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COMPUTER-ASSISTED ANALYSIS OF EXPERIMENTAL DATA FROM POST-MORTEM PORCINE LUNG TISSUE DURING RADIOFREQUENCY ABLATION TO EVALUATE THE CONDUCTANCE RESPONSE

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Abstract: *Radiofrequency ablation (RFA) is a minimally invasive technique used in the treatment of cancer. The application of RFA in the treatment of lung tumors has gained increasing research attention in the search for improvements in the technique. Variation in quantities such as impedance and power determine the efficiency of treatment. Electrical concepts such as power, impedance, and conductance are parameters that are evaluated during surgical procedures and in many cases interact with each other during the ablation process. Although studies have been performed to characterize these parameters in an ex-vivo environment with a variable post-mortem, they have not emphasized electrodynamic concepts during the application of the treatment signal. For an experiment using ex-vivo porcine lung tissue, we performed a computational analysis of the data obtained. For the preclinical test, an RFA device developed by the research group was used, applying a signal with a frequency of 500 kHz. The collected data were preprocessed using MATLAB®software tools. Models were created from the obtained conductance curves using the system identification technique. The system properties were evaluated using classical control theory. The computational model results confirmed that the tissue sections had conductance functions. Thus, it was possible to show the definition of the dynamic conductance of the tissue as a function of postmortem time. These results can be used as guidelines for optimizing the parameters used for RFA, taking into account the electrophysiological dynamics of the tissue. With the analysis of these quantities, it is possible to improve the performance of the devices and to obtain a better understanding of the tissue in order to develop new medical-surgical technologies.*

Keywords: *Radiofrequency ablation, Lung cancer, dynamic control, ex-vivo.*

1. INTRODUCTION

The most recent survey from 2020 identified lung cancer as the leading cause of death worldwide (Sung *et al.* and Ferlay *et al.*, 2021). The Global Cancer Observatory shows that the incidence rate for the same year for both sexes was 22.4 per 100 thousand population, behind only breast cancer and prostate cancer, each of which ranked first (Observatory, 2021). According to the National Cancer Institute (INCA), the number of lung cancer cases in Brazil for the triennium 2020 - 2022 is estimated at more than 30 thousand, occurring mainly in men (de Câncer, 2019).

The main cause of this disease is excessive smoking or passive exposure to tobacco (da Silva *et al.*, 2019). Other factors may be associated with this disease, such as exposure to chemicals, pollution, lung disease and genetics (Brey *et al.*, 2020). Diagnosis is primarily by chest radiography or computed tomography of the region, resources that are often not available to the general population, resulting in late diagnosis of the disease (Araujo *et al.*, 2018). Treatment depends on the stage of development of the disease and generally includes drug administration, surgical intervention, and even combination therapy protocols (de Câncer, 2021).

Although the treatment scenario has evolved over time, invasive surgical interventions represent a significant proportion of those performed for recovery, albeit with significant impact on patient survival (Gelatti and Lorandi, 2020). The treatment of lung cancer is still expensive and poorly standardised, which opens up space for the search for more effective and less expensive methods (Tanaka *et al.*, 2016).

In this context, it is known that radiofrequency ablation (RFA) is a minimally invasive technique used in tumour treatment to treat primary and secondary malignancies in clinical practise, where the thermal outcome is directly related

to the biological tissue focus of the application (Fang *et al.*, 2020; da Fonseca *et al.*, 2019). Many details of RFA biophysics remain to be modeled from a mathematical and theoretical perspective. One of the most pressing problems is to obtain a mathematical structure that can describe the interaction of the tissue with the applied signal to improve energy delivery (da Fonseca *et al.*, 2019).

Some researchers at the University of Brasilia (UnB) have been working on the analysis and use of RFA for applications in liver carcinomas. These studies are being conducted using a national technology developed by the Biomedical Engineering Laboratory (LaB/UnB) and funded by the Brazilian Ministry of Health (from Portuguese MS). It is called SOFIA (Software of Intensive Ablation) (de Siqueira Rodrigues Fleury Rosa, 2017). This medical aid device delivers up to 50 W of power and operates at a frequency of 500 kHz. Mathematical models have been used to propose treatment protocols and optimise the hardware of SOFIA devices (da Fonseca, 2017; Cavalcante *et al.*, 2018). These models can be obtained by constructing and identifying systems from data collected in *ex-vivo* experiments with the aim of evaluating the dynamics of the system (Monteiro *et al.*, 2019).

The potential of RFA is also being investigated for application in pleural tissue (de Paula and de Brito, 2018). To investigate the best potential of RFA in lung tissue and quantify the possible second-order dynamics of this relationship, we first sought to develop a mathematical model using system identification of data collected in an *ex-vivo* porcine animal model (non-clinical study). Three ablation powers (20, 25, and 30 W), the input signal to the system, and the tissue response to this stimulus, in this case measured indirectly during the experiment by tissue conductance, were used as the output signal of the system.

The study presented in this paper proposes to collect parameters that can contribute to future adjustments in the devices using controllers. For this purpose, an analysis of the transfer functions resulting from the models using classical control techniques was performed.

2. METHODOLOGY

The process of developing a medical device involves various testing phases and adaptations that go hand in hand with bench tests simulating the use of the device. In this way, experimental parameters will be obtained to build mathematical models and use them to make technical adjustments to the RFA devices in order to improve the efficiency of the devices and the effectiveness of the treatment.

2.1 Experimental test bed

A non-clinical experimental trial was conducted to collect data on the biological procedure of tissue ablation. The trial was conducted in an *ex-vivo* setting using pig lungs obtained from a slaughterhouse. The autopsy was performed within 30 minutes at a basal temperature of $37°C$. This temperature was not kept constant during the test. Standardised samples were prepared whose shape corresponded to a cubic shape with an edge length of 5 cm and which had a similar weight. These samples were divided into three experimental groups, each group containing three samples, namely: I) Experimental group for the application of 20 W power; II) Experimental group for the application of 25 W power; and III) Experimental group for the application of 30 W power. All groups used an ablation device developed by UnB (da Fonseca *et al.*, 2019) with a constant delivery of the listed powers. The termination criterion was the application time of 50 s. The electrode used in the application of the signal in all samples was of the LeVeen Standard 4.0 umbrella type from Boston Scientific, semi-open with a diameter of 2.5 cm. The Fig. 1 shows the configuration of the experimental table.

2.1.1 Data collected

During the ablation procedure, the electrode was inserted into the center of the sample for the time period specified in the protocol. Voltage and current data were acquired using a data acquisition system developed by the SOFIA group. This circuit is based on a single board computer, Raspberry Pi 3B, in conjunction with converters. Analog to Digital (ADC) and signal conditioning circuits. This system stores the measurement data in a spreadsheet to allow data analysis after the experiment.

2.2 Pre-processing of the data

The system to be analysed in this study has as its street the signal applied by the device SOFIA and as its output the tissue conductance parameter. To represent the input of the system, three sinusoidal signals with a frequency of 500 kHz and an amplitude of 200 V_{RMS}, 170 V_{RMS} and 140 V_{RMS}, respectively, were constructed to represent the powers applied in each of the experimental groups. To ensure an initial condition of zero for the input, a series of zeros with 100 samples was inserted at the beginning of the input vector, corresponding to 200 ms.

The conductance parameter was determined indirectly from the voltage and current data collected during the experiment. In this way, a script was created in Matlab® software to perform the linear interpolation between the points and ensure the equidistance and dimension of the vectors related to this data. With the vectorised data, the conductance values for each sample were calculated using Eq. 1.

$$G = \frac{i}{v} \tag{1}$$

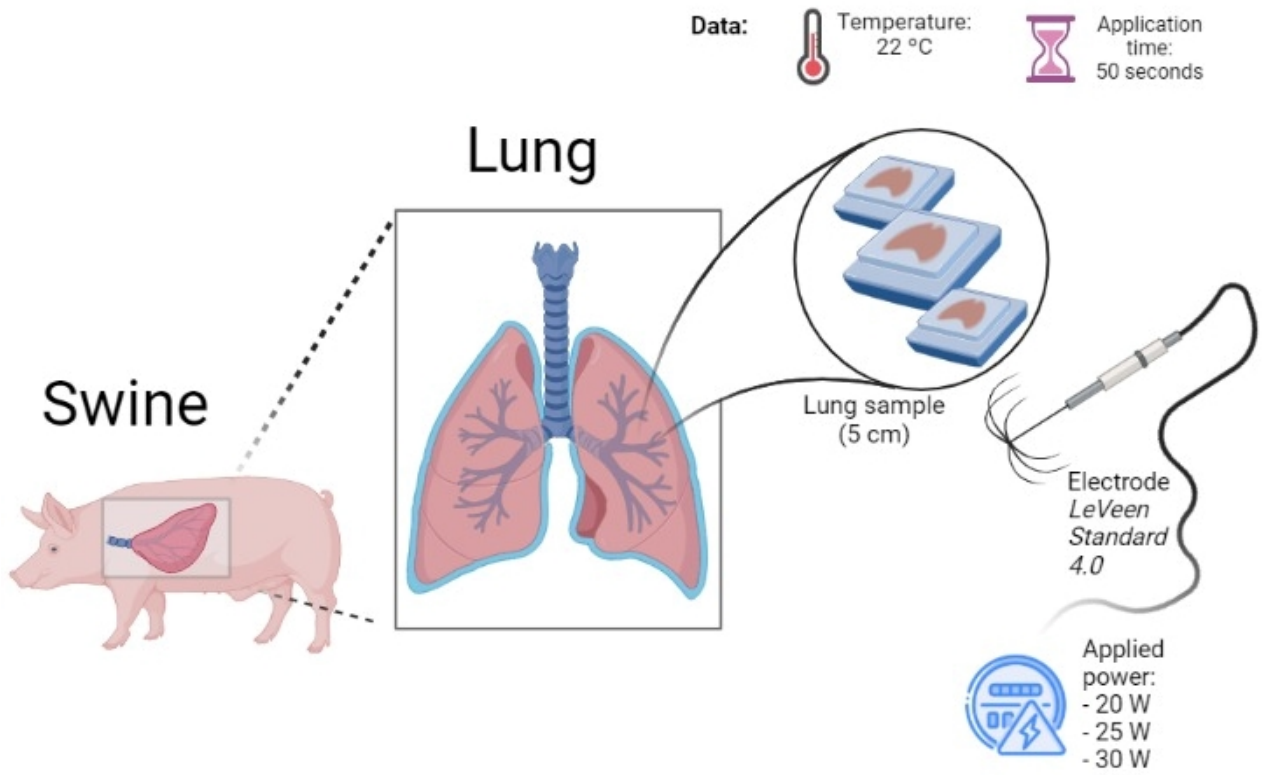


Figura 1: **Setup of the experiment used for the trial with pig parts *ex-vivo* and the SOFIA ablation equipment.**

where: G is the indirectly measured conductance, i is the measured current and v is the measured voltage.

These procedures were performed to ensure that the vectors containing the input and output data have the same dimension, a prerequisite for performing system identification.

2.3 System identification

The system identification procedure was performed using the Matlab® System Identification Tool. Three models were generated for each experimental group with the sinusoidal input signal and the conductance values of each sample as output. The vector with the average of the conductance values of each group was used as validation data for the models. The same procedure was applied to the three groups.

The system was represented by the mathematical model ARX (Auto Regressive with External Input) in the form of a transfer function. Estimates were made in the discrete time domain with a sampling time of 0.02 s. In each case, the number of poles and zeros was chosen to obtain the best estimation and validation.

In each group, the model with the best validation and estimation fit was selected to represent the power range being analysed. The models were represented in transfer functions. These functions were then reduced to the second degree using the balred function of Matlab® so that they could be analysed using classical control techniques.

2.4 Analyses

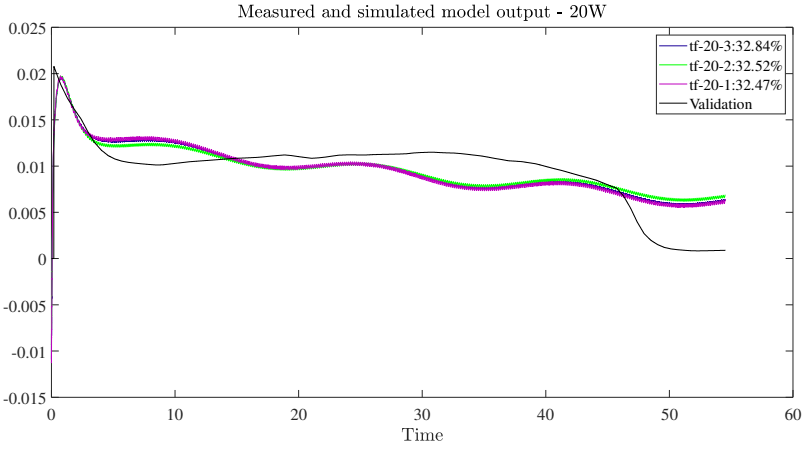
For the analysis of the discrete second order transfer functions obtained for the three power signals. First, the mapping of the poles and zeros was evaluated to determine the stability of the obtained models. The step response were observed to evaluate the time evolution and the behaviour in the permanent evaluation of the stability BIBO - Limited Input - Limited Output. Characterisation of these responses will be presented for future analysis.

3. RESULTS

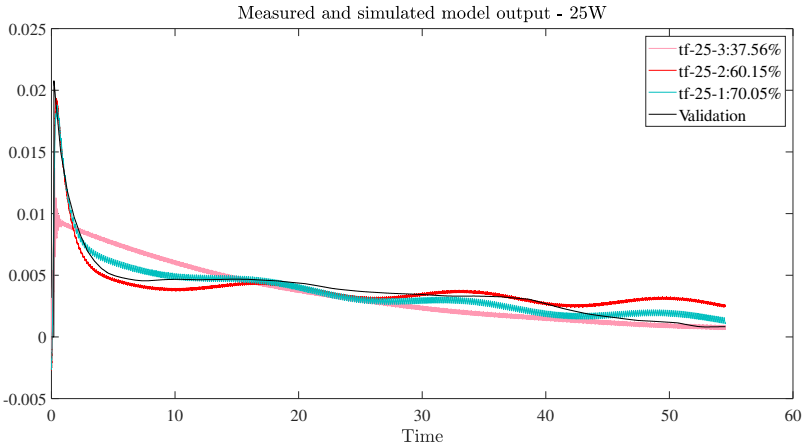
The Tab. 1 shows the results obtained for the three performance domains. No single selection criterion was used to choose the model, but in each case the best estimate FIT and the best validation FIT were sought. For the validation of the models, the average vector was used, which was calculated from the samples of the individual performance areas. In Fig. 2 it can be seen that the models followed the validating data. For the 20 W power the models were able to follow the behaviour for almost the whole sample, however in the final part there was a divergence, which possibly occurred due to an abrupt change in the data. The two other powers, 25 W and 30 W the models followed the reference in a satisfactory way.

Tabela 1: **Percentage results of validation fit and best fit of the models.**

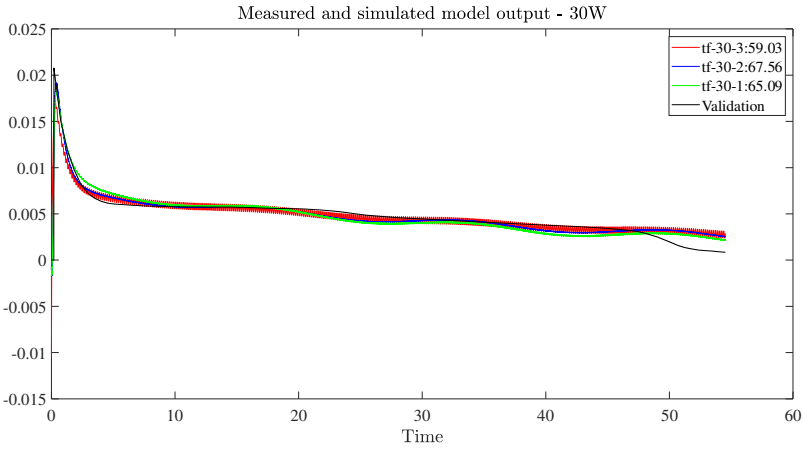
Experimental group	Sample	Fit to estimation data	Best fits
20 W	01	28.7%	32.46%
	02	30.84%	32.51%
	03	37.15%	32.84%
25 W	01	72.44%	62.09%
	02	58.58%	67.56%
	03	57.17%	59.03%
30 W	01	67.97%	70.05%
	02	60.31%	60.14%
	03	49.13%	37.55%



(a) 20 W



(b) 25W



(c) 30 W

Figura 2: **Models generated in the System Identification App of Matlab® for each power tested.**

Equations (2) through (4) present the second-order transfer functions that represent the mathematical models describing the dynamic response of lung tissue *ex-vivo* to the power stimulus applied by the RFA device. Then, the stability of the systems was evaluated using the map of the poles and zeros of the equations. The obtained result is shown in Fig. 3, where it can be seen that the systems are stable.

$$H_{20}(z) = \frac{-0.004136z^2 + 0.008315z - 0.004179}{z^2 - 1.998z + 0.9979} \tag{2}$$

$$H_{25}(z) = \frac{0.0001972z^2 - 0.0003999z + 0.0002028}{z^2 - 1.998z + 0.9976} \tag{3}$$

$$H_{30}(z) = \frac{0.0002793z^2 - 0.0005647z + 0.0002855}{z^2 - 1.997z + 0.9974} \tag{4}$$

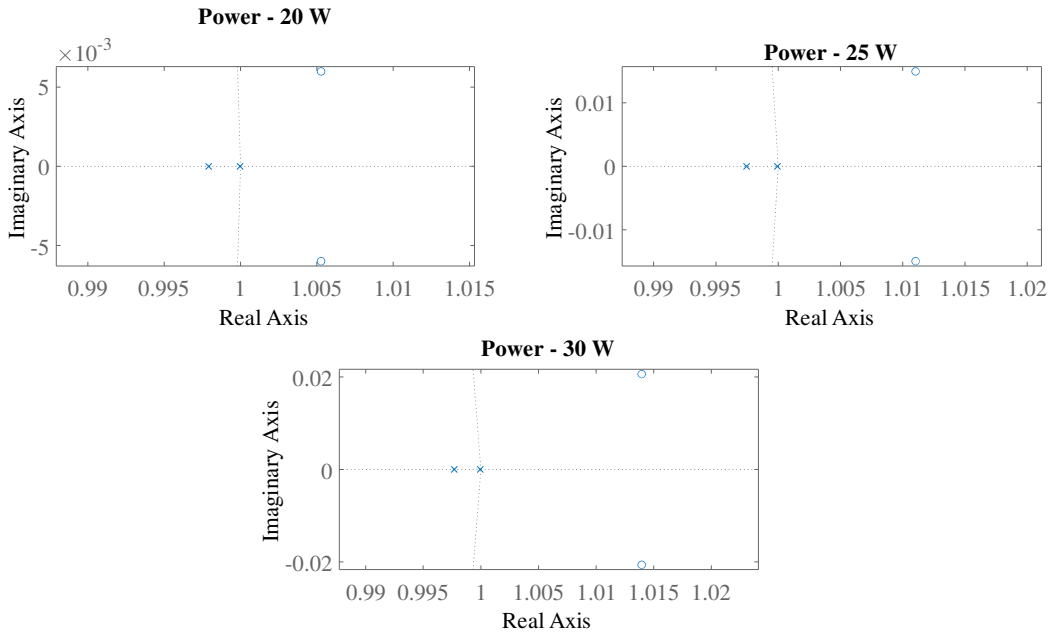


Figura 3: **Matlab's System Identification App poles and zeros diagram for each experimental group.**

To analyze the performance of the second-order systems, we focus on the transient response (dynamic response) of the three applied forces, whose parameters are shown in Tab. 2. The graph with the step response is shown in Fig. 4.

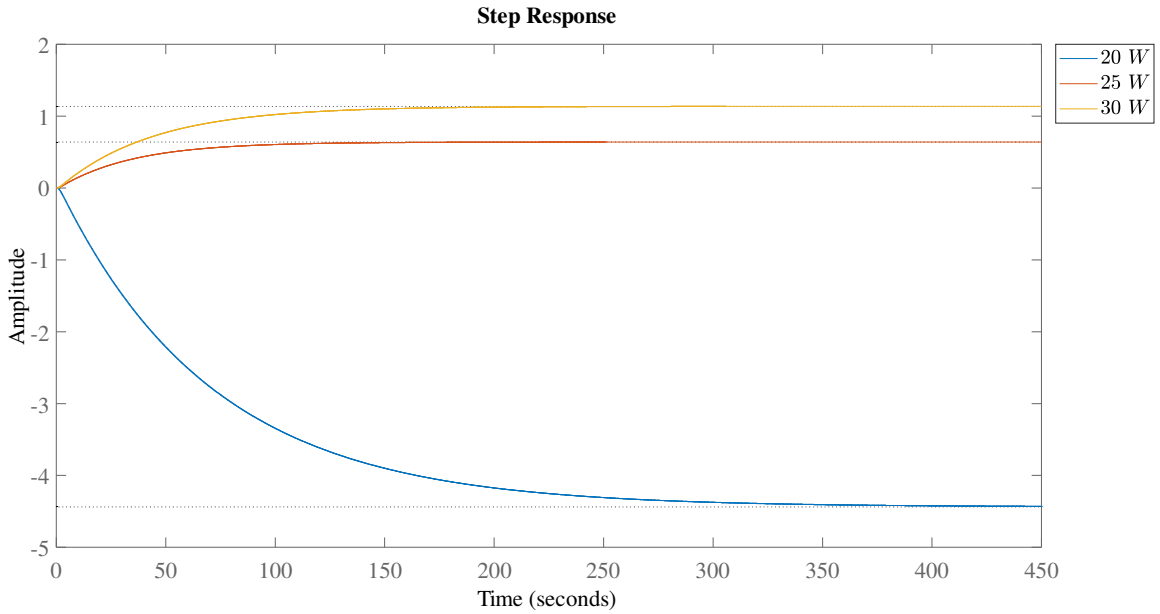


Figura 4: **Step response generated in Matlab's System Identification App for each experimental group.**

Tabela 2: **Parameters of the step responses for the obtained models.**

Parameter	**20 W**	**25 W**	**30 W**
RiseTime:	154.6258	94.4983	74.3178
SettlingTime:	276.5988	169.2102	133.2393
SettlingMin:	-4.4328	1.0237	0.5765
SettlingMax:	-3.9947	1.1365	0.6402
Overshoot:	0	0	0
Undershoot:	0	0	0
Peak:	4.4328	1.1365	0.6402
PeakTime:	475.9697	305.8455	250.9242

As in the Fig. 5, the signal exceeded the unit value, so it was necessary to control the system variables. Since all models obtained were discrete, it would be necessary to develop a discrete controller in future studies. It is expected that after the mesh is closed, the tissue response to the treatment will be optimised to minimise the regime error and maximise the results.

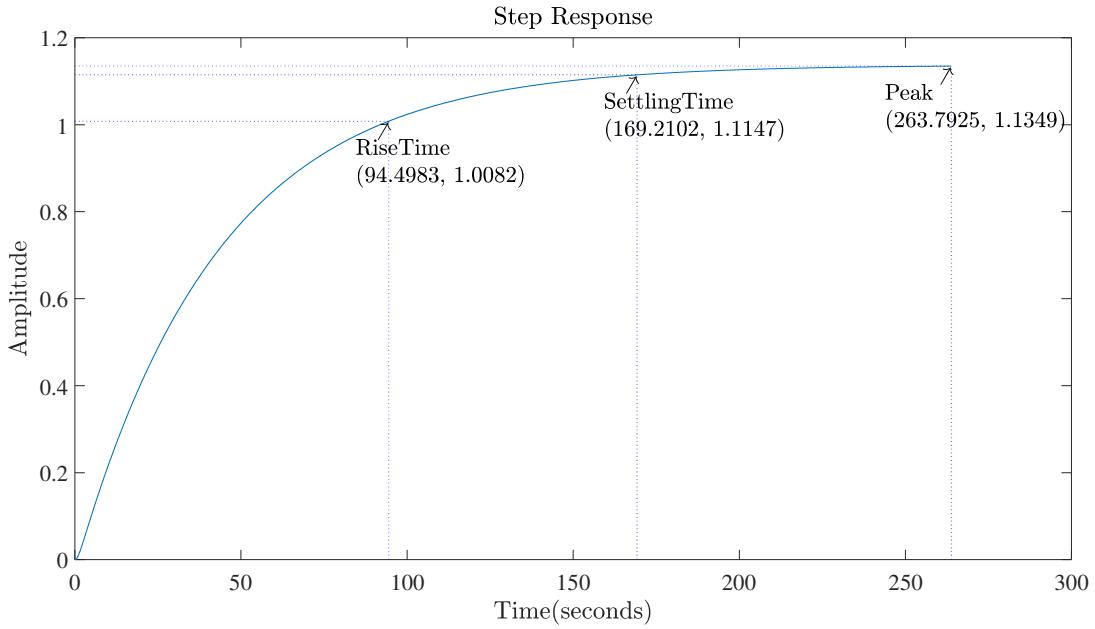


Figura 5: **Step response for 25 W generated in Matlab's System Identification App for each experimental group.**

4. RESULTS ANALYSIS

Testing biological systems using medical devices is an area of engineering where results need to be extended to support the development of mathematical models based primarily on data with simulations *ex-vivo*, *in-vivo* or agar models so that we can support the development of new devices. On the other hand, decisions should be made in data acquisition, model extraction, validation and analysis that restrict, simplify, and do not represent the real phenomenon (González-Suárez *et al.*, 2021). These results are intended to show a first way of identifying information without considering the underlying assumptions. They show that using a device with controlled and known (calibrated) output one can raise models with data collected in experiments and expand the understanding, in this case of tissue and its correlation with the input signal.

In this work, mathematical models were obtained to describe the behavior of the lung tissue when submitted to the ablation procedure. These models were represented by transfer functions in Z domain that have as input signal of the system the power emitted during the RFA procedure and as output signal the tissue conductance. A constant problem in the RFA procedure is the correlation of the power in the dynamic displacement of the tissue resistance curve. In the study by Labonté a model was presented that shows that a significant temperature difference occurs between the electrode and the tissue when the applied power is constant (Labonté, 1994). Therefore it becomes necessary to investigate which power favours the RFA procedure.

In our results the stability of the open loop systems was analysed from the map of poles and zeros in Fig. 3. In the three cases the poles of the equation are inside the unitary cicle, necessary condition for the systems to be stable. Despite presenting stability adjustments can still be implemented in the system to improve its response so it is important to know that the poles of the system are related to the velocity, while the zeros interfere in the amplitude (energy). The peak time data show that this dynamic response moment is reached in a longer time (slower) for a power value of 20 W than for the higher power of 30 W.

The dynamic response of the systems was evaluated from the unit step response. In Fig. 4, it is possible to notice that in the response for the 30 W power there is a positive steady state error that leads the response to exceed the upper limit. In contrast, when applied the power of 20 W this regine error is negative and causes the response not to converge to the unit value showing a dynamic behaviour different from the expected one. The power of 25 W, in this scenario, presents the best response by not exceeding the upper limit and presenting a median settling time. In this context, it is observed that neither the highest nor the lowest analyzed power present the ideal dynamics for the procedure, suggesting that a better heat propagation would happen with an intermediate power (25 W). Although the power of 25 W presents the best scenario of this study, it is necessary to implement controllers to adjust parameters such as overshoot and even to control the peak instant of response.

5. CONCLUSION

The device SOFIA is a Brazilian technology for RFA treatment, which is already consolidated for liver tissue and has great potential for expanding its use for other tissues such as lung and kidney. To this end, it is necessary to adjust the parameters of the signal emitted by the device so that the treatment can be optimised and adapted taking into account the characteristics of the organ on which it acts.

The goal of this work was to identify parameters that may help to adapt the device in a future scenario. To this end, three different power ranges (20, 25, and 30 W, respectively) were analysed and applied *ex-vivo* to porcine lung tissue. Mathematical models representing the dynamic response of lung tissue *ex-vivo* to the power stimulus of the RFA.

We conclude that a more detailed analysis of these parameters should be performed, taking into account other parameters such as the burn area, the frequency of the applied signal, the type of electrode used, and other power ranges. It is emphasised the importance of studying these parameters not only for the adaptation of the devices, but also for the adaptation of the treatment protocol proposed in the future.

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