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We propose to develop a multiscale, predictive model of Colorectal Cancer (CRC) that can be used both for clinical applications and to develop specific, testable hypotheses about CRC. We hypothesize that a multiscale mechanistic model of CRC can be constructed with state-of-the-art modeling methods developed in Professor Cristini's lab for integrating both discrete and continuum scales, can be validated with ex vivo tissue from surgical specimens provided by Dr Rasi and coworkers, and can be applied to current clinical problems in treating CRC and to develop specific, testable hypotheses about CRC metastasis.

Our hypothesis is based on the following observations. 1.) A stochastic model is required to account for critical mechanisms modified by the microenvironment that determine the local cell-scale behavior. 2.) It is too expensive to compute the behavior of the entire system with a stochastic model, and therefore a continuum model is required to predict the tissue-scale behavior. 3.) Using two different scales requires an integrated approach with rigorous upscaling. 4.) We have demonstrated that we can use ex vivo tissue from surgical specimens of epithelial tumors (obtained through Laser Capture Microdissection from rats) to develop a validation set of realistic input cell-scale parameters for the model with measurable tissue-scale quantities that correspond to model predicted values. Based on these observations and our results with an introductory series of cases, we propose the following specific aims:

Specific Aim 1: Construct Tissue- and Cell-scale models of CRC: An agent-based, cellular-model is developed to model CRC from the molecular and multicellular scales, with direct calibration from patient and animal molecular- (IHC) and cellular- (histopathologic measurements) scale data. In parallel, a continuum model of growth and motility in a three-dimensional, patient-calibrated is developed.

1a. Develop an agent-based, cell-scale model (ABCM) to describe the time and space dependence of tumor size determinant cell functions and the effects of the microenvironment on these functions.

Time and length scales: Order of minutes to hours and sub-micron to mm, respectively.

1b. Develop a continuum, tissue scale model of CRC based on partial differential equations (PDEs) that express conservation laws.

Time and length scales: Order of hours to days and sub-mm to cm, respectively.

Specific Aim 2: The equation-free approach is used to develop dynamic, bidirectional, mechanistic links between the patient-and animal-calibrated cell-scale model and the tissue-scale growth model, allowing information to flow freely throughout the multiscale framework.

2. Develop a rigorous and accurate mathematical framework for integrating the cellular- and tissue-scale models developed in 1a/b using upscaling methods and the equation free approach (EFA)

The multiscale model is used to generate 1) testable hypotheses on the molecular basis of CRC's carcinogensis and invasion using the mathematical model and comparing growth predictions from model simulations, and 2) to define ideal timing of therapies targeting specific markers.

We have completed preliminary work on the development of a mechanistic model that directly links measurements of subcellular and cellular data to a predicted size and shape of a tumor. Our model is also an important step in understanding the difference biological behaviors of metastasis growth in different microenvironments. We have formulated a flexible architecture that will allow us to formulate hypotheses concerning the causative mechanisms of invasion in future research.

References:

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