Average beta burst duration profiles provide a signature of dynamical changes between the ON and OFF medication states in Parkinson’s disease

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Abstract

Parkinson’s disease motor symptoms are associated with an increase in subthalamic nucleus beta band oscillatory power. But these oscillations are phasic, and there is a growing body of evidence suggesting that beta burst duration may be of critical importance to motor symptoms, making insights into the dynamics of beta bursting generation valuable. In this study, we ask the question “Can average burst duration reveal how dynamics change between the ON and OFF medication states?” Our analysis of local field potentials from the subthalamic nucleus demonstrates using linear surrogates that the system generating beta oscillations acts in a more non-linear regime OFF medication and that the change in the degree of non-linearity is correlated with motor impairment. Further, we pinpoint specific dynamical changes responsible for changes in the temporal patterning of beta oscillations between medication states by fitting to data biologically inspired models, and simpler beta envelope models. Finally, we show that the non-linearity can be directly extracted from average burst duration profiles under the assumption of constant noise in envelope models. This reveals that average burst duration profiles provide a window into burst dynamics, which may underlie the success of burst duration as a biomarker. In summary, we demonstrate a relationship between average burst duration profiles, dynamics of the system generating beta oscillations, and motor impairment, which puts us in a better position to understand the pathology and improve therapies such as deep brain stimulation.
Author summary

In Parkinson’s disease, motor impairment is associated with abnormal oscillatory activity of neurons in deep motor regions of the brain. These oscillations come in the shape of bursts, and the duration of these bursts has recently been shown to be of importance to motor symptoms. To better understand the disease and refine therapies, we relate the duration of these bursts to properties of the system generating them in the pathological state and in a proxy of the healthy state. The data suggest that the system generating bursts is more complex in the pathological state, and we show that a measure of this complexity is associated with motor impairment. We propose biologically inspired models and simpler models that can generate the burst patterns observed in the pathological and healthy state. The models confirm what was observed in data, and tell us how burst generation mechanisms could differ in the disease. Finally, we identify a mathematical link allowing to infer properties of the burst generating system from burst duration. This sheds some light on the significance of burst duration as a marker of pathology.

Introduction

The cardinal motor symptoms of Parkinson’s disease (PD) are slowness of movement (bradykinesia) or even inability to initiate movements, as well as rigidity due to increased muscle tone, and tremor. As suggested in [1], increased basal ganglia (BG) oscillatory activity in the beta band (13-35 Hz) has been correlated with worsening of motor symptoms, in particular bradykinesia and rigidity but not tremor [2–7]. It is believed that heightened synchrony in the beta band decreases the information coding capacity of the cortico-basal ganglia network [8], as recently confirmed [9]. PD is caused by a progressive loss of dopaminergic neurons, and can be successfully managed for a number of years by pharmacological treatment (the principal drug is Levodopa, a precursor of dopamine).

Physiological beta activity in the cortex is of phasic nature and comes in bursts [10–12]. In PD, besides the average level of synchrony, the temporal patterning of beta activity has more recently been shown to be of importance. Specifically, the proportion of longer bursts of activity in the beta band of subthalamic nucleus (STN) local field potentials (LFPs) OFF medication has been correlated with motor impairment [13]. It was also found that motor symptoms can be ameliorated by selectively shortening beta bursts of longer duration with STN adaptive deep brain stimulation (aDBS) [14]. Since then, STN bursts in PD patients have been shown to impact motor performance at the single trial level [15]. In another task, the percentage of time spent in beta bursts has been shown to be a better predictor of bradykinesia than average beta power [16], and it has been argued that temporal synchrony patterning may be more sensitive to clinical changes than average synchrony [17]. The clinical relevance of temporal synchrony patterning may extend to other PD motor symptoms, and STN beta burst duration has also been suggested as a potential biomarker for freezing of gait in PD [18]. Given this mounting body of evidence, providing insights into the dynamics of burst generation should put us in a better position to understand the pathology and treat it, in particular with targeted neurostimulation. In this study, we therefore ask the following question: can we relate observed changes in beta oscillations temporal patterning in PD between the ON and OFF medication states to changes in dynamical properties of the system generating beta oscillations?

In previous studies, STN beta bursts have been mostly studied based on one arbitrary threshold of the beta envelope as events above the threshold, potentially with
a minimum duration condition (examples of various thresholds shown in Fig 1A). Average burst duration and amplitude profiles describing the average burst duration and amplitude for a range of thresholds (see Fig 1A and Fig 1B for an illustration of average burst duration profiles) have been introduced [13,14]. However, they played a minor role and have not been considered systematically on an individual patient basis. Here, we leave behind the arbitrary choice of a threshold by relying on profiles across thresholds to provide an unbiased characterisation of beta oscillation temporal patterning. It has been established that STN beta burst duration is a better metric than burst amplitude to distinguish between the healthy and pathological states in an animal model of PD [19]. We begin our study by investigating in STN recordings of PD patients whether average burst duration profiles are better at distinguishing between the ON and OFF medication states than average burst amplitude profiles. We only observe changes in temporal patterning of beta oscillations in average burst duration profiles, and come to the conclusion that burst duration is the better metric as in [19]. We introduce a burst duration specific measure of non-linearity based on linear surrogates, and show that non-linearity is increasing from the ON to the OFF state, thereby presenting a first level of description of the dynamical changes associated with changes in the temporal patterning of beta oscillations. To support the relevance of these changes, we study the correlation of our non-linearity measure with motor symptoms.

Fig 1. Introducing average burst duration profiles. Average burst duration profiles are obtained by computing beta envelope average burst duration for a range of thresholds. An example is provided for three thresholds, where thick lines highlight the duration of individual bursts for the three thresholds in panel A, and the corresponding averages are identified with the same colour in panel B. Considering the time discretization of simple envelope models of the form $dx_t = -\mu(x_t)dt + \zeta dW_t$, where $\mu$ is the drift function, $W$ is a Wiener process, and $\zeta$ is a constant noise parameter, we illustrate with two example drift functions the link between envelope dynamics (panels C1 and C2, one-dimensional vector field also sketched with blue arrows) and average burst duration profiles (panels E1 and E2). The envelope models produce the black envelopes in panels D1 and D2, and beta oscillations (shown in grey in panels D1 and D2) can be obtained by adding a constant frequency phase equation. In C1, when $x$ moves away from the fixed point, it will be strongly attracted back. By contrast, in the case of C2, if $x$ is around 1, there is weak attraction towards the fixed point, allowing $x$ to stay at an elevated level for longer.

Many modelling studies have reported the generation of sustained beta oscillations in the context of PD, and identified several potential sources of exaggerated beta...
oscillations (see [20] for a review). However, reproducing the temporal patterning of beta oscillations has received little attention. It has been shown that models of the feedback loop formed by the STN and the globus pallidus pars externa (GPe) can generate realistic transient beta oscillations in response to beta frequency inputs from PD patient electroencephalogram (EEG) recordings [21], and in response to biologically inspired input patterns in healthy animals [22]. How model dynamics would need to change in the absence of correlated inputs to account for changes observed in the temporal patterning of beta oscillations in patients ON and OFF medication has not been reported. To confirm that more non-linearity is present OFF medication and delineate which types of circuit dynamics are associated with average burst duration profiles ON and OFF medication, we fit time discretized Wilson-Cowan (WC) models [23] of increasing complexity with uncorrelated inputs to selected patient data.

The time discretization of one dimensional stochastic processes can be used to simulate the Hilbert envelope of beta oscillations (see Fig 1C and Fig 1D). We call these models “envelope models”. Under simplifying assumptions, the envelope of a linear WC model was shown in [24] to be described by a particular envelope model. While the WC model is biologically inspired and describes the STN-GPe circuit, envelope models are simpler, can reproduce average burst duration profiles, and summarize the essence of the underlying dynamics. We use this to our advantage to pinpoint the simplest polynomial forms of envelope drift function representative of the ON and OFF medication states, and to derive an analytical expression for average burst duration profiles by identifying a first passage problem. Based on this result, we relate changes in average burst duration to changes in one specific parameter in the linear case.

Different envelope dynamics result in different average burst duration profiles (this is illustrated in Fig 1C, Fig 1D, and Fig 1E). To fully relate temporal patterning of beta oscillations to dynamics, we establish a mathematical link under general assumptions from average burst duration profile to envelope dynamics. This suggests that average burst duration profiles are a direct signature of envelope dynamics, and may be one reason why beta burst duration is found to be an important marker of pathology in experimental studies of PD. Further, we illustrate the relationship between burst duration and dynamics by recovering envelope dynamics in envelope model synthetic data, and in examples of patient data. This envelope dynamics inference method may find applications in other contexts, as it can be applied to any envelope time series.

Starting with the data, the paper’s narrative will be guided by the following questions. Is non-linearity increasing from the ON to the OFF state (surrogate analysis, neural mass model, and envelope model subsections)? Can the change in the degree of non-linearity help predict motor impairment (surrogate analysis subsection)? Which type of non-linearity is required to explain experimental average burst duration profiles (neural mass model and envelope model subsection)? How can we directly extract this non-linearity from average burst duration profiles (dynamics inference subsection)? The surrogate analysis is based on a statistical method which makes the least assumptions about the system, and is used to link dynamical changes with motor impairment. While the biologically inspired neural mass models describe the STN-GPe circuit, envelope models are particularly insightful as they can be used to study the dependence of average burst duration on model parameters, and provide a direct link from average burst duration to drift function.
Results

Comparing bursting features ON and OFF medication

Choice of bursting features

The activity at beta frequency comes in the shape of bursts, and several features could be analysed to capture the difference in beta bursting dynamics between medication state in STN LFPs. In addition to the power spectrum, we will consider the average burst duration profile, the average burst amplitude profile, and the probability density function (PDF) of the envelope. Bursts are commonly defined as events corresponding to the envelope being above a predefined threshold for more than 100 ms \cite{13,14}. Burst profiles across thresholds do not depend on an arbitrary threshold choice. Additionally, given a short time series, they make more efficient use of the data available than the burst distribution at a single threshold. This is because they rely on a mean value for a given threshold and the same time series is reused for all thresholds. Importantly, dynamical properties of the system are revealed by average burst duration profiles as will be detailed later.

Extracting bursting features

We extracted the power spectrum density (PSD) and the three features mentioned above from bilateral STN LFP recordings of 8 patients ON and OFF Levodopa \cite{2}. Recording duration ranged from 137 s to 366 s (mean duration 233 s). For a given patient and hemisphere, the channel with the highest beta peak was selected, and both the ON and OFF medication data were band-pass filtered $\pm 3$ Hz around the beta peak found in the OFF state (defined as the power spectrum maximum in the 13 to 35 Hz range). Power spectra were directly obtained from the filtered data. Next, the filtered data were individually z-scored to remove amplitude differences that could arise simply from a difference in mean beta power between the ON and OFF states, and highlight instead any possible differences in the temporal dynamics of beta amplitude (this z-scoring step has no effect on burst duration profiles as thresholds considered are individual to each time series). Beta envelopes were obtained as the smoothed modulus of the analytic signal of the filtered, z-scored data (smoothing span of 5 ms, about a tenth of a beta cycle). To allow for statistical analysis, time-series were then divided into five parts of equal length. For each segment, beta envelope PDFs were estimated, and burst duration and burst amplitude profiles were built as the average burst duration and amplitude for thresholds ranging from the 20\textsuperscript{th} to the 95\textsuperscript{th} percentiles of the envelope in steps of 5\%. We used the definition of bursts given above (including the minimum burst duration of 100 ms), and burst amplitude was defined as the maximum amplitude recorded during a burst.

Average burst duration profile is the relevant feature to discriminate bursting dynamics ON and OFF medication

Our statistical analysis reveals that average burst duration profile is the most powerful of the features analysed to discriminate bursting dynamics between conditions. Significant differences in mean burst duration and mean burst amplitude between the ON and OFF states were assessed by paired t-tests with false discovery rate (FDR) control at 5\% (more details on FDR correction in the subsection \textsuperscript{FDR correction} in the Methods section). We evaluated significant differences in mean envelope PDFs between the ON and OFF conditions using cluster-based permutation testing ($10^6$ permutations). The power spectra and the three bursting features are shown for the right hemispheres of the 8 patients in our dataset in Fig \textsuperscript{2}. Besides differences in the
power spectra which are known to be statistically significant, only burst duration profiles exhibit significant differences after FDR correction between the ON and OFF states. These significant differences are seen in most patients, although they are consistent across thresholds only for half the datasets. Besides a difference in mean power removed by z-scoring, amplitude statistics were not found to be significantly different ON and OFF medication as exemplified by the lack of significant differences in both average burst amplitude profiles and envelope PDFs for all patients. A similar picture is seen in left hemispheres LFPs (see supplementary Fig A in S1). We show in supplementary Fig B and C in S1 that profiles obtained ON medication are different from identically filtered white noise for the majority of hemispheres. This confirms that ON profiles are physiologically meaningful, despite the choice of filtering windows always centered on the beta peak OFF medication. We will therefore focus on average burst duration profiles in the rest of the paper, and we start by a linear surrogate analysis of the changes in these profiles.

**Fig 2. Power spectra and bursting features ON and OFF Levodopa (right hemispheres).** Each column corresponds to the right hemisphere of one of the eight patients. Each row corresponds to a bursting feature, the ON state is always in blue, and the OFF state in red. The first row shows power spectra, the second row average burst duration profiles, the third row average burst amplitude profiles, and last row envelope amplitude PDFs. Statistically significant differences under FDR control are indicated by black stars (three bursting features only).
Approaching dynamical changes using a linear surrogate analysis of average burst duration profiles

Our first approach to relating changes in the temporal patterning of beta oscillations between the ON and OFF states to dynamical changes is to consider the degree of non-linearity in the ON and OFF states. It is obtained by comparing average burst duration profiles ON and OFF medication to the profiles of their respective linear surrogates. In addition, we provide support for the relevance of these changes by reporting correlations with motor impairment.

Linear surrogates

Linear surrogates provide a way of testing for the presence of non-linearity in the system that generated an observed time-series [25]. Here linear system refers to a stationary linear stochastic process, an example of which is a stationary linear Gaussian process (in discrete time an auto-regressive moving average model or ARMA). As a reminder, an ARMA(p,q) model can be described as

\[ y_n = \sum_{i=1}^{p} a_i y_{n-i} + \sum_{i=0}^{q} b_i \epsilon_{n-i}, \] (1)

where \( \epsilon_i \) are independent Gaussian white noise increments. The value at time \( n \) is a linear combination of past values and noise terms.

Linear surrogates preserve the linear properties of the data (linear correlations) but erase any potential non-linear structure. Besides the mean and standard deviation, linear properties are limited to the auto-correlation at all lags in the time domain, which is equivalent to the power spectrum in the frequency domain via the Wiener-Khinchin theorem. Fourier transform (FT) surrogates are the most straightforward implementation of this idea: the Fourier phases of the data Fourier transform are randomized, but its Fourier amplitudes are kept, which ensures that upon inverse Fourier transform, the generated time series will share the same linear properties as the data but none of their potential non-linear properties. This corresponds to generating surrogates according to a stationary linear Gaussian process (ARMA in discrete time) that shares the same power spectrum as the data. Note that the coefficients and the order of the model need not be estimated and are not determined by the procedure.

Iterated amplitude adjusted Fourier transform (IAAFT) surrogates improve on FT surrogates by providing an exact match of the values in the surrogates and the values present in the data [26]. This corresponds to generating surrogates according to a stationary linear Gaussian process rescaled by an invertible, time-independent, non-linear measurement function:

\[ y_n = h(z_n), \] (2)

where \( h \) is the measurement function, \( z_n \) an ARMA model as described above, and \( y_n \) is constrained by the procedure to have the same PDF as the data, and approximately the same power spectrum. Thanks to \( h \), the requirement that \( y_n \) has a Gaussian noise structure is relaxed. The IAAFT surrogate method in particular, but also a number of other methods, have been successfully applied in various fields. For in-depths reviews of the methods available and their applications, see [27–29].

FT and IAAFT assume the data is stationary, which should be questioned in LFP recordings. In this work, even if the recordings used are short (on the order of 250 s), we rely on gradual wavelet reconstruction (GWR) surrogates, which can mitigate the nonstationarity issue. At the same time, GWR surrogates can quantify the strength of an effect by providing surrogates along a continuum parametrised by \( \rho \), where \( \rho = 0 \)
corresponds to IAAFT surrogates, and $\rho = 1$ corresponds to the data \cite{30}. More details on the GWR method can be found in \textbf{GWR surrogates} (Methods section). Nineteen GWR surrogates were computed from the filtered data for each patient and hemisphere, ON and OFF medication, and for each $\rho$ levels ranging from 0 to 0.9 in steps of 0.1 with an additional value at 0.99 (as close to the data as possible). A range of surrogates are shown in Fig. 11 (Methods section). Fixing the largest wavelet coefficient up to 10% of the total wavelet energy to the data values ($\rho = 0.1$) includes most of the data temporal variability in surrogates.

\textbf{Change in a burst duration specific measure of non-linearity in the ON and OFF states}

To evaluate dynamical changes between the ON and OFF states, we define a burst duration specific measure of non-linearity based on linear surrogates, and show that it is significantly greater OFF than ON medication.

We obtain average burst duration profiles and PSD from the filtered data and surrogates as in subsection \textbf{Extracting bursting features}, except that no segmentation is done and the surrogates are not filtered (as they already reproduce the spectrum of the filtered data). Average burst duration profiles of linear surrogates and filtered data are shown for the right hemispheres of the eight patients in Fig 4 for $\rho = 0$. Similar figures are provided for a range of $\rho$ levels for both hemispheres (supplementary Fig D and E in S1), and show that surrogates PSDs very closely match the data PSDs as expected.

As shown in Fig 3, panel A, we define a non-linearity measure specific to burst duration profiles as the sum of the squared differences between filtered data and linear surrogate burst duration profiles, relative to the square of the mean value of surrogate average burst duration profile. We refer to this measure as BDDLS, which stands for burst duration distance to linear surrogates. We call the difference in BDDLS OFF and ON medication BDDLSdiff.

Our burst duration specific measure of non-linearity, BDDLS, was found significantly greater OFF than ON medication from $\rho = 0$ up to $\rho = 0.6$ under FDR correction as shown in Table 1 (one-tailed Wilcoxon signed rank test, all patients and hemispheres). The BDDLS measures include a scaling by the square of the mean value of the surrogate average burst duration profile which ensures that the effect is not due to the profiles of data and surrogates having overall larger values OFF medication. Two conclusions can be drawn from the effect being significant up to $\rho = 0.6$. Firstly, the effect is not due to nonstationarity in the data (as mentioned earlier, GWR surrogates at $\rho = 0.1$ already look very similar to the data, and thus capture the major non-stationary features that may be present). Secondly, significance up to $\rho = 0.6$ implies that a limited amount of phase randomization in the surrogates is enough to start seeing a significant difference between BDDLS OFF and ON medication, hinting at a strong effect. More details on $\rho$ can be found in \textbf{GWR surrogates} (Methods section).

As a control, we calculated BDDLS OFF and ON medication for data band-pass filtered $\pm 3$ Hz around 35Hz, for $\rho = 0$. The control is here to show that there is no difference between BDDLS OFF and ON medication in another frequency band, and the choice of $\rho$ is therefore conservative (it is more likely to find a difference when the surrogates are the most different from the data). This effect is not found ($p = 0.449$, and see supplementary Fig F and Fig G in S1). This further suggests the effect does not come from differences in signal to noise ratio, as PSDs still vary considerably between the OFF and ON states in the controls. As BDDLS is greater in the pathological state, it is natural to ask whether BDDLSdiff correlates with motor impairment, which is what we focus on next.
Fig 3. Sketch of burst duration metrics. A: illustration of burst duration distance to linear surrogates in the OFF state (BDDLS OFF). BDDLS OFF is defined as the sum of squared differences between data and linear surrogate burst duration profiles for the OFF condition divided by the square of a scale. The scale is taken as the mean value of the OFF linear surrogate average burst duration profile. BDDLS ON is defined in a similar way, and BDDLSdiff is BDDLS OFF medication minus BDDLS ON medication. B: DURdiff is defined as the sum of the differences across thresholds between burst duration profiles OFF and ON medication.

Fig 4. Average burst duration profiles ON and OFF medication for data and GWR surrogates at $\rho = 0$ (right hemispheres). In all panels, data profiles are solid lines, while linear surrogate profiles are dashed lines. The OFF medication state is indicated in red, and the ON state in blue.

<table>
<thead>
<tr>
<th>$\rho$</th>
<th>0</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
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<th>0.6</th>
<th>0.7</th>
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<td>0.0010</td>
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<td>0.0012</td>
<td>0.259</td>
<td>0.510</td>
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Table 1. Statistical significance of medication state effect on BDDLS. Showing p-values for the test that BDDLS is greater OFF than ON medication (sign rank test, all patients, both hemispheres) as a function of the GWR surrogate parameter $\rho$. P-values in bold are smaller than 5%, while green indicates significance under FDR correction.
Clinical correlations

To show that the difference in BDDLS OFF and ON medication, BDDLSdiff, is indicative of motor impairment, we also consider two other metrics as possible predictors of motor impairment. The first one is the relative difference between PSD OFF and ON medication called PSDdiff (the difference has to be relative to allow an analysis across patients as PSD levels vary greatly), and the second one is the sum of the differences between burst duration profiles OFF and ON medication across thresholds called DURdiff (similar scale across patients). DURdiff is illustrated in Fig 3B. We measure motor impairment using the total unified Parkinson’s disease rating scale (UPDRS) OFF medication. The correlations we report are for predictors and total UPDRS OFF averaged across sides.

BDDLSdiff correlates with total UPDRS OFF. The correlation is statistically significant under FDR correction from $\rho = 0.1$ to $\rho = 0.5$ (Spearman’s correlation coefficients and associated p-values are shown in Table 2). This suggests a robust effect as explained previously. The other factors of interest PSDdiff (relative change in PSD) and DURdiff (change in burst duration) are also correlated with total UPDRS OFF medication (Spearman’s correlation of 0.500, $p = 0.216$, and of 0.476, $p = 0.243$, respectively). The lack of significance for these factors is likely due to the small sample size (8 subjects). The relationship between predictors and changes in clinical scores is plotted in supplementary Fig H in S1.

<table>
<thead>
<tr>
<th>$\rho$</th>
<th>0</th>
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<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
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<td>0.428</td>
<td>0.935</td>
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Table 2. Spearman’s correlations between BDDLSdiff and total UPDRS score OFF medication. Values presented as a function of the GWR surrogate level $\rho$, for both the total UPDRS difference. P-values in bold are smaller than 5%, while green indicates significance under FDR correction.

The three predictors considered are correlated (Spearman’s correlations are 0.500, $p = 0.216$ between BDDLSdiff for $\rho = 0.2$ and PSDdiff, 0.476, $p = 0.243$ between BDDLSdiff for $\rho = 0.2$ and DURdiff, and 0.952, $p = 0.001$ between DURdiff and PSDdiff). However, scaling BDDLs by the mean value of surrogate average burst duration profile decorrelates as much as possible BDDLSdiff from DURdiff. Moreover, non-linear correlations cannot be recovered from the PSD (the power spectrum only captures linear correlations) which implies that BDDLSdiff should contain information not present in PSDdiff if there is non-linearity in the system expressed in the bursting profiles.

We have made apparent that changes in temporal patterning in beta activity between medication states can be related to an increase in our burst duration specific non-linearity metric OFF medication, and that changes in the BDDLS metric are correlated with motor symptoms. Average burst duration profiles OFF medication rank higher on the BDDLS metric and can therefore be thought of as being generated by a more non-linear system than ON medication. To get a clearer idea of which specific dynamical changes could be at play between the ON and OFF states, we proceed to model one patient at each end of the BDDLS spectrum with biologically inspired models, and compare both dynamical systems.

Approaching dynamical changes using neural mass models

To investigate which particular changes to the dynamics of a biologically inspired model of the STN-GPe loop could account for the changes in the temporal patterning of beta oscillations between the OFF and ON condition, we fit WC models to patient data. We
choose patients whose average burst duration profiles deviate the least and the most from their linear surrogates. These patients are patient 3, left hemisphere, in the ON state (lowest BDDLS for $\rho = 0$, see supplementary Fig D in [S1], and patient 6, right hemisphere, OFF medication (most striking deviation from its linear surrogate and greatest BDDLS for $\rho = 0$, see Fig 3). We denote these datasets patients 3L ON and 3R OFF, respectively. We note that the average burst duration profile of patient 3L ON is close to its linear surrogate (for $\rho = 0$). Since the average burst duration profiles of linear surrogates all closely match when z-scored (see supplementary Fig I in [S1], it is likely that patient 3L ON should also be representative of linear systems in general.

Fitting a linear Wilson-Cowan model to the lowest BDDLS patient

We start by fitting to patient 3L ON the time discretization of a linear Wilson-Cowan model which describes the interactions between an excitatory and an inhibitory population of neurons. The discrete WC can be seen as a multivariate version of an ARMA model (equation (1)). The WC is a natural choice as it can be mapped onto the basal ganglia STN-GPe loop as shown in Fig 5, the STN being modelled as the excitatory population, and the GPe as the inhibitory population [31][32]. The LFP recordings used in this study are obtained from DBS electrodes implanted in the STN, and therefore we model the LFP signal by the activity of the excitatory population. STN and GPe are reciprocally connected, the STN receives a constant excitatory input from the cortex, while the GPe receives a constant inhibitory input from the striatum, and is also self-inhibiting. Uncorrelated inputs, specifically Gaussian white noise, are added to each population, and the STN activity, $E$, and the GPe activity, $I$, are described by the stochastic differential equations

$$
\begin{align*}
\frac{dE}{dt} &= \frac{1}{\Omega_E} (-E + f_\beta(\lambda_E - w_{IE}I)) dt + \zeta dW_E, \\
\frac{dI}{dt} &= \frac{1}{\Omega_I} (-I + f_\beta(-\lambda_I + w_{EI}E - w_{II}I)) dt + \zeta dW_I, 
\end{align*}$$

(3)

with $w_{PR}$ the weight of the projection from population “P” to population “R”, $\lambda_P$ the constant input to population “P”, $\Omega_P$ the time constant of populations “P”, $dW_E$ and $dW_I$ are Wiener processes, and $\zeta$ the noise standard deviation. In this attempt to describe the simplest average burst duration profiles, we use a linear activation function simply given by $f_\beta(x) = \beta x$, parametrized by a steepness parameter $\beta$.

The time discretized model is fitted to two features (also known as summary statistics) of the data, namely the data PSD and the data average burst duration profile.

![Fig 5. Mapping of the Wilson-Cowan model onto the STN-GPe loop.](image)
How fitting is carried out is described in “Fitting procedures” in the Methods section. As the model output $E$ models the centered LFP recordings, a model of the beta envelope is obtained by considering the Hilbert amplitude of $E$ (modulus of the analytic signal of $E$).

The best fit to patient 3L ON is shown in the first row of Fig 6 and we report the corresponding model parameters in supplementary Table A in S2. The linear WC model is able to reproduce both the data PSD and average burst duration profile ($R^2 = 0.726$, see Fig 6C1 and Fig 6D1). The input parameters $\lambda_E$ and $\lambda_I$ only contribute to transients in the linear WC model, and are therefore set to zero here. They will have an influence on the model output when non-linearity is introduced.

We have shown that a linear WC model can fit to the lowest BDDLS patient, and we next fit increasingly complex WC models to patient 6R OFF to investigate the OFF medication case.

Fitting Wilson-Cowan models to the highest BDDLS patient

The same procedure as before is used to fit the time discretized linear WC model to patient 6R OFF. The best fit is shown in Fig 6 third row, and we report the corresponding model parameters in supplementary Table A in S2. The linear WC model is able to reproduce the data PSD but does not fit well to the average burst duration profile ($R^2 = 0.312$ overall, see Fig 6C3 and Fig 6D3).

We next introduce the time discretization of a non-linear WC model, which is identical to the linear WC model (see Fig 5), except that its activation function

$$g_{\beta,\eta}(x) = \frac{\eta}{1 + e^{-\beta(x-1)}}$$

is non-linear and that connections carry a delay. The system of equations (3) is therefore modified as

$$
\begin{align*}
\frac{dE_t}{dt} &= \frac{1}{\Omega_E} (-E_t + g_{\beta,\eta}(\lambda_E - w_{IE}I_{t-\Delta_IE})) dt + \zeta dW_{E,t}, \\
\frac{dI_t}{dt} &= \frac{1}{\Omega_I} (-I_t + g_{\beta,\eta}(-\lambda_I + w_{EI}E_{t-\Delta_IE} - w_{II}I_{t-\Delta_{II}})) dt + \zeta dW_{I,t},
\end{align*}
$$

(5)

where $\Delta_{PR}$ is the delay from population “P” to population “R”, and $\eta$ a scaling parameter.

The best fit to patient 6R OFF obtained with the same fitting methodology as before is shown in the fourth row of Fig 6 and we report the corresponding model parameters in supplementary Table B in S2. The non-linear WC model with delays is able to reproduce well the data average burst duration profile and the data PSD ($R^2 = 0.91$, see Fig 6C4 and Fig 6D4).

In summary, this subsection has demonstrated that in a biologically inspired E/I model, reproducing the most striking average burst duration profile in the OFF condition requires the addition of delays and a non-linear (sigmoidal) activation function compared to typical ON profiles. The need for non-linearity agrees with the surrogate analysis carried out previously, but the present results also delineate the specific differences in dynamics of a biologically inspired model required to reproduce the two conditions studied.

In some cases, the envelope of E/I models can be related to what we call in this work “envelope models” (illustrated in Fig 1). Indeed, it was shown in [24] that the envelope of a linear WC model is a Rayleigh process, assuming the ratio of the $E$ and $I$ envelopes is constant, and the phase delay between $E$ and $I$ oscillations is constant. A Rayleigh process is in fact a particular type of envelope model. We next investigate whether a conclusion similar to that of this subsection on E/I models holds for envelope models that provide a direct, simpler description of envelope dynamics. Additionally, we will study envelope models analytically to obtain additional insights.
Fig 6. Best model fits. Showing best fits to patient 3L ON (first two rows), and patient 6R OFF (next three rows). Patient data is color coded in black, models in blue. Each row corresponds to a given model as labelled in blue. The first column shows twenty seconds of filtered LFP recording (A panels), while model oscillatory activity output is plotted in the second column (B panels). Data and model PSDs are compared in the third column (C panels), and data and model average burst duration profiles are shown in the last column (E panels, sem error bars).

Approaching dynamical changes using envelope models

To obtain the simplest polynomial dynamics describing the OFF and ON conditions (as represented by patient 6R OFF and patient 3L ON, respectively), we consider envelope models directly describing the LFP envelope and fit them to data. Further, to describe the dependence of burst duration on model parameters, we derive an approximate analytical expression for the average burst duration profile, and apply it to the model describing the ON condition.
Fitting envelope models to burst duration profiles

The time discretization of the simplest stochastic process with state dependent drift and uncorrelated white noise, the Ornstein-Uhlenbeck (OU) process, is in fact enough to model the average burst duration profile of patient 3L ON, which is representative of linear systems and of the ON condition. The OU process is described by the stochastic differential equation

\[ dx = -\theta x dt + \zeta dW, \]  

where \( W \) is a Wiener process, \( \theta \) a positive decay parameter, and \( \zeta \) the constant noise standard deviation. To illustrate the ability of such a system to also model oscillatory activity, the phase equation

\[ \dot{\phi} = 2\pi\nu \]  

is added, where \( \nu \) is a constant frequency. Oscillatory activity can then be generated as \( z(t) = x(t) \cos \phi(t) \).

To reproduce the average burst duration profile of patient 6R OFF, we extend the drift function of the OU model to include non-linear polynomial terms. Since degree two polynomials could not fit the data (not shown), we are considering the time discretization of a degree three model

\[ dx = (d_3 x^3 + d_2 x^2 + d_1 x + d_0) dt + \zeta dW, \]  

where \( d_0 \) to \( d_3 \) are constants. As before, the independent phase equation \( \dot{\phi} = 2\pi\nu \) is added to the envelope model.

The resulting models are fitted to the average burst duration profile of patient 3L ON, and patient 6R OFF, respectively. The frequencies \( \nu \) are adjusted to match the data peak frequencies, and the models are scaled so the standard deviation of \( z \) roughly matches that of the data. In the simple OU model, the envelope is prevented from being negative by shifting it by the absolute value of its 0.11th percentile, and setting values below that to zero. In the degree three model, a positive envelope is ensured by retaining only the absolute value of the next point at each integration step, which has a negligible impact on positive thresholds. Remaining model parameters are optimised (procedure in "Fitting procedures" in the Methods section) to obtain the best fit of the data average burst duration profile with \( x(t) \) directly modelling the \( \beta \) envelope.

The best fits to patient 3L ON and 6R OFF are shown in the second and last row of Fig 6, and we report the corresponding model parameters in supplementary Table C and Table D in S2, respectively. The OU model is able to reproduce the data average burst duration profile of patient 3L ON well (\( R^2 = 0.996 \) for burst duration only, see Fig 6D2), and so is the degree three model for patient 6R OFF (\( R^2 = 0.976 \) for burst duration only, see Fig 6D5). In both cases, oscillatory activity at the data peak frequency can be generated from the envelope model (Fig 6C2 and Fig 6C5).

As in the previous subsection, we conclude that reproducing the OFF average burst duration profile most strikingly different from its surrogate’s profile requires the addition of non-linearity compared to typical ON profiles, which can be reproduced with an OU model. The non-linearity takes the form of a degree three polynomial drift function. We have shown that envelope models can successfully model patient average burst duration profiles, and we next study analytically how to express average burst duration profiles as a function of envelope models dynamics.

Average burst duration and exterior problem mean first passage time

In order to study the dependence of burst duration on envelope model parameters, we seek an analytical expression for the average burst duration profile of envelope models. As recently noted in [24], the concept of average burst duration is related to the concept
of mean first passage time (MFPT, also known as mean exit time) in the exterior problem. Considering a threshold or boundary $L$ and a starting point $x_0 = L + \delta$, with $\delta > 0$, we denote the continuous time MFPT from $x_0$ to $L$ by $\tau_{x_0, L}$. It is defined by the expectation of the random variable $\inf \{ t \geq 0 : x_t \leq L \}$. At this point it should be clarified that the average burst duration of a continuous time stochastic process with Gaussian noise is always zero, as all trajectories starting from the threshold $L$ will cross it again in vanishingly short times. In addition, MFPTs in continuous time are systematically biased towards shorter first passage times since a continuous stochastic model is more likely to cross the boundary when close to it than its discrete time counterpart. However, we can adapt classical MFPT results from continuous time stochastic process literature to analytically approximate the average burst duration of the corresponding models in discrete time. In what follows, we use a tilde to distinguish quantities that can be measured readily in a time discretized system from the continuous system quantities.

Fig 7. First exit time and overshoot distribution. Showing a discrete realisation of an OU process overshooting the threshold $L$ by $\delta$, with a sketch of the overshoot probability density at $L$ in purple. The first exit time from $x_0$ to $L$ is the time taken to get below $L$ for the first time, starting from $x_0$.

To study the associated discrete time model with time step $dt$, we are considering the continuous case of a stochastic process

$$dx_t = \mu(x_t) dt + \zeta dW_t,$$

where we have assumed that the real valued drift function $\mu$ can depend on $x_t$, and that $\zeta$ is constant in time and space. Following a derivation similar to that reviewed in [34], we show in the Methods section (see "Continuous model MFPT") that the MFPT of the continuous system is given by

$$\tau_{x_0, L} = \frac{2}{\zeta^2} \int_{x_0}^{L} \int_{-\infty}^{+\infty} \frac{e^{-x_1^2}}{2\pi \sigma^2} \int_{x_1}^{+\infty} \mu(x) dx dx_1 dx.$$  

For the integral to converge, we require non-vanishing negative $\mu$ at $+\infty$, which is necessarily the case in models describing neural oscillations. Equation (10) cannot be applied to white noise only, where $\mu(x) = 0$. From there, we derive the average burst duration for the discretized model with time step $dt$. We show in the Methods section (see "Discretized model") how to correct for the systematic bias of the continuous model.
(Steps 1 and 2). We also detail there how to relate average burst duration and MFPT (Step 3): when crossing a threshold $L$ from below at the start of a burst, a discrete model will always overshoot the threshold, and the average burst duration at threshold $L$ can be related to MFPTs by taking into account the overshoot distribution at $L$ (see Fig 7). We finally obtain to first order in $\sqrt{dt}$ the average burst duration $\tilde{\tau}_L$ for the discrete time model as

$$\tilde{\tau}_L \approx \frac{\sqrt{2\pi dt}}{\zeta} \int_L^{+\infty} e^{-\frac{x^2}{2\zeta^2}} \mu(x) dx.$$  \hspace{1cm} (11)

Equation (11) provides a general relationship from drift function to average burst duration profile for the discretization of stochastic envelope models described by equation (9). As shown in Fig 8 this result applied to the OU model and the degree three model [equation (12) below and equation (48) in the Methods section] is very close to simulations.

![Fig 8. Simulations of average burst duration profiles for OU processes and the fitted degree three polynomial model.](image)

**Fig 8. Simulations of average burst duration profiles for OU processes and the fitted degree three polynomial model.** Average burst duration profiles from simulations of OU processes are compared to equation (12) for a range of decay parameters and $\zeta = 1$ in panel A. Similarly, average burst duration profiles from simulations of the fitted degree three polynomial envelope model are compared to equation (48) in panel B. Simulations are indicated by dashed lines (sem error bars), and analytical results by dotted lines. Simulations consist of five repeats of $10^5$ s, with a time step of 1 ms (simulations of the OU process are done according to the exact updating equation (17)).

**Increasing average burst duration in the OU model**

Building on the previous result, we highlight the dependence of average burst duration on model parameters and show how bursts can be lengthened in the discretized OU model, which is representative of the ON condition and of linear systems in general (see supplementary Fig I in S1). We are considering here the discretization of an OU process centered on zero [equation (6)]. Equation (11) gives, to first order in $\sqrt{dt}$,

$$\tilde{\tau}_L \approx \pi \sqrt{\frac{dt}{2\theta}} e^{-\frac{\theta L^2}{2}} \text{erfc} \left( \frac{\sqrt{\theta} L}{\zeta} \right),$$  \hspace{1cm} (12)
where erfc is the complementary error function. The dependence of average burst duration on parameters is easier to see when \( L \) is expressed as a percentile of the time series values, which is also how we present average burst duration profiles. Because of this choice, the shift introduced earlier to ensure the envelope stays positive will have no impact on the result.

We express the average burst duration of a discrete OU process as a function of threshold percentile using the stationary probability distribution of the OU process (see “OU” paragraph in the Methods section). We obtain

\[
\bar{\tau}_L \approx \pi \sqrt{\frac{2 dt}{\theta}} \left(1 - L\%\right) e^{\left\{erf^{-1}(2L\%-1)\right\}^2},
\]  

(13)

where \( L\% \) is the percentile rank (between 0 and 1) corresponding to the threshold \( L \). Equation (13) does not depend on the noise parameter \( \zeta \) (which only scales trajectories), and makes apparent a simple dependence of the average burst duration on the decay parameter. We can conclude that increasing the average burst duration for a given threshold corresponds to decreasing the decay in the OU model, which is what is intuitively expected.

We demonstrated that discretized envelope models can reproduce patient average burst duration profiles, and provided the polynomial form of the drift function required. In addition, the average burst duration profile of discretized envelope models can be approximated analytically, which yields insights into how model parameters influence average burst duration profiles. This analytical result opens the question of a reverse link from average burst duration profile to dynamics, which we investigate next.

**Average burst duration profiles are a signature of envelope dynamics**

In this subsection, we establish that average burst duration profiles are a signature of envelope dynamics by showing that the envelope drift function can be recovered from the average burst duration profile. This clarifies how a change in the temporal patterning of beta oscillation signals a change in dynamics.

**Relationship between envelope drift function and average burst duration profiles**

To highlight the importance of burst duration profiles as a marker of dynamics, we establish a link for a general class of stochastic processes with additive noise between the average burst duration profile, the noise standard deviation, and dynamics. We are considering a time discretization (time step \( dt \)) of the stochastic process given by equation (9). As a reminder, we assume that the real valued drift function \( \mu \) can depend on \( x_t \), and that the diffusion term \( \zeta \) is constant in time and space. We show in “Passage method” in the Methods section, that to first order in \( \sqrt{dt} \),

\[
\mu(L) \approx -\zeta \sqrt{\frac{2 dt}{\tau_L^2}} + \frac{\zeta \partial \bar{\tau}_L}{\bar{\tau}_L} \partial L.
\]  

(14)

Equation (14) highlights a direct relationship between envelope dynamics (drift function) and average burst duration in discrete time. This is essentially a local relationship (at threshold \( L \)), and the drift function can be estimated where the average burst duration profile is known. We call this estimation procedure the “passage method”, and show next that it can recover envelope dynamics in synthetic data and patient data.
Inferring dynamics in synthetic data from envelope models and in patient data with the passage method

To validate the method, we first test the passage method on synthetic data. We are considering envelope time series of 250 s (roughly the same length as data) and of 1000 s generated from an OU envelope model (same parameters as best fit to patient data, see supplementary Table C in S2) and a degree five polynomial envelope model (see equation (50) in “Passage method” in the Methods section, parameters given in supplementary Table E in S2). The degree five polynomial model provides more complex dynamics to infer than the degree three polynomial introduced earlier.

Dynamics from these time series are recovered using the passage method. We are considering three hundred thresholds, and applying smoothing to τ_L and its derivative (full details provided in “Passage method” in the Methods section). The results are shown in the first two rows of Fig 9. Approximations of the drift functions µ are recovered (Fig 9A1 and Fig 9A2), and the average burst duration profiles and inverse CDFs obtained from simulating the recovered dynamics approximate the synthetic data well (Fig 9B1 and Fig 9B2, and Fig 9C1 and Fig 9C2, respectively). Dynamics recovered from the longer time series and associated features are a better approximation than dynamics recovered from the shorter time series, although performance is reasonable for the shorter time series, which is approximately the duration of patient data recordings.

Given its success on synthetic data, the method is tested on patient data. We pick the patient that scores the highest on our burst duration specific non-linearity measure, patient 6R OFF (as for non-linear fits), and the same patient and hemisphere ON medication for comparison. The method is applied as before, with the additional estimation of the noise parameter and the time step (specifics of the application of the method to patient data detailed in “Passage method” in the Methods section). The results are shown in the last two rows of Fig 9. There is no ground truth to compare the recovered dynamics against (Fig 9A3 and Fig 9A4), but the average burst duration profiles and inverse CDF obtained from simulating the recovered dynamics are a good match to the data. We note that the dynamics inferred ON medication are closer to a straight line, which supports the hypothesis of more non-linearity OFF medication.

Comparison of the passage method with a direct method

To evaluate the performance of the passage method in extracting envelope dynamics from data, we compare our method with a simpler envelope recovery method that directly tries to estimate time derivatives from the envelope time series. Specifically, time derivatives are calculated as a first order difference, and the data is binned in 300 bins of equal width (same number of bins as the number of thresholds in our method) within which derivative values are averaged.

Both the simple method and the passage method are applied to envelope time series of a range of durations from 100 s to 1000 s generated by the OU model and the degree five polynomial model used in previous tests. The passage method is applied as described in “Passage method” in the Methods section, expect that no smoothing is applied to either the passage method or the direct method for a fair comparison. The sum of the squared errors between the recovered drift function µ and the corresponding ground truth is calculated for both methods for each time series, and the results are presented in Fig 10. The passage method is at a slight advantage in the OU case as well as in the degree five polynomial case.
Fig 9. Recovering envelope dynamics with the passage method. The method is applied to synthetic data (OU model in the first row, degree five polynomial model in the second row), and patient data (patient 6, right, ON medication in the third row, and patient 6, right, OFF medication in the last row). The recovered drift functions ($\mu$) are shown in the first column, and the average burst duration profiles and the inverse CDFs simulated from the recovered dynamics in the second and third column, respectively. Ground truths are provided when available (black dashed line). Synthetic data results are presented for 250 s and 1000 s of training data. In the last column, 5 s of simulated data from the recovered dynamics is compared to training data (panels D and E share the same time axis).
**Discussion**

In this study, we analysed PD patients STN LFP recordings in the beta band and first motivated the choice of average burst duration as a marker of the differences in bursting activity ON and OFF medication. We found a burst duration specific measure of non-linearity based on linear surrogates to significantly increase from the ON to the OFF medication state, and the change in this non-linearity measure to be correlated with motor impairment. We further narrowed-down dynamical changes underlying the changes in beta oscillation temporal patterning between medication states by fitting models to data. The biologically inspired WC model could reproduce a typical ON average burst duration profile with a linear activation function, while the most striking OFF profile required a non-linear activation function and the addition of delays. Similarly, envelope models, where the beta envelope is directly described by the discretization of a stochastic process with constant noise, required a linear drift function (OU process), and a degree three polynomial drift function, respectively. The simplicity of envelope models allowed to derive an approximate expression for average burst duration profiles (equation (11)), which clarified how model parameters affect average burst duration in the linear case. Further, we showed that the non-linearity can be directly extracted from average burst duration profiles using our “passage method” (based on equation (14)), demonstrating that average burst duration profiles are a signature of envelope dynamics. This sheds light on why burst duration has been suggested in multiple studies as an important biomarker in PD.

**Bursting features** Average burst duration profiles are an insightful and exhaustive way of characterising bursting dynamics. Average profiles across thresholds benefit from information from a range of thresholds and capture more about the system than the burst duration distribution at one threshold (which may only integrate dynamical information, and predominantly above the threshold). In fact, we demonstrate that average burst duration profiles are closely related to the dynamics of the beta envelope. They can also provide insights into bursts shape: the levelling of a burst duration profile at higher thresholds can be related to sharp and long bursts of high amplitude. Some
previous studies have used wavelet amplitude as the beta envelope to study bursting features [13,14], while we used the Hilbert envelope of the filtered signal. We found little difference between the methods as far as average burst duration is concerned (not reported). While a number of recent studies define bursts as Hidden Markov Model states [35,36] or using support-vector machines [37], we aim at providing a more complete dynamical picture of beta dynamics.

Besides the PSD, our statistical analysis of patient STN LFP recordings identified burst duration across thresholds as the feature most suited to distinguish between burst dynamics in the ON and OFF states. We highlight the importance of individually z-scoring the filtered data when comparing average burst amplitude profiles between medication states to control for differences simply due to differences in mean beta power. A similar result has been reported in a non-human primate study [19] where beta burst duration was found to be a better differentiator of healthy and pathological episodes in the STN. Deleting longer beta episodes resulted in a greater decrease of parkinsonian activity than deleting stronger episodes. In our patient analysis, the ON medication state gives an approximation to the physiological state. It is hypothesised that shorter bursts are more likely to be physiological, whereas longer burst are more likely to be pathological [13,14]. Longer bursts are known to be associated with more synchronization in the STN, but also across the motor network [38]. This results in less information coding capacity [8] and may underlie the motor symptoms.

**Surrogate analysis**  Our burst duration specific measure of non-linearity, BDDLS, provides a new dimension that can be used to analyse LFP recordings. Non-linearity here should be understood as non-linear correlations in the time series of interest (a sinusoid is considered linear, as it can be represented by an ARMA model, see “Linear surrogates”). We showed that, in the case of PD, the difference in BDDLS between medication states in STN LFPs is correlated with motor impairment. The correlation for \( \rho = 0 \) to 0.5 was on par or better than the correlation obtained with the relative difference in power and the difference in burst duration. However this should be re-evaluated on larger datasets. Predicting burst duration based on PSD alone will not be accurate for patients that have different average burst duration profiles than their linear surrogates, which is the case for most patients OFF medication. This is because the PSD only reflects linear correlations. Changes between the ON and OFF states are of one of three types. The first one is mostly “linear” changes (e.g. patient 5, right, in Fig 4 where both the ON and OFF average burst duration profiles are close to their surrogates and there is a large difference between surrogates). The second one is mostly “non-linear” changes (e.g. patient 4, right, in Fig 4 where the ON profile matches its surrogate and the OFF surrogate, and the OFF profile differs from its surrogate). The third one is both “linear” and “non-linear” changes (e.g. patient 6, right, in Fig 4 where the ON profile is close to its surrogate, and there is a large difference between surrogates and between the OFF profile and its surrogate). These categories could provide a basis to stratify patients, in particular if similar results could be obtained from non-invasive EEG recordings. The scaling by the mean value of the surrogate profile that was applied to BDDLS helped decorrelate BDDLS from the difference in burst duration (DURdiff). We defined DURdiff as a difference between data burst duration profiles for simplicity, but it may be the case that defining DURdiff as the difference between linear surrogates decorrelates BDDLSdiff and DURdiff further and improves predictive power.

Surrogate testing has been used to explore non-linearity in brain recordings in pathological states. In particular it has been reported that epileptic seizures are associated with non-linear brain dynamics, while little non-linearity was found in Alzheimer’s disease (reviewed in [39]). In the context of PD, we found an increase in a burst duration specific measure of non-linearity in the pathological state compared to
ON medication. From an information theoretic perspective, non-linear correlations between frequencies within the beta band may further reduce information coding capacity, and impair motor function. On a related note, scalp EEG recordings over the sensorimotor cortex of PD patients were found to have more pronounced non-sinusoidal features in the beta band OFF medication compared to ON medication [40] and OFF DBS compared to ON DBS [41]. Non-linear correlations between different frequencies in STN LFP rhythms have been reported to be greater OFF than ON medication [42]. STN LFPs were also described as more non-linear during resting tremor in PD [43], but our non-linearity measure is specific to burst duration in the beta band and may therefore be more specific to bradykinesia and rigidity.

Non-linear correlations are not seen in average power, and we showed that they are correlated with motor impairment, which has implication for aDBS in PD patients. A slow variant of aDBS provides stimulation according to average beta power on a 50 s time scale [44,45]. Slow aDBS will not address selectively the aspect of the pathology we highlighted in this study, since average power cannot reflect non-linear correlations. Providing aDBS according to a predictive algorithm based on the frequency information contained in a 300 ms window before burst onset was reported in PD to be very close in performance to optimised aDBS, i.e. to threshold based stimulation [46]. Moreover, it appears that pathological synchronization is established earlier than common thresholds used to define beta bursts [47]. Non-linear information not present in the features studied in [46] (windowed power spectra) may provide additional predictive power, and linear surrogates estimated on a slower time scale than real time could provide a useful baseline to compare current recordings against. The computational cost of GWR surrogates rules them out, but computationally cheaper IAAFT surrogates may be better cut out for the task. Although GWR surrogates were used in our study to account for potential non-stationarity in LFP recordings, a correlation with clinical scores was observed for $\rho = 0$, which corresponds to IAAFT surrogates. Average burst duration profiles and BDDLSdiff have been studied on a slow time scale (about 250 s of data). How little data can be used to reliably estimate BDDLSdiff remains to be explored, and other surrogate based non-linearity measures may be more suited to real-time use. Nevertheless, closed-loop DBS targeting non-linearity in the drift function might prove more selective in suppressing pathological oscillations than closed-loop DBS approaches based on amplitude. Additionally, amplitude thresholds in aDBS would need to change with medication and activity level, and a stimulation strategy not requiring an amplitude threshold would be simpler.

### Modelling burst duration profiles

As one could expect, linear models could fit to the average burst duration profile which scored the lowest on our burst duration specific measure of non-linearity. This profile was taken as a representative example of average burst duration profiles of linear systems, which were found to have a typical shape (potentially scaled and shifted). The linear models chosen were a linear WC model without delays and an OU envelope model. On the one hand, the architecture of the former can be mapped onto the STN and GPe populations [31][33], and it only has a few parameters, making it easier to constrain and less likely to overfit the data. On the other hand, the latter is perhaps the simplest stochastic envelope model with a non constant drift term, and is a simplification of the Rayleigh envelope model, which has been shown to describe the envelope of the linear WC model under certain assumptions [24] as mentioned in the Results section.

The data average burst duration profile that scores the highest on our burst duration specific measure of non-linearity could be modelled by more complex versions of the successful linear models, namely the non-linear WC with delays, and a degree three polynomial envelope model (the OU envelope model can be seen as a degree one
Polynomial model). Complexity was increased gradually to avoid overfitting. A linear WC model without delays could not fit the data, and a non-linear WC model without delays could not fit the data either (not shown), but the non-linear WC model with delays was successful. Similarly, a degree two polynomial was found to not fit the data (not shown) before the degree three polynomial was introduced.

Dynamical changes identified in both models between medication states deserve further discussion. While it could be tempting to conclude from the WC fits that delays are necessary to reproduce the data from patient 6R OFF, the degree three polynomial envelope model suggests that non-linearity is enough to reproduce the data and that delays are not necessarily required in all models. The levelling off at high thresholds of an average burst duration profile such as that of patient 6R OFF could be explained by larger oscillations getting stability from an additional attractor. Multistability could be a dynamical interpretation of such features in the average burst duration profile, and could open the door to a dynamical definition of bursts as events in the vicinity of an attractor at larger amplitude. However, multistability turns out not to be a requirement since the best fit degree three polynomial model to patient 6R OFF, and the dynamics inferred by the passage method applied to the same patient, do not exhibit multistability but produce an average burst duration profile close to the data (see Fig 6, Fig 9A4, and Fig 9B4). The “bump” seen in Fig 9A4 is not indicative of multistability since it does not cross the horizontal axis, but suggests an attractive influence at the corresponding amplitude level. It is unclear how this attractive influence could be interpreted in terms of physiological processes at this point.

It is well known that simple Wilson-Cowan (WC) models [23] of the STN-GPe loop can generate sustained beta oscillations without the need for correlated inputs [33, 48], but whether that is the case for transient beta has not been reported. The finding that a simple STN-GPe WC model with uncorrelated noise as inputs can reproduce the most complex average burst duration profile of the dataset, i.e. realistic transient beta oscillations, brings support to the theory that the STN-GPe loop could play a predominant role in the generation of pathological beta activity [49–51].

**Analytical expression of average burst duration in envelope models**

Standard first-passage results are available for continuous time stochastic processes (see for instance [34]), but their application to time-discretized systems is not immediate. While we derive in this study a three-step correction to obtain the average burst duration profile of envelope models in discrete time (assuming time-independent but possible state-dependent drift function and constant diffusion term across space and time), other related approaches are worth mentioning. Perhaps the most relevant is a continuity correction introduced in the financial literature to price continuous barrier options [52]. The correction consists in shifting the continuous barrier to account for discrete monitoring of prices, but is not applicable when the initial price is close to the barrier. As a result, this approach cannot be successfully used for bursts, since they start very close to the barrier (the distribution of initial points is given by the overshoot distribution). Alternatively, algorithms have been suggested to approximate continuous first passage time distributions with simulations [53–55]. In the specific case of the OU model, approximations are directly available for the first passage density of the discretized model, but their complexity makes them unpractical [56, 57].

Discrete models are required to model burst duration, however the dependence of our results on the time step is worth discussing. As mentioned in the Results section, discrete models are required to model burst duration since the average burst duration for a continuous stochastic process with Gaussian noise is always zero. As expected, the average burst duration given by equation (11) goes to zero as the time step goes to zero. Moreover, the dependence of average burst duration on the time step predicted by...
The present work contributes a result for a more general class of models, that includes a general drift function that can depend on the position, and additive noise constant in time and space (“complicated dynamics, simple noise”). However, the model cannot include delays, and dynamics cannot be recovered in the vicinity of the derivative of the MFPT being zero at the threshold considered. As is manifest in equation (14), when average burst duration and its derivative are considered only at a given threshold, only the decay parameter and the time step play a role in the expression. For a given time step, it is therefore possible to identify an envelope decay in a dataset by fitting an OU burst duration profile to its average burst duration profile. The decay could be assimilated to the real part of the eigenvalues of a broader class of linear envelope models. In the context of simple integrate and fire neuron models, firing can be related to the first passage of an OU process, and the associated decay parameter is estimated in [58] by considering inter-spike interval statistics. In our work, Equation (13) clarifies the role played by the decay parameter, and predicts that a linear system modelling beta bursts will be made more pathological when its decay parameter is reduced, which makes intuitive sense. This may correspond to changes in average burst duration described as “linear” in the “Surrogate analysis” part of the discussion. In the degree three model case, dependence on model parameters cannot be studied directly contrary to the OU case, but the integral expression given by equation (48) could facilitate numerical analysis as it can be evaluated numerically much faster than the model can be simulated and subjected to burst duration quantification. Also of experimental interest, the burst duration distribution for a given threshold can be obtained analytically for OU processes as an infinite series, but is hard to evaluate numerically since it involves confluent hypergeometric functions of the second kind, their zeros and derivatives (equation (90) in [34]).

From average burst duration profiles to dynamics  The link we established from average burst duration profiles to drift function suggests that average burst duration profiles are a window into envelope dynamics. As detailed in the introduction, burst duration has been experimentally identified as an important marker of pathology for PD, and the present finding shed some light on the dynamical significance of burst duration. The uncovered link (equation (14)) is true for a general envelope model, with a general drift function that can depend on the position, and additive noise constant in time and space (“complicated dynamics, simple noise”). However, the model cannot include delays, and dynamics cannot be recovered in the vicinity of the derivative of the MFPT being zero at the threshold considered. As is manifest in equation (14), when average burst duration and its derivative are considered only at a given threshold, only
local information on the dynamics is available.

The relationship naturally provides a method to infer envelope dynamics from data, which we call the passage method. We applied the passage method successfully to synthetic data, and recovered envelope dynamics from patient data for patient 6R, ON and OFF medication. In this case study, envelope dynamics OFF medication are found more linear than ON. The range of \( x \) values are lower for the ON state, and the OFF state is mostly linear in this region, which could suggest the ON state may correspond to a sub-regime of the OFF state, and non-linearity could come in when oscillations become larger.

The passage method favorably compared to a simple, direct method. The better performance of the passage method on synthetic data may be related to a better robustness to noise. The noise parameter has to be estimated and is accounted for in the passage method, which is not the case in the direct method. This might be advantageous provided that constant additive noise is a good approximation for the dataset at hand. Comparison of the passage method with state of the art dynamics inference methods that account for stochasticity such as dynamical Bayesian inference (DBI) \cite{59,61} is out of the scope of this paper, but would provide more insight into the performance of the passage method. DBI was not specifically designed to recover envelope time series, and assumes basis functions to represent dynamics, but could be applied to envelope dynamics inference. Additionally, the direct method can be improved using multiple linear regressions and derivative estimates with various time lags \cite{62}, in particular for linear dynamics. The passage method may find productive applications in other parts of the neurosciences – for instance in the field of memory, where beta and gamma bursts \cite{63}, and the duration of sharp wave ripples \cite{64} have been found to be related to memory – and beyond.

**Methods**

We present in this section some methodological details on data analysis, model fitting, the derivation of average burst duration in envelope models, and the passage method.

**FDR correction**

All statistical tests in this study were performed under FDR control at 5%. This ensures that the expectation of the number of false positives over the total number of positives is less than 5% when many statistical tests are performed. The null hypothesis was rejected relatively frequently in this study (for example 13 out of 25 times in the linear surrogate analysis section), and the total number of tests is not a good estimator of the number of true null hypotheses. The total number of tests is the estimator used in the original Benjamini and Hochberg procedure \cite{65}. Instead, we rely on a better estimator of the number of true null hypothesis \cite{66}, and use an FDR control procedure based on it (adaptive linear step-up procedure, reviewed in \cite{67}).

**GWR surrogates**

The GWR method is based on a maximal overlap discrete wavelet transform (MODWT) implementation of the IAAFT algorithm first described in \cite{68} and later refined in \cite{69}. The algorithm details are available in \cite{30}, but the basic ingredients are fixing a proportion of the MODWT wavelet coefficients, and applying the IAAFT algorithm to each scale and to the dataset as a whole. Surrogates can be computed along a continuum parametrised by \( \rho \), where \( \rho = 0 \) corresponds to IAAFT surrogates, and \( \rho = 1 \).
corresponds to the data. The fixed coefficients are related to \( \rho \) as follows. The energy of a signal of length \( N = 2^J \) is proportional to

\[
\Xi = \sum_{j=1}^{J} \sum_{i=1}^{N} W_{j,i}^2
\]

where \( W_{j,i} \) is the wavelet coefficients at scale \( j \) and temporal position \( i \). Let us define an energy threshold \( \Xi_0 = \rho \Xi \). Going from the largest to the smallest, squared wavelet coefficients are summed irrespective of scale and position until \( \Xi_0 \) is reached. Coefficients that contributed to the sum are fixed for this level of \( \rho \). An example of surrogates for a range of \( \rho \) values is given in Fig 11.

![Fig 11. Filtered LFP for patient 6L OFF (black), and corresponding GWR surrogates for a range of \( \rho \) levels (blue). Most of the data temporal variability is already accounted for at \( \rho = 0.1 \). The plots share the same time axes.](image)

**Fitting procedures**

We describe in this subsection the fitting procedure used to fit all the models of this study to data. Slight differences between models will be highlighted when applicable. The general fitting procedure is similar to what was used in \[70\]. For each fit, random sets of model parameters are generated from uniform distributions with appropriate bounds. For envelope models, all parameters are accepted. For WC models, parameters impacting the PSD and the average burst duration profile are coupled, and to improve optimisation efficiency, parameters are accepted when the PSD peak of the corresponding model is within 1 Hz and 30% in magnitude of the data PSD peak. The
first 5000 sets of parameters are optimised in parallel on a supercomputer with the generalized pattern search algorithm [71,72]. We use Matlab’s implementation of the algorithm with the “positive basis 2N” poll method. Parameters are put on a similar scale to improve search robustness. A mesh size of $10^{-5}$, and a function call budget of 600 calls are used.

At each optimisation step, the optimiser returns the cost

$$c = \frac{1}{N_f} \sum_{n=1}^{N_f} \left( \frac{\sum_{i=1}^{N_n} (y_{n,i}^{\text{data}} - y_{n,i}^{\text{model}})^2}{\sum_{i=1}^{N_n} (y_{n,i}^{\text{data}} - y_{n}^{\text{mean}})^2} \right),$$

(16)

where $N_f$ is the number of features, $y_n$ the features considered, $N_n$ the length of $y_n$, and $y_n^{\text{mean}}$ the mean of the data feature $n$. For envelope models, the PSD is not considered in the optimisation, while for other models both the PSD and the average burst duration profiles are considered. At the end of the procedure, the fit with the highest $R^2 = 1 - c$ is deemed the best fit. Model simulations are performed with an Euler–Maruyama scheme, except for the OU model which is simulated according to the exact updating equation [73]

$$x(t + \delta t) = x(t) e^{-\theta \delta t} + n \sqrt{\frac{\zeta^2}{2 \theta}} (1 - e^{-2\theta \delta t})$$

(17)

where $n$ are independent samples of the standard normal distribution. The time step used in all cases was $10^{-3}$ s, roughly equivalent to the data sampling rate. At each optimisation step, the features (average burst duration for all models, plus PSD for WC models) are computed on five repeats of 1000 s and are averaged over the five repeats. The average burst duration profiles are computed from the model envelope (model output for envelope models, modulus of the analytic signal of the model output for WC models), based on the same thresholds and minimum burst duration as for data analysis (see “Extracting bursting features”).

**Average burst duration in an envelope model**

**Continuous model MFPT**

To derive the average burst duration of the time discretization of the stochastic process described by equation (9), we start by drawing on classic results for the continuous time stochastic process itself. We consider the MFPT problem on $[L, +\infty)$ with a single boundary at $x = L$, and a reflective boundary at $x = +\infty$. The backward Fokker-Planck operator corresponding to the continuous time stochastic process reads

$$\mathcal{L}^*_x \tau_{x_0,L} = -1,$$

(19)

where $\mathcal{L}^*_x$ is the backward Fokker-Planck operator acting on the starting point $x_0$. Equation (19) is a first order differential equation in $T(x_0) = \frac{\partial \tau_{x_0,L}}{\partial x_0}$

$$\frac{\partial T}{\partial x_0} + \frac{2\mu(x_0)}{\zeta^2} T = -2 \frac{2\zeta^2}{\zeta^2},$$

(20)
whose solution reads
\[
T(x_0) = \left( A - \frac{2}{\zeta^2} \int_{+\infty}^{x_0} e^{\frac{2}{\zeta^2} \int_0^1 \mu(x) dx} dt \right) e^{-\frac{2}{\zeta^2} \int_0^{x_0} \mu(x) dx},
\]
where \( A \) is an integration constant, which is zero in the continuous case (reflective boundary at \(+\infty\)). We can therefore write \( T \) as
\[
T(x_0) = \frac{2}{\zeta^2} \int_{x_0}^{+\infty} e^{\frac{2}{\zeta^2} \int_0^1 \mu(x) dx} dt L, (22)
\]
Integrating \( T(x_0) \), we obtain the MFPT as
\[
\tau_{x_0,L} = \int_L^{x_0} T(x) dx,
\]
where we have used the absorbing boundary condition at \( L (\tau_{L,L} = 0) \). This leads to the expression for the MFPT in the continuous model presented in the Results section [equation \([10]\)]. Finally, for \( x_0 = L + \delta \) and \( \delta \ll L \), the mean first passage time close to the boundary \( \tau_{L+\delta,L} \) can be approximated by
\[
\tau_{L+\delta,L} \approx \delta T(L).
\]

**Discretized model**

We now consider a time discretization of the stochastic process described by equation \([9]\) with time step \( dt \), and derive an expression for the average burst duration of the discretized model in three steps. We correct for the systematic bias of the continuous model MFPT and MFPT derivative in steps 1 and 2, respectively. In step 3, we relate average burst duration and MFPT. We remind the reader we use a tilde to distinguish quantities that can be measured readily in a discretized system from the continuous system quantities introduced earlier. For clarity of exposition, we also denote with a hat and double hat intermediate quantities that will be introduced as the derivation progresses. The three steps will make use of the transition probability for \( \tau_{L,L} \).

\[
p(x,t' + dt|x',t') \approx \frac{1}{\sqrt{2\pi dt\zeta}} \exp \left\{ -\frac{(x-x')^2}{2dt\zeta^2} \right\}, \tag{25}
\]

**Step 1: MFPT bias** When close to the boundary \( x = L \), the continuous model is more likely to cross the boundary earlier, which makes for a systematic under-estimation of the discrete MFPT by the continuous model. The first correction to the continuous MFPT \( \tau_{x_0,L} \) is therefore to add a constant correction \( \hat{\tau}_{L,L} \) to it, which describes the average additional time taken by the discrete model once close to the boundary:
\[
\hat{\tau}_{x_0,L} = \tau_{x_0,L} + \hat{\tau}_{L,L}. \tag{26}
\]

Another way of looking at it is that in the continuous model, all trajectories starting from the threshold will cross the boundary in vanishingly short times, which is reflected by the boundary condition \( \tau_{L,L} = 0 \). This is not the case for the discrete model, as some trajectories starting at \( L \) will end up above \( L \) a time step later. In fact, by considering trajectories starting at \( L \) and the transition probability for one time step \( dt \), \( \hat{\tau}_{L,L} \) can be estimated as
\[
\hat{\tau}_{L,L} = \int_{-\infty}^0 dt \frac{1}{2} \delta^0(x) dx + \int_0^{+\infty} (\hat{\tau}_{L+x,L} + dt) \delta^0(x) dx, \tag{27}
\]

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where $p^x(z) = p(L + x + z, t' + dt| L + x, t')$, and the burst duration of a trajectory starting at $L$ but ending below $L$ a time step later has been approximated by $\frac{d\tau}{dt}$. Using equation (20), we find

$$\tilde{\tau}_{L,L} = (1 - \alpha)\frac{dt}{2} + \int_0^{+\infty} \tau_{L+z,L} p^0(z) dz + \alpha \tilde{\tau}_{L,L} + \alpha dt,$$

(28)

with $\alpha = \int_0^{+\infty} p^0(z) dz$. Therefore

$$\tilde{\tau}_{L,L} = \frac{1 + \alpha dt}{1 - \alpha} + \frac{1}{1 - \alpha} \int_0^{+\infty} \tau_{L+z,L} p^0(z) dz.$$

(29)

As $p^0$ decays quickly away from $L$ for small $dt$, we use equation (24), and obtain to first order in $\sqrt{dt}$

$$\tilde{\tau}_{L,L} = \frac{T(L)}{1 - \alpha} \int_0^{+\infty} z p^0(z) dz.$$

(30)

To first order in $\sqrt{dt}$, $p^0(z) = p(L + z, t' + dt| L, L')$ is even (see equation (25)) and $1 - \alpha = \alpha$. Therefore,

$$\tilde{\tau}_{L,L} = T(L) \frac{\int_0^{+\infty} z p^0(z) dz}{\int_0^{+\infty} p^0(z) dz} = \tilde{\Gamma} T(L),$$

(31)

where $\tilde{\Gamma}$ is the average step above $L$ starting from $L$. To first order in $\sqrt{dt}$, $\Gamma$ does not depend on $\mu$ and $L$ and is given by

$$\tilde{\Gamma} \approx \sqrt{\frac{2dt}{\pi \zeta}}.$$

(32)

**Step 2: MFPT derivative** As the discrete model is less likely to cross the boundary when close to it, the derivative of the MFPT at the boundary will also be affected. We model this effect with a correction to the continuous model through a non-zero $A$ [integration constant in equation (21)]. We define

$$A_0 = A \left( \frac{2}{\zeta^2} \int_{L}^{+\infty} e^{\frac{x^2}{\zeta^2}} f^{(1)}(p(x)dx) \right)^{-1},$$

(33)

in such a way that the corrected MFPT derivative at the boundary $\tilde{T}(L)$ equals $(A_0 + 1)T(L)$. To show that $A_0$ should not be zero in the discrete time case and provide an approximation of its value, we are going to approximate $\tilde{T}(L)$ by

$$\frac{\partial \tilde{\tau}_{L+\delta,L}}{\partial \delta} \bigg|_{\delta=0},$$

where $\tilde{\tau}_{L+\delta,L}$ is defined next and will explicitly take into account the distribution of the first time step from $L + \delta$, similarly to what was done in the previous paragraph. We are assuming here that most of the difference in the derivative with the continuous case comes from the first time step, and that the MFPT will subsequently evolve according to equation (26). Starting from $L + \delta$ and considering explicitly the first time step and its associated transition probability, we can write

$$\tilde{\tau}_{L+\delta,L} = \int_{-\infty}^{-\delta} \frac{dt}{2} p^\delta(z) dz + \int_{-\delta}^{+\infty} (\tilde{\tau}_{L+\delta+z,L} + dt)p^\delta(z) dz.$$

(34)
With the change of variable \( x = \delta + z \), we obtain to first order in \( \sqrt{dt} \)
\[
\hat{\tau}_{L+\delta,L} = \int_0^{+\infty} \hat{\tau}_{L+x,L} p^\delta(x-\delta)dx.
\]  

(35)

Making use of \( \hat{\tau}_{L+x,L} = xT(L) + \hat{\Gamma}T(L) \) [see equations \([24], [26], \) and \([31]\)], we express
\[
\hat{\tau}_{L+\delta,L} = \int_0^{+\infty} (x + \hat{\Gamma})p^\delta(x-\delta)dx.
\]  

(36)

From there, we obtain to zeroth order in \( \sqrt{dt} \) \((A_0 + 1\) will multiply a \( \sqrt{dt} \) factor in the final expression) \n\[
\left. \frac{\partial \hat{\tau}_{L+\delta,L}}{\partial \delta} \right|_{\delta=0} = \left( \frac{1}{2} + \frac{1}{\pi} \right)T(L),
\]  

(37)

which yields \( A_0 = \frac{1}{2} - \frac{1}{\pi} \approx -0.18 \). This provides a rationale for a non-zero \( A_0 \) in the discretization and a good approximation of the optimal value of \( A_0 \), which was found empirically to be \( A_0 = \frac{\pi}{\pi+1} \approx -0.12 \) (the discrepancy may come from considering only the contribution from the first time step). We use this latter value in what follows, and obtain for the MFPT in the discretized model
\[
\tilde{\tau}_{L+x,L} \approx x\tilde{T}(L) + \hat{\Gamma}\tilde{T}(L) = \frac{2\pi}{\pi+4}(x+\hat{\Gamma})T(L),
\]  

(38)

for \( x \ll L \), with \( T(L) \) given by equation \([22]\).

**Step 3: overshoot distribution** We have just obtained an approximation for the MFPT in the discretized model \([equation \([38]\)]\), and the last step is to derive from this result the average burst duration for the discretized model as a function of the threshold \( L \). In the discretization, unless simulations are started exactly at \( L \) before every single burst is analysed (which is not compatible with modelling data), the distribution of boundary overshoots from below has to be taken into account (see Fig. 7 in the Results section). Averaging equation \([38]\) over the overshoot distribution of density \( \chi \) gives the average burst duration \( \tilde{\tau}_L \) that can be measured from one long time series of the discretized model as
\[
\tilde{\tau}_L = \int_L^{+\infty} \tilde{\tau}_{x_0,L}(x_0)dx_0.
\]  

(39)

Contrary to \( \tilde{\tau}_{L,L} \), the notation \( \tilde{\tau}_L \) does not imply an exact start of trajectories from \( L \) before each burst. We also note that the contribution of boundary overshoots from above when getting back to \( L \) at the end of the burst is negligible compared to stopping exactly at the threshold as it cannot change \( \tilde{\tau}_L \) by more than a time step. This is not the case at the beginning of a burst as the further away from the threshold, the less likely a premature end of the burst is, which has a drastic influence on burst duration. As \( \chi_L \) decays quickly away from \( L \) for small \( dt \) (the average overshoot scales with \( \sqrt{dt} \) as we will see in equation \([43]\), equation \([39]\) can be approximated by
\[
\tilde{\tau}_L \approx \tilde{T}(L) \int_0^{+\infty} \delta\chi_L(L + \delta)d\delta + \tilde{\tau}_{L,L} = (\tilde{\Delta}_L + \tilde{\Gamma})\tilde{T}(L),
\]  

(40)

where \( \tilde{\Delta}_L \) is the average overshoot at threshold \( L \). An approximation for the average overshoot can be obtained by considering the probability of the state \( x \) given that \( dt \) before, the state was anywhere below \( L \), which is given by
\[
p_L(x,dt) = \int_{-\infty}^{L} p(x,t' + dt|x',t')p_\infty(x')dx',
\]  

(41)
where \( p_\infty(x) \) is the stationary probability density of the process normalised by its integral over \((-\infty, L]\) and \( p \) is the transition probability to first order in \( \sqrt{dt} \) introduced earlier [equation (25)]. The overshoot density is

\[
\chi_L(x_0) = \frac{p_L(x_0, dt)}{\int_{-\infty}^{+\infty} p_L(x, dt) dx}.
\]  

(42)

For small \( dt \) the stationary probability density contribution reduces to a constant that cancels out in the overshoot density. The average overshoot is obtained to first order in \( \sqrt{dt} \) as

\[
\bar{\Delta}_L \approx \frac{1}{2} \sqrt{\frac{\pi dt}{2}} \zeta,
\]  

(43)

which does not depend on the drift function \( \mu \) (to first order in \( \sqrt{dt} \)) and as a result does not depend on \( L \) either. We will therefore drop the subscript \( L \) and simply denote the average burst duration by \( \bar{\Delta} \).

This leads to a direct relationship between \( \bar{\tau}_L \) and \( T(L) \),

\[
\bar{\tau}_L \approx (\bar{\Delta} + \bar{\Gamma}) T(L) \approx \sqrt{\frac{\pi dt}{2}} \zeta T(L),
\]  

(44)

and the full expression presented in the Results section for the average burst duration of a discretized envelope model to first order in \( \sqrt{dt} \) is

\[
\bar{\tau}_L \approx \sqrt{\frac{2\pi dt}{\zeta}} \int_{\lambda}^{+\infty} e^{\frac{-x^2}{2\zeta^2}} \mu(x) dx.
\]  

Application to two envelope models

OU We are considering here the discretization of an OU process centered on zero [equation (6)]. To highlight the dependence of average burst duration on parameters, we are going to express equation (12) (in the Results section, direct application of the previous result) with \( L \) as a percentile of the time series values. The stationary probability density for our centered OU process is

\[
p_\infty(x) = \sqrt{\frac{\theta}{\pi \zeta^2}} e^{-\frac{\theta x^2}{\zeta^2}},
\]  

(45)

and the associated cumulative distribution function (CDF) \( \Phi \) reads

\[
\Phi(x) = \frac{1}{2} \left\{ 1 + \text{erf} \left( \frac{\sqrt{\theta} x}{\zeta} \right) \right\},
\]  

(46)

where \( \text{erf} \) is the error function. Let us denote by \( L\% \) the percentile rank (between 0 and 1) corresponding to the threshold \( L \). By definition, \( \Phi(L) = L\% \), and therefore

\[
\frac{\sqrt{\theta} L}{\zeta} = \text{erf}^{-1} \left( 2L\% - 1 \right).
\]  

(47)

This leads to an expression for the average burst duration of a discrete OU process as a function of threshold percentile rank:

\[
\bar{\tau}_L \approx \pi \sqrt{\frac{2dt}{\theta}} \left( 1 - L\% \right) \left( \text{erf}^{-1}(2L\%-1) \right)^2.
\]
Degree three polynomial  We are considering here the discretization of a degree three polynomial envelope model [equation (8)]. The direct application of the general expression for \( \tilde{\tau}_L \) obtained previously provides an approximation for the average burst duration of this model to first order in \( \sqrt{dt} \), which reads

\[
\tilde{\tau}_L \approx \frac{\sqrt{2\pi dt}}{\zeta} \int_{L}^{+\infty} e^{-\frac{1}{2} \zeta^2 (\Lambda(x) - \Lambda(L))} dx,
\]

(48)

with

\[
\Lambda(x) = \frac{d_3}{4} x^4 + \frac{d_2}{3} x^3 + \frac{d_1}{2} x^2 + d_0 x
\]

The average burst duration expression for the degree three polynomial model is not as simple as in the OU case, but it can easily be evaluated numerically.

Passage method

From average burst duration profile to envelope dynamics  We are concerned here with the time discretization of the continuous-time stochastic process described by equation (9), where we are assuming the real valued drift function \( \mu \) can depend on \( x_t \), and the diffusion term \( \zeta \) is constant in time and space. Provided that the derivative of the first passage time \( T(x_0) \) is never zero, the differential equation satisfied by \( T \) [equation (20)] can be re-arranged into

\[
\mu(x_0) = -\frac{1 + \frac{1}{2} \zeta^2 \frac{\partial T}{\partial x_0}}{T(x_0)}.
\]

(49)

We have shown previously that in the discretized system considered, there is a simple relationship to first order in \( \sqrt{dt} \) between the average burst duration \( \tilde{\tau}_L \) at threshold \( L \) and \( T(L) \) [equation (44)]. Thus, to first order in \( \sqrt{dt} \),

\[
\mu(L) \approx -\zeta \sqrt{\frac{\pi dt}{2}} + \frac{\zeta \frac{\partial \tilde{\tau}_L}{\partial L}}{\tilde{\tau}_L},
\]

which we discuss in the Results section.

Preparation of synthetic data  Simulation of the synthetic data used to test envelope dynamics recovery was performed with the same methods as in “Fitting procedures”. Synthetic data were generated by the OU model introduced before, and by a degree five polynomial model given by

\[
dx = \gamma x \prod_{i=1}^{4} (x - x_i) + \zeta dW,
\]

(50)

where \( \gamma \) is a coefficient, the \( x_i \) are roots, and \( \zeta \) a constant noise parameter (parameters values given in supplementary Table E in [22]). OU synthetic data were shifted as before, while for the degree five model, only the absolute value of the next point was retained at each integration step. For patient data the envelope was obtained as the modulus of the analytic signal of the filtered data as in “Extracting bursting features”.
Envelope dynamics recovery  Three hundred thresholds equally spaced from one
fiftieth to 90% of the maximum envelope value are considered (extreme thresholds
will not yield reliable measures). At each threshold, the average burst duration \( \bar{\tau}_L \) is
obtained, and the resulting curve is smoothed across thresholds (LOWESS method,
which stands for locally weighted scatterplot smoothing, smoothing span of threshold
range divided by eight). The derivative of \( \bar{\tau}_L \) is then estimated numerically and
smoothed (LOWESS, smoothing span of threshold range divided by five). In the case of
patient data, the first 10% to 20% of both \( \bar{\tau}_L \) and its derivative are not smoothed as the
fast decay of \( \bar{\tau}_L \) at the left edge of the profile is not handled properly by the smoothing
function. Finally, the drift function \( \mu \) is reconstructed based on equation (14). The
noise parameter \( \zeta \) is simply taken as the known value used to generate the envelope for
synthetic data, and is estimated for data (24% and 27% of the time series deviation, for
OFF medication and ON medication, respectively). These values were obtained for
patient data by adjusting the noise parameter so the burst duration profile and the
envelope inverse CDF of the inferred dynamics best match the data. The time step \( dt \) is
taken as the time step used for forward simulation for synthetic data, and as the time
scale of variation of the envelope for data (roughly a beta cycle, 0.05 seconds). The
mean of the drift function is learnt by considering all the data available, while sem error
bars are obtained by dividing all the data available in four segments and repeating the
learning process on each segment (noise parameter fixed to the value used for the mean).

Simulation of inferred envelope dynamics  The inferred dynamics are known at
300 equally spaced points between \( x_{\text{min}} \) and \( x_{\text{max}} \), so we define

\[
\mu(x(i)) = \begin{cases} 
\mu(x_{\text{min}}) & x(i) < x_{\text{min}}, \\
\mu(x_{\text{max}}) & x(i) > x_{\text{max}}, \\
\mu_{\text{interp}} & \text{otherwise},
\end{cases} 
\tag{51}
\]

where \( \mu_{\text{interp}} \) is the linear interpolation of \( \mu \) between the closest \( x \) points framing \( x(i) \)
at which \( \mu \) is known. Forward simulations of the inferred envelope dynamics are then
performed according to equation 9 with a Euler–Maruyama scheme (the time step is
taken as \( dt \)). Additionally, at each integration step, only the absolute value of the next
point \( x(i+1) \) is retained to prevent the envelope from becoming negative. Five repeats
of ten times the data duration are simulated. The resulting envelopes are used to
compute the mean and sem error bars of the average burst duration profile and the
inverse CDF of the inferred envelope dynamics.

Supporting information

S1 Supplementary Figures. Supplementary Figures pertaining to data analysis
are presented here.

S2 Supplementary Tables. Supplementary Tables pertaining to fits, and testing of
the passage method are presented here.

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References


