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SimCardioTest - Simulation of Cardiac Devices & Drugs for in-silico Testing and Certification

Technical Report

D 5.1: REPORT ON THE IN-SILICO TRIAL OF PACING LEADS & CATHETERS

Work Package 5 (WP5)
IN-SILICO TRIALS & DATA SCIENCE

Task Lead: UBx, France
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DELIVERABLE INFORMATION

Deliverable number	D5.1
Deliverable title	Report on the in-silico trial of pacing leads & catheters
Description	In silico trial that determines the proportion of population that undergoes loss-of-capture due to fibrosis after implantation of a bradycardia pacemaker in the right ventricle
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Comments	This deliverable was delayed as we had to overcome technical difficulties when setting up the final computational pipeline.

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Executive Summary

This report constitutes the SimCardioTest WP5 deliverable D5.1 due in December 2023 (M36) related to use case 1.

Here, we describe the way to conduct an in-silico trial with the bradycardia pacemaker and cardiac tissue computer model developed during the project. The computational pipeline that was provided for integration in the cloud-based platform has been run off-line, on a different computational platform, and integration on the cloud-based platform is being finalized. This pipeline was used to characterize improvement in the electrical properties, in the context of tissue fibrosis, of a new lead design with respect to a known one. The credibility of the computational model was assessed for computing electrical threshold curves, a context of use that is sufficiently close to the clinical trial.

Acronyms

Acronym	Meaning
WP2	Work Package 2
SCT	SimCardioTest
IST	In Silico Trials
CEPS	Cardiac Electro Physiology Simulator

Preamble

NOTE: This section is identical for deliverables D5.1, D5.2 and D5.3.

In-silico trials based on computational models and simulation (CM&S) represent a revolutionary approach in the field of medical research and development. In-silico trials can be used in the development and regulatory phases of a new therapy, with the goal of reducing, refining and sometimes partially replacing clinical trials by the mean of individualized simulations of specific patients and sub-populations, and the synthetic effect on them of the targeted treatment [1,2]. In-silico trials are gaining visibility and increasing acceptance by regulatory authorities ([3,4], with a focus on cardiology), and dedicated organizations have been created, such as the Virtual Physiological Human institute (https://www.vph-institute.org), which promotes the implementation of CM&S to optimize clinical trials, and the Avicenna alliance (https://avicenna-alliance.com), founded by the European commission to develop the research roadmap for in-silico medicine, put it into policy and ensure the development of a regulated in-silico market. However, the widespread adoption and acceptance of in-silico trials requires a standardized framework to ensure consistency, reliability, and regulatory compliance. Recognizing this need, efforts are underway to establish Good Simulation Practice (GSP) guidelines. Scheduled for publication in 2024, the book "Toward Good Simulation Practice" (https://link.springer.com/book/9783031482830) is the result of the joint work of 138 In-silico Trials experts working in academia, the medical industry, regulatory bodies, hospitals and consultancies. This initiative aims to create a unified approach that will enhance the credibility and acceptance of in-silico trials across the scientific and regulatory communities.
To complement the standardization effort, there is a clear need for the community to agree on protocol and reporting standards. Inspired by the well-established Good Clinical Practice (GCP) framework, a protocol has been created within SimCardioTest to drive researchers through an efficient and effective deployment of in-silico trials. Each Use Case implemented in WP2-3-4 performed a specific in-silico trial based on the proposed in-silico protocol, and carried out via the secure standardized cloud-based platform developed in SimcardioTest. Deliverables D5.1-2-3 reports the details and results of the in-silico trials for Use Case 1, 2 and 3 respectively.

[1] Pappalardo, F., Russo, G., Tshinanu, F. M., & Viceconti, M. (2019). In silico clinical trials: concepts and early adoptions. *Briefings in bioinformatics*, *20*(5), 1699-1708.
[2] Viceconti, M., Juárez, M. A., Curreli, C., Pennisi, M., Russo, G., & Pappalardo, F. (2019). Credibility of in silico trial technologies—a theoretical framing. *IEEE journal of biomedical and health informatics*, *24*(1), 4-13.
[3] Miller, C., Konduri, P., Bridio, S., Luraghi, G., Terreros, N. A., Boodt, N., ... & Hoekstra, A. (2023). In silico thrombectomy trials for acute ischemic stroke. *Computer Methods and Programs in Biomedicine*, *228*, 107244.
[4] Rodero, C., Baptiste, T. M., Barrows, R. K., Keramati, H., Sillett, C. P., Strocchi, M., ... & Niederer, S. A. (2023). A systematic review of cardiac in-silico clinical trials. *Progress in Biomedical Engineering*.
In-silico protocol development process;

IN-SILICO PROTOCOL DEVELOPMENT PROCESS

The in-silico trials realized for each UC within SimCardioTest whose results are reported in deliverables D5.1, D5.2 and D5.3, have been carried out following a common in-silico protocol, developed within the project. The objective was to have a standardized template allowing to organize and perform all relevant steps to execute, analyse and assess an in-silico trial. This process, together with the realization of the subsequent in-silico trials, required coordination across all UC's partners, IST, and Inria. Here below we list the different phases and main meetings we organized during the period M24-M36.

Table 1. *Main phases in the development of the standardized in-silico trial protocol and in-silico trial set-up.*

Date	Participants	
21/06/2022	UPV, SIMULA, EXC, IST, Inria	Preliminary discussion based on UC3 and initial protocol draft
20/07/2022	UPV, SIMULA, EXC, IST, Inria	Follow-up discussion and continuous improvement of the first draft.
07/11/2022	Inria	Communication of the template for in-silico protocol to all UC's partners.
18/11/2022	UBX, UPF, UPV, IST, Inria	WP5 meeting on in-silico trial protocol design.
20-21/03/2023	All UC's partners, IST, Inria	One day hands-on on in-silico trials during the annual SimCardioTest GA to specialize an in-silico protocol for a selected QoI and at least one CoU per UC.
March to November 2023	All UC's partners, IST, Inria	Regular monthly UC-specific meetings for updates on the advancements on the in-silico trials, refinement of the protocol, and of the UCs' dedicated interfaces.
07/11/2023	All SCT partners	Half-day workshop on in-silico trials.
November to December 2023	All UC's partners, IST, Inria	The protocols are finalized, in-silico trials are run offline. The integration of the latest version of the codes advanced in parallel. Regular monthly UC-specific meetings are organized for coordination.

1 Introduction

1.1 BACKGROUND INFORMATION

Bradycardia is a common, frequent occasion for cardiac consultation, and may have diverse origins. The guidelines in [1] are a reference for the evaluation of patients with bradycardia or conduction delay. Novelty in these guidelines with respect to the previous one from 2008 are reported in [2].

Our work is placed in the general context of bradycardia that requires a permanent pacing protocol to be treated. According to [1,2] (see e.g. [1, Fig. 6 p e89]), the principal indication for permanent pacing strategy is the management of sinus node diseases. Permanent pacing requires a pacemaker, which is composed of a pulse generator (electronics and battery), and leads which are implanted in the cardiac tissues. Bradycardia related to sinus node diseases are usually treated with a main lead implanted in the right ventricle. Sinus node disease is considered in [1] a non-life-threatening condition, the main benefit of the treatment being symptom relief and quality of life improvement.

This type of treatment exists since the 1950s, and has made remarkable progress since then, although various complications may still occur (see [3]). For instance, it is a long-lasting device, whose management on a long term is crucial to actually treat the disease. Among other parameters, capture threshold (*i.e.* the minimum energy required to stimulate, that is, capture, the heart with a pulse generator external to the heart) is a critical measurement to assess and predict the pacemaker's performance at implantation and on the long term follow-up. Hence, capture threshold has to be accurately evaluated.

Among the various complications, changes in capture threshold is a known phenomenon, reported earlier in [4], with causes more recently listed in [5]. Capture threshold increase may result in loss of capture, which requires immediate assessment and therapy. It is a crucial problem for patients depending on the pacing function, and may require hospitalization and reprogramming of the device. Typical evolution of threshold to capture along time are reported in [6], where a plateau of the capture threshold is typically reached 16 weeks after implantation.

We developed a computational model of the pulse generator and leads connection to a generic cardiac tissue through contact impedance, as reported in deliverable D2.2. The computer model has undergone a systematic verification and validation as reported in deliverable documents D6.1 and D6.2. This work has been carried out in the context of using the model to evaluate the complete capture threshold curve, also known as Lapicque curve (see D6.1 and 6.2). Hence, the model is well suited to conduct trials concerning loss of capture due to changes in the cardiac tissue, or may be well suited to study some dysfunction of the device (like connection issues). According to [5], these causes cover the main reasons for long-term loss of capture. In the trial proposed below, we focus on a well-known phenomenon, which is loss of capture due to fibrosis [6,5,4] that develops on the long term (months to years after the implantation). Fibrosis related to inflammation or exit blocks are less frequent with steroid-eluting tip leads, but they are well documented (*e.g.* in [6]), so that they constitute a good compromise for evaluating the interest of in-silico trials for pacemakers.

The risk matrix analysis from D6.2 showed that the simulation outputs from the computational model are a moderate factor in the decision, and an incorrect decision would not adversely affect

patient safety or health, but might result in a nuisance to the physician or have other minor impacts. The benefit of the clinical trial presented here is mainly to assess the improved efficiency of the energy delivery of a new lead design with respect to a reference one, resulting typically in energy saving and increased battery life. Errors in this evaluation would result in more patients that need reprogramming of the device.

Here, the reference device modeled is based on a typical pacemaker lead (VEGA™ lead from Microport CRM) and implanted pacemaker (BOREA™ from Microport CRM). All the parameter inputs, such as the detailed dimensions of the lead and electronic components of the pacemaker, were provided to infer the contact impedance model values (according to [10]) prior to the in-silico trials.

1.2 OBJECTIVES

Our question of interest states as follows: what are the changes of the energy delivery properties of a new pacemaker lead design, with respect to a reference one? The population of interest consists of persons who require a permanent pacemaker treatment for a sinus node disease, and it is very large [1]. We focus on people who would benefit from implantation of a bradycardia permanent pacemaker treatment for whom the recommendation is to implant the pacing lead in a healthy region of the right ventricle. The trial targets device companies running preliminary studies on the interest of developing new lead designs. Our objective is to evaluate the changes, and in particular to assess improvement, in the threshold to capture of a new, prospective, lead design with respect to an existing one. We would like, in particular, to evaluate how much the capture-threshold changes in the 16 weeks after implantation as described in [6]. It applies when loss of capture is caused by modification of tissue conduction properties in the vicinity of the tip electrode.

Primary objective. Our primary objective is to compare the proportion of the population for whom the initial setting of the device does not capture any more, i.e. who experienced loss-of-capture, due to fibrosis or exit block (as explained in the previous section).

Secondary objectives. Our secondary objective is to evaluate the changes in capture threshold after implantation due to fibrosis or exit blocks, with respect to new lead designs.

2 Study Design

2.1 VIRTUAL POPULATION DEFINITION

The population represented in this trial contains subjects who would benefit from implantation of a bradycardia permanent pacemaker treatment for which the recommendation is to implant the pacing lead in a healthy region of the right ventricle. We assume homogeneity of the conduction and excitation properties near the tip electrode of the device, among these patients.

In practice, as specified below, the population is not defined in terms of number of patients, but represented by a stochastic parameter in the equations, which represents the expected statistical evolution of fibrosis at the tip electrode, after it has fully developed (typically 16 weeks according to [6]) for a set of patients with leads in initially healthy regions of the cardiac tissue. This distribution of fibrosis on the population of patients is an input parameter in the computational pipeline.

2.2 INTERVENTION DEFINITION

For any patient, the initial intervention consists in implanting a pacing lead in a healthy region of his or her right ventricle. Afterward, the pulse generator is programmed according to the specific pathology and patient. It is strongly based on the capture threshold that has been measured at the time of implantation.

2.3 IN-SILICO TRIAL DESIGN

Cardiac capture is a local characterization of the excitability properties around the tip of the pacing lead, so that the in-silico capture threshold detection for a patient is done on a small region of diameter 4 cm around the tip electrode of the pacing lead (see Figure 1). The computational model assumes capture to be directly related to two types of factors:

- the local conduction and excitation properties of the cardiac tissue at the site of the pacing (tip) electrode, on the cardiac side;
- the geometry of the lead and electrodes, and the main electric characteristics of the pulse generator, on the device side.

Figure 1: *Example of computational mesh used to determine capture or non-capture. This specific mesh is built from the specifications of the Microport VEGA lead. Both translucent and solid red volumes depict the cardiac tissue, while the surrounding wireframe outlines the region simulating blood.*

The trial is designed as follows.

First, the lead is assumed implanted in healthy tissue. A threshold detection test is run with cardiac tissue parameters from the literature [7,8], lead characteristics input by the user, and a pulse duration fixed by the user, within the range of values allowed by the pulse generator, and common in clinical practice. For a fixed pulse duration (see Results section), the threshold is a voltage, searched among a set of predefined voltages of the pulse generator. In practice, it is an interval with lower and upper bounds v_L and v_U among the predefined values 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00 V. The search is realized by decreasing the voltage. For sake of security, the voltage value just above the last voltage to capture is retained as the final value for the permanent pacing therapy in the computational model. In comparison, +0.5 to +1 V is applied in clinical practice. During

this search, we determine if an action potential is triggered by monitoring the volume of tissue in which the transmembrane voltage exceeds a threshold value (-40mV), at two different times t_1 = 5 ms and t_2 = 10 ms post-stimulation pulse. We consider that there is an action potential when the volume at t_2 is larger than the one at t_1. In the case of a non-capturing stimulation, this volume rapidly tends to 0, a few milliseconds after stimulation.

Second, fibrosis is assumed to have installed and stabilized, so that the local conduction and excitation properties of the cardiac tissue are altered. This evolution is diverse and patient dependent, so that we expect the level of fibrosis to be randomly distributed on the population of virtual patients. We chose a distribution rule characterized by a scalar parameter with normal distribution, as specified below. Given the random distribution of fibrosis among the population, the second step in the trial aims at measuring the fraction of the total population that undergoes loss of capture (primary objective). The search for this fraction of the population amounts to recompute capture thresholds for a wide range of the parameter that encode tissue alteration. When done for several leads the changes in capture thresholds can be estimated (secondary objective).

For a fixed individual, fibrosis is supposed to be at maximum on the tip lead axis, and decrease to no fibrosis (healthy tissue) as a function of the distance to the tip axis. This decay of fibrosis follows a sigmoid function, which half value (50% fibrosis level) is reached at a distance d from the tip axis (see

Figure *2*). This distance and sigmoid function characterize the local fibrosis distribution for a virtual patient. We assume the virtual population to have this distance d randomly distributed among individuals, following a normal law N(d0,sigma) of average distance d0 and standard deviation sigma (see

Figure *2*). We modify the physical properties in the fibrotic tissue according to the literature, by lowering the electric conduction as in [8] and decreasing ionic currents down to 60% of their initial value [9], proportionally to the local fibrosis level.

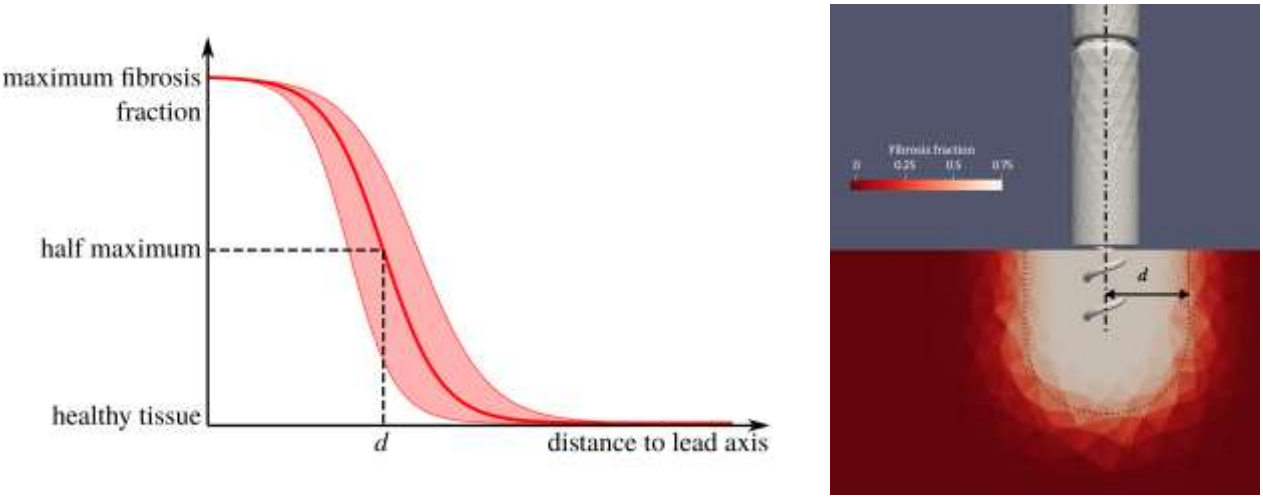

Figure 2: *Distribution of fibrosis level from maximum (tip lead axis) to minimum (healthy tissue) through the half maximum value d (left). The average, second and third quartile of the population model are also represented. Representation of the fibrosis level (in level of white) around the tip lead for a fixed value of d (right).*

A typical value of the average distance d0 is twice the radius of the tip lead.

Due to the specific phenomena of interest, namely a threshold detection (all-or-nothing phenomena), and since the capture duration is initially fixed, we expect the capture threshold to decrease monotonically with the increase in the fibrosis radius d = N(d0,sigma). Hence loss of capture is perfectly determined by a critical value d_c, such that loss of capture occurs only for d>d_c. The proportion of the population that undergoes loss-of-capture is then perfectly determined by the integral above d_c of the distribution function associated to the normal law (see Figure 3).

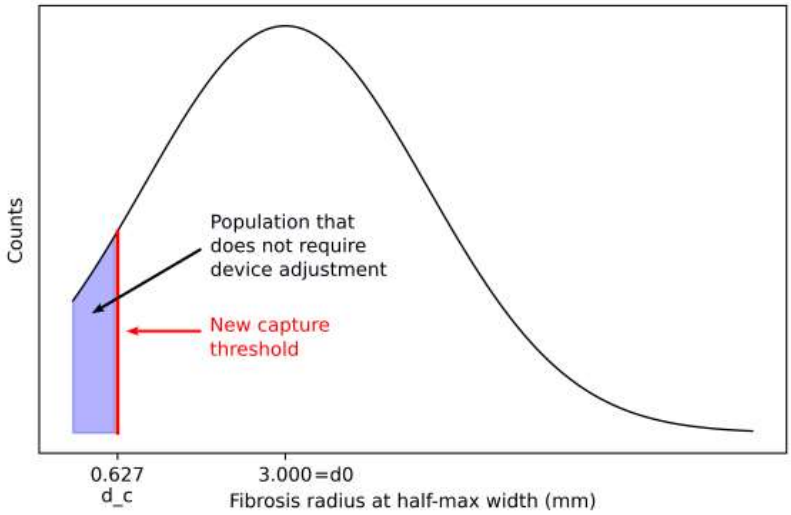

Figure 3: Example of computation of the proportion of population that requires adjustment of stimulation parameters. The shape of the population distribution is parametrized from the web platform.

In practice, the population characteristics, namely average distance d0 and standard deviation sigma can be modified by the user of the cloud-based platform.

3 Evaluation Plan

3.1 EVALUATION METRICS

Our primary objective is evaluated by studying the fraction of the population that undergoes loss-of-capture, which is a direct quantity output by the computational pipeline (see Figure 3. This number can be evaluated for each lead design, and for various settings of the population statistics. These numbers can then be compared, the smaller being the better result.

Our secondary objective is evaluated because capture thresholds intervals (v_L and v_U) can be output at the first step of the computational pipeline (threshold at implantation), and at its end (threshold after fibrosis fully develops). Again, this may be done on any number of lead design and population input statistics. In this case, the situations of smallest increase of capture interval are preferred.

Each run of the pipeline computes the fraction of population and capture thresholds for one lead, so that at least two pipelines have to be run (a reference, and a new lead).

3.2 STATISTICAL DESIGN AND DATA ANALYSIS

The computational pipeline outputs one number which already has a statistical meaning, namely the fraction of a population that will lose capture due to fibrosis.

4 In-silico Trial Simulation Plan

The trials are executed by running several times the computational pipeline described below. The user enters the values of the quantities listed in Table 1.These values are threefold: (1) parameters of the geometrical and electrical properties of the lead to be tested; (2) duration of the pulse to be used for actually pacing; (3) average and standard deviation of the population participating to the trial.

Table 1: *Parameters that are adjustable on the IST web-platform.*

Parameter name	Lower bound	Upper bound	Default value	Source of default value
Stimulation duration (ms)	0.10	10.00	1.00	-
Lead diameter (mm)	6.00	20.00	6.96	Microport VEGA lead
Ring size (mm)	1.00	20.00	7.07	
Ring distance (mm)	6.00	20.00	6.38	
Ring contact capacitance (μF)	10^{-5}	none	5.55	Fitted with bench experiment data
Ring contact resistance (kOhm)	10^{-5}	none	0.03	
Tip contact capacitance (μF)	10^{-5}	none	18.74	
Tip contact resistance (kOhm)	10^{-5}	none	2.0	
Fibrosis radius mean (mm)	0	2	1.0	
Fibrosis radius stdev (mm)	10^{-6}		1.0	

Each of these values is set among a predefined set of meaningful ones, which correspond to biomedical relevant ones, for which the computational pipeline is expected to run successfully. There may be mutual exclusion criteria for groups of parameters but, for now, they cannot be determined *a priori*. For instance, geometrical parameters that lead to impossible meshing, or physical properties of contact that make the numerical solvers diverge.

These inputs are sent to a Python script that performs the steps below.

- Meshing: we use the gmsh software http://gmsh.info/ to generate a 3D mesh of the lead, for which most of the parameters are taken from a reference design (Microport VEGA lead) and are fixed.
- Detection of voltage capture threshold interval.
- Detection of capture threshold interval with changing fibrosis level.

With the determined threshold in fibrosis, the pipeline provides the percentage of population that undergoes loss-of-capture and is eligible for reprogramming the pulse generator.

The last two steps of the pipeline are described in section 2.3. They rely on CEPS, which is an in-house software that implements a numerical solver for the models required for this project (see D2.2, D6.1, D6.2, and documentation). The computational cost of each pipeline is determined mostly by the quality of the generated mesh and the desired accuracy of the final step. With 200 realizations of the distance d describing the fibrosis (determined to cover 99.9% of the input population), the pipeline runs CEPS about 15 times, for a total runtime of nearly 2.5 hours on 24 CPUs. Of course, this would depend on the hardware architecture used for the computations.

5 Results

At the time of writing, the code integration into the in-silico trials web-based platform has not been completed. We then provide results that were generated offline, on a different computational server. The complete pipeline described above (python scripts and its internal steps), which was used to compute the results shown in this section, has been provided to IST for later integration, by the end of the project. The usage of the current platform version is shown in the associated video (Demonstration UC1 In Silico Trial). The web-based interface is already implemented, as depicted on Figure 4 For instance, the input numbers from Table 1 are entered by a user as shown on Figure 5 The pipeline will be fully integrated in the platform by the end of the project.

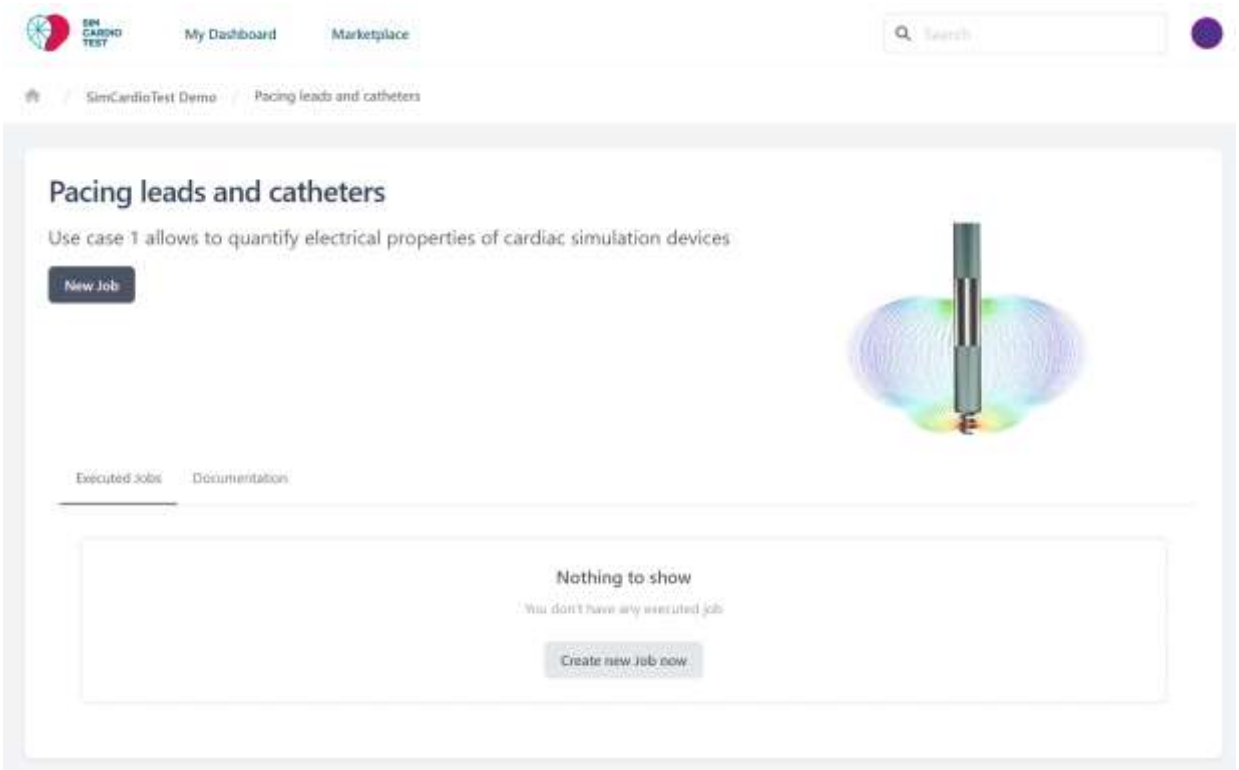

Figure 6

Figure 4: *Web homepage of the Use Case 1 workflow.*

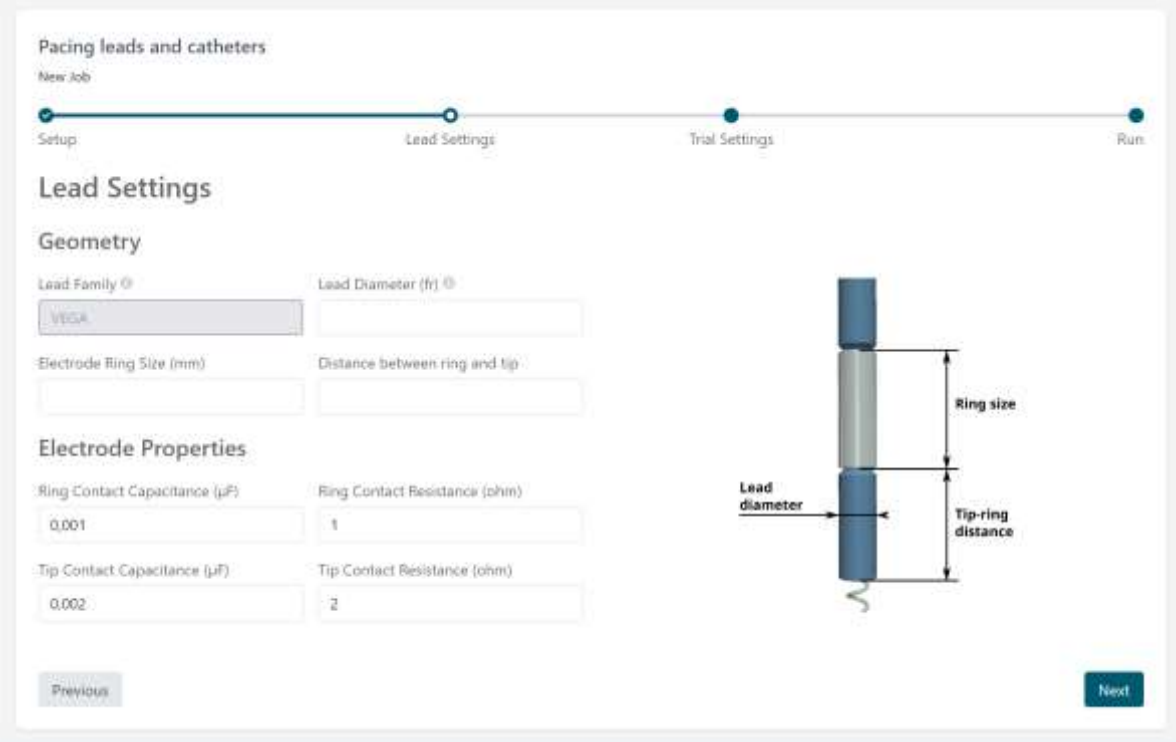

Figure 5: *Web interface for lead settings inputs to be inserted by the user.*

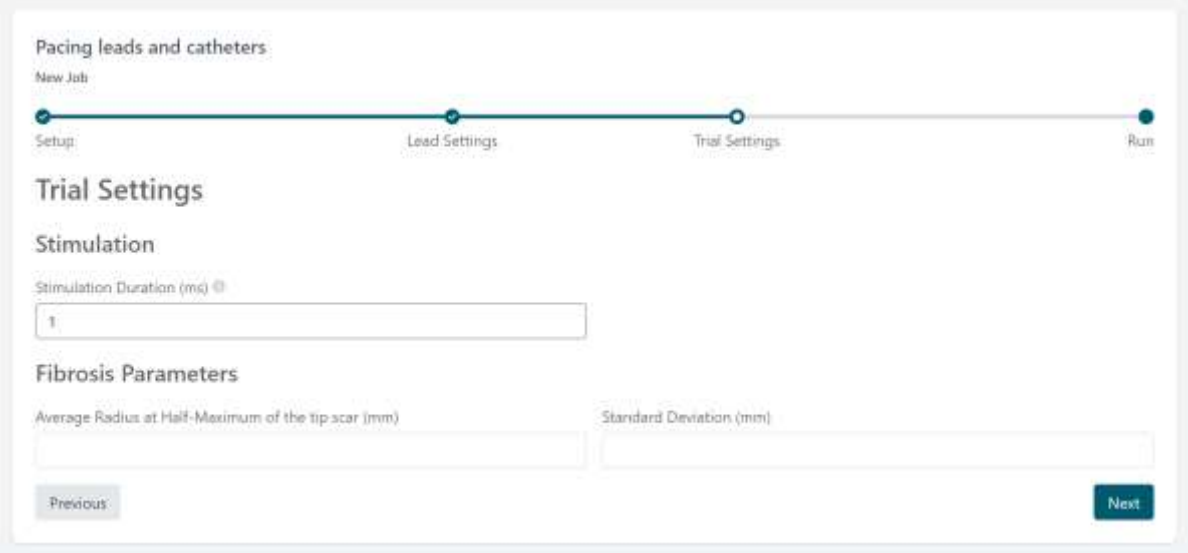

Figure 6: *Web interface for trial settings inputs to be inserted by the user.*

We first ran the pipeline with the original design of the Microport VEGA lead, with stimulation durations of 0.25, 0.5 and 1 ms. The voltage thresholds (upper bound) were found at 2 V, 1.25 V and 0.75 V, respectively (Table 2). Therefore, the voltages used to find the fibrosis thresholds were 2.5 V, 1.5 V and 1 V, respectively, with results compiled in Table 3.

For comparison, we ran pipelines with the same stimulation parameters and electrode contact properties for a second design of the lead, with slightly smaller lead diameter (7 to 6 mm), and much smaller ring electrode size (7 to 2.5 mm), see Figure 7.

Figure 7: *Lead designs tested for this report. Left: meshed from original Microport VEGA lead dimensions. Right: custom diameter and ring electrode size.*

We report the final results of these pipelines in Table 4, in terms of percentages of the input population that does not undergo loss-of-capture, i.e. for whom the initial settings still trigger action potentials.

Table 2: *Detection of minimum voltage required to trigger an action potential, for two different lead designs and three different stimulation durations*

Lead Design 1 (Microport Vega)						Lead Design 2 (Custom)					
0.25 ms		0.5 ms		1 ms		0.25 ms		0.5 ms		1 ms	
Voltage (V)	Capture	Voltage (V)	Capture	Voltage (V)	Capture	Voltage (V)	Capture	Voltage (V)	Capture	Voltage (V)	Capture
0.25	No	0.25	No	0.25	No	0.25	No	0.25	No	0.25	No
1.50	No	1.00	No	0.75	No	1.50	No	1.00	No	1.00	No
2.00	No	1.25	No	1.00	Yes	2.50	No	1.25	Yes	1.25	Yes
2.50	Yes	1.50	Yes	1.50	Yes	3.00	Yes	1.50	Yes	1.50	Yes
3.00	Yes	4.00	Yes	4.00	Yes	4.00	Yes	4.00	Yes	4.00	Yes
4.00	Yes										

Table 3: *Detection of fibrosis radius d above which capture is not possible anymore, using a voltage deduced from Table 2.*

Lead Design 1 (Microport Vega)						Lead Design 2 (Custom)					
0.25 ms		0.5 ms		1 ms		0.25 ms		0.5 ms		1 ms	
Fibrosis RHMW (mm)	Capture	Fibrosis RHMW (mm)	Capture	Fibrosis RHMW (mm)	Capture	Fibrosis RHMW (mm)	Capture	Fibrosis RHMW (mm)	Capture	Fibrosis RHMW (mm)	Capture
0.00	Yes	0.00	Yes	0.00	Yes	0.00	Yes	0.00	Yes	0.00	Yes
0.28	Yes	0.57	Yes	0.57	Yes	0.28	Yes	0.57	Yes	0.57	Yes
0.43	Yes	0.62	No	0.62	Yes	0.33	Yes	0.62	Yes	0.72	Yes
0.48	Yes	0.72	No	0.67	No	0.38	No	0.67	No	0.77	No
0.53	No	0.86	No	0.72	No	0.43	No	0.72	No	0.86	No
0.57	No	1.15	No	0.86	No	0.57	No	0.86	No	1.15	No
1.15	No	2.36	No	1.15	No	1.15	No	1.15	No	2.36	No
2.36	No	4.77	No	2.36	No	2.36	No	2.36	No	4.77	No
4.77	No	9.60	No	4.77	No	4.77	No	4.77	No	9.60	No
9.60	No			9.60	No	9.60	No	9.60	No		

Table 4: *Percentages of population for which the pacemaker still captures (blue area on figure Figure 3, for different normal distributions of fibrosis parameters. The mean and standard deviation of these distributions are user-defined inputs of the pipeline.*

Fibrosis distribution parameters		Lead Design 1 (Vega)			Lead Design 2 (Custom)		
d Mean	d STD	0.25 ms	0.5 ms	1 ms	0.25 ms	0.5 ms	1 ms
3.0	2.0	3.92 %	4.87 %	5.36 %	2.61 %	5.36 %	6.40 %
0.0	0.5	77.37 %	82.19 %	86.21 %	51.47 %	75.34 %	84.79 %

The results in Table 2 show that, right after implantation in a healthy tissue, the threshold to capture for the new lead design 2 is decreased for a pulse duration of 0.5 ms (1.50 to 1.25 V), but increased for the other two tested durations, 0.25 ms (2.5 to 3 V) and 1 ms (1 to 1.25 V). Decrease in threshold to capture is an improvement that we look for.

Our primary objective is answered by Table 4. It shows two situations. First, if the average extend of fibrosis is assumed equal to 0 with a small standard deviation of 0.5 mm, then for lead 1, 77 % to 86 % of the population remains in capture range after the fibrosis has installed permanently. In comparison, these numbers are 51 % to 84 % for the lead design 2, meaning that lead design 2 achieves poorer performance. Second, if the average extend of fibrosis is large (3 mm) with a large standard deviation (2 mm), then in any case only a very small fraction of the population remains in the capture range, 4 % to 5 % on lead design 1, and 2 % to 6 % on lead design 2. Anyway, in this case, lead design 2 improves the performance for pulse durations of 0.5 ms and 1 ms (resp. 4.87 % to 5.36 %, and 5.36 % to 6.40 %).

Our secondary objective is addressed through Table 3. The results are consistent with the ones from the primary objective: the extend of fibrosis for which loss of capture occurs increased for pulse durations of 0.5 and 1 ms, and decreased at 0.25 ms.

6 Conclusions and Discussion

This report describes how the cloud-based platform can be used to realize an in-silico trial for new, prospective pacemaker bradycardia leads. In previous deliverable documents (D2.1, D2.3, D6.1 and D6.2), we fixed standard input and output for the computational pipeline (D2.1) that is the basis of this in-silico trial, explained how the model was conceived and calibrated (D2.2), carried out thorough verification (D6.1) and validation (D6.2) procedures in order to demonstrate the credibility of the computational model. To date, the validation process is still on-going, because it involves complex, difficult to schedule, animal experiments. In particular, we still have to complete experiments involving scar tissue, equivalent of the fibrosis model described in this report.

The credibility of the model has been studied in view of computing complete threshold (Lapicque) curves for a given lead and pulse generator, in the context of using the computation to reproduce the threshold detection tests carried out on animal heart in diverse conditions. The context of use of the model for the trial proposed in this report is sufficiently close to the previous one for the answer to be credible, as soon as the complete validation process is finished.

The trial relies nonetheless on a few additional assumptions: implantation sites are supposed to be all identical and perfectly healthy, the development of tip fibrosis has been simplified to an axi-symmetric region, and characterized by its extend only.

In practice, this may be far from the clinical reality. Anyway, it is a first step towards more realistic setups, that allows tractable computations with our model (in terms of CPU complexity). It may be extended to establish a computational model that remains robust and reflects better the lead placement in real tissue, and associated electrical energy delivery. For instance, the angle of the lead with respect to the tissue surface may be varied, as well as the depth of the tip electrode in the tissue. A more general population could be considered, that would have diverse tissue properties at the implantation site, like space-dependent values of the conductivity coefficients and ionic properties. The same computational model could be used, but the cloud-based interface would have to be generalized to account for all these new parameters.

Another possible generalization would be to use the model to study the loss-of-capture due to connection issues with the device. It amounts to change the equivalent electrical circuit to account for known issues, like short-circuit between the tip and ring wire or current leakage due to deterioration of the insulating material. It would anyway require to review the validation study in this new context.

Finally, some patients receive concomitant medication, which is sometimes known to alter the capture threshold [5]. These patients were discarded from the current trial, but could be included in another trial, by coupling the work done in UC3 to understand drug effects on ion channels (which are one of the characteristics of excitability) to our model (UC1) on pacemaker models.

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