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Jacobian Problem and Genetic Networks

Mau-Hsiang Shih

Department of Mathematics, National Taiwan Normal University,

88 Sec. 4, Ting Chou Road, Taipei 116, Taiwan

E-mail : mhshih@math.ntnu.edu.tw

The Jacobian conjecture is a long standing problem in *algebraic geometry.* The conjecture was formulated by O. H. Keller in 1939 (see the excellent surveys by Bass-Connell-Wright[1] and van den Essen[2]), and also listed as one of 18 mathematical problems for 21st century by Steve Smale[3]. Mathematicians hope to unlock its mystery. Here we propose a network perspective of the Jacobian conjecture.

One of the fundamental tasks of biology is to understand cell differentiation. Recent biological progress, including the regulation of genes, gives us new insights into the mystery of differentiation. In 1961, Jacob and Monod[4] had discovered that genes coupled of promoters can act as switches to turn the genes on and off. (It was the work for which they later won the Nobel Prize in Physiology or Medicine.) As one gene is turned on, it leads to the production of proteins that can work upon the promoters of other genes. Every cell contains a number of such regulatory genes, and triggers a gene network coupled of complicated interactions.

Each gene is regarded as a basic processing unit in the network; it has two states - the "on" state of gene i is denoted by $x_i = 1$, and the "off" state is represented by $x_i = 0$. For a network made up of n genes, the state of the network is thus determined by the vector $x = (x_1, x_2, \ldots, x_n)^T$, and the n-cube $\{0,1\}^n$ is the network's phase space.

A type of cell resulting from cell differentiation might be associated with a permanent expression of corresponding genes. In that case, we have the transition function $F : \{0,1\}^n \to \{0,1\}^n$ associated with the gene network, and each choice of the steady state of F would respond to an assembly of genes guiding the differentiation of cells (a steady state has no changes under any updating of genes). This motivates us to have a mathematical interpretation of cell differentiation on the finding of multiple steady states of the gene network. A famous conjecture to characterize the structural properties for the occurrence of multiple steady states is proposed by René Thomas in 1981[5].

Thomas' Conjecture. *A necessary condition for the occurrence of multiple steady states of gene network is the presence of a positive circuit among complicated interacting genes.*

Let us introduce the notion of *discrete derivative* of F evaluated at $x \in \{0,1\}^n$, that is,

$$F'(x) = (f_{ij}(x)),$$

where $f_{ij}(x) = 1$ if $f_i(x) \neq f_i(\widetilde{x}^j)$, and $f_{ij}(x) = 0$ otherwise. Here $\widetilde{x}^j$ means the changing state of jth component of x. For a discrete $F'(x)$, we have a corresponding interaction graph $G(F'(x))$. The following theorem is a reformation of a combinatorial version of the Jacobian conjecture[7].

Theorem 1. *Given a complex network of interacting n genes and let $F : \{0,1\}^n \to \{0,1\}^n$ be the transition function associated with the network. If F has multiple steady states or has no steady states, then circuits exist in an interaction graph $G(F'(x))$ for some x in $\{0,1\}^n$.*

A further study of Theorem 1 will be given by adding a sign to each edge in the interaction graph $G(F'(x))$ and counting the attribution of each circuit lurking in $G(F'(x))$. A new graph method would be applied to solve the Thomas' Conjecture in full generality, and will appear in the forthcoming pape by Shih & Tsai.

For an $n \times n$ 01-matrix A, the boolean spectral radius of A, denoted as $\rho(A)$, is defined to be the maximum of boolean eigenvalues of A. One can prove that $\rho(A) = 0$ iff $G(A)$ has no circuits. Thus Theorem 1 has the following analytic boolean counterpart[7].

Theorem 2. *Let $F : \{0,1\}^n \to \{0,1\}^n$. If $\rho(F'(x)) = 0$ for all x in $\{0,1\}^n$, then F has a unique fixed point.*

Theorem 2 answers to the "Combinatorial Fixed Point Conjecture", a combinatorial version of the Jacobian conjecture[6].

To prove Theorem 2, we need the following lemma[7]. Let $x \in \{0,1\}^n$; for each $k = 1, 2, \ldots, n-1$ and for each choice of $k+1$ distinct integers $i_1, \ldots, i_{k+1}$ (which are arranged in any order) from $\{1, \ldots, n\}$, we define

$$x\,[\,\{i_1, \ldots, i_k\} \mid i_{k+1}\,] \equiv \{\, y \in \{0,1\}^n;\ y_{i_{k+1}} = x_{i_{k+1}},\ y_j = x_j \text{ for all } j \neq i_1, \ldots, i_k \,\},$$

$$x\,[\,\{i_1, \ldots, i_k\} \mid \bar{i}_{k+1}\,] \equiv \{\, y \in \{0,1\}^n;\ y_{i_{k+1}} = \overline{x}_{i_{k+1}},\ y_j = x_j \text{ for all } j \neq i_1, \ldots, i_k, i_{k+1} \,\}.$$

We call $x\,[\,\{i_1, \ldots, i_k\} \mid i_{k+1}\,]$ a *k-subcube* generated by x.

Lemma. *Let $F : \{0,1\}^n \to \{0,1\}^n$. If $\rho(F'(x)) = 0$ for all x in $\{0,1\}^n$, then for each x in $\{0,1\}^n$ and for each $k = 1, \ldots, n-1$ and for each choice of $k+1$ distinct integers $i_1, \ldots, i_{k+1}$ (which are arranged in any order) from $\{1, \ldots, n\}$, there exists a unique point $\alpha \in x\,[\,\{i_1, \ldots, i_k\} \mid i_{k+1}]$ such that $f_j(\alpha) = \alpha_j$ for all $j = i_1, \ldots, i_k$. (Geometrically, this means that the image of this element α belongs to n hypercube which is a kind of "orthogonal" to the k-subcube.)*

The spectral condition "$\rho(F'(x)) = 0$ for all $x \in \{0,1\}^n$" implies that F leaves a unique point invariant. And on toward microscopic perspectives: the spectral condition also implies that for each $k = 1, \ldots, n-1$ and for each k-subcube the boolean function F leaves a unique point in the k-subcube having k components invariant in a very regular pattern indeed. This lemma triggers us to understanding the collective behavior in systems of many components interacting simultaneously. Finally, the author wishes to thank Professor Christophe Soule (at IHES in Paris) for informing that Theorem 2 fits nicely in René Thomas' conjecture.

References

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