Understanding vascular patterns in leukaemia with geometry and topology

HeKa seminar

PSC, Monday 18 September

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PhD: 2019-2023 (4 years)
Defense: 22 September 2023

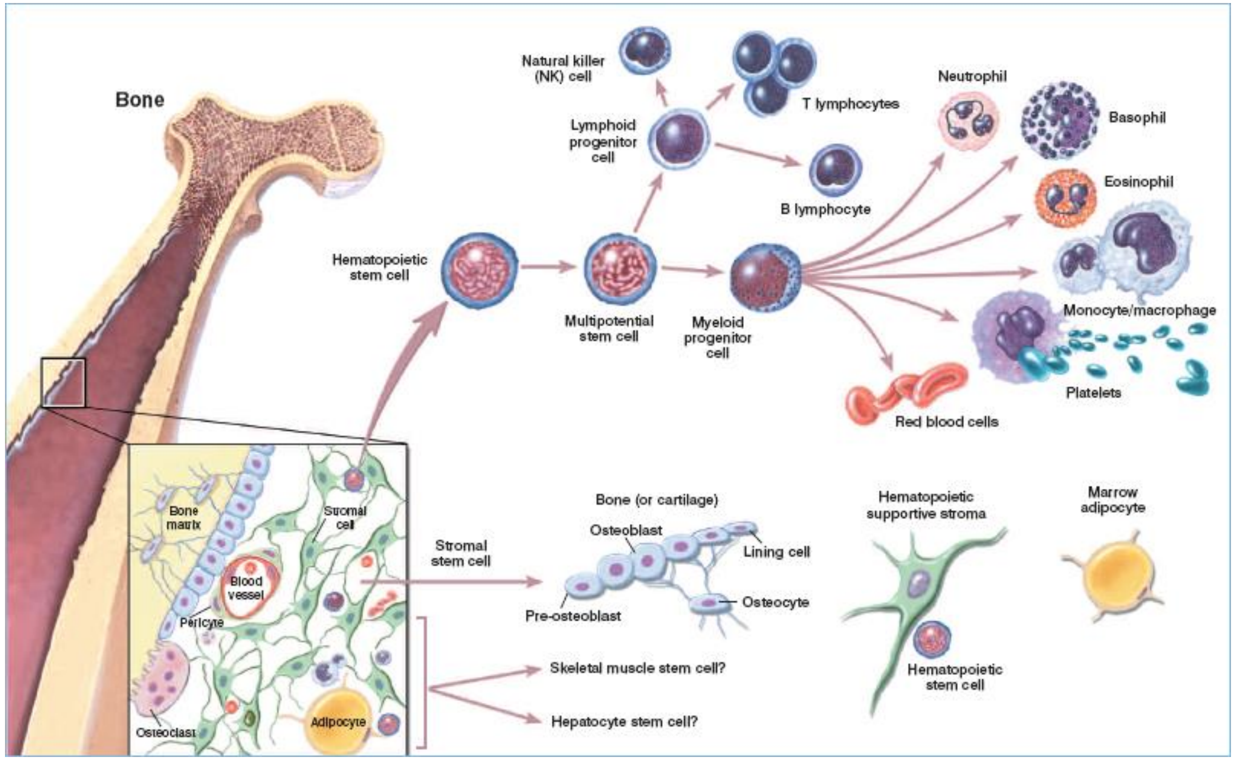
Imperial College London (maths, Anthea Monod)
The Francis Crick Institute (biology, Dominique Bonnet)

Introduction

Acute Myeloid Leukaemia

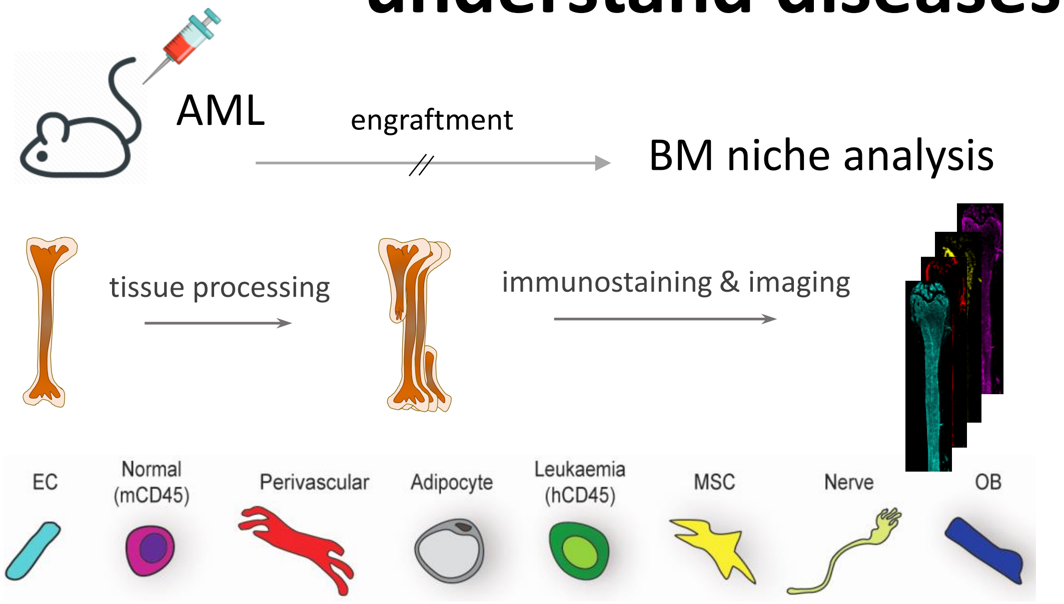
AML arises after accumulation of mutations in HSCs. Tissues get infiltrated by proliferative and dysfunctional haematopoietic cells.

- high clonal heterogeneity
- AML affects the bone marrow environment for its own proliferation
- drug resistance, relapse after therapy
- global picture of how AML interacts with bone marrow niches?
- **vascular morphology and AML?**



Credits : Terese Winslow & Lydia Kibiuk (2001)

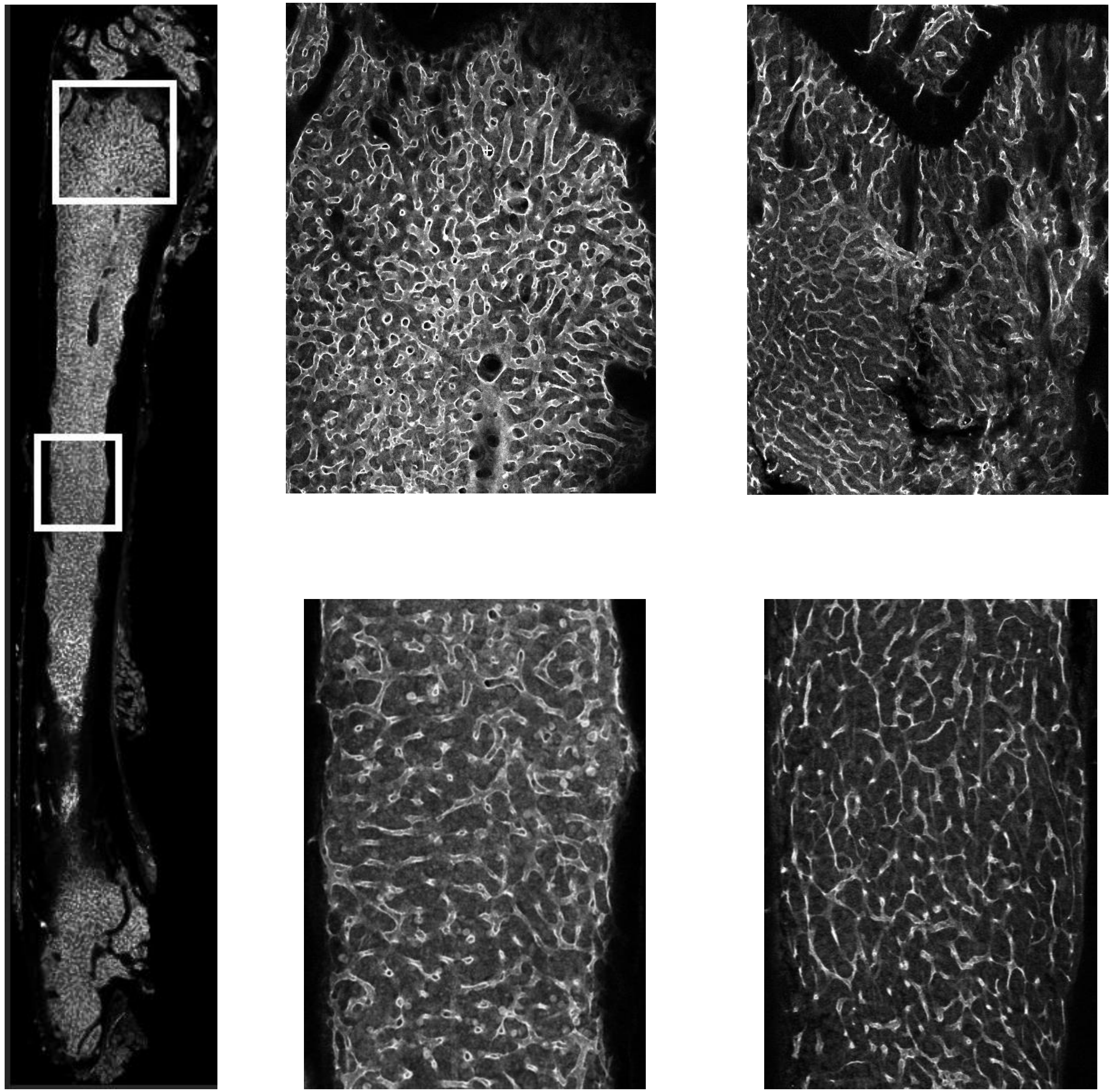
Quantify shape textures to understand diseases



27 entire femurs

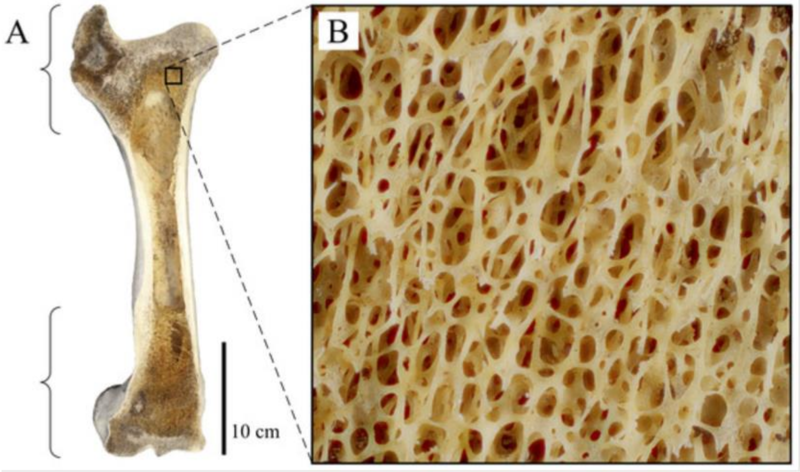
- 4 CTRL (0%)
- 4 MNC (53%-86%)
- 7 U937 (1%-10%)
- 3 HL60 (23%-25%)
- 6 P1 (10%-76%)
- 3 P2 (59%-90%)

data: Antoniana Batsivari



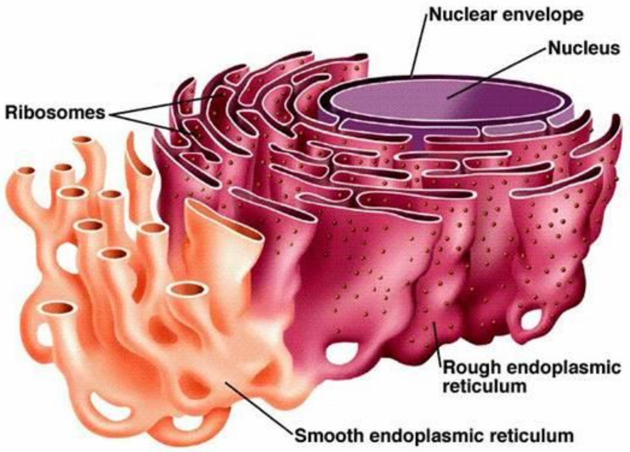
vessels healthy after engraftment

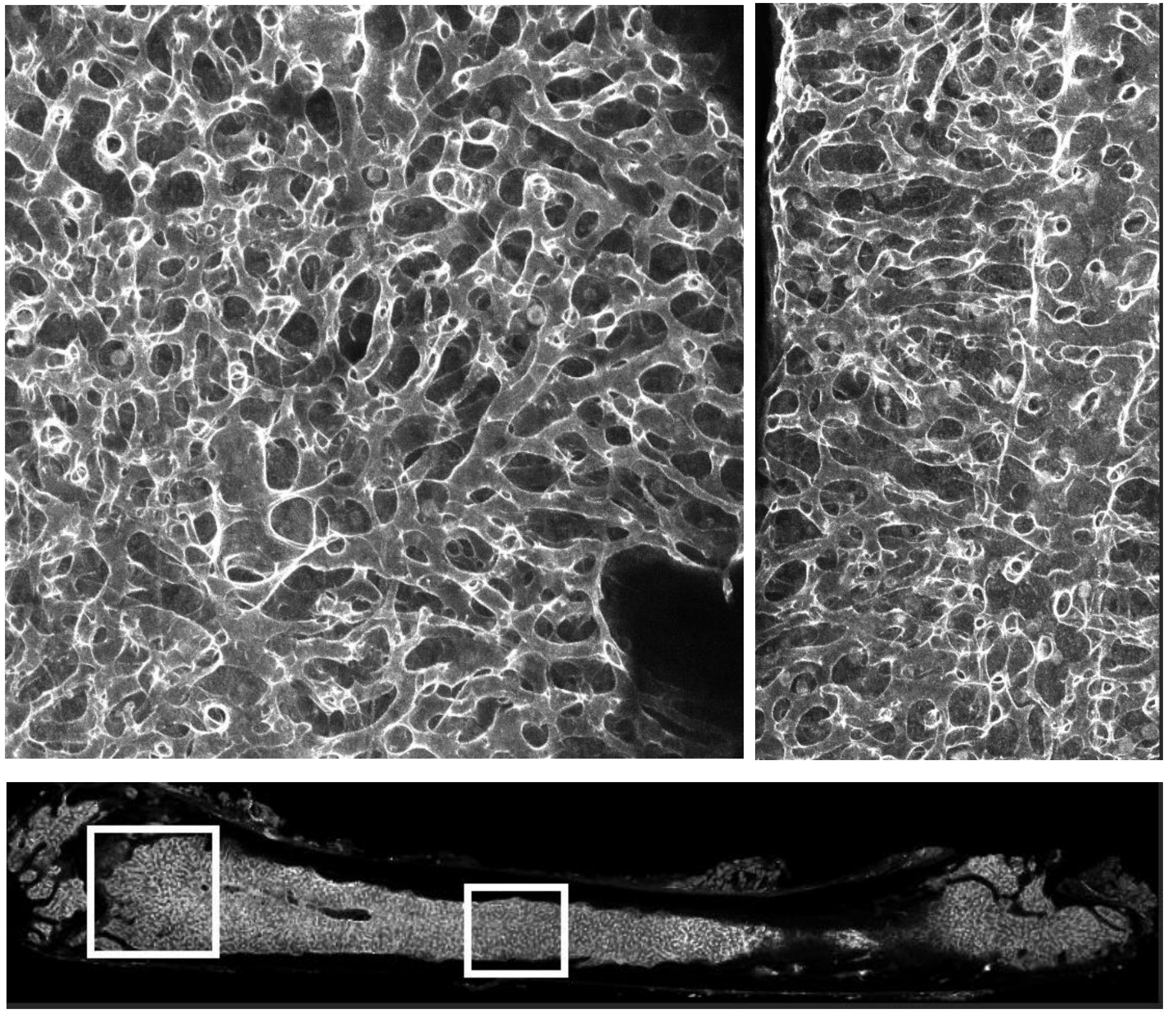
Tubular shapes, branching membranes

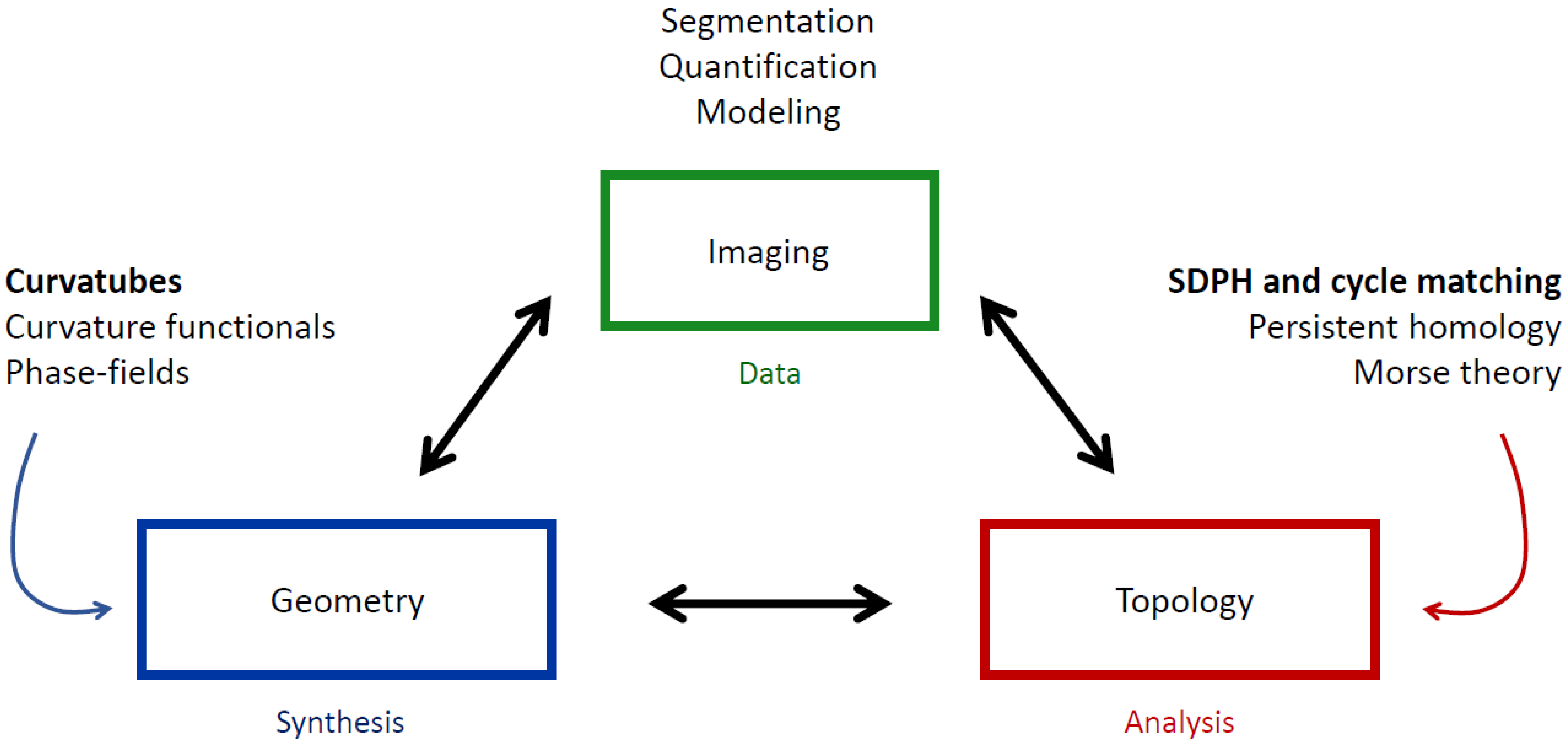


Trabecular bone has plates and rods, from Bishop et al., PeerJ (2018)

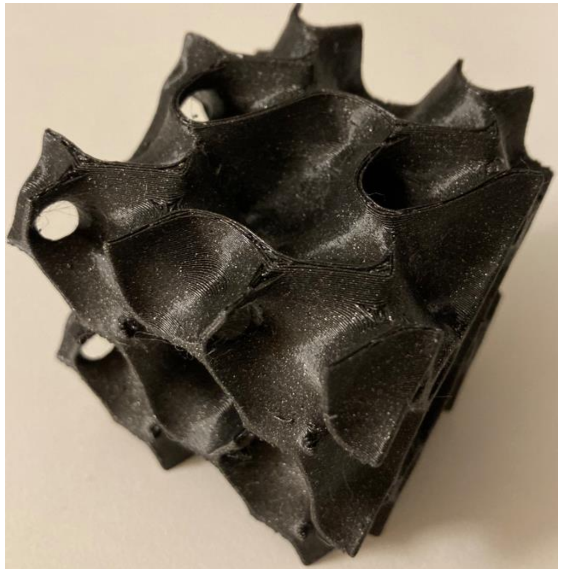
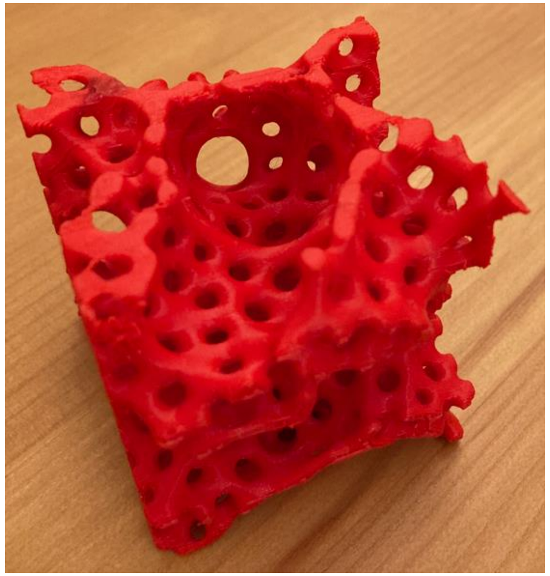
Endoplasmic reticulum has sheets and tubules






Segmentation
Quantification
Modeling
Imaging
Data
Curvatubes
Curvature functionals
Phase-fields
SDPH and cycle matching
Persistent homology
Morse theory
Geometry
Synthesis
Topology
Analysis

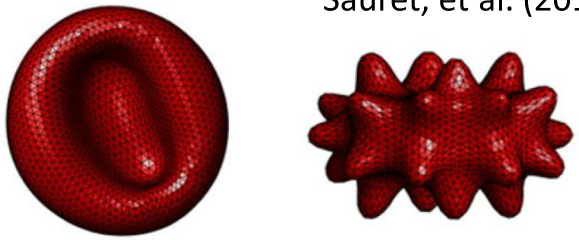
I. Curvatubes


Generation of Tubular and Membranous Shape Textures with Curvature Functionals, Anna Song, *J Math Imaging Vis* (2021)

Energy-minimizing surfaces

Geekiyanage, Balanant, Sauret, et al. (2019)



$$\mathbf{E}_A(\mathcal{S}) = \int_{\mathcal{S}} 1 \, dA$$

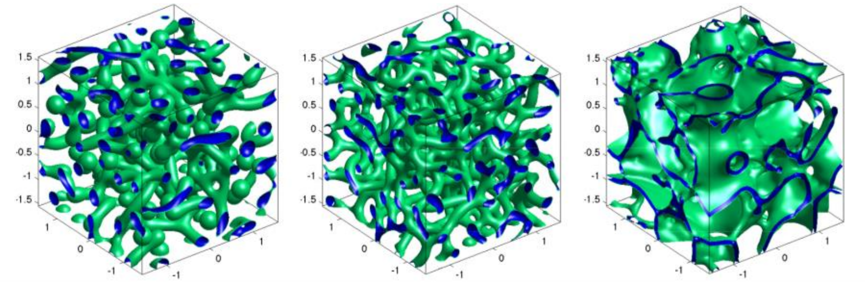
area

$$\mathbf{E}_{\mathrm{W}}(\mathcal{S}) = \int_{\mathcal{S}} H^2 \, dA$$

Willmore (1960')

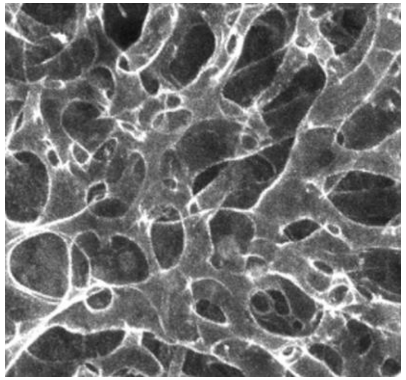
$$\mathbf{E}_{\mathrm{H}}(\mathcal{S}) = \int_{\mathcal{S}} \left(\frac{\chi_b}{2} (H - H_0)^2 + \chi_G K \right) dA$$

Helfrich (1970') and beyond



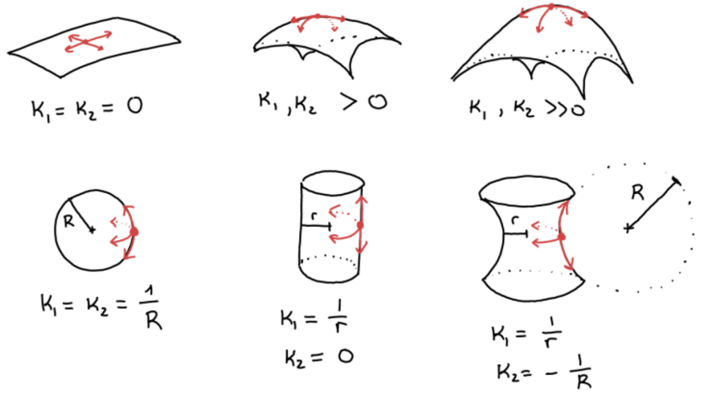
Kraitzman & Promislow (2014)

FCH model (2012)
not curvature-based



General 3D shapes?

Branching, tubular, membranous, porous, spherical…
Bone marrow vessels?

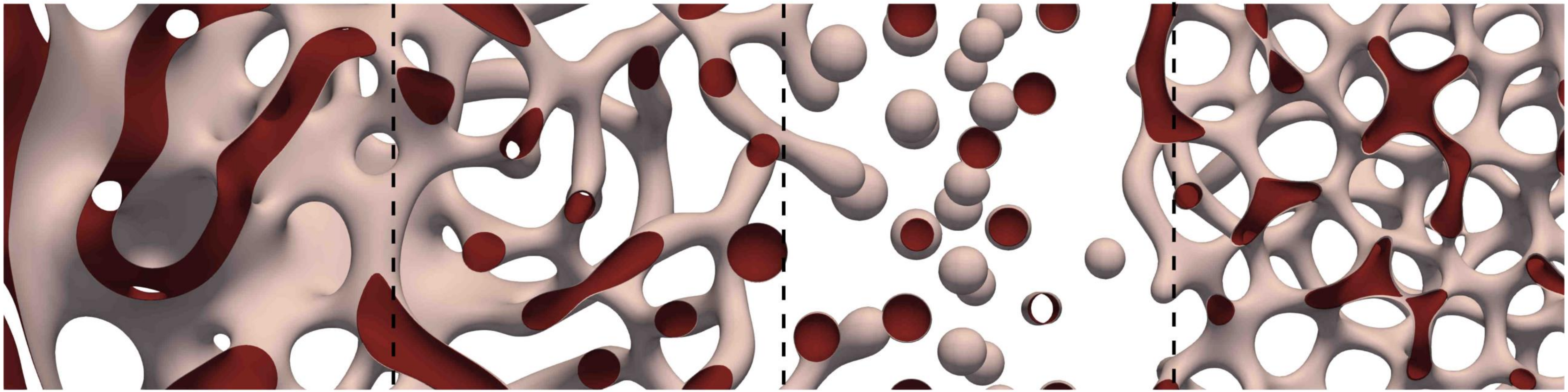


"Curvatubes" functional

$$\mathbf{F}(S) = \int_S p(\kappa_1, \kappa_2)\, dA$$

$$p(x, y) = \sum_{|\alpha| \leq 2} a_\alpha (x, y)^\alpha$$

can be asymmetric



$H^2 + \kappa_1^2 + \kappa_2^2$

$(H - 20)^2 + 5\,\kappa_2^2$

$(H - 25)^2 + (\kappa_1 - 12.5)^2 + (\kappa_2 - 12.5)^2$

$(H - 45)^2 + (\kappa_1 - 45)^2 + 10\,\kappa_2^2$

Main contributions

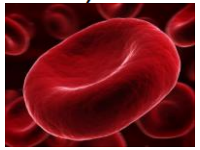
$$\mathbf{E}_A(\mathcal{S}) = \int_{\mathcal{S}} 1\, dA$$

minimal surfaces (1750')

$$\mathbf{E}_{\mathrm{W}}(\mathcal{S}) = \int_{\mathcal{S}} H^2\, dA$$

Willmore (1960')

$$\mathbf{E}_{\mathrm{H}}(\mathcal{S}) = \int_{\mathcal{S}} \left(\frac{\chi_b}{2}(H - H_0)^2 + \chi_G K \right) dA$$

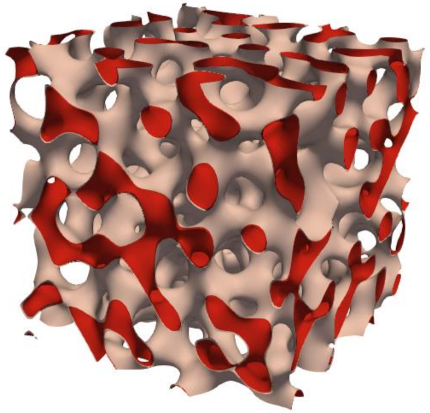


Helfrich (1970')

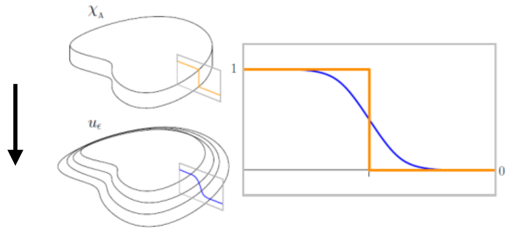
$$\mathbf{F}(\mathcal{S}) = \int_{\mathcal{S}} p(\kappa_1, \kappa_2)\, d A$$

Curvatubes (2021)

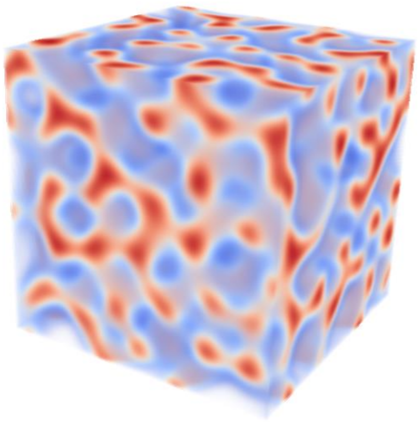
$$\mathbf{F}(\mathcal{S}) = \int_{\mathcal{S}} p(\kappa_1, \kappa_2)\, d A$$



2D surface energy
hard to simulate



$$\mathcal{E}_\epsilon(u) = \int_\Omega p(\kappa_{1,u}^\epsilon, \kappa_{2,u}^\epsilon)\, \epsilon |\nabla u|^2\, dx$$



3D phase-field energy
easy to simulate on GPUs

https://github.com/annasongmaths/curvatubes

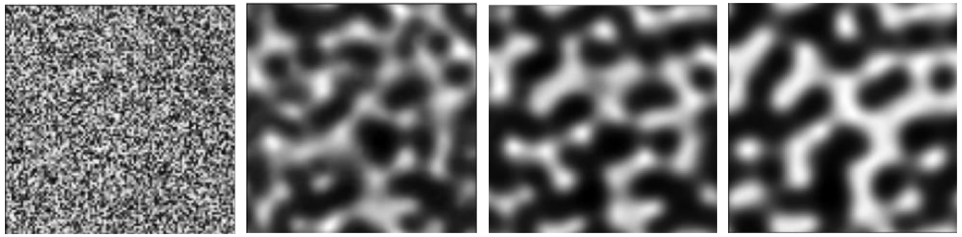
Algorithm

curvatubes

parameters inside energy

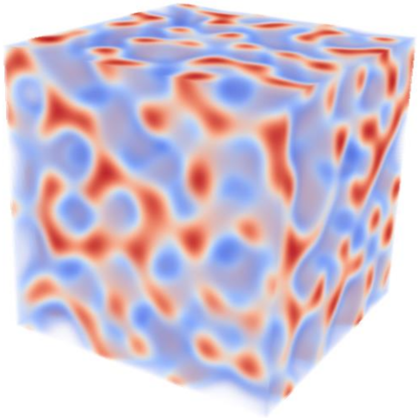
$$\dot{u} = \Delta \frac{\partial \mathcal{F}_\epsilon}{\partial u}$$

random initialization



=

phase-field

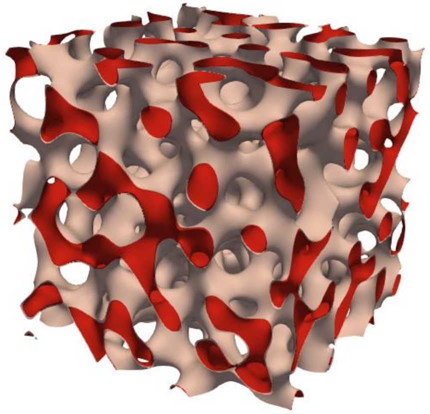


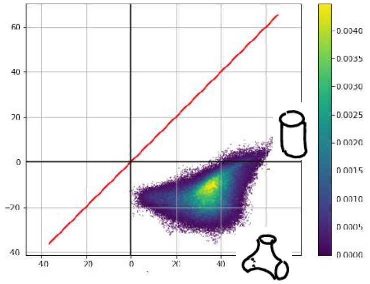
$$\mathcal{F}_\epsilon(u) = \int_\Omega \Big[\frac{a_{2,0}+a_{0,2}-a_{1,1}}{2\epsilon} \|\mathcal{M}_u^\epsilon\|^2 + \frac{a_{1,1}}{2\epsilon} (\mathrm{Tr}\mathcal{M}_u^\epsilon)^2 + \frac{a_{2,0}-a_{0,2}}{2\epsilon} \mathrm{Tr}\mathcal{M}_u^\epsilon \sqrt{(2\|\mathcal{M}_u^\epsilon\|^2 - (\mathrm{Tr}\mathcal{M}_u^\epsilon)^2)^+} + \frac{a_{1,0}+a_{0,1}}{2} |\nabla u| \mathrm{Tr}\mathcal{M}_u^\epsilon + \frac{a_{1,0}-a_{0,1}}{2} |\nabla u| \sqrt{(2\|\mathcal{M}_u^\epsilon\|^2 - (\mathrm{Tr}\mathcal{M}_u^\epsilon)^2)^+} + a_{0,0}\, \epsilon |\nabla u|^2 \Big] \, dx.$$

Pytorch
GPU
Adam or L-BFGS

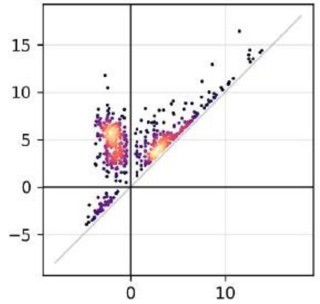
outputs

surface





curvature diagram

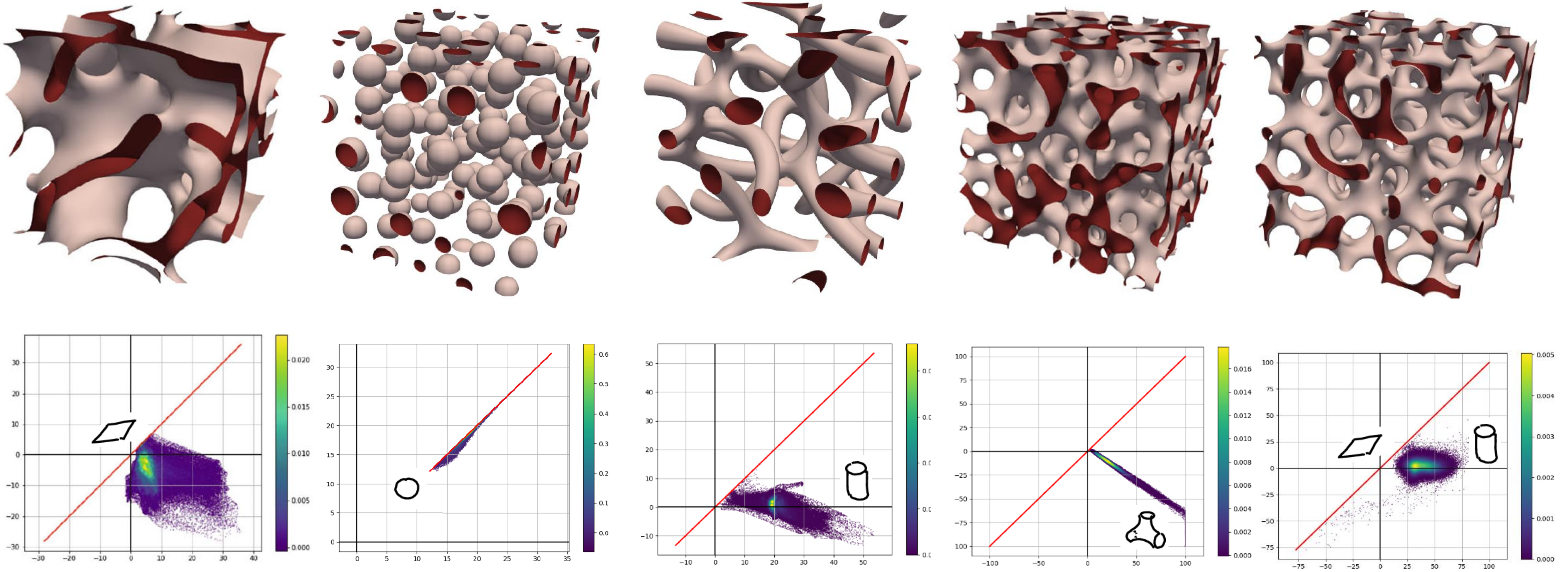


persistence diagram

other features...

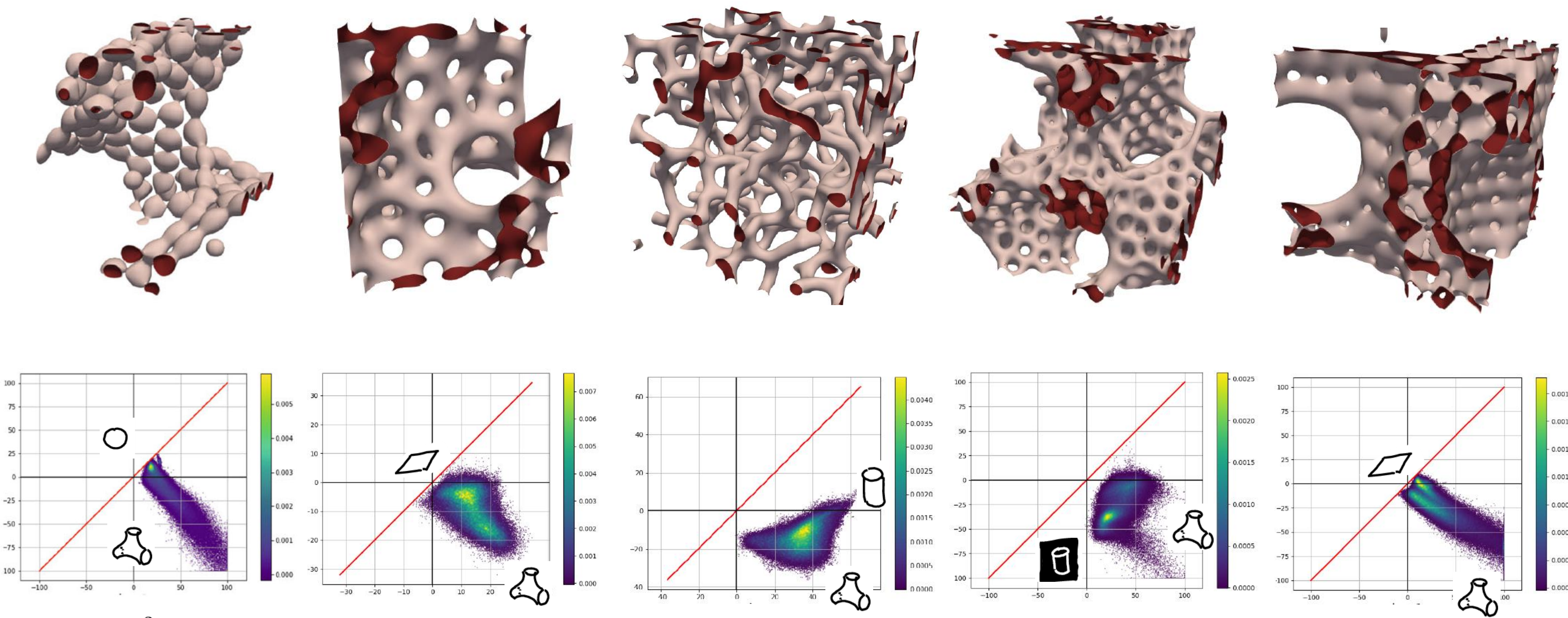
Basic shape textures

Natural form $h_2(H - H_0)^2 + k_1 K + \alpha(\kappa_1 - \kappa_1^0)^2 + \beta(\kappa_2 - \kappa_2^0)^2$



$H^2 + \kappa_1^2 + \kappa_2^2$ | $(H-25)^2 + (\kappa_1 - 12.5)^2 + (\kappa_2 - 12.5)^2$ | $(H-20)^2 + 5\kappa_2^2$ | $(H-5)^2 + 0.8K + \kappa_2^2$ | (no natural form)

Complex shape textures



$(H - 28)^2 + 1.55K$

(no natural form)

(no natural form)

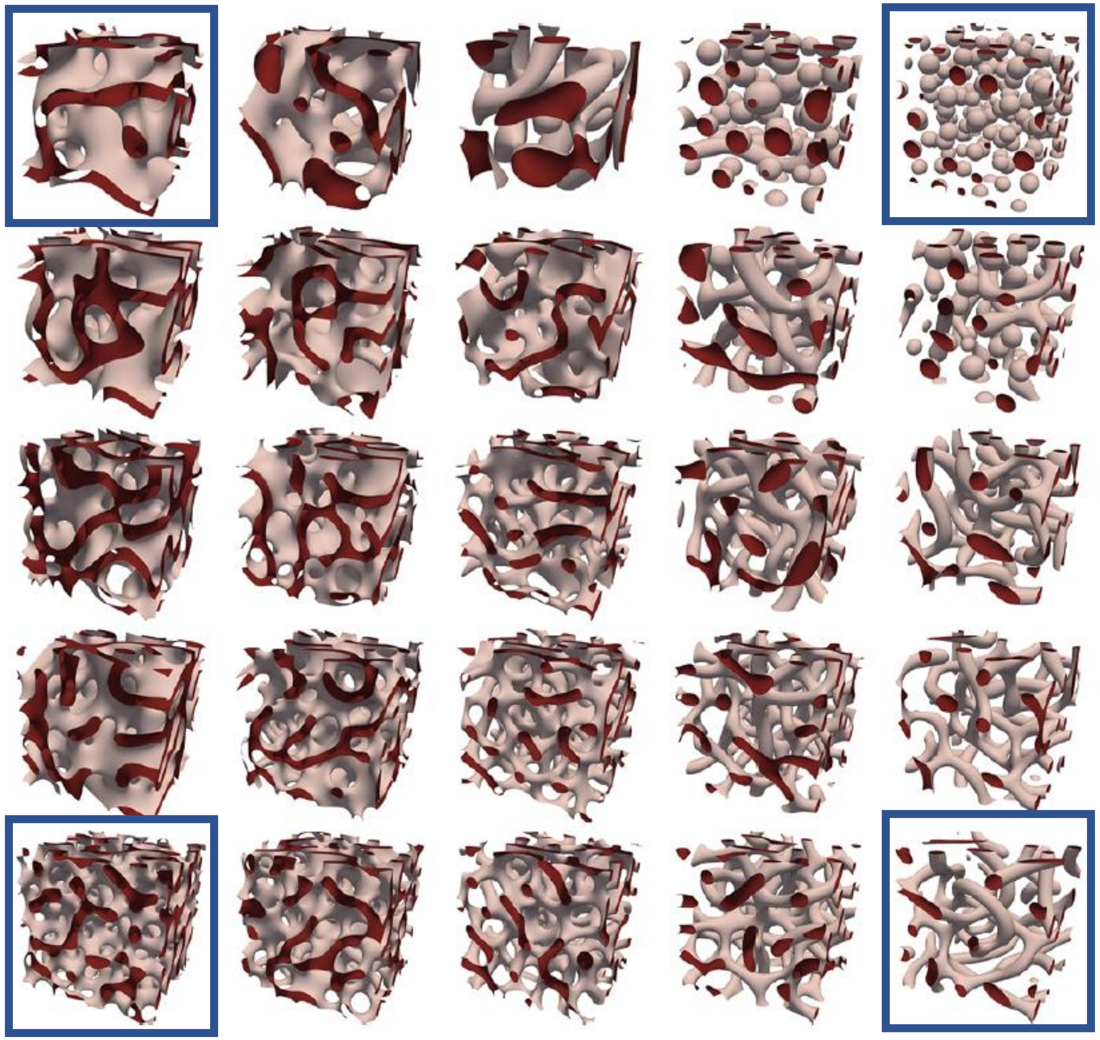
(no natural form)

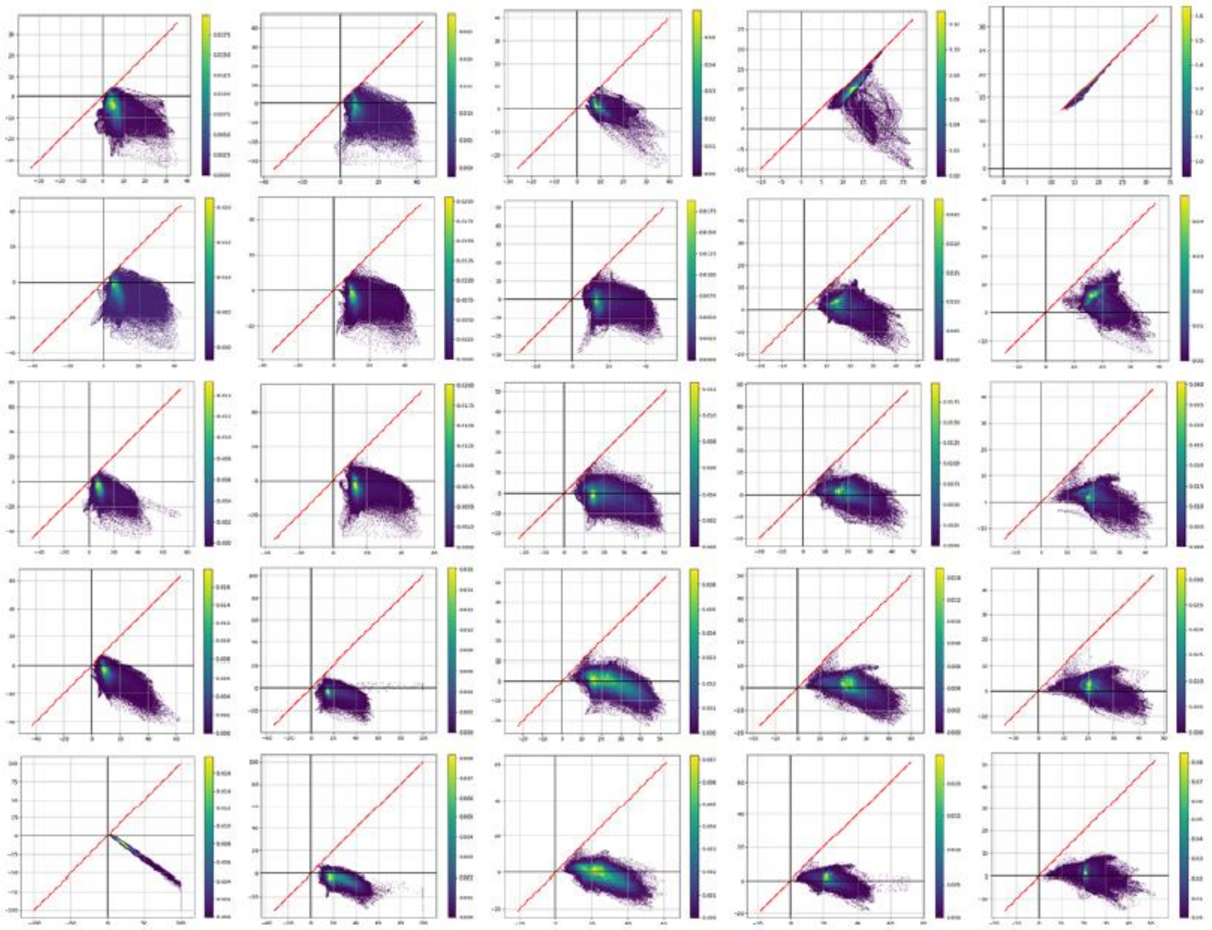
(no natural form)

Continuity of shapes and of textures

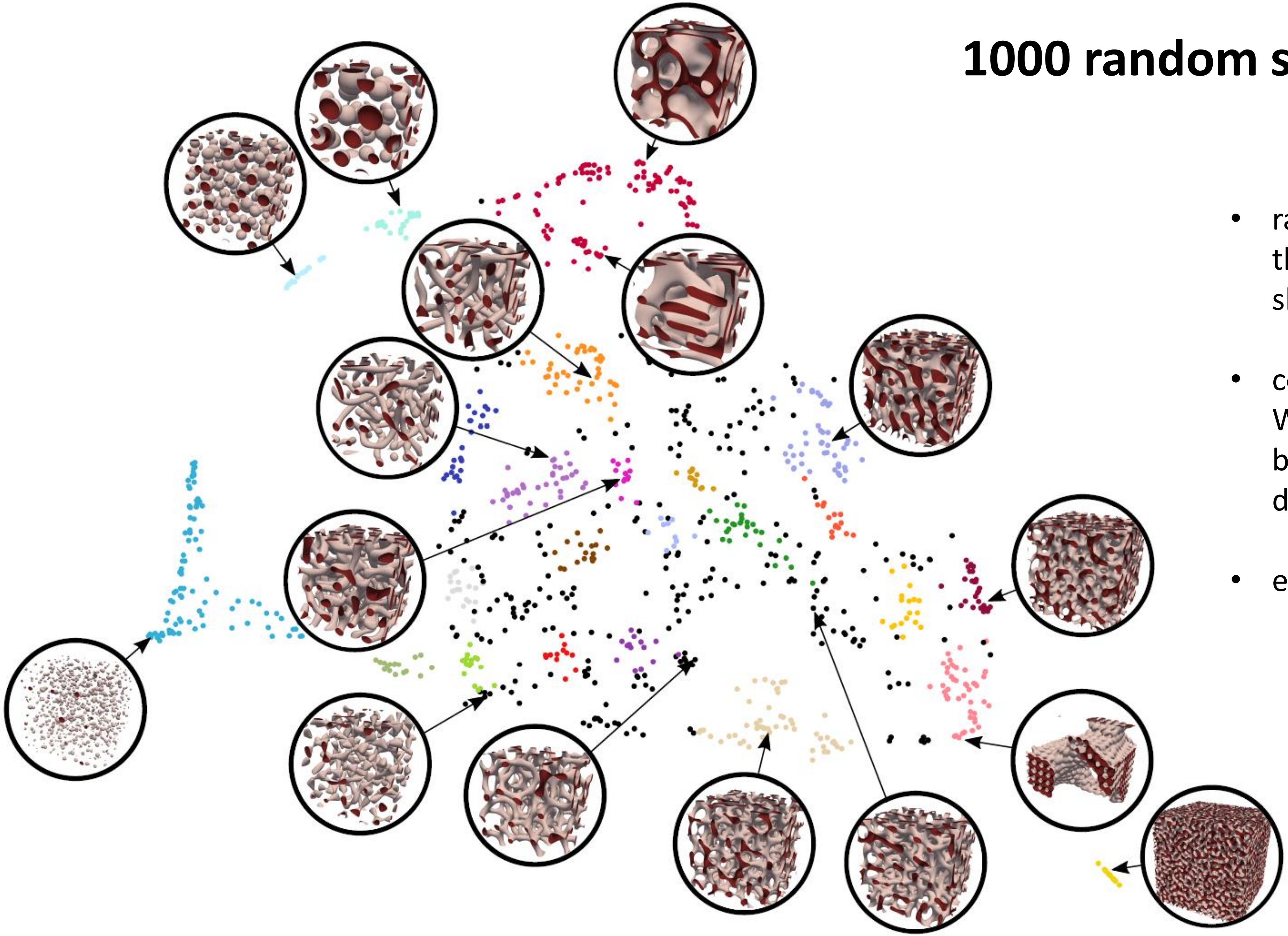
same initialization
different energies

bilinear interpolation between 4 shape parameters leads to continuum of morphologies



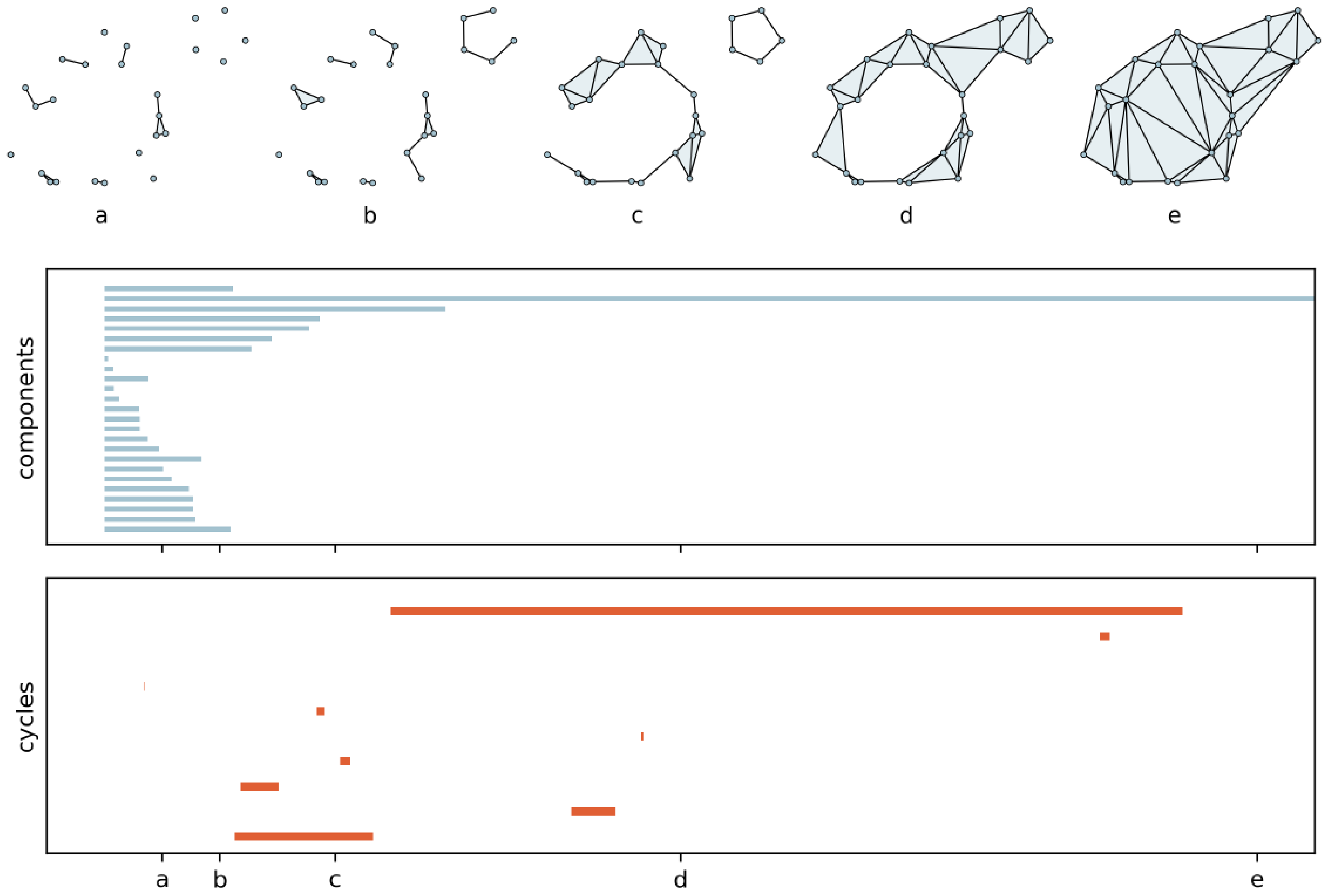


1000 random shapes in UMAP



- randomly chosen coeffs, then accept only “valid” shapes
- compute pairwise Wasserstein distances between curvature diagrams
- embed in 2D using UMAP

II. Topological Data Analysis (TDA) for vascular quantification



Persistent homology :

- tracks evolution of topological features
- summarizes birth-death times in barcodes

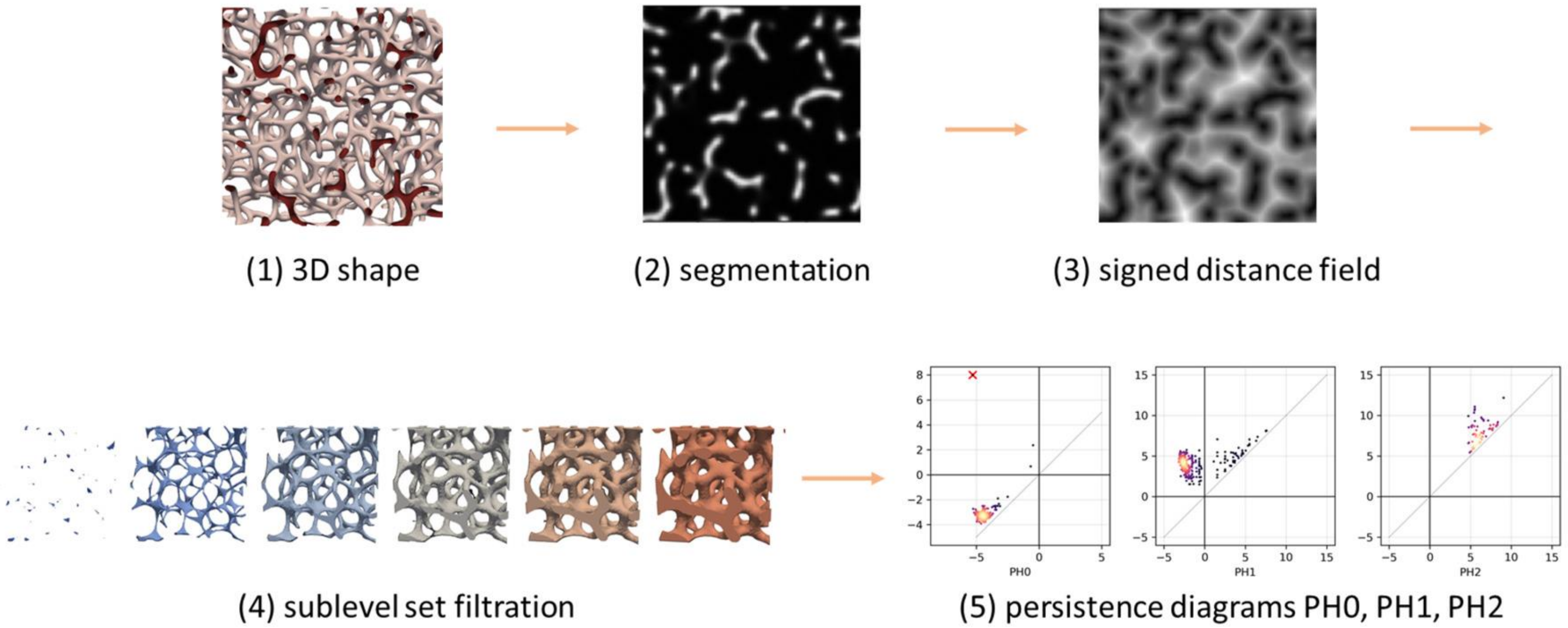
PH0:
components

PH1:
cycles

PH2:
cavities

PHk:
k-dim holes

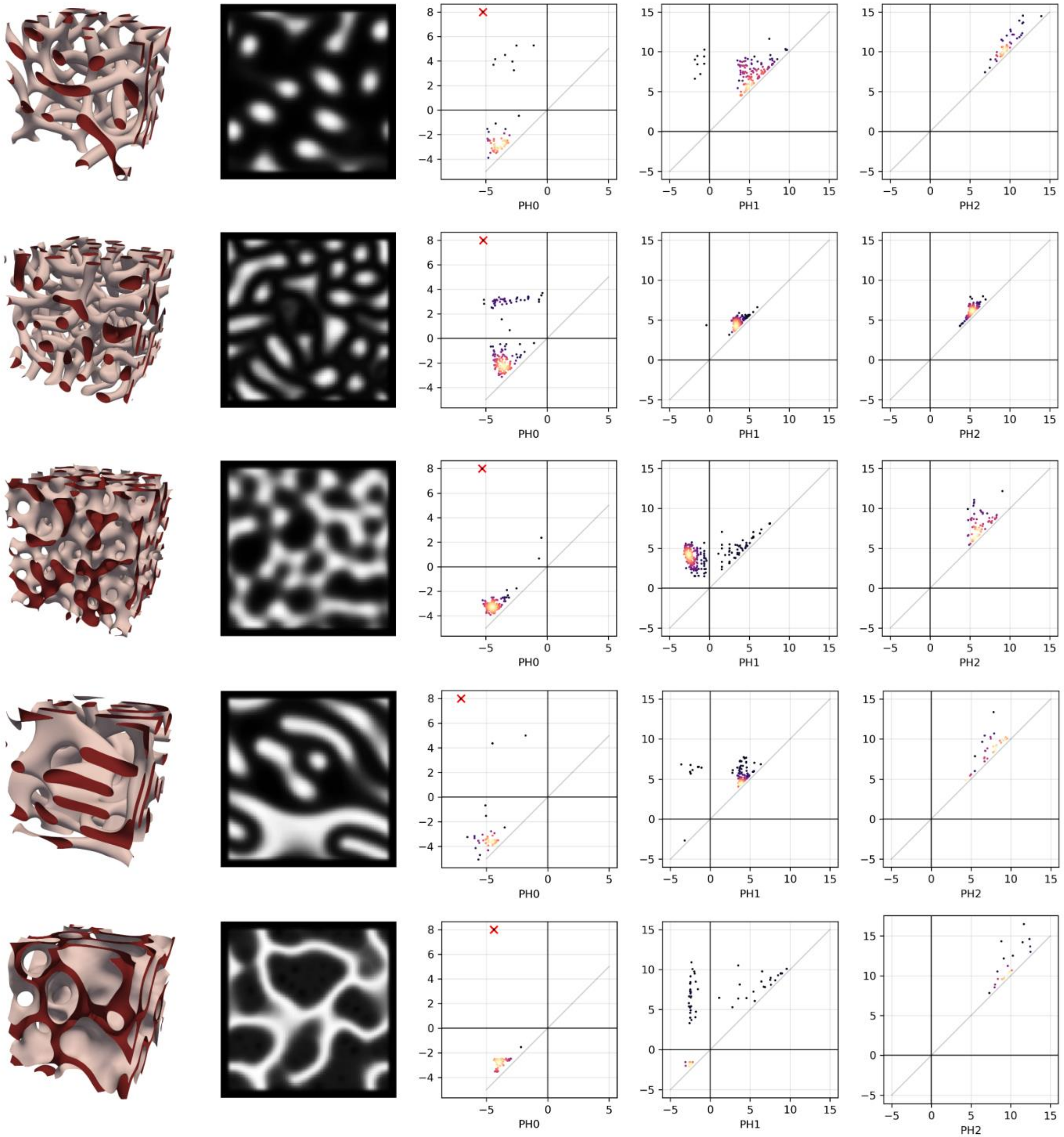
SDPH method


(1) 3D shape
(2) segmentation
(3) signed distance field
(4) sublevel set filtration
PH0
PH1
PH2
(5) persistence diagrams PH0, PH1, PH2

- five textures generated with curvatubes

- sometimes visually hard to describe how different

- but SDPH can easily discriminate



Theoretical investigation

Generalized Morse Theory of Distance Functions to Surfaces for Persistent Homology
Anna Song, Ka Man Yim, and Anthea Monod (arxiv, 2023)

Setting

SDPH used by (Delgado-Friedrichs *et al.*, 2014, 2015; Herring *et al.*, 2019; Moon *et al.*, 2019; Pritchard *et al.*, 2023) in the discrete cubical setting. Here, we consider distance fields to smooth surfaces.

Let Ω^- be a bounded open set with C^k boundary $\mathcal{S} = \partial\Omega^-$, $k \geq 2$. Then

$$\mathbb{R}^n = \Omega^- \sqcup \mathcal{S} \sqcup \Omega^+.$$

$$\text{Define} \quad d = \mathrm{dist}(\cdot, \Omega^-) - \mathrm{dist}(\cdot, \Omega^+).$$

Consider the sublevel set filtration $X_\bullet$ where

$$X_t = \{x \in \mathbb{R}^3 \mid d(x) \leq t\}.$$

Compute the persistence diagrams

$$\mathrm{PH}(d) : \forall s \leq t, \quad H(X_s) \to H(X_t).$$

General aims

Are SDPH diagrams **well-defined**?

How to **interpret** SDPH diagrams?

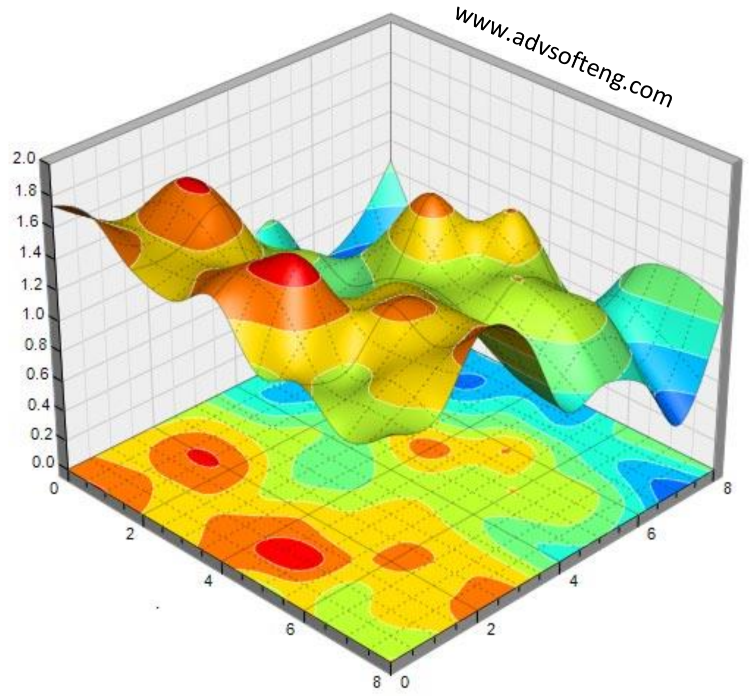
What do they **quantify** in shapes?

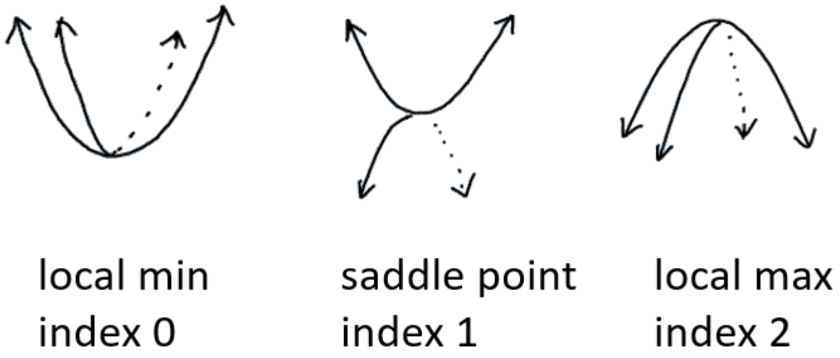
notion of **critical points**

Smooth Morse theory and PH

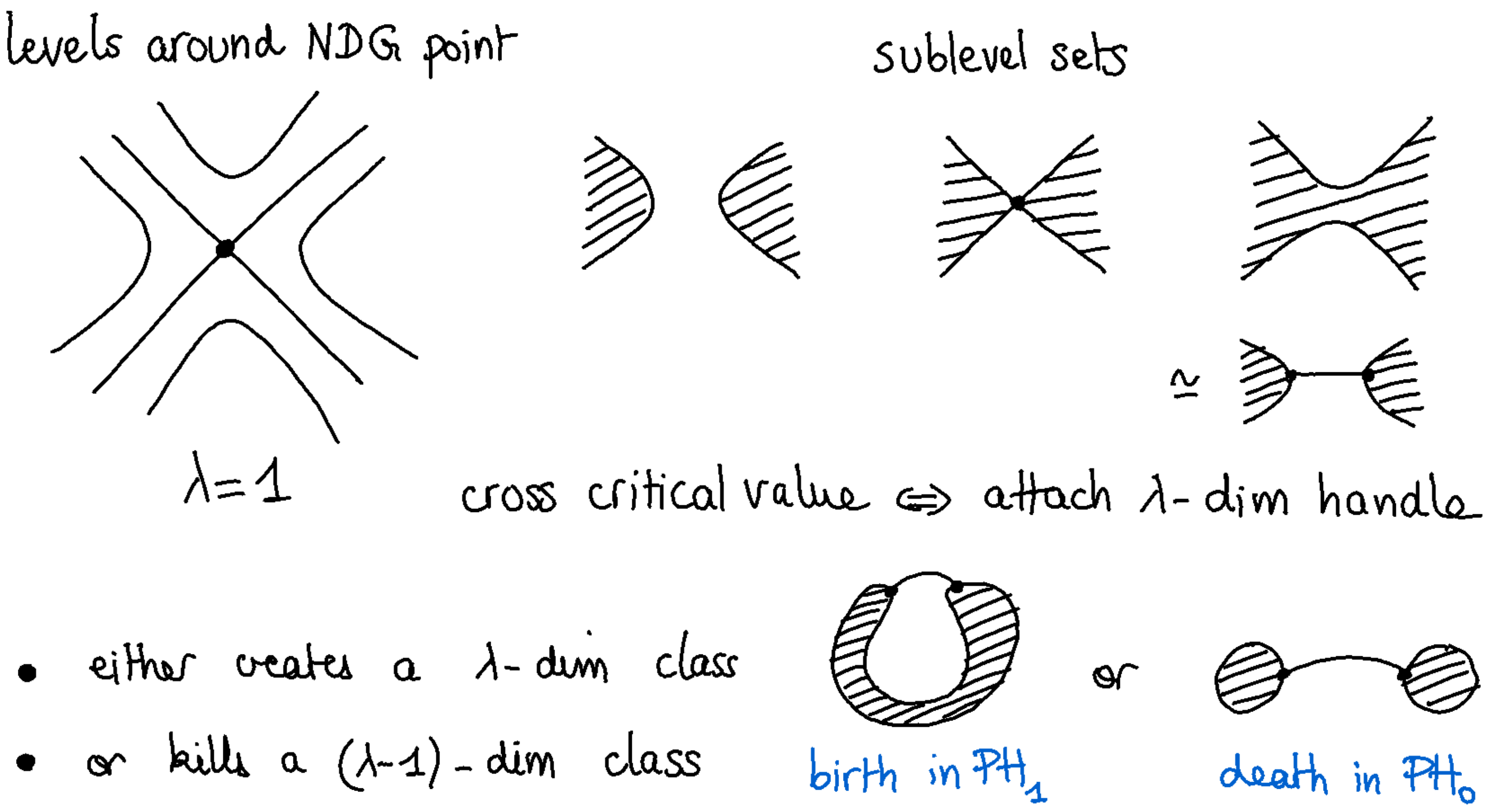
Morse theory studies **non-degenerate critical points** of smooth functions, at which

$$f \underset{\text{diffeo}}{\sim} \text{cst} - \sum_{i=1}^{\lambda} x_i^2 + \sum_{i=\lambda+1}^{n} x_i^2 .$$





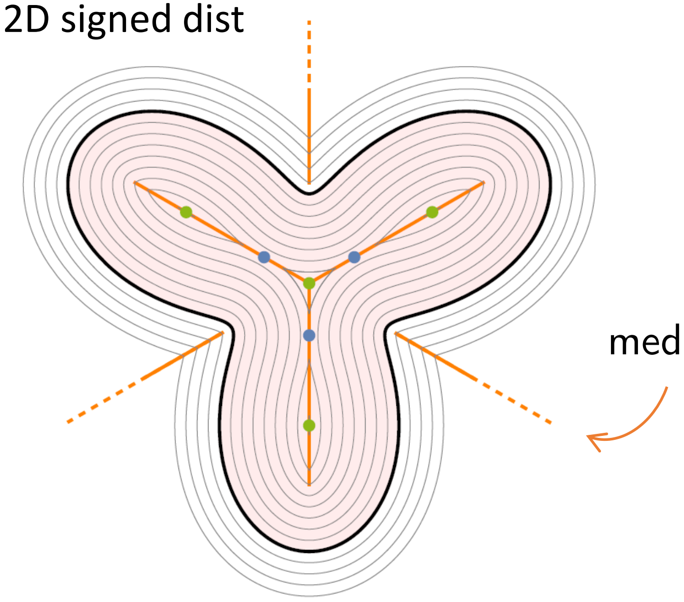
Morse theory relates a smooth proper Morse function f to $\mathrm{PH}(f)$ through the **isotopy lemma** and **handle attachment lemma**. Typically, births and deaths in $\mathrm{PH}_k(f)$ pair **critical points** with indices $(k, k+1)$.



Problem

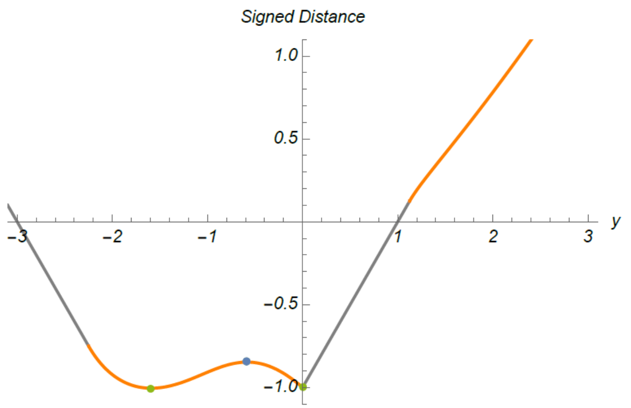
However, distance functions generated by smooth boundaries $\mathcal{S}$ **are not smooth**, especially on the medial axis $\mathcal{M}_{\mathcal{S}}$.

2D signed dist



medial axis

nonsmooth profile on vertical axis



Contribution: Morse theory for (signed) distance functions

Theorem (Isotopy lemma for signed distance)

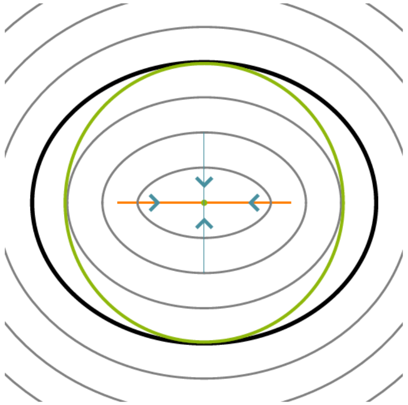
Let $a < b$ in $\mathbb{R}$. Suppose that $d^{-1}[a, b]$ contains no critical point of d (it is compact). Then $d^{-1}(-\infty, a]$ is a deformation retract of $d^{-1}(-\infty, b]$, and therefore they are homotopy-equivalent.

Theorem (Handle attachment lemma for signed distance)

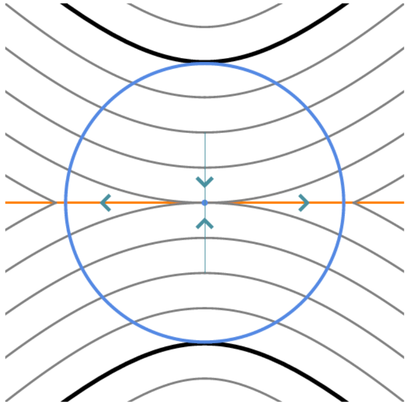
At a Min-type NDG critical point $x \in \mathbb{R}^n \setminus \mathcal{S}$ with index λ and value $d(x) = c$, if the interlevel set $d^{-1}[c - \epsilon, c + \epsilon]$ contains no other critical point for some $\epsilon > 0$, then

$$d^{-1}(-\infty, c + \epsilon] \simeq d^{-1}(-\infty, c - \epsilon] \cup e^{\lambda}.$$

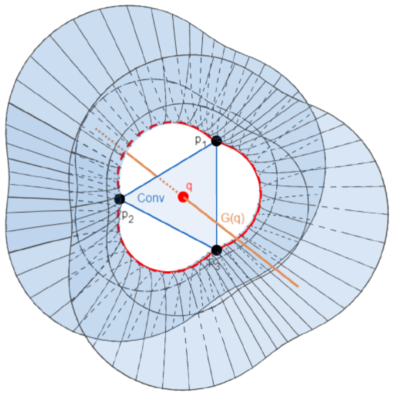
non-degenerate



$\mu = 1 + 1$



$\mu = 1 + 0$



$\mu = 2 + 0$

Theorem (Genericity)

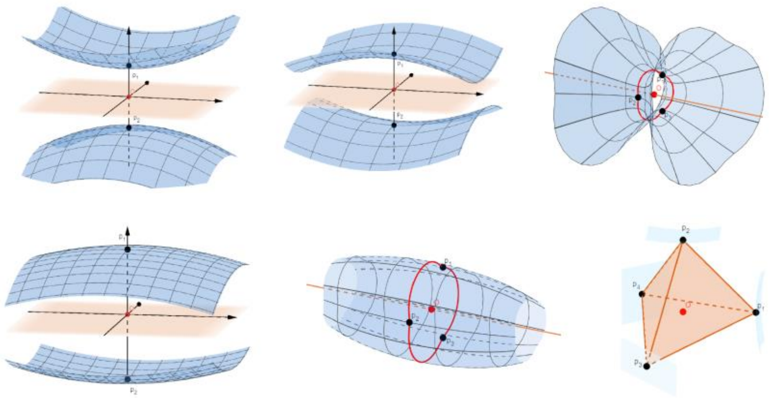
For generic embeddings of a C^k-smooth ($k \geq 3$) closed orientable surface into $\mathbb{R}^3$, the induced signed distance d admits only a finite number of critical points, that are all non-degenerate.

Corollary (SDPH)

For generic 3D shapes, the SDPH module PH_k can be decomposed into a finite sum of $\{[b_i, d_i)\}$ intervals pairing NDG points with indices $(k, k+1)$.

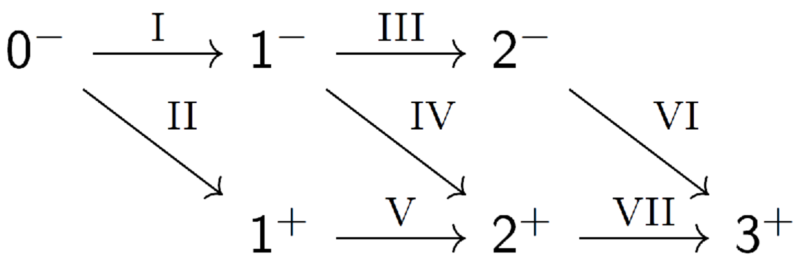
	$\lambda = 0$	$\lambda = 1$	$\lambda = 2$	$\lambda = 3$
$d < 0$	**type** 0^- 3 subtypes	**type** 1^- 2 subtypes	**type** 2^- 1 subtype	
$d > 0$		**type** 1^+ 1 subtype	**type** 2^+ 2 subtypes	**type** 3^+ 3 subtypes

Table: **Classification of NDG critical points of d in dimension 3.**

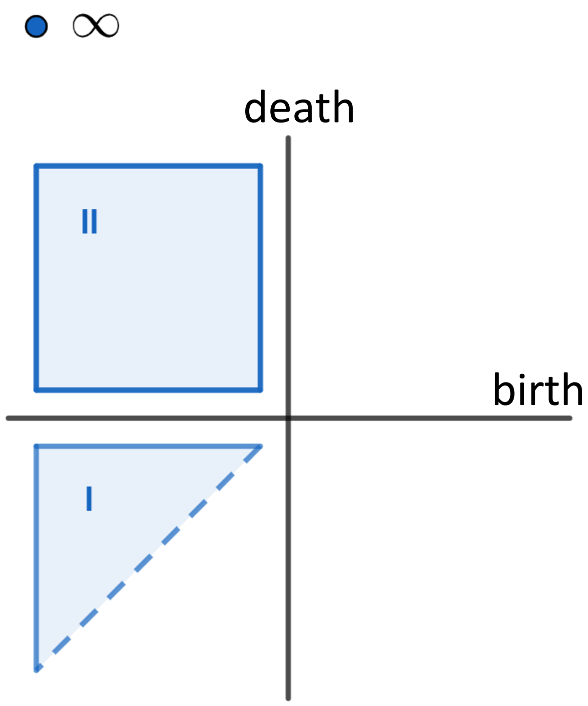


(subtypes)

SDPH diagrams in theory

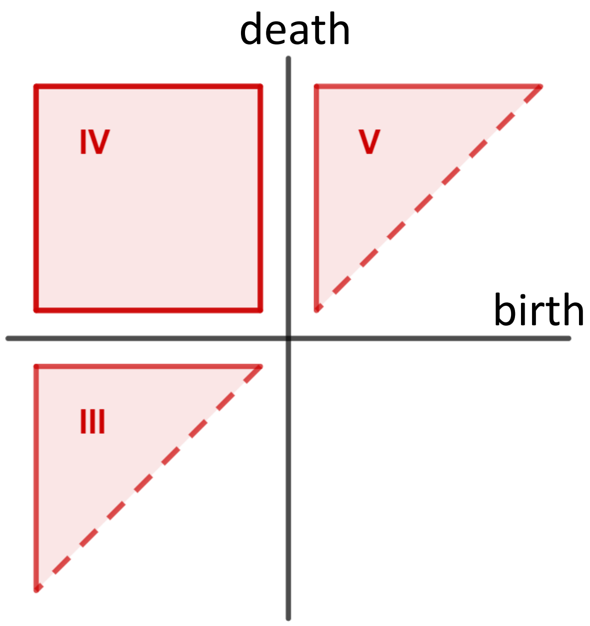


birth/death of components



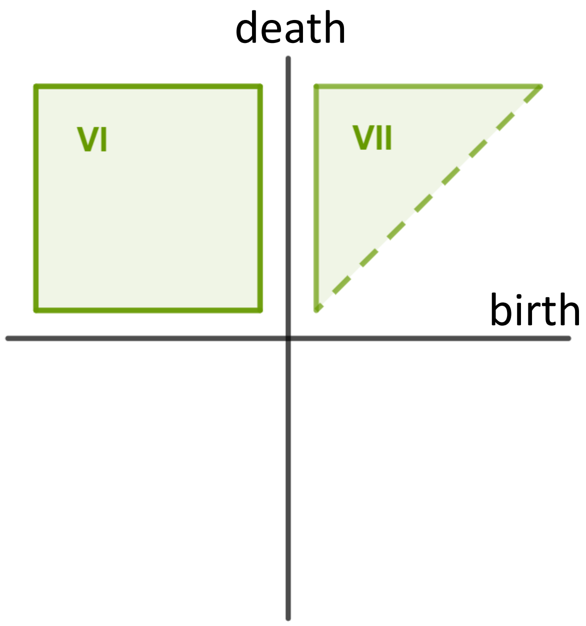
PH_0

birth/death of loops



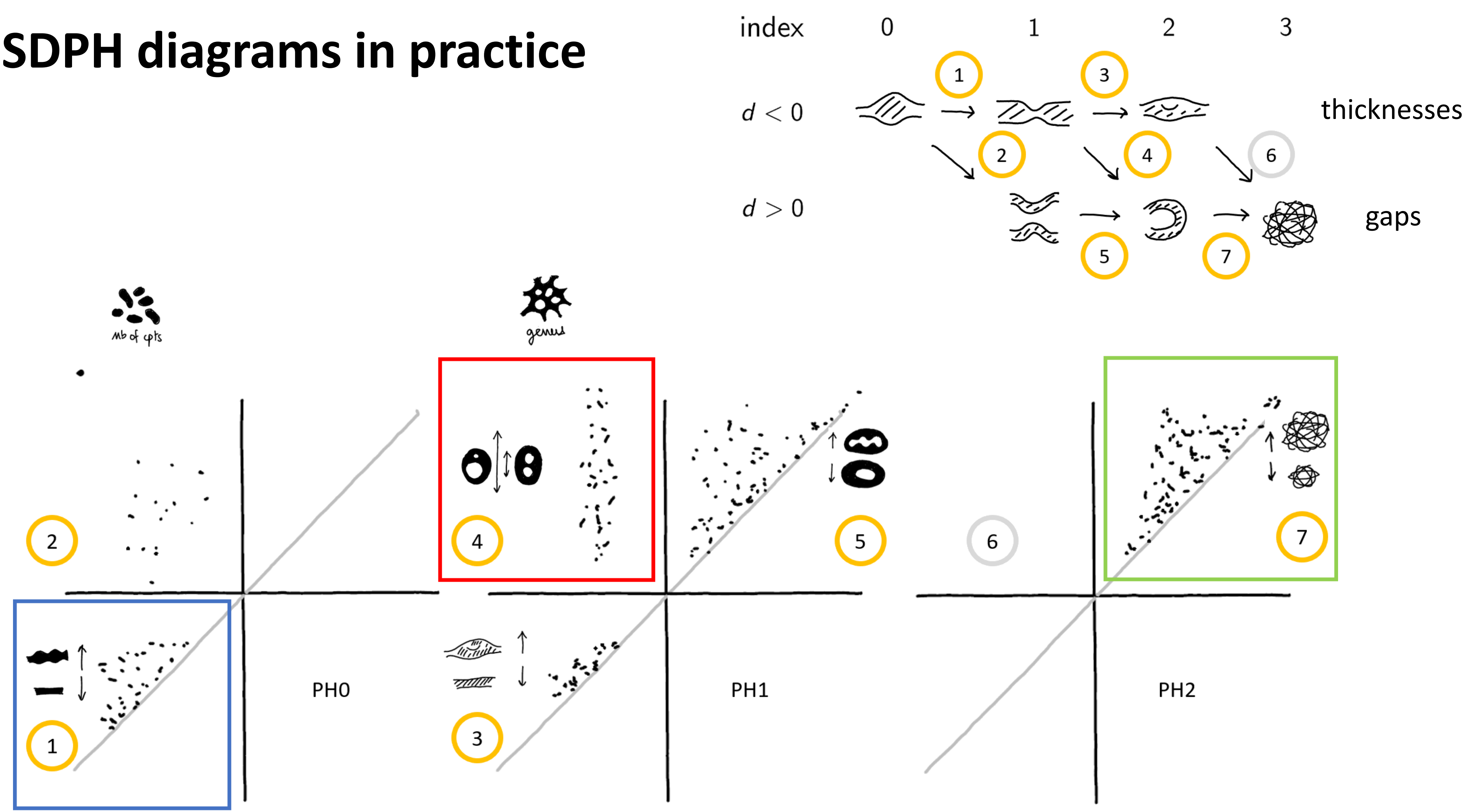
PH_1

birth/death of cavities



PH_2

SDPH diagrams in practice



Take-home message

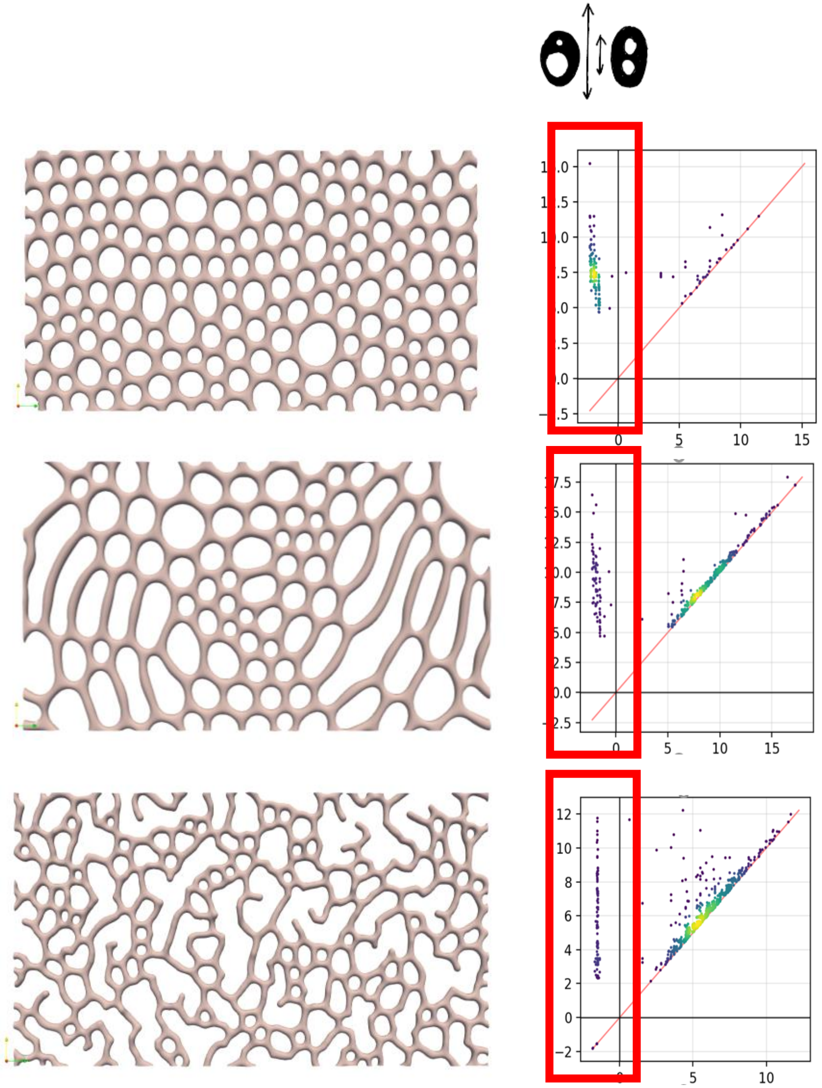
Persistent homology describes shapes by **pairing their critical points**.

- one (b,d) point in the diagram = two critical points in the shape
- a critical point is either a creator / destroyer of a topological feature

- each critical point carries a value: a **critical size**
- no need to measure thicknesses and interspaces by hand! no annotation!
- long-lived features are more significant

--> SDPH diagrams quantify the **texture of shapes**

Examples

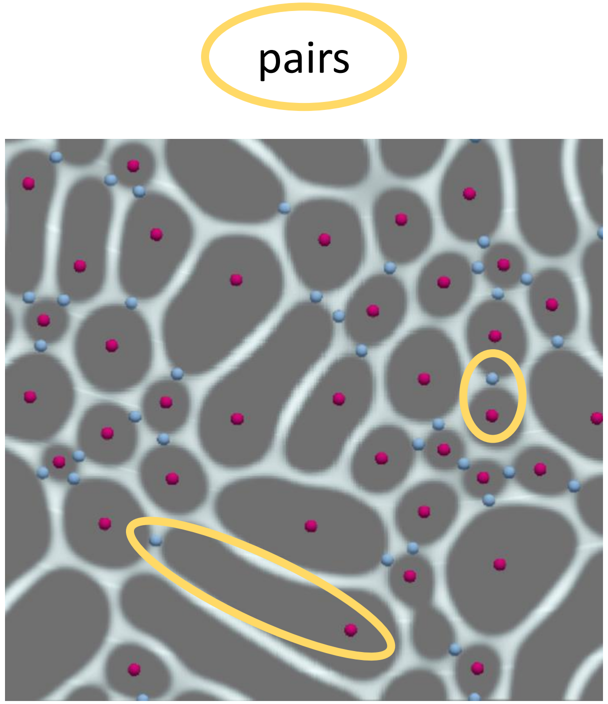


PH1

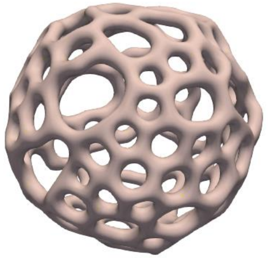
PH1

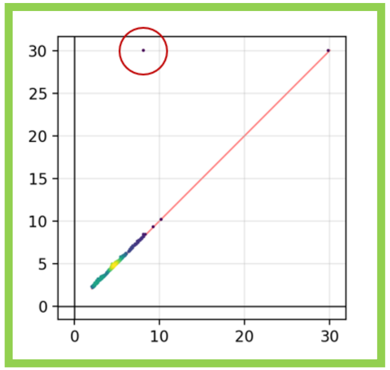
PH1

Increasing loop heterogeneity induces larger spread in PH1 NW.



Creator-destroyer critical points (blue-red).



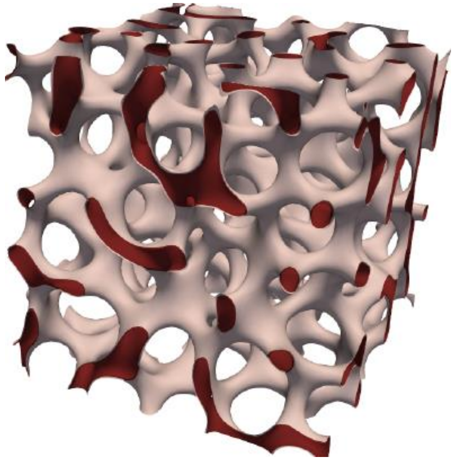


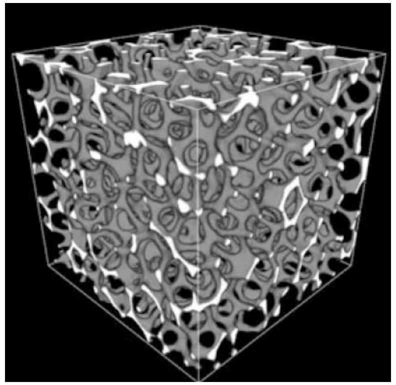
PH2

PH2 NE measures bubble interspaces.

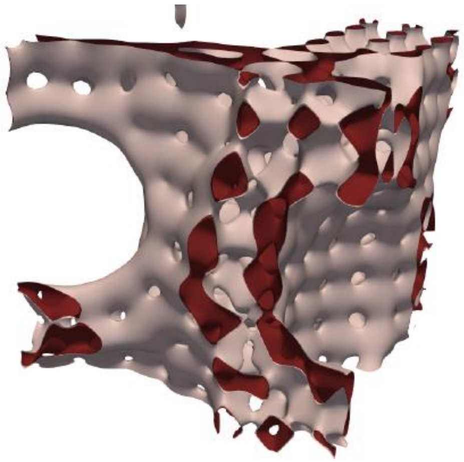
By pairing (creator –destroyer) critical points, SDPH quantifies the **texture of shapes.**

III. Data, imaging, applications

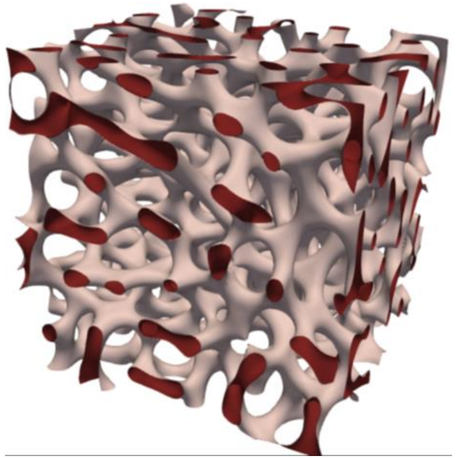




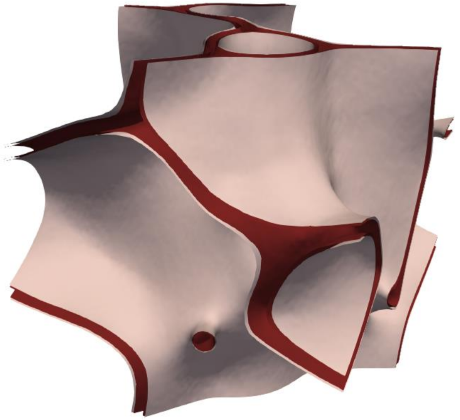
μCT image of open aluminium foam

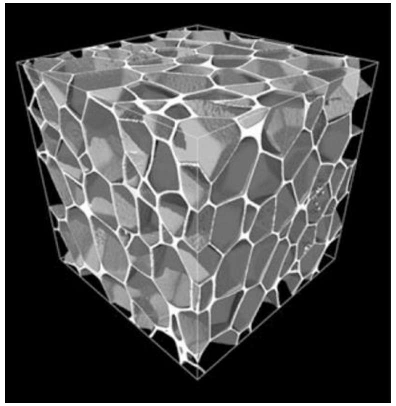


lamina cribrosa behind the eye

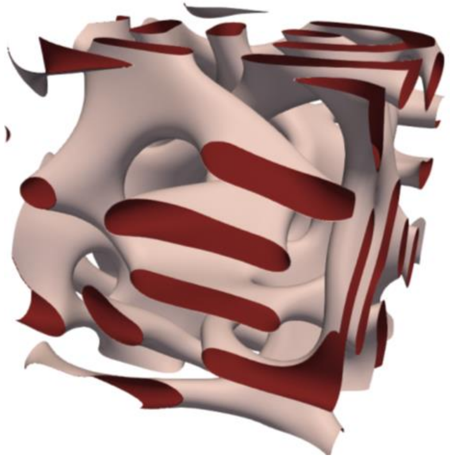


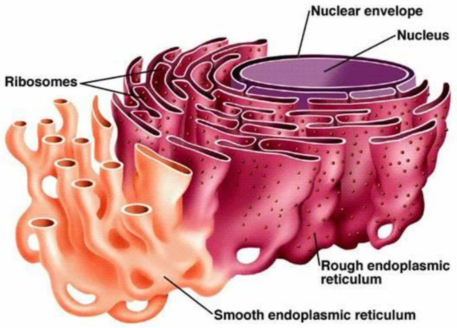
trabecular bone





μCT image of closed polymer foam

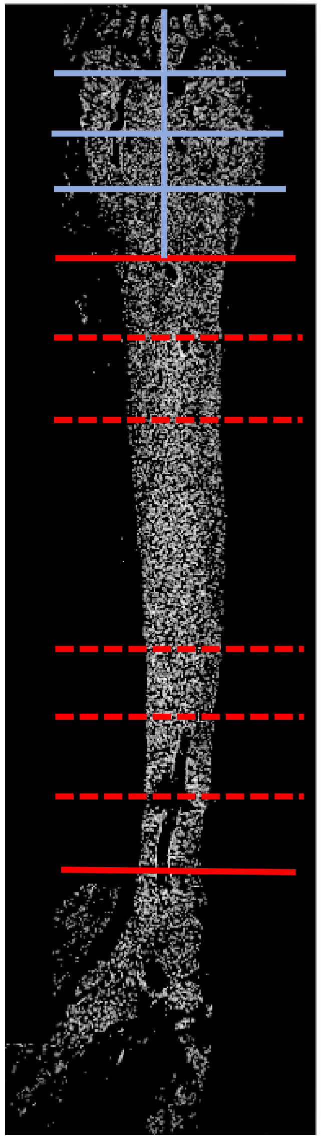


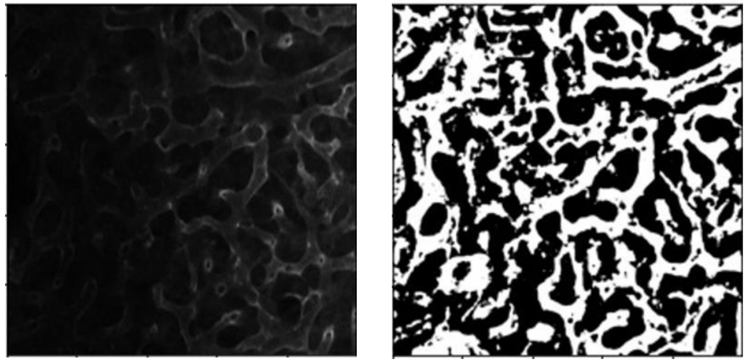


endoplasmic reticulum

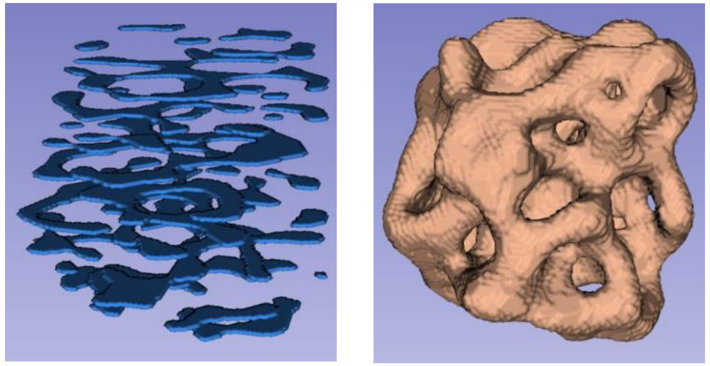
3D data (slices)
300 GB

Application: leukaemia in bone marrow vessels



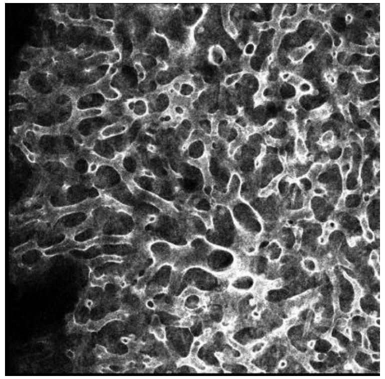


Niblack local thresholding

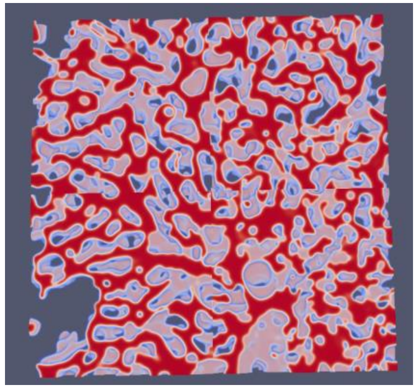


Willmore 3D reconstruction

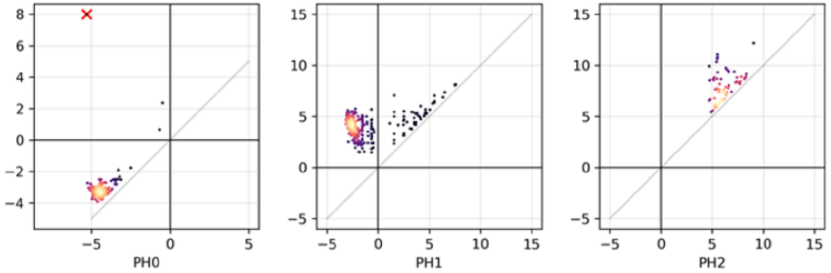
E = Reg + Fid



original data

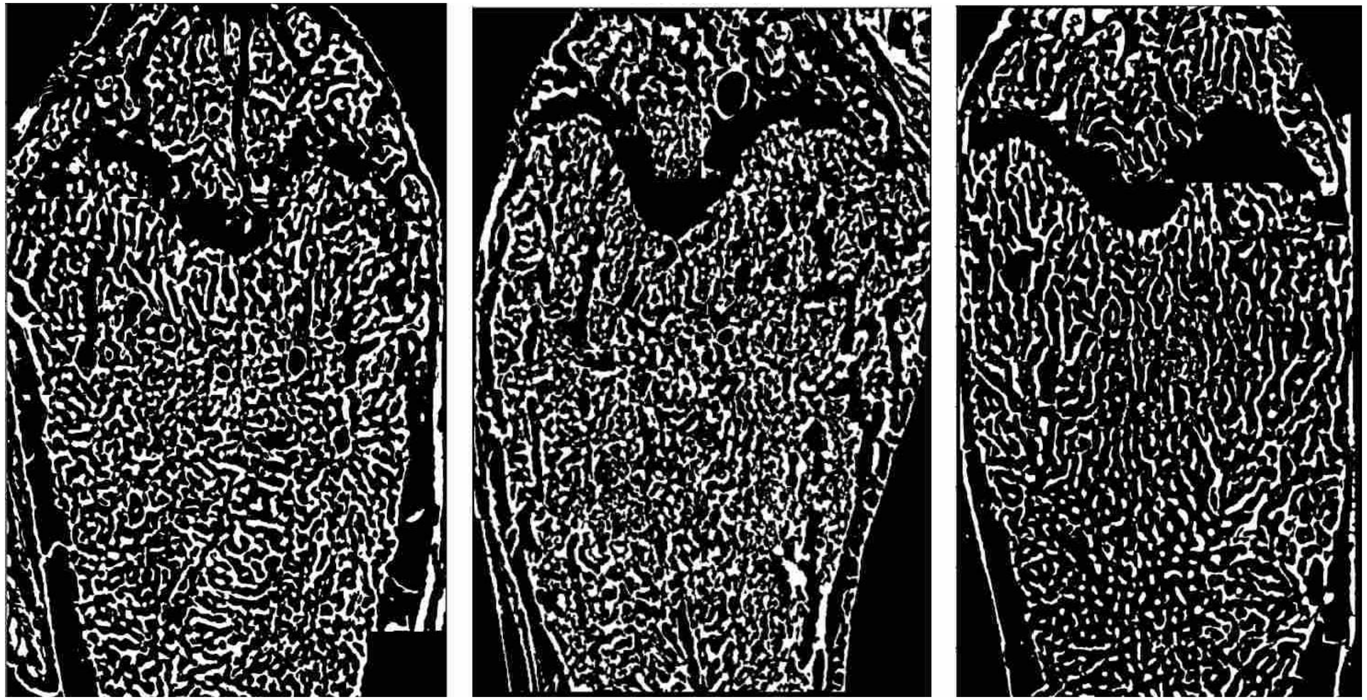


3D segmented data



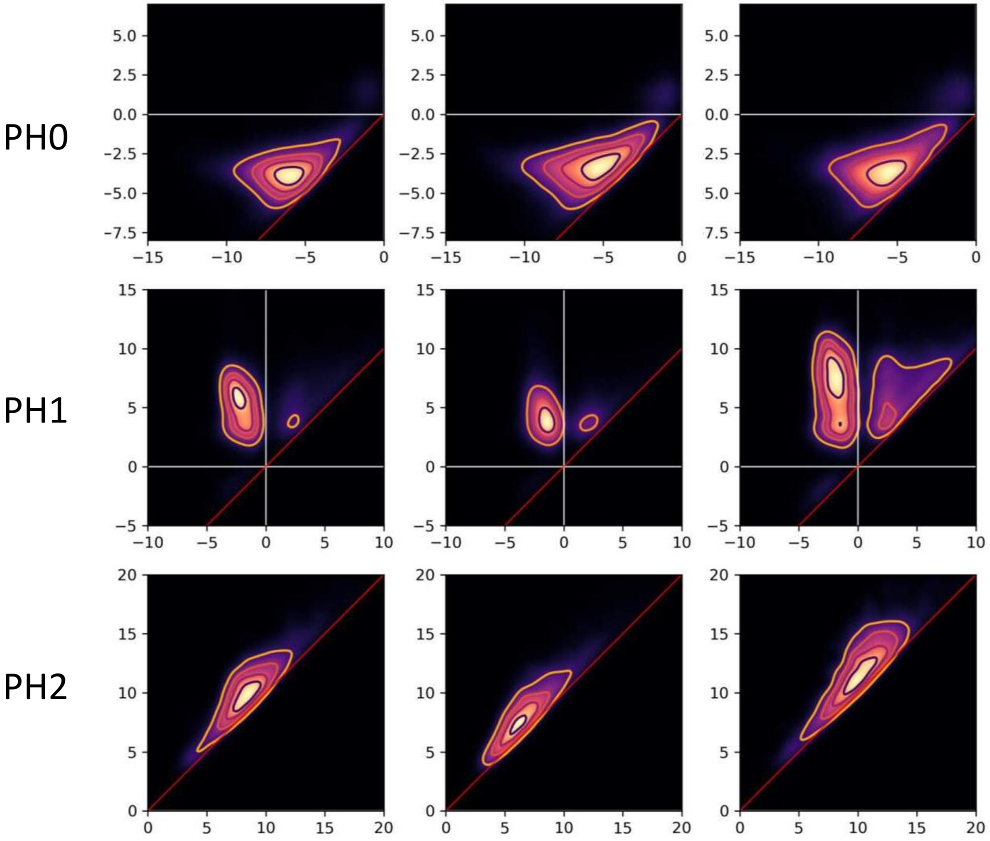
SDPH diagrams

Vessels at three stages



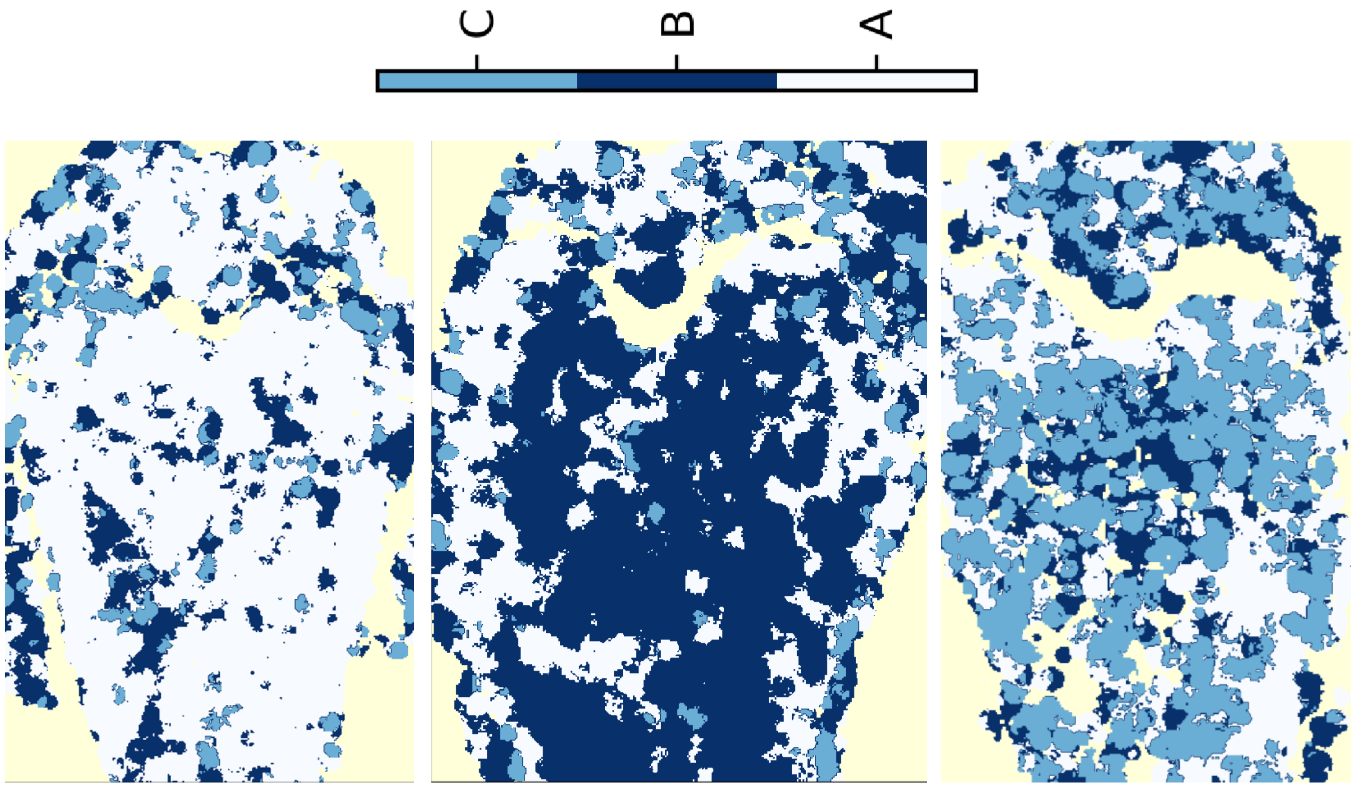
CTRL | Early | Late

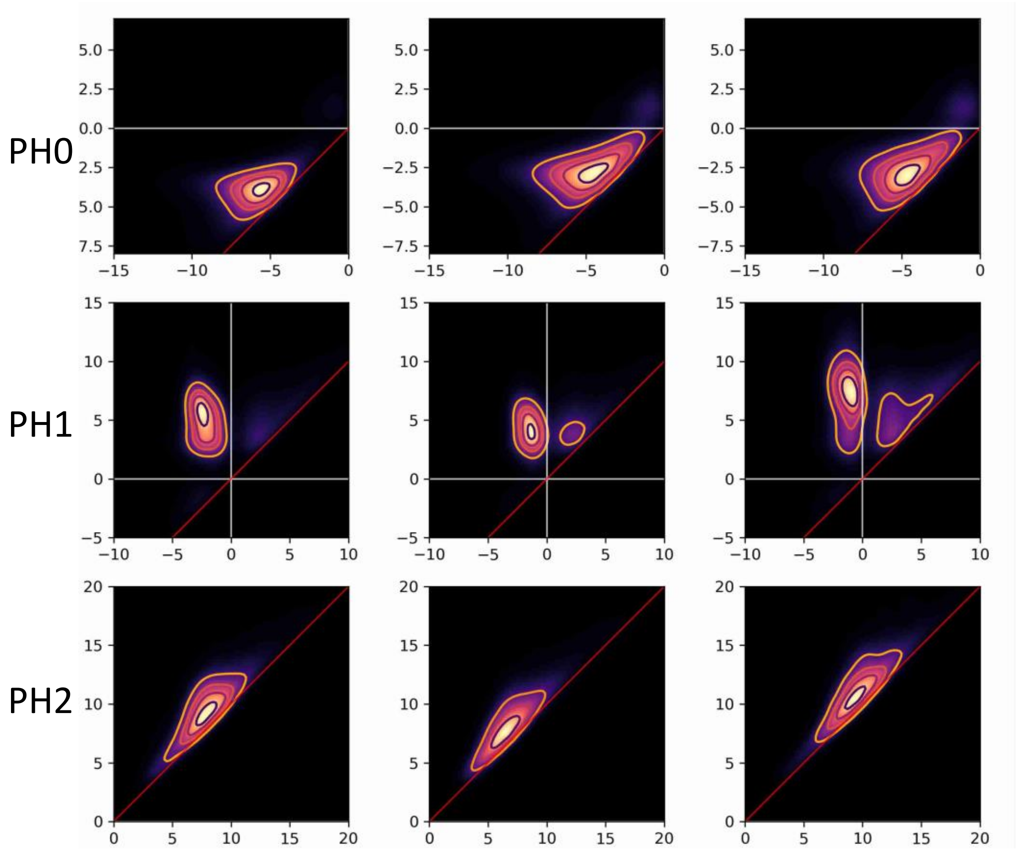
CTRL at 0% | U937 at 10% | P2 at 59%



CTRL at 0% | U937 at 10% | P2 at 59%

Spatial texture decomposition





CTRL — CTRL at 0%

Early — U937 at 10%

Late — P2 at 59%

Texture A

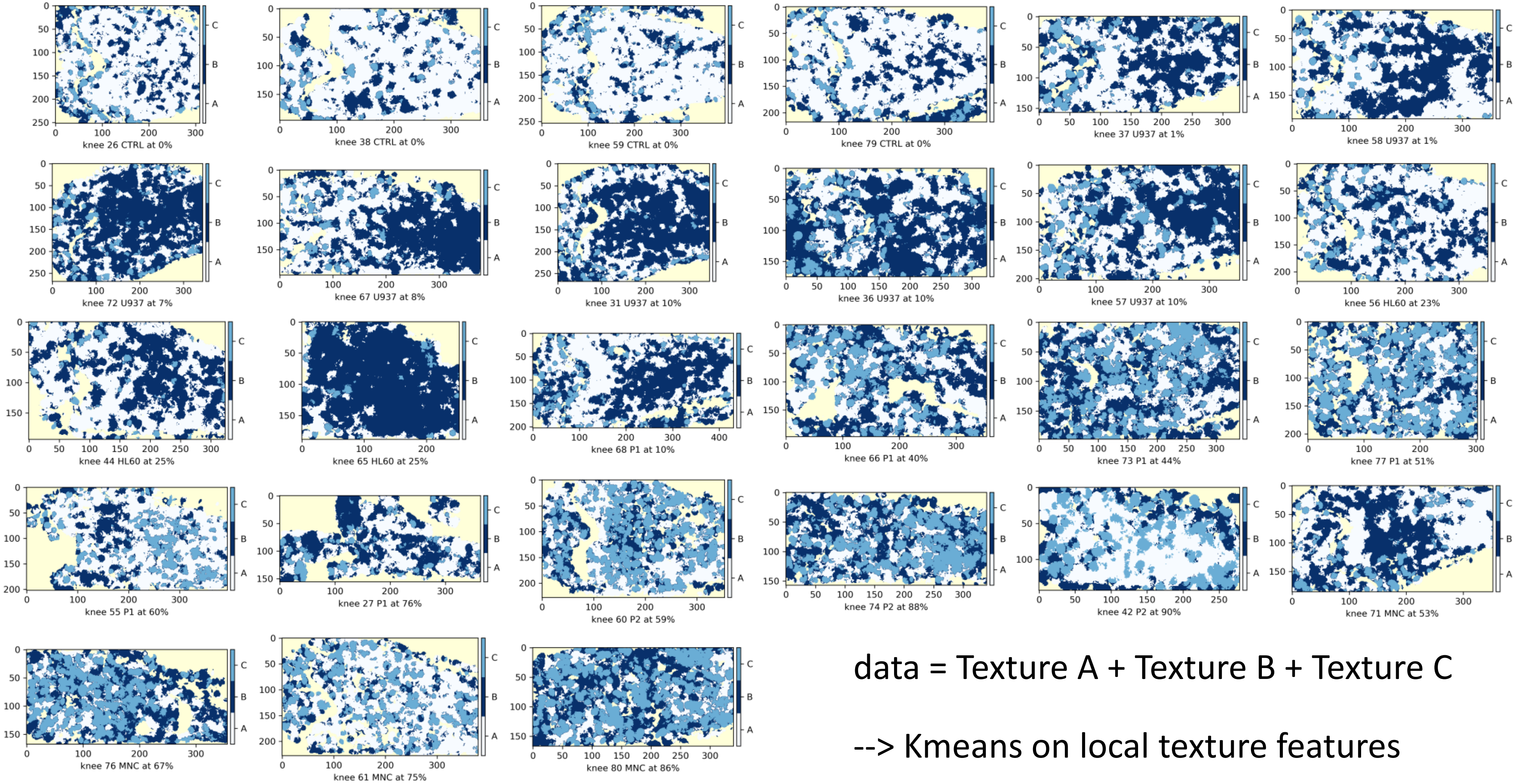
Texture B

Texture C

B v.s. A
- angiogenesis
- thin vessels
- small loops
- dense network

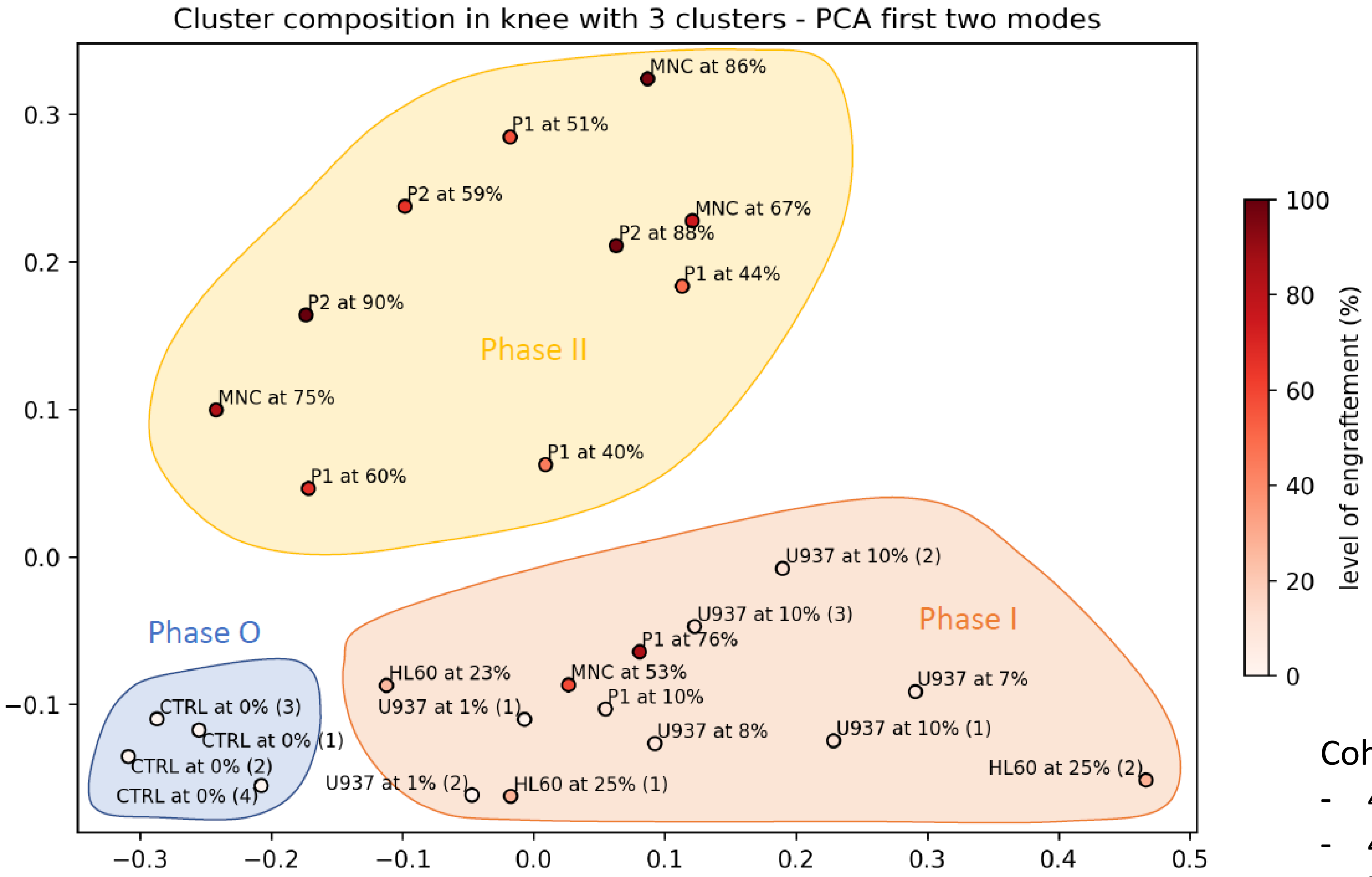
C v.s. A
- thin vessels
- heterogeneous loop sizes
- sparser network

Spatial texture decomposition



data = Texture A + Texture B + Texture C

--> Kmeans on local texture features



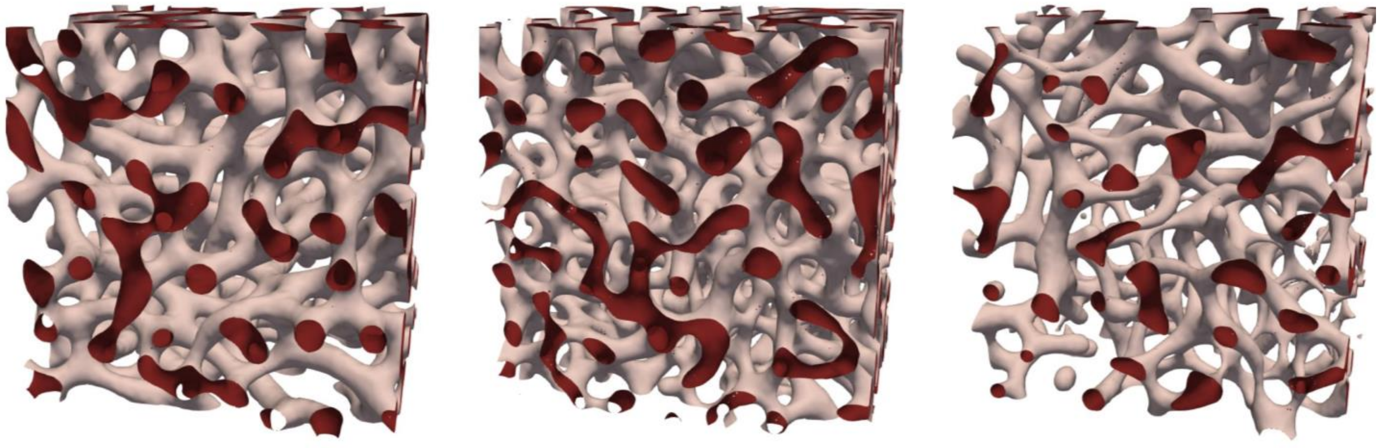
Evolution in three phases : Phases O, I, II

Dominant Textures A, B, C

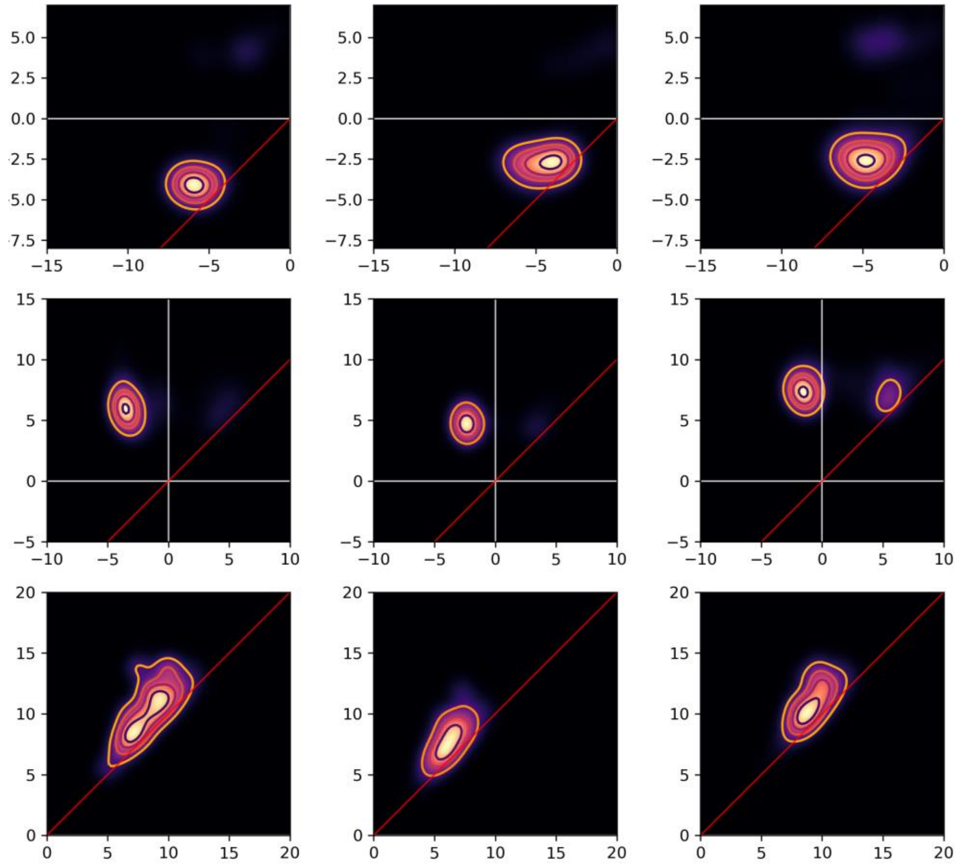
Cohort:

- 4 CTRL (0%)
- 4 MNC (53%-86%)
- 7 U937 (1%-10%)
- 3 HL60 (23%-25%)
- 6 P1 (10%-76%)
- 3 P2 (59%-90%)

Emulating real textures with curvatubes



Emulated A Emulated B Emulated C

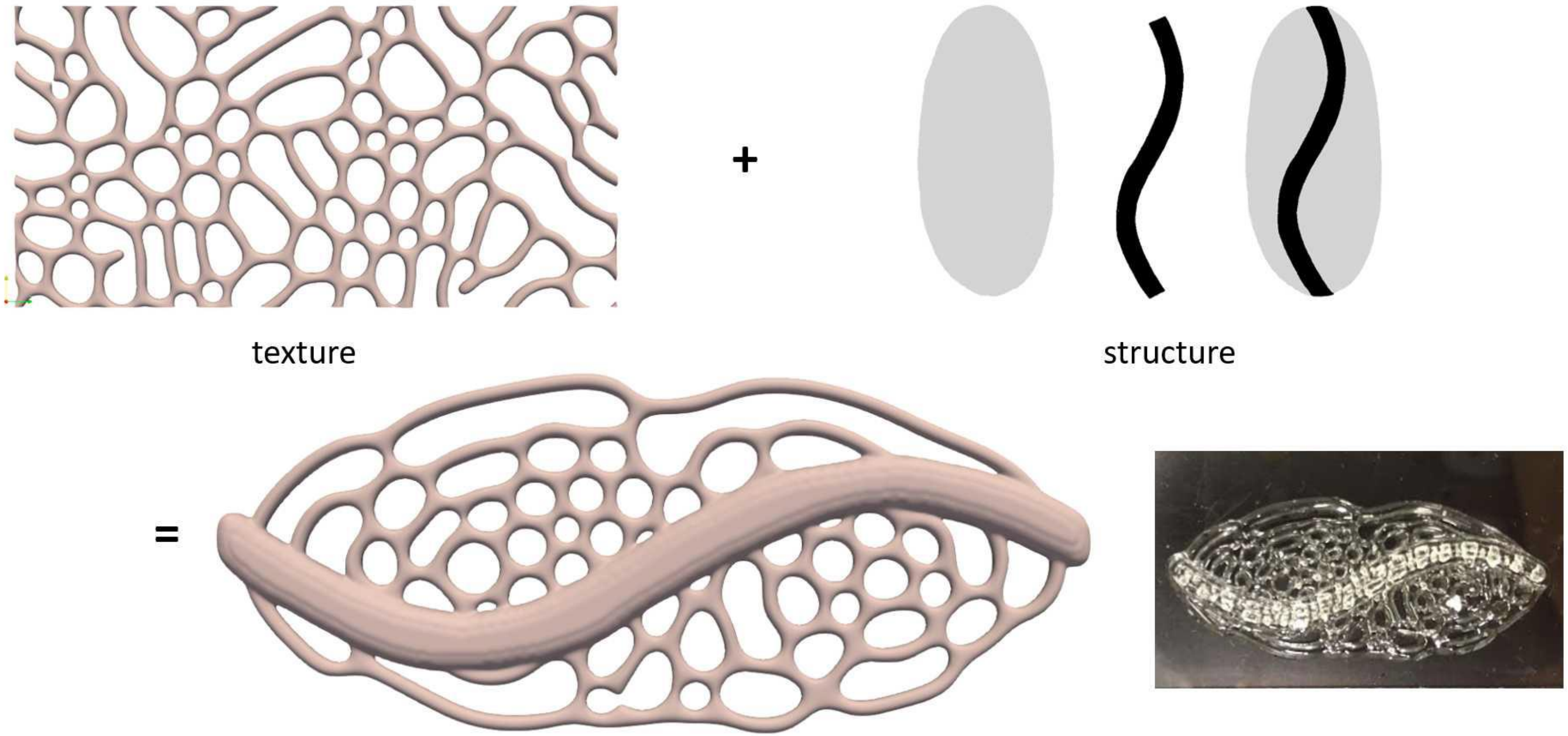


Emulated A Emulated B Emulated C

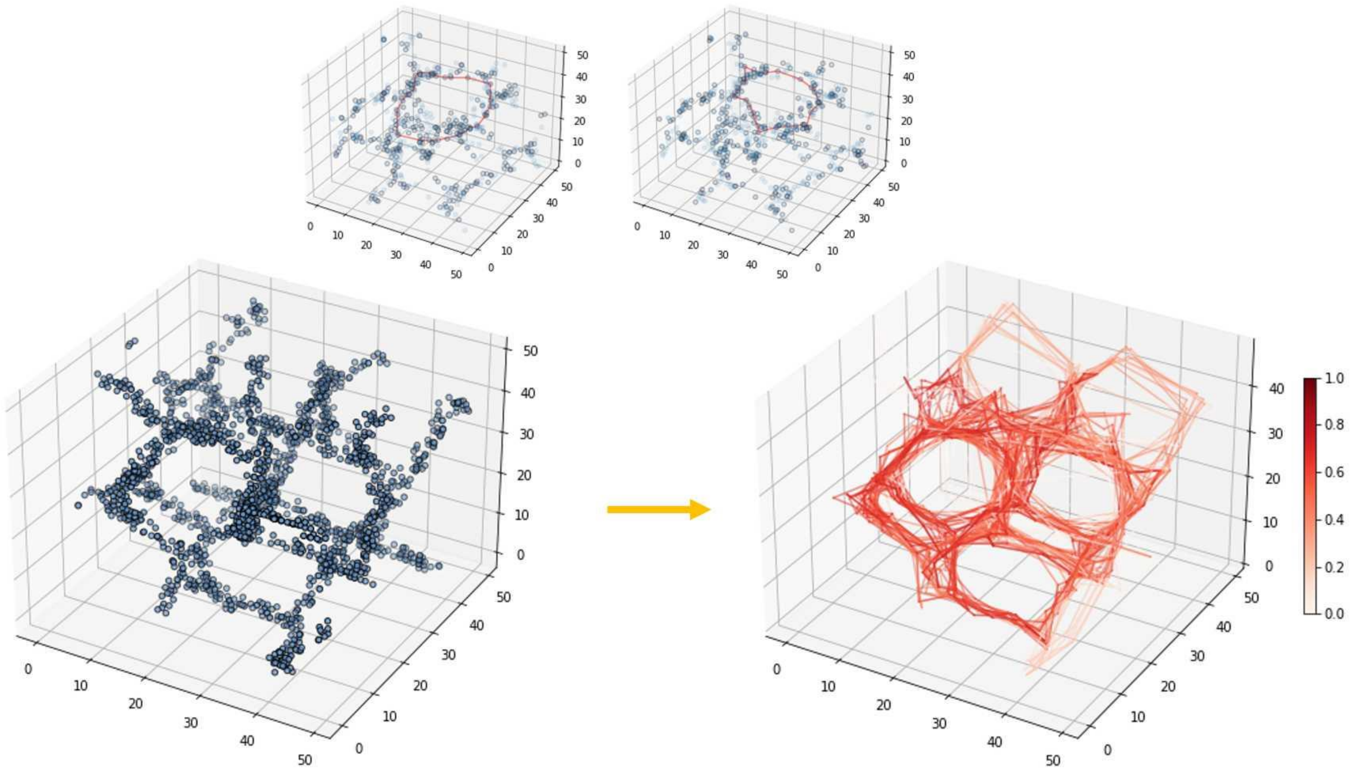
Bayesian Optimization w.r.t. SDPH diagrams

Non-linear impact of AML

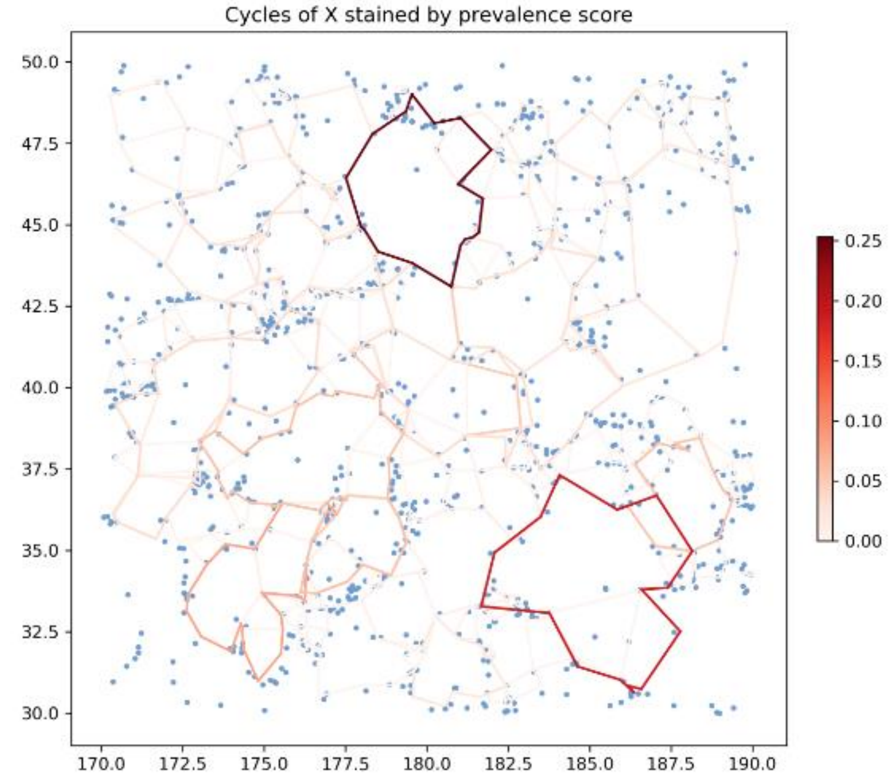
Other project: 3D bioprinting vessels



Other project: Finding “true cycles” in data



network data



cosmic web data

Fast Topological Signal Identification and Persistent Cohomological Cycle Matching, Ines Garcia-Redondo, Anthea Monod, Anna Song (arXiv 2022)

Conclusion:

Maths + AI + Biology = ♥

Thank you!

Questions?