MS4: Multiscale Modeling in Cancer: From Genotype to Phenotype I

Nonlinear Networks Dynamics and Opposite Effects of Wnt5a on Motility in Melanomas

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Understanding how networks react to molecular targeting is important in biological sciences and medicine. Here, we encounter unusual nonlinear dynamics after targeting of Wnt5a, which enhances motility in 3/5 melanoma cell lines and represses motility in the other two. To explain this behavior we develop an optimization-driven general method for recovering networks from perturbation experiments. The models, consisting of ordinary differential equations representing signed directed graphs, are applied to a set of seven proteins that are key in classifying melanomas and in predicting biological phenotypes. To dampen the noise in biological data, we perform four replicates of each protein assay. Predictions from the computed networks were validated by motility experiments. The results uncover key principles of nonlinear molecular dynamics with wide implications in biological and medical sciences. Furthermore, the methodology and models are applicable to a wide range of biological networks.

Modeling of in Vivo Experiments of Metastatic Initiation and Tumor-Tumor Spatial Interactions

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Little is known about the detailed mechanisms of metastasis establishment in a distant organ, due to lack of experimental means to observe the process at this early stage. To resolve this further, we conducted a theoretical study based on data from an orthotopic murine experimental system of metastatic renal cell carcinoma. We first confronted our temporal data of total number of cells in the lungs with a mathematical model for the total metastatic burden dynamics. The results suggested as inadequate a naive theory of metastatic development where metastases would spread from the primary tumor and then grow independently from each other as well as from other parts of the system. Instead, we propose that metastatic germs growing from one or few cells could be aggregating, resulting in a similar total mass but a lower number of metastases. This led us to investigate the effect of tumor-tumor spatial interactions on the global metastatic burden dynamics. A novel mathematical model based on pressure-mediated growth was derived and shown able to fit the growth of metastatic lung nodules retrieved from magnetic resonance imaging (MRI) data. As a non trivial outcome from this analysis and under our modeling assumptions, the model predicted that total growth of two neighboring tumors was considerably impaired (31% 1.5% size reduction), as compared to the growth of two independent tumors. Our results provide a quantitative assessment of how much individual tumors growth is suppressed when tumors are in contact interactions. Moreover, they have implications for theories of metastatic development and suggest that global metastatic dynamics could emerge from the combined effects of fractionation of the total mass and spatial interactions between metastatic germs.

Data Assimilation in Lung Metastases Modeling: Towards Patient Calibrated Models Using Imaging Devices

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Data assimilation in lung metastases modeling: towards patient calibrated models using imaging devices Lung metastases are a therapeutical challenge as some as slowly evolving while others show an aggressive growth. This makes it difficult for clinicians to determine which nodule is to be treated

first on patients where many are present. As this patients are often weak and old, they seek to avoid any unnecessary invasive intervention.

In collaboration with Institut Bergoni (Bordeaux, France), we have developed a spatial mathematical model for the growth of these nodules and a data assimilation technique to recover its patient specific parameters from a sequence of medical images. This talk will describe the different challenges that had to be overcome and some results on clinical cases.

Level Set Segmentation Using Non-Negative Matrix Factorization with Application to MRI

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We present a new deformable model for image segmentation based on the level set method (LSM) and probabilistic non-negative matrix factorization (PNMF). The proposed model characterizes the histogram of the image, calculated over the image blocks, as nonnegative combinations of basic histograms computed using the PNMF algorithm. These basic histograms form a clustering of the image. Our model also takes into account the intensity inhomogeneity or bias field of medical images. In a level set formulation, this clustering criterion defines an energy in terms of the level set functions that represent a partition of the image domain. The image segmentation is achieved by minimizing this energy with respect to the level set functions and the bias field. Our method is compared, using brain MRI, to two other state-of-the-art level set methods that are based on k-means clustering and local Gaussian distribution fitting. It is shown that the proposed PNMF LSM is less sensitive to model parameters, more robust to noise in the image and, at the same time, has a higher convergence rate. These advantages are due to the fact that the proposed approach i) relies on the histogram for local clustering rather than image intensities, and ii) does not introduce additional model parameters to be simultaneously estimated with the bias field and the level set functions.