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Optimal Model Parameter Estimation from EEG Power Spectrum Features Observed during General Anesthesia

Meysam Hashemi¹ · Axel Hutt^{2,3} · Laure Buhry^{4,5,6} · Jamie Sleight⁷

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Abstract

Mathematical modeling is a powerful tool that enables researchers to describe the experimentally observed dynamics of complex systems. Starting with a robust model including model parameters, it is necessary to choose an appropriate set of model parameters to reproduce experimental data. However, estimating an optimal solution of the inverse problem, i.e., finding a set of model parameters that yields the best possible fit to the experimental data, is a very challenging problem. In the present work, we use different optimization algorithms based on a frequentist approach, as well as Monte Carlo Markov Chain methods based on Bayesian inference techniques to solve the considered inverse problems. We first probe two case studies with synthetic data and study models described by a stochastic non-delayed linear second-order differential equation and a stochastic linear delay differential equation. In a third case study, a thalamo-cortical neural mass model is fitted to the EEG spectral power measured during general anesthesia induced by anesthetics propofol and desflurane. We show that the proposed neural mass model fits very well to the observed EEG power spectra, particularly to the power spectral peaks within δ - (0 – 4 Hz) and α - (8 – 13 Hz) frequency ranges. Furthermore, for each case study, we perform a practical identifiability analysis by estimating the confidence regions of the parameter estimates and interpret the corresponding correlation and sensitivity matrices. Our results indicate that estimating the model parameters from analytically computed spectral power, we are able to accurately estimate the unknown parameters while avoiding the computational costs due to numerical integration of the model equations.

Keywords Parameter estimation · Optimization · Stochastic differential equation · Spectral power · General anesthesia

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Introduction

Although mathematical modeling plays a key role in describing the dynamics of complex systems, it still remains a challenging problem (Banga and Balsa-Canto 2008; van Riel 2006; Stelling 2004; Kell 2004). In order to build a successful model that allows one to reveal the mechanism underlying a complex system, we first need to select a robust model whose output is consistent with *a priori* available knowledge about the system dynamics (Kitano 2002; Rodriguez-Fernandez et al. 2006a; Rodriguez-Fernandez et al. 2013). The selected model should be able to reproduce, at least qualitatively, observed specific features in experimental data. This task is referred to as *structure identification* (Lillacci and Khammash 2010; Tashkova et al. 2011). The subsequent task is *parameter estimation* (Ashyraliyev et al. 2008, 2009). After the model identification, one needs to determine the unknown model parameters from the measurements. Since the output of a model depends on the values of its parameters, reproducing

Q1

19 specific features of the experimental measurements requires
20 selecting a suitable set of the unknown parameters. There-
21 fore, parameter estimation is a very important component of
22 the model developing procedure. Broadly speaking, given
23 a set of experimental data and a particular mathematical
24 model, the aim of parameter estimation (also known
25 as model calibration) is to identify the unknown model
26 parameters from the measurements for which substituting
27 the estimated parameters in the model equations reproduces
28 the experimental data in the best possible way (Rodriguez-
29 Fernandez et al. 2006a). Nevertheless, finding a set of model
30 parameters which accurately fits the recorded data is an
31 extremely difficult task, especially for nonlinear dynamic
32 models with many parameters and constraints. Numerical
33 integration of differential equations and finding the best
34 parameter values in the entire search domain, i.e. find-
35 ing the global minimum, are two major challenges in the
36 parameter estimation problems (Zhan and Yeung 2011). In
37 particular for biological systems, these challenges need to
38 be addressed in nonlinear high-dimensional models.

39 In general, there are two broad classes of approaches
40 for solving parameter estimation problems: the frequentist
41 (classic) inference and Bayesian (probabilistic) estimation
42 (Kimura et al. 2005; Myung 2003; Gelman et al. 2004).
43 Both approaches have been applied successfully in a wide
44 range of scientific areas with different applications while
45 one over the other is preferable in specific problems (Green
46 and Worden 2015; Prasad and Souradeep 2012; Lillacci and
47 Khammash 2010; Ashyraliyev et al. 2009). Bayesian infer-
48 ence gives the full probability distribution of the parameters
49 rather than single optimal values as in frequentist infer-
50 ence. However, the former approach is more complex and
51 more expensive in terms of computational cost than the
52 latter (Lillacci and Khammash 2010). In practice, the fre-
53 quentist framework is more simple and more suitable for
54 high-dimensional models (Tashkova et al. 2011).

55 It is important to point out that there are various algo-
56 rithms in both frequentist and Bayesian inferences, and no
57 single algorithm is the best for all problems or even for a
58 broad class of problems (Mendes and Kell 1998; Gelman
59 et al. 2004; Haario et al. 2006; Girolami and Calderhead
60 2011; Kramer et al. 2014). Specifically, in the frequentist
61 approach the choice of the optimization technique com-
62 monly depends on the nonlinearity of the model and its con-
63 straints, on the problem dimensionality as well as on the *a*
64 *priori* knowledge about the system.

65 In the present study, we employ different algorithms
66 within both frequentist and Bayesian inference frame-
67 works. As frequentist techniques, we apply the Levenberg-
68 Marquardt (LM) algorithm as a gradient descent local
69 search method, the algorithm by Hooke and Jeeves (HJ) as
direct local search method, in addition to Particle Swarm

Optimization (PSO), Differential Evolution (DE), Genetic
Algorithm (GA), and Covariance Matrix Adaptation Evolu-
tion Strategy (CMA-ES) as stochastic global search meth-
ods that have previously been compared and/or shown to
be efficient for fitting electrophysiological neuronal record-
ings (Buhry et al. 2012). We also use Metropolis-Hastings
(MH) and Simulated Annealing (SA) as the most estab-
lished Monte Carlo Markov Chain (MCMC) algorithms,
which are widely used in the Bayesian framework. Fur-
thermore, we evaluate the performance of aforementioned
algorithms to determine which method is more suitable for
each of the parameter estimation problem considered in this
study.

It is well known that the dynamics of a majority of
biological systems can be described by a set of coupled
Ordinary Differential Equations (ODEs) or Delay Differen-
tial Equations (DDEs) (Mendes and Kell 1998). Moreover,
biological systems are often subject to external random
fluctuations (noise) from signal stimuli and environmen-
tal perturbations (Daunizeau et al. 2009; Breakspear 2017).
Despite the importance of stochastic differential equations
(SDEs) in brain stimulation (Deco et al. 2009; Herrmann
et al. 2016) and describing biological systems (Wilkinson
2011; Hutt et al. 2016), their parameter inference by a
rigorous analytical approach have received relatively little
attention and substantial challenges remain in this context.
This motivated us to focus on the parameter estimation of
systems whose dynamics are governed by SDEs.

More precisely, a parameter estimation problem is shown
for a neurophysiological model describing recorded elec-
troencephalographic data (EEG) obtained under anesthesia.
We show that the proposed neural mass model is able to
fit very well to observed EEG spectral power peaks in the
 δ - (0 – 4 Hz) and α - (8 – 13 Hz) frequency ranges.
For illustration reasons, firstly two *in silico* parameter esti-
mation problems are presented using synthetic data. These
case studies consider very basic linear stochastic models and
illustrate in detail the analysis applied.

After the parameter estimation task, another important
challenge is the *identifiability* of the estimates (Ashyraliyev
et al. 2009; Rodriguez-Fernandez et al. 2006b). Identifi-
ability analysis allows one to estimate whether the model
parameters can be uniquely determined by the given exper-
imental data (Rodriguez-Fernandez et al. 2013). For each
considered case study, we employ different methods to
address this issue. The confidence regions of the estimates
are plotted and the correlation and sensitivity matrices are
analyzed to assess the accuracy of the estimates.

Several previous methods need to integrate differential
equations to estimate model parameters, which is a major
time consuming problem for the parameter estimation of
nonlinear dynamic systems (Tsai and Wang 2005). In this

121 work, we present a general methodological framework for
 122 estimating the parameters of systems described by a set of
 123 stochastic ODEs or DDEs. In our proposed scheme which
 124 is applicable in both frequentist and Bayesian inference
 125 frameworks, we compute analytically the power spectrum
 126 of model solutions by the aid of the Green's function and
 127 fit these to the spectral power of measured data. This com-
 128 bination of techniques provides high estimation accuracy
 129 in addition to a great advantage in terms of optimiza-
 130 tion speed, because it allows us to avoid the numerical
 131 integration of model equations.

132 The following section presents the acquisition proced-
 133 ure of experimental EEG under anesthesia. Then, we
 134 briefly review the parameter estimation algorithms and
 135 present the mathematical formulation of identifiability anal-
 136 ysis in details. Next, we provide the analytical derivation
 137 of system spectral power for the two synthetic case stud-
 138 ies and the thalamo-cortical model carried out in this work.
 139 The subsequent results section provides the performance
 140 of employed optimization algorithms for the synthetic and
 141 neurophysiological models. We can show the different sensi-
 142 tivity of model parameters in the thalamo-cortical model.
 143 Moreover, employing EAs yields very good model fits to the
 144 EEG spectral features within δ - and α -frequency ranges
 145 measured during general anesthesia. A final patient group
 146 study reveals which model parameters vary statistically sig-
 147 nificantly between experimental conditions and which are
 148 robust towards conditions.

149 **Materials and Methods**

150 **EEG Acquisition during General Anesthesia**

151 The details of the patient management and EEG acquisition
 152 is described in Sleigh et al. (2010). In brief, frontal (FP2-
 153 FT7 montage) EEG was obtained from adult patients under
 154 general anesthesia that was maintained using either propofol
 155 and fentanyl, or desflurane and fentanyl. The hypnotic drugs
 156 were titrated to obtain a bispectral index value of 40-50
 157 as per clinical guidelines. The EEG data were collected
 158 2 minutes before, and 2 minutes after, the initial skin
 159 incision. The signal was digitized at 128/sec and with
 160 14 bit precision. To remove line artefact it was band-pass
 161 filtered between 1 Hz and 41 Hz.

162 **Objective Function**

163 The most widely used criteria to evaluate the goodness of
 164 a model fit are the maximum likelihood estimation (MLE)
 165 and the least-squares estimation (LSE) (Bates and Watts
 1988; Villaverde and Banga 2013). MLE implies Bayesian

inference and was originally introduced by R.A. Fisher 166
 in 1912 (Aldrich 1997). It searches parameter space to 167
 obtain the parameter probability distributions that produce 168
 the observed data most likely (Kay 1993). In other words, 169
 the MLE assesses the quality of estimated parameters by 170
 maximizing the likelihood function (or equivalently the log- 171
 likelihood function which is easier to work mathematically). 172
 The likelihood function is the probability of obtaining 173
 the set of observed data, with a given set of parameter 174
 values. The set of parameters that maximizes the likelihood 175
 function is called the maximum likelihood estimator. On the 176
 other hand, choosing LSE method (frequentist inference), 177
 we search for the parameter values that minimize the 178
 sum of squared error (SSE) between the measured and 179
 the simulated data (Ljung 1999; Myung 2003). As it is 180
 widely known, if we assume that the experimental errors are 181
 independent and normally distributed and assuming that the 182
 measurement noise is uncorrelated and obeys a Gaussian 183
 distribution, the MLE is equivalent to LSE (Bates and Watts 184
 1980; Ljung 1999): 185

$$\operatorname{argmax}_p \{ \mathcal{P}(\mathbf{p}) \} = \operatorname{argmin}_p \{ \mathcal{E}(\mathbf{p}) \}, \quad (1)$$

where 186

$$\mathcal{P}(\mathbf{p}) = \ln \left(\prod_{i=1}^{N_y} \left(\frac{1}{2\pi\sigma_i^2} \right)^{\frac{1}{2}} \right) - \frac{1}{2} \left(\sum_{i=1}^N \left[\frac{(\hat{Y}_i - Y_i(t, \mathbf{p}))^2}{\sigma_i^2} \right] \right), \quad (2)$$

$$\mathcal{E}(\mathbf{p}) = \sum_{i=1}^{N_y} \left[\frac{(\hat{Y}_i - Y_i(t, \mathbf{p}))^2}{\sigma_i^2} \right], \quad (3)$$

where $\mathcal{E}(\mathbf{p})$ is the weighted least-squares fitness function, 187
 \hat{Y}_i denotes the measured data in the i -th data point, $Y_i(t, \mathbf{p})$ 188
 represents the corresponding model prediction at time point 189
 t_i , \mathbf{p} is the parameter vector being estimated, σ_i are 190
 the measurement errors (the variance of the experimental 191
 fluctuations), and N_y is the number of sampling points 192
 of the observed data. In addition, if we assume that all 193
 variances σ_i^2 are equal, Eq. 3 simplifies to the well-known 194
 chi-squared error criterion (Walter and Pronzato 1997) 195

$$\chi^2 = \sum_{i=1}^{N_y} (\hat{Y}_i - Y_i(t, \mathbf{p}))^2. \quad (4)$$

When minimizing the standard chi-squared error criterion 196
 failed to reveal the power peaks in certain frequency bands,

197 we employ a modified chi-squared error criterion referred
 198 to as the biased chi-squared function given by

$$\chi^2 = c_1 \sum_{i=1}^{N_1} (\hat{Y}_i - Y_i(t, \mathbf{p}))^2 + c_2 \sum_{i=N_1}^{N_2} (\hat{Y}_i - Y_i(t, \mathbf{p}))^2 + c_3 \sum_{i=N_2}^{N_3} (\hat{Y}_i - Y_i(t, \mathbf{p}))^2 + c_4 \sum_{i=N_3}^{N_y} (\hat{Y}_i - Y_i(t, \mathbf{p}))^2, \tag{5}$$

199 where c_1 , c_2 and c_3 c_4 are manually chosen constants
 200 depending on the observed spectral peaks in the estimation
 201 problem. Let us consider a power spectrum that exhibits
 202 two peaks in δ - (0 – 4 Hz) and α - (8 – 13 Hz) fre-
 203 quency ranges. We can choose N_1 , N_2 , and N_3 in such
 204 a way that the δ - and α - peaks fall within the ranges
 205 $[1, N_1]$ and $[N_2, N_3]$, respectively. Then, large values of c_1 ,
 206 c_3 forces the model output to be fitted with the observed
 207 spectral peaks within these frequency ranges. It is trivial that
 208 $c_1 = c_2 = c_3 = 1$ yields the standard chi-squared error
 209 criterion given by Eq. 4. To fit the model’s power spectrum
 210 to the empirical data, we take the logarithm of the spec-
 211 tral power i.e., $Y_i(t, \mathbf{p}) = \log(\text{PSD}_{model}(f_i, \mathbf{p}))$, where f_i
 212 is the i -th frequency value and \mathbf{p} contains all the unknown
 213 model parameters being estimated. Here, PSD_{model} is
 214 the analytically derived power spectrum derived in
 215 Section “Case Studies”.

216 **Parameter Estimation Algorithms**

217 Optimization methods can be broadly divided into two
 218 major groups known as local optimization methods and
 219 global optimization methods. Local optimization methods
 220 can be further subdivided into two categories. First, gra-
 221 dient based methods involve the use of derivative infor-
 222 mation, such as Levenberg-Marquardt and Gauss-Newton
 223 algorithms. Second, pattern search methods, such as Nelder-
 224 Mead simplex and Hooke-Jeeves algorithms, which involve
 225 the use of function evaluations only and do not need the
 226 derivative information. Local optimization methods start
 227 with an initial guess for the parameter values and, in
 228 order to obtain satisfactory results, one has to manually
 229 tune the initial parameters. Although the local search algo-
 230 rithms converge very rapidly to a solution, they can easily
 231 get trapped at a local minimum if the algorithm is not ini-
 232 tialized close to the global minimum (Moles et al. 2003;
 233 Mendes and Kell 1998; Rodriguez-Fernandez et al. 2006a;
 234 Hamm et al. 2007). To overcome such drawbacks, stochas-
 235 tic global optimization methods have been widely used for
 236 the solving of nonlinear optimization problems (Rodriguez-
 237 Fernandez et al. 2006b; Svensson et al. 2012; Tashkova
 238 et al. 2011). These methods need neither an initial guess for
 239 the parameters nor the gradient of the objective function.

Although stochastic global search methods cannot guaran-
 240 tee the convergence to a global optimum, they are particu-
 241 larly adapted to black-box optimization problems (Pardalos
 242 et al. 2000; Papamichail and Adjiman 2004; Lera and
 243 Dergeyev 2010). These methods are also usually more
 244 efficient in locating a global minimum than deterministic
 245 methods, which are based on the computation of gradient
 246 information (Georgieva and Jordanov 2009; Cuevas et al.
 247 2014).
 248

249 There are several types of stochastic global optimization
 250 methods, which are mostly based on biological or physical
 251 phenomena (Corne et al. 1999; Fogel 2000). Evolutionary
 252 algorithms (EAs) are stochastic search methods, which
 253 incorporate a random search principle existing in natural
 254 systems including biological evolution (e.g. GA inspired by
 255 mating and mutation), artificial evolution (if one does not
 256 deal with binary data), and social swarming behavior of
 257 living organisms. As an example for the latter algorithm,
 258 Particle Swarm Optimization is inspired by birds flocking
 259 and fish schooling.

260 In this study, we use the most popular optimization
 261 algorithms namely Levenberg-Marquardt (LM) algorithm
 262 and Hooke and Jeeves (HJ) algorithm selected from local
 263 search category, and Particle Swarm Optimization (PSO),
 264 Differential Evolution (DE), Genetic Algorithm (GA), and
 265 Covariance Matrix Adaptation Evolution Strategy (CMA-
 266 ES) from stochastic global search methods. Furthermore,
 267 we use Metropolis-Hastings (MH) and Simulated Annealing
 268 (SA) as the popular sampling algorithm belonging to Monte
 269 Carlo Markov Chain (MCMC) methods. In addition, to
 270 confirm our results obtained by MH, we have used PyMC,
 271 which is a probabilistic programming language to perform
 272 Bayesian inference in Python (Patil et al. 2010). The
 273 details of these algorithms are explained in Appendix A in
 274 Supplementary Material.

275 **Identifiability Analysis**

276 Once the model parameters have been estimated, it is nec-
 277 essary to determine the identifiability of the estimates, i.e.,
 278 whether the model parameters can be uniquely determined
 279 by the given experimental data (Raue et al. 2011, 2009;
 280 Quaiser and Monnigmann 2009). This task is referred to as
 281 *practical identifiability* of the estimates. Several approaches
 282 have been suggested to assess the reliability and accuracy
 283 of the estimated parameters. In what follows, we describe
 284 the most widely used metrics for assessing the accuracy of
 285 estimates.

286 **Confidence Regions**

287 A widely used method in statistical inference to assess
 288 the precision of estimated parameters is constructing the

289 confidence regions (Draper and Smith 1998; Rawlings et al.
290 1998). A confidence region with the confidence level of
291 $(1 - \alpha)\%$ is a region around the estimated parameter that
292 contains the true parameter with a probability of $(1 - \alpha)$.
293 Since the sum of squares function is quadratic in linear
294 models, the confidence regions for linear problems with
295 Gaussian noise can be obtained exactly as the ellipsoid (Kay
296 1993)

$$(\mathbf{p}^* - \mathbf{p})^\top C_{lin}^{-1} (\mathbf{p}^* - \mathbf{p}) \leq N_p \mathcal{F}_{N_p, N_y - N_p}^{1-\alpha} \quad (6)$$

297 It is centered at the estimated parameter \mathbf{p}^* with principal
298 axes directed along the eigenvectors of C_{lin}^{-1} , where C_{lin}
299 denotes the covariance matrix of the linear model, \mathcal{F} is
300 the Fisher distribution with N_p and $N_y - N_p$ degrees of
301 freedom, N_p and N_y are the number of model parameters
302 and the total number of data points, respectively.

303 In contrast, for nonlinear models there is no exact
304 solution to obtain the confidence regions (Marsili-Libelli
305 et al. 2003). In these cases, we have to approximate the
306 covariance matrix to extend (6) for nonlinear models leading
307 to (Seber and Wild 1997; Ljung 1999)

$$(\mathbf{p}^* - \mathbf{p})^\top C_{approx}^{-1} (\mathbf{p}^* - \mathbf{p}) \leq N_p \mathcal{F}_{N_p, N_y - N_p}^{1-\alpha} \quad (7)$$

308 Here C_{approx} is an approximation of covariance matrix and
309 it can be computed by either the Fisher information matrix
310 (represented by C_J), or the Hessian matrix (represented by
311 C_H).

312 Applying the Fisher matrix $C_J = FIM^{-1}$, the
313 approximate covariance matrix is given by (Rodriguez-
314 Fernandez et al. 2006a)

$$C_J = s^2 \left(J(\mathbf{p})^\top W J(\mathbf{p}) \right)^{-1}, \quad (8)$$

315 where $s^2 = \mathcal{E}(\mathbf{p}^*) / (N_y - N_p)$ is an unbiased approximation
316 of the measurement variance,

$$J(\mathbf{p}) = \frac{\partial Y(t, \mathbf{p})}{\partial \mathbf{p}} \Big|_{\mathbf{p}^*}$$

317 is an $N_y \times N_p$ matrix indicating the Jacobian matrix
318 evaluated at \mathbf{p}^* , and W is a weighting diagonal matrix
319 with elements $w_{ii}^2 = 1/\sigma_{ii}^2$ in the principal diagonal.
320 Consequently, by substituting (8) into (7), the confidence
321 region obtained with the Fisher matrix reads

$$(\mathbf{p}^* - \mathbf{p})^\top \left(J(\mathbf{p})^\top W J(\mathbf{p}) \right) (\mathbf{p}^* - \mathbf{p}) \leq N_p \frac{\mathcal{E}(\mathbf{p}^*)}{N_y - N_p} \times \mathcal{F}_{N_p, N_y - N_p}^{1-\alpha} \quad (9)$$

322 In another approach, the approximate covariance matrix
323 can be derived from the curvature of the objective function
324 through the Hessian matrix (Marsili-Libelli et al. 2003):

$$C_H = 2s^2 H(\mathbf{p})^{-1}, \quad (10)$$

where

$$H(\mathbf{p}) = \frac{\partial^2 \mathcal{E}(\mathbf{p})}{\partial \mathbf{p} \partial \mathbf{p}^\top} \Big|_{\mathbf{p}^*}.$$

Therefore, the confidence region based on Hessian matrix
reads

$$(\mathbf{p}^* - \mathbf{p})^\top H(\mathbf{p}) (\mathbf{p}^* - \mathbf{p}) \leq 2N_p \frac{\mathcal{E}(\mathbf{p}^*)}{N_y - N_p} \mathcal{F}_{N_p, N_y - N_p}^{1-\alpha} \quad (11)$$

325 It is important to note that if both approaches yield the
326 same confidence ellipsoids, the estimation converges to the
327 true parameters. Otherwise, any discrepancy between them
328 indicates an inaccurate estimation (Marsili-Libelli et al.
329 2003; Rodriguez-Fernandez et al. 2006b).

330 Another way of constructing the confidence regions in
331 non-linear models is known as the likelihood method. In this
332 approach, an approximate confidence region is defined as
333 all the parameter sets that satisfy (Donaldson and Schnabel
334 1985)

$$\mathcal{E}(\mathbf{p}) \leq \mathcal{E}(\mathbf{p}^*) \left(1 + \frac{N_p}{N_y - N_p} \mathcal{F}_{N_p, N_y - N_p}^{1-\alpha} \right). \quad (12)$$

335 In general, the confidence regions constructed by this
336 approach do not have to be elliptical. Furthermore, since
337 the (12) does not depend on the linearization, the confi-
338 dence regions obtained through the likelihood method are
339 more precise than those computed through the approxi-
340 mate covariance matrix (Schmeink et al. 2011). Generat-
341 ing likelihood-based confidence regions requires a large
342 number of function evaluations, which can be compu-
343 tationally expensive. Despite this fact, since minimiz-
344 ing an objective function with metaheuristic optimiza-
345 tion algorithms like PSO is performed through func-
346 tion evaluations, using them is a suitable way to
347 obtain the likelihood confidence regions (Schwaab et al.
348 2008). In this work, we employ the PSO algorithm
349 to compute the likelihood confidence regions which
350 will be compared with those obtained through the
351 covariance approximation.

Correlation Analysis

352 The correlation matrix quantifies the possible interrelation-
353 ship among the model parameters, which can be obtained
354 from the covariance matrix. The correlation coefficient
355 between the i -th and j -th parameter is defined by

$$R_{ij} = \frac{C_{ij}}{\sqrt{C_{ii} C_{jj}}} \quad (13)$$

356 where C_{ij} is the covariance between the i -th and j -th
357 parameter estimates (Rodriguez-Fernandez et al. 2006a).
358 By virtue of the conceptual definition of the correla-
359 tion coefficient, the correlation among parameters leads to

364 non-identifiability problems (Li and Vu 2013; Rodriguez-
 365 Fernandez et al. 2006b). Thus, highly correlated parameters
 366 cannot be uniquely estimated, because the output modifica-
 367 tion due to small change in one of the correlated parameter
 368 can be compensated by an appropriate change in the other
 369 parameter.

370 **Sensitivity Analysis**

371 Sensitivity analysis is an appropriate way to identify which
 372 model parameters contribute most to variations in model
 373 output due to the changes in model input (Rateitschak et al.
 374 2012). A local sensitivity coefficient measures the influence
 375 of small changes in one model parameter on the model
 376 output, while the other parameters are held constant (Ingalls
 377 2008; Zi 2011). The local sensitivity coefficients can be
 378 defined by (Brun et al. 2001)

$$\Gamma(p_j) = \mathcal{D}(J(\mathbf{p})^\top W J(\mathbf{p})), \quad (14)$$

379 where \mathcal{D} denotes the main diagonal elements of a matrix. In
 380 addition, the local sensitivity matrix can be determined by
 381 computing the curvature of the objective function through
 382 the Hessian matrix (Bates and Watts 1980)

$$\Lambda(p_j) = \mathcal{D}(H(\mathbf{p})). \quad (15)$$

383 The sensitivity analysis can shed light on the identifiabil-
 384 ity of model parameters. Making a small change in a very
 385 sensitive model parameter causes a strong response in the
 386 model output, which indicates that the parameter is more
 387 identifiable. On the contrary, a model parameter with low
 388 sensitivity is more difficult to being identified, because any
 389 modification in an insensitive parameter has no influence on
 390 the model output (Rodriguez-Fernandez et al. 2013).

391 **Case Studies**

392 Firstly, in order to illustrate the performance and capability
 393 of the parameter estimation method carried out in this work,
 394 we estimate the model parameters of two case studies:
 395 Case Study I) a stochastic damped harmonic oscillator, and
 396 Case Study II) a stochastic delayed oscillator. For each
 397 case we have generated *in silico* data, i.e., the measured
 398 data is generated artificially by adding noise to the model
 399 output obtained by simulating the model equations with
 400 a set of pre-chosen parameters referred to as the *true*
 401 values. Finally, in Case Study III) the parameters of a
 402 thalamo-ocortical model are inferred by fitting the model
 403 power spectrum to the EEG spectral power recorded under
 404 various experimental conditions. All the computations in the
 405 present work were implemented in Matlab (The Mathworks
 406 Inc., MA) on a Mac OS X machine with 2.5 GHz
 407 Intel Core i5 processor and 12 GB of 1333 MHz DDR3
 408 memory.

Case Study I: a Stochastic Damped Harmonic Oscillator 409

410 Consider a damped harmonic oscillator driven by a random
 411 stochastic force given by (Øksendal 2007)

$$\frac{d^2x}{dt^2} + \gamma \frac{dx}{dt} + \omega_0^2 x = \xi(t), \quad (16)$$

412 where ω_0 is the intrinsic angular frequency of the oscillator,
 413 and γ denotes the damping coefficient. The additive
 414 Gaussian white noise $\xi(t)$ obeys

$$\langle \xi(t) \rangle = 0, \quad \langle \xi(t)\xi(t') \rangle = 2\kappa\delta(t - t'), \quad (17)$$

415 where κ is the intensity of the uncorrelated driving noise,
 416 and $\langle \cdot \rangle$ denotes the ensemble average (Risken 1984; 1996).
 417 Using the Wiener-Khinchin theorem, the power spectrum
 418 of the stochastic differential equation (16) reads (Wang and
 419 Uhlenbeck 1945; Masoliver and Porrá 1993)

$$P(\omega) = \frac{2\kappa}{\sqrt{2\pi}} \frac{1}{(\omega^2 - \omega_0^2)^2 + \gamma^2\omega^2}, \quad (18)$$

420 where $\omega = 2\pi f$ denotes the angular frequency. It can
 421 be shown that the only maximum of $P(\omega)$ is located at
 422 $\omega_{max} = \sqrt{\omega_0^2 - \gamma^2/2}$, where $f_0 = \omega_0/2\pi$ is the resonant
 423 frequency of the system. In this case study, the vector of
 424 unknown parameters being estimated is $\mathbf{p}_I = (\kappa, \gamma, f_0)$
 425 with the constraint $\kappa, \gamma, f_0 > 0$.

Case Study II: a Stochastic Linear Delayed Oscillator 426

427 Consider a linear scalar delay differential equation in the
 428 presence of additive white noise given by

$$\frac{dy(t)}{dt} = ay(t) + by(t - \tau) + \xi(t). \quad (19)$$

429 where the noise $\xi(t)$ obeys the properties given by Eq. 17.
 430 The power spectrum of the corresponding solution is

$$P(\omega) = \frac{2\kappa}{\sqrt{2\pi}} \frac{1}{(a + b \cos(\omega\tau))^2 + (\omega + b \sin(\omega\tau))^2}, \quad (20)$$

431 where κ is the intensity of the additive white Gaussian noise.
 432 In this case study the vector of unknown parameters being
 433 estimated is $\mathbf{p}_{II} = (\kappa, a, b, \tau)$, where $\kappa > 0, \tau > 0$, and
 434 $a, b \in \mathbb{R}$.

Case Study III: a Thalamo-Cortical Model Reproducing the EEG Rhythms 435
 436

437 Case Study III aims to estimate the parameters of a
 438 neural mass model by fitting the power spectrum of
 439 the system to the recorded EEG data during awake and
 440 anesthesia conditions. To this end, we consider a reduced
 441 thalamo-cortical neuronal population model, which is able
 442 to reproduce the characteristic spectral changes in EEG
 443 rhythms observed experimentally during propofol-induced
 444

444 anesthesia (Hashemi et al. 2014; 2015). In the following,
 445 the model equations are given, then we derive the analytical
 446 expression for EEG power spectrum which will be fitted to
 447 the empirical spectra.

448 Consider the thalamo-cortical system shown schemati-
 449 cally in Fig. 1. The model consists of a network of three
 450 populations of neurons: cortical pyramidal neurons (E),
 451 thalamo-cortical relay neurons (S) which both are excita-
 452 tory glutamatergic neurons, and thalamic reticular nucleus
 453 (R) which is a thin shell of GABAergic cells surrounding
 454 the thalamus. The cortical pyramidal neurons (E) receives
 455 excitatory input from thalamo-cortical relay neurons (S)
 456 and projects back to the same nucleus. This reciprocal
 457 long-range excitatory interaction would generates a positive
 458 feedback which is associated with a conduction delay τ .
 459 However, the incessant excitation in this loop is prevented
 460 by the interposed inhibition to thalamo-cortical relay neu-
 461 rons (S) which originates from thalamic reticular nucleus
 462 (R). The thalamic reticular nucleus (R) receive excitatory
 463 input from axon collaterals of the cortical pyramidal neu-
 464 rons (E) and thalamo-cortical relay neurons (S), which the
 465 former input is associated with a constant time delay τ
 466 (Robinson et al. 2001a; Victor et al. 2011).

467 Following Hashemi et al. (2014, 2015), we denote the
 468 excitatory and inhibitory postsynaptic potentials (PSPs)

in the model's neuronal populations by V_a^c , where $a \in$ 469
 $\{E, R, S\}$ represents the pyramidal (E), relay (S), and 470
 reticular (R) neurons, respectively, and $c \in \{e, i\}$ indicates 471
 the excitatory and inhibitory synapses, respectively. The 472
 system dynamics are governed by the following set of 473
 coupled delay differential equations 474

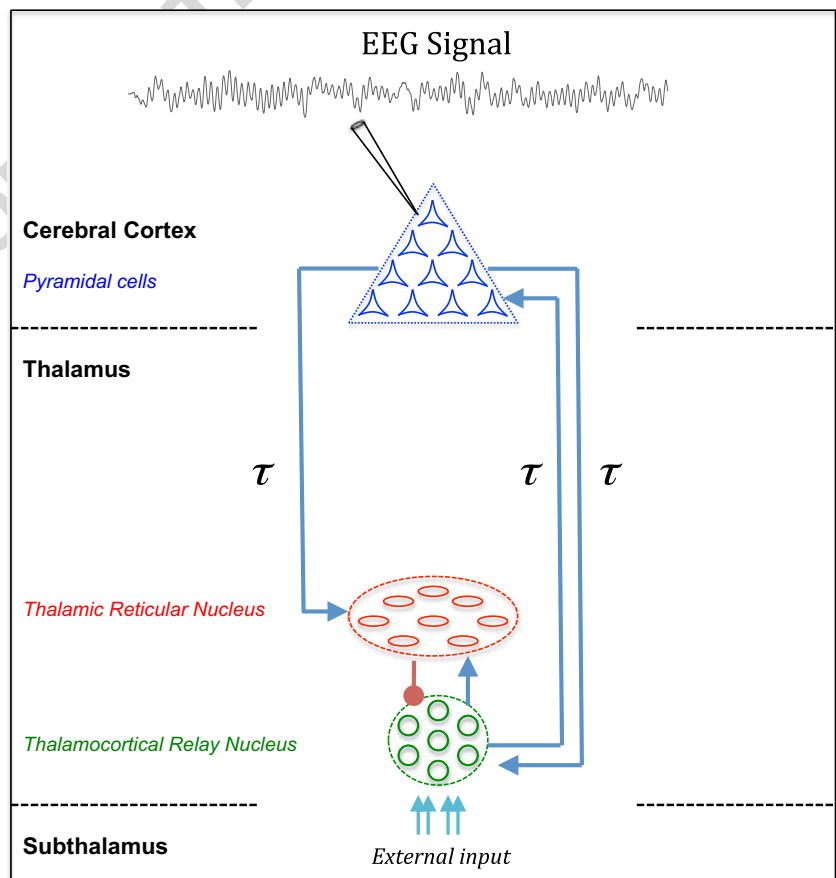
$$\begin{aligned} \hat{L}_e V_E^e(t) &= K_{ES} S_S [V_S^e(t - \tau) - V_S^i(t - \tau)], \\ \hat{L}_e V_S^e(t) &= K_{SE} S_E [V_E^e(t - \tau)] + I(t), \\ \hat{L}_i V_S^i(t) &= K_{SR} S_R [V_R^e(t)], \\ \hat{L}_e V_R^e(t) &= K_{RE} S_E [V_E^e(t - \tau)] + K_{RS} S_S [V_S^e(t) - V_S^i(t)] \end{aligned} \quad (21)$$

where the parameters K_{ab} are the synaptic connection stren- 475
 gths in population a originating from population b and τ is 476
 the transmission time delay between cortex and thalamus. 477
 The additional activity $I(t)$ introduces an external input to the 478
 system considered as a non-specific input to relay neurons 479

$$I(t) = I_0 + \xi(t), \quad (22)$$

where I_0 is the input mean value, and the noise $\xi(t)$ obeys 480
 the properties given by Eq. 17. According to previous 481
 studies, we assume that the EEG can be described in a 482
 good approximation by spatially constant neural population 483
 activity (Robinson et al. 2001a, b, 2002). Thus, under the 484

Fig. 1 Schematic diagram of the reduced thalamo-cortical model. The excitatory connections (glutamatergic) are indicated with blue arrows, while the inhibitory connections (GABAergic) are represented by red lines with filled circle ends. The connections between cortical pyramidal neurons (E) and the thalamus consisting of thalamocortical relay neurons (S) and thalamic reticular nucleus (R) are associated with a constant time delay τ



485 assumption of the spatial homogeneity, mean post-synaptic
 486 potentials in above equations do not depend on spatial
 487 locations. The parameters $S_a[\cdot]$ describe the mean firing rate
 488 functions for neuronal populations $a \in \{E, S, R\}$, in which
 489 they are generally considered as a standard sigmoid function

$$S_a(V) = \frac{S_a^{max}}{1 + e^{-c(V-V_a^{th})}}, \quad (23)$$

490 where S_a^{max} is the maximum firing rate of population a ,
 491 V_a^{th} indicates the mean firing threshold, and c denotes the
 492 slope of the sigmoid function at the inflexion-point V^{th} . The
 493 temporal operators $\hat{L}_{e,i}$ are given by

$$\hat{L}_e(\partial/\partial t) = \frac{1}{\alpha_e \beta_e} \frac{\partial^2}{\partial t^2} + \left(\frac{1}{\alpha_e} + \frac{1}{\beta_e}\right) \frac{\partial}{\partial t} + 1, \quad (24)$$

$$\hat{L}_i(\partial/\partial t) = \frac{1}{\alpha_i \beta_i} \frac{\partial^2}{\partial t^2} + \left(\frac{1}{\alpha_i} + \frac{1}{\beta_i}\right) \frac{\partial}{\partial t} + 1,$$

494 with $\alpha_e > \beta_e$, and $\alpha_i > \beta_i$, where α_e and α_i indicate the
 495 synaptic rise rates of the response functions for excitatory
 496 and inhibitory synapses in s^{-1} , respectively, and β_e and β_i
 497 denote the corresponding decay rate constants. Moreover,
 498 the delay term, τ , is zero if both the sending and receiving
 499 populations are in the thalamus while for the thalamo-
 500 cortical or cortico-thalamic pathways, the delay term is
 501 nonzero. For further details on model equation derivation
 502 see Hashemi et al. (2015).

503 Finally, since we assume that the EEG is generated
 504 by the activity of pyramidal cortical cells (Nunez and
 505 Srinivasan 2006; Rennie et al. 2002), and by virtue of the
 506 specific choice of external input to relay neurons, the power
 507 spectrum of the EEG just depends on one matrix component
 508 of the Green's function by (Hutt 2013; Hashemi et al. 2015)

$$P_E(\omega) = 2\kappa\sqrt{2\pi} \left| \tilde{G}_{1,2}(\omega) \right|^2, \quad (25)$$

509 where

$$\tilde{G}_{1,2}(\omega) = \frac{-K_1 \hat{L}_i e^{-i\omega\tau}}{\hat{L}_e(\hat{L}_e \hat{L}_i + G_{srs}) + e^{-2i\omega\tau}(G_{esre} - G_{ese} \hat{L}_i)}, \quad (26)$$

510 with $G_{ese} = K_1 K_2$, $G_{srs} = K_3 K_5$ and $G_{esre} = K_1 K_3 K_4$,
 511 and

$$\begin{aligned} \hat{L}_e &= \left(1 + \frac{i\omega}{\alpha_e}\right) \left(1 + \frac{i\omega}{\beta_e}\right), & \hat{L}_i &= \left(1 + \frac{i\omega}{\alpha_i}\right) \left(1 + \frac{i\omega}{\beta_i}\right), \\ K_1 &= K_{ES} \frac{dS_S[V]}{dV} \Big|_{V=(V_S^{*e}-V_S^{*i})}, & K_2 &= K_{SE} \frac{dS_E[V]}{dV} \Big|_{V=V_E^{*e}}, \\ K_3 &= K_{SR} \frac{dS_R[V]}{dV} \Big|_{V=V_R^{*e}}, & K_4 &= K_{RE} \frac{dS_E[V]}{dV} \Big|_{V=V_E^{*e}}, \\ K_5 &= K_{RS} \frac{dS_S[V]}{dV} \Big|_{V=(V_S^{*e}-V_S^{*i})}. \end{aligned}$$

512 In a reasonable approximation, we assume an instanta-
 513 neous rise of the synaptic response function followed by an
 514 exponential decay i.e., $\alpha_e \gg \beta_e$, and $\alpha_i \gg \beta_i$ (Hashemi

et al. 2017). This approximation reduces the second-order
 temporal operators $\hat{L}_{e,i}$ given by Eq. 24 to the first-order
 operators $\hat{L}_e = 1 + i\omega/\beta_e$, and $\hat{L}_i = 1 + i\omega/\beta_i$. Using
 this approximation, the sixth-order characteristic equation
 (the denominator of $\tilde{G}_{1,2}$ given by Eq. 26) simplifies to a
 third-order equation, which is more analytically tractable.
 In our previous study (Hashemi et al. 2017), we have
 shown that this simplification does not affect the spectral
 power in the delta and alpha ranges. Moreover, it is widely
 accepted that anesthetic agent propofol prolongs the tempo-
 ral decay phase of inhibitory synapses while the rise rates
 remain unaffected (Hutt and Longtin 2009; Hutt et al. 2015;
 Hashemi et al. 2014, 2015).

Taken together, by fitting the power spectrum of EEG given
 by Eq. 25 to the empirical spectra, we aim to estimate seven
 model parameters, namely, the power normalization $D =$
 $\sqrt{2\kappa K_1}$, the excitatory and inhibitory synaptic decay rates β_e ,
 and β_i , respectively, the axonal propagation delay τ , and the
 closed-loop gains G_{ese} , G_{srs} , and G_{esre} . Thus, the vector
 of unknown parameters being estimated is $\mathbf{p}_{III} = (D, \tau,$
 $\beta_e, \beta_i, G_{ese}, G_{srs}, G_{esre})$, where based on the physiological
 limits, all the parameters are restricted to be positive.

Furthermore, there are six inequality constraints on
 system parameters, which will be imposed over the chi-
 squared error function in spectral fitting problem. The
 first constraint is related to the synaptic rise and decay
 rate constants. Since response functions for the excitatory
 synapses exhibit a longer characteristic rise and decay times
 than the inhibitory synapses, thus $\alpha_e > \alpha_i$, and $\beta_e > \beta_i$
 (Constraint I). Following the analytical approach described
 in Forde and Nelson (2004) to obtain stability conditions
 for characteristic equation of DDEs, we have derived five
 analytical conditions for the stability of the considered
 thalamo-cortical system. According to this approach, we
 first investigate the conditions under which the system is
 stable in the absence of time delay ($\tau = 0$). Then, by
 increasing the delay value ($\tau > 0$), we seek to determine
 whether there exists a critical delay value for which
 the system becomes unstable. Since the power spectrum
 analysis is valid only if the system resting state is stable, we
 probe the conditions under which the introduction of time
 delay cannot cause a bifurcation. The following conditions
 guarantee that the system is stable when $\tau = 0$, and
 increasing the delay value does not change the stability of
 the system (see (Hashemi et al. 2017) for the details):

$$\beta_i(2 + G_{srs}) + \beta_e(1 - G_{ese}) > 0, \quad (\text{Constraint II})$$

$$1 + G_{esre} + G_{srs} - G_{ese} > 0, \quad (\text{Constraint III})$$

$$(2\beta_e + \beta_i) \left(\frac{2 + G_{srs}}{\beta_e} + \frac{1 - G_{ese}}{\beta_i} \right) - (1 + G_{esre} + G_{srs} - G_{ese}) > 0, \quad (\text{Constraint IV})$$

$$(\beta_e^2 \beta_i)^2 \left((1 + G_{srs})^2 - (G_{esre} - G_{ese})^2 \right) > 0, \quad (\text{Constraint V})$$

$$\Delta = 18\xi_2\xi_1\xi_0 - 4\xi_2^3\xi_0 + \xi_2^2\xi_1^2 - 4\xi_1^3 - 27\xi_0^2 < 0. \quad (\text{Constraint VI})$$

560 Results

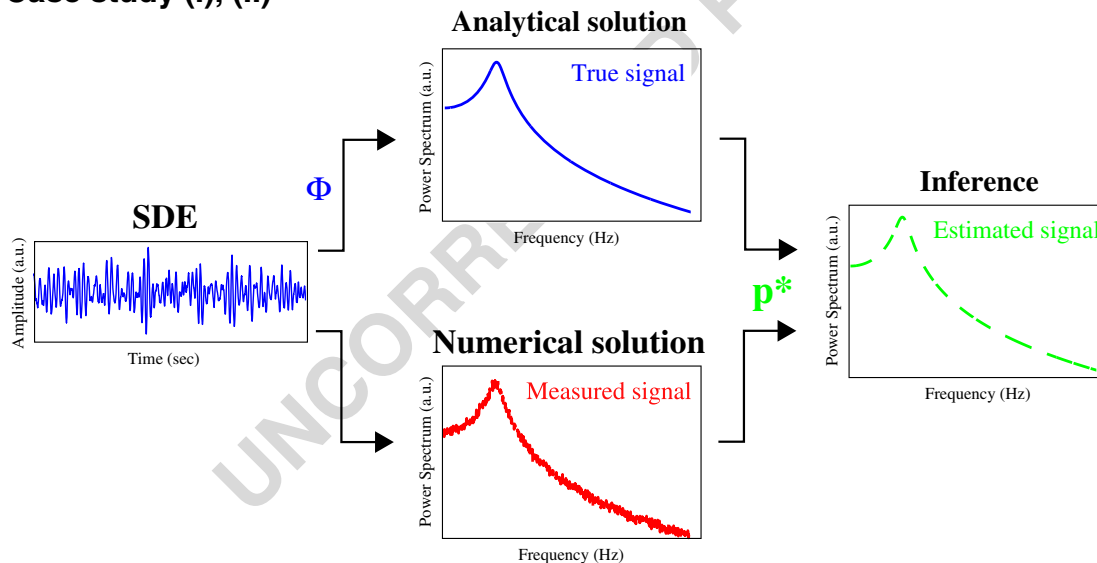
561 In the following, the results of model parameter estimation
 562 for the case studies described in the previous section are
 563 presented. The first two case studies aim to illustrate
 564 important features of the methods applied laying the ground
 565 for the analysis of recorded experimental data by a thalamo-
 566 cortical model. An outline of the parameter inference in
 567 this study is illustrated in Fig. 2. In Case Study I and
 568 II, the unknown parameters of set of SDEs (stochastic
 569 ordinary and delay differential equation, respectively) are
 570 inferred from pseudo-experimental data. As can be observed
 571 from the schematic illustration, in order to estimate the
 572 unknown parameters of a set of SDE, we transform the
 573 observation from time-domain to frequency-domain data.
 574 To this end, the power spectrum of the system is computed
 575 analytically by the aid of the Green's function to generate
 576 the true signal, i.e. the signal constructed by the nominal
 577 (true) parameters. In addition, the system spectral power
 578 is calculated numerically to acquire the measurement

579 signal by applying the Welch method. Then, the model
 580 parameters are estimated by fitting the experimental data to
 581 the corresponding model power spectrum. In general, the
 582 generated *in silico* data can be mathematically expressed
 583 as $\Psi = \Phi + noise$, where Φ and Ψ denote the noise-
 584 free observation (true signal) and the corresponding noisy
 585 data (measured signal), respectively. Finally, in the main
 586 Case Study III, the proposed parameter inference method
 587 is applied to the real experimental data set to estimate the
 588 parameters of a neural mass thalamo-cortical model (true
 589 signal) from the EEG spectral power (measured signal).

Case Study I

591 Case Study I deals with estimating the parameters of a
 592 stochastic damped harmonic oscillator by fitting the model's
 593 spectrum to a set of pseudo-experimental data. The result
 594 of this estimation is shown in Fig. 3. In Fig. 3a, the
 595 estimated power spectrum obtained by PSO is compared
 596 with the respective noise-free and the noisy spectra. From

Case study (I), (II)



Case study (III)

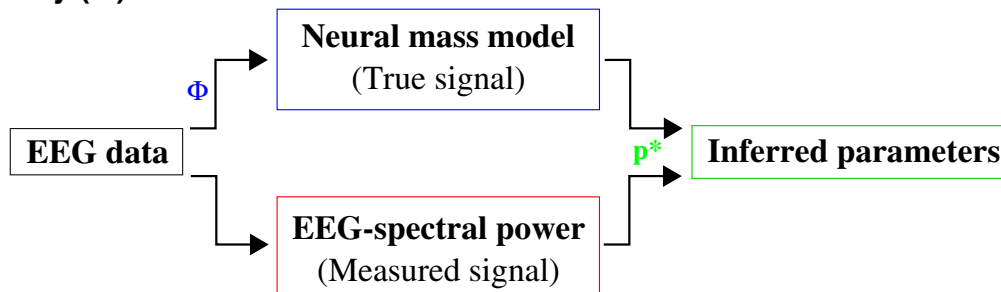


Fig. 2 Schematic illustration of parameter inference carried out in this work. In Case studies I and II, the true signal (analytical power spectrum, Φ) is fitted to the measured signal (numerical power spectrum,

Ψ). In a similar manner applied to real data measurement, in Case study III, the power spectrum of a neural mass model (true signal) is fitted to the EEG spectral power (measured signal)

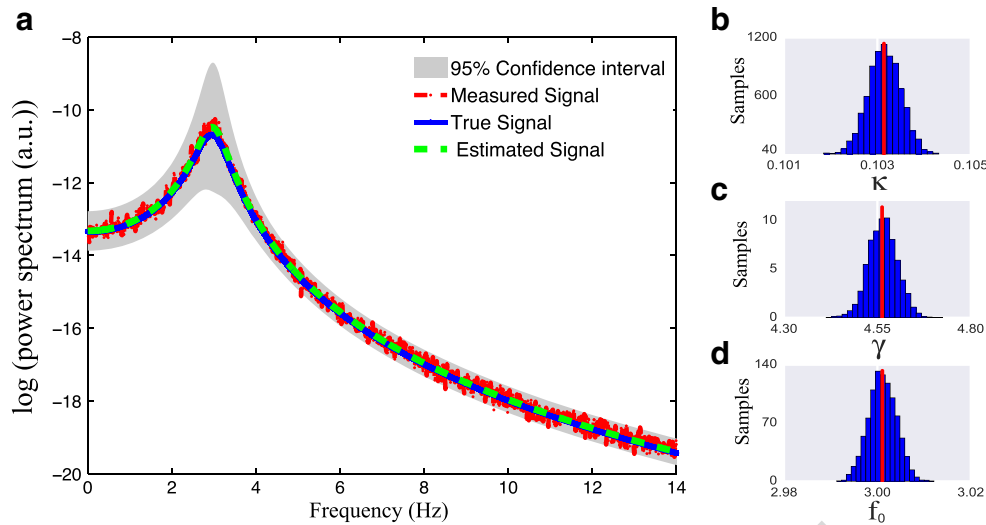


Fig. 3 Parameter estimation of a stochastic damped harmonic oscillator (Case Study I) from a set of noisy *in silico* data. **a** Estimated power spectrum is plotted versus the noise-free and the noisy spectrum, encoded in dashed green, solid blue, and dashed red lines, respectively. In addition, the grey shaded area represents the 95% confidence interval. The true and estimated parameters obtained by PSO are

$p_I = (\kappa, \gamma, f_0) = (0.1 \text{ mV}, 5.0 \text{ Hz}, 3.0 \text{ Hz})$, and $p_I^* = (\kappa, \gamma, f_0) = (0.103 \text{ mV}, 4.562 \text{ Hz}, 3.00 \text{ Hz})$, respectively. **b**, **c**, **d** Histogram of Markov chains constructed by the MH algorithm for parameters κ , γ and f_0 , respectively. The mean value of Markov chains (vertical red lines) indicate near identical estimates with those obtained by the PSO algorithm

597 the result, we observe that the estimated power spectrum
 598 is in very good agreement with the power spectrum
 599 computed from the given signal. The noise-free power
 600 spectrum was generated according to Eq. 18 with the true
 601 parameters $p_I = (\kappa, \gamma, f_0) = (0.1 \text{ mV}, 5.0 \text{ Hz}, 3.0 \text{ Hz})$.
 602 The estimated parameters $p_I^* = (\kappa, \gamma, f_0) = (0.103 \text{ mV},$
 603 $4.562 \text{ Hz}, 3.00 \text{ Hz})$ are very close to the true parameters p_I
 604 and yield the best-fit value $\mathcal{E}(p_I^*) = 0.6554$. It is worth
 605 pointing out that other EAs such as GA and DE yield similar
 606 estimations.

607 Moreover, using MCMC methods we can produce an
 608 estimate of the means and standard deviations of the inferred
 609 parameters. The histogram of Markov Chains constructed
 610 by the MH algorithm for model parameters κ , γ , and
 611 f_0 are shown in Fig. 3b, c and d, respectively. One can
 612 see that the Markov chains obey a Gaussian distribution,
 613 where the mean values (vertical red lines) indicate near
 614 identical estimates with those obtained by PSO algorithm.
 615 This result represents a very close agreement between the
 616 MLE and LSE obtained by the MH and the PSO algorithm,
 617 respectively.

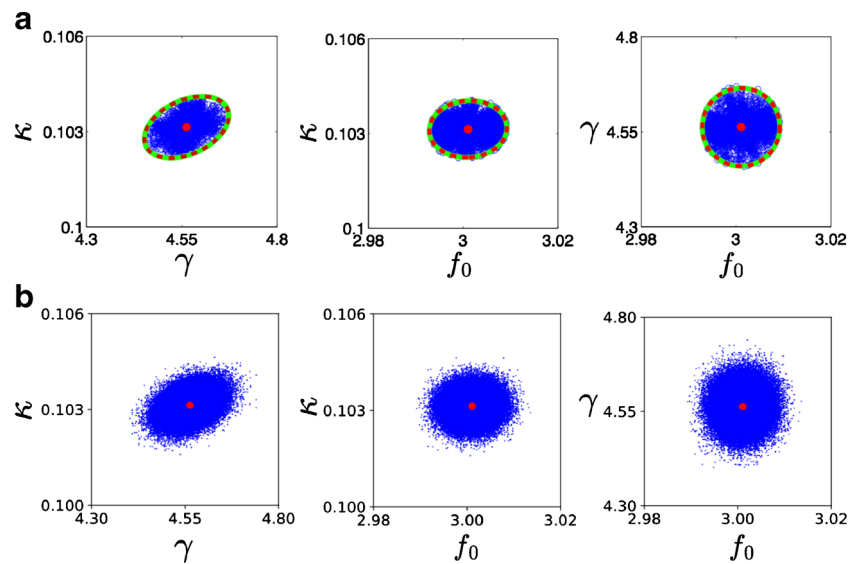
618 Once the model parameters have been inferred, one can
 619 determine the uncertainties in the parameter estimations.
 620 In order to assess the accuracy of the estimates shown in
 621 Fig. 3, we plot the confidence regions of the calibrated
 622 parameters. Figure 4 illustrates the 95% confidence regions
 623 for different pairs of parameter estimates in Case Study I.
 624 Covariance matrix estimation yields elliptical confidence
 625 regions, whereas the likelihood confidence regions are
 626 estimated by PSO algorithm. Since $J(p^*)^T W J(p^*) =$

$2H(p^*)$ the covariance matrix approximated by the Fisher 627
 Information Matrix (cf. Eq. 9) and Hessian matrix (cf. 628
 Eq. 11) are equal. This yields identical elliptical confidence 629
 regions, cf. dashed red and green lines in Fig. 4a. 630
 Considering the conceptual difference of Hessian and FIM 631
 approaches in the derivative terms, the exact coincidence 632
 of the ellipsoids obtained by these methods confirms that 633
 the accuracy in parameter estimations are well captured 634
 (Marsili-Libelli et al. 2003). Moreover, comparing the 635
 likelihood confidence regions (calculated from Eq. 12) 636
 with the elliptical confidence regions indicates that high 637
 inference precision have been obtained by PSO algorithm. 638
 This demonstrates further the benefits of the PSO algorithm 639
 in estimating the model parameters combined with a 640
 simultaneous computation of the confidence estimates. 641

To further confirm the reliability of the obtained 642
 confidence regions, we have also computed the 95% 643
 confidence regions by PyMC package (Patil et al. 2010). As 644
 presented in Fig. 4b, one observes very good agreement with 645
 the results illustrated in panel a. 646

An easy way to study the practical identifiability of an 647
 estimation is to plot the correlation matrix of the model 648
 parameters. Here, the local identifiability of the obtained 649
 estimations is evaluated based on the correlation analysis. 650
 For Case Study I, Fig. 5 displays the absolute value of 651
 the correlation coefficients obtained according to Eq. 13. 652
 The figure shows low correlation values in non-diagonal 653
 elements. The lack of correlation between the estimated 654
 parameters indicates that all the parameters are identifiable. 655
 Furthermore, we have carried out the sensitivity analysis 656

Fig. 4 Comparison of 95% confidence regions for different pairs of parameter estimates in Case Study I. **a** The ellipsoids encoded in dashed red and green lines show the confidence regions obtained by approximating the covariance matrix through the use of FIM and Hessian approaches, respectively. The regions constructed by the blue markers indicate the likelihood confidence regions produced by the PSO algorithm. **b** Confidence regions for model parameters obtained by MH algorithm. The regions are centered at the optimal parameters p_{II}^* illustrated by the filled red circles



657 for this case study (see the relevant result presented in
658 Appendix B in Supplementary Material) revealing that the
659 estimated parameters in this case study are captured in an
660 accurate manner.

661 Further it is interesting to take a closer look at the
662 convergence speed of different algorithms carried out in
663 Case Study I. Figure 6 shows the convergence functions,
664 i.e., The fitness values versus the function evaluations, for
665 LM, HJ, PSO, DE, GA, CMA-ES, MH, and SA algorithms
666 averaged over 100 runs. Although the fitness function of
667 all algorithms finally reach the global minimum, the local
668 search algorithms (LM and HJ) show a faster convergence
669 speed compared to the others, whereas the EAs (including
670 PSO, DE, GA, CMA-ES) indicate faster convergence
671 than MH and SA as MCMC algorithms. In addition, SA

converges finally to the minimum value in a damping
manner (when the temperature is reduced toward zero). In
contrast, the fitness function of MH keeps oscillating about
the minimum value.

Case Study II

In Case Study II, the power spectrum of a linear SDDE
is fit to a set of pseudo-experimental data. Note that this
case study poses a multimodal objective function, which is
a more challenging problem in finding the global minimum
compared to Case Study I as an example of unimodal
functions. Figure 7 illustrates the parameter inference of
the SDDE from a noisy measurement. The estimated power
spectrum shows a striking close match to the reference
spectrum in Fig. 7a. Here, the noise-free observations
are generated by substituting the true parameters $p_{II} =$
 $(\kappa, a, b, \tau) = (0.1 \text{ mV}, -17.3, -21.32, 0.2)$ in Eq. 20.
The fit based on PSO yields the optimal parameters
 $p_{II}^* = (\kappa, a, b, \tau) = (0.103 \text{ mV}, -18.4, -21.49, 0.2)$,
that is in very good agreement with the original model
parameters. The corresponding estimation's fitness function
value is $\mathcal{E}(p_{II}^*) = 33.19$. Furthermore, the histograms
of Markov Chains constructed by the MH algorithm for
model parameters κ, a, b and τ are shown in Fig. 7b–e,
respectively. We observe that the estimates calculated by
the MH (vertical red lines) are very close to those obtained
by PSO algorithm.

Figure 8 displays the confidence regions for all possible
pairs of the estimated parameters in Case Study II. Similar
to Case Study I, the elliptical confidence regions are
computed by covariance matrix estimation according to
Eqs. 9, and 11, whereas the likelihood confidence regions
are provided by PSO according to Eq. 12. One can see that
the ellipsoids constructed with covariance matrix estimation

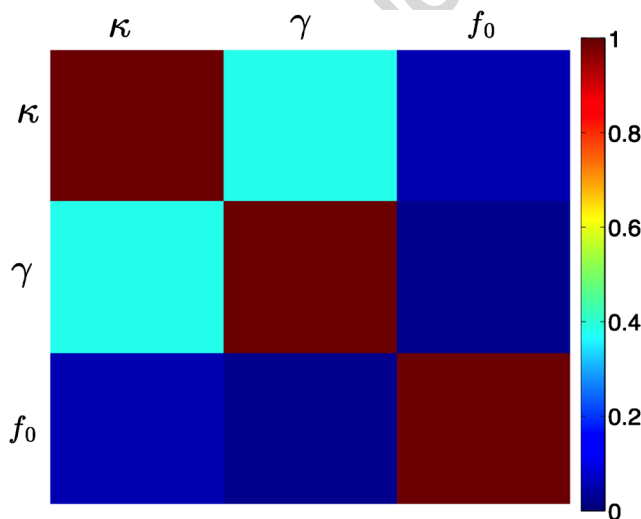
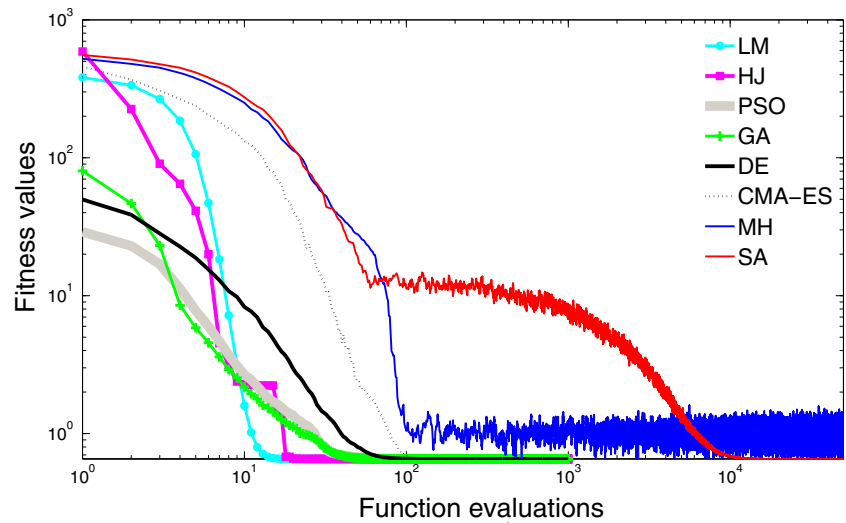


Fig. 5 Correlation matrix for Case Study I. The figure shows the absolute value of the correlation coefficients indicating lack of correlation between the estimated model parameters $\kappa, \gamma,$ and f_0

Fig. 6 Convergence functions of several optimization algorithms used in Case Study I. The fitness values versus the function evaluations in a log-log scale for different algorithms: LM and HJ as local search algorithm, PSO, DE, GA, CMA-ES from global search algorithms, and MH and SA known as sampling algorithms



705 using FIM and Hessian matrix coincide, because in this case
 706 study $J(\mathbf{p}^*)^T W J(\mathbf{p}^*) = 2H(\mathbf{p}^*)$. However, comparing
 707 the elliptical and likelihood confidence regions, there is
 708 a discrepancy between the regions evaluated based on
 709 covariance matrix and those computed through the PSO
 710 method.

711 In order to identify the origin of the discrepancy between
 712 elliptical and likelihood confidence regions observed in
 713 Fig. 8, we investigate the correlation among the model
 714 parameters. Figure 9 represents the correlation matrix of
 715 the model parameters in case study II. If two parameters
 716 are highly correlated, the change in model output caused
 717 by change in one parameter can be compensated by an

appropriate change in the other parameter. This prevents
 the parameters from being uniquely identifiable. In other
 words, for a pair of correlated parameters there exist many
 combinations that give almost the same value of fitness
 function. This aspect reflects a degeneracy of solutions,
 resulting from the non-uniqueness of the inverse problem
 solution. According to the absolute value of the correlation
 coefficients plotted in Fig. 9a, the parameters a and b are
 practically non-identifiable since they are highly correlated,
 whereas other pairs of parameters are uncorrelated. To
 overcome such problem, the pairs of correlated parameters
 must be removed analytically by introduction of new
 variables. In this case study, setting a candidate solution in

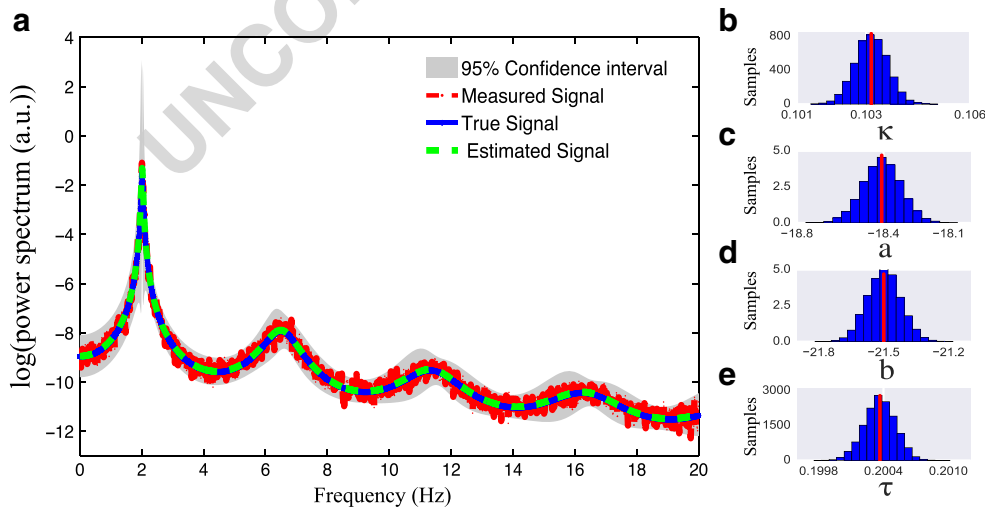
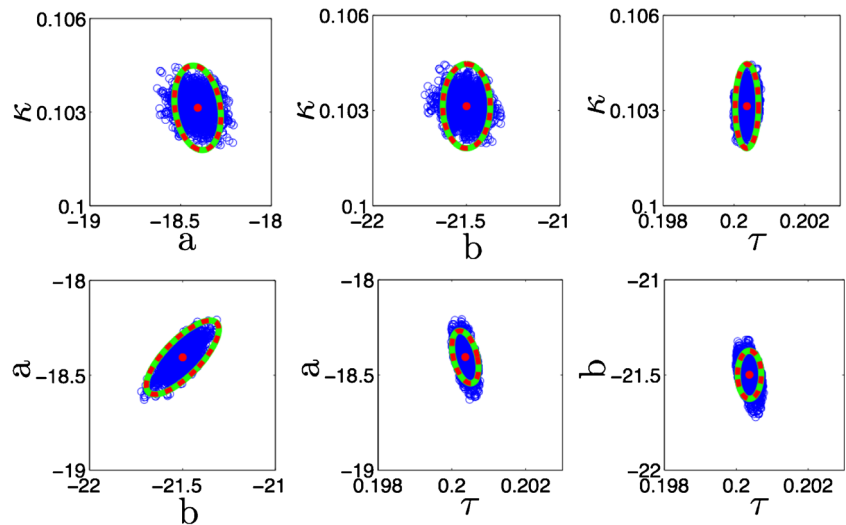


Fig. 7 Inferring the parameter values of a stochastic linear delay differential equation (Case Study II) from a set of *in silico* data. **a** The estimated power spectrum (dashed green line), the corresponding noise-free spectrum (blue line) and the spectrum from noisy measured data (dashed red line). The grey shaded area encodes the 95% confidence interval. The true and estimated parameters are

$p_{II} = (\kappa, a, b, \tau) = (0.1 \text{ mV}, -17.3, -21.32, 0.2)$, and $p_{II}^* = (\kappa, a, b, \tau) = (0.103 \text{ mV}, -18.4, -21.49, 0.2)$, respectively. **b, c, d, e** Histograms of Markov chains constructed by the MH algorithm for parameters κ , a , b and τ , respectively. The mean value of generated Markov chains (vertical red lines) are very close to the estimates obtained by the PSO algorithm

Fig. 8 Elliptical and likelihood confidence regions at 95% confidence level for each pair of estimated parameters in Case Study II. The ellipsoids are computed with the FIM information (in dashed red) and Hessian matrix (in green), whereas the likelihood confidence regions (in blue) are estimated by the PSO algorithm. The estimated parameters $\mathbf{p}_{II}^* = (\kappa, a, b, \tau) = (0.103 \text{ mV}, -18.4, -21.49, 0.201)$ are represented by filled red circles



731 the form of $y(t) = Ce^{\lambda t}$ yields the following nonlinear
 732 transcendental characteristic equation:

$$\lambda - a - be^{-\lambda\tau} = 0,$$

733 where, by inserting $\lambda = i\omega$, and separating the real and
 734 imaginary parts we obtain

$$\begin{aligned} a &= -b \cos(\omega\tau), \\ \Omega &= -b \sin(\omega\tau), \end{aligned} \tag{27}$$

735 or equivalently,

$$\begin{aligned} a &= \omega / \tan(\omega\tau), \\ b &= -\omega / \sin(\omega\tau). \end{aligned} \tag{28}$$

736 where $\omega = 2\pi\Omega$. Now, introducing the parameter Ω
 737 according to the above equations leads to a model equation
 738 containing three uncorrelated parameters: κ, Ω, τ (cf.
 739 Fig. 9b). As it is shown in Fig. 10a, for this set of uncorrelated
 740 parameters, the elliptical confidence regions coincide
 741 very well with the likelihood-based regions. These results
 742 indicate a precise estimation with uniquely identifiable estimates.
 743 Here, to compute the confidence regions of the model
 744 parameters, we employed the same approach as used in
 Fig. 8. In addition, the 95% confidence regions obtained

by PyMC are displayed in Fig. 10b. From Figs. 7 and 10,
 we observe very close agreement between the inference
 obtained by PSO and MH.

Finally, for this case study, we compare the performance
 of different algorithms used in this study. For the sake of
 fair comparison, the initial guesses in the MH and SA algo-
 rithms were created randomly within the parameter search
 space to have an identical strategy for starting condition
 with the EAs (i.e., PSO, DE, GA, CMA-ES). The parameter
 search space was limited in the range $[0, 20]$ for each param-
 eter. We have also applied the local algorithms LM and
 HJ, but nonlocal algorithms out-perform them clearly (LM
 and HJ algorithms failed to arrive at the global minimum).
 This is why we do not discuss their corresponding results
 in the following.

The results for 100 runs are reported in Fig. 11 and
 Table 1. We found that PSO, DE, GA, CMA-ES, SA, MH
 methods succeeded in finding the global minimum.

In addition, for each algorithm, the mean and minimum
 values of obtained fitness function, and the average of run-
 ning time are listed in Table 1. Although EAs reveal a high
 computational cost, they show a very good performance in
 finding the global solution. According to these results, PSO
 delivers slightly better solutions than other EAs, although

Fig. 9 Correlation matrix (absolute values) for Case Study II. **a** The estimated parameters are κ, a, b , and τ . From this panel, we observe that parameters a and b are highly correlated, which were causing identifiability problem. **b** Introducing the parameter Ω according to Eq. 27 yields a model with three uncorrelated parameters: κ, Ω, τ

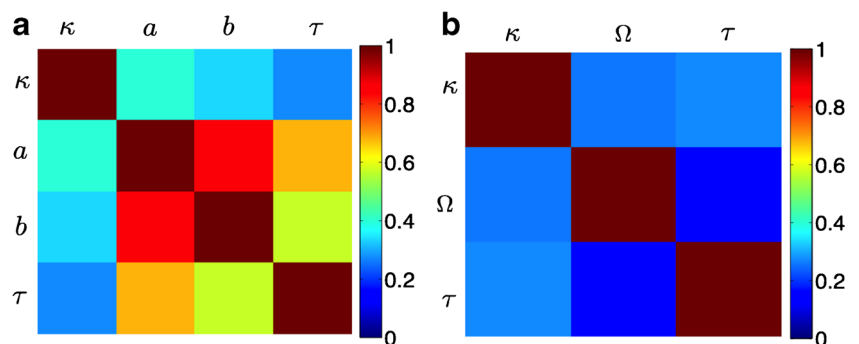
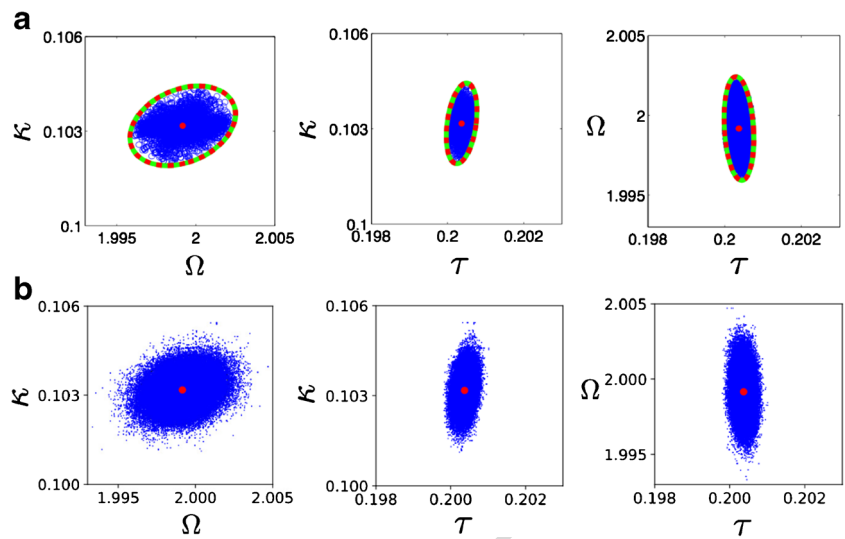


Fig. 10 Confidence regions for the parameters of Case Study II. **a** The elliptic and likelihood confidence regions for the uncorrelated parameters κ , Ω , and τ . **b** Confidence regions of the parameters built from MH algorithm. The regions are centered at the estimated parameters $p_{II}^* = (\kappa, \Omega, \tau) = (0.103 \text{ mV}, 1.99, 0.2)$



769 the employed EAs are competitive in finding the global
770 minimum.

771 **Case Study III**

772 The first two case studies were designed with the measured
773 *in silico* data. In the following, we identify the parameters
774 of a thalamo-cortical model described by a set of coupled
775 stochastic delay differential equations through the model
776 spectral fitting to the *in vivo* experimental data.

777 Figure 12 shows the power spectrum of the model
778 given by Eq. 25 fit to the power spectra of EEG recorded
779 over frontal and occipital head regions during awake and
780 anesthesia conditions. As a consequence of the very good
781 performance of the parameter estimation based on PSO, we
782 applied it to estimate model parameters optimally. Figure 12

shows a good prediction of the observed spectral power
features in experimental data.

It is important to point out that, in most of the datasets,
implementing a standard fitness function defined by the
discrepancy between the models output and the measured
data does not allow to fit well the spectral power peak in δ -
and α -frequency ranges (cf. the inset in Fig. 12a). Since
the δ - and α -peaks are important and informative signal
features observed during anesthesia, we employed a biased
chi-squared function given by Eq. 5 in order to fit the model
with the spectral power peak within these frequency ranges.
Taking a biased fitness function with more weight value in
 δ - and α -frequency bands, the model output is forced to
improve the fit of the corresponding experimental spectral
power peaks. For instance, in panel A, we set $c_1 = 20$,
 $c_2 = 1$, $c_3 = 10$, $c_4 = 1$ to capture the observed δ - and α -

Fig. 11 Comparing the performance of different algorithms through 100 independent runs in Case Study II. The red bars indicate the histogram of fitness function values (the number of counts of the best fitness value) obtained by PSO, DE, GA, CMA-ES, MH and SA algorithm

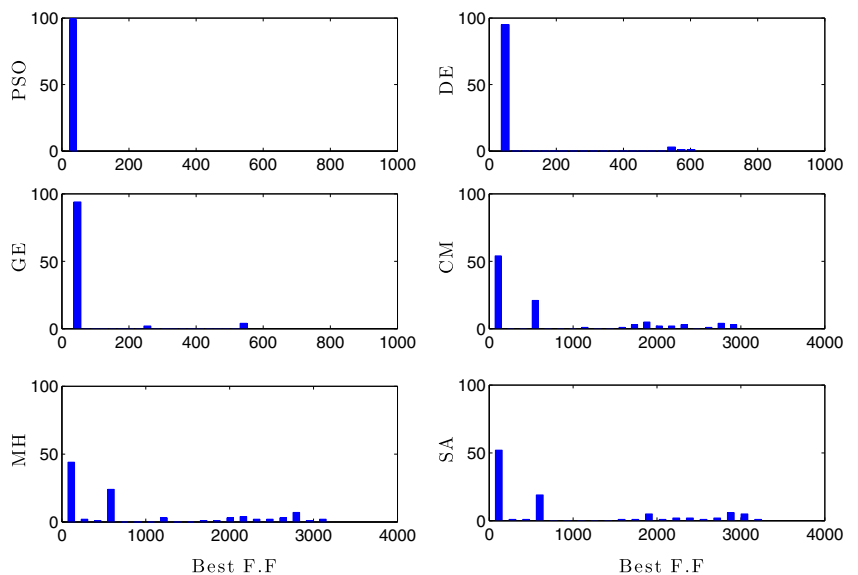


Table 1 Comparing the results obtained by different search algorithms achieved from 100 independent runs in Case Study II

Algorithm	Min	Counts	Mean	Time(s)
PSO	33.19	100	33.19	27.5
DE	46.22	95	58.73	27.9
GA	47.76	94	60.04	31.5
CMA	107.03	54	699.59	67.03
SA	112.09	52	825.90	116.3
MH	114.52	44	850.69	117.3

The best values of fitness function (minimum), the related counts, its mean value and the average of computational time (in second) for each algorithm are illustrated in the table

799 peak. It is trivial that $c_1 = c_2 = c_3 = c_4 = 1$ results in the
800 standard chi-squared function.

801 The sensitivity analysis of the fitness function to the
802 estimated parameters for this case study is shown in
803 Appendix B in Supplementary Mateial.

804 In order to demonstrate the power of the thalamo-cortical
805 neural mass model, it is fit to EEG spectral power of eight
806 patients recorded during pre- and post-incision anesthesia
807 induced by propofol and desflurane, as shown in Fig. 13.
808 In this figure, we also observe that the model fits measured
809 data very well in δ - and α -frequency bands. These results
810 indicate that the considered thalamo-cortical model in this
811 work is able to reproduce the specific features observed
812 in EEG spectral power data adequately. For completeness,
813 statistics of the estimated parameters are given in Fig. 14 for

all patients. Most parameters are stable over experimental 814
conditions and subjects, such as the thalamo-cortical 815
delay time τ . Conversely, the decay rates β_e and β_i 816
are significantly different under desflurane and propofol 817
anesthesia under the pre-incision condition ($p < 0.05$). 818
Moreover, the noise strength is significantly different under 819
desflurane and propofol anesthesia in both experimental 820
conditions ($p < 0.05$). The detailed parameter statistics for 821
each patient are reported in Appendix C in Supplementary 822
Material. 823

Discussion 824

In a great variety of scientific fields, stochastic differential 825
equations arise naturally in the modeling of systems due 826
to random forcing or other noisy input (Faisal et al. 2008). 827
Numerical integration of differential equations is a major 828
time consuming problem in the parameter estimation of 829
nonlinear dynamics describing biological systems (Liang 830
and Lord 2010). Furthermore, inferring the parameters of 831
SDEs are more problematic due to the inherent noise in 832
system equations. 833

Various previous methods attack the parameter inference 834
problem. It has been shown that a decoupling strategy 835
(slope approximation), that considers the derivative values 836
of system state variables, avoids numerical integration 837
altogether by fitting models to the slope of time-series 838
data (Almeida and Voit 2003; Voit and Almeida 2004). 839
However, this technique is not applicable in most inverse 840

Fig. 12 Fitting a reduced thalamo-cortical model to the EEG power spectra in awake and anesthesia conditions. In each panel, the spectral power of recorded EEG data is shown as a dashed red line. The fit EEG power spectra using standard chi-squared function are illustrated by green lines, whereas those obtained through the biased chi-squared function are shown by blue lines. Panels a and b illustrate the EEG spectral power over the frontal head region in awake and anesthesia conditions, respectively. The occipital EEG spectral power in awake and anesthesia conditions are displayed in panels c and d, respectively

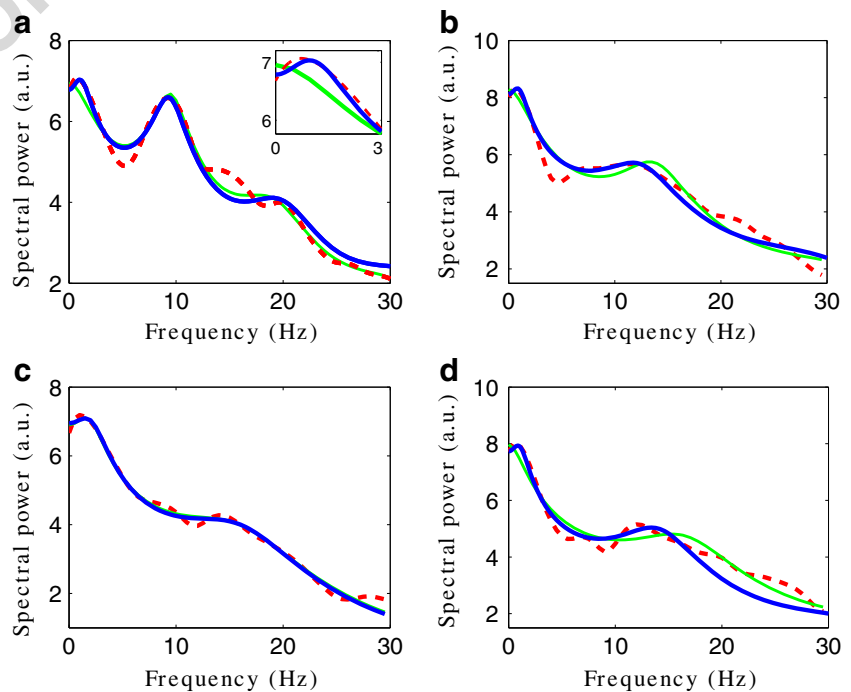
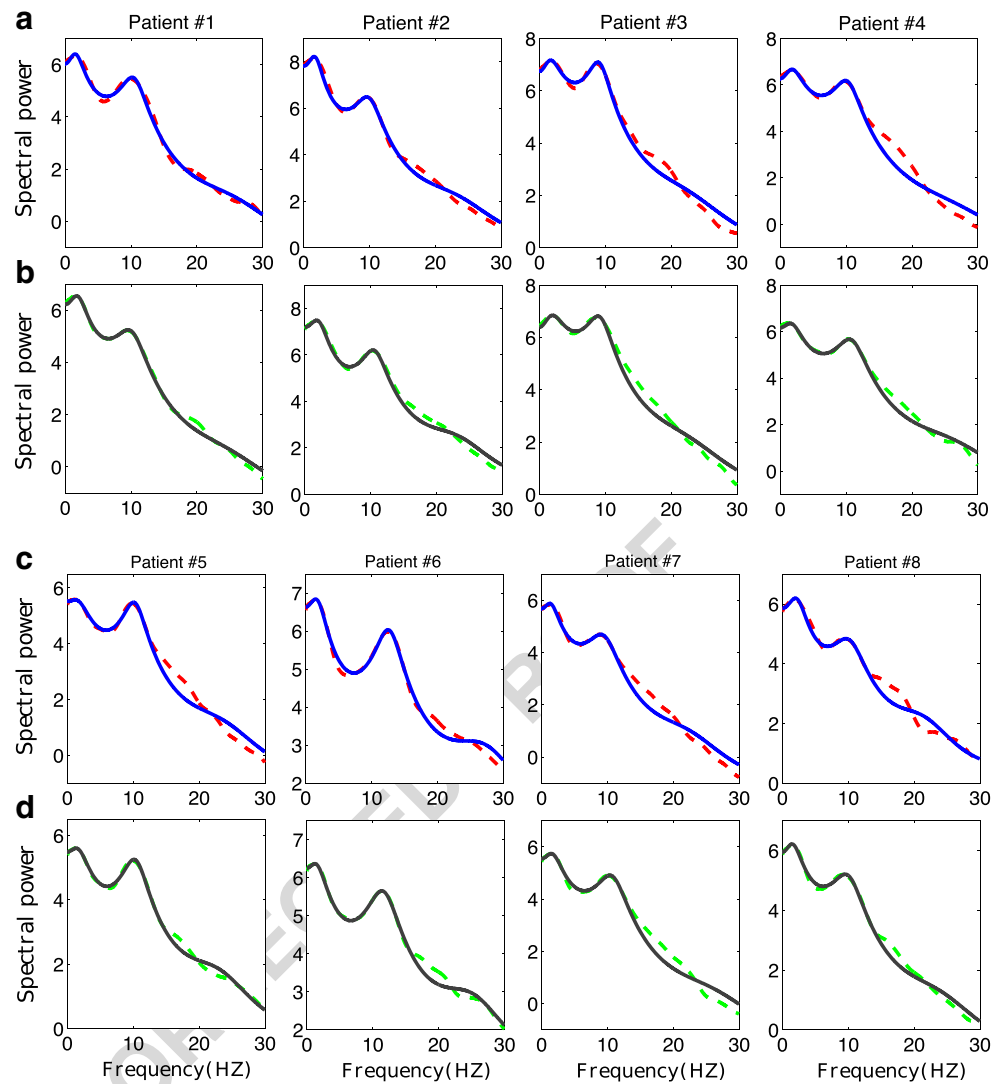


Fig. 13 Fitting a reduced thalamo-cortical model to EEG spectral power in pre- and post-incision anesthesia induced by propofol and desflurane. The recorded EEG data for eight patients are shown by dashed lines, whereas the corresponding fitted model are illustrated by solid lines. **a** The EEG power spectra recorded in pre- and **b** in post-incision condition induced by propofol are illustrated by dashed red and green lines, respectively. In addition, the solid blue and black lines depict the corresponding fitted thalamo-cortical model to experimental data. Panels **c**) and **d** show the the fitted mode against the spectral power of recorded EEG data during desflurane induced anesthesia in pre- and post-incision conditions, respectively



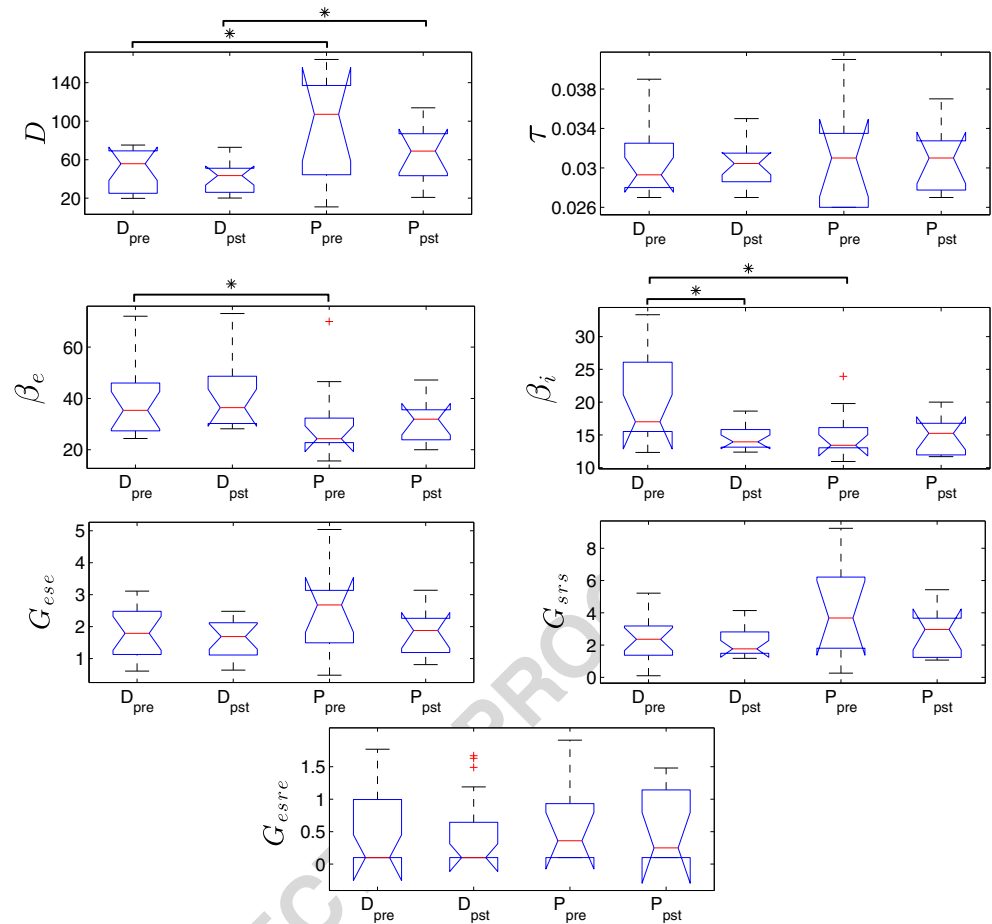
841 problems. For instance, if an equation is affected by a
 842 state variable for which there is no data available, then the
 843 decoupling technique cannot be applied to that equation.
 844 Moreover, this strategy cannot provides a model that is
 845 readily applicable to the computational simulation when the
 846 given time-series data contain measurement errors (Kimura
 847 et al. 2005).

848 In another work, Tsai and Wang (2005) have proposed
 849 a modified collocation approximation technique to convert
 850 differential equations into a set of algebraic equations. This
 851 method has the obvious advantage of avoiding numerical
 852 integration of differential equations. They have shown
 853 that their method yields accurate parameter estimation for
 854 S-system models of genetic networks what also saves
 855 much computational time. However, such an approximation
 856 cannot always be employed in general complex nonlinear
 857 inverse problems.

858 In the last decade, there have been several studies on
 859 fitting the neural population models to experimental data. In

neuroimaging literature, Dynamic Causal Modeling (DCM) 860
 has been used successfully to infer hidden neuronal states 861
 from measurements of brain activity (Friston et al. 2003; 862
 David et al. 2006; Pinotsis et al. 2012). It has been shown 863
 previously that characterizing neural fluctuations in terms 864
 of spectral densities leads to more accurate inference than 865
 stochastic scheme (Razi et al. 2015; Jirsa et al. 2017). 866
 However, in most of the previous studies, a rigorous 867
 analytical approach to overcome the inference difficulties 868
 due to the additive noise has received relatively little 869
 attention (Daunizeau et al. 2012; Ostwald et al. 2014; 870
 Ostwald and Starke 2016). In the technique presented 871
 in this study, we estimated the model parameters from 872
 the power spectrum derived analytically from the system 873
 equations. By the aid of the Green's function method, 874
 we can easily compute the power spectrum of a linear 875
 system whose dynamics are governed by a set of coupled 876
 stochastic ordinary or delay differential equations. By fitting 877
 the analytically computed spectral power to the spectral 878

Fig. 14 Statistics of the estimated parameters of the thalamo-cortical model for 25 patients during general anesthesia. Each boxplot shows the Kruskal-Wallis test statistic for the estimated parameters of the thalamo-cortical neural mass model fitted to EEG spectral power in pre- and post-incision anesthesia induced by propofol and desflurane. D_{pre} and D_{pst} stand for pre- and post-incision induced by desflurane, respectively. P_{pre} and P_{pst} stand for pre- and post-incision induced by propofol, respectively



879 power estimated from corresponding measurements, we can
 880 estimate the model parameters without solving the model
 881 equations. Hence we are able to avoid the computational
 882 costs of numerical integration, which dramatically reduces
 883 the computational time burden. Note that investigating the
 884 structural identifiability (model selection practice) in order
 885 to identify which model best explains the experimental data,
 886 is beyond the scope of the present manuscript. The reader
 887 is referred to further literature for a more detailed review of
 888 the model comparison (Daunizeau et al. 2009; Raue et al.
 889 2009; Penny 2012).

890 In general, the inverse problems can be solved by opti-
 891 mization algorithms and MCMCs methods (Myung 2003;
 892 Tashkova et al. 2011; Gelman et al. 2004). Optimization
 893 methods are simple and straightforward to minimize the
 894 error between the model prediction and the measured data
 895 (Mendes and Kell 1998; Moles et al. 2003; Kimura et al.
 896 2015). On the other side, many sampling algorithms and
 897 probabilistic programming languages have been created to
 898 perform Bayesian inference, especially for high dimen-
 899 sional and complex posterior distributions e.g., Carpenter
 900 et al. (2017) and Patil et al. (2010). This maximum like-
 901 lihood approach provides us uncertainty information in
 902 addition to the optimum value for each parameter. In the

present work, we have used several optimization algorithms
 as well as classical sampling methods (MH) to benefit from
 and compare both classic and probabilistic inferences.

We compared the performance of EAs including PSO,
 DE, GA, CMA-ES and the well-known sampling algorithms
 MH, and SA (Case Study I and Case Study II, cf.
 Figs. 6, and 11)). Our results show that in the case of a
 unimodal problem (single spectral peak), EAs outperform
 the sampling algorithms while they are computationally
 more expensive.

In recent years, many algorithms have been proposed to
 solve inverse problems (Rodriguez-Fernandez et al. 2006b;
 Kramer et al. 2014; Kimura et al. 2015). Notably, it is shown
 that both the choice of algorithm applied in the estimating
 problems and the formulation of the objective function
 plays a crucial role in reproducing the key features of the
 measured data (Kimura et al. 2005). This is confirmed
 by our study demonstrating that the specific choice of the
 fitness function, e.g. by weighting different signal elements,
 plays a decisive role in reproducing the key features of the
 measured data. We showed that using the standard least
 squares function the thalamo-cortical neural mass model
 fails to be fit to the spectral power peak observed in δ - and
 α -frequency ranges. This can be improved by adding more

927 weights to the fitness function in certain frequency bands
928 than the others, cf. Fig 12.

929 For each parameter estimation problem carried out in this
930 study, we also employed the practical identifiability analysis
931 to check the reliability of the estimates. The identifiability
932 analysis in this work comprised the Fisher Information
933 Matrix (FIM) to compute the sensitivity and the correlation
934 matrices, in addition to plotting the confidence regions for
935 estimated parameters. We illustrated that the identifiability
936 analysis can be easily exploited by plotting the confidence
937 regions according to the covariance approximation or by
938 employing PSO and MH algorithms. For instance, the
939 confidence regions obtained through Hessian and FIM
940 approaches were compared in Figs. 4 and 10. By virtue
941 of the conceptual difference between these approaches,
942 the exact coincidence of the ellipsoids obtained based on
943 Hessian and FIM information indicates that the estimated
944 parameters are uniquely identifiable and we were able to
945 obtain reliable estimates (Marsili-Libelli et al. 2003). To
946 further confirm the reliability of the shown confidence
947 regions, we have also compared the results obtained by the
948 PSO and the MH algorithms. As presented in Figs. 4 and 10,
949 we observed very good agreement with these approaches.

950 Furthermore, by measuring the sensitivity values, it
951 is possible to investigate how the system output will
952 change in response to small modification in the model
953 parameters (Rodríguez-Fernandez et al. 2006b, 2013).
954 This allows us to reveal which model parameters play a
955 decisive role in the model behavior. A high sensitivity
956 index for a parameter shows that the small changes on
957 that parameter cause a strong response in model output.
958 This indicates that the parameters with higher sensitivity
959 values are more identifiable than those parameters with
960 low sensitivity indices (cf. Appendix B in Supplementary
961 Material). The correlation plots also provide information
962 about the parameter identifiability. The lack of correlation
963 among the estimated parameters reveals that the parameters
964 are identifiable, as shown in Fig. 5. On the contrary, the
965 highly correlated parameters are not identifiable since there
966 exist combinations of them yielding an identical fitness
967 value, cf. Fig. 9. The high correlation between parameters
968 can also cause a discrepancy between the elliptical and
969 likelihood-based confidence regions, as illustrated in Fig. 8.
970 To surmount this problem, the pairs of correlated parameters
971 must be removed by introduction of new variables.

972 Up to now, few studies have investigated the parameter
973 estimation problems in the context of neural population
974 modeling, which is well-established to reproduce the
975 measured EEG data during different behavioral states. To
976 our best knowledge, the present study is the first that fits
977 a thalamo-cortical model to EEG spectral power peaks
978 observed in both δ - and α -frequency ranges. A pioneer
979 study by Bojak and Liley (2005) fitted a neural population

model comprising excitatory and inhibitory cortical neurons 980
to a set of pseudo-experimental data. In another study, 981
Rowe et al. (2004) have estimated the values of key 982
neurophysiological parameters by fitting the model's single- 983
peak spectrum to EEG spectra in awake eyes-closed 984
and eyes-open states. Although they have achieved good 985
predictions of the measured data, their data do not exhibit a 986
second spectral power peak as in our data in δ -frequency 987
range. Moreover, they have used a local search method (LM 988
method) which requires an initial guess for the parameters. 989
In a similar approach, Van Albada et al. (2010) have fit a 990
neural mass model to eyes-closed EEG spectra of a large 991
number of subjects to probe the age-associated changes 992
in the physiological model's parameters. Their findings 993
suggest that the inverse modeling of EEG spectral power is 994
a reliable and non-invasive method for investigating large- 995
scale dynamics, which allows us to extract physiological 996
information from EEG spectra. In line with these studies, 997
the data-driven approach presented in the current study 998
provides a proper guidance for fitting the thalamo-cortical 999
model to a large set of experimental recordings. This 1000
enables us to investigate the parameter changes during the 1001
transition from awake to anesthesia state, especially those 1002
parameters that cannot be measured directly. An important 1003
finding of our data-based analysis in fitting a thalamo- 1004
cortical model to the EEG spectra is that the model is 1005
heavily sensitive to the delay transmission in the system 1006
(cf. Appendix B in Supplementary Material). This is in 1007
agreement with previous studies suggesting that the location 1008
of spectral power peaks especially in alpha frequency range 1009
heavily depends to the delay values in the thalamo-cortical 1010
circuits (Robinson et al. 2001a, b; Rowe et al. 2004). 1011
Hence the transmission delay can provide a basis for the 1012
reproduction of certain features in experimental data seen 1013
at high concentration of anesthetics. For instance, a recent 1014
study by Hashemi et al. (2017) has considered the effect of 1015
anesthetics on the axonal transmission delay to reproduce 1016
the beta power surging observed in EEG power spectrum 1017
close to loss of consciousness. Inferring the parameter 1018
changes associated to the changes in brain activities from 1019
model fitting to a large data set remains to be investigated in 1020
future work. 1021

Conclusion 1022

The results obtained in the present work reveal that given 1023
a set of stochastic ordinary or delay differential equations 1024
(SDEs) and a set of experimental data, we are able to fit 1025
the model power spectrum to the related data with a high 1026
accuracy and very low computational costs by the aid of 1027
the Green's function method and evolutionary algorithms. 1028
We demonstrated that using evolutionary algorithms, the 1029

1030 proposed thalamo-cortical neural population model fits
1031 very well to the EEG spectral features within δ - and
1032 α -frequency ranges measured during general anesthesia.

1033 Moreover, we showed that in multimodal optimization
1034 problems, the use of a global optimization approach such as
1035 PSO or DE is required in order to accurately estimate the
1036 model parameters.

1037 Our analysis indicates further that one can employ a data-
1038 driven approach to provide new valuable insights into the
1039 mechanisms underlying the behavior of complex systems.
1040 This approach will provide an appropriate guidance in
1041 future brain experiments to better understand different
1042 behavioral activities. As a summary, this work can serve
1043 as a basis for future studies revealing biomarkers from
1044 physiological signals.

1045 Information Sharing Statement

1046 The authors do not have ethical approval to make the
1047 data set publicly available, as this did not form part of
1048 the subject consent process. Consequently, we do not
1049 have the written approval of the patients to publish
1050 their data and hence we refrain from making the data
1051 public. However, the data are available upon request
1052 from authors by contacting meysam.hashemi@univ-amu.fr
1053 and/or Jamie.Sleigh@waikatodhb.health.nz

1054 The source codes needed to reproduce the presented
1055 results are available on GitHub (<https://www.github.com/mhashemi0873/SpectralPowerFitting>).
1056

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