Check for updates

Sensitivity Analysis of a Cardiac Electrophysiology Model for the Occurrence of Electrical Alternans

Rodrigo B. Pigozzo, Rodrigo Weber dos Santos, and Bernardo M. Rocha(✉)

Graduate Program in Computational Modeling, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil
rodrigo.pigozzo@estudante.ufjf.br, {rodrigo.weber,bernardomartinsrocha}@ice.ufjf.br

Abstract. Cardiac arrhythmias are a serious health problem that can lead to sudden cardiac arrest, heart failure, and ultimately death. Electrical alternans is often seen in patients with cardiac arrhythmias, particularly those affecting the ventricles. Alternans is a beat-to-beat variation in the duration or amplitude of cardiac action potentials, which can be reflected in alterations of the electrocardiogram. Identifying and monitoring electrical alternans in patients with cardiac arrhythmias can be important in preventing serious complications and improving outcomes. In the context of computational modeling of the heart, there are several mathematical models representing the generation of the action potential on cardiac cells. Some of these models do exhibit alternans, while others do not manifest this behavior. Therefore, considering the relevance of alternans in the study of deadly arrhythmias, it is of great interest to identify which are the parameters from a given mathematical cell model that contribute the most to the occurrence of alternans. The main objective of this study was to understand the parameters that most impact quantities of interest related to alternans behavior using local and global sensitivity analysis. To this end, we focused in this work on a simplified model of the cardiac action potential and evaluated the significance of its parameters for the action potential duration and the maximum slope of the restitution curve, which are relevant for alternans behavior. Overall, this study provides initial insights into the mathematical models of cardiac electrophysiology and how to evaluate the impact of parameters on alternans.

Keywords: cardiac electrophysiology · action potential alternans · Mitchell-Schaeffer model · Sensitivity Analysis · Sobol Indices

1 Introduction

Cardiac arrhythmias affect the heart's rhythm, causing it to beat too fast, too slow, or irregularly, leading to serious health problems, including sudden car-

Supported by organization x.

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2023
O. Gervasi et al. (Eds.): ICCSA 2023 Workshops, LNCS 14104, pp. 44–58, 2023.
https://doi.org/10.1007/978-3-031-37105-9_4

diac arrest, heart failure, and death. Electrical alternans is often seen in patients with cardiac arrhythmias, particularly those affecting the ventricles. Alternans is a phenomenon in which there is a beat-to-beat variation in the duration or amplitude of cardiac myocytes action potentials, which are the electrical signals that stimulate the heart muscle to contract. Clinical experiments and measurements indicate that electrical alternans can be a precursor to dangerous arrhythmias, such as ventricular fibrillation or sudden death [21]. The alterations of properties at the cellular level can also be reflected in variations in the amplitude or shape of the electrocardiogram (ECG) waveform. Therefore, identifying and monitoring electrical alternans in patients with cardiac arrhythmias can prevent serious complications and improve outcomes.

Despite the importance of alternans in studying heart diseases, many mathematical models for the electrophysiology of cardiac myocytes cannot reproduce this phenomenon, while others do [4,6]. Although some techniques for promoting alternans in specific cardiac cell models exist [2], there is a lack of studies in the literature evaluating the role and impact of model parameters on the occurrence of alternans. A recent study [10] using a technique known as population modeling identified the ion channel that maximally affected the occurrence of APD alternans and found that relevant quantities of interest were sensitive to changes in the plateau calcium current of the cardiac cell model under consideration.

In this work, we identify the most relevant parameters for quantities of interest related to alternans promotion, such as the action potential duration and the maximal slope of the restitution curve. A simplified mathematical model of the cardiac action potential, such as the modified Mitchell-Schaeffer (MMS), was used in this study to limit the number of parameters under investigation since it consists of a two-variable model with four parameters. Both local and global sensitivity analysis (SA) methods [15], such as the one-at-a-time and Sobol indices, were used in this initial investigation to provide insight into the impact of the model parameters. The choice of the MMS model for this work is also based on the fact that analysis is available, which allows the evaluation of the model dynamics for a given set of parameters and a comparison with the results obtained via the sensitivity analysis. This is important for validating the approach presented in this work, especially considering that most realistic cardiac cell models in the literature have several variables and parameters for which no mathematical analysis is available to describe their dynamics.

The remainder of this document is organized as follows: in the next section, we present the mathematical models for cardiac electrophysiology and the computational methods used to analyze their alternans behavior. In Sect. 3, we present some numerical experiments using the sensitivity analysis tools, and in Sect. 4, our concluding remarks on the results and findings of this work are presented.

2 Mathematical Model and Methods

We begin this section by presenting the mathematical model for the generation of cardiac action potential used to investigate the electrical alternans phenomenon.

Some basic concepts related to alternans, such as the restitution curve, are introduced in the sequence. Mathematical and computational tools for sensitivity analysis of the cardiac cell model are also presented in this section.

2.1 Cardiac Cell Model

There is a vast literature on cell models for generating cardiac action potential based on ordinary differential equations (ODEs). The models range from the seminal model of Hodgkin and Huxley [7] to more recent human ventricular models [18]. For this work, we used the modified Mitchell-Schaeffer Model (MMS) [1], a simple model with two variables capable of reproducing electrical alternans, for which some analytical results are available. The MMS model modifies the original Mitchell-Schaeffer (MS) model to avoid pacemaker behavior when exploring the parameter space, which is crucial for sensitivity analysis and could hinder the exploratory analysis of alternans classification. The unwanted pacemaker behavior manifests as the transmembrane potential cyclically depolarises and repolarises without any applied external stimulus (see [1] for further details).

The MMS model consists of two variables: the transmembrane potential or voltage $v_m(t)$, and the gating variable $h(t)$, which satisfy the following ODEs:

$$\frac{dv_{\mathrm{m}}}{dt} = h\frac{(v_{\mathrm{m}} + \mathrm{a})\,(v_{\mathrm{m}} + \mathrm{a} - \lambda)\,(1 - v_{\mathrm{m}})}{\tau_{\mathrm{in}}} - \frac{v_{\mathrm{m}}}{\tau_{\mathrm{out}}} + J_{\mathrm{stim}}, \tag{1}$$

$$\frac{dh}{dt} = \begin{cases} \frac{1-h}{\tau_{\mathrm{open}}} & v_{\mathrm{m}} \le v_{\mathrm{gate}} \\ -\frac{h}{\tau_{\mathrm{close}}} & v_{\mathrm{m}} > v_{\mathrm{gate}} \end{cases}, \tag{2}$$

where J_{stim} is an externally applied stimulus current, v_{gate} is the activation threshold potential and the parameters τ_{in}, τ_{out}, τ_{open}, τ_{close} are time constants controling important features of the action potential. The parameters a and λ are set to 0 and v_{gate}, respectively, in the MMS model [1].

The first term on the right-hand side of Eq. (1) represents the inward current (J_{in}) whose strength is specified by the time constant τ_{in}. The second term is the outward current (J_{out}), which consists of a combination of the currents which decrease the membrane voltage, such as the potassium current. Likewise, in the inward current, the time constant τ_{out} controls the strength of the outward current. The gating variable h is open when $h = 1$ and closed when $h = 0$, as can be seen from Eq. (2). The parameters τ_{close} and τ_{open} are the time constants with which the gate controlled by the h variable closes and opens, respectively.

An action potential of the MMS model is presented in Fig. 1, which was generated using the baseline parameter values presented in Table 1.

2.2 Alternans

In cardiac electrophysiology, alternans is a beat-to-beat alternation in cellular action potential shape and duration [17], despite a constant pacing period (basic cycle length - BCL), that may lead to alternans in the T-wave of the ECG [22].

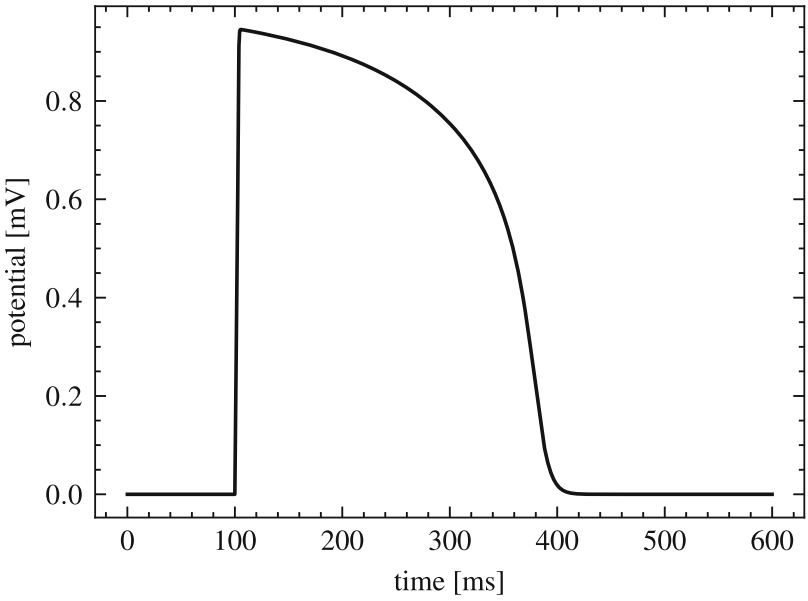

Fig. 1. Action potential generated by the MMS model when a external stimulus is appled at $t = 100$ ms for the baseline parameters: $v_{\text{gate}} = 0.13$, $\tau_{\text{in}} = 0.3$, $\tau_{\text{out}} = 6.0$, $\tau_{\text{open}} = 120$, and $\tau_{\text{close}} = 150$.

Table 1. Baseline parameter values for the MMS model, and the interval used for the SA of alternans behavior.

Parameter	Baseline value	Interval
τ_{in}	0.3	[0.1, 0.5]
τ_{out}	6.0	[2.0, 10.0]
τ_{open}	120.0	[40.0, 200.0]
τ_{close}	150.0	[50.0, 250.0]

An example of alternans of action potential for the MMS model is presented in Fig. 2 below.

The BCL can be expressed as the sum of the diastolic interval (DI) and APD. Alternans are often associated with dangerous arrhythmias like ventricular fibrillation [5]. Alternans can be observed in single cardiac cell simulations through the action potential restitution protocols, which are commonly used in cardiac electrophysiology to investigate the APD and the rate adaptation properties of cardiac cells. Essentially, APD restitution refers to the natural shortening of APD in response to faster heart rates.

2.3 Restitution Curve

The dynamics of a paced cardiac cell can be described through the restitution curve, which is obtained by plotting APD as a function of the basic cycle length

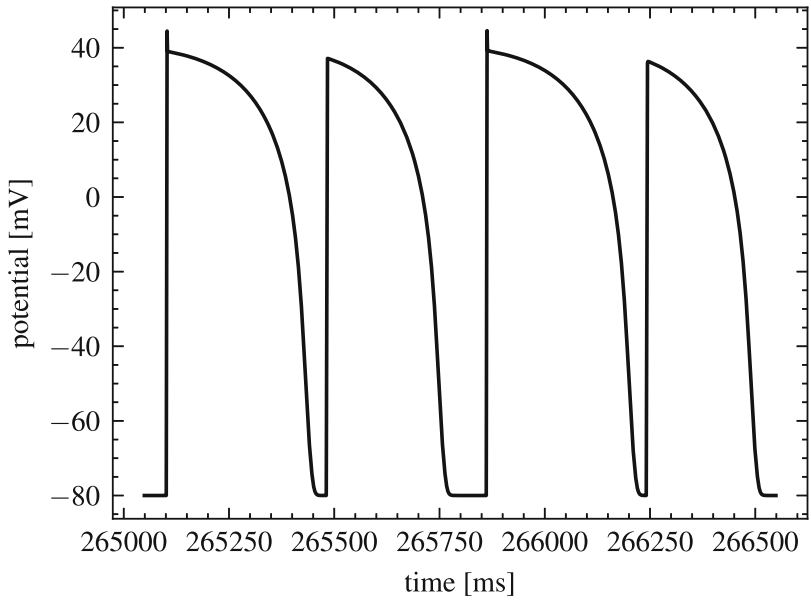

Fig. 2. APDs of the MMS Model and the occurrence of alternans. The model parameters used for generating this pulses are: $\tau_{\text{in}} = 0.1$, $\tau_{\text{out}} = 9.0$, $\tau_{\text{open}} = 100$, and $\tau_{\text{close}} = 120$.

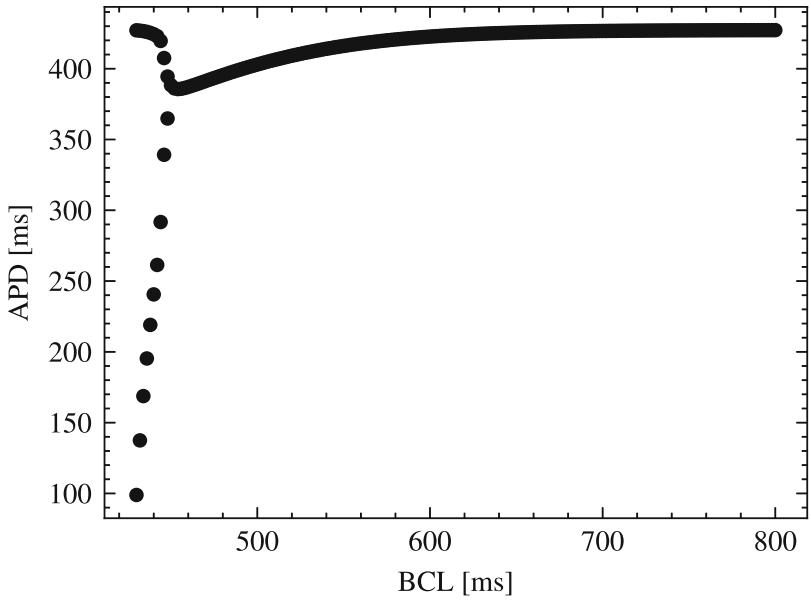

Fig. 3. Restitution curve of the MMS model and the occurrence of alternans at BCL of 320 ms. The model parameters used for generating this curve are: $\tau_{\text{in}} = 0.1$, $\tau_{\text{out}} = 4.3$, $\tau_{\text{open}} = 50.1$, and $\tau_{\text{close}} = 177.5$.

(period). Alternans occur when a period-doubling bifurcation appears on the restitution curve. Figure 3 shows an example of the restitution curve for the MMS model for a specific set of parameters $\{\tau_{\text{in}}, \tau_{\text{out}}, \tau_{\text{open}}, \tau_{\text{close}}\}$ which results in alternans (as observed near the BCL of 320 ms).

Two different pacing protocols are usually employed to generate the restitution curve: the S1S2 and dynamic protocols [13,19]. The S1S2 pacing protocol involves applying two stimuli (S1 and S2) to a cardiac cell at different intervals to study its response. In the protocol, a basic cycle length (BCL) and a certain number of beats (n_{beats}) are selected for the pacing of the S1 stimuli. Following n_{beats} of the S1 pacing, a second stimulus (S2) is applied at a range of coupling intervals (CI). When using a dynamic pacing protocol, a number of beats of the S1 pacing are given, and then the S1 cycle length is decremented until the minimum CI is reached.

The restitution curve can also be studied using the graphical approach proposed by [12], which is characterized by the dependence of APD on the preceding diastolic interval (DI). Defining the action potential duration of the next cycle as

$$APD_{i+1} = f(DI_i) = f(BCL - APD_i) \tag{3}$$

gives an iterative map (for a fixed period $BCL = APD_i + DI_i$), where f represents the function relating the new APD to its previous DI. As detailed in [12], it is said the restitution curve is stable when

$$|f'(DI_i)| < 1, \tag{4}$$

and when

$$|f'(DI_i)| > 1, \tag{5}$$

it represents a predictor for the occurrence of alternans. In other words, if the maximum slope of the restitution curve is greater than one, alternans may occur. Figure 4 shows an example of the APD and DI relation for the MMS.

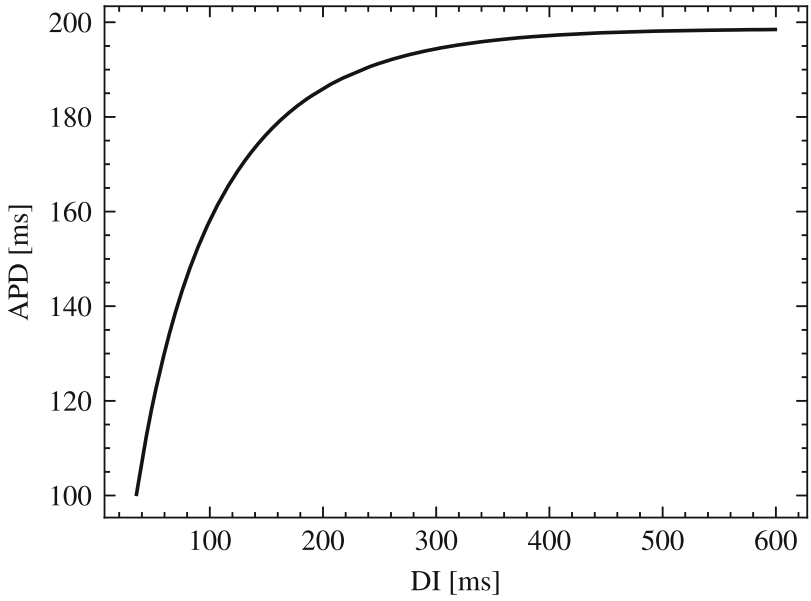

Fig. 4. Another example of restitution Curve for the MMS Model showing APD as a function of DI.

2.4 Restitution Curve for the MMS

Both the original MS [11] and the MMS [1] models, present an asymptotic derivation of the restitution curve, which is a closed expression relating APD and DI. For the MMS model it is given by:

$$\mathrm{APD}_{\mathrm{n+1}} = f(DI_i) = \tau_{\mathrm{close}} \ \ln\left(\frac{1-\left(1-h_{\mathrm{min}}^{\mathrm{MMS}}\right)e^{-\frac{\mathrm{DI}_{\mathrm{i}}}{\tau_{\mathrm{open}}}}}{h_{\mathrm{min}}^{\mathrm{mMS}}}\right), \tag{6}$$

where $h_{\mathrm{min}}^{\mathrm{MMS}}$ is given by

$$h_{\mathrm{min}}^{\mathrm{MMS}} = \left(1+\frac{\tau_{\mathrm{out}}}{4\tau_{\mathrm{in}}}\left(1-v_{\mathrm{gate}}\right)^2\right)^{-1}. \tag{7}$$

Therefore, to determine if, for a given set of parameters, the MMS model predicts the occurrence of alternans, the criterion was to verify if Eq. (6) satisfied the condition $|f'(DI_i)| > 1$.

2.5 Quantities of Interest

To evaluate the occurrence of alternans or not, two quantities of interest (QoI) were defined and evaluated via sensitivity analysis. The action potential duration (APD) and the maximum slope of the restitution curve (MaxSlope) for single

cardiac cells were considered QoIs. These quantities were defined and computed as follows:

- APD: Action potential duration measures the time taken from the depolarization to the repolarization during an action potential (see Fig. 1). We considered APD measured at 90% repolarization (APD90) as the metric for APD. It is calculated by determining the time interval between the peak of the action potential and the point at which the membrane potential has repolarized to 90% of its initial value.
- MaxSlope: This quantity was defined as the maximum slope of the restitution curve generated for the single cardiac cell using the dynamic pacing protocol. The maximum slope of the restitution curve (MaxSlope) was calculated using the gradient of the restitution curve (see Fig. 4), which was computed using second-order accurate central differences in the interior points.

2.6 Sensitivity Analysis

The investigation of how changes or fluctuations in model inputs impact the output of a mathematical model, whether it can be distinguished qualitatively or quantitatively, is known as sensitivity analysis (SA) [3]. There exists several techniques for performing SA in the literature, such as the local one-at-a-time (OAT), the elementary effects method (EE), Sobol' indices, and others.

SA can be used for many purposes: identifying important input variables, model calibration and validation, risk assessment, decision-making, and optimization [15]. SA can help better understand the behavior of complex systems, such as in the present case of alternans occurrence in mathematical cell models of the action potential.

In this work, we used the well-known Sobol indices [16] for conducting global sensitivity analysis of the MMS model with respect to quantities of interest relevant to the occurrence of alternans. Local SA through the OAT method was also evaluated to complement the results. Let Y be a scalar quantity of interest for which we want to assess the impact of the input parameters $\mathbf{X} = \{X_1, X_2, \ldots, X_D\}$. The first-order Sobol index expresses the direct influence of a parameter X_i on the variance of the quantity of interest Y and is given by:

$$S_i = \frac{\mathbb{V}\left[\mathbb{E}\left(Y \mid X_i\right)\right]}{\mathbb{V}(Y)} \tag{8}$$

where $\mathbb{E}$ denotes the expected value, $\mathbb{V}$ represents the variance, and $\mathbb{E}\left(Y \mid X_i\right)$ denotes the expected value of the output Y when the parameter X_i is fixed. The first order Sobol sensitivity index represents the expected reduction in the variance of the analyzed quantity when the parameter X_i is fixed.

The total Sobol index represents possible interactions between the input parameters and their effects on the Y quantity. For the input X_i it is denoted by S_{T_i}, and is given by:

$$S_{T_i} = \frac{\mathbb{E}\left[\mathbb{V}\left(Y \mid X_{\sim i}\right)\right]}{\mathbb{V}(Y)} = 1 - \frac{\mathbb{V}\left[\mathbb{E}\left(Y \mid X_{\sim i}\right)\right]}{\mathbb{V}(Y)} \tag{9}$$

where $X_{\sim i}$ represents all input parameters except the X_i parameter.

3 Numerical Experiments

In this section, we present details on the implementation and design of the numerical experiments, as well as the results of sensitivity analysis in terms of APD and the maximum slope of the restitution curve for the MMS model.

3.1 Implementation

The numerical simulations carried out in this work were performed using the `openCARP` simulation environment for cardiac electrophysiology [13]. To this end, the MMS model had to be implemented as a cell model in the environment. In particular, the simulations were based on existing `openCARP` modules for computing the APD of a single cardiac cell. The restitution curve was generated using the expression for the MMS model given by Eq. (6).

The computational experiments of this work were all carried out in a code implemented in the Python programming language with support for scientific computing through the `NumPy` and `SciPy` libraries [20].

In this work, the first order and total order Sobol sensitivity indices were calculated for quantities of interest (QoI) from the MMS Model using the Saltelli method [14] available in the `SAlib` library [9] for the Python programming language.

3.2 Design of Experiments

Table 1 shows the parameter space used for conducting the SA of the MMS model, which was selected such that the baseline values were centered between the lower and upper limits and considering a coefficient of variation of approximately 66%. Considering a total of $D = 4$ parameters under investigation, a total of $N * (2D + 2) = (N * 10)$ samples were used to carry out the sensitivity analysis via *Sobol indices*. The value of N was chosen as $N = 2^{10} = 1024$, resulting in a total of 10240 samples from which APD and the restitution curve had to be computed.

In addition, the one-at-a-time approach was performed by exploring the parameters using the lower limit, baseline value, and upper limit values (from Table 1) for the analysis of each parameter.

3.3 Sensitivities for APD

We begin by presenting the results of the OAT study for the APD of the MMS, which is presented for each parameter on Fig. 5. The results show that reducing τ_{in} increases the APD, while increases in the values of both τ_{out} and τ_{close} increases the APD. Results also indicates that τ_{open} has negligible effects on the APD.

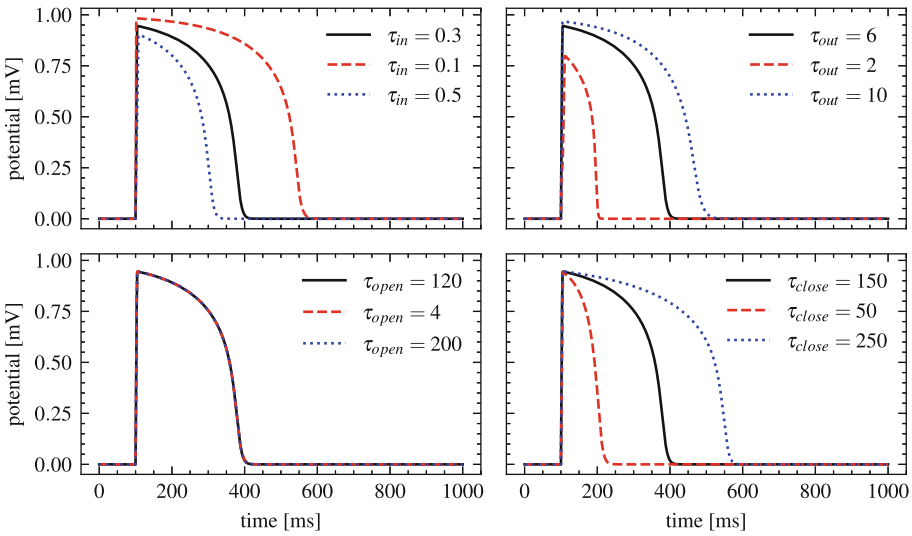

Fig. 5. Local one-at-a-time SA of the parameters of the MMS model for APD.

Figure 6 shows the results of the main and total Sobol indices for the APD considering the for time constant parameters. The results in terms of the main Sobol indices reiterates the OAT analysis made earlier since it indicates that the most influential parameter in the APD is, in fact, τ_{close}, and that τ_{open} parameter that does not impact the APD. From the total Sobol indices, one can observe that a small interaction between the parameters contribute to the variation on APD.

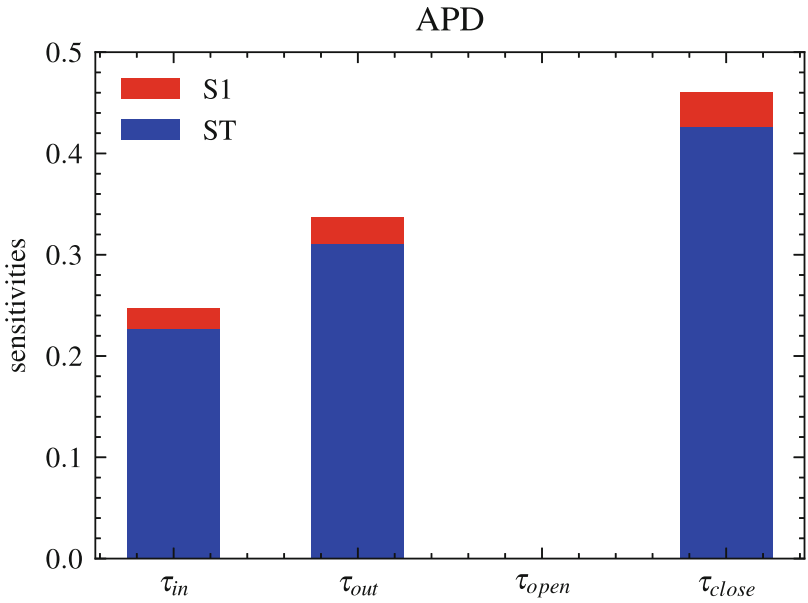

Fig. 6. The main (S1) and total (ST) Sobol indices calculated for the APD of the MMS model.

3.4 Sensitivities for Maximum Slope of the Restitution Curve

Here we present the results of sensitivity analyses for the maximum slope of the restitution curve, which can be used for the prediction of alternans. Figure 7 presents the results of the OAT study for MaxSlope, which indicate that τ_{in}, τ_{out}, and τ_{close} parameters influence this quantity significantly. The only exception is τ_{open} whose influence on the variation of the maximum slope is small.

Sobol sensitivity indices are reported in Fig. 8, which show that except for τ_{open}, the other three parameters have a significant impact on the analyzed QoI, as demonstrated via the main indices. For this quantity, it is interesting to observe that high-order interactions between the parameters are present, as can be observed via the total Sobol indices (when they are greater than the main indices).

3.5 Discussion

It is interesting to confront the results of the SA based on Sobol indices with knowledge from the analysis of the MS model which provide a reparametrization to allow a direct classification of the alternans behavior in terms of two parameters. This analysis is not yet available for the modified MS used in this work, however, it is expected that it should not be much different from the one available for the MS model, which we recall next, since the difference between the models is minimal.

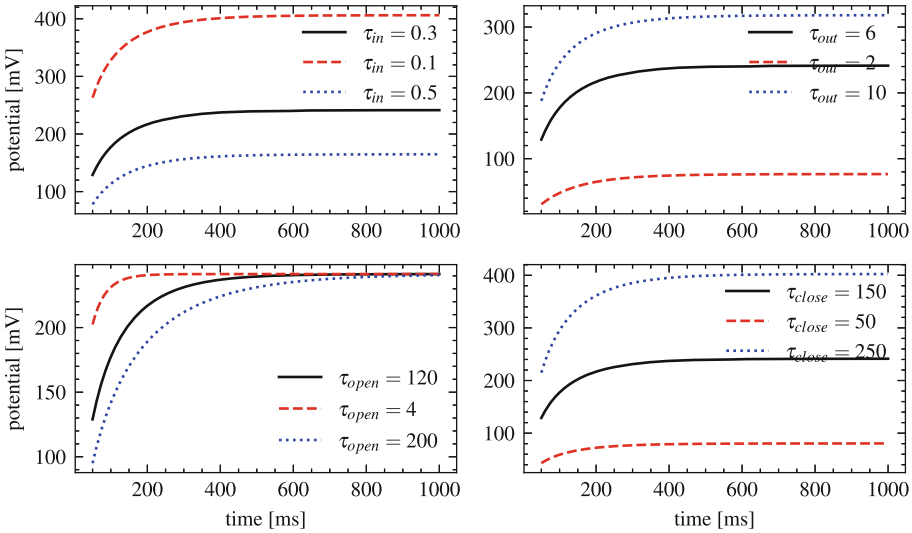

Fig. 7. Local one-at-a-time SA of the parameters of the MMS model for MaxSlope

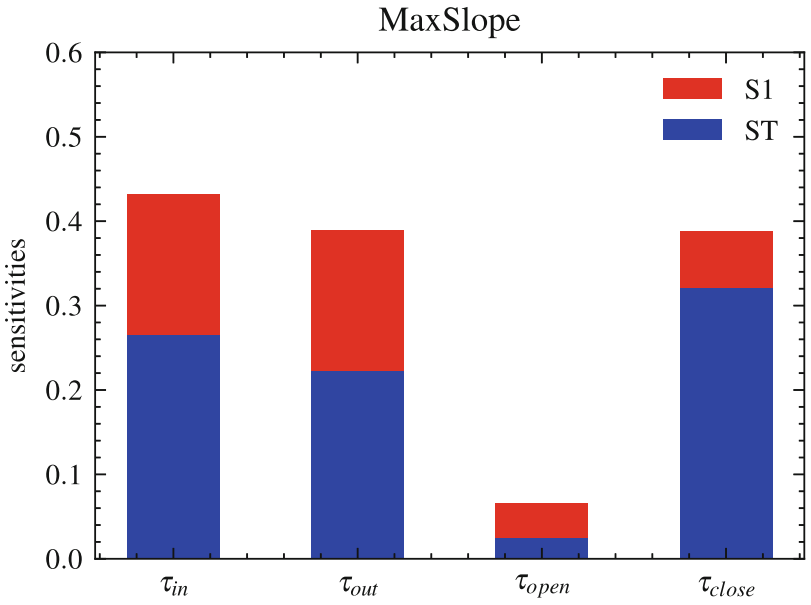

Fig. 8. The main (S1) and total (ST) Sobol indices calculated for the MaxSlope (maximum slope of the restitution curve) of the MMS model.

For the MS model [11] one can define dimensionless quantities that can be used to classify the behavior of the solutions. The following quantities are defined:

$$h_{\min} = 4\left(\frac{\tau_{\text{in}}}{\tau_{\text{out}}}\right), \quad h_{\text{thr}} = \frac{\tau_{\text{in}}}{\tau_{\text{out}}}\frac{1}{v_{\text{stim}}(1 - v_{\text{stim}})} \quad r = \frac{\tau_{\text{open}}}{\tau_{\text{close}}}. \tag{10}$$

The region in the parameter space defined by $r < 1$ and below the curve defined by the following relation

$$h_{\text{thr}} = \left(\frac{1}{1+r} \right), \tag{11}$$

characterizes solutions with alternans behavior, whereas the remaining regions of the parameter space do not present alternans.

Figure 9 below shows the parameter space defined in terms of r and h_{thr} for the classification of the solutions. The lines in blue is the curve represents Eq. (11), and the region denoted by γ is where alternans occurs.

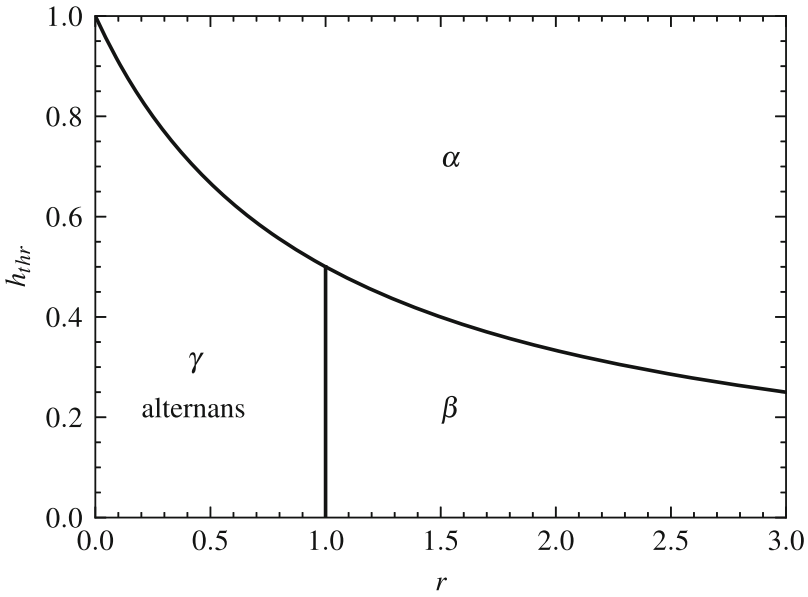

Fig. 9. Classification of the parameter space in the original MS model and the region γ where alternans occurs.

Comparing this information from the MS model and the results of the SA for the MMS in terms of the QoIs relevant for alternans behavior, one can notice that the role of the τ_{open} parameter has been neglected in both the local and global SA (via OAT and Sobol indices). However, analyzing the r parameter from Eq. (10), one can notice that τ_{open} is present, and it is relevant to result in values of r smaller than 1 (which is one of the conditions for the MS model to present alternans). From the graphical or schematic classification of the solution presented in Fig. 9 together with Eq. (10) for r, one can see that a given set of parameters on the right of $r = 1$ line and above the r_{thr} curve for which alternans does not occur, can be classified on the left where alternans occur by simply changing the value of the τ_{open} parameter. Therefore, its influence on the alternans behavior is relevant and was not captured by the local and global SA studies carried out.

4 Conclusions

In this work, we evaluated a mathematical model of cardiac electrophysiology with respect to complex dynamics known as alternans, a beat-to-beat variation in the shape and duration of the action potential. Local and global sensitivity analyses of quantities of interest, such as action potential duration and maximum slope of the restitution curve, which are relevant for the alternans behavior, were carried out for the modified Mitchell-Schaeffer model in terms of its four time constant parameters.

The results indicate that three of the four parameters significantly impact APD and the restitution curve's maximum slope for the parameter space explored in this work. However, previous analyses of the original model indicate that the four parameters are important for generating alternans dynamics. These findings clearly show the limitation of the classic Sobol indices for sensitivity analysis as the only metric for the classification of model behaviors. To summarize, these results highlight the need of other tools like regional sensitivity analysis [8,23,24] for the task of binary classification of model outputs based on the specified behavior definition.

Future works should explore techniques for the identification of the parameters that are more relevant for the alternans behavior. In addition to that, other possibilities for the extension of this work include the usage of surrogate models to accelerate the sensitivity analysis, the usage of other analytical findings of the MMS model to corroborate with computational studies, and also conducting the same type of study for more complex cardiac electrophysiology models with dozens of variables.

References

1. Corrado, C., Niederer, S.A.: A two-variable model robust to pacemaker behaviour for the dynamics of the cardiac action potential. Math. Biosci. **281**, 46–54 (2016)
2. Eastman, J., Sass, J., Gomes, J.M., Dos Santos, R.W., Cherry, E.M.: Using delay differential equations to induce alternans in a model of cardiac electrophysiology. J. Theor. Biol. **404**, 262–272 (2016)
3. Eck, V.G., et al.: A guide to uncertainty quantification and sensitivity analysis for cardiovascular applications. Int. J. Numer. Methods Biomed. Eng. **32**(8), e02755 (2016)
4. Elshrif, M.M., Cherry, E.M.: A quantitative comparison of the behavior of human ventricular cardiac electrophysiology models in tissue. PLoS ONE **9**(1), e84401 (2014)
5. Gizzi, A., Cherry, E.M., Gilmour, R.F., Jr., Luther, S., Filippi, S., Fenton, F.H.: Effects of pacing site and stimulation history on alternans dynamics and the development of complex spatiotemporal patterns in cardiac tissue. Front. Physiol. **4**, 71 (2013)
6. Gomes, J.M., Dos Santos, R.W., Cherry, E.M.: Alternans promotion in cardiac electrophysiology models by delay differential equations. Chaos: Interdisc. J. Nonlinear Sci. **27**(9), 093915 (2017)

7. Hodgkin, A.L., Huxley, A.F.: A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. **117**(4), 500 (1952)
8. Hornberger, G.M., Spear, R.C.: Approach to the preliminary analysis of environmental systems. J. Environ. Mgmt. **12**(1), 7–18 (1981)
9. Iwanaga, T., Usher, W., Herman, J.: Toward SALib 2.0: advancing the accessibility and interpretability of global sensitivity analyses. Socio-Environ. Syst. Model. **4**(18155), 10 (2022). https://doi.org/10.18174/sesmo.18155, https://sesmo.org/article/view/18155
10. Jeong, D.U., Marcellinus, A., Lim, K.M.: Sensitivity analysis of cardiac alternans and tachyarrhythmia to ion channel conductance using population modeling. Bioengineering **9**(11), 628 (2022)
11. Mitchell, C.C., Schaeffer, D.G.: A two-current model for the dynamics of cardiac membrane. Bull. Math. Biol. **65**(5), 767–793 (2003)
12. Nolasco, J.: A graphic method for the study of alternation in cardiac action potentials. J. Appl. Physiol. **25**(2), 191–196 (1968)
13. Plank, G., et al.: The openCARP simulation environment for cardiac electrophysiology. Comput. Methods Programs Biomed. **208**, 106223 (2021). https://doi.org/10.1016/j.cmpb.2021.106223
14. Saltelli, A., Annoni, P., Azzini, I., Campolongo, F., Ratto, M., Tarantola, S.: Variance based sensitivity analysis of model output. design and estimator for the total sensitivity index. Comput. Phys. Commun. **181**(2), 259–270 (2010)
15. Saltelli, A., et al.: Global Sensitivity Analysis: The Primer. Wiley, Hoboken (2008)
16. Sobol, I.M.: Global sensitivity indices for nonlinear mathematical models and their monte Carlo estimates. Math. Comput. Simul. **55**(1–3), 271–280 (2001)
17. Surawicz, B., Fisch, C.: Cardiac alternans: diverse mechanisms and clinical manifestations. J. Am. Coll. Cardiol. **20**(2), 483–499 (1992)
18. Tomek, J., et al.: Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block. Elife **8**, e48890 (2019)
19. ten Tusscher, K.H., Noble, D., Noble, P.J., Panfilov, A.V.: A model for human ventricular tissue. Am. J. Physiol. Heart Circulatory Physiol. (2004)
20. Virtanen, P., et al.: SciPy 1.0 contributors: SciPy 1.0: fundamental algorithms for scientific computing in python. Nat. Methods **17**, 261–272 (2020). https://doi.org/10.1038/s41592-019-0686-2
21. Wilson, L.D., Rosenbaum, D.S.: Mechanisms of arrythmogenic cardiac alternans. Europace 9(suppl_6), vi77-vi82 (2007)
22. You, T., Luo, C., Zhang, K., Zhang, H.: Electrophysiological mechanisms underlying t-wave alternans and their role in arrhythmogenesis. Front. Physiol. **12**, 614946 (2021)
23. Young, P.: Data-based mechanistic modelling, generalised sensitivity and dominant mode analysis. Comput. Phys. Commun. **117**(1–2), 113–129 (1999)
24. Young, P., Parkinson, S., Lees, M.: Simplicity out of complexity in environmental modelling: Occam's razor revisited. J. Appl. Stat. **23**(2–3), 165–210 (1996)