The Impact of Ordinary and Partial Differential Equations in Understanding Brain Cancer Progression and Improving Treatments: A Decade-long Study

T. Divya, *Member, IAENG,* and V. Ananthan

***Abstract*—Genetic disorders significantly impact human existence, often leading to serious health issues. Cancer is a genetic disorder caused by somatic mutations, which play a key role in its development and progression. Among the various forms of cancer, Brain cancer is a critical and potentially fatal disorder marked by uncontrolled cell proliferation in the brain. This kind of disorder can be modelled using mathematical frameworks. Mathematical tools, such as ordinary and partial differential equations, can be used to identify cancer cells. This report have a significant impact on cancer growth and progress. Hence, this research reviewed the reported mathematical models in brain cancer cell identification between 2011 and 2024 to gain awareness of progress. The primary objective of this research is to assist surgeons in developing effective treatment plans for eliminating malignant brain tumors.**

***Index Terms*—Brain cancer, Chemotherapy, Immune cells, Mathematical modelling, Ordinary differential equations, Partial differential equations**

I. Introduction

IN the modern era, the deadliest epidemic or pandemic that spreads across a vast region, and transcends international borders results in significant loss of life globally. The COVID-19 pandemic emerged as a global crisis in late 2019, spreading rapidly worldwide. There are widespread lockdowns and immense pressure on healthcare systems to eradicate the deadliest pandemic. Mathematical modelling played a critical role in understanding and managing the virus's spread, providing insights into transmission dynamics, predicting infection peaks, and assessing the impact of interventions like social distancing, quarantines, and vaccination campaigns. These models helped governments and health organisations make informed decisions to mitigate the crisis while guiding resource allocation and response strategies in an unprecedented global effort. As of November 17, 2024, the confirmed death toll from COVID-19 has reached 7,074,387 [1].

At present, a large number of individuals globally are affected by chronic illnesses like diabetes and cancer. These diseases have become increasingly common, putting considerable strain on worldwide healthcare systems. Cancer is the second leading cause of death worldwide. It has major drawback in identification at initial stage. Prolonged time, our body cells are damaged by various closed system and abnormal pressure. It can be transformed to cancer. These cancer cells multiply rapidly and spread throughout the body, potentially leading to death. According to the World Health Organization (WHO), breast cancer is a leading cause of cancer deaths globally. Commonly affected areas include the lungs, prostate, colon, rectum, brain, and blood. When cancer-causing agents infiltrate normal cells, they damage the DNA, causing proto-oncogenes within the DNA to activate as oncogenes. This process deactivates certain genes, leading to uncontrolled cell division.

In addition, various factors such as genetics, smoking, high-sugar diets, continuous exposure to radon, asbestos, UV radiation, and hormone replacement are causing cancer. The choice of treatment depends on the specific stage of cancer, classified into four stages. Stages 0-II involve cancers that have not spread, while stage III indicates cancer spread to nearby lymph nodes or surrounding tissues. Stage IV signifies that cancer has spread throughout the body. There are possibilities to live at least 20 years with cancer. This is due to effective treatment given by expert medical examiners.

In 1964, the Indian Cancer Society created the first cancer checklist in Mumbai, which included the urban population. The National Cancer Registry Programme (NCRP) was established by the Indian Council of Medical Research (ICMR) in 1981 in Chennai and Bangalore. Since 1986, many cancer institutes were established which includes Bhopal and New Delhi, owing to the increased number of cancer patients. In 2022, India reported 14.1 lakh new cancer cases, with 9.1 lakhs deaths [2]. Recently, many cancer Institutes have been established in various states of India due to the increased human cancer. Numerous studies and research were done on treatments for cancer, which has a lower survival rate. Early detection and effective treatments have improved survival rates, allowing many cancer patients to live longer. Initial diagnosis can be done through blood tests, imaging, or biopsies. Surgeons assess whether a tumor is treatable or malignant.

Mathematical modelling is used to understand real-world situations. It is used to predict and optimize the system's behaviour by mathematical language. There were numerous applications in the stability analysis of structures like buildings, bridges, dams, and to the signals, spreading of disease,

Manuscript received September 9, 2024; revised April 1, 2025.

This research was supported in part by School of Arts and Science, VMCC, VMRF (DU), India for providing PhD fellowship.

T. Divya is a Ph.D. Research Scholar at the Department of Mathematics, School of Arts and Science, Vinayaka Mission's Chennai Campus, Vinayaka Mission's Research Foundation (Deemed to be University), Paiyanoor - 603 104, Tamil Nadu, India. (e-mail: divyashankar1009@gmail.com).

V. Ananthan is an Associate Professor at the Department of Mathematics, School of Arts and Science, Vinayaka Mission's Chennai Campus, Vinayaka Mission's Research Foundation (Deemed to be University), Paiyanoor - 603 104, Tamil Nadu, India. (Corresponding author: e-mail: ananthan.avmts015@avsas.ac.in).

climate change prediction. Thus, it is a power tool which deals with future behaviour and outcomes. Mathematical modelling on medical field increases to the highest due to our climatic changes and pollutants, increased population, new arising pathogens in the environment etc.

Mathematical modelling is critical in expressing numerous processes encountered in medical research, such as spreading infectious sickness or creating abnormal cells in the human body. The most frequent cancer is the brain and spinal cord cancer. Many curable and optic pathway tumours benefit from effective referral mechanisms, resulting in earlier cancer detection in children. Many researchers put pressure to increase the efficacy of brain cancer treatments mathematically.

Hence, we have reviewed the mathematical modelling of brain cancer to help the world get out of cancer problems in detail.

II. Understanding the Impact of Differential Equations on Early Epidemic Dynamics

The treatments for any deadly diseases can be first illustrated mathematically through a differential system of models to check the validity and assurance of the drugs prescribed to the affected people. Daniel Bernoulli (1760) pioneered the concept of epidemiological inoculation modelling during an outbreak of smallpox in England. This infectious disease, which caused widespread fatalities, has origins that trace back as far as 1350 BCE, evidenced in Egyptian mummies [3]. Bernoulli's work in inoculation modelling eventually contributed to Edward Jenner's development of variolation in 1796, using cowpox material. This inoculation model against the disease increased the life up to 2 years. The first epidemic model was framed in 1927 [4].

$$\frac{ds}{dt} = -\lambda s \tag{1}$$

$$\frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} = \delta(a)\lambda s - \gamma(a) i \tag{2}$$

$$I(t) = \int_0^\infty i(a,t)da \tag{3}$$

$$\frac{\partial R}{\partial t} = \int_0^\infty \gamma(a) i(a,t)da \tag{4}$$

Kermack-Mckendrick theory has represented the pressure from infection as $\lambda = \int_0^\infty \beta(a) i(a,t)da$, with the Dirac delta function denoted as $\delta(a)$. a denote the age of infections. The growth of the infection is described by $I(t)$. The report assumed the transmission rate $\beta(a)$ was equivalent to the removal rate $\gamma(a)$. In 1932 and 1933, the same coworkers [4] expanded this model to more effectively account for birth, migration, and death rates attributed to partial immunity within human populations.

$$\frac{\partial s}{\partial t} = b_0 + b_s S + b_1 I + b_R R - \delta s - m_s S \tag{5}$$

$$\frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} = \delta(a)\lambda(s + \sigma R) - \gamma(a) i - \mu(a) - m_i(a) i \tag{6}$$

$$I(t) = \int_0^\infty i(a,t)da \tag{7}$$

$$\frac{\partial R}{\partial t} = \int_0^\infty \gamma(a) i(a,t)da - \sigma\lambda R - m_R R \tag{8}$$

He framed the equations using parameters like the birth rate (b_j) for state j and the death rate (m_j) for state j per capital. (b_0) is related with the rate of immigration of susceptible and individuals having partial immunity after recovery by ρ. This research expressed a stable solution for epidemic disease control.

In 1967, a freeze-dried vaccine was introduced for smallpox inoculation, eventually eradicating the disease. Epidemic models are used to identify mutation patterns, facilitate the mathematical prediction, control, and treatment of diseases. Otherwise, it leads to significant economic and financial impacts on public health. In the 20th century, mathematicians applied the law of mass action to understand epidemic behaviours. The model based on partial differential equations of Kermack-McKendrick was used to analyze the infectious diseases spread within a population over time [5]. This model helps clinicians to decide the growth of diseases and the exact treatment without any delay, as well as to predict the pattern of any future disease growth. This can be depicted using an algorithm.

A. An algorithm to predict the growth of disease mathematically

Step 1: Start

Step 2: Collect the exact or imprecise situations under knowledge.

Step 3: Estimate the parameters indulged, dependent and independent variables.

Step 4: Frame a mathematical formula to illustrate the situation.

Step 5: Solve Step 4 using numerical solutions of ordinary or partial differential equations.

Step 6: Examine the methodology that can be applied to solve the situation and predict it with mathematical solutions.

Step 7: Convert mathematical solution to practical solution.

Step 8: Then, plan for the reduction of the endemic problems.

Step 9: If Step 8 is False, Go to Step 3 and continue. Otherwise, Stop.

III. Brain Cancer

Brain cancer is also a major cause of cancer-related fatalities. It can be characterized by the abnormal growth of cells within the brain or nearby regions. It is classified into two types such as benign and malignant. Fig. 1 shows the model image of the Brain cancer [6].

The common brain tumor named Glioblastoma, in short Gliomas, has two categories. The primary stage of brain tumor also known as benign tumors originates from the brain, nerves, glands or membranes around the brain [7]. It is usually large in size, grows slowly, and does not spread to other body parts. The malignant stage is spreading from

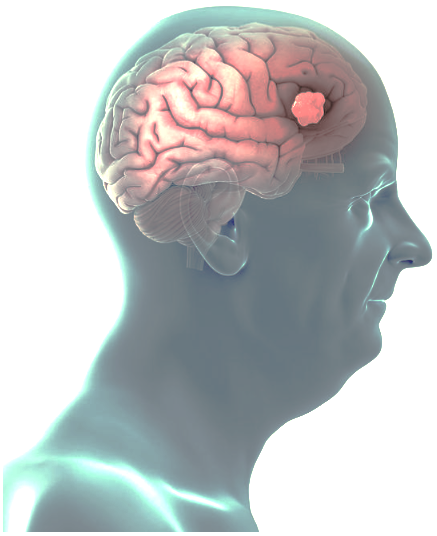

Fig. 1. Model image of Brain cancer [6]

one part to other parts of the body, thus causing lung, breast, skin, and kidney cancers [7]. The benign tumors can be easily operated through surgery [8]. Higher mortality rates were observed for stages III and IV [9], when compared with the Astrocytomas stage (Stage I curable). In contrast, malignant tumors grow and spread quickly within brain tissue. Hence, it is complicated to remove by surgery and leads to severe cancer. Some common symptoms of the brain cancer are confusion, hearing difficulty, nausea, vision problem, balance difficulty, speech difficulty, arms and legs weakness, headache, vomiting. In recent years, various treatments, including craniotomy surgery, endoscopic brain surgery, radiation therapy, radiosurgery, chemotherapy, and targeted therapy, have extended human life expectancy [10].

New treatments reduce the harnesses of the body's immune system to target and destroy cancer cells. Six immunotherapy options have received Food and Drug Administration approval for brain and nervous system cancers [11]. ZAP-X Gyroscopic Radiosurgery is an innovative technology for treating brain tumors, lesions, and various head and neck conditions. This advanced approach delivers highly precise radiation therapy while minimizing exposure to surrounding healthy tissues. Combining gyroscopic motion and targeted radiation enhances treatment accuracy and effectiveness. ZAP-X eliminates the need for invasive procedures, offering a non-invasive alternative for patients. Its cutting-edge design represents a significant advancement in radiosurgical treatment options. CARE T cells are evaluated in a phase I clinical trial to determine their safety and effectiveness. The study focuses on identifying a safe dosage, understanding how long the cells remain active in the body, and monitoring potential side effects [11]. Researchers aim to gather critical data to assess the therapy's potential benefits. This early-phase trial is a key step toward developing new treatments. The findings will inform future research and therapeutic applications.

An mRNA vaccine was tested in a clinical trial to enhance the immune system's ability to fight glioblastoma. This approach aims to train the immune system to recognize and attack cancer cells more effectively. Researchers are evaluating the vaccine's potential to stimulate a stronger and more targeted immune response. The trial represents a step forward in exploring innovative treatments for this aggressive brain cancer. Findings from the study could pave the way for new immunotherapy options. In April 2024, the United States Food and Drug Administration FDA approved tovorafenib treatment for patients 6 months and older with relapsed or refractory pediatric low-grade glioma harboring a BRAF fusion or rearrangement [11]. Recently FDA granted approval for vorasidenib treatment on August 6, 2024, for adults and children aged 12 and up with Grade 2 astrocytoma or oligodendroglioma. This approval is specific to tumors with susceptible IDH1 or IDH2 mutations. It applies to patients who have undergone surgery, including biopsy, subtotal resection, or gross total resection [11].

Procedure to combat brain cancer through innovative vaccines are stated below [11]

- Start
- Activate the immune system to fight glioblastoma cells
- Identify treatment options: Peptide-based vaccine and personalized neoantigen vaccine
- For the peptide-based vaccine: Focus on survivin, a molecule overexpressed in glioblastoma cells Design a vaccine to stimulate an immune response targeting survivin. Evaluate its potential to inhibit tumor growth
- For the personalized neoantigen vaccine: Analyze the patient's specific tumor for unique neoantigens. Develop a vaccine tailored to these neoantigens under expert guidance, Dr. Catherine J. Wu [11]
- Compare the effectiveness of both approaches in activating the immune system and reducing tumor progression
- End

IV. Dynamic Systems Analysis in Brain Cancer Research

An effective mathematical model integrating chemotherapy and radiation therapy has been analyzed [12]. Tumors can be removed without causing harm to the healthy regions of the brain [13][14]. Tumor growth in the brain has been studied by comparing clinical and experimental findings, highlighting the critical connection between theoretical models and experimental data [15]-[17]. When these genes malfunction, they cannot repair DNA damage, which can lead to the onset of cancer [18]. Advancements in understanding tumor growth have been supported by simulations, creating a dynamic process where theoretical frameworks inform experimentation, and experimental outcomes refine theoretical models [19]-[21]. Additionally, a neuroimage of a brain tumor was successfully simulated [22]. Genes involved in DNA repair are essential for correcting errors that arise during the process of DNA replication. Recently boosting the immune cells by injecting cytokines to reduce the cancerous tumors [23].

A linear regression model highlighted a rising trend in nervous system tumors [24]. A technique for solving nonlinear partial differential equations numerically was proposed [25]. Certain side effects associated with cancer treatments pose significant health risks, including weakened immunity, nausea, bruising, bleeding, respiratory issues, hair loss, mouth sores, heart complications, behavioural changes, and

more [26]. Consequently, numerous researchers are dedicated to reducing the adverse effects of cancer treatments.

The main goal is to reduce the side effects linked to cancer treatments. This article presents an extensive review of mathematical models for brain tumors, focusing on enhancing the understanding of brain cancer, its treatment options, and their associated side effects. Cancer progression is modelled mathematically through linear or non-linear differential equations, which provide an effective representation of tumor growth over time. This methodology encourages collaboration between clinicians and mathematicians to develop effective drugs, optimize treatment schedules and dosages, shrink tumors, and minimize harmful side effects.

The mathematical models developed by various researchers assist medical professionals in evaluating and identifying treatment options at the earliest stages. This article reviews research studies published between 2011 and 2024, providing a detailed overview of mathematical models for brain tumor growth. The goal is to offer valuable insights that can help clinicians enhance the effectiveness of brain cancer treatments.

This more reviewed on reports on brain tumor dynamics while excluding research on other cancer types and their behaviours. The objective of this review is to understand above brain tumor characteristics and improve treatment strategies. Through online searches, this work selected 32 relevant articles which have related the brain tumor and differential equations for detailed review. Further, this work have delivered a short review on pediatric brain cancer awareness and its reduction. This article offers a thorough overview to help readers comprehend the development and progression of brain tumors.

Rajibul et al. [27] provided a numerical solution using PDE for effective brain tumor growth prediction. They have used the finite difference method to solve the two-dimensional parabolic PDE. A new technique based on a parallel algorithm was incorporated to trace the brain tumor growth prediction. The report have plotted a two-dimensional plots for the brain tumor progression with different parameters. Further they used the Red-Black Gauss-Seidal method to solve mathematical tumor equation. The same research team used Gauss-Seidel with sequence algorithm to find better solutions to understand the growth of tumors and to emphasise treatment strategies. They also compared the results and concluded that the time taken for execution in GSRB with Parallel Virtual Machine (PVM) is about eight times faster than Gauss-Seidel with sequence algorithm.

In their work, they utilized a discrete type of PDE and implemented a parallel algorithm in the Red-Black Gauss-Seidal algorithm to predict brain tumor dynamics. The report used C-programming to compare the results of computing systems where the growth of tumor cells from 1-30 days at different rounds in grids. They have established a clear view about the growth of tumor cells for five rounds once in 6 days. On the sixth day, the count of tumor cells was 235-239 in number omitting decimals and observed that it has continuously increased to 743-758 cells at the end of 30 days.

The report concluded that the average daily tumor growth rate was 17 cells per day. The data obtained is relatively exact to the actual growth rate of tumor cells. They deduces that the tumor grows slowly, but the progression or transformation is independently faster than usual in brain cancer.

Glioma growth models have been refined by integrating brain topology into a three-dimensional, patient-specific mathematical model. Suarez et al. [28] determined this approach to employ a PDE to simulate cell proliferation and the invasion of surrounding healthy tissue. Daniel et al. [29] proposed a mathematical model to describe tumor growth in relation to blood flow within the brain. The authors defined $u*$ and $P*$ as the velocity vector of interstitial fluid flow and pressure, respectively. Additionally, μ and k represented dynamic viscosity and permeability. The tumor was conceptualized as having a spherical shape, and the interstitial pressure and blood flow velocity were analyzed using second-order differential equations with specified boundary conditions.

$$\frac{\mu}{k}u^* = \nabla P^* \; and \; \nabla u^* = a_1 - a_2 P^* \tag{9}$$

$$\left(\frac{\partial}{\partial t^*} + u^*\nabla\right) C_1 = D_1\nabla^2 C_1 - a_3 C_1 - a_4 C_2 \tag{10}$$

$$\left(\frac{\partial}{\partial t^*} + u^*\nabla\right) C_2 = D_2\nabla^2 C_2 - a_5 C_1 - a_6 C_2 \tag{11}$$

$$\frac{\partial P^*}{\partial r^*} = 0 \; at \; r^* = 0 \tag{12}$$

$$P^* = PB^* \bigwedge C_i = C^*_{B_i} \bigwedge \frac{\partial C_i}{\partial r^*} = T^*_i \; at \; r^* = R^*(t^*) \tag{13}$$

They simplified the given system of equations and derived solutions for blood flow velocity and pressure, providing insights into their behaviour and interaction.

$$P_0(r) = \frac{b_1}{b_2} + (P_B - \frac{b}{b_2})\frac{cos\sqrt{b_2}r}{cos\sqrt{b_2}} \tag{14}$$

$$u_0(r) = -\sqrt{b_2}\left(P_B - \frac{b_1}{b_2}\right)\frac{sin\sqrt{b_2}r}{cos\sqrt{b_2}} \tag{15}$$

They have also used constant coefficients, boundary conditions, and diffusion parameters, the non-zero constants $PB*$, a_1, a_2 for simulations from Tan et al. [30]. Additionally, the study analyzed the concentrations of Etanidazole and Cisplatin, a chemotherapy agent used to shrink the tumor. They have reported that medicine Cisplatin exhibited a higher concentration than Etanidazole when the tumor was assumed to be large. Finally, they concluded that tumor growth could be effectively monitored and managed by regulating the drug concentrations administered to brain tumor patients.

Khairia et al. [31] provided a solution for the stochastic PDE, used to measure tumor growth in time and space. They framed the mathematical model using the abdomen decomposition method.

$$v(x,t) = \varphi(x) + \int_0^t \frac{\partial^2 v(x,s)}{\partial x^2} ds - \frac{2-\sigma^2}{2}\int_0^t v(x,s) ds \tag{16}$$

The solutions are listed below

$$v_0(x,t) = \mu \tag{17}$$

$$v_1(x,t) = \frac{\sigma^2 - 2}{2}\mu(t) \tag{18}$$

$$v_2(x,t) = \left[\frac{(\sigma^2-2)^2}{4}\mu\right]\frac{t^2}{2} \tag{19}$$

$$v_n(x,t) = \left[\frac{(\sigma^2-2)^n}{2^n}\mu\right]\frac{t^n}{n!} \tag{20}$$

They defined the concentration of tumor cells in the brain at specific location x at time $t : v(x,t)$ with μ, ρ representing constants where $\mu = \alpha x + \beta$. The treatment strategy aims to ensure sufficient penetration into the tumor while carefully avoiding damage to the surrounding healthy tissue. This model assists clinicians in predicting whether the tumor size will grow or shrink over time under various treatment approaches, such as surgery, chemotherapy, or radiation therapy.

Cancer cell growth and chemotherapy treatments are comprehensively reviewed by Liu et al. [32]. The report proposed a novel approach in which nongenotoxic drugs selectively eliminate cancer cells while safeguarding healthy cells from the harmful effects of chemotherapy.

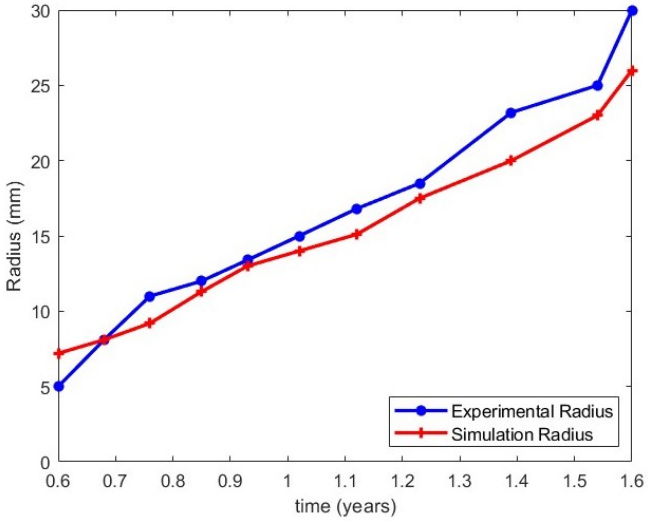

Fig. 2. The comparison between the experimental and simulation radius against time in days at $x^4 = 10$ mm/year [33]

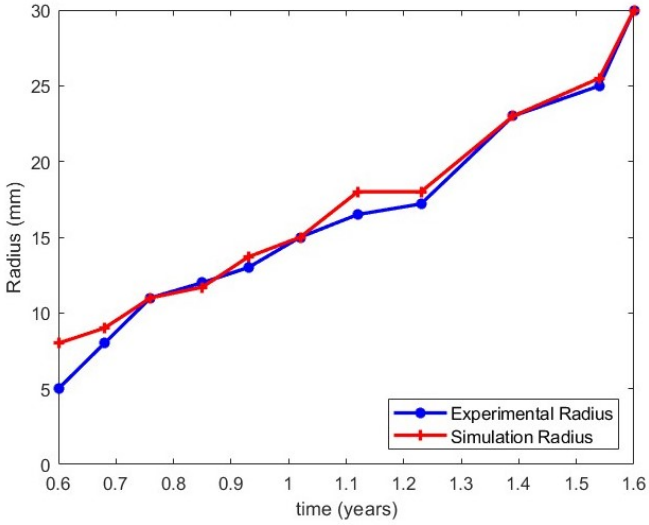

Fig. 3. The comparison between experimental and simulation radius against time in days at $x^4 = 11$ mm/year [33]

Wanjau et al. [33] formulated a PDE to model vascular brain tumors. Using the Adomian decomposition method to solve the PDE, they determined the tumor size following angiogenesis in cancer patients. Their findings demonstrated that this model accurately predicts the tumor radius within a specified time frame. The model incorporates the nutrient concentration $f(x)$ post-angiogenesis and the diffusion coefficient $D_c = \frac{\partial c}{\partial t} = D_c\Delta^2 c + f(x)$.

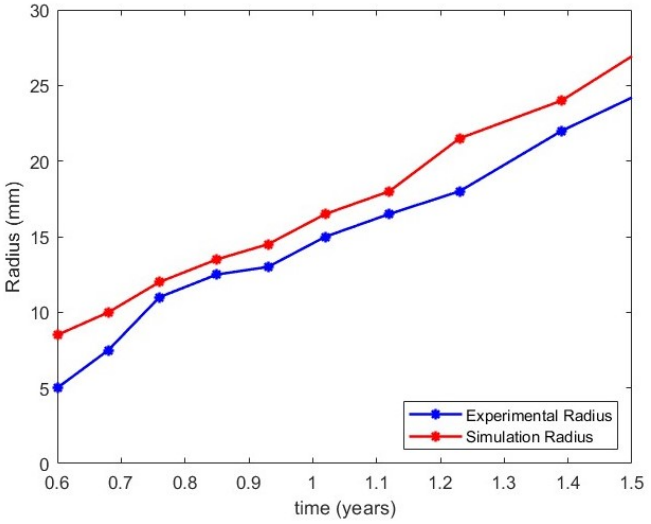

Fig. 4. The comparison between the experimental and simulation radius against time in days at $x^4 = 12$ mm/year [33]

They compared the experimental tumor radius with the simulated radius for nutrient diffusion x^4 at 10 mm, 11 mm, and 12 mm over the course of each year. This comparison yielded a highly realistic simulation, aiding surgeons in cancer management. On the 223^{rd} day, the experimental radius measured 5 mm, while the simulated radius was 7.2 mm, resulting in an error of 2.9 mm. By the 625^{th} day, the experimental radius had grown to 30 mm, with a simulation error of just 0.2 mm when the diffusion of nutrients was 10 mm. Similar comparisons were conducted for nutrient diffusion radii 11 mm and 12 mm by the researcher with the results illustrated graphically in Fig. 2, Fig. 3, Fig. 4.

Ghosh et al. [34] conducted an analysis on factors including patient characteristics, disease attributes, treatment protocols, and survival outcomes among 61 patients who received concurrent chemo-radiotherapy followed by adjuvant chemotherapy, showing low survival rates. Chemotherapy, in addition to surgery, can control the increase in tumor cells. Lestari et al. [35] provided the behaviour of cancer cells undergoing chemotherapy using a mathematical model. The rate of change of the effector cell, tumor cells, and the concentration of drugs given in chemotherapy treatment plays a vital role to reduce tumor. The authors concluded that the fixed point of the above system was asymptotically stable. The report inferred with increasing the concentration of drugs would decrease the number of cancer cells. They analysed the numerical simulations of the fixed points, which remained constant at 0.556 around the fifth day.

Hatchondo et al. [36] investigated the circadian rhythm across 12 distinct brain regions. The study involved samples collected from 30 healthy volunteers. Observations were made at three specific times: 7 : 30 AM, 1 : 30 PM,

and 5 : 30 PM. They modelled these fluctuations, where u represented the concentration of lactate and choline associated with brain development and formulated a nonlinear mathematical model as follows.

$$y' + \frac{ky}{k' + y} = a\ sin(bt + c) \tag{21}$$

$$y' + \frac{ky}{k' + y} = a\ sin^2(bt + c) \tag{22}$$

For $k, k', a, b > 0$ with the boundary condition $y' + \frac{ky}{k'+y} = a\ sin(bt + c)$ with $y(0) = y_0 \geq 0$. The authors proved the boundedness in the following theorems.

Theorem 4.1: The maximum solution y is defined on $\mathbb{R}^+$ with $T_* = +\infty$.

Theorem 4.2: The solution for condition $y' + \frac{ky}{k'+y} = a\ sin(bt + c)$ with $y(0) = 0 \geq 0$, then y is bounded.

Theorem 4.3: If $y_0 \geq 2\frac{a}{b}$ the solution for condition $y' + \frac{ky}{k'+y} = a\ sin(bt + c)$ with $y(0) = 0$, $y_0 \geq 0$, then y is bounded.

They observed that the model $y' + \frac{ky}{k'+y} = a\ sin(bt + c)$ is well derived and the numerical values simulated have a better prediction of the actual clinical data. The report further proved $y' + \frac{ky}{k'+y} = a\ sin(bt + c)$, $y(0) = y_0 \geq 0$ has less concentration of lactate and compared to actual medical data. The predicted values are significantly lower compared to the clinical data. This model is very beneficial to the medical field to understand the brain's circadian rhythm.

The Allee effect plays a key role to study cancer growth. Delitala and Ferraro [37] analyzed both single and dual cancer species by integrating the Allee effect into the growth equation. They inferred that the effect is strong when $A > 0$ and weak when $A < 0$. A single-clone cancer species was represented through the model.

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{k}\right)\left(1 - \frac{A + c}{x + c}\right) \tag{23}$$

The same researchers investigated the weak Allee effect by setting $A = 0$, which simplified the given equation as given below.

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{k}\right)\left(1 - \frac{x}{x + c}\right) \tag{24}$$

In their analysis, x was considered as the number of cancer cells, with r representing the rate of new differentiation of cancer cells and K denoting the maximum growth rate. They observed a exponential growth under a weaker Allee effect $A = 0$ with $r = 0.12$ for various values of c and its vector field. They further investigated whether the system would exhibit a similar response when c remained constant, but the production rate varied.

Niu et al. [38] have demonstrated that as immune cell levels increase, tumor size decreases over time, leading to improved survival rates. A review article highlighted the possibility of achieving high survival rates in glioblastoma cases by Brancato et al. [39].

Sinkala and Nkalashe [40] used Black-Scholas equation $\frac{\partial u}{\partial t} + \frac{1}{2}\sigma^2 x^2 \frac{\partial^2 u}{\partial x^2} + rx\frac{\partial u}{\partial x} - ru = 0$ to understand the spatial growth of brain tumor. Line symmetry analysis was applied to map the tumor equation to the Black-Scholes equation, providing valuable insights for surgeons studying brain tumors. They transformed the variable coefficient PDE into a constant coefficient PDE and utilized the four solutions of the Black-Scholes equation to derive the solution for the tumor equation.

Ramtekkar et al. [41] introduced a model utilizing PDE for detecting brain tumors in Magnetic Resonance Imaging (MRI) scans. This model incorporates deep learning techniques to classify brain tumor types and address neural network challenges. It enables clinicians to pinpoint the tumor's exact location and assess its impact on the brain. The study deduced that the model achieves an accuracy exceeding 99%.

Chandra and Bajpai [42] analysed the early-stage tumor growth and their segments using a PDE. They solved PDE using a mesh-free approach, and the resulting solution was employed to identify the regions of early tumor growth. Alharbi and Ranbely [43] introduced the normal-tumor = immune unhealthy diet model using ordinary differential equations (ODE). They modelled the system using tumor cells T, immune cells I and normal cells N. The behaviour of the stability at different equilibrium points is analysed below. The parameters are non-negative. r : grown-normal cells, γ : denotes grown-normal cells, β_1 : division rate of tumor, η : immune cells, γ : rate at which tumor cells attack the normal cells.

$$\frac{dT}{dt} = \alpha_1 T(1 - \alpha_2 T) + \beta_2 NT - \alpha_3 TI \tag{25}$$

$$\frac{dI}{dt} = \sigma - \delta I + \frac{\rho NI}{m + n} + \frac{\rho_1 TI}{m_1 + T} - \mu NI - \mu_1 TI \tag{26}$$

$$\frac{dN}{dt} = rN(1 - \beta_1 N) - \eta NI - \gamma NT \tag{27}$$

α_1 : the growth of tumor cells, α_2 : tumor cells that do not grow properly, β_2 : abnormal cells converted to tumors, α_3 : rate of tumor cells invaded into weak immune cells. The same authors concluded that the obtained solution is stable and investigated the impact of weak immune cells and an unhealthy diet as contributing factors to the growth of tumor cells.

Trobia et al. [44] utilized continuous differential equations to target and destroy glioma brain cells. The authors integrated chemotherapy into the model, showing its effectiveness in significantly reducing tumor size. Building on the mathematical framework established in Iarosz et al. [45], Trobia et al. refined the model to describe brain tumor growth better and provided evidence that chemotherapy can mitigate neuron destruction in the brain.

Dehingia et al. [46] combined chemotherapy with immunotherapy that enhanced ability to eliminate cancer cells more rapidly. This model is the improved version of the model framed by Tsygvintsev et al. [47]. The authors denoted qM as the gene therapy identifies the differences between tumor cells and normal cells. q meant a protein that activates immune cells. The differentiation of immunity cells rate was p, whereas the natural death rate is μ. $s(t)$ is a therapy that boosts immune system I at time t. The term a denotes the fixed rate at which cancer cells are eliminated during the application of gene therapy by Michaelis Menton term $\frac{aIM}{g+M}$. Under chemotherapy C, the immune $d_1 IC$ and cancer cells $d_2 MC$ undergo destruction. The authors framed the mathematical framework using above parameters to combine the above treatments to eliminate cancer cells.

Noviantria et al. [48] provided the progression of brain tumor growth, including the rate of tumor cell division and its spread to surrounding tissues, can be analyzed using exponential growth, logistic growth, and Gompertzian growth models. The study revealed that Gompertzian growth predicts tumor growth patterns approximately 2.8 times faster than the exponential or logistic models. Authors have employed the finite difference method to solve the model numerically and compared their findings with the results obtained by Ozugurlu [49].

Arora et al. [50] demonstrated that tumor cells initially proliferate without diffusion. After one month, the cells begin to diffuse, replicate, and their density increases to 0.1, eventually reaching 0.6. The authors documented the tumor growth rate over six months by analyzing its dynamics at 30-day intervals. The model was developed by extending Fisher's equations in the following manner.

$$\frac{\partial u(x,t)}{\partial t} = \nabla(D(x)\nabla u(x,t)) + \rho(x,t) - \alpha(x,t)u(x,t) \left(\frac{1 - u(x,t) + v(x,t) + w(x,t)}{u_*(x)}\right) u(x,t) \tag{28}$$

$$\frac{\partial v(x,t)}{\partial t} = -f((x,t,u(x,t),v(x,t),w(x,t)) \tag{29}$$

$$\frac{\partial w(x,t)}{\partial t} = -f((x,t,u(x,t),v(x,t),w(x,t)) + \alpha(x,t)u(x,t) \tag{30}$$

The study involves the diffusion coefficient $D(x)$ rate of proliferation $\rho(x,t)$, the carrying capacity $u_*(x)$ with $\alpha(x,t)$ representing the rate at which tumor cells are destroyed due to chemotherapy and radiotherapy treatments. They focused on addressing brain tumor reduction by applying the differential quadrature method using trigonometric B-spline functions. The numerical results illustrated that this model effectively preserves the behaviour and density of normal cells as well as those surrounding the brain tumor.

Lucci et al. [51] analysed the effects on healthy tissues surrounding a brain tumor. This has garnered significant attention in the research community as it helps shield neighboring tissues from cancer cells. In their research, they utilized MRI and DTI data from patients to characterize tumor density by considering both the solid and fluid phases of the brain's soft tissue. A multiphase mesh approach was employed to distinguish stress distribution between the fluid components and the brain's solid structure. Additionally, the model effectively facilitated simulations for radiotherapy and surgical procedures.

The toxicity associated with chemotherapy treatment was examined by Conti et al. [52]. This study introduced a mathematical model incorporating both chemotherapy and anti-angiogenic therapy, focusing on how these treatments reduce the nutrient supply to cancer cells. The researchers also identified optimal control strategies to balance the cytotoxic and anti-angiogenic effects in cancer treatment.

Nave [53] created a non-linear first-order ODE model to examine the effects of chemotherapy and immunotherapy treatments for brain tumors. The study tracked treatment schedules and drug dosages administered over intervals of 7, 14, 28 and 56 days, and compared the results with clinical data. A stronger correlation was observed between cancer cell growth and these time intervals.

Varsoliwala and Singh [54] developed a non-linear PDE to model the reduction of tumor growth. This study integrated chemotherapy and radiotherapy into the tumor growth equation and applied the Adomian decomposition method to solve it.

Nayied et al. [55] analysed the brain tumor growth by the numerical solution which was expanded using generalized Laguerre polynomials. The authors modeled the growth of brain tumors incorporating initial conditions from Avazzadeh et al. [56] and solved mathematically utilizing Haar wavelets and Fibonacci matrices. The quasilinearization method was employed to address the nonlinearity in the Burgess equation, examining the impact of medical therapies on brain tumor progression.

Sadique et al. [57] introduced a neural ODE to study the growth patterns of brain segments. Recent studies have also explored the killing capacity of tumor cells under the influence of chemotherapy. They denoted the change in tumor cell density as the sum of tumor cell diffusion and growth, minus the killing rate, represented mathematically as follows.

$$\frac{\partial U(x,t)}{\partial t} = D\frac{1}{x^2}\frac{\partial}{\partial x}\left(x^2\frac{\partial U(x,t)}{\partial x}\right) + \rho U(x,t) - k_t U(x,t) \tag{31}$$

where $U(x,t)$ is the amount of tumor cells in the location x at time t; D is diffusion coefficient; ρ is the rate of increase in tumor cells; k_t is the killing rate of tumor cells due to chemotherapy treatment in fractional order.

Romero et al. [58] combined ODE and PDE system together, comprised to three equations representing tumor, necrosis, and vasculature. This assisted the clinicians to study the biological characteristics of glioblastoma, including malignant tumor ring volume. Several mathematical models collected by Falco et al. [59] have shown potential to assist medical practitioners and significantly contribute to advancements in tumor management and improved patient outcomes, emphasizing the importance of preserving healthy cells during treatment. Mendoza et al. [60] provided a comprehensive understanding of brain tumor growth.

Paul et al. [61] recently conducted a thorough survey on brain tumor types and their growth patterns in patients from the northeastern region of India. Their study revealed that 68% of the patients were male, and 32% were female, from a sample of 100 individuals affected by brain tumors in the northeastern part of India. Clinical data collected from brain tumor patients indicated that 46% of cases were located in the lower region of Assam. Chemotherapy and Radiotherapy treatment were given to 61% of the patients, 22% undergone Radiotherapy. Beyond the treatments there were side effects due to radiation or the over dosages of drugs. Some 7% patients stopped their treatments and 10% dint endure treatments in India. The authors concluded that glioblastoma and astrocytoma were more aggressive brain cancers than other primary brain tumours in northeast India between 2017 and 2022.

Kumar et al. [62] examined the dynamics in brain tumor if a drug was being injected to the brain via the nasal route. The young researchers Raad et al. [63] recently examined the side effects of chemotherapy on brain tumors. It was inferred

that drug dosage can influence lactate production in the brain. Specifically, a dosage of 21.9 day^{-1} was shown to increase lactate concentration. Conversely, a reduction in tumor cells was associated with decreased lactate concentration was presented in their work as illustrated in Fig. 5.

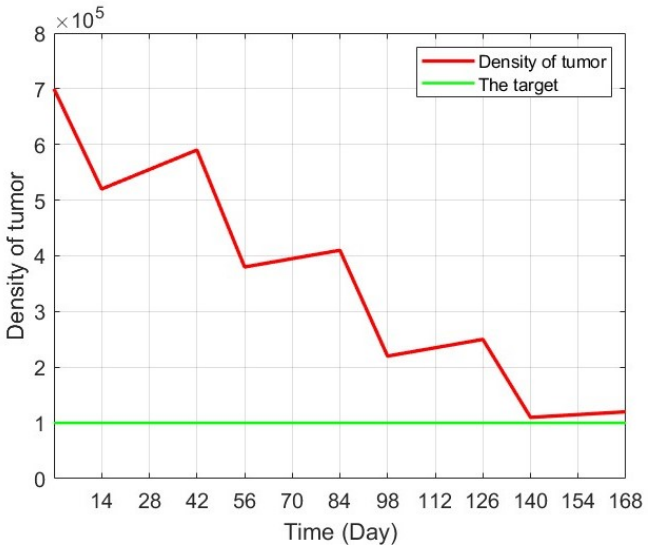

Fig. 5. Tumor cell decreases with a decrease in lactate concentration [63]

V. EXPLORING THE CHALLENGES OF BRAIN TUMORS IN CHILDREN

Brain tumors are not just a concern for adults; also affect children. Kartik et al. [64] provided a detailed survey in India: 8% to 12% of children were diagnosed with brain cancer, compared to 21% in the western regions of the country. A significant factor contributing to delayed treatment is the lack of awareness about childhood brain cancer. They stated that situation is critical in India, as the survival rate for children with brain cancer is less than 26.8%.

The government have launched various awareness campaigns to promote early detection and recognise the disease's symptoms. When cancer in children is detected early, it is often treatable; otherwise, it can lead to severe neurological issues. Magnetic Resonance Imaging (MRI) was introduced over 30 years ago and has significantly advanced the detection of cancer. However, despite the technological progress, public awareness remains low, contributing to the rise of malignant brain tumors. This lack of awareness is resulting in higher mortality rates, with children also being increasingly affected by brain cancer.

On a global scale, governments are running awareness campaigns to highlight the symptoms of brain cancer. Tamil Nadu is widely recognized for its impressive healthcare achievements, securing the second position in India for its advancements in the medical field. Despite this, brain cancer remains a substantial challenge within the state. The complexities surrounding the diagnosis and treatment of brain cancer continue to hinder progress in effectively managing the disease.

Early detection, while critical for improving outcomes, is often delayed due to limited awareness and insufficient access to specialized medical resources. Furthermore, the treatment of brain cancer, especially in its advanced stages, remains a formidable obstacle, as effective therapies are still limited and not universally accessible. This combination of diagnostic delays and treatment barriers contributes to the persistence of brain cancer as a major public health issue, underscoring the need for continued research, improved healthcare infrastructure, and greater public awareness to combat this life-threatening condition.

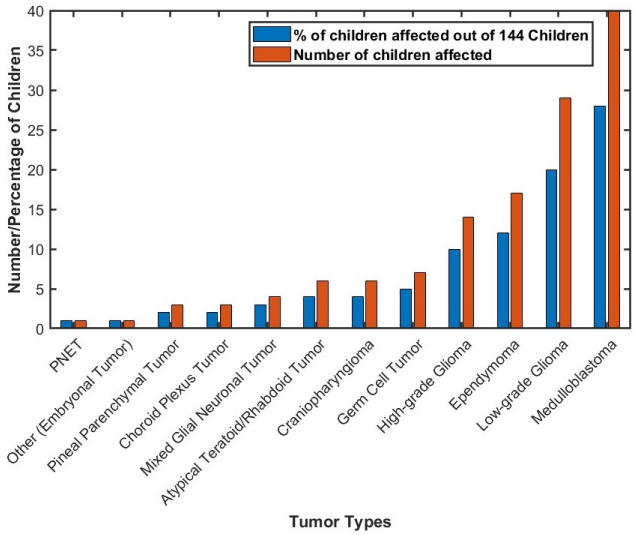

Fig. 6. Various types of brain tumors affected by children [64]

A study was conducted by the same authors to analyze the delays in diagnosing brain cancer and the types of tumors affecting children across eight leading cancer hospitals in Tamil Nadu shown in Fig. 6. They briefly focused on pediatric brain cancer cases reported between January 2018 and October 2020 in India. A total of 144 children with brain cancer were studied, with 40% being under 5 years old, 47% between 5 and 11 years, and 12% older than 12 years.

They effectively illustrated the various types of brain tumors and their specific locations within the brain shown in Fig. 7, drawing on data gathered from 144 pediatric cancer patients. This comprehensive study provided valuable insights into the distribution and characteristics of brain tumors in children, highlighting the diversity of tumor types and their distinct anatomical positions. The data revealed crucial patterns related to the age of the patients and the prevalence of different tumor locations, which are essential for understanding the progression and symptoms of pediatric brain cancer. By analyzing the collected information, the authors were able to offer a detailed picture of how these tumors manifest in the developing brain, underscoring the importance of early detection and targeted treatment strategies for young patients facing these challenges. Thus their research deduced that out of 144 children, 89 showed symptoms of vomiting, 68 experienced headaches, 64 faced motor difficulties, and 12 displayed an abnormal gait along with other associated issues.

In [65], Falco et al. reviewed the advantages and limitations of modeling glioma brain tumors and medulloblastomas, which primarily affect children. Their report also examined ependymomas, tumors originating in the ependymal cells of the brain or spinal cord. This review further included detailed analyses of studies where tumors were

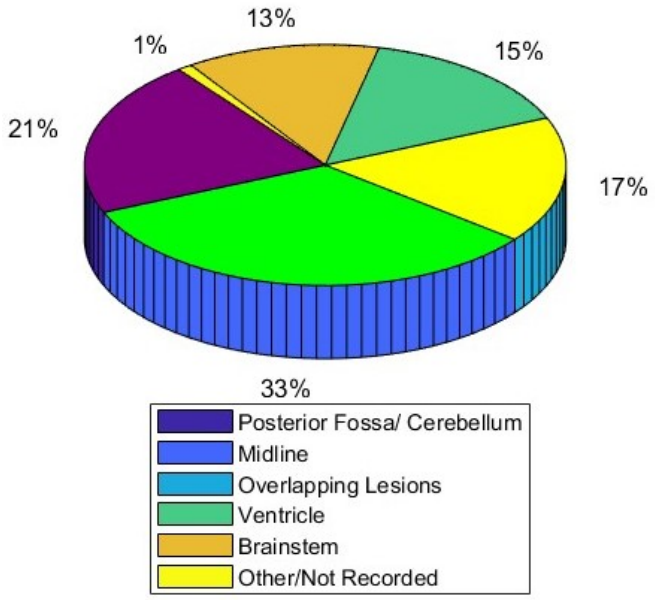

Fig. 7. The specific location of pediatric brain tumor [64]

induced in mouse brains to investigate tumor growth and the effectiveness of various therapies.

Faruqui et al. [66] have highlighted the factors contributing to brain cancer in children across different states of India. These investigations focus on identifying potential causes specific to various regions by the same authors [67]. The findings emphasize the need for localized research and interventions. Understanding regional variations can aid in developing targeted prevention strategies. Such studies are crucial for addressing the growing concern of pediatric brain cancer by Ahuja et al. [68] and Yadav et al. [69]. The issue of limited knowledge about pediatric cancer symptoms and treatment options was addressed by Ganguly et al. [70]. Many individuals are unaware of the early warning signs of the disease. This lack of understanding often delays diagnosis and treatment. Raising awareness is essential to improving early detection. Educating the public about available treatment options is equally important. Further studies should explore how the location of a tumor influences a child's symptoms, thus aiding in quicker and more accurate diagnoses. Improved training for cancer treatment and the development of effective referral pathways could lead to earlier diagnosis and better livelihood of children.

VI. Applications of Differential Equations in Modelling Dynamic Systems Across Various Fields

Chong et al. [71] framed a Lotka-Volterra ammensalism model using the fear effect to understand the dynamic behaviour of the model. By incorporating the impact of fear on species interactions, the study analyzed the changes in population dynamics and stability. The findings provide deeper insights into the role of behavioral responses in ecological systems, enhancing the understanding of species coexistence and interaction patterns. Simulation Study on Ideal Camera Angles for Inspecting Glossy Surfaces done by the author Tanaka [72]. Wang et al. [73] modelled a leveraging spatio-temporal patterns to identify anomalies in traffic flow data. By analyzing both spatial relationships and temporal trends, the model effectively detects irregularities, ensuring accurate monitoring and management of traffic systems. Their approach integrates advanced data processing techniques to enhance the reliability of anomaly detection in complex traffic networks.

An adaptive correlation graph neural ODE model is used to forecast traffic flow. The model dynamically captures the evolving correlations within traffic networks by integrating graph neural networks with the continuous modeling capabilities of ODEs. Bai et al. [74] provides a more accurate and flexible framework for predicting traffic patterns, effectively addressing the challenges of temporal variability and spatial dependencies in traffic flow data. Xiao et al. [75] designed a lightweight convolutional neural network (CNN) model to identify pests and diseases. Their model incorporated a gated multi-scale coordinate attention mechanism to enhance feature extraction and focus on critical regions. Bai et al. [76] presented a dual-graph attention neural controlled differential equation model for precise prediction of urban rail passenger flow. This innovative approach have improved prediction accuracy, offering valuable insights for urban transportation planning and management.

Jummannavar et al. [77] proved that the numerical solution of singular Lane-Emden type equations, often encountered in astrophysics and applied mathematics. It can be effectively tackled using clique polynomials. These polynomials, based on the combinatorial characteristics of graphs, provide a structured approach for approximating solutions to such nonlinear differential equations. This technique efficiently addresses the singularity in the equations, ensuring accurate and stable results. Consequently, the authors provided the use of clique polynomials offers a robust and efficient framework for solving singular Lane-Emden type equations numerically. Cahyono et al. [78] provided an analytical solution to the Lotka-Volterra model in the vicinity of its equilibrium point that has not been previously investigated by other researchers.

Vineetha ans Shiyas [79] established an effective different Genetic Algorithm variants in solving the complex Dynamic Facility Layout Problem. Yang et al. [80] presented a novel network model called the Image Guidance Encoder-Decoder Model (IG-ED). This model was specifically designed to optimize the process of image captioning. It focused on enhancing efficiency while also improving the accuracy of predictions. By leveraging advanced techniques, IG-ED aims to bridge gaps in existing methodologies. Their model offers a promising approach to achieving more reliable and effective image captioning results. Kamput and Dechsupa et al. [81] presented a modeling and verification approach for traffic right design models using a timed automaton called Uppaal. Their aim was to enhance the accuracy and reliability of traffic system simulations method. By applying Uppaal, the study verified the correctness of the traffic right designs in various scenarios. This approach offers a structured way to assess and optimize traffic flow models. The authors concluded that the use of Uppaal provides a rigorous framework for analyzing time-dependent behaviors in traffic systems.

Baokar et al. [82] designed a Memristive Neural Network (MNN) that demonstrates comparable accuracy to CMOS-based Deep Neural Networks (DNNs), while significantly

reducing power consumption. The authors showed that the MNN offered an alternative by leveraging memristive devices for energy-efficient processing. Despite the lower power usage, the network maintains high performance, making it suitable for resource-constrained applications. Their design highlighted the potential of memristive technology in neural network implementations. Ultimately, this approach provides a sustainable solution without compromising accuracy. Chen et al. [83] enhanced balun model that accurately incorporates differential-mode and common-mode mutual inductances.

Oghonyon et al. [84] focused on creating softcodes designed for the parallel processing of Milne's device (SPPMD). This approach employed an exponentially fitted method, which is particularly well-suited for solving certain special ordinary differential equations. Their method enhanced computational efficiency and accuracy by using parallel processing. The proposed softcodes are tailored to handle the unique challenges associated with ODE. Further, the report established advanced numerical methods for solving differential equations more effectively. Li and Wu [85] designed a compact and efficient object detection model based on YOLOv8, specifically for detecting small objects in aerial images captured by a Unmanned Ariel Vehicle.

VII. Conclusion

Mathematical modelling has become a vital asset in the biomedical field, offering significant advantages for simulating tumor behaviour and progression. These models are essential for gaining a deeper understanding of cancer dynamics and predicting how tumors evolve over time. This report enables the evaluation of various treatment options, including surgery, chemotherapy, gene therapy, and radiation therapy, by providing insights into their effectiveness and potential outcomes. This article highlights the role of mathematical models in deciphering the complexities of brain tumors, enhancing our awareness of symptoms, and optimizing treatment strategies. Advance in medical research, the integration of mathematical modelling continues to be instrumental in improving patient care and refining therapeutic approaches. This review article explored the diverse applications of modeling in various disciplines through the use of differential equations.

Acknowledgment

The authors would like to thank faculties of School of Arts and Science, VMCC for their invaluable insights, guidance, and encouragement in refining the technical writing and enhancing the quality of this review article.

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T. Divya (M'24) earned her Master of Science in Mathematics with a Gold Medal in 2017 from D.K.M. College for Women (Autonomous), affiliated with Tiruvalluvar University, Vellore, Tamil Nadu, India. She became a Member (M) of IAENG in 2024. She is currently pursuing her Ph.D. in the Department of Mathematics at the School of Arts and Science, Vinayaka Mission's Chennai Campus, Vinayaka Mission's Research Foundation (Deemed to be University), Paiyanoor, Tamil Nadu, India. She has published four research articles in Scopus-indexed journals. Her research interests include mathematical modelling, graph theory, and their applications.

V. Ananthan is an Associate Professor in the Department of Mathematics at the School of Arts and Science, Vinayaka Mission's Chennai Campus, Vinayaka Mission's Research Foundation (Deemed to be University), Paiyanoor, Tamil Nadu, India. He earned his Ph.D. in 2017 from the Vinayaka Mission's Research Foundation (Deemed to be University) in Salem, Tamil Nadu, India. With 13 years of teaching experience, he has contributed to numerous national and international journals through his research. His research interests include differential equations, difference equations and mathematical modelling.