

1139-92-217

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Detection of exponential rate of growth of antigen challenges by incoherent feedforward loops, and implications for immune/tumor modeling.

Since the early 1990s, many authors have independently suggested that self/nonsel self recognition by the immune system might be modulated by the rates of change of antigen challenges. This talk discusses an extremely simple and purely conceptual mathematical model that allows dynamic discrimination of immune challenges. 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. (Received February 11, 2018)