The Modeling of Cancer Progression and Immunotherapy

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Title: The Resonance Effect: From Mathematical Theory to Clinical Application in Cancer Drug Design

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Models of population dynamics, under various distributions of environmentally-inflicted loss processes, suggest that population persistence depends on the level synchronization of the environmental and population processes. Population growth is maximized when the environmental disturbance periodicity is an integer or fractional multiple of the population characteristic periodicity. This Resonance Phenomenon is observed in as diverse models as those of mussels in the inter-tidal zone under harsh weather regimes, those of humans exposed to pulsed measles vaccination policies and those of cancer and host cell populations under periodic chemotherapy. Based on the model analysis it was suggested that chemotherapy by cell-cycle phase-specific drugs can be optimized by drug schedules, employing the Resonance effect in conjunction with known differences in cell-cycle distributions of host and cancer cells. This method, termed *Z-Method*, was verified both *in vitro* and *in vivo*.

For tuning-up the method to clinical needs a new heuristic optimization method was developed, complying with complex criteria for treatment efficacy and the mathematical models of both pathology and physiology were upgraded to fit the breast cancer disease and the related chemotherapy induced myelosuppression. Quantitative predictions about the optimal administration of the chemotherapy supportive drug, TPO, were successfully validated in preclinical trials and the model-suggested optimal treatment schedule is routinely used in monkeys. The comprehensive cancer model now undergoes clinical trials in breast and brain cancer patients for its accuracy in predicting disease progression, metastatic formation and toxicity, and for its efficacy in optimizing the treatment schedules of drugs such as Docetaxel and Temozolomide. Success in these trials will pave the way for prediction-based drug development and for personalized drug treatment.