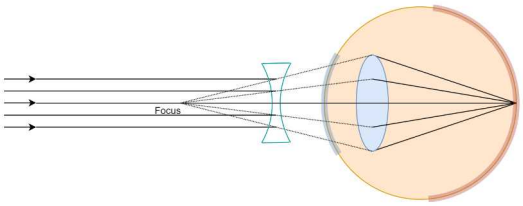

Breakthrough Adaptive insights into Emmetropization for Physiologic Myopia

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0. Abstract

Purpose: Recent investigations hint towards viability of axial shortening and existence of active emmetropization. We propose a novel theoretical framework considering recent investigations into the interplay between the visual environment and viewing habits for commonly observed uncomplicated (physiologic) myopia.

Methods: Survey of the current evidence pool about common myopia on PubMed. The search terms used were as follows: myopia progression, genetics, near work, lighting environment, emmetropization, outdoor exposure. etc.

Results: The breakthrough Continuous Adaptation Theory (CAT) with its two refractive equivalences, describes physiologic Myopia as a shift in refractive equilibrium between two opposing processes—myopization and emmetropization. Physiologic myopia results from 'push-pull' shift in refractive equilibrium from strenuous incidence of near-work (PULL) along with underutilisation of distance vision (PUSH) causing myopization to dominate. The lighting environment serves to steer adaptation from resulting blur due to defocus, possibly answering the decades-long open question of how eyes deduce the direction of adaptation from defocus.

Conclusions: Our theoretical framework predicts that the environmental stimulus responsible for physiologic myopia onset (in emmetropic eyes) is also responsible for its progression and results from identical processes. The resulting 'duals' provide valuable insight into slowing/stabilizing Myopia progression and even reducing it toward potential emmetropia.

Translational Relevance: Our breakthrough adaptive framework provides implementation details for indirect (sun)light therapy that holds potential for first-ever clinically significant long-term myopia regression.

0.1 Conflict of interest & ethics declarations

The author declares no competing interests.
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0.2 Keywords

Axial shortening, Myopia progression, Myopia regression, Emmetropization

0.3 Significance Statement

This article provides the first proper breakthrough toward properly understanding physiologic myopia.

1. Introduction

Myopia is a refractive error widely regarded as irreversible/irreducible with a largely suspected multifactorial etiology[1]. Extreme axial elongation[2] resulting from severely high myopia increases the risk of vision threatening complications including but not limited to open-angle glaucoma, cataracts, retinal tears that can lead to retinal detachment, and macular degeneration (myopic maculopathy)[3]. An estimated half of the world's population is expected to be myopic by 2050 if the current trends continue[4].

There is an urgent need for viable interventions that can stabilize or at least slow down myopia progression. Existing methods for myopia control have been shown to be incapable of directly affecting the consequence of myopia which is posterior axial elongation.

This article attempts to describe breakthrough insights from an adaptive equilibrium characterization for physiologic myopia. The governing insight behind such an approach is the possibility of axial shortening and evidence suggesting occurrence of active emmetropization. Our work is in stark contrast with conventional approaches, which are mostly dominated by empirical guesses for myopia.

2. Background: Survey of the current evidence pool

Article search for relevant literature was done on PubMed associated with non-pathologic/common myopia. The search terms included but were not limited to:

myopia progression, genetics, near work, lighting environment, emmetropization, outdoor exposure etc.

Particular emphasis was given on articles reporting unexpected findings about myopia.

The background summary follows the natural order:

Binary classification for myopia (physiologic vs pathologic) → Physiologic myopia (onset and progression/stabilization) → Associations of Myopia → Insights/implications from animal models of myopia → Shortcomings of current interventions for myopia

2.1 Physiologic Myopia vs Pathologic Myopia - a strictly modular classification

The term Myopia denotes refractive error resulting in the proper inability to bring distant objects into focus (image formation behind the retina even after relaxing accommodation) compared to an emmetropic eye. Myopia can be further classified on the basis of its origin as physiologic or pathologic[5].

Even high degree of refractive error due to physiologic myopia (increasing risk of sequelae) needs to be strictly distinguished from pathological myopia as well as pathological complications that can accompany highly severe forms of physiologic myopia[6]. Pathologic myopia is often associated with high myopia and complications of the fundus such as degeneration of the macula, optic nerve, or peripheral retina. Nevertheless, signs/complications associated with pathologic

myopia (for instance, posterior staphyloma) have been observed to occur in eyes without high myopia sometimes even in otherwise emmetropic individuals[7] [IMI Pathologic Myopia, May 2021].

For this article, physiologic myopia was strictly defined as 'myopia in the absence of other ocular anomalies', except for those from axial elongation. This is important from the standpoint of consistent classification—myopia can be either physiologic or pathologic (but not both) in the sense that highly severe physiologic myopia can also lead to pathological complications. These findings indicate differences in both the underlying pathways and origin. The benefits of this strict classification will become apparent later.

The scope of this article is restricted to physiologic myopia only. The term Myopia from now on in this article should be taken to mean physiologic Myopia unless stated otherwise.
A list of synonyms for both kinds of myopia is given below.

Physiologic Myopia (of which pseudomyopia is a precursor)	Pathologic Myopia
Common, childhood onset, uncomplicated, non syndromic/pathological, functional	Degenerative, malignant, syndromic

Myopia onset is primarily observed in early childhood, and mostly stabilizes in the mid twenties. However, both myopia onset and progression have been observed at all ages. This is confirmed by reports documenting adult onset/progression of myopia after enrolling in college[8]. The COVID-19 pandemic also resulted in reports of myopia onset and progression in both adults[9] and school-aged children[10] coincident with lockdown confinement.

The onset of myopia is usually considered as setting the stage for Myopia progression. This translates to a presumed etiology where worsening myopia is viewed as the natural course of disease progression.

2.2 Multifactorial associations necessitating stricter classification for myopia

For several decades, investigations have focused primarily on figuring out the suspected genetic causes of myopia. There are numerous studies investigating the associations of myopia with genetics. However, for physiologic AKA nonsyndromic myopia, evidence is now mounting that at most, there can only be genetic susceptibility in the face of mostly missing heritable markers ('heritability gap')[11]. To quote, *"A known genetic factor has been implicated in genesis and development of syndromic myopia (such as Marfan syndrome or congenital stationary night blindness). Nonsyndromic myopia has no clear association with a genetic mutation; however, polymorphisms in different genes are associated with nonsyndromic myopia"*.

There are multiple reports outlining the differences between myopia observed to be genetic and one that is environmental. This is unlike the mostly hereditary/parental nature of syndromic/pathologic myopia[12]. Our argument is further supported by the negative association between common Myopia and outdoor activity and the recently discovered protective effect of sunlight[13] on Myopia onset and progression.

2.2.1 Environmental and behavioral Associations of Physiologic Myopia

Myopia shows major associations with environmental and behavioral factors that cannot be explained by genetic considerations alone. Eyes, as an organ adaptive toward visual perception implies environmental factors that affect the eyes optically; for instance, object distance (deciding accommodation and vergence), contrast, and brightness/intensity (affecting the pupil) or their superposition are considered physiologic factors. Factors not optical in nature, for instance: hereditary, birth defects/congenital and environmental factors different from those mentioned above such as toxins, trauma, and other unidentified factors internal to the eye are considered pathological factors.

In regard to common myopia, its cause is commonly predicted to be a multifactorial interplay of environmental and lifestyle factors with a component of genetic susceptibility. Along with an increased incidence of near-work, myopia is strongly correlated with urban lifestyles and higher education. It includes but is not limited to jobs involving handling small things (watchmaking, quality control and inspection, for instance); reading, writing and time spent looking at digital displays, whether PC/Laptop/smartphone/tablet[14]. Myopia is not significantly associated with time spent doing near work after adjustment for other factors such as age, sex, ethnicity, parental myopia, school type, and outdoor activity. There were independent associations between closer reading distance (< 30 cm) and continuous reading (> 30 minutes) leading the study authors to speculate that intensity rather cumulative duration of near work was deciding factor for myopia. This particular study additionally reinforces the need for targeted workplace measures to reduce occupational exposure and mitigations such as allowances for regular breaks from near work[15].

2.3 Animal models of Experimental Myopia and Form Deprivation Myopia (FDM)

Of the large pool of studies documenting experimental myopia in animals, we expect only a subset of observations to actually extend to human eyes.

Both hyperopia and myopia occurred in young chicks when convex and concave lenses respectively were used indicating the ability of the eye to respond and direct axial changes in the opposite direction to compensate for the defocus. Additionally, eyes with myopic defocus (inducing hyperopia) had a disproportionately stronger response compared to similar duration of hyperopic defocus (inducing myopia) as long as the cycle time was maintained longer than 30 minutes[16]. Once the external defocus was removed, progression of experimental myopia slowed and then decreased and in some cases even emmetropia was achieved, suggesting that the built-in mechanism is able to detect and swiftly adapt to changes in external stimuli. The same was also observed in a higher primate (rhesus macaque[17]).

Efforts to induce FDM were successful even after Optic Nerve Section (ONS), indicating that the eye possesses internal mechanisms still capable of directing axial changes (which might also act as a fall back)[18]. This finding was further backed by hemi-retinal form deprivation influencing local axial changes in infant monkeys and chicks before eye-growth is completed. The study on infant rhesus macaques concluded that the effects of form deprivation on refractive development in primates are presumably mediated by presumably retinal mechanisms that integrate visual signals in a spatially restricted manner[19]. These observations are consistent with previous findings indicating that adaption occurs across multiple species, including higher primates (hinting similar possibilities for humans) and that the retina acts as the primary initiator of most localized changes.

2.3.1 Structural modifications to the Eye by Myopia

Hyperopic defocus using minus lenses resulted in the observation of rapid choroidal thinning, indicating AL compensation for the introduced defocus. Choroidal and scleral thinning was most prominent at the posterior pole compared to the equatorial regions of the eye[20].

Human eyes start to develop around the third week of gestation, and the process is mostly completed by the tenth week[21]. Eyes continue to grow rapidly after birth to the age of one to two years and then gradually until adult eyeball size is usually attained around the onset of puberty. The primary goal is to match the eye's axial length with power of its optical components in such a way that images of objects at infinity can be formed with relaxed accommodation (emmetropia). Eye size and shape at birth influences subsequent eye growth but is not observed to be associated with refractive error development later in life[22].

The distinctive nature of axial elongation in response to external environmental factors separate from eye growth is necessary to explain observed focally controlled ocular growth in infant monkeys and chicks. The eye responds to the superposition of growth and adaptive signals after birth [Josh Wallman and Jonathan Winawer, 2004]. Terming axial elongation as eye growth contradicts evidence hinting at existence of active emmetropization. Such a mechanism should be present and fully functional in human eyes (although the time period may differ) influencing axial length alongside growth signals[23]. Axial elongation due to myopia results in a marked shape change (elongation) distinct from overall (globe) growth. Hence, we prefer to use the term axial change (for both axial elongation and shortening) instead of axial growth. This approach also avoids irreversible connotations of the term growth, mistaking it for bodily growth of the eyes.

That Myopia can result from homeostatic control mechanisms inside the eye has been known for quite some time[24, 25]. These observations of structural changes accompanying axial elongation 2.3.1, suggest physiologic myopia shows signs of equilibrium and feedback (characteristic of adaptive systems according to control theory). From an adaptive standpoint, myopia progression is shift in equilibrium distinct from stabilized myopia. The observation that myopia onset/progression occurs at all ages strongly indicates that physiologic myopia should also be reduced beyond puberty.

2.4 Shortcomings of existing interventions for myopia

Myopia control/management refers to interventions[26] aimed at slowing/stabilizing myopia progression. This is distinct from refractive interventions such as lenses, contacts and surgical procedures meant to compensate for defocus (after subjective refraction[27]). The term "compensation" is better than the widely used correction in this regard. There can be no difference between refractive compensation by glasses, contacts, or refractive surgeries from an optical standpoint.

None of the existing methods truly and significantly affect the physical consequences of physiologic myopia. Currently, there is no widely accepted method directly targeting long-term consequences of posterior axial elongation[28].

The two most commonly used myopia control treatments, Ortho-K and atropine, do not account for or directly address the previously outlined environmental association of physiologic myopia. These widely used management options suffer from frequent rebound effects[29, 30]. Rebound effects after cessation of treatment show that the underlying mechanism and environmental factors behind myopia remain unaffected.

Recent investigations into peripheral defocus strategies (eg. DIMS) echo a shared observation—something other than defocus also plays a key role in myopia[31].

Notably, recent promising advancements in the form of light therapies have reported significant axial shortening beyond measurement uncertainty. RLRL[32] (Repeated Low-level Red Light) and High Environmental Illuminance therapies[33] have shown promise for Myopia management. Light therapies aim to emulate the response to daytime outdoor exposure and its known protective effect against Myopia onset/progression[34, 35]. However, reliable signs of significant myopia regression resulting from existing light therapies have yet to be identified. Further advancements are needed before such therapies can become the standard for myopia management.

3. Materials (separate)

4. Continuous Adaptive Theory (CAT)

This section aims to develop an adaptive theoretical framework explaining physiologic myopia.

This article utilizes prefixes such as *compensated* to denote an eye seeing with refractive interventions. The symbol ∞ should be taken to mean optical infinity[1].

The problem statements for out theoretical framework are as follows:

1. What are the top factors for physiologic myopia?
2. Arrive at the reason behind lack of a well established cause for physiologic myopia.
3. Why is common myopia considered permanent/irreducible in nature so far?
4. There is mounting evidence contradicting the widely presumed irreversibility of myopia and suggesting the possible existence of interventions that can reduce myopia. The primary goal is to develop a truly viable protocol/method for reducing physiologic myopia.

The underlying hypothesis of CAT is that ocular refraction is governed by homeostatic AKA adaptive equilibrium. The process that makes the eye less myopic/further hyperopic will be referred to as emmetropization, and its inverse will be referred to as Myopization according to our conventions[2]. It also implies that for a hyperopic eye to become emmetropic, myopization must dominate and vice versa.

4.1 Variable time-scale adaptive processes of the eye

Decoding the adaptive nature of the eye involves determining out how adaptive mechanisms inside the eye communicate, delivering images to the retina [Josh Wallman and Jonathan Winawer, 2004]. The two ways corresponding to two variables by which refraction is shifted/affected are: focal length or screen distance changes. The focal length aspect is somewhat complicated by two distinct ocular focusing elements inside the eye: – the cornea and the eye lens.

A lot has been already described about accommodation. Accommodation happens to be a very short-term (almost instantaneous) adaptive response decreasing the focal length of the eye lens.

1 10 m (≤0.1 D) or better instead of the usual 20 feet/6 metre

2 Emmetropization should not be confused with the term emmetropia/emmetropic. The former refers to a process (directional context) while the latter indicates refraction of the eye being neither hyperopic nor myopic (positional context).

The eye lens is unaccommodated while viewing objects at the eye's far point. A high-quality video of accommodation in action[36] can be accessed here: https://youtu.be/1yIpyitm6eE

Long-term axial changes (occurring on a time scale of several months or longer) due to myopia[37] mostly involve changes in the cornea (changes in the corneal curvature and ACD[38]) and thinning of the posterior sclera accompanying physical distancing of the retina[39].

Hypothesis H1: Predicts existence of a medium-term intermediate bridging response between the well-known short-term accommodation and long-term processes associated with axial changes. H1 proposes that this intermediate response precedes long-term axial changes to the retina and cornea. In addition to evidence pointing at existence of active emmetropization, H1 is strengthened further from continuous structures of iris, ciliary body and choroid comprising uvea. This medium-term shift should result in marked changes to both the ciliary body and choroid.

Intermediate changes to the ciliary body affecting the ciliary muscle state should result in shifts in the relaxed and accommodated power of the eye lens. The cornea then undergoes long-term changes to alleviate such ciliary shift. In the absence of extensive details, we speculate that observations reporting ciliary body thickening[[40], [41]] indicate myopic ciliary shift. Thickness changes to the choroid occur in tandem, acting as a precursor for displacement of the retina and associated scleral shape changes. Observations describing the inverse association[42] between choroidal thickness and posterior axial changes further strengthen our conviction. We expect these intermediate changes in the ciliary body and choroid to happen mostly before long-term changes are made to the cornea and retina, respectively.

4.2 Changes in refraction/focus range due to myopia

The eye experiences continuous changes while becoming myopic. The ability of the eye to undergo accommodation during this period is roughly constant. A myopic eye continuously gains additional close-range focusing capability while *sacrificing* the ability to observe distant objects compared to an emmetropic eye, as shown in Figure 1.

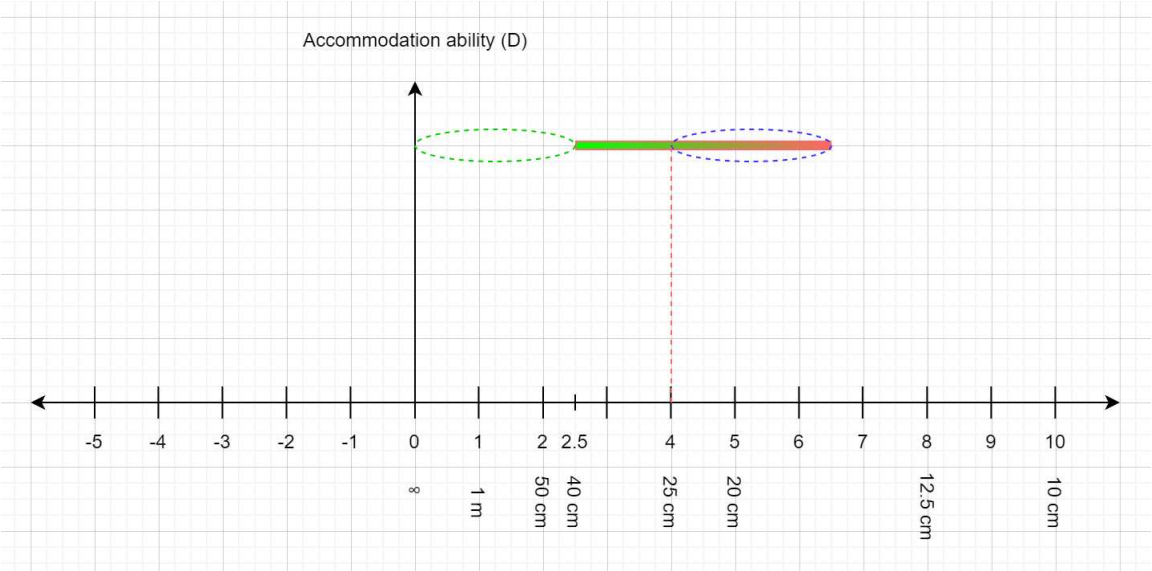

Figure 1 Compared to an emmetropic eye, the gained close-range observation capability by a Myopic eye (2.5 D) is shown with a blue dotted oval while its 'sacrificed' observation range is shown with a green dotted oval. The x-axis scale denotes refraction power/focal length of the eye optics.

The blue dotted oval denotes the gained focusing capability between myopic and emmetropic near points, while the green dotted oval denotes the lost focusing capability between the myopic far point and infinity (its emmetropic counterpart). It is already well known that myopia is associated with both an extended duration of near-work and lack of regular outdoor exposure. This shift in the observation range is in agreement with these well-established associations of myopia and hints at the possibility that both might constitute simultaneous requirements.

Hypothesis H2: Myopia results in the eye gradually gaining extra close-range capability while sacrificing the ability to observe distant objects; that can be explained as shift in refractive equilibrium due to hyperopic defocus from increased incidence of near work combined with underutilization of distant vision capability of the eye.

The simultaneous 'Push-Pull' analogy makes this even clearer. It hints that the eye undergoes axial changes trying to relieve accommodative fatigue induced defocus[43]. Due to limited extent of ciliary accommodation, underutilization of the focusing range extrema (here refers to distance vision capability) permits an even stronger response. An increased incidence of near work can be said to exert a 'PULL' while underutilization of distant vision capability exerts a 'PUSH'. The push criteria can alternatively be termed 'permitting' criteria because it allows pull criteria to make myopic changes. A push or pull in isolation should be insufficient toward shifting refractive equilibrium.

H2 explains one of the many unexplained mysteries of myopia: Why does a population not experience myopia onset/progression even with significant near-work incidence[44]? This hints that utilization of distant vision possibly counters adaptive signals from near work and that regular utilisation of distance vision capability can prevent myopia onset/progression. We invite others to verify the physical implications of our explanation. Our finding explains why near-work is correlated[45] with myopia but is not the only factor. Underutilization of distant vision capability (not the same as lack of near-work) is also a contributing factor for physiologic myopia[46].

4.3 Influence of lighting levels and the problem of deducing adaptive direction from defocus

The pupil of the iris[47] evolved as an aperture control mechanism to regulate the amount of light entering the eye. [Pupil size[48] in adults usually varies from 2 to 4 mm in diameter in brightly lit environments to 4 to 8 mm in the dark]. In this context, environmental light intensity can be said to relatively affect the pupil size in two ways: pupil constricting (bright) and pupil dilating (dim/dark) lighting.

A dilated pupil's shallower depth of field should theoretically demand additional accommodation in dim lighting for unchanged focus distance, resulting in hyperopic defocus. Myopization then tries to compensate for this hyperopic defocus.

Moreover, even very forgiving DOF calculations hint that the pinhole effect alone is not enough to explain the dramatic improvements in vision during the day. Suggesting the iris must somewhat mechanistically offset the ciliary muscle 'set-point' with its constricting 'tug'. This prediction too is supported by the continuous structure of iris and ciliary body permitting mechanistic interaction.

4.3.1 Pupil constricting lighting and the role of sunlight in the evolution of eyes

The human eye has evolved[49] from a simple light-sensing structure to an absurdly complex and highly specialized organ dedicated to vision. The scope of this article is limited to pointing out the role of sun as the only primal light source influencing evolution of eyes. By connecting the dots

further, it can be understood that human eyes must also show selectivity toward the intensity and (basically black body) spectrum of sunlight. This basically means that the best example of the aforementioned pupil constricting lighting environment is indirect sunlight. For the purpose of this article, indirect exposure to diffuse sunlight will be defined as the sun not directly in the visual field – whether visible directly (incident) or specularly reflected from mirrored surfaces/water/ice/snow.

4.3.2 Deciphering Form Deprivation

It is well known that near work in dimly lit lighting environments is directly associated with myopia[50]. Multiple studies have shown that myopia is the 'default' behavior of animal eyes when subjected to form deprivation in dim lighting environments[[51],[52] and [53]]. Form deprivation has also been successfully induced in higher primates (Rhesus Macaques[54]) meaning a similar response must exist in human eyes as well.

We want to point out that from the standpoint of optics, there is little difference between uniform blur produced by small amounts of hyperopic or myopic defocus. There is only so much information that can be conveyed by image formation alone. The eye must rely on clues other than image formation alone in order to deduce this information. This problem is further complicated by uneven distribution of rods and cones demarcating the central/foveal (photopic) and peripheral (scotopic) regions of retina[55].

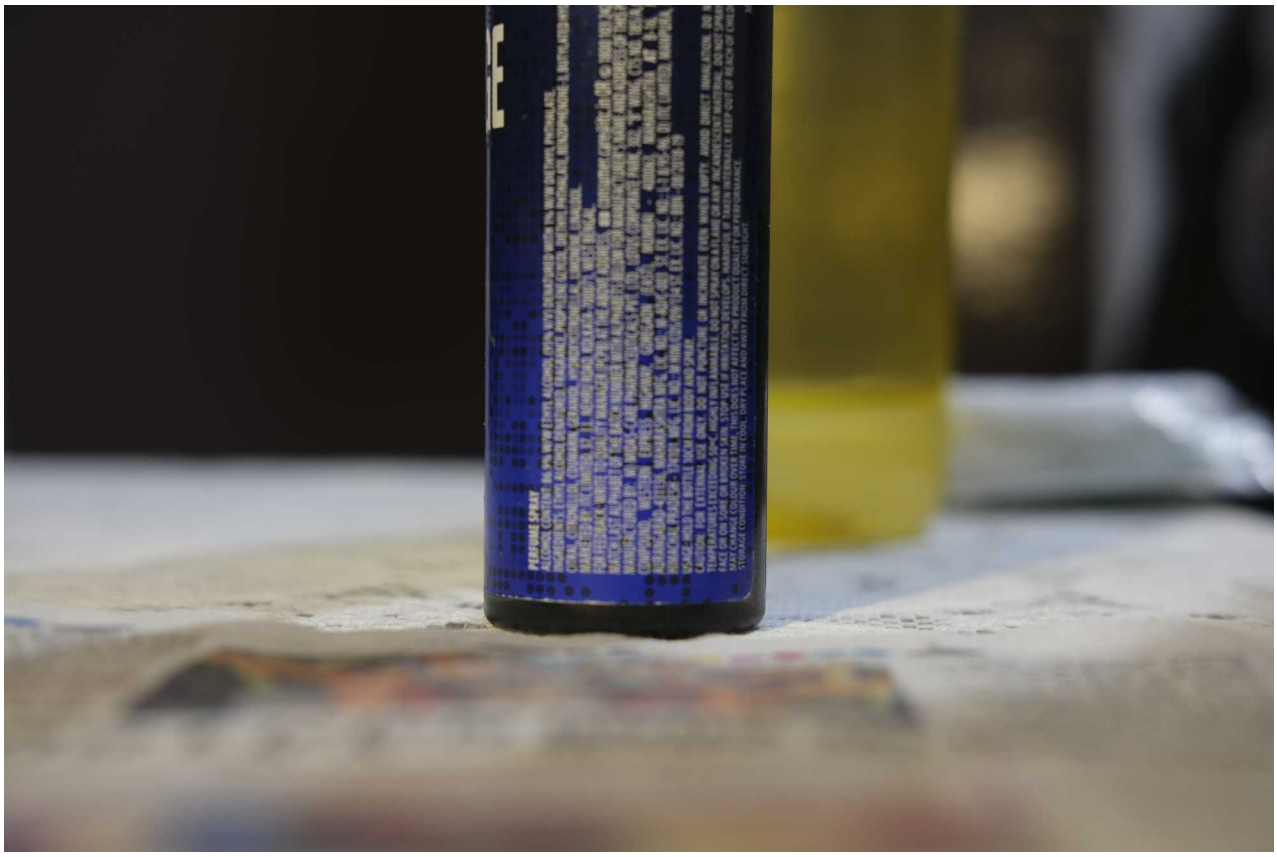

Figure 2 Two images taken at f = 35mm, f/4. Both images demonstrate strikingly similar blur from defocus in central text. Myopic or hyperopic defocus can be determined by checking the lowermost focused part of the image. (Best viewed side-by-side)

This observation alone implies that the mechanism inside the eye responsible for adaptive changes must be much more 'sophisticated in nature' than previously understood. FDM, as component of myopization, also makes evolutionary sense for maintaining refractive equilibrium along with emmetropization. Much debate has taken place as to whether FDM and lens-induced myopia are different[56]. However, our arguments inspire confidence that the mechanisms are indeed the same.

Hypothesis H3: H3 predicts pupil dilating lighting during near-work accelerates myopization by parallel activation of FDM pathways[57]. This is in addition to processes alleviating accommodative fatigue. Form deprivation Myopia is nothing but an essential component of myopization that responds directly to blur from defocus in lens-induced myopia.

It hints that possible efforts toward inducing emmetropization could be rendered ineffective/countered by the dominant nature of the FDM pathway under pupil dilating lighting. The activation of FDM pathway might explain why myopic defocus in primate eyes triggers further Myopization under pupil dilating lighting instead of the expected emmetropization, as expected from animal models.

We previously outlined how accommodative fatigue and underutilization of distant vision capability together shift refractive equilibrium toward Myopia. In this context, less than adequate lighting enhances myopization by parallel activation of the FDM pathway besides responding to accommodative fatigue. Lighting condition happens to be the last remaining puzzle piece in our understanding of physiological factors underlying Myopia[58]. This might also explain why highly myopic people experiencing active myopia progression can show sensitivity to bright lighting

environments, which normally do not significantly affect emmetropic individuals. Low lighting conditions also reduce the availability of information, increasing the chances of developing alignment errors and visual aberrations thereby making myopization inherently ‘inferior’ than emmetropization in this regard.

4.4 Refractive Equivalences for Physiologic Myopia

The similarities between an emmetropic eye and an eye compensated[3] for myopia can be subdivided into two equivalences. These result from simple equivalence of refraction.

4.4.1 Observational equivalence of far-point

The apparent far-point of a pseudo-emmetropic (best compensated uncomplicated myopic/hyperopic) eye is equivalent to the real far-point of an emmetropic eye at infinity. This equivalence cannot always be extended to the near-point due to the variation in accommodation ability and/or presbyopia.

The apparent far-point of a myopic eye with proper refractive compensation lies at infinity. This can be termed as ‘clamping’ of actual far-point due to refractive compensation, shown in Figure 3.

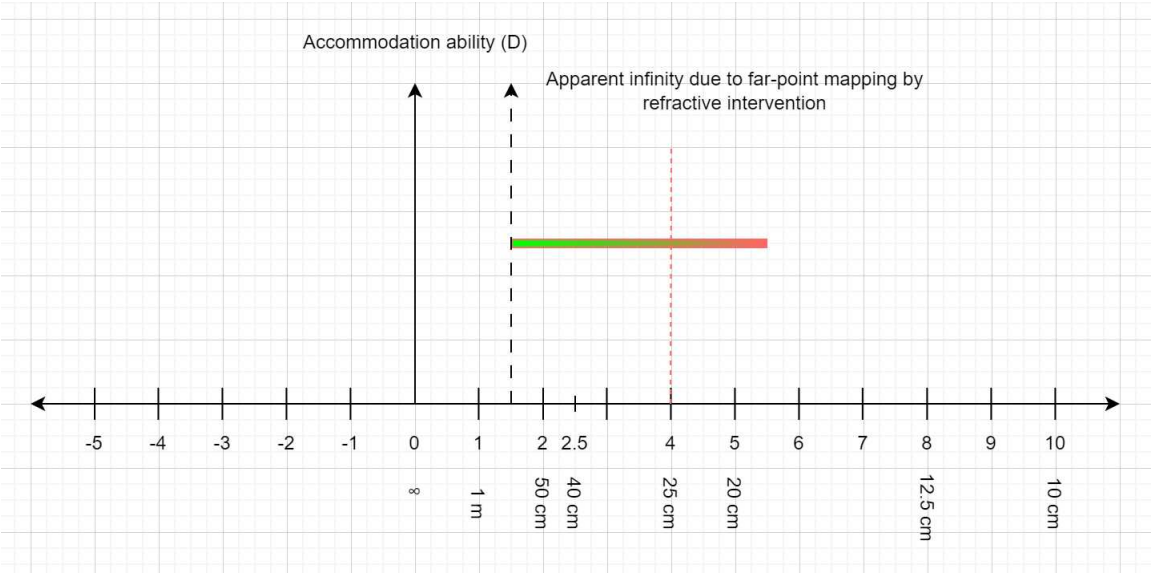

Figure 3 Clamped far-point of a Myopic eye (1.5 D) by refractive compensation

4.4.2 Behavioral/equilibrium equivalence of the refraction shift

Any refractive shift affects identically, both an emmetropic eye (onset of myopia) or an already myopic eye (myopia progression). This equivalence naturally extends to hyperopic shifts as well. This basically ensures that any viable method resulting in myopia regression should also force the development of hyperopia in emmetropic eyes.

3 Termed pseudo-emmetropic

5. Discussion

5.1 Implications from refractive equivalences

The equivalences outlined in section 4.4.1 basically guarantee the similarity between refractive equilibrium of a stabilized myopic eye and an emmetropic eye. Refractive state is in stable equilibrium because the process of myopization is in equilibrium with emmetropization for both (stabilized myopic and emmetropic) eyes, suggesting that conditions for an emmetropic eye to not experience myopia onset is identical for stabilizing myopia. Myopia progression is nothing but 'onset of myopia' in a myopic eye. Even in the absence of a widely agreed upon cause for myopia, these equivalences impose the weaker restriction that constrains the conditions responsible for myopia progression to match with conditions responsible for myopia onset.

In addition, stabilized myopic eyes shows behaviour closer to a stable emmetropic eye than to an eye experiencing active myopia progression. For hyperopic shift in refraction, myopic defocus is required because ciliary muscle is relaxed for distant work implying the lack of accommodation or accompanying fatigue. Myopic defocus emerges as a necessary but not sufficient[59] requirement for invoking emmetropization. We have already noted the role of pupil constricting lighting in overcoming FDM pathways. It should also explain to why progression of hyperopia unlike myopia progression is very rare[60]!

These equivalences alone signify the urgent need to revisit and properly isolate the behavior shown by stabilized myopia from that shown by progressive myopia in the pertinent literature and explain why efforts to gather insights about myopia from studies on refractive state alone failed to yield conclusive insights.

The breakthrough insights from these two refractive equivalences are summarized below in Table 1:

Table 1: Equivalences between a pseudo-emmetropic eye and an emmetropic eye

Myopic eye wearing best possible refractive compensation (pseudo-emmetropic eye)	**Emmetropic eye**
Failure to observe Myopia regression with best refractive compensation even after distance work	No observed hyperopia (shifting of far-point beyond infinity) even after (in-focus) distance work
Myopic shift observed as Myopia progression	Myopic shift observed as Onset of Myopia
Some population reports stabilized myopia even with significant near-work habits.	Some population reports no myopia even with significant near-work habits.
Apparent Far-point is at infinity	*Real* far-point is at infinity

The refractive state of a myopic/hyperopic eye is as '*valid'* as that of an emmetropic eye from the perspective of CAT. These equivalences combined with the lack of specific retinal

complications/anomalies inside the eye should serve to distinguish physiologic myopia from the pathologic kind. Physiologic myopia cannot be termed a disorder or disease. It is a consequence of processes responsible for maintaining refractive state in all functional eyes. This is evident from the self-consistency of our adaptive framework and the resulting behavioral equivalences.

5.2 'Genetics' of physiologic myopia

Physiologic myopia is shift in observation range brought by two opposing processes under dynamic equilibrium responding to temporal integration of visual signals. Any influence of genetics on these processes will not considerably alter the processes themselves—rather their rate and consequently the set-point of equilibrium. This is the primary reason why there can only be a genetic susceptibility component for physiologic Myopia, unlike the well-established mostly hereditary nature of pathologic myopia. The observation of FDM across animal species is one of the many hints of physiologic Myopia being an essential/fundamental/functional behavior of the eyes. This also means that basically all human beings with functional eyes can become myopic.

The heredity of myopia is frequently described as myopic individuals having more chances of a myopic parent. After accounting for the possibility that myopic children share a similar environment with their parents, it becomes unclear how much of a role heredity actually plays in the progression of physiologic myopia. It must also be noted that most current studies on parental myopia additionally fail to strictly isolate progressive and stabilized myopia[61, 62, 63] in line with the equivalences in section 4.4. These equivalences outline the urgent need to isolate all physiological variables from pathological ones. We expect definitive trends to emerge in studies when progressive myopia is properly isolated from stabilized myopia.

5.3 Changes in the accommodation-convergence reflex from myopia

Human eyes form a stereoscopic pair for depth perception, necessitating convergence[64]. Convergence basically involves simultaneous tilting in the axis of both eyes toward the object point in focus. This article is limited only to convergence aspects and behavior related to myopia.

For an adult emmetropic eye focusing on an object equidistant from both eyes, the relation between convergence angle θ and accommodation is governed by $\theta = \sin^{-1}\left(\frac{IPD \times Accommodation\,Power}{2}\right)$, where the Interpupillary distance (IPD) is the distance between the axes of both eyes. The angle between the respective image planes depicted in blue is the sum of convergence angle of both eyes (Figure 4).

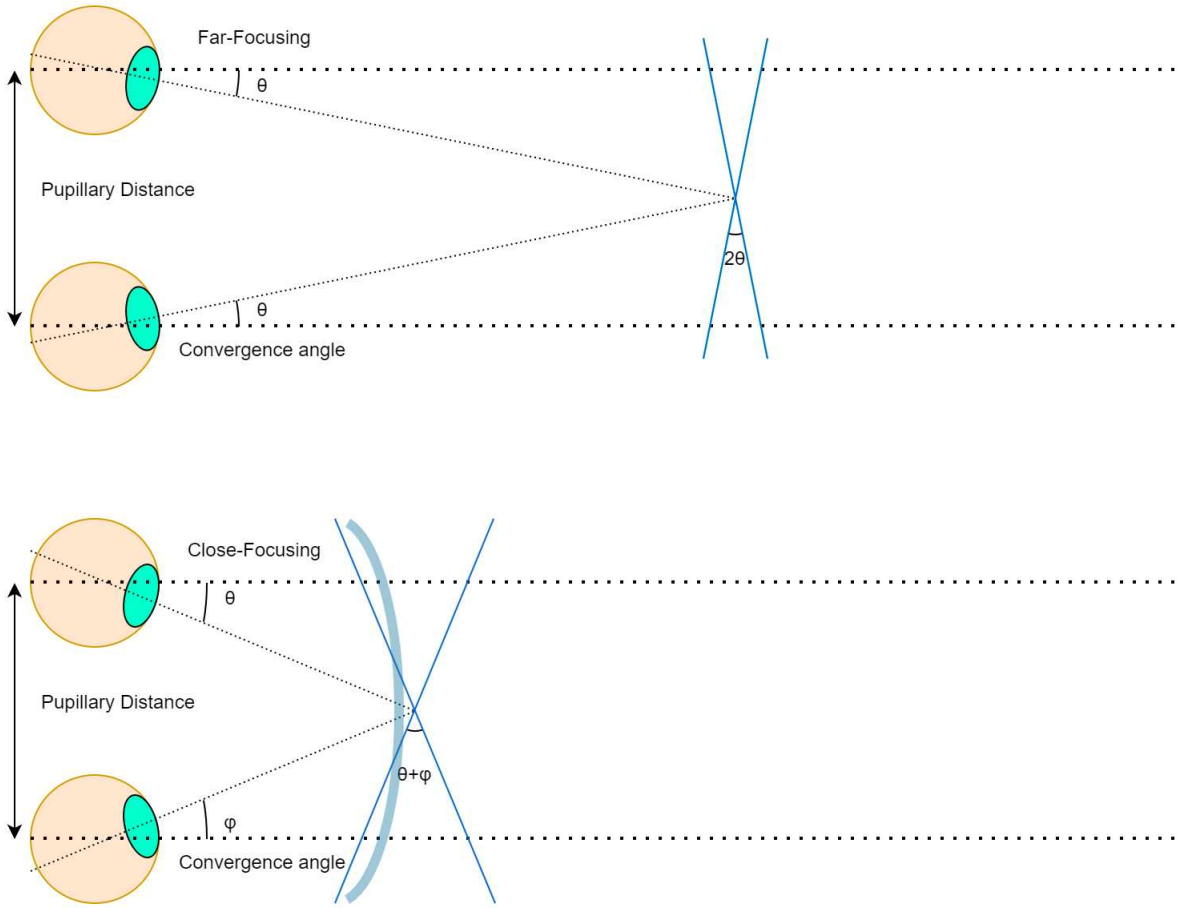

Figure 4 Depiction of convergence with observed distance compared to observing at infinity. Note the increasing angle between the perceived image planes shown in blue as focusing distance gets closer.

The average IPD (63 mm) was used giving 1.8°±0.1° convergence angle for each eye per Dioptre of accommodation. For symmetric focusing at 25 cm (+4 D accommodation), the eye needs to converge by ~ 7.2°. An increase in the angle between perceived image planes for stereoscopic fusion as the focusing distance comes closer should also be noted.

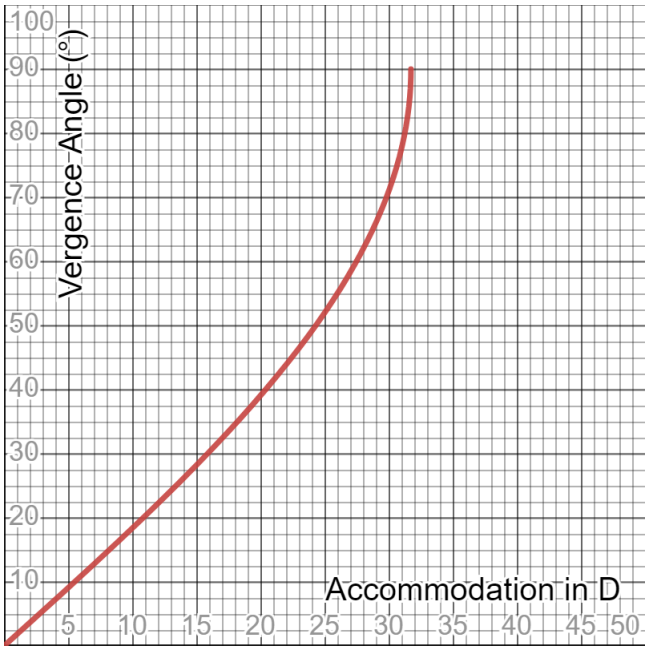

Figure 5 A plot of convergence angle with accommodation (IPD: 63 mm)

As shown in Figure 5, the reflex acts in a mostly linear fashion even beyond the usual accommodation ability for the eye (4 to 5 D). It is not a mere coincidence that the range of ciliary accommodation lies mostly within the contraction range of extraocular muscles responsible for convergence. The extraocular muscles responsible for convergence start hitting their limits at close-up distances characteristic of severe myopia.

For an emmetropic eye with the far-point at infinity, the reflex ideally acts at all observable distances. The same applies to a pseudo-emmetropic eye also with the best possible refractive compensation. For an uncompensated myopic eye with its far point no longer at infinity, accommodation starts only when convergence 'reaches' distances closer than the far-point. For distances beyond the myopic far point, the eyes remain unaccommodated. This can be termed as the introduction of **convergence lag** in myopia[65]. In both cases, the reflex starts acting only when the observed distances reach closer than far point of eye, whether myopic or emmetropic.

The roughly cylindrical nature of converged image plane distortion with its axis normal to the line joining both eyes suggested its connection with astigmatism. It predicts the presence of small, baseline levels of astigmatism in the population primarily involved with significant close-up near-work. How this particular form of cylindrical image plane distortion affects ocular biometry has yet to be properly investigated. It is possible that fully compensating for this form of astigmatism may result in discomfort and increase astigmatism (progression). Astigmatism of this form is best left under-compensated unless it perceptibly affects vision.

It is possible that subsequent conflict and recalibration of the accommodation-convergence reflex play crucial roles in influencing reports of initial discomfort associated with major changes in refraction. The common observation of discomfort stabilizing in the span of a few days hints that the convergence reflex is also recalibrated within this time frame.

An important finding from all of these studies is that, convergence also starts becoming significant at much closer distances of near work. A myopic person can always relax accommodation by wearing simple plus lenses or by not wearing glasses for lower levels of myopia but cannot avoid

convergence. Prisms are contraindicated because of the potential possibility of disrupting accommodation-convergence reflex.

5.4 Proposed mechanism underlying physiologic myopia

Section 4.1 describes short-term, medium-term and long-term processes that are responsible for maintaining the refraction of an eye in accordance with its visual environment. We have also described how an emmetropic eye becomes myopic in section 4.2.

The onset of myopia is predicted to result mainly from the ciliary muscle 'tiring' out during threshold near-work (also see pseudo-myopia/NITM)[66]. This accommodative fatigue of the ciliary results in imperceptible levels of hyperopic defocus, which eyes try to compensate for by becoming myopic in the long run. Doing near work closer to the focusing limit results in faster exhaustion of the ciliary muscle. Defocus near work predictably results in the superposition of defocus response in addition to extreme accommodation. This myopization route is termed AFiM, short for Accommodation Fatigue induced Myopia. In addition, these findings imply that the eyes can respond to relieve accommodative fatigue in addition to existing observations of eyes responding to the superposition of growth signals, defocus, and pathological factors. The scope of CAT is limited to physiological factors only.

In the absence of suitable interventions, the ciliary body starts developing changes to adapt to accommodative fatigue. It is expected that a person with myopic ciliary shift will possess a markedly better ability to sustaining near work for a longer time and suppress near work induced strain signaling. A myopic shift in the ciliary could also result in discouragement toward utilization of distance vision capability in the form of excessive tear formation, rapid uncontrolled blinking, increased sensitivity toward bright lighting and signaled discomfort (HARE[67]), thereby establishing a subtle feedback loop.

Underutilization of distant vision capability in the presence of ciliary body changes then initiates long-term axial changes to alleviate this myopic shift. Subsidence of external factors causing myopia results in equilibrium being established again. The ciliary body gradually returns to its normal state, **preserving** the axial state observed as stabilized myopia.

We have already mentioned that a component of astigmatism should result from increasing angle between image planes at closer distances in section 5.3. Another component of astigmatism is expected to result from adaptive anisotropic changes that ocular components can undergo during myopia. The 'recalibration' of the accommodation-convergence reflex as convergence lag mentioned earlier is also predicted to occur alongside myopia.

5.5 Predicted requirements for emmetropization

If physiologic myopia indeed involves a shift in refractive equilibrium, it should be possible to shift refractive equilibrium toward emmetropia. To summarize our findings, section 4.2 covers why accommodative strain from near-work coupled with underutilization of distant vision capability should cause onset/progression of myopia. Section 4.3 outlines why defocus in pupil dilating lighting triggers FDM pathways. Section 4.4 establishes the refractive equivalence between behavior shown by a best compensated myopic eye and an emmetropic eye. A (pseudo) emmetropic eye and an eye with very low myopia should differ only in their ability to focus on distant objects.

For emmetropization, we need to determine the adaptive 'duals' of the factors behind myopization. Implementing these duals need to be augmented with management of near work which can cause myopization. These findings are tabulated in Table 2.

Table 2: Establishing duals of physiological factors required for myopization

Factors resulting in Myopization	**'Duals' for inducing Emmetropization**
Accommodative strain induced hyperopic defocus from near-work (PULL)	Myopic defocus (exposure beyond myopic far-point) (PULL)
Underutilization of the distance vision capability. (PUSH)	Near-work management to reduce accommodative causing Myopization in the first place with convergence. (underutilization of near vision capability) (PUSH)
Myopization is accelerated under pupil dilating lighting due to parallel activation of FDM pathway	Emmetropization requires pupil constricting lighting environment (preferably indirect sunlight) in order to overcome FDM pathways

These duals provide the first ever breakthrough insights into the physical requirements for emmetropization. They expand our explanatory framework, explaining why earlier attempts[68] investigating undercorrection for myopia failed.

The distances beyond the far point (myopic defocus) that need to be exposed under pupil constricting lighting lie inside the green oval for a myopic eye shown in Figure 1. We will refer to this as Actual Distance Viewing (ADV from now on). The benchmark pupil constricting lighting is indirect sunlight on a clear sunny day. Because emmetropization needs pupil constricting lighting, it should also be slightly faster (superior) due to the availability of more information.

This hints that the commonly observed phenomenon of myopia stabilization coinciding with mid-twenties must be linked to changes caused by environmental and lifestyle factors from attaining adulthood and conscious improvements in viewing habits, including eye-strain awareness during increased near work. This also makes it easy to explain adult myopia progression.

The framework of CAT naturally implies that changes from emmetropization should be somewhat countered by myopization due to 'ordinary work' during the rest of the day. This temporal integration aspect hints at a recovery rate less than the predicted recovery rate. The refractive state of an eye undergoing myopia regression is expected to follow a stair-step function with slight regressions below baseline, as shown in Figure 6. The time difference between each dip (scale exaggerated for clarity) is the rolling window (which can also be termed the emmetropization window) for temporal integration. This rolling window itself is some multiple of days. Its expected range is 2-4 days for most human eyes.

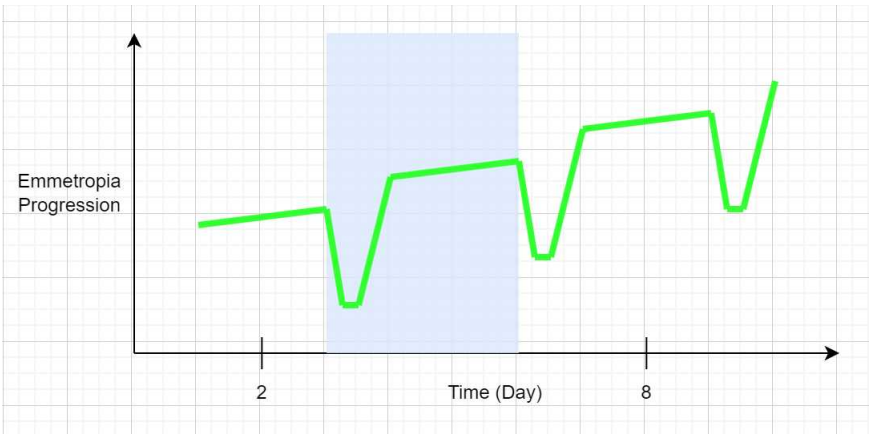

Figure 6: A not to scale exaggerated plot of Refraction vs time for myopia regression

The adaptive nature of the process also implies that the requirements for myopia regression are stricter than just stabilizing myopia. This happens to be the 'dual' of observing a population subset with significant near-work habits not becoming myopic.

5.6 Changes to the Field of View from Axial Changes

The FoV depends on the screen distance, taken as the distance of the central retina from the optical center of the lumped lens (Combined Retinal Distance [CRD]). Axial length is assumed proportional to CRD. The resulting FoV reduction can then be estimated as *emmetropic AL* ÷ *myopic AL*. This process is similar to how focal length changes affect FoV. For instance, an emmetropic AL of 23 mm and myopic AL of 25 mm estimate a myopic FoV of ~ 0.92× the emmetropic FoV.

One such study considering FoV changes in highly myopic subjects was performed by {Yanming Chen; Ji Liu; Yining Shi} for pathological myopia[69]. On the basis of optics alone, the effects of shrinking FoV should start resembling 'tunnel vision effect' and slight zoom with increasingly severe myopia. This also predicts that people managing myopia regression experience consequent FoV expansion.

5.7 Predicting the duration of long-term axial changes

There are two approaches for predicting the duration of long-term AL changes. Both approaches should converge at similar estimates. The first approach considers that both myopization and emmetropization make changes at similar time scales. By extension, time scale for emmetropization can be estimated from the data on myopia progression[70]. Emmetropization should be slightly faster than myopization because it demands pupil constricting lighting with extra available information.

The second approach involves estimating axial elongation from the degree of myopia and current AL measurements. This is detailed below. For an emmetropic eye, the CRD equals inverse of focal power of eye focused for infinity. We assume CRD $\propto$ AL, denoting their ratio CRD/AL as β.

The CRD for a myopic eye can subsequently be estimated giving ΔAL, as shown below.

$$\text{Lens relation}: \quad \frac{1}{s} - \frac{1}{u} = \frac{1}{f}$$

$$\text{Here, elongated or myopic CRD serves as screen distance } (s) \text{ and emmetropic eCRD serves as focal length } (f)$$

$$\frac{1}{CRD} + \frac{1}{-u} = \frac{1}{f}$$

$$\text{emmetropic CRD } (f) = \frac{-u \times CRD}{-u + CRD}$$

$$\text{if we assume CRD / AL as } \beta, \text{ where AL is the current myopic axial length, then}$$

$$\text{Predicted Axial Elongation, } \Delta AL \text{ from Myopia} = AL - \frac{f}{\beta} = \frac{\beta \times (AL^2)}{-u + \beta \times AL}$$

$$\text{For instance, a myopic eye wearing prescription of } -4\ D \text{ corresponding to a far-point of roughly } 25\ cm \text{ will give } u \text{ as } -25\ cm \text{ for the formula.}$$

If the AL and degree of myopia for a non severe myopic eye are known, this formula estimates Axial elongation provided β remains constant. Measuring the long-term rate of AL changes then provides a rough estimate of the time period required for axial changes.

5.8 Strengths and Limitations of CAT

This article provides a high-level description of physiologic myopia which is a distinct subset of myopia. The proposed framework of CAT might very well be the first such explanation managing to consistently and convincingly explain nearly all clinically relevant aspects of physiologic myopia, including but not limited to its onset, progression and even seemingly irreducible nature in humans.

The strengths of CAT is the novel adaptive equilibrium description of physiologic myopia. The resulting equivalences succinctly explain why studies on stabilized myopes have thus far been mostly an exercise in futility because of their equivalence to emmetropes. CAT is the only description of myopia consistent with the evolution of eyes as a visual organ.

Moreover, we want to stress that the simplistic model upon which CAT builds cannot account for differencess between peripheral and central vision or for other non-physiological factors that can otherwise possibly contribute to myopia. Because CAT redefines pathological Myopia from physiologic myopia, the theory naturally breaks down for pathological myopia due to unpredictable alterations to the underlying adaptive mechanism maintaining refractive equilibrium.

6. Conclusions

The first and foremost conclusion from CAT is evidence favors our explanation that physiologic myopia behaves similar to a process under active equilibrium.

In other words, emmetropization ⇌ myopization for when eyes experience no shift in refraction with time. One of these two processes must dominate to cause a shift in equilibrium. For an eye to experience active myopia onset/progression, myopization must dominate over emmetropization. The opposite must be true for hyperopic changes to the eye.

Our findings also reliably establish that an eye can never be in know of its absolute refractive state. The eye only undergoes relative changes based on the quality (defocus) of image formation on retina based on the visual lighting environment.

The theory naturally suggests that myopic defocus implemented strictly under a pupil constricting lighting environment (inducing emmetropization) is the only viable strategy that can result in physiologic myopia regression. The theory obviously predicts adaptive and thus reversible component of axial elongation. Our findings indicate active intervention is necessary to disrupt 'myopic feedback loop' in people experiencing active myopia progression. This is covered in more details in the appendix. We expect the sheer predictive ability of CAT to also provide fast insights into near-work interventions for truly effective clinical myopia regression in the very near future.

6.1 Summing up the Continuous Adaptive Theory (CAT)

A tabulation of the predicted differences between myopization and emmetropization processes is given below:

Table 3: Physiological requirements for factors determining refractive equilibrium

Equilibrium shift by the process	Myopization (Onset/Progression of Myopia)	Emmetropization (Myopia regression)
Visual stimulus 'PULLing' the adaptive equilibrium	Near work accommodative strain resulting in fatigue induced hyperopic defocus. This is exacerbated in pupil dilating lighting environment.	Myopic defocus under pupil constricting lighting that overcomes FDM pathway
Visual stimulus 'PUSHing' the adaptive equilibrium	underutilization of distance vision capability	Near-work management including distancing and periodic breaks as signaled by the eye. (underutilization of near vision)
Accelerator Light levels	Pupil dilating utilizing FDM pathways	Pupil constricting to overcome FDM pathways
Accommodative shift in the ciliary/feedback loop causing shift in Observation Range (far-	Myopic	Hyperopic

point and near-point)		
Secondary refractive errors	Results in aberrations and progression of refractive errors like astigmatism (inferior)	Corrects aberrations and refractive errors (Superior)
Field of View	Shrinks	Expands
Time Interval	Observed rate of Myopia progression	faster than Myopia progression due to extra light information

6.2 The informal Law of Physiologic Myopia

Given time and effort, physiologic myopes should be able to approach emmetropia at par but usually better than their current visual performance with the best possible refractive compensation.

This law encapsulates our bold prediction from CAT, signifying the error-correcting, superior nature of emmetropization.

6.3 Further research

Predicting a concise set of requirements that must be satisfied for physiologic myopia regression presents a massive opportunity for the scientific community.

1. Optimal degree and form of myopic defocus under pupil constricting lighting that safely maximizes the rate of emmetropization. Further optimization of the lighting environment and daytime distant vision requirements.
2. Whether insights from this article can be utilized toward Hyperopia reduction.
3. Experimental studies trying to observe form-deprivation hyperopia under pupil constricting lighting.
4. Further investigations into the role of the mechanistic interaction between the iris and ciliary in the context of the emmetropization.
5. Corporate, industrial and lawmaker roles in promoting myopia prevention guidelines for near work jobs.

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