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Research Article

MATH IN PLANT PATHOLOGY: IS THE EARLY BLIGHT OF TOMATO ONE MORE EXAMPLE OF THE GOLDEN RATIO?

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ARTICLE INFO ABSTRACT

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The spiral is a common pattern in nature, with *Nautilus pompilius* often cited as a prime example of the mathematical principles behind spiral growth, such as the "logarithmic spiral." In plant biology, sunflower seeds are arranged in spirals that follow the Fibonacci sequence, optimizing space and minimizing shadowing among the seeds. The Fibonacci spiral and numbers are also prevalent in nature, appearing in the arrangement of leaves, the structure of pinecones, and the scales of pineapples. This pattern reflects how plants grow efficiently, maximizing space for each leaf and the amount of light they receive. Our study on microorganisms causing early blight disease in tomatoes, such as *Alternaria solani*, reveals that Fibonacci numbers frequently appear in the lesion patterns of the fungus. Moreover, our data show that these Fibonacci numbers approach the "golden ratio" (approximately 1.618), suggesting that this pattern optimizes resource allocation for fungal mycelial growth within plant tissue and enhances reproductive success of the fungus.

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INTRODUCTION

Tomato is one of the most agriculturally significant crops and is highly susceptible to fungal infections caused by *Alternaria* species. Among these, *A. solani* and *A. alternata* are particularly damaging, causing severe diseases such as early blight, attributed to *A. solani*, and brown spot, caused by *A. alternata* (Schmey et al., 2024). The symptoms of these diseases, including the early blight/brown spot complex, primarily manifest as foliar lesions that begin as brown spots. Depending on the species, these spots often develop characteristic concentric rings, eventually leading to severe defoliation and substantial yield losses (Schmey

et al., 2024; Singh et al., 2014).

Early blight lesions typically start as small, brown spots on tomato leaves and progressively enlarge into dark brown to black lesions, often displaying targetlike concentric rings on the leaf surface. These distinctive bullseye-like spots make early blight symptoms relatively easy to identify. On the affected leaves, *A. solani* produces mycelium within the plant tissue, while conidia form on conidiophores that emerge from the mycelium on the leaf surface (personal observation). The conidia, which are dark, multicellular, and septate, play a critical role in the spread and survival of the pathogen. During infection, conidia are primarily disseminated by wind and rain splash. Once they land on susceptible plant tissue, they germinate, penetrate, and colonize the host tissue via mycelium, causing the characteristic symptoms of early blight. Effective management of these diseases necessitates an integrated approach, including the use of resistant varieties and timely fungicide applications.

To date, no explanation has been provided for the efficiency of the harmony and the formation of the intricate structures and patterns observed in *Alternaria* rings on the tomato leaves.

In nature, organisms such as the nautilus (*Nautilus pompilius* L.) and snails like *Helix pomatia* create shells composed of chambers that increase in size as the organism grows, enabling them to occupy the outermost chamber (Ward et al., 1980, 1981). Specifically, the nautilus expands by adding compartments of consistent shape, differing only in scale. This growth pattern is widely observed in nature. For example, the fruits of a pineapple are typically arranged in two interlocking helices. Similarly, natural phenomena such as hurricanes and ocean waves frequently exhibit geometric structures and mathematical principles, demonstrating inherent patterns of organization (Carson et al., 1978; Socha, 2007; Minarova, 2014; Oosterhoff, 2018).

In plants, phyllotaxis, the arrangement of leaves, seeds, or petals around a stem, often follows spiral patterns closely approximating the Golden Ratio, as seen in sunflower heads. Spiral patterns are also evident in structures like pinecones and pineapples, where the numbers of spirals adhere to Fibonacci sequences. This arrangement minimizes shading among leaves, ensuring optimal light absorption for photosynthesis. By adopting growth patterns aligned with the Golden Ratio, plants maximize efficiency, reducing the energy needed to produce new leaves, branches, or seeds. Such adaptations allow plants to thrive in competitive environments by optimizing resource utilization (Strauss et al., 2019; Jean-Paul, 2021).

In biology, the nautilus shell is often cited as a classic example of the Golden Ratio due to its distinctive spiral form. This spiral shape is an example of a logarithmic spiral, also known as an equiangular spiral. In a logarithmic spiral, the distance between successive turns increases as the spiral expands outward, but the overall shape remains consistent. This property, known as selfsimilarity, ensures that the spiral looks the same at any scale. The logarithmic spiral form of the nautilus shell enables the organism to grow without altering its shape (Bartlett, 2019; Kaur et al., 2021). As the nautilus matures, it adds progressively larger chambers to its shell in a precise spiral pattern, maintaining its proportions and structural integrity. This growth strategy is biologically and evolutionarily efficient, as it allows the nautilus to expand while preserving the protective structure of its shell.

Similarly, many plants exhibit spiral arrangements in the organization of their leaves, seeds, or petals, often associated with patterns linked to the Golden Ratio. This arrangement optimizes sunlight exposure and facilitates the efficient packing of seeds in structures such as sunflower heads. A comparable growth pattern may also be present in the *Alternaria* fungus, which could maximize spore survival and germination by adopting efficient, stable, and reproductive strategies. This raises an intriguing scientific question: could the mathematical harmony observed in natural forms create target-like rings on leaf surfaces, reflecting a universal tendency toward efficiency and balance, even in pathogens like *Alternaria*?

Exploring this phenomenon further could shed light on how such mathematical principles intersect with plant pathology, particularly in relation to the target-like rings formed on leaves during the early blight disease of tomatoes. By integrating mathematical models with biological processes, this study has the potential to deepen our understanding of the natural world and pave the way for innovative strategies to enhance plant health and productivity.

MATERIALS AND METHODS

Symptoms of early blight caused by A. solani

As noted earlier, the most distinctive symptom of early blight is the formation of brown to dark-brown lesions on the leaves, often exhibiting a concentric ring pattern resembling a target (Figure 1). These lesions typically measure 1-2 cm in diameter and initially appear as irregular brown spots (Figure 2a) or larger brown areas with characteristic dark-brown rings within the lesion (Figure 2b). Early blight symptoms primarily develop on older, lower leaves before progressively moving upward (Figure 2c).

The symptoms usually begin as small necrotic spots on the younger leaves, which gradually enlarge and can eventually lead to the collapse of entire leaflets. According to Adhikari et al. (2017), some authors include *A. alternata* among the species responsible for early blight. However, unlike *A. solani*, *A. alternata* does not produce concentric rings on tomato leaves (Bessadat et al., 2021). Instead, it causes brown spot disease, which starts as small brown spots dispersed across the leaf surface (Schmey et al., 2024).



Figure 1. Characteristic rings or target structures on tomato leaf caused by early leaf blight, *A. solani*.

Concerning the disease cycle, *A. solani* reproduces asexually in the form of either conidia or mycelia, which may serve as primary sources of inoculum (Adhikari et al., 2017). Infection occurs during warm and humid conditions. Conidia germ tubes penetrate host tissue directly or enter through stomata or wounds, thereby causing infection (leaf lesions). Initially, conidiophores develop on the lesion and produce conidia, which are subsequently dispersed rapidly by wind and rain splash. This facilitates the continuation of the disease cycle, infecting healthy parts of the same plant or other plants (Adhikari et al., 2017).

The early blight disease on tomato plants begins with the appearance of small, brownish spots on the lower leaves. These spots gradually grow larger and form concentric rings. The rings are formed by the fungus sporulation, which consists of abundant structures of conidiophores produced in the central area of the leaf lesion. Each conidiophore frequently produces a chain of conidia, which are essential for the survival and pathogenicity of the fungus. This biological process will be further elaborated and explained in detail in this study, including mathematical aspects.



Figure 2. Early blight disease of tomato. Early blight spots start as irregular brown spots with characteristic rings leaf structure (a), and the formation of large brown spots of early blight, showing characteristic dark-brown rings within the lesion (b). Early blight spots start on the older, lower leaves and progressing upward (c).

An example of golden ratio application in biology

As pointed out above, the shell of *H. pomatia*, like many gastropods, follows a spiral pattern. This spiral is often a

logarithmic spiral, similar to that seen in the nautilus shell. The logarithmic spiral in shells allows for continuous, proportional growth without changing shape, which is efficient for both protection and the accommodation of the snail's growing body.

Based on geometric structures using the Spiral of Theodorus (Theodorus of Cyrene (Greek: $\Theta\epsilon\delta\delta\omega\rho\sigma\varsigma$ ò Kυρηναῖος, 465-398 BC), we can construct the snail's body (Gautschi, 2010). In detail, as Figure 3 shows, we start with a left-angled triangle where one of the legs has length 1, and the other leg has length $\sqrt{2}$, and contiguous left triangles, always attaching a new triangle with the hypotenuse of the previous triangle as the longer lengths equal to $\sqrt{3}$, $\sqrt{4}$, ..., $\sqrt{7}$ (Figure 3a) we use geometry for visual representation of the snail's body chambers (Figure 3b).

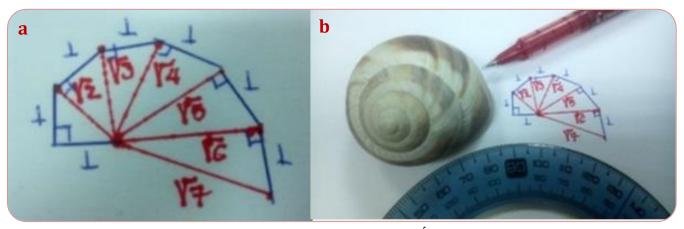


Figure 3. The spiral of Theodorus up to the triangle with a hypotenuse $\sqrt{7}$ (figure 3a). Using the spiral of Theodorus, we create the snail's (Helix pomatia) body chambers (figure 3b).

Apart from the Spiral of Theodorus, the Fibonacci sequence, also known as Fibonacci numbers, and the nautilus shell is connected through a spiral pattern exhibited by the shell, known as the Fibonacci spiral or the golden spiral (Bartlett, 2019). Mathematically, the Fibonacci sequence explains that the chambers in the nautilus shell grow in a logarithmic spiral pattern. Each chamber is added in a way that reflects the Fibonacci sequence, with the size of each chamber corresponding to a Fibonacci number, for example, 0, 1, 1, 2, 3, 5, 8, 13, and so on. These numbers play a fundamental role in number theory and are often encountered in algebraic expressions, equations, and mathematical patterns. Moreover, the Fibonacci sequence is closely related to the golden ratio (ϕ), an irrational number approximately equal to 1.618. Therefore, the snail body pattern (Pandey, 2023), can be seen in the order of the Fibonacci spiral (Figure 4a), where each number is the sum of the two preceding ones, for example, 0, 1, 1, 2, 3, ... (Figure 4b and 5a). In summary, those spiral galaxies have often been modeled as logarithmic spirals e.g. an arithmetic spiral (also known as Archimedean spiral) is a continuous curve that grows outward with a constant difference in radius or as a golden spiral that grows outward by a factor of the golden ratio (ϕ) with each quarter turn left as presented

with a graph of Figure 4b. In our graph (Figure 4b), the golden spiral is created by connecting the corners of squares whose side lengths are successive Fibonacci numbers (1, 2, 3). This pattern, logarithmic spiral growth (Figure 3b), allows the organism to grow without changing shape Figure 4b, which is grown outward by a factor of the golden ratio (Pandey, 2023).



Figure 4. A Fibonacci spiral presents the snail body (figure 4a and 4b). Snail shell exhibits logarithmic.

The Fibonacci sequence

The Fibonacci sequence (Wall, 1960) is a series of numbers in which each number is the sum of the two preceding ones. It usually starts with 0 and 1. Therefore, the sequence is 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, and so on.

The sequence can be defined by the recurrence relation: F(n) = F(n-1) + F(n-2), with initial conditions: F(0) = 0, F(1) = 1

So, each subsequent number in the sequence is the sum of the two preceding numbers. For example, to find the fourth Fibonacci number (F (3)), the preceding numbers are:

F(3) = F(2) + F(1) = 1 + 1 = 2

Similarly, to find the fifth Fibonacci number (F (4)), the preceding numbers are:

F(4) = F(3) + F(2) = 3 + 2 = 5

The Fibonacci sequence has numerous interesting properties and applications in mathematics and nature. Some notable aspects of mathematics include:

Golden ratio

The ratio of consecutive Fibonacci numbers converges to the golden ratio, donated by the Greek letter phi (φ), which is approximately equal to 1.6180339887 or ($\varphi \approx$ 1.618). This ratio has aesthetic and mathematical significance and is often found in various aspects of art, architecture, and nature.

Relationship between Fibonacci numbers and the golden ratio

As we progress along the Fibonacci sequence and calculate the ratio of consecutive numbers (e.g., 21/13, 34/21, 55/34, and so on), the values converge towards

the golden ratio. In mathematical terms, if F(n) represents the nth Fibonacci number, the limit of F(n+1)/F(n) as n approaches infinity is equal to the golden ratio.

Mathematically, this relationship is expressed as: $\lim_{n\to\infty} F(n+1)/F(n) = \phi i$

or φ is considered as a sequence of convergent such as: $\phi = (1/1, 2/1, 3/2, 5/3, 8/5, 13/8, 21/13, 34/21, 55/34 \dots)$

Some notable aspects of the natural world include:

Shell spirals

Some seashells, such as the nautilus, exhibit spiral patterns that can be related to the Fibonacci sequence (Bartlett, 2019).

Sunflower seed heads

The seeds in the center of a sunflower head are arranged in spiral patterns, often forming two sets of spirals, one winding clockwise and the other counterclockwise (Minarova, 2014).

Leaf arrangement and phyllotaxis

The arrangement of leaves on a stem, known as phyllotaxis, often follows a spiral pattern derived from the Fibonacci sequence (Minarova, 2014).

The Fibonacci spirals

The Fibonacci spiral is closely related to the Fibonacci sequence and the golden ratio (Schneider, 2016). When we draw squares based on the Fibonacci sequence (Figure 5a) and connect their corners with quarter circles (Figure 5b), the resulting spiral approximates a logarithmic spiral, and the ratio of the distances between successive arcs converges towards the golden ratio.

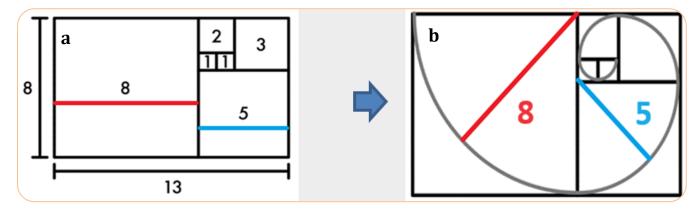


Figure 5. Squares are drawn based on the Fibonacci sequence as is seen in figure a. Based on Fibonacci numbers we have squared patterns (figure a) of side length 1, of length 1+1=2, 1+2=3, of 2+3=5 (square at bottom edge, of side length 5 blue line), of 3+5=8 (of side length 8 red line) and so on. The Fibonacci spiral (figure b) is a geometric pattern that emerges when we draw quarter circles with radii based on the Fibonacci sequence e.g. 5 (blue line) or 8 (red line).

Based on the above mentioned, we tested the hypothesis that the symptoms of the early blight disease of tomato are symmetrical and follow a radial pattern or grow with the same sequence, the Fibonacci sequence, and apart the shape (quantiles), the lines like the lengths of two-line segments (the long side and the short side) have the same ratio of side lengths. The present research work discusses and provides evidence for this hypothesis.

Methodology, the study of early blight lesions, process calculus

We studied leaves of tomato plants with early blight lesions and found a distinctive "bulls-eye" pattern of rings that can be seen with low magnification (20×), as shown in Figures 6a and 6b. Using ImageJ software (Vagelas et al., 2011; Vagelas, 2021), we examined individual lesions and converted color images to black and white (Figure 7). For image analysis, we utilized the free software ImageJ, which can be downloaded from https://imagej.net/ij/index.html. First, we adjusted the image's color balance by selecting Image > Adjust > Brightness/Contrast and Image > Adjust > Color Balance (Figure 7a). Next, we converted the RGB image to grayscale by selecting Image > Type > 8-bit. After that, we transformed the grayscale image into black and white by selecting Process > Binary > Make Binary, as shown in Figure 7b.

We then checked and applied a Fibonacci golden spiral to these images, as demonstrated in Figure 8. We utilized a Golden Ratio Generator (https://goldenratio.club/) to analyze the golden ratio in our blackand-white images. First, we overlaid the Fibonacci spiral onto our images. We then used the apply command to fix the golden spiral overlay, as shown in Figures 8a, 8b, 8c, and 8d. After that, we employed the ruler using the ImageJ program to obtain numerical data (length) from the fixed Fibonacci golden spiral squared patterns by selecting Analyze > Measure. These numerical measurements were taken by assessing the short and long lengths, as indicated in Figure 5. So, for each lesion, apart from the Fibonacci series, we calculated the number preceding it. By dividing the shorter portion (short length, as indicated by the blue line in Figure 5b) of a line by the longer portion (long length, as shown by the red line in Figure 5a), we calculated the inverse phi (φ). This inverse phi (φ), also known as the Golden section, equals 0.61803, while the Golden Number Phi (Φ)

equals 1.61803. The Golden Ratio, specifically the Golden section phi (φ), is well known to appear in nature, especially in botany, and represents a fundamental mathematical structure that is ubiquitous. Further, we utilized the Fibonacci golden spiral pattern and tested the phi (φ) hypothesis as shown in Table 1 on the symptomatology of tomato leaves, depicted in Figures 8a, b, c, and d.

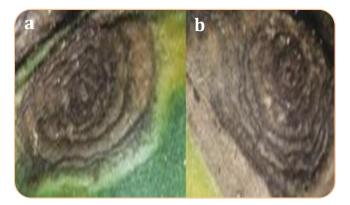


Figure 6. Early blight of tomato. Early blight symptoms (early blight spots) start as irregular brown spots, that appear on tomato leaves (a) and with the formation of dark, concentric rings within the lesion (a, b).

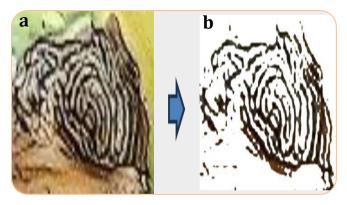


Figure 7. Improved image visualization (a) and converted image to black and white (b) using the ImageJ software. For image visualization we used commands Image > Adjust > Brightness/Contrast and Image > Adjust > Color Balance and for black and white we used commands Process > Binary > Make Binary.

Statistical Analysis

An analysis of variance was performed on all datasets using the JASP 0.18.3 open-source software suite (https://jasp-stats.org/). Further, we used Raincloud Plots in JASP to draw meaningful conclusions from a dataset presented in Figure 9. Plant Protection, 08 (04) 2024. 691-700

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Table 1. A golden relationshi	p between the two lesion	parts, the smaller- sort leng	th a) and the larger- long length (b)
	P	P) (a	······································

1 st Replicate Fig.8a portion (length)			2 nd Replicate Fig.8b			3 rd Replicate Fig.8c portion (length			4 th Replicate Fig.8d portion (length		
			portion (length								
а	b	a/b	а	b	a/b	а	b	a/b	а	b	a/b
0.7	1.2	0.583	0.6	1,2	0.692	0.8	1.4	0.571	1.1	2	0.55
1.2	1.9	0.631	1.2	2	0.591	1.4	2.3	0.608	2	3.2	0.625
1.9	3.1	0.612	2	3.2	0.625	2.3	3.8	0.605	3.2	5.2	0.615
3.1	5.1	0.607	3.2	5.4	0.592	3.8	5.9	0.644	5.2	8.3	0.626
5.1	8.1	0.629	5.4	8.9	0.606	5.9	9.7	0.608	8.3	13.6	0.610
Mean(±S.E. mean) 0.612±0.009 0.621±0.019			0.607±0.012					0.605±0.014			
F(n)	x _{6a} =	0.629	F(n)	x _{6b} =	0.606	F(n)	x _{6c} =	0.608	F(n)	x _{6d} =	0.610
						$\varphi_{experimental} = (x_{6a} + x_{6b} + x_{6c} + x_{6d}) / 4 = 0,613$					

Where: a= smaller portion (sort length), b larger portion (long length) as presented by figure 5. S.E. mean= the Std Error of Mean.

RESULTS

In Figure 8, the Fibonacci Golden spiral pattern perfectly matches all the lesions caused by the Alternaria fungus on tomato leaves. In this set of leaves (Figure 8), the geometry of each lesion pattern is arranged in a spiral pattern. To be specific, the Golden spiral, formed by using quarter-circle arcs inscribed in squares derived from the Fibonacci sequence, fits the leaf lesion patterns in all figures 8a, 8b, 8c, and 8d.

Moreover, numerical data the length ratio data (Table 1), obtained through the analysis of those spirals indicates that the φ experimental value is approximately 0.613 (or Phi = 1.613) comparable and very close to the Fibonacci value of (φ) of 1.618. So, data from Table 1 supported the hypothesis that all patterns of Figure 8 fit the dimensions of the Golden spiral. Using the values from the sequence of the two portion lengths, where the smaller part (a) is divided by the larger part (b) as shown in Table 1, we concluded that there was no statistical **697**

difference between the figures (p = 0.847). Moreover, a raincloud plot (Figure 9), illustrates the raw data, probability density, and summary statistics, including the median and quantiles. This plot combines individual data points, a violin plot, and a boxplot, and shows that these values are very close to the Golden Ratio, approximately 0.61 or φ = 1.61. The raincloud plot (Figure 9) highlights important aspects of the data. First, the raw data (Table 1) aligns with the central tendency. Second, both groups (refer to Figures 8b and 8d or Figures 8b and 8c, in the v-axis of Figure 9), contain an outlier that is not significant. Third, the data distribution (box plots) appears similarly compact, indicating that further inspection or more data are not required. Plotting means and F(n) values from Table 1, we concluded that there was no statistical difference between them (p = 0.765). The raincloud plot (Figure 10) shows that both means and F(n) values (Table 1) are close together, with the means associated with F(n) values.

DISCUSSION

It has been observed that the Fibonacci sequence and the Golden Ratio (Phi = 1.618) are evident in biology and nature, present in various organisms such as the nautilus, snails, pinecones, ocean waves, and hurricanes (Minarova, 2014; Bartlett, 2019; Turner et al., 2023). Our study revealed that leaf symptoms caused by the parasitic fungus A. solani on plants follow the Fibonacci spiral pattern and the Golden Ratio (Wall, 1960), Specifically, our data show that plant lesions caused by the fungus A. solani produce a pattern similar to Fibonacci Rectangles spiral in a quarter turn, and they increase in size by a factor of Phi (approximately 1.618). This suggests a significant connection between the science of plant pathology and the Fibonacci sequence, with phenomena such as the early blight disease of tomatoes showing a connection of disease lesions to the "golden ratio", which is approximately 1.618.

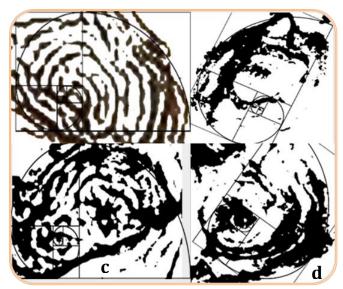


Figure 8. The Early blight disease of tomato lesions, fitted on the Golden Rectangle or with approximations to the Golden Spiral.

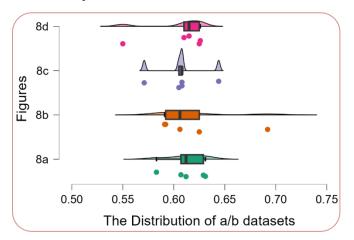


Figure 9. The Raincloud plot provides an overview of the raw data, its distribution, and important statistical properties for two portion lengths, where the smaller part (a) is divided by the larger part (b), as shown in Table 1.

Based on the data presented above, we believe that the Fibonacci sequence is frequently observed in nature, playing a significant role in the survival and dispersal of organisms, such as plants e.g. the distribution of sunflower seeds. It is well known that the arrangement of sunflower seeds in Fibonacci patterns can create optimal conditions for seed development. Based on that, we believe that the *Alternaria* plant pathogen follows a similar pattern for its survival and spread. These arrangements may enhance the efficiency of resource use and space occupation, which could facilitate the dispersal of plant pathogens.

In nature, infectious plant diseases are mainly caused by fungi on leaves. They are initially characterized by small spots that quickly enlarge. As lesions expand, new lesions develop and can affect entire leaves. Some fungi species, such as *A. solani* or *A. tomatophila* (Gannibal et al., 2014), cause leaf lesions, known as leaf spot disease of tomato. These lesions present initially as small circular spots, which progress into irregular lesions with concentric rings later. Tomato early blight spots on leaves start as irregular brown spots that grow in targetlike rings around a bull's eye of dead tissue later. Based on this, mathematics shows that this arrangement, like phyllotaxis, follows a spiral pattern that approximates the Golden Ratio (Wall, 1960; Turner et al., 2023).

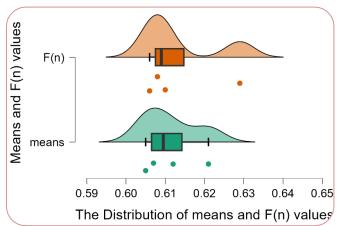


Figure 10. Raincloud plot, which provides an overview of the raw data, its distribution, and important statistical properties between the means and the F(n) values as presented in Table 1.

The spiral pattern likely facilitates efficient fungus development on the leaf surface, contributing to the optimal distribution of fungus conidia. This pattern, following the Golden Ratio (Wall, 1960), is particularly important for fungus development in limited spaces, as it ensures structural stability and efficient conidia production without wasting space. We believe that this spiral growth pattern contributes to both the structural stability of the fungus and its distribution in the plant environment, maximizing reproductive output and the spread of fungus spores. Through the spiral growth pattern, fungus mycelia likely allocate resources, such as nutrients, more effectively for conidia production. Stopping the Fibonacci pattern in *Alternaria* development is complex and requires a deep understanding of pathogen biology, growth mechanisms, environmental factors, genetics, and plant resistance factors that may influence or modify these patterns.

Mathematics provides a framework for modeling complex biological processes, allowing researchers to predict and analyze the spread of plant diseases. By applying mathematical models, we can gain insights into the dynamics of pathogen infection, disease progression, and the effectiveness of control measures. Considering the example of *Alternaria* disease of this research we present a different application of mathematics combining the precision of mathematics with the complexity of plant pathology linked to the pathogen efficacy of space occupation for spread and survival.

CONCLUSION

In general, we believe that the fungus *A. solani* exhibits a spiral growth pattern similar to that of sunflowers, or *H. pomatia* body's chambers. This pattern optimizes resource allocation for mycelia development within the plant tissue and enhances its reproductive success by ensuring that more conidia are produced in a confined space. This phenomenon serves as an example that highlights the profound relationship between mathematics and the natural world.

In summary, the occurrence of the Golden Ratio in the context of the Early Blight disease of tomatoes serves as yet another example of mathematical patterns in plant pathology.

AUTHORS' CONTRIBUTIONS

IV carried out the conceptualization, investigation, writing-original draft preparation, writing-review, editing, visualization, and supervision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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