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Towards reliable spike-train recordings from thousands of neurons with multielectrodes

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The new generation of silicon-based multielectrodes comprising hundreds or more electrode contacts offers unprecedented possibilities for simultaneous recordings of spike trains from thousands of neurons. Such data will not only be invaluable for finding out how neural networks in the brain work, but will likely be important also for neural prosthesis applications. This opportunity can only be realized if efficient, accurate and validated methods for automatic spike sorting are provided. In this review we describe some of the challenges that must be met to achieve this goal, and in particular argue for the critical need of realistic model data to be used as ground truth in the validation of spike-sorting algorithms.

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Introduction

The electrical recording of spikes — the extracellular signatures of neuronal action potentials — is among the oldest [1] and most commonly used recording techniques in neuroscience. Accurate and reliable recording of the sequence of spikes from individual neurons is crucial as such spike trains appear to be the main carrier of information in mammalian neural systems. Despite its importance, the problem of reliably deciphering the recorded signal from an electrode in terms of spike contributions from the various neurons located in its vicinity is still largely unresolved. This spike-sorting problem is akin to the well-known 'cocktail-party problem' of tuning into one of the conversations at a busy party [2], and the development of automatic computerized spike-sorting methods has been an active research topic for several decades [3–5]. However, spike sorting is still an art as much as a science, and in most neuroscience labs spike sorting still involves a large manual component. This is not only very labor intensive, the sorting will by its nature be idiosyncratic, and the estimated spike trains will depend on who is doing the analysis [6,7].

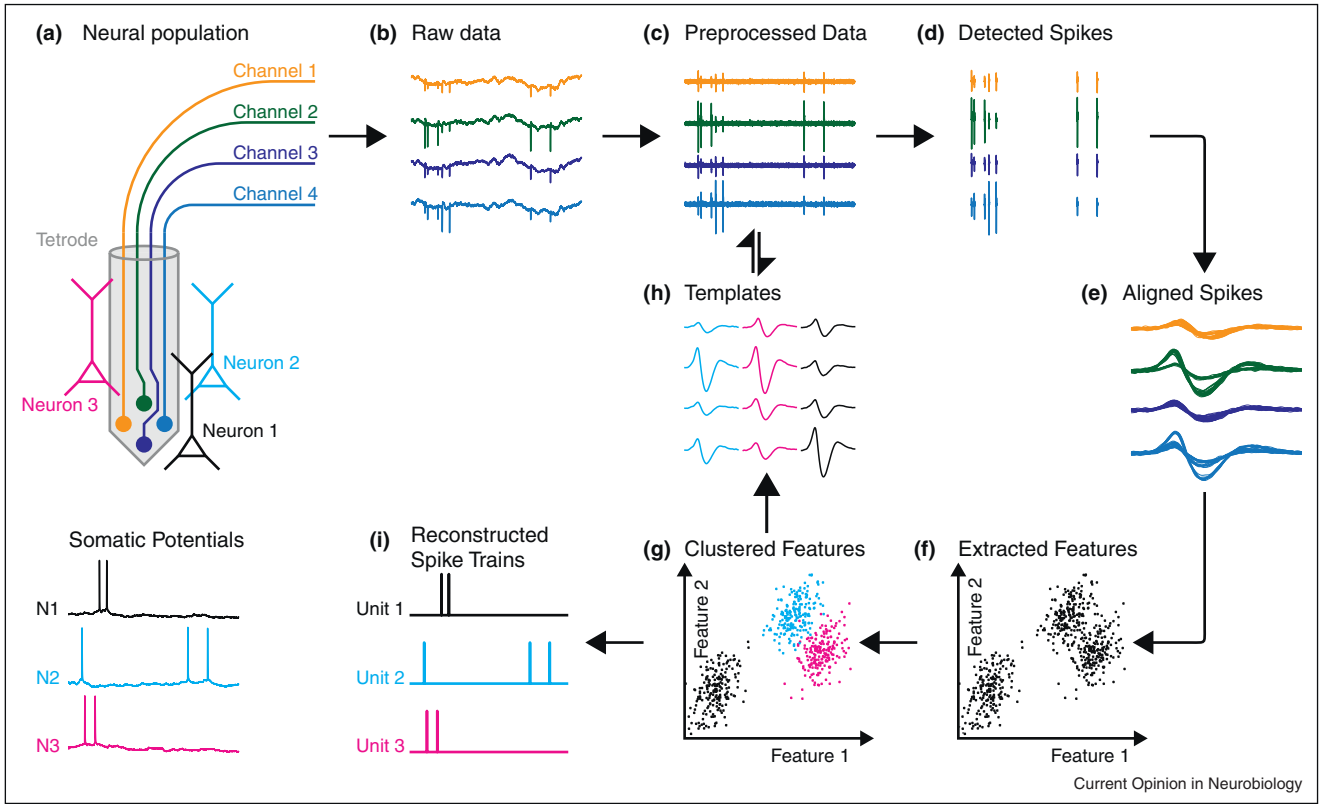
The new generation of silicon-based multielectrodes [8,9] with hundreds or more electrode contacts [10,11•,12•] offers exciting opportunities for dramatically increasing the yield and allowing for simultaneous spike-train recordings from thousands of neurons. However, this potential can only be realized if these advances in electrode hardware are accompanied by the development of validated automatic methods for spike-train extraction and quality estimation. Such algorithms would ideally operate in real-time to allow for continuous monitoring of recordings and use in closed-loop therapeutic [13] and brain–machine interface applications [14].

As illustrated in Figure 1, spike-train estimation from raw potential traces involves many steps. In addition to the obvious prerequisite of suitable recording electrodes and measurement electronics, all these must be performed adequately for successful spike-train estimation. In this short review, some key challenges in this processing chain will be discussed. We argue that the design and use of detailed mock experiments in a computer-model setting will be crucial for the development and validation of the necessary signal-analysis methods at each processing step. In such models the ground-truth, that is, the true underlying spike trains, will be known so that the estimation error can be readily assessed. The forward modeling of realistic extracellular signatures of spikes is an essential part of this. This was a central question discussed at the recent workshop 'Validation of Automatic Spike-Sorting Methods' held in Ski, Norway in May 2011 (see www.g-node.org/spike) and will also be a key point addressed in this review.

Challenges of automatic spike sorting

Spike sorting is an umbrella term lumping together the several stages involved in extracting single-neuron spike

Figure 1



Overview of spike-sorting process. Electrodes record changes in the extracellular electrical potential **(b)** caused by action potentials of neurons in its vicinity **(a)** [intracellular potentials of three spiking example neurons (N1, N2, N3) are depicted in lower left panel]. For the detection and analysis a highpass or bandpass filter is usually used to remove the low-frequency part of the potential **(c)**. The optimal procedure for detection of spikes, especially in multielectrode recordings, is still is an unsolved problem but simple voltage thresholding is commonly used **(d)**. For most spike-sorting procedures the extracted spike waveforms need to be temporally aligned on a common feature like the position of the voltage peak **(e)** before features are extracted from every waveform **(f)**. The feature extraction is crucial for decreasing the dimensionality of the data to the most informative dimensions. This can be done by, for example, using principal component analysis [4] or wavelets [49]. Clustering, that is, finding the number of clusters and their position in the feature space **(g)**, is highly susceptible to the choice of those features. Individual clusters should contain all spikes of one putative neuron only and are commonly assumed to exhibit multivariate normal [48] or *t*-distributions [50]. The average waveform of all spikes belonging to one cluster is called the 'template' of that neuron **(h)**. The outcome of the clustering is often a statistical model of the data (e.g., number of neurons, templates, covariance matrices) that can be used for quality estimation of the sorting result (see Figure 2 and [30••,48]) and derivation of a classifier for yet unclassified spikes (e.g., template matching).

trains from raw extracellular recordings [5]. This is illustrated in Figure 1 and described in more detail in its caption for a recording with a 'tetrode', a commonly used multielectrode with four closely spaced electrode contacts [15,16]. The analysis steps of the recorded potential traces can be organized as follows: (1) preprocessing of raw data (b → c in Figure 1), (2) spike detection (c → d), (3) extraction of spike waveforms from the data and their alignment (d → e), (4) feature extraction (e → f), (5) clustering (f → g), and (6) classification (g → i). Despite considerable efforts invested in developing algorithms and software, no generally applicable, easy-to-use and properly validated tool for fully automatic spike sorting, that is, the automatic processing of steps 1–6, is presently available. One obvious reason is the wide variety of recording types, such as *in vivo* recordings for various brain areas both in acute and chronic settings, and *in vitro* recordings for nervous tissue slices or in cultures. Also a wide range of recording hardware is used, varying both in the size, number and geometrical arrangement of electrode contacts and in electrode impedances. The consequence of this diversity is that a spike-sorting procedure working well in one setup may fail in others.

Spikes may be detected by electrodes up to 100 μm or more away from the somata of the firing neurons [8,10,17]. This implies that spikes typically will be recorded by several contacts on a multielectrode, that is, the electrodes will have overlapping 'sampling volumes'. This feature has been utilized to improve sorting quality when recording with stereotrodes [18] or tetrodes [15,16]. Tetrode recording is now commonplace in many labs, and the spike-sorting pipeline illustrated in Figure 1 has been used successfully for many years for such data.

The recent advent of high-density multielectrode arrays (MEAs) with hundreds of closely spaced contacts [10,11•,12•] poses serious problems for traditional spike-sorting methods. With large high-density probes, any one neuron will be recorded from several nearby channels, but there is no natural way to divide the channels into smaller groups which pick up non-overlapping sets of cells. The development of algorithms to deal with this new type of data is thus a high priority. For *in vitro* recordings with large dense MEAs (such as in retinal explants), algorithms based on fitting data as a sum of template waveforms are widely used [10]. In retina, a discrete population of ganglion cells is responsible for essentially all spiking activity picked up on the MEA. For *in vivo* recordings, the electrodes detect the spikes from thousands of neurons, most of which are too small in amplitude to be spike sorted. It is thus unclear whether the same spike-sorting approach will work for recordings of the mammalian brain *in vivo*. Further difficulties arise from waveform variability during bursting, as well as the ubiquitous LFP signal. At present, therefore, two (suboptimal) strategies are used for sorting high channel count data recorded *in vivo*. In the first, the data is processed 'en bloc', that is, all recording contacts are considered simultaneously [10]. This has the advantage that the methods developed for tetrode data can be applied directly or with minor modifications only. However, with MEAs recording from more and more neurons, synchronous firing events that constitute a severe problem for spike sorting become the rule, not the exception. In the second approach ('divide-and-conquer') the array of electrodes is split into groups of electrodes with overlapping sampling volumes (where each electrode may belong to several groups), and spike sorting is then performed for the electrode groups individually. This offers the advantage that computational demand scales only linearly with the number of electrodes. However, as one cell may be detected by several electrode groups, a second step is required, where neurons seen by several groups are identified. Although this is typically done manually, the development and verification of algorithms for this step are important [19] (but see also http://code.google.com/p/caton/).

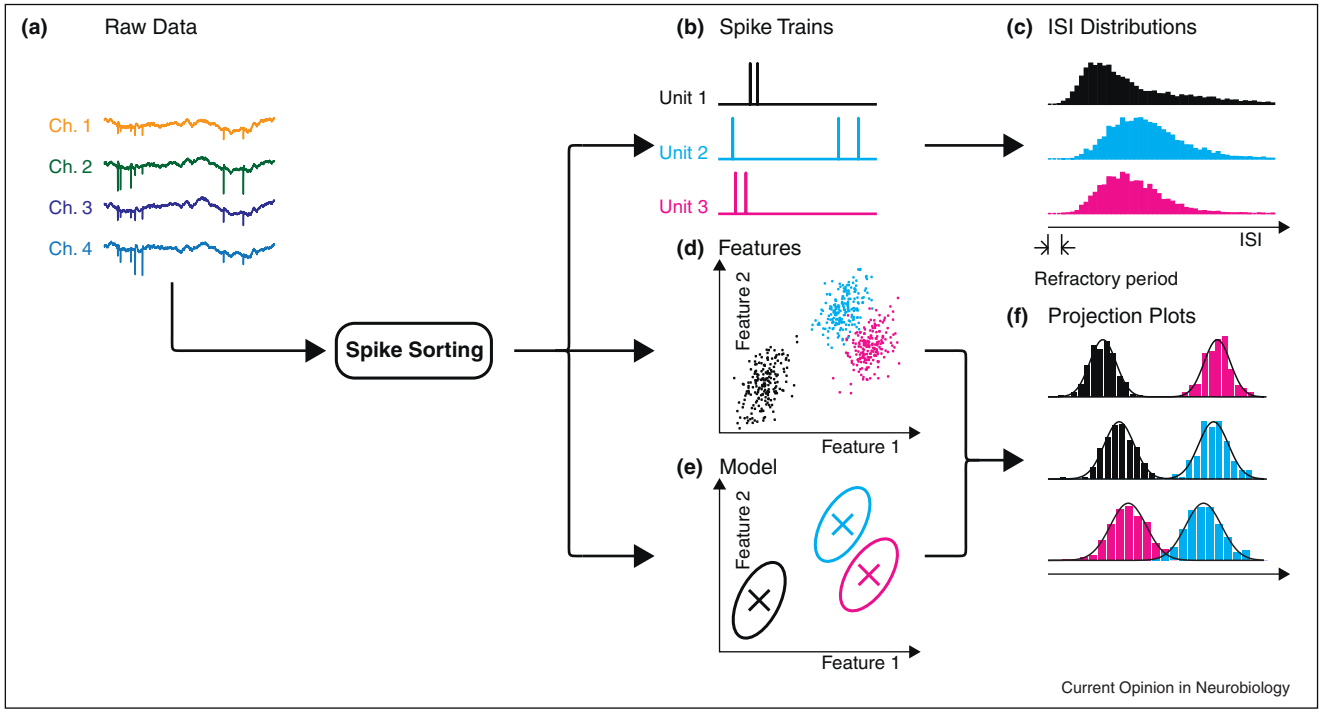
For long-lasting recording sessions 'cluster stability' becomes an issue as the electrode may drift, that is, move, with respect to the neural tissue. Further, for week-long recordings the extracellular environment surrounding the electrode contact may change due to, for example, glia cell movements or growth. This may lead to movement of cluster centers in feature space (Figure 1g), new clusters appearing, and existing clusters vanishing, merging or separating [20]. While most approaches seem to ignore the problem and process all data 'en bloc', some have addressed it by modeling the electrode drift explicitly and incorporating it into the spike-sorting procedure [20,21]. Another approach has taken advantage of the slowness of the drift and solved the problem in an iterative way: (i) extract a classifier from a short chunk of data, (ii) apply this classifier to the next data chunk, (iii) update the classifier, and then repeat the steps (i)–(iii) on a new chunk of data. In essence this latter approach is a simplified version of the former where the time courses of model parameters are approximated as piecewise constant functions in time. The method is simple to implement and gives large run-time reductions as the clustering is performed on a smaller sample [22,23].

In many preparations spike amplitude and shape are found to vary depending on the time since the previous spike of the same neuron, the prime example being bursting neurons [24,25]. If unaccounted for, such dependence on interspike interval may result in classification errors [7,16]. This problem has not received as much attention as it should, but some solutions have nevertheless been proposed. One has involved a flexible, nonparametric estimation of the cluster shapes of single units since a consequence of such waveform dynamics will be 'elongation' of clusters [26]. This approach can be numerically efficient, especially if one uses 'Bagged Clustering' algorithms [27], but the implicit assumption that a single unit gives rise to a single connected cluster may be problematic. This problem has been dealt with by explicit modeling of the waveform dependence on the interspike interval [28], but this implies about a tenfold increase in computational burden. Another approach takes advantage of the overlapping sampling volumes of the contacts in tetrodes and other modern multielectrodes: if the waveform from a particular neuron as recorded on one contact can be predicted by applying a linear filter to the waveform of the same neuron recorded on another contact, these filters can be used as input features to the clustering algorithm. The key idea is that these filters predominantly will be determined by the position of the neuron with respect to the electrodes and thus vary less with the spike waveforms [29].

Validation of automatic spike-sorting algorithms

Spike-sorting methods should ideally provide not only a best estimation of spike trains, but also a measure of the sorting reliability. A thorough recent review of methods that can be used in the absence of ground-truth data can be found in [30••], and some easily implemented tests are illustrated in Figure 2. A thorough evaluation of spike-sorting algorithms is difficult to do, however, without proper ground-truth test data, that is, spike-sorting data for which the true underlying spike trains are known. With such data the performance can be evaluated directly by comparison of the estimated and ground-truth spike trains, that is, by calculation of false detections, misses of detections, and classification errors of spikes [7,28,31,32]. An obvious approach for obtaining such ground-truth data is to combine extracellular recordings with simultaneous

Figure 2



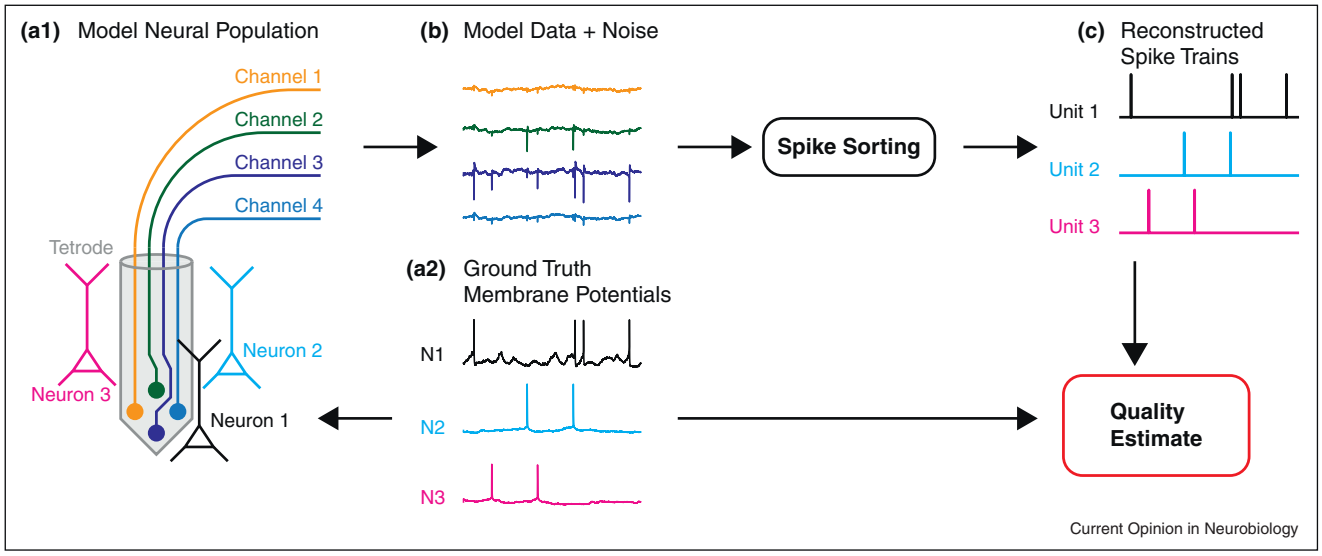
Examples of spike-sorting validation techniques applicable without knowledge of the true spike trains (ground truth) [30••]. After spike sorting of the raw recorded signals **(a)** the resulting spike trains **(b)** can be checked for biological plausibility by, for example, computing the interspike interval (ISI) **(c)** and inspected for violation of a refractory period. Using a dynamic multidimensional data visualization software like GGobi (www.ggobi.org), cluster separation can be judged visually **(d)**. The assumptions of model-based sorters, for example, assuming a mixture of Gaussian or *t*-distribution for the clusters, can be checked by finding for each pair of clusters a direction along which the separation of the spikes of these two clusters is optimal, that is, determining the optimal linear discriminant. The overlap of the densities of spikes from each pair of clusters projected onto this optimal direction can then be theoretically obtained, compared to the empirical distribution to validate the model assumptions, and used as a measure of the probability of misclassification [48] **(e)** and **(f)**. The linear discriminant approach applies only if the different clusters have a common covariance matrix. Otherwise, the quadratic discriminant can be used instead.

intracellular recordings of individual spike trains of neurons that contribute to the recorded extracellular potentials. Such data has been provided from the optic lobe of locusts [31], from pyramidal cells in rat hippocampus *in vivo* [33,7], and Purkinje cells in *in vitro* rat cerebellum [28], and successfully used to evaluate performances of automatic spike-sorting algorithms [7,28,31].

Such dual recordings are difficult to do, however, and the yield in terms of the number of ground-truth spike trains will by nature be limited. An attractive alternative has thus been to use synthetic test data obtained from modeling [32,34–38]. In one approach synthetic data has been constructed based on extracellular spike shapes extracted from real data, superposed in a stochastic manner to incorporate a plausible underlying spike-train statistics [10,32,34,36]. Noise has either been added by hand [35] or by summing contributions from numerous distant neurons [32,36]. Another approach, illustrated in Figure 3, has taken advantage of the well-known biophysical cable properties of neurons, and in particular the link between intracellular and extracellular potentials provided by volume conduction theory [17,39,40]. This theory allows for detailed simulation of the extracellular signature of spikes and, for example, how it depends on the position of the electrode relative to the soma [17,39–44]. Such modeling typically proceeds in two steps: First, the transmembrane neuronal currents during action-potential firing are calculated using a neural simulator such as *NEURON* (www.neuron.yale.edu) or *GENESIS* (www.genesis-sim.org). Secondly, the extracellular potential is found by summing over the transmembrane current of each compartment inversely weighted with the distance between the neuronal compartment and the virtual electrode [40].

This scheme has already seen preliminary use in generating synthetic spike data mimicking a rat hippocampal network [35,36] (and synthetic multiunit activity (MUA) data mimicking cortical population activity [43]). However, the use in the context of generating spike-sorting test data is still in its infancy. With thousands of reconstructed neuronal morphologies becoming available through public databases such as NeuroMorpho.org, there

Figure 3



Validation of spike-sorting methods by use of ground-truth data obtained from biophysically detailed modeling of extracellular potentials accompanying action-potential firing. **(a1)** A population of (in this case three) spiking model neurons is placed around a virtual multielectrode (in this case a tetrode). Ground-truth somatic membrane potentials **(a2)** and the neuronal transmembrane currents needed to evaluate the corresponding extracellular traces using an electrostatic forward-modeling formula [40,17], are calculated with standard multicompartmental modeling of spiking neurons [39–43,17]. Alternatively, recorded intracellular action potentials can be imposed directly as an electric boundary condition in the soma of the multicompartmental model neuron [17]. Noise can be added to the calculated extracellular traces as desired **(b)**. The model 'raw data' are then used to reconstruct the spike trains **(c)** following the standard spike-sorting procedure depicted in Figure 1. These estimated spike trains can then be compared with the known ground-truth spike trains read directly out from the somatic membrane potentials **(a2)**.

is in practice no limit to the variety of test data that can be made. These digitized morphologies are readily imported into neural simulators to be supplemented with suitable ionic conductances to make models with plausible action-potential firing. A simplifying trick to avoid the arduous exercise of fitting the parameters of active ionic conductances is to impose recorded somatic intracellular potentials directly into the soma compartment in the corresponding simulation [17]. For example, bursting dynamics, where the subsequent spikes in a burst have different extracellular signatures [24,25], can be implemented by imposing the intracellular potential trace recorded from a bursting neuron. Model neurons with appropriate firing statistics can then be placed at appropriate positions around the electrode to mimic the system of interest. Effects of electrode drift can be taken into account [45] and noise added at wish [38]. A particularly interesting prospect is to combine synthetic test data with experimental data [10]: here model data from one or several neurons, for which the ground-truth spike times are exactly known, is added to experimental recordings incorporating the noise situation at hand. The performance of the spike-sorting algorithms for the spiking model neurons can then be evaluated in a standard way. The biophysical forward-modeling scheme which assumes a frequency-independent, isotropic and inhomogeneous electrical conductivity in the extracellular medium may be modified if warranted [44]. Likewise, the effect of the size and shape of the electrode and in particular electrode contact can be modeled in detail and included in the scheme [46,47•]. But it should be kept in mind that test data do not have to be biophysically realistic in all ways in order to be useful. After all, if an aspiring spike-sorting algorithm fails already on relatively simple test data, it will be difficult to trust it in an even more challenging experimental setting.

Outlook

Methods for spike sorting of arrays of tetrodes are well developed and, if not optimal and validated, good enough to be used routinely to record from up to ~200 neurons simultaneously *in vivo*. The new generation of high-density MEAs presents the potential to record from thousands of neurons *in vivo*, but new algorithms must be developed to spike-sort this data. The problem of developing optimal and validated methods for extraction of spike trains from this data, is not only difficult but also well defined, and likely tractable. The basic physical processes of the entire recording and estimation chain appear well understood so that accurate mock experiments, in which the ground truth is known, can be constructed in simulations. A coordinated international effort is needed, however, and to stimulate this process we have set up a website where researchers with spike-sorting test data can meet researchers developing spike-sorting algorithms and other signal analysis methods. This

web site, www.g-node.org/spike, is hosted by the German national node of the International Neuroinformatics Coordinating Facility (INCF, www.incf.org), an organization set up to stimulate global use of neuroinformatics to solve neuroscience problems.

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