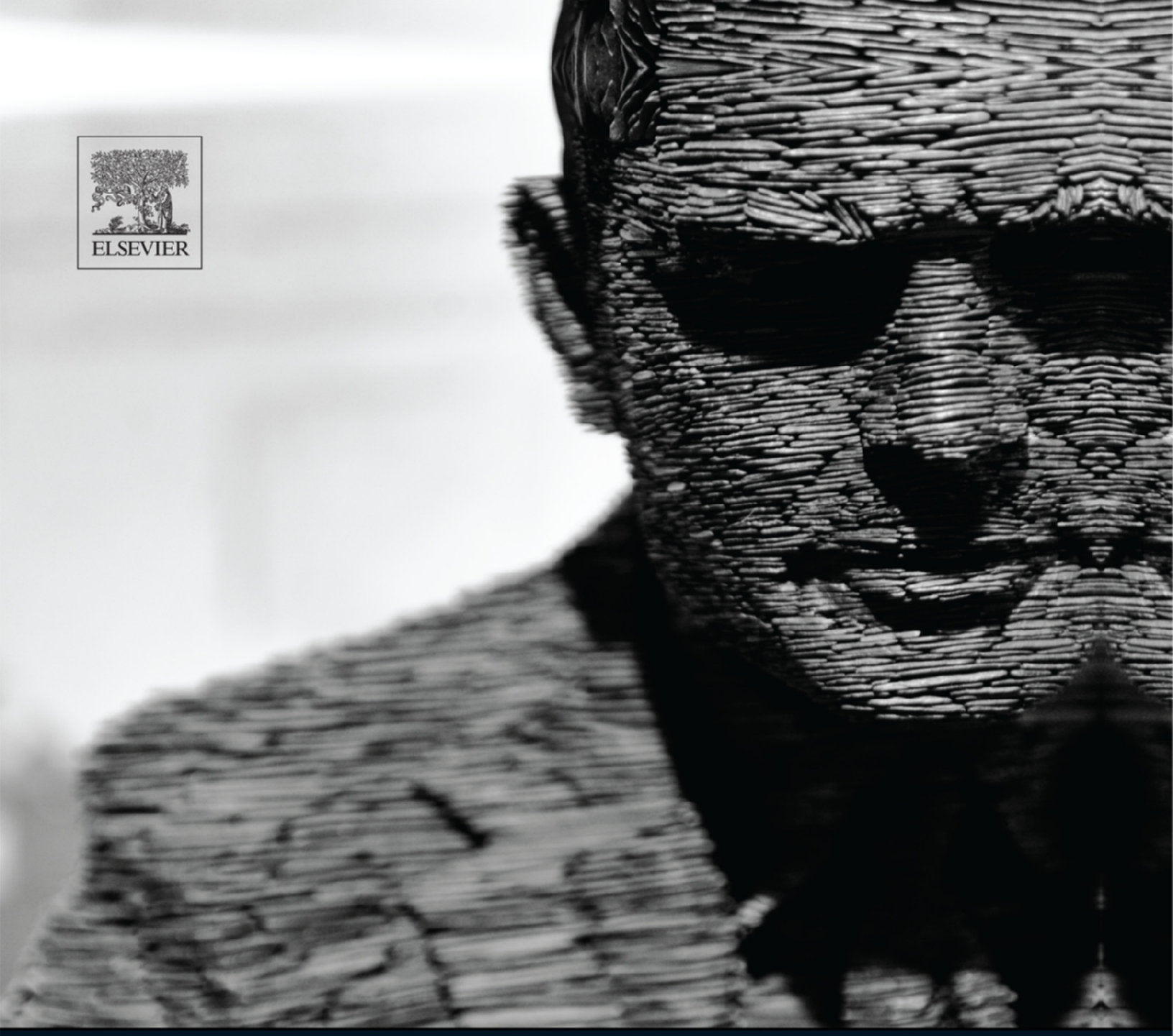

ALAN TURING

HIS WORK AND IMPACT

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included in the Collected Works, but it is clear just from the comment he made to Robin Gandy (see Hodges (1983, p. 431)) that his new ideas were 'intended to defeat the argument from design'.[2]

The development of any organism, and above all a complex one such as a human being, is a truly remarkable process. We each begin as a single cell and eventually become an adult made up of approximately 10^{15} cells of about 200 different types organised in a very complicated arrangement and able to cooperate to carry out many vital functions. This would be an impressive enough accomplishment if it were done under the supervision of an intelligent craftsman; in fact, it happens through nothing more than a series of interrelated physical and chemical processes. The genes play an important role in this, but we cannot just say that the genes create the form and let it go at that. The genes can only influence development through their effects on chemical reactions, and they themselves have to be turned on and off at appropriate times. Important though developmental genetics is, ultimately it is the physics and chemistry that we have to understand.

While the later stages of development are often complicated and hard to understand in detail, perhaps the greatest difficulty in principle is at the very beginning. Once a pattern of some sort has been established, it can serve as the basis for the next stage and so on. But how does the process start? The original cell is not, to be sure, totally symmetric; it has a polarity induced by the point of entry of the sperm, but this does not seem enough to determine the structure that is to appear. How does a pattern appear in a region that has nothing to serve as a template – or, equivalently, where does the template come from? This was what Turing saw as the fundamental problem.

Reference

Hodges, A., 1983. Alan Turing: The Enigma, Burnett Books, London.

And Philip K. Maini wonders at —

TURING'S THEORY OF MORPHOGENESIS

Alan Turing's paper, 'The chemical basis of morphogenesis' (Turing, 1952) has been hugely influential in a number of areas[3]. In this paper, Turing proposed that biological pattern formation arises in response to a chemical pre-pattern which, in turn, is set up by a process which is now known as *diffusion-driven instability*. The genius of this work was that he considered a system which was stable in the absence of diffusion and then showed that the addition of diffusion, which is naturally stablising, actually caused an instability. Thus, it was the *integration* of the parts that was as crucial to the understanding of embryological development as the parts themselves – patterns *emerged* or *self-organisd* as a result of the individual parts interacting. To see how far ahead of his time he was,

[2] Peter Saunders continues with further comments on this aspect of the morphogenesis work in his Introduction in the *Collected Works*. But see his contribution later in this chapter – *Defeating the Argument from Design* – for his recent thinking on the topic.

[3] 3,459 citations – ISI web of science 25/4/11.

one has to note that it is only now in the post-genomic era of systems biology that the majority of the scientific community has arrived at the conclusion he came to some 60 years ago.

Turing termed these chemicals 'morphogens'. For example, in phyllotaxis, an area in which he was interested, if the morphogen was a growth hormone, then a spatially non-uniform pre-pattern in it could cause symmetry breaking in a ring of cells leading to branching or leaf formation. More generally, if the morphogen determined cell fate, then the model could be used to describe patterning phenomena in a variety of settings (see, for example, Murray (2003)).

The Turing model was generalised in 1972 by Gierer and Meinhardt (see Meinhardt, 1982 and references therein) to the idea of activator–inhibitor systems and the general patterning principle of 'short-range activation, long-range inhibition' or 'local-activation, lateral inhibition (LALI)'. They also showed how the model could be used to explain regulation as well as normal patterning. Many subsequent models for biological pattern formation have been proposed based on very different biology, for example, (i) the theory of chemotaxis in which cells are proposed to move up gradients in chemicals (known as chemoattractants) so that the patterns are in cebu now.

Idensity (see, for example, Keller and Segel (1970)); (ii) the mechanochemical [4] theory of morphogenesis in which it is proposed that the physical interaction of cells with extracellular matrix leads to instabilities from which spatially varying patterns in cell density emerge (Murray, 2003, and references therein); (iii) neural models in which the neuroscretory system leads to growth and pigmentation (Boettiger et al., 2009). These models also have very different mathematical forms from the original parabolic system of equations proposed by Turing, some involving hyperbolic and/or elliptical terms, while others are of integro-partial differential equation type. However, they all generate pattern by the LALI principle. As a result of this, one can draw general conclusions on how patterns will depend on domain length and geometry, leading to mathematically derived notions of developmental constraints and the evolution of and morphogenetic rules for certain patterns (for example, cartilage formation in the vertebrate limb – see Murray (2003)).

The notion that something as complicated as patterning in developmental biology can be described by two equations appears fanciful but this was recognised by Turing, who stated in his paper:

> 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.

His model may be thought of as being applied at a certain scale, with the link to other scales appearing via the parameters (production, decay and interaction rates). So, for example, in the application to fish pigmentation patterns, while the model is assumed to operate on the tissue level, the parameters would arise from interactions occurring from the genetic level upwards (Kondo, 2002; Watanabe et al., 2006). Understanding how biological function arises through the integration of processes interacting on very different spatial and temporal scales is perhaps *the* greatest challenge facing developmental biology this century.

The Turing model for morphogenesis has provoked much controversy. For example, it does not account for factors such as chemotaxis, mechanics, etc., subsequently modelled as mentioned above. While Turing patterns have been shown to exist in chemistry (see, for example, Bánsági et al. (2011) and references therein) their existence in biology is still highly controversial. While the existence of morphogens is now widely accepted, it is still not at all clear if patterns arise by the mechanism proposed by Turing. While a vast number of organisms obey the developmental constraints arising

[4] In fact Turing mentioned that it may be possible to take mechanical effects into account within the framework he had developed.

from LALI models and a great number of experimental manipulations give results consistent with the Turing model (or extensions thereof) to actually *prove* that a pattern arises via a Turing mechanism would require one to know the precise chemical interactions of the morphogens and show that the parameters satisfy the inequalities necessary for diffusion-driven instability to occur. This is a far way off but encouraging recent progress has been made. For example, Garfinkel et al. (2004) investigated in vitro the self-organising properties of multipotential adult vascular mesenchymal cells. They identified BMP-2 and MGP as qualitatively satisfying all the conditions necessary for a Turing morphogen pair and showed that the cells aggregate into stripe, spot and labyrinthine patterns in response to various manipulations precisely as predicted by the Turing model. Sick et al. (2006) propose that WNT and DKK may be a Turing morphogen pair involved in the patterning of hair follicles in mice. They showed that experimental manipulation of the system leads to results that are qualitatively similar to those predicted by a Turing mechanism.

Adding fuel to the debate was the discovery that one of the candidates for a Turing pattern, the periodic pattern of expression of pair-rule genes in *Drosophila*, is actually not formed via diffusion-driven instability but an asymmetry is already inherited from the mother and this leads to a cascade of patterning interactions (Akam, 1989). This is very different from the Turing model which assumes that pattern arises de novo. However, again this was recognised by Turing, who said in his famous paper, 'Most of an organism, most of the time, is developing from one pattern to another rather than from homogeneity into a pattern'.

Not only are there biological issues about the Turing model, there are also mathematical concerns. It is known that the model exhibits multiple stable steady states and this means that it can be very sensitive to noise and stochasticity in, for example, initial conditions (Bard and Lauder, 1974) or slight changes in domain shape (Bunow et al., 1980). Therefore, the patterns produced are not robust. In some cases, this may not be a problem (for example, for certain pigmentation patterns), but in other cases, for example, limb development, it may be crucial. It has been shown that using different types of biologically relevant boundary conditions can improve robustness (Dillon et al., 1994) as can domain growth (Crampin et al., 1999). In the latter case, it has been shown that growth can enhance selection of certain patterning modes at the expense of others. It is observed that biological pattern often arises behind a moving front (either in growth or a critical parameter) and in the context of the Turing theory for morphogenesis, this would be explained by noting that such a process keeps the patterning domain small, and on such domains pattern selection can be easily controlled. Very recently, it has been shown that the model is highly sensitive to the inclusion of gene transcription delays in the kinetics (see Seirin Lee et al. (2011) and references therein).

Not only has the Turing model challenged biologists to prove/disprove the existence of LALI morphogens. It has also challenged several generations of mathematicians. While the equations look relativity simple, the vast array of patterning behaviours it produces (many of which were computed by Turing in his paper) is astonishing. While the linear theory is well understood (presented by Turing himself), the nonlinear theory is largely intractable. Early analysis investigated the weakly nonlinear case where amplitude equations could be derived using perturbation approaches (see, for example, the book by Britton (1986), for the general theory) and are valid in the vicinity of primary bifurcation points. Although Turing studied and computed the linear system, he does mention the nonlinear problem and, in an *ad hoc* way, derives the amplitude equation that many found later multi-timescale analysis. Group symmetry approaches have also been used to study the problem of mode interactions (see Comanici and Golubitsky (2008) and references therein). Away from the primary bifurcation points one has to resort, by and large, to numerical computation, except in certain cases of very slow activator diffusion in which spike solutions form. These solutions have complex behaviour in which they move to certain parts of the domain to stabilise and spikes may also coalesce with other spikes (see, for example, Ward et al. (2002) and references therein).

Applications of Turing's work to developmental biology are too numerous to list but include limb development, pigmentation patterning, hair and feather germ formation, tooth morphogenesis, phyllotaxis, hydra patterning and regeneration. Moreover, ideas of self-organisation now abound in biology, chemistry and ecology. The stimulus for a lot of this work stems from Turing's original ideas. Thus, his paper has significantly advanced the field and the paper is being cited almost every-day[5]. Advanced computational power now means that the model is trivial to simulate and explore (Kondo and Miura, 2010) and it is envisaged that this will result in its impact increasing instead of waning. George Box is quoted as making the very truthful statement, 'all models are wrong, but some are useful'. Although still very controversial, Turing's theory for morphogenesis provided a paradigm shift in our way of thinking, which has stimulated countless experimental programmes and resulted in novel experiments being carried out that may not otherwise have been undertaken. It has also generated new mathematical and computational problems that have advanced those fields considerably.

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