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Saccadic and smooth pursuit eye movements: Computational modeling of a common inhibitory mechanism in brainstem

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ABSTRACT

The oculomotor system coordinates different types of eye movements in order to orient the visual axis, including saccade and smooth pursuit,. It was traditionally thought that the premotor pathways for these different eye movements are largely separate. In particular, a group of midline cells in the pons called omnipause neurons were considered to be part of only the saccadic system. Recent experimental findings have shown activity modulation of these brainstem premotor neurons during both kinds of eye movements. In this study, we propose a new computational model of the brainstem circuitry underlying the generation of saccades and smooth pursuit eye movements. Similar models have been developed earlier, but mainly looking at pure saccades. Here, we integrated recent neurophysiological findings on omnipause neuron activity during smooth pursuit. Our computational model can mimic some new experimental findings as the similarity of "eye velocity profile" with "omnipause neuron pattern of activity" in pursuit movement. We showed that pursuit neuron activity is augmented during catch-up saccades; this increment depends on the initial pursuit velocity in catch-up saccade onset. We conclude that saccadic and pursuit components of catch-up saccades are added to each other nonlinearly.

Primates use saccadic and pursuit eye movements to keep the image of objects on the fovea. Saccades are discrete movements that turn eyes quickly to the target. Since their velocity is high, visual feedback is not used to guide eye movements. Smooth pursuit movement is a continuous movement which smoothly tracks the moving object.

Reticular formation cells are the final common pathway in oculomotor control. The reticular formation contains a number of saccade-related areas, providing direct input to the oculomotor neurons which have a "burst-tonic" discharge pattern. The tonic neurons (TN) provide tonic activity [6], while burst neurons emit a high-frequency burst of action potentials before the beginning of saccades. Burst neurons are grouped into two different categories: long-lead burst neurons (LLBNs) and medium-lead burst neurons (MLBNs). A group of excitatory MLBNs named excitatory burst neurons (EBNs), emit high-frequency action potentials that determines the dynamics of saccadic eye movements. During periods of fixation, EBNs are kept under the constant inhibition of omnipause neurons (OPNs) in stem cell. OPNs fire at a constant rate during fixation periods and stop firing (or pause) before and during all saccades, irrespective of their amplitude or direction [12].

Traditionally pursuit has been viewed to be driven by motion signals and mediated by pathways connecting visual areas in the cerebral cortex to the motor regions of cerebellum [10]. Recent findings, however, show that this view needs to be reconsidered. Pursuit includes an extended network of cortical areas and, of these, the pursuit-related region in the frontal eye fields seems to exert the most direct effect [11]. Recently, some pathways including basal ganglia, the superior colliculus, and reticular formation nuclei are identified to be involved in pursuit; these routes were previously thought to be associated only with saccade control [4,11,12]. It has been experimentally revealed that some brain stem neurons are involved in both saccade and pursuit movements. Among them, OPNs are the most important ones. OPNs, the inhibitory effects of which were determined earlier on saccade generation, may also be involved in gating pursuit. OPNs regulate pursuit gain through their inhibitory effect on pursuit neurons (PN) in the vestibular and prepositus nuclei, analogous to the way that they are believed to gate the occurrence of saccades through inhibitory effects on EBNs. However, the exact circuit is not yet known.

In this paper, we propose a new computational model that couples saccade and pursuit systems at the level of omnipause neurons

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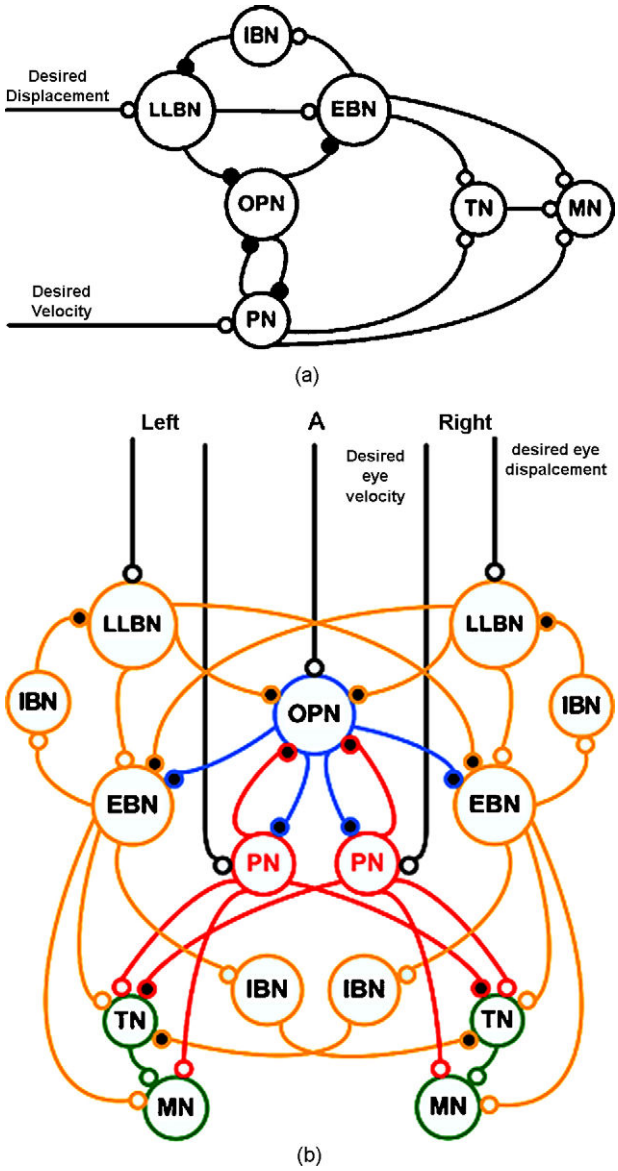

Fig. 1. Our proposed model for saccadic and smooth pursuit movements in final premotor pathways at the level of brain stem, in order to control (a) an extraocular muscle, (b) an antagonist pair of muscles in saccadic and smooth pursuit eye movements. Small white and black circles correspond to excitatory and inhibitory connections, respectively. MN: motor neuron.

through hypothetical reciprocal inhibitory connections between PNs and OPNs. Our model has the ability to show the properties of both movements as well as the role of OPN as an inhibitory mechanism and predicts the behavior of PNs. We propose new ideas for saccadic and pursuit components of "catch-up saccades" (i.e., performing saccadic movement during a pursuit, whenever it is unable to reach the target).We will also investigate whether these two components of catch-up saccades are linear or not.

A compartment of our model that controls an extraocular muscle is depicted in Fig. 1a. We have used the previous saccade generator (SG) model proposed by Grossberg in [5] that is one of the most complete models [6]. We extended this model so that it can account for both pursuit and saccade eye movements and is consistent with most known anatomical connections [13]. Inputs to the model are "desired displacement" and "desired velocity" of the eye that are used in saccadic and pursuit systems, respectively.

In this model, OPN is active due to the arousal input (A) from higher brain centers like superior colliculus, provided that no saccadic and pursuit inputs are applied [3]. OPN has inhibitory effects on EBN and PN. When a desired displacement is applied to the model, LLBN will be activated and consequently will stop OPN [15]. The LLBN excites the corresponding EBN [5]. The EBN excites TN and IBN. The IBN is excited through EBN and has an inhibitory connection to LLBN that closes a feedback loop between LLBN, EBN, and IBN. TN integrates EBN activity [5] and applies it to the motor neuron.

EBN is directly connected to the motor neuron to generate fast saccadic movements. At the end of saccade, IBN will stop LLBN activity. When a desired velocity is applied to the model, the activity of PN increases. As OPN and PN are connected through reciprocal inhibitory connections, their activity is regulated with each other; hence, by activation of PN, OPN activity decreases but never stops. In this case, OPN and PN form a feedback loop in which OPN activity can change the gain of feedback pathway. TN integrates PN activity and applies it to the motor neuron.

Fig. 1b depicts the proposed model of final premotor pathway in the level of brain stem to control an antagonist pair of muscles in saccadic and smooth pursuit eye movements.

Each neuron in the model is described with a differential equation based on the conductance model of membrane [7]. Since no experimental recording of PN exists, we proposed a hypothetical equation for it. The total model results show compatibility with experimental data in [12].

Eqs. (2), (3), (4), (5), (6), (7), and (10) are adopted from [5], but Eq. (10) is modified in order to obtain better performance in both movements. We proposed Eqs. (8) and (9) to describe PN activity. Finally, the transfer functions of motor neurons and the eye plant (Eqs. (11)–(13)), are adopted from [1], with changed time scales.

r, l, and *h are* suffixes referring to right side, left side, and horizontal plane of the model, respectively.

LLBN (indexed by L in equations) is a part of SG that has an inhibitory input from IBN (B) and an excitatory saccadic input (SI). SI is the desired eye displacement. LLBNs are leaky integrator neurons with a passive decay rate of 1.3.

$$\frac{dL_l}{dt} = -1.3L_l + \mathrm{SI}_l - 2B_l \tag{2}$$

and

$$\frac{dL_r}{dt} = -1.3L_r + \mathrm{SI}_r - 2B_r \tag{3}$$

EBNs (E) receive excitatory inputs from the ipsilateral LLBNs and are inhibited by contralateral LLBNs and OPN (P). We have:

$$\frac{dE_l}{dt} = -3.5E_l + (2 - E_l)(5L_l + 1) - (E_l + 1)(10L_r + 20g(P)) \tag{4}$$

and

$$\frac{dE_r}{dt} = -3.5E_r + (2 - E_r)(5L_r + 1) - (E_r + 1)(10L_l + 20g(P)) \tag{5}$$

IBNs (B) are excited by ipsilateral EBNs and are leaky integrators with a passive decay rate of 2.4:

$$\frac{dB_l}{dt} = -2.4B_l + 3E_l \tag{6}$$

and

$$\frac{dB_r}{dt} = -2.4B_r + 3E_r \tag{7}$$

PNs (PN) have reciprocal inhibitory connections with OPN (P) and are excited by the pursuit input (PI) which is the desired eye

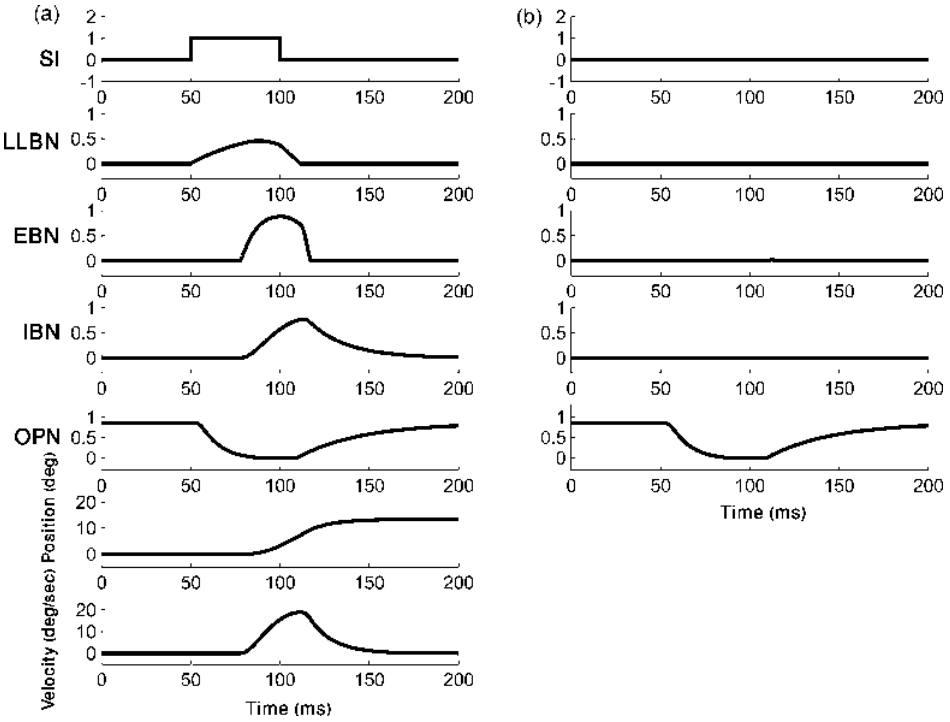

Fig. 2. Activity profiles of the left (a) and right (b) side of the model in response to setting the left saccadic input to 1, between 50 and 100 ms.

velocity. Hence:

$$\frac{d\mathrm{PN}_r}{dt} = -3.5\mathrm{PN}_r + \mathrm{PI}_r - 5P \times \mathrm{PN}_r \tag{8}$$

and

$$\frac{d\mathrm{PN}_l}{dt} = -3.5\mathrm{PN}_l + \mathrm{PI}_l - 5P \times \mathrm{PN}_l \tag{9}$$

OPNs (P) are initially active, unless inhibited by LLBN or PN. They have inhibitory inputs from all LLBNs and ipsilateral PN and are excited with an external excitatory electrical stimulation (J). $g()$ is a sigmoid function and is tuned so that a single active inhibitory $g()$ term from LLBNs can stop OPN activity:

$$\frac{dP}{dt} = -0.2P + (1-P)(1.2+J) - 3.5(P+0.4)(g(L_l + g(L_r)) - P(\mathrm{PN}_l + \mathrm{PN}_r) \tag{10}$$

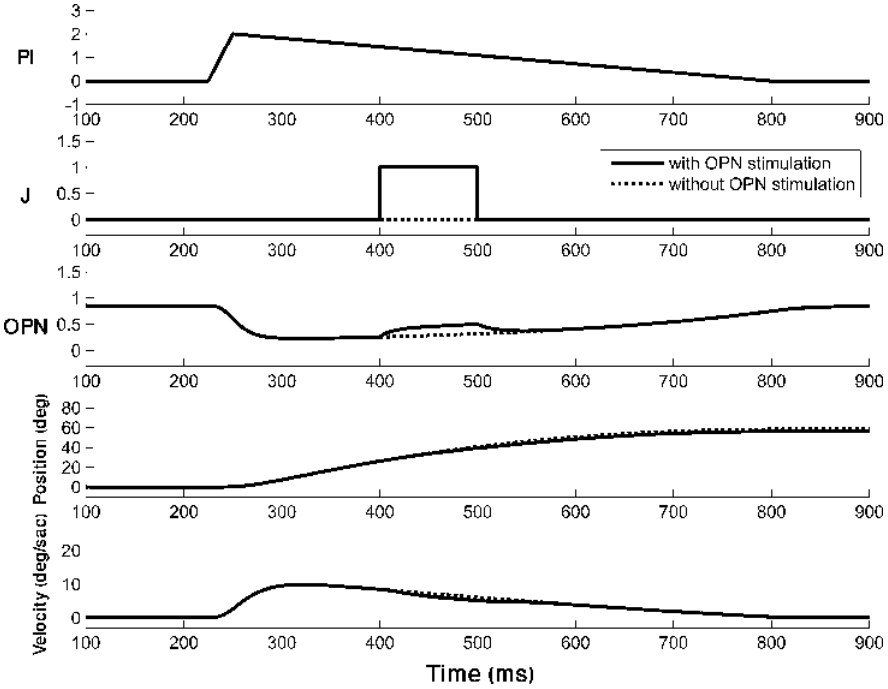

Fig. 3. Simulation of OPN activity along with eye velocity profile in response to the triangular desired eye velocity (PI) and pulsed J stimulation in horizontal plane. Thick and dotted lines show results in the presence and absence of OPN stimulation, respectively. Pursuit input (PI) is applied in both cases.

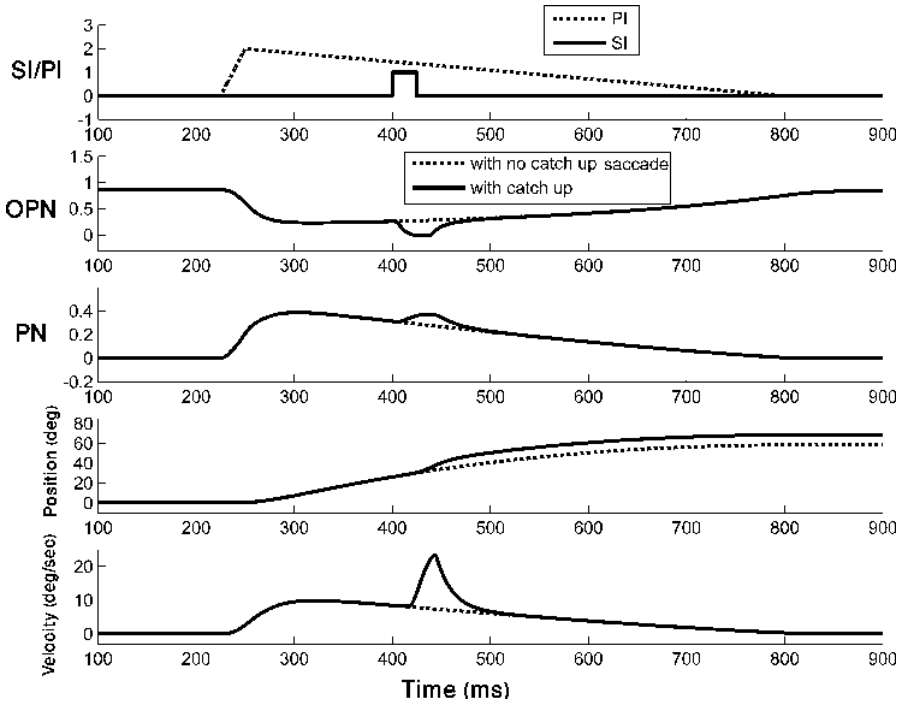

Fig. 4. Simulation of model activities with a forward catch-up saccade during pursuit in horizontal plane. Saccadic Input (SI) is set to 1 in the interval of 400–425 ms and pursuit input (PI) is the desired eye velocity. Continuous and dotted lines correspond to catch-up saccade and pure pursuit movement, respectively.

Tonic and motor neurons of the horizontal plane, which provide the pulse-step motor commands for eye plant dynamics [1], are described as:

$$H_h(s) = \frac{M_{ch}(s)}{V_{dh}(s)} = K\left(T_1 + \frac{1}{s}\right) \tag{11}$$

$$V_{dh} = (\mathrm{PN}_r - \mathrm{PN}_l) + (E_r - B_L) \tag{12}$$

where $T_1 = 3.5$ and $K = 26$ are compatible with the results of [5]. V_{dh} is the desired eye velocity in horizontal plane and M_{ch} is the horizontal motor command fed to the eye.

Horizontal eye plant is described with a transfer function that has two poles and acts as a low-pass filter [1]:

$$H_{\mathrm{eye}h}(s) = \frac{1}{(T_1T_2)s^2 + (T_1 + T_2)s + 1} \tag{13}$$

where $T_1 = 3.5$ and $T_2 = 0.26$. The input is the horizontal motor command (M_{ch}) and the output is the horizontal eye position in degrees.

The sigmoid function that maps the x between 0 and 1 is:

$$g(x) = \frac{x^4}{0.1^4 + x^4} \tag{14}$$

In this function, the power 4 controls the sharpness of the sigmoid and the parameter 0.1 determines the value of x at which the function $g(x)$ equals 0.5 [5].

Simulations were done with Simulink package in Matlab, using ode4 (4th order Runge-Kutta) solver and fixed step-size of 1 ms. Each simulation time unit is 50 ms in real world. Model parameters are optimized based on least mean square (LMS) algorithm to be compatible with experimental results.

Activity profiles of the model during a typical saccade are depicted in Fig. 2. The LLBNs in the model show a prelude of activity. The EBN burst begins after the onset of LLBN activity. The antagonist EBN produces a small burst at the end of a saccade. This antagonistic rebound may function as a braking pulse to decelerate the eye at the end of a saccade. As found experimentally, the OPN stops firing during a saccade [5].

It is shown experimentally that OPN activity pattern during smooth pursuit is similar to eye movement velocity [12]. Fig. 3 (dotted lines) shows the activity of OPN and eye velocity in response to desired eye velocity input (PI). Triangular input is applied at 225 ms. It has a positive slope and reaches to 2 at 250 ms and then decreases by a negative slope to 0 at 800 ms. It is obvious that in pursuit movement, the profiles of desired eye velocity (input of the model) and the modeled eye velocity (output of the model) are similar; however, the OPN pattern of activity is the mirror image of this profile.

To stimulate OPN, we use an excitatory input J that excites all OPNs. Fig. 3 shows activity simulation of OPN and eye velocity profile in response to the triangular desired eye velocity (PI) and pulse stimulation of J in horizontal plane. J is set to 1 in the interval of 400–500 ms. Eye movement velocity is decreased during OPN stimulation.

Now we evaluate the model when both movements are done concurrently or one movement switches to another. This occurs when during tracking a target, pursuit cannot reach it; so a catch-up saccade is performed to decrease visual error. Catch-up saccades are typically preceded and followed by pursuit movements. When catch-up saccade direction is the same as pursuit, it is defined as forward saccade, whereas when the direction is opposite, it is called reverse saccade. Saccades which start with stationary state are called control saccades.

To simulate forward catch-up saccades, we added pulsed SI to the pursuit movement of previous sections (Fig. 4).

Then, we investigated the effect of mean pursuit velocity and saccadic input amplitude variations on PN activity during catch-up saccades. We applied the previous pursuit and saccadic inputs. Saccadic inputs were applied in different pursuit velocities to the left side of the model in order to generate forward catch-up saccades. For each initial pursuit velocity, different SI amplitudes were examined. Each saccadic input duration was 25 ms. We compared the activity of PN in saccade containing cases, with saccade-less

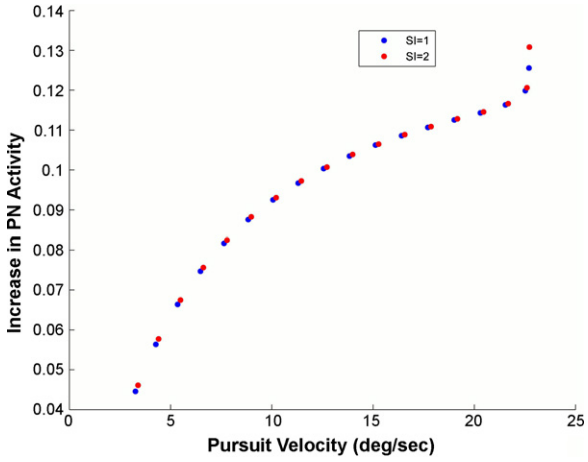

Fig. 5. The effect of different saccadic input amplitudes on PN activity for different mean pursuit velocities.

ones and plotted the increased activity of saccade containing cases against the mean pursuit velocity (Fig. 5).

In this paper, we propose a new model of the brainstem underlying the generation of saccades and smooth pursuit movements.

In our model, when the pursuit movement is being performed, OPN pattern of activity is similar to the eye velocity (see Fig. 3) which is similar to physiological evidences[12]. In addition, OPN and PN neurons of the model become synchronized as a result of their reciprocal inhibitory connection. This finding can encourage experimental studies on PN.

Some researchers [9] showed that electrical micro-stimulation on OPN during saccadic movement slows or stops the movement. Missal and Keller [12] studied this effect on pursuit movement and showed that OPN stimulation decreases eye movement.

Similar to [5], our simulation (Fig. 3) indicates that although OPN stimulation in both saccade and pursuit decreases eye velocity, they have some key differences. OPN stimulation during saccade stops or slows movement; however, in pursuit, it decreases pursuit eye movement but mostly never stops it. Our results are in accordance with the experimental study of Missal and Keller, in which, electrical stimulation decelerated the pursuit movement in both directions [12]. In our study, OPN electrical stimulation causes a decrement, although lower than [12].

Since OPN activity stops during saccades and reaches its maximum in resting, it may be considered as a gate for saccades. Moreover, as a result of reciprocal inhibitory mechanism between OPN and PN in pursuit, OPN also acts as a gain controller.

Missal and Keller [12] studied OPN during horizontal pursuit and catch-up saccades. During catch-up saccades, mean spike density of OPN decreases to zero, which is similar to our simulation (Fig. 4).

In Fig. 6, v_d^* is the sum of activity of ipsilateral PN and EBN, minus the activity of contralateral IBN. This figure shows that v_d^* has a similar profile to the eye velocity, but has a trivial difference with it, as a result of low-pass filtering effect of motor neuron and eye plant models. Thus, we can claim that catch-up saccades are composed of saccadic and pursuit components which are generated by EBN and PN, respectively. However, the manner in which these two components interact is controversial.

It had never been clearly demonstrated whether smooth pursuit motor commands are stopped during catch-up saccades. An early study by Jurgens and Becker [8] showed that there is a nonlinear summation of saccadic and pursuit eye movements. However, some newer studies [14] supposed a linear summation between them. Brouwer et al. [2] found out that there is a continuous superposition between saccadic and pursuit commands. They compared forward and reverse catch-up saccades with control ones. In their study, when these three kinds of saccades had the same duration, reverse saccades had lower velocity and amplitude than control

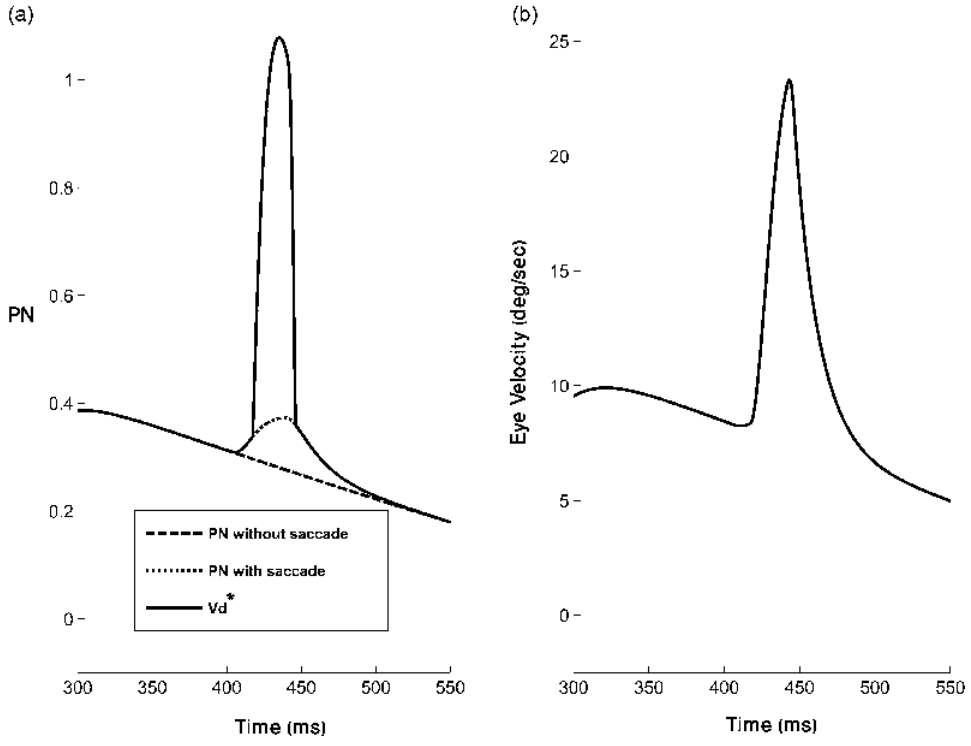

Fig. 6. (a) v_d^*: the sum of pursuit and saccadic commands before entering the TN. (b) Eye velocity simulation during a forward catch-up saccade (the lowest panel of Fig. 4 in large scale). Note the similarity between the shape of velocity profile and the shape of v_d^*.

saccades, whereas forward saccades had higher velocity and amplitude. Hence, they concluded that it is necessary to consider the pursuit component in catch-up saccades, i.e., subtract it in reverse saccades and add it in forward ones. Brouwer et al. [2] subtract a mean pursuit velocity (V_{PURS}) from peak velocity (V_{MAX}) of catch-up saccade to determine corrected peak velocity (V^*_{MAX}):

$$V^*_{MAX} = V_{MAX} - V_{PURS} \quad (15)$$

where $V_{PURS} = (V_P + V_N)/2$, V_P is eye velocity over the interval of 25 to 75 ms before saccade onset, and V_N is eye velocity during 25–75 ms after saccade offset.

In fact, these calculations are done with the assumption that during catch-up saccades, pursuit component of eye velocity could not be affected by catch-up saccades.

A major difference between our simulation and previous ones is that based on our model, as a result of inhibitory mechanism between PNs and OPNs, by stopping OPNs activity during catch-up saccades, PN activity and consequently pursuit component of eye movement increases (the dotted line in Fig. 6a). We have studied the effect of changes in saccadic input amplitude along with the initial pursuit velocity before catch-up saccade on PN activity variation (see Fig. 5). Our results suggest that PN activity was not affected by the strength of saccadic input but was influenced by initial pursuit eye velocity before catch-up saccade onset. Therefore, there is a nonlinear component that varies by changes in initial pursuit velocity before the onset of catch-up saccade; i.e., it increases by increasing initial pursuit velocity. In forward catch-up saccades, this nonlinear component is added to the peak eye velocity (V_{MAX}) while in reverse saccade, it is subtracted from it. Hence, a nonlinear summation of saccadic and pursuit components occurs.

In this paper, we proposed a new model that couples saccade and pursuit systems at the level of omnipause neurons. We suggest that PNs might have reciprocal inhibitory connections with OPNs, and their activity will increase during catch-up saccades. The amount of this increment depends on the amplitude of pursuit eye velocity in catch-up saccade onset. In addition, in catch-up saccades, as a result of interaction of saccadic and pursuit components, both of them change nonlinearly.

Similar modeling could be a guide for predicting future experimental studies. For example, our research suggests that it is worthy to record the activity of PN during pursuit and catch-up saccades. This recording will be a proper tool to validate our hypothesis about the behavior of PNs. Also, it would help to understand the pathophysiology of some vision disorders as ocular dyskinesia of Parkinson's disease.

References

[1] G. Blohm, L.M. Optican, P. Lef'ever, A model that integrates eye velocity commands to keep track of smooth eye displacements, J. Comput. Neurosci. 21 (1) (2006) 51–70.
[2] S. Brouwer, M. Missal, G. Barnes, P. Lef'ever, Quantitative analysis of catch-up saccades during sustained pursuit, J. Neurophysiol. 87 (2002) 1772–1780.
[3] J.A. Buttner-Ennever, A.K. Horn, V. Henn, B. Cohen, Projections from the superior colliculus motor map to omnipause neurons in monkey, J. Comp. Neurol. 413 (1) (1999) 55–67.
[4] C.J. Erkelens, Coordination of smooth pursuit and saccades, Vision Res. 46 (2006) 163–170.
[5] G. Gancarz, S. Grossberg, A neural model of the saccade generator in the reticular formation, Neural Netw. (1998) 1159–1174.
[6] B. Girard, A. Berthoz, From brainstem to cortex: computational models of the saccade generation circuitry, Prog. Neurobiol. 77 (4) (2005) 125–251.
[7] S. Grossberg, Studies of Mind and Brain, Kluwer/Reidel, Amsterdam, 1982.
[8] R. Jurgens, W. Becker, Is there a linear addition of saccades and pursuit movements? in: G. Lennerstrand, P. Bach-y-Rita (Eds.), Basic Mechanisms of Ocular Motility and Their Clinical Implications, Pergamon, Oxford, UK, 1974, pp. 525–529.
[9] E.L. Keller, Control of saccadic eye movements by midline brainstem neurons, in: R. Baker, A. Berthoz (Eds.), Control of Gaze by Brainstem Neurons, Elsevier, New York, 1977, pp. 327–336.
[10] E.L. Keller, S.J. Heinen, Generation of smooth-pursuit eye movements: neuronal mechanisms and pathways Neurosci. Res. 11 (1991) 79–107.
[11] R.J. Krauzlis, Recasting the smooth pursuit eye movement system, J. Neurophysiol. 91 (2004) 591–603.
[12] M. Missal, E.L. Keller, Common inhibitory mechanism for saccades and smooth-pursuit eye movements, J. Neurophysiol. 88 (2002) 1880–1892.
[13] C. Scudder, C. Kaneko, A. Fuchs, The brainstem burst generator for saccadic eye movements. A modern synthesis, Exp. Brain Res. 142 (2002) 439–462.
[14] J. Smeets, H. Bekkering, Prediction of saccadic amplitude during smooth pursuit eye movements, Hum. Move. Sci. 19 (2000) 275–295.
[15] K. Yoshida, Y. Iwamoto, S. Chimoto, H. Shimazu, Saccade-related inhibitory input to pontine omnipause neurons: an intracellular study in alert cats, J. Neurophysiol. 82 (1999) 1198–1208.