

The nonlinearity of regulation in biological networks

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The extent to which the components of a biological system are (non)linearly regulated determines how amenable they are to therapy and control. To better understand this property termed ‘regulatory nonlinearity’, we analyzed a suite of 137 published Boolean network models, containing a variety of complex nonlinear interactions, using a probabilistic generalization of Boolean logic that George Boole himself had proposed. Leveraging the continuous-nature of this formulation, we used Taylor decomposition to approximate the models with various levels of nonlinearity. A comparison of the resulting series of approximations of the biological models with appropriate random ensembles revealed that biological regulation tends to be less nonlinear than expected. A further categorical analysis of the biological models revealed that the nonlinearity of cancer and disease networks could not only be sometimes higher than expected but are also relatively more variable. We show that this variation is caused by differences in the apportioning of information among the various orders of nonlinearity. Taken together, our results suggest, but do not imply, that biological regulation may have evolved to be more linear on average, and certain systems such as cancer may have, on the other hand, evolved to be more nonlinear.