UNDERSTANDING THE SPREAD OF COLOR BLINDNESS VIA POPULATION GENETICS MODEL

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Abstract. Color blindness is a lifelong disease caused by damage to the eye's nerve cells' pigment that reacts to color and light. As a result, a person suffering from this disease will have difficulty distinguishing specific or all colors. Although only a small number of people suffer from this disease, and it does not harm the sufferers, this disease can interfere with their daily activities. Interestingly, the proportion of color-blind people varies by ethnicity, geographic area, and gender. We construct a mathematical model to understand population dynamics in the spread of genetic-based color blindness with a particular concern of gender factors, involving a random mating process between men and women. The stability of the equilibrium point is analyzed in detail, and the model's suitability with the Hardy-Weinberg equilibrium principle is examined. We found that the proportion of color-blind people in the future (equilibrium) depends on the initial conditions of the population and is more sensitive to the initial condition of the color blind women than that in men or carrier women. Furthermore, we also found that the ratio of color blindness in men is constantly higher than in women. Finally, the numerical simulations of data in Korea and Northern European countries are presented to confirm our analytical results.

Keywords: color blindness; mathematical model; dynamical population; mathematical genetics.

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1. INTRODUCTION

In the human eye, there are rods and cones that function to receive visual signals. The part that is most sensitive to light is the rods. Meanwhile, the cone part plays a role in conveying color information in the form of a signal that is passed in the retina and then reaches the lateral geniculate nucleus (LGN) [1]. Insights into the structural features of these rods and cones have been studied in molecular genetics. Human vision consists of three classes of spectrally different photoreceptor cells cone, known as trichromatic. Each cone class classifies a different part of the spectrum: red or long-wave sensitive (LWS), green or medium-wave sensitive (MWS), and blue or short-wave sensitive (SWS) [2]. Isolated cone photoreceptor dysfunction can cause vision loss known as achromatopsia which is a type of color blindness desease [3]. In general, color blindness which is also known as color vision deficiency, is a lifelong disease caused by damage to the pigment in the eye's nerve cells that react to color and light. This condition causes the sufferer not to be able to see a color properly [4]. The cell damage occurs because of an abnormality in the X chromosome inherited from parents to their offspring. In addition, it is also known that inherited color vision deficiencies are caused by the rearrangement of genes that arise through unequal homologous recombination in women during the meiosis event [5, 6, 7, 8].

Even though only a small number of people suffer from this deficiency and it may not risk their health, color blindness might still affect their lives. Interestingly, the proportion of color blind people varies across different ethnicities, geographical areas, and sexes. For example, the prevalence for the red-green color blindness, which is the most common form of color blindness [8], is about 8% in men and 0.4% in women of the European Caucasian population [9, 10, 11, 12], about 4% to 6.5% in Chinese men and 0.4% to 1.7% in Chinese women [13, 14], about 4% to 6.85% in Japanese men [15], and about 6% to 7.2% for African-American which has risen possibly due to intermarriages [16, 17]. A complete review of the prevalence of the color deficiency population is discussed in [18]. This raises some intriguing questions, e.g., how color blindness spreads in a population, why the proportion of color blind people in some populations is higher than in others, and how the composition of the normal and color blind people and their genetic makeup vary in the population.

The genetic characteristics in a population can be modeled via a continuous approach. This approach was pioneered by Fisher [19], Wright [20], Crow and Kimura [21]. Since then, numerous works have been dedicated to describe various phenomena of genetic characteristics in population, for example, [22, 23, 24, 25]. In [22], James F. Selgrade and Gene Namkoong modeled competition between two species involving genetic variation factors with a system of differential equations. They present an analytical study of the stability of the polymorphic and monomorphic equilibrium associated with the extinction of a species. A more general study of the mathematical concept of genetics can be found in [23], where the construction of the mathematical model involves Mendel's theory of inheritance. This encourages the involvement of random mating factors, selection factors, and gene classification at a particular locus. The cases studied there are general cases for diploid species at one locus and multiple loci.

Genetic mathematical modeling is indeed limited in its use. However, in modern population genetics, genetic analysis plays an essential role in anticipating and controlling the condition of genetic frequency distribution in the next generation, for example, to look at the genetic distribution of insecticide resistance in mosquitoes from generation to generation [24, 26]. Recently, mathematical modeling has also been applied to investigate the spread of X-linked recessive diseases in a population using a discrete approach [27] and a continuous approach [28]. Some X-linked recessive diseases are red-green color blindness, which is the topic of this paper, hemophilia, and Duchenne/Becker muscular dystrophy. In the discrete approach [27], they assume that the diseases rarely affect the women, and hence the affected women sub-population is neglected in the model. For color blindness, however, the existence of affected women (color blind women) cannot be neglected since they can be born from color blind fathers and color blind mothers or carrier mothers. In the continuous approach [28], the affected women sub-population was then taken into account in the model as well.

In this work, we construct a mathematical model to describe the dynamics of color blindness in the population. The model is generally similar to that developed in [28], except that we take the natural mortality into account and exclude the spontaneous genetic mutation factor. Although our model is simple, it turns out that the model is hard to analyze. Utilizing the Hardy-Weinberg principle, we found that the proportion of people with color blindness at the

equilibrium depends on their initial proportion in the population, and is more sensitive to the initial condition of the color blind in women than that in men or carrier women. As a result, we could determine in what condition color blindness will dominate the population. Using this information, we may control the spread of color blindness by intervening in the proportion of the population. In addition, we also found that the ratio of color blindness in men is constantly higher than in women. Finally, we apply our model using available data to describe color blindness in some Northern European countries and the Republic of Korea. We found that higher initial color blindness in one area does not necessarily result in higher color blindness at equilibrium conditions. With these results, our work will complement the existing literature to study the dynamics of X-linked recessive diseases, specifically on the spread of color blindness in the population.

2. Mathematical Model of Colorblinds in Population

2.1. Mendel's segregation law. Normal humans have 23 pairs of chromosomes, of which 22 homologous pairs are called autosomes, while the other pairs are called sex chromosomes. A woman has a pair of XX chromosomes, and a man has a pair of XY chromosomes. If both X chromosomes of a woman are chromosome carrying the gene for color blindness, she will be color blind; but if only one of her X chromosomes is chromosome carrying the gene for color blindness, she will be a carrier. On the other hand, if a male has chromosome carrying the gene for color blindness, he will be color blind [8, 29, 30].

Consider a population that consists of normal men and women, color blind men and women, and carrier women. Suppose that the X-chromosome responsible for the color deficiency is denoted by X^c. Thus, normal women will have genotype XX, color blind women will have genotype $X^c X^c$, carrier women will have genotype XX^c, normal men will have genotype XY, and color blind men will have genotype $X^c Y$. Based on Mendel's law of segregation [31], the results of random mating in the population is given in the Punnett Square table in Table 1. As can be observed from the table, normal parents will produce normal offspring (green cells), while color blind parents will produce color blind offspring (gray cells). However, if the mother is color blind whereas the father is normal, their sons will be color blind, and their daughters

will be carriers. On the contrary, if the mother is normal but the father is color blind, their sons will be normal, but the daughters will be carriers.

TABLE 1. Punnett square to describe possibility for color blindness. Here the different parent pairs and their offspring are illustrated; the top row shows the three different female types that can mate with two different male types (shown in the first column).

♂ × ♀		XX		XXᶜ		XᶜXᶜ	
		X	X	X	Xᶜ	Xᶜ	Xᶜ
XY	X	XX	XX	XX	XXᶜ	XXᶜ	XXᶜ
	Y	XY	XY	XY	XᶜY	XᶜY	XᶜY
XᶜY	Xᶜ	XXᶜ	XXᶜ	XXᶜ	XᶜXᶜ	XᶜXᶜ	XᶜXᶜ
	Y	XY	XY	XY	XᶜY	XᶜY	XᶜY

2.2. Mathematical model.

Let W_n denotes the number of normal women XX, W_b the number of color blind women X^cX^c, W_c the number of carrier women XX^c, M_n the number of normal men XY, and M_b the number of color blind men X^cY in the population. These variables are listed in Table 2.

TABLE 2. Variables notation and their interpretation.

Notation	Interpretation
W_n & w_n	Number & proportion of normal females, respectively
W_b & w_b	Number & proportion of color blind females, respectively
W_c & w_c	Number & proportion of carrier females, respectively
M_n & m_n	Number & proportion of normal males, respectively
M_b & m_b	Number & proportion of color blind males, respectively

Consider the sub-population of the normal female, XX. From Table 1, we observe that the sub-population XX may increase due to the mating between XX and XY and also between XX^c

and XY. Since the probability that a normal male produces gametes X is half, then half of the sub-population XY contributes to the increase of the sub-population XX. The same thing also applies to the sub-population XX^c.

If we assume that the number of men and women in the population is equal, then the rate at which the sub-population XX increases due to the mating between normal men XY and normal women XX is

$$
\underbrace{\frac{M_n/2}{(W_n + W_b + W_c + M_n + M_b)/2}}_{\substack{\text{probability of 1 female XX to mate 1 male XY,} \\ \text{equal to the ratio of male XYs and total men (half of population)}}} \times \underbrace{W_n}_{\text{number of normal female XX}},
$$

and due to the mating between normal men XY and carrier women XX^c is

$$
\frac{M_n/2}{(W_n + W_b + W_c + M_n + M_b)/2} \times \frac{W_c}{2}.
$$

Thus, the number of births of the XX sub-population per unit time Δt is:

$$
W_n(t + \Delta t) \approx W_n(t) + \Delta t \frac{2\alpha}{N(t)} \left(\frac{1}{2} W_n(t) M_n(t) + \frac{1}{4} W_c(t) M_n(t) \right),
$$

where $N = W_n + W_b + W_c + M_n + M_b$ is the total population and α is the intrinsic growth rate of the population.

Using the same argument for the other sub-populations and involving the natural mortality rate of each sub-population, after limiting the time series under $\Delta t \to 0$, we arrive at a model

$$
\begin{aligned}
\frac{dW_n}{dt} &= \frac{2\alpha}{N} \left(\frac{1}{2} W_n M_n + \frac{1}{4} W_c M_n \right) - \delta W_n, \\
\frac{dW_b}{dt} &= \frac{2\alpha}{N} \left(\frac{1}{4} W_c M_b + \frac{1}{2} W_b M_b \right) - \delta W_b, \\
\frac{dW_c}{dt} &= \frac{2\alpha}{N} \left(\frac{1}{4} W_c M_n + \frac{1}{2} W_b M_n + \frac{1}{2} W_n M_b + \frac{1}{4} W_c M_b \right) - \delta W_c, \\
\frac{dM_n}{dt} &= \frac{2\alpha}{N} \left(\frac{1}{2} W_n M_n + \frac{1}{4} W_c M_n + \frac{1}{2} W_n M_b + \frac{1}{4} W_c M_b \right) - \delta M_n, \\
\frac{dM_b}{dt} &= \frac{2\alpha}{N} \left(\frac{1}{4} W_c M_n + \frac{1}{2} W_b M_n + \frac{1}{4} W_c M_b + \frac{1}{2} W_b M_b \right) - \delta M_b.
\end{aligned}
\tag{1}
$$

where δ is the natural death rate. By adding all equations in (1), we have:

$$
\frac{dN}{dt} = \left(\frac{\alpha}{2} - \delta \right) N.
\tag{2}
$$

Notice that since the factors that are involved in the model are only birth and death, in this case, we have a Malthusian model that may be valid for a short period of time. Nevertheless, we will show that even with this model, we still gain some important insight in the dynamics of color blindness.

To simplify our observation, we scale each sub-population to the total population, N. Thus,

$$w_i(t) = \frac{W_i(t)}{N(t)} \text{ for } i = n, b, c.$$

(3)
$$m_j(t) = \frac{M_j(t)}{N(t)} \text{ for } j = n, b.$$

where w_i denotes the proportion of the sub-population W_i and m_j denotes the proportion of the sub-population M_j. Thus, for example,

$$\frac{dw_n}{dt} = \frac{1}{N^2}\left(\frac{dW_n}{dt}N - W_n\frac{dN}{dt}\right)$$

$$= \frac{1}{N^2}\left(\left[\frac{2\alpha}{N}\left(\frac{1}{2}W_nM_n + \frac{1}{4}W_cM_n\right) - \delta W_n\right]N - W_n\left(\frac{\alpha}{2} - \delta\right)N\right)$$

$$= 2\alpha\left(\frac{1}{2}w_nm_n + \frac{1}{4}w_cm_n\right) - \delta w_n - \frac{\alpha}{2}w_n + \delta w_n$$

(4)
$$= 2\alpha\left(\frac{1}{2}w_nm_n + \frac{1}{4}w_cm_n - \frac{1}{4}w_n\right)$$

Therefore, system (1) turns into

$$\frac{dw_n}{dt} = 2\alpha\left(\frac{1}{2}w_nm_n + \frac{1}{4}w_cm_n - \frac{1}{4}w_n\right),$$

$$\frac{dw_b}{dt} = 2\alpha\left(\frac{1}{4}w_cm_b + \frac{1}{2}w_bm_b - \frac{1}{4}w_b\right),$$

(5)
$$\frac{dw_c}{dt} = 2\alpha\left(\frac{1}{4}w_cm_n + \frac{1}{2}w_bm_n + \frac{1}{2}w_nm_b + \frac{1}{4}w_cm_b - \frac{1}{4}w_c\right),$$

$$\frac{dm_n}{dt} = 2\alpha\left(\frac{1}{2}w_nm_n + \frac{1}{4}w_cm_n + \frac{1}{2}w_nm_b + \frac{1}{4}w_cm_b - \frac{1}{4}m_n\right),$$

$$\frac{dm_b}{dt} = 2\alpha\left(\frac{1}{4}w_cm_n + \frac{1}{2}w_bm_n + \frac{1}{4}w_cm_b + \frac{1}{2}w_bm_b - \frac{1}{4}m_b\right).$$

Since we assume that the number of men and women are equal, i.e., $w_n + w_b + w_c = m_n + m_b = 1/2$, then

$$w_c = \frac{1}{2} - w_n - w_b,$$

(6)
$$m_n = \frac{1}{2} - m_b.$$

As a result, the model can be reduced to a three-dimensional system of ordinary differential equations, namely

$$\frac{dw_n}{dt} = \frac{\alpha}{2}\left(\frac{1}{4} - \frac{1}{2}[w_n + w_b + m_b] - w_n m_b + w_b m_b\right),$$

(7)
$$\frac{dw_b}{dt} = \frac{\alpha}{2}\left(\frac{m_b}{2} - w_b + w_b m_b - w_n m_b\right),$$

$$\frac{dm_b}{dt} = \frac{\alpha}{2}\left(\frac{1}{4} - \frac{1}{2}[w_n - w_b] - m_b\right).$$

Notice that using the time scaling

(8)
$$\tilde{t} = \frac{\alpha t}{2},$$

the factor $\alpha/2$ on the right-hand side of system (7) can be removed. Thus, the factor α only stretches or shrinks the dynamics of the model.

2.3. Equilibrium points and their stability. System (7) has an equilibrium point

(9)
$$\left(w_n^\infty, w_b^\infty, m_b^\infty\right) = \left(2\left(m_b^\infty\right)^2 - 2m_b^\infty + \frac{1}{2}, 2\left(m_b^\infty\right)^2, m_b^\infty\right),$$

which implies the dependency on the value of the color blind men proportion at the steady-state condition. If we let $m_b^\infty = u$, and noticing (6), the equilibrium point above can be rewritten as

(10)
$$\left(w_n^\infty, w_b^\infty, m_b^\infty\right) = \left(2u^2 - 2u + \frac{1}{2}, 2u^2, u\right),$$

where u is an arbitrary constant with $0 \le u \le \frac{1}{2}$. Therefore, model (7) has infinitely many equilibrium points that do not depend on the model's parameters, which makes the model's analysis not trivial. From local stability analysis, we found the eigenvalues

$$\lambda_1 = -\frac{3}{4}\alpha, \lambda_2 = -\frac{1}{2}\alpha, \lambda_3 = 0.$$

To determine the stability, the dynamics at the center manifold are investigated in the equilibrium point's vicinity. Here the dynamics at the one-dimensional center manifold are given by

$\frac{du}{dt} = 0$. This dynamics can be easily seen as a consequence of the one-dimensional manifold of equilibrium point that we have. Hence, we have stable a equilibrium point.

3. GENETIC FREQUENCY

3.1. Hardy-Weinberg equilibrium. Assuming that (1) population size is very large, (2) mating is random, (3) no mutation, (4) migration and natural selection occur in population, (5) organism is diploid, (6) sexual reproduction occurs, and (7) discrete or non-overlapping generation, Hardy-Weinberg equilibrium states that the allele and genotype frequencies in a population will not change from generation to generation [31, 32]. According to Lange, after a long time, the normal allele frequencies in men and women will be equal [33]. The same thing also applies to the frequency of the color blind allele.

Consider the female population that consists of $W_n(t)$, $W_b(t)$, and $W_c(t)$ in (1). Normal women have two X chromosomes, color blind women have two X^c chromosomes, and carrier women have one X and one X^c chromosomes. Therefore, in female population, the sum of all X chromosomes is $2W_n(t) + W_c(t)$, while the sum of all X^c chromosomes is $2W_b(t) + W_c(t)$. Thus, the frequency of normal allele chromosomes in women is

$$
\begin{aligned}
p_w(t) &= \frac{2W_n(t) + W_c(t)}{2W_n(t) + 2W_b(t) + 2W_c(t)} \\
&= \frac{W_n(t) + \frac{1}{2}W_c(t)}{W_n(t) + W_b(t) + W_c(t)}
\end{aligned}
$$

(11)

Dividing both denominator and numerator by the total population $N(t)$, we have

(12)
$$
p_w(t) = \frac{w_n(t) + \frac{1}{2}w_c(t)}{w_n(t) + w_b(t) + w_c(t)}
$$

Let q_w be the frequency of color blind allele chromosomes in women. Then,

(13)
$$
q_w(t) = \frac{w_b(t) + \frac{1}{2}w_c(t)}{w_n(t) + w_b(t) + w_c(t)}.
$$

Now consider the male population that consists of $M_n(t)$ and $M_b(t)$. Since normal men have only one X chromosome and color blind men have only one X^c chromosome, the amount of all X chromosomes and X^c chromosomes in the male population is $M_n(t)$ and $M_b(t)$, respectively.

Thus, the frequency of normal allele chromosomes in men is

$$(14) \qquad p_m(t) = \frac{M_n(t)}{M_n(t) + M_b(t)}.$$

After dividing both denominator and numerator by the total population $N(t)$, the frequency becomes

$$(15) \qquad p_m(t) = \frac{m_n(t)}{m_n(t) + m_b(t)}.$$

Furthermore, the frequency of the color blind allele chromosomes in men is

$$(16) \qquad q_m(t) = \frac{m_b(t)}{m_n(t) + m_b(t)}.$$

Notice that $p_w(t) + q_w(t) = 1$ and $p_m(t) + q_m(t) = 1$, and hence the genetic variation in men and women remains constant.

Let $p_w^{(n)}$ and $p_m^{(n)}$ represent the normal allele frequency of women and men after n generations, respectively. A daughter will receive each X chromosome from her mother and her father, therefore

$$(17) \qquad p_w^{(n)} = \frac{1}{2}p_w^{(n-1)} + \frac{1}{2}p_m^{(n-1)}.$$

On the other hand, a son will receive an X chromosome only from his mother, thus

$$(18) \qquad p_m^{(n)} = p_w^{(n-1)}.$$

From these two equations, we obtain [33]

$$
\begin{aligned}
\frac{1}{3}\left(2p_w^{(n)} + p_m^{(n)}\right) &= \frac{1}{3}\left(2\left(\frac{1}{2}p_w^{(n-1)} + \frac{1}{2}p_m^{(n-1)}\right) + p_w^{(n-1)}\right) \\
&= \frac{1}{3}\left(2p_w^{(n-1)} + p_m^{(n-1)}\right) \\
&\ \vdots \\
(19) \qquad &= \frac{1}{3}\left(2p_w^{(0)} + p_m^{(0)}\right)
\end{aligned}
$$

where $p_w^{(0)}$ and $p_m^{(0)}$ are the initial frequencies of the normal alleles in women and men, respectively. The last equation shows that genetic variation between generations remains constant and

thus implies a Hardy-Weinberg equilibrium. Therefore, we can rewrite it as

$$(20) \qquad \frac{1}{3}\left(2p_w^{(n)} + p_m^{(n)}\right) = p,$$

where p is a constant value. In addition, from (17) and (20) we conclude that

$$
\begin{aligned}
p_w^{(n)} - p &= \left(\frac{1}{2}p_w^{(n-1)} + \frac{1}{2}p_m^{(n-1)}\right) - \frac{3}{2}p + \frac{1}{2}p \\
&= \left(\frac{1}{2}p_w^{n-1} + \frac{1}{2}p_m^{(n-1)}\right) - \frac{3}{2}\left(\frac{1}{3}\left(2p_w^{(n-1)} + p_m^{(n-1)}\right)\right) + \frac{1}{2}p \\
&= \left(-\frac{1}{2}\right)\left(p_w^{(n-1)} - p\right) \\
&\ \ \vdots \\
(21) \qquad &= \left(-\frac{1}{2}\right)^n \left(p_w^{(0)} - p\right)
\end{aligned}
$$

This means that the difference between $p_w^{(n)}$ and p reduced by half in each generation and $p_w^{(n)}$ approaches p in a zigzag manner. The male frequency $p_m^{(n)}$ shows the same behavior, but behind $p_w^{(n)}$ by one generation [21].

Let

$$(22) \qquad p(t) = \frac{1}{3}(2p_w(t) + p_m(t))$$

which is expected to be the continuous version of the Hardy-Weinberg equilibrium in (20). The dynamics of the genetic variations obtained by the discrete model in (20) and by the continuous model in (22) are shown in Fig. 1. As can be observed, the equilibrium from continuous model in Fig. 1(a) is exactly the same as the equilibrium in the discrete model (note that in the discrete model, the dynamics in Fig. 1(a) is shown in generation time scale, whereas in continuous model, the dynamics in Fig.1(a), is shown in year time scale). This can be understood because of the following reason. Recall our assumption that the proportion of men and women is equal, that is

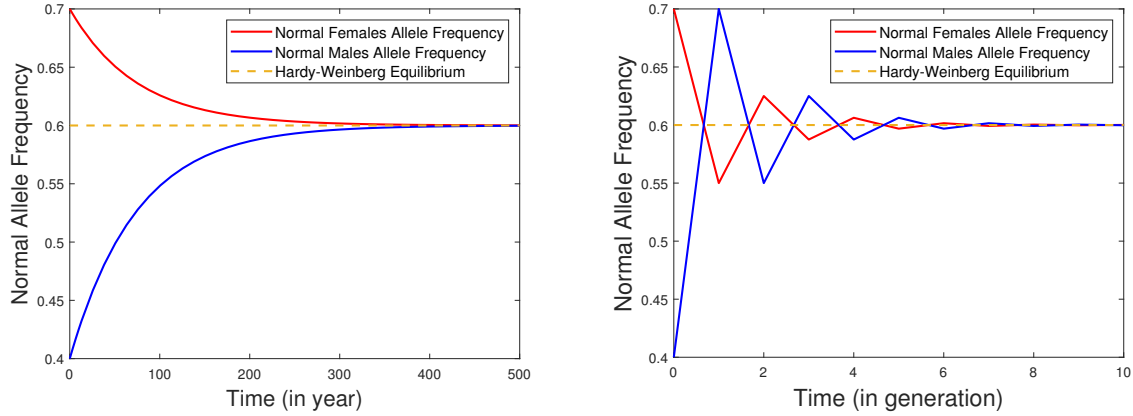$$(23) \qquad w_n(t) + w_b(t) + w_c(t) = m_n(t) + m_b(t) = \frac{1}{2}.$$

FIGURE 1. Comparison of normal allele frequency that changes with time resulted from continuous (left) and discrete (right) approaches with initial conditions $(w_n^0, w_b^0, w_c^0, m_n^0, m_b^0) = (0.3, 0.1, 0.1, 0.2, 0.3)$.

Differentiating (22) and using (12) and (15), we find

$$
\begin{aligned}
\frac{dp}{dt} &= \frac{1}{3}\left(2\frac{dp_w}{dt} + \frac{dp_m}{dt}\right) \\
&= \frac{2}{3}\left(2\frac{dw_n}{dt} + \frac{dw_c}{dt} + \frac{dm_n}{dt}\right) \\
&= \frac{2}{3}\left(\frac{dw_n}{dt} - \frac{dw_b}{dt} + \frac{dm_n}{dt}\right) \\
&= 0
\end{aligned}
$$

(24)

Therefore, when the proportion of men and women is equal, the value of $p(t)$ is constant throughout the time and hence the Hardy-Weinberg equilibrium holds.

Furthermore, if the initial frequencies $p_w(0)$ and $p_m(0)$ are known, (22) can be rewritten as

$$
\begin{aligned}
p &= p(0) \\
&= \frac{1}{3}\left(2p_w(0) + p_m(0)\right) \\
&= \frac{1}{3}\left(\frac{2w_n^0 + w_c^0}{w_n^0 + w_b^0 + w_c^0} + \frac{m_n^0}{m_n^0 + m_b^0}\right) \\
&= \frac{2}{3}\left(2w_n^0 + w_c^0 + m_n^0\right)
\end{aligned}
$$

(25)

where w_n^0, w_c^0, m_n^0 denote the initial proportion of normal women, carrier women, and normal men, respectively. Let p_w^∞ and p_m^∞ represent the frequency of chromosomes of the normal alleles in women and men in equilibrium condition, respectively. Substituting the equilibrium condition in (10) into (12), the frequency p_w^∞ can be written as

$$
\begin{aligned}
p_w^\infty &= \frac{w_n^\infty + \frac{1}{2} w_c^\infty}{w_n^\infty + w_b^\infty + w_c^\infty} \\
&= 1 - 2u
\end{aligned}
$$

(26)

In the same way, the frequency p_m^∞ can also be expressed as

$$
(27) \qquad p_m^\infty = 1 - 2u
$$

Thus, following (22), we have

$$
\begin{aligned}
p^\infty &= \frac{1}{3}(2p_w^\infty + p_m^\infty) \\
&= \frac{1}{3}(2(1 - 2u) + 1 - 2u) \\
&= 1 - 2u
\end{aligned}
$$

(28)

Since $p(t)$ is constant, then $p^\infty = p(0) = p$. Due to (25) and (28), we have

$$
(29) \qquad u = \frac{1}{2}\left[1 - \frac{2}{3}\left(2w_n^0 + w_c^0 + m_n^0\right)\right]
$$

By relation in (23), after some calculations, the equation above turns into

$$
(30) \qquad u = \frac{1}{3}(2w_b^0 + w_c^0 + m_b^0)
$$

4. DEPENDENCY OF THE EQUILIBRIUM POINT ON THE INITIAL CONDITION

Notice that the equilibrium point of the full system (5) is

$$
(31) \qquad \left(w_n^\infty, w_b^\infty, w_c^\infty, m_n^\infty, m_b^\infty\right) = \left(2u^2 - 2u + \frac{1}{2}, 2u^2, 2u - 4u^2, \frac{1}{2} - u, u\right).
$$

This means the proportion of all sub-populations depends on the constant u, which represents the proportion of color blind men at steady-state. From (30) we found that when the proportion

of men is equal to the proportion of women, we can determine the value of u based on the initial

conditions of the system, and hence also the equilibrium point (31). Let

$$(32) \qquad\qquad\qquad\qquad f : \mathbf{x}_0 \mapsto u$$

defines a map from initial condition $\mathbf{x}_0 = (w_n^0, w_b^0, w_c^0, m_n^0, m_b^0)$ to a real number $u \in [0, \frac{1}{2}]$, with

$$(33) \qquad\qquad\qquad u = f(\mathbf{x}_0) = \frac{1}{3}(2w_b^0 + w_c^0 + m_b^0)$$

and

$$(34) \qquad\qquad\qquad\qquad \gamma : u \mapsto \gamma(u)$$

defines a map from u to $\gamma(u)$ which is the equilibrium point, i.e.,

$$(35) \qquad\qquad \gamma(u) = \left(2u^2 - 2u + \frac{1}{2}, 2u^2, -4u^2 + 2u, \frac{1}{2} - u, u \right).$$

Then, the equilibrium point $\mathbf{x}_{eq}$ can be obtained as follows [6]:

$$(36) \qquad\qquad\qquad\qquad \mathbf{x}_{eq} = (\gamma \circ f)(\mathbf{x}_0).$$

Observe that due to (6), we have

$$(37) \qquad\qquad\qquad\qquad w_b + w_c = \frac{1}{2} - w_n$$

Since $w_n \in \left[0, \frac{1}{2}\right]$, then

$$(38) \qquad\qquad\qquad\qquad 0 \leq w_b + w_c \leq \frac{1}{2}$$

Therefore, when m_b^0 is fixed to a constant value, for example $m_b^0 = 0$ or $m_b^0 = 0.5$, all possible

value of u can be described as a surface depicted in Fig 2a). For other values of m_b^0 with

$0 < m_b^0 < 0.5$, the surfaces of u are similar to those in Fig. 2a), where the bigger the value of

m_b^0, the higher the surface of u. From this figure, we see that the value of u, which represents the

proportion of color blind men at steady-state, is more sensitive to the changes of w_b (the color

blind women) than to w_c (the carrier women). This can be understood because the dynamics of

the color blind men sub-population M_b, based on (5), are influenced by the color blind women

W_b stronger (by a factor $1/2$) than by the carrier women W_c (by a factor $1/4$).

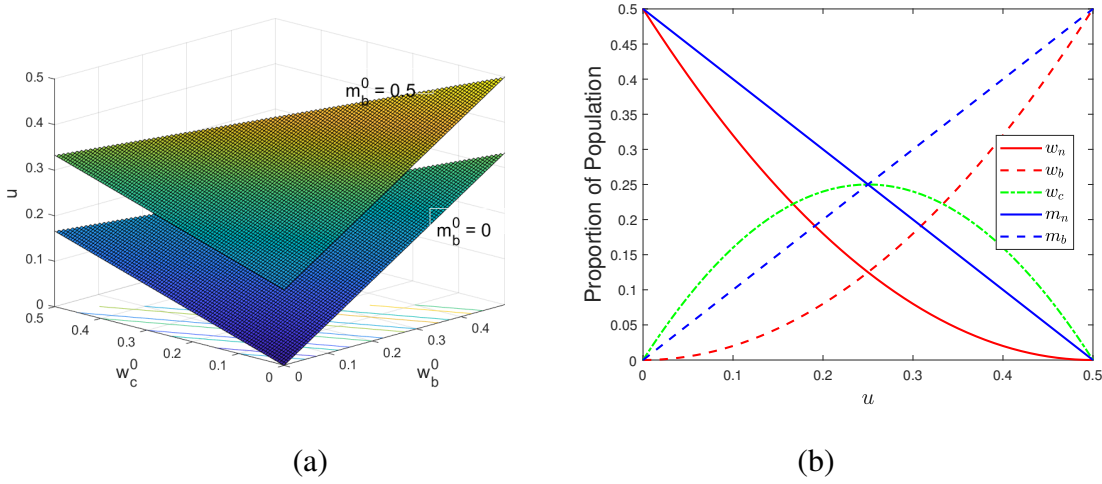(a)   (b)

FIGURE 2. (a): Surface of u as function of (w_b^0, w_c^0) when $m_b^0 = 0$ and $m_b^0 = 0.5$. For other values of m_b^0, the surfaces will be in-between those two surfaces. (b) Proportion of population in the equilibrium point of the model as function of u.

When u changes, then the proportion of each sub-population also changes, as shown in Fig. 2b). For example, when $u = 0$, the proportion of the normal, color blind, and carriers population is $(w_n + m_n, w_b + m_b, w_c) = (1, 0, 0)$, which means that there will be no color blind people in the population. But when $u = \frac{1}{2}$, the proportion becomes $(w_n + m_n, w_b + m_b, w_c) = (0, 1, 0)$, which indicates that all people will be color blind. Observe from Fig. 2a), that $u = 0$ occurs only if $w_b^0 = w_c^0 = m_b^0 = 0$, that is when all people in the population have normal vision. In contrast, $u = 1/2$ occurs if only $w_b^0 = m_b^0 = 1/2$, that is when all people in the population are color blind. When $u = \frac{1}{4}$, we found $(w_n + m_n, w_b + m_b, w_c) = \left(\frac{3}{8}, \frac{3}{8}, \frac{1}{4}\right)$, and thus the proportion of normal people is the same as that of color blind people. Furthermore, we also observe that when $0 \leq u < \frac{1}{4}$, the proportion of normal people is larger than the proportion of color blind people $(w_n + m_n > w_b + m_b)$, whereas when $\frac{1}{4} < u \leq \frac{1}{2}$, the proportion becomes the opposite $(w_n + m_n < w_b + m_b)$.

Another essential thing to note is that the proportion of normal men is always more prominent than the normal women $(m_n > w_n)$ and the proportion of color blind men is also more prominent than the color blind women $(m_b > w_b)$. In a nutshell, the result in Fig. 2a) can be summarized as shown in Table 3.

TABLE 3. Characteristic of population at steady state according to the value of u.

	$0 \leq u < \frac{1}{4}$	$\frac{1}{4} < u \leq \frac{1}{2}$	$u = \frac{1}{4}$
Normal population	$w_n^\infty < m_n^\infty$	$w_n^\infty < m_n^\infty$	$w_n^\infty < m_n^\infty$
Color blind population	$w_b^\infty < m_b^\infty$	$w_b^\infty < m_b^\infty$	$w_b^\infty < m_b^\infty$
women population	$w_n^\infty > w_b^\infty$	$w_n^\infty < w_b^\infty$	$w_n^\infty = w_b^\infty$
men population	$m_n^\infty > m_b^\infty$	$m_n^\infty < m_b^\infty$	$m_n^\infty = m_b^\infty$

Suppose $\mathscr{H}_\infty = w_n^\infty + m_n^\infty$ and $h_\infty = w_b^\infty + m_b^\infty$ denotes the proportion of the normal population and the proportion of the color blind population at equilibrium, respectively. Notice that the uppercase letter($\mathscr{H}$) is used to represent people with dominant gene and lowercase letter (h) is used to represents people with recessive gene.

Let

$$\Omega_1 = \left\{ (w_n^0, w_b^0, w_c^0, m_n^0, m_b^0) \mid 0 \leq \frac{1}{3}(2w_b^0 + w_c^0 + m_b^0) < \frac{1}{4} \right\},$$

(39)
$$\Omega_2 = \left\{ (w_n^0, w_b^0, w_c^0, m_n^0, m_b^0) \mid \frac{1}{4} < \frac{1}{3}(2w_b^0 + w_c^0 + m_b^0) \leq \frac{1}{2} \right\},$$

$$\Omega_3 = \left\{ (w_n^0, w_b^0, w_c^0, m_n^0, m_b^0) \mid \frac{1}{3}(2w_b^0 + w_c^0 + m_b^0) = \frac{1}{4} \right\}.$$

Then, based on Table 3 we see that

- if $\mathbf{x}_0 \in \Omega_1$, then in the equilibrium state, we get $\mathscr{H}_\infty > h_\infty$.
- if $\mathbf{x}_0 \in \Omega_2$, then in the equilibrium state, we get $\mathscr{H}_\infty < h_\infty$.
- if $\mathbf{x}_0 \in \Omega_3$, then in the equilibrium state, we get $\mathscr{H}_\infty = h_\infty$.

Let $\mathscr{H}_0 = w_n^0 + m_n^0$ and $h_0 = w_b^0 + m_b^0$ denote the initial proportions of the normal population and the color blind population, respectively. Since we assume that the proportion of men and women is the same, then $m_n^0 + m_b^0 = \frac{1}{2}$. Now consider the situation where $\mathscr{H}_0 > h_0, m_n^0 < m_b^0$, and $w_n^0 > w_b^0$. Since $m_n^0 < m_b^0$, then

(40)
$$2m_n^0 < m_n^0 + m_b^0 = \frac{1}{2} \iff m_n^0 < \frac{1}{4}.$$

Notice that $\mathscr{H}_0 > h_0$ or $w_n^0 + m_n^0 > w_b^0 + m_b^0$. Therefore,

$$u = \frac{1}{3}\left(2w_b^0 + w_c^0 + m_b^0\right)$$

$$< \frac{1}{3}\left(w_b^0 + w_c^0 + w_n^0 + m_n^0\right)$$

(41)
$$< \frac{1}{3}\left(\frac{1}{2} + \frac{1}{4}\right) = \frac{1}{4}$$

Since $u < \frac{1}{4}$, the initial condition belongs to Ω_1 which gives equilibrium state $\mathcal{H}_\infty > h_\infty$. In the same way, for other initial conditions, we obtain equilibrium states as summarized in Table 4.

TABLE 4. Equilibrium state according to different initial conditions

Initial condition		$w_n^0 > w_b^0$	$w_n^0 < w_b^0$	$w_n^0 = w_b^0$
$\mathcal{H}_0 > h_0$	$m_n^0 > m_b^0$	$\mathcal{H}_\infty > h_\infty$	anything is possible	$\mathcal{H}_\infty > h_\infty$
	$m_n^0 < m_b^0$	$\mathcal{H}_\infty > h_\infty$	–	–
	$m_n^0 = m_b^0$	$\mathcal{H}_\infty > h_\infty$	–	–
$\mathcal{H}_0 < h_0$	$m_n^0 > m_b^0$	–	$\mathcal{H}_\infty < h_\infty$	–
	$m_n^0 < m_b^0$	anything is possible	$\mathcal{H}_\infty < h_\infty$	$\mathcal{H}_\infty < h_\infty$
	$m_n^0 = m_b^0$	–	$\mathcal{H}_\infty < h_\infty$	–
$\mathcal{H}_0 = h_0$	$m_n^0 > m_b^0$	–	$\mathcal{H}_\infty < h_\infty$	–
	$m_n^0 < m_b^0$	$\mathcal{H}_\infty > h_\infty$	–	–
	$m_n^0 = m_b^0$	–	–	$\mathcal{H}_\infty = h_\infty$

Thus, for example, when the initial condition satisfies $\mathcal{H}_0 > h_0$, $w_n^0 > w_b^0$, and $m_n^0 > m_b^0$, then $\mathcal{H}_\infty > h_\infty$, that is in the equilibrium, the proportion of normal population will be higher than that of the color blind population. The "-" sign in the table represents a case that needs no consideration because it contradicts the assumption on the initial condition. In the cases where $\mathcal{H}_0 > h_0$, $w_n^0 < w_b^0$, and $m_n^0 > m_b^0$, any equilibrium state is possible. For example, the initial condition $(0.1, 0.2, 0.2, 0.4, 0.1)$ gives a conclusion $\mathcal{H}_\infty > h_\infty$, the initial condition $(0.1, 0.35, 0.05, 0.45, 0.05)$ gives a conclusion $\mathcal{H}_\infty < h_\infty$, and the initial condition $(0.125, 0.25, 0.125, 0.375, 0.125)$ gives the conclusion $\mathcal{H}_\infty = h_\infty$.

5. NUMERICAL SIMULATION

In this section, we apply our model to data from some Northern European countries and Korea where the population proportions are given in Table 5 and Table 6 [34]. As can be noticed from the tables, the average proportion of men and women in those countries is almost equal. Therefore, we assume that the number of men is always the same as that of women throughout the time. Furthermore, since we do not have detailed information on the number of carrier women, for simplicity, we also assume that the number of normal women is equal to that of carrier women.

Observe that actually, the role of birth rate parameter α and death rate parameter δ vanish when we work in the dimensionless system, as mentioned at the end of Section 2.2 (recall that parameter α only stretches or shrinks the dynamics behavior of the model). However, since we analyze the stability of the non-zero equilibrium points, for our analysis to make sense, the population should not be extinct. Therefore, we need to keep $dN/dt \geq 0$, which implies that $\alpha \geq 2\delta$. In this simulation, we take

$$\alpha = \frac{2}{65}\frac{1}{\text{year}}, \quad \delta = \frac{1}{65}\frac{1}{\text{year}},$$

so that the total population is constant. Remark that in the following simulations, we apply the model in (7) where the proportion of each sub-population to the total population is used to represent their quantity so that their total is one at any time.

TABLE 5. The sex ratio population in Northern Europe countries [34].

Country	Male (%)	Female (%)
Denmark	49.7	50.3
Finland	49.3	50.7
Iceland	50.2	49.8
Norway	50.5	49.5
Sweden	50.1	49.9
Average	49.96	50.04

TABLE 6. The sex ratio population in Republic of Korea [34].

Country	Male (%)	Female (%)
Republic of Korea	50.1	49.9

Notice that the model that we derive deals with the mating adult population. Therefore, for simplicity, in our numerical simulation, we assume that the numbers in Table 5 and Table 6 are related to color blindness in the adult population.

5.1. Northern Europe. From [9, 10, 11, 12], we know that the percentage of color blindness in European Caucasian people is 8% in men and 0.4% in women, thus

$$(42) \quad W_n + W_c = 0.996 \left(\frac{1}{2} N \right), \ W_b = 0.004 \left(\frac{1}{2} N \right), \ M_n = 0.92 \left(\frac{1}{2} N \right), \ M_b = 0.08 \left(\frac{1}{2} N \right),$$

or in proportion,

$$(43) \qquad w_n + w_c = 0.498, \quad w_b = 0.002, \quad m_n = 0.46, \quad m_b = 0.04.$$

It is easy to see that $w_n + w_b + w_c + m_n + m_b = 1$. Since we assume that the number of normal women and carrier women is the same, then

$$(44) \qquad\qquad\qquad w_n = 0.249, \quad w_c = 0.249.$$

We consider those values as initial condition in our model, therefore

$$(45) \qquad\qquad (w_n^0, w_b^0, w_c^0, m_n^0, m_b^0) = (0.249, 0.002, 0.249, 0.46, 0.04).$$

Since the initial proportion of normal people is higher than that of the color blind and since Hardy-Weinberg equilibrium holds, we conclude that based on Table 4 people with normal vision will dominate the population in the future. Additionally, based on Table 3, the proportion of men and women with normal vision will be higher than those with color blindness. Here we find $u = 0.0977$, and therefore, the corresponding equilibrium point is

$$(46) \qquad\qquad (w_n^\infty, w_b^\infty, w_c^\infty, m_n^\infty, m_b^\infty) = (0.3237, 0.0191, 0.1572, 0.4023, 0.0977).$$

We also obtain that the frequency of the normal allele will converge to the equilibrium frequency $p = 0.8047$. The numerical simulation is presented in Fig. 3.
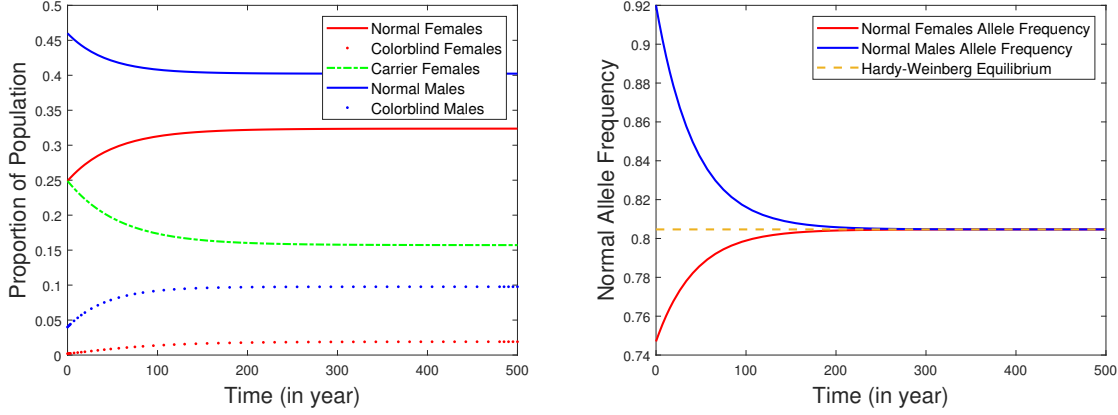

FIGURE 3. Numerical simulation of (a) the color blind model and (b) the corresponding Hardy-Weinberg equilibrium for Northern European countries' population.

As can be observed from Figure 3, as time goes by, the proportion of the color blind people and normal women increase, whereas the proportion of normal men and carrier women decrease. Although the proportion of normal men decreases with time, their number is still higher than the proportion of color blind people. Thus, people with normal vision are still dominating the population. We also observe that the decrease of normal male proportion and the increase of normal female proportion are consistent with the dynamics of their allele frequencies where the normal female's allele frequency increases but the normal men frequency decreases. The genetic variations, however, are constant throughout the time.

5.2. Korea. The percentage of color blindness in Korea is 5.9% in men and 0.44% in women [35]. Therefore, in proportion,

(47) $w_n + w_c = 0.4978, \quad w_b = 0.0022, \quad m_n = 0.4705, \quad m_b = 0.0295.$

So we set the initial condition for Korea as

(48) $(w_n^0, w_b^0, w_c^0, m_n^0, m_b^0) = (0.2489, 0.0022, 0.2489, 0.4705, 0.0295).$

Again, we see that the initial proportion of normal people is higher than that of the color blind. Hence, based on Table 4, we conclude that people with normal vision will dominate

the population in the future, and the proportion of men and women with normal vision will be higher than those with color blindness. In this case, we find $u = 0.0943$ and the corresponding equilibrium point is

$$(49) \qquad (w_n^\infty, w_b^\infty, w_c^\infty, m_n^\infty, m_b^\infty) = (0.3292, 0.0178, 0.1530, 0.4057, 0.0943).$$

Furthermore, the frequency of the normal allele will converge to the equilibrium frequency $p = 0.8115$. The numerical simulation is presented in Fig. 4.
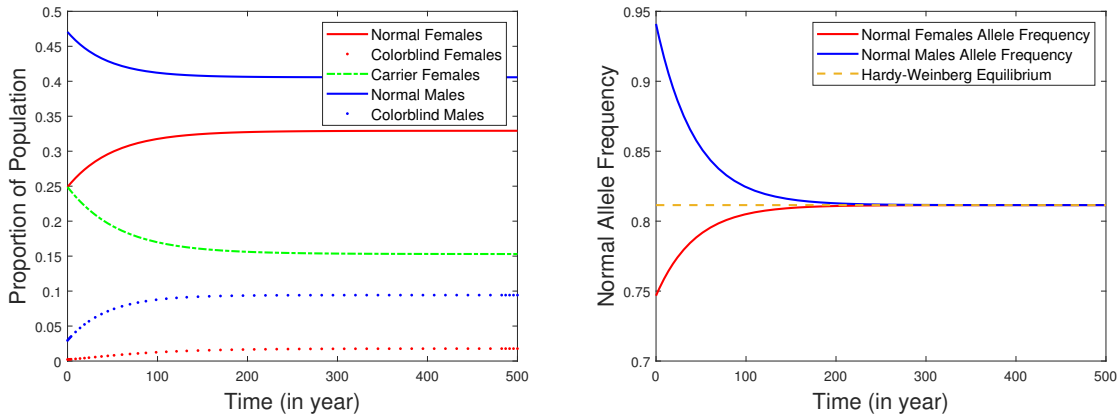

FIGURE 4. Numerical simulation of (a) the color blind model and (b) the corresponding Hardy-Weinberg equilibrium for Korea population.

As we can see from Figure 4, the trend in Korea is quite similar to that in the Northern European countries' population where proportion of color blind people increases but the proportion of carrier women decreases. Although the trend is similar, there is an exciting result to notice if we compare the initial conditions in those countries, i.e., (45) and (48), with their equilibrium points in (46) and (49). In Northern Europe, the color blindness in men is initially higher than that in Korea (m_b^0(Northern Europe) $= 0.04$, whereas m_b^0(Korea) $= 0.0295$) and ends up consistently in the future, as can be observed from the equilibrium points ($m_b^\infty = 0.0977$ vs $m_b^\infty = 0.0943$). However, it is on the other way around for the women. In Northern Europe, the color blindness in women is initially slightly lower than that in Korea (w_b^0(Northern Europe) $= 0.002$, whereas w_b^0(Korea) $= 0.0022$). However, the color blindness Northern European women ends up higher than that in Korea w_b^∞(Northern Europe) $= 0.0191$ vs w_b^∞(Korea) $= 0.0178$. This is because the value of u in Northern Europe is higher than that in Korea, and therefore, based on

Figure 2b), the proportion of color blind people in Northern Europe will also be higher. Recall from (30) that the value of u is determined by w_b^0, w_c^0, and m_b^0. By comparing the initial conditions in (45) and (48), we see that the initial proportion of color blind in men, m_b^0, in Northern Europe is almost two times that in Korea. On the other hand, the values of w_b^0 and w_c^0 are slightly different, which is why the value of u in Northern Europe is higher.

6. DISCUSSION AND CONCLUSION

We have developed a mathematical model to describe the spread of color blindness in the population. This model is based on the continuous approach and Mendel's segregation law, resulting in a set of differential equations. The model has equilibrium point that does not depend on the model's parameters and thus making the model hard to analyze. Despite this condition, utilizing the Hardy-Weinberg principle, we could deduce the equilibrium points' dependencies on the model's initial condition. Using this dependency, which is reflected by the value of u as a function of w_b^0, w_c^0, and m_b^0, we could determine at what condition color blindness will dominate the population, as shown in Table 4. The bigger the value of u, the higher the proportion of the color blind population. It can be observed from formulae (30) and Fig. 2a) that the value of u depends on the initial condition of carrier and color blind women and also on the initial condition of color blind men. This result might hint at controlling color blindness in the population. This could be done, for example, by suggesting a couple conduct a genetic screening before committing to having children. In this way, the couple will realize the risk for their children. Since in addition to the color blind men, the value of u also depends on the proportion of carrier and color blind women, and is more sensitive to the color blind women, the screening can be more prioritized for the women.

We further observed via our model that color blindness in men is always higher than that in women. This result is consistent with the fact that color blindness is inherited via the X chromosome. Our result is also in good agreement with finding from many researchers, for example [18, 36].

In our model, we consider cases where the number of men and women in the population is equal. While this may be a strong assumption, there are many places where the proportions of men and women are nearly equal, for example, in some Northern European countries, South

Korea, the Netherlands, and Australia [34]. The ratio is even the same in Cyprus, Azerbaijan, Cameroon, Ethiopia, Ecuador, Honduras, Costa Rica, and some other countries. Therefore, we think the assumption is still acceptable, although a more general assumption would be preferable. We also assume that color blindness does not reduce a person's chances of marrying a woman/men they like. If this factor is considered in the model, we may have a factor to control color blindness.

In our work, we exclude the mutation factor from our model. From the genetic point of view, the effect of the mutation factor in the model can be included as a fitness level, which is the weight of a gene or allele in the model. Basically, this factor can be incorporated into our model. However, since we would like to focus on the phenotypic dynamics of color blindness, the presence of mutation factors becomes less significant. This is why we incorporate the birth rates and natural death rates in our model where both of them are terms used to describe the phenotypic conditions. Thus, we leave the mutation factor for future work. Further, we consider the adult population in our model, and for simplicity, we assume that the numbers related to color blindness in Table 5 and Table 6 occur in the adult population. Certainly, it will be interesting to see the dynamic behavior of color blindness in the children and adults population, but we leave it for future work.

Since only factors of births and deaths are involved in the model, we end up with a Malthusian model. Nevertheless, even with this model, we find some important insights that are discussed above. Therefore, we can utilize this model as a start to study some basic features of the dynamics of the spread of color blindness in a population. Furthermore, this model can be further extended, for example, by introducing logistic factors, which will make it more realistic. Finally, although in our paper we focus on the genetic disease that leads to color blindness, in general, the approach can also be applied to model the dynamics of other genetic diseases, including, for example, the lethal one. However, we may need to make some adjustments to adapt to the particular situation that the disease may have.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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