International Journal of Heat and Mass Transfer 106 (2017) 570–572

Contents lists available at ScienceDirect

International Journal of Heat and Mass Transfer

journal homepage: www.elsevier.com/locate/ijhmt

Critical time scales for morphogen gradient formation: Concentration or gradient criteria?

Matthew J. Simpson

School of Mathematical Sciences, Queensland University of Technology, Brisbane 4001, Australia

ARTICLE INFO

Article history:
Received 2 June 2016
Received in revised form 8 September 2016
Accepted 9 September 2016
Available online 13 September 2016

Keywords:
Reaction–diffusion
Steady state
Transient
Critical time
Mean action time

ABSTRACT

We extend some recent analysis regarding an approximation of the time scale required for a transient morphogen concentration profile to approach steady state. Motivated by experimental observations, we consider the time scale required for the spatial gradient of morphogen concentration to approach steady state. The analysis shows that the spatial gradient approaches steady state faster than the associated concentration profile approaches steady state. For typical parameter values, this difference in time scales appears to be significant because it is comparable to the time scale of a typical experiment.

1. Introduction

Solutions of reaction–diffusion equations are typically classified as being either a transient solution, or a steady state (equilibrium) solution. The steady state solution of a reaction–diffusion equation is the long time limit of a particular transient solution. Strictly speaking, an infinite amount of time is required for a transient solution to reach steady state [1–3]. Unfortunately, this formal mathematical definition is impossible to implement for practical purposes because we can never wait for an infinite time to pass before we make use of a steady state solution. This observation has motivated many previous researchers to define a *critical time*, which is a finite estimate of the amount of time required for a transient solution of a reaction–diffusion equation to effectively reach steady state [1–3].

Some previous definitions of critical times involve obtaining both the transient and steady state solutions of the problem of interest and then defining the critical time to be the amount of time required for the transient solution to approach the steady state solution within some predefined tolerance [1–3]. In contrast, the concept of mean action time (MAT) has also been used as an estimate of the critical time for reaction–diffusion equations [4–7]. An attractive feature of using MAT as a critical time is that it can be calculated without explicitly calculating the transient solution of the reaction–diffusion equation [4–7].

The development of an embryo into a complex organism, characterised by different types of tissues, is thought to be driven by changes in cell type and cell function in different spatial locations during development [8,9]. This kind of spatial information is provided by concentration fields of molecules that are called *morphogens* [8,9]. It is widely thought that this kind of spatial information is controlled by reaction–diffusion mechanisms, and can therefore be predicted and understood in terms of mathematical models that describe reaction–diffusion processes [10–13]. Spatial gradients of morphogens were first proposed from a theoretical point of view without direct experimental evidence [8,9]. Subsequent experimental evidence supports the idea that spatial differences in morphogen concentration can control spatial information about cellular function during development [14]. In their 2005 study, Rogulja and Irvine [15] provide experimental evidence suggesting that the spatial gradient, or slope, of a morphogen concentration field regulates cell proliferation in developing tissues. The work of Rogulja and Irvine is important because it suggests that the spatial gradient, or shape, of the morphogen field is a key driver of development rather than the concentration of the morphogen. Since this discovery in 2005, there have been many further discoveries that provide additional insight into how morphogens regulate development [16,17]. A key question that is relevant to the study of how morphogens drive development is to determine the amount of time required for a morphogen field to develop from an underlying reaction–diffusion process. This question has been addressed in terms of examining the amount of time required for a morphogen profile to effectively reach steady state

E-mail address: matthew.simpson@qut.edu.au

http://dx.doi.org/10.1016/j.ijheatmasstransfer.2016.09.026
0017-9310/

[10,11], and in the current work we examine the question of how long does it take for the shape of the morphogen profile to effectively reach steady state.

In this work we will use MAT as a critical time for of a mathematical model of morphogen gradient formation. In particular, we will explore the question of whether the critical time for the concentration profile, $c(x,t)$, is different to the critical time for the spatial gradient of the concentration profile, $\partial c(x,t)/\partial x$.

2. Results and discussion

The spatio-temporal evolution of a morphogen concentration profile is typically modeled using

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc, \tag{1}$$

where $c(x,t)$ is the morphogen concentration, $D > 0$ is the diffusivity and $k > 0$ is the decay rate [10,12]. To approximate the time taken for the initial concentration profile, $c_0(x) = c(x,0)$, to effectively reach the steady state solution, $c_\infty(x) = \lim_{t\to\infty} c(x,t)$, we make use of the following definitions

$$F(t;x) = 1 - \left[\frac{c(x,t) - c_{\infty(x)}}{c_0(x) - c_\infty(x)}\right], \tag{2}$$

$$f(t;x) = \frac{\mathrm{d}F(t;x)}{\mathrm{d}t} = -\frac{\partial}{\partial t}\left[\frac{c(x,t) - c_{\infty(x)}}{c_0(x) - c_\infty(x)}\right], \tag{3}$$

for which we have $F(0;x) = 0$ and $\lim_{t\to\infty} F(t;x) = 1^-$. For many transitions $F(t;x)$ increases monotonically with t so we can interpret $F(t;x)$ as a cumulative distribution function [5–7]. The mean of the probability density function, $f(t;x)$, which can be written as

$$T(x) = \int_0^\infty t f(t;x)\,\mathrm{d}t, \tag{4}$$

is known as the MAT [4]. The MAT provides us with a finite estimate of the amount of time taken for the transient solution of the reaction–diffusion equation to effectively asymptote to the corresponding steady state solution. One of the benefits of working with MAT is that it is possible to solve for $T(x)$ using $c_0(x)$ and $c_\infty(x)$ alone, without needing to solve for the transient solution of Eq. (1), $c(x,t)$ [4–6].

The aim of this technical note is to apply Eq. (1) to model the formation of a morphogen gradient profile and to examine whether the MAT for $c(x,t)$ is different to the MAT for $\partial c(x,t)/\partial x$.

2.1. Concentration criteria

To model the spatial evolution of a morphogen concentration profile we consider Eq. (1) on $0 \leqslant x < \infty$. With $c_0(x) = 0, \lim_{x\to\infty} c(x,t) = 0$ and $\partial c/\partial x = -Q/D$ at $x = 0$, we have $c_\infty(x) = Q\mathrm{e}^{-x\sqrt{k/D}}/\sqrt{Dk}$ [10,11]. Typical $c_0(x)$ and $c_\infty(x)$ profiles are shown in Fig. 1(a).

To solve for $T(x)$, we apply integration by parts to Eq. (4), giving

$$T(x) = \frac{1}{h_1(x)}\int_0^\infty c_\infty(x) - c(x,t)\,\mathrm{d}t, \tag{5}$$

where we define $h_1(x) = c_\infty(x) - c_0(x)$ for notational convenience. To arrive at this expression for $T(x)$ we make use of the fact that $c(x,t) - c_\infty(x)$ decays to zero exponentially fast as $t \to \infty$ [5,6]. Differentiating Eq. (5) twice with respect to x gives

$$(T(x)h_1(x))' = \int_0^\infty c'_\infty(x) - \frac{\partial c}{\partial x}\,\mathrm{d}t, \tag{6}$$

$$(T(x)h_1(x))'' = \int_0^\infty c''_\infty(x) - \frac{\partial^2 c}{\partial x^2}\,\mathrm{d}t, \tag{7}$$

where the prime notation indicates ordinary differentiation with respect to x. Combining Eqs. (6) and (7) with Eq. (1) leads to a boundary value problem

$$D(T(x)c_\infty(x))'' - kT(x)c_\infty(x) = -c_\infty(x), \tag{8}$$

where, in this case with $c_0(x) = 0$, we have $h_1(x) = c_\infty(x)$. The boundary condition at $x \to \infty$ is given by Eq. (5) which implies that we have $\lim_{x\to\infty}(T(x)c_\infty(x)) = 0$. The boundary condition at $x = 0$ is given by Eq. (6) which implies that we have $(T(0)c_\infty(0))' = 0$. With these boundary conditions and our expression for $c_\infty(x)$, the solution of Eq. (8) is

$$T(x) = \frac{1}{2k} + \frac{x}{\sqrt{4kD}}, \tag{9}$$

which shows how the MAT depends on position, x, and the parameters in Eq. (1), D and k.

2.2. Gradient criteria

Instead of focusing on the morphogen concentration, $c(x,t)$, some experimental evidence suggests that the spatial gradient, $\partial c(x,t)/\partial x$, plays a key role in regularing development [15]. The aim of this techical note is to examine, and compare, $T(x)$ associated with $\partial c(x,t)/\partial x$ with $T(x)$ associated with $c(x,t)$, for the same physical problem. Eq. (1) is invariant under the transformation $g(x,t) = \partial c(x,t)/\partial x$, so we have

$$\frac{\partial g}{\partial t} = D\frac{\partial^2 g}{\partial x^2} - kg. \tag{10}$$

Transforming the initial and boundary conditions gives $g_0(x) = 0, \lim_{x\to\infty} g(x,t) = 0$ and $g(0,t) = -Q/D$, which in turn gives the steady state profile as $g_\infty(x) = -Q\mathrm{e}^{-x\sqrt{k/D}}/D$. Profiles in Fig. 1 (b) show $g_0(x)$ and $g_\infty(x)$ for the transition previously depicted in Fig. 1(a).

To calculate the MAT for the transition in terms of the gradient variable, $g(x,t)$, we repeat the same calculation that we performed previously except now the expressions for the steady state solution, $g_\infty(x)$, is different. Applying integration by parts to Eq. (4) gives

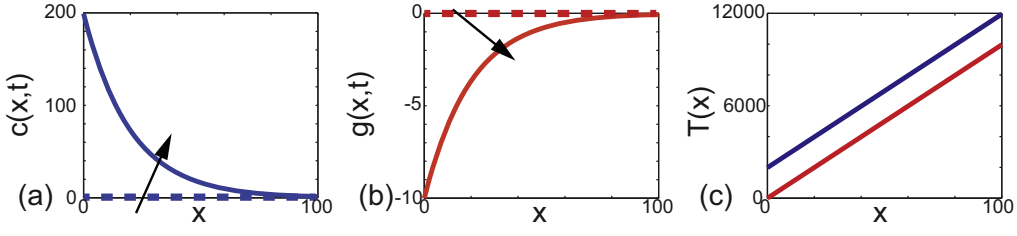

Fig. 1. (a) $c_0(x)$ (dashed blue), $c_\infty(x)$ (solid blue); (b) $g_0(x)$ (dashed red), $g_\infty(x)$ (solid red); (c) $T(x)$ for concentration criteria (blue) and gradient criteria (red). $D = 0.1\ \mu\mathrm{m}^2\mathrm{s}^{-1}$, $k = 2.5 \times 10^{-4}\ \mathrm{s}^{-1}$ [13], $Q = 1$. Physical scales are μm and s. (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this article.)

$$T(x) = \frac{1}{h_2(x)} \int_0^\infty g_\infty(x) - g(x,t)\,\mathrm{d}t, \tag{11}$$

where, in this case, we have $h_2(x) = g_\infty(x) - g_0(x)$ and we note that $g(x,t) - g_\infty(x)$ approaches zero exponentially fast as $t \to \infty$ [5,6]. Differentiating Eq. (11) twice with respect to x to give

$$(T(x)h_2(x))' = \int_0^\infty g'_\infty(x) - \frac{\partial g}{\partial x}\,\mathrm{d}t, \tag{12}$$

$$(T(x)h_2(x))'' = \int_0^\infty g''_\infty(x) - \frac{\partial^2 g}{\partial x^2}\,\mathrm{d}t. \tag{13}$$

Combining Eqs. (12) and (13) with Eq. (10) leads to

$$D(T(x)g_\infty(x))'' - kT(x)g_\infty(x) = -g_\infty(x), \tag{14}$$

where, in this case with $g_0(x) = 0$, we have $h_2(x) = g_\infty(x)$. Since we apply a Dirichlet boundary condition at $x = 0$, we have $T(0) = 0$ [18]. The boundary condition at $x \to \infty$ is given by Eq. (11) which implies that we have $\lim_{x\to\infty}(T(x)g_\infty(x)) = 0$. With these boundary conditions and our expression for $g_\infty(x)$, the solution of Eq. (14) is

$$T(x) = \frac{x}{\sqrt{4kD}}. \tag{15}$$

Comparing Eq. (9) with Eq. (15), we see that the MAT for $c_0(x)$ to approach $c_\infty(x)$ is always greater than the MAT for $g_0(x)$ to approach $g_\infty(x)$. This difference is precisely $1/(2k)$, and the difference in time scale does not depend on position, x. Using Kicheva's parameter estimates ($D = 0.1\ \mu\mathrm{m}^2\,\mathrm{s}^{-1}$, $k = 2.5 \times 10^{-4}\ \mathrm{s}^{-1}$) [13], the analysis indicates that $g(x,t)$ becomes effectively steady approximately 2000 s before $c(x,t)$ (Fig. 1(c)). Since this difference is comparable to the time scale of Kicheva's experiments [13], it appears to be an experimentally significant difference.

3. Conclusions

In summary, we have shown that the same mathematical technique used to approximate the amount of time taken for $c_0(x)$ to approach $c_\infty(x)$ can also be used to approximate the amount of time taken for $g_0(x)$ to approach $g_\infty(x)$, where $g(x,t) = \partial c(x,t)/\partial x$. Given that certain experiments indicate that the spatial gradient of morphogen concentration can play an important role in regulating development [15], we suggest that any analysis of $T(x)$ associated with concentration data ought to be compared with estimates of $T(x)$ for concentration gradient data since previous parameter estimates indicate that the difference between $T(x)$ based on these different criteria can be significant because the difference in time scales is comparable to typical experimental time scales.

Acknowledgments

This work is supported by the Australian Research Council (FT130100148). I thank Emeritus Professor DL Sean McElwain for pointing out the relationship between Eqs. (1) and (10), and I appreciate the helpful comments of two referees.

References

[1] R.I. Hickson, S.I. Barry, G.N. Mercer, Critical times in multilayer diffusion. Part I: exact solutions, Int. J. Heat Mass Transfer 52 (2009) 5776.
[2] R.I. Hickson, S.I. Barry, G.N. Mercer, Critical times in multilayer diffusion. Part II: approximate solutions, Int. J. Heat Mass Transfer 52 (2009) 5784.
[3] R.I. Hickson, S.I. Barry, H.S. Sidhu, G.N. Mercer, Critical times in single-layer reaction diffusion, Int. J. Heat Mass Transfer 54 (2011) 2642.
[4] A. McNabb, G.C. Wake, Heat conduction and finite measures for transition times between steady states, IMA J. Appl. Math. 47 (1991) 193.
[5] A.J. Ellery, M.J. Simpson, S.W. McCue, R.E. Baker, Critical time scales for advection-diffusion-reaction processes, Phys. Rev. E. 85 (2012) 041135.
[6] A.J. Ellery, M.J. Simpson, S.W. McCue, R.E. Baker, Moments of action provide insight into critical times for advection–diffusion–reaction processes, Phys. Rev. E. 86 (2012) 031136.
[7] M.J. Simpson, F. Jazaei, T.P. Clement, How long does it take for aquifer recharge or aquifer discharge processes to reach steady state?, J Hydrol. 501 (2013) 241.
[8] L. Wolpert, Positional information and the spatial pattern of cellular differentiation, J. Theor. Biol. 25 (1969) 1.
[9] F. Crick, Diffusion in embryogeneis, Nature 225 (1970) 420.
[10] A.M. Berezhkovskii, C. Sample, S.Y. Shvartsman, How long does it take to establish a morphogen gradient?, Biophys J. (2010) 99; L59.
[11] A.M. Berezhkovskii, C. Sample, S.Y. Shvartsman, Formation of morphogen gradients: local accumulation time, Phys. Rev. E (2011) 83, 051906.
[12] A.B. Kolomeisky, Formation of a morphogen gradient: acceleration by degradation, Phys. Chem. Lett. 2 (2011) 1502.
[13] A. Kicheva, P. Pantazis, T. Bollenbach, Y. Kalaidzidis, T. Bittig, F. Julicher, M. Gonzalez-Gaitan, Kinetics of morphogen gradient formation, Science 315 (2007) 521.
[14] H. Ashe, J. Briscoe, The interpretation of morphogen gradients, Development 133 (2006) 385.
[15] D. Rogulja, K.D. Irvine, Regulation of cell proliferation by a morphogen gradient, Cell 123 (2005) 449.
[16] J. Briscoe, S. Small, Morphogen rules: design principles of gradient-mediated embryo patterning, Development 142 (2015) 3996.
[17] T. Akiyama, M.C. Gibson, Decapentaplegic and growth control in the developing Drosophila wing, Nature 527 (2015) 325.
[18] F. Jazaei, M.J. Simpson, T.P. Clement, An analytical framework for quantifying aquifer response time scales associated with transient boundary conditions, J. Hydrol. 519 (2014) 1642.