Journal of Statistical Physic, Vol. 52, Nos. 3/4, 1988

Comment on a Genetic Application of Square-Lattice Kauffman Models

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Received April 8, 1988

Biological genes are argued to have an infinite range of interaction, in agreement with the original Kauffman model and in disagreement with recent modifications which put them on a lattice with nearest neighbor interaction.

KEY WORDS: Kauffman model; lattice model; genetics; biology.

Recent simulations[1] have investigated a special kind of Kauffman random Boolean network model for genetics, where each gene is either on or off, depending in a fixed way on whether k neighbor genes are on or off. These genes are assigned to the sites of a lattice and one asks, for example, if subsets of them are percolating, i.e., form one connected network of neighboring sites.

The dynamical properties of this class of cellular automata have been the theme of many papers referring to problems gathered from theoretical physics in the recent years. In particular, Stauffer[1] refers to biological problems,[2–6] where Kauffman automata were formulated for the first time, i.e., problems of genetic regulation.[7,8]

To check the biological applicability of these modified models, it is advantageous to separate the properties of the model structure, i.e., implicit assumptions about the structure of the phenomenon, from its results and to investigate both of them separately.

The causal texture of the genome, i.e., the regulative interaction of the genes, is projected onto a lattice, each site representing a formal gene. The

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0022-4715/88/0800-1129$06.00/0

neighborhood of a gene is defined, for example, to be the four orthogonal neighbors on the square lattice, i.e., the von Neumann neighborhood of cellular automata. This projection implies two structural characteristics we want to investigate in detail below:

1. Such a lattice gene directly interacts only with its spatially nearest neighbors. This implies that only a strictly limited spatial neighborhood of the gene is taken into consideration. But gene of higher organisms (eukaryotes) are arranged on several linear DNA molecules, the chromosomes.[5] Within the nucleus characteristic for the eukaryotes, they permanently change their relative position, thus changing the distance between them. To guarantee a limited spatial neighborhood one either has to choose the range of interaction of a gene very small, only covering its direct neighbors on the same chromosome, or assume a mechanism that fixes the chromosomes, thus avoiding a change in their distances.

Both assumptions contradict biological findings. Interactions between genes on different chromosomes are well known[9] and the temporal variability of the spatial distances of the genes is commonly accepted.

Furthermore, there is a second reason to call the idea of a spatially limited interaction critical: Genetic regulation is based upon interaction of a gene with a regulatory macromolecule. Most commonly the macromolecule is a protein.[5] But proteins are assembled only outside the nucleus, far away from the genes, in distances often exceeding the size of the nucleus.[6] It moves throughout the cell until it influences suitable genes in the nucleus. Biological findings[10] indicate a homogeneous density of such proteins throughout the cell. Therefore the typical distance the information of a gene has to cover before it can become regulatory effective is much larger than the distances between the genes inside the nucleus. Spatial distances between the genes of a cell seem to be irrelevant for regulation.

Therefore we assume that the regulatory interaction of the genes is essentially independent of their spatial distance.

2. The activity of a square-lattice gene is determined only by its neighbors.

The assumption that the activity of a gene depends only on its position stands in gross contradiction to biological results, which show that the ordered and coordinated regulation of a gene is independent of its position within the genome.[2–4] For example, one can inject in early embryonal cells of the fruit fly *Drosophila* carrying a well-known genetic defect an intact version of the faulty gene. So-called *P*-vectors insert this gene at a randomly chosen position between other genes.[2] It is found that the regulation due to the inserted gene and its expression are totally normal, i.e., well-ordered and coordinated with the other genes.

Therefore we have to assume that the pattern of activity of a gene is mostly independent from its position.

Based upon these structural considerations, not only square-lattice models, but all geometrically structured models with elements having fixed spatial relations seem unsuitable to describe the causal texture of the genome, at least if they contain a fixed spatial projection between genes and sites. Not geometrical structures, but more general topological structures with an infinite range of interaction are necessary to describe the biological phenomenon, as Kauffman originally proposed.[7,8].

However, to be a useful tool for understanding a given problem, a theoretical model does not necessarily have to provide a structural equivalence in all aspects. One often finds it sufficient that it shows a comparable and eventually an interpretable behavior: What questions were raised in refs. 1?

Of the behavior found for lattice models,[1] the geometrical interpretation via percolation concepts has not been claimed to have biologial significance. Periods and limit cycles seem to us biologically significant if one follows Kauffman[7,8] and identifies biological cell types with mathematical limit cycles. Most relevant for biological applications seem to us the investigations of stability against minor changes (mutations, damage spreading).[1,7,8]

Since their introduction,[7,8] Kauffman's random Boolean networks have found great acceptance, above all in theoretical physics. Its originally general and topological structure was replaced by a geometrical one, making possible many physical interpretations. The original infinite-range Kauffman model seems to us much more applicable than recent lattice versions. One could modify their structure again or investigate possible modifications in the interpretation of sites and neighbors on the lattice, thus replacing spatial ideas by functional ones. Both suggestions will be presented in a subsequent paper.

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