BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

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Department of Medicine
Channing Division of Network Medicine

Channing Network Science Seminar

July 19 (Friday), 2019, 11am @ 5th-floor conference room

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Dynamical aspects of antigen recognition, tumor/immune interactions, and spontaneous versus induced evolution of drug resistance during cancer treatment

This talk will consist of two related parts. The first part, which we published in (Cell Systems, 2017) addresses dynamic pathogen recognition. Since the early 1990s, many authors have independently suggested that self/nonself recognition by the immune system might be modulated by the rates of change of antigen challenges. This work introduces an extremely simple and purely conceptual mathematical model that allows dynamic discrimination of immunechallenges. The main component of the model is a motif which is ubiquitous in systems biology, the incoherent feedforward loop, which endows the system with the capability to estimate exponential growth exponents, a prediction which is consistent with experimental work showing that exponentially increasing antigen stimulation is a determinant of immune reactivity. Combined with a bistable system and a simple feedback repression mechanism, an interesting phenomenon emerges as a tumor growth rate increases: elimination, tolerance (tumor growth), again elimination, and finally a second zone of tolerance (tumor escape). This prediction from our model is analogous to the "two-zone tumor tolerance" phenomenon experimentally validated since the mid 1970s. Moreover, we provide a plausible biological instantiation of our circuit using combinations of regulatory and effector T cells.

The second part of the talk will be based mostly upon the recently published paper (Greene, Gevertz, and Sontag, ASCO Clinical Cancer Informatics, 2019), and deals with the following topic. Resistance to chemotherapy is a major impediment to the successful treatment of cancer. Classically, resistance has been thought to arise primarily through random genetic mutations, after which mutated cells expand via Darwinian selection. However, recent experimental evidence suggests that the progression to resistance need not occur randomly, but instead may be induced by the therapeutic agent itself.This process of resistance induction can be a result of genetic changes, or can occur through epigenetic alterations that cause otherwise drug-sensitive cancer cells to undergo "phenotype switching". This relatively novel notion of resistance further complicates the already challenging task of designing treatment protocols that minimize the risk of evolving resistance. In an effort to better understand treatment resistance, we have developed a mathematical modeling framework that incorporates both random and drug-induced resistance. Our model demonstrates that the ability (or lack thereof) of a drug to induce resistance can result in qualitatively different responses to the same drug dose and delivery schedule. The importance of induced resistance in treatment response led us to ask if, in our model, one can determine the

resistance induction rate of a drug for a given treatment protocol. Mathematically, we show that the induction parameter in our model is theoretically identifiable. We provide also a solution to an associated optimal control (preprint, arXiv, 2019).

Bio: Eduardo Sontag received his undergraduate degree from the University of Buenos Aires and his Ph.D., from the University of Florida, both in mathematics. In January 2018, after a 40-year career at Rutgers, he became a University Distinguished Professor in Electrical and Computer Engineering and in BioEngineering at Northeastern University. He has authored over five hundred research papers, and is a fellow of several societies, including IEEE, AMS, and SIAM. Sontag has been awarded several major prizes, including the Reid Prize in Mathematics by SIAM, the 2002 Bode Prize and the 2011 Control Systems Field Award by the IEEE.

Hosted by Yang-Yu Liu