Medical Sciences

Progressive Myopia and Lid Suture Myopia are Explained by the Same Feedback Process: a Mathematical Model of Myopia

Antonio Medina[1,*], Peter R. Greene[2]

[1]Massachusetts Institute of Technology, Research Laboratory of Electronics, Cambridge, MA 02139, USA. [2]BGKT Consulting Engineers, Bioengineering, Huntington, NY 11743, USA

Objective: Progressive myopia in humans and lid-sutured myopia in primates have been considered to be different processes. This report seeks to establish the connection between progressive myopia in humans and lid suture myopia in macaque monkeys. Methods: We followed the axial length of 4 lid-sutured macaque monkeys over an 18 month period. Their axial length is directly related to myopia. We also studied the myopia progression in corrected human subjects. Macaques and humans exhibit a linear time course of myopia progression when lid-sutured or corrected with lenses, respectively. Results: A linear progression is observed in lid-sutured eyes of four macaques, $r = 0.94$, $p < 0.05$. Human progressive myopia and lid-suture myopia can be modeled by the same feedback process. In both cases the functional equivalent is the opening of the feedback loop. Conclusions: The open loop feedback process predicts a linear progression of myopia. This prediction was confirmed in human subjects and it is now confirmed in our macaque subjects. This process also explains the very rapid rate of myopia progression of lid sutured eyes. *Journal of Nature and Science, 1(6):e121, 2015*

Emmetropia | emmetropization | myopia | Laplace transform | feedback | ultrasound

Nomenclature

r = correlation coefficient
p = significance level
d = diopters
t = time [years]
s = complex variable in the Laplace or s domain
k = emmetropization system time constant [years]
R = uncorrected refractive error [*d*]
A = initial refraction at birth [*d*]
F(s) = emmetropization transfer function
o(t) = system output or response [*d*]
G(s) = forward or open loop transfer function
i(t) = input to the feedback system [*d*]
O(s) = output function in the Laplace or s domain
L{ } = Laplace transform
L^{-1}{ } = inverse Laplace transform
(A/k)t = open loop response function to step A input
R/k = ramp slope or myopia progression rate, human [*d*/year]
A/k = ramp slope or myopia progression rate, macaque [*d*/year]

Introduction

Myopia has an estimated prevalence of 41% among adults in the United States, and the myopia prevalence is increasing [1]. Among Asian populations, the prevalence is even higher with rates as high as 60% among adolescents aged 11 to 17 years in China [2].

The course of myopia typically follows a pattern that begins with an initial emmetropic phase, followed by a myopic onset that usually occurs in the early school years, which is followed by a myopic depression that tends to stabilize in the mid to late teenage years [3]. These are general trends, early or late onset myopia is also possible and a more modest progression may occur during early adulthood before fully stabilizing [8].

Several facts are established that allow us an understanding of refraction development of the eye as a system. Emmetropization and refractive development is a feedback process in humans [5-9]. There is now considerable evidence showing that there is feedback control of emmetropization in humans and animals, and that refractive development can be manipulated experimentally [10].

Emmetropic or uncorrected eyes follow an exponential development of refractive error in humans. An exponential development is the response of a first-order feedback system to a constant-level step input signal [7]. If we can identify the input signal or stimulus, we can define the complete system by simple observation and Laplace transformation. The system transfer function is the ratio of the output and input in the s-domain. Such a transfer function will quantitatively model, not only the mechanism of emmetropization, but also the effect of lenses and lid suture.

The existence of an input signal is supported by the fact that the refraction of the eye is alterable with external stimuli, including lid suture [10,11,12,13]. Medina and Fariza [7] showed that corrective lenses applied to the eye are step input stimuli to the emmetropization system and that the response of a first order feedback system to an input determined by the power of the corrective lenses fits refraction data from ametropic subjects that wore those lenses.

The transfer function of the emmetropization system **F(s) = 1/(ks+1)** produces the observed output **o(t) = A** $\mathbf{e^{-t/k}}$ if a step input of value A is present. In this equation t represents time. The step input A is assumed to be close to the refractive error at birth while the final level the system seeks is around zero diopters, somewhat negative for those who develop myopia.

A system with transfer function **F(s) = 1/(ks+1)** can be represented as a feedback system of unitary feedback and forward function **G(s) = 1/ks**. The open loop transfer function of transfer function **F(s) = 1/(ks+1)** is therefore **G(s) = 1/ks**. Lid suture opens the feedback loop. The response of the open loop system to input A is a ramp whose slope is A divided by the time constant k as illustrated in Fig. 1 and derived in the Appendix. From [8], adapted for step input A.

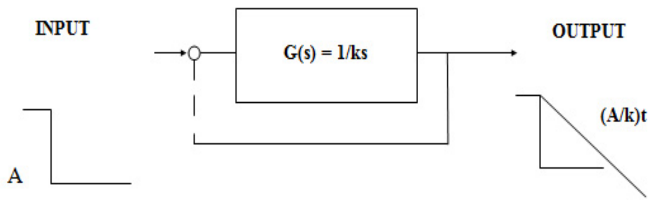

Figure 1. Open loop transfer function of the feedback system of transfer function 1/(ks+1). Broken lines denote the loop is open. This function models continuous correction or visual form deprivation (constant error). The variables are t, time and s, complex variable.

Medina [8] showed that myopes that are fully corrected continuously place the emmetropization feedback system in an open loop condition. Continuous correction alters the feedback loop rendering it inoperative. He also found that refractive data from the eyes of 13 myopic subjects followed straight lines with slope (R/k)t as predicted by the model, Fig. 2.

Conflict of interest: No conflicts declared.
*Corresponding Author: Antonio Medina, PhD. MultiVision Research, 1590 Adams Ave., Costa Mesa, CA 92628. Office: (714)-248-5689
E-mail: puerta@alum.mit.edu

Methods

The axial length of four macaque right eyes whose eyelids were sutured soon after birth was monitored. Suturing of the lids prevents the error detector from functioning by placing the feedback system in an open loop situation, similar to the continuously corrected myope. To test the hypothesis, we fitted with straight lines the axial length vs. age plots of these eyes. Axial length is proportional to refractive error [14]. Conventional lid-suture procedures were used [12]. Under anesthesia, cycloplegic refraction when eyes were open, and axial length were measured via retinoscopy with trial lenses and using a hand held acoustic transducer. Axial length was measured ultrasonographically with a Sonometrics A-scan digital Biometric Ruler. It was calibrated with a block of lucite of known dimensions and sound speed. The ultrasonic Crystal had a frequency of 15 MHz; the average speed of sound was set to 1545 m/s, corresponding to the speed in normal phakic eyes. From 10 to 20 measurements were obtained per eye and then averaged, allowing a repeatability of measurement within +/-0.2 mm.

Removable stitches were used so the lids could be opened at 6 month intervals, to verify ultrasound measurements with lids closed and degree of myopia. The axial length measurements were used for this report instead of the refractions because they were more frequent. The macaques were born with several diopters of hyperopia and developed myopia very quickly as previously reported [11, 12].

This study was approved by the institution review board. The experiments adhered to the EU Directive 2010/63/EU for animal experiments.

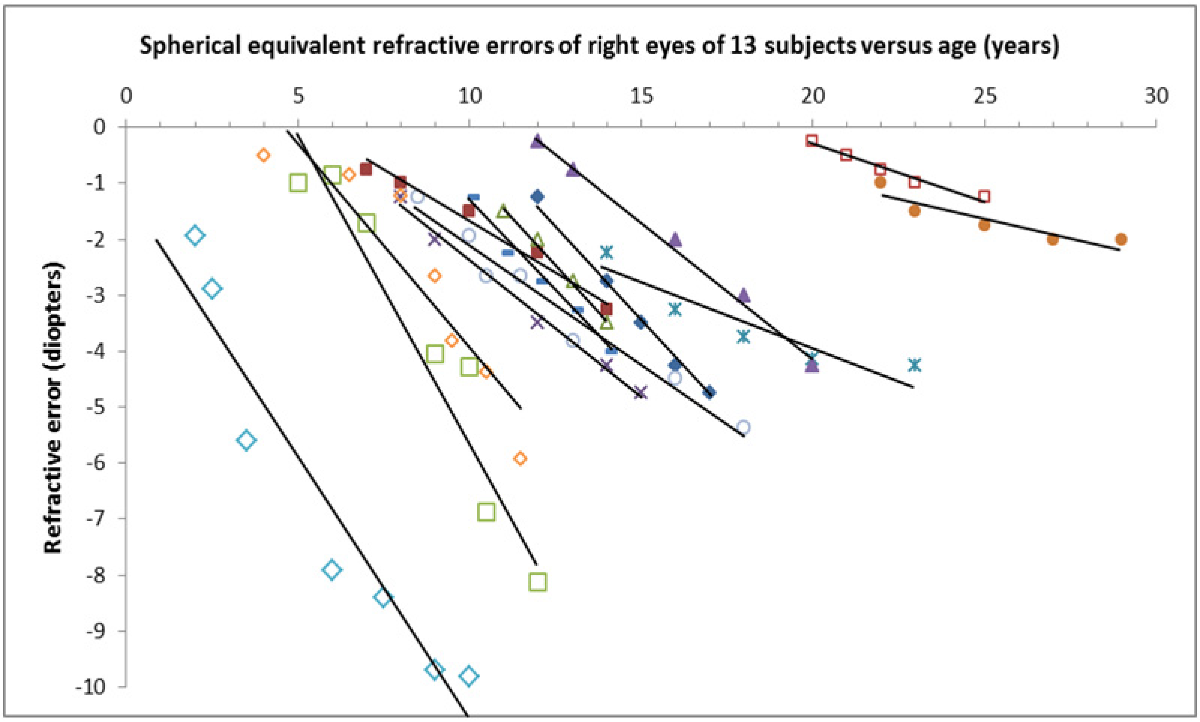

Figure 2. Refractive errors of right eyes of 13 myopic human subjects vs. age (symbols) and linear prediction of open loop system, solid lines, (from [8]).

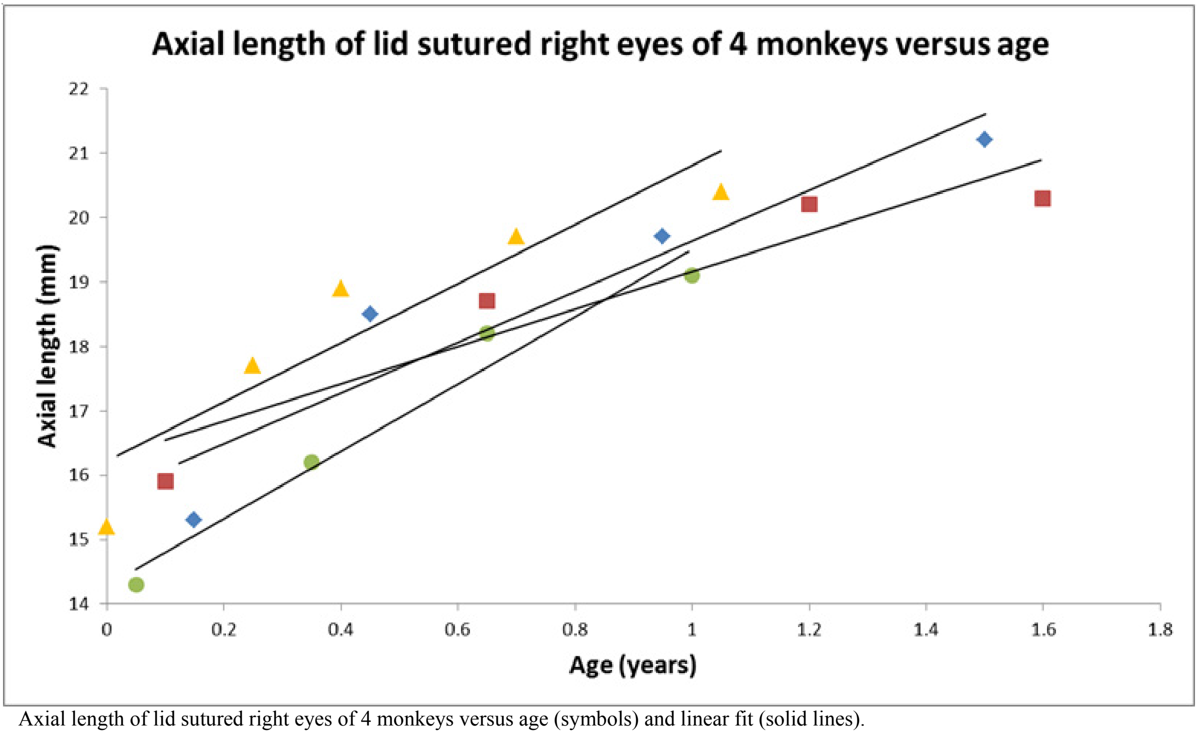

Figure 3. Axial length of lid sutured right eyes of 4 monkeys versus age (symbols) and linear fit (solid lines).

Results

A linear fit is a good approximation of the macaques' axial length vs. age plots. The Pearson correlation coefficient r ranges 0.93 to 0.98, with a mean $r = 0.94$, $p < 0.05$. See Fig. 3. The slopes range 3 to 5 mm/year, with an average slope of 4.2 mm/year. Since the axial length and refraction are strongly correlated this rate corresponds to -15.5 diopters/year based on a conversion factor of 3.7 diopters/mm [14].

Myopia progressed very quickly during eye suture. The last data points are under the straight line regressions for all monkeys, suggesting commence of saturation.

Discussion

We have applied the Laplace transformation to the refractive development of eyes experimentally manipulated. We find that the observed results agree with the predictions by a first-order feedback system.

The axial length and myopia progression of our macaques follow straight lines, the same as myopia progression in humans. Figs. 2 and 3.

We found in this study that the average rate of myopia progression in macaques is -15.5 diopters year, with a range of -11 to -40, while it was reported to be in the range of -0.2 to -1.0 in humans [8]. The feedback model predicts, and the results confirm that the myopia progression rate will be higher for lid sutured monkeys than for humans because this rate is determined by the slope of the straight lines predicted by the model. In humans this slope is **R/k**, while in monkeys it is **A/k**. A is the refraction at birth, which is usually greater than R, the uncorrected myopic end refraction.

The connection between progressive myopia and experimental myopia in animals is established and described by the same model. The model predicts a linear progression of myopia in both cases.

The feedback model does not account for stabilization. Linear progression of myopia cannot continue forever. There must be a limit or saturation of the physiological mechanism. We notice that our monkeys start to stabilize at about 6 to 12 months of age. This eventual stabilization is not contained in the model, but is observed in progressive human myopes [3,4,15] and lid-sutured monkeys [12]. The stabilization of myopia allows an exponential fit for myopia time course that includes progression and saturation, but lacks any feedback model support. While exponential functions may fit refractive development, our results suggest that a linear progression is the correct description for the progression of lid–suture myopia and corrected myopia prior to saturation.

Conclusions

Uncorrected primates, both macaques and humans, exhibit an exponential time course of their refractive error, however corrected subjects exhibit a linear time course. The effect of external manipulation on emmetropization, e.g., lid-suture and continuous correction with lenses, can be predicted from the feedback transfer function.

Lid-suture myopia and human myopia can be modeled as the response of the emmetropization system to an unnatural input. In both conditions the functional equivalent is the opening of the emmetropization feedback loop. Myopia progression is predicted by the feedback model and results from such conditions. The similarity between lid-suture and progressive myopia is clear when working in the s-domain.

The same linear progression outcome is predicted in both conditions based on the transfer function alone. The meaning of open loop in the temporal domain is that lid-suture and continuous correction of myopia maintain a steady stimulus that emmetropization will try to alter without success. Emmetropization efforts result in myopization with the only arrest provided by physiological limits saturating the process.

This study has potential implications for future study and clinical care. The model predicts a rapid myopia progression for primates (lid sutured monkeys and humans that develop myopia) with a short emmetropization time −the time it takes to reach emmetropia− because the magnitude of the myopia progression rate, or ramp slope, is inversely proportional to the emmetropization time constant k. Therefore a child who develops myopia at an early age will have a fast myopia progression and will likely end with high myopia. Similarly, a child with less hyperopia than the average is at greater risk for developing myopia sooner. This prediction of the feedback model has already been observed [16]. A practical application which deserves further research is the prediction that the use of corrective lenses increases the rate of myopia progression and possibly the final myopia, therefore indicating that correction of myopia should be delayed and substantially reduced. Such research is critically needed given the conflicting literature on the use of undercorrection [17] and the small amount of undercorrection tested in those studies. A further question for future research extending to emmetropia and spherical ametropia in general is whether subjects with the same constants A, R and k develop different refractive error if they are differently corrected for their present refractive error. Such research will elucidate the practice of correcting young subjects and ultimately the prevention of myopia.

Appendix

The Laplace transform of the step input i(t) = A is (Equation 1):

$$\mathbf{I(s) = A/s} \tag{1}$$

The output of the system in the s-domain is the input times the transfer function as shown in Equation 2 :

$$\mathbf{O(s) = I(s)G(s) = (A/s)(1/ks) = A/ks^2} \tag{2}$$

The output in the time domain is the inverse Laplace transform of the output in the s-domain. Equation 3 shows the inverse transform:

$$\mathbf{o(t) = L^{-1}\{ A/ks^2 \} = (A/k)t} \tag{3}$$

Acknowledgments

Partial funding for this work was provided by a NIH-NEI Research Grant.

[1] Vitale S, Sperduto RD, Ferris FL. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Arch Ophthalmol.*, 2009; 127:1632–1639.

[2] Congdon N, Wang Y, Song Y, et al. Visual disability, visual function, and myopia among rural Chinese secondary school children: the Xichang Pediatric Refractive Error Study (XPRES): report 1. *Invest Ophthalmol Vis Sci.*, 2008;49:2888–2894.

[3] Thorn F, Gwiazda J, Held R. Myopia Progression is specified by a double exponential growth function. *Optom Vis Sci.*, 2005;82:286-297.

[4] Bullimore MA, Jones LA, Moeschberger ML, Zadnik K, Payor RE. A retrospective study of myopia progression in adult contact lens wearers. *Invest Ophthalmol Vis Sci.*, 2002; 43:2110–2113.

[5] Medina A. A model for emmetropization: predicting the progression of ametropia. *Ophthalmologica*, 1987;194:133-139.

[6] Medina A. A model for emmetropization: The effect of corrective lenses. *Acta Ophthalmologica*, 1987;65:565-571.

[7] Medina A and Fariza E. Emmetropization as a First-Order Feedback System. *Vis. Res.*, 1993;33(21):21-26.

[8] Medina A. The Progression of Corrected Myopia. *Graefe's Arch. Clin. Exp. Ophthalmology*, 2015;253(7). DOI 10.1007/s00417-015-2991-5.

[9] Medina A. El Origen de las ametropias: Que es emetropia?. *Arch. Soc. Esp. Oftalmologia*, 1980;40(2):156-161.

[10] Meyer C, Mueller MF, Duncker GI and Meyer HG. Experimental animal models are applicable to human juvenile-onset Myopia. *Surv. Ophthalmol.*, 1999;4:93-102.

[11] Raviola E and Wiesel TN. An Animal Model of Myopia, *New England J. Med.*, 1985;312(25):1609-1615.

[12] Greene PR and Guyton DL. Time Course of Rhesus Lid-Suture Myopia. *Exp. Eye Res.*, 1986;42:529-534.

[13] Hoyt CS, Stone RD, Fromer C, and Billson FA. Monocular axial myopia associated with neonatal eyelid closure in human infants. *Am. J. Ophthalmol.*, 1981;9:197-200.

[14] Greene PR. Optical constants and dimensions for the myopic, hyperopic, and normal rhesus eye. *Exp. Eye Res.*, 1990; 51:351-360.

[15] The COMET Group. Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). *Invest Ophthalmol Vis Sci.*, 2013;54:7871–7883.

[16] Zadnik K, Sinnott LT, Cotter SA, Jones-Jordan LA, Kleinstein RN, Manny RE, Twelker JD, Mutti DO for the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study Group. Prediction of Juvenile-Onset Myopia. *JAMA Ophthalmol*. 2015; DOI:10.1001/jamaophthalmol.2015.0471.

[17] Goss DA. Effect of spectacle correction on the progression of myopia in children-a literature review. *J Am Optom Assoc.*, 1994;65(2):117-28.