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Fitting rVOR responses using current models

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Abstract— **The slow phase velocity of the rVOR response to a step of constant velocity head rotation is best represented by a model with two time constants. Two main models, based on different physiological hypotheses, have been proposed in the literature. Although their structures and their parameters are different, these two models have often been considered mathematically identical. Here we compare them, highlighting their differences and showing which parameters are more representative and giving hints on which model to use when fitting rVOR responses having different morphologies.**

I. INTRODUCTION

THE mathematical model of a biological system, developed to investigate the physiological process underling a recorded response, always requires a trade off between the mathematical and the physiological guided choices. Indeed a complex physiological model can be a powerful tool, but if its parameters are not all identifiable based on the available experimental data, no physiological conclusion can be drawn. From a mathematical point of view, a desired response to a given input can be achieved by different model structures. The choice between these structures has to take into account, not only the physiological background, but also if the states of the model are observable given the response of the biological system to a known input.

The rotational vestibulo-ocular reflex (rVOR) stabilizes vision by generating eye movements compensatory of head rotations. Semicircular canals (SCC) in the inner ear are sensible to rotational accelerations but, due to their mechanical properties, they integrate head accelerations, thus providing a velocity signal. This signal is carried through the brainstem and then reaches the ocular motor neurons innervating eye muscles. Sustained head velocity rotations in darkness evoke a nystagmic response with a slow phase velocity (SPV) showing a fast increase followed by a slow decay. The signal recorded from SCC's afferents in monkeys shows a similar behavior, but it decays faster than eye movement velocity. It is currently believed that a central processing stage, commonly called velocity storage mechanism (VSM), lengthens the time constant of the SCC process. The eye velocity responses of rVOR to a step of head velocity have been often modeled using a single exponential [1], as if the VSM processing operates a perfect substitution of the SCC time constant. This model, although not always accurate, allows to estimate a gain and a time constant of the rVOR response. It has been shown that in most cases the SPV envelope of the rVOR response to a step input is better represented by a sum of two exponentials with different time constants [2], one for the SCC and one for the VSM. Two main models of the rVOR, based on different physiological hypotheses, have been suggested: the model proposed by Raphan and Cohen [2] and the one proposed by Robinson [3]. These two models have been considered mathematically indistinguishable [3], since they provide the same input-output relationship, yet their structures and the roles of their parameters are different. Our main goal here is to analyze the two models to enlighten the different roles of the model parameters in generating a specific output. By determining when the estimated parameters are more or less reliable, the weaknesses and strengths of the two models will be shown. The two models will be briefly described in the next section, while a comparative analysis will be carried out in the subsequent section. The last section draws the conclusions and suggests which model is preferable when fitting rVOR responses having different morphologies. To distinguish the variables of the two models, the apex "C" will be used for Cohen's model and "R" for the Robinson's one.

II. THE RVOR MODELS

The rVOR produces eye movements that are compensatory of head rotation. This is usually shown mathematically by a negative sign in the input-output transfer function, which, for simplicity, will be neglected in the following.

A. *Raphan's and Cohen's Model*

The model proposed by Raphan and Cohen assumes that the rVOR velocity command results from the sum of two separate pathways. The first one is called "direct pathway" as it carries the SCC afferents' signal directly to the ocular motor neurons. The second one, called "indirect pathway", processes the afferents' signal through a pure integrator within a negative feedback loop, representing the VSM. A graphical representation of the model is given in fig.1.

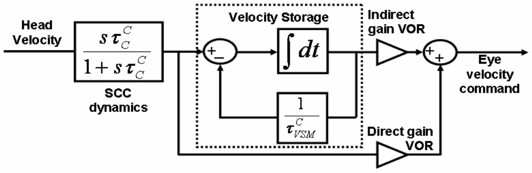

Figure 1: Block diagram of Raphan and Cohen's model

The eye velocity response to a unit step of head velocity predicted by the model is expressed by the equation

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$$\dot{\theta}^C = g_0^C e^{-t/\tau_C^C} + g_1^C \frac{\tau_C^C \tau_{VSM}^C}{\tau_C^C - \tau_{VSM}^C}\left(e^{-t/\tau_C^C} - e^{-t/\tau_{VSM}^C}\right) \quad (1)$$

where g^C_0 and g^C_1 represent the direct and indirect gains, respectively, while τ^C_C and τ^C_{VSM} are the time constants of the SCC and VSM, respectively. Previous studies using this model on humans [4], as well as studies on monkeys [6], suggested a range of 3-7 s for τ^C_C. Ramat et al.[5] have shown that neglecting the mechano-neural transduction [6] in the rVOR models results in an under-estimation of the time constants. As our focus here is the estimate of the model parameters and not its physiological accuracy or the values of these parameters, we will neglect the MNT in the following considerations. In the parameter estimation procedures we will constrain the values of the time constants based on the common consensus from the literature, i.e. $\tau^C_C \in [3,7]$ seconds and $\tau^C_{VSM} \in [8\text{-}40]$ seconds.

B. Robinson's Model

The model proposed by Robinson hypothesizes a single rVOR pathway carrying the SCC signal through the brainstem to the ocular motor neurons. The VSM activity is modeled as a positive feedback loop along this pathway, with a leaky integrator and a gain on the feedback line. A graphical representation of the model is given in fig.2.

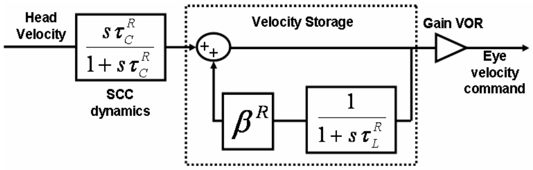

Figure 2: Block diagram of Robinson's model

The model prediction of the output eye velocity response to a unit step of head velocity is:

$$\dot{\theta}^R = g_0^R \left(\frac{\beta^R}{\tau_L^R} e^{-t\frac{1-\beta^R}{\tau_L^R}} - \frac{\tau_C^R - \tau_L^R}{\tau_C^R \tau_L^R} e^{-t/\tau_C^R} \right) \Bigg/ \left(\frac{1}{\tau_C^R} - \frac{1-\beta^R}{\tau_L^R} \right) \quad (2)$$

where τ^R_C and τ^R_L are the time constants of the SCC and of the leaky integrator, respectively, while β^R is the gain on the feedback line and g^R_0 is the gain of the rVOR. To ensure stability β^R is always smaller than 1, thus $\tau^R_L/(1- \beta^R)$, which represents the long time constant of the response, is longer than τ^R_L. The bounds for τ^R_C are 3-7 s, as suggested by previous studies on monkeys [6], β^R ranges between 0 and 1 and τ^R_L can be either larger or smaller than τ^R_C.

III. ANALYSIS OF THE OUTPUTS OF THE MODEL

The state-space equations of a model can be directly obtained using the coefficients of its transfer function written in Laplace transform notation. The Cohen's and the Robinson's state-space equations are, respectively:

$$\begin{cases} \dot{x}^C(t) = \overbrace{\begin{bmatrix} -\frac{1}{\tau_C^C} & 0 \\ -\frac{1}{\tau_C^C} & -\frac{1}{\tau_{VSM}^C} \end{bmatrix}}^{A} x^C(t) + \overbrace{\begin{bmatrix} 1 \\ 1 \end{bmatrix}}^{B} u^C(t) \\ y^C(t) = \overbrace{\begin{bmatrix} -\frac{g_0^C}{\tau_C^C} & g_1^C \end{bmatrix}}^{C} x^C(t) + \begin{bmatrix} g_0^C \end{bmatrix} u^C(t) \end{cases} \quad (3a)$$

$$\begin{cases} \dot{x}^R(t) = \overbrace{\begin{bmatrix} -\frac{1}{\tau_C^R} & 0 \\ -\frac{1}{\tau_C^R} & -\frac{1-\beta^R}{\tau_L^R} \end{bmatrix}}^{A} x^R(t) + \overbrace{\begin{bmatrix} 1 \\ 1 \end{bmatrix}}^{B} u^R(t) \\ y^R = \overbrace{\begin{bmatrix} -\frac{g_0^R}{\tau_C^R} & \frac{g_0^R \beta^R}{\tau_L^R} \end{bmatrix}}^{C} x^R(t) + \overbrace{\begin{bmatrix} g_0^R \end{bmatrix}}^{D} u^R(t) \end{cases} \quad (3b)$$

where $x^C(t)$ and $y^C(t)$ are the state and the output vectors of the Cohen's model, while $x^R(t)$ and $y^R(t)$ are those of Robinson's one. $u^C(t)$ and $u^R(t)$ are the respective input vectors. The observability of a system is a measure of whether the internal states of the system can be inferred by knowledge of its external outputs, i.e. if it is possible, in our context, to identify both elements of the state vector from the eye movements of the subject. Since both models have two states equations, their internal states are not observable when the determinants of the matrix built as $\begin{bmatrix} C \\ CA \end{bmatrix}$ equals 0; i.e. its rank is less than 2.

Therefore, the internal states of the step response of Cohen's model are not observable when the parameters satisfy the following equation:

$$\frac{g_1^C}{g_0^C} = \frac{1}{\tau_C^C} - \frac{1}{\tau_{VSM}^C} \quad (4)$$

Equation 4 can also be obtained by finding the gain g^C_1 that cancels the direct pathway contribution, i.e. the first term in the right-hand side of (1). This changes (1) to a single exponential, expressed by the equation:

$$\dot{\theta}^C = g_0^C e^{-t/\tau_{VSM}^C} \quad (5)$$

If the data are fitted using a set of parameters satisfying (4), only the estimates of τ^C_{VSM} and g^C_0 are reliable and they represent the time constant and the gain of the rVOR response, respectively. Both g^C_1 and τ^C_C are not constrained by (5), thus any couple of parameters that satisfies (4), given τ^C_{VSM} and g^C_0, generates the same output.

On the other hand, the step response of Robinson's model does not allow to infer the internal states when

$$\tau_L^R = \tau_C^R \quad (6)$$

When (6) is satisfied the exponential with time constant τ^R_C is canceled in (2). This results in a single exponential output, represented by the equation:

$$\dot{\theta}^R = g_0^R e^{-t\frac{1-\beta^R}{\tau_L^R}} \quad (7)$$

Although producing similar outputs, (4)-(5) and (6)-(7) are different. In Cohen's model (4) binds all the parameters while in Robinson's one only the two time constants have to satisfy (6) while β^R is free. Moreover (5) allows the estimation of two parameters while (7) gives no information about the actual values of τ^R_L as only $\tau^R_L/(1- \beta^R)$ and g^R_0 can be estimated.

Besides these differences, both models become non completely observable when attempting to fit a response that can be approximated by a single exponential.

However, different constraints for the model parameters arise from their structures when they are optimized to fit a specific response, and this can play a role in the choice of one or the other model. To enlighten these differences, two families of output curves, fitting two different morphologies of rVOR responses, have to be kept separate. For simplicity these two kinds of output will be first introduced showing how they are generated by Cohen's model. Then the corresponding equations for Robinson's model will be presented and discussed.

The possible output morphologies of Cohen's model are separated by (4). When the left-hand side of the equation is lower than the right-hand side, the model output is dominated by the direct pathway. Indeed, in these conditions $g^C{}_1$ is lower than the fraction of $g^C{}_0$ needed to cancel the direct pathway contribution, and the response is dominated by a single exponential with $\tau^C{}_C$ as time constant and $g^C{}_0$ as gain. The fit of the response using two exponentials can be ambiguous, as the reliability of the indirect pathway parameters is entrusted to a small part of the information. Special care has to be taken when considering the time constant estimate for the direct pathway in these conditions. In fact although a large misestimation of $g^C{}_1$ is unlikely (it would change the balance between the two pathways), a small error would be negligible to the overall fit, yet it would change the amount of information accounted for by the VSM activity, potentially leading to a significant error in estimating $\tau^C{}_{VSM}$.

The opposite condition occurs when $g^C{}_1/g^C{}_0$ is larger than the value on the right-hand side of (4). In this condition the indirect pathway dominates the response and the output of the model would initially decay more slowly than (5). Later in the response, the slope would became more negative and then align with (5) by its end. The beginning behavior occurs because the sum of the coefficients of the two exponential monomers of (1) having $\tau^C{}_C$ as time constant is negative, i.e. the resulting exponential function grows. If the indirect pathway contribution is strong enough, the output curve can also be constant, or even rise, in the beginning. In these conditions the model simulates a so-called "plateau response", which represents a common behavior of the rVOR. Thus, the relationship between the left- and right-hand side of (4) discriminates between the possible behaviors of the model, as described above. In the following we will refer to the ratio $g^C{}_1/g^C{}_0$ as R^C.

A simple equation relating R^C to the initial model output can be obtained by calculating the derivative of (1), normalized with respect to $g^C{}_0$, at time t = 0:

$$R^C = \frac{g_1^C}{g_0^C} = \frac{1}{\tau_C^C} + \left.\frac{\partial \dot{\theta}_{norm}^C}{\partial t}\right|_{t=0} \qquad (8)$$

Equation 8 shows that the model generates a plateau output (derivative in $t=0$ larger than 0) when R^C is larger that the inverse of $\tau^C{}_C$, independently by the values of $\tau^C{}_{VSM}$.

The time $T^C{}_{peak}$, at which the plateau reaches its maximum value, is expressed by

$$T_{peak}^C = \frac{\tau_C^C \tau_{VSM}^C}{\tau_{VSM}^C - \tau_C^C} \ln\left(\left(\frac{1}{R^C}\left(\tau_C^C - \tau_{VSM}^C\right) + \tau_C^C \tau_{VSM}^C\right) \Big/ \left(\tau_C^C\right)^2\right) \qquad (9)$$

Once $T^C{}_{peak}$ is defined, we can write an equation describing the decay of eye velocity, normalized with respect to its peak value:

$$\dot{\theta}_{Norm}^C(t_{decay}) = \frac{\tau_{VSM}^C e^{-\frac{t_{decay}}{\tau_{VSM}^C}}}{\left(\tau_{VSM}^C - \tau_C^C\right)} - \frac{\tau_C^C e^{-\frac{t_{decay}}{\tau_C^C}}}{\left(\tau_{VSM}^C - \tau_C^C\right)} \qquad (10)$$

where t_{decay} represents the time after $T^C{}_{peak}$. (10) is independent from R^C, thus the gains do not determine the timing of decay of a plateau output, but only scale its amplitude. From (9) it can be seen that different triplets of parameters can give the same $T^C{}_{peak}$, thus (9) alone does not allow a unique solution when fitting a plateau response. However (10) can be used to produce a set of points as large as the number of time points in the data after $T^C{}_{peak}$. As (10) is a sum of two exponential functions with independent time constants, there is a unique pair of $\tau^C{}_C$ and $\tau^C{}_{VSM}$ that generates a given curve when in plateau response conditions (Fig.3).

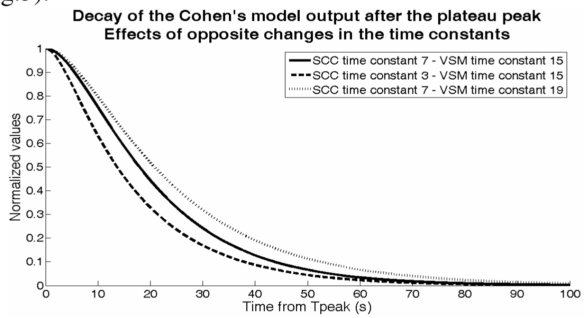

Figure 3: Dashed line (reduction of $\tau^C{}_C$) shows a marked difference in the first part, while dotted line (increase of $\tau^C{}_{VSM}$) mainly changes in the middle part. Thus opposite changes cannot compensate each other in every points of the curve.

In Robinson's model (6) is the boundary between the two behaviors, equivalent to (4) for the Cohen's one. When $\tau^R{}_L$ is larger than $\tau^R{}_C$, the charging rate of the feedback loop is too slow to compensate the decay rate of the SCC signal, thus the output is similar to that of a single exponential with time constant $\tau^R{}_C$. Differently from Cohen's model, the estimate of the other time constant $\tau^R{}_L$ is quite reliable. Indeed its value determine the relative weight of the two exponentials in (2) since $\tau^R{}_C$ is constrained, being the dominant time constant in this kind of response, and β^R multiplies only the first exponential of (2).

Considering (2), when $\tau^R{}_L$ is smaller than $\tau^R{}_C$ the coefficient of the second exponential is negative, thus causing a slower decay in the begging of the response. If $\tau^R{}_C$, satisfies the following equation:

$$\tau_C^R \geq \tau_L^R / \beta^R \qquad (11)$$

then the model produces a plateau response. (11), which was obtained with the same approach used for (8), is a strong constraint for the possible values of the model parameters. Indeed since $\tau^R{}_C$ has usually limited to at most 7 s, (11) implies that $\tau^R{}_L/(1-\beta^R)$, i.e. the time constant of the VSM, is also bounded by $\beta^R/(1-\beta^R)\ \tau^R_C$.

The time of the peak of the plateau output is expressed by:

$$T^R_{peak} = \frac{\tau^R_C \tau^R_L}{\tau^R_L - \left(1-\beta^R\right)\tau^R_C} \ln\left(\frac{\left(\tau^R_C - \tau^R_L\right)\tau^R_L}{\beta^R\left(1-\beta^R\right)^2\left(\tau^R_C\right)^2}\right) \quad (12)$$

The decay after the peak of the plateau is represented by the equation:

$$\dot{\theta}^R_{Norm}(t_{decay}) = \frac{1}{\left(\tau^R_L \big/ \left(1-\beta^R\right) - \tau^R_C\right)} * \left(\frac{\tau^R_L}{\left(1-\beta^R\right)} e^{-t_{decay}\frac{\left(1-\beta^R\right)}{\tau^R_L}} - \tau^R_C e^{-\frac{t_{decay}}{\tau^R_C}}\right) \quad (13)$$

Equation 13 is equivalent to (10) since τ^C_{VSM} in Cohen's model corresponds to $\tau^R_L/(1-\beta^R)$ in Robinson's model. Nevertheless, in (13) all the parameters have a role in determining the decay after the peak, a significant difference with respect to Cohen's model. Yet, τ^R_L and β^R cannot be directly evaluated from (13), because they always appear together in the ratio $\tau^R_L/(1-\beta^R)$. Nevertheless, the logarithm within (12) depends on β^R and τ^R_L separately, thus taking (12) and (13) together allows estimating all the parameters.

IV. CONCLUSIONS

Fitting the SPV of the rVOR response to a step of constant velocity head rotation using a model with two time constants instead of one usually results in lower residuals. Moreover two time constants allow a better investigation of the process underlying the reflex as one can account for the peripheral and the other for the central processing stages. The main drawback to this approach is that sometimes eye velocity traces mask a part of the internal process and show a single exponential behavior.

Two main models [1][2] have been proposed to fit the rVOR responses with two time constants. Avoiding the discussion on the physiological hypotheses behind them, we have investigated their mathematical properties as well as the role of their parameters in fitting different types of rVOR responses. Besides the different structures, their responses to a step of head velocity are similar in many aspects:

1) Both models can fit all rVOR response morphologies

2) Both use four parameters, one being a scaling factor

3) They do not allow to observe their internal state when the output behaves a single exponential

Nevertheless, two differences arise when fitting a single exponential trace:

1a) All the parameters of Cohen's model are involved in the equation that defines the observability of the internal states of the system, while two parameters (g^R_0 and β^R) are not involved in the observability equation for Robinson's model.

2a) Cohen's model allows to estimate two parameters (g^C_0 and τ^C_{VSM}) when fitting a single exponential response, while the only reliable value using Robinson's model is the gain g^R_0 as the time constant is a derived value ($\tau^R_L/(1-\beta^R)$).

In this condition Cohen's model is preferable as it allows estimating the VSM parameters, while Robinson's hypothesis quantifies the decay rate of the eye velocity curve only.

When the central processing activity is weak, the parameters that represent the peripheral activity ([g^C_0; τ^C_C] and [g^R_0;τ^R_C]) dominate the fit. Here the main difference is that Robinson's model uses mainly τ^R_L (the leaky integrator time constant) to weight the two exponentials, while Cohen's model use the ratio of the gains R^C. Thus the more reliable parameters are [g^C_0; g^C_1; τ^C_C] and [g^R_0; τ^R_C; τ^R_L]. Indeed as in this condition both models rely on a little amount of information to evaluate the central contribution, the estimate of the long time constant can be critical. This suggests using Robinson's model in these conditions, since it allows estimating both model time constants.

The rVOR response called "plateau response" is the response that strictly requires the use of a two time constants model, since it cannot be approximated by a single exponential. In modeling terms it is the most important kind of response since it allows to infer the processing underlying the reflex. The model differences for fitting plateau responses can be summarized as follows:

1b) Cohen's model fits a plateau response when the ratio between the direct and indirect gain (R^C) is larger then the inverse of the SCC time constant (without dependence upon the VSM time constant). In order to fit a plateau response Robinson's model imposes an upper bound, related to the SCC time constant ($\beta^R\tau^R_C/(1-\beta^R)$), to the longest time constant. The parameter β^R has also a major role in determining the time of the peak eye velocity.

2b) The decay after the peak can be written as a function of τ^C_C-τ^C_{VSM} in Cohen's model, allowing their estimate. The same function in Robinson's model involves all the parameters except g^R_0 and allows to estimate τ^R_C but not τ^R_L. As for condition 2a, the derived value $\tau^R_L/(1-\beta^R)$ is the only one that can be estimated.

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