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Patterning by genetic networks and modular principle

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Abstract. We consider here the morphogenesis (pattern formation) problem for some genetic network models. First, we show that any given spatio-temporal pattern can be generated by a genetic network involving a sufficiently large number of genes. Moreover, patterning process can be performed by an effective algorithm. We also show that Turing's or Meinhardt's type reaction-diffusion models can be approximated by genetic networks.

These results exploit the fundamental fact that the genes form functional units and are organised in blocks (modular principle). Due to this modular organisation, the genes always are capable to construct any new patterns and even any time sequences of new patterns from old patterns. Computer simulations illustrate analytical results.

1. Introduction

In this paper we consider pattern formation problem in the developmental biology. Mathematical approaches to this problem start with the seminal work by A. M. Turing [36] devoted to pattern formation from a spatially uniform state. Turing's model is a system of two reaction-diffusion equations. After [36], similar phenomenological models were studied by numerous works (see [19,23] for the review). Computer simulations based on this mathematical approach give patterns similar to really observed ones [19]. However, there is no direct evidence of Turing's patterning in any developing organism ([42], p.347). The mathematical models are often selected to be mathematically tractable and they do not take into account actual experimental genetic information.

Moreover, within the framework of the Turing-Meinhardt approach some important theoretical questions are left open. For example, whether there exist "universal" mathematical models and patterning algorithms that allow to obtain any, even very complicated, patterns. In fact, a difficulty in using of simple reaction-diffusion models with polynomial or rational nonlinearities is that we have no patterning algorithms. To obtain a given pattern, first we choose a reasonable model (often using intuitive ideas) and later we adjust coefficients or nonlinear terms by

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numerical experiments (an excellent example of this approach is given by the book of H. Meinhardt on pigmentation in shells [20]).

To overcome this algorithmic difficulty we use genetic circuit models. We are going to show that they can serve as "universal models", which are capable to generate any spatio-temporal patterns by algorithms. The gene circuits were proposed and investigated by many works [7, 10, 22, 26, 30, 31, 33, 35] (for the review see [33]) in order to use available genetic information, to take into account some fundamental properties of gene interaction and understand mechanisms of cell gene regulation.

In this paper we investigate the model from [22, 26], which is similar to the well studied Hopfield neural networks. This model describes activation or depression of one gene by another and have the following form:

$$\frac{\partial y_i}{\partial t} = R_i \sigma \left(\sum_{j=1}^m K_{ij} y_j - \theta_i(x) - \eta_i \right) - \lambda_i y_i + d_i \Delta y_i, \quad (1.1)$$

where m is the number of genes included in the circuit, $y_i(x, t)$ are the concentration of the i -th protein, λ_i are the protein decay rates, R_i are some positive coefficients and d_i are the protein diffusion coefficients. We consider (1.1) in some bounded domain Ω with a boundary $\partial\Omega$.

The real number K_{ij} measures the influence of the j -th gene on the i -th one. The assumption that gene interactions can be expressed by a single real number per pair of genes is a simplification excluding complicated interactions between three, four and more genes. Clearly such interactions are possible, however in this case the problem becomes mathematically much more complicated. Since the pair interaction is capable to produce any patterns, it seems reasonable to restrict our consideration only to such interaction.

The parameters η_i are activation thresholds and σ is a monotone function satisfying the following assumptions

$$\sigma \in C^\infty(\mathbf{R}), \quad \lim_{z \rightarrow -\infty} \sigma(z) = 0, \quad \lim_{z \rightarrow +\infty} \sigma(z) = 1, \quad (1.2)$$

$$\left| \frac{d\sigma}{dz} \right| < C \exp(-c|z|), \quad \sigma'(0) = 1. \quad (1.3)$$

The well known example is $\sigma(z) = (1 + \tanh z)/2$.

The functions $\theta_i(x)$ are other activation thresholds depending on x . They can be interpreted as densities of proteins associated with the maternal genes.

This model takes into account only three fundamental processes: (a) decay of gene products (the term $-\lambda_i y_i$); (b) exchange of gene products between cells (the term with Δ) and (c) gene regulation and protein synthesis. Notice that this model of gene circuit can be considered as a Hopfield's neural network [14] with thresholds depending on x and where diffusion is taken into account. The Hopfield system is the first model of so-called attractor neural network, both fundamental and simple. Analytical methods for the Hopfield models were developed in [9, 37–39].

Let us fix a function σ satisfying (1.2), (1.3) and functions θ_i . On the contrary, we consider $m, \mathbf{K}, \lambda_i, d_i, R_i$ and η_i as parameters to be adjusted. We denote the set of these parameters by \mathbf{P} :

$$\mathbf{P} = \{m, \mathbf{K}, \eta, \lambda, d, R\}. \quad (1.4)$$

Model (1.1) allows to use data on gene regulation (see [26], where the least square approximation of experimental data and simulated annealing were used to determine the values of the parameters \mathbf{P}).

In order to study (1.1), many previous works used numerical simulations. For example, the work [31] is devoted to the segmentation in *Drosophila*, in [30] the authors analyse complex patterns occurring under a random choice of the coefficients K_{ij} .

Let us formulate now mathematically our main problem.

Problem 1.1 (Universal pattern generation problem for gene circuit model).

Let $T_0 > 0$ and $T_0 < T$. Given a function $z(x, t), x \in \Omega, t \in [0, T]$ and a positive number ϵ , to find the parameters \mathbf{P} such that the solution of system (1.1) with initial conditions $y_j = 0$ satisfies

$$\sup_{x,t} |z(x, t) - y_1(x, t)| < \epsilon, \quad x \in \Omega, \quad t \in [T_0, T]. \quad (1.5)$$

Let us consider a biological interpretation of this mathematical formulation. We assume that the cell states depend on expression of some genes; we can thus identify observed patterns of cell differentiation with gene expression patterns. Let us consider these expression patterns as continuous functions $z(x, t)$, where $x \in \Omega, t \in [0, T]$ and $T > 0$. For example, we can assume that $z \in [0, 1]$ and if z is close to 1, the gene is expressed otherwise the gene is not expressed.

We consider gene circuits including a single "output" (structural) gene $y_1 = Y_{out}$ and m_1 "hidden" (regulating) genes. The output gene can change the cell states and therefore can predetermine an output pattern z . The hidden genes do not influence directly the cell states, they are involved only in an internal cellular gene regulation.

Notice that given pattern z can depend on time t . This fact is important since real biological structures are usually dynamical. For stationary patterns z (independent of time) the solution of pattern problem is simple and follows from the well known results on neural networks (see Sect. 2).

The main results can be described as follows.

A) We show that, roughly speaking, any pattern formation process based on a reaction-diffusion model can be performed as well by a genetic network, with a sufficiently large number of the genes. For each reaction-diffusion model one can find an approximating gene network, with the almost same pattern formation capacity. This result justifies, to some extent, Turing-Meinhardt's models from a genetic point of view. Indeed, these models can be considered as gene circuits.

B) The second result asserts that, under natural conditions on maternal genes densities θ_i , the universal pattern generation problem always has a solution. Moreover, there is a constructive and numerically effective algorithm that allows us to find a circuit generating a given pattern.

Notice that this result is also valid in the absence of diffusion. Indeed, in our approach, spatial signalling is not provided by the diffusion process, but by space-depending thresholds θ_i .

Our conditions on maternal gene concentration are necessary and sufficient: if they do not hold, it is not possible to approximate any patterns within an arbitrarily small error. On the contrary, if they are valid, it is possible. If we deal with one-dimensional case (for example, we consider a differentiation along anterior-posterior axis), then our conditions mean existence of a morphogene gradient along this axis. For *Drosophila* this morphogene is *bicoid*. So, we show that a simple bicoid gradient is capable to produce any chain of complicated time transformations leading to complex spatial one-dimensional patterns. This result is in an agreement with biological observations [1,42]. To create any two-dimensional patterns, we need at least two independent gradients, along anterior-posterior and dorso-ventral axes.

C) We show that the modular organisation and sigmoidal interaction are effective tools to form complex hierarchical patterns.

Indeed, we show that new, more refined structures, can be obtained by using of previous old structures. Also we illustrate that existence of an old structure make it easier to produce a new complex one. This property might help to understand the usual idea "morphogenesis repeats evolution" [27], see Sect. 4 and 6.

The paper is organised as follows. In the next section we explain main biological and mathematical ideas beyond these results, in particular, we find connections with multilayered network theory and the Hopfield model. In Sect. 3 we describe the connection between the reaction-diffusion models and gene circuit systems. In Sect. 4 we formulate mathematically pattern formation problem and describe main ideas of patterning algorithms. Sect. 5 presents computer simulations illustrating our analytical results. In particular, as an illustration, we approximate numerically, by gene circuit, a reaction-diffusion system for pigmentation of sea shells proposed by [20]. Sect. 6 contains a discussion and concluding remarks.

All complicated and tedious mathematical details can be found in the Appendix.

2. Main mathematical instruments

In this section we remind main ideas and results of neural network theory important below. To simplify our statement, we omit some non-essential mathematical details (for details, see [38]).

2.1. Multilayered neural networks

The neural networks usually consist of a large number of neurons. Each neuron is connected to other neurons by directed links with their associated weights. After absorbing the inputs, each neuron produces its activation as an output signal to other neurons. Each neuron sends a single signal to several neurons at the time. Typical problems which may be solved by such nets are pattern classification, storing patterns and optimal control problems (see [8]).

The simplest example is a single-layer network having one layer of weights. The network consists of n input neurons X_j , $j = 1, \dots, n$ and an output neuron Y . Each X_j is connected to Y with an associated weight w_j . The output Y is given by

$$Y = \sigma\left(\sum_{j=1}^n w_j X_j - h\right), \quad (2.1)$$

where h is a threshold and σ is a strictly monotone function satisfying (1.2) and (1.3).

Network (2.1) can solve only simple classification problems. More powerful, a multilayer neural network with p layers consists of one layer of input neurons, an output neuron and $(p - 1)$ hidden layers. For $p = 2$, the corresponding equations can be written for instance as

$$Y = \sigma\left(\sum_{k=1}^m B_k z_k - h\right), \quad (2.2)$$

$$z_k = \sigma\left(\sum_{j=1}^n A_{kj} q_j - \eta_k\right), \quad (2.3)$$

where q_j are states of the input neurons. The remarkable property of this network playing the key role in this paper is that any input-output map of the form $(q_1, q_2, \dots, q_n) \rightarrow F(q_1, q_2, \dots, q_n)$, where F is a continuous function, can be approximated by a network (2.2)–(2.3) with a sufficiently large m and appropriate weights A_{kj} and B_k .

We shall use below, for brevity, notation

$$\mathbf{A}_j q = \sum_{l=1}^m A_{jl} q_l. \quad (2.4)$$

Since σ is monotone, the assertion that network (2.2)–(2.3) approximates any output, can be reformulated as follows: by the quantity $\Psi = \sum_{k=1}^m B_k z_k$ we can approximate any function, within an arbitrarily small error. This fact results from the following well known assertion (see, for example, the works [3, 9, 15, 38]).

Let us consider function $\Psi(q, \mathbf{A}, B, \eta)$ of vector argument $q = (q_1, \dots, q_m) \in \mathbf{R}^m$ depending on the following parameters: the number $m > 1$, an $m \times n$ matrix \mathbf{A} , and the vectors B and $\eta \in \mathbf{R}^m$. This function is defined by

$$\Psi(q, \mathbf{A}, B, m, \eta) = \sum_{k=1}^m B_k z_k = \sum_{k=1}^m B_k \sigma(\mathbf{A}_k q - \eta_k). \quad (2.5)$$

We consider this function in a bounded ball Ω_R , consisting of vectors q such that $|q|^2 = q_1^2 + \dots + q_m^2 < R^2$.

Lemma 2.1 (Approximation Lemma). *If σ is monotone and satisfies conditions (1.2)–(1.3), then for any continuous function $Q(q)$ defined in the ball Ω_R and for any positive number ε , there exist a number $m \geq n$, matrices \mathbf{A} and m -vector η and B such that*

$$|Q(q) - \Psi(q, \mathbf{A}, B, m, \eta)| < \varepsilon, \quad q \in \Omega_R. \quad (2.6)$$

In other words, given pattern Q and $\varepsilon > 0$, we can always find weights \mathbf{A} and B such that the output of network (2.2)–(2.3) approximates this pattern, up to precision ε .

Approximation (2.6) can be obtained by the multilayered network theory (see [9, 13, 15]) or by an application of wavelet type extensions [38]. For wavelet theory see [21]. It is well known that the approximations by (2.5) are numerically effective as the dimension n of the vector q increases. We know constructive algorithms allowing to adjust the parameters \mathbf{A} , B , m , θ (see [3] and references therein).

Notice that the number m of the coefficients B depends polynomially on "complexity" of the pattern Q and the precision ε . More "complex" the pattern, greater m . This complexity can be measured by the integral [3]

$$\text{Comp}(Q) = \int |\omega| |\hat{Q}(\omega)| d\omega, \quad (2.7)$$

where $\hat{Q}(\omega)$ is the Fourier transform of the function Q . This means that more oscillating functions (patterns) have larger complexities.

2.2. Large time behaviour of the Hopfield networks

The Hopfield network [14] is a system of coupled oscillators defined by the differential equations

$$\frac{dy_i}{dt} = R_i \sigma \left(\sum_{j=1}^m K_{ij} y_j - \eta_i \right) - y_i. \quad (2.8)$$

Here y_i are neuron states depending on time, K_{ij} is a matrix determining a neuron interaction (synaptic matrix), η_i are thresholds. Genetic model (1.1) can be considered as a generalisation of the Hopfield system such that the neuron states and the thresholds depend on a space variable x and the diffusion is taken into account.

We are going to apply some methods developed to investigate attractors of the Hopfield neural networks. We recall that dynamics (2.8) is dissipative and thus an attractor always exists (on the attractor theory see publications [4, 11, 16, 18, 28, 34] among many others).

Dynamics of (2.8) sharply depends on the synaptic matrix \mathbf{K} . If the matrix \mathbf{K} is symmetric, the attractor usually consists of many equilibria. Such stable large time behaviour can be applied to the pattern recognition and associative memory problems.

The large time behaviour of y can become very complex if \mathbf{K} is non-symmetric. For instance, depending on \mathbf{K} , neuron states can form complicated coherent

structures that evolve periodically or even chaotically in time. These coherent patterns can be described as follows.

Any (symmetrical or non-symmetrical) $m \times m$ matrix \mathbf{K} of rank n can be represented as a product of two matrices \mathbf{A} and \mathbf{B} , i.e.,

$$\mathbf{K} = \mathbf{A}\mathbf{B}, \quad (2.9)$$

where \mathbf{A} has size $m \times n$ and \mathbf{B} has size $n \times m$,

Let us introduce the new variables

$$q_l(t) = \sum_{j=1}^m B_{lj}y_j(t) = \mathbf{B}_l y(t), \quad (2.10)$$

where $l = 1, 2, \dots, n$.

The dynamical equations for q have the following form

$$\frac{dq_l}{dt} = -q_l + \Psi_l(q, \mathbf{A}, \mathbf{B}, m, \eta), \quad (2.11)$$

where Ψ_l are defined by equations similar to (2.5). Time evolution of the new variables q_l controls the dynamics of all the neuron states y_i . Indeed, we have

$$\frac{dy_i}{dt} = -y_i + \sigma(\mathbf{A}_i q - \eta_i). \quad (2.12)$$

The functions $y(t)$ can be expressed through $q(t)$ in a simple way by linear equations (2.12).

Below we will use new control parameters \mathbf{P} , we denote $\mathbf{P} = \{n, m, \mathbf{A}, \mathbf{B}, \eta\}$ fixing $R_i = 1, \lambda_i = 1, d_i = 0$.

Let us formulate now the following assertion (analogous to the results of [38, 39]) describing the complexity of time behaviour of the circuits.

Lemma 2.2. *By the network parameters \mathbf{P} , dynamics (2.11) can be specified within an arbitrarily small error. More precisely, for any n , any given continuous functions $Q_l(q)$ defined on bounded domain Ω , and for any $\epsilon > 0$, we can choose parameters \mathbf{P} such that*

$$|Q_l + \lambda q_l - \Psi_l(q, \mathbf{A}, \mathbf{B}, m, \eta)| < \epsilon, \quad q \in \Omega, \quad l = 1, 2, \dots, n. \quad (2.13)$$

Therefore, any structurally stable dynamics can be generated by system (2.8).

This result shows that the variables q_j can exhibit complicated dynamics, periodic or chaotic. In particular, any kind of stable chaos can occur in the dynamics of our systems, for example, the Smale horseshoes, Anosov flows, the Ruelle-Takens-Newhouse chaos, etc. [2, 24, 25, 29, 32, 41].

In general, greater the neuron number m , more complex this time dynamics. Thus, the neuron states y_j also can demonstrate a complicated dynamics however, if $n \ll m$, all the m neuron states are strongly correlated since they can be defined through a relatively small number of the hidden variables.

For a proof of Lemma 2.2 see [38].

In the next section we shall show that the gene networks can simulate, in a sense, any reaction-diffusion systems.

Notice that some fundamental and simple biological principles are beyond the mathematics. The genes are organised in blocks. The local cell differentiation and growth processes are governed by a collective action of these blocks.

3. Approximation of reaction-diffusion systems by gene networks

We consider, for simplicity, the case of two component reaction-diffusion systems

$$\frac{\partial u}{\partial t} = d_1 \Delta u + f(u, v), \quad (3.1)$$

$$\frac{\partial v}{\partial t} = d_2 \Delta v + g(u, v). \quad (3.2)$$

The phenomenological approach based on (3.1)–(3.2) gives excellent results for some pattern formation problems (for example such as shell pigmentation [20]), where nonlinearities can have the following typical form [20]

$$f = f_M(u, v) = \alpha v \left(\frac{u^2}{1 + \alpha_1 u^2} + \beta_1 \right) - \kappa_1 u, \quad (3.3)$$

$$g = g_M(u, v) = \beta_2 - \alpha v \left(\frac{u^2}{1 + \alpha_1 u^2} + \beta_1 \right) - \kappa_2 v. \quad (3.4)$$

We suppose here that all constants $\alpha, \beta_i, \alpha_1, \kappa_k$ are positive.

In these equations, u and v are unknown functions of the space variables $x = (x_1, x_2, x_3)$ defined in a bounded domain Ω .

System (3.1)–(3.2) must be complemented by standard initial and boundary conditions.

Suppose the system of equations that governs patterning is two-component system (3.1)–(3.2), where nonlinearities f and g are continuous functions. The general multi-component case can be studied in a similar way. Assume solutions of (3.1)–(3.2) remain globally bounded, i.e., for some positive constants C_i we have the estimate

$$|u(x, t)| < C_1, \quad |v(x, t)| < C_2, \quad (3.5)$$

for all $t > 0$, if it holds for $t = 0$. Let us define the domain D_{C_1, C_2} as follows:

$$D_{C_1, C_2} = \{(u, v) : 0 \leq u < C_1, 0 \leq v < C_2\}. \quad (3.6)$$

We suppose that initial condition belongs to D_{C_1, C_2} for each x .

Our goal is to show that, for a given reaction-diffusion system (3.1)–(3.2) we can always find an “ ϵ -equivalent” circuit (1.1). Namely, for this equivalent circuit there exists a smooth map $b(y) : (y_1, y_2, \dots, y_m) \rightarrow (u, v)$ transforming the gene concentrations to the reagent concentrations and such that time evolution of u, v is defined by a new reaction-diffusion system with nonlinearities $\Phi_1(u, v), \Phi_2(u, v)$, ϵ -close to nonlinearities $f(u, v), g(u, v)$. Roughly speaking we can say that any reaction-diffusion system can be realized as a gene circuit.

To this end, we use *Modular Principle*. Let us consider a system (1.1) having a special block structure. Namely, we assume that there exist two kinds of the genes. We denote these groups of the genes by y and z , where vector $y(x, t)$ contains m_1 components and $z(x, t)$ contains m_2 components. Naturally, $m = m_1 + m_2$. We consider system (1.1) of the special form

$$\frac{\partial y_i}{\partial t} = \sigma(\mathbf{K}_i^{yy}y + \mathbf{K}_i^{yz}z - \theta_i) + d_1 \Delta y_i, \quad (3.7)$$

$$\frac{\partial z_i}{\partial t} = \sigma(\mathbf{K}_i^{zy}y + \mathbf{K}_i^{zz}z - \bar{\theta}_i) + d_2 \Delta z_i. \quad (3.8)$$

Here we use notation (2.4) and matrices \mathbf{K}^{yy} , \mathbf{K}^{zz} , \mathbf{K}^{zy} and \mathbf{K}^{yz} describe interactions between different groups of the genes.

In general, these interactions are not symmetric, i.e., \mathbf{K}^{yz} is not equal to the transpose of \mathbf{K}^{zy} .

The coefficients d_1 and d_2 coincide with the diffusion coefficients in equations (3.1) and (3.2).

We choose the entries of the matrices \mathbf{K}^{yy} , \mathbf{K}^{zz} , \mathbf{K}^{zy} and \mathbf{K}^{yz} as follows:

$$K_{ij}^{yy} = a_i b_j, \quad K_{ij}^{yz} = \gamma_i \bar{b}_j, \quad (3.9)$$

and

$$K_{ij}^{zy} = \bar{\gamma}_i b_j, \quad K_{ij}^{zz} = \bar{a}_i \bar{b}_j, \quad (3.10)$$

where $a_i, \bar{a}_i, \gamma_i, \bar{\gamma}_i, b_i, \bar{b}_i$ are unknown coefficients.

Let us define "collective variables"

$$u = \sum_{i=1}^{m_1} b_i y_i, \quad v = \sum_{i=1}^{m_2} \bar{b}_i z_i. \quad (3.11)$$

After some calculations (see the Appendix, part 1) we obtain

$$\frac{\partial u}{\partial t} = d_1 \Delta u + \Phi_1(u, v), \quad (3.12)$$

and

$$\frac{\partial v}{\partial t} = d_2 \Delta v + \Phi_2(u, v), \quad (3.13)$$

where

$$\Phi_1(u, v) = \sum_{i=1}^{m_1} b_i \sigma(a_i u + \gamma_i v - \theta_i), \quad (3.14)$$

$$\Phi_2(u, v) = \sum_{i=1}^{m_2} \bar{b}_i \sigma(\bar{a}_i v + \bar{\gamma}_i u - \bar{\theta}_i). \quad (3.15)$$

Applying Lemma 2.1, we notice that for any $\epsilon > 0$ there exist numbers m_1, m_2 , vectors $a, b, \bar{a}, \bar{b}, \gamma, \bar{\gamma}$ and $\theta, \bar{\theta}$ such that

$$|\Phi_1(u, v) - f(u, v)| < \epsilon, \quad |\Phi_2(u, v) - g(u, v)| < \epsilon \quad (3.16)$$

for all u, v from some bounded domain.

This proves the main result of this section:

Proposition 3.1 (Realization of reaction-diffusion systems by circuits).

Consider problem (3.1)–(3.2) whose solutions remain in a domain D_{C_1, C_2} .

Then, if functions f, g are continuous, for any $\epsilon > 0$, there exist such a system (1.1) with a sufficiently large number m and coefficients $r = (r_1, r_2, \dots, r_m)$ and $s = (s_1, s_2, \dots, s_m)$ such that the functions

$$u = ry = \sum_{i=1}^m r_i y_i, \quad v = sy = \sum_{i=1}^m s_i y_i \quad (3.17)$$

satisfy the system

$$u_t = d_1 \Delta u + \tilde{f}(u, v) \quad (3.18)$$

$$v_t = d_2 \Delta v + \tilde{g}(u, v), \quad (3.19)$$

where

$$|f(u, v) - \tilde{f}(u, v)| < \epsilon, \quad (3.20)$$

$$|g(u, v) - \tilde{g}(u, v)| < \epsilon \quad (3.21)$$

for $(u, v) \in D_{C_1, C_2}$.

Therefore, any reaction-diffusion patterning processes on a bounded time interval $[0, T]$ can be performed as well by genetic networks. In other words, the pattern capacity of the gene circuits on bounded time intervals are not less than the pattern capacity of reaction-diffusion systems.

To conclude this section, let us notice that an inverse problem, namely an approximation of a neural network by a reaction-diffusion system has been considered in [6] and [38].

4. Programming of spatio-temporal patterns by gene circuit models

In this section we state an analytical algorithm resolving the following problem: given spatio-temporal pattern, to find a gene circuit generating this pattern. We show that this problem can be solved even without diffusion ($d_i = 0$). In our approach the space signalling is provided by space-depending activation thresholds. It is important from the biological point of view since the molecular transport is often performed by non-diffusional mechanisms [1]. For time discrete networks, similar results were obtained in [40].

Beside multilayered network theory (Lemma 2.1) we also use the following result.

Theorem 4.1 (Superposition Theorem). *Let us consider a family \mathcal{F} of gene circuits (1.1) with the parameters $\mathbf{P}^1, \mathbf{P}^2, \dots, \mathbf{P}^p$, where the functions θ_i are fixed and identical for all the circuits. Assume these networks generate the output patterns $Y^1 = y_1^1(x, t), Y^2 = y_1^2(x, t), \dots, Y^p = y_1^p(x, t)$.*

Then, for any $\epsilon > 0$ and for any continuous positive function $F(u_1, \dots, u_p)$, there is a network (1.1) generating an output pattern $y_1 = Y$ such that

$$|F(Y^1(x, t), Y^2(x, t), \dots, Y^p(x, t)) - Y(x, t)| < \epsilon. \quad (4.1)$$

This result can be interpreted as a *Superposition Principle*. If given circuits are capable to produce patterns Y^1, Y^2, \dots, Y^p , for any function $F(u_1, \dots, u_p)$ there is a new circuit, which can approximate the pattern z of the form $z = F(Y^1, \dots, Y^p)$, in other words, "superposition by F " of these previous patterns. This result also has interesting biological corollaries; we discuss it in Sect. 6.

Let us describe first the outline of the proof. The proof is based on *Modular Principle*. We suppose that an unknown interaction matrix \mathbf{K} of the network can be decomposed in blocks. Some blocks contain the known matrices \mathbf{K}^s corresponding to s -th network of given network family. An additional block determines an interaction between new genes and the genes involved in the networks of the family \mathcal{F} . This structure allows us to apply the approximation results of the multilayered network theory [3, 5, 13, 15] (see Lemma 2.1). This assumption about the structure of the matrix \mathbf{K} also is in agreement with contemporary ideas in molecular biology [12, 43]. The proof (which, by *Modular Principle*, is quite straightforward) can be found in the Appendix.

Since the basic element of the proof of Superposition Principle is Lemma 2.1, and the proof of this Lemma gives us an algorithm, therefore we obtain a complicated but quite constructive algorithm resolving the patterning problem. Moreover, we can estimate the number of the genes $N(z)$ involved in patterning process as a function of the pattern complexity defined by (2.7). Namely, using the results of the work [3], we find that $N(z)$ depends polynomially on $\text{Comp}(z|u)$, where $\text{Comp}(z|u)$ is a conditional complexity of z respectively given patterns u . To explain this relation and its biological meaning, let us consider a simple example.

Suppose our problem is to construct a periodic one-dimensional pattern $z(x) = \sin kx$, where k is a large number. Our target pattern therefore is sharply oscillating. Moreover, we have no stored (old) patterns u_i and thus $\text{Comp}(z|u) = \text{Comp}(z)$ is proportional to k . In this case, to resolve the pattern approximation problem, the network have to involve many genes.

Assume now that there are old patterns u_i and, in particular, the patterns of the form $\sin k_0x, \cos k_0x$, where $k_0 < k$ but $k_0 \gg 1$. In this case the function z can be expressed through u_i as a polynomial of degree $P = k/k_0$. Thus $\text{Comp}(z|u)$ is much less $\text{Comp}(z)$ for large k_0 and k .

Roughly speaking, a complex target pattern may be simple respectively to another complex pattern. We discuss a biological interpretation of this property in Sect. 6.

Using Theorem 4.1, we can resolve now the pattern programming problem. Suppose the functions $\theta_i(x)$ possess the following property. They can be considered as "coordinates" in the domain Ω , i.e., there exist continuous functions g_i such that

$$x_i = g_i(\theta_1(x), \theta_2(x), \dots, \theta_m(x)), \quad x \in \Omega, \quad i = 1, \dots, n. \quad (4.2)$$

This condition holds, for example, if $m = n$ and for each i , the function $\theta_i(x)$ is a strictly monotone function of only one variable x_i . A biological example can be given by the distribution of maternal genes in *Drosophila* [42].

Let us prove first an auxiliary mathematical result.

Lemma 4.1. *Suppose that condition (4.2) holds. Then any continuous function $F(x_1, \dots, x_n, t)$ can be represented as a function of $n + 1$ variables*

$$\bar{Y}_1 = \sigma(\theta_1(x))(1 - \exp(-\gamma t)), \quad (4.3)$$

$$Y_i = \sigma(\theta_i(x))(1 - \exp(-\kappa t)), \quad (4.4)$$

for $i = 1, \dots, n$, where κ and γ are two different positive constants.

Proof. To prove this lemma, let us observe that

$$\log Y_1 - \log \bar{Y}_1 = f(t), \quad (4.5)$$

where $f(t)$ is a strictly monotone function of t . Therefore, t can be written as a function of Y_1 and \bar{Y}_1 . Then any $\theta_i(x)$ can be presented as a function of Y_i , Y_1 and \bar{Y}_1 . Using (4.2), one obtains that each x_i is a function of the variables Y_s , $s = 1, 2, \dots, n$ and \bar{Y}_1 . The lemma is proved. \square

Let us formulate the main result of this work. This result means that any patterning process can be realized by a gene circuit.

Theorem 4.2. *Suppose that condition (4.2) holds. Then for any continuous positive $z(x, t)$, $x \in \Omega$, $t \in [0, T]$, any positive $T_0 < T$ and ϵ there is a system (1.1) such that the solution of this system satisfies the estimate*

$$|z(x, t) - y_1(x, t)| < \epsilon \quad x \in \Omega, \quad t \in [T_0, T]. \quad (4.6)$$

Before start to prove Theorem, let us notice that in the case $d_i = 0$ (diffusion coefficients vanish) condition (4.2) is actually necessary in order to resolve any patterning problem. In other words, if it does not hold, there is a pattern, which cannot be ϵ -approximated for any ϵ . Indeed, if $d_i = 0$, solutions of (1.1) are vector function y of variables t and θ_i . If (4.2) does not hold, for some s the pattern $y_1(x, t) = x_s$ cannot be ϵ -approximated for any ϵ . For $d_i \neq 0$ condition (4.2) can be replaced by a weaker one but we will not consider this question here.

Proof. Theorem 4.2 results from Lemma 4.1 and Theorem 4.1. We take a network generating \bar{Y}_1 , Y_1 , Y_2, \dots, Y_n . This network has the following structure:

$$\frac{\partial \bar{y}_1}{\partial t} = -\gamma \bar{y}_1 + \gamma \sigma(\theta_1), \quad (4.7)$$

$$\frac{\partial y_i}{\partial t} = -\kappa y_i + \kappa \sigma(\theta_i), \quad (4.8)$$

for $i = 1, \dots, n$. We observe now that $y_i = Y_i(x, t)$ and $\bar{y}_1 = \bar{Y}_1(x, t)$. This completes the proof. \square

5. Computer simulations

We first illustrate the results of Sect. 3: we approximate the reaction-diffusion system (3.1)–(3.4) by a gene network. For this we approximate functions (3.3) and (3.4) by sigmoidal functions in order to satisfy inequalities (3.16).

This is a problem of nonlinear approximation since functions Φ_1 and Φ_2 depend linearly on b_i and \bar{b}_i but nonlinearly on a_i, γ_i, θ_i and $\bar{a}_i, \bar{\gamma}_i, \bar{\theta}_i$. Coefficients b_i and \bar{b}_i can be calculated by the classical least square method, but other coefficients have to be determined in a proper way. For instance, we could choose these coefficients randomly and select the best values (or a satisfying value), however this is usually too long when the search space is large. Here this random method cannot be used due to the fact that the functions (3.3) and (3.4) depend on two variables. If we approximate a function of a single variable, this simple random method can be useful and we apply it below.

To make this nonlinear approximation, we use an iterative approach proposed by Jones [17] (see also Barron [3]). Jones' result is an iterative version of Approximation Lemma 2.1: under the conditions of this lemma one can find a sequence of approximating functions $(\Psi(q, A, B, \eta, m))_{m \in \mathbb{N}}$ (denoted $(\Psi_m)_{m \in \mathbb{N}}$ for brevity) satisfying

$$|Q(q) - \Psi_m|^2 \leq C/m, \quad (5.1)$$

where C is a constant depending on Q . As already mentioned in Sect. 2, Barron [3] has related C to the Fourier transform of Q . For more oscillating functions Q , the constant C is greater. This constant can be considered as a measure of complexity of Q .

Jones' sequence is defined as follows: $\Psi_1 = B_1 \sigma(A_1 q - \eta_1)$, where B_1, A_1, η_1 give an almost minimal value of $|Q(q) - \Psi_1|$. Then, for any $m \geq 2$, $\Psi_m = \alpha_m \Psi_{m-1} + B_m \sigma(A_m q - \eta_m)$, where α_m, B_m, A_m and η_m give an almost minimal value of $|Q(q) - \Psi_m|$. Barron [3] formulates precise conditions on these almost minimal values in order to obtain equation (3.16), but we do not use these conditions here. The important point we use is that optimising only one sigmoidal function each time, Jones' sequence is able to achieve $O(1/m)$ approximation. This permits to avoid a global optimisation of all the coefficients involved nonlinearly. The linearly involved coefficients α_m and B_m can be computed by the least square method and the nonlinearly involved coefficients A_m (which are two-dimensional like q) and η_m can be determined by a random method. Such approach allows us to approximate functions (3.3) and (3.4). The numerical parameters were $\alpha = 8, \alpha_1 = 1, \beta_1 = 0, \kappa_1 = 2, \beta_2 = 1, \kappa_2 = 0$. In this case system (3.1)–(3.4) with Neumann boundary conditions has an homogeneous equilibrium solution $u_0 = \beta_2/\kappa_1, v_0 = (\kappa_1^2 + \alpha_1 \beta_2^2)/(\alpha \beta_2)$. On the segment $[0, L]$ with $L = 60$, and with $d_u = 1, d_v = 50$, this equilibrium is unstable with respect to some non-homogeneous perturbations. Using an initial perturbation on u at the left side ($u(t = 0, x) = 2u_0$ for $x \in [0, L/10]$), one obtains a non-homogeneous stationary solution (so-called Turing structure). Moreover, the perturbation spreads to the right like a wave. See [20] p. 30. This behaviour is presented in fig. 5.1. We approximated Meinhardt's model by a gene network, with 600 genes (300 to ap-

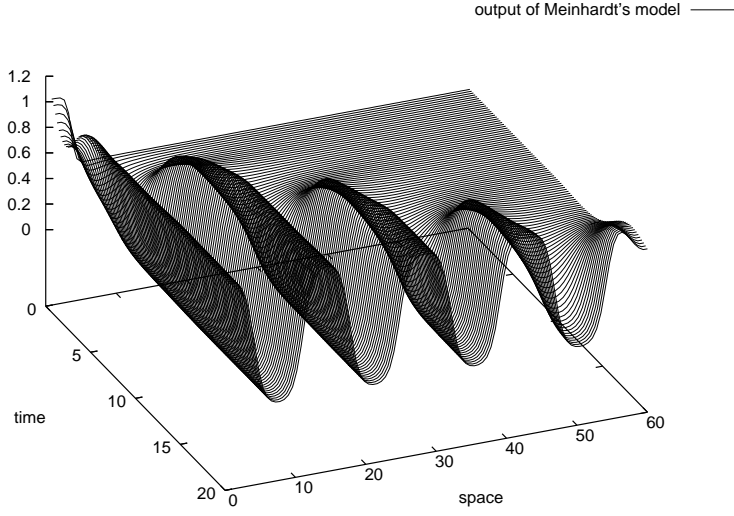


Fig. 5.1. Solution of Meinhardt's model.

proximate function (3.3) and 300 for (3.4)). The behaviour is qualitatively similar to the solution of Meinhardt's model. See fig. 5.2.

The second point we illustrate is the universal pattern generation problem: given a spatio-temporal pattern, to find a gene network generating pattern.

We first generate spatio-temporal patterns with one spatial dimension. The corresponding gene network can be defined as follows:

$$\frac{\partial y_1}{\partial t} = \kappa(\sigma(\theta_1(x)) - y_1), \quad (5.2)$$

$$\frac{\partial \bar{y}_1}{\partial t} = 2\kappa(\sigma(\theta_1(x)) - \bar{y}_1), \quad (5.3)$$

$$\frac{\partial u_j}{\partial t} = \lambda(R_j\sigma(K_j y_1 + \bar{K}_j \bar{y}_1 - \eta_j) - u_j), \quad j = 1, \dots, m, \quad (5.4)$$

$$\frac{\partial y_{\text{out}}}{\partial t} = \lambda(\sigma(\sum_{j=1}^m u_j) - y_{\text{out}}). \quad (5.5)$$

Notice that diffusion is absent and positional information is provided by the space-dependent threshold $\theta_1(x)$. In this one-dimensional case, the condition on θ_1 means that this function is strictly monotone.

As it is shown in Sect. 4, t and x are functions of (y_1, \bar{y}_1) . Namely,

$$t = -\frac{1}{\kappa} \log\left(\frac{\bar{y}_1}{y_1} - 1\right) \quad (5.6)$$

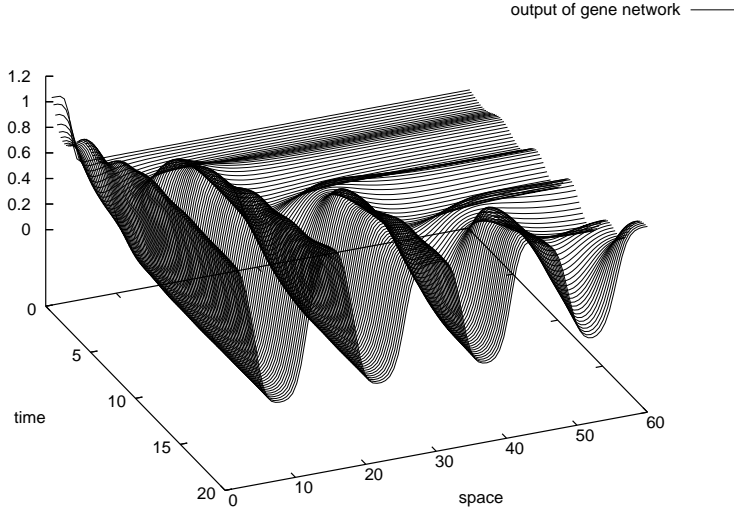


Fig. 5.2. Approximation of Meinhardt's model by a gene network.

and

$$x = \theta_1^{-1}(\sigma^{-1}(\frac{y_1^2}{2y_1 - \bar{y}_1})). \quad (5.7)$$

Thus any $z(t, x)$ can be presented as a function of (y_1, \bar{y}_1) :

$$z(t, x) = z(\text{time}(y_1, \bar{y}_1), \text{space}(y_1, \bar{y}_1)) = Z(y_1, \bar{y}_1). \quad (5.8)$$

Notice that y_{out} approximates $r = \sigma(\sum_{j=1}^m u_j)$ as $\lambda \rightarrow \infty$. In turn, r approximates $\sigma(\sum_{j=1}^m R_j \sigma(T_j y_1 + \bar{T}_j \bar{y}_1 - \theta_j))$. Hence, to solve the pattern generation problem, we have to determine the coefficients $R_j, T_j, \bar{T}_j, \theta_j$ such that $\sum_{j=1}^m R_j \sigma(T_j y_1 + \bar{T}_j \bar{y}_1 - \theta_j)$ approximates $\sigma^{-1}(Z(y_1, \bar{y}_1))$. It is possible if Z is a continuous function.

The problem is thus to approximate a function of two variables (y_1 and \bar{y}_1). This problem is intractable with the least square and the random methods, and we use here again Jones' iterative approximation method (see above).

To avoid singularities at the lines $y_1 = \bar{y}_1$ and $2y_1 = \bar{y}_1$, we have approximated this function Z in the image of the bounded rectangle $[T_0, T_1] \times [x_0, x_1]$ by the map $(t, x) \mapsto (\sigma(\theta_1(x))(1 - e^{-\kappa t}), \sigma(\theta_1(x))(1 - e^{-2\kappa t}))$, which is a one-to-one map of (t, x) .

Fig. 5.3 and 5.4 present the output of system (5.2)–(5.4) approximating the function $0.1(\sin(8t) + \sin(16t))$ and $0.025(1 + \tanh(10t - 0.5))\sin(8x)$, respectively, for $t \in [0, 1]$ and $x \in [0, 1]$. We have used 1000 sigmoidal functions for these simulations.

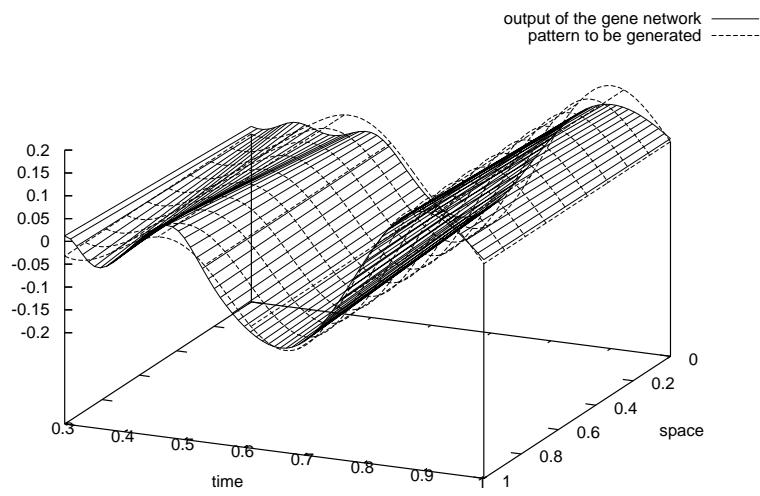


Fig. 5.3. Generation of $0.1(\sin(8t) + \sin(16t))$ by a gene network.

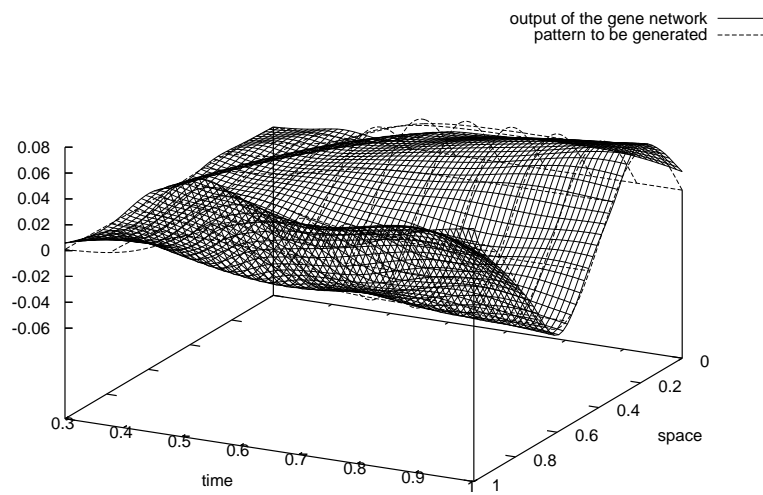


Fig. 5.4. Generation of $0.025(1 + \tanh(10t - 0.5)) \sin(8x)$ by a gene network.

Also we have generated spatio-temporal patterns with 2 space dimensions. The corresponding gene circuit is

$$\frac{\partial y_1}{\partial t} = \kappa(\sigma(\theta_1(x)) - y_1), \quad (5.9)$$

$$\frac{\partial y_2}{\partial t} = \kappa(\sigma(\theta_2(x)) - y_2), \quad (5.10)$$

$$\frac{\partial \bar{y}_1}{\partial t} = 2\kappa(\sigma(\theta_1(x)) - \bar{y}_1), \quad (5.11)$$

$$\frac{\partial u_j}{\partial t} = \lambda(R_j\sigma(K_j^1 y_1 + K_j^2 y_2 + \bar{K}_j \bar{y}_1 - \eta_j) - u_j), \quad j = 1, \dots, m, \quad (5.12)$$

$$\frac{\partial y_{\text{out}}}{\partial t} = \lambda(\sigma(\sum_{j=1}^m u_j) - y_{\text{out}}). \quad (5.13)$$

The time t , the spatial coordinates x_1 and x_2 can be expressed as functions of (y_1, y_2, \bar{y}_1) :

$$t = -\frac{1}{\kappa} \log\left(\frac{\bar{y}_1}{y_1} - 1\right), \quad (5.14)$$

$$x_1 = g_1\left(\sigma^{-1}\left(\frac{y_1^2}{2y_1 - \bar{y}_1}\right), \sigma^{-1}\left(\frac{y_1 y_2}{2y_1 - \bar{y}_1}\right)\right) \quad (5.15)$$

and

$$x_2 = g_2\left(\sigma^{-1}\left(\frac{y_1^2}{2y_1 - \bar{y}_1}\right), \sigma^{-1}\left(\frac{y_1 y_2}{2y_1 - \bar{y}_1}\right)\right). \quad (5.16)$$

Hence, any continuous function $z(t, x_1, x_2)$ can be represented as a function of (y_1, y_2, \bar{y}_1) , which has to be approximated by Jones' method in order to solve the pattern generation problem. Since t , x_1 and x_2 are singular in $y_1 = \bar{y}_1$ and $2y_1 = \bar{y}_1$, these functions were approximated in the image of the cubic domain $[T_0, T_1] \times [x_{1,0}, x_{1,1}] \times [x_{2,0}, x_{2,1}]$ by the map $(t, x_1, x_2) \mapsto (\sigma(\theta_1(x))(1 - e^{-\kappa t}), \sigma(\theta_2(x))(1 - e^{-\kappa t}), \sigma(\theta_1(x))(1 - e^{-2\kappa t}))$.

Fig. 5.5 presents the output of system (5.9)–(5.13) approximating the function $0.01((x_1 - 0.5)^2 - (x_2 - 0.5)^2)$ for $(x_1, x_2) \in [0, 1]^2$. This function is independent of time, but time-dependent functions have also been approximated (it is not shown). We have used 1000 sigmoidal functions for this simulation.

The last point we illustrate is the superposition principle and its relation with the conditional complexity (see Sect. 4). The superposition Theorem 4.1 states that a given network generating a pattern $u(t, x)$ and a given continuous function F , one can devise a new network generating $F(u)(t, x)$. The number of the genes involved in this new network depends on the complexity of the target pattern. This complexity can be defined by the Fourier transform of the pattern [3]. We define the conditional complexity $\text{Comp}(F(u)(t, x)|u(t, x))$ as the complexity of $F(u)(t, x)$ considered as a function of $u(t, x)$. The point is that

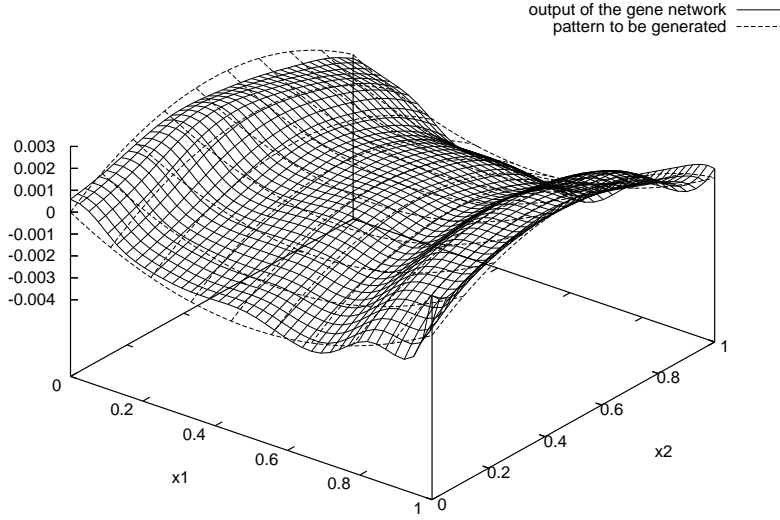


Fig. 5.5. Generation of $0.01((x_1 - 0.5)^2 - (x_2 - 0.5)^2)$ by a gene network.

$\text{Comp}(F(u)(t, x)|u(t, x))$ can be much less than $\text{Comp}(F(u)(t, x))$. So generating $F(u)(t, x)$ through $u(t, x)$ we may use much less genes than generating $F(u)(t, x)$ directly (or, if the same gene number is involved, a better precision may be achieved).

We illustrate this fact by generating $\cos(8t)$ for $t \in [0, 2\pi]$. We produce this time function directly and, moreover, we first generate $\cos(t)$, then $2\cos^2(t) - 1 = \cos(2t)$, later $2\cos^2(2t) - 1 = \cos(4t)$ and finally $2\cos^2(4t) - 1 = \cos(8t)$. The network generating $\cos(8t)$ directly is

$$\frac{\partial y_1}{\partial t} = 1, \quad (5.17)$$

$$\frac{\partial u_j}{\partial t} = \lambda(R_j \sigma(K_j y_1 - \eta_j) - u_j), \quad j = 1, \dots, m, \quad (5.18)$$

$$\frac{\partial y_{\text{out}}}{\partial t} = \lambda\left(\sum_{j=1}^m u_j - y_{\text{out}}\right), \quad (5.19)$$

where R_j , K_j and η_j are chosen so that $\sum_{j=1}^m R_j \sigma(K_j t - \eta_j)$ approximates $\cos(8t)$.

The network producing $\cos(8t)$ indirectly is

$$\frac{\partial y_1}{\partial t} = 1, \quad (5.20)$$

$$\frac{\partial u_j^1}{\partial t} = \lambda(R_j^1 \sigma(K_j^1 y_1 - \eta_j^1) - u_j^1), \quad j = 1, \dots, m_1, \quad (5.21)$$

$$\frac{\partial y_2}{\partial t} = \lambda \left(\sum_{j=1}^{m_1} u_j^1 - y_2 \right), \quad (5.22)$$

$$\frac{\partial u_j^2}{\partial t} = \lambda (R_j^2 \sigma(K_j^2 y_2 - \eta_j^2) - u_j^2), \quad j = 1, \dots, m_2, \quad (5.23)$$

$$\frac{\partial y_3}{\partial t} = \lambda \left(\sum_{j=1}^{m_2} u_j^2 - y_3 \right), \quad (5.24)$$

$$\frac{\partial u_j^3}{\partial t} = \lambda (R_j^2 \sigma(K_j^2 y_3 - \eta_j^2) - u_j^3), \quad j = 1, \dots, m_2, \quad (5.25)$$

$$\frac{\partial y_4}{\partial t} = \lambda \left(\sum_{j=1}^{m_2} u_j^3 - y_4 \right), \quad (5.26)$$

$$\frac{\partial u_j^4}{\partial t} = \lambda (R_j^2 \sigma(K_j^2 y_4 - \eta_j^2) - u_j^4), \quad j = 1, \dots, m_2, \quad (5.27)$$

$$\frac{\partial y_{\text{out}}}{\partial t} = \lambda \left(\sum_{j=1}^{m_2} u_j^4 - y_{\text{out}} \right), \quad (5.28)$$

where R_j^1, K_j^1 and η_j^1 have been chosen so that $\sum_{j=1}^{m_1} R_j^1 \sigma(K_j^1 t - \eta_j^1)$ approximates $\cos(t)$ and R_j^2, K_j^2 and η_j^2 have been chosen so that $\sum_{j=1}^{m_2} R_j^2 \sigma(K_j^2 x - \eta_j^2)$ approximates $2x^2 - 1$.

We have used the same number of equations in the two cases, namely 52, (so, $m = 50$ in equation (5.18)) and we have compared the precision achieved. For the indirect approximation, we have chose $m_1 = 32$ and hence, $m_2 = 5$.

The target pattern is defined by a function of a single variable. In this case and with a small number of the genes, using of Jones' method is not obligatory. Actually, here by the least square method for the linear coefficients and a random choice for the nonlinear ones we achieve a better precision.

Fig. 5.6 presents the results. The patterns computed by systems (5.17)–(5.19) and (5.20)–(5.28) are denoted respectively "direct approximation" and "indirect approximation".

6. Conclusion

It is shown that the genetic networks with binary interaction of the genes have a formidable patterning capacity. They can produce any spatio-temporal patterns. Moreover, it is proved that any reaction-diffusion systems can be approximated by genetic circuits. This result allows to connect earlier phenomenological mathematical reaction-diffusion models and more biologically realistic genetic circuits.

Let us emphasise that, by these circuits, pattern programming can be performed. This means that, for a given pattern, a circuit that builds this pattern, can be found by effective and universal algorithms. One of the most astonishing biological revelations of the past twenty years is that much of the basic machinery of development is essentially the same, not in all vertebrates but in all the major phyla

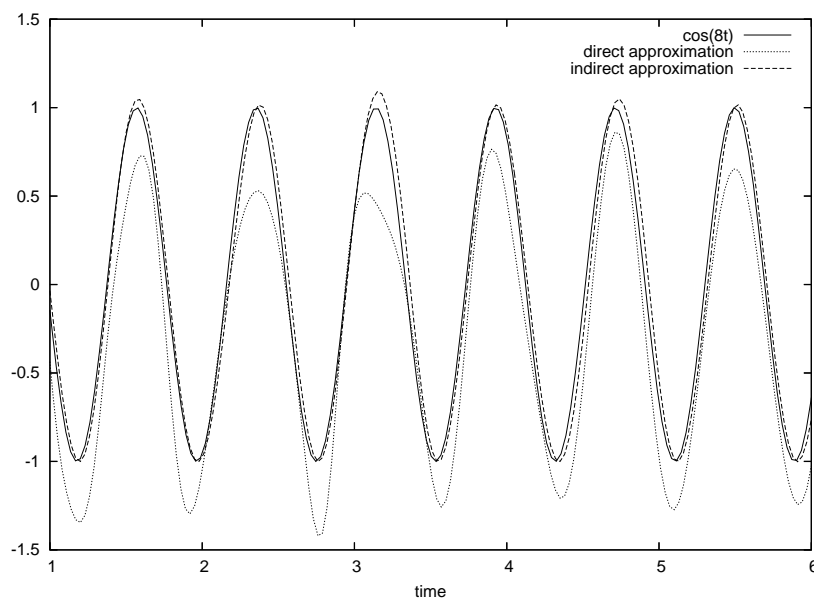


Fig. 5.6. Improvement of approximation by superposition principle.

of invertebrates too [42]. We show therefore that this machinery can be described by simple gene circuit models.

This pattern programming holds on a basic biological principle: on modular organisation of genes. Genes are organised in blocs. Notice that the modular principle is confirmed by experimental data of molecular biology (see [1, 12, 42] and references therein).

We have demonstrated that this modular structure entails an interesting property, which can be named "superposition principle". This superposition property means that new patterns can always be obtained by previous (old) patterns.

As an elementary example explaining a biological interpretation of superposition principle we can consider flappers, wings and legs of tetrapodes. It is well known that they consist of the same basic elements (numerus, cubitus, radius, carpe) but jointed in different ways (see [27]). Different joinings give wings for birds, legs for dogs, flappers for whales etc. When mammals penetrated in water, evolution did not invented flappers from zero. Evolution used earlier created patterns to obtain flappers. Thus, the superposition principle allows us to understand why the gene number grows relatively slow in evolution (remind that *Drosophila* has the 14000 genes, *C. elegans* has the 19000 and *Homo sapiens* has the 30000 genes). Indeed, as we have explained in Sect. 4 and 5, the gene number growth is not directly proportional to the pattern complexity; this number is proportional to conditional pattern complexity relatively already stored patterns. This conditional quantity may be small even if the target pattern is very complex.

We can thus conclude that the modular organisation of gene interaction leads to a minimisation of time and genes in a process of invention of new biological struc-

tures. A famous basic evolutionary law asserts that the ontogenesis summarises the phylogenesis [27]. This paper suggest that this law is a direct consequence of gene network organisation.

A. Appendix

A.1. Derivation of equations (3.12) and (3.13)

Equations (3.7) and (3.8) can be rewritten as

$$\frac{\partial y_i}{\partial t} = \sigma(a_i u + \gamma_i v - \theta_i) + d_1 \Delta y_i, \quad (\text{A.1})$$

$$\frac{\partial z_i}{\partial t} = \sigma(\bar{a}_i v + \bar{\gamma}_i u - \bar{\theta}_i) + d_2 \Delta z_i. \quad (\text{A.2})$$

Multiplying the i -th equation in (A.1) by b_i and taking the sum over i , we obtain (3.12) and (3.13).

A.2. Boundedness of solutions of the Meinhardt equations

Solutions of (3.1)-(3.2) stay bounded: they lie in the domain D_{C_1, C_2} for all times if the corresponding initial data are in this domain.

Let us show that condition (3.5) holds with appropriate C_1, C_2 . Let us choose such C_i that

$$\alpha C_2 (C_1^2 (1 + \alpha_1 C_1^2)^{-1} + \beta_1) < \kappa_1 C_1 \quad (\text{A.3})$$

and

$$\beta_2 < (\alpha \beta_1 + \kappa_2) C_2. \quad (\text{A.4})$$

First we choose a large C_2 to satisfy (A.4) and then we can take a constant C_1 large enough to satisfy (A.3). Now we can prove that the domain D_{C_1, C_2} is an invariant rectangle for (3.1)-(3.2). This means that on the boundaries $u = C_1$ and $v = C_2$ the vector field (f, g) is directed inside D_{C_1, C_2} .

This assertion follows from (A.3) and (A.4).

A.3. Proof of Superposition Theorem

We consider a large network involving a number of genes. First, it involves the genes y_i^s , $i = 1, \dots, m_s$, where $s = 1, \dots, p$, participating in given networks. The corresponding dynamics is defined by the equations

$$\frac{\partial y_i^s(x, t)}{\partial t} = R_i^s \sigma \left(\sum_{j=1}^{m_s} K_{ij}^s y_j^s - \theta_i(x) - \eta_i^s \right) - \lambda_i^s y_i^s, \quad x \in \Omega, \quad t \geq 0, \quad (\text{A.5})$$

where $s = 1, \dots, p$.

Moreover, the large network includes additional genes v_k . The time evolution of the corresponding concentrations $v_k(x, t)$ is defined by the following equations

$$\frac{\partial v_k(x, t)}{\partial t} = b_k \sigma \left(\sum_{j=1}^p M_{kj} y_1^j(x, t) - \eta_k \right) - \lambda v_k, \quad x \in \Omega, t > 0. \quad (\text{A.6})$$

At last, the genes $v_k(x, t)$ determine the time evolution of the output gene y_1 as follows:

$$\frac{\partial y_1(x, t)}{\partial t} = R \sigma \left(\sum_{j=1}^{m_0} S_{kj} v_k(x, t) \right) - \lambda y_1, \quad x \in \Omega, \quad t > 0. \quad (\text{A.7})$$

We set the zero initial conditions for all the concentrations

$$v_k(x, 0) = y_1^k(x, 0) = y_1(x, 0) = 0.$$

Let us prove the auxiliary lemma.

Lemma A.1. *Given a function $z(t) \in C^1[0, T]$, positive numbers ϵ and $\delta < T$, there are a function $w \in C[0, T]$ and a positive coefficient λ such that the solution of the Cauchy problem*

$$\frac{dX(t)}{dt} = -\lambda X(t) + w(t), \quad X(0) = 0, \quad t \in [0, T] \quad (\text{A.8})$$

satisfies the following inequality

$$|X(t) - z(t)| < \epsilon, \quad t \in [\delta, T]. \quad (\text{A.9})$$

Proof. The proof of this lemma is elementary. Indeed, let us set

$$w = \frac{dz(t)}{dt} + \lambda z(t), \quad X = z + \tilde{X}.$$

Then (A.8) entails

$$\frac{d\tilde{X}(t)}{dt} = -\lambda \tilde{X}(t), \quad \tilde{X}(0) = -z(0).$$

Thus,

$$|\tilde{X}(t)| \leq |z(0)| \exp(-\lambda t).$$

To complete the proof of the lemma, we set

$$\lambda > -\delta^{-1} \log(|z(0)|^{-1} \epsilon).$$

□

Notice that the lemma also holds for $z \in C[0, T]$, since any continuous function can be approximated by a smooth function. Moreover, if given z is a superposition of the form $z = z(y^1(t), \dots, y^p(t))$, where y^s are defined by some system of autonomous differential equations, then w can also be represented as a superposition: $w = w(y^1(t), \dots, y^p(t))$.

To finish the proof of Theorem 4.1, it is sufficient to prove that for any continuous function of the form $w(x, t) = w(y_1^1(x, t), \dots, y_1^p(x, t))$, where $x \in \Omega$, $t \in [0, T]$ and $\epsilon > 0$, there exists such a choice of the parameters $M_{kj}, \eta_k, \lambda, b_k, S_k$ and R in (A.6) and (A.7) that the solutions $v_k(x, t)$ of (A.6) satisfy the estimate

$$|w(y_1^1(x, t), \dots, y_1^p(x, t)) - R\sigma(\sum_{k=1}^{m_0} S_k v_k)| < \epsilon, \quad (\text{A.10})$$

for any $x \in \Omega$, $t \in [\delta, T]$. Using the monotonicity of σ and choosing a sufficiently large R , we simplify the last estimate and obtain

$$|W(y_1^1(x, t), \dots, y_1^p(x, t)) - \sum_{k=1}^{m_0} S_k v_k| < \epsilon, \quad x \in \Omega, \quad t \in [\delta, T], \quad (\text{A.11})$$

where $W(x, t)$ is given.

Let us take sufficiently large $\lambda > 0$. Using (A.11) and (A.6), we obtain

$$|v_k(x, t) - \lambda^{-1} b_k \sigma(\sum_{j=1}^p M_{kj} y_1^j(x, t) - \eta_k)| < \epsilon/4. \quad (\text{A.12})$$

Denote $\beta_k = \lambda^{-1} S_k b_k$. Now, to finish the proof, it is sufficient to find the parameters

M_{kj}, η_k, β_k such that

$$|W(y_1^1(x, t), \dots, y_1^p(x, t)) - \sum_{k=1}^{m_0} \beta_k \sigma(\sum_{j=1}^p M_{kj} y_1^j(x, t) - \eta_k)| < \epsilon/4, \quad (\text{A.13})$$

where $x \in \Omega$, $t \in [\delta, T]$. The existence of this approximation follows from the multilayered network theory (see Lemma 2.1).

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