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A Multivariate Logistical Model for Identifying the Compressive Sensitivity of Single Rat Tactile Receptors as Nanobiosensors

Tactile sensation is a complex manifestation of mechanical stimuli applied to the skin. At the most fundamental level of the somatosensory system is the cutaneous mechanoreceptor. The objective here was to establish a framework for modeling afferent mechanoreceptor behavior as a nanoscale biosensor under dynamic compressive loads using multivariate regression techniques. A multivariate logistical model was chosen because the system contains continuous input variables and a singular binary-output variable corresponding to the nerve action potential. Subsequently, this method was used to quantify the sensitivity of ten rapidly adapting afferents from rat hairy skin due to the stimulus metrics of compressive stress, strain, their respective time derivatives, and interactions. In vitro experiments involving compressive stimulation of isolated afferents using pseudorandom and nonrepeating noise sequences were completed. An analysis of the data was performed using multivariate logistical regression producing odds ratios (ORs) as a metric associated with mechanotransduction. It was determined that cutaneous mechanoreceptors are preferentially sensitive to stress (mean $OR_{max}=26.10$), stress rate (mean $OR_{max}=15.03$), strain (mean $OR_{max}=12.01$), and strain rate (mean $OR_{max}=7.29$) typically occurring within 7.3 ms of the nerve response. As a novel approach to receptor characterization, this analytical framework was validated for the multiple-input, binary-output neural system. [DOI: 10.1115/1.4002750]

Keywords: skin mechanics, tactile sensation, cutaneous mechanoreceptors, logistic regression, mechanosensitivity

1 Introduction

Recently, nanoscale probes have been developed to study interactions at the cellular and molecular level in real time, providing biosensors that have far higher sensitivity than conventional methods. As an example, nanoscale cantilevers have been used to measure the deflection induced by surface stresses, in which target molecules attach themselves to the sensitized surface of the cantilever [1]. In the specialized sensory organs, mechanosensitive ion channels act as the mechanotransducers responsible for the sensations of hearing, touch, vibration, local gravity, kinesthesis, and osmoreception [2]. Mechanoreception provides sensory feedback on organ volume and pressure, including the mechanoreceptors explored here.

Tactile skin mechanoreceptors transduce mechanical stimuli such as applied vibration, stretching, and pressure into a binary action potential. Nerve endings associated with mediating cutaneous sensation are classified as Meissner's corpuscles, Merkel cells, Pacinian corpuscles, or Ruffini corpuscles. Both the intensity and duration of the stimulation are encoded by the frequency of action potentials. However, mechanoreceptors exhibit adaptation when subjected to prolonged stimulation. This adaptation is either rapid or slow and each type of adaptation encodes different information [3]. Rapidly adapting (RA) receptors (Meissner and Pacinian corpuscles) encode higher frequency mechanical changes such as those produced by vibration. RA receptors fire at the onset and offset of a stimulus at or above the nerve's threshold and are generally quiet in between. RA afferents may also respond with a high frequency burst of action potentials at the onset of the stimulus where the burst rate is a function of the magnitude of the initial stimulation. The more intense or rapid the deformation of a single corpuscle, the higher the burst rate of nerve impulses generated in its neuron. If the stimulation is continuous but static in magnitude, a RA afferent will adapt, resulting in a decrease in the frequency of action potentials until none are observed. At this point, any change in the stimulus from this static state will again prompt a volley of action potentials followed by the same pattern. Rapidly adapting afferents, therefore, tend to encode a stimulus rate.

Tactile nerves respond to a plurality of local stimuli, making it difficult to ascertain whether a mechanoreceptor responds more readily to in-plane tensile strains or to transverse compressive stresses [4–6]. It is often difficult to correlate components of a stimulus to the observed nerve response since the stimulus component controlled in the experiment may influence other components of the stimulus such that there is no clear input/output relationship. The situation is further confounded when component interactions are encoded by the receptor. However, one can gain a more rigorous understanding of the incipient behavior of the system by analyzing the description of higher-order interaction terms through recently proposed models [7].

Multivariate logistical regression (MLR) is a mathematical technique in which multiple continuous explanatory variables, or covariates, are correlated with a dichotomous response variable. This model provides an alternative to common regression methods that attempt to predict the best estimate of a continuous output variable. The technique was first employed in epidemiological studies to determine which habits and predispositions best predicted a particular disorder [8]. The explanatory variables could be age, weight, quantifiable eating habits, and disorder history.

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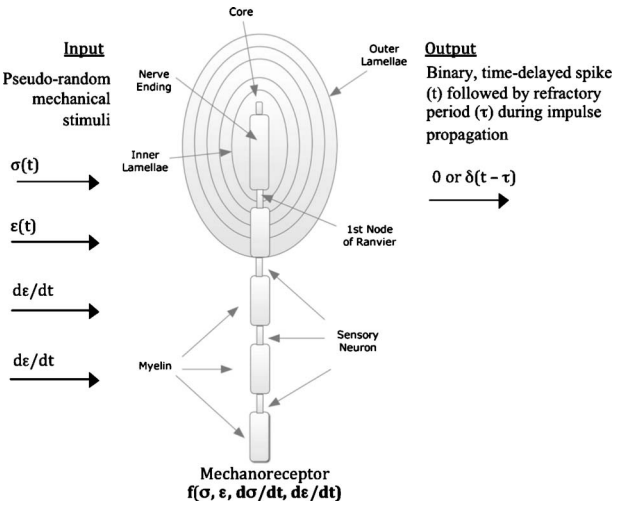

Fig. 1 Schematic of the mechanical and statistical modeling approach as functionally interrelated through single nerve mechanotransduction. Individual components of the rapidly adapting nerve are noted with the oval corpuscles having longitudinal and transverse dimensions ranging from 156 μm to 2025 μm and 88 μm to 1249 μm (in monkeys), respectively, as dependent upon location and distribution [23].

The response variable would be the presence or absence of the disorder, expressed in binary. Recently, this technique has examined the presence of postoperative conditions based on preoperative variables including the time between diagnosed symptoms and surgical intervention as associated with cauda equine syndrome [9]. MLR quantifies the relative contribution that each explanatory variable has upon the response. This is completed without any predisposition toward known input/output correlations and accounting for confounded interactions among explanatory variables (such as age, height, and weight in growing individuals).

In this study, a multivariate logistical model was used to characterize the in vitro behavior of isolated rapidly adapting mechanoreceptor afferents present in rat hairy skin (Fig. 1). The explanatory variables were controlled, time-sampled compressive loading states expressed as normal stress, normal strain, their respective time derivatives, and interactions. The binary response variable was the presence or absence of a nerve action potential. As the average thickness of the concentric flattened cells of lamellae found in the outer zones is on the order of 200 nm [10], the study of these nerves may contribute to the development of biomimetic nanotechnology. As such, we explored the function of this nanoscale biosensor to test the hypothesis that rapidly adapting mechanoreceptors are preferentially sensitive to compressive stress and the rate of change of compressive strain.

2 Methods

2.1 Experimental Approach. One or two patches of skin (~10 mm in diameter) were identified from the inner hindlimb of seven anesthesized Sprague-Dawley rats (adults of either gender). Skin patches were depilated and removed with an intact saphenous nerve following a procedure approved by the Institutional Animal Care and Use Committees from the University of Massachusetts Medical School and Worcester Polytechnic Institute. The

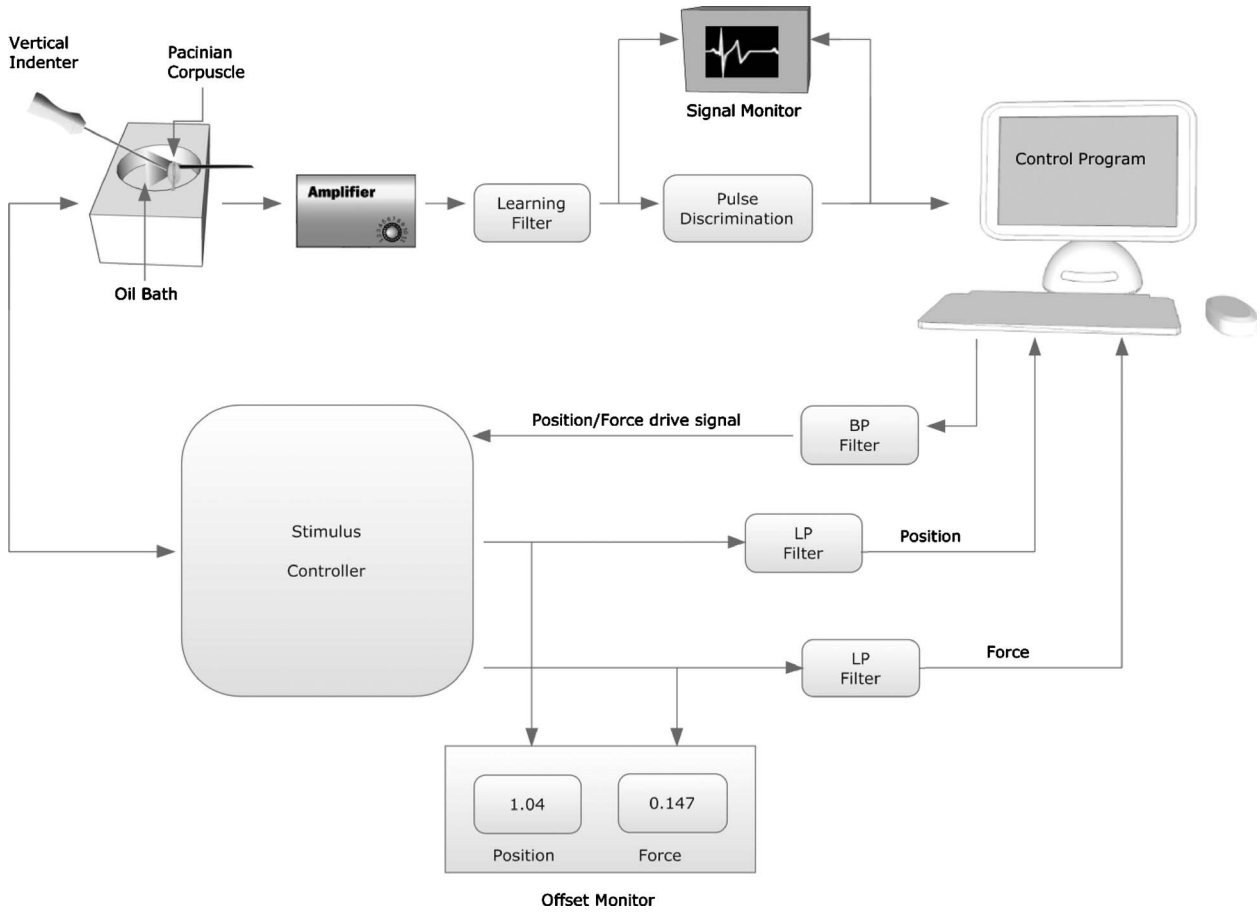

Fig. 2 Illustration of the experimental setup, control loop scheme, and data acquisition arrangement. The applied time-dependent mechanical stimulus was established in either force or displacement control.

nerve fibers corresponded to a single, identifiable afferent and were isolated from each rat skin section (n=10) as previously reported [4]. Each skin patch was transferred onto a rigid support substrate in a plastic chamber and bathed in physiologic interstitial fluid (hydroxyethylpiperazine ethanesulfonic acid solution). Each skin sheet was stretched to its original dimensions (as determined by a circle drawn on the skin prior to excision) via uniformly attached hooks.

The lever arm of an actuator (model 300B lever system, Aurora Scientific, Inc., Richmond Hills, Ontario) was positioned to apply either position-controlled (± 2 mm range, ~ 1 μm resolution) or force-controlled (± 50 g range, ~ 30 mg resolution) transverse loading to each skin patch (Fig. 2). Skin thickness was recorded during the unloaded state as the position differential between the surface of the skin and the supporting substrate. The afferent nerve-skin sample was stimulated at its most sensitive point with one of three actuator-controlled indenting tips (flat with 4.2, 16.6, or 34.2 mm^2 circular cross sections). Before cyclic loading, the actuator tip was pre-indented approximately 300–600 μm and held for several seconds. This pre-indentation, referred to as "stimulus neutral," prevented any loss of contact between the skin surface and actuator during dynamic stimulation. Both position and force voltage readings were recorded from the "stimulus neutral" baseline. The indented position and force of the tip were controlled using nonrepeating noise (10 min period) and pseudorandom noise (0.5 s period) input waveforms [6,11–13]. Nonrepeating noise sequences have the advantage of covering all possible input combinations that occur naturally. With nonrepeating noise input, rich waveform stimuli can be applied in a relatively short period of time. Pseudorandom input facilitated the verification of the logistical regression technique and was used to evaluate the effects that the time varying properties of skin have upon the receptor response. These waveforms were generated algorithmically using a noise generator (model 8057A, Hewlett-Packard Co., Palo Alto, CA) with1 kilohertz output bandwidth, 0.5–80 Hz band-pass filtered (Fig. 3). The microdissected nerve corresponding to each single, identifiable rapidly adapting afferent was positioned through a chamber wall into an oil filled recording chamber where it was wrapped around an electrode submersed in this nonconductive bath for action potential measurement. Both the mechanical input and nerve signal output were sampled at 2 kHz for ~ 1 min with custom software and analog-to-digital converters. Up to three trials of load-controlled and eight trials of deformation-controlled stimulation were applied to each afferent-skin sample (k=105 total trials). Stimulus magnitude was also iteratively controlled at 1, 2, 4, 6, and 8 times the nerve threshold. The acquired force and deformation data were then normalized into stress, strain, time derivatives, and their mathematical interactions for followup logistic regression analysis. All predictors were approximately Gaussian in distribution and nondimensionalized such that the input variables had means=0 and standard deviations=1 for direct comparisons of relative influence [14].

2.2 Analytical and Statistical Modeling. Multivariate logistic regression was performed on each data set, modeling the effect of each explanatory variable ($X_i = \sigma$ or s, ε or e, $d\sigma/dt$, $d\varepsilon/dt$) and first-order interaction terms ($\sigma \times \varepsilon$, etc.) on a binary (Y=1 or 0) nerve response using a maximum likelihood estimation technique (SPSS base with regression model v10, Chicago, IL). The fully constructed multivariate model for all input and output variables was as follows:

$$Y = \frac{e^{\beta_0+\sigma\beta_1+\varepsilon\beta_2+(d\sigma/dt)\beta_3+(d\varepsilon/dt)\beta_4+\sigma\varepsilon\beta_5+\sigma(d\sigma/dt)\beta_6+\varepsilon(d\varepsilon/dt)\beta_7+(d\sigma/dt)(d\varepsilon/dt)\beta_8}}{1 - + e^{\beta_0+\sigma\beta_1+\varepsilon\beta_2+(d\sigma/dt)\beta_3+(d\varepsilon/dt)\beta_4+\sigma\varepsilon\beta_5+\sigma(d\sigma/dt)\beta_6+\varepsilon(d\varepsilon/dt)\beta_7+(d\sigma/dt)(d\varepsilon/dt)\beta_8}} \quad (1)$$

While the overriding goal was to define the influences of the mechanical input variables via the associated coefficients (β_i), a metric of interest in logistic regression is the antilog $\psi(X_i)$, also interpretable as the odds ratio (OR) of a factor X_i

$$\psi(X_i) = e^{\beta_i} \quad (2)$$

The magnitude of the OR represents the difference in probability of a positive outcome (here a neuronal spike) given a one-unit change in the input (mechanical stimulus) variable relative to the probability of the outcome without the change in the stimulus. The OR is thus a measure of the strength of association between an input variable X and the outcome variable Y [4,7,8,15,16]. When the explanatory variables are normalized as they were here, the OR can be interpreted as a unitless quantitative measure of the strength of association between the explanatory variable and the response, directly relative to all other explanatory variables included in the model. Therefore, the OR was used to compare afferent behavior among mechanoreceptors under dynamic compressive loads of varying magnitudes.

Since an evoked action potential may correspond to a stimulus before the action potential is recorded, ORs were calculated for explanatory variable combinations that occurred up to 100 ms before the observed action potential. This approach effectively decouples the stimulus variables across samples, ensuring independency among explanatory variables that had been confounded in time by discrete sampling [4].

Nerve responses were followed by absolute and relative refractory periods during which no magnitude of stimuli and elevated stimuli elicited an action potential, respectively [4,13]. In order to break this cross-sample dependency, post-spike sample points were assigned positive (binary 1) outcomes and added to the model as categorical (discrete) explanatory variables. An OR was calculated for each and a number of data samples post-spike were discarded if they were calculated to be protective against spikes (OR <1). The regression coefficients and odds ratios were then recomputed for each explanatory variable.

Secondary one-way analyses of variance (ANOVA) and a repeated measure ANOVA were conducted on the experimental design variables as statistical influences of the regression metrics (JMP v5.0.1, SAS Institute, Inc., Cary, NC). The distinct influence of stimulus type, control regime, stimulus intensity, trial, rat, and nerve were examined, where $p<0.05$ was considered statistically influential. Tables and plots were constructed from means $\pm$ standard deviations, 95% confidence intervals (CIs), and distribution frequencies.

3 Results

Aggregate influences of all the experimental variables were fully characterized over the offset times leading to nerve signal responses (Fig. 4 and Table 1) where any OR >1 indicated a strong association. Afferent sensitivity at 2 times threshold compression indicated that the $d\sigma/dt$ and $d\varepsilon/dt$ stimuli were highly correlated with the neural firings up to 10 ms prior to the observed action potential. At higher intensity compressive loading (up to 8 times threshold), σ, ε, $d\sigma/dt$, and $d\varepsilon/dt$ were also correlated with a neural response. The accuracy of the logistical model can also

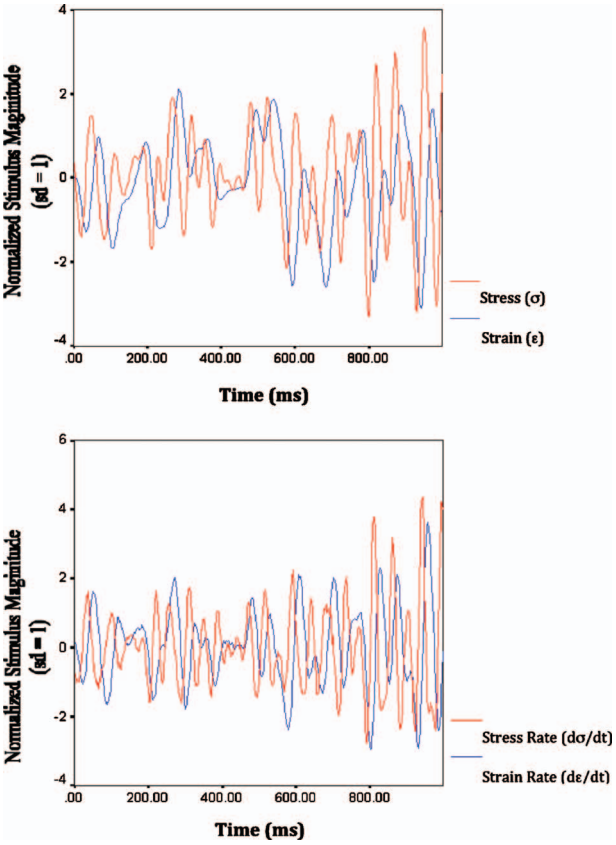

Fig. 3 Representative normalized plots of the applied dynamic mechanical stimulus (stress and strain) as well as their time derivatives. The input waveform was a nonrepeating, pseudo-random noise function. Here, normalization was conducted by subtracting the means and dividing by the standard deviations. This allowed for all input variables to be represented nondimensionally within the model.

be seen when comparing the probability of an observed impulse versus a predicted coefficient (8.6% maximum error) and by examining the response frequency of maximum ORs occurring at specific offset times (Fig. 5).

In previous tensile stretch experiments [7], spike responses were also strongly associated with $d\sigma/dt$, weakly associated with the $d\varepsilon/dt$ and with σ, and had no association with ε. Here, the statistical influence of the model coefficients were consistently significant (ORs excluding 1.0 within the 95% CI) for compressive $d\varepsilon/dt$ sensitivity while interaction terms were consistently insignificant (ORs including 1.0). Many of the controlled study variable also maintained a strong influence on the identified ORs (Table 2).

Based on preliminary investigation and the characterization of nerve responses using linear cross-correlation and stimulus-response plots [6], it was expected that the nerve responses of rapidly adapting afferents would correlate strongly with compressive stress, strain, and the energy conveyed to the skin (a σ-ε interaction term) rather than their time derivatives. However, as noted, the time derivatives were highly correlated with the neural firings up to 20 samples (10 ms) prior to the observed action potential. Furthermore, during this 10 ms interval, both σ and ε were protective against nerve responses since their odds ratios were less than 1. Both the σ-ε and $d\sigma/dt$-$d\varepsilon/dt$ interaction terms had ORs around 1, indicating that these stimulus components have a statistical significance within the model but not an influence on the nerve response.

4 Discussion

Through the controlled application of mechanical stimuli to the excised skin samples, stresses and strains were isolated in their relationship with the measured nerve-cell response. This simplified approach identified a subset of the many in vivo mechanical variables that traverse the tissue with orientation (anisotropy) and location (heterogeneous) dependencies constantly influencing the dynamic properties of the tissue and the mechanotransductive response. The strength of the presented findings should be further validated by identifying similar patterns across several afferents, in multiple experimental contexts. Although not fully addressed, an analytic foundation has been made to pursue issues such as stress-relaxation, the fit of the model to the system, the statistical significance of each interaction term, and regions of the stimulus state space in which there are few samples.

In previous studies, RA mouse afferents' that have limited directional selectivity in vitro however emphasized that the stresses, with which neuronal responses are associated, are unknown in situ (e.g., limb extension can cause orthogonal direction strains to be strongly negative, which would lower any stresses along the adjacent direction) [17]. They hypothesized that the viscoelastic response of the skin influences the dynamic response of cutaneous RA neurons. Utilizing a similar MLR analysis, they concluded that skin samples with lower dynamic response contained RA afferents with a lower sensitivity to dynamic stimuli. In seeking relationships between spike responses and mechanical stimuli, it is necessary to know which of the many potential component(s) of mechanical stimuli are actually causing the action potential.

It is extremely difficult to produce accurate in vivo tactile stimuli. Some of the non-nociceptive somatosensory research previously performed has depended on unnatural stimuli such as electric pulses [18,19]. Although pneumatics and finger clips have been used in order to investigate the human non-nociceptive sensory system, such stimulation activates multiple tactile receptors. The application magoencephalography indicated that the response to on- and off-stimuli was remarkably similar. Prominent somatosensory evoked magnetic fields (SEFs) were evoked not only by the onset of tactile-on stimuli but also by tactile-off stimuli generated by the removal of a constant mechanical pressure. It was assumed that the observed peaks of SEF were caused by the RA mechanoreceptors, which tend to fire only during the initial application and removal of constant stimuli, which are important in the detection of changes in the displacement of the skin.

In a recent experiment, SEFs were actuated by mechanical versus electrical stimulation of an index finger from human subjects in order to objectively establish the existence of compressive/decompressive stimuli-related SEFs [20]. Mechanical stimulation was administered to the index-pulp of each subject utilizing a nonmagnetic mechanical stimulator applied at 3 times the sensory-threshold. Primary sensorimotor responses to mechanical stimuli were detected in all subjects, whereas electrical stimuli to index finger pulp could not evoke any sensorimotor responses. Based on these results, the neural interaction between the inputs of different sensory afferents was assumed to suppress SEFs while the mechanical stimuli delivered a more selective tactile sensory input without nontactile input (proprioceptive, thermal, etc.). Overall, sensorimotor responses can be consistently detected with mechanical stimuli rather than electrical stimuli, supporting the experimental design of our study and others [21,22,24].

The methodology developed in this work presented a statistical model to describe the afferent behavior of individual skin mechanoreceptors. We believe that this contributes to a more complete understanding of tactile sensation while identifying the functional response of this biological nanoscale sensor with both medical and engineering implications.

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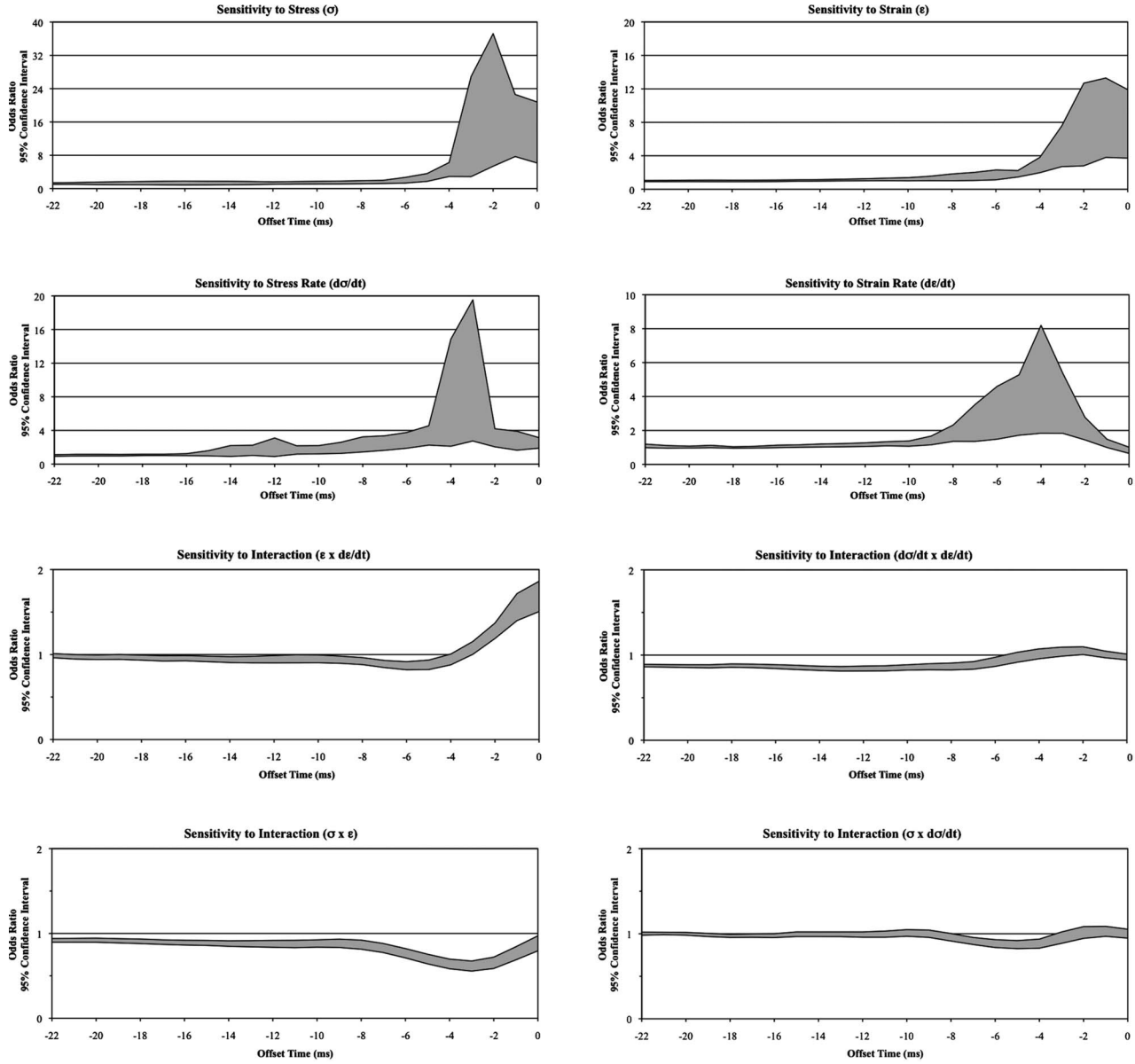

Fig. 4 95% confidence intervals of ORs as an aggregate influence of all experimental variables represented over the offset times leading to a nerve signal response. ORs>1.0 indicate a probabilistic likelihood of predicting the nerve signal based on the direct mechanical stimulus, its time-derivative, or a stimulus interaction.

Table 1 Descriptive statistics (means ± standard deviations) of all ORs throughout the offset times (only the maximum ORs indicated within the collection period) and the offset time associated with resulting maximum ORs

Stimuli	Overall mean ORs (±sd)	Mean of maximum ORs (±sd)	Mean offset time at maximum OR (ms)
Stress (σ or s)	5.04 (±11.97)	26.10 (±87.81)	−5.81
Strain (ε or e)	2.94 (±6.82)	12.01 (±31.46)	−3.51
Stress rate ($d\sigma/dt$)	3.08 (±7.31)	15.03 (±44.74)	−3.68
Strain rate ($d\varepsilon/dt$)	1.72 (±2.24)	7.29 (±18.23)	−7.28
Interactions			
$\sigma \times \varepsilon$	0.82 (±0.19)	1.14 (±0.25)	−7.78
$\sigma \times d\sigma/dt$	0.97 (±0.09)	1.31 (±0.27)	−6.98
$\varepsilon \times d\varepsilon/dt$	1.03 (±0.13)	1.90 (±0.88)	−3.06
$d\sigma/dt \times d\varepsilon/dt$	0.91 (±0.14)	1.18 (±0.21)	−5.10

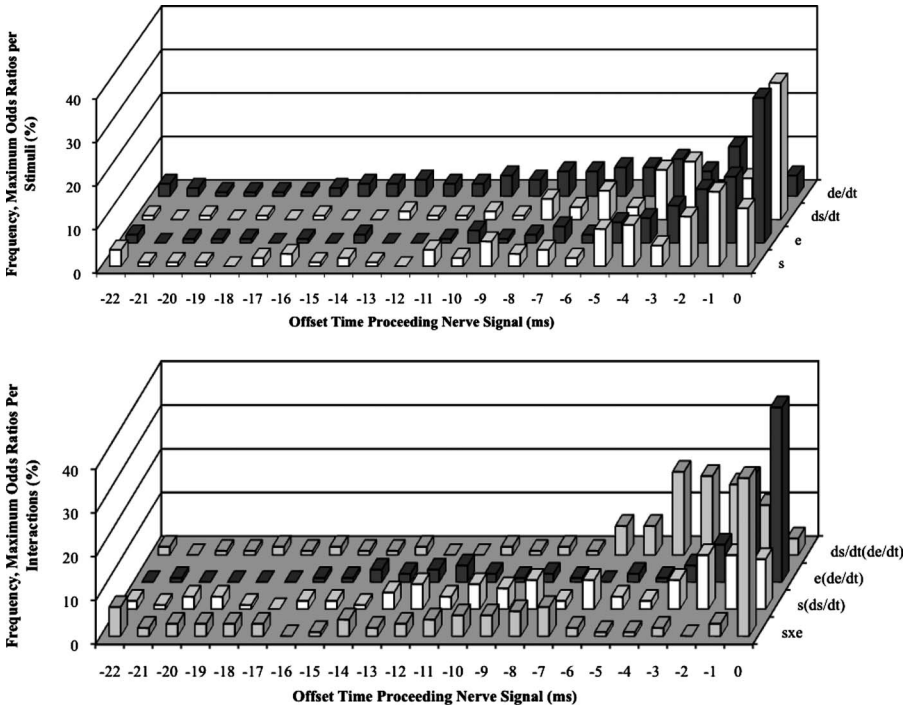

Fig. 5 The response frequency of a maximum OR occurring at a specific offset time leading to a nerve signal based on the direct mechanical stimulus, its time-derivative, or a stimulus interaction

Table 2 Summary of comparative univariate statistical analyses addressing the probability of each controlled variable as an influence on maximum ORs and the associated offset time. In addition, the statistical results of a repeated measures analysis are shown for all resulting OR metrics through offset time.

One-way ANOVA of maxima		
Influencing variable	Dependency of max ORs	Dependency of time at max OR
Stimulus	p=0.0001	p=0.0001
Control	p=0.0248	p=0.4616
Intensity	p=0.0863, R=−0.187	p=0.0003, R=0.124
Trial	p=0.0006, R=−0.119	p=0.5255, R=0.022
Rat	p=0.0002 [a]	p=0.0001 [a]
Nerve	p=0.0004 [a]	p=0.0001 [a]
Repeated measures analysis of all ORs		
Between stimuli	0.0001	
Within stimuli (time)	0.0001	

[a]Two of the donor rats and their associated nerves had consistently larger odds ratios and shorter offset times.

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