数理解析研究所講究録
第1704巻 2010年 138-142

成長するドメインにおける、遺伝子発現の時間遅れがパターン形成に与える影響について

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1 はじめに

Turing's pattern formation mechanism exhibits sensitivity to the details of the initial conditions suggesting that, in isolation, it cannot robustly generate pattern within noisy biological environments. Nonetheless, secondary aspects of developmental self-organisation, such as a growing domain, have been shown to ameliorate this aberrant model behaviour. Furthermore, while in-situ hybridisation reveals the presence of gene expression in developmental processes, the influence of such dynamics on Turing's model has received limited attention. Here, we novelly focus on the Gierer-Meinhardt reaction diffusion system considering delays due the time taken for gene expression, while incorporating a number of different domain growth profiles to further explore the influence and interplay of domain growth and gene expression on Turing's mechanism. We find extensive pathological model behaviour, exhibiting one or more of the following: temporal oscillations with no spatial structure, a failure of the Turing instability and an extreme sensitivity to the initial conditions, the growth profile and the duration of gene expression. Our results emphasise that gene expression dynamics induce unrealistic behaviour in Turing's model for multiple choices of kinetics and thus such aberrant modelling predictions are likely to be generic. They also highlight that domain growth can no longer ameliorate the excessive sensitivity of Turing's mechanism in the presence of gene expression time delays. The above, extensive, pathologies suggest that, in the presence of gene expression, Turing's mechanism would generally require a novel and extensive secondary mechanism to control reaction diffusion patterning.

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2 モデル

Consider a uniformly growing one dimensional domain, $x \in [0, L_0 L(t)]$, where L_0 is the initial domain length and $L_0 L(t)$ is the domain length, an increasing function of time, with $L(0) = 1$. Let c_p denote the p^{th} biochemical concentration, $p \in \{1, 2\}$, for a general two component reaction-diffusion system. On the above domain, standard conservation arguments give (Crampin et al., 1999)

$$\frac{\partial c_p}{\partial t} + \frac{\partial}{\partial x}(\alpha(x,t)c_p) = \sum_{q=1,2} \frac{\partial}{\partial x}\left(\mathcal{D}_{pq}\frac{\partial c_q}{\partial x}\right) + F_p(\boldsymbol{c}(x,t)),$$

where $F_p(\boldsymbol{c}(x,t))$ denotes the reaction kinetics, $\alpha(x,t)$ is the domain growth velocity field and $\mathcal{D}_{pq}$ are the components of a diffusion matrix. The latter is taken to be constant and diagonal below and is written in the form $\mathcal{D}_{pq} = \mathrm{diag}(\epsilon^2 D, D)$ with $\epsilon < 1$; this bound entails that c_1 has the shorter spatial range of the morphogens and is thus the activator.

Gene expression time delay models are influenced at location (x,t) by the gene expression instigated within the cells a time τ earlier, where τ is the gene expression time delay. However, due to domain growth, these cells were not at spatial location x at time $t - \tau$. Instead these cells were previously located at x_τ; an explicit expression can be found by backtracking along the characteristic generated by the velocity vector field starting at (x,t) (Gaffney and Monk, 2006). However, an explicit expression is not required below due to the consideration of Lagrangian coordinates.

In the presence of gene expression time delays, we thus have the reaction term $F_p(\boldsymbol{c}(x,t))$ generalises to

$$F_p(\boldsymbol{c}(x,t), \boldsymbol{c}(x_\tau, t-\tau)).$$

For convenience we relabel $(c_1, c_2) \to (u, v)$, and $(F_1, F_2) \to (f, g)$. We non-dimensionalise concentrations by $(\hat{u}, \hat{v}) = (Uu, Vv)$, length via $\hat{x} = x/L_0 \in [0, L(t)]$, time by $\hat{t} = t/T_S$, and the velocity vector field by $\hat{\alpha} = T_s\alpha/L_0$. Then the reaction diffusion system, with gene expression time delays, reduces to the form

$$\begin{aligned}
\frac{\partial u}{\partial t} + \alpha\frac{\partial u}{\partial x} &= \frac{\epsilon^2 T_s D}{L_0^2}\frac{\partial^2 u}{\partial x^2} + \gamma f(u(x,t), v(x,t), u(x_\tau, t-\tau), v(x_\tau, t-\tau)) - \frac{\partial \alpha}{\partial x}u, \\
\frac{\partial v}{\partial t} + \alpha\frac{\partial v}{\partial x} &= \frac{T_s D}{L_0^2}\frac{\partial^2 v}{\partial x^2} + \gamma g(u(x,t), v(x,t), u(x_\tau, t-\tau), v(x_\tau, t-\tau)) - \frac{\partial \alpha}{\partial x}v,
\end{aligned} \tag{1}$$

where γ is a constant and hats are dropped for convenience.

Following Crampin et al. (1999), consider Lagrangian coordinates (X,t) where X is the initial position of a tissue element moving with the flow α. The movement of tissue as a result of growth can be described in terms of the mapping between the Eulerian coordinate, x, and the Lagrangian coordinate X:

$$x = \Gamma(X,t), \quad \Gamma(X,0) = X \in [0,1], \quad \Gamma(0,t) = 0 \ \text{ for } t > 0.$$

Uniform growth implies $x = \Gamma(X,t) = X L(t)$ and hence

$$\alpha(x,t) = X\dot{L}(t) = x\frac{\dot{L}(t)}{L(t)} \tag{2}$$

with the fractional dilation rate given by

$$\frac{\partial \alpha}{\partial x} = \frac{\dot{L}(t)}{L(t)}.$$

Now we transform the spatial coordinates to the unit interval via the mapping

$$(x(t), t) \to \left(\frac{x(t)}{L(t)}, t\right) = (\bar{x}, t) \text{ where } \frac{x(t)}{L(t)} \in [0, 1]. \tag{3}$$

Note that $x(t-\tau)/L(t-\tau) = X = x(t)/L(t)$ from (2). The fact the Lagrangian coordinate is time invariant, by construction, implies $\bar{x} = \bar{x}_\tau$. Thus on implementing the above mapping one finds

$$(u(x_\tau, t-\tau), v(x_\tau, t-\tau)) \xrightarrow{(3)} (u(\bar{x}, t-\tau), v(\bar{x}, t-\tau)) \stackrel{def}{=} (u_\tau, v_\tau).$$

In addition the first order convective terms cancel in the reaction diffusion equations. Hence the gene expression time delay system (1) can be expressed in the form

$$\begin{aligned} \frac{\partial u}{\partial t} &= \frac{\epsilon^2 d}{L^2(t)} \frac{\partial^2 u}{\partial x^2} + \gamma f(u, v, u_\tau, v_\tau) - S(t)u, \\ \frac{\partial v}{\partial t} &= \frac{d}{L^2(t)} \frac{\partial^2 v}{\partial x^2} + \gamma g(u, v, u_\tau, v_\tau) - S(t)v, \end{aligned} \tag{4}$$

where bars are once more dropped for convenience, $x \in [0, 1]$, $d = T_s D/L_0^2$ and domain dilation also dictates the rate of biochemical dilution via $S(t) = \dot{L}(t)/L(t)$.

For the specific kinetic functions and growth rate functions, see Seirin-Lee et al. (2010); Crampin et al. (1999).

3 結果

In the absence of time delays this model once more reproduces a self-similar cascade of peak insertion patterning. For very small gene expression time delays one instead finds a self-similar cascade of peak splitting; this is depicted in plots **1a**, **1a1**. As the gene expression time delay is increased even slightly, temporal oscillations occur and the self-similar cascade, and indeed all spatial structure, is lost as illustrated in plots **1a3**, **1a4**. This also occurs for linear and logistic growth (results not shown). In contrast to the ligand internalisation models, the patterning lags and sensitivity are not as profound, but the loss of spatial structure entails that patterning cannot emerge regardless.

Our results emphasise that previously observed pathologies are not limited to a special choice of kinetics or representation of the gene expression dynamics and are therefore more likely to be generic. Nonetheless, different choice of kinetics and sub-cellular dynamics do yield different modelling predictions. Hence we also no longer have the expectation that all systems exhibiting a Turing instability will behave in a remotely similar way on a growing domain given gene expression dynamics. This is also important in constructing models of developmental self-organisation on growing domains, as it is clear that choosing the simplest

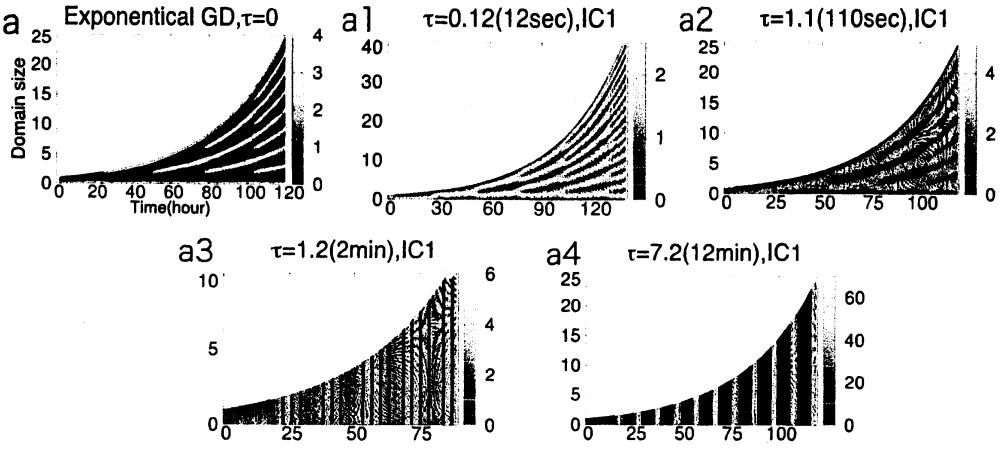

Figure 1: **Model I-S**. In the above plots results are presented for Model I-S, where morphogen-cell interactions are instigated on the cell surface via reversible ligand binding, with saturation of activator induced activator production. The horizontal axis in all plots represents time, in units of hours, and the vertical axis gives the domain size, in units of the initial domain length which corresponds to 10^{-2}cm or approximately 10 cell lengths. The label IC1 denotes the time-independent initial condition. The domain is exponentially growing with a growth parameter of $\delta_{exp} = 0.0015$ which corresponds to a doubling time of approximately 25 hours using the timescale $T_s = 100$ seconds. Finally note that the non-dimensionalised gene expression time delay, τ, is given above each plot with its dimensional size in brackets.

kinetics, a common strategy as illustrated in Miura et al. (2006), is inappropriate. Further, investigations of the Turing space for a given choice of kinetics, even for growing domains, such as those derived and considered in Alber et al. (2008) for limb self-organisation, should assess numerous additional factors given the presence of gene expression. These include the prospect of excessive patterning lags, the possibility of oscillations and extreme sensitivity, to the initial conditions, to the domain growth profile, to the representation of the signal transduction dynamics and, finally, to the duration of the gene expression time delay.

References

Alber, M., Glimm, T., Hentschel, H., Kazmierczakd, B., Zhanga, Y., Zhua, J., Newman, S., 2008. The morphostatic limit for a model of skeletal pattern formation in the vertebrate limb. Bull. Math. Biol. 70, 460–483.

Crampin, E. J., Gaffney, E. A., Maini, P. K., 1999. Reaction and diffusion on growing domains: Scenarios for robust pattern formation. Bull. Math. Biol. 61, 1093–1120.

Gaffney, E. A., Monk, N. A. M., 2006. Gene expression time delays and Turing pattern formation systems. Bull. Math. Bio 68, 99–130.

Miura, T., Shiota, K., Morriss-Kay, G., Maini, P. K., 2006. Mixed-mode pattern in

Doublefoot mutant mouse limb-Turing reaction-diffusion model on a growing domain during limb development. J. Theor. Biol. 240, 562–573.

Seirin-Lee, S., Gaffney, E. A., Monk, N. A. M., 2010. The influence of gene expression time delays on Gierer-Meinhardt pattern formation systems. Bull. Math. Biol., DOI10.1007/s11538–010–9532–5.