Traversing Geodesics to Grow Biological Structures

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Abstract

Biological tissues reliably grow into functional structures from simple starting states during development. Throughout this process, the energy of a tissue changes depending on its natural resistance to deformations such as stretching, bending, shearing, and torsion. In this paper, we represent tissue structures as shapes and develop a mathematical framework to discover paths on the tissue shape manifold to minimize the total energy during development. We find that paths discovered by gradient descent and the geodesic algorithm outperform naive shape interpolation in energetic terms and resemble strategies observed in development. Broadly, these tools can be used to understand and compare shape transformations in biology and propose optimal strategies for synthetic tissue engineering.

1 Introduction

In biological tissues, shape and function are inextricably linked. For instance, the intricate architecture of the heart allows it to efficiently deliver oxygenated blood to the body. During cardiac development (cardiogenesis), a single population of early precursors fuses into the primitive heart tube and must undergo a series of precise loopings, rotations, and partitions, while simultaneously functioning as a pump [1]. As a result, congenital heart malformations [2, 3] are the most common fatal birth defects in infants, for whom birth defects are the number one cause of death. Of the many possible paths from an initial form to a final form, why do biological tissues transform in the manner as observed? From the perspective of physics, as a tissue changes shape, it traverses an energy landscape determined by its natural resistance to deformations from a resting state.

To better understand this problem, we design a mathematical approach inspired by AI to discover minimum-energy strategies for growing a folded rigid tubular structure from an initially round tissue. We generate candidate paths for this simple morphological operation using naive interpolation, an algorithm for geodesic (locally low-energy) paths, and gradient descent. We find that geodesic and gradient descent paths open up the tissue at the opposite end from the site of folding, thus bypassing closed intermediates with high tensile energy. Broadly, our work supplies tools for understanding biological development and discovering novel strategies for synthetic tissue engineering.

2 Mathematical framework

2.1 Preliminaries

In our mathematical framework adapted from [4, 5], we represent an organic structure as a 2-dimensional shape, wherein the sampled coordinates of the shape are vertices of the shape manifold ($\mathcal{S}$) = $\mathbb{R}^{mx2}$, where m is the number of vertices and '2' refers to the 2 axes x and y. In addition, we define an energy function ($E(s) = \mathbb{R}^n$), that maps an organic structure s to the energy space ($\mathbf{E}$). The energy space is a vector in $\mathbb{R}^n$, where the n elements correspond to n separable energies, whose relative contributions can be balanced based on the properties of the tissue being examined. In this

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work, we approximate a rigid tissue as a covalent solid, or a network of stretchable bonds connected by bendable joints. Thus, a shape's energy is the sum of the stretching and bending energies of its constituent bonds and joints (Fig. 1A).

$$E(s,t) = \begin{bmatrix} E_{\text{stretch}} \\ E_{\text{bend}} \end{bmatrix} = \begin{bmatrix} B \sum_{i=0}^{m-1} \left(\ell_i - \ell_i^{(0)}(t)\right)^2 \\ K \sum_{i=0}^{m-2} \left(\theta_i - \theta_i^{(0)}(t)\right)^2 \end{bmatrix} \tag{1}$$

Here, B and K are the stretching and bending moduli (analogous to a material's bulk modulus and bending rigidity). The stretching energy is the spring potential for a spring described by the vector $\mathbf{r}_j = s_{j+1} - s_j$ with resting length $\ell_j^{(0)}(t)$, and the bending energy is the harmonic angle potential for the signed bending angle between $\mathbf{r}_j$ and $\mathbf{r}_{j+1}$ with resting angle $\theta_j^{(0)}(t)$. Spring lengths and bending angles were calculated as

$$\ell_j = \|\mathbf{r}_j\|_2\,, \quad \theta_j = \text{Sgn}(\mathbf{r_j} \times \mathbf{r_{j+1}}) \arccos\left(\frac{\mathbf{r}_j \cdot \mathbf{r}_{j+1}}{\|\mathbf{r}_j\|_2\, \|\mathbf{r}_{j+1}\|_2}\right), \tag{2}$$

where Sgn is the signum operator.

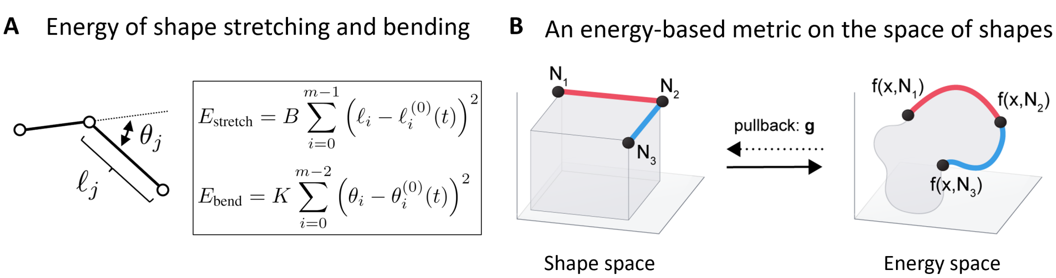

Figure 1: (A) Energy of a structure is evaluated by modeling the bonds as a flexible network of nodes with pre-defined resting lengths and angles. (B) Geometric framework for growing biological structures. Three biological structures (N1,N2,N3) in shape space $\mathcal{S}$ and their relative distance in the Energy space. Growth of biological structures is analyzed by asking how movement in shape space changes the energy through introduction of a pullback metric $\mathbf{g}$

Objective: Our goal is to find a path ($\gamma(t)$) between two organic structures ($\mathbf{s_1}$, $\mathbf{s_f} \in \mathcal{S}$) while optimizing relevant energy terms, based on the developmental process being modeled.

2.2 Metric Tensor construction

To formalize the notion of energy change as the structure (2D shape) changes, we evaluate how infinitesimal perturbation in the shape manifold ($\mathcal{S}$) impacts movement in the energy space ($\mathbf{E}$) by constructing a metric tensor (Fig 2B). To construct the metric, we ask how the energy changes ($\mathbf{E}$) as the 2D shape is infinitesimally changed from $\mathbf{s_1} \in \mathcal{S}$ by $\mathbf{ds}$.

$$E(\mathbf{s_1} + \mathbf{ds}) \approx E(\mathbf{s_1}) + \mathbf{J_{s_1}}\, \mathbf{du}, \tag{3}$$

where $\mathbf{J_{s_1}}$ is the Jacobian of $E(\mathbf{s_1})$ and $J_{i,j} = \frac{\partial E_i}{\partial s^j}$, evaluated at $\mathbf{s_1}$.

In this work, we evaluate the change in energy ($d_E(\mathbf{ds}, \mathbf{g_{s_1}})$) by calculating the Euclidean distance between the energy vectors corresponding to shapes $\mathbf{s_1}$ and $\mathbf{s_1} + \mathbf{ds}$. (Please note that general (non-Euclidean) distance measures can be constructed on the output space, but we focus on the Euclidean case for clarity).

$$d_E(\mathbf{ds}, \mathbf{g_{s_1}}) = \sqrt{|E(\mathbf{s_1} + \mathbf{ds}) - E(\mathbf{s_1})|^2} = \sqrt{\mathbf{ds}^T\, (\mathbf{J_{s_1}}^T\, \mathbf{J_{s_1}})\, \mathbf{ds}} = \sqrt{\mathbf{ds}^T\, \mathbf{g_{s_1}}\, \mathbf{ds}} \tag{4}$$

$$d_E(\mathbf{ds}, \mathbf{g_w}) = \sqrt{\mathbf{ds}^T \mathbf{g_s} \mathbf{ds}} \tag{5}$$

where $\mathbf{g_{s_1}} = \mathbf{J_{s_1}}^T\, \mathbf{J_{s_1}}$ is the metric tensor evaluated at the point $\mathbf{s_1} \in \mathcal{S}$ and $d_E(\mathbf{ds}, \mathbf{g_s})$ is the distance moved in output space when the weights are perturbed by $\mathbf{ds}$ at $\mathbf{s} \in \mathcal{S}$.

2.3 Constructing minimal energy paths in the shape manifold

Our objective is to find a path in the shape manifold ($\mathcal{S}$) between two 2D shapes ($\mathbf{s_1}$ and $\mathbf{s_2}$), representing biological tissue structures at separated time-intervals during the developmental process (as shown in Fig. 2A), such that the total energy consumed during the transformation is minimized.

Mathematically, we want to find a curve $\mathcal{C} \in \mathcal{S}$, with start and end points $\mathbf{s_1}$ and $\mathbf{s_2}$ respectively, such that the integrated energy of the transformation is minimized.

$$L(\mathcal{C}) = \int_{\mathcal{C}} d_E(\mathbf{ds}, \langle \mathbf{g_w}(\mathbf{x}) \rangle) \tag{6}$$

$$= \int_{\mathcal{C}} \sqrt{\mathbf{ds^T} \langle \mathbf{g_s} \rangle \mathbf{ds}} \tag{7}$$

On parameterizing the curve traversed ($\mathcal{C} \in \mathcal{S}$) by $\gamma : [0, 1] \to \mathcal{S} \in W$, wherein $\gamma(0) = \mathbf{s_1}$, $\gamma(1) = \mathbf{s_2}$, the differential element along the path ($\mathbf{ds}$) can be rewritten as:

$$\mathbf{ds} = \frac{d\gamma}{dt} dt, \quad \mathbf{s} = \gamma(t)$$

The total length of the path parameterized by $\gamma(t)$ is:

$$L(\gamma) = \int_0^1 \sqrt{(\frac{d\gamma}{dt}(dt))^T \langle \mathbf{g}_{\gamma(t)}(\mathbf{x}) \rangle (\frac{d\gamma}{dt}(dt))} \tag{8}$$

$$L(\gamma) = \int_0^1 \sqrt{\frac{d\gamma(t)}{dt}^T \langle \mathbf{g}_{\gamma(t)} \rangle \frac{d\gamma(t)}{dt}}\, dt, \tag{9}$$

Let Ω be the set of all piecewise differentiable curves from $\mathbf{s_1}$ to $\mathbf{s_2}$ in the shape manifold ($\mathcal{S}$), we want to find γ^* such that:

$$L(\gamma^*) = \min_\gamma L(\gamma) \quad \forall \gamma \in \Omega \tag{10}$$

Therefore, minimizing L(γ) enables the discovery of low-energy paths in the shapes manifold between two shapes, corresponding to biological structures at different stages of development. We find the geodesic path from the source to the target shape by applying the path-straightening approach [6, 7]. The algorithm is seeded with the linear path as the starting path, and the shapes along the linear path are adjusted in order to minimize the total energy of the path.

3 Results

We seek to study how cells and tissues traverse the energy landscape between disparate "source" and "target" structures. During development, the same tissue structure is often generated in different ways depending on the developmental context, suggesting the existence of multiple paths in the energy landscape with different energetic trade-offs. For instance, a tube is a fundamental unit of many tissues and organs, and yet tubes form in a variety of ways, including wrapping, budding, and hollowing/cavitation [8]. Let us consider growing a tube from a rigid aggregate of uniform, adhesive cells. Initially, the tissue would adopt a spherical configuration due to surface tension. Two mechanisms for tube-formation, wrapping and budding, involve creating high positive and negative curvature on opposing ends of a folding structure, resulting in a wrinkle or dimple. To represent this process in 2D, we start from a circular source shape and specify a folded target shape (a hollow annulus prior to fusion of the tube), assuming the tissue is rigid throughout.

We assume that this transformation is thermodynamically favorable such that $\lim_{t\to\infty} \ell_j^{(0)}(t) = \ell_{j,\, s_2}$, $\lim_{t\to\infty} \theta_j^{(0)}(t) = \theta_{j,\, s_2}\ \forall j$. As in development, the tissue will eventually relax to its target shape in the absence of external forces. We begin with the simple case where resting lengths and angles are constant ($\ell_j^{(0)} = \ell_{j,\, s_2}$ and $\theta_j^{(0)} = \theta_{j,\, s_2}$).

We first generate a naive path by linearly interpolating Cartesian coordinates for each point in the shape (Fig 2A, top). In this naive path, the source shape gradual involutes on the bottom side and stretches on the top in order to fold into the target shape, remaining closed throughout. We then apply

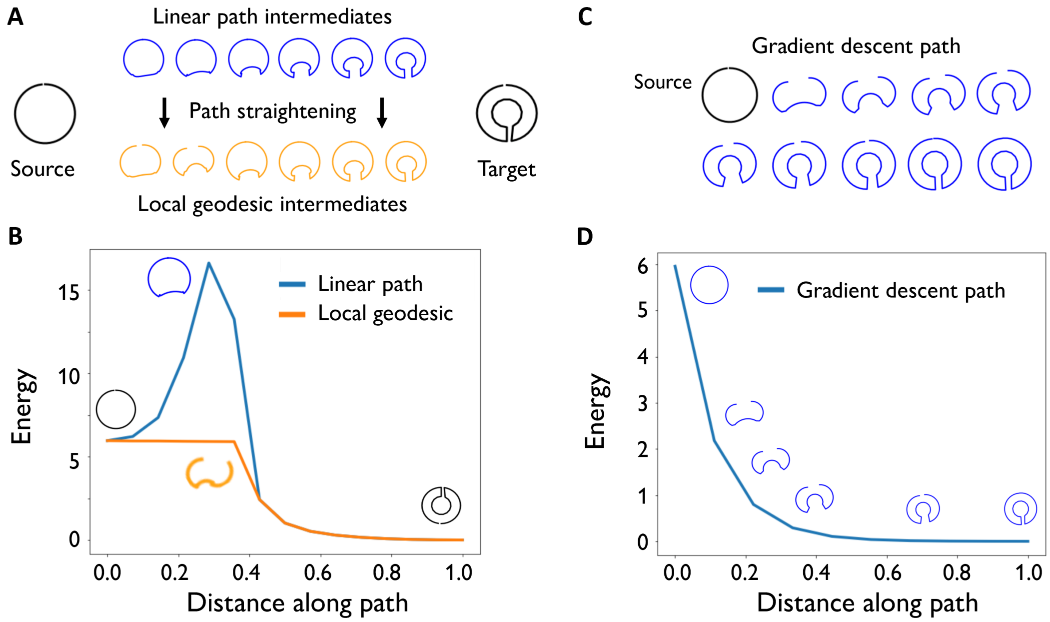

Figure 2: (A) Source and Target shape as we move in the shape manifold. Path Straightening algorithm finds the local Geodesic beginning from the linear path in the shape space. (B) Geodesic path minimizes the energy of the path between source and target structures. (C) Gradient descent minimization of the energy of the source shape, discovers a string of open-networks before converging at the target shape. (D) The energy along the path that traverses the gradient of the energy function is demonstrated here.

a path straightening algorithm to the linear path. The resulting local geodesic path involves a sudden opening of the structure (Fig. 2A, bottom). Plotting the energy along both paths (Fig. 2B) reveals that the unfolding intermediate corresponds to the highest-energy shape in the linear path, suggesting that the geodesic is bypassing an energy barrier during involution. We further find that a gradient descent algorithm applied to the source shape generates a path that similarly opens up the structure, allowing the right and left arms to move independently as it converges to the target (Fig. 2CD).

We hypothesize that as involution occurs at one end of the tissue, the other end must transiently stretch in order to preserve a closed configuration. The geodesic and gradient descent paths avoid this high-energy intermediate by transiently opening the structure topology. This result highlights the potential for mechanical forces to exert long-range effects in development, whereby morphological events seemingly isolated to one region of an embryo can in fact be enabled by changes occurring in distant regions [9].

4 Discussion

Our preliminary experiments suggest that we can use structural modeling and a mathematical framework to find energy-efficient paths between biological structures that avoid energy barriers encountered by naive shape interpolation. Because each path provides a program for each element of the biological tissue to follow, they can be seen as a set of cell-level instructions for transforming a biomaterial as a whole. Such instruction sets could be useful for the engineering of a next generation of synthetic lab-grown tissues with defined morphology.

This approach also could be extended in order to reverse-engineer the material properties (energy function parameters) of a developing/deforming tissue by minimizing the distance between experimental and model-predicted shape trajectories. This method would enable measurement of a tissue's material properties in a much less invasive fashion than current methods and with greater spatial and temporal resolution.

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