ETH zürich

Lecture 4: Morphogen Gradients on Growing Domains

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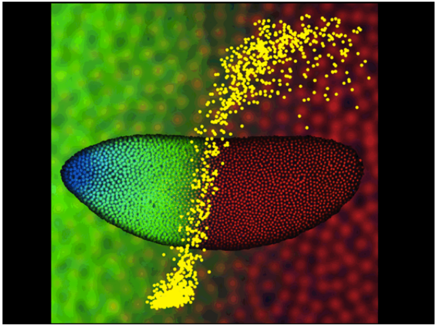
MSc Computational Biology 2019/20

Contents

Previous Lectures

Morphogen Gradients

- What is a morphogen gradient?
- Can diffusion create gradients?
- Robustness of morphogen gradients



A simple 1D diffusion model

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}; \quad 0 \leq x \leq L$$

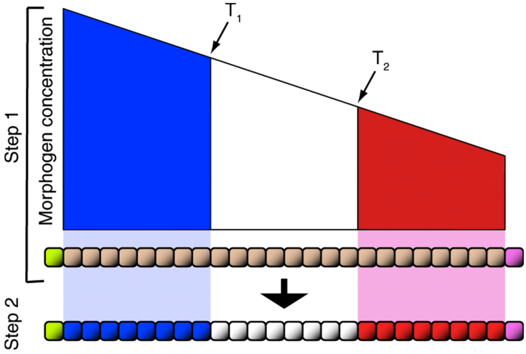
$$IC: \; c(x,0) = 0 \quad x > 0$$

$$BC: \; c(0) = c_0 \qquad c(L) = 0$$

<u>Steady-state solution:</u>

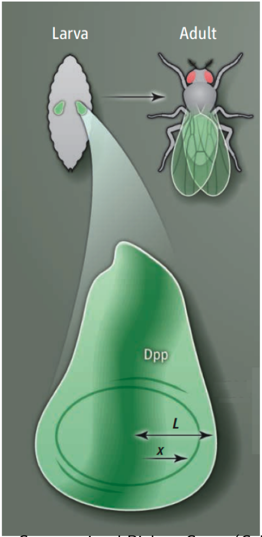
$$c(x) = c_0 \frac{L-x}{L}$$

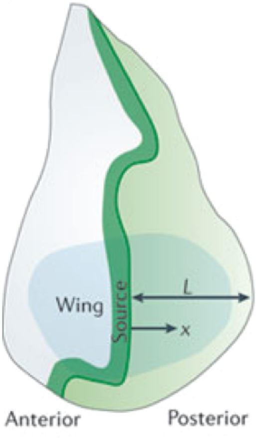
French Flag Model (Wolpert)

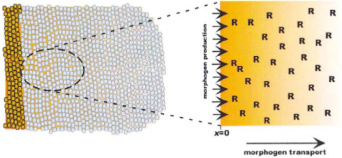


Jaeger et al (2008) Development

The Dpp Gradient in the *Drosophila* wing disc

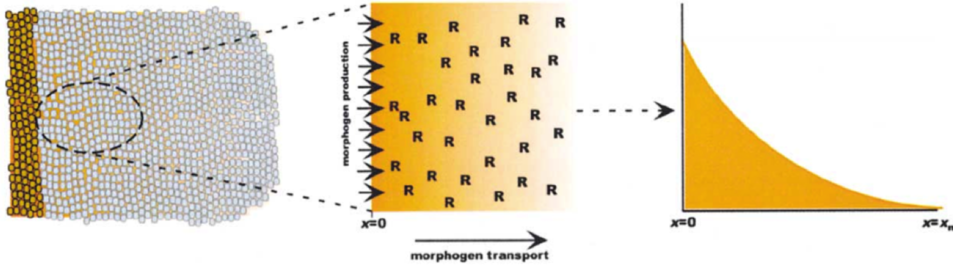






Dpp is secreted continously from the stripe at the AP boundary into the domain.

STANDARD MODEL: boundary at infinity



Steady-state solution:

$$PDE: \quad \frac{\partial c}{\partial t} = D\Delta c - kc; \quad 0 \leq x \leq L$$

$$IC: \quad c(x,0) = 0$$

$$BC: \quad c(0,t) = c_0 \qquad c(x \to \infty) = 0$$

$$c(x) = c_0 \exp\left(-\frac{x}{\lambda}\right)$$

$$\lambda = \sqrt{\frac{D}{k}}$$

What model for Morphogen Gradients?

$$\begin{aligned} 1D\ Domain: &\quad 0 \leq x \leq L \\ PDE: &\quad \frac{\partial c}{\partial t} = D\Delta c - f(c) \\ IC: &\quad c(x>0,0) = 0 \end{aligned}$$

Degradation Term $f(c)$

- none $\Rightarrow$ linear gradient
- linear $\Rightarrow$ exponential gradient
- non-linear $\Rightarrow$ powerlaw gradient

Boundary Conditions

- Fixed concentration at both boundaries, i.e. $c(0,t) = c_0$ & $c(L) = 0$
- Fixed concentration at source, zero concentration at infinity, $c(0,t) = c_0$ & $c(x \to \infty) = 0$
- Flux boundary conditions, i.e. $\left.\frac{\partial c}{\partial x}\right|_{x=0} = -j$ & $\left.\frac{\partial c}{\partial x}\right|_{x=L} = 0$

Scaling with domain size

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc \qquad + IC \quad + BC$$

Re-scaling position as $\zeta = x/L$, $0 < \zeta < 1$, yields

$$\frac{\partial c}{\partial t} \quad = \quad \frac{D}{L^2}\frac{\partial^2 c}{\partial \zeta^2} - kc \qquad + IC \quad + BC.$$

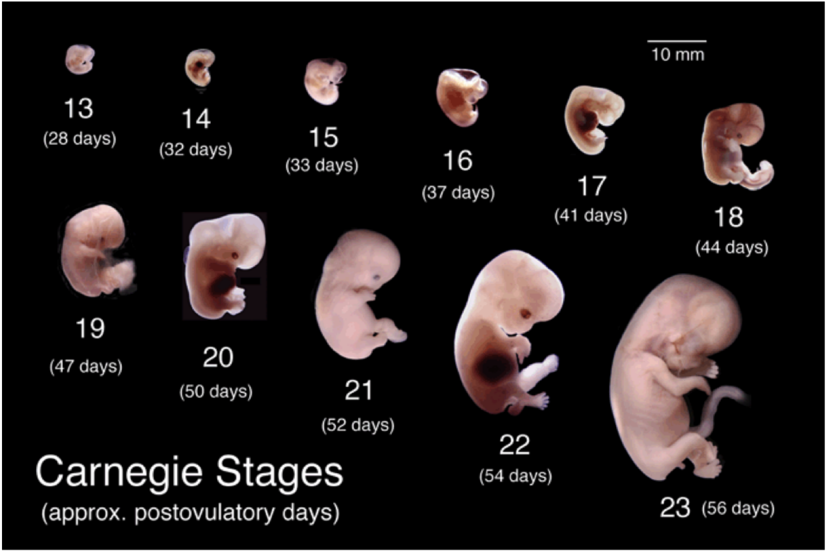
We then have as steady-state solution

$$c = c_0 \exp\left(-\zeta/\lambda^*\right) \quad \text{with} \quad \lambda^* = \sqrt{\frac{D}{k}\frac{1}{L^2}}.$$

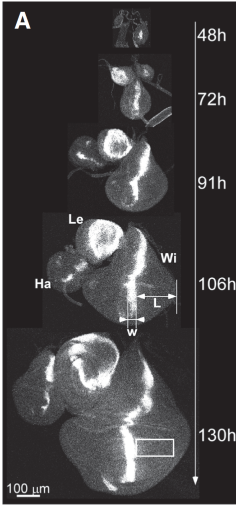
To achieve scaling on domains of different lengths L require $\frac{D}{k} \propto L^2$.

Signaling Models on Moving Domains

Human Embryonic Development



Growth & Patterning



Growth can have a significant impact on patterning processes because

- the growing tissue transports signaling molecules, and
- molecules become diluted in a growing tissue.

In the following we will discuss the impact of growth on the spatio-temporal distribution of signaling factors.

Conservation of Mass

The total temporal change of $c_i(\boldsymbol{x}, t)$ in the volume Ω must be equal to the combined changes in the domain due to fluxes $\boldsymbol{j}$ across the boundary and reactions $R(c)$ inside the domain:

$$\frac{d}{dt}\int_{\Omega} c_i(\boldsymbol{x}, t) d\boldsymbol{x} = \int_{\partial\Omega} \boldsymbol{j} \cdot \boldsymbol{n}\, dS + \int_{\Omega} R(c) d\boldsymbol{x}$$

According to the Divergence Theorem

$$\int_{\partial\Omega} \boldsymbol{j} \cdot \boldsymbol{n}\, dS = -\int_{\Omega} \nabla \cdot \boldsymbol{j}\, d\boldsymbol{x}$$

$$\frac{d}{dt}\int_{\Omega} c_i(\boldsymbol{x}, t) dV = \int_{\Omega} \left(-\nabla \cdot \boldsymbol{j} + R(\boldsymbol{c})\right) d\boldsymbol{x} \tag{1}$$

Leibniz integral rule

$$\frac{d}{dt}\left(\int_{a(t)}^{b(t)} f(x,t)\,dx\right) = f\left(b(t),t\right)\cdot\frac{d}{dt}b(t) - f\left(a(t),t\right)\cdot\frac{d}{dt}a(t) + \int_{a(t)}^{b(t)} \frac{\partial}{\partial t} f(x,t)\,dx,$$

where $-\infty < a(t), b(t) < \infty$.

Leibniz integral rule

$$
\begin{aligned}
\frac{d}{dt}\left(\int_{a(t)}^{b(t)} f(x,t)\,dx\right) \quad &= \quad f\left(b(t),t\right)\cdot\frac{d}{dt}b(t) - f\left(a(t),t\right)\cdot\frac{d}{dt}a(t) \\
&\quad + \int_{a(t)}^{b(t)} \frac{\partial}{\partial t} f(x,t)\,dx,
\end{aligned}
$$

where $-\infty < a(t), b(t) < \infty$.

In case of constant bounds, we obtain

$$
\frac{d}{dt}\left(\int_{a}^{b} f(x,t)\,dx\right) = \int_{a}^{b} \frac{\partial}{\partial t} f(x,t)\,dx.
$$

Reaction-Diffusion Equations on static domains

In case of a constant domain Ω, the Leibnitz integral rule yields

$$\frac{d}{dt}\int_{\Omega} c_i(\boldsymbol{x}, t)dV = \int_{\Omega}\{D_i\Delta c_i + R(c_k)\}dV$$

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$$\int_{\Omega}\left(\frac{dc_i(\boldsymbol{x}, t)}{dt} - D_i\Delta c_i - R(c_k)\right)dV = 0$$

Reaction-Diffusion Equations on static domains

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$$\int_\Omega \left(\frac{dc_i(\boldsymbol{x},t)}{dt} - D_i \Delta c_i - R(c_k) \right) dV = 0$$

$$\int_\Omega \left(\frac{\partial c_i(\boldsymbol{x},t)}{\partial t} - D_i \Delta c_i - R(c_k) \right) dV = 0$$

Reaction-Diffusion Equations on static domains

Since

$$\int_\Omega \left(\frac{\partial c_i(\boldsymbol{x}, t)}{\partial t} - D_i \Delta c_i - R(c_k) \right) dV = 0 \tag{2}$$

holds for any domain Ω, we must have

$$\frac{\partial c_i(\boldsymbol{x}, t)}{\partial t} - D_i \Delta c_i - R(c_k) = 0, \tag{3}$$

and we obtain the well-known reaction-diffusion equation

$$\frac{\partial c_i}{\partial t} = D_i \Delta c_i + R(c_k). \tag{4}$$

If the domain is evolving in time, then we would need to determine the time-derivatives of the boundaries.

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Alternatively, we can map the time-evolving domain Ω_t to a stationary domain $\Omega_{\boldsymbol{\xi}}$ using a time-dependent mapping.

$\boldsymbol{\xi} = [\xi_1, \xi_2, \xi_3]^T$ denotes the spatial coordinate in the stationary domain.

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$\boldsymbol{\xi} = [\xi_1, \xi_2, \xi_3]^T$ denotes the spatial coordinate in the stationary domain.

The mapping is described by the Jacobian of the transformation:

$$J = \begin{pmatrix} \frac{\partial x_1}{\partial \zeta_1} & \frac{\partial x_1}{\partial \zeta_2} & \frac{\partial x_1}{\partial \zeta_3} \\ \frac{\partial x_2}{\partial \zeta_1} & \frac{\partial x_2}{\partial \zeta_2} & \frac{\partial x_2}{\partial \zeta_3} \\ \frac{\partial x_3}{\partial \zeta_1} & \frac{\partial x_3}{\partial \zeta_2} & \frac{\partial x_3}{\partial \zeta_3} \end{pmatrix}. \tag{5}$$

In short-hand notation, we write

$$J = \frac{\partial \mathbf{x}}{\partial \boldsymbol{\xi}} = \frac{\partial(x_1, x_2, x_3)}{\partial(\xi_1, \xi_2, \xi_3)}. \tag{6}$$

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In short-hand notation, we will write

$$J = \frac{\partial \boldsymbol{x}}{\partial \boldsymbol{\xi}} = \frac{\partial(x_1, x_2, x_3)}{\partial(\xi_1, \xi_2, \xi_3)}. \tag{8}$$

Geometrically, the determinant of J represents the dilation of an infinitesimal volume as it follows the motion:

$$d\Omega_t = dx_1 dx_2 dx_3 = \det J \, d\xi_1 d\xi_2 d\xi_3 = \det J \, d\Omega_{\boldsymbol{\xi}}. \tag{9}$$

For the left hand side of eq. (1) we then obtain, using the Reynolds transport theorem,

$$
\begin{aligned}
\frac{d}{dt}\int_{\Omega_t} c_i(\boldsymbol{x},t)\, d\Omega_t &= \frac{d}{dt}\int_{\Omega_\xi} c_i\left(\boldsymbol{x}(\boldsymbol{\xi},t),t\right)\det J\, d\Omega_\xi \\
&= \int_{\Omega_\xi}\left[\frac{dc_i}{dt}\det J + c_i\frac{d(\det J)}{dt}\right] d\Omega_\xi \\
&= \int_{\Omega_\xi}\left[\frac{\partial c_i}{\partial t} + \boldsymbol{u}\cdot\nabla c_i + c_i\nabla\cdot\boldsymbol{u}\right]\det J\, d\Omega_\xi \\
&= \int_{\Omega_t}\left[\frac{\partial c_i}{\partial t} + \nabla\cdot(c_i\boldsymbol{u})\right] d\Omega_t
\end{aligned}
$$

where $d(\det J)/dt = \nabla\boldsymbol{u}\det J$ and $\boldsymbol{u} = \frac{d\boldsymbol{x}}{dt}$ the velocity field.

We thus obtain as reaction-diffusion equation on a growing domain:

$$\left.\frac{\partial c_i}{\partial t}\right|_{\boldsymbol{x}} + \nabla \cdot (c_i \boldsymbol{u}) = D_i \Delta c_i + R(c_i). \tag{10}$$

$|_{\boldsymbol{x}}$ indicates that the time derivative is performed while keeping $\boldsymbol{x}$ constant.

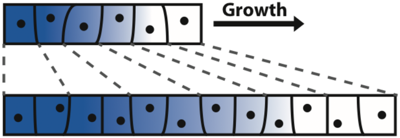
The terms $\boldsymbol{u} \cdot \nabla c_i$ and $c_i \nabla \cdot \boldsymbol{u}$ describe advection and dilution, respectively.

If the domain is incompressible, i.e. $\nabla \cdot \boldsymbol{u} = 0$, the equations further simplify.

The Lagrangian Framework

The Lagrangian Framework

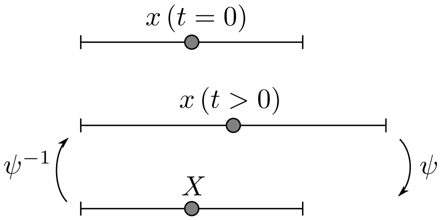
In growing tissues cells move. It can be beneficial to take the point of view of the cells and follow them. This is possible within the Lagrangian Framework.



To illustrate the differences between the Eulerian and Lagrangian framework consider a river. The Eulerian framework would correspond to sitting on a bench and watching the river flow by. In the Lagrangian framework we would sit in a boat and travel with the river.

The Lagrangian Framework

Mapping between the Frameworks



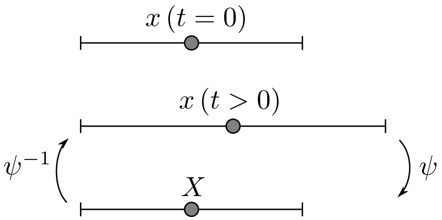
At time $t = 0$, we label a particle by the position vector $\boldsymbol{X} = \boldsymbol{x}(0)$ and follow this particle over time.

At times $t > 0$, the particle is found at position $\boldsymbol{x} = \psi\,(\boldsymbol{X}, t)$. Here $\boldsymbol{x}$ is the spatial variable in the Eulerian framework, and $\boldsymbol{X}$ in the Lagrangian framework.

If initially distinct points remain distinct throughout the entire motion then the transformation possesses the inverse $\boldsymbol{X} = \psi^{-1}\,(\boldsymbol{x}, t)$.

The Lagrangian Framework

Mapping between the Frameworks



A one dimensional domain is stretched. A point on the domain, initially at $x(t=0)$ is advected and later found at position $x(t>0)$.

At all times, the Eulerian coordinate system can be mapped to the Lagrangian coordinate system using a mapping function ψ, and vice versa using its inverse ψ^{-1}.

In case of uniform growth, the point stays at the same position in the Lagrangian coordinate system for all times and thus can be labeled by X.

The Eulerian and the Lagrangian Framework

Any quantity F (i.e. a concentration $F = c_i$) can therefore be written either as a function of

- Eulerian variables $(\boldsymbol{x}, t)$
- Lagrangian variables $(\boldsymbol{X}, t)$.

To indicate a particular set of variables we thus write either

- $F = F(\boldsymbol{x}(\boldsymbol{X}, t), t)$ as the value of F felt by the particle instantaneously at the position $\boldsymbol{x}$ in the Eulerian framework, or
- $F = F(\boldsymbol{X}, t)$ as the value of F experienced at time t by the particle initially at $\boldsymbol{X}$ (Lagrangian Framework).

The Eulerian and the Lagrangian Framework

In the Lagrangian framework we now need to determine the change of the variable F following the particle.

In the Eulerian framework, we are determining $\left.\frac{\partial F}{\partial t}\right|_{\boldsymbol{x}}$, the rate of F apparent to a viewer stationed at the position $\boldsymbol{x}$.

The Material Derivative

The time derivative in the Lagrangian framework is also called the material derivative:

$$\frac{dF}{dt} = \frac{dF(\boldsymbol{x}(\boldsymbol{X},t),t)}{dt} = \frac{dF(\boldsymbol{X},t)}{dt} \tag{11}$$

and follows as

$$\begin{aligned} \underbrace{\frac{dF(\boldsymbol{X},t)}{dt}}_{Lagrangian} &= \left.\frac{\partial F}{\partial t}\right|_{\boldsymbol{x}} + \frac{\partial F}{\partial x_k} \underbrace{\frac{\partial x_k(\boldsymbol{X},t)}{\partial t}}_{=u_k} \\ &= \underbrace{\left.\frac{\partial F}{\partial t}\right|_{\boldsymbol{x}} + \boldsymbol{u}\cdot\nabla F}_{Eulerian}\,. \end{aligned} \tag{12}$$

Note that the advection term $\boldsymbol{u}\cdot\nabla F$ vanishes in the material derivative as compared to the Eulerian description.

The Spatial Derivative

We can now also write the Eulerian spatial derivatives in terms of the Lagrangian reference frame using the Jacobian of the transformation

$$J = \frac{\partial(X_1, X_2, X_3)}{\partial(x_1, x_2, x_3)}. \tag{13}$$

Geometrically, $\det(J)$ represents the dilation of an infinitesimal volume as it follows the motion:

$$dX_1 dX_2 dX_3 = \det(J) dx_1 dx_2 dx_3. \tag{14}$$

Arbitrary Lagrangian-Eulerian (ALE) Method

Arbitrary Lagrangian-Eulerian (ALE) Method

The arbitrary Lagrangian-Eulerian (ALE) method is a generalization of the well-known Eulerian and Lagrangian domain formulations.

In the Eulerian framework, the observer does not move with respect to a reference frame (Equation 10). Large deformations can be described in a simple and robust way, but tracking moving boundaries can lead to non-trivial problems.

In the Lagrangian framework, on the other hand, the observer moves according to the local velocity field. The convective terms are zero because the relative motion to the material vanishes locally, and the equations simplify substantially (Equation 12). However, this comes at the expense of mesh distortions when facing large material deformations.

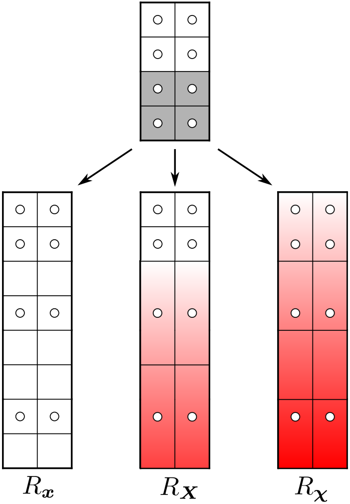
Arbitrary Lagrangian-Eulerian (ALE) Method

In the ALE framework, finally, the observer is allowed to move freely and describe the equations of motions from his viewpoint.

This allows for the flexibility to deform the mesh according to e.g. moving boundaries, but also for the possibility to freely remodel the mesh independent of the material deformations.

Although the problem of mesh distortion is much reduced as compared to the Lagrangian formulation, remeshing might still be required when confronted with complex deformations.

Reference Frame Paradigms



The grey shaded material of the initial domain is stretched threefold. Material particles (circles) are attached to the continuum. In the Eulerian domain $R_{\boldsymbol{x}}$ the mesh does not move as opposed to the Lagrangian domain $R_{\boldsymbol{X}}$ and ALE domain $R_{\boldsymbol{\chi}}$. The red color denotes the magnitude of mesh velocity $\boldsymbol{v}$. In the Lagrangian domain, the mesh velocity coincides with the material velocity field $\boldsymbol{u}$, whereas in the ALE domain the mesh velocity can be chosen arbitrarily.

Arbitrary Lagrangian-Eulerian (ALE) Method

In the ALE framework, the reaction-diffusion equation reads:

$$\left.\frac{\partial c_i}{\partial t}\right|_{\boldsymbol{x}} + \boldsymbol{w} \cdot \nabla c_i + c_i \nabla \cdot \boldsymbol{u} = D_i \Delta c_i + R\left(c_i\right) \tag{15}$$

where $\partial_t c_i\big|_{\boldsymbol{x}}$ denotes the time derivative with fixed $\boldsymbol{x}$ coordinate. $\boldsymbol{w} = \boldsymbol{u} - \boldsymbol{v}$ is the convective velocity (i.e. the relative velocity between the material and the ALE frame) and $\boldsymbol{v}$ the mesh velocity. In the case of $\boldsymbol{v} \equiv \boldsymbol{u}$, i.e. the mesh is attached to the material, the Lagrangian formulation (Equation 12) is recovered. On the other hand, when setting $\boldsymbol{v} \equiv 0$, we get back the Eulerian formulation (Equation 10). In between, the mesh velocity $\boldsymbol{v}$ can be chosen freely, which can be exploited to being able to track large deformations.

Example - Uniform Growth

Example - Uniform Growth

The benefit of working in a Lagrangian reference frame is directly apparent in case of a uniformly growing domain. In case of uniform growth in one spatial dimension we have

$$x(t) = L(t)X, \tag{16}$$

where $L(t)$ is the time-dependent length of the domain.

Since the stretching factor $L(t)$ is independent of the spatial position, the Lagrangian reference frame X corresponds to a stationary domain.

Example - Uniform Growth

To transform a PDE for the concentration c

$$\frac{\partial c}{\partial t} + \nabla \cdot (cu) = D\frac{\partial^2 c}{\partial x^2} + R(c) \tag{17}$$

from Eulerian coordinates $x(t) = L(t)X$ to Lagrangian coordinates X, we use

$$\frac{\partial X}{\partial x} = \frac{1}{L(t)} \qquad u = \frac{dx}{dt} = \dot{L}(t)X \qquad \frac{\partial u}{\partial X} = \dot{L}(t). \tag{18}$$

Example - Uniform Growth

$$x(t) = L(t)X, \quad \frac{\partial X}{\partial x} = \frac{1}{L(t)} \qquad u = \frac{dx}{dt} = \dot{L}(t)X \qquad \frac{\partial u}{\partial X} = \dot{L}(t)$$

$$\begin{aligned}
\frac{dc}{dt} + c\frac{\partial u}{\partial x} &= D\frac{\partial^2 c}{\partial x^2} + R(c) \\
\frac{\partial c}{\partial t} + c\,\underbrace{\frac{\partial u}{\partial X}}_{\dot{L}(t)}\,\underbrace{\frac{\partial X}{\partial x}}_{1/L(t)} &= D\frac{\partial^2 c}{\partial X^2}\underbrace{\left(\frac{\partial X}{\partial x}\right)^2}_{1/L(t)^2} + R(c) \\
\frac{\partial c}{\partial t} + c\dot{L}(t)\frac{1}{L(t)} &= D\frac{\partial^2 c}{\partial X^2}\left(\frac{1}{L(t)}\right)^2 + R(c)
\end{aligned}$$

Example - Uniform Growth

As reaction-diffusion equation for $c = c(X,t)$ on an uniformly growing domain, we then obtain a rather simple formula, i.e.

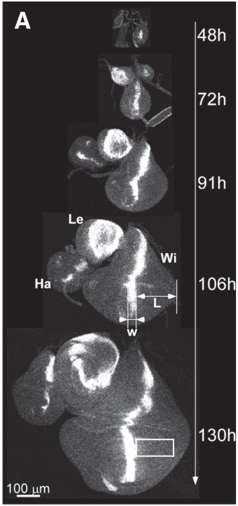
$$\frac{dc}{dt} = \frac{\partial c}{\partial t} = \frac{D}{L(t)^2}\frac{\partial^2 c}{\partial X^2} - \frac{\dot{L(t)}}{L(t)}c + R(c).$$

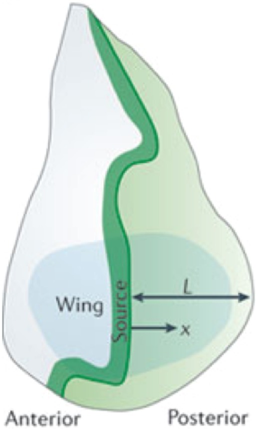
In case of linear growth, $L(t) = L(0) + v \cdot t$, this further simplifies to

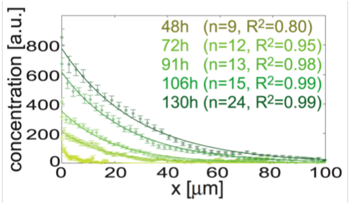
$$\frac{dc}{dt} = \frac{\partial c}{\partial t} = \frac{D}{L(t)^2}\frac{\partial^2 c}{\partial X^2} - \frac{v}{L(t)}c + R(c).$$

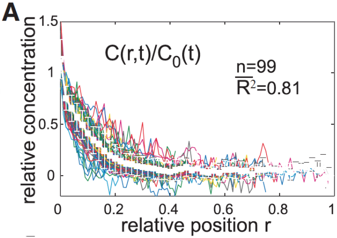
Morphogen Gradient Scaling on Growing Domains

The Dpp Gradient scales with the growing wing disc domain

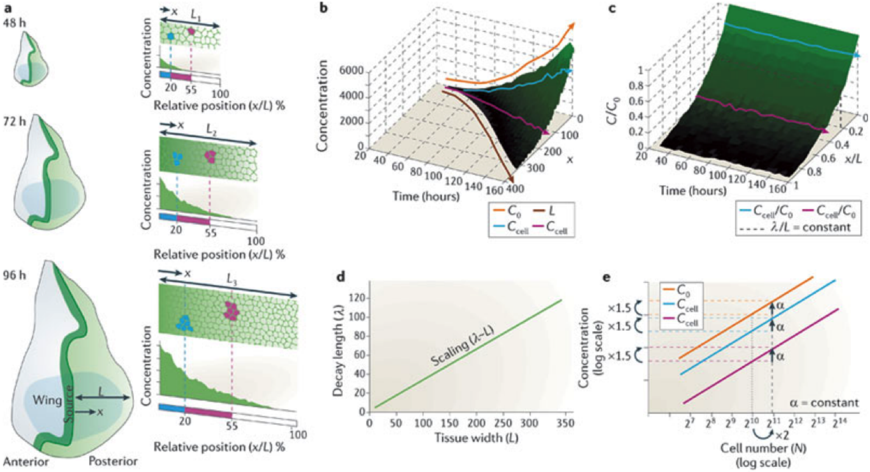








The Dpp Gradient scales with the domain



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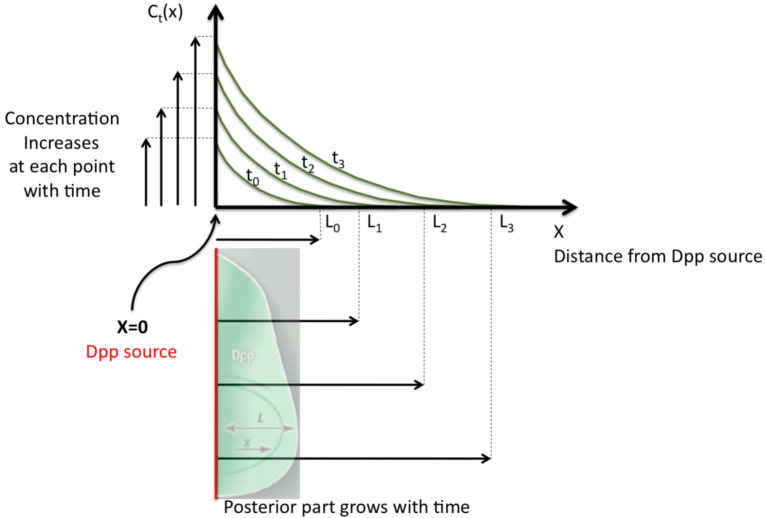
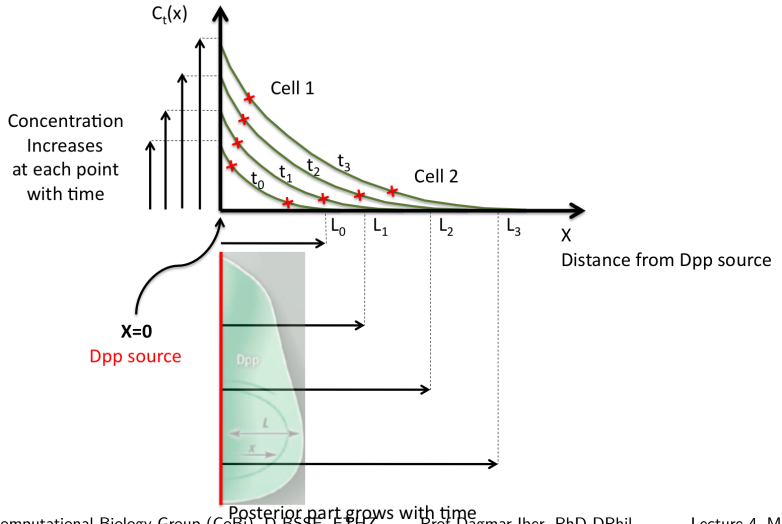
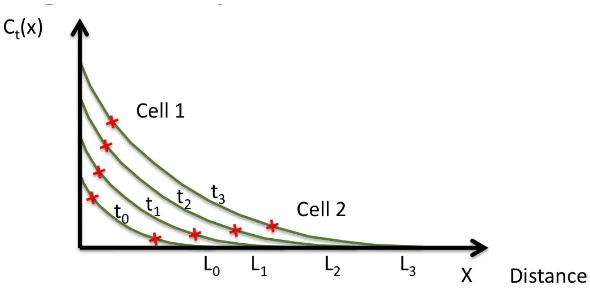
The Dpp Gradient scales with the domain



The Dpp concentration seen by cells over time.



An exponential gradient



Observation:

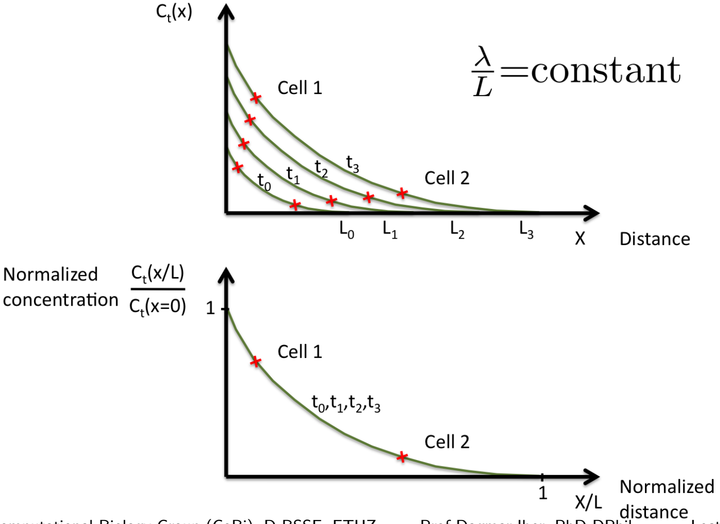
$$\frac{\lambda}{L} = \text{constant} \quad , \; \lambda = \sqrt{\frac{D}{\kappa}}$$

For any t:

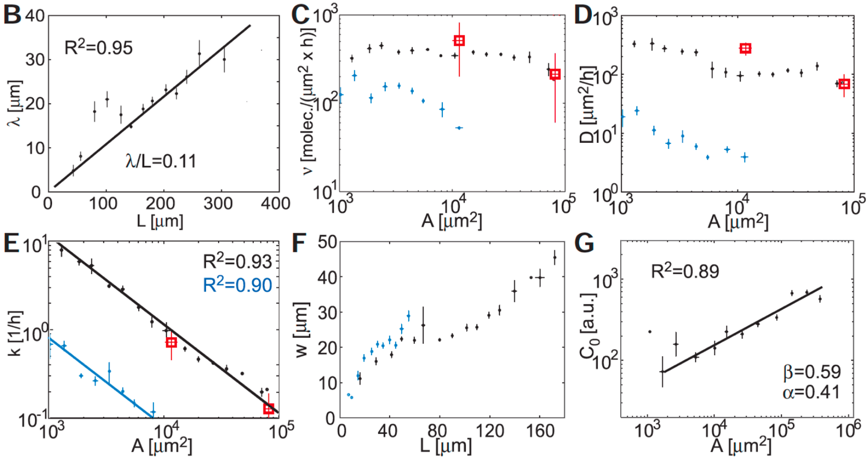
$$C_t(x) = C_0 e^{-\frac{x}{\lambda}}$$

$$(t = t_0) : C_{t_0}(x) = C_{0_{t_0}} e^{-\frac{x}{\lambda_{t_0}}}$$
$$(t = t_1) : C_{t_1}(x) = C_{0_{t_1}} e^{-\frac{x}{\lambda_{t_1}}}$$
$$(t = t_2) : C_{t_2}(x) = C_{0_{t_2}} e^{-\frac{x}{\lambda_{t_2}}}$$
$$(t = t_3) : C_{t_3}(x) = C_{0_{t_3}} e^{-\frac{x}{\lambda_{t_3}}}$$

The Dpp profiles scale on a growing domain



How does λ scale with L?



$$\lambda^* = \sqrt{(D^*/k^*)} : D = const, \; k \sim 1/A \sim 1/\Lambda^2$$

Dynamic Scaling on a Growing Domain

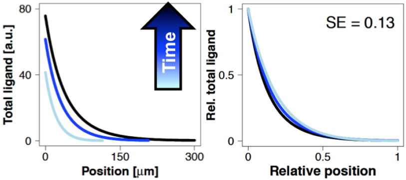
Advection-Diffusion system scales almost perfectly

Model

- **Diffusion equation** on 1D growing domain

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - u\frac{\partial c}{\partial x} - c\frac{\partial u}{\partial x}$$

- **Linear growth speed** of domain based on previously measured data
- **Constant influx of Dpp** from the left boundary
- Dpp transported by **Diffusion & Advection**



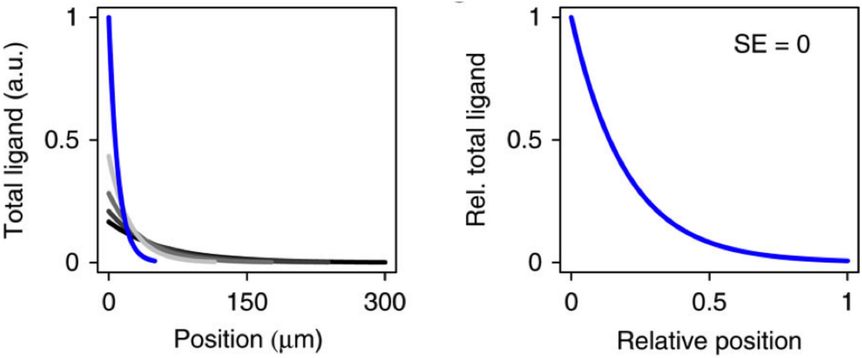
Observations & implications

- Concentration at left boundary **continuously increasing**
- **Strong overlap between normalized gradients** of different time points
- Surprisingly **low scaling error** (0 = perfect scaling, 1 = no scaling)

Further analysis revealed: Scaling effect caused by pre-steady state dynamics due to absence of degradation

Evaluation of scaling quality

We speak of scaling if two gradients on differently sized domains overlay when normalized with respect to their maximal value and plotted on domains that have been normalized with respect to their maximal length.



Evaluation of scaling quality

To evaluate the quality of scaling, we seek to determine the extent, to which the gradients are shifted over time on the normalized domain, $X \in [0,1]$.

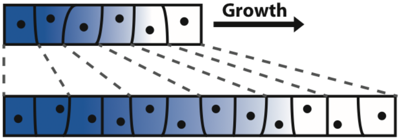
Accordingly, we define the scaling error SE as

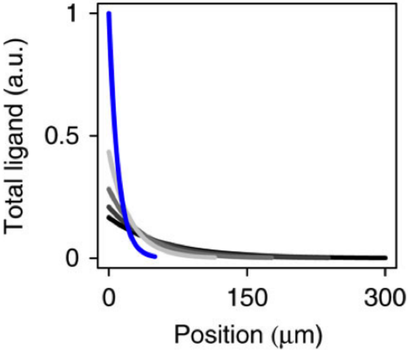
$$SE = \frac{\Delta X}{X}, \tag{19}$$

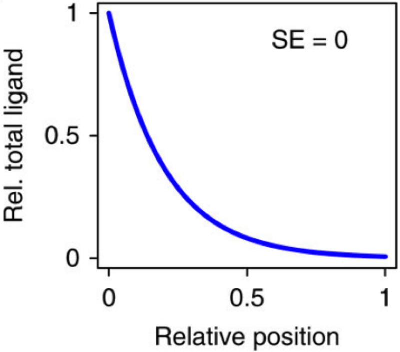
where ΔX specifies the difference of the position X at which a given normalized concentration $\frac{c(x,t)}{c(0,t)}$ is attained by the different gradients.

Advection & Dilution of a gradient

$$\frac{\partial c}{\partial t} = -\underbrace{u\frac{\partial c}{\partial x}}_{\text{advection}} - \underbrace{c\frac{\partial u}{\partial x}}_{\text{dilution}}$$







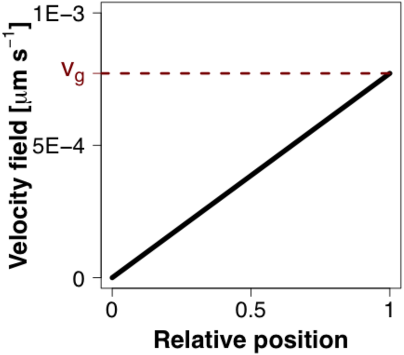
Dilution of a gradient

$$\frac{\partial c}{\partial t} = - \underbrace{u\frac{\partial c}{\partial x}}_{\text{advection}} - \underbrace{c\frac{\partial u}{\partial x}}_{\text{dilution}}$$

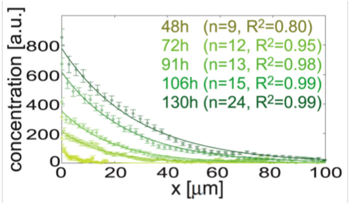
Dilution in case of linear uniform growth is spatially uniform:

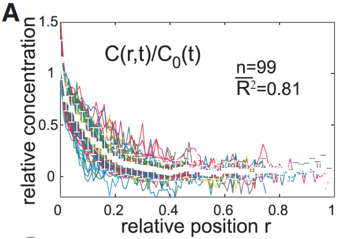
$$\frac{\partial u}{\partial x} = \frac{v}{L(t)}$$

$\Rightarrow$ Gradient Shape remains preserved.



Definition of Gradient Expansion





Consider a gradient concentration profile $c(x,t)$ on a growing domain of length $L(t) = L(0) + v \cdot t$, with growth speed v. We define the mean squared displacement of the gradient as

$$E[x^2] = \frac{\int_0^{L(t)} x^2 c(x,t)dx}{\int_0^{L(t)} c(x,t)dx} \tag{20}$$

We will show that in case of

Advection: $\sqrt{E[x^2]} \sim t$

Diffusion: $\sqrt{E[x^2]} \sim \sqrt{t}$

Advection of a gradient

Consider an initial distribution U with mean μ_0 and variance $\sigma_0^2 = 0$:

$$E[U^2] = Var(U) + (E[U])^2 = \sigma_0^2 + \mu_0^2.$$

$$\text{Impact of Growth:} \qquad U = V(t)\frac{L(0)}{L(t)}$$

$$E[V^2] = Var(V) + (E[V])^2 = a^2(Var(U) + (E[U])^2) = a^2 E[U^2]$$

using

$$Var(aU) = a^2 Var(U); \qquad E[aU] = aE[U]$$

$$\text{For} \quad a = \frac{L(t)}{L(0)}: \qquad E[V^2] = \left(\frac{L(t)}{L(0)}\right)^2 (\sigma_0^2 + \mu_0^2)$$

Concentration Gradient

$$c(z,0) = c(0,0)\exp\left(-z/\lambda\right) \quad \text{on} \quad z \in [0,\infty) \tag{21}$$

$$E[z^2] = \frac{\int_0^\infty z^2 c(z,t)dz}{\int_0^\infty c(z,t)dz} = 2\lambda^2 \tag{22}$$

$$\text{Impact of Growth:} \qquad z = x\frac{L(0)}{L(t)}$$

$$E[x^2] = 2\lambda^2\left(\frac{L(t)}{L(0)}\right)^2 \quad \Rightarrow \quad \sqrt{E[x^2]} = \sqrt{2}\lambda\frac{L(t)}{L(0)} \tag{23}$$

Advection on uniformly, linearly growing domain results in gradient expansion proportional to time.

Impact of Diffusion

$$\frac{\partial c}{\partial t} = \underbrace{D\frac{\partial^2 c}{\partial x^2}}_{\text{diffusion}} \tag{24}$$

For a Dirac Delta function $\delta(x)$ as initial condition, the solution on an infinite domain is

$$c(x,t) = \frac{1}{\sqrt{4\pi D t}} \exp\left(-\frac{x^2}{4Dt}\right). \tag{25}$$

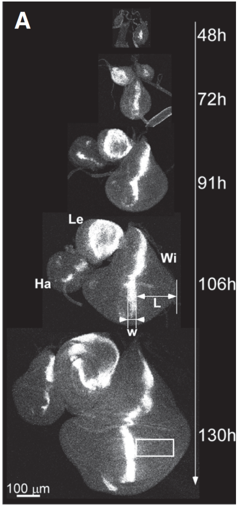
The variance is the second central moment of a random variable U,

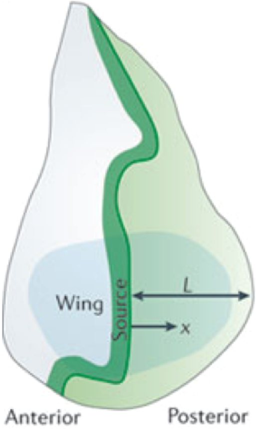
$$Var(U) = E[U^2] - (E[U])^2 \quad \Leftrightarrow \quad E[U^2] = Var(U) + (E[U])^2.$$

such that with $\mu = 0$ and $\sigma^2 = 2Dt$,

$$E[x^2] = \sigma^2 - \mu^2 = 2Dt. \tag{26}$$

Impact of Flux Boundary Condition





In the wing disc model, we have flux boundary conditions at the left boundary,

$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = -j_{in}.$$

Zero-flux at the left boundary

Let us first consider zero-flux boundary conditions, $\left.\frac{\partial c}{\partial x}\right|_{x=0} = 0$. We have

$$c(x,t) = \frac{\sqrt{2}}{\sqrt{2\pi D t}} \exp\left(-\frac{x^2}{4Dt}\right), \tag{27}$$

which is the half-normal distribution with $\sigma^2 = 2Dt$. Given the variance and mean of the half-normal distribution, we have

$$E[x^2] = \sigma^2(1 - \frac{2}{\pi}) + \left(\frac{\sigma\sqrt{2}}{\sqrt{\pi}}\right)^2 = \sigma^2 = 2Dt \tag{28}$$

This is the same expectation value of x^2 as in the normal distribution.

Flux boundary conditions

In our model, we still have a slightly different situation in that we have a constant influx at the left-hand side boundary instead of a given initial distribution,

$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = -j_{in}.$$

We can approximate our inhomogeneous Neumann boundary condition at $x = 0$ as a mixture distribution of half-normal distributions with different end times tend, $t_{end} = \frac{i}{k}t$ with $i = 0, 1, 2, \ldots, k$. For large k, the following is therefore a good approximation

$$c(x,t) \approx \frac{1}{k+1}\sum_{i=0}^{k} \frac{\sqrt{2}}{\sqrt{2\pi D t \frac{i}{k}}} \exp\left(-\frac{x^2}{4Dt\frac{i}{k}}\right). \tag{29}$$

Flux boundary conditions

$$c(x,t) \approx \frac{1}{k+1}\sum_{i=0}^{k} \frac{\sqrt{2}}{\sqrt{2\pi D t \frac{i}{k}}} \exp\left(-\frac{x^2}{4Dt\frac{i}{k}}\right)$$

$E[x^2]$ of this mixed distribution is then the weighted sum of the individual expectation values, $E_i[x^2] = 2D\frac{i}{k}t$, which range from $E_i[x^2] = 0$ to $E_i[x^2] = 2Dt$, such that

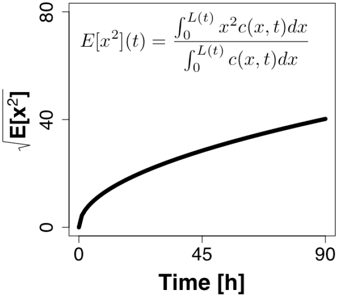
$$E[x^2] = \frac{1}{k+1}\sum_{i=0}^{k} E_i[x^2] = Dt. \qquad (30)$$

Thus,

$$\sqrt{E[x^2]} = \sqrt{Dt}. \qquad (31)$$

Diffusion expands gradient with square-root of time

$$\frac{\partial c}{\partial t} = D\frac{\partial^2}{\partial x^2}$$



Dirac Delta function as IC:

$$\mathbf{c(x,t)} = \frac{\mathbf{1}}{\sqrt{\mathbf{4\pi Dt}}}\exp\left(-\frac{\mathbf{x^2}}{\mathbf{4Dt}}\right)$$

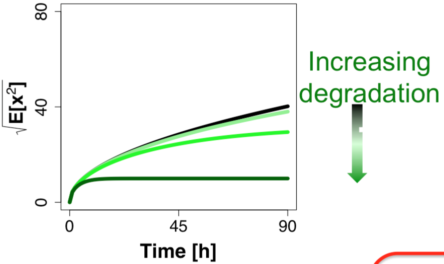
Flux Boundary condition:

$$\sigma^2 = Dt$$

Diffusion: $\lambda \sim \sqrt{t} = \sqrt{\frac{L(t)}{v} - \frac{L_0}{v}}$

Perfect scaling: $\lambda \sim L(t)$

Degradation limits diffusion-driven gradient expansion because of pre-steady state nature of expansion



Pre-steady state effect

Degradation limits diffusion-driven gradient expansion

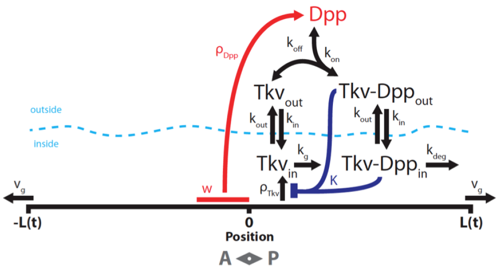
Diffusion: $\lambda \sim \sqrt{t} = \sqrt{\frac{L(t)}{v} - \frac{L_0}{v}}$

Perfect scaling: $\lambda \sim L(t)$

Fried and Iber, *Nat. Commun.*, 2014.

Detailed Model of Dpp Dynamics in the Wing Disc

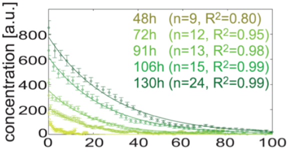
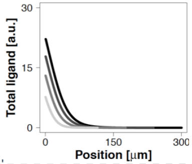
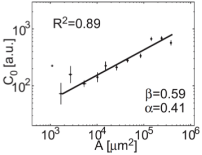
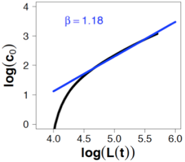
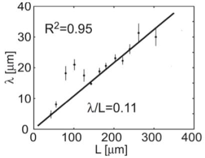
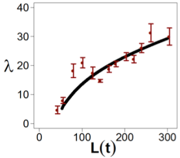
Wing disc model



Key features

- Dpp **produced in a small stripe** posterior to AP boundary
- Dpp can **bind and unbind receptor** Tkv
- Complex can be **rapidly internalized** and can downregulate production of receptor
- Complex and receptor can be degraded, the **complex however at a slow rate** (min. half-life required:10h)

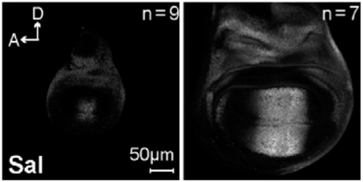
All experimental data can be explained by model

	Experimental data	Model results	Match
Exponential gradient			✓
Incrasing amplitude			✓
Scaling			✓

Dpp target genes scale with tissue size

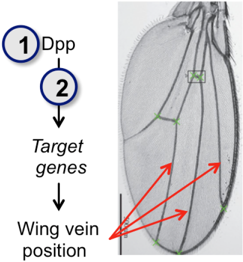
Dpp target genes

- Dpp gradient is known to **determine expression domain of downstream target genes** in the wing disc
- The expression boundaries of downstream target genes **determine the position of wing veins**
- Expression domains of target genes, e.g. sal and dad-GFP, have been found to scale well with tissue size



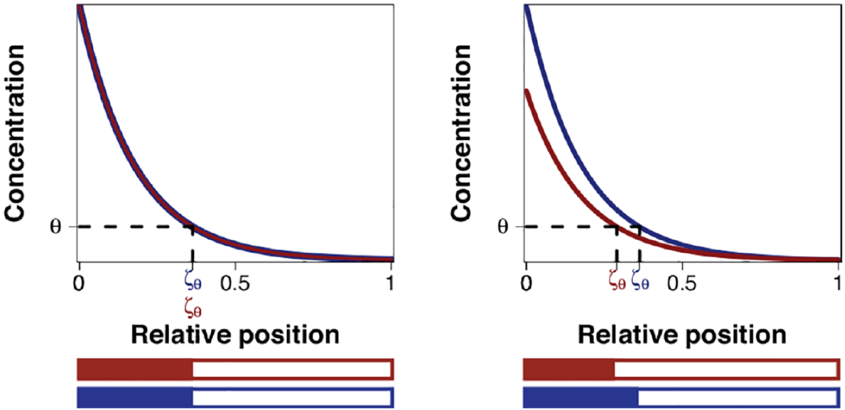
Source: **Hamaratoglu et al., *PLOS Biology*, 2011.**

Wing vein patterning



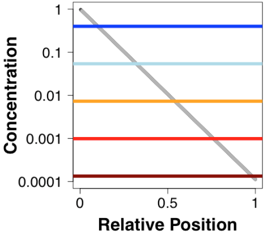
How is the morphogen gradient read out?

How to read out an increasing, scaled gradient?



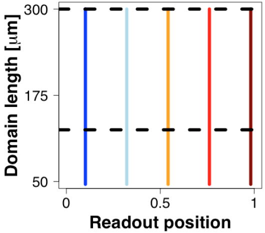
Threshold-based read-out: Perfect scaling of morphogen results in perfect scaling of target genes

Concentration profile (log-scale)



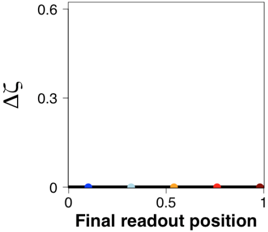
Normalized concentration profiles of perfectly scaling gradients **overlap for all time points**

Rel. read-out position during growth



Relative read-out position constant over time for all concentration thresholds

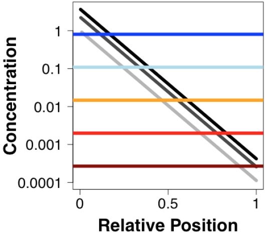
Deviation of rel. read-out position



Zero deviation of relative read-out positon over time

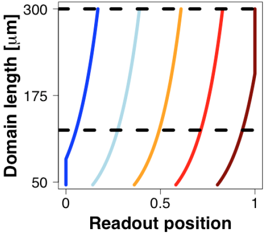
Threshold-based read-out: Increasing gradient shifts read-out position over time

Concentration profile (log-scale)



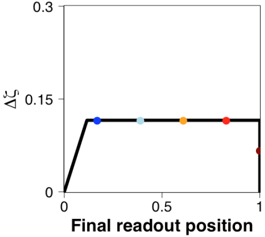
Normalized concentration profiles of increasing perfectly scaling gradient **no longer overlap**

Rel. read-out position during growth



Relative read-out position shifts over time for all concentration thresholds

Deviation of rel. read-out position



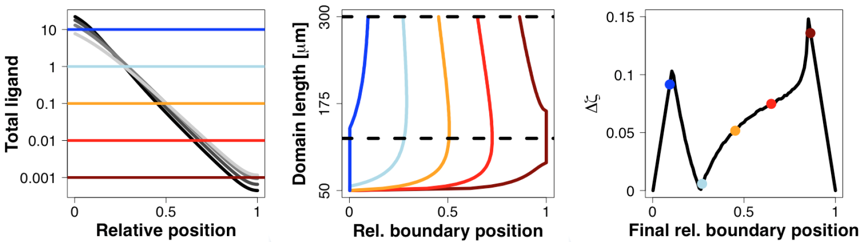
Large deviation of relative read-out positon over time

Imperfect scaling and an increasing amplitude result in stable read out region

Concentration profile (log-scale)

Rel. read-out position during growth

Deviation of rel. read-out position

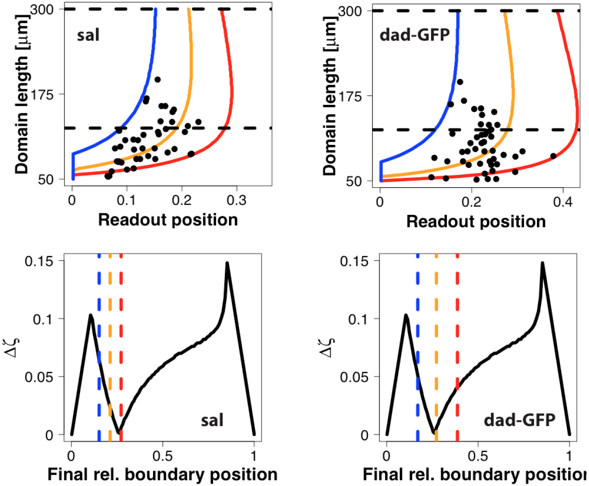


Normalized concentration profiles of imperfectly scaling gradient overlap in one region

Relative read-out position is stable over time for certain concentration thresholds

Zone where devation of the relative read out position is **minimal over time**

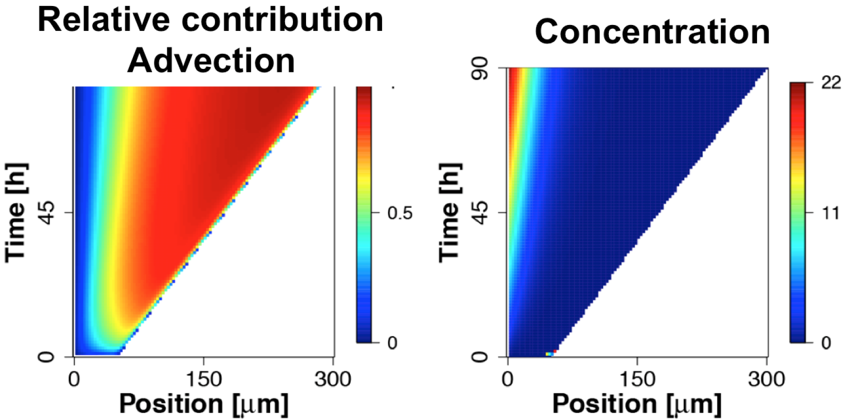
Expression domains of *sal* and *dad*-GFP are within stable region



Conclusion

- A general mechanism for dynamic (imperfect) scaling of morphogen gradients
- The scaling mechanism requires pre-steady state kinetics and therefore a low degradation rate of the morphogen
- Imperfect scaling can explain the biological data in the *Drosophila* wing disc
- Simple threshold-based read out mechanism is sufficient to explain scaling of target genes
- Imperfect scaling and an increasing amplitude cooperate in such a way that the readout position is stable over time
- Several target genes of Dpp in the Drosophila wing disc are within the stable readout zone

Dpp Transport is dominated by diffusion



- Diffusion dominates in the front of the tissue
- Advection dominates at the end of the tissue

Thanks!!

Thanks for your attention!

Slides for this talk will be available at:
`http://www.bsse.ethz.ch/cobi/education`