VueBox™
Quantification Toolbox

Instructions for use

CONTENTS

1 INTRODUCTION

1.1 ABOUT THIS MANUAL

In this manual, examples, suggestions and warnings are included to help you to start using the VueBox™ software application and to advise you on important items. This information is indicated using the following symbols:

	The *caution symbol* indicates important information, safety precautions, or warnings.
	The *stop* symbol highlights important information. You should stop and read before continuing.
	The *bulb* symbol indicates a suggestion or an idea that simplifies the use of VueBox™. It can also refer to information available in other chapters.

1.2 INTERPRETING SYMBOLS OF THE PRODUCT

Symbol	Location	Description
REF	User Manual	Product name and version
	User Manual	Manufacturer's name
	User manual	Production Year and month
CE1253	User Manual	Conformity assessment procedure according to directive 93/42/EEC Annex II.3 Classification according to directive 93/42/EEC, Ann. IX: class IIa according to rule 10

1.3 DEFINITIONS

ROI	Region Of Interest
PE	Peak Enhancement
WiAUC	Wash-in Area Under Curve
RT	Rise Time
TTP	Time To Peak
WiR	Wash-in Rate
WiPI	Wash-in Perfusion Index
WoAUC	Wash-out AUC
WiWoAUC	Wash-in and Wash-out AUC
FT	Fall Time
WoR	Wash-out Rate
QOF	Quality Of Fit
rBV	Regional Blood Volume
mTT	Mean Transit Time
PI	Perfusion Index
TSV	Tabulation-Separated Values

1.4 SYSTEM DESCRIPTION

VueBox™ is a software package useful for the quantification of blood perfusion, based on clips acquired in Dynamic Contrast Enhanced Ultrasound, in radiology applications (cardiology excluded).

From the analysis of a time sequence of 2D contrast images, perfusion parameters are calculated, such as wash-in rate (WiR), peak enhancement (PE), rise time (RT) or area under curve during wash-in (WiAUC). Time parameters (e.g. RT) can be interpreted in absolute terms, and amplitude parameters (e.g. WiR, PE and WiAUC) in relative terms (vs. values in a reference region). VueBox™ can display the spatial distribution of any of these (and other) parameters, synthesizing time sequences of contrast images into single parametric images. Models are provided for the two most common modes of administration: bolus (wash-in / wash-out kinetics) and infusion (replenishment kinetics after destruction).

1.5 INTENDED USE

VueBox™ is intended to assess relative perfusion parameters in radiology applications (cardiology excluded), based on 2D DICOM datasets acquired in Dynamic Contrast Enhanced Ultrasound examinations.

1.6 SAFETY PRECAUTIONS

Please read the information in this section carefully before using the program. This section contains important information on safe operation and handling of the program as well as information on service and support.

STOP Only trained and licensed medical practitioners are authorized to use the system.

STOP Any diagnosis based on the usage of this product must be confirmed by a differential diagnosis prior any treatment according to common medical sense.

STOP Only 2D DICOM datasets of Dynamic Contrast Enhanced Ultrasound examinations for which a calibration file is available should be processed.

1.7 INSTALLATION AND MAINTENANCE

CAUTION Bracco Suisse SA assumes no liability for problems attributable to unauthorized modifications, additions or deletions to Bracco Suisse SA software or hardware, or unauthorized installation of third party software.

STOP As manufacturer and distributor of this product, Bracco Suisse SA is not responsible for safety, reliability and performance of the system, if:
- the product is not operated in accordance with the operating manual
- the product is operated outside of its operating conditions
- the product is operated outside of the specified operating environment.

1.8 PATIENT AND USER SAFETY

STOP The user must be satisfied with the suitability and completeness of clips acquired in a study, prior to analysis with VueBox™. If not, acquisitions have to be repeated. For information about performing contrast acquisitions for reliable perfusion quantification, please refer to the operating instructions provided by the manufacturer of your ultrasound equipment as well as to Bracco's Application note "Protocol for performing reliable perfusion quantification".

CAUTION The information contained in this manual is intended only for the operation of Bracco Suisse SA application software. It does not include information on echocardiograms or general ultrasound acquisition. Please refer to the operating instructions of your ultrasound equipment for further information.

1.9 MEASUREMENT

CAUTION The user is responsible for a suitable choice of ROI (Region of interest), in order to include contrast-ultrasound data only. ROI should not include any overlays such as texts, labels or measurements and should be drawn on ultrasound data acquired with a contrast-specific mode only (i.e. no Fundamental B-Mode or Color Doppler overlays).

CAUTION The user is responsible for determining if artifacts are present in the data to be analyzed. Artifacts can severely affect the analysis outcome and require a reacquisition. Examples of artifacts are:
- obvious discontinuity due to a jerky motion during acquisition or because the acquisition plane changed;
- excess shadowing in images;
- poorly defined anatomy or evidence of distorted anatomical representation.

STOP In the case of a poorly reconstructed image, as determined by the above criteria (e.g. artifacts) or by the user's clinical experience and training, measurements should not be made and must not be used for any diagnostic purposes.
The user must ensure the accuracy of the images and measurement results. Acquisitions should be repeated if there is the slightest doubt as to the accuracy of images and measurements.

CAUTION The user is responsible for a suitable length calibration. In case of incorrect usage, wrong measurement results may occur.
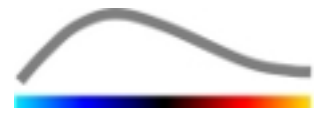
CAUTION The user should always make sure to select the appropriate calibration according to the ultrasound system, probe and settings used. This control should be performed for each clip to be analyzed.

2 INSTALLATION

2.1 SYSTEM REQUIREMENTS

	Minimum	Proposed
CPU	Intel® Pentium 4 520	Intel® Core 2 Duo E8400 or better
RAM	1 GB	2 GB or more
Disk Space	40 GB	80 GB or more
Graphics Card	Nvidia GeForce 8500GT 512DDR Minimum Resolution **1024x768**	Nvidia GeForce 8800GT 1024DDR Resolution **1280x1024 and higher**
Monitor	17'' SVGA (CRT)	19'' TFT Flat Screen or higher
Additional Requirements		
Operating System:	Microsoft® Windows™ XP (SP2), 32 bit Microsoft® Windows™ VISTA (SP1), 32 bit / 64 bit Microsoft® Windows™ 7, 32 bit / 64 bit	
Screen text size	96 dpi	

Please make sure that your screen resolution fulfills the minimum requirement and that your **DPI** (Dots Per Inch) setting is set at **96**.

2.2 INSTALLATION OF VUEBOX™

The installation package of VueBox™ includes the following mandatory prerequisites:

- Microsoft .NET Framework 4.0
- SAP Crystal Report Runtime Engine for .NET Framework 4.0
- Visual C++ 2010 Runtime Libraries

During the installation procedure, you will be automatically prompted if any of these prerequisites needs to be installed.

Please perform the following steps in order to install VueBox™:

1. close all applications,
2. run the *setup.exe* installation package located in VueBox™ installation folder,
3. accept the installation of the **prerequisites** (if not already installed),
4. select the installation folder and press **Next**,
5. follow the on-screen instructions,
6. at the end of the installation, press **Close**.

The installation is now complete. VueBox™ can be started from the *VueBox* folder in the start menu or more directly using the desktop shortcut.

VueBox™ can be uninstalled through the **Add / Remove** software feature from the Windows **control panel**.

2.3 ACTIVATION OF VUEBOX™

At first start-up, VueBox™ launches an activation process that will validate and unlock the copy of the software application.

In this process you will be prompted to enter the following information:

- Serial number
- E-mail address
- Hospital / Company name.

The activation needs to communicate these information to the activation server. This can be performed automatically through the **online activation**, or manually using the **e-mail activation**.

In the **online activation**, VueBox™ will be activated and unlocked automatically, by simply following the on-screen instructions.

In the **e-mail activation**, an e-mail including all necessary information for the activation of VueBox™ will be generated and you will be asked to send it to the activation server (e-mail address will be displayed). Within a few minutes, you will receive an automatic reply by e-mail including an **unlock code**. This **unlock code** will be required at the next start-up of VueBox™ to finalize the activation process.

Please note that this activation process, either through the online or the e-mail method, needs to be performed **only once**.
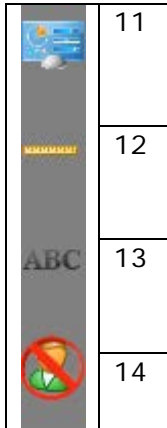
3 GENERAL REVIEW TOOLS

3.1 INTERFACE ELEMENTS

3.1.1 MAIN TOOLBAR

1	2	3	4	5	6	7	8	9	10

Item	Function	Available in mode			Comments
		Clip editor	Motion comp.	Result	
1	Clip editor		X	X	Return to the clip editor mode.
2	Length Calibration	X	X	X	Set a known distance in the image to calibrate for length and area measurements.
3	Copy ROI	X	X	X	Copy all ROI of the current active window into the ROI database.
4	Paste ROI	X	X	X	Paste selected ROI set from the ROI database.
5	Motion compensation	X	X		Apply spatial realignments on all images using a specific reference image.
6	Perfusion quantification	X	X		Perform perfusion quantification.
7	Save result			X	Store a result file (analysis result context) into the result database.
8	Export data			X	Export selected data (e.g. quantification data, screenshots, movies).
9	About	X	X	X	Display the about screen.
10	Exit	X	X	X	Close all clips opened and exit the software.

3.1.2 SIDE TOOLBAR

		Available in mode			
Item	Function	Clip editor	Motion comp.	Result	Comments
11	Import / Export user settings	X	X	X	Import / export user settings (i.e. ROI, result and display preset databases).
12	Length Measurement	X	X	X	Measure distances in the image.
13	Annotations	X	X	X	Add text labels on images.
14	Anonymize	X	X	X	Hide patient's name and identification.

4 FUNCTIONAL REFERENCE

To get instant help on working with VueBox™, double-click on the manual shortcut icon located on the desktop.

You will need Adobe Acrobat Reader® to display the software manual. If Adobe Acrobat Reader® is not installed on your system, please download the latest version from www.adobe.com.

4.1 USER INTERFACE

VueBox™ is a multiple window interface software application. The possibility to process several clips in separate child windows comes in handy for the user who, for example, wants to analyze different cross-sections of a given lesion at the same time. Another example is the case of a user who is interested to compare a given lesion imaged at different dates. Each analysis is performed in an individual, independent child window. VueBox™ is also multitasking, as each child window can execute processing at the same time while keeping the parent interface responsive. Furthermore, calculations that are demanding in terms of computing power, such as computing the perfusion quantification, have been optimized to benefit from multicore processors when available, a technology called parallelization.

When VueBox™ is launched, a start page is shown indicating the software name and version number. From this start page, clips can be opened; recent clips and recent analyses, if applicable, can be quickly reopened. Moreover, when a recent clip is selected, its associated analyses (i.e. previously saved analysis contexts) are accessible and can be restored.
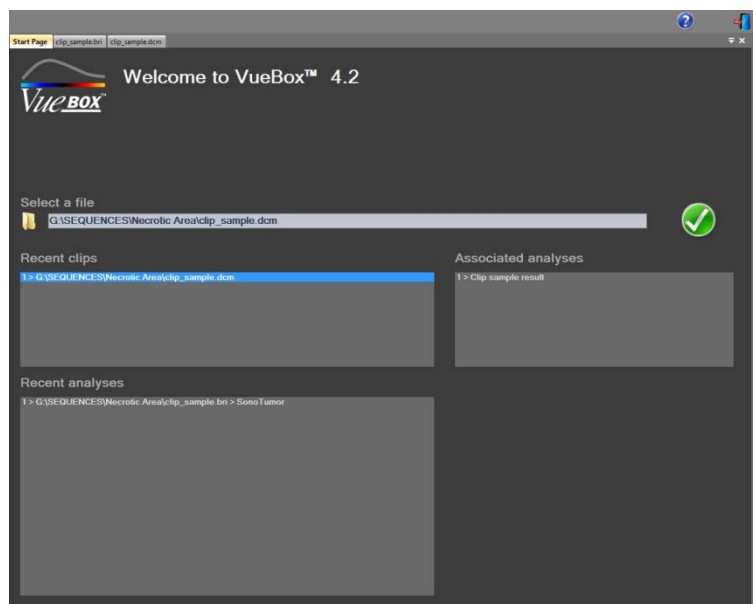

Figure 1 – VueBox™ start page

Once a clip is opened, a one-quadrant view is displayed, including the video settings toolbar, the clip editor as well as the remaining functionalities useful prior to launching the analysis process (e.g. ROI drawing toolbar, etc.).
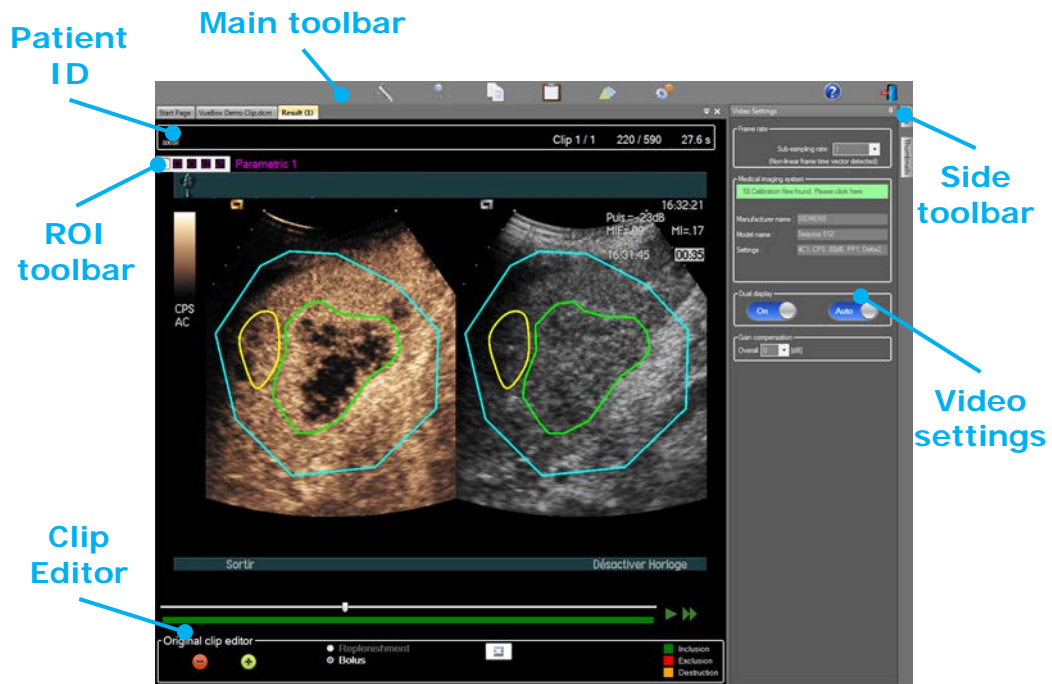
Figure 2 - One-quadrant view

Finally, when the perfusion data processing is completed, results are presented in a four-quadrant view, where time-intensity curves, parametric images, time intensity curves and perfusion parameter values are displayed.
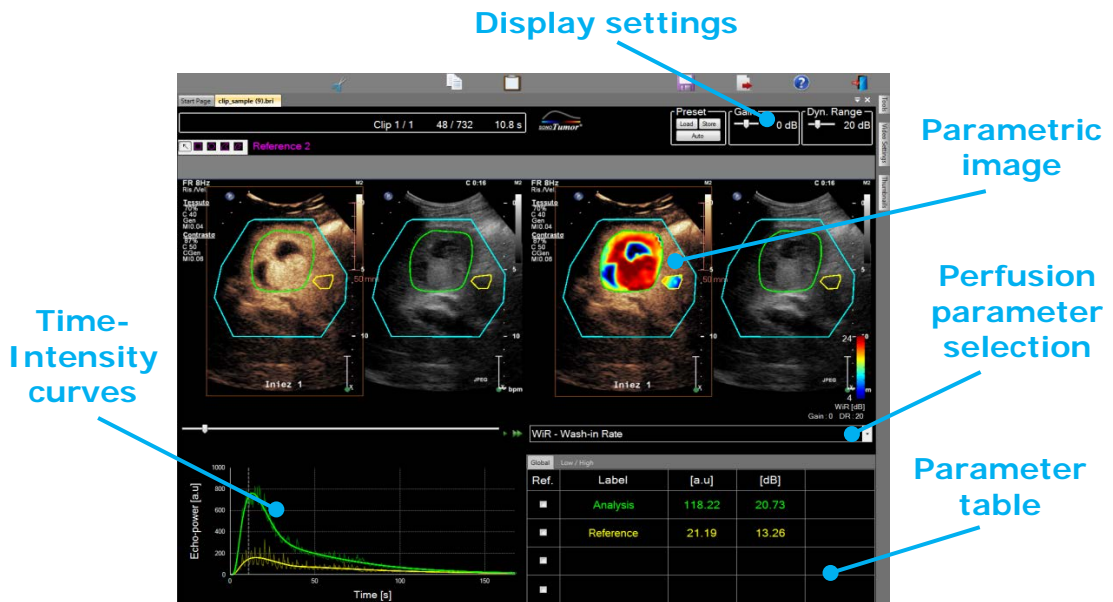

Figure 3 - Four-quadrant view

4.2 GENERAL WORKFLOW

The application workflow is easy and intuitive for a routine clinical use. It consists of the following steps:

1. Load a dataset
2. Adjust video settings

3. Remove unwanted images with the clip editor

4. Draw several ROI

5. Apply motion compensation if needed

6. Perform quantification

7. Visualize, save and export results

4.3 SUPPORTED DATASETS

VueBox™ supports contrast ultrasound 2D DICOM clips of systems for which linearization tables are available (also called calibration files). Color Doppler clips, B-mode clips and contrast/B-mode overlay displays are not supported.

In general, bolus clips longer than 90 seconds are recommended so as to include wash-in and wash-out phases. Replenishment clips can be substantially shorter.

4.4 VIDEO SETTINGS

Figure 4 - Video settings panel
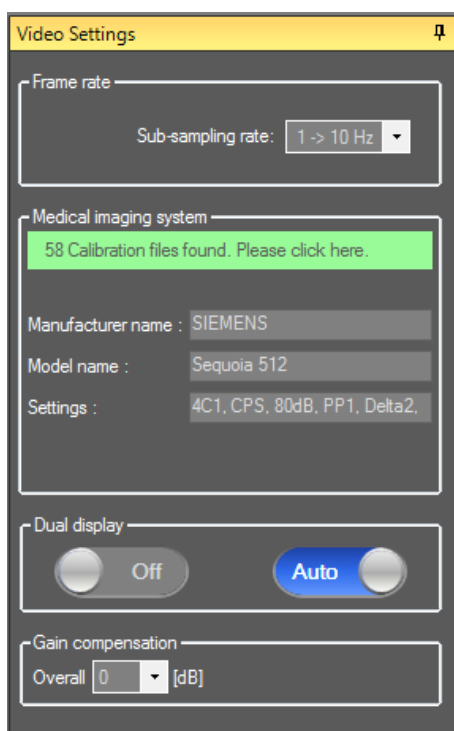
The video settings panel is shown when a clip is loaded in the software. In this panel, you need to:

- define the desired **sub-sampling rate** if needed, so as to reduce the number of frames to be processed (**optional**),

- select the appropriate **ultrasound system and settings** used for the acquisition so as to apply the correct linearization function to the image data (**mandatory**),

- activate the **dual display** mode if the clip was recorded with both contrast and fundamental B-mode images side-by-side (or above each-other) on screen (**optional**),

- select the **gain compensation** so as to compensate for gain variations across different exams in order to be able to compare results of a given patient at different visits (**optional**).

Bracco recommends activating the dual display mode when available, as this feature increases the robustness of the motion compensation algorithm.

Default values are kept in memory from one session to another (e.g. last ultrasound system used, etc.). Therefore, it is important to make sure that these settings are correct before continuing with the analysis.

The user should make sure that the clip frame rate read from the DICOM file and displayed in the video settings panel is correct before pursuing the analysis. An incorrect frame rate may result in a wrong time base and, thus, affect the computed values of perfusion parameters.

4.5 CALIBRATION FILES

Calibration files contain the appropriate linearization function and color map correction for a given ultrasound system and specific setting (i.e. probe, dynamic range, color map, etc.). Using calibration files, the VueBox™ can convert video data extracted from DICOM clips into echo-power data, a quantity directly proportional to the instantaneous concentration of contrast agent concentration at each location in the field of view.

Calibration files are distributed to users according to their ultrasound system(s) (e.g. Philips, Siemens, Toshiba, etc.) and can be added to VueBox™ by a simple drag & drop into the VueBox™ user interface.

The most common settings are available for each ultrasound system. However, new calibration files can be generated, with specific settings, upon users' request.

Please contact your local Bracco representative for more information on how to obtain additional calibration files.

4.6 CLIP EDITION

4.6.1 PRINCIPLE

The clip editor module allows you to limit the analysis to a specified time window, and also to exclude unwanted images from processing (either isolated or in ranges).

As illustrated on the figure below, the clip editor may be used to retain, within the wash-in and wash-out phases of a bolus, only the images within a relevant time interval. If the destruction-replenishment technique is applied during the experiment, the clip editor automatically defines selectable replenishment segments by including images between two destruction events only.

(a) BOLUS

(b) REPLENISHMENT

Image status bar:

Display settings

Parameter table

Destruction event
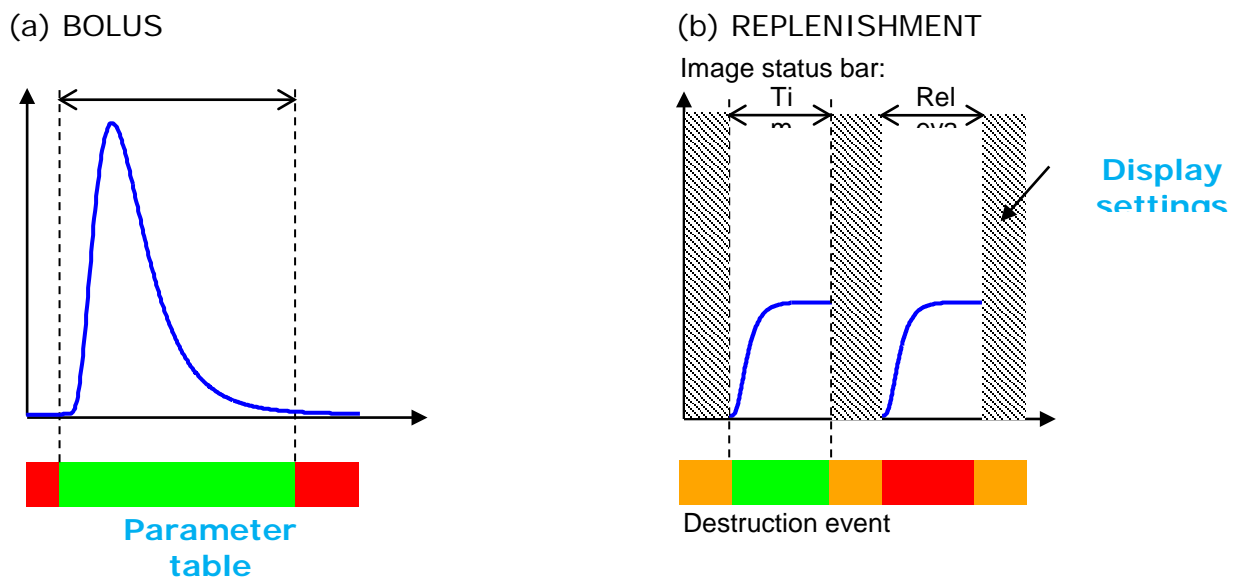
Time-Intensity curves

al examples of clip edition

CAUTION Using the bolus perfusion model, the user should make sure to include both wash-in and wash-out phases. Not doing so may affect the outcome of the perfusion data processing.

4.6.2 INTERFACE ELEMENTS

Figure 6 shows a screenshot of the interface elements in the clip editor in the replenishment mode.
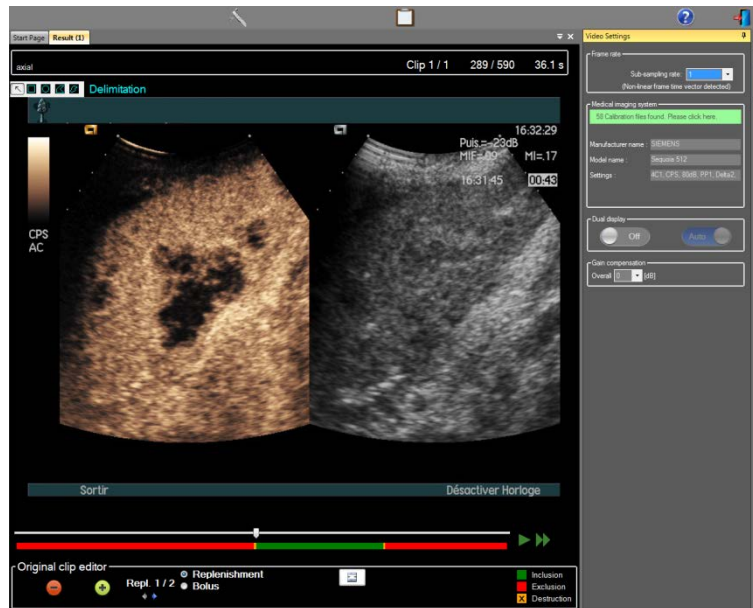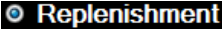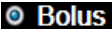

Figure 6: User interface in the clip editor in the replenishment mode.

Element	Name	Function
Image display		
60 / 286	**Image number**	shows the order number of the currently displayed image as well as the total number of images available in the clip.
2.8 s	**Time indicator**	shows the time instant of the currently displayed image.
	Zoom In / Out	increases or decreases the image size.
	Image slider	selects the image to be displayed. If the cursor points to an excluded image, a red frame appears around it.
	Image status bar	shows excluded and included image ranges in red and green, respectively. Destruction images are shown in orange.
	Play	runs the movie player.
	Fast play	runs the movie player in fast mode.

Clip editor

⊖	**Exclude**	sets the exclusion mode.
⊕	**Include**	sets the inclusion mode.
Ⓡ	**Reset**	reset the clip edition to default (for targeted mode only)
⊙ Replenishment	**Replenishment**	enables the destruction / replenishment mode (only available if clip contains destruction images)
⊙ Bolus	**Bolus**	enables the bolus mode.
◀ ▶	**Replenishment selector**	selects the previous/next replenishment segment (only available if the clip includes destruction-replenishment segments)

4.6.3 WORKFLOW

EXCLUDING IMAGES

To exclude a range of images:

1. Move the **Image slider** to the first image to be excluded

2. Click the **Exclude** ⊖ button

3. Move the **Image slider** to the last image to be excluded.

INCLUDING IMAGES

To include a range of images:

1. Move the **Image slider** to the first image to be included

2. Click the **Include** ⊕ button

3. Move the **Image slider** to the last image to be included

CHANGING THE RANGE OF EXCLUDED IMAGES

To change the range of excluded images:

1. Move the mouse pointer over the **Image status bar** to any border of a range of excluded images (■■)

2. When the pointer's shape changes to a vertical split ⧻, drag the border to change the range of excluded images.

MOVING THE RANGE OF EXCLUDED IMAGES

To move the range of excluded images:

1. Move the mouse pointer over the **Image status bar** to any border of a range of excluded images (■■)

2. When the pointer's shape changes to a vertical split ⧻, press the **Shift** key and drag the range of excluded images to the desired position.

4.6.4 CLIP CONCATENATION

The clip concatenation, or combination, is the process of pooling clips together to build up a single sequence of images. Using this feature, a set of clips recorded in chronological order by an ultrasound scanner can be processed. The concatenation function is useful when the ultrasound system has a limited clip recording time per DICOM file.

Bracco recommends concatenating clips with a clip-transition delay ≤ 15 seconds.

	Concatenate clip	opens and concatenates a clip with the current clip.
	Move up selected clip	moves up the selected clip in the Clip selector list.
	Delete selected clip	removes the selected clip from the Clip selector list.
	Move down selected clip	moves down the selected clip in the Clip selector list.
	Transition delay	sets the transition delay (in seconds) between the beginning of the selected clip and the end of the previous one to account for this delay in the analysis.
	Clip selector	selects a clip in the list.

4.6.5 FLASH IMAGE DETECTION

The selection of the perfusion model (i.e. Bolus or replenishment) can be performed in the clip editor. So as to reduce the risk of selecting a wrong model (e.g. the replenishment model for a bolus injection), the replenishment button becomes active only if the software has detected flash images in the clip. The flash detection is an automatic process launched every time a clip is loaded in VueBox™.
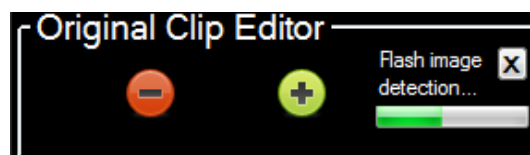
Figure 7 - Flash image detection

The automatic flash image detection progress can be seen in the clip editor toolbar as shown in the figure above. In some cases, this detection may not be accurate. Therefore, you may want to cancel it when the automatic detection is not accurate or fails. To cancel this flash image detection or to remove unwanted flash images:

1. if the detection is still being performed, click on the "X" button to stop it.

2. If the detection is completed, click on the destruction orange square located in the clip editor caption (with a "X" letter inserted).

However, the "Replenishment" model will not be accessible anymore. Therefore, if you want to process destruction / replenishment clips with the replenishment model, you will need to identify flash images manually by placing the image slider at the desired location and pressing the "F" keyboard key on each destruction frame.

4.7 REGIONS OF INTEREST

4.7.1 PRINCIPLE

With the help of the **ROI toolbar**, you can define up to five **Regions of Interest** on images of the clip using the mouse; a mandatory ROI named Delimitation and up to four generic ROI. The Delimitation ROI is used to delimit the processing area. It must thus exclude any non-echographic data, such as text, colorbars or image borders. A first generic ROI (e.g. ROI 1) usually includes lesion if applicable and a second generic ROI (e.g. ROI 2) may include healthy tissue to serve as reference for relative measurements. Note that ROI names are arbitrary and can be entered by the user. An additional two ROI are available to user's discretion.
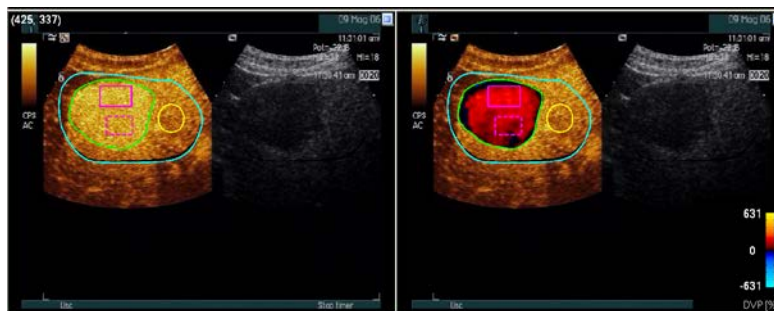

Figure 8 - Example of Regions of interest

4.7.2 INTEFACE ELEMENTS

Figure 9: ROI toolbar

The **ROI toolbar** (located in the upper-left corner of the image viewer) offers tools to draw four different shapes. The **ROI label** on the right of the toolbar identifies the current region to be drawn, and may be edited by clicking on it.

Button	Name	Function
↖	**Select**	allows to select / modify a region of interest.
▣	**Rectangle**	draws a rectangular shape.
◎	**Ellipse**	draws an elliptical shape.
⬠	**Polygon**	draws a closed polygonal shape.
⬡	**Closed curve**	draws a closed curvilinear shape.

4.7.3 WORKFLOW

DRAWING A ROI

To draw a rectangular or elliptical ROI:

1. Select a shape in the ROI toolbar (■ or ●)
2. Move the mouse pointer to the wanted location in the B-mode image (left side) or the contrast image (right side)
3. Click and drag to draw the ROI.

To draw a closed polygonal or curved ROI,

1. Select a shape in the ROI toolbar (◣ or ◢)
2. Move the mouse pointer to the wanted location in the B-mode image (left side) or the contrast image (right side)
3. To add anchor points, click repeatedly while moving the mouse pointer
4. Double-click at any time to close the shape.

DELETING A ROI

To delete a ROI:

1. Right click in the image to set the ROI selection mode or click the ⬉ button
2. Move the mouse pointer to any border of the ROI
3. Select the ROI using the left or right mouse button
4. Press either the DELETE or BACKSPACE keys.

MOVING A ROI

To change the location of a ROI:

1. Right click in the image to set the ROI selection mode or click the ⬉ button
2. Move the mouse pointer to any border of the ROI
3. When the pointer shape changes to a double-arrow, click and drag the ROI to a new location

EDITING A ROI

To change the location of anchor points of a ROI:

1. Right click in the image to set the ROI selection mode or click the ⬉ button
2. Move the mouse pointer to any anchor point of the ROI
3. When the pointer shape changes to a cross, click and drag the anchor point to a new location.

COPYING AND PASTING ROI

Regions of interest can be copied into a ROI library and pasted at a later time point, in any clip analysis. To copy all the ROI currently drawn:

1. Click the ![icon] button in the main toolbar

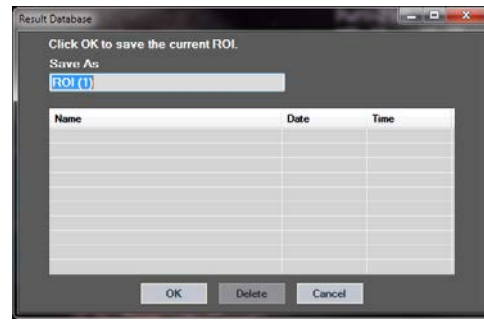2. Set a name or accept the default generated one and press the OK button

Figure 10 - Copying ROI into library

To paste ROI from the library:

1. Click the ![icon] button in the main toolbar

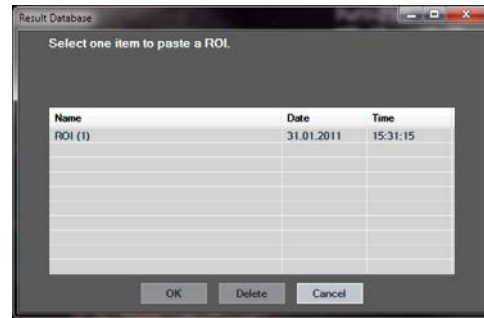2. Select the item in the list and press the OK button

Figure 11 - Pasting ROI from library

4.7.4   DUAL DISPLAY MODE

The dual mode is active when a clip is split into two image areas: contrast and fundamental B-mode. Each image area may be identified by its orientation marker, usually the logo of the ultrasound scanner manufacture, showing the scan orientation of the probe.

Figure 12 - Dual display mode with automatic or manual detection options

In this mode, ROI can be drawn on any side (i.e. contrast or B-mode) provided that that the contrast side is manually determined by the user. This operation is performed by first enabling the dual display mode in the video settings panel and then by left-clicking on the orientation marker of the contrast image. VueBox™ delineates the orientation marker using a white rectangle and detects the corresponding marker on the B-mode side automatically.

Figure 13 - Orientation marker detection in dual display mode

In some cases, similar orientation markers on both contrast and B-mode images may not be available. Thus, the automatic detection cannot be performed and the manual selection of landmarks within both images should be chosen.

To activate dual display with automatic detection (i.e. both probe orientation markers are available):

1. Set the ![On toggle button] toggle button to "On" in the dual display section of the video settings panel

2. Make sure that the ![Auto toggle button] toggle button is set to "Auto"

3. Click on the probe orientation marker of the contrast image

4. Control that the corresponding orientation marker located on the B-mode image is correctly detected

To activate dual display with manual landmarks selection (i.e. no or different probe orientation markers present):

1. Set the ![On toggle button] toggle button to "On" in the dual display section of the video settings panel

2. Set the ![Manual toggle button] toggle button to "Manual"

3. Click on an image landmark of the contrast image

4. Click on a corresponding image landmark of the B-mode image

5. Note: By pressing the left mouse-button in the vicinity of each landmark, a magnifying tool is activated to help the user position a cursor in a very precise way

CAUTION   The user should make sure to select the correct orientation marker (i.e. on the contrast-image side). Otherwise, all ROI may be inverted and all analysis results will be invalid.

CAUTION   In the manual landmarks selection mode, the user should carefully select a pair of image landmarks spaced in exactly the same way as the B-mode and contrast images. Otherwise, ROI positioning may be incorrect and this may degrade both image registration and analysis results.

4.8 LENGTH CALIBRATION AND MEASUREMENT

The Length Calibration tool is required for performing length and area measurements of anatomical objects in the images. It consists in identifying a known distance in any image of the clip. Once the line is drawn, the effective corresponding distance in mm needs to be entered.

To calibrate:

1. click the length calibration ✎ button,

2. draw a line on a known distance in the image (e.g. along a calibrated depth scale),

3. in the Length calibration dialog box, type the known corresponding distance in mm.

Once the Length calibration has been defined, areas of regions of interest will be listed in cm^2, in the quantitative parameter table.

The lengths within the images can be measured with the Length measurement tool ▬. The first Measurement tool 🎚 is called *ruler* and is used for drawing straight lines. The second one 🎚 is called *cross ruler* and is able to draw a "cross", 2 lines perpendicular to each other.

To make a length measurement:

1. click the length measurement ▬ button,

2. select the type of ruler in the ROI toolbar (line or cross),
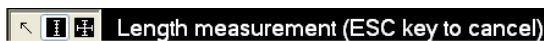
3. draw the ruler on the image by holding down the left mouse button and drag the line to change its length. The ruler direction, location and size can be modified with the same procedure,

4. the cross ruler follows the same principle. The user must know that the perpendicular line may be shifted by moving the mouse in the direction opposite to the first line.

CAUTION The accuracy of the measurement tools was verified and the following error should be taken into account:

Error on Length (horizontal and vertical)   < 1%

Error on Area   < 1%

4.9 ANONYMIZATION OF CLIP

The Anonymize Clip Tool 🚫 is useful for presentations, lectures or any occasions in which the patient information must be removed to comply with privacy protection. This tool is available at any processing stage of VueBox™. The user can move or resize the anonymization mask to hide the patient name. This mask is automatically filled with the most prominent color from the portion of the image covered.

The general workflow is as follows:

1. Click the Anonymize 🚫 button.

2. Adjust and move the Anonymize mask (rectangular shape) to where the information to be hidden is located in the image.
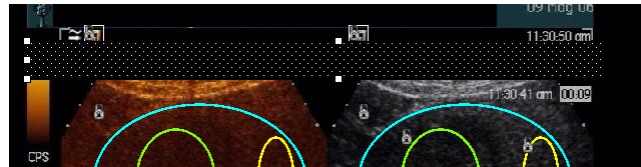
Figure 14 - Anonymization mask

4.10 ANNOTATION

The Annotation Tool ^{ABC} is used for labeling important parts of the image (for instance, the lesion type). After selecting the tool, click at a desired location for the annotation in the image. Then, the software displays a dialog box in which you may enter text. Annotations can be moved or deleted exactly like ROIs, using either the DELETE or BACKSPACE key.

4.11 MOTION COMPENSATION

4.11.1 PRINCIPLE

Motion compensation is a key tool for allowing reliable perfusion assessments. Motion in a clip can be due to internal organ movements, such as breathing, or to slight probe movements. Manual alignment of individual images is extremely time-consuming and thus not proposed in VueBox™. VueBox™ provides an automatic motion correction tool to correct in-plane breathing-motion and probe movements by spatially realigning anatomical structures with respect to a user-selected reference image.
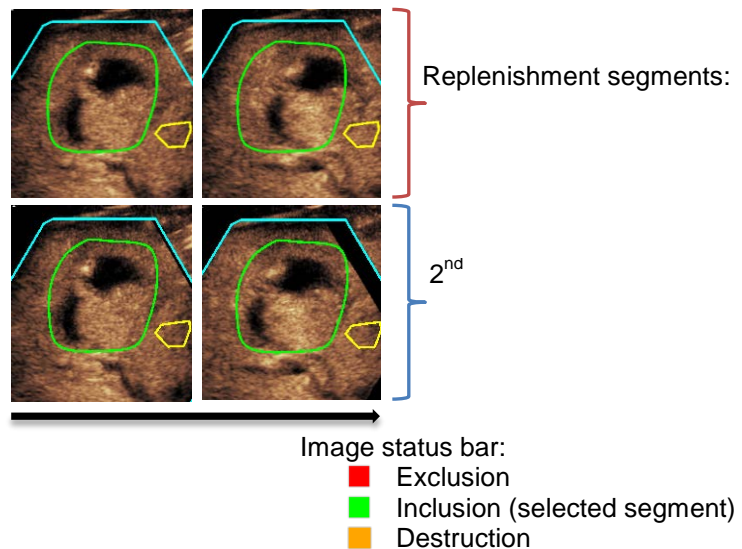

Figure 15 - Motion compensation example

4.11.2 WORKFLOW

To apply motion compensation:

1. Move the **Image slider** to choose a reference image

2. Click the 🔺 button in the main toolbar

3. Once motion compensation is applied, the native clip editor is replaced by a motion-corrected clip editor, where the clip resulting from the motion compensation process can be further edited. At this stage, colors of the **Image status bar** (■■) representing excluded and included image ranges are set to blue and violet, respectively.

4. Check the accuracy of the motion compensation by scrolling through the clip using the **Image slider** (motion compensation is considered a success if the images are spatially realigned and any residual motion is deemed acceptable)

5. If the motion compensation is unsuccessful, try one of the following:

6. Use the scissors and select another reference image and click the ![button] button again to re-apply **Motion compensation**.

7. Use the Clip editor to exclude any images thought to be degrading the result of motion compensation, such as out-of-plane movements, and then re-apply **Motion compensation**.

CAUTION	The user is responsible for checking the accuracy of the motion compensation before pursuing the clip analysis. In case of failure, incorrect results may occur.
CAUTION	The user should exclude any out-of-plane images using the clip editor before performing a motion compensation.
CAUTION	The user should avoid performing motion compensation when the clip does not contain any motion as this may degrade slightly the analysis results.

4.12 PERFUSION DATA PROCESSING

4.12.1 PRINCIPLE

The **Perfusion data processing (or perfusion quantification)** feature represents the core of the VueBox™ functionality and performs quantification in two steps. Video data are first converted into echo-power data, a quantity directly proportional to the instantaneous concentration of contrast agent concentration at each location in the field of view. This conversion process, called **linearization**, takes into account color or greyscale rendering, the dynamic range of log-compression used during the clip acquisition and compensates for contrast gain as well as mean Time-Gain Compensation (TGC) value within the contrast box, as long as pixel intensity is not truncated or saturated. The echo-power data as a function of time, or **Linearized signals,** are then processed to assess blood perfusion, using a curve-fitting approach with a parametric **Perfusion model**. The parameters derived from such a model are called **Perfusion parameters** and are useful for relative estimates of local perfusion (e.g. in terms of relative blood volume or relative blood flow). For instance, theses parameters may be particularly useful for assessing the efficacy of given therapeutic agents at different times. In the next sections, the concepts of linearized signal, perfusion modeling and parametric imaging are explained further.

4.12.2 LINEARIZED SIGNAL

A linearized (or echo-power) signal represents echo-power data as a function of time at either the pixel level or in a region of interest. The linearized signal results from a linearization process of the video data and is proportional to the local ultrasound agent concentration. As it is expressed in arbitrary units, only relative measurements are possible. For instance, let's consider echo-power amplitudes at a given instant in two ROI, one in a tumor and one in surrounding parenchyma. If the echo-power amplitude is twice as high in the tumor than in the parenchyma, this means that the concentration of ultrasound contrast agent in the lesion is close to double that present in the parenchyma. The same is true at the pixel level.

4.12.3 CONTRAST ARRIVAL DETECTION

At the beginning of the perfusion quantification process, when the **Bolus model** is selected, the arrival of contrast is detected within the ROIs. The time of contrast arrival is automatically determined as the instant when the echo-power amplitude rises above the background (wash-in phase), and is represented by a red line. As shown in the **Contrast arrival detection** dialog box, this instant remains a suggestion which may be modified by dragging the red cursor line. After pressing the OK button, all images preceding the

selected instant will be excluded from the analysis and the clip time origin will be updated accordingly. This instant should be shortly before contrast arrival in any region.
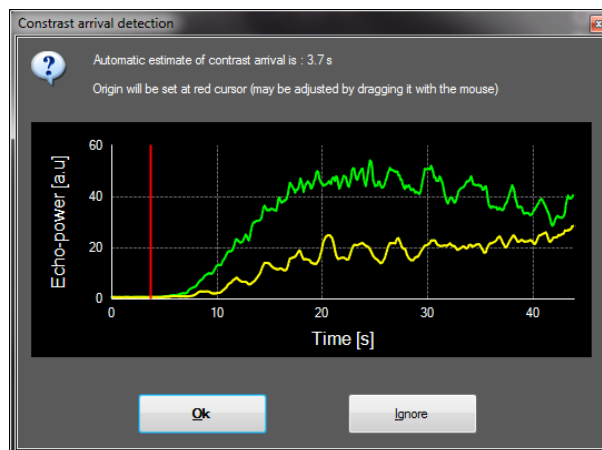

Figure 16 - Contrast arrival detection dialog box

| CAUTION	The automatic contrast arrival detection is to be considered as a suggestion only. The user should make sure to review this suggestion before pressing OK.

4.12.4 SKIP DUPLICATE IMAGES

Duplicate images (i.e. two or more consecutive similar images) may be found when a clip was exported from the ultrasound scanner at a frame rate higher than the acquisition frame rate (e.g. 25 Hz instead of 8 or 15 Hz). In this case, duplicate images are found in the clip. In order to insure a correct analysis as well as reliable time-related parameters, the duplicate images have to be discarded. To do so, when the clip is being loaded in memory, the software compares each frame with the previous one and discards any duplicate ones. This operation is automatic and requires no user intervention.

4.12.5 PERFUSION MODELS

Perfusion estimates in VueBox™ are made by a curve fitting process that adjusts the parameters of a mathematical model function to fit the experimental linearized signal in an optimal way. In the context of ultrasound contrast imaging, the mathematical function is called **Perfusion model** and **is chosen to** represent either bolus kinetics or replenishment kinetics following bubble destruction. Such models serve to estimate sets of **Perfusion parameters** for quantification purposes. These parameters can be divided into three categories: those representing an amplitude, a time and a combination of amplitude and time. Firstly, amplitude related parameters are expressed as echo-power, in a relative way (arbitrary units). Typical amplitude parameters are the peak enhancement in a bolus kinetics, or the plateau value in a replenishment kinetics, which may be associated with relative blood volume. Secondly, time related parameters are expressed in seconds and refer to the timing of the contrast-uptake kinetics. As an example of time parameter in a bolus, the rise time (RT) measures the time that a contrast echo signal takes to go from baseline level to peak enhancement, a quantity related to bloodflow velocity in a portion of tissue. Finally, amplitude and time parameters may be combined so as to produce quantities related to the blood flow (= blood volume / mean transit time) for replenishment kinetics or the wash-in rate (= peak enhancement / rise time) for bolus kinetics

For **Bolus** kinetics, VueBox™ provides the following parameters, illustrated in the figure hereafter:
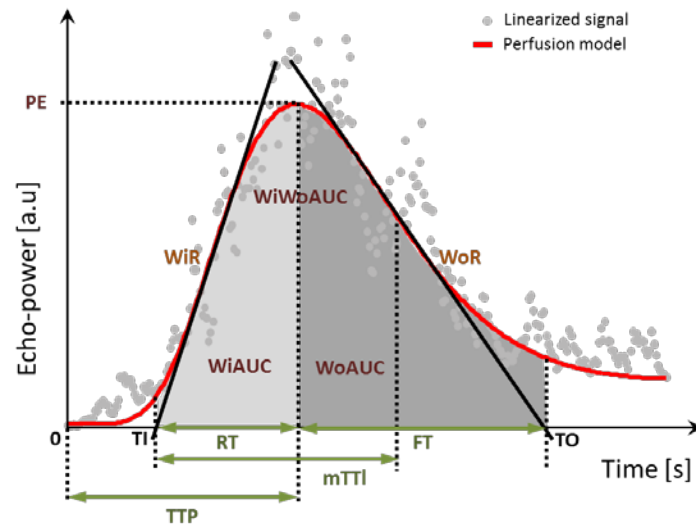
PE	Peak Enhancement	[a.u]
WiAUC	Wash-in Area Under the Curve (*AUC (TI:TTP)*)	[a.u]
RT	Rise Time (*TTP – TI*)	[s]
mTTl	mean Transit Time local (*mTT – TI*)	[s]
TTP	Time To Peak	[s]
WiR	Wash-in Rate (*maximum slope*)	[a.u]
WiPI	Wash-in Perfusion Index (*WiAUC / RT*)	[a.u]
WoAUC	Wash-out AUC (*AUC (TTP:TO)*)	[a.u]
WiWoAUC	Wash-in and Wash-out AUC (*WiAUC + WoAUC*)	[a.u]
FT	Fall Time (*TO – TTP*)	[s]
WoR	Wash-out Rate (*minimum slope*)	[a.u]
QOF	Quality Of Fit between the echo-power signal and *f(t)*	[%]

Where TI is the instant at which the maximum slope tangent intersects the x-axis (or offset value if present), and TO is the instant at which the minimum slope tangent intersects the x-axis (or offset value if present).

For **Replenishment** kinetics, VueBox™ provides the following parameters, illustrated in the figure hereafter:
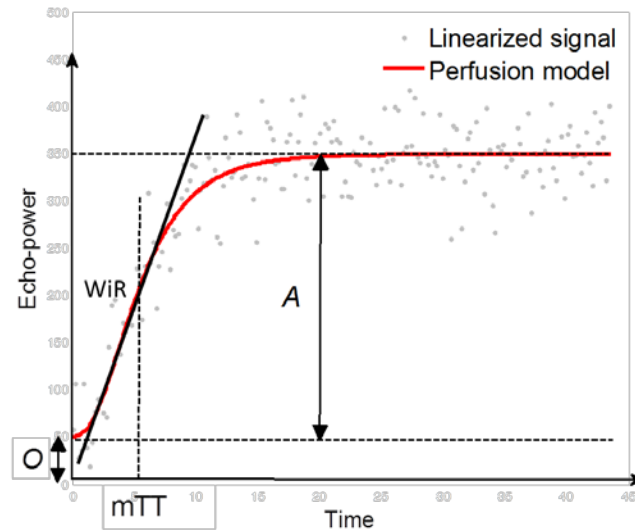
rBV	relative Blood Volume (A)	[a.u]
WiR	Wash-in Rate (*maximum slope*)	[a.u]
mTT	mean Transit Time	[s]
PI	Perfusion Index (rBV / mTT)	[a.u]
QOF	Quality Of Fit between the echo-power signal and *f(t)*	[%]

where [a.u] and [s] are arbitrary unit and second, respectively.

CAUTION	The user must ensure that the right perfusion model was selected before performing the perfusion data processing otherwise analysis results may be incorrect.
CAUTION	The user must ensure that perfusion kinetics are not affected by any vessel or artifact.
CAUTION	In the replenishment perfusion case, the user must ensure that the plateau value is reached before considering analysis results.

4.12.6 MEASUREMENT ACCEPTANCE CRITERIA

CAUTION	The accuracy of the calculated and measured parameters was verified and the following error should be taken into account:

Calculated & Measured parameters	Tolerance
$f(t)$	± 15%
WiAUC	± 15%
RT	± 15%
mTTI	± 15%
TTP	± 15%
WiR (Bolus)	± 15%
WiR (Replenishment)	± 15%
WiPI	± 15%
WoAUC	± 15%
WiWoAUC	± 15%
FT	± 15%
WoR	± 15%
rBV	± 15%
mTT	± 15%
rBF	± 15%
QOF	± 15%

4.12.7 PARAMETRIC IMAGING

VueBox™ can perform spatial rendering of any perfusion parameter, in the form of a color-rendered parametric map. This map synthesizes the time sequence of images into a single parametric image. Parametric imaging may enhance the information content of the contrast examination.

This technique may be particularly useful for making qualitative analyses in the course of a therapeutic monitoring performed on a given small-animal. In the example of using the destruction-replenishment technique, the efficacy of a substance inhibiting angiogenesis may be assessed by observing parametric images of relative blood volume (rBV) in a tumor, before and in the course of therapeutic treatment, reflecting the state of tumor perfusion resulting from the neovasculature. A second benefit of parametric images is the spatial visualization of tumor response to the treatment, or its effects on healthy surrounding parenchyma.

Note that in order to perform qualitative analyses on the basis of parametric images, certain recommendations must be made:

- the clips must represent the same anatomical cross-section from one exam to another;

- acquisition of contrast-ultrasound sequences must be performed using identical system settings (primarily transmit power, display settings, gain, TGC, dynamic range and post-processing);

- only parametric images of the same perfusion parameter can be compared.
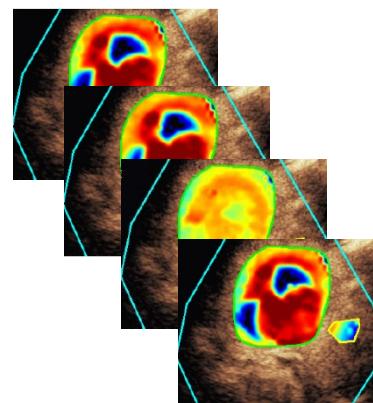
Figure 17 - Parametric images example

4.12.8 WORKFLOW

To perform **perfusion data processing**:

1. click the ⚙ button,

2. in the Bolus case only, accept, modify or ignore the automatic contrast arrival detection,

3. review the result in the result window.

4.13 RESULT WINDOW

4.13.1 INTERFACE ELEMENTS

Once the perfusion quantification processing is completed, VueBox™ switches from the clip editing mode to the result mode. The display-layout in the result mode comprises four quadrants (Q1-Q4). The four-quadrant representation combines all results within one display, namely

- Original clip (Q1);

- Processed clip or parametric image (Q2);

- Chart displaying time intensity curves (linearized and fitted signals) in each ROI (Q3);

- Table listing the computed parameter values in each ROI (Q4).

Q1 displays the original clip and Q2 a processed clip or a parametric image, depending on the selection in the Parametric image view menu. Each parametric image has its own colormap, which is rendered in the colorbar located in the lower-right corner of Q2. For amplitude perfusion parameters, the colormap ranges from blue to red, representing low to high amplitudes, respectively. As regards time parameters, the colormap is a reversed version of the colormap used for amplitude parameters.

In Q3, the colors of the traces match those of the ROI. When a ROI is moved or modified, its corresponding signals and computed values are automatically and immediately recalculated and displayed in Q4. The ROI labels may be changed by editing the data in the left column cells (Q4).

Figure 18 - User interface in result mode

Control	Name	Function
PE ▾	**Parametric image view**	allows the selection of parameter to be displayed.

Finally, relative measurements can be displayed in the **Q4** table by checking one of the ROI as a reference (in the Ref. column). Relative values are displayed in [%] and [dB] for amplitude-related parameters and in [%] for time-related parameters.
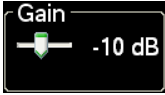
Ref.	Label	[a.u]	Ref [%]	Ref [dB]
☐	Whole Kidney	79.4	266.52	4.26
☑	Medulla	29.8	100.00	0.00
☐	Cortex	91.9	308.34	4.89

WiR - Wash-in Rate

Figure 19 - Quantitative parameter table

4.13.2 ADJUSTABLE DISPLAY PRESETS

Above Q2, sliders are provided to adjust the gain and the dynamic range (log-compression) of the processed image displayed in Q2, in a way similar to a standard ultrasound scanner.

Slider / control	Name	Function
Preset / Load Store / Auto	**Preset**	stores, restores and auto scales display preset (gain and dynamic range of all parametric images).
Gain / -10 dB	**Gain**	controls the gain applied to the current processed image (Q2). (-60dB to +60dB)
Dynamic / 20 dB	**Dynamic range**	controls the dynamic range of log-compressed applied to the current processed image (Q2). (0dB to +60dB)
PE	**Parametric image view**	allows the selection of parameter to be displayed.

4.13.3 AUTO-SCALED DISPLAY PRESETS

Display presets (i.e. gain & dynamic range) for each parametric image are automatically adjusted once the perfusion quantification processing is completed using the built-in auto-scaling function. However, this adjustment is to be seen as a suggestion and may need further manual fine tuning. Below, an example of a parametric image prior and after auto-scaling is applied:
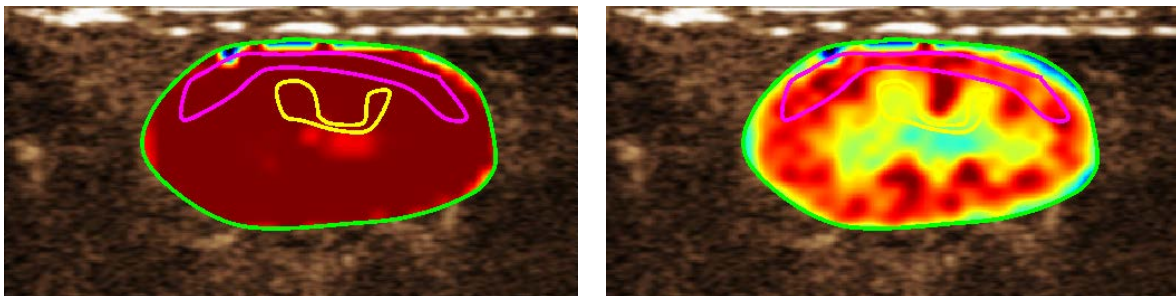
Figure 20 : Parametric image prior and after display presets auto-scaling

4.13.4 STORING / LOADING DISPLAY PRESET

Display preset can be stored into a dedicated library and loaded at a later time point. To store the preset for all parametric images:

1. Click the [Store] button in the preset toolbar

2. Set a name or accept the one generated by default and press the OK button
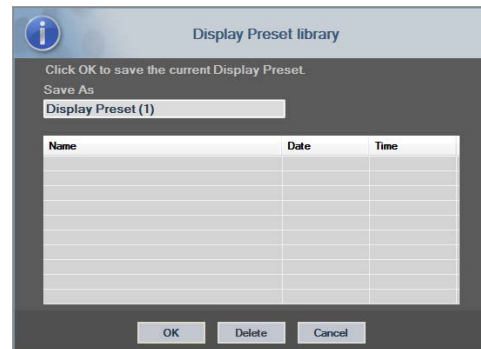
Figure 21 : Storing display presets into library

To load display presets from the library:

1. Click the [Load] button in the preset toolbar

2. Select the item in the list and press the OK button
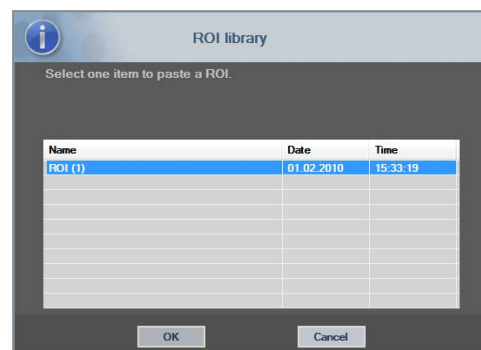
Figure 22 : Loading display presets from library

4.13.5 ANALYSIS RESULT DATABASE

Each clip associates a result database in which the whole context of each analysis result can be stored. This enables restoration of the result at a later time by selecting the corresponding clip (previously analyzed) in the start page of VueBox™.
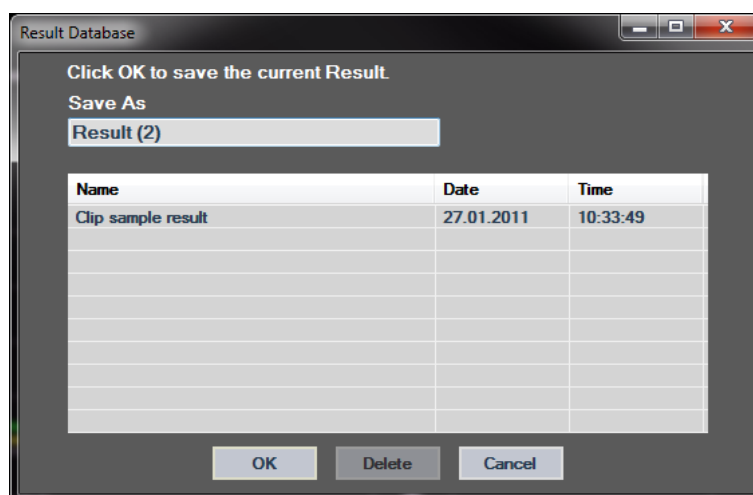
Figure 23 - Result database dialog box

The result database is automatically displayed when saving a result or loading a clip for which previous analyses exist.

To save the current result:

1. Click the 🖫 button in the main toolbar
2. Under **Save as**, type the result name
3. Click the OK button.

To overwrite a result:

1. Click the 🖫 button in the main toolbar
2. Select a result in the list
3. Click the OK button.

To remove a result:

1. Click the 🖫 button in the main toolbar
2. Select a result in the list
3. Click the DELETE button.

4.14 EXPORT ANALYSIS DATA

4.14.1 PRINCIPLE

VueBox™ offers the possibility to export numerical, image and clip data to a user defined directory. For example, the numerical data are particularly useful for carrying out further analyses in a spreadsheet program. The image data are a set of screenshot containing both the regions of interest and parametric images. These images allow to perform qualitative comparisons between successive studies in the course of a therapeutic follow-up on a given patient. As a second example of qualitative analysis, the processed clips may provide a better assessment of the contrast-uptake over time. Still images or processed clips may also be useful for documentation or presentation purposes. Finally, an analysis report summarizing qualitative (i.e. still images) and quantitative (i.e. numerical data) information can be generated.

> **CAUTION**
> The user should always review the consistency of the exported results (i.e. images, numerical data, etc.).

4.14.2 INTERFACE ELEMENTS

The figure below shows a screenshot of the interface elements in export mode.
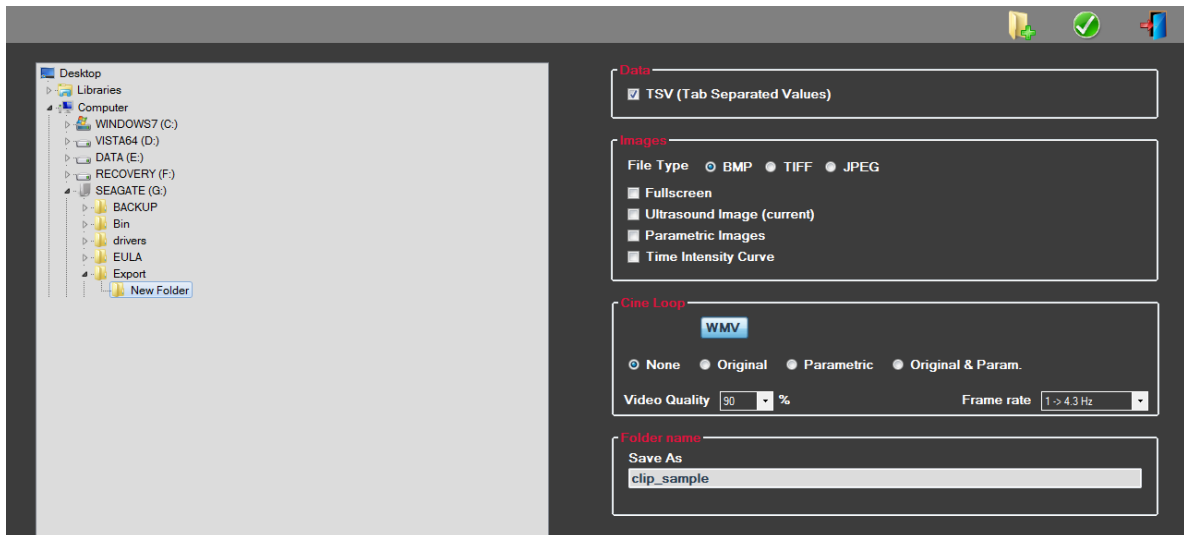
Figure 24: User interface in export mode

Name	Function
Data	
TSV	exports a tabulated text file (XLS extension) including time intensity curves and perfusion estimates.
Images	
Full screen	exports a screenshot of the front panel (All 4 quadrants).
Ultrasound image (current)	exports the current ultrasound image with its ROIs (Quadrant 1).
Parametric images	exports all parametric images (Quadrant 2).
Time Intensity Curve	exports an image of the chart (Quadrant 3).
Clip	
Original	exports the original clip.
Parametric	exports the processed clip.
Native & Parametric	exports both the original and processed clips in a side-by-side view mode.
Video Quality	quality of the exported clip (in percent).
Frame rate	video frame rate of the exported clip (sub-sample factor).
Analysis Report	
Generate report	generates the analysis report and display the report generator dialog box.

Folder name

Save as   indicates the folder name where the result files will be saved.

4.14.3 WORKFLOW

To export data:

1. Click the ➡ button
2. Select a target directory in the left panel
3. Under **Data**, **Images** and **Clip** in the right panel, choose the type of results to export
4. Under **Option,** type a folder result name
5. Click the OK button in the main toolbar to export the results in the specified folder result name.

4.14.4 ANALYSIS REPORT

The analysis report summarizes both qualitative (i.e. still images) and quantitative (i.e. numerical data) information in a single, customizable, easy-to-read report. The report is divided into two parts: a header and a body.

The header contains the following information:

Hospital-related information	Patient- and exam-related information
• Hospital name • Department name • Professor name • Phone & fax numbers	• Patient ID • Patient name • Physician name • Exam date • Patient birth date • Contrast agent used • Indication for exam

Hospital-related information are editable and are saved from one session to another. Patient- and exam-related information are automatically extracted from the DICOM dataset header, if present, and may be edited if not present.

The body of the report contains the following information:

- an image of the analyzed clip including ROI,
- a chart representing the average signal within available ROI,
- the perfusion model selected,
- a parametric image and quantitative values, in absolute and relative terms, for each perfusion parameters,
- an editable comment field.

Perfusion parameters can be dynamically added or removed from the analysis report, thus reducing or increasing the number of pages. The user selection is saved from one session to another.

Figure 25 - Analysis report, header modification interface
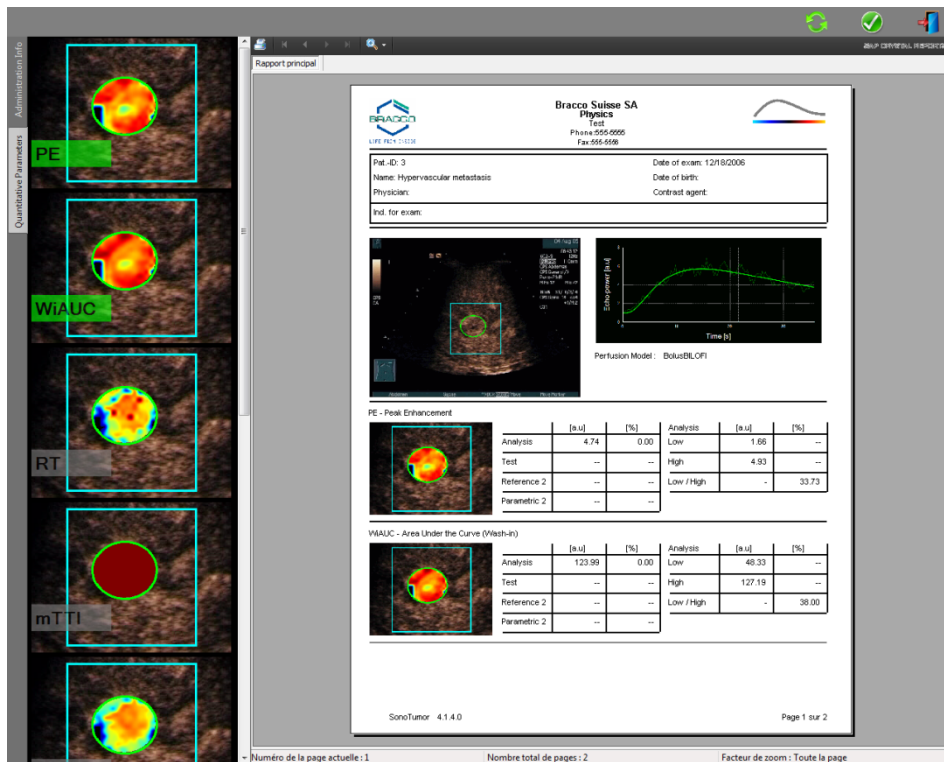
Figure 26 - Analysis report, quantitative parameter selection

Finally, the report is automatically saved into a finalized PDF file.

4.15 IMPORT AND EXPORT USER SETTINGS

User settings such as ROI, result and display preset databases, can be exported into a single file (with 1 ".sharp" extension) and reimported at a later time. This function may be useful for sharing results between users or when transferring the software to another computer.

To export user settings:

1. Click the button from the side toolbar

2. Select export location

3. Click the button.

To import user settings:

1. Click the button from the side toolbar

2. Choose Copy from... option by clicking the button

3. Select user settings file location and choose user settings file from the list

4. Click the button.

4.16 ABOUT SCREEN

Information about the software such as version number and software manufacturer can be found in the about screen.

To display the about screen:

1. Click the button in the main toolbar.

5 QUICK GUIDE

This section describes the two typical workflows to perform an analysis with VueBox™.

5.1 BOLUS ANALYSIS

1. Open a Bolus clip in **VueBox™.**
2. Adjust the linearization settings in the **Video Settings** panel.
3. Define the images to be excluded using the **Clip editor**.
4. Draw ROI successively as desired.
5. Move the **Image slider** to choose a reference image for motion compensation.
6. Click the button to launch the **motion compensation**.
7. Review the motion compensated clip using the **Image slider.**
8. If the **Motion compensation** is unsuccessful, try one of the following:
9. Select another reference image and click the button again to re-apply **Motion compensation.**
10. Click the button to return to the **Clip editor** and exclude any images thought to be degrading the result of motion correction, such as out of plane movements, and then re-apply **Motion compensation.**
11. Once satisfied with motion compensation, click the button to launch the **Perfusion Data Processing**.
12. Accept or select another instant in the **Contrast arrival detection** dialog box.
13. If needed, adjust the **Gain** and **Dynamic range** sliders for each parametric image or check **Apply preset** to apply the user preferences.
14. Click the button to export data
15. Click the button to store the context.

5.2 REPLENISHMENT ANALYSIS

1. Open a Replenishment clip in **VueBox™.**
2. Wait for the **flash detection** to be completed. If necessary, set flash images manually by using the F keyboard key.
3. If multiple segments are present, select the replenishment segment to be analyzed with arrow buttons ( ).
4. Draw multiple ROI successively as desired.
5. Move the **Image slider** to choose a reference image for motion correction.
6. Click the button.
7. Review the motion compensated clip using the **Image slider.**
8. If the **Motion compensation** is unsuccessful, try one of the following:
9. Select another reference image and click the button again to re-apply **Motion compensation.**

10. Click the ✂ button to return to the **Clip editor** and exclude any images thought to be degrading the result of motion correction, such as out of plane movements, and then re-apply **Motion compensation.**

11. Once satisfied with motion compensation, click the ⚙ button to launch the **Perfusion Data Processing**.

12. If needed, adjust the **Gain** and **Dynamic range** sliders for each parametric image or check **Apply preset** to apply the user preferences.

13. Click the ⮕ button to export data.

14. Click the 💾 button to store the context.

6 INDEX

REF   VueBox™ v4.2

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 Software Applications

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