Scaling of morphogenetic patterns

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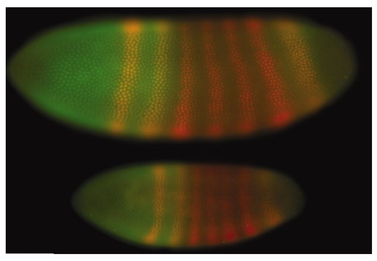
Abstract

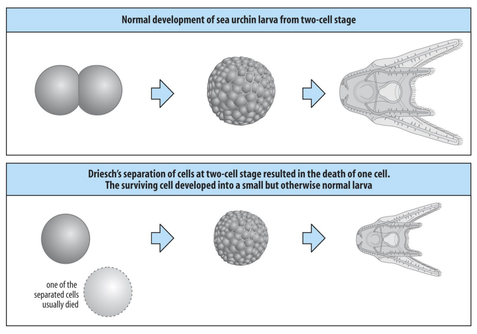
An important property of developmental processes is their robustness with respect to the developmental conditions and particularly their scaling with the size of developing object. Simple patterns like that described by the "French Flag" model do indeed scale. However the exponential patterns forming in systems with decay or Turing patterns do not. In this presentation we show the way of extension of common models describing morphogenetic patterns, which allows their scaling and gives a possible explanation for it.

Scaling of morphological patterns

One of the most intriguing and important features of biological patterns is their ability to scale with the size of the object where they form [1]. This feature is a manifestation of a more general property of morphological structures to be robust with respect to variations in the developmental conditions. Developing embryos are exposed to a certain "development noise" i.e. environmental factor, genetic variability and random difference. Despite these fluctuations, the outcome of development is precise and reproducible, indicating that the mechanisms regulating patterning and growth of organs are robust and able to damp the effects of the variations.

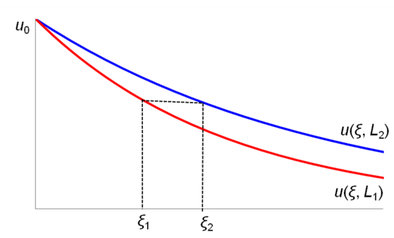


In Drosophila, development along the anterior-posterior axis is scaled with embryo length [2].



Scaling of sea urchin larva in Hans Driesch experiment [1]

Definition of scaling factor



Exponential profiles as functions of relative position ($\xi=x/L$) for two mediums of different sizes.

Let us consider a morphogenetic profiles occurring in two objects of different sizes, say L_1 and L_2. These profiles can be described by functions $u(\xi, L_1)$ and $u(\xi, L_2)$ where $\xi=x/L$ gives a coordinate in the range [0,1] for both objects.

Definition: The profile is scaled across the two objects if

$$u(\xi, L_1)=u(\xi, L_2) \text{ for any } \xi.$$

Generally this is not true and from $u(\xi_1, L_1)=u(\xi_2, L_2)$ it doesn't follow that $\xi_1=\xi_2$. For this case we can introduce the scaling factor in the following way. Assume that $u(\xi_1, L_1)=u(\xi_2, L_2)$. For small differences in L and in ξ we can write:

$u(\xi_2, L_2) \approx u(\xi_1, L_1) + u'_\xi(\xi_2-\xi_1) + u'_L(L_2-L_1)$; so that from $u(\xi_1, L_1)=u(\xi_2, L_2)$ it follows

$u'_\xi(\xi_2-\xi_1) + u'_L(L_2-L_1) = 0$

From the above formula the relocation of the level point is given as: $\xi_2-\xi_1 = -\frac{u'_L}{u'_\xi}(L_2-L_1)$

i.e. the deformation of the profile is proportional to the change in the size of the system with the coefficient of proportionality representing scaling factor: $\boxed{S = -\left(\frac{\partial u}{\partial L}\right)\left(\frac{\partial u}{\partial \xi}\right)^{-1}}$

Scaling of exponential profile

Let us consider the system with degradation:

$$\frac{\partial u}{\partial t} = D_1\frac{\partial^2 u}{\partial x^2} - k_1 u$$

Morphogen in this system forms a stationary exponential profile of characteristic length given as:

$$\lambda = \sqrt{\frac{D_1}{k_1}}$$

In the system with fast diffusion and/or slow degradation the concentration profile can be readily represented by a horizontal line associated with a constant level of morphogen. This constant level is scaled with the size of the medium if constant flux boundary conditions are implemented [3].

This observation can be used to scale exponential profiles by constructing a system when a scaled horizontal profile is bound to the exponential.

The system:

$$\frac{\partial u}{\partial t} = D_1\frac{\partial^2 u}{\partial x^2} - k_1 u v^2; \qquad \frac{\partial v}{\partial t} = D_2\frac{\partial^2 v}{\partial x^2} - kv$$

Boundary conditions:

$$u(x=0)=u_0,\ \left.\frac{\partial u}{\partial x}\right|_{x=L} = j_L; \qquad \left.\frac{\partial v}{\partial x}\right|_{x=0} = -j_0, \left.\frac{\partial v}{\partial x}\right|_{x=L} = j_1$$

Solution:

$$u \approx u_0 e^{-\frac{x}{L}\frac{D_2(j_0+j_1)}{k}\sqrt{\frac{k_1}{D_1}}}; \qquad v \approx \frac{D_2(j_0+j_1)}{kL}$$

Pattern formation in Turing model

Turing model is commonly used for describing of spatially extended activator-inhibitor systems:

$$\frac{\partial u}{\partial t} = D_1\frac{\partial^2 u}{\partial x^2} + \gamma_1(au+bv); \qquad \frac{\partial v}{\partial t} = D_2\frac{\partial^2 v}{\partial x^2} + \gamma_2(cu+dv)$$

where (a, c)>0 (activation) and (b, d)<0 (inhibition) [4].

Patterning takes place due to diffusion of the inhibitor. That is, when morphogens don't diffuse the homogeneous state (u=v=0) is stable:

$$trace = f_u + g_v < 0; \quad Det = f_u g_v - f_v g_u > 0$$

The loss of stability is associated with high diffusion of the inhibitor and takes place under the following condition:

$$f_u D_2 + g_v D_1 > 2\sqrt{D_1 D_2 (f_u g_v - f_v g_u)}$$

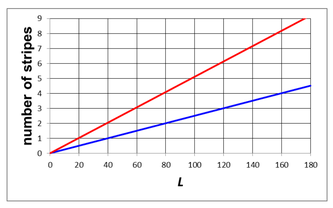
Case of multiple unstable modes

Generally the patterns forming due to Turing instability are not unique. There can be many unstable special modes in the same system [4]. Extending the Turing model with cubic terms on the RHS:

$$\frac{\partial u}{\partial t} = D_1\frac{\partial^2 u}{\partial x^2} + \gamma_1(au+bv) - \alpha_1 u^3;$$

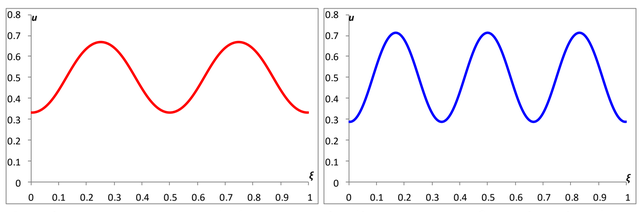
$$\frac{\partial v}{\partial t} = D_2\frac{\partial^2 v}{\partial x^2} + \gamma_2(cu+dv) - \alpha_2 v^3.$$

lets to avoid infinite concentrations arising for unstable modes of solution and observe patterns of different periodicity arising in the same system. Coexistence of different patterns creates difficulties in maintenance of scaling.



Shown simulations are performed using the following parameter values: a=1, b=−2, c=3, d=−4, D_1=1, D_2=20, $\alpha_1=\alpha_2$=0.1 and $\gamma_1=\gamma_2$=0.04.

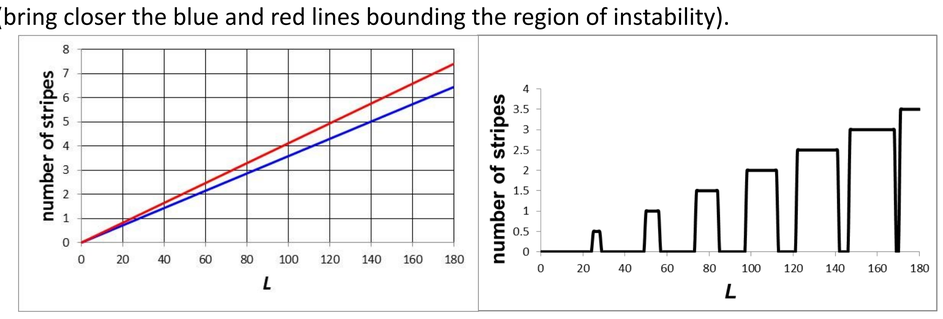
Each horizontal line between red and blue lines corresponds to a pattern of different special periodicity.



Stationary two– and three-periodic patterns forming in the same model medium in computer simulations

Case of unique unstable mode

By variation of model parameters it is possible to reduce the number of unstable modes (bring closer the blue and red lines bounding the region of instability).



There is either none or only one unstable mode in a shown range of medium sizes when γ_1=0.04 and γ_2=0.053.

In our simulations, we set the values of the model parameters so that only one unstable mode exists for a wide range of medium sizes. For example, in the model illustrated by this figure, in the case of the medium size L=160, we can only have 3 stripes.

Scaling in the extended (three-variable) Turing model

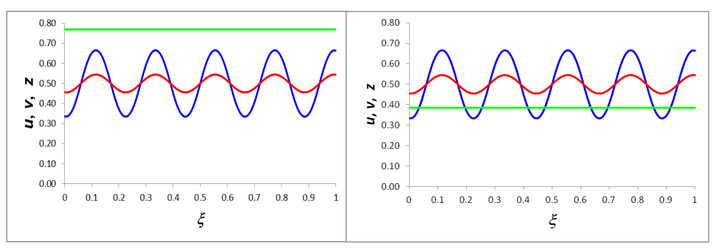
To introduce scaling into the Turing model we have extended it with the third variable satisfying two conditions:

1. Additional variable (z) is maintained at a constant level which depends on the size of the medium.
2. Additional variable affect the kinetics rate of two original variables so that space scaling of the pattern is proportional to the medium size.

$$\frac{\partial u}{\partial t} = D_1\frac{\partial^2 u}{\partial x^2} + \left(\gamma_1(au+bv) - \alpha_1 u^3\right)z^2$$

$$\frac{\partial v}{\partial t} = D_2\frac{\partial^2 v}{\partial x^2} + \left(\gamma_2(cu+dv) - \alpha_2 v^3\right)z^2$$

$$\frac{\partial z}{\partial t} = D_3\frac{\partial^2 z}{\partial x^2} - kz$$



The above graphs show patterns forming in the extended Turing model for the case of two different medium lengths (L_2=2L_1). The green curve represents the concentration of the new variable (z) which is constant. The blue and red curves show u- and v-profiles respectively. Profiles of u and v are identical for these two medium sizes—indicating the perfect scaling.

Conclusion

- Robustness and scaling are important features of developing biological systems. Recent observations [3] confirm that scaling of biological patterns takes place at the level of morphogen gradients.
- Many research groups are working to reveal mechanisms underlying robustness and scaling of biological patterns. There are many indications that the scaling is based on the discrete nature (with discrete entities represented by cells or nuclei) of biological objects. This comes to play even the patterning is considered in continuous models [5].
- Here we have proposed a hypothetical mechanism of scaling which can take place during morphogenetic patterning and differentiation of cells in tissues and which is not necessarily relied on the discrete nature of biological objects. This mechanisms is based on two assumptions:
  1. There is a morphogen which is produced with a constant rate and this rate doesn't depend on the size of the tissue. This morphogen is degraded everywhere in the tissue so that the overall degradation rate is proportional to the size of the medium. In addition this morphogen diffuses quickly enough to maintain the same level all over the tissue.
  2. This morphogen affects the kinetics rates in the activator/inhibitor system responsible for patterning in the tissue in a way that the kinetics of morphogens depends on the size of the tissue and scaling of morphogenetic pattern can take place.
- The next task would be to explore whether there are experimental evidences supporting proposed mechanism of scaling.

References:

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