

# Treatment Methods Combining Physics and Medicine: Their Incorporation Into a Theoretical Model for Glioblastoma Treatment Selection

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Medicine has advanced with innovative treatment approaches that combine physics and medicine such as bioresonance and tumor-treating fields (TTFields). Bioresonance makes use of electromagnetic signals the human body emits to diagnose and treat diseases. Tumor-treating field systems deliver intermediate-frequency, alternating electric fields to the supratentorial brain through transducer arrays attached to the scalp of patients and are FDA-approved for glioblastoma (GBM) treatment. GBM is a fast-growing and aggressive brain tumor. This study proposes a theoretical model that would aid physicians in determining the most suitable treatment plan for patients with GBM. The inputs of the model include tumor volume and shape, tumor location, patient age and MGMT promoter methylation status, recurrence status, as well as medical history. The model serves as the foundation of a neural network. If patient data were to be input, the neural network would analyze it, make use of backpropagation to adjust the weights for each input using gradient descent to reduce error, and produce a percentage for possible treatments based on their suitability for the patient. The current standard treatment for GBM is surgical resection, followed by adjuvant temozolomide (TMZ) combined with radiotherapy (RT). However, the model includes TTFields given that they are FDA-approved for GBM treatment. Bioresonance in combination with chemotherapy is also included as bioresonance improves overall health and quality of life. The theoretical approach of this study can be applied to other types of tumors. The paper could also inspire studies in bioresonance and how it could be integrated into standard cancer treatment.

**Keywords:** Physics; Medicine; Cancer Treatment and Therapies; Glioblastoma (GBM); Tumor-Treating Fields (TTFields); Bioresonance

## Introduction

### Literature Review

Physics is the study of matter and governs principles behind gravitational, electromagnetic, and nuclear force fields<sup>1</sup>. It is the driving force behind a vast number of fields, including medicine. Emerging treatment options utilize physics for innovative treatments that could change the way healthcare is viewed. This paper will present two of those treatment approaches: bioresonance and tumor-treating fields, both of which are currently being researched.

Bioresonance is an alternative treatment that uses electromagnetic signals the human body emits to diagnose and treat diseases, which result from the disruption of normal cellular electromagnetic communication due to interference of a pathogenic microorganism<sup>2</sup>. Human cells have resonant frequencies<sup>3</sup>. In recent years, researchers have measured some of these frequencies, the rates at which cells would naturally oscillate in normal conditions<sup>3</sup>. Bioresonance is based on the magnetic field spectral analysis of living organisms, allowing for differentiation

between normal and abnormal frequencies that are emitted by our bodies<sup>2</sup>. The first electronic device that could receive and return electromagnetic frequencies to or from the body with the use of electrodes was created by Franz Morell electrical engineering technician Erich Rasche in the 1970s<sup>2</sup>.

*Spooky2*, a company that produces machinery to treat people with bioresonance, provided information on some of their machines. Cold Laser Mode uses safe, non-thermal light photons to accelerate the body's natural restoring processes, being useful for pain, joint and neurological problems, wounds and burns, dental issues, lymph node swelling, tinnitus, bone and tissue regeneration<sup>4</sup>. *Spooky2* Pulse sweeps above and below each frequency in a program that patients are undergoing until it finds the value that works best for them and provides them with a ranking of frequencies according to how well they work for them<sup>4</sup>. *Spooky2* Digitizer can be used for scanning biological samples such as urine, saliva, etc., and the results are accurate because of the high ratio of pathogens within the sample<sup>4</sup>. The machine is suited for finding pathogens and sending result frequencies for health improvement<sup>4</sup>. Furthermore, the company

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also has a scalar machine. Scalar fields introduce energy, which restores cell communication and exposes the diseased cells to the body's defenses<sup>4</sup>. Mitochondria are the power stations of cells, and scalar fields charge the mitochondria, thus giving cells energy to open and remove the blockages<sup>4</sup>. Many people have reported to the company that they have seen improvement in their chronic migraine, chronic fatigue, and sleep disorders<sup>4</sup>.

Studies have been done to showcase the effect bioresonance can have when it comes to combating different diseases or illnesses. It is assumed that weak, coherent, and low-frequency electromagnetic oscillations are carriers of information on a biophysical level, and one study, which was placebo-controlled and double-blind, aimed to examine if bioresonance could have an impact on smoking cessation<sup>5</sup>. Each group in the study consisted of 95 smokers between the ages of 18 and 75, with the bioresonance treatment being monitored after 1 week, 2 weeks, 1 month, and 1 year<sup>5</sup>. The results of the experiment were successful in showcasing the efficacy of bioresonance therapy and the lack of any adverse side effects to it<sup>5</sup>. A comparison was made with varenicline, an effective pharmacological solution, and the results were similar in effectiveness, yet varenicline tended to cause unpleasant side effects<sup>5</sup>.

Currently, several treatment methods combine physics with medicine to heal people. An example is the use of tumor-treating fields as a therapy for glioblastoma. GBM is the most common primary malignant brain cancer, with median overall survival (OS) ranging from 12 to 18 months<sup>6</sup>. It is fast-growing and aggressive, invading nearby brain tissue<sup>7</sup>. The TTFields system delivers intermediate-frequency, alternating electric fields to the supratentorial brain through transducer arrays attached to the shaved scalp of the patient<sup>8</sup>. The therapy consists of two main components: the delivery system, encompassing insulated transducer arrays and the electric field generator, and the frequency and intensity<sup>9</sup>. The transducer arrays are composed of nine insulated ceramic discs with a high dielectric constant which are separated from the skin through a layer of conductive hydrogel and which are attached to a flexible circuit board<sup>10</sup>. There are no ion concentration changes in the cells nor electrolysis, and the arrays have eight temperature sensors that continuously monitor temperature<sup>10</sup>. If the array exceeds 41°C, the device will shut off and sound an alarm<sup>10</sup>. The two perpendicular electrodes of the arrays allow for the transcutaneous delivery of electric current<sup>9</sup>. The application of alternating electric fields happens transcutaneously through the placement of the electrodes on the skin's surface<sup>9</sup>. The magnitude of the electric field is directly proportional to the potential difference between the electrodes and inversely proportional to the distance between them<sup>9</sup>.

The intensity and frequency of the applied electric fields dictate the efficacy of TTFields therapy<sup>9</sup>. For glioblastoma treatment, the appropriate frequency is 20KHz, while for malignant melanoma, a frequency of 150KHz is used<sup>9</sup>. These targeted frequencies hinder heat generation, as well as nerve and muscle

stimulation, minimizing the risk of adverse effects following therapy<sup>9</sup>.

In various preclinical studies, it was shown that the TTFields could arrest the division in cancer cells through the hindering of mitotic spindle formation and normal cytokinesis by disrupting cytoplasmic furrow formation<sup>11</sup>. The effects of the alternating electric fields are selective for cancer cells and spare non-mitotically active cells<sup>10</sup>. The field is uniform inside quiescent cells, so the oscillating electric forces only cause the ions and dipoles to vibrate; on the other hand, the nonuniform field within dividing cells induces forces that push dipoles toward the furrow<sup>12</sup>. When it comes to their therapeutic effect across cell lines, the fields possess directional specificity, alongside frequency and intensity dependence<sup>8</sup>. The system runs paired array layouts to generate an optimal configuration that delivers maximal electric field intensity to the tumor site, which happens through the employment of the measures of head size and distances from predetermined fiducial markers to tumor margins<sup>8</sup>. Studies have been done to further explore the effectiveness of this treatment method. The pilot trial was conducted with ten patients who had recurrent glioblastoma and received the treatment for 280 weeks without any serious adverse effects from the procedure<sup>13</sup>. The drug for glioblastoma multiforme is called bevacizumab, yet the tumor can develop resistance to it or grow more aggressive<sup>11</sup>. A phase III (EF - 11) trial, which is what got the device its FDA approval, compared the NovoTTF therapy with the most appropriate chemotherapy according to physicians in patients with recurrent GBM from seven different countries<sup>11</sup>. More than 80% of the participants had undergone at least two chemotherapies, with 20% experiencing recurrence while they were on bevacizumab. Out of the 116 patients who chose the NovoTTF Therapy, 78% completed the full treatment course of 4 weeks. A comparable median OS was demonstrated with the NovoTTF Therapy in comparison to the chemotherapy, as well as fewer adverse events and improved quality of life. A common effect of the NovoTTF Therapy was skin irritation due to the transducer arrays; other common adverse events associated with chemotherapy were generally absent<sup>11</sup>.

The mechanism of action of TTFields includes impacts on mitosis, autophagy, cell adhesion and motility, stimulation of antitumor immune responses, as well as improved permeability of the blood-brain barrier (BBB)<sup>14</sup>. Evidence suggests that TTFields can affect the microenvironment of the tumor to advance antitumor immune responses. GBMs generally express immune checkpoint proteins and are not vastly immunogenic<sup>14</sup>. Nevertheless, GBMs could be "heated up" for immune-mediated tumor control. Moreover, the effects on TTFields reach several cellular processes. One important example is their effect on preventing DNA damage response. Cancer cells exposed to TTFields have a reduced DNA repair capacity and are more susceptible to DNA-damaging agents<sup>14</sup>. Therefore, these cells could be more vulnerable to treatments like chemotherapy. TTFields could

also impede cancer cell motility through microtubules and actin dynamics regulation. Changes in the cells' signaling pathways are caused, resulting in impacted direction and velocity of cell migration<sup>14</sup>. Finally, TTFields increase the permeability of the BBB<sup>14</sup>. This results from the disruption of microtubules in cells that triggers the dislocalization of tight junction proteins that hold the BBB together into the cytoplasm<sup>14</sup>. In vitro data further suggests that the treatment can cause pore formation in the plasma membranes of cancer cells, which could help with the delivery of anticancer therapies while leaving noncancerous cells intact<sup>14</sup>.

The treatment approach and prognosis of GBM are intertwined with the molecular characteristics of the cancer<sup>9</sup>. Specifically, MGMT promoter methylation is significant<sup>9</sup>. MGMT is a DNA repair enzyme, known as O<sup>6</sup>-methylguanine-DNA methyltransferase<sup>15</sup>. Patients who harbor a methylated MGMT promoter show better responses to alkylating chemotherapy and generally survive longer, demonstrating enhanced post-progression survival<sup>9</sup>. TTField therapy targets cells in their division phase. The alternating electric field generates dielectrophoretic forces that hinder the functioning of microtubules, cilia, and mitotic spindles<sup>9</sup>. This disruption results in the debilitation of the overall mitotic process, which prevents cancer cell proliferation<sup>9</sup>.

Overall, TTFields therapy could synergistically improve the antitumor effects of radiotherapy and chemotherapy through the blockage of homologous recombination repair in irradiated tumor cells. GBMs cannot be totally resected due to their highly invasive and metastatic characteristics; TTFields can impede tumor metastatic speed, seeding, and growth<sup>16</sup>. TTFields also impact the directionality of cancer migration by changing the organization and dynamics of microtubules and actin<sup>16</sup>. Moreover, the treatment reduces the expression levels of VEGF, the basis of tumor growth, HIF1- $\alpha$ , the basis of invasion, MMP2, the basis of metastasis, and MMP9, the basis of recidivism<sup>16</sup>.

Cilia are present in over 30% of glioma cells, promoting cancer growth, migration, differentiation, and resistance to TMZ<sup>16</sup>. TTFields have previously been found to suppress primary cilia in both low-grade and high-grade glioma cell lines<sup>16</sup>.

#### ***TTFields combined with radiotherapy***

The therapy improves the efficacy of radiation in glioblastoma cells. According to preclinical evidence, the combination of radiation and TTFields hinders GBM cells from migrating and invading; it also encourages cell apoptosis, DNA damage, and mitotic abnormalities<sup>16</sup>.

#### ***TTFields combined with chemotherapy***

GBM develops resistance to chemo due to activated DNA repair, angiogenesis, immune escape, and stem cell development<sup>16</sup>. The BBB also contributes to the chemoresistance of the cancer. Preclinical data of combining TTFields with TMZ therapy has shown that using TTFields and alkylation agents resulted in additive or synergistic outcomes for GBM patients<sup>16</sup>.

Cells which are resistant to TMZ responded well to the treatment, showcasing the clinical potential of this combined approach. TTFields could make GBM cells increasingly sensitive to TMZ; this means similar or perhaps better therapeutic effects could be attained with lower dosages, reducing overall toxicity<sup>16</sup>.

In 2009, a phase 3 controlled trial (EF-14) focused on the efficacy of TTFields combined with TMZ maintenance therapy for ndGBM patients<sup>16</sup>. The trial included 695 patients who had undergone surgery and chemoradiotherapy<sup>16</sup>. Of that group, two-thirds were treated with TTFields (18 h/d) alongside adjuvant TMZ. The rest were treated according to the standard adjuvant TMZ maintenance therapy. An interim analysis from 2015 concluded that the median progression-free survival (PFS) of the group treated with both TTFields and TMZ was 7.1 months, and the median OS was 20.5 months. On the other hand, the PFS for the TMZ-alone group was 4.0 months, and the median OS was 15.6 months.

A final report from 2017 discussed how the addition of TTFields to TMZ therapy following chemoradiotherapy helped improve patient outcomes. The OS rose from 16.0 months (achieved using solely TMZ therapy) to 20.9 months, while the PFS increased from 4.0 months to 6.7 months<sup>16</sup>.

The FDA has further approved TTFields for the treatment of mesothelioma<sup>17</sup>. Malignant mesothelioma, an aggressive form of cancer, occurs in the thin layer of tissue that covers the majority of internal organs<sup>18</sup>. Diagnosis of the illness can be difficult, and traditional diagnosis methods include pleural fluid cytology obtained through thoracentesis, needle biopsy of pleural tissue under CT, video-assisted thoracoscopy surgery with direct visualization and biopsy of pleural nodules, as well as open thoracotomy<sup>19</sup>. The causes of mesothelioma are known<sup>20</sup>. According to Penn Medicine, if a patient presents with symptoms pointing to that type of cancer, the first question a doctor would ask is about asbestos exposure<sup>20</sup>. Another important point is family history and whether someone in the patient's family has been diagnosed with mesothelioma<sup>20</sup>. People who were exposed to high levels of asbestos during their lives are likely to develop mesothelioma. When the fibers are inhaled or swallowed, they can go to the lining of the lungs (pleura), abdomen (peritoneum), or heart (pericardium) where they cause inflammation to the cells, resulting in scar tissues that can later lead to cancer. Malignant mesothelioma tumors form in the scar tissues 20 to 50 years after the exposure. Pleural mesothelioma forms when the asbestos fibers are inhaled and stick in the lining of the pleura. 12% of mesotheliomas happen to people who have genetic changes like BAP1 tumor predisposition syndrome, an inherited disorder which results from modifications in the BAP1 gene that increases the likelihood of having mesothelioma. Therefore, if a patient has family members who are diagnosed with mesothelioma, genetic testing should be considered<sup>20</sup>. Regarding TTFields, a study was done to test

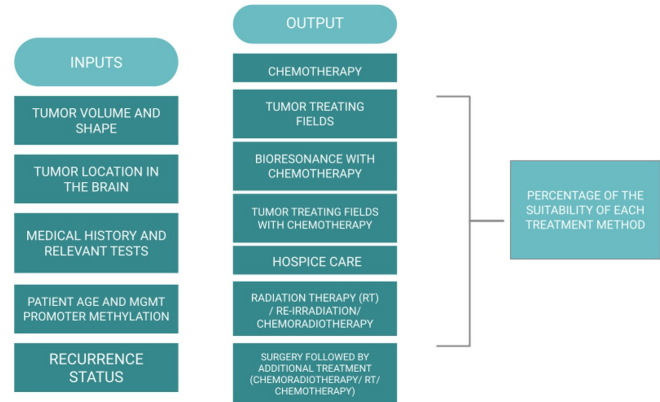
the activity of TTFields delivered to the thorax combined with systemic chemotherapy for patients with unresectable malignant pleural mesothelioma<sup>21</sup>. The trial was single-arm and phase 2 one where patients older than eighteen with an Eastern Cooperative Oncology Group performance status of 0-1 and at least one measurable or evaluable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma received TTFields at a frequency of 150 kHz to the thorax alongside concomitant chemotherapy with intravenous pemetrexed, 500 mg/m<sup>2</sup> on the first day, as well as intravenous platinum, cisplatin 75 mg/m<sup>2</sup> on the first day or carboplatin area under the curve 5 on the first day, every twenty-one days for six cycles. The single adverse effect associated with the TTFields was skin reaction. TTFields (150 kHz) delivered to the thorax in combination with pemetrexed and platinum was an active and safe treatment option for unresectable pleural mesothelioma, yet further investigation should be done<sup>21</sup>.

### Project Aim

The initial direction of the project was to build a neural network that could help doctors determine the most suitable treatment options for patients with GBM. Doctors would have input medically relevant information about the patient such as tumor volume and shape, tumor location, medical history, age and MGMT promoter methylation, as well as recurrence status. Then the neural network would have provided a percentage of suitability for each output (the outputs are different treatment options). However, to successfully train a neural network that could have a valuable impact on the way diagnosis and treatment are looked at, a significant amount of data samples is required. Therefore, it was necessary to be in close communication with FDA-approved clinics and companies that produce machinery and treat cancer patients. The aim was to obtain the medical factors that play a role in the diagnosis of patients, what treatment they got, and how their condition improved without the disclosure of any personal information that could lead to the identification of a patient. Nevertheless, despite long correspondence over several weeks and an offer for a non-disclosure agreement to be signed given that the data was required purely for academic purposes, there was no success in receiving the necessary information.

After realizing the high barrier that exists in obtaining patient data, the direction of the project was adapted. The current goal of this paper is to present a working theoretical model with a focus on GBM and innovative treatment options. Figure 1 outlines the inputs and outputs for the developed model. It addresses cases where cancer has already been diagnosed, so surgery is included as one of the treatment methods. Besides the standard chemotherapy and radiotherapy, TTFields are included as an output, alongside TTFields with chemotherapy, since they are FDA-approved for the treatment of GBM. Bioresonance is not yet proven as a cancer treatment, but it can be effective

in improving the overall health of the patient while they are undergoing standard cancer treatments. Therefore, it is included in the outputs alongside chemotherapy. The goal of this model is to aid physicians and outline the importance of treatments methods such as TTFields and bioresonance.



**Fig. 1** Doctors will input patient information such as tumor shape, relevant test results, tumor location, patient age, and medical history. Then they will receive a percentage for the most suitable treatment plan for a specific patient.

Regression predictive modeling is the process of approximating a mapping function from specific inputs to a continuous output; the output variable is a real value such as a floating point value<sup>22</sup>. Given that the end goal is to receive a specific percentage number regarding the most appropriate treatment plan for patients, the neural network can be classified as regression.

The hidden layers in a neural network are intermediary stages between the inputs and output. They contain neurons (also known as nodes) that interact with the data<sup>23</sup>. Each node in a layer connects to a node in the next layer, and information about the data is passed down in this manner<sup>23</sup>. Data flows through the input to the first layer of nodes, which reacts to it and passes down information to the following layers<sup>23</sup>. The extraction and processing of local information performing convolution on input data happens through trainable filters with a specified size<sup>24</sup>.

### Results

The theoretical model will assess the characteristics of patients with GBM and based on the treatment options available, it will produce a specific percentage for each of them based on how suitable they might be. This recommendation could be used as a second opinion by doctors to help them in their work. Given that GBM still needs to be researched further, this model will only provide the foundation for what could come next. If a doctor was presented with a patient with recurrent GBM, they could either propose a second surgery followed by chemotherapy or re-irradiation followed by additional treatment. With a disease

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like GBM, it can be difficult to determine the most appropriate treatment plan given that GBM cells have gained genetic and metabolic adaptations to be able to sustain tumor growth, including modifications in energetic metabolism, invasive capacity, migration, and angiogenesis; therefore, it is a challenge to find therapeutic targets<sup>25</sup>. Usually, the first step in treatment will always be surgery if it is applicable to the patient since it is associated with longer survival<sup>26</sup>. In the cases where it is not possible to operate, other treatment options include radiotherapy, chemotherapy with TMZ, and TTFields.

### Example Output Scenarios

#### *Patient 1 (Good Prognosis)*

This is an imaginary scenario for a patient. The patient is 45 years old, with an irregularly shaped, yet contained tumor. The tumor is in an operable location and has a diameter of 6 cm. It is methylated, and the patient is not experiencing major health issues.

In this case, an example output of the model could be the following: surgery followed by additional treatment would get assigned 40%, TTFields with chemotherapy - 15%, radiation therapy/chemoradiotherapy - 15%, TTFields - 10%, chemotherapy - 10%, hospice care - 5%, bioresonance with chemotherapy - 5%. Surgery followed by additional treatment such as radiotherapy or chemotherapy would be the most optimal treatment option. Usually, radiation therapy is recommended after surgery<sup>27</sup>. It could also be combined with chemotherapy<sup>27</sup>.

#### *Patient 2 (Poor Prognosis)*

This second patient is 73 years old. The tumor shape is highly infiltrative and the tumor itself is not in an easily accessible location. The diameter of the unmethylated tumor is 8 cm. Furthermore, this is a recurrent glioblastoma in less than 6 months, and the patient has diabetes. The patient previously underwent chemoradiotherapy.

In this case, an example output of the model could be the following: hospice care would get assigned 40%, TTFields - 20%, TTFields with chemotherapy - 15%, bioresonance with chemotherapy - 10%, chemotherapy - 6%, re-irradiation - 5%, surgery followed by additional treatment - 4%. In this case, TTFields might be the most optimal treatment option or TTFields coupled with chemotherapy if the patient wants to try something further besides hospice care. When there is recurrence, chemotherapeutic possibilities are often constrained<sup>9</sup>. On the other hand, TTFields therapy has showcased good tolerance and minimal systemic side effects, which makes it a good option for recurrent glioblastoma patients like the one in this scenario who might not be able to undergo further surgeries or aggressive treatments<sup>9</sup>. Moreover, for recurrent GBM, TTFields have demonstrated comparable effectiveness to standard chemotherapy in terms of OS<sup>9</sup>. RT treatment is rarely considered when the cancer relapses, which is why it does not receive a high

percentage in this scenario<sup>28</sup>.

### Discussion

This paper aims to emphasize the impact of treatments such as bioresonance and TTFields which combine physics and medicine. A theoretical model of a neural network that can help doctors identify the optimal treatment plan for their patients with GBM was developed, which includes TTFields. In terms of bioresonance, there is still not enough research on the topic even if there are papers that highlight its positive impact on human health. This is why this work could inspire a larger number of studies in that field and in how bioresonance could be integrated into standard cancer treatment to improve overall health. The paper also presents the importance of further research into GBM in all age groups that are affected by it. Limitations to the model could arise from the fact that there are still studies that need to be conducted to provide a clear understanding of the disease.

Assuming patient data was available, this model could have actual results to work with and its real-world impact would be more evident. Other experiments that could be done based on this paper would be a deeper study on various types of tumors and innovative approaches to treating them. Lastly, in the interviews with surgeons and oncologists that were conducted for this paper, an interesting point about predictive genetic testing came up, which sparked the idea of creating a program that could predict the likelihood of someone having cancer.

### Methods

This paper focuses on presenting a model for a neural network that could optimize the work of doctors. The process of obtaining actual data to work with was difficult, which outlined ethical considerations in the field and the necessity of being mindful when working with patient information. Extensive research was required to select the inputs that would go into the model in order to ensure that it was an accurate representation of the treatment plans available. The main approach involved adhering only to trusted journals, books, and websites after filtering by keywords such as “Glioblastoma”, “TTFields”, “Bioresonance”, “Regression Predictive Modelling”, and “Treatment plans for brain cancer”. The publication date and study design were evaluated for each source to ensure that the information is up-to-date. Oncologists and surgeons were also consulted. This section, therefore, serves to present in detail each of the inputs after an examination of the diagnosis approach for glioblastoma.

The cause of this cancer type has not been clearly defined<sup>29</sup>. It tends to occur in adults between the ages of 65 and 74, with men being affected more than women. The majority of people diagnosed with the disease do not have prior family history. Nevertheless, a study concluded that patients with immediate

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relatives who have developed glioblastoma have twice the risk of contracting the same kind of brain cancer<sup>29</sup>. To diagnose the cancer, several procedures could be done. One is a neurological exam to examine vision, balance, coordination, and reflexes since issues within these areas might give insight into the part of the brain the glioblastoma affects<sup>27</sup>. Magnetic resonance imaging (MRI) and imaging tests such as CT and positron emission tomography (PET) are used to diagnose the cancer as well<sup>27</sup>. Lastly, a biopsy in which a sample of tissue is removed for testing is another option in diagnosis since the sample is sent for testing where it can be determined whether the cells are cancerous and if they are glioblastoma cells<sup>27</sup>.

According to Dr. John Andrew Ridge, “doctors need to know your cancer’s stage to advise the best treatment options”<sup>30</sup>. Cancer staging is of use for a doctor to understand the seriousness of the cancer and the patient’s prognosis. According to Dr. Ridge, “it’s important to remember, however, that the prognosis with staging is based on large groups of people with similar tumors. But staging cannot predict with absolute certainty what will happen to you”<sup>30</sup>. This was discussed in an interview for this paper conducted with Professor Elena Aleksandrova, a Bulgarian surgeon and oncologist, who explained that stage of cancer is important for mapping out a prognosis, yet there are cases where patients with early stages of cancer pass away quickly and cases where patients with cancer at a later stage live longer<sup>31</sup>. Regarding glioblastoma grading, by definition, it is a central nervous system tumor of grade IV histological malignancy, which outlines the aggressiveness of the cancer<sup>32</sup>. Therefore, grade is not going to be an input that goes into the neural network since the focus is solely on glioblastoma. However, if this model were to be applied to other types of cancer, stage would be an input that will require a stride of one.

The standard treatment procedure for GBM begins with surgical resection<sup>26</sup>. In another interview conducted for this paper with Professor Nikolay Gabrovski, a Bulgarian neurosurgeon, he outlined that he looks at a patient’s MRI, tumor location in the brain, whether or not it is pressing on the brain, the patient’s age, as well as the tumor’s localization<sup>33</sup>. Family history does not impact his decision to operate<sup>33</sup>. Surgery is usually proposed to patients who are in good condition, below the age of 70, and with a tumor that is accessible for removal<sup>34</sup>. In order to make the input of tumor location understandable for the program, specific categories for the patients and whether or not they are able to undergo surgery need to be defined. The cases for which a tumor could be considered inoperable are the following: there are no clear borders and difficulty in distinguishing the tumor from healthy tissues; the tumor is very close to areas in the brain that are vital for vision, language, and body movements; surgery would reduce function significantly<sup>35</sup>. These are the main categories doctors usually take into account, yet it is important to mention that there are cases when an “inoperable” tumor could be removed by a surgeon with a high level of specialized exper-

tise<sup>35</sup>. In the rest of the cases with appropriate tumor location in the brain, surgery would usually be the first step of treatment<sup>35</sup>. Nevertheless, while surgery is usually the first step in the process, it has to be followed by additional treatment, which is outlined in Dr. Steven Toms’s explanation: “In glioblastoma, tumor cells can be found far from where the tumor is seen on an MRI. So, I set expectations from the very first conversation that, even when the postoperative MRI looks perfect, there are tumor cells left behind that will come back unless treated”<sup>36</sup>.

After surgery, the standard treatment is radiotherapy and chemotherapy<sup>32</sup>. Surgical treatment in combination with chemotherapy and radiotherapy prolongs the survival time by up to 202 weeks for young people<sup>32</sup>. For patients below the age of 70, radiotherapy and adjuvant temozolomide are recommended, a protocol that improved survival in a randomized phase III trial<sup>34</sup>. RT is administered for six weeks with a dose of 60 grays, and temozolomide is given daily during the RT and then for six cycles of five days per month in the month following the RT<sup>34</sup>. Regarding the input of age, treatment of elderly patients is a challenge. Age is one of the most pressing prognostic factors for survival in GBM patients, and a study of 1,578 patients from 3 trials demonstrated that age  $\geq$  50 was the factor with a connection to poor prognosis<sup>37</sup>. However, there is not an understanding of the difference of the biological behavior of the GBM between younger and older patients; potential treatments are influenced by an understanding of the genetic, molecular, and cellular mechanism of the illness<sup>37</sup>. Nevertheless, based on research that has been done, conclusions can be drawn for this theoretical model. Prognosis is poor for elderly people, and there is restricted response to treatment due to aggressive tumor biology, as well as risk of intolerance of aggressive treatments such as surgery and adjuvant radio-chemotherapy<sup>38</sup>. First, regarding surgery, both age and severity of comorbidities are of importance in determining the aggressiveness of the resection in elderly patients<sup>39</sup>. A case-control study from Johns Hopkins University assessed patients over the age of 65 who underwent resection versus those who underwent biopsy, concluding that the median survival of those who had undergone resection was longer<sup>39</sup>. A further retrospective trial on 142 elderly patients who had GBM that was newly diagnosed found that overall survival was better in extended resection over biopsy<sup>38</sup>. Regarding radiotherapy, a French multi-institutional randomized trial of 85 elderly patients with GBM who were at least 70 years old and with a KPS score of 70 or higher was conducted<sup>40</sup>. The patients were split into two groups: one receiving RT and supportive care and the other receiving only supportive care<sup>40</sup>. Median overall survival and progression-free survival times were 29.1 and 14.9 weeks for the first group, and 16.9 and 5.4 weeks for the second group<sup>40</sup>. Also, the radiotherapy did not cause deterioration in the KPS, in quality of life related to health, nor in cognitive functions in comparison with the palliative care<sup>40</sup>. Standard radiotherapy is a treatment option for patients

between the ages of 60 and 70 if their performance status is good<sup>40</sup>. However, randomized controlled studies have shown that short-course radiotherapy offers similar survival benefits and a shorter treatment time, so it could be a better option for elderly patients<sup>40</sup>. Third, regarding chemotherapy, temozolomide is an effective treatment option for elderly patients and is associated with enhancement in quality of life and functional status<sup>40</sup>. Here it is important to note that response to this treatment is associated strongly with MGMT promoter methylation status<sup>40</sup>. TMZ was given as adjuvant monotherapy to patients above the age of 70 in a phase II study<sup>38</sup>. Standard schedule of 150-200 mg/m<sup>2</sup>/daily for 5 days every 28 days was followed, and the treatment was tolerated well, with its efficacy being greater with patients with MGMTp methylation<sup>38</sup>. Combined hypofractionated radiotherapy and chemotherapy with TMZ followed by adjuvant TMZ could be suitable for elderly patients if they have good performance status and MGMTp-methylated tumors<sup>38</sup>. For those without MGMTp methylation, hypofractionated radiotherapy could be suitable<sup>38</sup>. If the patients have poor clinical status or require an extensive field for RT, yet are with MGMTp methylation, monotherapy with TMZ is the fitting treatment plan<sup>38</sup>. Last, in a randomized trial of 637 patients, the addition of TTFIELDS to maintenance temozolomide chemotherapy resulted in improvement in progression-free survival and overall survival compared to TMZ alone, so TTFIELDS are a possible addition to the treatment plan of elderly patients<sup>41</sup>. Overall, if elderly patients who are in good clinical conditions pre or post operation are treated according to the same standard of care, their results could be similar to those of younger patients even though they could be affected further from clinical deterioration following chemoradiotherapy<sup>42</sup>. However, longer PFS and OS are usually linked with MGMT promoter methylation<sup>42</sup>.

### **Quantification of each input**

For this neural network model, each input needs to be quantified so that it can be properly incorporated.

#### **Tumor volume and shape**

Tumor volume is currently being investigated as a prognostic factor<sup>43</sup>. There are inconclusive results as some studies validate its role in prognostic value while others do not<sup>43</sup>. Normally, the tumor diameter at the time of diagnosis is approximately 4 cm<sup>32</sup>. Data from a study of 645 patients showed that in 38% of patients, the tumor diameter at the diagnosis was less than 5 cm<sup>32</sup>. In 56% of cases, it was within 5–10 cm, and in 6% of patients, the tumor was larger than 10 cm<sup>32</sup>. Interestingly, the shape of the tumor often can offer more insight into treatment planning, so this will be one focus area for the theoretical model<sup>43</sup>. Irregularly shaped tumors could be MGMT promoter methylated, yet their complex and large area is in contact with brain tissue, predicting shorter survival rates<sup>43</sup>. Infiltration happens at the margin of tumors, making tumor shape and surface area more representative of

infiltrative capacities than tumor volume<sup>43</sup>.

In order to accurately input tumor shape into the neural network model, it is important to quantify it. One way to achieve that is through lacunarity analysis and fractal dimension<sup>44</sup>. Lacunarity is a quantifiable measure of how shapes fill spaces, while fractal dimension is a measure of the consistency of a shape with itself in different spatial scales<sup>44</sup>. Higher lacunarity is present in disconnected and more heterogeneous shapes, while high fractal dimension is present for very self-consistent shapes<sup>44</sup>. For GBM specifically, a study of 95 patients found that fractal dimension and lacunarity, when applied to pretreatment necrotic regions shown on T1-weighted MRIs with gadolinium contrast (T1Gd MRIs), can distinguish overall survival and progression-free survival<sup>44</sup>.

A new study was done with 402 patients with primary GBM. The following was required: a T1Gd MRI and T2/FLAIR imaging, the patient's age at diagnosis, sex, and OS data, as well as no significant cystic tumor components<sup>44</sup>. Both lacunarity and fractal dimension values of imaging abnormalities were calculated through T1Gd MRI and T2/FLAIR images for three distinct tumor regions. There were statistically significant associations between the morphological metrics and survival outcomes, including OS and PFS<sup>44</sup>.

To calculate the lacunarity and fractal dimension values, a FracLac plugin for ImageJ was used<sup>44</sup>. The FracLac software utilizes a box-counting algorithm. For fractal dimension, grids with varying box sizes are placed over a specific region, with the number of boxes being recorded for each grid. Afterwards, the log of this number is plotted against the log reciprocal of each box's length<sup>44</sup>. The gradient of this regression line is the fractal dimension. Regarding lacunarity, the variation in pixel distribution within each box was recorded<sup>44</sup>. Both standard deviation ( $\sigma$ ) and mean ( $\mu$ ) of pixel counts within the boxes were computed<sup>44</sup>. Lacunarity is calculated as  $\left(\frac{\sigma}{\mu}\right)^2$ . A similar calculation technique could be used for the neural network to quantify tumor size and analyze it properly.

To properly incorporate the quantified data into the model, min-max scaling could be used to adjust the lacunarity and fractal dimension values so that they are in the range between 0 and 1<sup>45</sup>. The formula for this operation is the following<sup>45</sup>:

$$X_{\text{normalized}} = \frac{X - X_{\text{min}}}{X_{\text{max}} - X_{\text{min}}}$$

#### **Tumor location**

Glioblastomas can occur in various regions of the brain, and tumor location influences treatment approach and patient outcomes, which means that it is important to assess it accurately. Decision on whether or not surgery is done is dependent on tumor location<sup>46</sup>. Expected residual tumor volume (eRV) and expected resectability index (eRI) could predict whether a tumor

can be resected<sup>46</sup>. The eRV can be derived from patients' MRI images using a resection probability map, while the eRI is calculated from the tumor volume. Various surgical classifications exist such as preoperative diagnostic imaging with structural MRI, task-based functional MRI, resting-state functional MRI, magnetoencephalography, or transcranial magnetic stimulation<sup>46</sup>. Another good source of information that could be applied in this theoretical model to quantify data is resection probability maps, which are based on a great number of prior resections. Resection probability maps have been utilized to predict surgical outcomes, assess brain plasticity, and compare resection success among surgical teams<sup>46</sup>. A recent advancement for the maps involves quantifying tumor resectability, which provides an estimate of the expected residual tumor portion<sup>46</sup>. The maps are derived from patients, and outline the likelihood of tumor resection at a 1 mm<sup>3</sup> resolution in standard brain space (MNI-152 template)<sup>46</sup>. The map is created using pre- and postoperative tumor segmentations. A leave-one-out approach can be applied to determine resectability<sup>46</sup>. In this case, the patient's preoperative tumor segmentation can be applied to filter the probability map from other patients. Following that, the resection probabilities of masked voxels are integrated, which will give the expected resectable volume<sup>46</sup>. The difference between the preoperative tumor volume and the expected resectable volume, in milliliters, yields eRV. On the other hand, dividing the expected resectable volume by the preoperative tumor volume calculates the eRI, which will be between 0.0 and 1.0. 0.0 represents a non-resectable tumor; 1.0 represents a completely resectable tumor<sup>46</sup>.

For the theoretical model in this paper, the tumor could be mapped onto a template like MNI-152. MRI images and segmentation will be used to define its boundaries. Then resection probability maps, alongside eRV and eRI will quantify the likelihood of a successful resection.

Additionally, a different option to incorporate tumor location would be a quadrant-based approach. The brain can be divided into four primary quadrants. Then, within each primary quadrant, the classification can be further refined through the use of sub-quadrants, which would allow for a precise localization of the tumor.

#### **Medical History/Relevant Tests**

Patients with glioblastoma will often report a short medical history, which will likely include progressive focal neurologic deficits such as motor weakness, sensory loss, memory loss, language deficits, and visual impairments<sup>47</sup>. In some cases, patients could experience headaches, nausea and vomiting, and personality changes, all of which are symptoms of increased intracranial pressure (ICP)<sup>47</sup>. Other medical history would include documentation of previous and ongoing health conditions and allergies, surgeries, as well as medications<sup>48</sup>. As mentioned above in the paper, the relevant tests include: a neurological exam, MRI, CT, PET, and a biopsy.

One approach for quantifying the medical history data into

the model would be the development of a risk factor scoring system; numerical values will be assigned to various aspects. Each component can be scored on a scale from 1 to 10 based on its potential impact on treatment decisions. These scores can then be input into the network. Additionally, another interesting option would be the utilization of natural language processing (NLP) techniques, which could be used to extract relevant information from patients' medical records<sup>49</sup>.

#### **Patient age and MGMT Promoter Methylation**

As mentioned above in the paper, increasing age is connected with worse prognosis, with mortality to incidence ratio exceeding 0.8 for all patients above the age of 35<sup>50</sup>. However, the MGMT status also has to be taken into account when looking at treatment options for patients. The MGMT gene, which is positioned on chromosome 10q26, encodes a DNA-repair protein which removes alkyl groups from guanine's O<sup>6</sup> position, an important DNA alkylation site<sup>51</sup>. The MGMT gene is involved with DNA repair and in the resistance to alkylating drugs of glioma cells<sup>51</sup>. A study was done with 41 newly diagnosed GBM patients who were treated at the 10th Military Research Hospital and Polyclinic, Poland, from 2011-2014<sup>51</sup>. The patients underwent surgical resection and then radiation and chemotherapy with alkylating agents. 43% were found to be methylated; 26 had a gross total resection and 15 had a subtotal resection<sup>51</sup>. Patients with a methylated MGMT promoted had a median survival of 504 days, while those without methylation had a median survival of 329 days<sup>51</sup>. The median age of the patients was 53; for the group younger than 53 years, those with methylation had a longer OS of 639 days in comparison to those without methylation who had an OS of 433.5 days<sup>51</sup>. Therefore, the value of MGMT promoter methylation as a predictive biomarker is widely accepted; it is its prognostic value that still is not proven and has contradictory findings<sup>51</sup>.

Currently, the following treatment options are available when age and MGMT methylation status are considered. Patients younger than 70 years and with good performance status can undergo fractionated standard brain RT alongside concurrent and adjuvant TMZ<sup>52</sup>. Alternating electric field therapy could also be included<sup>52</sup>. Patients younger than 70 years with poor performance status can undergo hypofractionated RT with or without concurrent or adjuvant TMZ, or TMZ alone. Both of these options do not consider MGMT methylation status<sup>52</sup>.

Patients who are older than 70 years, have good performance status, and MGMT promoter-methylated tumors can undergo hypofractionated RT plus concurrent and adjuvant TMZ or standard RT plus concurrent and adjuvant TMZ and alternating electric field therapy<sup>52</sup>. Patients above the age of 70 with good performance status and MGMT unmethylated tumors could receive standard brain RT alongside concurrent and adjuvant TMZ and alternating electric field therapy<sup>52</sup>. Finally, patients above the age of 70 with poor performance status (regardless of MGMT methylation status) could undergo hypofractionated

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brain RT, TMZ therapy, or palliative care<sup>52</sup>.

Regarding the quantification of age for this model, it could be used directly or categorized into groups (<50, 50-60, 61-70, 71-80, ≥80). Regarding MGMT Promoter Methylation Status, one approach for its incorporation into the model would be representation as a binary variable: 0 for unmethylated and 1 for methylated.

### **Recurrence status**

Recurrence status is another factor in GBM treatment, which is why it is included as an input for the neural network. GBM tumors that respond to first-line therapy often recur, and there is no standard approach to their treatment<sup>53</sup>. GBM can come back anywhere in the brain or the spinal cord<sup>54</sup>. Nevertheless, recurrences are usually close to the original tumor site<sup>54</sup>. When the GBM is progressive or recurrent, treatment options could include reoperation, reirradiation, chemotherapy, TTFs, and antiangiogenic therapy (for example, VEGF inhibitors)<sup>55</sup>. The challenging aspect is the malignant reprogramming evolution of glioblastoma stem cells, low or partial response to immunotherapy, the diffusely infiltrative nature of the disease, the poor delivery of drugs to the brain tumors, as well as the inefficiency of current treatment options<sup>55</sup>. The invasive nature of the tumor means it infiltrates normal brain regions, prohibiting surgical recession of the entire tumor and leading to a high rate of post-treatment progression and recurrence<sup>55</sup>. Sometimes it could be that patients with recurrent GBM are recommended to participate in clinical trials of new therapies<sup>49</sup>. Patients with a young age, recurrence after 6 months, and with good performance status could undergo more aggressive treatment<sup>56</sup>. First, second surgery could be offered to patients who are with a localized relapse in areas that are not eloquent and to whom a complete or subtotal resection of the tumor could be done<sup>57</sup>. Patients who could undergo another surgery have to have a good performance status, alongside an indolent tumor history, which is measured as a prudential time from the first surgery<sup>57</sup>. However, only 20-30% of patients with a recurrent tumor are candidates for a second surgery, and the median OS after that is variable<sup>57</sup>. Regarding re-irradiation, it is an option for patients with small volume recurrence, if it is done at a distance from the first round of radiation therapy and if surgery is not suggested as a result of the eloquent tumor location<sup>56</sup>. Furthermore, the time period between the first radiation and the recurrence should be looked at, and there should be at least a 6-month time period<sup>56</sup>. Re-irradiation is usually given as a single high dose for small tumor volumes, known as stereotactic radiotherapy, or divided into fractions for larger tumor volumes, which is known as hypofractionated radiotherapy<sup>58</sup>. Re-irradiation could be done by external beam radiotherapy or brachytherapy, whose nature is invasive, yet could be tried for superficial tumors<sup>56</sup>. However, there are various aspects which make re-irradiation complicated such as the fact that there is no criteria for the selection of patients, alongside insufficient research on total dose, optimal

fractionation, and volume<sup>57</sup>. Temozolomide, Bevacizumab, and Nitrosureas are agents that have shown moderate activity in treating recurrent GBM<sup>56</sup>. Chemotherapy here could be given alone or after surgery, and it could also be given along or after radiotherapy<sup>56</sup>. However, the blood-brain barrier is a limiting factor to the delivery of most chemotherapeutic agents<sup>56</sup>. A new combination of chemotherapy drugs could be recommended for those with recurrent GBM or a stronger dose/accelerated delivery cycle of the same drugs<sup>54</sup>. Lastly, TTFields will be discussed as a potential option for recurrent GBM. The company that manufactures the machines has said that TTFields could be used alone as a treatment option if surgery and radiation did not work for the patient and if the patient tried chemotherapy<sup>36</sup>. Regarding recurrence, a binary variable representation could be used to quantify it. '1' will be assigned if there is a recurrence and '0' if there is not. The location of recurrence could also be described in three categories: if the tumor appears at the original site, if it appears in a close brain region, and if it develops far from the original site.

In order for the program to function, there has to be a multitude of neuron layers within it. Initially, weights are randomly assigned to the input/output pairs. By training the program repeatedly with a substantial amount of data, backpropagation will adjust the weights for each of the input variables using gradient descent to reduce error. Based on the importance of the various inputs explained above, this neural network will identify the appropriate weights to lead to an output suggestion that is most accurate based on current medical guidelines. In this case, after the weights are assigned, the physician's suggested result will have to be compared with the program output. This will determine the overall accuracy of the neural network.

The importance of each input variable is learned as the network optimizes the weight assignments, ensuring that clinically relevant factors have the strongest influence on the output. Each output will have a probability score based on its effectiveness for a given patient. The treatment probabilities will be generated through a softmax activation function, which converts output scores into probabilities; the values are in the range (0,1) and sum up to 1<sup>59</sup>. The treatment option with the highest probability would be the most favorable recommendation; if it aligns with the opinion of physicians, this would support the accuracy of the neural network.

Each layer of the network would utilize backpropagation to modify weights and reduce error in treatment predictions. The probability will be computed according to the following equation<sup>59</sup>:

$$\frac{e^{z_i}}{\sum_{j=1}^K e^{z_j}}$$

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