

Deep Model Generalization in Medical Image Segmentation

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Medical Image Segmentation at a Glance

Medical Image Segmentation at a Glance

Spectrum of medical image segmentation methods

- Deformable models, such as snakes, active contours, level-set [T. McInerney and D. Terzopoulos D. MedIA 1996]
- Statistical inference via parametric or nonparametric probability models [D. Pham, C. Xu, and J. Prince Annu Rev Biomed Eng 2000]
- Multi-atlas based segmentation via registration and label fusion [J. Iglesias and M. Sabuncu MedIA 2015]
- Discriminative classifier based methods

$$
F_{\theta}(X) \to Z \in R^z
$$
; $C_{\phi}(Z) \to Y \in R^c$ $X \to F_{\theta}(\cdot) \circ C_{\phi}(\cdot) \to Y$ Deep Learning

End-to-end 3D Networks for Semantic Segmentation

3D models

- Encode richer spatial information - Fit to domain knowledge

- Short-cut connection facilitate information flow
- Mutli-scale feature fusion for pixel-wise prediction

[Chen et al. NeuroImage 2018]

Skip connection Deep supervision

- Enhance gradients with explicit loss propagation - Speed up training process

[Dou et al. MICCAI 2016; MedIA 2017]

[[]Liu et al. IEEE Access 2020]

Improve Computational Efficiency by Network Design

H-DenseUNet: Hybrid Densely Connected UNet for Liver and Tumor Segmentation

 (b)

 (a)

Improve Computational Efficiency by Network Design

3D RoI-aware U-Net for Accurate and Efficient Colorectal Tumor Segmentation

How can AI Segmentations Influence Clinicians?

- saving 40% time, per case
- process 1 more cancer patient in 1 hour *Do more calculations …*

A Gallery of Image Segmentation Scenarios

Open Problems

Weak label usage, e.g., semi-supervised learning; noisy-label training; unsupervised learning, active learning.

Data scarcity issue, e.g., transfer learning; data augmentation; limited data training.

Interpretability issue, e.g., uncertainty estimation; explainable deep learning; relationship and causality.

Clinical oriented, e.g., large-scale validation; beyond imaging data;

Model generalization.

Model Generalization in Real World Conditions

Data-driven method is sensitive to data mismatch

• **Low data quality at inference**

- artefacts,
- missing modality,
- unseen severe cases, etc.

- **Data heterogeneity**
	- different vendors,
	- imaging protocols,
	- patient population

Loss for disentangled appearance code:

 $\mathcal{L}_{\mathrm{KL}} = \sum_{i=1}^{M} \mathbb{E}[D_{\mathrm{KL}}(p(a_i)||\mathcal{N}(\mathbf{0},\mathbf{I}))]$

Loss for reconstruction with content code:

 $\mathcal{L}_{\text{rec}} = \sum_{i} ||D_i^r(z, a_i) - x_i||_1$, where $z = \mathcal{F}(\delta_i c_1, ..., \delta_M c_M)$

C. Chen, Q. Dou, et al. "Robust Multimodal Brain Tumor Segmentation via Feature Disentanglement and Gated Fusion", MICCAI, 2019.

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[D. Castro, I. Walker, and B. Glocker. 2019]

Tackling Data Heterogeneity: does Normalization Help?

An empirical study on the impact of scanner effects with brain imaging

Construct an **age- and sex-matched** dataset with T1-weighted brain MRI from n = 592 individuals, where 296 subjects (146 F) are taken each from the Cam-CAN and UKBB, to simulate a somewhat 'best case scenario' to **remove population bias**.

Very **careful pre-processing** is conducted, including: 1) reorientation, 2) skull stripping, 3) bias field correction, 4) intensitybased linear registration (rigid and affine) to MNI space, 5) whitening for intensity normalization

Site classification with random forest binary classifier

B. Glocker et al. "Machine Learning with Multi-site Imaging Data: An Empirical Study on the Impact of Scanner Effects." Medical Imaging meets NeurIPS Workshop, 2019.

Related work: [Shafto et al., 2014; Taylor et al., 2017; Sudlow et al., 2015; Miller et al., 2016; Alfaro-Almagro et al., 2018]

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A case study with prostateT2-weighted MRI image segmentation

Q. Liu, Q. Dou, et al. "MS-Net: Multi-Site Network for Improving Prostate Segmentation with Heterogeneous MRI Data", IEEE Trans. on Medical Imaging, 2020. Related work: [Karani et al. MICCAI 2018; Gibson et al. MICCAI 2018; John et al. ISBI 2019]

Q. Liu, Q. Dou, et al. "MS-Net: Multi-Site Network for Improving Prostate Segmentation with Heterogeneous MRI Data", IEEE Trans. on Medical Imaging, 2020.

Unpaired Multi-modal Learning with Knowledge Distillation

Distill activations per-class:

$$
\mathbf{z}_c^i = \frac{1}{\sum_n |\mathcal{S}_c^n|} \sum_n \sum_{(w,h) \in S_c^n} z_{nwhi},
$$

$$
\mathbf{p}_c^i = \frac{\exp(\mathbf{z}_c^i/T)}{\sum_j \exp(\mathbf{z}_c^j/T)},
$$

Minimize probability divergence:

$$
\mathcal{L}_{\rm kd} = \frac{1}{C} \sum_c \left(\mathcal{D}_{\rm KL}(\mathbf{q}_c^a || \mathbf{q}_c^b) + \mathcal{D}_{\rm KL}(\mathbf{q}_c^b || \mathbf{q}_c^a) \right),
$$

where $\mathcal{D}_{\rm KL}(\mathbf{q}_c^a || \mathbf{q}_c^b) = \sum \mathbf{q}_c^a \log \frac{\mathbf{q}_c^a}{\mathbf{q}_c^b}.$

Q. Dou, Q. Liu et al. "Unpaired Multi-modal Segmentation via Knowledge Distillation", IEEE Trans. on Medical Imaging, 2020.

Q. Dou, Q. Liu et al. "Unpaired Multi-modal Segmentation via Knowledge Distillation", IEEE Trans. on Medical Imaging, 2020.

Unsupervised domain adaptation through pixel-level alignment

C. Chen, Q. Dou, et al. "Semantic-Aware Generative Adversarial Nets for Unsupervised Domain Adaptation in Chest X-ray Segmentation." MICCAI-MLMI'18 (Oral)

Related work: [Y. Huo et al., ISBI 2018; Z. Zhang et al. CVPR 2018; Y. Zhang et al. MICCAI 2018]

Tackling Data Heterogeneity with UDA

Image-to-image transformation with generative adversarial nets

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Tackling Data Heterogeneity with UDA

Unsupervised Domain Adaptation: Feature-level Alignment

Train a source domain segmentation model

• joint cross-entropy loss and dice loss

$$
\mathcal{L}_{\text{seg}} = -\sum_{i=1}^{N^s} \sum_{c \in C} w_c^s \cdot y_{i,c}^s \log(\hat{p}_{i,c}^s) - \lambda \sum_{c \in C} \frac{\sum_{i=1}^{N^s} 2 y_{i,c}^s \hat{y}_{i,c}^s}{\sum_{i=1}^{N^s} y_{i,c}^s y_{i,c}^s + \sum_{i=1}^{N^s} \hat{y}_{i,c}^s \hat{y}_{i,c}^s}
$$

Q. Dou, C. Ouyang*, et al. "Unsupervised Cross-Modality Domain Adaptation of ConvNets for Biomedical Image Segmentations with Adversarial Loss.." IJCAI 2018.*

Unsupervised Domain Adaptation: Feature-level Alignment

Unsupervised learning with adversarial loss

domain adaptation module (generator):
$$
\min_{\mathcal{M}} \mathcal{L}_{\mathcal{M}}(X^t, \mathcal{D}) = -\mathbb{E}_{(\mathcal{M}_A(x^t), F_H(x^t)) \sim \mathbb{P}_g}[\mathcal{D}(\mathcal{M}_A(x^t), F_H(x^t))]
$$

$$
\text{domain critic module (discriminator):} \quad \min_{\mathcal{D}} \mathcal{L}_{\mathcal{D}}(X^s, X^t, \mathcal{M}) = \quad \mathbb{E}_{(\mathcal{M}_A(x^t), F_H(x^t)) \sim \mathbb{P}_g}[\mathcal{D}(\mathcal{M}_A(x^t), F_H(x^t))] \ - \qquad \qquad \mathbb{E}_{(\mathcal{M}_A^s(x^s), F_H(x^s)) \sim \mathbb{P}_s}[\mathcal{D}(\mathcal{M}_A^s(x^s), F_H(x^s))], s.t. \, \|\mathcal{D}\|_{L \leq K}.
$$

21 *Q. Dou*, C. Ouyang*, et al. "Unsupervised Cross-Modality Domain Adaptation of ConvNets for Biomedical Image Segmentations with Adversarial Loss.." IJCAI 2018. Related work: [K Kamnitsas et al. IPMI 2017]*

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$$

 $\mathbb{P}(\mathcal{M}_A(x^{\nu}), F_H(x^{\nu})) \sim \mathbb{P}_q \downharpoonright \mathcal{L}$ (v $\mathcal{M}_A(\omega)$), \mathcal{L}_H \mathcal{D} $\mathbb{E}_{(M_A^s(x^s),F_H(x^s))\sim \mathbb{P}_s}[\mathcal{D}(M_A^s(x^s),F_H(x^s))], s.t.$ $\|\mathcal{D}\|_{L\leq K}$

22 *Q. Dou*, C. Ouyang*, et al. "Unsupervised Cross-Modality Domain Adaptation of ConvNets for Biomedical Image Segmentations with Adversarial Loss.." IJCAI 2018. Related work: [K Kamnitsas et al. IPMI 2017]*

Related work: [DANN, Ganin et al. JMLR 2016; ADDA, Tzeng et al. CVPR 2017; CycleGAN, Zhu et al. ICCV 2017]

Unsupervised Domain Adaptation: Synergistic Alignment

C. Chen, Q. Dou et al. "Synergistic Image and Feature Adaptation: Towards Cross-Modality Domain Adaptation for Medical Image Segmentation", AAAI, 2019. (Oral) Related work: [DANN, Ganin et al. JMLR 2016; ADDA, Tzeng et al. CVPR 2017; CycleGAN, Zhu et al. ICCV 2017]

A brief overview of existing approaches

Domain Generalization

Problem setting: train on multiple source domains and **directly** generalize to unseen domains

Regularization for generic semantic features

- adversarial feature alignment for domain invariance [Li et al. ECCV 2018]
- decompose networks parameters to domain-specific/invariant [Khosla ECCV 2012]
- data augmentation based methods [Shankar et al. ICLR 2018; Volpi et al. NeurIPS 2018]
- multi-task or self-supervised signals [Ghifary et al. ICCV 2015; Carlucci et al. CVPR 2019]

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Tackling Data Heterogeneity for Domain Generalization

Domain Generalization with Gradient-based Meta-learning

Model-agnostic learning: MAML (model-agnostic meta-learning) [Finn et al. ICML 2017]

- MLDG: directly applying episodic training paradigm [Li et al. AAAI 2018]
- MetaReg: meta-learning of weights regularization term [Balaji et al. NeurIPS 2018]
- Episodic training with alternative model updates [Li et al. ICCV 2019]

- meta-learning

learning/adaptation

Episodic training paradigm

Available domains: $D = \{D_1, D_2, ..., D_K\}$ Neural network is composed of: $F_{\psi} \circ T_{\theta}$

Learning with explicit simulation of domain shift:

At each iteration, split into meta-train D_{tr} and meta-test D_{te} Update the parameters one or more steps with gradient descent:

 $(\psi', \theta') = (\psi, \theta) - \alpha \nabla_{\psi, \theta} \mathcal{L}_{\text{task}}(\mathcal{D}_{\text{tr}}; \psi, \theta)$

Then, apply meta-learning step, to enforce certain properties to be exhibited on held-out domain D_{te} , to regularize semantic features

Global Class Alignment

Inter-class relationships concept is domain-invariant and transferable

• In each domain, compute class-specific mean feature vector:

$$
\bar{\mathbf{z}}_c^{(k)} = \frac{1}{N_k^{(c)}} \sum_{n:y_n^{(k)}=c} F_{\psi'}(\mathbf{x}_n^{(k)}) \approx \mathbb{E}_{D_k}[F_{\psi'}(\mathbf{x}) | y = c]
$$

- Compute soft label distribution: $\mathbf{s}_{c}^{(k)} = \text{softmax}(T_{\theta}(\bar{\mathbf{z}}_{c}^{(k)})/\tau)$
- With $(D_i, D_j) \in D_{tr} \times D_{te}$, regularize consistency of inter-class alignment:

$$
\ell_{\text{global}}(D_i, D_j; \psi', \theta') = \frac{1}{C} \sum_{c=1}^C \frac{1}{2} [D_{\text{KL}}(\mathbf{s}_c^{(i)} \, \| \, \mathbf{s}_c^{(j)}) + D_{\text{KL}}(\mathbf{s}_c^{(j)} \, \| \, \mathbf{s}_c^{(i)})]
$$

(Note: complexity of pairs is controllable via mini-batch sampling in large-scale scenarios.)

MASF: Model-Agnostic Learning of Semantic Features

Local Sample Clustering

feature clusters with domain-independent class-specific cohesion and separation

Use a *metric-learning* approach, with an embedding network and operates in semantic feature space:

• obtain a learnable distance function:

 $d_{\phi}(\mathbf{z}_n, \mathbf{z}_m) = ||\mathbf{e}_n - \mathbf{e}_m||_2 = ||M_{\phi}(\mathbf{z}_n) - M_{\phi}(\mathbf{z}_m)||_2$

• metric-learning can rely on contrastive loss [Hadsell et al. CVPR 2006]:

 $\ell_{\text{con}}^{n,m} = \begin{cases} d_{\phi}(\mathbf{z}_n, \mathbf{z}_m)^2, & \text{if } y_n = y_m \\ (\max\{0, \xi - d_{\phi}(\mathbf{z}_n, \mathbf{z}_m)\})^2, & \text{if } y_n \neq y_m \end{cases}$

• or triplet loss [Schroff et al. CVPR 2015]:

$$
\ell_{\rm tri}^{a,p,n} = \max\{0, d_{\phi}(\mathbf{z}_a, \mathbf{z}_p)^2 - d_{\phi}(\mathbf{z}_a, \mathbf{z}_n)^2 + \xi\}
$$

Medical application of brain tissue segmentation

- data acquisition differences in scanners, imaging protocols, and many other factors
- posing severe limitations for translating learning-based methods in clinical practice
- segmentation of 3 brain tissues: white matter, gray matter and cerebrospinal fluid
- 4 domains corresponding to 4 hospitals

MASF: Model-Agnostic Learning of Semantic Features

Datasets

- 1. Multi-Modality Whole Heart Segmentation (MMWHS) Challenge <http://www.sdspeople.fudan.edu.cn/zhuangxiahai/0/mmwhs/> <https://github.com/carrenD/Medical-Cross-Modality-Domain-Adaptation>
- 2. MICCAI 2019 MS-CMRSeg Multi-sequence Cardiac MR Segmentation Challenge <https://zmiclab.github.io/mscmrseg19/>
- 3. MICCAI iSeg 2019 Challenge 6-month Infant Brain MRI segmentation from Multiple Sites http://iseg2019.web.unc.edu
- 4. ISBI 2019 CHAOS Challenge CT-MRI Abdominal Multi-Organ Segmentation https://chaos.grand-challenge.org
- 5. Prostate Segmentation, with several public datasets, i.e., NCI-ISBI 2013 dataset, I2CVB dataset (include multiple sites), PROMISE12 dataset (include multiple sites)
- 6. Chest X-Ray, with several public datasets, i.e., ChestX-ray14 NIH, CheXpert, PadChest, Mimic-CXR MIDL 2019: <https://openreview.net/forum?id=S1gvm2E-t4>

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Paper & Code Available at:

Thanks for your attention! Q & A

