Solving reaction-diffusion equation for embryos that scale with their length

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Problem: Spatial patterning due to simple diffusion of a morphogen

Consider a morphogen $Morph$, whose concentration is M, diffusing and degrading along a line. This line represents the proximal-distal axis of a developing embryo. The one-dimensional reaction-diffusion equation that describes the concentration M along the line is

$$\frac{\partial M}{\partial t} = D\nabla^2 M - G(M) \tag{1}$$

where D is the diffusion coefficient of $Morph$, and $G(M)$ is a degradation rate of $Morph$ (so it is never negative) and is a function of M.

(**a**) Assume that M does not degrade at all. The embryo's proximal end is at $x = 0$ and its distal end is at $x = \infty$ (i.e., the embryo has one boundary, at $x = 0$). Note that as x approaches ∞, we have $M \to 0$. Assume that at $x = 0$, the concentration of M is always a constant, M_0. Find the steady-state concentration profile M for this infinitely long embryo.

(**b**) Now, assume that the embryo has a finite length, L, with the proximal end at $x = 0$ and the distal end at $x = L$. The morphogen still does not degrade. Solve the reaction-diffusion equation (Eq. 1) to find the steady-state concentration $M(x)$. Use the following boundary conditions: $M(x = 0) = M_0$ and $M(x = L) = 0$. The boundary condition at $x = L$ is called the **absorbing boundary condition**.

(**c**) Show that the solution you found in (b) proportionally scales with the proximal-distal length L of the embryo. That is, show that if L changes by a factor β while the boundary conditions remain the same, then $M_L(x/L) = M_{\beta L}(x/L)$ where M_L is the solution that you found in (b) and $M_{\beta L}$ would be the solution to Eq. 1 for the embryo with length βL.

(**d**) Derive equations (24) and (25) in lecture note 5. You can use any result from the lecture note, in particular Eq. (22), and your starting point is Eq. (11b) in lecture note 5.

Solutions: Spatial patterning due to simple diffusion of a morphogen

(**a**) Here we have $G = 0$. For a steady-state profile $M(x)$, we then have

$$0 = \frac{d^2M}{dx^2} \tag{2}$$

Evidently, the steady-state concentration-profile does not depend on the diffusion coefficient D. As mentioned in the lecture note, this equation with the prescribed boundary conditions has a unique solution. So once we guess a solution and find that it's indeed a solution of Eq. 2 that matches the boundary conditions, we have found the only solution that there is. Since Eq. 2 states that M should not have its slope ever changing at any position x, a natural guess is a linear function:

$$M(x) = Ax + B \tag{3}$$

where A and B are constants. Note that Eq. 3 indeed satisfies Eq. 2. Now, we need $M(0) = M_0$. Thus $B = M_0$. And to have $M(L) = 0$, we need $A = -M_0/L$. Thus we have

$$M(x) = M_0\left(1 - \frac{x}{L}\right) \tag{4}$$

By an infinitely long embryo, we mean that L is finite but very large (we can never set x to be *exactly* an infinity for an embryo). Above solution still holds even for a hypothetical, "infinitely" long embryo. Note that as we take $L \to \infty$, we have

$$M(x) = \lim_{L\to\infty} M_0\left(1 - \frac{x}{L}\right) = M_0 \tag{5}$$

Thus, we obtain a constant concentration, M_0 everywhere. Physically, this occurs because there must be a source of the morphogen at $x = 0$ (or just to the left of $x = 0$, such as $x = -\epsilon$) that is keeping the concentration at $x = 0$ fixed at M_0. So the morphogens at $x = 0$ diffuse out to the rest of the infinitely long embryo ($x > 0$)and are simultaneously replenished by the source at $x = 0$.

(**b**) Eq. 4 is the solution.

(**c**) Let us call the solution Eq. 4 as $M_L(x)$. The solution for an embryo of length βL is

$$M_{\beta L}(x) = M_0\left(1 - \frac{x}{\beta L}\right) \tag{6}$$

Let $x = \alpha L$, where $0 \le \alpha \le 1$. Then

$$\begin{aligned}
M_L(\alpha L) &= M_0(1-\alpha) && \text{(7a)}\\
&= M_0\left(1 - \frac{\beta\alpha}{\beta}\right) && \text{(7b)}\\
&= M_0\left(1 - \frac{\beta x}{\beta L}\right) && \text{(7c)}\\
&= M_{\beta L}(\beta x) && \text{(7d)}\\
&= M_{\beta L}(\beta\alpha L) && \text{(7e)}\\
&= M_{\beta L}(\alpha(\beta L)) && \text{(7f)}\\
&= M_{\beta L}(\alpha L_{\text{new}}) && \text{(7g)}\\
& && \text{(7h)}
\end{aligned}$$

where $L_{new} = \beta L$ is the length of the embryo after it's been scaled by the factor β. This shows that the morphogen gradient scales with the length of the embryo. In other words, the absolute distance x does not matter, only the fractional length α matters in determining the morphogen concentration.

(**d**) **First-order degradation of the morphogen**: The reaction-diffusion equation with a first-order degradation term, $G(M) = \alpha_M M$, is given by Eq. 11b in lecture note 5:

$$\tau \frac{\partial M}{\partial t} = \lambda^2 \frac{\partial^2 M}{\partial x^2} - M \tag{8}$$

where $\tau = 1/\alpha_M$ is called **characteristic time** and $\lambda = \sqrt{D_M/\alpha_M}$ is called the **characteristic length** (these are also respectively called **diffusion time** and **diffusion length**). Note that λ is actually a function of the expander concentration E. In steady-state, we have $\partial M/\partial t = 0$ and $\lambda = \lambda_s$, where λ_s is the steady-state function (due to the expander's steady-state concentration profile, $E_s(x)$). Thus we obtain

$$0 = \frac{d^2 M}{dy^2} - M \tag{9}$$

where $y \equiv x/\lambda_s$. The boundary conditions are

$$\eta_M = -D_M \frac{dM_s}{dx}\bigg|_{x=0} \implies \frac{\lambda_s \eta_M}{D_M} = -\frac{dM_s}{dy}\bigg|_{y=0} \qquad \text{at } x = 0\text{: constant flux (by Fick's law of diffusion)} \tag{10a}$$

$$M_s(x = L) = \epsilon \qquad \text{at } x = L\text{: constant concentration} \tag{10b}$$

where η_M and ϵ are constants. Eq. 10a indicates that we can write $M_s(x)$ is a function of y, $f(y)$ (i.e., $M_s(x) = f(y)$). In other words, x does not appear by itself and always appears with λ_s as x/λ_s. Let us now solve Eq. 9. We have

$$0 = \frac{d^2 f}{dy^2} - f \tag{11}$$

Plugging $f(y) = Ce^{ay}$ into Eq. 11, we find that $a^2 - 1 = 0$. Thus, the general solution of Eq. 11 is

$$f(y) = Ae^{y} + Be^{-y} \tag{12}$$

where A and B are constants that depend on the boundary conditions (Eqs. 10a- 10b). First of all, we must have $A = 0$ since the solution should still hold for a very long embryo (i.e., $L \to \infty$). If $A \neq 0$, then the e^y term will diverge to infinity as $y \to \infty$ while the e^{-y} goes to zero (and thus B does not have to be zero). So, we have reduced Eq. 12 to

$$f(y) = Be^{-y} \tag{13}$$

Applying the two boundary conditions to Eq. 13, we have

$$\frac{\lambda_s \eta_M}{D_M} = B \tag{14a}$$

$$\epsilon = Be^{-L/\lambda_s} \tag{14b}$$

We assume here that the expander concentration is uniform throughout the embryo, and hence $\lambda_s = \lambda_s([E])$ is a constant (i.e., both $D_M(E)$ and $\alpha_M(E)$ are constants).
By Eq. 14a, we have

$$M_s(x) = \frac{\lambda_s \eta_M}{D_M} e^{-x/\lambda_s} \tag{15}$$

Eq. 14b states that ϵ must be a particular value for the steady-state with these two boundary conditions. To determine this value, we note that the expander concentration, $[E]$, must also be at a steady-state for otherwise, λ_s would change over time, meaning that M_s would not be a steady-state solution. In lecture note 5, we discussed that increasing the expander concentration would increase the morphogen's diffusion (i.e., increases D_M) and decrease the morphogen's degradation (i.e., decreases α_M). Thus, increasing the expander concentration would increase $\lambda_s = \sqrt{D_M/\alpha_M}$. We also stated in lecture note 5 that the expander has a very fast diffusion, leading to the equalization of its concentration throughout the embryo (thus the assumption above that the steady-state concentration fo the expander is uniform). This means that if the expander production is not turned off at any point inside the embryo, then the expander produced at a given point will quickly spread and even out, leading to a higher uniform concentration of itself. This, in turn, would increase λ_s, causing the M_s to change, which we cannot have since the M_s must be a steady-state solution. Thus we the expander production rate, but not necessarily its concentration inside the embryo, must be zero everywhere inside the embryo, including at $x = L$ where the morphogen concentration is the lowest and hence the expander-production rate is the highest - recall that this is because the morphogen represses the expander production (see lecture note 5). Thus we see that if we ensure that the expander-production rate at $x = L$ is zero, then we are also ensuring that its production rate, which is lower at all other locations, is zero as well. Recall that the expander-production rate is given by the sigmoidal function:

$$\frac{\partial E(x)}{\partial t} = \frac{V}{T_{\text{rep}}^h + M(x)} \tag{16}$$

where V and T_{rep} are constants and M is the morphogen concentration. Assuming a very high (infinite) Hill coefficient h, the production of the expander would be nearly (exactly) zero if M is larger than or equal to T_{rep}. Thus we can argue that in order to have zero production of the expander at $x = L$, we need $\epsilon \geq T_{\text{rep}}$. Setting $\epsilon = T_{\text{rep}}$, we have

$$T_{\text{rep}} = M_s(x = L) \tag{17a}$$

$$\implies T_{\text{rep}} = \frac{\lambda_s \eta_M}{D_M} e^{-L/\lambda_s} \tag{17b}$$

$$\implies \frac{L}{\lambda_s} = ln\left(\frac{\lambda_s \eta_M}{D_M T_{\text{rep}}}\right) \tag{17c}$$

$$\implies \frac{1}{\lambda_s} = \frac{1}{L} ln\left(\frac{\lambda_s \eta_M}{D_M T_{\text{rep}}}\right) \tag{17d}$$

$$\implies \frac{1}{\lambda_s} = \frac{\mu}{L} \tag{17e}$$

where

$$\mu \equiv ln\left(\frac{\lambda_s \eta_M}{D_M T_{\text{rep}}}\right) \tag{18}$$

Thus Eq. 15 becomes

$$M_s(x) = \frac{L \eta_M}{D_M \mu} e^{-\mu x/L} \tag{19}$$

This is the result that the problem asked for. Note that the first-order degradation does not yield a perfect scaling - Eq. 19 has the L appearing outside the exponential without a x to go with it.

Second-order degradation of the morphogen: We now assume that the morphogen degrades as

$$G(M) = \alpha_M \frac{M^2}{M_T} \tag{20}$$

where M_T is a constant and α_M is a function of the expander concentration (i.e., $\alpha_M = \alpha_M([E])$). The reaction-diffusion equation is now

$$\frac{\partial M}{\partial t} = D_M \nabla^2 M - G(M) \tag{21a}$$

$$\implies \frac{\partial M}{\partial t} = D_M \frac{\partial^2 M}{\partial x^2} - \alpha_M \frac{M^2}{M_T} \tag{21b}$$

$$\implies \tau \frac{\partial M}{\partial t} = \lambda^2 \frac{\partial^2 M}{\partial x^2} - \frac{M^2}{M_T} \tag{21c}$$

$$\implies 0 = \frac{d^2 M_s}{dy^2} - \frac{M_s^2}{M_T} \qquad \text{(for a steady-state concentration-profile)} \tag{21d}$$

where $\lambda \equiv \sqrt{D_M/\alpha_M}$, $\tau = 1/\alpha_M$, $y \equiv x/\alpha_M$, and M_s is the steady-state concentration of the morphogen. Note that y is still a dimensionless position variable since α_M, like in the first-order degradation scenario, is a unit of length. Eq. 21d indicates that we can write M_s is a function of y (i.e., $M_s = f(y)$). Unlike in the case of first-order degradation, we cannot just assume that $f(y) = Ce^{ay}$ then plug it into Eq. 21d and then proceed. This is because Eq. 21d is not a linear equation (unlike its counterpart in the case of first-order degradation) (i.e., exponential solutions work for linear equations but not necessarily for non-linear equations like Eq. 21d). In fact, you can check that the exponential does not work by plugging in $f(y) = Ce^{ay}$ into Eq. 21d (you'll find that a^2 must equal an exponential that varies over space - a non-sense). To proceed, we manipulate Eq. 21d so that we collect alike variables together and separate them from the other variables:

$$0 = \frac{d^2 f}{dy^2} - \frac{f^2}{M_T} \tag{22a}$$

$$\implies 0 = \frac{du}{dy} - \frac{f^2}{M_T} \qquad (\text{where } u \equiv df/dy) \tag{22b}$$

$$\implies 0 = \frac{du}{df}\frac{df}{dy} - \frac{f^2}{M_T} \tag{22c}$$

$$\implies 0 = u\frac{du}{df} - \frac{f^2}{M_T} \tag{22d}$$

$$\implies \frac{f^2}{M_T} df = u du \tag{22e}$$

We then integrate Eq. 22e to find a **general, steady-state solution f(y) to the reaction-diffusion equation with a second-order degradation (Eq. 21d)**:

$$\int \frac{f^2}{M_T} df = \int u du \tag{23a}$$

$$\implies \frac{2f^3}{3M_T} + A = u^2 \qquad (\text{where } A \text{ is a constant}) \tag{23b}$$

$$\implies -\sqrt{\frac{2f^3}{3M_T} + A} = \frac{df}{dy} \qquad (\text{take the negative root since } f \text{ should decrease}) \tag{23c}$$

These are complicated functions. Let's see if we can simplify them by using the two boundary conditions, Eqs. 10a- 10b. Applying the boundary condition at $y = L/\lambda_s$ (Eq. 10b) to Eq. 23c, we obtain

$$\left.\frac{df}{dy}\right|_{y=L/\lambda_s} = -\sqrt{\frac{2\epsilon^3}{3M_T} + A} \tag{24}$$

where $f(L/\lambda_s) = \epsilon = T_{rep}$ (by the argument given in the previous section on first-order degradation scenario). Let us assume that T_{rep} is very small. In fact, let us assume that $T_{rep} \approx 0$. Let us also assume that the embryo is sufficiently long that the morphogen has an extremely shallow gradient at $x = L$. That is,

$$\left.\frac{df}{dy}\right|_{y=L/\lambda_s} \approx 0 \tag{25}$$

Eq. 24 then becomes

$$A = 0 \tag{26}$$

Before moving on, note that our two assumptions here - (1) T_{rep} is a very small concentration (i.e., nearly but not exactly zero), and (2) L is sufficiently large that the morphogen gradient is very shallow (i.e., $df/dy|_{y=L/\lambda_s} \approx 0$) - are consistent with each other. We would indeed expect that a very long embryo to have an extremely low morphogen concentration and shallow morphogen gradient at the distal end ($x = L$). With $A = 0$, Eq. 23c is now simple to solve by integrating as follows:

$$\int dy = -\int df \sqrt{\frac{3M_T}{2f^3}} \tag{27a}$$

$$\implies y + B = \sqrt{6M_T} f^{-1/2} \qquad \text{(where } B \text{ is a constant)} \tag{27b}$$

$$\implies f(y) = \frac{6M_T}{(y+B)^2} \tag{27c}$$

$$\implies M_s(x) = \frac{6M_T}{(x/\lambda_s + B)^2} \qquad \text{(since } y = x/\lambda_s\text{)} \tag{27d}$$

$$= \frac{6M_T\lambda_s^2}{(x + \lambda_s B)^2} \tag{27e}$$

Applying the boundary condition at $y = 0$ (Eq. 10a) to Eq. 27c, we obtain

$$\frac{\lambda_s \eta_M}{D_M} = \frac{12M_T}{B^3} \tag{28a}$$

$$\implies B = \left(\frac{12M_T D_M}{\lambda_s \eta_M}\right)^{1/3} \tag{28b}$$

Finally, combining Eq. 27e with Eq. 28b yields

$$M_s(x) = \frac{6M_T D_M}{\alpha_M \left(x + \left(\frac{12M_T D_M^2}{\alpha_M \eta_M}\right)^{1/3}\right)^2} \tag{29a}$$

$$= \frac{6M_T D_M}{\alpha_M (x + C)^2} \qquad \left(\text{where } C \equiv \left(\frac{12M_T D_M^2}{\alpha_M \eta_M}\right)^{1/3}\right) \tag{29b}$$

Technically, we are done at this point. But it is unclear from Eq. 29b whether scaling occurs or not (and in fact, merely glancing at it suggests that no scaling occurs). This is because the equation does not contain any factors of L. Let rewrite Eq. 29b by explicitly showing all factors of L. To do this, recall that we had assumed that L is very large in Eq. 25. Specifically, we assume a large embryo so that Eq. 25 is satisfied and $L \gg C$. Then Eq. 29b, after applying the boundary condition $M_s(L) = T_{rep}$, becomes

$$M_s(L) \approx \frac{6M_T D_M}{\alpha_M L^2} \tag{30a}$$

$$\implies T_{rep} \approx \frac{6M_T D_M}{\alpha_M L^2} \tag{30b}$$

$$\implies L^2 = \frac{6M_T D_M}{\alpha_M T_{rep}} \tag{30c}$$

Then we use Eq. 30c to introduce a factor of L^2 in Eq. 29b:

$$M_s(x) \approx \frac{L^2 6 M_T D_M}{L^2 \alpha_M x^2} \tag{31a}$$

$$= \frac{6 M_T D_M}{\alpha_M L^2} \frac{1}{(x/L)^2} \tag{31b}$$

$$= \frac{T_{rep}}{(x/L)^2} \qquad \text{(by Eq. 30c)} \tag{31c}$$

Eq. 31c shows that the 2nd order degradation of the morphogen achieves a nearly perfect scaling (under the assumption that L is sufficiently large - "sufficiently large" means satisfying Eq. 25 and $L \gg C$).