

From response to stimulus: adaptive sampling in sensory physiology

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Sensory systems extract behaviorally relevant information from a continuous stream of complex high-dimensional input signals. Understanding the detailed dynamics and precise neural code, even of a single neuron, is therefore a non-trivial task. Automated closed-loop approaches that integrate data analysis in the experimental design ease the investigation of sensory systems in three directions: First, adaptive sampling speeds up the data acquisition and thus increases the yield of an experiment. Second, model-driven stimulus exploration improves the quality of experimental data needed to discriminate between alternative hypotheses. Third, information-theoretic data analyses open up novel ways to search for those stimuli that are most efficient in driving a given neuron in terms of its firing rate or coding quality. Examples from different sensory systems show that, in all three directions, substantial progress can be achieved once rapid online data analysis, adaptive sampling, and computational modeling are tightly integrated into experiments.

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Introduction

High-quality experimental data are precious. Physiological recordings from neurons are more easily lost than established, and the duration of any single experiment is almost always shorter than one wished. Therefore, an important aspect of experimental design in sensory physiology concerns the selection of stimuli. In general, stimuli are designed to characterize a neural system or test a hypothesis about its structure, dynamics, or function. The hypothesis itself might be derived from a previous observation or theoretical framework, such as the energy model

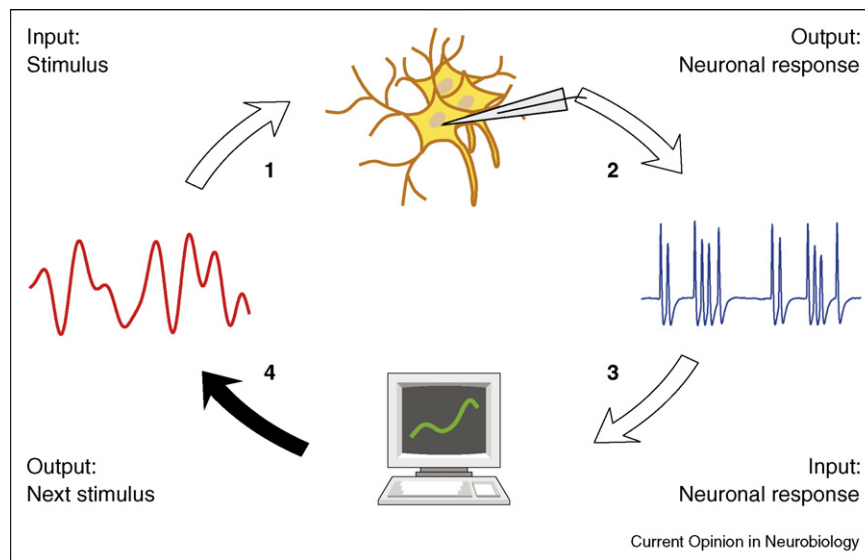
in early vision [1], leading to an iterative process of data acquisition, data analysis, hypothesis generation, and new stimulus design. Each step in this process has traditionally been carried out separately.

In this review, we discuss how one can use adaptive sampling methods to speed up hypothesis-driven neuroscience by analyzing neural responses *while* a cell is being recorded and using the results of this analysis to determine the stimuli that should be presented next – all during the same recording session. Of course, using their intuition and expert knowledge, neurophysiologists often do just this – when they manually vary the parameters of a visual grating to determine the receptive field of a neuron or when they adjust the intensity of a sound stimulus to measure the threshold curve of an auditory neuron. While this is exactly the conceptual framework for closed-loop approaches we have in mind, that is, exploiting neural responses *online* to determine which stimulus to present next, their full potential can only be reached in a fully automated set-up (Figure 1). In the following, we therefore focus on recent computer-based approaches. For the sake of concreteness, we limit our review to sensory systems explored with sensory stimuli in a closed-loop setting and do not cover dynamic-clamp studies [2,3,4] nor brain–computer interfaces [5].

How to speed up experiments: optimal sampling strategies

Many experiments start with some standard stimulation protocol that allows the researcher to identify or characterize a sensory neuron. In the visual system, this may be the receptive field of a neuron, in the auditory system its threshold curves over sound frequencies. In several laboratories, such protocols have been automated; for instance, instead of determining the characteristic frequency of an auditory neuron by stepping through sine tones with pre-determined, equally spaced frequencies, some physiologists use a simple line-search algorithm to iteratively zoom down onto the right frequency or apply automated threshold tracking to assess the tuning curve [6–8]. Visual receptive fields can be determined in a related though much higher-dimensional online procedure: Already in the 70s, the ‘algorithm of pattern extraction’ (Alopex) was introduced to achieve fast, yet accurate measurements [9]. Similar tasks arise in the characterization of neuronal populations; for recordings of multiple neurons, rapid automated screening for connected cell pairs can be used to determine which pairs are suited for more detailed experimental testing [10].

Figure 1



Closed-loop experiments and adaptive sampling. First, the sensory system under investigation is presented with an initial stimulus such as a sound wave or a color image. Second, the neural system converts this input stimulus into an output response—the membrane potential of a single neuron, a multi-unit signal as measured in an extracellular recording, a calcium or EEG signal and so on. Third, this response is measured and recorded with a computer system. If necessary, spikes are automatically detected and sorted online. Following this data pre-processing, the neural response is further analyzed according to the theoretical framework underlying the specific experiment. Fourth, a new stimulus is generated on the basis of the results of this analysis thus closing the loop. Iterating this loop, stimuli can be generated that reflect the particular response characteristics of the studied system. As discussed in this review, such an adaptive sampling strategy has various advantages.

Despite these specific successes, closed-loop methods have not been used widely in sensory physiology. This may be because computational demands were too high when these methods were first introduced or their performance did not reach initial expectations. After all, automated algorithms tend to be susceptible to uncontrolled response fluctuations or changing conditions inherent of most biological experiments.

Recent conceptual and technical advances, however, should lead us to reconsider closed-loop methods. For instance, a study by Lewi *et al.* [11^{••}] does not only show how to measure receptive fields more efficiently but more importantly suggests an approach to do so in an optimal, most time-saving way. The authors present a novel method that, given a set of already acquired neural responses, determines which stimulus should be presented next so that the recorded data provide as much information about the structure of the receptive field as possible (Figure 2). The method is computationally feasible and fast; in addition, it can account for neural adaptation and shifting experimental conditions.

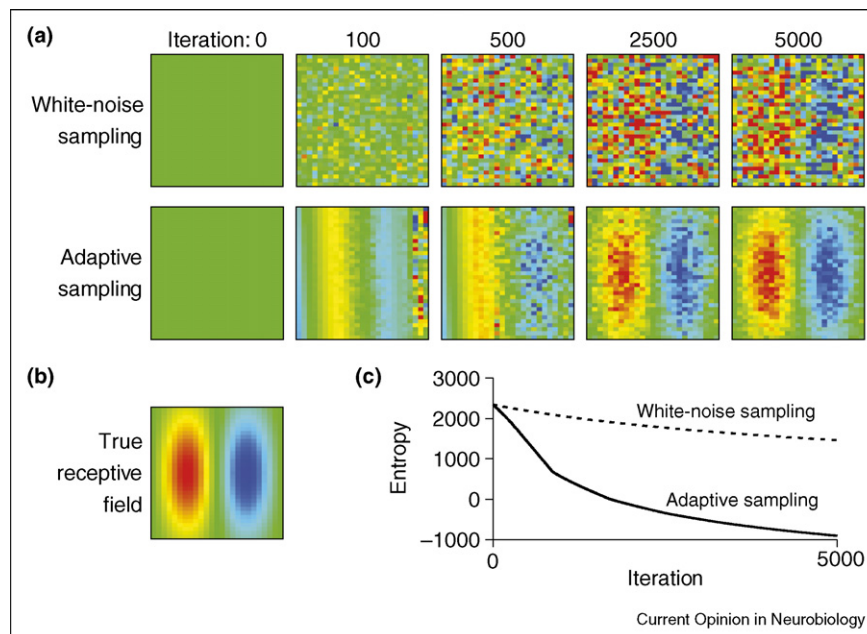
The principle that each successive stimulus should provide as much information as possible about the investigated system has been exploited in several algorithmic suggestions for experimental stimulus selection [12,13]. In psychophysics, for example, a standard problem akin to

the assessment of receptive fields and tuning curves is the measurement of psychometric functions [14]. Often, these are characterized by few parameters only, such as the range and maximal slope of a predetermined class of sigmoid functions. After each trial one can present the stimulus that maximizes the information we can gain about these parameters, thus making optimal use of experimental time [15].

Discriminating between alternative models: the iso-response method

The above methods show how experiments can be made more efficient once a particular underlying model has been identified. If there are several competing models, however, the first goal is often not to estimate their parameters most efficiently but to compare their validity. Is there a smart way to do so? Obviously, a primary objective is to identify some feature that clearly distinguishes between the alternative models. But how do we find such a characteristic feature? Here, again, closed-loop approaches are helpful in that they allow us to efficiently look for a new and possibly unexpected type of signature; instead of a standard experimental procedure that measures the response for a given stimulus and compares it with the predictions of the different models, we can alternatively identify those stimuli that correspond to a *fixed response* and use them to assess the performance of the different models (Figure 3).

Figure 2



Adaptive estimation of receptive fields, as demonstrated by a numerical simulation study. **(a)** The top row shows how the structure of a receptive field builds up gradually when a standard neurophysiological approach is used. Here, white-noise stimuli are presented and the receptive field is estimated as the spike-triggered average. The bottom row shows results from an adaptive sampling technique in which each new stimulus is selected such that it maximizes the information gained about the receptive field. **(b)** The true receptive field. **(c)** The uncertainty of the estimates, quantified by the entropy of the parameter distribution, drops far more rapidly for the adaptive sampling technique than for white-noise sampling (data provided by courtesy of J Lewi).

Sets of stimuli that yield the same response – also called *iso-response stimuli* – have a straightforward advantage: they are largely independent of the neural output non-linearity. The dynamics of how a neuron, for example, converts its summed activation into a firing rate are unimportant if all comparisons are made on the basis of identical firing rates. Instead, measurements of iso-response stimuli can more easily explore the processing of sensory or synaptic input into the neuron [16]. For this reason, such measurements have been used for a long time in auditory physiology to characterize neural tuning to sound frequency [6,17,18]. In addition, iso-response stimuli correspond to the level sets of a neural input-output relation and thus directly reveal invariances with respect to stimulus variations that might hint at biophysical mechanisms and also be of functional relevance (Figure 3).

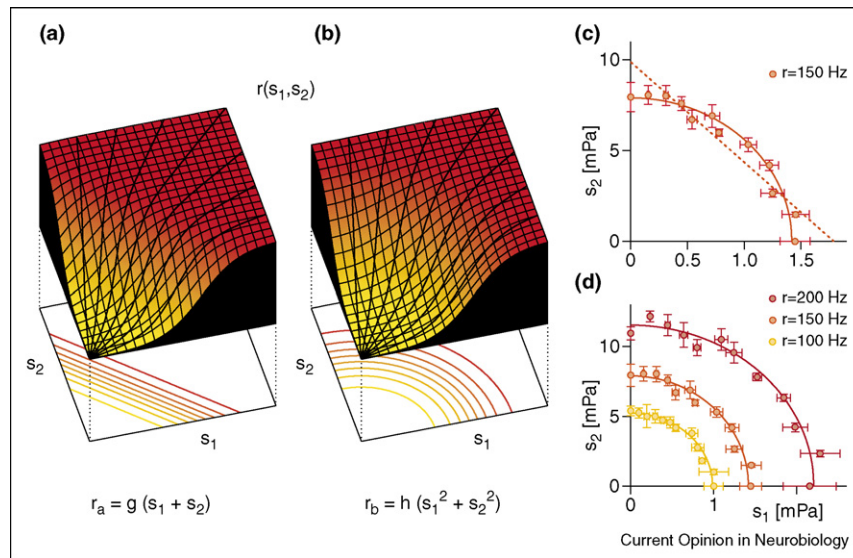
Methodologically, setting a desired neural response is, of course, not quite as straightforward as specifying a particular stimulus. But the implementation of fast, automated-search algorithms in a closed-loop approach allows us to efficiently tune in on a specific response and thus make the iso-response approach feasible even for fairly limited recording times. The response measures that are specified are not restricted to spike rate or intracellular

membrane potential. By applying this approach to the occurrence probability of a single spike, for example, it can be used to analyze signal processing with a temporal resolution much finer than the limits imposed by neural output variability, that is, spike-time jitter [19^{••}]. In addition, the iso-response approach offers the possibility to precisely control adaptation mechanisms that are triggered by the neuron's spiking activity. This can be used to distinguish between adaptation that is *caused* by spike generation and adaptation that results from upstream mechanisms, such as synaptic depression, channel inactivation, or mechanical fatigue [20].

Searching for the most efficient stimuli

Neural stimulus-response relations are often too complex to be explained by simple dynamical models. On the other hand, it is very difficult to accurately determine the many parameters of a model that covers morphological or biophysical details [21]. This calls for approaches that go beyond a dynamical-system view of neural processing. Progress can be made by formulating a hypothesis about the neural code used to represent information about the sensory world. Here, a standard assumption is that neurons encode specific stimulus features in their individual firing rates; they fire strongly when a particular feature is present and weakly or not at all when the feature is absent.

Figure 3



Discrimination of alternative response relations using the Iso-Response Method. **(a and b)** A hypothetical two-dimensional stimulus space is spanned by the variables s_1 and s_2 . The drawn surfaces represent the response $r(s_1, s_2)$ for two different models, which take the linear (a) and quadratic sum (b) as the argument of a sigmoid non-linearity. Although the two input-output scenarios are fundamentally different, both produce exactly the same one-dimensional response functions $r(s_1)$ and $r(s_2)$, respectively, as seen by the black areas at the sides of the surface blocks. Furthermore, any measurement along a radial direction, as is common in physiological experiments, will produce similar sigmoid response curves in both cases, as seen by the thick black lines running along the surfaces. The iso-response manifolds $r = \text{const}$ (here: one-dimensional curves) below the surface plots, however, give a clear signature of the different underlying processes. **(c)** Iso-firing-rate curves for an auditory neuron stimulated by superpositions of two pure tones. The measured pairs of amplitudes s_1 and s_2 corresponding to a firing rate r of 150 Hz are shown together with the iso-firing-rate curves for the two scenarios which now correspond to sound-amplitude integration (a) and sound-energy integration (b), respectively. The straight line for the amplitude hypothesis deviates systematically from the data, whereas the ellipse obtained from the energy hypothesis provides an excellent fit. The different scales on the axes reflect the strong frequency dependence of the neuron's sound sensitivity. **(d)** As expected from the sound-energy model, iso-response lines for different output firing rates are scaled ellipses (panels c and d adapted from reference [16], with permission. Copyright 2002 by the Society for Neuroscience).

Several techniques have been proposed to search for the particular stimulus or stimulus feature that maximizes a neuron's firing rate; these include the Alopex algorithm already mentioned, which is based on stimulus-response correlations [9,22–24]. Alternatives are the simplex algorithms known from numerical optimization methods [25], genetic algorithms [26], and approaches based on estimating gradients [27,28*]. To keep stimuli within physical bounds, searches are performed under a given set of constraints, for instance, a fixed visual contrast or a fixed sound intensity. In particular, for higher brain areas, it may be advantageous to search rapidly through a large set of pre-determined natural stimuli and progressively narrow them down to those that elicit the highest firing rates [29].

The search for optimal stimuli has been of particular interest for auditory neurophysiologists in their quest for organization principles that resemble those found in the visual system [22,25,26,28*]. Automated closed-loop approaches have therefore been considered a highly promising concept in this respect [30], and indeed, optimization algorithms such as those mentioned above do

succeed in finding sensory stimuli that yield high firing rates. However, the overall impact of these studies has been limited, perhaps because identifying stimuli that cause strong responses does not necessarily assess the information-processing role of the investigated neuron. This concerns the auditory system as well as other sensory modalities. It therefore remains a matter of debate how useful the very concept of stimuli that are 'preferred' – in terms of the elicited firing rates – really is [31].

An alternative and more general approach is based on the assumption that a suitable measure of neural coding is the average Shannon-Information that a cell conveys about sensory stimuli [32]. Accordingly, a neuron is then characterized by the stimulus *ensemble* that maximizes the cell's information rate. In the same way as firing-rate-based optimality approaches, this framework requires specific assumptions about how information about the outside world is represented in the neuron's activity pattern. However, the assumed neural code need not be limited to a firing-rate description but can include temporal aspects too. A recent study shows how to find such optimal stimulus ensembles in a closed-loop setting

(Figure 4) and how they depend on assumptions about the neural code [33,34^{••}]. Comparing these different optimal stimulus ensembles with each other and with the set of natural stimuli opens up the possibility to use quantitative information-theoretic methods to investigate questions of neural coding and code efficiency from a neuroethological point of view.

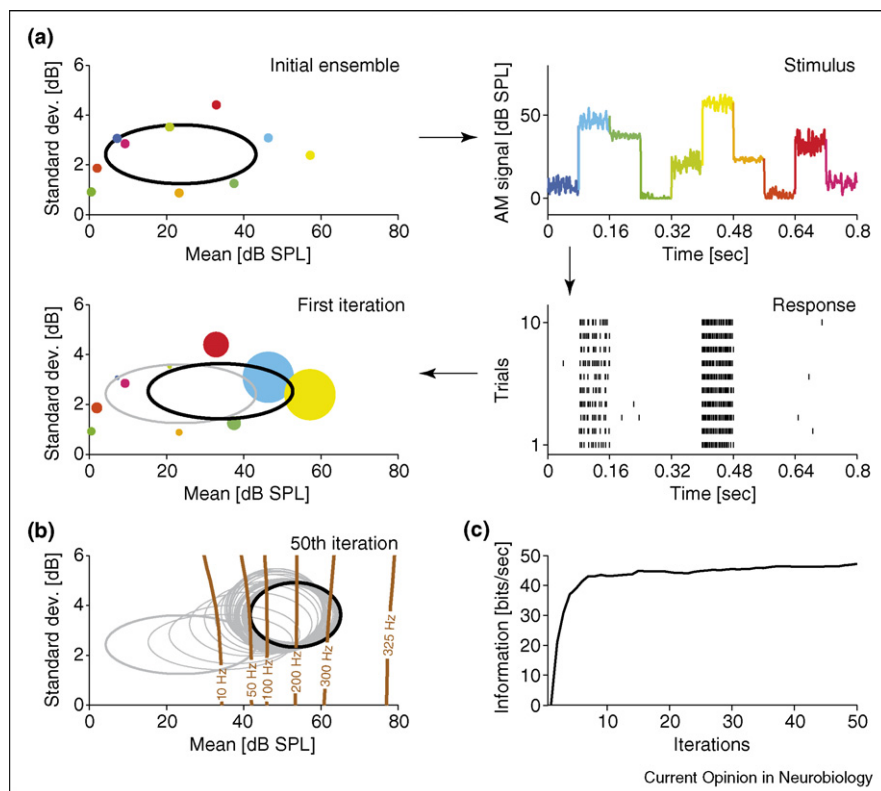
With specific assumptions about the neural code, one can search for particularly stable sensory representations by directly using the neuron's output – after some proper transformation – as a subsequent input into the same neuron [35]. Similar approaches have also been used to investigate signal propagation in neuronal populations with a feed-forward [36] or recurrent connectivity [37,38]. Re-injecting the recorded neuronal spike train as an electric input into the neuron closes the loop in these investigations and allows one to simulate inter-

actions in neuronal populations based on a single recorded neuron.

Technical challenges

Online data analysis, closed-loop experiments, and adaptive sampling are powerful techniques that bear substantial advantages in many different experimental scenarios; from making standard receptive-field characterizations faster and more efficient to allowing novel experimental designs that search for stimulus ensembles that are optimal in an information-theoretical sense. The benefits of all these closed-loop experiments, however, do not come for free; automating the data acquisition and analysis creates the need for a particular robustness of the experimental system and a certain degree of predictability of potential outcomes of the experiment so that the closed-loop system can be programmed to automatically generate suitable reactions.

Figure 4



Iterative search for optimal stimulus ensembles (OSEs). **(a)** In this analysis of an auditory receptor neuron, stimuli are sets of ten 80 ms-long snippets of white-noise amplitude modulations of a sine-wave carrier. Sample mean and standard deviation (colored dots in top-left panel) are drawn from a two-dimensional Gaussian distribution whose standard deviation is represented by the black ellipse. The stimuli are played repeatedly (top-right panel), resulting in spike-train responses that vary slightly from trial to trial (bottom-right panel). On the basis of the responses from several trials, the contribution of each stimulus to the mutual information is estimated; this contribution is depicted by the size of the colored dots representing the individual snippets (bottom-left panel). The contributions are taken as weight factors to update the parameters of the Gaussian distribution that is thus shifted toward the more important stimuli (new black ellipse). The updated stimulus ensemble is then used to draw new, additional test stimuli. **(b)** For a longer sample run with multiple iterations, intermediate estimates of the OSE (grey) rapidly converge to the final OSE (black). As shown by the iso-firing-rate lines, the OSE is centered at the steepest part of the tuning curve and triggers responses that cover almost the full range of firing rates. As desired, the OSE is thus indeed located in the most informative region in stimulus space. **(c)** Accordingly, the information rate initially grows rather fast with each iteration until it saturates after about 20 iterations. (adapted from reference [34], with permission. Copyright 2005 by Cell press).

For the large field of extracellular recordings from neurons *in vivo*, the first hurdle to be taken on the way to reliable closed-loop experiments is the notorious spike-sorting problem [39,40]. While many techniques for determining which measured voltage peaks correspond to the action potentials of a single neuron still rely on offline processing and human intervention during the sorting process, new and fully automated methods are under way [41–43,44*], but will yet have to demonstrate their reliability under generic experimental conditions.

Intracellular recordings alleviate the spike-sorting problem, as the membrane potential can be used directly as a response measure and spikes can be robustly detected by simple threshold criteria [45]. But changing experimental conditions due to, for example, fatigue of the neural preparation or drifts in the recording quality, may ‘confuse’ the automated analysis and lead it to track these artificial changes instead of the more interesting actual neural dynamics. And the more complex the automated analysis gets [35], the more care has to be taken with respect to spurious artifacts and unforeseen pitfalls such as non-converging oscillatory solutions or local minima in the search for optimal stimulus parameters.

Conclusions

If the challenges and caveats of closed-loop experiments and adaptive-sampling strategies can all be properly addressed, substantial advancements are to be expected in measurement efficiency and experimental design, similar to what has already become possible in other biological research areas [46]. Quantitative assessments of data efficiency will underscore the importance of these technological developments. This goal has been accomplished for information-theoretic optimal sampling schemes: In general, adaptive sampling will speed up experiments by a constant factor, and this factor grows with the dimensionality (i.e. the number of parameters) of the underlying mathematical model [47**]. Hence, especially when there are many parameters involved, as is the case for receptive-field models, adaptive sampling techniques are clearly superior to traditional non-adaptive techniques. Thanks to the dramatic improvements in processor speed and memory capacity, this mathematical result translates directly into large potential experimental gains. Already now, fast and efficient control programs (see, e.g., <http://www.relacs.net>) allow one to include even sophisticated online information theoretic calculations, as in reference [34**], into closed-loop experiments.

It is mostly for this reason of experimental efficiency that more and more experimental studies will involve adaptive-sampling techniques in the future. This advancement will boost – and be boosted by – theoretical approaches to neuroscience, from non-linear dynamics and probability theory to theoretical biophysics and neural computation. As a result, mathematical theory

and computational modeling will be tightly integrated into the data acquisition and analysis process and lead to important changes in the conceptual framework and everyday practice of sensory physiology.

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