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Patterns and dynamics, homage to Pierre Coullet / *Formes et dynamique : hommage à Pierre Coullet*

The biological frontier of pattern formation

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ABSTRACT

Morphogenetic patterns are highly sophisticated dissipative structures. Are they governed by the same general mechanisms as chemical and hydrodynamic patterns? Turing's symmetry breaking and Wolpert's signalling provide alternative mechanisms. The current evidence points out that the latter is more relevant, but reality is still far more complicated.

1. Dissipative structures: from hydrodynamics to chemistry

The end of the last, and the beginning of this century was the heyday of general theory of pattern formation far from equilibrium that brought under a common roof symmetry breaking phenomena that had always fascinated people, but only marginally touched earlier the mainstream science. One of the high points of this drive was the Advanced Study Institute PHYSBIO organized in 2002–2008 by Pierre Coullet together with the late Lorenz Kramer. As it is clear from this abbreviation, already at that time the centre of attention of nonlinear science was moving from general theories to the huge unexplored territory of biological patterns, of which morphogenesis presents the most challenging problems. This tendency has only strengthened since.

First scientific studies of what would be encompassed by the term "dissipative structures" [1], in Faraday's vibrating liquid layers [2] and Bénard convection [3], originated in fluid mechanics. This was an inspiration and example, but it was natural and non-controversial; after all, everybody is used to a play of sea waves and river currents. Perhaps it was only the regularity of patterns, the hexagonal tiling resembling the crystalline order that maintains itself far from equilibrium calmness, which was unusual and thought provoking?

It was not hydrodynamic but chemical structures that excited the pioneering work of the mid-20th century, since they promised to show the way to understanding the basic mechanism of morphogenesis [4] and evolution [5,6]. The paper bearing the ambitious title "The chemical basis of morphogenesis" [4] (winged by the fame of the Turing machine and Enigma Code but more cited than read) ends on a humble note: "It must be admitted that the biological examples which it has been possible to give in the present paper are very limited. This can be ascribed quite simply to the fact that biological phenomena are usually very complicated".

The rational message to be extracted from the 36 long pages is that the formation of chemical patterns requires, in the simplest setting, combining a slowly diffusing activator with a rapidly diffusing inhibitor. This principle, that can be established in a few lines by linear stability analysis of a two-component reaction–diffusion system, is prominent in model pattern-forming systems [7,8], and has been later clearly formulated in a general form [9]. General problems become easy

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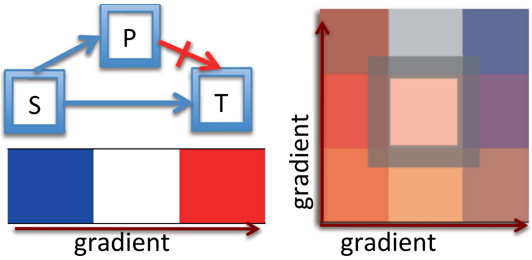

Fig. 1. On the left, the scheme of a feed-forward loop and Wolpert's "French flag". On the right, nine expression domains of the "Franco-German flag"; the frame indicates the zone of influence of the ligand produced in the middle square.

in retrospect; even nonlinear features of model patterns can be explored analytically using the scale separation between the diffusional lengths of the two species [10], but particular realisations of general principles overgrow by details like a ship's hull by barnacles.

Much attention has been paid to the Belousov–Zhabotinsky (BZ) reaction displaying dazzling chemical waves [11]; much later, stationary patterns have been also observed in precision experiments [12,13]. Patterns and waves on a finer scale, with added anisotropy observed on catalytic surfaces, earned the Nobel prize to Ertl [14]. Simple reaction-diffusion systems served as reasonable, if not quantitative, models of these patterns, even though the precise mechanism of the BZ reaction is disputed to this day. The same models were successfully applied to more complicated phenomena, such as desert vegetation patterns [15]. To be fair, generic models, such as the complex Ginzburg–Landau [16] or Swift–Hohenberg [17] equations reproduce qualitatively the same variety of patterns. Generalised models of this kind are equally applicable to chemical, hydrodynamical, optical, and population patterns [18]. But does the Turing mechanism indeed qualify as the chemical basis of morphogenesis?

2. Wolpert *vs.* Turing

There is a strong general reason why the answer should be negative, at least as far as it concerns animal development. Observed chemical patterns, as well as patterns in model computations, are repetitive, and their apparent variety is caused either by a difference in initial conditions or by random inputs. On the contrary, the morphogenetic process starting from an undifferentiated eggshell is unique and precise, with variegated features emerging at precise locations. Repetitive patterns are common in plants where the symmetry-breaking scenario may be applicable [19], but even there common spiral patterns arise from self-organization in an iterative growth process [20] rather than Turing-like symmetry breaking. Superficially realistic animal coat patterns modelled by solving the FitzHugh–Nagumo equations [21] have no connection with the actual intricate three-layer mechanism [22].

A rival morphogenetic scenario, supported by the evidence accumulated during half a century [23–25], has been put forward by Wolpert [26]. Unlike Turing patterns emerging on a homogeneous background, patterns of animal development are governed by morphogens emanating from a certain source, thereby breaking the symmetry of a featureless background, and the positional information is provided by *morphogenetic gradients*.

The Turing and Wolpert scenarios do have common features and can be even combined [27]. Interaction of activating and repressing agents is necessary also in Wolpert's scenario, and the essential feature of acting genetic schemes is a *feed-forward* motif [28]. The simplest patterning scheme involves a single incoherent feed-forward loop $S \to P$, $S \to T$, $P \dashv T$ that includes two activating ($\to$) links with different thresholds initiated by the same signal S (induced by a morphogen M), and an inhibiting ($\dashv$) link from the intermediate protein P to the target. This scheme generates the classical "French flag" pattern [26], as in the left-hand panel of Fig. 1, with the target T expressed in the middle ("white") interval, where the signal level is below the higher threshold of the link to the protein P and above the lower threshold of the direct link to the target. Differences in diffusivities of morphogens also play a role in localising activating or repressing thresholds, although there is no reason for the latter being less diffusive. And, of course, all morphogenetic patterns are dissipative structures in a wide sense, as they are actively driven and sustained far from equilibrium.

Repetitive patterns do occur; for example, the formation of fingers has been reproduced by a rather realistic two-dimensional simulation [29]. Fingers have, however, to be generated at a proper location, which requires positional information, and in a predetermined number, which requires scale invariance. Even in development processes generating repetitive regular patterns, such us segmentation [30], hair follicle or feather formation [31,32], or the development of ommatidia in the *Drosophila* eye [33,34], these patterns do not emerge on a homogeneous background as a result of random fluctuations, but are generated by a morphogenetic wave propagating in a predetermined direction.

The "French flag" scheme can be straightforwardly extended to two-dimensional (2D) patterns under the combined action of crossed gradients. A common example of 2D signalling is found in combined anterior–posterior and dorsal–ventral gradients in a developing *Drosophila* eggshell [35]. A second signal, generated by a morphogen with the gradient in the direction normal to that of the first signal, may induce 2D patterning that can be presented, extending Wolpert's simile, as the nine-colour superposition of French and German flags, as in the right-hand panel of Fig. 1 [36]. For example, expression