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Dynamics of Expanding Inhibitory Fields

Glass (1) has discussed certain statistical properties of systems in which random initiation of structures is followed by the establishment around each structure of a growing zone of inhibition within which new structures cannot be formed. Glass found that the saturation density of structures (n^*) in systems in which the inhibitory field spreads at a uniform velocity is given by

$$n^* = k_d (F_d / \nu)^{d/(d+1)} \quad (1)$$

where d is the dimensionality of the system, F_d (units: $l^{-d}t^{-1}$) is the rate of random structure initiation, $\nu(lt^{-1})$ is the rate at which the inhibitory fields spread, and k_d is a dimensionless constant which depends on d . Although Glass was unable to find explicit expressions for the k_d , he did find by computer simulation that for $d = 1$, $k_1 \approx 0.830$.

By attacking the problem in a different manner, I have obtained expressions for the fraction of area covered by inhibitory fields at time t and for the expected density of structures at time t . The value of k_d in Eq. 1 is then easily obtained.

Two cases must be examined. In the first, the fields may interpenetrate freely, and thus do not interfere with one another's growth. In the second, a field stops growing upon contact with the edge of another field: there is no further growth of either field along the arc where they intersect. Fortunately, in the situation in which the fields grow at a uniform rate, the solutions of these two cases are the same. The former case, in which the fields can interpenetrate freely, is mathematically simpler and will be explored first.

Consider first an infinite one-dimensional system. If a line segment of length L is marked off at random on a line containing randomly distributed structures of density λ_1 , then the probability R that no structures will be found within the segment is given by the zero-category Poisson term $e^{-\lambda_1 L}$. Equivalently, if structures are being formed along a line at the rate $F_1(l^{-1}t^{-1})$, then the probability that no structures will be formed within the segment of length L in the time t will be $e^{-F_1 L t}$. If L is not constant, but is a continuously varying function of time, this probability is given by

$$R = \exp \left[-F_1 \int_0^t L(\xi) d\xi \right] \quad (2)$$

The integral defines a space-time volume U ; R is then the probability that no structure is located in U .

Consider now an infinite one-dimensional system free of structures at time $t = 0$. Note that if no structure is formed closer to a randomly selected point P than a distance $\nu\xi$ before time $(t - \xi)$, then no field can have reached P by time t . By use of the above arguments, it can be seen that a space-time volume U' can be defined for this problem such that if no structure is formed within U' , then point P will be free of inhibitory fields at time t . The volume of U' is calculated in the present case by letting $L(\xi) = 2\nu(t - \xi)$. The probability that no structure will be formed within U' is then given by Eq. 2 provided that all of U' is available for structure formation (that is, that no part of U' is occupied by field associated with some structure outside U'). This condi-

tion will always be satisfied if the inhibitory field spreads at a constant rate.

But if the fields can freely interpenetrate, it is also true that the fields associated with any and all structures in U' will reach P by t . Therefore P will not be covered by inhibitory field at time t if and only if U' is free of structures. Thus we can calculate $\phi_1(t)$, the probability that a randomly chosen point is not covered by an inhibitory field at time t , and equivalently the expected fraction of points and hence length not covered by inhibitory fields at time t , by writing $L(\xi) = 2\nu(t - \xi)$ in Eq. 2, obtaining

$$\begin{aligned} \phi_1(t) &= \exp \left[-F_1 \int_0^t 2\nu(t - \xi) d\xi \right] \\ &= e^{-F_1 \nu t^2} \end{aligned} \quad (3)$$

We can use Eq. 3 to calculate the density of structures $n_1(t)$ at time t . Since the rate of structure formation per unit length not covered by inhibitory fields per unit time is F_1 , it follows that

$$\frac{dn_1}{dt} = F_1 \phi_1 \quad (4)$$

so that the density of structures at time t is

$$n_1(t) = \int_0^t F_1 \phi_1 dt \quad (5)$$

The saturation density n_1^* is simply the limit of n_1 as $t \rightarrow \infty$, so that

$$n_1^* = \int_0^\infty F_1 \phi_1 dt = (\pi/4)^{1/2} (F_1/\nu)^{1/2} \quad (6)$$

Thus k_1 in Eq. 1 equals $(\pi/4)^{1/2} \approx 0.886$, which is in good agreement with Glass's computer estimate (2).

This method is readily extended to higher dimensions by replacing $L(\xi)$ by an appropriate higher-dimensional form. For example, in two dimensions $F_1(l^{-1}t^{-1})$ is replaced by $F_2(l^{-2}t^{-1})$ and $L(\xi)$ by a two-dimensional target area $A(\xi) = \pi\nu^2(t - \xi)^2$. Thus in two dimensions the time course of areal coverage by inhibitory fields is given by

$$\phi_2(t) = \exp(-\pi F_2 \nu^2 t^3/3) \quad (7)$$

from which it follows that

$$n_2(t) = \int_0^t F_2 \phi_2 dt \quad (8)$$

whence

$$n_2^* = (\pi/3)^{-1/3} (F_2/\nu)^{2/3} \int_0^\infty e^{-\eta^3} d\eta \quad (9)$$

where η is a dummy variable.

In d dimensions we replace F_1 ($1-t^{-1}$) with $F_d(1-t^{-d})$. Since the volume of a hypersphere of unit radius in d dimensions is $\omega_d = \pi^{d/2}/\Gamma[(d+2)/2]$ (3), it follows that $L(\xi)$ can be replaced by the d -dimensional volume

$$V_d(\xi) = \omega_d v^d (t - \xi)^d \quad (10)$$

so that

$$\phi_d(t) = \exp[-F_d \omega_d v^d t^{d+1}/(d+1)] \quad (11)$$

By use of a change of variables $\eta = [F_d \omega_d v^d / (d+1)]^{1/(d+1)} t$, we can obtain immediately

$$n^* = [\omega_d / (d+1)]^{-\frac{1}{d+1}} \times (F_d / v)^{\frac{d}{d+1}} \int_0^\infty e^{-\eta^{d+1}} d\eta \quad (12)$$

Thus the functional dependence of n^* on $(F_d/v)^{d/(d+1)}$ expressed in Eq. 1 is confirmed, and the values of Glass's constant k_d are given by

$$k_d = [\omega_d / (d+1)]^{-\frac{1}{d+1}} \int_0^\infty e^{-\eta^{d+1}} d\eta = \omega_d^{-\frac{1}{d+1}} (d+1)^{-\frac{d}{d+1}} \Gamma\left(\frac{1}{d+1}\right) \quad (13)$$

The case where field expansion stops upon contact with another field can now be considered. I will demonstrate that if growth proceeds at the constant rate v , the solution in the case in which field growth stops upon contact is identical to that in the case where fields can interpenetrate freely. Thus, it will be shown that Eqs. 11 to 13 represent analytical solutions to the problem posed by Glass (1), regardless of whether or not the fields can interpenetrate.

A demonstration of the identity of solution of the two cases can be based on Huygens' principle (4), which states that each point on an advancing wave front can be considered as a new point source of waves. In our case, we can consider each point covered by an inhibitory field at a particular time to be a focus from which a new field is spreading. Since the rate at which the field spreads is a constant, and so is independent of the age of the field (or ages of the fields, in the case of interpenetration) at a point, the field radiating from each point spreads at the same rate.

There are two sets of points covered by a field: those on the edge of the field (boundary points) and those inside (interior points). Since the fields of the

interior points spread at the same rate as those of boundary points, the fields of interior points can never grow past the boundary, and therefore can never affect the spread of the inhibitory fields into areas not covered by field. Once a boundary point becomes an interior point through the coalescence of two previously disjoint fields, it cannot affect the further evolution of the system. Thus it does not matter whether the field stops growing or continues growing when it contacts another field: The point of contact has become an interior point and no longer influences the dynamics of the system.

This proof is valid in all dimensions, so that Eqs. 11 to 13 constitute a solution to the problem when growth rate is constant regardless of whether or not the fields can interpenetrate.

Glass (1) originally formulated this problem with reference to questions of structure dispersion in many disciplines. My interest in this problem is more restricted: I have been studying the colonization dynamics of organisms which grow radially and compete for space. For this reason I have found it desirable to distinguish the two cases which might arise, that in which field interpenetration occurs and that in which there is no field interpenetration. Mathematically, this distinction is not necessary when the growth rate is constant, since then the solution to both cases is the same in all dimensions. But the fact that two distinct cases exist must be kept in mind if these methods are to be applied in situations in which the rate of spread of the inhibitory field is a function of structure age: in these situations the Huygens argument does not apply, and the solutions to the two cases may be different.

ROBERT A. ARMSTRONG

Department of Ecology and Behavioral Biology, University of Minnesota, St. Paul 55101

References and Notes

1. L. Glass, *Science* **180**, 1061 (1973).
2. The value $k_1 = (\pi/4)^{1/2}$ is obtained whether the fields can or cannot interpenetrate, as shown later in the text. The comparison with Glass's computer estimate is made here for convenience, although his simulation was done by assuming that the fields did not interpenetrate.
3. R. Courant, *Differential and Integral Calculus* (Interscience, New York, 1949), vol. 2, p. 302.
4. Huygens' principle arises in the study of wave phenomena in optics. Any optics textbook will contain a discussion of this principle. The use of an argument based on Huygens' principle was suggested to me by R. P. McGehee.
5. I thank R. J. Taylor, R. P. McGehee, and D. B. Siniff for reviewing the manuscript. Their suggestions were most helpful. Supported by NIH training grant 5 TO1 GMO1779.

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Glass (1) presented a model wherein regularity appeared in the spacing of randomly initiated structures. The regularity arose from the assumption that a structure, once formed at a point, produces a growing inhibitory field about it in which new structures may not start. The process starts with a fully available (white) volume and ends when the inhibited (black) regions cover the entire space. One of the central problems of the model is the calculation of the mean number of structures formed at saturation. The result depends on the dimensionality of the space and on the assumption made about the growth of the inhibitory field (that is, two modes of growth were considered, constant velocity and diffusion). The essential parameters of the theory are F , the rate of formation of new structures per unit volume, per unit time, and v , the velocity of growth of the inhibitory field (or D , the diffusion constant, in the case of the latter growth model). Glass presents arguments that the average number of structures formed in the process is given by

$$N^* = k_d \left(\frac{F}{v}\right)^{d/(d+1)} V \quad (1)$$

for the uniform velocity case and

$$N^* = k'_d \left(\frac{F}{D}\right)^{d/(d+2)} V \quad (2)$$

for the case of diffusion. Here d is the dimensionality and V the volume of the space in which the process occurs. Estimates are presented for k_1 and verified by computer simulation.

In this comment, I will show how the k_d and k'_d may be calculated analytically and we present the results for one-, two-, and three-dimensional spaces. In addition, we state results that may be obtained by similar methods for the average distribution of lengths of white intervals in the one-dimensional, uniform velocity case.

The basis of the analytical calculation is the recognition of the fact that the quantity $\phi(t)$, defined by Glass as the average fraction of the line that is white at time t (and still available for the formation of new structures), is also the probability that a typical point is still white. For the uniform velocity model, neglecting end effects, the probability that a point is white at time t_0 is equal to the probability that no new structure was initiated in an isosceles triangle in $x-t$ space, whose base is of length $2vt_0$ and altitude is t_0 (see Fig. 1). If no initiation takes place in this

region the typical point under consideration will still be white at time t_0 . The equation of the sides of the triangle is

$$x = x_0 \pm v(t_0 - t) \quad (3)$$

If we break up the time interval $(0, t_0)$ into small ones $dt_1, dt_2, \dots, dt_j, \dots, dt_n$, then the probability that no initiations have occurred in any of the "strips" into which the triangle has been divided is

$$\phi(t_0) = \prod_{j=1}^n [1 - 2Fv(t_0 - t_j)dt_j] \quad (4)$$

Taking the natural logarithm of Eq. 4, we get

$$\ln\phi(t) = \sum_{j=1}^n \ln[1 - 2Fv(t_0 - t_j)dt_j] \quad (5)$$

For sufficiently small dt_j , the logarithm may be expanded and the sum replaced by an integral with the result

$$\ln\phi(t_0) = - \int_{t'=0}^{t_0} 2Fv(t_0 - t')dt' \quad (6)$$

from which

$$\phi(t) = e^{-Fv t^2} \quad (7)$$

As the average rate of formation of new structures is equal to the product of F with the available white length, we have

$$\frac{dN}{dt} = FL e^{-Fv t^2} \quad (8)$$

Integrating from $t=0$ to $t=\infty$, the result for the average number of structures formed in the process is

$$N^* = L \frac{\pi^{1/2}}{2} \left(\frac{F}{v}\right)^{1/2} \quad (9)$$

whence $k_1 = \pi^{1/2}/2 = 0.8862$.

The same procedure may be followed for any number of dimensions and for either diffusion or constant velocity growth. Glass's formulas, Eqs. 1 and 2, are verified and the results for the k_d and k'_d are

$$k'_d = \left(\frac{d+1}{C_d}\right)^{\frac{1}{d+1}} \left(\frac{1}{d+1}\right)! \quad (10)$$

and

$$k_d = \frac{1}{2} \left(\frac{1}{d}\right)^{\frac{d}{d+2}} \left(\frac{d+2}{C_d}\right)^{\frac{2}{d+2}} \left(\frac{2}{d+2}\right)! \quad (11)$$

Here C_d are constants associated with the volume elements in d -dimensional space and are given by

$$C_1 = 2; \quad C_2 = \pi; \quad C_3 = \frac{4\pi}{3} \quad (12)$$

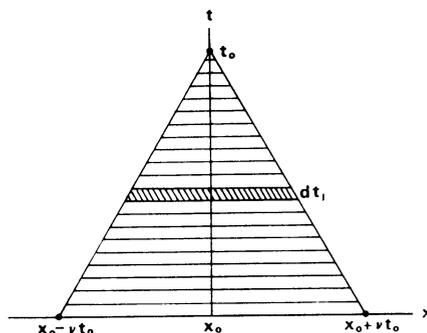


Fig. 1. Region x - t space in which no initiations may occur for x_0 to be white at time t_0 .

The numerical values of the k_d and k'_d are

$$\begin{aligned} k_1 &= 0.8862 & k_2 &= 0.8794 & k_3 &= 0.8960 \\ k'_1 &= 0.6617 & k'_2 &= 0.3535 & k'_3 &= 0.2463 \end{aligned} \quad (13)$$

We see that the analytical result for k_1 , 0.8862, is within the limits (0.707, 1.225) predicted by Glass in the portion of the text which follows his equation 8. It is to be compared with the value of 0.830 which he obtains by means of computer simulation.

As pointed out by Glass, our Eq. 8 and his equation 1 should be valid only in the limit of L going to infinity. For $(v/F)^{1/2}$ not negligible with respect to L , k_1 may be a function of L and there may indeed be a real discrepancy between the analytical results presented here and the results obtained in a computer simulation with a finite L . Further analytical results may be obtained by similar methods. If $s(l,t)dl$ is the number of white strips along the line with length between l and $l + dl$, one may show that

$$s(l,t) = L(Ft)^2 e^{-Fv t^2} e^{-F l^2} \quad (14)$$

and the total number of white sequences at time t is

$$s(t) = \int_{l=0}^{\infty} s(l,t) dl = L F t e^{-Fv t^2} \quad (15)$$

At present, however, we have not been

able to obtain any analytical results about the correlation among centers of structures.

JULIUS L. JACKSON

Department of Chemical Engineering and Material Sciences, Wayne State University, Detroit, Michigan 48202

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20 August 1973

I proposed in my report (1) that regular spatial patterns of structures can be generated by a process of random structure initiation followed by locally spreading inhibition which prevents new structure formation in ever widening regions surrounding each structure. Professor B. N. Boots of the Department of Geography, Columbia University, has informed me that this model, which I believed to be novel, was previously proposed as a mechanism for phase transformations in solids (2). Armstrong's and Jackson's results for the saturating densities for systems with inhibitory fields expanding with constant velocity are in agreement with previous computations (3). The model has also been applied to study the kinetics of phase transformations in solids (4) and dynamic processes in geography (5).

LEON GLASS

Institute for Fundamental Studies, Department of Physics and Astronomy, University of Rochester, Rochester, New York 14627

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4. J. Burke, *The Kinetics of Phase Transformations in Metals* (Pergamon, Oxford, 1965).
5. B. N. Boots, thesis, Rutgers University (1972); *Geografiska Ann. Ser. B* **55**, 34 (1973).
6. I thank B. N. Boots, Department of Geography, Columbia University, for bringing the earlier work in this field to my attention.
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Analysis of Neutrality in Protein Polymorphism

Yamazaki and Maruyama (1) used published gene frequency data in conjunction with some theoretical calculations to conclude that the data in question yield evidence in favor of the "neutral mutations theory." We have severe reservations about a number of

the theoretical calculations used by them. Here we discuss two of these points, relating respectively to calculations on mutation rate and to the problem of population structure and subdivision.

We review first the mathematical

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Robert A. Armstrong, Julius L. Jackson and Leon Glass

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