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1 **Changes in Neuronal Entropy in a Network Model of the Cortico-**
2 **Basal Ganglia during Deep Brain Stimulation**

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19 **Abstract**

20 Neuronal entropy changes are observed in the basal ganglia circuit in Parkinson's disease (PD).
21 These changes are observed in both single unit recordings from globus pallidus (GP) neurons
22 and in local field potential (LFP) recordings from the subthalamic nucleus (STN). These
23 changes are hypothesized as representing changes in the information coding capacity of the
24 network, with PD resulting in a reduction in the coding capacity of the basal ganglia network.
25 Entropy changes in the LFP and in single unit recordings are investigated in a detailed
26 physiological model of the cortico-basal ganglia network during STN deep brain stimulation
27 (DBS). The model incorporates extracellular stimulation of STN afferent fibers, with both
28 orthodromic and antidromic activation, and simulation of the LFP detected at a differential
29 recording electrode. LFP sample entropy and beta-band oscillation power were found to be
30 altered following the application of DBS. The firing pattern entropy of GP neurons in the
31 network were observed to decrease during high frequency stimulation and increase during low
32 frequency stimulation. Simulation results were consistent with experimentally reported changes
33 in neuronal entropy during DBS.

34 **Introduction**

35 Parkinson's disease (PD) is a neurodegenerative disease characterized by a triad of motor
36 symptoms; bradykinesia, akinesia, and tremor. Recent research has focused on identifying
37 signals from the central and peripheral nervous system which can be used to quantify the
38 disease state and symptom severity. These signals are commonly referred to as disease
39 'biomarkers'. Clinical and experimental studies have identified several potential biomarkers for
40 PD, such as increased oscillatory activity in the beta frequency band (13-30 Hz) recorded from
41 the cortico-basal ganglia circuit [1], betagamma band (60-200 Hz) phase-amplitude coupling in
42 the primary motor cortex [2], and changes in neuronal entropy in the basal ganglia network [3].
43 Deep brain stimulation is an effective treatment for PD which has been shown to have
44 measurable effects on these biomarkers. These effects include reducing beta-band oscillatory
45 activity [1], reducing betagamma band phase-amplitude coupling [2], and regularizing neural
46 firing rates in the basal ganglia network [4], [5].

47 Firing pattern entropy, calculated using single unit recordings from the basal ganglia network,
48 and sample entropy, calculated from the STN local field potential (LFP), are two entropy
49 measures with observable changes during PD. Firing pattern entropy quantifies an upper bound
50 on the information embedded in a spike train. Spike trains from globus pallidus (GP) neurons
51 are shown to have increased firing pattern entropy during PD, with this being reduced to near

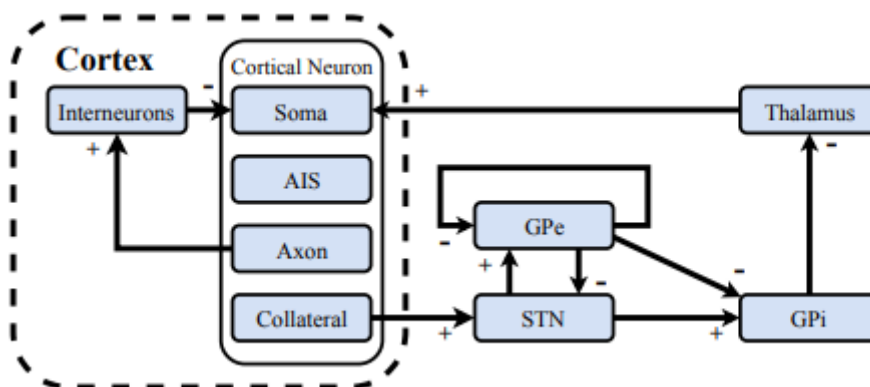
52 healthy levels during effective DBS [3]–[6]. Sample entropy is a measure for assessing the
53 complexity of physiological time series signals. In [7], it was shown that there was an inverse
54 relationship between beta-band oscillation power and betaband sample entropy in the STN LFP.
55 Furthermore, in [7] LFP sample entropy was utilized to distinguish between PD patients who
56 experienced freezing of gait episodes and those who did not.

57 Computational modelling allows the investigation of network dynamics which may be difficult
58 to access during clinical practice. Here a computational model of the corticobasal ganglia
59 network is utilized to investigate changes in basal ganglia neuronal entropy during DBS. Single
60 unit recordings from GP neurons are utilized to assess changes in firing pattern entropy, while
61 the STN LFP is simulated to assess changes in sample entropy and beta-band oscillatory activity
62 during DBS. The results from the computational model are compared with results from clinical
63 and experimental studies. Quantifying changes in basal ganglia entropy may lead to an
64 improved understanding of the relationship between oscillatory activity and entropy in the
65 network, and how this relationship is modified during PD and DBS.

66 **Methods**

67 A physiologically based model of the cortico-basal ganglia network incorporating extracellular
 68 DBS and simulation of the STN LFP was utilized [8]. The structure of the network model is
 69 presented in Fig. 1 and includes the closed loop formed between the cortex, basal ganglia and
 70 thalamus. The major model components include single compartment, conductance-based
 71 biophysical models of the STN, globus pallidus externa (GPe), globus pallidus interna (GPi) and
 72 thalamus, each of which have been validated and employed in previous modelling studies [8]–
 73 [10]. The cortex is represented by a network of interneurons and multi-compartment cortical
 74 neurons. Each component is described in greater detail below.

75 Six hundred cells consisting of one hundred STN, GPe, GPi, thalamic, interneuron and cortical
 76 neurons were connected through excitatory and inhibitory synapses, AMPA and GABA_A,
 77 respectively. The STN neurons received direct excitatory input from the cortex via the
 78 hyperdirect pathway and inhibitory input from the GPe. Each STN neuron received excitatory
 79 input from five cortical neurons and inhibitory input from two GPe neurons. Each GPe neuron
 80 received inhibitory input from one other GPe neurons and excitatory input from two STN
 81 neurons. Each GPi neuron received excitatory input from a single STN neuron and inhibitory
 82 input from a single GPe neuron. Each thalamic neuron received inhibitory input from a single
 83 GPi neuron. Cortical neurons received excitatory input from a single thalamic neuron and
 84 inhibitory input from a single interneuron. Interneurons received excitatory input from a single
 85 cortical axon. All connections within the network were randomly assigned.



86

87 **Figure 1:** Schematic diagram of the cortico-basal ganglia model. Excitatory and inhibitory
 88 connections are indicated with a + or –, respectively.

89 The presence of pathologically exaggerated beta oscillations in the cortico-basal ganglia
 90 network, typically observed in PD, were simulated by varying synaptic gains within the network
 91 in accordance with [11]. An increased cortical drive to the STN, due to strengthening of the

92 hyperdirect pathway, led to the emergence of beta oscillations within the network and the STN
93 LFP.

94 *A. Cortex*

95 The model used to simulate the cortex consisted of cortical neurons and interneurons. The
96 cortical neuron model included a soma, axon initial segment (AIS), main axon, and axon
97 collateral. The cortical neuron soma and interneuron models are based on the regular spiking
98 neuron model developed by Pospischil et al. [12]. The model used to simulate the AIS, main
99 axon, and axon collateral is based on results from the experimental and modeling study in [13].
100 The membrane potentials of the cortical compartments and interneurons are described by

$$C_m \frac{dv_m}{dt} = -I_l - I_{Na} - I_K - I_{Kd} - I_M - \sum_k I_{syn}^k \quad (1)$$

101

102 Where C_m is the membrane capacitance, I_l is the leak current, I_{Na} is the sodium current, I_K is the
103 potassium current, I_{Kd} is D potassium current, I_M is a slow, voltage dependent potassium current,
104 and I_{syn} are synaptic currents. The cortical soma model excluded the I_{Kd} current. The cortical
105 AIS, main axon and axon collateral segments did not include the I_M current. Finally, cortical
106 interneurons did not include either the I_{Kd} or I_M currents. Further details regarding the
107 parameters used can be found in [12], [13].

108

109 *B. Subthalamic Nucleus*

110 The STN model incorporates a physiological representation of STN neurons developed by
111 Otsuka et al. [14]. The model captures the generation of plateau potentials, which are believed
112 to play an important role in generating STN bursting activity in PD. The membrane potential of
113 an STN neuron is given by

$$C_m \frac{dv_m}{dt} = -I_l - I_{Na} - I_K - I_A - I_L - I_T - I_{Ca-K} - \sum_k I_{syn}^k \quad (2)$$

114

115 Where C_m is the membrane capacitance, I_l is the leak current, I_{Na} is a sodium current, I_K is a
 116 Kv3-type potassium current, I_A is a voltage dependent A-type potassium current, I_L is an L-type
 117 long lasting calcium current, I_{CaK} is a calcium activated potassium current, and I_{syn} are synaptic
 118 currents. Further details can be found in [14].

119 *C. Globus Pallidus and Thalamus*

120 The models used to simulate GPe, GPi, and thalamic neurons are based on those presented by
 121 Rubin and Terman in [15]. The membrane potential of a GP neuron is described by

$$C_m \frac{dv_m}{dt} = - I_l - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - \sum_k I_{syn}^k \quad (3)$$

122

123 Where C_m is the membrane capacitance, I_l is the leak current, I_{Na} is the sodium current, I_K is a
 124 potassium current, I_{Na} is a sodium current, I_T is a low-threshold T-type calcium current, I_{Ca} is a
 125 voltage-dependent after hyperpolarization potassium current, and I_{syn} are synaptic currents.
 126 Thalamic neurons were modelled similarly, with the exception of excluding I_{Ca} and I_{AHP} in the
 127 thalamic model. Further details regarding the GPe, GPi, and thalamus models can be found in
 128 [15].

129

130 *D. Synapses*

131 Individual synaptic currents, I_{syn}^k , were described by

$$I_{syn}^k = R_k (V_m - E_{rev}) \quad (4)$$

132

133 Where I_{syn}^k is the k^{th} synaptic current, R_k represents the kinetics of the onset and decay of
 134 current following a presynaptic spike for synapse k , and E_{rev} is the reversal potential for the
 135 appropriate type of synapse. Further details regarding the synaptic models can be found in [16].

136

137 *E. Application of DBS and LFP Simulation*

138 The extracellular potential due to a current source, I_x , at time t was calculated as

$$V_x(t) = \frac{I_x(t)}{4\pi\sigma r_x} \quad (5)$$

139

140 Where σ is the conductivity of a homogenous, isotropic medium representing brain tissue. The
 141 distance from a point in extracellular space to the current source I_x , or vice versa, is given as r_x .
 142 For simulating the voltage applied to cortical collaterals due to a monopolar stimulation
 143 electrode, r_x was the distance between each collateral segment and the stimulation electrode,
 144 while I_x was a square wave current source with 130 Hz frequency, 60 s pulse width and varying
 145 amplitude. Cortical collaterals were assigned a random position in a 2 mm radius of
 146 extracellular space around the stimulation electrode.

147 To simulate the recording of the LFP using a differential recording electrode, STN neurons, like
 148 the cortical collaterals, were assigned positions in a 2 mm radius of extracellular space around
 149 the stimulation electrode. Each recording electrode was positioned 1.365 mm away from the
 150 stimulation electrode, with each recording electrode being placed either side of the stimulation
 151 electrode. The LFP recorded at each recording electrode was then calculated as the summation
 152 of the total extracellular voltages due to each STN neuron's synaptic currents in the extracellular
 153 space, where I_x corresponds to the synaptic currents of an STN neuron of distance r_x away from
 154 one of the recording electrodes.

155 *F. LFP Sample Entropy*

156 Sample Entropy was calculated as the negative natural logarithm of the estimated conditional
 157 probability that two sequences similar for m points remain similar at the next point, where self-
 158 matches are not included in calculating the probability [17]. It is defined as

$$SampEn(m, r, N) = - \ln[A^{m+1}(r)/A^m(r)] \quad (6)$$

159

160 Where $A^{m+1}(r)$ represents the number of vector pairs (within the time series) of length $m + 1$
 161 whose mutual distance is less than a tolerance r , and $A^m(r)$ equals the number of vector pairs
 162 (within the time series) of length m whose mutual distance is less than r . Here the length of the
 163 vector pairs, m , denotes the embedding dimension. The mutual distance between the vector
 164 pairs was calculated using the Chebyshev distance between the pairs, with m and r set to 4 and
 165 20% of the standard deviation of the data respectively

166 *G. Firing Pattern Entropy*

167 The firing pattern entropy of a spike train was calculated by binning the inter spike intervals of
 168 the train in logarithmic time, as in [18]. The leftmost and rightmost bin edges were set just
 169 below, or just above, the smallest and largest inter spike intervals observed, respectively, in
 170 each population. The entropy of the spike train was then calculated using Shannon Entropy

$$H(X) = - \sum_{i=0}^{N-1} P_{ISI_i} \log_2(P_{ISI_i}) \quad (7)$$

171

172 Where H is the entropy of spike train X , P_{ISI_i} is the probability of inter spike interval i
 173 occurring in the spike train, and N is the number of inter spike interval bins.

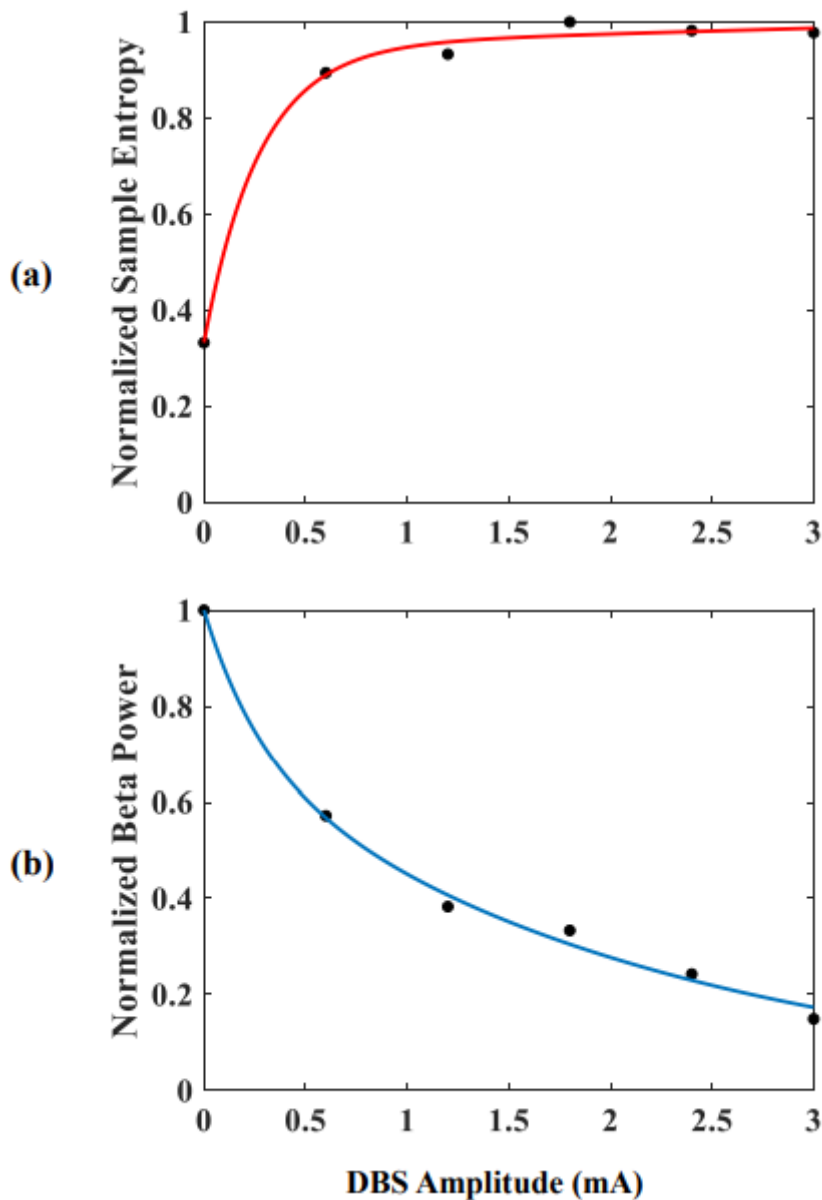
174 *H. Simulation Details*

175 The model was implemented in Python using the API package PyNN [19] with NEURON
 176 v7.6.5 as the model simulator. A timestep of 0.01 ms was used for simulations. Post-processing
 177 was done using custom scripts in MATLAB (The MathWorks, Inc., Natick, MA). To examine
 178 LFP sample entropy the LFP was first down-sampled and low-pass filtered at 100Hz to remove
 179 stimulation artifact. To examine the magnitude of beta-band oscillations in the LFP the LFP was
 180 band-pass filtered between 10 and 35 Hz, full-wave rectified and averaged by low-pass filtering
 181 at 2 Hz.

182 **Results**

183 *A. LFP Sample Entropy*

184 The effect of varying stimulation amplitude on the STN LFP sample entropy was investigated
 185 using a fixed frequency and pulse width of 130 Hz and 60 μ s, respectively, Fig. 2 (a). A
 186 progressive increase in the sample entropy was observed as the stimulation amplitude increased.
 187 For comparison, the corresponding magnitude of beta-band oscillations in the LFP is given in
 188 Fig. 2 (b).

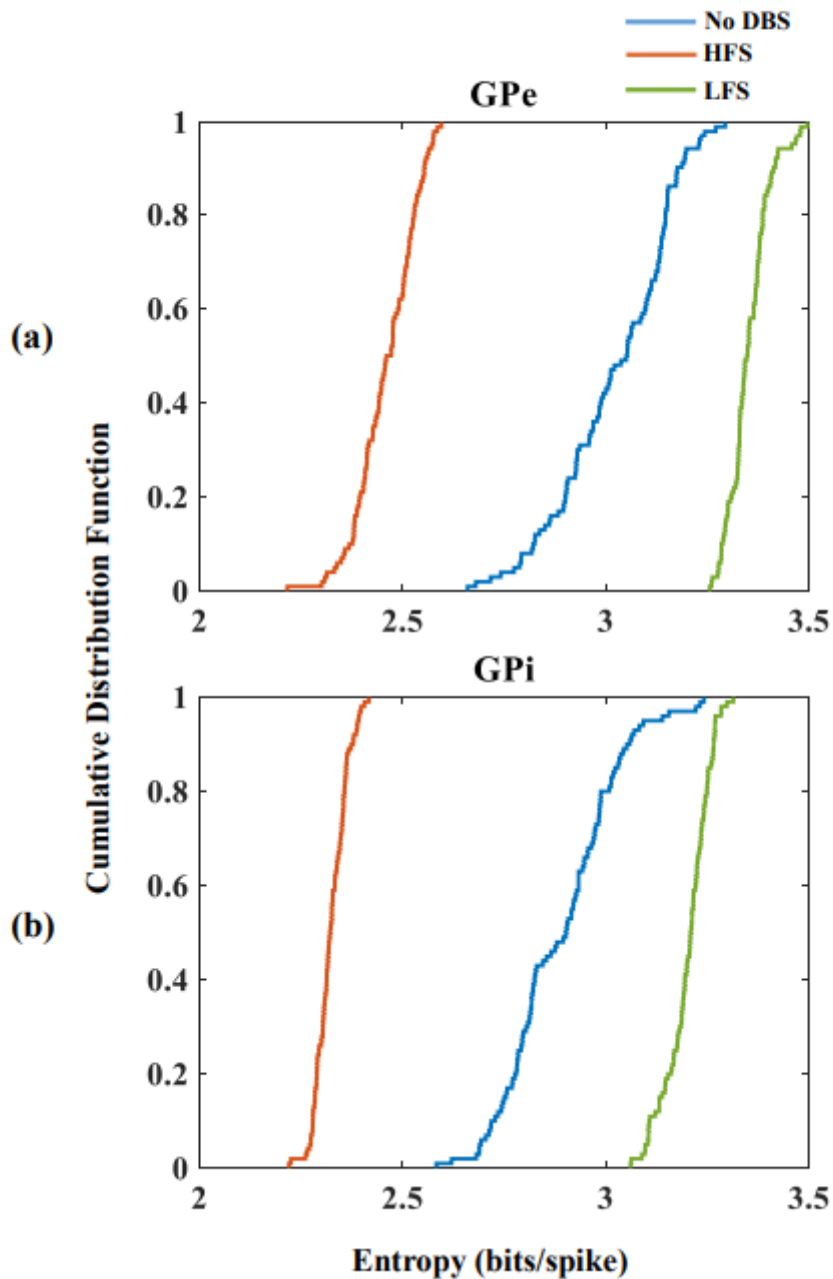


189

190 **Figure 2.** Normalized STN LFP (a) sample entropy and (b) beta-band oscillation power as a
 191 function of DBS amplitude.

192 *B. Firing Pattern Entropy*

193 The effect of varying stimulation frequency on the firing pattern entropy of GPe and GPi
 194 neurons was investigated using a fixed amplitude and pulse width of 3 mA and 60 μ s,
 195 respectively. Fig. 3 shows the cumulative distribution of the firing pattern entropy for each
 196 population. Firing pattern entropy was reduced following the application of high frequency
 197 stimulation (HFS), with a frequency of 130 Hz, and increased following the application of low
 198 frequency stimulation (LFS), with a frequency of 20 Hz.



199

200 **Figure 3.** Cumulative distributions of the firing pattern entropy for the (a) GPe and (b) GPi
 201 neuron populations due to high frequency and low frequency stimulation.

202 Discussion & Conclusion

203 The aim of this study was to investigate changes in neuronal entropy due to extracellular DBS
 204 in a computational model of the cortico-basal ganglia network during PD. The model includes
 205 extracellular stimulation of cortical afferent fibers projecting to the STN and simulation of the

206 resulting LFP. This allows for comparison with clinical and experimental results which have
207 previously investigated entropy changes in the cortico-basal ganglia network during PD. Sample
208 entropy was observed to have an inverse relationship with beta-band oscillation power, Fig. 2.
209 In [7], an inverse relationship was observed between beta-band sample entropy and beta-band
210 oscillation power taken from STN LFP recordings in freely moving patients during three
211 movement tasks. Here, a distinction was not made between frequency bands when calculating
212 sample entropy. However, effective DBS did result in similar behaviour, with beta-band power
213 decreasing, and sample entropy increasing in the LFP for increasing DBS amplitude.

214 Firing pattern entropy in GP neurons decreased during HFS, and increased during LFS of the
215 STN, Fig. 3. These results agree with those presented in [4]–[6] and support the hypothesis that
216 effective DBS regularizes firing patterns in GP neurons. The computational model presented
217 displays changes in neuronal entropy consistent with those presented in clinical and
218 experimental literature. These results suggest that investigation into basal ganglia entropy
219 changes during PD and DBS may elucidate the relationship between network entropy and
220 oscillation power during disease progression. Moreover, these results support further
221 investigation of the utilization of entropy-based measures in closed-loop DBS strategies.

222

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