ON STOCHASTIC GROWTH AND FORM

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Many models of biological development at the cellular level are deterministic;[1-6] i.e., the rules of growth contain no elements of probability, so that a given configuration of starting cells always yields a pattern which is the same in every detail. These patterns are usually highly symmetric[1, 2, 5, 6] or quite irregular.[3, 4] Probabilistic models have been considered for analogues of growth of bacterial colonies,[7, 8] theories of cellular movement in dissociated and reaggregated embryonic tissues,[9] and differentiation of hydroid colonies.[10] In most cases the over-all form is approximately circular,[7, 8, 10] spherical,[9] or occasionally elliptical[8] (due to an externally imposed nutrient gradient).

This article presents a simple model for the growth of a stochastically generated spiral (a "snail," if you wish), and the preliminary results of a computer program written to execute the rules of growth. A general viewpoint of a developing organism as an ensemble of interacting, probabilistic, decision-making units is outlined, and also a scheme for exploiting such models. If forms generated by stochastic growth rules may be shown to be reasonably stable, then the amount of information necessary to specify the development of an organism may be considerably less than has been estimated.[14]

Growth Rules for a Stochastic Spiral.—Two kinds of cells are assumed: type I (Inside), and type S (Shell). They grow on a square planar lattice. With one exception (to be mentioned later), all interactions are steric: the only thing that prevents a cell from growing is the other cells which may already occupy its nearest-neighbor sites. "Growth" of a cell means that the cell remains where it is, but produces another which then occupies an adjacent site that was previously empty. A cell cannot grow (or "reproduce") if it already has four nearest neighbors. One cell, I or S, grows at a time.

All I cells which are not completely surrounded (the "active" ones) have equal probabilities of dividing next. All empty sites around the chosen cell have equal probabilities of receiving the new I cell.

One S cell is designated the "leader." It is the only S cell that may divide. The cell it produces becomes the new leader. Growth is directional: the leader cell grows the new S cell into the site to its left (relative to the vector from the cell from which it grew, directed to itself), provided that site is available. If it is not available, growth is into the forward site. If *that* is not available, then growth is to the right. If the leading S cell is surrounded by other cells, then the cell it grew from becomes the new leader, and growth towards the left is attempted again by this cell. In other words, if the leading S cell becomes trapped by other cells, the first exposed cell down the chain of consecutive S cells resumes growth.

These growth rules are reasonably analogous to those which may be used by certain real cells. The random growth of I cells is similar to the growth of tumors. The behavior of S cells is reminiscent of apical meristem in plants, which only grows at the tip of a shoot, inhibiting growth further down. If the apical meristem is cut off, growth resumes at a lower point. Also, vines tend to spiral in one direction.[12]

The starting configuration of cells in this study was always ISZ, the Z cell on the right designating the initial leading S cell.

There is one free parameter for this system: the ratio r of the specific (per cell) growth rate of active I cells (the ones which are not surrounded), to that of the leading S cell. In other words, given i active I cells, the probability that a particular one of these will be the next cell to divide is $P_I = rP_S$ (where P_S is the probability that the leading S cell will divide). The total proba-

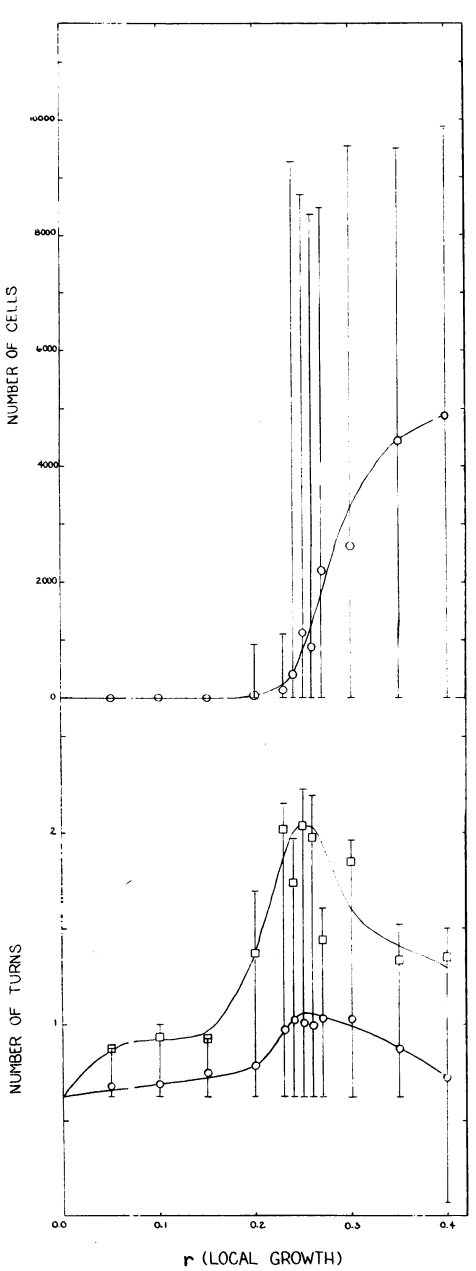

FIG. 1

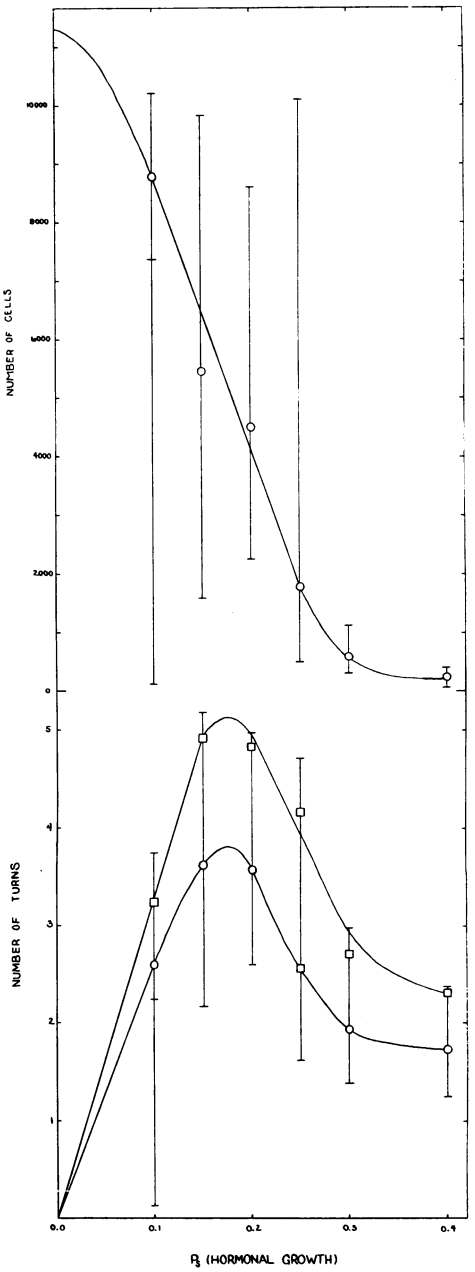

FIG. 2

FIGS. 1 AND 2.—○, Mean value; □, mean value of the three spirals with the most turns. Thirty to thirty-three cases were run for each value of r or P_S. The bars indicate extrema. The smallest "spiral," which sets the lower limit in size, is $\overset{*}{\underset{*}{ISZ}}$ (see Figs. 3–6). At $P_S = 0.1$ in Fig. 2, there was one case in which the S cells were completely surrounded early in growth. The extra bars indicate the minima of size and number of turns when this case is disregarded.

bility that any one of the active I cells will divide next is iP_I. Thus, since $P_S + iP_I = 1$, $P_S = 1/(1 + ri)$.

If each cell grows at a specific, intrinsic rate, independent of the rest (except for steric interference), then r is a constant. This is designated "local" growth. At high values of the constant r, the I cells will tend to surround the S cells, and vice versa. At an intermediate value of r there should be some probability of a compromise, resulting in an over-all form which is roughly spiral.

If the leading S cell could "count" the number of active I cells, for example, by being sensitive to a hormone diffusing from them, and its rate of growth were proportional to this count, a feedback mechanism with rather fine control would be established. In this case $1/r = P_S/P_I = i/r'$, or $P_S = 1/(1 + r')$. r' is a new constant. In other words, under this kind of "hormonal growth" P_S is a constant. This growth rule will tend to give a "phonograph" spiral, i.e., the spiral of Archimedes. If the growth of the leading S cell were instead inhibited in proportion to i, logarithmic spirals might be obtained. Only the former case has been investigated so far.

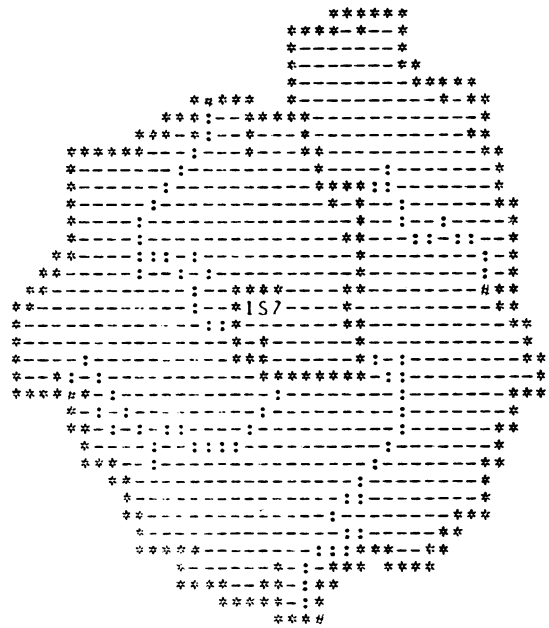

FIG. 3.—The best spiral obtained under local growth. $r = 0.25$. Rings every 200 additional cells. Symbols for Figs. 3–6: (I), initial I cell; (S), (Z), initial S cells, Z being the initial leading S cell; (—), I cells; (*), S cells. I cells are labeled (:) at fixed intervals, thus giving growth rings; (#) indicates the position of the leading S cell when a growth ring was labeled. The forms are slightly distorted, since the cells are printed 5 horizontal to 4 vertical.

The computer program carrying out these rules of growth was written in Fortran IV and run on the IBM OS/360 model 50 computer at the University of Oregon. The random number generator used was that recommended by MacLaren and Marsaglia[11] as the most uniform.

Growth continued until either the available array (120X120) was filled, or either cell type completely surrounded the other. The growing forms were centered, if room was left, when they grew to an edge. Up to 10 min of computing time were required for each form to grow.

Results.—Some examples of the forms which were grown are shown in Figures 3–6. For both local and hormonal growth there were somewhat narrow ranges of the free parameter in which the most spiral turns were obtained ($r = 0.25 \pm 0.05$ and $P_S = 0.20 \pm 0.05$, respectively). Thus the appearance of spirals is in a sense a critical point phenomenon. This is reflected in the large change in mean size over these ranges (see Figs. 1 and 2).

However, under local growth spirals with approximately two or more turns are of low frequency ($\sim$10%) even in the critical range. The reason for the low viability seems to be that at the beginning of growth the S cells have a high probability of enclosing the I cells, before the latter have a chance to increase their numbers. This could be called a critical stage of growth, and is reminiscent of nucleation of a new phase. Because of this critical stage a bimodal distribution of sizes is obtained, which accounts for the enormous variance in size under local growth (see Fig. 1).[16]

On the other hand, hormonal growth near its critical point gave spirals of many

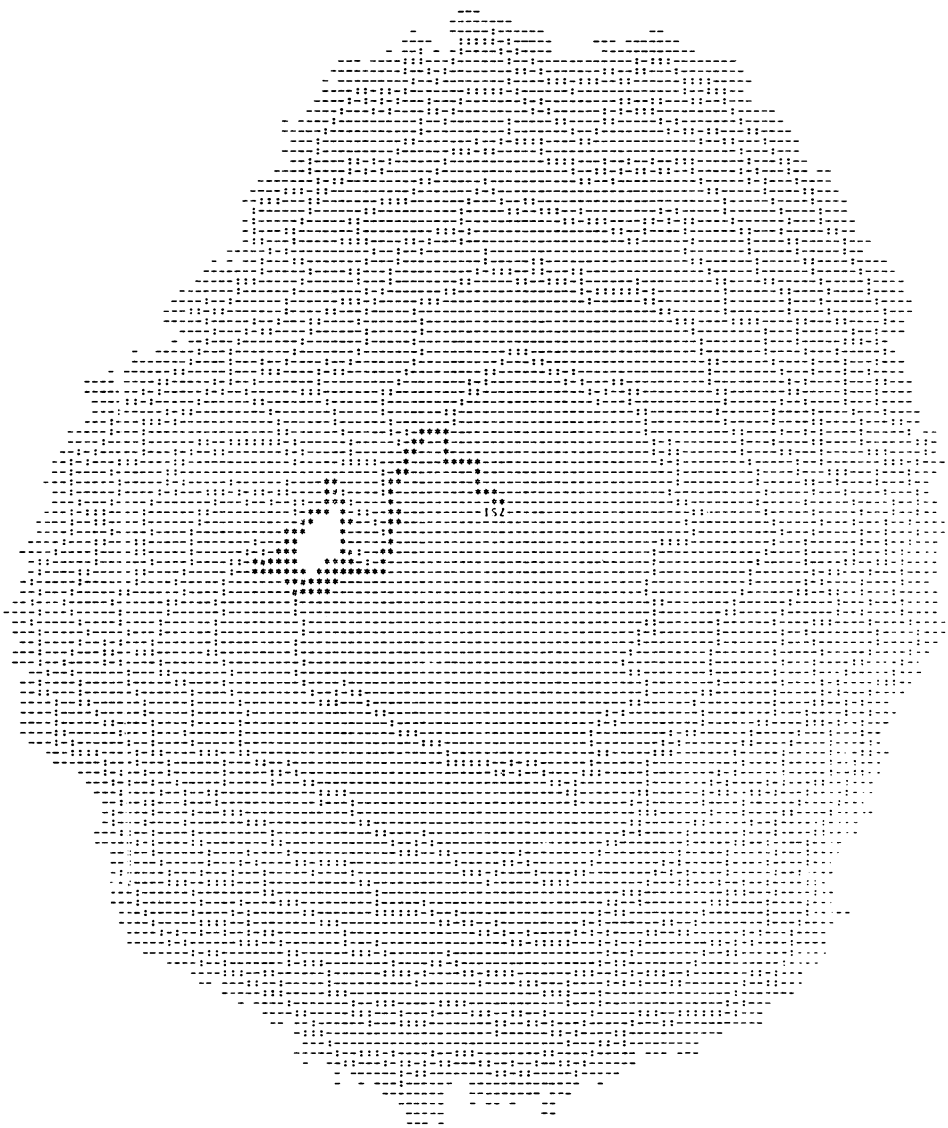

FIG. 4.—Local growth, $r = 0.4$. Rings every 1400 additional cells. The S cells have been surrounded and are winding up in a cavity.

turns almost 100 per cent of the time. Thus, whereas strictly local cellular interactions would have guaranteed sufficient viability for the "survival" of such an organism at the beginning of the evolution of life, addition of a hormonal mechanism would have conferred a large advantage.

A General Model for Development.—To a first approximation, a developing organism or colony might be regarded as an ensemble of units (cells or individuals) each capable of making certain decisions.[17] These decisions may be based on the state of the unit itself and the environment in which it finds itself.

For a living cell the local environment would include the configuration of cells

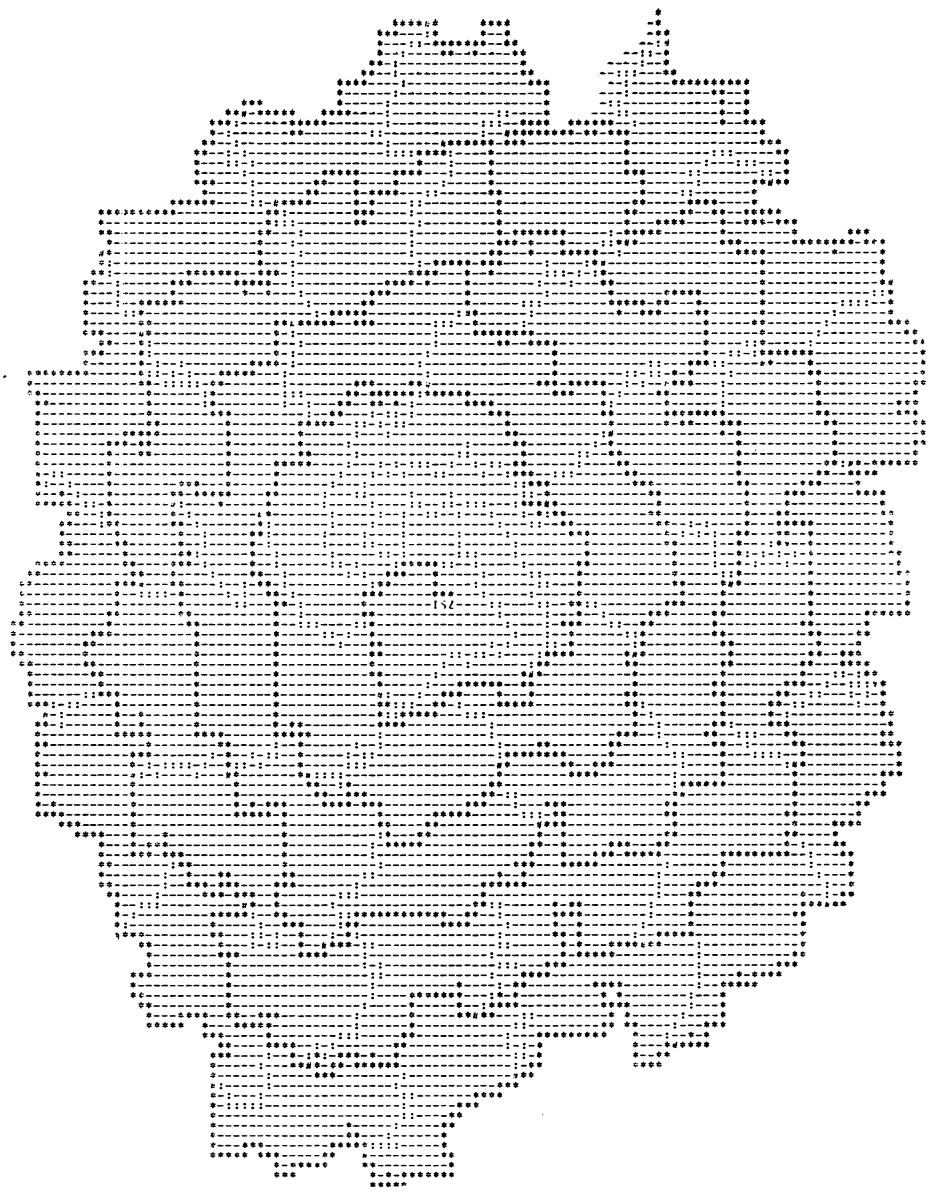

FIG. 5.—The best spiral otained under hormonal growth. $P_S = 0.15$. Rings every 200 additional cells.

around it, and the chemical and electrical messages (surface interactions, hormones, nerve impulses, etc.) it receives from cells near and far.

The internal "state" of a cell would include its state of differentiation, a limited "memory," and perhaps an internal clock. A cell's polarity, such as that of the *S* cells, would be a simple example of its memory. Thus, based on its state and its local environment, each cell occasionally or continually makes decisions about what to do next. It could, for example, (1) do nothing; (2) reset its internal clock;

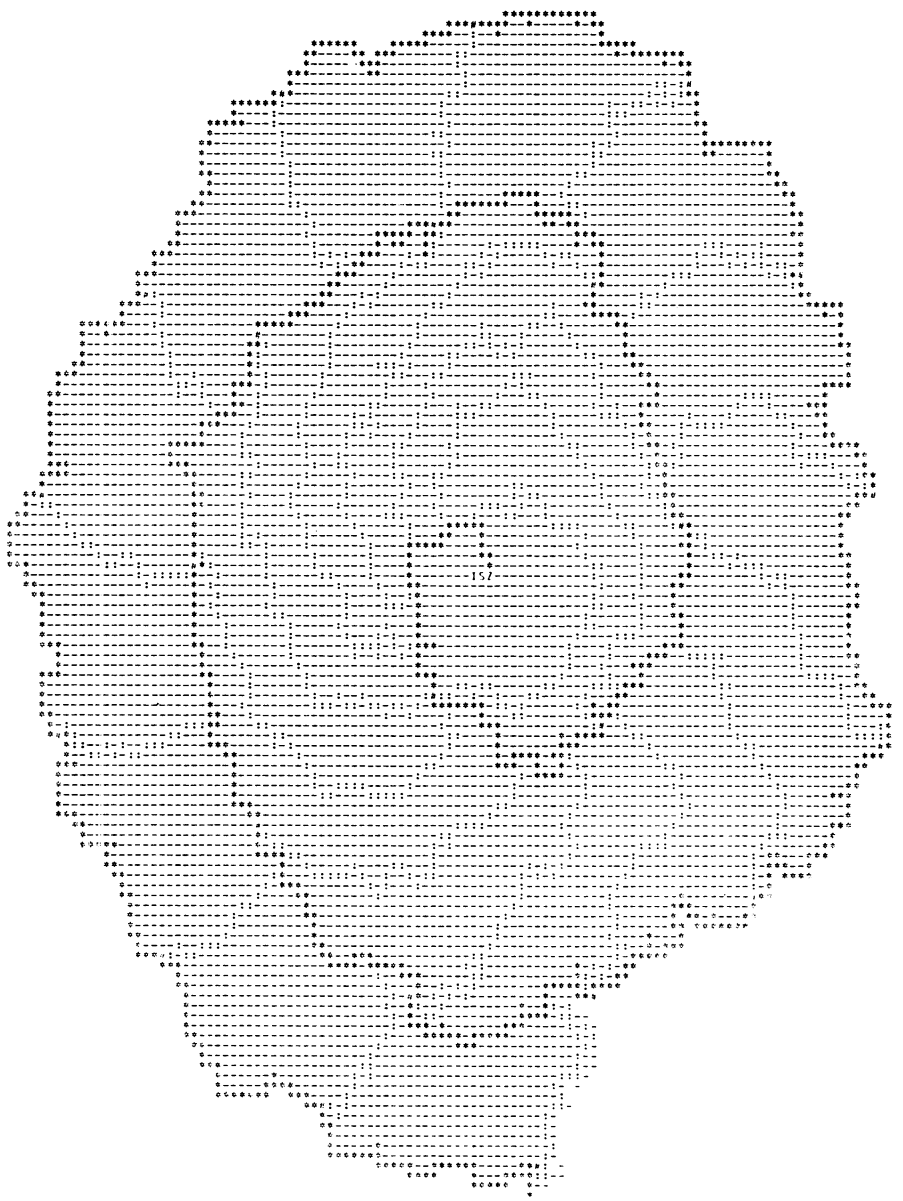

FIG. 6.—Hormonal growth. $P_S = 0.1$. Rings every 400 additional cells.

(3) differentiate to another cell type; (4) send messages to other cells; (5) divide; (6) eat a neighbor; (7) fuse with a neighbor; (8) expand or shrink; (9) move elsewhere; (10) die. Many of these actions are not mutually exclusive. A "decision" might involve a subset or sequence of them.

The resulting interactions between cells would be probabilistic for at least four reasons. (1) Thermodynamic fluctuations, inaccuracies in the division process, etc., will lead to variations in the internal state of a cell and its local environment, so

that in the "same" circumstances it may not make the same decision. (2) Due to these fluctuations, the internal clocks of the cells may go out of synchrony. Then development could not depend on precise timing of events. (3) The number of possible local environments might be enormous. A cell could probably not distinguish them all, and thus it might, for example, assume all local environments are of a few types. The one it is in may not fit neatly into any of these pigeonholes, or may fit poorly into more than one. Such a pattern recognition scheme is thus subject to a certain amount of "error." (4) The initial configuration of the constituents of the "egg" may vary from individual to individual. For instance, the positions of the starting cells for the stochastic spirals could be varied.

Genetic control of development is regarded as indirect in this model. Specific genes for specific forms and patterns may not be necessary. Instead, the genes would presumably be partially responsible for determining the rules governing interactions of the embryonic cells, i.e., the proclivity of a cell to react in a given way in a given local environment. The result of these interactions is the over-all form.

Experimental Evidence for Variability in Development.—Obtain two leaves of approximately the same size from the nearest dicotyledonous bush or tree. These leaves will probably differ in the fine structure of the venation, the left-right order of the branching of the main veins, and the over-all shape. Count the number of main branches and lobes, if any. Some leaves may be grossly different from the norm in over-all shape. One is unlikely to find two identical leaves on a single plant, even though it is presumably genetically homogeneous.

Discussion.—The general model presented above is much richer than the simple rules used to generate stochastic spirals. It may also have a greater potential, perhaps yielding forms of greater complexity and regularity. As with the stochastic spirals, these forms might develop only in certain critical ranges of the growth constants.

The following approach is proposed for future work. Let an organism grow according to a set of rules $\mathbf{R}$. $\mathbf{R}$ may be regarded as a vector whose components are a set of independent "growth constants," such as r or P_S for the spirals. Choose at random n slight variations from $\mathbf{R}$, $\mathbf{R} + \Delta\mathbf{R}_i$, $i = 1, \ldots, n$, and grow the corresponding organisms (say, using a computer). Those which show hints of some form or pattern which is aesthetically pleasing or biologically important are selected and the process is repeated. In other words, an experimenter's relationship to these organisms would be analogous to that of an animal breeder to his stock: he carefully selects individuals having traits he wants to develop.[13] By continuing this process of domestication for a number of generations, one might learn the complete set of forms generable from a given set of rules.

It should be possible to manipulate computer-grown "organisms" in much the same way as embryos may be manipulated. For instance, "transplants" could be made, growth in the presence of physical barriers could be observed, and the cells could, at any stage, be "dissociated and reaggregated." If the computer organism's rules were intended to represent the growth of a real organism, the results of such manipulations would be a severe test of the correctness of these presumed rules. M. Braverman and R. G. Schrandt[10] see future research in "the form of a continuous dialogue between questions and suggestions arrived at through computer genera-

tions, and biological experiments and observations answering and proving these."

What actual environments real cells find themselves in, how well they can discriminate among these, and what decisions they can make must be learned by experimental embryologists. But the result of the cells' myriad interactions and decisions is a macroscopic organism, reasonably constant in form, despite perhaps largely stochastic processes occurring on the microscopic level.[15] Perhaps such processes can be studied in a future statistical mechanics of growth and form.

Summary.—It has been shown that a biologically significant form,[12] the spiral, may be generated by the statistical interaction of two cell-like units obeying different growth rules. This is a very simple case of a general model of development in which the cells are regarded as decision-making units, each cell making decisions according to its own state and its local environment. Reasons are given why somewhat probabilistic growth rules should be expected for cells in real organisms. A scheme based on domestic animal and plant breeding is presented which would help discover the full potential of this and similar models.

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[16] Professor F. Helfferich (personal communication) has suggested that the critical growth constant for spirals growing under the local growth rule could somehow be estimated by considering the average number and direction of sites available to both active *I* cells and the leading *S* cell. Similarly, the statistics of the process should be analogous to that of a random walk on a line between two absorbing barriers, the *S* cells ultimately either enclosing the *I* cells or becoming swamped out by them. Long walks would correspond to spirals of many turns.

[17] This model ignores physical forces, for instance, which are very important in development.