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Modeling Mendel's Laws on Inheritance in Computational Biology and Medical Sciences**

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Abstract

The current research article is based on a simple and practical way of employing the computational power of widely available, versatile software MS Excel 2007 to perform interactive computer simulations for undergraduate/graduate students in biology, biochemistry, biophysics, microbiology, and medicine in college and university classroom setting. To accomplish this important motive, we developed the necessary computer algorithm, which used a built-in pseudo-random number generating function in MS Excel 2007, to computer model two basic Mendel's Laws of heredity for plant and animal species. We performed more than 18,000 computer simulations to investigate the behavior of dominant and recessive genes to verify two basic Mendel's Laws of heredity. Our simulation work corroborates the experimental observations of Mendel's research on inheritance in *Pisum hybrids*. When we compare our results of simulated data with that of experiments done on *Drosophila melanogaster*, fruit fly extensively being used as a model organism to study genetics and development, an exceedingly good agreement between the simulated and the experimental data has been observed for the F2 generation.

1. INTRODUCTION

Gregor Mendel's famous research paper [1] on inheritance in *Pisum* hybrids formed a sound basis for the study of modern genetics, but the importance of Mendel's work was not completely realized till the beginning of twentieth century. Mendel was born in country-side (Heinzendorf, the Czech Republic) in a country-side family. In 1847, he was ordained as a priest, and was ultimately elected to the position of Abbott. In 1851, he was sent by the Church to study natural science at the University of Vienna, so that he could defend the theory of intelligent design. After completing his studies, he systematically and painstakingly investigated for seven years 28,000 *Pisum* plants in his father's orchard with an idea of developing new varieties of plant and sheep through cross-breeding. In 1865, he presented his research findings to the Natural History Society of Brünn, and the following year, he published his most prominent paper on the laws of dominance, segregation, and independent assortment [1]. Mendel himself was very much interested in the question of evolution theory of Darwin [2], but unfortunately, he performed experiments with an idea in his mind to support

the theory of intelligent design. He worked in the tradition of Kölreuter and Gärtner [3], investigating Linnaeus's theory [4] that hybrids might have played an important role in evolution process, and consequently, his experiments were designed to explore a fundamental difference between hybrids and species. On page 40 of his textbook [5], Mendel writes, "Thus with a relatively small number of experimental plants the result could be only approximately correct and occasionally could deviate not inconsiderably." Mendel believed that the mechanisms of evolution might have existed in the organisms themselves, but they could not be directly observed, so it was necessary to investigate the aggregate behavior of a large amount of data collected and to analyze these data using statistical techniques, concluding that mathematics should play an important role in the formulism corresponding to any experimental scientific research.

The basic aim of Mendel's experiments on hybrids was to provide the detailed evidence that his predecessors were unable to figure out. To achieve his goal, he initiated discussion of the evolutionary significance of hybrids by making a clear distinction between "variable" and "constant" hybrids [6]. The progeny of variable hybrids would display reversion, while constant hybrids would breed exactly the same way. Mendel's main objective was to find out which environment could give rise to which types of hybrids, and whether or not constant hybrids could be produced in a reproducible experiment. Mendel's research was largely ignored by others, although it was not completely unknown to biologists of the time. They thought Mendel's work was not so important, because even Mendel himself was unable to realize the importance of his laws, and their real practical applicability to different kinds of species. Mendel thought that his laws could be applied only to certain categories of special species such as *Pisum* hybrids but not to other general classes of species. Nevertheless, controversial nature of Mendel's laws was vigorously promoted in Europe by Bateson [7], who coined a new term "genetics", "gene", and "allele" to describe many of its traits. The model of heredity was highly debated by other biologists as it implied that heredity was discontinuous, contrary to the apparently continuously changing observables. Several biologists also did not care about Mendel's theory for numerous years, since they were not sure that it could be applied to all plant and animal species. Consequently, they generally concluded that there seemed to be very few true Mendelian attributes existing in nature. However, later research work done by biologists and statisticians like Fisher [8] gave some concrete evidence that if multiple Mendelian factors were involved for individual traits, they could produce the diversified results observed in nature overtime. Thomas Morgan [9] and his associates later on integrated the theoretical model of Mendel with the chromosome theory of inheritance, where it was assumed that the chromosomes of cells held the actual hereditary information, and created what is now popularly known as classical genetics [10]. Thus, classical genetics of Thomas Morgan [10] was extremely successful in establishing Mendel's laws of heredity on a firm footing.

As pointed out by Fisher [8] that if the results of Mendel's experiments on *Pisum* hybrids [1] are carefully examined, one would immediately conclude that it was highly desirable to

formulate a mathematical model, which would reproduce the experimental results on hybrids. Although mathematics, computer science and statistics are not considered to be a part of natural sciences, it is not possible during these days to avoid the use of mathematics and statistics from the model construction. Strictly speaking, computer science (in conjunction with modern mathematical computational tools such as MS Excel 2007, MatLab, Mathematica, Maple etc.) provide essential algorithm and logic in terms of high level programming languages such as C++, C#, Visual Basic, Java, Pearl etc. to construct successful and relevant model of any experimental scientific research or discovery. Thus, mathematics, statistics and computer science provide basic essential and viable tools and framework to model theoretically or empirically almost all the natural phenomena of modern scientific exploration, including two Mendel's laws of inheritance. This is the ultimate aim of the present research paper, in which we intend to use very powerful, computational Microsoft software system, Excel 2007, to model Mendel's laws of heredity in genetics.

Although a lot of research work has been done to build theoretical models to explain Mendel's laws of heredity [11], very scanty work has been done using Microsoft Excel 2007. As far as we are aware of, only one investigator has employed Excel 2003 to build model on Mendel's laws of inheritance, which explains the behavior of recessive genes only [12] and none of the investigators, so far, have tried to build theoretical and empirical model on the behavior of dominant genes to verify Mendel's laws of genetics.

From past ten years, our department is teaching MS Excel software system based course to a general audience of students of biochemistry, biology, medicine, computer science, chemistry, biophysics, physics, mathematics, education, music and business majors, and it is one of the most popular service courses in our university. In this course, we generally develop and discuss several scientific applications with the help of MS Excel software system to enhance the basic understanding of our students in the above mentioned disciplines. We believe that Mendel's Laws simulations would be an additional MS Excel based application that could be an extremely useful teaching/learning tool not only for the undergraduate students of biology, biochemistry, biophysics and medical sciences of SUNY Fredonia but also for other universities/colleges. It would be taught even in the graduate school in the near future as promised by one of my colleagues in the Department of Oral Biology, University of Buffalo.

The organization of the present manuscript is done as follows: Section 2 is devoted to a brief description of MS Excel 2007 computational and graphical capabilities. Section 3 deals with the theoretical formalism and algorithm for Mendel's laws of heredity, and it also reports actual computer simulation work on recessive and dominant genes in tabular and graphical form. Section 4 gives a brief experimental work on *Drosophila melanogaster* for F2 generation and compares it with our simulated data obtained from MS Excel 2007 software system. Finally, conclusions of the present investigation are presented in Section 5.

2. A BRIEF DESCRIPTION OF MS EXCEL "INSERT FUNCTION" AND "INSERT CHART" GROUPS

Before starting our formal computer simulation work on interactive application of MS Excel 2007 to model Mendel's laws of heredity, a few words about Excel's 2007 "*Insert Function*" and "*Insert Chart*" Groups may be in order. In Fig. 1(a), we show an actual screen-shot of MS Excel 2007 "*Insert Function*" Group, which is very natural and the students/instructors can grasp its mastery pretty easily. In the screen-shot of Fig. 1(a), we display one category of selected functions, e.g., "*Logical*" category, which is highlighted. To its left side, there are different kinds of functions to be selected from "*Select a function*" window. One can see all the built-in Excel 2007 functions corresponding to "*Logical*" function category and the AND( ) function is ready for use. For the present investigation, we employed two functions from the "*Logical*" category: IF( ), and AND( ) functions. In addition, three more built-in functions are used in this study and these are: COUNT( ), SUM( ) and RAND( ) functions.

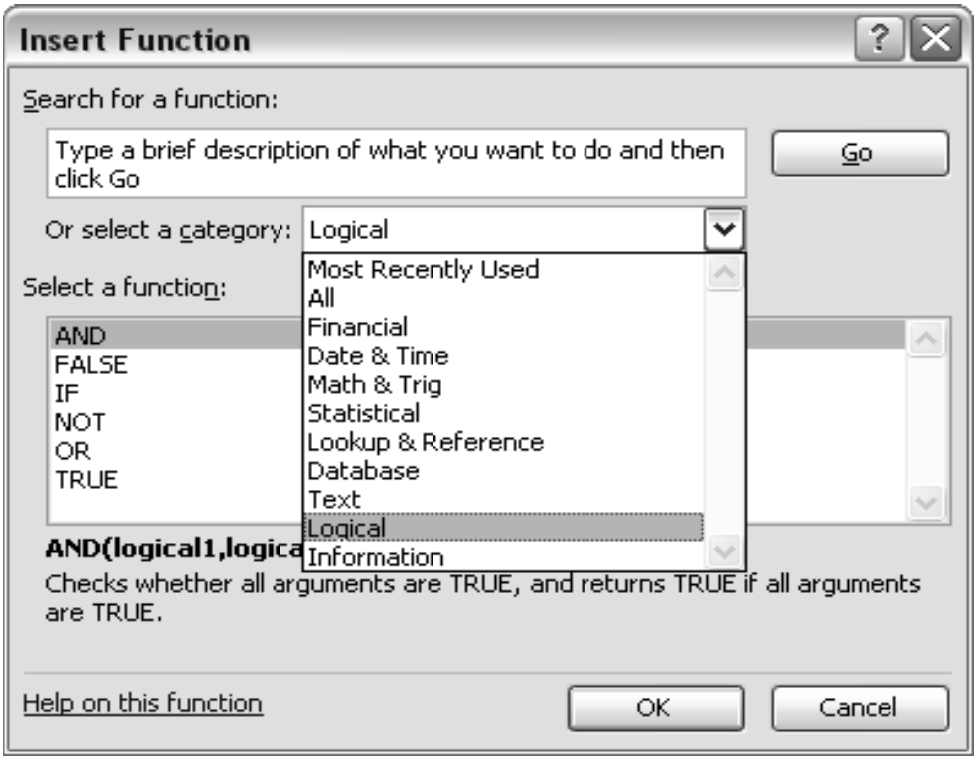

Fig. 1(a): A typical view of MS Excel 2007 of "*Insert Function*" group, in which various built-in logical functions can be used during computational work.

A screen-shot of an "*Insert Chart*" Group of MS Excel 2007 is shown in Fig. 1(b), which is frequently used for graph plotting. For further details of MS Excel interfaces and Groups, we may make a reference to our former investigation [13]. Each spreadsheet in Excel is composed of 256 columns, 65536 rows and one may insert a large number of spreadsheets in a workbook [14], the number of rows in a single spreadsheet is a measure of the number

simulations that can performed during a single computation, i.e., almost 66000, which was not possible even with old versions of IBM Mainframes of seventies.

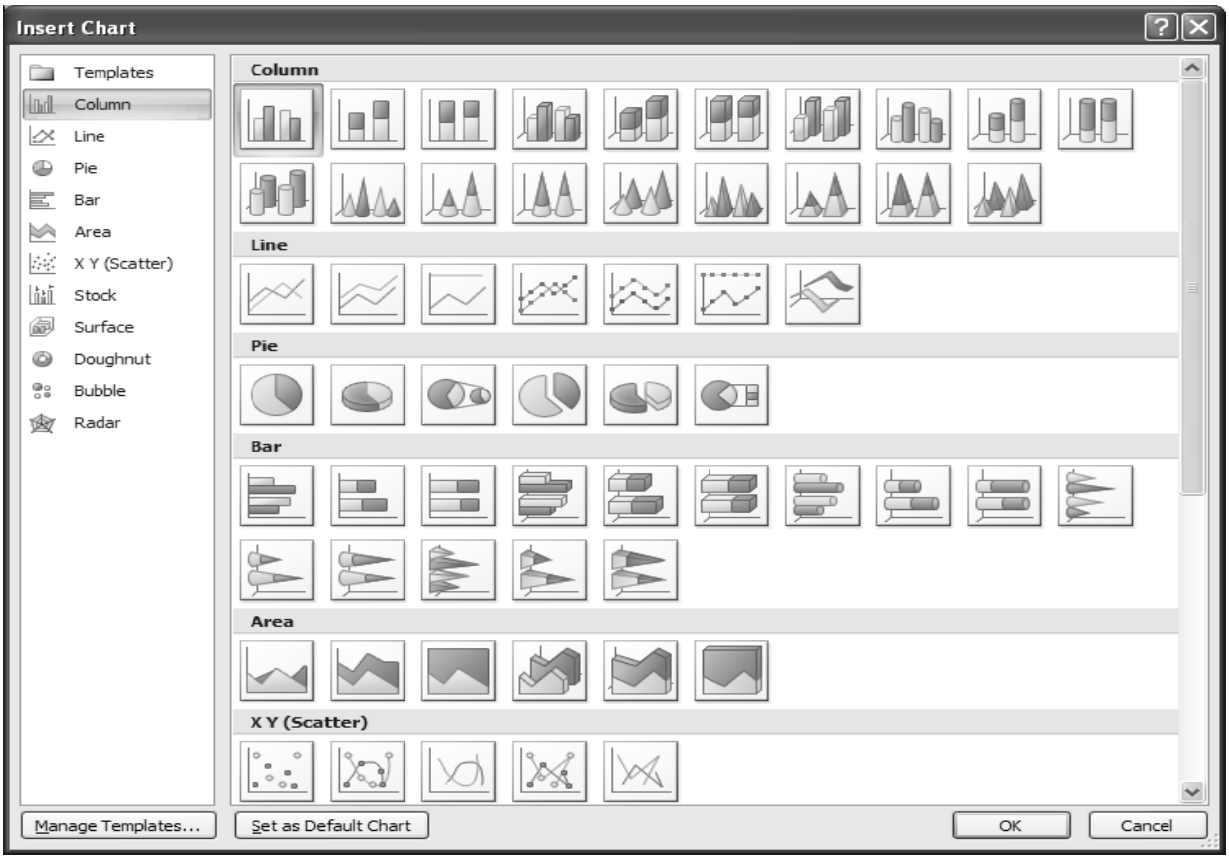

Fig. 1(b): A typical view of "*Insert Chart*" group of MS Excel 2007 in which graph plotting capabilities can be basically used to plot several kinds of charts.

3. COMPUTER SIMULATIONS OF MODELING MENDEL'S LAWS OF HEREDITY AND DISCUSSION OF RESULTS

To perform the simulations to model progeny through fertilization between males (♂) and females (♀), we start with one gene and we use the idea of Mendel's Laws for *Pisum* hybrids [1]. We begin with two alleles of the gene, D and r, where D and r stand for dominant and recessive alleles, respectively. With two alleles, there are four possible combinations: DD, Dr, rD and rr or DD, 2Dr, rr. As only two alleles are involved during fertilization, each allele has 50% contribution for the production of progeny and this condition must be implemented in the computer simulations. In this study, we performed more than 18,000 computer simulations and only 12 simulations are shown in Table 1. In column four of Table 1, tag 1 stands for the progeny due to recessive gene pair, whereas tag 0 stands for the offspring due to dominant gene pair. The rr progeny will constitute about 25% of the total progeny. If neither of the two alleles has any selective disadvantage, the ratio of their population in successive generations should stay constant as observed by Mendel through his research on *Pisum* hybrids [1]. This

is what is found through the computer simulations of data presented in column four of Table 2, where this ratio has been found to be nearly constant (e.g., its average value equals 1.99). The ratio of the rr progeny to the total progeny, which is 0.25, is plotted in Fig. 2 for ten generations and shown with filled triangles (▲). This ratio is also reflected in the plot for the total progeny (filled squares in Fig. 2 and the column on Trials in Table 2) versus the plot for the rr progeny (filled diamonds in Fig.2 and the column on progeny in Table 2).

Table 1: Computer simulations that start with male and female genes with recessive and dominant traits, and progeny of different traits are produced.

Female Gene	Male Gene	Progeny Phenotype	Recessive/Dominant Tag
dominant	recessive	dominant	0
recessive	dominant	dominant	0
recessive	recessive	recessive	1
dominant	recessive	dominant	0
recessive	dominant	dominant	0
recessive	dominant	dominant	0
dominant	recessive	dominant	0
recessive	recessive	recessive	1
dominant	recessive	dominant	0
dominant	dominant	dominant	0
recessive	recessive	recessive	1
recessive	recessive	recessive	1

Table 2: Results of computer simulations that give rise to recessive-gene progenies for 11 generations. Here *n* stands for generation index and *n* = 1 is for the first generation etc.

Recessive Phenotype in the Progeny				
Generation, *n*	**Trials, T_n**	**Progeny, P_n**	**P_{n+1}/P_n**	**P_n/T_n**
1	18	5	1.80	0.28
2	36	9	1.89	0.25
3	72	17	2.24	0.24
4	144	38	2.26	0.26
5	288	86	1.95	0.30
6	576	168	1.84	0.29
7	1160	309	1.98	0.27
8	2300	613	1.94	0.27
9	4600	1189	1.97	0.26
10	9200	2347	1.99	0.26
11	18400	4672	-	0.25

The best fit exponential function through the data points (filled diamonds) for the sum total

number of simulations for each generation of recessive genes is given by

$$y = C_1 \, e^{0.693x}, \tag{1}$$

where, the value of constant, C_1 = 9.008 and that of exponent, e_1 = 0.693. Exactly the same way, the first best-fit exponential function through the data points for the total number of progenies (filled squares) for each generation of recessive genes is given by

$$y = C_2 \, e^{0.691x}, \tag{2}$$

where the value of constant, C_2 = 2.410 and of exponent, e_2 = 0.691. It will be a good idea to compute the ratio of constants C_1 and C_2. This ratio $C_2/C_1 \approx 27\%$, which proves that only almost a quarter of the total population in a given generation comes from the contribution of recessive genes, and rest of the population in the same generation is from the contribution of dominant genes, which is pretty interesting outcome of the present simulations. The two exponents, e_1 and e_2, in Eq. (1) and Eq. (2) have exactly the same value as expected, which indicates that the population of recessive gene pairs will not increase overtime.

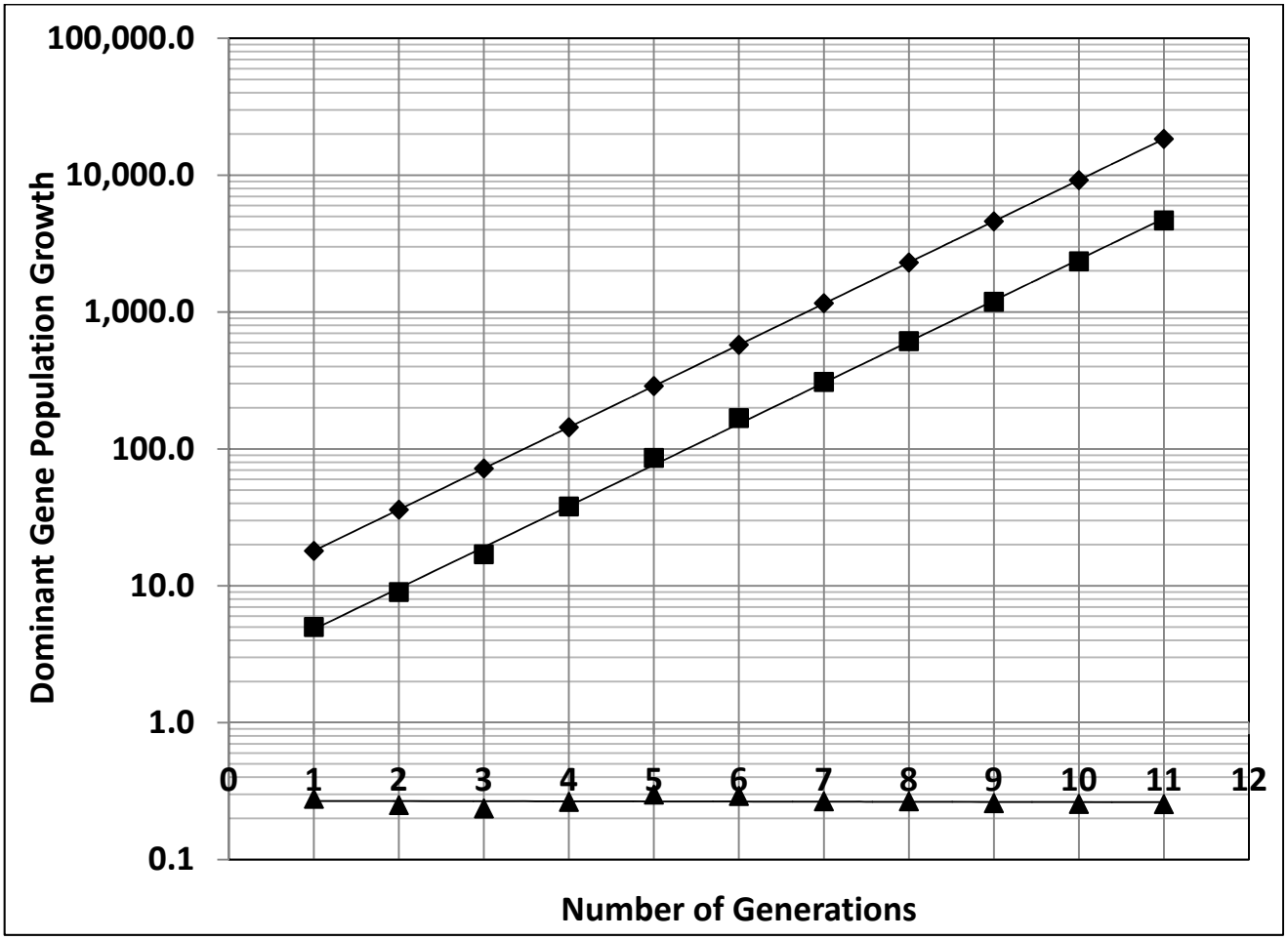

Fig. 2: A plot of population growth of progenies due to recessive genes and ratio of baby population in successive generations as a function of the number of generations. Symbols used in this diagram are: (1) Diamonds (♦) represent starting dominant/recessive gene pairs for a given generation, (2) squares (■) are for population growth due to recessive gene-pairs and (3) triangle (▲) is the ratio of two successive progenies due to recessive genes.

As shown by Mendel that the population growth of progeny produced by the contribution of dominant genes in a given generation, $P_n(D)$, should be expressed in terms of the progeny produced by the recessive genes, $P_n(r)$. Following similar arguments of Ref. [1], one can write an empirical mathematical correlation between the two progenies in the first generation with $n = 1$:

$$P_1(D) = \Sigma\, P_1(\text{Total}) - \Sigma\, P_1(\text{r}). \tag{3}$$

Here, $\Sigma\, P_1(\text{Total})$ and $\Sigma\, P_1(\text{r})$ stand for the sum of total population in the first generation and the sum of the recessive population in the first generation respectively.

For second and subsequent generations, the correlation between the population growth due to dominant and recessive progenies can be expressed as

$$P_n(D) = K(2^n - 1)P_n(r), \tag{4}$$

where n = 1, 2, 3, 4, 5, 6, …….etc. is a running index for 1st, 2nd, 3rd, 4th, 5th, 6th, …etc. generation, respectively. Here, we have used $K = 4$ for the first and subsequent generations. Multiplier factor, $(2^n - 1)$ used in expression of Eq. (4) has odd values, which are shown in 2nd column of Table 3. The results of these computations are displayed in Table 3 and are plotted graphically in Fig. 3. It is clear from Table 3 that starting from the second generation and for subsequent generations, the ratio of off-spring in a given generation to the number of simulations in the same generation increases exponentially, which indicates that the population due to dominant genes should increase or explode in subsequent generations, as observed by Mendel in *Pisum* hybrids. The population in the second generation is four times than that in the first generation. The ratio of populations in third and second, fourth and third, fifth and fourth and of all the subsequent pairs of generations is more or less equals to four. These findings corroborate the experimental results of Mendel on *Pisum* hybrids [1].

The best-fit exponential functions through the three sets of computed data points are represented by Eq. (5) – Eq. (7). Each function when plotted on semi-log scale looks like a straight line plot as depicted in Fig. 3. The first best-fit exponential function passes through the dominant/recessive gene-pair data points (♦) for all the generations, and is given below:

$$y = C_1' e^{0.693x} \tag{5}$$

Here, once again, $C_1^{'}$ = C_1 = 9.008 and exponent has a value $e_1^{'}$ = 0.693, which is exactly the same as in Eq. (1). This function also has exactly the similar form as that of Eq. (1), because Eq. (1) and Eq. (5) represent the same number of starting dominant/recessive gene pairs for a particular generation.

Table 3: Computer Simulations for the contribution of dominant genes in the population growth in several generations are displayed in Table 3, where ratio of the progeny population growth increases in accordance with Mendel's Laws [1].

Dominant Genes (Constants)				
Generation	**Multiplier**	**Staring Dominant/Recessive gene pairs, $P_n(Dr)$**	**Progeny, $P_n(D)$**	**Ratio, $P_n(D)/P_n(Dr)$**
1	1	18	20	1.1
2	3	36	108	3.0
3	7	72	476	6.6
4	15	144	2280	15.8
5	31	288	10664	37.0
6	63	576	42336	73.5
7	127	1160	156972	135.3
8	255	2300	625260	271.9
9	511	4600	2430316	528.3
10	1023	9200	9603924	1043.9
11	2047	18400	38254336	2079.0

The second best-fit exponential function passes through the dominant gene pairs (■) for all the generations and is given below:

$$y = C_2^{'} e^{1.419x} \quad (6)$$

Here, $C_2^{'}$ = 7.153 and exponent $e_2^{'}$ = 1.419. By comparing constants $C_2^{'}$ and $C_1^{'}$ through their ratio $C_1^{'}/C_2^{'}$ = 1.260, we obtain an important information of the intercept of each plot, i.e., the intercept of dominant gene progeny population graph is almost equals that of the starting dominant/recessive gene-pairs plot. In the same way, the ratio of exponents $e_2^{'}/e_1^{'}$ = 1.419/0.693 = 2.048 indicates that the slope of dominant gene progeny population plot is a little more than two times the starting dominant/recessive gene-pairs plot, which is also obvious from Fig. 3.

The third best-fit exponential function in Fig. 3 is for the ratio of progeny corresponding to the dominant gene pairs, $P_n(D)$, to the starting population of dominant/recessive gene-pairs, $P_n(Dr)$:

$$y = C_3' e^{0.726x}, \quad (7)$$

where C_3' = 0.794 and the exponent in Eq. (7) is e_3' = 0.726. The behavior of ratio of progeny of the dominant gene pairs, $P_n(D)$, to the starting population of dominant/recessive gene-pairs, $P_n(Dr)$ has very similar nature as that of the starting population of dominant/recessive gene-pairs, $P_n(Dr)$. This conclusion can be easily drawn from Fig. 3, in which two plots represented by the data points corresponding to diamonds (♦) and triangles (▲) are almost parallel to each other, showing that their slopes should be almost equal. If one looks at the values of e_1' = 0.693 and e_3' = 0.726, one can perceive that their values almost match and, therefore, their slopes are almost equal.

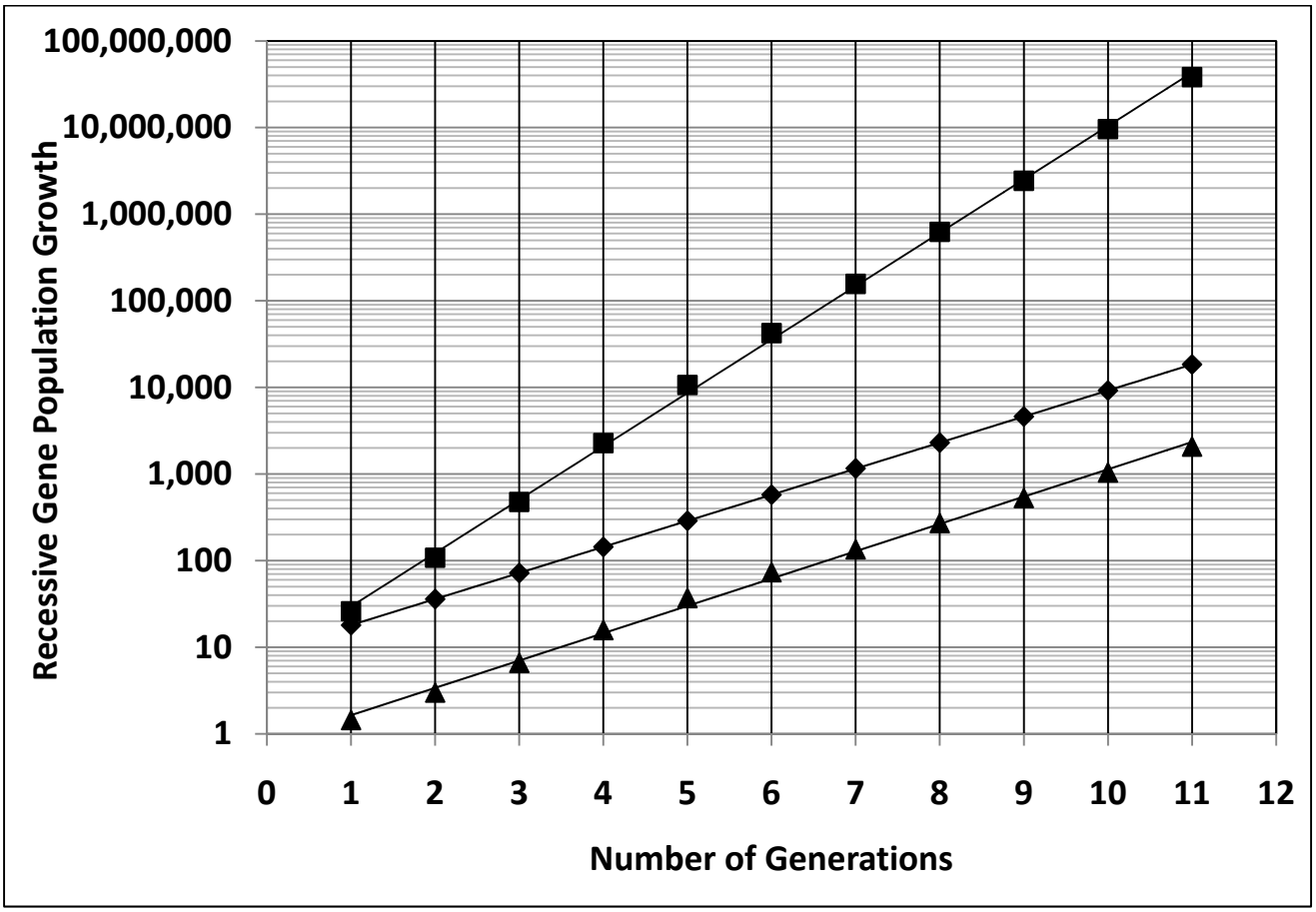

Fig. 3: A plot of population growth of progenies due to dominant genes and ratio of progeny population in successive generations as a function of number of generations. Symbols used in this diagram are: (1) filled diamonds (♦) represent starting dominant/recessive gene pairs for a given generation, (2) filled squares (■) are for population growth due to dominant genes and (3) filled triangles are (▲) the ratio of progeny due to dominant genes to the starting pairs of dominant/recessive genes.

Table 4: F2 generation data of a cross between Lobe and wild-type alleles

	Number of F2 flies			
Phenotypes	**Female**	**Male**	**Total**	**Percentage**
Homozygous Lobe	14	13	27	29%
Heterozygous	21	22	43	46%
Homozygous wild-type	12	11	23	25%
Total	47	46	93	100%

4. EXPERIMENTAL DATA ON DROSOPHILA MELANOGASTER (FRUIT FLY)

Encouraged by the results of monohybrid crosses work performed by Mendel on *Pisum* hybrids [1], which lead to the idea that certain traits appeared in offspring should be according to a ratio determined by the characteristic of that trait, fruit fly, *Drosophila melanogaster,* could be a very good candidate to verify Mendel's laws in biology laboratories. Therefore, fruit fly species is frequently being used to demonstrate the different results of a monohybrid cross, and to figure out whether or not these results would give rise to expected ratios. In a typical monohybrid cross, individuals with one pair of contrasting traits are mated. Variations in these inherited traits arise from alternative forms of a gene, known as alleles. Dominant alleles always appear in the phenotype and recessive alleles are only sometimes expressed in the phenotype [15]. Therefore, it is quite important to investigate the effect that genes have on certain traits, which are expressed in an organism. Though organisms develop and change according to the different environment in which they are confined, genetic inheritance still plays a very significant role. In one particular article on the Genetics of flowering time in chickpeas, it was found that despite the environmental changes, two genetically inherited traits affected flowering time. Simple inheritance, as was first proposed by Mendel, can also affect many different traits and characteristics of organism [16]. An organism with a pair of the same alleles is said to by homozygous for a particular trait, while an organism with a pair of different alleles is heterozygous for the trait. The pair of alleles segregates during gamete formation so each gamete receives only one trait. This is known as Mendel's law of segregation of alleles [15]. Fruit flies are used in experimental studies because they pass through metamorphosis in just 10-14 days, they have a short life cycle, possess high degrees of genetic variability, are convenient, and inexpensive to study [17]. In a monohybrid cross, a 3:1 ratio is expected in the F2 offspring, which is also predicted by our simulation work, e.g., see Table 2 for recessive genes. An experimental mating was performed in a laboratory under controlled experimental conditions of temperature, using Lobe (L), a mutation that results in altered morphology of the eyes. This mutation offers the advantage that the heterozygous phenotype is distinct from the homozygous phenotype and can be monitored in the F2 progeny. A sample of 93 offspring was analyzed in the F2 generation. Number of homozygous mutant, heterozygous and homozygous wild-type offspring is recorded in Table 4. The percentage of various phenotypes observed in the experimental data conforms to Mendel's laws of inheritance. Thus, the ratio between homozygous mutant, heterozygous and homozygous wild-type offspring is 29%, 46%, 25%,

which is close to 1:2:1 and the ratio between homozygous wild-type (the recessive allele in this case) to offspring showing Lobe (the dominant allele) either in the homozygous or the heterozygous form, is close to 1:3. These findings are expected on the basis of Mendel's laws on inheritance.

5. CONCLUDING REMARKS

In the current investigation with the latest version of MS Excel 2007 software system, we have successfully presented for the undergraduates at senior level and for the graduate students in college and university classroom setting, the interactive simulations of Mendel's laws of heredity. We start with two pairs of dominant and recessive genes, perform the computer simulations with help of pseudo-random number generating function, and performed more than 18,000 Monte Carlo simulations. We implement the condition of 50% probability of each dominant and the recessive allele contributing to the offspring. Simulations were performed for more than ten generations. The results of the simulations for recessive gene progeny corroborate the predictions of Mendel's laws on *Pisum* hybrids. Theoretical formulism has been extended to create recursive formula for the progeny of dominant genes, and the theoretical results, once again, match with predictions of Mendel's laws of inheritance. Both for recessive and dominant allele progenies, graphs of their population growth are plotted as a function of the number of generations. The least squares, best-fit exponential functions have been obtained for recessive and dominant allele progenies and their biological implications have been discussed to support the implosion of population of progeny from the recessive gene parents, and explosion of progeny from the dominant gene parents. The present investigation proves that progeny with recessive genes will not survive in successive generations. However, the progeny from the dominant genes parents shall survive and it will explode overtime. These findings are in line with Darwin's theory of survival of the fittest [2].

In summary, we may conclude that the present paper has two important implications both for biosciences, computer science and medical science curriculum: (i) In biological and medical sciences the students learn how to employ versatile software system such as MS Excel 2007 software system [13] to simulate the basic concept of Mendel's laws of heredity, whereas (ii) in computer science, students could visualize the real time application of this fundamental concept of biosciences in a virtual laboratory.

Additionally, we have compared the results of our computer simulated data with that of experiments performed on *Drosophila melanogaster*, the fruit fly extensively being used as a model organism to study genetics and development, and an exceedingly good agreement between simulated and experimental data is observed for F2 progeny.

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