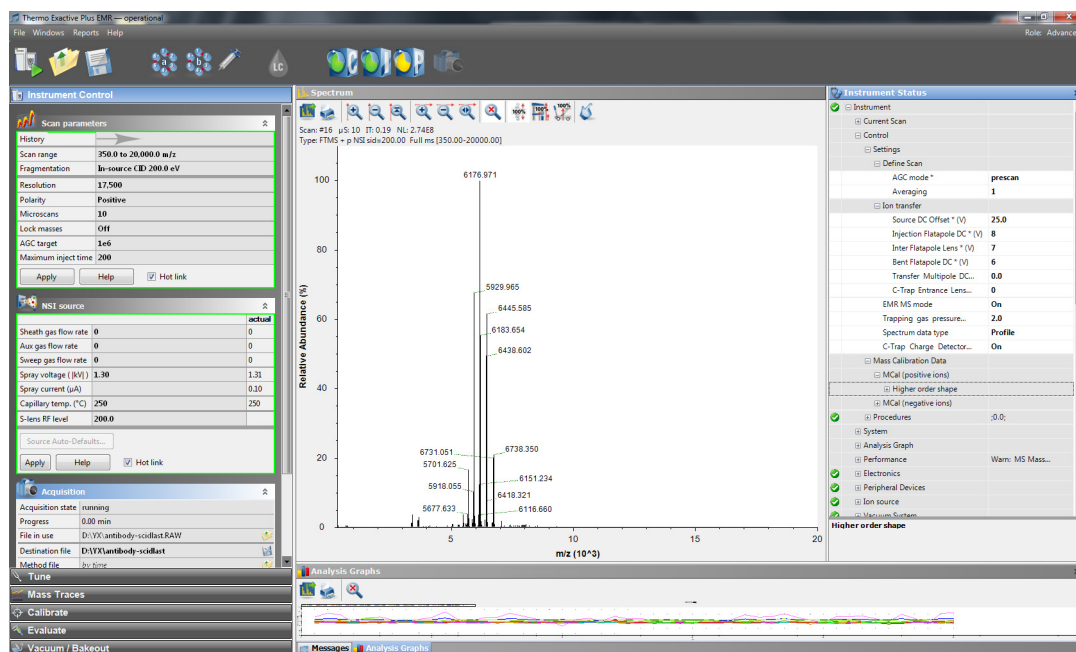
1. Set the instrument to EMR mode:
 - a. If it is not already open, display the instrument status window.
 - b. In the tree view, expand the Instrument > Control > Settings item.
 - c. Set EMR MS mode to **On**.
2. Set the scan parameters to the following:
 - a. Mass range can be extended to up to m/z 20000. The first mass should be set to m/z 350 or higher.
 - b. Calibrate the instrument using the cesium iodide (CsI) solution provided during the installation.
 - c. Using *default_CsI.mstune*, perform an EMR Mode Calibration for both EMR eFT Parameter and EMR Mass Calibration. During the calibration, make sure that the spray is stable.



An example of a measurement of a CsI solution is given in the figure below.



- d. Use the appropriate tune file:
 - For proteins such as mAb in native state, use *default_mAb.mstune*.
 - For large proteins assemblies in native state, use *default_GroEL.mstune*.
- e. For proper desolvation, activate In-source CID and HCD. If necessary, fine tune.
- f. In the instrument status window under Instrument > Control > Define Scan, always set Spectra averaging to 1 before a new acquisition. Once you have established a good signal, you can set Spectra averaging to a higher value for best results. The figure below shows an example of a measurement of an mAb mixture.





After you have entered the scan parameters of your experiment, you can finally start to acquire data.

❖ To perform data acquisition

- Specify the acquisition parameters in the Acquisition window:
 - In the Destination file field, type the full path (Drive:\path\file name) of the raw file that is used to store the acquired data. Alternatively, click the  button to the right of the text box to open a dialog box to browse your directories. See figure right.
 - Click into the Acquisition time field to open the dialog box. Select the continuously option button to specify that the acquisition will continue until you click **Stop**. The Acquisition time field shows *continuously*.
- Click the **On/Off/Standby** button to take the mass spectrometer out of the Standby mode or Off mode and turn it On.
- Click the **Syringe Pump** button to start the syringe pump.
- In the Acquisition window, click **Start** to initiate the data acquisition. The spectrum window shows a real-time display of the mass spectrum. The data are saved in the selected raw file.
- Click **Stop** to stop the acquisition.

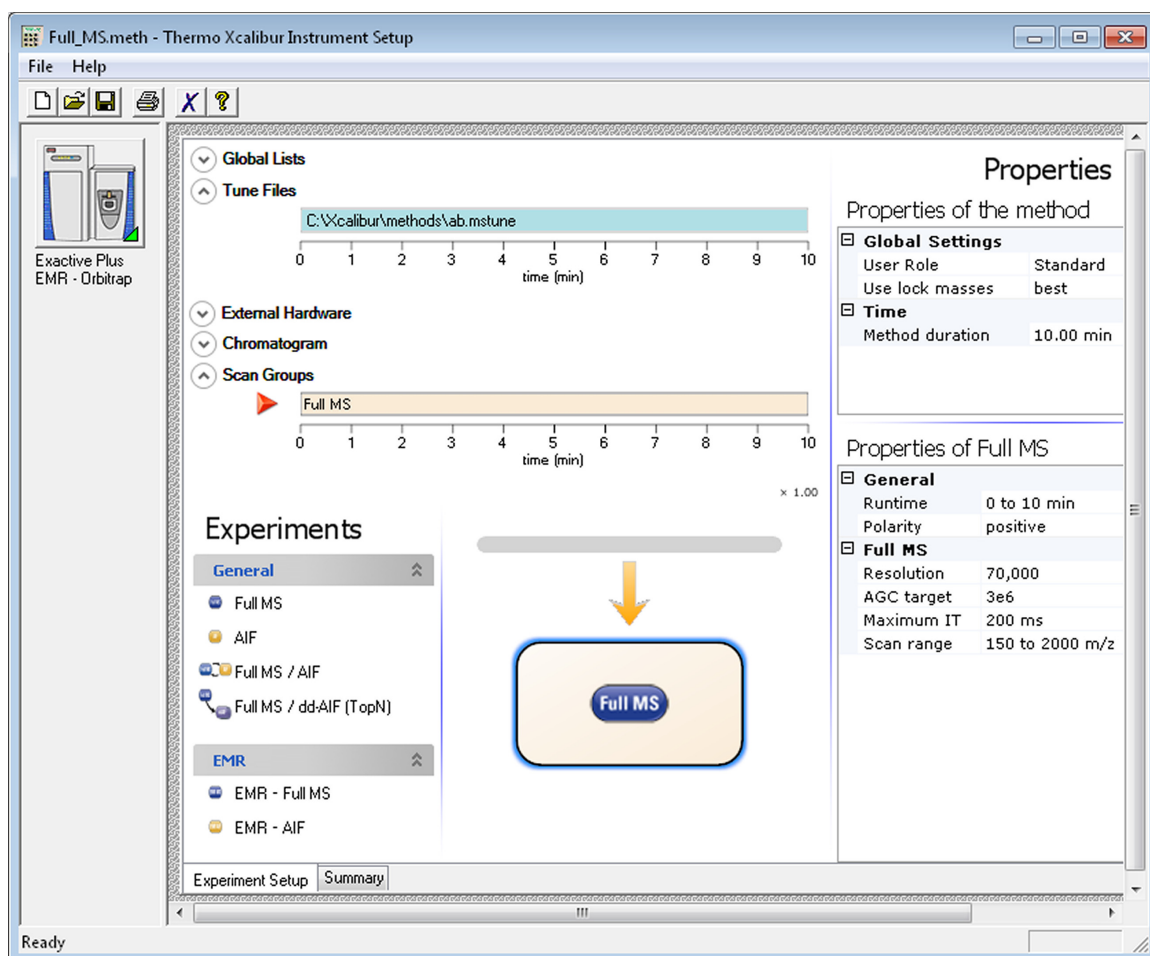
Acquisition	
Acquisition state	off
Progress	0.00 min
File in use	unknown
Destination file	C:\Xcalibur\data\ESI_HCD
Method file	by time
Acquisition time	continuously
Sample	
Comment	
On start	don't wait
After acquisition	stay on
Start Pause Help	

The following example describes how to create an instrument method in the Instrument Setup view of Xcalibur. You can then use the instrument method to acquire data with the Exactive Plus EMR mass spectrometer. The tune file used in the instrument method is used for data acquisition. In the Exactive Plus EMR Tune software, make sure that your tune file has appropriate settings and save it accordingly.

❖ To set up an instrument method

- Display the Instrument Setup page in Xcalibur:
 - Choose **Start > Programs > Thermo Xcalibur > Xcalibur** to display the Xcalibur Home Page window.
 - Choose **GoTo > Instrument Setup** to display the Instrument Setup window.
 - If necessary, click **Exactive Plus EMR - Orbitrap MS** in the View bar to display the Method Editor.
- In the Method Editor, drag an experiment symbol (for example, Full MS) from the Experiment pane (bottom left) to the gray bar in the Graph pane. A corresponding time bar is displayed in the Scan Groups pane.
- Edit the fields of the Properties pane (right) to set up the experiment parameters. Refer to the *Exactive Plus EMR Software Manual* or the Exactive Plus EMR Tune Help for a description of the available parameters.
- Assign a tune file:
 - On the External Hardware pane, click the  **Tune Files** icon to expand the Tune Files pane.
 - In the Properties of Tunefiles pane, click the Base Tunefile field.
 - Click the  button to open a dialog box.
 - Browse for the tune file (for example, ab.mstune) and assign it to the experiment.
- Click  on the toolbar to save the new instrument method:
 - In the Save As dialog box, enter the name (Full_MS.meth, for example) and the location for your instrument method. Then click **Save**.
 - In the File Summary Information Dialog Box, enter a comment as header information for your instrument method. Then click **OK** to close the dialog box.

The instrument method can now be used to acquire data with your Exactive Plus EMR mass spectrometer, either from the Xcalibur Sequence Setup or from the Exactive Plus EMR Tune window. The figure below shows the example of an instrument method that was set up as described above.

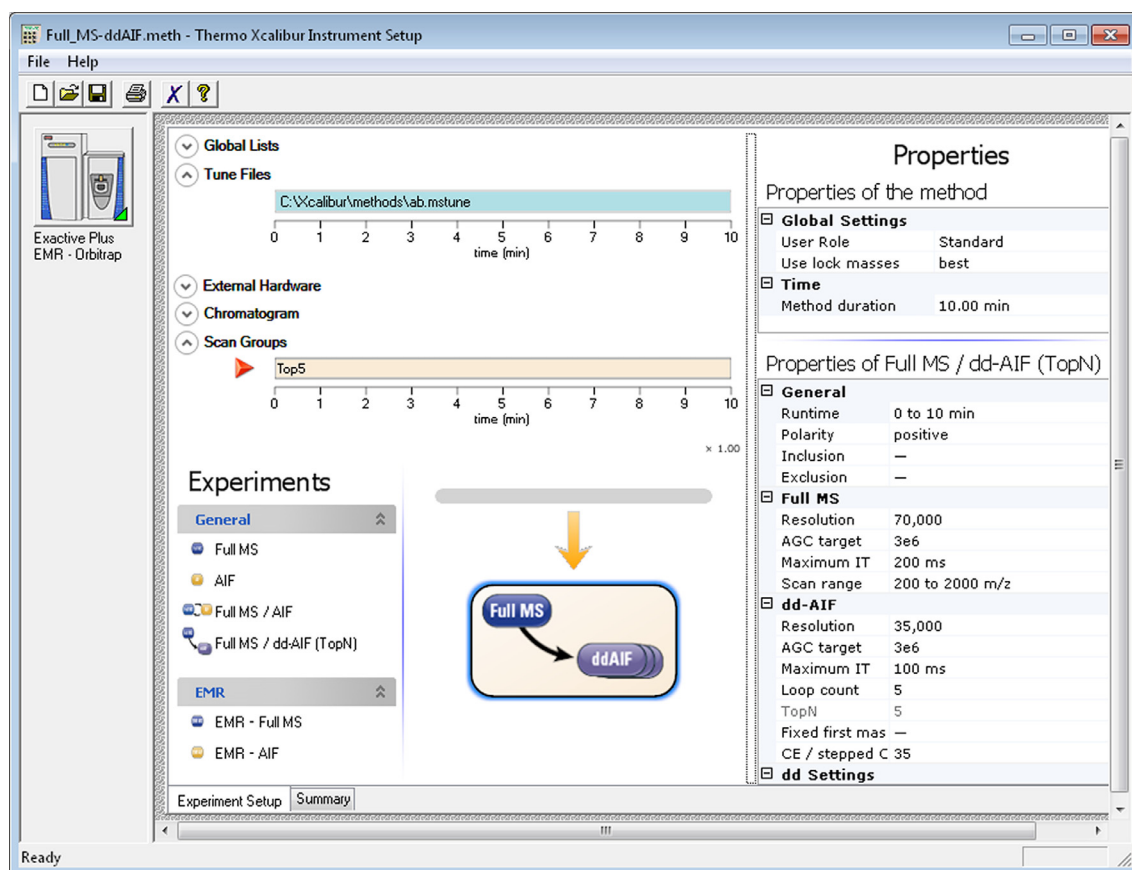


Performing Data Dependent AIF Experiments

❖ To set the scan parameters for a dd-AIF Experiment

- Display the Instrument Setup page in Xcalibur:
 - Choose **Start > Programs > Thermo Xcalibur > Xcalibur** to display the Xcalibur Home Page window.
 - Choose **GoTo > Instrument Setup** to display the Instrument Setup window.
 - Click **Exactive Plus EMR - Orbitrap MS** in the View bar to display the Method Editor.
- In the Method Editor, drag a Full MS/dd-AIF (TopN) template from the Experiment panel (bottom left) to the gray bar in the Graph pane. A corresponding time bar is displayed in the Scan Group pane.
- Edit the fields of the Properties panel (right) to set up the experiment parameters. Refer to the *Exactive Plus EMR Software Manual* or the Exactive Plus EMR Tune Help for a description of the available parameters.
- Assign a tune file:
 - On the Global Settings pane, click the **Tune Files** icon to expand the Tune Files pane.
 - In the Properties of Tunefiles pane, click the Base Tunefile field.
 - Click the button to open a dialog box.
 - Browse for the tune file (for example, ab.mstune) and assign it to the experiment.
- Click on the toolbar to save the new instrument method:
 - In the Save As dialog box, enter the name (Full_MS-ddAIF.meth, for example) and the location for your instrument method. Then click **Save**.
 - In the File Summary Information Dialog Box, enter a comment as header information for your instrument method. Then click **OK** to close the dialog box.

The instrument method can now be used to acquire data with your Exactive Plus EMR mass spectrometer, either from the Xcalibur Sequence Setup or from the Exactive Plus EMR Tune window. The figure below shows the example of an instrument method that was set up as described above.

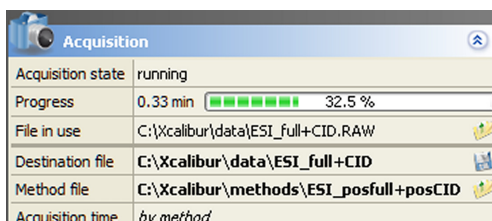
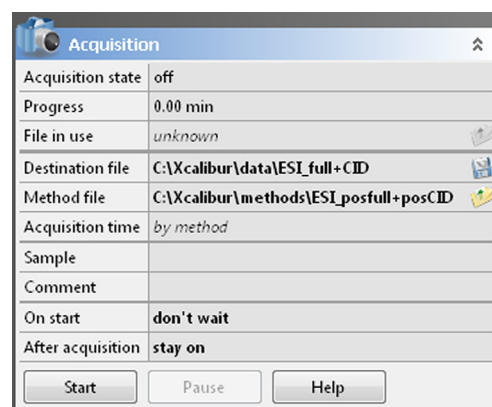


Running the MS

This section shows an example of how to use an instrument method to run the Exactive Plus EMR mass spectrometer.

❖ To run the Exactive Plus EMR mass spectrometer with an instrument method

- Specify the acquisition parameters in the Acquisition window of Exactive Plus EMR Tune, as follows:
 - In the Destination file field, type the full path (Drive:\path\file name) of the raw file that is used to store the acquired data. See figure right.
 - In the Method file field, click the  button to the right of the field to browse the computer for the instrument method file that was created in the previous topic. The Acquisition time field shows *by method*.
- Click the **On/Off/Standby** button to take the mass spectrometer out of the Standby mode or Off mode and turn it On.
- Click the **Syringe Pump** button to start the syringe pump or start a separate pump for infusion experiments.
- In the Acquisition window, click **Start** to initiate the data acquisition:
 - The Start button is replaced by a Stop button.
 - The Acquisition state changes to *running*.
 - A progress bar indicates the completed percentage of the acquisition. See figure right.
 - Icons appear on the toolbar to indicate an active data acquisition.



After Operation

Trademarks

- If necessary, Exactive Plus EMR Tune appends a time stamp to the name of the destination raw file to prevent overwriting existing files.

When the Scan parameters window and the Spectrum window are monitored, it is possible to view how Exactive Plus EMR Tune changes the values according to the settings defined in the instrument method.

The acquisition ends when the acquisition time defined in the instrument method has expired. To display the raw file with the acquired data in Qual Browser, click the  button in the File in use field.

When the measurement is finished, Thermo Fisher Scientific recommends that you leave the Exactive Plus EMR mass spectrometer in Standby mode and not in Off mode to provide the best mass accuracy for the next analysis.

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