

Computer Models of Brain Tumor Metastasis

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Abstract

A computer model of brain tumor metastasis is developed and simulated using the language Mathematica. Diffusion of cancer cells through regions of gray and white matter is differentiated resulting in realistic asymmetric tumor growth. Applications include the precise treatment of a patient's "future tumor" with focused radiation, and modelling the effects of chemotherapy.

1 Introduction

Cancerous tumors, or neoplasms, arise from the mutation of one or more cells which undergo uncontrolled growth thereby impairing the functioning of surrounding normal tissue. There are many different cancers each with their own characteristics. This work shall only be concerned with brain tumors, and in particular gliomas or glioblastomas, which make up about half of all primary brain tumors diagnosed; they are particularly dreadful tumors with a dismal prognosis for survival. Gliomas are highly invasive. The improvements in computerized tomography (CT) and magnetic resonance imaging (MRI) over the last decades have resulted in earlier detection of glioma tumors. Despite this progress, the benefits of early treatment have been minimal. For example, even with surgical excision well beyond the grossly visible tumor boundary, regeneration near the edge of resection ultimately results, eventually leading to death. This failure of resection is analogous to trying to put out a forest fire from behind the advancing front. The action of the fire

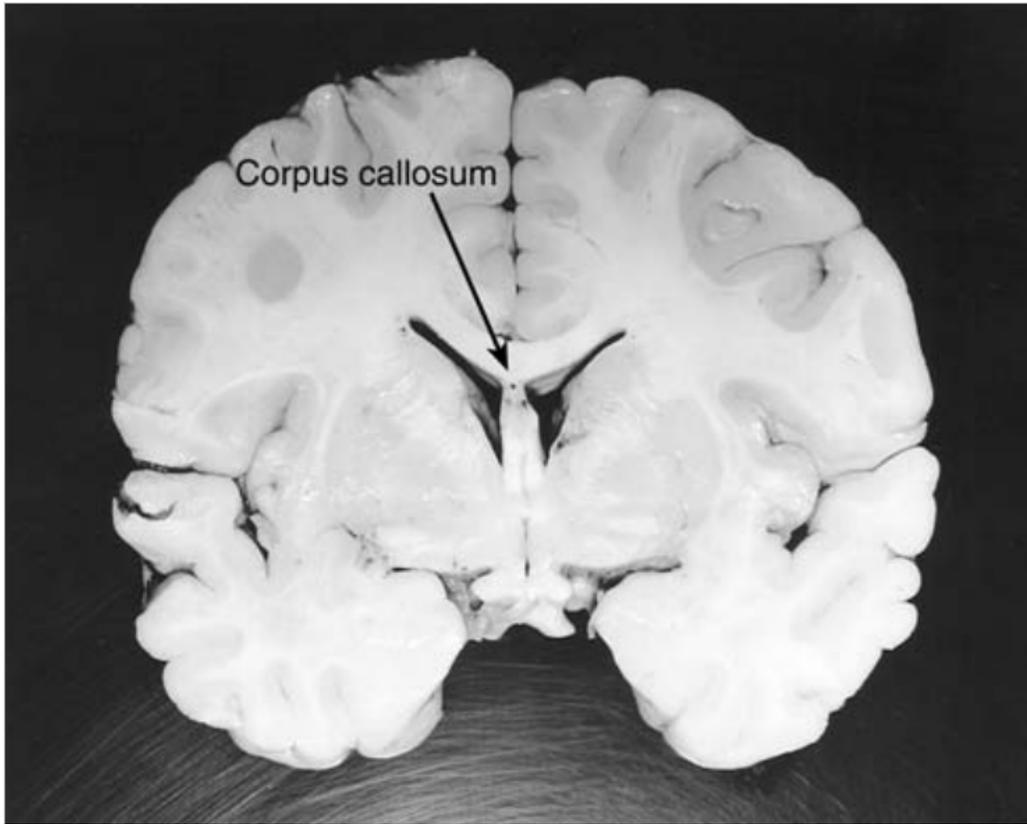


Figure 1: Cross-section of a human brain showing fibrous white matter and the corpus callosum which connects the left and right cerebral hemispheres.

(tumor growth) is primarily at the periphery.

The brain basically consists of two types of tissue: gray matter and white matter. Gray matter is composed of neuronal and glial cell bodies that control brain activity while the cortex is a coat of gray matter that covers the brain. White matter fiber tracts are myelinated neuron axon bundles located throughout the inner regions of the brain. These fibers establish pathways between gray matter regions. The corpus callosum is a thick band of white matter fibers connecting the left and right cerebral hemispheres of the brain. Within each hemisphere, there are several white matter pathways connecting the cortex to the nuclei deep within the brain.

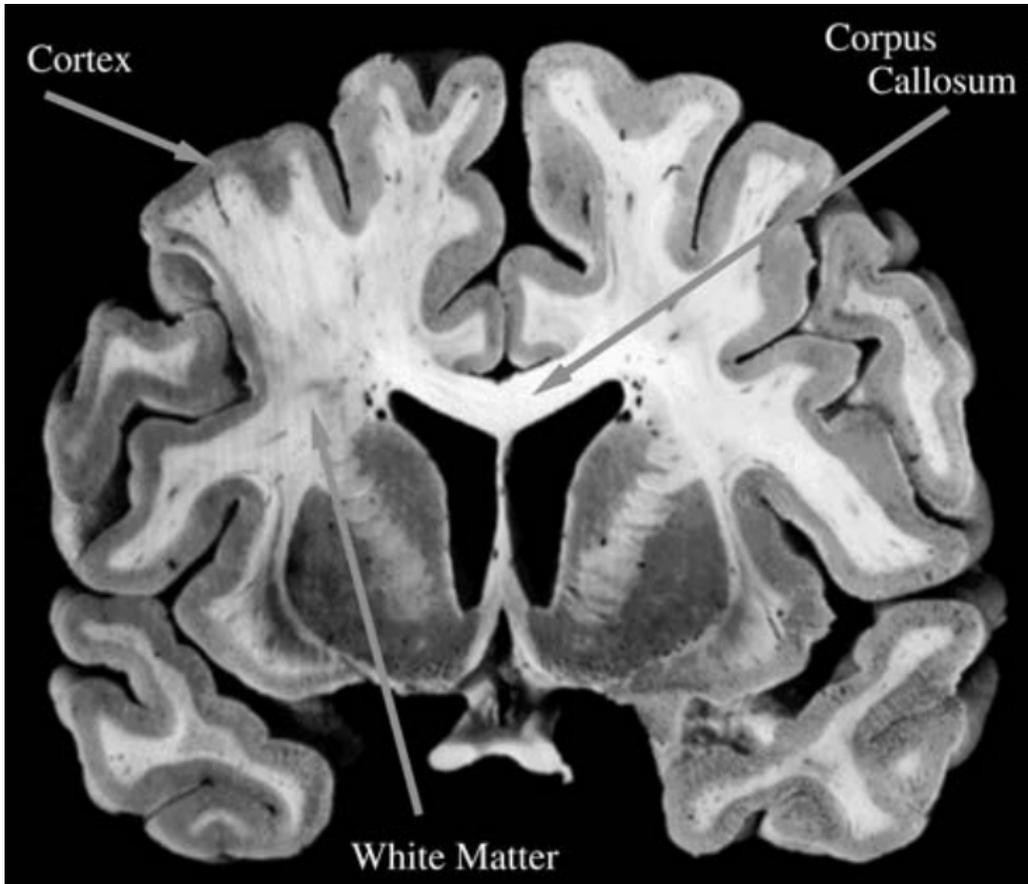


Figure 2: The cortex consists of gray matter and is connected to other gray matter regions by white matter fiber bundles. The corpus callosum is a white matter tract connecting the left and right cerebral hemispheres.

Gliomas are neoplasms of glial cells (neural cells capable of division) that usually occur in the upper cerebral hemisphere but which can be found throughout the brain. Astrocytomas, originating from an abnormally multiplying astrocyte glial cell, are the most common gliomas. Depending on their aggressiveness (grade), astrocytomas are further divided into several subcategories. Astrocytomas are the least aggressive or lowest grade, anaplastic astrocytomas are the more aggressive or mid-grade and glioblastomas are the most aggressive or highest grade. Tumor grade indicates the level of malignancy and is based on the degree of anaplasia (deformity in behavior and form) seen in the cancerous cells under a microscope. Gliomas often contain several different grade cells with the highest grade or most malignant grade of cells determining the grade, even if most of the tumor is lower grade. There is still no general clinical agreement on the grading.

Generally, the higher-grade cancer cells are more capable of invading normal tissue and so are more malignant. However, even with their invasive abilities, gliomas very rarely metastasize outside the brain.

The prognosis for patients with neoplasms affecting the nervous system depends on many factors. A major element in the prognosis is the quantitative evaluation of the spatiotemporal infiltration of the tumor, taking into account the anatomic site of the tumor as well as the effectiveness of the various treatments.

Since the modelling developed in this paper has a practical bearing on patient treatment, it is necessary to give more detailed medical information which is an important part of realistic medical modelling.

Difficulties in Treating Brain Tumors An enormous amount of experimental and some theoretical work has been devoted to trying to understand why gliomas are so difficult to treat. Unlike many other tumors, gliomas can be highly diffuse. Experiments indicate that within seven days of tumor implantation in a rat brain, glioma cells can be found throughout the central nervous system. Most glioma treatments are directed locally to the bulk mass when, in fact, the action of tumor growth and invasion is elsewhere.

There are various, regularly used, treatments for gliomas, mainly chemotherapy, radiation therapy and surgical intervention. Resection, the surgical removal of an accessible tumor, has a poor history of success. Recurrence of tumor growth at the resection boundary is well-documented. Most believe that the distantly invaded cells are responsible for tumor regeneration following surgery. Since the density of cancerous cells (remaining after resection) is highest at the resection boundary, regrowth seems most probable at this location. Silbergeld and Chicoine suggested the hypothesis that damaged brain tissue at the resection site releases cytokines that recruit the diffusely invaded tumor cells. Nevertheless, both explanations are consistent with the argument that the diffuse nature of gliomas is fundamentally responsible for tumor recurrence near the resection boundary. The difference is that the former is a physical model and the later is more biochemical.

Chemotherapy essentially uses specialized chemicals to poison the tumor cells. The brain is naturally defended from these and other types of chemicals by the intricate capillary structure of the blood-brain barrier. Water-soluble drugs, ions and proteins cannot permeate the blood-brain barrier but lipid-soluble agents can. Recently, agents have been devised to temporarily disrupt the blood-brain barrier. Many chemotherapeutic treatments are cell-cycle-dependent: the drugs are triggered by certain phases of the cell cycle. Silbergeld and Chicoine have observed that motile cells distant from the bulk tumor do not appear to enter mitosis so cell-cycle specific drugs and standard radiation therapy have limited effectiveness. Not only that, gliomas are often heterogeneous tumors. Those drugs that do reach the cancerous cells are hindered by drug resistance commonly associated with cancer cell heterogeneity. While one cell type is responsive to treatment and dies off, other types are waiting to dominate. This phenomenon requires a model which includes cell mutation to drug resistance cells, in other words a polyclonal model.

The biological complexity of gliomas makes treatment a difficult undertaking. For planning effective treatment strategies, information regarding the growth rates and invasion characteristics of tumors is crucial. The use of mathematical modelling can help to quantify the effects of resection, chemotherapy and radiation on the growth and diffusion of malignant gliomas. In this work, some light is shed on certain aspects of brain tumor treatment with the aim of helping to determine better, or even optimal, ther-

apeutic regimes for patients. A major goal is the development of interactive computer models with which the effects of various treatment strategies for specific tumors could be examined. This work goes some way in achieving this goal.

2 Basic Mathematical Model of Glioma Growth and Invasion

Like all tumors, the biological and clinical aspects of gliomas are complex and the details of their spatiotemporal growth are still not well understood. In constructing models therefore we have to make some major assumptions. We start with as simple a model as is reasonable and build up from it. The simplest theoretical models involve only the total number of cells in the tumor, with growth of the tumor usually assumed to be exponential, Gompertzian, or logistic. Such models do not take into account the spatial arrangement of the cells at a specific anatomical location or the spatial spread of the cancerous cells. These spatial aspects are crucial in estimating tumor growth since they determine the invasiveness and the apparent border of the tumor. It is necessary to try and determine the extent of infiltration of the tumor in most treatment situations, such as estimating the likely benefit of surgical resection. One of the surprising aspects of this work is how a very simple deterministic model can provide meaningful and helpful clinical information with a direct bearing on patient care.

In this section we develop a mathematical model for the spatiotemporal dynamics of tumor growth. Importantly we can estimate the model parameters, including the proliferation, or growth rate, and the diffusion coefficient of the cells from clinical data obtained from successive CT scans of patients.

Once we have established the feasibility of reconstructing some of the kinetic events in invasion from histological sections, it will be possible to investigate other gliomas with different characteristic growth patterns, geometries and the effects of various forms of therapy using the same types of data from other patients. The growth patterns essentially define the gross and microscopic characteristics not only of the classical tumors of different degrees of malignancy but also of mixed-gliomas.

Previous mathematical modelling used a theoretical framework to describe the invasive nature of gliomas, both with and without treatment regimes, by isolating two characteristics: proliferation and diffusion. Here diffusion represents the active motility of glioma cells. These models showed that diffusion is more important in determining survival than the proliferation rate of the tumor. In vivo studies show that malignant glioma cells implanted in rats quickly invade the contralateral hemisphere of the brain dispersing via white matter tracts. The diffusion of glioma cells in white matter is different from that in the gray matter and is included in a more realistic model.

The basic model considers the evolution of the glioma tumor cell population to be mainly governed by proliferation and diffusion. Tumor cells are assumed to grow exponentially. This is a reasonable reflection of the biology for the timescale with which we are concerned, namely, the time to the patient's death. Silbergeld and Chicoine suggested that diffusion is a good approximation for the tumor cell motility. A very good review of glioma invasion is given by Giese and Westphal. It can be shown that diffusion reasonably models the cell spreading dynamics observed in vitro.

Let $c(\mathbf{x}, t)$ be the number of cancer cells at a position \mathbf{x} and time t . We take the basic model as a modified diffusion equation

$$\frac{\partial c}{\partial t} = \nabla \cdot \mathbf{J} + \rho c$$

where ρ (time⁻¹) represents the net rate of growth of cells including proliferation and death (or loss). The diffusional flux of cells, \mathbf{J} , we take as proportional to the gradient of the cell density:

$$\mathbf{J} = D\nabla c$$

where D (distance²/time) is the diffusion coefficient of cells in brain tissue (and in our model will depend on tissue "whiteness"). The theoretical models, referred to above, considered the brain tissue to be homogeneous so the diffusion and growth rates of the tumor cells are taken to be constant throughout the brain. This is not the case, of course, when considering tumor invasion into white matter from gray. With constant diffusion the governing equation is then

$$\frac{\partial c}{\partial t} = D\nabla^2 c + \rho c.$$

This model gives reasonable agreement with the CT scans on which the model is based and has given surprisingly good results in predicting survival times under various treatment scenarios. Although the models gave surprisingly good results, they contain several basic simplifications which can now be reconsidered. For example, given a source of glioma cells at a given location, for numerical simplicity, considered the ‘front’ of detectable cells propagates symmetrically out from the source. They all knew that clinical observation indicated that, in fact, symmetry in growth of the tumor is not the case. The first model we discuss here deals with this aspect as well as tissue heterogeneity.

White matter serves as a route of invasion between gray matter areas for glioma cells. The diffusion coefficient for glioma cells is larger in the white matter than in the gray matter. In vivo studies show that malignant glioma cells implanted in rats quickly invade the contralateral hemisphere of the brain dispersing via white matter tracts. The model we study now incorporates the effects of the heterogeneous tissue on the cell diffusion and tumor growth rates to emulate more accurately the clinically and experimentally observed asymmetries of the gross visible tumor boundaries.

Model with Spatial Heterogeneity We can account for spatial heterogeneity in our model by taking the diffusion coefficient D to be a function of the spatial variable, \mathbf{x} , thereby differentiating regions of gray and white matter. This gives as our governing equation,

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\mathbf{x})\nabla c) + \rho c.$$

We take zero flux boundary conditions on the anatomic boundaries of the brain and the ventricles. So, if B is the brain domain on which the equation is to be solved, the boundary conditions are

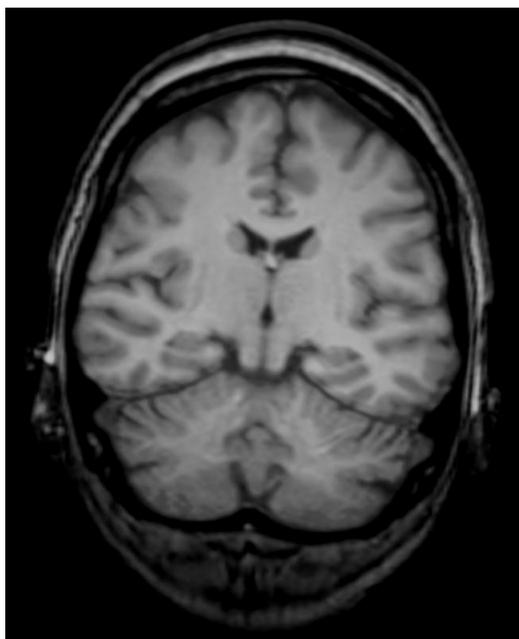
$$\mathbf{n} \cdot D(\mathbf{x})\nabla c = 0 \quad \text{for } \mathbf{x} \text{ on } \partial B,$$

where \mathbf{n} is the unit normal to the boundary ∂B of B . With the geometric complexity of an anatomically accurate brain (which we shall in fact use) it is clearly a very difficult analytical problem and a nontrivial numerical problem, even in two dimensions.

3 A Computer Simulation of Brain Tumor Growth

Here we model brain tumor growth using the language Mathematica. The first step is to import an image of a brain scan clearly showing areas of gray and white matter.

```
img2 = Import["~/Desktop/notebooks/brain-crop.jpg"]
```



Next we convert the image to grayscale and sharpen the image.

```
img3 = Sharpen[ColorConvert[img2, "Grayscale"]]
```

The key realization is that the diffusion coefficient is proportional to and can be gotten from the image data. The following command produces an interpolating function.

```
diffcoeff =
ListInterpolation[ImageData[img3], InterpolationOrder -> 3]
```

It is important to know the dimensions of the data, which in this case was 798×654 .

```
Dimensions[ImageData[img3]]
```

Next we define a region such that $-y \leq 0$, $-1 + y \leq 0$, $-x \leq 0$ and $-1 + x \leq 0$.

```
boundaries = {-y, y - 1, -x, x - 1};
omega = ImplicitRegion[And @@ (# <= 0 & /@ boundaries), {x, y}];
```

Next we use `NDSolveValue` to produce an interpolating function `sol[t,x,y]` that represents the density of cancer cells on the image. In practice we solve

$$\text{Div} \left[\frac{1}{500} D^4(\mathbf{x}) \cdot \text{Grad } u(t, x, y) \right] + 0.025u(t, x, y) - \frac{\partial u}{\partial t} == 0$$

with the initial condition

$$u(0, x, y) == \text{Exp} \left[-1000((x - 0.6)^2 + (y - 0.6)^2) \right]$$

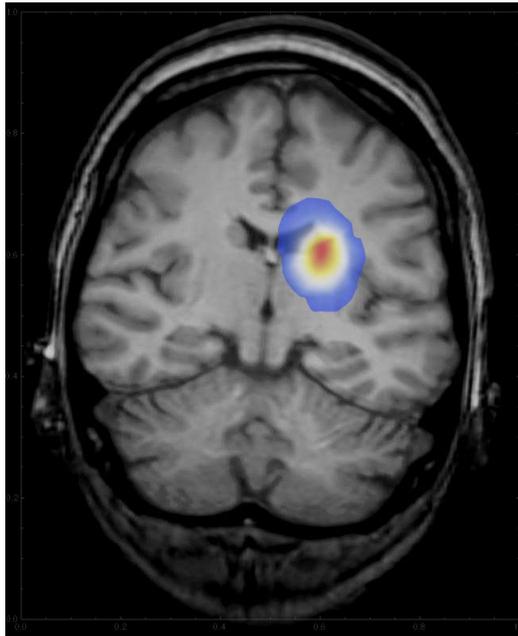
```
sols = NDSolveValue[{{Div[
  1./500.*(diffcoeff[798.*x, 654*y])^4*
  Grad[u[t, x, y], {x, y}], {x, y}] - D[u[t, x, y], t] +
  0.025*u[t, x, y] ==
  NeumannValue[0., x >= 1. || x <= 0. || y <= 0. || y >= 1.]}},
  {u[0, x, y] == Exp[-1000. ((x - 0.6)^2 + (y - 0.6)^2)]},
  u, {x, y} \[Element] omega, {t, 0, 20},
  Method -> {"FiniteElement",
  "MeshOptions" -> {"BoundaryMeshGenerator" -> "Continuation",
  MaxCellMeasure -> 0.002}}]
```

Note that we start with an initially Gaussian distributed tumor and describe its growth from there. Also, I took the fourth power of the diffusion

coefficient, which changes the relation between grayscale and diffusion rate. You can change the coefficient to get different patterns for the growth.

That done, we can now compose the brain image with that of a contour plot of the solution. Here we display the tumor at time $t = 2$.

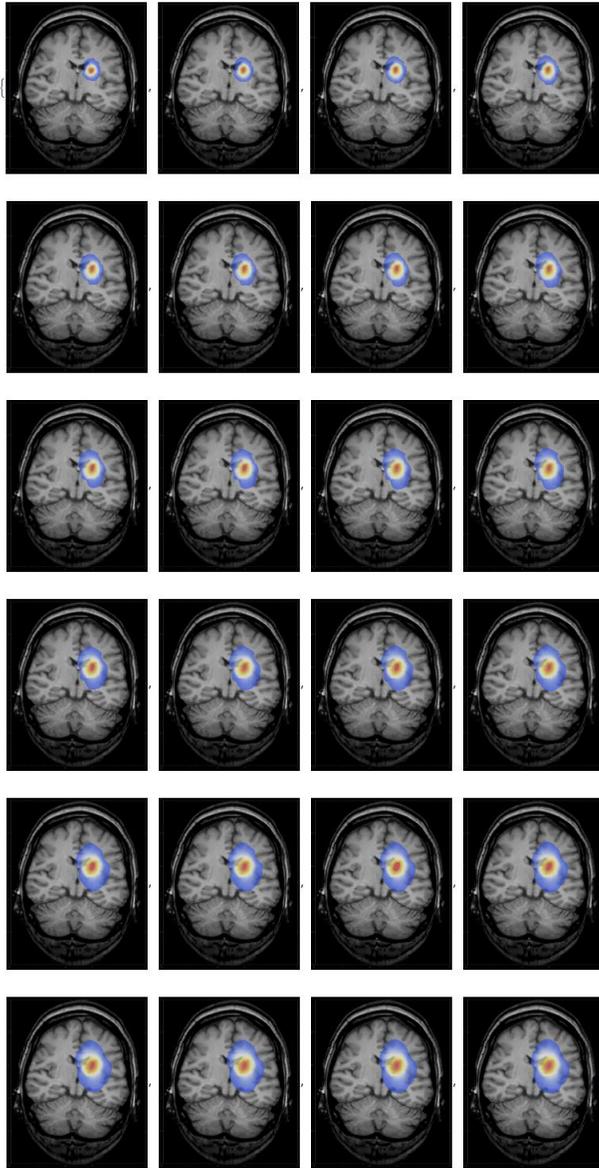
```
ImageCompose[img3, {ContourPlot[
  Max[sols[t, x, y], 0] /. t -> 2, {y, 0, 1}, {x, 0, 1},
  PlotRange -> {{0, 1}, {0, 1}, {0.01, All}}, PlotPoints -> 100,
  Contours -> 200, ContourLines -> False, AspectRatio -> 798./654.,
  ColorFunction -> "Temperature"], 0.6}]
```



We can now simulate tumor growth in a series of images taken at successive times.

```
frames = Table[
  ImageCompose[
    img3, {ContourPlot[
      Max[sols[d, x, y], 0] /. d -> t, {y, 0, 1}, {x, 0, 1},
      PlotRange -> {{0, 1}, {0, 1}, {0.01, All}}, PlotPoints -> 100,
```

```
Contours -> 200, ContourLines -> False, AspectRatio -> 798./654.,  
ColorFunction -> "Temperature"], 0.6}], {t, 0, 11.5, 0.5}]
```



These frames can be exported into an animation.

```
ani = ListAnimate[frames, DefaultDuration -> 20,
```

```
Paneled -> False] /. (AppearanceElements -> _) ->
(AppearanceElements -> {})

Export["animation1.avi", ani]
```

References

- [1] J.D. Murray. *Mathematical Biology II: Spatial Models and Biomedical Applications*. Springer, New York, 2003.
- [2] D.L. Silbergeld. *J. Neurosurg.* , 86:525-531, 1997.
- [3] D.L. Silbergeld. *J. Neuro-Oncol.* , 10:179-185, 1991.