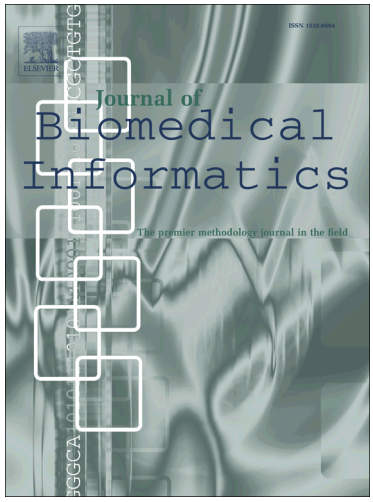

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Dynamic Strategy for Personalized Medicine: An Application to Metastatic Breast Cancer

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Abstract

We compare methods to develop an adaptive strategy for therapy choice in a class of breast cancer patients, as an example of approaches to personalize therapies for individual characteristics and each patient's response to therapy. Our model maintains a Markov belief about the effectiveness of the different therapies and updates it as therapies are administered and tumor images are observed, reflecting tumor response. We compare three different approximate methods to solve our analytical model against standard medical practice and show significant potential benefit of the computed dynamic strategies to limit tumor growth and to reduce the number of time periods patients are given chemotherapy, with its attendant side effects.

Keywords: breast cancer, dynamic treatment strategy, personalized medicine, Markov Decision Process

Personalized medicine offers the potential of selecting the best therapies depending on patient characteristics, medical history, and observed response to treatment. We seek to develop a framework to model the effectiveness of different therapies and develop a strategy tailored to a patient or class of patients. In this paper we consider breast cancer patients who are hormone receptor-positive and we use approximate algorithms to construct therapy strategies that incorporate clinical observations about tumor response to therapy.

Breast cancer is one of the most common cancers with 231,840 estimated new cases and 40,290 estimated deaths among US women in 2015. [1] Roughly 6% of all breast cancer cases reported from 2005 to 2011 are metastatic breast cancer cases. Breast cancer can be *hormone receptor-positive* for estrogen (ER+) and/or progesterone (PR+), where hormone therapy is most effective. This is the most prevalent of the three therapeutic categories for breast cancer, comprising 2/3 of all cases. Recent studies have also shown that targeted therapy in combination with hormone therapy, i.e. everolimus plus exemestane, is even more effective than many hormone therapies and chemotherapies. [2, 3] Because hormone therapy, as well as targeted therapy, induce fewer side effects than chemotherapy, it is usually the first-line therapy for hormone receptor-positive breast cancer patients.

Oncologists face challenging questions when treating metastatic hormone-receptor positive patients, including

(1) ***Is the current therapy effective?***

We say that a therapy is currently *effective* for a patient if it is more likely that the tumor size will decrease than increase. According to a systematic review of metastatic breast cancer therapies, [4] the rate of *objective tumor response* (defined as the tumor being less than half its initial size for at least 4 weeks), varies from 19% to 56% across therapies. There is considerable uncertainty, in the measurement of tumor size from radiological images, in the response of a tumor even to an effective therapy, and in the high probability that the measurement of tumor size will not change significantly in the two weeks between hospital visits. Together this makes it difficult to determine whether the current therapy is effective. This is exacerbated by the current practice of waiting three months between mammograms.

Unfortunately, tumors can develop resistance to therapies. The probability that a particular therapy is effective declines over time. This decline in effectiveness is observed whenever the patient receives that therapy or, to a lesser extent, another therapy from the same family, with similar functional mechanisms.