Modelling of activator-inhibitor dynamics via nonlocal integral operators

Roumen Anguelov, Stephanus Marnus Stoltz

Abstract This paper proposes application of nonlocal operators to represent the biological pattern formation mechanism of self-activation and lateral inhibition. The blue-green algae *Anabaena* is discussed as a model example. The patterns are determined by the kernels of the integrals representing the nonlocal operators. The emergence of patters when varying the size of the support of the kernels is numerically investigated.

Roumen Anguelov
Department of Mathematics and Applied Mathematics, University of Pretoria, Pretoria, South Africa
e-mail: roumen.anguelov@up.ac.za

Stephanus Marnus Stoltz
Department of Mathematics and Applied Mathematics, University of Pretoria, Pretoria, South Africa
e-mail: stoltstep@gmail.com

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1 Introduction

The theory of pattern formation through local self-activation and long range inhibition accounts for much of the observed pattern forming regulatory phenomena [5]. This mechanism is captured mathematically by considering two species, activator and inhibitor, with different spatial diffusivity, so that the resulting model is a system of reaction diffusion equations. The formation of patterns occurring in such systems under certain conditions was discovered by Alan Turing in 1952. Independently of Turing's work, Gierer and Meinhardt derived in 1972 their *Theory of Biological Pattern Formation* showing that patterns occur only if local self-enhancing reaction is coupled with an antagonistic reaction of long range [5, 8]. The theory was embedded in a model comprising a system of reaction diffusion equations satisfying the Turing conditions. This model is now known as the Gierer-Meinhardt model. It is used as a mathematical model for pattern formation in many different settings. For example, the Brusselator model for trimolecular chemical reactions is a particular case of it [12, 3].

Here we propose modelling of the activation-inhibition mechanism of pattern formation by using nonlocal integral operators. This approach was pioneered in [7] for modelling of vegetation patterns. It turns out that the short range of the activation and the long range of the inhibition can be adequately represented via the supports of the kernels of the respective integrals. An advantage of using the nonlocal operator model from the point of view of its theoretical and numerical analysis is that it does not require smoothness of the solution with respect to the spatial variable.

2 A motivating example: The blue-green algae *Anabaena*

Patterns appear everywhere in the living world, from cell level to level of ecosystems. Gierer and Meinhardt showed that, irrespective of the level of complexity of the system, patterns are produced via the coupling of self-activation with lateral inhibition. Then, it is natural to try to understand this mechanism on simple systems. In this sense, the algae *Anabaena* provides a good example [9]. It is a single cell organism. However, the individual algae attach to form chains or filaments. Most of the cells are vegetative, focused on photosynthesis. In every 7-10 vegetative cells a cell differentiates and becomes a nitrogen fixating cell called heterocyst. This simple one-dimension pattern is very important as it spatially separates two incompatible processes: the oxygen-evolving photosynthesis (in vegetative cells) and oxygen-sensitive nitrogen fixation (in heterocysts) [1]. The control of the pattern formation is attributed to a peptide, which is produced and released by cells differentiating as heterocysts. This peptide inhibits the development of the other vegetative cells into heterocyst [14]. The biology of the heterocyst has been studied intensely with varied approaches [11]. However, many processes and genetic mechanisms are not yet well understood [10]. Theoretical and mathematical models have been developed using different tools, e.g. cellular automata [6], genetic networks [4, 10]. In this paper we

model the spatial interaction of the processes of self-activation and lateral inhibition, which produces the well-known pattern of vegetative cells and heterocysts. We use integral operators in a single differential equation rather than the Turing mechanism as in the Gierer-Meinhardt model.

3 The mathematical model

In most general terms we consider the spatial distribution over a domain Ω of a substance, species or utility, which we denote by U. Usually $\Omega \subseteq \mathbb{R}^n$, where $n = 1, 2$ or 3. Let $u(t,x)$ denote the spatial density of U at time t and a space location $x \in \Omega$. The forces of self-activation and lateral inhibition on U are considered to be nonlocal in the sense that their values at given time t and space point x depend not only on the value of u at (t,x), but on the values of u at time t at all points of the spatial domain Ω or at least a neighborhood of x of positive measure. Using the approach in [7], the nonlocal self-activation and lateral inhibition forces can be represented via integral operators as follows.

$$\text{Self-activation: } A(u;t,x) = \int_\Omega k_1(y-x)u(t,y)(1+bu(t,y))dy. \tag{1}$$

$$\text{Inhibition: } I(u;t,x) = \int_\Omega k_2(y-x)(1-u(t,y))dy. \tag{2}$$

Here b is a positive constant. Further, the kernels k_1, k_2 of the integral operators are nonnegative and such that

$$\int_\Omega k_1(x)dx = \int_\Omega k_2(x)dx = 1. \tag{3}$$

Typically these function are centrally symmetric with most of the volume under the graph concentrated around the origin. Possibly the simplest choice is

$$k_i(x) = \begin{cases} \varepsilon_i \text{ if } ||x|| \le L_i, \\ 0 \text{ otherwise,} \end{cases} \quad i = 1,2,$$

where ε_i, $i = 1,2$, are such that (3) holds. The model represents the relationship

$$\text{Rate of change} \propto \text{Activation} \times \text{Inhibition}.$$

Further, we need to take into account that the Inhibition, as defined in (2) could be negative at (t,x), while $u(t,x) = 0$ and $u(t,\cdot)$ is nonnegative over Ω. Hence, with a modification to exclude the possibility of obtaining negative values, the model is

$$\frac{\partial u(t,x)}{\partial t} = \begin{cases} rA(u;t,x) \times I(u;t,x) & \text{if } u(t,x) > 0 \\ 0 & \text{otherwise} \end{cases}, \tag{4}$$

where r is a positive constant.

4 Pattern formation

It is easy to observe that in the space independent case of model (4), obtained when $L_1 \to 0$ and $L_2 \to 0$, the model is reduced to a well known cubic growth equation with nonnegative equilibria 0 and 1, which are unstable and stable, respectively. Further, $u = 0$ and $u = 1$ are spatially homogeneous equilibria of (4), but the stability is not necessarily preserved.

It turn out that for positive values of L_1 and L_2 the positive spatially homogeneous equilibrium is unstable and stable patterns are established. Note that the value of L_1 indicates the size of the neighborhood providing support, while L_2 indicates the size of the neighborhood providing inhibition. In essence, the patterns are formed through the Gierer-Meinhardt mechanism of self-activation and lateral inhibition. However, this mechanism is represented in model (4) via integral operators rather then via system of reaction-diffusion equation with the Turing conditions, [8].

We perform numerical experiments with a one-dimensional model inspired by the considered example of the blue-green algae *Anabaena*. Here U can be consider the nitrogen-fixation capacity and $u(t,x)$ denotes its distribution along the length of a filament at time t. The self-activation length is the length of a cell. The inhibition length is determined by how far the messenger peptide is spread, e.g. 4-5 cells. In the simulations we used $r = 1$, $b = 0.5$ and $L_1 = 5$. As we vary $d = L_2/L_1$, different patterns are obtained. Two patterns obtained for $d = 4$ are presented on the graphs in Figure 1.

These pattern are stable with respect to small perturbation. Although, every run tends to produce slightly different pattern, they have common essential characteristics: they consist of pulses of similar magnitude and fairly regularly spread over the domain. If we modify the model by restricting the vertical height of the pulses, which is the usual case in practice, e.g. the maximum nitrogen-fixating capacity of a heterocyst, the patterns become much more regular, visually indistinguishable one from the other. A graph is given in Figure 2.

The frequencies of the pulses is determined by the value of d. On Figure 3, patterns produced for different values of d are presented using a color theme to represent the values of u (yellow is high, blue is low). One can observe how as d increases the pulses get more spaced.

5 Conclusion

It is widely accepted that the Turing mechanism for systems of reaction-diffusion equations is appropriate way for modeling pattern formation. In fact, it seems that it is widely believed that it is the only way, particularly given that Gierer and Mein-

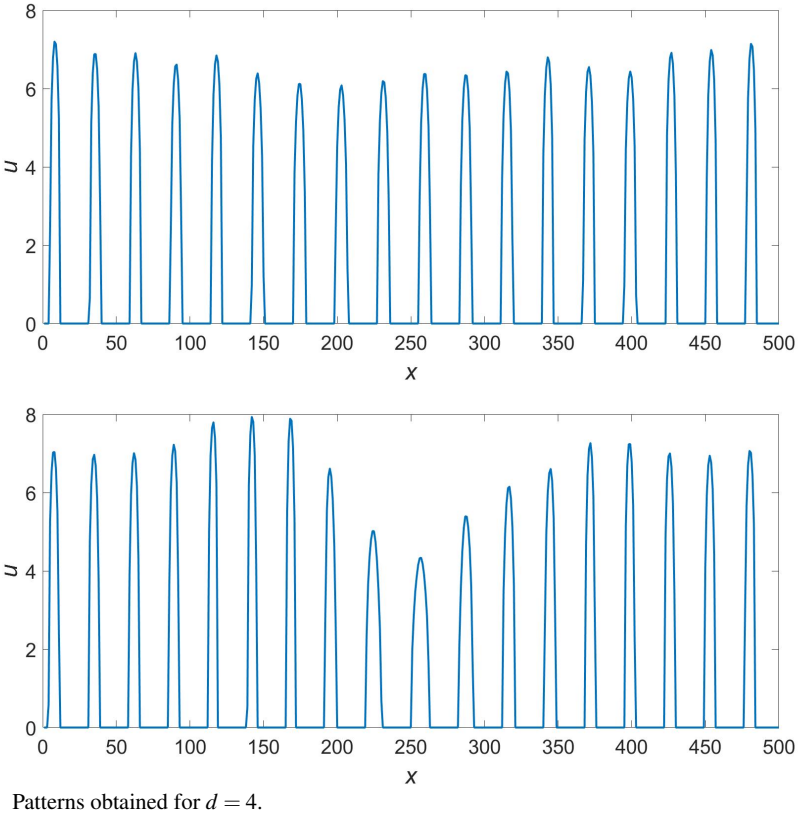

Fig. 1 Patterns obtained for $d = 4$.

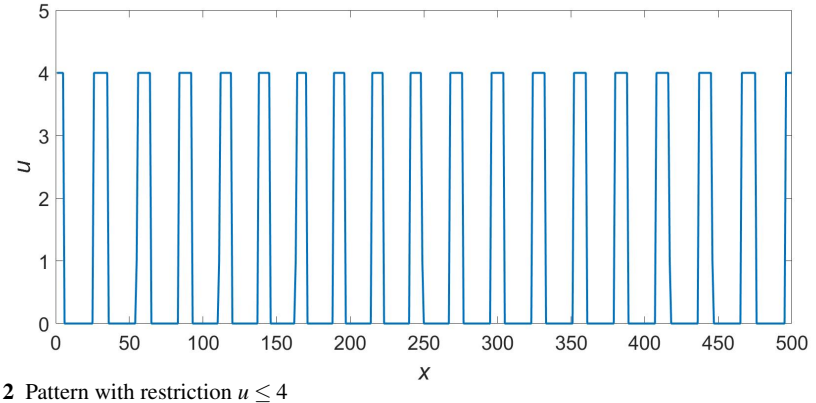

Fig. 2 Pattern with restriction $u \leq 4$

hardt derived independently the same model to represent their principle of self-activation and lateral inhibition, [8]. In this work we suggest that reaction-diffusion

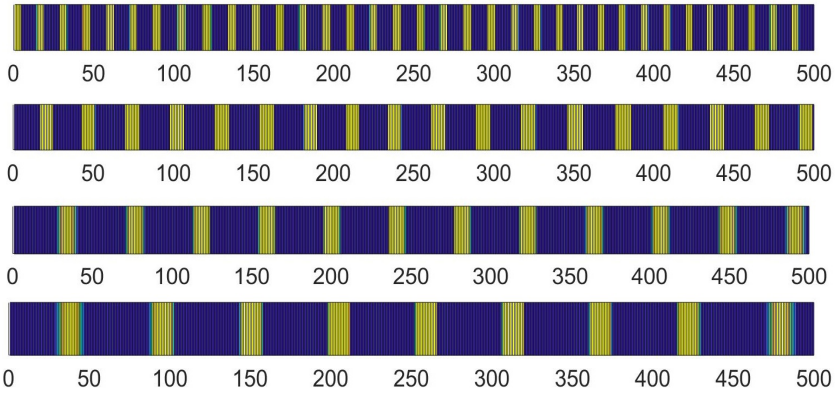

Fig. 3 Patterns for $d = 2, 4, 6, 8$

systems are not a unique way of modelling spatial interactions and pattern formation. We propose a model, where the pattern formation mechanism is formulated in term of integral operators, representing the self-activation and the lateral inhibition forces driving the model's dynamics. Numerical simulations for the one dimensional case show pattern relevant to the blue-green algae *Anabaena*.

There has been quite substantial recent development of the theory of equations involving nonlocal operators, e.g. see [2]. However, there is no theory as yet on pattern formation in such equations. Here we presented a mainly numerical investigation on the pattern appearing when varying the support of the respective kernels. The theoretical analysis of this pattern formation mechanism is an open issue, well-deserving of a research attention.

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