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Indirect Inference Used to Identify Models of Vestibular Nerve Response in Isolated Inner Ear

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Abstract—Measuring nerve signal response from the balance organs of mammals is a challenging task in a live specimen (in vivo). Using data obtained instead from a set of isolated (in vitro) preparations from mice, and using a similar experimental method to the typical in vivo procedure, we fit model parameters to the in vitro system to investigate its nerve response dynamics. First, a non parametric transfer function is obtained for the system using several preprocessing steps, and then indirect inference is used as an identification tool to fit two model structures already present in the literature. The ability of each structure to fit the experiment data is assessed, and the resultant model fits are compared with typical in vivo models for mice. The results suggest that the vestibular nerve dynamics in vitro are similar to those modelled from in vivo data, particularly for nerve afferents classified as ‘irregular’ in the literature.

I. INTRODUCTION

Inner ear organs of the balance (vestibular) system can be considered inertial sensors, and since they are tethered to the skull they generate signals related to head motion [1]. During head movements, specialised sensory cells within the vestibular organs convert the relative displacement of inner ear fluid into electrical signals [2]. These signals are then transmitted to nerve fibres that convey the encoded head motion to the central nervous system (CNS) [1], [2]. Head motion information is encoded in the nerve fibre as a temporal sequence of short duration (2 - 4 ms), all-or-none electrical impulses, called action potentials (APs). APs are the result of consistent and repeatable rise and fall, or ‘spikes’, in the nerve fibre’s membrane potential.

In mammals, APs are technically challenging to record in live (in vivo) preparations since the vestibular organs and their associated nerves are buried deep within the hardest bone of the skull. In addition, the precise action of drugs on the balance organs and their nerves cannot be determined since it is impossible to control the local environment surrounding them. To overcome this, a recently developed [3] surgically isolated (in vitro) preparation of mice inner ear organs was used to collect the data analysed in this paper. This preparation allows unrestricted access to vestibular organs and the nerves that carry the balance signals to the CNS, while still remaining functionally active.

Two models in the literature have described intact, in vivo nerve response dynamics for sinusoidal head rotation in mice

[4], [5]. Although similar, the two models deviate at frequencies above 2 Hz. To determine if either or both in vivo models could be applied to nerve response dynamics recorded under in vitro conditions, it is required to adequately model the nerve response properties of our isolated preparation. One of the models poses issues for obtaining unbiased parameter estimates due to the presence of a fractional zero term in the model structure, and this motivates the choice of indirect inference as the identification algorithm. Indirect inference avoids the problem of constructing and optimising a likelihood function for complex models by estimating a misspecified model of simple structure, and iteratively simulating the complex system.

Following the introduction, Section II provides some further background on the details of gathering data from a vestibular organ, and how our experimental setup differs from previous studies. The structure of the two in vivo models is also addressed in this section. Section III develops the motivation and theory behind indirect inference for system identification, and discusses its application to the data presented in this paper. The progression from raw experiment data to frequency response data is treated in Section IV, where we discuss some issues with the processing methodology and analyse the error this could introduce. The indirect inference model fitting results are the focus of Section V, and we compare the performance of both in vitro models in several contexts. Finally, some conclusions are drawn in Section VI.

II. PROBLEM SETTING

A. Experimental Method

In many ways, the data collection method used in this paper follows very closely the methods adopted for in vivo experiments. A sinusoidal stimulus is applied to the organ of interest at frequencies ranging from 0.01 Hz to 10 Hz, and the ‘spike rate’ of vestibular nerve fibres are measured to determine the gain and phase shift at each test frequency. There are, however, two significant differences in recording conditions between in vivo and in vitro that are likely to affect nerve response dynamics. First, experiments using in vivo preparations were recorded at normal body temperature (37°C), but to improve the viability of the isolated preparation and extend the duration of recordings, experiments under in vitro conditions were done at room temperature (22°C). The other significant difference is the manner in which inner ear fluid movement was generated. In vivo experiments use natural head rotations to stimulate fluid movement within vestibular organs. Due to technical

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reasons, rotating the isolated organs was not an option and therefore the *in vitro* preparation was subject to a different stimulus. We used a linear micro-actuator with a range of up to 30 microns to generate displacement of inner ear fluid by indentation of the compliant membrane surrounding the balance organs. These indentations were used to simulate the fluid movement that occurs during natural head movements. Previous studies suggest that the transformation from mechanical indentation to an equivalent rotational stimulus is independent of frequency from 0.03Hz to 10Hz in pigeons [6], and for frequencies less than 2Hz in toadfish [7]. While the invariant frequency range is not known for mice, it is possible that the data at higher frequencies may not directly correspond with the results that would be obtained using rotation.

B. Vestibular Models

Classical studies have attempted to model the macromechanics of the vestibular organs, and in particular the semicircular canals that detect rotational head movements. The most successful model is similar to an overdamped torsion pendulum and was first proposed by [8]. Since then, the model has been refined so that the subtle geometrical features of these vestibular organs are taken into account [9]. All versions of the torsion pendulum model, however, lead to a second-order differential equation that relates the angular acceleration of the head to the displacement of the inner ear fluid in the semicircular canal.

During sinusoidal head rotation, the nerve responses are close to sinusoidal with non-linear distortion of less than 10% [10]. Gains and phases are constant even as peak velocity varies over a wide range. Throughout the frequency range from 0.03 Hz to 0.5 Hz, gains and phases are also close to those expected from a torsion pendulum model. Above 0.5 Hz, however, there are progressive phase leads and gain enhancements not predicted by the model. Precisely what cellular mechanisms contribute to the high frequency discrepancies are not clear, but any of the transduction steps between head motion and nerve fibre discharge may contribute. In an attempt to model this effect, fractional operators at higher stimulus frequencies have been introduced to correct for these deviations [10], [11], [12].

The first model of mouse vestibular nerve response that we consider in this paper was published in [4]. The transfer function is based on the familiar torsion pendulum model, but eschews the high frequency correction. They argue that most previous models are aimed at larger animals such as squirrel monkeys, chinchillas, rats, and guinea pigs, and therefore do not take into account the smaller dimensions of the mouse semicircular canal. They conjecture that a high frequency fractional operator in small animals is redundant. The resulting model structure, which will henceforth be labelled ‘Model 1’, is given by

$$G_{Model1}(s) = \frac{g(t_L s)(t_z s + 1)}{(t_L s + 1)(0.001s + 1)}.$$

Note that while the model has a fixed pole, the frequency of the pole is too high to have an appreciable effect on dynamics in the frequency range of interest.

The second model structure we consider is found in [5], which contains a fractional operator for high frequency corrections, and was also applied to the semicircular canals of mice. We label the structure ‘Model 2’, and it is given by

$$G_{Model2}(s) = \frac{g(t_L s)(0.2s + 1)^k}{(t_L s + 1)(0.007s + 1)}.$$

Again, we see a fixed fast pole in the model, along with a fixed fractional zero location. The exponent, k , is a parameter to be estimated, and its value is expected to be between 0 and 1.

III. INDIRECT INFERENCE

Indirect inference is an estimation technique which is based on the explicit use of a misspecified model. Data is collected from the real system and is used to identify parameters of a model which generally possesses a structure that is different to that of the real system, i.e. the misspecified model. A model more representative of the real system is simulated, using an initial guess for its parameters, to obtain a second set of input/output data. An iterative procedure is then started where a second misspecified model, of the same structure as the first, is identified using the simulated data. A cost function which is dependent on a measure of the distance between the two misspecified models is minimised. During the optimisation procedure, the parameters of the simulated model are updated until a stopping criterion is reached. This yields a final set of parameters for the simulation model which are the estimated parameters for the real system. Figure 1 provides an illustration of the procedure [13].

Note that during the misspecified model estimation step, the estimate obtained will generally be non-consistent. However, a consistent estimate is obtained with indirect inference due to the simulations performed on a representative model structure of the real system within an optimisation procedure. So far, statistical properties such as consistency and asymptotic normality have been proven for time series models only (i.e. not considering systems with a measurable deterministic input) [14].

In general terms, identification of dynamical systems is a difficult task, even when the system structure is known. For example, in Maximum Likelihood Estimation, maximisation of a nonconvex function is usually involved. Additionally, for some systems, it is not possible to write down the likelihood function in an explicit form. This is the case for the Model 2 structure examined in [5], which contains a fractional zero term where the non-integer exponent is a parameter to be estimated. In this situation, indirect inference allows us to instead maximise a misspecified likelihood function to obtain parameters for use in the optimisation loop.

In this paper, indirect inference was applied in the frequency domain context using the steps listed below:

Fig. 1. Implementation of Indirect Inference

- 1) Obtain the average phase and magnitude values from the vestibular system data to generate a ‘mean’ non-parametric transfer function, $\overline{G}(j\omega)$.
- 2) Using $\overline{G}(j\omega)$, estimate a “misspecified” model ($\hat{G}_{MT}$) which is based on a 20th order ARX model structure.
- 3) Set initial parameter values for the ‘real’ model structure, G_S , using the values obtained for live specimens in the corresponding literature.
- 4) Evaluate G_S at the required frequencies to produce another non-parametric transfer function, $G_S(j\omega)$.
- 5) Using $G_S(j\omega)$, estimate the parameters of a model ($\hat{G}_{MS}$) having the same structure as used in step 2.
- 6) Estimate an updated set of parameters for G_S by minimising a measure of the distance between the estimated parameters for $\hat{G}_{MT}$ and $\hat{G}_{MS}$. In this paper, the cost function was designed such that

$$\hat{\theta}_S = \arg \min_{\theta} \|\hat{G}_{MT}(\hat{\theta}_{MT}) - \hat{G}_{MS}(\hat{\theta}_{MS})\|_2 \quad (1)$$

where $\hat{\theta}_{MT}$ and $\hat{\theta}_{MS}$ are the estimated parameters for $\hat{G}_{MT}$ and $\hat{G}_{MS}$ respectively, and $\|\cdot\|_2$ denotes the H2 norm. Note that the appropriate cost function depends on the parameter $\hat{\theta}_{MS}$ which, in turn, depends on the parameter θ .

- 7) Repeat steps 4 – 6 until a specified stopping criterion is reached.

IV. DATA PREPROCESSING

A. Processing Method

In analysing nerve response, the initial data collected is a time signal of the electric potential measured from individual nerve fibres. From the raw signal, the rate at which the nerve produces ‘spikes’ is determined using a binning procedure. First, the spikes are detected and converted to latency events

Fig. 2. Spike density histogram and its fitted sinusoid at 0.1 Hz

which are aligned in time to the sinusoidal excitation signal. To compute the spike density, every period of the excitation signal is divided, for historical reasons, into 40 bins. The spikes are assigned to these bins in order to produce a histogram for each period, and the periods are then combined to produce an average histogram for the total record. To determine the gain and phase of the spike density relative to the excitation signal, a sine wave is fitted to the histogram in a least squares sense. Figure 2 presents a typical spike density histogram, along with the fitted sinusoid. The amplitude value obtained from the curve fit is in units of *spikes/bin*, and is divided by the stimulus to obtain a gain value in *spikes/s/μm*. The phase shift between the stimulus and response sinusoid is also computed. When data is collected for a range of stimulus frequencies, a non parametric transfer function is formed from the gain and phase values extracted at each frequency.

Fig. 3. Comparing phase estimates using the start- and middle-of-bin time vector alignments

B. Phase Estimation Errors

The gain and phase data analysed in this paper has been taken from a large dataset which was preprocessed several years ago, and an investigation of the binning method used revealed the potential for sub-optimal phase estimates in the dataset. When fitting sinusoids to the spike histograms, the time vector was aligned with the start point of each bin, which should generate some error compared to using the optimal alignment at the middle point of each bin. As the number of bins per period increases, the effect will become negligible. To quantify the errors which are introduced in a 40-bin processing scheme, a small subset of the large dataset was reanalysed from raw data using both the ‘start-of-bin’ and ‘middle-of-bin’ alignment for the time vector. It was found that start-of-bin phase estimates contained a small positive bias, but when compared to the variance of the phase estimates, this bias was not significant in magnitude. The result is shown in Figure 3.

In the context of modelling, it is just as important to quantify the change in model-fit between start-of-bin and middle-of-bin processing methods. Using the mean gain and phase estimates obtained from each method, parameters were obtained for Model 1 and Model 2 using the indirect inference approach. These models were compared to two in vivo model estimates obtained in the literature for the same structures (‘Regular’ in [4] for Model 1 and ‘Regular’ in [5] for Model 2). The metrics used for comparison were normalised Mean Square Error (MSE), Total Absolute Error (TAE) and Worst Case Error (WCE), where the complex error vector was formed from the difference between models of in vitro data and their corresponding literature model at the test frequencies, i.e.

$$e_k = \frac{G_{lit}(j\omega_k) - G_{model}(j\omega_k)}{|G_{lit}(j\omega_k)|}, \quad (2)$$

TABLE I
GOODNESS OF FIT TO LITERATURE MODELS USING START-OF-BIN AND MIDDLE-OF-BIN ALIGNMENT

Model Structure	Time Vector Alignment	MSE	TAE	WCE
Model 1	start-of-bin	3.88	10.73	3.64
Model 1	middle-of-bin	4.11	11.84	3.51
Model 2	start-of-bin	11.03	19.25	6.25
Model 2	middle-of-bin	12.22	21.39	6.13

where $G_{model}(j\omega)$ is our model estimate, $G_{lit}(j\omega)$ is the corresponding literature model, and e_k and ω_k are the k^{th} normalised error value and test frequency respectively. The MSE, TAE and WCE are computed on the normalised error vector, assumed to be of length N , in the following way:

$$MSE = \frac{1}{N} \sum_{k=1}^N e_k \bar{e}_k, \quad (3)$$

$$TAE = \sum_{k=1}^N |e_k|, \quad (4)$$

$$WCE = \max_k \{|e_k|\}. \quad (5)$$

A summary of the comparison metrics is given in Table I for both model structures and using both time vector alignments. The use of start-of-bin alignment on the small dataset is seen to have only a slight effect on the fitted models, with all error metrics changing by less than 10% with respect to the middle-of-bin equivalents. The result suggests that using the large dataset for model identification will not incur significant errors, although the binning procedure was not performed in an optimal fashion.

V. RESULTS

Using a large dataset which consisted of 133 individual transfer functions obtained in separate in vitro experiments, a ‘mean’ transfer function, $\overline{G}(j\omega)$, was formed for use in the indirect inference algorithm. The two models were fit to the mean data, with results shown in Figure 4. The analytic forms are presented in Table II.

To assess the ‘goodness of fit’ for each model structure, several metrics were employed as comparison tools. The first metric comes directly from the initial model estimation, where we take the final value of the indirect inference cost function, J , as an indicator of how well the model fit the data. The other error metrics come from a separate validation exercise, where the large data set was split randomly into two

TABLE II
TRANSFER FUNCTION MODELS

Model Structure	Indirect Inference Output
Model 1	$\frac{0.487(0.777s)(0.007s+1)}{(0.777s+1)(0.001s+1)}$
Model 2	$\frac{0.312(0.896s)(0.2s+1)^{0.431}}{(0.896s+1)(0.007s+1)}$

Fig. 4. Experimental and modelled gain and phase

sets of equal size. The first set produced a mean transfer function used to generate a model estimate, $G_{model}(j\omega)$, while the mean result for the second set, $G_{val}(j\omega)$, was used as validation data to generate normalised MSE, TAE and WCE values for both model types, using the same method described in (3), (4) and (5). In this case, the normalised error vector was formed from the difference between the modelled and validation transfer function at each test frequency;

$$e_k = \frac{G_{val}(j\omega_k) - G_{model}(j\omega_k)}{|G_{val}(j\omega_k)|}.$$

A comparison of the error metrics obtained for each model is presented in Table III, which indicates a stronger fit for the Model 2 structure in 3 out of the 4 measures.

While the structure of Model 2 appears to provide better predictions of the system behaviour, this does not necessarily reveal how close the dynamics of the in-vitro system are to the dynamics observed in the literature for in-vivo experiments on mice. For this reason, the fits obtained for Model 1 and Model 2 were compared to the fits obtained in [4] and [5], where the same model structures were used to identify in-vivo dynamics. We employ the same error metrics as in the validation tests, but in this case, the errors are generated

TABLE III
GOODNESS OF FIT MEASURES FOR BOTH MODEL STRUCTURES

Model Structure	J	MSE	TAE	WCE
Model 1	7.95	0.37	4.10	0.83
Model 2	4.29	0.36	3.72	1.05

TABLE IV
ERRORS BETWEEN IN-VIVO MODEL FITS FROM LITERATURE AND
CURRENT IN-VITRO MODEL FITS

Literature Model Fit	MSE	TAE	WCE
Model 1 - Regular	4.33	12.44	2.92
Model 1 - Irregular	0.21	3.15	0.54
Model 2 - Regular	17.32	21.32	8.77
Model 2 - High Gain Irregular	0.17	2.72	0.59
Model 2 - Low Gain Irregular	2.05	8.76	1.98

Fig. 5. Comparing in vitro data to in vivo models in literature

as the difference between $G_{model}(j\omega)$ for the relevant model structure, and model fits for several in-vivo classifications given in the literature. Naturally, Model 1 fits in [4] are compared with this paper's fit for Model 1, and the Model 2 fits in [5] are treated with respect to our Model 2 fit. The results are given in Table IV.

From Table IV, it is seen that the models obtained from the in-vitro dataset are closest to the 'Irregular' model in [4] and 'High Gain Irregular' model in [5]. These two models are plotted in Figure 5, along with the in vitro data obtained for this paper, and it can be seen visually that the dynamics observed for the in vitro system match closely to those dynamics observed in live mice.

VI. CONCLUSIONS

We investigated the nerve dynamics of vestibular organs in vitro through the use of indirect inference as a modelling tool. The parameters for two common transfer function model structures could be estimated well using the indirect inference algorithm applied on frequency domain data, even though the misspecified model had a time domain ARX structure. In the case of Model 2, an indirect technique allowed us to avoid the difficult task of constructing a likelihood function for the non linear structure.

While the binning procedure used for the estimation

dataset was found to generate errors due to a misaligned time vector, the effect of the introduced error was not significant compared to the variance of the data, and did not cause large changes in the model estimates obtained.

Using the large dataset to estimate parameters for the Model 1 and Model 2 structures, validation techniques suggested that Model 2 was able to fit the data slightly better. The distance between in vitro and in vivo dynamics was also of interest, and it was found that the data and model estimates obtained in this paper are closest to the ‘Irregular’ and ‘High Gain Irregular’ models obtained in [4] and [5] respectively.

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