

MATHEMATICAL MODELLING OF NEURONAL PROCESSES  
WITHIN THE OCULOMOTOR SYSTEM.

F. del Pozo; Sendra, A.; Delgado-García, (1) J. M. and Portaencasa, R.

Dept. de Cibernética y Análisis Numérico. Facultad de Informática. Universidad Politécnica. Madrid. Spain.

(1). Dept. Fisiología. Facultad de Medicina. Sevilla. Spain.

Abstract

It is presented a mathematical model of the oculomotor plant, based on experimental data in cats. The system that generates, from the neuronal processes at the motoneuron, the control signals to the eye muscles that moves the eye. In contrast with previous models, that base the eye movement related motoneuron behavior on a first order linear differential equation, non-linear effects are described: A dependency on the eye angular position of the model parameters.

Introduction

Any approach to the study of the brain is intended to understand finally how the brain processes information, which, we assume, is the substrate for behavior. And dealing with information-processing systems, the theoretical work based on signal theory, information theory and control system theory, seems the adequate framework to cover that objective. Since the possibilities of any mathematical modelling tool, to provide a quantitative description of phenomena, however, rely on the adequate knowledge of the neuronal networks of interest (the connection between nerve cells) and the activity of the cells involved; our efforts have to be focused on the those neural systems both functional-anatomically identified and with most of their circuits accesible to exploration (measurement of cell activity).

The oculomotor system, the system that controls eye movements, appears as one of the main candidates, considering that its functional and conceptual features<sup>12</sup> clearly provide quite enough system description; and signal measurements are possible since the recent improvement of the techniques for recording the activity of functional and anatomically identified single neurons in alert behaving animals<sup>6, 10, 11</sup>.

Within the oculomotor system, five mayor subsystems can be outlined for those species with a structure similar to that of man: 1) The vestibulo-ocular reflex subsystem, that allows to maintain the visual

image fixed in the retina during head movements. Eye compensation control signals, to hold eye position in space, are generated from the semicircular canals that sense head acceleration. 2) The optokinetic subsystem, that complements the previous one, under slow movements where the canals do not operate correctly, and uses the image slip as the error signal that generates the control commands. 3) The saccadic subsystem whose purpose is to reorient the eye quickly in space to minimize the interval during which vision is lost. 4) The vergence subsystem with the aim of adapting binocular vision to targets at different distances; and 5) The smooth pursuit subsystem intended to track moving target with smooth eye movements.

This communication is limited to an important part of the oculomotor system, in terms of neuronal information processing, which is the common final structure of all the five subsystems mentioned: The oculomotor plant; that is, the system that process the signals transmitted and conditioned by the different subsystems involved in any type of eye movement, generating the control signal to the eye muscle that finally moves the eye. A further limitation of the work here presented is that only the horizontal component of the eye movement is considered for modelling purposes. Restriction which is founded on anatomical and functional bases, since there are a pair of eye muscles acting on the horizontal plane innervated by a specialized class of motoneurons: abducens neurons.

A model of the oculomotor plant.

Since the introduction of the techniques of single neuron recording in alert behaving animals, the eye related behavior of the abducens motoneurons has been extensively studied. After a first stage of qualitative descriptions, in 1970 a mathematical model, due simultaneously to Fuchs and Luschei<sup>4</sup>, Robinson<sup>9</sup> and Schiller<sup>13</sup>, was published. It relates the motoneuron discharge rate  $R(t)$  in spikes  $\text{sec}^{-1}$  to the eye instantaneous angular position  $\Theta(t)$  in degrees (positive in the pulling direction of the muscle—the so called on-direction) measured in the plane of action of the muscle that the cell being considered innervates. The model is a first order constant coefficient linear differential equation as follows:

$$R = k(\Theta - \Theta_T) + r \frac{d\Theta}{dt} \quad R \geq 0$$

where, under static fixation of the eye, there is a linear relationship between the firing rate of the motoneuron and eye position, being  $k$  (spikes sec<sup>-1</sup> deg sec<sup>-1</sup>) the proportionality constant that corresponds to the muscle force required to oppose the elastic elements of muscle-eyeball mechanical system. And  $-k\Theta_T$  the firing rate when the eye is centered at zero degrees; or  $\Theta_T$  the threshold angle, that is, for any  $\Theta$  smaller than  $\Theta_T$ , the motoneuron remains silent. When the eye moves, the rate  $R(t)$  is incremented by a term proportional to the eye velocity, that corresponds to the additional force required to overcome the viscous impedance of the mechanical structure; being the constant  $r$  defined in (spikes sec<sup>-1</sup>) (deg sec<sup>-1</sup>)<sup>-1</sup>.

This model has been generally accepted since its publication and only a few minor modifications have been reported; such as the introduction of a second order term proportional to eye acceleration, whose effect is only significant under abrupt changes in velocity as in saccadic movements<sup>8</sup>.

### Methods

#### Experimental methods.

Experiments were carried out in alert cats. Animals were previously implanted with silver ball electrodes to record their electrooculogram (both in the horizontal and vertical planes) and also with a holding system to restrain their heads during recording sessions. Recordings were carried out with glass micropipettes in selected areas of the brain stem through a transcerebellar approach. A more detailed account of the experimental set has been published elsewhere<sup>1</sup>.

The activity of isolated motor or premotor neurons were recorded during spontaneous and vestibular or visual induced eye movements in the alert behaving animal. Only eye movements related neurons were recorded. To further improve the reliability of the results, only identified neurons were considered for analysis.

Neuronal identification was achieved by antidromic activation of their somas from their axonal projections. Activation was carried out by chronically implanted stimulating electrodes located in neuronal projection sites: abducens nerve, oculomotor nucleus, anterior vermis of the cerebellum, etc.<sup>1,14</sup>.

A system was developed for the automatic and simultaneous recording of neuronal activity, angular position of the eyes and selected experimental inputs.

#### Experimental data acquisition and processing system.

For the acquisition, graphic display and processing of the recorded data, a system controlled by a HP9845B computer and a set of programs were implemented. Unit activity of the registered neurons was converted into a point process by filtering, window discrimination and measuring the interspike interval sequence. The operation is performed by a computer-

controlled counter that transfer to the computer, in a high speed mode, the intervals between neuron action potentials; so that, no lost of information is guaranteed under the shortest expected intervals with the fast test play-back magnetic tape speed. Analog data (angular position in both eyes and experimental variables) were connected to high speed A/D converters, where sampling is provided by a computer-controlled timer, that also synchronize the counter operation in order to get exact temporal correspondence between the different data channels. Digitized analog data were stored momentarily, after multiplexing, in an auxiliary buffer while the point process is being acquired, and are transferred into the computer, through the system bus, upon completion of that operation. Finally, data are stored in a flexible disc together with file codes and acquisition variables.

In order to allow the visual inspection of the transferred data and the systematic selection of records in a great amount of cells for further processing the program enabled the display, upon selection, of the angular position and/or velocity of both eyes with the cellular activity point process. Each partial acquisition can be saved or erased according to its relevance for posterior analysis. It was also possible to select partial segments of a given file using a cursor over the CRT screen and store them with separated codes. Ordinate scales were defined from calibration records on the magnetic tape. Hard-copies of the CRT display can be obtained with a thermal printer. After the presentation of a transferred block, the program automatically continue with a new acquisition.

Figures 1 and 3 show examples of the graphic displays obtained with the program. In both cases, sampling rate was selected to 1/40 msec<sup>-1</sup> (this rate was used generally during the stage of initial inspection of data, since it allows a convenient 40 sec duration of each acquisition block with adequate time resolution for this purpose). The data segments shown in both figures are cursor selected and expanded portions of a 40 sec total duration file. The data presented have not been manipulated in any way to show the clear correlation that exists between the static and dynamical behavior of the eyes and motoneuron activity, which has been represented at the bottom of the figures by the inverse of the time intervals between spikes, also included (represented below) as they are obtained after the window discriminator.

### Results

#### Motoneuron behavior during fixation.

During steady fixation, each motoneuron discharges at a constant rate, as can be predicted from the model of the oculomotor plant presented, if we assume, as is generally the case in the literature, that the model is linear and time invariant. In other words, the relationship between the discharge rate of each motoneuron and the fixation angle is completely described by the constant parameters  $k$  and  $\Theta_T$ . Parameters are usually estimated by linear regression analysis applied for each motoneuron, to the bidimensional random variable  $(R, \Theta)$ , under steady fixation conditions.

Reviewing published results, (only papers with

identified motoneurons), some departures from the model have been considered (without an adequate quantitative evaluation) to account for the experimental residual variability: 1) Non-linear effects; some kind of dependence on the fixation angle of the model parameters. 2) Hysteresis effect 3, 5; at a given position, the firing rate tend to be higher when that angle is reached through an on-transition (the motoneuron acting as the agonist) than when it is reached after an off-transition (with the motoneuron acting as the antagonist). 3) State of alertness of the animal; that could be related to a general state of responsiveness of the whole system. 4) Adaptation processes; when the animal repeatedly fixated a steady target. 5) Crosstalk effects; between the different projection planes of the eye movement subsystem.

21 functional and antidromic identified motoneurons from three cats, were analyzed to provide some insight on the previous points. In a first stage, steady fixation coefficients, obtained by linear regression techniques, revealed a  $k$  value with a broad distribution range, from 3 to 12 spikes  $\text{sec}^{-1} \text{deg}^{-1}$  lightly peaked around 8; and a threshold value  $\Theta_T$  also with a broad dispersion ranging from 0 to 10 degrees right with a higher density around 6, 5 deg. right.

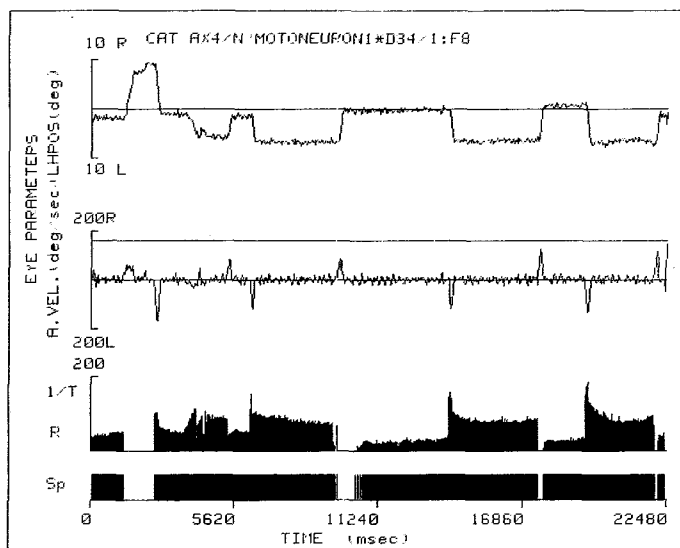


Fig. 1. Activity of an identified abducens motoneuron (Ax4 - M1) (left side) during spontaneous fixation eye movements of the cat. From top to bottom: The angular position of the left eye in the horizontal plane (LHPOS) in degrees (scale: 10 deg. left (L) - 10 deg. right (R)). The corresponding eye velocity (AVEL) in  $\text{deg. sec}^{-1}$  (scale: 20  $\text{deg. sec}^{-1}$  left - 200  $\text{deg. sec}^{-1}$  right). The inverse of the intervals (T) between consecutive action potentials (instantaneous firing rate R) (scale: 200 spikes  $\text{sec}^{-1}$ ). The point process (Sp) obtained from the motoneuron action potentials passing through a window discriminator.

A closer approach in the regression analysis can be followed in the figures 1 and 2. Figure 1, shows the activity during spontaneous fixation eye movements of the cat of a functional and antidromically identified motoneuron (Ax4 - M1) that innervates the external horizontal muscle of the left eye. The meaning of

the signals shown can be followed from the figure legend. The data points (R,  $\Theta$ ) are obtained by averaging the R and  $\Theta$  (horizontal angular position of the left eye-LHPOS) values in the interval within a pair of cursors that are positioned in the desired eye fixation time ranges.

A first conclusion can be obtained from figure 1: The firing rate profile, during steady fixation, can hardly be assumed, as is the normal situation in the published literature, to be constant; on the contrary, it evolves in time following, in a first qualitative description, a monotonic pattern whose sense depends on the direction of the previous transition. This finding, in contrast with previous models <sup>10, 11</sup>, that consider: motoneuron activity shows a pulse-step increase in the firing rate during saccadic movement in the on-direction, followed by a constant value which corresponds to the new steady position, could explain, at least, part of the high residual variation in the relationship between the angle of the fixation and the firing rate. Moreover, it could disclose some properties of the mechanisms involved in the integration of information at the motoneuron level of the oculomotor system.

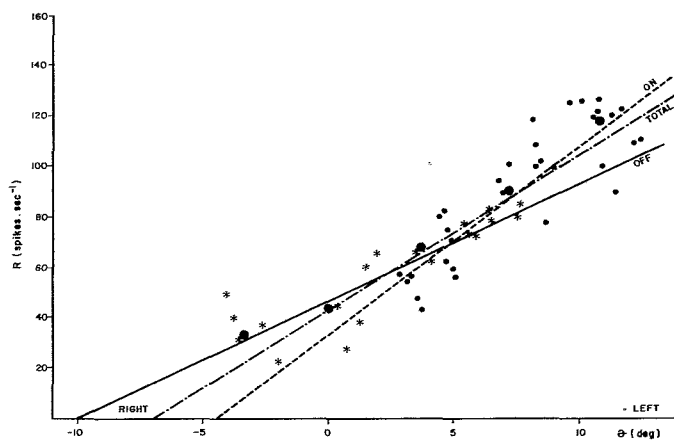


Fig. 2. Linear regression analysis, for the same motoneurons showed in the Fig. 1. (Ax4 - M1), of the bidimensional random variable (R,  $\Theta$ ). Full points correspond to steady fixation states following an on-direction eye transition. Star points are those for steady fixation states following an off-direction eye transition. The regression lines for both set of data are plotted as well as the total data samples (TOTAL). Biggest size full points represent the firing rate when the eye passes through the associated angular position with instantaneous zero velocity (see text for details).

A practical consequence, in relation to the interpretation of the (R,  $\Theta$ ) regression analysis, is that regression coefficients depends on the time interval from the transition where data samples are taken.

As a matter of fact, the differences founded in the  $k$  and  $\Theta_T$  values, for several states of alertness (greater values of R, for a given  $\Theta$ , as the level of alertness increases), could be explained taking as

a basis the observed phenomena: since the state of alertness is frequently evaluated by the number of eye fixation per unit of time; thus, as the alertness of the animal increases, the mean value of the fixation interval duration decreases, and the firing rate samples become closer to eye transitions.

Also, the hysteresis effect could be explained on those basis, if we take into account the opposite sign of the motoneuron firing rate evolution profiles during fixation after an on or off transition.

To overcome, as much as possible, those effects, the data points  $(R, \theta)$  considered for regression analysis (fig. 2) were selected exclusively from those fixation intervals long enough to assume that the firing profile is close to its asymptotic value (if this asymptotic value can be defined!).  $(R, \theta)$  points of the same motoneuron selected in figure 1 are plotted in figure 2. Three regression lines have been obtained; one for eye fixations after on-transition ( $k = 7.5; \theta_T = -4.42$  deg), another for eye fixation after off-transition ( $k = 4.6; \theta_T = -10$  deg) and the third one constructed from the total number of data points ( $k=6.15, \theta_T=-6.95$ ) Several non-linear models: exponential, logarithmic and polynomial (up to third order), not included in the figure, were also fitted to the data.

An analysis of variance, applied to the regression models, showed the following results: The best fit corresponds to the linear model when it is estimated separately from on-direction and off-direction data samples. The residual variance increases when the model is fitted to all the data point, which, on the other hand, is smaller than the residual variance obtained for the non-linear models.

These results could rise on two different (not necessarily mutually exclusive) interpretation: 1) As a supporting evidence of the hysteresis effect, or/and 2) Considering that, within the angular range of motoneuron activity ( $\theta > \theta_T$ ), on-direction and off-direction fixation data points will show, on the scatter diagram, a greater density for high and low, respectively, eye angular deviations (see figure 2); the obtained results suggest some kind of non-linear effect or  $k$  dependency on the eye angular position.

Also, in the figure 2, it has been included five points (biggest size full points), obtained by a dynamical test of the oculomotor plant that will be presented in the next paragraph, that correspond to the firing rate when the eye pass through those five eye positions with instantaneous zero velocity. It can be observed how close they follow the two component linear model; and then, it could be taken as a supporting evidence of the non-linear interpretation mentioned; since the  $k$  dependency on  $\theta$ , cannot be associated, in this case, to the hysteresis effect.

#### Motoneuron behavior during slow eye movements (vestibular induced).

While the motoneuron behavior during fixation is independent on which subsystem of the oculomotor system is involved, during eye movements, the velocity component of the differential equation, depends very much on which subsystem commands the movement

(their objectives are different from the system control point of view).

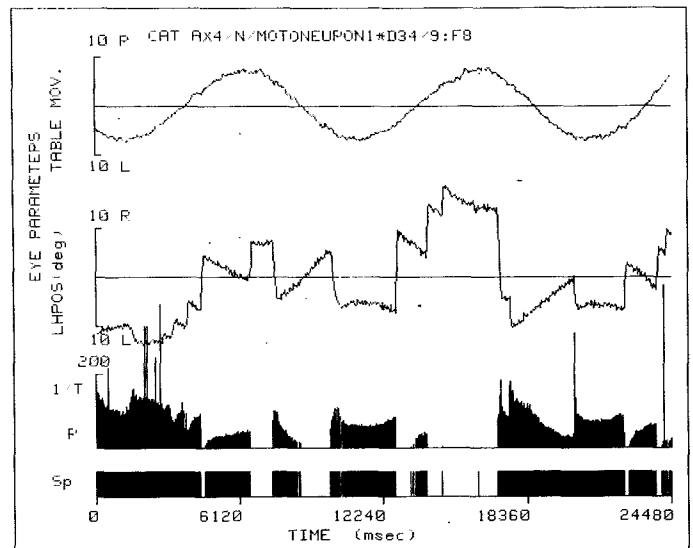


Fig. 3. Activity of an identified abducens motoneuron (same one of previous figures) during vestibular stimulation (sinusoidal head rotation). From top to bottom: The absolute angular position in space of the animal head (TABLE MOV.). The absolute angular position of the left eye in the horizontal plane (LHPOS). The other two signals are identical to those of figure 1. Vertical scales are those of figure 1.

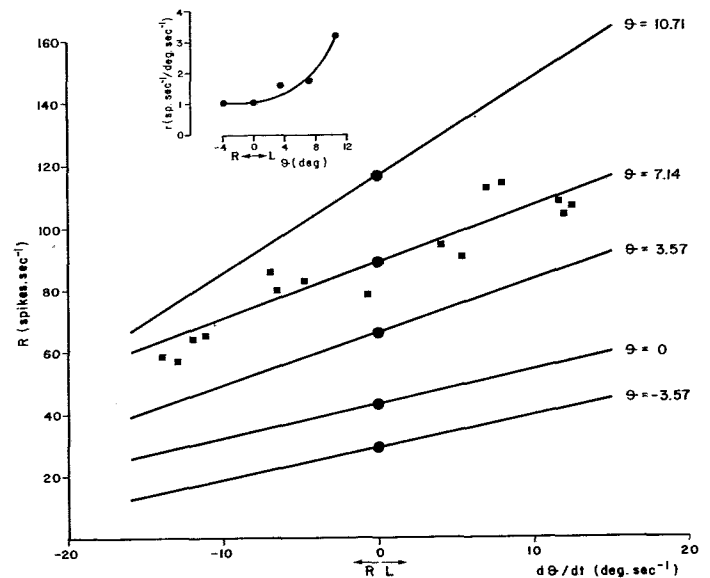


Fig. 4. Linear regression analysis of the random variable  $(R, \dot{\theta})$  during slow eye movements under sinusoidal vestibular stimuli, for different values of the eye angular position ( $\theta = -3.57$  to  $10.71$ ;  $3.57$  deg. apart). To avoid confusion, only the data samples for  $\theta = 7.14$  deg. have been plotted. Biggest size points  $(R, \dot{\theta}/\dot{\theta} = 0)$  correspond to the same type of figure 2. The coefficient  $r$  (spikes  $\text{sec}^{-1}/\text{deg. sec}^{-1}$ ) (slope of the regression lines) is represented as a function of  $\theta$ .

This experimental evidence suggests that the various subsystems generate their own signals according to their purpose, being added together to produce at the motoneuron a unique eye position command. Robinson<sup>12</sup> considers that, at the oculomotor plant, however, the velocity component of the model is the same for any type of eye movement, changing only the value of the coefficient  $r$ .

Since our purpose is to review the adequacy of the velocity component included in the differential equation of the oculomotor plant, we limit our presentation to a specific type of eye movement: Slow movements (in the range  $\pm 12 \text{ deg. sec}^{-1}$ ) induced by vestibular stimuli.

13 functional and antidromically identified motoneurons from 3 cats were analyzed. The procedure to estimate the coefficient  $r$  can be followed from figure 3 in which it has been represented the activity of the same motoneuron (Ax4 - M1) of previous examples, under sinusoidal vestibular stimulation. The meaning of the different signal plotted is included in the corresponding legend.

The data points of the bidimensional random variable  $(R, \dot{\theta})$  were obtained by selecting an horizontal cursor at a given eye angle  $\theta_i$  and positioning the vertical cursor at the crossing points  $t_i$  where  $\theta(t_i) = \theta_i$ . Only the crossing points corresponding to slow movements with a  $R(t_i) \neq 0$ , were considered for analysis. At the selected times  $t_i$ , the instantaneous eye velocity  $\dot{\theta}(t_i)$  and instantaneous firing rate  $R(t_i)$  were measured. To avoid the effect of the analog channel noise, it was implemented a selectable width smoothing algorithm.

The results obtained for  $\theta_i = 0$  (when the eye passes through the origin of the eye angles) showed a linear correlation coefficient generally greater than 0.9 and  $r$  values in the range 0.26 to  $1.78 \text{ sp. sec}^{-1} / \text{deg. sec}^{-1}$  for the motoneurons analyzed.

Repeating the procedure at different values of  $\theta_i$ , it would be expected, under the assumptions of the model, a family of parallel lines ( $r$  independent of  $\theta_i$ ) and equally spaced for equal increments of  $\theta_i$  ( $k$  independent of  $\theta_i$ ). Figure 4, shows the regression lines corresponding to the random variable  $(R, \dot{\theta})$  for five different values of  $\theta_i$ , 3.57 degrees apart. Several conclusions can be drawn: 1) For any angular position  $\theta_i$ , the linear model showed the minimum residual variance (in the figure, only the data points for  $\theta = 7.14$  have been represented to avoid confusion) within the  $\pm 12 \text{ deg. sec}^{-1}$  eye velocity range. 2) At any eye velocity, within the range considered, the increments of the firing rate due to equal increments of  $\theta_i$  (3.57 deg.) are not uniform but rather increasing with the angular position  $\theta_i$ , where  $\dot{\theta}$  was evaluated. The predicted values by the linear regression models of figure 4 for  $\dot{\theta} = 0$ , that is,  $(R, \dot{\theta} / \dot{\theta} = 0)$ , will define five  $(R, \theta_i)$  points (biggest size full points in figure 4) that, according to the differential equation of the model, have also been represented on the scatter diagram under fixation conditions (fig. 2). It can be observed how well they fit the two slopes linear model  $(R, \theta)$  obtained under static conditions. Since at any  $\dot{\theta}$ , within experimental range considered, and, as a particular case,

at  $\dot{\theta} = 0$ , the increment in the firing rate for equal increments of the eye angle is not constant; it can once more be realized the existence of a dependency on  $\theta$  of the  $k$  value of the model, being greater as the eye angle increase in the pulling direction of the eye muscle. 3) The slopes of the regression line of figure 4, are not constant for the different  $\theta_i$ , but they increase with  $\theta_i$ . A plot of the  $r$  value (slope of the regression lines in  $\text{spikes sec}^{-1} / \text{deg. sec}^{-1}$ ) is also included in the figure 4. A conclusion is evident; the  $r$  coefficient depends on the eye angle, increasing in a rather fast way for large angular distances from the origin in the pulling direction of the eye muscle. In other words, the constancy of the coefficient of the velocity component of the model can only be assumed within a limited angular range of the eye movement in the horizontal plane.

### Conclusions

The results presented herein show the need of a deep revision of the, generally accepted, first order linear time invariant model, that relates the instantaneous firing rate of the abducens motoneuron to the angular horizontal component of the eye position in space. In terms of the mathematical characterization of the non-linear effects suggested by the included results on the behavior of the system (oculomotor plant), during steady fixation and slow vestibular induced eye movements.

An obvious prolongation of this research, now in progress on the data already acquired, is the application of similar procedures to other types of eye movements and ranges of velocity (wide frequency range sinusoidal vestibular stimuli and fast movement-saccadic) from the set of recorded motoneurons; taking into account the individual differences. With the purpose of getting a formal representation of the relationship between the model coefficients and the eye angular position; both for each motoneuron and for the set of cells.

Data are also being analyzed from a different approach: harmonic analysis, applied to the system under sinusoidal vestibular stimulation and restricted to a range of stimuli amplitude and frequency, to assume that a linearization approximation is appropriate.

Also, the mathematical characterization of the firing profiles during steady fixation after an on and off eye transition, will help to elucidate the existence of a significant hysteresis effect and the hypothetical model parameters dependency on the level of alertness. On the other hand, a better understanding of the non-linearities mentioned can be obtained, since the variance of the firing rate experimental samples will be reduced. An finally, and more important, the modelling of the firing profiles under fixation and those associated to eye saccades between fixation, is an unavoidable step to cover the purpose to extend the oculomotor plant model to saccadic eye movements.

Further studies should be done to include previous result in the structural and functional description of how the information content of the neural signal

at the output of abducens motoneurons is transduced to eye movements, taking into account both, the mechanical properties of the muscle-eyeball structure and the fact that the model parameters ( $k$ ,  $\Theta_T$ ,  $r$ ) defined for each motoneuron are different within wide dispersion ranges. It has to be considered, that the proposed model relates a single neuron feature, its firing rate, to a global feature, the eye angular position due to the compound activity of many motoneurons. That is, the oculomotor model can be interpreted as a causal model, only under the dangerous assumption<sup>12</sup> that the motoneuron set can be described by a typical "mean behaving" motoneuron.

A final word is to express our conviction that any further progress to understand how is processed the information within the oculomotor system, and any other system that could be defined in the brain, has to be based on two main pillars: A data acquisition system to handle in some flexible and structured way a great amount of data and the intensive application of the available mathematical tools, mainly those of control system analysis and model identification and estimation statistics.

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