

1 **Cortical neuronal activity determines the dynamics of local sleep homeostasis**

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11

Abstract

12 The homeostatic regulation of sleep manifests as a relative constancy of its total daily amount, and the
13 compensation of sleep loss by an increase in its subsequent duration and intensity. Theoretical
14 descriptions of this phenomenon define “Process S”, a variable with dynamics dependent only on sleep-
15 wake history and whose levels are reflected in EEG slow wave activity. While numerous hypotheses
16 have been advanced regarding the substrate and role of Process S, such as synaptic or energy
17 homeostasis, it remains unclear whether these dynamics are fundamentally driven by a need to
18 homeostatically regulate specific variables, or by an unknown innate process which enforces that a
19 certain daily sleep quota is obtained. Sleep is typically defined based on brain-derived criteria, such as
20 behaviour or EEG power spectra, and variation in brain activity during wakefulness has been linked to
21 variation in Process S accumulation. We therefore hypothesised that Process S dynamics might be
22 related to the quantity and characteristics of spiking activity in cortical neurones. Specifically, we
23 assumed that Process S changes as a function of the deviation of neuronal firing rate from a locally
24 defined set point. To relate these dynamics explicitly to patterns of spiking activity, we incorporated the
25 occurrence of network spiking off periods as both the defining measure of Process S and as the
26 determinant of its rate of decay. This approach was able to describe the time course of Process S,
27 crucially without explicit knowledge of the animal’s global sleep-wake state. This work provides a
28 conceptual advance in our understanding of the substrate of sleep homeostasis and provides important
29 links between local and global aspects of sleep regulation.

30

Introduction

31 According to traditional theory, the need for sleep accumulates during wakefulness and dissipates
32 during sleep. Despite decades of research, it is still uncertain precisely which biological variables form
33 the substrate of sleep need, what characteristics of wake challenge their stability and how sleep
34 mediates the restoration of homeostasis. More fundamentally, it remains unclear whether homeostatic
35 sleep regulation reflects an active process, dynamically shaping daily sleep architecture in response to
36 a physiological need for the homeostatic regulation of specific variables, or whether it corresponds
37 instead to an unknown innate process which ensures only that a certain daily quota of sleep is obtained.

38 The earliest theories of sleep homeostasis supposed the existence of a single variable, termed Process
39 S, which describes sleep drive at the global level (Borbély, 1982). This variable is assumed to always
40 increase during wakefulness, independently of its content, and to decline during sleep. It is widely
41 acknowledged that homeostatic sleep pressure is reflected in the levels of slow wave activity (SWA, 0.5-
42 4 Hz spectral power) observable during NREM sleep in neurophysiological field potentials, such as
43 electroencephalogram (EEG) or local field potential (LFP).

44 Current views on the origin of sleep homeostasis emphasise its local and activity-dependent component
45 (Krueger & Tononi, 2011; Rattenborg et al., 2012; Tononi & Cirelli, 2014). It was shown that SWA is far
46 from uniform across the brain, and that the behavioural and cognitive content of waking, beyond merely
47 its duration, influences subsequent SWA magnitude (Huber et al., 2004; Vyazovskiy & Tobler, 2008;
48 Rector et al., 2009; Murphy et al. 2011; Fisher et al., 2016). Indeed, many candidate mechanisms for the
49 substrate of sleep homeostasis implicate processes occurring at a cellular and network level. These
50 include the maintenance of cellular homeostasis (Reimund 1994; Mackiewicz et al., 2007; Vyazovskiy &
51 Harris, 2013; Bellesi et al., 2016), the replenishment of energy stores (Scharf et al., 2008), the influence
52 of sleep-related signalling molecules such as adenosine or cytokines (Krueger et al., 2008), and the
53 regulation of imbalanced synaptic strength (Tononi & Cirelli 2003; Vyazovskiy et al., 2008; Liu et al.,
54 2010). Although the equivalence of these processes with Process S has not been conclusively
55 demonstrated (Frank & Heller, 2019), the existing evidence supports the relevance of sleep-wake
56 dependent differences in neuronal activity for understanding the regulation of sleep.

57 Cortical neuronal activity is generally higher during waking compared to sleep (Vyazovskiy et al., 2009;
58 Hengen et al., 2016; McKillop et al., 2018). Lower spike firing typical of sleep is due, at least in part, to
59 regular periods of widespread synchronous network silence, termed off periods, intruding on ongoing
60 activity (Steriade et al., 1993a; Steriade et al., 2001; Sanchez-Vives & Mattia, 2014). Importantly, off
61 periods in neural populations are thought to underpin slow wave dynamics at the level of the field
62 potential (Steriade et al., 1993b; Massimini et al., 2004; Buzsáki et al., 2012) and their properties reflect
63 homeostatic sleep need (Vyazovskiy et al., 2009; McKillop et al., 2018; Saberi-Moghadam et al., 2018).

64 Neuronal firing rates typically fluctuate around a homeostatic set point, which is characteristic for
65 individual cells and variable across the population (Turrigiano, 2011; Hengen et al., 2013; O’Leary et al.,
66 2014; Styr et al., 2019). The homeostatic regulation of firing rates may depend on processes occurring
67 specifically in sleep and wakefulness (Grosmark et al., 2012; Hengen et al., 2016) and evidence suggests
68 that firing rates change as a function of time spent awake, conditional on wake’s behavioural quality
69 (Vyazovskiy et al., 2009; Fisher et al., 2016). Additionally, the magnitude and direction of state-
70 dependent changes in firing rate differs between neurons, depending on brain region and their
71 individual firing rate set point (Miyawaki & Diba 2016; Watson et al., 2016; Miyawaki et al., 2019). Firing
72 rate homeostasis may occur above the individual cell level (Slomowitz et al., 2015), as network level
73 mechanisms dependent on the NREM sleep slow oscillation constrain the distribution of population
74 firing rates within an optimal functional range (Levenstein et al., 2017).

75 Overall, evidence suggests that the homeostatic regulation of sleep and of neuronal firing rates may be
76 intrinsically related, however, this functional link remains incompletely defined. Mathematical
77 modelling approaches present an opportunity to begin addressing this problem. To this end, we develop
78 quantitative models of Process S, describing its temporal dynamics on a local level in terms of spiking
79 activity and off periods, instead of global sleep-wake history. We find that the magnitude of the deviation
80 of multi-unit firing rate from a locally specified set point carries sufficient information to account for
81 empirically derived patterns of SWA. We then introduce the total time spent in off periods as an
82 alternative measure for Process S with more local origins than SWA, and account for the time course of
83 this variable in terms of two opponent processes dependent on spiking rate and off period occurrence.

84

Materials & Methods

85 **Animals, surgery & husbandry**

86 Chronic electrophysiological recordings from six male young adult (4.8 – 5.7 months old, mean 5.2
87 months) C57BL/6J mice were analysed here. This data set is a subset of that used in a previous study
88 (McKillop et al., 2018). The animals were surgically implanted with electrodes for the continuous
89 recording of electroencephalography, electromyography and cortical neuronal activity. EEG screw
90 electrodes (Fine Science Tools) were inserted into the skull unilaterally above the frontal cortex
91 (primary motor area: anteroposterior 2mm, mediolateral 2mm) and bilaterally above the occipital
92 (primary visual area: anteroposterior 3.5mm, mediolateral 2.5mm) cortex. One occipital screw
93 (contralateral to the frontal screw) served as the ground electrode and an additional screw located
94 above the cerebellum served as the reference. A pair of stainless steel wires were inserted into nuchal
95 muscle for the recording of electromyogram (EMG). A polyimide-insulated tungsten microwire array
96 (Tucker-Davis Technologies) was implanted through a craniotomy window into the frontal cortex
97 (primary motor area: anteroposterior 2mm, mediolateral -2mm), contralateral to the EEG screw. The
98 array comprised 16 wire channels of 33µm diameter, arranged in 2 rows of 8, with columnar separation
99 of 250µm, row separation of 375µm and tip angle of 45 degrees. One row of wires was 250µm longer
100 than the other to account for cortical curvature. A silicone gel (KwikSil, World Precision Instruments)
101 was used to seal the craniotomy, and dental acrylic cement used to stabilise all the implanted electrodes.
102 Surgeries were performed under isoflurane anaesthesia (4% induction, 1-2% maintenance). Analgesics
103 were given immediately before surgery (1-2 mg/kg metacam and 0.08 mg/kg vetergesic, subcutaneous
104 injection) and for at least 3 days during recovery following surgery (1-2 mg/kg metacam, oral). In
105 addition, immunosuppressant (0.2 mg/kg dexamethasone) was given the day before surgery (oral),
106 immediately before surgery (subcutaneous injection) and during recovery for at least 2 days (oral).
107 Animal wellbeing was closely monitored during recovery until a stable return to baseline was observed
108 for at least 2 days. All procedures were performed under a UK Home Office Project License and
109 conformed to the Animal (Scientific Procedures) Act 1986.

110 Mice were housed individually following surgery. Two weeks after surgery, mice were transferred, still
111 individually, to custom made Plexiglas cages (20.3x32x35 cm), containing a running wheel (Campden
112 Instruments), which were placed within ventilated sound-attenuated Faraday chambers (Campden
113 Instruments). The animals were exposed to a standard 12hr-12hr light dark cycle, with food and water
114 available *ad libitum*. Mice were allowed to habituate to the recording chamber and to attachment of the
115 recording cables for a minimum of three days before recordings began.

116 **Experimental design**

117 All the data analysed here were collected over two days of experimental recording. The first day served
118 as a baseline, while the animals were completely undisturbed. A sleep deprivation protocol was
119 enforced at light onset on the second day, immediately after the baseline day, and lasted 6 hours. Sleep
120 deprivation was performed using novel object presentation. During this period, experimenters
121 constantly monitored both the behaviour and ongoing neurophysiological recordings of the mice. As
122 soon as any animal showed signs of sleepiness (such as stillness with eyes closed, or slow waves in the
123 EEG), novel objects were introduced to the cage (such as cardboard, colourful plastic and tissue paper)
124 in order to encourage wakefulness. During the 6-hr sleep deprivation period, these mice slept 6.0 ± 3.1
125 minutes (mean \pm sd) only.

126 **Data collection & pre-processing**

127 Data acquisition was performed using a Multichannel Neurophysiology Recording System (Tucker Davis
128 Technologies). EEG, EMG and microwire array LFP signals were filtered (0.1-100 Hz), amplified (PZ5
129 NeuroDigitizer preamplifier, TDT) and stored locally (256.9 Hz sampling rate). Custom written Matlab
130 scripts were used for signal conversion and data pre-processing. The LFP, EMG and EEG signals were
131 filtered again offline between 0.5 - 100 Hz (4th order Type II Chebyshev filter) and resampled at 256 Hz.
132 Extracellular multi-unit spiking was additionally obtained from each microwire array channel, recorded
133 at 25 kHz and filtered 300 Hz – 5 kHz. An amplitude threshold (at least 2 standard deviations, minimum
134 $-25\mu\text{V}$) was used to identify putative spikes. Individual spikes were saved as a voltage waveform
135 comprising 46 data samples (0.48ms before to 1.36ms after threshold crossing) plus a time stamp of

136 occurrence. Spiking activity from each channel was cleaned offline for artefacts using the Matlab spike
137 sorting software Wave_clus (Quiroga et al., 2004). All putative single unit clusters identified by the
138 algorithm from the same channel were merged, excluding only noise spikes. MUA firing rate for each
139 channel was calculated in 4-second epochs as the mean number of spikes per second.

140 Vigilance states were scored manually by visual inspection with a 4-second epoch resolution (using the
141 software SleepSign, Kissei Comtec). Vigilance states were classified as waking (low amplitude but high
142 frequency EEG with high or phasic EMG activity), NREM sleep (presence of EEG slow waves, a signal of
143 a high amplitude and low frequency, and a low level of EMG activity) or REM sleep (low amplitude, high
144 frequency EEG, and low EMG). For this analysis, over the six mice, a total of 78 out of 96 channels could
145 be analysed (minimum of 10 out of 16 from one mouse). The excluded channels were characterised by
146 an unstable MUA firing rate, including a large drift in firing which was persistent and sleep-wake state
147 independent. For the off occupancy models described below, 75 out of 96 channels were used; a further
148 3 channels had to be excluded because multi-unit firing rates, while stable, were too low to yield a
149 reasonable estimate of the occurrence of off periods.

150 **Slow wave activity**

151 Each EEG and LFP signal was processed to extract a measure of the SWA. Signal segments were extracted
152 within windows of 4-second duration and 1-second spacing (giving 3-second overlap), and Hann
153 tapered. A Fourier Transform was applied to each signal segment and the mean power in the slow wave
154 range (frequencies from 0.5 to 4 Hz) was calculated. This measure was smoothed by finding the median
155 over five temporally adjacent overlapping segments, yielding a SWA measurement for each sequential
156 4 second epoch. For normalisation within each channel, SWA values were then expressed as a
157 percentage of the mean SWA calculated over all artefact-free epochs scored as NREM sleep in the
158 baseline 24 hours. The median value of the SWA during each continuous NREM sleep episode served as
159 an estimate of Process S. NREM sleep episodes shorter than 1 minute (15 epochs) were excluded, as in
160 a previous study modelling Process S in mice (Guillaumin et al., 2018). Brief awakenings (short arousals
161 accompanied by movement, lasting ≤ 20 seconds) were excluded from analysis but were not considered
162 to be the ending of a NREM sleep episode.

163 **Off periods detection and definition of “off occupancy”**

164 One aim of this study was to develop measures of Process S independent of the EEG, and so we focused
165 on off periods which are the neuronal counterpart of slow waves. Off periods refer to brief interruptions
166 of spiking activity which occur synchronously across many recording sites, last approximately 70-
167 100ms (Vyazovskiy et al., 2009), and are coincident with the positive deflection of LFP slow waves
168 (McKillop et al., 2018). In these studies, off periods were detected by pooling spikes over all channels
169 and identifying inter-spike intervals (ISIs) that exceed some long duration threshold. However, pooling
170 spikes removes the ability to compare local differences, and if an off period does not involve all channels
171 it will go undetected. To overcome this limitation, off periods were defined separately for each channel
172 by looking at the co-occurrence of local slow waves and spiking silence.

173 There is no universally accepted method for slow wave detection, and a recent comparison suggests that
174 a simple amplitude threshold based approach, while in theory adequate, may underperform due to
175 channel differences in overall LFP amplitude and large amplitude fluctuations of higher frequencies
176 (Bukhtiyarova et al., 2019). For this reason, the LFP was first filtered from 0.5 to 6 Hz (4th order
177 Butterworth filter), and a threshold defined individually for each channel, using the median plus one
178 median absolute deviation of the peak amplitude of all positive half waves (including all vigilances
179 states, but excluding epochs with artefacts). All positive half waves with peak amplitude above threshold
180 were then considered to be slow waves.

181 Next, for each LFP slow wave, the multi-unit spike preceding and following the slow wave peak was
182 identified and the corresponding ISI determined. The distribution of these ISIs which coincide with slow
183 waves was often (in 64 out of 75 channels) unambiguously bimodal, allowing the threshold to be
184 selected at the local minimum between these two modes. When there was no evidence of bimodality a
185 value of 120ms was chosen, corresponding to the maximum value selected for the other channels. All
186 inter-spike intervals aligned to slow wave peaks with duration exceeding the threshold were considered
187 off periods. Finally, the metric termed off occupancy was defined, for each 4-second epoch, as the
188 percentage of time spent in a detected off period during that epoch. Just as with SWA (see above), the
189 median value of off occupancy over NREM sleep episodes was used to represent the level of Process S.

190 **Model fitting and parameter optimisation**

191 Three theoretical models were used to describe the time course of Process S (see Results). The model
192 equations were solved using a discrete time approximation, iteratively updating the value of modelled
193 Process S in time steps of 4 seconds (Euler method). The fitting of various models to a particular channel
194 of data is equivalent to finding the optimal choice of parameters to achieve the closest match between
195 simulation and empirical SWA/off occupancy. In all models, the initial value of Process S was included
196 as an additional free parameter. The selection of parameter values for model fitting was achieved using
197 a semi-automated approach. First, an algorithmic methodology was established, which depends
198 primarily on the definition of an error metric to assess fit quality between modelled Process S and
199 empirical data. For each animal, NREM sleep episodes were identified with a duration of at least 1
200 minute. For each NREM sleep episode ($n=1:N$), the median empirical SWA/off occupancy (X_n), and
201 similarly the median modelled value of Process S (S_n), were computed. The error metric (E) is defined
202 as the sum of absolute differences between model and data, weighted by the relative episode duration
203 (w_n). This weight was defined as the absolute duration (d_n) of the NREM sleep episode in seconds,
204 normalised by the total duration of all episodes.

$$205 \quad E = \sum_{n=1:N} w_n \cdot |X_n - S_n|$$

$$206 \quad w_n = d_n / \sum_{i=1:N} d_i$$

207 Algorithmic parameter optimisation was performed separately for each channel, aiming to minimise
208 this error metric. This was achieved using the Matlab function *fminsearch*, which uses the Nelder-Mead
209 simplex algorithm (Lagarias et al., 1998). Many parameter combinations produce very similar dynamics.
210 Therefore, there exist many possible optimal (or near-optimal) parameter regimes and so algorithmic
211 optimisation is sensitive to initial values. For this reason, initial values for the parameters were first set
212 manually, aided with the use of a custom-made Matlab graphical user interface. Manually selected values
213 were then fed into the algorithmic optimisation. Final parameter values were visually inspected to
214 ensure that this optimisation produced an improvement of fit.

215 The final fit quality of a model to the data was expressed as the median percent error (E^*). This is
216 calculated by finding the absolute difference between median empirical (X_n) and simulated (S_n) SWA/off
217 occupancy for each NREM sleep episode, expressed as a percentage of the empirical SWA/off occupancy
218 in that episode. E^* is then defined as the median over all NREM sleep episodes of these difference values.
219 This alternative error metric is used for presentation of results because it has more comprehensible
220 units (percentage of empirical SWA/off occupancy) compared to the error metric, with arbitrary units.

$$221 \quad E^* = \text{median}_{n=1:N} \left[\frac{|X_n - S_n|}{X_n} \cdot 100\% \right]$$

222 **Statistical analyses**

223 The correlation between wake duration, wake firing rates and changes in SWA was calculated separately
224 for each LFP channel. We first identified episodes of NREM sleep of at least 1-minute duration (exactly
225 as for modelling) and obtained the median SWA in each episode. We then identified which intervening
226 time periods, between two NREM episodes, comprised at least 80% wake and lasted at least 5 minutes.
227 We then calculated Pearson correlation coefficients between i) the duration of these wake periods, ii)
228 the mean multi-unit firing rate during these periods, and iii) the change in median SWA from preceding
229 to the following NREM sleep episode.

230 Analysis of variance was performed to explore factors influencing model parameters and fit quality
231 using the Matlab functions *anova1* (one-way) and *anovan* (two-way with unequal group size). For the
232 rate parameters, ANOVA was calculated after applying a log transform. The effect size (η^2) is calculated
233 for a factor as its sum of squares divided by the total sum of squares in the ANOVA and reflects the
234 fraction of the variance accounted for by that factor.

235 To summarise the results in figures, boxplots were included alongside individual data points. These
236 indicate the median, 25th and 75th percentile, with whiskers extending to the most extreme value which
237 falls within 150% of the interquartile range of the box. For these plots, results from individual channels
238 were typically pooled across animals. In some cases, where indicated, channels from the same animal
239 were presented as separate populations.

240

Results

241 We selected a dataset of chronic recordings of frontal electroencephalogram (EEG) alongside local field
242 potential (LFP) and multi-unit activity (MUA) spiking from primary motor cortex from six mice. These
243 recordings were made continuously over 48 hours, starting at light onset, while the mice were freely
244 behaving within their cage and exposed to a standard 12hr-12hr light-dark cycle. At light onset of the
245 second day a sleep deprivation protocol was enforced for 6 hours, involving the presentation of novel
246 objects. Outside of this sleep deprivation period, mice were undisturbed and able to sleep at will.

247 **Process S dynamics can be described as a function of vigilance state history**

248 NREM sleep can be defined and distinguished from waking by the presence of high amplitude slow (0.5
249 - 4Hz) waves in the EEG. The average EEG spectral power in the slow wave range (termed slow wave
250 activity; SWA) in NREM sleep varies as a function of the animal's recent sleep-wake history, and this
251 relationship has been captured in a classical quantitative theory using the concept of "Process S"
252 (Borbély, 1982; Daan et al., 1984). Process S describes a variable whose magnitude can be estimated
253 using the level of SWA during NREM sleep, reflecting the intensity of sleep, and which is interpreted as
254 corresponding to the homeostatic component of sleep drive (Franken et al., 1991a; Achermann et al.,
255 1993; Huber et al., 2000a; Vyazovskiy et al., 2007; Guillaumin et al., 2018). Theoretically, this Process S
256 follows simple dynamics; during wake it increases according to a saturating exponential function
257 towards an upper asymptote, and similarly during NREM sleep it decays exponentially towards a lower
258 asymptote. There are many published variants of the precise equations for this model, but crucially, all
259 these variants use the sleep-wake state history of the animal as the key predictive variable for Process
260 S. Here, the specific equations used are:

$$\text{Wake/REM Sleep: } \frac{dS}{dt} = \alpha(S_{max} - S(t))$$

$$\text{NREM Sleep: } \frac{dS}{dt} = -\beta(S(t) - S_{min})$$

261 Where S represents the level of Process S, S_{max} and S_{min} are upper and lower asymptotes, and α and β
262 are rate parameters. The first equation is applied when the animal is scored to be awake or in REM sleep
263 and the second equation is applied when it is scored to be in NREM sleep. Here, we use the typical

264 approach of applying the wake dynamics equation to REM sleep (Franken et al., 1991a; Huber et al.,
265 2000a; Vyazovskiy et al.; 2007), but for simplicity do not set separate parameters for wake vs. REM
266 sleep. For convenience, S is expressed in units equivalent to those of SWA. This classical formulism is
267 later abbreviated as model CI-SWA. Process S as described by these simple dynamics accounts for the
268 time course of empirical SWA with high accuracy. We applied this model to SWA derived from the frontal
269 EEG of all animals, and as expected obtained a high quality fit (Figure 1A).

270 **Neuronal firing rates are associated with Process S dynamics and vigilance state distributions**

271 Whichever specific processes within the brain underpin these state-dependent dynamics for Process S ,
272 it is likely associated in some way to neuronal spiking activity. Spiking patterns differ characteristically
273 between wake and NREM sleep, due to the presence of off periods in NREM sleep which typically
274 coincide with slow waves in both EEG and LFP (Figure 1B). The occurrence of such spiking off periods
275 cause firing rates to be typically much lower during NREM sleep compared to wake and REM sleep. In
276 this dataset, the mean multi-unit firing rate averaged over all periods of wake was larger than the firing
277 rate averaged over all periods of NREM sleep in every recording channel and every animal (Figure 1C).

278 Because the slow oscillation is underpinned by local neuronal dynamics, it is expected to be highly
279 heterogeneous across the neocortex. Regional differences in SWA dynamics have been previously
280 described, for example between frontal and occipital EEG derivations (Werth et al., 1996; Huber et al.,
281 2000b), and can be accounted for within the classical Process S model through the selection of locally
282 variable values for model rate parameters (Zavada et al., 2009; Rusterholz & Achermann, 2011;
283 Guillaumin et al., 2018). To explore whether spike firing rates might account for some of the variation
284 in the rate of Process S increase, we correlated the change in LFP SWA from one NREM sleep episode to
285 the next, when separated by wakefulness lasting at least 5 minutes, with the mean spike firing rate
286 during this intervening wake period, and with the duration of that wake period. Correlation coefficients
287 were obtained separately for each recording channel, and pooled across animals. As expected, we
288 obtained large positive correlation coefficients between the duration of a period of wakefulness and the
289 change in LFP SWA in all channels (mean=0.66, sd=0.13; Figure 1D). Importantly however, the change
290 in LFP SWA was on average also positively correlated with firing rate (mean=0.27, sd=0.30; Figure

291 1D,E), meaning that, generally, a higher firing rate during waking was associated with a larger increase
292 in SWA in subsequent NREM sleep. Interestingly, these phenomena were not independent, as a positive
293 correlation was also found between wake episode duration and firing rate (mean=0.35, sd= 0.33; Figure
294 1D). These results further support the possibility that neuronal activity is associated with Process S
295 dynamics and vigilance state distributions. To test this hypothesis we next turned to a quantitative
296 modelling approach.

297 **Process S dynamics can be described as a function of neuronal firing rates**

298 We first sought to determine whether a model expressing Process S dynamics solely as a function of
299 local multi-unit neuronal firing rates might describe the levels of sleep SWA in the corresponding LFP
300 with comparable accuracy to the classical model dependent on vigilance states at the global level. The
301 classical Process S model was used as a starting point for the development of a novel firing rate
302 dependent alternative. To do this, the equations of the classical model were adapted in two ways. Firstly,
303 an instantaneous firing rate threshold (F_{θ}) was introduced as a new model parameter to replace the
304 wake vs. sleep criterion, assuming an increase in Process S when the threshold is exceeded and decrease
305 when firing is below. Conceptually, this firing rate threshold resembles a set point; a target firing rate at
306 which the dynamics are stable. Secondly, we assumed that the rate of change of Process S is proportional
307 to the difference between firing rate and this threshold. Introducing this change to the equations ensures
308 that the rate of change of S is equal to zero exactly at the set point, and a continuous function of firing
309 rate around this value. This version of the model is later abbreviated as Fr-SWA. The equations are:

$$F(t) > F_{\theta}: \quad dS/dt = \alpha(S_{max} - S(t))(F(t) - F_{\theta})$$

$$F(t) < F_{\theta}: \quad dS/dt = -\beta(S(t) - S_{min})(F_{\theta} - F(t))$$

$$F(t) = F_{\theta}: \quad dS/dt = 0$$

310 We applied this novel model, alongside the classical model, to describe SWA dynamics at the LFP level,
311 by finding parameter values that would minimise the difference between empirical SWA and modelled
312 Process S. The two models were fit to the SWA from each LFP channel separately, using the multi-unit
313 firing rate from the same channel for the firing-rate-dependent model. The models were also fit to the

314 SWA obtained by averaging the LFP (and firing rate) over the whole population of channels within the
315 same mouse.

316 Figure 2 shows two examples of the fit of both models, first to SWA derived from the average LFP, and
317 also to SWA derived from a single LFP channel (these examples are from the same animal as in Figure
318 1A). The overall pattern of Process S dynamics is similar at both recording levels, and to the
319 corresponding EEG, and is well described by both the classic and novel firing-rate-based model.
320 Throughout the dataset, this purely firing-rate-dependent model described the overall dynamics of LFP
321 SWA during NREM sleep to a comparable accuracy as the classical model, as reflected in the median
322 percent error deviation between modelled and empirical SWA (Figure 3B). Both the model type and
323 animal have a highly significant effect on the median percent error of the model fit to individual LFP
324 channels, although there is no significant interaction (Model: $F_{(1,144)} = 25.9$, $p = 1.1 \times 10^{-6}$; Animal: $F_{(5,144)}$
325 $= 30.2$, $p = 6.3 \times 10^{-21}$; Model x Animal: $F_{(5,144)} = 1.65$, $p = 0.15$; two-way ANOVA unequal groups). Errors
326 were higher for the novel model, importantly however, the differences in fit quality due to the model
327 type are small relative to the effect size of the particular animal and channel, on which fit quality
328 depends much more strongly (Model: $\eta^2 = 0.079$; Animal: $\eta^2 = 0.459$; Model x Animal: $\eta^2 = 0.025$; Channel
329 (residuals): $\eta^2 = 0.437$). The errors of the model fit on the averaged LFP and on the EEG (classical model
330 only) are also shown in Figure 3B, and are more explicitly compared in Figure 3C. We do not find any
331 significant effect of the field potential level (EEG, average LFP, single LFP) on the model error ($F_{(2,171)} =$
332 0.2 , $p = 0.82$, one-way ANOVA).

333 The distributions of final optimised parameters are shown in Figure 3D-G for the classic model and
334 Figure 3H-L for the firing rate based model. Most parameters in both models were significantly different
335 between animals, with the exception of S_{min} in the firing rate dependent model (Cl-SWA α : $F_{(5,77)} = 4.03$,
336 $p = 2.8 \times 10^{-3}$; Cl-SWA β : $F_{(5,77)} = 8.65$, $p = 1.9 \times 10^{-6}$; Cl-SWA S_{max} : $F_{(5,77)} = 14.35$, $p = 9.8 \times 10^{-10}$; Cl-SWA S_{min} :
337 $F_{(5,77)} = 12.42$, $p = 1.1 \times 10^{-8}$; Fr-SWA α : $F_{(5,77)} = 8.33$, $p = 3.0 \times 10^{-6}$; Fr-SWA β : $F_{(5,77)} = 9.27$, $p = 7.5 \times 10^{-7}$; Fr-
338 SWA F_{θ} : $F_{(5,77)} = 14.3$, $p = 1.0 \times 10^{-9}$; Fr-SWA S_{max} : $F_{(5,77)} = 6.64$, $p = 3.9 \times 10^{-5}$; Fr-SWA S_{min} : $F_{(5,77)} = 2.16$, $p =$
339 0.07 ; one way ANOVA). The optimised rate parameters for EEG and averaged LFP data consistently fall
340 within the range of the single channel population (Figure 3D-L). The relationship between the optimal

341 firing set point and state specific firing rates is shown in Figure 3M. Firing rate threshold was z-
342 normalised (subtract mean, divide by standard deviation) separately with respect to the distribution of
343 firing rates in wake, NREM and REM sleep. This shows, as expected, that the set point is typically below
344 mean firing in wake (-1.0 ± 0.6 ; mean \pm sd), well above mean firing in NREM sleep (1.6 ± 1.1), and slightly
345 above mean firing of REM sleep (0.7 ± 1.1). These were all significantly different from zero (wake: $p =$
346 1.6×10^{-13} , NREM: $p = 1.9 \times 10^{-14}$, REM: $p = 3.4 \times 10^{-7}$, two-sided Wilcoxon signed rank test). Figure 3N
347 further shows the state dependent distribution of average firing rate, expressed as a percentage of the
348 chosen firing set point parameter. Mean firing was $182 \pm 57.6\%$ of the firing rate set point during wake,
349 $61.8 \pm 17.6\%$ during NREM sleep, and $84.2 \pm 31.8\%$ during REM sleep. Again, these distributions were
350 all significantly different from 100% (Wake: $p = 6.7 \times 10^{-14}$, NREM: $p = 2.0 \times 10^{-14}$, REM: $p = 5.4 \times 10^{-5}$). Note
351 that, in a few channels, the optimal firing rate threshold is actually above the mean firing rate during
352 waking. This occurs when the waking firing rate distribution overlaps substantially with the NREM sleep
353 firing rate distribution but has a heavier tail. REM sleep, in this dataset, is typically associated with firing
354 below the set point, and therefore Process S decrease, albeit at a reduced rate compared to NREM sleep
355 (Figure 3O). Interestingly, there are no significant correlations between the model fit error and the
356 threshold normalisation relative to any one vigilance state (Wake: $p=0.06$, $r=0.21$; NREM: $p=0.35$, $r=-$
357 0.11 ; REM: $p=0.94$, $r=-0.01$), suggesting that there is no clear relationship between the firing rate set
358 point and firing rate distribution of any one particular state.

359 **Process S can be defined in terms of neuronal spiking off periods**

360 When considering the relationship between multi-unit firing rates and LFP slow waves, a conceptual
361 complication arises due to the different origins of the LFP and MUA from within the same channel. While
362 the MUA firing rate represents the activity of only a few individual neurones, factors such as volume
363 conduction result in spatial smoothing of the LFP signal, and as such it represents the combined activity
364 of neurones covering a cortical area potentially on the order of several millimetres (Kajikawa &
365 Schroeder, 2011). This means that when a slow wave is detected in the LFP, it is not guaranteed that
366 local neurones which contribute to the MUA are necessarily in an off period. Similarly, not every long
367 interspike interval occurs during a slow wave. An estimation of the occurrence of off periods may be

368 obtained by combining LFP and spiking data (Figure 4A). Slow wave detection was performed on each
369 LFP over the whole 48hrs, including all vigilance states (0.5-6 Hz filter followed by an amplitude
370 threshold, values shown in Figure 4C). All multi-unit inter-spike intervals (ISIs) which coincide with the
371 peak of detected slow waves were identified. The distribution of the duration of these ISIs was often (64
372 out of 75 channels) unambiguously bimodal (Figure 4B). This could be interpreted as evidence of the
373 existence of two spiking states occurring locally during the more widespread network slow oscillation;
374 high frequency spiking (on period) and extended silence (off period). Note that these two distributions
375 do not simply correspond exactly to sleep vs. wake conditions, because bimodality is often evident in
376 the distribution of slow wave coincident ISIs from NREM sleep only, or even from REM sleep only (Figure
377 4B). The distribution of slow wave coincident ISIs (over all vigilance states) was used to define an ISI
378 duration threshold for the detection of off periods, separately for each channel. The values used for this
379 threshold are shown in Figure 4D. The average multi-unit firing rate aligned to the peak of slow waves
380 in detected off periods reveals a clear suppression of firing, consistent with expectations (Figure 4E). A
381 rebound increase in average firing is visible in this example channel immediately after the off period, as
382 has been previously documented in some cortical neuronal populations (Chauvette et al., 2010). The
383 total fraction of time each channel spends in off periods was calculated over all 4-second epochs, and
384 termed the “off occupancy”. Off occupancy defined in this way is high in NREM sleep and low in both
385 wake and REM sleep (Figure 4F). The existence of a non-zero frequency of local cortical off periods has
386 been previously reported during wakefulness (Vyazovskiy et al., 2011; Vyazovskiy et al., 2014; Fisher et
387 al., 2016), and REM sleep (Funk et al., 2016). The off occupancy measure displays similar temporal
388 dynamics to LFP (and EEG) SWA over both sleep deprivation and spontaneous sleep and wake (Figure
389 4G).

390 **Process S dynamics, defined using off periods, can be described as a function of vigilance states**
391 **or neuronal firing rates**

392 In order to investigate whether the off occupancy measure reflects Process S, we applied the classical
393 state based model to the time course of off occupancy, exactly as was done with single channel SWA. The
394 classical model was applied with its equations unchanged, and is abbreviated as Cl-Off. Figure 5A shows

395 an example of the resulting Process S time course obtained in this way with a high quality of fit. In
396 contrast, some changes were introduced to the firing-rate-based model in order to describe off
397 occupancy dynamics. We considered that the different dynamics above vs. below a particular firing rate
398 set point may be due to two opponent processes simultaneously active in dynamic opposition but with
399 differential magnitude in wake vs. NREM sleep. Specifically, we consider a Process S increasing term
400 which is proportional to instantaneous firing rate, and a Process S decreasing term which is proportional
401 to the time spent in off periods (off occupancy). The equation used is:

$$402 \quad \frac{dS}{dt} = \alpha F(t)(S_{max} - S(t)) - \beta X(t)(S(t) - S_{min})$$

403 In this model, one term drives S towards an upper asymptote (S_{max}) in proportion to firing rate (F), while
404 the other drives S towards a lower asymptote (S_{min}) in proportion to the off occupancy (X). Again, two
405 rate parameters α & β are required. This model behaves similarly to previous models because firing is
406 high in wake and low in NREM sleep, whereas off occupancy is high in NREM sleep and low in wake. This
407 variant of the model is abbreviated as Fr-Off. Figure 5A includes also the fit from this model,
408 demonstrating a high level of agreement between the two models and an accurate fit to the data.

409 The distribution over all animals and channels of the median percent errors for the fits from both models
410 is shown in Figure 5C. As before, the model type and animal has a significant effect (Model: $F_{(1,138)} = 8.06$,
411 $p = 5.2 \times 10^{-3}$; Animal: $F_{(5,138)} = 17.2$, $p = 3.2 \times 10^{-13}$; Model x Animal: $F_{(5,138)} = 0.52$, $p = 0.76$; two-way ANOVA
412 with unequal groups) and the classic model achieved a slightly lower median percent error. However,
413 this effect was again very weak compared with the variation in fit quality between animals and channels
414 (Model: $\eta^2 = 0.034$; Animal: $\eta^2 = 0.367$; Model x Animal: $\eta^2 = 0.011$; Channel (residuals): $\eta^2 = 0.588$).

415 Figure 5D shows the distribution of values for the change in modelled Process S from one time step to
416 the next resulting from the firing-rate-based model (Fr-Off), in wake, NREM sleep and REM, pooling all
417 animals, channels and time. Unlike in the previous firing-rate-based model, REM sleep is now typically
418 associated with Process S increase. The distributions of final optimised parameters are shown in Figure
419 5E-H for the classic model and Figure 5I-L for the firing rate and off occupancy model. Most parameters
420 in both models were different between animals to a high significance level (Cl-Off α : $F_{(5,74)} = 2.4$, $p =$
421 0.047 ; Cl-Off β : $F_{(5,74)} = 2.29$, $p = 0.055$; Cl-Off S_{max} : $F_{(5,74)} = 9.49$, $p = 6.4 \times 10^{-7}$; Cl-Off S_{min} : $F_{(5,74)} = 16.79$, p

422 = 8.0×10^{-11} ; Fr-Off α : $F_{(5,74)} = 9.86$, $p = 3.9 \times 10^{-7}$; Fr-Off β : $F_{(5,74)} = 5.14$, $p = 4.6 \times 10^{-4}$; Fr-Off S_{max} : $F_{(5,74)} =$
423 10.08 , $p = 2.8 \times 10^{-7}$; Fr-Off S_{min} : $F_{(5,74)} = 10.25$, $p = 2.3 \times 10^{-7}$; one way ANOVA). Notably, the weakest
424 evidence for inter-animal differences were for α and β in the classic model.

425 **Modelling identifies local variation in Process S dynamics**

426 All four modelling approaches described here suggest the existence of variability in Process S between
427 recording channels, indicating that a local component determines its dynamics. Figure 6A-D illustrates
428 this diversity, showing the overlaid time courses of Process S for all channels within a single
429 representative animal, expressed as a percentage of their individual maximum value for normalisation
430 purposes. Although the models all fit empirical SWA or off period occupancy with generally high
431 accuracy, there are nonetheless differences between models in the precise shape of Process S. The
432 average Process S over all channels was also calculated for each model and compared with the Process
433 S derived from applying the classical model to EEG SWA (Figure 6E). This reveals that Process S derived
434 from modelling LFP SWA more closely resembles Process S derived from EEG SWA than Process S
435 derived from off occupancy. This suggests that global Process S calculated at a higher spatial scale might
436 reflect an averaging across a manifold of local Processes S that exist on a finer spatial level.

437

Discussion

438 Here, we show that Process S can be quantitatively described entirely in terms of measures based on
439 neuronal spiking activity, without reference to global vigilance states. A model was outlined whereby
440 the integrated history of multi-unit firing rates, relative to a firing rate set point, predicted the temporal
441 dynamics of LFP SWA. The accuracy of this model was demonstrated in a dataset of recordings from
442 mouse frontal cortex over 48 hours, including both voluntary sleep and wake, and sleep deprivation. A
443 novel metric for Process S was then presented, termed off occupancy, which measures the fraction of
444 time a neural population spends in off periods, defined by the coincidence of LFP slow waves and multi-
445 unit spiking silence. The modelling approach was combined with the off occupancy metric and tested on
446 the same dataset to present a quantitative framework for understanding dynamics of sleep pressure at
447 a highly local level in terms of neural spiking and off periods.

448 Central to this modelling perspective is the assumption that the generation of spikes by a neural network
449 is in some way correlated with an increase in sleep pressure, and that this manifests in the subsequent
450 expression of slow waves and off periods, reflecting Process S. The energetic cost of spiking is high
451 (Attwell & Laughlin 2001), the regulation of a neurone's firing rate set point is linked to cellular
452 energetics (Styr et al., 2019; Vergara et al., 2019), and neurones are susceptible to cellular stresses that
453 can result from sustained metabolic load, such as oxidative stress (Wang & Michaelis 2010; Cobley et al.,
454 2018; Kempf et al., 2019). Furthermore, spiking activity may be mechanistically associated with synaptic
455 plasticity, and it was suggested that firing rates are an important determinant of overall changes in
456 synaptic strength, with higher spiking leading to greater changes (Graupner et al., 2016; Lappalainen et
457 al., 2019). Compensatory processes exist within neurones to oppose cellular stress and related
458 homeostatic challenges (Kültz 2005) and off periods could provide the opportunity for neurones to
459 prioritise such processes, therefore mediating the restorative benefits of sleep (Vyazovskiy & Harris,
460 2013). Similarly, off periods are associated with distinct synaptic plasticity rules (Gonzalez-Rueda et al.,
461 2018), and so their prevalence and patterning is likely also related to whatever regulation of synaptic
462 strength occurs during sleep (Tononi & Cirelli 2014; Timofeev & Chauvette 2017; Seibt & Frank, 2019).

463 According to this view of sleep homeostasis, in principle, regulation can occur entirely at the local level,
464 within cortical networks or perhaps even single neurones. Indeed, this is reflected in our results through
465 the differences between channels both with respect to the accuracy of the model and in the values of
466 optimised parameters. Why then is global sleep preferred over a hypothetical state including
467 asynchronous local off periods, which presumably could be used to sustain longer periods of
468 behavioural wakefulness? It has been argued previously that it is ecologically optimal to synchronise off
469 periods and undergo dedicated periods of total behavioural shutdown, because local off periods during
470 waking impair behaviour (Vyazovskiy et al., 2011; Rattenborg et al., 2012). Mechanistically, the
471 occurrence of off periods might be obstructed by strong synaptic coupling and shared neuromodulatory
472 tone. Indeed, it has been observed that the degree of coupling between an individual neurone's firing
473 and the population firing rate, is variable between cells but characteristic to an individual neurone and
474 likely reflects total synaptic strength with its neighbours (Okun et al., 2015). Some neurones may
475 therefore be less able to express asynchronous off periods than others.

476 The preference for global sleep, despite its fundamentally local mechanisms, may be evidence that sleep
477 homeostasis ultimately does not serve a single specific local function. Instead, the recent history of local
478 activities, by alteration of the local propensity to generate off periods (Process S), may be integrated
479 over neuronal populations through intrinsic network mechanisms, in order to produce a sleep
480 propensity signal that estimates the total time spent awake with great accuracy. The brain would
481 thereby aim to enforce a daily quota of sleep, which could have many physiological and ecological
482 benefits, rather than initiating sleep in response to the homeostatic need of one specific regulated
483 variable (Vyazovskiy, 2015). The overall accuracy of both firing-rate-based and vigilance-state-based
484 models supports this possibility, as does the evidence that homeostatically regulated cellular variables
485 can actually be stable during extended wakefulness and that maintenance processes in sleep are
486 ultimately prophylactic (Vyazovskiy & Harris, 2013). In this case, the sleep quota typically required by
487 the brain would be determined by the neural population(s) that regularly accumulate sleep pressure
488 the fastest. In order to maximise the efficiency of global sleep, single neuronal activities may be
489 modulated such that sleep pressure accumulates, on average, as uniformly as possible. This is consistent
490 with recent reports that sleep regulates the population level firing rate distribution (Watson et al., 2016;

491 Levenstein et al., 2017; Miyawaki & Diba, 2019) and could account for sleep's link with synaptic and
492 firing rate homeostasis, reconciling the local origins of sleep pressure accumulation with the global level
493 of its dissipation.

494 Here, spike firing rate is used to represent the level of neural activity because it is convenient to record,
495 locally variable, and directly linked to neuronal functionality. However, no strong claim is made that
496 firing rates are necessarily causally responsible for the accumulation of sleep pressure. Indeed, it would
497 likely be possible to obtain a reasonable quantitative account of sleep homeostasis using any
498 physiological variable (or set of variables) that are consistently higher in either the wake or sleep state.
499 For example, a model assuming that Process S increases in proportion to local cortical temperature,
500 which drops by $\sim 2^{\circ}\text{C}$ when falling asleep (Franken et al., 1991b) and which has been mechanistically
501 implicated in sleep regulation (Hoekstra et al., 2019), might also provide a plausible description of
502 Process S dynamics. Importantly, these results demonstrate that firing rates are a useful measurable
503 correlate of the processes that directly underpin Process S, and therefore firing rate variance resulting
504 from differences in experience and behaviour may well account for the variance in Process S
505 accumulation in normal individuals, between waking periods and between cortical regions.

506 It should be addressed explicitly that the novel firing rate based models typically slightly under-perform,
507 relative to the classic model, in terms of minimising the error between simulation and empirical data.
508 There are a number of reasons why a limit on the accuracy of the model is to be expected, related to
509 technical restrictions rather than conceptual ones. In this approach, each MUA channel records only a
510 few randomly sampled nearby neurones, which may have very different spiking properties, and so
511 grouping these as a single measure of local network activity is somewhat artificial. It may be valuable to
512 explore genetic and pharmacological manipulations of firing rate in order to further test this model's
513 validity. Unfortunately, the effects of any manipulation on the accumulation, expression and dissipation
514 of sleep pressure, separately to the effects on firing, is unknown, and so this may be hard to interpret.
515 For example, a recent study found that systemic atropine administered during behavioural wakefulness
516 produces slow wave activity, reducing spiking (as measured by c-Fos) yet increasing the duration of
517 subsequent NREM sleep (Qiu et al., 2015). While this was interpreted as evidence that spiking activity

518 is not related to sleep pressure accumulation, the direct effects of atropine on Process S and the
519 functional significance of the resulting induced slow oscillation are unclear. Similarly, another study
520 found that optogenetic activation of cortex during sleep, despite raising firing rates to waking levels,
521 was accompanied with decreased Process S (lower SWA and fewer off periods) during subsequent
522 NREM sleep (Rodriguez et al., 2016). Again, it is difficult to disentangle the direct effects of this
523 stimulation, which is not physiologically realistic, on the mechanisms surrounding the accumulation,
524 expression and dissipation of sleep pressure. On the other hand, these results might be interpreted as
525 evidence that the expression of the level of Process S involves an integration of homeostatic sleep need
526 across neural populations and therefore local firing rate manipulations are not able to substantially
527 influence Process S dynamics at a global level.

528 It is reasonable to assume that sleep homeostasis unfolds on multiple time scales and Process S as
529 defined by these models describes a relatively fast one, approaching its upper asymptote after
530 continuous wakefulness on a time scale of hours. The inclusion of processes acting over longer or
531 shorter time scales might explain discrepancies in all these models, however, the challenge remains to
532 identify what these could be. Furthermore, the role of REM sleep in Process S dynamics has not been
533 explicitly addressed or considered in the construction of these models. Depending on the model variant,
534 REM sleep is associated either with small increase or small decrease in Process S, because firing rates
535 are low in REM sleep (closer to NREM sleep than waking) and yet off period occupancy is also low (closer
536 to wake levels than NREM sleep). It is possible that REM sleep might represent a homeostatically neutral
537 state, in which the level of Process S changes little, or not at all (Vyazovskiy & Delogu, 2014).

538 In summary, Process S is reflected in both slow wave activity and the occurrence of local off periods, and
539 its dynamics can be quantitatively described using information derived from local spike firing rates and
540 off periods. Such a description has comparable accuracy to the classical model of Process S, dependent
541 only on global sleep-wake history. This result has important implications for our understanding of the
542 nature of sleep homeostasis and these novel models provide a methodology to quantify and compare
543 Process S dynamics, potentially between different cell types and brain regions.

544

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712

Figure Legends

713 **Figure 1.** Cortical spike firing patterns are associated with the dynamics of Process S. **A)** An example of
714 the classical state-based Process S model (blue) describing the dynamics of frontal EEG SWA (median
715 per NREM sleep episode, black bars) over 48 hours in one representative animal. Sleep deprivation
716 occurred as indicated at light onset of the second day and lasted 6 hours. Scored vigilance states are also
717 shown. **B)** An example of frontal electroencephalogram (EEG), primary motor cortical local field
718 potentials (LFP), corresponding raw signal with multi-unit activity (MUA), and detected spikes, in
719 representative segments of waking and NREM sleep. Slow waves and synchronous spiking off periods
720 are visible in NREM sleep but not wakefulness. **C)** The distribution of mean firing rate during wake,
721 NREM and REM sleep over the whole dataset, in addition to the difference in mean firing rate in wake
722 compared to NREM sleep (all are positive, reflecting higher firing in wake). Points indicate channels
723 grouped by animal (left to right), but boxplots reflect channels from all animals treated as a single
724 population. **D)** Distribution of correlation coefficients, calculated within each single channel, between
725 wake episode duration (Duration), the change in slow wave activity (dSWA), and mean firing rate (mean
726 FR). Points indicate channels grouped by animal (left to right), but boxplots reflect channels from all
727 animals treated as a single population. **E)** An example scatter plot of the correlation between the change
728 in median SWA from one NREM episode to the next and the mean firing rate during the intervening
729 period of wakefulness. This channel is representative because it has the median correlation coefficient
730 of all channels.

731 **Figure 2.** Slow wave activity dynamics at the LFP level can be modelled using multi-unit spiking
732 information. **A)** An example from one representative animal modelling the SWA averaged over all LFP
733 channels, of both the classical model (blue) and novel firing-rate-based model (orange), calculated from
734 the firing rate also averaged over all LFP channels (brown). **B)** An example of both models applied to
735 the SWA of a single LFP channel, which came from the same animal as used in **A**.

736 **Figure 3.** The fit quality and parameters for both classical and firing-rate-based models of LFP SWA. **A)**
737 Equations for the classic state-based model (blue) and novel firing-rate-based model (orange). **B)** For
738 each animal, the distribution over channels of the median difference between the model and empirical

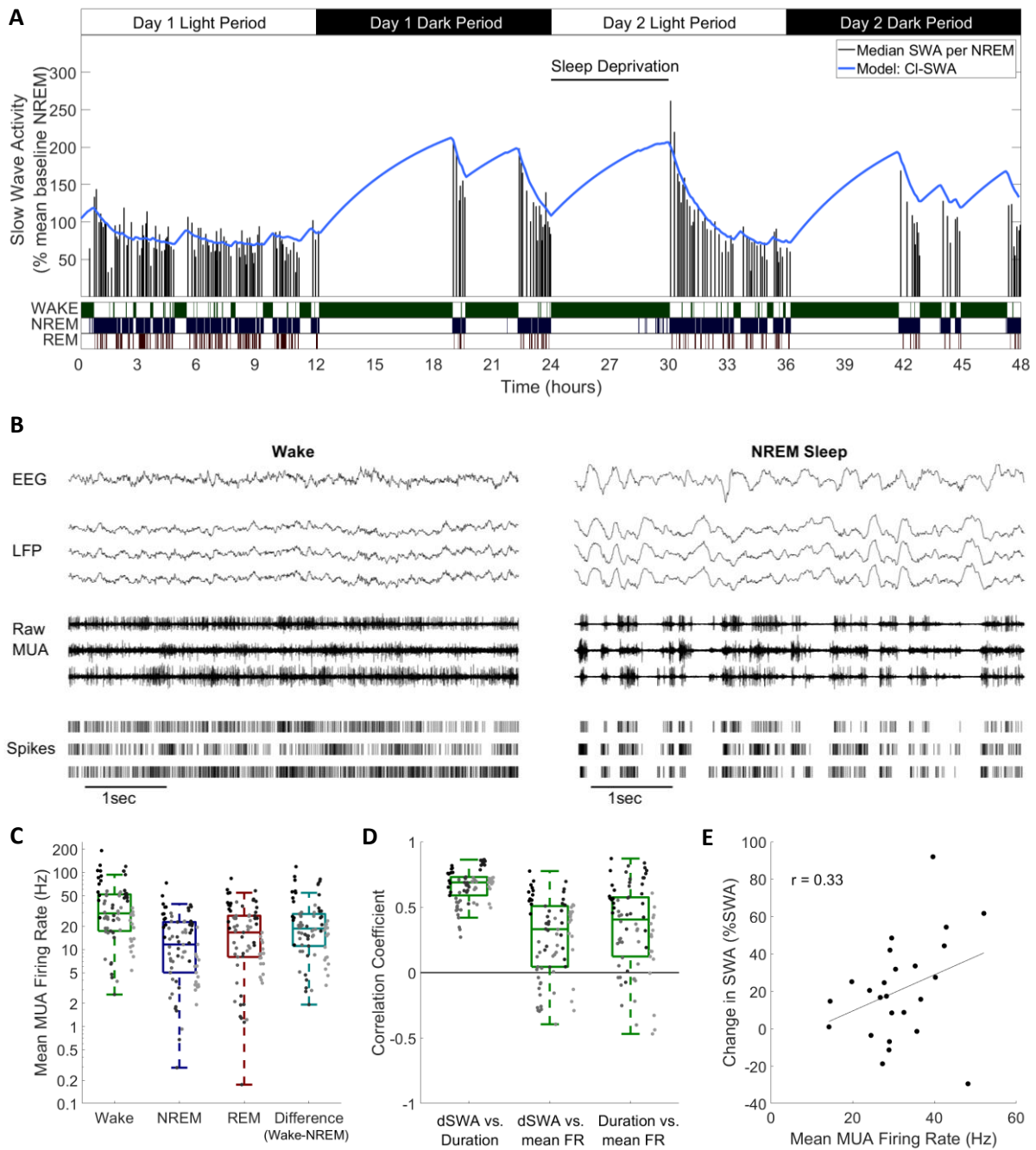
739 SWA, expressed as a percentage of empirical SWA, for both classic and firing-rate-based models. **C)** The
740 same median percent error, grouped over animals and models, separately showing errors at the level of
741 single LFP, averaged LFP and EEG. **D-G)** The distribution of values used for each parameter in the classic
742 model and **H-L)** in the firing-rate-based model, with boxplots plotted separately for each animal. The
743 black lines indicate the values obtained from modelling the averaged LFP SWA and firing rate over all
744 channels within an animal. Additionally, the red lines in **D-G)** give the parameter value obtained from the
745 model of the frontal EEG SWA of that animal. **M)** The distribution of the final optimised value for the
746 firing rate set point parameter (F_{θ}) of the firing-rate-based model, z-normalised to the distribution of
747 firing rates within wake, NREM and REM sleep. Points indicate channels grouped by animal (left to
748 right), but boxplots reflect all channels treated as a single population. **N)** The distribution of mean firing
749 rate in wake, NREM and REM sleep, expressed as a percentage of the firing rate set point parameter (F_{θ}).
750 Points indicate channels grouped and coloured by animal, but boxplots reflect all channels treated as a
751 single population. **O)** The distribution of values of the change in Process S ($\Delta S/\Delta t$) from one 4-second
752 time step to the next derived from the Fr-SWA model in wake, NREM sleep and REM sleep. All mice,
753 channels and time are pooled.

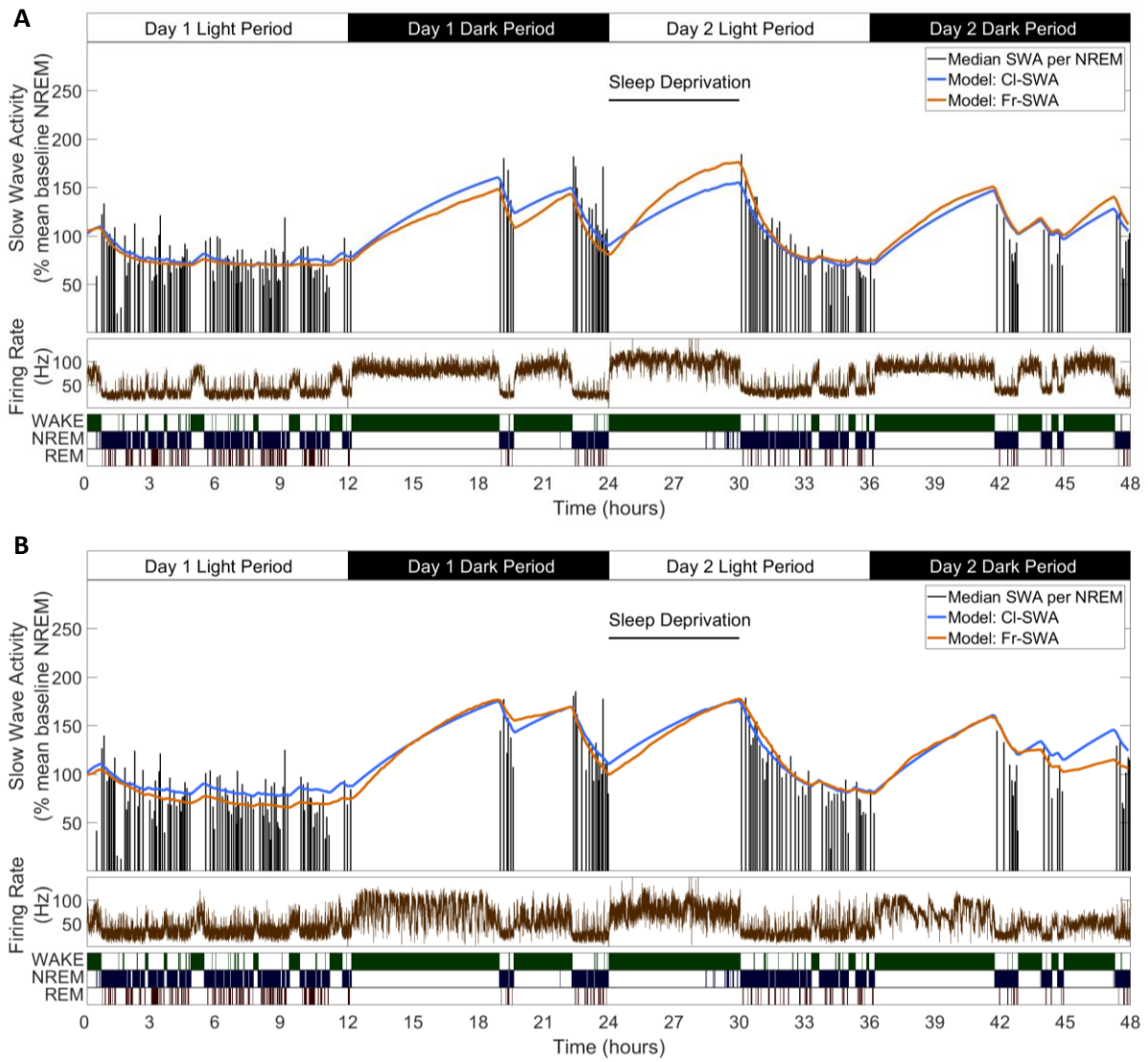
754 **Figure 4.** The definition of off periods and off occupancy. **A)** An example section of LFP (raw in grey,
755 0.5-6Hz filtered in black) and simultaneous MUA spikes. During this time window, the filtered LFP
756 crosses the amplitude threshold (265 μ V for this channel, red line) five times. The multi-unit inter-spike
757 interval aligned to two of these peaks exceeds the duration threshold (85ms for this channel) and so
758 two off periods are detected (grey boxes). ISIs aligned to the other three out of five crossings (asterisks)
759 are too short to be considered off periods. **B)** Histograms of multi-unit inter-spike intervals aligned with
760 detected slow waves for this example channel. The four plots show, from left to right, ISIs over the whole
761 recording and separately ISIs from wake, NREM and REM sleep only. The ISI duration threshold (red
762 line) is selected using the histogram of all ISIs (leftmost) at the minimum between the two modes. **C)**
763 The distribution of LFP amplitude and **D)** ISI duration threshold values used for definition of off periods
764 for each channel, with boxplots plotted separately for each animal. **E)** The mean multi-unit firing rate
765 over a 1-second period centred on the peak of detected slow waves, calculated over all slow waves
766 within one example channel with 1-millisecond resolution. **F)** Distributions of mean off occupancy (%)

767 for all channels averaged over wake, NREM and REM sleep. Points indicate channels grouped by animal
768 (left to right), but boxplots reflect all channels treated as a single population. **G)** Off occupancy is shown
769 alongside EEG and LFP SWA for an example channel over 48 hours. Traces represent these values
770 calculated at 4-second resolution (light grey), in addition to the median value per NREM sleep episode,
771 as used for model fitting (black bars). Firing rate (brown) and scored vigilance states are also shown.

772 **Figure 5.** Process S is reflected in an LFP channel's off occupancy and its dynamics are described well
773 by both state-based and firing-rates-based models. **A)** An example of the novel model based on firing
774 rates and off occupancy (purple), and the classic state-based model (blue), with optimised parameters
775 describing the dynamics of off occupancy (median per NREM episode, black bars) over 48 hours. Sleep
776 deprivation occurred as indicated at light onset of the second day and lasted 6 hours. Firing rate
777 (brown), off occupancy (value per 4-second epoch, grey) and scored vigilance states are also shown. **B)**
778 Equations for the classic state based model (blue) and firing-rate-and-off-occupancy-based model for
779 off occupancy (purple). **C)** For each animal, the distribution over channels of the median difference
780 between the model and empirical off occupancy, expressed as a percentage of the off occupancy, for both
781 classic and firing-rate-based models. **D)** The distribution of values of the change in Process S ($\Delta S/\Delta t$)
782 from one 4-second time step to the next derived from the Fr-SWA model in wake, NREM sleep and REM
783 sleep. All mice, channels and time are pooled. **E-H)** The distribution of optimised values used for each
784 parameter in the classic model and **I-L)** the firing rate model, with boxplots plotted separately for each
785 animal.

786 **Figure 6.** The time course of Process S is similar between models and individual channels. Process S
787 time courses, expressed for each channel as a percentage of the maximum value, overlaid for all channels
788 within a single representative animal obtained from **A)** the classic state-based model applied to LFP
789 SWA, **B)** the firing-rate-based model applied to LFP SWA, **C)** the classic state-based model applied to off
790 occupancy, **D)** the firing-rate-based model applied to off occupancy. In these panels the black line
791 indicates the mean Process S over all channels. **E)** The mean Process S calculated over all channels is
792 now plotted in colour (Cl-SWA light blue, Fr-SWA orange, Cl-Off dark blue, Fr-Off purple), and the red
793 line indicates the Process S obtained by applying model Cl-SWA to the EEG derived SWA.





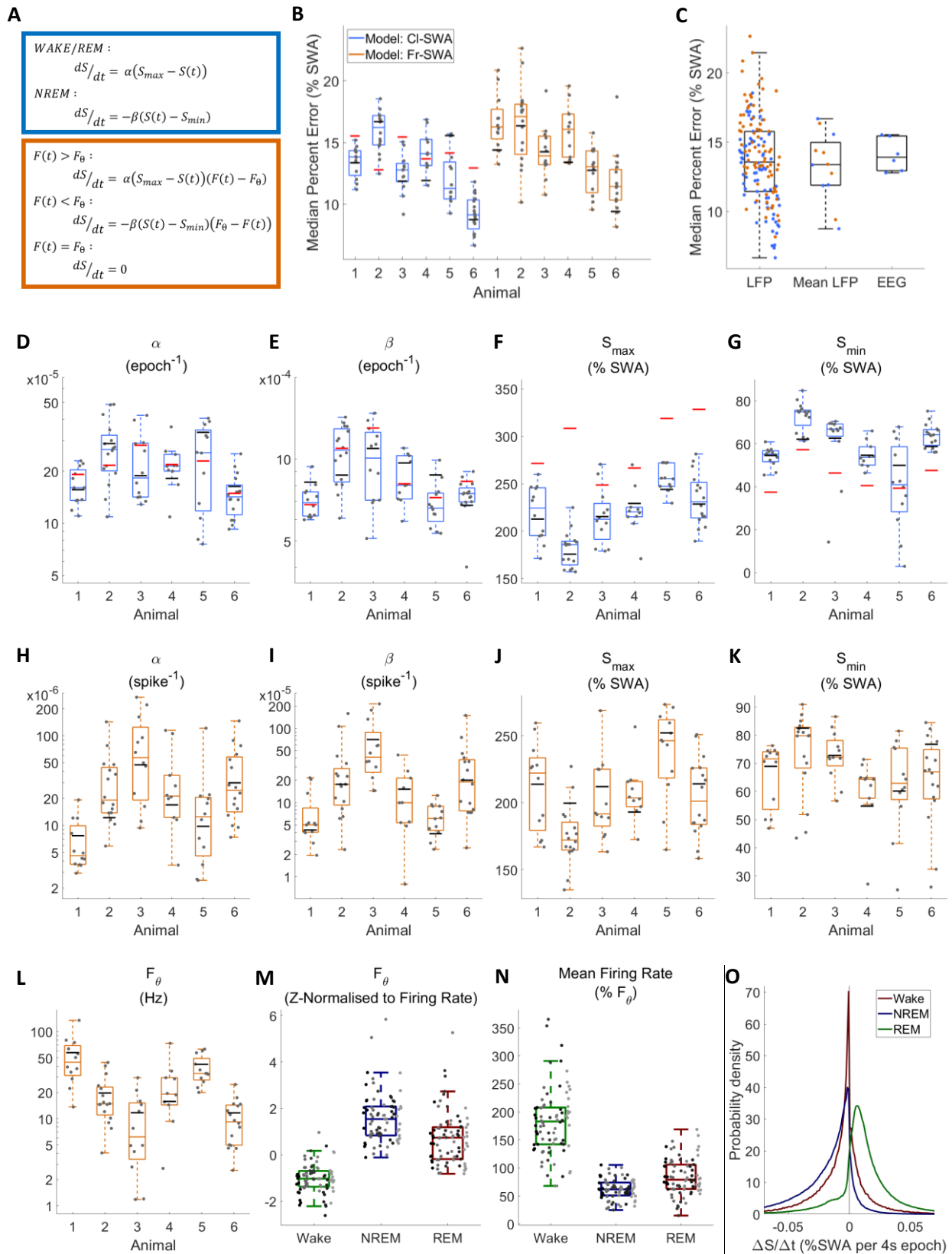


Figure 3

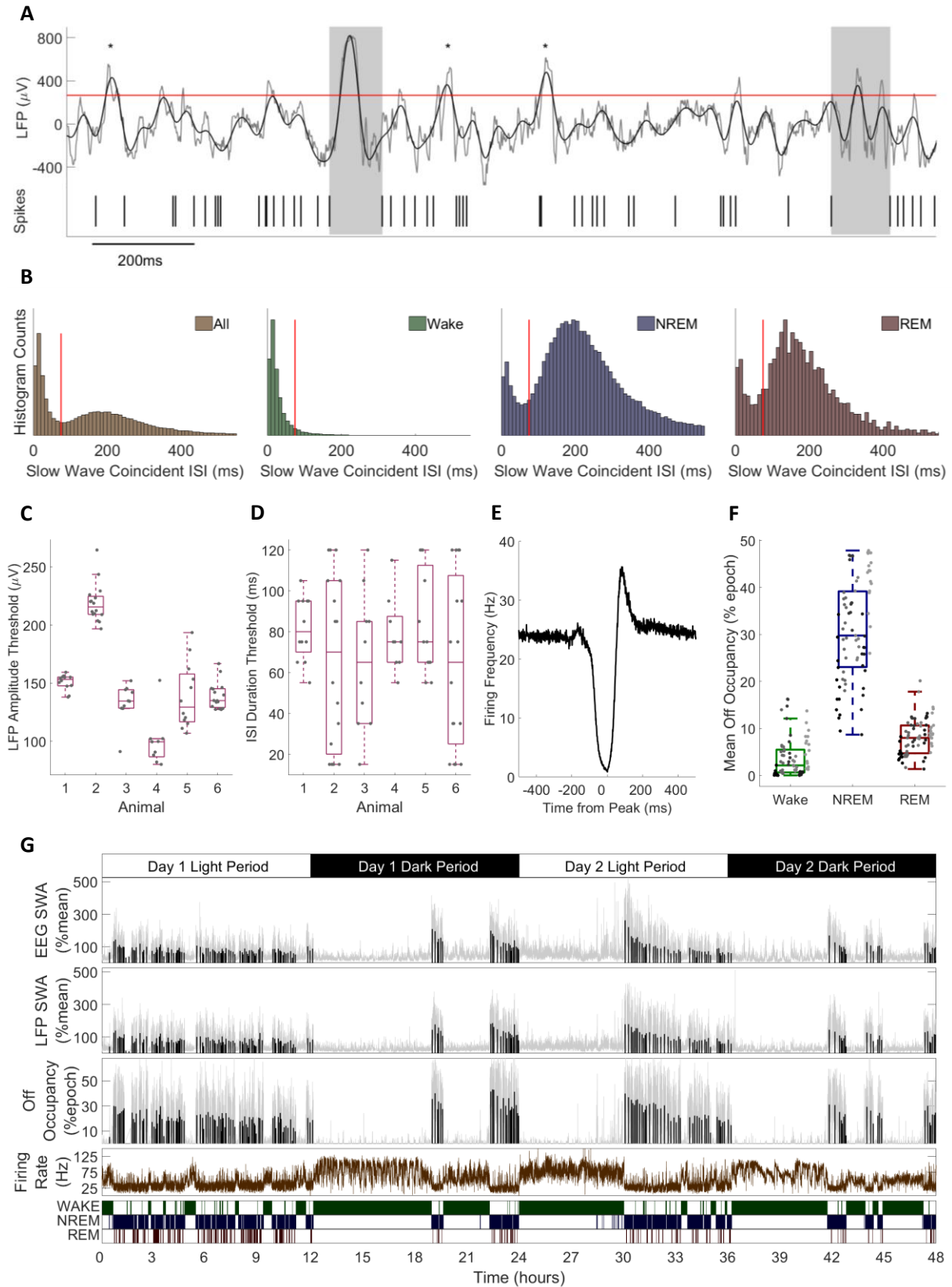


Figure 4

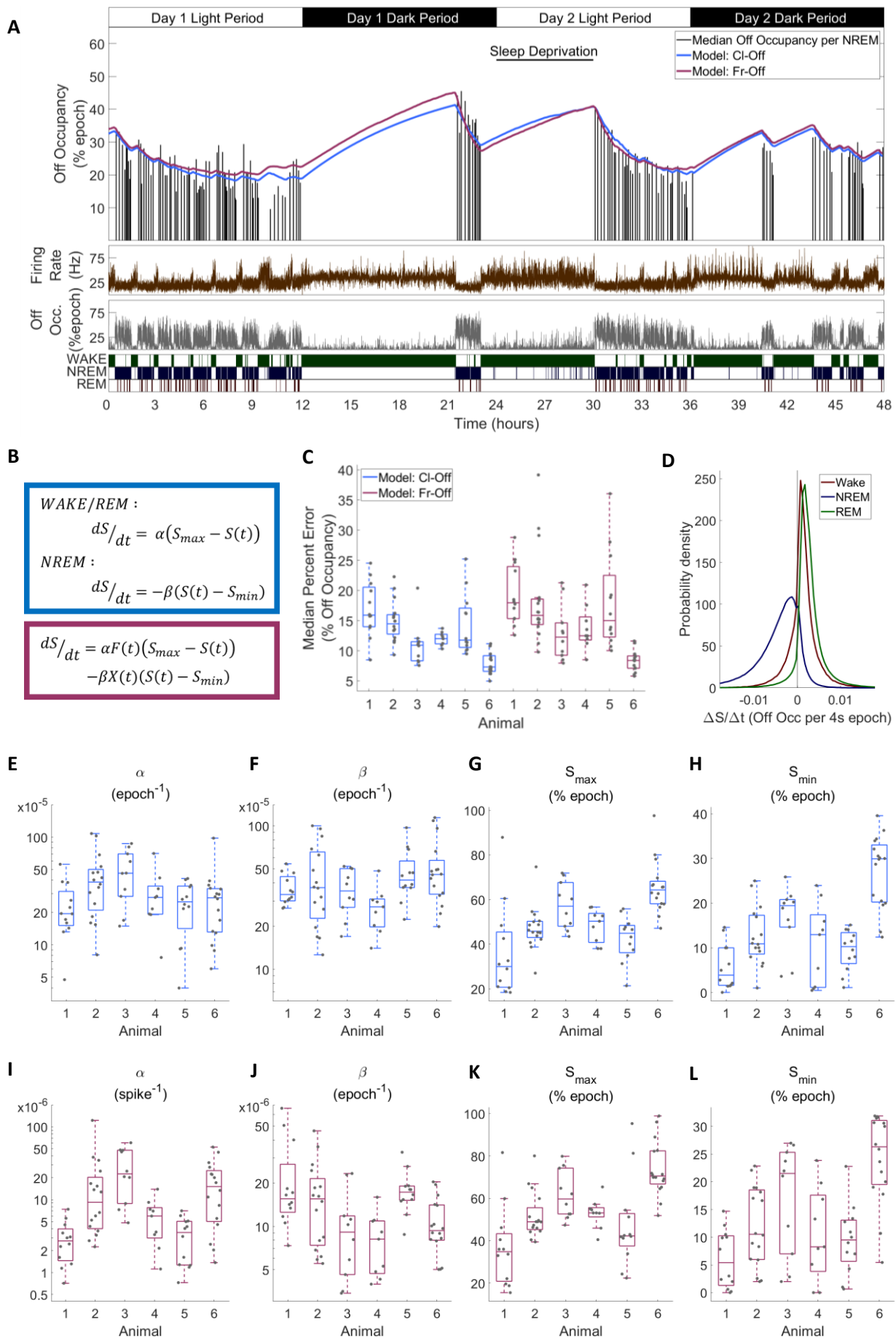


Figure 5

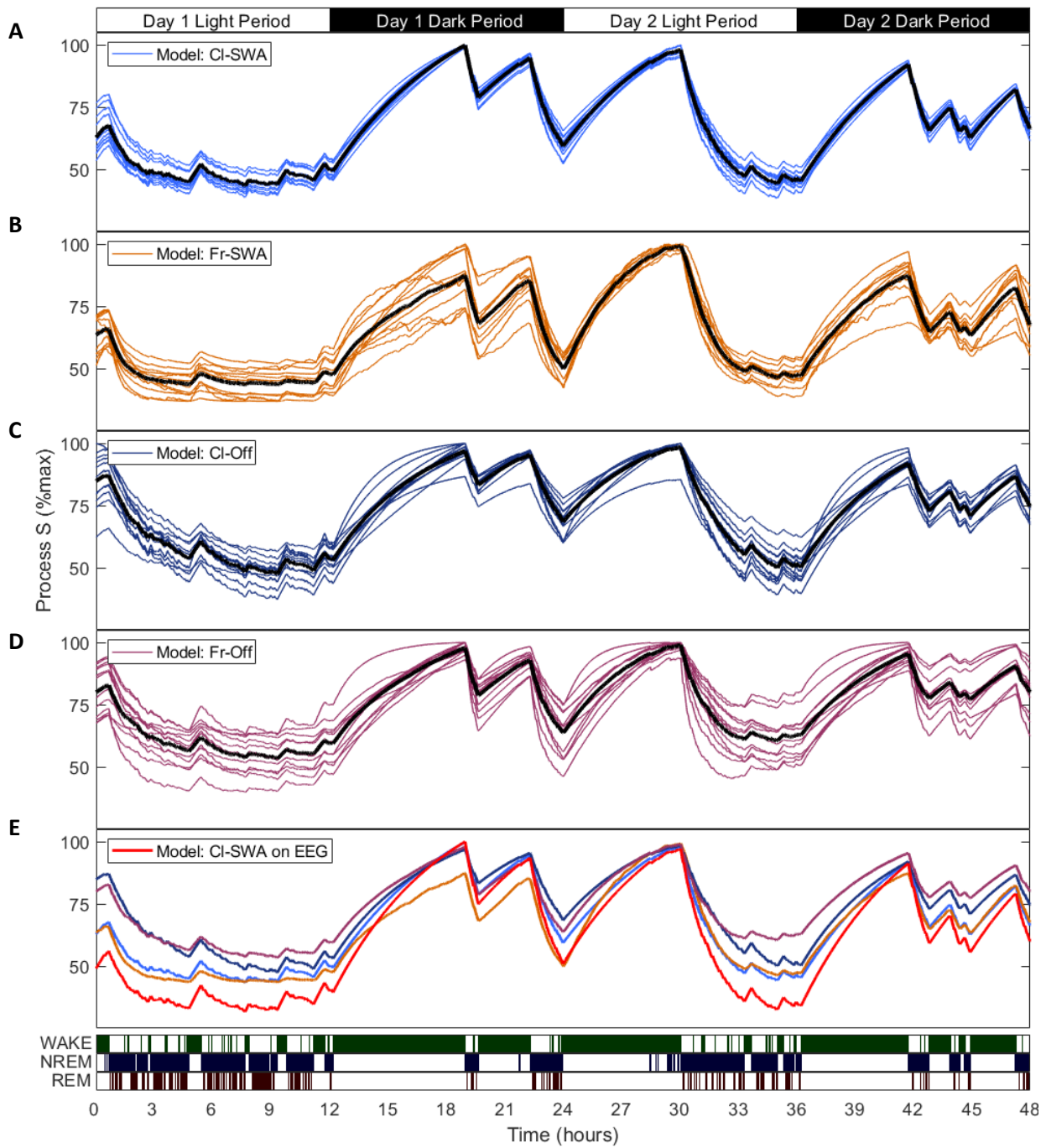


Figure 6