Singular pulse patterns in the Gierer-Meinhardt equation
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Chapter 1

Biological pattern formation

The growth of plants and animals is a highly intriguing process. A fully developed organism is a complex arrangement of many different structures, yet it grows from a single fertilised cell. In the initial stages of its development, an organism grows by cell division only, forming a sphere of identical cells, but after this first stage, more and more structure appears. The formation of structures out a less structured tissue is known as morphogenesis (from the Greek words μορφή = shape and γένεσις =creation). Though many processes are involved in morphogenesis, the result is a highly reproducible arrangement of the various structures.

The variety of structures arises, because different cells develop in different ways, a process known as (biological) differentiation. Differentiation is a complex process, which involves many phenomena like cell division, cell movement, gene activation and changes in the shape of the cells. Irrespective of the exact mechanisms of differentiation, the point I want to address here is the fact, that the way the cells develop depends on their position in the tissue. Hence, there must exist some mechanism to 'tell' the cells, where they are in the tissue. Of course, the genes play an important role in the differentiation process, but as the genetic information is the same in all cells, the genes alone can not provide the necessary spatial information. Hence, we assume that differentiation is triggered by a patterned signal, called the morphogenetic field. Therefore, morphogenesis is also called (biological) pattern formation.

Disclaimer

This introduction is not aimed at providing a full description of the differentiation process. Instead, I focus on one mechanism to generate spatial information in the developing tissue. The choice for this mechanism was made purely on mathematical grounds and I make no claim towards its biological relevance. I also am aware that it underexposes the role played by the genes in the differentiation process. In defence of the mechanism that I am about to describe, I point to the reaction-diffusion models, that have been used to reproduce biological patterns, including the patterns on sea shells (see especially [53]), patterns on mammal coats [58, 60] and the regeneration of
polyps [31, 52]. However the mechanisms behind these examples of biological pattern formation remain unclear. More information on biological pattern formation can be found in the literature [51, 60].

1.1 Modelling pattern formation

As the underlying mechanisms remain unclear, it is essential to develop (mathematical) models of biological pattern formation. The complexity of a fully developed organism seems to rule out any kind of model, but fortunately the differentiation pattern is not formed for the organism as a whole. Instead, development is built up of individual steps, which in many cases only occur when previous steps have been completed. For example, in a human embryo the arms are formed first as a (shapeless) bud, and only later smaller structures like the hands are formed in these buds. Furthermore, many of the developmental steps occur in a small part of the embryo and can proceed independently from the processes in the rest of the embryo. Using the same example, the development of, say, the right hand is not influenced by the processes involved in the formation of the left hand. Thus, the patterns formed in the individual developmental steps are relatively simple.

Despite the relative simplicity of the individual developmental steps, it is still not easy to model them, as there are many phenomena such a model needs to incorporate. Arguably, the most important problem is the fact that during differentiation, structure appears from a less structured starting point. Hence, any morphogenetic model must be able to form spatial patterns spontaneously from a uniform state.

1.2 Reaction-diffusion systems

A frequently used type of models for the development of a morphogenetic patterns, is the class of reaction-diffusion systems, in which it is assumed that differentiation is triggered by concentration patterns of certain chemicals, called morphogens. In this approach the developing tissue is considered as a chemical reactor, where the morphogens can react with each other. Thus, the tissue is considered as a continuous medium, without a direct influence of the cell boundaries, so that the morphogens can diffuse freely. On the other hand, the influence of the tissue is not completely ignored, as the composition of the tissue influences the chemical properties of the morphogens. One can think here for example of the influence on the reaction rates of the concentration of enzymes that facilitate the morphogen reactions. Therefore, the influence of the tissue enters the model through parameters like the diffusion rate and the reaction rates. This is especially important if the pattern formation process follows an earlier differentiation process, which made the composition of the tissue nonhomogeneous. However, these spatial effects are easily incorporated by including space-dependent parameters (see Section 1.3 on the Hydra for an example).
1.2. Reaction-diffusion systems

Turing

The differentiation patterns necessarily evolve from a state, where the morphogens are distributed equally over the tissue. Hence, the fundamental question in the reaction-diffusion approach is: How do spatial concentration patterns emerge from a uniform initial condition? Since the patterns appear spontaneously, they must be triggered by the always-present fluctuations around the uniform state. However, it seems that the diffusion of the morphogens smoothens any fluctuations. The question was answered by Alan Turing's\textsuperscript{1} 1952 paper "The chemical basis of morphogenesis" [80], which can safely be called the foundation for reaction-diffusion equations as a model for (biological) pattern formation. In this paper Turing showed that under the right conditions, diffusion does not prevent, but actually stimulates pattern formation: he showed that in a system with a uniform state that is stable in the absence of diffusion, the uniform state can destabilise if diffusion is introduced in the system. The crucial condition for this diffusion-driven instability is that the two components diffuse at a (very) different rate. Turing predicted that the instability would lead to complex spatial patterns. Such patterns were observed experimentally only in 1990 [7]; the main reason for the long time it took to discover these patterns was this condition on the ratio of diffusion rates.

Note that Turing's diffusion-driven instability does not contradict the normal notion of diffusion as a smoothing effect. In fact, we will see below that it is actually the smoothing out of one of the components that -in combination with the effects of the reactions- leads to pattern formation.

Activator-inhibitor

Unfortunately Turing's analysis was restricted to linear reaction rates, which makes the reactions biochemically infeasible. The Turing mechanism was extended to nonlinear reaction-diffusion systems in 1972 by Gierer and Meinhardt [31], who showed that the crucial conditions for pattern formation in reaction-diffusion systems are local self-activation and long-range inhibition.

A straightforward realisation of these principles is an activator-inhibitor system. An activator-inhibitor system consists of two chemicals; a slowly diffusing activator, that stimulates its own production and a rapidly diffusing inhibitor, that is produced by the activator and reduces the production rate of the activator. Due to the autocatalytic property of the activator, a small local increase in the activator concentration is amplified. The increase in activator concentration triggers the production of the inhibitor, which diffuses rapidly into the surrounding tissue. Therefore the inhibitory effect at the peak is initially not strong enough to prevent the peak from growing further, but the diffusing inhibitor prevents the formation of new peaks in activator concentration in the surrounding tissue. The high inhibitor concentration in the tissue around the initial peak also prevents the spreading of the activator peak into the surrounding tissue, i.e. it keeps the peak localised. When the activator peak...
has become large enough, the high inhibitor production blocks further growth of the activator concentration. The difference in diffusion rates of the activator and the inhibitor is crucial: if the activator diffuses too fast (or the inhibitor too slow), the activator can invade the entire tissue before the inhibitor can prevent this.

The final result of this process is a localised peak in the activator concentration, whose form is determined by the balance of the (net) activator production and its diffusion. Hence, the form of the peak is independent of the initial perturbation. Of course, the position of the peak depends on the position of the initial trigger of the activator concentration. The activator-inhibitor mechanism allows for the formation of multiple activator peaks, but due to the long-range effect of the inhibitor, there exists a minimum distance between two peaks. Once one or more activator peaks are formed, new peaks can only be formed in places where the inhibitor concentration is low. This means that there exists a kind of self-regulation mechanism with respect to the positioning of different structures in activator-inhibitor models [51]. A similar self-regulation mechanism is observed in nature in situations, where multiple structures of the same form, maintain a certain distance from each other: consider for example, the positioning of stomata on plant leaves.

Different mechanisms exist for the activation and inhibition. Most important are the activator-substrate systems, in which a chemical, called the substrate, is used up in the activator production. Thus, if the activator concentration increases locally, the substrate is consumed locally, but if it flows in rapidly from the surrounding tissue, it is depleted over a large area. Then, no peaks in activator concentration can be formed in this larger area.

The linear equations used by Turing in his 1952 paper were of activator-inhibitor type. It can also be shown that a linear system with an autocatalytic activator and a inhibitor can exhibit Turing instabilities if the inhibitor diffuses (much) more rapidly than the activator.

1.3 The Hydra and the GM-equation

The work of Gierer and Meinhardt [31] was aimed at modelling the growth and regeneration of the Hydra, a type of fresh-water polyps. The Hydra is considered as a model organism for morphogenesis for its relative simplicity and its fast reproduction. The animal is a few mm long and consists of about 100,000 cells of only a small number of different types. The polyps consist of a foot, a body column, which encloses the digestive channel, a head region, containing the mouth, and the tentacles, surrounding the head region. Small pieces of Hydra can regenerate to a complete new animal, maintaining the orientation of the original animal.

For biological reasons, Gierer and Meinhardt modelled the growth of a new head on a piece of the Hydra using an activator-inhibitor model. The activator promotes the formation of a head, while the inhibitor prevents the formation of secondary heads. After the removal of the original head, the production of the inhibitor stops and the inhibitor concentration decays rapidly. In the absence of the inhibitor a new peak in activator concentration can form following the general activator-inhibitor
mechanism outlined above. The new peak in activator concentration initiates the development of a new head. The peak in activator concentration at the position of the new head also leads to the production of the inhibitor, thus preventing the formation of secondary heads. To explain the orientation-preserving regrowth of the head, Gierer and Meinhardt assumed that the ability of the tissue to produce the activator, called the source density, varies over the body of the Hydra. The source density depends on things like the presence of enzymes and chemicals needed in the reactions. They assumed that a graded source density was laid down by an earlier pattern formation process. The graded source density implies that the area closest to the original head is the most suitable for the production of the activator, so that the new head grows there.

The Gierer-Meinhardt equation

To illustrate their theory, Gierer and Meinhardt introduced the following set of reaction-diffusion equations, referred to as the classical Gierer-Meinhardt equation,

\[
\begin{align*}
V_t &= d_v V_{xx} - \nu V + \frac{a \rho V^2}{U} + \rho_0 \rho, \\
U_t &= d_u U_{xx} - \mu U + b \rho V^2,
\end{align*}
\]

where \(V\) is the activator concentration, \(U\) is the inhibitor concentration and \(\rho = \rho(x)\) is the source density. The diffusion rates \(d_v\) and \(d_u\) satisfy \(d_u \gg d_v\). The terms \(\nu V\) and \(\mu U\) are the decay terms; they correspond to the disappearance of the activator and inhibitor due to the interaction with the surrounding tissue. The autocatalytic reaction term is given by \(a \rho V^2/U\); note that the \(V^2\)-term grows faster with \(V\), than the linear decay \(\mu V\). The activator stimulates the inhibitor production through the \(b \rho V^2\)-term. The basic activator production \(\rho_0 \rho\) provides the necessary activator to start the pattern formation. The spatial coordinate is along the Hydra from head to foot; for the modelling one dimension is sufficient.

Remark 1.1 In the style of Alan Turing\(^2\), I do apologise for springing these partial differential equations (PDE) on the non-mathematical reader. PDE's are used to express the evolution over time of a time- and space-dependent quantity, in situations where the time-evolution depends not only on the quantity itself, but also on spatial differences in this quantity. The first line of this equation states that the rate of change of the activator concentration \( (V_t = \partial V/\partial t)\) in a point \(x\) is the sum of the change due to diffusion \( (d_v V_{xx} = d_v \partial^2 V/\partial x^2)\), the (negative) activator decay \( (\nu V)\), the autocatalytic production \( (c \rho V^2/U)\) and a basic production \((\rho_0 \rho)\) independent of the activator concentration.

Extensions of the simple model

The simple two component system used for the modelling of the (re)growth of the head can be extended to include several other phenomena in the growth and repro-

\(^2\)I Quote from [80] "Certain readers may have preferred to omit the detailed mathematical treatment of §§6 to 10. For their benefit the assumptions and results will be briefly summarized, with some change of emphasis.".
duction of the Hydra. The gradient in the source density can be explained, if one assumes that the source density follows the inhibitor concentration but on a much longer time scale[47]. Note that this corresponds to experimental observations, which show that polarity reversal takes days, whereas the formation of a new head region takes only about six hours. The polarity of the tissue can be reversed by removing the head and transplanting it on the 'wrong' side of (part of) the body column. At its new location the head produces the inhibitor, which diffuses into the tissue, preventing the formation of a new head at the normal position closest to the original head. After the inhibitor concentration is settled, the source density slowly adapts to the new situation. Also the positioning of the foot and the tentacles with respect to the head can be explained with simple extensions of the two component model [52].

**Remark 1.2** It is important to note that the gradient in the source density is not essential for the pattern forming properties in the system. For a constant source density patterns can be formed but the orientation is lost. This is also observed in experiments; clumps of mixed up cells from all parts of the Hydra can develop to fully grown polyps[30].