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Supracellular Structural Principle of Multicellular Organisms

Norio Suwa

(Present address) 1-33 Kotakecho, Nerima, Tokyo 176, Japan

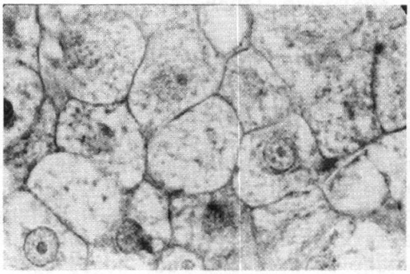
All the supracellular structures made of compact aggregates of constituent units are subordinate to a single structural principle. It is a particular space division called equilibrium space division (ESD) by the author. Three-dimensional ESD is characterized by polyhedral space division in which three faces unite to make an edge and four edges converge to a vertex. It is a geometrical expression of the second law of thermodynamics corresponding to the state of minimized potential energy of the system of constituent units assembled by uniform centripetal force. The field of force is provided by tension of connective tissue encapsulating and lobulating parenchymal mass. Any polarization of extraneous force produces lower-dimensional ESD, which precipitates anisotropic structures. ESD is a statistical process under incomplete mechanical restriction and cannot entirely be reduced to deterministic mechanism. Supracellular structures are accordingly not directly prescribed by genetic information derived from the template function of DNA molecules. Ample freedom in the structural principle is interpreted as the morphological background of remarkable adaptability of organisms.

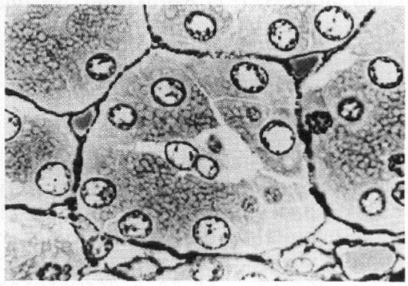
The present report deals with the general supracellular structural principle which universally underlies all the tissues and organs of multicellular organisms. Detailed discussions of the problem are found in Suwa (1981a), Suwa (1981b) and Suwa (1982). It would seem to be the established concept on the structures beyond the cell level that a number of similar cells are grouped together with different amount of intercellular substance to make a tissue. A variety of tissues are then assembled to construct an organ. It appears as if there were nothing ambiguous in these conventional definitions of tissues and organs. In reality, however, they are entirely devoid of the viewpoint, how the cells and larger constituent units are "grouped" or "assembled". There are a number of different ways in filling the three-dimensional space even with the same sample of units, and the analysis of structural principle would be indispensable for the understanding of the nature of multicellular organisms.

There are two important findings in this respect. One of them is the structural isotropy in the majority of tissues and organs. Their histological appearances are practically not influenced by the direction of the sectional plane in the three-dimensional space. This is easily ascertained in many organs, such as liver, pancreas, lung and so forth.

Anisotropic arrangement of structural units as observed in the renal medulla is considered later.

The other important finding is that on the section of every tissue or organ made of compact cell aggregates three cellular borders converge to a point. This structural pattern is observed not only on the cell level





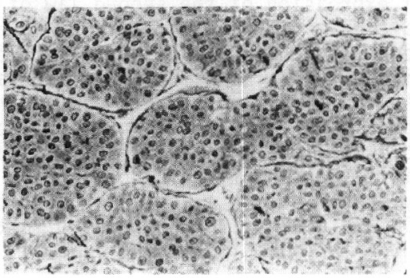


Fig. 1-a (upper left) Aggregate of liver cells is demonstrated. Note that three border lines of cells converge to a point.
Fig. 1-b (upper right) Normal pancreatic acini. Three border lines of acini unite to a point.
Fig. 1-c (lower left) Alveoli of liver cell cancer are shown. The boundaries of alveoli are made of blood spaces, and three sections of blood spaces converge to a point.

but also on larger structural units such as pancreatic acini, thyroid follicles and pulmonary alveoli. Pathological structural units, for example nodules of cirrhotic livers and cancer alveoli exhibit likewise the same pattern.

Now, the lines and points on the sectional plane give information of faces and edges in the three-dimensional space, respectively. The histological finding that three borderlines of constituent units converge to a point indicates polyhedral space division, where three faces unite to make an edge. But the condition of space division is still undertermined, because the number of edges converging to a corner is not yet defined. Geometrically, any even number of edges not smaller than four may be connected at a corner, if only the local condition at a certain corner is considered. However, only the case of four edges is acceptable for biological structures. This is confirmed by serial sections. Direct observation on very thick sections may also be helpful, while the focussed level is continuously shifted. Accordingly, we can define the polyhedral space division of supracellular structures completely by the following conditions. Namely, three faces unite to make an edge, and four edges converge to a corner.

This characteristic space division can be perfectly reproduced by constructing the Voronoi polyhedron around each of randomly packed hard spheres of equal diameter. Brief comments would be necessary on the concepts of random packing of spheres and the Voronoi polyhedron. Random packing of spheres means the aggregate of a sufficiently large number of

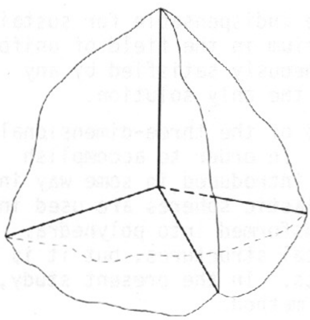


Fig. 2

Local conditions of space division by supracellular structures are demonstrated. Note that three faces unite to make an edge and four edges converge to a vertex.

hard spheres packed as tightly as possible under extraneous force acting centripetally and uniformly from every direction. The size of spheres may be variable, but only the case of equal spheres is taken into consideration. For example, we can suppose small steel balls of a ball bearing held tightly in the palm.

The arrangement of spheres in random packing is irregular, or it cannot be reduced to the pile of any geometrically definable elementary sphere groups. In other words, the same spatial arrangement cannot be reproduced by repeated trials even with the same sphere sample. Random packing is essentially a statistical process and is not susceptible of any simple geometrical approach.

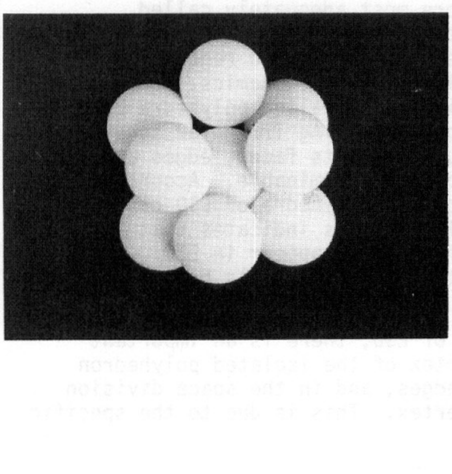


Fig. 3

Aspects of random packing are demonstrated with a small number of ping-pong balls. Note irregular configuration of spheres. The sphere at the center is supported by three contact spheres in every direction.

In spite of the irregularity, this particular sphere aggregate has two important characteristics. One of them is isotropic sphere arrangement or the expected number of spheres intersected by a test plane is the same irrespective of the position and direction of the latter. The other is that possible dislocation of a sphere in any direction is always stopped by three supporting contact spheres. This means that there are at least three contact spheres on every hemisphere. This is obviously necessary to establish stable mechanical equilibrium of the sphere aggregate.

The afore-mentioned two conditions are indispensable for sustaining a three-dimensional sphere pile in equilibrium in the field of uniform centripetal force. They cannot be simultaneously satisfied by any regular sphere pile, and random packing is the only solution.

Hard spheres can occupy only about 64% of the three-dimensional space, however tight they might be packed. In order to accomplish complete space division, polyhedra must be introduced in some way into the sphere group. For example, soft and plastic spheres are used instead of hard ones, compressed uniformly and transformed into polyhedra. This may be the most suitable model for biological structures, but it is not accessible to simple mathematical treatments. In the present study, polyhedra are constructed by the following method.

We suppose now a point in the interspherical space and define the distance of the point from an adjacent sphere by the length of the extraspherical portion of the line connecting the point with the sphere center. We take then around a sphere such a region that all the points within it are situated nearer to this particular sphere than to any other one. The region will demarcate a polyhedron around the sphere, and it is called the Voronoi polyhedron.

The borders of the polyhedra made around all the spheres of the pile are the faces on which every point is situated at equal distances from the surfaces of every two adjacent spheres. When the spheres are unequal in size, the faces are hyperboloidal. In the case of equal spheres, the faces become planes.

The Voronoi polyhedra made around all the spheres of random packing accomplish complete division of a three-dimensional space. Stable mechanical equilibrium in a field of uniform centripetal force is ensured by the configuration of spheres underlying the polyhedra. This particular space division may be therefore most adequately called "equilibrium space division" or ESD. It corresponds to the state of minimum potential energy of the sphere system and may be regarded as a geometrical expression of the second law of thermodynamics. Individual Voronoi polyhedra in ESD are consequently simply called polyhedra of ESD. A polyhedron of ESD is irregular in shape reflecting irregular sphere configuration of random packing. The number of its faces, edges and verteces are variable and only statistically determinable. According to Coxeter(1961), the mean number of faces of polyhedra of ESD can be theoretically derived as approximately 13.4. This indicates that 13-faced and 14-faced polyhedra will most frequently appear in ESD. The result is in agreement with the observation on plant cells by Dodd(1944), Marvin(1939) and Matzke(1939, 1946).

In spite of the statistical nature of ESD, there is an important invariable topological character. A vertex of the isolated polyhedron is always made by convergence of three edges, and in the space division by polyhedra four edges converge to a vertex. This is due to the specific

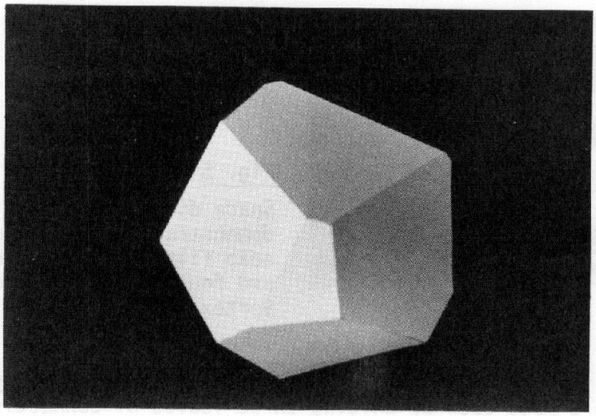


Fig. 4
An example of polyhedron of ESD is presented. Note irregular shape and invariable topological character that a vertex is always made by convergence of three edges.

sphere configuration of random packing, in which each sphere is supported by three contact spheres in any direction.

With this particular topological character and isotropic orientation of the faces, ESD perfectly reproduces the supracellular structural principle. The result has important implication. It indicates that the cells and supracellular structural units are not endowed with capacity to prescribe definitely the positions of their neighbors. In this respect, biological structures are fundamentally different from crystals. In crystals interatomic force determines a certain definite configuration of the constituent atoms. Such a mechanism brings about a regular structure, but cannot produce the pattern of random packing of spheres. The principle of biological structures consists in assembling constituent units only under the restriction that a unit is excluded from the space preoccupied by another. This is also the reason why the stereological methods are effectively applied to biological structures. Stereological methods mostly presuppose the random distribution of objects. Although strict random distribution cannot be realized by compact biological structures, minimum restriction in the structural principle makes a good approximation possible.

Now, we have to consider the mechanism, which produces ESD in organisms. ESD is widely observed in nature, regardless of the difference of organic and inorganic structures. One of the classical examples is the space division by soap foam. The force sustaining the structure is the surface tension on soap film, which is converted to pressure vertical to film surfaces and compresses enclosed air. The same mechanism is also working in supracellular structures. The organs are encapsulated and lobulated by connective tissue. The tension of connective tissue septa evidently generates force which sustains the three-dimensional organ structure. The connective tissue septa, however, do not usually separate and enclose parenchymal masses completely. They are abundantly perforated by thick parenchymal bridges. The tension is

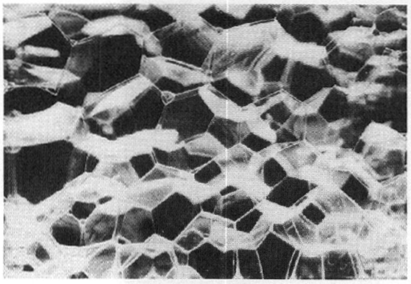


Fig. 5

Space division by soap foam is demonstrated. Three faces of soap films unite to make an edge and four edges converge to a vertex.

then produced from more or less limited regions in the vicinity of the edges, which are made each by uniting three leaves of connective tissue septa. In extreme cases membraneous character is practically lost from connective tissue. If parenchymal mass is cohesive enough, strings of connective tissue fibers perforating it along the edges of ESD can bear the tension to hold a three-dimensional structure. Normal human liver is a good example.

This organ is practically devoid of septal connective tissue, and connective tissue is localized in the limited region of portal triads. However, if the portal triads are connected with imaginary borderlines, polyhedra of ESD are visualized on the histological section as hepatic lobules. Hepatic lobules may also appear as real structures, when the lobular borders exhibit different staining behavior.

Three-dimensional ESD is possible only in the field of uniform centripetal force. Any polarization of extraneous force disintegrates three-dimensional structures and produces lower-dimensional ones. They may be two-dimensional structures or one-dimensional ones. Even in such cases no specific structural principle is present other than ESD of lower dimensions.

Two-dimensional ESD is produced when additional force is acting which compresses constituent units against a certain plane. The resulting structures is a sheet-like one, and ESD is realized on the plane. It is reproduced by dividing a plane with the Voronoi polygons made around each of a large number of circles gathered as closely as possible under uniform centripetal force acting on the plane. Stable mechanical equilibrium is attained by so arranging the circles that the dislocation of a circle in any direction on the plane is always stopped by two contact circles. In other words, there are at least two contact circles on every hemicircle. We suppose now a point in the intercircular space and the line connecting it with the center of an adjacent circle. The distance from the point to the circle is then defined by the length of the portion of the line outside the circle. The common side of the Voronoi polygons of two adjacent circles is the locus of points which are situated in equal distances from the two circles. It gives a hyperbolic curve, because the difference in the length of the lines connecting a point on the locus with the centers of the two adjacent circles should always be equal to the difference in the radii of the circles and therefore constant. If the circles are all equal in size, the side of the Voronoi polygons becomes a straight line. It is further important that three common sides of the Voronoi polygons invariably converge to a point and make the common vertex of three Voronoi polygons. This geometrical behavior is due to the particular circle arrangement that there are always at least two contact circles present on every hemi-circle.

Typical examples of two-dimensional ESD are the cellular arrangements of epithelial and endothelial linings. The characteristic pattern of convergence of three cellular borderlines to a vertex has been confirmed by observation.

One-dimensional ESD develops when stretching force is added along a certain axis. The result is a thread-like structure. In organisms, one-dimensional ESD appears so combined with two-dimensional ESD as to make a three-dimensional structure. For example, muscle fiber bundles conform to one-dimensional ESD in their longitudinal direction, but their transverse sections exhibit the pattern of two-dimensional ESD.

The afore-mentioned considerations can be summarized as follows. Three-dimensional ESD is possible only under uniform centripetal force. Any polarization of the field of force lowers the dimension of the space to be divided. The principle of ESD is nevertheless valid, and apparent difference in the appearance of lower-dimensional structures can be attributed to different pattern of polarized force.

In some organs there is remarkable anisotropy of their structures. Renal medulla and digestive tract are good examples. When an organ is made of compact three-dimensional cell aggregates, structural anisotropy can be realized only by development of some lower-dimensional space division. Because it is possible to interpret this also from ESD under polarized force, we can generalize the application of the principle of this particular space division to the structural analysis of all the organs, irrespective of possible intervention of anisotropic components. ESD is a geometrical expression of the second law of thermodynamics, and we can conclude that all the supracellular structures are subordinate to this single physical law, in spite of their highly manifold appearances. There is no other structural principle specific to the biological system.

The most important character of ESD is that it is produced by a statistical process under incomplete mechanical restriction. Two different restrictions are inherent to this particular space division. One of them is that a unit cannot enter the space preoccupied by another. The other is the field of centripetal force which gathers the units toward a certain point. However, these restrictions are not sufficient in order to prescribe the positions of individual units definitely, and there is still ample freedom in the configuration of the system particularly in three-dimensional ESD.

The severer the restriction is, the less becomes the freedom in the configuration of the system. In extreme cases the units would be mechanically so closely interdependent that any single unit could not be deleted without complete destruction of the whole structure. Such a condition would be roughly visualized by an arch made by wedge-formed bricks. In complete absence of restriction, on the contrary, the arrangement of the units will follow the random distribution. The condition is devoid of any structure. It may be assimilated for example by bacterial suspension in liquid medium.

It is clear that neither of the two extreme patterns can reproduce the supracellular structural principle of multicellular organisms. Some restrictions are indispensable for producing and maintaining a structure of any kind. However, they cannot be so strict as to exclude significant participation of statistical process. Without the latter it would be impossible for an organ to survive its partial injury.

For example, cirrhosis can develop through regenerative process after partial liver damage. Regenerative growth of liver cells proceeds under spatial restriction of connective tissue septa. Connective tissue is not only increased in quantity but also exhibit septal formation, which is absent in the normal liver. Stronger restriction is then imposed upon the parenchymal growth. If the structure of the normal liver were already subordinate to such a strict restriction that all the liver cells should be interdependent in their positions, any partial destruction of the organ would result in its complete disintegration. It would be impossible for the liver to sustain its organ character and to adapt to stronger restrictions. The situation may be comparable to numerous cracks extending over the tempered front glass of a motor car from a single small bullet hole, while a shot into water does not cause any structural change of the latter. The wonderful adaptability of organisms to changing conditions is largely dependent on statistical character incorporated into the organ structure.

The present analysis of the structural principle leads further to a certain interpretation of the morphogenetic mechanism of multicellular organisms. The generally accepted view on the development of the shapes and structures of an organism would be that they are brought to existence according to the genetic information depending upon the molecular structure of DNA. The way of thinking is here a deterministic one, and its validity has been so far established as to derive successfully protein structures out of the template function of DNA molecules. However, the route of this deterministic thinking cannot simply be extended beyond the cell level. Genetic information may direct cell proliferation and differentiation, which result in the formation of some field of force. From this stage on, supracellular structures are produced only by participation of statistical process. It is impossible to assume genetic information which could determine the final supracellular structure in such a way as to prescribe the position of every cell. Even in "cloned" individuals their structures could not be identical in every respect, because there is inevitably some uncertainty in the cellular arrangement.

The present study is an attempt at demonstrating that a statistical process under incomplete restriction precipitates a certain structure, which is essentially not influenced by genetic information. Such an approach is expected to liberate morphology from the restraints of specific biological concepts and to make it accessible to general scientific thinking.

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Q: Prof. Suwa, I congratulate you of this fine presentation of a general principle. As you said, it is a general principle, but can you imagine any condition in which this principle would be violated under pathological circumstances? (Y. Collan)

A: Dr. Collan, there is no exception to the rule. The structural principle here mentioned is valid regardless of the difference of pathological and normal structures.