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Design of Optimal Stimulation Patterns for Neuronal Ensembles Based on Volterra-type Hierarchical Modeling

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Abstract

This paper presents a general methodology for the optimal design of stimulation patterns applied to neuronal ensembles in order to elicit a desired effect. The methodology follows a variant of the hierarchical Volterra modeling approach that utilizes input-output data to construct predictive models that describe the effects of interactions among multiple input events in an ascending order of interaction complexity. The illustrative example presented in this paper concerns the multi-unit activity of CA1 neurons in the hippocampus of a rodent performing a learned Delayed-Non-Match-to-Sample (DNMS) task. The multi-unit activity of the hippocampal CA1 neurons is recorded via chronically implanted multi-electrode arrays during this task. The obtained model quantifies the likelihood of having correct performance of the specific task for a given multi-unit (spatiotemporal) activity pattern of a CA1 neuronal ensemble during the “Sample Presentation” phase of the DNMS task. The model can be used to determine computationally (off-line) the “optimal” multi-unit stimulation pattern that maximizes the likelihood of inducing the correct performance of the DNMS task. Our working hypothesis is that application of this optimal stimulation pattern will enhance performance of the DNMS task due to enhancement of memory formation and storage during the “Sample Presentation” phase of the task.

Keywords

Multi-unit neurostimulation; Nonlinear modeling; Hippocampal activity

1. Introduction

Neural prostheses are currently designed to mitigate neurological deficits of various kinds. Among them, considerable attention has been given to neuromotor and neuromuscular deficits as well as sensory deficits [1–10]. Less attention has been given so far to the replacement of lost cognitive function (memory, language, decision making, planning etc.) due to damage in central parts of the brain that are not explicitly neurosensory or neuromotor. With proper recognition of the complexity of this task, we have pursued this goal in the rodent hippocampus by combining advanced methods of system modeling with computational neuroscience and multi-electrode recordings during specialized experiments [11–34]. We take the view that a cognitive neuroprosthesis must mimic functionally the activity of the damaged neural system that it seeks to replace. To achieve this goal, we follow the input-output approach, whereby “silicon neurons” (i.e. a man-made electronic

system) emulate the target neural activity insofar the input-output transformational properties of the damaged neurons.

Our group has focused over the last 12 years on the development of a cognitive prosthesis for the hippocampus, a region of the brain responsible for the formation of new long-term memories [15–18]. We have sought to Design of Optimal Stimulation Patterns for Neuronal Ensembles Based on Volterra-type Hierarchical Modeling develop a neuroprosthesis that emulates the input-output transformation of information by ensembles of neurons in parts of the hippocampus which may become damaged by stroke (selective loss of CA1 neurons), epileptic activity (preferential damage to CA3) or head trauma (preferential damage to hippocampal hilar neurons). Alzheimer's disease and other forms of dementia are also associated with loss of neurons throughout the hippocampal formation, although preferentially within the entorhinal layers that serve as input/output gateways of the hippocampus. In the context of such a hippocampal prosthesis, the design of appropriate multi-unit stimulation patterns attains a critical role.

This paper presents a new approach for designing the optimal multi-unit stimulation pattern (OMUSP) that employs a *multi-input Volterra-type model* describing the effect of *any* multi-unit (spatiotemporal) stimulation pattern applied to the CA1 region (through the specific set of electrodes implanted in the hippocampus) upon the likelihood of triggering the desired outcome of the Delayed-Non-Match-to-Sample (DNMS) behavioral task. This model is obtained from the experimental data through a new methodology that employs the concept of “Triggering Likelihood Functions” (*TLF*) of various orders of interaction – i.e. the *n*-th order *TLF* describes how *n* spikes in the epoch of neuronal activity interact to influence the observed outcome. These interactions can be within the same neuron (self-*TLFs*) or between different neurons (cross-*TLFs*). A hierarchical *TLF*-based model is subsequently constructed that defines the “Event Triggering Likelihood” (ETL) for any given pattern of neuronal activity. This model is distinct from previously published Multi-Input/Multi-Output (MIMO) Volterra models [15–18, 30–32] in that it maps the activity of the CA1 region (input of this model, but output for the previous MIMO models) onto the output which is the desired behavior (Sample-to-Nonmatch in this study) and not time-series data as in the previous MIMO models. This *TLF*-based model can be used to design the OMUSP by maximizing a utility function that is computed by these models and is akin to the likelihood of eliciting the desired (DNMS) outcome instead of alternative outcomes (e.g. Delayed-Match-to-Sample in this study).

Section II of this paper presents the new methodology of OMUSP design. Section III presents the obtained OMUSP (based on the *TLF* model) for the DNMS task in rodents and evaluates their performance. Section IV presents the conclusions of this study, following discussion of its main results.

2. Methodology

2.1. Experimental Methods

Male Long-Evans rats were trained for a two lever, spatial Delayed-Nonmatch-to-Sample (DNMS) task with randomly occurring variable delay intervals between 2 and 40 s. The rats performed the task by pressing initially a lever presented in one of two positions in the “Sample Phase” (left or right). The lever was then retracted and the delay phase was initiated. For the duration of the delay phase, the animal was required to nose-poke into a lighted device on the opposite wall. Following termination of the delay phase the nose-poke light was turned off, both levers were extended and the animal was deemed to have a correct response when pressing the other lever than the one pressed during the Sample Phase

(“Nonmatch Response”). The animal was rewarded after a correct response. Figure 1 illustrates the four phases of the DNMS experiments.

Spike trains were recorded through multi-electrode arrays implanted in the CA1 region of the rat hippocampus during performance of the described DNMS task. An array of 16 electrodes was surgically implanted into the hippocampus, with 8 electrodes in the CA3 (input) region and 8 electrodes in the CA1 (output) region. Spike data were sorted and recorded during the various phases of this experiment and the behavioral responses were timestamped with a 25 μ s resolution. Five sessions of recordings were selected from each rat. Each session included about 100 trials of DNMS tasks of which approximately two-thirds were successfully performed for long delays. These experiments were conducted in the labs of Dr. Deadwyler and Dr. Hampson at Wake-Forest University and have been described in detail in previous publications [17, 27–30].

During the micro-stimulation experiments the animals received model-determined multi-unit patterns of stimulation of CA1 during the sample phase of one-third of the trials. Stimulation trials were selected randomly and were equally distributed with respect to trial types (left/right lever and delay). The selected pattern of stimulation pulses was applied to the appropriate 16 CA1 recording/stimulating electrodes. Each stimulus pulse consisted of a 1 ms bipolar square wave (0.5 ms per phase) with constant current 10 to 250 μ A (0.1 to 5 V). Adjacent recording electrodes were paired to permit bipolar stimulation. Stimulation pulses were delivered at minimum 50 ms inter-spike intervals to reduce the risk of kindling and seizure. Stimulation pulses were delivered by a fully programmable custom asynchronous 16 channel stimulator manufactured for WFUHS by Triangle Biosystems, Inc (Durham, NC). Optimal multi-unit stimulation patterns (OMUSP) for each type of trial (left or right) were computed from 5 days prior recordings, then one of the two distinct OMUSPs (left or right) was delivered starting within 100 ms of identification of right or left trial initiation (i.e. sample lever presentation). The application of the OMUSP took place 5 days after the collection of the data that were used to design it following the presented methodology.

2.2. Data Preparation

In this study, we analyzed the data around the “Sample Presentation” phase of each experiment. The spike-train data over 20 s peri-event intervals were extracted (i.e. starting 10 s before and stopping 10 s after the Sample Presentation). The spikes were “binned” at 50 ms binwidth for further analysis, when the peri-event mean-firing-rate (MFR) was between 0.25 and 5 spikes/s – otherwise the data were not analyzed as likely due to interneurons. The CA1 and CA3 interneurons have baseline firing rates of Theta frequency (6–10 Hz) and higher [35] and show indistinct correlations to these events. For this reason, they are traditionally excluded from assessment of hippocampal memory encoding [36]. Hippocampal pyramidal cells fire with a baseline firing rate of up to 5 Hz and have been shown to be the principal output cells of hippocampus that encode spatial position [37], task phase [38] and associational memory [39].

2.3. Modeling Methodology

The development of the multi-input *TLF* model that describes the relation between CA1 multi-unit activity and DNMS outcome is based on the available experimental data and comprises the computation of the *TLFs* up to 2nd order. The computation of these *TLFs* requires the initial computation of “*Triggering Likelihood Distributions*” (*TLDs*) of 1st and 2nd order that are peri-event histograms of all CA1 *spike combinations* related to the DNMS event that are appropriate for the respective order. The 1st order *TLD* is the customary peri-event histogram that has been extensively used before. However, the 2nd order *TLD* is novel and quantifies the interactions between pairs of spikes in the past epoch of the monitored

CA1 neurons (coming from the same or different neurons) that correspond to the correct DNMS outcome. The computation of the 1st order TLD_1 and 2nd order TLD_2 are illustrated in the schematic of Figure 2. In general, the computation of the Q^{th} order TLD entails counting the number of times each specific *combination of Q spikes* at various latencies within the past epoch of a CA1 neuron (*self-TLD*) or multiple CA1 neurons (*cross-TLD*) corresponds to a correct outcome of the DNMS task at the reference time. It is evident that the values of the TLD s cannot be negative.

Using the computed TLD s, we can subsequently compute the TLF s of various orders by removing the effects of lower order interactions. For instance, for the 1st order TLF , we must subtract the baseline activity μ_i (representing the spontaneous activity of the neuron) to obtain:

$$TLF_1(i;L_i)=TLD_1(i;L_i)-\mu_i \quad (1)$$

where i is the neuron index and L_i is the latency. Thus, the 1st order TLF (like the TLF s of all orders) may take negative values (unlike the TLD s which cannot) representing possible inhibitory effects. The TLF s quantify the net impact (excitatory or inhibitory) of any given multi-unit stimulation pattern upon the likelihood of a desired behavioral outcome. The 2nd order cross- TLF for neurons i and j is computed from $TLD_2(i, j; L_i, L_j)$ by subtraction of the outer product of the respective TLD_1 's as:

$$TLF_2(i, j; L_i, L_j)=TLD_2(i, j; L_i, L_j)-TLF_1(i;L_i) \cdot TLF_1(j;L_j) \quad (2)$$

For any given multi-unit stimulation pattern, $S(t)$:

$$S(t)=\sum_i \sum_n \delta[t-L_i(n)] \quad (3)$$

where i and n denote neuron and spike index, respectively, we can compute the *Event-Triggering Likelihood (ETL)* using the obtained TLF s:

$$ETL\{S(t)\}=\sum_i \sum_n TLF_1\{i;L_i(n)\}+\sum_{i_1,i_2,n_1,n_2} TLF_2\{i_1,i_2;L_{i_1}(n_1),L_{i_2}(n_2)\}+\text{higher order TLF contribution} \quad (4)$$

The ETL is the sum of the contributions of the TLF s of all orders (self- and cross-) for all stimulation spikes in the multi-unit pattern $\{L_i(n)\}$. This ETL is a measure of the total impact of the given multi-unit stimulation pattern, $S(t)$. Figure 3 illustrates the procedure for the ETL computation from the TLF_1 's and TLF_2 's (self- and cross-) of the monitored CA1 neurons, obtained for correct or incorrect trials of the DNMS task.

2.4. Design of Optimal Multi-Unit Stimulation Patterns

Using this TLF -based model of ETL impact, the design of the *optimal multi-unit stimulation pattern* (OMUSP) for a given mean firing rate (MFR) is now possible via maximization of a utility function, Q , through off-line computation of the ETL values of the alternative outcomes for all possible patterns. For instance, in the DNMS task of this paper, there are two possible outcomes: Nonmatch (correct) and Match (incorrect). Thus, the utility function Q is defined as the difference between the ETL values for the Nonmatch minus the Match response:

$$Q_n=Q\{S_n(t)\}=ETL_{\text{CORRECT}}\{S_n(t)\}-ETL_{\text{INCORRECT}}\{S_n(t)\} \quad (5)$$

both computed for the same OMUSP using the respective TLF-based models, as indicated in the diagram of Figure 4. Therefore, the criterion for designing the OMUSP is the maximization of the utility function Q (a performance index) that takes into account all possible (competing) outcomes.

The maximization of the utility function Q seeks the placement of the appropriate number of stimulation pulses in 8 “search segments” of 2 s each (before and after the reference event for each of the 4 neurons) which may have distinct functional characteristics, so that Q attains the maximum value. The number of possible patterns in each “search segment” is determined by the combinations of 40 bins (2 s divided by 50 ms) taken by M , where M denotes the number of appropriate stimulation spikes defined by the observed average activity over baseline in the respective “search segment” (this was in the range 2–4 spikes over 2s in this study). This may result in a very large number of Q computations. To make this maximization task more efficient, we can use specialized search techniques (e.g. back/forth-step iterative techniques) but these engender the usual pitfalls of iterative search procedures (e.g. possible entrapment in local minima, dependence on initialization etc.). The maximization procedure used in this study included the following steps: (1) determine the number M of stimulation spikes that will be placed in each of the 8 “search segments” on the basis on the observed activity of each neuron before/after the reference event; (2) select a sequence of the 8 “search segments”; (3) starting with the first “search segment”, place one spike at the location that maximizes Q and then proceed with positioning one spike sequentially in each of the other “search segments” so that Q is maximized after each new placement; (4) upon completing the placement of one spike in each of the “search segments”, continue with placing a second spike sequentially and so on until the selected number of M pulses is reached in each “search segment”. This procedure is repeated for a different sequence of “search segments” until all have been used. Then, we select the stimulation pattern that resulted in the highest Q value among the maxima of each sequence. This procedure requires fewer computations of Q than the exhaustive search (on the order of 10^{10} in this study).

3. Results

3.1. Computed TLFs from experimental data

Illustrative examples of the computed TLF_1 s and TLF_2 s for 4 CA1 neurons of rodent 1154 (left-lever trials) are shown below. The selected neurons are: #77, 78, 85, and 87. The number of utilized trials was 84 with correct outcomes and 23 with incorrect outcomes in this example. The TLF_1 s resulting from the respective TLD_1 s after subtraction of the baseline values (1.94, 0.72, 0.71, and 1.39 spikes/s for Nonmatch response, and 1.74, 0.57, 0.68 and 1.28 spikes/s for Match response, respectively) and application of zero-phase 21-point smoothing, are shown in Figure 5. It is evident that the TLF_1 patterns are distinct for the correct and incorrect responses, as well as across different neurons. We note, however, that some TLF_1 peaks are common for the correct and incorrect response (e.g. around 0.8 s for neuron #85). This result is supportive of the basic premise of our work, namely that distinct behaviors (Nonmatch or Match) correspond to distinct patterns of neuronal activity, although occasional common features may also exist, probably due to factors common in both competing behaviors. The latter observation supports the maximization of the *difference* of the performance metrics (the *ETL* functions) for the two competing behaviors, so that the effect of the common features is eliminated.

Our analysis of second-order interactions yields 4 self- TLF_2 s and 6 cross- TLF_2 s of these 4 CA1 neurons for the Nonmatch (correct) response and an equal number for the Match (incorrect) response that are shown in Figures 6 and 7. Differences are observed in the 2nd order TLFs between the Nonmatch (correct) and Match (incorrect) responses. We observe

2nd order facilitatory interactions (positive values) and inhibitory interactions (negative values) of roughly equal magnitude in the self- TLF_2 of these 4 CA1 neurons shown in Figure 6 (not exceeding 0.005 in absolute value). However, the values of the cross- TLF_2 s, shown in Figure 7, are considerably larger and mostly positive (facilitatory) with values often exceeding 0.005. Thus the cross- TLF_2 s appear to have a more significant effect on the behavioral outcome than the self- TLF_2 s. The sign and the magnitude of the TLF values have specific functional meaning. Note that the numerical values of the TLF s ought to be viewed as akin to conditional probabilities (although they, unlike probabilities, may take negative values) contributing to the likelihood of the behavioral outcome for the respective pattern of CA1 spikes. In order to compare the relative contributions of the TLF_1 and TLF_2 values, we note that the number of pair-spike combinations in each neuron epoch is much larger than the number of individual spikes (close to a square relation) and, therefore, the relative cumulative contribution to the ETL by the TLF_1 s and the TLF_2 s must be assessed in the context of the prevailing MFR. For instance, if we consider a stimulation interval of 4 s and a MFR of 2 spikes/s, then the TLF_2 values must be multiplied by 3.5 to be compared with the TLF_1 values. Thus, in the presented example, a TLF_1 value of 0.05 is comparable to a TLF_2 value of 0.014 in terms of relative contribution to the ETL . In light of this, the contributions of the TLF_1 s are comparable to the contributions of the cross- TLF_2 s, but much larger than the contributions of the self- TLF_2 s in this example.

3.2. Optimal Multi-Unit Stimulation Patterns

In order to design the optimal multi-unit stimulation pattern (OMUSP) for these 4 CA1 neurons, we compute the utility function Q that equals the difference of the ETL values corresponding to correct and incorrect responses for all combinations of CA1 activity patterns using the computed TLF_1 s and TLF_2 s (see Methods). The number of spikes in these putative multi-unit firing patterns is consistent with the experimentally observed mean firing rates (MFRs) above the baseline value of background/spontaneous activity for each neuron and before/after the reference event (Sample Presentation in this case). The pattern that maximizes Q is the OMUSP.

As an illustrative example, we show in Figure 8 the locations of the OMUSP spikes (red bars) that maximize the likelihood of the Nonmatch response being elicited in rodent 1154 (left column), as opposed to the Match response (right column), for the left-lever task (left column) and the right-lever task (right column). The specificity of these optimal stimulation patterns is evident. The difference of the computed TLF_1 s for the correct (Nonmatch) minus the incorrect (Match) response is also shown in Figure 8 for each neuron in order to demonstrate that the location of each stimulation spike of the designed OMUSP does not necessarily correspond to high values of this difference (representing the first-order effects captured by the TLF_1 s – i.e. the conventional peri-event histograms) – a fact that indicates the significance of the second-order effects captured and quantified by the TLF_2 terms (self and cross) of the ETL model.

The computational evaluation of the designed OMUSP is performed through 10,000 independent Monte Carlo simulations of the TLF -based model in the presence of uncorrelated (Poisson) spontaneous activity at the experimentally observed level. The Monte-Carlo simulations under the Null Hypothesis H_0 are performed for random (Poisson) spontaneous activity. Note that the level of random spontaneous activity for the Null Hypothesis is increased relative to the Alternate Hypothesis H_a (OMUSP superimposed on random spontaneous activity) to match the additional average stimulation power provided by the OMUSP spikes.

These simulations yield the histograms of Q values shown in Figure 9 for the Null Hypothesis H_0 (blue line) and the alternate Hypothesis H_a (red line). The shift of the H_a

histogram seen in Figure 9 towards higher computed Q values indicates an effect by the OMUSP on the rodent performance. We emphasize the importance of increasing the level of random spontaneous activity for the Null Hypothesis in order to match the additional average stimulation power provided by the OMUSP spikes, so that we eliminate possible performance biases due to the overall level of average stimulation. Thus, the observed shift of the H_a histogram can be viewed as being strictly due to the precise timing of the OMUSP spikes. The statistical significance of this shift and the separation of the two histograms can be quantified by a “measure of mean separation” (MMS), which is defined as:

$$\text{MMS} = \frac{\mu_{H_a} - \mu_{H_0}}{\sqrt{\sigma_{H_a}^2 + \sigma_{H_0}^2}} \quad (5)$$

where μ_{H_a} (σ_{H_a}) and μ_{H_0} (σ_{H_0}) denote the mean (standard deviation) values of the histograms under H_0 and H_a respectively. Significant separation of the two histograms (e.g. MMS value greater than 2.0) implies that the performance of the OMUSP is satisfactory, because it shows that the performance index Q resulting from application of the OMUSP is not likely to be due to statistical reasons of chance related to random background activity. The MMS value for the correct (Nonmatch) left-lever response of rodent 1154 (left-lever) is 2.40, while it is 4.63 for the right-lever response.

In order to examine whether the OMUSP is distinct for the left-lever versus the right-level correct Nonmatch response, we show in Figure 8 the resulting OMUSP for the right-lever Nonmatch response (since the previously presented results were for the left-lever Nonmatch response). It is evident that the OMUSPs for the two cases are distinct. The computational evaluation of the right-lever Nonmatch OMUSP of rodent 1154 is shown in Figure 9 and indicates a highly significant MMS value of 4.63.

The same analysis was repeated for data from additional rodents, resulting in distinct OMUSP patterns with similar performance characteristics based on the computational evaluation using Monte-Carlo simulations of the *TLF*-based model. In total, experimental data from six different rodents, with multiple experimental sessions each, have been analyzed so far. However, the critical means of evaluation and validation of the efficacy of the designed OMUSP are offered only by actual experiments utilizing these stimulation patterns (see below).

3.3. Experimental Evaluation of Designed OMUSPs

We tested experimentally the efficacy of the designed OMUSP using the aforementioned methodology by applying these stimulation patterns to 4 CA1 neurons in two rodents: 1154 and 1181, over 10 experimental sessions of 100 trials each. To evaluate the OMUSP performance, we also tested these two rodents with random spikes (control experiments) with the same MFR as the OMUSP. The specifics of the stimulation procedure are presented in Methods. Figure 10 shows the observed performance of the OMUSP in these two rodents (red lines) and the performance for the control experiments (blue lines) for various imposed delays between the sample presentation and the response time. Generally, as the delay increases, the performance degrades in both OMUSP and controls. We observe consistent improvement of performance (percentage of correct Nonmatch responses) of about 10% on the average for the OMUSP experiments over all delays for both rodents, with slightly greater improvement due to OMUSP for longer delays.

4. Conclusion

We have presented a new methodology for the design of optimal multi-unit stimulation patterns (OMUSP) for neuronal ensembles that maximize the likelihood of inducing a desired behavioral outcome. The presented methodology utilizes a Volterra-type hierarchical model that accounts for high-order interactions and allows the computation of a performance index – the maximization of which yields the OMUSP in each case. The key entities in this model are the Triggering Likelihood Functions (*TLF*) which are computed from experimental data in each case. The computational evaluation of the designed OMUSP is performed with Monte Carlo simulations of the *TLF*-based model under the appropriate Null and Alternate Hypotheses, incorporating random (Poisson) background/spontaneous activity comparable to that observed in the experimental data. The computational evaluations demonstrated significant performance improvement for the OMUSP stimulation (Alternate Hypothesis) versus random stimulation (Null Hypothesis) for the same mean firing rates. The ultimate validation of the efficacy of the designed OMUSP was sought with actual experiments in two rodents utilizing the respective OMUSP stimulation patterns. The experimental results yielded significant improvement of about 10 % in correct average performance under OMUSP stimulation versus control experiments of random stimulation with the same mean firing rates. The percent improvement was slightly higher for longer imposed delays.

It would be interesting in future studies to compare the resulting OMUSPs by using *TLF*1s only with the OMUSPs from *TLF*1s and *TLF*2s. It would be also interesting to examine the degree of performance degradation when we use OMUSPs for the incorrect (Matched) responses or other random patterns. We must also seek to elucidate in future studies the intriguing fact that we can get such marked behavioral shift in an entire animal by stimulating only a few neurons in the hippocampus. This fundamentally important question can be explored by stimulating more and more neurons and/or selecting different tasks of variable complexity.

Further experimental testing of the efficacy of this approach is required and it is currently ongoing. The effects of key operational parameters (e.g. number of stimulated neurons, mean firing rates of stimulation etc.) are also currently examined and will be reported in the near future.

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Figure 1. Description of the DNMS experiments showing four different phases: Sample Presentation, Sample Response, Delay, and either Match (incorrect) or Nonmatch (correct) Response.

Figure 2.

Schematic illustrating the computation of the 1st order TLD₁ (left) using data from 5 trials and of the 2nd order TLD₂ (right) using a single trial (for simplicity of illustration). In practice, the data from hundreds of such trials are merged to compute the TLDs.

Figure 3. Block diagram showing the ETL computation from the TLF_1 's and TLF_2 's (self- and cross-) of the CA1 neurons, obtained for correct or incorrect trials of the DNMS task.

Figure 4.

Block diagram showing the computations required for the design of the optimal multi-unit stimulation pattern (OMUSP) via maximization of the utility function Q that is defined by the ETL values of Nonmatch (correct) and Match (incorrect) TLF-based models according to Equation (5).

Figure 5.

The computed TLF₁s of 4 CA1 neurons of rodent 1154 for Sample-to- Nonmatch (left) and Sample-to-Match (right) responses around the “Sample Presentation” phase of the DNMS task (i.e. zero is the time of Sample Presentation). These plots are the same as the conventional peri-event histograms after subtraction of the baseline (estimate of the background/spontaneous activity) and application of zero-phase smoothing.

Figure 6.

The computed self-TLF₂s of 4 CA1 neurons of rodent 1154 for the correct Sample-to-Nonmatch response (left column) and the incorrect Sample-to-Match response (right column) around the “Sample Presentation” phase of the DNMS task (i.e. the origin is the time of Sample Presentation). These plots describe the interactions between pairs of spikes in the epoch of the respective neuron as they influence the behavioral outcome. The effects of 1st order interactions, described by the TLF₁s of Figure 5, have been subtracted. The diagonal values are zero by definition (no interaction of a spike with itself).

Figure 7.

The computed cross-TLF₂s of 4 CA1 neurons of rodent 1154 for the the correct Sample-to-Nonmatch response (left column) and the incorrect Sample-to-Match response (right column) around the “Sample Presentation” phase of the DNMS task (i.e. the origin is the time of Sample Presentation). These plots describe the interactions between pairs of spikes from different neurons as they influence the behavioral outcome. The effects of 1st order interactions have been subtracted.

Figure 8.

The designed OMUSP pulses (red bars) for 4 CA1 neurons of rodent 1154 using the proposed TLF-based methodology for the left-lever (left) and right-lever (right) Sample-to-Nonmatch responses. The blue lines are the differences of the TLF_1 s for the correct (Nonmatch) minus the incorrect (Match) response, representing 1st-order analysis similar to conventional peri-event histograms. The timing of the OMUSP spikes does not always coincide with the peaks of the TLF_1 difference, suggesting the importance of 2nd-order interactions accounted by the computed TLF_2 s. Distinct differences are evident in the respective OMUSP for left-lever and right-lever tasks, demonstrating the task-specificity of the designed OMUSP.

Figure 9.

The histograms of Q values for the left-lever (left) and right-lever (right) Sample-to-Nonmatch responses of rodent 1154, obtained from 10,000 Monte-Carlo simulations under the null (H_0) and alternate (H_a) hypotheses (see text). The MMS values for the left-lever (left) and right-lever (right) Nonmatch response are 2.40 and 4.63, respectively.

Figure 10.

Performance of the optimal multi-unit stimulation patterns (OMUSP) designed for two rodents: 1154 (left) and 1180 (right), using the presented methodology. The abscissa is the imposed delay between the Sample Presentation and the response time. The ordinate is the mean percentage of correct (Nonmatch) responses for each delay over 10 experimental sessions of 100 trials each. The results for the OMUSP experiments are shown in red and for the control experiments (random stimulation of the same MFR) are shown in blue. Significant improvement of performance (~10%) is evident, especially for longer delays.