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Review

Theoretical analysis of mechanisms that generate the pigmentation pattern of animals

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ABSTRACT

Mechanisms of animal skin pigment pattern formation have long been of interest to developmental and mathematical biologists. Although there has been a well-studied theoretical hypothesis—the reaction–diffusion system—that is able to reproduce the variety of skin patterns, a lack of molecular evidence has kept it just a hypothesis. In this review, we summarize the results of theoretical studies to date for researchers not familiar with their mathematical underpinnings, and we discuss future approaches that will more fully integrate mathematical models and experimental analyses.

Contents

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1. Introduction

Many animals have fascinating color patterns on their skin, which play important roles in many kinds of behavior such as shoaling, mate choice, camouflage, and antagonistic displays. How these skin patterns form is a long-held but still unsolved question. There have been two principle avenues towards solving the problem. Classic genetic studies have long been done for with pigmented domestic mammals, birds and fishes. Many strains of different pigmentation patterns have been isolated and relationships between mutants analyzed mainly by the breeding [1–3]. However, as the species used in such analysis were not standard model animal of molecular genetic studies, it had been difficult to identify the underlying molecular mechanism in such animals. There is also a long history of theoretical study on this subject [4–6]. With many characteristic pattern shapes, mathematical methods have shed light on the logic of underlying mechanisms: although mathematical studies cannot identify the involved genes or signaling pathways that function in the pattern-forming event, they can predict fundamental behaviors of skin patterns and can suggest the necessary conditions for their formation. Emergence of zebrafish as a model organism for developmental genetics has made it possible to combine the two kinds of studies because both "molecular genetic" and "mathematical" approaches are possible with this species [7–10]. In this review, we summarize theoretical studies of the reaction–diffusion (RD) system, a representative mathematical model that explains the patterning phenomena, and we show how this model can explain the specific characteristics of animal skin patterns.

2. Common characteristics of animal skin patterns

Although there is large diversity in skin pattern, there are some common characteristics that can suggest underlying mechanisms.

2.1. Diversity among the closely related species

Most skin pigment patterns can be roughly classified into three basic patterns: spots, stripes, and polygons (i.e., reverse spots). As many animals have the skin of continuous coloration, "uniform pattern" can be counted as another skin pattern. It is interesting to note that some species in the same family or genus often have different patterns. Catfish species shown in Fig. 1 belong to the same family, Loricariidae [11] and their skin patterns differ despite morphological similarities in other respects. As they are phylogenetically very close, molecular mechanisms at work are likely to be very similar; i.e., an essentially similar pattern-forming system can form very different patterns, such as spots, stripes, and polygons. There are many other examples showing this pattern diversity in the family of fish (Tetraodontidae, Siganidae, Labridae, and Serranidae [12]) and frogs (Dendrobatidae [13]), suggesting that flexibility of the underlying mechanism is a common feature among the pigmented animals.

2.2. Autonomy

The second characteristic of animal skin patterns is that they appear independent of the internal tissues or the body structures. For example, the fishes shown in Fig. 1 have uniform skin patterns across their entire bodies. In spite of the structural difference of the internal tissues, both the patterns and the length of the repetitive units are almost identical. This fact is very interesting when considering the nature of the underlying patterning mechanisms, because the distance of the repetitive units is much larger than the size of a single cell. How do cells know how wide stripes should be? In the case of striped pattern of segmentation genes in Drosophila, positional information comes from morphogen gradients that function as a prepattern. However, in the case of skin pattern, it has not been possible to find such a prepattern, suggesting that many skin patterns are formed autonomously without reference to an external prepattern.

2.3. Robustness

The third interesting characteristic of animal skin pattern is its robustness against perturbation. In some tropical fish, when skin patterns are disturbed by injury or transplantation, or when growth of the fish enlarges the spacing of the patterns, rearrangement of the pattern is induced, and this restores the original spacing [14–16]. The third interesting characteristic of animal skin pattern is its robustness against perturbation. In some tropical fish, when skin patterns are disturbed by injury or transplantation, or when growth of the fish enlarges the spacing of the patterns, rearrangement of the pattern is induced, and this restores the original spacing.

3. A mathematical model that satisfies characteristics of animal pigment patterns

From the characteristics of the skin pattern explained earlier and extensive empirical analyses [16–18], it is clear that formation of skin pigment patterns cannot be explained by the function of single molecules or a simple prepattern-based mechanism. Although there is no known molecular mechanism that is capable of explaining all the characteristics of pigment patterns, a well-established mathematical model, called the RD system, can explain these characteristics very well [4].

3.1. The RD system

In 1952, Turing presented a ground-breaking idea that a combination of reaction and diffusion of the putative chemical substances can generate spatial patterns in his work entitled "The chemical basis of morphogenesis" [4]. He studied the behavior of a complex system in which two substances interact with each other and diffuse at different diffusion rates, which is known as the RD system. Turing proved mathematically that such a system can form stable periodic patterns in the field even from a uniform state. In the 1970s [4,5,19,20], theoretical studies of the RD system with computer simulation showed that this model can produce most of the 2D patterns found in the skin of animals.

3.2. Necessary conditions for stationary pattern formation in the RD system: "local enhancement and long-range inhibition"

The RD system is described by partial differential equations, which mathematically deal with the synthesis, decay and diffusion of the hypothetical substances. Although many different types of equations can generate the stable periodic pattern, they share a common property, "local enhancement and long-range inhibition," which is thought to be the necessary condition for pattern formation [21,22]. The simplest type of these equations, the activator–inhibitor model, is shown in Fig. 2a and is represented as follows [6]:

$$\frac{\partial u}{\partial t} = a - bu + \frac{u^2}{v(1+u^2)} + D_u \Delta u$$
$$\frac{\partial v}{\partial t} = -v + u^2 + D_v \Delta v$$

Here u and v are the concentrations of activator and inhibitor. a, b, D_u, and D_v represent the parameters. In the model, the acti-

Fig. 1. Pigment pattern diversity in catfish, family Loricariidae. The most frequently seen skin pigment patterns are spots, stripes and polygons. This diversity of the pattern is often seen in the species belonging to an identical family or genus. Pictures are species in the family Loricariidae.

vator is supposed to activate the synthesis of both activator and inhibitor, whereas the inhibitor inhibits the function of activator, and the diffusion rate of inhibitor is set much larger than that of the activator. The dynamic behavior of the system is represented schematically in Fig. 2b–d. Graphs in Fig. 2b–d show the concentration of activator and inhibitor in the 1D field. Fig. 2b shows how the periodic peaks emerge from a random pattern. In the central region of Fig. 2a, the concentration of the activator is set relatively higher than in other regions as an initial condition. By the self-enhancing nature of the activator, the concentration of activator increases at the center, followed by the increase of inhibitor at the region (Fig. 2c). As the diffusion rate of inhibitor is much larger than that of the activator, substantial amounts of inhibitor move toward the lateral regions, and depress the activator function, decreasing the activator concentration there. Eventually, this system amplifies the minor concentration difference and stabilizes the border of the concentration peaks and valleys (Fig. 2d). This system also has the ability to regulate the width of the peak or valley regions. When a wide region has a high concentration of activator, diffusion cannot decrease the inhibitor concentration at the center. Then the high inhibitor stops activator synthesis, and decreases the activator concentration to divide the wide peak. At the valley of the activator concentration, activator production is suppressed by the inhibitor diffusing from the neighboring region. However, if the low activator region is too wide, inhibitor cannot reach to the middle of the region; then the inhibition of the activator synthesis is lost at this region and the activator synthesis starts to insert a new peak. These effects occur continuously at all places in the field, and give rise to evenly distributed wave-like patterns, the spacing of which is determined by parameter values of the equations.

(This explanation is only for giving a rough image of the RD mechanism. For more "mathematical" explanations, please refer [5,23,24])

4. Ability of the RD system to form the variety of observed patterns in nature

4.1. Basic three patterns: spots, stripes, and polygons

Shapes of the RD patterns are sensitive to parameter values of the differential equations, and using this property, it is possible to generate various patterns with almost identical equations. The relationship between the parameter values and the 2D patterns has been studied extensively using computer simulations. Among the parameters in the equation, Meinhardt pointed out that the value that determines the upper limit of activator synthesis is particularly important to pattern outcome [24]. Fig. 3 shows the relationship between the shape of 1D wave and the 2D patterns. When the upper limit of activator synthesis is high, the wave peaks become high and pointed. On the contrary, when the upper limit is low, the wave peaks become bold, and the valleys become pointed. The former parameter value makes the spot pattern, whereas the latter parameter value makes polygons. When this parameter is set at an intermediate value, the system forms a stripe pattern. Therefore, it is possible to generate the three basic periodic patterns—spots, stripes, and polygons, just by changing a single parameter in the RD

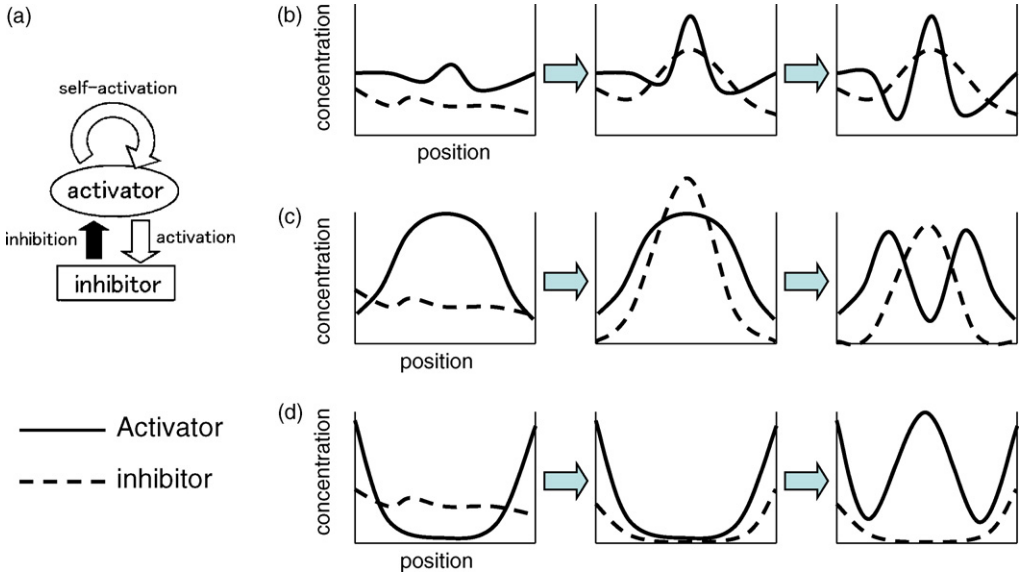

Fig. 2. Schematic explanation of the reaction–diffusion mechanism. (a) Interaction network of a simple RD model called "activator–inhibitor model". (b) A process of periodic pattern formation in the 1D field originated from a random pattern. (c) A process of division of a broad peak. (d) A process of new peak insertion. The dynamic properties shown in this figure are common among most of RD models that satisfies the necessary conditions for the stable pattern formation, "local activation and long-range inhibition". Solid lines and dotted lines represent the concentration of activator and inhibitor, respectively.

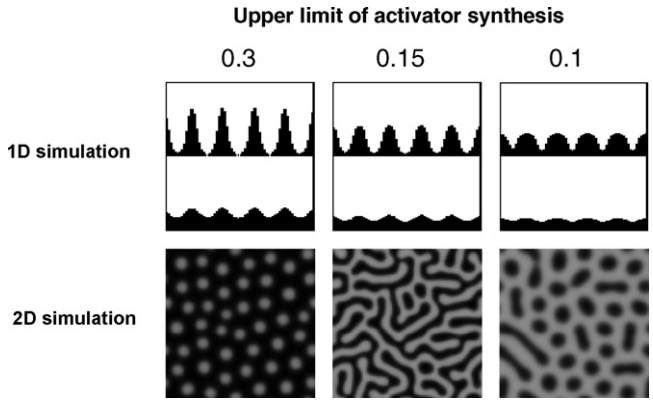

Fig. 3. Difference in the shape of the 1D waves and 2D patterns depending of a parameter value in the equation. When the upper limit of the activator synthesis is high, the wave peaks becomes pointed and spot pattern forms in the 2D field. When the parameter is low, the wave peaks become rounded and polygon (reverse spots) pattern forms. Stripes form when the parameter value is intermediate. Simulations are performed as described in [10].

equation. It is notable that most of the pigmentation patterns seen in animal skin belong roughly to one of these three patterns.

4.2. Complex 2D patterns

Although the pure RD systems can generate only the basic patterns described earlier, it is possible to generate more realistic and complex patterns by adding some additional conditions.

4.2.1. Leopard spots

One of the complex but relatively common animal patterns is the so-called leopard spots. To generate the leopard pattern, one first needs to make a spot pattern, and then the field should be enlarged, which corresponds to the growth of the animal. Enlargement (growth) of the field (skin) enlarges each spot. But as the RD system has a tendency to keep the size of the spots, they divide into 2–4 daughter spots of original size to form the characteristic leopard spots, which is very similar to the skin pattern of a leopard (Fig. 4b and d). With the parameter value that favors stripes instead of spots, enlargement of the field generates rings, which is similar to the patterns seen in the skin of jaguars (Fig. 4a and c). Such spots and rings also can be made by changing the diffusion rate after the simple spot pattern is formed [25].

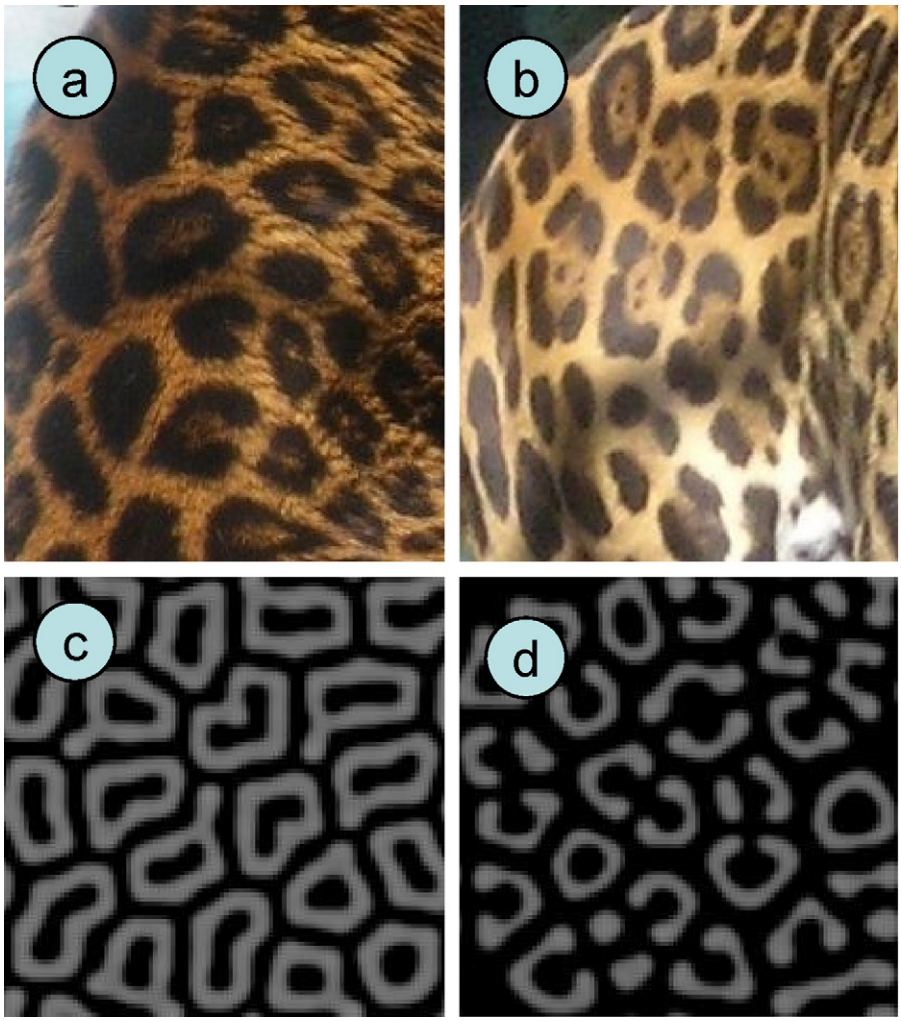

Fig. 4. Dividing spots and ring pattern in the animals and simulations (a) skin pattern of a jaguar; (b) skin pattern of a leopard; (c and d) simulated pattern of RD mechanism in the growing field. Simulations are performed as described in [10].

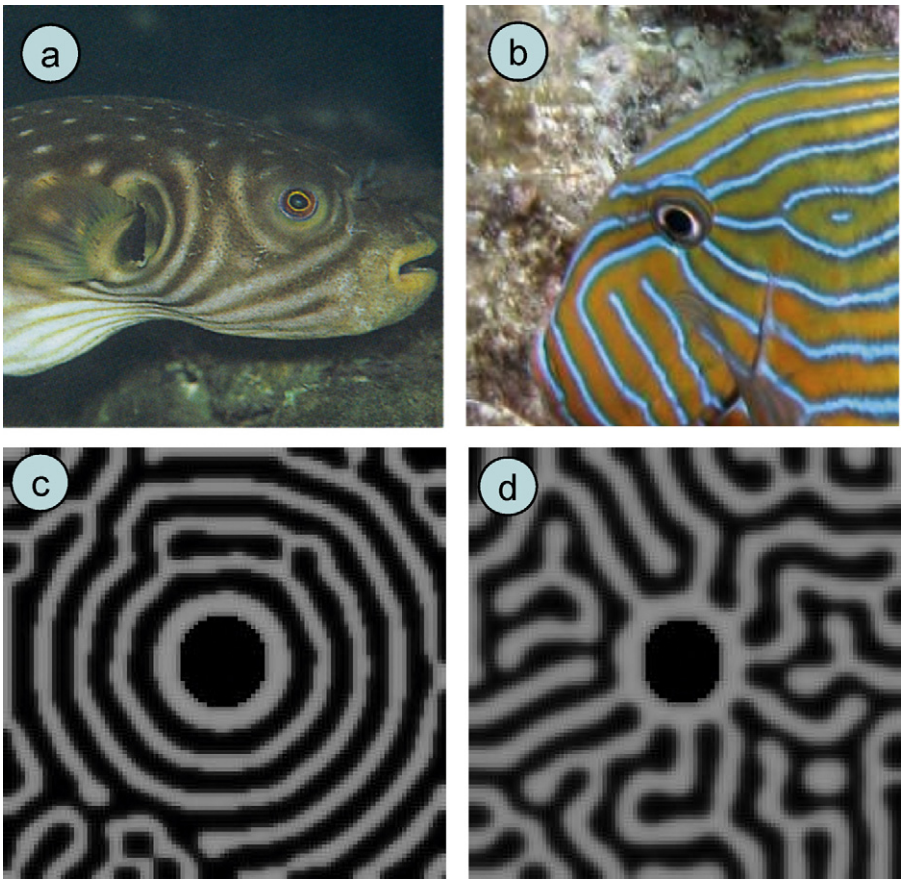

Fig. 5. Directionality of the stripes near the boundary stripes tend to run along or vertical to the field boundary made by the eyes of fish and the simulation. (a) *Arthoron mappa*, (b) *Acanthrus lineatus*, and (c and d) simulated pattern besides the circle boundary. Simulations are performed as described in [10] with the following modification of specific boundary conditions. In the simulation shown in Fig. 3c, the activator concentration in the center part of the field (black circle) is fixed at low level. This boundary condition induces the quick formation of stripes along the boundary. As the newly formed stripes induce additional stripes in the neighboring region, concentric ring pattern was generated. In the simulation shown in Fig. 3d, it was supposed that the pattern formation occurred by the two steps. In the first step, the reaction and diffusion occurred only around the edge of the center circle boundary, which formed the periodic around the edge. Then the reaction and diffusion were made active in all other regions. The periodic pattern around the center circle acted as the patterning cores and formed the radial stripes. Finer simulations of the fish pattern around the fish eyes are described by Sanderson et al. [29]. Fish pictures are courtesy of Tokai University Press.

4.2.2. Directionality of the stripes

Most stripe patterns seen in animals have specific directionality. As the RD system lacks directional information, additional conditions are required to orient the stripes. Shoji et al. [26,27] have shown that adding even very small directionality to the diffusion can orient stripes, and suggested that the scales of the fish may be the origin of this directionality. Boundary conditions are also able to specify stripe directionality near the edge of the patterning field [28]. Stripes of the RD system tend to run parallel or vertical to a fixed boundary, which is a common characteristic of nonlinear waves. In the fish skin, the eyes create such an edge, and as shown in Fig. 5, the stripes become concentric or radial to the round boundary [29].

4.2.3. More complex patterns

The additional conditions described here can be used in combination to generate more complex patterns. For example, a gradual changing of the parameter value which determines the basal production of activator causes the resulting pattern to change from spots to polygons, which are seen in *Plectorhinchus lineatus* (Fig. 6a and c), and a gradual enlargement of the fields in a specific direction is capable of making a complex pattern like that of whale sharks (Fig. 6b and d). Extensive studies with RD models thus suggest that an RD system can generate nearly all animal skin patterns having spatial periodicity [30,31].

5. Autonomy of the RD pattern and the real skin pattern

One of the remarkable properties of the RD mechanism is its independence from the prepattern. As explained earlier, the system amplifies the minor difference of concentration and regulates the width of the peaks and valleys to get the periodic pattern of uniform spacing. The shape and the spacing are determined only by the equation and the parameter values. Pigment patterns on real skin also can appear largely independent of internal structure, suggesting the autonomy of the pattern-forming process. Experimental results with zebrafish have shown more directly the autonomous property of the underlying mechanism. Using a temperature sensitive allele of the *panther* mutant, Parichy et al. eliminated two classes of pigment cells (blacks melanophore and yellow xanthophores) in the adult zebrafish, and observed the regeneration of the pattern in the body and on the tail fin. Their result on the body is consistent with a patterning mechanism that is autonomous to the pigment cells or the presence of persisting cues [9]. On the fin, however, the directionality of the stripes was lost, showing the autonomous nature of the pattern-forming process (Fig. 7a). Using a laser to kill pigment cells in a specific area of body trunk, Yamaguchi et al. got almost an identical result (Fig. 7b). When all the pigment cells in a broad region were killed, the regenerated stripes sometimes lost their directionality and the resulting patterns were very similar to that

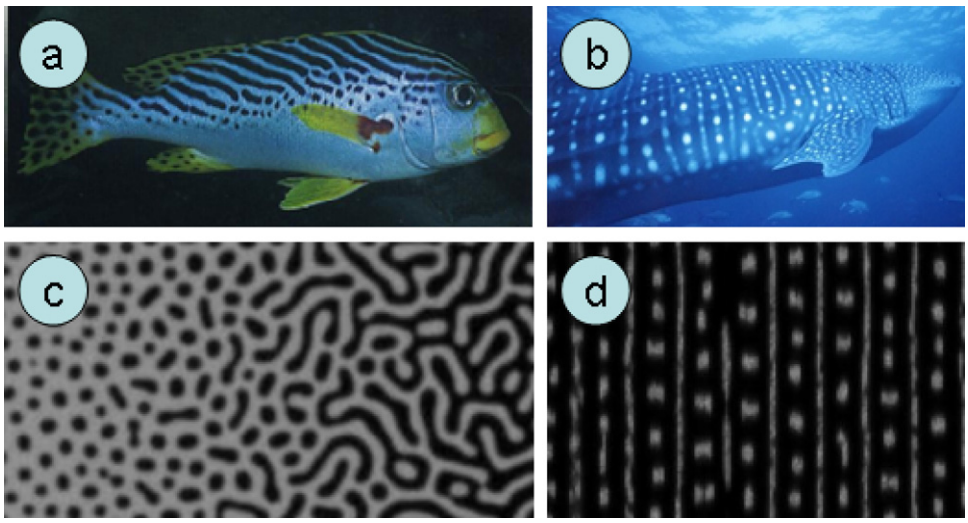

Fig. 6. Complex 2D patterns seen in the fish (a) *Plectorhinchus lineatus*. (b) Whale shark. (c) A parameter value corresponding to the basal synthesis of the parameter in the activator inhibitor model is gradually changed in the 2D field. (d) Stripe pattern is formed in the growing 2D field. Details of the simulation and the used equations were described in [42]. Fish pictures are courtesy of Tokai University Press.

generated by an RD mechanism from a random initial condition [15].

6. Robustness of the RD pattern and the real skin pattern

Another important characteristic of the stationary pattern made by an RD mechanism is its robustness against the perturbation. As far as the patterning mechanism functions, the resulting pattern is not fixed, but is able to autonomously rearrange to recover original spacing in a manner that is very specific to the RD mechanism. By comparing the simulation and the rearrangement of the real skin pattern, one can further test whether an RD mechanism really underlies pattern formation or not in vivo.

6.1. Rearrangement of the pattern induced by the growth

When an animal with a stripe pattern grows, the spacing of the stripes becomes wider. Therefore, growth of the body continuously changes the spacing of the pattern. If the pattern is made by an RD mechanism, some rearrangement must occur to keep the original spacing. According to RD simulations, the manner of rearrangement differs depending on the types of stripes. If stripes

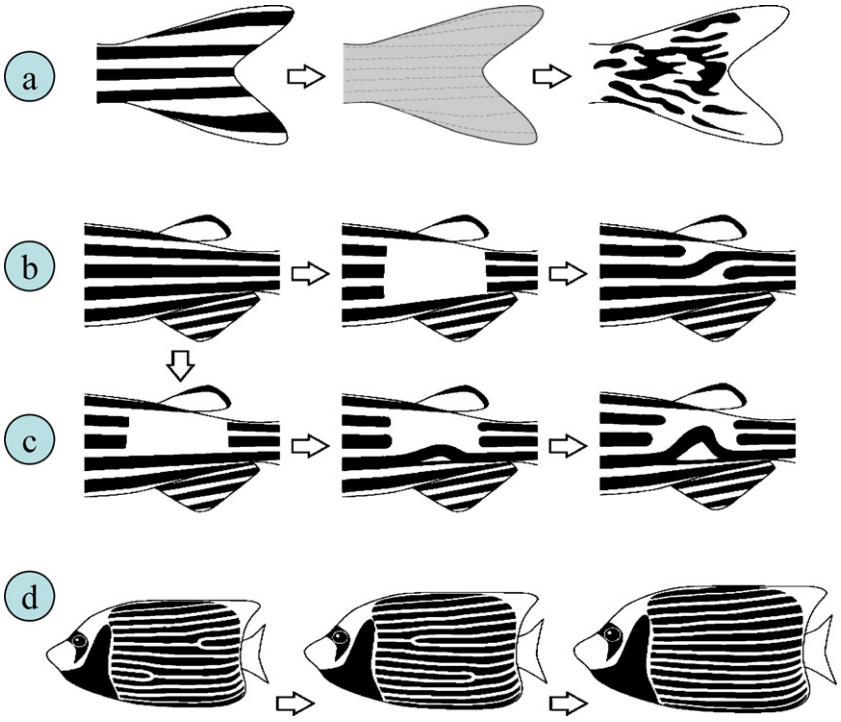

Fig. 7. Results of pattern regeneration experiments. (a) Pigment cells in the fin were eliminated by temperature-sensitive mutation [9]. (b) Pigment cells (both melanophores and xanthophores) were killed by laser [15]. (c) Dorsal movement of a melanophore stripe induced by melanophore elimination in the dorsal region [15]. (d) Division of stripes induced by the fish growth [14].

exhibit branch points, their division occurs by the horizontal movement of the branch points; if the stripes contain no branch points, new stripes emerge between the old stripes. Kondo et al. observed in vivo exactly these changes predicted by simulation in tropical angelfish, *Pomacanthus imperators*, and *Pomacanthus semicirculatus* (Fig. 7d) [10,14].

6.2. Rearrangement of the pattern induced by artificial perturbation

Yamaguchi et al. used laser ablation of the pigment cells to artificially perturb the pattern, and observed a strange but predicted change to the striped pattern of zebrafish [15]. They ablated the melanophores in the dorsal two stripes, and continuously eliminated new melanophores developing in the area. This operation made a broad region lacking melanophores, and induced a dynamic dorsal movement of the remaining ventral melanophore stripe to fill the space. The rearrangement started by bending and dorsally moving of the more ventral band, and ended by forming a bell-shaped pattern to fill the vacant space (Fig. 7c). It is interesting to note that the region of xanthophores reappeared at the ventral side of moving black band, suggesting that the black stripe did not simply get wider but moved by keeping the width. This dynamic movement of the pattern also possesses the typical property of an RD mechanism, and is reproducible by the simulation.

7. RD model as the working hypothesis for the molecular genetic study

7.1. Other mathematical models those are able to form the similar patterns

In the RD mechanism, signals of the reactions are spatially transferred by diffusion. By applying different values for diffusion constants to the substances, it is possible to satisfy the necessary conditions of Turing pattern formation, "local activation and long-range inhibition". It is notable, however, that diffusion is not essential to achieve this necessary condition. It is also possible to satisfy the necessary condition with neuronal networks [32], mechanical pressure [33], or cell migration [34], and mathematical models using these factors have been developed. As there models do not require "diffusion" *per se*, these are not RD models in the formal sense. However, as long as these models satisfy the identical necessary condition, the mathematical equations become similar, and their pattern-forming abilities are almost identical to RD models. In order to find out to which mathematical model the biological systems resemble most, identification of the signaling mechanisms is required. If future experiments reveal that patterns result only from local interactions, different theoretical models will need to be constructed. In this regard, Caicedo-Carvajal and Shinbrot presented an interesting mathematical model in which the pigment patterns are made by only the local effect among two kinds of particles, which represent the pigment cells in the fish skin [35]. It is supposed that the cell–cell binding affinities between the homophilic and heterophilic contact are different. They showed that their model can reproduce most of zebrafish pigment patterns from the random conditions. However, the pattern-forming ability of their model has a serious limitation because it does not contain the long-range interaction. The stripe pattern made by the simulation is only two-cell width because the mechanism cannot specify the distance wider than three cells. It seems to be impossible to reproduce the rearrangement of the stripes observed in the tropical fish (Kondo S., personal communication). From the experimental observation so far made, involvement of the long-range effect should be essential for many animal patterns.

7.2. Molecular genetic studies on the pigmentation of zebrafish

As the zebrafish is a model animal on which the advanced molecular technology is available, finding the specific dynamics of an RD pattern opens the possibility of identifying the molecular level network of the hypothetical mechanism. Recent progress has made it possible to investigate the molecular bases of pigment pattern formation in zebrafish. The pattern of skin pigmentation in zebrafish is determined by the distribution of three types of pigment cell in the hypodermis: melanophores, the main component of dark stripes; xanthophores, the main component of light stripes; and iridophores [9,17,36,37]. To understand how the stripe pattern forms, several mutant genes responsible for abnormal skin pigmentation have been isolated [38–45] and the molecular functions of these genes have been investigated [9,46,47,48,18,49,50].

These mutant genes can be classified into two categories: those with a defect in the development of pigment cells; and those with normal development of pigment cells, but a disrupted pattern in adult fish. Molecular genetic studies of the mutants in the first category have shown that *nacre* (*mitf*), *sparse* (*kit*), *shady* (*ltk*), *picasso* (*erbb3*) and *rose* (*ednrb1*) are required for the development of melanophores, and that *panther* (*fms*) is required for the development of xanthophores [38,40,39,45,51,41]. Interestingly, when either type of pigment cell misdevelops, other pigment cells fail to localize to their normal positions [40,9]. This fact suggests that interaction between pigment cells plays a critical role in the generation of skin pigmentation pattern, a notion that has been confirmed by cell transplantation studies [16,47]. Mutants of *jaguar* (*obelix*) [47] and *leopard* [8] belong to the second category. In these mutants, development and distribution of the pigment cells is normal in embryos and young fish. In adult fish, although the development of pigment cells is normal, their spatial arrangement (pattern) is changed, suggesting that these genes are specifically required for pattern formation. Positional cloning of these latter two mutants identified the affected genes as encoding a potassium channel, Kir7.1 [44], and a gap junction, connexin41.8 [43], respectively. How these molecules are involved in the pigment pattern formation is still unknown.

7.3. Consistency of the mathematical model with the experimental results

Many different types of hypothetical network that are capable of generating the RD pattern have been presented to date. In most of them, the putative network is composed of the interactions among the diffusible chemicals. Meanwhile, molecular genetic studies have suggested that two types of pigment cells, melanophores and xanthophores, play a major role in the patterning mechanism. This difference is not a serious one because it is also possible to compose the equivalent network with the interacting two types of cells (melanophores and xanthophores). For example, if the pattern is large relative to the cell size, the density of the cells can be used as the concentration of the chemicals in the original RD equation. Therefore, there is no theoretical difficulty in applying the RD model to the experimental data of zebrafish.

8. Future directions

As shown earlier in this article, the RD system is capable of generating most of the animal pigmentation patterns, and explaining many of their characteristics. However, as there are many different models with equivalent ability to form the patterns, it is impossible

to identify the real mechanism only by the mathematical analysis. On the other hand, the dynamic characteristics of the skin pattern suggest that the usual techniques of the molecular biology are not enough to clarify the hidden mechanism. Therefore, combinatorial use of both strategies should be required to clarify the hidden mechanism. The mathematical studies have shown that the necessary conditions for the skin pattern formation are "local enhancement and long-range inhibition [24]." Therefore, according to the theory, two kinds of interactions, which differ in the effective distance and function oppositely, must exist among the pigment cells. Finding such interaction in the fish skin, and the identification of the molecules involved in the interaction will solve the long-asked question, "how does the animal pigment pattern form?"

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