Matematica, Cultura e Società

Rivista dell'Unione Matematica Italiana

Deborah Lacitignola

The Mathematical Beauty of Nature and Turing Pattern Formation

Matematica, Cultura e Società. Rivista dell'Unione Matematica Italiana, Serie 1, Vol. **1** (2016), n.2, p. 93–103.

Unione Matematica Italiana

<http://www.bdim.eu/item?id=RUMI_2016_1_1_2_93_0>

Matematica, Cultura e Società. Rivista dell'Unione Matematica Italiana, Unione Matematica Italiana, 2016.

Matematica, Cultura e Società – Rivista dell'Unione Matematica Italiana
Serie I, Vol. 1, N. 2, Agosto 2016, 93-103

The Mathematical Beauty of Nature and Turing Pattern Formation

Deborah Lacitignola
Università di Cassino e del Lazio Meridionale
E-mail: d.lacitignola@unicas.it

There are more things in heaven and earth,
Horatio, Than are dreamt of in your philosophy.
(W. Shakespeare - Hamlet)

Sommario: *Esiste davvero una bellezza matematica della natura? E la rivoluzionaria idea di Turing può fornire una chiave per decifrarla? In questo articolo si cerca di rispondere a questi interrogativi illustrando la genesi, le basi teoriche e l'impatto scientifico della teoria di Alan Turing sulla "pattern formation". Il quadro che emerge è quello di una teoria ancora di grande attualità, che continua ad affascinare per la sua forte interdisciplinarietà e per i tanti progressi che ha permesso di ottenere sia in ambito matematico che in campo chimico e biologico.*

Abstract: *Does it really exist a mathematical beauty of nature? And the revolutionary Turing's idea can be a key to decipher it? In this paper we try to answer these questions by describing the origins, the theoretical basis and the scientific impact of Alan Turing's theory on pattern formation. The picture that emerges is that of a highly topical theory, that still fascinates because of its strong interdisciplinary features and for the many advances that it has allowed to obtain in mathematics as well as in chemistry and in biology.*

1. – Shapes of Nature: patterns everywhere

Nature – because of the enormous variety of its shapes and structures – has always been the inspiring muse of a great number of writers, painters and poets. What is perhaps less known is that this great variety of shapes and structures has as well surprised, intrigued and excited a large number of mathematicians who have always tried to find regularities in the great diversity of natural patterns in order to decipher their mysteries.

To the question: What do fishes have in common with the desert sand dunes?, who would not answer right away: Nothing at all? Surprisingly, a careful look at both, fishes and sand dunes, suggests that the answer is not so obvious. And it is not the only surprising thing. Looking at the fishes, one cannot be struck by the large variety of coat markings that may exhibit stripe, labyrinthine or spot patterns. Similarly, it is impressive to see the occurrence of the same type of structures in landscapes also at different scales.

The notable circumstance that – as for fish coat markings and sand dunes – many patterns in nature exhibit structures that are strongly reminiscent of the ones found in many other different contexts, has suggested the very fascinating idea that such scenarios – although belonging to very different worlds – might be explained within a common theoretical framework.

Accettato: il 18 luglio 2016.

Therefore, questions as *"Do these patterns really have anything in common?"* and *"How do these patterns arise?"* have produced stimulating researches in the mathematical field of nonlinear dynamics, with the aim to understand and describe the constitutive mechanisms underlying such kind of processes.

In this regard, a first methodological answer was provided by the Scottish biologist and mathematician Sir D'Arcy Wentworth Thompson that – with a beautiful merging of natural history, biology, mathematics and physics – put together in the monumental book *On growth and form* [54], all that was then known about patterns and forms in nature, paving the way for the scientific understanding of the mechanisms underlying plant and animal pattern formation. In his book, Thompson suggestively describes the problem of biological form at many levels of organisation [54]

> 'The waves of the sea, the little ripples on the shore, the sweeping curve of the sandy bay between the headlands, the outline of the hills, the shape of the clouds, all these are so many riddles of form, so many problems of morphology, and all of them the physicist can more or less easily read and adequately solve'

and aims to apply mathematics and physics in a descriptive way,

> 'My sole purpose is to correlate with mathematical statement and physical law certain of the simpler outward phenomena of organic growth and structure or form'

His precious description of the *mathematical beauty* of nature deeply fascinated Alan Turing and highly contributed to the birth of the mathematical theory of morphogenesis.

2. – Alan Turing and pattern formation

After the Second World's war, Alan Turing – already well known in the field of mathematical logic and cryptology – began working on the project *'building a brain'* focussed on the construction of an electronic computer, [49]. As a consequence, he ripened a growing interest in the brain structure, becoming more and more involved in the problem of its biological development. The first results of this interest appeared in 1948 and in 1950 when Turing published two papers highlighting the relation between (i) genes and brain structure [56] (ii) human mind and computer [57].

Two years later, Alan Turing published 'The chemical basis of morphogenesis' [58], a paper that is now considered a milestone for the mathematical theory of morphogenesis. In this pioneering paper, he clearly declares

> 'The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organisms'.

To lower the complexity of the problem, when describing the zygote, Turing neglected both the electrical properties and the internal structure of the cell, taking initially into account only its chemical and mechanical properties. However, also the

> 'interdependence of the chemical and mechanical data adds enormously to the difficulty'

so that Turing only considered cases where

> 'the mechanical aspect can be ignored and the chemical aspect is the most significant' [58]

and assumed genes (or proteins and enzymes) acting only as catalysts for spontaneous chemical reactions, which regulate the production of other catalysts. Turing proposed a hypothetical chemical reaction that could spontaneously break the symmetry in an initially uniform mixture of chemical compounds. Such symmetry breaking – triggered by random disturbances – could occur because of the interplay of two main processes – reaction and diffusion – involving certain chemical 'species': reaction is the process that creates and destroys such chemicals; diffusion is the action of spreading chemicals through the tissue. Turing hypothesized that if one of the reacting pair of chemicals was a growth hormone, the symmetry breaking would result in a spatially non-uniform growth and hence to the development of structures, i.e. spatial patterns. For this reason, he evocatively called these chemicals

morphogens, choosing the word morphogen *'to convey the idea of a form producer'*, [58]. The related chemical system is called a reaction-diffusion system. Turing's analysis showed that, by properly choosing system kinetics, it was possible to obtain a steady state that – although stable in the absence of diffusion – could become unstable when diffusion was introduced. Moreover the difference in the diffusion rates of the chemicals was a necessary, but not a sufficient condition for such diffusion-driven instability to occur. Turing's results appeared in a certain sense counterintuitive since diffusion usually acts as a stabilizing and a homogenizing process. Hence, Turing's revolutionary intuition was to show that the interplay of two stabilizing processes can cause instability and lead to the arising of spatial structures. This pattern forming mechanism is now known as diffusion-driven instability (or Turing instability) and the pattern is said to emerge or self-organize.

Since Turing predicted the phenomenon of diffusion-driven instability, it took almost 40 years for Turing patterns to be *created* in a real chemical reaction. In fact Turing patterns were first experimentally observed in 1990 by De Kepper's group [13] that carried out an oscillatory chemical reaction involving chlorite and iodide ions and malonic acid (CIMA) in a thin layer of gel that was continuously fed from opposite directions with fresh reagents. Following Turing's scheme: (i) the CIMA reaction is described by an activator and inhibitor system; (ii) different rates of diffusion have been introduced in the CIMA reaction by conducting it in a polymer gel. The CIMA's reaction spatial organization properties were later confirmed by Ouyang and Swinney [47] who observed that the patterns disappeared if the gel was warmed above $18\,^{\circ}\mathrm{C}$ and reappeared by cooling again the gel. Moreover, by increasing the iodide concentration or lowering the malonic acid concentration, they showed that symmetry could be broken in different ways so that stripe as well as spot patterns could be observed.

This experimental observation of Turing structures in a real chemical phenomenon determined a renewed interest in Turing pattern formation as shown by the large number of theoretical [28, 50], computational [33, 60] and experimental studies in the field [2, 32]. Turing's diffusion-driven instability is now universally recognized as one of the leading mechanisms of spatial self-organization in reaction diffusion systems and has become the subject of extensive studies in a variety of different applied contexts.

3. – The mathematics behind Turing patterns

Investigations on Turing patterns within the reaction-diffusion modeling framework, often require the combined use of both the linear stability analysis and the nonlinear bifurcation theory. The simplest model that can give rise to diffusion-driven instability involves two chemicals – the activator u and the inhibitor v – and reads as:

$$\frac{\partial w}{\partial t} = D\Delta w + F(w) \tag{1}$$

with zero flux boundary conditions on a 2D rectangular domain. In the adimensional system (1),

$$w = \begin{pmatrix} u \\ v \end{pmatrix}, \quad D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix}, \quad F = \begin{pmatrix} f(u,v) \\ g(u,v) \end{pmatrix},$$

where: (i) w contains the system variables, i.e. the concentrations $u(r,t)$ and $v(r,t)$ of the two chemicals at the spatial position $r = (x,y)$ and time t, on the 2D rectangular domain; (ii) the diagonal matrix D contains information about the diffusion coefficients, i.e. $d = d_v/d_u$ is the ratio between the diffusion coefficients d_u and d_v of the two chemicals; (iii) F accounts for the reaction kinetics through the source terms $f(u,v)$ and $g(u,v)$; (iv) Δ stands for the Laplacian operator $\partial^2/\partial x^2 + \partial^2/\partial y^2$.

Linear stability analysis allows one to derive conditions in order that the homogeneous steady state P_e can undergo diffusion-driven instability. Following Turing's, one has hence to require that P_e is stable in the absence of diffusion but looses its stability when diffusion is considered, [43].

The homogeneous equilibrium $P_e = w_e = (u_e, v_e)$ verifies $F(w_e) = 0$ and its stability can be analyzed by studying the system behavior when a small inhomogeneous perturbation δw is introduced in the neighborhood of w_e, i.e. $w = w_e + \delta w$. The perturbation δw can be written in terms of its spectral

decomposition given by:

$$\delta w(r,t) = \sum_j c_j e^{\lambda_j t} e^{-i\mathbf{k}\cdot\mathbf{r}}, \tag{2}$$

where $\mathbf{k} = (k_1, k_2)$ is the wave number vector and $\mathbf{r} = (x, y)$ the spatial variable. Hence, the wave modes k_j rule the spatial part whereas the related eigenvalues $\lambda_j = \lambda(k_j)$ account for the temporal part and describe the growth rate of the perturbation. By substituting (2) in (1) and retaining only the linear terms, one obtains for each k_j the equation:

$$\left|\lambda_j I - J(u_e, v_e) + Dk_j^2\right| = 0,$$

where $J(u_e, v_e)$ is the Jacobian matrix evaluated at the steady state P_e. Such equation provides the characteristic polynomial of (1):

$$\lambda^2 + \left[k^2(1+d) - tr(J(u_e, v_e))\right]\lambda + h(k^2) = 0, \tag{3}$$

with

$$h(k^2) = k^4 d - k^2(J^e_{22} + dJ^e_{11}) + det(J(u_e, v_e)).$$

To predict the unstable wave numbers one makes use of the dispersion relation $\lambda(k)$, obtained by solving (3). The growing modes look like $We^{i\mathbf{k}\cdot\mathbf{r}}e^{\lambda(k)t}$, where W is the amplitude and $\lambda(k)$ is the growth rate defined by the dispersion relation. Hence, those wave numbers k characterized by $Re(\lambda(k)) < 0$ will decay whereas those such that $Re(\lambda(k)) > 0$ will grow exponentially. Among them the wave number k_{max}, corresponding to a maximum positive value of $Re(\lambda(k))$, represents the most unstable mode. At the onset of instability $\lambda(k_c) = 0$ holds and, at bifurcation, a single mode with wave number k_c is driven unstable for $d \approx d_c$. By (3), such critical wavenumber is given by:

$$k_c^2 = \frac{J^e_{22} + d_c J^e_{11}}{2d_c} = \sqrt{\frac{det(J(u_e, v_e))}{d_c}} \tag{4}$$

and the characteristic length of the pattern emergent at $d \approx d_c$ is $\lambda_c = \dfrac{2\pi}{k_c}$. Here J^e_{ij} stands for the ij entry of the Jacobian matrix evaluated at the equilibrium $P_e = (u_e, v_e)$ and d_c is the critical value of the diffusion coefficient d which is chosen as a bifurcation parameter.

For the general system (1), it can be easily shown that the Turing space – consisting of parameters resulting in Turing instability – is bounded by the following set of inequalities:

$$\begin{aligned} &J^e_{11} + J^e_{22} < 0; \quad J^e_{11}J^e_{22} - J^e_{12}J^e_{21} > 0; \\ &dJ^e_{11} + J^e_{22} > 0; \quad \frac{(J^e_{22} + dJ^e_{11})^2}{4d} > det(J(u_e, v_e)). \end{aligned} \tag{5}$$

The first two inequalities are derived by stability considerations on the homogeneous equilibrium P_e in the absence of diffusion, the others are obtained, as (4), by considerations on the onset of instability when diffusion is introduced. We refer to [43] and references therein for the explicit derivation of the system of inequalities (5). Moreover conditions (5) also indicate that $d > 1$ is a necessary condition for diffusion-driven instability to occur, meaning that the homogeneous steady state P_e cannot be unstable with respect to small spatial perturbations if both the chemicals have the same diffusion coefficients.

When conditions for diffusion-driven instability are all met, because of the destabilizing effect of diffusion, at least one mode is unstable with respect to small spatial perturbations and grows exponentially with time. The wave number k_{max} represents hence the mode that – growing faster than the others – dictates the length scale of the emerging spatial pattern as $t \to \infty$.

The linear stability analysis described above – which is developed under the assumption of small perturbations of the homogeneous steady state – turns out to be an efficient tool for the following tasks: (i) determine the bifurcation thresholds for the arising of diffusion-driven instability; (ii) identify the Turing space; (iii) approximate the characteristic length of the resulting patterns. By applying this technique one is instead not capable to gain any information about the *morphology* of the resulting pattern. For example, stripe patterns and spot patterns are two typical morphologies for reaction-diffusion systems in two spatial dimensions [43], but to establish which one is selected by the system, linear stability analysis is not enough and the use of nonlinear bifurcation theory is required.

In Turing systems, bifurcation analysis can be fruitfully employed to investigate possible qualitative changes in the stability of different patterns when a bifurcation parameter – typically the distance to the onset – is varied. The starting idea is to

express the system variables $\mathbf{w} = (u, v)$ as a superposition of unstable and stable Fourier modes:

$$\mathbf{w} = \mathbf{w_0} \sum_{\mathbf{k}_j} W_j \, e^{i\mathbf{k}_j \cdot \mathbf{r}} + W_j^* \, e^{-i\mathbf{k}_j \cdot \mathbf{r}},$$

where W_j and W_j^* are the amplitudes of the modes $\mathbf{k}_j$ and $-\mathbf{k}_j$ respectively. The unstable modes have slow dynamics whereas the stable modes relax quickly. Near the transition from a homogeneous steady state towards a pattern, it is hence possible to derive a reduced description of the resulting patterns in terms of their amplitude. The time evolution of the amplitudes W_j of the unstable modes $\mathbf{k}_j$, with $j = 1, \ldots, n$ is in fact described by the following general set of n nonlinear differential equations

$$\frac{dW_j}{dt} = \lambda_c W_j + f_j(W_1, W_2, ..., W_n). \tag{6}$$

In system (6) the linear part accounts for the linear growth predicted by the positive eigenvalue of the linearized system, see equation (3), whereas the nonlinear terms $f_j(W_1, W_2, \ldots, W_n)$ describe the nonlinear coupling of the unstable modes. The next step will be to derive the normal form for the amplitude equations related to a particular morphology, e.g. spots or stripes, and determine the coefficients of the normal form in terms of the system parameters. To this aim, various complex mathematical techniques can be applied to detect the exact form of the nonlinear terms f_j.

One of these methods is the weakly nonlinear analysis which has been employed as a mean to predict and characterize the emerging patterns [6, 19, 19, 20]. Its key idea is that – close to the bifurcation value – the pattern evolves on a slow time scale so that, by using the method of multiple scales, one can derive an evolution equation for the amplitude of the pattern. The system variables and the bifurcation parameter are hence expanded in a small parameter ε and the coefficients of the amplitude equations are then obtained through the solvability conditions of the resulting linear differential equations at different degrees of ε.

An alternative approach is based on the center manifold reduction [9, 10, 24] that essentially exploits the decoupling between the fast dynamics of the decaying components of the system, and the slow dynamics of the marginal stable modes on the center manifold. System dynamics near a bifurcation can be hence suitably described in a low-dimensional space of *amplitudes* through the so-called amplitude equations. In fact, in the neighborhood of a local bifurcation, the motion of the system variables in the r-dimensional center manifold W^c can be described by r amplitudes y_i, $i = 1, \ldots, r$, which are coordinates of a point $\mathbf{y}$ in the center subspace E^c with respect to a basis of eigenvectors (related to the critical eigenvalues) of the linearized vector field. A set of differential equations for the amplitudes y_i and a transformation $h(\mathbf{y})$ from E^c to W^c can hence be derived to describe the dynamical evolution of the system variables on the center manifold. Once the general amplitude equation is obtained, the relevant coefficients can be determined directly in terms of the original vector field and the amplitude equations can be used to capture the qualitative behavior of the system, see i.e. [24, 25, 30]. At this point, investigations on the stability properties of the morphology under study can be easily performed by using the linear stability analysis on the obtained system of the amplitude equations. For further details on nonlinear bifurcation methods, we refer to specific literature on this topic [15, 34].

The methods presented above allow one to gain insight into the essential mathematical features of Turing pattern formation, enabling to detect the bifurcation thresholds for the arising of the diffusion-driven instability phenomenon and to characterize the morphological structures expected at the onset of instability. In addition, topological methods as the Leray-Schauder degree theory can also be used to prove the existence of non constant steady states as in [55, 63] and hence to deduce the existence and non-existence of patterns. The combined use of the bifurcation and topological theories allows a more complete characterization of the emerging patterns. In fact, bifurcation techniques gain insights into the rough spatial profile of the patterns even if such results only hold in the neighboring of the bifurcation point whereas the Leray-Schauder degree theory provides results holding for a larger parameter region, but with none information about the pattern profile. To make the picture even more complete, rigorous computational methods – as the one proposed in [7] – can be used to compute global

bifurcation diagrams of non constant steady states for systems of PDEs allowing to answer specific questions about the number of non constant coexisting steady states or about the behavior of the solutions on the global bifurcating branches.

4. – Evidences from chemistry, questions from biology

To evaluate if Turing mechanism can actually be considered as a common underlying process promoting pattern formation in physics, chemistry and biology, a methodological shift in the usual way of employing mathematics is strongly required. At this regard, the different role played by chemistry and biology is particularly enlightening.

As just stressed in the previous Sections, the first experimental validation of Turing's theory of pattern formation was obtained – although 40 years later Turing's intuition – by the means of the CIMA chemical reaction. From then on, a great deal of work has led to the validation of the ideas of Turing in the chemical context (i.e. [17, 50, 60, 61]) and, very recently, also whithin the alloy electrodeposition framework (i.e. [3, 4, 31]) providing tangible examples of the fruitful interplay between mathematical modeling – with its analytical and numerical results – and the experimental validation of those results. As interestingly stressed in [61], within the chemical context, experiments can be performed under strictly controllable conditions and the relevant parameters can be manipulated in order to generate patterns. As a consequence, chemical systems can provide rigorous experimental validation of Turing's theoretical predictions and have become a privileged tool in order to elucidate the fundamental issues about pattern formation.

Differently from chemistry, the existence of Turing patterns in biology has been a long-debated question. However, also in the field of biology, much progress has recently been made in this direction. For example in [46, 59] a possible application of the Turing mechanism is pointed out at least for three biological situations. The first one is the feather bud formation in birds whose patterning was investigated by Jung et al. [27] that identified a number of activators and inhibitors (morphogens) involved in the process, hence suggesting a possible explanation of this phenomenon in terms of the Turing mechanism. A further example is given by hair follicle patterns of mammals that have been theoretically related to the Turing mechanism by a number of well established mathematical models, i.e. [11, 44], even if the existence of specific morphogens has been clearly stated only quite recently. In fact, by using a combined experimental and computational modeling approach, Sick et al. [53] suggested a couple of activator-inhibitor (i.e. WNT and DKK) functioning as morphogens to determine the hair follicle spacing in mice and provided in vivo corroboration of the reaction-diffusion mechanism for epidermal appendage formation. In addition Mou et al. [41] identified the Ectodysplasin receptor (Edar) and its inhibitor, the bone morphogenetic protein (BMP), as a further activator-inhibitor pair in follicles localisation. Finally, for the Drosophila melanogaster, a number of morphogens were identified just as the components of the gene control networks involved in patterning, [46, 59]. A further interesting case study regards the investigations in vitro of the self-organising properties of multipotential adult vascular mesenchymal cells. In the research performed by Garfinkel et al. [21], the pair BMP-2 and MGP were qualitatively recognized as a Turing morphogen pair and it was shown that – just as predicted by the Turing model – cells may aggregate into stripe, spot and labyrinthine patterns according to the different manipulations performed on the system, [40].

Along with these advances about morphogens and their identifications, much of the progress in the biological field is also due to the new role played by the mathematical modeling. In fact, just as it happened before in the case of the chemistry, mathematical models have recently been combined with the experimental observations also in biological systems. In particular, mathematical models have been recognized as *dynamic* tools that can actively support the experimental activities and provide a platform to test old and new hypotheses. In this regard, the case of the Drosophila melanogaster appears to be quite enlightening since mathematical models for Drosophila oogenesis have suggested experiments that otherwise would have not been thought (and performed) and have hence highly

improved the current understanding of the underlying biology, [46, 52]. On the other hand, both experiments and biological observations can also suggest further refinements to the existing mathematical models so that they can become less rough approximations of the complex biological realities they attempt to describe.

For a long time Turing mechanism was deemed as not capable to provide reliable spatial patterns under normal biological variation, [1, 8]. The main criticism in considering Turing models as possible pattern generators within the biological framework, has been the lack of robustness of the related Turing structures because of their sensitivity to the initial conditions.

It is in fact well known that, for a given set of system parameters, reaction-diffusion systems may exhibit a multiplicity of spatial structures and can hence be very sensitive to noise and stochasticity in the initial conditions. As a consequence, the resulting patterns lack in robustness and a precise control of the initial conditions is necessary in order a specific pattern to be selected. Surprisingly, in some cases, this pattern sensitivity to the initial conditions may not be a problem as for example in models for animal coat markings, [42]. In fact looking at pigmentation patterns, it is striking to observe that different members of the same species – although sharing a common pattern typology (e.g. stripes in the case of the zebras) – display their unique own pattern, just like the fingerprints for human beings. In this case, a large variability in patterns is highly desirable. In other contexts, as for the limb development, such sensitivity may become a big problem that can, however, be partially overcome by considering the influence of domain growth on pattern forming systems. This substantially corresponds to enrich the Turing paradigm with a more realistic feature since growth is one of the key processes in development and can have crucial effects on the occurrence of spatial heterogeneity since it is capable to change the dynamics of the patterning mechanisms, [37].

In particular, Kondo and Asai [29] investigated the fish pigmentation patterns of the marine angelfish Pomocanthus as its size doubled and indicated a Turing-like mechanism as responsible for the development of the skin pigmentation. Starting from this work, the effects of growth in reaction-diffusion models for fish skin patterns have first been investigated by the means of numerical simulations [48, 62]. A large amount of theoretical work has then focused on this topic gaining evidences that, when coupled with growth, robust pattern formation can occur without a sensitivity to the initial conditions, via a cascade of instabilities with bifurcations driven by the evolution of the domain [12, 36, 39]. The process of growth in fact can enhance a selection of certain patterning modes at the expense of the others and, in addition, enables the models to produce a dynamics much richer than in the case of fixed domains. Domain growth can hence be considered as a mechanism responsible for increasing robustness in pattern formation.

Within the biological framework, the Turing mechanism was also criticized with regard to the scale-invariance question. In Turing patterns, the number of spots or stripes is in fact proportional to the system size, whereas in many biological systems such number is often invariant against the change of the size and the system exhibits a proportionality of the scale of the pattern to the system size. Biological examples in this direction are offered by patterns in Hydra and Dictyostelium discoideum slugs or in the development of Drosophila melanogaster [22, 26].

To obtain scale-invariance, different mechanisms have been proposed: for example, Othmer and Pate [45] showed that scale-invariance could be achieved by the means of a biologically plausible modification of the Turing model. They required morphogen diffusivities to be proportional to L^2 (where L is the system-size) showing that this could be obtained if the diffusion constants depend on the concentration of a diffusible regulatory species produced at a constant rate by all the cells. Hunding and Sorensen [23] similarly discussed a simple mechanism to explain such concentration-dependent diffusion by an auxiliary chemical factor. In [26], a possible mechanism of proportion regulation is discussed based on the control of the reaction rate in reaction-diffusion systems. This can be obtained by the introduction of a morphogen which itself does not convey positional information [64], but works as a carrier of information on the size of the system. It is hypothesized that the concentration of this morphogen changes with

some power of the system size thereby influencing the rate of reaction in the Turing system and producing scale invariance.

More recently, the problem of identifying those mechanisms that regulate scaling of patterns has been widely reviewed and discussed in [59].

In particular, the control of the pattern scale by a size-sensor molecule – a modulator that regulates the reaction and transport characteristics of the morphogen – has been proposed as a generic mechanism able to produce scale invariance. Modulators can be used, either in active or passive way, to adjust the characteristic time scales of diffusion and/or reaction in a size-dependent manner in order to achieve the proper proportions of morphogen patterning. Here, in regard to the scale-invariance question, it is interestingly deduced that

> 'the scaling of spatial patterns during development can result from any of a number of diverse mechanisms. Despite the fact that the details of each scaling mechanism vary, they all must incorporate size information into the modulation of transport, reaction and production rates appropriately, in order to adjust the intrinsic scale and amplitude of the patterning species. Proper scaling requires at least one species that properly encodes the size of the tissue being patterned in order that the distribution of other species be scale invariant', [59].

In conclusion, the lack of robustness due either to the patterns sensitivity to the initial conditions or to their scale-dependence, can be satisfactorily overcome by acting on the Turing model through suitable refinements that, increasing the complexity of Turing's paradigm, drive the system towards an higher degree of realism. This is not surprising since Turing himself was well aware that, because of the many simplifications, his model represented a severe approximation of a real biological system:

> 'This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge' [58]

Turing knew that the attempt to fully explain something as complex as the patterning in developing systems with a simple two-equation model was rather utopian and that further more realistic refinements would be needed to deeply understand the general features related to the growth of form in nature.

5. – The scientific impact of Turing's theory

Self-organisation is currently a widespread concept in chemistry, biology and ecology but questions as 'Do chemical, biological and ecological patterns really have anything in common?' still represent an open challenge. Although the role of the Turing mechanism in chemistry has been well elucidated, in the biological context the Turing model has challenged – and continues to challenge – several generations of biologists as well as of mathematicians.

Biologists faced the arduous task to prove the existence of morphogens in biological systems and still have the challenge to corroborate or contradict, often with a complex series of experiments, the theoretical findings coming from Turing's theory and from its ramifications. Mathematicians have been challenged by the complexity arising behind the apparent simplicity of the Turing model: an amazing variety of spatial and spatio-temporal patterns has in fact been detected in the many mathematical models exhibiting the Turing mechanism and the development of complex mathematical techniques has been necessary to fully characterize the emerging dynamics. The nonlinear bifurcation theory, the fully nonlinear theory of Turing patterns as well as the computational methods developed to rigorously characterize the bifurcation branches are clear examples in this direction. Furthermore, the problem of Turing pattern formation on growing domains as well as the one of identifying the mechanisms that regulate scaling in Turing patterns are two challenging tasks which have recently stimulated much theoretical and computational works.

However, along with the many still open challenges stemming from Turing's original idea, what is astonishing in Turing's theory is the strongly interdisciplinary nature of the resulting research. We are now well aware that in chemistry, as well as in biology, the development of Turing's theory has caused a paradigm shift in the usual way of 'thin-

king', making the fruitful interplay between mathematical modeling and experimental verifications an essential matter of fact. In this way of making science, experiments have stimulated the arising of new mathematical problems and mathematical theories have suggested to carry out experiments that otherwise would not have been perhaps even thought.

In a certain sense, we can say that Turing's theory acted as a driving force to bring the scientific methodology proposed in physics by Galileo – which was based on the innovative combination of experiments and mathematics [51] – beyond the boundaries of physics, allowing the galilean approach to become a concrete paradigm for the scientific progress both in chemistry and in biology. In this paradigm, nature and maths must be the main actors of the same scientific discovery process. In his beautiful book 'Il Saggiatore', Galileo already wrote about this *strange pair*, nature and maths:

> 'Philosophy [nature] is written in that great book which ever is before our eyes – I mean the universe – but we cannot understand it if we do not first learn the language and grasp the symbols in which it is written. The book is written in mathematical language, and the symbols are triangles, circles and other geometrical figures, without whose help it is impossible to comprehend a single word of it; without which one wanders in vain through a dark labyrinth.' [18]

The lesson emerging from the talented Turing's idea and from the fascinating research stemming from it is that, in this great book 'which ever is before our eyes', the mathematical beauty of nature is still far from being fully revealed so that questions as 'What do fishes have in common with the desert sand dunes?' no longer seem so obvious and are actually waiting for reliable answers.

Acknowledgments. This work has been performed under the auspices of the Italian National Group for Mathematical Physics (GNFM-Indam). I sincerely wish to thank Maria Groppi for the welcome invitation to contribute with this article to 'Matematica, Cultura e Società – Rivista dell'Unione Matematica Italiana' and two anonymous reviewers for their interesting comments on the paper. I would also like to thank Benedetto Bozzini and Ivonne Sgura – my *travel companions* in the ongoing discovery of the fascinating world of pattern formation – for the many inspiring discussions on the subject.

References

[1] J. Bard, I. Lauder, *How well does Turing's theory of morphogenesis work?*, J. Theor. Biol. **45** (1974), 501–531.

[2] P. Borckmans, G. Dewel, A. De Wit, E. Dulos, J. Boissonade, F. Gauffre, P. De Kepper, *Diffusive instabilities and chemical reactions*, Int. J. Bif. and Chaos **12** (2002), 2307–2332.

[3] B. Bozzini, D. Lacitignola, C. Mele, I. Sgura, *Coupling of morphology and chemistry leads to morphogenesis in electrochemical metal growth: a review of the reaction-diffusion approach*, Acta Applic. Mathematicae **122** (2012), 53–68.

[4] B. Bozzini, D. Lacitignola, C. Mele, I. Sgura, *Morphogenesis in metal electrodeposition*, *Note di Matem.* **32** (2012), 7–46.

[5] B. Bozzini, D. Lacitignola, I. Sgura, *Spatio-temporal organisation in alloy electrodeposition: a morphochemical mathematical model and its experimental validation*, Journal of Solid State Electrochemistry **17** (2013), 467–479.

[6] B. Bozzini, G. Gambino, D. Lacitignola, S. Lupo, M. Sammartino, I. Sgura, *Weakly nonlinear analysis of Turing patterns in a morphochemical model for metal growth*, Computers & Mathematics with Applications **70** (2015), 1948–1969.

[7] M. Breden, J.P. Lessard, M. Vanicat, *Global bifurcation diagrams of steady states of systems of PDEs via rigorous numerics: a 3-component reaction-diffusion system*, Acta Applicandae Mathematicae **128** (2013), 113–152.

[8] B. Bunow, J.P. Kernevez, G. Joly, D. Thomas, *Pattern formation by reaction-diffusion instabilities: application to morphogenesis in Drosophila*, J. Theor. Biol. **84** (1980), 629–649.

[9] T.K. Callahan, E. Knobloch, *Symmetry-breaking bifurcations on cubic lattices*, Nonlinearity **10** (1997), 1179.

[10] T.K. Callahan, E. Knobloch, *Pattern formation in three-dimensional reaction-diffusion systems*, Physica D **132** (1999), 339.

[11] J.H. Claxton, *The determination of patterns with special reference to that of the central primary skin follicles in sheep*, J. Theor. Biol. **7** (1964), 302–317.

[12] E. Crampin, E.A. Gaffney, P.K. Maini, *Reaction and diffusion on growing domains: scenarios for robust pattern formation*, Bulletin Mathematical Biology **61** (1999), 1093–1120.

[13] V. Castets, E. Dulos, J. Boissonade, P. De Kepper, *Experimental evidence of a sustained standing Turing-type nonequilibrium chemical pattern*. Phys. Rev. Lett. **64** (1990), 2953.

[14] J.D. Crawford, *Introduction to bifurcation theory*, Rev. Mod. Phys. **63** (1991), 991–1037.

[15] M.C. Cross, P.C. Honenberg, *Pattern formation outside the equilibrium*, Reviews in Modern Phys. **65** (1993), 851–1112.
[16] G.C. Cruywagen, P.K. Maini, J.D. Murray, *Biological pattern formation on two-dimensional spatial domains: a nonlinear bifurcation analysis*, SIAM J. Appl. Math. **57** (1993), 1485–1509.
[17] I.R. Epstein, J.A. Pojman, O. Steinbock, *Introduction: Self-organization in non equilibrium chemical systems*, Chaos **16** (2006), 037101.
[18] G. Galilei, *Il Saggiatore*, 1623.
[19] G. Gambino, M.C. Lombardo, M. Sammartino, *Turing instability and traveling fronts for a nonlinear reaction-diffusion system with cross-diffusion*, Math. Comp. Simul. **82** (2012), 1112–1132.
[20] G. Gambino, M.C. Lombardo, M. Sammartino, *Pattern formation driven by cross-diffusion in a 2D domain*, Nonlinear Analysis: Real World Applications **14** (2013), 1755–1779.
[21] A. Garfinkel, Y. Tintut, D. Petrasek, K. Bostrom, L.L. Demer, *Pattern formation by vascular mesenchymal cells*, Proc. Nat. Acad. Sci. USA **101** (2004), 9247–9250.
[22] B. Houchmandzadeh, E. Wieschais, S. Leibler, *Establishment of developmental precision and proportions in the early Drosophila embryo*. Nature **415** (2002), 798–802.
[23] A. Hunding, P.G. Sorensen, *Size adaptation of Turing prepatterns*, J. Math. Biol. **26** (1988), 27–39.
[24] M. Ipsen, F. Hynne, P.G. Sorensen, *Amplitude equations and chemical reaction-diffusion systems*, Int. J. Bifurc. Chaos **7** (1997), 1539–1554.
[25] M. Ipsen, F. Hynne, P.G. Sorensen, *Systematic derivation of amplitude equations and normal forms for dynamical systems*, Chaos 8 (1998), 834–852.
[26] S. Ishihara, K. Kaneko, *Turing pattern with proportion preservation*, J. Theor. Biol. **238** (2006), 683–693.
[27] H.S. Jung, P.H. Francis-West, R.B. Widelitz, T.X. Jiang, S. Ting-Berreth, C. Tickle, L. Wolpert, C.M. Chuong, *Local inhibitory action of BMPs and their relationships with activators in feather formation: implications for periodic patterning*, Dev. Biol. **196** (1998), 11–23.
[28] R. Kapral, K. Showalter, *Chemical Waves and Patterns*, Kluwer Academic Publishers, 1995.
[29] S. Kondo, R. Asai, *A reaction-diffusion wave on the skin of the marine angelfish Pomacanthus*, Nature **376** (1995), 765–768.
[30] D. Lacitignola, B. Bozzini, I. Sgura, *Spatio-temporal organization in a morphochemical electrodeposition model: analysis and numerical simulation of spiral waves*, Acta Applicandae Mathematicae **132** (2014), 377–389.
[31] D. Lacitignola, B. Bozzini, I. Sgura, *Spatio-temporal organization in a morphochemical electrodeposition model: Hopf and Turing instabilities and their interplay*, European Journal of Applied Mathematics **26** (2015), 143–173.
[32] K.J. Lee, W.D. McCormick, Q. Ouyang, H.L. Swinney, *Pattern Formation by Interacting Chemical Fronts*, Science, New Series **261** (1993), 192–194.
[33] T. Leppanen, M. Karttunen, K. Kaski, R.A. Barrio, *Turing systems as models of complex pattern formation*, Braz. J. Phys. **34** (2004), 368–372.
[34] T. Leppanen, *The Theory of Turing Pattern Formation*, in *Current Topics in Physics in Honor of Sir Roger Elliot*, Imperial College Press, Eds. K. Kaski and R.A. Barrio, 190–227, 2005.
[35] Y.J. Li, J. Oslonovitch, N. Mazouz, F. Plenge, K. Krischer, G. Ertl, *Turing-type patterns on electrode surfaces*, Science **291** (2001), 2395–2398.
[36] A. Madzvamuse, E.A. Gaffney, P.K. Maini, *Stability analysis of reaction-diffusion systems with time-dependent coefficients on growing domains*, Journal of Mathematical Biology **61** (2010), 133–164.
[37] P.K. Maini, E.J. Crampin, A. Madzvamuse, A.J. Wathen, R.D.K. Thomas, *Implications of domain growth in morphogenesis*. In *Mathematical Modelling & Computing in Biology and Medicine*: 5th ESMTB Conf. 2002, vol. **1**, 67–73, 2003.
[38] P.K. Maini, *Using mathematical models to help understand biological pattern formation*. Comptes Rendus Biologies **327** (2004), 225–234.
[39] P.K. Maini, T.E. Woolley, R.E. Baker, E.A. Gaffney, S. Seirin Lee, *Turing's model for biological pattern formation & the robustness problem*, J.R. Soc.Interface Focus **2** (2012), 487–496.
[40] P.K. Maini, *And Philip K. Maini Wonders at - Turing's Theory of Morphogenesis in Alan Turing: His Work and Impact, 1st Edition, 684–689*, edited by S. Barry Cooper, J. van Leeuwen, 2013.
[41] C. Mou, B. Jackson, P. Schneider, P.A. Overbeek, D.J. Headon, *Generation of the primary hair follicle pattern*, Proc. Natl. Acad. Sci. U.S.A. **103** (2006), 9075–9080.
[42] J.D. Murray, *A pre-pattern formation mechanism for animal coat markings*. J. Theor. Biol. **88** (1981), 161–199.
[43] J.D. Murray, *Mathematical Biology II; Spatial models and biomedical applications, 3rd edition*, Springer, 2002.
[44] B.N. Nagorcka, J.R. Mooney, *The role of a reaction-diffusion system in the formation of hair fibres*, J. Theor. Biol. **98** (1982), 575–607.
[45] H.G. Othmer, E. Pate, *Scale-invariance in reaction-diffusion models of spatial pattern formation*, Proc. Natl. Acad. Sci. **77** (1980), 4180–4184.
[46] H.G. Othmer, K. Painter, D. Umulis, C. Xue, *The intersection of theory and application in biological pattern formation*, Math. Model. Nat. Phenom. **4** (2009), 3–79.
[47] Q. Ouyang, H.L. Swinney, *Transition from a uniform state to hexagonal and striped Turing patterns*, Nature **352** (1991), 610–612.
[48] K.J. Painter, P.K. Maini, H.G. Othmer, *Stripe formation in Juvenile Pomacanthus explained by a generalized Turing mechanism with chemotaxis*, PNAS **96** (1999), 5549–5554.
[49] S. Roth, *Mathematics and biology: a Kantian view on the history of pattern formation theory*, Dev. Genes Evol. **221** (2011), 255–279.
[50] F. Sagués, I.R. Epstein, *Nonlinear Chemical Dynamics*, Dalton Trans. (2003), 1201–1217.
[51] M. Sharratt, Galileo: *Decisive Innovator*. Cambridge: Cambridge University Press, 1994.
[52] S.Y. Shvartsman, C.B. Muratov, D.A. Lauffenburger, *Modeling and computational analysis of EGF receptor-mediated cell communication in Drosophila oogenesis*, Development **129** (2002), 2577–2589.
[53] S. Sick, S. Reinker, J. Timmer, T. Schlake, *WNT and DKK determine hair follicle spacing through a reaction-diffusion mechanism*, Science **314** (2006), 1447–1450.

[54] D.W. Thompson, *On Growth and Form*, Cambridge University Press, 1917.
[55] C. Tian, Z. Ling, Z. Lin, *Turing pattern formation in a predator-prey-mutualist system*, Nonlinear Analysis: Real World Applications **12** (2011), 3224–3237.
[56] A.M. Turing, *Intelligent machinery*, In: *The Essential Turing*, Oxford University Press, 1948, (reprinted 2004).
[57] A.M. Turing, *Computing machinery and intelligence*, Mind **59** (1950), 433–460.
[58] A.M. Turing, *The chemical bases of morphogenesis*, Phil. Trans. Royal Soc. London **B 237** (1952), 37–72.
[59] D.M. Umulis, H.G. Othmer, *Mechanisms of scaling in pattern formation*, Development **140** (2013), 4830–4843.
[60] V.K. Vanag, I.R. Epstein, *Design and control of patterns in reaction-diffusion systems*, Chaos **18** (2008), 1–11.
[61] V.K. Vanag, I.R. Epstein, *Pattern formation mechanisms in reaction-diffusion systems*, Int. J. Dev. Biol. **53** (2009), 673–681.
[62] C. Varea, J.L. Aragon, R.A. Barrio, *Confined Turing patterns in growing systems*, Phys. Rev. **E 56** (1997), 1250–1253.
[63] J. Wang, J. Wei, J. Shi, *Global bifurcation analysis and pattern formation inhomogeneous diffusive predator-prey systems*, J. Differential Equations **260** (2016), 3495–3523.
[64] L. Wolpert, *Positional information and the spatial pattern of cellar differentiation*, J. Theor. Biol. **25** (1969), 1–47.

D. Lacitignola

The author is researcher in Mathematical Physics at the University of Cassino and Southern Lazio (Italy). Her teaching activities are concerned with applied mathematics and mathematical modelling. Her research interests are focussed on nonlinear dynamical systems, bifurcation theory, pattern formation mechanisms in reaction-diffusion systems and mathematical modelling with applications to biology, chemistry and life sciences.