SYMMETRY OF TURING'S MORPHOGENETIC EQUATIONS*

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ABSTRACT: We investigate the symmetry properties of the coupled second-order partial differential equations used by A. M. Turing, to describe the kinetics of chemical reactions that can lead to geometrical symmetry breaking in living embryos. It is shown that the equations possess a richer symmetry algebra than can be found by the usual extensions of the classical work of Lie. The significance of some of the symmetries is discussed.

I. INTRODUCTION

How is it that the cells of a living organism, all of which arise by growth and division from the union of a single egg and sperm cell, become different from each other? This question characterizes one of the great mysteries of contemporary biology — the mystery of cell differentiation.

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Sometime after its fertilization the egg of an animal divides, the resulting two cells grow and divide, and this process continues, leading to the formation of a blastula – a polygonal shell of perhaps 2^5 cells. Experiments show that in many animals all of the cells in the blastula can be considered equivalent. If one or several of them are carefully separated from the rest, each can independently develop into a whole animal.

However, as the quasi-spherical blastula continues to grow, there comes a time when the cells are no longer biologically equivalent. This decrease in effective biological symmetry is also accompanied by the development of a depression at some point on the sphere. As this depression deepens, the decrease in biological symmetry is emphasized geometrically and the embryo is said to become a gastrula.

This transformation of the highly symmetrical blastula into the less symmetrical gastrula poses the problem of cell differentiation in its simplest form. If it is solved at this level, then one can in fairness ask the biochemist to answer in some detail the question, "How is it that a sphere develops into a horse?"

The question just stated is due to *A. M. Turing*, who seems to have outlined the only answer to it that is at once logically, mathematically, physically, chemically, and biologically possible.[1]

As it is logically necessary that an object with geometrical symmetry group G in an homogeneous environment will evolve in time to an object with the same symmetry, it must be true that in an embryo small deviations from the polygonal, essentially spherical, symmetry of the blastula become determinative. This is physically possible only if the evolving biochemical system becomes unstable to small "perturbations" that change its geometrical symmetry. If these "perturbations" were simply those of the rough and tumble of embryonic life, there would be no inheritance of characteristics – no phyla, classes, orders, genera or species, whatsoever – no biology as we know it.

It may be admitted then, either that the "perturbations" are supplied by the genetic material in the cells, and/or that the genetic material determines directly or indirectly the effect that the "perturbations" may have upon the system. Since the genetic material itself is not a miniature replica of the full grown organism, it is evident that it does not act directly, impressing the image of a homunculus upon the developing embryo. Rather, it must mediate chemical reactions that are unstable to perturbations, and these must lead to a change in the local or global symmetry of the embryo, a change that is essentially independent of adventituous perturbations. Only a subclass of all perturbations can be amplified.

The facts of biology thus suggest that there exist chemical reactions that, though beginning in a homogeneous environment, develop spatially inhomogeneous distributions of reactants, either in solution or in a gel, and do so in a determinate manner.

The biological importance of such reactions was recognized in the 1930's by Alvin Weinberg[2], who showed that a pair of coupled chemical reactions in solution could give rise to a spatially inhomogeneous distribution of reactants, both inside and outside a spherical cell, if the reactants diffuse at different rates through the solution and the cell membrane. Further additions to the theory of such reactions were contributed by N. Rashevsky.[3] A fairly simple example of a coupled series of reactions that developed inhomogeneously in an initially homogeneous solution in vitro has been recently discovered.[4]

II. THE KINETIC EQUATIONS

Consider a sequence of chemical reactions involving substances "X" and "Y" and let their respective concentrations be X, Y. We shall suppose these concentrations to be functions of time t, and of position r. In Turing's theory of morphogenesis these substances are termed morphogens and Turing supposes that at least one of them favors the growth or development of a cell in which its concentration is changed. He considers diffusion to take place between cells in this case, and also considers reactions in an initially homogeneous medium. We consider only the latter. The local rate of production of "X" is $\partial X/\partial t$ and that of "Y" is $\partial Y/\partial t$. If "X", "Y" diffuse through the solution and have diffusion tensors M, N then the kinetic equations are of the form

$$\frac{\partial X}{\partial t} = f(X,Y) + \sum_i \frac{\partial}{\partial r_i} M^{ii} \frac{\partial}{\partial r_i} X \ ,$$

$$\frac{\partial Y}{\partial t} = g(X,Y) + \sum_i \frac{\partial}{\partial r_i} N^{ii} \frac{\partial}{\partial r_i} Y \ , \tag{1}$$

where r_i are the Cartesian coordinates. The functional form of f and g is determined by the particular reaction sequence. In Turing's theory this is probably to be considered an inherited characteristic though Turing himself does not say so.

Suppose that $f = g = 0$ when $x = h$, $y = k$ throughout the solution. Then the system is in a steady state which may or may not be an equilibrium state.[5] That is, the steady state is characterized only by the requirement:

$$\partial X/\partial t = \partial Y/\partial t = 0 \ .$$

Letting $X = x + h$, $Y = y + k$, and expanding f and g in Taylor series, one obtains

$$\frac{\partial x}{\partial t} = ax + by + R_1 + \sum_i \frac{\partial}{\partial r_i} M^{ii} \frac{\partial}{\partial r_i} x \ ,$$

$$\frac{\partial y}{\partial t} = cx + dy + R_2 + \sum_i \frac{\partial}{\partial r_i} N^{ii} \frac{\partial}{\partial r_i} y \ , \qquad (2)$$

where R_1, R_2 are terms that are not linear in the macroscopic fluctuations x, y. The behavior of the solution near the steady state ($x = 0$, $y = 0$) is determined by the linear terms in eqs. (2). The equations obtained by dropping R_1, R_2 are easily solved, and the results have been discussed by Turing for the case when the solution is confined within a thin annular region, and for the case when it is confined between two concentric spherical surfaces of slightly different radii. He also investigated the case of three morphogens.

For our purposes here it is sufficient to consider the case of two reacting substances confined within a thin annulus. The fluctuations u^1 and u^2 of their concentrations are considered to be functions of the time $x^1 = t$, and of $x^2 = \theta$ where θ is an angular coordinate measured from an origin at the center of the annulus. We also assume that the diffusion tensors are constants. We may then write the linearized kinetic equations as

$$\frac{\partial u^1}{\partial x^1} = k_{11} u^1 + k_{12} u^2 + d_1 \frac{\partial^2 u^1}{(\partial x^2)^2} \ ,$$

$$\frac{\partial u^2}{\partial x^1} = k_{21} u^1 + k_{22} u^2 + d_2 \frac{\partial^2 u^2}{(\partial x^2)^2} \ . \qquad (3)$$

The solutions of these equations are

$$u^1 = \sum_m C_m^1 u_m^1 , \qquad u^2 = \sum_m C_m^2 u_m^2 , \tag{4}$$

$$u_m^1 = \left(A_m^1 e^{p_m x^1} + B_m^1 e^{p'_m x^1} \right) e^{imx^2} ,$$

$$p \neq p' \tag{5}$$

$$u_m^2 = \left(A_m^2 e^{p_m x^1} + B_m^2 e^{p'_m x^1} \right) e^{imx^2} ,$$

Here p and p' are the two roots of the equation

$$(p - k_{11} + d_1 m^2)(p - k_{22} + d_2 m^2) = k_{12} k_{21} . \tag{6}$$

The constants A^1, B^1, A^2, B^2 are restricted only by the relation

$$A_m^1 (p_m - k_{11} + d_1 m^2) = k_{12} A_m^2 ,$$

$$B_m^1 (p'_m - k_{11} + d_1 m^2) = k_{12} B_m^2 . \tag{7}$$

Turing proposes that microscopic fluctuation phenomena are sufficiently varied to ensure that, even when the initial state of the system is the steady state, subsequently any of the coefficients C_m^1, C_m^2 can become non-zero. He then concentrates attention upon those values of m for which p_m, p'_m have the largest positive real part. It is these particular solutions that grow most rapidly with time, and may therefore be expected to dominate the behavior of the system after an initial induction period.

III. CLASSICAL SYMMETRIES OF THE LINEARIZED EQUATIONS

Eqs. (3) will be said to be invariant under the transformation $u^k \to \overline{u}^k$, $x^i \to \overline{x}^i$ if they retain the same form when expressed in the new variables, the constants $k_{11}, \ldots d_2$ being understood to remain unaltered.

It is apparent that the equations are *not* invariant under time reversal $x^1 \to \overline{x}^1 = -x^1$ though they are invariant under the space inversion $x^2 \to \overline{x}^2 = -x^2$.

They are not in general invariant under the exchange $u^1 \leftrightarrow u^2$, but are invariant under the reflection $u^1 \to -u^1, u^2 \to -u^2$. In the classical theory of the local symmetry of differential equations (3) one considers transformations

$$\bar{x}^i = x^i + \epsilon\xi^i(x,u) \ , \qquad x \equiv (x^1, x^2) \ , \ u \equiv (u^1, u^2) \ , \qquad (8)$$
$$\bar{u}^k = u^k + \epsilon\eta^k(x,u) \ ,$$

where ϵ is an arbitrarily small parameter, and the quantities x, u are treated as independent variables.[6] The simplest way to apply the classical method to a set of second order equations, is to convert the set to a canonical set of first order equations by defining auxiliary variables. We therefore let

$$u^3 \equiv \frac{\partial u^1}{\partial x^1} \ , \qquad u^4 \equiv \frac{\partial u^2}{\partial x^1} \ ,$$
$$u^5 \equiv \frac{\partial u^1}{\partial x^2} \ , \qquad u^6 \equiv \frac{\partial u^2}{\partial x^2} \ . \qquad (9)$$

whence eqs. (3) become

$$u^3 = k_{11}u^1 + k_{12}u^2 + d_1 \frac{\partial u^5}{\partial x^2} \ ,$$
$$u^4 = k_{21}u^1 + k_{22}u^2 + d_2 \frac{\partial u^6}{\partial x^2} \ . \qquad (10)$$

The classical method applied to the six equations (9, 10) then leads to a set of six determining equations for the Lie generators:

$$Q = \xi^i(x,u)\frac{\partial}{\partial x^i} + \eta^k(x,u)\frac{\partial}{\partial u^k} \ , \quad i = 1,2; \ k = 1, \ldots 6 \ ,$$
$$x \equiv (x^1, x^2) \ , \qquad u \equiv (u^1, \ldots u^6) \ . \qquad (11)$$

Solving these equations one obtains the following linearly independent generators:

$$Q_1 = \frac{\partial}{\partial x^1}, \quad Q_2 = \frac{\partial}{\partial x^2},$$

$$Q_3 = \sum_{k=1}^{6} u^k \frac{\partial}{\partial u^k}, \quad Q_v = \sum_{k=1}^{6} v^k \frac{\partial}{\partial u^k}, \tag{12}$$

where v^1 and v^2 satisfy the same equations (3) as u^1, u^2, respectively, and

$$v^3 \equiv \frac{\partial v^1}{\partial x^1}, \quad v^4 \equiv \frac{\partial v^2}{\partial x^1}, \quad v^5 \equiv \frac{\partial v^1}{\partial x^2}, \quad v^6 \equiv \frac{\partial v^2}{\partial x^2}. \tag{13}$$

These are the only classical generators that are admitted by the equations (3) for arbitrary values of the constants $k_{11} \dots d_2$. The generators Q_1, Q_2 are the generators of time and space translations. The operator Q_3 generates dilatations of the variables u^i, and of course commutes with Q_1, Q_2. In the remaining generators Q_v the functions $v^1(x^1, x^2)$, $v^2(x^1, x^2)$ may be chosen from the non-denumerable infinity of solutions (v^1, v^2) of the original equations.

Each of these operators may be exponentiated to yield a one-parameter subgroup which leaves the equations invariant. The condition $u(\theta) = u(\theta + 2\pi)$ requires that Q_2 generates $SO(2)$. If further boundary conditions are imposed, the remaining operators may no longer generate one-parameter subgroups.

In Turing's theory of morphogenesis, microscopic fluctuation phenomena are held responsible for the transformation of a steady state into a state inhomogeneous in time and/or space. These fluctuation phenomena may be said to set the initial conditions at $t = t_0$ pertinent to a given problem. Thus while it is true that for all τ, $u^k(t + \tau, \theta)$ is a solution if $u^k(t, \theta)$ is a solution, $u^k(t + \tau, \theta)$ does not in general represent the actual chemical state of the system for $t + \tau < t_0$. It may also not represent the chemical state for times $t + \tau > t_0 + \delta t$ if the non-steady state stimulated is not one that amplifies the perturbation rapidly, so that further microscopic fluctuation phenomena are effectively setting up new initial conditions with macroscopic consequences.

Finally, it is important to note that the only group operators that can convert the steady state $u^1 = 0$, $u^2 = 0$ into any other solution, are the operators obtained by exponentiating the Q_v. Unfortunately, knowledge of operators of this type presupposes a knowledge of solutions of the original differential equations whose symmetries are being studied.

IV. NEW SYMMETRIES

Recently it was discovered that partial differential equations may possess larger continuous groups of symmetries than those considered in the classical theory.[7] These arise when one allows infinitesimal transformations of the form

$$\begin{aligned} \bar{x}^l &= x^l + \epsilon \xi^l (x, u, u_i, u_{ij}, \ldots) , \\ \bar{u}^k &= u^k + \epsilon \eta^k (x, u, u_i, u_{ij}, \ldots) , \\ \bar{u}_l^k &= u_l^k + \epsilon \eta_l^k (x, u, u_i, u_{ij}, \ldots) , \end{aligned} \tag{14}$$

where as before $x = (x^1, x^2)$, $u = (u^1, u^2)$ and

$$u_i \equiv \frac{\partial u}{\partial x^i} , \quad u_{ij} \equiv \frac{\partial u_j}{\partial x^i} , \quad \text{etc.} \tag{14a}$$

For linear equations it is simplest to treat only the x^i as independent variables and suppose the generators of the transformation to be matrix operators that act upon the vector $U = (u^1, u^2)^T$. Thus we write

$$Q = q^0 + q^1 \frac{\partial}{\partial x^1} + q^2 \frac{\partial}{\partial x^2} + + q^{11} \frac{\partial^2}{(\partial x^1)^2} + q^{12} \frac{\partial^2}{\partial x^1 \partial x^2} + q^{22} \frac{\partial^2}{(\partial x^2)^2} + \ldots , \tag{15}$$

where q's are 2×2 matrices whose elements are, in general, functions of x^1, x^2. The invariance requirement then reduces to

$$WQU = \quad \text{if} \quad WU = 0 \ , \tag{16}$$

where

$$W = K + D \frac{\partial^2}{(\partial x^2)^2} - I \frac{\partial}{\partial x^1} \ ; \ K \equiv \begin{bmatrix} k_{11} & k_{12} \\ k_{21} & k_{22} \end{bmatrix} , \ D = \begin{bmatrix} d_1 & 0 \\ 0 & d_2 \end{bmatrix} , \ I \equiv \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} . \tag{16a}$$

Using methods described previously[7], one derives the following determining equations for the q's, if derivatives of order no higher than two are allowed:

$$\begin{aligned}
&(Kq^0 - \overline{q}^0 K) + Dq^0_{22} - q^0_1 - 2\overline{q}^2_2 K = 0 \ , \\
&(Kq^2 - \overline{q}^2 K) + Dq^2_{22} - q^2_1 + 2Dq^0_2 = 0 \ , \\
&(Kq^1 - \overline{q}^1 K) + Dq^1_{22} - q^1_1 + 2(\overline{q}^2_2 - \overline{q}^{12}_2 K) + (\overline{q}^0 - q^0) = 0 \ , \\
&(Kq^{12} - \overline{q}^{12} K) + Dq^{12}_{22} - q^{12}_1 + 2Dq^1_2 + (\overline{q}^2 - q^2) = 0 \ , \\
&2\overline{q}^{12}_2 + (\overline{q}^1 - q^1) = 0 \ , \\
&\overline{q}^{12} - q^{12} = 0 \ .
\end{aligned} \tag{17}$$

Here

$$q^0_1 \equiv \frac{\partial q^0}{\partial x^1} \ , \ \text{etc.} \ ; \quad \overline{q}^0 \equiv Dq^0 D^{-1} \ , \ \text{etc.} \tag{17a}$$

Solving these one obtains, for arbitrary $k_{11}, \ldots d_2$, $(d_2 \neq d_1)$ the following generators

$$Q_0 = I\ ,\quad Q_1 = I\,\frac{\partial}{\partial x^1}\ ,\quad Q_2 = I\,\frac{\partial}{\partial x^2}\ ,$$

$$Q_3 = \begin{bmatrix} 0 & \alpha \\ \beta & \gamma \end{bmatrix} - \begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix} \frac{\partial}{\partial x^1}\ ,\quad Q_4 = Q_3 Q_2\ ,\quad Q_5 = (Q_1 + 2Q_3)\, Q_2\ ,$$

$$Q_6 = \frac{x^2}{2}\left\{\left(\frac{1}{d_1} + \frac{1}{d_2}\right) Q_3 + \frac{1}{d_1}(Q_1 - \gamma I)\right\} + \left\{x^1 (Q_1 + 2Q_3 - \gamma I) - \begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix}\right\} \frac{\partial}{\partial x^2}\ , \tag{18}$$

where

$$\alpha \equiv \frac{d_2}{d_1 - d_2}\, k_{12}\ ,\quad \beta \equiv \frac{d_1}{d_1 - d_2}\, k_{21}\ ,\quad \gamma \equiv \frac{d_1}{d_1 - d_2}\, k_{22} - \frac{d_2}{d_1 - d_2}\, k_{11}\ . \tag{18a}$$

(The operators $Q_3, \ldots Q_6$ can be converted to a more symmetrical form by adding to them multiples of Q_0, Q_1, Q_2, but this complicates their commutation relations). We note first of all that while Q_0, Q_1, Q_2 each have their analog in the classical generators, the same is not true of Q_3, Q_4, Q_5, Q_6. The infinitesimal operators obtained from the generators $Q_3, \ldots Q_6$ all have the property of being able to convert one solution $U(x^1, x^2)$ into another solution $\overline{U}(x^1, x^2) \neq U(x^1 + \epsilon\xi^1, x^2 + \epsilon\xi^2)$. That is, their effect is not one induced by a linear transformation of the independent variables. Furthermore none of them commute identically with the operator W, though they do so on the space of solutions U.

The operators $Q_0, Q_1, Q_2, Q_3, Q_4, Q_5$, mutually commute. However, commutators involving the operator Q_6 do not close on the algebra $Q_0, \ldots Q_6$. The algebra containing these six operators is an infinite parameter Lie algebra: So also is the algebra containing Q_0, Q_1, Q_2, Q_3, and Q_6.

Because Q_3, Q_4, Q_5 commute with the time translation operator Q_1, they cannot convert a solution, constant in time, into one varying in time: Because they commute with Q_2, they cannot convert a solution that is spatially isotropic into one that is anisotropic. Neither of these statements is true of Q_6, however.

V. SOME REMARKS ON THE GENERATOR Q_6

It is evident from the preceding that the generator Q_6 plays a central role in the Lie algebras and Lie groups admitted by eqs. (3). Acting upon a solution U, it gives

$$Q_6 \begin{bmatrix} u^1 \\ \\ u^2 \end{bmatrix} = \begin{bmatrix} \frac{\theta}{2}\{-\frac{1}{d_1}(\gamma u^1 - u^1_t) + (\frac{1}{d_1}+\frac{1}{d_2})\alpha u^2\} + t(-\gamma u^1_\theta + 2\alpha u^2_\theta + u^1_{\theta t}) \\ \\ \frac{\theta}{2}\{(\frac{1}{d_1}+\frac{1}{d_2})\beta u^1 + \frac{1}{d_2}(\gamma u^2 - u^2_t)\} + t(2\beta u^1_\theta - u^2_{\theta t} + \gamma u^2_\theta) - u^2_\theta \end{bmatrix} . \tag{19}$$

where

$$u^1_\theta \equiv \frac{\partial u^1}{\partial \theta} \quad , \quad \text{etc.} \tag{19a}$$

In establishing the connection between diffusion in solution and diffusion between cells. Turing equates d_i to μ_i/n^2, where μ_i is the permeability of the cell membrane to component i, and n is the number of cells per radian. We may suppose that prior to cell differentiation, n continues to increase without making much change in the chemical kinetics. This is equivalent to saying that the d_i decrease while the k_{ij} are kept constant until the cell differentiation takes place.

In the limit $n \to \infty$ (i. e. $d_1 \to 0$, $d_2 \to 0$), the original equations (3) reduce to the θ-independent equations which can give rise to temporally-organized solutions but not spatially-organized solutions.[5] Thus the cell differentiation must take place long before the system approaches this limit.

Some interesting features may be seen in the other limit $n \to 0$ (i. e. $d_1 \to \infty$, $d_2 \to \infty$). In this case we have

$$Q_6 \rightarrow \left\{ t\left(\begin{bmatrix} -\gamma & 2\alpha \\ 2\beta & \gamma \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ 0 & -1 \end{bmatrix} \frac{\partial}{\partial t} \right) - \begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix} \right\} \frac{\partial}{\partial \theta} \quad , \tag{20}$$

while all the other generators retain the form given by eqs. (18). This limiting form of the Q_6 operator commutes with all the other generators on the space of solutions U, thus forming a completely closed Lie algebra on the solution space. The action of this operator on the θ-independent solutions is destructive. However, even at the earliest stages of the growth of the system, chemical species can never attain infinite diffusibilities. This, of course, means that the Lie algebra containing Q_6 is never really closed, but, most importantly, the presence of Q_6 allows it to generate θ-independent structures, which is the condition essential to cell differentiation. Although the non-zero solutions U are necessarily functions of t, one can see in eqs. (19), that new t-dependent structures should be generated if θ-dependent structures are developed.

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RESUMEN

Se investigan las propiedades de simetría de las ecuaciones diferenciales parciales de segundo orden acopladas, usadas por A.M. Turing para describir la cinemática de las reacciones químicas, que pueden llevar al rompimiento de la simetría geométrica en los embriones vivos. Se muestra que las ecuaciones tienen álgebra mucho más rica en simetría que la que se puede encontrar en las extensiones usuales del trabajo clásico de Lie. Se discute el significado de algunas de las simetrías.