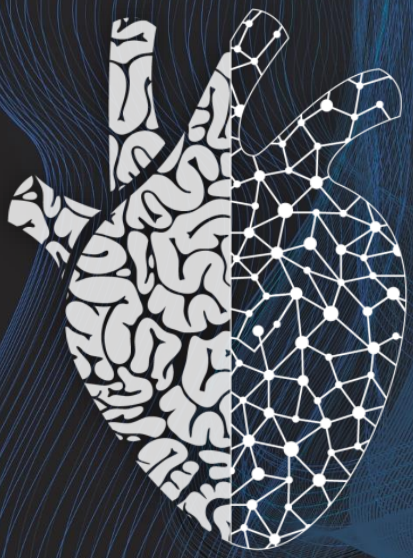
N.I.C.E.

USER MANUAL

VERSION 1.5



X|SPLINE

IMPROVING CRT.
BEYOND PREDICTION.

INFORMATION ON THE MANUFACTURER:

XSpline S.p.A.

Via Ressel 2/F, 39100 – Bolzano, Italy

Tel: +39 0471 200372 - Fax: +39 0471 539338

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WARNING

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1.5	19/03/2025	N.I.C.E. User Manual update Intended patient population (2.3)	XSpline	XSpline

TABLE OF CONTENTS

1 INTRODUCTION

1.1. NAME OF THE DEVICE

This user manual refers to the device named N.I.C.E. (below called “the device” or “the system”), composed by a user interface to create and navigate a patient study, and a simulator, below called “VizTool”, which can be accessed through the user interface.

N.I.C.E. has two possible configurations:

- stand-alone system: the software runs on a Personal Computer, Windows compatible, and certificated medical PC;
- web-based system: the software system is in the cloud, and it is accessible over a network connection using HTTPS.

This manual covers the use of both configurations.

Version of the device: 1.0.0

1.2. NAME OF THE MANUFACTURER AND HEADQUARTERS

N.I.C.E. is manufactured by:

XSpline S.p.A., via Ressel 2F, 39100, Bolzano – Bozen (Italy).

Tel. +39-0471-200372 Fax +39-0471-539338
E-mail: info@xspline.com Website: www.xspline.com
XSpline specializes in the development, production and marketing of innovative solutions in the field of software as a medical device.

1.3. GENERAL FEATURES OF THE DEVICE

1) The device DOES NOT contain:

- *Medicinal products, human blood products or plasma*
- *Tissues or cells of human origin or their derivatives*

- *Tissues or cells of animal origin or their derivatives, as referred to in Regulation (EU) 722/2012.*

2) The device DOES NOT imply specific conditions of preservation or handling.

3) The device IS NOT provided in a sterile state.

4) The device IS NOT disposable.

5) The device DOES NOT consist of substances or substance aggregates intended to be introduced in the human body through an orifice or applied on the skin, or that are absorbed by the human body or locally dispersed within it.

The manual contains information for the safe handling of the device with the components listed.

- *Always read the instructions for use before using N.I.C.E.*
- *The manual is part of the product and should always be at hand.*
- *Illustrations show functions by way of example and may differ from the actual look of N.I.C.E.*

These instructions have been designed to help you gain an understanding of the operation and possible applications of our device. For optimal utilization of all functions, we recommend that you thoroughly study this manual prior to beginning operation.

2 BEFORE STARTING

2.1 INTENDED PURPOSE

The medical device N.I.C.E. is intended for:

“N.I.C.E. is intended for the acquisition, analysis, and display of cardiac electrophysiological data and mapping to assist physicians for Cardiac Resynchronization Therapy (CRT).”

2.2 INTENDED USERS

The device is intended to be used by a cardiologist with experience in cardiac electrophysiology and CRT and with a strong professional background (at least 5 years in the related field) and who attends training in system/device usage, with no interaction with the patient, through self-application according to the instructions for use.

2.3 INTENDED PATIENT POPULATION

N.I.C.E. is specifically designed for adult individuals over 18 years of age who are undergoing the electrophysiology (EP) –procedure of Cardiac Resynchronization Therapy (CRT). The target population for N.I.C.E. includes patients who require cardiac electrophysiological data acquisition, analysis and display of cardiac electrophysiological data.

2.4 INDICATIONS FOR USE

N.I.C.E. is indicated for pre-procedural and post-procedural evaluation by cardiologists and cardiac electrophysiologists in patients undergoing the cardiac electrophysiological procedure of Cardiac Resynchronization Therapy (CRT). It facilitates visualization of cardiac structures through 3D reconstruction from DICOM CT tomography data, generates electrical activation maps, aids in assisting cardiac electrophysiological procedures.

2.5 CONTRAINDICATIONS

The use of the N.I.C.E. software does not have any known contraindications.

2.6 FUNCTIONAL DESCRIPTION

N.I.C.E. is a Medical Device for medical professionals, specifically cardiologists and cardiac electrophysiologists.

N.I.C.E. is a medical software package used to collect, archive, and display clinical information and health documentation referring to electrophysiologists procedures destined patients.

N.I.C.E. is a class B medical device, a software package which processes medical images, cardiac electroanatomical information, and patient data.

N.I.C.E. has two possible configurations:

- stand-alone system: the software runs on a Personal Computer, Windows compatible, and certificated medical PC;
- web-based system: the software system is in the cloud, and it is accessible over a network connection using HTTPS.

N.I.C.E. has no parts or materials that will be in contact with tissues or body fluids.

N.I.C.E., given DICOM CT images of torso and heart, and given a digital standard 12-lead electrocardiogram, provides visual 3D information about the heart anatomy and the morphology of coronary veins through an automatic segmentation procedure of cardiac structures. Additionally, it generates an epi- and endocardial electrical activation map, which provides an opportunity to visualize the latest activation zone and reach the target zone for successful Cardiac Resynchronization Therapy (CRT) procedures.

N.I.C.E. approach is to provide all the relevant information about the patients' heart and coronary sinus anatomy and the propagation of the electric stimulus, using routine and non-invasive clinical data (computer tomography and 12-channel ECG) as input. In this way, the electrophysiologist will be able to make informed decisions on the ideal LV lead placement for each patient ahead of any kind of conventional invasive intervention, or even plan alternative implantation beforehand.

N.I.C.E. gives the possibility to the physician to make a pre-procedural evaluation, with no interaction with the patient and is designed to be used by qualified medical professionals and the users are solely responsible for making all final patient management decisions.

2.7 DEVICE CLAIMED AND INTENDED CLINICAL BENEFITS

The device offers several clinical benefits that contribute to improved patient care and treatment outcomes:

1. Epi-Endocardial Activation Mapping: The device enables detailed mapping of patients scheduled for cardiac resynchronization therapy (CRT). This information is crucial for accurately diagnosing and selecting appropriate treatment approaches for these patients, leading to more effective management of their conditions.

2. Individual Patient Anatomy Identification: By utilizing the device, healthcare professionals can accurately visualize the entire cardiac structures of an individual patient. This capability aids in the identification of any existing pathologies, allowing for early detection and appropriate intervention, ultimately improving patient outcomes.

3. Visualization of Coronary Veins: The device facilitates the visualization of coronary veins, aiding healthcare professionals in identifying the optimal location for left ventricular (LV) lead implantation during or before cardiac resynchronization therapy (CRT). This ensures precise lead placement, enhancing the effectiveness of CRT and improving patient response to treatment.

4. Improvement of cardiac resynchronization therapy outcome: Through its advanced features, the device aims to reduce non-responders to specific treatments. This valuable information allows cardiologists to tailor treatment strategies and interventions, potentially increasing the response rate among patients.

By harnessing these clinical benefits, healthcare providers can make more informed decisions, individualize treatment plans, and enhance the overall quality of care for patients with cardiac conditions.

2.8 DATA SECURITY

2.6.1 AVAILABILITY

The system is based on a regularly backed-up server platform which guarantees data availability.

2.6.2 CONFIDENTIALITY

Passwords and sensitive data are protected and not easily accessible. Data separation is guaranteed, and the system complies with the current privacy legislation.

2.6.3 INTEGRITY

The database features all the referential integrity functions existing in all the versions of Oracle Databases.

2.7 SAFETY ISSUES

N.I.C.E. has no direct interactions with the patient or with the clinical protocols, minimizing the risk for the patient.

However, a fault in the device can consist in:

- *no information for the clinician, which leads to time wasted for the clinician and to follow usual clinical protocols;*
- *wrong information, which can lead to false non-responders or longer CRT: for this reason, the output of the device must be always interpreted by an experienced cardiologist;*
- *personal data violation, e.g. if patient data is erroneously inserted in the device. Please make sure no personal patient data is inserted in the device.*

See also section 2.9 “Warnings and precautions”.

2.7.1 TRAINING

The use of the device is restricted to authorized hospital staff duly trained for its use.

XSpline team will support the training process during the first usage of the device and will support any request for help.

2.7.2 CYBERSECURITY

The responsibility for medical device security is shared among stakeholders, such as healthcare facilities, providers, and manufacturer of the device. Neglecting cybersecurity measures could lead to compromised device performance, data loss (whether medical or personal), threats to the availability or integrity of data, and potential exposure of other interconnected devices or networks to security risks.

However, any information potentially added to the device during the usage is visible only to the institute's staff. The device does not handle any personal data of the patient. The tracking of the patient is sole responsibility of the user. The tracking shall be made using the Internal Code chosen by the user.

Please, contact XSpline upon detection of a cybersecurity vulnerability or incident.

Implement a stringent policy governing the services accessible via the Internet on the computer where N.I.C.E. is installed. Utilize a firewall to enforce this policy and prevent unauthorized access. Additionally, refrain from connecting the computer to public networks to minimize security risks.

2.8 SOFTWARE AND HARDWARE SPECIFICATIONS

2.8.1 HARDWARE SPECIFICATIONS

N.I.C.E. has two possible configurations:

- stand-alone system: the software runs on a Personal Computer, Windows compatible, and certificated medical PC;
- web-based system: the software system is in the cloud, and it is accessible over a network connection using HTTPS.

Stand-alone system: there are no hardware specifications, as the hardware is provided, and the software is installed by the manufacturer.

For storage and disposal, please refer to the user manual of the manufacturer of the certified medical PC provided. For disposal, also follow WEEE specifications.

Web based system: Minimum display resolution: HD ready – 1280x720 (recommended Full HD – 1920x1080), display and browser zoom set to 100%.

2.8.2 SOFTWARE SPECIFICATIONS

- *Compatible OS: Windows 10*
- *Compatible browser: Mozilla Firefox 72.x or more recent, Chrome 80.x or more recent, Edge 90.x or more recent*

2.9 WARNINGS AND PRECAUTIONS

⚠ *Warning! The information given by N.I.C.E. is purely intended to improve pre-interventional preparation. The final decision on how to intervene on the patient is exclusive responsibility of the surgeon, based on ECG and Echo parameters according to current guidelines.*

⚠ *Warning! Only XSpline S.p.A. qualified personnel are authorized to perform configuration, installation, maintenance, and repairs.*

⚠ *Warning! N.I.C.E. will not function without an active internet connection. Ensure you have a stable and active internet connection before using the device.*

⚠ *Warning! Make sure all persons tasked with operating the device have read and understand the safety information and operating instructions.*

⚠ *Warning! N.I.C.E. must be used in conformity with hospital information management procedures.*

⚠ *Warning! The device does not handle any personal data of the patient. The tracking of the patient is sole responsibility of the user. The tracking shall be made using the Internal Code chosen by the user.*

⚠ *Warning! The Internal code of the patient chosen by the user shall not contain any data of the patient, including name, surname, date of birth or any other sensitive data that can lead to losing the patient's confidentiality (i.e. health card code).*

⚠ *Warning! Make sure to load and insert the actual data and images coherently for the patient. The correctness of the data inserted and uploaded is unique responsibility of the user.*

⚠ *Warning! Strictly follow CT Protocol provided together with this manual. Any CT image that does not respect the protocol standards*

might not provide high quality segmentations and simulation results might be unreliable.

Only authorized staff may use the product. The User Manual is exhaustive. Any use different from what is described in this User Manual is strictly prohibited as it may lead to unexpected results.

The screenshots must be taken purely as examples.

Disclaimer: no patient personal data is detained in the device, in the database nor anywhere else.

2.9.1 HOW TO REQUEST MORE COPIES

To request more copies of this manual and the paper format, please get in touch with XSpline S.p.A, contact details given below. The time period for the supply of paper format is 7 days.

If you wish to consult an electronic version of this manual, please open the cloud website (https://nice.xspline.com/login-nice) and click “Open Manual” button for the latest version or open the link https://nice.xspline.com/public/documents/documentation$user-manual and select the version of the device of which you wish to consult the manual.

2.9.2 HOW TO REPORT A SERIOUS INCIDENT

Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient established.

2.9.3 HOW TO REPORT A PROBLEM

If you encounter any problem, malfunctions, serious incidents/adverse events, or any other issue on the device or about this manual, please let us know by getting in touch directly with XSpline SpA, contact details given below.

Any feedback or suggestions for improvement is also welcome.

2.9.4 CONTACT DETAILS

E-mail: info@xspline.com Website: www.xspline.com

Tel. +39-0471-200372 Fax +39-0471-539338

XSpline S.p.A., via Ressel 2F, 39100, Bolzano – Bozen (Italy).

3 ICONS LEGEND

	Manufacturer
	Medical Device
	Read the electronic instructions for use
	CE marking with notified body number
	Unique Device Identifier
	Catalogue number

4 ACCESS TO THE SYSTEM

N.I.C.E. can be accessed through two different methods, according to the chosen configuration of the system:

- For stand-alone system, double click on N.I.C.E. icon from the desktop provided to you.

- For the web system, from the following URL: https://nice.xspline.com/

The login page is shown in Figure 1. For Admin Users, also use this login page to access your functionalities: please refer to paragraph “14. Admin User page” to view the part of the manual referring to these pages.

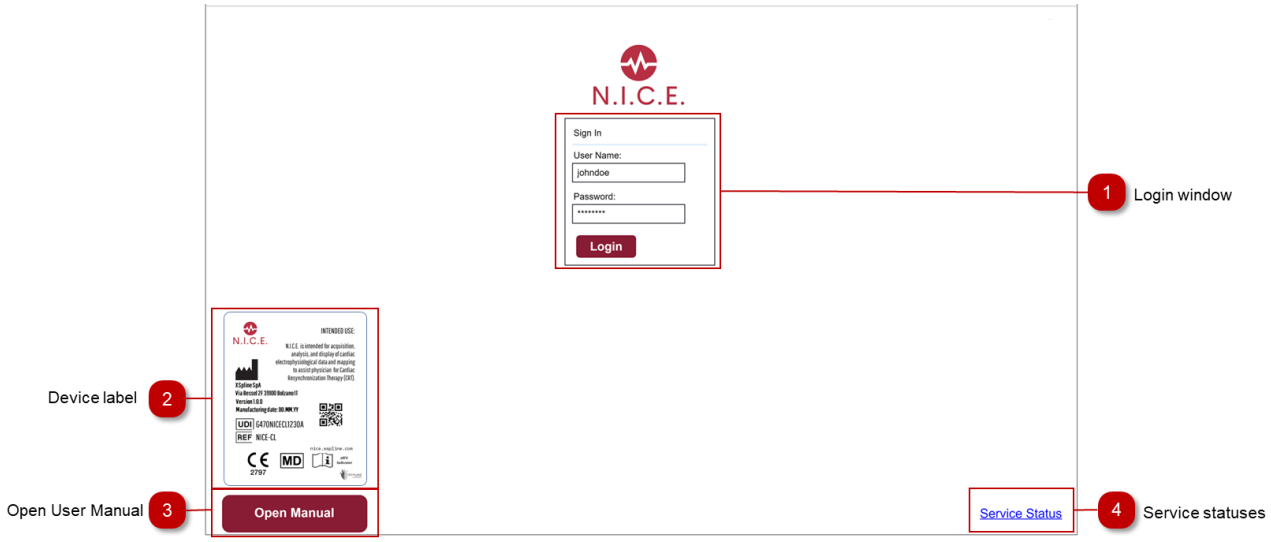


Figure 1 N.I.C.E. Login page

1	LOGIN WINDOW	To access the system, enter your credentials in the login window.
2	DEVICE LABEL	Label of the N.I.C.E. device, with UDI, intended use, details of the manufacturer and logos.
3	OPEN USER MANUAL	Use this button to access the electronic version of this manual. No credentials required.
4	SERVICE STATUS	Use this link to open the “System Status” page.

When accessing the system, user credentials are required (Figure 2)

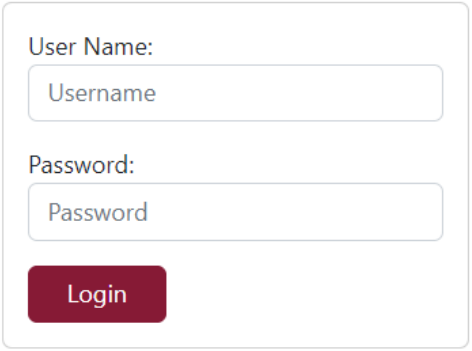


Figure 2 N.I.C.E. login window

After inserting the credentials (Username and password), the user can access the system.

In any of the following pages, the user can find the following user menu on the top right of the page (Figure 3):

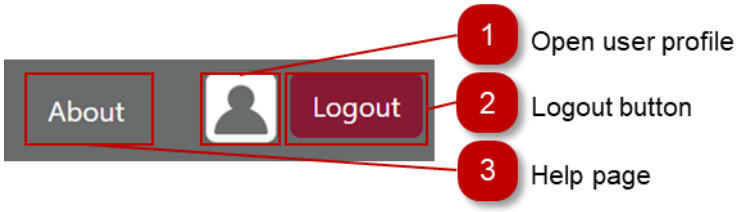


Figure 3 User Menu

1	OPEN USER PROFILE	Use this button to access the user profile page and change password.
2	LOGOUT BUTTON	Use this button to safely logout from current user.
3	HELP PAGE	Use this button to access the help page, where the electronic version of this manual is also available.

When selecting the “Open user profile” icon, the user is redirected to the page with user details and the function to change password:

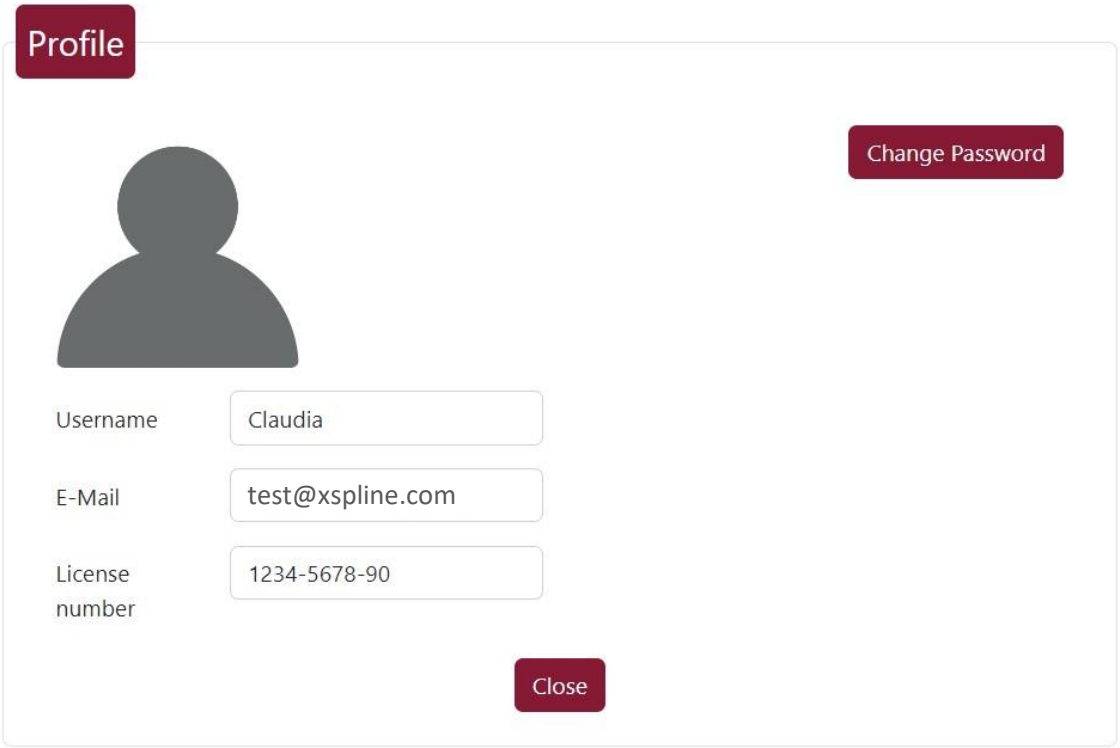


Figure 4 User profile and change password

After filling out the fields with the old password and the new password and saving the changes, the user receives a confirmation of the password change and, from that moment onwards, the user can enter the system using the new password.

In addition, the system informs the user of the expiration date of their password (as marked in red in Figure 3). Passwords expire after 180 days and the system pre-alerts the user 7 days before expiration.

The password entered by the user must comply with the following requirements:

- *Be at least 8 characters*
- *Contain at least one digit*
- *Contain at least an uppercase character*
- *Contain at least a lowercase character*
- *Contain at least a special character*

After 60 minutes of no activity, the session expires, and the user is required to enter username and password to access again.

5 ABOUT

By clicking the button “About”, the About page opens in a new tab (Figure 5).

Figure 5 Help page

This page contains the version of the device, a description of the device, manufacturer information and the button to open the manual.

6 SYSTEM STATUS PAGE

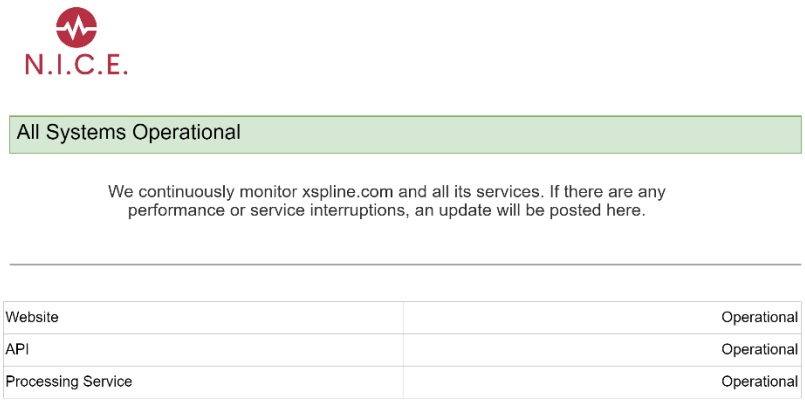


Figure 6 Service status page

This page contains the status of various systems: website, API, and Processing Service.

If N.I.C.E. is presenting any issue, you can check this page. However, for any issue, please get in touch with XSpline directly.

7 PATIENT LIBRARY

After inserting the credentials (Username and password), the user can access the application main page:

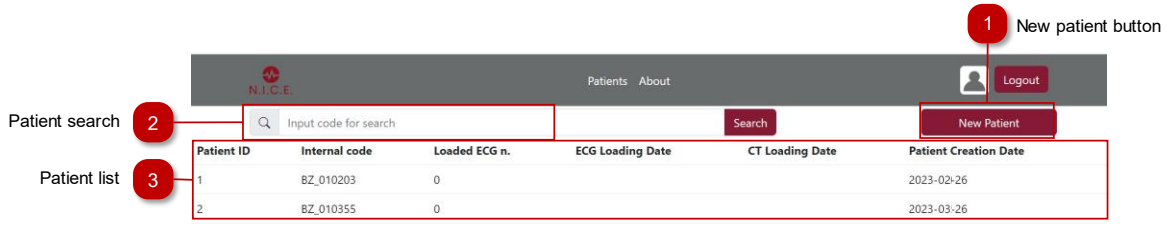


Figure 7 Patient library page

1	NEW PATIENT BUTTON	Use this button to create a new patient case.
2	PATIENT SEARCH	Use this button to search a patient by "Internal Code" or parts of it.
3	PATIENT LIST	This table shows all the patients created in the center relative to the connected user.

To create a new patient, simply input the "Internal Code" that you wish to use in order to trace the patient and the relative results to your hospital archives.

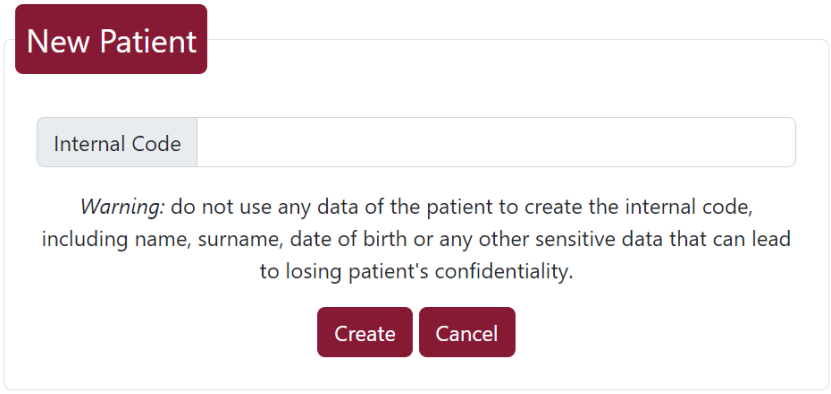


Figure 8 New Patient creation window

Warning: the Internal code of the patient chosen by the user shall not contain any data of the patient, including name, surname, date of birth or any other sensitive data that can lead to losing the patient's confidentiality (i.e. health card code).

The system will also automatically create a Patient ID for any trouble-shooting purposes, and a correspondent entry will be saved in the library.

After creating the patient, the patient page will open with the two following tabs:

- *General information*
- *Study.*

8 PATIENT GENERAL INFORMATION

The Patient Page opens automatically on the "General information" tab when a patient is created or opened through the library. This tab shows the identification details, processing status and a space for comments, as shown in Figure 9:

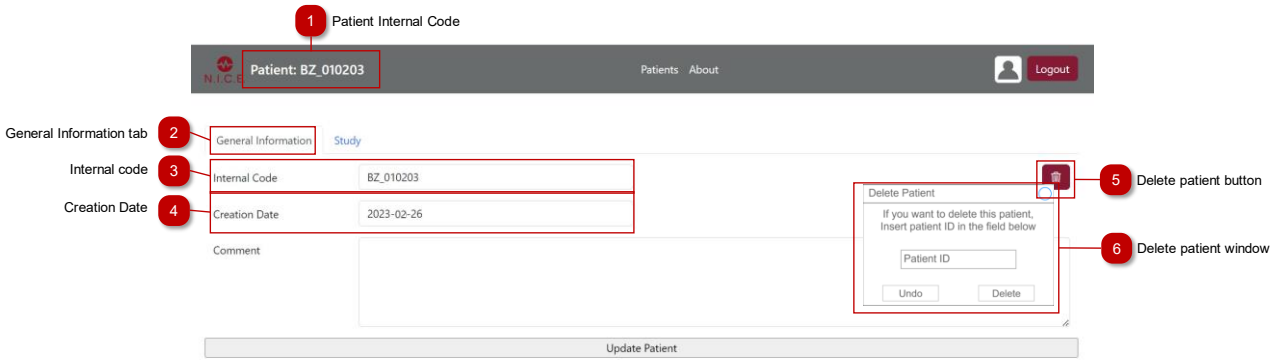


Figure 9 Patient general information page

1	PATIENT INTERNAL CODE	Patient Internal Code, to trace the patient and the relative results to your hospital archives.
2	GENERAL INFORMATION TAB	When a patient is created, this tab opens by default.
3	INTERNAL CODE	Patient Internal Code for hospital tracking purposes, inserted during patient creation.
4	CREATION DATE	Information on the date of creation of the patient in the database.
5	DELETE PATIENT BUTTON	Use this button to delete the patient from the library: this will open a confirmation window.
6	DELETE PATIENT WINDOW	Confirmation window: to proceed with patient deletion, insert patient ID (this is a safety precaution).

9 PATIENT STUDY

The second Patient page tab is “Study". In this tab it is possible to upload patient data such as CT and ECG studies, delete the data, and visualize the results of N.I.C.E. simulations through the VizTool by clicking the corresponding button.

When the Study is empty (Figure 10), it is possible to upload the CT Study of the patient by clicking the button “Add CT”.

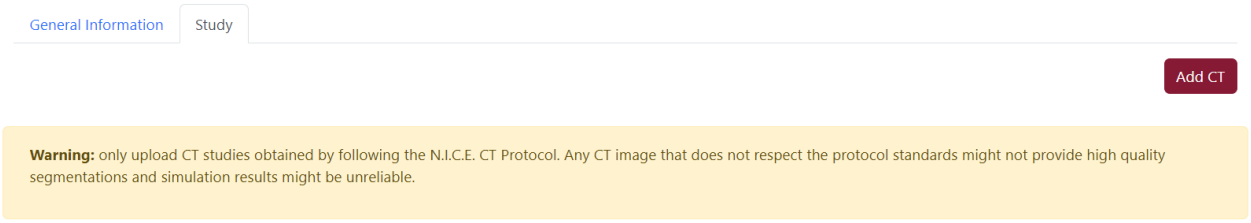


Figure 10 Study tab of the Patient page, before any data is uploaded.

A drag-and-drop dialog appears, and during the upload, and a status bar shows the uploading process (Error! Reference source not found.)

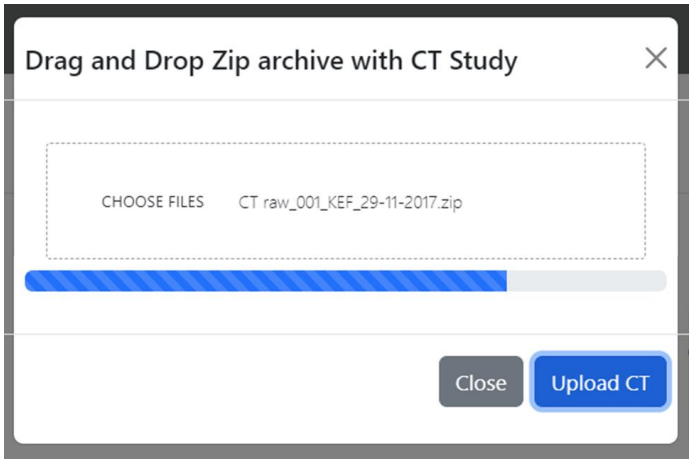


Figure 11 Drag-and-drop dialog.

After the CT is uploaded, the "Add ECG" button appears. Error! Reference source not found. shows the Study page when the CT and ECG files have been uploaded.

Warning: only upload CT studies obtained by following the N.I.C.E. CT protocol. Any CT image that does not respect the protocol standards might not provide high quality segmentations and simulation results might be unreliable.

Warning: only upload ECG files in one of the following formats: DICOM, PhysioNet, Sierra, XML. Any ECG file of a different format is not suitable for Activation Map generation and the automatic processing will not be initiated.

The successful upload operations automatically start the segmentation process, the Activation Map generation, and the Target Point calculation, which can be viewed through the VizTool (described in the following chapter) through the buttons at the bottom of the cards.

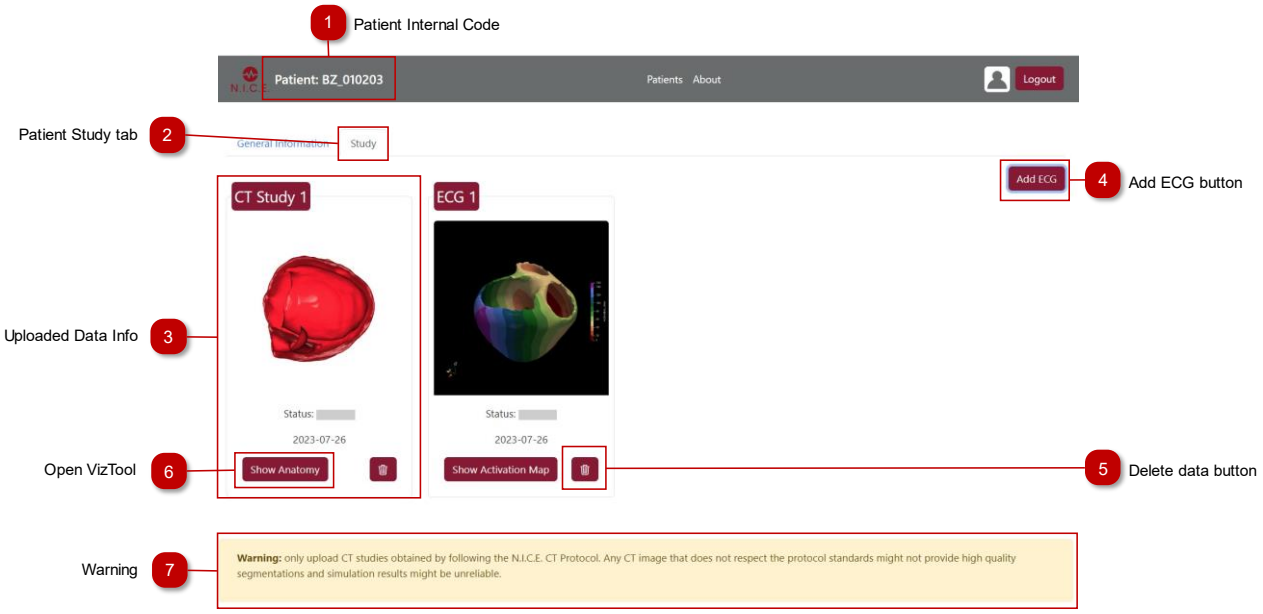


Figure 12 Patient study page

1	PATIENT INTERNAL CODE	Patient Internal Code, to trace the patient and the relative results to your hospital archives.
2	PATIENT STUDY TAB	Use this page to upload CT/ECG data or to visualize the simulation results.
3	UPLOADED DATA INFO	This window shows information about the corresponding study: the data file name and the date of upload. Here also the status of the elaboration is shown.
4	ADD DATA BUTTON	Use this button to upload a CT study (only one allowed) or an ECG of the same patient.
5	DELETE DATA BUTTON	Use this button to delete the selected patient data from the library: this will open a confirmation window.
6	OPEN VIZTOOL	Use this button to open the VizTool with the corresponding data: on the CT Study it will show only the geometry, on the ECG study it will show the geometry and the

		corresponding activation map. This button is only active if data has been loaded and the data elaboration is finished.
7	WARNING	Warning about CT study upload: please read carefully before uploading

N.I.C.E. VIZTOOL

N.I.C.E. VizTool can be opened from the patient page in the N.I.C.E. main interface: please read the paragraph “Patient Study”.

10 INTRODUCTION

N.I.C.E. VizTool is a software tool that allows 3D visualization of segmented cardiac districts: coronary veins and ventricles (Figure 13).

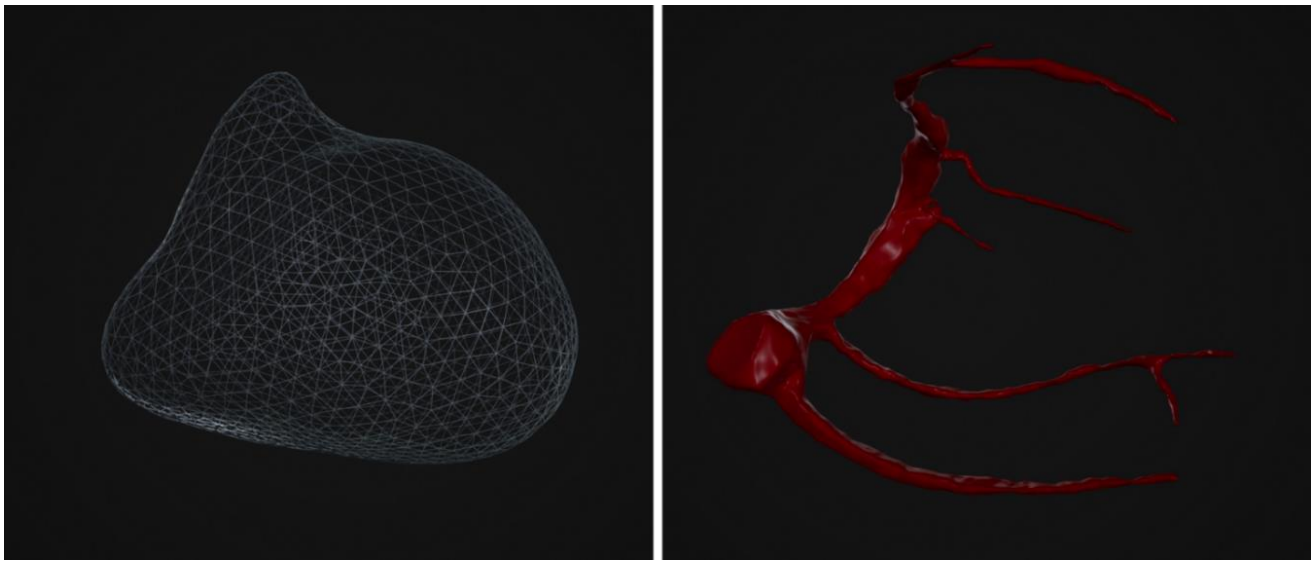


Figure 13 Segmented Ventricles (left) and coronary veins (right

This includes the output of color maps to visualize information about the diameters of the coronary veins and the electrical functions of the ventricles, measuring functions and tracing of a center line in the veins.

A software 3D simulation also allows to follow the catheter on its way between defined entrance and end points, with different perspectives, external to the vein and internal (Figure 14).

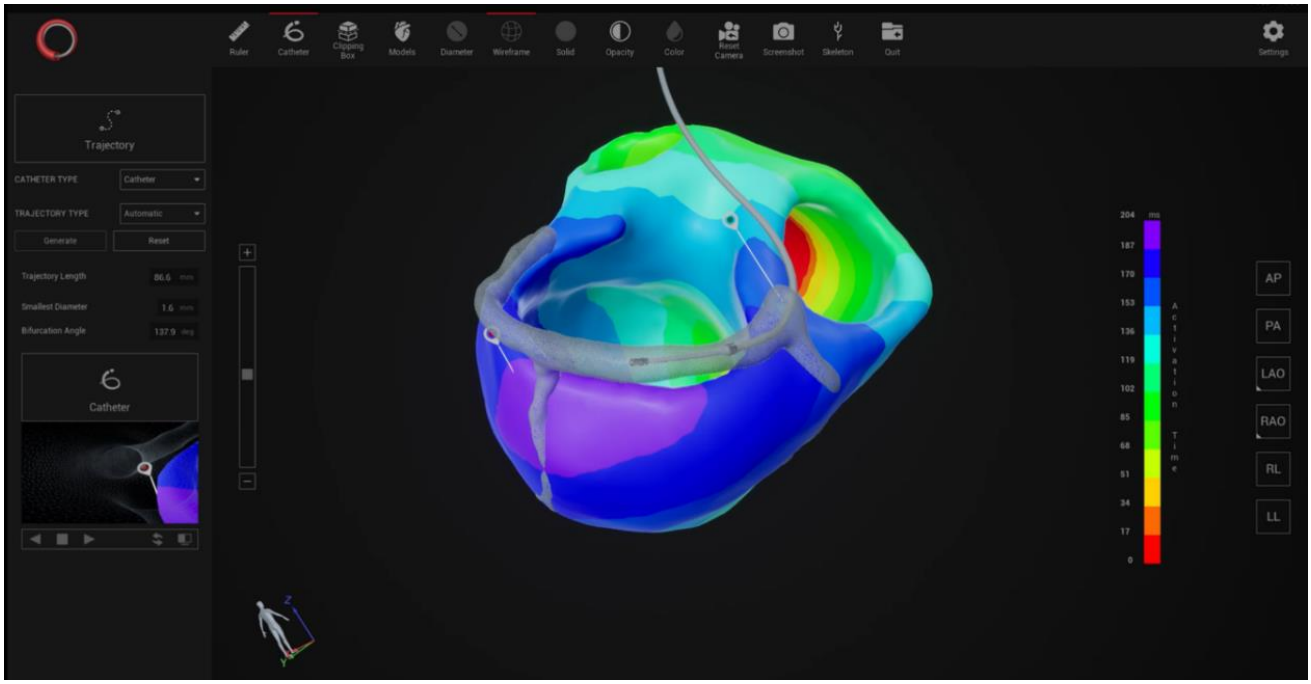


Figure 14 Simulation of catheter insertion

10.1 MAIN VIEW

N.I.C.E. VizTool can be opened through N.I.C.E. interface, in the "Patient Study" page (see Paragraph 9). The main view is the following:

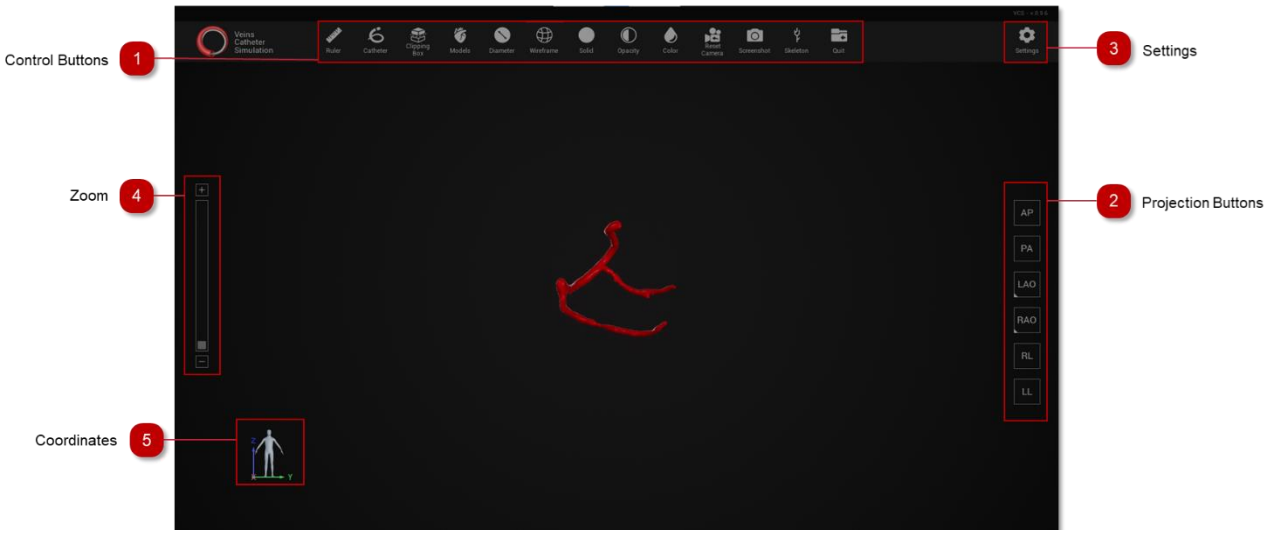


Figure 15 Main View of vVizTool

1	CONTROL BUTTONS	The control buttons enable/disable the visualization properties and functions

		included in the program. These properties and functions are the main components of the program, designed to assist the operator in their decision-making process. See “Control Buttons” paragraph.
2	PROJECTION BUTTONS	The Projection Buttons rotate the view to a position correspondent to the standard heart projections. See “Projection Buttons” paragraph.
3	SETTINGS	The Settings button toggles the Settings menu, where the user can customize the properties of the program. See “Settings” paragraph.
4	ZOOM	The Zoom bar adjusts the zoom level of the camera. Default setting is the lowest (bottom position).
5	COORDINATES	Coordinates Reference animation indicates the orientation of the (rotated) 3D image of the heart, relative to the body.

10.2 COMMANDS TO INTERACT WITH THE 3D OBJECTS

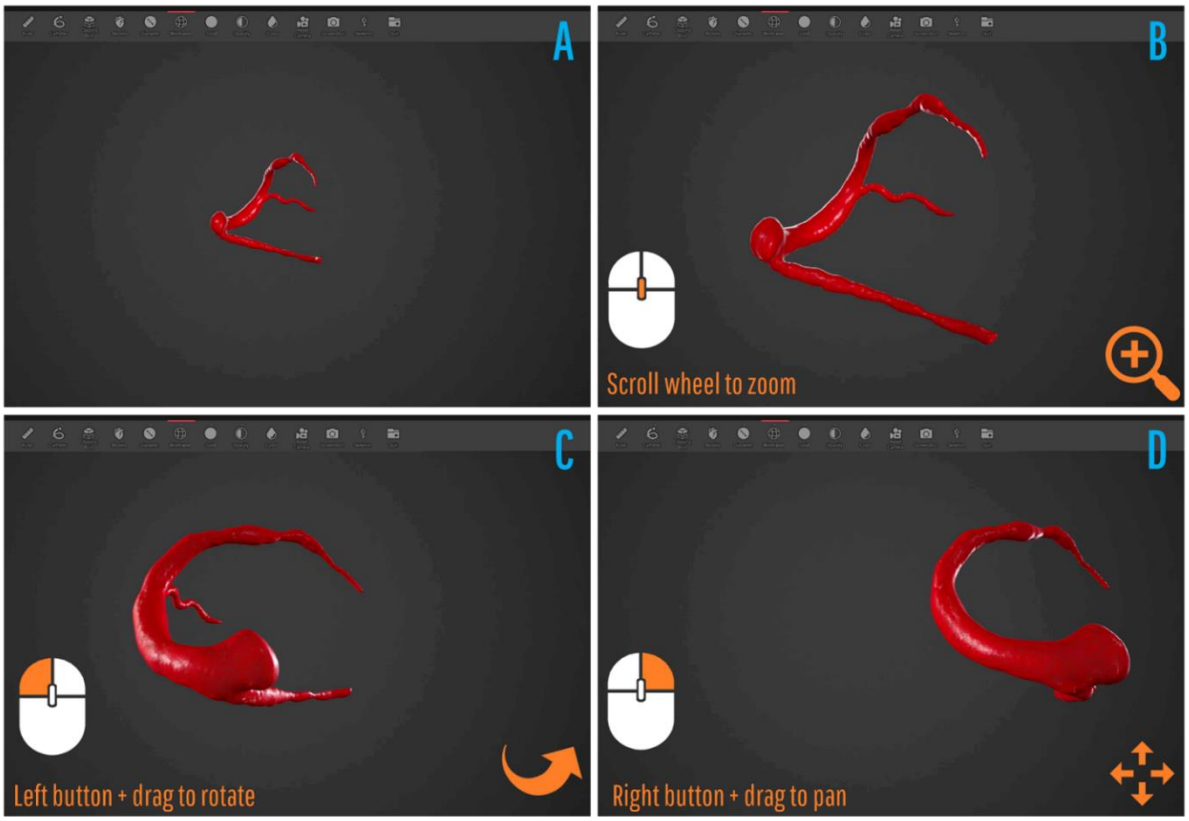


Figure 16 Commands to interact with the object

The user can interact with the visualized 3D object (Error! Reference source not found..A) using the mouse:

- *zoom using the mouse wheel (Figure 16.B)*
- *rotate by left click & drag (Figure 16.C)*
- *pan by right click & drag (Figure 16.D).*

11 CONTROL BUTTONS

The Control Buttons (Figure 17) can be found at the top of the screen (Error! Reference source not found.). These represent all the main functions of the software.

Figure 17 Control Buttons at the top of the screen

11.1 RULER

Ruler is a function to measure distances between two points of the veins, directly on the 3D image.

The Euclidean or Geodesic distance path between two end points (A and B), chosen by clicking with the left mouse button right on the image, will be visualized on the vein segmentation (Figure 18). Their calculated distance (Distance output) will be visible on the ruler menu.

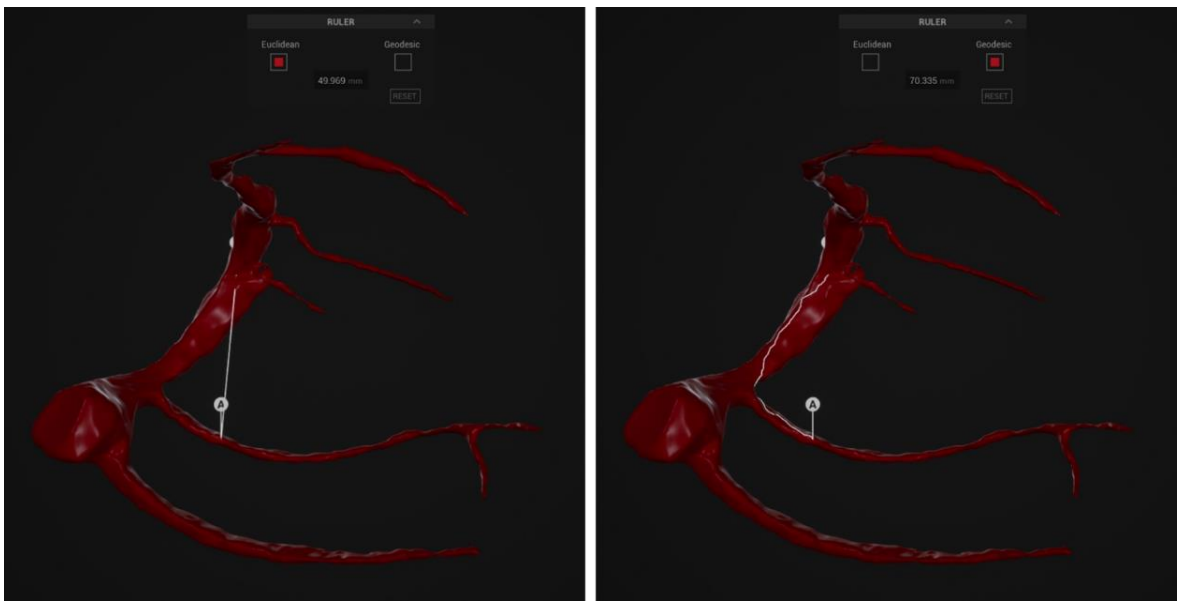


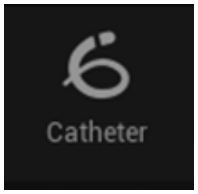
Figure 18 Visualization of Euclidean (left) and Geodesic (right) distance between point A and point

The Ruler button toggles the Ruler menu (Figure 19). The Ruler menu provides tools to pick either Euclidean or Geodesic distance and to read the relative measure.

Figure 19 Ruler menu

1	MINIMIZE MENU	The Minimize button toggles the minimization of the menu.
2	DISTANCE SELECTION	Pick the type of distance to calculate between two selected points (A to B) using the relevant tick box: Euclidean (straight line) or Geodesic (shortest path on the vessel wall surface). After choosing, you may pick points A and B on the 3D image
3	DISTANCE OUTPUT	In the distance output box, the numerical value of the measure (Euclidean or Geodesic) is displayed.
4	RESET BUTTON	The reset button sets the ruler options to their default values.

11.2 CATHETER



Catheter is a function that simulates the delivery of the catheter for the implantation of the pacemaker lead.

One of the main functions of the software is the Catheter simulation: pick an entrance point and an endpoint, read the trajectory stats, pick a catheter type, and watch the animation of the catheter moving through the

trajectory (Figure 20), from two different points of view (external and internal). To visualize the path more clearly, it is suggested to use this function with wireframe rendering.

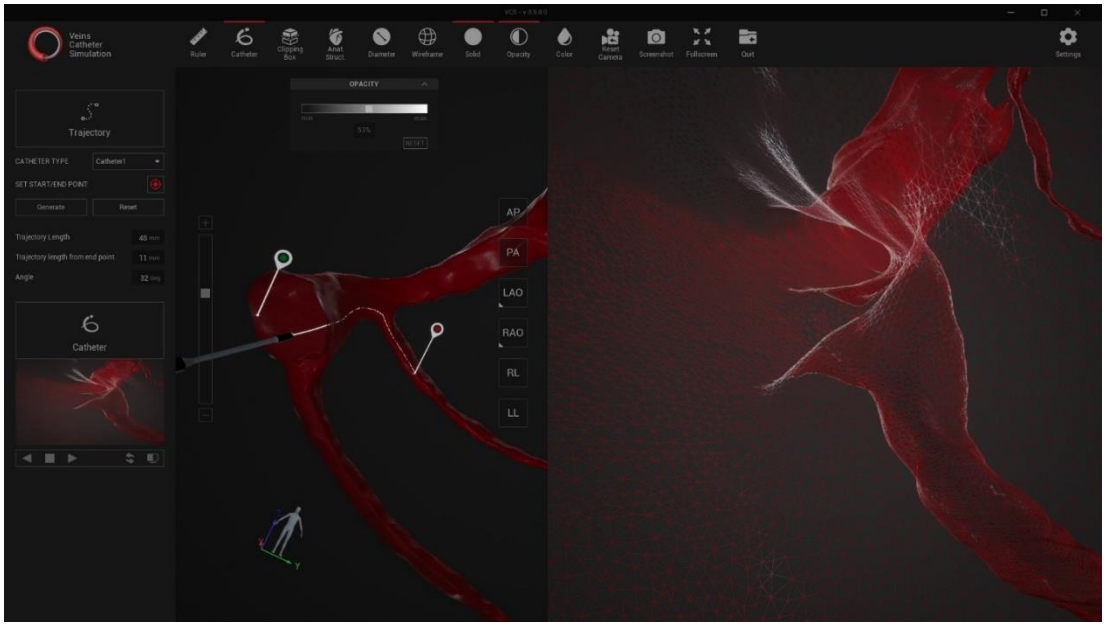


Figure 20 Catheter insertion simulation

The Catheter button toggles the catheter menu, which allows to customize the catheter delivery simulation (Figure 21).

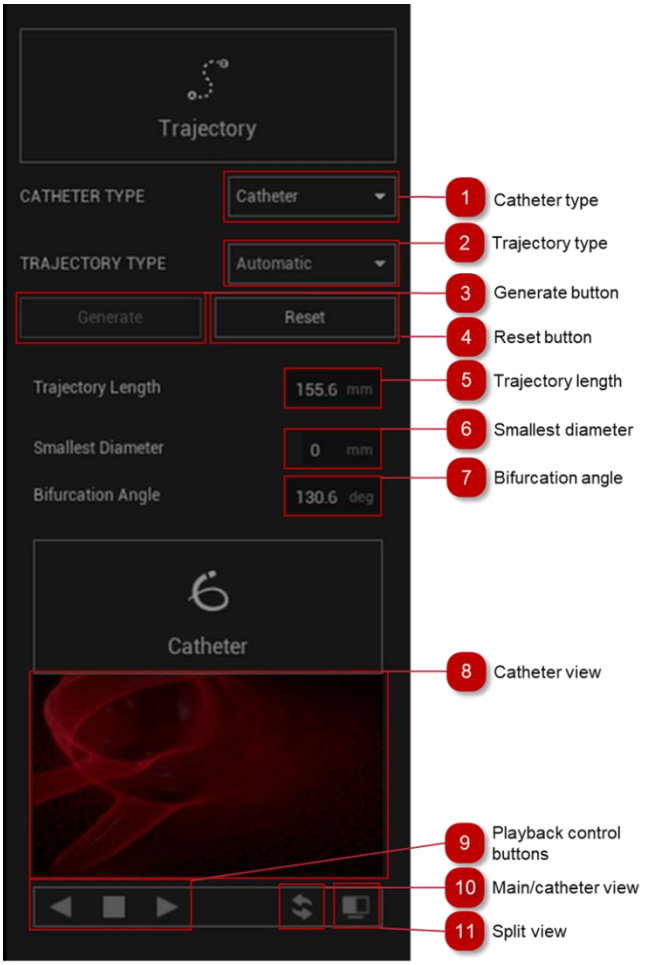


Figure 21 Catheter menu

1	CATHETER TYPE	Choose the type of catheter to visualize in the simulation through a drop-down menu.
2	TRAJECTORY TYPE	Choose between "Automatic", where start and end point are automatically calculated, and "Manual" to be able to pick the points. A crosshair icon will appear, click to pick the entrance point first and the end point after.
3	GENERATE BUTTON	Start the simulation of the catheter delivery. This operation might take some time.
4	RESET BUTTON	Reset the variables of catheter delivery simulation to their default values.
5	TRAJECTORY LENGTH	Length of the calculated trajectory between start and end points.

6	SMALLEST DIAMETER	Smallest coronary diameter in the calculated trajectory between start and end points.
7	BIFURCATION ANGLE	Bifurcation angle in the calculated trajectory between start and end points.
8	CATHETER VIEW	Catheter view shows the point of view from the catheter tip. During the catheter introduction simulation, it moves inside the vessel according to the catheter movement.
9	PLAYBACK CONTROL BUTTONS	The playback control buttons start, stop, and reverse the playback of the catheter introduction simulation.
10	MAIN/CATHETER VIEW	The main/catheter view button toggles the main view between the standard external view and the catheter tip view.
11	SPLIT VIEW	The split view button splits the main view into two sections, arranged side by side: one portraying the view from the standard camera, one from the catheter tip.

11.3 CLIPPING BOX

Clipping Box is a function that allows to visualize sections of the 3D segmented vein and ventricle.

The Clipping Box button toggles the clipping Box function, which creates a bounding box delimiting the area containing the 3D image (Figure 22).

Moving the clipping planes along the 3D axes of the image will cut out the parts of image that remain outside the clipping box, showing the resulting section of the vein/ventricle.

It is possible to hold shift + left mouse button to select a specific plane and drag it in the desired direction.

Figure 22 The Clipping box function creates a bounding box around the 3D image

Additionally, the Clipping Box button toggles the Clipping Box menu, which can be used to select additional options to move the clipping planes:

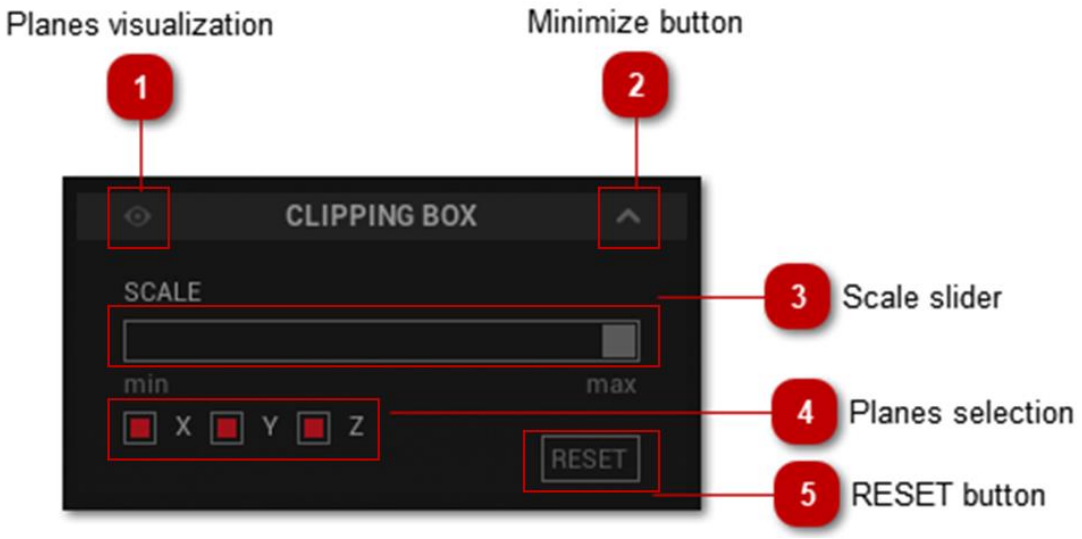
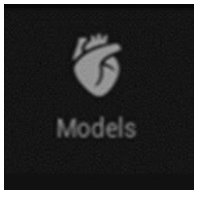


Figure 23 Clipping Box menu

1	PLANES VISUALIZATION	Toggles the visualization of the clipping planes.
2	MINIMIZE BUTTON	The Minimize button toggles the minimization of the menu.
3	SCALE SLIDER	Adjust the position of the clipping planes along the selected axis, symmetrically.
4	PLANES SELECTION	Choose along which axes the clipping planes can move.
5	RESET BUTTON	The reset button sets the clipping planes position to the default value.

11.4 MODELS



This function allows to select the preferred anatomical visualization.

The Models button toggles the visualization of: ventricles and veins (Vein + Ventricle), veins only (Vein), segmented ventricles only (Ventricle). The option “Activation map” can be selected only when either Vein + Ventricle or Ventricle are also selected (Figure 24).

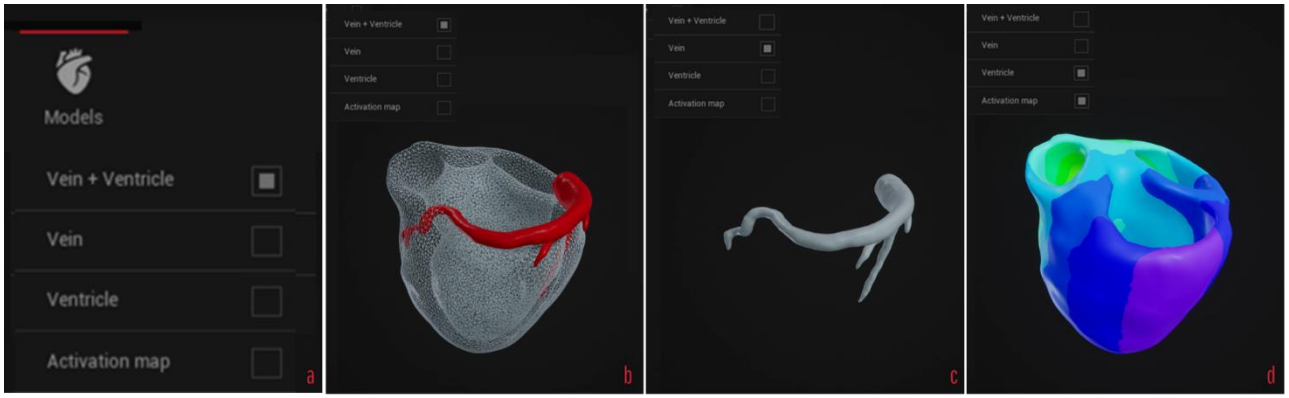
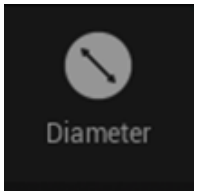


Figure 24 Models menu (a) and visualizations: Vein + Ventricle (b), Vein (c), Ventricle & Activation map (d).

11.5 DIAMETER



This button shows a colormap of the veins based on the diameter of the vessel. Each color shows the diameter of the vein in millimeters at the selected level (Figure 25).

To activate this function, please select Wireframe first.

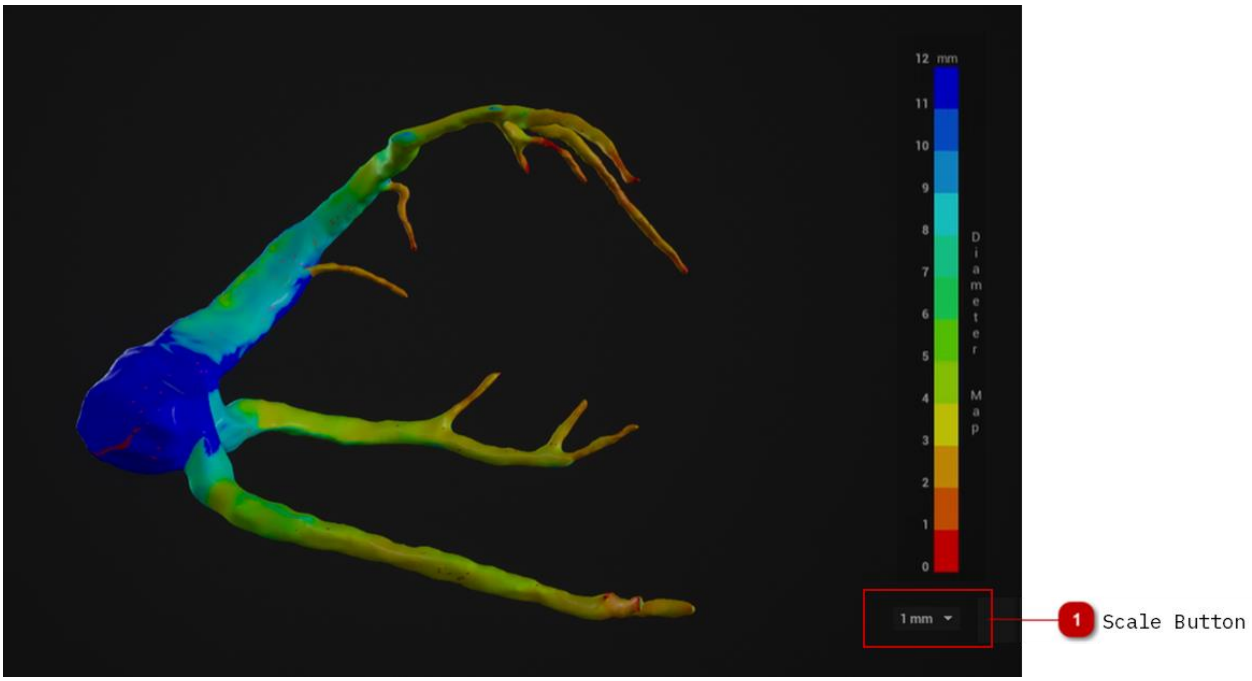


Figure 25 Scale button (on the bottom right) adjusts the distance color scale

1	SCALE BUTTON	This button allows to adjust the color scale by assigning a specified number of

		millimeters to each color (1, 2, 3, 4 or 5 mm).

11.6 RENDERING BUTTONS

WIREFRAME

The Wireframe button enables the wireframe rendering of the segmented vein and ventricle (Figure 26, left).

SOLID

The Solid button enables the solid rendering of the segmented vein and ventricle (Figure 26Error! Reference source not found., right).

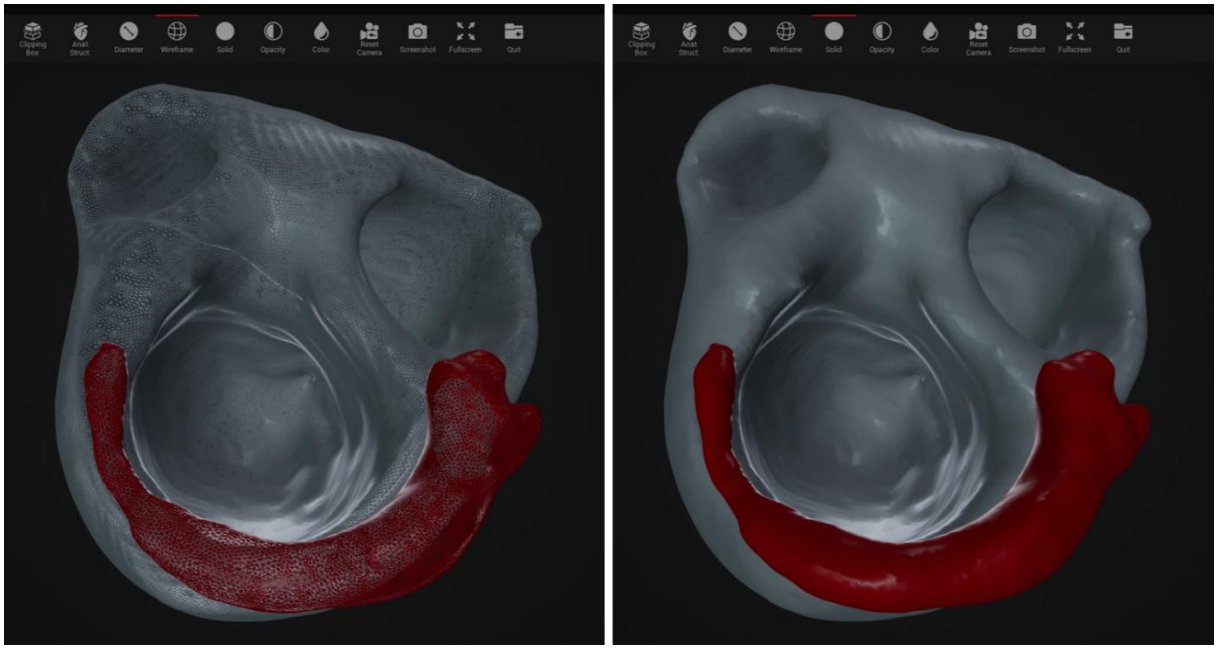
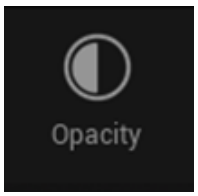


Figure 26 Segmented vein and ventricle with wireframe (left) and solid (right) rendering

11.7 OPACITY



The Opacity button toggles the Opacity menu, which sets the opacity level for the segmented vein or ventricle (Error! Reference source not found.).

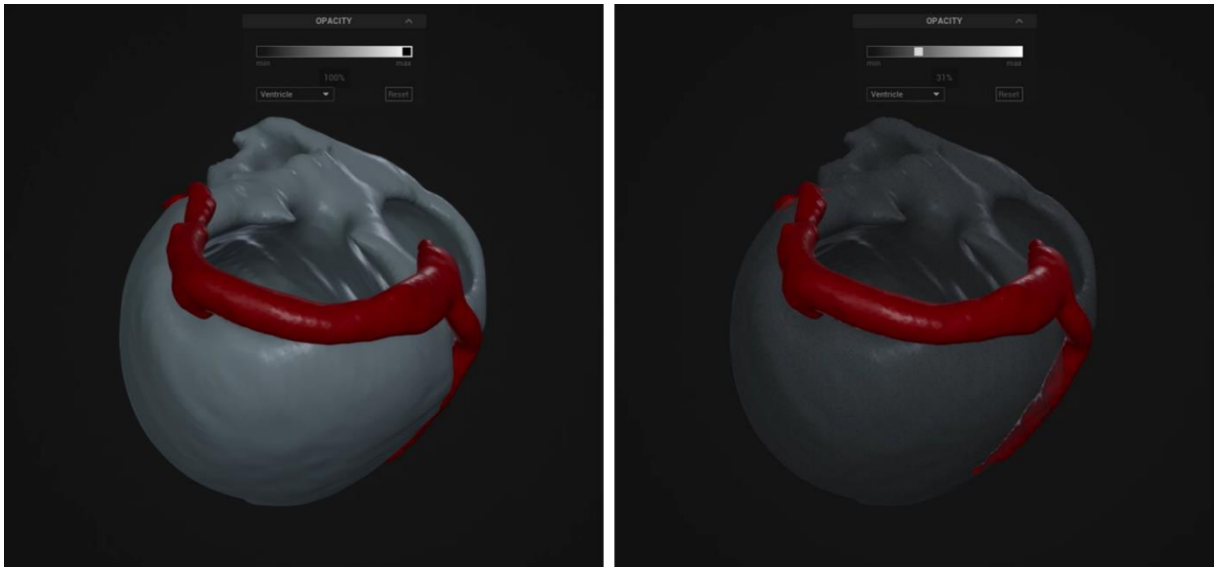


Figure 27 Changing the opacity of the ventricle from 100% (left) to 30% (right)

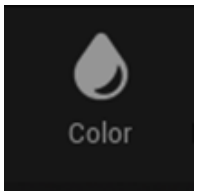
Through the Opacity menu the opacity setting can be modified for each anatomical structure (Figure 28)

Figure 28 Opacity Menu

1	MINIMIZE MENU	The Minimize button toggles the minimization of the menu.
2	OPACITY SLIDER	The opacity slider adjusts the opacity of the segmented vein or ventricle.
3	RESET BUTTON	The RESET button sets the opacity level to the default value (100%).

4	ANATOMICAL STRUCTURE	Pick the structure you are changing the opacity of, between vein and ventricle

11.8 COLOR



The Color button toggles the Color menu, which allows the user to customize the color of the segmented vein (Figure 29) or ventricle.

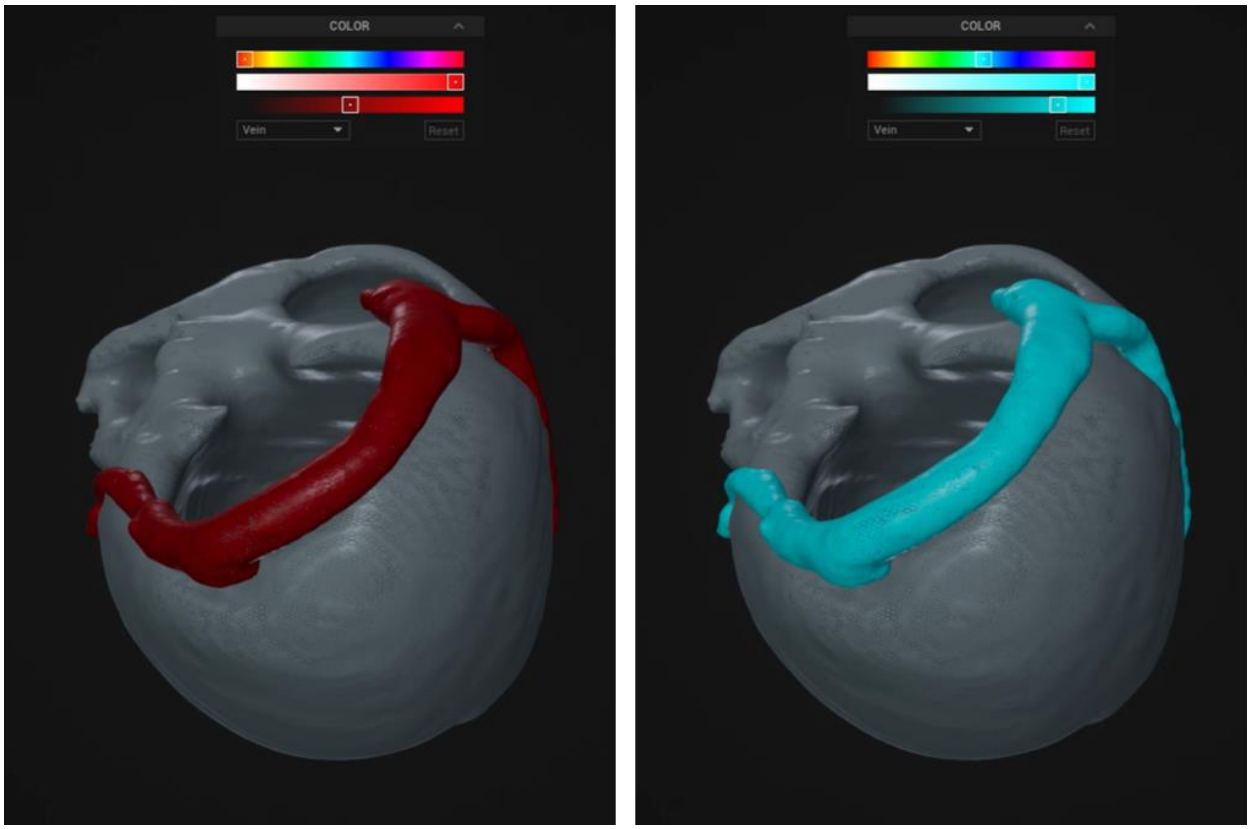


Figure 29 Color function on the Vein. Default color (left), light-blue color with higher contrast (right).

Through the Color Menu the color, brightness and contrast settings can be modified for each anatomical structure (Figure 30)

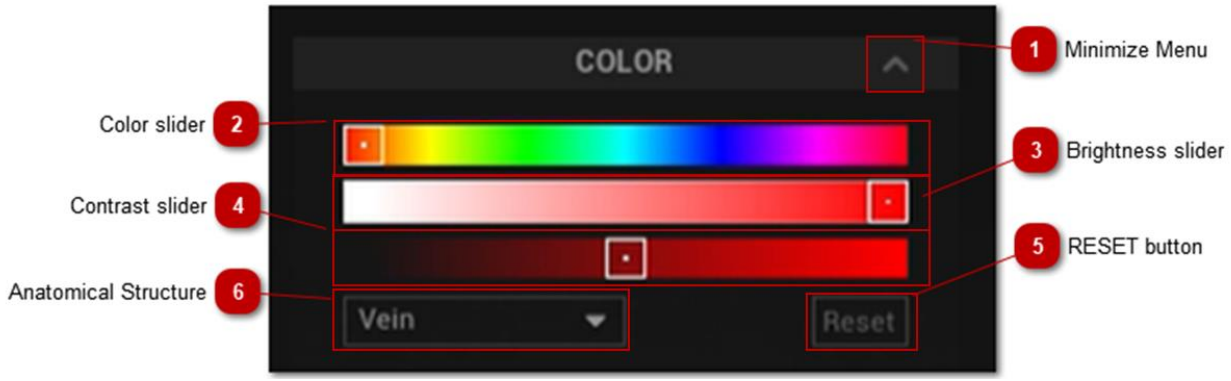
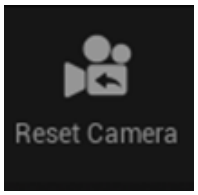


Figure 30 Color Menu

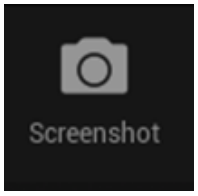
1	MINIMIZE MENU	The Minimize button toggles the minimization of the menu.
2	COLOR SLIDER	Pick the color of the segmented vein or ventricle.
3	BRIGHTNESS SLIDER	Adjust the brightness of the vein or ventricle.
4	CONTRAST SLIDER	Adjust the contrast of the vein or ventricle.
5	RESET BUTTON	Set Color, Brightness and Contrast levels to default.
6	ANATOMICAL STRUCTURE	Pick the structure you are changing the color of, between vein and ventricle

11.9 RESET CAMERA



This button resets the image to the center of the visualization area and to default plane (AP, AnteroPosterior) and rotation.

11.10 SCREENSHOT



Take a screenshot of the view, with the visualization options that are active on the screen.

A confirmation window will appear (Figure 31)

Figure 31 Screenshot Confirmation Window

Example in Figure 32:

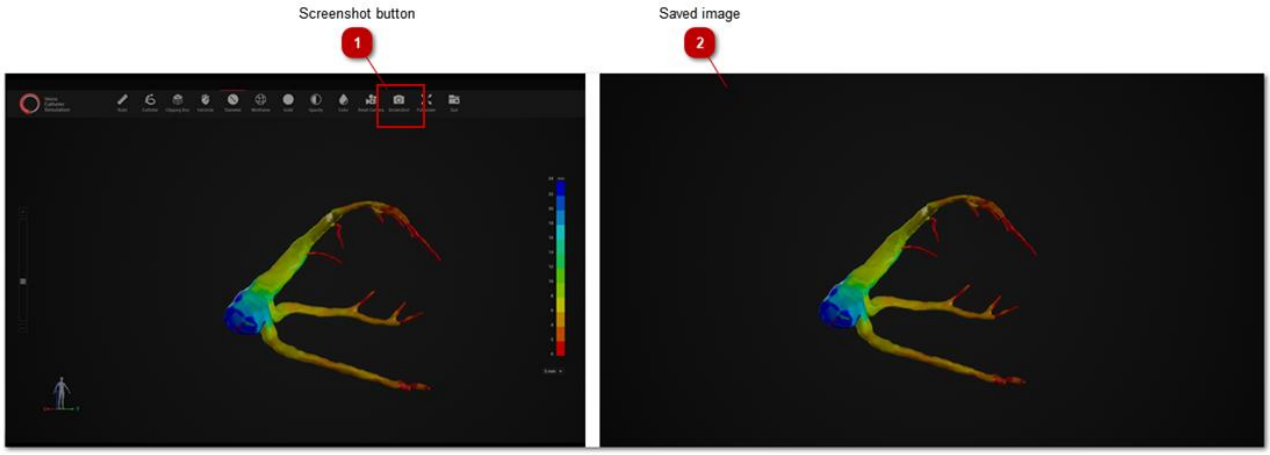


Figure 32 Example of figure as seen on the screen (left) and the saved image (right)

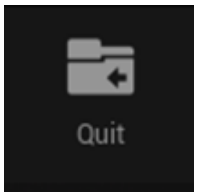
11.11 SKELETON

The Skeleton Button shows the center line of the Coronary Sinus, used to calculate the Trajectory (see relevant paragraph) and its length.

By selecting this option, the center line appears in the model of the vein.

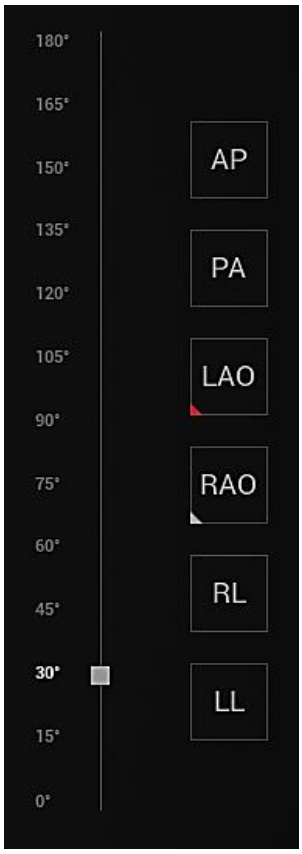
By hovering with the mouse on the center line, an info box appears: the diameter of the vein in that point, and the bifurcation angle of that branch with the main branch.

11.12 QUIT



Press the Quit button to quit and close the program and return to the main N.I.C.E. interface.

12 PROJECTIONS BUTTONS



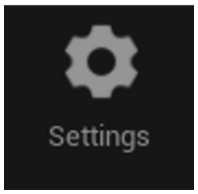
The Projection Buttons rotate the object to a position correspondent to the standard heart projections:

- *Frontal plane: Anterior-Posterior (AP) or Posterior-Anterior (PA) axis*
- *Oblique plane: Left Anterior Oblique (LAO) or Right Anterior Oblique (RAO) axis. For these 2, it is possible to pick the rotation angle (Oblique) from the Frontal plane towards either its Left side or its Right side (see image).*
- *Sagittal plane: Right to Left (RL) or Left to Right (LR) axis.*

It is possible to rotate the view or shift from the central point also using the mouse:

- *left button - rotate*
- *right button - pan*
- *scroll wheel up - zoom in*
- *scroll wheel down - zoom out*

13 SETTINGS



The Settings button toggles the Settings menu, which is subdivided into four sub-menus: GAME and GRAPHICS. Click on the single entries to display the submenus.

13.1 GAME

The settings menu "Game" (Figure 33) shows the Game settings.

Figure 33 Game settings menu

Game settings can be adjusted through three commands:

- *Rotate Sensitivity regulates the software sensitivity to the rotation command (mouse movement with left button pressed).*
- *Zoom Sensitivity regulates the software sensitivity to the zoom command (mouse scroll wheel).*
- *Pan Sensitivity regulates the software sensitivity to the panning command (mouse movement with right button pressed).*

13.2 GRAPHICS

The settings menu "Graphics" (Figure 34) shows the options for Display and Graphics.

Figure 34 Graphics settings menu

Display settings can be modified through the command Rendering resolution to adjust the resolution.

Graphics quality can be changed among the different modes (Low, Medium, High, Ultra) using the arrows. The Preset quality is set to Ultra.

14 ADMIN USER PAGE

14.1 INTRODUCTION TO THE ADMIN USER

The Admin User is a type of user with administrative rights, but no access to the pages of N.I.C.E. related to the patients of the hospital.

The role of the Admin User is to manage the Users of their hospital:

- *view the list of users,*
- *add a new user,*
- *change password,*
- *disable a user.*

14.2 ADMIN USER HOME PAGE

After the login, the Admin User will see the list of the registered user of the center, or the centers, related to the given license number.

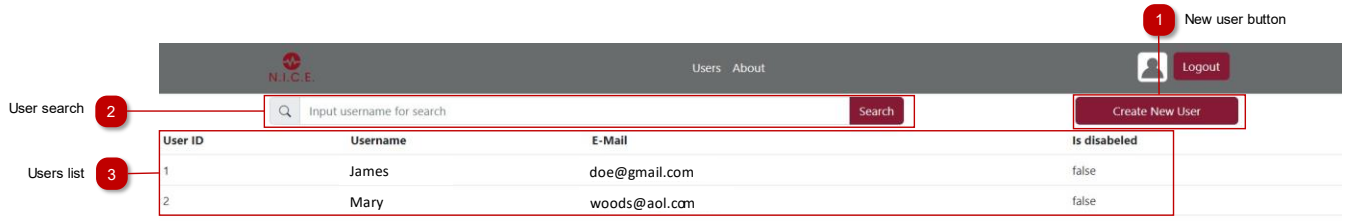


Figure 35 Admin User homepage

1	NEW USER BUTTON	Use this button to create a new user.
2	USER SEARCH	Use this button to search a user by "UserName", "Email" or parts of them
3	USERS LIST	This table shows all the users managed by the admin and the following information: username, email, and whether the user is disabled.

14.3 CREATE NEW USER

Use this page (Figure 36) to create a new user, generate a first-access password and associate it with a license number.

The password can be changed by the user on their first access.

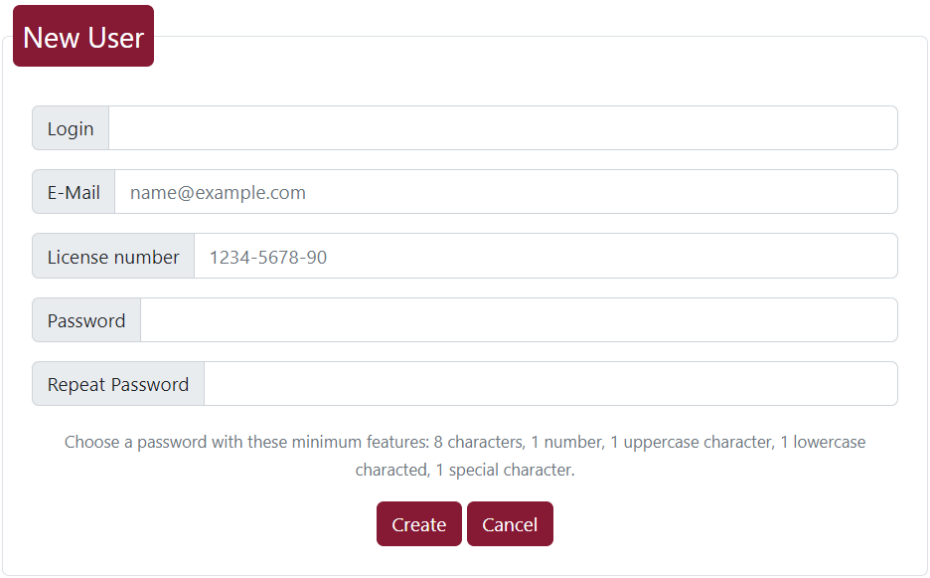


Figure 36 New User registration page

14.4 EDIT USER PROFILE

The Admin User can change the details of the user or disable them at any point (Figure 37).

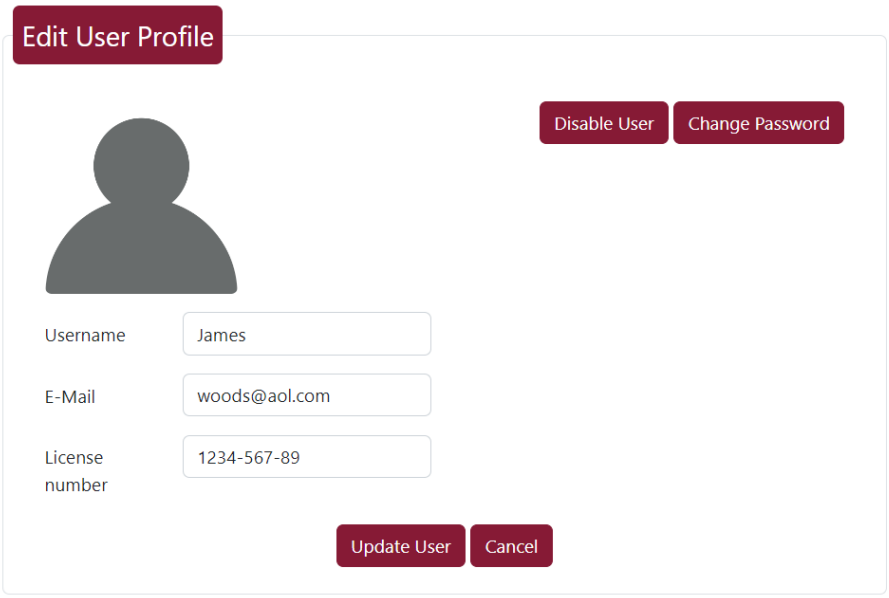


Figure 37 Edit User page

Clicking the buttons “Disable User” and “Save changes” will generate a confirmation window.

15 NOTIFICATION SERVICE

From the Admin Panel, you have access to the setup of Default Notifications service.

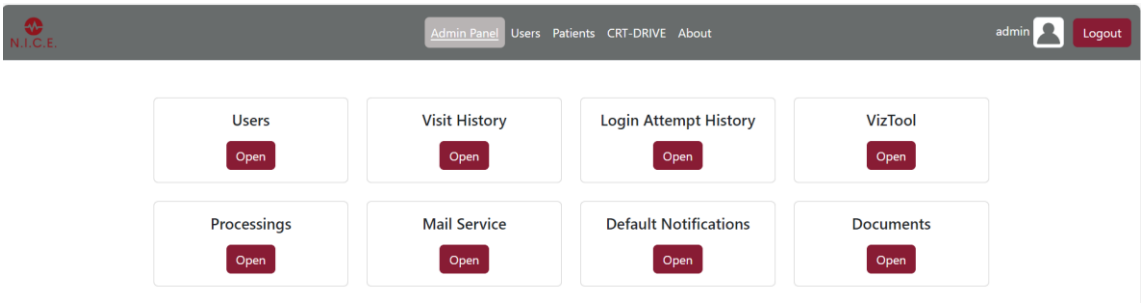
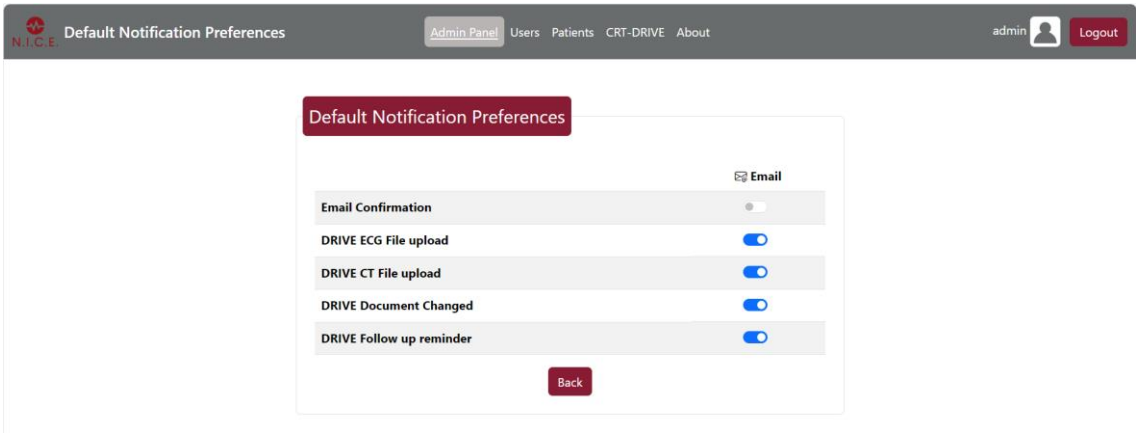


Figure 38 Admin Panel

1.4. SETUP

By default four services are enabled and managed through emails:



- *DRIVE ECG File upload:* those who enable this setting, will receive an email notification whenever an ECG file has been uploaded in the CRT-drive study. The email contains information about the patient, with the relative link to directly access the patient page.
- *DRIVE CT File upload: :* those who enable this setting, will receive an email notification whenever a CT file has been uploaded in the CRT-drive study. The email contains information about the patient, with the relative link to directly access the patient page.
- *DRIVE Document Changed: :* those who enable this setting, will receive an email notification whenever any new data has been changed in the CRT-drive study. The email contains information about the patient, with the relative link to directly access the patient page.
- *Follow up reminders:* those who enable this setting, will receive an email as reminder for follow up visits.

  Once defined the follow-up visit expected date as 180 days from the CRT implantation day, a specific timeline will be followed to send out reminders:
  - 2 weeks before the expected date
  - 1 week before the expected date
  - 3 days before the expected date
  - 1 day before the expected date
  - The expected date
  - 1 day after the expected date (!)
  - 3 days after the expected date (!)
  - 1 week after the expected date (!)
  - Every 7 days until the data are uploaded.

  (!) means that the follow up visit has been missed and there is a high risk for the patient to be excluded from the CRT-DRIVE clinical

trial. In this case, the email will encourage to upload the data as soon as possible.

ANNEX I

1. MEASUREMENT ACCURACY

The accuracy of all the measurements computed in N.I.C.E. depends on the input DICOM image resolution and the ECG measurements.

Activation Map

The accuracy of the non-invasive N.I.C.E. maps are assessed through comparison with invasive CARTO data, recognized as the gold standard for activation maps. The comparison yields an average correlation coefficient of 0.80 (the closer to 1, the better).

Segmentation

For segmentation tasks, the Dice score serves as a measure of overlap between two samples, with a higher score indicating better agreement. The segmentation of the Coronary Sinus, utilizing the N.I.C.E. method, resulted in an average Dice score of 0.79 ± 0.07. Additionally, the Dice scores for the wall, left ventricle (LV), and LV classes achieved by the model are 0.71 ± 0.14, 0.89 ± 0.06, and 0.78 ± 0.15, respectively.

Vein Parameters

The Spearman correlation coefficient is employed to assess measurement efficacy of the vein parameters. The coefficient yields the following results: vein diameter measurements exhibit a correlation coefficient of 0.97, vein angle measurements indicate a coefficient of 0.85, and vein lengths demonstrate a coefficient of 0.99.

2. PERFORMANCE CHARACTERISTICS

It is recommended to not perform other CPU and RAM intensive tasks during the computation of N.I.C.E.

The System shall be able to store for each user group at least 100 cases, with at least 2.5 Gb available per patient case.

Maximum timeframe is defined as 1 hour from successful loading of input data (for a single full process).