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SPIKE SEPARATION BASED ON SIMMETRIES ANALYSIS IN PHASE SPACE

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The present study introduces an approach for automatic classification of extracellularly recorded action potentials of neurons based on geometrical approach. Neuronal spikes are considered as geometrical objects, namely trajectories in phase space. It is shown that for spikes, generated by the same neuron, it is possible to find such symmetry transformation under which their trajectories are invariant in phase space. On the other hand, the phase trajectories of spikes generated by other neurons change significantly under action of that transformation. Thus it is possible to define a special symmetry transformation that only typifies the spikes of the given neuron. The proposed algorithm is explained and an overview of the mathematical background is given. The method was tested on simulated data and showed good results in real experiments.

INTRODUCTION

Analysis of populations of neurons represents an important step for better understanding of brain functioning. The present theories of brain functioning stress accent on the neuronal interactions in term of syncronized firing across many neurons, or spatio-temporal interactions and presence of specific patterns. Many such neuronal interactions cannot be observed with recording from single neuron. Thus, analysis of neuronal populations does not simply provide an additive scheme for increase experimental data but make possible to detect some features of brain functioning that could never be observed with recording of only single neuron.

The basic hypothesis used to detect and separate action potential of neurons assumes that spikes generated by the same neurons have similar shapes and these shapes are unique and conservative for each recorded neuron. The shape of neuron spikes detected by the electrode depends on the distance, relative position, properties of the media, e.g., presence and distribution of glia cells, between electrode and neurons. The shape also depends on resistance of electrode and neuron. Thus, even if two neurons are identical, their action potential detected at the microelectrode can be different and, thus, spikes from such neurons could be separated.

The number of different methods used in the neurophysiology for spike sorting dramatically increases. One of the most popular methods is template matching. These techniques use templates that represent some typical waveform shapes of neurons in time domain. A classification of a candidate spike is done by its comparison to all templates and selecting the best matching one. The recent trends include appearance of more computationally expensive methods, such as neural networks wavelet transforms.

There are many basic problems should be solved for successful spike sorting. The first basic question concerns the number of different types of neurons that should be separated in the experimental data. The usual practice is to use a «supervisor», i.e. the experimentator, who can provide a preliminary classification of data, e.g. selection of template spikes, based on his experience and knowledge. This is, for example, a feature of Multi Spike Detector (MSD) software (Alpha Omega Ltd., Nazareth) that is based on the template matching algorithm of. However, even if number of classes is identified, the separation of spikes remains very difficult problem due to extracellular and intracellular noise that can disturb the form of the action potential.

The extracelular noise is usually taken into account by the most of models as an additive noise. The intracellular noise that can produce variation in the spike waveform is more difficult to account for. Recently we have proposed a new method for spike sorting that consider the problem of spike sorting in phase space and describe the spike waveform as an ordinary differential equation with perturbation [1]. This approach made possible to account for both extracellular and intracellular noise. The differential equation describing the activity of a neuron was supposed to have a limit trajectory in phase space, and noise was treated as deviation of the signal from that trajectory. Current study provides further development of this idea. As contrasted to [1], we proposed a numerical method that takes into account that the variety of spike waveforms generated by the same neuron cannot be only explained by influence of both kinds of noise on some «typical» for a given neuron impulse, but is should be considered as a whole. Therefore, the new theoretical background uses a wider class of differential equations, not necessarily describing self-oscillating systems. Another principal difference is that the activity of a neuron is described by a symmetry transformation in phase space. Criterion of classification is the steadiness of the portrait in phase space of a spike against the transformation that corresponds to the given neuron. A computational method for modeling transformations is introduced and tested.

1. MATHEMATICAL STATEMENT OF THE PROBLEM

Let us consider a microelectrode signal $x(t) = x_0(t) + \xi(t)$ that is observed at discrete times $t = 0,1,\ldots$. Here $\xi(t)$ is a sequence of independent identically distributed random variables with zero mean and finite variance ($\sigma_\xi^2 < \infty$). The signal $x(t)$ is characterized by the occurrence of repeated intervals with amplitudes significantly exceeding the variance of $\xi(t)$. These intervals are assumed to be the occurrences of neuronal discharges, i.e. the spikes.

Let us suppose that every observed spike $x_i(t)$ of the i-th neuron is a solution of an ordinary differential equation with perturbation

$$\frac{d^3x}{dt^3} = f_i\left(x, \frac{dx}{dt}, \frac{d^2x}{dt^2}\right) + F\left(t, x, \frac{dx}{dt}, \frac{d^2x}{dt^2}\right), \tag{1}$$

where $F(\cdot)$ is a perturbation function. The perturbation function $F(x,...,t)$, bounded by a small value, is a random process with zero mean and small correlation time $\tau^* << T$. The solution of the equation

$$\frac{d^3x}{dt^3} = f_i\left(x, \frac{dx}{dt}, \frac{d^2x}{dt^2}\right) \tag{2}$$

describes a self-oscillating system. The duration of spikes is limited, so we can suppose that $x(t)$ is defined on some interval $(a;b)$. In practice parameters *a* and *b* are chosen manually by an expert. Set of differential equations

$$\begin{cases} \dfrac{dx^{(0)}}{dt} = x^{(1)}, \\ \dfrac{dx^{(1)}}{dt} = x^{(2)}, \\ \dfrac{dx^{(2)}}{dt} = f_i\left(x^{(0)}, x^{(1)}, x^{(2)}\right), \end{cases} \tag{3}$$

where $x^{(k)}$ is the k -th derivative of $x(t)$ is equivalent to (2).

If function f_i is defined in open domain $D \subset R^3$ then any solution *x(t)* of (3) induces phase trajectory $\vec{X}(t) = \left(x^{(0)}(t), x^{(1)}(t), x^{(2)}(t)\right)^T$. In this case the trajectory is also an integral curve for (3). The theorem about existing of a solution for an ordinary differential equation applies that for an arbitrary point $p \in D$ exists such integral curve $\vec{X}_p(t)$ that $\vec{X}_p(t_0) = p$ for some t_0 and $\vec{X}_p(t)$ is a solution of (3).

The equation (3) induces local one-parameter group G on D [2]. Let us define some action $g_\tau \in G$ on D. Consider integral curve $\vec{X}_p(t)$ that passes *p* when $t = t_0$. Then

$$g_\tau : p \mapsto \vec{X}_p(\tau + t_0) \tag{4}$$

i.e., $g_\tau(p)$ describes the state of system (3) at time moment $\tau + t_0$ under initial conditions *p*.

If the action of G on D is known we can introduce a criterion that allows to determine whether an arbitrary function *x(t)*, defined on interval $(a;b)$, is a solution of (3). That is, $\vec{X}(t) = \left(x^{(0)}(t), x^{(1)}(t), x^{(2)}(t)\right)^T$ is an integral curve for (3) if and only if

$$g_\tau\left(\vec{X}(t-\tau)\right) = \vec{X}(t) \tag{5}$$

for any $t \in (a;b)$ and any permissible $\tau \in (-\varepsilon; +\varepsilon)$.

Let us consider set Φ of all curves

$$\vec{\varphi}:(a;b)\to D\,. \tag{6}$$

A natural distance function on Φ can be given as

$$\rho(\vec{\varphi}_1(\cdot),\vec{\varphi}_2(\cdot))=\sqrt{\int_a^b(\vec{\varphi}_1(t)-\vec{\varphi}_2(t))^2\,dt}\;. \tag{7}$$

The action of G on Φ can be defined as:

$$g_\tau(\vec{\varphi}(\cdot))(t)=g_\tau(\vec{\varphi}(t-\tau)). \tag{8}$$

If $\vec{\varphi}(t)$ is a solution of (3) if and only if $g_\tau(\vec{\varphi}(\cdot))=\vec{\varphi}(\cdot)$ for any permissible $\tau\in(-\varepsilon;+\varepsilon)$. This statement is a formalization of (5) in terms of functions.

Let us introduce a deviation function

$$\Delta_\tau:\Phi\to R\,, \tag{9}$$

$$\Delta_\tau:\vec{\varphi}(\cdot)\mapsto\rho(g_\tau(\vec{\varphi}(\cdot)),\vec{\varphi}(\cdot))\,. \tag{10}$$

In other words, Δ_τ is a numerical criterion that shows how accurately an arbitrary phase trajectory $\vec{\varphi}(t)$ can be described by differential equation (2). $\vec{\varphi}(t)$ is a solution of (3) if and only if $\Delta_\tau(\vec{\varphi}(\cdot))=0$ for any permissible τ.

Consider an arbitrary spike $x(t)$ that solves system (1) and its phase trajectory $\vec{\varphi}(t)$. Point $p=\vec{\varphi}(t_0)$ gives an initial condition for system (1). If the perturbation $F(t,x,\frac{dx}{dt},\frac{d^2x}{dt^2})$ is small enough then the phase trajectory $\vec{\varphi}(t)$ of $x(t)$ will stay close to phase trajectory $\vec{X}_p(t)$ of some solution $x_p(t)$ of undisturbed system (3) for $t\in(t_0-\varepsilon;\,t_0+\varepsilon)$, where ε is small enough (Fig.1).

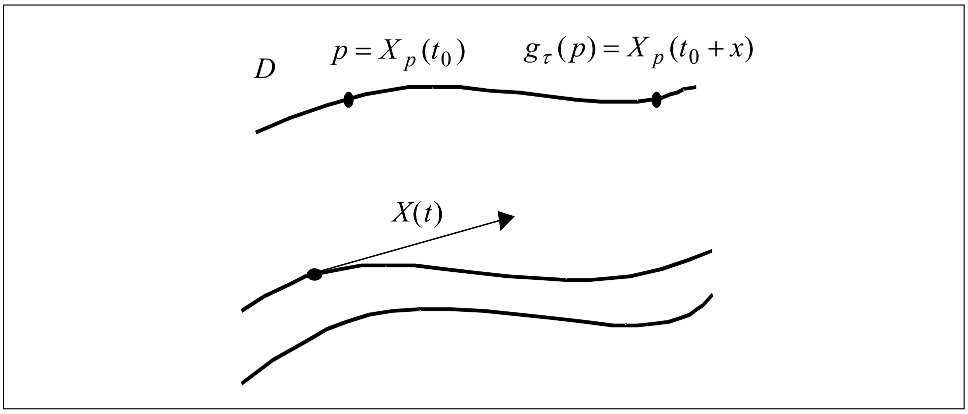

Fig. 1. Vector field on D and its integral curves that correspond to solutions of equation (3). The action of g_t on point p is shown

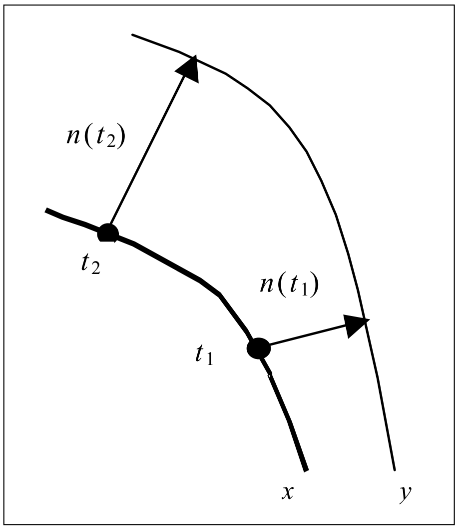

Fig. 2. The deviation of spike $y(t)$ relative to spike $x(t)$. Deviation vector $n(t)$ at time points t_1 and t_2

It is true for any $t_0 \in (a;b)$. Therefore the phase portrait $\vec{\varphi}(t)$ of the observed spike will be locally steady against the transformation with group G for every $t_0 \in (a;b)$. Deviation function (10) makes it possible to obtain a numerical criterion for the whole interval $(a;b)$. The greater is the influence of the perturbation F, the greater is the value of Δ_τ (Fig.2).

So, one of the differences of the method presented from our previous work [1, 3–6] is that we do not put into accordance to the undisturbed system the only limit phase trajectory, but characterize it by group of transformations G, which describes the whole set of solutions of (2). We also have developed some ideas on symmetry application [8, 9]. The other difference is that instead of calculating the distance between the phase trajectory $\vec{\varphi}(t)$ of an observed spike and the limit trajectory chosen as a sample for a given neuron we analyze the steadiness of $\vec{\varphi}(t)$ against the action of group G. The set of integral curves that correspond to all solutions of equation (3) defines a vector field V on D. Suppose we know how group G acts on subset D of phase space. Then we can estimate how well the following spike classification criterion can be.

2. DESCRIPTION OF ALGORITHM STEPS

The algorithm to separate neuronal spikes several intermediate steps:

1. Spike detection from the noisy signal;
2. Calculation of distances between the phase trajectories of the detected spikes;
3. Detection of spikes that hypothetically belong to the same neuron;
4. Building a numerical model of transformation group that correspond to every neuron observed;
5. Classification of spikes.

The three first steps were performed similar to our previous analysis and are described in details in elsewhere [1, 4, 5]. In this article we only briefly summarize the main implementation details and parameters of calculations of these steps that are important to reproduce our work. The vector field approach (steps 4 – 5) is described in details and main differences between old and new algorithm are emphasized.

The first 4 steps corresponded to the training phase on which the number of spike classes was estimated and the vector field for each class was constructed. In order to perform this analysis few tens of spike occurrences, usually corresponding to few minutes of recording time were required. Like in our previous approach a human expert could participate at step 3 were the number of spike classes were detected.

2.1 Spike detection from the noisy signal and derivative calculation methods. The derivatives of the signal were calculated following [1]. We represent time signals used at Fig. 3–9.

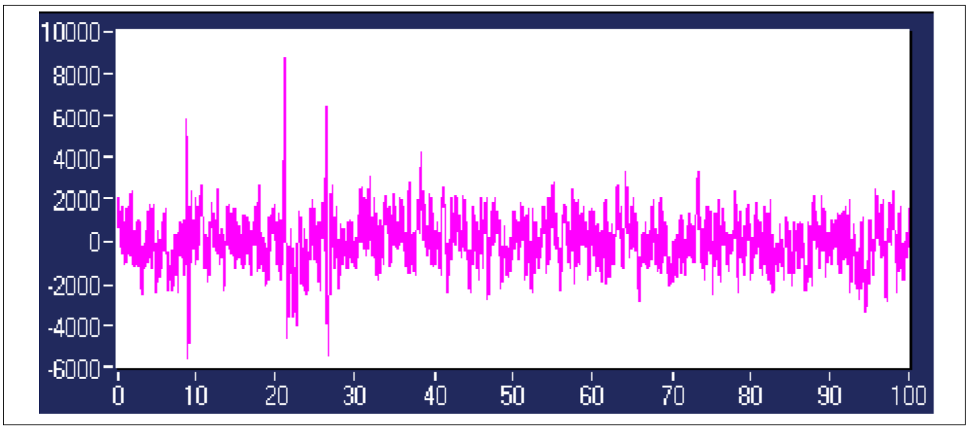

Fig. 3. 100 ms trial of brain activity observed in real experiment

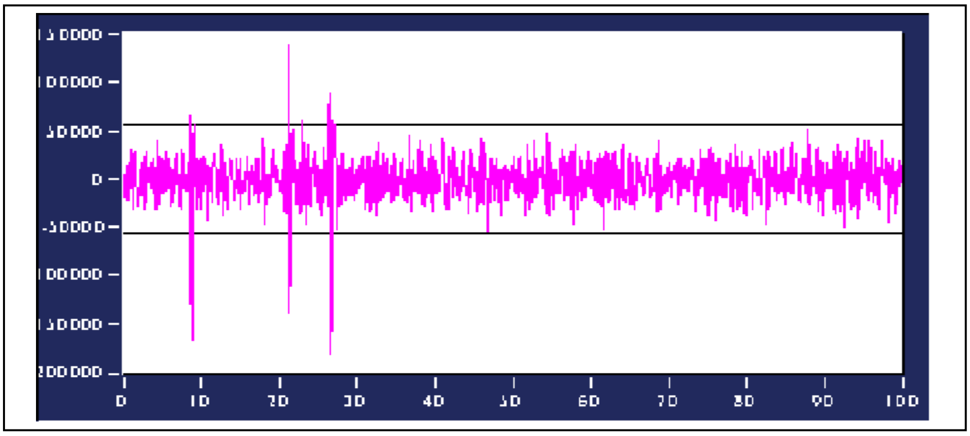

Fig. 4. 100 ms trial of first derivative with detected spikes

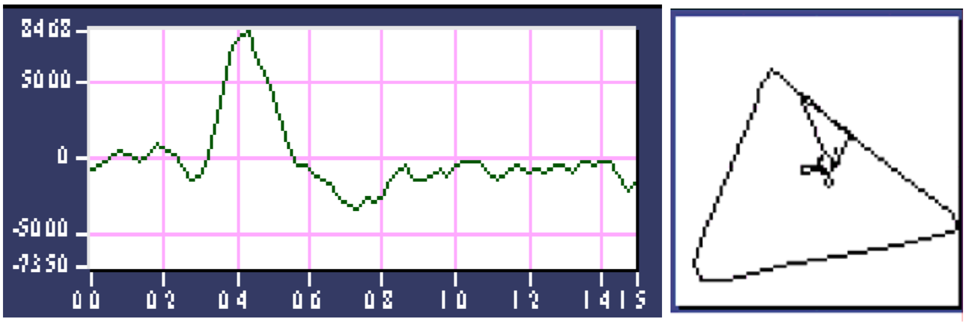

Fig. 5. Spike templates one and its portraits in phase space. The centers of the spikes are at 0.41 ms

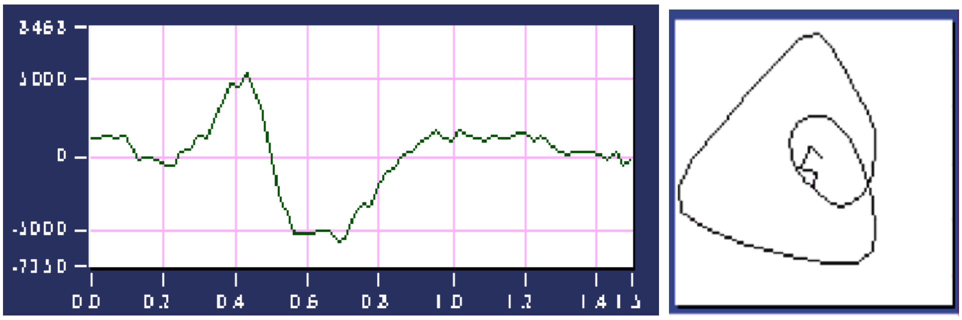

Fig. 6. Spike templates two and its portraits in phase space. The centers of the spikes are at 0.41 ms

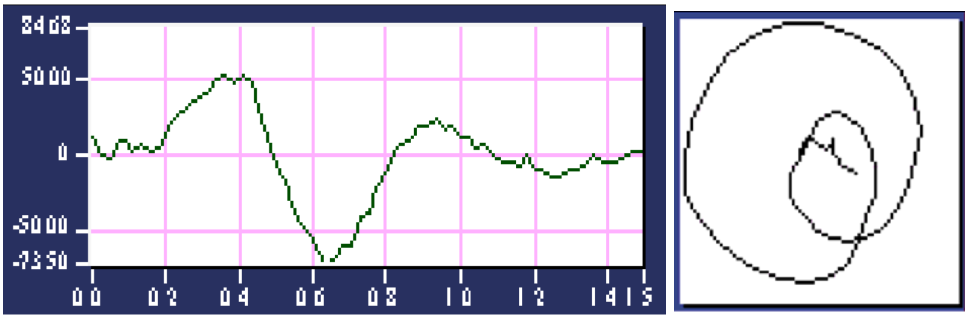

Fig. 7. Spike templates three and its portraits in phase space. The centers of the spikes are at 0.41 ms

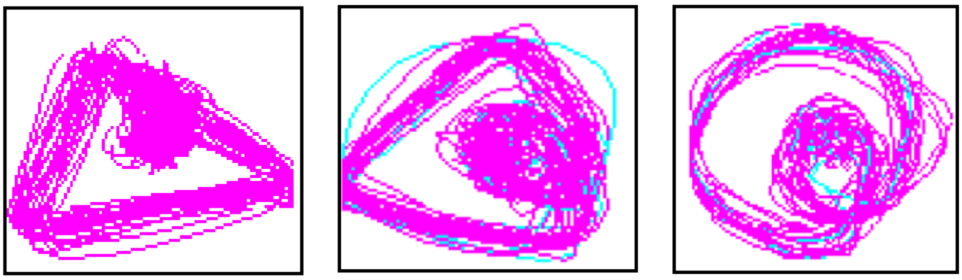

Fig.. 8. Spike portraits in phase space for three modeled neurons. In other words, they are projections of vector fields on R^2, which describe the activity of each of the three neurons

The estimation of the variance σ^2 was calculated for the second derivative. The time intervals in which the latter exceeded $c\sigma$ were accepted as centers of potential spikes. Coefficient c was chosen by an expert manually with regard of spike amplitude and noise level. In our experiments, it equaled to 3.

The derivatives of function $x(t)$ were estimated using integral operators

$$D_\alpha^i x(t) = \int_R \omega_\alpha^i \left(t-\tau\right) f\left(\tau\right) d\tau \,, \tag{11}$$

where ω_α^i is the i-th derivative of kernel function ω_α, which satisfies the following conditions [1]:

i. $\omega_\alpha(t) = 0$, if $|t| > \alpha$;

ii. $\int_R \omega_\alpha(t)\,dt = 1$;

iii. ω_α has *i* continuous derivatives.

The piece-wise polynomial kernel functions ω_α^i were used (Fig. 9).

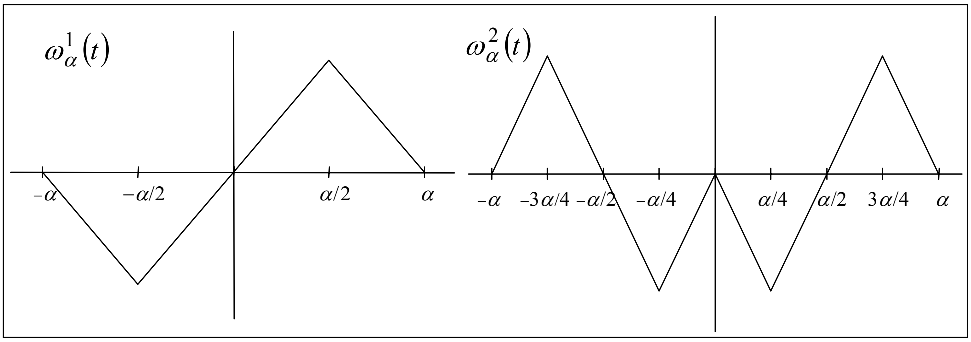

Fig. 9. The kernel functions used to estimate the first and second derivative of the signal

The integral operator $D_\alpha^i x(t)$ acts also as a band-pass filter of the signal $x(t)$ and its low and high cutoff frequencies are functions of parameter α. Since the duration of neuronal spikes are in the range of several ms, we selected parameters α to have the low cutoff frequency of 1 kHz for both kernels. The same approach to select smoothing parameters was used in our previous study (1).

2.2. Distance function for phase trajectories used for estimation of spike classes. Let $x(t)$, where $t \in (a;b)$, be an arbitrary spike, $x^1(t)$ and $x^2(t)$ be the evaluation of its first and second derivatives respectively. Then $\vec{x}(t) = \left(x^1(t), x^2(t)\right)^T$ describes the phase trajectory of that spike. In order to estimate the deviation of trajectory $\vec{y}(t)$ from $\vec{x}(t)$ we define such vector $\vec{n}(t)$, that $\vec{x}(t) + \vec{n}(t) = \vec{y}(\omega(t))$ for some $\omega(t)$, and $\vec{n}(t)$ is normal to $\vec{y}(\omega(t))$ [1]. The norm of $\vec{n}(t)$ can be calculated as

$$\left\|\vec{n}(x(\cdot), y(\cdot))(t)\right\|^2 = \min_{t' \in [t-c;t+c] \cap [a;b]} \left(\left(x^1(t) - y^1(t')\right)^2 + \left(x_2(t) - y_2(t')\right)^2 \right). \tag{12}$$

Then we can introduce a difference function for phase trajectories of spikes $x(t)$ and $y(t)$ [1] as

$$d(x(\cdot), y(\cdot)) = \min\left(\tilde{d}(x(\cdot), y(\cdot)), \tilde{d}(y(\cdot), x(\cdot))\right). \tag{13}$$

where

$$\tilde{d}(x(\cdot), y(\cdot)) = \min \sqrt{\int_0^a w(t) \left\|\vec{n}(x(\cdot), y(\cdot))(t)\right\|^2 (t)\,dt} \tag{14}$$

and

$$w(t)=\begin{cases}\dfrac{t}{a_1}, & t\in[0;a_1),\\ 1, & [a_1;a_2],\\ \dfrac{a-t}{a-a_2}, & (a_2;a]\end{cases} \tag{15}$$

is some weight function. In our implementation $a_1 = 0{,}5\,\text{ms}$, $a_2 = 1\,\text{ms}$ and $a_2 = 2\,\text{ms}$. For N detected spikes matrix of pair-wise distances between trajectories $D = \{d_{i,j}\}$, $i, j = 1..N$, where $d_{i,j} = d(x_i(\cdot), x_j(\cdot))$, was calculated.

2.3. Selection of the number of spike classes. On this step we formed classes of spikes using the set of spikes accumulated during few first minutes of recordings. Spikes generated by the same neuron must belong to one class. The difficult problem of this step is an absent of *apriori* information about the possible number of spike classes (neurons) that are recorded by the microelectrode. An iterative procedure for detection the number of spike classes was used [1].

In the beginning each spike was considered as a new class. Let C_i be the *i*-th class of spikes, s_j be the j-th accumulated spike, c_i be the central spike of class C_i, R be the radius of that class, i.e. the maximum allowed distance from the central spike to other spikes of C_i.

1. A new center c_i of class C_i was found as

$$c_i = \underset{s_j\in C_i}{\arg\min} \sum_{s_k\in C_i} d(s_j, s_k). \tag{16}$$

2. Spikes s_j with $d(c_i, s_i) \le R_i$ were added to the class, and spikes with $d(c_i, s_i) > R$ were deleted from each class i.

3. Overlapped classes were determined. All pairs of classes C_i, C_j and their intersection $I = C_i \cap C_j$ were determined. Each class C_j was deleted if more than 50% of its spikes belonged to the class C_j.

4. Steps 1, 2 and 3 were repeated. As it was shown in [1], such iterative process converges to stable centers of the classes. However, a larger training set is required for smaller values of R.

5. The remaining classes were analyzed by a human expert who performed further elimination of classes with small number of spikes. The user also selected the parameter R.

Notice, that up to this step both our previous and new method were exactly the same.

2.4. Numerical representation of vector field. Vector fields were constructed for each spike class. The vector field that characterized the activity of a neuron was described by phase trajectories of the most typical representatives of its class. The center of the class and several of the most close to it spikes were selected. The whole vector field was represented as a set of its integral curves. Let V_i be a vector field that correspond to i-th neuron, and $\vec{X}_{i,j}(t) = \left(x_i(t), \dfrac{dx_i}{dt}(t), \dfrac{d^2x_i}{dt^2}(t)\right)^T$ be a phase portrait of the j-th spike of the i-th class, i.e. one of the integral curves of the field V_i. In order to obtain the value of vector $V_i(m)$ for an arbitrary point $m \in D$ all curves from the vector field are analyzed. A minimum Euclidean norm $\left\| m - \vec{X}_{i,j}(t_0) \right\|$ is detected for some t_0 and j and vector $\frac{d\vec{X}_{i,j}}{dt}(t) = \left(\frac{dx_i}{dt}(t), \frac{d^2 x_i}{dt^2}(t), \frac{d^3 x_i}{dt^3}(t) \right)^T$ is selected as an estimation of vector $V_i(m)$.

2.5 Spike classification and probabilistic analysis of the deviation function. Consider phase portrait $\vec{\varphi}(\cdot) \in \Sigma$ of an arbitrary spike, vector field V_i and some action of group G on it: $g_\tau(\vec{\varphi}(\cdot))(t) = g_\tau(\vec{\varphi}(t-\tau))$. We propose the following iterative algorithm for calculation trajectory

$$\vec{\varphi}'(t) = g_\tau(\vec{\varphi}(\cdot))(t-\tau). \tag{17}$$

Consider $\vec{S}_0 \in R^3$. Let $\vec{S}_0 = \vec{\sigma}(t-\tau)$. Let us choose step of integration Δt. During the k-th iteration we calculate

$$\vec{S}_{k+1} = \vec{S}_k + \Delta t V_i\left(\vec{S}_k\right). \tag{18}$$

The iterations repeat until $k\Delta t < \tau$. The last value of vector $\vec{S}_k$ is the estimation of point $\vec{\sigma}(t)$ of the transformed trajectory.

Deviation function (9) was calculated for trajectory $\vec{\sigma}(t)$. Let us consider the distribution of (9). Spike $x(t)$, which is a solution of system (1), can be represented as $x(t) = x_0(t) + \xi(t)$, where $x_0(t)$ is some solution of (2) and $\xi(t)$ is the influence of perturbation $F\left(t, x, \frac{dx}{dt}, \frac{d^2 x}{dt^2}\right)$. Assume that $\xi(t)$ is a random process with a zero mean and small correlation time. Taking into account that the signal was read at discrete time points spikes $x(t), x_0(t)$ and noise $\xi(t)$ can be represented as sequences x_j, $x_{0,j}$ and ξ_j, where $j = 1 \ldots n$. In our implementation we considered ξ_j as a random sequence of independent normally distributed values. The estimation of the first and second derivatives x_j^1 and x_j^2 are obtained as a linear combination (10) of x_j:

$$x_j{}^1 = \sum_k A_k^1 x_k = \sum_k A_k^1 \left(x_{0,k} + \xi_k\right) = \sum_k A_k^1 x_{0,k} + \sum_k A_k^1 \xi_k = x_{0,j}^1 + \xi_j^1, \tag{19}$$

$$x_j{}^2 = \sum_k A_k^2 x_k = \sum_k A_k^2 \left(x_{0,k} + \xi_k\right) = \sum_k A_k^2 x_{0,k} + \sum_k A_k^2 \xi_k = x_{0,j}^2 + \xi_j^2, \tag{20}$$

where A_k^1 and A_k^2 are the values at k-th time point of kernels ω_α^1 and ω_α^2 respectively, $x_{0,j}^1$ and $x_{0,j}^2$ are the estimation of the first and second derivatives of spike $x_0(t)$, ξ_j^1 and ξ_j^2 are normally distributed random quantities with zero mean.

Consider transformed portrait (17) of spike $x(t)$. Assume than $x(t)$ is close to $x_0(t)$. Then during the iterative procedure (18) of transformation with vector field the values of $\vec{S}_k$ will stay close to phase portrait $\vec{x}_0(t)=$ $=\left(x_0(t),\frac{dx_0}{dt}(t),\frac{d^2x_0}{dt^2}(t)\right)^T$ of spike $x_0(t)$. Assuming that Δt is the sampling interval and taking into consideration the numeric representation of vector field we can suppose that

$$V_i(\vec{x}_{0,j}) \approx \left(x_{0,j+1}-x_{0,j}, x_{0,j+1}^1-x_{0,j}^1, x_{0,j+1}^2-x_{0,j}^2\right)^T. \qquad (21)$$

The iteration (18) becomes

$$\vec{S}_{k+1} \approx \vec{S}_k + \left(x_{0,j+1}-x_{0,j}, x_{0,j+1}^1-x_{0,j}^1, x_{0,j+1}^2-x_{0,j}^2\right)^T. \qquad (22)$$

Thus transformed with field V_i portrait $x'(t)$ of spike $x(t)$ is close to the trajectory described by $\vec{x}_{0,j}+\vec{\xi}'_j$, where $\vec{\xi}'_j=\left(\xi_j,\xi_j^1,\xi_j^2\right)^T$. Then the deviation function (9) squared for the first and second derivatives of spike $x(t)$ will equal to

$$\alpha_\tau^{\,2}(\vec{x}_j)=\sum_k\left(\left(\xi_k^1\right)^2+\left(\xi_k^2\right)^2\right). \qquad (23)$$

It has χ^2 distribution with known parameters. It makes possible to find a confidence interval δ with given confidence probability p for the spike class observed. If the value of $\alpha_\tau^{\,2}(\vec{\sigma}(\cdot))$ does not exceed threshold δ then we consider spike $x(t)$ to be generated by the corresponding neuron, the activity of which is described by (1) and vector field V_i.

3. NUMERICAL RESULTS ON SPIKES RECOGNITION

Inverse Fourier transform was used to generate 50 seconds trial of an artificial noise with evenly distributed phases and magnitude that represented $1/f$ noise signature. The sampling frequency was 44 kHz. 3 different templates of spikes that were obtained in real experiment, in 10000 instances of every template, were imposed additively on the noise. Spikes did not overlap. The duration of every spike equaled to 2.43 ms, the duration of the whole experiment was 1097 s.

Comparison of new and template matching method

Template	Symmetry group			Template matching in phase space		
	Unclassified	Misclassified	Error index	Unclassified	Misclassified	Error index
I	32	0	32	10	12	15.6
Ii	103	120	158.1	122	165	205.2
Iii	94	22	96.5	165	76	181.7

Unclassified — number of spikes of the given class that were not detected or were referred to another class. Misclassified – number of impulses that belong to another class or represent noise but were classified as spikes of the given class.

$$ErrorIndex = \sqrt{(unclassified)^2 + (misclassified)^2}\ .$$

4. DISCUSSION

The method described in the article is an elaboration of the method based on template matching in phase space [1]. The stages of spike detection and forming spike classes are generally similar to the latter. The principal difference of the method presented from template matching is the implementation of spike classification after spike classes are formed. The template matching method characterizes the whole class of spikes generated by the same neuron by the phase portrait of its typical spike. As contrasted to another methods [9], the method based on symmetries analyses uses computational modeling of vector field that conforms the differential equation describing the activity of the chosen neuron and thus it is more stable against alterations of spike form. It showed better results than the former and can be useful in experiments, where spike tend to change their form.

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