Lectures on Mathematics

Some Mathematical Questions in Biology

in the Life Sciences Volume 14

Lectures on Mathematics in the Life Sciences

Volume 14

Some Mathematical Questions in Biology

The American Mathematical Society
Providence, Rhode Island

Proceedings of the 1981 Symposium on
Mathematical Biology held at the Annual Meeting of the
American Association for the Advancement of Science
in Toronto, Canada, January 8, 1981.

edited by
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Library of Congress Catalog Card Number 77-25086
International Standard Book Number 0-8218-1164-9
International Standard Serial Number 0075-8523
1980 Mathematics Subject Classifications: 92–06, 93A05, 92A09.

Printed in the United States of America

FOREWORD

This volume contains the lectures which were presented at the Fifteenth Symposium on Some Mathematical Questions in Biology, held on January 8, 1981 in Toronto, Canada, in conjunction with the annual meeting of the American Association for the Advancement of Science. The symposium was jointly organized and sponsored by the American Mathematical Society and the Society for Industrial and Applied Mathematics under the auspices of Section A, Mathematics, of the AAAS.

The papers presented in this Symposium deal with two principal areas of theoretical biology, the first focusing on several problems of developmental biology, the second on recent work in biomechanics. Meinhardt and Gierer consider the organization of pattern, using models extending their celebrated work on regulation in systems of reaction-diffusion equations. Emphasis in their presentation is on the role of sequencing as a means of generating structures with a high degree of internal regulation. Lacker and Peskin treat a related but unusual example of modeling, whose aim is to explain the process of control of ovulation number (number of maturing follicles per cycle) in mammals. A system of differential equations is used to describe the regulation of follicle growth by circulating hormones. In a sense Lacker and Peskin also are concerned with (temporal) sequencing of pattern as determined by the integral number of maturing follicles. The third paper in this set, by Percus and myself, deals with some elementary mechanical models of the movement of cells and cell aggregates. Here the interest is in exploring the morphogenetic consequences of relatively simple instructions at the cell level, involving measures of cell-cell adhesion.

The lectures by Koehl and Weinbaum deal with quite different

problems of biomechanics, but there is common ground in their innovative application of classical properties of viscous fluids moving at low Reynolds numbers. Koehl is interested in the feeding behaviors of copepods and their relation to food particle size. The complexity of behavior associated with particle capture poses a number of intriguing questions for theoreticians interested in time-dependent Stokes flows, which raises issues complementary to theories of propulsion at low Reynolds number. Weinbaum discusses methods which are well suited for such applications, and gives a comprehensive review of their implications for pore-particle problems arising in models of transport through membranes.

The final lecture, by Mochon, deals with the mechanics of human locomotion in a series of models of increasing complexity, and highlights the useful role which this kind of analysis can play in many related problems of human movement.

On behalf of all the participants I would like to extend our thanks to the staff of the American Mathematical Society for their capable assistance with all phases of planning the Symposium and preparing these Proceedings.

Stephen Childress
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June 18, 1981

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GENERATION OF SPATIAL SEQUENCES OF STRUCTURES DURING DEVELOPMENT OF HIGHER ORGANISMS

Hans Meinhardt and Alfred Gierer

ABSTRACT. Sequences of structures are frequently encountered during development of higher organisms. Different mechanisms can be envisaged for its formation: (i) the two-step process of generation of positional information and its interpretation and (ii) the direct sequential induction of structures. Positional information can be generated by local autocatalysis combined with long range inhibition or by cooperation of compartments. Mutual induction of structures requires a long range activation of locally exclusive states. This mechanism seems to be appropriate for developmental systems in which experimental evidence indicates that a control of a correct neighbourhood of structures exists. It will be shown under which conditions a sequence of structures is more stable than one very large element or an alternation of only two structures. This mechanism allows a self-regulatory intercalary regeneration of missing elements. In a two-dimensional field of cells, a stable stripe-like arrangement of structures with a long extension in one dimension and a short extension in the other can be obtained. The proposed interactions are provided in the form of coupled non-linear partial differential equations. Computer simulations show that the proposed models are free of internal contradictions and that their regulatory behavior is in agreement with experimental observations.

1. POSITIONAL INFORMATION VERSUS DIRECT INDUCTION OF ADJACENT STRUCTURES.

The complexity of structures of a higher organism must be generated during its development; it cannot already exist in a hidden form within the egg cell. The generation of structures signifies that at a particular location something is formed which is not formed in the surrounding. Experimental evidence suggests that whole sequences of structures are under a common developmental control. For instance, the implantation of a second "organizer" (Spemann, 1938) consisting of a small piece of tissue derived from the dorsal lip of an amphibian blastopore, can induce a complete new embryo. A common developmental control for many structures which are arranged in an ordered sequence appears necessary not only to form every structure of an organism but also to obtain their correct spatial relationship. A mechanism which is able to generate sequences of structures in space consists in the formation of a graded distribution of

a substance, the morphogen, across a field of cells. The local concentration can provide positional information and determine the future pathway of the cells (Wolpert, 1969, 1971). Many experiments concerning early insect embryogenesis are quantitatively explicable under this assumption (Meinhardt, 1977).

A characteristic property of a positional information scheme is that cell determination is affected only by the local concentration of the morphogen but not by the state of determination of cells in the neighbourhood. The corresponding behavior has been observed in many instances; for instance, upon ligation of early insect embryos, regeneration of the sequence of segments is incomplete, leaving gaps which are not repaired (Sander, 1975). Similarly, gaps occurring spontaneously in "bicaudal"-embryos of Drosophila (Nüsslein-Volhard, 1977) remain unrepaired.

Other developmental systems behave differently. For instance, portions removed from a particular segment of an insect leg regenerate. Confrontation of normally non-adjacent cells initiates a respecification (and frequently a proliferation) of the cells at the discontinuity which leads to a repair of the gap.

We have proposed molecular mechanisms for the generation and interpretation of positional information and for the control of neighbouring structure (Gierer and Meinhardt, 1972, 1974; Meinhardt and Gierer, 1974, 1980; Meinhardt, 1977, 1978a,b). In the present article, we provide a review of these models, pointing out differences and similarities and compare the behavior of these models with some key experiments.

2. PATTERN FORMATION BY AUTOCATALYSIS AND LATERAL INHIBITION. We have shown (Gierer and Meinhardt, 1972, 1974) that patterned distributions of substances can be generated by an interaction of a short-ranging autocatalytic and a long-ranging antagonistic substance. Some possible interactions should be discussed briefly to demonstrate similarities and differences with mechanisms enabling control of adjacent structures.

The following interaction between an autocatalytic activator $a(x)$ and the inhibitor $h(x)$ leads to stable patterns:

$$\frac{\partial a}{\partial t} = \frac{ca^2}{h} - \mu a + D_a \frac{\partial a^2}{\partial x^2} \qquad (1a)$$

$$\frac{\partial h}{\partial t} = ca^2 - \nu h + D_h \frac{\partial^2 h}{\partial x^2} \qquad (1b)$$

The reaction is such that in a small field (smoothing out of any spatial inhomogeneity by diffusion) only a single stable steady state is possible corresponding to a near-uniform distribution in space. In a larger field, the local autocatalysis allows an amplification of small deviations from the steady state while due to the long-ranging inhibition, an activator increase in one part of the field is coupled to a decrease in other parts until the pattern becomes stabilized. It is a property of such a system that in a growing field, after surpassing of a critical extension, an activator maximum is formed at one margin, leading to a graded - and thus polar - concentration profile (Fig.1a). An activator maximum has many properties of the classical organizer: it can "regenerate" after its removal. The regeneration of hydra tissue, and the induction of secondary axis in hydra, show properties characteristic for this type of pattern formation. Another property of a classical organizer is the possibility

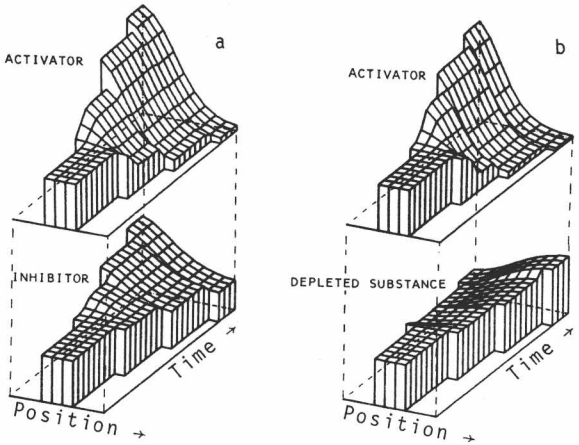

Fig.1: Pattern formation by autocatalysis and lateral inhibition. The interaction between the autocatalytic activator and either the inhibitor (Fig.a, Eq.1) or the depleted substance (Fig.b, Eq.2) leads to a stable patterned distribution of both substances. Assumed is a linear array of cells growing at both margins; the concentrations are plotted as function of position and time. Pattern formation requires an area exceeding that of the activator range. At that size, the activator maximum appears at one boundary of the field since a non-marginal maximum would require space for two slopes. Therefore, this mechanism can generate positional information changing monotonically in the field of cells to be organized.

of its induction by unspecific manipulations. According to the model, a local inhibitor decrease caused, for instance, by injury or local irradiation can lead to a second activator maximum (second organizer region).

The effect antagonistic to autocatalysis need not be provided by an inhibitor but may result from the depletion of a precursor s required for the synthesis of the activator:

$$\frac{\partial a}{\partial t} = ca^2s - \mu a + D_a \frac{\partial^2 a}{\partial x^2} \qquad (2a)$$

$$\frac{\partial s}{\partial t} = c_o - ca^2s - \nu s + D_s \frac{\partial^2 s}{\partial x^2} \qquad (2b)$$

A simulation is shown in Fig.1b. This reaction has somewhat different properties, sometimes distinguishable on the basis of experimental observations (Meinhardt, 1978a). For instance, additional maxima cannot be induced by an unspecific reduction caused by radiation damage or leakage of one of the components.

The autocatalytic effect need not be due to a single component, but may be hidden in a reaction chain. An example is given by two substances, a and b, each repressing the production of the other. An increase of a leads to a decrease in production of b and the lowering of b leads to a further increase of the production of a. Pattern formation requires that an increase of a at a particular location is coupled to a decrease of a in the surroundings, requiring a further substance with a long diffusion range. An example of an interaction scheme of this type in which no component is autocatalytic per se is the following:

$$\frac{\partial a}{\partial t} = \frac{\mu}{\kappa + b^2} - \mu a \qquad (3a)$$

$$\frac{\partial b}{\partial t} = \frac{\mu . c}{\kappa + a} - \mu b \qquad (3b)$$

$$\frac{\partial c}{\partial t} = \nu(a - c) + D_c \frac{\partial^2 c}{\partial x^2} \qquad (3c)$$

The substance c supports the production of b but in the system as a whole it has the function of a long-range inhibitor since it is antagonistic to the (hidden) autocatalysis. Fig.2 shows the formation of a regular periodic structure in a growing field according to this interaction.

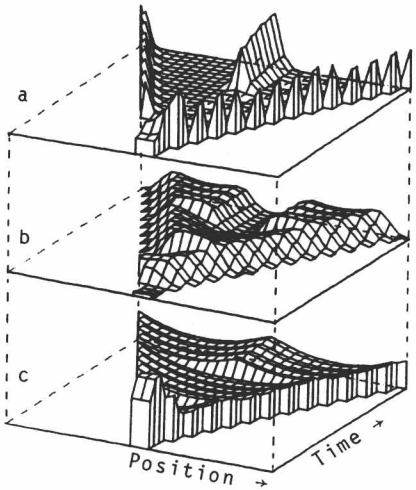

Fig.2: Formation of a periodic pattern in a growing array of cells. Two substances are assumed (plotted in the corresponding subpictures a and b) which inhibit each others production (Eq.3). This inhibition of an inhibition is equivalent to an autocatalytic reaction. A long-ranging substance (Fig.c) stabilizes the pattern since it is antagonistic to this hidden autocatalysis. Starting from an almost homogeneous distributions, with growth, the system passes through a polar and a symmetrical pattern until regular periodic patterns occur.

3. POSITIONAL INFORMATION AND ITS INTERPRETATION. As mentioned, pattern formation by autocatalysis and lateral inhibition allows the formation of a graded distribution of a substance. The local concentration is a measure for the distance from the maximum and can therefore be used as positional information: If the selection of a particular developmental pathway is under the control of the local concentration of such a morphogen, spatial sequences of structures can be specified.

A challenging biological system to test such a model is the determination of segments in a developing insect embryo. Experiments have been performed in which the normal development has been disturbed (see Sander, 1976) leading to an abberant development. It was shown that many of these experiments become quantitatively explainable under the assumption that the activator maximum is confined to a small fraction of the egg located at the posterior (rear) pole and that the long-ranging inhibitor with its graded distribution across the whole egg supplies the proper positional information (Meinhardt, 1977). The explanatory power of that model is

illustrated with one example. Unspecific manipulations such as UV-irradiation, puncturing of the anterior pole or centrifugation of the egg can lead to a completely symmetrical development in which the head and the thoracic segments become replaced by a second, mirror-symmetric set of abdominal structures (Kalthoff and Sander, 1968; Schmidt et al., 1975; Rau and Kalthoff, 1980). According to the model, the activator maximum is located at the posterior (abdominal) pole; therefore, the inhibitor concentration has its minimal value at the anterior pole. There, any further reduction of the inhibitor concentration can trigger autocatalytic activation, leading to a second activator maximum which causes a second abdomen to be formed. In agreement with the model, the induction of the second maximum is an all-or-none effect and the pattern of segments formed is nearly independent of the dose of UV-irradiation. The transition from a polar to a symmetrical pattern is connected with a characteristic alteration of the segment formed in the center of the egg. This alteration is described in a straightforward manner by a positional information scheme. Let us enumerate the segments from the head to the abdomen 1,2...16. The segment formed in the center of a normally developing egg is the segment 5, a thoracic segment. After induction of a symmetrical development, the plain of symmetry is around segment 9, leading to a pattern 16...9...16. According to the model, after induction of the second activator maximum, inhibitor diffuses from both sites into the center, leading to an increase of the inhibitor concentration (positional information) and therefore to the formation of more posterior structures there.

The final spatial complexity of an organism is not generated by the interpretation of just one gradient or of two orthogonal gradients. Additional positional information systems are required to determine the finer details. The interpretation of the primary positional information leads to a subdivision into discrete patches of differently determined cells, and positional information for subpatterns can be generated, within the patches, by a cooperation of such "compartments" (Meinhardt, 1980). The common boundary region of at least two such patches may become a new source region of further morphogens. Many experiments concerning the determination of insect appendages are explainable under this assumption.

4. GENERATION OF SEQUENCES OF STRUCTURES BY LONG-RANGE ACTIVATION OF LOCALLY EXCLUSIVE STATES. While in a positional information scheme the cells ignore the determination of their neighbours and respond only to a local morphogen concentration, some developmental systems indicate a strong control of correct neighbourhood. An example is the proximo-distal as well as the circumferential sequence of structures within an insect leg. Artificially induced gaps are repaired (Bohn, 1965; French, 1978). Moreover, gaps produced by grafting of surplus structures on an existing stump lead to a duplication of the excessive structures (Fig.3). To give a brief description of some experimental key results let us denote the sequence of structures such as parts of a leg segment, in proximo (close to the body)-distal dimension, with 123...9. An experimentally produced leg segment containing the structures 12/89 will replace the missing structures by intercalary regeneration, forming the complete sequence 123456789 (the intercalated elements are underlined). The corresponding experiment with surplus structures, e.g. 1234567/23456789 would lead to an even longer leg 12345676543456789. Removal of an internal part of a leg will never occur under natural circumstances such as the bite of a predator. That the organism is nevertheless able to regenerate suggest that the role of this mechamism is not the repair after artificial remo-

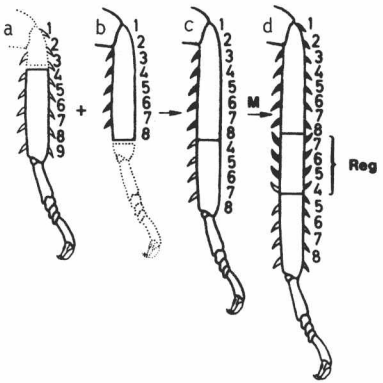

Fig.3: Duplication of excessive parts of a cockroach leg (after Bohn, 1970). Experimental juxtaposition of originally non-adjacent pattern elements (a-c) leads after one or two molts (M) to intercalary regeneration of the missing elements (Reg) at the site of the gap (d). This experimental result indicates that it is not the normal pattern of the leg segment but the neighbourhood of elements of the sequence of structures which is under developmental control.

val of parts but that it is a component in the generation of the structures during normal, undisturbed embryonic development. For instance, it is possible that initially only the terminal structures, e.g. 1 and 9 are layed down and that the remaining structures are filled in by intercalation.

The formation and stability of an abnormal mirror-symmetric sequences such as ... 45676543234 ... is particularly instructive in discriminating between types of models. For instance, it can be ruled out that the internal organisation of the leg segment is controlled by a morphogen gradient, formed by a source at one side and by a sink at the other side since such a model cannot account for the intercalation of structures in a reverted sequence. It rather appears that regeneration results from direct mutual or consecutive induction of neighbouring states. We have proposed explicit models for this type of pattern formation (Meinhardt and Gierer 1980). Molecular interactions are introduced such that two or more locally exclusive states of activation can be generated, with neighbouring states stabilizing each other in analogy to a symbiosis.

5. HOW TO GENERATE STABLE LOCALLY EXCLUSIVE STATES. Cell determination is considered to be an all-or-none event shifting the cell into a new stable state that can be transferred to daughter cells upon proliferation. Presumably, determination corresponds to the activation of particular genes out of a set of alternative genes, the others becoming repressed. The stability of a state of determination requires some positive feedback of a gene on its own activity. Alternative feedback loops are assumed to compete with each other in such a way that only one loop can be activated in a given cell (Meinhardt, 1978b). A kinetic interaction with this property is described in Eq.4.

$$\frac{dg_i}{dt} = \frac{c_i g_i^2}{r} - \alpha g_i \qquad (4a)$$

$$\frac{dr}{dt} = \sum c_i g_i^2 - \beta r \qquad (4b)$$

Each one of a set of alternative genes i (i = 1,2...n). is activated by an activator g_i acting autocatalytically on its own production as described by the term ($c_i g_i^2$). Autocatalysis is counteracted by the action of a common repressor r. Each active gene produces and reacts upon this repressor. It is further assumed that gene activator and repressor

are destroyed by normal first-order kinetics. These equations are formally related to the equations describing the pattern forming reaction (Eq.1). This similarity is not accidental: in pattern formation, the synthesis of a substance is enhanced at a particular location and suppressed at others. In cell determination a particular gene is assumed to be activated and the alternatives repressed, corresponding to pattern formation in an abstract "gene space".

A simple example for two mutually exclusive states is given by the following equation:

$$\frac{\partial g_1}{\partial t} = \frac{\alpha}{\kappa+g_2^2} - \alpha g_1 \qquad (5a)$$

$$\frac{\partial g_2}{\partial t} = \frac{\alpha}{\kappa+g_1^2} - \alpha g_2 \qquad (5b)$$

For interactions according to Eq.4 or 5, a state with uniform equal activation of all genes is unstable. Any slight advantage of one state leads to the exclusive activation of this particular state, and to the repression of the alternative state(s).

6. LONG RANGE ACTIVATION OF THE LOCALLY EXCLUSIVE STATES. Such mutual exclusive activation of cell states can lead to defined spatial sequences of different structures if, in addition, cells in any given state cause and stabilize activation of a different state in the neighbourhood via diffusable substances s_i.

$$\frac{\partial g_i}{\partial t} = \frac{c s_j g_i^2}{r} - \alpha g_i + D_g \frac{\partial^2 g}{\partial x^2} \qquad (6a)$$

$$\frac{\partial s_i}{\partial t} = \gamma g_i - \gamma s_i + D_s \frac{\partial^2 s}{\partial x^2} \qquad (6b)$$

$$\frac{\partial r}{\partial t} = \sum c s_j g_i - \beta r \quad \text{with } i,j = 1,2;\ i \neq j \qquad (6c)$$

The (small) diffusion of the g_i-molecules is of importance for size-regulation and for the coherence of g_i-regions.

Let us consider the simplest case of two states (g_1, g_2) and s with a near-uniform steady state with equal concentrations g_1 and g_2

throughout the field. Since s_1 or s_2 distributes over larger space by diffusion, a local increase of g_1 will increase further by self-enhancement, but the accompanied increase in s_1 concentration favours g_2-activation in the surroundings. Therefore, two neighbouring patches of high g_1 and of high g_2 concentration respectively, are formed (Fig.4).

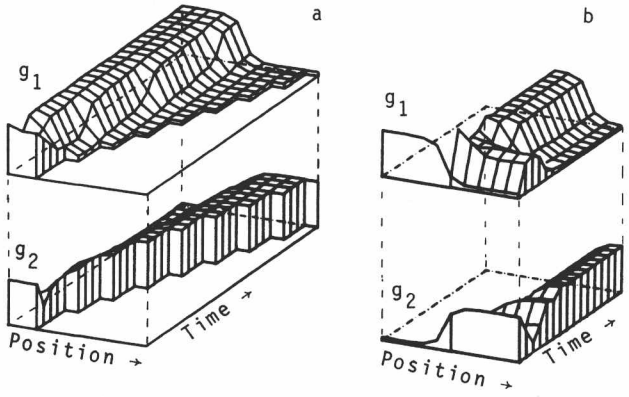

Fig.4: Size-regulation. A system of two feedback loops (g_1 above, g_2 below) which compete with each other locally but support each other over a longrange (Eq.6) show pattern formation with good size regulation. (a) Proliferation of the cells with high g_2-concentration leads to an increased support of the g_1-feedback loop. At the zone of transition between high g_1 and high g_2, some of the cells switch from a high g_2 concentration to a high g_1 concentration and the correct proportion of both areas is maintained. (b) Removal of the cells in which the g_1-loop is active leads to a new pattern formation in the remaining cells, resulting in a new equal partition into a g_1 and a g_2 area.

7. EQUIVALENCE OF MULTICOMPONENT SYSTEMS WITH AUTOCATALYSIS-LATERAL INHIBITION. Pattern formation by mutual lateral activation of locally exclusive states may seem, at first sight, as a mechanism qualitatively different from pattern formation by autocatalysis and lateral inhibition which can lead to gradients and other morphogenetic fields specifying positional information as described in section (2). However, a closer analysis shows that this is not the case; rather, mutually exclusive lateral activation can be subsumed under a generalization of the theory of autocatalysis and lateral inhibition (Gierer, 1981). It was shown by mathematical analysis that the conditions of autocatalysis and lateral inhibition are necessary requirements for the simplest case of two com-

ponents independent of details of models. The conditions can be generalized to some extent to multiple-component systems. The generalization cannot be based on determining whether or not an individual substance is autocatalytic. As shown in section (2), patterns can be formed even if no single component of the system is in itself autocatalytic, because autocatalysis may result from inhibition of inhibition. However, if in a multicomponent system there are two subsets of components distinguished by ranges (e.g. due to different diffusion rates) and if the short-range subset is autocatalytic as a system (perhaps by inhibition of inhibition), whereas the long-range subsystem is crossinhibiting (thus preventing an overall autocatalytic explosion), spatial patterns can be generated. Requirements are that redistribution of molecules belonging to the inhibitory subset is sufficiently large and that of the activating subset sufficiently small. This is a generalization of the two-factor theory of autocatalysis and lateral inhibition to more than two components. In molecular terms, it implies that activation and inhibition need not be properties of individual components but can be features of systems of such components. The models for sequences of structures based on lateral activation as described in this paper are of this type.

This can be directly demonstrated for the case of activation of two locally exclusive states as exemplified by Eq.(6). Let us introduce a parameter transformation, with the sums and differences as new parameters: $a_s = g_1+g_2$, $a_d = g_1-g_2$, $s_s = s_1+s_2$, $s_d = s_1-s_2$. The subsystem a_s, s_s is of no particular interest. The system of the differences a_d, s_d, however, is closely related to the activator/inhibitor system in the context of the theory of lateral inhibition. The near-uniform state corresponds to $a_d = 0$, $s_d = 0$; upon pattern formation, activating g_1 in one and g_2 in another part of the field, the difference $a_d = g_1-g_2$ is autocatalytic, forming a gradient across the field. At the same time, $s_d = s_1-s_2$ forms a gradient of the same orientation but with a wider range across the field due to larger diffusion rates. Since s_2 cross-activates g_1 and as s_1 cross-activates g_2, the difference $s_d = s_1-s_2$ inhibits $a_d = g_1-g_2$: it acts by lateral inhibition. Aside from this qualitative demonstration of the inhibiting function of s_d, it has been shown that in the linear approximation of deviations from the uniform distribution there is a definitive mathematical correspondence of the difference parameter a_d with activation, and of s_d with inhibition. The mathematical decision