Modelling the Probabilistic Neural Activation in Deep Brain Stimulation: Influence of Uncertainty in the Parameters of the Electrode-Tissue-Interface

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***Abstract*—Deep brain stimulation (DBS) is a neurosurgical method of stimulating deep brain areas with electrical pulses to treat symptoms of neurodegenerative disorders. To date in human DBS, these pulses are commonly voltage controlled resulting in a formation of an electrical double layer at the electrode-tissue-interface, which influences the time-dependent voltage response and neural activation in the proximity of the stimulated target. The aim of this study was to investigate the effect of uncertainties in these parameters. A probabilistic method based on a multi-dimensional polynomial expansion in combination with computationally efficient sparse grid integration technique was used. The results suggested that the influence of uncertainty in the parameters of the electrical double layer on the investigated quantities is negligible in volume conductor models of DBS.**

I. Introduction

Deep brain stimulation (DBS) is a widely employed neurosurgical method to treat the symptoms of motor skill disorders such as Parkinson's disease (PD), essential tremor and dystonia by implanting a stimulation electrode in a group of nuclei situated at the base of the forebrain, the basal ganglia [1]. Although the method has become a common procedure in these clinical fields [2], the fundamental mechanisms of action of DBS remain uncertain [3]. To date many computational models have been developed to gain more insight into these mechanisms. A number of these models have concentrated on the computation of the neural activation and time-dependent voltage response in the proximity of the stimulated target to investigate the extent of activation in dependence of the applied stimulation pulse. In human DBS, voltage controlled stimulation pulses are commonly used for the treatment. In this stimulation mode the voltage response in the proximity of the stimulated target is not only influenced by the material properties of brain tissue, but also by the electrode-tissue interface at the electrode contact surface known as the electrical double layer. The properties of this layer can be modelled by using a constant phase element, which describes its resistive and capacitive electrical properties. The parameters of the constant phase element are based on an experimental study and subject to uncertainty [4]. Current computational models only consider one set of parameters and do not take into account the influence of uncertainties on the solution.

The aim of this study was to investigate the sensitivity of the time dependent voltage response and volume of tissue activated (VTA) of a unipolar and voltage controlled DBS electrode setup on the uncertain parameters of this double layer. A probabilistic approach was implemented by using a polynomial expansion known as polynomial chaos (PC) to approximate these probabilistic quantities. The computationally expensive deterministic model, which combines a finite element volume conductor model of the human brain and a multi-compartmental neuron model, was used to compute the coefficients of this polynomial expansion using a sparse grid integration technique, which resulted in an computational efficient method to compute the probabilistic voltage response and VTA compared to traditional probabilistic sampling methods such as Monte Carlo simulations.

II. Methods

A. Polynomial Chaos

The probabilistic voltage response and VTA are approximated by a set of orthogonal polynomial basis functions $\psi(\boldsymbol{\xi})$ of the uniformly distributed random variables $\boldsymbol{\xi} = (\xi_1, \dots, \xi_M)$ in $\mathcal{U}[-1,1]$, where M is the number of independent random model parameters. This expansion is known as the polynomial chaos (PC) [5]. For uniformly distributed random variables, products of Legendre Polynomials form the optimal set of basis functions for the polynomial expansion. In practice this expansion is truncated at a number P_{out} of basis functions, resulting in the polynomial expansion

$$Z = \sum_{i=0}^{P_{\text{out}}} c_i \psi_i(\boldsymbol{\xi}) \ . \tag{1}$$

The coefficients c_i are determined by projecting Z on each basis function $\psi_i(\boldsymbol{\xi})$ and exploiting its orthogonality in the domain $\Omega = [-1,1]^M$

$$c_i = \frac{1}{\langle \psi_i(\boldsymbol{\xi}), \psi_i(\boldsymbol{\xi}) \rangle} \int_{\Omega} Z(\boldsymbol{\xi}) \psi_i(\boldsymbol{\xi}) f(\boldsymbol{\xi}) \, \mathrm{d}\boldsymbol{\xi} \ , \tag{2}$$

with the probability density function $f(\boldsymbol{\xi})$ and $i = 0, 1, \dots, P_{\text{out}}$. The integral is evaluated numerically by using nested Smolyak sparse grids $S(L, M)$ with the grid level $L = 2^L + 1$ for $L > 1$, as described in [6], and traditional tensor grids in combination with the one-dimensional Clenshaw-Curtis rule [7]. The magnitude of the uncertainty is determined by the relative standard deviation σ_r

$$\sigma_r = \frac{\sigma}{\mu} \tag{3}$$

with the mean μ and the standard deviation σ.

B. Human Brain Model

A 3D volume conductor model of the human brain based on segmented magnetic resonance images of the digital brain atlas, the SRI24 multi-channel brain atlas, was developed. The model comprises (1) an ellipsoid resembling the geometry of the brain, (2) spatial information of gray matter, white matter, and cerebrospinal fluid, and (3) a realistic model of the cylindrical stimulating electrode Mo. 3387 of the vendor Medtronic. The electrode is positioned in the stimulated target area, the subthalamic nucleus. The mesh was refined manually at the electrode contact surfaces and the proximity of the stimulated target area until the deviation of the total current was below 1 %, which resulted in approximately 1.4 million elements. The material properties of the brain tissue types were determined from [8]. A detailed description of the model can be found in [9].

C. Time-Dependent Voltage Response

For the computation of the time-dependent voltage response, a hybrid method combining Fourier finite element method (FFEM) [10] and equivalent circuit representation of the electrical properties of the volume conductor model was developed. In this method a common stimulation pulse used in DBS therapy is transformed into the frequency-domain using a fast Fourier transform (FFT), scaled and phase shifted by the transfer function obtained from the equivalent circuit representation of the volume conductor model at each location of interest, and transformed back into the time-domain using an inverse FFT. This approach has the advantage of requiring only one FEM evaluation instead of 512 - 2,000 for the classical FFEM to obtain the transfer function [11], [12]. The equivalent circuit representation for voltage controlled stimulation consists out of the resistance R_{t} and capacitance C_{t} of the volume conductor model and the electrode-tissue-interface, which is modelled by a constant phase element (CPA), which impedance Z_{CPA} is given by the following equation

$$Z_{\mathsf{CPA}} = \frac{K}{A(\mathrm{j}\omega)^{\beta}} \tag{4}$$

with the electrode contact surface area A, the imaginary unit j, the angular frequency ω, the coefficient K, and the exponent $\beta \in [0, 1]$. Both parameters K and β were modelled as uniformly distributed random variables based on literature data [4] with a relative standard deviation of 50 % and 10 % of K and β, respectively (Table I). A quasi-static approximation of the time-harmonic Maxwell's equations was used to compute the field distribution inside the brain model. Boundary conditions were applied to the boundaries of the model, representing perfect conductors at the active electrode contact (1 V) as well as electrical ground at the bottom of the brain model (0 V) and insulation at the remaining electrode body as well as the exterior boundary of the model, respectively. The inactive electrode contacts were set to a floating potential, i.e. no net current flow crosses their surface. The finite element software COMSOL Multiphysics 4.2a was used to perform the deterministic computations. Iteration was stopped when the 2-norm of the residual was below $1 \cdot 10^{-6}$.

TABLE I
RANDOM MODEL PARAMETERS $\mathcal{U}[a, b]$ OF THE CONSTANT PHASE ELEMENT

Parameter	Boundaries		Mean	Uncertainty
	a	b		
K	0.21	2.93	1.57	50 %
β	0.7	1.0	0.85	10 %

D. Volume of Tissue Activated

The multi-compartmental axon model developed by McIntyre *et al.* [13] was used to determine the extent of the volume of tissue activated surrounding the electrode. The axons comprised 21 nodes of Ranvier and were arranged perpendicular to the coronary plane in a rectangular 7×18 grid, with a spacing of 0.5 mm normal and parallel to the electrode's central axis respectively. The model was implemented using NEURON 7.1 in conjunction with the Python interpreter [14]. The computed time-dependent voltage response was applied to the neuron model as an extracellular potential at each node to compute the required threshold to elicit an action potential. The VTA for a certain threshold was computed by integrating the according threshold isoline using disk integration method and subtracting the volume of the electrode geometry.

III. RESULTS

To investigate the influence of uncertainties in the parameters of the electrical double layer on the voltage response and neural activation in a volume conductor model of DBS, different cases were defined, in which (1) the exponent β, (2) the coefficient K, (3) the exponent β and the coefficient K were modelled as probabilistic parameters. The influence on the probabilistic time-dependent voltage response was determined by computing its average RMS value at the nodes of a 4x4 grid with 0.5 mm spacing in the proximity of the active electrode contact in the coronary plane. The probabilistic VTA and its relative standard deviation was computed for a stimulation amplitude of $V = -1$ V.

To ensure the accuracy of the computed probabilistic quantities, the convergence of the relative error of their variances was determined. The results showed a decreased convergence rate for the sparse grid integration technique, compared to the tensor grid integration technique (Fig. 1). Nevertheless, the relative error of the variance of the voltage response for the sparse grid integration technique was below 0.1 % for a

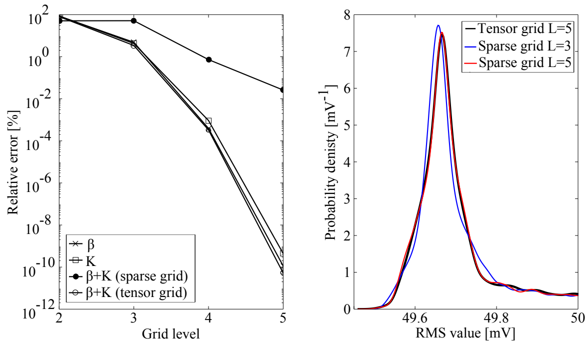

Fig. 1. (Left) Relative a posteriori error of the variance of the root mean square (RMS) value of the time-dependent voltage response 1 mm from the active electrode contact for the random model parameters (1) β, (2) K, (3) $\beta+K$ with sparse grid integration, and (4) $\beta+K$ with tensor grid integration. (Right) Probability density function of the RMS value for the random model parameters $\beta + K$ with (1) tensor grid of level $L = 5$, (2) sparse grid of level $L = 3$, and (3) sparse grid of level $L = 5$.

TABLE II
RELATIVE STANDARD DEVIATION OF THE AVERAGE RMS VALUE OF THE TIME-DEPENDENT VOLTAGE RESPONSE IN THE PROXIMITY OF THE ACTIVE ELECTRODE CONTACT IN THE CORONARY PLANE.

Parameter	Parameter uncertainty [%]	Voltage response uncertainty [%]
β	10	0.47
K	50	0.01
β & K	10 & 50	0.66

grid level of 5, which corresponds to 65 deterministic model evaluations, and agreed well with the probability density function of the RMS value of the voltage response for tensor grid integration technique, which required 1089 deterministic model evaluations. The relative standard deviation of the probabilistic voltage response, which was determined by its average RMS value in the proximity of the active electrode contact, was between 0.01 % for an uncertain parameter K and 0.66 % for the uncertain parameters β and K (Table II). These magnitudes in the uncertainty of the voltage response are substantially smaller than the parameter uncertainties of 10 % for β and 50 % for K. Both parameters influenced more the waveform shape of the time-dependent voltage response than the amplitude (Fig. 2). The probability densities of the RMS values of the voltage response showed a strong asymmetric distribution. For the case, where β and K were modelled as probabilistic parameters, a broadening of this density is noticeable compared to the cases, where only β or K were uncertain.

The relative standard deviation of the probabilistic VTA remained between 1.47 % for an uncertain K and 2.68 % for β and K modelled as random parameters (Table III). These magnitudes in the uncertainty of the VTA are larger than the magnitudes obtained for the probabilistic voltage response. To ensure a relative error of the variance of the VTA of below 1 % a sparse grid of level $L = 7$ was required resulting in 705 necessary deterministic model evaluations.

TABLE III
MEAN VALUE μ, STANDARD DEVIATION σ, AND RELATIVE STANDARD DEVIATION σ_r OF THE PROBABILISTIC VTA FOR A STIMULATION AMPLITUDE OF $V = -1$ V.

Parameter	VTA uncertainty		
	μ [mm^3]	σ [mm^3]	σ_r [%]
β	85.53	1.80	1.57
K	85.68	1.59	1.47
β & K	85.66	2.68	1.91

IV. DISCUSSION

Based on the uncertainties in the parameters of the electrical double layer, which were modelled as random uniform variables, the probabilistic voltage response and VTA was computed in a finite element model of the human brain coupled with a multi-compartmental nerve fibre model. The results suggested that the influence of uncertainties of these parameters with the defined magnitude on the probabilistic voltage response and VTA is negligible in volume conductor models of DBS. Compared to a parameter uncertainty of 10 % for the exponent β and 50 % for the coefficient K of the constant phase element impedance Z_{CPA} the relative standard deviation of the voltage response and VTA was below 0.7 % and 2.7 %, respectively. It is assumed that this minor influence on these quantities arises from voltage divider, which is formed by the constant phase element and the resistance as well as capacitance of the brain tissue resulting in only a partial effect of the uncertainties in the parameters of the electrical double layer on the voltage response and, therefore, on the VTA [10]. The influence of the uncertainties in the exponent β was larger than for the coefficient K. For the case, in which both parameters were modelled as random variables, a slight increase in the influence of their uncertainties was noticeable.

The slower convergence rate of the sparse grid integration technique compared to that of the tensor grid integration technique results from higher order functional dependencies in the deterministic model equations resulting in strongly asymmetric probability density functions [6]. These non-smooth properties are assumed to mainly affect the convergence rate of the sparse grid integration technique and, therefore, also show the limitations of this method. However, the accuracy reached with this method was sufficient to compute the desired probabilistic quantities in a good agreement with the computationally expensive tensor grid integration technique. For the computation of the probabilistic voltage response, 65 deterministic model evaluations were required using sparse grids compared to 1089 using tensor grids. To ensure the defined accuracy for the computation of the probabilistic VTA, sparse grids with a level $L = 7$ were necessary resulting in 705 deterministic model evaluations.

Despite the simplified computation of the VTA by a disk integration method, which assumes homogeneous material properties in the proximity of the stimulated target, the method provides a first estimation of the sensitivity of the neural activation on the parameters of the electrical double layer.

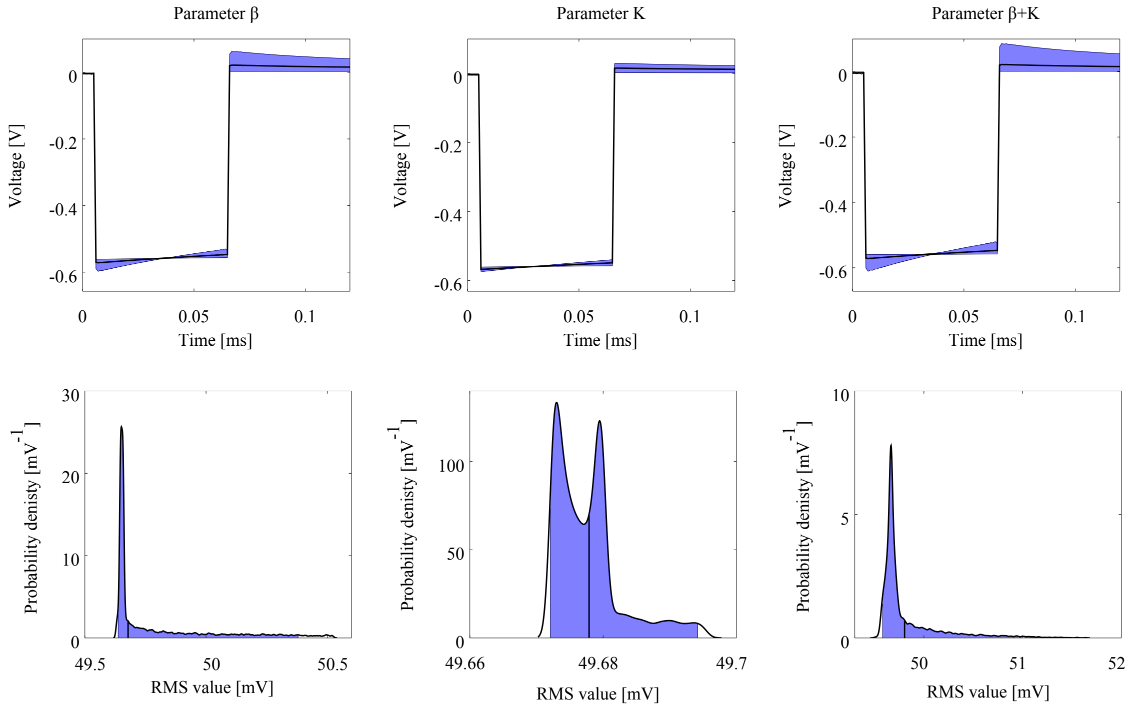

Fig. 2. Representative probabilistic voltage response 1 mm from the active electrode contact and the corresponding probability density of its RMS value for (1) β, (2) K, and (3) β as well as K modelled as uncertain parameters. Mean value and probability between the 0.025 and 0.975 quantile are illustrated.

V. Conclusion

We proposed a computationally efficient method to investigate uncertainties in the parameters of the electrical double layer on the probabilistic voltage response and VTA in a volume conductor model of DBS. Error bounds for the magnitude of uncertainty in these quantities were computed. The results suggested that the voltage response and VTA are less sensitive to the uncertainties in the parameters of the electrical double layer.

Acknowledgment

The authors are grateful to DFG (German Science Foundation) for funding our project in the Research Training Group 1505/1 ”welisa”. The authors would like to thank Peadar Grant from the School of Electrical, Electronics & Communications Engineering of the University College Dublin, Ireland for the advice on the computation of the neural activation in volume conductor models of DBS. The authors wish to acknowledge the Research IT Service at the University College Dublin and the SFI/HEA Irish Centre for High-End Computing (ICHEC) for providing HPC resources that have contributed to the research results reported within this paper.

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