

TITEL

Masterthesis

der Mathematisch-Naturwissenschaftlichen Fakultät
der Eberhard Karls Universität Tübingen

Erstkorrektor:

Zweitkorrektor: Prof. Dr. Jan Benda

Lehrbereich für Neuroethologie

vorgelegt von

Alexander Mathias Ott

Abgabedatum: 30.11.2017

Eigenständigkeitserklärung

Hiermit erkläre ich, dass ich die vorgelegte Arbeit selbstständig verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt habe.

Außerdem erkläre ich, dass die eingereichte Arbeit weder vollständig noch in wesentlichen Teilen Gegenstand eines anderen Prüfungsverfahrens gewesen ist.

Unterschrift

Ort, Datum

Contents

1	Abstract	2
2	Introduction	2
3	Materials and Methods	3
3.1	Notes:	3
3.2	Leaky Integrate and Fire Model	3
3.3	Data Generation	4
3.4	Stimulus Protocols	4
3.5	Fitting of the Model	4
3.6	Henriette's structure:	4
4	Results	5
5	Discussion	5
6	Possible Sources	5
6.1	Henriette Walz - Thesis	5
6.1.1	Nervous system - Signal encoding	5
6.1.2	electrosensory system - electric fish	6
6.1.3	P-Units encoding	7
6.1.4	Chapter 4 - other models	8

1 Abstract

2 Introduction

1. electric fish
 - (a) general: habitat,
 - (b) as model animal for ethology
 - (c) electric organ + eod
 - (d) sensory neurons p- and t(?) -type
2. sensory perception
 - (a) receptor - \bar{z} heterogenic population
 - (b) further analysis limited by what receptors code for - P-Units encoding
 - (c) p-type neurons code AMs
3. goal be able to simulate heterogenic population to analyze full coding properties - \bar{z}
many cells at the same time needed - \bar{z} only possible in vitro/ with model simulations
4. Possible to draw representative values for model parameters to generate a population
?

3 Materials and Methods

3.1 Notes:

1. Data generation
 - (a) How data was measured / which data used
 - (b) How data was chosen - i at least 30s baseline, 7 contrasts with 7 trials
 - (c) experimental protocols were allowed by XYZ (before 2012: All experimental protocols were approved and complied with national and regional laws (file no. 55.2-1-54-2531-135-09). between 2013-2016 ZP 1/13 Regierungspräsidium Tübingen and after 2016 ZP 1/16 Regierungspräsidium Tübingen)
 - (d) description of data - i Baseline properties, FI-Curve with images made from cells
 - (e) make a point of using also bursty cells as part of what is new in this work!
2. behavior parameters:
 - (a) which behaviors were looked at / calculated and why (bf, vs, sc, cv, fi-curve...)
 - (b) how exactly were they calculated in the cell and model
 - (c) stimulus protocols
3. Construction of model
 - (a) Explain general LIF
 - (b) parameters explanation, dif. equations
 - (c) Explain addition of adaption current
 - (d) note addition of noise + factor for the independence from step size
 - (e) addition of refractory period
 - (f) check between alpha in fire-rate model adaption and a-delta in LIFAC
4. Fitting of model to data
 - (a) which variables were determined beforehand (None, just for start parameters)
 - (b) which variables were fit
 - (c) What method was used (Nelder-Mead) and why/(how it works?)
 - (d) fit routine ? (currently just all at the same time)

3.2 Leaky Integrate and Fire Model

also show function with membrane resistance before explaining that is is unknown an left out: $\tau_m \frac{dV}{dt} = -V + I$ (TODO: restructure sounds horrible)

The P-units were modeled with an noisy leaky integrate-and-fire neuron with an adaption current (LIFAC). The basic voltage dynamics in this model follows equation 1. The voltage is integrated over time while also exponentially decaying back to zero. When a voltage threshold is reached the voltage is set back to zero and a spike is recorded. The currents in this model carry the unit mV as the the cell bodies of p-units are inaccessible

during the recordings and as such the resistance of the cell membrane is unknown (TODO: ref mem res p-units) .

The current can be split into three parts: the adaption current, the input current and the bias current (Eq. 2). The input current is the stimulus from outside the cell, the bias current models the general activity of the cell and the adaption current models a combination of the M-type, mAHP-type and sodium adaption currents (TODO: ref Benda 2005) .

The adaption current is modeled as an exponential decay with the time constant τ_A and a strength called Δ_A (Eq. 3). Δ_A is multiplied with the sum of events in the spike train ($\delta(t)$) of the model cell itself. For the simulation using the Euler integration this results in an increase of I_A by Δ_A in every time step where a spike is recorded. (TODO: image of model simulation with voltage adaption and spikes?)

Finally a noise current and an absolute refractory period were added to the model. The noise ξ is drawn from a Gaussian noise with values between 0 and 1 and divided by $\sqrt{\Delta t}$ to get a noise which autocorrelation function is independent of the integration step size Δt . After an excitation of the model the voltage is kept at zero for the duration of the refractory period.

$$\tau_m \frac{dV}{dt} = -V + I \quad (1)$$

$$I = \alpha I_{Input} - I_A + I_{Bias} \quad (2)$$

$$\tau_A \frac{dI_A}{dt} = -I_A + \Delta_A \sum \delta(t) \quad (3)$$

$$\tau_m \frac{dV}{dt} = -V + I_{Bias} + \alpha I_{Input} - I_A + \sqrt{2D} \frac{\xi}{\sqrt{\Delta t}} \quad (4)$$

3.3 Data Generation

The data for this master's thesis was collected as part of other previous studies (TODO: ref other studies) . The collection method provided here is only an overview for the exact details see (TODO: link papers) . The in vivo intracellular recordings of P-unit electroreceptors of *Apteronotus leptorhynchus* were done in the lateral line nerve . The fish were anesthetized with MS-222 (100-130 mg/l; PharmaQ; Fordingbridge, UK) and the part of the skin covering the lateral line just behind the skull was removed

general anesthetic MS-222 (100-130 mg/l; PharmaQ; Fordingbridge, UK) local anesthetics Lidocaine (2%; bela-pharm; Vechta, Germany) immobilization with (Tubocurarine; Sigma-Aldrich; Steinheim, Germany, 25–50 μ l of 5mg/ml solution)

3.4 Stimulus Protocols

3.5 Fitting of the Model

3.6 Henriette's structure:

1. data generation - recordings
2. model simulations - construction of model

3. Simulation protocols
4. Data analysis - calculation of behavior parameters
 - (a) calculation of baseline parameters
 - (b) calculation of fit curve parameters
 - (c) stimuli step SAM(?) noise(?)
 - (d) goodness of fit
 - (e) sensitivity analysis (influence of par on model)

4 Results

1. how well does the fitting work?
2. distribution of behavior parameters (cells and models)
3. distributions of parameters
4. correlations: between parameters between parameters and behavior
5. correlation between final error and behavior parameters of the cell -¿ hard to fit cell types
6. (response to SAM stimuli)

5 Discussion

6 Possible Sources

6.1 Henriette Walz - Thesis

6.1.1 Nervous system - Signal encoding

1. single neurons are the building blocks of the nervous system (Cajal 1899)
2. encoding of information in spike frequency - rate code(first description(?) Adrian 1928) also find examples! (light flash intensity Barlow et al. 1971,)
3. encoding info in inter spike intervals (Singer and Gary 1995)
4. encoding time window (Theunissen and Miller 1995) "This time window is the time scale in which the encoding is assumed to take place within the nervous system
5. encoding is noisy (Mainen and Sejnowski 1995, Tolhurst et al 1983, Tomko and Crapper 1974 -¿ review Faisal et al 2008) in part because of stimulus properties but also cell properties (Ion channel stochasticity (van Rossum et al., 2003))
6. noise can be beneficial to encoding -¿ "stochastic resonance" (weak stimuli on thresholding devices like neurons, noise allows coding of sub threshold stimuli) (Benzi et al., 1981)

7. single neurons are anatomically and computationally independent units, the representation and processing of information in vertebrate nervous systems is distributed over groups or networks of cells (for a review, see Pouget et al., 2000)
8. It has been shown that the synchrony among cells carries information on a very fine temporal scale in different modalities, from olfaction (Laurent, 1996) to vision (Dan et al., 1998)
9. In the electrosensory system it was shown before that communication signals change the synchrony of the receptor population (Benda et al., 2005, 2006) and that this is read out by cells in the successive stages of the electrosensory pathway (Marsat and Maler, 2010, 2012; Marsat et al., 2009).
10. An advantage of rate coding in populations is that it is fast. The rate in single neurons has to be averaged over a time window, that is at least as long as the minimum interspike interval. In contrast, the population rate can follow the stimulus instantaneous, as it does not have to be averaged over time but can be averaged over cells (Knight, 1972a).
11. In a population of neurons subject to neuronal noise, stochastic resonance occurs even if the stimulus is strong enough to trigger action potentials itself (supra-threshold stochastic resonance described by Stocks, 2000; see Fig. 1.1 B
12. Cells of the same type and from the same population often vary in their stimulus sensitivity (Ringach et al., 2002) as well as in their baseline activity properties (Gussin et al., 2007; Hospedales et al., 2008)
13. Heterogeneity has been shown to improve information coding in both situations, in the presence of noise correlations, for example in the visual system cells (Chelaru and Dragoi, 2008) or when correlations mainly originate from shared input as in the olfactory system (Padmanabhan and Urban, 2010)
14. A prerequisite to a neural code thus is that it can be read out by other neurons (Parker and Bullock, 1968).
15. Development and evolution shape the functioning of many physiological systems and there is evidence that they also shape the encoding mechanisms of nervous systems. For example, the development of frequency selectivity in the auditory cortex has been shown to be delayed in animals stimulated with white noise only (Chang and Merzenich, 2003). Also, several encoding mechanisms can be related to the selective pressure that the energetic consumption of the nervous system has exerted on its evolution (Laughlin, 2001; Niven and Laughlin, 2008). These findings confirmed earlier theoretical predictions that had proposed that coding should be optimized to encode natural stimuli in an energy-efficient way (Barlow, 1972). - importance of using natural stimuli as the coding and nervous system could be optimized for unknown stimuli features not contained in the artificial stimuli like white noise.

6.1.2 electrosensory system - electric fish

1. For decades, studies examining the neurophysiological systems of weakly electric fish have provided insights into how natural behaviors are generated using relatively simple sensorimotor circuits (for recent reviews see: Chacron et al., 2011; Fortune,

2006; Marsat and Maler, 2012). Further, electrocommunication signals are relatively easy to describe, classify and simulate, facilitating quantification and experimental manipulation. Weakly electric fish are therefore an ideal system for examining how communication signals influence sensory scenes, drive sensory system responses, and consequently exert effects on conspecific behavior.

2. The weakly electric fish use active electroreception to navigate and communicate under low light conditions (Zupanc et al., 2001).
3. In active electroreception, animals produce an electric field using an electric organ (and this electric field is therefore called the electric organ discharge, EOD) and infer, from changes of the EOD, information about the location and identification of objects and conspecifics in their vicinity (e.g. Kelly et al., 2008; MacIver et al., 2001). However, perturbations result not only from objects and other fish, but also from self-motion and other factors. All of these together make up the electrosensory scene. The perturbed version of the fish's own field on its skin is called the electric image (Caputi and Budelli, 2006), which is sensed via specialized receptors distributed over the body surface (Carr et al., 1982).
4. In *A. leptorhynchus*, the dipole-like electric field (electric organ discharge, EOD) oscillates in a quasi-sinusoidal fashion at frequencies from 700 to 1100 Hz (Zakon et al., 2002) with males emitting at higher frequencies than females (Meyer et al., 1987).
5. The EOD of each individual fish has a specific frequency (the EOD frequency, EODf) that remains stable in time (exhibiting a coefficient of variation of the interspike intervals as low as 2×10^{-4} ; Moortgat et al., 1998).
6. During social encounters, wave-type fish often modulate the frequency as well as the amplitude of their field to communicate (Hagedorn and Heiligenberg, 1985).
7. Communication signals in *A. leptorhynchus* have been classified into two classes: (i) chirps are transient and stereotyped EODf excursions over tens of milliseconds (Zupanc et al., 2006), while (ii) rises are longer duration and more variable modulations of EODf, typically lasting for hundreds of milliseconds to seconds (Hagedorn and Heiligenberg, 1985; Tallarovic and Zakon, 2002). (OLD INFO ? RISES NOW OVER MINUTES/HOURS)

6.1.3 P-Units encoding

1. In baseline conditions (stimulus only own EOD), they fire irregularly at a certain baseline rate. Action potentials occur approximately at a certain phase of the EOD cycle, they are phase-locked to the EOD, but only with a certain probability to each cycle. The baseline rate differs from cell to cell (compare the two example cells in Fig. 2.2 A and B, Gussin et al., 2007)
2. Since tuberous receptors are distributed over the whole body and the EOD spans the whole surrounding, all P-units of a given animal are stimulated with a similar stimulus (see Kelly et al. (2008) for an exact model of the EOD). Their noise sources are, however, uncorrelated (Chacron et al., 2005b).

3. In response to a step increase in EOD amplitude, P-units exhibit pronounced spike frequency adaptation (Benda et al., 2005; Chacron et al., 2001b; Nelson et al., 1997; Xu et al., 1996).

6.1.4 Chapter 4 - other models

1. Kashimori et al. (1996) built a conductance-based model of the whole electroreceptor unit and were able to qualitatively reproduce the behaviour of different types of tuberous units.
2. Nelson et al. (1997) constrained a stochastically spiking model by linear filters of the previously determined P-unit frequency tuning.
3. Kreiman et al. (2000) used the same frequency filters to stimulate a noisy perfect integrate-and-fire neuron with which they investigated the variability of cell responses to random amplitude modulations (RAMs).
4. To reproduce the probabilistic phase-locked firing and the correlations of the ISIs, Chacron et al. (2000) used a noisy leaky integrate-and-fire model with refractoriness as well as a dynamical threshold.
5. Benda et al. (2005) used a firing rate model with a negative adaptation current to reproduce the high-pass behaviour of P-units.

6.2 Zakon: Negative Interspike Interval Correlations Increase the Neuronal Capacity for Encoding Time-Dependent Stimuli

1. P-type electroreceptors on their skin detect amplitude modulations (AMs) of this field caused by nearby objects or conspecifics (for review, see Bastian, 1981; Zakon, 1986).