

Invasive Behaviors of Growing Solid Tumors

Fang Jin¹, Yao-Li Chuang^{1,*}, Steven Wise², Xiaoming Zheng³,
John Lowengrub^{1,4,5}, Hermann Frieboes^{6,1}, Vittorio Cristini^{6,7}

1. Mathematics Department, University of California, Irvine, Irvine, CA, USA
2. Mathematics Department, University of Tennessee, Knoxville, TN, USA
3. Mathematics Department, University of Michigan, Ann Arbor, MI, USA
4. Chemical Engineering and Materials Science Department,
University of California, Irvine, Irvine, CA, USA
5. Biomedical Engineering Department, University of California, Irvine,
Irvine, CA, USA
6. School of Health Information Science, University of Texas,
Houston, TX, USA
7. Department of Biomedical Engineering, University of Texas, Austin, TX, USA

*E-mail: ychuang1@math.uci.edu

Introduction

A growing solid tumor is a complex biological system. The basic structure involves cell-cell and cell-matrix adhesion, mechanical stress, cell motility, as well as nutrient induced cell proliferation and death [1, 2, 3, 4]. In response to various environmental conditions, tumors may exhibit morphological instability, giving rise to invasive behaviors of tumors [5]. Hypoxia can further induce more complex mechanisms of tumor growth, such as cell mutations and angiogenesis. Mutations change cell properties and essentially make the tumor a heterogeneous system. Angiogenesis interactively modifies the nutrient source and enhances the anisotropy of the system. Both mechanisms generally increase the morphological instability, helping the tumor invade surrounding tissues.

The Mathematical Model

In an attempt to control tumor growth and to prevent tumors from developing invasive shapes, we need to understand the factors that may affect the morphology of a tumor. In our study, we adopt a diffusive interface model to describe the basic structure of tumor growth [1, 3]. The full model consists of fourth-order nonlinear advection-reaction-diffusion equations (of Cahn-Hilliard-type) for tumor cells. For our model simulations, we adopt a finite-difference multi-grid method with adaptive mesh grids [1, 6, 7]. The results qualitatively match the clinical observations.

Mutation and Angiogenesis

Our basic model can be extended to include hypoxic behaviors such as tumor cell mutations and tumor induced angiogenesis. To add mutations to the model, we treat mutation cells as an additional sub-species of tumor cells. While the equations of tumor cells are of Cahn-Hilliard-type and generally expensive to solve, an advantage of our model is that the fourth-order terms of a master equation governing the total tumor density are decoupled from

those of the sub-species. Therefore, only the master equation has to be solved as a fourth-order equation, and it is relatively cheaper to add multiple sub-species to our basic tumor model [2]. Our simulations show that mutation species of certain properties may trigger the morphological instability of an originally stable tumor, as shown in Fig. 1(Left). In addition, we model tumor induced angiogenesis by coupling our tumor growth model to a capillary growth model. We adopt a gradient-based, circular random walk model for the capillary growth [8, 9]. The choice of the model allows us to capture essential microscopic phenomena of capillaries, such as tip splitting and anastomosis, while generating a more natural look of capillary profiles. The tumor cells release angiogenetic factors to induce the capillary growth; in turn, the capillaries provide nutrient, which is essential for tumor growth. Fig. 1(Right) shows an example of simulating the coupled tumor and capillary models.

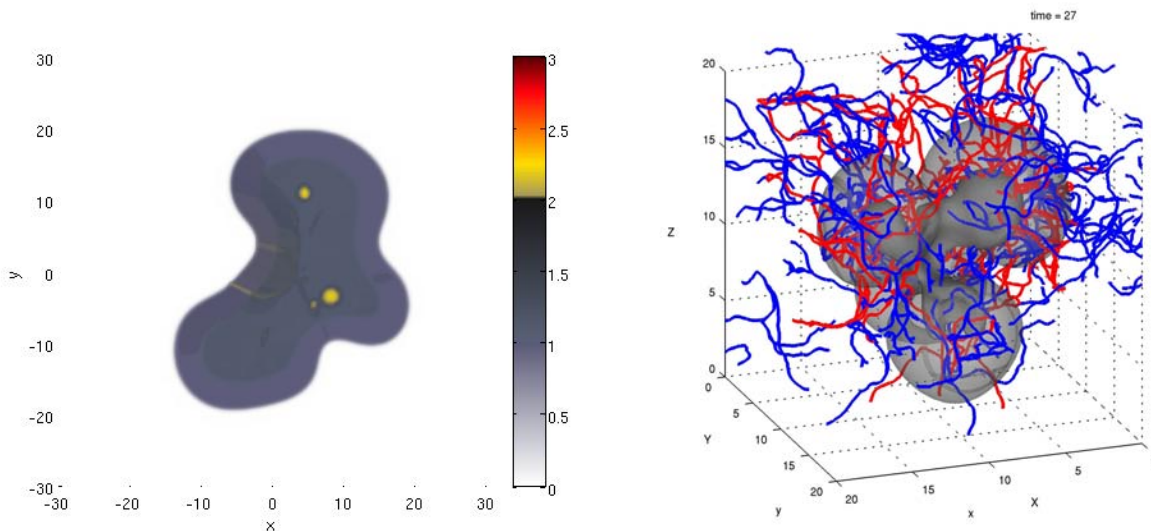


Figure 1: Left: Morphological instability of tumor growth due to mutations. The mutation tumor cells are denoted by yellow regions. Right: Tumor growth with angiogenesis. The red curves are anastomosed capillaries while the blue ones are not. Only the anastomosed capillaries supply nutrient.

Future Prospects

Various therapies have been proposed to treat tumors. Given the complex nature of a tumor, the results of these treatment sometimes contradict one another. We hope our model can provide useful *in silico* experiments, explaining the success and failure of the treatments in the context of various environmental conditions [2, 3, 5].

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