"Eppur (non) si muove": why cellular movements may not be essential to the formation of Turing patterns in biology.

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In this essay we comment on our recent paper "Pigment cell movement is not required for generation of Turing patterns in zebrafish skin" [1]. The main aims of this narrative are essentially three: to tell the background story behind our work; to provide some basic information which may be useful to understand our paper especially for the readers who are less familiar with theoretical concepts; to propose additional comments and interpretation on the meaning of our results for the developmental biology community. This essay was specifically written under request for the audience of *The Node* blog (thenode.biologists.com).

When Catarina Vicente (Community Manager of *The Node*) proposed us to write a post about our recent paper on pattern formation in zebrafish [1] we were very glad for the opportunity she was giving us to tell the background story about our work in this blog. We are not biologists (we are two theoretical chemists working in the field of nonlinear chemistry and self-organization) and our experience in developmental biology before undertaking this research essentially consisted in having read some books and papers about biochemical self-organization, in having discussions with colleagues, and in attending a few seminars. We think we have somewhat "improved" since then, but we must admit that we still feel like neophytes in the community of developmental biologists. This was the main reason why we were so happy about Dr. Vicente's invitation: we took it as an opportunity to present our outsiders' point of view on a quite debated question related to morphogenesis, and we very much hope to gain inspiring feedbacks from it. But for the very same reason, we were initially afraid to stumble into the typical communication issues that arise when scientists of different fields meet each other in multidisciplinary topics. We thus decided to write our post in an informal way and also include information that may be considered elementary knowledge by most readers, but that we hope will make this post more accessible to those who are completely new to the topic. We also hope that it may be interesting for many scientists to have a look at familiar concepts from a slightly different perspective.

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ALAN TURING AND THE REACTION-DIFFUSION MECHANISM

Morphogenesis and nonlinear chemistry share a special bond since the British mathematician Alan Turing published his seminal paper *On the chemical basis of morphogenesis* [2], which set the basis for a theoretical development of both disciplines. The basic question that Turing wanted to answer was: How can a system with such a high degree of symmetry as an egg cell (essentially a sphere) develop organisms with a much lower degree of symmetry (i. e. living beings)? The question is far from being solved still today, but it certainly was a very challenging one in the mid 1950s when the paper came out. Although one can intuitively grasp that morphogenesis has to stem from the basic laws of chemistry and physics, it was far from obvious at the time how such a symmetry breaking phenomenon could spontaneously emerge in reactive systems. The typical understanding of directionality of chemical reactions provided by equilibrium thermodynamics was that all reactive systems will eventually tend to converge towards their equilibrium state, which typically comes in the form of a spatially homogeneous configuration. Much of the effort to clarify the thermodynamical conditions behind symmetry-breaking phenomena in chemical systems was carried out by Ilya Prigogine and the Brussels school in the 1960s, but in his paper Turing already provided a key mechanism, as well as its mathematical formulation, to account for the central phenomenon of pattern formation.

The pivotal idea of Turing is that [2]

> 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 pat-

tern or structure due to an instability of the homogeneous equilibrium[1], which is triggered off by random disturbances.

This mechanism has since then being referred to as the *reaction-diffusion (RD) mechanism*, and the corresponding stationary patterns as *Turing patterns*. Some of the controversy surrounding Turing patterns in biology often arose from some fundamental disagreement on the names used to describe these structures. We thus think that it is worth spending some time on RD systems before moving forward, in order to clarify the discussion.

From a molecular point of view, a chemical reaction is essentially an exchange of atoms between two or more molecules (or molecular segments of the same molecule). At a molecular scale, chemical reactions are thus non-local events between units which are located at different positions in space. However, theoretical approaches to reactive systems are often based on a much coarser level of description. One usually subdivides the whole space inside a system into a collection of infinitesimal volumes Δ_V. Within each infinitesimal volume a molar concentration c_i can be defined as

$$c_i = \frac{N_i}{N_A \Delta_V}\,, \tag{1}$$

where N_i is the number of particles of each species i. The microscopic details of the chemical reactions are disregarded and one focuses solely on the numbers of particles. This coarse graining is at the basis of the classical mathematical formulation of chemical kinetics in terms of continuous differential equations of the form

$$\frac{\partial c_i}{\partial t} = f_i - \nabla \cdot \mathbf{J}_i\,, \tag{2}$$

but in order to be properly applied, two opposite requirements must be fulfilled:

1. The volume Δ_V must be large enough so as to contain a statistically significant number of molecules. In such a way, continuous concentrations can be defined.

2. The volume Δ_V must be small enough so that the concentration gradients across space are smooth. A continuous spatial coordinate can thus be used to describe the system.

If the above two conditions are satisfied, each sub-volume can be seen as a single "point" of space in which the molecules are in a well-mixed state. One can then assume that chemical reactions will only occur between molecules in the same infinitesimal volume and reactions can therefore be considered as local events. This local description of chemical kinetics produces the scalar term f_i in the right hand side of (2). A similar approach can be used for processes that are not really chemical reactions, as long as one can define events taking place between the units composing a system whose outcome is to change the number of units. From this point of view a wolf killing a rabbit or a cell undergoing mitosis may be both considered as "reactions", although not chemical ones.

The other molecular phenomenon central to Turing's mechanism is diffusion. Due to its importance in several areas of science, there are many slightly different interpretations of the word "diffusion". We define here molecular diffusion as a motion of the molecules of the system which can be described as a Brownian motion. By extension, we will use the expression "cellular diffusion" when the motion of a biological cell can be described in the same way. In the coarse-grained framework discussed above, a diffusive motion represents a displacement of a molecule (or cell) from one point in space to an adjacent one. The concentration fluxes $\mathbf{J}_i$ for the ith species will have in this case the form:

$$\mathbf{J}_i = -D_i \nabla c_i\,. \tag{3}$$

Plugging (3) into (2) produces the well known Laplacian term $D_i \nabla^2 c_i$, which is typical of Fickian diffusion. We would like to stress at this stage that while this Laplacian description is the coarse grained representation of a molecular Brownian motion, the converse statement is not always true: not all Laplacian formulations necessarily imply a Brownian motion of microscopic units. The Laplacian is just a mathematical operator which propagates a certain information (in this case the concentration fields) across space, but the physical reasons behind this propagation can be very diverse. Indeed Laplacian formulations can be found in many different fields ranging from heat conduction to nonlinear optics. This very point is essential to understand one of the key messages of our work and we felt that it was important to stress it even at the cost of sounding trivial to many readers.

Another important remark is that not all RD dynamics produce evolution laws which undergo a dynamical instability in the sens of Turing. The usual way to assess the emergence of an instability is to perform a *linear stability analysis* of the evolution equations. Shortly said, one linearizes the system of equations (2) around a homogeneous steady state and then looks at the response of such mathematical system to a small perturbation around this state of reference. It is convenient in practice to consider perturbations of the form $\exp[\omega t + \mathrm{i} k \mathbf{r}]$, where t is the time and $\mathbf{r}$ a generic spatial coordinate. If both ω and k are real numbers, the above perturbation describes a function which can exponentially grow ($\omega > 0$) or decay ($\omega < 0$) in time and which is periodic in space with

[1] Intended as the mathematical equilibrium of the set of equations describing the dynamics of the system, or in other words any reference homogeneous steady state solution of the latter.

wavenumber k. The outcome of the linear stability analysis is usually expressed in the form of a mathematical relation between ω and k, which depends on the parameters of the system. If for a certain range of parameters the growth rate ω of the perturbation is always negative, the reference steady state cannot be destabilized with spatially periodic perturbation and we will therefore observe a spatially homogeneous configuration. If however, upon tuning the control parameters of the system, ω becomes non-negative for a particular wavenumber $k = k_T$, the homogeneous steady state can be destabilized by perturbations having this very wavenumber. In such case, the state of the system which will be eventually observed is a time-invariant, periodic in space pattern of concentrations with the corresponding wavelength. The particular combination of values of the different parameters for which the instability appears is commonly referred to as a *Turing instability* or *Turing bifurcation*.

The occurrence of this instability is the very reason why stationary patterns with an intrinsic wavelength can be generated with RD equations. The original model proposed by Alan Turing - as well as several other pattern-generating models - undergo precisely this type of instability, which led in practice to an identification of the terms "Turing instability", "Turing patterns" and "reaction-diffusion mechanism". We hope that the short discussion above has made it clear that these terms express in fact different concepts. As their meaning varies slightly from one field of research to another, we find it convenient to adopt here the following definitions:

- A *Turing instability* or *Turing bifurcation* is a mathematical condition for which the growth rate ω of a linearized set of dynamical equations becomes non-negative for a single value of the wavenumber k of the applied perturbation.

- A *Turing pattern* is a time-stationary and space-periodic state of a system generated by a Turing bifurcation. We additionally require that the physical system whose dynamical equations undergo the Turing bifurcation is in a state of thermodynamical non-equilibrium.

- A *reaction-diffusion mechanism* is any mechanism which involves *(a)* interactions between the units of a system whose outcome is to change the number of units in the system, and *(b)* physical movements of these units in space which can be described as Brownian motion.

Notice that according to the latter definition, the fact that a system can be described by a set of partial differential equations with scalar and Laplacian terms is not enough to classify it as a reaction-diffusion system. Classical pattern-generating models such as the Brusselator [3] or the Geirer-Meinhardt model [4] are examples of reaction-diffusion systems, but Turing patterns can be generated by other classes of systems (as for example in nonlinear optics [5]).

TURING PATTERNS WITHOUT DIFFUSION? THE RIDDLE OF THE ZEBRAFISH STRIPES

As most of the readers of this blog probably know very well, zebrafish is a widely used model organism for many different studies in genetics and developmental biology. Our interest however is in what gave the zebrafish its name: coloured skin patterns. Since we don't want this post to be a repetition of the information written in our paper and since we want to keep the tone of the discussion informal, we won't attempt a comprehensive review of the studies on zebrafish patterning here. Instead we want to take this opportunity to express our personal point of view on, and our perception of, these studies.

Our interest in zebrafish patterning began in 2012, when we attended a very intriguing seminar by Shigeru Kondo at a Gordon Research Conference on "Oscillations & Dynamic Instabilities in Chemical Systems". In his talk, Kondo showed a set of fascinating experiments that he and his group had been carrying out. In a nutshell, their aim was to investigate the dynamical response of the skin patterns of both adult and young zebrafish after partial ablation by a laser. They compared the observed regeneration dynamics to the output of numerical integrations performed on a typical RD system (the Geirer-Meinhardt model) subject to analogous initial conditions [6]. The visual matching between the two was simply astonishing: the dynamics of the experimental and theoretical patterns were practically identical, right down to the smallest detail. Moreover, the experiments clearly showed that the stripes of the zebrafish possess an intrinsic wavelength, which was recovered even after total ablation of the pattern. Needless to say, these results initially convinced us that the likelihood of the zebrafish patterns being Turing patterns generated by some sort of RD mechanism was very high.

A more detailed look at their results led us however to change our mind quite rapidly. Magnification of the experimental pattern shows that it is not formed by continuous gradients of concentrations of some molecular species across the skin, as one would expect in RD systems. It is made instead of a discrete clustering of pigment cells of essentially two types: black melanophores and yellow xantophores. The number of cells within each wavelength is surprisingly small (on the order of tens of cells) compared to the numbers one would need to define local reaction rules according to the coarse-graining discussed above. The fact that cells do not properly "react" in a chemical way and the intrinsically discrete character of the systems were strong hints that an explanation of the pattern formation in terms of a RD mechanism was,

after all, likely not a good one. We thought at first that both these limitations could nevertheless be overcome. If the pigment cells could be shown to interact analogously to the molecules of a chemical oscillator and, most importantly, if they could move through the skin of the fish with a Brownian-like motion, then one might end up with a set of approximated RD evolution equations for the populations of cells on the fish skin. However we soon understood that this was not the case.

Indeed, the cell-to-cell interactions which are at the core of the pattern formation mechanism cannot be interpreted as reaction rules acting locally. More specifically, the cells show two different kinds of interactions with two different ranges. When melanophores and xantophores are in close contact, they exhibit contact-mediated interactions which tend to decrease the lifespan of both cells [7]. We will call this mutual inhibition the *short-range interactions*. However the presence of xantophores at a certain distance h from a given position on the fish skin increases both the rate at which melanophores appear as well as their survivability at that place [8]. An interesting observation is that this distance roughly coincides to half of the wavelength of the pattern. We will refer to this feedback as the *long-range interaction*. Although the exact biological mechanism by which xantophores promote the appearance of new melanophores is not known, there is very strong evidence that the increased survivability is mediated by protrusions of melanophores which trigger a delta-notch signaling at their tip when they enter in contact with xantophores [9]. This is supported by the fact that the length of these protrusions is also roughly equal to the distance at which the long-range interaction occurs. Our unverified hypothesis is that since the precursors of melanophores and xantophores are everywhere present below the hypodermis of the fish, a similar interaction may occur between xantophore on the hypodermis and melanophores below it at distance h. This would have the effect of favoring the presence of melanophores at that distance below the hypodermis, and subsequently increase the likelihood that melanophores would "appear" there. In any case, whatever the actual mechanism responsible for the interaction, the important information for us is that the existence of such long-range feedback is strongly proven by the experiments.

Aside from the non-local character of the cellular interactions, there is an even bigger problem when invoking a reaction-diffusion for this system: the pigment cells do not diffuse across the skin of zebrafish. They do exhibit some degree of mobility but their movement, which has been characterized in vitro as a run-and-catch motion [10], cannot be represented as a Brownian motion. Even more importantly, this motion is not enough by itself to induce a migration of the pigment cells into separate domains [2] [11]. In other words, cells are in a first approximation almost immobile.

We must admit that the challenge posed by the experimental findings was one of the most intriguing problems we ever came across. We were in the presence of what looked like, and dynamically behaved like a Turing pattern but it couldn't be cast into a reaction-diffusion system. For a long time we considered the solution of this riddle out of our reach, and we waited for more experimental findings on the actual motion of the cells in vivo to be published. However, as new studies confirmed the absence of extensive motion of cells, we came to realize that no important piece of the puzzle was missing and that the answer to the absence of motion was just before our eyes.

We knew that when chemical reactions are described at the nanoscale they cannot be interpreted as local processes occurring at a single point in space anymore, because the size of the molecules cannot be neglected with respect to the scale of the mathematical description. More importantly for our purpose, the fact that two reacting molecules are located at different positions means that chemical reactions are not local, but are propagating in space. In mathematical terms, t his effect translates into "virtual" diffusion terms [12] even if the molecules are immobile because the reaction itself can induce a redistribution of the nature of molecules in space. We thus thought that since such an effect exists for immobile molecules on catalytic surfaces, something similar could also be found for pigment cells sitting on the skin of zebrafish.

A NEW MECHANISM: DIFFERENTIAL GROWTH

The question we wanted to answer was essentially the following: Is the the nonlocal character of the short-range and long-range interactions able to create a "virtual movement" of cells across the zebrafish skin, and to generate in such a way a pattern with an intrinsic wavelength?

This hypothesis was not easy to confirm. Not only does it require that nonlocal interactions can generate flux terms for the cellular populations, but also these fluxes

[2] One of our initial guesses was that the short-range movement shown by the pigment cells could have been important in shaping the fine details of the stripes, more particular the small gap observed between two adjacent stripes. Because of the nature of our model, we could not test this hypothesis ourselves, but we recently discovered a preprint paper by A. Volkening and B. Sandstede titled *Modeling stripe formation in zebrafish: an agent-based approach* which independently proves this hypothesis true with a different modelling approach.

need to combine with other terms produced by the interactions to produce, in the end, a Turing bifurcation. To test our hypothesis, we thus needed a simple mathematical model which is also biologically relevant. In order to make sure that the real reason behind pattern formation was the presence of non-local interactions (and not a sophisticated cell movement like the run-and-catch motion observed in vitro), we decided to completely remove any form of cellular motion from our model. Alwasy for the sake of simplicity, we did not include explicitly a third type of pigment cell (iridophores) whose role was shown to be important in the pattern formation on the body of the fish [13], but negligible in fin patterning [14]. We again focused on the simplest possible model one could deduce from the experiments and we decided to take into acocunt their presence only implicitly: xantophores and melanophores are known to rest on separate layers of iridophores [15], and this forbids the possibility that two of these pigment cells stay on top of each other. Finally, to have the simplest possible description of this situation, we imagined the skin of the fish as a regular lattice where each box could contain at most one melanophore, one xantophore, or none of the two.

With our modelling framework now well-defined, we introduced the short-range and long-range interactions reported in the literature as stochastic processes occurring with different probabilities. An initial problem we had was to establish precise cellular rules for the interactions, based on the experimental data. As an example, the short-range inhibition of xantophores by melanophores can be implemented in many different ways, each implying a different number of interacting melanophores and xantophores. Such details are very important when modelling non-linear behaviors in reactive systems. For example, it can be mathematically proven [16] that in order to generate temporal oscillations in a chemical system with two dynamical variables, it is necessary to have at least one elementary step whose molecularity is strictly larger than 2. Introducing tri-cellular steps however would have implied a degree of cooperativity between cells which could not be justified with the available experimental knowledge. Again, we opted here for the simplest possible implementation of the short-range and long-range feedbacks, so we assumed that they are just due to pairwise cell-to-cell interactions.

For the sake of completeness we also included the spontaneous differentiation and death of both pigment cells on the skin of the fish. On one hand, several studies show that the early stage of the pattern development is characterized by a pre-pattern formed by a single band of iridophores in the middle portion of the trunk of the fish [13]. This band inhibits the growth of melanophores on top of them and therefore guides the differentiation of new pigment cells on the skin of the fish. On the other hand, the ablation experiments by Kondo et al. mentioned before show that when the pattern is ablated on the skin of adult fish, melanophores and xantophores randomly appear everywhere on the skin. In our quest for simplicity, we decided not to make any particular assumption on the positions where pigment cells appear on the skin, and we simply modelled the differentiation process as a random birth process over the whole space[3]. We could however qualitatively reproduce the effect of having a pre-pattern by imposing special initial and boundary conditions in the simulations of our model.

Once the full model was built, the last step was to find a simple yet representative set of parameters which would trigger the pattern formation. For a theoretician there are generally two ways to make this choice. The first is to extrapolate numbers from quantitative fitting of experimental data. The second is to use the experiments as a guideline to make suitable approximations and then explore a reasonable region of parameter space around these values. Since our aim was not to make quantitative comparison with experiments but rather to prove a general principle, we opted for the second choice. The seven steps of our final model can be cast into essentially four classes of processes: two "natural births" (the spontaneous differentiations), one "induced birth" (the long-range interaction), two "natural deaths" and two "induced deaths" (the short-range interactions). By reading the available literature we developed the idea that the induced birth and death processes are much faster than their natural counterparts. We therefore decided to set to zero the probabilities of these natural processes. That left us with just four processes: the spontaneous differentiation of xantophores, the differentiation of melanophores induced by long-range xantophores and the mutual killing of pigment cells promoted by the short-range interactions. In order to further reduce the number of parameters, we set the probabilities of the induced deaths to be equal. Although this approximation may not exactly correspond to the values which could be obtained from a quantitative fitting of the experiments, it allowed us to simplify a lot the mathematical analysis of our equations without losing generality. All these approximations left us with only three control parameters: the probability of xantophore differentiation b_X, the probability of having a long range interaction l_X, and the spatial extent of the long range interaction h.

By performing stochastic simulations of this model, we observed that as soon as l_X was larger than b_X, the sys-

[3] To this regard, we feel like we should somehow apologize to the biology community for the choice of jargon we made in our paper: we there call "birth" what should more correctly be called "differentiation". The reason of this choice is that the name commonly used in the stochastic mechanics literature for the class of processes we used is "birth/death" processes, so we felt that the model could be more easily understood by a broader audience of also non-biologist scientists if we stuck to these names.

tem would form stationary patterns with well-defined geometry and wavelength. This was an incredible achievement for us, because it shows that despite its extreme simplicity, our model is able to reproduce the most important experimental observations:

- stationary patterns with intrinsic wavelength can spontaneously emerge without cellular motion;
- patterns with different geometries (spots, stripes and reverse spots) can be generated by the model when varying the numerical value of l_X (which mimics the effect of having different mutants of the same genus with different geometrical patterns);
- the half-wavelength of the patterns (regardless of their geometry) is roughly equal to the length of the long range interaction;
- the wavelength is recovered after perturbation or ablation of the pattern;
- imposing a pre-pattern rule similar to the one observed in the experiment (a single band of iridophores in the middle of the trunk) guides the orientation of the striped pattern parallel to it.

We were also very positively surprised by the simplicity of the selection rule for the pattern's geometry: the length h of the long-range interaction controls the wavelength of the pattern, while the "strength" l_X of the same interaction controls the topology (spots, stripes or reverse spots).

With these results, the only missing piece was to mathematically prove (via a linear stability analysis) what the origin of the patterns observed in the simulations was. To keep the mathematical analysis on the familiar grounds of classical of RD systems, we decided to perform the analysis on the mean-field (non-stochastic) limit of our model. The corresponding set of evolution equations has the form of a RD system, but one must be very careful neither to interpret the scalar terms in these equations as coming from reaction, nor the Laplacian terms as coming from diffusion. As we said earlier, the mathematical representation of the continuous limit of a process should not be identified with the process itself, and different physical mechanisms can lead to equations having the same form. Earlier in this post we also briefly explained how the scalar and Laplacian terms in reaction-diffusion models are obtained. We will not present here a similar explanation for our model, because the details can be found in our paper, which is freely available. The stability analysis showed that a Turing bifurcation is possible for values of l_X larger than b_X, as observed in the simulations. We could moreover show that the values of the half-wavelength of the pattern and of h at the onset of the instability are very close to each other. This represented the mathematical proof that the fact that the half-wavelength of the pattern and the length of the long-range interaction are found to be approximately the same is not a trivial occurrence to be expected *a priori*, but the result of being close to a Turing instability.

Our results prove that biological patterns with an intrinsic wavelength can be generated from a Turing bifurcation, without any need to invoke cellular motion. The necessary condition is to have non-local cellular interactions at play in the system. This mechanism is intrinsically different from the reaction-diffusion mechanism proposed by Turing, although we believe that the pattern thus generated have the right to be called Turing patterns, because they result from a Turing bifurcation generated by a nonequilibrium process. The key ingredient to form the patterns is that cells can "be born" and die with different rates, or in more mathematical words can have different growth rates, depending on their surrounding. In order to give a unambiguous connotation to this mechanism and distinguish it from other pattern-generating ones, we proposed to call this mechanism *differential growth*. Differential growth promotes a non-trivial redistribution of cells across space by combining short-range and long-range cellular interaction in an appropriate way. In such situations cellular migration becomes accessory to pattern formation, so one cannot rule out the possibility of having Turing patterns solely on the basis of the lack of extensive cellular movements.

As a final note, we would like to mention a very interesting article which has recently been published in Development [17]. The authors propose a way to rationalize the different patterns-generating mechanism under a common mathematical framework and try to derive simple rules for the control parameters, which can be used as a guide for the design of experiments. Although all the mechanisms taken into account fall under the "short-range activation and long-range inhibition" type, the physical origins of these mechanism are very different, and so are the constraint rules on the parameters. It is interesting to note that the only mechanism for which the authors could not calculate a simple parametric constraint is precisely the type of mechanism we consider here ("cellular via cell contact signals"). We think that the main difficulty in deriving simple rules is generally due to the lack of simple models directly derived from the basic physical processes. We hope that our model can fill this hole for the contact-mediated pattern formation and allow for a simpler interpretation of experiments. For reaction-diffusion systems, classical toy models can be used to derive the general rule that 'the inhibitor must diffuse faster than the activator'. For the class of systems which fall under the differential growth mechanism, our model suggests that 'the inhibitor must grow faster than the activator', provided that the growth of the former is controlled by a long-range positioning of the latter.

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