GOMPERTZ KINETICS IN DEVELOPMENTAL FIELDS: AN INFORMATION THEORY APPROACH

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Abstract

A model for cell proliferation in developmental fields is derived from information theory using a few biological postulates. The model provides an explanation for the success of the Gompertz equation in describing the growth of embryonic, neoplastic, and regenerative systems. Although this equation has been applied to many growth phenomena, its use has been entirely empirical. A theoretical justification for the use of the Gompertz equation in characterizing developmental processes is presented. The model also accounts for a reported relationship among the parameters of the Gompertz equation. A method for quantification and comparison of the determination of developmental fields at different levels of organization is suggested.

Keywords: Developmental Field; Gompertz Equation; Information Theory; Developmental Biology

1. Introduction

Information theory has been productively utilized in many different biological disciplines including molecular genetics, evolution, neurobiology, and behavioral biology (Bossert, 2018; Pardo, 2019; Zambrano and Galindo-Cortes, 2018). Quastler, 1958 and Reza, 1961 may provide an introduction to this subject for biologists unfamiliar with it. See also Gatlin, 1972 and Soucek and Carlson, 1976. However, many previous attempts to use information theory in developmental biology "…have been either faulty, meaningless, or trivial." (Apter and Wolpert, 1965) In the present paper, I apply information theory to the formal aspects of the problem of cell proliferation in developmental fields (Flowers and Crews, 2020; Tkacik and Gregor, 2021). A developmental field "…can be defined operationally as the domain within which changes in the presumptive fates of cells (regulation) can occur in response to surgical manipulation." (French, Bryant, and Bryant, 1976) A remarkable variety of developmental systems have been characterized by the Gompertz equation (Akin et al., 2020; Castaneda et al., 2019; Fornalski et al., 2020; Geng et al., 2017; Vaghi et al., 2020; Yang et al., 2020). See Table 1. The model detailed below provides a theoretical rationale for the empirical success of the Gompertz equation in describing the growth kinetics of embryonic, regenerative and neoplastic systems at many levels of organization.

2. Conceptual Milieu for the Model

The area of biology to which information theory has been most extensively applied seems to be molecular genetics. Gatlin (1972) provides a careful and lucid description of this work, and she states, "Life may be defined operationally as an information processing system - a structural hierarchy of functioning units - that has acquired through evolution the ability to store and process the information necessary for its own accurate reproduction." She points out that under this definition, the smallest unit of life is the cell, although the definition is also applicable to multicellular organisms. I will accept this statement as a starting point for my work.

Developmental systems are constructed by one or more of the following processes: cell proliferation, programmed cell death, cell migration, cell secretion, cell adhesion, and cell hypertrophy (see references in Wessells, 1977). Often several processes occurring simultaneously are required for proper structural and functional development. However, it is legitimate to consider each of these processes separately for analytical

purposes. In this paper, my treatment is limited to the problem of cell proliferation in developmental fields.

The following three statements are well supported by the biological literature and are incorporated into the model as *a priori* postulates.

(a) Developmental fields are comprised of some specific, minimum number of cells (here termed N_0),i.e. Any aggregation of such cells which is smaller than the minimum number will not show the properties which define a developmental field (Grobstein and Zwilling, 1953; Wolpert, 1969; Montgomery and Coward, 1974).

(b) Individual developmental fields are each endowed with some sort of "pattern" which specifies their uniqueness and their future structure and functional capacities (French et al., 1976).

(c) There exists an intrinsic timing factor within fields which determines their rates of cellular proliferation and of pattern expression (Summerbell, Lewis, and Wolpert, 1973). The timing factor of the field will be called D_1. The rationale for and implications of this assignment are discussed in a later section.

3. Derivation of the Model

In this section, a form of the Gompertz equation is derived by consideration of developmental processes in the light of information theory principles.

(a) The Process of Determination

The growth of a developmental field requires a time series of determinatory events restricting the number of pathways of biochemical differentiation which a cell and its progeny can follow. Present technology has been inadequate to elucidate in detail the mechanics of the physical switching networks by which determination occurs. For our present purposes, a "state of determination" of an individual cell in a developmental field at a given time will be defined as the total restrictions on the cell's biochemical differentiation which previous determinatory events have imposed. The "state of the system" will refer to the state of the entire developmental field at a given time. It is a function of the states of determination of the field's constituent cells.

The essence of the growth of a developmental field is that its individual cells become "more different" from each other. As individual cells become more restricted in the biochemical pathways they can follow, the number of different types of cells increases. Consider a set, X_t, of all possible cell types that could exist, as a result of previous

determinatory events, at a given time in the growth of the field. This set will consist of states of determination, x_{m_t} . The number of possible states of determination at a given time will be a_t , so $X_t=\{x_{1_t},x_{2_t},x_{3_t},\ldots,x_{a_t}\}$. As time progresses and the cells become "more different" from each other, the number of elements, a, of the set, X, will obviously increase. So, as t increases, a_t increases. One may define a logarithmic measure, H_{max}, of the number, a, of possible states of determination at a given time, so $H_{max_t} = \log a_t$. In this system, as t increases, H_{max_t} will increase.

There is obviously some probability distribution of the elements of any set X_t. Some cell types, certain states of determination, are more probable results of any determinatory event than are others. Indeed, some possible states of determination must occur with a small frequency or even not at all. Thus the actual state of the system at any given time will involve a frequency distribution of some subset, S_t, of X_t consisting of only those states of determination which are actually present in cells.

I will assume that at any given determinatory event, the mechanism or process which selects the actual set, S_t, of states of determination from the set, X_t, of possible states of determination is a Markov process, and that this is true at every time, regardless of the number of elements in X_t. As discussed below, this situation is largely analogous to a system which Gatlin (1972) describes, in which the state of the system at any given time is considered as the output of a Markov process, even though the overall process is not stationary.

It is possible at any time to compute a measure called H-Markov, H_M, depending on the probability distribution of the actual states of determination in the set S_t. Gatlin provides a general method for calculating H_M. A method tailored to developmental systems is suggested below.

(b) The concept of information content

Gatlin defines a quantity which she calls information content or information density (Id) or stored information. I will now relate this concept to "information content" in a developmental field. We will assume that each determinatory event, z, occupies a finite but short time interval and that in the aggregate we may treat determination as a continouous process. In analogy with her equation (48) one may write:

$$Id(t_z) = Hmax(t) - H_M(t) \qquad (1)$$

This equation states that the information content of a determinatory event may be measured as an entropy value. This value represents both how many of the possible states are excluded by that determinatory decision as well as how much the states that are represented diverge from equiprobability and independence (see Gatlin, chap. 3). This definition of determinatory information content from an information theory perspective is in excellent accord with the way the term "information content" is applied to determinatory events in developmental biologic theory. A determinatory event chooses certain developmental pathways, concomitantly excluding other pathways and skewing the probabilities toward specific final differentiated states. The usefulness of the present approach is that such determinatory information can now be quantified (see methods described below and in Gatlin's chap. 3).

Information content may also be viewed from another perspective. Hmax, as I have defined it, may be considered a valid measure of the maturity of a developmental field. As a field gets older and has more possible states of determination, Hmax incrases. In this context, it is entirely appropriate to view the information content of any determinatory event, z, as proportional to the change in Hmax over the time interval of the determinatory event, so $Id(t_z) \alpha \Delta Hmax(t) / \Delta(t)$. We may also write $Id(t_z)=c \cdot \Delta Hmax(t)/\Delta t$, where c is a constant. Since we have assumed that each determinatory event occupies a discrete but short time interval and overall we may treat determination as a continuous process, one may write

$$Id(t_z) = c \cdot \frac{dHmax(t)}{dt} \qquad (2)$$

Note that the value of c depends on the time units chosen.

(c) Developmental pattern

The concept of "pattern" in developmental systems will now be considered. As mentioned above, the biological literature provides support for the thesis that all developmental fields have some sort of inherent pattern. There are many papers concerning the theoretical nature of such patterns, and all biologists have a good understanding of what is referred to as a developmental pattern. Yet I

know of no papers presumptuous enough to claim that they can fully characterize the nature of developmental pattern. The essence of the phenomenon of pattern remains elusive in current developmental biology (probably due to present technological limitations). In contrast, the concept of pattern is very precisely defined and quantified in information theory. It is represented by the concept of "redundancy," which specifies "...how much the entropy has been lowered from its maximum value...."(See equation (3) below.) However, redundancy(pattern) in information theory is also "...a measure of all the ordering, constraints, rules, etc., that have been imposed on the system." (Gatlin, 1972) Although it is not possible for developmental biologists today to fully characterize the phenomenon of pattern, their conception of it is absolutely consistent with the more general definition of information theory pattern just quoted. For that reason, it is entirely valid to represent the developmental pattern at a given time as R(t) for the present analysis. To conclusively prove or disprove the validity of this association will require a fuller delineation of potential determinatory pathways than is technologically feasible at present. The symbol R_0 will be used to indicate the initial pattern of the field, Developmental redundancy may be characterized in accord with Gatlin's equation (51) as,

$$R(t) = \frac{Hmax(t) - H_M(t)}{Hmax(t)} \qquad (3)$$

(d) The Model

This section completes the derivation of the model I propose for cell proliferation in developmental fields. Let us now substitute equation (1) into equation (3) to obtain $R(t)=Id(t_z)/Hmax(t)$, or

$$Id(t_z) = R(t)\cdot Hmax(t) \qquad (4)$$

The substitution of equation (2) into equation (4) provides:

$$c\cdot\frac{dHmax(t)}{dt} = R(t)\cdot Hmax(t) \qquad (5)$$

Letting C=1/c, we may also write:

$$\frac{dHmax(t)}{dt} = C\cdot R(t)\cdot Hmax(t) \qquad (6)$$

The concept of pattern development as an interlocking stepwise process whose future course is influenced by its present state is well accepted in developmental biology (see Wessells, 1977,

chapters 6 and 17). This may be written as dR/dt = f(R(t)). Since it was postulated above (c) that there is an intrinsic timing factor, D_1, which governs the expression of pattern in time (dR/dt), we may write dR/dt = D_1R(t). However, the pattern or "prepattern" is indeed "unfolding" in time, so we introduce a negative sign:

$$\frac{dR(t)}{dt} = -D_1 R(t) \qquad (7)$$

Equations (6) and (7) are equivalent to the pair of differential equations which Norton et al. (1976) used to define the Gompertz equation. Their solution to these equations in the present notation is:

$$Hmax(t) = Hmax(0)\ Exp[\frac{C \cdot R_0}{D_1}(1-Exp(-D_1 t))] \qquad (8)$$

In analogy with Gatlin's equation (49), one may write:

$$Id(t_z) = D_1(t) + D_2(t) \qquad (9)$$

The biological import of the term D_2 will be discussed in a subsequent section. By substituting this equation into equation(4) we have

$$R(t) \cdot Hmax(t) = D_1(t) + D_2(t) \qquad (10)$$

I have postulated that the timing factor, D_1, is constant throughout the growth of an individual field. With this in mind, and setting the expression to the inception of the field, time zero, writes

$$R_0\, Hmax_0 = D_1 + D_{2_0} \qquad (11)$$

The mathematical discussion to this point has been in many respects analogous to Gatlin's model for the evolution of the DNA of organisms. Gatlin views the DNA of each organism as the output of a Markov process, so associated with the DNA of each species is an Hmax, R, D_1 and D_2. She then shows that D_1 is about constant for all organisms for most of evolution and that an equation analogous to equation (l0) characterized the evolutionary (time) development of the DNA. I have herein viewed the "state" of a developmental field with respect to determination at any given time as the output of a Markov

process. I have then shown mathematically that equation (10) characterizes the time development of the field. Experimental evidence supporting this is discussed below. (It should be noted that this system is different from Gatlin's in that in her system the Hmax does not change as time progresses.)

Now let us consider, in the individual growing field the relationship between the number of cells and the maturity of the system with respect to differentiation. As mentioned previously, Hmax may be considered an index of the maturity of a developmental field. It is obvious that there is some general relationship between N(t) and Hmax(t) since there are fewer cells when a field is young and little determined, and cell number increases as determination of the field increases. Thus, we may write,

$$N(t) = k\,Hmax(t) \qquad (12)$$

Using equation (12), we may substitute for Hmax(t) in equations (8) and (11) to obtain

$$N(t) = N_0 \exp\left(\frac{C \cdot R_0}{D_1}\left(1-\exp(-D_{1_t})\right)\right) \qquad (13)$$

and

$$R_0 N_0 = k \cdot (D_1 + D_{2_0}) \qquad (14)$$

Equation (13) is the form of the Gompertz equation utilized by Norton et al.,1976. Equation (14) defines the relationship among the parameters of the Gompertz equation. Only recently have investigators looked for and found correlation among the parameters of the Gompertz equation (Brunton and Wheldon, 1978).

Methods for computing all parameters (N_0, R_0, D_1, D_{2_O}, and k) in equations (13) and (14) are discussed below. The value of C depends on the time units chosen, e.g. days or weeks. Should the value of C change the values of the other parameters would also be modified. In the seminal paper by Laird, Tyler and Barton (1965), the value of C is, in effect, conveniently set to 1. The model I propose for cell proliferation in developmental fields is formally defined by equations (13) and (14).

4. The Timing Factor and Initial Determination of Developmental Fields

It was postulated that there exists an intrinsic timing factor within fields which determines their rates of cellular proliferation and of pattern expression. Now, I will describe why one may assign the term D_1 to this timing mechanism.

Associated with each determinatory event is a set X_t, and there exists some probability distribution of the elements of any set X_t. That is, some states of determination are more probable to result from the Markov process governing the determinatory event than are other states of determination. In analogy, with Gatlin's mathematical definition of D_1, one may define D_1 in a developmental context as the "divergence from equiprobability" of the elements of the set X_t. Thus if all the states of determination in X_t are equally probable, $D_1=0$, and if some are more likely than others, $D_1>0$. Also, D_1 is here postulated to be constant throughout the growth of an individual field. Focusing on the inception of the field, t=0, *we* see that if $D_1>0$, some of the states of determination in X_0 are more probable than others. If we examine two fields with different D_1's, then the field with the highest "divergence from equiprobability" of its possible states of determination will be more determined from the beginning. For each subsequent determinatory event, the probabilities will continue to be more skewed in the field with the higher D_1. Thus the field with the higher D_1 should take fewer determinatory events, and therefore less time to reach a terminally differentiated state, than the field in which the possible states of determination at any event are more nearly equiprobable. Thus, having defined D_1 in a developmental context in a manner consistent with Gatlin's mathematical definition, clearly D_1 is also a valid measure of the intrinsic timing factor of a developmental field.

Let us now specifically examine the relationship of D_1 to the growth period of a field. It can be demonstrated that if two different fields grow by Gompertz kinetics, and differ only in the value of D_1, the field with the larger D_1 will have a shorter growth period (i.e. will reach a given percent of its upper asymptote in less days than the other field; see equation (8)). Baranowitz,Maderson and Connelly (1979) demonstrate that if the Gompertz equation is written in a form where the parameter herein called D_1 is replaced such that $-\ln B = D_1$ for $O>B>1$, then the field with the smaller B will have a shorter growth period. Therefore, a larger D_1 will indicate a shorter growth period. D_1, of course, can be determined from the regression routine (see below). Since the technology necessary to fully characterize physically the different states of determination is not yet

available, it is not yet practical to compute D_1 using Gatlin's direct equations (chapter 2).

We may define D_2 in equation (9) by analogy with Gatlin's definition. In a developmental system, D_{2_t} represents the "divergence from independence" of the elements of the set X_t. If for every two elements, X_{ut} and X_{vt}, the probability $p(X_{ut}|X_{vt}) = p(X_{ut})$ then $D_2 = 0$. If $p(X_{ut}|X_{vt}) \neq p(X_{ut})$ for any elements of X_t, then $D_2 > 0$. Thus D_2 is a measure of the divergence from independence of the states of determination of X_t. D_2 can be obtained by regression (see below). Again, since the technology to physically identify the different states of determination is not yet available, it is not yet practical to directly compute D_2 using Gatlin's equations (chapter 2).

Investigators have heretofore obtained parameters N_0, R_0 and D_1 by regression using equation (13) as the model (Laird, 1964, 1965, 1966a; see references in Brunton and Wheldon, 1978). They have then computed k and a term containing D_{2O} by regressing the parameters obtained from equation (13) to a variant form of equation (14). However, this practice is less than desirable since the first regression really proceeds under the assumption that the parameters N_0, R_0 and D_1 are independent, which empirically they are not. It would seem preferable in the future to devise a single regression algorithm incorporating both equations (13) and (14) into the regression model. Once the parameters in equations (13) and (14) are known, one could, if desired, compute H_{MO} in equation (1) from equations (12), (9), and (1).

One must be extremely cautious in evaluating the literature for values of D_1, D_{2_0} and k. First, almost all of the reports in the literature involve regressions on pooled measurements taken from groups of organisms at different time points in the growth of a particular system. Of course, this only provides an average curve. It would be better to take measurements of individual systems, perhaps using some noninvasive, nondestructive technology such as tomography or ultrasonography. Second, although the theory herein presented is applicable without modification to such "classical" developmental fields as embryos and regenerating structures, it is unclear exactly how it applies to neoplastic and postnatal growth which do not quite fit in the "classical" definition of a developmental field.

The model presented above should make it possible to compare the initial determination and growth periods of different developmental systems (embryonic, regenerative, and neoplastic) in a given species by merely comparing their D's under standardized experimental conditions. Interspecies comparisons will require a great deal of caution in experimental methodology.

5. Initial Cell Number and Initial Determination in Developmental Fields

I have postulated a relationship between the initial cell number, N_0, of a developmental field and its $Hmax_0$, so $N_0 = k \cdot Hmax_0$.

The importance and usefulness of this concept may be more concretely demonstrated by consideration of two classical developmental riddles.

First, many workers have commented that amphibian regeneration seems to represent the reactivation of an embryonic morphogenetic program. Yet this program must operate on a scale, in the adult, with many times the number of cells that were present in the embryonic structure. In our present theoretical context, we may simply view regeneration as just involving a change in the term k, with all other aspects of the embryonic morphogenetic program otherwise unchanged.

Second, at certain stages an embryonic field can be divided into two parts and each will give rise to perfectly normal adult structures; yet each will have a smaller than normal number of cells. Again, we may view this as simply a change in k, with all other aspects of the embryonic morphogenetic program unchanged.

The work of Brunton and Wheldon (1978) can be easily related to the present model and provides estimates of the value of k for some neoplastic systems. They reanalyzed most published reports of tumors with Gompertz growth kinetics and demonstrated a linear relationship between the parameters R_0 and D_1 (which are alpha and beta respectively in their notation). By dividing both sides of equation (14) by N_0, we obtain a linear form equivalent to theirs:

$$R_0 = \frac{k(D_1)}{N_0} + \frac{k\,D_{2_0}}{N_0} \qquad (15)$$

The second term for all tumors is shown by them to be close to zero, so we can simplify this to,

$$R_0 \cong \frac{k(D_1)}{N_0} \qquad (16)$$

If we let $K = k/N_0$ then: (17)

$$R_0 \cong K(D_1)$$

Brunton and Wheldon show that K is about constant for all tumors of a given species of animal. If N_0 can be determined eventually for each tumor, then the $Hmax_0$ for each tumor could be computed. One could then compare the initial determination of different tumors with each other and with the tissues from which they arose.

The fact that the second term in equation (15) is about zero for tumors is most interesting. It implies that D_{2_0} is about zero, and therefore that states of determination emerge almost independent of each other in neoplasms. This is in good accord with the ubiquitous reports of bizarre, seemingly randomly distributed histological cell types occurring in neoplasms. In contrast, one would expect that D_{2_0} would be greater than zero for "well-organized" systems such as embryos or regenerates. Unfortunately,the sorts of computations Brunton and Wheldon made on neoplasms have not yet, to my knowledge, been made on embryonic or regenerative systems. Thus, D_{2_0} for such systems has not yet been calculated.

6. Information Theory Implications for Developmental Fields

The equations of information theory utilized by Gatlin are ultimately derived from the classical Shannon equation. It is of interest that there exist proofs (see Reza, 1969 and other proofs he cites) that within the mathematical postulates under which information theory is constructed, the Shannon equation is unique - no other expression can govern information theory. It is not presently clear how to relate the postulates in that mathematical proof to the biological world. (See Quastler, 1958 for a simplified interpretation of some of these concepts.) However, the relationship between the Gompertz equation and information theory, as well as the vast empirical applicability of the equation, at least suggest the possibility that under certain biological conditions, this equation may be the only one governing cell proliferation in developmental fields.

Acknowledgments

I am grateful to Dr. S.N. Salthe for suggesting to me that some relationship might exist between the Gompertz equation and information theory and for critical review of an earlier draft of this paper. I appreciate the assistance of W. Lerner and P. Eap in preparation of the manuscript.

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Table 1

DEVELOPMENTAL SYSTEMS WITH GOMPERTZ GROWTH KINETICS*

Level of Organization	Growth Type	System		References
Cells and Tissues	Neoplastic	Human:	IgG Multiple Myeloma	1
		Hamster:	Fortner Plasmacytoma No. 1, Melanotic Melanoma No. 1	
		Mouse:	B-16 Melanoma, Adenocarcinoma 755, L1210 leukemia (ip), Lewis Lung, Sarcoma 180, C3H, Krebs, Ehrlich, MC_1M, $6C_3HED$, DBA Lymphoma, El_4, Osteosarcoma	
		Rabbit:	Brown Pearce	
		Rat:	Transplantable Mammary Carcinoma, DMBA-induced, Walker 256, R39 Sarcoma, Flexner-Jobling	
Organs	Embryonic	Human:	Adrenals, brain, heart, kidneys, liver, lungs, pancreas, thymus, thyroid, spleen	2
		Chick:	Brain, eye, gizzard, heart, intestine, liver, lungs, mesonephros, metanephros, spleen	
Body Regions	Embryonic	Human:	Head, forelimbs, hindlimbs, trunk	2
		Chick:	Head, forelimbs, hindlimbs, trunk, neck	
	Regenerative	Lizard:	Tail	3,4
		Newt:	Tail	4
	Postnatal	Rat:	Head, forelimbs, hindlimbs, trunk	2
Organisms	Embryonic	Human, guinea pig, mouse, rat, sheep, chicken, crow, duck, goose, jungle fowl, pheasant quail, pigeon, turkey		5
	Postnatal**	Human, chimpanzee, rhesus money		6
		Cat, crow, dog, goat, guinea pig, hamster, horse, rabbit, rat, shrew, swine, chick, duck, quail, goose, turkey		7
Populations		Human		8

*This table is intended to be illustrative but not comprehensive. Often more than one species of animals cited demonstrate Gompertz kinetics. See references.

**A form of the Gompertz equation designed to take into account linear accumulation of extracellular (non-living) substances in postnatal growth was used for some of the postnatal studies.

(1) See references in Laird, 1964 and Brunton and Wheldon, 1978; (2) Laird, 1965; (3) Baranowitz et al., 1977; (4) Baranowitz et al., 1979 (5) Laird, 1966a; (6) Laird, 1967; (7) Laird, 1966b; (8) Shryock and Siegel, 1973