**149b Sources of Switch-like Behavior in Simple and Complex Biochemical Networks: Understanding the Action of a Cancer Target, Dihydrofolate Reductase**

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Clear understanding of the delicate relationship between biochemical reaction network structure and the capacity for switch-like behavior will be essential if we are to manipulate signaling and regulation for directed purposes. Some recent theory serves to distinguish, on the basis of network architecture, between complex networks that have the capacity to engender bistability and very similar ones that do not. In particular, the theory reveals something that is not generally appreciated: Some seemingly elementary classical mass action mechanisms for a *single* overall reaction involving a *single* enzyme are already sufficiently complex as to carry the seeds of bistability in simple physico-chemical settings. Thus, to understand how biochemical networks might give rise to switch-like behavior, it is important to understand sources of bistability not only “in the large” -- that is, at the level of multi-reaction pathways -- but also at the detailed level of individual enzyme-catalyzed reactions.

We shall provide a cursory description of recent developments in reaction network theory, operating both “in the large” and at the level of a single enzyme-catalyzed reaction. An example of switching at the single-reaction level will be afforded by a detailed study of the action of dihydrofolate reductase, which is crucial to the synthesis of DNA and which is the target of a standard chemotherapy agent, methotrexate. We conjecture that such bistability might serve a natural regulatory purpose but that it might also confound the quantitative understanding of methotrexate's action.