Fitting Local Field Potentials Generating Model of the Basal Ganglia to Actual Recorded Signals

George L. Tsirogiannis, *Student Member, IEEE,* George A. Tagaris, Damianos Sakas and Konstantina S. Nikita, *Member, IEEE*

***Abstract*—A population level model of the basal ganglia has been shown to reliably reproduce the local field potential (LFP) activity recorded from subthalamic nucleus (STN) during typical microelectrode recording sessions. The purpose of the present work is to investigate optimization methods that can be used to fit that model to actual recorded LFPs. For that, we utilize data derived from seven parkinsonian subjects prior to the permanent implantation of the deep brain stimulation (DBS) electrode. For the fitting, five optimization methods are used, combined with two methods for estimating the error between the actual recorded and the model predicted LFP signals in the frequency domain. The procedures are focused on re-generating the characteristic beta peak of the STN LFP. The results indicate that the model is able to reproduce the beta peak in various frequencies in the range of both low and high beta, while at the same time, the values of the critical parameters bringing the model in that area of behavior reveal the crucial role of the synaptic strengths in Parkinson's disease pathophysiology.**

I. Introduction

MICRO- electrode recordings (MERs) are routinely acquired during typical electrode implantation procedures for the deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease [1]. Neurologists empirically assess the resulting recording at each point anticipating the properties of the underlying tissue. The acquisition takes place prior to the final fixation of the stimulating electrode's tip and after overnight removal of anti-parkinsonian drugs. Usually, the recording session consists of moving the micro-electrode along a predefined line grid of points that includes the theoretical target. The latter is the Posterior part of the STN, having been approximately defined by analysis of patient's MRI data.

The MERs gathered in that way are information rich, containing both local field potentials (LFPs) and spiking activity [2]. It is thought that the former is contained in the low range of the frequency spectrum, whereas the latter appears in the high frequencies [3]. That's why the usual cut-off frequency used for separating these two kinds of activity via low-pass filtering is 100 Hz [4].

Both LFPs and spiking activity carry a wide spectrum of activity patterns, most of which remain to be identified and established. However, in what particularly concerns the content of the LFPs, an established pattern observed in the LFPs of the STN of parkinsonian subjects is the dominant high, sharp peak in the beta band [5]. This is thought to reflect the pathological behavior of the basal ganglia and the STN in particular, in Parkinson's disease. Functionally, it is associated with the kinetic problems characterizing parkinsonian subjects, as it is thought to be produced by the mechanisms generating the characteristic kinetic stiffness.

Moving from the facts about the LFPs towards a modeling perspective, these mechanisms are simulated in order to reproduce the beta peak in various frequencies, providing insights about both the signals and the underlying functionality. This is described in a recent work [6], where the authors present a biologically plausible population level model of the basal ganglia that generates LFPs of the STN. The model has provided indications concerning the role of the duration and the amplitude of the post-synaptic potentials (PSPs) in the pathophysiology of Parkinson's disease. At the same time, the simulations have revealed the conditions under which the LFPs of the STN express a high peak in the beta band and the root mechanistic cause for that.

Using this model, the present work aims at taking advantage of actual recorded LFP data to constrain the model's critical parameters of PSP amplitude and duration. This is performed in order to fit its reproduced LFPs of the STN to the recorded ones, which express the characteristic beta band peak. To achieve that, five different optimization algorithms are combined with two distinct measures of distance (error objective functions) between LFPs. The actual recordings have been derived from seven parkinsonian subjects having undergone the DBS surgical procedure. In the following sections, we first describe in detail the acquisition procedure and the selected recorded signals for the fitting. Then, a brief presentation of the population level

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G. L. Tsirogiannis is with the Biomedical Simulations and Imaging Laboratory, School of Electrical and Computer Engineering, National Technical University of Athens, Iroon Polytechneiou 9, 15773 Athens, Greece (corresponding author; phone: +30-210 772 2968; fax: +30-210 772 2320; e-mail: tsi@biosim.ntua.gr).

G. A. Tagaris is with the Department of Neurology, "G. Gennimatas" General Hospital of Athens, Greece (e-mail: tagaris@otenet.gr).

D. Sakas is with the Parkinson's Disease Surgical Treatment Unit, Department of Neurosurgery, University of Athens, "Evangelismos" Hospital, Greece (e-mail: sakasde@med.uoa.gr).

K. S. Nikita is with the Biomedical Simulations and Imaging Laboratory, School of Electrical and Computer Engineering, National Technical University of Athens, Iroon Polytechneiou 9, 15773 Athens, Greece (e-mail: knikita@cc.ece.ntua.gr).

model of the basal ganglia is given, followed by the fitting methodology used. Finally, the results and the conclusions of this work are summarized.

II. Recorded Local Field Potential Signals

The recorded signals that we used to fit the output of the model to have been derived by the typical recording procedure generally outlined in the introduction. Specifically, the signals are acquired by means of an array of five microelectrodes in cross formation (known as Ben Gun) [7], entering in parallel into the brain tissue. The different electrodes are referenced by an anatomical term indicating position, namely Central, Anterior, Posterior, Lateral and Medial. The distance between the tips of the peripheral electrodes from the central is 2 mm. The original sampling frequency of the recordings is 24 KHz and their duration 10 s. The line grid of the points in the brain where recordings actually take place varies for each subject, but there is a general pattern that dictates a range between -4 mm and +2 mm (the reference is the pre-determined theoretical target inside the STN considered to lie at 0 mm). The usual intermediate stops of the electrode tips are at -3, -2.5, -2, -1.5, -1, -0.5, 0, +0.5, +1, +1.5 mm points. At each of these positions, usually 2 recordings are performed. Therefore, a total of 24 recordings are generated for each one of the five electrodes in the array, providing a total of about 120 recordings for each subject.

For each set of recordings, not all of the acquired signals are originated from the STN. In practice, the exact distribution of the brain sources producing the signals depend both on the specific line grid used for the recordings and on the insertion angle of the electrodes. The electrode that produced the recording matters as well, because the labeling of the points follows the Central electrode's course. Finally, the individual anatomy of each subject plays important role as well. In spite of these, it is expected that the probability of a recording to origin from the STN gets higher when it corresponds to points closer to the 0 mm point. Thus, since in this work we are interested in recordings from the STN that exhibit a dominant beta peak in their power spectral density (PSD) function, we limit our exploration to the recordings from the Central electrode in the range of -2 to +2 mm points, analyzing them in terms of their PSD function. Eventually, we end up in selecting one representative recording from each subject (denoted by s33, s36, s42, s50, s51, s52, s54), acquired from the Central electrode in positions that are summarized in the legend of Fig. 1. In that figure, the PSD functions of all the seven selected recordings are depicted. It is interesting to observe that each recording exhibits the characteristic peak in different frequency points, though all lying in the beta range (from low beta: 15 Hz, to high beta: 35 Hz). Also, although not presented here due to space limitations, from the overall available recordings we have noticed that the beta peak, when present, persistently appears at the same frequency point for all the recordings from the same subject. That indicates a quite interesting personalized pattern for the exact point of the peak.

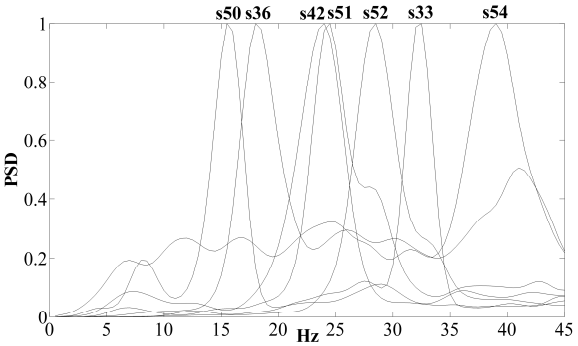

Fig. 1. PSD functions of the seven selected LFP recordings, one from each subject. Subject's identifier is presented above the corresponding trace. These PSD functions are the targets for model fitting. The respective position of the central electrode for each recording is: s33 0, s36 -1, s42 0, s50 0, s51 -0.5, s52 +1, s54 -0.5 (all in mm).

III. The Population Level Model Of The Basal Ganglia

The full description of the population level model of the basal ganglia, on which the present fitting approach is based, is out of the scope of this work. However, we provide a brief report, focusing on the properties of the model that are mostly relevant to the fitting to LFP data.

The modeling formulation is based on the early works of Lopes Da Silva [8], [9], Freeman [10] and Zetterberg [11]. They have suggested a methodology with which rhythms of the cortical structures can be modeled and explained. Recently, Wendling *et al.* [12], [13] have also used that methodology to generate depth-EEG signals in epileptic states. In our previous work, we have adapted the methodology to model the basal ganglia's LFP generating mechanisms, incorporating all major nuclei and an extensive set of pathways [6]. A block diagram of the model is presented in Fig. 2.

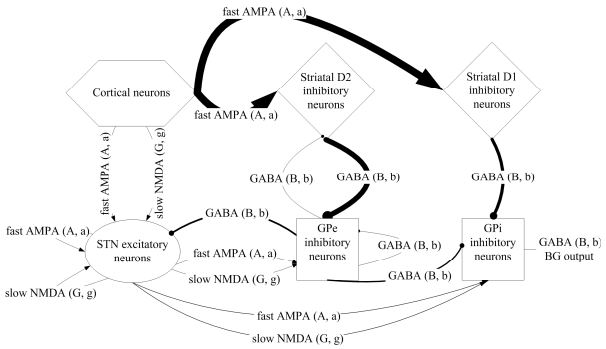

Fig. 2. Block diagram of the population level model of the basal ganglia that is fitted to the PSD of the recorded LFP recordings.

The primary output of the model is the LFP activity from the STN, while at the same time the firing rates of the nuclei over time are obtained. The model is governed

by a total number of 52 parameters, 17 of which control the excitability of the populations, 11 are synaptic constants and 24 are related to the amplitudes and the durations of the post-synaptic potentials (PSPs) of each synaptic pathway. The latter are considered to be the critical parameters, being affected by the lack of dopamine taking place in Parkinson's disease [14]. Under that condition, the desensitization of dopamine receptors leads to intensification (D2 receptors) or dampening (D1 receptors) of the PSPs. Through the simulations of the model, it is shown that it is this modification of the values of all the synaptic parameters that consists the critical alteration leading to the parkinsonian state. The latter is identified by the expressed beta peak in the model generated LFPs and the consistent to clinical observations firing rates of all the nuclei.

Because of this significance of the synaptic parameters, we have chosen these to be the set of free parameters for fitting the model's output to the recorded LFPs. The model is mathematically equivalent to a set of 24 differential equations, thus fitting to 24 free parameters is a feasible task.

IV. Fitting Methodology

The fitting approach is based on the measurement of the error between the recorded and the predicted signals from the model. This error is normalized in the [0, 1] range and corresponds to a distance estimation, which is attempted to be minimized by means of several optimization algorithms. As error measures, we have selected two different objective functions: the Root Mean Squared Error ($RMSE = \sqrt{\frac{\sum_{i=1}^{N}(x_i - y_i)^2}{N}}$) and the Pearson Correlation Coefficient ($PCC = \frac{1}{N}\sum_{i=1}^{N}(\frac{x_i - \bar{x}}{s_x})(\frac{y_i - \bar{y}}{s_y})$) of the PSD functions of the signals (thus, both methods work in the frequency domain). The PSD functions of both actual and simulated LFPs are obtained by the Welch's modified periodogram method. Also, because we focused our approach at reproducing the beta band peak, we only considered the range of frequencies up to 45 Hz.

The optimization algorithms used are a mesh-adaptive direct search algorithm [15]-[17], the classic genetic algorithm [18]-[21], simulated annealing [21]-[23], and two combinations of the genetic algorithm and simulated annealing with the direct search algorithm. Bound constrains were used for all methods, reflecting the plausible physiological values of the free parameters. Details about the algorithms and the parameters used for each are summarized in Table I. The optimal set of values for the parameters of each method was decided by extensive performance evaluation trials. The fitting results obtained by different sets of parametric values were compared and the best set in terms of minimum and mean fit error was chosen for each method. The trials were performed twice, for both objective functions. Thus, some parameters had different values for RMSE and PCC methods.

TABLE I
FITTING METHODS

METHOD	PARAMETERS	REFERENCES
Direct-Search Mesh Adaptive Algorithm (DS)	Accelerate Mesh: Off (RMSE), On (PCC) Scale Mesh: On Mesh Tolerance: 10^{-4} Function Tolerance: 10^{-5} X Tolerance: 10^{-4} Function Evaluations: 3000	[15]-[17]
Genetic Algorithm (GA)	Populations: 2x50 (RMSE), 1x100 (PCC) Selection: stochastic uniform Mutation: adaptive feasible Crossover: 80%, scattered, 5 elite individuals Migration: 10% both directions, 3 generations Function Tolerance: 10^{-5} Generations: 30	[18]-[21]
Simulated Annealing (SA)	Initial Temperature: 1000 (RMSE), 5000 (PCC) Temperature and Annealing Function: Fast Function Tolerance: 10^{-5} Function Evaluations: 3000	[21]-[23]
GA+DS	Parameters of the single algorithms with half function evaluations each (3000 total)	
SA+DS	Parameters of the single algorithms with half function evaluations each (3000 total)	

The constraining of the parameter of the allowed maximum function evaluations (or the maximum number of generations for GA) is referred as the computational budget of the methods. That is used to control the necessary time for the methods to be completed, according also to the time needed for the evaluation of the objective function.

All the fitting procedures were performed in the Matlab 7.5 environment and run in a standard desktop PC, with an Intel Core 2 Duo processor and 2 GB of RAM. Because of the stochasticity of the fit for each trial (imposed either by the algorithm and/ or the random selection of the initial point), we repeated each method 40 times, in order to increase the possibility of obtaining the best possible fit result. Every trial needed about half an hour to complete, so each case (determined by the optimization algorithm, the error estimation method and the specific LFP target used) took about 20 hours. Since there were 70 cases (5 optimization algorithms x 2 error estimation methods x 7 possible target signals), a total of 1400 computational hours were necessary, divided in two parallel threads, because of the use of the two-core processor.

V. RESULTS

The overall fitting results are initially concentrated according to the specific targeted LFP recording and the objective function used. Then, for each LFP, the set of parametric values giving both the best RMSE and PCC errors is selected. Table II summarizes the best fit result for each of the seven LFP recordings used, regarding the best error achieved and the method that led to that. Table III presents the methods' mean errors of all trials for all cases considered.

TABLE II
FITTING PERFORMANCE

LFP	BEST FIT RMSE ERROR	BEST FIT PCC ERROR	BEST FIT METHOD
s33	0.0284	0.0165	DS RMSE
s36	0.2284	0.3919	SA+DS PCC
s42	0.0240	0.0084	GA PCC
s50	0.054	0.0279	DS PCC
s51	0.0664	0.0741	DS RMSE
s52	0.0317	0.0166	DS PCC
s54	0.0588	0.0684	DS RMSE

TABLE III
METHODS PERFORMANCE

LFP	Mean RMSE (0-100, 40 trials)					Mean PCC (0-100, 40 trials)				
	DS	GA	SA	GA + DS	SA + DS	DS	GA	SA	GA + DS	SA + DS
s33	4	3.7	10	5.3	12	76	10	22	13	33
s36	23	21	22	21	22	56	45	49	53	51
s42	2.7	2.8	8.2	3.5	10	57	1.6	12	2.6	18
s50	9.8	9	15	11	17	43	9.7	32	25	46
s51	7.6	7.9	11	8.7	12	65	13	23	17	29
s52	5.2	5.4	10	5.8	11	55	7.5	18	8.6	24
s54	8.3	12	15	12	16	51	22	30	34	41
Avg	13.5	14	13.8	14.6	14.3	58	23	27	28	35

It turns out that the DS method produces most of the best fits (5/7). The rest two are given by the GA and the combination of SA with DS. Regarding the mean error of all trials, DS is the best for the RMSE, but is suffers a large error for the PCC objective function. The best in the latter case is the GA, which is not significantly worse than DS in the RMSE case. SA is second best for both RMSE and PCC. The combinatory schemes are worse in all cases.

In order to further analyze the performance of the optimization methods and probably select one of them, we must take into account the factor of computational budget with which we performed the fitting trials. The reason of using it was on the one hand to benchmark the methods with strict computational requirements, implying an importance for this factor in selecting the best method. On the other hand, computational budget had a practical meaning, allowing all the series of trials not to need too much time to complete.

Because of the special characteristics of each optimization algorithm, it is expected that the GAs are more likely to perform better if the budget is allowed to be increased. That is because DS follows a path towards a local minimum that is in most cases adequately approached by the given budget. No escape from that minimum is then feasible for DS. SA on the other hand follows the drop of the temperature parameter, which is always completed with the given budget. In contrast, GAs may continue seeking for a best local minimum throughout the evolution of generations, broadly covering the error hyper-plane with a diversity of different individuals. So, since GAs are good enough (if not best) for the given computational budget, they are more probable of giving even better results by loosening it. Considering also the ability of DS to find good fits (exhibiting a rather best-or-nothing behavior), maybe the combination of GAs with DS could also be more productive with increased computational budget.

Regarding the objective functions, PCC is more efficient, giving 4/7 best fits, although RMSE has been also proven capable of providing successful fitting results. GAs are the best with PCC, with GA+DS combination closely following, so it seems that the methods of GA with PCC and GA+DS with PCC are those that we will select for further work in trying to find the best possible fits.

Regarding the present fitting results, the best fitted LFP PSDs for all subjects are depicted in Fig. 3. Despite some inaccuracies, fitting the model to every signal's beta peak is successful, irrespectively of the exact frequency point of the peak in the beta range. That enables us to consider the model as being capable of reproducing the characteristic parkinsonian signs in a personalized fashion.

Fig. 4 summarizes the sets of values of the parameters that produce the best fit to each of the seven selected actual recordings. Twenty-four (24) subplots are included, one for each free parameter that varies during the fitting. Any single subplot contains 7 distinct points, reflecting the value of the corresponding parameter for the best fit to each of the seven signals. Overall, it is evident that several parameters are driven to the range of pathological values for each subject. In fact, if we specifically consider the strength of the pathways by co-examining for each both the amplitude and duration parameters, in most cases at least one of these parameters is driven to pathological values. Therefore, since only the amplitude or the duration is enough for any pathway to be characterized pathological, most pathways do seem to turn pathological for the best fit to be achieved.

In order to establish this tendency of the critical parameters, we also performed two extra series of trials where we bounded either the amplitude or the duration of the synaptic pathways within the range of normal values. Using only the best fitting method in each case, as derived by the full approach, it turned out that in this way the model is never getting successfully fitted. The final errors of the trials kept being high and the traces were far from expressing any match to the actual PSDs.

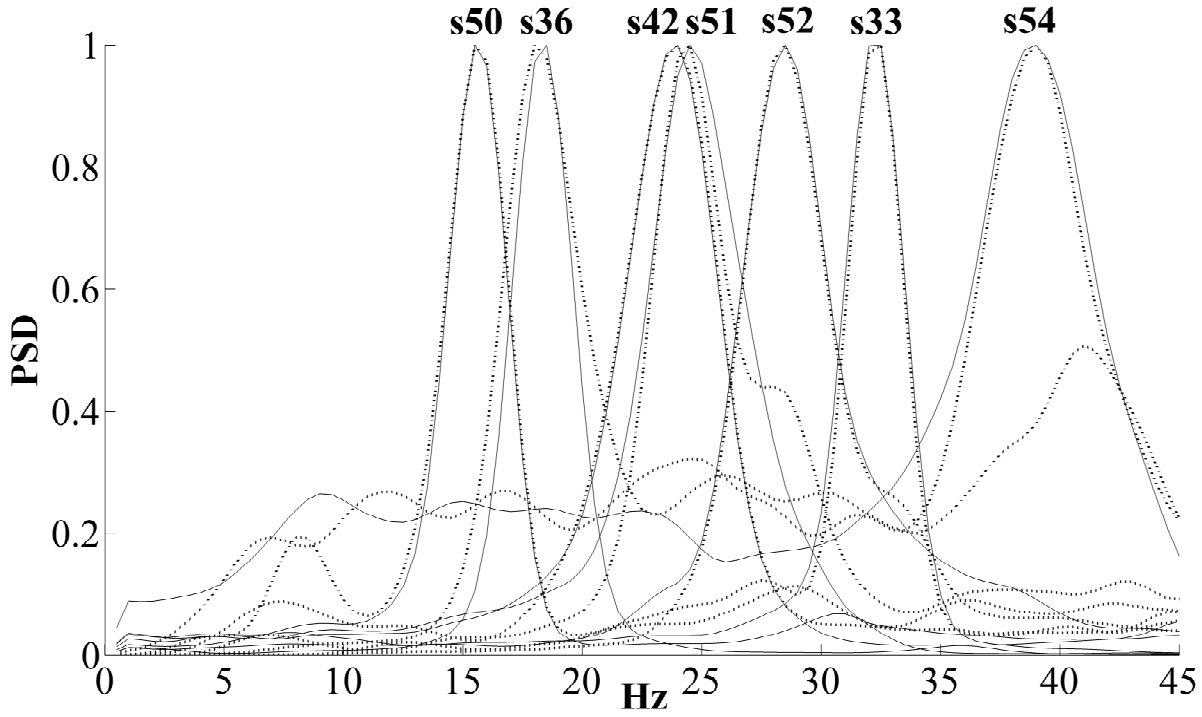

Fig. 3. The fitting results for all seven selected LFP PSD functions. Solid lines correspond to the simulated best fitted PSDs. Dotted lines are the actual recorded LFPs' PSDs. Subject identifier is noted on the top of the traces.

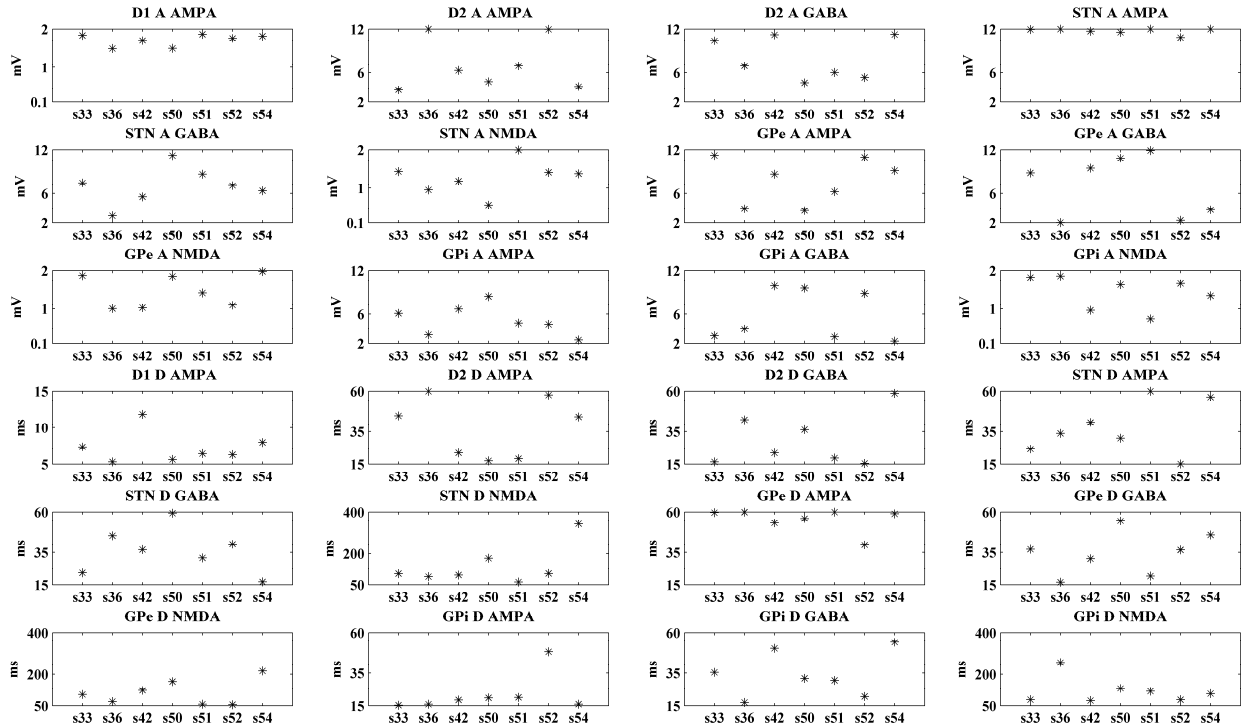

Fig. 4. The values of the 24 free parameters after fitting to each LFP PSD function. For each subject, the best achieved fit is considered. In the subplots' titles, A stands for amplitude and D for duration. The limits of the vertical axes correspond to the bounds of the values of each parameter during fitting. The middle value is considered to be the transition point from the normal to the pathological range. In all but the two D1 subplots, the lowest value is the normal one, while the highest is the extreme pathological. Seven points are drawn in each subplot, each one giving the best fitted value of the presented parameter for the corresponding LFP.

VI. CONCLUSIONS AND FURTHER WORK

The importance of this work lies at the direct linking of neurophysiological data from a relatively high level of description, such as the LFPs, with a biophysically plausible model that can reveal indications about the pathophysiology of the basal ganglia. So far, from what is presented in this work, we can conclude the following:

- The utilized population level model of the basal ganglia is able to reproduce the characteristic beta band peak.
- The reproduction can be achieved for various frequency points in the beta range, suggesting that the model can be used for personalized approaches.
- The beta band peak can only be expressed if the critical parameters are allowed to take values within the assumed pathological range. That is determined by modifying the normal values of amplitudes and durations of the PSPs, according to the hypothesized effect of dopamine depletion.
- The modification of the synaptic parameters is therefore crucial for the model to function in a parkinsonian-like behavior. This indication physiologically suggests a pivotal role of synaptic strength in Parkinson's disease.

Technically, further elaboration is necessary in order to finalize the obtained results, by driving the fitting procedures to their best potential. That was not the primary goal of this work, since the investigation of the approaches presented here demanded the exploration of several possible tools and algorithms. Concluding about the methods used, we can note the emergence of some best guidelines:

- Both RMSE and PCC error estimation methods are efficient, but PCC is preferable.
- Genetic algorithms are on average the most efficient optimization method, but direct-search algorithm provides most of the best fit results.
- The combination of genetic algorithms and direct search bears the best potential for leading to the best possible fits.

Further work will be consisted of loosening computational budget's requirements and narrowing the selection of algorithms. That will enable the finding of the best possible fit to each LFP signal, making more reliable the final best fitted values of the parameters and the analysis of their specific contributions to the position of the beta peak in frequency. Another way that remains to be explored is the fitting in the time domain, which may extend and complete current approaches' conclusions.

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