A BILATERAL MODEL FOR COORDINATED CONJUGATE AND VERGENCE EYE MOVEMENTS

by

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Abstract

Traditionally, the Oculomotor Control System (OCS) has been considered as composed of several independent subsystems acting in parallel, where each dedicated subsystem controls a particular type of conjugate or disjunctive eye movement. Previous mathematical models built upon this assumption have mainly focused on input-output relationships, being difficult to relate to anatomy. This fact may limit the application of such models in the clinical environment A new integrated approach for the modelling of the OCS is proposed, compatible with both known anatomy and physiology. This study presents a single, bilateral model capable of predicting the general characteristics (dynamics) of vergence and the vestibulo-ocular reflex (VOR) during slow phase eye movements. The present study is motivated by growing evidence of interactions between conjugate and vergence premotor activities.

The model relies on the sharing of neural signals among several premotor structures located on both sides of the brainstem A new possible role for the superior colliculi in the control of slow phase and vergence eye movements is suggested The proposed model incorporates the presence of near response cells located in the midbrain including modulation of their discharge rate with vergence angle The bilateral model proposes a distributed vergence integrator whose slow discharge accounts for the vergence relaxation pattern found after binocular occlusion. The model reproduces very recent physiological data concerning the activity profiles of abducens interneurons and extraocular motoneurons during vergence responses and can provide tentative explanations for changes in VN modulation during VOR responses at different vergence levels. Additional extensions of the model can easily include burst cell populations for the simulation of fast vergence responses, and their interaction with conjugate saccades or vestibular quick phases.

Résumé

Par convention, le système de contrôle oculomoteur (OCS) a été representé par plusieurs sous-systèmes indépendants agissant en parallel, où chaque système est dédié au contrôle d'un certain type de mouvements conjugués ou de vergence. Les modèles mathématiques basés sur cette préconception se sont concentrés sur des relations globales reliant les entrées aux sorties, sans faire le lien à l'anatomie. Ce fait réduit leur utilité dans les environnements cliniques. Une nouvelle conception intégrée pour le modelling du OCS est proposée ici, qui est compatible avec et l'anatomie, et la physiologie du système Cette étude présente un seul modèle bilatéral et intégré, capable de prédire les caractéristiques générales (dynamique) de la vergence et du réflexe vestibulo-oculaire (VOR) pendant les réponses lentes de ce système. L'étude présentee ici est motivée par le nombre croissant d'observations démontrant de fortes interactions entre la vergence et la version dans les activitées prémoteures du CNS.

Notre modèle se base sur le partage des signaux nerveux entre plusieurs structures neurales situées sur les deux côtes du tronc cérébral. Un nouveau rôle est postulé pour le collicule supérieur (SC) dans le contrôle des mouvements lents des yeux en vergence ou en version Le modèle proposé inclu la présence de cellules nommées "near-response" dans le mésencephalon qui modulent leur décharge avec l'angle de vergence Le modèle bilatéral propose une structure distribuée pour l'intégrateur de vergence, dont la décharge lente aprés occlusion binoculaire cause la perte graduelle de l'angle de vergence. Le modèle reproduit des données très récentes sur les décharges des motoneurones extraoculaires et des interneurons du noyau abducens pendant les changements d'activité au niveau du noyau vestibulaire pendant des réponses VOR à différents niveaux de vergence. Des extensions du modèle pourraient facilement inclure les populations de cellules "burst" associées aux saccades, pour la simulation de la vergence rapide et son interaction avec les saccades conjugées, ou phases rapides du VOR.

Claims to Originality

1. The proposed model constitutes the first bilateral model for the unified, simultaneous control of conjugate and vergence ocular responses.
2. The model of this thesis is the first bilateral model for vergence control developed fully on physiological and anatomical grounds
3. The model [illegible] selective changes in the functional activity of shared pathways [illegible] nt dynamics in a single, bilateral structure. As a result, [illegible] conjugate integrators are distributed entities within the model [illegible] localized structures as previously suggested.
4. The model postulates a new role for the superior colliculus in the control of slow eye movements. The colliculus acts as a proportional derivative controller within a neural element feedback loop. The model representation of collicular activity is consistent with neurophysiological and lesion studies
5. The bilateral, symmetric structure of the model makes it possible to reproduce recently observed characteristics in the discharge of premotor and motor centers in response to visual and vestibular stimuli. the proposed model appropriately simulates the firing rate of vergence cells, abducens and oculomotor motoneurons, abducens internuclear neurons and vestibular nuclei cells.
6. The model structure makes it possible to evaluate the influences of sensory and/or neural imbalances at different premotor and motor levels, as well as examine the resulting asymmetric ocular responses.

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I. INTRODUCTION

I.1 General considerations

Living creatures, in their struggle for survival, have developed a series of intricate and complex physiological systems to enable them to get food, find shelter and avoid danger. No sensory system is more versatile than vision in helping to achieve such objectives. Consequently it is not surprising to find that vision is among the first sensory systems to develop among vertebrates and invertebrates. Species with vision systems built around two eyes have a significant evolutionary advantage over those having monocular (one single eye) systems. Portions of the visual field sensed by each eye superimpose, making it possible to obtain more detailed information concerning the visual scene by comparing image differences in the two eyes. Vision using two eyes, or binocular vision, is essential for depth perception (stereopsis) and the accurate identification of targets in three dimensional space.

Among the tasks necessary for survival, one of the most relevant is the coordination of the eyes and the body in order to achieve free and stable movement in space. In particular, the concordant interaction between the position of the eyes relative to the head, and the position of the head on the body is a very important issue usually forgotten in our daily lives.

In order to achieve a stable and clear vision, it is necessary to count on a system capable of making fast and accurate corrections in eye position and velocity. The oculomotor control system (OCS) is the neural system in charge of making such adjustments. The OCS monitors and corrects eye position in the head, taking into account the relative orientation of the head on the body and the body in space. The objective of this control action is to orient gaze towards spatial targets or, when necessary, maintain a desired gaze in space. In this context, gaze is the position of the line of sight in space.

It can be defined as the sum of eye position relative to the head and head position relative to space.

It is easy to understand that in real world conditions, the achievement of stable vision has capital importance. Stable vision constitutes a platform to enable proper performance of higher level visual processes, such as color detection and form recognition. Scientists, aware of this importance, have dedicated numerous efforts during the last years to the study of the OCS. Implications of a better knowledge of OCS organization and function have been widely recognized. In medicine, oculomotor control research can help assess the guiding principles of central nervous system (CNS) action. It can also provide useful information for the development of non invasive diagnostic tools for the detection of pathologies involving the CNS. In the areas of robotics and artificial vision, oculomotor control research can help in the construction of efficient and accurate artificial gaze orienting and gaze holding systems. Such systems provide basic functionalities required to obtain an effective artificial attentive vision. By minimizing motion induced blur and ensuring fixation, gaze holding systems can simplify computations and facilitate visual interpretation (Coombs and Brown, 1991).

As an advantage in its study, the OCS exhibits a relative simplicity compared to other physiological systems, such as body postural control. Nevertheless, this simplicity does not make the OCS behave in a trivial manner. On the contrary, it possesses a diversity of responses that make it a specially suitable framework for deducing the control strategies followed by the CNS. Among the reasons justifying the relative simplicity of the OCS, we can mention:

Single joint system

Different from limb control, the OCS behaves as a single joint system. The OCS controls ocular movements in three angular and three linear coordinates. Since linear translation of the eyeball in the orbit is not significant, the coordinate system of eye movements is usually expressed in terms of horizontal, vertical and torsional angles referred to the head (Torsion is the rotation angle described around the line of sight).

Absence of cocontraction

In peripheral motor control cocontraction is used to minimize the unwanted influence of disturbance torques on the joint. Cocontraction consists on the simultaneous activation of agonist and antagonist muscles with the objective of making a joint stiffer. An agonist muscle acts in favor of the movement, while the antagonist opposes to the movement. In the OCS, however, the muscle activation pattern is simpler, never actively causing cocontraction (Galiana, 1990). Cocontraction of extraocular muscles produces linear translation of the globe into the orbit, an effect considered unimportant. Normally, an increase in tension in an agonist muscle is paired to a decrease in tension in the antagonist.

No stretch reflexes

Again, in peripheral control there is a continuous gradation of muscle activation by means of neural feedback signals arising in muscle spindles and tendon organs. This modulation process, known as the stretch reflex is not used in the control of eye movements, even though muscle tendon organs and spindles are found in eye muscles. Several studies have shown the existence of projections from proprioceptors in eye muscles to premotor areas in the brainstem (Ashton et al.; 1984, 1988), but nonetheless proprioceptive feedback seems not to have a detectable short term influence on oculomotor responses (Keller and Robinson, 1971; Daunicht and Dieringer, 1986). Apparently, peripheral feedback in the OCS is used mainly during motor learning or adaptation processes in order to fine tune control parameters.

Accessibility of the control centers for study.

The centers known to control ocular movements are located in the brainstem or higher in the cranial cavity. This fact enables researchers to perform experiments in unanesthetized animals with relative ease, recording patterns of neuronal activity during behavioral experiments following the surgical implantation of microelectrodes at premotor and motor sites.

I.2 Types of eye movements

Eye movements are elicited by a variety of stimuli, both sensory and cognitive. Sensory stimuli can be vestibular in nature, such as body rotation in the dark, or visual, such as the movement of a textured surface across the visual field or the displacement of a target of interest. Cognitively driven eye movements are elicited, for instance, when the subject imagines the presence of a target in the dark and moves the eyes in the appropriate direction. Cognitive stimuli have been proven to noticeably affect ocular responses to sensory stimuli (Barnes, 1988; Howard et al., 1989).

Ocular movements typically consist of patterns of fast and slow phases. As seen in Figure I.1 the eye movement record resembles a zig-zag (sawtooth like) succession of segments. This pattern is known as ***ocular nystagmus***. Ocular nystagmus was initially examined in the light of qualitative behavioral considerations. According to this trend, the segments of longer duration and less velocity were named slow phases. The segments characterized by higher average velocities and shorter durations were named fast phases. It is believed that fast phases serve to reduce the position error between the ocular response and the stimulus. Slow phases reduce the velocity error between the stimulus and the eye. Both slow and fast phases reflect the existence of changes in the functional activity of OCS elements. This functional modulation is partly due to the existence of mechanical and neural limits on the ocular response The OCS can not sustain extended angular deviations without resetting eye position in the orbit, a task which is accomplished by fast phases of nystagmus. It is important to mention that nystagmus has been recently shown to help overcome the restrictions in eye movement imposed by neural limits, extending the linear range of a particular kind of ocular response (Galiana,1991).

In general terms, three kinds of nystagmic responses have been described so far, receiving the names of vestibulo-ocular, pursuit and optokinetic nystagmus. Vestibulo-ocular and optokinetic nystagmus are considered to be reflex responses with the objective of stabilizing vision. Pursuit nystagmus is assumed to be an active response in order to track objects appearing in the visual field. Fast phases of pursuit nystagmus are called ***saccades*** while fast phases of vestibulo-ocular nystagmus are named ***quick phases***. Another kind of volitional ocular response, vergence eye movements, have

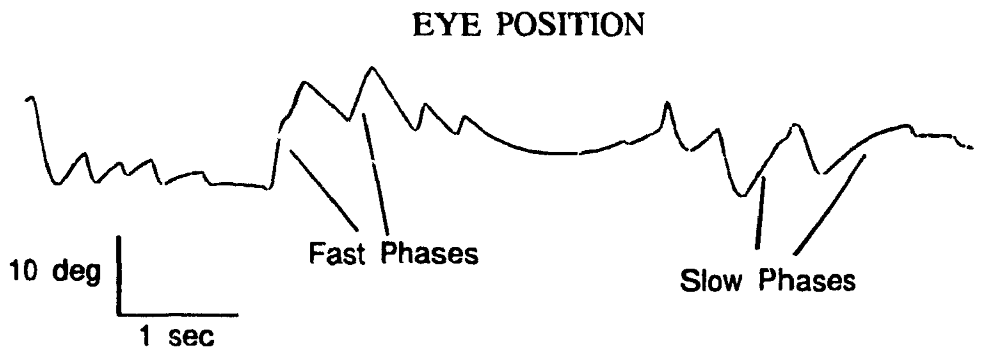

Figure I.1: Record showing the principal qualitative characteristics of eye movements.

been shown to contain both slow and fast velocity segments as well (Semmlow et al., 1986; Mays, pers. comm. 1992; Zee et al., 1992).

In particular, five main types of eye movements have been the subject of detailed attention by researchers:

1. VESTIBULO-OCULAR REFLEX: When the head/body is rotated as a unit, the eyes move in the direction opposite to the rotation. Such a compensatory reflexive movement stabilizes the line of sight in space. This kind of ocular movement is called the vestibulo-ocular reflex (VOR) since the sensors producing the afferent signals needed for accomplishing the movement are located in the inner ear, specifically in the vestibular apparatus. The velocity of slow phase segments of the vestibulo-ocular reflex is opposed (out of phase) to head velocity. Quick phases of nystagmus redirect the eyes in the direction of head/body rotation, resetting eye position. The vestibulo-ocular response can be modified according to the particular characteristics of visual stimuli presented to the subject, so that the reflex can be either suppressed or enhanced (Schultheis and Robinson, 1981; Barnes, 1988). The VOR can also be affected by variations in the state of alertness and attention. It is influenced by cognitive stimuli as well, such as imagining the presence of a target in space (Barr et al.,

1976; Howard et al., 1989). VOR experiments are usually performed in the dark, rotating the subject on a motorized chair.

2. SACCADES: Fast phases of pursuit nystagmus, better known as saccades, are used to direct gaze toward rapidly moving objects The goal of this kind of ocular movement is to quickly correct eye position, aligning the target of interest with the fovea, the retinal area of highest visual sensibility. Saccades are not only voluntarily produced, but they also are generated spontaneously, 2 to 3 times per second. Since they have an orienting function, saccades are tightly coupled with free head movements. Saccades can have overall angular displacements between 3 min arc and 90 deg, reaching velocities as high as 700 deg/s in primates. Between stimulus onset and the generation of the saccadic response there is a dead time, also known as latency. Saccade latency is variable, with average times between 200 and 250 ms. However, latency is significantly reduced in express saccades reaching values of only 70 to 80 ms, when target selection is done before asking for action (Guitton et al., 1990; Guitton, 1991).

3. OPTOKINETIC RESPONSE: As a complement for the VOR, the optokinetic response (OKR) serves to stabilize the visual scene on the retina The OKR produces slow compensatory movements in the direction of visual image displacement together with fast resetting ocular movements (saccades) in the opposite direction. This alternating sequence of eye responses with different dynamics is known as optokinetic nystagmus (OKN) The slow compensatory phases of OKN are believed to be composed of two major components the "direct" and the "indirect" (or "velocity storage") component (Cohen et al , 1977). The direct component is characterized by an abrupt increase in eye velocity after optokinetic stimulus presentation. In humans, the direct component reaches 90% of stimulus velocities up to 30 deg/s. The direct component is linked to voluntary tracking of the visual stimuli (see smooth pursuit eye movements below) and seldom surpasses 120 deg/s in human subjects. On the other hand, the indirect component is slower and more gradual than the direct component. The slower rise in eye velocity characteristic of the indirect component is thought to be produced by a reflex mechanism. Optokinetic

response experiments are performed with the subject's head stationary, placed at the center of a rotating drum. The drum has a textured surface, usually composed of parallel stripes.

4. SMOOTH PURSUIT: When a target of interest is detected by the subject in its visual field, first a saccadic movement occurs in order to fixate ("foveate") the object. The target is then followed, with slow conjugate eye movements. Smooth pursuit consists of versional eye movements with the head/body stationary, which enable the subject to see a slowly moving target and maintain it on the fovea Angular target velocities which can be properly tracked are usually in the range of 1 to 30 deg/sec. However, tracking velocities up to 100 deg/s have been reported (Meyer et al., 1985). Smooth pursuit is a voluntary movement which requires an appropriate degree of attentiveness and motivation on the part of the subject. This movement is believed to be primarily elicited by target velocity as perceived in the foveal or parafoveal areas. Nevertheless, smooth pursuit is also evoked by sustained errors in target position on the peripheral retina (Kommerell, 1986). After stimulus presentation, there exists a delay in the generation of the pursuit movement, in the range 100 - 150 ms (Robinson, 1965). In the laboratory environment, smooth pursuit is tested asking the subject to follow a small visual target moving over a dark or homogeneous background.

5. VERGENCE: Vergence eye movements are disjunctive displacements of the eyes in opposite directions in order to fuse the image of far or near objects, preventing diplopia or "double vision". When the eyes move towards the nose the movement is called convergence. When they move towards the temporal side (outwards) the movement is called divergence. Vergence movements are, on average, slower and smoother than conjugate eye movements, lasting about 1 second (Hain and Zee, 1989). There is a latency of 130 - 250 ms (Krishnan et al., 1973) in this kind of movements. In the laboratory environment during slow vergence tracking, maximal velocities of approximately 5 deg/sec can be reached over a range of 15 degrees. However, segments of considerably higher velocities have been consistently observed for greater stimulus velocities

(Semmlow et al., 1986). Vergence eye movements are generally assumed to occur in the horizontal plane and are specified by the angle between the lines of sight of each eye. However vergence can also occur in the vertical and frontal planes (Kertesz, 1983; Hain and Zee, 1989). Vertical vergence eye movements are significantly slower than vergence in the horizontal plane, taking up to 8 seconds for completion (Kertesz, 1983). Vergence can be produced by the presence of a diversity of stimuli, including binocular disparity, accommodation (Ciuffreda and Kenyon, 1983) , target proximity (Wick and Currie, 1991a) and other factors such as perspective and target angular size change (Erkelens and Regan, 1986). Binocular disparity and accommodation are considered primary clues to vergence, while the other factors mentioned above constitute high-level or secondary clues to vergence (Cumming and Judge,1986). Binocular disparity arises from the non correspondence of retinal images on the fovea of both eyes when the target moves towards or away from the subject. Vergence eye movements produced by disparity are known as disparity vergence.

The effect of binocular disparity on vergence can be appreciated by means of a common experience. If a weak horizontal prism is suddenly presented in front of one eye of a subject who is binocularly fixating a target, the disparity produced by the shift of the image as a result of the action of the prism makes the eye verge unilaterally. This experience can be extended to both eyes introducing prisms in front of them (at the same time) in order to elicit vergence (Ogle,1967). Accommodation is a binocular response which modifies the curvature of the lens in the refocusing effort to fixate a target. Accommodation induces vergence An experiment carried out by Muller in 1826 constitutes a classical example of this. With one eye occluded and the other fixating a target, if a negative lens is introduced in front of the exposed eye, the other converges. The origin of this movement is the accommodation performed to refocus the target. Accommodation and vergence are related, one interacting with the other. Accommodation produces vergence, as it has been mentioned, and vergence also induces accommodation (Ciuffreda and Kenyon, 1983; Semmlow and Hung, 1983; Wick and Currie, 1991b). The convergence produced by accommodation is called accomodative-convergence while accommodation induced by convergence is called convergence -accommodation.

In general terms, the different eye movements described above can be grouped into two major categories according to the nature of the ocular response. The VOR, saccades, smooth pursuit and optokinetic response are known as ***conjugate*** eye movements, characterized under normal circumstances by nearly symmetrical deviations of both eyes in a common direction. During conjugate movements the eyes behave like a pair of horses yoked to a sleigh As stated before, ***vergence*** eye movements consist of opposite displacements of the eyes in the convergent or divergent directions in order to fuse the image of objects moving in depth.

I.3 Oculomotor system organization

One interesting aspect to consider while studying the oculomotor system (OCS) is its general structure (see Figure I 2). It has the same basic elements of any control system. There is a plant which must be controlled: the eye plant which is composed of the eye globe and extraocular muscles. There is a set of sensorial devices whose function is to transduce stimuli into nerve impulses and generate the appropriate signals which will be transformed in a way that can be processed by the controller; the central nervous system (CNS). The CNS produces command (motoneural) signals in order to drive the eye plant and cause movements of the eyes according to a particular strategy. When the subject is in the light, elements of the visual scene provide clues to modify the time course of eye movements. Therefore, note the presence of feedback when the stimuli under consideration are visual. In the absence of visual stimuli, such as body/head rotation in the dark, the OCS can be regarded as a cascade of the elements mentioned above.

Consequently, the general structure of the OCS can be described in terms of three major components: the sensors, the central processing stage and the eye plant.

I.3.1 Sensors

The two principal sensory transducers are the retina and the vestibular system. The retina, a complex layer of sensitive tissue located in the inner part of the eyeball, contains specialized cells for the perception of light and colors. It is a truly sensitive extension of the brain, formed by an intricate hierarchy of processing cells ranging from light sensitive cells (cones and rods) up to bipolar, horizontal, amacrine and ganglion

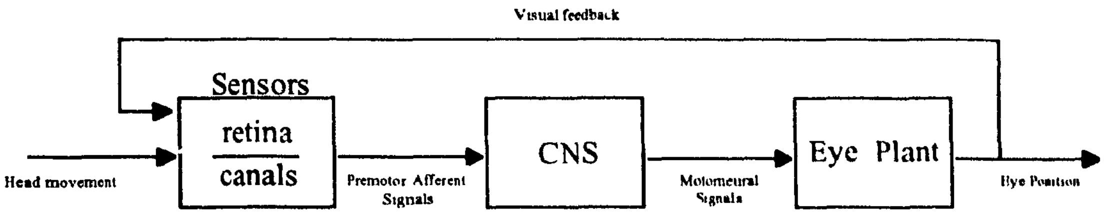

Figure I.2: General structure of the oculomotor control system (OCS)

cells which provide different levels of increased sensory integration. The complexity of the retina is remarkable, so that it has been discovered via immunohistochemical analysis that some of the five classes of sensory cells mentioned above may comprise 15-20 different subtypes (Karten et al., 1990). The final output of the process of sensory integration at the retinal level is found on ganglion cells, whose axons group together to form the optic nerve. There are three major kinds of retinal ganglion cells: on-center cells, off-center cells and on-off cells. On-center cells increase their activity with the increment in the brightness of the stimulus placed in their receptive fields Of-center cells, on the contrary, increase their discharge rate as the stimulus presented in their receptive fields becomes darker. On-off cells are responsive to changes in luminance associated with moving stimuli crossing their receptive fields. The output from ganglion cells conveys the necessary visual information to be handled by the central processing stages in the CNS. Forming an on-off channel system, ganglion cells ensure an expeditious transmission of target position and target velocity information to the CNS. They provide enhanced contrast sensitivity as well (Schiller, 1990)

The vestibular system acts as a transducer for the measurement of linear acceleration and angular rotation of the head. It is composed of very small (around 10 mm across in man) structures located in the labyrinth of the inner ear (see Figure I.3). The vestibular components sensing linear acceleration are the otoliths (utricule and saccule), bowl shaped organs disposed in a roughly orthogonal manner. Both utricule and saccule are filled with endolymph, a liquid similar to the intracellular fluid. Their internal walls are composed of a special hairy epithelium, which in turn, is covered by a gelatinous plaque (statoconia) formed by calcium carbonate crystals. Linear acceleration

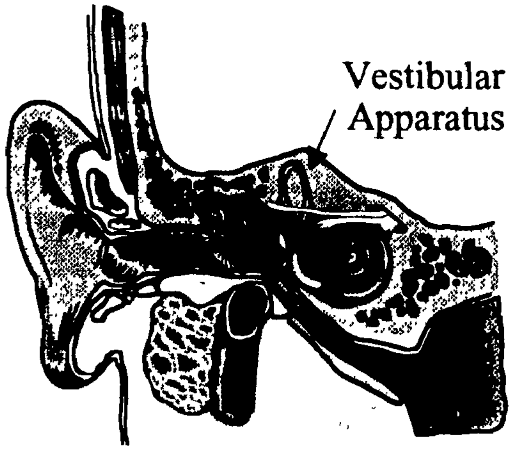

Figure I 3 Location of the Vestibular apparatus in the inner ear

causes an inertial force that produces movement of the statoconia and subsequent bending of hair cells. The firing rate of the sensory cells changes as a result of the movement.

The semicircular canals sense the angular acceleration of the head by means of the orthogonal arrangement of three semicircular ducts in each ear. The ducts have their origin in the utricle and are filled with endolymph. There is an enlarged section next to the utricule where lies the ampulla, a structure internally covered by hair cells. These hair cells are overlayed by a gelatinous formation: the cupula. Rotational movements produce flow of the endolymph contained in the canal lying in the plane of motion. This flow causes movement of the cupula which in turn deflects hair cells. The deflection modulates the activity of hair cells whose outputs converge to form the vestibular nerve.

I.3.2 Central processing stages

The processing of sensory information by the CNS has been considered to be a specialized process according to the particular ocular response evoked by the stimulus. In correspondence with this idea, the central process has been regarded as a collection of several independent, separate processing subsystems, each of them in charge of controlling a specific type of eye movement. As seen in Figure I.4, each of the above mentioned subsystems linearly combine their outputs at the motoneuron level (Mn), in order to drive the eye plant. However, it is worth mentioning that this classical view of

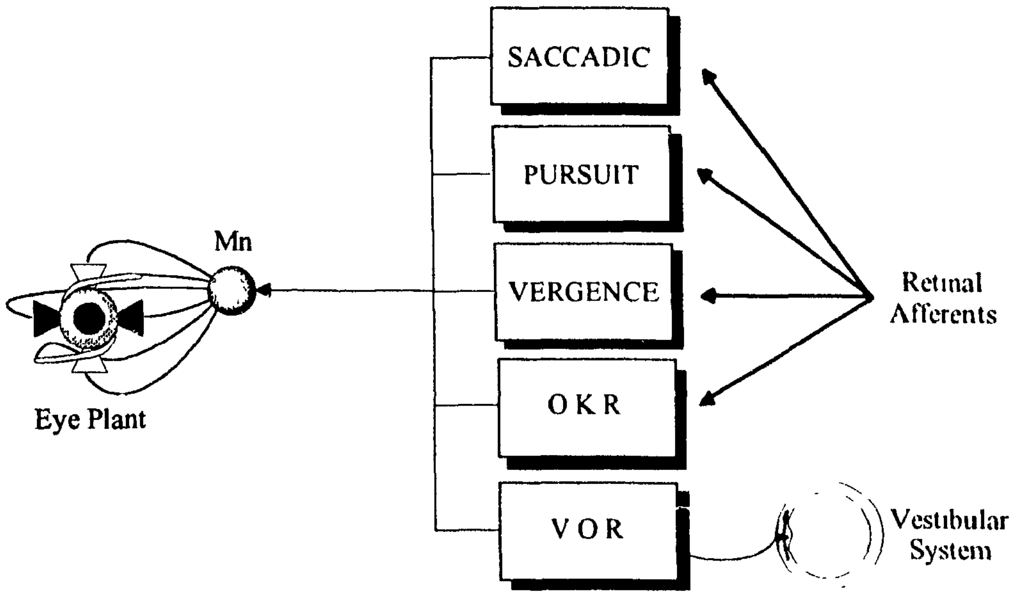

Figure I.4 General organization of the OCS at the central processing level

oculomotor organization at the central processing level deserves to be reexamined in the light of recent observations. New studies, using behavioral and neurophysiological data, suggest that this independence is not true (Enright, 1984; Judge and Cumming, 1986; Steinman et al., 1990).

I.3.3 The eye plant

The eyeball (*bulbus oculi*) is a nearly spherical structure, around 2.5 cm in diameter, protected by a bony cavity in the skull: the orbit. Six extraocular muscles (see Figure I.5) rotate the eye in the orbit. These muscles are grouped in three agonist/antagonist pairs, so that activation of an agonist is usually coupled to a relaxation of the corresponding antagonist. Eye movements in the horizontal plane (naso-temporal) are governed by the lateral and the medial recti. Medial recti causes the eyes to rotate inwards, towards the nose (adduction), while lateral recti rotate the eyes towards the temporal side, that is outwards (abduction). The superior and inferior oblique primarily produce rotation of the eyes around the line of sight in the frontal

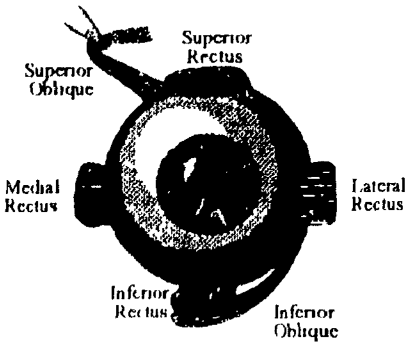

Figure I.5 Eye plant's extraocular muscles

plane (torsional movements). The superior and inferior recti mainly elevate and depress the eyeballs in a plane parallel to the midsagital head plane.

I.4 Objective of research

As mentioned above, the Oculomotor Control System (OCS) has traditionally been considered as composed of several independent subsystems acting in parallel, where each dedicated subsystem controls a particular type of conjugate or disjunctive eye movement (see review by Büttner and Büttner, 1988; Luebke et al.,1988; Robinson, 1981b) However, there is no strong evidence supporting this idea, since several neurophysiological studies have reported premotor structures in the brain involved in the control of more than one type of eye movements.

Mathematical models based upon the idea of parallel, independent subsystems, have been built in order to describe the OCS. Such previous models have mainly focused on input-output relationships, being difficult to relate to anatomy (Hung et al., 1986; Krishnan et al., 1977; Robinson et al., 1986). This fact may limit the application of such models in the clinical environment, where it is desirable to correlate patients' dysfunctional ocular responses with lesions or alterations of specific neurological sites.

Taking into account the aforementioned limitations and inconsistencies, it is attractive to postulate an integrated approach for the modelling of the OCS (Steinman et al., 1990). Models developed on this basis should reflect known anatomical and physiological facts. This study seeks to follow this new approach. It presents for the first time a single, bilateral model compatible with both known neuroanatomy and neurophysiology, capable of predicting the general characteristics (dynamics) of vergence and the vestibulo-ocular reflex (VOR) during slow phase eye movements This thesis is motivated by growing evidence of interactions between conjugate and vergence premotor activities To our present knowledge, there is no reported model of vergence and VOR together that follows the integrated methodology of this study A bilateral model of the VOR alone was proposed for the first time by Galiana (Galiana and Outerbridge,1984). Galiana's model included both slow and quick phases of the VOR. At this stage the integration of vergent responses is restricted to slow dynamics without rapid eye movements.

I.5 Thesis Outline.

The thesis is organized into 5 chapters:

Chapter 2 reviews tendencies in the mathematical modeling of the oculomotor system. The discussion focuses on previous models of vergence and the vestibulo-ocular reflex.

Chapter 3 surveys current neurophysiological knowledge about the role of several brainstem and midbrain centers in vergence and VOR control. The function of premotor structures relevant to the model is examined.

Chapter 4 describes the proposed bilateral model for coordinated vergence and conjugate eye movements. Results from simulations performed on the model are presented and analyzed.

Chapter 5 concludes the thesis giving possible directions for future work.

II. MODELING THE OCS

II.1 General remarks

A mathematical model is an abstract description of a real world process by means of mathematical concepts. Mathematical models are formulated with the intention of giving a deeper insight into the nature and characteristics of the process, as well as assessing its possible outcomes. In this sense, a well conceived mathematical model can lead to accurate predictions about the evolution of a system's state for different operating conditions.

Numerous efforts have been dedicated to modelling either the CNS itself (as a whole) or any of its constituent subsystems (the Oculomotor Control System (OCS) among them). Such models can be grouped into three major categories (Reeke et al., 1990):

Neurobiological models

Neurobiological models concentrate on the function or development of a specific brain area or subdivision of the CNS. These models can help unveil the particularities of neuronal function that can be important for higher-level processes. They can also provide clues on the best way to incorporate neurophysiological properties into more comprehensive models of the CNS. In the formulation of neurobiological models the idea of division of labor has been preeminent, with separate centers controlling the different aspects of the motor response under study. It has been acknowledged that a close correspondence with neurophysiology is the key factor in obtaining successful models. The great majority of models proposed for the OCS belong to this category.

Connectionist models

These kinds of models have received considerable attention in the past years. Based on neural network theory, connectionist models focus on the idea of parallel distributed processing of information, via highly interconnected arrays of individual processors. The interactions among processors (artificial neurons) can be changed according to adaptive schemes or "learning rules". The learning process is carried out in an instructional manner, with correct output responses being forced on the system from the very beginning. The architectures used in these neural network models have been regarded as unbiological and simplistic compared to real biological systems. Nonetheless, structures built upon connectionist principles have shown to be effective in solving problems in areas different from OCS modeling. Neural networks have been used with good results in optimization tasks, pattern recognition, control systems and signal processing.

Artificial Intelligence models

Models within this category seek to describe human intelligent behaviour in terms of symbolic information transformations carried out in the CNS. It is a priori assumed that concrete reality can be divided in classes with a specific language to describe them. This reduces the analysis of complex perceptual and behavioural processes to the consideration of simple sequential actions. Artificial intelligence models have primarily been applied to the description of higher level, cognitive processes.

A novel approach now in its early stages, synthetic neuronal modeling, considers the CNS as a whole system, possessing common structures capable of controlling the different motor responses according to a general, unified set of strategies and principles. This modeling scheme includes three levels of interaction: the environment, the phenotype and the CNS itself (Reeke et al; 1990).

Since the early studies of Westheimer and Robinson, most models in the area of oculomotor research have focused on behavioral data. The proposed neurobiological models paid limited attention to related physiological and anatomical facts. This tendency led to the formulation of a large number of lumped, "black box" parametric models where the emphasis was placed on input-output relationships only. This has been so partly because of the unavailability of neurophysiological data in these earlier studies. In the past decade, however, the appearance of sophisticated instrumentation has made it possible to obtain reliable neurophysiological information from experiments on alert, behaving animals. As a result, there is a more recent trend to develop OCS models with structural elements related to physiology.

Since a given transfer function can have an infinite number of realizations, previous lumped models of the OCS have proposed many arbitrary, sometimes meaningless model structures. The parameters in the majority of those models had little or no connection to known physical quantities within the OCS. Model elements usually can not be identified as particular anatomical sites and their outputs do not resemble recorded neural activity.

Most reported mathematical models of VOR and vergence have used linear parametric formulations. Some models have utilized cascades of linear dynamic and static non-linear elements. In the next section we will review the most relevant contributions to VOR and disparity vergence models, trying to concisely reflect the basic properties of each of them. The models examined restrict their consideration to eye movements performed in the horizontal plane.

II.2 Models of the Vestibulo-ocular reflex (VOR)

Two major approaches have been followed for the modeling of the VOR. One of them assumes the existence of parallel linear networks each one responsible for the fast and slow phases of VOR response. The other assumes the use of linear feedback elements in a two sided symmetrical structure. This last approach effectively represents the bilateral nature of the CNS. The functional connectivity of the linear feedback elements is strategically modulated during nystagmus in order to generate both slow and fast phases (Galiana and Outerbridge, 1984; Galiana, 1991).

Parallel processing models

The general scheme of parallel processing models is presented in Figure II.1. It consists of two parallel dedicated processes. The slow compensatory process generates the envelopes of the slow phase eye velocity, out of phase with respect to head velocity. The fast phase block is activated during quick phases in attention to a particular strategy of the CNS. Such models assume that the major goal of the CNS should be the generation of an appropriate eye velocity pattern, opposite to head velocity during slow phases. In the formulation of this hypothesis, it is a priori assumed that the slow phase process is operating in steady state, so that interactions between the slow compensatory and the fast resetting mechanism are considered unimportant. However, recent studies have suggested that the strategy followed by the CNS has to be reexamined with a broader perspective. Experiments done with sinusoidal rotation of subjects in the dark have shown that gaze tracks head position (Katsarkas et al., 1991). Quick phases are indeed an essential part of the VOR and their dynamic interaction with slow phases of nystagmus helps extend the linear range of the response (Galiana, 1991; Katsarkas et al., 1991). Therefore it is necessary to analyze responses using transient analysis methods, rather than assuming the presence of an ongoing slow process operating in steady state (Galiana, 1990)

Both slow and fast processes transform an estimate of head velocity coming from the canal sensors and produce an internal representation of the desired eye velocity profile. This estimate of eye velocity, generated internally and not a result of sensory feedback, is known in the literature as efference copy. The eye velocity estimate is then fed into a compensatory stage, formed by the parallel arrangement of a neural integrator (NI) and a feedforward gain G. The purpose of this stage is to provide compensation for the eye plant dynamics so that the actual eye velocity profile follows the velocity efference copy. This occurs when the compensatory stage produces a cancelation of the single pole of the eye plant, that is when G equals the value of the dominant time constant of the eye plant. The pole-zero cancellation extends the bandwidth of the system above the eye plant cut-off frequency.

The motoneural compensation block was first proposed by Robinson (Skavensky and Robinson,1973; Robinson,1981). It was found that abducens motoneurons of an alert monkey modulate their firing rates according to eye position and eye velocity.

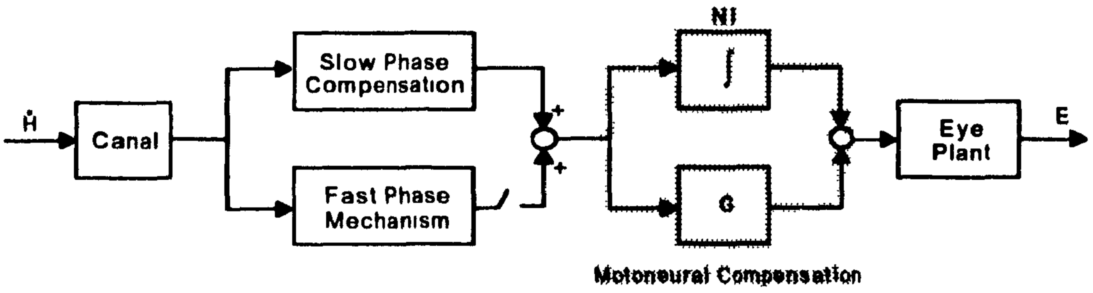

Figure II.1 General schema of parallel processing models of the VOR

Hence, it is required that efference copies of both eye position and eye velocity be available at the motoneuron level. The neural integrator provides the integration function necessary to produce the eye position estimate (Robinson, 1981b). However, it should be mentioned that the integration effect is not perfect, since gaze can only be held for a finite period of time (20 to 70 seconds in humans) after removal of sensory inputs (Becker and Klein, 1973; Leigh and Zee, 1991). Therefore, more recent lumped parameter models of the proposed compensation stage have described the conjugate NI as a leaky integrator, that is a single pole low pass filter with a large time constant.

The classical view of motoneural compensation implies the existence of the NI as a localized structure producing a pure position signal. Neurophysiological evidence is difficult to reconcile with this idea, since lesion and pharmacological studies in several areas of the brain have caused deterioration of the neural integration function (Cannon and Robinson, 1987; Godeaux et al. 1990; Mettens et al., 1991).

Slow phase dynamics are due to the so called "velocity storage" mechanism, an effect seen in VOR responses during constant velocity stimulation. When a subject is rotated at constant velocity the observed envelope of eye velocity decays at a slower rate than that expected from the dynamics of the canal sensor. The velocity storage mechanism accounts for this accumulation or "storage" of the vestibular signal. It has been suggested that velocity storage helps obtain a better estimate of head velocity from the canal signal. On the other hand, velocity storage would help make the sensation of rotation more persistent after vestibular responses have ceased.

From the control systems point of view, the velocity storage mechanism acts as a lag-lead compensator producing a cancellation of the canal pole. The introduction of a new pole, closer to zero, extends the low-frequency response of the VOR.

One of the approaches for modelling the velocity storage (Robinson, 1977) clarifies the concepts expressed above (Figure II.2). The canal transfer function consists of a single lag element with a zero (see chapter 4). From this transfer function it can be easily inferred that the canal sensor functions as a high pass filter of head velocity. The velocity storage is achieved by means of a positive feedback loop with a single pole low pass filter in the feedback path. This low pass filter is assumed to be an internal model of canal dynamics. Simple mathematical manipulations show that compensation is achieved when $T_o = T_c$. The time constant (T_{vor}) of the velocity storage transfer function can be tailored by manipulating b, according to the expression:

$$T_{vor} = \frac{T_o}{1-b} \qquad \text{(Eq. 2.1)}$$

Let us remember that it is assumed that VOR dynamics can properly be assessed from the envelopes of slow phase segments. Thus, the cascade of the canal, velocity storage, NI and eye plant transfer functions yields the following simplified VOR transfer function :

$$\frac{E(s)}{H(s)} = -k\frac{s\,T_{vor}}{s\,T_{vor}+1} \qquad \text{(Eq. 2.2)}$$

Where:

E(s) = Laplace transform of the angular position of the eye in the orbit
H(s) = Laplace transform of the angular position of the head in space
k = VOR gain
T_{vor} = VOR time constant

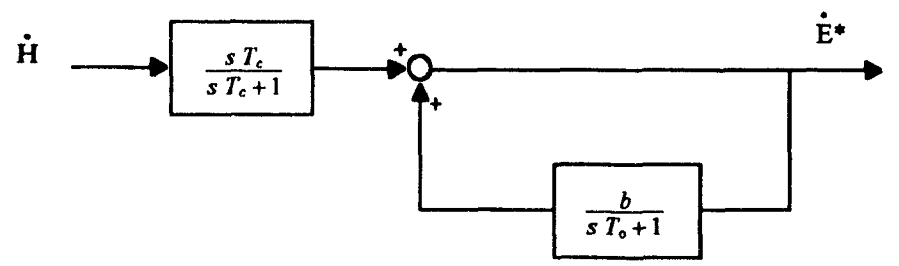

Figure II.2 Robinson's realization of the velocity storage mechanism

As a simplification, the influence of adaptation in canal dynamics has been omitted from the above transfer function (Barnes, 1980; Robinson,1981a). This influence is small, probably employed to maintain balanced canal sensors. Also, the transfer function above does not include an additional zero at 3.3 Hz in the canal transfer function (Robinson, 1981b). However, the impact of this zero in the overall VOR dynamics is small in the normal bandwidth of head movements (0.028 Hz to 3.3 Hz).

Typical values of T_{vor} are 21 sec in humans, 12 seconds in cats and around 16 seconds in monkeys (Robinson, 1981b). The high frequency gain k of the VOR varies according to cognitive and sensory factors, as mentioned in the introduction. In the dark, the gain for passive head rotations approximates 0.6 in alert humans. However if the subject is asked to imagine a fixed object in the room the gain climbs to nearly 1 (Barr et al., 1976). The VOR is significantly suppressed if the subject imagines a head fixed object in the dark In this case the gain drops to about 0.35 (Howard et al., 1989). In the light the gain of the reflex approaches 1, thanks to a pursuit related mechanism (Robinson, 1981b).

Quick phases of the VOR are produced by the activation of a heterogeneous group of cells called "bursters". These cells are located in the paramedian pontine reticular formation (PPRF) of the brainstem (Büttner and Büttner; 1988a,b; Leigh and Zee, 1991). Burst cells fire prior to quick phases and saccades, remaining silent during slow phases. The firing rate of burst cells is strongly correlated with eye velocity. This correlation is not entirely linear, so the firing rate is affected by a nonlinearity or nonstationarity (Robinson, 1981a,b). Burst cells constitute a source of premotor commands for motoneurons during quick phases, with axons projecting directly to extraocular and premotor nuclei (Büttner and Büttner; 1988b). Since burst cells output gives an estimate of eye velocity, a classical approach proposed is that they directly project to the motoneural compensation stage described above (Robinson,1981a)

It was early suggested that rapid eye movements are governed by a position feedback control system where desired eye position (target goal) is continuously compared with an internal estimation of eye trajectory (Yasui and Young, 1975; Young, 1977). On this theoretical basis and taking into account the already mentioned relationship between quick phase generation and burst cell activation, Robinson (Robinson, 1975) described the fast phase mechanism as a SISO position servo (Figure II.3). In this "local feedback" model the vestibular signal is assumed to be preprocessed in order to provide an internally generated estimate of target position (T) in the anticompensatory direction. The motor error signal e_m is an angular position error computed from the difference of the target estimate and the efference copy of eye angular position. The motor error drives the burst cells (bursters sensitivity = B) which generate an estimate of eye velocity. The static non-linearity in the forward path is included to model saturation effects which limit the velocity of the movement (Robinson, 1981a). The rest of the model includes the motoneural compensation stage formed by the NI and a forward path. As shown before, the output of this stage drives the eye plant.

Within the linear range of operation, the eye angular position in Laplace transforms is proportional to:

$$E(s) \propto \frac{1}{T_f s + 1} T(s) \, ; \qquad T_f = \frac{1}{B} \qquad \text{(Eq. 2.3)}$$

As Equation 2.3 implies, eye position is a low pass filtered version of the target goal, as required during quick phases. The value of T_f necessary to simulate high speed transients during fast phases of the VOR, is in the range 20-50 ms. Hence, the minimum required burster sensitivity will have a value of 20. The burster cells output is indeed related to the velocity of the eye movement.

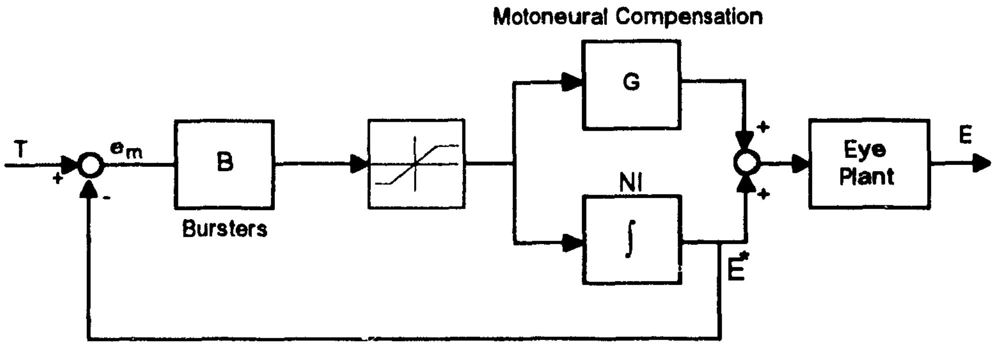

Figure II.3 Local feedback model for quick phase generation

This relationship can be expressed in Laplace transforms as:

$$B_c(s) = \frac{s}{T_f s + 1} T(s) \qquad \text{(Eq. 2.4)}$$

One inconvenience of this model is that it assumes that the burst generator is the only source of motoneural drive. It has been suggested that the generation of burst activity necessary for quick phase activation is a conjoint process where not only burst cells but also different premotor centers participate (Galiana, 1990; Guitton et al., 1990). Neurophysiological findings do not point towards the existence of parallel dedicated processes for both slow and quick phases of the VOR, but rather towards the convergence of premotor signals onto shared pathways in the brainstem (Galiana, 1991).

Bilateral feedback models

A more comprehensive and sophisticated model of the VOR was proposed by Galiana and Outerbridge (1984), taking into account the anatomical connectivity and the neurophysiological characteristics of premotor centers controlling the VOR. The model, in contrast to previous lumped models of the VOR, truly reflects the inherent bilaterality of the CNS. The bilateral feedback model relies on a selective, distributed processing of premotor information. This is achieved via positive feedback loops on each side and across the midline (indicated as a segmented line in the figures). The model can simulate reported activity patterns of known premotor nuclei of the VOR, including modulation of their activity by cerebellar pathways (Galiana and Outerbridge, 1984). Premotor centers are explicitly indicated in the simplified version of the model shown in Figures II.4 and II.5 (Galiana, 1990; 1991): the left and right vestibular nuclei (VR and VL) and the right and left prepositus hypoglossi (PHR and PHL). Details about the neurophysiology of these premotor structures will be covered in Chapter III.

During slow phases (see Figure II.4) the model has bilateral symmetry with reciprocal inhibition of the vestibular nuclei on both sides of the brainstem. This results in a positive teedback loop (with gain g^2) across the midline. This mutual inhibition effect, known as "commissural coupling", has been reported in the literature (Nakao et al., 1982). Each vestibular nucleus ipsilaterally drives a neural filter (NF(s)) in a positive feedback loop whose gain is controlled by a gain element (b). The neural filters are internal models of the eye plant and provide an internal estimate or "efference copy" (E^*) of eye position. This choice of modelling components is justified by neurophysiological studies which have shown that the prepositus hypoglossi is a center providing eye position estimates (Highstein and McCrea, 1988). The distributed processing of neural signals via positive feedback loops enables the model to perform the function of mathematical integration analogous to that of NI in traditional lumped models. Hence, in the bilateral model appropriate compensation for eye plant dynamics is achieved at the vestibular nuclei level. It is important to mention that central processing and motoneural compensation are combined within the model so there is no need for separate processing and compensatory stages.

During quick phases, burst cell activity causes changes in the feedback pathways, for example silencing of selected commissural and premotor pathways (Nakao et al., 1982). In the model this results in the asymmetrical structure of Figure II.5 and is characterized by the loss of strong commissural coupling between vestibular nuclei and the appearance of a negative feedback loop around the NF (Galiana and Outerbridge, 1984; Galiana, 1990; 1991). This has been called "structural modulation", a term which refers to the modifications in the functional components of the model structure during quick phases, without implying the existence of changes in the anatomical connectivity of premotor centers. What the "structural modulation" concept rather suggests is the occurrence of selective changes in the functional connectivity of premotor centers.

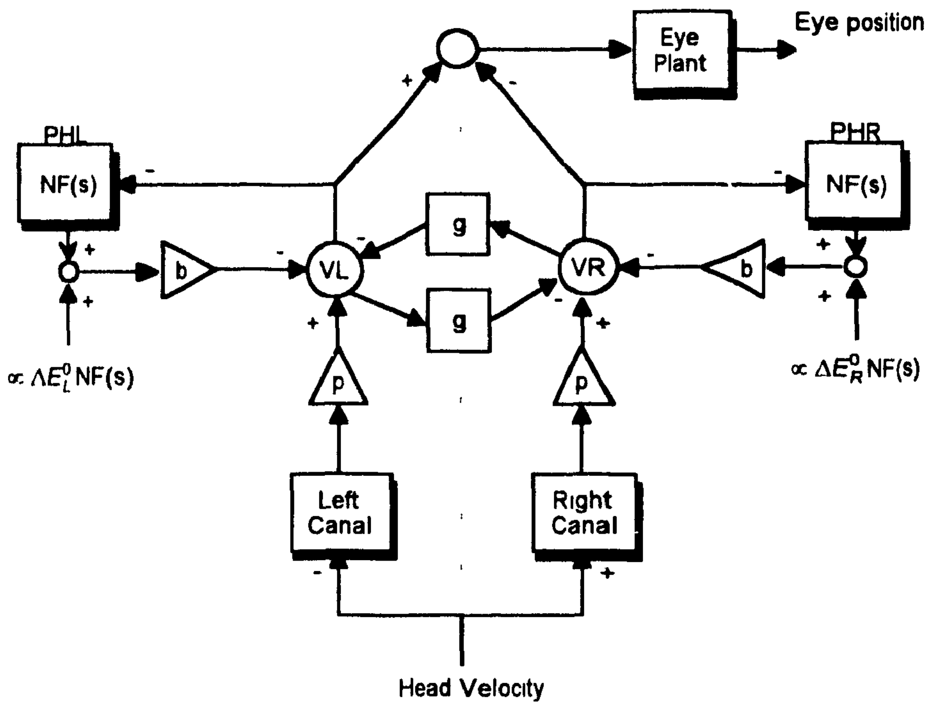

Figure II.4 Bilateral model of the VOR during slow phase. Movements in the rightward direction are considered positive

These functional changes, accomplished by the silencing of motor and premotor antagonists to the movement (Nakao et al., 1982; Büttner and Büttner, 1988b), enable a structure whose anatomical connections exhibit significantly different dynamics during quick phases. The asymmetric model structure during quick phases is dominated by centers contralateral to the direction of head movement (here the left side, since it is assumed head rotation to the right), linked to burst cells ipsilateral to the direction of head movement.

In the bilateral model, interactions between slow and fast phases are significant and occur at the premotor level, not downstream as in the classical models. Since steady state operating conditions are not assumed, transient analysis techniques are used to evaluate model responses In this transient analysis approach, the passing of information concerning initial eye position at the end of each segment is of great importance, since it can alter the apparent dynamics of the reflex (Galiana, 1991; Rey, 1992).

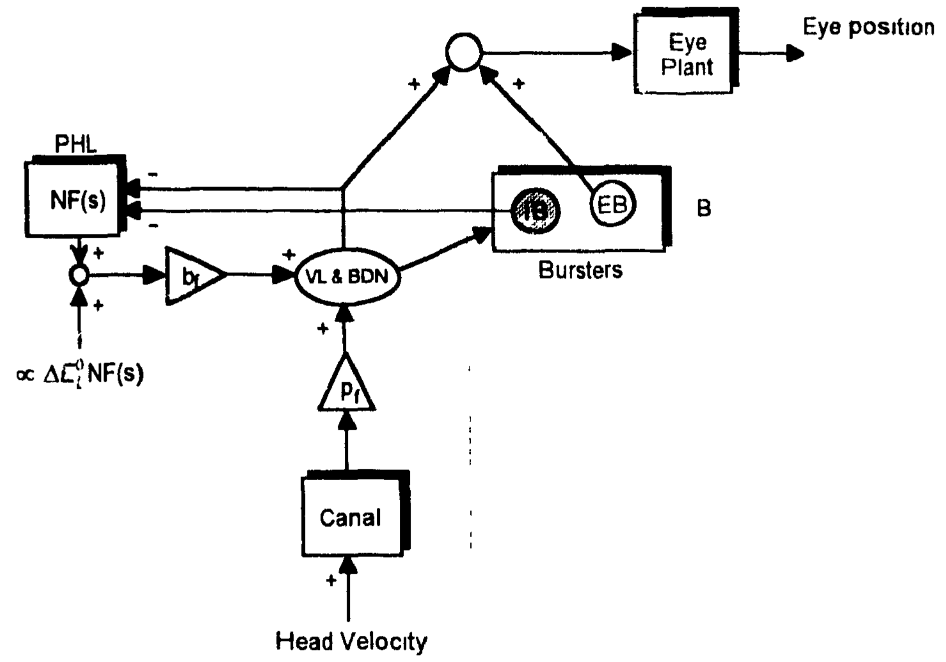

Figure II.5 Bilateral model of the VOR during quick phases.

In summary, the bilateral model considers fast and slow phases of nystagmus as transient responses, taking into account the effect of initial conditions at the output of the internal models (NF) of the eye plant.

Assuming linear balanced canal sensors (one canal decreases its activity by the same amount the other increases it), the premotor drive during slow phases will be related to the difference of vestibular nuclei signals (Galiana, 1991):

$$V_L(s) - V_R(s) = \frac{-2p\ \Delta C(s)}{(1 - b\ NF(s) - g)} + \frac{T(\Delta E_R^o - \Delta E_L^o)}{(Ts+1)(1 - b\ NF(s) - g)} \qquad \text{(Eq 2 5)}$$

Where:

ΔC(s) = Laplace transform of canals' firing rate modulation

ΔE = Initial conditions on the outputs of the neural filters

NF(s) = Internal models of the eye plant, $\frac{k}{Ts + 1}$

$V_{L,R}(s)$ = Laplace transform of vestibular nuclei signals

With sustained vestibular stimuli, the resulting angular eye position after the contributions of initial conditions have died out will be:

$$E(s) = \frac{-2\,G\,\Delta C(s)}{T_{vor}s + 1} \qquad \text{(Eq. 2.6)}$$

and

$$G = \frac{p}{(1 - bk - g)}; \qquad T_{vor} = \frac{T(1 - g)}{(1 - bk - g)} \qquad \text{(Eq. 2.7)}$$

In the normal range of head movements, the canal modulation $\Delta C(s)$ provides an estimate of head angular velocity. Therefore, Equation 2.6 is equivalent to the proposed transfer function for describing VOR dynamics (see Eq. 2.2). Equation 2.6 appropriately predicts that eye angular position will be out of phase with respect to head angular displacement for large values of T_{vor}. As seen in Equation 2.7, the time constant of the reflex T_{vor} can be made larger than the time constant of the internal filters and will strongly depend upon the commissural and dc gain of ipsilateral loops. An extensive description of the mathematical analysis of the bilateral model can be found in the original paper by Galiana and Outerbridge (1984).

During quick phases of the VOR (see Figure II.5) burst cell activity (excitatory (EB) and inhibitory (IB) burst cells) produces changes in the premotor functional connectivity and directly contributes to the motoneural drive (Nakao et al., 1982; Büttner and Büttner, 1988b) . This is represented in the model by means of:

1. A change in the feedback loop around the NF, which is now negative. The loop gain is partly controlled by the shared action of the left vestibular nucleus (VL) and left burster-driving-cells (BDN's) (Ohki et al., 1988). BDN's receive afferents from the vestibular nucleus and project to bursters as depicted in the model.
2. Bursters are represented as a neuron pool with gain B. Burst cell output modulates the internal model of the eye plant, via known projections to the PHL (Büttner and Büttner, 1988b; Highstein and McCrea, 1988).

3. Burst cells directly drive the motoneurons, causing eye movements in the direction of head rotation (see review by Keller,1991)
4. Information about right canal discharge rate predominantly modulates BDN's activity. This is interpreted in the model as a change in the effective sensitivity of the canal input, which is now depicted as p_f.

Now, the premotor drive also depends on the left vestibular nucleus signal (Galiana, 1991):

$$V_L(s) = \frac{G_f \Delta C(s)\,(Ts+1)}{(T_f s+1)} + \frac{T_f \Delta E_l^{o}(s)}{(T_f s+1)} \qquad \text{(Eq. 2 8)}$$

where:

$$G_f = \frac{p_f}{(1+kb_f+kb_f B)}; \qquad T_f = \frac{T}{(1+kb_f+kb_f B)} \qquad \text{(Eq 2 9)}$$

The resulting angular eye position, without taking into account the contribution of initial conditions, responds to the total drive from both burst cells and the VL:

$$E(s) \propto \frac{(1+B)\,G_f \Delta C(s)}{(T_f s+1)} \qquad \text{(Eq 2 10)}$$

According to Equation 2.10, angular eye position is a low pass filtered version of the canal output. In the canal passband, the eye angular position is in phase with head velocity, as required for the generation of fast ocular movements in the direction of head rotation. The quick phase time constant T_f can be made much smaller than the time constant of the internal models of the eye plant (Equation 2 9) This holds for positive b_f, p_f and k as described in the bilateral model (Galiana, 1991)

Different from any other previous model, the bilateral model is capable of generating very realistic nystagmus patterns. The strategy proposed by Galiana for the activation of quick phases is simple and concordant with physiological and anatomical observations. It has been convincingly shown that the occurrence of nystagmus helps extend the linear range of the VOR beyond that of the premotor centers (Galiana, 1991). In those cases where nonlinearities are present not only at the central processing level but also at the vestibular sensory stage (canal sensors) the bilateral structure exhibits substantial linearizing properties during slow phases (Smith and Galiana, 1991).

II.3 Disparity vergence models

Initial experiments in the study of vergence eye movements concentrated on obtaining experimental data in the time domain for a variety of different test inputs (Rashbass and Westheimer, 1961; Riggs and Niehl, 1960). Later studies developed linear non-parametric descriptions of the disparity vergence system, particularly in the frequency domain (Krishnan et al., 1973). On the basis of this accumulated data, mathematical models of increased complexity were built. Let us examine the most important ones.

Toates' Model of the vergence system

A simplified schematic of the vergence system model proposed by Toates, is seen in Figure II.6 (Toates, 1974). The disparity vergence system is modeled as a single input - single output (SISO), unity feedback dynamic system. The input to the model is target vergence, or the desired eye vergence angle. The controlled variable is eye vergence angle, or in simpler words, vergence angle. The error signal is the binocular disparity, or angular position error between target vergence and vergence angle. The model includes linear dynamic and static non-linear elements in the forward path, as can be seen in the figure.

The binocular disparity signal is multiplied by a gain of K1 corresponding to the radius of the eye. The binocular disparity is so converted into a measurement of the linear separation of retinal points from the fovea. This retinal error is processed by a pure delay block which is meant to represent the latency found in the generation of vergence eye movements. The pure delay is assumed to be 160 ms.

The delayed retinal error is then fed into a limiter. This limiter accounts for reported velocity saturation effects in vergence eye movements (Rashbass and Westheimer, 1961; Semmlow et al.,1986). When the binocular disparity exceeds a certain value, the

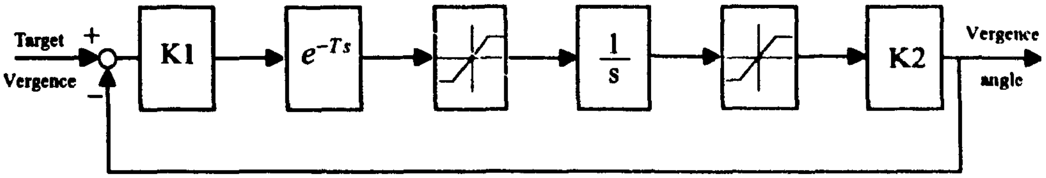

Figure II.6 Toate's model of the disparity vergence system

vergence velocity reaches a limit, remaining constant even if the binocular disparity is further increased. Then, note the presence of a pure integrative element. This block is included to model the open loop response characteristics of the disparity vergence system. For open loop disparity step inputs, both in humans and monkeys, the system reacts like an integrator (Cumming and Judge, 1986; Rashbass and Westheimer, 1961). The second limiter is included to represent the range of achievable vergence responses. The resulting motoneural signal drives the eye plant, which is modeled as a static gain element K2. This is an oversimplification of the inherent characteristics of the oculomotor plant, which has been shown to posses dynamic behaviour (Skavensky and Robinson, 1973; Keller, 1991). Since the model has a pure integrator in the loop transfer function, there is no steady state error for disparity step inputs. This is inconsistent with the small steady state error or fixation disparity that has been observed for step inputs (Schor, 1980; Schor, 1986): fixation disparity is in the range of 5-20 minutes of arc for most tested step disparity amplitudes.

In addition, this model fails to predict adequate eye responses when the gain is set to ensure a bandwidth of approximately 1 Hz, as has been reported for humans and monkeys (Cumming and Judge, 1986; Krishnan and Stark, 1977) As seen in Figure II.7, the predicted response to step inputs is oscillatory and reaches its final value in more than one second. Consequently, the predicted responses exhibit a settling time too large compared to actual recorded vergence eye movements, which settle within approximately one second after stimulus onset.

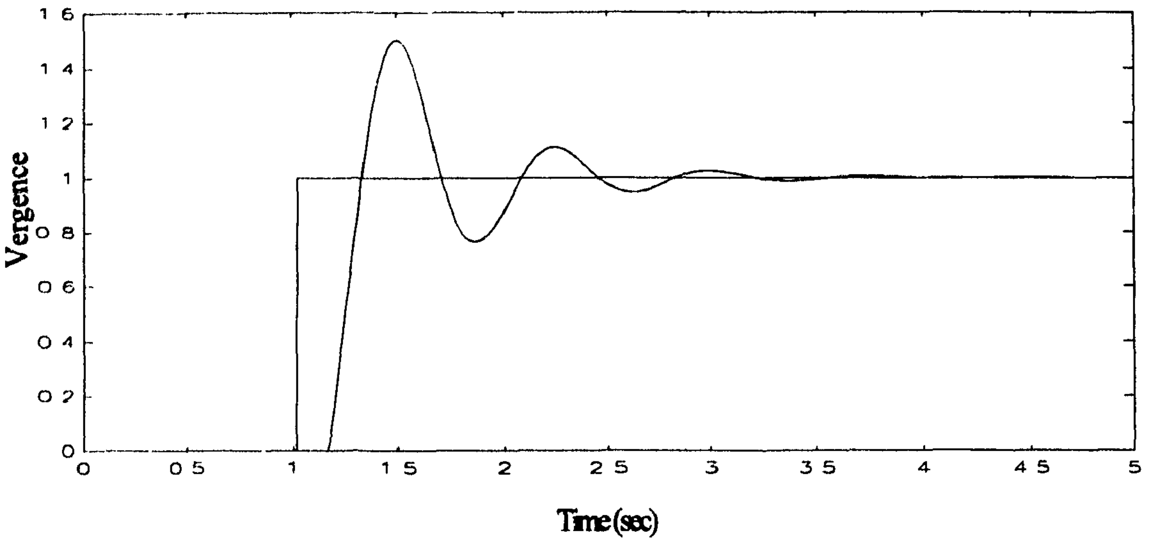

Figure II.7 Toate's model step response for $K_1 \times K_2 = 6.25$

It is also worth mentioning that, given the lumped or collapsed topology of this model, it is not possible to individually predict the position of each eye during the course of vergence movements.

Parallel integral-derivative model

A more comprehensive model of disparity vergence was proposed by Krishnan and Stark (1977). The model is linear dynamic with unity feedback and does not include any static non-linearity. As seen in Figure II.8, the model is also a single input - single output (SISO). The controller is modeled with two separate parallel elements in the forward path, one of them is derivative and the other integral. The derivative block is intended to speed up the transient response of the system with no steady state effect for step inputs. The integrative behaviour of the disparity vergence system is modeled by means of a leaky integrator with a time constant of 10 seconds. The high gain of the integral element enables the model to predict a small steady state error (fixation disparity) . The 10 seconds time constant is also included to simulate the slow decaying relaxation response found in "no target" conditions (see figure 10.8 in Krishnan and Stark, 1983). "No target" conditions are present when the lights are suddenly turned off after the subject has been steadily fixating a target. However, a time constant of 10 seconds is too large to accurately match the observed slow decay. As Krishnan and Stark

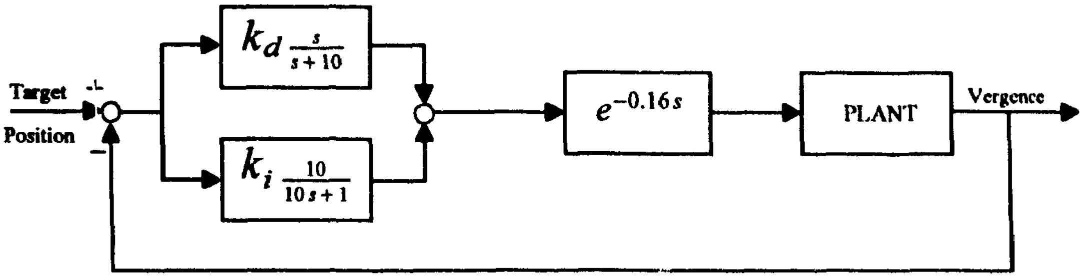

Figure II.8 Heuristic model of the disparity vergence system

reported, the relaxation response lasts about 16 seconds, suggesting a time constant smaller than 10 seconds.

The gains k_i and k_d are varied to simulate the differences in the dynamics of vergence eye movements performed in the convergent and divergent directions. It has been observed in some experiments that convergent movements are somewhat faster than divergent movements. However, it has also been noted that there is a noticeable intersubject variability so that for certain individuals there only are subtle differences in divergent and convergent dynamics.

A pure delay block with a value of 160 ms accounts for the latency of vergence responses. The model of the eye plant is based on previous work by Cook and Stark (Cook and Stark,1968; Krishnan and Stark,1983) which takes into account the viscoelastic properties of the eye ball and extraocular muscles. A simplification of this eye plant model leads to a single pole low-pass filter with a time constant in the range of 40-50 ms (Krishnan and Stark, 1983). This time constant is very small compared to the time constant employed in a widely accepted model of the eye plant (Skavensky and Robinson, 1973).

It should be mentioned that, even though this model provides a reasonably good fit to frequency response data, it cannot explain reductions in the phase lag seen in sinusoidal responses (Rashbass and Westheimer, 1961). Rashbass and Westheimer noted that the observed phase lags for sinusoidal stimulation were small compared to the values predicted by the presence of a pure delay. It has been suggested that a prediction operator within the system could account for the reduction in the phase lag (Krishnan et al.,1973).

Dual-mode dynamic model

This model (Hung et al.,1986) deviates from the consideration of the vergence system as a slow continuous linear feedback system. Several studies have pointed out the occurrence of fast (saccadic) vergence responses with higher velocities than those observed during vergence tracking at low velocities (Semmlow et al.,1986; Zee et al., 1992). This fact was interpreted by Hung and coworkers as an indication of the presence of a dual structure with separate, alternate control strategies. Experiments performed by the same scientists (Semmlow et al.,1986) using ramp inputs at different velocities, showed that responses to high velocity ramps (2-9 deg/s) consisted of successions of small step responses. The final position of each step matched the stimulus position. This was described by Hung et al. as a sample and prediction mechanism where the stimulus velocity is processed to give an estimate of the future position of the target. However, this effect may be caused not only by anticipation mechanisms (Krishnan et al., 1977), but by the presence of a fast mode controller seeking to reduce the position error between the stimulus and the eye. This kind of strategy was mentioned above (Chapter I), as the one used during fast phases of nystagmus. This potential explanation could point towards the reevaluation of vergence eye movements as another kind of nystagmic response.

As seen in Figure II.9, the model consists of both slow and fast dynamic blocks arranged in positive feedback loops. The vergence error VE or binocular disparity is computed from the difference of the vergence stimulus VS and the vergence response VR, using a negative feedback loop. The sum of the fast and slow dynamic element outputs generates VR1, a motor signal driving the eye plant. The slow component block is driven by the disparity delayed by 200ms (Figure II.10). This delayed version of disparity is applied to position and velocity error limiters which regulate the operating range of the slow component block. The position error limiter is set to a value of 1 degree. Note the presence of an ideal differentiator to produce the velocity error signal, which in turn controls the gain element in the error velocity limiter. The gain of this element, within the prescribed range of velocity error, is unity. For velocities above 2 deg/s the gain is set to zero, nulling the output of the slow component. The output

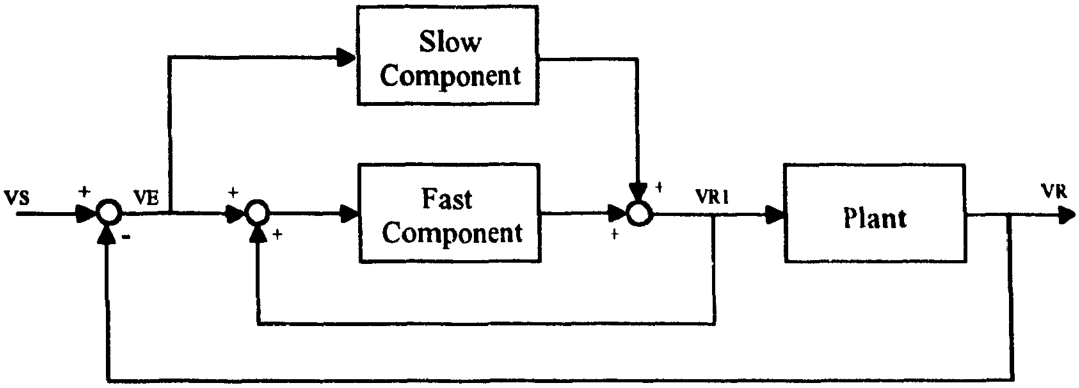

Fig II.9 General structure of dual-mode dynamic model of Vergence

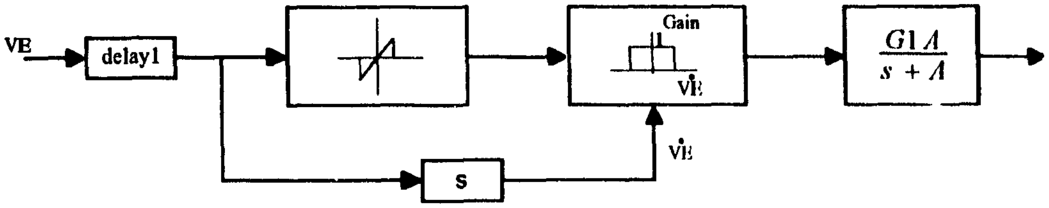

Fig II.10 Slow component of dual-mode dynamic model of Vergence

signal of the velocity limiter is fed into a low-pass filter which represents the dynamics of the slow component block. The low pass filter has a time constant of 10 seconds (A=0.1) as in the integral element of Krishnan's model. Gain G1 was empirically set to 30.

The fast component block is meant to represent the sample and prediction mechanism, as seen in Figure II.11. It is driven by the sum of the vergence error VE and VR1 delayed by the block DELAY2. The values of delay used were 50 ms for predictable stimuli and 200 ms for unpredictable stimuli. A delay of 50 ms for predictable targets was included to partially account for the reduction in phase lag found in sinusoidal

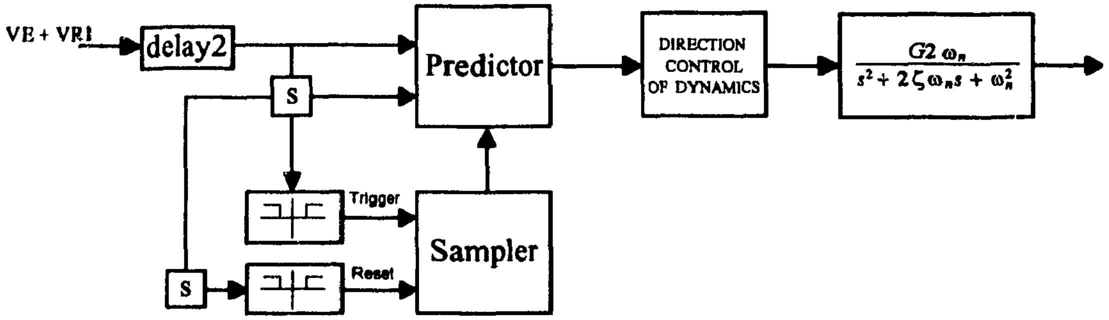

Fig II.11 Fast component of dual-mode dynamic model of Vergence

responses. The sum of VE and VR1 provides an estimate of the position of the target. The velocity and acceleration of the target position estimate are used to trigger and reset the sampler. When the velocity of VE + VR1 is above a threshold of 1.7 deg/s the sampler triggers. When there is an abrupt change in the velocity of VE + VR1 above a threshold level (increase in the acceleration above a certain limit) the sampler is reset. The sampler controls the timing of the predictor, using a sampling period of 500 ms. The predictor computes the future position of the target from information about the position and velocity of the target. The predictor generates an estimate of the future position of the target after a sampling interval and produces a step signal to match that future position. The direction of the step (convergent or divergent) is controlled by a special block in order to ensure correct matching. Finally the output of the direction control block is filtered using a second order low-pass filter. The filter order was arbitrarily selected, only to ensure a good fit with observed vergence responses to disparity steps. The parameters were empirically set; the dc gain G2=0.95, the damping ratio 0.4 for convergence and 0.6 for divergence. The natural frequency used was 12 rad/s and 8 rad/s for convergence and divergence respectively. Differences in the parameter values for convergence and divergence were justified on the basis of matching subjects' responses in the convergent and divergent directions.

Unfortunately, the eye plant model is not described in detail. Only a brief reference states that it *"represents the mechanical properties of the eyeball and musculature and is assumed to have unity gain for the vergence simulation"* (Hung et al. 1986). Therefore, the eye plant model used is vague and can not be specifically related to previous accepted models of the oculomotor plant.

Model responses for sinusoidal, step and ramp-stop stimuli are, with some exceptions, in good agreement with recorded vergence responses. However, predicted model outputs for pulse stimuli differ greatly from observed responses: they showed an overshoot in the return phase, a fact not observed in actual vergence measurements. It should be noted again that a time constant of 10 seconds for the slow process does not permit the model to simulate correct responses in "no target" conditions.

The dual dynamic model suffers from the same inconsistencies as its predecessors and other black box models: the model structure is selected arbitrarily, with no further constraints than those of providing a close match to observed responses. There is little or no relation between the constitutive elements of the model and identifiable anatomical sites. The function of individual model elements does not resemble neurophysiological findings reported in the literature and it is not possible to evaluate individual eye responses during vergence.

The dual-mode dynamic model was not developed taking into account reported neurophysiological or anatomical data, but nonetheless there is indeed evidence for a bimodal control of vergence. Premotor centers coding vergence position and vergence velocity signals have been reported (Judge and Cumming, 1986; Mays, 1984; Mays et al., 1986; Zhang et al.,1992). It has been suggested that vergence burst neurons (Mays et al., 1986) which modify their discharge rate with the velocity of the vergence movement would provide the input to a motoneural compensation stage similar to that of parallel processing models of the VOR. Hence, the function of mathematical integration would be provided by a "vergence integrator" operating in parallel with a direct pathway (Leigh and Zee, 1991). The effect of the "vergence integrator" is evidenced during "no target" conditions. The dynamic characteristics of the vergence integrator are different from the conjugate NI, whose time constant is significantly larger (see above). However, there is no reported physiological evidence supporting the thesis that both neural and vergence integrators are separate entities.

In contrast to lumped models of the VOR and vergence reviewed above, the model of this thesis was developed in close relationship to anatomical and physiological facts related to vergence and the VOR. The following chapter will cover in detail the neurophysiology and the anatomical connectivity of the neural elements represented in the proposed bilateral model.

III. NEUROPHYSIOLOGY BACKGROUND

Efforts for accurately describing vergence or any other oculomotor response strongly depend upon the choice of a correct, meaningful model structure. The model structure can only be proper if it is based on the underlying neuroanatomical and neurophysiological aspects related to the motor response studied. Aware of this fact, the model described in this thesis considered the physiological and anatomical basis of vergence and the VOR as a guiding factor for the selection of the model structure. The following sections will briefly examine the anatomy and physiology of known and putative premotor areas controlling vergence and the VOR. The oculomotor centers reviewed below are reflected in the topology of the proposed bilateral model for coordinated VOR and vergence eye movements. The discussion which follows will primarily refer to primates, unless otherwise noted.

III.1 General anatomical organization of CNS

The nervous system is a complex arrangement of neural control centers and physical channels for the transmission of information known as nerves. In general terms, the central nervous system can be considered as composed of two interdependent parts: the peripheral nervous system (PNS) and the central nervous system (CNS). The CNS comprises the brain and the spinal cord, while the PNS is formed by the cranial and spinal nerves. Both the CNS and PNS integrate sensory information coming from different locations in the body, controlling perceptual processes and voluntary motor responses. The PNS and CNS also govern autonomic body functions such as regulation of temperature and respiration.

The CNS is the nervous system subdivision controlling oculomotor responses. The brain, locus of the neural centers relevant to oculomotor control, is composed of the cerebellum, the cerebral hemispheres and the brainstem. The brainstem is part icularly rich in the number of oculomotor control structures it contains (see Figure III.1). It is subdivided into four anatomical regions: the diencephalon, the mesencephalon, the metencephalon and the myelencephalon. The last two mentioned subdivisions (myelencephalon and metencephalon) constitute the hindbrain, also known as rhombencephalon.

The diencephalon is the dorsalmost brainstem region. It is composed of four major nuclear subdivisions, all related functionally to the cerebral cortex: the hypothalamus, the thalamus, the epithalamus and the subthalamus. The hypothalamus is involved in the regulation of visceral, autonomic and endocrine functions such as metabolic activity, temperature regulation and sleep. It is also implicated in the control of emotional behaviour. The thalamus is an egg shaped structure which occupies a large portion of the diencephalon. It is involved in the distribution of sensory information to the cerebral cortex, the integration of motor functions and the control of cerebral cortex activity. It has been suggested that the thalamus is implicated in the control of saccades (Robinson et al., 1986; Schlag-Rey and Schlag, 1981, 1984). The subthalamus is located ventral to the thalamus and lateral to the hypothalamus. It is believed that the subthalamus plays a role in the control of vertical saccades (King and Fuchs, 1979).

The mesencephalon or midbrain is the least differentiated and smallest part of the brainstem. Three major subdivisions can be distinguished: the tectum, the tegmentum and the crura cerebri. The crura cerebri and the tegmentum are separated by the substantia nigra, a structure involved in the control of saccadic eye movements (Guitton, 1991). The tectum area is composed of four little hills: the superior and inferior colliculi. The region adjacent to the tectum, immediately rostral to the superior colliculi is known as pretectum, an area involved in the pupillary light reflex. The inferior colliculi contain cells sensitive to the frequency of auditory stimuli, so it is believed that the inferior colliculus serves as a relay nuclei in passing on auditory information to the thalamus. The superior colliculi constitute an important vision center where multimodal sensory information converge (Grantyn, 1988; Guitton, 1991). The superior colliculus is involved in the control of saccadic eye movements and orienting responses (Guitton, 1991; Guitton et al., 1990). Some studies have suggested that the superior colliculus is also implicated in the control of vergence and accommodation (Cowey et al., 1984; Cowey 1985). The mesencephalon contains two important motor nuclei: the trochlear and the

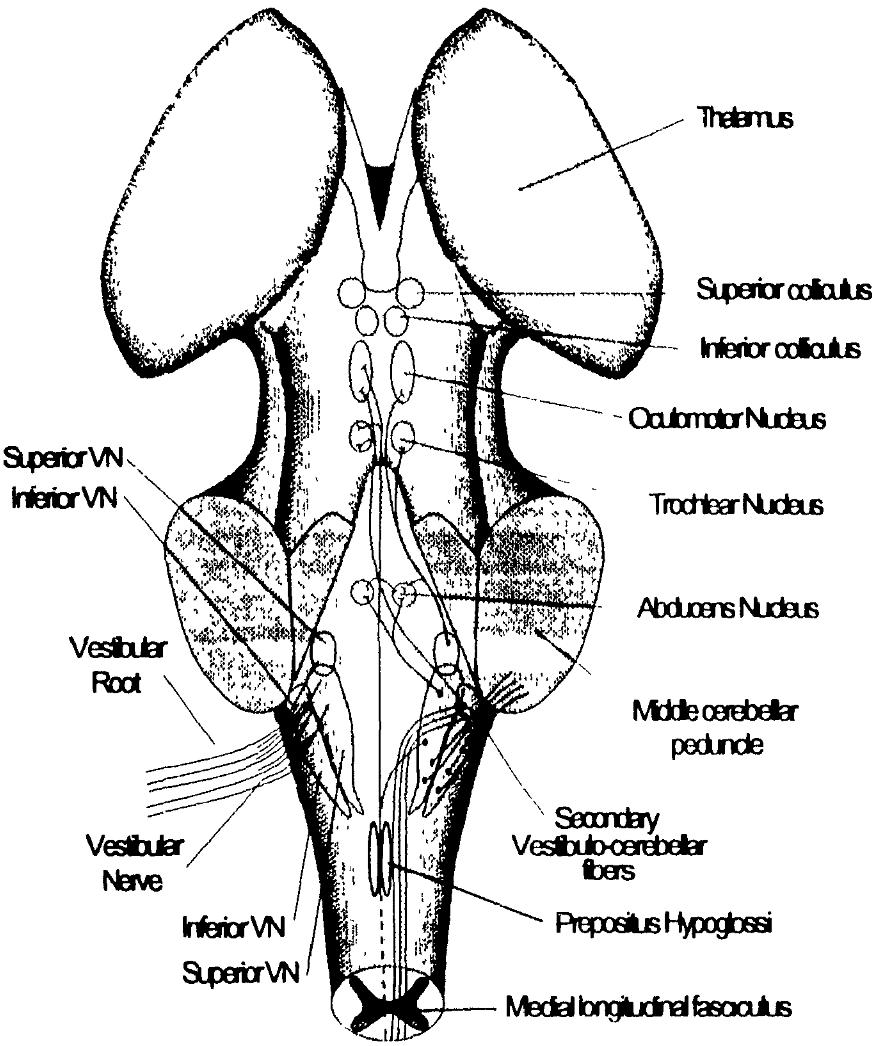

Figure III.1 Posterior view of the brainstem showing relevant premotor and motor areas involved in oculomotor control. Adapted from Rey (1992) "New algorithms for Classification and Identification of the vestibulo-ocular reflex".

oculomotor nuclei. Both nuclei accommodate motoneurons responsible for the activation of ocular muscles during conjugate and vergence eye movements (Evinger, 1988; Spencer and McNeer, 1991). Recent studies have located a special population of "near response" cells whose discharge rate is modulated by both vergence and accommodation (Mays, 1984; Judge and Cumming, 1986; Zhang et al , 1992).

The metencephalon, also called the pons, is a clearly differentiated region occupying the rostral part of the hindbrain. It is composed of two major areas: A large ventral region or pons itself, and a dorsal region known as pontine tegmentum. The dorsal subdivision of the pons contains many pontine nuclei which play important roles in oculomotor control. Among them, both the vestibular nuclei and the abducens nuclei deserve special mention. The vestibular nuclei is a premotor center responsive during all types of eye movements including vergence (see review by Büttner and Büttner, 1988a; Tomlinson et al., 1991 pers. comm.). The abducens nuclei are motor nuclei controlling the lateral recti muscles and oculomotor nuclei activity via a special subset of cells called abducens internuclear neurons (AbIn). Another important region within the dorsal pons is the pontine reticular formation, an area where burster cells are located.

The myelencephalon or medulla is the most caudal brain region, directly arising from the termination of the spinal cord. Several cranial nerves have their origin in the medulla which are involved in the control of somatic and visceral functions. Just to name a few of them, the hypoglossal nerve which innervates the skeletal muscles of the tongue; the vagus nerve which reaches different muscles and viscera of the larynx, the pharynx , trachea and esophagus; the glossopharingeal nerve which conveys information related to tactile sense, temperature and pain from areas in the tongue, the pharynx and the Eustachian tube. Perhaps the medullary region of greatest relevance to oculomotor control is the one containing the nuclei prepositus hypoglossi (PH). The PH has been consistently indicated as an "efference copy" center where internally derived information concerning eye position and velocity is generated (McCrea, 1988).

III.2 Extraocular motor nuclei: Abducens and Oculomotor nuclei

The abducens and oculomotor nuclei are the two motor centers which innervate eye muscles causing ocular movements in the horizontal plane. These muscles are the lateral recti, which rotate the eye towards the temporal side (abduction) and the medial recti which move the eyeball towards the nose (adduction). The placement and relative actions of these muscles are very similar in both frontal-eyed and lateral-eyed animals (Spencer and McNeer, 1991).

The oculomotor nuclei are located in the rostral mesencephalon, limited laterally by the medial longitudinal fasciculus, a region containing the axons of motoneurons driving the eye muscles. Motorneurons in the oculomotor nucleus project to the ipsilateral medial rectus (MR), the ipsilateral inferior oblique (IO), the contralateral superior rectus (SR) and the ipsilateral inferior rectus (IR) muscle (Evinger, 1988) A special subpopulation of oculomotor nucleus motoneurons, the oculomotor internuclear neurons, project to the abducens nucleus (Langer et al, 1986), the spinal cord and the cerebellum (Sekiya et al., 1984) but their physiological role is still unclear Afferents to the oculomotor nucleus include contralateral abducens interneurons (AbIn) (McCrea et al, 1986), the pretectal area (Weber and Harting, 1980) and the prepositus hypoglossi (PH) (McCrea, 1988).

The abducens nuclei are small groups of cells located in the dorsal pons Efferents from the abducens nucleus innervate the ipsilateral lateral rectus (LR) muscle (Langer 1986; McCrea et al., 1986; Evinger, 1988). A special population of abducens neurons, the internuclear abducens neurons (AbIn), cross the midline and project rostrally via the contralateral medial longitudinal fasciculus (MLF) to motoneurons in the contralateral oculomotor nucleus (OMN) (Evinger, 1988) The abducens nucleus receives direct afferents from the contralateral superior colliculus (Langer et al, 1986, Guitton, 1991), the ipsilateral pontine reticular formation, the prepositus hypoglossi (McCrea, 1988) and the vestibular nuclei (Highstein and McCrea, 1988). The afferents from the contralateral vestibular nucleus are excitatory while those from the ipsilateral vestibular nucleus are inhibitory (Highstein and McCrea, 1988).

Motoneurons in the abducens and oculomotor nucleus participate in the control of both conjugate and vergence eye movements (Mays and Porter, 1984, Keller, 1991, Gamlin and Mays, 1992). When performing a conjugate gaze deviation, abducens motoneurons ipsilateral to the direction of movement increase their firing rate Motoneurons in the oculomotor nucleus contralateral to gaze deviation increase their activity as well, mainly as a result of the excitatory drive provided by ipsilateral AbIn which also increase their firing rate. An opposite pattern of activation occurs in the ipsilateral oculomotor nucleus and the contralateral abducens nucleus, where motoneurons decrease their discharge rate. As a result, supposing an eye movement to the right, the left medial rectus and the right lateral rectus would increase their tension while the left lateral and right medial rectus would decrease it.

During convergence, motoneurons in both oculomotor nuclei augment their firing rate while motoneurons in both abducens nuclei decrease their discharge rate (Mays and Porter, 1984; Gamlin et al., 1989a,b; Gamlin and Mays, 1992; Keller, 1992). The activity profile of motoneurons during convergence is consistent with the need of increasing the tension of both medial recti and decreasing the tension of both lateral recti. An opposite motoneural activity pattern is seen in divergent eye responses. Very recently, it has been shown that the discharge rate of motoneurons in the oculomotor nuclei is related to both eye position and velocity (Gamlin and Mays, 1992). A similar relationship has been reported for conjugate eye movements (Skavensky and Robinson, 1973). The motoneuron firing rate displays transient changes attributable to the eye velocity component. This velocity component together with the position related component enable motoneurons to compensate for the dynamic characteristics of the oculomotor plant.

The behaviour of abducens internuclear neurons (AbIn) during vergence is similar to that of abducens nucleus motoneurons (Gamlin et al., 1989a,b). The discharge rate of AbIn decreases with convergence angle and increases with divergence angle. Thus, the activity pattern of AbIn conveys an "inappropriate" signal for ocular vergence (Gamlin et al, 1989), since motoneurons in the oculomotor nucleus (OMN) increase their firing rate with convergence angle. Consequently, a direct signal arriving to the OMN should overcome the effect of the inappropriate AbIn signal. It has convincingly been argued that this signal comes from near response cells located in the vicinity of the OMN (Mays, 1984; Judge and Cumming, 1986; Gamlin et al., 1989a,b; Zhang et al., 1991; Zhang et al., 1992).

III.3 The Vestibular Nuclei

The vestibular nuclei are important centers intervening in the control of all types of eye movements. The role of the vestibular nuclei in the mediation of the VOR is significant, serving as an intermediate stage for the processing of vestibular information coming from the semicircular canals. The vestibular nuclei relay the vestibular nerve signals to the motor nuclei, in what has been named the "3 neuron arc" of the VOR; that is the most direct pathway linking vestibular stimuli to oculomotor responses. The vestibular nuclei are actually nuclear complexes, containing a variety of differentiated sub-nuclei which send efferents to diverse structures in the brainstem, the cerebellum and the spinal cord (Highstein and McCrea, 1988).

Primary vestibular afferents arising from the semicircular canals and otolith organs innervate almost the totality of regions of the vestibular nucleus (Highstein and McCrea, 1988; In cat: Mannen et al., 1982). Other afferents to the vestibular nucleus include the PH, the spinal cord, the vestibulo-cerebellum, the ipsi- and contralateral vestibular sub-nuclei and the reticular formation (Highstein and McCrea, 1988). Of particular interest are the heavy commissural projections from the contralateral vestibular nucleus at the level of the superior and medial subdivisions (Ito et al., 1985; Highstein and McCrea, 1988). These commissural projections play an important role in the dynamics of the VOR and the process of vestibular compensation, as reflected in simulations performed in a recent model of the VOR (Galiana and Outerbridge, 1984; Galiana et al., 1984).

Efferent vestibular nucleus neurons project, among other areas, to the thalamus, the reticular formation, the spinal cord, the PH, the cerebellum, the ipsi- and contralateral vestibular nucleus and the extraocular nuclei (Highstein and McCrea, 1988). With regards to the horizontal VOR, the vestibular nucleus project to the abducens nuclei. The projection to the contralateral abducens nucleus is excitatory, while the projection to the ipsilateral abducens nucleus is inhibitory (McCrea et al., 1987). The connections reach both abducens motoneuron and abducens internuclear neurons (AbIn). AbIn, in turn make an excitatory projection to medial rectus motoneurons within the contralateral OMN.

From the physiological point of view, vestibular nucleus neurons encode a wide variety of information in their discharge rate. The identified neurons can be classified in six different groups according to the nature of their response (reviewed in Highstein and McCrea, 1988):

1. Neurons modulating their firing rate with the magnitude of eye position relative to the head and the magnitude of head velocity. These cells, known as position-vestibular-pause (PVP) neurons, remain silent during saccadic eye movements.

2. Neurons which carry an eye position related component (position-burst cells). Position-burst cells burst for saccades in their preferred direction and pause during saccades in the opposite direction.
3. Neurons which respond similarly to primary vestibular afferents.
4. Gaze velocity neurons which modulate their discharge rate according to eye velocity in space.
5. Neurons which carry signals similar to those of primary vestibular afferents but that pause during saccades (vestibular-pause cells).
6. Neurons which modulate their activity with eye position, without bursting or pausing for saccades (position cells).

In addition to the identified classes of vestibular neurons mentioned above, preliminary reports suggest that a population of cells within the vestibular nucleus modulate their discharge rate with vergence (Tomlinson et al., 1991 pers. comm.). These vestibular cells decrease their firing rate proportionally to the convergence angle. These very recent findings, stress the role of the vestibular nuclei as a multimodal center for eye movement control.

III.4 The Nucleus Prepositus Hypoglossi (PH)

The nuclei prepositus hypoglossi are columns of medullary neurons located in the dorsomedial region next to the vestibular nuclei. The nuclei extend from the rostral portion of the hypoglossal nuclei (from which they received their name) to the caudal pole of the abducens nuclei (McCrea, 1988; Keller, 1991). Preceding studies have revealed that PH activity is strongly correlated with eye movements (In cat: Lopez Barneo et al., 1982). This fact, together with the extensive and varied connectivity of the PH, makes the PH an important premotor center involved in controlling all kinds of eye movements.

The projections to the PH are numerous. The principal afferents to the PH include (McCrea, 1988): the perihypoglossal nuclei, the ipsi- and contralateral PH, vestibular nuclei, paramedian medullary reticular formation, the ipsilateral paramedian pontine reticular formation (PPRF), pretectum, abducens and the oculomotor nuclei, trochlear nuclei, the central mesencephalic reticular formation and the superior colliculi (mainly contralateral). As can be seen in the list above, the PH receives a variety of inputs from identified structures involved in eye movement control.

The most important efferents from the PH reach the vestibular nuclei, the ipsi- and contralateral PH, cerebellar cortex and nuclei, abducens nuclei (mainly contralateral), the PPRF (mainly contralateral), oculomotor nucleus (mainly the ipsilateral medial rectus subdivision), trochlear nuclei, superior colliculi (mainly contralateral), mesencephalic reticular formation (mainly ipsilateral) and the thalamus (McCrea, 1988). Recent studies in the guinea pig (Corvisier and Hardy, 1991) suggest that the projections from the PH to the contralateral superior colliculus are both inhibitory and excitatory.

The aforementioned characteristics in the activity pattern of PH neurons led to the consideration of the PH as an efference copy center. The PH distributes information concerning eye position and velocity to different target structures in the brain. The PH may not be the unique efference copy center in the brainstem, since it has relatively few neurons responsive during vertical eye movements (McCrea, 1988). Moreover, recent lesion studies (Cannon et al., 1937) suggest that the PH together with the vestibular complex form part of a distributed conjugate neural integrator. It should be mentioned that this fact had been previously suggested by Galiana (Galiana and Outerbridge, 1984) on theoretical grounds. PH lesions not only compromise gaze holding, but also cause long lasting oculomotor deficits, including asymmetrical vestibular and optokinetic responses as well as hypometric saccades (Kaneko and Fuchs, 1991).

In summary, the PH generates internally derived estimates of eye position and velocity which, via PH efferents, are conveyed to premotor structures where they are processed to produce the required drive to motoneurons (McCrea, 1988).

III.5 The Superior Colliculus

The superior colliculus (SC) is a complex, multilayered structure involved in the control of coordinated head and eye orientation towards objects of interest in space. The activity of the SC has been consistently related to the planning and generation of saccadic eye movements (Grantyn, 1988; Guitton, 1991; Munoz and Guitton, 1991a). However, lesion studies have shown that the SC is not essential for the execution of visually triggered saccades. Studies suggest that there exists redundancy in the control of saccadic eye movements and that another suprareticular structure, the frontal eye fields (FEF), acts in parallel, complementing the action of the SC (Guitton, 1991). The SC has a wide involvement in controlling visuomotor responses. It has been shown that the SC plays an important role in the control of gaze, via projections to the spinal cord and premotor structures in the brainstem (Munoz and Guitton, 1989). A comprehensive model of gaze control which takes into account the role of the SC in generating coordinated head and eye rapid eye movements, has been proposed by Galiana and coworkers (Guitton et al., 1990).

The superior colliculus is also related to other oculomotor and visual aspects in addition to saccadic and gaze control. Experiments with cortical and collicular lesions in cats (Sprague, 1991) suggests that the SC participates in form discrimination, a perceptual process long believed to be carried out only within the visual cortex. Collicular ablation in monkeys produces inattentiveness to visual stimulus in the visual field contralateral to the lesion. This "sensory neglect" effect is partially caused by a reduction in the visual sensitivity (Albano et al., 1982). Lesion studies involving the SC have shown significant impairment in vergence following collicular/FEF ablation (Cowey, 1984). Accommodation is also impaired when the lesion includes both SC and pretectal areas (Cowey, 1985).

The SC in mammals is a laminated structure which can be subdivided, *a grosso modo*, into two major regions (Grantyn, 1988; Guitton, 1991):

1. Superficial region: Composed of the three dorsalmost areas; the stratum zonale, the stratum griseum superficiale (SGS) and the stratum opticum (SO).
2. Deep region: Constituted by the four ventral-most strata.

The activity of the superficial layer is sensory related. This layer contains neurons which respond to visual stimuli. Afferents to the superficial region of the SC arise in the retina, FEF, extrastriate visual cortical areas, striate cortex, pre-motor cortex and pretectum, among other areas. Efferents from this region project to the pretectum, the dorsal lateral and ventral lateral geniculate nuclei, parabigeminal nucleus and the lateral posterior-pulvinar complex (reviewed by Guitton, 1991). There is evidence which confirms the existence of intracollicular pathways connecting the superficial and deep layers (Grantyn, 1988). In consequence, it is reasonable to expect that the sensory information conveyed by superficial neurons be transmitted to cells in the deep region in order to produce the required transformations for generating motor responses.

Neurons in the superficial region respond to visual stimuli placed in a restricted area of the contralateral visual hemi-field. This limited region is known as the neuron's receptive field. The topographic organization of neurons in the superficial region constitutes a retinotopic map of the visual space, ranging from 0 to 80 degrees of the contralateral visual field (Munoz et al., 1991). This means that the location of a point in visual space is coded by the position of a visually responsive cell whose receptive field coincides with the position of the point in the contralateral visual field. This internal collicular representation of target position should be processed in order to yield an appropriate premotor drive to motoneurons. Premotor information coding occurs in the time domain; therefore a transformation process from spatial to motor coordinates should take place in the SC: the so called spatio-temporal transformation.

The retinotopic map in the superficial layers is heterogeneous in the sense that the central visual field occupies more area of the collicular surface than the peripheral visual field. This property is known as magnification factor (Guitton, 1991). The effects of the magnification factor are compensated by the larger receptive fields of peripheral visual field neurons, so any target in space ends up activating an equivalent area of the superficial region of the SC (McIlwain, 1986).

Neurons in the superficial layers respond to targets placed in their corresponding receptive fields with a latency in the range of 40-80 ms. Some of this neurons (ENVIS) exhibit an enhanced response linked to motivational factors; i e. the monkey expects the target to appear (Guitton, 1991). It has been postulated that cells in the superficial layers are mainly activated by the position of the target in the visual field, without taking into account the velocity, orientation, luminance or shape of the stimulus. Recent experiments suggest that the response of superficial neurons is indeed correlated with some of the before mentioned factors. Robinson and coworkers (1991) found cells in the superficial layers of the SC which modulate their firing rate with the velocity of a small target crossing their receptive fields. Some of these cells preferentially discharge to low speed stimuli (low speed tuned cells) such as those used during laboratory evaluation of vergence responses. It is interesting to mention that the identified cells responded to real motion of the target, and a significant number of neurons showed strongly suppressed responses to self induced motion caused by pursuit of saccadic eye movements. The suppression effect is dependent on the luminance level and it is probably due to the influence of an extraretinal signal (Robinson et al., 1991). The reported activity of these cells is compatible with studies suggesting that the SC is involved in movement detection. Experiments in rhesus monkeys evidenced a reduction in movement discrimination after collicular damage (Cowey et al., 1984).

In experiments with immobilized and anesthetized monkeys, Davidson and Bender (1991) found that most cells in the deeper superficial layers (lower half SGS and SO) were responsive to differences in the direction and velocity of a target moving relative to a textured background. The selective properties of the neurons were unaffected by the absolute magnitude of speed and direction of both target and moving background, only the relative differences were important. Responses were strongly suppressed when the target and background moved in the same direction at the same velocity. The suppression effect was minimal when the target moved in the opposite direction to that of background. Neurons responded to low stimulus velocities (2 to 40 deg/s) and their responses were maximal when the background remained stationary (no suppression). Some neurons showed speed selectivity, independent of the directions of the target and background. From the results of these experiments, it is possible that the SC be able to compute or at least convey the differences in speed and direction between the target and the surrounding visual field.

The intrinsic organization and connectivity of the deep layers is more elaborate than that of the superficial area. Neurons in this region are spatially organized in a motor map concordant with the retinotopic map of the superficial layers. Therefore, the excitation of a neuron in the motor map will trigger a movement to the spatial location specified by the corresponding neuron in the retinotopic map. The deep collicular region receives visual, somatosensory and auditory information and produces motor responses related to eye, pinna and head movements (Guitton, 1991). Afferents originate in the retina, ipsilateral visual and auditory cortex, contralateral SC (commissural projections), inferior colliculus, trigeminal nucleus, spinal cord, PH, contralateral vestibular nucleus, ipsilateral substantia nigra, FEF and cerebellar nuclei (reviewed by Grantyn, 1988). Since the organization of the deep collicular layers seems to agree with that of a modular structure, it is possible that the processed information be distributed across several parallel output channels. The characteristics of the efferent information will obviously depend upon the targeted structures.

Several types of efferent neurons with diverse sensory and motor discharges have been identified. In experiments with monkeys, Moschovakis and colleagues (1988), classified collicular efferents into three different morphological groups: X, L and T. The somatodendritic and physiological characteristics of some of these cells closely resemble those of identified presaccadic neurons in cat. Of particular interest for oculomotor and gaze control are the tectoreticular and tectoreticulospinal neurons in cat (known together as TR(S)Ns), which correspond to type X and type X-T cells in monkeys (Guitton, 1991). TR(S)Ns activity precedes the generation of eye and head movements in both head fixed and head unrestrained conditions (Munoz and Guitton, 1989; 1991). These cells play an important role in the sensorimotor transformation required for accurate control of gaze shifts (Guitton and Munoz, 1991). Recent evidence have shown that TR(S)Ns also fire during the execution of slow eye movements, such as pre- and postsaccadic drift (Olivier at al., 1991).

TR(S)Ns cross the midline to join a contralateral thick group of axons called predorsal bundle and distribute profusely in the brainstem. The projections to the mesencephalon and diencephalon are bilateral while connections to the pons and the medulla are contralateral (Grantyn, 1988). Particularly important are the strong contralateral connections with the abducens nucleus, medullary and paramedian pontine reticular (PPRF) formations and the PH. Additional target structures include the mesencephalic reticular formation, substantia nigra, facial nucleus, as well as various thalamic and cerebellar nuclei (Guitton, 1991; Grantyn, 1988). Tecto-reticulo-spinal neurons (TRSN) project directly to the spinal cord, at the level where motoneurons controlling neck muscles have their somata (Grantyn, 1988). TRSN directly participate in the control of head movements during orienting responses towards targets whose eccentricity exceeds the limits of the oculomotor range (Guitton et al., 1990). In experiments with rats, King and coworkers (1991), showed that induced modulation of the firing rate of collicular efferents was correlated with the amplitude and velocity of head movements. These authors claimed their results are compatible with the hypothesis postulated by Guitton and coworkers (Guitton et al., 1990).

Two major subclasses of TR(S)Ns have been identified (Munoz and Guitton, 1989; Guitton and Munoz, 1991): (1) "rostral" or "fixation" TR(S)Ns which are active during fixation of a target of motivational significance, and (2) "caudal" or "orientation" TR(S)Ns which modulate their discharge rate before and during the execution of gaze orienting tasks. The receptive fields of fixation tecto-reticulo-(spinal) neurons (fTR(S)Ns) are small, and represent the central region of the visual field (area centralis representation). Orientation tecto-reticulo-(spinal) cells (OTR(S)N), on the other hand, map the visual field region around the area centralis representation.

Both kinds of neurons respond to multiple sensory and cognitive stimuli with sustained and phasic discharges, depending on the behavioural nature of the task performed (orientation or fixation) and the degree of attentiveness of the animal. Sensory mediated TR(S)Ns activity is influenced by visual, somatosensory and auditory stimuli presented in their receptive fields. Predictive discharges are observed when the animal anticipates the appearance of a target in a location in space corresponding to the neuron's receptive field (Munoz and Guitton, 1991).

Visual, auditory and somatosensory receptive fields of OTR(S)Ns neurons are in register with the retinotopic map of superficial layers. The responses to visual stimuli are characterized by sustained and phasic discharges, with a mean latency for stimuli onset of approximately 60 ms (Guitton and Munoz, 1991). OTR(S)Ns have directional preference for stimuli moving away from the center of the central visual field. The directional selectivity is highest for movement of the stimulus in a direction parallel to the horizontal meridian. Discharges for somatosensory, visual and auditory stimuli presented in their receptive fields are significantly reduced when the animal attentively fixates a target in space (Guitton and Munoz, 1991).

The firing rate of OTRS(N)s is enhanced when the cat performs an orienting response directed towards the spatial locus of the stimuli. These neurons fire tonically in relation to the difference between the position of the target and gaze in space. The discharge is maximal for a particular position of the target relative to gaze. Accordingly, it has been postulated that OTR(S)Ns encode gaze position error (GPE) and closely resemble the activity of identified presacadic neurons in the primates (Munoz and Guitton, 1991).

When the motivational significance of a target is such that the animal decides to orient its line of sight towards the stimulus, a pattern of sustained discharge is found in OTR(S)Ns whose position in the motor map corresponds to the GPE vector. As gaze shift progresses and consequently, instantaneous GPE reduces, and the zone of sustained activity moves towards the rostral pole of the colliculus. When the orientation movement finishes, the activity of OTR(S)Ns is significantly suppressed and "fixation" TR(S)Ns (fTR(S)Ns), mapping the area centralis (GPE=0 degrees), fire maximally (Munoz et al., 1991a; Munoz and Guitton, 1989; 1991). OTR(S)Ns and fTR(S)Ns also fire steadily in situations when the animal anticipate the appearance of a target. Suppressed or weak responses are evoked by the disappearance of a target lacking motivational importance ("no target" conditions) (Munoz and Guitton, 1991).

OTR(S)Ns have a phasic component in their firing rate related to the execution of gaze shifts in the preferred direction for both head restrained and head free conditions (Munoz et al., 1991b). The discharge is maximum for visually triggered orienting movements, with weaker firing rates for predictive or spontaneous gaze shifts. The phasic bursts are strongly correlated with eye (Berthoz et al., 1986) and gaze velocity (Munoz et al., 1991b) in head fixed and head free situations. Taking into account that information regarding target velocity can be received from the superficial layers, it may be possible that collicular efferents encode both gaze position and gaze velocity errors. The computation at the collicular level of a gaze velocity error would be consistent with the reported changes in the velocity of the orienting movement following sudden increases in OTR(S)Ns discharges (Munoz et al., 1991b). As Guitton and Munoz (1991) pointed out , TR(S)Ns form a heterogeneous population in which the dominance of phasic or sustained components is observed in subpopulations of cells. So, it is possible that cells with predominantly sustained discharge independently combine their outputs, at the level of SC target structures, with the outputs of mainly phasic cells.

On the basis of observed characteristics of TR(S)Ns discharges, Guitton and coworkers postulated that SC lies in a feedback loop where information about instantaneous gaze position error is spatially coded and distributed to other premotor structures in the brainstem (Guitton et al., 1990; Munoz et al., 1991b). The idea of placing the SC in a feedback loop for the control of saccadic eye movements was first introduced by Keller (1981) and has been recently endorsed by other researchers (Waitzman et al., 1991).

III.6 Near response cells

Very recently, neurophysiological studies have unveiled the presence of neurons in the monkey midbrain whose activity is related to both vergence and accommodation (Mays, 1984; Judge and Cumming, 1986). These neurons, known collectively as "near response" cells are primarily located in the mesencephalic reticular formation, dorsal and dorsolateral to the oculomotor nucleus. Some near response neurons were also identified in the vicinity of the superior colliculus and pretectal area (Judge and Cumming, 1986; Mays et al., 1986).

Antidromic identification studies have shown that near response cells mainly project to the ipsilateral oculomotor nucleus, at the level of its medial rectus subdivision (Zhang et al., 1991). However, since stimulation of near response cells causes simultaneous activation of both oculomotor nuclei, and hence adduction of both eyes, it has been suggested that a coupling may exist between near response cells located on both sides of the brainstem (Zhang et al., 1991).

Cells whose firing rate is primarily influenced by vergence are called "vergence" cells while those cells which predominantly discharge in relation to accommodation are named "accommodation" cells (Judge and Cumming, 1986; Zhang et al., 1992). In an experiment in which vergence and accommodation components were not assessed separately, Mays (1984) found near response neurons which linearly increased their firing rate with convergence angle. He gave the name of "convergence cells" to this neurons. The same study revealed the existence of "divergence cells" whose discharge rate is inversely proportional to vergence angle. Nonetheless, divergence cells were encountered less frequently that convergence cells (Mays, 1984).

Some vergence cells have a burst activity correlated with instantaneous vergence velocity (Mays et al., 1986). These neurons carrying a vergence-velocity signal are called vergence "burst" neurons. Both convergence and divergence burst neurons were identified: convergence burst cells abruptly increase their firing rate for convergence eye movements while divergence burst neurons do the same for movements in the divergent direction. Like divergence neurons, divergence burst cells were found far less often than convergence burst cells. It should be mentioned that vergence cells form a continuum where cells carry both vergence position and velocity signals in different proportions. As a consequence of this tonic, burst and burst-tonic vergence cells have been positively identified (Mays, 1984; Mays et al., 1986) Near response cells also form a continuum: accommodation and vergence components have a wide distribution, with some neurons even having negative vergence and accommodation coefficients (Zhang et al., 1992). Therefore, the signals found in near response cells discharges ranged from mainly vergence related to mainly accommodation related.

Studies have shown that the activity of near response cells is unaffected by smooth pursuit and saccadic eye movements (Mays, 1984; Judge and Cumming, 1986; Mays et al., 1986). Judge and Cumming (1986) also found that the firing rate of near response cells during sinusoidal vergence tracking, had a phase lead significantly higher than that of motoneurons. Discharges for a given vergence demand were very similar during binocular, monocular and accommodation open loop (no blur cues) viewing. This led the authors (Judge and Cumming, 1986) to conclude that near response cells are involved in the motor output path of vergence responses. This finding is in agreement with experiments performed by Mays and coworkers (1986) which evidenced that the firing rate of vergence burst cells is correlated with vergence velocity and not with disparity velocity (Mays et al., 1986).

The next chapter will illustrate how the anatomy and physiology of motor and premotor centers discussed in previous sections are closely reflected in the structure and functionality of the proposed bilateral model.

IV. MODEL ANALYSIS AND SIMULATION

IV.1 General considerations

The following chapter describes the proposed mathematical model for coordinated control of vergence and the VOR during slow phase eye movements. The model was developed taking into account the physiology and anatomical connectivity of premotor and motor centers governing both VOR and vergence responses. The neurophysiological and anatomical characteristics of the neural structures represented in the model have been discussed previously in this work (see Chapter III). The model focuses on disparity vergence and does not consider other sensory cues, such as accommodation or target angular size change. This is by no means a limitation since, without undermining the relative importance of other cues, disparity is widely acknowledged as the primary stimulus for eliciting vergence. Nevertheless, it is important to say that we believe the proposed model constitutes a solid ground on which additional sensory inputs affecting vergence may be included. Sensory drive for the VOR is represented in the model via inputs carrying estimates of head angular velocity coming from balanced semicircular canals.

Only eye movements performed in the horizontal plane are considered. The neural elements depicted in the model are assumed to operate in their linear ranges; in consequence no static non-linearities affecting VOR or vergence are delineated. For ease of exposition, variables in the model are incremental: only deviations in activity from resting rate are considered.

The coordinate system utilized for representing eye and head angular deviations can be seen in Figure IV.1, which illustrates the angular position variables reflected in the proposed model. The target initially at p is supposed to move to point q along the segmented line. The angular positions of each eye at the initial fixation point (p) are E_L and E_R for the left and right eye respectively. The angular position of the target at q is

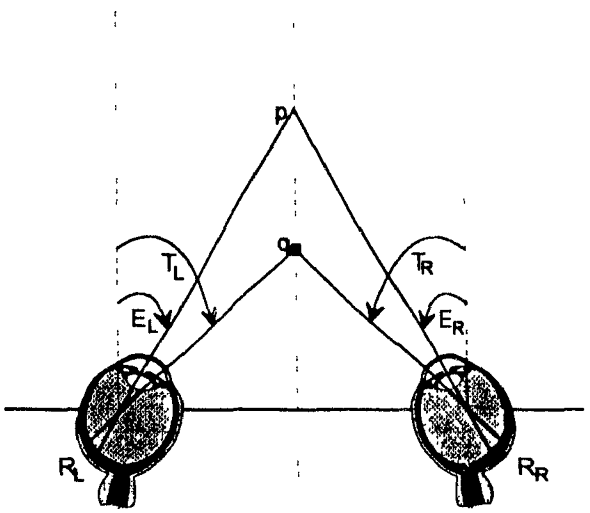

Figure IV.1 Coordinate system for the proposed bilateral model

described by means of T_R and T_L, both angles relative to zero vergence position When vergence angle is zero, the eyes look parallel at infinity so $E_L = E_R = 0$ degrees Adducting angles (in the nasal direction) are considered positive, abducting angles (in the temporal bone direction) are negative.

With this choice of a coordinate system it is very easy to express mathematically the values of the target vergence and vergence angles:

$$\text{Vergence angle} = E_R + E_L \qquad \text{(Eq 4 1)}$$

$$\text{Target vergence} = T_R + T_L \qquad \text{(Eq 4 2)}$$

The movement of the target generates angular position errors between the target and each eye. These errors, known as retinal disparities (R_R and R_L), are given by:

$$R_R = T_R - E_R \qquad \text{(Eq 4 3)}$$

$$R_L = T_L - E_L \qquad \text{(Eq 4 4)}$$

It is inferred from the expressions above that the binocular disparity, or in other words the angular position error between target vergence and vergence angle, can be computed by simply adding the right and left retinal disparities.

IV.2 Model description

A general schematic of the proposed model is shown in Figure IV.2. The model has a bilateral, symmetric structure with distributed connections which reflect the anatomy of the neural centers discussed in Chapter III. Arrows indicate the direction of information inflow/outflow within the model. Variables placed next to each projection represent the sensitivity or strength of the projection. According to usual conventions, "s" represents the Laplace complex variable. The segmented line (midline) signals the imaginary division between right and left sides of the brainstem.

In contrast to previous models of vergence, the proposed model is multiple-input multiple-output (MIMO) and allows simultaneous control of the angular positions of the left and right eye. This feature is particularly advantageous for the analysis of asymmetric responses and the evaluation of interactions between VOR and vergence. The inputs to the model are vestibular signals arising in the semicircular canals on each side (C_R and C_L) and the right and left angular positions of the target relative to zero vergence (T_R and T_L). The outputs from the model are the angular positions of the right and left eye (E_R and E_L).

Note the presence of multiple feedback loops located ipsilaterally and across the midline. Reciprocal inhibitory connections between the right and left vestibular nuclei (VN) form a feedback loop with gain g^2 between both sides of the brainstem. Mutual inhibitory projections between the VN and the ipsilateral prepositus hypoglossi (PH) are represented in the model as pathways with gains b and b1 on each side. The PH are depicted as neural low pass filters (F(s)) whose output signals are conveyed to the contralateral superior colliculus (SC), ipsilateral VN and vergence cells (Vc) located in the midbrain. Note that in order to simplify the drawing, the SC has been transposed: the right SC is depicted on the left side of Figure IV.2 while the left SC is on the right side. The rest of the neural elements in the figure reflect their anatomical distribution on both sides of the midline. The neural filters are linear dynamic models of the eye plant which provide internal estimates (efference copies) of eye position. The influence of initial conditions ($E^{*}(0)$) at the output of neural filters is also considered. The SC lies in a feedback loop computing position and velocity errors between the target and PH outputs on each side. In agreement with studies showing the presence of velocity and

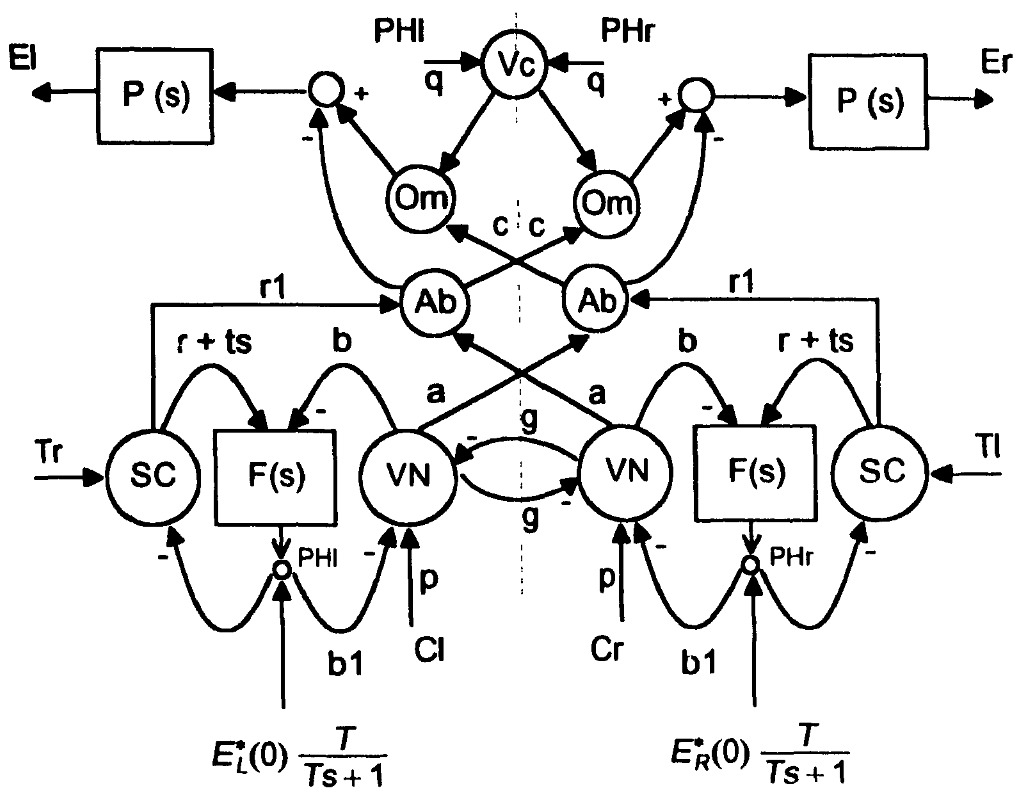

Figure IV.2 General schematic of the proposed bilateral model. The superior colliculi have been transposed to simplify picture

position related components in the collicular discharge (see Chapter III), the SC in the proposed model acts as a proportional derivative controller whose output signal varies linearly with the values of the instantaneous retinal disparity and retinal disparity velocity. The "anticipatory" action of a derivative control strategy helps to speed up the transient response of the system, having no effect on the dc steady state response.

According to neurophysiology, excitatory pathways transmit the collicular output to the contralateral abducens nuclei (Ab) and the contralateral PH. Abducens internuclear neurons (AIN) projecting via the medial longitudinal fasciculus (MLF) to the contralateral oculomotor nucleus are represented via pathways with gain c crossing the midline. The output signals from motoneurons conjointly drive P(s), first order linear dynamic models of the eye plant. Since oculomotor nucleus motoneurons control adducting movements in the horizontal plane (positive direction in the model), a connection with unity gain is included between the oculomotor nucleus (Om) and the eye plant. Complementary considerations justify the pathway with gain -1 between the Ab and P(s).

Near response cells with firing rates mainly related to vergence (Vc) are depicted in the bilateral model. Vergence cells located in the mesencephalic reticular formation receive ipsilaterally output signals from the PH and send projections (gain q) to the Om. Here we support the thesis of a potential coupling among vergence cells located in opposite sides of the brainstem (Zhang et al., 1991), therefore representing them as a collapsed pool of neurons.

IV.3 Model analysis

Analysis methods

The model schematic was reduced to its signal-flow graph equivalent and transfer functions for each of the sensory inputs were computed at the level of the eye, vestibular nuclei, vergence cells and motor nuclei by using Mason's rule. According to this formula the transfer function between the input $X_i(s)$ and the output $Y_j(s)$ is given by:

$$H_{ij}(s) = \frac{\sum_k G_{ijk}\Delta_{ijk}}{\Delta} \qquad \text{(Eq. 4.5)}$$

where G_{ijk}= Gain of the kth path from variable $X_i(s)$ to variable $Y_j(s)$
Δ = Determinant of the signal flow graph
Δ_{ijk} = Cofactor of the path G_{ijk}

By using the superposition theorem the contributions of each sensory input were linearly added to determine angular position of the eyes and the firing rates of motor and premotor elements of the model. The transfer matrix of the system was transformed to express output signals as linear filtered combinations of common mode and differential mode inputs. As a result both common mode and differential mode transfer functions for each kind of sensory input were computed. This method has the advantage of expressing output signals as functions of physical quantities relevant to the analysis of vergence and the VOR. For instance, the angular position of each eye can be expressed as the summation of contributions from common mode and difference mode target angular positions:

$$E_{R,L}(s) = H_c(s)\,[T_R(s) + T_L(s)] \quad \pm \quad H_d(s)\,[T_R(s) - T_L(s)] \qquad \text{(Eq. 4.6)}$$

The common mode transfer function $H_c(s)$ relating target vergence to eye angular position is proportional to the vergence transfer function. The difference mode transfer function $H_d(s)$ gives an estimate of the influence of target eccentricity on eye position (a measure of the eccentricity of the target is provided by $T_R(s) - T_l(s)$).

Model analysis was performed on an IBM RISC 6000 workstation with the aid of XMaple, a symbolic computation package for the X Windows environment originally developed by the University of Waterloo. Using XMaple's high level language, several script modules were written to automate the process of transfer function computation and determination of model parameters at different functional levels. Modules were thoroughly tested and debugged both manually and using Mint, a syntax checker within the XMaple program.

Eye Plant model

A simple first order model was chosen for representing the dynamics of the eye plant. This model has proven to be an accurate predictor of the relation between eye angular position and motoneural firing rate for movements with spectral content up to 4 Hz approximately. Skavensky and Robinson (1973) in experiments performed on monkeys found that the firing rate modulation of abducens motoneurons ($\Delta M(t)$) was correlated with the velocity and position of eye trajectory:

$$\Delta M(t) = k\,e(t) + r\,\dot{e}(t) \qquad \text{(Eq. 4.7)}$$

As a result, the following first order transfer function can be used to approximate eye plant dynamics:

$$P(s) = \frac{E(s)}{\Delta M(s)} = \frac{1/k}{r/k\,s + 1} = \frac{K_e}{T_e s + 1} \qquad \text{(Eq. 4.8)}$$

where K_e = 0.25 deg/spikes.sec^{-1} and T_e = 0.24 seconds.

The internal neural filters in the proposed bilateral model are also first order low pass filters with dynamics similar to that of the eye plant:

$$F(s) = \frac{K}{Ts + 1} \qquad \text{(Eq. 4.9)}$$

Vestibular sensors

The dynamics of the semicircular canals have been the subject of many studies which have explored both non-linear and linear aspects of canal function. Without taking into account non-linearities or adaptation effects, the majority of previous studies coincide in modelling the canals as high pass filters of angular head velocity (Goldberg and Fernandez, 1971; Melvill Jones, 1991). A first order linear model of canal dynamics is given by:

$$\frac{C(s)}{\dot{H}(s)} = \frac{c_s T_c s}{T_c s + 1} \qquad \text{(Eq. 4.10)}$$

where $C(s)$= Laplace transform of the firing rate modulation of canal primary fibers
$\dot{H}(s$ = Laplace transform of head's angular velocity
c_s = Canal sensitivity (high frequency gain)
T_c = Canal's time constant

Approximate values for c_s and T_c are 0.4 spikes.sec^{-1}/deg.sec^{-1} and 6 seconds respectively.

Central process

The following section describes the obtained transfer functions for different vestibular and visual stimuli combinations. The influence of initial conditions at the output of the neural filters in shaping eye responses will be described. Neural elements in the model are assumed to operate in their linear ranges and their output signals represent modulations in the firing rate above resting activity.

Let us examine the output signals at the ocular level. The angular position of each eye, for zero initial conditions and no vestibular stimuli, can be expressed as:

$$E_R(s) = \left[G_{cv} \frac{T_{cv} s + 1}{T_{cm} s + 1} (T_R(s) + T_L(s)) + G_{dv} \frac{T_{dv} s + 1}{T_{dm} s + 1} (T_R(s) - T_L(s)) \right] \frac{K_e}{T_e s + 1}$$

$$E_L(s) = \left[G_{cv} \frac{T_{cv} s + 1}{T_{cm} s + 1} (T_R(s) + T_L(s)) - G_{dv} \frac{T_{dv} s + 1}{T_{dm} s + 1} (T_R(s) - T_L(s)) \right] \frac{K_e}{T_e s + 1} \qquad \text{(Eq. 4.11)}$$

For a symmetric bilateral structure, adding both eye positions in order to find the vergence angle results in a cancellation of the difference mode terms. Therefore, the vergence angle can be written as:

$$E_R(s)+E_L(s) = 2K_e G_{cv} \frac{T_{cv}s+1}{(T_{cm}s+1)(T_e s+1)} (T_R(s)+T_L(s)) \qquad \text{(Eq. 4.12)}$$

Finally, making the zero's time constant approximate the eye plant time constant ($T_{cv} \cong T_e$) in order to compensate for eye plant dynamics, the resulting expression for the vergence transfer function is:

$$\frac{E_R(s)+E_L(s)}{T_R(s)+T_L(s)} \propto \frac{G}{T_{cm}s+1} \qquad \text{(Eq. 4.13)}$$

where G is the dc steady state vergence gain and T_{cm} is the system's common mode time constant. Equation 4.13 is compatible with time and frequency response studies which suggest that the vergence system can be described as a single pole low pass filter with time constant close to that of the eye plant (Rashbass and Westeimer, 1961; Krishnan and Stark, 1977; Hain and Zee, 1989). The vergence time constant (T_{cm}) as a function of model parameters is given by:

$$T_{cm} = \frac{(T+Kt)(1+g)}{(1+g)(1+Kr) - bKb1} \qquad \text{(Eq. 4.14)}$$

As Equation 4.14 shows, the model predicts a potential increase in bandwidth for a decrease in the mutual inhibition effect ($bKb1$) between ipsilateral VN and PH. The common mode time constant would also be affected in the event of variation of the adaptive commissural coupling (g) across the midline. Given the limited number of neurophysiological studies on vergence, these predictions remain to be tested by more comprehensive experiments than those already reported. It is also important to note that an increase in the common mode time constant can result from a significant decrease in collicular discharge, as would occur in total darkness with no cognitive inputs (Guitton, 1991).

Assuming visual inputs only, the motoneural output signal at the level of the oculomotor nuclei is:

$$Om_L(s) = G_{com}\frac{T_{zom}s+1}{T_{cm}s+1}(T_R(s)+T_L(s)) - G_{dom}\frac{T_{z1om}s+1}{T_{dm}s+1}(T_R(s)-T_L(s))$$

$$Om_R(s) = G_{com}\frac{T_{zom}s+1}{T_{cm}s+1}(T_R(s)+T_L(s)) + G_{dom}\frac{T_{z1om}s+1}{T_{dm}s+1}(T_R(s)-T_L(s)) \qquad \text{(Eq.4.15)}$$

Note that the model predicts a combination of eye velocity and position components in the motoneuron output signals, in agreement with a very recent study concerning oculomotor nuclei function during vergence eye movements (Gamlin and Mays, 1992). For symmetric vergence ($T_R(s)=T_L(s)$), the difference mode terms cancel and the eye velocity sensitivity of oculomotor nuclei motoneurons is proportional to T_{zom}:

$$T_{zom} = \frac{(1+g)(2qKt+r1cT)-acb1Kt}{(1+g)(2qKt+r1c)-cb1K(ar+br1)} \qquad \text{(Eq. 4.16)}$$

Similar considerations apply for abducens nuclei motoneurons, whose discharge rate is related to both eye velocity and position:

$$Ab_R(s) = -G_{cab}\frac{T_{zab}s+1}{T_{cm}s+1}(T_R(s)+T_L(s)) - G_{dab}\frac{T_{z1ab}s+1}{T_{dm}s+1}(T_R(s)-T_L(s)) \qquad \text{(Eq. 4.17)}$$

$$Ab_L(s) = -G_{cab}\frac{T_{zab}s+1}{T_{cm}s+1}(T_R(s)+T_L(s)) + G_{dab}\frac{T_{z1ab}s+1}{T_{dm}s+1}(T_R(s)-T_L(s))$$

Again, for symmetric vergence eye movements the difference mode terms go to zero leaving the common mode terms only. It is easy to see that for positive G_{cab}, both abducens motoneurons and internuclear neurons (AIN) decrease their firing rate during convergence. The model prediction described by Equation 4.17 agrees with previous reported studies (Mays and Porter, 1984; Gamlin et al., 1989a,b) which showed a decrease in the firing rate and the presence of burst-tonic discharges in AIN and abducens motoneurons. The velocity sensitivity of abducens motoneurons is proportional to T_{zab}:

$$T_{zab} = \frac{(1+g)(1+r1T)-ab1Kt}{r1(1+g)-b1K(ar+r1b)} \qquad \text{(Eq. 4.18)}$$

For visual stimuli only and symmetric vergence eye movements, the equation describing the modulation of VN efferents is:

$$VN_{R,L}(s) = -G_{cvn}\frac{T_{cvn}s + 1}{T_{cm}s + 1}(T_R(s) + T_L(s)) \qquad \text{(Eq. 4.19)}$$

Note the presence of components associated with the velocity and position of the vergence response. The VN output signal is predicted to decrease for increasing convergence angles, with dynamics approximate to that of vergence. Signals similar to that described above have been recently observed in neurophysiology experiments which analyzed VN behaviour during symmetric vergence (Tomlinson, 1991; pers. comm.).

With zero initial conditions, the following expression relates the output signal from vergence cells to vestibular and visual inputs:

$$V_c(s) = G_{cvc}\frac{T_{cvc}s + 1}{T_{cm}s + 1}(C_R(s) + C_L(s)) + G_{tvc}\frac{T_{tvc}s + 1}{T_{cm}s + 1}(T_R(s) + T_L(s)) \qquad \text{(Eq. 4.20)}$$

The lack of difference mode terms in Equation 4.20 is the result of the symmetry of the bilateral inputs reaching vergence cells. The model predicts an increase in the modulation of vergence cells with increasing convergence angles, a fact recently reported in experiments with monkeys (Mays, 1984; Judge and Cumming 1986, Zhang et al., 1992). In agreement with these studies, Equation 4.20 predicts the presence of burst-tonic discharges in the firing rate of vergence cells (see also Mays et al., 1986). Moreover, the model predicts that the firing rate of vergence cells will be unaffected by conjugate VOR movements as long as the canals are balanced. This prediction, however, remains to be tested.

In the dark, assuming no cognitive goals, the absence of visual stimuli cause the collicular efferents to considerably decrease their modulation leading to the model structure shown in Figure IV.3. Note that the collicular loop is not present now and that projections from the SC to the contralateral Ab are silenced. Under these conditions, the angular position of the eyes for balanced canals is described by Equation 4 21:

$$E_L(s) = \left[-G_{cd}\frac{T_{dd}s + 1}{T_{dmd}s + 1}(C_R(s) - C_L(s)) + \frac{G_{c0}}{T_{cmd}s + 1}(E^*_R(s) + E^*_L(s)) - \frac{G_{d0}}{T_{dmd}s + 1}(E^*_R(s) - E^*_L(s))\right]\frac{K_e}{T_e s + 1}$$

$$E_R(s) = \left[G_{cd}\frac{T_{dd}s + 1}{T_{dmd}s + 1}(C_R(s) - C_L(s)) + \frac{G_{c0}}{T_{cmd}s + 1}(E^*_R(s) + E^*_L(s)) + \frac{G_{d0}}{T_{dmd}s + 1}(E^*_R(s) - E^*_L(s))\right]\frac{K_e}{T_e s + 1}$$

(Eq. 4.21)

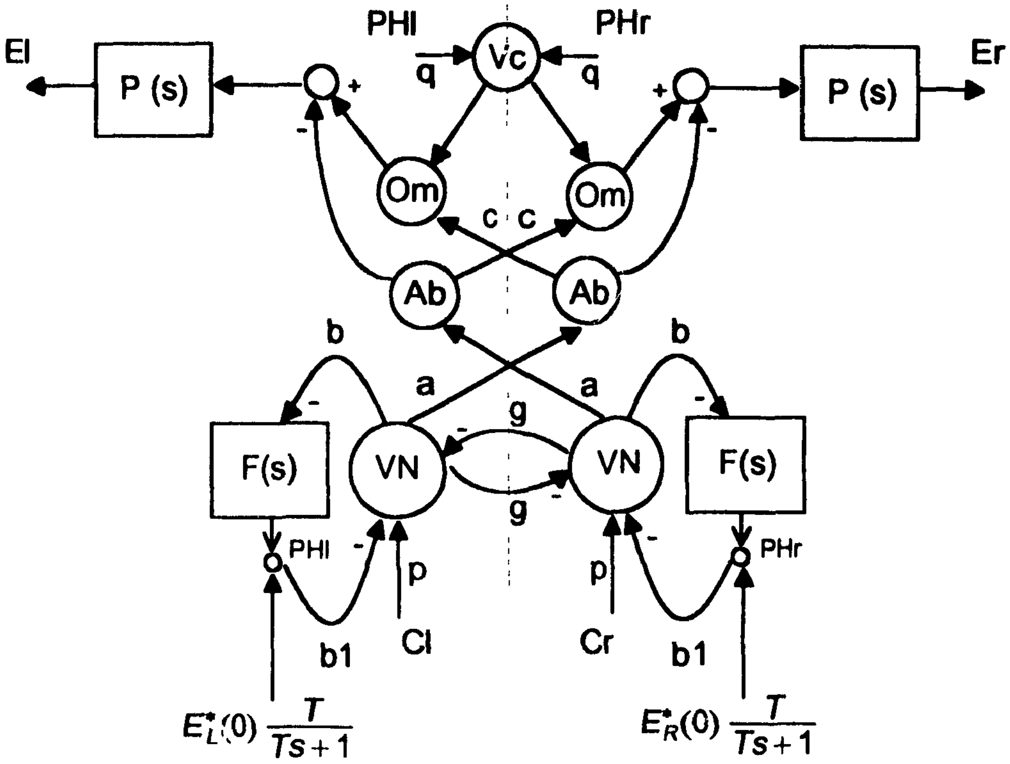

Figure IV.3 Model schematic during "no target" conditions

As required for proper VOR function during slow phases, an increase in canal modulation causes each eye to rotate in a direction opposed to head movement. Defining the VOR transfer function as the ratio of the Laplace transform of conjugate eye velocity and the Laplace transform of head velocity, with zero initial conditions:

$$\frac{s(E_R(s)-E_L(s))}{2\,\dot{H}(s)}=\frac{2\,G_{cd}\,K_e\,s^2\,T_c\,(T_{dd}s+1)}{(T_cs+1)(T_{dmd}s+1)(T_es+1)} \qquad \text{(Eq. 4.22)}$$

Making T_{dd} approximate T_e in order to provide compensation for eye dynamics, the resulting VOR gain in the passband (w >> $1/T_{dmd}$, $1/T_c$) is given by:

$$\text{VORgain} = \frac{2G_{cd}K_e}{T_{dmd}} = \frac{(c+1)apc_sK_e}{(g-1)T_e} \qquad \text{(Eq. 4.23)}$$

where T_{dmd}, the time constant of the reflex, can be much larger than the canal time constant:

$$T_{dmd} = \frac{T(1-g)}{1-g-bKb1} \qquad \text{(Eq. 4.24)}$$

Equations 4.22 and 4.23 are equivalent to previously postulated expressions for the VOR transfer function and gain (Galiana, 1991). As previously noted by Galiana (Galiana and Outerbridge, 1984) the commissural gain g plays an important role in determining the gain of the reflex and could constitute a putative site to partially govern adaptation processes (Galiana et al., 1984). From Equation 4.24 it is inferred that the dynamics of the reflex would also be altered as a result of changes in the commissural coupling and/or in the dc gain of the VN loop ($bKbl$).

The difference and common mode terms related to initial conditions at the output of the internal filters ($E_R^*(0)$, $E_L^*(0)$) respond as decreasing exponentials with time constants T_{dmd} (refer to Equation 4.24) and T_{cmd}:

$$T_{cmd} = \frac{(1+g)T}{1+g-bKb1} \qquad \text{(Eq. 4.25)}$$

As seen, initial conditions can significantly affect the time course of slow phase VOR, since the dynamics of vestibular and initial condition terms are comparable. With regards to vergence, by comparing Eq. 4.14 and 4.24 it is evident that the silencing of collicular efferents can cause a considerable increase in the common mode time constant of the system, which would account for the slow dynamics of vergence during "no target" conditions.

IV.4 Model simulation

Simulation Methods

Simulations were performed on an IBM RISC 6000 workstation and on a 80386 DX25 personal computer using SIMULAB, a graphical interface to MATLAB, the systems analysis and identification package by The Mathworks Inc. Time increments for the simulations were fixed to 10 msec, providing an effective sampling frequency well above the Nyquist rate. Responses were obtained at different premotor and motor sites in the model using ramp, sinusoidal and step input signals.

Choice of model parameters

Model parameters were selected to approximate observed premotor and motor dynamic responses in monkey. In order to satisfy stability requirements, closed loop poles were placed in the open left half complex plane. The common mode time constant of the system was set to 160 msec, compatible with previous studies on the frequency and time response characteristics of vergence. The vergence gain was fixed near 1, in order to simulate reported values of fixation disparity for target vergence step inputs. In agreement with published data (Smith and Galiana, 1991), model parameters provide a VOR gain of 0.5 for sinusoidal rotation in the dark, together with a reflex time constant of 15 seconds. In order to account for the slow decay of vergence holding found in "no target" conditions, the common mode time constant of the system with no collicular modulation (see Figure IV.3) was set close to 5 seconds. The steady state position sensitivity of vergence cells was adjusted to 15 spikes.sec^{-1}/deg, within the range of previously reported primate data (Zhang et al., 1992). To satisfy these conditions a unique set of parameters was used in all the simulation tests for different experimental conditions. Table 4.1 summarizes the complete parameter set employed for the simulation runs:

PARAMETER	VALUE
a	0.4
b	0.11
b1	12.06
c	6.71
c_s	0.4
g	1/58
K	0.75
K_e	0.2
p	0.48
q	16

Table 4.1 Model parameters used during the simulations

r	1
r1	0.97
t	- 0.16
T	0.25
T_c	6
T_e	0.2

Table 4.1 Model parameters used during the simulations

Simulation Results

Several computer simulations were run to test the bilateral model performance The parameter set of Table 4.1 was used in every simulation irrespective of the functional changes in model structure associated with the silencing of premotor pathways in different experimental conditions. The simulations performed can be divided into four groups related to the nature of the tested response: vergence open loop, vergence closed loop, responses to vestibular stimuli and fixation decay in the dark

- **Vergence open loop response**

Previous experiments performed in both humans and monkeys characterized the vergence response under "open loop" conditions by using electronic feedback to make the vergence angle control the vergence stimulus (Rashbass and Westheimer, 1961; Cumming and Judge, 1986). According to observed responses to step disparities, it was postulated that the vergence system acts like an integrator. Vergence records obtained for open loop conditions showed ramp like movements over a short period of time (only a couple of seconds long, refer to Rashbass and Westheimer, 1961; Cumming and Judge, 1986). Consequently, previous models of vergence have included a slow process represented by an ideal or in some cases, "leaky" integrator with very large time constants (see Chapter II). The limitations of the aforementioned models are not going to be repeated here, but it is important to stress that the very short duration of observed data can lead to biased estimations of the gain and dynamics for open loop conditions. This becomes evident in Figure IV.4, the result of a simulation performed in the model with the collicular loop opened (see Figure IV.2). The vergence angle resembles a ramp signal and a subjective analysis in the presence of measurement noise could evaluate the gain of a pure integrator as being in the 3 to 4 deg.sec^{-1} / degree disparity range, compatible with reported values (see Rashbass and Westheimer, 1961). In fact the bilateral system behaves as a "leaky" integrator with only a 5 second common mode time constant!.

- **Closed loop vergence response**

The closed loop vergence response to disparity ramp stimuli is shown in Figure IV.5. The upper trace represents the trajectory of the target, a slow ramp with a velocity of 1 deg/sec. The vergence angle (lower trace), follows the input with a steady state gain close to 1. This simulation performed on the bilateral model is compatible with previous studies which analyzed vergence time responses to ramp inputs (Semmlow et al., 1986).

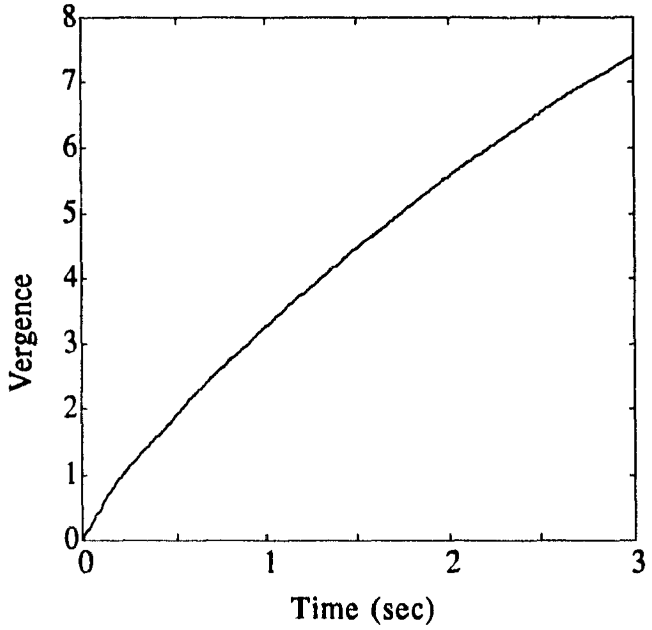

Figure IV.4 Open loop vergence response to 1 deg step disparity

Let us now examine the output signals from the neural elements of the bilateral model under closed loop conditions. The target vergence used for the simulations was a ramp signal with a 1 deg/sec slope. As shown in Figure IV 6 and IV 7, the model simulates the decrease in the firing rate of abducens motoneurons (Abmn) and AIN during convergence. The steady state gain predicted by the simulations agrees with reported values (Mays and Porter, 1984; Gamlin et al., 1989a): for Abmn the convergence gain is near -2.25 spikes.sec^{-1}/deg (see Figure IV.7) while for AIN projecting via the MLF the convergence gain is close to -8 spikes.sec^{-1}/deg (see Figure IV.6).

The firing rate of the oculomotor nuclei during convergence is depicted in Figure IV.8. Note the rapid transient increase in the discharge rate, which evidences the presence of a velocity related component. Then the firing rate increases proportional to the convergence angle. The characteristics mentioned above are consistent with a very recent study on the dynamic properties of medial rectus motoneurons during vergence (Gamlin and Mays, 1992). The predicted velocity sensitivity of approximately 1.4 spikes.sec^{-1}/deg.sec^{-1} is very close to the mean value (1 52 spikes sec^{-1}/deg.sec^{-1}) found in the cell population studied by Gamlin and Mays (1992) However, the

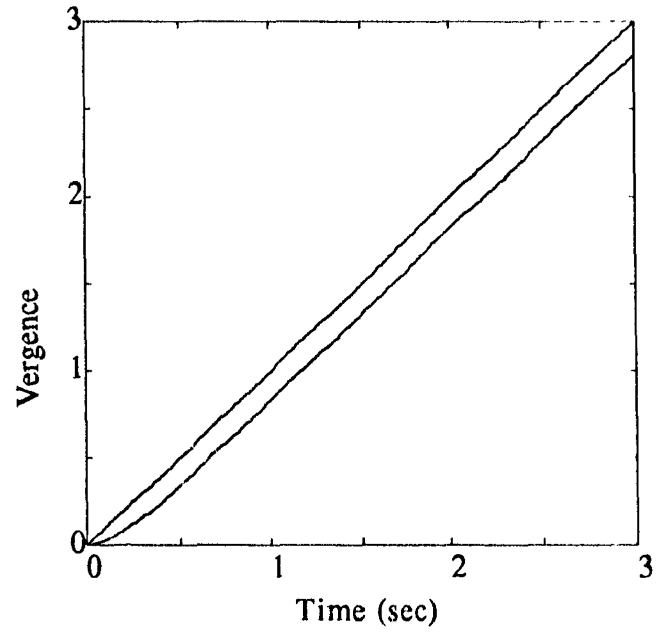

Figure IV.5 Closed loop vergence response to 1 deg/sec ramp stimulus

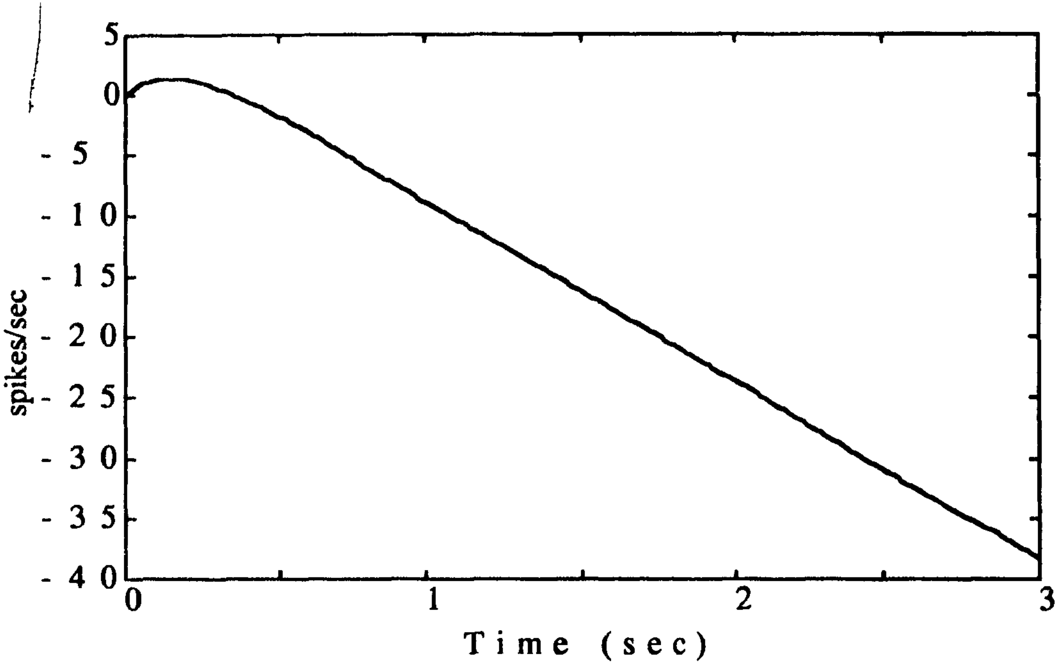

Figure IV.6 AIN firing rate for a 1 deg/sec ramp disparity input

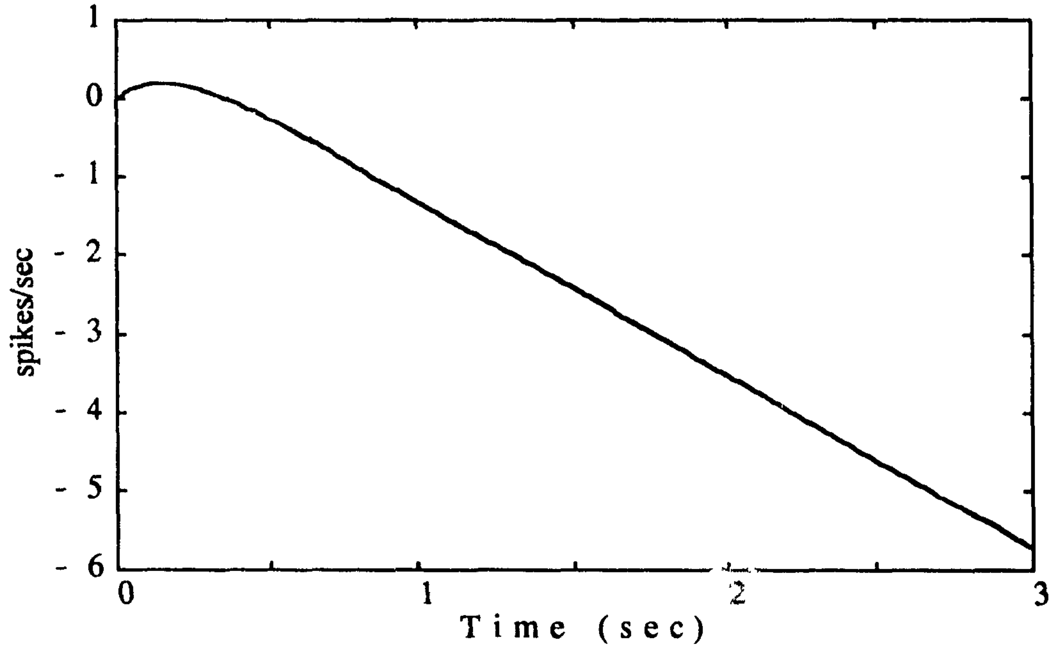

Figure IV.7 Abmn discharge rate for 1 deg/sec ramp disparity input

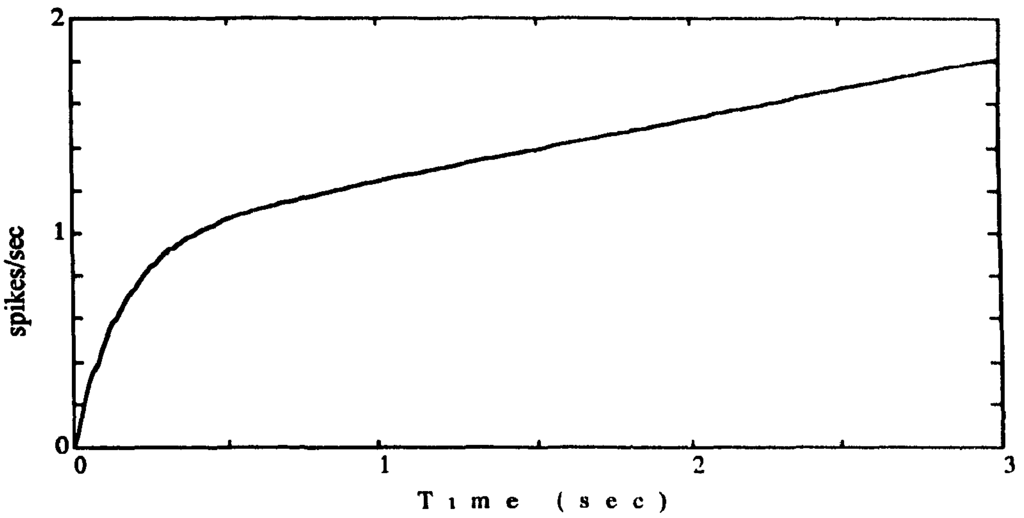

Figure IV.8 Oculomotor nucleus firing rate for 1 deg/sec ramp stimulus

predicted steady state gain (around 0.4 spikes.sec^{-1}/deg) falls within the lower range of reported values.

In agreement with previous studies (Mays, 1984; Judge and Cumming, 1986; Zhang et al., 1992) the simulated firing rate of vergence cells increases proportionally to the vergence angle (see Figure IV.9). The steady state gain is 15 spikes sec^{-1}/deg, consistent with reported values (Judge and Cumming, 1986; Zhang et al., 1992). From comparing the simulated activity of AIN, motoneurons and vergence cells it becomes clear that the increment in the firing rate of vergence cells overcomes the "inappropriate" decreasing discharge rate of AIN, resulting in an adequate drive for oculomotor nuclei motoneurons.

As stated earlier in this chapter, the model predicts a decrease in the firing rate of both vestibular nuclei with convergence angle. This effect (Tomlinson, 1991; pers. comm.) is shown in Figure IV.10, which depicts the VN output signal for a 1 deg/sec ramp disparity input. The position sensitivity predicted by the bilateral model is close to 5.5 spikes.sec^{-1}/deg.

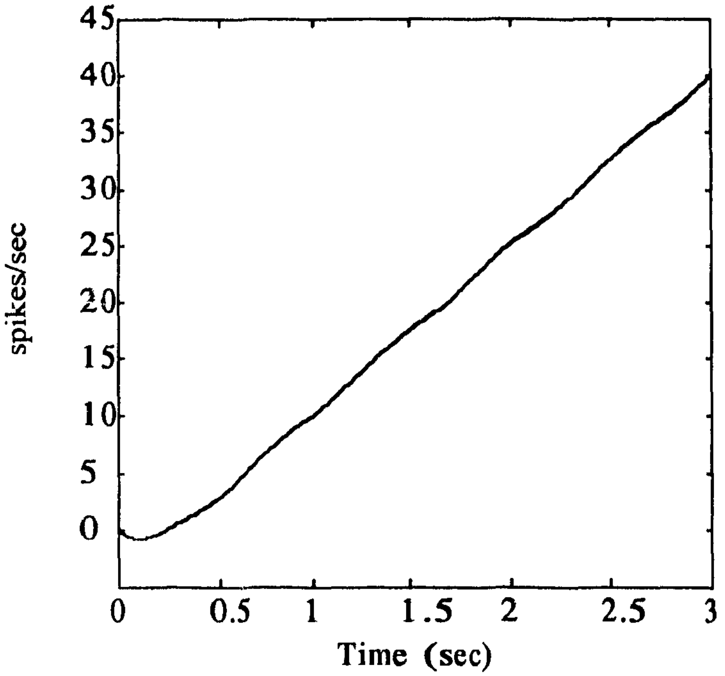

Figure IV.9 Vergence cells firing rate for 1 deg/sec ramp stimulus

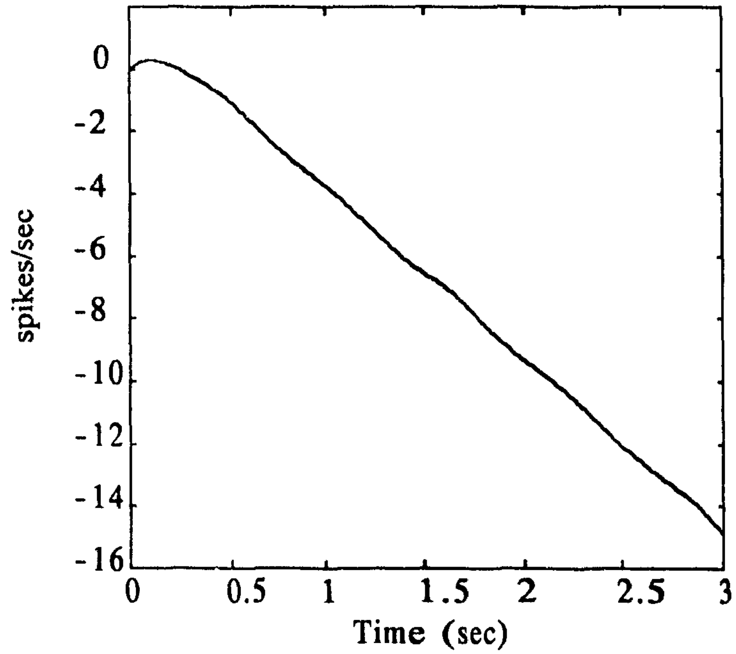

Figure IV.10 Vestibular nucleus firing rate for 1 deg/sec ramp stimulus

◆ Model response to vestibular stimuli

For sinusoidal rotation in the dark, the model accurately simulates slow phase VOR responses (refer to Figure IV.11). The input signal representing head velocity is a sinusoid with a frequency of 1/6 Hz and 10 deg.sec^{-1} peak amplitude. In steady state, the conjugate eye velocity is appropriately out of phase with head velocity, which results in compensatory eye movements to stabilize gaze. As seen in the figure, the VOR gain is 0.5, compatible with prior works on VOR modelling (Smith and Galiana, 1991).

◆ Fixation decay in the dark

Finally, let us examine the bilateral model response to initial conditions at the PH outputs. After a period of symmetrical fixation of a near target, if the lights are turned off suddenly and there are no cognitive inputs demanding the maintenance of fixation after target disappearance, the bilateral model reduces to the scheme of Figure IV.3. The inputs to the model are now weighted impulses representing equal initial conditions on the neural filters at the time of light to dark transition. Figure IV.12 shows the predicted vergence response during "no target" conditions, assuming the initial fixation of a target whose vergence demand is 1 degree. The vergence angle decays very slowly in an exponential manner, with a time constant of 5 seconds. The model response shown in Figure IV.12 is a very good approximation to observed vergence relaxation for "no target" conditions (for example see Figure 8 in Krishnan and Stark, 1977). In contrast, equal and opposite initial conditions on PH filters would correspond to previous fixation on an eccentric far target: here, the conjugate angle would decay slowly towards the rest position with a time constant of 15 seconds, as observed during experiments evaluating gaze holding in the dark. The response for assymetrical fixation (unequal initial conditions at the filters' outputs) will consist of the combination of two decaying exponentials with time constants of 5 and 15 sec, as reflected by Equation 4.21. As a result both common and difference modes will influence observed responses

Only a few of the wide properties of this model have been illustrated here. The following chapter will examine some of the implications resulting from model characteristics. Some proposals for future studies will be suggested.

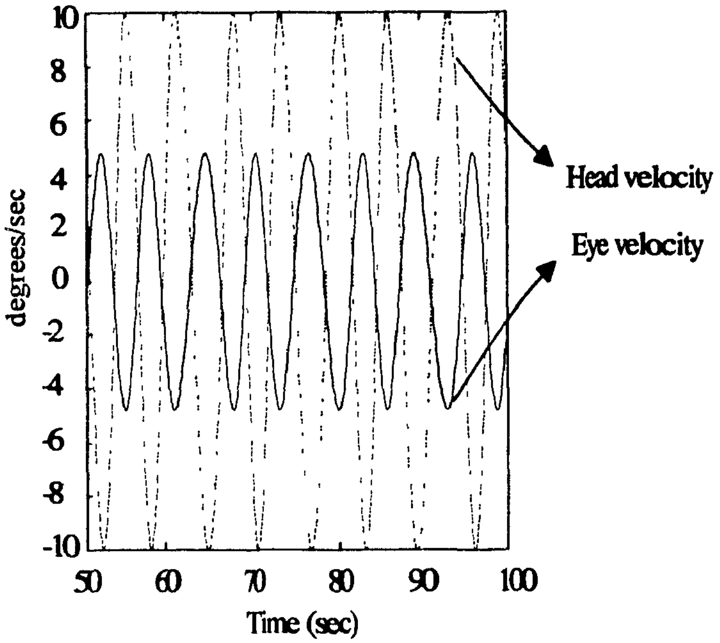

Figure IV.11 VOR response for sinusoidal rotation in the dark. f=1/6 Hz

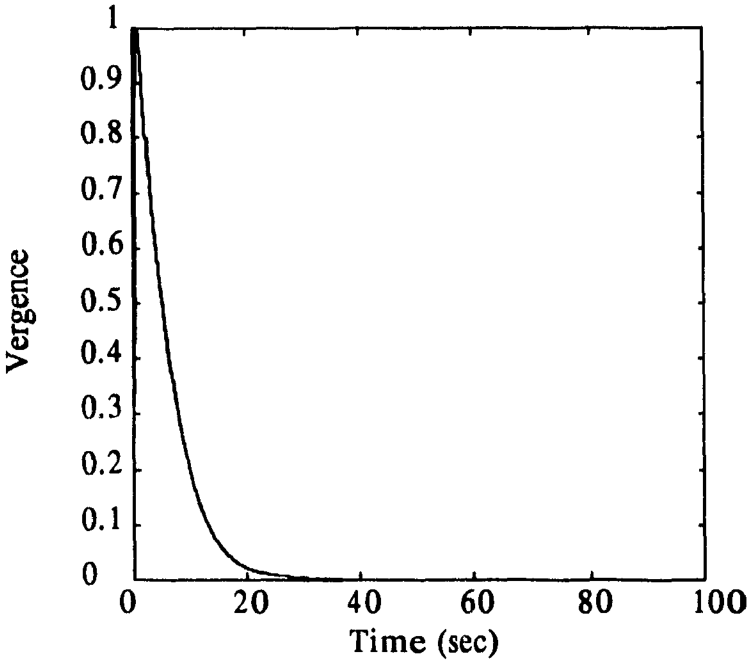

Figure IV.12 Vergence decay during "no target" conditions

V. DISCUSSION

The results of this work have described the properties of a bilateral structure in the coordinated control of vergence and VOR slow phase eye movements. In the context of vergence control, and different from previous dynamic models of vergence, the proposed bilateral model has a remarkable complexity as a consequence of its close relations to neurophysiology and anatomy. The model structure is compatible with known anatomical and physiological facts; a characteristic unfortunately not found in the majority of preceding studies on vergence modelling. These earlier models proposed structures based on input-output relationships, representing a system inherently bilateral in nature as a collapsed, single sided arrangement of dynamic elements. In consequence, previous models of vergence cannot predict the individual responses of each eye; a highly desirable characteristic for the analysis of asymmetric responses. Moreover, previous lumped vergence models cannot reproduce activity patterns of neural centers controlling vergence: the model elements are arbitrary and their outputs do not resemble neuronal firing rates.

The bilateral model from this thesis does not suffer from the above mentioned limitations of earlier models. The distinctive properties of the proposed model and some of their implications will be discussed in the following sections.

Anatomical and physiological consistency

The elements in the model can be easily recognized as representing known anatomical sites at premotor and motor levels. The connectivity of the neural centers involved in VOR and vergence control is properly reflected in the distributed connections depicted in the model. The proposed bilateral model is capable of reproducing the neural activity profiles of several brainstem nuclei, including modulations in their discharge rate with both visual and vestibular stimuli. The model appropriately simulates the decrease in the firing rate of both abducens internuclear neurons (AIN) and abducens motoneurons with convergence angle; as has been previously reported in neurophysiological experiments (Mays and Porter, 1984; Gamlin et al., 1989a). The firing rate of oculomotor nucleus motoneurons is also adequately simulated: the discharge rate increases linearly, proportional to movement amplitude in the convergent direction. The presence of components in the discharge which are related to eye velocity and position is reflected in the simulations performed on the model: results are compatible with recently reported observations on the dynamic properties of medial rectus motoneurons during vergence eye movements (Gamlin et al., 1992).

Vergence cells

One of the novelties introduced by the proposed model is the representation of vergence cells located in the midbrain. Results from model simulations show that the predicted discharge rate of vergence cells is consistent with activity profiles recorded in neurophysiological experiments (Mays, 1984; Judge and Cumming, 1986; Zhang et al., 1992). The simulations show an increase in the firing rate with increasing convergence angles, which results in a excitatory drive to oculomotor nucleus motoneurons. The bilateral model corroborates Mays' (1984) hypothesis that such an excitatory action from vergence cells overcomes the inhibitory influence of the AIN pathway, producing an appropriate increase in the activity of oculomotor motoneurons.

The proposed model places vergence cells in the motor output path, consistent with observations made by Judge and Cumming (1986) relating near response cell activity to the motoneural drive of vergence. These authors suggested the superior colliculus as a possible afferent structure, via known projections to the paraoculomotor area. However, in agreement with current neurophysiological knowledge, the superior colliculus in the bilateral model is concerned with processing of sensory information, in particular the transformation of retinal disparity and retinal disparity velocity into premotor and motor commands. Studies performed by Mays and coworkers (Mays et al., 1986) on vergence burst neurons confirmed that the firing rate of near response cells is related to the vergence response and not to its sensory drive. In consequence, we chose not to include direct projections from the colliculus to the vergence cells but rather represent known strong afferents from the prepositus hypoglossi carrying efference copies of eye position. This model representation, consonant with anatomy and physiology, stresses the relationship between vergence cell activity and vergence response since, as a result, the neural drive for vergence cells in the model is proportional to the instantaneous efference copy of vergence angle. Nonetheless, our choice does not rule out the possibility that collicular afferents could directly modulate the discharge rate of vergence cells.

One important prediction from the bilateral model concerns vergence cell activity during vestibular stimulation. Previous experiments have examined the influences of conjugate eye movements on the firing rate of vergence cells. However, only movements evoked by visual stimuli were studied. It was found that conjugate saccades and smooth pursuit eye movements do not modulate the activity of vergence cells (Mays, 1984; Judge and Cumming, 1986; Mays et al., 1986). Along this line, the bilateral model predicts that conjugate eye movements elicited by vestibular inputs coming from balanced semicircular canals will not cause modulation in the discharge rate of vergence cells. A potential functional implication of this model prediction involves slow phase VOR in the presence of vision: during compensatory movements in which the main goal is stabilize gaze in one particular point of space, it is convenient not to change the plane of fixation since this would contribute to a blurred image of the scene and deteriorate visual interpretation. The modulation of vergence cells activity as a result of vestibular imbalances might imply the appearance of vergence during high speed head rotation in the non-linear ranges of the canals.

The bilateral model as a platform for multisensory oculomotor control

One curious finding concerning sensory inputs and vergence cell modulation, arises from the studies of Judge and Cumming (1986). Within the examined population of mesencephalic neurons, the authors found cells whose activity was influenced by somatosensory inputs. Judge and Cumming labeled these neurons "other cells", and suggested that their activity was caused by muscle spindle afferents arising in the jaw muscle. However, it is important to mention that Guitton and Munoz (1991) in experiments with cats, found that tecto-reticulo-spinal neurons (TR(S)N) modulate their discharge rate with somatosensory inputs. Although Judge and Cumming (1986) did not clearly state if the group of "other cells" only responded to somatosensory stimuli and not to vergence or accommodation, it is possible that the colliculus could participate in the generation of a somatosensory-related drive to these cells (or near response neurons located in the vicinities) by means of distributed connections such as the ones represented in the bilateral model. Since visual, auditory and somatosensory collicular maps are coextensive (Guitton and Munoz, 1991) it would be relatively easy to include additional weighted inputs to the bilateral model, each one representing different sensory modalities. In this sense, the bilateral model of this thesis could provide the basis of a comprehensive model for multisensorial control of eye movements.

The bilateral model and the unified control of vergence and version

The lack of modulatory influences from conjugate movements on the activity of near response cells have been interpreted as evidence supporting the widespread idea of the independence of vergence and conjugate systems (Mays, 1984; Mays et al., 1986; Zhang et al., 1992). This traditional view of oculomotor organization considers the oculomotor system as composed of several separate subsystems controlling the different ocular responses. The outputs from each independent subsystems are linearly combined at the level of ocular motoneurons (Robinson, 1981b; Büttner and Büttner, 1988; Luebke and Robinson, 1988; Zee et al., 1992), implying that interactions between responses only occur at the periphery, in the extraocular motor nuclei. The bilateral model of this thesis provides evidence to refute such an assumption. A single, two sided structure founded on physiological and anatomical basis, is capable of adequately controlling two dissimilar eye movements: vergence and the VOR. The distributed processing of information through shared pathways enables the model to properly simulate the dynamics of vergence and VOR during slow phases. Interactions between ocular responses in the bilateral model occur at the central processing stage and not at the motor level, as has been suggested before. The proposed scheme is consistent with neurophysiological and behavioural observations. In experiments using target motions that demanded both vergence and version, Enright (1984) found that eye trajectories could not be predicted by a simple addition of conjugate and vergence commands as would be expected from subsystems acting in parallel. Moreover, vergence was accelerated during saccades, with a significant proportion of the total vergence movement occurring during disconjugate saccades. Similar effects were reported by Cumming and Judge (1986) in experiments with monkeys. These researchers found that during asymmetrical vergence, the movements are not smooth but are often interrupted by vergent saccades which cause transient increases in vergence velocity. More recently, Busettini and coworkers (1991) in experiments on the interactions between vergence and the optokinetic response (OKR) found that vergence modulated optokinetic and vestibulo-ocular responses in a very similar way, suggesting that both compensatory movements share a common structure. The above mentioned findings together with physiological evidence showing that central shared pathways are active during the different ocular responses (see Introduction), justify the existence of a bilateral structure for the coordinated control of eye movements such as the one proposed in this thesis.

Simultaneous binocular control

The two sided structure of the proposed model makes it possible to achieve simultaneous binocular control with separate processing of sensory stimuli on each side. Consequently, in the bilateral model one can examine individual eye responses, a very advantageous characteristic which enables to simulate the effects of central or peripheral asymmetries on eye movements. Asymmetric eye movements also occur as a result of asymmetrical vergence demands (for instance binocular tracking of a target moving in depth along the line of sight of one eye), interactions between conjugate and vergence movements or pathological conditions: the bilateral model constitutes a tool which may help in the study of such unsymmetric responses. The effects caused by sensory or neural imbalances on the activity of central brainstem areas represented in the model can readily be evaluated as well. Interestingly, slightly unequal movements are also observed in normal subjects when responding to symmetric vergence demands. As a result, many subjects with normal binocular vision exhibit an uneven distribution of the fixation disparity between the two eyes (Irving and Robertson, 1991)· the dominant eye is defined as the eye with the less fixation disparity. This condition can be simulated in the bilateral model by changing the sensitivity of pathways which increase the vergence gain of the dominant eye. Weather the observed unequal distribution is the result of small central or peripheral asymmetries is still unknown, but in any case the influence of such imbalances may be evaluated with the bilateral model as a tool.

Interactions between the VOR and vergence

Another interesting topic which may be investigated by using the model is the interaction phenomena between vergence and vestibulo-ocular responses. Recent evidence suggests that the VOR gain increases with vergence angle in order to achieve accurate stabilization of retinal images from near targets (Snyder at al., 1991). Changes in the VOR gain take place before the completion of the vergence movement, suggesting that interaction processes between VOR and vergence occur at central sites. Similar modulatory effects are observed for head rotations around off-center vertical axis (Snyder and King, 1992); in this case the associated translational movement of the head generates linear vestibulo-ocular responses which complement the action of the VOR.

When the head is linearly translated in space along the intra-aural (IA) or dorsoventral (DV) axis, excitation of the otoliths in the vestibular apparatus generates compensatory eye movements known as the linear (LVOR) or translational (TVOR) vestibulo-ocular reflex (Paige and Tomko, 1991a; Schwarz and Miles, 1991). The LVOR is also influenced by viewing distance: the gain varies inversely with target distance (Paige, 1991; Paige and Tomko, 1991b; Schwarz and Miles, 1991). The similitude between the modulation of both VOR and the LVOR with vergence, together with anatomical and physiological evidence (see Introduction and Chapter III) suggest both responses share a common central structure. The basis for this structure may be provided by the proposed bilateral model: additional inputs representing the directional dynamics of otolith organs can be included at the level of the vestibular nuclei in the model. The two sided symmetry of the bilateral model will generate compensatory movements in the horizontal plane in response to linear head motion along the IA axis.

Providing a comprehensive explanation for the mechanisms of vergence-(L)VOR interactions by using the bilateral model, deserves further studies and probably modifications to the model structure. Nevertheless, a tentative explanation for the observed phenomena may be associated with the observed decrease in the vestibular nucleus discharge as a result of increasing vergence angles (see Chapter IV). The decrease in the activity of the vestibular nuclei coupled with non-linearities affecting their output, can bring the operating point (analogous to a dc bias) for a given convergence angle to a zone where the gain of vestibular afferents is higher (parameter a in the bilateral model). Such an increase in the sensitivity of vestibular afferents would result in a higher VOR gain (refer to Equation 4.23).

Role of the Superior colliculus

In agreement with lesion (Cowey et al., 1984; Cowey, 1985) and physiological studies (Olivier et al., 1991), we have proposed a new role for the superior colliculus in the context of feedback control of slow eye movements. The colliculus in the bilateral model acts as a proportional derivative controller in response to instantaneous variations of eye motor error. This model representation of collicular activity during slow eye movements, although speculative, is consistent with neurophysiological studies on the characteristics of collicular firing rate during saccades (Berthoz et al , 1986; Guitton, 1991; Guitton et al., 1990; Munoz and Guitton, 1991; Munoz et al., 1991a,b) and the patterns of collicular discharges in response to visual stimuli (Guitton and Munoz, 1991; Robinson et al., 1991).

New approach for modelling both Conjugate and Vergence integrators

On the basis of collicular properties, the bilateral model may provide tentative explanations for recent findings concerning vergence relaxation in the dark, with "no target" conditions. It has been proposed that the slow decay of vergence responses is the result of the slow discharge of a vergence integrator that operates in parallel with a forward path (Leigh and Zee, 1991; Zee et al., 1992). This motoneural compensation stage is analogous to the one used in lumped models of conjugate eye movements (refer to Chapter II). The neural drive for the "vergence integrator" would be provided by vergence burst neurons (Mays et al., 1986) whose discharge rate encode instantaneous vergence velocity. According to this idea, the "vergence integrator" is a localized structure, which implies that the integration function could be deteriorated by damaging a particular brainstem site. However, this seems improbable judging from neurophysiological studies concerning the performance of the "conjugate" neural integrator (see chapter II). It is also important to mention that Mays and coworkers (1986) found a wide distribution of velocity and position components in the discharge of vergence cells the great majority of neurons in the population studied had both tonic and burst discharges. Consequently it is dubious that an ideal, "vergence velocity neuron" (Zee et al., 1992) feeding a vergence integrator could exist.

The bilateral model predicts the presence of position and velocity related components in the firing rate of vergence cells, as previously shown by Mays and colleagues (1986). The mathematical function of integration is a distributed property of the model and it is not confined to a particular site. Selective changes in the activity of collicular pathways in the model make it possible to obtain sluggish dynamics during "no target" conditions Simulated responses using the proposed bilateral model are consistent with observed vergence relaxation data (Krishnan and Stark, 1977). In addition, the bilateral model shows how the convergence of multiple pathways at premotor and motor structures generate appropriate velocity and position components at the level of motoneurons Hence, the model of this thesis demonstrates that a separate compensation stage is not needed to provide compensation for eye dynamics.

Other aspects of vergence function which may find some clarifications in the bilateral model are the sensitivity suppression effects observed during vergence responses to different kinds of visual stimuli (reviewed in Hung et al., 1990). Vergence sensitivity to rapid light flashes diminishes before and during the motor response. Similar suppression phenomena are seen for movements of the background and for small changes in target disparity. Interestingly, the visual sensitivity of the superficial layers of the colliculus has been found to decrease for differences in the relative direction and speed of a target against a moving background (Davidson and Bender, 1991). The sensitivity curves show a characteristic U shaped profile which could be easily used for representing, in the bilateral model, changes in the collicular discharge as a result of variations in the sensitivity of the superficial layers. It is also important to mention that sudden changes in room light level do not significantly affect collicular activity during saccades made to a target with motivational significance (Munoz and Guitton; 1991). This functional property of the colliculus may provide a clue to explain the reduction of vergence sensitivity to brief changes in illumination. Since sensitivity suppression effects have also been reported for conjugate eye movements (e. g. saccades) the bilateral model could also provide a basis for further developments destined to explain such phenomena

Clinical significance

The proposed model may constitute a useful tool in the analysis of the effects of lesions or the evaluation of disease states. For instance, one abnormality affecting vergence, internuclear ophthalmoplegia, may very well be evaluated by using the bilateral model. The syndrome of internuclear ophthalmoplegia is characterized by the loss of adduction for conjugate eye movements but not for convergence Adducting saccades in the affected eye are hypometric, horizontal smooth pursuit movements are seriously impaired and vergence responses have higher gains These deficits are believed to be caused by damage of the AIN-medial longitudinal fasciculus pathway ipsilateral to the affected eye (Gamlin et al., 1989b). In contrast to any previous model of vergence, the bilateral model may help to quantify the extension of the lesion by comparing real eye records with simulated outputs from the model in which the gain of the AIN projections (parameter c in the model) is varied in order to imitate lesion effects. The development of anatomically relevant models like the one presented in this study, could lead to non-invasive diagnostic tools, replacing more costly imaging techniques in some cases.

Applications to robotic control

Another potential field of knowledge which could benefit from the properties of the bilateral model is robotic eye control. A very recent work in this area has acknowledged the advantages that biological modelling may offer for the design of more accurate and efficient artificial vision systems (Coombs and Brown, 1991) However, the internal models of the vergence and conjugate controllers used in this study were extremely simplistic compared to previous models of oculomotor control The controllers are single sided and operate in parallel, independently from each other. The above mentioned facts limit the efficiency of the system and produce suboptimal interactions between the different conjugate and vergence control modes The use of a controller with a bilateral structure, like the one proposed here, may provide a superior performance by virtue of its close relationship to physiology and generate functional interactions Also, it is reasonable to expect a reduction in the computation time required for generating the controller output signal, since the use of integrated, more compact systems minimizes computing requirements.

Original Contributions

The following section summarizes the original contributions of this thesis which have been discussed above:

1. The proposed model constitutes the first bilateral model for the unified, simultaneous control of conjugate and vergence ocular responses.
2. The model of this thesis is the first bilateral model for vergence control developed fully on physiological and anatomical grounds.
3. The model shows how selective changes in the functional activity of shared pathways generate different dynamics in a single, bilateral structure. As a result, the vergence and conjugate integrators are distributed entities within the model and not separate, localized structures as previously suggested.
4. The model postulates a new role for the superior colliculus in the control of slow eye movements. The colliculus acts as a proportional derivative controller within a neural element feedback loop. The model representation of collicular activity is consistent with neurophysiological and lesion studies.
5. The bilateral, symmetric structure of the model makes it possible to reproduce observed characteristics in the discharge of premotor and motor centers in response to visual and vestibular stimuli: the proposed model appropriately simulates the firing rate of vergence cells, abducens and oculomotor motoneurons, abducens internuclear neurons and vestibular nuclei cells.
6. The model structure makes it possible to evaluate the influences of sensory and/or neural imbalances at different premotor and motor levels, as well as examine the resulting asymmetric ocular responses.

Directions for future Work

- **Development of a model for Vergence nystagmus**

The most immediate extension to the proposed model will be the development of a complementary scheme for the control of fast vergence (Semmlow, 1986; Leigh and Zee, 1991). Interestingly, the neural substratum for the "saccadic" vergence generator has close similitudes to its conjugate counterpart: during rapid vergence movements, the activity of cells coding vergence velocity (vergence burst neurons) is released by the silencing of omnipause neurons (Mays, pers. comm., 1992; Zee et al., 1992). The participation of the superior colliculus in an integrated scheme of rapid eye movement control seems likely, taking into account that the importance of its role in saccade generation has been demonstrated. Hence, it is possible that a common neural structure be involved in the control of both conjugate and vergence rapid eye movements. Extensions to the model of this thesis, reflecting the neurophysiological and anatomical basis of rapid eye movement control, may result in a bilateral structure capable of controlling both slow and rapid modes of vergence and conjugate eye movements. A good starting point for the development of a bilateral model extension for the visual control of rapid eye movements is the model postulated by Galiana (Guitton et al.,1990), which stresses the function of the superior colliculus in saccade generation and the control of gaze. In Galiana's model the superior colliculus, within a feedback loop, computes instantaneous gaze motor error by comparing desired gaze position with internal estimates of eye and head position. Collicular efferents drive several brainstem areas, including the vestibular nuclei and burst cells. In this model, vestibular afferents from the semicircular canal provide estimates of head velocity at the level of the vestibular nucleus Galiana's model is a good predictor of rapid gaze shifts with or without head perturbations (Guitton et al., 1990; Guitton, 1991).

- **Study of the interactions between vergence and accommodation**

Another interesting area in which the proposed bilateral model will serve as the basis for further developments is the study of vergence-accommodation interactions. Several models have already been postulated to explain the interdependence phenomena between vergence and accommodation (Hung and Semmlow, 1980; Schor and Kotulak, 1986; Zhang et al., 1992). However, these models are lumped, and in some cases, only address steady state relations between accommodation and vergence In consequence, the limitations found in interaction models are similar to the ones encountered in conventional disparity vergence models. Modifications to the model of this thesis may eventually result in a more complete scheme for describing vergence-accommodation interactions.

- **Characterization of response latencies**

Among our objectives for future work is the modelling of vergence response latency. Previous measurements of vergence latency have been subjective: no systematic methodology, such as correlation techniques, have been applied to obtain reliable measures of the delay within the system A preliminary simulation performed in the bilateral model shows that, system dynamics together with smaller physiological delays may account for the characteristics of disparity vergence step responses reported in some studies (Semmlow et al., 1986). We modeled the latency in the TR(S)N response to visual stimuli as a pure delay with a value of 60 ms, in agreement with reported data (Guitton and Munoz, 1991). A pure delay of only 50 ms was included within the collicular loop in the bilateral model to account for the observed latency in the generation of motor responses following TR(S)N activation (Munoz et al, 1991b) As Figure V 1 shows, the vergence response to a disparity step along the midline shows an initial rapid increase in vergence velocity, followed by an overshoot. The predicted output from the bilateral model is similar to the recorded disparity step responses of Semmlow and coworkers (1986; Hung et al., 1986). It is important to mention that we expect the model structure to vary as we try in the near future to represent other premotor circuits involved in saccadic vergence control. However, for rapid pure vergence demands along the midline, both colliculi remain active and the principles illustrated here remain valid.

This theoretical work uncovers the potential of a single bilateral structure for the complex coordination of visual tasks and body movement Response modes are coupled in the bilateral model: reported evidence suggests that real oculomotor responses are coupled as well. Consequently, traditional experimental protocols designed on the basis of the independence between subsystems should be reviewed We intend to do some experimental work to test the principles of unified control of version and vergence illustrated by the model of this thesis.

We believe that the trend initiated by Galiana (Galiana and Outerbrige, 1984; Galiana, 1990;1991) on the bilateral, homeomorphic modelling applied to oculomotor control will lead to further developments in the area. This modelling scheme has appealing capabilities for explaining interactions between control modes, offering unique advantages for the interpretation of behavioural and neural responses. We intend to continue our future research along this line.

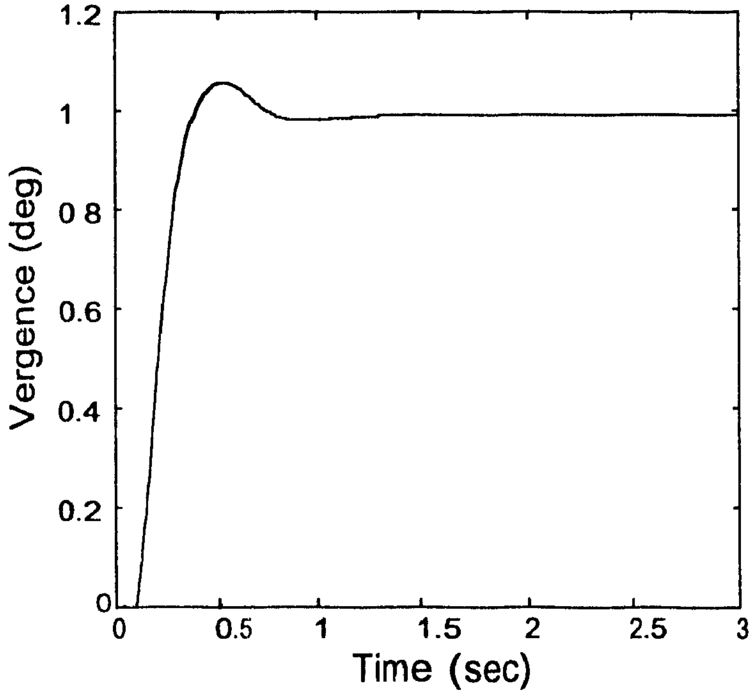

Figure V.1 **Step response of the bilateral model with built in delays. Collicular loop delay=50 ms. Visual responsiveness delay=60 ms.**

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