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Homogeneity and identity tests for unidimensional Poisson processes for neurophysiological peri-stimulus time histograms.

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Abstract

The first characterization of the response of a neuron to a stimulus is the peri-stimulus time histogram (PSTH). From a statistical viewpoint the PSTH is an estimator of the intensity of the inhomogeneous Poisson process describing (asymptotically) the aggregated responses of the neuron to repeated presentations of the stimulus. The PSTH is often used to address qualitatively two questions: i) is the neuron responding to the stimulation? ii) are the responses of a neuron to two different stimuli different? We propose here quantitative answers based of the PSTH. The observed state space is first finely binned before applying a variance stabilizing transformation. The homogeneity ("Is the neuron responding?") is then addressed by using a linear smoother estimator for the scaled Poisson process intensity before building a confidence set containing this estimator. The identity ("Are the two responses identical?") is addressed by constructing the cumulative sum of the difference of the scaled PSTH obtained with the two stimuli. This cumulative sum tends under the null hypothesis towards a canonical Brownian motion. Minimal surface domains containing the totality of a given fraction of the realizations of a canonical Brownian motion are available, allowing us to build an identity test. Our motivating dataset arises from our own experimental work and is publicly available. Our proposed methods are implemented in publicly available and documented codes for either R or Python.
1 Introduction

Neurophysiologists often repeat the presentation of a given stimulus, e.g., an odor when studying the olfactory system, and then, observe neuronal outputs (sequences / trains of action potentials / spikes). The outputs are time aligned on the stimulus onset and their sum is generally modeled as a uni-dimensional Poisson process—a key result from the theory of point processes states that if the successive responses are independent, the resulting process converges towards an inhomogeneous Poisson process (T. Brown 1978; Grigelionis 1963; Valerie Ventura et al. 2002). This paper focuses on two classical questions in neurophysiology: i) is the process homogeneous (is the neuron responding to the stimulation)? ii) are two given observations identical (are the responses to two different stimuli different)?

A classical approach is to build the peri-stimulus time histogram or PSTH (George L. Gerstein and Kiang 1960; Perkel, G. L. Gerstein, and Moore 1967), an estimator of the intensity of the Poisson process describing the aggregation of the successive responses. The PSTH has been around for a long time and remains the first descriptive statistics used when characterizing stimulus / response relations in neurons. When constructing the PSTH, the automatic bin width choice, or more generally the bandwidth choice when smooth estimates are looked for, has rarely been touched upon (Kaufman, Valérie Ventura, and Kass 2005; Pouzat and Chaffiol 2009; Reynaud-Bouret et al. 2013; Shimazaki and Shinomoto 2007, 2010; Wallstrom, Liebner, and Kass 2007) despite of its importance. Only pointwise confidence intervals have been proposed to date (Dörrscheidt 1981; Pouzat and Chaffiol 2009) meaning that the PSTH is rarely used as a quantitative tool. The assessment of differences between two PSTH has received some attention (Dörrscheidt 1981; Ellaway 1978; Tam 2009; Ushiba et al. 2002) going generally through an examination of the cumulative difference of the PSTH and linking this question to the interpretation of cumulative sum charts (Hawkins and Olwell 1998; Siegmund 1985). The quantitative evaluation of the difference has nevertheless not been farther than the definition of pointwise intervals that can be appropriate for change point detection but fall short of addressing the overall difference issue.

We propose to finely bin the observed state space before applying a variance stabilizing transformation (L. D. Brown, Cai, and Zhou 2010). The homogeneity is then addressed by using a linear smoother (Wasserman 2006) estimator for the scaled Poisson process intensity before building a confidence set containing this estimator (Sun and Clive R. Loader 1994). The prior variance stabilization is important since we justify the construction of the
confidence sets by using Gaussian processes and this requires the observation errors to be IID and to follow a Gaussian distribution. One may notice that the smoothing bandwidth choice is not crucial: the null hypothesis is homogeneity of the process and a constant intensity cannot be over-smooth with a linear smoother. In a second time, we address the question of identity of two observed processes by applying a common binning on two observations followed by variance stabilization and subtraction, bin per bin of the two scaled processes. The resulting sequence of differences should then be, under the null hypothesis of identity, a sequence of IID draws from a centered Gaussian distribution with a known variance. We take into account multiple comparisons by first constructing the cumulative process (the differences contained in the successive bins are added one by one in the bin order) that should under the null hypothesis—and after proper rescaling—converge towards a standard Brownian motion as stated in Donsker’s theorem (Billingsley 1999; Durrett 2009). The question then boils down to testing if the rescaled difference process is compatible with a standard Brownian motion. We use the results of Kendall, Marin, and Robert 2007 to build a minimal surface domain within which a prescribed fraction of the observed standard Brownian motions will be entirely contained. The combination of Donsker’s theorem with the minimal surface domain allows us to built a test. This test is free since it does not depend on the true common underlying intensity of the two observed process under the null hypothesis. The proposed tests are implemented in two software environments: R and Python. The technique used in the second test can clearly be applied to any context where a sufficient number (50 or more) of tests are performed.

This article is organized as follows. Section 2 presents briefly the neuronal data used in this article and the kernel based linear smoother used in section 3. Section 3 presents the homogeneity test based on the confidence set construction. Section 4 presents the identity test. A simulation study of the sample size sensitivity of the identity test is presented in Section 5. In Section 6, a discussion of the proposed test is carried out and perspectives are presented. A companion document allowing readers to reproduce the complete analysis presented in this article in both R and Python is available on demand to the first author.
2 Peri-stimulus time histograms and their smooth estimates

2.1 The neurophysiological data and the two questions

Our dataset arises from our own experimental work and is publicly available—either as part of our R package STAR (on the CRAN) or from the zenodo server (DOI:10.5281/zenodo.14281, Pouzat and Chaffiol 2015)—and are fully described in Pouzat and Chaffiol 2009. After recording the spontaneous activity for a few minutes, a cockroach (Periplaneta americana) was stimulated with an odor: citronellal, terpineol or a 50/50 mixture of the two. The recordings were made from the first olfactory relay of the insect with an interval between stimulations long enough for the effect of the former to have disappeared when the next comes. After a preprocessing called spike sorting (Einevoll et al. 2012), sequences of action potentials or spike trains are extracted from the continuous raw data. We then get data representations called raster plots (Fig. 6, in the Appendix). The main conclusions are:

- Neuron 1 is excited (its discharge frequency increases) by the stimulation.
- Neuron 3 is inhibited with a delay (its discharge frequency decreases after the stimulation).
- Neuron 2 is not clearly responding.

A second question of interest is to conclude if the responses for the same neuron stimulated with different odors are identical or not (Fig. 7, in the Appendix).

2.2 The "classical" peri-stimulus time histogram

As mentioned in the introduction, the aggregated process ("summation" of all the responses) converges, under smooth assumptions, towards an inhomogeneous Poisson process. A peri-stimulus time histogram (PSTH) (George L. Gerstein and Kiang 1960; Perkel, G. L. Gerstein, and Moore 1967), is, in statistical terminology, a piecewise constant estimator of the Poisson process intensity, $\lambda(t)$, built conditionally on a bin width of duration $\delta$. The number of spikes falling in each of the $k$ bins (from all the trials realigned on the stimulus onset) is counted and noted $\{y_1, \ldots, y_k\}$. These observations are realizations from a set of Poisson random variables $\{Y_1, \ldots, Y_k\}$ with
parameters:
\[
 n \int_{t_i - \delta/2}^{t_i + \delta/2} \lambda(u) \, du \approx n \lambda(t_i) \delta , \quad i = 1, \ldots, k ,
\]  
(1)
where \( t_i \) is the center of a class (bin) and \( n \) is the number of stimulations. The piecewise constant estimator of \( \lambda(t) \) is then defined by:
\[
 \hat{\lambda}(t) = y_i / (n\delta) , \quad \text{if} \quad t \in [t_i - \delta/2, t_i + \delta/2) .
\]  
(2)

2.3 Variance stabilization before smooth estimation

Our goal here is not intensity estimation per se, but the construction of a confidence set containing the actual \( \lambda(t) \) (for all \( t \)), with a given probability. We first transform the Poisson regression problem to a Gaussian regression by stabilizing the variance (Anscombe 1948; L. D. Brown, Cai, and Zhou 2010) with a square root transform.

Let \( X_{i,j} \) be the number of spikes falling in bin \( i \) for trial \( j \) and let \( Y_i = \sum_{j=1}^{n} X_{i,j} \) be the aggregated process. As noted by Anscombe 1948, an improvement to the square root transform is given by transforming \( Y_i \) as:
\[
 Z_i = 2 \sqrt{(Y_i + 1/4)/n} .
\]  
(3)
The effect of this variance stabilizing transformation is illustrated on Fig. 1. The bin width should be chosen large enough to have a few events per bin most of the time. We used \( \delta = 25 \) ms in Fig. 1 giving us a typical count between 3 and 4 before the stimulus onset. In our application, choosing this bin width is not a problem since we can always increase our "stationary" regime recording duration, before presenting the stimuli, in order to have a reliable estimate of the spontaneous frequency of the neuron. The bin width is then the targeted count divided by the product of the spontaneous frequency and the number of trials.

2.4 Smooth estimation: Nadaraya-Watson estimator

After variance stabilization, we have a Gaussian regression setting:
\[
 Z_i = r(t_i) + \epsilon_i \sigma ,
\]  
(4)
where the \( \epsilon_i \) i.i.d. \( \mathcal{N}(0, 1) \). Following Wasserman 2006 we use a Nadaraya-Watson estimator:
\[
 \hat{r}(t) = \sum_{i=1}^{k} l_i(t) Z_i .
\]
The functions $l_i$ are defined by:

$$l_i(t) = \frac{K \left( \frac{t-t_i}{h} \right)}{\sum_{j=1}^{k} K \left( \frac{t-t_j}{h} \right)} .$$

(5)

In this article we use the tricube kernel: $K(t) = 70/81 \left( 1 - |t|^3 \right)^3 \mathbb{I}(t)$, where $\mathbb{I}(t)$ is the indicator function.

Since after variance stabilization the variance is known we can set our bandwidth by minimizing Mallows’ $C_p$ criterion instead of using cross-validation. More explicitly, we minimize:

$$(1/k) \sum_{i=1}^{k} (Z_i - \hat{r}(t_i))^2 + 2\sigma^2 \left( \frac{\sum_{i=1}^{k} l_i(t_i)}{k} \right).$$

Fig. 2 illustrates this procedure with the data of Fig. 1. Note that the
optimal bandwidth (225 ms) is nearly ten times larger than the initial bin width (25 ms).

Figure 2: Nadaraya-Watson estimator of Neuron 1 response to citronellal. Left: Mallows’ Cp score vs bandwidth. Right: variance stabilized spike counts per bin (black) and Nadaraya-Watson estimator with optimal bandwidth.

3 Confidence set and homogeneity test

Let $S$ is a large class of functions, we would like to provide a confidence envelop $B = \{s \in S : u_1(t) \leq s(t) \leq u_2(t), \forall t \in [a, b]\}$, such that:

$$\Pr \{r \in B\} \geq 1 - \alpha$$

(6)

for all $r \in S$ (Wasserman 2006). Since smooth estimators exhibit a bias that does not disappear even with large sample sizes, we built sets around $\tau = E(\hat{r}) = \sum_{i=1}^{k} l_i(t) r(t_i)$. Moreover we have:

$$\text{Var}(\hat{r}(t)) = \sigma^2 \sum_{i=1}^{k} l_i(t)^2 = (1/n) \|l(t)\|^2 .$$

Since the stabilized variance is equal to $1/n$.

We consider a confidence band for $\tau(t)$ of the form:

$$I(t) = \left( \hat{r}(t) - c \|l(t)\|/\sqrt{n}, \hat{r}(t) + c \|l(t)\|/\sqrt{n} \right) ,$$
with $c > 0$ and $a \leq t \leq b$.

Following Sun and Clive R. Loader [1994] and Wasserman [2006] we have:

$$\Pr \{ \tau(t) \notin I(t) \text{ for some } t \in [a,b] \} = \begin{cases} 
\Pr \left\{ \max_{t \in [a,b]} \frac{|r(t)-\tau(t)|}{\|l(t)/\sqrt{n}\|} > c \right\}, \\
\Pr \left\{ \max_{t \in [a,b]} \frac{\sum_{i=1}^{k} (\epsilon_i/\sqrt{n}) l_i(t)}{\|l(t)/\sqrt{n}\|} > c \right\}, \\
\Pr \left\{ \max_{t \in [a,b]} |W(t)| > c \right\},
\end{cases}$$

where $W(t) = \sum_{i=1}^{k} \epsilon_i l_i(t)/\|l(t)\|$ is a Gaussian process.

The constant $c$ is given by solving the tube formula (Sun and Clive R. Loader [1994]) for the distribution of the maximum of a Gaussian process:

$$\alpha = \Pr \left\{ \max_{t \in [a,b]} \left| \sum_{i=1}^{k} \epsilon_i l_i(t)/\|l(t)\| \right| > c \right\} \approx 2 \left( 1 - \Phi(c) \right) + \frac{\kappa_0}{\pi} \exp \left( -\frac{c^2}{2} \right),$$

and $\kappa_0 \approx (b-a)/h \left( \int_{a}^{b} K'(t)^2 dt \right)^{1/2}$.

Fig. 3 illustrates the construction of a 95% confidence set for Nadaraya-Watson estimator of the citronellal response of Neuron 1. Although Wasserman [2006] describes a strategy to take the fact that the smoother bandwidth was set from the data, we won’t need it here since our purpose is to test the homogeneity of the intensity of the process. If the underlying intensity is homogeneous, the (transformed) intensity should be a constant (that is, a horizontal line on a graph like Fig. 3).

Note that linear smoothers cannot oversmooth a constant function since Eq. (5) imposes a normalization. We can therefore decide than we would be willing to miss some actual non-stationarities on a short time scale by using a bandwidth slightly longer that the latter, giving us a reduced estimator variance. Our knowledge of the (cockroach olfactory) system tells us that typical responses last 100 ms to 1 s so in the case of the "dubiously responding" Neuron 2, we set our bandwidth to 1 s and get the result illustrated on Fig. 4 allowing us to reject the null hypothesis of non-response at a 0.95 level.

4 Identity test

We now turn to our second question: the identity of the responses of a given neuron to two different stimuli; and look for an answer that does not require any hypothesis on the underlying process intensity, when the latter is actually the same for the two situations. We could clearly use our previous
Figure 3: Nadaraya-Watson estimator of Neuron 1 response to citronellal. Variance stabilized data (black) Nadaraya-Watson estimator (blue) and 0.95 confidence band (red).

confidence set construction, setting the guaranteed probability of containing the actual smooth intensity through a Bonferroni like correction, such that the two bands would not overlap at, at least, one time point with a given frequency under the null hypothesis of identity. But we can find a more direct answer that is also, in principle, better since the inequality in Eq. \(6\) becomes (asymptotically) an equality.

We nevertheless start as before by using a sequence of Poisson random variable as a proxy for our process through time discretization. So when we compare the citronellal and terpineol responses of Neuron 1, we use a bin width of 25 ms and get to set of observations: \(\{y_{\text{citron}}^1, \ldots, y_{\text{citron}}^k\}\) and \(\{y_{\text{terpi}}^1, \ldots, y_{\text{terpi}}^k\}\). We also stabilize the variance as we did before ( \(z_i = 2\sqrt{(y_i + 0.25)/n}\) ) to get: \(\{z_{\text{citron}}^1, \ldots, z_{\text{citron}}^k\}\) and \(\{z_{\text{terpi}}^1, \ldots, z_{\text{terpi}}^k\}\). Our null hypothesis is that the two underlying inhomogeneous Poisson processes are the same, that is:

\[
z_{\text{citron}}^i = r(t_i) + \epsilon_{\text{citron}}^i \sigma \quad \text{and} \quad z_{\text{terpi}}^i = r(t_i) + \epsilon_{\text{terpi}}^i \sigma,
\]
leading us to:

\[ \frac{Z_{\text{terpi}}^i - Z_{\text{citron}}^i}{\sqrt{2\sigma}} = \epsilon_i. \] (7)

We therefore want to test the null hypothesis \( H_0 \): the collection of observed differences \( \frac{Z_{\text{terpi}}^i - Z_{\text{citron}}^i}{\sqrt{2\sigma}} \sim \mathcal{N}(0,1) \). Under \( H_0 \) we can apply Donsker theorem (Billingsley [1999], Durrett [2009]): under \( H_0 \) the sequence of processes:

\[ S_k(t) = \frac{1}{\sqrt{k}} \sum_{i=1}^{[kt]} \frac{Z_{\text{terpi}}^i - Z_{\text{citron}}^i}{\sqrt{2\sigma}}, \quad 0 \leq t \leq 1, \]

converges in law towards a canonical Brownian motion.

It is direct to construct \( S_k(t) \) and check if the observed trajectory looks Brownian or not. Ideally, we would like to define a domain in \([0,1] \times \mathbb{R}\) containing the realizations of a canonical Brownian motion with a given probability. To have a reasonable power, we would like the surface of this
domain to be minimal, but Kendall, Marin, and Robert [2007] showed that the upper boundary of this minimal surface domain is given by:

\[ u^*(t) \equiv \sqrt{-\frac{W_{-1}(-((\kappa t)^2))}{t}}, \quad \text{for} \quad \kappa t \leq 1/\sqrt{e} \]

where \( W_{-1} \) is the secondary real branch of the Lambert W function (defined as the solution of \( W(z) \exp(W(z)) = z \)); \( \kappa \) being adjusted to get the desired probability. A simpler to work with and almost minimal surface domain has its upper boundary given by: \( u(t) = a + b\sqrt{t} \) (Kendall, Marin, and Robert [2007]). An efficient and simple algorithm for adjusting \( a \) and \( b \) or \( \kappa \) is found in C. R. Loader and Deely [1987]. The comparison between the citronellal and terpineol responses of Neuron 1 is shown on Fig. 5. The comparison of even and odd stimulus number for terpineol has been added to the figure as a control since we do not expect here any difference in the underlying intensity.

![Graph](image)

Figure 5: Almost minimal surface domains with probabilities 0.95 (dashed red) and 0.99 (red) of containing an observed canonical Brownian motion. Black: terpineol - citronellal; blue: odd terpineol trials - even terpineol trials.
5 Sample size sensitivity of the Brownian motion based test

We estimated the coefficients $a$ and $b$ of the "square root boundary" for various values of the "coverage probability", that is probability to have a realization of a canonical Brownian motion entirely inside the domain (bounded by the square root boundary). We used the numerical method of C. R. Loader and Deely [1987] that also yields an absolute bound on the probability. We thus obtained the results of Table 1.

Table 1: Coefficient $a$ and $b$ for (upper) boundaries given by $a + b\sqrt{t}$ ensuring a given coverage probability. Values have been rounded to the third digit giving enough precision to reproduce the results of Table 2.

<table>
<thead>
<tr>
<th>Cov. Prob.</th>
<th>a</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.99</td>
<td>0.312</td>
<td>2.891</td>
</tr>
<tr>
<td>0.98</td>
<td>0.308</td>
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</tr>
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<tr>
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<tr>
<td>0.93</td>
<td>0.296</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>0.90</td>
<td>0.292</td>
<td>2.077</td>
</tr>
</tbody>
</table>

We then performed a Monte Carlo simulation drawing for each sample size, 100000 replicates. For each replicate, the approximate Brownian motion was obtained by constructing its cumulative sum and rescaling it. The number of replicates crossing the 10 domains defined by the 10 sets of coefficients of Table 1 was computed. The results are reported as "Agresti-Coull" 95% confidence intervals (L. D. Brown, Cai, and DasGupta [2001]) for the empirical coverage probability in Table 2. We can see that the empirical coverage probability approaches systematically its nominal (asymptotic) value from above. We can use this table to correct for the sample size: if a sample size of size 50 is considered and if a coverage probability of 0.95 is requested, the coefficients giving an asymptotic coverage probability of 0.93 should be used.

6 Discussion

Although PSTH have been heavily used for more than 50 years (George L. Gerstein and Kiang [1960], Wall [1959]) and despite of serious attempts at
Table 2: Limits of the "Agresti-Coull" 95% confidence intervals of the empirical coverage probability for various sample sizes (horizontal) and various nominal coverage probabilities (vertical). The third decimal of the intervals limits have been rounded upward, respectively downward for the upper, respectively lower, limit.

<table>
<thead>
<tr>
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<th>50</th>
<th>75</th>
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<th>250</th>
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<tbody>
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<td></td>
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<td></td>
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<tr>
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building a quantitative tool out of an essentially descriptive one (Dörrscheidt 1981; Ellaway 1978; Ushiba et al. 2002), this report contains, to our knowledge, the first construction of PSTH based quantitative tests for two very common questions in neurophysiology:

1. Is a given neuron responding "on average" to a given stimulus?

2. Are the responses of a given neuron to two different stimuli the same?

Essential for the validity of our tests is the convergence of the "aggregated responses" making the PSTH towards an inhomogeneous Poisson process. This is a well established result (T. Brown 1978; Grigelionis 1963; Valérie Ventura et al. 2002), but practitioners still have to check that enough stimuli have been used for the convergence to have been reached. Our methods require a discretization of the observed (aggregated) process bringing the problem into an easier to deal with Poisson regression framework. The bin width setting, giving 3 or more events in each of the bins making the PSTH, is not a limitation of our procedure. Experimentalists can in practice always record enough data—in the "spontaneous regime"—to get an estimate of the
neurons basal firing rate necessary to set the bin width. After discretization, a well known variance stabilizing transformation (Anscombe 1948; L. D. Brown, Cai, and Zhou 2010) makes the answer to the first question above a direct application of (advanced) textbook methodology (Wasserman 2006) through the construction of a confidence set / band. It should nevertheless be noted that we are not the first to use variance stabilizing transformation in a neuronal spike train analysis context: Brillinger and colleagues did it in 1976 (D. R. Brillinger, Bryant, and Segundo 1976). The confidence band can also be used to estimate the response delay, a parameter of interest in neurophysiology: once a response threshold has been set, it is enough to find the two times at which the two boundaries of the confidence band cross that threshold in the upward direction.

We address the second question using a cumsum chart (Hawkins and Olwell 1998), a tool that has also already appeared in the present context (Ellaway 1978; Tam 2009; Ushiba et al. 2002); but we bring two decisive improvements. Working with the difference of two observed PSTH makes our test free. The combination of Donsker’s theorem (Billingsley 1999; Durrett 2009) with the Brownian confidence domain (Kendall, Marin, and Robert 2007) provides the first global test for an absence of drift in a cumsum chart context. Our simulation study shows that when 250 of more bins are used (a realistic number in practice) the actual test coverage probabilities are very close to the nominal ones for the most commonly used values (Table 2). They also show how to set the nominal value in order to get the right target value for as few as 50 bins.
References


Reynaud-Bouret, Patricia et al. (2013). “Spike trains as (in)homogeneous Poisson processes or Hawkes processes: non-parametric adaptive estimation and goodness-of-fit tests”.


## A Raster plots of the analyzed data

The usual way of presenting "raw" spike train data when a stimulus has been repetitively applied is the *raster plot* also referred to as a *dot display* (Eggermont [1990], Glaser and Ruchkin [1976], Wall [1959]) (David R. Brillinger [1992] uses the term *raster plot*): neuronal responses are displayed one above the other aligned on the stimulus onset; individual spikes are represented by a dot, a tick or any other suitable glyph. Fig. 6 shows 20 successive responses to a 0.5 s air puff of citronellal of three simultaneously recorded neurons. Fig. 7 shows 20 successive responses of neuron 1 of Fig. 6 to 3 different odors: citronellal, terpineol and a 50/50 mixture of the two.

![Raster plot example](image)

**Figure 6:** Example of 20 stimulations with citronellal for 3 simultaneously recorded neurons in the first olfactory relay of an insect. Each tick represents a spike occurrence. The first stimulation is at the bottom and the 20th at the top. Stimulations are delivered during 500 ms (gray background)—in fact the opening time of the valve diverting the continuous flux of moist air through a vial saturated with the odor; the odor presentation on the insect antenna does not stop when the valve closes but approximately 500 ms later—.
Figure 7: Neuron 1: 20 stimulations with citronellal, terpineol and a mixture of the two.