Title: A generative model of electrophysiological brain responses to stimulation: an approach to study perceptual stability

Abbreviated title: A model of electrophysiological brain responses

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Abstract: Each brain response to a stimulus is, to a large extent, unique. However this variability, our perceptual experience feels stable. Standard decoding models, which utilise information across several areas to tap into stimuli distributed representations and processing, are fundamentally based on averages and, therefore, can focus precisely on the features that are most stable across stimulus presentations. But what are these stable features that may sustain stable perception across experiences is still poorly understood. This question is difficult to address in the absence of a generative model of the signal. Here, I introduce *genephys*, a generative model of brain responses to stimulation publicly available as a Python package that, when confronted with a decoding algorithm, can reproduce the structured patterns of decoding accuracy observed in real data. Using this approach, I characterise how these patterns may be brought about by the different aspects of the signal, which in turn may translate into distinct putative neural mechanisms. In particular, the model shows that the features in the data that support successful decoding —and, therefore, likely reflect stable mechanisms of stimulus representation— have an oscillatory component that spans multiple channels, frequencies and latencies of response; and an additive, slower response with a specific (cross-frequency) relation to the phase of the oscillatory, faster component. At the individual trial level, still, responses are found to be highly variable, which can be due to various factors including phase noise and probabilistic activations.

Significance statement: Except for psychotic patients, human perception is quite stable: our feel is relatively consistent across different presentations of the same stimulus. However, brain responses are, at many levels, very different each time. Still, there must be a space of activity where projected brain responses are relatively stable so that they can support stable perceptual experiences. A proper characterisation of the mechanisms underlying this space

will be useful to understand what underlies unstable perception in disease, for instance in psychotic patients.

Introduction

There are virtually infinite manners by which a constant stimulus can impinge into the sensorium of an animal. For instance, our noses have many receptors that can sense a given odorant molecule, but only a small subset of those are excited each time the odour is perceived (Axel, 1995). Similarly, photons hit and excite photoreceptors in the retina randomly and sparsely for a given presented image (Dowling, 1987). An important aspect of sensation and perception is that never the exact same receptors are excited every time we perceive and, still, our perceptual experiences are quite stable. So the brain must have a way to transit from lack of invariance at the microscopic sensory level toward invariance at the macroscopic level, which ultimately supports the invariant aspects of conscious perception and behaviour. However, we observe significant variability in the brain responses at the trial level (Stein, et al., 2005; McIntosh, et al., 2008; Garrett, et al., 2013), including at the earliest layers of the perceptual hierarchy (Croner, et al., 1993; Freeman, 1978) —that is, each perceptual experience is associated with a unique neural trajectory that does not repeat. The gap between stability in subjective perception and the changing nature of brain responses in an important question in neuroscience. Here, I investigate the distributed aspects of brain activity that are most stable across experimental repetitions, and are therefore most likely to support stable perceptual experiences.

Decoding analysis uses a multivariate machine learning algorithm to predict the identity of the observed stimulus from brain data (Haxby, et al., 2014; Stokes, et al., 2015), producing a set of algebraic subspaces (one per time point) where the brain signals maximally discriminate between conditions, and yielding a measure of accuracy across time that reflects how much information the data conveys about the stimuli. The assessment, via decoding accuracy, of how the discriminative space changes throughout the trial offers a view of the properties of stimulus representation and processing. However, it is not straightforward to know what specific aspects of the signal cause the patterns of decoding accuracy that we observe in perceptual experiments. Without this capacity, it is hard to link these patterns to actual neural mechanisms.

To help fill this gap, I introduce a generative model of multichannel electrophysiological activity (e.g. EEG or MEG) that, under no stimulation, exhibits chaotic phasic and amplitude fluctuations; and that, when stimulated, responds by manipulating certain aspects of the data, such as ongoing phase or signal amplitude, in a stimulus-specific manner. Specifically, in every trial, each channel may or may not respond to stimulation, according to a certain probability. When a channel responds, it can do it in different ways: (i) by phase resetting of the ongoing oscillation to a given target phase and then entraining to a given frequency, (ii) by an additive oscillatory response independent of the ongoing oscillation, (iii) by modulating the amplitude of the stimulus-relevant oscillations, or (iv) by an additive non-oscillatory (slower) response. Each of these effects can arguably be underpinned by distinct neural mechanisms. I named this model *genephys* by *gen*erative model of *e*mpirical electro*phys*iological signals. This model is empirical in the sense that it purely accounts for the features in the signal that are observable, without making any assumption about the underlying neurobiological causes; that is, it can generate signals that, depending on its parametrisation, can share empirical properties with real data. In particular, when confronted with a decoding algorithm, the data generated by this model can show, depending on its configuration, patterns of decoding accuracy with similar characteristics to we observe in real data.

Using real data during a visual experiment as a benchmark, I observed that two different mechanisms can produce realistic decoding results as we see in real visual perception: either phase resetting to a stimulus-specific phase followed by frequency entrainment, or an additive oscillation with a stimulus-specific phase. Either way, a cross-frequency coupling effect is also necessary, where an additive slower response holds a specific phasic relation with the oscillatory (faster) response. Furthermore, the stimulus-related oscillations need to span multiple channels, and have a diversity of frequencies and latencies of response. Other experimental paradigms can be investigated with g*enephys*, which is publicly available as a Python package[1].

Methods

A generative model of empirical electrophysiological signals: *genephys*

[1] https://test.pypi.org/project/genephys, https://github.com/vidaurre/genephys

While the system is unperturbed, *genephys* is based on sampling spontaneously varying instantaneous frequency and amplitude (square root of power) time series, f^{rest} and a^{rest} respectively, that are analytically combined to form the sampled signal x. Amplitude and frequency are allowed to oscillate within ranges r^f and r^a. Instantaneous frequency here refers to angular frequency, from which we can obtain the ordinary frequency in Hertz as $\frac{F}{2\pi} f^{\text{rest}}$, where F is the sampling frequency of the signal. Both f^{rest} and a^{rest} are sampled separately from an autoregressive process of order one, endowing them with chaotic, non-oscillatory dynamics. Given autoregressive parameters $b^f, b^a < 1$, and Gaussian-noise variables e_{f_t}, e_{a_t}, I generate f^{rest} and a^{rest} for a given channel as

$$
\begin{aligned}
f_0^{\text{rest}} &= e_{f_0} \\
f_t^{\text{rest}} &= b_f\, f_{t-1}^{\text{rest}} + e_{f_t} \qquad \text{for t > 0} \\
a_0^{\text{rest}} &= e_{a_0} \\
a_t^{\text{rest}} &= b_a\, a_{t-1}^{\text{rest}} + e_{a_t} \qquad \text{for t > 0.}
\end{aligned}
$$

Without stimulation, a phase time series φ^{rest} is then built as

$$
\begin{aligned}
\varphi_0^{\text{rest}} &= 0 \\
\varphi_t^{\text{rest}} &= \varphi_{t-1}^{\text{rest}} + f_t^{\text{rest}}
\end{aligned}
$$

Then, given some Gaussian-distributed measurement noise ϵ_t with standard deviation σ_ϵ, I build x (in absence of stimulation) as

$$
x_t^{\text{rest}} = a_t^{\text{rest}} \sin \varphi_t^{\text{rest}} + \epsilon_t
$$

This process is done separately per channel and per trial. Note that, under no stimulation, the channel time series are therefore (asymptotically) uncorrelated. We can think of them as dipoles in brain space. We can induce correlations for instance by projecting these time series into a higher-dimensional space, which we can consider to be in sensor space, or by using correlated noise. Altogether, this generates chaotic oscillatory data akin to real data.

When a stimulus is presented at time point τ of the trial, a perturbation is introduced into the system on the p channels that are stimulus-relevant, which can be a subset of the total number of channels. When a channel is not relevant, it does not respond; when it is relevant, it responds to the stimulus stochastically:

Prob (channel j responds | channel j is relevant) = θ_j

Prob (channel j responds | channel j is not relevant) = 0

Where θ_j is a hyperparameter representing a certain probability. In simpler words, relevant channels might respond in some trials, but not in others. In all the simulations, I set all channel probabilities to a single value, $\theta_j = \theta$, but other configurations are possible.

Given some stimulus presentation at time point τ, a channel may respond:

- By phase-resetting to a condition-specific target phase, and then, when the target phase is reached, by frequency entraining to a target frequency.
- By adding a transient, oscillatory response with a condition-specific phase, amplitude and frequency.
- By increasing the (absolute) amplitude of the ongoing oscillation following stimulus presentation (with no phase effect).
- By adding a transient, non-oscillatory response with a condition-specific amplitude.

To implement these effects, I use an double logarithmic response function, asymmetric around the time of maximum effect $t_{\max}$. For the left side (before $t_{\max}$), this function is parametrised by: δ_1, reflecting the latency of the response in number of time points; and δ_2, reflecting how many time points it takes the logarithmic function to go from zero to its maximum before it changes to the logarithmic function. Therefore $t_{\max} = \delta_1 + \delta_2 + \tau$. I introduce some noise in δ_1 per trial to make the timing of the response to vary, as per $\delta_1 \sim \mathrm{Uniform}(0, \sigma_{\delta_1})$, where σ_{δ_1} is a model hyperparameters. This latency noise could be fixed for all channels (absolute stochastic latency) or per channel (relative stochastic latency). It is also possible to use different parametrisations per channel. For example, we can induce a diversity of latencies for the different channels by using different values of δ_1 per channel — so that some channels (e.g. those more closely related to primary sensory areas) respond

earlier than others (e.g. those related to associative areas). Once the activation reaches its maximum at $t_{\max}$, the decay is also parametrised by a logarithmic function with a parameter δ_3, reflecting how many time points it takes the logarithmic function to go from its maximum to zero. A different response function can be used for each type of effect. In the **Supplemental Information** there is a full mathematical specification of the response function.

With respect to the phase-reset and frequency entrainment effect, the phase reset occurs before $t_{\max}$, when the target phase is reached. For each trial and channel,

$$\varphi_t = \varphi_{t-1} + (1 - g_t) f_t^{\text{rest}} + g_t \ \nabla_t \qquad \text{with}$$

$$\nabla_t = \begin{cases} \varphi^k - \varphi_t, & \text{if } \varphi^k - \varphi_t \in [-\pi, \pi] \\ \varphi^k - \varphi_t - 2\pi, & \text{if } \varphi^k - \varphi_t > \pi \\ \varphi^k - \varphi_t + 2\pi, & \text{if } \varphi^k - \varphi_t < \pi \end{cases}$$

Where, for each trial, φ^k is randomly sampled from a von Mises distribution with mean the target phase $\overline{\varphi^k}$ and standard deviation σ_φ; ∇_t is the polar gradient between the target phase and the ongoing phase φ_{t-1}; and g_t is the value taken by the response function at time point t. After $t_{\max}$, phase-resetting is over, and the phase entrainment period starts,

$$\varphi_t = \varphi_{t-1} + g_t \, f^k + (1 - g_t) \, f_t^{\text{rest}}$$

The system then entrains to a possibly stimulus-specific, possibly channel-specific, target frequency f^k, with a strength that logarithmically decreases as t moves away from $t_{\max}$.

With respect to the additive oscillatory response, we consider a sinusoidal oscillator, which is damped by the action of the response function g_t:

$$y_t = g_t \, \alpha^k \sin(\omega^k t + \gamma^k)$$

.

Here, α^k reflects the amplitude of the additive oscillation, ω^k its frequency, and γ^k its phase.

For the amplitude modulation, I apply a multiplying factor to the ongoing amplitude time series:

$$a_t = (1 + g_t\, m^k)\; a_t^{\text{rest}}$$

where m^k is a proportional increment; for example, $m^k = 0.1$ would produce an increment of 10% in amplitude at $t_{\max}$.

With respect to the additive non-oscillatory response, we have:

$$z_t = g_t\, s^k$$

where s^k is sampled from a Gaussian distribution, $\mathcal{N}\,(\overline{z^k}, \sigma_z)$, where $\overline{z^k}$ is stimulus-specific.

Given these elements, the signal is built as

$$x_t = a_t \sin \varphi_t + z_t + y_t + \epsilon_t$$

This model can be trivially extended to have correlated noise ϵ_t across channels, which would also make the channels non-independent.

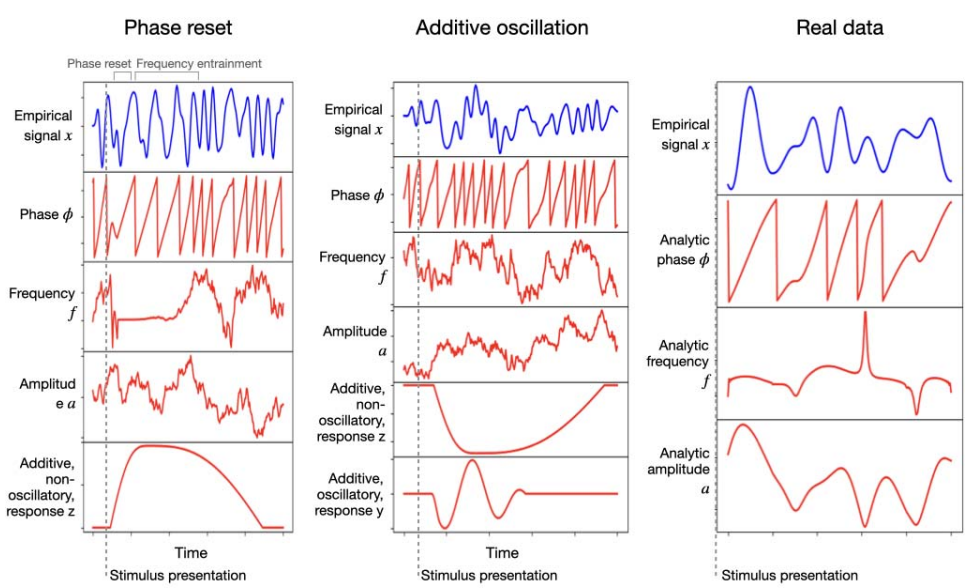

Figure 1. Left and middle: single-trial example of the generated signal (in blue) and its constitutive components (in red): instantaneous phase, frequency and amplitude, as well as an additive non-oscillatory and oscillatory response components; the left panel reflects a phase resetting plus frequency entrainment effect, while the middle panel corresponds to an additive oscillatory component. Right: real (filtered) magnetoencephalography data collected during passive viewing; the red curves are the analytically computed phase, frequency and amplitude (via the Hilbert transform).

Figure 1 shows two examples of how the effect of stimulation looks for one trial and one channel. The left panel corresponds to a phase resetting plus frequency entrainment effect, and the middle panel corresponds to an additive oscillation; both are accompanied by an additive non-oscillatory response. Here, the sampled signal x is shown in blue on top, and the phase φ, frequency f, amplitude a, additive non-oscillatory response z, and additive oscillatory response y are shown in red underneath. For comparison, the right panel shows real magnetoencephalography data from a passive visual experiment where a number of images are shown to the subjects at a rate of one image per second (Cichy, et al., 2016); the measured (filtered) signal is shown in blue, while the red curves correspond to analytical phase, frequency and amplitude (computed via the Hilbert transform on the filtered signal). **Table 1** summarises all the hyperparameters that configure the model.

Parameter	**Math. notation**
Frequency autoregressive parameter	b_f
Amplitude autoregressive parameter	b_a
Frequency range	r_f
Amplitude range	r_a
Measurement noise standard deviation	σ_ϵ
Channel activation probability	θ
Number of relevant channels	p
Latency of response	δ_1
Other response function parameters	δ_2, δ_3
Target phase, mean	$\overline{\varphi^k}$
Target phase, standard deviation	σ_φ
Additive oscillatory response, phase	γ^k
Additive oscillatory response, amplitude	α^k
Additive oscillatory response, frequency	ω^k
Amplitude modulation	m^k

Additive non-oscillatory response, mean	$\overline{z^k}$
Additive non-oscillatory response, standard deviation	σ_z

Table 1: *genephys* configuration hyperparameters.

Decoding accuracy to characterise structured invariance

One possible approach to characterise the stable aspects of brain responses to stimulation is the analysis of average evoked responses potentials or fields (ERP/F) (Dawson, 1954; Steven & Kappenman, 2011; Pfurtscheller & Lopes da Silva, 1999). However, this is limited because perceptual experiences emerge from activity patterns across multiple brain areas acting in a distributed fashion, whereas ERP/Fs are separately evaluated channel by channel. Also, ERP/F analyses are not concerned with what aspects of the signal carry specific information about the stimulus —i.e. they are not predictive of the stimulus (Kragel, et al., 2018).

I instead focus on decoding, which finds patterns of differential activity between conditions across channels and throughout time in a multivariate way (Grootswagers, et al., 2017). I use linear discriminant analysis (LDA), which estimates a projection or subspace in the data that maximally discriminate between conditions. Throughout the trial, this set of projections reflects information about the dynamics of stimulus processing.

Specifically, I use the temporal generalisation matrix (TGM), a $T \times T$ matrix of decoding accuracies (where T is the number of time points in the trial), such that one decoding model is trained per time point and tested on every time point of the trial using cross-validation (King & Dehaene, 2014). This way, the diagonal of the TGM reflects how well can we can decode information time point by time point, while the off-diagonal of the TGM shows how well decoding models generalize to time points different from those where they were trained. As illustrated in **Supplemental Figure 1**, where I show a real-data TGM from a subject performing a simple visual task (Cichy et al., 2016; Vidaurre et al, 2019), the TGM exhibits some characteristic features that we often see throughout the literature. First, there is a strong diagonal band that is relatively narrow early in the trial, often surrounded by areas of worse-than-baseline accuracy. Then, the accuracy on the diagonal becomes progressively wider and weaker, expanding until relatively late in the trial. Also, there are bands of higher-than-

baseline accuracy stemming vertically and horizontally from the time points of maximum accuracy after a brief period of depression, which often show oscillatory behaviour throughout the band. Central to this paper is the observation that the variability of brain responses to stimuli are structured in a specific manner, and that the TGM can reflect various aspects of this structure —but not others. Below, I explore *genephys'* configuration space in relation to its ability to produce patterns of decoding accuracy similar to these from real data.

Results

In the experiments below, I confront *genephys* to classification-based decoding analysis to characterise the stochastic nature of the subspace of brain activity that carry stimulus-specific information. In each simulation, I generated 10 data sets per combination of parameters, each with N=250 trials and 250 time points per trial (i.e. one second for a sampling frequency of 250Hz). For simplicity, only one spontaneous oscillation was sampled, with (angular) frequencies broadly ranging between 0.01 and 0.25π. The number of channels is set to 32. All All TGMs reflect cross-run averages.

For comparison, I use magnetoencephalography (MEG) data recorded while participants viewed object images across 118 categories, as presented in (Cichy, et al., 2016). Each image category were presented 30 times each. Presentation occurred during the first 500ms of the trial, and trials were 1s long, sampled at 250Hz. The multi-channel sensor-space data, epoched around the presentation of each visual stimulus, can be used to train a decoder to predict which visual image is being presented (Cichy, et al., 2016; Vidaurre, et al., 2021). Here, I decoded whether the image corresponded to an animate category (a dog) or inanimate (a pencil).

Oscillatory components underlying the observed decoding patterns

In real data, we often see oscillatory patterns in the TGM, indicating that the subspace of brain activity that carries information about the stimulus must have some oscillatory element. At least two distinct mechanisms may be behind this phenomenon: first, an ongoing oscillation might reset its phase and then entrain to a given frequency in a stimulus-specific fashion; second, a stimulus -specific oscillatory response might by added to the signal after stimulus presentation on top of the existing ongoing oscillation. Essentially, the difference between the two is that, in the phase resetting case, the ongoing oscillations are altered; while

in the other case the additive oscillation coexists with the ongoing oscillations. Next, I use *genephys* together with decoding analysis to compare between these two alternatives, showing that both can produce decoding patterns similar to what we observe empirically in real experiments.

In the simulations, all 32 channels convey information but with a relatively low activation probability ($\theta = 1/6$). For phase resetting and frequency entrainment, I considered a diverse range of entrainment frequencies (between 0.1 and 0.2 in angular frequency) and latencies of response ($\delta_1 = 0$–160ms) across channels. For the additive oscillatory, I similarly considered a similar range of frequencies and latencies of response across channels. (I will show below that channel stochasticity and frequency diversity are both important to produce realistic decoding patterns). The difference between the two fictitious stimuli lied in their different target frequencies (that is, $\overline{\varphi^k}$ for phase resetting and γ^k for the additive oscillation; see specification of the model in **Methods**). I also included an additive non-oscillatory response with a stimulus-specific amplitude, which (as I will also show later) is important to produce realistic decoding results. I did not optimise the parameters of the model to reflect the fine details from real data TGMs, since TGMs vary across subjects (see **Supplementary Figure 2**) and across experimental paradigms (King & Dehaene, 2014).

Figure 2 (top) shows TGMs together with one-channel ERPs (where each stimulus is represented by a different tonality of blue or red; bottom) for the sampled signal x and its various constitutive elements: ongoing phase φ, frequency f, amplitude a, additive non-oscillatory response z, and, when applicable, an additive oscillatory response y. The left panels show results for phase reset plus frequency entrainment, where we can see an effect on the ongoing phase. The middle panels show results for the additive oscillation; here, there is no effect on the ongoing phase, and, instead, the additive oscillatory component y is shown at the bottom. The right panels show an example from real data, where phase, frequency and amplitude were computed analytically using the Hilbert transform on the filtered data.

Although the exact details differ from the right panels of the figure, both types of effects produce patterns reproducing the characteristic signatures of real data. These include the strong diagonal, the vertical/horizontal bands of high generalisation accuracy, and the broadening of accuracy in later stages of the trial (see **Supplementary Figure 1**). Note that

phase resetting plus frequency entrainment is, everything else held constant, a stronger effect than an additive oscillatory response. This is because, for the latter, the ongoing oscillations (here, non-stimulus specific) can interfere with the phase of the additive response, impeding cross-trial phase locking throughout the trial; while, for phase resetting, the ongoing oscillation *is* the effect and there is therefore no interference. In this particular example, anyway, the range for the additive oscillation (0.1–0.2) was much narrower than that of the ongoing oscillation (0.01–0.25π), making the interference more unlikely; that is, the ongoing oscillation phase is approximately averaged out, and treated as noise by the decoding algorithm.

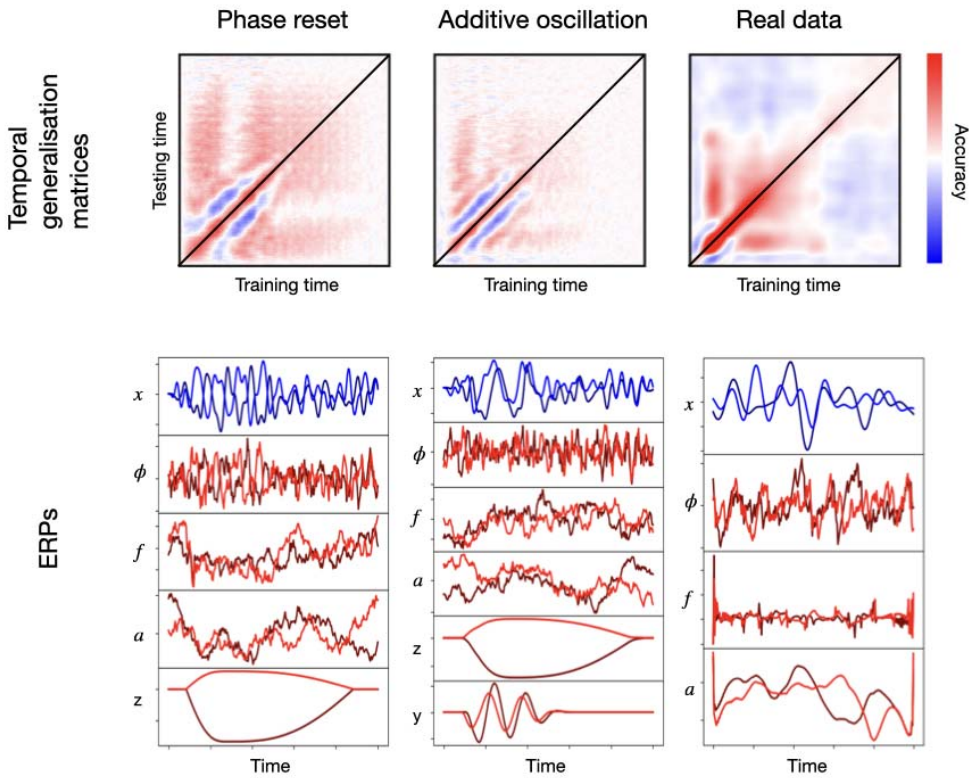

Figure 2. Examples of two configurations based on phase resetting and frequency entrainment (left) and additive oscillatory responses (middle), shown together with results obtained from real data (right). At the top, temporal generalisation matrix (TGM) from standard decoding analysis; on the bottom, average evoked responses (ERP/F) for the sampled signal (blue) and its components (red), for the two stimuli (represented as different tonalities of blue or red).

The distribution of stimulus-specific information spans multiple channels and is stochastic

Next, I use *genephys* to show that the stimulus-specific information spans a large number of channels, and do so stochastically. I focus on the additive oscillatory response effect, which, as shown in the previous section, can produce comparable results to phase resetting followed by frequency entrainment.

I varied the number of relevant channels p as well as the probability of activation θ for the relevant channels, so that the subset of channels that activate is different for every trial. **Figure 3** shows the TGMs for various combinations of p and θ, from a configuration where there are few relevant channels that always respond ($p = 1, \theta = 1$) to another where there are many relevant channels that only respond sparsely ($p = 32,\ \theta = 1/8$). As previously, channels have diverse frequencies and latencies of response; and an additive non-oscillatory response is also included as an effect.

Contrary to empirical TGMs (which have a relatively stylised diagonal), having only a few relevant channels (first three panels of **Figure 3**) produces unrealistically geometric patterns. This indicates that, in real data, the subspace of the data that contains information about the stimulus needs to be multi-dimensional; that is, that the amount of relevant channels must be relatively high (as in the fourth panel of **Figure 3**). However, this must occur in combination with an unstable informational contribution of the channels (in this case expressed by having probabilistic activations), or else the decoding accuracy would become unrealistically perfect. In summary, the subspace of brain activity that carries out information about the condition is highly stochastic at the single trial level.

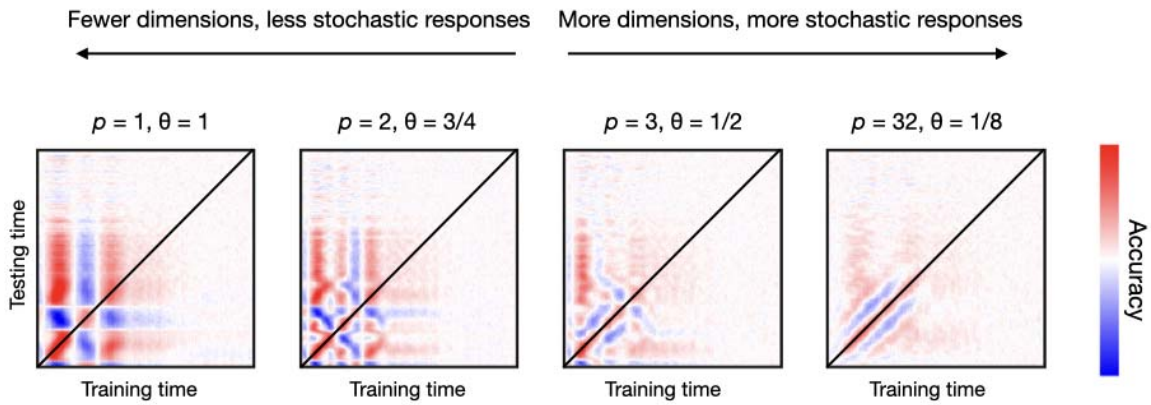

Figure 3. Having more dimensions (channels) carrying stimulus-specific information, but with a larger degree of stochasticity, produces more realistic decoding patterns than having fewer dimensions with a lower degree of stochasticity. Here stochasticity referred to the channels' probability of activation.

Frequency entrainment span multiple frequencies and latencies

In the previous sections, I showed that a noisy, additive oscillation effect (or phase reset effect) across multiple channels can generate decoding patterns as we see in real data. Next, I demonstrate that the effect must span a diversity of frequencies across channels,), as well as a diversity of latencies of response. In real data, frequency diversity can be expressed as, for example, a gradient of frequencies from primary towards more associative areas; while diversity in latency could reflect phenomena such that primary areas respond earlier than associative areas.

For frequency diversity, each channel is endowed with a different effect-related frequency that are not multiples of each other, i.e. different values of ω^k between 0.1 and 0.2 in angular frequency. For latency diversity, channels do not respond simultaneously but with different values of δ_1 between 0 and 120ms (see the specification of the model in **Methods**). **Figure 4** shows a two-by-two design. On the left column, I set *genephys* to have a uniform frequency of response, while on the right column it uses a diversity of frequencies. On the top row, we have a uniform latency of response (i.e. all channels have the same latency of response),

whereas on the bottom row we have a diversity of latencies of response. See **Supplemental Figure 3** for a similar result with phase resetting followed by frequency entrainment.

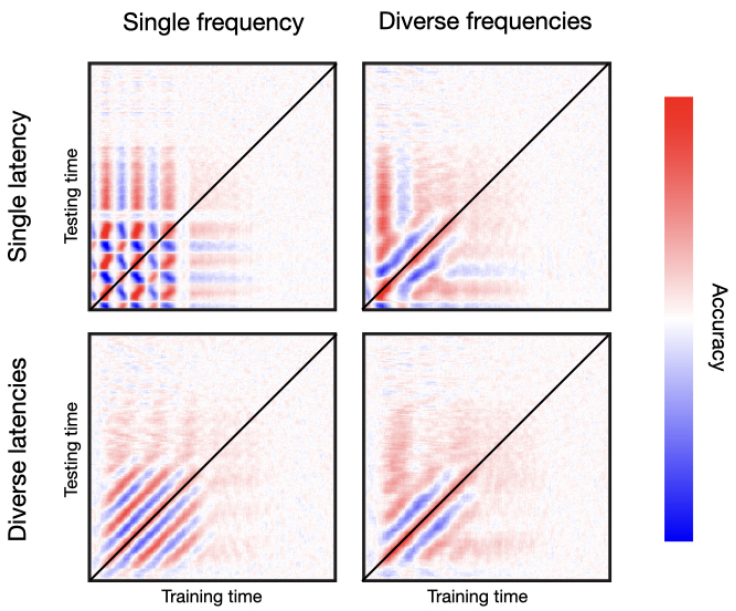

Figure 4. Oscillatory responses to stimulation occur in a diversity of frequencies and latencies across channels. Top row, single latency of response; bottom row, diverse latencies across channels; left column, single frequency; right column; diverse frequencies across channels.

As mentioned, real data normally yield a relatively tight band of high decoding accuracy along the diagonal, often accompanied from contiguous parallel bands of below-baseline. Critically, the fact that we do not typically observe a chequer pattern means that the trajectory of phase across channels does not repeat itself periodically. If it did, it would show patterns as in the top left panel, where the uniformity of frequencies and latencies gives rise to an unrealistically regular pattern —such that a decoder trained at a certain time point will become equally accurate again after one cycle at the entrained frequency. Having a diversity of frequencies but not of latencies produces another regular pattern consisting of alternating, parallel bands of higher/lower than baseline accuracy. This, shown in the bottom left panel, is not what we see in real data either. Having a diversity of latencies but not of frequencies gets us closer to a realistic pattern, as we see in the top right panel. Finally, having diversity of both frequencies and latencies produces the most realistic pattern, as we can see by comparing to the examples in **Figure 2** or in **Supplemental Figure 2**, and many others

throughout the literature (King & Dehaene, 2014). Similar conclusions can be drawn from **Supplemental Figure 3**, where the effect is based on phase resetting and subsequent frequency entrainment.

In summary, these results show that it is not only important for the stimulus-relevant subspace of activity to be high-dimensional in space, but also in the time domain.

A slower additive component must be coupled with the oscillatory response

In real data, we normally also see a general broadening of decoding accuracy in the TGM as time progresses throughout the trial (see **Figure SI-1**). This is often interpreted as neural representations becoming more stable at latter stages of the trial, which is putatively linked to memory encoding and higher cognitive processes.

In **Figure 5A**, I show that this effect can be reproduced on synthetic data through the addition of a slowly-progressing, non-oscillatory response. Specifically, I set up a response function such that, after stimulus presentation, the non-oscillatory additive response ramps up to a stimulus-specific target value in about 100s, and then slowly decays to vanish at around 800ms. Also, I modulate the strength of the oscillatory response using values of $\overline{z^k}$ (see **Methods**) that differ between the two stimuli by a magnitude that ranges from 0.0 (no difference) to 1.0 (for reference, the examples in **Figure 2** had difference of 0.5). As seen in **Figure 5A**, the broadening of decoding accuracy gets stronger as the difference in the slow response increases.

Another feature commonly seen on real data are the vertical and horizontal bars of high accuracy stemming from the time point of maximum accuracy (see **Figure SI-1**), which is sometimes interpreted as evidence of recurrence of the stimulus representations in the brain.

I show in **Figure 5B** that this feature emerges from the following property in the data: that the amplitude differences of the slow component must be consistent with the phase differences of the oscillatory component. For example, if the phase difference of the oscillatory component between stimulus A and B is positive at the time of maximum activation ($t_{\max}$), then the difference in amplitude of the slower component has to be also

positive throughout the trial —i.e. the two effects must be in-phase. That was the case for all panels of **Figure 5A**. For **Figure 5B**, while keeping a difference between the values of z^k equal to 0.5 (as in the middle panel of **Figure 5A**), I varied the phase consistency between the oscillatory and the non-oscillatory components. In the leftmost panel, the oscillatory and the non-oscillatory components are in-phase for all channels, while in the rightmost panel, they are anti-phase for all channels; in between, 25%, 50% and 75% of the channels are in-phase (and 75%, 50% and 25% are anti-phase, respectively). As observed, the type of phase consistency between the oscillatory and the non-oscillatory component has a strong impact on the TGM. In particular, an in-phase relation bears the most consistent patterns with the real data shown throughout the paper.

Altogether, these results reflect the importance of a specific form of cross-frequency coupling in order to obtain results as we observe in real experiments.

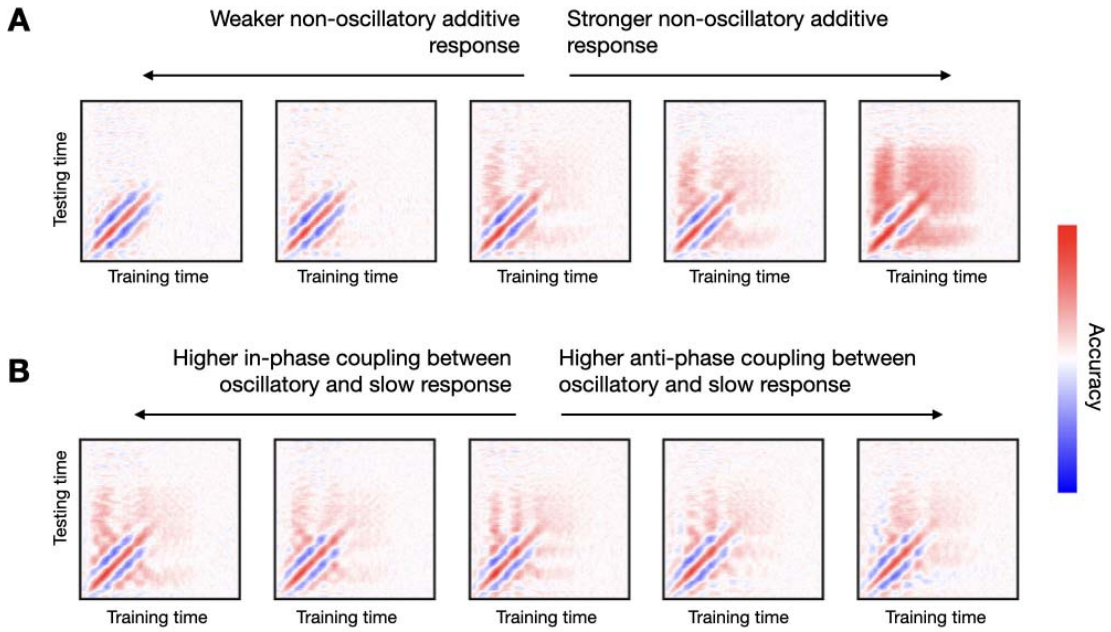

Figure 5. An additive non-oscillatory response produces an slow expansion of decoding accuracy toward the end of the trial. **A**: By increasing the strength of the non-oscillatory response, the broadening of accuracy becomes more prominent. **B**: Changing the nature of the phasic relationship between the slower and the faster (oscillatory component) greatly changes the TGM, from all in-phase (left) towards all anti-phase (right).

Amplitude increases modulate the size of the effect

Are modulations in the amplitude of the stimulus-specific oscillation necessary for the effects we observe in real data? They are not, but they can enhance the already existing patterns.

I generated various data sets, all with the same phase modulation based on additive oscillatory components. In each of them, I applied a different amount of amplitude enhancement, from no increase to a five-fold increase —which, critically, did not entail any effect on the signals' phase. Note that an amplitude effect without a phase effect would not result in any phase locking across trials, and therefore could not lead to any decoding accuracy. Having applied decoding analysis, I looked at two characteristic features of the TGM: (i) the diagonal, and (ii) a vertical cut stemming from the time point of maximum accuracy. **Figure 6** shows the results. As observed, the main features are present in all runs

regardless of the size of the amplitude effect, although they were more prominent for higher amplitude modulations.

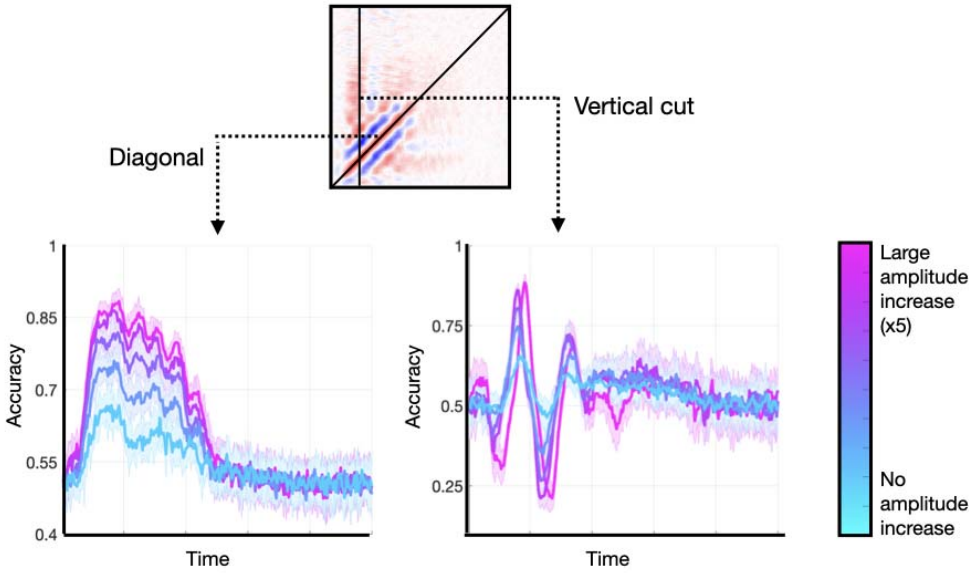

Figure 6. Amplitude enhancement of the stimulus-relevant oscillation is not strictly necessary to produce realistic results, but it can enlarge the effects. Two features of the TGM are highlighted: the diagonal, and a vertical cut at the time point of maximum accuracy.

Discussion

Brain's responses to even the simplest stimuli are characteristically variable. This is not surprising, given the brain's plasticity, and that it never stops generating ever-changing endogenous activity. It also speaks to the brain's degeneracy (Edelman & Gally, 2001) —i.e. the fact that there are many possible neural trajectories that can achieve a single purpose. How this variability translates into behaviour and experience is however an open question. Anyhow, it seems reasonable that, at some level, brain responses must keep some invariant aspects so that our perceptual experiences remain stable. Here, I investigated, using a novel generative model, the most stable aspects of brain responses to stimuli as seen through the lens of decoding accuracy, which is by definition based on averaging.

Previous work has analysed the nature of brain responses to perceptual stimulation using average evoked responses (Sauseng, et al., 2007), arguing either for a predominant role of

additive responses (Shah, et al., 2004; Mazaheri & Jensen, 2006) or phase resetting (Makeig, et al., 2002). These studies looked at the average response to a given stimulus, but did not investigate what aspects of the data carry information about the identity of the stimulus; this is the focus of this paper and the goal of the proposed model.

It is important to note that the list of effects that I have explored is non-exhaustive. For example, I have considered additive oscillatory responses in the form of sinusoidal waves. Another possibility could be to have additive oscillatory responses that are non-linear, i.e. with a tendency to spend more time in certain phases (for example, having wider peaks than throughs); in this case, even in the absence of phase locking between trials, we could potentially have a significant evoked response due to phase asymmetry (Nikulin, et al., 2007). For simplicity, I have considered independent sources of activity that exhibit correlations only through the induced effect. In practice, brain areas are in constant communication even in the absence of stimulation. Alternatives where sources are modelled as coupled oscillators (Breakspear, et al., 2010; Cabral, et al., 2014), or where there is correlated noise, are also possible. Also for simplicity, I have considered that every channel has only one fundamental frequency (besides the additive oscillation); in practice, multiple ongoing frequencies coexist and interact, potentially affecting the TGM if they are do not completely average out across trials. Finally, the inherent stochasticity of the stimulus-specific space of activity can take various forms; here, I have explored a probabilistic activation of the channels, but others, such as noise in the phase distribution, are also possible and can be readily be simulated using *genephys*.

Importantly, I have shown that standard decoding analysis can differentiate between these explanations only to some extent. For example, it cannot trivially disambiguate between phase-resetting and additive oscillatory components, except for the fact that phase resetting might lead to higher accuracy —but this could be balanced by manipulating the signal-to-noise ratio of the signal. In future work, alternatives to standard decoding analysis might be used to disentangle these sources of variation (Vidaurre, et al., 2019). In order to explore the space of configurations more effectively, an automatic exploration of the hyperparameter space using, for instance, Bayesian optimisation (Lorenz, et al., 2017) is an alternative for future consideration.

Overall, the results obtained from applying *genephys* suggest that the stable aspects of brain activity regarding stimulus processing are underpinned by phasic modulations of an oscillatory component coupled with a slower component in a very specific manner. The subspace of brain activity induced by the effect is high-dimensional in both the spatial domain (it must span many channels) and the frequency domain (it must involve a great diversity of frequencies and exhibit a diversity of latencies). This effect may be accompanied by an amplitude modulation. Above and beyond these average patterns, the stimulus-specific subspace of brain responses is highly stochastic at the trial level. Moving forward, the evidenced role of oscillations and slow responses in stimulus processing, together with its high dimensionality in space and frequency, may point at a relevant role for largely distributed neural ensembles besides more localised circuits.

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Conflicts of interest: None

Code accessibility: The model is available as a Python package in PyPI.

Bibliography

Axel, R., 1995. The molecular logic of smell. *Scientific American*, pp. 154-159.

Breakspear, M., Heitmann, S. & Daffertshofer, A., 2010. Generative models of cortical oscillations: neurobiological implications of the Kuramoto model. *Frontiers in human neuroscience*, p. 190.

Cabral, J. et al., 2014. Exploring mechanisms of spontaneous functional connectivity in MEG: How delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. *NeuroImage*, pp. 423-435.

Cichy, R. M., Pantazis, D. & Oliva, A., 2016. Similarity-based fusion of MEG and fMRI reveals spatio-temporal dynamics in human cortex during visual object recognition. *Cerebral Cortex*, pp. 3563-3579.

Croner, L., Purpura, K. & Kaplan, E., 1993. Response variability in retinal ganglion cells of primates. *Proceedings of the National Academy of Sciences*, pp. 8128-8130.

Dawson, G. D., 1954. A summation technique for the detection of small evoked potentials. *Electroencephalography & clinical neurophysiology*.

Dowling, J. E., 1987. *The retina: an approachable part of the brain.* s.l.:Harvard University Press.

Edelman, G. & Gally, J., 2001. Degeneracy and complexity in biological systems. *Proceedings of the National Academy of Sciences* , pp. 13763-13768.

Freeman, W. J., 1978. Spatial properties of an EEG event in the olfactory bulb and cortex. *Electroencephalography and Clinical Neurophysiology,* pp. 586-605.

Freeman, W. J., 2000. *How brains make up their minds.* New York: Columbia University Press.

Garrett, D. D. et al., 2013. Moment-to-moment brain signal variability: A next frontier in human brain mapping?. *Neuroscience & Biobehavioral Reviews,* pp. 610-624.

Grootswagers, T., Wardle, S. G. & Carl, T. A., 2017. Decoding Dynamic Brain Patterns from Evoked Responses: A Tutorial on Multivariate Pattern Analysis Applied to Time Series Neuroimaging Data. *Journal of Cognitive Neuroscience,* Issue 29, p. 677–697.

Haxby, J. V., Connolly, A. C. & Guntupalli, S., 2014. Decoding Neural Representational Spaces Using Multivariate Pattern Analysis. *Annual review of neuroscience,* pp. 435-456.

King, J.-R. & Dehaene, S., 2014. Characterizing the dynamics of mental representations: the temporal generalization method. *Trends in cognitive sciences,* pp. 203-210.

Kragel, P. A., Koban, L., Feldman Barrett, L. & Wager, T. D., 2018. Representation, pattern information, and brain signatures: from neurons to neuroimaging. *Neuron,* pp. 257-273.

Lorenz, R., Hampshire, A. & Leech, R., 2017. Neuroadaptive Bayesian optimization and hypothesis testing. *Trends in Cognitive Sciences,* pp. 155-167.

Makeig, S. et al., 2002. Dynamic Brain Sources of Visual Evoked Responses. *Science,* pp. 690-694.

Mazaheri, A. & Jensen, O., 2006. Posterior α activity is not phase-reset by visual stimuli. *Proceedings of the National Academy of Sciences,* pp. 2948-2952.

McIntosh, A. R., Kovacevic, N. & Itier, R. J. J., 2008. Increased Brain Signal Variability Accompanies Lower Behavioral Variability in Development. *PLOS Computational Biology,* p. e1000106.

Nikulin, V. et al., 2007. A novel mechanism for evoked responses in the human brain. *European Journal of Neuroscience,* pp. 3146-3154.

Pfurtscheller, G. & Lopes da Silva, F., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clinical Neurophysiology,* pp. 1842-1857.

Sauseng, P. et al., 2007. Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion. *Neuroscience,* pp. 1435-1444.

Shah, A. S. et al., 2004. Neural Dynamics and the Fundamental Mechanisms of Event-related Brain Potentials. *Cerebral Cortex,* p. 476–483.

Stein, R. B., Gossen, E. R. & Jones , K. E., 2005. Neuronal variability: noise or part of the signal?. *Nature Reviews Neuroscience,* p. 389–397.

Steven, L. J. & Kappenman, S. E., 2011. *The Oxford handbook of event-related potential components.* s.l.:Oxford university press.

Stokes, M. G., Wolff, M. J. & Spaak, E., 2015. Decoding Rich Spatial Information with High Temporal Resolution. *Trends in Cognitive Sciences,* pp. 636-638.

Vidaurre, D. et al., 2019. Temporally unconstrained decoding reveals consistent but time-varying stages of stimulus processing. *Cerebral Cortex,* pp. 863-874.

Supplemental methods: The response function

Assuming the stimulus was presented at time point τ within a given trial, and that both t and τ are expressed in number of time points, the response function is asymmetric around $t_{\max}$, when the function takes the value 1.0 from both sides. In the experiments above, both left and right parts are logarithmic. Mathematically,

$$g_t = \mathrm{G}(t;\, \tau) = 0.0, \text{ if } t < \delta_1 + \tau$$

$$g_t = \mathrm{G}(t;\, \tau) = -\log\left(1 + \left(\frac{\delta_1+\delta_2+\tau-t-1}{T_1}\right)^{\varsigma_1}\right) + C_1, \text{ if } t \in [\delta_1 + \tau, \delta_1 + \delta_2 + \tau]$$

$$g_t = \mathrm{G}(t;\, \tau) = -\log\left(1 + \left(\frac{\mathrm{t}-\tau-\delta_1-\delta_2-1}{T_2}\right)^{\varsigma_2}\right) + C_2,$$

$$\text{if } t \in [\delta_1 + \delta_2 + \tau, \delta_1 + \delta_2 + \delta_3 + \tau]$$

$$g_t = \mathrm{G}(t;\, \tau) = 0.0, \text{ if } t > \tau + \delta_1 + \delta_2 + \tau + 1 + T_2,$$

where

- δ_1 reflects the latency of the response in number of time points,
- δ_2 is how many time points it takes the left logarithmic function to go from 0.0 to 1.0,
- δ_3 is how many time points it takes the right logarithmic function to go from 1.0 to 0.0,
- $t_{\max} = \delta_1 + \delta_2 + \tau$ is the time point of maximum response (i.e. the changing point between the two functions),
- C_1,C_2,T_1,T_2 are normalisation constants chosen such that the logarithmic functions are bounded between 0.0 and 1.0, and $\mathrm{G}(t_{\max};\, \tau) = 1.0$ from both sides.
- ς_1 and ς_2 determine the shape of the logarithmic functions (here chosen to 2 and 4 respectively).

Note that, thanks to the normalisation constants, both the left and the right side of the response function take values between 0.0 and 1.0. There is also the possibility of using an

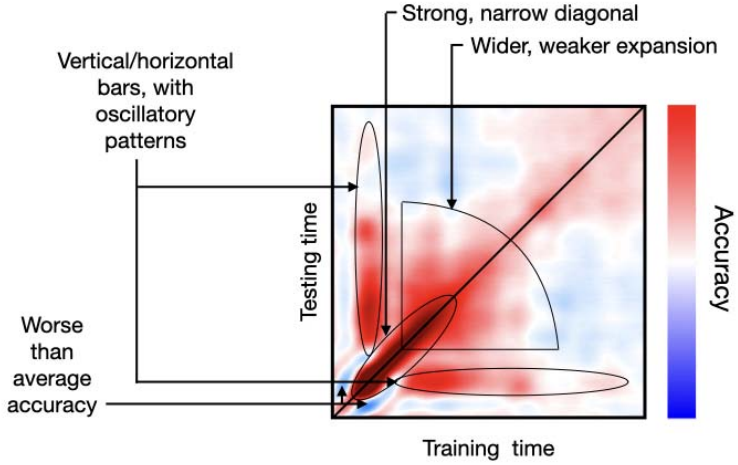
exponential function —which is faster to decay— in either side, but I did not use it in the experiments. For example, in the left part, this would take the form:

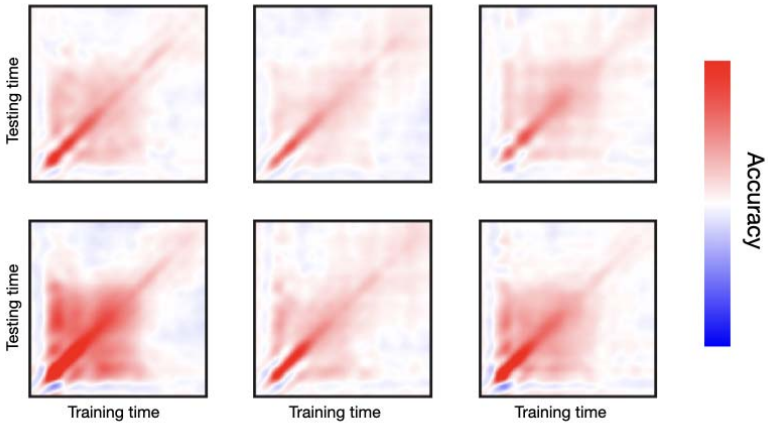
$$\frac{e^{-\frac{0.5\,(\delta_1+\delta_2+\tau-t)^2}{C_3}}}{C_4}\ ,$$

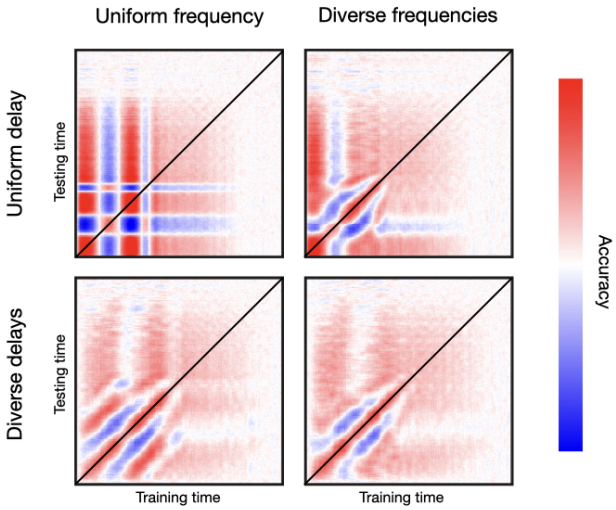
where C_3 and C_4 are normalisation constants.

Supplemental figures

Supplemental Figure 1: Example of real TGM, where the different characteristic features have been highlighted.





Supplemental Figure 2: TGMs from six real data example subjects performing a passive viewing paradigm

Supplemental Figure 3: Phase reset plus frequency entrainment effect. Top row, single latency of response; bottom row, diverse latencies across channels; left column, single frequency; right column; diverse frequencies across channels.