A personalized model of prostate cancer progression under hormonal therapy

The prostate is a vital component of the male reproductive anatomy, which produces an alkaline fluid that is one of the key constituents of semen. Additionally, prostatic epithelial cells also produce prostate specific-antigen (PSA), that aids in sperm motility. Unfortunately, the prostate is also one of the most common sites of cancer incidence, with prostate cancer being the second most common type of cancer affecting men in the United States. In 2010 alone, more than 200,000 cases were diagnosed, resulting in 32,000 deaths.

Like the epithelial cells from which they chiefly originate, prostate cancer cells depend on male sex hormones (androgens) for growth and survival, and also produce PSA. Thus, an increased level of PSA in blood serum is used as a prognostic indicator for tumor burden. Cancer progression depends in part on the complex interactions between testosterone, DHT (a more active form of testosterone), and androgen receptors (which bind to, and are activated by testosterone and DHT). Figure 1 shows a simplified schematic of the intracellular reactions involving these chemicals.

In a metastatic setting, the first line of treatment is the elimination of testosterone, via chemical castration or ‘androgen ablaton’. However, such interventions are not curative as cancer cells evolve to a castration-resistant state via mutations in the androgen receptor-signaling pathway (see Figure 1), resulting in disease progression and ultimately death. It is thought that the selective pressures created by the continuous application of androgen ablation are responsible for this castration-resistant state. Consequently, it has been proposed that replacing constant androgen ablation with periodic androgen suppression, where treatment is switched on and off depending on predefined clinical objectives such as threshold PSA may bestow improved disease control with fewer treatment related toxicities.

With a view to identifying who will benefit from such a strategy, and personalizing therapy at an individual level, MBI Postdoctoral Fellow Harsh Jain and collaborators Avner Friedman (Department of Mathematics, OSU) and Steven Clinton (Director, Genitourinary Oncology Clinic, Wexner Medical Center, OSU) have developed mathematical models of prostate cancer progression in response to anti-androgen therapy. The models comprise of coupled ordinary (ODE) and partial differential equations (PDE) describing the temporal and spatial dynamics of key biochemical species, such as cancer cells, testosterone, DHT and androgen receptors. For instance, using mass action kinetics, the reactions in Figure 1 may be converted to a system of nonlinear ODEs. Singular perturbations are used to simplify model equations and analyze model behavior. An important feature of the models is the inclusion of “personalized” parameters, which address the heterogeneity in the predicted course of the disease under various androgen-deprivation schedules.

Model simulations are able to capture a variety of clinically observed outcomes for (averaged) patient data under different intermittent and continuous schedules.
Significantly, the model predicts that in most cases intermittent scheduling can lead to more rapid treatment failure as compared to continuous treatment. However, under certain conditions, such as if androgen-dependent cancer cells have a competitive advantage over resistant cells, or when resistant cells are in fact androgen repressed (unable to survive high androgen levels), intermittent therapy can delay the onset of resistance. Further, the models highlight the limited potential of PSA as a prognostic tool, and suggest that intermittent therapy scheduling should also take into account additional factors such as cancer cell turnover rates.

The long-term research goal of Jain and collaborators is to develop a comprehensive and highly personalized model of metastatic prostate cancer response to a range of treatments, with demonstrated predictive power. This requires the identification of new biomarkers for clinically significant disease; quantification of biomarker heterogeneity in the population; biomarker validation in predicting patient response and disease significance; and quantifying the effects of bone tissue healing on the growth of metastases and vascular morphology on PSA leakage. The resulting model will provide treatment outcome predictions in response to different therapeutic strategies, by estimating patient-specific parameters that are updated by observed patient responses on an ongoing basis, thus helping clinicians in optimizing therapeutic strategies.