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# ALAN TURING´S WORK ON MORPHOGENESIS

# *EL TRABAJO DE ALAN TURING EN MORFOGÉNESIS*

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**ABSTRACT:** In this work we will discuss on the contribution made by Alan Turing (1912-1954) towards a mathematical foundation of Developmental Biology. To do so, we will briefly review the approach he laid out in his only published work on the subject, and then describe the impact of his work on Mathematics on one hand, and on Biology on the other.

**KEY WORDS:** Pattern Formation; Developmental Biology; Activator-Inhibitor systems.

**RESUMEN:** En este artículo debatiremos la contribución hecha por Alan Turing (1912-1954) a la fundamentación matemática de la Biología del Desarrollo. Para ello, repasaremos brevemente su punto de vista en el único trabajo que publicó sobre este tema, y describiremos su impacto tanto en las Matemáticas como en la Biología.

**Palabras clave**: Formación de patrones; Biología del Desarrollo; Sistemas de activación e inhibición.

## 1. TURING´S PROPOSAL: A MATHEMATICAL THEORY OF DEVELOPMENT

Alan Turing published a single paper on what we now call Mathematical Biology (Turing, 1952). He had however a keen interest in biological problems, and left unfinished a number of manuscripts on issues such as phyllotaxis, the way in which leaves are spatially distributed in plants (see *http://www.turingarchive.org/*). Interestingly enough, the word Mathematics does not appears in the title of that work (The chemical basis of morphogenesis, see Ref. Turing, 1952). However, the approach in that article is deeply mathematical, and some of the results derived in it have had a considerable influence in Physics and Mathematics, where they fueled a whole new area known as Pattern Formation. This happened, though, only after his ideas had remained largely forgotten for many years. The impact of Turing´s approach in Biology is arguably far more modest, and his vision remains out of the main stream even today.

In his work (Turing, 1952), Turing was concerned with morphogenesis, a key issue in what it is today called Developmental Biology. Roughly speaking, the term morphogenesis is used to describe the whole set of processes by which a fully grown living being unfolds from a fertilized embryo. How such a complex object as an adult person could develop from a quite small, almost homogeneous initial stage, poses a formidable scientific problem. Indeed, many of its crucial aspects remain largely unknown, in spite of the outstanding amount of information gathered on that area during the last century.

It has been long suspected before Turing that chemical substances should be instrumental in morphogenesis. Such assumption is however made precise in the very first lines of (Turing, 1952) with unmatched precision:

> *…It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system...*

And now a key technical point is stated:

> *…The investigation is chiefly concerned with the onset of instability…*

In Turing´s approach simplicity is crucial. A few lines below, our author makes clear that he only intends to make use of a few basic physical principles to address his ambitious goal:

> *…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 organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts…*

Simple his proposal may be, but mastering it requires some background, which is precisely described:

> *...The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry…*

These few remarkable lines encode the gist of Turing´s ideas on morphogenesis. Chemical species, which mediate the shaping of unfolding living patterns (such as organs or limbs), are postulated to operate according to a number of physical mechanisms, which are reduced to a bare minimum. In fact, only two such principles are discussed in detail. The first of them is diffusion, which accounts for random, unbiased molecular motion at the microscopic scale. The second is represented by chemical reactions, whereby new molecular substances are generated from the interactions between existing ones. It was shown in (Turing, 1952) that, from the point of view of mathematical modelling, reaction and diffusion suffice to explain the appearance of nontrivial patterns which were initially absent in a featureless initial medium. Mechanical aspects, however important they may be in practice, are not dealt with in the paper (Turing, 1952). That makes life simpler for the modeller, but has been a source of criticism ever since.

As recalled before, biological patterns are proposed to be the consequence of instabilities arising from a homogeneous state, which was initially stable from the point of view of reaction kinetics (described mathematically in terms of ordinary differential equations, ODEs). Such instabilities are a result of (arbitrarily small) random disturbances which introduce heterogeneity in such medium. This in turn induces diffusion (represented in mathematical terms by partial differential equations, PDEs). Diffusion is a mass transport mechanism, which in an attempt to suppress


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heterogeneity, moves chemicals from regions where their concentrations are higher (with respect to the global spatial average) to others where they are lower. Oddly enough, and this was one of Turing's significant mathematical contributions (Turing, 1952), this attempt to return to homogeneity results in the onset of unbounded disturbance growth when at least two reacting chemical substances are considered; see the Appendix at the end of this paper for further details.

Turing was well aware that his suggestion that symmetry breaking could be induced by arbitrarily small random disturbances might (and actually did) look surprising at first glance. In (Turing, 1952), page 41, he wrote:

> *…There appears superficially to be a difficulty confronting this theory of morphogenesis, or, indeed, almost any other theory of it. An embryo in its spherical blastula stage has spherical symmetry, or if there are any deviations from perfect symmetry, they cannot be regarded as of any particular importance, for the deviations vary greatly from embryo to embryo within a species, though the organisms developed from them are barely distinguishable. One may take it therefore that there is perfect spherical symmetry. But a system which has spherical symmetry, and whose state is changing because of chemical reactions and diffusion, will remain spherically symmetrical forever. (The same would hold true if the state were changing according to the laws of electricity and magnetism, or of quantum mechanics.) It certainly cannot result in an organism such as a horse, which is not spherically symmetrical…*

Turing´s answer to his own carefully worded statement goes as follows (Turing, 1952, p. 42):

> *…There is a fallacy in this argument. It was assumed that the deviations from spherical symmetry in the blastula could be ignored because it makes no particular difference what form of asymmetry there is. It is, however, important that there are some deviations, for the system may reach a state of instability in which these irregularities, or certain components of them, tend to grow. If this happens a new and stable equilibrium is usually reached, with the symmetry entirely gone…*

We have already noticed that the seemingly counterintuitive fact that symmetry breaking could be induced by any small, random perturbation is supported in (Turing, 1952) by means of a simple mathematical model (cf. Appendix). However, the final statement in the previous excerpt, namely the fact that eventually "*a new and stable equilibrium is usually reached, with the symmetry entirely gone"* would require for its justification of additional, and highly sophisticated, mathematical tools of a nonlinear nature. We shall presently return to this point in Section 2 below.

Turing´s description of the initial stages of Pattern Formation in an embryo as a diffusion-induced destabilization of an initially stable, homogeneous steady state instantly appeals to a mathematically-minded reader for various reasons. It is elegant, simple, looks quite general and can be illustrated by means of elementary arguments. However, it just looks too good to be true, and the limitations of his approach were apparent to Turing himself. As a matter of fact, in page 37 in (Turing, 1952), a few lines after his already quoted excerpt at the beginning of his note, he plainly declared:

> *…In this Section a mathematical model of the growing embryo will be described. 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…*

Indeed, the Mathematics behind Turing´s arguments were known to their author to be insufficient to fully achieve his purpose. A key technical limitation in his work is that significant results could only be obtained under the assumption of linearity in the equations involved. This is plainly declared in a final Section 13 of (Turing, 1952, cf. p. 71 there), where a few conclusions are gathered:

> *…The 'wave' theory which has been developed here depends essentially on the assumption that the reaction rates are linear functions of the concentrations, an assumption which is justifiable in the case of a system just beginning to leave a homogeneous condition. Such systems certainly have a special interest as giving the first appearance of a pattern, but they are the exception rather than the rule. Most of an organism, most of the time, is developing from one pattern into another, rather than from homogeneity into a pattern. One would like to be able to follow this more general process mathematically also…*

The last goal is acknowledged to be out of reach by the author at that time (1952).

> *…The difficulties are, however, such that one cannot hope to have any very embracing theory of such processes, beyond the statement of the equations…*

(Turing, 1952, loc. cit.). Nevertheless, Turing conceived a possible way out of this stalemate by embracing what we would today call Computational Biology:

> *…It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis. It might even be possible to take the mechanical aspects of the problem into account as well as the chemical, when applying this type of method. The essential disadvantage of the method is that one only gets results for particular cases…*

It may well be guessed from the previous sentences that Turing clearly foresaw the impending power of computers, a technology that he himself contributed to develop, as a tool to address biological problems, developmental and otherwise. However, state-of-the-art computers in 1952 where unable to yield any scientific breakthrough in a mathematically-based theory of Pattern Formation.

## 2. THE IMPACT OF TURING´S IDEAS IN MATHEMATICS AND BIOLOGY

How was Turing´s work received at his time? It would be fair to say that his proposals remained largely forgotten during the fifties and the sixties of previous century. Several facts conspired to that effect. To begin with, his untimely death in 1954, only two years after (Turing, 1952) was published, prevented him from further developing his ideas and methods. Moreover, some momentous events happened at that time which contributed to diverting biologists attention away from Turing´s work.

Indeed, only one year after (Turing, 1952) appeared, Watson and Crick published their seminal work on the structure of DNA (Watson and Crick, 1953) that led generations of scientists to dig deeper and deeper into genetics. On the other hand, in the same year 1952 A. Hodgkin and A. Huxley published the first of a series of articles (Hodgkin and Huxley, 1952) concerned with a key issue in neuroscience, that of modelling the propagation of signals in nerves. Oddly enough, Mathematics was paramount to the techniques used in Watson and Crick (1953) (crystallography) and in Hodgkin and Huxley (1952) (numerical simulation of ODEs) systems. Why it was that mathematical modelling failed to appeal to developmental biologists?

It could well be that Crystallography had been grounded on Mathematics and Physics since its very beginning, and that Neurosciences were ripe enough to benefit from mathematical tools while Developmental Biology was not. In a way, the question was related to that of selecting a problem which was at the same time important and within reach of already existing mathematical techniques. It is interesting in this respect to read what Francis Crick, a physicist turned biologist, revealed to Lewis Wolpert, a distinguished developmental biologist, during a scientific interview. Their dialogue went as follows:

> Lewis Wolpert*: How do you choose your theoretical work?*
>
> Francis Crick*: Well, what I do is, not choose a problem, but to choose a subject, and then try to move around in this subject until I find an idea that yields: something that clicks together.*
>
> *I don´t say that I am going to try and solve such and such problem, because it may turn out, especially in biology, that it´s insoluble. The problem of how proteins fold up, for example. We showed great discrimination in not choosing that problem. It has not been solved to this day.*
>
> *The way I work is to take a given area and to look at problems which look as if they might be tractable, as we thought the genetic code would be.*

(see Wolpert and Richards, 1988 for the whole interview). One may wonder if a mathematical theory of developmental was tractable at all in the absence of sufficient computer power. This came soon afterwards, though, and its staggering increase since the late sixties has definitely shifted the balance in modellers minds from theory to large-scale simulations, a trend that is clearly dominant nowadays. As a matter of fact, even the comparatively low computing level in the early seventies was enough to take a step further form (Turing, 1952), as we will see next.

### 2.1. Beyond linearity. Activator-inhibitor systems

In the context of morphogenesis, one had to wait for twenty years until a further significant step with respect to (Turing, 1952) was provided. This was achieved by the nonlinear activator-inhibitor theory due A. Gierer and H. Meinhardt (1972). The authors summarized their approach in that work as follows:

> *…The hypothesis is being stated that the elementary process in pattern formation may be the formation of a primary pattern of two morphogens, one acting as*



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*activator, and one with inhibitory effect, the inhibition being derived from, and extending into a wider area. Activator and inhibitor react auto -and cross catalytically on their sources…*

A key point is now immediately made:

*… Since linear relations will not suffice, non-linear equations have to be postulated…*

As a striking difference with the situation in 1952, the basic nonlinear activator-inhibitor proposed in Gierer and Meinhardt (1972) could be easily simulated in 1972, and the results of such simulations revealed the emergence of patterns that are rendered stable by the effect of the nonlinearity retained in the model. Actually, since the publication of Gierer and Meinhardt (1972), the study of systems of this type (see for instance Koch and Meinhardt, 1994) has been mostly done by means of numerical simulations. Fully rigorous analysis (proving in particular existence and uniqueness of solutions) has indeed become a rarity in this context. See however (Rothe, 1984), where the systems proposed in Gierer and Meinhardt (1972) were rigorously studied.

As a matter of fact, there are understandable reasons for this shift from theory to simulations. It is beyond question that biological processes are exceedingly complex, and therefore most models, if manageable, have to keep to a few assumptions and disregard the rest, including obviously those that remain unknown at the time. To compare various modelling alternatives, there seems to be no better way than to check what their predictions are, and computational methods help in this respect more than any other mathematical technique. In particular rigorous analysis, with its characteristically long time scale to achieve results, and the difficulties inherent to its own method, is no match for educated computer guesses when it comes to exploring a largely unknown field. This has contributed to widening the gap between theory and simulations that shows no signs as yet of being filled.

In the years since Gierer and Meinhardt (1972) was published, a large number of articles using reaction-diffusion equations to address biological (and not merely developmental) problems has been produced; see for instance Murray (2003) and its references. In this way, the subject of Mathematical Biology has established itself as a branch of contemporary Mathematics that attracts a large following. Its status among biologists is however quite a different matter, as we shall discuss below.

### 2.2. The Impact of Turing´s work in Biology

While the interest in using mathematical models in Biology has been steadily increasing among mathematicians and physicists ever since (and arguably before) the publication of (Turing, 1952), the situation is quite different as far as biologists are concerned. In fact, Turing's approach, and mathematical modelling in general, has yet to be accepted in most Biology quarters, with the single possible exception of Ecology and related fields. It is beyond the scope of this article to provide a full account, not to say a reasonable explanation, of the reasons behind biologists' misgivings with respect to Mathematics. Instead, we shall content ourselves with sketching a few points which will hopefully shed some light onto that situation.

To begin with, many biologists consider living beings to be simply too complex to be amenable to anything close to mathematical modelling, whose realm should be accordingly confined to that of inorganic matter. This belief runs deep both in science and philosophy since the very origins of scientific thought. No less a master than Aristotle (ca 384 BC - 322 BC) pronounced Mathematics valid only to deal with immaterial things with these terse words:

*…The minute accuracy of mathematics is not to be demanded in all cases, but only in the case of things which have no matter. Hence (mathematical) method is not that of natural science; for presumably the whole of nature has matter…*

(see Aristotle, 1998; see also the web link: *http://classics.mit.edu/Aristotle/metaphysics.html*). It has taken Mathematics almost two thousand years to gain a solid grasp as a key method in Physics, and only after such minds as Galileo and Newton have made their mark there. In our days no one would seriously challenge the principle that Mathematics is *the* tool to understand matter, from atoms to stars. When it comes to living beings, however, the situation is very different.

An illuminating view on the stance taken by many biologists with respect to Mathematics is given by Evelyn Fox Keller in (Keller, 2002). She provides there a penetrating account of what she refers to as "untimely births of Mathematical Biology". An example of that situation is provided by the career of Nicholas Rashevsky (1899-1972), founder of a journal that eventually became the Bulletin of Mathematical Biology, currently one of the leading publications in that field. In 1934 Rashevsky, presented at Cold Spring Harbor (CSH), then at the initial stages of its current role as a

beacon for cutting-edge Biology worldwide, his mathematical model of cell division. Rashevsky´s approach was a classical one in physics, where simplified situations are considered first (for instance, cells may assumed spherical to start with) to be later generalized once a few relevant conclusions have been derived from such simplified cases. The answer found in CSH to his approach was disappointing. In particular, as recalled in (Keller, 2002), E. B. Wilson, a leading biologist of his generation, prepared a short paper discussing Rashevsky´s proposals, which contained statements as the following:

*…Science need not be mathematical,*
*Simply because a subject is mathematical it need not therefore be scientific…*

Moreover, to summarize the exchanges between Rashevsky and Wilson, E. Ponder, director of CSH at that time wrote:

*…One point upon which there seems to be pretty general agreement is that there is little relation between the amount of which has been done on the mathematics of (biological) growth and the clarification of the subject which has resulted…*

*…It is futile to conjure up in the imagination a system of differential equations for the purpose of accounting for facts which are not only very complex, but largely unknown…*

*…What we require at the present time is more measurement and less theory…*

These words, written less than twenty years *before* the publication of (Turing, 1952) represent an anticipated and complete rebuttal of Turing´s approach. There is an ominous ring in a sentence declaring that what we need is "more measurement and less theory". Indeed, theories, so appreciated in Physics, are looked down upon by many distinguished developmental biologists, to keep to the field that Turing himself selected to study. This statement is plainly explained by Hans Meinhardt in (Gordon and Beloussov, 2006). There he says:

*…Why do models (in Biology) have only a limited reputation? My own experience is that experimentalists are not very enthusiastic if it turns out that a process was correctly predicted. They worked hard to find the basic principles by themselves. Frequently the prediction is then handled more as a speculation, if not completely ignored.*

*This is very different to the habit in physics where an experimental observation would be in no way diminished if it is preceded by a theoretical prediction, on the contrary…*

A bit later in Gordon and Beloussov (2006), Meinhardt provides a pungent comment that could be extended to the difficulties that new ideas usually find when they are formulated:

*…The reception of some of my models had a strange history. First they were regarded as unrealistic or misleading: "cannot be". More or less abruptly this changed later into: "that is trivial, how else should it be?" This switch had different time constants in different communities. Both attitudes provide the freedom to ignore the theoretical work…*

Despite a general unfriendly welcome, the use of Reaction-Diffusion models to address biological problems has slowly gained ground as time has elapsed. Even hardliners nowadays consider it appropriate to refer to it, although not without due reservations. For instance, in the book *Principles of Development* (Wolpert *et al*., 1999), whose principal author is Lewis Wolpert (already mentioned here), Reaction-Diffusion mechanisms are dealt with in page 317 in Chapter 10 (devoted to organogenesis) in the 1999 edition. An interesting description of stripe formation in fishes is provided as a possible example of application of these mathematical methods. The text referred concludes, though, with the following cautionary statement:

*…Nevertheless, there is as yet no direct evidence for a reaction-diffusion system patterning any developing organism…* (chapter 10, p. 317).

However, a number of molecular agents have been identified as candidates to mediate such processes, and their number continues to increase (Meinhardt, 2008).

## 3. CONCLUDING REMARKS

Despite the obstacles found, some of which have been briefly addressed here, there is currently a larger interaction between biomedical scientists, mathematicians and physicists that has ever been in the past. It is beyond the scope of this note to report on some of the exciting scientific frontiers where this collaboration is already bearing fruit. Of course, the sheer complexity of living beings represents a formidable barrier that has to be overcome case by case for this collaboration to succeed. That was certainly foreseen in the concluding sentence in (Turing, 1952) which accurately summarized what was achieved there:


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*…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. Taking this in combination with the relatively elementary mathematics used in this paper one could hardly expect to find that many observed biological phenomena would be covered. It is thought, however, that the imaginary biological systems which have been treated, and the principles which have been discussed, should be of some help in interpreting real biological forms…*

There is a long way to go following the path laid out in Turing´s celebrated paper. This seems to be a task for many generations of scientists, and it appears to be currently well on its way.


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## APPENDIX: TURING'S INSTABILITY IN A NUTSHELL

The following argument, taken from pages 42 and 43 in Turing (1952), illustrates the manner in which breakdown of symmetry or homogeneity sets in the case of a pair of contiguous cells, having initially nearly the same contents.

Consider two cells I and II, and two substances (morphogens) X, Y present on them (c.f. Figure A below).

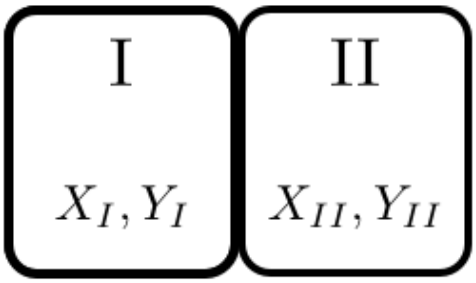


**Figure A:** Two similar cells (I and II) where two morphogens X,Y are present. The respective concentrations in I and II are denoted by means of indexes I and II.

Chemical reactions will be assumed among X and Y of a linear nature and given by

(A1) $$\frac{dX}{dt} = 5X - 6Y + 1,$$

(A2) $$\frac{dY}{dt} = 6X - 7Y + 1.$$

Note that if both morphogens have concentrations X = Y = 1 in both cells, there is equilibrium of a stable nature, as can be seen from the study of the eigenvalues associated to (A1), (A2). Suppose now that, due perhaps to some fluctuation, the initial values in I and II turn out to be:

(A3) $$X_I = 1.06,\ Y_I = 1.02 \quad ; \quad X_{II} = 0.94,\ Y_{II} = 0.98$$

According to (A1), (A2), X and Y are produced by chemical action at rates 0.18 and 0.22 in the first cell, and destroyed at the same rate in the second. As a consequence of the heterogeneity introduced by (A3), a diffusion mechanism sets in. Suppose that flow due to diffusion from the first cell to the second occurs at a rate 0.5 for the first morphogen , and 4.5 for the second (Note that the ratio of the second diffusivity to the first one is 9, about one order of magnitude). The combined reaction-diffusion process may now be represented by the following equations:

(A4) $$\frac{dX}{dt} = 5X - 6Y + 1 - 0.5(X_I - X_{II}),$$

(A5) $$\frac{dY}{dt} = 6X - 7Y + 1 - 4.5(Y_I - Y_{II}).$$

Let $\xi(t)$ be the perturbation induced in each morphogen starting from an initial value $\xi(0)=0.02$ in (A3). It then follows from (A4), (A5) that for any $t>0$,

(A6) $$\xi' = 2\xi$$

so that an exponential drift away from equilibrium is induced by the initial perturbation (A3). Note that negative values for morphogen concentrations should be discarded. Actually, when application of the previous formulae result in the concentration of a morphogen in a cell becoming negative, it should be understood that it is instead removed only at the rate at which it is reaching that cell by diffusion.


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