Neural Posterior Estimation of hierarchical models in neuroscience

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Résumé – L'objectif principal de la recherche expérimentale en neurosciences est de comprendre les mécanismes bio-physiques qui sont à l'origine de phénomènes neuronaux complexes. Lorsque le but est de reproduire informatiquement des signaux cérébraux réalistes, cela implique généralement l'inférence des paramètres de modèles stochastiques non-linéaires. Cette tâche est d'autant plus difficile si le couplage de certains paramètres conduit à des modèles intrinsèquement indéterminés. Nous présentons une méthode capable de lever une telle indétermination en étendant les développements récents de l'inférence par simulation (SBI) aux modèles hiérarchiques bayésiens. L'idée est d'exploiter l'information incluse dans un ensemble d'observations supplémentaires partageants les mêmes paramètres globaux, afin de fournir une estimation plus précise des paramètres couplés. Nous appliquons cette méthode à un modèle neuronal connu, le *Jansen & Rit Neural Mass Model* pour étudier quelles informations supplémentaires permettent d'obtenir les meilleures estimations de paramètres pour des signaux EEG.

Abstract – Understanding the bio-physical mechanisms underlying complex neuronal phenomena is the main focus of experimental research in neuroscience. When trying to computationally replicate realistic brain signals, it typically involves inferring the parameters of stochastic non linear models. This task becomes particularly challenging when the coupling of certain parameters leads to intrinsically indeterminate models. We present a method that is capable of removing such indeterminacy by extending recent developments in simulation-based inference (SBI) to hierarchical Bayesian models. The idea is to exploit additional information conveyed by an auxiliary set of observations sharing the same global parameters, in order to provide more accurate estimates of the coupled parameters. We demonstrate this method on the well known *Jansen & Rit Neural Mass Model* and use it to investigate what extra information best improves the parameter estimates on EEG signals.

1 Introduction

Sophisticated experimental technologies help us to observe complex neuronal behavior at different scales. But understanding the bio-physical mechanisms that drive such phenomena remains a challenging task: computational neuroscientists usually face the dilemma of either creating carefully designed, highly interpretable mechanistic models but rely on ad-hoc parameter tuning [1], or resort to purely data-driven models built for statistical inference, but with limited mechanistic insight [2].

Simulation-Based Inference (SBI) allows to perform statistical Bayesian inference in cases where the likelihood of the data is intractable (e.g. due to the non-linear or non-differentiable behavior within the model). They only require access to a simulator capable of generating samples from the underlying mathematical model. Building on the recent advances in deep learning combined with active learning techniques and probabilistic programming [3], new algorithms have been developed. Core elements are neural density estimators that learn different quantities in the Bayes' formula such as the likelihood function [4], the likelihood-to-evidence ratio [5], or the posterior distribution [6]. Methods based on neural posterior estimation [7, 8] have shown to scale to complex mechanistic models in neuroscience where they outperform traditional methods [9] based on Approximate Bayesian Computation (ABC). They also show that resulting *full* posterior distribution allows to visualize intrinsic uncertainties in the parameter space, that are typical for stochastic and non-linear dynamics of neuronal activity [7].

Stochasticity is not the only source of uncertainty when estimating the parameters in a computational neuroscience model. In a number of practical contexts, some parameters are strongly coupled. Formally, this means that the likelihood function $p(\mathbf{x}|\boldsymbol{\theta})$ is non-injective w.r.t. $\boldsymbol{\theta}$: one can find $\boldsymbol{\theta} \neq \boldsymbol{\theta}'$ such that $p(\mathbf{x}|\boldsymbol{\theta}) = p(\mathbf{x}|\boldsymbol{\theta}')$. This can lead to highly structured posteriors (e.g. "banana shapes" in Fig. 4 of [7]). A particular case is when certain *global* parameters $\boldsymbol{\beta}$ can be shared among observations obtained for different *local* parameters $\boldsymbol{\alpha}$.

Hierarchical Bayesian Models are the central tool to model data with nested subpopulations as can be found in topic models or population genetics [10]. They share statistical strength across observations and result in sharper posteriors and more reliable estimates for global and local parameters. In the situation where we have an observation of interest $\mathbf{x}_0$ and a set of extra observations $\mathcal{X} = \{\mathbf{x}_1, \dots, \mathbf{x}_N\}$ with $\mathbf{x}_i \sim p(\mathbf{x} \mid \boldsymbol{\alpha}_i, \boldsymbol{\beta})$, the posterior distribution can be factorized as:

$$p(\boldsymbol{\alpha}_0, \boldsymbol{\beta} \mid \mathbf{x}_0, \mathcal{X}) = p(\boldsymbol{\alpha}_0 \mid \boldsymbol{\beta}, \mathbf{x}_0)\, p(\boldsymbol{\beta} \mid \mathbf{x}_0, \mathcal{X})\,. \quad (1)$$

Approaches for SBI in hierarchical models exist, but are limited. Ref. [10] extends Approximate Bayesian computation (ABC) into a two-step procedure in which local and global variables are estimated. Ref. [11] and [5] extend amortized likelihood ratios to deal with global parameters, but cannot do inference on local parameters.

In this work we present HNPE [12], an extension of neural posterior estimation [6] that was published at the 2021 NeurIPS conference. The authors validate this method, showing that it converges to the true global and local parameter values of complex hierarchical models in neuroscience. We propose a follow-up with additional experimental results about how the use of extra-observations can influence inference quality, with an application to real electroencephalography (EEG) data.

2 Methods

Approximating the posterior distribution. Our goal is to approximate $p(\boldsymbol{\alpha_0}, \boldsymbol{\beta} \mid \mathbf{x}, \mathcal{X})$ in a setting where the likelihood function of the hierarchical Bayesiam model is intractable and we only have access to samples from a simulator. MCMC methods commonly used for posterior estimation are thus not applicable. To bypass such difficulty, we employ tools from simulation based inference (SBI) to directly estimate an approximation to the posterior distribution using a conditional neural density estimator trained over simulations of the model. More specifically, we use *Hierarchical Neural Posterior Estimation* (HNPE) [12] a neural posterior estimation procedure that relies on normalizing flows, i.e. invertible neural networks capable of transforming data points sampled from a simple base distribution (e.g. Gaussian) to approximate any probability density function [13].

In HNPE, we approximate the target posterior distribution based on its factorization (1) as follows:

$$\begin{aligned} p(\boldsymbol{\beta} \mid \mathbf{x}_0, \mathcal{X}) &\approx q_{\boldsymbol{\phi_1}}(\boldsymbol{\beta} \mid \mathbf{x}_0, f_{\boldsymbol{\phi}_3}(\mathcal{X})) \\ p(\boldsymbol{\alpha}_0 \mid \boldsymbol{\beta}, \mathbf{x}_0) &\approx q_{\boldsymbol{\phi}_2}(\boldsymbol{\alpha}_0 \mid \boldsymbol{\beta}, \mathbf{x}_0) \end{aligned} \tag{2}$$

where $q_{\boldsymbol{\phi_1}}$ and $q_{\boldsymbol{\phi}_2}$ are normalizing flows. The function $f_{\boldsymbol{\phi}_3}$ is a *deepset* neural network [14] used to aggregate the extra observations via a learnable weighted average operation and is crucial for imposing the invariance to permutation of the extra observations in $\mathcal{X}$.

The parameters $\boldsymbol{\phi} = \{\boldsymbol{\phi}_1, \boldsymbol{\phi}_2, \boldsymbol{\phi}_3\}$ are estimated by minimizing the average Kullback-Leibler divergence between the true posterior distribution $p(\boldsymbol{\alpha}_0, \boldsymbol{\beta} | \mathbf{x}_0, \mathcal{X})$ and our approximation $q_{\boldsymbol{\phi}}(\boldsymbol{\alpha}_0, \boldsymbol{\beta} | \mathbf{x}_0, \mathcal{X})$ over all possible values of $\mathbf{x}_0$ and $\mathcal{X}$:

$$\min_{\boldsymbol{\phi}} \ \mathbb{E}_{p(\mathbf{x}_0, \mathcal{X})} \Big[\mathrm{KL}(p(\boldsymbol{\alpha}_0, \boldsymbol{\beta} \mid \mathbf{x}_0, \mathcal{X}) \| q_{\boldsymbol{\phi}}(\boldsymbol{\alpha}_0, \boldsymbol{\beta} \mid \mathbf{x}_0, \mathcal{X})) \Big] \ .$$

We may rewrite the optimization problem in terms of each of its parameters to get

$$\min_{\boldsymbol{\phi}_1, \boldsymbol{\phi}_2, \boldsymbol{\phi}_3} \quad \mathcal{L}_{\boldsymbol{\alpha}}(\boldsymbol{\phi}_2) + \mathcal{L}_{\boldsymbol{\beta}}(\boldsymbol{\phi}_1, \boldsymbol{\phi}_3) \tag{3}$$

with

$$\begin{aligned} \mathcal{L}_{\boldsymbol{\alpha}}(\boldsymbol{\phi}_2) &= -\mathbb{E}_{p(\mathbf{x}_0, \mathcal{X}, \boldsymbol{\alpha}_0, \boldsymbol{\beta})} \left[\log(q_{\boldsymbol{\phi}_2}(\boldsymbol{\alpha}_0 \mid \boldsymbol{\beta}, \mathbf{x}_0)) \right] \ , \\ \mathcal{L}_{\boldsymbol{\beta}}(\boldsymbol{\phi}_1, \boldsymbol{\phi}_3) &= -\mathbb{E}_{p(\mathbf{x}_0, \mathcal{X}, \boldsymbol{\alpha}_0, \boldsymbol{\beta})} \left[\log(q_{\boldsymbol{\phi}_1}(\boldsymbol{\beta} \mid \mathbf{x}_0, f_{\boldsymbol{\phi}_3}(\mathcal{X}))) \right] \ . \end{aligned}$$

In practice we minimize the Monte Carlo approximation of our objective function (3) using a training set of n i.i.d. data samples $(\mathbf{x}_0^j, \mathcal{X}^j)$ generated from our hierarchical stochastic simulator for a given prior $p(\boldsymbol{\alpha}, \boldsymbol{\beta}) = p(\boldsymbol{\alpha}|\boldsymbol{\beta})p(\boldsymbol{\beta})$ that describe our initial knowledge of the parameters (e.g. the range of possible values):

1. Sample a set of parameters from the prior distribution $p(\boldsymbol{\alpha}, \boldsymbol{\beta})$ such that $\boldsymbol{\beta}^j \sim p(\boldsymbol{\beta})$ and $\boldsymbol{\alpha}_i^j \sim p(\boldsymbol{\alpha}|\boldsymbol{\beta}^j)$ with $j = 1, \ldots, n$ and $i = 0, \ldots, N$.
2. For each (i, j)-pair, generate $\mathbf{x}_i^j \sim p(\mathbf{x}|\boldsymbol{\alpha}_i^j, \boldsymbol{\beta}^j)$ so that each observation $\mathbf{x}_0^j$ is accompanied by its corresponding N extra observations $\mathcal{X}^j = \{\mathbf{x}_1^j, \ldots, \mathbf{x}_N^j\}$.

We can now train our neural density estimators by minimizing the empirical losses:

$$\begin{aligned} \mathcal{L}_{\boldsymbol{\alpha}}^n &= -\tfrac{1}{n} \textstyle\sum_{j=1}^n \log(q_{\boldsymbol{\phi}_2}(\boldsymbol{\alpha}_0^j \mid \boldsymbol{\beta}^j, \mathbf{x}_0^j)) \\ \mathcal{L}_{\boldsymbol{\beta}}^n &= -\tfrac{1}{n} \textstyle\sum_{j=1}^n \log(q_{\boldsymbol{\phi}_1}(\boldsymbol{\beta}^j \mid \mathbf{x}_0^j, f_{\boldsymbol{\phi}_3}(\mathcal{X}^j))) \ . \end{aligned}$$

This training proceedure can be used in a sequential manner to further improve inference quality and simulation efficency by using the running estimate of the posterior distribution to guide further simulations toward regions of the parameter space compatible with a specific choice of $\mathbf{x}_0$ and $\mathcal{X}$. This is useful when the observed data is scarce and/or difficult to obtain or simulations of the model are costly. See [12] for more details of the algorithm and its implementation.

The simulator model. *Neural Mass Models* are a class of nonlinear models from computational neuroscience that, based on physiologically motivated stochasitc differential equations, are able to replicate oscillatory electrical signals experimentally observed with electroencephalography (EEG). These models of cortical columns are used in large-scale simulators [15] and serve as building blocks for several simulation studies in cognitive and clinical neuroscience [16]. We consider the stochastic version of the Jansen & Rit Neural Mass Model (JR-NMM) and use the C++ implementation in the supporting code of [9]. The output $\mathbf{x}$ of this generative model is a time series obtained by taking as input a set of four parameters $\boldsymbol{\theta} = (C, \mu, \sigma, g)$. While C influences the oscillatory behavior, (μ, σ) and g impact the amplitude of $\mathbf{x}$: the gain factor g represents the amplifier (resp. attenuator) for measurements of physiological signals with small (resp. high) amplitude (characterized by (μ, σ)). The reader is referred to [12] for the full description of the stochastic differential equations and the bio-physical parameters defining the neural mass model.

Here, the coupling-effect of parameters g and (μ, σ) on the amplitude of the output signal is what leads to indeterminacy in the posterior-estimation problem: the same observed signal $\mathbf{x}_0$ could be generated with larger (smaller) values of g and smaller (larger) values of μ and σ. Fortunately, it is common to record several chunks of signals within an experiment, giving us access to auxiliary signals $\mathbf{x}_1, \ldots, \mathbf{x}_N$ obtained with the same instrument setup (i.e. the same gain g). We can therefore use the above presented framework of hierachical modeling with $\boldsymbol{\alpha} = (C, \mu, \sigma)$ and $\boldsymbol{\beta} = g$.

Experimental data. In our numerical illustrations with real data, we consider EEG recordings of brain signals taken from a public dataset [17] in which subjects were asked to keep their eyes open or closed during periods of 8 seconds. For each subject we have access to 10 epochs, five of which correspond to *open eyes*, and the rest to *closed eyes* events. We refer to [12] for more details on the dataset.

3 Results and discussion

All experiments used the `sbi` package [18] and the code at `https://github.com/plcrodrigues/HNPE`. We use the same experimental setup as in [12] to train HNPE with $R = 2$ rounds and $n = 50\,000$ training samples of simulated data from the JR-NMM.

Experiment 1. HNPE has already shown to provide a sharper posterior when using multiple extra-observation [12]. We now aim to answer the following question: is the indeterminacy problem solved by the *quantity* or the *diversity* of the extra observations? We therefore consider the following two cases for a given observed signal $\mathbf{x}_0 \sim p(\mathbf{x}|\boldsymbol{\theta}_0)$ simulated using a given set of ground-truth parameters $\boldsymbol{\theta}_0$:

— **Case 1 - No Diversity** (BLUE): the extra observations are generated with the *same* parameters, i.e. $\mathbf{x}_i \sim p(\mathbf{x}|\boldsymbol{\theta}_i)$ with $\boldsymbol{\theta}_i = \boldsymbol{\theta}_0 = (C_0, \mu_0, \sigma_0, g_0)$. We use multiple realizations of the same generative model, exploiting quantity, but without diversity.

— **Case 2 - Diversity** (ORANGE): the extra observations are generated with *different* local parameters (but still share the same global one), i.e. $\mathbf{x}_i \sim p(x|\boldsymbol{\theta}_i)$ with $\boldsymbol{\theta}_i = (C_i, \mu_i, \sigma_i, g_0)$. We here exploit access to both quantity and diversity of the extra observations.

Figure 1 shows that *quantity* indeed sharpens the posterior: the gray posterior where $N = 0$ is wider than the orange and blue ones obtained for $N = 9$. However, *diversity* is needed to get a correct estimate of the global parameter g, otherwise the result is *biased*. Indeed even a small offset in the gain-estimate (bottom-right subplot) leads to poor estimates of (μ, σ): the second and third diagonal subplots show a gap between the orange and the blue peak locations. Other experiments allowed us to confirm that over (resp. under) estimating the gain leads to under (resp. over) estimating μ and σ.

Experiment 2. We now consider an observation $\mathbf{x}_0$ of EEG-data with the goal of revealing what extra-information should be considered to get the best possible estimates consistent with the *closed* or *open eyes*-states. To do so, we consider the following three cases of extra-information:

— **Case 1 - No Diversity** (BLUE): The extra-observations are chosen amongst signals corresponding to the *same state* as the one of the observed signal.

— **Case 2 - Maximum Diversity** (ORANGE): The extra-observations are chosen amongst signals corresponding to the state *different* from the one of the observed signal.

— **Case 3 - Medium Diversity** (PINK): An *equal mix of both states* are considered for the extra-observations.

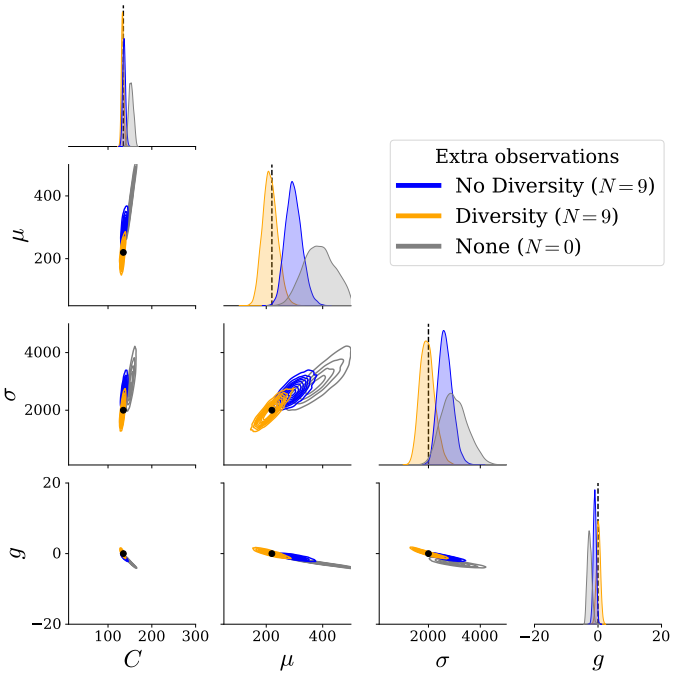

FIGURE 1 – Posterior estimates for the parameters of the JR-NMM obtained for an observation $\mathbf{x}_0$ simulated using the same ground-truth parameters (represented with black dots) as the ones used in Figure 3 of [12]. The different posteriors correspond to the cases with (ORANGE) or without (BLUE) diversity in the extra-observations ($N = 9$) and are compared to the case where no extra-observations (GRAY) are used ($N = 0$).

We can see in Figure 2 that contrasting $\mathbf{x}_0$ with maximum diversity (ORANGE) leads to sharper marginal posteriors, than for the other two cases (BLUE and PINK). Furthermore, we observe that the different posteriors disagree in the estimation of g and μ: the 2 bottom diagonal subplots show a gap between the orange and blue marginals while the pink one appears as a weighted average covering the union of their value ranges. They agree on the estimate for C (as expected), but also on the parameter μ, which is not usually the case if the gain-estimates differ (cf. Figure 1). However, this is probably due to the small number of extra-observations, which was solely chosen for comparison purposes.

If the state of the observed signal is known, the best posterior-estimate seems to be the one that uses extra-observations corresponding to the different state, as diversity increases accuracy according to Experiment 1. However, if the observed state is not known, one should rather consider the third case, where equally mixing both states results in larger posteriors, but with less risk for overconfident and false estimates. Note that in this case we would even have access to more than $N = 4$ extra-observations leading to sharper posterior-estimates as the one shown in Figure 4 of [12].

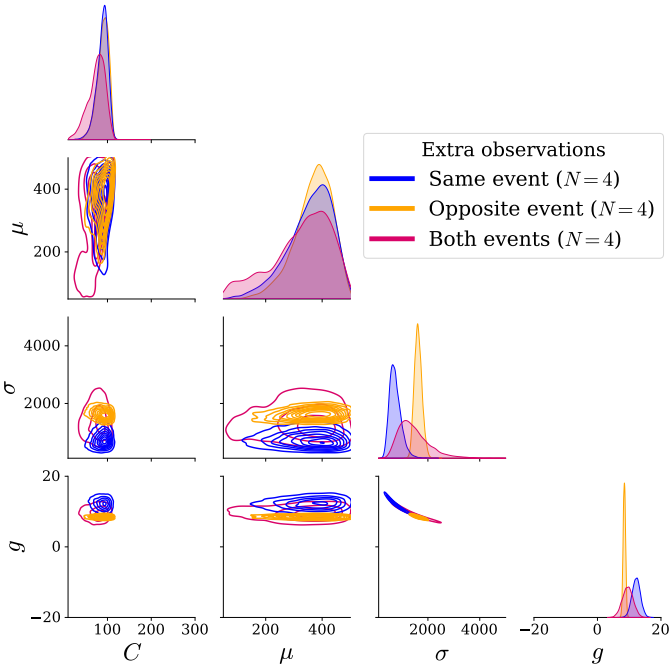

FIGURE 2 – Posterior estimates for the parameters of the JR-NMM obtained for a real human EEG signal recorded in an *open eyes*-state. We compare the posteriors obtained for three different sets of $N = 4$ extra-observations: in blue (resp. orange) they are chosen to belong to the same (resp. opposite) state as the observed signal, and in pink, we chose 2 of each.

Conclusion

The HNPE approach evaluated here considers some parameters to be global in an SBI context. Doing so allows to alleviate some indeterminacy in the posterior estimates of coupled parameters. Considering neural mass models, Experiment 1 showed that *diversity* in the extra-observations is crucial to get a *precise* and *correct* estimate of the gain, and thus of the corresponding coupled parameters μ and σ, hence removing the indeterminacy without introducing any bias. Experiment 2 confirmed on EEG-data that the sharpest posteriors are obtained by using maximally contrasted information in the extra observations.

This work shows that HNPE with carefully chosen extra-observations can be used for reliable fitting and inference of complex models in neuroscience based on stochastic non-linear differential equations, and therefore opens the door to new biologically informed descriptions of brain dynamics.

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