ADVANCED BIOPHYSICS

Biological pattern formation

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Abstract

In this essay we will critically explore Turing's reaction-diffusion models as a mechanism for pattern formation in the domain of living systems. More specifically, we will be mostly concerned about the question to what extent Turing's mechanism underlies the formation of stripes in the skin of zebrafish.

Introduction

A big puzzle in Biology can be translated into the question of how can a complex organism come from a single cell? Alan Turing [1] shed light on the question by proposing a reaction-diffusion model to describe the process of pattern formation. In his mental mechanism, for a pattern to emerge, it was necessary the presence of two interacting morphogens[1] that while diffusing would react with one another which would break spatial symmetry giving rise to the observed patterns. This principle was revolutionary but counterintuitive seeing that diffusion mostly takes an stabilizing role in a system. However, Gierer and Meinhardt [3] performed linear stability analysis to show that this compromise between diffusion and reaction must be under very strict conditions for the system to generate a pattern, i.e., if local autocatalysis and long- ranging inhibition is involved.

Grounded on deductive-nomological and mechanistic accounts of explanation, i.e., the integration between mechanisms and their mathematical counterparts as an approach for modeling of biological phenomena, we regard the qualitative and quantitative description of a model as its fundamental properties [4]. More specifically, as for its qualitative description, we refer to the experimental evidences of the causal contributions of the mechanisms. Regarding its quantitative description, we refer to the down to minute generation of quantitative dynamic-details of the phenomena through the mathematical counterparts of the proposed mechanisms [2]. To simplify the wording, we refer to the later properties as *empirical consistency* and *predictive precision* respectively.

Moreover, as for a "measure" of confidence in a model, we refer to its *robustness*. How invariant are the model's results under different assumptions [2]? To do this in a systematic way, we categorise *model robustness* in *parameter robustness*[3] and *structural robustness* [4]. Upon doing so, we are now able to use formal logic in our critical analysis of the models described in the next sections. This essay is

[1] "The shape-formers": they can be molecules, hormones, genes and etc.
[2] In this hypothetical inductive-deductive cycle, we take falsifiability implicitly into account seeing that we are dealing with models that are certainly falsifiable.
[3] How sensitive is the model to perturbations in the range of the parameters.
[4] How invariant is the model under more realistic representations.

organized as follows. Firstly, we briefly introduce Turing's reaction diffusion models. Secondly, we analyse the Yamaguchi-Yoshimoto-Kondo´s mechanism as a model for the formation of stripes in the skin of *zebrafish* and we refer to its insights and drawbacks related to pigment patterning. Subsequently, we explain the Bullara-Dekker's model and we put it into perspective with Yamaguchi-Yoshimoto-Kondo´s model followed by a critical discussion of the simulations. Lastly, we conclude the essay by summarising it and by providing a concise discussion hereof.

Turing's reaction diffusion model

In 1951, Alan Turing published his grounding-breaking paper [1] concerning pattern formation. The underlying principle is that an instability can emerge from the interaction of two stabilizing processes. More specifically, two interacting morphogens while diffusing keep on reacting with each other which ends up breaking spatial symmetry giving rise to the observed patterns. This mechanism is translated into the following dynamical equations

$$\begin{aligned} \frac{\partial u}{\partial t} &= D_u \nabla^2 u + f(u,v), \\ \frac{\partial v}{\partial t} &= D_v \nabla^2 v + g(u,v), \end{aligned} \tag{1}$$

where u, and v stand for the concentrations of the involved morphogens, D_u, and D_v are the respective diffusion coefficients and $f(u,v)$ and $g(u,v)$ are the reaction kinetics[5]. It is consistent with the proposed mental mechanism seeing that the dynamics of the morphogens is fully determined by the compromise between the diffusion and the chemical reaction processes. From intuition to a precise description, how can we mathematically define *Turing patterns*? In fact, they are stable, time-independent, spatially heterogeneous solutions of (1). To generate these inhomogeneous steady states, one must perturb the system away from its equilibrium which is done when diffusion of the morphogens drives the system unstable in time. Having defined that, and recalling from the theory of partial differential equations that it is not to easy to analytically solve the system (1), we can reasonably assume that a solution of (1) reads

$$e^{pt} e^{iqx}, \tag{2}$$

with $p > 0$ and $q \in \mathbb{R}$ being the wave-number of a Fourier mode. Upon doing so, by drawing on (2), we can perform linear stability analysis of (1) to arrive at the conditions

[5]This system is closed when augmented with suitable boundary and initial conditions.

$$
\begin{aligned}
&f_u + g_v < 0,\\
&f_u g_v - f_v g_u > 0,\\
&D_u g_v + D_v f_u > 2\sqrt{D_u D_v}\sqrt{(f_u g_v - f_v g_u)} > 0,
\end{aligned}
\tag{3}
$$

under which *Turing patterns* can emerge [5]. In other words, if (3) holds then $p > 0$ and one has that e^{pt} will grow unstable in time leading the system to a dramatic change in its spatial structure, embodied into the term e^{iqx}, which, in turn, will cause the pattern to form. Depending on the sort of problem to be studied, the reaction kinetics of (1) is modified which gives rise to a large class of reaction diffusion models [7] . However, can we provide examples of reaction kinetics from which Turing patterns emerge and resemble biological patterns very closely? In fact, it has been shown that a lot of observed biological patterns [6] can be computationally reproduced[6] by using an idealized phenomenological reaction-diffusion system whereby the reaction kinetics hypothetically describes the interaction between an inhibitor and an activator. This system was proposed by Gierer and Meinhardt [3] and it reads as follows[7]

$$
\begin{aligned}
&f(u,v) = c_1 - c_2 u + c_3 \frac{u^2}{(1+ku^2)v},\\
&g(u,v) = c_4 u^2 - c_5 v,
\end{aligned}
\tag{4}
$$

where c_1, c_2, c_3, c_4 and c_5 are the *deterministic* rates of the reactions[8]. The parameter k is a measure of the saturation of the activator u. In $(4)_1$, one sees that the activator u has a positive feedback on itself, degrades, and also saturates, depending on k, and has a negative feedback of the inhibitor v. In $(4)_2$, one sees that the inhibitor v degrades and has a positive feedback of the activator u. However, we want to translate this mental process into a biological context. Can we now give a biological meaning to the abstract conditions showed in (3) with respect to the Gierer-Meinahardt kinetic system (4)? In fact, for this specific kinetics, it is not too difficult to show that the conditions (3) are reduced to the single rational rule

$$
D > (3 + 2\sqrt{2})c,
\tag{5}
$$

[6]In the sense of being very similar to the observed biological pattern. In contrast, we will use "reproduced down to minute" to mean a down to minute description of the observed biological phenomenon.
[7]This is the dimensionless form of the original kinetic system.
[8]These are thought to be estimated from empirical data.

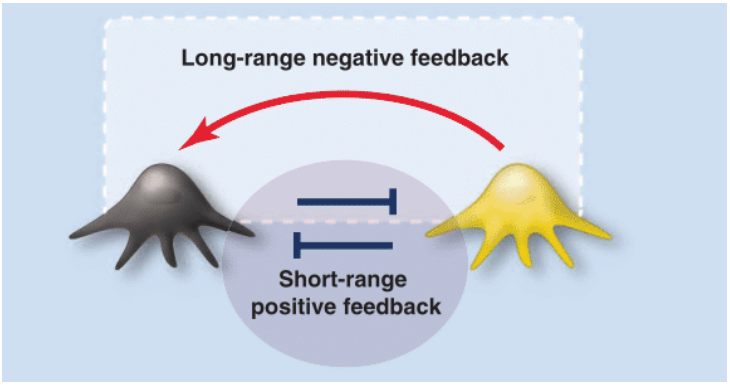

Figure 1 Yamaguchi-Yoshimoto-Kondo's mechanism. Here, we see that the yellow cells have a long-range negative feedback on this circuit while the black cells have a short-range positive and also negative feedback, seeing that they can saturate.

where

$$D = D_v/D_u, \tag{6}$$

and

$$c = c_4/c_3. \tag{7}$$

Hence, if (5) holds then Turing patterns can emerge for the Gierer-Meinahardt reaction kinetics (4). More specifically, one has that the inhibitor v must diffuse sufficiently "faster" than the activator u, i.e., $D_v > D_u$, and that the activator must "produce" enough of itself, i.e., $c_3 > 0$ sufficiently large, so that the condition (5) holds. Or equivalently, if local autocatalysis and long-ranging inhibition is involved then Turing patterns emerge for the reaction kinetics (4). Despite being at a hypothetical level, Geirer-Meinhardt's model is able to reproduce a lot of observed biological patterns [6] which suggests that an activator-inhibitor system is sufficient to yield a biological pattern. This is *conceptual insightful* because it provides normative insights. However, what about a down to minute reproduction of a biological phenomenon? Is there a real living system in which we can actually find Turing patterns? In other words, is there a living system for which Turing‘s mechanism provides a down to minute generation of quantitative dynamic-details of pattern formation? A positive answer to this question would definitely validate the model at the molecular level. From now to the end of this essay, we will be entirely concerned about this question.

Yamaguchi-Yoshimoto-Kondo's model

In 2007, grounded on the normative insight provided by Geirer-Meinhardt's model[9], Yamaguchi, Yoshimoto and Kondo [8] proposed a mechanism[10] to explain

[9] We refer to the inclusion of an adequate activator-inhibitor system.

[10] There is actually no reason for us to name this model in this way. In fact, their proposed model is precisely the Gierer-Meinhardt's model. However, thereby we

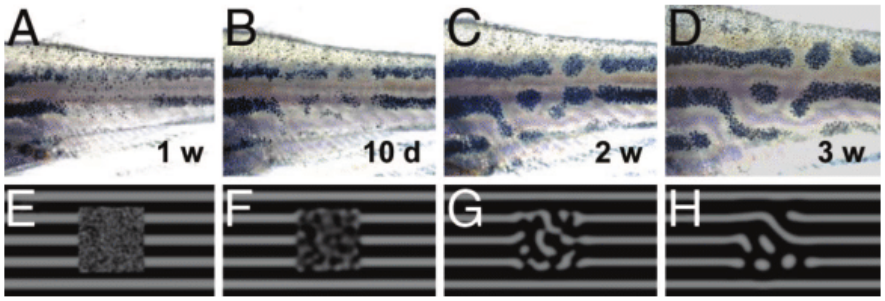

Figure 2 (A-D) Regeneration of stripes: A) One week after ablation of melanophores and xanthophores in the body of zebrafish. B) After 10 days, segregation of the cells can be observed. C) After 2 weeks, we see clearly the formation of a pattern but segregation still takes place. D) After three weeks, regeneration process seems to be completed and a stationary pattern can be clearly seen in the ablated region. (E-F) Simulation of Yamaguchi-Yoshimoto-Kondo's model. Parameters: $a = 0; b = 1.2; c = 0.4; D_u = 1 \times 10^{-2}; D_v = 20 \times 10^{-2}$. To reproduce ablation, the center region in (E) was replaced by a random pattern. In the simulations, u, the activator, stands for the white stripes while v, the inhibitor, stands for the black stripes. (Methods) As for the ablation, they used a laser to break each pigment cell in the ablated region. Regarding the recordings, a time-lapse technique was applied by using a digital camera during $\approx 50 - 60$ days.

the formation of stripes in the skin of *zebrafish*. The pigment cells in zebrafish´s skin comprise *melanophores* (the black cells), *xanthophores* (the yellow cells) and *iridophores* (the white cells) [10]. In 2003, Hirata et al [11] reported that the distribution of melanophores and xanthophores mainly determines the pigment pattern in the hypodermis of zebrafish. Presumably based on this information, Yamaguchi et al [8] performed an experiment in which they used a pulse laser system[11] to ablate all the *melanophores* and *xanthophores* from the target region without damaging the *iridophores*. After having erased the whole pattern from the ablated region[12], figure 2, they observed that the regeneration process took place leading the ablated region to form new stripes. The observation was consistent with Turing's mental mechanism, seeing that ablating the target region drove the "system" away from its equilibrium. Hence, they hypothesize that the formation of the stripes is controlled by the interactions between *melanophores* and *xanthophores*, figure 1, or rather, that long-ranging inhibition of *xanthophores* and local autocatalysis of *melanophores* is sufficient to give rise to the observed pigment pattern in zebrafish. Mathematically, this mechanism is translated into the following dynamical equations

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want to draw the reader's attention to a specific context, i.e., zebrafish as a model organism to unravell the underlying mechanism of pigment pattern formation in vertebrates.

[11] With a microscope attached to it.

[12] The ablated region was in the body not in the fins.

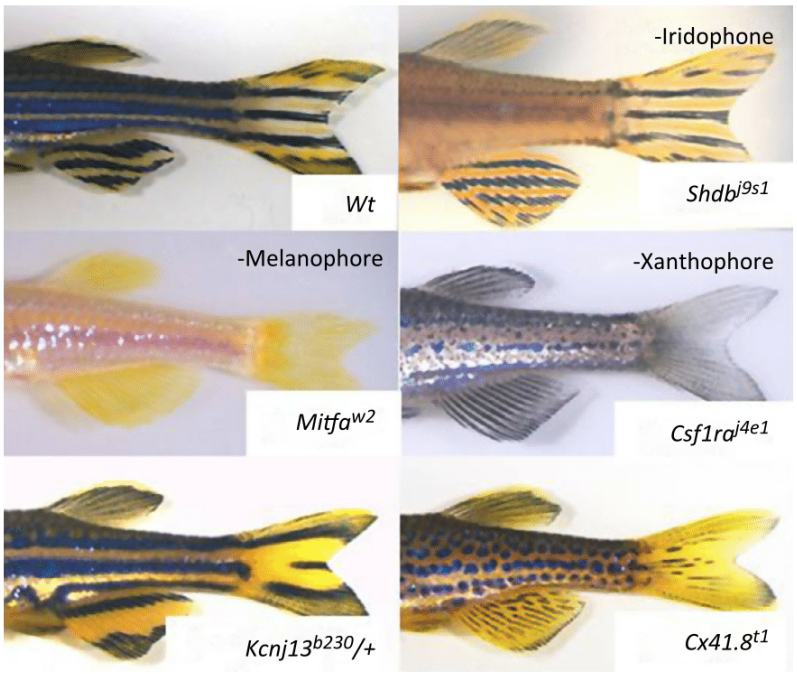

Figure 3 Pigmentation pattern in a mutant zebrafish. In this 3×2 matrix we have that: (1-1) The wild type zebrafish exhibiting the stripes. (2-1) Mutant zebrafish lacking melanophores, total lost of stripes in the body and fins. (2-2) Mutant zebrafish lacking xanthophores, total lost of pattern in the body and fins. (1-2) The mutant zebrafish lacking iridophores, total lost of stripes in the body, but, pattern left unaffected in the fins. What does it suggest? This certainly suggests that, perhaps, melanophores and xanthophores are sufficient for patterning in the fins what implies that the mechanism underlying pigment patterning in both regions, body and fins, is different. However, (3-1) and (3-2) show two mutants in which the pattern changes in the same way continuously from the body to the fins which strongly suggests that the underlying mechanism is the same in the body and in the fins.The names of the mutant genes are displayed on the lower right side of each picture.

$$\begin{aligned}\frac{\partial u}{\partial t} &= D_u\nabla^2 u + c_1 - c_2 u + \frac{u^2}{(1+ku^2)v},\\ \frac{\partial v}{\partial t} &= D_v\nabla^2 v + u^2 - v,\end{aligned} \tag{8}$$

where, u, the activator, stands for the concentration of black cells, *melanophores*, and v, the inhibitor, represents the concentration of yellow cells, i.e., *xanthophores*. Therefore, the dynamics of this model reduces to the Gierer-Meinhardt's reaction kinetics (4).

Regarding *empirical cosistency*, there are few issues. In 1999, Lister [9] reported that in a mutant zebrafish, lacking *melanophores*, no pigment pattern forms in the body or in the fins. In 2000, Parichy et al [12] showed that in a mutant zebrafish, lacking production of *xanthophores*, no pigment pattern forms in the body or in the fins. These facts are certainly consistent with Yamaguchi-Yoshimoto-Kondo's hypothesis. However, in 2013, Frohnhofer et al. [13] carried out an experiment in which

a mutant zebrafish, lacking *iridophores*, produced no pattern in the body but left the pigment pattern in the fins unaffected. These results, figure 3, suggests that the mutual interactions among the pigment cells account for pigment pattern in zebrafish. In other words, a model cannot disregard the interactions between *melanophores* and *iridophores* or the interactions between *xanthophores* and *iridophores*. Moreover, in 2014, Mahalwar et al. [14] reported that pigment pattern formation occurs even though the pigment cells do not have an extensive movement [13]. With long-term imaging procedure, they observed that the melanophores barely move while the movement of xanthophores is limited to the boundary region between stripe and interstripe. The observation is a precise description of the pigment pattern seeing that the stripes, consisting of melanophores, are surrounded by a thin layer of iridophores (interstripes) which, in turn, is covered by xanthophores. This suggests that xanthophores repelling the melanophores and attracting the iridophores causes the pigment pattern to emerge. In other words, if diffusion cannot be the driving force of pigment pattern formation then other forms of cell-cell interaction must better account for the pattern formation process. These facts are really harmful for Yamaguchi-Yoshimoto-Kondo's model seeing that the interactions between *melanophores* and *xanthophores* through diffusion have been assumed to play the major role in their mental mechanism. This suggests that their model is just a subset of a more complex molecular process underlying the pigment pattern formation in zebrafish.

As for *predictive precision*, although they were able to reproduce a regeneration process culminating in the formation of a striped-pattern, figure 2, the " down to minute dynamics" requirement is not met. However, their simulations cannot be seen as mere coincidences but, instead, as evidences for the hypothesis that the underlying mechanism is in a more complex system of regulatory interactions. What can we say about the robustness of this model? With respect to *parameter robustness*, there are some remarkable points. In 1982, Murray [17], drawing on the conditions (3), showed that the parameter space[14] of Gierer-Meinhardt's model is constrained to fine-tuning. In fact, he showed that slightly changes in the parameters can have a negative impact on the results of the model seeing that Turing patterns might no longer emerge. He also showed that the same point in the parameter space could stand for different Turing patterns owing to small variations in the initial conditions. Furthermore, he showed that the parameter space of this model allow the parameters to take negative values what is biologically unrealistic[15]. Therefore, Yamaguchi et al [8] had to adjust the parameters to cause the system to develop stripes. For example, they reported that k[16] was set equal to 0.4 given that slightly smaller and larger values thereof were giving rising to spots or network. If we now consider *structural robustness*, they did not test the model across more realistic assumptions such as the compelling effects of growth, noise and gene-expression delays [15].

[13]Roughly speaking, there is formation of pattern even though the pigment cells do not diffuse.
[14]The parameter domain wherein Turing patterns can emerge.
[15]These parameters stand for reaction rates.
[16]A measure of the saturation of the activator u.

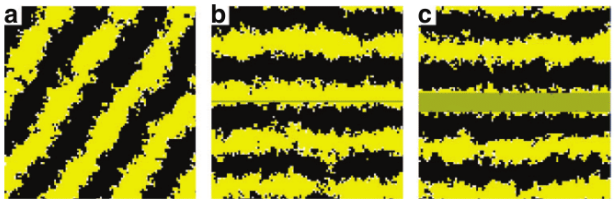

Figure 4 Striped pattern with 1×10^9 Monte Carlo steps. (Parameters) $b_M = d_X = d_M = 0; b_X = s_X = s_M = 1; l_X = 2.5; h = 16$. (Initial conditions) Uniform without *xanthophores* and *melanophores*. (a) Pattern evolves. (b) and (c) They simulated the effects of *iridophores* (shadded band), which are assumed to inhibit *melanophores*.

Bullara-Dekker's model

In 2007, grounded on the experimental results reported by Mahalwar et al. [14] as to the mechanical behavior of the pigment cells[17], Bullara and De Decker [16] proposed a minimal cell-based mechanism[18] to explain pigment pattern formation in the skin of zebrafish. This reads as follows. Despite being immobile, pigment cells can interact locally and non-locally with each other. This compromise of local and non-local biological interactions of *melanophores* and *xanthophores* causes the growth rates of these cells to differ significantly from each other. This *differential growth* culminates in a redistribution of these cells in the hypodermis which, in turn, gives rise to the observed pigment patterning. Mathematically[19], this mechanism can be translated into the following *average evolution equations*

$$\frac{d\langle X_i\rangle}{dt} = b_X\langle S_i\rangle - d_X\langle X_i\rangle - \frac{1}{2}s_M[\langle X_i, M_{i-1}\rangle + \langle X_i, M_{i+1}\rangle], \tag{9}$$

and

$$\begin{aligned}\frac{d\langle M_i\rangle}{dt} &= b_M\langle S_i\rangle - d_M\langle M_i\rangle - \frac{1}{2}s_X[\langle M_i, X_{i-1}\rangle + \langle M_i, X_{i+1}\rangle] \\ &\quad + \frac{1}{2}l_X[\langle S_i, X_{i-h}\rangle + \langle S_i, X_{i+h}\rangle],\end{aligned} \tag{10}$$

where X_i, *xanthophores*, M_i, *melanophores*, and S_i, neither of the latter ones[20], denote the boolean variables describing the node i. The brackets denote the averages of the boolean variables at each time[21]. Hence, intuitively, (9) and (10) describes the time evolution of the "growth rates" of the *xanthophores* and *melanophores*. How are the "growth rates" of *melanophores* and *xanthophores* affected according to their mental mechanism? Or rather, what are the local and non-local rules underlying the interactions between these cells? 1) Firstly, they assume that *xanthophores* and

[17]Here we recall that it was reported that melanophores barely move and that xanthophores have a non-extensive movement.
[18]Without the inclusion of the interactions with the iridophores in the model.
[19]To define cell interactions is convenient to consider a discrete model in which the hypodermis is modelled as a regular lattice.
[20]By construction $X_i + M_i + S_i = 1$.
[21]$\langle A_i, B_j\rangle$ denotes the average of having A at node i and B at node j.

melanophores can emerge at random anywhere in the hypodermis not yet occupied by neither of them. Thus, b_X and b_M represent the "birth rates" of *xanthophores* and *melanophores* in node i. 2) Secondly, they assume that these cells can die due to ageing processes leaving the corresponding node available to be occupied again. So, d_X and d_M stand for the respective "death rates". 3) Thirdly, they assume a "short-range effect" which accounts for the effect of direct contact or competition for nutrients. In other words, cells of the same type surrounding a cell of another type have an inhibitory effect on it. The corresponding "short-range rates" are given by s_M and s_X[22]. 4) Lastly, they assume a positive effect on the "growth rate" of *melanophores* when *xanthophores* are at a distance h. The strength of this "long-range effect" is captured by l_X. Having described the nature of the effects on the expression of the "growth rates", how is the stripped pattern formed then? In fact, short-range interactions segregate[23] the cells. However, only short-range effect is not sufficient to generate a pattern with a finite wavelength. The argument for this claim rests on the assumption that the cells can randomly appear anywhere in the hypodermis what, only under short-range effect, gives rise to a domain wherein the different clusters of *melanophores* (dark cells) and *xanthophores* (yellow cells) have an indefinite size. This implies that the distance between two clusters of dark cells is not uniformly distributed so one cannot have a finite wavelength. How to generate a pattern with a finite wavelength then? To do this, it is necessary to control the distance at which these clusters of *melanophores* can emerge and it is done by including a long-range inhibitory effect which, in fact, limits the region wherein the *melanophores* can emerge. If this distance h sets the boundary of this 'forbidden region' then one expects to get a finite wavelength of $2h$. The strength of this inhibition is given by the parameter l_X. Hence, the smaller is l_X, the smaller is the "growth rate" of *melanophores* which culminates in a domain only consisting of *xanthophores*. On the other hand, the higher is l_X, the higher is the "growth rate" of *melanophores* which will presumably give rise to the stripped pattern.

As for *empirical consistency*, although their model relies on molecular based facts, there is an intriguing issue. In fact, they assume that *melanophores* and *xanthophores* are immobile. The assumption seems to be reasonable for the former. And for the latter? The authors argue that there is no evidence of large-scale movement of *xanthophores*. Besides that, cell movement does not necessarily imply pattern formation. We think that the argument is plausible given the context[24] of their modelling. However, further investigations should be conducted to answer this question properly. As for *predictive precision*, we see in figure 4 that they could reproduce the stripped pattern in the simulations. Therefore, Bullara et al [16], under molecular based assumptions, showed that a compromise between short-range activation and long-range inhibition, as in Yamaguchi-Yoshimoto-Kondo´s model,

[22]They also assume that the short range effects are larger than the death effects, i. e., $s_M > d_X$ and $s_X > d_M$.

[23]It also implies that the cells of the same type have a "short range activation" seeing that, when locally clustered, they only favor the appearance and permanence of cells belonging to the same type.

[24]Their main goal is to get insight into the underlying mechanism given all the compelling evidences against Yamaguchi-Yoshimoto-Kondo´s model.

is sufficient to reproduce the observed pigment pattern even though the cells are immobile. In contrast with Yamaguchi-Yoshimoto-Kondo´s model, this compromise is not driven by diffusion but, instead, by local and non-local biological interactions between the cells culminating in different growth rates. Their results strongly suggest that a better understanding of the respective complex regulatory network of cells involved in pigment patterning will further help us to formulate better models to unravel the underlying mechanism of this biological process.

Conclusion

As we have seen through this essay, it is very unlikely that diffusion-driven instability underlies pigment pattern formation in the skin of zebrafish. How can we unravell the underlying mechanism then? To do so, it is necessary to know how information is carried out by the cells. In order to properly answer this, it is necessary to understand the complex regulatory network involved in the respective biological process. Hence, from this perspective, a biological pattern is a systemic property and not an isolated event. This is in line with the field of systems biology wherein one tries to account for systemic properties of the organism. What is the most adequate modelling strategy then? What kind of models should we expect/propose then? This is a question whose answer depends on the sort of data being analyzed. In fact, *Metabolomics* provides us with "quantitative data", which calls for a continuous approach. On the other hand, *Genomics* yields "qualitative data", which calls for a discrete approach. Hence, toward the description of systemic properties, the mix of data types suggests a formalism through which we can either project our reasoning onto the continuous level or onto the discrete level. Therefore, hybrid models seem to be necessary to properly describe biological phenomena.

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