Research Statement

Xiaoling Hu (xihu3@mgh.harvard.edu)
https://huxiaoling.github.io/

My long-term vision is to develop advanced AI systems that can significantly enhance disease diagnosis and treatment, transforming healthcare through technology. Although remarkable strides have been made in data-driven approaches due to the increasing availability of large-scale datasets, the challenge of effectively leveraging the data remains at the forefront. In practice, simply applying brute-force methods to data without considering its structure, topology, or geometric properties can limit the success of models, particularly when faced with the complex, heterogeneous data that is common in biomedical contexts. Another pervasive challenge is that the data itself is often far from ideal, especially in healthcare settings. Data may be noisy, incomplete, imbalanced, or otherwise imperfect, which makes it difficult to rely on conventional models that are designed to work optimally with clean, well-labeled, and extensive training datasets. The over-reliance on pristine training sets has emerged as a major bottleneck in the development of AI systems that perform well in real-world applications, where such ideal datasets are rare.

To overcome these challenges, my current research interest lies in the intersection of *machine learning* (**ML**), *computer vision* (**CV**), *medical image computing* (**MIC**), and *topological data analysis* (**TDA**), and is focused on **developing innovative algorithms that are both theoretically sound and empirically effective in diverse and imperfect data contexts, with a particular emphasis on biomedical applications**. Specifically, my work revolves around the following core themes:

1. **Topology-Driven Deep Image Analysis**
2. **Trustworthy Machine Learning**
3. **Multimodal AI and Generative AI (GenAI)**
4. **Healthcare Applications**

Each of these themes addresses critical gaps in current AI research, especially when applied to complex, imperfect data in the healthcare domain. In the following sections, I will delve deeper into my recent contributions within these areas, highlighting key achievements and outlining the future directions of my work. I believe that by combining rigorous theoretical insights with practical, application-driven innovation, we can develop AI solutions that are more adaptable, interpretable, and reliable, ultimately making a profound impact on the healthcare industry.

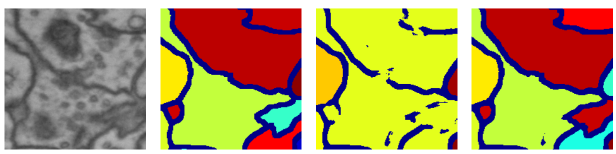
Research Progress

1 Topology-Driven Deep Image Analysis

Despite the strong predictive power of deep learning methods, they are mostly learning pixel-wise representations, thus creating significant barriers in scalable annotation and downstream analysis. The first direction of my research is to explore beyond pixel-wise representations: *How can we learn topological representations to understand the topology, structure, and geometry for image tasks*?

As a pioneer in topology-driven deep image analysis, I have focused on designing novel topology-preserving deep image segmentation algorithms [1, 2, 3, 4, 5, 6, 7, 8, 9]. Also, I have proposed to leverage topological tools to reason structures directly for biomedical imaging tasks [10, 11].

Topology-preserving deep image segmentation. Image segmentation, i.e., assigning labels to all pixels of an input image, is crucial in many computer vision tasks. State-of-the-art segmentation methods learn high-quality feature representations through an end-to-end trained deep network and achieve satisfactory per-pixel accuracy. However, these segmentation algorithms are still prone to errors on fine-scale structures, such as small object instances, instances with multiple connected components, and thin connections. These fine-scale structures may be crucial in analyzing the *functionality* of the objects. TopoLoss [1] is a *pioneer end-to-end deep segmentation network with guaranteed topological correctness*. In particular, based on *persistent homology*, I proposed a *differentiable topological loss* that enforces the segmentation results to have the same topology as the ground truth, i.e.,

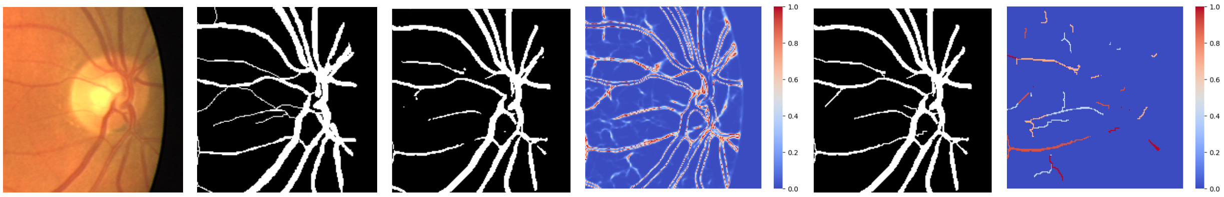


(a) Ori (b) GT (c) Baseline (d) Ours

Figure 1: Illustration of the importance of topological correctness in a neuron image segmentation task. **(a)** an input neuron image. **(b)** ground truth segmentation. **(c)** result of a baseline method without topological guarantee. **(d)** My method.

having the same Betti number (number of connected components and handles). A neural network trained with such a loss will achieve high topological fidelity without sacrificing per-pixel accuracy. I have shown that when the topological loss is decreased to zero, the segmentation is guaranteed to be topologically correct, i.e., have identical topology as the ground truth. These fine-scale structures are crucial in analyzing the functionality of the objects. See Figure 1 as an example.

Deep structural reasoning for biomedical imaging. Beyond topology-preserving deep image segmentation, I have also developed advanced deep learning methods that integrate structural understanding into biomedical image analysis [10, 11]. More specifically, I proposed *novel deep learning-based method that directly learns the topological / structural representation of images* [10, 11]. To move from pixel space to structure space, I applied the classic discrete Morse theory to decompose an image into a Morse complex, consisting of structural elements like branches, patches, etc. These structural elements are hypothetical structures one can infer from the input image. These approaches emphasize leveraging both the spatial and functional relationships inherent in biological structures, such as organs, tissues, and cellular formations, to potentially enhance interpretability and diagnostic accuracy. By embedding topological/structural/geometric priors and reasoning capabilities into deep neural networks, these methods can better capture complex anatomical relationships as well as measure structural level uncertainty (Figure 2). The uncertainty maps provide hints for downstream human-in-the-loop proofreading and improve reasoning efficiency. This structural reasoning not only aids in providing more accurate predictions but also in building robust models that generalize well across diverse patient populations and imaging modalities, paving the way for improved diagnostic tools in medical applications.



(a) Image (b) GT (c) Pro.UNet (d) Pixel Uncer. (e) Ours (f) Stru. Uncer.

Figure 2: Illustration of structural segmentation and structure-level uncertainty. Compared with Probabilistic-UNet (Figure 2(c)-(d)), the proposed method [10] is able to generate structure-preserving segmentation maps (Figure 2(e)), and structure-level uncertainty (Figure 2(f)).

2 Trustworthy Machine Learning: Reliability, Interpretability, and Robustness

Despite the power of deep networks, their overconfidence is a common issue. For example, in autonomous driving and computer-aided diagnosis, analyzing low-confidence samples/regions can help identify subpopulations of events or patients that deserve extra consideration. *A good model should know both what it knows and what it does not know*, thus reliability and interoperability are essential in the deployment of the models. On the other hand, training powerful deep neural networks usually requires a large amount of data. While *the obtained data are usually not ideal, especially in healthcare scenarios*. How to train robust models under imperfect data scenarios (e.g., missing modalities) is of great value and remains challenging in practice.

I have developed novel algorithms for uncertainty estimation applied to both curvilinear structure data [10, 11] and unlabeled data [12, 13], enhancing model interpretability and demonstrating their reliability. Additionally, I have created robust algorithms to address practical challenges under imperfect data conditions, including crowd counting [13], lesion segmentation [14], and brain tumor segmentation [15].

Learning with reliability and interpretability. In fields such as healthcare, finance, and autonomous systems, the ability to understand and trust the predictions made by algorithms is paramount. Reliable models are those that consistently yield accurate results across diverse datasets and conditions, reducing the risk of unexpected failures. Simultaneously, interpretability allows stakeholders ranging from clinicians to data scientists to grasp how specific features influence outcomes, fostering confidence in the model's applications. Learning with reliability and interpretability is essential in developing models that not only perform well but also provide transparent insights into their decision-making processes. I have proposed novel algorithms for uncertainty estimation applied to both curvilinear structure data [10, 11] and unlabeled data [12, 13]. By combining these two aspects, we can leverage advanced machine learning techniques while ensuring ethical considerations and regulatory compliance are met, ultimately promoting more responsible and effective use of artificial intelligence in critical decision-making contexts.

Learning with robustness. Robustness ensures that a model remains accurate and reliable even when faced with noisy inputs, adversarial attacks, or shifts in data distribution. By incorporating techniques such as data augmentation, regularization, and ensemble methods, developers can create systems that generalize well across different scenarios, minimizing overfitting to specific datasets. Learning with robustness is a vital aspect of developing machine learning models that can withstand variations and uncertainties in real-world data. The focus on robustness is particularly crucial in high-stakes domains such as healthcare, finance, and autonomous driving, where errors can have significant consequences. I have created robust algorithms to address practical challenges under imperfect data conditions, including crowd counting [13], lesion segmentation [14], and brain tumor segmentation [15]. Ultimately, learning with robustness enhances the resilience of models, allowing them to adapt to changing environments while maintaining performance and trustworthiness.

3 Empowering Clinical and Biomedical Applications

As mentioned above, *my long-term vision is to develop advanced AI systems that can significantly enhance disease diagnosis and treatment, transforming healthcare through technology*. Besides developing novel algorithms with firm theoretical foundations, I have also collaborated with radiologists and ophthalmologists and applied the developed algorithms to challenging practical problems.

I have utilized machine learning tools for brain image analysis [16, 17, 18, 19, 20, 21]. Also, I have developed algorithms for segmentations of Electron microscopy (EM), vessel, tumor, and lesions [1, 14, 15] as well as pathology image analysis [22, 23, 24].

Brain image analysis. Brain image analysis involves the application of advanced imaging techniques and computational methods to study the structure and function of the brain. Utilizing modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET), researchers can obtain detailed visual representations of brain anatomy and activity. The analysis typically encompasses various tasks, including segmentation, registration, and classification, which aid in identifying abnormalities such as tumors, lesions, or neurodegenerative diseases. With the integration of machine learning and artificial intelligence, brain image analysis has significantly advanced, enabling more accurate diagnostics and personalized treatment strategies. Specifically, I have used topological tools for lesion counting [16], estimated uncertainty for image registration [17, 19], designed generative AI (GenAI) and scalable methods for brain image segmentation [20, 21], and developed multimodal models for brain imaging [18]. This interdisciplinary field not only enhances our understanding of brain disorders but also contributes to ongoing efforts in neuroscience research and clinical practice.

General biomedical applications. General biomedical applications encompass a wide range of technologies and methodologies aiming at improving health outcomes, diagnostics, and treatment strategies. This field integrates principles from biology, medicine, engineering, and data science to address complex challenges in healthcare. Key applications include the development of medical imaging techniques for enhanced visualization of biological structures, the use of bioinformatics for analyzing genomic data to identify disease markers, and the implementation of wearable devices that monitor patient health in real time. Additionally, advancements in telemedicine facilitate remote consultations, making healthcare more accessible. I have worked on EM, vessel, tumor, and lesion segmentations [1, 14, 15] as well as pathology image analysis [22, 23, 24]. Also, I have developed multimodal [15, 25] and GenAI methods [24, 26] to solve biomedical problems.

As interdisciplinary research continues to flourish, general biomedical applications hold great promise for personalized medicine, drug discovery, and public health initiatives, ultimately contributing to more effective and efficient healthcare delivery systems.

Ongoing and Future Work

In summary, my research lies in the intersection of *machine learning* (**ML**), *computer vision* (**CV**), *medical image computing* (**MIC**), and *topological data analysis* (**TDA**). I primarily focus on developing algorithms that investigate the properties of complex data and learn from imperfect datasets. Beyond these themes, I am keenly interested in addressing a wide range of challenges within the broader context of medical AI. Specifically, I aim to extend my research from the **Data, Model, Application** perspectives respectively in the future:

- ***Data: exploring underlying features of data***. How can we efficiently utilize data while considering its structural properties? By investigating structural, topological, and geometric priors, we may be able to guide the effective training of deep neural networks. However, until recently, research has predominantly focused on purely data-driven methods. Incorporating structural, geometric, and topological information into deep neural networks is especially crucial for biomedical data. I have begun to make progress in this direction [1, 2, 3, 4, 6, 7, 8, 9, 10, 11]. And how do accurate structures influence downstream analyses, such as quantification? Based on my current work, I am poised to take the next step: quantifying how topology- and geometry-aware segmentation results impact downstream analyses. By extracting topology- and geometry-informed features, we can conduct various interesting analyses, such as diagnosing retinal diseases and predicting the risk of aortic aneurysm rupture. Figure 3 illustrates a pipeline for this downstream analysis. This is an ongoing direction that I will continue to explore further.

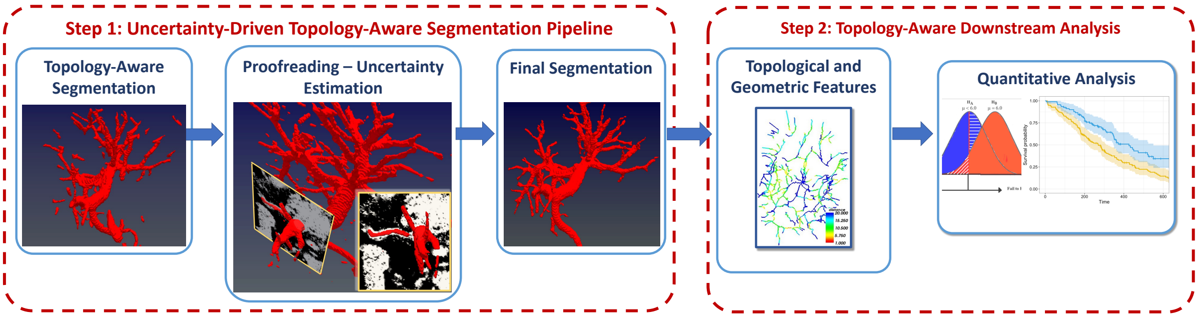


Figure 3: Workflow for uncertainty-driven topology-aware segmentation, and the downstream topology/geometry aware analysis.

- ***Models: trustworthy models with reliability, interpretability, and robustness***. How confident is the model in its predictions? While many existing algorithms claim to achieve high performance, it is crucial to assess their reliability, especially in biomedical contexts. *A model should understand both what it knows and what it does not know*. My recent work on structure-wise uncertainty estimation for curvilinear structure data [10, 11] and confidence estimation using unlabeled data [12] takes a step in this direction. A pertinent research question arises from this work: *How can we utilize uncertainty estimation in unsupervised contexts*? I have applied the uncertainty estimation approach to crowd counting tasks and achieved promising results [13]. I believe that the proposed reliable uncertainty estimation method can benefit even more unsupervised scenarios.

  Another question is how we can develop algorithms and models that maintain robust performance even when faced with imperfect data. The effectiveness of current data-driven methods heavily relies on large amounts of labeled training data. However, in practical biomedical contexts, gathering labeled data can be cost-prohibitive and time-consuming, often requiring specialized domain knowledge. This reliance on diverse, high-quality training datasets significantly limits model applicability in complex scenarios characterized by imperfect data, such as *missing modalities or limited human labeling*. Furthermore, the uncertainty estimation I have been working on may provide insights for handling imperfect data. For instance, *can we focus on the most uncertain samples or regions to enhance training in these challenging conditions*? I have recently begun to explore this intriguing direction [12, 13, 14, 15].

- ***Applications: empowering clinical and biomedical scenarios***. Applications in clinical and biomedical scenarios play a crucial role in transforming healthcare through innovative technologies and methodologies. By harnessing data-driven approaches, such as artificial intelligence, machine learning, and advanced imaging techniques, healthcare professionals can enhance diagnostic accuracy, personalize treatment plans, and improve patient outcomes. These applications empower clinicians to analyze complex medical data, identify patterns, and make informed decisions in real time, thereby streamlining workflows and optimizing resource allocation. Additionally, they facilitate early detection of diseases, enabling timely interventions that can significantly alter the course of patient care. My recent works span from radiology [1, 14, 15] to pathology applications [22, 23, 24]. More recently, I have leveraged machine learning tools to deal with brain image analysis [16, 17, 18, 19]. As these technologies continue to evolve, they hold the promise of revolutionizing the way medical professionals approach diagnostics, treatment, and patient management, ultimately leading to more efficient and effective healthcare delivery.

Over the next few years, I will continue to develop intelligent AI systems that assist in diagnosis and disease treatment. I am eager to pose meaningful and impactful research questions and to create innovative and effective solutions from both theoretical and empirical perspectives. I also enjoy collaborating with experts in medical imaging, computer vision, machine learning, and related fields, including computational geometry, radiology, ophthalmology, and digital pathology. Working together, we can tackle these challenges and advance the frontiers of healthcare technology.

References

[1] **Xiaoling Hu**, F. Li, D. Samaras, and C. Chen, “Topology-Preserving Deep Image Segmentation,” in *NeurIPS*, 2019.

[2] **Xiaoling Hu**, Y. Wang, F. Li, D. Samaras, and C. Chen, “Topology-Aware Segmentation Using Discrete Morse Theory,” in *ICLR*, 2021.

[3] **Xiaoling Hu**, “Structure-Aware Image Segmentation with Homotopy Warping,” in *NeurIPS*, 2022.

[4] **Xiaoling Hu**, X. Chen, Y. Liu, E. Z. Chen, T. Chen, and S. Sun, “Deep Statistic Shape Model for Myocardium Segmentation,” *arXiv preprint arXiv:2207.10607*, 2022.

[5] M. Xu, **Xiaoling Hu**, S. Gupta, S. Abousamra, and C. Chen, “Semi-supervised Segmentation of Histopathology Images with Noise-Aware Topological Consistency,” in *ECCV*, 2024.

[6] J. Yang*, **Xiaoling Hu***, C. Chen, and C. Tsai, “3D Topology-Preserving Segmentation with Compound Multi-Slice Representation,” in *ISBI*, 2021.

[7] J. Yang*, **Xiaoling Hu***, C. Chen, and C. Tsai, “A Topological-Attention ConvLSTM Network and Its Application to EM Images,” in *MICCAI*, 2021.

[8] S. Gupta*, **Xiaoling Hu***, J. Kaan, M. Jin, M. Mpoy, K. Chung, G. Singh, M. Saltz, T. Kurc, J. Saltz, *et al.*, “Learning Topological Interactions for Multi-Class Medical Image Segmentation,” in *ECCV*, 2022.

[9] **Xiaoling Hu**, X. Lin, M. Cogswell, Y. Yao, S. Jha, and C. Chen, “Trigger Hunting with a Topological Prior for Trojan Detection,” in *ICLR*, 2022.

[10] **Xiaoling Hu**, D. Samaras, and C. Chen, “Learning Probabilistic Topological Representation Using Discrete Morse Theory,” in *ICLR*, 2023.

[11] S. Gupta, Y. Zhang, **Xiaoling Hu**, P. Prasanna, and C. Chen, “Topology-Aware Uncertainty for Image Segmentation,” in *NeurIPS*, 2023.

[12] C. Li, **Xiaoling Hu**, and C. Chen, “Confidence Estimation Using Unlabeled Data,” in *ICLR*, 2023.

[13] C. Li, **Xiaoling Hu**, S. Abousamra, and C. Chen, “Calibrating Uncertainty for Semi-Supervised Crowd Counting,” in *ICCV*, 2023.

[14] J. Yang, N. Mehta, G. Demirci, **Xiaoling Hu**, M. S. Ramakrishnan, M. Naguib, C. Chen, and C.-L. Tsai, “Anomaly-guided weakly supervised lesion segmentation on retinal OCT images,” *MedIA*, 2024.

[15] A. Konwer, **Xiaoling Hu**, J. Bae, X. Xu, C. Chen, and P. Prasanna, “Enhancing Modality-Agnostic Representations via Meta-Learning for Brain Tumor Segmentation,” in *ICCV*, 2023.

[16] **Xiaoling Hu**, A. Sorby-Adams, F. Barkhof, W. Taylor Kimberly, O. Puonti, and J. E. Iglesias, “*P-Count*: Persistence-Based Counting of White Matter Hyperintensities in Brain MRI,” in *MICCAI-TGI3*, 2024.

[17] K. Gopinath*, **Xiaoling Hu***, M. Hoffmann, O. Puonti, and J. E. Iglesias, “Registration by Regression (RbR): a framework for interpretable and flexible atlas registration,” in *MICCAI-WBIR*, 2024.

[18] P. Liu, O. Puonti, **Xiaoling Hu**, D. C. Alexander, and J. E. Iglesias, “Brain-ID: Learning Contrast-agnostic Anatomical Representations for Brain Imaging,” in *ECCV*, 2024.

[19] **Xiaoling Hu**, K. Gopinath, P. Liu, M. Hoffmann, K. Van Leemput, O. Puonti, and J. E. Iglesias, “Hierarchical Uncertainty Estimation for Learning-based Registration in Neuroimaging,” in *ICLR*, 2025.

[20] **Xiaoling Hu**, O. Puonti, J. E. Iglesias, B. Fischl, and Y. Balbastre, “Learn2Synth: Learning Optimal Data Synthesis Using Hypergradients,” in *ICCV*, 2025.

[21] **Xiaoling Hu**, P. Liu, D. Zemlyanker, J. W. Ramirez, O. Puonti, and J. E. Iglesias, “Scalable Segmentation for Ultra-High-Resolution Brain MR Images,” *arXiv preprint arXiv:2505.21697*, 2025.

[22] M. Hasan, **Xiaoling Hu**, S. Abousamra, P. Prasanna, J. Saltz, and C. Chen, “Semi-Supervised Contrastive VAE for Disentanglement of Digital Pathology Images,” in *MICCAI*, 2024.

[23] W. Huang, **Xiaoling Hu**, S. Abousamra, P. Prasanna, and C. Chen, “Hard Negative Sample Mining for Whole Slide Image Classification,” in *MICCAI*, 2024.

[24] C. Li, **Xiaoling Hu**, S. Abousamra, M. Xu, and C. Chen, “Spatial Diffusion for Cell Layout Generation,” in *MICCAI*, 2024.

[25] W. Huang, M. Xu, **Xiaoling Hu**, S. Abousamra, A. Ganguly, S. Kapse, A. Yurovsky, P. Prasanna, T. Kurc, J. Saltz, *et al.*, “RankByGene: Gene-Guided Histopathology Representation Learning Through Cross-Modal Ranking Consistency,” *arXiv preprint arXiv:2411.15076*, 2024.

[26] M. Xu, S. Gupta, **Xiaoling Hu**, C. Li, S. Abousamra, D. Samaras, P. Prasanna, and C. Chen, “TopoCellGen: Generating Histopathology Cell Topology with a Diffusion Model,” in *CVPR*, 2025.