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BEHAVIOR OF GENE NETS

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Warren McCulloch was deeply interested in how accurate the workings and wirings of a nerve net must be for adequate function. I visited him for three months in 1967 to pursue at M.I.T. my parallel interest in the requirements for orderly dynamic behavior in a gene net. The genetic system whose developmental deployment generates a brain, and that brain, are highly ordered structures. The operon model was by then well established, and the view of a cellular control system of 104-105 genes whose molecular products regulated one another's activities was pointing towards a coherent formulation of the problem of cellular differentiation. The work McCulloch and I undertook was to characterize the typical behaviors of gene nets of binary devices, subject only to constraints on the number of "genes" in a net, N, and the number of genes regulating any given gene's activity, K.

Unlike neurons, for which threshold boolean functions are plausible idealizations, no restriction to threshold functions for gene control is likely. Indeed, subsequent evidence on the gene tof in bacteriophage lambda (1) shows it is not regulated by a threshold boolean function. Hence, in the work co-authored with McCulloch, we allowed all possible boolean functions of K variables in a net of N binary genes. We found, by computer simulation, and a few theorems, highly localized patterns of oscillations, and remarkable stability properties when all genes received two inputs.

Since McCulloch's death, I have been able to show that these highly localized dynamical properties are consequences of a simple class of boolean functions, which I call "canalizing". It appears that virtually all known regulated genes, when idealized as binary variables, are regulated by canalizing functions (1), which are defined by the simple property that at least one control variable has one state which alone determines one state of the regulated locus, regardless of the states of other control variables.

Were I now to recast those earlier efforts, I would say that the epistemological problem confronting cell biology is to find ways to use small scale information about genetic control systems - such as the typical number of genes directly regulating any given gene's activity, and constraints on the class of control rules governing the activity of the regulated gene, in order to find the expected implication of those small scale behaviors for the large scale structure and dynamic behaviors of the entire control system. This approach requires assessing the average properties of the ensemble of large gene nets built consistent with the small scale constraints, and suggests attempting to explain first those large scale features which are most insensitive to the details of the "wiring diagram". That simple local constraints in a model chemical system seem to impose such enormous global order led McCulloch to close our article with a typically lyric phrase: "Life is the inevitable consequence of chance and number."

And perhaps it is. I confess that possibility, hinting profound global dynamic order deriving from very simple kinetic properties of macromolecular catalysts, continues to fascinate me.

REFERENCE:

1. Kauffman, Stuart. 1974. *The Large Scale Structure and Dynamics of Gene Control Circuits: An ensemble Approach*. J. Theor. Biol. 44: 161-190.