How gap genes make their domains: An analytical study based on data driven approximations

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We consider a mathematical formulation of the problem of protein production during segment determination in the *Drosophila* blastoderm, together with some preliminary results of its analytical study. We reformulate the spatial difference equations as a set of nonlinear partial differential equations and obtain their dimensionless form in the continuum limit. Using previous results obtained by the gene circuit method, we find an asymptotic statement of the problem with a small parameter. Some results of the comparison method applied to the model are obtained, and exact stationary upper solutions are derived. They exhibit distinctive features of localized bell-shaped structures. © *2001 American Institute of Physics.* [DOI: 10.1063/1.1349890]

The central problem of developmental biology is to understand how an organism constructs itself from an egg. This is a dynamical process for which a state description picture was first introduced by Turing. In this article we first briefly review a phenomenological approach to obtaining specific dynamical equations for the process of segment determination in the fruit fly *Drosophila*. This approach, called Gene Circuits, has been successful in solving a number of biological problems. Next we present the initial results of a project to characterize the behavior of the equations analytically, particularly with regard to genes of the gap class, which are expressed in localized bell-shaped expression domains. We transform the Gene Circuit ordinary differential equations into dimensionless partial differential equations by taking the limit as the size of cell nuclei approaches zero. We formulate a minimal instance of the gap gene system generating a stripe of pair-rule gene expression that can be expressed in terms of a small parameter. We then construct upper and lower limits for an analytic solution, and demonstrate that the equation for the upper limit, of interest in its own right as the equation for an uncoupled gene, is integrable. We demonstrate that the upper limit equation indeed has a solitary domain as a solution, and lastly we show that if the regulation-expression term of the equations is approximated by a cubic polynomial, the solitary domain can be obtained as an exact solution in terms of elliptic functions.

I. INTRODUCTION

Recent developments in functional genomics have resulted in a revival of interest in dynamical models of gene networks as well as in nonlinear reaction-diffusion models in the context of developmental biology. The interest of theoreticians in this problem is long-standing: Many theoreticians, beginning with Turing, formulated models of pattern formation with interesting theoretical properties, and some of these dealt with the biological system considered here.[1–7] Many of the postulated state variables in these models were not observable, however, and this adversely affected their credibility with mainstream biologists. A technological revolution has made the fundamental variables of biological pattern formation observable, and has led to a reawakening of interest in models among the mainstream biological community. This has led to a conceptual difficulty: while nearly all of the analysis of ''Turing Systems'' has been based on properties of the linear system near homogeneity, actual biological systems are, in Turing's words, ''developing from one pattern into another, rather than from homogeneity into a pattern'' (Ref. 8, pp. 71–72). Turing recognized that such fully nonlinear systems could be modeled as well, by treating ''particular cases in detail with the aid of a digital computer,'' but that ''...one cannot hope to have any embracing *theory* of such processes'' (Ref. 8, p. 72). Turing's observation raises a difficult problem for the future of functional

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genomics and developmental biology: we may find ourselves with extremely large models that give correct biological behavior numerically but in which the reasons for this correct behavior are not understood by humans.

Nevertheless, the famous and colorful Belousov–Zhabotinsky reaction and the theory which followed[9,10] demonstrate that a useful theoretical understanding of a nonlinear pattern formation system can be obtained. These results dramatically illustrate the necessity and feasibility of obtaining human understanding of pattern formation in developmental biology through the application of modern mathematics to molecular biology. For these reasons, we believe that new mathematical (that is, analytical) approaches to complex problems in gene regulation and pattern formation are of fundamental importance.

In this article we outline the first steps of an analytical attack on a particular pattern formation system. We review key features of a particular biological system that is particularly suited to theoretical analysis, and review past work in formulating a description of it in terms of a particular set of phenomenological ordinary differential equations (ODE's). We then present new results in which we reformulate the system in terms of dimensionless partial differential equations (PDE's). Using results which come from the biological analysis, we introduce a small parameter that allows us to separate the mathematical problems for gap genes and pair-rule genes in order to answer particular pattern formation questions. Certain features of the biology are then used to show how results from the theory of nonlinear quasi-parabolic equations can be used to construct upper and lower bounds for an analytic solution. Finally, we derive an analytic solution for the upper bound which has certain biologically correct features. The work reported here has the limitation that it does not analytically produce features of the pattern that answer specific biological questions. We nevertheless believe the results to be important. They are the foundation for a conceptual and analytic characterization of a set of equations with clear biological relevance which up to now have been treated by entirely numerical methods.

We also direct the reader to recent ODE-based work both in this issue of *Chaos* and elsewhere. These studies include an analysis of the robustness of a late acting component of the segmentation system[11] and an analysis of the statistical properties of ensembles of networks.[12]

A. The biological system

The pattern formation system we consider controls segment determination in the fruit fly *Drosophila*. Like other arthropods, the body of a fruit fly is composed of repeating units called segments. Not all segments are identical: for example, three of them contain a pair of legs and the others do not. Differences between segments are controlled by the famous homeotic (HOX) genes, while the segments themselves are under the control of a completely separate set of genes known as segmentation genes. Segments form in a two step process. First comes *determination*, which classically means that a cell has stably selected a particular tissue type it will develop into. Developmental biologists refer to this ''destination'' tissue type as a cell's *fate*. The actual formation of that tissue type is called *differentiation*. Immediately following the deposition of a *Drosophila* egg, a rapid series of nuclear divisions takes place, without the formation of cells. Between the sixth and ninth nuclear divisions, the nuclei migrate to the outside or ''cortex'' of the egg and form an approximately ellipsoidal shell of cells known as the ''syncytial blastoderm.'' Four synchronous nuclear divisions take place during the syncytial blastoderm stage. Following the 13th nuclear division a long interphase, called cleavage cycle 14A, takes place during which time cell membranes invaginate between the nuclei and seal them off into cells.[13] At about the time cellularization is complete, a complex set of folding motions called gastrulation begins. Twenty-two hours later, the egg hatches. It is during cleavage cycle 14A that segment determination takes place.[14]

Segment determination in *Drosophila* is under the control of about 40 genes. Slightly less than half of these are concerned with the initial determination event, while the other half maintain the determined state. It is reasonably certain that the complete set of segmentation genes are known, since they were found by a procedure known as ''saturation mutagenesis.'' In this procedure, mutants affecting a particular function are generated repeatedly until no new genetic loci are found. Thus, using pregenomics technology, we can be sure that we have all of the genetic players in hand.[15]

The segmentation genes are divided into four classes: maternal coordinate genes, gap genes, pair-rule genes, and segment polarity genes. This classification was originally based on the phenotypes of mutants. Embryos mutant for gap genes contain a large gap in the body pattern of about five to eight segments, pair-rule mutants are missing pieces of body pattern with a spatial periodicity of two segments, while segment polarity mutants are missing them with a periodicity of one segment. Mutants in maternal coordinate genes have phenotypes in which the overall coordinates of the embryo is altered; they are called maternal because the phenotype of the zygote depends on the genotype of the mother.

The expression patterns of the segmentation genes in the blastoderm are loosely comparable to their phenotypes in mutants. While there are many maternal coordinate genes, their actual input to the segmentation system takes place via the products of three genes, *bicoid (bcd)*, *caudal (cad)*, and *hunchback (hb)*, which are expressed as three monotonic gradients of protein at the time when the zygotic segmentation genes are first activated. Of these three genes, *bcd* is entirely maternal while both *cad* and *hb* are expressed from both the maternal and zygotic genomes. Gap genes are expressed in one or two broad domains about 10 to 20 nuclei wide which gradually intensify and sharpen during the blastoderm period. Pair-rule genes are initially expressed almost uniformly but late in the blastoderm period resolve to seven distinct stripes three to four nuclei wide. Examples of maternal coordinate, gap, and pair-rule gene expression patterns are shown in Fig. 1. The segment polarity genes are not expressed until gastrulation, where they appear as 14 to 17 single cell wide stripes. Two segment polarity genes, *engrailed (en)* and *wingless (wg)*, which are expressed in adjacent rows of cells, are the final output of the segmentation system. Their expression is stable through the life of the fly,

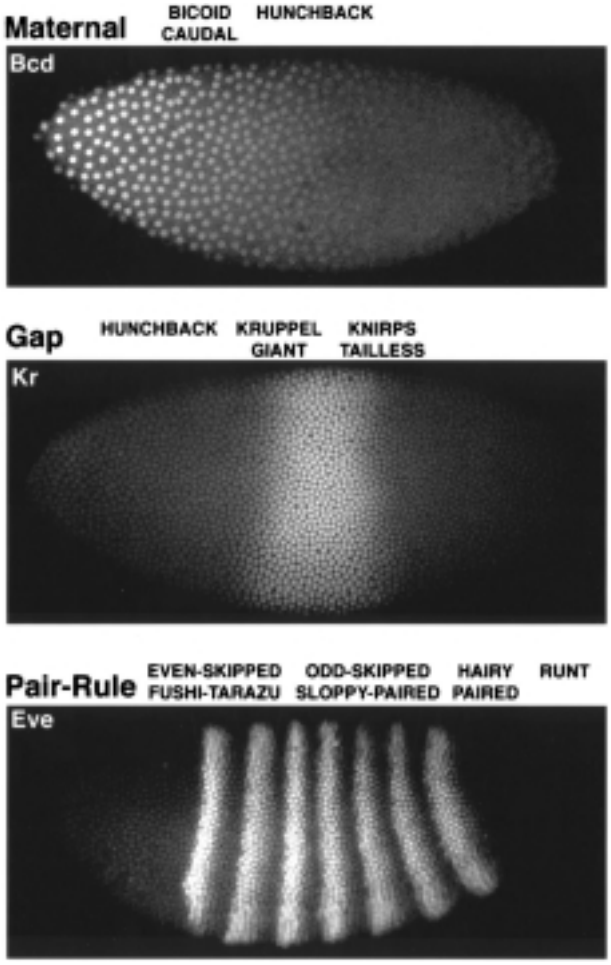

FIG. 1. Examples of expression patterns of each of the three classes of segmentation genes that are expressed during the blastoderm stage of development. The members of each class are listed in smaller type to the right of the name of the class. Each image is labeled with the name of the protein shown; Bcd denotes Bicoid protein, Kr denotes Kruppel protein, and Eve denotes Even-skipped protein. Each image is a confocally scanned blastoderm stage embryo; that showing Bcd is cleavage cycle 12, while the other two embryos are cleavage cycle 14A. The embryos are fluorescently labeled with polyclonal antibodies. The serums were raised and the embryos were fixed and stained as described (Ref. 22); each dot is a single nucleus. Anterior is to the left and dorsal is up. Each embryo is about 0.5 mm long.

and they form the two sides of the borders of ''parasegments,'' which are 180° out of phase with the segment borders that appear after hatching.[16–18]

B. The gene circuit approach

The blastoderm is a uniquely favorable system for theoretical studies of development for three reasons. First, the expression of segmentation genes is to a very good level of approximation a function only of distance along the anterior-posterior (A-P) axis, and so a one dimensional model is effective. Because the blastoderm is a syncytium, cell-cell interactions can be treated in terms of the diffusion of protein products of genes. Most importantly, the state of the system is given by the concentrations of protein products of segmentation genes. Prior to gastrulation, nuclear divisions and morphology are under maternal control, as shown by the absence of zygotic mutants which affect these processes. Segmentation genes are coupled to each other prior to gastrulation, since mutations in one segmentation gene typically affect the expression of others, but they are dynamically uncoupled from the rest of the embryo. This affords an opportunity, rare in biological systems, to do a clean dynamical analysis with all relevant biological information in hand.

One of the authors, in collaboration with D. H. Sharp, has developed an approach to the analysis of the segment determination system as a network using an approach called ''Gene Circuits.'' [19,20] The use of the word ''circuits'' is intended to suggest a relationship with the full molecular picture analogous to that between Maxwell's equations for the EM field and the usual circuit level description of an electrical device. For many calculations involving electromagnetism, a full set of partial differential equations (PDEs) for the EM field are approximated by ordinary differential equations (ODEs) that can be readily written down from a diagrammatic representation with idealized and repeated components (a circuit diagram) and are much easier to calculate with than the exact PDEs. Similarly, in the Gene Circuit method we represent each gene phenomenologically in terms of how its rate of protein synthesis depends on the local concentration of various regulators, without attempting to represent the explicit state of active chromatin at the molecular level. Note that with Gene Circuits the (currently unknown) exact model is a statistical model of some sort, not a PDE. In this article we will examine a PDE which is an *approximation* to the circuit ODEs in the continuum limit.

The Gene Circuit method has four parts: (1) Construct a theoretical model,[19,21] (2) obtain gene expression data,[22] (3) fit the model to the data by large scale numerical optimization, and (4) learn new biology from the model. Active research is taking place in all four areas, including the amassing of a large database of quantitative gene expression data,[23–26] new optimization methods,[27] and biological results,[28,29] some of which are predictive and acknowledged as such by experimentalists.[30–32] In this article we will be concerned with mathematical analysis of the equations themselves, and so we review their main features below.

The state variables in the method are concentrations of segmentation gene products (proteins). The change in time of concentrations of these products is governed by three basic processes:

(1) direct regulation of protein synthesis from a given gene by the products of other genes (including auto-regulation as a special case);
(2) diffusion of protein molecules between cell nuclei; and
(3) decay of protein concentrations.

To model these, we consider a one-dimensional strip of nuclei running along the A-P axis. Indexing the position of a cell nucleus along the A-P axis by i, and denoting the concentration of the ath gene product in nucleus i, which is a function of time, by $v_i^a(t)$, we write

$$\frac{dv_i^a}{dt} = R_a g\left(\sum_{b=1}^{N} T^{ab} v_i^b + m_a v_i^{\mathrm{Bcd}} + h_a\right) + D_a(v_{i+1}^a - 2v_i^a + v_{i-1}^a) - \lambda_a v_i^a, \quad a = 1,\ldots,N, \tag{1}$$

where N is the number of zygotic genes included in the circuit. The first term on the right hand side of the equation describes gene regulation and protein synthesis, the second describes the exchange of gene products between neighboring cell nuclei, while the third represents the decay of gene products. In (1), T^{ab} characterizes the regulatory effect of gene b on gene a, the term $m_a v_i^{\mathrm{Bcd}}$ describes the input from the maternal gene *bcd* with v_i^{Bcd} being the concentration of Bcd protein in nucleus i and m_a being the regulatory coefficient of *bcd* acting on zygotic gene a. R_a is the maximum rate of synthesis from gene a, h_a summarizes the effect of uniformly distributed maternal transcription factors on gene a, D_a is the diffusion coefficient, and λ_a is the decay rate of the product of gene a. The function g is a ''regulation-expression function'' of an argument η, which plays the role of the ''source function'' in the nonlinear reaction-diffusion problem, and has the form

$$g(\eta)=\frac{1}{2}\left(\frac{\eta}{\sqrt{1+\eta^2}}+1\right). \tag{2}$$

The precise functional form is arbitrary. In general, the only restriction on function $g(\eta)$ is that its graph be monotonic and bounded, with a single maximum of the first derivative. Such curves are called ''sigmoids'' by biochemists and ''kinks'' by mathematicians, and it has been shown that dynamical behavior depends on the overall shape and slope of the curve rather than its precise functional form.[33]

All the parameters in (1) are defined by phenomenology and, therefore, remain unknown at the outset. They cannot be found from *in vitro* experiments because there is currently no faithful *in vitro* assay for regulated transcription in eucaryotes. Hence the parameters are found by fitting numerical solutions of (1) to gene expression patterns. This is formulated as a least squares optimization problem, which is solved by the method of simulated annealing, requiring intensive computation. Useful solutions are obtained, but these can be studied only by numerical methods. The overall behavior of the equations is not well understood, and hence analytical investigation of the model is of fundamental importance.

We begin this investigation in the next section by casting (1) to continuous dimensionless form. In Sec. IV we will formulate a theorem resulting from the parabolic maximum principle applied to the equations under study. This theorem provides the equations for upper and lower solutions of the problem, which are solved in the stationary case in Sec. V. Finally we obtain an implicit stationary upper solution and, under some assumptions, find its explicit form, which is shown in the graphs. Section VI contains a discussion of the results for the upper solution, and possible types of the equation for the lower solution.

II. THE MODEL EQUATIONS AS DIMENSIONLESS PDEs

In (1), the diffusion coefficient D_a is measured in units of inverse time, so that

$$D_a=\frac{1}{T_a^{\mathrm{diff}}}, \tag{3}$$

where T_a^{diff} is the characteristic time scale for the diffusion of product v_i^a to the neighboring nuclei. We introduce an average distance l between neighboring nuclei and take the continuum limit for very small l, so that $i\to x\in\mathbf{R}$, $v_i^a(t)\to v^a(x,t)$. Supposing that T_a^{diff} is proportional to l^2, we can write

$$T_a^{\mathrm{diff}}=\gamma_a l^2, \tag{4}$$

and from (3) one gets the continuum representation of the diffusion terms in Eqs. (1):

$$D_a(v_{i+1}^a-2v_i^a+v_{i-1}^a)\overset{1 \text{ is small}}{\approx}\frac{1}{\gamma_a}\partial_x^2 v^a(x,t). \tag{5}$$

Let us define the dimensionless independent variables ξ and τ as follows:

$$\xi=\frac{x}{L},\quad \tau=\frac{t}{T}\Rightarrow\partial_t=\frac{1}{T}\partial_\tau,\quad \partial_x=\frac{1}{L}\partial_\xi, \tag{6}$$

where L and T are space and time scales, respectively. Equations (1) can now be written in the form

$$\frac{1}{R_aT}\partial_\tau v^a(\xi,\tau)=g\left(\sum_{b=1}^{N}T^{ab}\cdot\frac{R_bT}{R_bT}\cdot v^b+m_a(\xi)\right)+\frac{1}{\gamma_aL^2R_a}\cdot\frac{T}{T}\cdot\partial_\xi^2 v^a-\frac{\lambda_a}{R_a}\cdot\frac{T}{T}\cdot v^a, \tag{7}$$

where $m_a(\xi)=m_a v^{\mathrm{Bcd}}(\xi)+h_a$.

We now introduce $\Lambda_a=R_aT$ that represents the amount of gene product a that would be produced during time period T if the linear growth law with the rate R_a is assumed to be valid. A dimensionless dependent variable u^a is defined therefore as $u^a=v^a/\Lambda_a$, and (7) takes the form

$$u_\tau^a=g\left(\sum_{b=1}^{N}T^{ab}\Lambda_b u^b+m_a(\xi)\right)+\frac{T}{\gamma_aL^2}u_{\xi\xi}^a-\lambda_aTu^a. \tag{8}$$

From (4), we have $\gamma_a=T_a^{\mathrm{diff}}/l^2$, and the dimensionless coefficient with the second spatial derivative of u^a in (8) has the form

$$\tilde{D}_a=\frac{T}{\gamma_aL^2}=\left(\frac{l}{L}\right)^2\frac{T}{T_a^{\mathrm{diff}}}=\left(\frac{l}{L}\right)^2TD_a. \tag{9}$$

The dimensionless coefficient with respect to u^a in the last term on the right hand side of (8) can be written as

$$\tilde{\lambda}_a=\lambda_aT=\frac{T}{T_a^{\mathrm{dec}}}, \tag{10}$$

where T_a^{dec} means the characteristic time scale of the decay of gene product a. Taking into consideration the dimensionless regulation matrix as $\tilde{T}^{ab}=T^{ab}\Lambda_b=T^{ab}R_bT$, one can finally write system (1) in the form of the following coupled dimensionless PDEs:

$$\partial_\tau u^a=\tilde{D}_a\partial_{\xi\xi}^2u^a+g\left(\sum_{b=1}^{N}\tilde{T}^{ab}u^b+m_a(\xi)\right)-\tilde{\lambda}_au^a. \tag{11}$$

The space scale L can be defined as the length of the A-P axis of a fly egg, i.e., $L \simeq 0.5$ mm. The time scale T should be the time interval between the end of nuclear cleavage 13 and the onset of gastrulation, because expression levels increase from hardly detectable to maximum levels in that time. For a given number n of nuclei along the A-P axis ($n \simeq 100$), one can determine the quantity $l = L/n \simeq 0.005$ mm. Then we have defined the correspondence between the initial dimensional parameters D_a, λ_a and the dimensionless ones $\tilde{D}_a$, $\tilde{\lambda}_a$, as well as between the dependent variables v^a and u^a.

Note that from now on we will omit all tildes in (11) and for simplicity write (x,t) instead of (ξ, τ) for dimensionless space and time variables.

III. STATEMENT OF THE PROBLEM WITH A SMALL PARAMETER

As reviewed in Sec. I, the two major classes of zygotic segmentation genes which act during the blastoderm stage are the gap and pair-rule genes. The pair-rule genes produce periodic patterns (stripes), while the gap genes form one or two localized bell-shaped expression domains. A key result from both Gene Circuits[28] and experimental studies[34–40] is that the formation of one pair-rule stripe expressed from certain pair-rule genes can be analyzed by considerating inputs from two overlapping gap-gene domains. This is a postulate:

Postulate 0: The pairwise (only 2 gap genes considered) repression of the pair-rule gene is sufficient to form one of its stripes.

Specific numerical results from the analysis of experimental data[31] lead to further postulates, as follows:

Postulate 1: The diagonal terms of the regulation matrix T^{ab} are positive.

Postulate 2: The off-diagonal ones are negative.

Postulate 3: All of the pair-rule gene's ''outputs'' are zero: pair-rule genes do not regulate gap genes, so that $T^{a \leftarrow \text{pair-rule}} \simeq 0$ for a denoting any gap gene.

Postulate 4: The pair-rule gene's product has an extremely low diffusivity.

Writing u to denote the pair-rule gene's product and v^a for the products of gap genes, we then reduce (11) to

$$\begin{aligned} u_t &= \varepsilon u_{xx} + g(T^{00}u - T^{01}v^1 - T^{02}v^2 + m_0) - \lambda_0 u, \\ v^1_t &= D_1 v^1_{xx} + g(T^{11}v^1 - T^{12}v^2 + m_1) - \lambda_1 v^1, \\ v^2_t &= D_2 v^2_{xx} + g(T^{22}v^2 - T^{21}v^1 + m_2) - \lambda_2 v^2. \end{aligned} \tag{12}$$

In this system all T^{ab}, $a, b = 0,1,2$, are positive because of Postulates 1 and 2; the second and the third equations do not directly depend on the first one due to Postulate 3; ϵ may be considered as a small parameter by Postulate 4. Finally in (12) there are only three equations. This is the simplest biologically meaningful model for describing the formation of a pair-rule stripe by Postulate 0. This condition can provide also a general matching rule for the final result of solving system (12).

The typical initial conditions for system (12) are as follows. The initial value of u is either zero, or a monotonic spatial gradient. Initial values for the gap genes' v^a are not zero if v^a is also the maternal gene (*hb*; *cad*, while both maternal and zygotic is not a classical gap gene), and zero otherwise.

The equation for u in system (12) contains the small parameter ϵ. This means that we can solve it by means of the usual asymptotic perturbation method, finding a solution as the power series expansion in ϵ. The coefficients in that expansion will depend on the gap-genes inputs v^1 and v^2 (in accordance with Postulate 0). Thus the main problem is to find out what kinds of patterns can provide a solution to the gap gene part of the system (12) and how far the borders of those patterns can spread. The following sections partially answer these questions.

IV. UPPER AND LOWER SOLUTIONS

The essence of the comparison method[41,42] is to find the so-called upper and lower solutions, which are functions bounding a solution to the problem under study. It is well known that the main advantage of this method is the fact that very often the upper and lower solutions provide stable limits of a genuine solution at large times.[43–45] A rigorous proof of this fact is rather complicated from a mathematical point of view. By now, various approaches exist to study the asymptotic stability of upper and lower solutions,[43–45] but the problem of a proper choice between them in a particular nonlinear problem remains an open question. However, the equations themselves for upper and lower estimates of a genuine solution can be derived easily, following standard theorems (the maximum principle) that are valid for quasi-parabolic equations.

Applying the version of the maximum principle, formulated in Ref. 42, to Eq. (11), we get the following.

Theorem: Let $\vec{y} = (y^1,\ldots,y^N)$ and $\vec{w} = (w^1,\ldots,w^N)$ be either classical or weak solutions to the following equations:

$$\begin{aligned} w^s_t &= D_s w^s_{xx} + g(T^{ss}w^s + m_s(x)) - \lambda_s w^s, \\ y^s_t &= D_s y^s_{xx} + g\left(T^{ss}y^s + \sum_{r \neq s} T^{sr}w^r + m_s(x)\right) - \lambda_s y^s, \\ & s = 1,\ldots,N, \end{aligned} \tag{13}$$

with some initial values $\vec{y}_0(x)$ and $\vec{w}_0(x)$, respectively. Consider the gap gene system

$$v^s_t = D_s v^s_{xx} + g\left(\sum_{r=1}^{N} T^{sr}v^r + m_s(x)\right) - \lambda_s v^s, \quad s = 1,\ldots,N, \tag{14}$$

with some initial value $\vec{v}_0(x)$. If $\vec{y}_0(x) \leqslant \vec{v}_0(x) \leqslant \vec{w}_0(x)$ for all real x, then $\vec{y}(x,t) \leqslant \vec{v}(x,t) \leqslant \vec{w}(x,t)$ for all $0 < t < \infty$. Functions $\vec{y}(x,t)$ and $\vec{w}(x,t)$ are called lower and upper solutions, respectively, for the system (14).

Sketch of the proof: The proof of the theorem is based on the following fact, quite transparent from a practical point of view. Consider two systems

$$\begin{aligned} w^s_t &= D_s w^s_{xx} + H_s(x, w^1,\ldots,w^N), \\ y^s_t &= D_s y^s_{xx} + G_s(x, y^1,\ldots,y^N), \quad s = 1,\ldots,N, \end{aligned} \tag{15}$$

with some smooth source functions H_s and G_s, nondecreasing with respect to w^k and y^k, respectively, for all $k \neq s$. It can be shown[41] that $w^s \geqslant y^s$ at any time, if it is true at the initial moment and $H_s \geqslant G_s$ later. Using this fact, one concludes that solutions of (15) will provide the upper and lower estimates of solution to (14), if we take the source functions in the form[42]

$$G_s(x,\vec{y}) = \inf_{\vec{y}\leqslant\vec{v}\leqslant\vec{w}} F_s(x,v_1,\ldots,v_{s-1},y_s,v_{s+1},\ldots,v_N),$$
$$H_s(x,\vec{w}) = \sup_{\vec{y}\leqslant\vec{v}\leqslant\vec{w}} F_s(x,v_1,\ldots,v_{s-1},w_s,v_{s+1},\ldots,v_N), \tag{16}$$

where $F_s(x,v^1,\ldots,v^N)$ is the source function for system (14), i.e.,

$$F_s(x,\vec{v}) = g\left(\sum_{r=1}^{N} T^{sr}v^r + m_s(x)\right) - \lambda_s v^s, \quad s=1,\ldots,N.$$

Calculating (16) and substituting the result into (15), we get (13), which completes the proof.

To make a better approximation to the solution $\vec{v}$, we should supply each of the two systems in (13) with the same initial conditions as for $\vec{v}$.

V. STATIONARY UPPER SOLUTION

Inspection of (13) shows that the equations for the upper solution $\vec{w}$ become uncoupled. Thus, one has N equations for functions w_s which are of the same type but with different coefficients. Since the upper solution equation can also be interpreted as describing a single autoregulating gene, its behavior is also of interest in its own right. We cannot solve them yet because of the special form of function $g(\cdot)$. However, in the stationary case, we may find the general solution to the corresponding equations (i.e., a solution to nonlinear ordinary differential equations of second order, depending on two arbitrary integration constants) if m_s is assumed to be constant. This assumption corresponds to considering an embryo whose mother was a homozygous mutant for the *bcd* gene; such mutants do form gap domains, but in altered positions compared to wild type.[46]

A. Implicit solution

In what follows, let us omit for brevity the index s in the stationary version of the equation for the upper solution w^s. Then it yields

$$D\frac{d^2}{dx^2}w + g(Tw+m) - \lambda w = 0, \tag{17}$$

where m is constant from now on and $w = w(x)$. Multiplying it by $w' \equiv dw/dx$ and integrating with respect to x over the interval $[x_0,x]$, one finds the first integral of (17) in the form[44,47]

$$K = P(w) + D\left(\frac{dw}{dx}\right)^2, \tag{18}$$

where $K = D(w'(x_0))^2$, and the function $P(w)$ is defined as

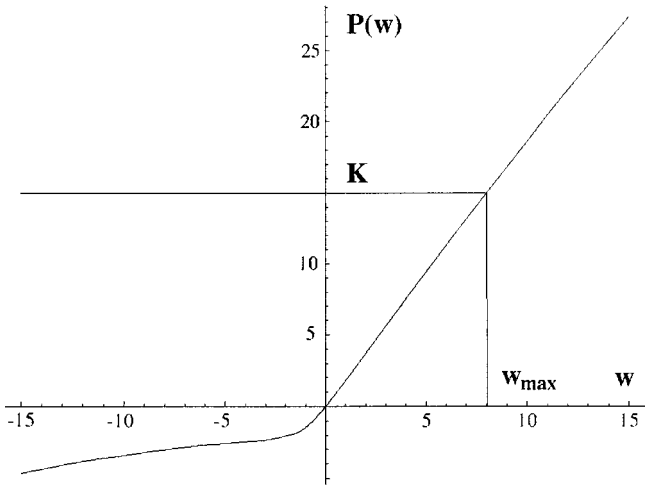

FIG. 2. The function $P(w)$ for $w_0=0$, $T=1$, $m=1$ and $\lambda=0.01$.

$$P(w) = 2\int_{w_0}^{w} (g(T\tilde{w}+m) - \lambda\tilde{w})\,d\tilde{w},$$

and the point x_0, along with the values $w_0 = w(x_0)$ and $w'(x_0)$, are arbitrary.

Equation (18) has the form of a conservation law for a mechanical system having a ''total energy'' K, ''time'' x, ''coordinate'' w and ''mass'' $2D$, while $P(w)$ can be interpreted as the potential energy of the system. Hence, we immediately find the integral of motion for such a system (the implicit solution):

$$x - x_1 = \pm\sqrt{D}\int_{w_1}^{w} \frac{d\tilde{w}}{\sqrt{K - P(\tilde{w})}}, \tag{19}$$

where x_1 and $w_1 = w(x_1)$ are arbitrary, but w_1 must be in a region where there exists a motion.

The form of the stationary upper gap-solution $w(x)$ is defined by a trajectory of ''coordinate'' w. The latter depends on the form of the ''potential energy'' $P(w)$ and a choice for the ''total energy'' K.

If the function g is given by (2), then $P(w)$ can be written explicitly as

$$P(w) = (w-w_0)(1-\lambda(w+w_0)) + \frac{1}{T}(\sqrt{1+(m+Tw)^2} - \sqrt{1+(m+Tw_0)^2}).$$

This function is shown in Fig. 2 for $w_0=0$, $T=1$, $m=1$ and $\lambda=0.01$.

It is seen from Fig. 2 that, for all $K>0$, the ''coordinate'' w exhibits quasi-hyperbolic motion, starting and finishing at value $-\infty$, and taking a maximum value $w_{\max}(K)$ which is defined by the equation

$$P(w_{\max}) = K.$$

Because w is the stationary upper bound for a chemical concentration, which can never be negative, we must drop the negative part of w and consider the domain of $x \in \mathbf{R}$ where w is positive and where, therefore, our approach is valid.

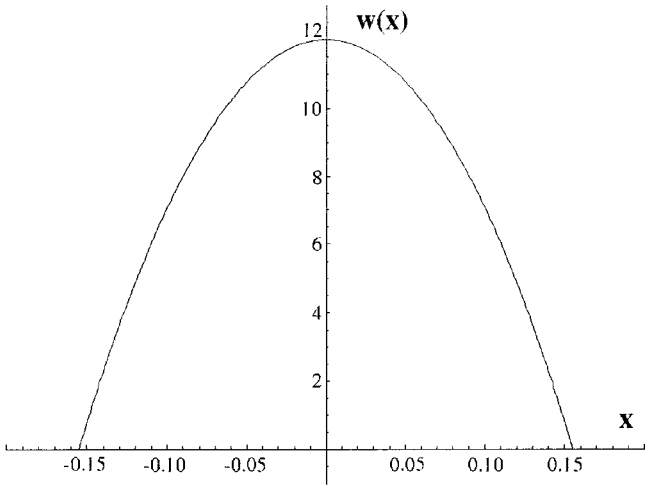

FIG. 3. The positive part of the numerical solution $w(x)$ of (20) for $D=0.03$, $T=1$, $m=1$, $\lambda=0.01$ and $K=22.2$.

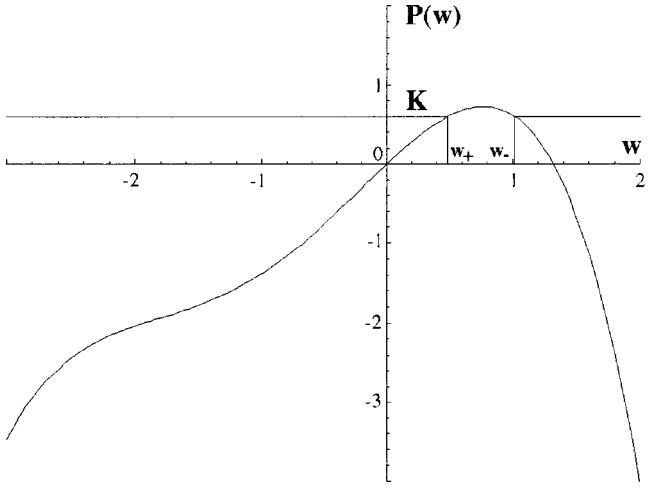

FIG. 5. The function $P(w)$ for cubic g and $D=0.03$, $T=1$, $m=1$, $\lambda=0.01$ and $K=0.6$.

Taking $x_1=0$ and $w_1=w_{\max}(K)(w'(0)=0)$, we can rewrite (19) in the form

$$x=\pm\sqrt{D}\int_{w}^{w_{\max}(K)}\frac{d\tilde{w}}{\sqrt{K-P(\tilde{w})}}. \tag{20}$$

The results of numerical integration of (20) for $D=0.03$, $T=1$, $m=1$, $\lambda=0.01$ and $K=22.2$ are shown in Fig. 3.

From (20), it follows that the borders x_+ and x_- of the localized pattern of $w(x)$ shown in Fig. 3, that is to say the points defined by the equality $w(x_\pm)=0$, are determined as

$$x_\pm=\pm\sqrt{D}\int_{0}^{w_{\max}(K)}\frac{d\tilde{w}}{\sqrt{K-P(\tilde{w})}}. \tag{21}$$

They represent upper estimates for the limits of a gap genes' expression domains.

B. Explicit solution

In general, we cannot calculate the inversion of the integral in (20) in order to get an explicit solution. However, if the cubic approximation for function $g(\cdot)$ is assumed to be valid, the inversion can be made easily in terms of elliptic functions.

Expanding $g(\cdot)$ in the Taylor series and omitting higher terms, we obtain

$$g(\eta)=\frac{1}{2}\left(\frac{\eta}{\sqrt{1+\eta^2}}+1\right)\simeq\frac{1}{2}+\frac{\eta}{2}-\frac{\eta^3}{4}.$$

This approximation is valid between 30% and 70% of total transcriptional capacity and is illustrated in Fig. 4. Then the ''potential energy'' $P(w)$ is a polynomial of fourth order and has the form shown in Fig. 5. It is seen from Fig. 5 that for not very large positive values of K two types of motion of the ''coordinate'' w exist with either maximum or minimum values w_+ and w_-, respectively.

The implicit solution (20) now takes the form

$$x=\pm\sqrt{D}\int_{w}^{w_+(K)}\frac{d\tilde{w}}{\sqrt{R_4(\tilde{w})}}, \tag{22}$$

where $R_4(w)\equiv K-P(w)$ is a polynomial of fourth order. This polynomial has two complex and two real (w_+ and w_-) roots. The integral in (22) is an elliptic one of the first kind.[48] Thus it can be inverted in terms of elliptic functions. Denot-

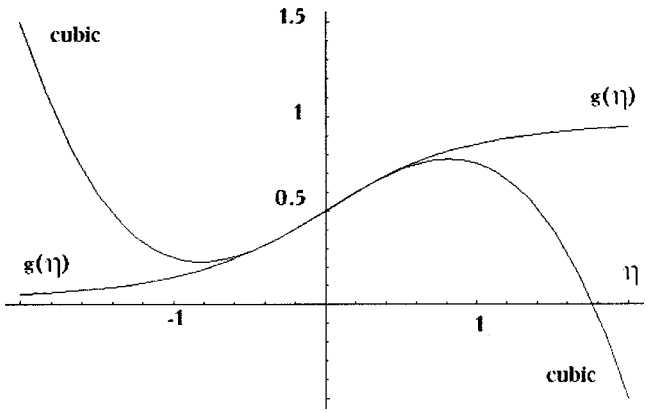

FIG. 4. Comparison between the function $g(\eta)$ and its cubic approximation.

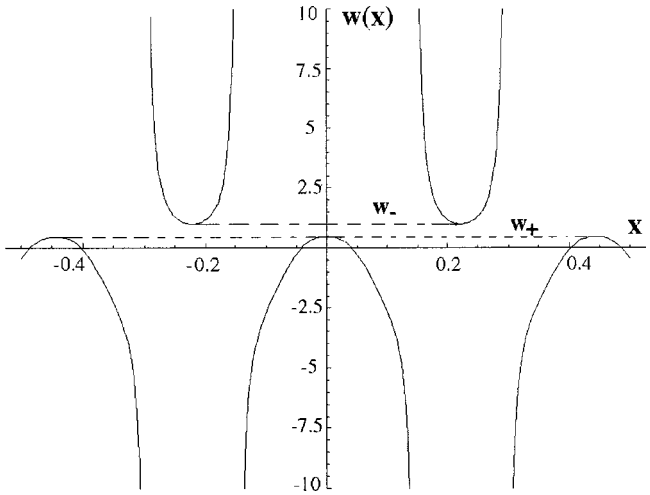

FIG. 6. Solution (23) for $D=0.03$, $T=1$, $m=1$, $\lambda=0.01$ and $K=0.6$.

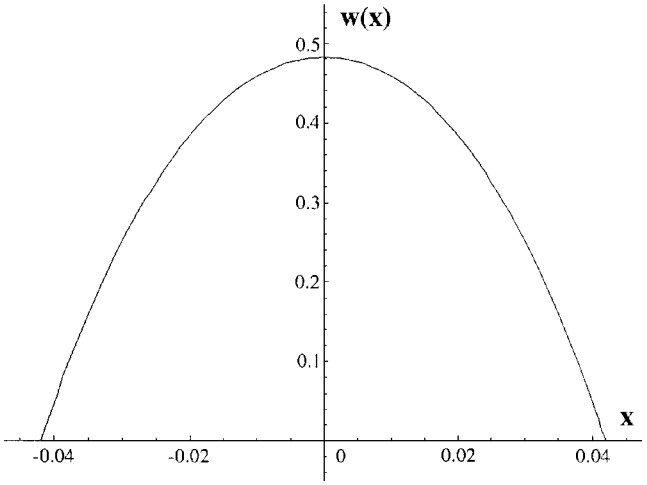

FIG. 7. The positive part of the biologically interesting branch of solution (23) for the same parameters as for Fig. 6.

ing a complex root of $R_4(w)$ and its complex conjugate by c and $\overline{c}$, respectively, and inverting the implicit solution, we get the explicit solution in the form

$$
\begin{aligned}
&w(x)=\frac{Bw_+-Aw_-+(Aw_-+Bw_+)E(x)}{(A+B)E(x)-A+B},\\
&A^2=(w_+-\mathrm{Re}\,c)^2+(\mathrm{Im}\,c)^2,\\
&B^2=(w_--\mathrm{Re}\,c)^2+(\mathrm{Im}\,c)^2,\\
&E(x)=cn\left(\sqrt{\frac{AB}{8D^2}}x,M\right),\\
&M\equiv k^2=\frac{(A+B)^2-(w_+-w_-)^2}{4AB}.
\end{aligned}
\tag{23}
$$

The graph of (23) is shown in Fig. 6, and its positive real part in Fig. 7. This appears similar to the pattern in Fig. 3 and to the *Kr* pattern in Fig. 1. This may indicate that the polynomial approximation to $g(\eta)$ preserves key features of the equations.

VI. DISCUSSION AND CONCLUSIONS

In this article we presented the initial results of an undertaking to characterize the segmentation process in *Drosophila* embryo analytically, based on the phenomenological model earlier proposed for this problem.[19,28,29,31]

We showed how to reduce the model equations to PDEs of the well-known nonlinear reaction-diffusion type. The use of this form of the model equations is attractive for analytical studies because of a number of classical results which can be applied in this case. We also discussed the dimensionless form of resulting PDEs, obtained by the introduction of characteristic time and space scales T and L. These have quite natural values: the space scale L is just the length of the A-P axis of a fly egg, while the time scale T should be equal to the 50 min time interval from the end of nuclear cleavage 13 to the onset of gastrulation, which is the biologically critical time for segment determination.

We showed how to introduce a small parameter into the model. This step allows us to separate the part of the model equations concerning the pair-rule genes from the one concerning the gap genes. Thus the latter becomes the main object under consideration, while the solution of the pair-rule system is determined by it as the series expansion in terms of the small parameter. This statement of the problem is applicable to any pair-rule stripe that forms by gap gene input, which includes six of seven *even-skipped* stripes, and many stripes formed by other pair-rule genes such as *hairy* or *runt*.

In Secs. IV and V we derived some preliminary results of application of the comparison method to the model equations for gap genes. Using the standard comparison theorem for parabolic equations, we found the system of equations for upper and lower solutions. The system for the upper solution appears to be uncoupled, while the system for the lower solution depends on the upper solution. Assuming $m_s(x) \equiv \mathrm{const}$ and using the mechanical formalism, we investigated allowed stationary upper solutions, which constitute upper bounds for the genuine solution of the gap gene system. They were described by the corresponding implicit solution and, inverting it, we obtained explicit stationary upper solution in terms of elliptic functions, when the cubic approximation to the model function $g(\cdot)$ is assumed. The graphs of these solutions show localized patterns with the borders having position described by formula (21).

In general, one cannot get stationary lower solutions $y^s = y^s(x)$ in a way similar to that used for upper solutions because of the dependence of the corresponding equations on upper solution $w^s(x)$ [see (13)]. However, using some facts noted in the proof of the Theorem in Sec. IV, we can find a lower estimate for lower solution. Indeed, because of $T^{sr} < 0$ for $s \neq r$, we have

$$
g\left(T^{ss}y^s+\sum_{r\neq s}T^{sr}w^r+m_s\right)\geqslant g\left(T^{ss}y^s+\sum_{r\neq s}T^{sr}W^r+m_s\right),
$$

where $W^r=\max_{x\in\mathbf{R}}w^r(x)$. Hence, $y^s(x,t)\geqslant z^s(x,t)$, where z^s is a solution to

$$
\begin{aligned}
&z^s_t=D_sz^s_{xx}+g\left(T^{ss}z^s+\sum_{r\neq s}T^{sr}W^r+m_s\right)-\lambda_sz^s,\\
&\qquad s=1,\ldots,N.
\end{aligned}
$$

After the solution $w^s(x)$ was obtained in the way described earlier, we can find stationary solution to the last equation in a similar way. Finally, we conclude that any solution v^s to the model equations obeys inequality $z^s\leqslant v^s\leqslant w^s$ and lies in this interval.

Although developed in the context of a very specific problem, many of the techniques used here may have wide applicability. The maximum principle applied in Sec. IV to the reaction-diffusion system is valid for a wide range of PDEs of different types.[41] In particular, this theorem is valid for systems of quasi-linear PDEs which contain not only the second derivative in space, as is the case in reaction-diffusion systems (describing the diffusive coupling between cells), but also a nonlinear term containing the first spatial derivative.

The maximum principle is formulated both for classical (smooth) and weak (discontinuous) solutions to those PDEs. Thus, various features of spatial discontinuity can be modeled using mathematical formalism of weak solutions. All the solutions derived in Sec. V are stationary, and cannot be used for modeling any patterns oscillating in time. At the same time, solutions similar to (23) can be obtained for more complicated stationary equations. Exact stationary solutions in terms of elliptic functions to nonlinear reaction-diffusion equations with polynomial both diffusive and reaction terms were obtained in Refs. 47 and 49.

The use of elliptic functions is both important and natural. The reason for this is that, depending on their own parameters, these functions may describe analytically a wide variety of behavior of solutions, including localized and periodic patterns, and even sharp spatial discontinuities, which can be done by means of the Weierstrass elliptic functions.

Nevertheless, the analytical results obtained in the article must be regarded as preliminary because the upper solutions derived in Secs. IV and V provide the analytical limits to a genuine solution to the problem.

For this reason they do not relate directly to the patterns observed in experiments. However, we mentioned in the beginning of Sec. IV that these upper and lower solutions may provide the asymptotic limits of the genuine solution at large time scales. A rigorous mathematical proof of this fact needs further consideration. Such studies may reveal a value of the constant K in the implicit solution (20). Some values of this constant were given for calculations in order to find general functional features of numerical solution to (20).

On the other hand, the equation (17) derived for the upper solutions may describe a gene system consisting of one gene and, therefore, may be of inherent interest itself. For example, one can imagine modeling the placement of gap domains by a set of solutions to (17) with a very weak coupling that is slowly turned up from zero. Whether such a treatment has biological utility must be checked carefully as both the biological system and its dynamical representation become better characterized.

We believe that the work presented here establishes the feasibility of an analytic approach to the segmentation problem, but much remains to be done. A central objective is to numerically solve the PDEs with biological parameters derived from phenomenological studies of experimental data. This will allow us to assess which features of the biology are and are not preserved in the analytical approach. With these tools in hand, we will be in position to exploit the results given here to obtain deeper insight into both developmental biology and nonlinear mathematics.

ACKNOWLEDGMENTS

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