Critical Point in Self-Organized Tissue Growth

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(Received 25 October 2017; revised manuscript received 20 February 2018; published 11 May 2018)

We present a theory of pattern formation in growing domains inspired by biological examples of tissue development. Gradients of signaling molecules regulate growth, while growth changes these graded chemical patterns by dilution and advection. We identify a critical point of this feedback dynamics, which is characterized by spatially homogeneous growth and proportional scaling of patterns with tissue length. We apply this theory to the biological model system of the developing wing of the fruit fly Drosophila melanogaster and quantitatively identify signatures of the critical point.

DOI: 10.1103/PhysRevLett.120.198102

How tissues grow to their correct size and become spatially patterned during development is a key question in biology. Specific signaling molecules, called morphogens, control tissue patterning and growth [1–3]. These morphogens are locally produced and secreted. They spread in the target tissues, where they form long-range graded concentration profiles [2,16] see numerical examples of pattern scaling in development revealed scaling of the Dpp concentration profile with respect to compartment size [2,33–37]. One major class of mechanisms introduces an additional chemical species, termed expander, whose concentration depends on tissue size. It regulates morphogen dynamics and thereby scales its pattern [2,33–35].

Several mechanisms of growth control have been proposed [37–42]. One suggestion is that morphogen gradients control growth by a “temporal growth rule” [2,43], where the local growth rate in the target tissue is set by relative temporal changes of the local morphogen concentration. This growth rule in conjunction with an expander

FIG. 1. Minimal model for growth control in biological tissues by scaling morphogen gradients. (a) The wing imaginal disk of the fruit fly is a two-dimensional epithelial sheet with a source releasing Dpp molecules (red) at the anterior-posterior compartment boundary (dark red). We consider a simplified morphogen system with a source at the left boundary. Panels (b)–(f) show numeric solutions of Eqs. (1) and (2) for k = 0. Color code defined in (b) applies to all panels [in (c) and (e) most lines overlap]. (b) Spatial profiles for morphogen concentration C0 for different tissue lengths. (c) Rescaled concentration profiles from (b) collapse on a master curve, thus showing scaling (inset: log-normal plot). (d) Amplitude C0 of the concentration profile obeys a power-law relationship with tissue length ℓ. (e) Self-consistently regulated growth becomes spatially homogeneous after an initial transient period. (f) Growth slows down inversely with time [solid line: Eq. (10)]. Parameters are D = 0.1 μm²/s [12], ν = 1 conc/s, w = 0.1ℓ, ε = 0.83 [2], β = 2/(1 + ε).
mechanism for gradient scaling can account for the homogeneous growth observed in the wing imaginal disk [2,35] and may also apply to other tissues [37,44]. It has further been suggested that the temporal growth rule by itself could yield gradient scaling, without the need of an additional expander mechanism [35].

In this Letter, we propose a theoretical framework for the interplay between gradient scaling and growth control. In this framework, spatially homogeneous growth and exact scaling of chemical gradients both emerge as features of a critical point of the growth dynamics. This approach provides a mechanism for the homogeneous growth and gradient scaling observed during the growth of the wing disk of the developing fly.

**Morphogen dynamics and growth control.**—We consider a minimal two-dimensional system with morphogen of concentration \(C(x,t)\) as function of position \(x = (x,y)\) and time \(t\). Morphogen dynamics is governed by local production in a specified source region \(s(x,t) > 0\), by effective diffusion with diffusivity \(D\), and effective degradation with rate \(k\), as well as by advection and dilution of molecules due to tissue growth. Further, we consider a temporal growth rule by which the relative rate of change of the morphogen concentration controls the local rate \(g\) of area growth [2], characterized by the dimensionless parameter \(β\). Together, morphogen dynamics and growth control are described by

\[
D_x C = \nabla \cdot (D \nabla C) - (k + g) C + s, \quad g = \frac{1}{\beta} \frac{D_x C}{C},
\]

where \(\nabla\) is the gradient operator. The convective time derivative \(D_t = \partial_t + u \cdot \nabla\) accounts for the local cell velocity field \(u(x,t)\) of the growing tissue, which obeys \(g = \nabla \cdot u\) [2].

We consider a morphogen source aligned parallel to the \(y\) axis with \(s(x,t) = \lambda\) in the interval \(0 ≤ x ≤ w(t)\) and \(s(x,t) = 0\) elsewhere; see dark red region in Fig. 1(a). The width of the morphogen source is denoted \(w(t)\) and \(v\) is a production rate. We consider morphogen profiles \(C(x,t)\) and growth profiles \(g(x,t)\) that only vary along the \(x\) axis. We choose reflecting boundary conditions at the domain boundaries, \(x = 0\) and \(x = \ell\). We account for a possible intrinsic anisotropy of tissue growth by the anisotropy parameter \(ε = (\partial_x s(r)) / (\partial_y s(r))\). Thus, tissue area scales as \(A \sim \ell^{1+ε}\), where isotropic growth corresponds to \(ε = 1\).

**Scaling of morphogen patterns.**—Scaling of concentration profiles is defined by the property that the time-dependent concentration \(C(x,t)\) can be written as

\[
C(x,t) = C_0(t) \xi(x/\ell),
\]

where \(\xi(r)\) with \(r = x/\ell\) is a scaling function that characterizes a time-independent shape of the concentration profile and \(C_0(t)\) is a time-dependent amplitude of the profile. An example exhibiting this scaling property is shown in Figs. 1(b) and 1(c). It has been suggested that \(C_0\) in Eq. (3) obeys a power law [2] of the form

\[
C_0(t) \sim \ell'(t)^{q/2}. \quad (4)
\]

Scale invariance captured by scaling functions together with power laws often occurs near critical points [45]. This raises the question of whether a critical point is underlying the scaling of morphogen patterns.

**Growth control and conditions for scaling.**—Dynamic solutions of Eqs. (1) and (2) exist, which scale as described by Eqs. (3) and (4) and for which growth is homogeneous, as we show next. This requires that the source width scales linearly with tissue length, \(w(t) \sim \ell(t)\).

Homogeneous growth with \(g(x,t) = g_0(t)\) implies that the relative position \(r = x/\ell\) of a material point does not change in time. In this case, the temporal growth rule Eq. (2) simplifies to \(βg_0 = \partial_t \ln(C_0)\). By definition, \(g_0\) is proportional to the relative change in tissue length, \(g_0 = (1 + ε) \partial_r \ln(\ell)\). Thus, we obtain the power law of Eq. (4) with exponent

\[
q = β(1 + ε). \quad (5)
\]

This exponent takes a specific value, as we show now. Combining Eqs. (1) and (2), we have

\[
0 = \nabla \cdot (D \nabla C) - [k + (1 + β)g] C + s, \quad (6)
\]

which holds at all times. For homogeneous growth, the time-dependent rate

\[
k_g = k + (1 + β)g \quad (7)
\]

is position independent, and the solution to Eq. (6) reads

\[
C(x,t) = \frac{v}{k_g} \left[ 1 - \frac{\sinh(\ell/\lambda - w/\lambda)}{\sinh(\ell/\lambda)} \cosh(\lambda x) \right] \quad x ≤ w \quad \xi_r \quad x > w, \quad (8)
\]

where \(λ = \sqrt{D/k_g}\) is a decay length. The time dependence of \(C(x,t)\) arises from the time dependencies of \(\ell', λ,\) and \(k_g\). From Eqs. (8) and (2), we find that growth is homogeneous if and only if concentration profiles scale. This is the case if \(λ \sim \ell'\) and \(w \sim \ell'\). Such scaling occurs if \(k_g \sim \ell'^{-2}\). Hence, \(C_0 \sim v/k_g\) obeys the power law Eq. (4) with \(q = 2\). Together with Eq. (5), we thus find that scaling can occur if the growth feedback parameter \(β\) takes a critical value \(β_c = 2/(1 + ε)\).

**Growth dynamics and the effect of morphogen degradation.**—The time dependence of homogeneous growth can be found using \(k_g \sim \ell'^{-2}\), Eq. (7), and \(g_0 = (1 + ε) \partial_r \ln(\ell)\), which together defines a differential equation for \(\ell'(t)\). The solution depends on the value and time dependence of the
degradation rate $k$. For the simple case $k = 0$, a numerical solution to Eqs. (1) and (2) is shown in Fig. 1, highlighting that for $\beta = \beta_c$, after a short transient, growth is indeed homogeneous and concentration profiles scale.

We can obtain explicit expressions for the growth dynamics at this critical point $\beta = \beta_c$, revealing that growth is unbounded and the growth rate slows down as $t^{-1}$:

\[
\ell'(t) = \ell(0)[1 + 2g_0(0)t/(1 + \epsilon)]^{1/2},
\]

\[
g_0(t) = \frac{g_0(0)}{1 + 2g_0(0)t/(1 + \epsilon)};
\]

see Fig. 1(f) and Ref. [46]. Interestingly, the growth rate in the long-time limit $g_0(t) \approx (1 + \epsilon)/(2t)$ becomes independent of the initial conditions.

Exact scaling and spatially homogeneous growth is also found at $\beta = \beta_c$ for a finite but constant degradation rate $k = k_0 > 0$. In this case, the growth rate decays exponentially,

\[
g_0(t) = \frac{g_0(0)e^{-t/\tau}}{1 + 2\tau g_0(0)(1 - e^{-t/\tau})/(1 + \epsilon)},
\]

with characteristic timescale $\tau = (1 + \beta_c/\epsilon)/(2k_0)$. As a consequence, growth arrests at a final size $\ell^*$ [35,46],

\[
\ell^* = \ell(0)[1 + g_0(0)(1 + \beta_c)/k_0]^{1/2}.
\]

Note that for $k_0 \to 0$, final size $\ell^*$ diverges as $\ell^* \sim k_0^{-1/2}$. Next, we consider the degradation rate as a function of tissue length, $k = k(\ell^*)$, e.g., regulated by an expander [2,33,47–49]. Let us consider the case of exact scaling of the degradation rate with tissue size in the form $k \sim \ell^{-2}$. For $\beta = \beta_c$, we again find spatially homogeneous growth as well as exact pattern scaling, which is again described by Eqs. (9) and (10). In particular, growth is unbounded; see Fig. 2. If, however, we add a small constant value $k_0$ to the degradation rate $k = k_0 \sim \ell^{-2}$, growth arrests at a finite size given by Eq. (12).

These cases illustrate that at $\beta = \beta_c$, we can find either unbounded or bounded growth, depending on the behavior of the degradation rate $k$. In general, growth arrest can be observed if there exists a final size $\ell^* > \ell(0)$, for which $k_0(\ell^*) = k(\ell^*)$. This follows from Eq. (7) [46].

**Critical point of growth control.**—We now explore the behavior for $\beta \neq \beta_c$. In this case, the system does not exhibit exact pattern scaling and growth becomes spatially inhomogeneous; see Figs. 2(a)–2(c) for an example. For $\beta < \beta_c$, $g(r,t)$ is decreasing with $r$, while for $\beta > \beta_c$, $g(r,t)$ is increasing with $r$; see Fig. 2(b) and Ref. [46]. As before, the growth dynamics depends on the degradation rate; see Fig. 2(d). Growth is always unbounded for $k = 0$. For $k = k_0 > 0$, growth arrests at a finite final size $\ell^*$ for all values of $\beta$. In the case of $k \sim \ell^{-2}$, growth arrests for $\beta > \beta_c$ and the growth rate $g(t)$ decays exponentially with characteristic time $\tau$. The final size $\ell^*$ diverges as $\beta$ approaches the critical point $\beta_c$ from above. For $\beta < \beta_c$, growth is unbounded. Thus, $\beta = \beta_c$ exhibits distinct features of a critical point such as scale invariance of the concentration profile and divergent length scales. For $k \sim \ell^{-2}$ this critical behavior includes a transition between bounded and unbounded growth.

Only at the critical point, exact pattern scaling and homogeneous growth occurs. However, in the vicinity of the critical point, patterns scale and growth is homogeneous.
to a good approximation, reflecting signatures of the critical point [46]. Interestingly, a control of the degradation rate by an expander molecule can maintain approximate scaling even away from the critical point if the growth rate is small compared to the degradation rate. In this case, \( k_g \approx k \sim \ell^{-2} \), and growth inhomogeneities do not perturb scaling strongly; see Fig. 2(a). Yet, even in this case of almost exact gradient scaling, inhomogeneity of growth occurs depending on \( \beta \); see Fig. 2(b).

So far we have focused on the case where the source width \( w \) grows proportional to tissue length \( \ell \). We now discuss situations where the source width is not proportional to tissue length. To simplify the discussion, we consider a source width \( w \sim \ell^\gamma \) with \( 0 \leq \gamma < 1 \), which interpolates between the cases of a constant source width \( (\gamma = 0) \) and a source width proportional to tissue length \( (\gamma = 1) \). Solving Eqs. (1) and (2) for different values of \( \gamma < 1 \), we again find similar behaviors as described for \( \gamma = 1 \). For example, two growth regimes can be distinguished, depending on the value of \( \beta \). For \( \beta < (\gamma + 1)/(1 + \epsilon) \), growth is unbounded and the growth rate as a function of time is well fit by a power law, while for \( \beta > (\gamma + 1)/(1 + \epsilon) \), growth is bounded and the growth rate is well fit by an exponential; see Fig. 2(e). Note that along the line \( \gamma = 2\beta/\beta_c - 1 \) we observe signatures of the critical point even for \( \beta < \beta_c \); see Fig. 3 and Ref. [46].

Homogeneous growth and gradient scaling in the wing imaginal disk of the fruit fly.—Growth dynamics and spatial profiles of the morphogen Dpp have been quantified in the wing imaginal disk of the fruit fly D. melanogaster. Growth of the wing disk is approximately homogeneous and the growth rate decays exponentially with a timescale of 30–60 h [2,50]. Dpp profiles scale to a good approximation and their amplitude \( C_0 \) is well fit by a power-law relation with tissue area with exponent \( \tilde{\beta} = q/(1 + \epsilon) \) ranging from 0.5 to 0.7 depending on the data set [2,46]. Furthermore, homogeneous growth can be accounted for by the temporal growth rule Eq. (2) with scaling Dpp profiles [2]. We show in Figs. 3(e)–3(g) experimental data on Dpp profile amplitude \( C_0 \), tissue area \( A \) and decay length \( \lambda [2] \) together with numerical values obtained by solving Eqs. (1) and (2). This comparison shows that the continuum model can account for growth and Dpp concentration gradient dynamics in the wing imaginal disk. The parameter values used in Fig. 3 are indicated in Fig. 2(e) as a blue dot. Estimating the growth anisotropy \( \epsilon [2,50] \) suggests that the growth parameter \( \beta \approx 0.7 \) is smaller than \( \beta_c \approx 1.1 \). Thus, the wing disk is not exactly critical. Deviations from criticality also arise because the source width in the wing imaginal disk increases less than linearly with tissue length. Experimental estimates locate \( \gamma \) within the range 0.2–0.9 [2,46], and our simulation fits experimental data of growth and morphogen dynamics with \( \gamma = 0.3 \); see Figs. 2(e), 3(e)–3(g). Therefore, scaling and homogeneous growth are only approximate, and result as signatures of the nearby critical point. Interestingly, the fly mutant Hh-CD2 differs from control animals in that its source width is constant [2].

Hh-CD2 can be represented here by exponents \( \gamma = 0 \) and \( \beta = 0.7 [46] \), which locates its growth dynamics far from the boundary line between unbounded growth and growth arrest. From this observation we predict that scaling should be less precise and growth nonhomogeneous for Hh-CD2 as compared to control fly wings. Indeed, our analysis of Dpp-decay lengths is consistent with less precise scaling in Hh-CD2 [46].

Conclusion.—We presented a theory for self-organized growth of tissues regulated by a dynamic morphogen profile and a temporal growth rule. We find that both exact scaling of the morphogen profile and homogeneous growth are mutually dependent and arise as features of a critical point. We determine a concise condition for scaling...
and homogeneous growth in terms of a critical feedback strength. We reveal characteristic features of the presented mechanism. First, the amplitude of morphogen profiles obeys a power-law relationship with tissue length. Second, there exist distinct regimes of growth arrest and unbounded growth in which spatial profiles of growth differ. Third, scaling itself is independent of many details of the dynamic equations if the system is close to criticality. In particular, scaling does, in principle, not require an expander mechanism and could occur even in the absence of a feedback on tissue length [35]. However, an expander can alter the growth dynamics. Note that an expander regulation that provides the relation $k \sim \ell^{-2}$ leads to unbounded growth at the critical point. Reliable growth termination can be achieved by an offset in the scaling relation, e.g., $k - k_0 \sim \ell^{-2}$. Such behavior could occur, for example, in the case of delayed expander regulation.

We applied our theory to the dynamics of morphogen gradients and growth during the development of the wing imaginal disks of the fruit fly. Chosen parameters, which are consistent with previous experiments, correspond to $\beta < \beta_c$ but are close to the boundary in parameter space separating bounded from unbounded growth [Fig. 2(e)]. We find that nonlinear scaling behavior of the Dpp source, as quantified in Ref. [2], may place the wing disk in the regime of bounded growth even for a supercritical growth parameter. Our work suggests that in the wing imaginal disk an expander mechanism ensures that growth arrests, while the scaling of Dpp profiles and the spatial homogeneity of growth result as robust signatures of a critical point. The framework presented here could be applied to other systems, such as the eye imaginal disk of the fly, which is an example of a nonstationary Dpp source that orchestrates growth [43].

We thank Maria Romanova-Michaelides and Zena Hadjivasiliou for discussions. D. A.-H., F. J., and M. G.-G. acknowledge support from the DIP of the Canton of Geneva, SNSF, the SystemsX epiPhysX grant, the ERC (Sara and Morphogen), the NCCR Chemical Biology program, and the Polish-Swiss research program. S. W. and B. M. F. acknowledge support from the German Federal Ministry of Education and Research (BMBF), Grant No. 031 A 099, and DFG through the Excellence Initiative by the German Federal and State Governments (cluster of excellence caed).

D. A.-H. and S. W. contributed equally to this work.

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