Understanding the sensory and motor behavior of accommodation in progressive myopic children

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Introduction: Accommodation and vergence, in unison, help in maintaining a clear and single binocular vision, a linchpin for normal vision development. Under natural viewing conditions, accommodation and vergence systems mutually interact with each other through a unique cross-link mechanism. Based on the empirical data from visually normal adults, several control theory models were proposed to predict the behavior of accommodation and vergence. Progressive myopic children, however, exhibit a transient but consistent abnormal accommodative behavior which is not predicted by the currently accepted models. Progressive myopes exhibit high accommodative adaptation, elevated AC output coupled with high accommodative lags. Several predictions, both sensory and motor origin, have been proposed to explain this behavior however they failed to predict this behavior completely. Furthermore, empirical conclusions on the impact of myopia over accommodation and blur sensitivity were mostly based on data obtained from adult population. Accordingly, this dissertation examined the sensory and motor mechanism of accommodation in young children with and without progressive myopia. Data from children were also compared to adults.

Methods: 12 children (8-13 years), 6 myopic and 6 non-myopic, and 6 naïve adults (25-33 years) were recruited for the purpose of this dissertation. Varying demands of accommodation were stimulated using a Badal optical system and recorded using custom-built dynamic photorefraction system (DPRS). Theoretical and empirical designs were developed to identify the ideal sampling rate necessary to measure a dynamic accommodative response. First and second order main sequence relationship and strength of the cross-link (CA) response was tested in the first experiment. In the second experiment, blur discrimination thresholds were tested psychophysically using simulated blur targets at two different stimulus demands. Furthermore, objective DOF and sensitivity of accommodative system to blur were examined using known demands of lens defocus and compared across different subject groups.

Results: The new custom built high speed photorefractor (DPRS) was found to be superior in measuring dynamic accommodation compared to the commercially available Power Refractor ($p < 0.001$). The current dissertation makes four major contributions to the field of accommodation and myopia: first, a motor deficit such as a sluggish or rigid plant cannot explain the abnormal behavior of accommodation in myopes. This was established based on the findings of a similar first and second order main sequence relationship between myopes and non-myopes ($p > 0.05$). Also, CA/C measures were not found to be attenuated as would be expected with a rigid plant. Novel simulations with reduced blur sensitivity coupled with a motor recalibration of AC gain did predict the myopic behavior. Second, atypical response patterns of accommodation such as the dynamic overshoots and double step responses were reported to exist with blur-driven accommodation. These patterns were suggested to occur due to an incorrect initiation of the response based on the similar main sequence findings between typical and atypical responses. Refractive error had no influence on the frequency of the atypical response in children. However, the influence of age reflects a developmental pattern in these dynamic atypical responses. Third, young progressive myopes showed large DOF and reduced accommodative sensitivity to lens defocus compared to non-myopes and adults. However, the ability to detect blur was similar between myopes and non myopes. Finally, depth of focus was found to increase with an increase in the stimulus demand. This change in the depth of focus was strongly correlated to a change in the microfluctuations but was independent of changes in the pupil size.

Discussion: These findings confirm that school aged myopic children exhibit an altered pattern of accommodation. The pattern appears to be associated to progressive myopia but cannot be readily explained by current motor models of accommodation and vergence. Empirical data and model simulations suggest that a sluggish or rigid motor plant (lens and ciliary muscle) cannot predict this altered behavior completely. The current dissertation speculates a reduced sensory gain (or reduced blur sensitivity) as the prime factor coupled with a compensatory motor recalibration in the accommodative convergence cross link. The large lags of accommodation reflect a large objective depth of focus in myopes. However, the capacity to detect blur was found to be independent of the retinal defocus present in the myopic eyes. The elongating eye of a progressive myopes appears to compensate the persistent retinal defocus on the retina by some form of a perceptual adaptation.

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Chapter 1

Literature review

1.1 Accommodation

Accommodation is a dynamic, optical change in the dioptric power of the eye allowing the point of focus of the eye to be changed from distant to near objects and vice versa[1]. Human accommodation is achieved by changing the curvature of the crystalline lens with the aid of the lens capsule, ciliary muscle, choroid and suspensory zonules (together known as the accommodative apparatus). Although there are several theories to explain the mechanism of accommodation[2,3], the most widely accepted one was given by Helmholtz [4]. This was later modified by several other researchers[1,5–8].

In an unaccommodated state, a relaxed ciliary muscle exerts increased tension on the suspensory zonules which in turn flattens the lens and holds it in a conoid shape. Blur is the primary stimulus to accommodation[1,9,10]. Proximity and retinal disparity can also stimulate accommodation[11–13]. The visual blur pathway starts at the level of the retinal cone receptors. Visual information then passes through optic nerve, reaches the lateral geniculate body and then transmitted to area V1 (visual cortex) for further processing. The neural signal is finally translated into a motor command at the level of the Edinger-Westphal (EW) nucleus in the midbrain. Although, the exact pathway to the Edinger-Westphal nucleus is unclear, the information could be derived from several areas in the cortex, midbrain and cerebellum[14–20]. The efferent pathway involves transmission of the motor commands from the EW nucleus to the ciliary muscle in the eye via the oculomotor nerve[21,22]. When the motor command reaches the ciliary muscle, it contracts and releases the tension on the zonular fibers. This allows the elastic forces of the crystalline lens capsule to mold the lens to make it steeper. Other changes include decrease in the lens equatorial diameter, an increase in lens axial thickness along with an increase in curvature resulting in an increase in the overall refractive power. Furthermore, the autonomic nervous system innervation on accommodation is composed of both inhibitory (sympathetic) and excitatory (para-sympathetic) input[23–25]. Along with the changes in pupil and vergence system, accommodation system ensures that a clear and single image is maintained. This synkinetic association between accommodation, vergence and constriction of pupil is termed as the near triad[12,26].

1.1.1 Static aspects of accommodation

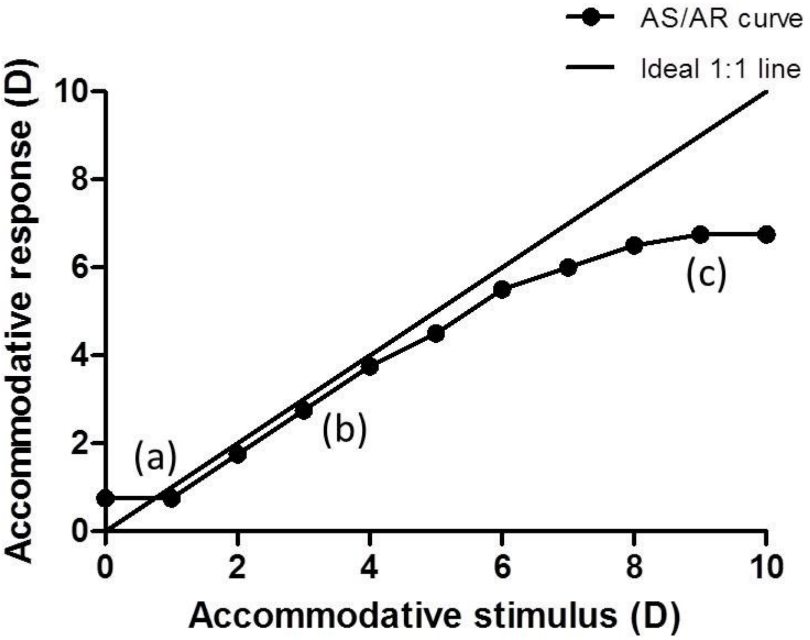

Figure 1-1: Accommodative stimulus-response function. This image is adapted from Ciuffreda, 1983.

The stimulus to accommodation (AS) is defined as the reciprocal of the target distance in meters and is expressed in the units of diopters (D). The accommodative response (AR) is the change in the dioptric power of the crystalline lens for a given stimulus demand. For an ideal optical system, response is equal to the stimulus demand. If the accommodative response is greater than the stimulus provided, it is called as a lead of accommodation. Conversely, if the response is less than the stimulus, it is called as a lag. The static aspects of accommodation are typically quantified using an AS-AR curve[12,27,28]. The accommodative stimulus (AS) response (AR) is a sigmoid shaped function[29,30]. As shown in figure 1-1, the solid linear line indicates a perfect 1:1 agreement between the accommodative stimulus and response (AS=AR). A typical static accommodative response curve can be divided into three distinct zones, (a) an initial non-linear zone (between 0 to 1.0D) where the response is more than the accommodative stimulus (AR>AS) due to the tonic level of the accommodation. (b) Linear zone, where a proportionate increase in the accommodative response is seen with the stimulus. Subjects tend to exhibit some lag in the accommodation response (i.e. AR<AS). This can be attributed to the sensory and optical factors such as depth of focus[31–33], spherical aberrations[34] etc. (c) Saturation zone or functional presbyopia, defines the maximum limit of accommodation.

1.1.2 Components of accommodation

The total accommodative response is composed of four components, tonic (or resting state), reflex, vergence and proximal accommodation[11].

1.1.2.1 Tonic accommodation

In the absence of an accommodative stimulus (blur), the accommodative mechanism assumes an intermediate resting position. This resting position is believed to reflect the tonicity of the ciliary muscle and a balance between the sympathetic and parasympathetic innervations[35,36]. Tonic accommodation can measured under stimulus-free scenarios such as dark room, bright empty field, pinholes or using difference of Gaussian targets (DOG)[37–40].

1.1.2.2 Reflex accommodation

Blur is the primary stimulus to accommodation. A reflex response to a blur input is limited to about 2.0D[10] and is constrained by the optical factors such as the size of the pupil. This constrain represents the depth of focus which is described as the dioptric extent of defocus that won't affect the perceptual quality[32] and can be influenced by several factors such as pupil size and target characteristics[32].

1.1.2.3 Vergence accommodation

Vergence (or convergence) accommodation is an accommodative change driven by the vergence system in the absence of an accommodative stimulus[13,41]. Clinically, the strength of the vergence driven accommodative response is quantified as CA/C ratio. Vergence driven accommodative response is measured using prisms in the absence of an accommodative stimulus (using either pin-holes or DOG target). The CA/C ratio represents the change in the accommodative response (D) produced by a unit change (prism diopters, Δ) in the vergence stimulus (stimulus CA/C) or the vergence response (response CA/C). Typical CA/C ratios range between 0.02 – 0.16D/ Δ[13,41,42].

1.1.2.4 Proximal accommodation

An accommodative response change due to perceived distance or knowledge of apparent nearness of an object of interest is termed as proximal accommodation[37,43,44]. Apparent change in the size or distance, voluntary effort or awareness of surround have been reported to influence the accommodative response.

1.1.3 Dynamic aspects of accommodation

An oculomotor response can also studied using its dynamic or time-varying properties. The dynamic aspect of accommodation can be described using its dynamic characteristics such as response time, latency, velocity and acceleration[45–51]. Latency (sec) is the time taken to initiate an accommodative response after the start of the stimulus. As shown in figure 1-2, the dioptric difference between the start (A) and the end point (B) of a response is called as amplitude of the response (D). The time between the start and the end points of a response is called as the response time or the movement time. Accommodative mechanism typically exhibits a latency of approximately 350-500msec and takes approximately one second to complete the response[47,50,52,53]. Differentiation of the response trace over time results in the velocity trace, a first order dynamic parameter. Peak velocity (D/sec) is the maximum velocity attained during the response and the time taken to reach that point from 0D/sec is called time to peak velocity. Differentiation of the velocity trace further results in an acceleration trace, a second order dynamic parameter. Peak acceleration (D/sec^2) is the maximum acceleration attained during the response and the time taken to reach that point from 0D/sec^2 is called time to peak acceleration. An age related trend was noted in the dynamic aspects of accommodation such as peak velocity and acceleration[45,46,51,54].

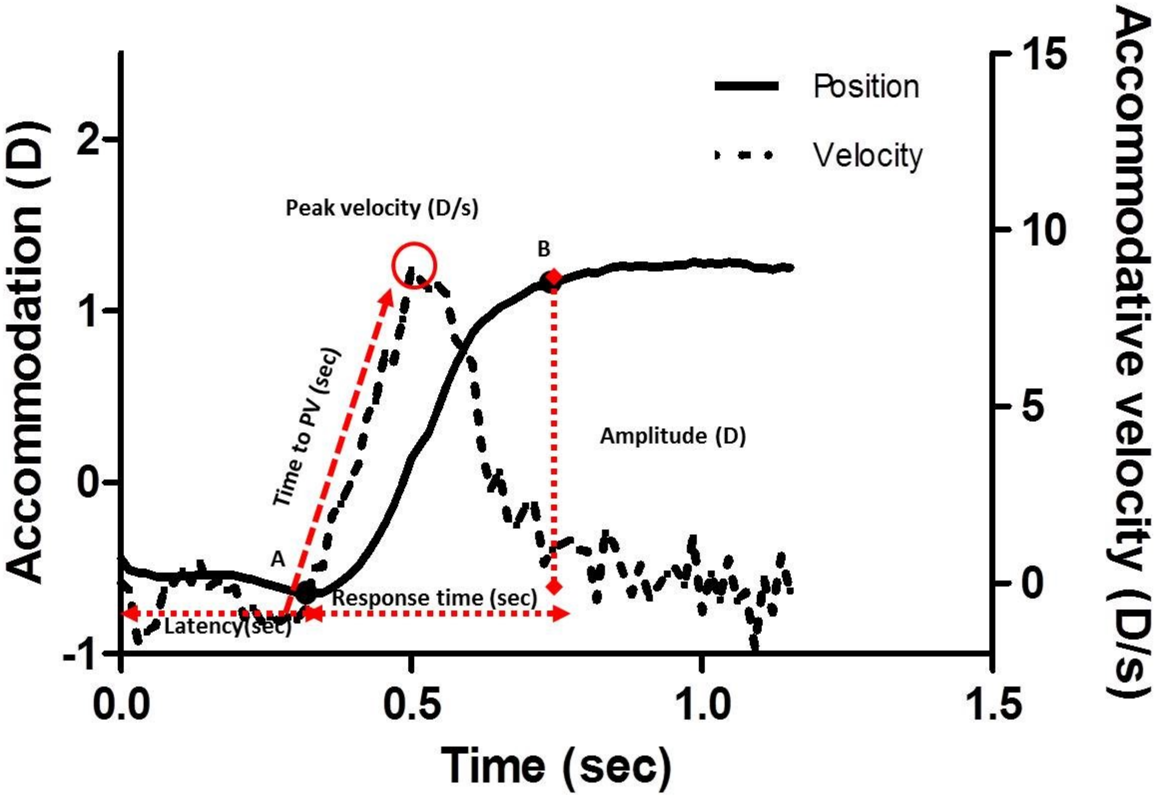

Figure 1-2: Dynamic aspect of an accommodative response to a 2D step stimulus.

Main sequence, however, is the most commonly employed parameter to quantify the dynamic property of the oculomotor system. It was first used to quantify saccadic eye movements[55,56] but was later employed to describe vergence[57] and accommodation[49,58]. Main sequence is typically quantified as first and second order main sequence. A first order main sequence relationship is obtained by plotting accommodative response velocity (D/s) as a function of accommodative response (D). Similarly, second order relationship is obtained by plotting accommodative response acceleration (D/s^2) over the accommodative response (D). Stimulus magnitude, start point and age were found to influence the linearity of the first order main sequence relationship[49,59,54]. However, the cue to accommodation (blur or disparity) did not appear to influence either the dynamic characteristics or the main sequence relationship[50,60].

1.1.4 Accommodative interactions and adaptation

Accommodation and vergence exhibit a unique cross-coupled behavior. Retinal blur input can elicit a vergence response through the accommodative convergence (AC) cross-link even when the vergence system is kept under open loop conditions[61]. Similarly, as described before, retinal disparity can elicit an accommodative response through the convergence accommodation (CA) cross-link mechanism. These cross-links are typically quantified as AC/A and CA/C ratio[41,62–64]. Similar to CA/C ratio, the strength of accommodative convergence cross-link (i.e. AC/A) ration can quantified as the change in the vergence response (prism diopters, Δ) produced by a unit change (D) in the accommodative stimulus (stimulus AC/A) or the accommodative response (response AC/A). Typical stimulus AC/A ratio ranges between 4-6Δ/ D[65]. Response AC/A are usually higher given the lags present in an accommodative response.

Similar to other motor systems, oculomotor systems such as accommodation and convergence exhibit motor adaptation. This process is essential in maintaining an optimal and stable motor control. When the stimulus to accommodation is sustained, depending on the duration and the magnitude of the stimulus, the new response will be directionally biased[66–69,39,70–73]. This phenomenon of adaptation was first noted in vergence[11,68] followed by the accommodative system[67]. Both fusional vergence and blur accommodation were believed to be composed of two sub-controllers with a varying time-constant: a fast reflex component followed by a slow adaptive component. The slow component has a longer decay rate proportional to the duration and magnitude of the stimulus leading to motor adaptation. This adaptive component reduces the response errors caused by the reflex response and is masked in darkness[39].

1.1.5 Control theory models of accommodation and vergence

Biological systems have been typically simplified and analyzed using control theory. The behavior of oculomotor systems such as saccades[74,75], vergence[76,77] and accommodation[27,77–80] have been predicted using control theory models. A control model system consists of several sub-systems (neural controllers and motor plants) designed in such a way that a desired output is obtained for a particular input[81,82]. Control systems, in general, can be of two types, open (no feedback) and closed loop (with a feedback mechanism). Feedback mechanism compares the output of the system to the input (error) to ensure accuracy in the response. Given the behavior, motor systems are typically quantified using a negative feedback mechanism wherein the response output is continuously compared to the stimulus input to ensure accuracy.

1.1.5.1 Dynamic model of accommodation

Based on the empirical data[29,67,39,72,79,83–87], accommodation and vergence have been modelled as two closed loop (negative feedback) systems that interact with each other through a unique crosslink mechanism (accommodative vergence, AC and convergence accommodation, CA). There are other models[79,88] developed for accommodation, however, Schor's model was chosen for this dissertation since it accurately predicts the cross-link behavior following adaptation[89]. In the model (Figure 1-3), retinal blur and disparity are modelled as the primary inputs to accommodation and vergence respectively. If inputs are greater than the system's dead zone (accommodation: depth of focus (DOF); vergence: Panum's fusional area (PA)), the input will feed into the neural controllers. The neural controllers are modelled as two leaky integrators that build up the innervation in response to the input provided. The controllers basically indicate the neural mechanism which transforms a physical stimulus such as blur or disparity into a motor command for accommodation (lens and ciliary muscle) or vergence (extra-ocular muscles) plants.

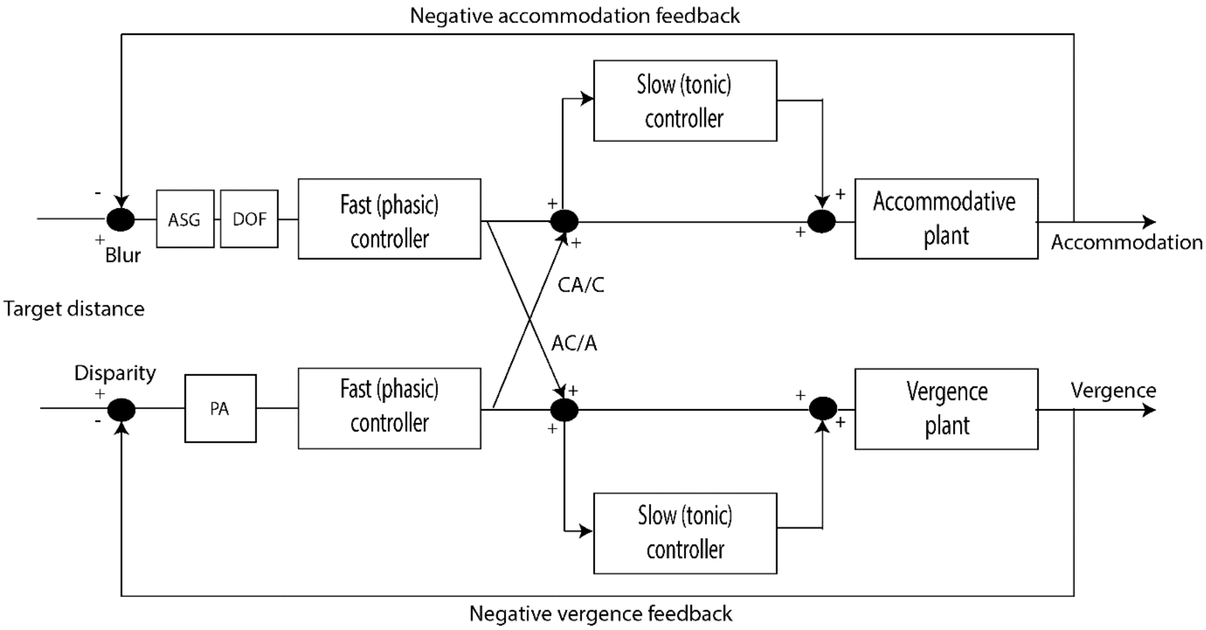

Figure 1-3: Simplified model of accommodation and vergence along with their cross-coupled interactions and feedback mechanisms. This image is adapted from the model proposed by Schor[66].

The two integrators with a variable time constant represent the fast and slow controllers responsible for the reflex and adaptive response of the system respectively[71,90]. The controllers represent the population of the phasic and tonic cells in the midbrain which variably increase their firing rate when exposed to a physical stimulus[15,16,18,19,91]. Although the two controllers differ mathematically in the way they innervate the motor plant, they behave similarly to maintain the steady state of the response. The phasic system also provides a cross-link input to the other system (AC or CA response). When the near stimulus is sustained, as the tonic system replaces the phasic system over time, the cross-link input is gradually reduced[72,89,92]. For example, AC output is reduced as tonic accommodative takes over the phasic accommodation. Similarly, a reduction is noted in the CA with vergence adaptation. Therefore, these cross-link channels, modeled as gains, are placed between the two controllers. The slow adaptive system is proposed to reduce the stress on the phasic system and also to ensure balance between the two cross-coupled mechanisms. Finally, the motor signals are sent from the midbrain (controllers) to the plant (accommodative apparatus and extraocular muscles) to produce a motor response. The negative feedback mechanism ensures the accuracy of this final motor response by feeding back the error signal (Error: (response) - (stimulus)).

1.1.5.2 Pulse step model of accommodation

The dynamic cross-coupling model (Figure 1-3) proposed previously assumed that the accommodation system receives a step innervation which would cause a proportional increase in the response amplitude, velocity and acceleration[93–95]. However, there were a number of studies that refuted this assumption of a pure step innervation. First, EW neurons showed a gradient change rather than an abrupt change in the firing pattern for a particular accommodative stimulus[18,19]. Second, the presence of a saccade influenced the peak velocity of accommodation but not the overall response magnitude[96]. This suggests that the reflex system contains two components, one responsible for the response initiation or dynamic characteristics and the other one for response accuracy. Finally, peak acceleration and peak velocity behave differently with response magnitude and age[45,49,58]. This suggests that the reflex component responsible for the dynamic characteristics has different subcomponents responsible for acceleration and velocity of the movement. To address these discrepancies, a pulse step model of accommodation was proposed to fit the empirical data[76,97–99] accurately.

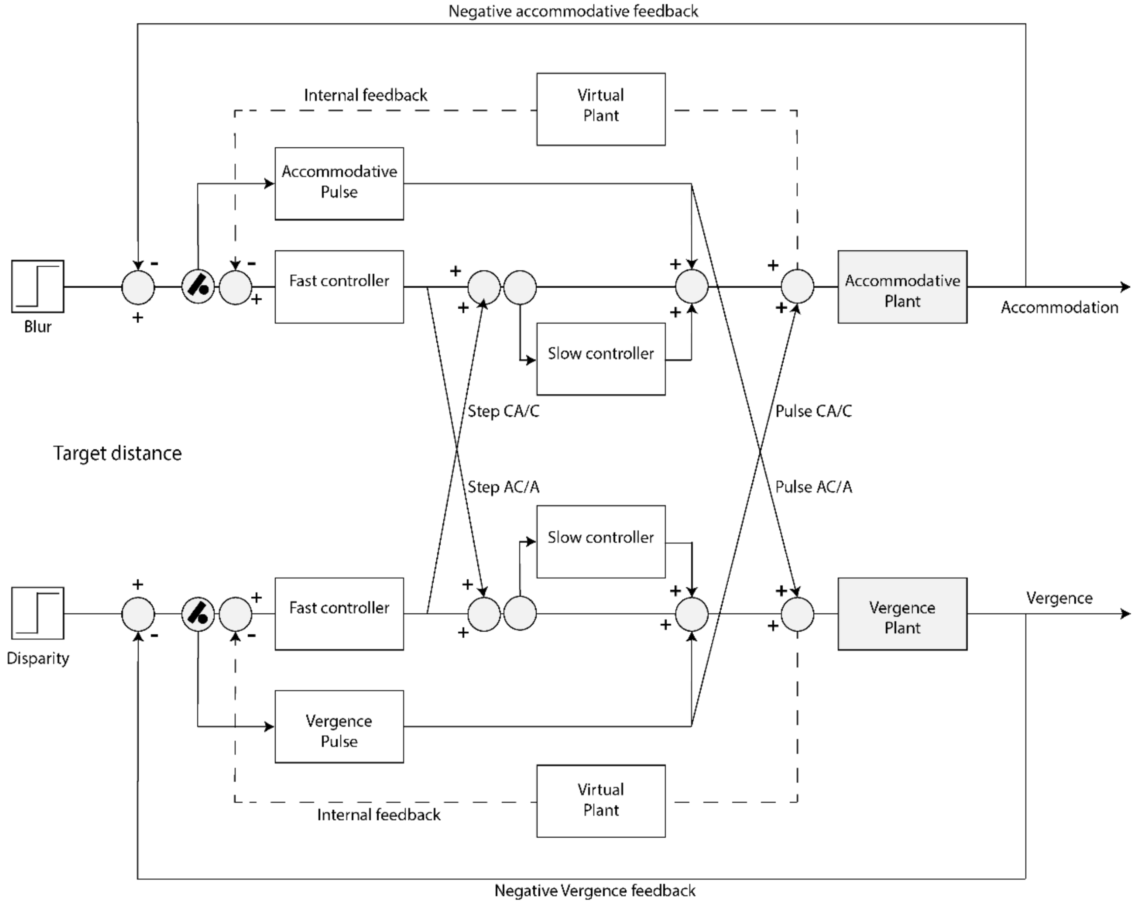

Figure 1-4: Pulse step model of accommodation and vergence along with their cross-link interactions. (This image is adapted from the model proposed by Maxwell et al.[65])

According to the model[97], the accommodative mechanism comprises of two modules, a biomechanical module (accommodative apparatus)[95,100] and a neural module[18,19,94,101,102]. The biomechanical module details the agonist-antagonist linkage between the active (ciliary muscle) and passive elements (lens, zonules and choroid) of the accommodative apparatus. The neural module consists of two leaky integrators representing the fast (phasic) and slow (tonic) controllers. The reflex fast controller is modelled as an open loop (fixed height-variable width) pulse signal coupled with a closed loop (variable height) step signal responsible for the dynamic characteristics and accuracy of the response respectively. The pulse signal was modelled based on the behavioral data which showed that the peak velocity increased proportionally with stimulus amplitude but not peak acceleration[45]. While the fixed height of the **pulse** signal codes for peak acceleration, the variable width of pulse codes for the peak velocity of the response. The height of the closed loop **step** signal indicates the error (response-stimulus) detected by the system and it decreases as the system makes a response. The step signal is always under the influence of an internal feedback system (virtual plant) to ensure the accuracy of the response without any over or undershoots. The two signals (pulse and step) were speculated to integrate at the level of Edinger-Westphal nucleus which is then transformed by the accommodative plant to make an accommodative response. The slow controller responsible for adaptation is similar to the one described previously (Figure 1-2). Given the behavioral evidence on the relationship between the disparity driven and cross-link driven vergence response[76], a pulse and step crosslink channels were modelled which code for the dynamic and static aspect of the cross-link response. This pulse step linkage of accommodation was a better fit to the empirical data[18,45,50,51,58,69,96] currently available compared to the previously proposed dynamic cross-coupling model.

1.1.6 Development of accommodation

Several studies in the 20th century examined the developmental pattern of accommodation in early childhood by measuring both static and dynamic aspects of accommodation to different targets, spatial cues responsible to drive the response at different ages, accommodative vergence interactions etc[63,103–113,42,114–120]. These studies have concluded that: (1) Vergence develops before accommodation. (2) Both static (quantified either using the slope of AS-AR curve or response lags) and dynamic (quantified by examining the peak velocity of a response to a particular stimulus) aspects of accommodation are adult like by 3-6months of age. Accommodation is either fixed to particular response level or is variable before this age. (3) Overall, infants and toddlers exhibit a larger steady state error and longer response latencies compared to the adults. (3) Proximal cues appeared to be more effective in driving an accommodative response during the early infancy (< 14 weeks) compared to blur and disparity cues. However, older infants were equally responsive to blur, disparity and proximity cues. (4) Both AC and CA cross-links were present in children. Infants had an adult like AC/A ratio but a higher CA/C ratio compared to the adult population.

1.2 Myopia

Myopia, commonly known as near-sightedness, is a refractive anomaly where the axial length of the eyeball progressively grows beyond its correct focal distance. As a result, parallel rays from a distant target will be focused in front of the retina with accommodation at rest. It is commonly corrected using spectacles or contact lenses. Myopia can be classified based on either the magnitude of refractive error (low (up to -3D); moderate (-3D to -6D); high myopia > -6D) or age of onset (congenital (myopia at birth); early or juvenile onset myopia (6-15 years); late onset myopia >15 years), or based on pathology (simple or pathological myopia). Global trends indicate that uncorrected myopia is the leading cause of visual impairment[121,122]. High myopia is also typically associated with sight-threatening complications such as retinal degenerations, retinal detachments and open angle glaucoma[123]. Myopia has reached epidemic proportions in Asian countries[124] and affects about 40% of the population in North America[125–127]. A recent study showed global trends projecting at a billion people with high myopia by 2050[122].

1.2.1 Development of myopia

Several studies have looked at the role of genetic and environmental factors in the development of myopia. However, the nature and the relative influence of these factors over the development of the refractive error remains unknown[128–131]. These studies found that the risk of developing childhood myopia increases in children with myopic parents. However, based on the recent studies, it appears that environmental factors could definitely modulate the susceptibility defined by the genes[130,132,133].

1.2.1.1 Animal models

Studies on animals including chicks and primates found that the growth of the eye can be regulated by the quality of retinal imagery[130,134–136]. Earlier studies on form deprivation myopia (FDM) induced using lid suture[137] or translucent diffuser[134,138] suggested that eye growth can be regulated by reducing retinal imagery quality and laid the foundation to our modern day understanding of refractive error development. Later, several studies induced a retinal image defocus using convex and concave lenses. They found that the defocused image on the retina regulated the direction of the axial growth of the eyeball[8,87,136,139]. While a concave lens induced a hyperopic defocus and increased the rate of the eyeball growth, opposite was noted with convex lens with a decreased growth rate. However, these effects are limited to the critical period and appeared to be reversible after the removal of the lens. This ability to rapidly alter the direction of growth suggests that the visual system can detect the polarity of blur and adjust the growth rate accordingly. Interestingly, these growth patterns were noted even in animals with an ablated fovea[140], sectioned optic nerve[141], and no Edinger-Westphal nucleus[142]. Peripheral refraction[143] or local mechanisms[144–147] were shown to influence the eye growth, however, the exact mechanism to detect the sign of defocus remains uncertain. Given this evidence, a simple explanation for the human myopic development and progression would be presence of a hyperopic defocus on the retina. Accordingly, researchers hypothesized that the presence of excessive accommodative lags during near work would cause a hyperopic defocus on the retina leading to axial elongation (or myopia)[131,148].

1.2.2 Myopia and accommodation

1.2.2.1 Near work and outdoor activity

Near work has been shown to increase the risk of myopia onset[124,131,133,149–154]. Reduced outdoor activity coupled with increased near work (or an increased amount of time spent indoors) have been found to be consistently associated with the onset of myopia and its progression[124,129,155,156]. Accommodation was suspected to be a possible link between near work and myopia onset. Accordingly, several aspects of accommodation were examined to understand this possible link with near work.

1.2.2.2 Accommodation in myopia

1.2.2.2.1 Blur driven accommodation

Accommodation was found to be reduced in progressive myopic individuals compared to their non-myopic peers[148,157–162]. Accommodation response was found to be reduced when stimulated through negative lenses compared to a stimulus change due to a physical change in the target position[148,162]. Reduced accommodation to lenses was attributed to poor blur sensitivity and improvement in the response with physical change in targets reflected the influence of proximity cue on the final accommodative response. Several investigations consistently showed that adult myopes are less sensitive to blur or defocus information to drive an appropriate accommodative response[157,160,163–168]. However, a study on progressive myopic children reported that blur detection and discrimination thresholds are similar between myopic and non-myopic children[164]. A hyperopic defocus on the retina induced due to this reduced accommodative behavior was speculated to be a causative factor for myopia onset. However, there were conflicting results on whether a reduced accommodative behavior was present at the time of onset of myopia[158,159,169–171]. Based on these studies, it is inconclusive whether accommodation was reduced before or after the onset of myopia in children. Also, studies found no correlation between the lag of accommodation and the rate of progression of early-onset myopia[172]. Interestingly, studies found that this reduced behavior of accommodation is present only with progressive and not stable myopia[157,161].

1.2.2.2.2 Other components of accommodation

Unlike blur accommodation, vergence driven accommodative response (CA/C ratio) was found to be similar in adult myopes compared to non-myopes[173–177]. Tonic levels of accommodation have also been examined as a function of the refractive status on both adults and children. Most of these studies found that progressive myopes exhibit low levels of tonic accommodation compared to emmetropes and hyperopes[174,178–181,38,182,183]. Furthermore, studies on accommodative adaptation found a difference in the magnitude and decay rate of tonic adaptation[174,178,180,184–192]. The pattern was noted with both early and late onset myopia. This abnormal adaptive behavior was proposed to either indicate a deficit in the sympathetic innervation[193] or an imbalance between the sympathetic and parasympathetic supply to the accommodative plant[25].

1.2.2.3 Vergence in myopia

There is a very limited on the behavior of the vergence mechanism in progressive myopes. Several studies reported that progressive myopia is associated with a near esophoria (or an over-converged near phoria)[194,195]. The strength of accommodative vergence cross-link, typically quantified as the AC/A ratio, was found to be different in different refractive groups. Both gradient and calculated response AC/A ratios were found to be elevated in myopes compared to emmetropes[169,174,196,197]. This elevated level of AC/A ratio was also linked to the onset of myopia[169]. However, stimulus AC/A ratio was found to be similar between myopic and non-myopic individuals[197]. The greater response ratio was attributed to the reduced accommodative behavior. Vergence adaptation was found to be reduced in progressive myopic children compared to the emmetropes[186,198]. The direction and magnitude of the near phoria was found to influence the behavior of the slow adaptive response in both myopes and emmetropes[186,199].

1.2.3 Available treatment options for myopia

Based on evidence from both animal and human models[130,136,200], several theories about the development and progression of myopia have been proposed. This led to the development of treatment options that target and control these theoretical predictions[201,202]. One such theory described in the previous section was the presence of a hyperopic defocus on the retina caused by reduced accommodation to near objects. Treatment options such as progressive additional lenses (PALs), bifocals, multi-focal contact lens etc. have been developed accordingly to control for reduced accommodation[203–208]. Conflicting results were obtained on the efficacy of bifocals or PALs over myopia control with some reporting no/ limited success and others reporting a successful reduction of myopia[203,204,206,209]. A large multi-center clinical trial (COMET) found a statistical but not a clinical significant effect of PALs on the progression rate compared to single vision lenses. A closer inspection showed that the treatment was more effective only in children with larger esophoria (>5PD) coupled with high lags of accommodation (>1.50D) compared other myopic population[209,210].

Other treatment options include orthokeratology[211–213], special lens designs for treating peripheral refraction[214–216], atropine[217–221], lenses with base-in prisms[222] etc. All these interventions have been reported to significantly reduce the progression of myopia when compared to single vision spectacle correction[201]. Taken as a whole, only pharmacological treatment options such as atropine and peripheral defocus contact lens have been found to produce moderate effects (≈ 0.50 – 0.70D) on the rate of myopic progression in children[201,218].

1.3 Rationale and objectives

Progressive myopes, both children and adults, exhibit an abnormal pattern of accommodation. As described previously, several studies explored the accommodative behavior in myopes and reported it to be abnormal. However, this work was either limited to adults whose progression status remained unclear or limited to one particular abnormal pattern of high accommodative response lags. Firstly, it is important to identify the progression status of the myopic subject since the abnormal accommodative behavior is associated only with progressive and not stable myopia. Second, the abnormal behavior of accommodative mechanism is not just limited to high accommodative response lags and needs to be further explored in order to fully understand the impact of progressive myopia on accommodative mechanism and its cross-link interactions with the vergence mechanism.

Progressive myopes exhibit an accommodative behavior characterized by high response lags that increase with the demand, elevated response AC/A, high accommodative adaptation, reduced vergence adaptation and a normal CA/C. These patterns are not predicted by the currently accepted models of accommodation and vergence (figure 1-3). There is no evidence which comprehensively explains this altered behavior of the accommodative mechanism in progressive myopes. Why do progressive myopic children show a reduced accommodation? How can a reduced reflexive response drive a high cross-link and adaptive response? Is there a deficit in the underlying sensory or motor mechanism of accommodation which then leads to this altered behavior? Can it be explained by a motor deficit in the accommodative apparatus (ciliary muscle or lens) of the eye? Or are the high lags in the accommodation due to their reduced sensitivity to blur? Is it because they cannot detect or process blur efficiently or is it a combination of both motor and sensory deficits? Also, most of the studies reviewed before were done on adult myopes who may or may not be progressive. There is a very limited evidence on accommodative behavior in progressive myopic children compared to the adult myopes.

Accordingly, this dissertation examines the sensory and motor mechanism of accommodation in progressive myopic children. The major objectives and hypotheses of this thesis are as follows:

1) Understand the motor mechanism of accommodation in the eye. Does the dynamic behavior of accommodation differ between myopic and non-myopic children? Would there be an impact of age on this dynamic behavior?

Based on the available evidence on the ciliary muscle and lens of the eye, myopes might show a sluggish dynamic behavior and reduced accommodation to both blur and disparity.

2) Understand the sensory mechanism of accommodation. Are myopic children less sensitive to blur? If yes, is it reduced because of a deficit in blur detection or blur processing or both?

Based on available empirical evidence on blur sensitivity, myopes might show a reduced ability to detect and process blur information compared to the non-myopic children.

Chapter 2

Dynamic Photorefraction System (DPRS)

2.1 Instrumentation

2.1.1 Eccentric photorefraction

Eccentric photorefraction is a rapid video-based objective technique used to measure the refractive status and accommodation of the eye[1–3]. Both theoretical[4,5] and empirical investigations[1,2,6] showed that the eccentric arrangement of the IR LEDs produce a linear pattern of the intensity distribution across the pupil. This pattern was found to vary depending on the type and magnitude of the refractive error. Other than defocus, optical factors such as pupil size, fundus brightness and ocular aberrations can influence the intensity distribution across the pupil[1,2,4,5,7,8]. Furthermore, non-optical factors such as working distance, camera limiting aperture and source eccentricity also can affect the intensity distribution[1,2,6,9,10]. Therefore, it is very important to control these factors to ensure accuracy across individuals.

2.1.2 Need for a custom built high speed photorefractor?

Photorefractors are commonly used as either screening tools[3,11] or for research purposes[12]. For the purpose of my research on young school aged children, a custom built high speed photorefractor would allow the necessary resolution to measure dynamic properties of accommodation. It would also provide a manual control to make necessary calibration adjustments for each subject. One of the primary disadvantages with currently available commercial photorefraction technology is that they work on outdated platform such as Windows 98 (Power Refractor, Multi-channel systems, Germany) which is no longer technically supported. Also, dioptric estimates obtained from most of the commercially available systems are based on an average calibration factor. Unfortunately, this would reduce the accuracy of the estimate given the individual variation in the optical factors such as pupil size, fundus brightness and ocular aberrations. Theoretical evidence suggests that errors of over a 1D can occur if changes in the pupil size and fundus brightness are not accounted during the estimation of the refractive error[4,5]. Finally, given the low sampling rate of the currently available systems (for e.g. Power Refractor works at 25Hz), estimation of the first and second order dynamic characteristics of accommodation might be inaccurate[13].

2.1.3 Dynamic photorefraction system: high speed photorefractor

Accordingly, I designed a video-based eccentric photorefractor with a higher sampling frequency (70 Hz) during my Masters[9,14,15]. The configuration of this photorefractor was based on the design proposed previously[6]. The dynamic photorefractor is a fire-wire charge coupled device (CCD) camera (PROSILICA CAM (EC750), Allied Vision Technologies, Canada) with multiple infra-red (IR) light emitting diodes (LEDs) set at the knife-edge covering the bottom half of the camera. A total of 44 LEDs arranged in 8 rows with a maximum eccentricity of 45mm were mounted on an aluminum plate and then fixed onto the camera. The peak wavelength of the LED source was 895nm. Infrared LEDs were incorporated at multiple eccentricities to extend the range of measurement, enhance the precision and to decrease the dead zone of the instrument[2,4].

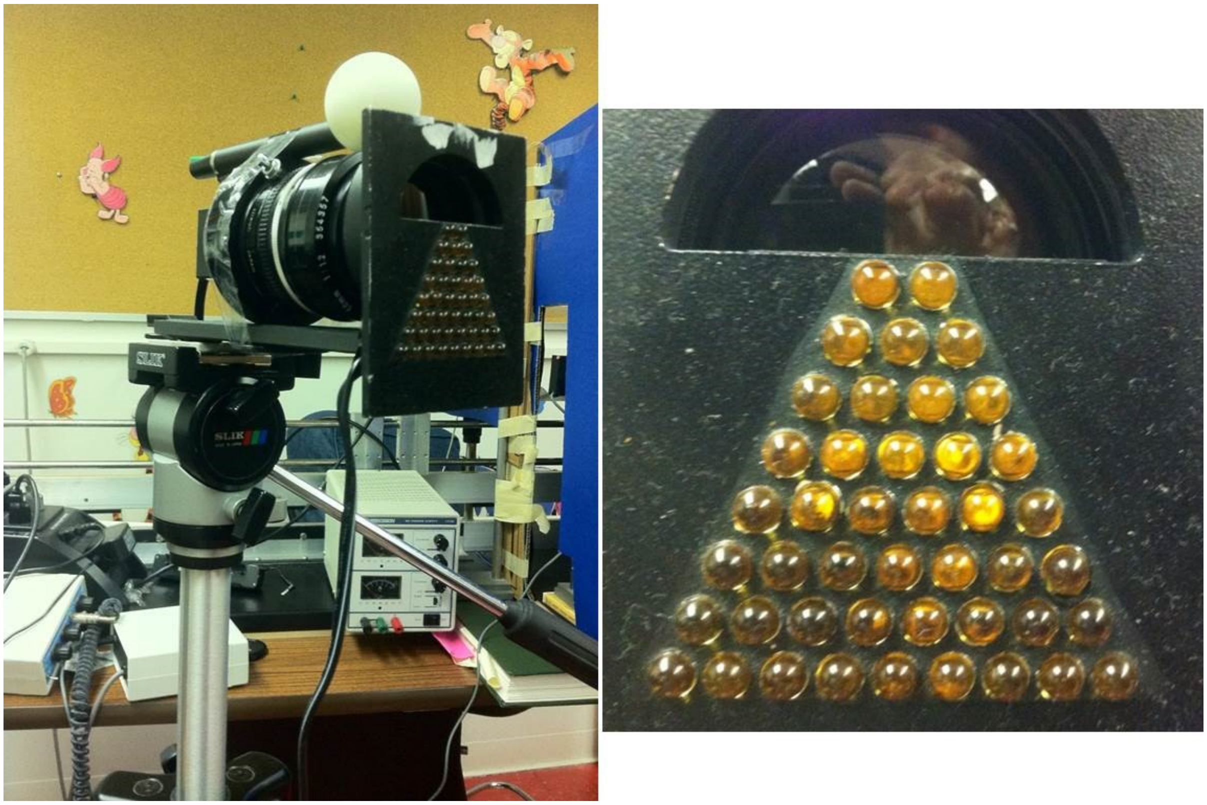

Figure 2-1: Dynamic high speed photorefractor. This image was reprinted from my Master's thesis.

It is a Fire-wire charge coupled device (CCD) camera (PROSILICA CAM (EC750), Allied Vision Technologies, Canada) with infra-red (IR) light emitting diodes (LEDs) set at the knife-edge covering the lower half of the camera.

2.1.4 Dynamic photorefractor: analysis algorithm

One of the most important components in the current photorefraction systems is the underlying analysis algorithm which converts the photorefraction data into defocus measures (in units of diopters). Accordingly, a novel offline analysis algorithm that allows a rapid and accurate estimation of pupil size, fundus brightness and refraction was designed. All the components of this algorithm have been described previously[9,14]. A video converter module would first convert and breakdown the video output from the photorefractor so that individual frames of the video data can be accessed. A circular pupil would be then detected and defined using an iterative process at the level of each frame. In simple words, this process would involve identifying the points (edge points) on the image where the intensity difference between two neighboring pixels is greater than a pre-set threshold value. Given the criterion, pixel points across the Purkinge image were often assigned as the edge points. Therefore, two post processing steps involving four neighbor connected components were employed to address this issue: first, if the connected components consists of too few pixels (i.e. less than 3), it was considered as a noise component; Second, if the ratio between the number of pixels and the area of the bounding rectangle was greater than a predefined threshold, those edge points were removed. The second step usually eliminated the edge points resulting from the Purkinge reflection as they contained tightly clustered edge points or pixels. This step is followed by another iterative process to determine the exact pupil boundary. The identified circular pupil is then divided into multiple vertical columns which are one pixel wide. The slope of the intensity gradient across the central vertical meridian would then be used to identify the sign and magnitude of refraction. The diameter of the circular fit defines the pupil diameter and average pixel intensity across the vertical meridian defines the fundus brightness.

2.1.5 Calibration

Since the defocus output from photorefraction is in the units of slope (or gradient) of intensity distribution across the pupil, it needs to be converted into a meaningful dioptric estimate of refraction. Three different calibration procedures were chosen to ensure that the final refractive measures obtained are accurate without any influence of the optical variations such as pupil size, fundus brightness or aberrations.

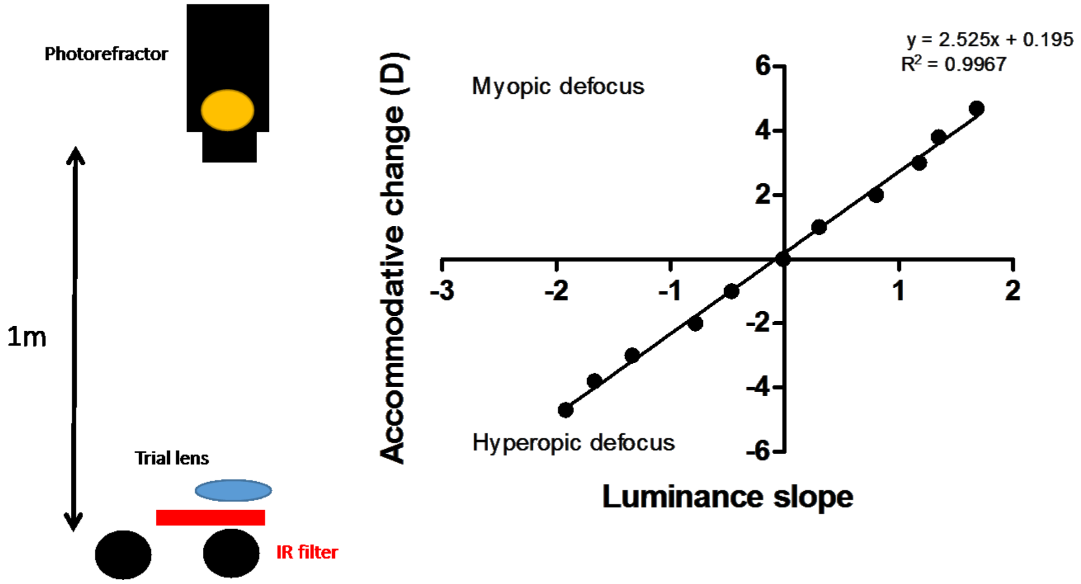

Figure 2-2: Individual relative calibration. This image was reprinted from my Master's thesis.

(a) Photorefractor is aligned to the subject's right eye and is typically placed 1m away. The visible spectrum is filtered out using an IR filter placed in front of the right eye. The subject would view a high contrast target placed at 3m with the left eye. (b) Photorefraction output (luminance slope) is plotted as a function of the induced refractive error. A linear regression fit would then be used to define the relationship.

2.1.5.1 Relative calibration

Several studies have described a calibration procedure to accurately convert photorefractive output into dioptric measures of refractive error or accommodation[1,2]. Individual relative calibration should be done on every subject to minimize the effect of individual variation in the optical components such as pupil size, fundus brightness or ocular aberrations. The relative calibration trial involves the interpretation of the intensity distribution patterns across the pupil when known magnitude of lens defocus is induced. This is typically achieved by placing trial lenses (ranging between +5D to -5D) over an IR filter which renders visible light. The relative change in the photorefraction output to this induced lens defocus is plotted and linear regression equation is obtained to define the relationship. The slope of this linear regression fit is called as the conversion factor (Figure 2-2). The repeatability in measuring conversion factors was also tested on five subjects using Bland-Altman plots[14]. The coefficient of repeatability was 0.20 which would be ≈0.05D and is clinically insignificant. Empirical calibration trials also showed that the instrument has a very small dead zone and is sensitive to smaller changes in the defocus of < ± 0.25D in magnitude.

2.1.5.2 Pupil size calibration

As described in the first chapter, an accommodative response to a near stimulus is accompanied by changes in both pupil size and vergence. This behavior is termed as the near triad. Theoretical and empirical evidence suggests that estimation errors of about a diopter can occur if changes in the pupil size are not taken into account[1,2,5]. As it is difficult to control the pupil size without affecting the accommodative response, a different parameter was necessary to control or minimize the effect of changes in pupil size to near targets. Previously, the impact of a changing pupil size was found to be minimized when the conversion factor was corrected based on the individual's fundus brightness. This was achieved by plotting the fundus brightness obtained from fifteen subjects as a function of their respective pupil size. A linear regression fit was then used to define the relationship and equation was built into the system to ensure that final refractive estimate would be accurate even with a changing pupil size. Accuracy in estimating the pupil size was also tested previously[14] and maximum error obtained was clinically insignificant (0.02mm).

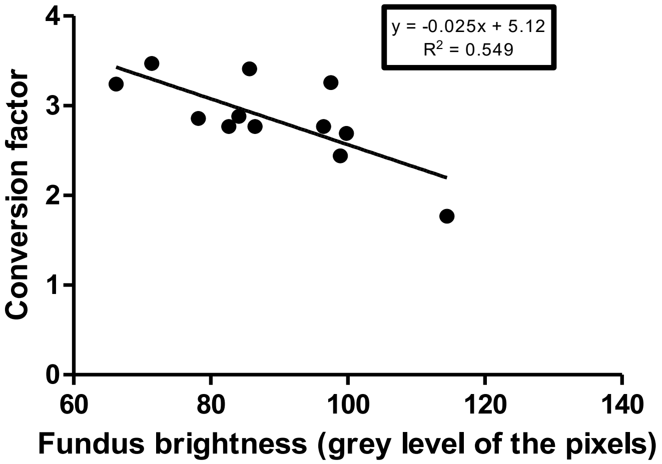

Figure 2-3: Pupil size calibration. This image was reprinted from my Master's thesis.

Conversion factors obtained from each subject using individual (relative) calibration were plotted as a function of their respective fundus brightness. Linear regression analysis showed negative correlation between the fundal brightness parameter and the conversion factor. The regression fit equation obtained was y= -0.025x+5.12, where x represents the average fundal brightness value obtained from the subject at that particular frame and y is the conversion factor to be calculated for that particular frame. This equation was built into the system to ensure that refractive estimates were accurate without being influenced by a changing pupil size.

2.1.5.3 Absolute calibration

The accuracy of the dynamic photorefraction system in measuring the accommodative response, quantified in terms of a response gain (= response/stimulus), was also tested on subjects (7 adults (29.57±2.69 years) and 2 children (11±1.4 years)) previously[14]. Accommodative gains obtained from the dynamic photorefraction (0.84±0.11) were compared to the dynamic retinoscopy (0.87±0.15). Dynamic photorefraction system underestimated the accommodative gains (≈ 0.5D) compared to the dynamic retinoscopy[14]. Given that I am interested in relative changes in accommodation in adults and children, this underestimation of the absolute measure would not impact my future work. However, to ensure that the absolute values of refraction are accurate, a correction factor (0.5D) was built into the system[14].

2.2 What is an ideal sampling rate to measure dynamic accommodation?

The dynamic photorefraction system (DPRS) was designed and calibrated on children and adults during my Masters. However, there were a few questions that still remain unanswered. Is this new photorefractor superior to the commercially available one in measuring the dynamic accommodation? If yes, what is the ideal sampling rate necessary to measure dynamic accommodative characteristics such as peak velocity and peak acceleration? Are the main sequence measures obtained previously using a 25Hz photorefractor accurate? Therefore, the first project in my PhD was to confirm that this new custom built DPRS is superior to the currently available technology in measuring dynamic accommodation. Previous studies on accommodative microfluctuations reported that frequencies that are of accommodative origin were typically less than 5Hz (this work was cited by Campbell[16] but the original work was a French publication by Arnulf et al.,[17]). These investigations concluded that to record the dynamic steady state errors accurately, optometers should operate at a rate of at least 10 Hz. However, it is unknown whether this frequency spectra from the steady state errors applies to the first and second order dynamics accommodation and disaccommodation. I also wanted to test to see if the accuracy of measuring dynamic accommodation would be improved with the new high speed photorefractor. Accordingly, two studies were performed in order to estimate the ideal sampling frequency required to measure accommodative position, velocity and acceleration accurately.

2.2.1 Study I: Spectral analysis of dynamic accommodation

Signal transformation procedures such as Fast Fourier transformation (FFT) are typically employed to perform frequency analysis on signals or responses[18]. In FFT, time domain signals or responses are converted into frequency domain. Information in a response could be accurately measured only when sampled (S) at a rate that is twice the peak frequency (f_{max}) present in its time domain response signal. If the signal is sampled at a rate higher than that limit (i.e. $S > 2*f_{max}$), no further information can be extracted[19,20]. However, when the signal is measured at a lower rate ($S < 2*f_{max}$), it leads to aliasing or underestimation of the response. Fourier representation of a time domain response that is T seconds long with n signal elements is given by,

$$X(t) = \frac{A_0}{2} + \sum_{n=1}^{\infty} (A_n \cos\frac{2\pi t}{T} + B_n \sin\frac{2\pi t}{T})$$

Where X (t) is the time domain response, 2π/T is the frequency of the response. A_n and B_n are the coefficients of the nth cosine and sine elements in the response respectively.

Accordingly, the present study uses Fast Fourier transformation[18] to quantify the ideal sampling rate necessary to accurately measure the dynamic characteristics of both accommodation and disaccommodation.

2.2.1.1 Methods

12 children (8-13 years) and 6 naive adults (Age: 20-35 years) were recruited from the clinic database at the School of Optometry and Vision Science, University of Waterloo. Informed consent was obtained from the parents for a child and was obtained directly from the adult

subjects. The study followed the tenets of Declaration of Helsinki and received ethical approval from the University of Waterloo office of research ethics review board. Subjects with strabismus, amblyopia, anisometropia > 1.00D, astigmatism > 1.00D and with best corrected visual acuity of less than 6/6 were excluded. All the subjects with refractive error were habitual contact lens wearers and wore the lens during the study.

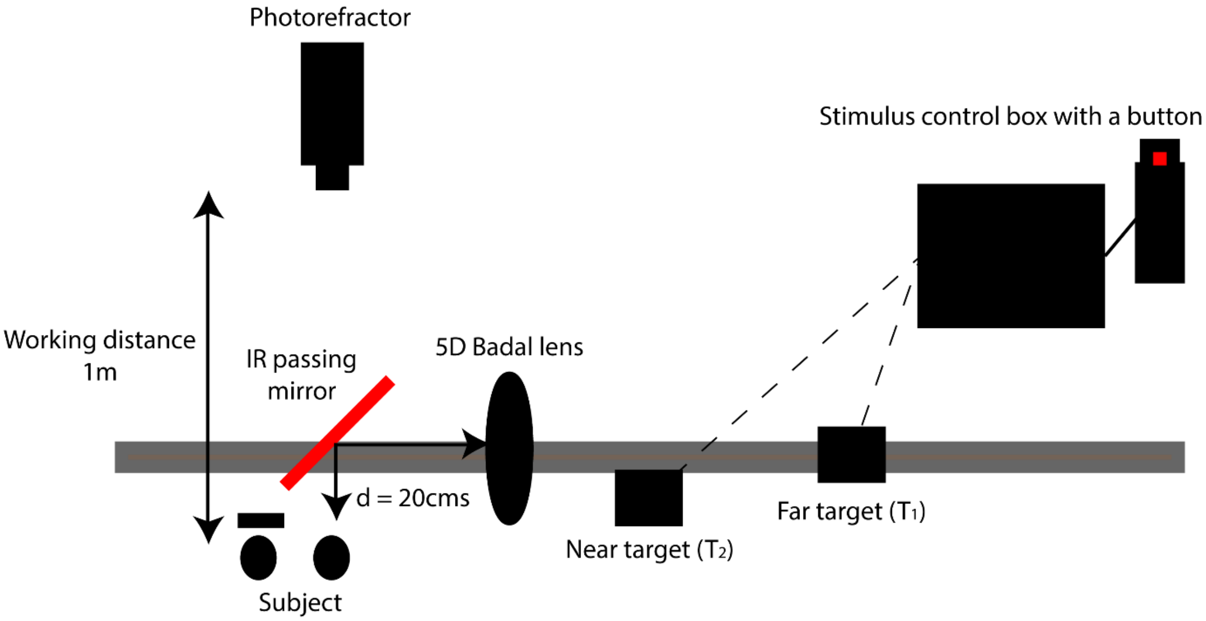

Figure 2-4: Experimental design to stimulate accommodation and disaccommodation.

The subject was seated 1m away from the photorefractor with the left eye occluded. An IR passing mirror (Optical cast IR filter, Edmund Optics, USA) was placed in front of the right eye for an orthogonal presentation of the accommodative targets along with a continuous measure of accommodation using the dynamic photorefractor. High contrast targets (T1, T2) were placed at different distances from the +5D Badal lens to create various accommodative and disaccommodative demands. Step stimuli were presented using a stimulus control tool box with a button that helps in switching the target distance instantly.

2.2.1.2 Instrumentation

As described above, **Dynamic photorefractor** (**DPR**, PROSILICA CAM (EC750), Allied Vision Technologies, BC, Canada), a custom built eccentric photorefractor was used to measure accommodation and disaccommodation.

2.2.1.3 Experimental design

Accommodation was stimulated using a Badal optical system[21]. As shown above (Figure 2-4), the subject was seated 1m away from the photorefractor. An IR passing mirror (Optical cast IR filter, Edmund Optics, USA) in front of the subject allowed an orthogonal presentation of the step targets along with a continuous measure of accommodation using the photorefractor. Two high contrast targets (T1, T2; black on white vertical lines that were illuminated using white LEDs) were placed at different distances from a +5D Badal lens to create various accommodative and disaccommodative demands without a change in the angular size of the target. While the far target was always at infinity, near one was moved to various distances to create demands ranging from 1-3D (1D steps). The accommodative demand was instantly switched from one distance to the other using a stimulus control tool box with a button. This switch was connected to the dynamic photorefraction system through an input-output control box allowing a time stamp to be created with the onset of the stimulus. Stimulus order and presentation time was randomized to avoid predictability or learning effects.

2.2.1.4 Procedure

After an initial assessment of the anterior chamber, both eyes of each subject were dilated using 2.5% Mydfrin (Phenylephrine hydrochloride). This was done to optimize the photorefraction measures by providing a larger pupil size (> 4mm). The left eye was occluded throughout the experiment to open the loop of the vergence system. Practice trials were given in order to familiarize the subjects with the procedures involved. Single step responses to both accommodation and disaccommodation were presented using a Badal system and recorded using the photorefractor. During the measurement trial, subjects viewed at the high contrast target (white on black) through the Badal lens and were instructed to make sure that the edges of the target were always clear and sharp. Multiple trials (ranging from 6-12) were conducted for each stimulus level of accommodation and disaccommodation and each trial lasted for 5-10 sec. The stimulus presentation time was varied from 2-5 sec after the initiation of the trial to avoid prediction. Frequent breaks were given to both children and adults between the trials to avoid fatigue effects on accommodation and disaccommodation.

2.2.1.5 Data analysis

Final position traces (units of diopters) obtained from the DPRS were used for further dynamic analysis on MATLAB (Mathworks, Inc., MA, USA). Velocity (diopters/s) and acceleration (diopters/s^2) profiles were obtained by differentiating the response traces using a 2-point-difference algorithm. Velocity threshold criterion[1] was used to identify start and end points of the dynamic accommodative response. An inverse of this criterion was used for disaccommodative responses.

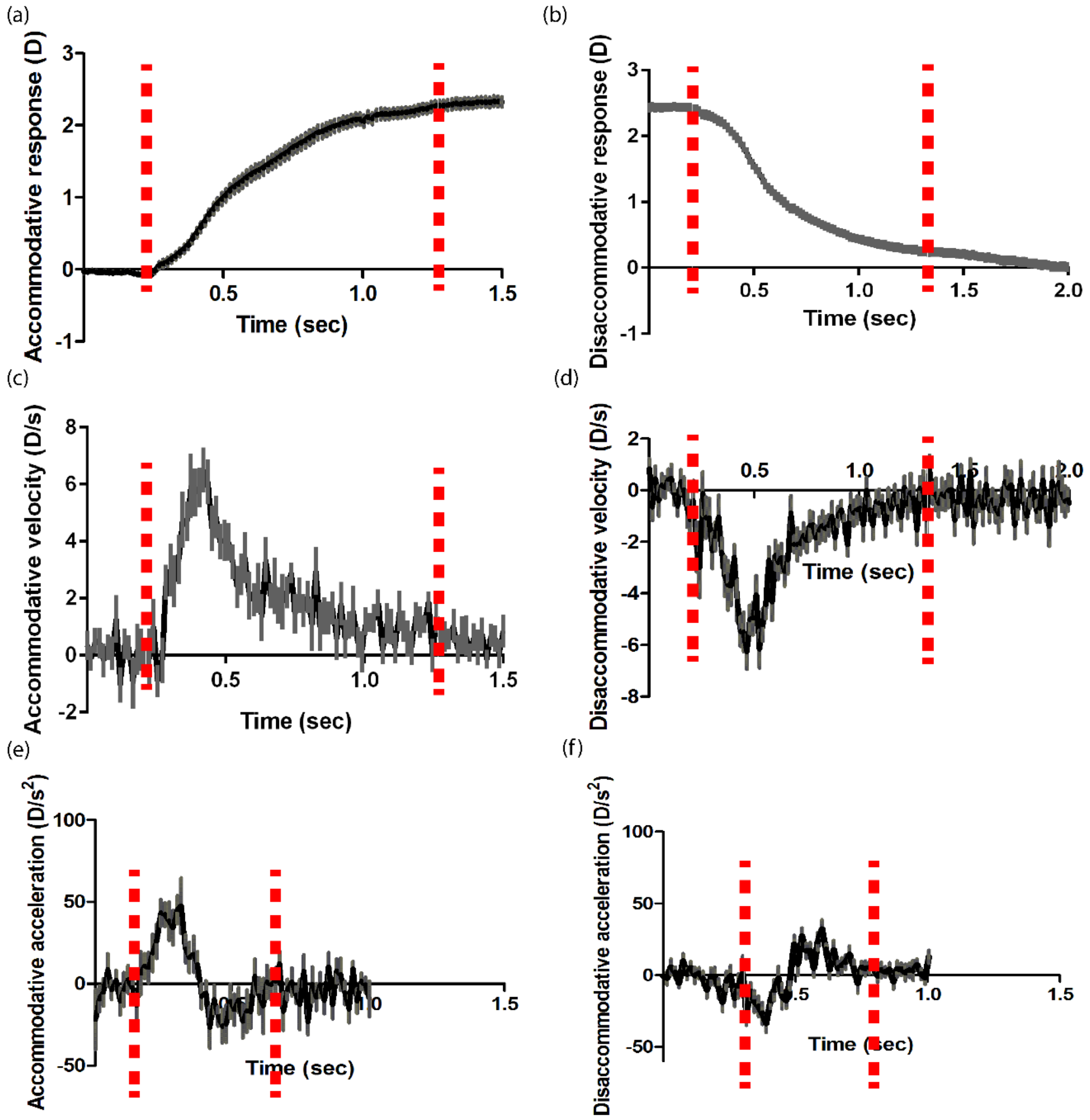

Figure 2-5: Typical dynamic accommodative and disaccommodative traces obtained to a 3D stimulus.

The solid line indicates the mean value and shaded area indicates the standard error in the response. The red dotted lines indicate the start and end points of the dynamic traces and FFT was applied only on this area.

Fourier transformation (FFT) was then applied on the individual unsmoothed position, velocity and acceleration traces obtained from all the subjects. As shown in Figure 2-5, FFT was applied only to the dynamic response between the two red dotted lines i.e. between the start and end points of the response. Ideal sampling rates for measuring the accommodative and disaccommodative position, velocity and acceleration traces were estimated using the peak frequency obtained from FFT. Instrument or measurement noise was identified by applying Fast Fourier transform on the measurements with a static model eye. The power spectrum due to noise was removed from the final accommodation frequency data to ensure that the measures were valid (Figure 2-6).

2.2.1.6 Results

Accommodation data were obtained from 12 children (11.16 ± 1.83 years) and 6 adults (26.16 ± 3.37 years). Figure 2-6 shows the FFT output (mean and SE) obtained from unsmoothed accommodative and disaccommodative traces (mean and SE) measured across different accommodative demands (1-3D, 1D steps). The typical frequencies present in a dynamic position and velocity trace were limited to frequencies less than 10Hz. For acceleration, frequencies ranging from 15 - 35Hz were present. The ideal sampling rate (Nyquist rate) was calculated using the peak frequency present in the response. As shown in figure 2-6, stimulus direction (accommodation or disaccommodation) and demand (1/2/3D steps) had no influence on the range of frequencies present in a dynamic response. Based on the FFT data, the ideal sampling rate should be at least 5Hz, 10Hz and at least 70Hz to accurately measure accommodative position, velocity and acceleration respectively.

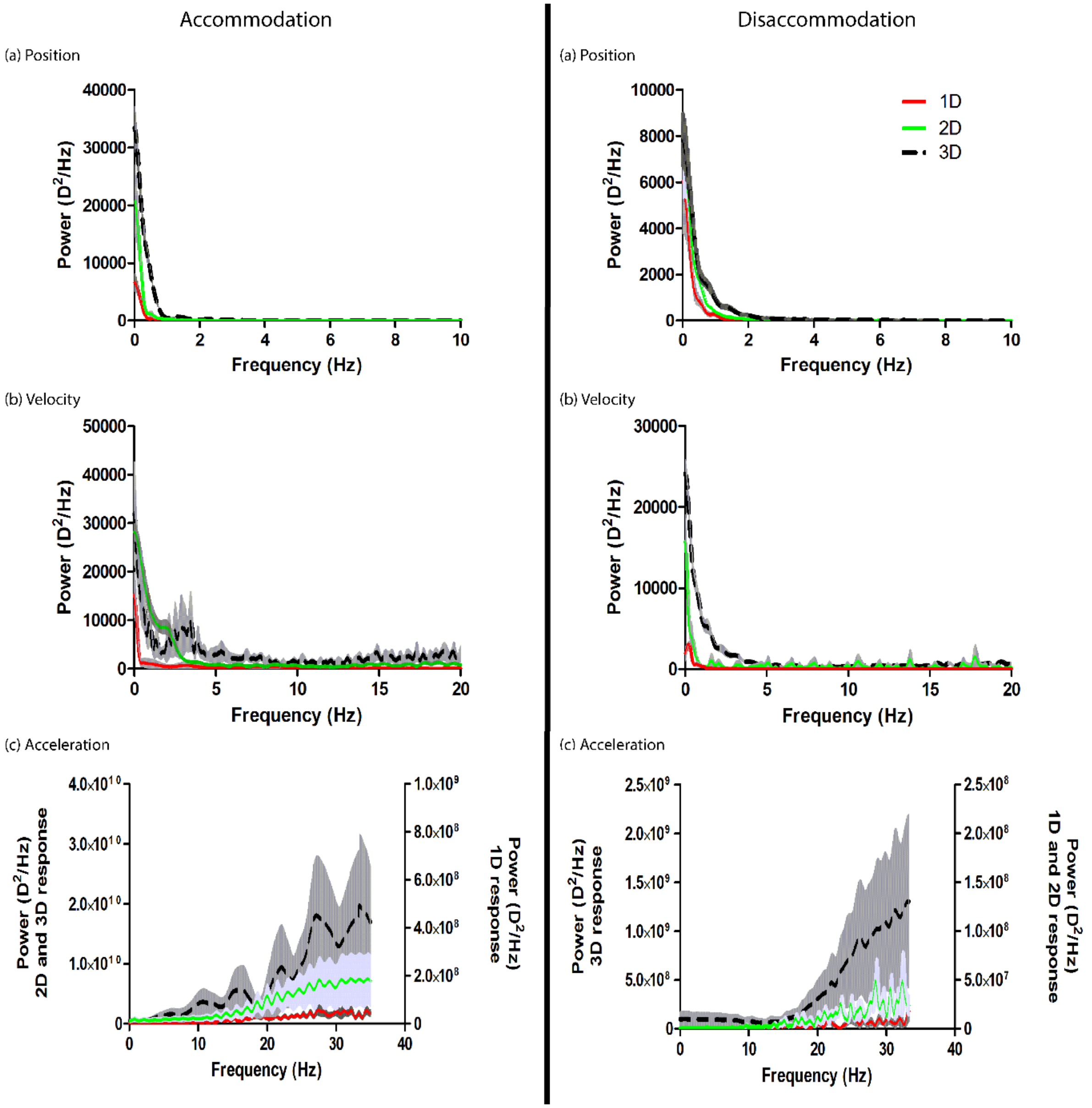

Figure 2-6: Fourier analysis of dynamic accommodation and disaccommodation.

Unsmoothed time domain traces of position (a), velocity (b) and acceleration (c) obtained were converted into frequency domain using fast Fourier analysis across different accommodative demands, 1D (red line), 2D (green line) and 3D black dotted line). The connecting lines indicate the mean values and shaded area indicates the standard error.

2.2.2 Study II: Effect of sampling rate on the main sequence relationship

Main sequence (MS) relationship has been commonly used to describe the dynamic aspect of a motor system[22–24]. It is the rate of change of velocity or acceleration as a function of the response amplitude. The slope of the MS profile defines the ability of the dynamic motor system. The present study compares three photorefractor conditions to understand the impact of sampling rate on the main sequence relationship.

2.2.2.1 Methods

Three adult subjects (26, 28 and 32 years) were recruited later for the second study where the dynamic main sequence was compared when measured at different sampling rates. Informed consent was obtained separately for this study visit. For main sequence comparison,

- Accommodation was measured on the 3 subjects using two photorefractors, a custom built eccentric DPR (70Hz) and a commercially available PowerRefractor (25Hz) on two separate days. The order was randomized.
- Accommodation was recorded using the Dynamic photorefractor (DPR). Data were subsequently analyzed at two sampling rates. First, the data were analyzed at its original sampling rate (DPR - 70Hz). It was then down sampled to 30Hz and re-analyzed (DPR – 30). This was done to understand the influence of differing analysis algorithms which might occur with the previous comparison.

2.2.2.2 Instrumentation

Dynamic photorefractor (**DPR**, PROSILICA CAM (EC750), Allied Vision Technologies, BC, Canada): As described in the first section (study 1).

PowerRefractor (PR, Multichannel systems, Reutlingen, Germany) is a commercially available photorefractor that works at a sampling rate of 25Hz, providing an output every 40 milliseconds. Numerous studies[3,12] have used it to measure static and dynamic characteristics accommodation on both children and adults. This was one of the first few photorefractors to successfully calibrate the optical principle of eccentric photorefraction for use in measures of accommodation.

2.2.2.3 Experimental design

The design used was similar to that described above. Similar procedures (as in study 1) were followed on two separate visits while accommodation data from the two subjects were recorded using the two photorefractors.

2.2.2.4 Data analysis

Dynamic accommodative and disaccommodative position traces obtained from the DPR were then loaded into MATLAB for further analysis. Velocity (diopters/s) and acceleration (diopters/s^2) profiles were obtained by differentiating the response traces using a 2-point-difference algorithm. All the traces were subsequently smoothed using a 100 msec window. Velocity threshold criterion was used to identify the start and end of the response. The start of the response was the first point where the velocity exceeded 0.5 D/s and continued to do so for the next 100 msec. Similarly, end of the response was identified as the point where velocity fell below 90% of peak velocity and continued to do for the next 100ms. The start and the end points obtained using this criterion were later confirmed by visual inspection.[22]

Amplitude (Diopters) was defined as the dioptric difference between the start and end points. Highest values on the velocity and acceleration traces were defined as the peak velocity (D/s) and peak acceleration (D/s^2) respectively. "First order main sequence" relationship was defined by plotting the accommodative and disaccommodative peak velocities as a function of their respective response amplitudes. Similarly "Second order main sequence" relationship was peak acceleration as a function of the response amplitude. Historically, linear regression was used to identify the main sequence relationship. However, given the variability in the velocity/acceleration and amplitude measures, a bivariate regression analysis such as Deming regression was chosen in the current study. Regression and other statistical analysis were performed using GraphPad Prism (GraphPad Software Inc., USA).

2.2.2.5 Results

Accommodative traces were obtained on three adults (26, 28 and 32 years). Figure 2-7 shows the main sequence characteristics of both accommodation and disaccommodation obtained from the three photorefractors conditions. For accommodation (Fig 2-7 (a, b)), Deming regression slopes of velocity and acceleration were significantly different from zero ($p < 0.01$). For accommodative velocity, the MS slopes were similar between the three conditions (DPRS (70Hz): 2.69x + 2.05; PR: 2.58x + 0.73; DPRS (30Hz): 2.34x + 1.06; PR: 2.58x + 0.73; Slopes: $F_{2, 66} = 0.120$; $p = 0.88$). However, the intercepts were significantly lower ($F_{2, 68} =$

4.653; $p = 0.01$) with PR ($p = 0.01$) and DPRS 30 ($p = 0.02$). Similarly, for accommodative acceleration, the MS slopes were similar between the three measurements (PR: 8.40x + 4.32; DPRS 70: 12.93x + 21.38; DPRS 30: 8.93x + 8.31; Slopes: $F_{2, 66} = 0.164$; $p = 0.84$) but the intercepts were significantly lower ($F_{2, 68} = 19.79$; $p < 0.0001$) with PR ($p < 0.0001$) and DPRS 30 ($p < 0.0001$). For disaccommodative velocity (Figure 2-7 (c)), the MS slopes of velocity were similar between the three photorefractor conditions (PR: 1.94x + 0.09; DPRS 70: 2.38x + 0.55; DPRS 30: 1.63x + 0.80; Slopes: $F_{2, 56} = 0.686$; $p = 0.50$). However, the intercepts were significantly lower ($F_{2, 58} = 4.017$; $p = 0.02$) with PR ($p = 0.04$) and DPRS 30 ($p = 0.04$). For disaccommodative acceleration, the MS slopes were similar between the three photorefractor conditions (PR: 3.46x + 7.52; DPRS 70: 12.70x + 10.72; DPRS 70: 6.82x + 4.93; Slopes: $F_{2, 56} = 2.130$; $p = 0.13$) but the intercepts were significantly lower ($F_{2, 58} = 24.145$; $p < 0.0001$) with PR and DPRS 30 ($p < 0.0001$).

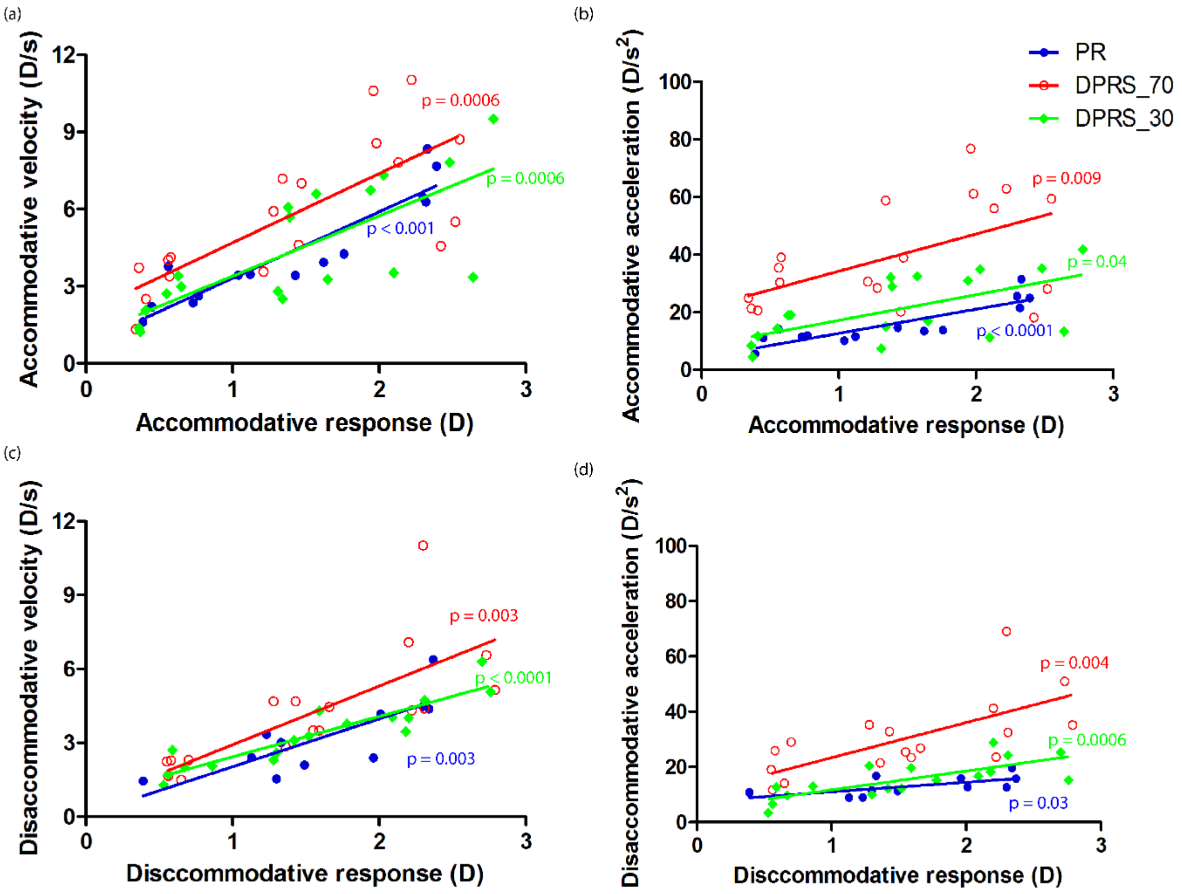

Figure 2-7: Main sequence data were compared between PR (blue) and DPR 70 (red) and DPR 30 (green). Deming regression was used to fit the MS data of velocity and acceleration for both accommodation (a, b) and disaccommodation (c, d). P value shows the difference between the slope of the regression fits from a zero slope.

2.2.3 Discussion

FFT was used to transform the time domain dynamic accommodative and disaccommodative responses into frequency domain. The peak frequency present in each dynamic response was identified and then used to calculate the ideal sampling rate required to avoid aliasing. In agreement with the previous investigation[17], position and velocity data showed frequencies less than 5Hz. However, higher frequencies were found with acceleration. Frequencies present in a dynamic response were similar in both accommodation and disaccommodation. Also, frequencies present in a particular dynamic response (position, velocity or acceleration) appeared to be independent of the stimulus demand (figure 2-6). To measure accommodative position, velocity and acceleration accurately, the sampling rate should be at least 5Hz, 10 Hz and 70 Hz respectively. For acceleration, frequencies higher than 35Hz may have been present in the response as the analysis was limited with the instrument's sampling rate (70Hz). It is possible that higher frequencies might have occurred as a result of plant noise, especially in the acceleration responses. However, it is difficult to isolate plant noise at this point due to the technological limitations.

Main sequence characteristics were compared between the two photorefractors that operate at different sampling rates. Peak velocity and acceleration dynamics were significantly underestimated when sampled at 25Hz as shown by the difference in the intercepts ($p < 0.05$). Although FFT data on velocity traces showed frequencies < 10Hz, it is unclear at this point why peak velocity was significantly underestimated at lower sampling rates (25Hz). Interestingly, the slope ($p > 0.10$) of main sequence appeared to be independent of the sampling rate suggesting that level of underestimation was consistent across all the stimulus demands presented during the course of this experiment. This confirms our FFT finding of similar frequencies being present in a particular dynamic response irrespective of the stimulus demand presented. Furthermore, this confirms that the previous measures of the velocity and acceleration main sequence characteristics are accurate[25–27] although the absolute values may have been underestimated. Higher frequencies obtained in the FFT data might be questionable at this point given that the plant noise was not isolated, however, empirical evidence obtained from the second study suggests that low sampling instruments such as autorefractors can significantly underestimate the first and second order dynamic behavior of accommodation.

2.3 Conclusion

The two studies described above conclude that instruments that work at higher sampling rate would be necessary to measure dynamic accommodation accurately. Accommodative dynamics such as peak velocity and acceleration were significantly underestimated at lower sampling rates (25 and 30 Hz). Therefore, a high speed photorefraction system would be necessary to measure dynamic characteristics of accommodation and disaccommodation accurately. Accordingly, the new custom built high speed DPRS was used to measure dynamic accommodation in this dissertation.

Chapter 3

Motor mechanism of accommodation

This chapter is published as follows:

Labhishetty V, Bobier WR. Are high lags of accommodation in myopic children due to motor deficits ? Vision Res. 2017; 130:9–21.

3.1 Summary

Introduction: Children with progressive myopia exhibit an abnormal pattern of high accommodative lags coupled with high accommodative convergence (AC/A) and high accommodative adaptation. This pattern is not predicted by the current models of accommodation and vergence. Reduced accommodative plant gain and reduced sensitivity to blur have been suggested as potential causes for this abnormal behavior in progressive myopes. These etiologies were tested by altering sensory and motor parameters in the Simulink model of accommodation and vergence. Only simulations with a reduced plant gain predicted this altered behavior in myopes. Accordingly, the hypothesis of a motor plant deficit was tested in myopes and the behavior was compared with non-myopic children and adults.

Methods: Static and dynamic blur accommodation (BA) measures were taken using a Badal optical system on 12 children (6 emmetropes and 6 myopes, 8–13 years) and 6 adults (20–35 years). A high speed dynamic photorefractor was used to record accommodative responses to various step stimuli (1-3D, 1D steps). Other critical parameters such as CA/C, AC/A, and accommodative adaptation were also measured.

Results: Usable BA responses were classified as either typical or atypical responses. Typical accommodation data confirmed the abnormal pattern of myopia along with an unchanged CA/C. Main sequence relationship remained invariant between myopic and nonmyopic children. An overall reduction was noted in the first and second order response dynamics such as peak velocity and acceleration with age.

Discussion: Taken as a whole, neither a reduced plant gain nor reduced blur sensitivity could predict the abnormal accommodative behavior completely. A model adjustment reflecting a reduced accommodative sensory gain (ASG) coupled with an increased AC cross-link gain and reduced vergence adaptive gain does predict these empirical findings in myopes. Based on these findings, reduced blur sensitivity in myopes is compensated by a motor recalibration of AC cross-link to balance the vergence behavior even with a reduced accommodation.

3.2 Introduction

As described in the first chapter, progressive myopes, both adults and children, exhibit an accommodative behavior characterized by high accommodative response lags[1–8] coupled with an elevated response AC/A[7,9–11], and high accommodative adaptation[11–13]. These patterns are not predicted by the currently accepted models of accommodation and vergence[14,15]. According to the Schor's model, high accommodative adaptation would be associated with a low and not high AC/A. Similarly, high adaptation would be associated with a small and not a large response lag. Other altered behavior includes high steady state fluctuations[16–18], reduced vergence adaptation[11,19] and a large depth of focus[20,21]. There have been conflicting results on whether this altered behavior of accommodation occurs before or after the onset of myopia[5,7,8,22]. Interestingly, this abnormal behavior is associated only with progressive but not stable myopia[2,23–25]. However, these abnormal patterns of accommodation do not appear to be causative because correction of the lags does not reduce the myopic progression to a significant clinical level[4,26–29].

3.2.1 Motor and sensory etiology

The etiology of this abnormal pattern of accommodation in myopes is unknown, however, there is evidence that suggests both motor and sensory origin. Several studies have attributed the abnormal behavior of accommodation seen in myopes to the difference in the accommodative plant, namely the lens and ciliary muscle [10,30–32]. Specifically, studies showed differences in the growth patterns of the crystalline lens [10,22,30–35] and the thickness of the ciliary muscle [36–43]. Previous work showed that the equatorial growth of the crystalline lens ceases earlier in myopes compared to the non-myopes[22,32,44]. These studies proposed that the failure of lens growth to compensate for the axial growth of the eyeball would lead to a prolate shaped eyeball with an increased tension on choroid and lens. This increased tension was predicted to make the lens more rigid and impede accommodation. Similarly, several studies also suggested that the ciliary muscle (CM) was thicker in myopes, more specifically posterior fibers. Also, CM movement was shown to be diminished during accommodation in myopes. Although this evidence is consistent with a rigid or sluggish plant, it is still unclear whether these "plant" differences would cause these abnormal patterns of accommodation[22,45].

Progressive myopes, both children and adults, are less sensitive to blur or defocus [1,2,13,20,21,46]. These studies suggested that this reduced ability to perceive blur would lead to an increased depth of focus (DOF) thereby leading to a reduced accommodative response. In agreement with this speculation, studies examined the depth of focus both objectively[20] and subjectively[21] and found that myopes exhibit a significantly larger depth of focus compared to their non-myopic peers. Increased levels of higher order aberrations were also speculated to increase the depth of focus in myopes by degrading the retinal image quality, ultimately leading to an inaccurate accommodation[47–49]. Studies looking at genetic mutations found an altered behavior in the information processing at the level of the retina in myopes[50]. We speculate that these mutations might influence blur processing, possibly decreased the system's sensitivity to blur. Jiang (1997)[51] proposed a modification to the static model of accommodation to explain the flatter accommodation stimulus-response curve (AS-AR) in myopes. Accommodative sensory gain (ASG) was added along with the dead space operator (DOF) in the model to account for various sensory factors that detect blur. He proposed that the flatter AS-AR curve in myopes compared to emmetropes could be due to a reduced accommodative sensory gain (ASG) or increased DOF or both.

3.2.2 Model simulations

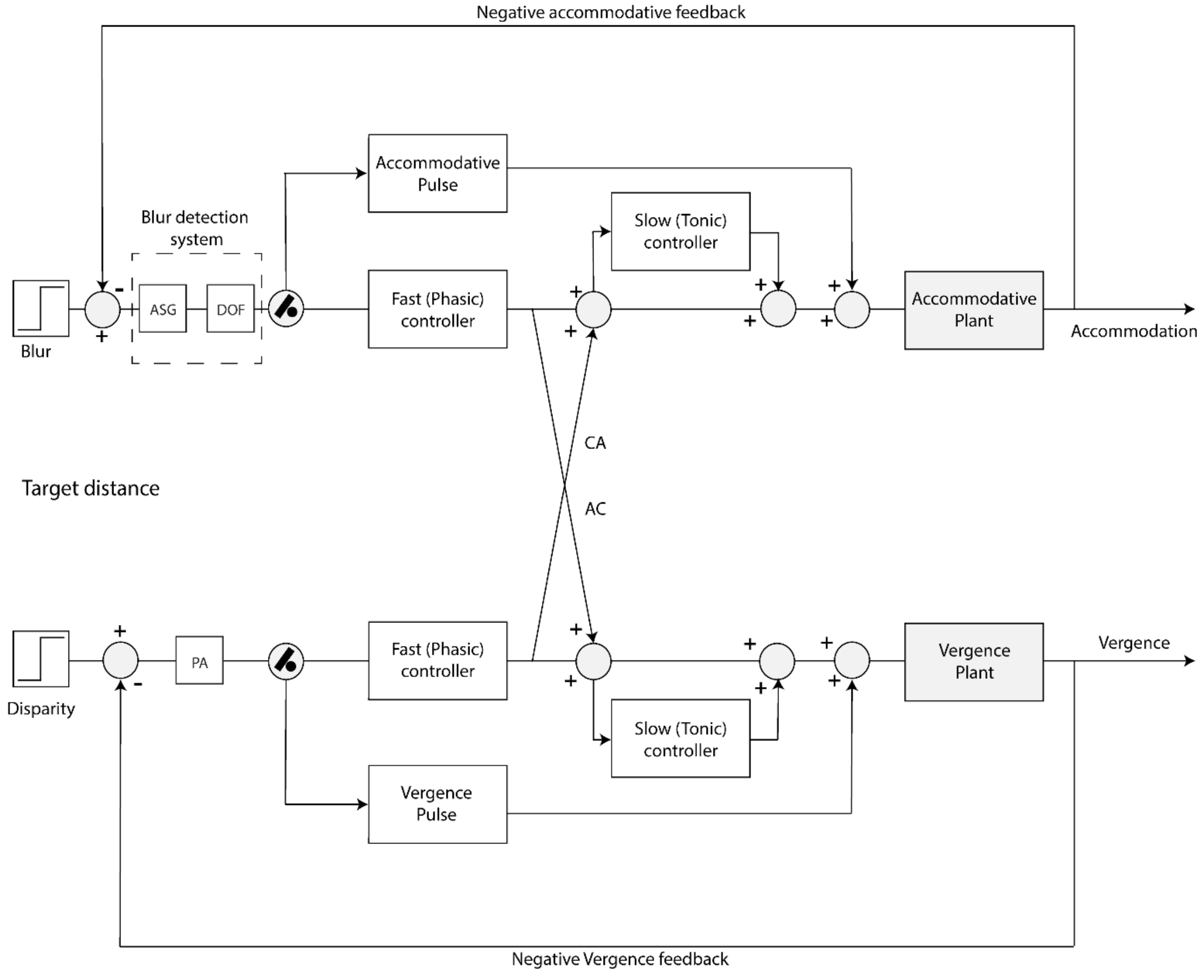

Figure 3-1: Pulse step model of accommodation and vergence (adapted from Maxwell, 2010).

For simplicity, the internal feedback and the pulse cross-link mechanism were not shown. The ASG (Jiang, 1997) parameter was included into this model to represent the sensory mechanism of accommodation. (DOF: Depth of focus; PA: Panum's area).

Taken as a whole, empirical data suggests that the abnormal pattern of accommodation could either reflect a motor plant deficit (i.e. a rigid lens and/ or a sluggish ciliary muscle), or sensory processor deficit (i.e. Increased DOF or reduced ASG) or perhaps a combination of both. A Simulink model (MATLAB) was devised, as shown in figure 3-1, by including the ASG component into the currently accepted model of accommodation (Figure 1-4).

We adjusted the parameters in the model to see if the modification predicted the myopic behavior. For example, the accommodative plant gain was reduced to simulate the empirical evidence on a rigid or sluggish plant. Simulations were carried out to determine if these deficits would predict the abnormal accommodative behavior. Table 3-1 below lists the outcomes of the model adjustments.

Table 3-1: Model adjustments and the predicted accommodative behavior.

Hypothesis	**Prediction**	**Simulink parameter**	**Accommodative behavior (model predictions)**
1) Motor deficit (rigid plant)	Reduced plant gain	Plant gain Actual gain: 1.75 Altered gain: 1.25, 0.75	1. Increased accommodative lag. 2. High AC/A and accommodative adaptation. 3. Reduced peak velocity and acceleration. 4. Reduced CA/C
	Reduced fast controller gain	Fast controller (phasic) gain Actual gain:2.5 Altered gain: 2.0, 1.5, 1.0	1. Increased accommodative lag. 2. Unchanged AC/A 3. Reduced accommodative adaptation 4. Unchanged CA/C 5. Reduced peak velocity and acceleration

2) Sensory deficit (reduced blur sensitivity)	Large depth of focus (DOF)	Dead zone Actual DOF: ± 0.14 Altered DOF: ±0.25,0.35	1. Increased accommodative lag. 2. Unchanged AC/A 3. Reduced accommodative adaptation 4. Reduced peak velocity and acceleration. 5. Unchanged CA/C
	Reduced accommodative sensory gain (ASG)	ASG gain Actual gain:1 Altered gain: 0.8, 0.6, and 0.4.	1. Increased accommodative lags. 2. Unchanged AC/A 3. Reduced adaptation 4. Reduced peak velocity and acceleration. 5. Unchanged CA/C
	Altered internal feedback mechanism	Virtual plant gain Actual gain:1.75 Altered gain: 1.25, 0.75	1. Accommodative leads 2. High AC/A and accommodative adaptation. 3. Increased peak velocity and acceleration. 4. Unchanged CA/C
3) Sensory motor interaction (altered feedback sensitivity)	Increased feedback gain	Feedback gain: Actual gain:1 Altered gain: 1.2, 1.4 and 1.6	1. High response lags 2. Unchanged AC/A 3. Unchanged CA/C 4. Reduced peak velocity and acceleration. 5. Low accommodative adaptation

4) Combination of a sensory and motor deficit	Reduced plant gain and increased DOF	Plant gain Actual gain: 1.75 Altered gain: 1.25, 0.75 Dead zone Actual DOF: ± 0.14 Altered DOF: ±0.25,0.35	1. Increased accommodative lag. 2. High AC/A and accommodative adaptation. 3. Reduced peak velocity and acceleration. 4. Reduced CA/C 5. Increased esophoria over time
	Reduced plant gain and ASG	Plant gain Actual gain: 1.75 Altered gain: 1.25, 0.75 ASG gain Actual gain:1 Altered gain: 0.8, 0.6, and 0.4.	1. Increased accommodative lag. 2. High AC/A and accommodative adaptation. 3. Reduced peak velocity and acceleration. 4. Reduced CA/C 5. Increased esophoria over time

As shown in table 3-1, model simulations with a reduced accommodative plant gain predicted the abnormal behavior found in myopes. However, this hypothesis of a rigid plant was never tested in progressive myopes, either children or adults. A rigid plant, as shown in table 3-1, would predict an altered main sequence (reduced rate of change of velocity and acceleration over response amplitude) and a reduced accommodative response to both blur and disparity. To date there has been no measure of main sequence characteristics of the blur-driven accommodative responses in myopic children. While our group previously found no attenuation of convergence accommodation (CA) in children, they do point out that CA output might have been prolonged due to the decreased vergence adaptation found in the myopic children[53].

Previous investigations, except one[5], examined accommodative behavior to targets changing in depth where both proximal and blur cues would be found together. Proximal cues could confound the isolation of a purely sensory (blur) or motor (plant) deficit. Static behavior of accommodation was found to be reduced when stimulated using optical (negative) lenses compared to targets changing in depth[1]. Negative lenses do not control image size, in fact, image size decreases with increasing defocus levels which is actually opposite to a normal proximal cue under natural conditions. Measures of blur driven accommodation (BA) are typically achieved by using a simple Badal optical system where changes in the stimulus do not result in retinal image size changes[54]. One study looked at blur driven accommodative lags using a Badal system in children, however, they did not characterize the main sequence relationship[5]. The purpose of this investigation was to examine the hypothesis of a rigid accommodative plant explaining the abnormal behavior of accommodation in young progressive myopes. Responses from myopes were compared to an age matched group of non-myopic children along with adults.

3.3 Methods

12 school aged children, 6 myopes & 6 emmetropes (Age: 8-13 years), and *6 naive adults* (Age: 21-35 years) were recruited from the optometry clinic at the School of Optometry and Vision Science, University of Waterloo. Sample size calculations for this study were done based on the pilot data on the accommodative response lags obtained from 3 myopes and 3 non-myopes (Appendix A). Informed consent and assent was obtained after a verbal and a written explanation of the study from the parents and children respectively. Consent was obtained directly from adult subjects. The study followed the tenets of Declaration of Helsinki and received ethical approval from the University of Waterloo office of research ethics review board.

Children were classified into two refractive groups based on their cycloplegic refraction. The myopic group (MYP) had equivalent spheres between –1.25D to -7.00D. Also, based on their clinical history, it was confirmed that all the myopic children had a progression rate of >0.5D/year over the last two years. Emmetropic children (EMM) had equivalent spheres between +0.50D to 0D. Adult group (ADT) had 4 stable myopes and 2 emmetropes. They were not subdivided into refractive groups given the empirical evidence on accommodative dynamics being similar between the stable myopes and emmetropes[23,55,56]. Subjects with no strabismus, no amblyopia, anisometropia < 1.00D, astigmatism < 1D along with a best corrected visual acuity of 6/6 in both eyes were included. All the myopes, both adults and children, were habitual soft contact lens wearers and wore their contact lenses during the study.

3.3.1 Experimental design and instrumentation

Data were collected over two visits, a screening visit to confirm the visual status of the subject and an experimental visit to measure the response dynamics to various accommodative stimuli.

3.3.1.1 First visit: Visual and other accommodative parameters

During the screening visit, baseline clinical measures including distance and near visual acuity, stereopsis, cycloplegic retinoscopy, and phoria (distance and near) measurement using cover test were performed on all the subjects.

3.3.1.1.1 PowerRefractor and its principle

During the first visit, accommodation was measured using a commercially available eccentric infra-red (IR) photorefractor, (PowerRefractor, MultiChannelSystems, Germany)[19,57,58]. The PowerRefractor works on the principle of eccentric photorefraction[59–61]. It works at a sampling rate of 25Hz and can measure accommodation in both monocular and binocular modes.

The Power Refractor consists of a triangular array of six light emitting diode (LED) segments placed around the closed circuit device (CCD) camera which is connected to a portable personal computer. Each segment contains nine infra-red LED's. The working range of the instrument extends from +4D to -6D. Infra-red light from the eccentric light source returns back to the CCD camera after reflection from the eye. The estimate of optical defocus is determined from the intensity of the luminance profile across the pupil. The slope of the intensity profile across the pupil varies with the magnitude and polarity of the refractive error and is converted into refractive error or accommodation (units of diopters) based on an inbuilt calibration equation[57,60]. However, to control for individual variations in the pupil size and fundal reflectance, both relative and absolute calibration need to be performed to ensure the accuracy of the final estimate[19,62]. Relative calibration were performed on all our subjects. An infrared (IR) filter (Kodak 87B, IR filter, Rochester, NY) was placed in front of the right eye which blocked visible light but permitted the IR light source of the PowerRefractor to obtain measurement. The left eye of the subject viewed a high contrast target placed at 4m. A series of lens defocus (ranging from +5D to -1D in 1D step) were then placed over the IR filter to induce refractive errors. Photorefraction measures were recorded for 2s and for each lens and averaged. This lens range was chosen based on the expected levels of stimulus demands tested during the visit. The resulting photorefraction measure for each lens defocus was then plotted as a function of induced refractive error. Linear regression fits were used to estimate the relationship between induced and measured refraction. The regression slope equation was then used to obtain accurate accommodative measures. Absolute calibration was not performed during this visit and instead a previously estimated correction factor (0.4D)[19] was used to get the final accommodation estimate.

3.3.1.1.2 Accommodative parameters

Horizontal near phoria was measured using a modified Thorington technique – MTT and was quantified using a custom designed tangent scale placed at 33cms[19,63]. The tangent scale consisted of a small central light source and a horizontal row of letters and numbers on either side. Each letter/number was separated by 3.3 mm (subtends 1Δ change at a distance of 33cm). Gradient response AC/A (Accommodative convergence per diopter of accommodative response) was quantified as the change in the phoria with negative lenses. Accommodation response to lenses was recorded for 2s using the PowerRefractor.

Resting focus was measured using a difference of Gaussian (DOG) target placed at 3m in a dark room with the left eye of the subject occluded. The peak spatial frequency present in the target was 0.18cpd. The DOG target used does not stimulate accommodation when viewed through a series of negative lenses and has been tested before in the laboratory[64,65].

- Accommodative adaptation was measured as the difference in the resting focus before and after the near task. The child was then asked to watch an animated movie (sustained accommodation) presented on a LCD display at 25cms for 20mins without any break.
- Stimulus CA/C was quantified as the instant change in the accommodative response to known prisms when the child was fixating at the DOG placed at 3m. Stimuli ranging from 5Δ - 15Δ (5Δ steps) were placed in front of the left eye. A consensual change in the accommodation was measured from the right eye for 5s and then averaged.

3.3.1.2 Second visit: Blur driven accommodation

The experimental visit followed the screening visit by not more than 10 days. During the second visit, each subject was dilated using a drop of 2.5% Mydfrin (Phenylephrine hydrochloride) in both the eyes following an initial anterior chamber assessment. This optimized the photorefraction measures by ensuring a large pupil size (>4mm).

3.3.1.2.1 Dynamic photorefraction system (DPRS)

DPRS consists of two major components, a high speed dynamic photorefractor coupled with an offline analysis algorithm[66]. The dynamic photorefractor and the components involved in the analysis algorithm have been described elsewhere (chapter 2). The DPRS was previously calibrated and validated on children and adults[68]. To control for individual variations in the fundal brightness and pupil size, relative calibration was performed on each subject. The calibration procedure followed was similar to one described in chapter 2.

3.3.1.2.2 Badal optical system

The experimental visit followed the screening visit by not more than 10 days. A simple Badal optical system was used to present accommodative and disaccommodative stimuli. The subject was seated 1m away from the photorefractor with the left eye occluded (figure 3-2). An IR passing mirror (Optical cast IR filter, Edmund Optics, USA) allowed an orthogonal presentation of the accommodative targets along with a continuous measure of accommodation using the dynamic photorefractor (see below). Two targets were manually placed at different distances from a +5D Badal lens. Each target was a high contrast (white on black) vertical line that was back illuminated using a white LED. A small horizontal offset was present between the two targets (maximum offset was 1.5° for a 3D stimulus). While the far target was always set at optical infinity, the near target was moved to various distances from the Badal lens to create various demands (1-3D, in 1D steps). Step stimuli were presented using a stimulus control tool box with a button that allowed for an instantaneous switch in the target distance. In other words, as shown in figure 3-2, the subject viewed only one high contrast target at a time, either the far target or the near target. This switch was connected to an input-output control box that was further connected to the dynamic photorefraction system. This allowed a time stamp to be created when the target distance was switched. The order and presentation time of the step stimulus was varied to avoid predictability.

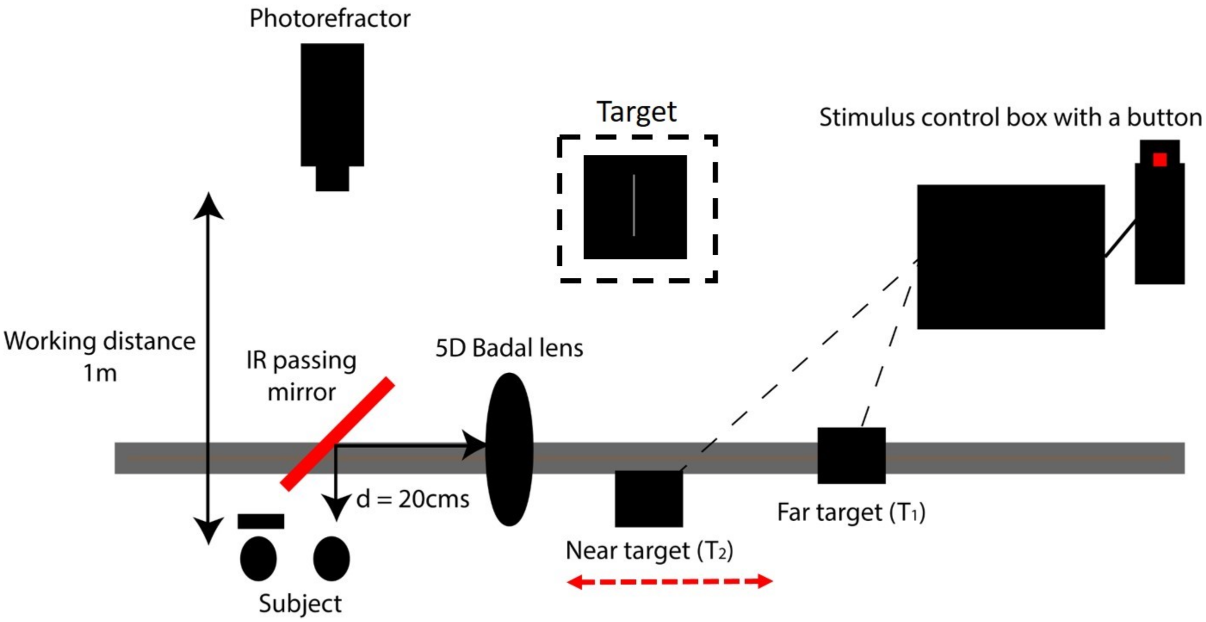

Figure 3-2: Badal optical system to stimulate accommodation and disaccommodation. Subjects viewed at a high contrast vertical line (white on black) through the Badal lens.

3.3.1.2.3 Procedure

The left eye of the subject was covered with an eye patch during the study to open the loop of the vergence system. The photorefractor was aligned to the right eye of the subject. Prior to the start of the study, 2-3 practice trials were given to each subject in order to familiarize them with the experimental procedures. During the measurement trial, subjects viewed at the high contrast target (white on black) through the Badal lens and were instructed to make sure that the edges of the target were always clear and sharp. Accommodative and disaccommodative step responses were recorded over 3 different stimulus amplitudes (1-3D in 1D steps). Six trials were conducted for each stimulus demand. Each trial lasted for approximately 5-10 seconds. The stimulus presentation time was controlled by the experimenter and was varied from 2-5 sec after the initiation of the trial to avoid prediction. Dynamic step responses were recorded for at least 3-5 sec after the presentation of the stimulus. The order of stimulus presentation was randomized. Frequent breaks were given to the subject between the trials.

3.3.1.3 Data analysis

Final position traces (units of diopters) over time obtained from the DPRS were then loaded into MATLAB for further analysis. Velocity (diopters/s) and acceleration (diopters/s^2) profiles were obtained by differentiating the response traces using a 2-point-difference algorithm. Position, velocity and acceleration traces were subsequently smoothed over a 100 msec window. It is a simple moving average with the middle of the smoothing window aligned to the sample point. The start and end of the response were identified using the velocity-criterion algorithm[69]. The start of the response was the first data point on the position trace where the velocity exceeded 0.5 D/s and continued to do so for the next 100 msec. Similarly, the response was considered to be completed when the velocity fell below 90% of peak velocity and remained at that level for the next 100ms. The start and the end points obtained using this criterion were later confirmed by visually inspecting each trace. An inverse of this criterion was used for the disaccommodative responses. Typical responses were characterized by an initial exponential increase (accommodative) or decrease (disaccommodative) in the amplitude followed by a small asymptotic change to the final steady state (figure 3-3). A transient rise in the velocity corresponded to a change in the accommodative position. Latency (msec) was defined as the time taken for the initiation of the response after the presentation of the stimulus and was ≈ 250 - 300msec. Amplitude (Diopters) was defined as the dioptric difference between the start and end points. The time taken to reach the end point from the starting point was defined as the response time (msec). The maximum values in the velocity and acceleration traces were defined as the peak velocity (D/s) and peak acceleration (D/s^2) respectively. "First order main sequence" relationship was obtained by plotting the peak velocities as a function of their respective response amplitudes. Similarly "Second order main sequence" relationship was defined by plotting peak acceleration as a function of the response amplitude. The time taken to reach the peak velocity value from 0 D/s is defined as the time to peak velocity (TPV in msec) and the total time taken for acceleration from 0D/s^2 to reach peak and decrease back to 0D/s^2 was defined as the total duration of acceleration (TDA in msec). Historically the main sequence relationship has been analyzed using a univariate regression. However, given the variability noted in both the velocity/acceleration measures and response amplitudes, a bivariate regression would appear to be more suitable. A bivariate analysis produced a better fit to the data (R squared) with significantly steeper slopes compared to a simple univariate analysis. Therefore, bivariate regression (Deming regression) was used for analyzing the main sequence relationship for both accommodation and disaccommodation. Deming regression and other statistical analysis were performed using GraphPad Prism (GraphPad Software Inc., USA) and STATISTICA (StatSoft, Inc., USA). For repeated measures ANOVA (Rm ANOVA), subject group (Myopes, emmetropes and adults) was considered as a between factor and stimulus amplitude (1D, 2D & 3D) as within factor.

Table 3-2: Critical visual and accommodative parameters (mean ± SD) obtained from all our subjects.

Parameter	EMM	MYP	ADT	P value
Age (years)	11.16 ± 1.83	11.16 ± 1.0	26.5 ± 3.56	-
Refractive error (D)	0 ± 0.25D	-3.7 ± 2.0	-1.91 ± 1.61	-
Near phoria (Δ) (-ve: exo; +ve: eso)	-1.83 ± 2.13	1 ± 3.57	-0.83 ± 0.98	-
Stimulus AC/A ratio (Δ/D)	4.00 ± 0.63	4.50 ± 0.50	-	0.17
Response AC/A ratio (Δ/D)	4.16 ± 0.57	6.66 ± 1.09	-	0.005
Stimulus CA/C ratio (D/Δ)	0.07 ± 0.009	0.05 ± 0.006	-	0.29
Accommodative adaptation (D)	0.08 ± 0.04	0.25 ± 0.05	-	0.0001
Tonic accommodation levels (D)	0.52 ± 0.07	0.28 ± 0.09	-	0.0006

3.4 Results

Accommodation data were obtained from 12 children, 6 myopes (11.16 ± 1.00 years) & 6 emmetropes (11.16 ± 1.83 years), and 6 adults (26.16 ± 3.37 years). Mean refractive error along with other critical visual parameters are provided in table 3-2. Given the off line nature of the analysis, efforts were made to ensure that each subject provided at least 6 usable measures for each stimulus level. In adults, each subject was tested at 3 stimulus levels with 6 trials for each target position for a total of 36 trials including both accommodation and disaccommodation. With children, response trials involved head and eye movements, significantly larger number of blinks etc. which corrupt the data. Therefore, more trials (6-12 trials per stimulus demand) were performed on children to ensure that the required number of data trials were obtained from each child. Measures were categorized into usable and unusable responses. The latter included measures with blinks, head movements and/ or poor photorefractor image quality. Usable traces were further divided into Typical and Atypical responses. Atypical responses were excluded from further analysis and would be described and analyzed separately in chapter 4. For the analysis of accommodative dynamics, the first 4 typical responses were considered. This allowed equal representation of the subjects' responses in the final group results without any individual bias.

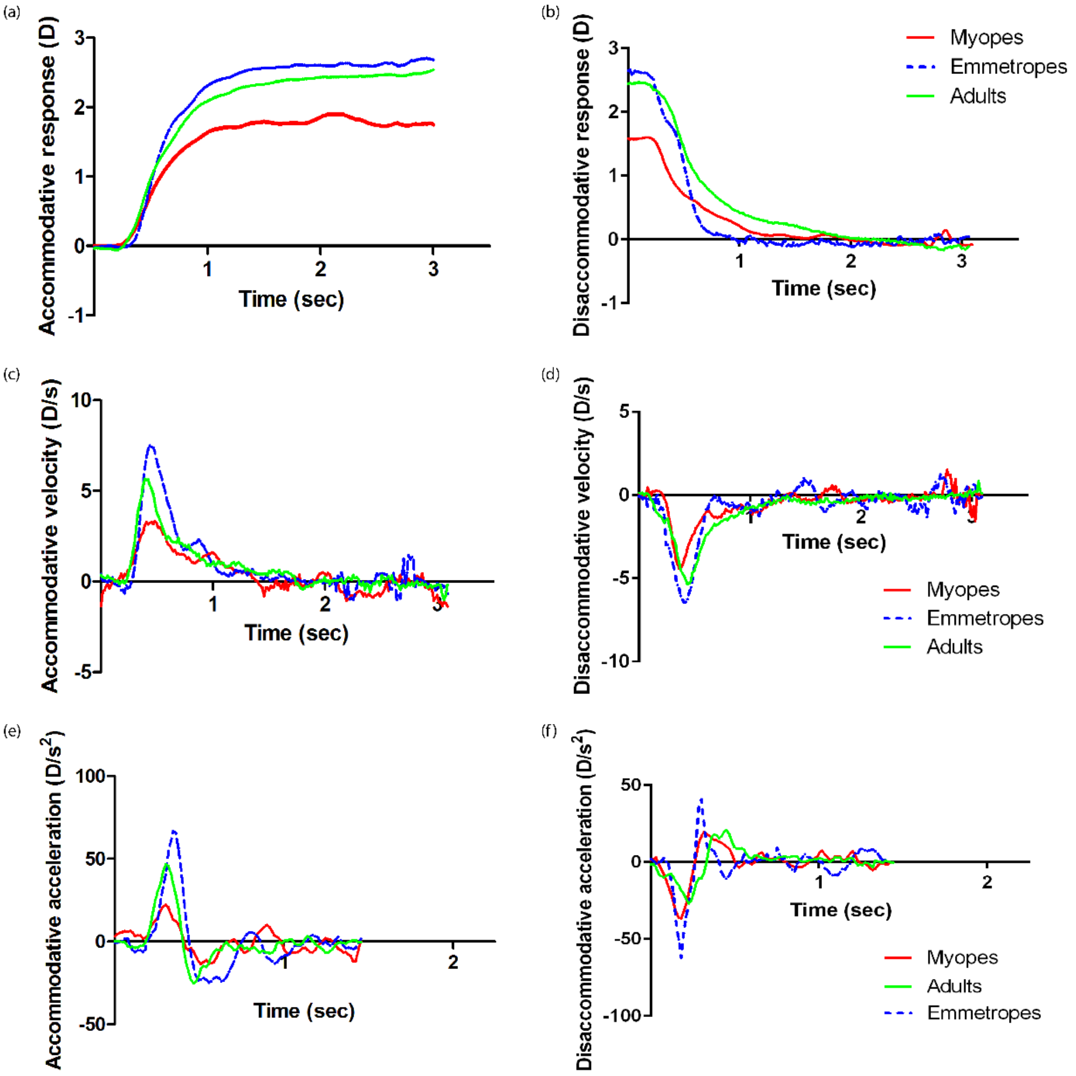

Figure 3-3: Typical accommodative and disaccommodative traces for a 3D stimulus demand.

Group averaged accommodative and disaccommodative position (3a, 3d), velocity (3b, 3e) and acceleration (3c, 3f) traces were plotted as a function of time. The data were normalized and averaged across different observers within each group.

3.4.1 Temporal characteristics

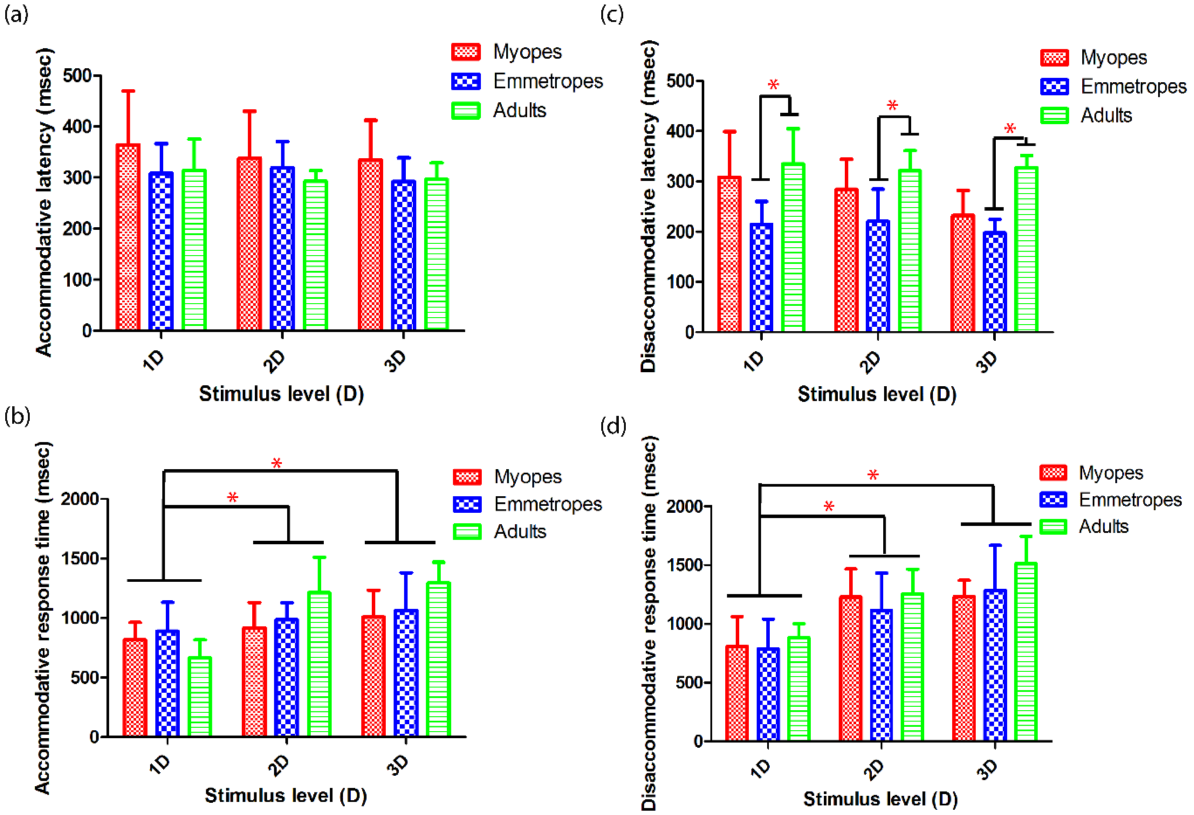

Figure 3-4: Latency and response time of accommodation and disaccommodation across the three groups and stimulus demands. The errors bars indicate the standard deviation. Asterisk symbols indicate the level of significance ('*' – p < 0.05).

Figure 3-4 shows the mean latency and response time exhibited by subjects in the three groups for both accommodation (figure 3-4 (a, b)) and disaccommodation (figure 3-4 (c, d)). For accommodation (ACC), repeated measures ANOVA (Rm ANOVA) showed that the latency was not significantly different between the three groups (F (2, 15) = 1.22, p = 0.32) and stimulus demands (F (2, 30) = 1.00, p = 0.37). However, for disaccommodation (DACC), latency was significantly different between the three groups (F (2, 15) = 12.39, $p < 0.001$) but not across the stimulus demands (F (2, 30) = 2.38, p = 0.10). Post hoc (Tukey HSD) analysis showed that ADT exhibited significantly longer latencies compared to the EMM across all the stimulus demands ($p < 0.05$). For both ACC and DACC, the response time was significantly different between the three stimulus amplitudes (ACC: F (2, 30) = 12.37, $p < 0.001$; DACC: F (2, 30) = 32.99, $p < 0.0001$) but not across the three groups (ACC: F (2, 15) = 1.44, p = 0.27; DACC: F (2, 15) = 1.11, p = 0.35). Post hoc Tukey suggested that the response time was significantly smaller for a 1D stimulus compared to the larger demands across all the groups ($p < 0.05$).

3.4.2 Accommodative response

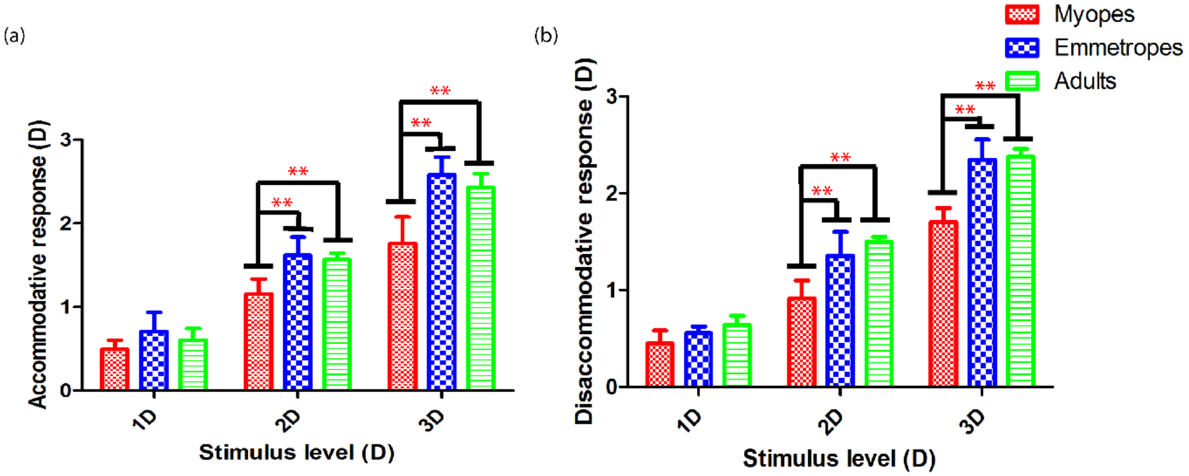

Figure 3-5: Response amplitude of accommodation (a) and disaccommodation (b) in relation to the stimulus demand across the three groups. Error bars indicate the standard deviation. Asterisk symbols indicate the level of significance ('' – $p < 0.001$).**

For both ACC and DACC, repeated measures ANOVA showed that the response amplitude was significantly different between the three groups (ACC: F (2, 15) = 29.0, $p < 0.0001$; DACC: F (2, 15) = 37.7, $p < 0.001$) and between stimulus demands (ACC: F (2, 30) = 355.30, $p < 0.0001$; DACC: F (2, 30) = 659.80, $p < 0.0001$). Further, a significant interaction was noted between the groups and stimulus demands (ACC: F (4, 30) = 5.20, $p = 0.003$; DACC: F (4, 30) = 8.1, $p < 0.001$). As shown in figure 3-5, post hoc analysis showed that MYP exhibited significantly reduced response amplitudes compared to other groups for demands larger than 1D ($p < 0.01$) of both accommodation and disaccommodation.

3.4.3 First and second order main sequence

Figure 3-6 (a, b) shows the velocity main sequence (MS) of the three groups. The slopes of the velocity MS for all the groups were significantly different from a zero slope ($p < 0.0001$). For ACC, although the slopes of the MS were not significantly different between the MYP vs EMM (F (1, 91) = 0.06, $p = 0.79$) and MYP vs ADT (F (1, 124) = 1.86, $p = 0.17$), a statistically significant difference in the slope of MS was noted between the EMM vs ADT (F (1, 121) = 4.15, $p = 0.04$). Also, the intercept of MS was significantly different between MYP and ADT (F (1, 125) = 4.16; $p = 0.04$). For DACC, the slopes of the MS were not significantly different between the MYP vs EMM (F (1, 102) = 0.14, $p = 0.70$), MYP vs ADT (F (1, 123) = 0.01, $p = 0.89$), and EMM vs ADT (F (1, 123) = 0.14, $p = 0.70$). However, the intercept of MS was significantly different between the EMM vs ADT (F (1, 124) = 11.74; $p = 0.0008$) and MYP vs ADT (F (1, 124) = 10.02; $p = 0.001$).

Time to peak velocity (TPV) was also compared across the three groups for accommodation and disaccommodation (figure 3-6 (c, d)). The slopes of the TPV over the response amplitudes were not significantly different from zero ($p > 0.05$). No significant difference was noted in the slope of TPV between MYP vs EMM (ACC: F (1, 91) = 0.45, $p = 0.50$; DACC: F (1, 102)

$= 0.63$, $p = 0.42$), MYP vs ADT (ACC: $F(1, 124) = 0.009$, $p = 0.92$; DACC: $F(1, 123) = 0.78$, $p = 0.37$) and EMM vs ADT (ACC: $F(1, 121) = 0.58$; $p = 0.44$; DACC: $F(1, 123) = 0.01$; $p = 0.91$). However, for DACC, the intercept of the TPV was significantly different between EMM and ADT ($F(1, 124) = 9.48$; $p = 0.002$).

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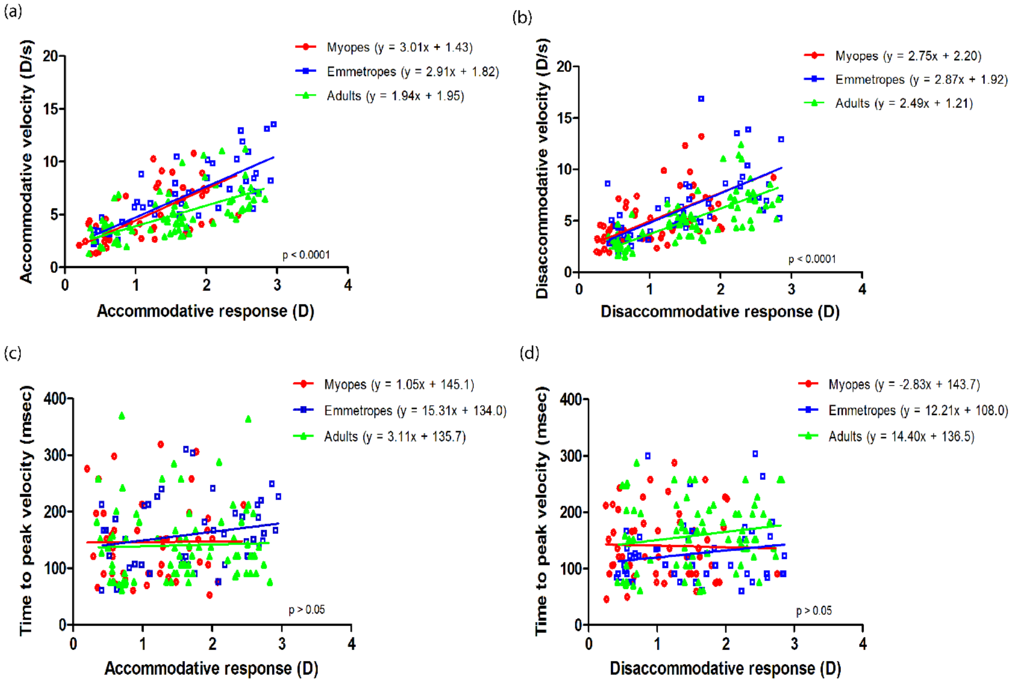
Velocity main sequence



Acceleration main sequence

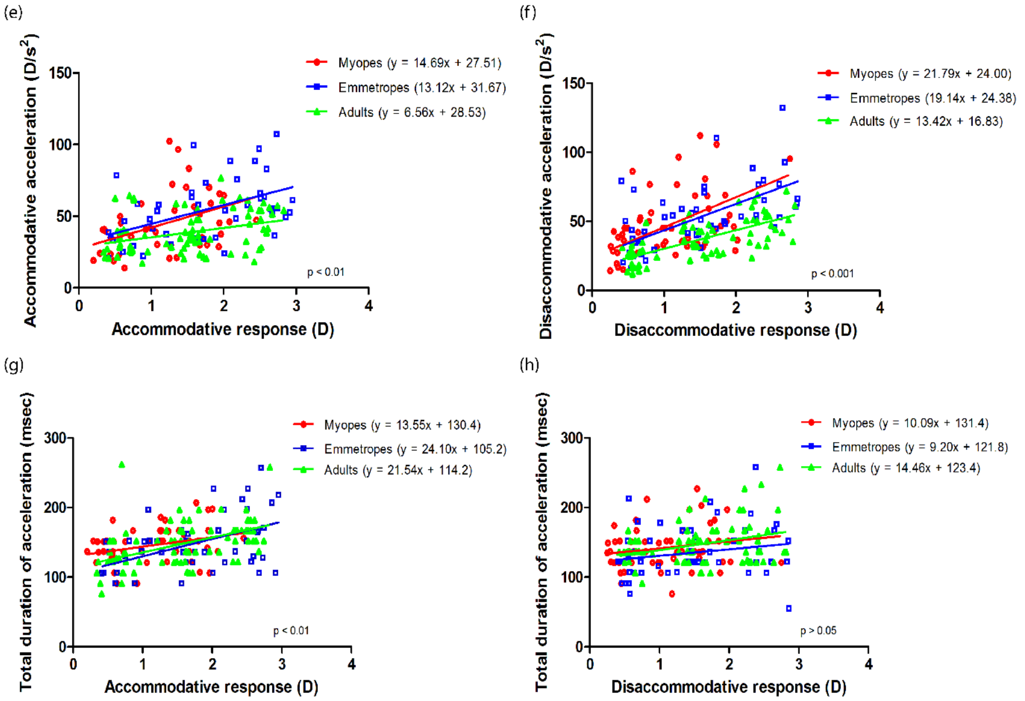


Figure 3-6: Main sequence characteristics of accommodation and disaccommodation.

(a, b) Peak velocity was plotted as a function of the response amplitude for both accommodation and disaccommodation. (b, d) Time to peak velocity was plotted as a function of response amplitude. (e, f) Peak acceleration was plotted as a function of the response amplitude for both accommodation and disaccommodation. (g, h) Total duration of acceleration was plotted as a function of response amplitude. As indicated in the picture, red circles indicate data from myopes, green circle from adults and blue squares indicate emmetropes. Solid lines represent Deming regression fits. Given the variance in both x and y variables of the main sequence plot, a simple linear regression was not used. P values indicate the level of difference of the MS slopes from a zero slope.

Figure 3-6 (e, f) represents the acceleration main sequence of the three groups. The slopes of the acceleration MS for all the groups were significantly different from a zero slope ($p < 0.05$). The slopes of the MS were not significantly different between the MYP vs EMM (ACC: F (1, 91) = 0.0004, p = 0.98; DACC: F (1, 102) = 0.002, p = 0.95) and MYP vs ADT (ACC: F (1, 124) = 1.60, p = 0.20; DACC: F (1, 123) = 0.77, p = 0.37), and EMM vs ADT (ACC: F (1, 121) = 2.19, p = 0.14; DACC: F (1, 123) = 1.44, p = 0.23). But the intercept of MS was significantly different between the MYP vs ADT (ACC: F (1, 125) = 8.06, p = 0.005; DACC: F (1, 124) = 30.56; $p < 0.0001$), and EMM vs ADT (ACC: F (1, 122) = 22.13; $p < 0.0001$; DACC: F (1, 124) = 37.24, $p < 0.0001$). Total duration of acceleration (TDA) was also compared across the three groups (Figure 3-6 (g, h)). For accommodation, the slopes of the TDA over the response amplitudes were significantly different from zero ($p < 0.01$) except for MYP ($p > 0.05$). For disaccommodation, the slopes of the TDA over the response amplitudes were significantly different from zero all the three groups ($p < 0.05$). No significant difference was noted in the slope of TDA between MYP vs EMM (ACC: F (1, 91) = 1.11, p = 0.29; DACC: F (1, 102) = 0.002, p = 0.95), MYP vs ADT (ACC: F (1, 124) = 0.86, p = 0.34; DACC: F (1, 123) = 0.29, p = 0.58) and EMM vs ADT (ACC: F (1, 121) = 0.10; p = 0.74; DACC: F (1, 123) = 0.42; p = 0.51).

3.5 Discussion

In agreement with the previous studies, myopic children exhibit significantly larger response lags which increase with stimulus demand. However, myopic children showed a main sequence relationship similar to the emmetropes. Other dynamic characteristics such as latency, response time were not significantly different between the two refractive groups (myopes and non-myopes) for both accommodation and disaccommodation. Adults showed an overall reduction in the response dynamics such as peak velocity and acceleration compared to children. The present investigation also confirms the previous findings of high response AC/A, high accommodative adaptation and unchanged CA/C.

3.5.1 Dynamic accommodation and myopia

A reduced accommodative plant gain would explain the pattern of high lags of accommodation coupled with an elevated response AC/A and high accommodative adaptation. However, it cannot explain the findings of similar disparity driven accommodative response (CA/C) and MS relationship found in progressive myopes compared to emmetropes. Also, given that these patterns of accommodation normalize after myopia progression ceases[23], it would be difficult to imagine a motor plant deficit that could be temporary. A sensory deficit modelled as either a large DOF or reduced ASG would predict the patterns of reduced blur accommodation, unchanged MS relationship and CA/C. However, it would not predict the abnormal pattern of high response AC/A and high adaptation. Previously, studies have suggested that the abnormal behavior of accommodation may be due to an increased effort to accommodate given the remote accommodative resting state in corrected MYPs compared to EMMs[12,70]. In agreement, tonic accommodative levels were lower in progressive myopic children compared to the non-myopic children. An increased effort to accommodate would lead to larger accommodative lags that increase with demand and would elevate both stimulus as well as response AC/A. However, consistent with the previous investigation, we found a similar stimulus AC/A between myopic and non-myopic children[10] despite their differences in response AC/A . This suggests that the resulting accommodative convergence for a given target distance remains constant even with a reduced accommodative response. This might suggest an increase in the AC cross-link gain to compensate for reduced accommodation.

A novel model simulation (Table 3-3), however, does predict the empirical evidence. This was achieved by including an elevated AC cross-link gain, a reduced slow vergence controller and a reduced ASG. Based on the simulations, I propose that the reduced blur sensitivity (ASG) seen in the myopic children might have been compensated by a motor recalibration wherein the gain of the accommodative convergence crosslink is increased. A larger gain of the crosslink would be necessary to maintain sufficient levels of vergence given the reduced accommodation. The capacity to increase AC gain is consistent with past studies on adults [71–73]. The gains in AC/A linkage are more difficult to change in adults compared to the adaptive system gains. However, since the direction of such adjustments appear to be necessary for children undergoing increases in inter-pupillary distance (IPD) with age, perhaps this adjustment is more plastic at a younger age[74]. The transient nature of this recalibration in the AC gain could be in the response to the reduced blur sensitivity which improves when myopia stabilizes. The increase in accommodative adaptation was modelled by reducing the gain of slow vergence controller (i.e. reduced vergence adaptation) in myopes. Vergence adaptation was found to be reduced in myopic children compared to the non-myopes[52]. A stronger slow accommodative controller may also be necessary to turn off the high AC cross-link and avoid esophoria with sustained viewing[75].

Table 3-3: Myopia model of accommodation and vergence

Hypothesis	Prediction and Simulink parameter	Agreement with empirical evidence	Disagreement with empirical evidence
Motor (AC/A) adjustment to compensate for reduced ASG	**Reduced ASG** Actual gain: 1 Altered gain: 0.8,0.6, 0.4 **High AC gain** Actual gain: 0.65 Altered gain: 0.7, 0.85, 1.15 **Reduced slow vergence controller gain** Actual gain: 1.5 Altered: 1.2, 1.0	1. High response lags 2. High accommodative adaptation 3. High response AC/A 4. Unchanged stimulus AC 5. Unchanged stimulus CA/C 6. Unchanged main sequence	None

3.5.2 Dynamic accommodation and age

Dynamic characteristics of accommodation and disaccommodation have been extensively studied on adults [60,65,69,76,77]. Previously, one investigation found that accommodative acceleration was independent of the response amplitude[69]. However, a positive acceleration MS (i.e., peak acceleration increased proportionately with an increase in the accommodative demand) was noted in all our subject groups. Given that both the current and previous study had a similar age range of subjects and measured blur only accommodation, this discrepancy cannot be explained. This positive MS relationship noted in the current study would imply that similar to other motor systems such as vergence, accommodative pulse innervation would increase proportionately with the response amplitude. Except the latency of the disaccommodative response, temporal behavior of the accommodative system was similar between the adults and children. It is difficult to comment on this difference since a change in the plant dynamics with age should have affected the overall temporal behavior of the accommodative mechanism and not just the disaccommodative latency. A small sample could be one of the potential explanation for this pattern. This is the first study to examine the age related pattern of second order main sequence. In agreement with previous studies and model predictions, a reduced first and second order main sequence profile was noted in adults compared to the children[78–81].

3.6 Conclusion

Empirical data from the present study suggests that the abnormal behavior of accommodation in myopic school children couldn't be explained by a purely motor or sensory model. Based on the current understanding of the accommodation, a reduced blur sensitivity coupled with a motor recalibration of the AC cross-link would predict this transient but consistent behavior seen in progressive myopic children. Atypical response behavior of blur driven accommodation and disaccommodation would be examined in the next chapter. Also, the influence of refractive error and age was tested.

Chapter 4

Dynamic atypical behavior of blur driven accommodation

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4.1 Summary

Introduction: Traditionally, accommodation has been considered as an overdamped system. Previously, atypical response patterns such as the dynamic overshoots were reported to exist only unnatural scenarios such as a stereoscopic viewing condition. However, atypical response patterns were noted even with blur driven accommodation in the previous chapter. The current investigation examines each atypical pattern and provides an explicit explanation to these response patterns.

Methods: Static and dynamic blur accommodation (BA) measures were taken using a Badal optical system on 12 children (6 emmetropes and 6 myopes, 8–13 years) and 6 adults (20–35 years). A high speed dynamic photorefractor was used to record accommodative responses to various step stimuli (1-3D, 1D steps).

Results: Usable BA responses were classified as either typical or atypical responses. Response integrals for double steps and dynamic overshoots ranged from 0.28D – 1.46D (0.78D ± 0.35D) and 0.2D – 1.15D (0.42D ± 0.21D) respectively. Atypical patterns were noted only in accommodation but not disaccommodation. Main sequence relationship remained invariant between typical and atypical responses. An overall reduction was noted in the frequency of atypical responses with age ($p < 0.001$).

Discussion: Taken as a whole, atypical response behavior exists with blur driven accommodation. Main sequence data suggests that atypical responses occur to inaccurate response initiation. The reduction in the frequency of atypical responses with age reflects a

developmental pattern of dynamic accommodative mechanism probably the internal feedback mechanism.

4.2 Introduction

The current study examines the atypical response behavior of accommodation in children and adults noted in the previous chapter. Atypical response patterns were those that did not conform to the expected typical exponential pattern of an accommodative response change. These patterns were noted to be more frequent in children (myopes and emmetropes) compared to adults. Close inspection showed that these patterns were not limited to poor attention and appeared to show immaturities in the dynamic properties of accommodation. While there was no a priori reason for this to differ between myopic and non-myopic children, it was important to determine if they did differ between the refractive groups. These patterns have not described previously with blur driven accommodative responses. One study which tested accommodation in children reported these response but have never fully investigated the patterns in children1. Therefore, given the consistency of these patterns in children, the frequency of pattern was tested in the current study both within and across the groups. Also, the influence of age and refractive error was tested.

Accommodation is a dynamic, optical change in the dioptric power of the eye to focus objects at various distances[1]. As described in chapter 1, static and dynamic aspects of accommodation have been well established[2–14] and have been modelled accordingly[15–19]. Based on the neural and biomechanical modules described previously[20], the accommodative mechanism is represented using a pulse and a step innervation which predicts the dynamic and static behavior respectively. As described previously, a typical response is characterized by an initial exponential increase in the amplitude followed by a small asymptotic change to the final steady state (figure 4-1 (a)).

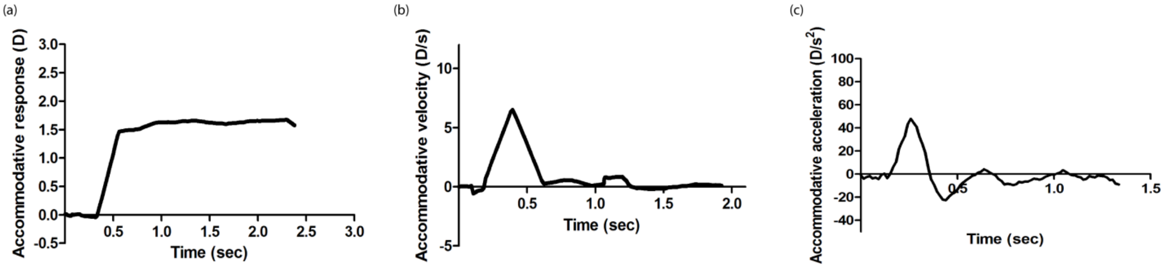


Figure 4-1: Typical accommodative position, velocity and acceleration traces for a 2D demand.

Accommodative position (a), velocity (b) and acceleration (c) traces were plotted as a function of time. (a) While a typical initiation of the response occurs approximately 300 msec after the presentation of the stimulus, total response occurs within a second. Velocity (D/s) and acceleration (D/s2) traces were obtained by differentiating the position traces.

4.2.1 Atypical responses: Response damping

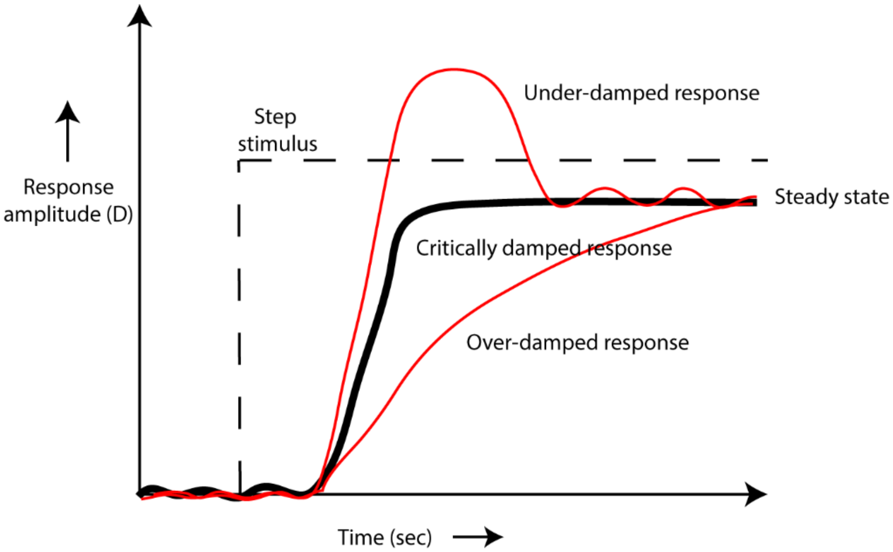


Figure 4-2: Types of damped responses that can occur with a transiently stimulated motor system. For a step stimulus (dotted line), the response of the motor system can vary depending on the amount of damping.

A typical control (motor) system would operate to restrict the error in the system to zero. Unlike the oculomotor systems, in an ideal system, when the stimulus input and the response output match, the motor system would then act to maintain the new desired steady state. With an increase in the difference between the input and output (i.e. error), a proportional increase would occur in the system's effort and speed to reduce the error. A motor system would respond transiently when exposed to a change in the steady state equilibrium (for e.g. error caused by a step stimulus described in the models identified previously[19]). This transient change in the steady state to reduce the error can be of three types based on the amount of damping[21] (figure 4-2), (1) Critically damped or typical response, whereby the system would reach the desired new steady state (or equilibrium) as quickly as possible without any oscillations. (2) Over damped, where the system reaches the equilibrium without oscillations but slower than a critically damped response. A system with low response gain would usually lead to an over damped response (3) If the output returns to the steady state with oscillations that decrease in magnitude overtime, it is termed as an underdamped response or a response with dynamic overshoots. This usually would happen with a system that would exert a response with a high gain causing overshoot before reaching the final steady state.

4.2.2 Atypical responses: Oculomotor system

Atypical patterns have been reported in saccades, vergence and accommodation. Studies on adults showed atypical saccadic patterns such as the dynamic overshoots and saccadic oscillations[22–25]. These atypical patterns were predicted to be due to either an unstable[25] or an inaccurate pulse generator[22]. Also, atypical patterns such as the double step responses found were shown to exist with the vergence system [26,27]. Double step responses exhibit an initial undershoot followed by a corrective response to reach the desired steady state. These studies predicted that atypical patterns in vergence occur due to an inaccurate response initiation like the saccades. Recently, several studies[6,28–31] reported atypical accommodative response patterns, specifically underdamped responses, to step stimuli. Two major findings from these studies include, (1) the existence of dynamic accommodative overshoots under a stereoscopic environment where vergence and accommodative demands were incongruent. (2) Higher frequency of dynamic overshoot responses were associated with subjects with excessive convergence driven accommodation (CA/C) output. The accommodative response to a stereoscopic target was suggested as a combination of the transient convergence accommodation phase followed by the blur driven accommodation phase. Another investigation found an increased proportion of atypical patterns of accommodation such as the overdamped response in their younger visually normal (3-5 year old) subjects compared to the older ones (20-30 year old)[6]. However, they did not quantify or categorize these atypical patterns other than to separate them from normal responses. They attributed those atypical responses to the limited attention levels of their younger subjects.

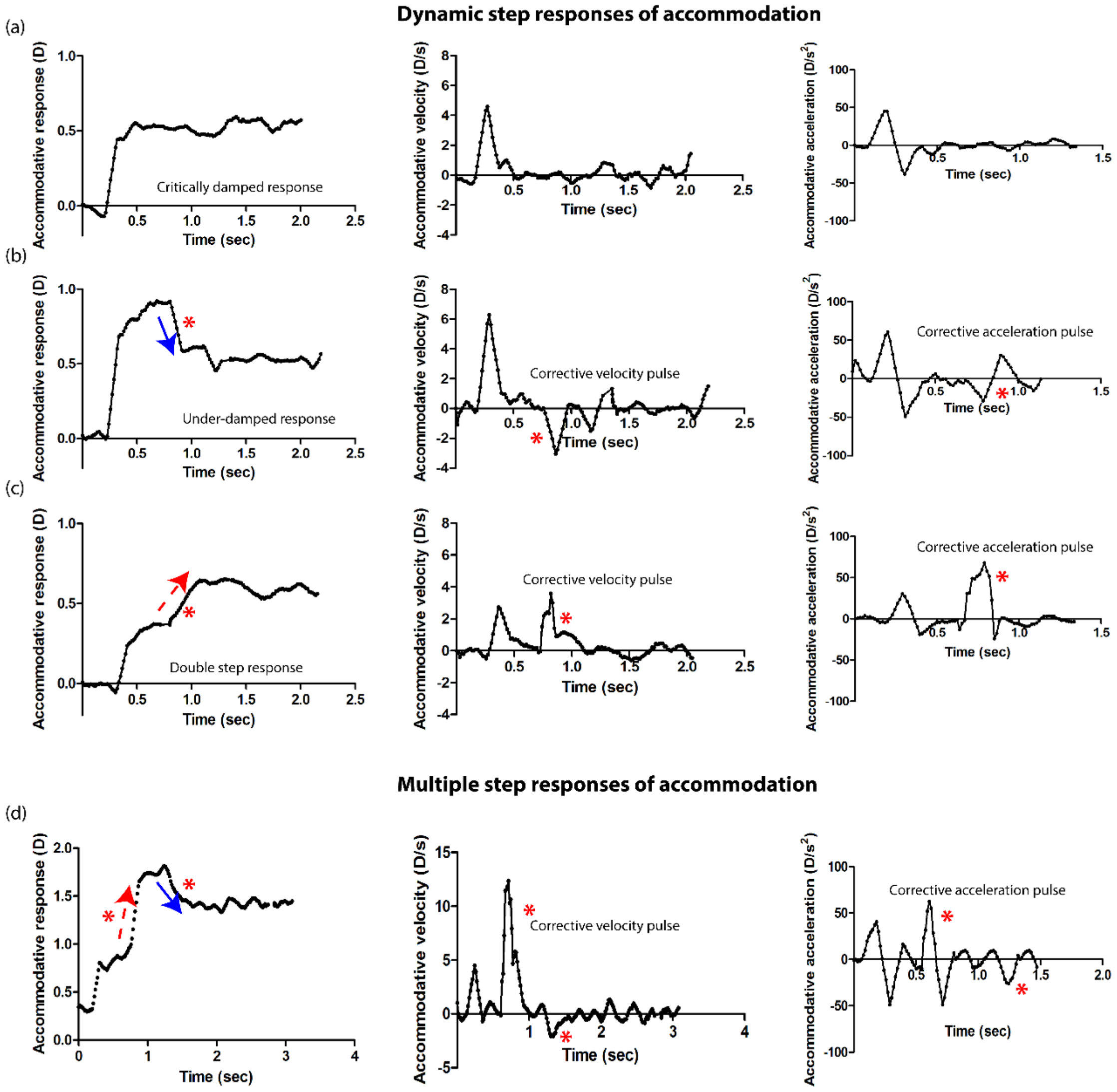


Figure 4-3: Individual representative typical and atypical accommodative traces to a step stimulus.

A typical (critically damped) accommodative response to a 1D stimulus is accompanied by the resulting velocity and acceleration traces (a). The system achieved the steady state without any oscillations. (b) An atypical underdamped response shows an initial dynamic overshoot that occurred due to an inaccurate acceleration and velocity pulse followed by a corrective response (*). Similarly (c) represents a double step (undershoots) response. An initial undershoot is followed by a corrective response in the same direction to reach the final steady state. (d) Multiple step response to a 2D stimulus from the same subject.

As noted in the previous chapter, the responses from the usable dynamic traces obtained from our children and adult subjects were categorized as either typical or atypical responses. Only typical responses were analyzed in the previous chapter to compare the dynamic accommodative behavior between school aged progressive myopes, non-myopes and adults. In the current chapter, we will be defining and examining the atypical patterns noted in the blur-driven accommodative response. The analysis was aimed to understand and answer three questions, (1) why do these atypical accommodative responses occur? (2) Given that myopic children have poor blur sensitivity, do they make more atypical responses compared to their non-myopic counterparts? (3) And finally, is there any age-related pattern to these atypical responses?

4.3 Data distribution and analysis

Table 4-1: Distribution of various response patterns in accommodation and disaccommodation obtained in the chapter 3.

		Accommodation			
Groups	***Typical***	***Typical with blinks***	***Atypical I***	***Atypical II***	***Unusable***
Myopes (MYP)	55	7	30	15	28
Emmetropes (EMM)	49	5	25	16	21
Adults (ADT)	84	3	7	3	11
		Disaccommodation			
MYP	69	7	7	18	26
EMM	59	6	5	16	29
ADT	80	6	1	5	16

As shown in table 4-1, accommodative measures obtained from the 12 children, 6 myopes (11.16 ± 1.00 years) & 6 emmetropes (11.16 ± 1.83 years), and 6 adults (26.16 ± 3.37 years) were categorized into usable and unusable responses. The latter included measures with blinks, head movements and/ or poor photorefractor image quality and were discarded. Usable accommodative traces were further divided into Typical and Atypical responses (figure 4-3).

Subjects showed a variety of atypical responses and were broadly classified as either Atypical I or II responses. Atypical I responses were classified into three types (figure 4-3), (1) **Under-damped responses or dynamic overshoots**, where the responses showed overshoots before reaching the final steady state. (2) **Double step responses or dynamic undershoots,** where a second corrective response followed an initial undershoot. (3) **Multiple step responses**, where the final steady state was achieved after multiple error responses (fig 4-3(d)). Alternatively, Atypical II responses were classified into two types, (1) Flat responses, or responses that did not show a change in the steady state or responses that did not fit the velocity threshold criterion, which was typically used to define an accommodative response. These responses usually occurred at 1D or 2D stimulus demands. (2) Ill sustained responses, wherein the change in the accommodative response was not sustained. Given the consistency of these atypical response patterns in both the age groups, it was important to carefully examine and analyze these patterns of blur-driven accommodation.

4.3.1 Atypical response characteristics

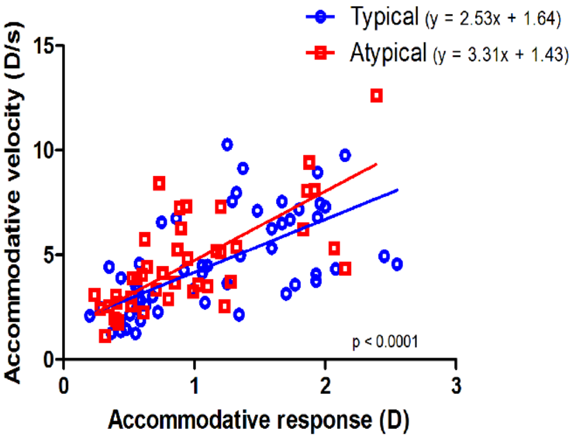
An atypical pattern was found in the responses where the steady state was reached but not in a smooth exponential manner as described above. These responses were categorized as atypical I responses. They were characterized by either an initial over or undershoot followed by a corrective response (figure 4-3). Velocity and acceleration traces were characterized by two or more peaks that corresponded to an erroneous and subsequent corrective response. Amplitude (Diopters) was defined as the dioptric difference between the start and end points for both initial and corrective responses. The start and end points were determined using the velocity threshold criterion as described previously. To measure the amount of over (figure 4-3 (b)) or undershoot (figure 4-3 (c)), an initial response was defined as the difference between the position at onset to the first local maximum that occurred before the initiation of a second response. A response differential for the corrective response was calculated as the difference between the initial erroneous position reached to the final steady state[28]. The maximum values in the velocity and acceleration trace were defined as the peak velocity (D/s) and peak acceleration (D/s^2) respectively. These parameters were defined separately for both erroneous and corrective responses. First (velocity) and second (acceleration) order main sequence relationship for accommodation were compared between the typical and atypical I responses. Since the number of atypical measures were unequal in the three groups (Table 4-1), they were quantified based on their proportion, i.e. number of atypical responses over the total number of usable (typical and atypical) responses in each subject and group. For disaccommodation, there was a significant reduction in the frequency of atypical patterns in all the groups (Table 4-1). Since there were fewer atypical disaccommodative responses (only double steps), further analysis was not performed. The impact of refractive error, age and stimulus demand on the frequency of atypical I responses was tested for accommodation. Also as described in the previous chapter, a bivariate regression (Deming regression) was used for analyzing the main sequence relationship given the variance in both accommodative response and the dynamic characteristics (peak velocity or acceleration).

4.4 Results

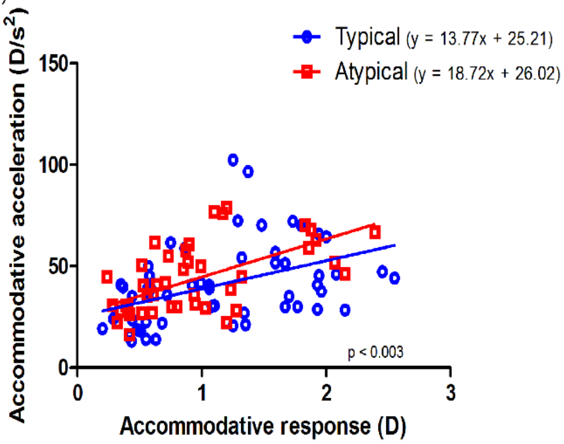
Response integrals for double step accommodative responses and dynamic overshoots ranged from 0.28D – 1.46D (0.78D ± 0.35D) and 0.2D – 1.15D (0.42D ± 0.21D) respectively. Rm ANOVA was used to compare the response patterns between the three groups and the three stimulus amplitudes. While the frequency of the useable responses were not different (F (2, 15) = 1.59; $p = 0.23$), the frequency of other response patterns was significantly different (F (3, 45) = 141.17, $p < 0.0001$) between the groups. Post hoc Tukey suggested no significant difference in the frequency of atypical responses between MYP and EMM ($p > 0.05$). However, a significant difference was noted in the frequency of atypical responses between children and adults ($p < 0.05$). The frequency of response patterns was also significantly different (F (3, 153) = 81.30; $p < 0.0001$) between the three stimulus amplitudes. Post hoc (Tukey) suggested that atypical II i.e. flat and ill-sustained responses occurred more with 1D compared to 2 and 3D stimulus ($p < 0.05$). Furthermore, no individual bias was noted within the three groups (MYP: F (5, 12) = 0.79; $p = 0.57$; EMM: F (5, 12) = 1.60; $p = 0.23$); ADT: F (5, 12) = 1.85; $p = 0.17$).

4.4.1 Main sequence characteristics

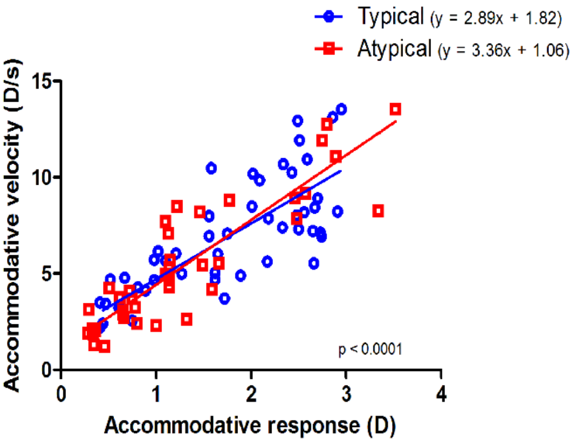
(a)



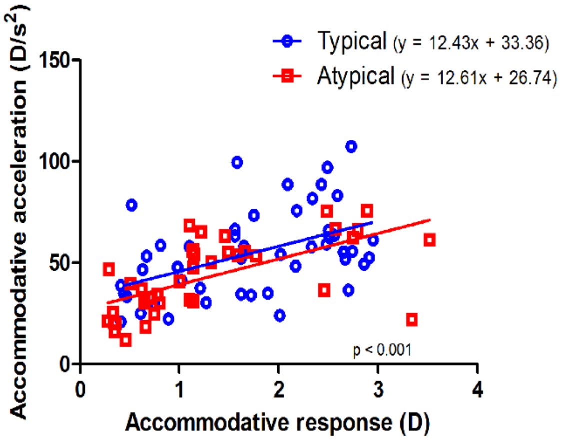
(b)



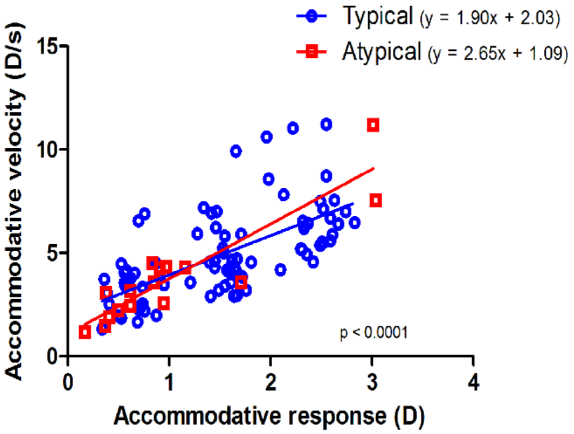
(c)



(d)



(e)



(f)

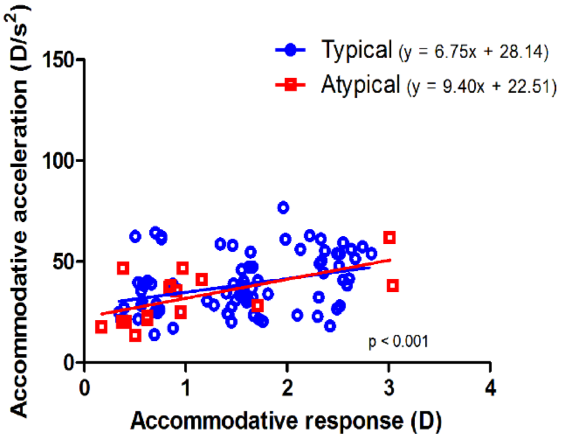


Figure 4-4: Velocity and acceleration main sequence of atypical accommodative responses.

Peak velocity (a, c, e) and peak acceleration (b, d, f) were plotted as a function of the response amplitude for myopic children (a, b), emmetropic children (c, d) and adults (e, f). While the red squares in the picture indicate atypical responses, blue circles indicate data from the typical responses. The solid lines indicate the deming regression fits. Overall, no significant difference was noted in the main sequence slopes between typical and atypical responses (p>0.1).

Velocity and acceleration main sequence (MS) were compared between the typical and atypical responses in children and adults (figure 4-4). For the MS analysis, both initial and corrective pulses were considered. The slopes of the velocity main sequence were not significantly different between the typical and atypical responses in all the groups (MYP: p = 0.25; EMM: p = 0.23; ADT: p = 0.13). Similarly, the slopes of the acceleration main sequence were not significantly different in all the groups (MYP: p = 0.38; EMM: p = 0.89; ADT: p = 0.53).

4.5 Discussion

Atypical patterns of blur driven accommodation were recorded, characterized and analyzed from all the three groups (myopic children, emmetropic children and adults). Atypical responses were more consistent in children with and without myopia compared to the adult subjects. While atypical II responses may suggest varying levels of attention, others (atypical I) may reflect a developmental pattern of the motor system.

4.5.1 Atypical responses: Control theory implications

Studies on accommodation under stereoscopic conditions have suggested that atypical patterns occur due to an excessive CA output that constitutes the initial part of the response under binocular viewing conditions[28,30]. However, our data shows that atypical response patterns do exist with blur only accommodation. We speculate that these atypical patterns of accommodation might occur due to an inaccurate pulse innervation or response initiation. Therefore, they cannot be purely explained based on the system (accommodation or vergence) that drives the response (Figure 4-5).

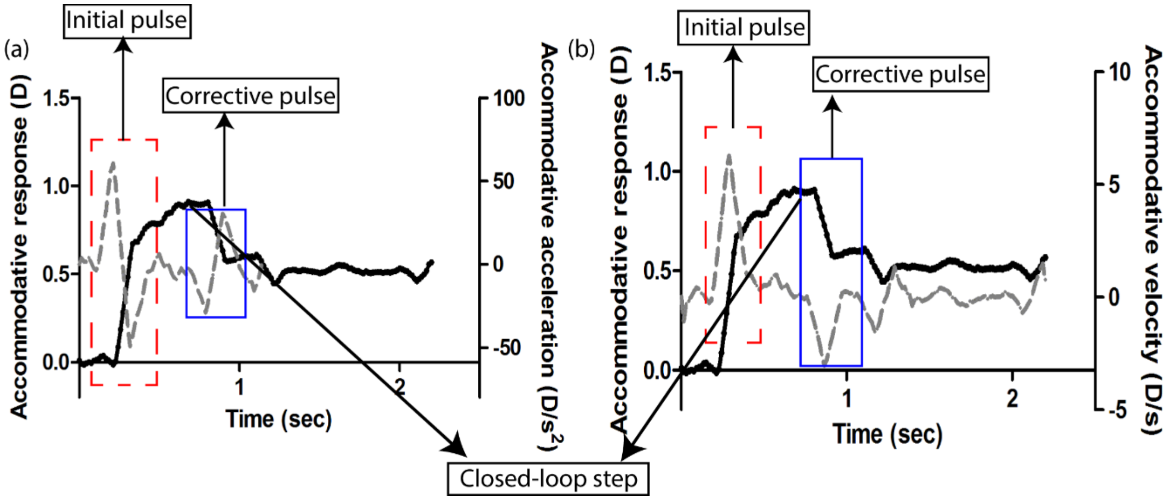


Figure 4-5: Modelling of an underdamped pulse-step response to a 1D step stimulus where an open loop, pre-programmed pulse is followed by a closed loop step (visually guided).

A typical response would occur when the pulse and step output accurately match the input. Based on our data, we predict that an atypical response occurs due to an inaccurate pulse innervation. Accommodative response (solid black line) along with (a) acceleration and (b) velocity (dotted gray line) were plotted as a function of time. An excessive initial pulse output (indicated by dashed red box) leads to an overshoot in the response. The error would be detected by the internal feedback of the step system. This would initiate a corrective response (shown in the solid blue box) to reach the final steady state.

Given the similar main sequence relationship between the typical and atypical I patterns, an initial inaccurate pulse might explain the over or undershoots. The visually guided step system might then detect this error and initiate a corrective response to reach the final steady state. Our results are in agreement with the current models wherein the oculomotor systems such as accommodation and vergence are characterized by a preprogramed pulse system coupled with a visually guided step system[27,40,41]. The lack of atypical responses in disaccommodation in our study might be due to the fact that all the responses were directed close to the resting levels of accommodation[40]. Recent investigation on adults found under-damped disaccommodative responses[40]. They reported that the frequency of under-damped responses is reduced when the end point was close to the resting level compared to the other proximal end points. Given this finding, they suggested that during a disaccommodative response, the system is always initiated towards a constant resting level which could be altered mid-way to a desired new steady state.

4.5.2 Atypical responses: Refractive error

As described in the previous chapter, myopes exhibit reduced blur sensitivity compared to their non-myopic counterparts[32–34]. Given this reduced behavior, we hypothesized that myopic children probably would show a reduced frequency of atypical responses compared to emmetropes. This was expected given that the blur mechanism in myopes is unable to detect or process an error in the final response and probably would remain in that undesired steady state without even detecting the persisting optical defocus on the retina. However, empirical data on children with and without myopia suggested that the frequency of atypical responses is similar between the refractive groups. This suggests that myopes similar to emmetropes actually detected the error in the response and made a corrective response to compensate it. Surprisingly, even after making the corrective response, myopes showed higher response lags compared to the non-myopes. We speculate that the response lags result from the reduced sensitivity of the system to blur and atypical responses might reflect an error in the initial pulse (response) innervation. The data on the main sequence characteristics prove that an inaccurate response initiation would actually lead to the atypical response patterns.

4.5.3 Atypical responses: Age

As described in Chapter 1, development of accommodation has been well studied[35–38]. Taken as whole, these studies suggested that accommodation would be "adult-like" by the age of 2-3 years. However, this conclusion was based on the response accuracy or static aspect of the accommodative response. Based on the data obtained in the current study, the dynamic behavior of accommodation appears to be in a recalibration mode adapting to the changes in the natural scene even during the early childhood. In agreement with the previous study[6], empirical data obtained from this current study suggests that atypical responses occur at a higher frequency rate in children (30-35%) compared to adults (<10%). We suspect that the atypical response patterns in children could be part of a calibration process in the internal feedback system to respond quickly and accurately to varying accommodative stimuli. It would be interesting to see if learning effects have any influence on the frequency of these response patters. This behavior is not surprising since such a dynamic recalibration would be necessary in both accommodation and vergence mechanism as children undergo changes in the dimensions of the head such as increasing inter-pupillary distance[39] (IPD) etc. with age.

4.6 Conclusion

Atypical response patterns such as dynamic overshoots and double step responses exist with blur driven accommodation. These responses appear to occur due to an inaccurate initiation of the response. The frequency of atypical responses decrease with age reflecting a developmental pattern of the dynamic accommodative mechanism probably, the internal feedback mechanism.

Chapter 5

Sensory mechanism of accommodation

5.1 Summary

Introduction: Children with a progressive myopia exhibit a unique pattern characterized by high accommodative response lags. This pattern was attributed to the larger depth of focus (DOF) in myopes. However, most of these studies were done on adults where the progression of myopia has attenuated considerably. The current study quantifies the blur sensitivity of progressive myopic children by measuring accommodative changes to lens induced defocus and comparing this objective measure of their depth of focus to a psychophysical measure of blur discrimination.

Methods: 12 children (8-13 years), 10 of them were recruited from the previous study, and 6 naïve adults (20-35 years) participated in the study. A range of optical lens defocus (0 to ±1.50D, 0.25 steps) was randomly induced while the subject viewed a high contrast target placed at either 50 or 25cms through a Badal optical system. Objective DOF was quantified as the blur magnitude that induced a consistent change in accommodative steady state measured with the DPR system. Also, micro fluctuations were compared before and after the introduction of optical blur across different stimulus demands. Blur detection thresholds were quantified using a 2 alternate forced choice adaptive staircase presentation performed at two working distances (50cms & 25cms), where angular size was held constant.

Results: Blur detection thresholds were similar between myopes, emmetropes and adults. However, accommodative lags and objective lags were significantly larger in myopic children compared to the other two groups ($p < 0.0001$). Furthermore, both objective and subjective measures of blur sensitivity were significantly larger at 4D demand compared to the 2D demand ($p < 0.0001$).

Discussion: Taken as a whole, young myopes can detect blur similar to the non-myopic peers, however, they exhibit larger depth of focus. Based on the findings, a reduced sensitivity to the retinal blur which appears to be compensated by some form of a perceptual adaptation to preserve the subjective percept of clarity.

5.2 Introduction

As shown in chapter 3, progressive myopic children exhibit larger accommodative response lags compared to the non-myopic children [1–4]. It is also well established that these myopic children are also associated with an abnormal accommodative behavior wherein high lags are associated with high response AC/A and high accommodative adaptation [5,6]. However, it is not clear whether the high lags reported in these progressive myopic children reflects a large depth of focus coupled with a reduced ability to perceive or process blur. Blur sensitivity is typically quantified in terms of depth of focus (DOF), defined as the change in the image plane off the retina that can be tolerated without perceiving blur. This is typically examined by changing the object position in physical space and can be measured both subjectively [7–10] and objectively [9–13]. Blur sensitivity can also tested subjectively using a blur discrimination task wherein the subjects would observe and compare targets with varied levels of blur [13,14]. While objective measures of blur sensitivity determine the defocus magnitude necessary to induce a consistent change in accommodation, subjective measures would estimate the subjective criterion of either blur detection or discrimination with no influence of accommodation.

Both objective and subjective measures of depth of focus were found to be reduced in myopes [7,15]. However, these studies were mostly limited to adult myopes who were likely to be not progressive. Given the evidence that the abnormal traits of accommodation are limited to progressive and not stable myopia [16,17], the evidence of blur sensitivity in progressive myopia remains unclear. As far as we know, objective DOF was not tested in progressive myopic children. One study, however, found that subjective blur discrimination thresholds were similar in progressive myopic children compared to their non-myopic peers[14]. However, the accommodative behavior to these blurred images was not tested and may not reflect a true measure of subjective measure of blur sensitivity. The capacity to perceive blurred images would involve both cognitive and perceptual processes which may not be required during objective DOF measures involving reflexive accommodative responses to retinal blur. If myopes indeed adapt to blur as suggested previously [18–20], a greater disparity would be expected between the ability to perceive blur and depth of focus in myopes. However, objective DOF and its correlation to the subjective measures of blur sensitivity has not been tested in progressive myopic children.

Traditionally, increased accommodative lags and microfluctuations found at closer distances have been attributed to a larger DOF that results from a reduction in the pupil size which acts to reduce the retinal blur circle. Several studies reported that the accommodative lags and microfluctuations increase with stimulus demand significantly more in progressive myopes compared to the non-myopes [1,21–23]. Recent investigation reported a correlation between DOF and accommodative micro-fluctuations [24]. When DOF was modulated by manipulating luminance level and pupil size, they found a consistent change in the magnitude of microfluctuations. In a separate study, this group also found that the increased magnitude of microfluctuations at closer distances was independent of changes in pupil size [21]. Another investigation on young emmetropic adults found a relationship between objective DOF and stimulus demand [9]. They also reported that the change in DOF with stimulus demand was correlated with only accommodative microfluctuations and not pupil size. Given that progressive myopes show greater accommodative lags and microfluctuations with stimulus demand compared to non-myopes, differences in blur sensitivity (both objective and subjective) would be expected as a function of stimulus demand between the refractive groups independent of the changes in pupil size.

Accordingly, the current study examined both objective and subjective estimates of blur sensitivity in progressive myopic children. Data from myopic children was then compared to non-myopic children and adults. Objective DOF and sensitivity of accommodation to defocus were examined using a Badal optical system. Given the cognitive ability of our younger subjects, a simple blur detection task was designed to test the subjective ability to perceive blur. Furthermore, correlation between these blur estimates and the magnitude of accommodative lag was tested in all the three groups. Finally, the influence of accommodative stimulus demand on response lags, accommodative microfluctuations, blur discrimination measures and objective DOF was also be tested.

5.3 Methods

12 school aged children, 6 myopes & 6 emmetropes (Age: 9–14 years), and 6 naïve adults (25 -32 years) were recruited from the optometry clinic at the University of Waterloo. Five of the six myopes were recruited from the previous study (chapter 3). Sample size calculations for this particular study were done based on the pilot data on the Objective DOF obtained from 3 myopes and 3 non-myopes (Appendix A). All the myopic subjects had a history of >0.5D/year change in the refractive error over the last 3 years. Informed consent and assent was obtained after a verbal and a written explanation of the study. The study followed the tenets of

Declaration of Helsinki and received ethical approval from the University of Waterloo office of research ethics review board. Classification of children into two refractive groups were similar to ones described in the previous chapter (Chapter 3). All the myopes were progressive and had an increase of >0.5D in their refractive error in the last year. There were 4 emmetropes and 2 stable myopes in our adult subgroup. Given that their accommodative behavior (Chapter 3) and objective DOF were similar, they were not subdivided based on refractive error. All the myopic subjects were habitual contact lens wearers and wore their lens during the study. Although all but one of the children were from the previous study (Chapter 3), critical visual parameters such as the distance and near visual acuity, near phoria and cycloplegic refraction were measured again to confirm the visual status of all the children. The measurement session followed the screening session by not more than a week. During the measurement session, objective DOF and blur discrimination thresholds were collected over two visits.

5.3.1 Objective depth of focus (DOF)

5.3.1.1 Experimental design

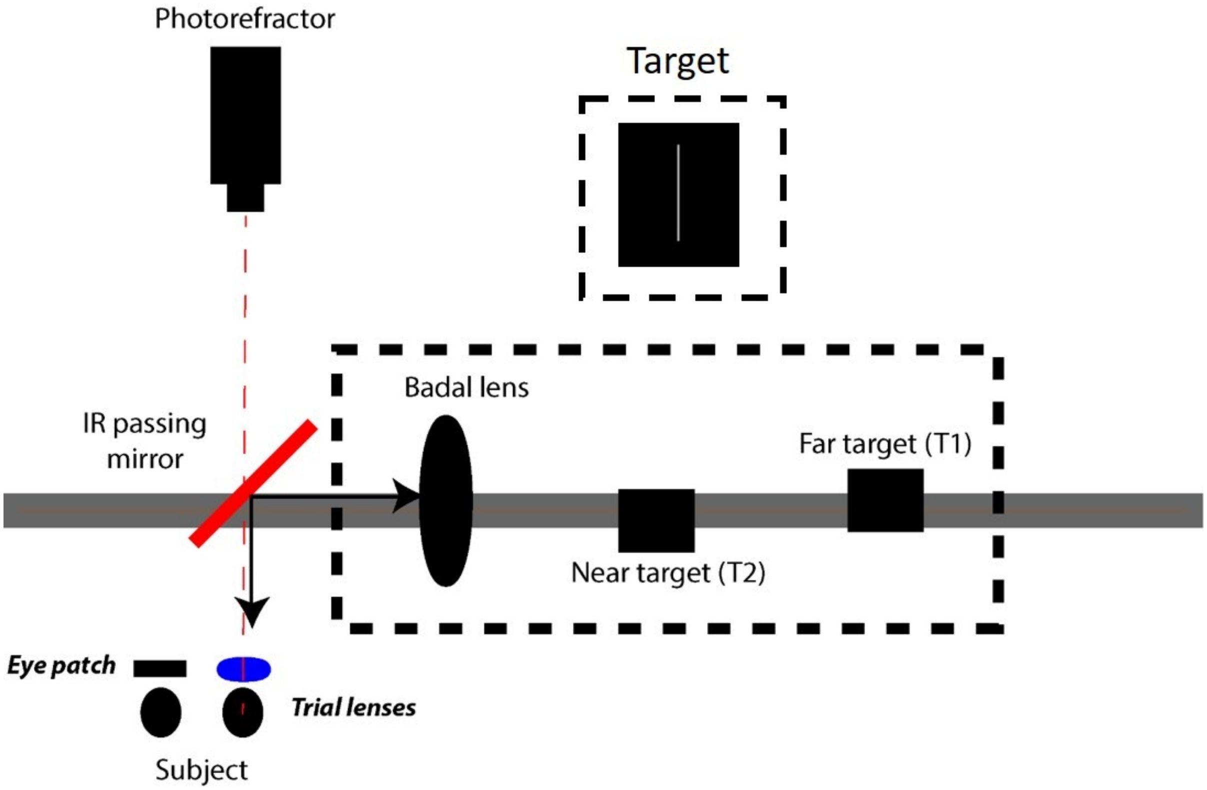


Figure 5-1: Badal optical system to stimulate accommodation and disaccommodation. Subjects viewed at a high contrast vertical line (white on black) that instantly switched from one distance to the other through a Badal lens.

A simple Badal optical system was used to present an accommodative stimulus similar to that described in the chapter 3. The child was 1m away from the dynamic photorefractor with an eye patch over the left eye. An IR passing mirror (Optical cast IR filter, Edmund Optics, USA) allowed an orthogonal presentation of the accommodative targets along with a continuous measure of accommodation (figure 5-1). Two targets were manually placed at different distances from a +5D Badal lens. While the far target was set at optical infinity, the near target was moved from the Badal lens to create two accommodative demands (2 and 4D). Step stimulus was presented using a stimulus control tool box with a button that allowed for an instantaneous switch in the target distance. In other words, as shown in figure 5-1, the subject viewed only one high contrast target at a time, either the far target or the near target. The order and presentation time of the step stimulus was varied to avoid predictability.

5.3.1.2 Instrumentation

Accommodative change was recorded using a custom built dynamic photorefractor (PROSILICA CAM (EC750), Allied Vision Technologies, Canada) and is described in detail in chapter 2. DPRS works at a sampling frequency of 70Hz, giving an output every 0.014 seconds. Photorefraction videos were later analyzed offline using the dynamic photorefraction system for refractive estimations [5,25]. The calibration procedures followed in this study were similar to ones described previously [26,27].

5.3.1.3 Procedure

One drop of 2.5% phenylephrine hydrochloride was instilled in both eyes of the child following an initial anterior chamber assessment. The left eye of the subject was covered with an eye patch during the study. This allowed a monocular presentation of the stimulus to open the loop of the vergence system. The dynamic photorefractor was aligned with the right eye. Prior to the start of the study, 2-3 practice trials were given to each subject to familiarize them with the experimental procedures involved. Each trial lasted for 15-25s. During the measurement trial, subjects viewed at the high contrast target (white on black) through the Badal lens and were instructed to make sure that the edges of the target were always clear and sharp. After the initiation of the trial, the stimulus presentation time was varied from 2-5s to avoid prediction. After the presentation of the stimulus, the accommodative response was recorded for 5-10s. A lens was then introduced in front of the right eye and the resulting accommodative response to lens was recorded for the next 5-10seconds. Single step accommodative responses to different lenses were recorded over 2 different stimulus amplitudes (2D and 4D demand). *Eleven lens conditions* were used for a 2D stimulus demand and *fifteen conditions* were used for 4D demand (table 5-1). The range of lenses selected was based on the measures of accommodative lags noted previously for each stimulus demand[2,5]. Three trials were conducted for each lens condition. The order of the stimulus demand and the lens condition selected for a particular stimulus demand was randomized. Frequent breaks were given to the child between the lens conditions.

Table 5-1: Lens conditions employed used to measure objective blur thresholds

Stimulus demand	Placebo condition	Plus lens defocus	Minus lens defocus
2D demand (50cm)	Plano lens	+0.25D to +1.00D (0.25D steps)	-0.25D to -1.00D (0.25D steps)
	Size lens (1.5% magnification lens)		
	No lens		
4D demand (25cm)	Plano lens	+0.25D to +1.50D (0.25D steps)	-0.25D to -1.50D (0.25D steps)
	Size lens (1.5% magnification lens)		
	No lens		

Three placebo lens conditions were used to quantify the influence of proximity and size cues on the final accommodative response. A plano lens was used to quantify the influence of the proximity cue which can occur due to the placement of the lens close to the patient's eyes. Also, the addition of an ophthalmic lenses changes the perceived magnification of the image, a size (2% magnification) lens was also used. Also, a no lens condition was used to understand the baseline steady state fluctuation in the accommodative response over time. Impact of the all the lens conditions including the placebo lenses (size and proximity cues) were compared to this baseline no-lens condition to identify changes in the accommodative state. Objective blur threshold was quantified as the first lens defocus (plus and minus) that induced a consistent change in the steady state position of accommodation.

5.3.1.4 Analysis

Accommodation data affected by blinks, head or large eye movements were discarded. The remaining data points were used for analysis. Accommodative response amplitudes were measured by averaging the response trace for at least 5s (350 data points) before and after the lens was placed in each condition. For the no lens condition, the accommodative response was measured by averaging the response data from the initial and final 5s of the trial after the response was made. The difference between the accommodative response before and after the induced lens defocus was defined as the accommodative response change. For each lens condition, three accommodative response change measures were obtained which were later averaged. Steady state fluctuation was defined as the standard deviation of the response and was calculated both before and after the placement of a lens. Repeated measures ANOVA was used to compare the steady state fluctuations across the stimulus demands and groups. For simplicity, the effect of plus lenses and minus lenses were analyzed separately for each demand and compared between the two refractive groups. Two different types of analysis were chosen to identify the sensitivity of accommodative system to blur. First, to examine the rate of change of accommodation, response change was plotted as a function of the lens induced defocus. Linear regression fits were used to examine the rate of change of accommodation with lens defocus and was tested at both 2 and 4D demand. One way ANOVA was used to identify differences in the linear regression slopes obtained from each group at both 2D and 4D stimulus demand. At each demand, objective DOF was quantified as the first lens defocus that induced a statistically significant change in the accommodative response. Objective thresholds were compared using a repeated measures ANOVA with group as a between factor and stimulus demand as a within factor.

5.3.2 Blur detection thresholds

5.3.2.1 Experimental design

Simulated retinal blur was created by applying an image processing technique to the high contrast targets used to measure the objective DOF. This was done to simulate the dioptric blur experienced by a subject with an out of focus image on the retina. This was programmed as a psychophysical task using Psykinematix (KyberVision Japan LLC) on a calibrated Macbook Pro (Apple Inc., USA) Retina Display screen (1024X768 pixels). The range of luminance levels of the targets was 140-180 cd/m^2 and was measured using Minolta Chroma meter CS-

100 (Minolta Camera Co. Ltd., Japan). The influence of luminance changes on our threshold measurements was also tested and found no significant effect (Appendix A). Gaussian blur was converted into dioptric blur based on the mathematical models described previously[28].

5.3.2.1.1 Blur detection stimulus

The angular size of the high contrast vertical line target (white on black) were first defined such that it would mimic the high contrast target used to measure objective DOF. The height (6°) and thickness (0.2°) of the high contrast vertical line target (white on black) was first created. Simulated blur was created based on the optical and mathematical approximations presented previously[28]. The approximate relationship between the blur circle diameter (degrees) with defocus (D) and pupil diameter was given by[28],

$$\text{blur circle (B)} = pD$$

Where p is the pupil diameter defined in meters and was kept constant at 3mm. D was the defocus in diopters and was kept variable. A cylinder shaped filter was then created with the radius given by the blur variable (B). The stimulus was then transformed into Fourier space and multiplied with the filter (convolution) to obtain blurred image in Fourier space. Inverse Fourier transformation was applied to obtain the final blur stimulus. This stimulus was designed in collaboration with Dr. Arijit Chakraborthy (personal communication).

A control experiment was performed on 3 subjects from the adult subgroup (25, 26 and 29 years old) at 50 and 25cm. The purpose was to determine whether the blurring of one target induced a significant change in accommodation. A 5min dark adaptation period was given prior to the start of the experiment. Two targets (no blur and 1D blur) were presented successively at the center of the Macbook screen for 5s each with an inter-stimulus interval of 5s. Accommodative response from the right eye was continuously recorded using the dynamic photorefraction system (DPRS). This was repeated at two working distances, 25cm and 50cm from the subject (figure 5-2). The extent of the targets were adjusted to subtend a constant angular size at each distance.

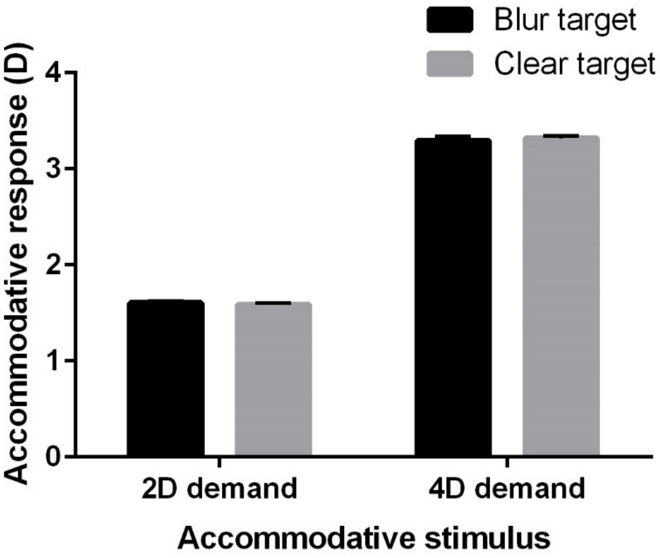


Figure 5-2: Accommodative response was measured while the subjects looked at the no blur and 1D blur targets both at 2D and 4D demand. Error bars indicate the standard error (SEM).

These simulated targets did not result in any significant change in the accommodative steady state at either 50cm (2D) or 25cm (4D) working distances in any subject. Therefore, targets were used to quantify the subjective blur thresholds in children using an adaptive psychophysical design.

5.3.2.2 Procedure

Blur detection thresholds were determined using a 2 alternate forced choice (AFC) paradigm (figure 5-3). Subjects looked at the screen placed at either 50cm or 25 cm with their left eye occluded. Two targets (reference and test), which were spatially separated, were presented on the screen with different levels of blur. The reference target was always maintained at 0 D blur and the test target blur began with 1D. Stimuli were presented for 10 secs for each blur condition with an inter-stimulus interval of 2 seconds to control for blur adaptation. The spatial position of the targets were randomized to avoid predictability. The subject was asked to compare the two targets and identify the target that is blurred. The magnitude of the blur was subsequently varied in steps of 0.1 D in a 2-down 1-up adaptive staircase. In other words, two correct responses increased the level of difficulty by decreasing the blur magnitude of the test target and one incorrect response increased the magnitude of blur. The staircase was terminated after 6 reversals and the blur detection threshold was calculated from the average of last 5 reversals. Furthermore, catch trials were included in the staircase (10% of the total trials) whereby a test target of 2D blur was presented along with the reference to enhance the motivation levels of the subjects. Pupil size was recorded for 5 sec with the dynamic photorefractor initially while the subject was performing the task at both the working distances.

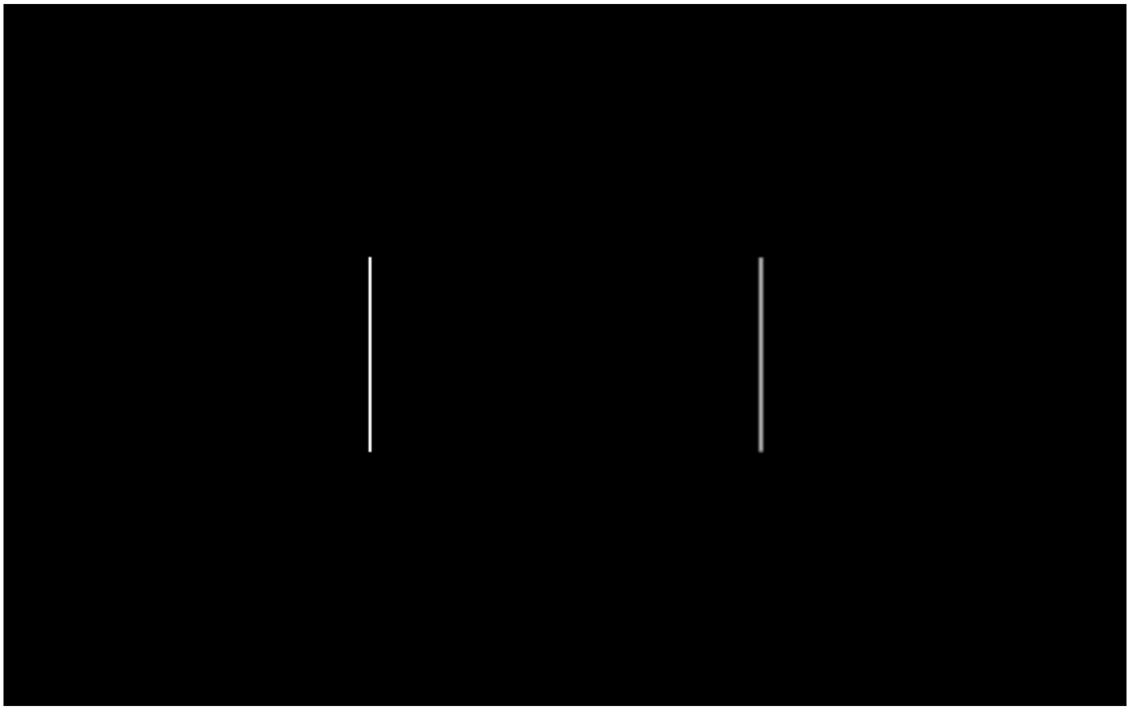


Figure 5-3: Blur detection task where two targets (reference and test), which were spatially separated, were presented on a screen. An example of simulated blur level of 1D is shown in this picture.

5.4 Results

Table 5-2: Visual parameters of children, both myopes and non-myopes, and adults.

Parameter	Myopes	Non-myopes	Adults
No .of participants	6	6	6
Age (years)	12.16 ± 1.47	12.08 ± 1.35	28 ± 2.82
Refractive error (D)	-3.31 ± 2.16	0.10 ± 0.09	-0.70 ± 1.28
Near phoria (Δ) **(‘+’ eso; ‘-’ exophoria)**	1.00 ± 2.36	-1.5 ± 2.25	-1.33 ± 1.63

5.4.1 Sensitivity of accommodation and objective DOF

The pupil measures obtained at both the working distances from the myopes (2D: 5.31±0.60mm; 4D: 4.9±0.61mm), non-myopes (2D: 5.35±0.37mm; 4D: 5.15±0.42mm) and adults (2D: 5.17±0.28mm; 4D: 4.72±0.38mm). DOF and the sensitivity of accommodation were analyzed separately across the stimulus demand (2/ 4D) and the direction of defocus (plus/ minus lens).

5.4.1.1 Minus lenses

For a 2D (50cm) demand, repeated measures ANOVA showed a significant difference in the DOF between the three groups (F = 31.0; p <0.0001) and the change in the accommodative response to different lens defocus (F = 1564.1; p <0.0001). There was also interaction found in the accommodative change noted to different lenses across the groups (response change*group: F = 58.6, p<0.0001). Post hoc (Tukey) analysis showed that a statistically significant change in the response occurred post -0.25D lens for emmetropes and adults. However, the change was post -0.50D in myopes. Accommodative response change was plotted as a function of the lens condition (figure 5-4 (a)). Linear regression fits were used to identify the rate at which accommodative system responds to different level of minus lens defocus. The slopes (table 5-3) were significantly different between myopes and emmetropes (F (1, 56) = 30.35; p <0.0001) and myopes and adults (F (1, 56) = 36.92; p <0.0001) but not between adults and emmetropes (F (1, 56) = 1.79; p =0.18).

For a 4D (25cm) demand, repeated measures ANOVA showed a similar pattern where significant differences were obtained between the groups (F = 28.3; p <0.0001) and the change in the accommodative response to different lenses (F = 732.9; p <0.0001). There was also interaction found in the accommodative change resulting from different lens defocus across the groups (change*group: F = 48.6, p<0.0001). Post hoc (Tukey) analysis showed that a statistically significant change in the accommodative response occurred post -0.75D in myopes and -0.50D lens in both emmetropes and adults. Accommodative response change was plotted as a function of the lens condition (figure 5-4 (b)). The slopes of the linear regression fits were used the sensitivity of accommodative system to different level of minus lens defocus at 4D demand. The slopes (table 5-3) were significantly different between myopes and emmetropes (F (1, 80) = 115.23; p <0.0001), myopes and adults (F (1, 80) = 61.95; p <0.0001) but not between adults and emmetropes (F (1, 80) = 1.53; p = 0.21).

Table 5-3: The slopes of the linear regression fits for accommodative response parameters such as response change and microfluctuations across the three groups.

Type of defocus and stimulus demand	Slope of the regression fits		
	Myopes	**Emmetropes**	**Adults**
Minus lens (2D)	$y = 0.13x - 0.20$	$y = 0.20x - 0.25$	$y = 0.22x - 0.26$
Minus lens (4D)	$y = 0.08x - 0.15$	$y = 0.17x - 0.29$	$y = 0.16x - 0.28$
Plus lens (2D)	$y = -0.14x + 0.23$	$y = -0.20x + 0.26$	$y = -0.19x + 0.22$
Plus lens (4D)	$y = -0.08x + 0.17$	$y = -0.18x + 0.32$	$y = -0.18x + 0.33$
Micro-fluctuations	$y = 0.03x - 0.06$	$y = 0.05x - 0.07$	$y = 0.03x - 0.04$

5.4.1.2 Plus lenses

For a 2D (50cm) demand, repeated measures ANOVA showed a significant difference between the groups (F = 11.5; p <0.001) and the change in the accommodative response to different lenses (F = 1417.0; p <0. 0001). There was also interaction found in the accommodative change resulting from different lenses across the groups (change*group: F = 35.7, p<0.0001). Post hoc (Tukey) analysis showed that a statistically significant change in the response occurred post +0.25D lens for emmetropes and adults. However, the change occurred post +0.50D for myopes. The slopes of the linear regression fits (figure 5-4 (c)) were significantly different between myopes and emmetropes (F (1, 56) = 25.01; p <0.0001) and myopes and adults (F (1, 56) = 7.66; p <0.007) but not between adults and emmetropes (F (1, 56) = 1.54; p = 0.27).

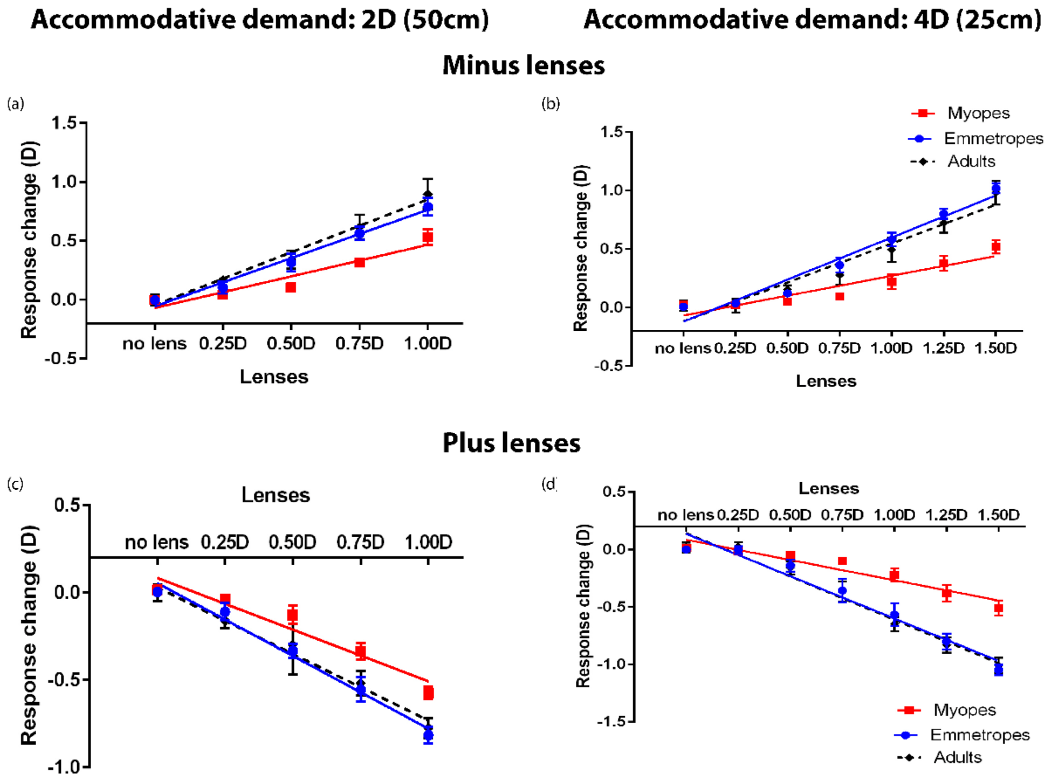


Figure 5-4: Sensitivity of accommodation to lenses

Accommodative sensitivity was quantified by plotting accommodative response change as a function of minus and plus powered lens defocus obtained at two different accommodative demands, 50cm (a, c) and 25cm(b, d). Change in the accommodative response to different lenses was plotted for all the groups (blue: Emmetropes; red: Myopes; black dotted line: Adults). Error bars indicate the standard deviation in the response change to a particular lens. Slopes across all the groups at different stimulus demands were significantly different from zero ($p < 0.0001$).

For a 4D (25cm) demand, repeated measures ANOVA showed a similar pattern where significant differences were found between the three groups (F = 14.5; p <0.0001) and in the response change to different lenses (F = 226.4; p <0. 0001). There was also interaction found in the accommodative change to different lenses across the groups (change*group: F = 161.5, p<0.0001). Post hoc (Tukey) analysis showed that statistically significant change in the accommodative response occurred post +0.50D lens in emmetropes and adults and post +0.75D in myopes. Accommodative sensitivity was tested by plotting the response change as a function of the lens condition (figure 5-4 (d)). The slopes (table 5-3) of the linear regression fits were significantly different between myopes and emmetropes (F (1, 80) = 105.55; p < 0.0001), myopes and adults (F (1, 80) = 128.82; p < 0.0001) but not between adults and emmetropes (F (1, 80) = 0.16; p = 0.68). Since the sphericity was violated, all the p values were adjusted based on the G-G test of sphericity.

5.4.1.3 Placebo lenses

Placebo lenses were tested to identify any spurious influence resulting from proximal and magnification (size) cues possibly induced by the placement of the lenses before the eye (figure 5-5). Placebo conditions included plano lens, size lens and a no lens condition and were tested at both stimulus demands in each group separately. Placebo lenses did not induce a statistically significant change in accommodation at both the accommodative demands in myopes ((2D) F = 2.905; p = 0.14; (4D) F = 0.05; p = 0.83), emmetropes ((2D) F = 0.49; p = 0.515; (4D) F = 1.3; p = 0.30) and adults ((2D) F = 3; p = 0.22; (4D) F = 0.51; p = 0.54).

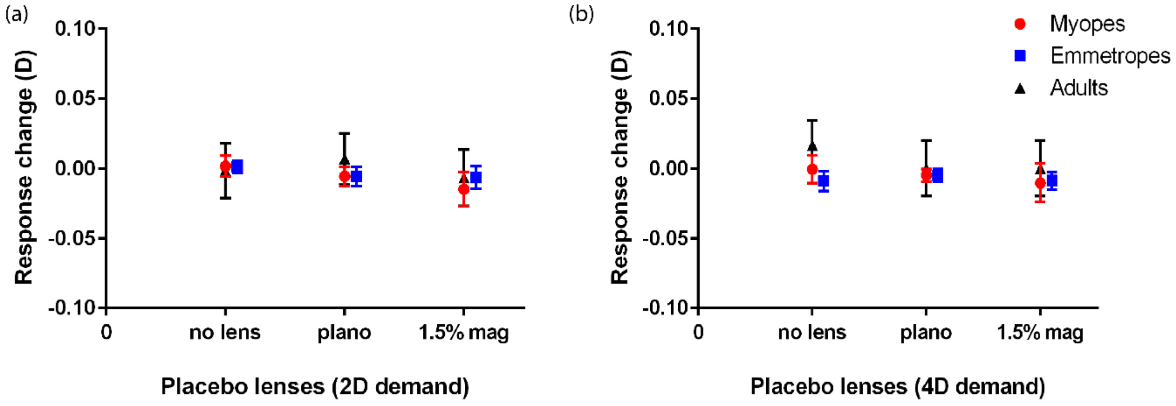


Figure 5-5: Placebo lenses and accommodation.

Placebo lenses were used to understand the influence of optical and proximity cues on the final accommodative response at two working distances. The change in the response to different placebo conditions were quantified in all the groups (blue: emmetropes; red: myopes; black: adults). Error bars indicate the standard error in the response change to the lens.

5.4.1.4 Objective depth of focus (DOF)

Repeated measures ANOVA was used to test objective blur thresholds across the three groups. Stimulus demands and type of lens defocus (plus or minus) were used as within factors. ANOVA showed that there were significant differences across the groups (F = 35.2; $p < 0.0001$) and stimulus demands (F = 107.6; $p < 0.0001$) but not across the type of defocus (F = 0.2; p = 0.81). Post hoc (Tukey) analysis showed that objective DOF was significantly larger in myopes compared to both emmetropes and adults ($p < 0.001$). Objective DOF was significantly larger at 4D demand compared to 2D demand in all the three groups ($p < 0.01$).

5.4.1.5 Accommodative steady state errors

As shown in figure 5-6, the magnitude of accommodative microfluctuations were plotted as a function of the accommodative demand. Linear regression fits were used to test the rate of change of microfluctuations with a change in the accommodative stimulus in each group. The slopes of the regression fits were significantly different between myopes and emmetropes (F (1, 56) = 59.31; $p < 0.0001$), myopes and adults (F (1, 56) = 8.81; $p < 0.004$) but not between adults and emmetropes (F (1, 56) = 0.0009; p = 0.97). However, the intercept of the slopes between adults and emmetropes was significantly different (F (1, 57) = 7.35; $p < 0.008$). This suggests that emmetropes showed larger variability in their accommodative steady state compared to the adults at all the stimulus demands.

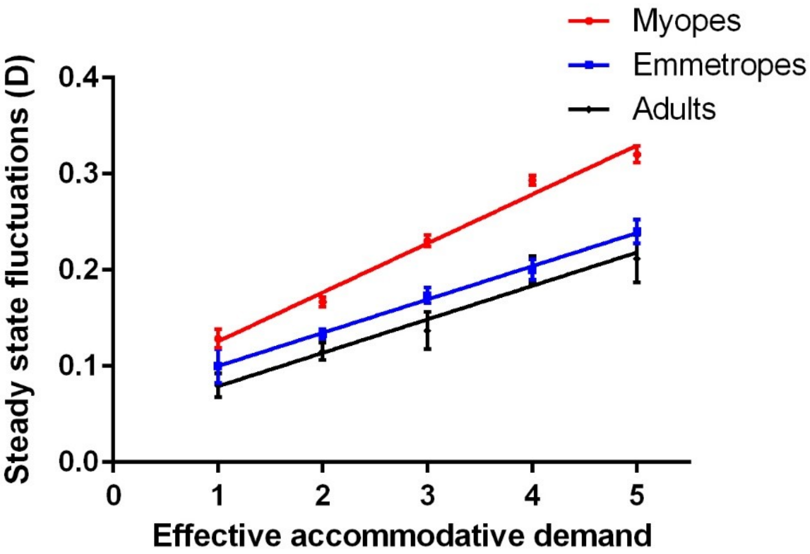


Figure 5-6: Steady state fluctuations in the accommodative response were plotted as a function of the effective accommodative stimulus.

Linear regression fits were used to identify the rate of change of the microfluctuations in myopes (red), adults (black) and emmetropes (blue). Microfluctuations showed a linear correlation with the accommodative demand in both the groups ($p < 0.0001$). Error bars indicate the standard error.

5.4.2 Blur detection thresholds

The pupil measures were obtained at both the working distances from all the three groups, myopes (2D: 5.28±0.68mm; 4D: 4.96±0.76mm), adults (2D: 5.10±0.36mm; 4D: 4.74±0.44mm) and emmetropes (2D: 5.41±0.67mm; 4D: 4.98±0.65mm). Repeated measures ANOVA was used with groups as the between factor and stimulus demands as the within factor. It showed a significant difference in the blur detection thresholds between demands ($F = 642.3$; $p < 0.0001$) but not across the groups ($F = 1.80$; $p = 0.19$). Post hoc (Tukey) showed that the subjective blur thresholds at 4D demand were significantly larger than the thresholds obtained at 2D demand ($p < 0.001$).

5.4.3 Pupil size and depth of focus

Repeated measures ANOVA was used to test the difference in pupil size across the stimulus demand and refractive groups. There was no significant difference in pupil size across the groups (F = 0.65; p = 0.536) or experimental design (F = 0.07; p = 0.79). However, significant difference in the pupil size was noted across the stimulus demands (F = 21.57; p < 0.001) with smaller pupils at closer demand (4D) compared to 2D demand.

The influence of the difference in the pupil size over the subjective and objective estimates of blur sensitivity across the stimulus demands was tested using repeated measures analysis of covariance (ANCOVA). The three groups (adults, myopes and emmetropes) were considered as between factors. The difference in the blur detection threshold or objective DOF between the two stimulus demands was considered as the dependent variable and difference in the pupil size between the two demands was taken as a covariate. No significant influence of the changes in the pupil size on the detection thresholds (F (1, 14) = 0.07; p = 0.78) and DOF (F (1, 14) = 0.87; p = 0.36) was noted across the two stimulus demands.

5.4.4 Blur thresholds and accommodation

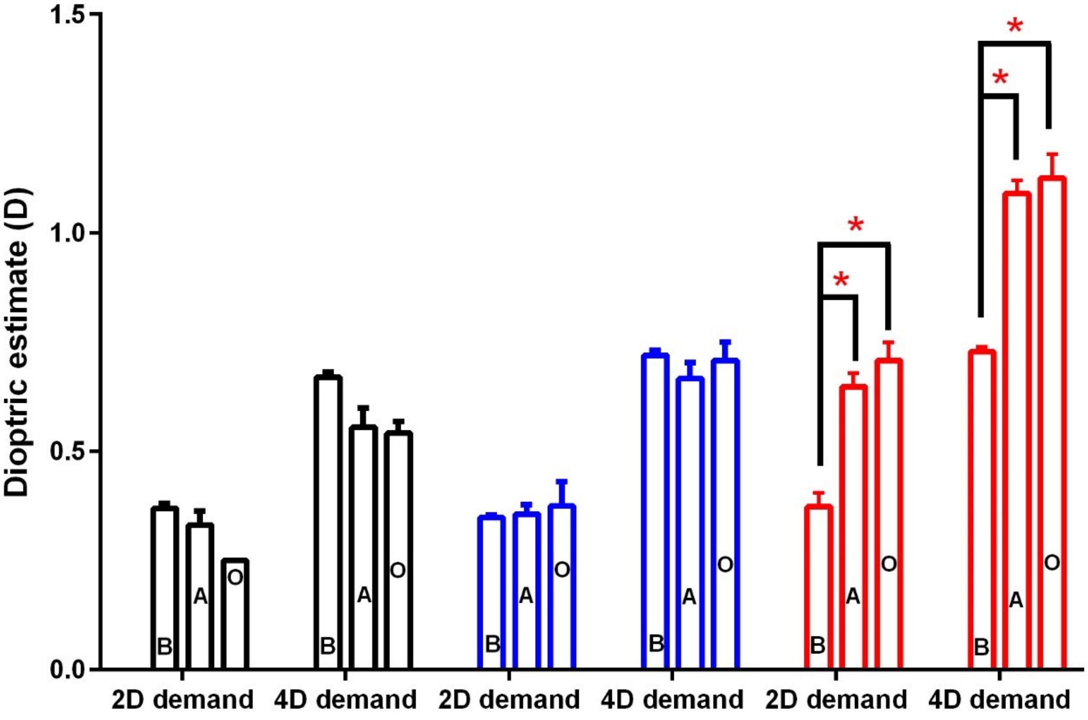


Figure 5-7: Subjective blur detection thresholds (B), accommodative lags (A) and objective DOF (O) were compared at each demand in all the three groups: myopes (red, non-myopes (blue) and adults (black). Asterisk symbols indicate statistical significance ($p < 0.001$). Error bars indicate the standard error (SE).

Accommodative lags were compared with objective DOF and blur detection thresholds in myopic and non-myopic children along with adults (figure 5-7). Repeated measures ANOVA was used to test the difference with group as the between factor and the three parameters including accommodative lags, objective and subjective thresholds as the within factors. At 2D demand, repeated measures ANOVA showed a significant difference between the groups ($F = 80.99$; $p < 0.0001$) and across the three parameters ($F = 6.52$; $p < 0.004$). Post hoc (Tukey) analysis showed that objective measures were similar to accommodative lags in all the three groups ($p > 0.80$). Furthermore, detection thresholds were similar to objective thresholds and accommodative lags only in emmetropes ($p > 0.90$) and adults ($p > 0.55$). However, detection thresholds were significantly smaller compared to objective DOF ($p = 0.01$) and accommodative lags ($p = 0.001$) in myopes ($p < 0.001$). Similarly at 4D demand, ANOVA showed a significant difference across the groups ($F = 77.7$; $p <0.0001$) and between the three parameters ($F = 12.63$; $p <0.001$). Post hoc (Tukey) analysis showed that objective measures were similar to accommodative lags in both the groups ($p>0.95$). However, subjective thresholds were similar to objective thresholds and accommodative lags only in emmetropes ($p>0.90$) and adults ($p > 0.45$) but not in myopes ($p<0.0001$). Objective DOF and accommodative lags were significantly larger in myopic children compared to emmetropes at both the working distances ($p<0.0001$).

5.5 Discussion

There were three major findings in this study, (1) Depth of focus and blur discrimination thresholds were influenced by accommodative stimulus demand; (2) Progressive refractive error had an influence on depth of focus but not on the ability to detect blur information. In other words, young myopes can detect blur similar to emmetropes, however, are less sensitive to accommodative response lags leading to an increase in the retinal defocus. (3) Finally, DOF, blur detection thresholds and accommodative error were comparable in emmetropes and adults but not in myopes suggesting that myopes may undergo a process of blur adaptation to attenuate the influence of the persistent retinal defocus.

5.5.1 Depth of focus and target distance

Depth of focus and the discrimination thresholds were tested at two different working distances to understand their impact on the final accommodative response. There was a clear trend of an increase in the depth of focus coupled with a decrease in the blur discrimination ability as the stimulus demand increased. Depth of focus was reported to be influenced by several factors including pupil size, luminance, retinal image size, contrast etc.[29]. Target characteristics such as contrast, luminance, and the range of spatial frequency content were kept under control when quantifying blur discrimination threshold and depth of focus. Retinal image size was kept constant at each working distance in both objective and subjective paradigms. Although phenylephrine controlled the pupil size without affecting accommodation[30,31], the difference in the pupil sizes was significant between the two working distances ($p < 0.05$). However, the difference in the pupil size did not appear to explain the relationship between stimulus demand and the behavior of the blur mechanism. Several studies showed that significant changes in the DOF would occur only with smaller pupil sizes (<2mm) due to diffraction effects[32]. Also, given the range of pupil sizes tested in this study, a change of not more than 0.1- 0.2D is expected in the DOF with the variation in the pupil size[32]. Within the range of pupil sizes tested, bivariate regression analysis suggested that the pupil size does not influence either the depth of focus or blur discrimination thresholds (figure 5-7 (b)). Recently, studies found that depth of focus was correlated with accommodative microfluctuations[9,24]. In agreement with these studies, bivariate regression analysis showed the magnitude of accommodative microfluctuations predicts the size of the depth of focus (figure 5-8 (a)).

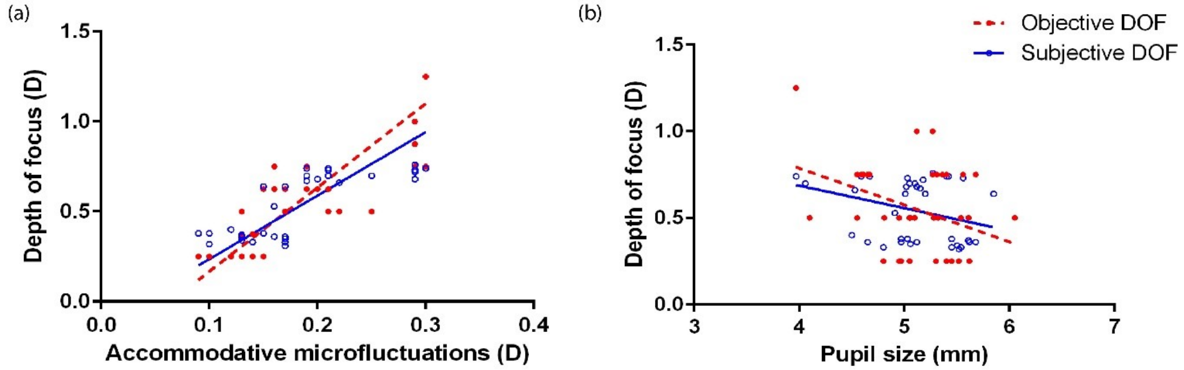


Figure 5-8: Depth of focus and blur discrimination thresholds were plotted as a function of the magnitude of the microfluctuations (b) and pupil size (a).

A bivariate regression (deming) analysis was used to examine the influence of pupil size and accommodative microfluctuations on given the variation in both x and y axis. (a) The slope of the regression fits for both DOF ($y= 4.66x - 0.30$) and discrimination thresholds ($y= 3.53x - 0.11$) as a function of microfluctuations was statistically significant from zero ($p < 0.0001$). (b) However, the slope of the regression fits for both DOF ($y= -0.21x + 1.63$; $p = 0.11$) and discrimination thresholds ($y= -0.13x + 1.20$; $p = 0.10$) DOF as a function of pupil size was not statistically significant from zero.

The findings of increasing microfluctuations, depth of focus and accommodative lags with increasing stimulus demand cannot be explained by a constant DOF parameter that is used in the current models of accommodation and vergence[33–35]. A gain parameter[36] such as the accommodative sensory gain (ASG) would predict this behavior of DOF with an increase in the stimulus demand. This would also indicate that the simulations in the previous chapter using ASG were actually a better representative of the sensory blur mechanism than what was modelled previously[33]. It is difficult to comment at this point on why the DOF behaves in this manner but I speculate that this increased optical blur at closer distances might be used to extract depth information from a given natural scene[37,38]. Also, the dioptric gradient is significantly larger up-close compared to objects placed closer to the far point. For example, imagine two scenarios (1) person looking at a computer screen placed at 30cm; (2) and a person looking at a tree 6m away. A change in the fixation in the first case would cause a significantly larger shift in the dioptric defocus compared to the second case with an object at the far point. Therefore, it would be logical to have a larger depth of focus (i.e. ability to tolerate defocus) up-close compared to objects farther away.

5.5.2 Depth of focus: accommodation

Objective DOF was obtained at two different accommodative demands using both plus and minus lenses. The data were comparable to another study that measured objective thresholds at 25cms on adult myopes[15]. Also, in agreement with another previous study on adults[9], our data showed that the DOF increases proportionally with the accommodative demand. However, our DOF data were significantly larger compared to the data reported in the previous study[9]. This could be due to differences in the type (range) of blur (lens induced defocus (0.25D steps) or targets in physical space (0.1D steps)) and age of the participants (children or adults). Some of the major differences between the current study and the previous investigations which examined the objective depth of focus include the age of the participants and more importantly, step changes in the blur were presented in this study compared to a ramp (slow) change in blur employed in the previous studies. Step changes in blur were employed in the current study to avoid the impact of both blur and accommodative adaptation. Blur detection thresholds also showed a proportional increase with an increase in the accommodative demand in all the three groups. Given that this behavior was noted in adults too, the influence of the level of cognitive ability or subject's mental maturity can be ruled out. One study looked at the blur discrimination thresholds with a similar design[14]. Although the measures were taken at a different working distance (40cm) with different types of targets, the overall trend appears to be comparable. With respect to the magnitude of the discrimination thresholds, there are conflicting results on adults with some showing smaller[11,13] and others larger thresholds[8,9] than the data reported in the current study. These differences could be attributed to factors such as the age of participants (children or adults) and type of blur used (simulated blur or targets in physical space), range of pupil size tested, target characteristics etc.

Previous studies on adults which compared subjective and objective blur sensitivity measures found inconsistent results[9–11,13,39]. The current study found different patterns in the three groups. In the current study, measures were taken to employ a comparable design for both objective and subjective measures of blur sensitivity. Data from the non-myopic children and adults showed that the objective DOF and blur detection thresholds were not statistically significant from each other. As pointed out previously, there were several factors such as the design, age groups, pupil size, target characteristics etc. which could have influenced these differences in blur sensitivity measures between the studies. Furthermore, previous study found an age related change in the subjective but not objective DOF [39]. However, we did not find any such related pattern in either objective DOF or detection thresholds. Factors such as age range, experimental design could have influenced these differences between the two studies.

5.5.3 Blur sensitivity and myopia

We examined several parameters of accommodation and blur in this current study and compared them between myopic and non-myopic children. Blur sensitivity was quantified in terms of the subject's ability to detect blur (detection thresholds) and their ability to translate the blur information into an accommodative response (objective DOF). In agreement with a previous study[14] that employed a similar experimental design, our data suggested no difference in the blur discrimination ability between myopes and emmetropes. However, another study on adults which compared the detection thresholds did show a difference between myopes and non-myopes[7]. Although both the studies employed a blur discrimination task, the current study used simulated blur with a natural viewing environment compared to using to a Badal optical system. Other differences include use of cycloplegia, age group of myopic subjects, progression status etc. The current study also looked at the sensitivity of accommodation to blur along with the objective DOF. The rate of change of accommodation to changing lens defocus (figure 5-4) was significantly reduced in myopes compared to the emmetropic children and adults. This suggests that the accommodative system is less sensitive to blur in children with progressive myopia. Myopes also exhibited larger objective DOF which was proportional to their accommodative lags (or errors). Furthermore, in agreement with the previous studies[21,22,40], the steady state microfluctuations increased with increasing demand, more significantly in myopes compared to emmetropic children and adults.

Taken as a whole, progressive young myopes can detect blur similar to their non-myopic peers. However, they show reduced sensitivity to retinal defocus which could explain their large errors of accommodation. It would be interesting to see if this pattern would be any different with the degree and age of onset of myopia. It is also interesting that progressive myopes can detect or discriminate blur similar to the non-myopes even with a defocused image on the retina. This disparity between perceived blur and retinal defocus could reflect some form of a perceptual adaptation to preserve the subjective sense of clarity or visual resolution even with a defocused image on the retina. If altered blur sensitivity is indeed the root cause of myopia with accommodative errors being a mere byproduct, it would also explain the ineffectiveness of near addition lenses to arrest myopia progression. There is no direct evidence to prove that eye growth causes altered blur sensitivity. However, there is data from animal models which show that alterations occur at the level of retina, specifically, in the pathway from the photoreceptors to ON-bipolar cells involving dopaminergic amacrine cells[41]. This may be an indirect evidence but it shows that cells involved in visual information processing are altered in case of myopia.

5.6 Conclusion

Objective DOF was a better predictor of the accommodative response lags compared to the blur detection ability of the subject. In the previous chapter, we hypothesized that myopes recalibrate their motor response to compensate for the reduced blur sensitivity. Based on the data from the current study, we confirm that progressive myopes do exhibit reduced blur sensitivity when measured as a function of depth of focus and accommodative sensitivity to blur. However, this reduction was not found when myopes were asked to detect the blurred target. This reduced blur sensitivity of the growing eye appears to be compensated by some form of a perceptual adaptation to maintain the visual resolution even with a defocused retinal image.

Chapter 6

General discussion and implications

Accommodation and vergence, in unison, help in maintaining a clear and single binocular vision, a linchpin for normal vision development. With blur as the primary stimulus[1,2], accommodation has been proposed to be controlled by two controllers with variable time constants, a fast reflex system and a slow tonic system[3,4]. Under natural viewing conditions, accommodation and vergence systems mutually interact with each other through AC and CA cross-links[3,5]. Based on the empirical data from adults, several control theory models were proposed to predict the behavior of accommodative sensory and motor controllers to various stimuli[6–9]. Progressive myopic children, however, exhibit a transient but consistent abnormal accommodative behavior which is not predicted by one of the currently accepted models[10]. Progressive myopes exhibit high accommodative adaptation, elevated AC/A coupled with high and not low accommodative lags[11–18]. Several predictions, both sensory and motor origin, have been proposed to explain this behavior however they failed to explain this behavior comprehensilvely[11,14,19–25]. Furthermore, empirical conclusions on the impact of myopia over accommodation and blur sensitivity were mostly based on data obtained from adult population. Accordingly, this dissertation examined the sensory and motor mechanism of accommodation in young children with and without progressive myopia. Data from children were also compared to adults. While the dynamic behavior of accommodation and the strength of the convergence driven accommodation (CA/C) were assessed to quantify the motor mechanism, subject's ability to discriminate and process blur/ defocus information was used to quantify the sensory mechanism of accommodation. This is the first investigation to provide an empirical evidence on the age related pattern of the second order dynamic behavior of accommodation and disaccommodation. Furthermore, this was the first study to examine objective DOF in children with and without myopia. Novel model simulations were designed to explain the altered behavior of accommodation in progressive myopic children. It should be noted that only Schor's models were used in this dissertation since they predicted the interaction between the cross-link and slow tonic controller accurately[5,26]. The development of the dynamic behavior of accommodation was also examined by comparing accommodative responses obtained from children and adults. This was the first study to successfully record and analyze atypical response patterns of blur driven accommodation. Furthermore, this thesis also examines the ideal sampling frequency necessary to accurately measure various aspects of accommodation. Both theoretical and empirical approaches were employed to identify the ideal sampling rate necessary to measure dynamic accommodation accurately.

6.1 Myopia and accommodation

The primary aim of the project was to understand the altered behavior of accommodation in children with progressive myopia. Progressive myopic children exhibit high accommodative response lags[18,27,28], elevated AC/A[14–17], high accommodative adaptation[12,29,30], high steady state fluctuations[31,32], reduced vergence adaptation[10], normal CA/C and a large depth of focus[21,22]. These findings contradict several predictions proposed by the currently accepted models of accommodation and its cross-coupled interactions with the vergence system[8,33].

First, empirical data on visually normal adults suggested that high response lags should be coupled with a low and not a high AC/A[5]. Second, the behavior of the phasic system should predict the behavior of the tonic system i.e. high reflex response lags won't be accompanied by high accommodative adaptation[34]. Third, an inverse relationship between the cross-links i.e. a high AC/A should be associated with a low and not normal CA/C[35,36]. The only prediction that holds valid in progressive myopes is the inverse relationship between the accommodative and vergence slow controller systems[3].

Previous studies predicted that this altered behavior can be explained by a either a sensory (blur) deficit or a motor (plant) deficit or a combination of both. One of other major explanations for this altered behavior was the increased effort to make an accommodative response in myopes[17,37]. This was proposed based on two findings: first, a rigid or sluggish accommodative plant in myopes[20,24,38]; Second, low tonic levels of accommodation in myopic children[12,39]. However, the findings of a similar accommodative main sequence characteristics and a similar stimulus AC/A ruled out the possibility of a motor deficit and an increased effort of the system respectively. Also, given that this behavior is transient[13,40], it would be difficult to imagine a motor deficit that is temporary. Instead, novel model simulations suggest that a reduced sensory ability to process blur coupled with a high cross-link (AC/A) gain could comprehensively explain this transient but consistent behavior in myopes. It is fascinating that this altered accommodative behavior returns to normal in stable myopes and cannot be explained at this point based on our data[13,40]. Myopes also show a reduced sensitivity to blur[21,22,41]. Increased higher order aberrations were suggested to lead to a poor retinal image quality ultimately leading to an inaccurate accommodative response[42]. However, there is conflicting evidence on alterations in the blur mechanism. Studies on adults found that myopes exhibit a reduced ability to detect and process blur ultimately leading to high response lags. However, one study on myopic children suggested that myopes can detect and discriminate blur similar to the non-myopic children[43]. In agreement, my findings (chapter 5) suggest that myopes can perceive blur similar to non-myopes however cannot translate that information completely to a motor (accommodative) response.

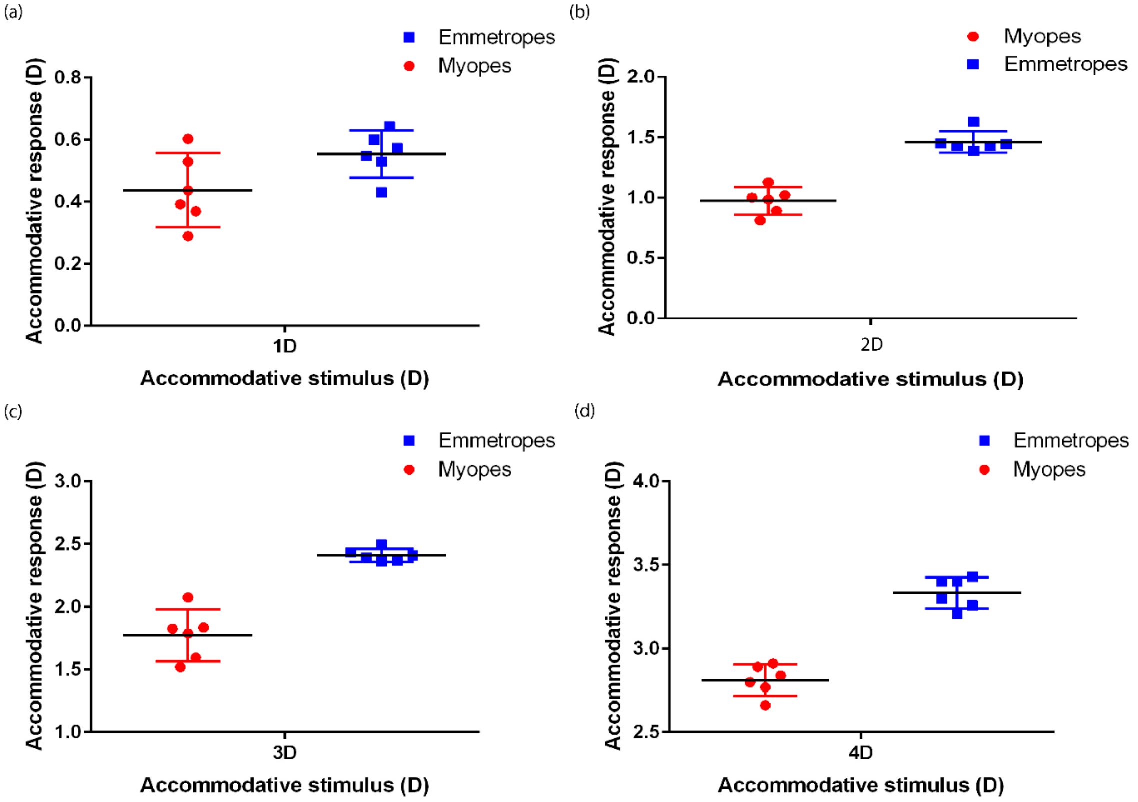


Figure 6-1: Accommodative response accuracy data obtained from individual subjects (both myopic and non-myopic children) at stimulus demands ranging from 1-4D, 1D steps (a, b, c, d). Taken as a whole, myopic children showed more variability compared to non-myopes. The mean difference in the response accuracy increased with stimulus demands and was consistent across the subjects in each group. Except at

1D demand, myopic children consistently showed a reduced response accuracy compared to the non-myopic children.

These differences would make sense given that these are two separate mechanisms, one probably being cortical and the other involving the midbrain and/ or its interaction with the cortical mechanisms. Taken as a whole, a reduced blur sensitivity of the growing eye in myopes might be compensated by two adaptive mechanisms: a motor recalibration of the cross-link and adaptive mechanisms coupled with a perceptual adaptation to preserve the image resolution even with a persistent defocus on the retina. If altered blur sensitivity is indeed the root cause of myopia with accommodative errors being a mere byproduct, it would also explain the ineffectiveness of near addition lenses to arrest myopia progression. There is no direct evidence to prove that eye growth causes altered blur sensitivity. However, there is data from animal models which show that alterations occur at the level of retina, specifically, in the pathway from the photoreceptors to ON-bipolar cells involving dopaminergic amacrine cells. This may be an indirect evidence but it shows that cells involved in visual information processing are altered in case of myopia.

6.2 Experimental conditions to stimulate blur driven accommodation

The results of this study pertain specifically to the response of young myopes to a blur cue. It should be noted that under natural viewing conditions, several other cues such as proximity and vergence are available to drive accommodation effectively in young myopes. Based on the limited evidence, it would appear that they would take advantage of other cues such as proximity11 and vergence10 to reduce the degree of accommodative lag. The static behavior of accommodation was found to be reduced when stimulated using optical (negative) lenses compared to targets changing in depth. However, negative lenses do not control image size, in fact, image size decreases with increasing defocus levels which is actually opposite to a normal proximal cue under natural conditions. It is difficult to speculate the degree of defocus that young myopes would experience in more naturalistic conditions. Also, it is unclear whether all progressive myopes fully compensate for the reduced blur response using other cues and needs further examination. Given that the abnormal pattern of accommodation in progressive myopes exists with blur driven accommodation, the aim of this experimental thesis was to isolate and vary the blur cue by controlling the influence of the other factors such proximity or vergence under experimental conditions. The presence of proximal cues could confound the isolation of a purely sensory (blur) or motor (plant) deficit. Therefore, I have chosen an experimental design that can effectively isolate only the blur cue and minimize other cues such as proximity and vergence which could influence the accommodative response.

6.3 Depth of focus: Implications on the blur mechanism

Depth of focus (DOF) is defined as the variation in the plane of image on the retina of the eye which can be tolerated without inducing an objectionable lack of sharpness or focus of the image[44]. This can measured subjectively[45–47] and objectively[48,49]. This parameter was modelled as a constant in the one of the currently accepted models of accommodation and vergence[8]. Given the influence of sensory parameters such as luminance and contrast on the accommodative response, an additional parameter, accommodative sensory gain (ASG), was proposed into the static model to predict the behavior[50]. ASG was also suggested to predict the static accommodative behavior of progressive myopic children. Although some studies point out to a measurement bias[51], it has been well established that accommodative lags increase with a change in the stimulus demand. It was proposed that these response lags and fluctuations occur within the range of the depth of focus, therefore, would not affect the perceptual quality[52]. However, both objective DOF and blur discrimination thresholds data from my study points out that our ability to tolerate blur increases with increasing stimulus demand similar to the behavior of the accommodative system (Figure 5-7). Several studies found that the DOF can be influenced by various factors including the target characteristics (Luminance, contrast, spatial frequency, and wavelength), pupil diameter, retinal image size, visual acuity, retinal eccentricity, refractive status (emmetropic or ametropic) and age. As described in the previous chapter, for a particular subject, target characteristics (luminance, spatial frequency, and contrast) and retinal image size were kept constant at both the working distances. Pupil size was kept relatively constant using a low dose mydriatic drug (2.5% phenylephrine). Although the pupil size was smaller at a closer working distance, the effect on the measures of blur sensitivity was too small. Also, based on previous theoretical and empirical evidence, the pupil variations noted in the current study should not account >0.2D of change in the DOF[53]. Furthermore, in agreement to previous studies, accommodative micro-fluctuations was a better predictor of the DOF than the pupil size[49,54].

This evidence provides a novel insight into the blur mechanism and its influence on the accommodative behavior at different working distances. The data in this work suggest that a constant DOF, as modelled currently, may not be an accurate depiction of the blur system. A gain parameter, such as the ASG, might be a better representation of the blur mechanism. This behavior of the blur mechanism could prove useful in locating objects in a natural scene. Several studies found that blur can be a useful cue in identifying the depth of target along with its spatial localization[55,56]. I speculate that the optical blur induced during the response lags might be a purposeful error (well within the perceptual thresholds) to localize various objects in a natural scene. Also, the dioptric gradient is significantly larger up-close compared to objects placed closer to the far point[56]. Therefore, it would be logical to have a larger depth of focus (i.e. ability to tolerate defocus) up-close compared to objects farther away.

6.4 Atypical accommodative responses: Control theory implications

This is the first study to successfully record and analyze atypical responses with blur driven accommodation in both children and adults. There were three major outcomes from this study: first, atypical responses exist with blur only accommodation and cannot be completely explained by the influence of the CA cross-link input as described previously[57,58]; Second, given the similar first and second order main sequence relationship between typical and atypical responses (Figure 4-4), an error in the response initiation could be attributed to the atypical response patterns. Finally, an age related pattern is noted in the frequency of the atypical responses indicating a possible developmental pattern of the dynamic aspect of accommodation probably the internal feedback mechanism.

6.5 Future work

As described previously, progressive myopic children exhibit an abnormal accommodative behavior. One such alteration includes reduced vergence adaptation. Although with the current work, I did try to establish the accommodative mechanism, there is still a limited evidence about the vergence behavior. Previous studies[10] in the lab and data from the current study suggest that myopic children exhibit an elevated AC/A, normal CA/C and reduced vergence adaptation. Predictions made by the currently accepted models suggest that a reduced vergence adaptation should be associated with a high and not a normal CA[3,35,36]. They also suggest that an elevated AC would be associated with a high and not low vergence adaptation. It is unclear how the phasic vergence behaves in progressive myopic children given the findings of a normal CA/C coupled with reduced vergence adaptation. As far as we know, there are no investigations that had examined the vergence behavior in myopic children. A reduced phasic vergence system would predict a reduced vergence adaptation coupled with a reduced/ sluggish CA output. It would interesting to examine the dynamic behavior of the CA cross-link in progressive myopes. A sluggish phasic system would exhibit a sluggish CA response without affecting the overall amplitude of the cross-link response[59]. Also, previous studies quantified vergence adaptation based on the decay of the CA cross-link output over a period of 15 min (CA measurement every 3 minutes)[29,60]. However, recent investigation proposed a better and a rapid way of quantifying the adaptive behavior of the vergence system[61]. It would be interesting to examine the reproducibility of these two techniques in testing the adaptive behavior of vergence in progressive myopic children. It would be useful to test the vergence behavior in myopes given the recent evidence of a moderate treatment efficacy of base-in prisms to halt myopia progression[62–64]. The sensory blur mechanism has also been established in children with and without myopia. Given the influence of the stimulus distance on accommodative behavior and DOF, it would be logical to test this across a wide range of stimulus distances to better understand the linearity of these mechanisms and also the concept of the depth of focus. Studies on adults showed that myopes have an ability to adapt to persistent blur by transiently altering their blur sensitivity and accommodative behavior[41,65,66]. This ability to modify the existing behavior was termed as perceptual adaptation. The most intriguing finding is that this behavior is noted only in myopes and not their emmetropic peers. It would interesting to see if progressive myopic children exhibit such a behavior. In this current dissertation, efforts were made to avoid such adaptation effects by providing step changes in blur that were presented transiently with an inter-stimulus interval. One common parameter that consistently exists in most of theories related to myopia development is the altered blur mechanism. Retinal (cellular), genetic or neural correlates of mechanisms related to blur processing would help us better understand the development and progression and myopia. This insight would probably help us in designing better and effective treatment strategies. The findings of atypical response patterns in this dissertation were incidental and were not hypothesized at the beginning of the study. These responses were not expected for two reasons, first, there was no previous evidence of any dynamic atypical patterns in blur driven accommodation; second, unlike saccades and vergence, accommodation was always considered as an over-damped system based on accommodation measures obtained from adults[67,68]. This was the first study to successfully record and analyze atypical responses with blur driven accommodation. Based on the main sequence data comparing typical and atypical responses, we concluded that similar to saccades[69] and vergence[70], atypical accommodative responses can occur due to an error in response initiation (Figure 4-5). Given the finding of an increased frequency of atypical response patterns in children compared to adults, this behavior was hypothesized as a development pattern of the dynamic behavior of accommodation possibly the internal feedback mechanism. Although the accommodative motor plant (ciliary muscle and lens) is different between myopes and emmetropes, there was no difference in the frequency of atypical response patterns. Therefore, I chose to propose a sensory recalibration process instead of a mechanical factor (changes in the accommodative plant with age) to explain this developmental pattern of atypical responses. Studies examining this behavior across a wider age range might provide a better insight into this developing pattern of the dynamic accommodative mechanism.

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Chapter 1

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Appendix A

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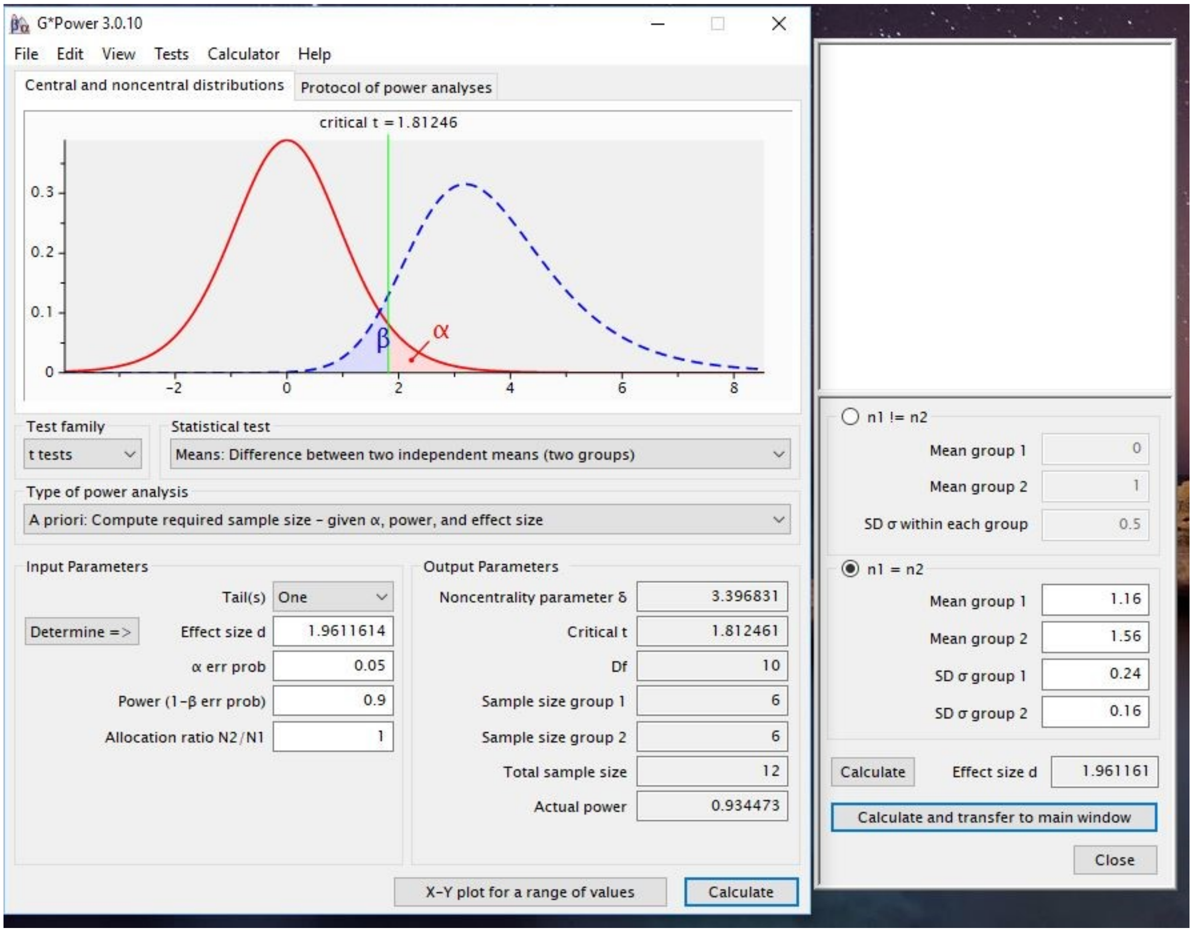
Appendix A

Sample size calculations and control experiments

Sample size calculations

Sample size calculations for both the studies are described in this section. Also, appropriate justifications were provided for the effect size calculations for unknown parameters. Power analysis were performed using the G*Power software.



Test family: t tests

Statistical test: Means: Difference between two independent means (two groups)

Type of power analysis: A priori: Compute required sample size – given α, power, and effect size

Input Parameters

Tail(s): One

Effect size d: 1.9611614

α err prob: 0.05

Power (1-β err prob): 0.9

Allocation ratio N2/N1: 1

Output Parameters

Noncentrality parameter δ: 3.396831

Critical t: 1.812461

Df: 10

Sample size group 1: 6

Sample size group 2: 6

Total sample size: 12

Actual power: 0.934473

○ n1 != n2

Mean group 1: 0

Mean group 2: 1

SD σ within each group: 0.5

● n1 = n2

Mean group 1: 1.16

Mean group 2: 1.56

SD σ group 1: 0.24

SD σ group 2: 0.16

Effect size d: 1.961161

Figure A- 1: Sample size calculation obtained from G*Power.

Study I: Motor deficit hypothesis

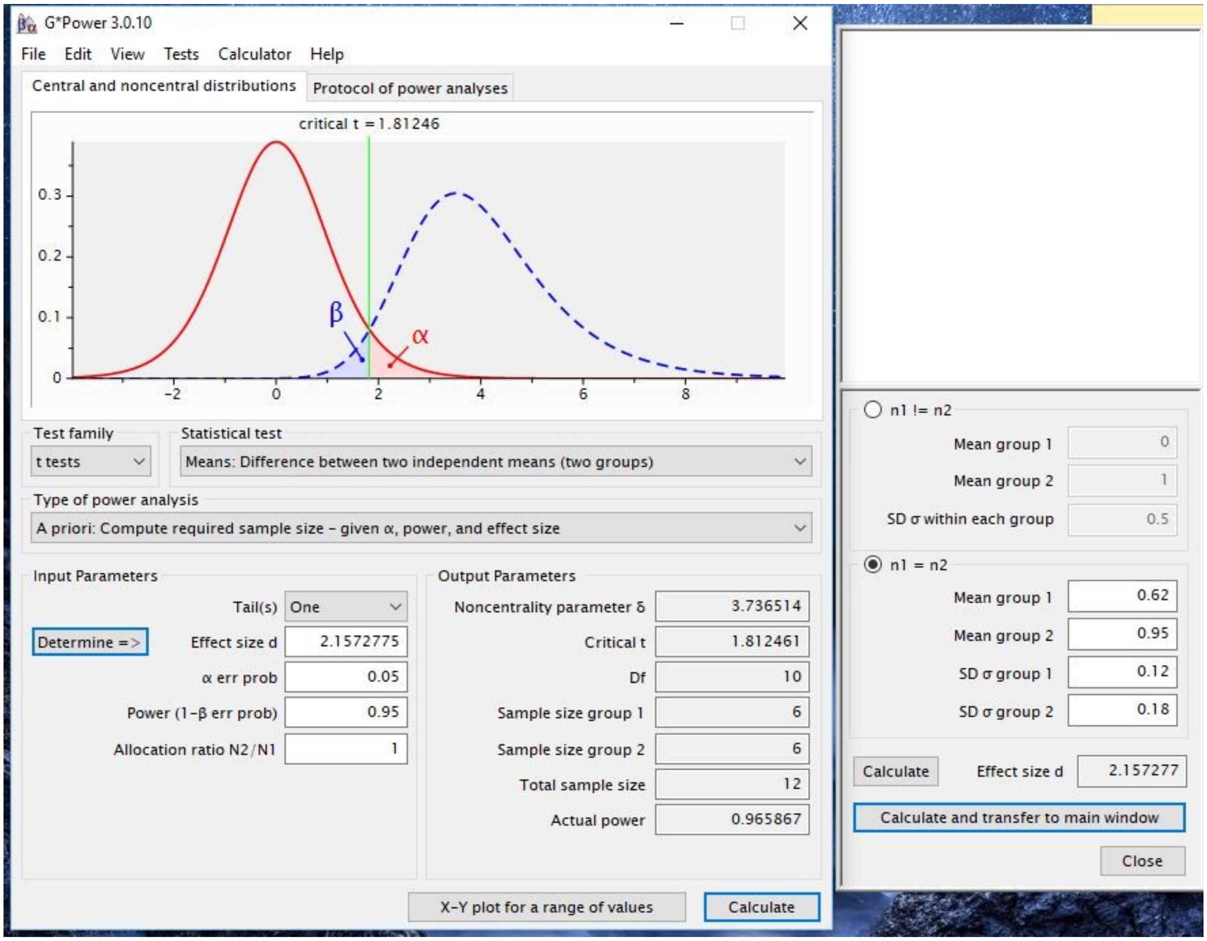
Sample size calculations for this particular study were done based on the pilot data on the accommodative response lags obtained from 3 myopes and 3 non-myopes. The experimental design used to measure accommodative lags was similar to the one described in Chapter 3. As shown in figure A-1, the mean and standard deviation obtained from the myopes (1.16 ± 0.24D) and non-myopic children (1.56 ± 0.16D) were used to calculate the effect size. Based on the effect size, a sample size of 6 subjects/ group was calculated (with $\alpha = 0.05$; Power $(1-\beta) = 0.90$).

However, there were parameters such as the main sequence relationship that was not different between the two groups. Given that this was a small sample, there are chances of a type II error. There were two approaches to address this issue: (1) Sample size calculations were first taken based on a known effect size. This known effect size was taken from another study[1] which reported a difference in the main sequence relationship between two age groups. This study hypothesized a difference in the main sequence based on the differences in the accommodative motor plant between their younger (10-30 years) and the older group (>40 years). The mean difference in the main sequence slopes between their younger and older subjects was 1.6. The sample size calculated based on this difference was less than the sample recruited in this particular study for each group. (2) In addition, effect size was also calculated based on the actual data obtained from each group in the current study. The mean difference between myopes and non-myopes was very small (0.1). There are two questions that arise from this finding, is the difference meaningful? If yes, based on the effect size calculations (@ $\alpha =$

0.05; Power (1-β) = 0.90), a sample of 894 would be necessary to prove that the groups are different. In our study, the mean difference between the groups was less than 1/10th of what was reported as a meaningful difference in the main sequence relationship between two groups in a previous study (mean difference in the previous study = 1.6 compared to the current study = 0.1). Therefore, I conclude that the sample size used in this particular study is adequate to obtain any meaningful differences between the two refractive groups.

Study II: Sensory deficit hypothesis

Sample size calculations for this particular study were done based on the pilot data on the Objective DOF obtained from 3 myopes and 3 non-myopes. The experimental design used to measure accommodative lags was similar to the one described in Chapter 5. As shown in figure A-2, the mean and standard deviation obtained from the myopes (0.95 ± 0.18D) and non-myopic children (0.62 ± 0.12D) were used to calculate the effect size. Based on the effect size, a sample size of 6 subjects/ group was calculated (with $\alpha = 0.05$; Power (1-β) = 0.90).



Test family: t tests
Statistical test: Means: Difference between two independent means (two groups)
Type of power analysis: A priori: Compute required sample size – given α, power, and effect size

Input Parameters
Tail(s): One
Effect size d: 2.1572775
α err prob: 0.05
Power (1-β err prob): 0.95
Allocation ratio N2/N1: 1

Output Parameters
Noncentrality parameter δ: 3.736514
Critical t: 1.812461
Df: 10
Sample size group 1: 6
Sample size group 2: 6
Total sample size: 12
Actual power: 0.965867

○ n1 != n2
Mean group 1: 0
Mean group 2: 1
SD σ within each group: 0.5
● n1 = n2
Mean group 1: 0.62
Mean group 2: 0.95
SD σ group 1: 0.12
SD σ group 2: 0.18
Effect size d: 2.157277

Figure A- 2: Sample size calculation obtained from G*Power.

However, there was a parameter (blur detection threshold) that was not different between the two groups. As mentioned before, there were two approaches taken to answer this question: (1) Sample size calculations based on a known effect size. This known effect size was taken from another study[2] which reported a difference in the blur detection ability between adult myopes and non-myopes. The mean difference reported in the blur detection ability was 0.12D. Sample size calculated based on this reported difference was less than the sample recruited in the current study. (2) In addition, effect size was also calculated based on actual data obtained from myopic and non-myopic children in the current study. The mean difference between the two groups was very small (0.01). There are two questions that arise from this finding, is the difference meaningful? If yes, based on the effect size calculations (@ $\alpha = 0.05$; Power $(1-\beta) = 0.90$), a sample of 584 would be necessary to prove that the two groups are different. In our study, the mean difference between the groups was less than 10% of what was reported as a meaningful difference in a previous study (mean difference in the previous study = 0.12D compared to the current study = 0.01D). Also, in agreement with our data, another study[3] which used a similar design reported a similar level of mean difference in the blur discrimination discrimination ability between myopic and non-myopic children. They had a larger sample (40 subjects) than ours and yet did not find any difference in the discrimination ability. Therefore, I conclude that the sample size used in this particular study is adequate to obtain any meaningful differences between the two refractive groups.

Control experiment – Luminance

This experiment was done to rule out possible influence of luminance difference between the reference and blur target on the final blur discrimination measures. First, luminance of the blur target (different levels) was measured along with the reference (no blur) target using Minolta Chroma meter CS-100 (Minolta Camera Co. Ltd., Japan). The luminance of the blur target was then plotted as a function of the dioptric approximate of the target.

Table A-1: Luminance measures of high contrast targets with varied levels of blur filters.

Dioptric filter (D)	Luminance (cd/m^2)
1	139.1333333
0.9	145.95
0.8	154.6666667
0.7	165.5
0.6	166.15
0.5	166.5333333
0.4	167.5666667
0.3	170.8
0.2	175.65
0.1	178.5
0	180.85

A linear regression equation, as shown below, was used to quantify the relationship between luminance and the dioptric estimate, where x is the luminance estimate and y is the corresponding dioptric value.

$$\boldsymbol{y\ (D) = \left(-0.0239 * x\left(\frac{cd}{m2}\right)\right) + 6.85}$$

Psychophysical experiment

The procedure employed for calculating the luminance thresholds was similar to the blur discrimination task described previously. Luminance thresholds were determined using a 2 alternate forced choice (AFC) paradigm. Subjects looked at the screen placed at either 50cm with their left eye occluded. Two targets (reference and test), which were spatially separated, were presented on a screen with different levels of luminance. The reference target was always maintained at the maximum luminance (i.e. luminance of a no blur target (L)) and the test target luminance value that is half of the maximum luminance (L/2). Stimuli were presented for 10 secs for each condition with an inter-stimulus interval of 2 seconds. The spatial position of the targets were randomized to avoid predictability. The luminance value was subsequently varied within a 2-down 1-up adaptive staircase, whereby the luminance went down (for correct responses) or up (for wrong responses) by 50% until the first reversal and 25% thereafter. The staircase was terminated after 6 reversals and the luminance threshold was calculated from the average of last 5 reversals. The final luminance value was converted into the dioptric approximate by using the regression equation as was shown above.

The experiment was performed initially on six naïve adults. The measures of blur discrimination threshold and luminance threshold were obtained on two separate days. The blur estimates obtained based on the luminance threshold values were significantly larger than the actual blur discrimination thresholds. This suggests that the difference in the luminance cue would not explain the magnitude of blur discrimination thresholds in our subjects.

Table A-2: Comparison between actual blur discrimination thresholds and blur thresholds calculated based on the luminance values.

Subject	Blur discrimination threshold (D)	Blur threshold (D) estimate based on the luminance measures (cd/m^2)
1	0.32	0.8302
2	0.38	1.4994
3	0.46	2.2403
4	0.4	0.7824
5	0.36	0.9019
6	0.32	0.7107