# Some historical aspects of Turing's Morphogenesis

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**Abstract**

This is a to-be-expanded historical account of Turing's theory of morphogenesis which accompanies the article, "Beyond the blueprint: reimagining Turing's Morphogenesis for the next generation of biology." We also refer to [1] and the introduction of [2] for other historical aspects.

## 1 Origins

Alan Turing conceived one of theoretical biology's enduring models (see Box 1), in a landmark work [3]: the highly challenging problem of how the early embryo acquired its form, tackled through a model poised between complexity and pragmatism. Containing some of the earliest numerical simulations of biological phenomena, it also presaged the near ubiquitous modern use of digital computing within theoretical biology.

At the time, appropriate avenues for publication were thin on the ground. Unlike the Hodgkin & Huxley model [4], published the same year in the Journal of Physiology and accompanied by experiments, Turing's paper was purely theoretical. The only journal dedicated to mathematical biology at the time – the Bulletin of Mathematical Biophysics[1] – was established in 1939, but Turing may have been unaware of its existence[2]. As a Fellow of the Royal Society, its Philosophical Transactions was natural, but even that dictated a binary choice: Series A or B, the physical or biological sciences? Notwithstanding the significant amount of mathematics, biologists were Turing's target audience and the paper subsequently appeared in Series B, in a volume sandwiched by articles on the metabolism of flying locusts [5] and the morphology of species belonging to the plant genus *Stauropteris* [6]. While Turing took pains to make the paper accessible, it was clearly an outlier.

In the immediate years following its publication, it received little attention[3]: some positive remarks for a role in phyllotaxis [7] and insect sensory bristle formation [8, 9], but also doubt [10]. Attention from the mathematical community was negligible until the 1960s, but on 'rediscovery' interest grew rapidly. As the field of theoretical and mathematical biology blossomed from the 1970s onwards, it became engrained in the consciousness and the near-default model for explaining pattern formation phenomena in biology and beyond.

Yet, the biological community remained unconvinced. As early as the 1950s, Waddington had expressed scepticism[4] as to whether Turing's "chancy" mechanism could play any part in truly important processes [10]. Bard and Lauder suggested it was suitable for mosaic patterns like hair follicles, but nothing regulatory or of deep biological importance [11]. While some convincing-looking applications had emerged, well into the 1980s any 'evidence' was largely restricted to a similarity in patterning. Fundamentally, where was the validation for Turing's proposal, and what was the scope of the theory?

[1]Later renamed the Bulletin of Mathematical Biology.
[2]Turing did not appear to have any previous intersection with this nascent field.
[3]Turing's premature death in 1954 deprived us of its proponent.
[4]"Probably the processes which (Turing) and Henke have discussed play a part only in the quasi-periodic dapplings and mottlings which often fill up relatively unimportant spaces." See [10], p.423.

**Box 1: Turing's paper**

Turing's paper is crammed with originality and we briefly comment on some details, including the central question, the proposed model, and the analytical approach. At the core was the challenging problem as to how the developing organism could acquire structure and form (morphogenesis), which was posed by Turing as a problem of *symmetry breaking*: how could a near-symmetrical mass of cells self-organise to create spatial structure of the emerging anatomy?

The proposed model relied on – using his own words – "quite simple" assumptions: the diffusion of and reaction between chemical species, coining the term *morphogen* to describe these players. Conceivably, if the morphogens could resolve into a spatially varying pattern, Fig. **??**(a)i, then this pattern could direct the subsequent morphogenesis of the embryo.

Turing first modelled this for a discrete number of cells, conveniently arranged into a circular ring, but subsequently for a continuous tissue. It is the latter form that is now standard, mathematically stated as a *reaction-diffusion* system where each equation describes the spatial and temporal dynamics of one of the morphogens, Fig. **??**(a)ii. At least two morphogens are needed, and when there are exactly two it is common to refer to them as an *activator* and *inhibitor*, a terminology that arises from the influential work of Gierer and Meinhardt [12] and the idea of patterning though *local activation and lateral inhibiton (LALI)*, Fig. **??**(a)iii.

To show that such a model could address the symmetry breaking challenge, Turing devised a *stability analysis*: exploring whether it would be possible for a uniform-in-space steady state morphogen distribution – representing a symmetric initial state – to become unstable in a manner that leads to a spatially periodic pattern. Making this mathematically tractable required a *linearity assumption*, where general forms for the reaction are replaced with linear forms. The analysis is only valid as long as the morphogen distributions remain close to the uniform steady state, but this would still reasonably describe the onset of a process that could lead to patterning.

Crucially, this approximation allowed Turing to demonstrate that there were a number cases where the steady state could become unstable. In particular, the emergence of a *periodic pattern with a characteristic wavelength*, Fig. **??**(c)i. As the icing on the cake, Turing demonstrated the feasibility of the proposed model through some early numerical simulations. Few had access to a suitable machine, but one of Turing's duties was to write software for the Manchester Mark 1. This formed the prototype of the Ferranti Manchester Universal Electronic Computer, the first commercially available electronic general-purpose stored program digital computer, and its sales brochure describes PDEs for "(t)he distribution of growth hormone in biological tissue" as an example of one of the problems that had been solved on the machine [13].

## 2 Growth of a theory

Turing's classic paper is cited frequently and widely[5] and an array of connected terminology has emerged: reaction-diffusion, Turing (sometimes diffusion-driven) instabilities, self-organisation, symmetry-breaking, dissipative systems, local activation and lateral inhibition (LALI). One-size-fits-all definitions are tricky to pin down and, while general concepts can be more important than precise definitions, different interpretations can be a source of confusion, particularly in arguments of what constitutes evidence for a given theory.

The broad terminology is the natural consequence of the many branches stemming from Turing's work. As a model it can be viewed both conceptually (explaining the concept of self-organisation) and mechanistically (expressed in terms of reaction and diffusion processes). Its rediscovery in the 1960s brought it to the attention of diverse disciplines – mathematics, biology, physics, chemistry etc – with studies that would widen it out or narrow it down. Growing interest in symmetry breaking and dissipative systems [15] linked it to self-organising phenomena beyond morphogenesis: as examples, Rayleigh–Bénard convection in fluid mechanics, the Belousov-Zhabotinskii reaction in chemistry, and aggregation of social amoebae. The textbook-style expositions possible under just two morphogens

[5] Aronson defined a classic as a "work which is often cited but seldom read" [14].

[16] clarified its counter-intuitive notions, such as the possibility of a diffusion-driven instability despite diffusion generally being a homogenising or stabilising process.

The notion of LALI emerged independently[6] with the suggestion that embryonic patterning events could arise through processes of activator-inhibitor or substrate depletion [12, 18]. The intuitive and biologically palatable terms, alongside prototypical kinetics and striking (at the time) numerical simulations, broadened its appeal to those daunted by more mathematical treatments. Such is the influence of this work that for many LALI is practically synonymous with Turing's idea, though there are important distinctions (see later). Reinterpretations in the context of ecosystems, such as predators and prey [16], lifted its range of application even further.

Turing's analysis was relatively simple in purely mathematical terms[7], but its importance lies in acting as a blueprint for demonstrating self-organisation across distinct phenomena captured by qualitatively similar mechanisms. As examples, chemotaxis models [20], mechanochemical models [21], and non-local adhesion models [22] can all exhibit spontaneous pattern formation and all fall under a general class of systems that display a Turing instability, even if the biological processes by which this is achieved may be quite distinct. This common root can allow lines to be drawn to LALI: for example, in the Keller-Segel chemotaxis model, it is the positive feedback between chemotaxis and attractant production that provides a form of local activation, and the depletion of cells from the surroundings that provides a lateral inhibition.

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[7] One of the peer reviews remarked that "the mathematics was not very deep, and that the mathematician would not get any new principles from it" [19].

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