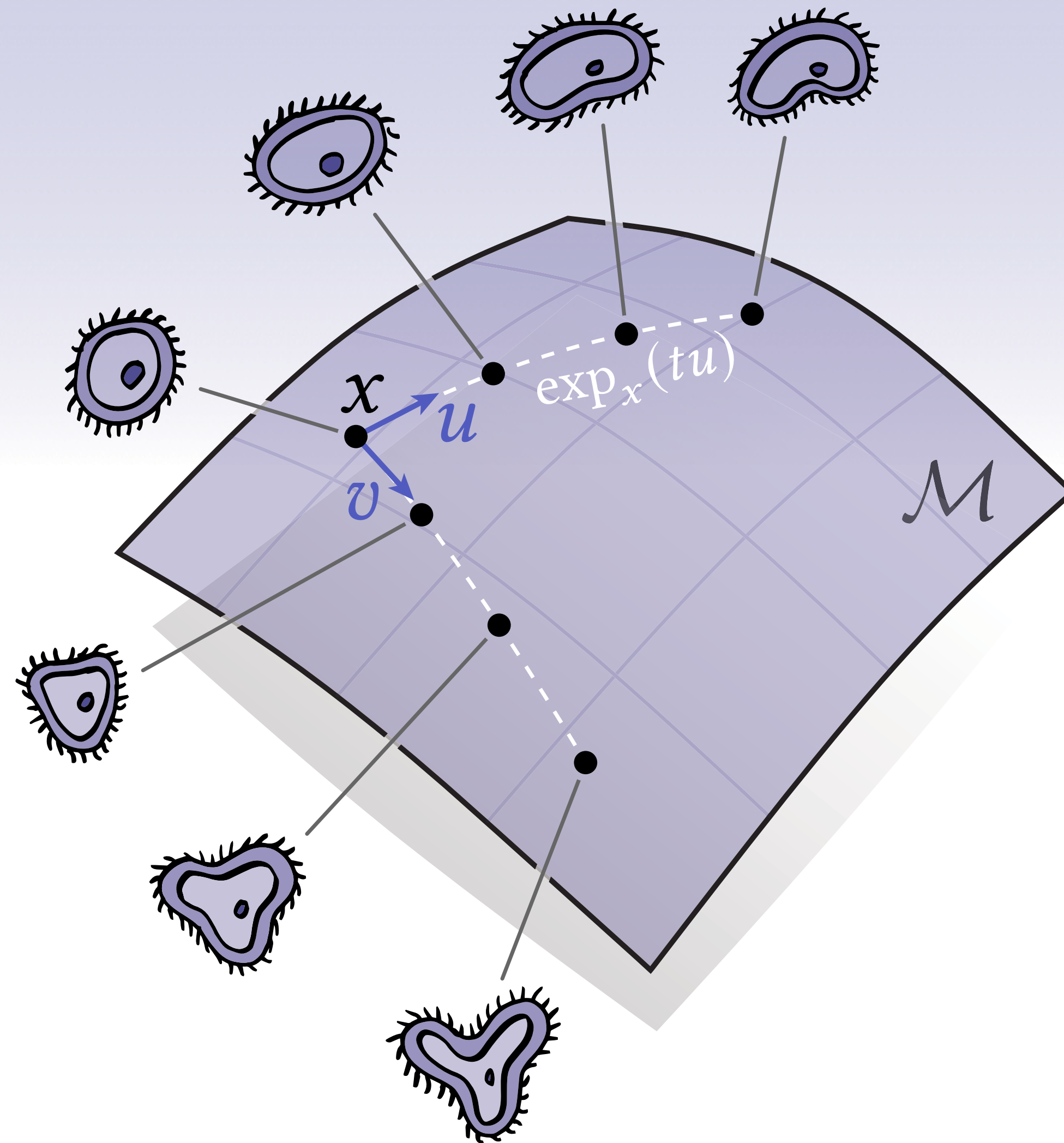


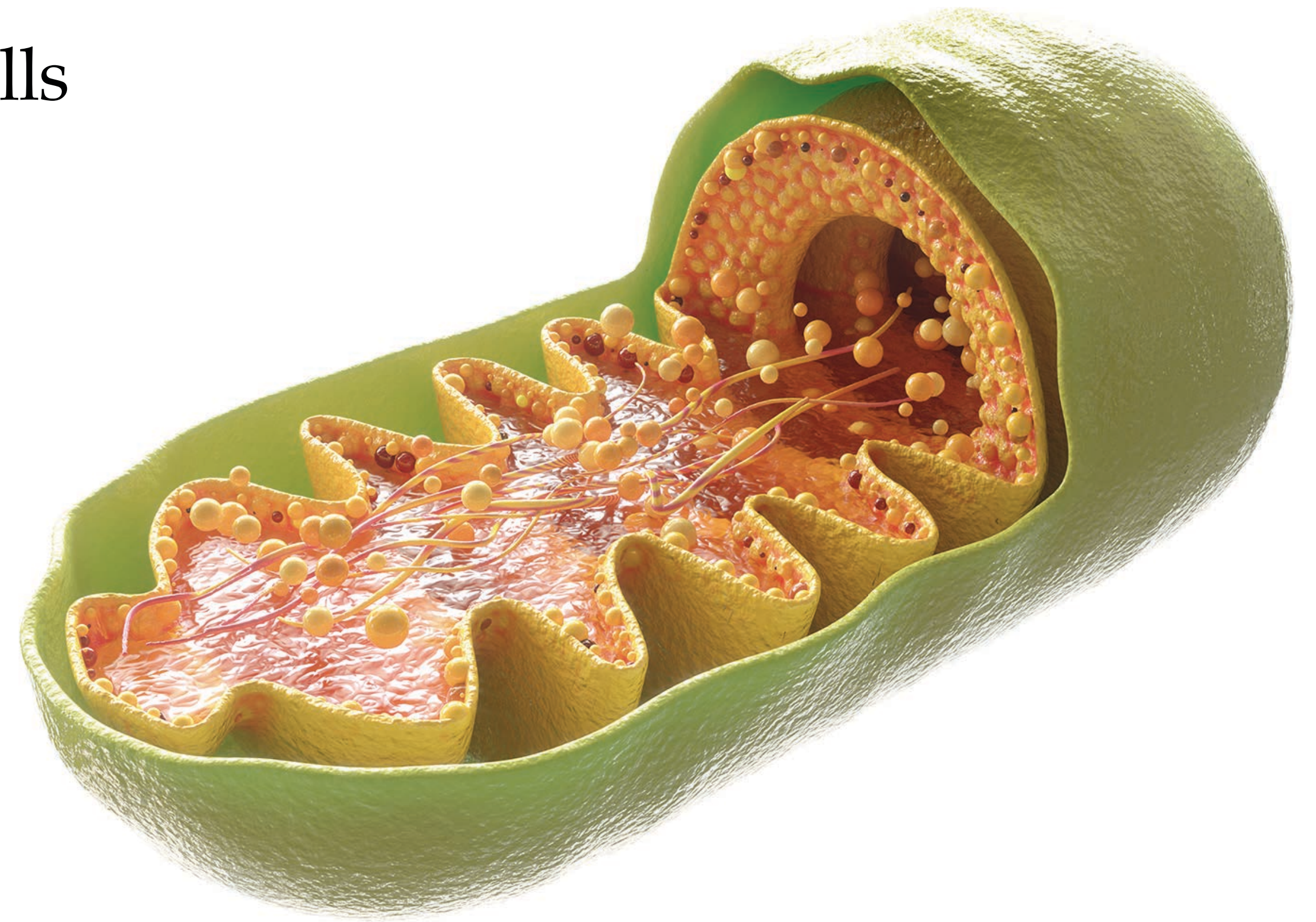
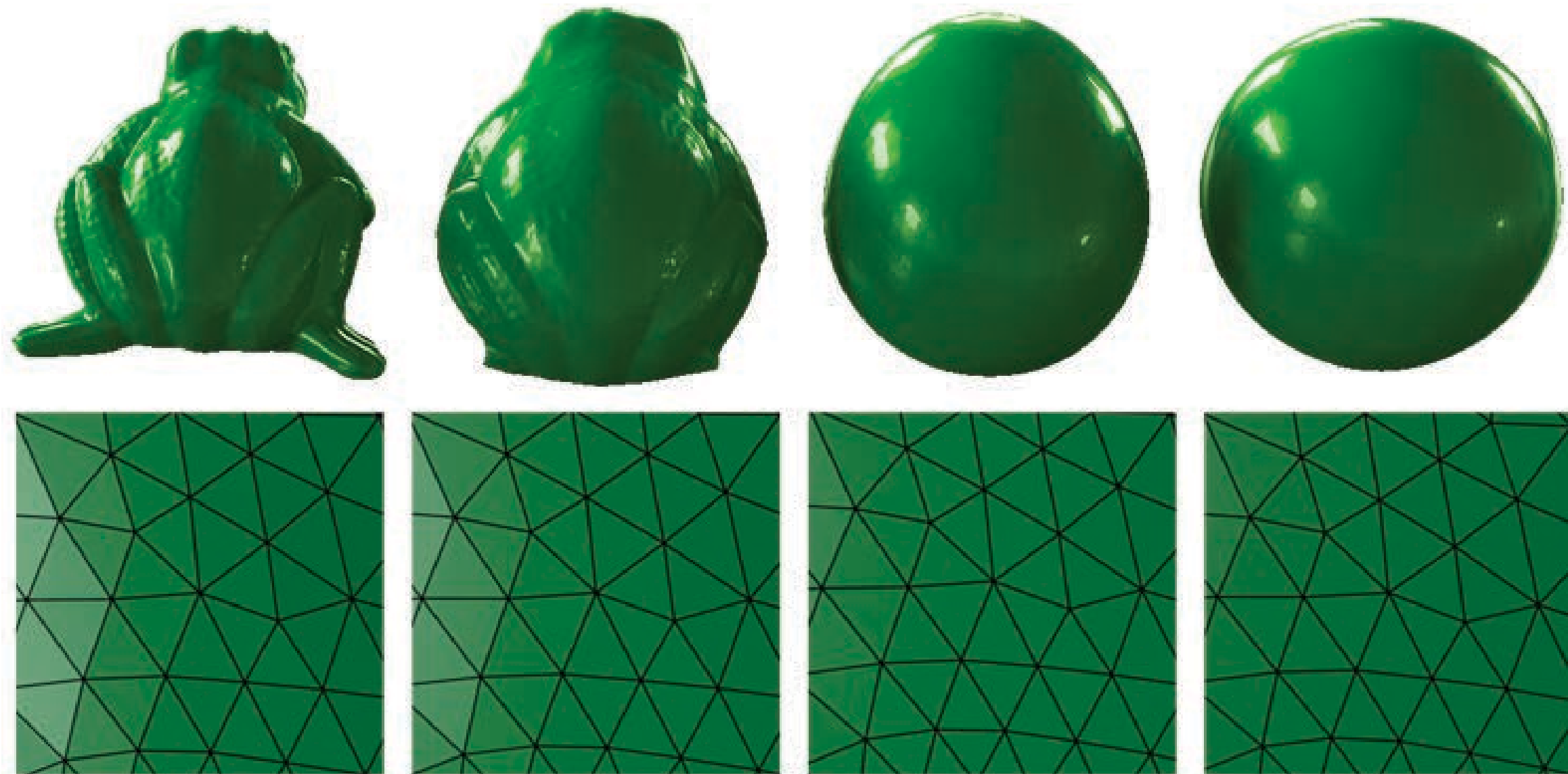


SHAPE SPACES FOR BIOMEMBRANES?

Keenan Crane • Carnegie Mellon University • February 27, 2024

Disclaimer

- *I am not a biologist!*
- My work focuses on differential geometry & numerical methods
- Please forgive me if I sound naïve about cell biology...
- ...**But**: there is an awful lot of **geometry** in cells
 - *can probably learn a lot from each other!*



Motivation: Nonlinear Data Analysis

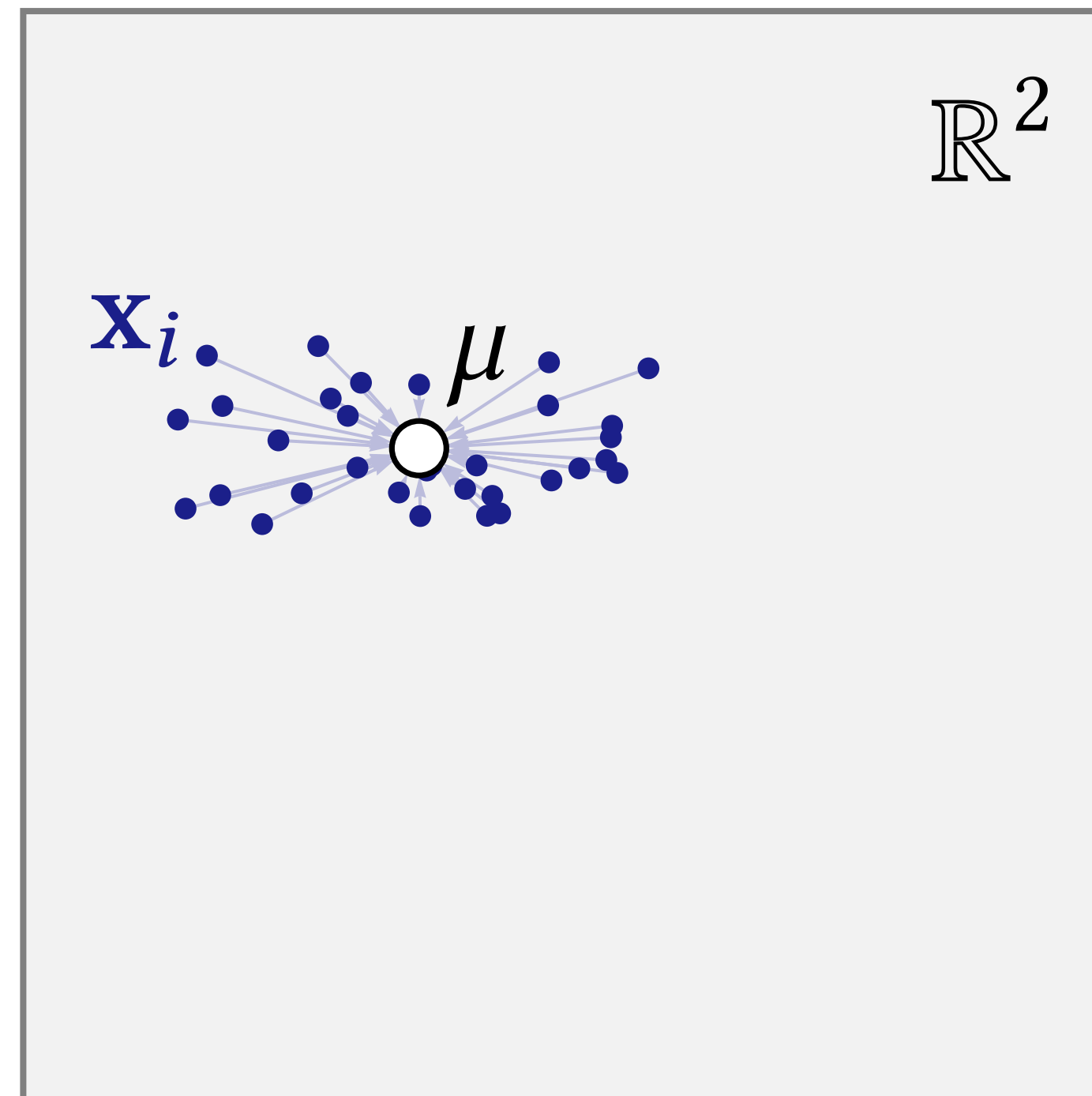
Standard statistical tools give meaningless answers for many kinds of data.

LINEAR

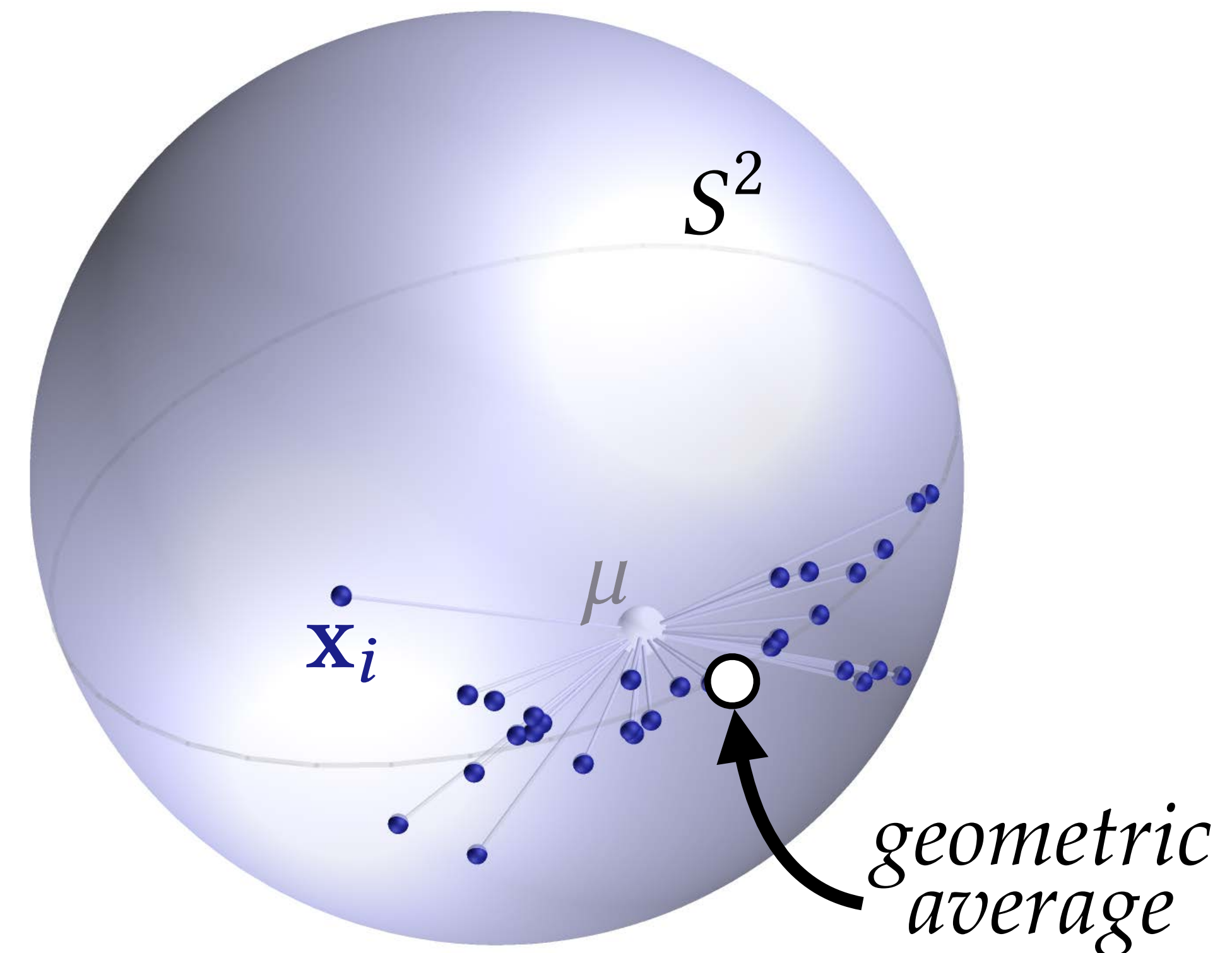
*Simple example: average
noisy measurements $\mathbf{x}_i$*

$$\mu := \frac{1}{n} \sum_{i=1}^n \mathbf{x}_i$$

(mean statistic)



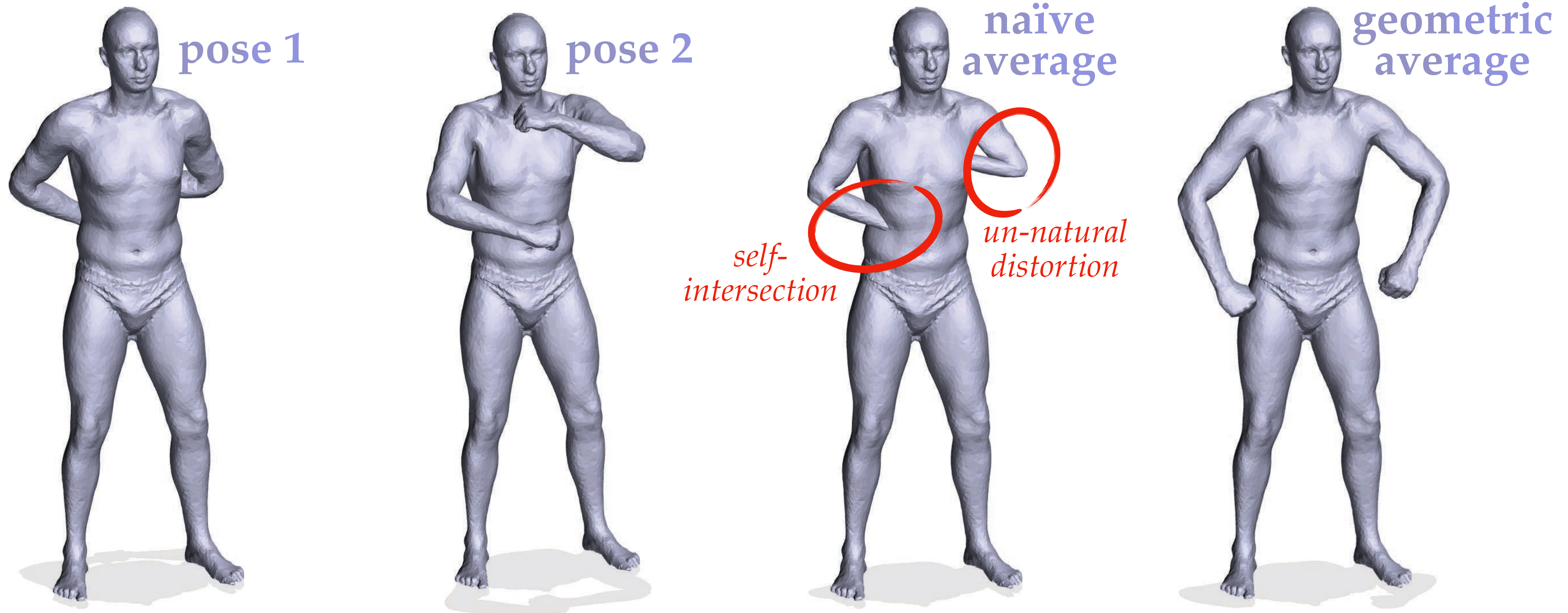
NONLINEAR



“mean” not even on sphere!

Motivation: Statistical Shape Analysis

Shape data also lives on a curved *shape space*...

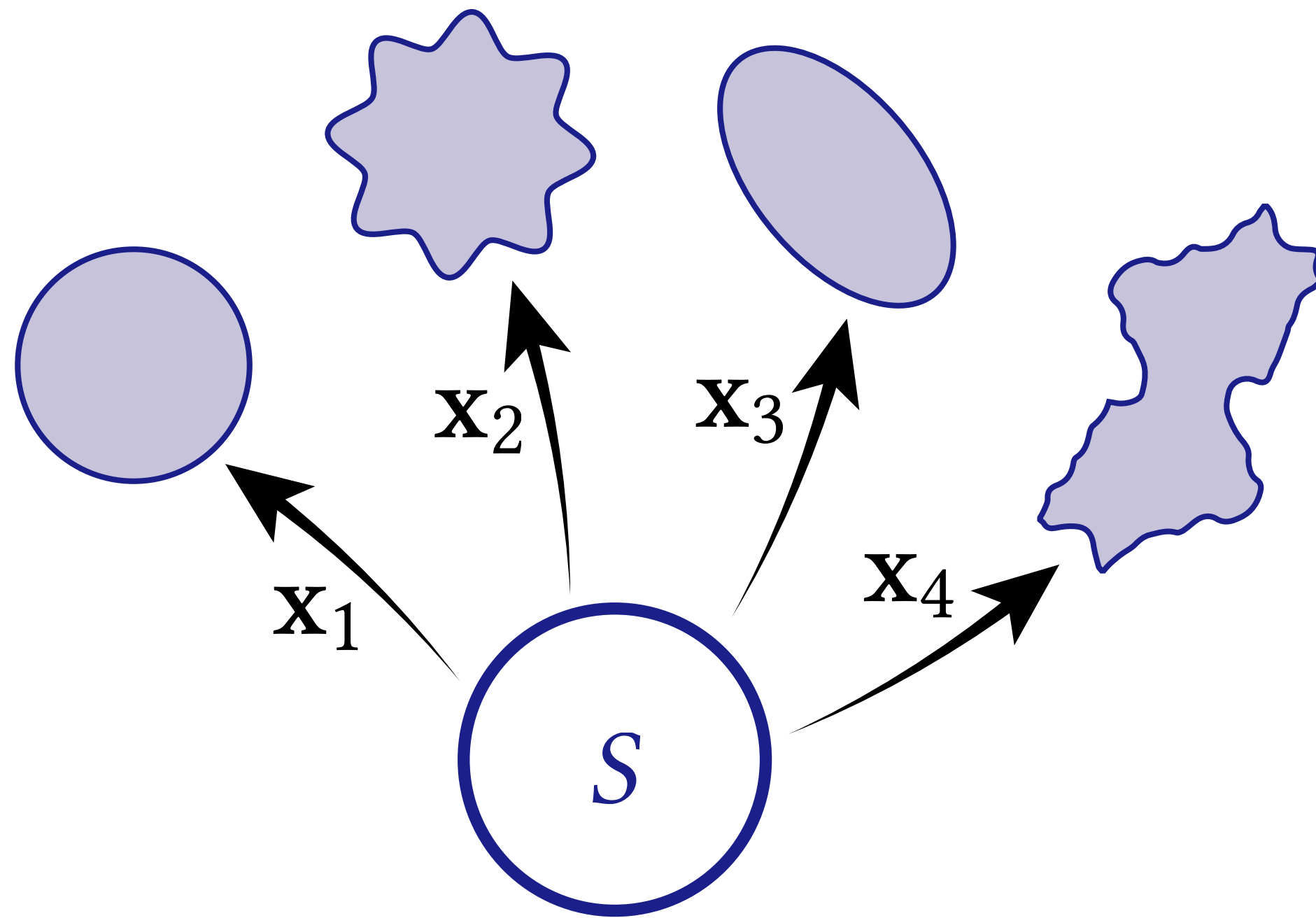


Key idea: obey the geometry of the space where the data lives

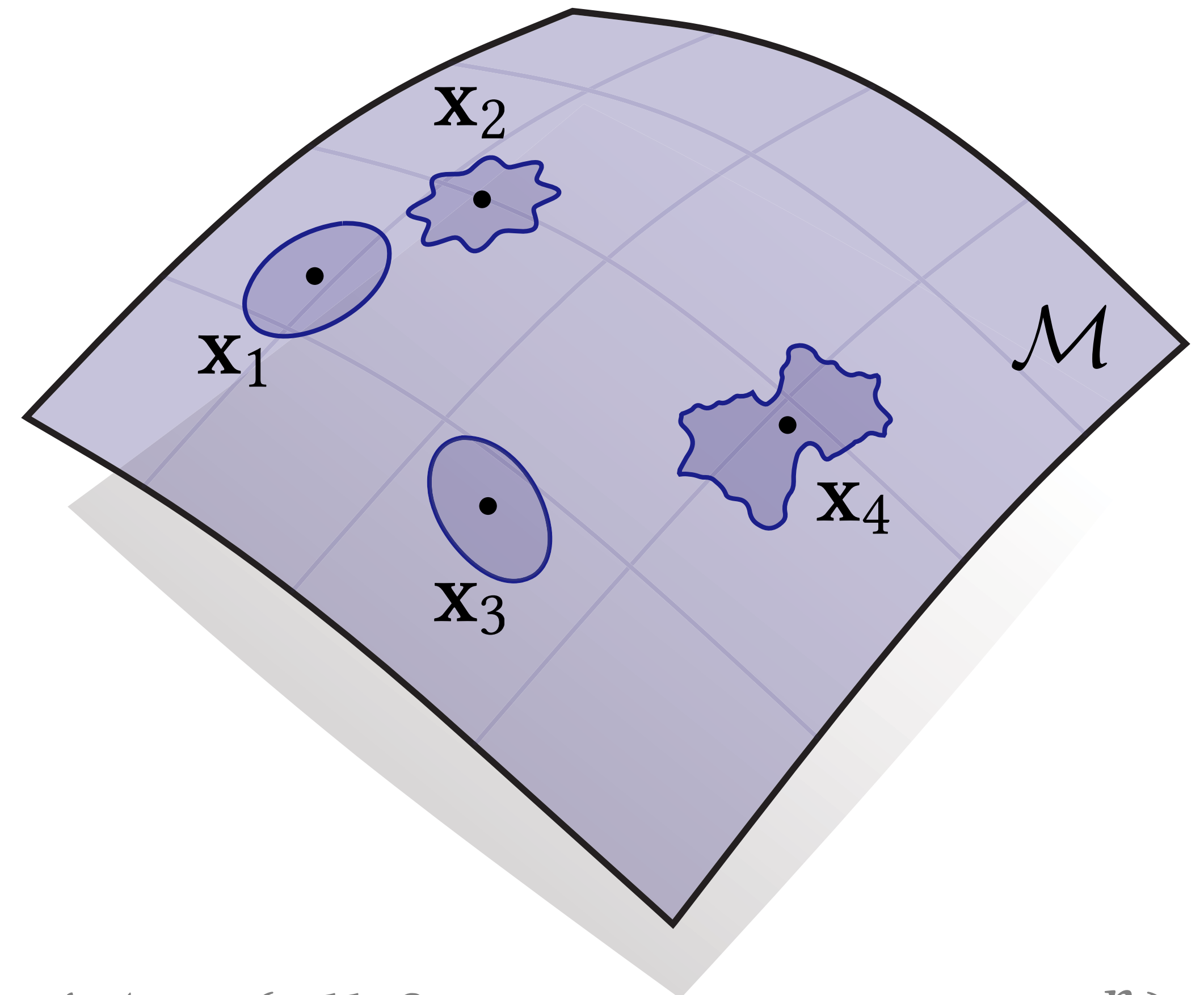
Riemannian Shape Spaces

shape configurations $\leftrightarrow$ points in $\mathcal{M}$

e.g., closed loops in the plane



shape space



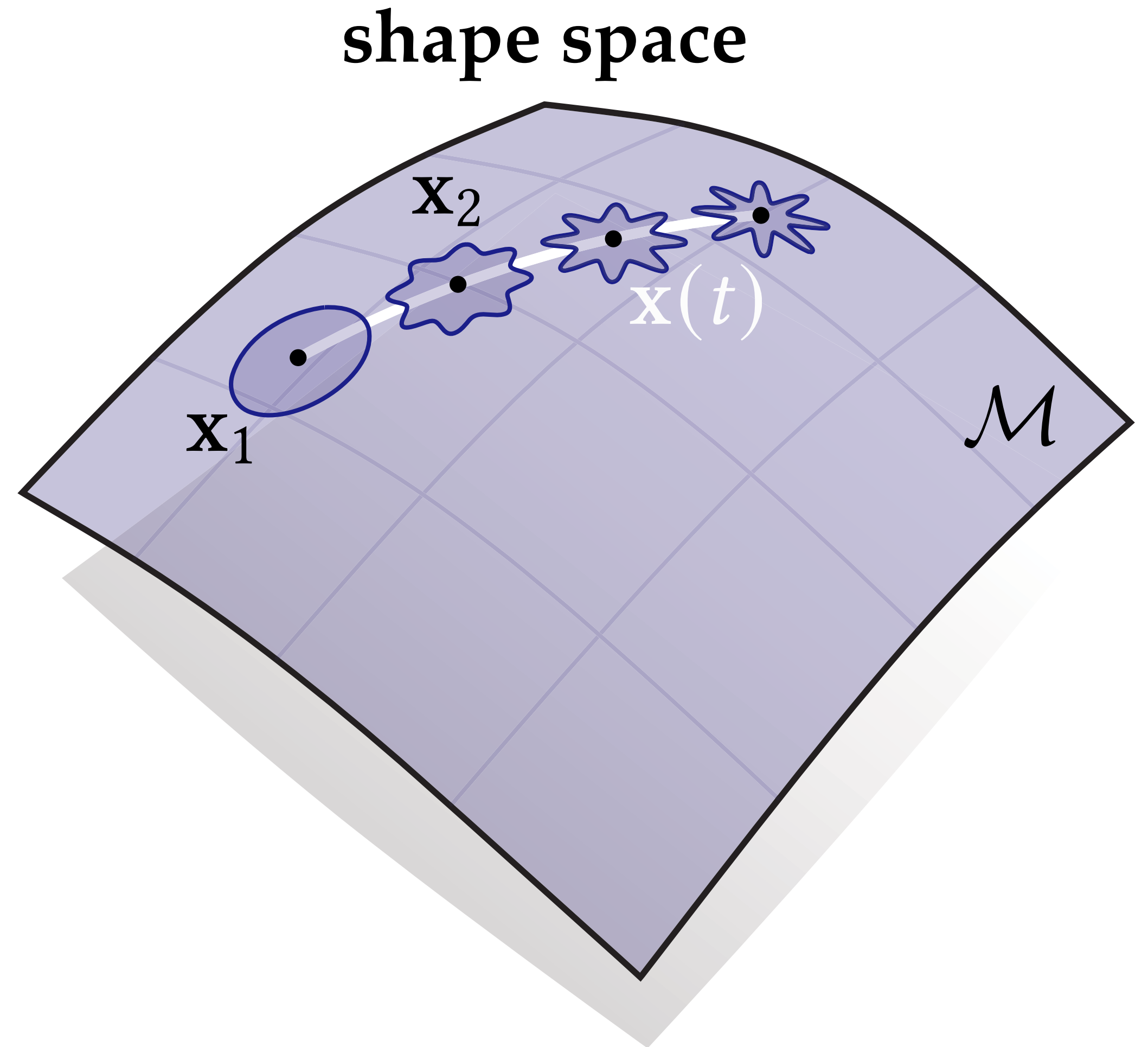
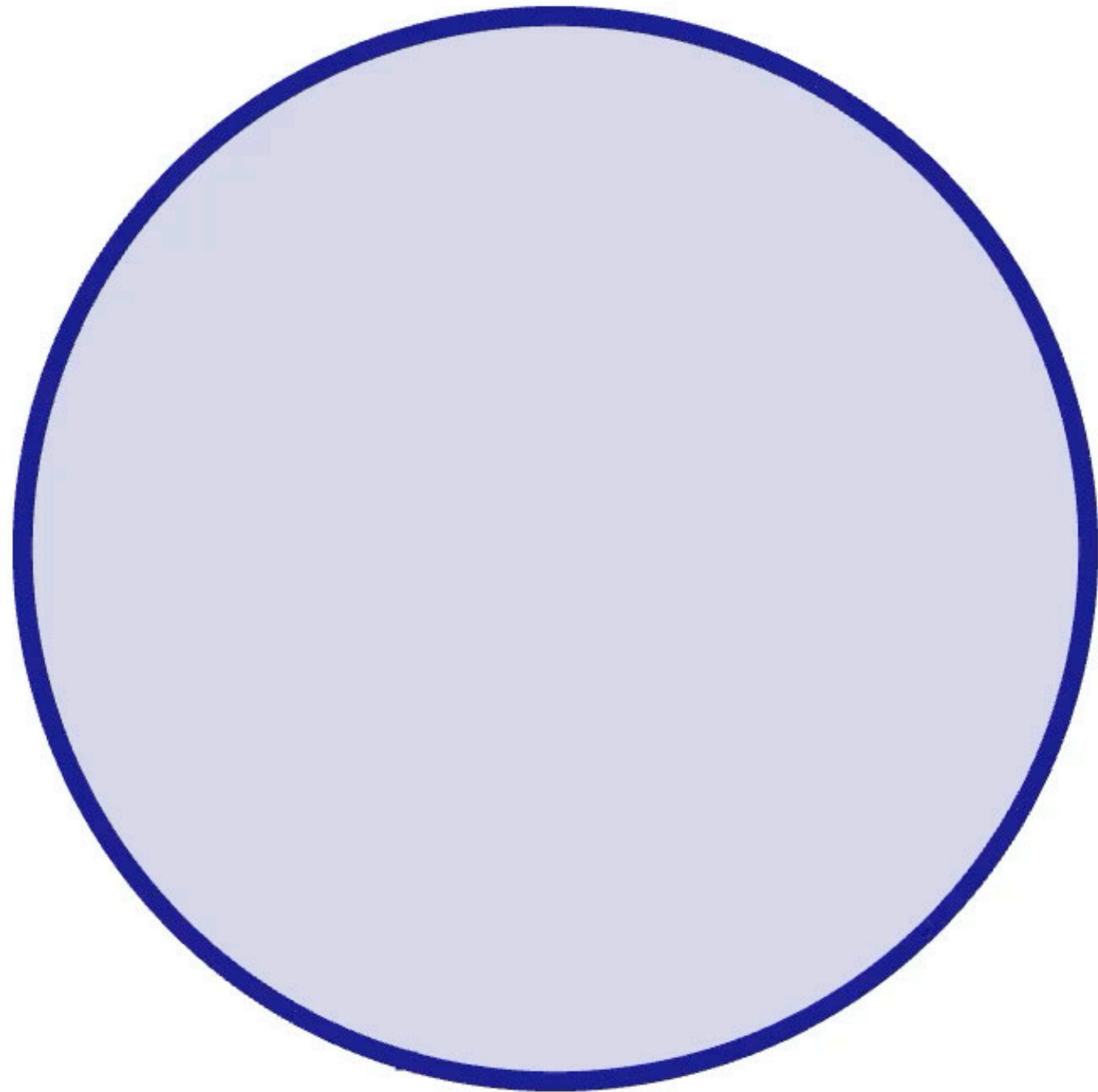
$$\mathcal{M} = \{\text{all functions } \mathbf{x} : S \rightarrow \mathbb{R}^n\}$$

Key idea: each **configuration** of a shape viewed as a **point** in a “curved space”

Riemannian Shape Spaces

shape configurations $\leftrightarrow$ points in $\mathcal{M}$

shape trajectories $\leftrightarrow$ curves on $\mathcal{M}$



$$\mathbf{x}(t) : [0, 1] \rightarrow \mathcal{M}$$

Riemannian Shape Spaces

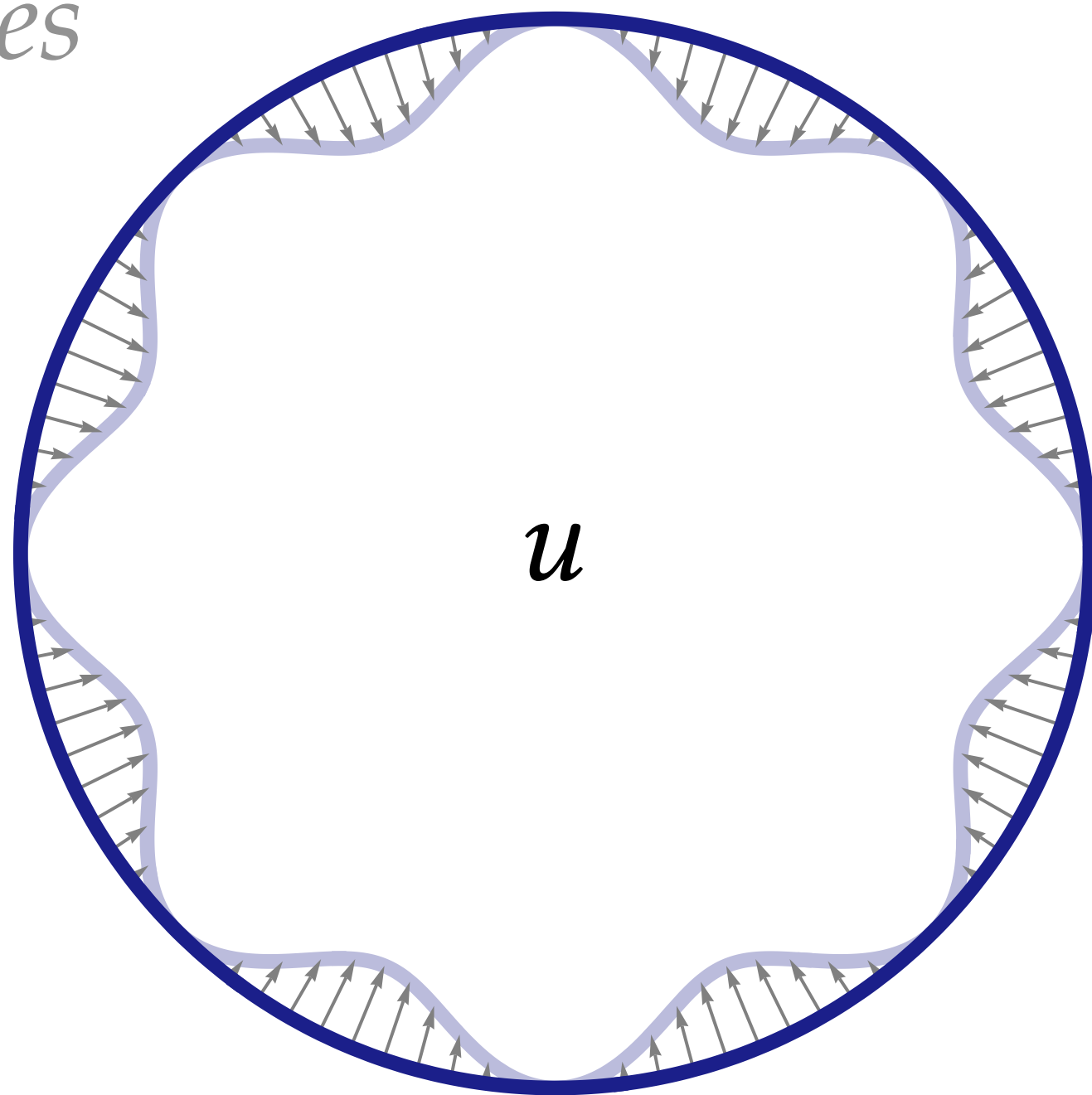
Key idea: shape space is not just a set!
Must assign a cost to small deformations...

shape configurations $\leftrightarrow$ points in $\mathcal{M}$

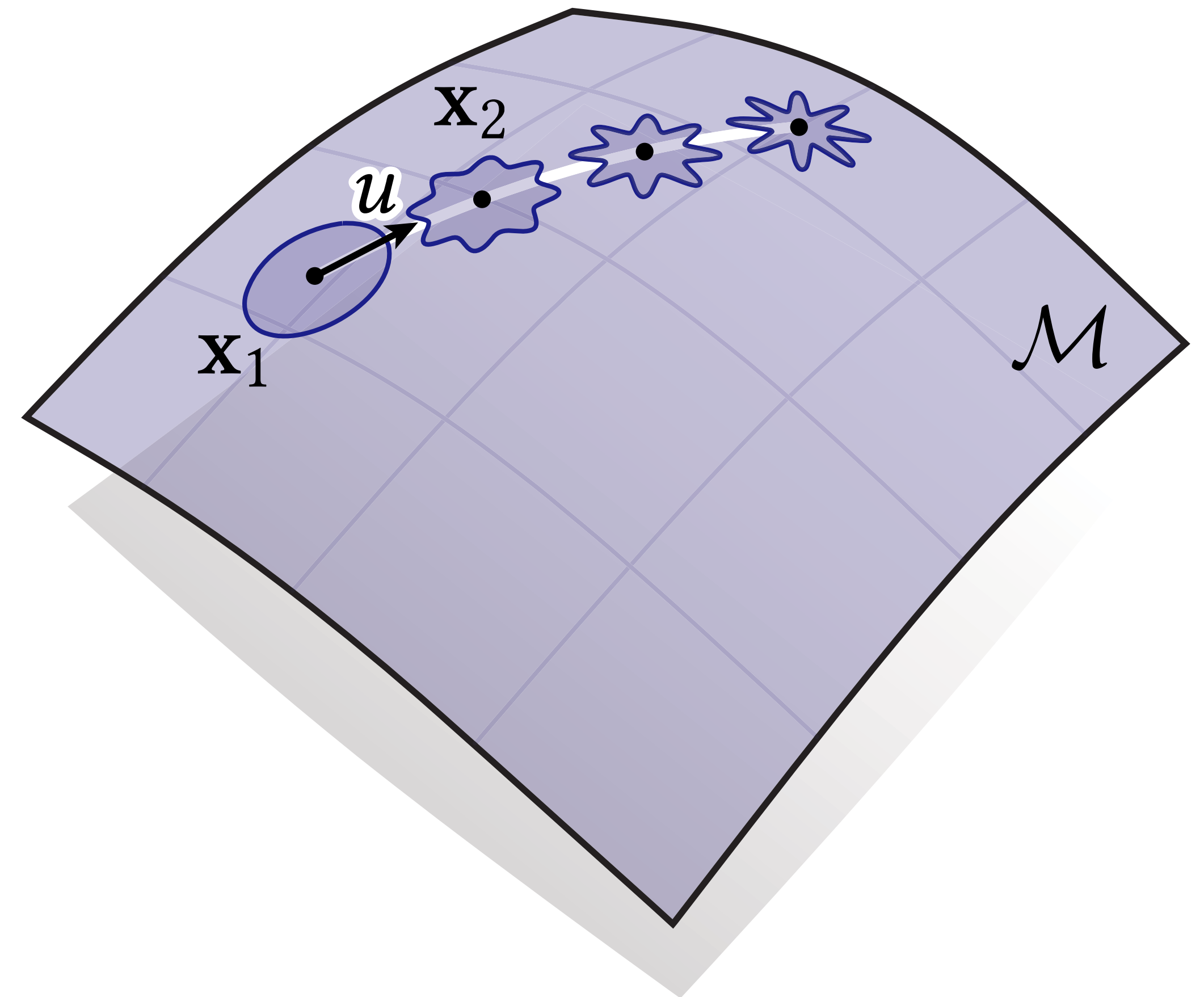
shape trajectories $\leftrightarrow$ curves on $\mathcal{M}$

small deformations $\leftrightarrow$ tangent vectors

i.e., velocities



shape space



$$u \in T_x \mathcal{M}$$

Riemannian Shape Spaces

Key idea: shape space is not just a set!
Must assign a cost to small deformations...

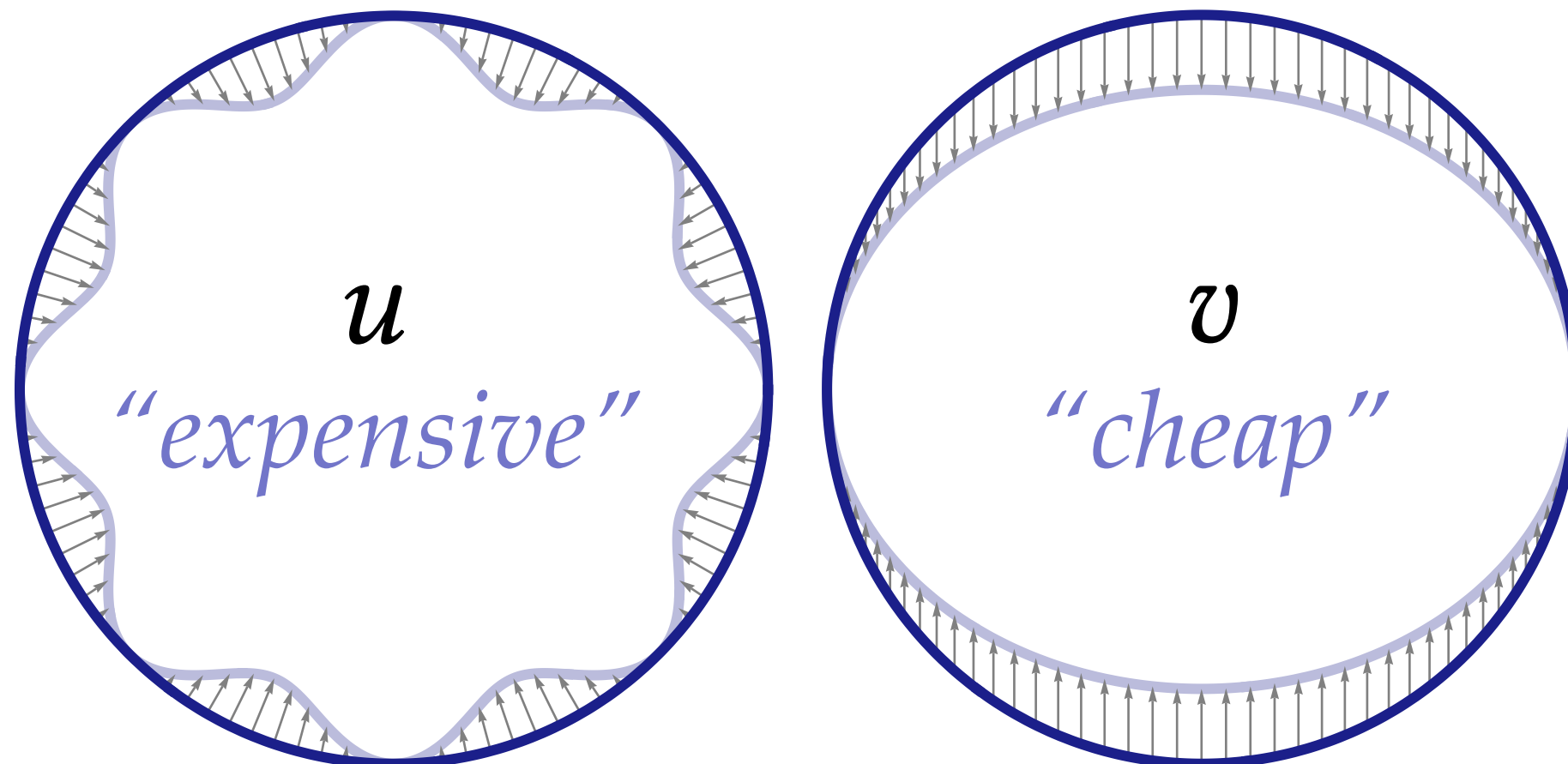
shape configurations $\leftrightarrow$ points in $\mathcal{M}$

shape trajectories $\leftrightarrow$ curves on $\mathcal{M}$

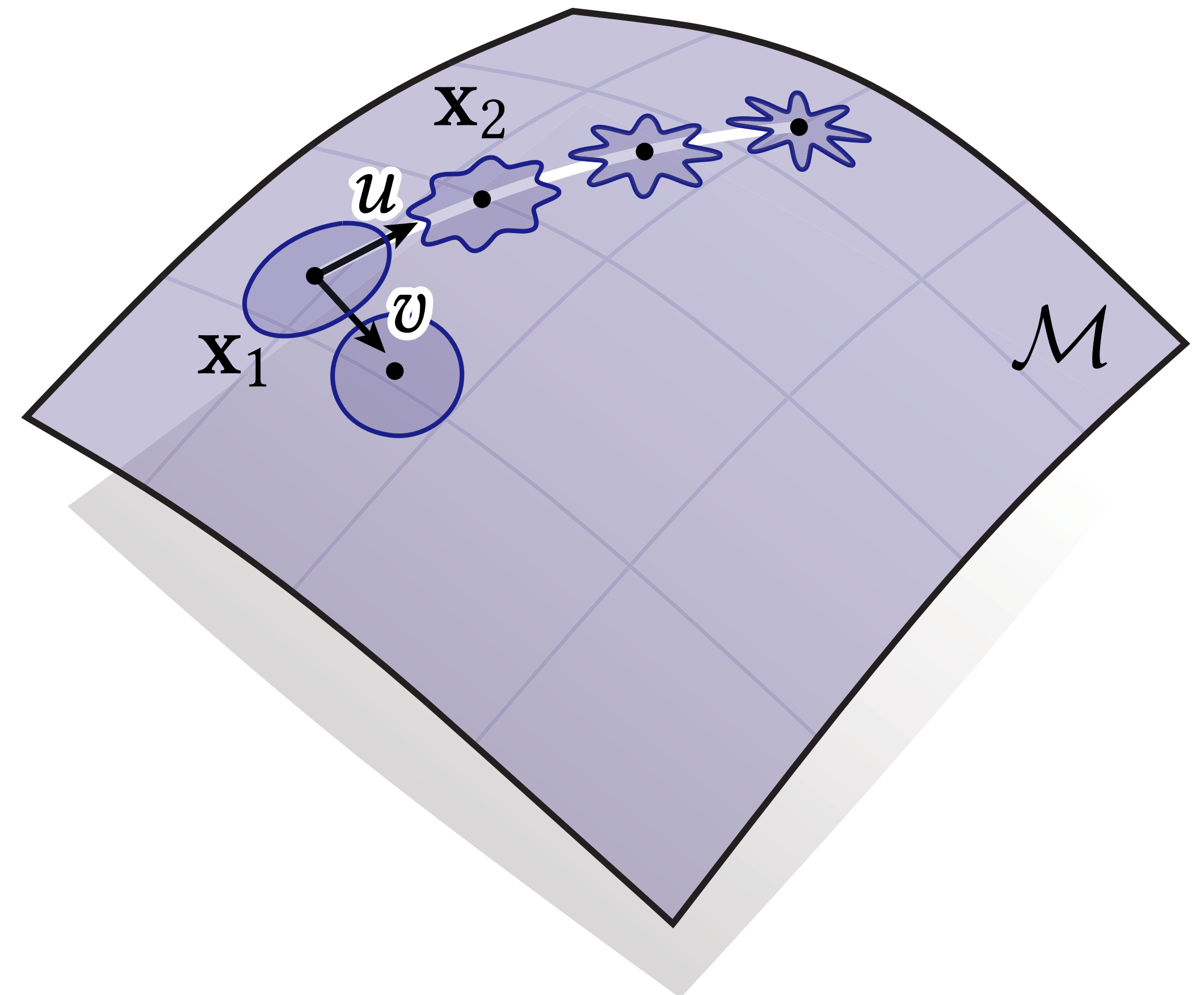
small deformations $\leftrightarrow$ tangent vectors

cost of small deformation $\leftrightarrow$ Riemannian metric g
(inner product)

$g(u, u)$ is big
 $\iff$
 u is expensive



shape space



$$g_x : T_x \mathcal{M} \times T_x \mathcal{M} \rightarrow \mathbb{R}_{\geq 0}$$

Riemannian Shape Spaces

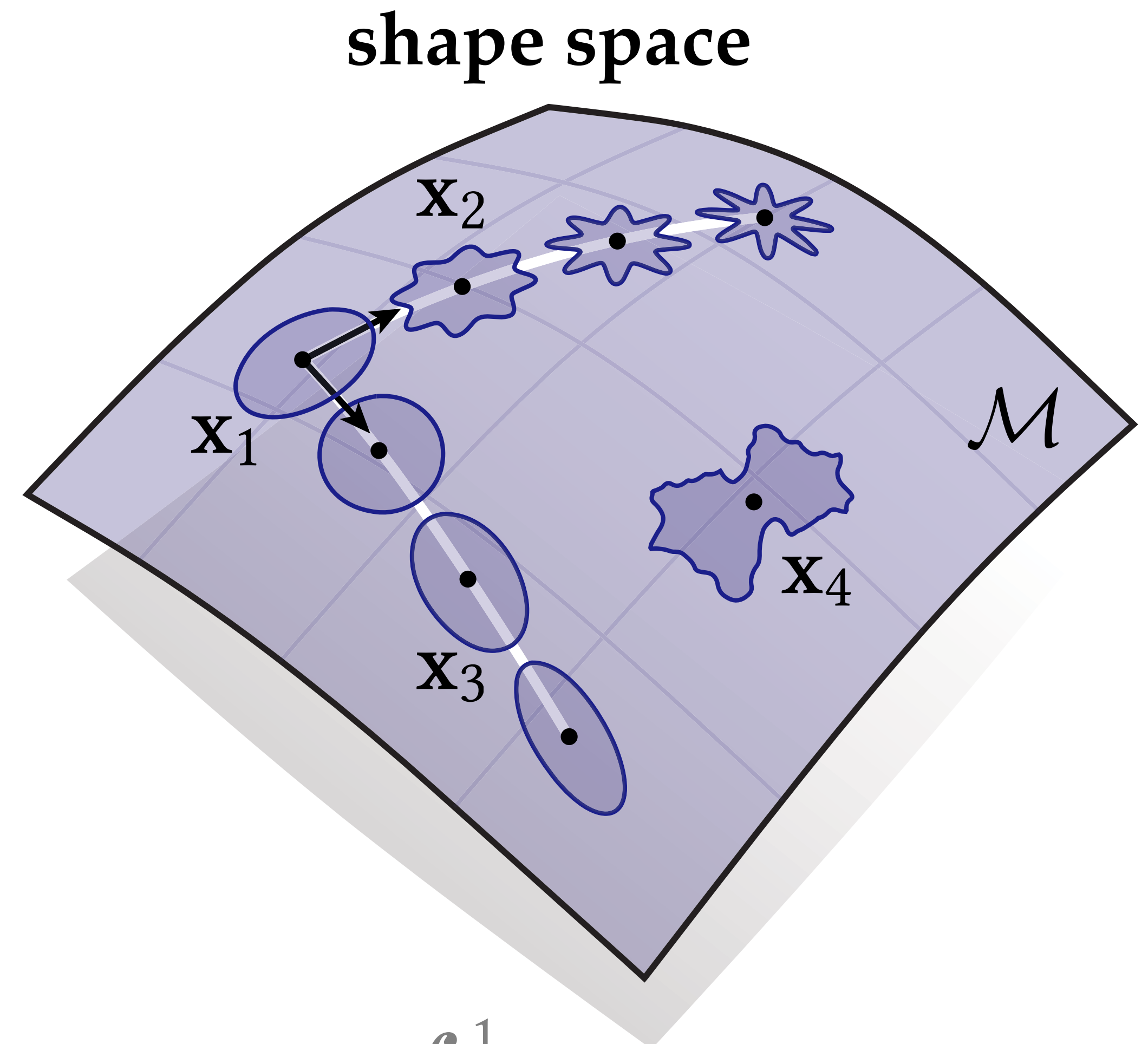
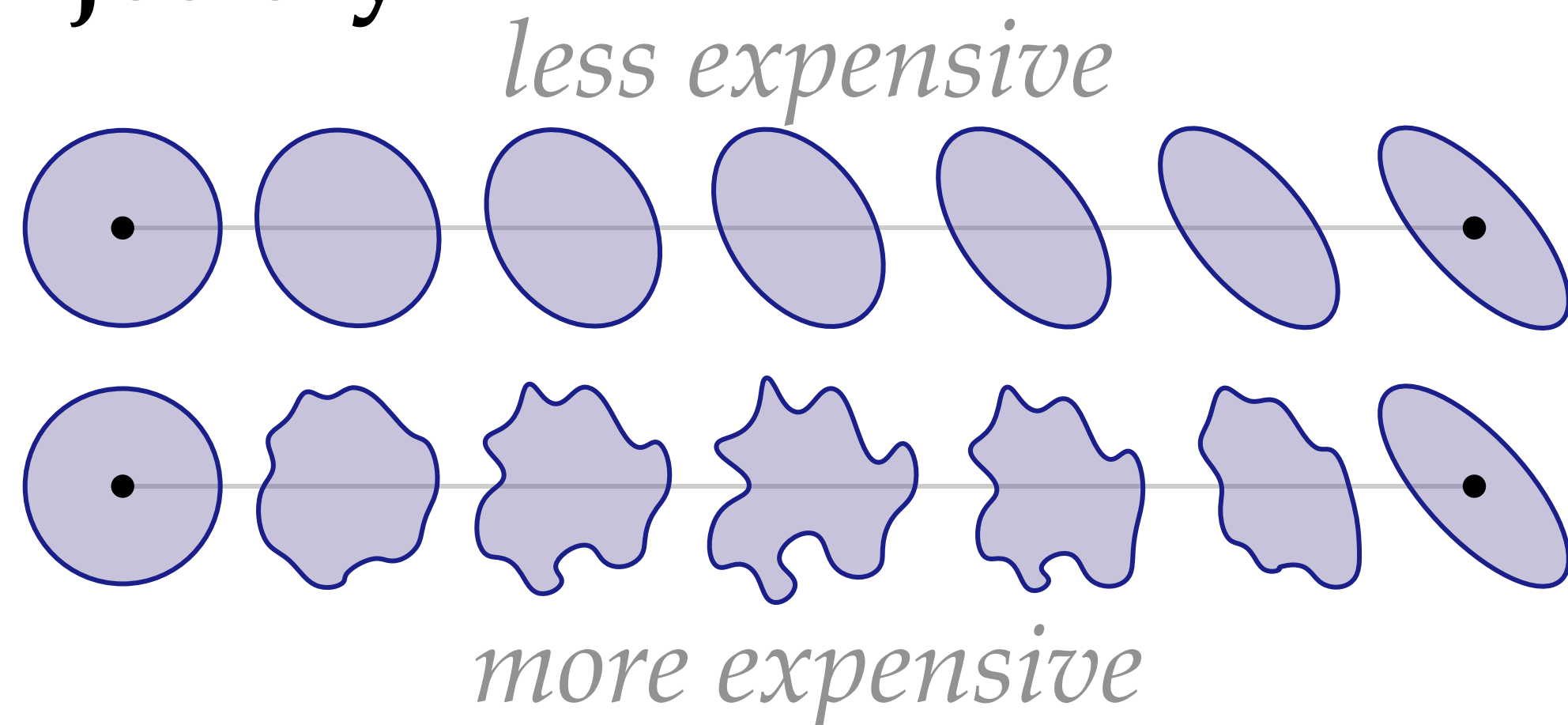
shape configurations $\leftrightarrow$ points in $\mathcal{M}$

shape trajectories $\leftrightarrow$ curves on $\mathcal{M}$

small deformations $\leftrightarrow$ tangent vectors

cost of small deformation $\leftrightarrow$ Riemannian metric g

cost of shape trajectory $\leftrightarrow$ path energy $\mathcal{E}$

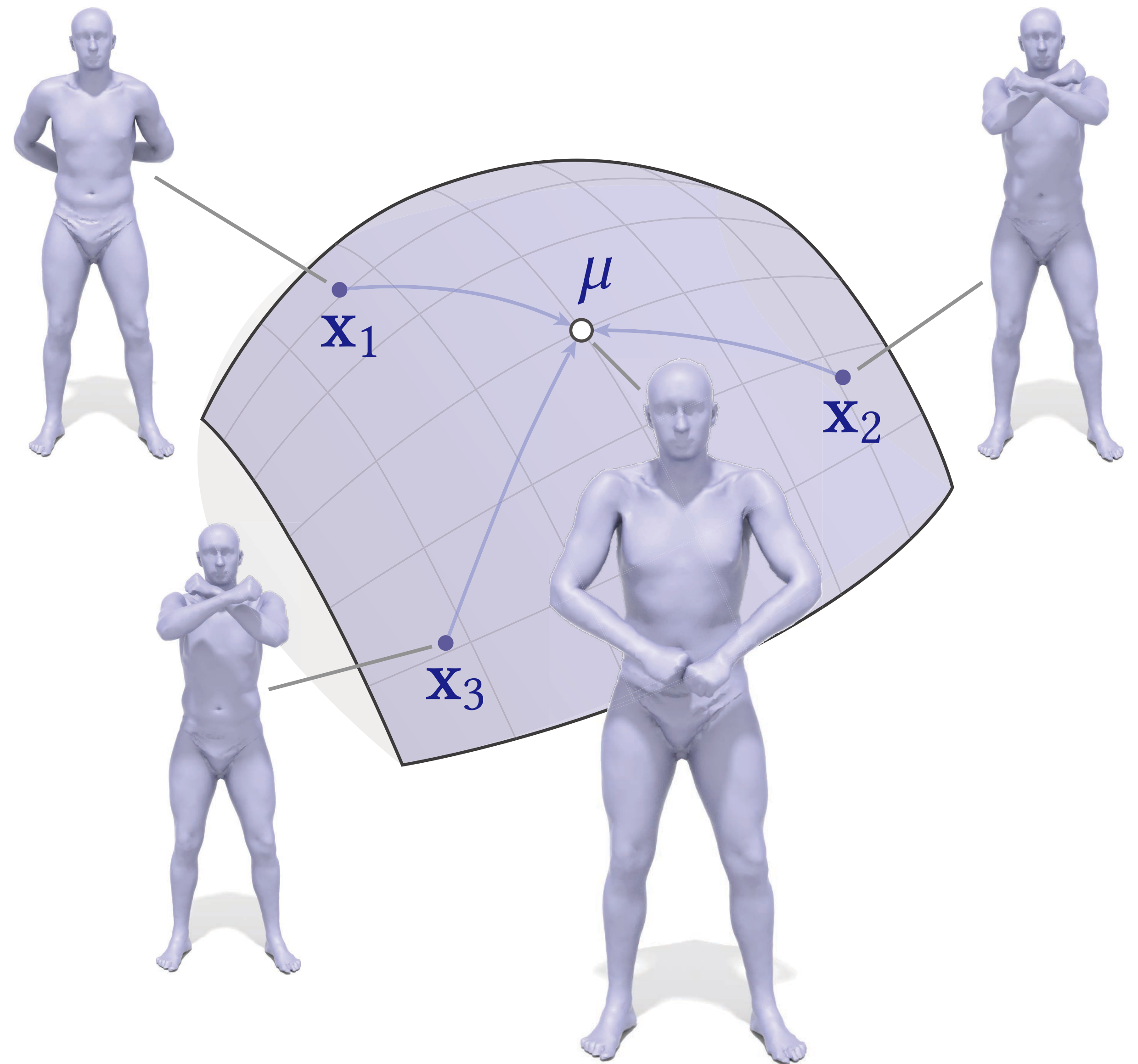


$$\mathcal{E}(\mathbf{x}(t)) = \int_0^1 g_{\mathbf{x}(t)}(\dot{\mathbf{x}}(t), \dot{\mathbf{x}}(t)) dt$$

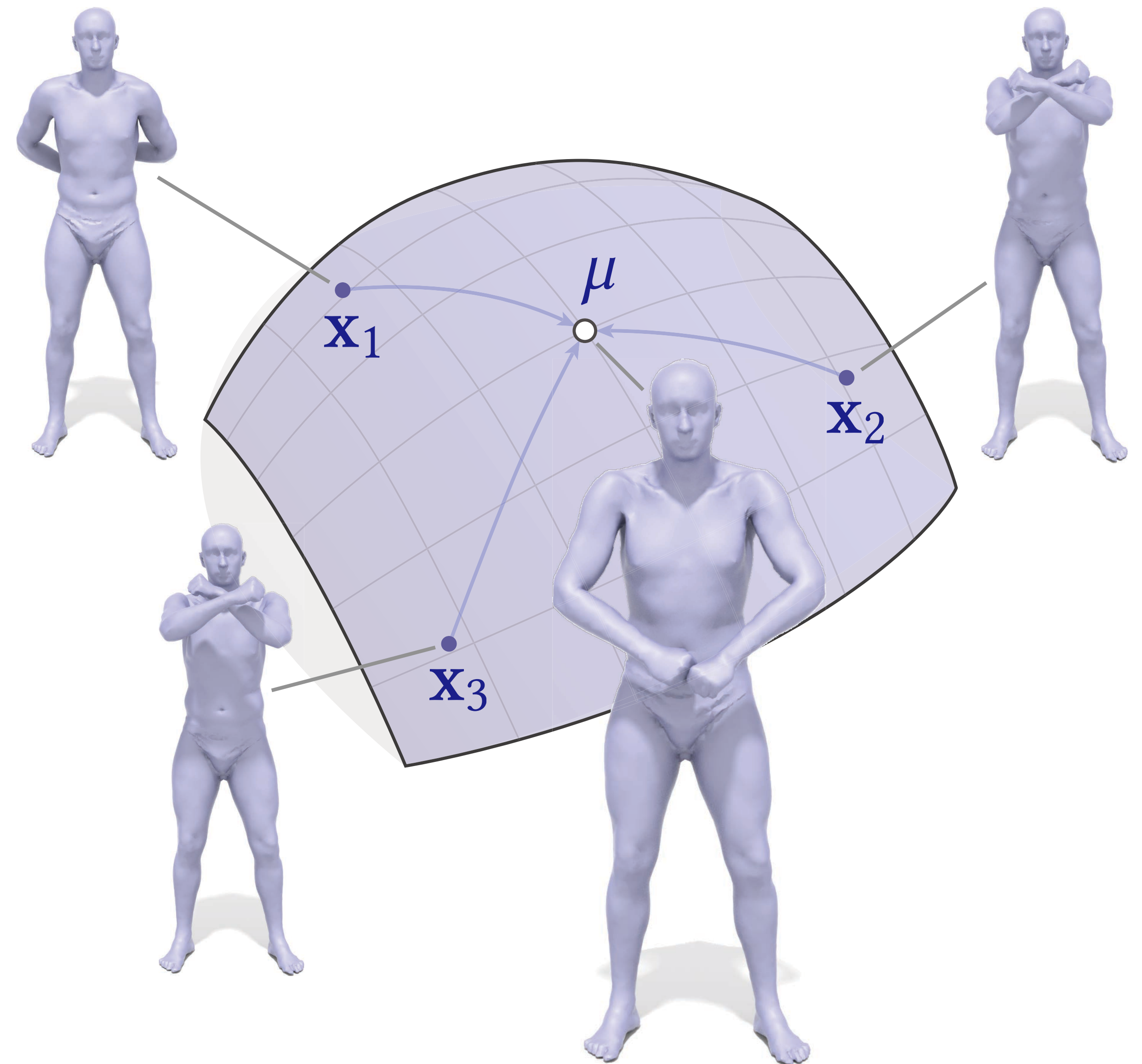
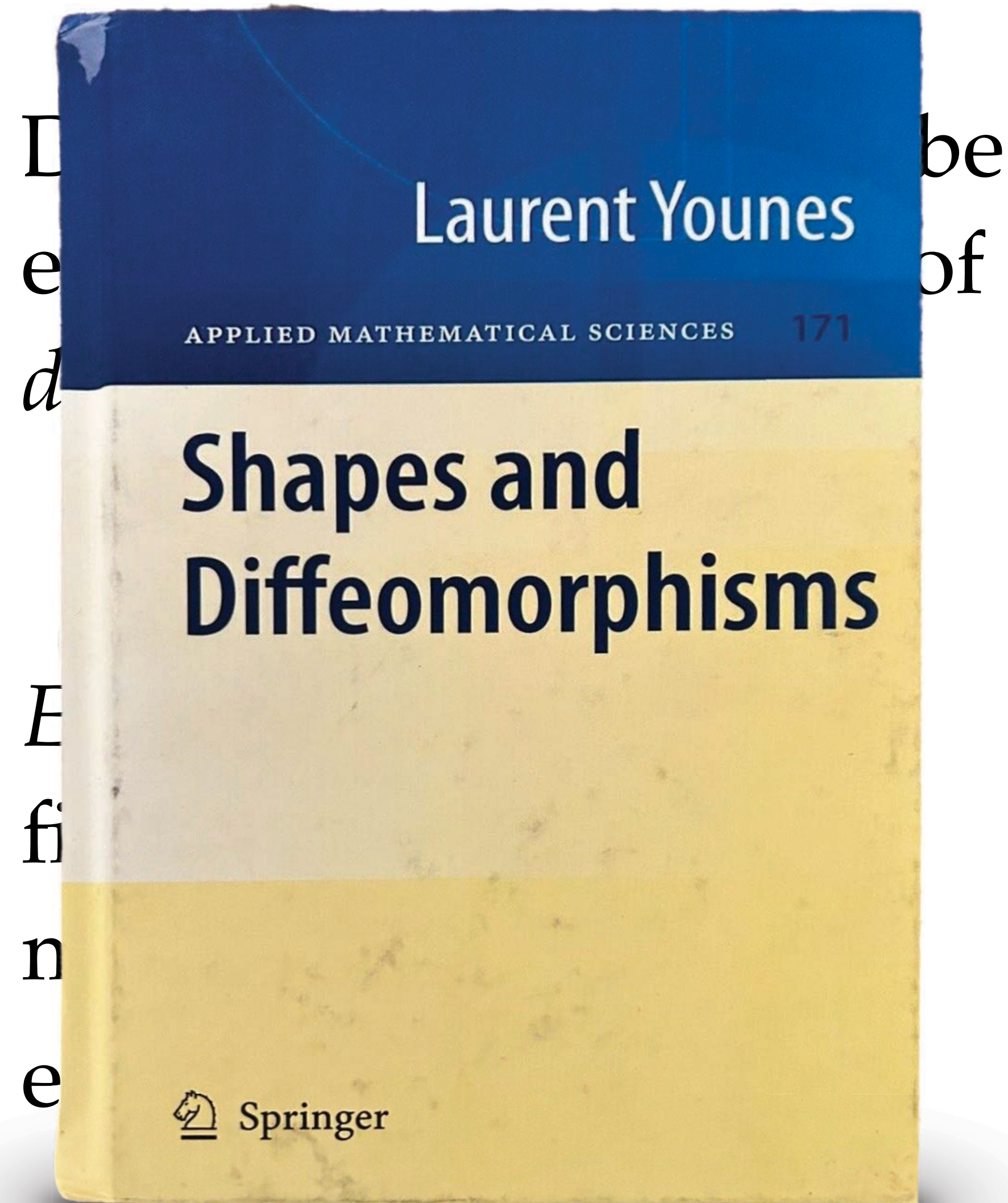
Data Analysis in Riemannian Shape Space

Data analysis can now be expressed in language of *differential geometry*.

E.g., to define “mean,” find point μ that minimizes sum of path energy to all points $\mathbf{x}_i$.



Data Analysis in Riemannian Shape Space



Question: what's the “right” **shape space** for representing / analyzing high-resolution cell data?

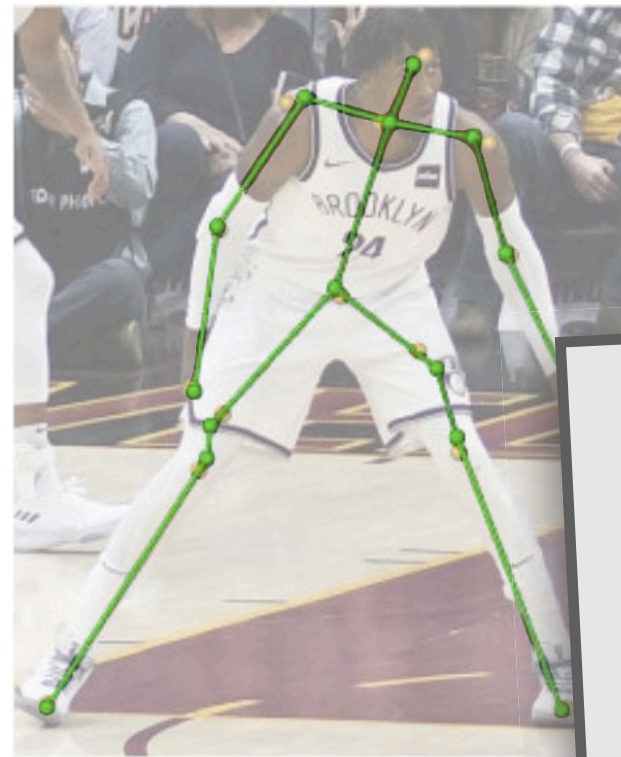
Shape Spaces for Biomembranes—Challenges

- **Several key challenges** (*plenty I'm not thinking about!*):
 1. Need good continuum models (see Deserno 2015, Argudo et al 2016, ...)
 - e.g., dynamics, growth, evolution, ...
 2. Incorporate data beyond shape (e.g., chemical concentrations)
 3. Empirical data should inform shape space definition
 4. Need good numerical discretization
 - handles large shearing
 - allows topology changes
 - models non-local forces (e.g., electrostatic repulsion)

Some Common Shape Space Frameworks

landmarks

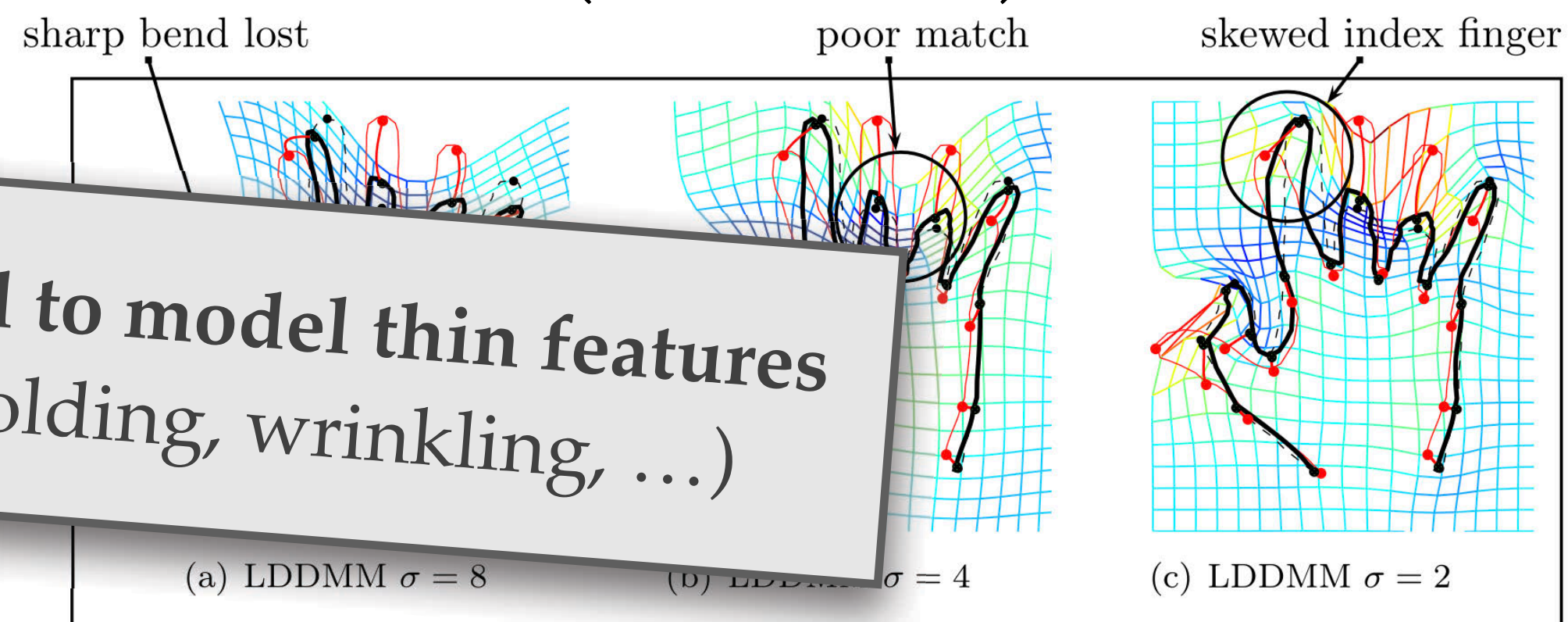
(Kendall shape space)



discards most information
(keeps just a few points)

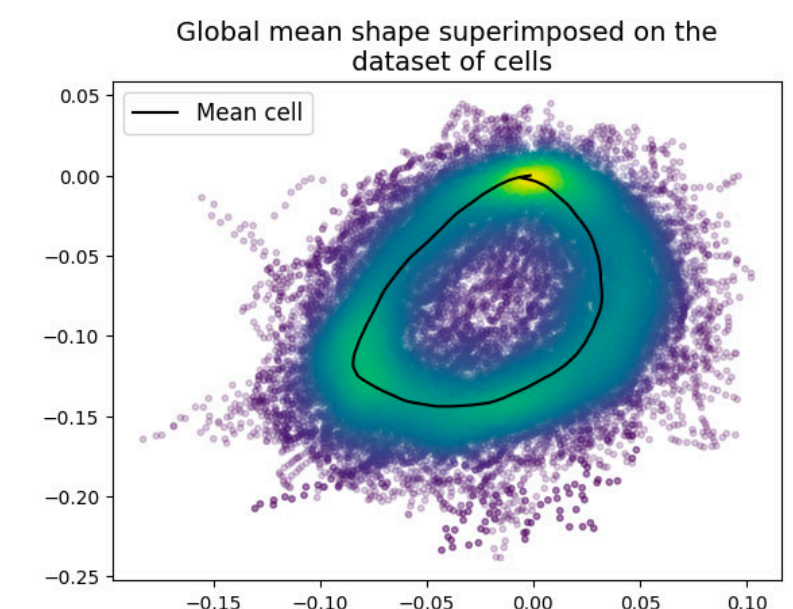
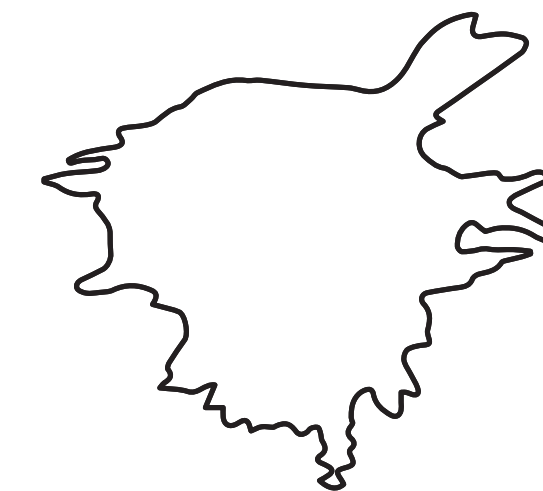
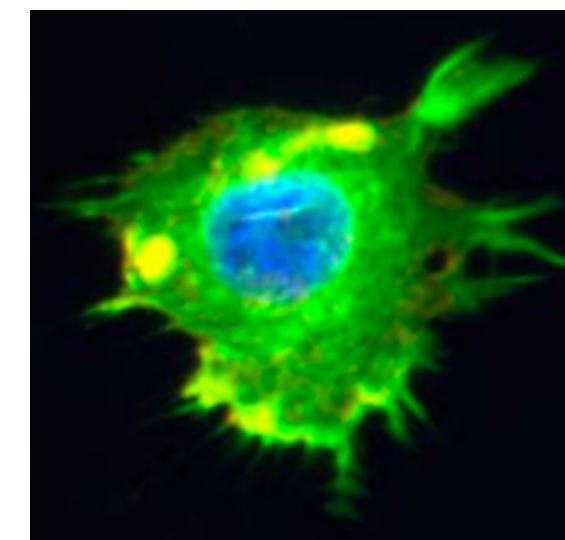
deformations of space

(LDDMM)

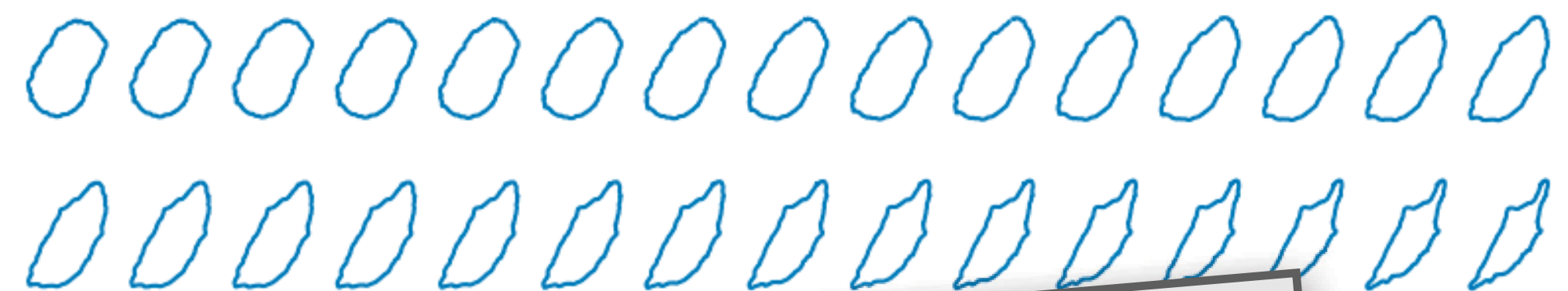


2D boundaries

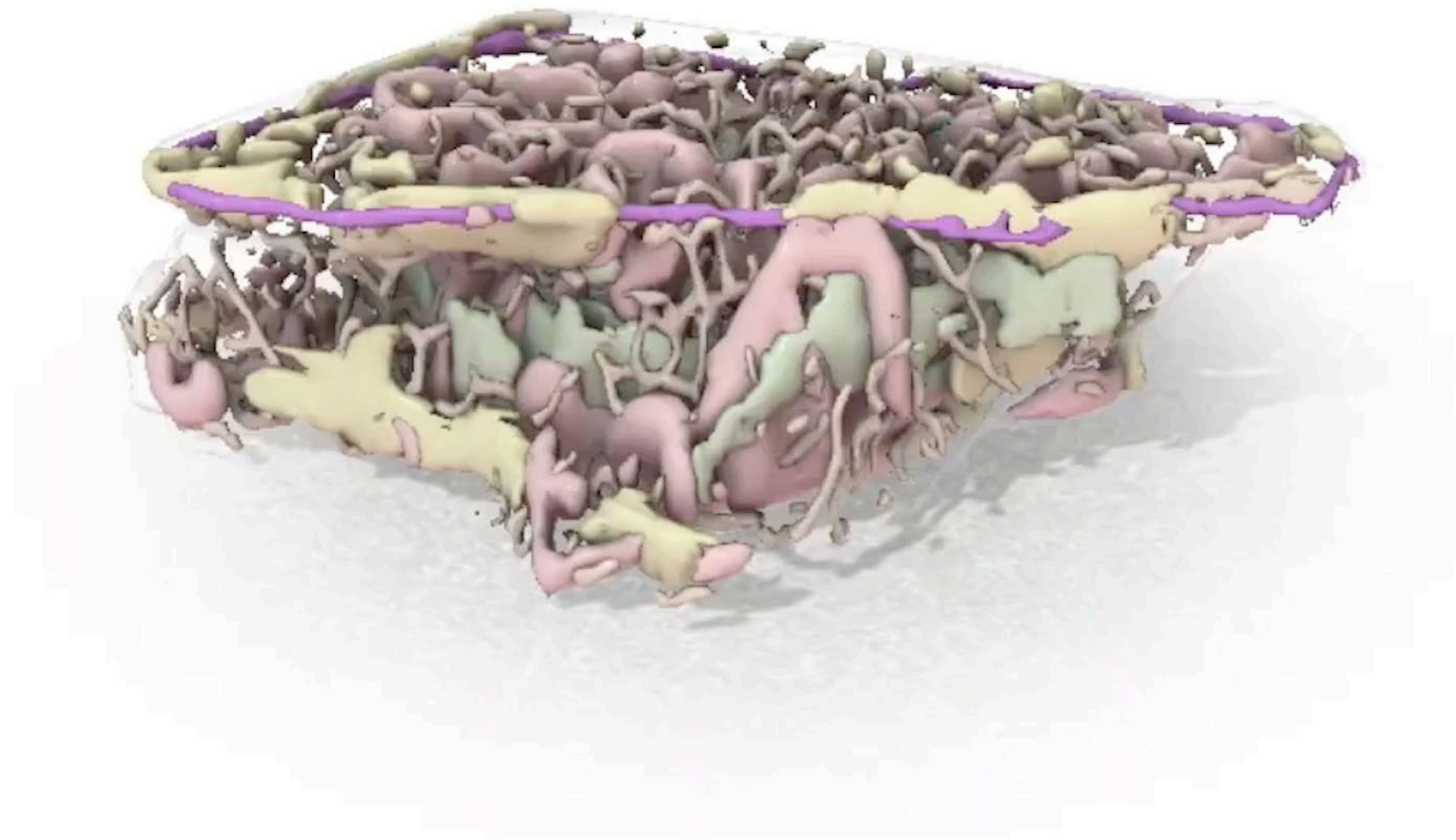
(spaces of elastic curves)



Geodesic between two cells



discards all information
about 3D geometry



If we have 3D cell data, shouldn't our shape space model 3D configurations?

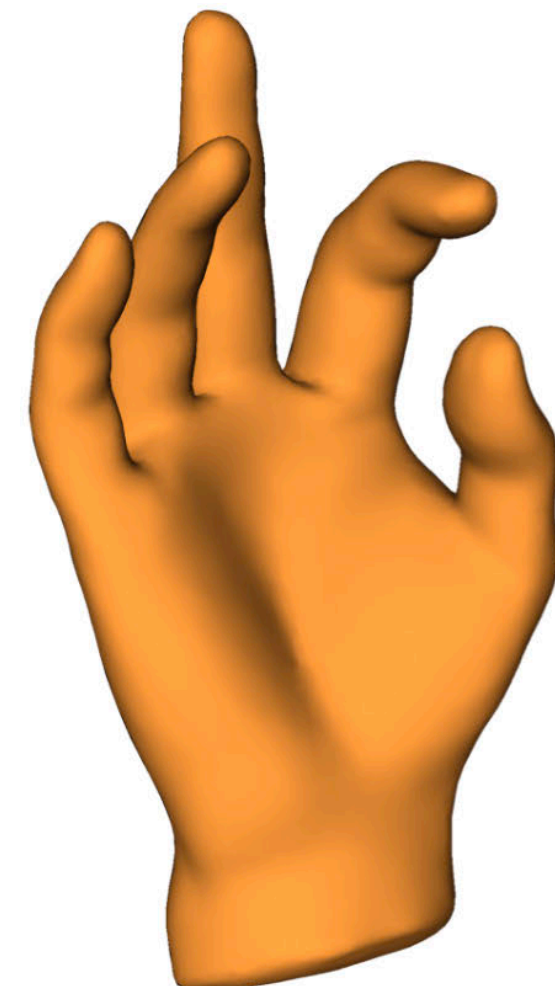
Shape Space of Elastic Shells

configuration space: embeddings of thin elastic shell

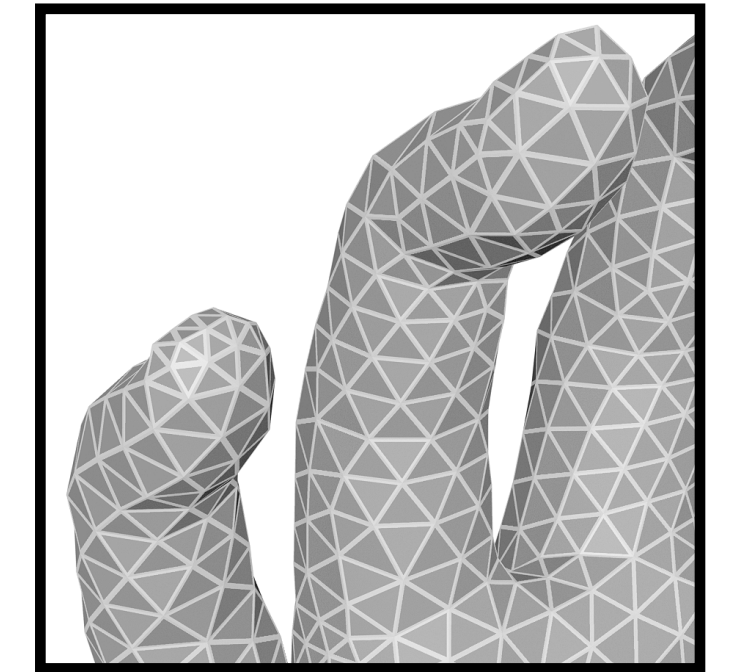
Riemannian metric: penalize *viscous dissipation*

e.g., “cheapest” path (geodesic)

start



end



*discretized
via fine mesh*

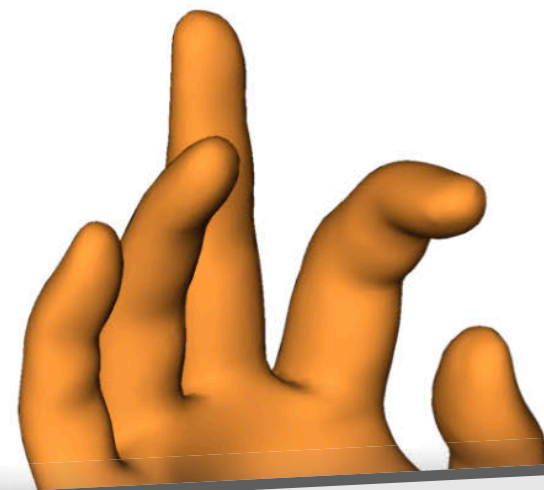
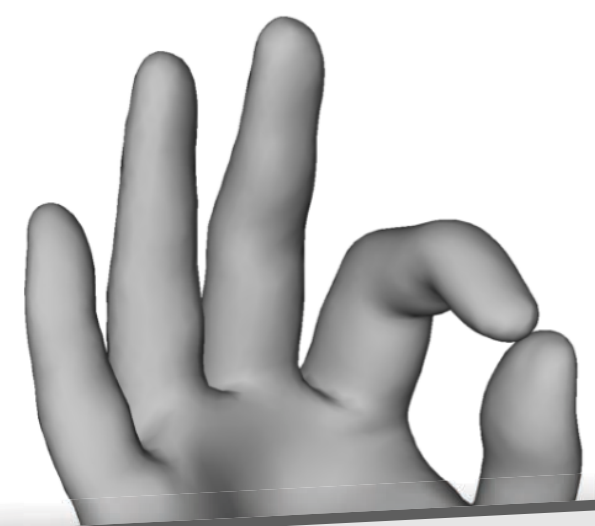
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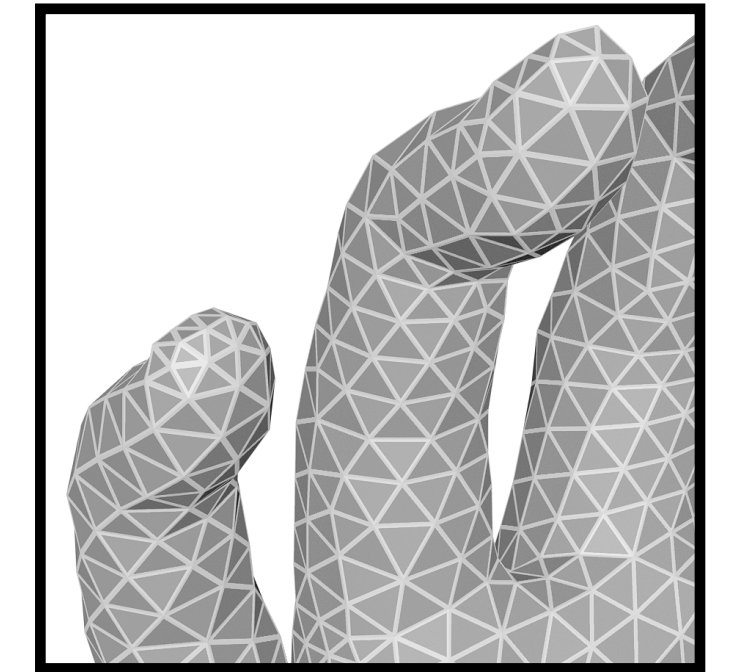


end



Also: elastic shells are a natural model for many biomembranes!

Problem: designed for macroscopic elastic shells...



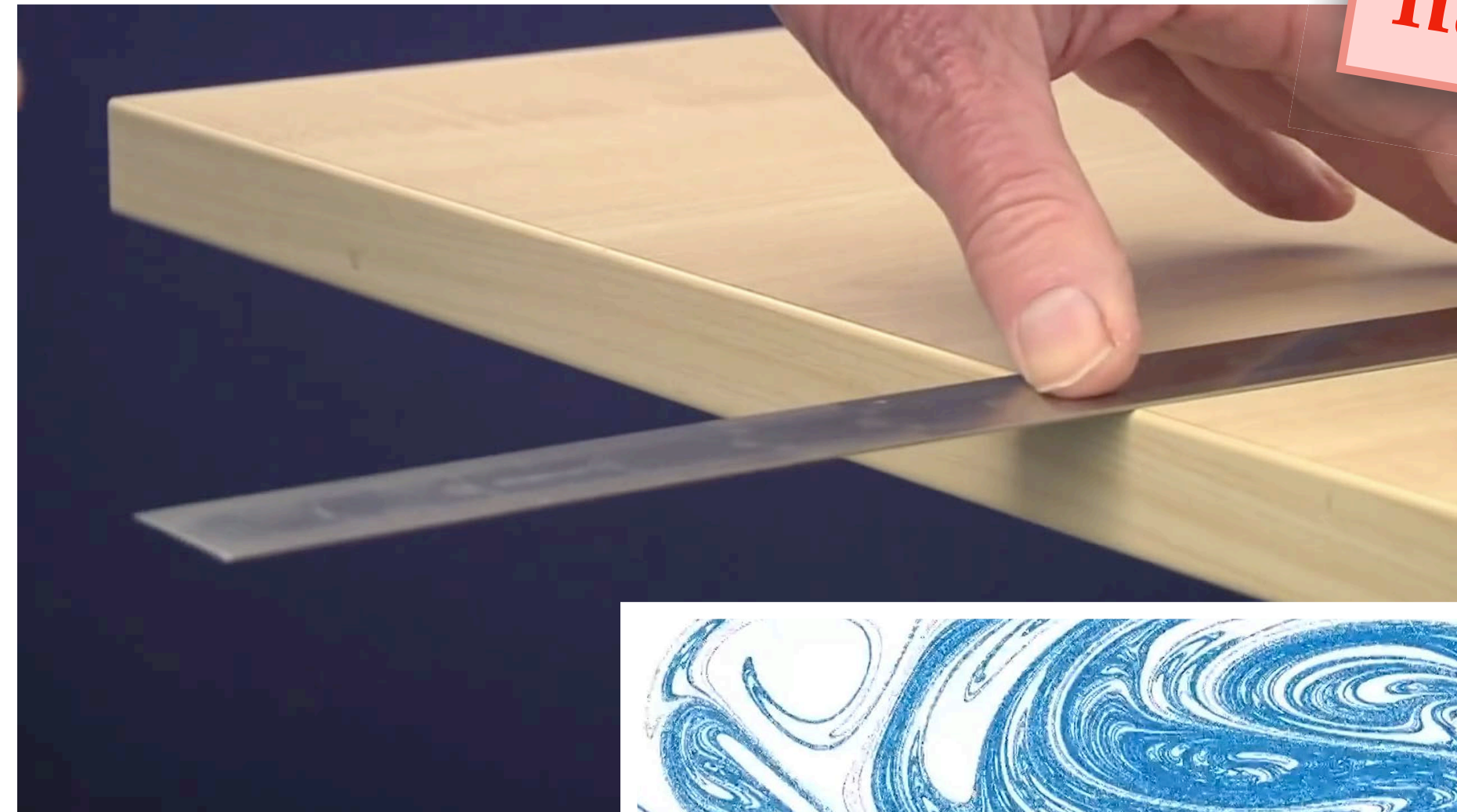
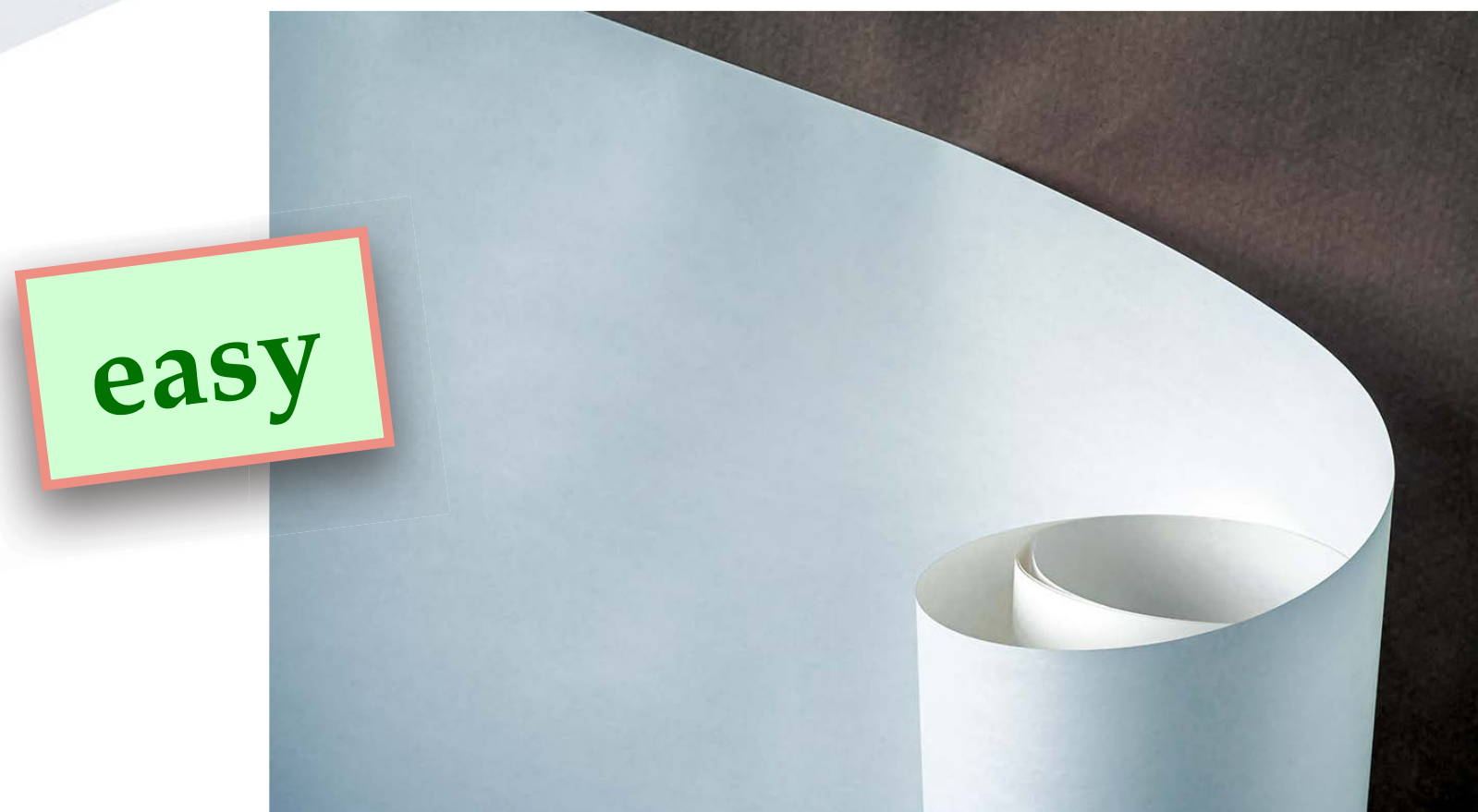
discretized via fine mesh

- uses full 3D geometry ✓
- handles fine structures / close contact ✓
- easy to augment w/ additional data ✓

Heeren et al, “Exploring the Geometry of the Space of Shells” (2014)

Challenge—Shearing

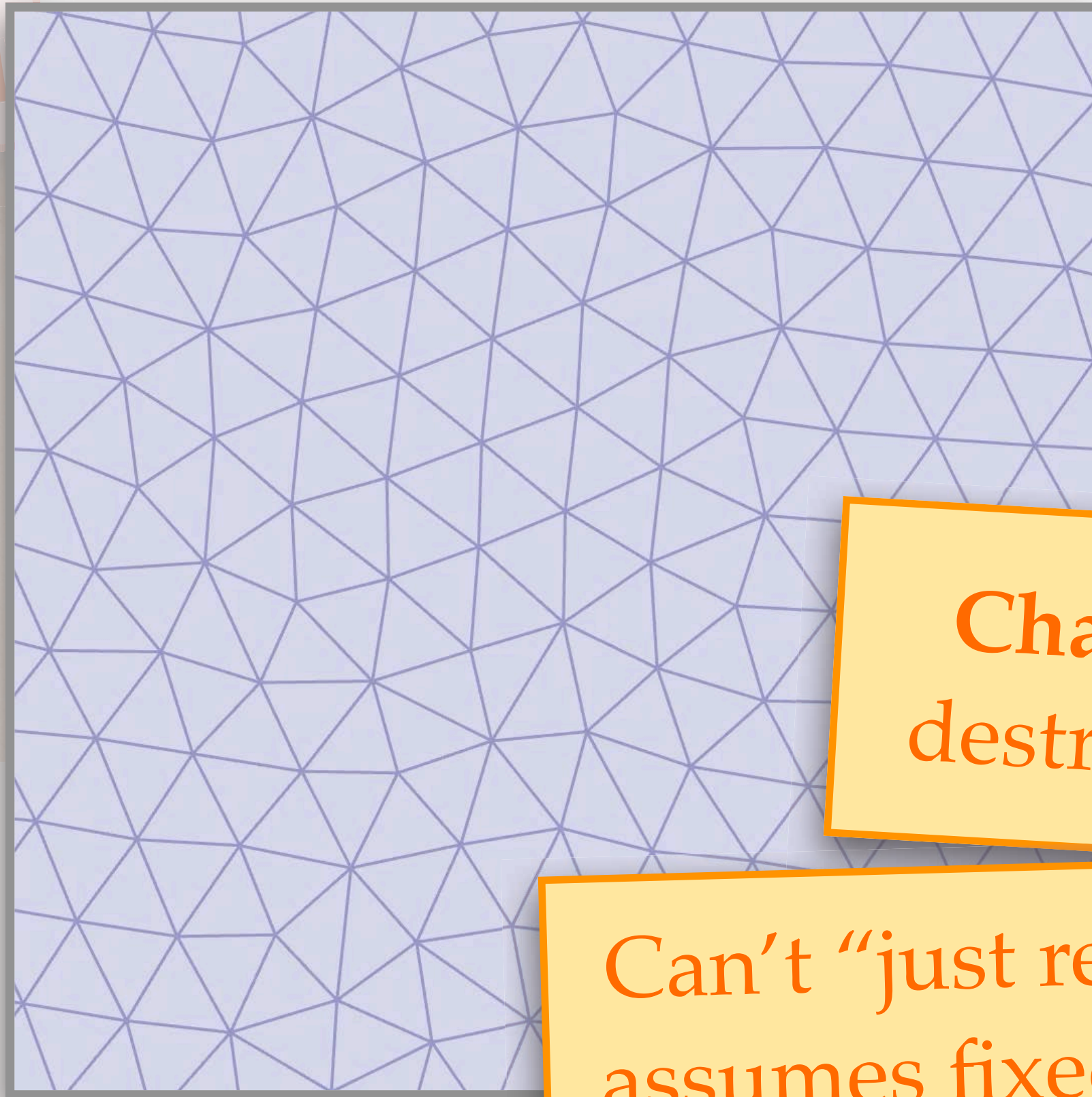
- **Macroscopic shell:** hard to shear; easy to bend (*e.g.*, paper)
- **Biomembrane:** hard to bend; easy to shear (*e.g.*, bilipid)



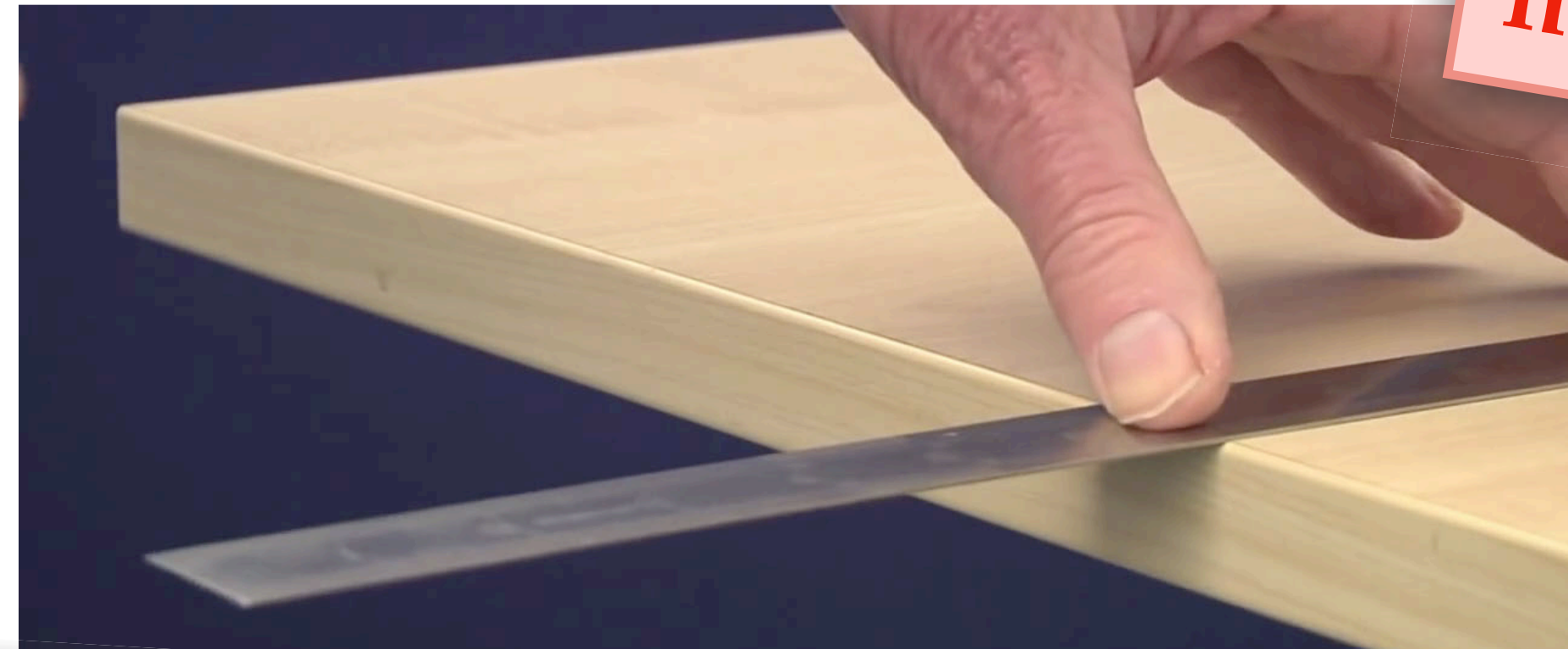
Challenge—Shearing

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- **Biomembrane:** hard to bend; easy to shear (*e.g.*, bilipid)

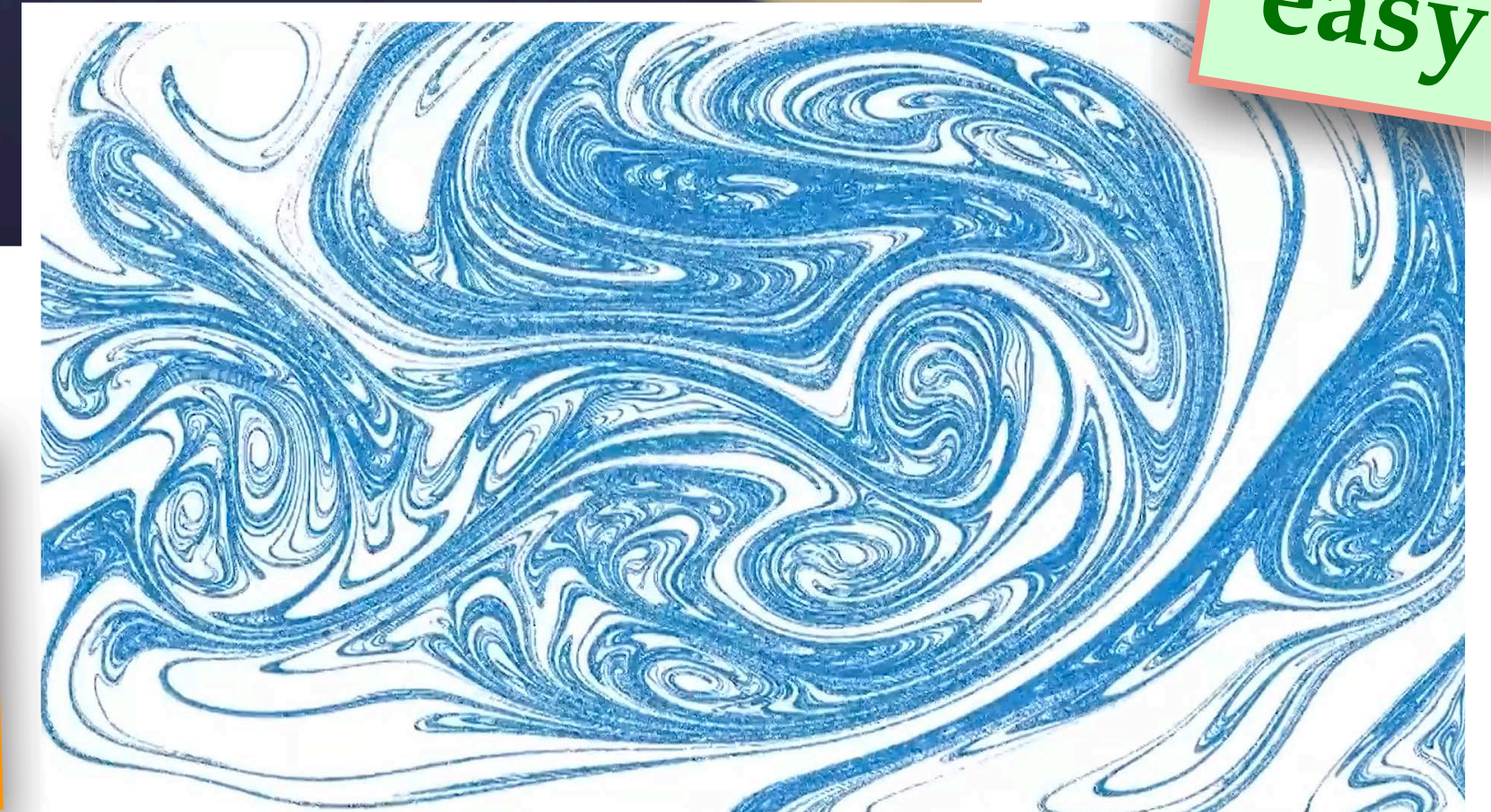
hard



hard



easy

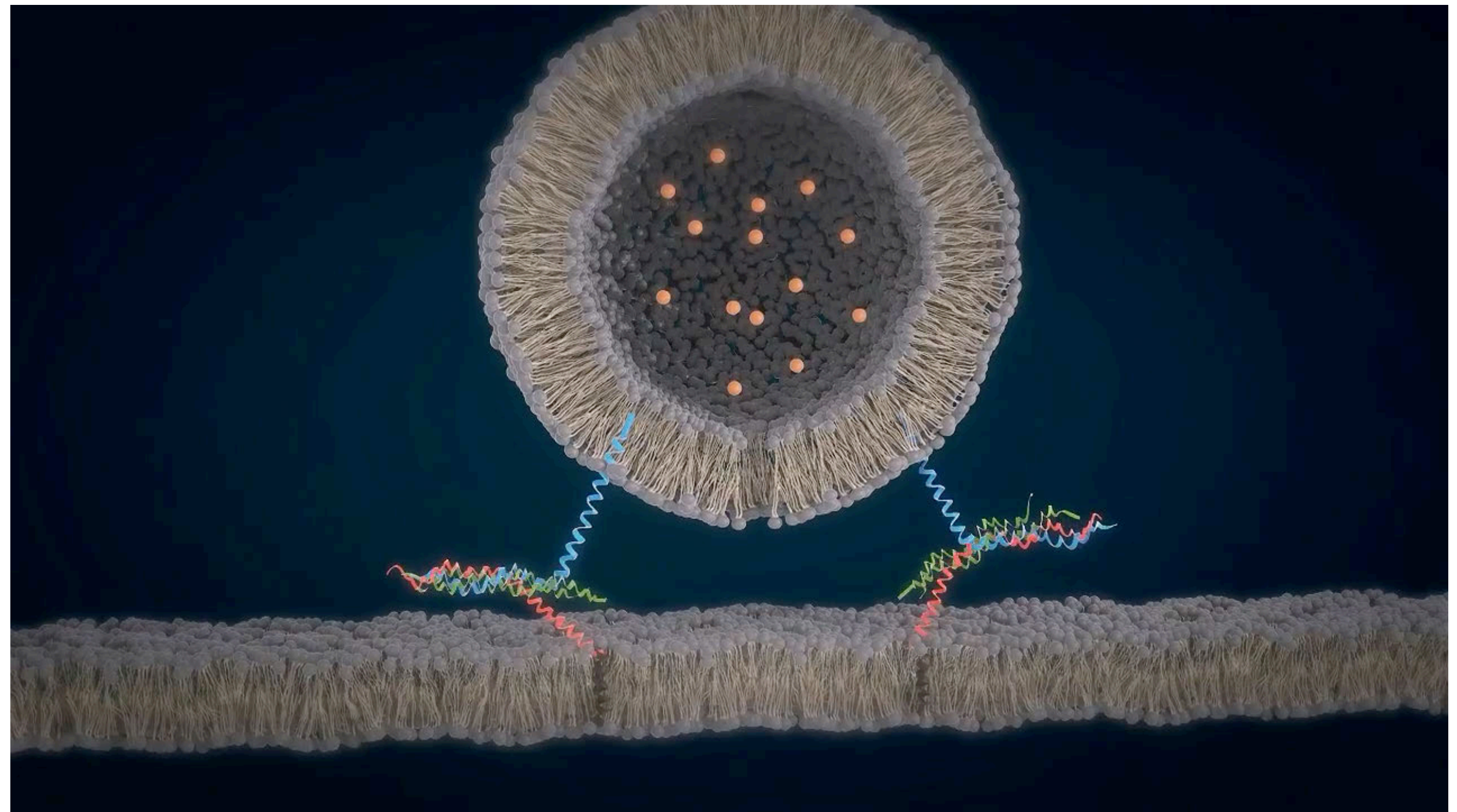
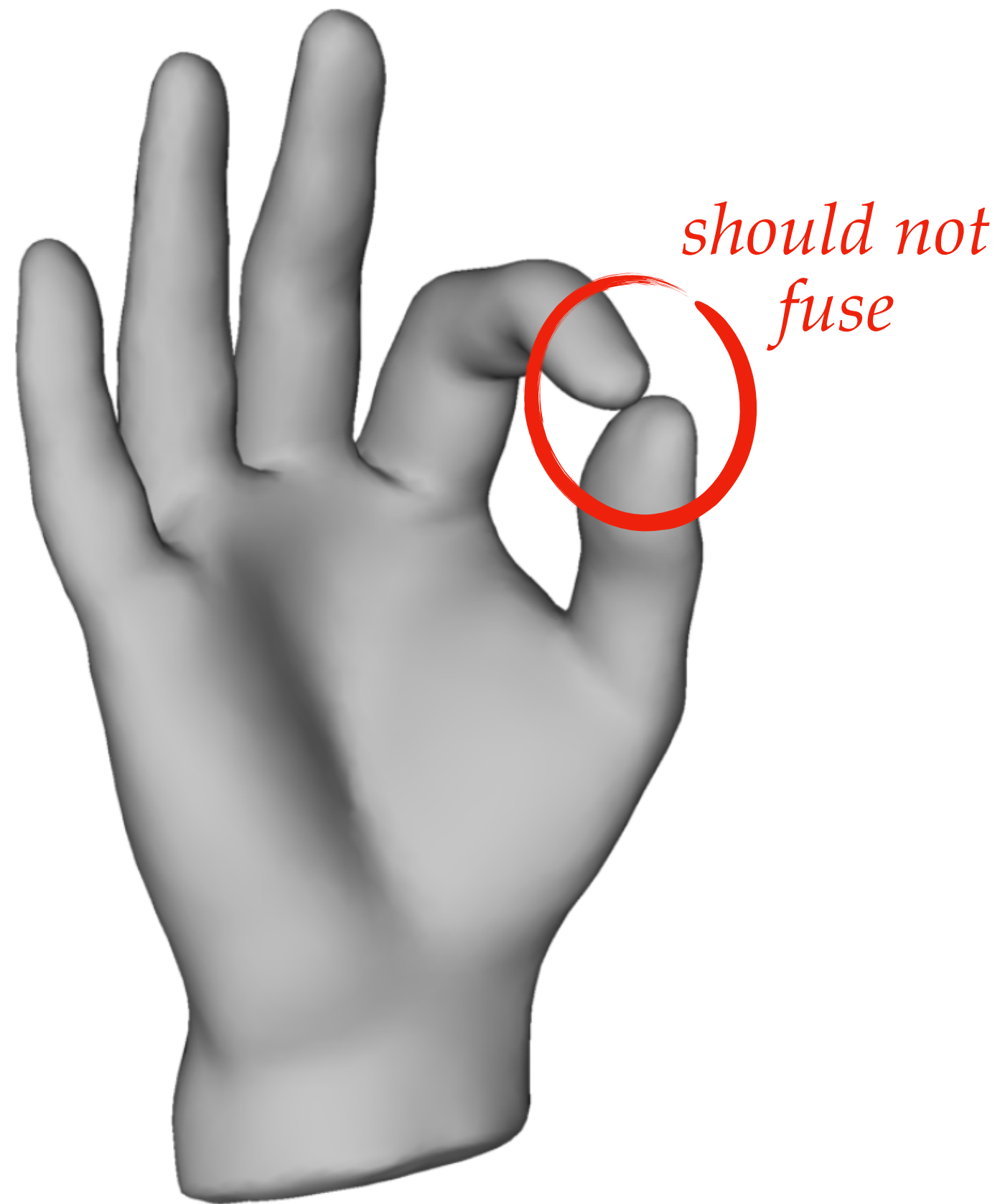


Challenge: shearing destroys mesh quality.

Can't "just remesh": shape space assumes fixed mesh connectivity.

Challenge—Topology Changes

- **Macroscopic shell:** shouldn't merge when in close contact (e.g., hand)
- **Biomembrane:** merging / splitting is critical (e.g., vesicle fusion)



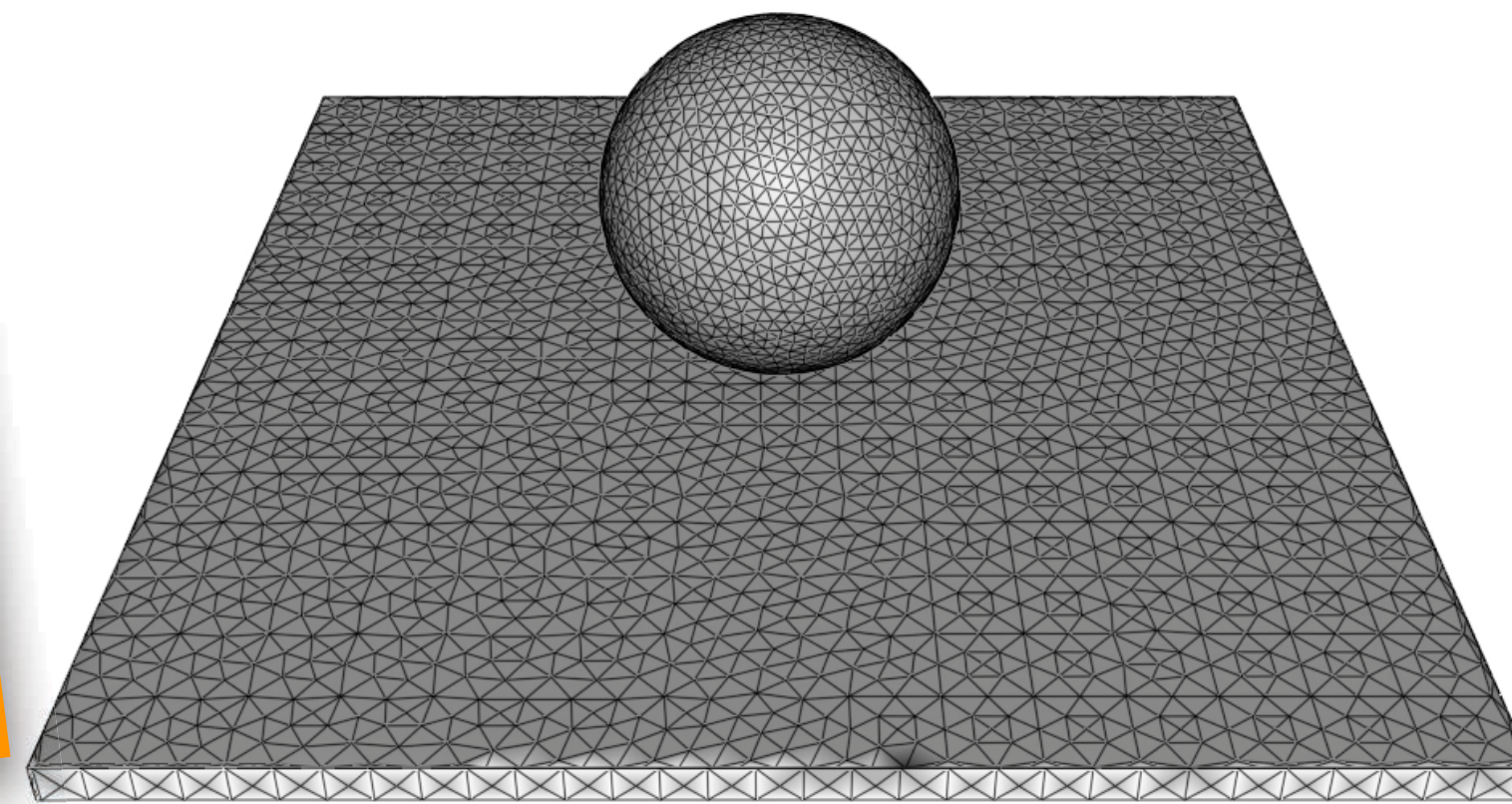
Challenge—Topology Changes

- **Macroscopic shell:** shouldn't merge when in close contact (e.g., hand)
- **Biomembrane:** merging / splitting is critical (e.g., vesicle fusion)

should not

Again: shape space assumes
fixed mesh connectivity

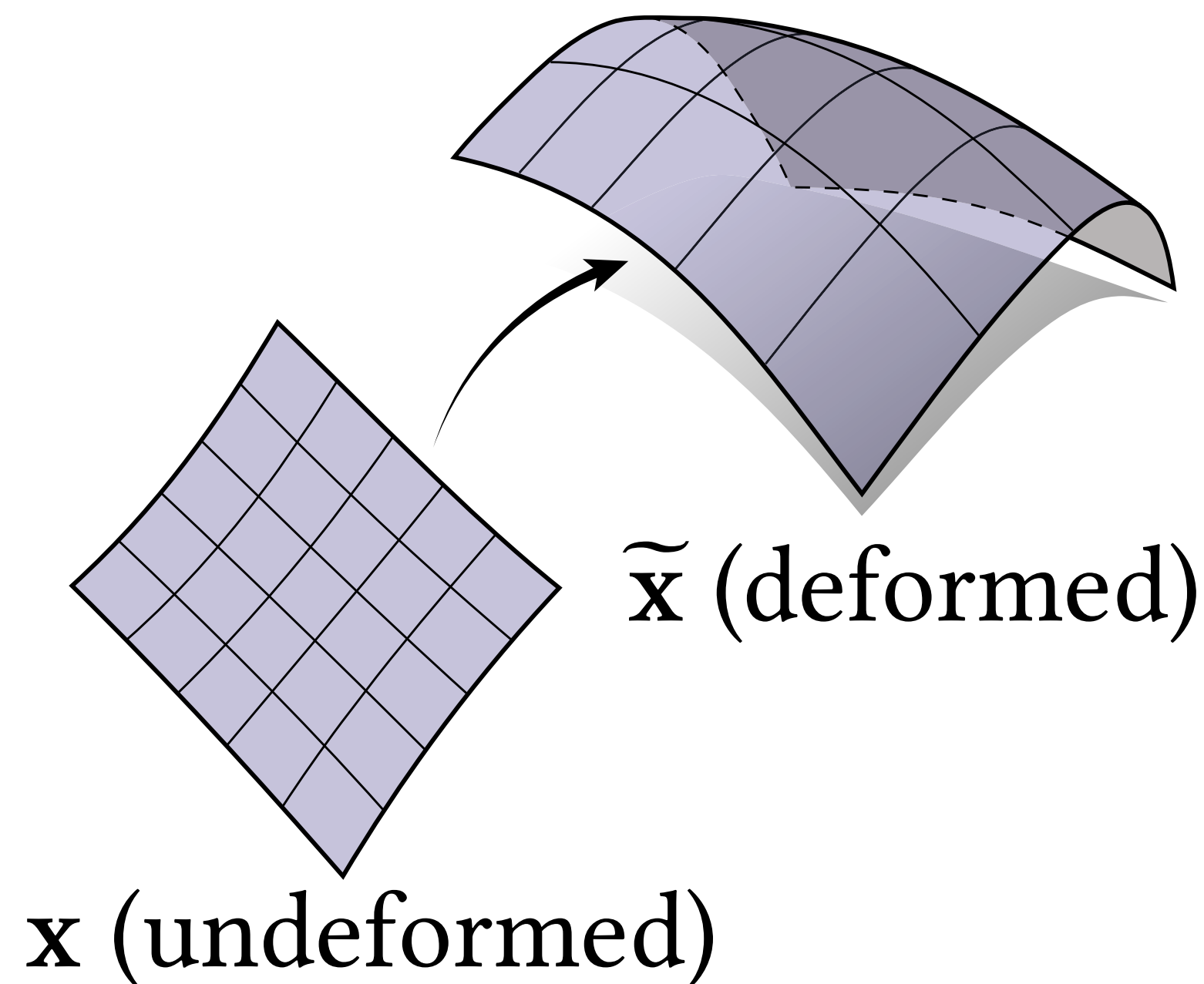
Bigger challenge: what is Riemannian
configuration space for surfaces with
dynamic topology?



Challenge—Data Beyond Geometry

- **Macroscopic shell:** state determined by geometry (positions in space)
- **Biomembrane:** geometry interacts w / chemistry (mechanochemical)

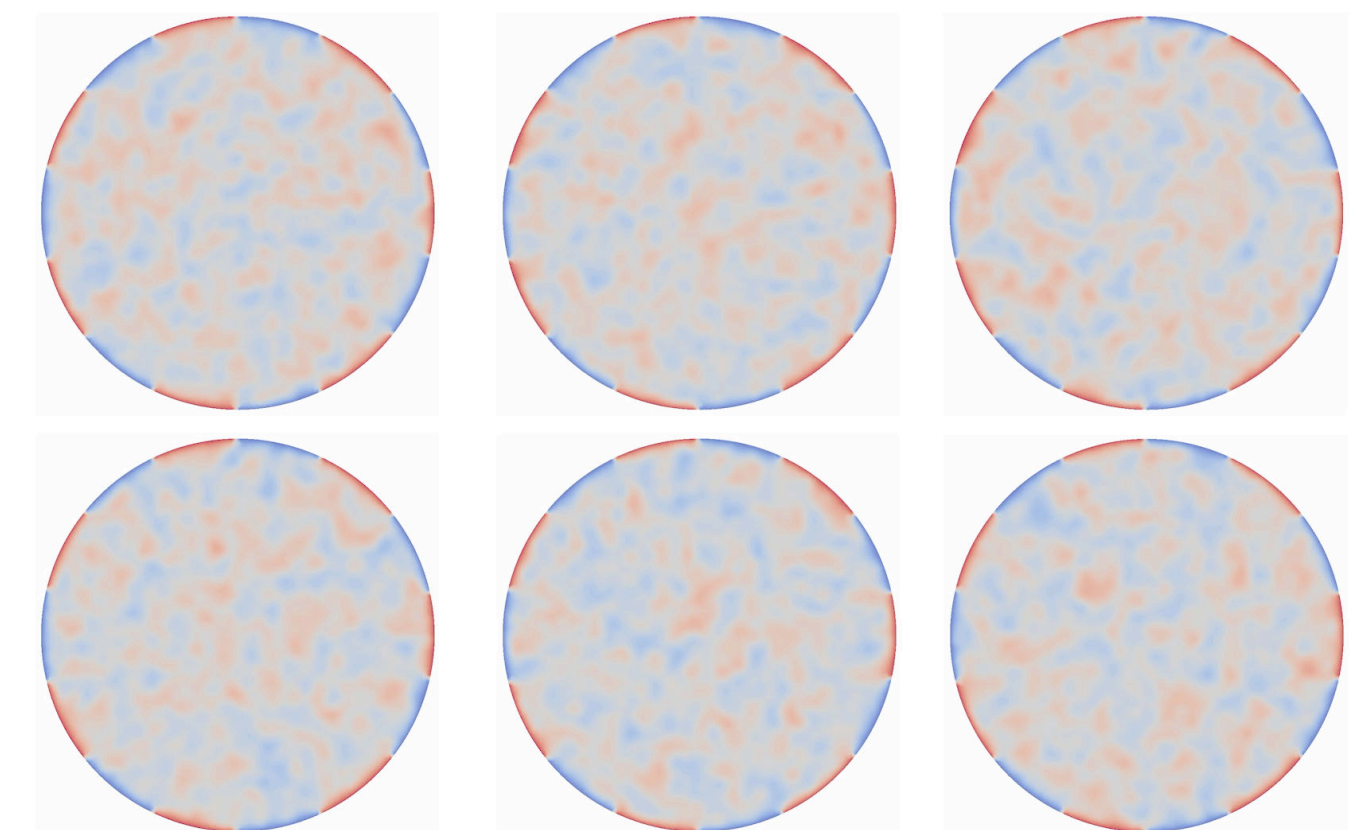
geometry: Riemannian metric $g(u,v)$ comes from *Hessian of elastic potential* $\mathcal{W}(\mathbf{x}, \tilde{\mathbf{x}})$



$$g(u, v) := \nabla^2 \mathcal{W}(\mathbf{x}, \mathbf{y})|_{\mathbf{y}=\mathbf{x}}(u, v)$$

chemistry: Hessian of chemical variational principle?
(e.g., Modica-Mortola functional $\Rightarrow$ reaction-diffusion)

Challenge: how does chemistry influence the Riemannian metric?

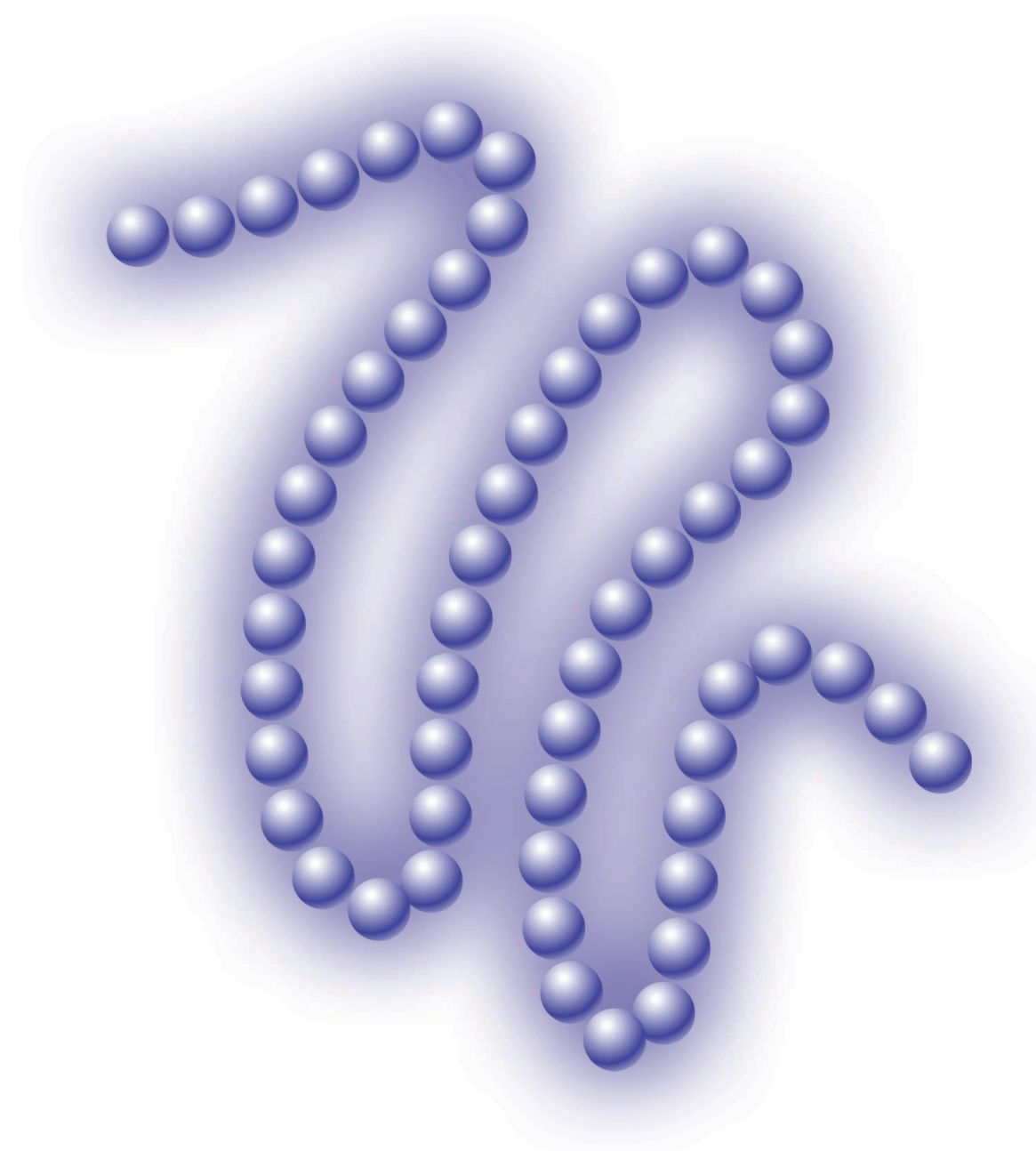


Challenge—Nonlocal Effects

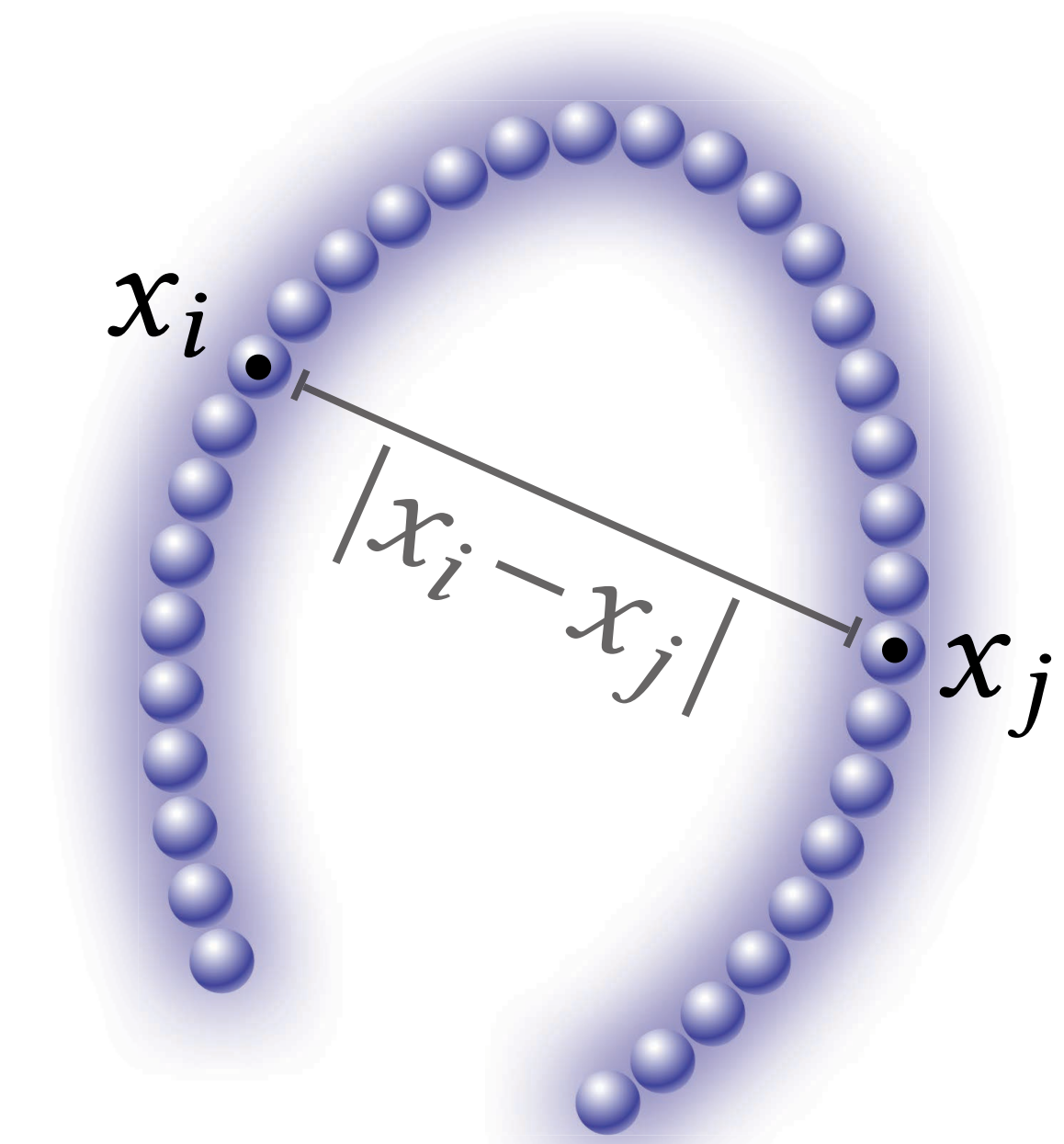
- Many phenomena depend on interaction between distant points
 - **macroscopic shells:** contact modeled as a *repulsive potential*
 - **biomembranes:** electrostatic repulsion, heat transfer...

e.g., Coulomb potential

$$\Phi(\mathbf{x}) = \sum_i \sum_{j \neq i} \frac{1}{|\mathbf{x}_i - \mathbf{x}_j|^2}$$



bigger Φ



smaller Φ

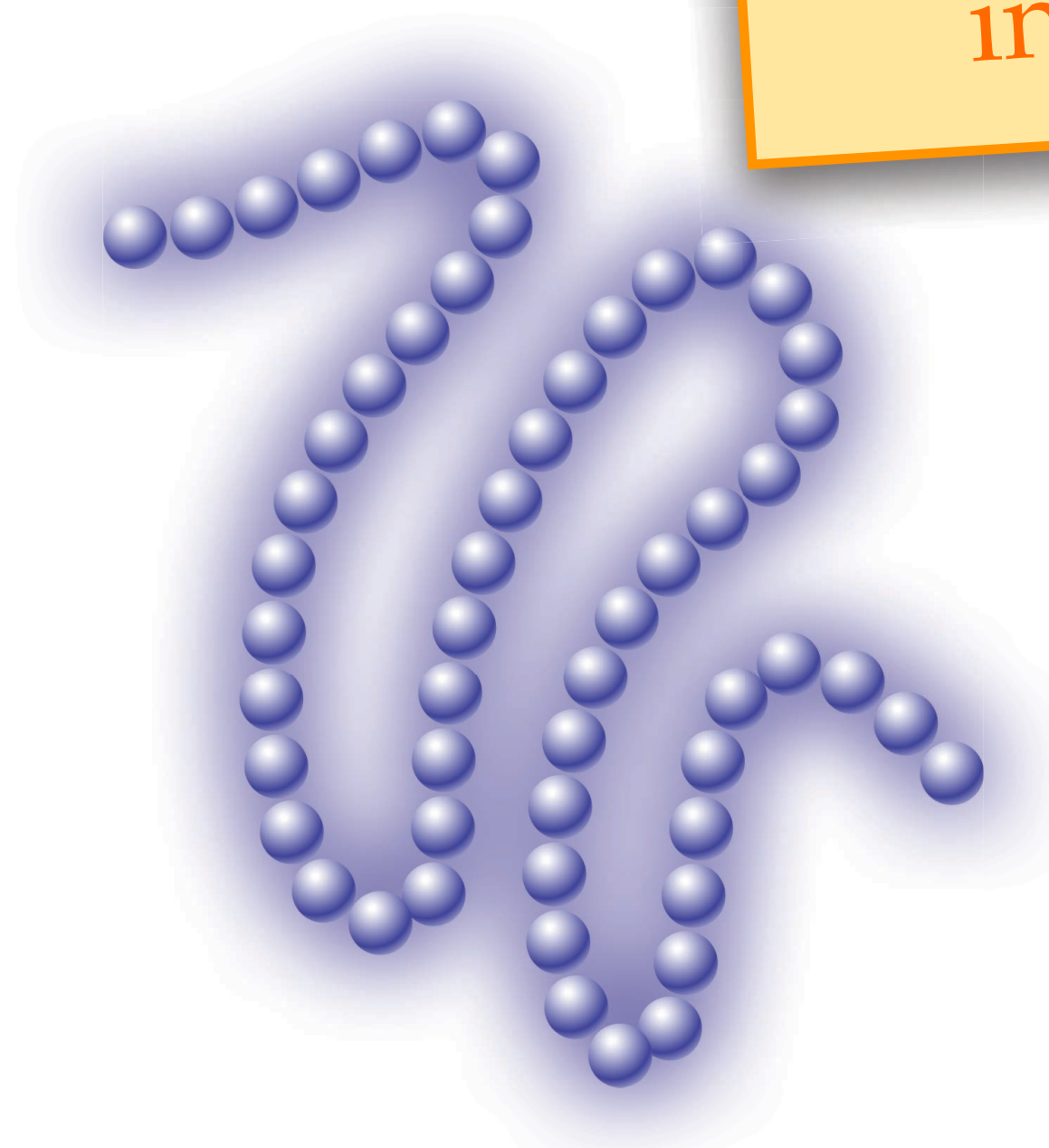
Challenge—Nonlocal Effects

- Many phenomena depend on interaction between distant points
 - **macroscopic shells:** contact modeled as a *repulsive potential*
 - **biomembranes:** electrostatic repulsion, he

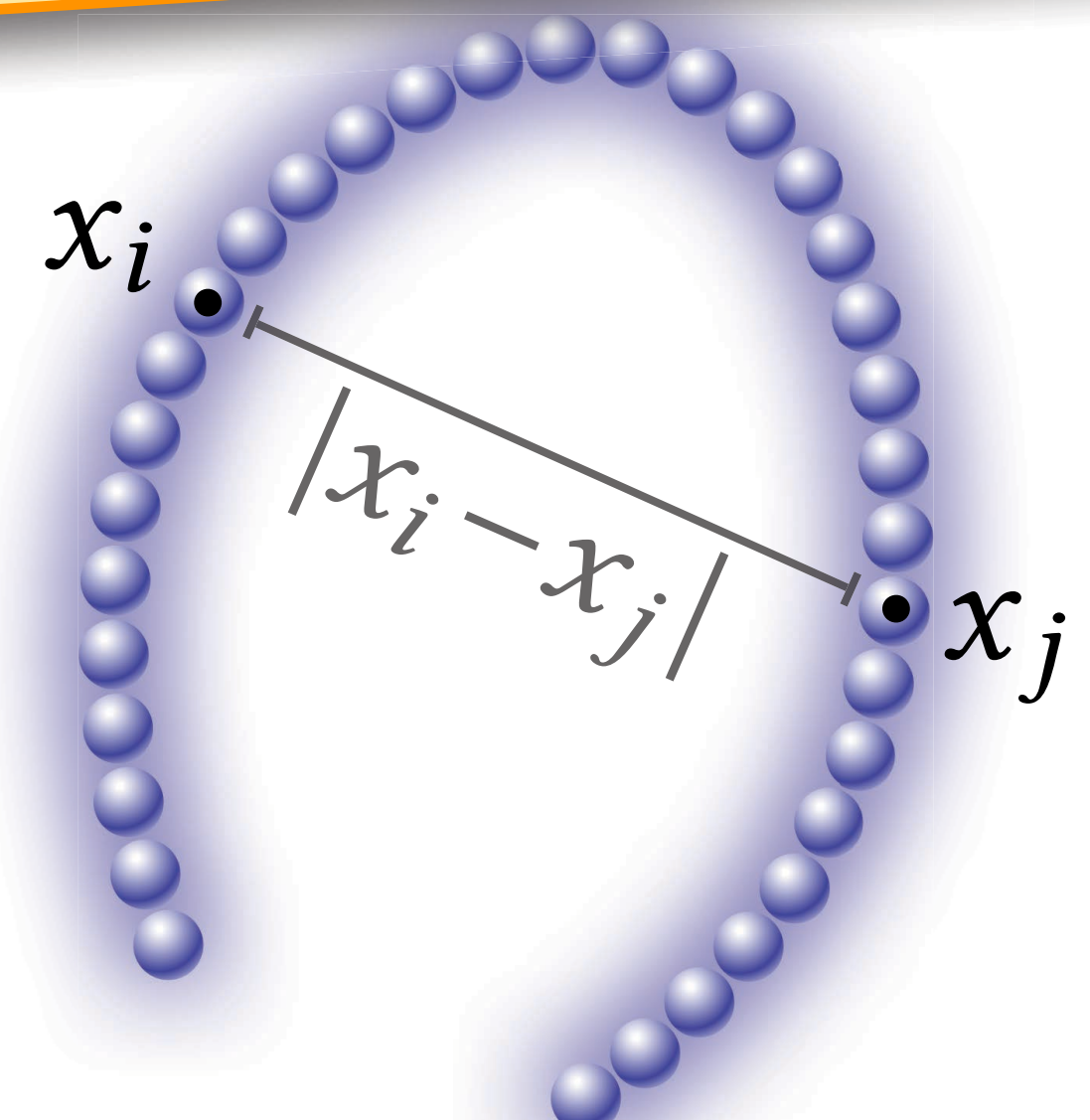
Challenge: how do you incorporate a nonlocal potential into a Riemannian metric?

e.g., Coulomb potential

$$\Phi(\mathbf{x}) = \sum_i \sum_{j \neq i} \frac{1}{|x_i - x_j|^2}$$



bigger Φ

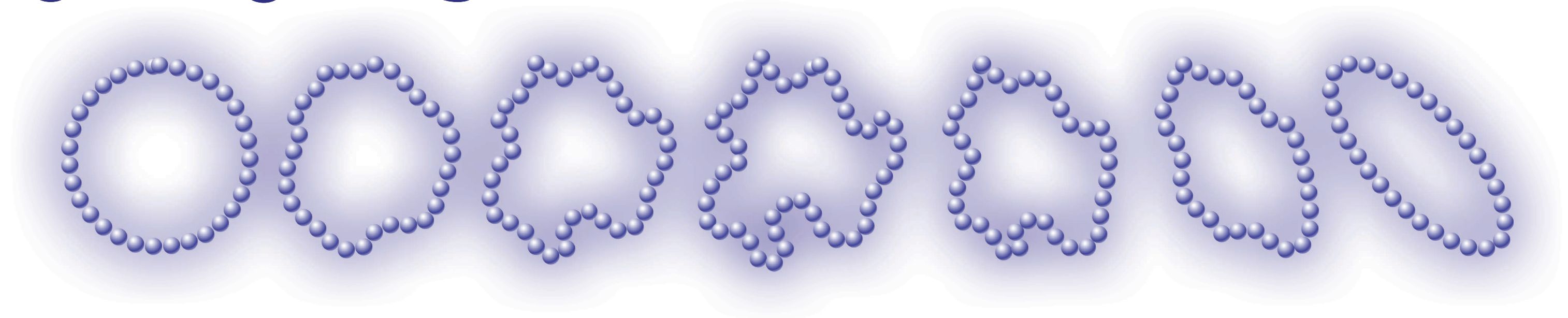
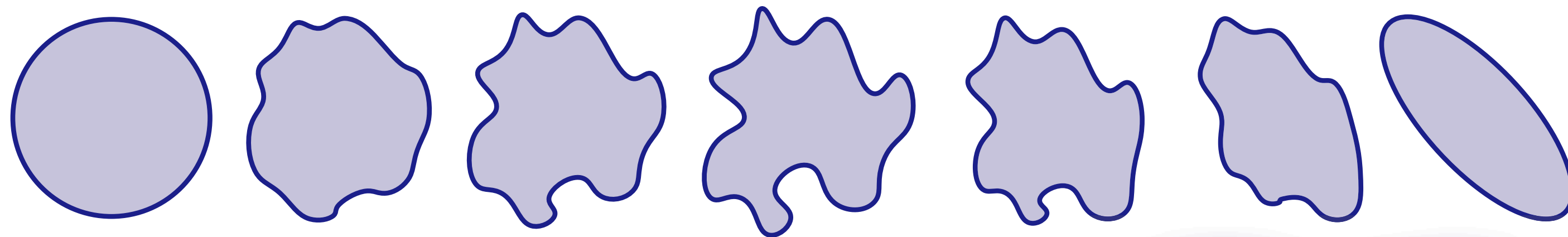


smaller Φ

Nonlocal Forces—Naïve Approach

One idea: simply add repulsive potential to cost of any path

$$\mathcal{E}(\mathbf{x}(t)) = \int_0^1 \overset{\text{viscous}}{\underset{\text{dissipation}}{g_{\mathbf{x}(t)}(\dot{\mathbf{x}}(t), \dot{\mathbf{x}}(t))}} dt + \int_0^1 \overset{\text{total potential}}{\underset{\text{over time}}{\Phi(\mathbf{x}(t))}} dt$$



Nonlocal Forces — Naïve Approach

One idea: simply add repulsive potential to cost of any path

path
energy

viscous
dissipation

total potential
over time

$$\mathcal{E}(\mathbf{x}(t)) = \int_0^1 g_{\mathbf{x}(t)}(\dot{\mathbf{x}}(t), \dot{\mathbf{x}}(t)) dt + \int_0^1 \Phi(\mathbf{x}(t)) dt$$

Problem: geometry just wants to “explode” in middle of any trajectory



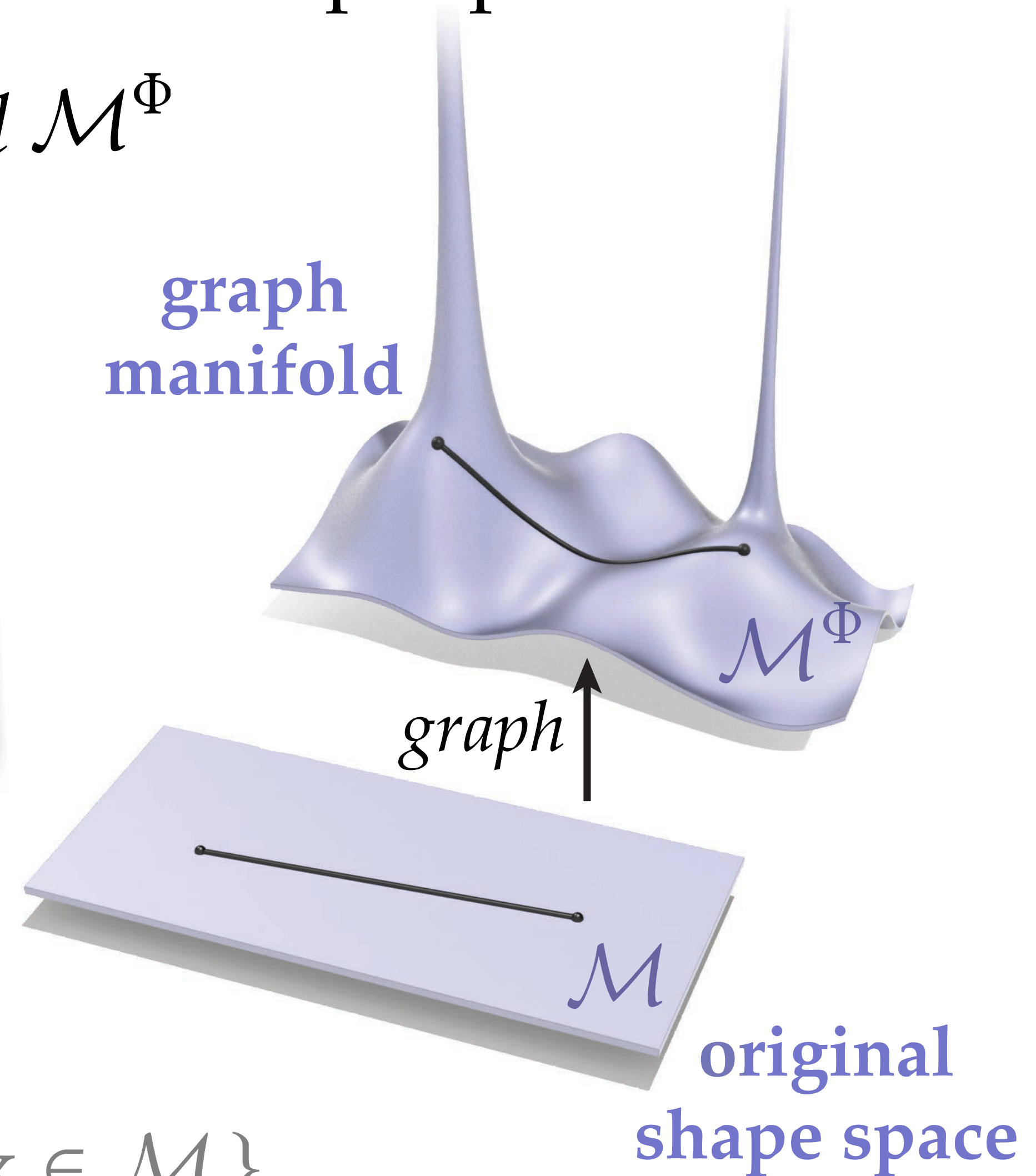
Graph Manifold

- **Alternative:** imagine “graphing” potential Φ over shape space $\mathcal{M}$
 - defines a new shape space — *graph manifold* $\mathcal{M}^\Phi$
 - *Intuition:* hiking along a mountain trail



maintain roughly
constant elevation
(potential) along
trajectory

physical motivation:
Occam's razor

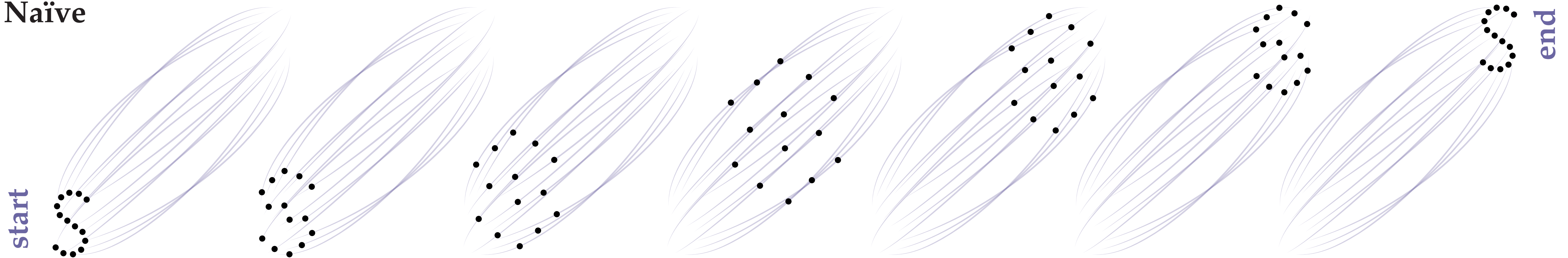


Sassen, Schumacher, Rumpf, C.
“Repulsive Shells” (2024)

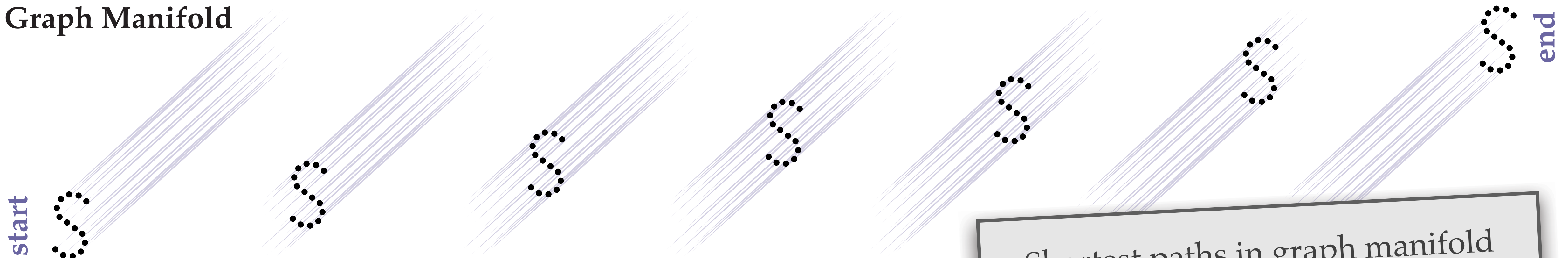
$$\mathcal{M}^\Phi = \{(\mathbf{x}, \Phi(\mathbf{x})) \mid \mathbf{x} \in \mathcal{M}\}$$

Naïve vs. Graph Manifold

Naïve



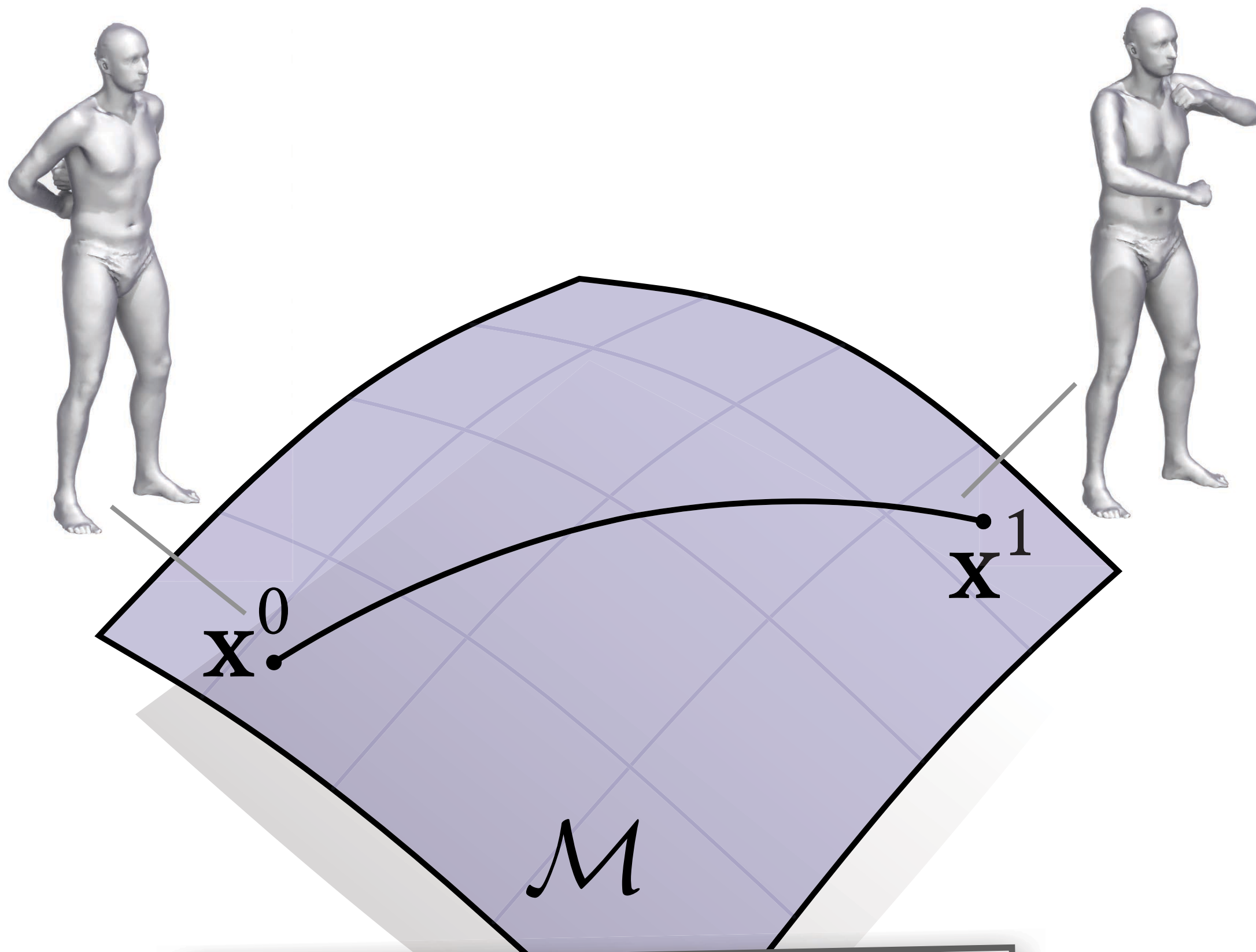
Graph Manifold



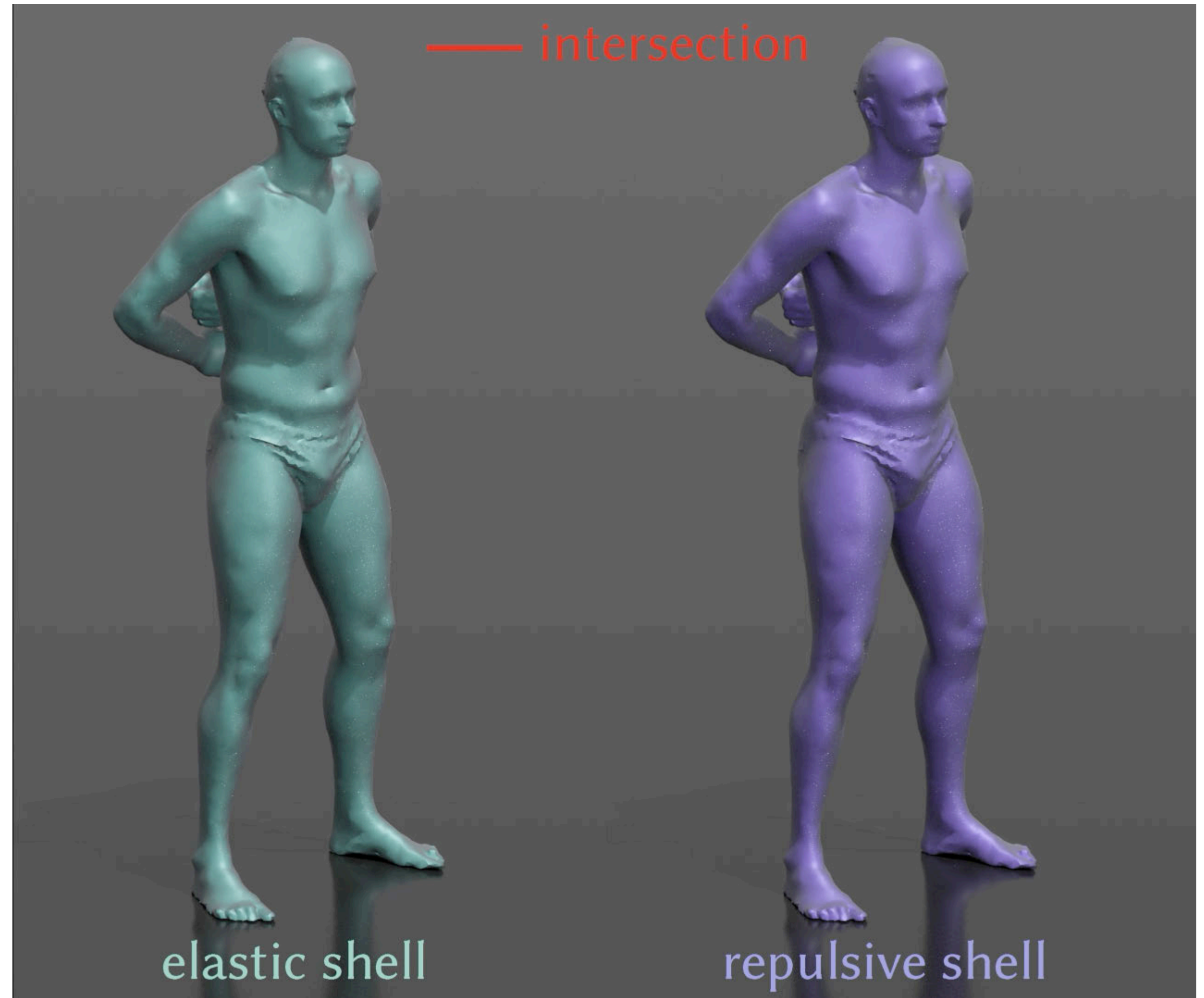
Shortest paths in graph manifold correspond to “more likely” motions.

Graph Manifold — Interpolation (Geodesics)

Task: given start/end configuration, determine *likely* trajectory

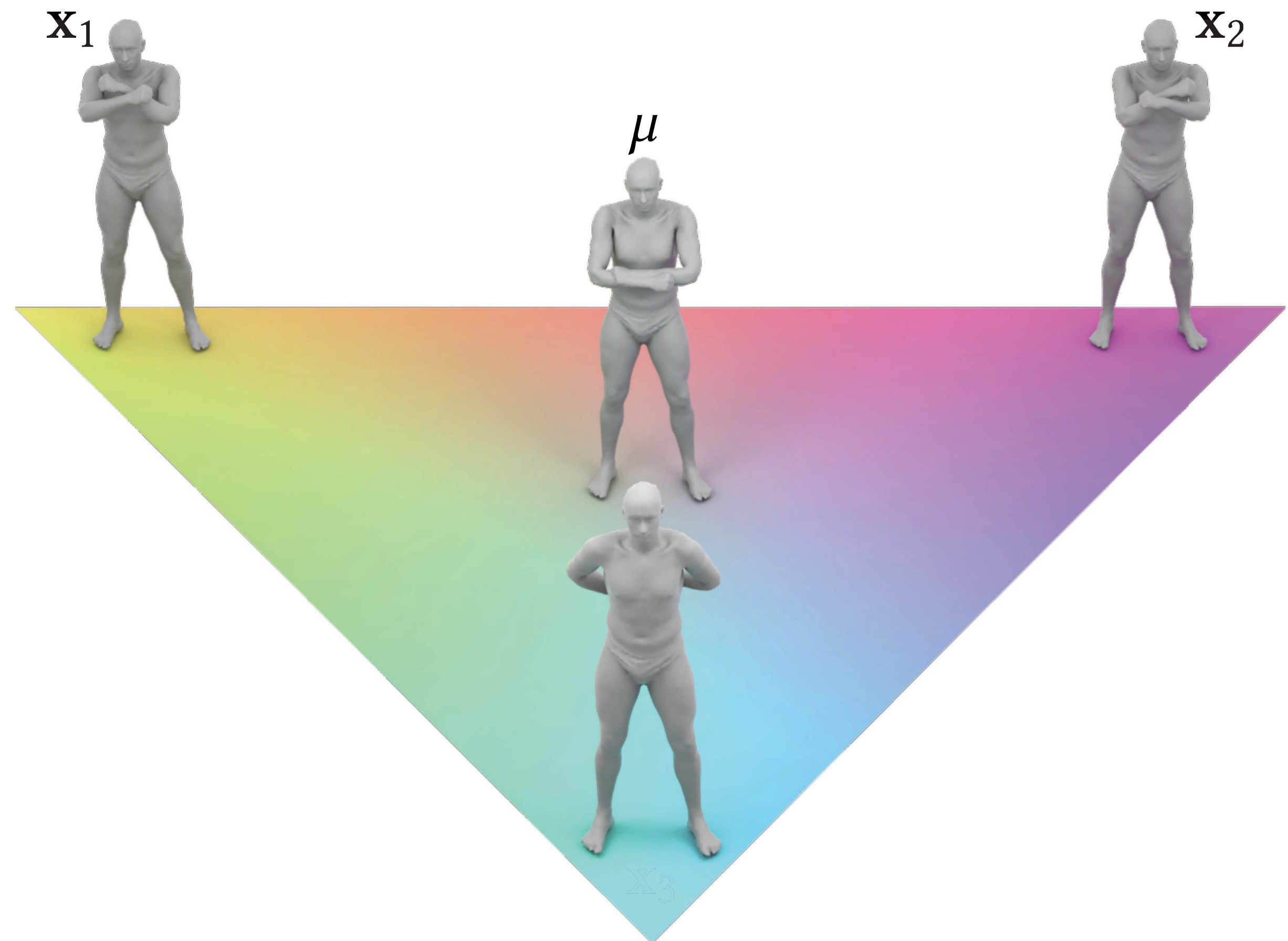
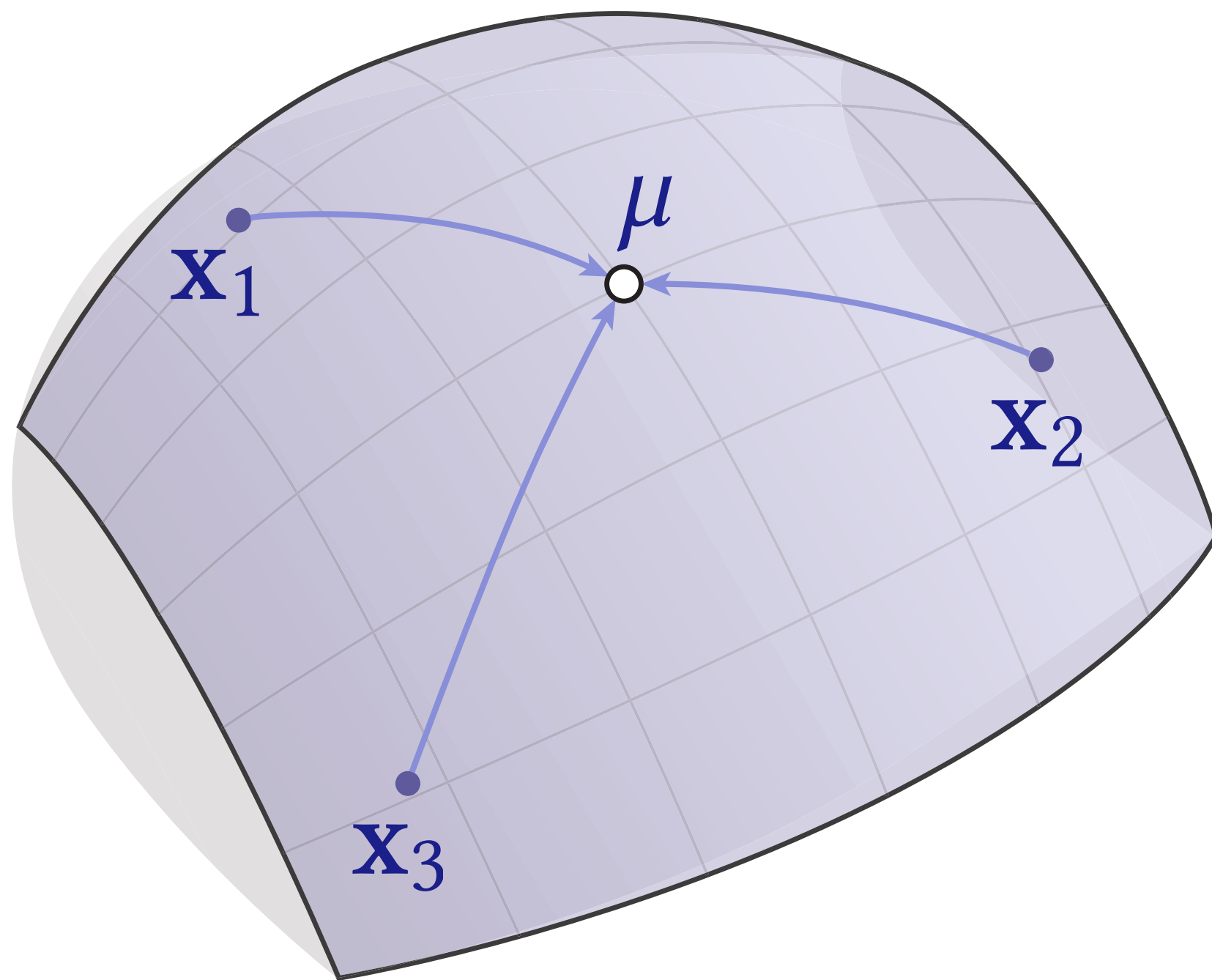


Basic building block for other statistical operations...



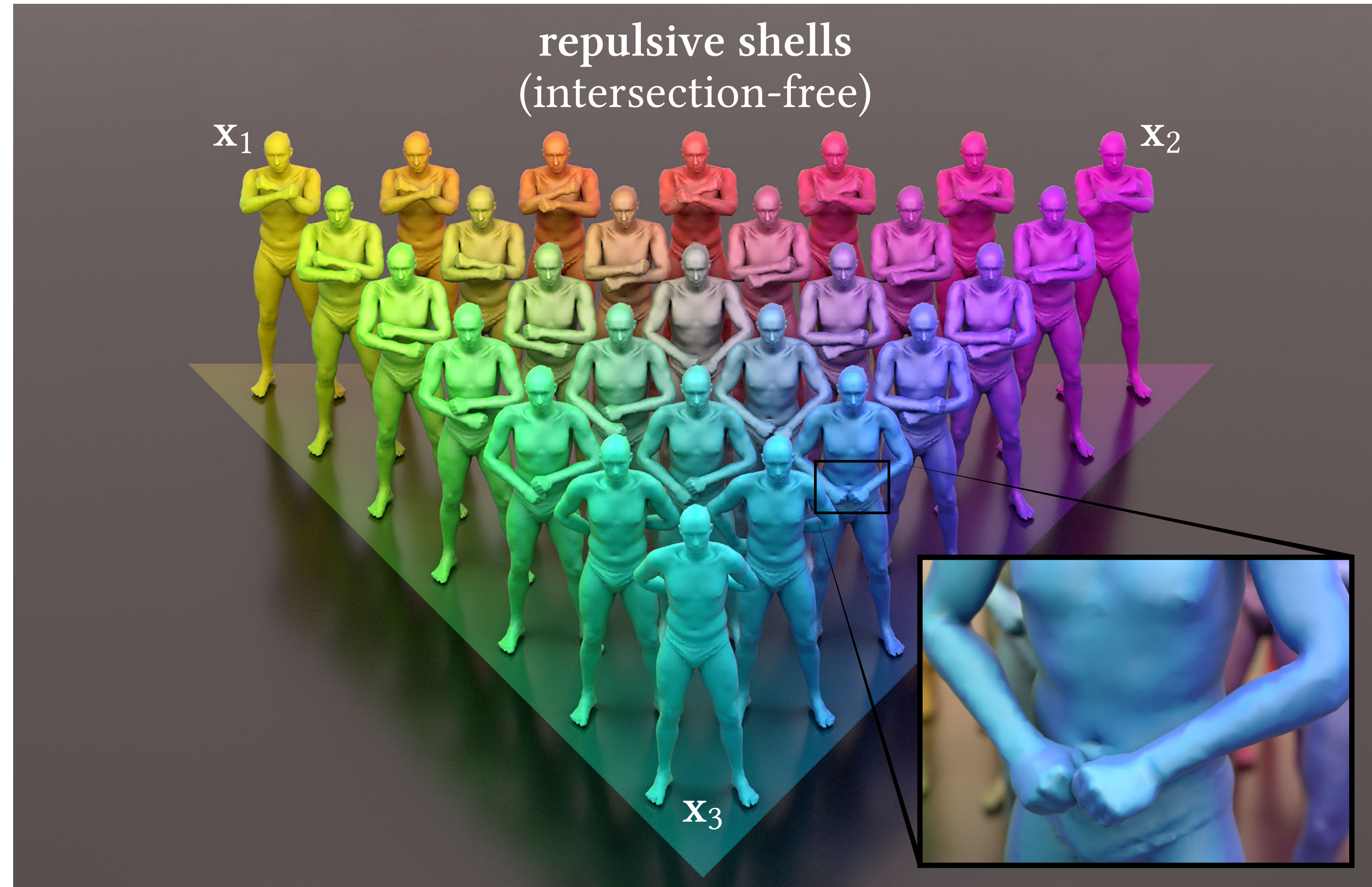
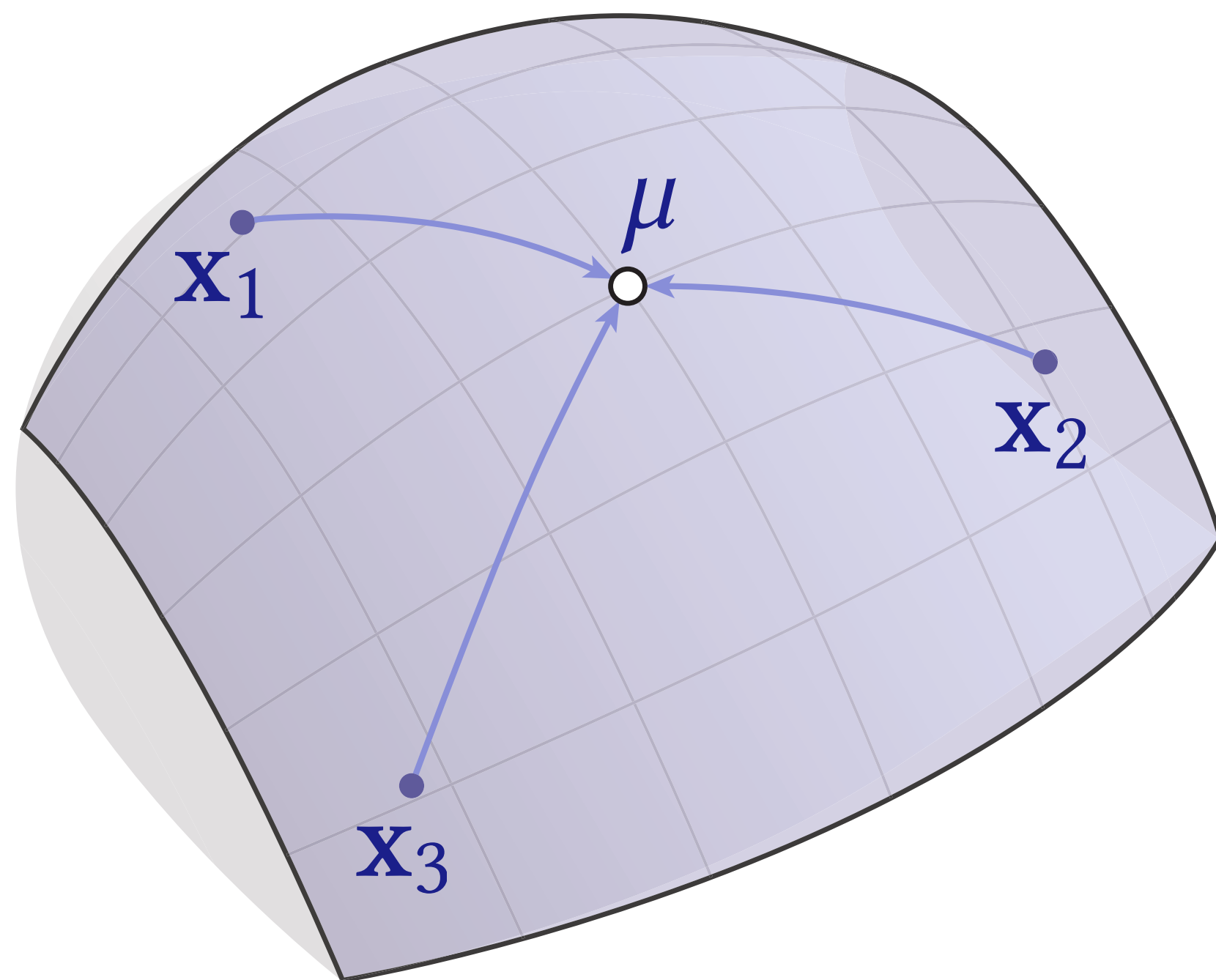
Graph Manifold — Averaging (Fréchet Mean)

Task: given several poses, find a (weighted) average



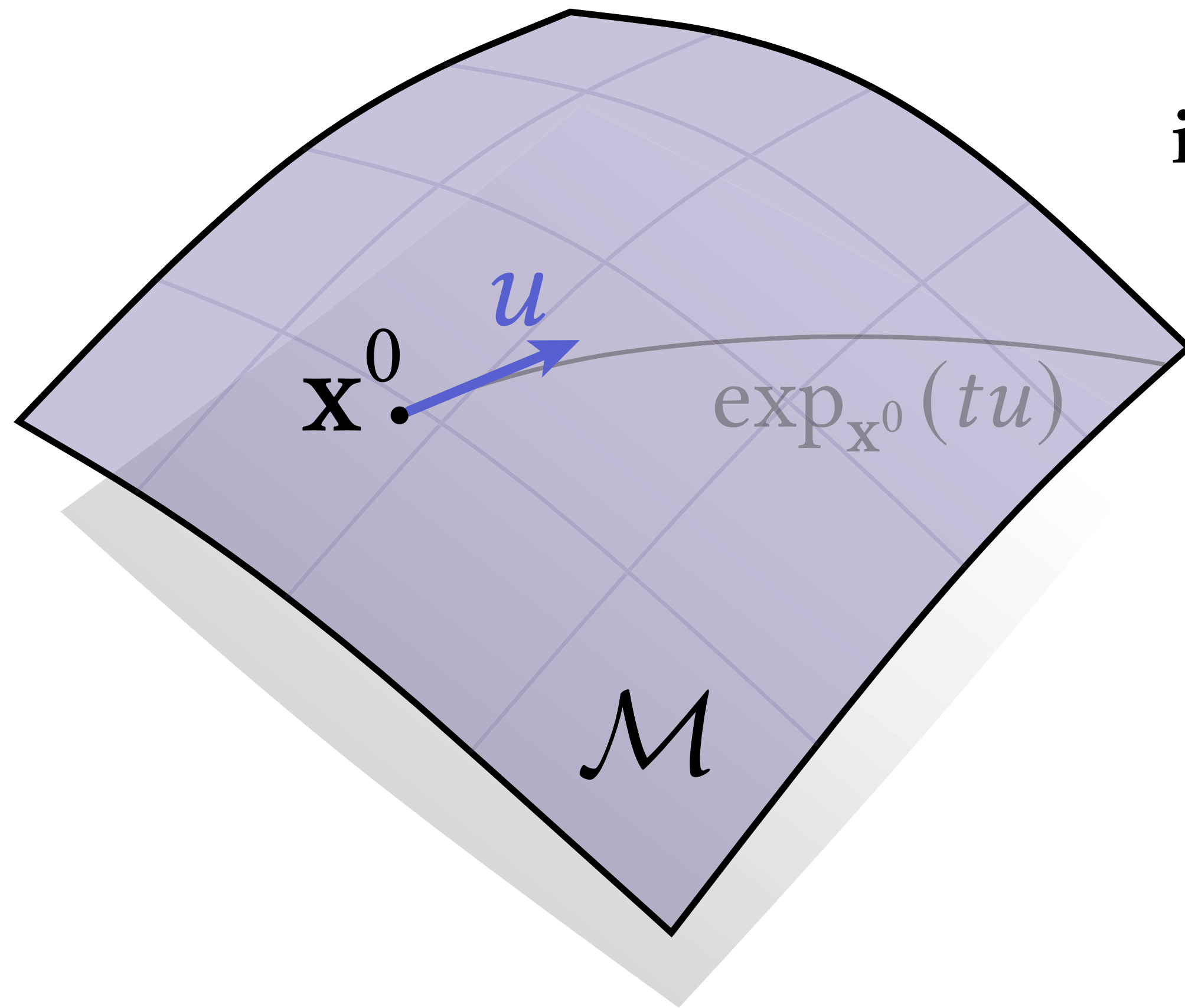
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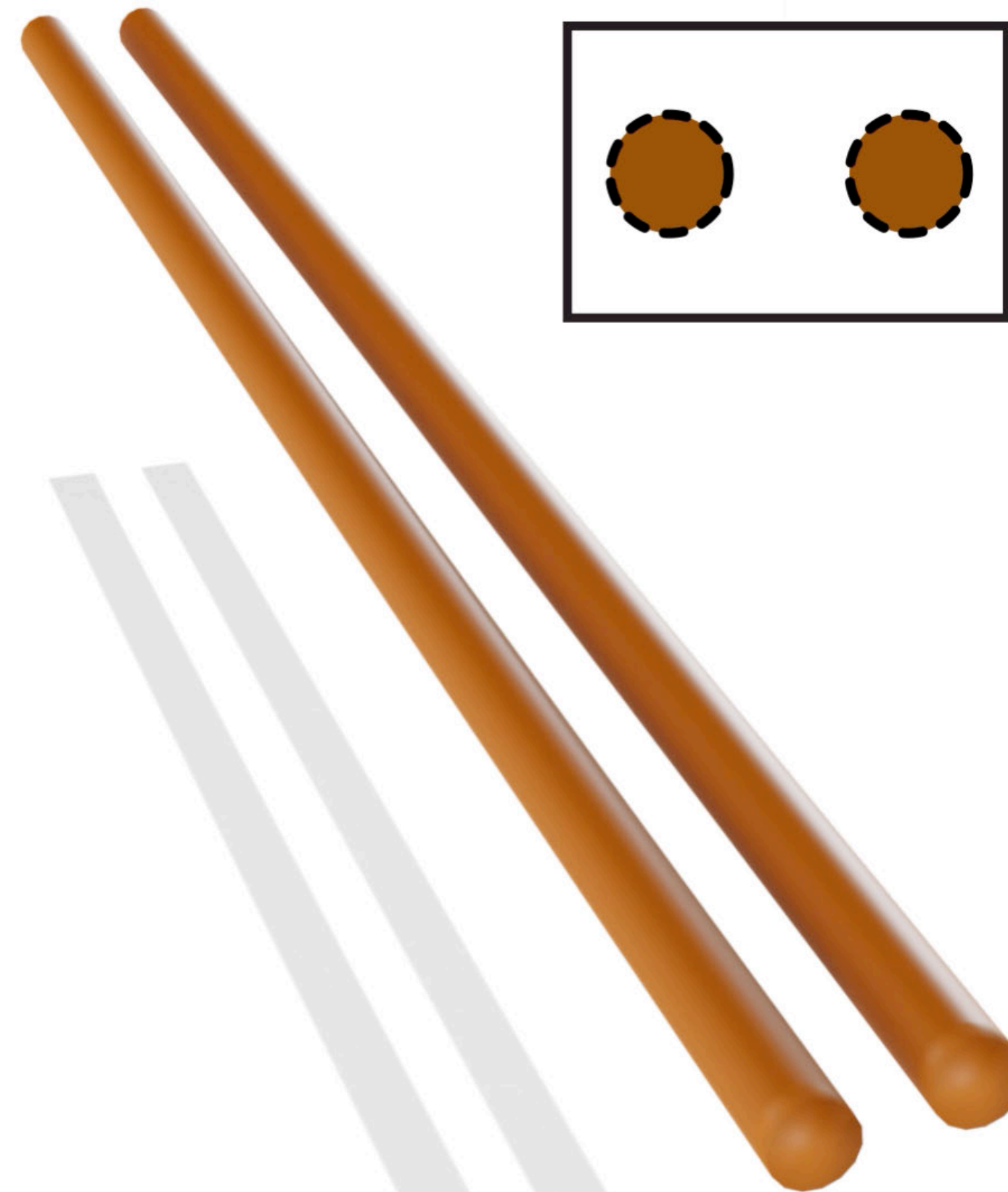


Graph Manifold — Extrapolation (Exponential Map)

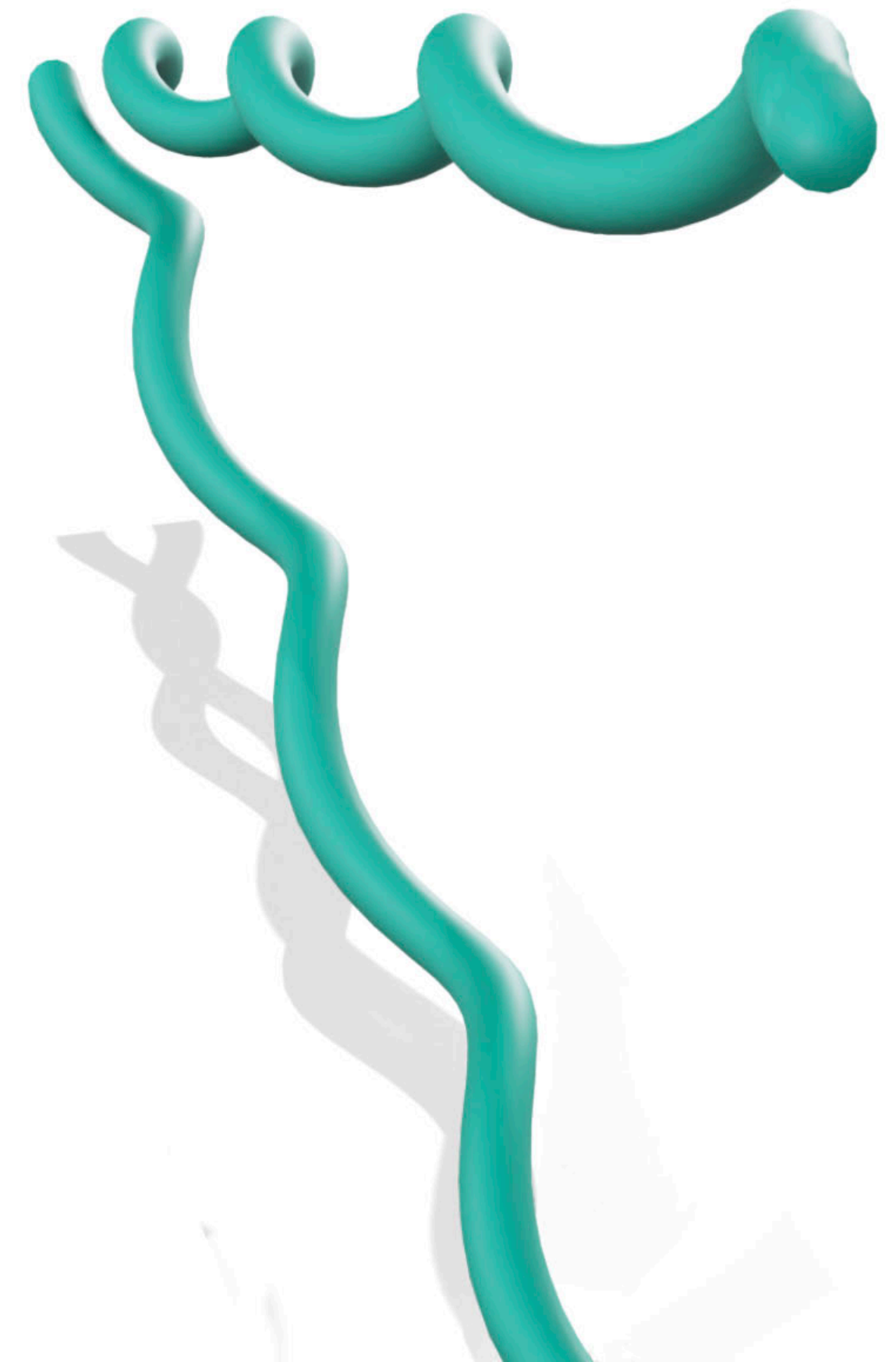
Task: predict how a small / motion deformation might continue/evolve



initial motion (small twist)

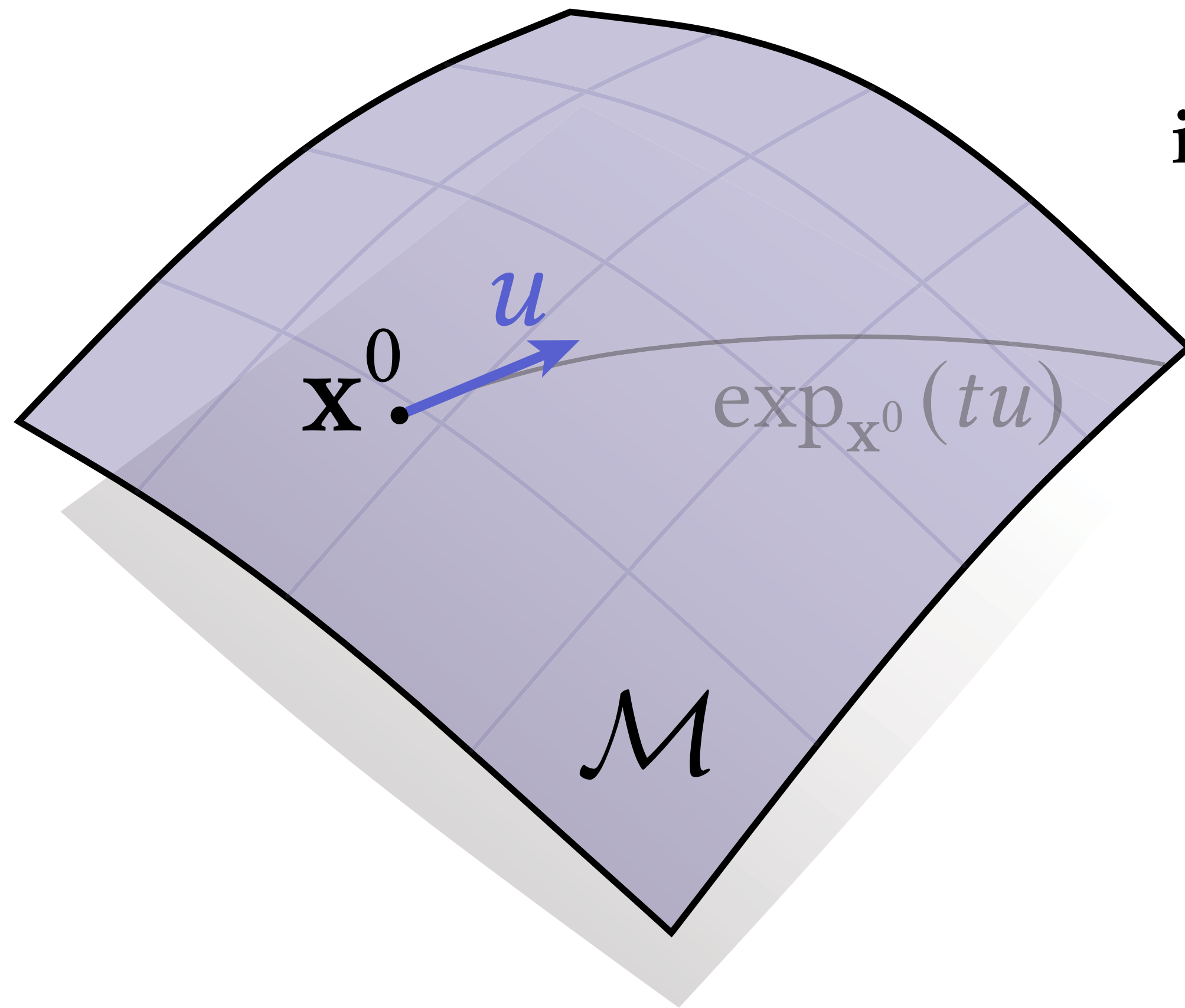


extrapolation
(purely elastic)

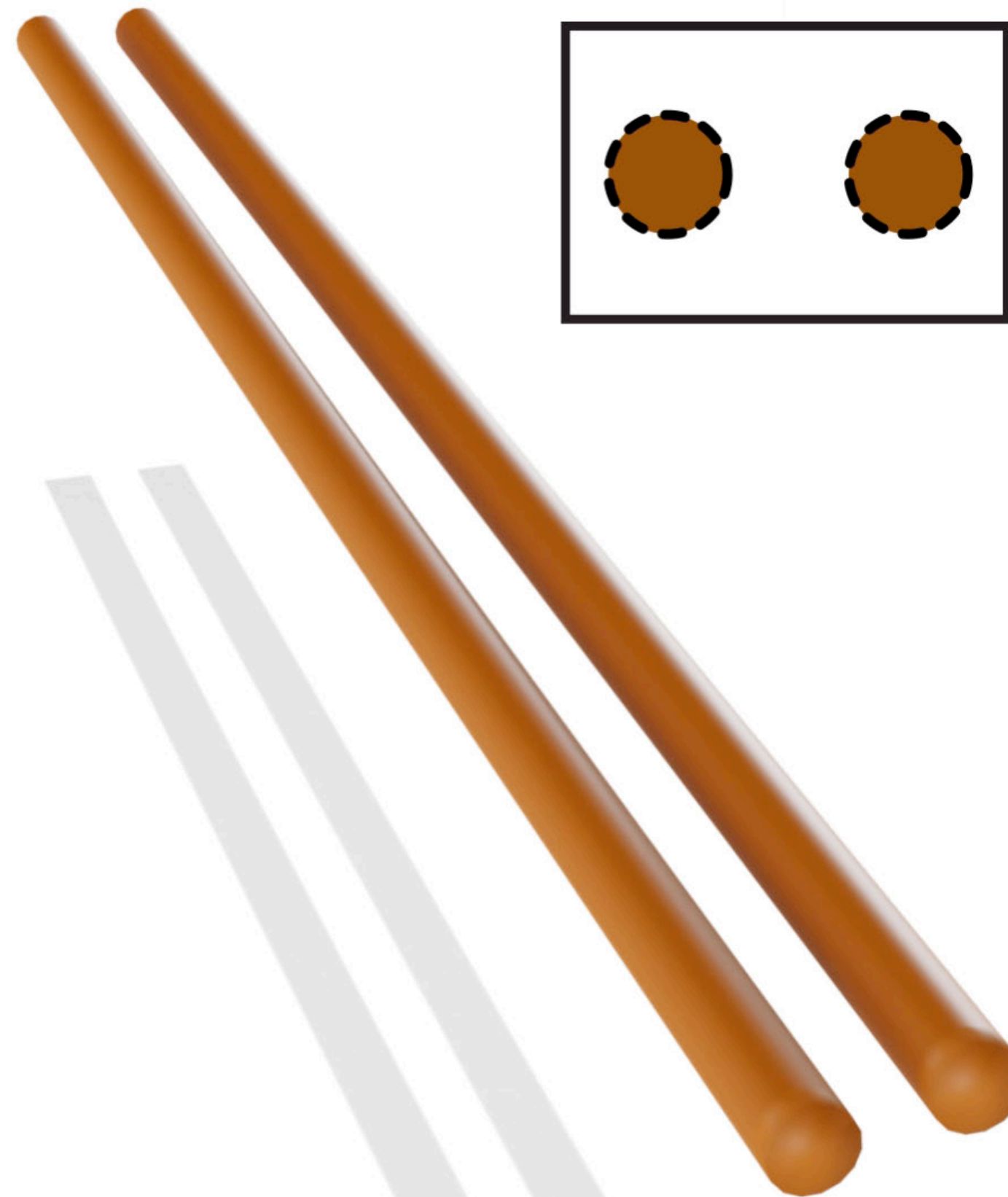


Graph Manifold — Extrapolation (Exponential Map)

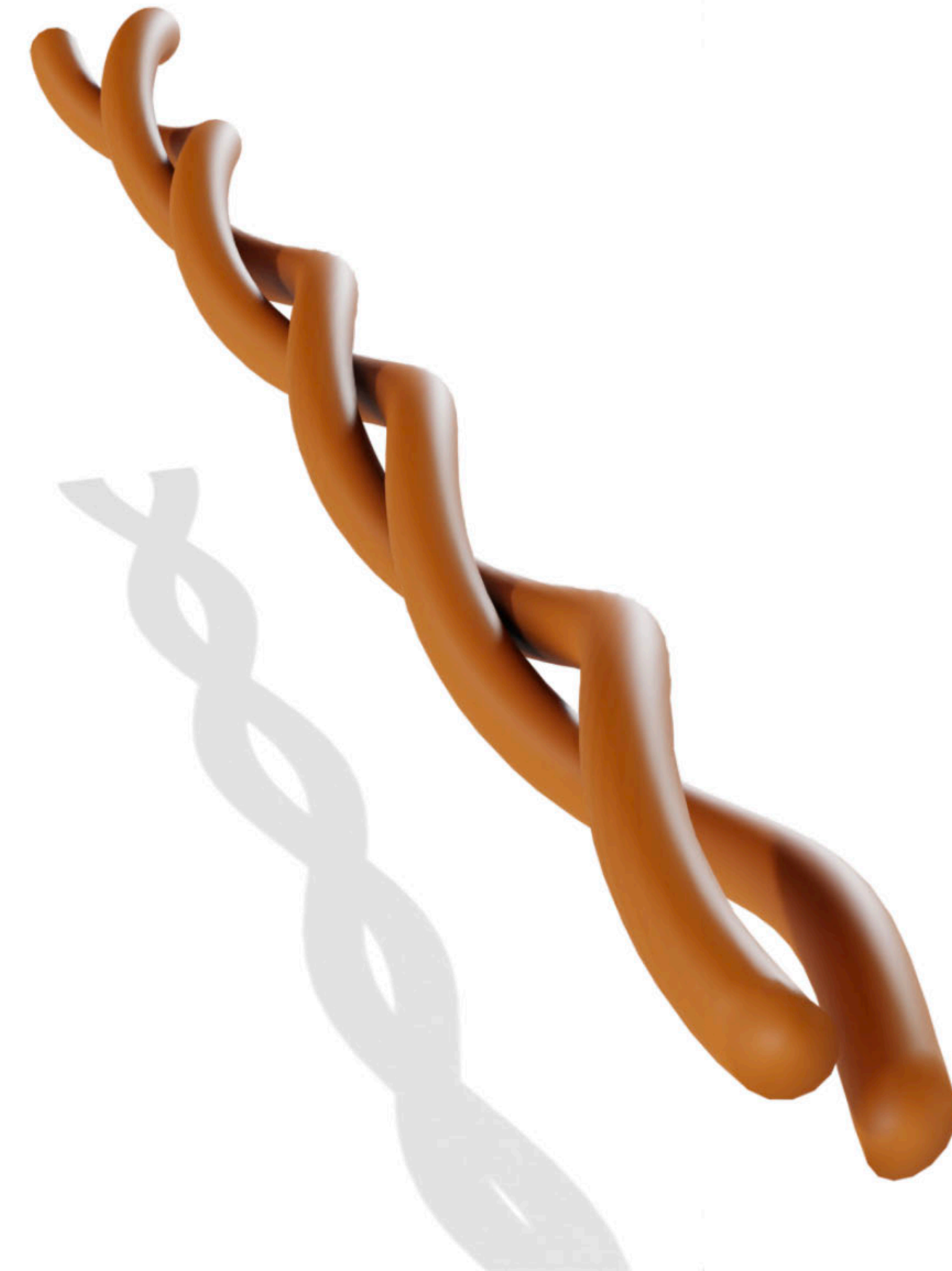
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initial motion (small twist)

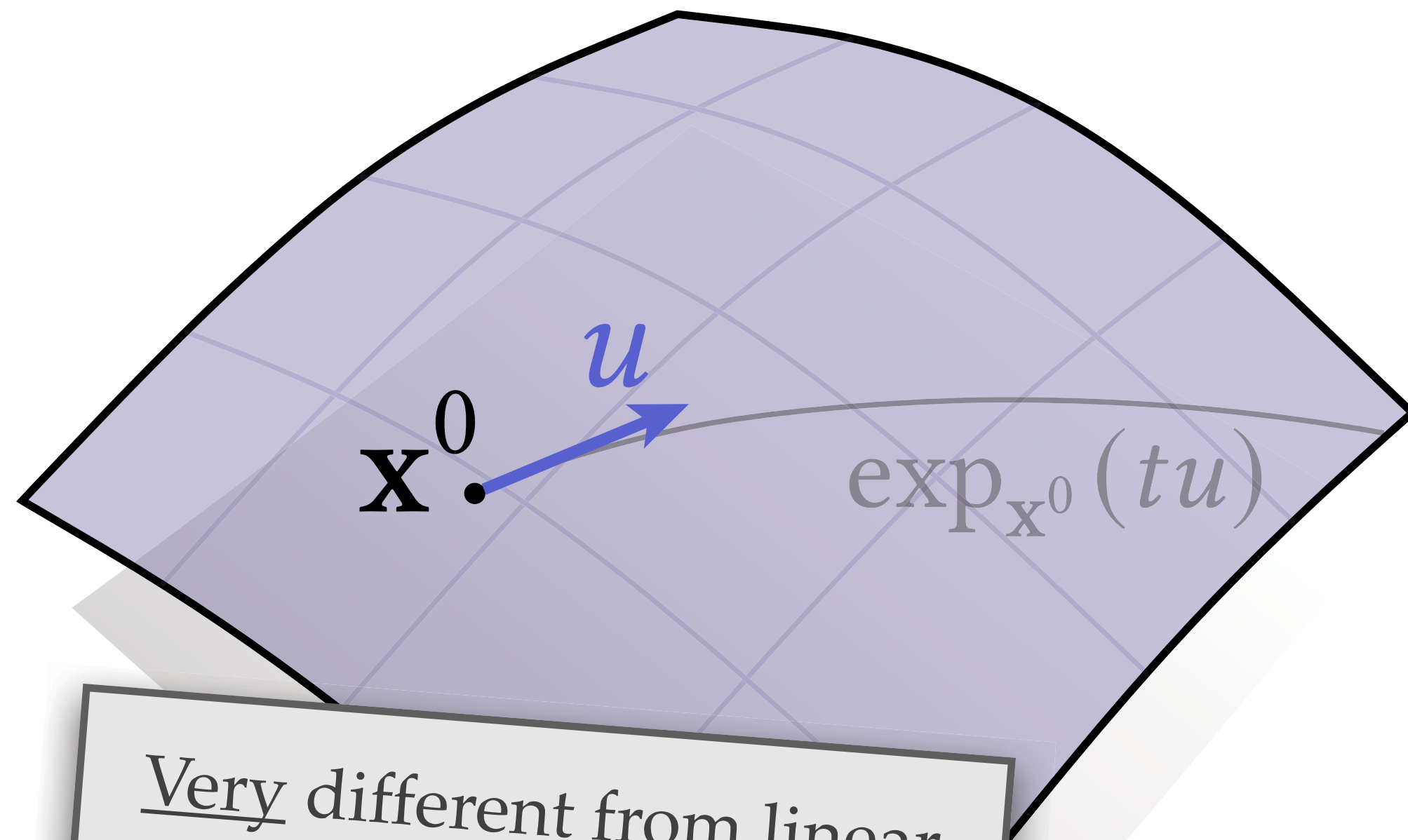


extrapolation
(elastic + repulsive)



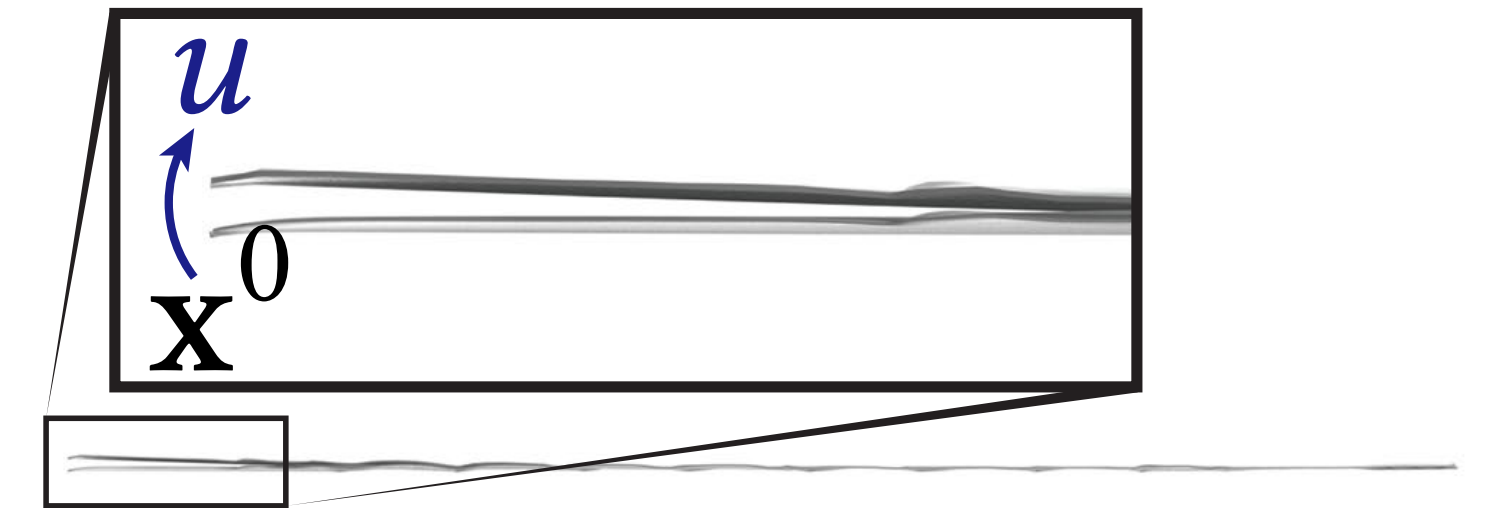
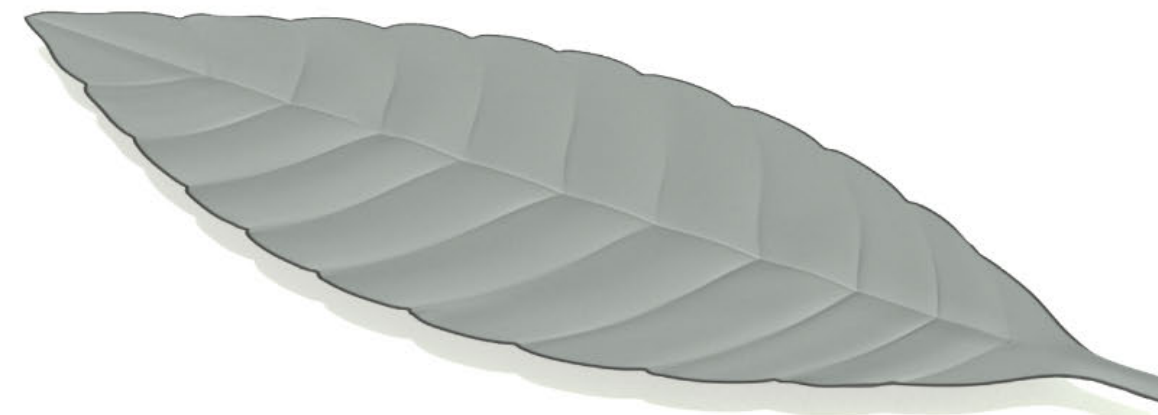
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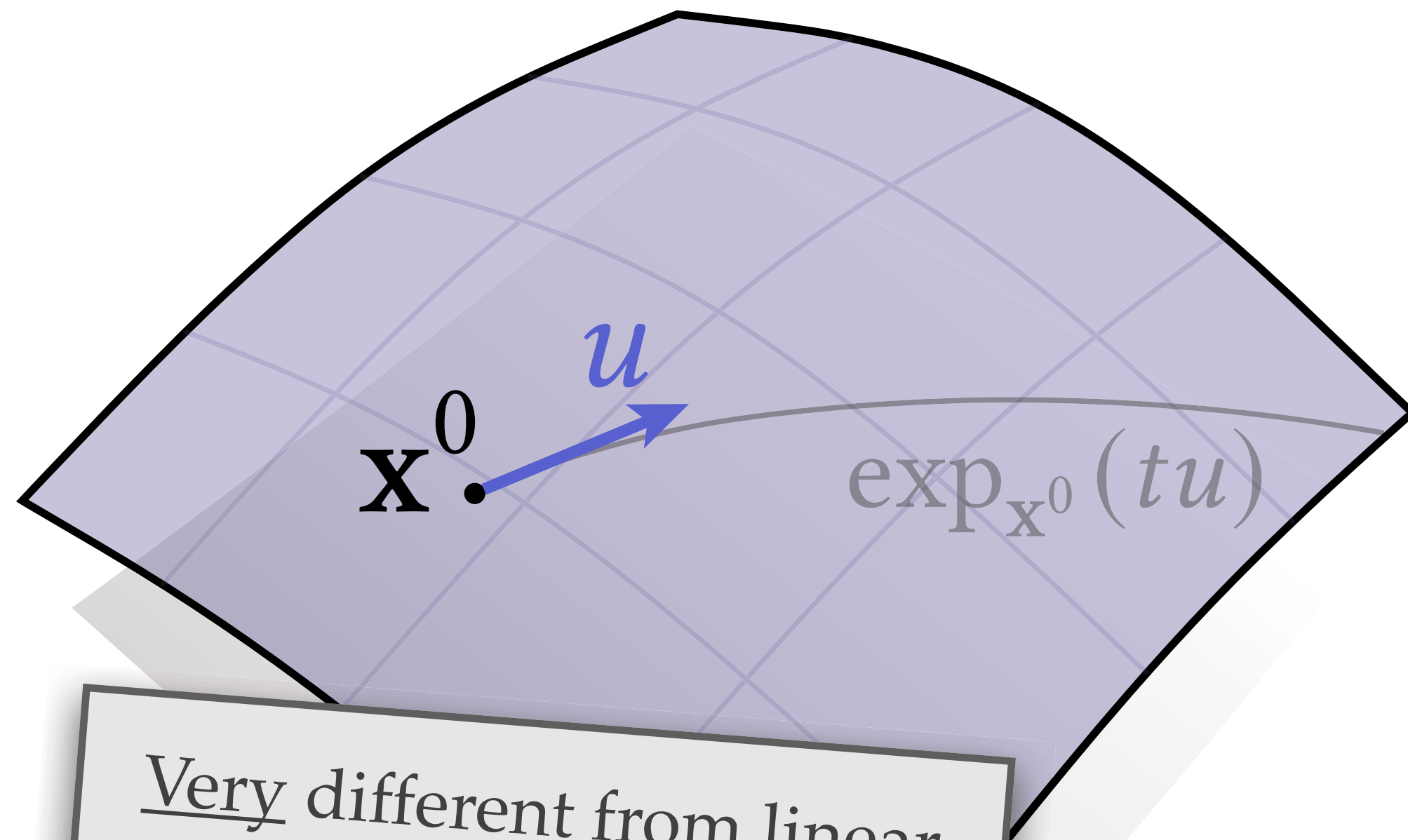
Very different from linear extrapolation!

Key point: Riemannian perspective enables us to make highly nonlinear, physics-based predictions.



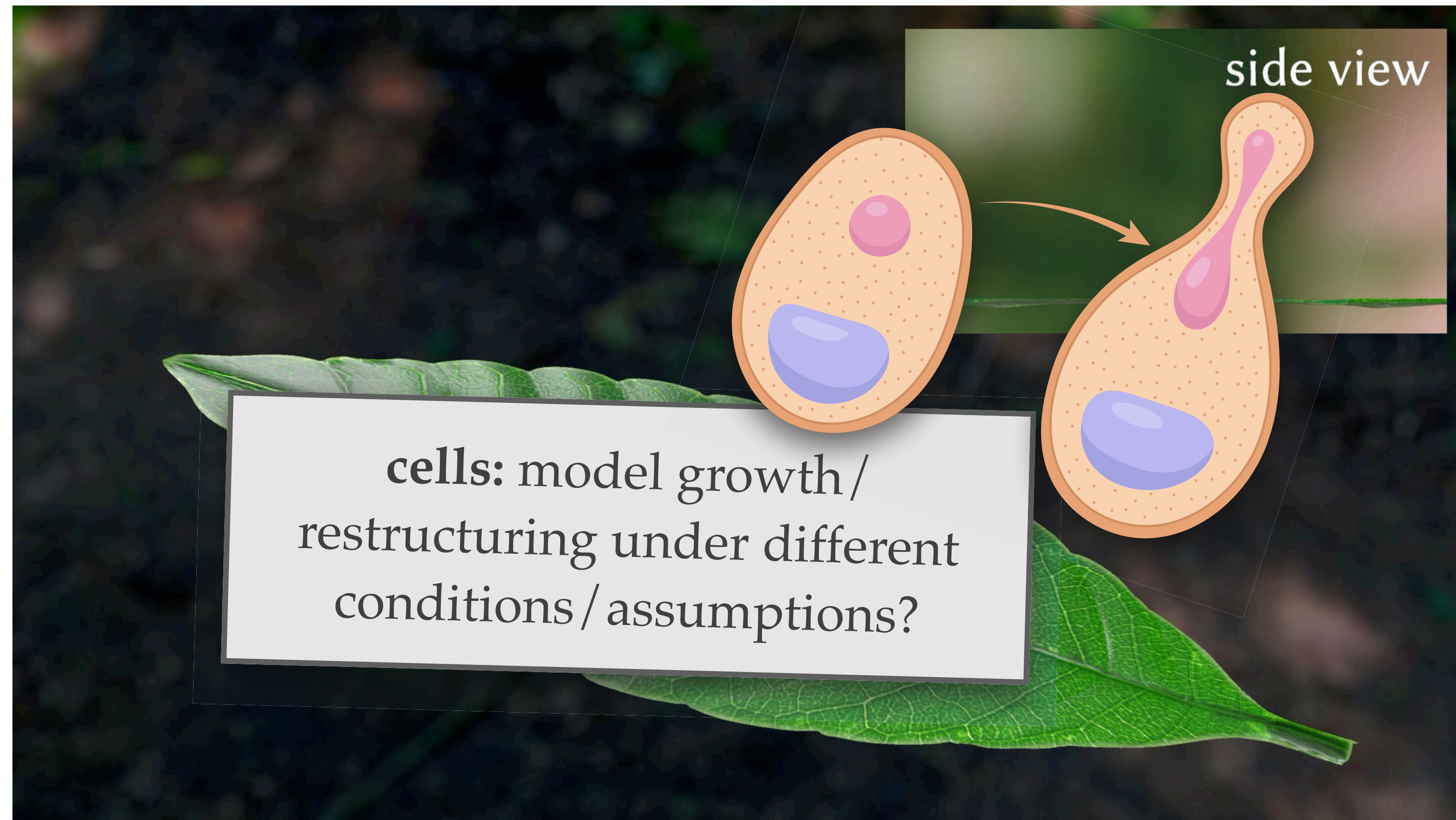
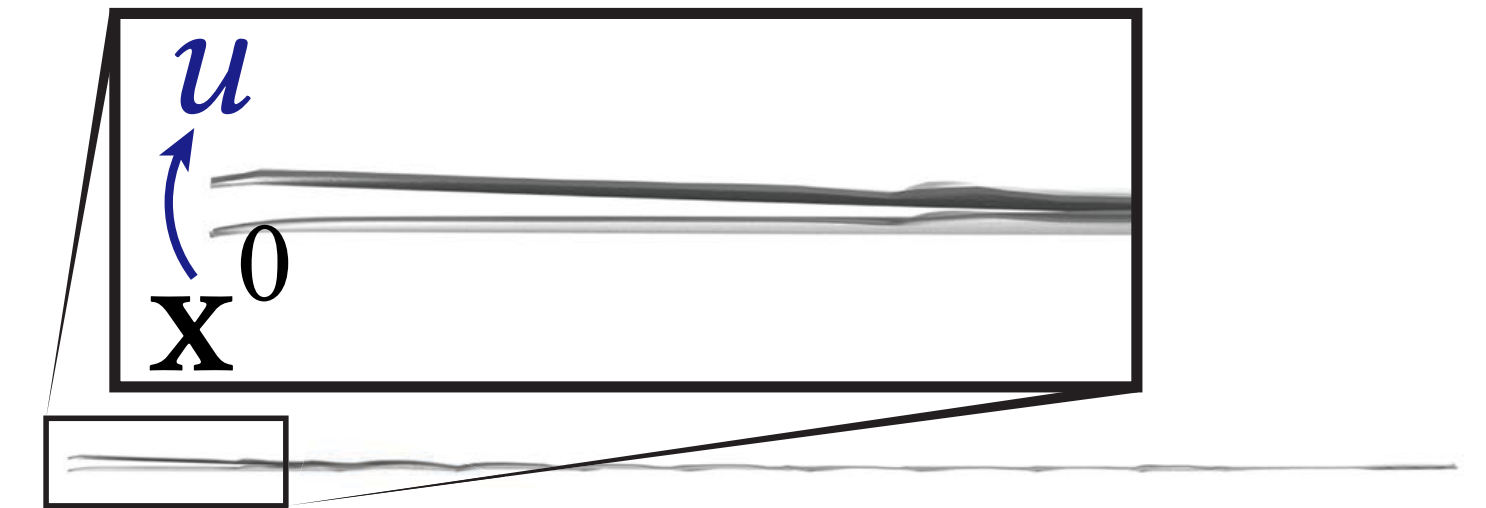
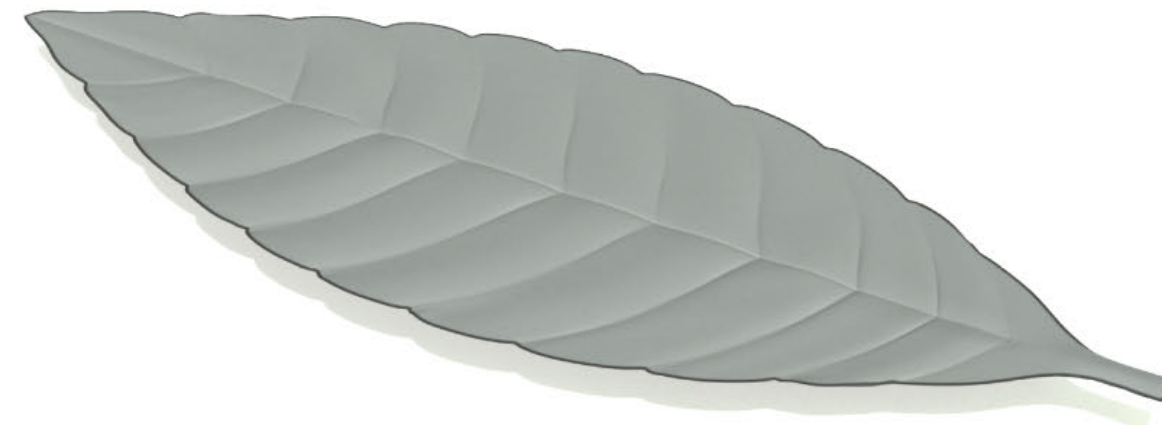
Graph Manifold — Extrapolation (Exponential Map)

Task: predict how a small / motion deformation might continue/evolve



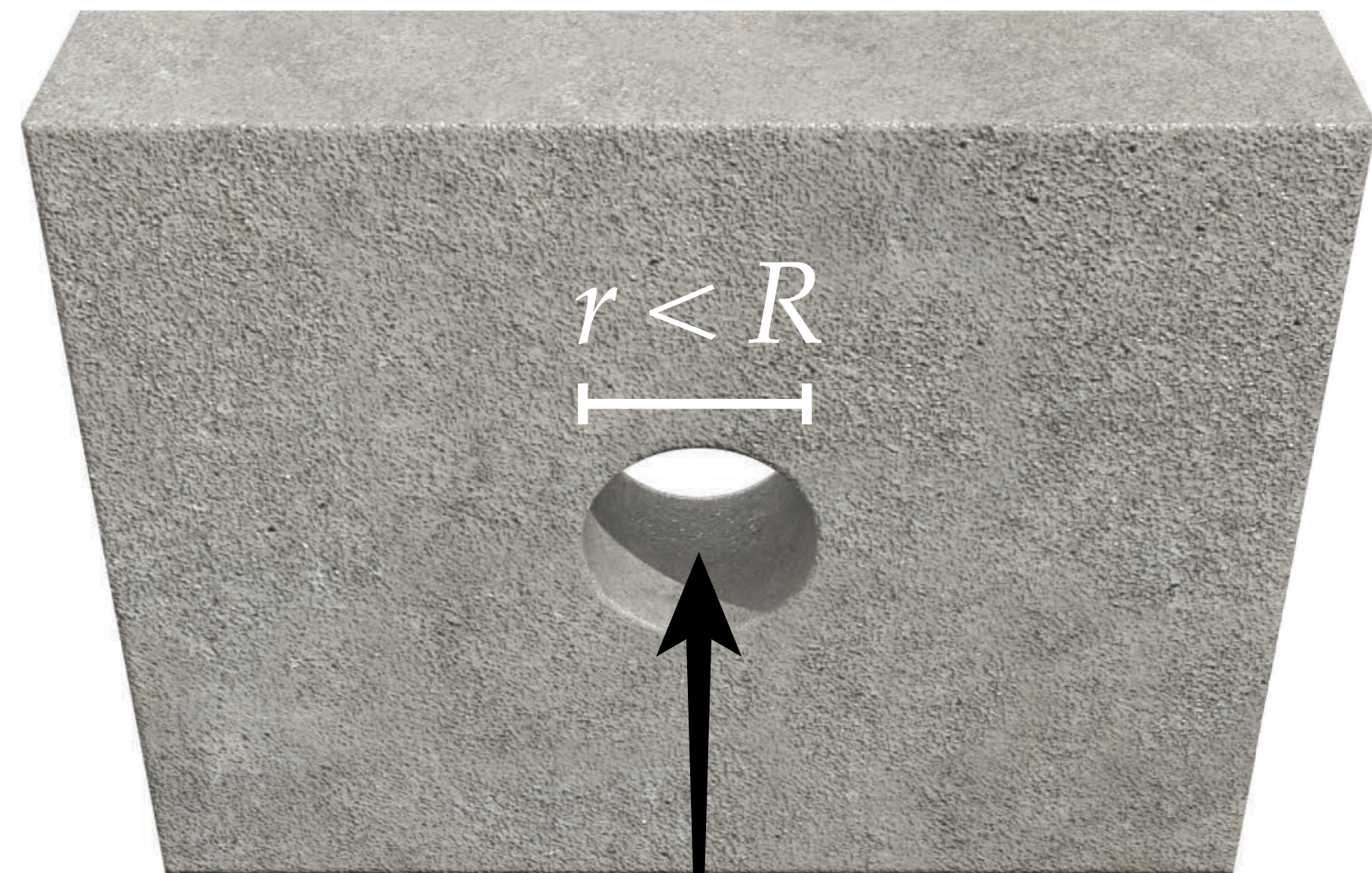
Very different from linear extrapolation!

Key point: Riemannian perspective enables us to make highly nonlinear, physics-based predictions.



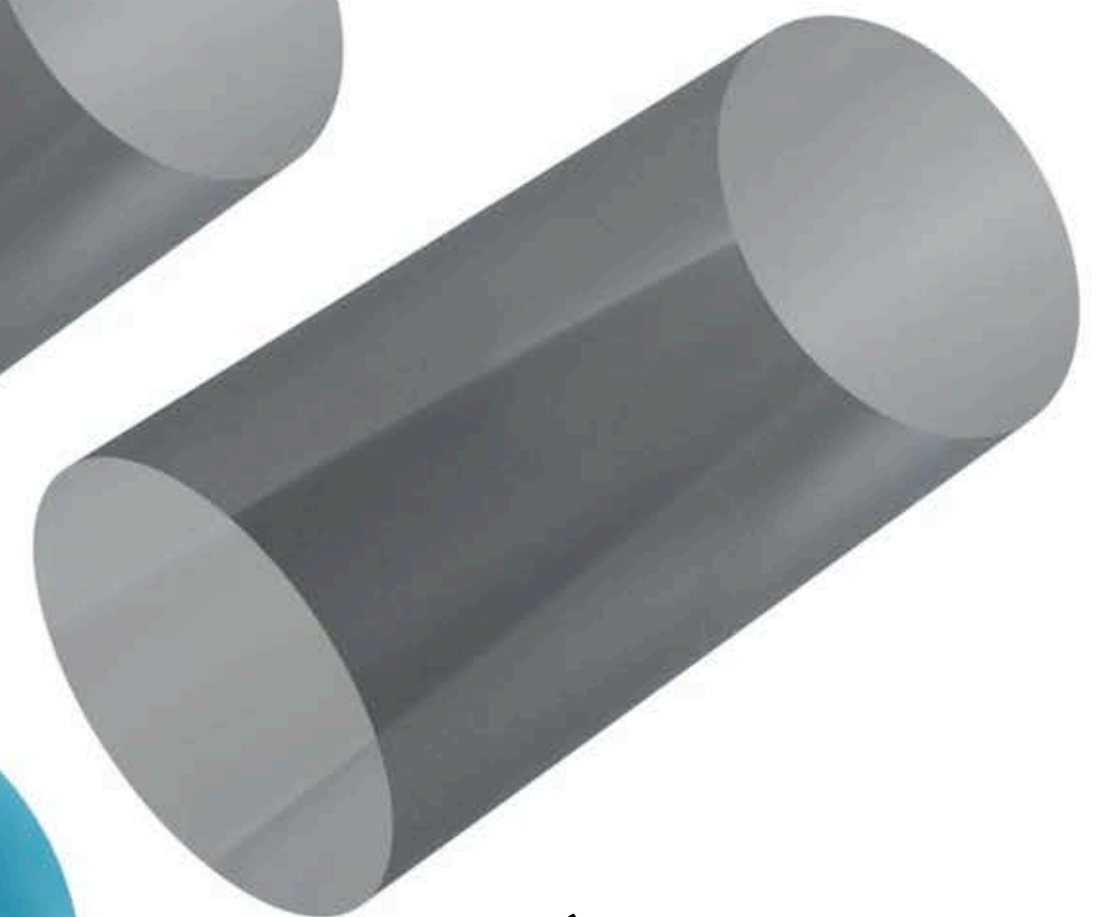
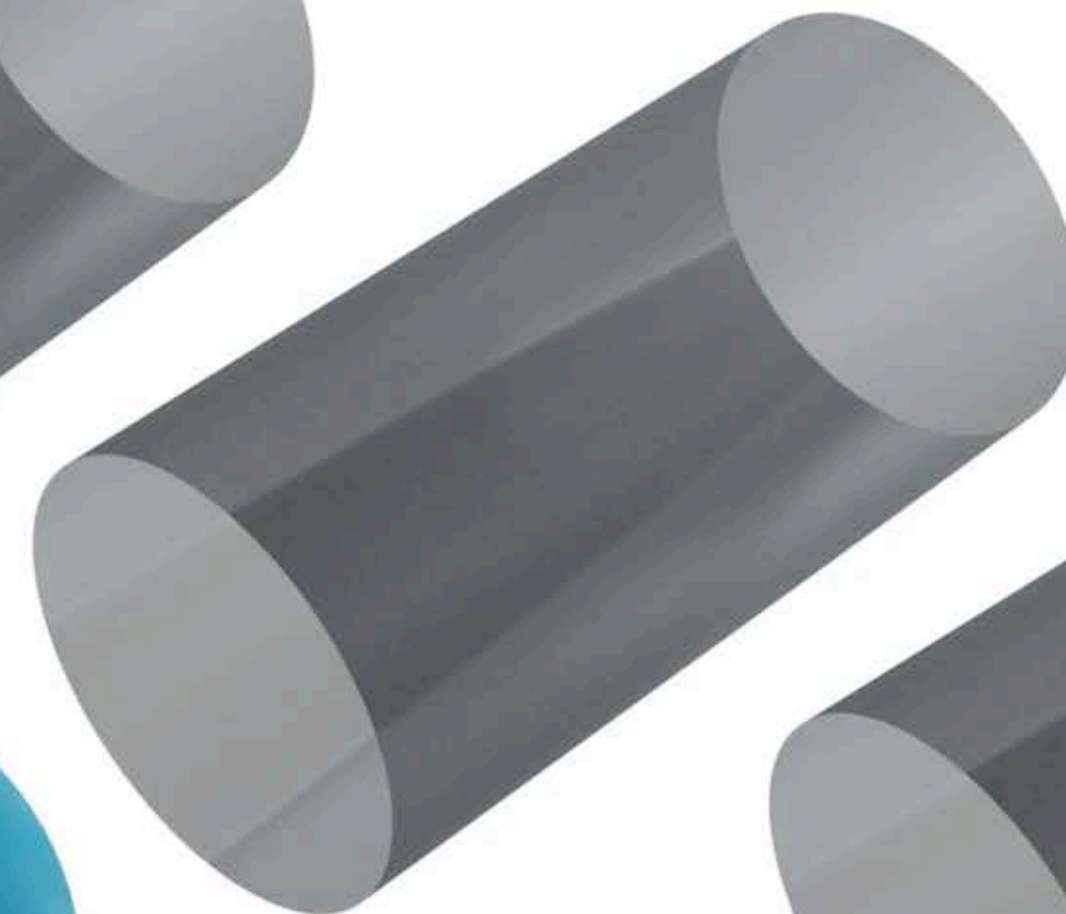
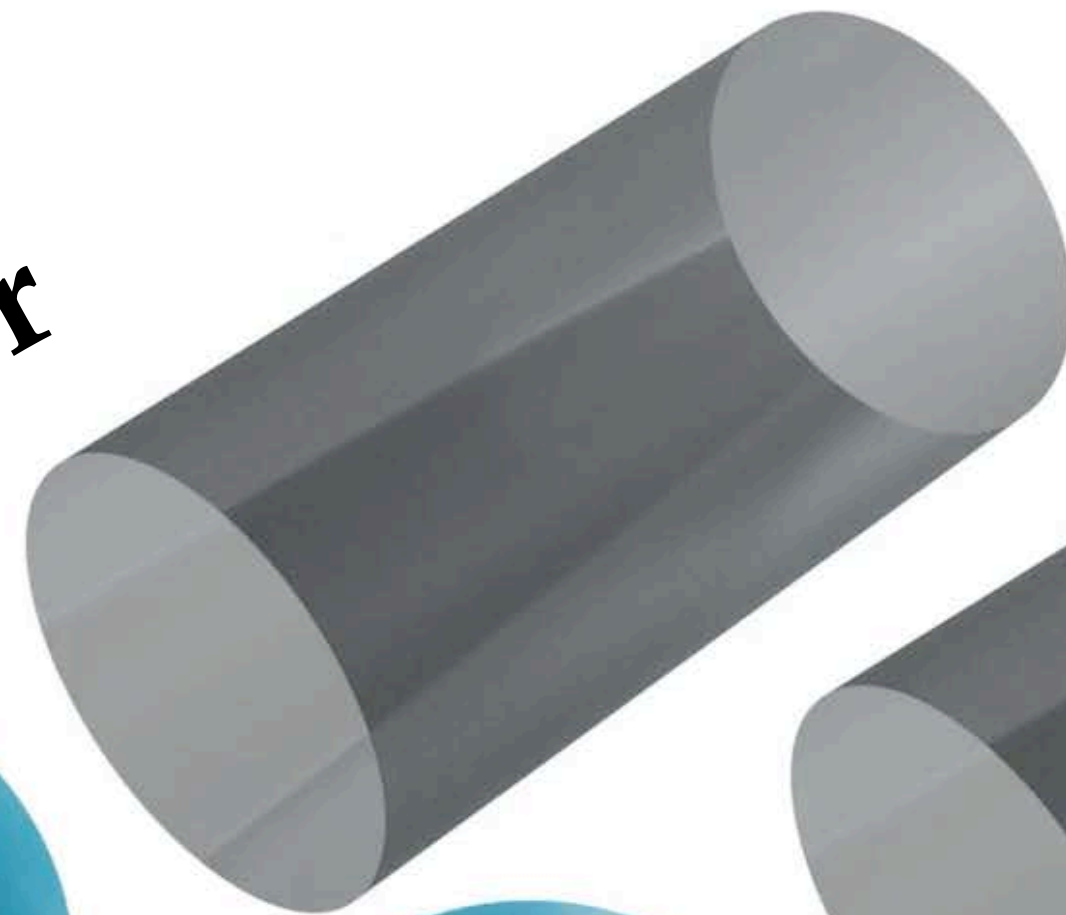
cells: model growth/
restructuring under different
conditions/assumptions?

Graph Manifold — Path Planning



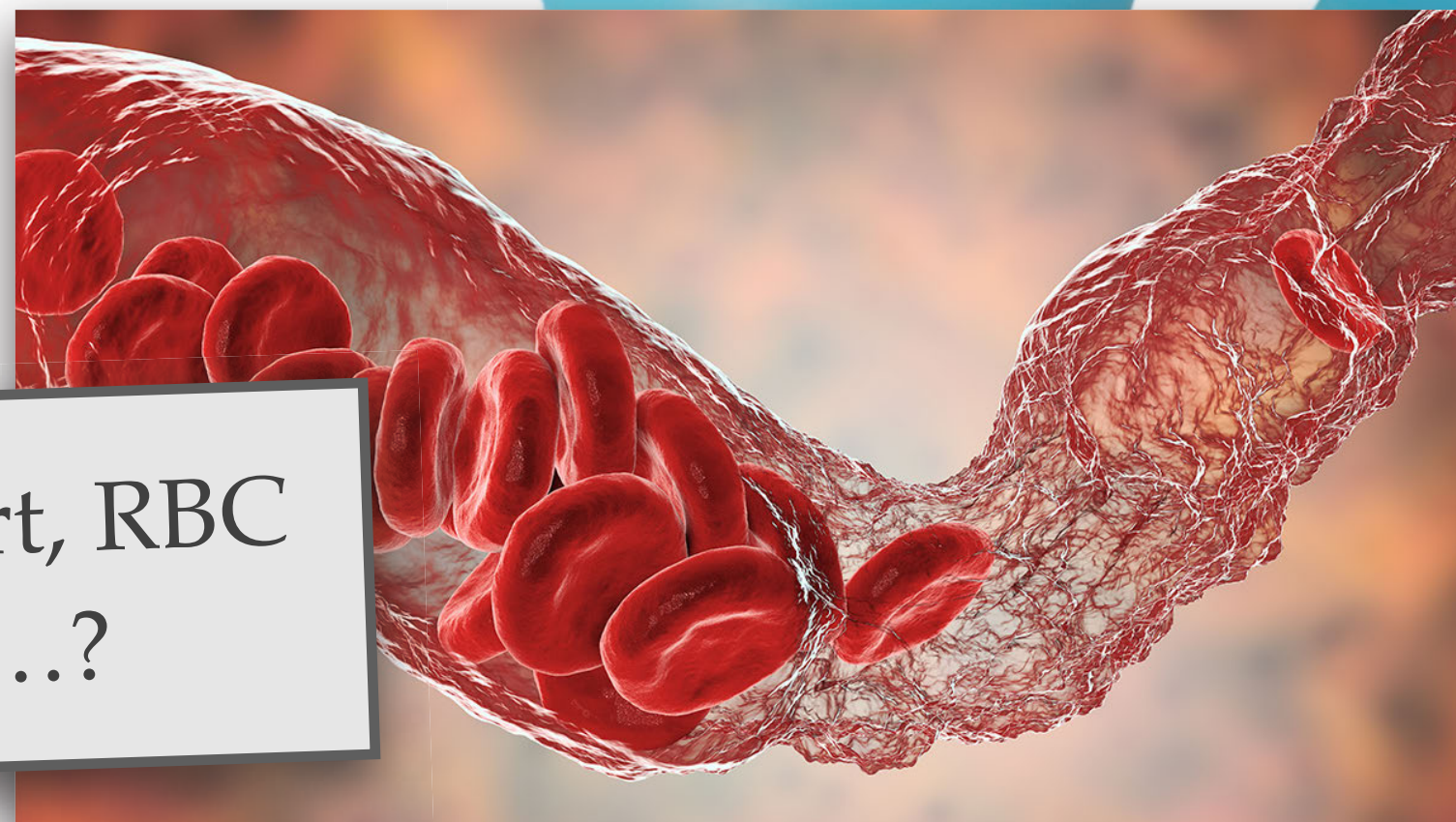
Deform in *anticipation* of obstacles—don't just slam on breaks at moment of impact.

softer



stiffer

cells: vesicle transport, RBC
microcirculation...?



Motion in Near-Contact



Motion in Near-Contact

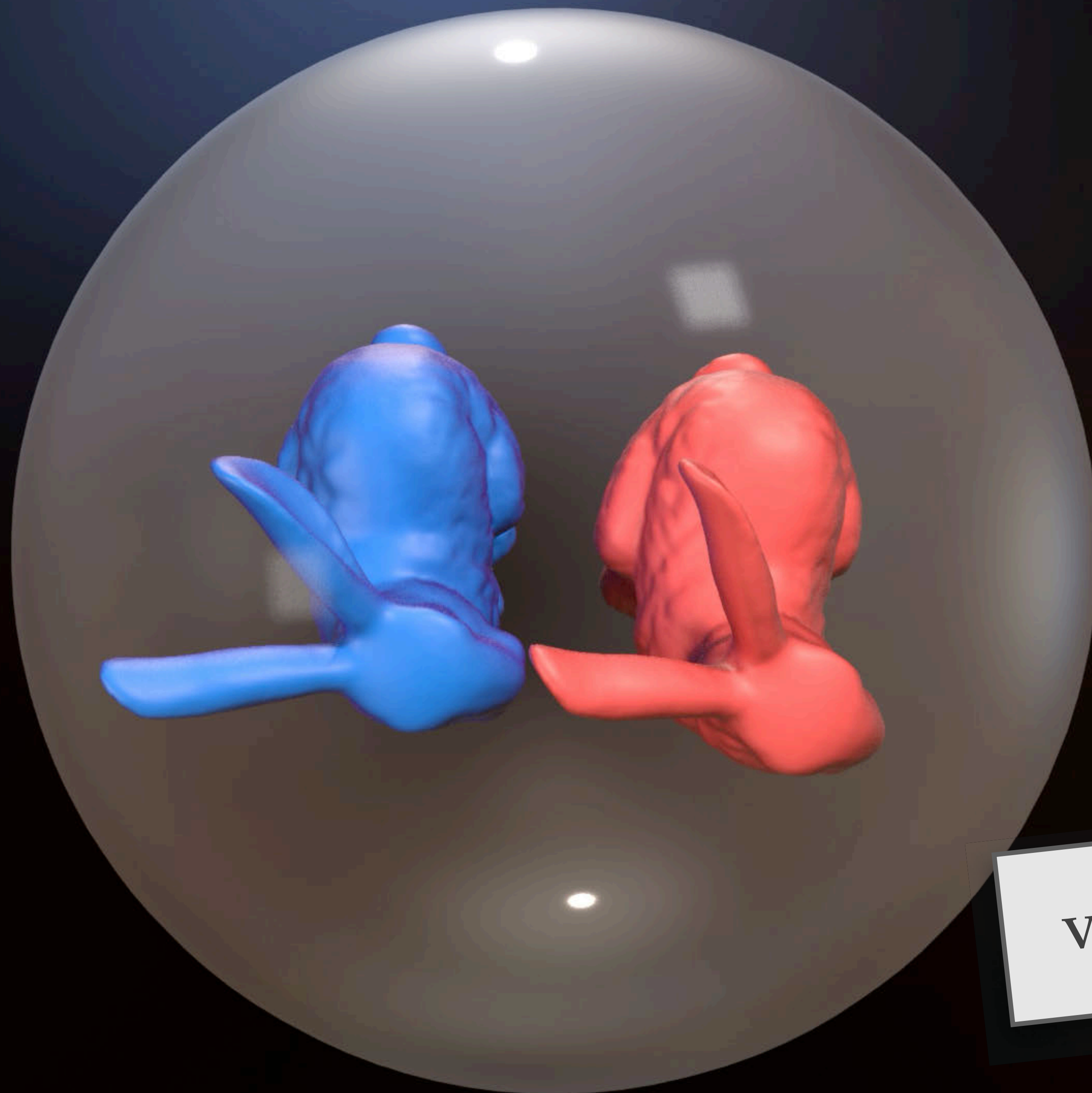
Extremely hard
(impossible) to capture
with volumetric models
(e.g., LDDMM)



biomembranes: highly folded structures
(mitochondria, golgi apparatus, ER, ...)

Packing Sheets in Tight Spaces

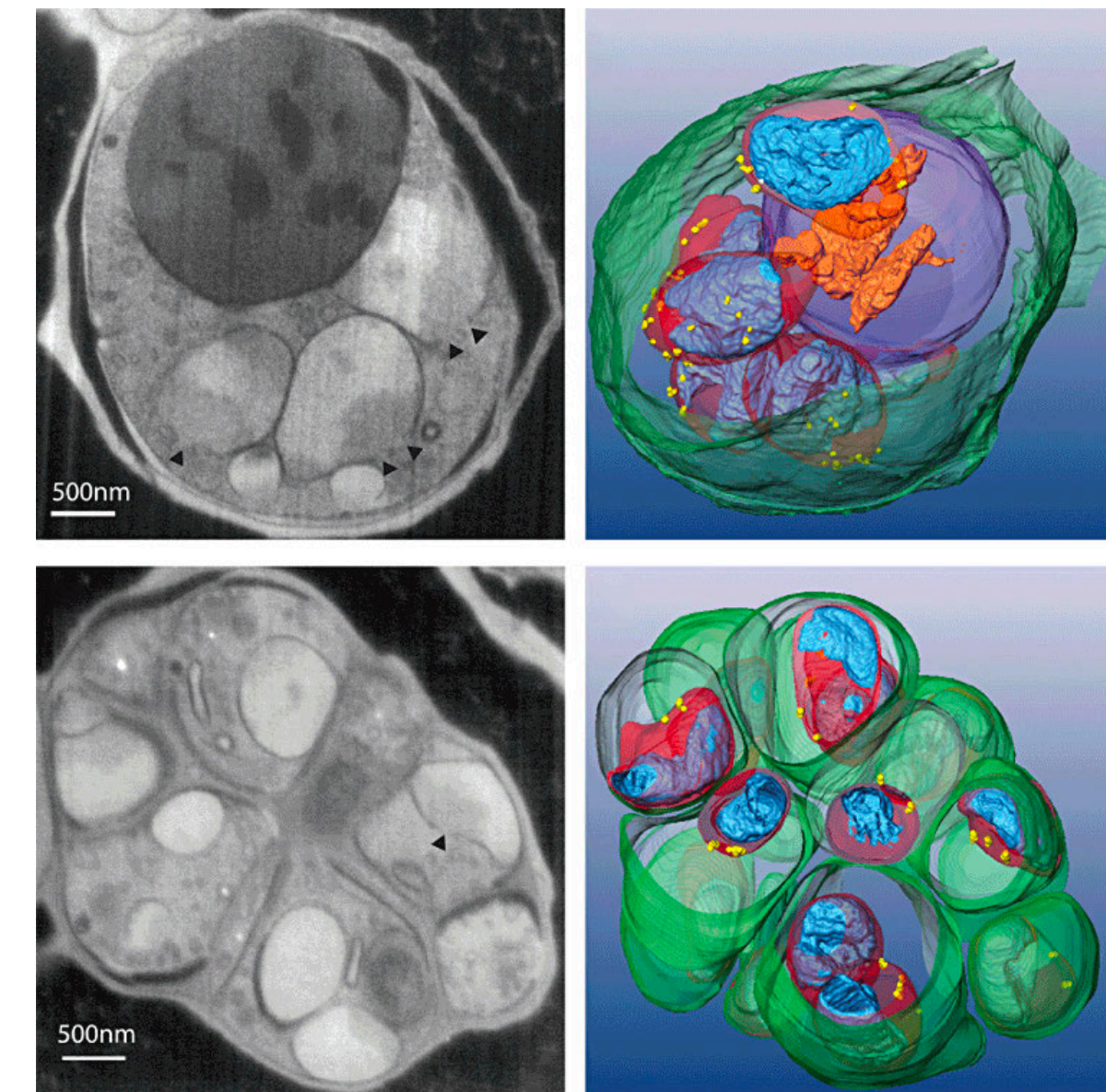
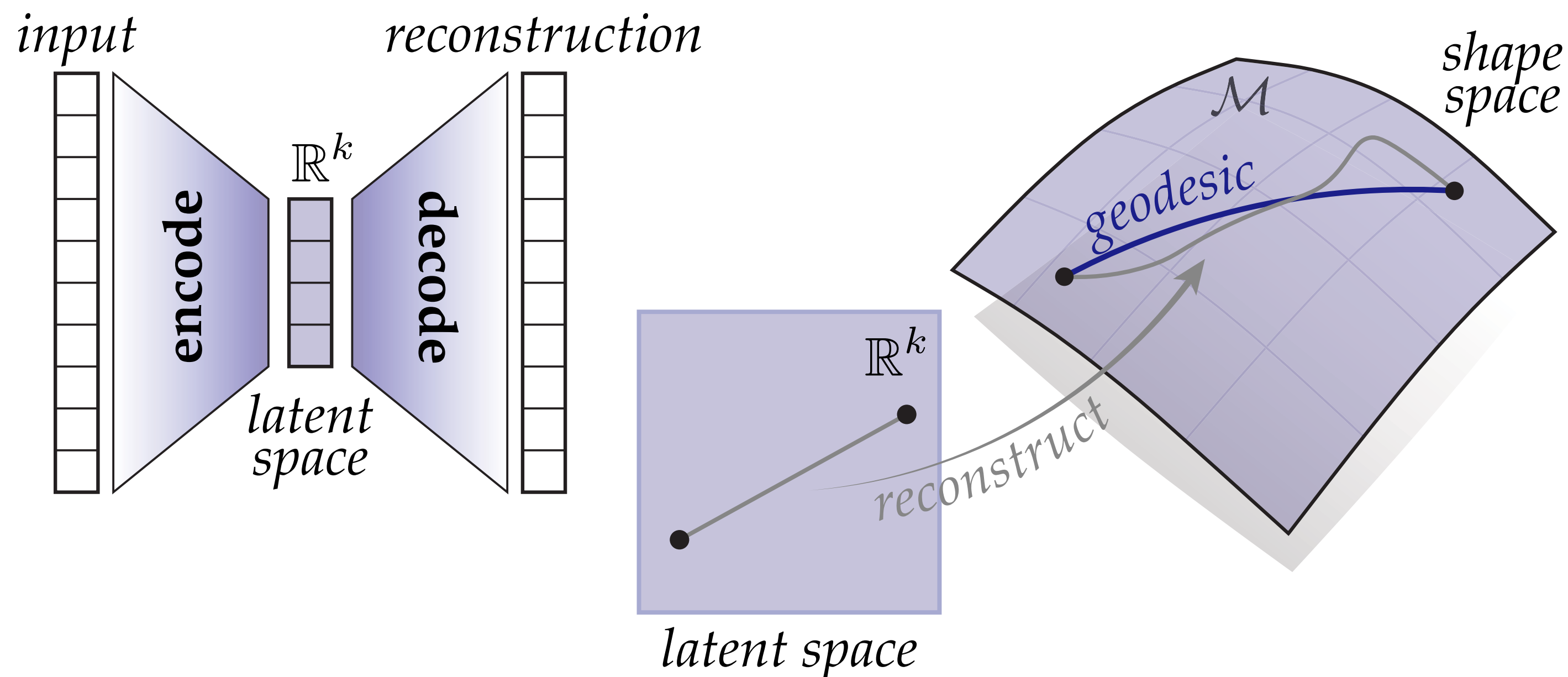
above



Very numerically robust.

Final Challenge—Incorporating Data

- **Q:** How to incorporate **data** into shape space—and physical priors in learned models?
- Two complementary possibilities:
 1. use data to help “learn” shape space metric?
 2. use shape space metric to regularize learned latent space?
 - *e.g.*, straight lines in latent space should have small path energy



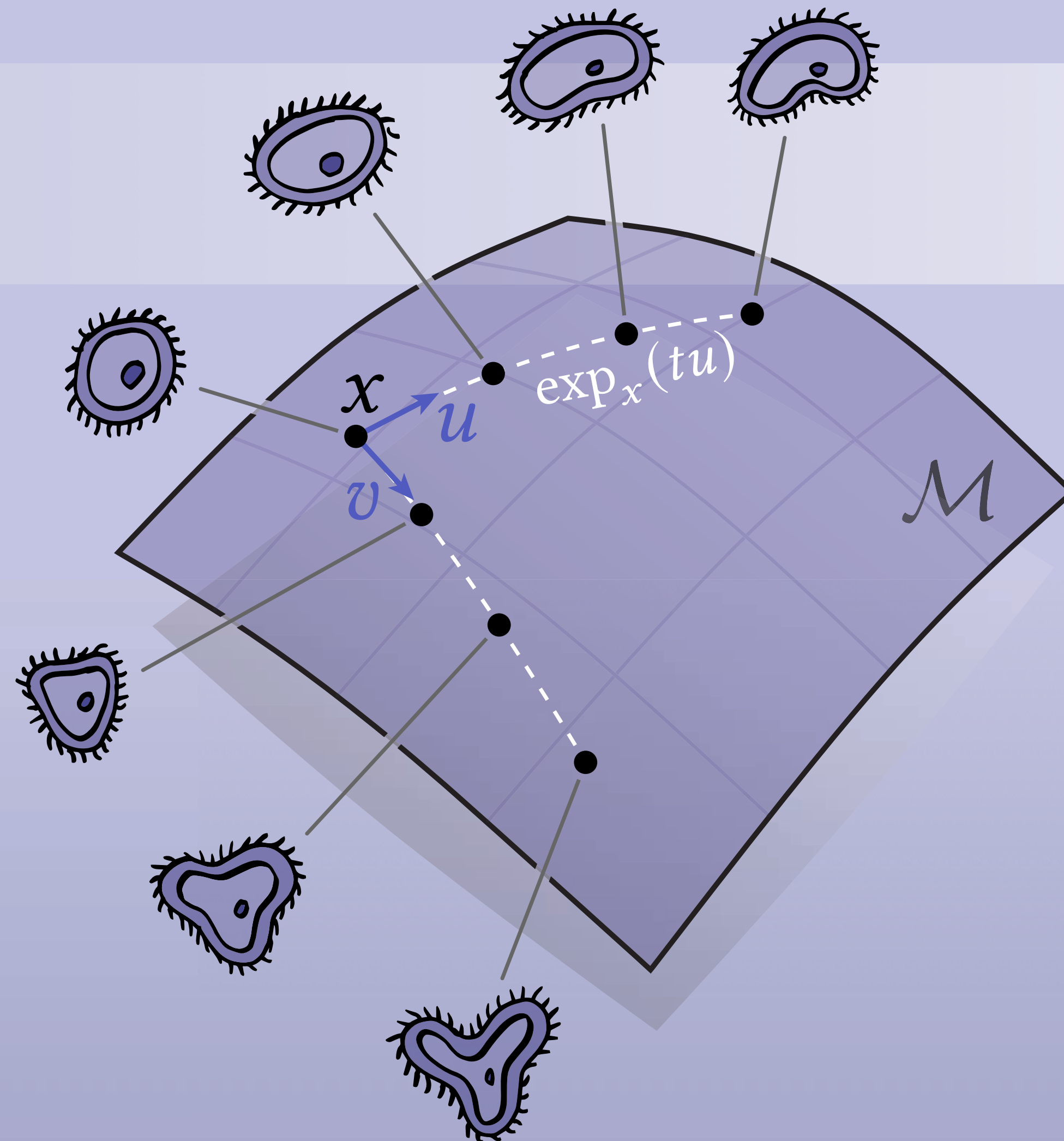
Problem: entire model still based on simple geometric considerations

Summary

- Is it **valuable** to develop high-resolution Riemannian shape spaces for cell data?
 - Certainly useful for *visualization* (human-centric understanding)...
 - **What other questions/tasks are aided by high-resolution analysis?**
- Have some good tools to lean on (shape spaces, mesh-based numerics, repulsion, ...)
- In general lots to explore, many challenges
- Which phenomena should we try to model? (mechanical, chemical, thermal...)
- Are there suitable continuum models? (must play well with shape space formulation)
- Can we cook up a good numerical discretization?
 - many challenges (shearing / adaptive meshing, topology changes, long-range forces)
- How do we incorporate empirical data? (latent space regularization as one proposal)

I understand only small pieces of this puzzle—glad to chat more!

Thanks!



SHAPE SPACES FOR BIOMEMBRANES?