Metric dynamics for membrane transformation through regulated cell proliferation

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Abstract

This study develops an equation for describing three-dimensional membrane transformation through proliferation of its component cells regulated by morphogen density distributions on the membrane. The equation is developed in a two-dimensional coordinate system mapped on the membrane, referred to as the membrane coordinates. When the membrane expands, the membrane coordinates expand in the same manner so that the membrane is invariant in the coordinates. In the membrane coordinate system, the transformation of membrane is described with a time-derivative equation for metric tensors. By defining relationships between morphogen density distributions and the direction and rate of cell division, trajectories of membrane transformation are obtained in terms of the morphogen distributions. An example of the membrane transformation is shown numerically.

1 Introduction

Arthropods have diverse morphologies (Regier et al., 2010). Those morphologies are made by molting; new epidermis can have significantly different shape from the old ones through morphogen-regulated proliferation and/or apoptosis of the component cells (Warren et al., 2013). While understandings of gene networks for the regulation have been accumulating rapidly, it is still not clear how the three-dimensional morphologies of epidermis are generated by morphogen distributions on it. For efficient investigation on the mechanism underlying this process, this study develops an equation for metric dynamics describing three-dimensional transformation of a membrane (corresponding to the new epidermis) through proliferation of its component cells regulated by morphogen density distributions on it. A unit element in this equation, referred to as the metric-dynamics equation, is a (sufficiently) small domain of a membrane, which still has many cells. In
Numerical calculation of the metric-dynamics equation may be more efficient than the approaches explicitly describing cell divisions.

This paper is structured as follows. Section 2 derives the metric-dynamics equation. Section 3 numerically shows development of a horn-like structure, as an application example. Section 4 discusses strong and weak points of the equation.

2 Derivations of metric-dynamics equation

We assume three-dimensional Euclidean coordinate system $\mathbf{R} = (X, Y, Z)^T$ and a membrane sheet expressed as a two-dimensional flat plane $Z = 0$. On the plane, we map a two-dimensional coordinate system $\mathbf{r} = (x, y)^T$. When the membrane sheet shrinks, expands and/or be bent, this coordinate system also changes in the same manner, so that in this membrane coordinates the membrane sheet is invariant. Thus, any point in the membrane coordinate system does not change its position through the dynamics. In other words, in this coordinate system cell division is not followed by growth of the divided cells.

2.1 Metric tensor based on cellular distance

The membrane is expressed as $\mathbf{R}(\mathbf{r}) = (X(\mathbf{r}), Y(\mathbf{r}), Z(\mathbf{r}))^T$. We assume that $\mathbf{R}(\mathbf{r}) = (x, y, 0)^T$ holds at the initial state. As cell proliferation proceeds, $(X(\mathbf{r}), Y(\mathbf{r}))^T$ deviates from $(x, y)^T$, and $Z(\mathbf{r})$ deviates from the flat plane $Z(\mathbf{r}) = 0$.

We assume that in coordinate system $\mathbf{R}$ the average cell of any small (but still sufficiently large for having many cells) region on the membrane is isotropic and its diameter is equal to a positive constant $\sigma (\ll 1)$, i.e., isometric embedding. Then, the number $\Delta l$ of cells penetrated by the line segment between $\mathbf{R}$ and $\mathbf{R} + \Delta \mathbf{R}$ on the membrane is expressed as $|\Delta \mathbf{R}|/\sigma$ with an additional isotropic-scaling of axes. Then a cellular distance $\sigma \Delta l$ can be expressed with the corresponding two points $\mathbf{r}$ and $\mathbf{r} + \Delta \mathbf{r}$ as

$$
\sigma^2 \Delta t^2 = a \Delta x^2 + 2ab \Delta x \Delta y + c \Delta y^2
= \begin{pmatrix} \Delta x \\ \Delta y \end{pmatrix}^T \begin{pmatrix} a & b \\ b & c \end{pmatrix} \begin{pmatrix} \Delta x \\ \Delta y \end{pmatrix}
= \Delta \mathbf{r}^T G \Delta \mathbf{r}
= \Delta \mathbf{r}^T W^T W \Delta \mathbf{r}
$$

by choosing appropriate coefficients $a, b, \text{and} c$, where a symmetric matrix $G = W^T W$ is the metric tensor at $\mathbf{r}$, and $W$ is its Cholesky decomposition.

With the metric, we introduce a two-dimensional locally geodesic coordinates $\hat{\mathbf{r}}$ around an arbitrary point $\hat{\mathbf{r}}$,

$$
\hat{\mathbf{r}} - \hat{\mathbf{r}} = W \left[ (\mathbf{r} - \hat{\mathbf{r}}) + \frac{1}{2} \begin{pmatrix} (\mathbf{r} - \hat{\mathbf{r}})^T \Gamma^x (\mathbf{r} - \hat{\mathbf{r}}) \\ (\mathbf{r} - \hat{\mathbf{r}})^T \Gamma^y (\mathbf{r} - \hat{\mathbf{r}}) \end{pmatrix} \right],
$$

$$
\mathbf{r} - \hat{\mathbf{r}} = W^{-1} (\mathbf{r} - \hat{\mathbf{r}}) - \frac{1}{2} \begin{pmatrix} [W^{-1}(\mathbf{r} - \hat{\mathbf{r}})]^T \Gamma^x [W^{-1}(\mathbf{r} - \hat{\mathbf{r}})] + \ldots \\ [W^{-1}(\mathbf{r} - \hat{\mathbf{r}})]^T \Gamma^y [W^{-1}(\mathbf{r} - \hat{\mathbf{r}})] + \ldots \end{pmatrix},
$$

(2)
with \( \Gamma^x \) and \( \Gamma^y \) that contain Christoffel symbols of the second kind,

\[
\Gamma^x = \begin{pmatrix}
\Gamma_{xx}^x & \Gamma_{xy}^x \\
\Gamma_{yx}^x & \Gamma_{yy}^x
\end{pmatrix},
\Gamma^y = \begin{pmatrix}
\Gamma_{xx}^y & \Gamma_{xy}^y \\
\Gamma_{yx}^y & \Gamma_{yy}^y
\end{pmatrix},
\Gamma_{ji}^k = \sum_m \frac{1}{2} G_{km}^{-1} \left( \frac{\partial G_{im}}{\partial x_j} + \frac{\partial G_{jm}}{\partial x_i} - \frac{\partial G_{ji}}{\partial x_m} \right),
\]

(3)

where \( G_{km}^{-1} \) is \((k, m)\) component of \( G^{-1}\) and \( G_{im} \) is \((i, m)\) component of \( G\).

Then in coordinate system \( \tilde{\mathbf{r}} \) the average cell is isotropic with constant diameter in the neighborhood of \( \hat{\mathbf{r}} \), where \( \sigma^2 \Delta l^2 = |\Delta \tilde{\mathbf{r}}|^2 \) holds. From Eqs. (2) we see at an arbitrary position \( \hat{\mathbf{r}} \)

\[
\nabla_{\hat{\mathbf{r}}} \mathbf{r} = \tilde{\nabla} \mathbf{r} = W^{-1},
\nabla_{\hat{\mathbf{r}}} \tilde{\mathbf{r}} = \nabla \tilde{\mathbf{r}} = W,
\]

(4)

where \( \tilde{\nabla} \) and \( \nabla \) mean \( \nabla_{\hat{\mathbf{r}}} \) and \( \nabla_{\mathbf{r}} \), respectively.

### 2.2 Membrane transformation induced by morphogen distribution

We assume two types of morphogens: \( \alpha \) and \( \eta \). Their density distributions on the membrane are described in \( \mathbf{r} \), as \( \alpha(\mathbf{r}) \) and \( \eta(\mathbf{r}) \). Morphogens \( \alpha \) and \( \eta \) control directed and non-directed cell division, respectively. For \( \alpha \), we assume that directed cell division occurs in the direction of gradient of \( \alpha \) in coordinate system \( \tilde{\mathbf{r}} \), denoted by \( \tilde{\nabla} \tilde{\alpha} \), with its rate proportional to \( b(\tilde{\nabla} \tilde{\alpha}) \). For \( \eta \), the rate of non-directed division is assumed to be proportional to \( \eta(\mathbf{r}) \).

Then from time \( t \) to \( t' = t + \Delta t \), \( \Delta \tilde{\mathbf{r}} \) changes into \( \Delta \tilde{\mathbf{r}}' \), satisfying

\[
\Delta \tilde{\mathbf{r}}' = \left[ I + \left( c_\alpha b(|\tilde{\nabla} \tilde{\alpha}|) \frac{\tilde{\nabla} \tilde{\alpha} \tilde{\nabla} \tilde{\alpha}^T}{|\tilde{\nabla} \tilde{\alpha}|^2} + c_\eta I \right) \Delta t \right] \Delta \tilde{\mathbf{r}}
\]

(5)

with proportionality coefficients \( c_\alpha \) and \( c_\eta \), where \( (\mathbf{r}) \) is omitted. Without loss of generality, we assume that \( \alpha(\mathbf{r}) \) and \( \eta(\mathbf{r}) \) are scaled so that \( c_\alpha = c_\eta = 1 \). The cellular distance between \( \mathbf{r} \) and \( \mathbf{r} + \Delta \mathbf{r} \) at \( t' = t + \Delta t \) is given by

\[
\sigma^2 \Delta l'^2 = \Delta \tilde{\mathbf{r}}'^T \Delta \tilde{\mathbf{r}}' = \Delta \tilde{\mathbf{r}}'^T [I + A \Delta t]^T [I + A \Delta t] \Delta \tilde{\mathbf{r}}.
\]

(6)

### 2.3 Metric dynamics in membrane coordinate system

To express Eq. (6) in the membrane coordinate system, we express density distribution of \( \alpha \) in coordinate system \( \tilde{\mathbf{r}} \) as

\[
\tilde{\alpha}(\tilde{\mathbf{r}}) = \frac{\alpha(\mathbf{r})}{\|W\|} = \frac{\alpha(W^{-1} \tilde{\mathbf{r}} + \ldots)}{\|W\|}.
\]

(7)
which gives a relationship
\[ \nabla \tilde{\alpha} = \nabla_{\hat{r}} \tilde{\alpha} = \frac{\nabla_{\hat{r}}^{\alpha}(W^{-1} \hat{r} + \ldots)}{\|W\|} = \frac{1}{\|W\|} \nabla_{\hat{r}}^{T} r \nabla_{r} \alpha = \frac{1}{\|W\|} W^{-1} \nabla_{r} \alpha. \] (8)

Here we assume that
\[ b(|\nabla \tilde{\alpha}|) = \|G\| |\nabla \tilde{\alpha}|^2, \] (9)

which gives a simple result as follows. Substituting Eqs. (8) and (9) into Eq. (5) gives
\[ A = W^{-1} \nabla_{\alpha} \nabla_{\alpha}^{T} W^{-1} + \eta I, \] (10)

which upon substitution into Eq. (6) gives
\[ \sigma^2 \Delta t^2 = \Delta r^{T} W^{T} [(1 + 2\eta \Delta t) I + 2W^{-1} \nabla_{\alpha} \nabla_{\alpha}^{T} W^{-1} \Delta t + O(\Delta t^2)] W \Delta r \]
\[ = \Delta r^{T} [(1 + 2\eta \Delta t) G + 2\nabla_{\alpha} \nabla_{\alpha}^{T} \Delta t + O(\Delta t^2)] \Delta r \]
\[ = \Delta r^{T} [G + 2(\eta G + \nabla_{\alpha} \nabla_{\alpha}^{T}) \Delta t + O(\Delta t^2)] \Delta r \]
\[ = \Delta r^{T} G' \Delta r. \] (11)

Therefore, the time derivative of metric \( G \) is obtained as
\[ \frac{dG}{dt} = \lim_{\Delta t \to 0} \frac{G' - G}{\Delta t} = 2\eta G + 2\nabla_{\alpha} \nabla_{\alpha}^{T}. \] (12)

From this equation, the time derivative of linear cell density \( q(e) = \sqrt{e^{T} G e} \), which is the multiplication of \( \sigma \) by the number of cells penetrated by unit vector \( e \) in coordinate system \( r \), is given by
\[ \frac{dq(e)^2}{dt} = e^{T} \frac{dG}{dt} e = 2e^{T} [\eta G + \nabla_{\alpha} \nabla_{\alpha}^{T}] e, \] (13)
\[ \frac{dq(e)}{dt} = \frac{1}{q(e)} e^{T} [\eta G + \nabla_{\alpha} \nabla_{\alpha}^{T}] e. \] (14)

### 2.4 Solution of metric-dynamics equation

Solving Eq. (12) gives the metric and linear cell density after cell proliferation from time \( t = 0 \) to an arbitrary \( t = \tau \),
\[ G(\tau) = e^{2\eta \tau} \left[ \int_{0}^{\tau} 2\nabla_{\alpha} \nabla_{\alpha}^{T} e^{-2\eta t} dt + G_{0} \right], \] (15)
\[ q^2(e, \tau) = e^{T} G(\tau) e. \] (16)

with \( G_{0} = G(0) \). If \( \eta \) and \( \nabla_{\alpha} \) is constant along time, Eq. (15) is simplified into
\[ G(\tau) = \begin{cases} 
    \left[ G_{0} + \frac{\nabla_{\alpha} \nabla_{\alpha}^{T}}{\eta} \right] \exp(2\eta \tau) - \frac{\nabla_{\alpha} \nabla_{\alpha}^{T}}{\eta} & \text{for } \eta \neq 0 \\
    G_{0} + 2\tau \nabla_{\alpha} \nabla_{\alpha}^{T} & \text{for } \eta = 0.
\end{cases} \] (17)

To see the shape of the membrane given by Eq. (17), we consider that \( \alpha(r) \) is expressed in coordinate system \( R \) as a two-dimensional surface \( R_{a} = (x, y, \alpha(r))^{T} \). Then
distance between the two points on the surface, \( R_\alpha \) and \( R_\alpha + \Delta R_\alpha \) (corresponding to \( r \) and \( r + \Delta r \)), can be expressed as

\[
\sigma^2 \Delta l_\alpha^2 = \Delta x^2 + \Delta y^2 + |\nabla \alpha^T \Delta r|^2,
\]

\[
= \Delta r^T \left( \begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array} \right) \Delta r + \Delta r^T \nabla \alpha \nabla \alpha^T \Delta r
\]

\[
= \Delta r^T [I + \nabla \alpha \nabla \alpha^T] \Delta r, \tag{18}
\]

which gives

\[
G_\alpha = I + \nabla \alpha \nabla \alpha^T. \tag{19}
\]

Thus, the membrane may have a similar shape to that of \( R_\alpha \). Especially, \( G_0 = 2\tau I \) gives \( G(\tau) = G_\alpha \). Even for \( G_0 \neq 2c_\alpha \tau I \), a sufficiently large \( |\nabla \alpha| \) allows \( G(\tau) \approx 2c_\alpha \tau G_\alpha \).

### 2.5 Modification by other morphogens

Here we assume that distributions of \( \alpha \) and \( \eta \) are constant along time in the membrane coordinate system. In order to modify the basic membrane structure formed by morphogens \( \alpha \) and \( \eta \), we introduce additional morphogens \( \beta \) and \( \theta \). Morphogens \( \beta \) and \( \theta \) curve and twist the basic structure, respectively, as explained below.

First, \( \beta \) accelerates the rate of directed cell division in one side of the basic structure, and suppresses that in the other side, which can be realized by introducing an increasing function of \( [\nabla \hat{\alpha}^T \nabla \beta]_{t=0} = ||G_0||^{-1} \nabla \hat{\alpha}^T G_0^{-1} \nabla \beta \), denoted by \( g([\nabla \hat{\alpha}^T \nabla \beta]_{t=0}) \), into Eq. (5) as

\[
\Delta \hat{r}' = [I + g([\nabla \hat{\alpha}^T \nabla \beta]_{t=0}) \nabla \hat{\alpha} \nabla \hat{\alpha}^T + \eta I] \Delta t] \Delta \hat{r}. \tag{20}
\]

For simplicity, we choose \( g([\nabla \hat{\alpha}^T \nabla \beta]_{t=0}) = \exp([\nabla \hat{\alpha}^T \nabla \beta]_{t=0})^2 \). (Curving can also be realized by acceleration/suppression of non-directed cell division, by multiplying \( \eta I \) by \( [\nabla \hat{\alpha}^T \nabla \beta]_{t=0} \).)

Second, \( \theta \) rotates the direction of directed cell division by \( \theta \) in the initial geodesic coordinate system (i.e., rotation of \( \nabla \hat{\alpha} = ||W||^{-1} W^{-1T} \nabla \alpha \) by \( \theta \) in \( \hat{r} \) at \( t = 0 \)), which further transforms Eq. (20) into

\[
\Delta \hat{r}' = [I + O(\Delta t^2)] \Delta \hat{r}
\]

\[
+ (\exp([\nabla \hat{\alpha}^T \nabla \beta]_{t=0})^2 [W^{-1T} \Theta \nabla \alpha] [W^{-1T} \Theta \nabla \alpha]^T + \eta I] \Delta t] \Delta \hat{r}
\]

\[
= [W + (\exp(||G_0||^{-1} \nabla \alpha^T G_0^{-1} \nabla \beta)^2 W^{-1T} \Theta \nabla \alpha \nabla \alpha^T \Theta^T + \eta W) \Delta t + O(\Delta t^2)] \Delta r
\]

\[
= [W + (W^{-1T} \mathbf{a} \mathbf{a}^T + \eta W) \Delta t + O(\Delta t^2)] \Delta r,
\]

where

\[
\mathbf{a} = \exp(||G_0||^{-1} \nabla \alpha^T G_0^{-1} \nabla \beta) \Theta \nabla \alpha,
\]

\[
\Theta = W_0^T \Theta W_0^{-1T},
\]

\[
\Theta = \begin{pmatrix}
\cos \theta & \sin \theta \\
-\sin \theta & \cos \theta
\end{pmatrix}, \tag{22}
\]
and $W_0^TW_0 = G_0$. Then we obtain,
\[
\sigma^2 \Delta l^2 = \Delta r^T [G + 2((aa^T + \eta G) \Delta t) + O(\Delta t^2)]\Delta r, \tag{23}
\]
\[
\frac{dG}{dt} = 2aa^T + 2\eta G, \tag{24}
\]
\[
G(\tau) = \begin{cases} 
     [G_0 + \frac{aa^T}{\eta}] \exp(2\eta \tau) - \frac{aa^T}{\eta} & \text{for } \eta \neq 0 \\
     G_0 + 2\tau aa^T & \text{for } \eta = 0.
\end{cases} \tag{25}
\]

The above formulation uses $\tilde{\nabla} \tilde{\alpha}$ and $\tilde{\nabla} \tilde{\beta}$ at $t=0$ for the modification. We can also use $\tilde{\nabla} \tilde{\alpha}$ and $\tilde{\nabla} \tilde{\beta}$ at each time $t$ instead (i.e., removing the subscript ‘0’ from $G_0$ and $W_0$ in Eqs. (22)), which might be easier to realize in biological systems. However, this choice gives more complicated equation than Eq. (25).

In the beginning of subsection 2.1 we assume that at $t=0$ the membrane is flat, $R(r) = (X(r), Y(r), Z(r))^T = (x, y, 0)^T$, which implies $G_0 = I$ for all $r$. Even if $G_0$ varies along $r$, i.e., the membrane is not flat at the initial state, Eqs. (23-25) are unchanged.

3 Numerical calculation of membrane transformation

(a) \hspace{1cm} (b)

Figure 1: Transformation of a flat membrane through cell proliferation regulated by morphogens. Parameters are $\tau = 0.6$, $d_{\alpha} = 1$, $\sigma_{\alpha} = 0.5$, $c_{\alpha} = 30$, $c_{\beta} = -0.15$, and $c_{\theta} = 0.02$. (a) and (b) show the same membrane seen from different perspectives.

We show an example of numerical calculation of membrane transformation. For given density distributions of $\alpha$, $\eta$, $\beta$, $\theta$, and the initial metric $G_0$, we can calculate $G(\tau)$. The membrane structure $R(r) = (X(r), Y(r), Z(r))^T$ at $t = \tau$ can be calculated by solving
\[
\lim_{|\Delta r| \to 0} \left[ \frac{|R(r + \Delta r) - R(r)|^2}{\Delta r^T G(\tau) \Delta r} \right] = 1 \tag{26}
\]
with Eq. (25). In this example, for $\alpha$ we assume a distribution
\[
\alpha(r) = c_\alpha \left[ \exp\left(-\frac{|r - (d_{\alpha}, 0)|^2}{2\sigma_{\alpha}^2}\right) + \exp\left(-\frac{|r - (-d_{\alpha}, 0)|^2}{2\sigma_{\alpha}^2}\right) \right], \tag{27}
\]
which have two peaks for a sufficiently large $d_\alpha$. For the other morphogens, we assume

$$
\begin{align*}
\eta(r) &= 0 \\
\beta(r) &= c_\beta y \\
\theta(r) &= \begin{cases} 
  c_\theta & \text{for } x > 0 \\
  -c_\theta & \text{for } x < 0
\end{cases}
\end{align*}
$$

(28)

For efficiency in solving Eq. (26), we assume a bending elasticity of the membrane, and a weak water pressure from inside of the membrane (i.e., a constant outward pressure in parallel with the normal vector at each point on the membrane). Figure 1 shows a transformed membrane structure for $G_0 = W_0 = I$ (i.e., the initial membrane is flat), $\tau = 0.6, d_\alpha = 1, \sigma_\alpha = 0.5, c_\alpha = 30, c_\beta = -0.15, c_\theta = 0.02$.

4 Discussion

As the initial metric $G_0$ can vary along $r$ for the metric-dynamics equation, Eq. (25), the membrane transformation can be repeatedly applied to the same membrane by resetting morphogen distributions while keeping $G(\tau)$ (like as repeated molting of arthropods), which can generate various complex structures. Our approach may be more efficient than models describing cell-level dynamics, because the number of vertices required for describing the membrane may be smaller. On the other hand, a weak point of our approach is that we have to define relationships between the local properties of morphogen distributions (e.g., gradients) and the manners of local membrane extensions. Cell-based approaches can examine the validity of those relationships and improve them.

References

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