Lines and Nets:
Models of Filamentary Structures

M.A.Herrero

Abstract

We shall recall some reaction-difussion models which have been used to describe the growth of net-like structures, mainly in a biological context. In particular, a modified activator-inhibitor system proposed by Hans Meinhardt in 1976 will be considered, and some properties of their solutions will be analyzed.

1   Introduction

From a mathematical point of view, the subject of pattern formation can be roughly described as the study of the spatio-temporal structure of solutions to some dynamic equations. One is thus led to describe the actual shape (as well as the time variations thereof) of the solutions under consideration, instead than merely showing their existence (and perhaps deriving schemes to approximate them), as it is often the case in the functional analysis oriented theory of classical and weak solutions that has unfolded during the XX century.

Among the many fascinating structures that may lie encoded within a system of partial differential equations, I shall briefly deal here with those having a filamentary nature. These will eventually give raise to highly sophisticated networks in the course of their evolution. As a matter of fact, such filamentary structures are highly pervasive, in that they can be found in a number of situations, both organic and inorganic. For instance, expanding and interwoven needles make up the structure of spherulites, which in turn can be considered as nucleation units appearing in many processes in crystal growth (cf.[L] and [C]). Actually, net-like structures are known to occur in many phase separation problems (see for instance [P] for recent numerical

simulations in a general model dealing to percolating networks). We shall confine our attention here to a biological problem in which such ramifying systems naturally appear, and for which mathematical modelling is being actively pursued.

2 The growth of biological filamentary structures. A reaction-diffusion approach.

It is a well known fact that, in the course of their development, higher organisms rapidly grow to a size where passive diffusion (which is a slow, short-range transport mechanism as observed in [Cr]) becomes inappropriate to supply tissues with oxygen, water, nutrients and information. The solution found by Nature in the course of evolution has consisted in the invention of complex-shaped organs made up of long, branching filaments, that are eventually able to expand in a very efficient way into the surrounding organic matrix. Typical examples of such organs are provided by the blood vessels, the trachaea of insects and the nervous system of vertebrates, to mention but a few.

A question that naturally arises is that of understanding the way in which such involved networks are started, and how do they evolve (and self-repair) during their host lifetime. At the molecular level, the genetic programs that govern the formation of the tree-like branching structure of some animal organs (the Drosophila fly tracheal system, the mouse lung, ...) have begun to be elucidated only recently (see [MK] for a review of such results). On the other hand, considerable attention is being paid to understanding a related biological mechanism: angiogenesis. This last can be shortly described as the study of the behavior of the system of blood vessels, both under normal and pathological conditions. For a recent overview of results and current research directions, the reader is referred to [Y] and the literature quoted therein.

What is clear from the beginning is that, even in its simplest biological setting (perhaps represented by the airways of the fruit fly Drosophila Melanogaster), the problem just mentioned is a challenging one. Indeed, in the case mentioned above, each part of the system consists of an epithelial monolayer of cells, wrapped into a tubular structure. There are hundreds to millions of branches in each organ, and an exceedingly large amount of information has to be used to configure such network. For instance, for each

branch, the codifying system has to specify:

1. Where the branch buds, and in which direction it will grow,

2. What is the size and shape of any branch,

3. When and where in the branch a new generation of branches shall sprout.

Is it at all possible to provide accurate mathematical models to describe such phenomena?. This question can be viewed as a part of a more general one, namely: is it possible (and useful) to describe biological systems by means of mathematical equations?. It is certainly well beyond the scope of this note to make even a partial attempt to explore such fundamental question. I therefore shall content myself with making some remarks on just one of the models proposed to address this issue.

The second half of the XX century has witnessed the birth and subsequent growth of the so-called reaction-diffusion theory of pattern formation. The basic ideas behind such approach are explained by A. M. Turing in his groundbreaking article [T] as follows:

> "... a system of chemical substances, 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..."

Patterns (or structures) thus appear in the models as bifurcations from homogeneous states when some parameters are suitably modified. In particular, a crucial role is played by the respective diffusion coefficients of the morphogens involved. As it turns out, in many cases one realizes that, the more different these coefficients are, the more interesting the resulting patterns are. However, as Turing himself was aware of, linear models (as were those amenable to analysis at Turing's time) can have a very limited biological meaning. In particular, once an instability starts to grow in a linear system, there is no way to prevent its unlimited growth, and no stable (hence bounded) structure could ever be reproduced by any such model.

One of the first nonlinear models derived to account for the formation of stable nontrivial patterns was proposed by Gierer and Meinhardt in 1972

(cf. [GM]). In its simplest version, it consists of two coupled equations for an activator, $a(x,t)$, and an inhibitor $h(x,t)$, which read as follows:

$$\frac{\partial a}{\partial t} = D_a \frac{\partial^2 a}{\partial x^2} + \rho \frac{a^2}{h} - \mu a,$$

$$\frac{\partial h}{\partial t} = D_h \frac{\partial^2 h}{\partial x^2} + c a^2 - \nu h,$$

(see also [M1], Chapter 2). Here $a(x,t)$ represents an autocatalytic substance, which produces also its own antagonist $h(x,t)$. This last is a substance that blocks the action of $a(x,t)$. As to D_a, D_h, ρ, μ, c, and ν, these are positive parameters. A key assumption is that, in general, $D_h \gg D_a$. In other words, there is a long-range inhibition coupled to short-range self-enhancement of the activator substance $a(x,t)$. In this way, a local deviation from an average concentration will increase further (no nontrivial pattern could be formed otherwise), but at the same time such increase cannot grow without limits, so that eventually a stable steady state will unfold.

One may wonder whether this reaction-diffusion approach can be used to reproduce (and predict!) events related to the operation of a biological network. Actually, as early as in 1976, H. Meinhardt obtained for that purpose a simple model, and proceeded to numerically simulate some of its features. The basic assumptions made on the motion of the net can be summarized as follows:

H1. A local signal for filament elongation is generated by local self-enhancement of an activator substance $a(x,t)$, and long-range difussion of an inhibitor product $h(x,t)$.

This amounts to say that a and h obey an activator-inhibitor system as that previously described. However, to account for the motion of the net, new ingredients are to be taken into account. These are described below.

H2. Filaments grow in a surrounding media that directs the net motion by producing a growth factor $s(x,t)$, which is removed by the filaments as they expand.

At this juncture, it is worth pointing out that the existence of chemical substances exhibiting such type of behaviors is a well established biological fact since the discovery of the nerve growth factor (NGF) by Rita Levi-Montalcini in the fifties. Back to our model, the last element to be included is that membership into the net is considered as an irreversible decision:

H3. The signal mentioned in H1 produces an elongation of the filament by accretion of newly differentiated cells. Once such differentiation is achieved, it will be preserved for later times,

(see [M2] and [M3] for further details). After some simplifications, the mathematical model derived by Meinhardt under such assumptions can be written in the following manner:

$$
\begin{cases}
\dfrac{\partial a}{\partial t} = \varepsilon\,\Delta a + \dfrac{a^2 s}{h} - a + \Gamma_1\, y\,, \\[2mm]
\dfrac{\partial h}{\partial t} = \dfrac{1}{\varepsilon}\,\Delta h + (a^2 s - h) + \Gamma_2 y\,, \\[2mm]
\dfrac{\partial s}{\partial t} = \Delta s + \alpha\varepsilon(1 - s) - \alpha\, s\, y\,, \\[2mm]
\dfrac{\partial y}{\partial t} = \beta\left(\dfrac{y^2/\varepsilon}{1 + y^2/\varepsilon} - y + \varepsilon^2\, a\right)\,.
\end{cases}
$$

This can be viewed as a typical activator-inhibitor system, with an extra driving term s (a growth factor). The value $s = 1$ is the (normalized) saturation value of such factor. As to function y (which is not subject to diffusion), is a zero-one variable, accounting for everlasting incorporation into the net. Finally, letters ε, Γ_1, Γ_2, α and β represent positive parameters.

The system of four equations described above has recently been considered in [AHV], in the case of two space dimensions, under the assumption that:

$$
0 < \varepsilon \ll 1\,.
$$

This assumption allows us to use matched asymptotic expansions techniques in order to unravel the various time and space scales appearing during the evolution of the net, as well as to estimate the motion (that turns out to be quite slow) of each of its filaments. Furthermore, the asymptotic profiles of variables a, h, s and y over the net are obtained, and the mechanism by which new branches are generated (as well as the location of these new buds) has been explained. This may hopefully be a first step towards analysing important vessel growth phenomena (as for instance, those reviewed in [Y]). Controlling the rate and direction of expansion in such complex vascular systems stands out as a major open question to be dealt with.

Acknowledgements:

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