



# Program and Abstracts

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## Introduction

### Description

Tumor invasion marks one of the last stages of tumor progression and emerges from the combined effect of tumor cell proliferation, migration and microenvironment interactions such as tumor-induced vasculature, immune cells, etc.. In the case of glioblastoma, the most common primary brain tumor, cell invasiveness into the surrounding brain tissue is particularly critical and is typically related to a poor prognosis and quality of life.

Despite intense research efforts over the past years with many biological insights, very little clinical progress has been made, with median survival for glioblastoma still less than 2 years and cure an impossibility. The use of mathematical and computational methods has the potential to improve the understanding of the complex biology of this disease, which may allow for more rational and effective therapies.

In this minisymposium, colocated at the European Conference on Mathematical and Theoretical Biology (ECMTB) in Gothenburg, young and senior researchers present novel mathematical models proposed to decipher the complex nature of glioma invasion. Special attention is also given to studies that provide insights into the evolution of benign brain tumors to invasive malignant gliomas, including the most aggressive of them known as secondary glioblastoma.

### Organizers

Alvaro Köhn-Luque  
Center for High Performance Computing  
Dresden University of Technology  
Dresden, Germany

Jacob Scott  
Integrated Mathematical Oncology  
Moffitt Cancer Center  
Tampa, USA

Haralambos Hatzikirou  
Center for Advance Electronics  
Dresden University of Technology  
Dresden, Germany

Andreas Deutsch  
Center for High Performance Computing  
Dresden University of Technology  
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### Date and Location

The minisymposium will be held on **June 17, 2014** as part of the [European Conference on Mathematical and Theoretical Biology](#) in Gothenburg, Sweden. It will take place at [Chalmers Conference Center](#) (Chalmerplatsen 1, 412 58 Göteborg) in the **room Catella** from 14:10 till 18:30 (see full program below).

## Program

Time	Speaker	Title	Chair
14:10 - 14:20	Andreas Deutsch	Introduction	
14:20 - 14:45	Philip Gerlee	The Influence of phenotypic switching on tumor growth rate and cell density	Haralambos Hatzikirou
14:45 - 15:10	Katrin Boettger	Investigation of the effect of phenotypic plasticity on tumor growth	
15:10 - 15:35	Alicia Martínez-González	In-silico glioma models: what can we take advantage for the clinical practice?	
15:35 - 16:00	Coffee Break		
16:00 - 16:25	Kristin R. Swanson	Quantifying changes in glioma biology with treatment using modeling of edema formation and clinical imaging	Jacob Scott
16:25 - 16:50	Mathilde Badoual	An edema-based model for diffuse low-grade gliomas under radiotherapy	
16:50 - 17:15	Juan Carlos López Alfonso	Modeling dose-painting effects in radiotherapy by means of an agent based model	
17:15 - 17:40	Russel Rockne	A data-driven calibration of a nonlinear mechanistic model for DNA damage and repair: applications to radiosurgery and heavy ion irradiation treatment for glioblastoma	
17:40 - 18:05	Thomas Buder	Linear dependency between residual tumor fraction and regression probability can provide decision support after partial resection of pilocytic astrocytoma	
18:05 - 18:30	Alvaro Köhn-Luque Haralambos Hatzikirou Jacob Scott Andreas Deutsch	Round table discussion and closing	



## Abstracts

### The influence of phenotypic switching on tumour growth rate and cell density profiles

Philip Gerlee<sup>1</sup>

1. Integrated Mathematical Oncology. Moffitt Cancer Center, Tampa, USA

In this talk we will present results derived by analysing a previously proposed cell-based model of glioblastoma growth, which is based on the assumption that the cancer cells switch phenotypes between a proliferative and motile state [1]. The dynamics of this model can be described by a system of partial differential equations, which exhibits traveling wave solutions whose wave speed depends crucially on the rates of phenotypic switching. We show that under certain conditions on the model parameters, a closed form expression of the wave speed can be obtained, and using singular perturbation methods we also derive an approximate expression of the cell density profile. These new analytical results agree with simulations of the cell-based model, and importantly show that the inverse relationship between the wave front steepness and speed observed for the Fisher equation no longer holds when phenotypic switching is considered.

[1] Gerlee P, Nelander S (2012) The Impact of Phenotypic Switching on Glioblastoma Growth and Invasion. PLoS Comput Biol 8(6): e1002556



## Investigation of the effect of phenotypic plasticity on tumor growth

Katrin Boettger<sup>1</sup>

1. Innovative Methods of Computing. Center for High Performance Computing (ZIH)

Modeling tissues with cellular and subcellular resolution requires clever representations of single cell complexity. Too much detail can saturate even most powerful computers while too simplistic approaches have usually limited predictive power. As it is usual in sciences the demands and capabilities are orthogonal to each other.

To solve simple cell-sorting problem, in 1992 Graner and Glazier [Swat, 2012] introduced cellular Potts Model (CPM) which currently is one of the most popular ways to model tissues, organs or even organisms with single -cell -resolution. CPM represents cells as spatially extended domains and allows relatively faithful model representation of basic cellular behaviors such as adhesion, growth, death, mitosis, chemical secretion, absorption etc... Over the years CPM evolved to become one of the most popular methods used in single-cell-based tissue simulation

In this talk I will present CompuCell3D (CC3D) simulation environment [Graner and Glazier, 1992] that allows building running and testing CPM-based models of tissues. CC3D is an open source project with fairly rich set of tools that facilitate model construction, visualization and post-processing. CC3D has Python interpreter which gives modelers great flexibility in customizing their models without requiring code recompilation. In fact bulk of the typical CC3D model is written in Python. I will present brief demo of the CC3D package and conclude the talk by addressing most pressing software-related issues facing multi-cell tissue modeling community.

[Swat, 2012]

Maciej Swat, Gilberto L. Thomas, Julio M. Belmonte, Abbas Shirinifard, Dimitrij Hmeljak, James A. Glazier (2012). "Multi-Scale Modeling of Tissues Using CompuCell3D," In Anand R. Asthagiri, Adam P. Arkin ed. *Methods In Cell Biology*, Vol 110, pp. 325-366.

[Graner and Glazier, 1992]

Francois Graner, James A. Glazier (1992). "Simulation of biological cell sorting using a two-dimensional extended Potts model," *Phys Rev Lett.* 69. p. 2013-2016.

## ***In-silico* glioma models: what can we take advantage for the clinical practice?**

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Glioblastoma Multiforme (GBM), the most prevalent and lethal primary brain tumor, typically shows the formation of hypercellular regions called pseudopalisades which usually surround necrotic cores and thrombosed vessels and are almost exclusive of this tumor type. In addition, pseudopalisades over express hypoxia-inducible factors and secrete prothrombotic factors such as tissue factor [1].

We discuss how these regions represent a wave of tumor cells actively migrating away from central hypoxia after a vascular insult as it was proposed in [2]. The irreversible impact of hypoxia events in tumor evolution will also be discussed as well as the therapeutical implications of our results and how the combination of antioxidants and antithrombotics, with very low or none toxicities, reduces tumor invasion and sensitizes GBM cells to conventional radiotherapy and chemotherapy, hopefully increasing median patient survival times.

Our results suggest that therapeutic approach targeting blood coagulation decreases tumor invasion although its effect is limited in monotherapy [3]. This is mainly due to the fact that an inefficient local tumor oxygenation in the tumor even during very short periods of time may lead to irreversible tumor cell transformation to more aggressive phenotypes [4]. Finally, we show that an appropriate combination of antioxidants and antithrombotics, with minor toxicity, may substantially slow down tumor invasion and sensitize GBM to conventional therapies such as radiotherapy and temozolamide [5].

The theoretical approach is based on different mathematical models constructed on the basis of the migration/proliferation dichotomy hypothesis, and incorporate the interplay among several cell phenotypes, a necrotic core and the vasculature that evolves with the tumor progression. The experimental verification of our ideas, to be discussed in this talk, has used: (i) experiments in controlled microfluidic devices and (ii) Different stainings of tumor tissue and pathology analysis to test the pseudopalisading hypothesis, (iii) in vitro and



in vivo experiments to test the effectivity of the combined therapies (xenografts in mice and orthotopic tumor transplants with rats and mice).

The potential application of these results into the clinical practice is under study.

[1] Louis, D. N., Ohgaki, H., Wiestler, O. D. & Cavenee, W. K. (2007) *World Health Organization Classification of Tumours of the Central Nervous System*, 4th edn. Geneva: Renouf Publishing Co. Ltd.

[2] Rong, Y., Durden, D. L., Van Meir, E. G. & Brat, D. J. (2006) 'Pseudopalisading' necrosis in glioblastoma: A familiar morphologic feature that links vascular pathology, hypoxia, and angiogenesis. *J. Neuropathol. Exp. Neurol.*, 65, 529–539.

[3] A. Martínez-González, G. F. Calvo, L. Pérez-Romasanta, V. M. Pérez-García. Hypoxic cell waves around necrotic cores in glioblastoma: A mathematical model and its therapeutical implications, *Bulletin of Mathematical Biology* 74, 2875-2896 (2012).

[4] V. M. Pérez-García and A. Martínez-González. Hypoxic ghost waves accelerates the progression of high-grade gliomas. *Journal of Mathematical Biology* (submitted) (2013).

[5] A. Martínez-González, M. Durán-Prado, G. F. Calvo, F. J. Alcaín, L. Pérez-Romasanta, V. M. Pérez-García. Combined therapies of antithrombotics and antioxidants delay *in silico* brain tumor progression *Mathematical Medicine and Biology*, doi: 10.1093/imammb/dqu002 (2014).



## Quantifying changes in glioma biology with treatment using modeling of edema formation and clinical imaging

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2. Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, USA

Glioblastoma, the most aggressive form of primary brain tumor, is predominantly assessed with gadolinium-enhanced T1-weighted (T1Gd) and T2-weighted magnetic resonance imaging (MRI). Pixel intensity enhancement on the T1Gd image corresponds to the contrast agent leaking from the tumor-induced neovasculature, while hyperintensity on the T2/FLAIR images represents a mix of edema and infiltrated tumor cells. None of these modalities directly show tumor cells; rather, they capture abnormalities in the microenvironment caused by the presence of tumor cells. Thus, clinical assessment of disease response after treatments impacting the microenvironment remains challenging through the obscuring lens of MR imaging. Anti-angiogenic therapies have been used in the treatment of gliomas with spurious results ranging from no apparent response to significant imaging improvement with the potential for extremely diffuse patterns of tumor recurrence on imaging and autopsy. Anti-angiogenic treatment normalizes the vasculature, effectively decreasing vessel permeability and thus reducing tumor-induced edema, drastically altering T2-weighted MRI.

We extend a previously developed mathematical model of glioma growth to explicitly incorporate edema formation allowing us to directly characterize and potentially predict the effects of anti-angiogenics on imageable tumor growth. A comparison of simulated glioma growth and imaging enhancement with and without bevacizumab supports the current understanding that anti-angiogenic treatment can serve as a surrogate for steroids and the clinically driven hypothesis that anti-angiogenic treatment may not have any significant effect on the growth dynamics of the overall tumor cell populations. However, the simulations do illustrate a potentially large impact on the level of edematous extracellular fluid, and thus on what would be imageable on T2/FLAIR MR. Additionally, by evaluating virtual tumors with varying growth kinetics, we see tumors with lower proliferation rates will have the most reduction in swelling from such treatments.

## An edema- based model for diffuse low-grade gliomas under radiotherapy

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Diffuse low-grade gliomas are rare and initially slowly growing tumours. Treatments consist in the first place in surgery when possible, followed by chemotherapy or radiotherapy. However, despite technical progress in imaging techniques and therapeutic management, they remain incurable. The major obstacle to cure these tumors surgically lays in the fact that tumor cells migrate well beyond the tumor limits detected by imaging techniques, precluding to remove all tumor cells. Hence the tumor always recurs and an anaplastic transformation eventually occurs: angiogenesis is triggered and the tumor becomes more aggressive, quickly leading to the patients demise. Optimizing treatments, for example with modeling, could help to delay the tumor regrowth and the anaplastic transformation. We present here a model for the effect of radiotherapy on diffuse low-grade gliomas. We complemented a migration-proliferation equation by an equation describing the appearance and draining of edema, and we argue that the latter effect accounts for the long decrease of the tumour's radius (sometimes even years) after the end of the radiotherapy. Using our four-parameter model, we are able to fit the data of the evolution of the tumor radius along time, of 28 patients [1]. The model predicts a strong correlation between a high proliferation coefficient and a low progression-free gain of lifetime among the patients, in agreement with clinical studies [1]. Moreover, by measuring or fixing the values of the parameters, we show that it is possible to predict, at the time of the radiotherapy, the duration of the tumour's radius decrease.

[1] Pallud J. et al. Dynamic imaging response following radiation therapy predicts long-term outcomes for diffuse low-grade gliomas. *Neuro Oncol.* 2012;14:1-10.





## Modeling dose-painting effects in radiotherapy by means of an agent based model.

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Radiotherapy, the use of ionizing radiation to eliminate pathological tissues, is a treatment of choice for more than 50% of patients diagnosed with solid tumors. Technical and methodological advances have allowed radiation oncology to achieve local tumor control in a considerable number of patients. However, locoregional recurrence (LRR) after treatment remains a problem in many clinical settings. For instance, In Glioblastoma Multiforme (GBM), the most common and aggressive malignant primary brain tumor, LRR occurs in about 90% of cases. Such recurrence is often associated to the onset of radioresistance and is strongly correlated with the development of significant intratumoral heterogeneity. Unfortunately, current medical techniques are unable to deduce sufficient information about tumor heterogeneity by means of non-invasive methods.

In this talk a mathematical model for heterogeneous tumor growth is proposed, and the effects of different homogeneous and heterogeneous radiation dose distributions are investigated by means of computer simulations [1]. Specifically, an individual cell-based model is considered for a simplified situation where two different tumor cell phenotypes corresponding to GBM cell lines coexist in a tumor, which we assume to strongly differ in their respective cell cycle duration and radiosensitivity properties. As a consequence of such differences, the spatial distribution of the corresponding phenotypes, whence the resulting tumor heterogeneity can be predicted as growth proceeds. Moreover, heterogeneous dosimetries can be selected to enhance tumor control by boosting radiation in the region occupied by the more radioresistant tumor cell phenotype. When compared with homogeneous dose distributions currently delivered in clinical practice, such heterogeneous radiation dosimetries always yield better results than their homogeneous counterparts.

[1] J. C. L. Alfonso, N. Jagiella, L. Núñez, M. A. Herrero, D. Drasdo (2014) Estimating Dose Painting Effects in Radiotherapy: A Mathematical Model. PLoS ONE 9(2): e89380. doi: 10.1371/journal.pone.0089380.



## A data-driven calibration of a nonlinear mechanistic model for DNA damage and repair: applications to radiosurgery and heavy ion irradiation treatment for glioblastoma

Russel Rockne<sup>1</sup>

1. Department of Neurological Surgery, Northwestern University, Chicago, USA

Current radiation treatment options for the invasive primary brain tumor glioblastoma multiforme (GBM), consist of two modalities which are very different in terms of the amount of dose delivered, the distribution of dose in space, and perhaps, the biological effectiveness.

On one hand, the current standard of care for GBM consists of “conformal” or intensity modulated radiation therapy (IMRT) with daily treatments of 1.8 – 2 Gy over the course of several weeks to a total dose of approximately 60 Gy to a large treatment volume. On the other hand is stereotactic radiosurgery (SRS), which is a secondary radiation therapy treatment used after the disease has recurred. The spatial localization of the highly focused “radiosurgical” dose is achieved through the composition of small 3–5 mm spherical targets, created with multiple small beams. SRS is typically a single fraction treatment, with doses of up to 24 Gy or higher and used primarily for small lesions. It is a matter of contemporary debate as to whether or not biological response to radiation changes for doses higher than 10 Gy per fraction. Because of the different dose per fraction, dose delivery times, and potentially different biological responses to these two radiation treatments, mechanistic models of radiation-induced DNA damage and repair are often used to quantify and translate radiation dose into biological effect.

I present a mechanistic two-compartment nonlinear ODE model of radiation-induced DNA damage and repair, which includes sub-lethal and fatal DNA classes of damage which is based on physically measurable quantities of the radiation treatment. Analytic solutions for this model can be found and demonstrates orders of magnitude differences from the linearized approximation used pervasively in the literature, particularly in the SRS high dose range. Further, data-driven parameterization of the fully nonlinear model reveals superior model prediction and parameter stability across a wide range of experimental conditions compared to current model paradigms such as the linear-quadratic model. The dose-response data used to test the model includes a wide range of particles, energies, doses, dose rates and dose-fraction timing, motivated by current trends in radiation oncology, including fractionated SRS and heavy ion therapy. This mechanistic modeling approach at the DNA level is connected to a patient-specific tissue level reaction-diffusion model for GBM which includes spatial and temporal delivery and response to radiation therapy to investigate the net effect of these novel radiation treatment strategies in silico.

## Linear dependency between residual tumor fraction and regression probability can provide decision support after partial resection of pilocytic astrocytoma

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1. Innovative Methods of Computing. Center for High Performance Computing (ZIH), Technische Universität Dresden, Germany

Pilocytic Astrocytoma (PA) is a grade I brain tumor which is common in children. These tumors are often benign and have a good prognosis, but in some cases a more aggressive form is observed causing higher mortality. If possible, total resection is the treatment of choice and provides a good prognosis. In many cases, only partial resection is possible due to the location of the tumor. Then, the prognosis is largely unpredictable and there is controversy about further treatment and the required follow-up investigations. In some cases of partial resection, the tumors spontaneously regress, whereas in other cases they regrow or even progress to a more aggressive form. The dependency between residual tumor size and regression probability is not understood yet. However, it could provide clinicians decision support in two ways. First, it could help to decide whether a "wait and see" strategy or, alternatively, additional therapy with further risks is required after partial resection. Second, it could justify the risk of additional resections in certain cases if this would imply a significant increase of the regression probability. A mathematical model is introduced in order to investigate this dependency. The dynamics of the model is entirely determined by a risk coefficient  $\gamma$ . This parameter is obtained by incorporating epidemiological data about PA. It turns out that the dependency between residual tumor fraction and regression probability is approximately linear. These insights can support clinicians in their decision to adopt a wait and see strategy and to balance between the risk of operation or further therapies and the risks of possible regrowth and progression of PA.