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Genes Do Not Determine Biological Shape Directly

HONDA Hisao*

Hyogo University, Kakogawa, Hyogo 675-0101, Japan
E-mail: hihonda@humans-kc.hyogo-dai.ac.jp

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Abstract. Genes have been considered to determine biological shape. However, based on several studies of the self-organization of biological systems, I would like to point out that genes do not always determine biological shape directly, but produce dynamic units that are spontaneously assembled into a characteristic shape. The spontaneously assembling is affected by stochastic and environmental effects, and lead to the final shapes. Shapes of living organisms thus do not necessarily have an adaptive value. They are sometimes neutral.

1. Introduction

All living organisms have been succeeding in continuous reproduction. Organisms failing in reproduction have died and disappeared. In general, reproduction is not exclusive for living organisms, e.g. pieces of crystal could reproduce themselves by repetition of crystal destruction and growth (nuclei made by destruction of a crystal grow large crystals in supersaturated solution, and the crystals are destroyed into crystal pieces again...). For the continuous reproduction of the living organisms, information for the reproduction of an individual body is packed into a set of genes and separated from the metabolic system of the individual body construction (Fig. 1). Genes have two functions. They do not only act as a heredity factor that genes copy themselves for inheritance, but also as a blueprint on which an individual body is constructed.

I would like to discuss what information the blueprint contains. The blueprint does not instruct directly an egg in the final body shape, but how to make a shape. The genes determine proteins, and the proteins (as enzymes) catalyze material syntheses. These materials are organized into a complex, and these complexes are further organized into a more complicated complex. These processes are autonomous. Such an autonomous process is not exclusive for the construction of molecules. In a similar way, cells are also organized into a tissue autonomously. For example, adhesive cells aggregate into a cell mass. A cell aggregate consisting of two cell types sometimes shows a sorting-out phenomenon, i.e.

*Name in Japanese style. Family name is in capitals.

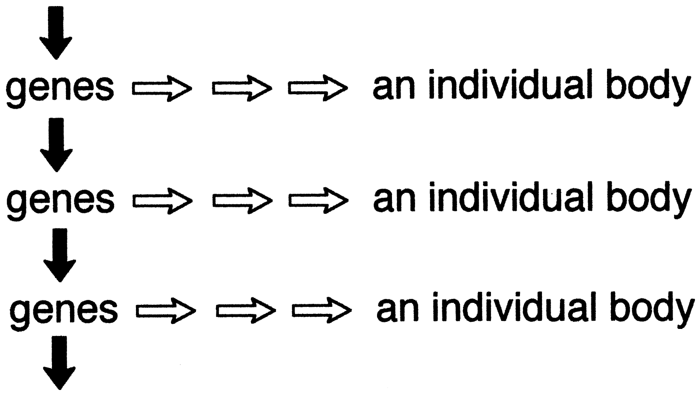


Fig. 1. Genes have two functions. They act as an inheritance factor in which genes copy themselves for heredity (top to bottom), and as a blueprint on which an individual body is constructed (left to right).

cells of one type which are strongly adhesive with each other are sorted to a cell mass, which is centered in the aggregate and surrounded with cells of the other type. The autonomous system of cells could be extended to tissues and higher organizations. Generally, genes produce dynamic units, which are spontaneously organized into a shape. I will show several self-organized processes of cells and tissues that I have been studying.

2. Processes of Self-Organization

2.*1*. *Colony patterns of the green algae* Pediastrum (HONDA, 1973)

Pediastrum biwae is a coenobial green algae in freshwater, and consists of 2^n cells (e.g., 32 cells), and shows characteristic cell patterns (a few concentric circular strings, a spiral string and so on, as shown in Fig. 2). These patterns form through random swimming of small cells (zoospores). The zoospore is approximated as a sphere which has two C-sites (presumptive connection sites) and one H-site (presumptive site for horn formation), and undergoes a series of changes in its properties (Fig. 3). The C-sites become connection sites then the zoospores form strings leading to the characteristic pattern. The H-site determines its fate, a horn or the third connection site according to absence or presence of other cells which limit its growth.

Genes produce zoospores (units) and units are spontaneously organized into one of *Pediastrum* patterns. Stochastic process produces variation of final patterns, e.g., three-cell centered, four-cell centered, five-cell centered concentric circular pattern, or spiral pattern (Fig. 2a–d). The theory was confirmed by the observation that a single clone of *Pediastrum* shows all of these various patterns (HONDA, 1973).

*2.2. Cell differentiation under the lateral inhibition control (*HONDA *et al*., 1990)

Cells in the neurogenic region of an insect (*Drosophila)* ectoderm have two alternative fates: either neuroblasts or epidermis. The fate is determined through a latarally inhibitory interaction among cells. Initially homogeneous cells are all competent to differentiate into

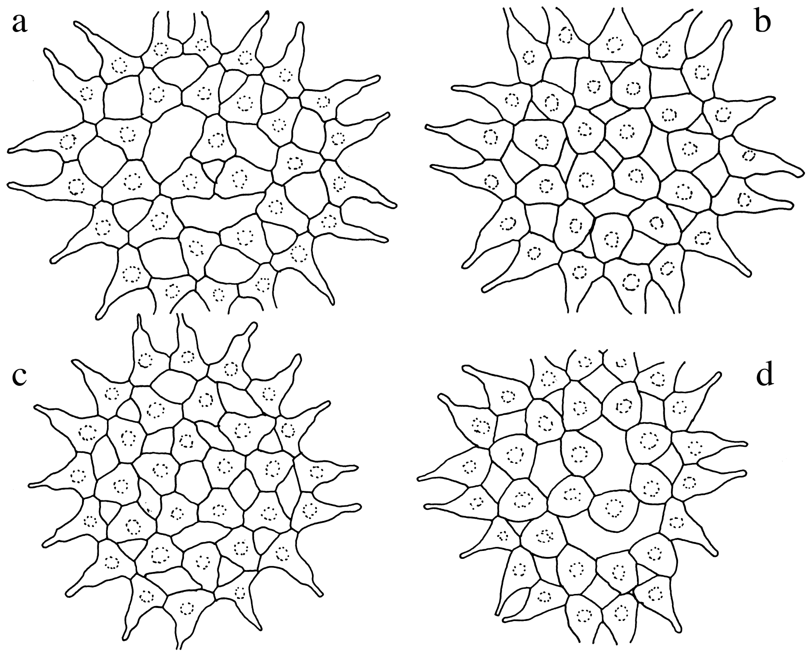


Fig. 2. Patterns of green algae *Pediastrum biwae*. Three-, four- and five-cell centered concentric circular patterns (a–c) and spiral pattern (d) (based on HONDA, 1973).

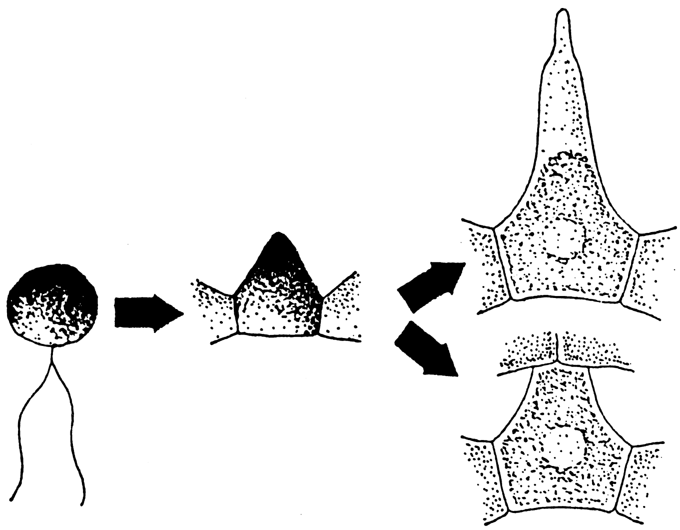


Fig. 3. Small cells (zoospores) undergo a series of changes during *Pediastrum* pattern formation: swimming zoospores, cells having two connection sites forming strings, and horn or triangle cells according to their position in a colony (based on HONDA, 1973).

neuroblasts. However, once a cell has differentiated as a neuroblast, it inhibits its immediate neighbors from following this pathway. Initiation of the cell differentiation is by chance. A distribution pattern of differentiated cells in the neurogenic region (Fig. 4) is a result of fluctuation of the initiation of individual cell differentiation. Genes determine only homogeneous (but competent) cells, but do not determine cell fates individually.

2.3. Checkerboard cellular pattern of the oviduct epithelium (HONDA *et al.*, 1986)

A peculiar cellular pattern resembling a checkerboard has been observed on the luminal surface of the oviduct epithelium of a quail (Fig. 5). The epithelium is a monolayer cell sheet and consists of two types of columnar cells, ciliated cells and gland cells assembled in alternating blocks. The two cell types form a checkerboard pattern. It was assumed that adhesion is stronger between unlike cells than between like cells because all cell boundaries in the checkerboard are edges along which unlike cells meet. The assumption was supported by a computer simulation (HONDA *et al.*, 1986). Genes produce two types of cells, and these cells are spontaneously organized into the checkerboard pattern.

2.4. Branching pattern formation of blood vessels (HONDA and YOSHIZATO, 1997)

Blood vessels in a blood branching system are formed by the selection of capillaries in the network (Fig. 6a). A positive feedback system participates in the formation of a

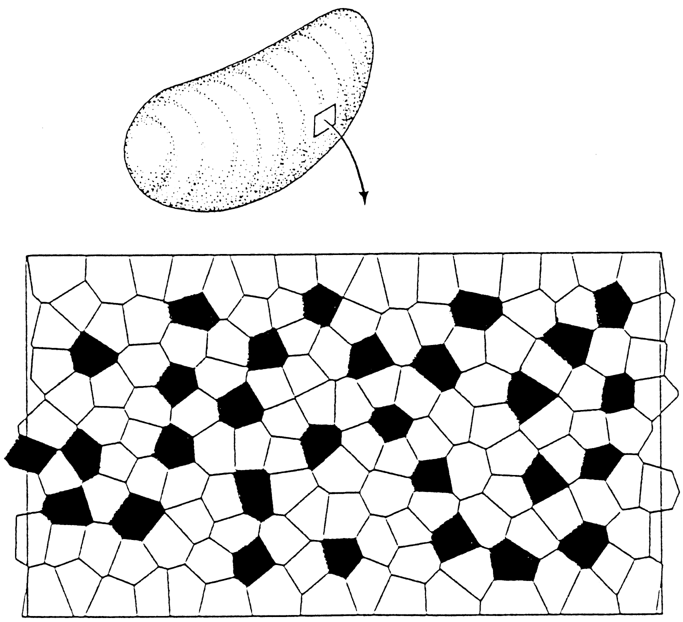


Fig. 4. Cells in the neurogenic region of an insect (*Drosophila*) ectoderm have two alternative fates: neuroblasts (solid polygon) or epidermis (open polygon). The fate is determined by the laterally inhibitory interaction among cells. A result of computer simulations (HONDA *et al.*, 1990).

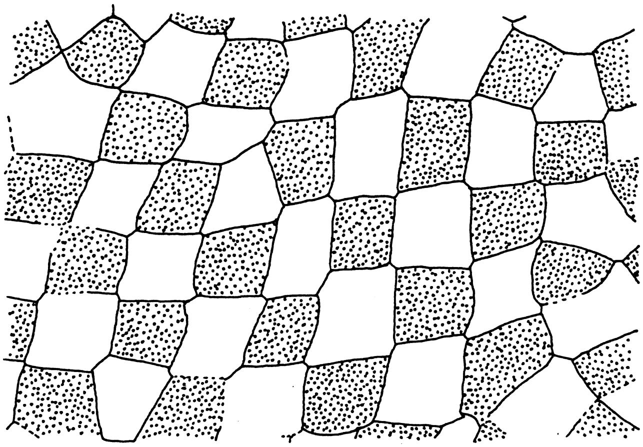


Fig. 5. An avian oviduct epithelial sheet consists of two types of cells, ciliated cells and gland cells assembled in alternating blocks. The formation of cell pattern is based on the differential affinity between cells (HONDA *et al.*, 1986).

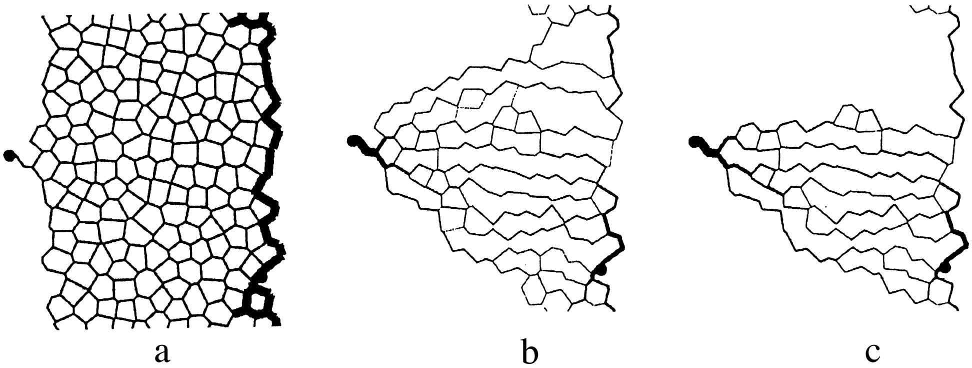


Fig. 6. Blood vessels in a blood branching system are formed by the selection of capillaries in the network (a). b and c, A sequential result of computer simulations under positive feedback control (HONDA and YOSHIZATO, 1997).

branching structure. Much used vessels are enlarged, whereas less used vessels are reduced in their size and finally extinguished (Figs. 6b and c). The enlarged vessels become major components of the branching system. Genes produce capillary vessels consisting of endothelial cells. The endothelial cells detect signals of the shearing force by blood flow and the blood pressure, and reform the vessels according to degree of detected signals. The vessels are dynamic units of the self-organization.

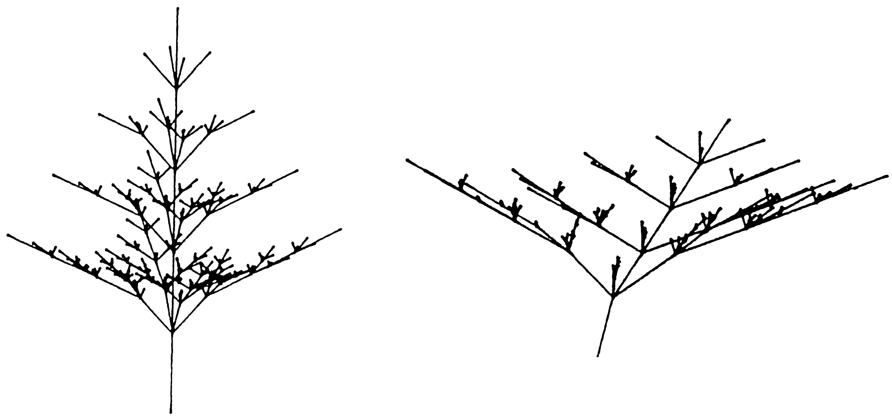
2.5. Branching structure of the Japanese strawberry tree Yamaboushi, Cornus kausa (HONDA *et al.*, 1997)

A crown of *Cornus kausa* consists of five-forked branchings showing various branching types. The branching type is determined by position within the crown and by the direction of the shoot with respect to gravity. A geometrical branching model is made that has parameters influenced by the direction of gravity. Computer simulations using the model successfully make realistic *Cornus* tree shapes (Fig. 7), and suggest that genes produce dynamic units having an ability of a physiological mechanism that responds to gravity and determines the orientation of themselves.

3. Discussion

I proposed genes produce dynamic structural units that are assembled into a characteristic shape spontaneously. The proposal leads to two important points. First, biological shapes are not determined solely by genes. They are determined by characteristics of the units (gene products) and the environment around the units. The environment sometimes varies by chance. Horn cells, one of the two fates of *Pediastrum* cells are determined by their peripheral position in a colony. The fate of cells in the neuroblast generating region is determined by fluctuating properties of surrounding cells. Transformation of branching blood vessels from capillary vessels is carried out through random positioning and functioning of capillary vessels and the positive feedback system. The branching type is determined by the interaction between the intrinsic branching rule and the gravity direction.

The second important point is that biological shapes are not always adaptive; they



a b

Fig. 7. A geometrical branching model that has parameters influenced by the direction of gravity. A whole tree (a) and a branch complex (b) of computer simulations using the model successfully make realistic *Cornus* tree shapes. Genes may regulate the type and orientation of branch units, but not the final pattern of the branch or the shape of the tree (HONDA *et al*., 1997).

sometimes may be neutral. Biological shapes are produced by self-organization. They are able to exist if they are not harmful to the function or survival of an organ or organism. *Pediastrum* shows various colony patterns, e.g. patterns having three, four and five centered cells (Fig. 2a–d). The variation of the patterns is due to the variables during the process of self-organization. These colonies having various patterns are considered to have a similar adaptive value with each other. The epithelium of hen oviducts shows a checkerboard pattern consisting of two types of cells. Even distribution of cilliary cells and gland cells on the inner surface of the oviduct tube seems to be convenient for egg transportation, but the complete intermixing of individual cells may be not necessary for smooth transportation. The checkerboard pattern may be simply a consequence of the process of self-organization. The final observable pattern or shape itself may not have a direct benefit.

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