



Unsupervised Discovery of 3D Hierarchical Structure with Generative Diffusion Features

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Abstract. Inspired by findings that generative diffusion models learn semantically meaningful representations, we use them to discover the intrinsic hierarchical structure in biomedical 3D images using *unsupervised* segmentation. We show that features of diffusion models from different stages of a U-Net-based ladder-like architecture capture different hierarchy levels in 3D biomedical images. We design three losses to train a predictive unsupervised segmentation network that encourages the decomposition of 3D volumes into meaningful nested subvolumes that represent a hierarchy. First, we pretrain 3D diffusion models and use the consistency of their features across subvolumes. Second, we use the visual consistency between subvolumes. Third, we use the invariance to photometric augmentations as a regularizer. Our models perform better than prior unsupervised structure discovery approaches on challenging biologically-inspired synthetic datasets and on a real-world brain tumor MRI dataset. Code is available at github.com/uncbiag/diffusion-3D-discovery.

1 Introduction

Deep neural networks (DNNs) have been successfully applied to various supervised 3D biomedical image analysis tasks, such as classification [11], segmentation [7], and registration [35]. Acquiring volumetric annotations manually to supervise deep learning models is costly and labor intensive. For example, the supervised training of 3D DNNs for segmentation requires the manual labeling of every voxel of the structures of interest for the entire training set. Additionally, the diversity of existing biomedical 3D volumetric image types (e.g. MRI, CT, electron tomography) and different tasks associated with them precludes image annotations for all existing problems in practice. Furthermore, experts may focus on annotating objects they are already aware of, thereby restricting the possibility of new structural discoveries in large datasets using deep learning. We hypothesize that the nested hierarchical structure intrinsic to many 3D biomedical images [13] might be useful for unsupervised segmentation. As a step in this direction, our goal in this work is to develop a computational approach for unsupervised structure discovery.

Recently, unsupervised part discovery in 2D natural images has gained significant attention [6, 8, 15]. These methods are based on the finding that intermediate

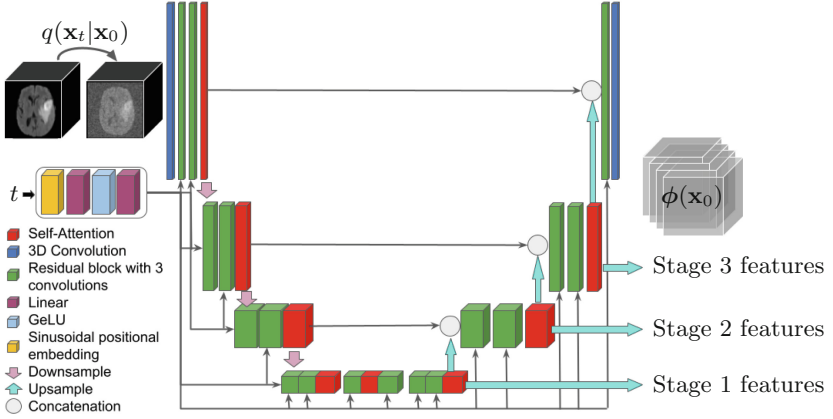


Fig. 1. Feature extractor. Given a clean 3D image \mathbf{x}_0 , we add Gaussian noise corresponding to diffusion timestep t to the image following the distribution $q(x_t|x_0)$ using Eq. (2). The noisy image \mathbf{x}_t is passed to our pretrained 3D diffusion model. We upsample intermediate activations to the original image size and use them as feature extractor ϕ for each voxel. Features from different stages of a U-Net-based ladder-like architecture for a diffusion model capture different hierarchy levels.

activations of deep ImageNet-pre-trained classification models capture semantically meaningful conceptual regions [8]. These regions are robust to pose and viewpoint variations and help high-level image understanding by providing local object representations, leading to more explainable recognition [15]. However, a naive application of part discovery methods to 3D volumetric segmentation is not feasible, due to the lack of good feature extractors for 3D biomedical images [5] and ImageNet-pretrained networks operate only on 2D images.

We hypothesize that deep generative models are good feature extractors for unsupervised structure discovery for the following reasons. First, these models do not require expert labels as they are trained in a self-supervised way. Second, the ability to generate high-quality images suggests that these models capture semantically meaningful information. Third, generative representation learning has been successfully applied to global and dense prediction tasks in 2D images [9] and has shown improvements in label efficiency and generalization [19].

Besides creating stunning image generation results, diffusion-based generative models [12] are applied to other downstream tasks. Several works use pre-trained diffusion models for 2D label-efficient semantic segmentation of natural images [1, 4]. In 2D medical imaging, diffusion models are used for self-supervised vessel segmentation [18], anomaly detection [27, 29, 31, 34], denoising [14], and improving supervised segmentation models [32, 33]. In 3D medical imaging, diffusion models are used for CT and MR image synthesis [10, 33]. Inspired by the success of unsupervised part discovery methods in 2D images and the effective abilities of diffusion models for many downstream tasks we hypothesize that feature representations of generative diffusion models discover intrinsic hierarchical structures in 3D biomedical images. Our work explores this hypothesis.

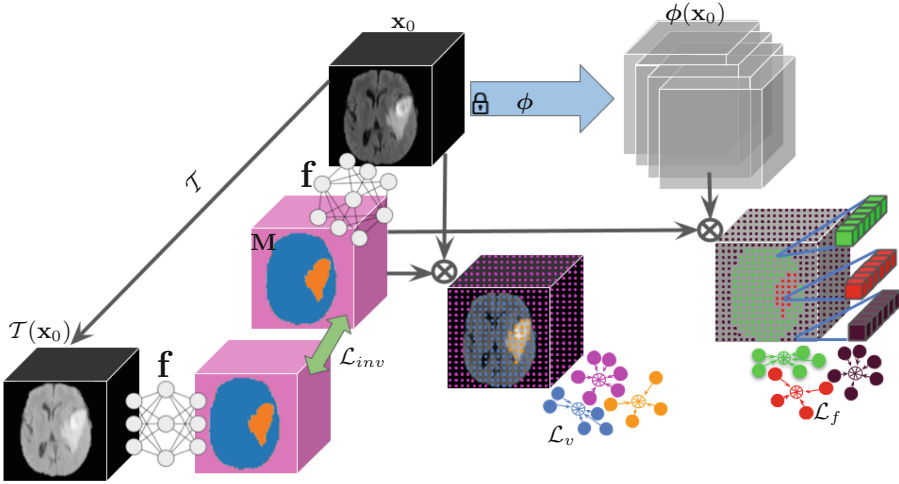


Fig. 2. Predictive unsupervised structure discovery. Our unsupervised segmentation network $\mathbf{f} : \mathbf{x}_0 \rightarrow \mathbf{M}$ is trained with three losses. Feature consistency loss \mathcal{L}_f encourages features $\phi(\mathbf{x}_0)$, extracted using diffusion models (see Fig. 1), of voxels belonging to the same parts to be similar to each other. Visual consistency loss \mathcal{L}_v encourages models to learn parts that align with image boundaries. Photometric invariance loss \mathcal{L}_{inv} encourages invariance in models to photometric transformation \mathcal{T} .

Our Contributions Are:

- 1) We pretrain 3D diffusion models, use them as feature extractors (Fig. 1), and design losses (Fig. 2) for unsupervised 3D structure discovery.
- 2) We show that features from different stages of ladder-like U-Net-based diffusion models capture different hierarchy levels in 3D biomedical volumes.
- 3) Our approach outperforms previous 3D unsupervised discovery methods on challenging synthetic datasets and on a real-world brain tumor segmentation (BraTS’19) dataset.

2 Background on Diffusion Models

Diffusion models [12] consist of two parts: a forward pass and a reverse pass. The forward pass is a T -step process of adding a small Gaussian noise, gradually destroying image information and transforming a clean image \mathbf{x}_0 into pure Gaussian noise \mathbf{x}_T . Each step $t \in \llbracket 1, T \rrbracket$ is:

$$q(\mathbf{x}_t | \mathbf{x}_{t-1}) := \mathcal{N}(\mathbf{x}_t; \sqrt{1 - \beta_t} \mathbf{x}_{t-1}, \sqrt{\beta_t} \mathbf{I}), \quad (1)$$

where $\{\beta_t\}_{t=1}^T$ is a variance schedule. With $\bar{\alpha}_t = \prod_{i=1}^t (1 - \beta_i)$, the noisy image \mathbf{x}_t at a timestep t , following $q(\mathbf{x}_t | \mathbf{x}_0) = \prod_{i=1}^t q(\mathbf{x}_i | \mathbf{x}_{i-1})$, can be written as:

$$\mathbf{x}_t = \sqrt{\bar{\alpha}_t} \mathbf{x}_0 + \sqrt{1 - \bar{\alpha}_t} \boldsymbol{\epsilon}, \quad \boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \mathbf{I}). \quad (2)$$

The reverse pass is a corresponding T -step denoising process using a neural network (usually, U-Net [28]) with parameters θ . For small noises, the reverse pass is also Gaussian:

$$p_{\theta}(\mathbf{x}_{t-1}|\mathbf{x}_t) := \mathcal{N}(\mathbf{x}_{t-1}; \boldsymbol{\mu}_{\theta}(\mathbf{x}_t, t), \boldsymbol{\Sigma}_{\theta}(\mathbf{x}_t, t)). \quad (3)$$

Practically, instead of $\boldsymbol{\mu}_{\theta}(x_t, t)$ and $\boldsymbol{\Sigma}_{\theta}(\mathbf{x}_t, t)$, models are designed to predict either the noise ϵ_t at timestep t , or a less noisier version of image \mathbf{x}_{t-1} directly.

3 Method

We formulate the 3D structure discovery task in biomedical images as an unsupervised segmentation into K parts. Given a one-channel 3D image $\mathbf{x}_0 \in \mathbb{R}^{1 \times H \times W \times D}$, our segmentation model \mathbf{f} predicts a mask $\mathbf{M} \in [0, 1]^{K \times H \times W \times D}$. For all voxels $u \in \llbracket 0, H-1 \rrbracket \times \llbracket 0, W-1 \rrbracket \times \llbracket 0, D-1 \rrbracket$, we have $\sum_{k=1}^K \mathbf{M}_{ku} = 1$. We use three losses for unsupervised training (see Fig. 2):

$$\mathcal{L} = \lambda_v \mathcal{L}_v + \lambda_f \mathcal{L}_f + \lambda_{inv} \mathcal{L}_{inv}. \quad (4)$$

For an arbitrary representation $\mathbf{h}(\mathbf{x}_0)$ of an image \mathbf{x}_0 with voxels u , the consistency of this representation $C(\mathbf{h}(\mathbf{x}_0))$ across K predicted parts in the form of segmentation \mathbf{M} is defined as:

$$C(\mathbf{h}(\mathbf{x}_0)) = \frac{1}{N} \sum_{k=1}^K \sum_u \mathbf{M}_{ku} \|\mathbf{z}_k - [\mathbf{h}(\mathbf{x}_0)]_u\|_2^2, \quad \text{where} \quad \mathbf{z}_k = \frac{\sum_u \mathbf{M}_{ku} [\mathbf{h}(\mathbf{x}_0)]_u}{\sum_u \mathbf{M}_{ku}}, \quad (5)$$

where N is the number of voxels. This is a form of volume-normalized K-means loss with z_k describing the mean feature value of partition k .

Feature Consistency. We pretrain generative 3D diffusion models and use them as feature extractors [4]. Noise is added to a clean image \mathbf{x}_0 based on Eq. (2) and the noisy image $\mathbf{x}_t \in \mathbb{R}^{1 \times H \times W \times D}$ is passed to the 3D diffusion model. Intermediate activations (either from different stages of ladder-like U-Nets or their concatenation, see Fig. 1) upsampled to the original image size serve as a p -dimensional feature extractor $\phi(\mathbf{x}_0) \in \mathbb{R}^{p \times H \times W \times D}$. The feature consistency loss encourages voxels corresponding to the same parts to have similar features:

$$\mathcal{L}_f = C(\phi(\mathbf{x}_0)). \quad (6)$$

Visual Consistency. The extracted features are upsampled from low spatial resolutions and therefore do not accurately align with image boundaries. To alleviate this problem, we use a voxel visual consistency loss:

$$\mathcal{L}_v = C(\mathbf{I}(\mathbf{x}_0)) = C(\mathbf{x}_0) \quad (7)$$

where $\mathbf{I}(\mathbf{x}_0)$ is the identity feature extractor, i.e. $\mathbf{I}(\mathbf{x}_0) = \mathbf{x}_0$.

Photometric Invariance. As biomedical images often show acquisition differences (e.g., based on MR or CT scanner), they can be heterogeneous in their voxel intensities [25]. Therefore, robustness of models to voxel-level photometric perturbations might be helpful for *unsupervised* discovery. We use the Dice loss [22] to encourage invariance to such a photometric transformation \mathcal{T} :

$$\mathcal{L}_{inv} = 1 - \frac{2 \sum_u [\mathbf{f}(\mathbf{x}_0)]_u [\mathbf{f}(\mathcal{T}(\mathbf{x}_0))]_u}{\sum_u [\mathbf{f}(\mathbf{x}_0)]_u^2 + \sum_u [\mathbf{f}(\mathcal{T}(\mathbf{x}_0))]_u^2}. \quad (8)$$

We assume our images are min-max normalized ($\mathbf{x}_0 \in [0, 1]$). We then use gamma-correction of the form $\mathcal{T}(\mathbf{x}_0) = \mathbf{x}_0^\gamma$ as a photometric transformation. We draw γ from the uniform distribution: $\gamma \sim U[\gamma_{min}, \gamma_{max}]$.

Table 1. Dice scores on the biologically inspired synthetic datasets. Our method outperforms all previous work on unsupervised 3D segmentation for all levels of hierarchy.

	Regular				Irregular		
	Level 1	Level 2	Level 3		Level 1	Level 2	Level 3
Çiçek et al. [7]	0.968	0.829	0.668	Semi-supervised	0.970	0.825	0.601
Zhao et al. [36]	0.989	0.655	0.357	Semi-supervised	0.978	0.641	0.333
Nalepa et al. [24]	0.530	0.276	0.112	Unsupervised	0.527	0.280	0.144
Ji et al. [16]	0.589	0.291	0.150	Unsupervised	0.527	0.280	0.144
Moriya et al. [23]	0.628	0.311	0.141	Unsupervised	0.525	0.232	0.094
Hsu et al. [13]	0.952	0.541	0.216	Unsupervised	0.953	0.488	0.199
Ours	0.986	0.577	0.397	Unsupervised	0.967	0.565	0.382
k -means	0.808	0.326	0.149	Non-DL	0.771	0.299	0.118
BM4D+ k -means	0.949	0.529	0.335	Non-DL	0.950	0.533	0.324

4 Experiments

4.1 Datasets

To compare with state-of-the-art unsupervised 3D segmentation methods we follow [13] and evaluate our method on challenging biologically inspired 3D synthetic datasets and a real-world brain tumor segmentation (BraTS’19) dataset.

The synthetic dataset of [13], consists of 120 volumes (80–20–20 split) of size $50 \times 50 \times 50$. Inspired by cryo-electron tomography images, it contains a three-level structure, representing a biological cell, vesicles and mitochondria, as well as protein aggregates. The intensities and locations of the objects are randomized without destroying the hierarchy. The regular variant of the dataset contains cubical and spherical objects, while the irregular variant contains more complex shapes. Pink noise of magnitude $m = 0.25$ which is commonly seen in biological data [30] is applied to the volume. Figure 3 shows sample slices of both variants.

The BraTS’19 dataset [2, 3, 21] is an established benchmark for 3D tumor segmentation of brain MRIs. Volumes are co-registered to the same template, interpolated to $(1\text{ mm})^3$ resolution and brain-extracted. Following [13], images are cropped to volumes of size $200 \times 200 \times 155$. As in [13], FLAIR images and corresponding whole tumor (WT) annotations are used for unsupervised segmentation evaluation with the same split of 259 high grade glioma training examples into 180 train, 39 validation, and 40 test samples. The official BraTS’19 validation and test sets are not used as their segmentation masks are not available.

4.2 Implementation Details

All diffusion models use the same architecture shown in Fig. 1. We pretrain them for $50k$ epochs with batch size 4, using an $L1$ loss between the denoised and the original images. We use the Adam optimizer, a cosine noise schedule, learning rate 10^{-4} and $T = 250$ steps. The first layer has 64 channels and this number is doubled for the proceeding downsampling layers. Due to memory constraints for BraTS’19, we trained diffusion models at $128 \times 128 \times 128$ resolution. However, the extracted features are upsampled to the original $200 \times 200 \times 155$ resolution.

Our segmentation networks (**f** in Fig. 2) use a 3D U-Net architecture [7, 28]. We trained them for 100 epochs using the Adam optimizer, a learning rate of $3 \cdot 10^{-4}$ and the losses in Eq. (4). We selected the epoch that gave the best average probability of the segmentation mask for all inputs [26] as our final model. Noisy images at timestep $t = 25$ are used as input to the diffusion models. Due to the

Table 2. Dice scores when using features from different stages of ladder-like U-Net-based diffusion models (see Fig. 1) for unsupervised segmentation of the different hierarchy levels of the synthetic dataset. Features at lower resolutions (Stage 1) are more suitable for discovering larger objects (Level 1). Intermediate features (Stage 2) are more suitable for intermediate discoveries (Level 2). Features at higher resolutions (Stage 3) are more suitable for more detailed discoveries (Level 3).

	Predictions		
	Level 1	Level 2	Level 3
Stage 1 features	0.986	0.366	0.273
Stage 2 features	0.923	0.577	0.327
Stage 3 features	0.878	0.489	0.397

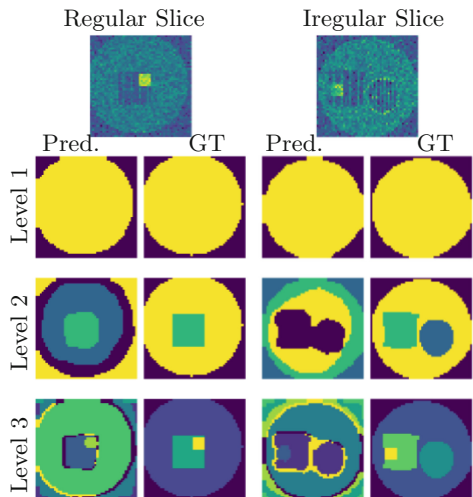


Fig. 3. Examples of unsupervised 3D structure discovery with our method on the biologically-inspired synthetic datasets. GT indicates ground truth.

memory limits, for BraTS’19, we used Stage 2 features, as they have the least number of channels. We set $\lambda_f = \lambda_v = \lambda_{inv} = 1$ and $\gamma \sim U[0.9, 1.1]$ for all cases. For all experiments we used Pytorch and 4 NVIDIA A6000 GPUs (48 Gb).

4.3 Results

We compare our method with state-of-the-art unsupervised 3D structure discovery approaches including clustering using 3D feature learning [23], a 3D convolutional autoencoder [24], and self-supervised hyperbolic representations [13].

For the synthetic datasets, we used $K = 2$ (background and cell) for Level 1, $K = 4$ (background, cell, vesicle, mitochondria) for Level 2, and $K = 8$ (background, cell, vesicle, mitochondria, and 4 small protein aggregates) for Level 3 predictions. The evaluation metric is the average Dice score on the annotated test labels. As the label order may differ we use the Hungarian algorithm to match the predicted masks with the ground truth segmentations. Table 1 shows the results for the regular and irregular variants of the cryo-ET-inspired synthetic dataset. Our models outperform all previous unsupervised work at all hierarchy levels. For some levels, our models even outperform semi-supervised methods (Çiçek et al. [7] used 2% of annotated data, Zhao et al. [36] used one annotated volume). We found that simple unsupervised denoising (BM4D [20]) followed by k -means clustering provides a good baseline, although vanilla k -means clustering on voxel intensities does not perform well due to noise. Results in Fig. 3 demonstrate that our proposed unsupervised method indeed discovers

Table 3. BraTS’19 results with ablation studies. Our method outperforms previous unsupervised methods in both the Dice score and the 95% Hausdorff distance.

	<i>Dice</i> WT \uparrow	<i>HD</i> 95 WT \downarrow	
1st place solution [17]	0.888	4.618	Supervised
^a Nalepa et al. [24]	0.211	170.434	Unsupervised
^a Ji et al. [16]	0.425	114.400	Unsupervised
^a Moriya et al. [23]	0.495	110.803	Unsupervised
^a Hsu et al. [13]	0.684	97.641	Unsupervised
Ours	0.719	27.838	Unsupervised
$\lambda_{inv} = 0$	0.696	38.645	Unsupervised
$\lambda_f = 0$	0.677	42.318	Unsupervised
$\lambda_v = 0$	0.671	41.801	Unsupervised
w/ Med3D [5] features	0.657	29.906	Unsupervised
k -means	0.439	63.811	Non-DL
Features k -means	0.471	45.917	Unsupervised
Med3D [5] k -means	0.231	55.846	Unsupervised

^a Dice and HD95 numbers for these models are taken from [13].

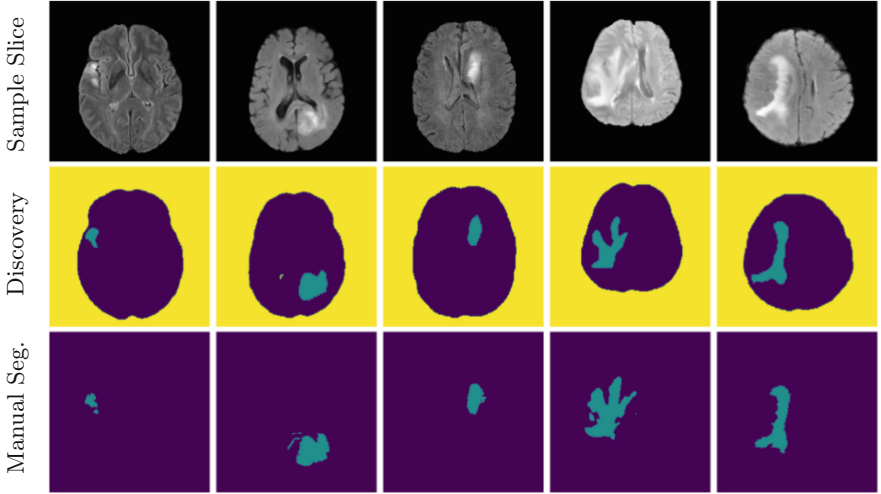


Fig. 4. Examples of discovered structures on BraTS’19. Our method discovers meaningful regions and detects tumors of different sizes in an unsupervised manner.

the hierarchical structure of different levels. We also show in Table 2 that features from early decoder stages of the U-Net-based diffusion models better discover larger objects in the hierarchy, features at intermediate stages better capture intermediate objects, and features at later stages better find smaller objects.

For the Brain Tumor Segmentation (BraTS’19) dataset, we use the whole tumor (WT) segmentation mask for evaluation, which is detectable based on the FLAIR images alone. We train segmentation models with $K = 3$ parts (background, brain, tumor). The evaluation metric, as in the BraTS’19 challenge [21], is Dice score and the 95th percentile of the symmetric Hausdorff distance, which quantifies the surface distance of the predicted segmentation from the manual tumor segmentation in millimeters. Table 3 shows that our model outperforms all prior unsupervised methods for both evaluation metrics. As an approximate upper bound we show for reference the reported results of the 1st place solution [17] on BraTS’19 which is based on supervised training on the full train set and evaluated on the BraTS’19 test set. The qualitative results in Fig. 4 show that our model can detect tumors of different sizes. Our predictions look smoother and do not capture fine details of tumor segmentations.

We perform ablation studies on the BraTS’19 dataset (Table 3: below the line). Measuring the impact of each loss, we see that the smallest performance drop is due to a deactivated invariance loss ($\lambda_{inv} = 0$) while deactivating the visual consistency ($\lambda_v = 0$) and feature consistency ($\lambda_f = 0$) losses results in larger, but similar performance drops. However, to achieve best performance all three components are necessary. We also perform k -means clustering on intensities and features. We observe that using our deep network model dramatically improves performance, although our losses are similar to k -means clustering.

This might be due to the fact that predictive modeling involves learning from a distribution of images and a model may therefore extract useful knowledge from a collection of images. To evaluate the significance of the diffusion features, we replaced our diffusion feature extractor with a 3D ResNet from Med3D [5] trained on 23 medical datasets. We use the “layer1_2_conv2” features as they showed the best performance. Although performance does not drop significantly when Med3D features are used with our losses, Med3D features do not produce good results when directly used for k -means clustering.

5 Conclusion

In this work, we showed that features from 3D generative diffusion models using a ladder-like U-Net-based architecture can discover *intrinsic* 3D structures in biomedical images. We trained predictive *unsupervised* segmentation models using losses that encourage the decomposition of biomedical volumes into nested subvolumes aligned with their hierarchical structures. Our method outperforms existing unsupervised segmentation approaches and discovers meaningful hierarchical concepts on challenging biologically-inspired synthetic datasets and on the BraTS brain tumor dataset. While we tested our approach for unsupervised image segmentation it is conceivable that it could also be useful in semi-supervised settings and that could be applied to data types other than images.

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