Bi-exponential description for different forms of refractive development

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It was recently established that the axial power, the refractive power required by the eye for a sharp retinal image in an eye of a certain axial length, and the total refractive power of the eye may both be described by a bi-exponential function as a function of age (Rozema, 2023). Inspired by this result, this work explores whether these bi-exponential functions are able to simulate the various known courses of refractive development described in the literature, such as instant emmetropization, persistent hypermetropia, developing hypermetropia, myopia, instant homeostasis, modulated development, or emmetropizing hypermetropes. Moreover, the equations can be adjusted to match the refractive development of school-age myopia and pseudophakia up to the age of 20 years. All of these courses closely resemble those reported in the previous literature while simultaneously providing estimates for the underlying changes in axial and whole eye power.

Introduction

The human eye undergoes an intricate refractive development between infancy and adolescence, culminating in the achievement and preservation of a sharp retinal image while the eye grows (Rozema, 2023; Rozema, Dankert, & Iribarren, 2023; Wood, Hodi, & Morgan, 1995). Refractive development occurs fastest during the first two years of life when the eye grows fastest (Mutti et al., 2005; Pennie, Wood, Olsen, White, & Charman, 2001; Rozema, 2023) by varying the growth rates of the different ocular components (Ehrlich et al., 1997; Mutti, 2007; Mutti et al., 2018; Pennie et al., 2001). At birth, the eye is typically hypermetropic (Edwards, 1991; Pennie et al., 2001; Wood et al., 1995), which gradually decreases through emmetropization, a continuous dynamic process that aims to fine-tune the refractive state of the eye to reach a sharp image on the retina (Pennie et al., 2001; Rozema et al., 2023). Although many factors contribute to emmetropization, it can be described in its most basic form as a fine-tuning of the axial length and the total optical power of the eye through coordinated growth to minimize spherical refractive errors (Rozema et al., 2023). However, emmetropia cannot always be achieved, as refractive development may be influenced by genetic, environmental, and lifestyle factors (Morgan & Rose, 2005). Several descriptive studies have explored early eye development and its underlying biometric changes, most notably Mutti and colleagues (2018), who examined individual ocular biometric parameters between infancy and early school age. Based in part on those works, a model was recently developed that describes the growth of refractive and biometric factors of the eye from before birth until adulthood as a bi-exponential function, a sum of two exponential functions (Rozema, 2023). These functions correspond with the two phases of ocular growth: genetically preprogrammed prenatal growth (or scaled growth) and postnatal coordinated growth. Inspired by this descriptive model, current work investigates the function of the different coefficients of the bi-exponential functions and whether these functions can be used to describe various healthy and pathological refractive development courses known from the literature.

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Methods

Model

The eye can be described as a simplified optical system that must balance two components: the axial length of the eye, here expressed in diopters as P_{ax} (or *axial power*), and the total refractive power of the eye, P_{eye}, consisting of the combined powers of the cornea and lens. These two parameters represent the power that the eye requires for a sharp retinal image and the power that the ocular optics can provide, respectively. Any difference between them would then correspond with the spherical refractive error S:

$$S = P_{ax} - P_{eye} \quad (1)$$

Consequently, the values of P_{ax} and P_{eye} must remain close to one another for the best chance of successful emmetropization.

Recently, it was established (Rozema, 2023) that, like most ocular parameters, P_{ax} and P_{eye} may be described by the following bi-exponential functions as a function of time t (age in years):

$$\begin{cases} P_{ax}(t) = a_0 + a_1 e^{a_2 t} + a_3 e^{a_4 t} \\ P_{eye}(t) = a_5 + a_6 e^{a_7 t} + a_8 e^{a_9 t} \end{cases} \quad (2)$$

where $a_0, \ldots, a_9$ are the model coefficients. Equation 2 corresponds to the fast initial scaled growth phase before and short after birth when retinal feedback is not yet active, followed by a second, slower growth phase during which the feedback controls (part of) the growth. As Equation 2 is purely descriptive, no interaction is assumed between P_{ax} and P_{eye}.

Note that, although most biometric parameters of the eye can be described by a bi-exponential function, refractive error S is a notable exception, as it displays more complicated, somewhat oscillating behavior (Rozema, 2023; Rozema et al., 2023). Hence, it was modeled by combining Equations 1 and 2, thus representing the relationship among all three parameters using a total of 10 coefficients a_i. These coefficients can be adjusted to match various courses of refractive development based on the literature (Jones et al., 2005; Mutti et al., 2018; Pennie et al., 2001), as well as those of pathologies such as school-age myopia and infant pseudophakia.

To simulate the sudden onset of school-age myopia, coefficients a_3 and a_7 were modulated by a Gompertz function (Gompertz, 1825), an asymmetric sigmoid function used for this purpose before in the literature (Thorn, Gwiazda, & Held, 2005):

$$\begin{cases} P_{ax}(t) = a_0 + a_1 e^{a_2 t} + a_3 (1 + G(t)) e^{a_4 t} \\ P_{eye}(t) = a_5 + a_6 e^{a_7 t} + a_8 (1 + G(t)) e^{a_9 t} \end{cases} \quad (3)$$

where $G(t) = \exp[-\exp(0.5 - 5 \cdot t)]$.

Courses of refractive development

Longitudinal refractive data from prior studies (Jones et al., 2005; Mutti et al., 2018; Pennie et al., 2001) demonstrate that there are several distinct courses in refractive development, ranging from normal to high hypermetropia or early myopia. Considering cycloplegic refractive errors, the following courses of refractive development can be identified:

1. *Modulated development*—At birth, the eye has a refractive error of about +2.5 diopters (D) and becomes more hypermetropic until a maximum value is reached at the age of 3 months. In the following months, the eye emmetropizes toward +1D, when the refractive error stabilizes under continued eye growth (Mutti et al., 2018; Pennie et al., 2001). The overall development displays the wavy behavior (Medina, 1980; Mutti et al., 2018) that gives it its name.
2. *Instant emmetropization*—The maximum hypermetropic refractive error is reached at birth, and the eye begins emmetropizing immediately, followed by homeostasis.
3. *Instant homeostasis*—The eye is born with a refractive error near +1D, negating the need for emmetropization, and immediately goes into homeostasis.(Mutti et al., 2018; Pennie et al., 2001; Rozema et al., 2023)
4. *Emmetropizing hyperopia*—This is similar to modulated development, but here emmetropization takes several years rather than 1 year.
5. *Persistent hypermetropia*—The eye is hypermetropic at birth and remains so over time.
6. *Developing hypermetropia*—The eye emmetropizes normally but gradually becomes hypermetropic with age.
7. *Infant myopia*—Although rare, some eyes are born with mild myopia. Although in some cases this myopia may emmetropize during the first year of life (Wood et al., 1995), this generally leads to high levels of myopia later on. This is seen in, for example, severely premature infants (Fledelius, 1996).
8. *School-age myopia*—The eye emmetropizes but gradually becomes myopic with age due to a combination of genetic, behavioral, and environmental factors affecting axial growth (Lingham, Mackey, Lucas, & Yazar, 2019;

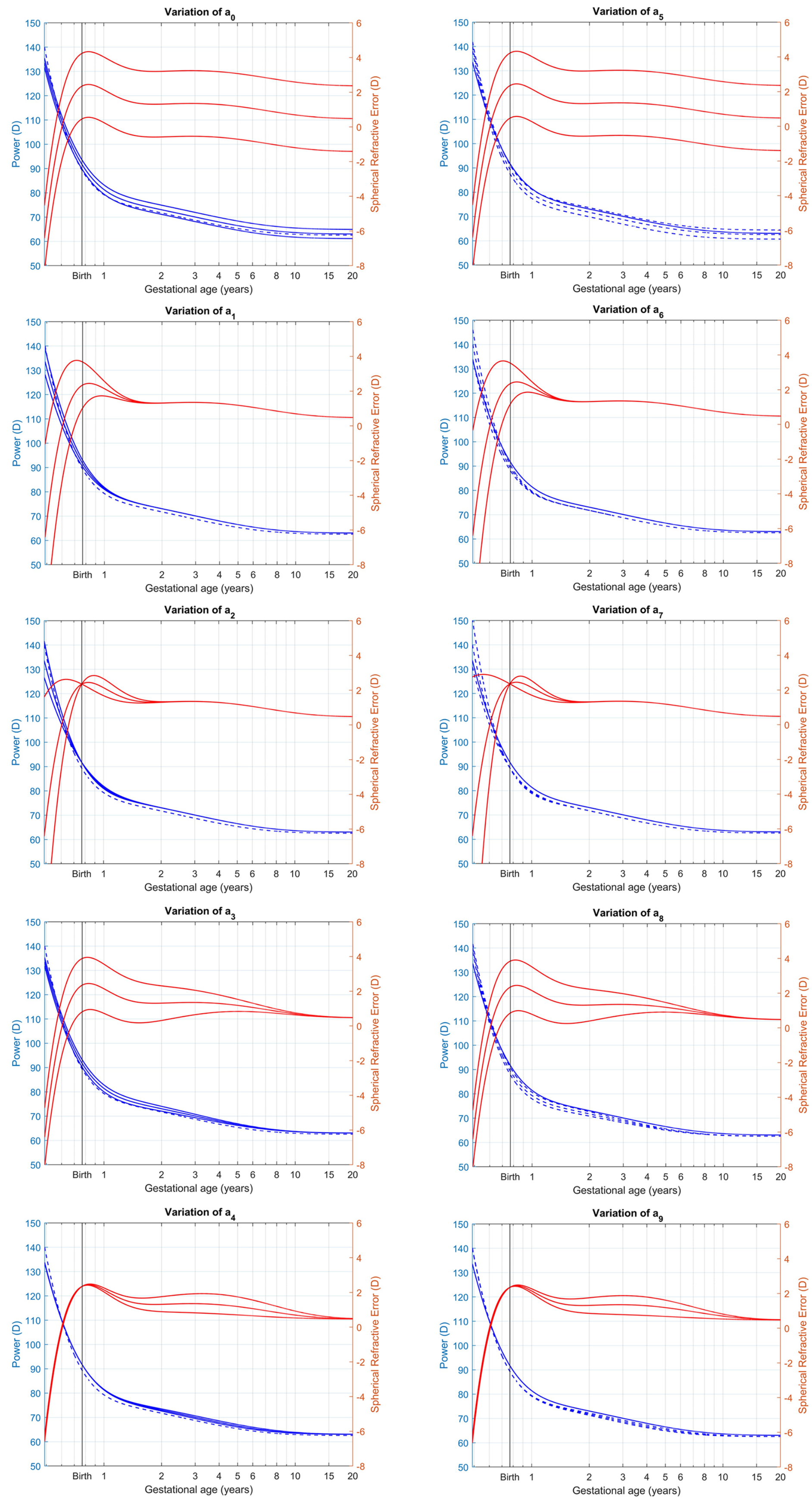


Figure 1. Influence of individual a_i parameters on *S* (red), axial (blue), and optical power (dashed blue). Middle red and blue lines correspond with the model from Rozema (2023).

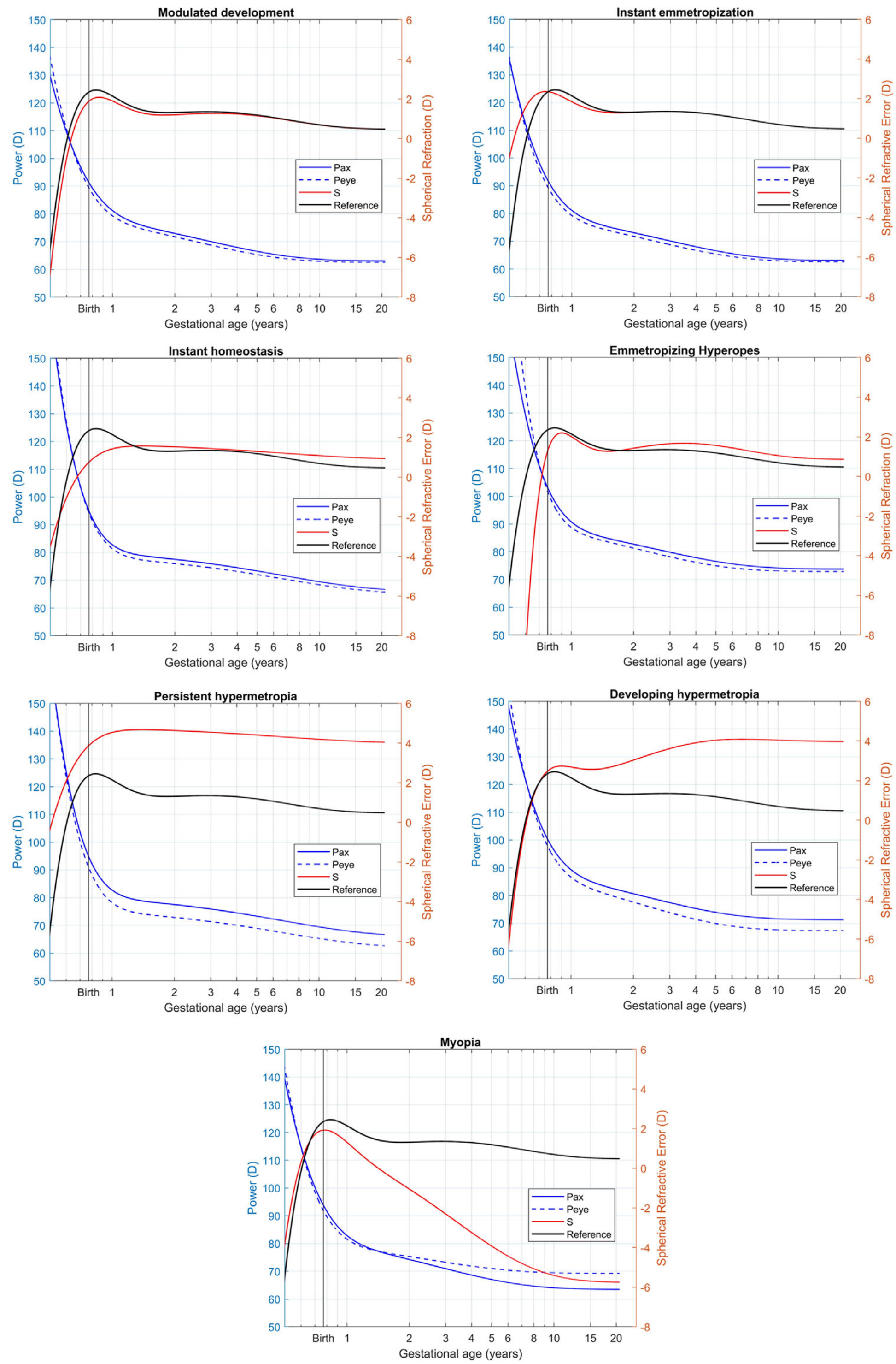


Figure 2. Simulated refractive development courses. The black line represents the references based on Rozema (2023).

Morgan et al., 2018; Rozema et al., 2023; Troilo et al., 2019). This case requires Equation 3.

9. *Infant pseudophakia*—Infants with congenital cataract must be treated at the earliest possible age to avoid negatively affecting their refractive development. Often such eyes are implanted with an intraocular lens. As such a lens has a fixed power, it hinders normal refractive development, leading to high myopia (Chan, Wong, Lam, & Yam, 2023; Hoevenaars, Polling, & Wolfs, 2010; McClatchey et al., 2000). This pathological course of development was added to test the

limits of what the bi-exponential description can handle.

Comparison with literature

Jones et al. (2005) published ocular component growth curves for emmetropes, emmetropizing hyperopes, persistent hyperopes, and myopes based on statistical fits for each ocular biometry variable as a function of age (Supplementary Material). These can be used to estimate the axial and whole eye power (Rozema, 2021) for comparison with the bi-exponential functions.

Results

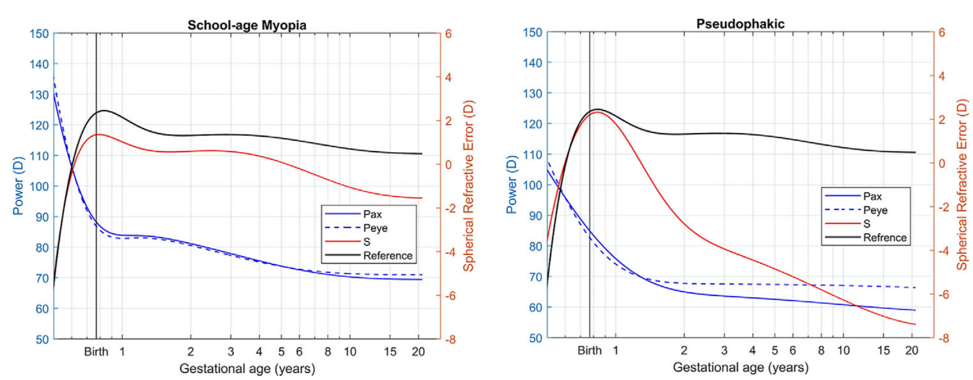
Influence of a_i parameter variations

To investigate the influence of the individual a_i coefficients on spherical refractive error S and the axial and ocular powers, each was varied by a certain percentage (a_0 and a_5 by ±3% and all others by ±10%) (Figure 1). Due to the symmetry in Equation 2, coefficients should be considered in pairs that affect the curves of P_{ax} and P_{eye}, respectively:

1. a_0 and a_5—The initial values of the axial and ocular powers; variations cause a vertical shift of the graphs.
2. a_1 and a_6—Amplitude of the axial and ocular powers during the scaled eye growth; lower values correspond with excessive eye growth, causing the focal point of the image to fall in front of the retina and resulting in myopia.
3. a_2 and a_7—Dampening of the scaled eye growth; these parameters determine the time scale over which this phase remains active and play a critical role in shaping the initial development.
4. a_3 and a_8—Amplitude of the axial and ocular powers during the coordinated eye growth, which is linked to the strength of the retinal feedback mechanism.
5. a_4 and a_9—Dampening of the coordinated eye growth; this determines the time scale over which the retinal feedback remains active but does not seem to affect the final refractive error.

Parameter	a_0	a_1	a_2	a_3	a_4	a_5	a_6	a_7	a_8	a_9
Modulated development	63.02	13.00	−4.98	15.20	−0.35	62.57	11.82	−5.85	14.96	−0.39
Instant emmetropization	63.04	13.29	−5.30	15.37	−0.35	62.57	11.82	−5.85	14.96	−0.39
Instant homeostasis	66.00	15.10	−6.50	13.84	−0.15	65.10	16.00	−6.50	13.08	−0.15
Emmetropizing hyperopes	73.77	14.78	−5.91	14.51	−0.40	72.90	13.90	−7.50	14.96	−0.50
Persistent hypermetropia	66.00	15.10	−6.50	13.84	−0.15	62.00	16.00	−6.50	13.08	−0.15
Developing hypermetropia	71.30	13.41	−5.50	15.68	−0.42	67.32	12.44	−6.21	18.15	−0.46
Myopia	63.50	13.41	−5.38	16.88	−0.37	69.26	12.54	−5.97	10.07	−0.42
School myopia	69.42	15.4	−5.07	17.57	−0.33	71	12.77	−5.99	16.05	−0.42
Pseudophakia	58.04	20	−2.55	6.84	−0.1	61	15	−3.7	6.68	−0.01
Reference (Rozema, 2023)	63.04	13.29	−4.98	15.37	−0.35	62.57	11.82	−5.84	14.96	−0.39

Table 1. Parameters required to simulate the above refractive development courses.



(A) (B)

Figure 3. Simulation of refractive development for school-age myopia (**A**) and pseudophakic eye (**B**) with the underlying changes in P_{ax} and P_{eye}.

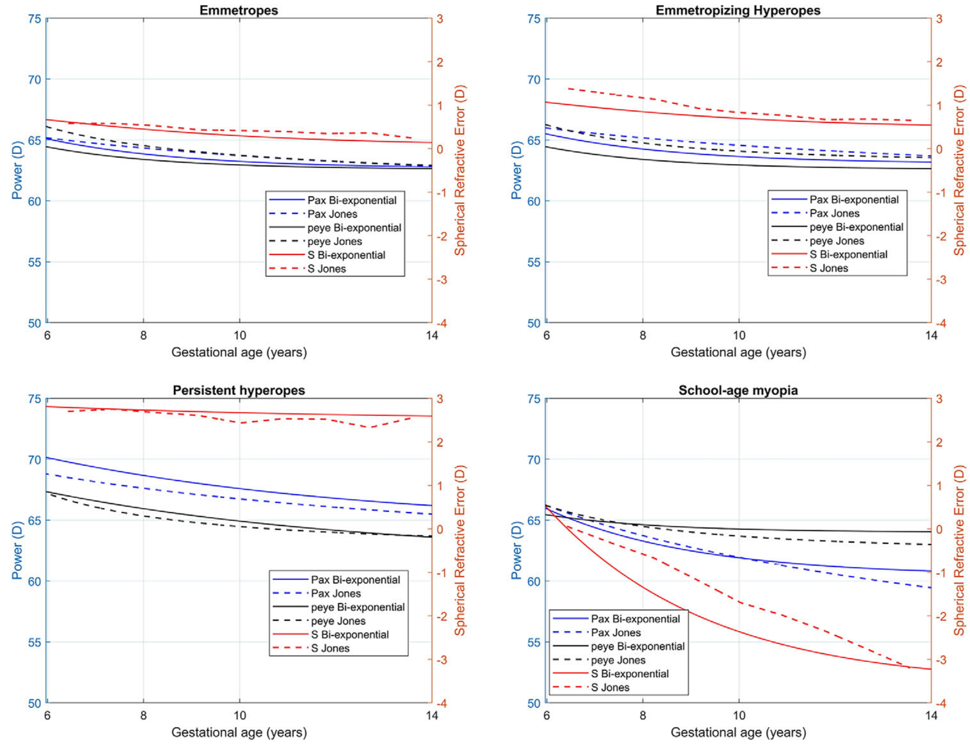


Figure 4. Comparison among four refractive development courses adapted from Jones et al. (2005) alongside their underlying changes in P_{ax} and P_{eye} with the results of bi-exponential function.

Simulation of normal refractive development courses

By making different combinations of the a_i coefficients, Equation 2 can simulate all forms of refractive development listed above. Examples of the changes in S, P_{ax}, and P_{eye} are shown in Figure 2, and the corresponding values for the a_i coefficients are provided in Table 1. The coefficient values for the population average are provided as a reference (Rozema, 2023). Equation 2 can also be adjusted to show the refractive development of pseudophakia and, with a small adjustment using Equation 3, school-age myopia (Figure 3). All of these courses closely resemble those reported in the previous literature.

Comparison with literature

Comparing the four refractive development groups identified by Jones et al. (2005) for ages between 6 and 14 years with the bi-exponential functions, it can be seen that both behave similarly for axial and optical powers, as well as spherical refractive error (Figure 4).

Discussion

This paper has explored how the coefficients of the bi-exponential growth functions can be used to successfully reproduce various courses of refractive development for emmetropic and ametropic eyes found in the literature (Figure 2), as well as pathological refractive developments, such as infant pseudophakia and school-age myopia (Figure 3). Consistent with previous literature (Chan et al., 2023), congenital cataract produced myopic shifts in pseudophakic eyes, indicating a greater risk of myopia due to the presence of the intraocular lens.

The bi-exponential description also reproduced the refractive development courses reported by Jones et al. (2005) for four refractive categories of children ages 6 to 14 years (Figure 4). In addition to reproducing the literature, these simulations also estimated the changes in P_{ax} and P_{eye} underlying the changes in refractive error. This is a distinct advantage over a simple description of the refractive error alone, especially given the observation by Benjamin, Davey, Sheridan, Sorsby, and Tanner (1957) that there is a considerable overlap between the ocular biometry values of emmetropes and ametropes between ±4D. It is therefore important to determine the underlying mismatch in ocular biometry, expressed as P_{ax} and P_{eye}, when trying to understand the origin of a refractive error.

Although bi-exponential growth functions provide a good description of the evolution of axial and whole eye power over time, these functions could conceivably be adapted further by considering the mutual influence between P_{ax} and P_{eye}, as well as the influence of external factors. Although the current model assumes independence between both parameters, real refractive development consists of intricate interactions between the optical and sensory components of the eye, crucial for achieving emmetropization. Such models were developed earlier by Medina (2022) and Medina and Fariza (1993), who described refractive error without intervention and a single exponential function, as well as by Hung and Ciuffreda (2000), who combined refractive error, axial length, and various scleral factors.

In conclusion, this work demonstrates the viability of bi-exponential functions to simulate diverse refractive development courses and offers insights into their differences. This research forms a foundation for future investigations into the complex interplay between ocular parameters during eye growth. Potential applications of the proposed descriptions may be the analysis of the refractive development profiles of individual eyes.

Keywords: bi-exponential function, refractive development, school-age myopia, pseudophakia

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