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ARTICLE

# Origin of Directionality in the Fish Stripe Pattern

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**The formation of stripe patterns in animal skin has been explained by the reaction-diffusion (RD) system, a hypothetical chemical reaction proposed by A. Turing. Although animal stripes usually have directionality, the RD model alone cannot explain how the direction is specified. To investigate the mechanism regulating the direction of stripes, we studied stripe pattern formation in two species of *Genicanthus* during sexual conversion. These species share almost identical morphologic properties, except for their stripe direction. In both species, spots transiently arise at random positions and then combine and rearrange to form directional stripes. Computational analysis has shown that diffusion anisotropy is very effective at specifying the direction of stripes formed by the RD system. Model simulations reproduce the transient dynamics of directional pattern formation observed in fish as well as the resulting stripes. In cases where the magnitude and direction of diffusion anisotropy of the substances are identical, the resulting stripes are not directional. However, if they differ, stripes become directional. As only a small difference in anisotropy is required for this effect, any kind of structure with directional conformation might cause a marked change in stripe direction. Scales are the most likely candidate structure for generating anisotropic interactions in skin. *Developmental Dynamics 226:627–633, 2003.* © 2003 Wiley-Liss, Inc.**

**Key words:** RD model; anisotropic diffusion; stripe directionality

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## INTRODUCTION

Turing (1952) demonstrated that spatially heterogeneous patterns could be formed out of a completely homogeneous field, in which two kinds of diffusible molecules react with one another and engage in random diffusion. A series of studies on reaction-diffusion (RD) systems have been performed to explain many examples of pattern formation during development. For example, Meinhardt (1982) showed that diverse stripe and spot patterns, observed in developmental pattern formation, could be generated by a simple system of chemical interaction between two factors. Moreover, Murray (1989) explained various phenomena of biological pattern formation, including pattern formation in animal pigmentation. Many animal species have characteristic coat patterns on the skin. The spatial scale of the coat pattern is much larger than the size of individual cells in the skin. In most cases, however, animals do not have any internal structure that looks similar to the coat patterns. Therefore, the positional information for the coat pattern must be generated autonomously in the skin. An RD mechanism provides an effective solution to this problem. Many mathematical studies have shown that the RD system is able to account for most of the animal coat pattern (Murray, 1989; Koch and Meinhardt, 1994).

The coat patterns of mammals are specified at birth, and simply enlarge as they grow. In contrast, however, the stripe patterns on fish skin, studied by Kondo and Asai (1995), change shape as fish grow. The number of stripes tends to increase with body size, but the width of each stripe and the distance between them remains almost unchanged. Kondo and Asai (1995) studied the skin patterns of several species of

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tropical fish and showed that changes in their skin patterns can be well explained by using a simple RD model. The matching of the dynamic change in the stripe patterns with the fish body size and the prediction of the simple model is spectacular. This finding strongly suggests that stripe patterns on fish skin depend on some spatial regulatory mechanism that can be usefully described by a RD model.

In this study, we focus on the directionality of stripes. Most stripes observed on fish skin are either parallel or perpendicular to the anterior–posterior (AP) axis, and the direction of stripes is characteristic to each species. For example, *Genicanthus melanospilos* have stripes perpendicular to the AP axis, whereas *Genicanthus watanabei* have stripes parallel to the AP axis (see Fig. 1). The direction of stripes has been considered important from both a behavioral and an ecological viewpoint. In the case of African cichlid fish, vertical stripes tend to be associated with living in rocky substrates or vegetation, whereas horizontal stripes are associated with schooling behavior (Seehausen et al., 1999).

On the other hand, little is known about the origin of the strong directionality of stripes in fish skin. As ordinal RD models generate undirectional stripes (labyrinth pattern), some additional conditions are required to force stripes to run in a specific direction. Of interest, the stripe direction often differs drastically among very closely related species. One such example is shown in Figure 1. Although both *G. melanospilos* and *G. watanabei* have almost identical body structure and have stripes with similar spacing, the direction of the stripes is different (horizontal or vertical). As the structural difference between the two *Genicanthus* species must be very small, the mechanism for specifying stripe direction must be quite sensitive.

In this study, we examined several candidate mechanisms that might underlie stripe directionality and tested whether the dynamics of pattern formation simulated from these mechanisms match the real fish pattern change or not. We found that standard RD models readily form directional stripes when anisotropic diffusion is incorporated, and the time course of pattern formation is highly similar to that of real fish.

## EMERGENCE OF STRIPE PATTERNS

To investigate the mechanism for determining stripe direction, we observed the emergence of stripe patterns in *Genicanthus,* in which two closely related species show different stripe directions. In both species, juveniles and females have no clear skin patterns but fish exhibit very clear directional stripe patterns during the sex transition from female to male (Masuda and Kobayashi, 1994). In the mating season, individuals with the largest body size change sex (Kuwarura, 1987). During sex changes, we can observe the formation of striped patterns. Figure 1 shows the pattern transition of *G. watanabei* and *G. melanospilos* starting from the female skin pattern, without clear stripes, and developing into the male skin pattern, with stripes. The dynamic change in the pattern suggests that we are not simply observing the appearance of a hidden pattern but rather visualizing the pattern-formation process itself. The characteristic steps (listed below) of this pattern transition are the same between the two species, except for the stripe directionality, suggesting that the basic mechanism of stripe formation is the same in both species.

(1) In both species, spots first appear at random positions, distributed evenly over the entire trunk region.
(2) Each spot becomes elongated according to the direction characteristic of the species.
(3) After approximately 3 weeks, the spots fuse with one another and form branching lines.
(4) Rearrangement of the lines, including reconnection and movement of junctions, makes the final pattern of completely parallel stripes. This step is completed within a few months.

The manner in which the stripes rearrange (step 4) is the same in *Genicanthus* and *Pomacanthus,* both of which belong to the same family. The standard RD model can successfully explain the rearrangement of stripes (step 4) (Kondo and Asai, 1995) but is unable to explain how the fixed directionality of stripes emerges (steps 1–3).

## REACTION-DIFFUSION MODEL

A series of transplant experiments performed by Kirschbaum (1975) revealed that pattern formation in pigment cells is controlled by unknown chemical factors in the dermal layer. Schliwa (1986) suggested that pigment pattern formation is controlled by the spatial distribution of two morphogens that react with one another and diffuse in a two-dimensional subepidermal layer. We introduce here an RD model that generates self-organizing patterns. In general, the RD model can be written as follows:

$$\frac{\partial u}{\partial t} = \Delta u + \gamma f(u,v),$$

$$\frac{\partial v}{\partial t} = d\Delta v + \gamma g(u,v), \qquad (1)$$

where $u$ and $v$ are the concentration of two hypothetical chemicals. $f(u,v)$ and $g(u,v)$ represent the chemical reaction terms. Reaction terms are multiplied by a rate constant $\gamma$, which rescales time and space without reducing calculation speed (Murray, 1989). The ratio of diffusion coefficients between the two substances $d$ is larger than 1 (Murray, 1989).

**Fig. 2. a:** *Cheilinus undulatus.* **b:** The stripe pattern around the operculum of *C. undulatus.* Scales exist in the upper left region. **c:** A scale from *Genicanthus watanabei.* The arrows show the orientation of the scale. The size and shape differ slightly, depending on the region of the fish body. Scales from *G. melanospilos* appear similar. **d:** Cross-section through the skin of *G. watanabei.* Tissue is cut from the center part of the trunk. The picture shown is from the stripe region. The picture from the inter-stripe region looks identical, except for the density of melanophores. The section from *G. melanospilos* appears similar. m, melanophore; e, epithelia; d, dermis; s, scale.

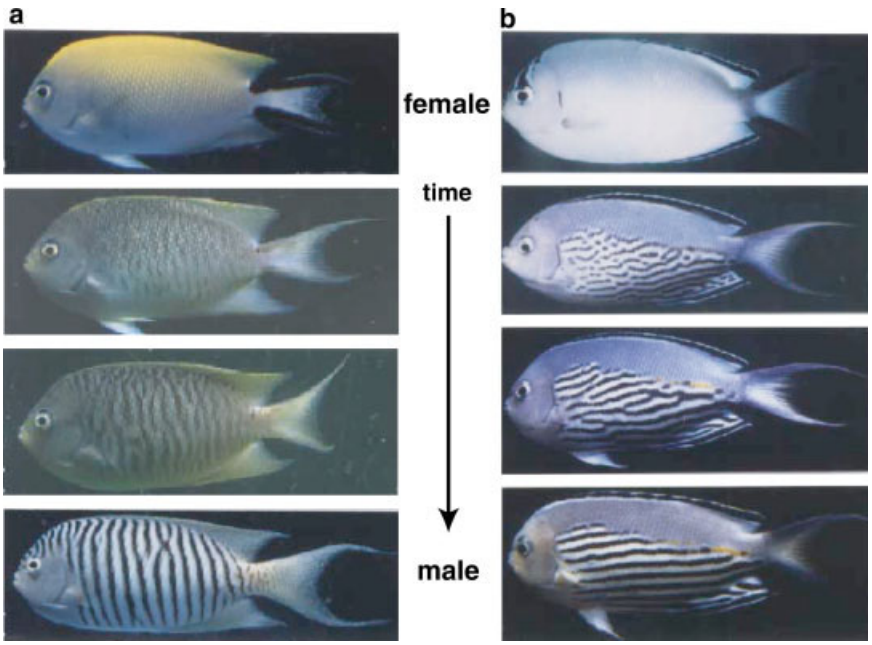


**Fig. 1.** The transition of stripe formation in the skin of (**a**) *Genicanthus melanospilos* and (**b**) *Genicanthus watanabei* during their sex change. The fish are maintained in the Tokai University aquarium. The male fish is removed from the flock of the *Genicanths watanabei* and *melanospilos*, and then the skin pattern change of one of the females is recorded. The pattern-forming processes are similar between these species, except for the stripe direction.

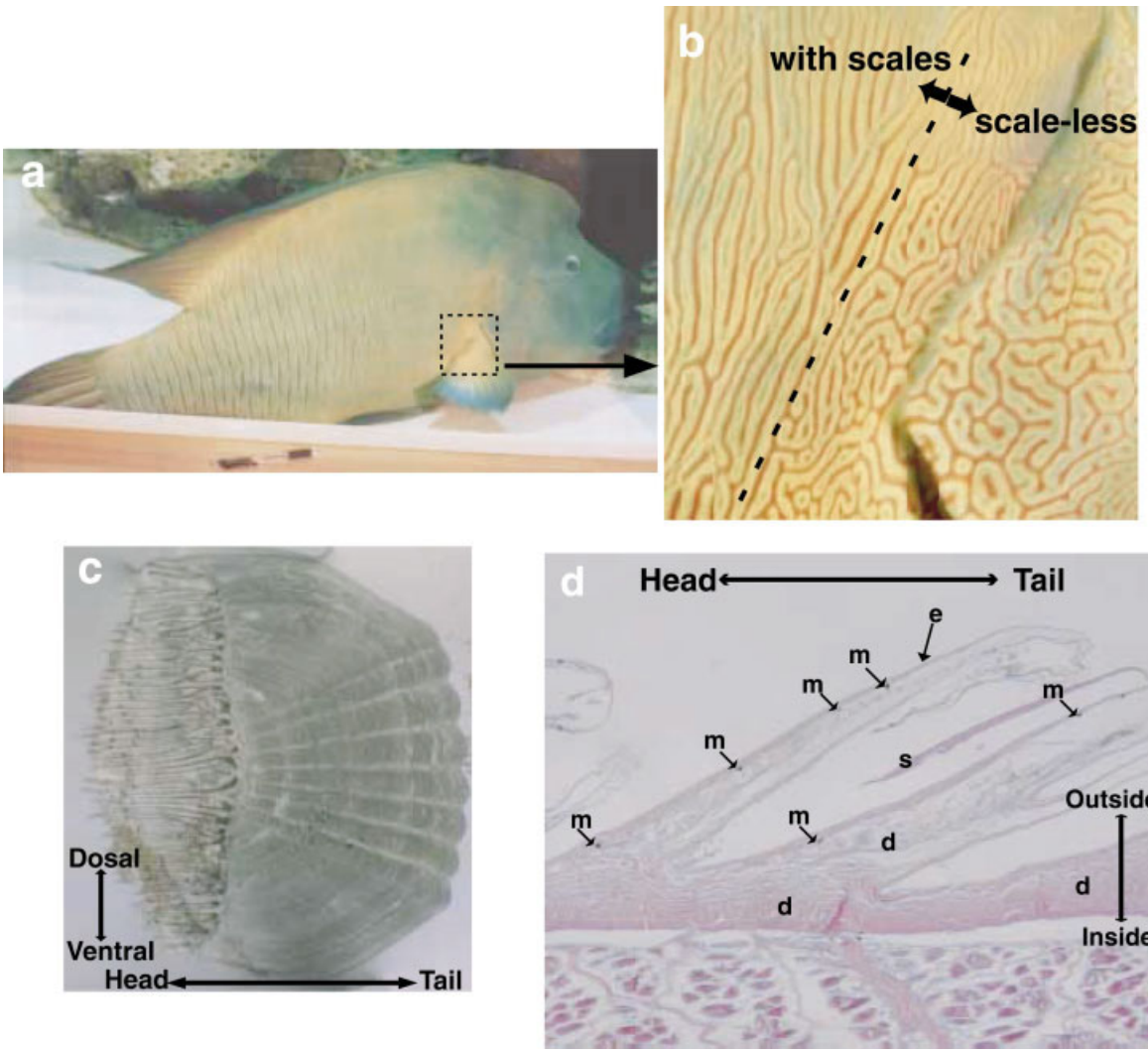


**Fig. 2.**

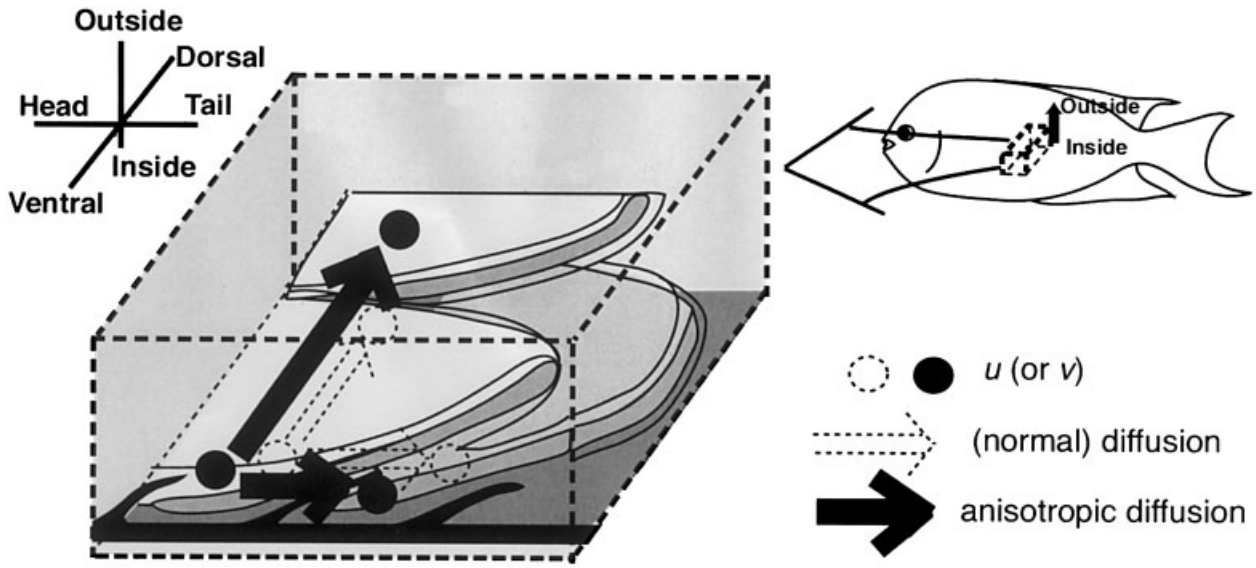


**Fig. 3.** Schematic structure of fish skin. Each scale comes out at the same direction along the anterior–posterior (AP) axis. This structural difference between the AP and DV axes might cause some directionality in diffusion. Diffusion along the AP axis passes through scales, whereas diffusion along the DV axis does not. In typical diffusion, substances diffuse equally in all directions (drawn by dotted arrow). In this study, we assumed that diffusion is enhanced along the *x* (or *y*) axis and reduced in the perpendicular direction, as shown with solid arrows. The positive $\delta$ indicates that diffusion along the *x*-axis is faster that that along the *y*-axis.

To show that the result of the simulation is not specific to a particular equation, but rather to the general property of the RD pattern, we used three different forms of reaction terms that satisfy the Turing conditions (e.g., Murray, 1989) and form stripes in a two-dimensional field. The equations we tested are the models of activator-depleted substrate type (Gierer and Meinhardt, 1972), linear type with saturation (Kondo and Asai, 1995; Asai et al., 1999), and activator–inhibitor type (Gierer and Meinhardt, 1972). Because we obtained basically the same results from all of these models, only the results from the activator-depleted substrate type model are shown below. We call *u* and *v* "activator" and "inhibitor," respectively, following the well-known class of the model with Turing's instability (also called activator–inhibitor model).

RD models differ in the range of parameters in which striped patterns, rather than spot patterns, are formed. In an activator–inhibitor model, Meinhardt (1989) pointed out that stripes are more easily formed when autocatalysis saturates. Adding a saturation term is a safe and reasonable way to form stripes, as substrates for any chemical reaction in a cell are not inexhaustible (Gierer and Meinhardt, 1972). The activator-depleted substrate model we used in this study includes a nonlinearity that constrains deviation from the equilibrium in a manner similar to saturation. We adopted the model with anisotropic diffusion to carry out analysis by using reaction terms of both types and obtained qualitatively the same results. Although stripe patterns generated by Turing's model have stable periodicity, the direction of the stripes varies depending on the initial distribution in two-dimensional space (Murray, 1989; Maini et al., 1997). If the studied domain is large enough, the spatial pattern includes stripes in each local area, but the direction of the stripes may change between different parts of the domain. When a random pattern is used as the initial condition, stripes with varying directionality form in different parts of the domain, resulting in a labyrinth pattern (Fig. 4a–d; Meinhardt, 1982; Murray, 1989; Maini et al., 1997). Thus, to explain the stable directionality of stripes observed in fish skin, the RD model needs to incorporate additional factors.

## SOME CANDIDATES FOR THE ORIGIN OF STRIPE DIRECTIONALITY

There are some candidates for a factor explaining the stability of stripe direction. The simplest is the "initial condition." When a weak stripe pattern is given as the initial condition, the resulting stripes tend to follow the original lines. The dynamics of pattern emergence in *Genicanthus*, however, show that there is no such prepattern, because in pattern transition, spots first emerge in a random distribution, and then combine to form stripes. Other possible candidates are the boundary condition (Fig. 4e–h) and the spatial gradient of reaction parameters (Fig. 4i–l), which are well studied and can explain some of the complex, striped animal patterns (Meinhardt, 1982; Lacalli et al., 1988; Dillon et al., 1994). Although both mechanisms can generate a directional stripe from a random pattern (Meinhardt, 1982; Lacalli et al., 1988), the lines are formed in an orderly manner, from a border (Fig. 4e–h,i–l). On the other hand, in *Genicanthus*, directional stripes are formed simultaneously.

## RD MODEL WITH ANISOTROPIC DIFFUSION

From transitional patterns, the origin of directionality is not localized, but instead works all over the skin. We hypothesize that scales are the most likely candidate for determining stripe directionality. Most fish with directional stripes have orderly scales arranged on the trunk. On the other hand, stripes in scale-less fish, such as the popper fish, usually have nondirectional patterns. Even in fish with directional stripes, scale-less regions of the skin are usually nondirectional (Fig. 2a,b).

Figure 2d shows a cross-section of *G. watanabei* skin, along with the AP axis. Melanophores are located beneath the skin epithelia where scales are present. *Genicanthus* scales are symmetric along the dorsal–ventral (DV) axis, and the anterior region of the scales is buried in the dermis of the fish skin (Fig. 2c). This conformation may cause some directionality in diffusion. Diffusion along the AP axis passes through scales, whereas diffusion along the DV axis does not. Therefore, the structure of fish skin likely causes some anisotropy in the diffusion of substances (Fig. 3), and the magnitude of the anisotropy might be different between the activator *u* and inhibitor *v* substances. To introduce anisotropic diffusion into the RD system, we used a standard method described by Kobayashi (1993). In brief, the diffusion coefficient depends on the direction of flux of the substance. As the simplest diffusion function model, we used periodic functions, which take a maximum or minimum value when the direction is parallel to the *x*-axis. The model can be written as follows:

$$\frac{\partial u}{\partial t} = \nabla \cdot (D_u(\theta_u)\nabla u) + \gamma f(u,v),$$

$$\frac{\partial v}{\partial t} = d\nabla \cdot (D_v(\theta_v)\nabla v) + \gamma g(u,v).$$

$$D_u(\theta_u) = \frac{1}{\sqrt{1 - \delta_u \cos 2\theta_u}},$$

$$D_v(\theta_v) = \frac{1}{\sqrt{1 - \delta_v \cos 2\theta_v}}, \quad (2)$$

where $\theta_u$ and $\theta_v$ indicate the angles of the gradient of the variables ($\theta_u = \tan^{-1}((\partial u/\partial y)/(\partial u/\partial x))$ *and* $\theta_v = \tan^{-1}((\partial v/\partial y)/(\partial v/\partial x))$). $\delta_u$ and $\delta_v$ indicate the magnitude of anisotropy of activator *u* and inhibitor *v* ($-1 < \delta_u < 1$, $-1 < \delta_u < 1$). A positive $\delta$ value indicates enlargement of diffusion in the direction of the *x*-axis, whereas a negative $\delta$ value indicates enlargement in the direction of the *y*-axis (Fig. 3b). If the absolute value of $\delta_u$ (or $\delta_v$) is large, then the distortion of the diffusion range of *u* (or *v*) is large.

In cases where the magnitude of anisotropy is identical between the activator *u* and inhibitor *v*, no stripe directionality will occur and the resulting pattern is almost the same as the pattern formed with no anisotropy (Fig. 4m–p: $\delta_u = 0.5$, $\delta_v = 0.5$). The absence of specific stripe directionality holds even if the value of the anisotropy is very large.

In cases where the magnitude of anisotropy differs between the activator *u* and the inhibitor *v*, however, stripes will run in a fixed direction. If the activator *u* diffuses faster along the AP axis and the inhibitor *v* diffuses evenly (Fig 4q–t: $\delta_u = 0.5$, $\delta_v = 0$), all the stripes will form parallel to the AP axis. In contrast, if the inhibitor *v* diffuses faster along the AP axis and the activator *u* diffuses evenly (Fig. 4u–x: $\delta_u = 0$, $\delta_v = 0.5$), then the resulting stripes will be parallel to the DV axis. Notably, not only the final stripe patterns but also the transient patterns are quite similar to those observed in *Genicanthus watanabei* and *G. melanospilos*.

The computational results shown in Figure 4 and 5 do not depend on the form of reaction terms or that of anisotropy. We performed the same analysis for the model with modified conditions—different parameter values in the reaction terms, different ratio of the two diffusion coefficients *d*, and different functional forms of diffusion anisotropy—and obtained very similar results. The robustness of these results is proven by the mathematical analysis shown in our theoretical study (Shoji et al., 2002).

Figure 5 summarizes the effect of anisotropy on the direction of stripes in the final spatial patterns. Generally, the effects of anisotropic diffusion of the activator *u* and inhibitor *v* are opposite. Resulting stripes tend to run parallel to the most-diffusive direction of activator *u*, and perpendicular to that of inhibitor *v*. The substance with the greater anisotropy decides the direction of the resulting stripes. A pattern with no directional stripes only occurs when the values of anisotropy are almost identical, and correspondingly, most fish with scales have directional stripes. In Figure 5, the direction of the resulting stripes at points O and A are opposite even though the anisotropy values are close: (0.64, 0.70) and (0.74, 0.70). This property of the model explains why the two species of *Genicanthus* have different stripe directionality, despite their almost identical morphology.

## DISCUSSION

In this study, we investigated the origin of stripe directionality by studying pattern changes in real fish and in computational models. Our results suggest that diffusion anisotropy may underlie this phenomenon. Our computational results described above do not depend on the form of reaction terms or on that of anisotropy. Therefore, the effect of diffusion anisotropy is a general property of stripe patterns made by RD systems.

Theoretical analysis in this study demonstrates that anisotropic diffusion in an RD model could explain many aspects of stripe pattern formation with directionality. This suggests that anisotropy in interactions between neighboring regions of fish skin can be responsible for stripe directionality. As only a small difference in anisotropy is required for the effect, any structure with directional conformation is likely to be the origin of stripe directionality. Although there are several possible candidates, we hypothesize that the most effective is the morphology of scales. Scales are plates directionally inserted in the dermis of the skin (Fig. 2d). They must cause some directional difference in the diffusion of substances, and in some cases, we found apparent correlations between the existence of scales and stripe directionality (Fig. 2b). Moreover, as the shape of scales is usually symmetric with respect to the body

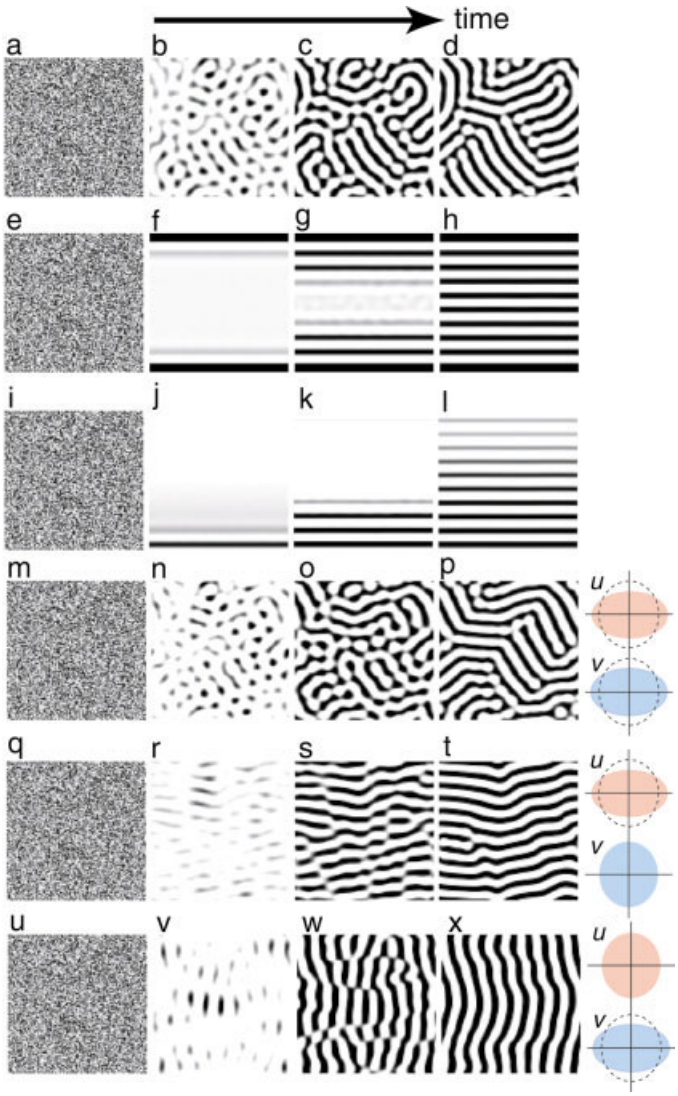


**Fig. 4.** Patterns obtained by computer simulations. We derived the spatial patterns formed after a long time calculation by computer simulation of the model given by equations (1) and (2). To remove the effect of the boundary, all simulations, except for those in e–h, were performed with the periodic boundary condition in a square domain of size: 1.0 × 1.0 (grid size:100 × 100, $\Delta x = 0.01$). The differential equations (1,2) are described according to the simple explicit scheme as follows:

$$u_{(i,j)}^{t+1} = u_{(i,j)}^{t} + \frac{\Delta t}{(\Delta x)^2}\begin{pmatrix} D_u(i-1,j)(u_{(i-1,j)}^{t} - u_{(i,j)}^{t}) + \\ D_u(i+1,j)(u_{(i+1,j)}^{t} - u_{(i,j)}^{t}) + \\ D_u(i,j-1)(u_{(i,j-1)}^{t} - u_{(i,j)}^{t}) + \\ D_u(i,j+1)(u_{(i,j+1)}^{t} - u_{(i,j)}^{t}) \end{pmatrix} + \Delta t\gamma f(u,v),$$

$$v_{(i,j)}^{t+1} = v_{(i,j)}^{t} + d\frac{\Delta t}{(\Delta x)^2}\begin{pmatrix} D_v(i-1,j)(v_{(i-1,j)}^{t} - v_{(i,j)}^{t}) + \\ D_v(i+1,j)(v_{(i+1,j)}^{t} - v_{(i,j)}^{t}) + \\ D_v(i,j-1)(v_{(i,j-1)}^{t} - v_{(i,j)}^{t}) + \\ D_v(i,j+1)(v_{(i,j+1)}^{t} - v_{(i,j)}^{t}) \end{pmatrix} + \Delta t\gamma g(u,v).$$

$D_u(i, j)$ and $D_v(i, j)$ are calculated at each site according to $D_u(\theta_u)$ and $D_v(\theta_v)$ in equation (2), whereas the gradient angles of the variables ($\theta_u$ and $\theta_v$) are determined by using the neighboring eight sites following equation (2). The mesh size ($\Delta t$) was $10^{-6}$ except when either $\delta$ is more than 0.5 in calculating equation (2). Otherwise, the mesh size is $5 \times 10^{-7}$. This size was chosen to satisfy the stability condition for numerical analysis. The initial distributions are close to the uniform distribution of $u$ and $v$ that are equal to the equilibrium of the ordinary differential equations with additional small random deviations. We used several initial distributions with different random deviations and confirmed the robustness of the result. We set the reaction terms as: $f(u,v) = A - u + u^2v$, $g(u,v) = B - u^2v$ (Schnackenberg, 1979), based on an activator-depleted substrate model that was originally proposed by Gierer and Meinhardt (1972). In all simulations, except those in Figure 4i–l, we chose the parameter values as $A = 0.025$, $B = 1.550$, $d = 20.0$, $\gamma = 10{,}000$, which make stripe patterns in a normal RD model (model 1) (Dufiet and Boissonade, 1992). **a–d:** Pattern formation under a periodic boundary condition. **e–h:** Pattern formation under a boundary condition fixed at zero at the top and bottom and periodic along the sides. **i–l:** Pattern formation from a model that assumes a spatial gradient of parameter $B$. The value of $B$ changes linearly, taking a maximum value of 1.8 at the top and a minimum value of 1.5 at the bottom of the space. **m–x:** Pattern formation from a model of anisotropic diffusion (model 2). The magnitude of anisotropy of these two substances are (m–p) $\delta_u = \delta_v = 0.5$; (q–t) $\delta_u = 0.5$, $\delta_v = 0$; (u–x) $\delta_u = 0$, $\delta_v = 0.5$.

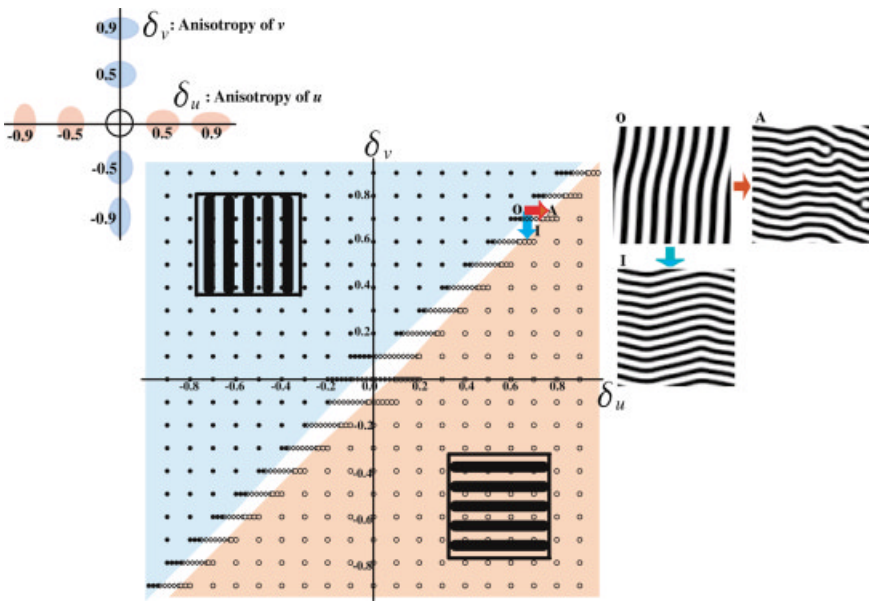


**Fig. 5.** Summary of the direction of stripe patterns obtained by the anisotropic diffusion model 2 with activator-depleted substrate type reaction terms in the same manner as Figure 4. Horizontal and vertical axes indicate $\delta_u$ and $\delta_v$, respectively. (The left-upper corner indicates the distortion of the diffusion range. The sizes of the ovals are different from the actual magnitude of diffusion.) Each point indicates the direction of the observed stripe: horizontal ($\nu$); vertical (•); or not determined (×). The method used to identify the direction of the stripes is shown in the accompanying study (Shoji et al., 2002). The direction is determined only by the difference between $\delta_u$ and $\delta_v$. A small difference in diffusion anisotropy can alter the final pattern to one with opposite directionality. Note the transition of the stripes by changing the $\delta_u$ (or $\delta_v$) from O to A (or I ). Quantitatively, the same results were obtained even if we used different reaction terms (Shoji et al., 2002; for example, $f(u,v) = Au - v + C$, $g(u,v) = Bu - v - 1$, ($0 \le u, v \le 10$), (Kondo and Asai, 1995; Asai et al., 1999)) or a different form of anisotropy (for example, $D_\sigma = 1 + \delta_\sigma \cos 2\theta_\sigma$, $\sigma = u$ or $v$, as proposed by Kobayashi, 1993).

axis, the diffusion anisotropy made by the scales should be parallel or perpendicular to the body axis, which is consistent with the fact that most fish stripes are horizontal or vertical.

Although we deduce that scales are the major origin of stripe directionality in fish, other candidate structures may also cause diffusion anisotropy. Such structures can form the directional stripes even in scaleless fish and other animals. Therefore, our model is applicable to many kinds of animals with stripes on their skin.

Another possible candidate structure is fiber protein located in the dermis of the skin. Collagen fibers in the dermis do not run in random directions but instead run with apparent directionality (Imayama and Braverman, 1989). If a substance related to the stripe pattern has some affinity for collagen or other fiber proteins, diffusion of the molecule would become directional and could cause some diffusion anisotropy. Blood vessels and neural fibers running in the skin can also cause stripe directionality. The directionality of such peripheral structures, however, is not evident compared with scales or collagen fibers. In the case of the zebra fish tail fin, stripes on the fin are parallel, despite the radial distribution of blood vessels and neurons (data not shown). Therefore, we presume that the effects of these structures, if any, are minor. Finally, muscle fibers located beneath the basal membrane of the skin produce some undulations of the skin sheet and may cause some directionality of diffusion in the skin. However, as the directional arrangement of muscular fibers does not match the directionality of stripes in fish, we assume that the effect of the muscular conformation is small.

Although the boundary condition model does not fit the case of *Genicanthus*, it can be adapted in some cases, such as the larval salamander, in which horizontal stripes arise from repulsion of melanophores from the forming lateral line (Parichy, 1996). In this case, the lateral line might act as the boundary condition. Whatever the effects of anisotropic diffusion, the drastic changes in stripe direction may occur even when there are rather minor differences between species. This may be evolutionarily significant because such small changes can initiate speciation.

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