Symbolic dynamics, reaction-diffusion systems and morphogenesis

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Conjoint with J. Reinitz (USA, Univ. of Chicago),
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I dedicate this talk to memory of Andreas Weber.

PLAN

1. Introduction
2. Reaction-diffusion systems (RDS)
3. Turing and Wolpert
4. Complexity of dynamics for RDS
5. Number of local attractors may be exponentially large
6. Symbolic dynamics, chaos and morphogenesis

Aim of study

The aim of this paper is to show that reaction-diffusion models are capable to generate a number of local attractors and to create a number of different cell developmental patterns. Our approach to that problem uses some basic ideas of A. Turing and L. Wolpert.

Wolpert and Turing

More 50 years ago, Lewis Wolpert proposed the positional information model to describe patterns of different cell types. This model is based on threshold concentrations of a morphogen diffusing in the tissue. 70 years ago, Alan Turing introduced the idea of patterns originated from a homogeneous states by reaction–diffusion mechanism. In both conceptual models, an organism is represented as a pattern consisting of different cells. The cells are "specialized", i.e., each type of cell performs a unique and special function and each of the order of $100 - 200$ different types of cells in multicellular organisms has different structures, sizes, shapes, and functions. Both approaches, Turing's and Wolpert's, assume that morphogens, special reagents, can change cell states.

Biological ideas

Turing pioneered the idea of a morhogen. Morphogens are special reagents, which can change cell states. Well-known morphogens include: decapentaplegic/transforming growth factor beta, Hedgehog/Sonic hedgehog, Wingless/Wnt, Bicoid and others. Ch. Nüsslein-Volhard identified the first morphogen, Bicoid, one of the transcription factors in the Drosophila syncytial embryos. The idea of positional information, which explains, how morphogen can work, was proposed by L. Wolpert. A morphogen spreads from a localized source at an edge of embryo and forms a concentration gradient across a developing tissue. That morphogen affects cell states, these states can be represented by the different colors of the French flag: high concentrations activate a "blue" gene, lower concentrations activate a "white" gene etc. (see Fig.).

French Flag model

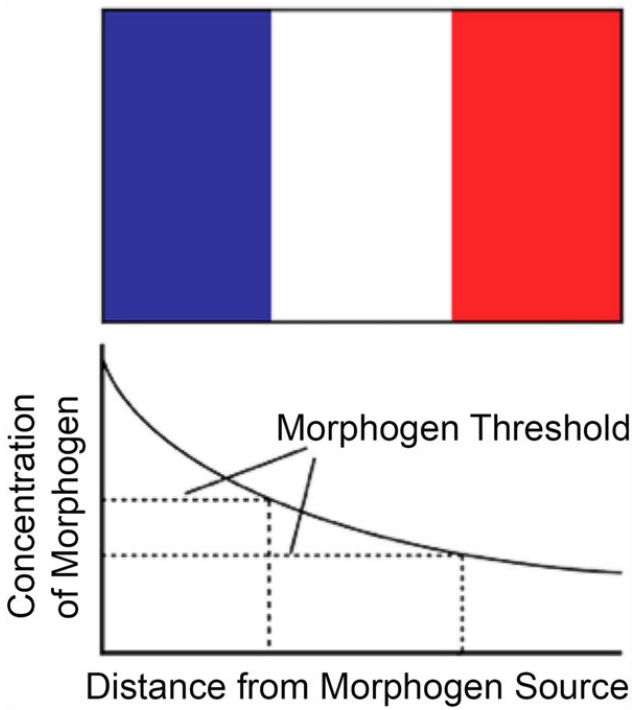


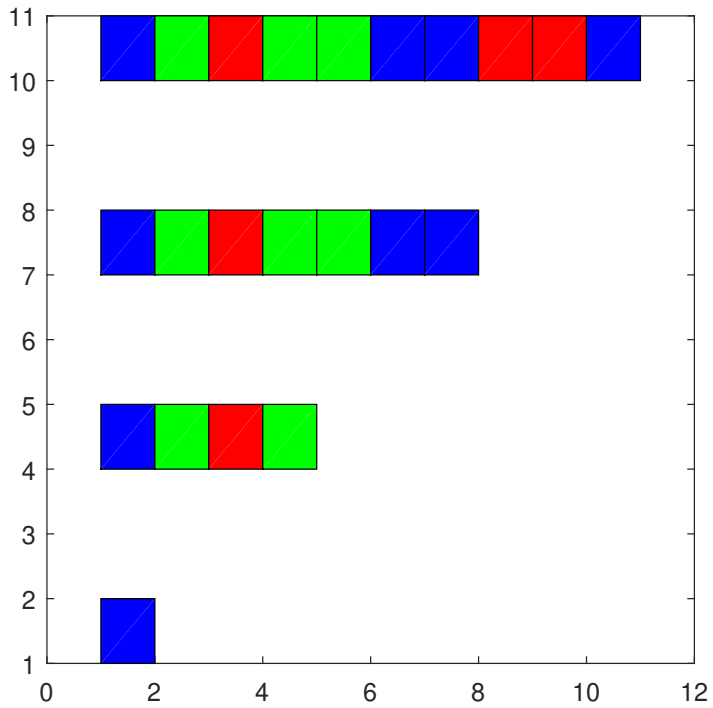
Figure: Famous French Flag model shows as an $1D$-organism consisting of three kinds of cells can be created by a positional information transfer via morphogen gradients. Proposed by L. Wolpert in 1960's, the model shows how embryonic cells can interpret genetic code to create a pattern. The cell fate is determined by a morphogen level.

Turing together with Wolpert

The Turing instability allows us to obtain periodical layered patterns, such as zebra stripes, however, we would like to have a model generating more complicated structures. We achieve it by a combination of Turing and Wolpert approaches using chaotic dynamics.

Our model is purely chemical. However, there are possible other models exploiting mechanical effects and waves.

Cell patterns



Cell pattern can be considered as a string in an alphabet (red, blue, green on Fig.). We would like to generate more complex patterns than French flag.

Reaction-diffusion systems (RDS)

We consider the following class of RDS with two reagents only:

$$u_t = d\Delta u + f(u, v) + \zeta, \tag{1}$$

$$v_t = D\Delta v + g(u, v) + \eta, \tag{2}$$

where $u = u(x, y, t)$ and $v = v(x, y, t)$ are unknown functions defined on $\Omega \times \{t \geq 0\}$, Ω is the strip $(-\infty, \infty) \times [0, 1] \subset \mathrm{R}^2$, $d, D > 0$ are diffusion coefficients, $\eta(x, y)$ and $\zeta(x, y)$ are smooth functions that can be interpreted as external sources independent of u, v.

Boundary conditions

$$\Omega = (-\infty, \infty) \times [0, 1],$$

$$u_y(x, y, t), v(x, y, t)|_{y=0,1} = 0,$$

$$u(x + 2\pi, y, t) = u(x, y, t), \quad v(x + 2\pi, y, t) = v(x, y, t),$$

η, ζ are 2π-periodical in x.

Assumptions

Suppose that

(**Bi**) *There exist* u_* *and* v_* *such that*

$$f_u(u_*, v_*) = 0, \quad f_v(u_*, v_*) = 0 \tag{3}$$

and

$$g_u(u_*, v_*) \neq 0; \tag{4}$$

(**Bii**) *The critical point* u_*, v_* *is non-degenerated, i.e., the Hessian* H_f *of the function* f *at the point* (u_*, v_*) *defined by*

$$\begin{pmatrix} f_{uu}(u_*, v_*) & f_{uv}(u_*, v_*) \\ f_{uv}(u_*, v_*) & f_{vv}(u_*, v_*) \end{pmatrix}$$

satisfies

$$\det H_f \neq 0. \tag{5}$$

Parameters

Let us introduce parameter P of our initial boundary valued problem (IBVP) as

$$P = \{\eta(\cdot,\cdot), \zeta(\cdot,\cdot), d_u, D_v\}.$$

Main Theorem

Theorem I. (S. Vakulenko, J. Dyn. Diff. Eqs. 2018) *Suppose assumptions* **Bi** *and* **Bii** *are satisfied. Then the family of the local semiflows $S^t(P)$ generates all finite dimensional hyperbolic dynamics (up to orbital topological equivalency) as we vary parameters P of our IBVP*.

Attractors may be chaotic. For semiflows defined by (2),(1) the following assertion is valid: either this semiflow $S^t(P)$ is monotone, or $S^t(P)$ can ϵ-realize all finite dimensional vector fields. Moreover, conditions to f, g have transparent chemical interpretation. They mean that the reagent v is neither an inhibitor nor an activator for u.

Comments

These results can be translated into biological language. Consider external sources $\eta(x, y)$ and $\zeta(x, y)$ in (2), (1) as spatial concentrations of certain morphogens. To obtain a complicated attractor, we need complicated functions $\eta(x, y)$ and $\zeta(x, y)$. We can thus consider those functions as carries a positional information that permits to create a complicated spatio-temporal structure (pattern). Moreover, in order to have a complex pattern $u(x, y, t), v(x, y, t)$ we need small coefficients d_u and $D_v >> d_u$, i.e., one reagent should diffuse much faster than the other one.

Comments

Under these conditions a positional information stored in functions η, ζ can be transformed to spatio-temporal structure with a complex large time behaviour. Our mechanism to generate complex structures is based on two fundamental ideas: Turing's idea to take $D_v \neq d_u$, and the Wolpert concept of positional information. Note that the idea to use a spatial heterogeneity was proposed still by Turing in his seminal paper.

Many local attractors

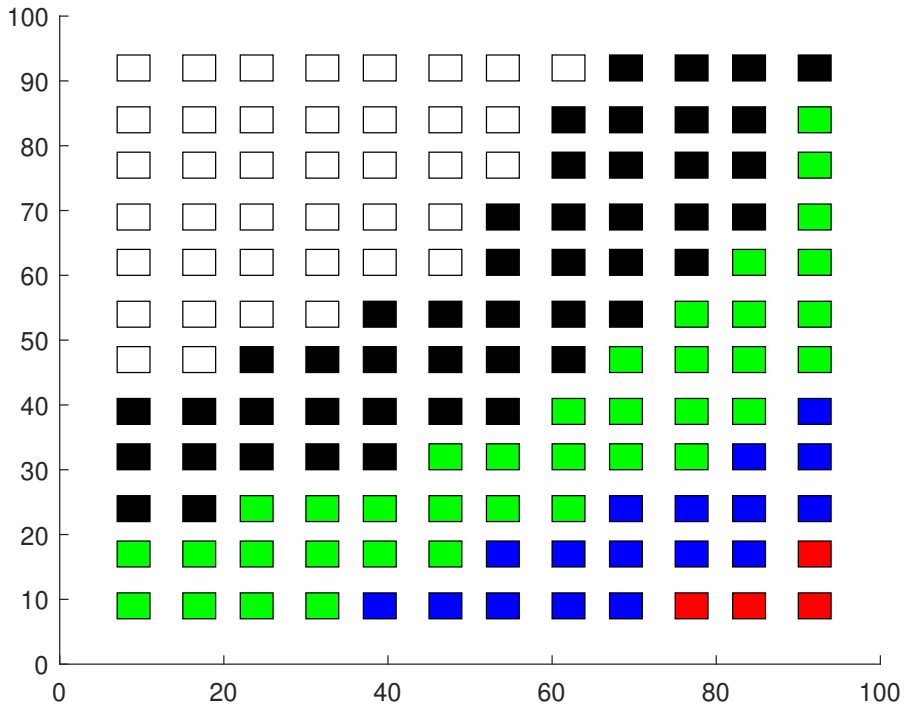
Assertion 1. *Generic open systems defined by eqs. (2) with $n \geq 2$ components define families of dynamical systems (semiflows) S_{P}^t enjoying the following property.*
For appropriate external gradients η, ζ the corresponding system S_{P}^t is capable to generate 2^{M_a} different structurally stable local attractors (which may be periodic or even chaotic), where $M_a > C_f d_u^{-1/4}$ and $C_f > 0$ is a constant depending on $f, g, D_v > 1$.

Many cell patterns

Assertion 2. *For appropriate P local semiflows defined by our IBVP. (2) are capable to realize any developmental programs by an appropriate morphogenetic operator $\mathcal{M}$. The maximal possible number of those programs is not less than $2^{M_{dvp}}$ with $M_{dvp} > \tilde{C}_f d_u^{-1/4}$.*

Morphogenetic operator transforms u-patterns into cell types, i.e. it is a map from space of smooth functions into space of strings. The simplest example is given by French flag model.

Cell developmental program



This picture illustrates a concept of developmental program. Different types of the cells are shown by different colors. The top row of the cells emerges at the last time moment t_n, the previous row appears at $t = t_{n-1}$ and the bottom row arises at the initial time $t = t_0$.

Chaos

To generate arbitrary strings we use chaos following C. Moore (1991). There is a wide broad in chaos definition. Features of a chaotic invariant set:

1. existence of infinite number of periodic trajectories
2. sensitivity with respect to initial data
3. positive Lyapunov exponents

A rigorious theory is developed for a special class of invariant sets, so-called hyperbolic sets. They can be fractal, like to Cantor sets, or smooth manifolds.

Reduction

Systems, which are capable to generate all hyperbolic dynamics we call "maximally dynamically complex" (or dynamically universal, if we use terminology of T. Tao). We reduce our RDS to an example of such system is

$$\frac{dx_i}{dt} = \sum_{j=1}^{N} W_{ij} x_j - \lambda x_i^2 \tag{6}$$

(the proof of universality see Vakulenko, Weber, Grigoriev, Studies in Applied Mathematics, 2015). We can vary N, W_{ij} by adjusting parameters P of our RDS.

Main trick

One can show that under an appropriate choice of P this system of a large dimension N can be decomposed into M_a almost independent shorted subsystems of dimension N/M_a of the same form. We adjust entries W_{ij} in such a way that each subsystem has two local attractors. Then the complete system has 2^{M_a} of local attractors.

Chaotic local attractor produces sequence of cell states in time

Suppose if morphogen concentration $u(x_c, t) \in U_j$, where U_j are domains, and x_c is a cell center, we obtain the cell of type j. Let for simplicity $j = r, b$. Then, to obtain a time sequence $a(t_1), ..., a(t_k)$ of cell types $a(t_j) \in \{r, b\}$, we should satisfy

$$u(x_c, t_j) \in U_j, \quad t_j = j\Delta T, \quad j = 1, ..., k.$$

Symbolic dynamics allows to resolve this problem by Bernoulli shifts and Markov partitions, (see C. Moore Nonlinearity, 1991, also S. Vakulenko, D. Grigoriev, New way for cell differentiation: Reaction, diffusion and chaotic waves, Biosystems (212), 2022).

Outline of proof

Our relation is equivalent

$$u(x_c, 0) \in S^{-t_j} U_j, \quad t_j = j\Delta T, \quad j = 1, ..., k.$$

where S^t is the semiflow. If the semiflow is mixing and chaotic on a hyperbolic set, this relation can be satisfied because

$$meas(A \cap S^t B) \to meas(A)\ meas(B) \quad t \to \infty.$$

French Flag model

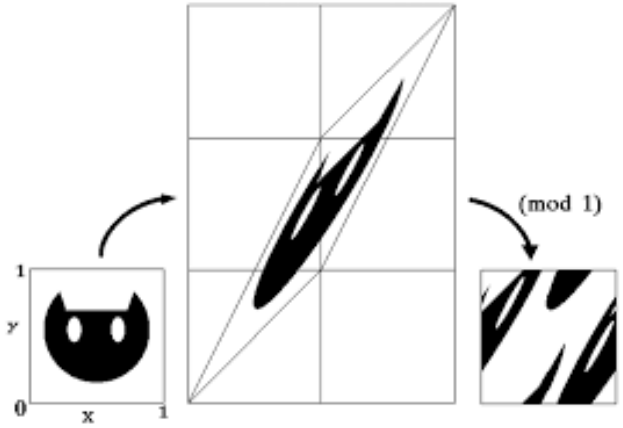


Figure: Famous Arnold cat picture shows mixing for some torus automorphisms.

Conclusion

1. methods of symbolic dynamics allow us to show that any cellular patten can be obtained by chaotic dynamics;
2. Turing mechanism + Wolpert gradients working together an open generic chemical system can generate exponentially many attractors and cellular patterns;
3. pattern and attractor control can be performed by gradients and diffusion coefficients only whereas reaction part can be fixed.

References

Main ideas on chaos and its connection with Turing machines can be found in:

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