

USE-Net: incorporating Squeeze-and-Excitation blocks into U-Net for prostate zonal segmentation of multi-institutional MRI datasets

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USE-Net: incorporating Squeeze-and-Excitation blocks into U-Net for prostate zonal segmentation of multi-institutional MRI datasets

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Abstract

Prostate cancer is the most common malignant tumors in men but prostate Magnetic Resonance Imaging (MRI) analysis remains challenging. Besides

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whole prostate gland segmentation, the capability to differentiate between the blurry boundary of the Central Gland (CG) and Peripheral Zone (PZ) can lead to differential diagnosis, since the frequency and severity of tumors differ in these regions. To tackle the prostate zonal segmentation task, we propose a novel Convolutional Neural Network (CNN), called USE-Net, which incorporates Squeeze-and-Excitation (SE) blocks into U-Net, i.e., one of the most effective CNNs in biomedical image segmentation. Especially, the SE blocks are added after every Encoder (Enc USE-Net) or Encoder-Decoder block (Enc-Dec USE-Net). This study evaluates the generalization ability of CNN-based architectures on three T2-weighted MRI datasets, each one consisting of a different number of patients and heterogeneous image characteristics, collected by different institutions. The following mixed scheme is used for training/testing: (i) training on either each individual dataset or multiple prostate MRI datasets and (ii) testing on all three datasets with all possible training/testing combinations. USE-Net is compared against three state-of-the-art CNN-based architectures (i.e., U-Net, pix2pix, and Mixed-Scale Dense Network), along with a semi-automatic continuous max-flow model. The results show that training on the union of the datasets generally outperforms training on each dataset separately, allowing for both intra-/cross-dataset generalization. Enc USE-Net shows good overall generalization under any training condition, while Enc-Dec USE-Net remarkably outperforms the other methods when trained on all datasets. These findings reveal that the SE blocks' adaptive feature recalibration provides excellent cross-dataset generalization when testing is performed on samples of the datasets used during training. Therefore, we should consider multi-dataset training and SE

blocks together as mutually indispensable methods to draw out each other’s full potential. In conclusion, adaptive mechanisms (e.g., feature recalibration) may be a valuable solution in medical imaging applications involving multi-institutional settings.

Keywords: Prostate zonal segmentation, Prostate cancer, Anatomical MRI, Convolutional neural networks, USE-Net, Cross-dataset generalization

1. Introduction

According to the American Cancer Society, in 2019 the Prostate Cancer (PCa) is expected to be the most common malignant tumor with the second highest mortality for American males [1]. Given a clinical context, several
5 imaging modalities can be used for PCa diagnosis, such as Transrectal Ultrasound (TRUS), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI). For an in-depth investigation, structural T1-weighted (T1w) and T2-weighted (T2w) MRI sequences can be combined with the functional information from Dynamic Contrast Enhanced MRI (DCE-MRI), Diffusion
10 Weighted Imaging (DWI), and Magnetic Resonance Spectroscopic Imaging (MRSI) [2]. Recent advancements in MRI scanners, especially those related to magnetic field strengths higher than 1.5T, did not decrease the effect of magnetic susceptibility artifacts on prostate MR images, even though the shift from 1.5T to 3T theoretically leads to a doubled Signal-to-Noise Ratio
15 (SNR) [3]. However, 3T MRI scanners permitted to obtain high-quality images with less invasive procedures compared with 1.5T, thanks to a pelvic coil that reduces prostate gland compression/deformation [4, 5].

Therefore, MRI plays a decisive role in PCa diagnosis and disease mon-

itoring (even in an advanced status [6]), revealing the internal prostatic
20 anatomy, prostatic margins, and PCa extent [7]. According to the zonal
compartment system proposed by McNeal, the prostate Whole Gland (WG)
can be partitioned into the Central Gland (CG) and Peripheral Zone (PZ) [8].
In prostate imaging, T2w MRI serves as the principal sequence [9], thanks
to its high resolution that enables to differentiate the hyper-intense PZ and
25 hypo-intense CG in young male subjects [10].

Besides manual detection/delineation of the WG and PCa on MR im-
ages, distinguishing between the CG and PZ is clinically essential, since
the frequency and severity of tumors differ in these regions [11, 12]. As
a matter of fact, the PZ harbors 70-80% of PCa and represents a target
30 for prostate biopsy [13]. Furthermore, the PZ volume ratio (i.e., the PZ
volume divided by the WG volume) can be considered for PCa diagnostic
refinement [14], while the CG volume ratio can help monitoring prostate hy-
perplasia [15]. Therefore, according to the Prostate Imaging-Reporting and
Data System version 2 (PI-RADSTM v2) [16], radiologists must perform a
35 zonal partitioning before assessing the suspicion of PCa on multi-parametric
MRI. However, an improved PCa diagnosis requires a reliable and automatic
zonal segmentation method, since manual delineation is time-consuming and
operator-dependent [17, 18]. Moreover, in clinical practice, the generaliza-
tion ability among multi-institutional prostate MRI datasets is essential due
40 to large anatomical inter-subject variability and the lack of a standardized
pixel intensity representation for MRI (such as for CT-based radiodensity
measurements expressed in Hounsfield units) [19]. Hence, we aim at au-
tomatically segmenting the prostate zones on three multi-institutional T2w

MRI datasets to evaluate the generalization ability of Convolutional Neural
45 Network (CNN)-based architectures. This task is challenging because images
from multi-institutional datasets are characterized by different contrasts, vi-
sual consistencies, and heterogeneous characteristics [20].

In this work, we propose a novel CNN, called USE-Net, which incorpo-
rates Squeeze-and-Excitation (SE) blocks [21] into U-Net after every Encoder
50 (Enc USE-Net) or Encoder-Decoder block (Enc-Dec USE-Net). The ratio-
nale behind the design of USE-Net is to exploit adaptive channel-wise feature
recalibration to boost the generalization performance. The proposed USE-
Net is conceived to outperform the state-of-the-art CNN-based architectures
for segmentation in multi-institutional studies, whilst the SE blocks (ini-
55 tially proposed in [21]) were originally designed to boost the performance
only for classification and object detection *via* feature recalibration, by cap-
turing single dataset characteristics. Unlike the original SE blocks placed
in InceptionNet [22] and ResNet [23] architectures, we introduced them into
U-Net after the encoders and decoders to boost the segmentation perfor-
60 mance with increased generalization ability, thanks to the representation of
channel-wise relationships in multi-institutional clinical scenarios, analyzing
multiple heterogeneous MRI datasets. This study adopted a mixed scheme
for cross- and intra-dataset generalization: (*i*) training on either each in-
dividual dataset or multiple datasets, and (*ii*) testing on all three datasets
65 with all possible training/testing combinations. To the best of our knowl-
edge, this is the first CNN-based prostate zonal segmentation on T2w MRI
alone. By relying on both spatial overlap-/distance-based metrics, we com-
pared USE-Net against three CNN-based architectures: U-Net, pix2pix, and

Mixed-Scale Dense Network (MS-D Net) [24], along with a semi-automatic
70 continuous max-flow model [25].

Contributions. Our main contributions are:

- **Prostate zonal segmentation:** our novel Enc-Dec USE-Net achieves accurate CG and PZ segmentation results on T2w MR images, remarkably outperforming the other competitor methods when trained on all
75 datasets used for testing in multi-institutional scenarios.
- **Cross-dataset generalization:** this first cross-dataset study, investigating all possible training/testing conditions among three different medical imaging datasets, shows that training on the union of multiple datasets generally outperforms training on each dataset during testing,
80 realizing both intra-/cross-dataset generalization—thus, we may train CNNs by feeding samples from multiple different datasets for improving the performance.
- **Deep Learning for medical imaging:** this research reveals that SE blocks provide excellent intra-dataset generalization in multi-institutional scenarios, when testing is performed on samples from the
85 datasets used during training. Therefore, adaptive mechanisms (e.g., feature recalibration in CNNs) may be a valuable solution in medical imaging applications involving multi-institutional settings.

The manuscript is structured as follows. Section 2 outlines the back-
90 ground of prostate MRI zonal segmentation, especially related work on CNNs.

Section 3 describes the analyzed multi-institutional MRI datasets, the proposed USE-Net architectures, the investigated state-of-the-art CNN- and max-flow-based segmentation approaches, as well as the employed evaluation metrics; the experimental results are presented and discussed in Section 4. Finally, conclusive remarks and future directions of this work are given in Section 5.

2. Related Work

Due to the crucial role of MR image analysis in PCa diagnosis and staging [2], researchers have paid specific attention to automatic WG detection/segmentation. Classic methods mainly leveraged atlases [19, 26] or statistical shape priors [27]: atlas-based approaches realized accurate segmentation when new prostate instances resemble the atlas, relying on a non-rigid registration algorithm [27, 28]. Unsupervised clustering techniques allowed for segmentation without manual labeling of large-scale MRI datasets [17, 29]. In the latest years, Deep Learning techniques [30] have achieved accurate prostate segmentation results by using deep feature learning combined with shape models [31] or location-prior maps [32]. Moreover, CNNs were used with patch-based ensemble learning [33] or dense prediction schemes [34]. In addition, end-to-end deep neural networks achieved outstanding results in automated PCa detection in multi-parametric MRI [35, 36].

Differently from WG segmentation and PCa detection, less attention has been paid to CG and PZ segmentation despite its clinical importance in PCa diagnosis [12]. In this context, classic Computer Vision techniques have been mainly exploited on T2w MRI. For instance, early studies combined classi-

115 fiers with statistical shape models [37] or deformable models [38]; Toth *et al.* [28] employed active appearance models with multiple level sets for simultaneous zonal segmentation; Qiu *et al.* [25] used a continuous max-flow model—the dual formulation of convex relaxed optimization with region consistency constraints [39]; in contrast, Makni *et al.* [40] fused and processed
120 3D T2w, DWI, and contrast-enhanced T1w MR images by means of an evidential C-means algorithm [41]. As the first CNN-based method, Clark *et al.* [42] detected DWI MR images with prostate relying on Visual Geometry Group (VGG) net [43], and then sequentially segmented WG and CG using U-Net [44].

125 Regarding the most recent computational methods in medical image segmentation, along with traditional Pattern Recognition techniques [45], significant advances have been proposed in CNN-based architectures. For instance, to overcome the limitations related to accurate image annotations, DeepCut [46] relies on weak bounding box labeling [47]. This method aims at
130 learning features for a CNN-based classifier from bounding box annotations. Among the architectures devised for biomedical image segmentation [48, 49], U-Net [44] showed to be a noticeably successful solution, thanks to the combination of a contracting (i.e., encoding) path, for coarse-grained context detection, and a symmetric expanding (i.e., decoding) path, for fine-grained
135 localization. This fully CNN is capable of stable training with reduced samples. The authors of V-Net [34] extended U-Net for volumetric medical image segmentation, by introducing also a different loss function based on the Dice Similarity Coefficient (*DSC*). Schlemper *et al.* [50] presented an Attention Gate (AG) model for medical imaging, which aims at focusing on

140 target structures or organs. AGs were introduced into the standard U-Net, so defining Attention U-Net, which achieved high performance in multi-class image segmentation without relying on multi-stage cascaded CNNs. Recently MS-D Net [24] was shown to yield better segmentation results in biomedical images than U-Net [44] and SegNet [51], by creating dense connections
145 among features at different scales obtained by means of dilated convolutions. By so doing, features at different scales can be contextually extracted using fewer parameters than full CNNs. Finally, also image-to-image translation approaches—e.g., pix2pix [52] that leverages conditional adversarial neural networks—were exploited for image segmentation.

150 However, no literature method so far coped with the generalization ability among multi-institutional MRI datasets, making their clinical applicability difficult [53]. In a previous work [54], we compared existing CNN-based architectures—namely, SegNet [51], U-Net [44], and pix2pix [52]—on two multi-institutional MRI datasets. According to our results, U-Net gener-
155 ally achieves the most accurate performance. Here, we thoroughly verify the intra-/cross-dataset generalization on three datasets from three different institutions, also proposing a novel architecture based on U-Net [44] incorporating SE blocks [21]. To the best of our knowledge, this is the first study on CNN-based prostate zonal segmentation on T2w MRI alone.

160 **3. Materials and Methods**

This section first describes the analyzed multi-institutional MRI datasets collected by different institutions. Afterwards, we explain the proposed USE-Net, the other investigated CNN-based architectures, as well as a state-of-

the-art prostate zonal segmentation method based on a continuous max-flow
165 model [25]. Finally, the used spatial overlap- and distance-based evaluation
metrics are reported.

3.1. Multi-institutional MRI Datasets

We segment the CG and PZ from the WG on three completely different
multi-parametric prostate MRI datasets, namely:

170 #1 dataset (21 patients/193 MR slices with prostate), acquired with a
whole body Philips Achieva 3T MRI scanner at the Cannizzaro Hospital
(Catania, Italy) [17]. MRI parameters: matrix size = 288×288 pixels;
slice thickness = 3.0 mm; inter-slice spacing = 4 mm; pixel spacing
= 0.625 mm; number of slices per image series (including slices without
175 prostate) = 18. Average patient age: 65.57 ± 6.42 years;

#2 Initiative for Collaborative Computer Vision Benchmarking (I2CVB)
dataset (19 patients/503 MR slices with prostate), acquired with a
whole body Siemens TIM 3T MRI scanner at the Hospital Center Re-
gional University of Dijon-Bourgogne (Dijon, France) [2]. MRI param-
180 eters: matrix size $\in \{308 \times 384, 336 \times 448, 360 \times 448, 368 \times 448\}$ pixels;
slice thickness = 1.25 mm; inter-slice spacing = 1.0 mm; pixel spac-
ing $\in \{0.676, 0.721, 0.881, 0.789\}$ mm; number of slices per image series
= 64. Average patient age: 64.36 ± 9.69 years;

#3 National Cancer Institute – International Symposium on Biomedical
185 Imaging (NCI-ISBI) 2013 Automated Segmentation of Prostate Struc-
tures Challenge dataset (40 patients/555 MR slices with prostate) *via*

The Cancer Imaging Archive (TCIA) [55], acquired with a whole body Siemens TIM 3T MRI scanner at Radboud University Medical Center (Nijmegen, The Netherlands) [56]. The prostate structures were manually delineated by five experts. MRI parameters: matrix size $\in \{256 \times 256, 320 \times 320, 384 \times 384\}$ pixels; slice thickness $\in \{3.0, 4.0\}$ mm; inter-slice spacing $\in \{3.6, 4.0\}$ mm; pixel spacing $\in \{0.500, 0.600, 0.625\}$ mm; number of slices per image series ranging from 15 to 24. Average patient age: 63.90 ± 7.17 years.

All the analyzed MR images are encoded in the 16-bit Digital Imaging and Communications in Medicine (DICOM) format. It is worth noting that even MR images from the same dataset have intra-dataset variations (such as the matrix size, slice thickness, and number of slices). Furthermore, inter-rater variability for the CG and PZ annotations exists, as different physicians delineated them. For clinical feasibility [10], we analyzed only axial T2w MR slices—the most commonly used sequence for prostate zonal segmentation—among the available sequences. In our multi-centric study, we conducted the following seven experiments resulting from all possible training/testing conditions:

- Individual dataset #1, #2, #3: training and testing on dataset #1 (#2, #3, respectively) alone in 4-fold cross-validation, and testing also on whole datasets #2 and #3 (#1 and #3, #1 and #2, respectively) separately for each round;
- Mixed dataset #1/#2, #2/#3, #1/#3: training and testing on both datasets #1 and #2 (#2 and #3, #1 and #3, respectively) in 4-fold

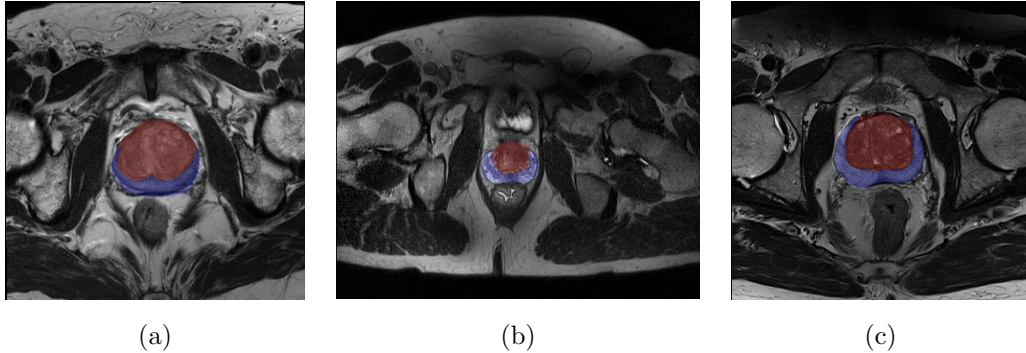


Figure 1: Examples of input prostate T2w MR axial slices in their original image ratio: (a) dataset #1; (b) dataset #2; (c) dataset #3. The CG and PZ are highlighted with red and blue transparent regions, respectively. Alpha blending with $\alpha = 0.2$.

cross-validation, and testing also on whole dataset #3 (#1, #2, respectively) separately for each round;

- Mixed dataset #1/#2/#3: training and testing on whole datasets #1, #2, and #3 in 4-fold cross-validation.

215 For clinical applications, such a multi-centric research is valuable for analyzing CNNs' generalization ability among different MRI acquisition options, e.g., different devices and functioning parameters. In our study, for instance, both intra-/cross-scanner evaluations can be carried out, because dataset #1's scanner is different from those of datasets #2 and #3. Fig. 1 shows
 220 an example image for each analyzed dataset; in the context of generalization among different datasets, Yan *et al.* [57] evaluated the average vessel segmentation performance on three retinal fundus image datasets under the three-dataset training condition, while pair-wisely assessing the cross-dataset performance on two datasets under the other one-dataset training condition.

225 Yang *et al.* [58] proposed an alternative approach using adversarial appearance rendering to relieve the burden of re-training for Ultrasound imaging datasets. Differently, we thoroughly evaluate all possible training/testing conditions (for a total of 21 configurations) on each dataset to confirm the intra- and cross-dataset generalization ability by incrementally injecting sam-
230 ples from the other datasets at hand.

With regard to the 4-fold cross-validation, we partitioned the datasets #1, #2, and #3 into 4 folds by using the following patient indices: $\{[1, \dots, 5], [6, \dots, 10], [11, \dots, 15], [16, \dots, 21]\}$, $\{[1, \dots, 5], [6, \dots, 10], [11, \dots, 15], [16, \dots, 19]\}$, and $\{[1, \dots, 10], [11, \dots, 20], [21, \dots, 30], [31, \dots, 40]\}$, respec-
235 tively. Finally, the results from the different cross-validation rounds were averaged to obtain a final descriptive value. These patient indices represent a permutation of the randomly arranged original patient ordering to portray a randomized partition scheme. This allowed us to guarantee a fixed partitioning among the different training/testing conditions with a general
240 notation valid for all datasets, regardless of the number of patients in each dataset.

Cross-validation strategies aim at estimating the generalization ability of a given model; the hold-out method fixedly partition the dataset into the training/test sets to train the model on the first partition alone and test it
245 only on the unseen test set data. Unlike the leave-one-out cross-validation with high variance and low bias, the k -fold cross-validation is a natural way to improve the hold-out method: the dataset is divided into k mutually exclusive folds of approximately equal size [59]. The statistical validity increases with less variance and less dependency on the initial dataset partition, av-

eraging the results for all the k cross-validation rounds. Consequently, the
 k -fold cross-validation is the most common choice for reliable generalization
results, minimizing the bias associated with the random sampling of the
training/test sets [59]. However, this statistical practice is computationally
expensive due to the k times-repeated training from scratch [60]. Moreover,
the results could underestimate the actual performance allowing for conser-
vative analyses [61]; thus, we chose 4-fold cross-validation for reliable and fair
training/testing phases, according to the number of patients in each dataset,
calculating the evaluation metrics on a statistically significant test set (i.e.,
25% of each prostate MRI dataset).

3.2. Prostate Zonal Segmentation on Multi-institutional MRI Datasets

This work adopts a selective delineation approach to focus on internal
prostatic anatomy: the CG and PZ, denoted by \mathcal{R}_{CG} and \mathcal{R}_{PZ} , respectively.
Let the entire image and the WG region be \mathcal{I}_Ω and \mathcal{R}_{WG} , respectively, the
following relationships can be defined:

$$\mathcal{I}_\Omega = \mathcal{R}_{WG} \cup \mathcal{R}_{bg} \text{ and } \mathcal{R}_{WG} \cap \mathcal{R}_{bg} = \emptyset, \quad (1)$$

where \mathcal{R}_{bg} represents background pixels. Relying on [7, 25], \mathcal{R}_{PZ} was ob-
tained by subtracting \mathcal{R}_{CG} from \mathcal{R}_{WG} meeting the constraints:

$$\mathcal{R}_{WG} = \mathcal{R}_{CG} \cup \mathcal{R}_{PZ} \text{ and } \mathcal{R}_{CG} \cap \mathcal{R}_{PZ} = \emptyset. \quad (2)$$

3.2.1. USE-Net: Incorporating SE Blocks into U-Net

We propose to introduce SE blocks [21] following every Encoder (Enc
USE-Net) or Encoder-Decoder (Enc-Dec USE-Net) of U-Net [44], as shown

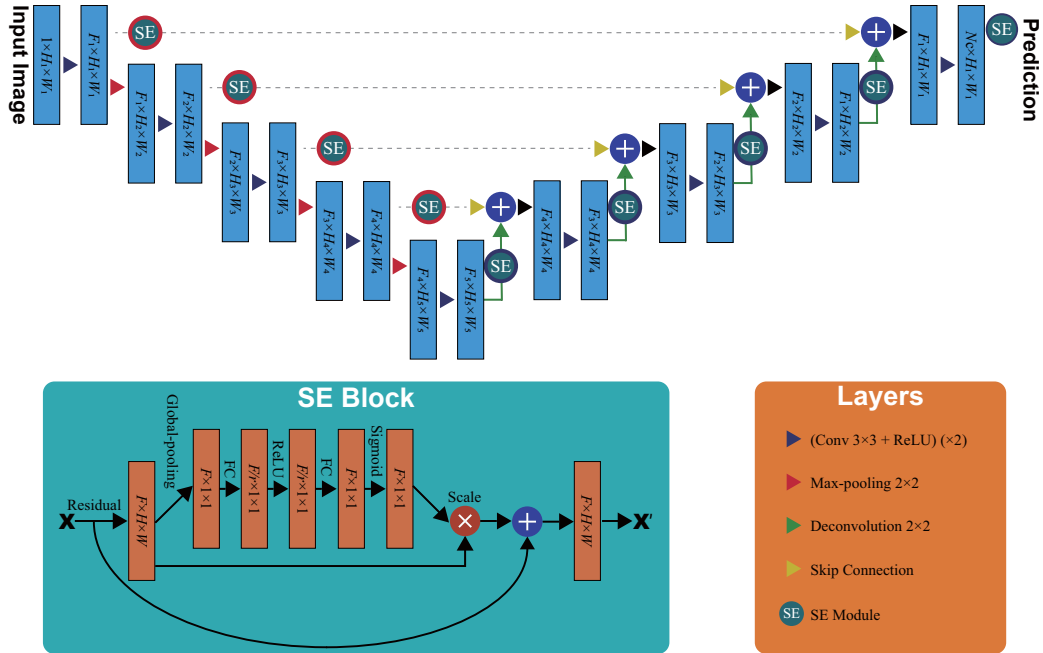


Figure 2: Scheme of the proposed USE-Net architecture: Enc USE-Net has only 4 (red-contoured) SE blocks after every encoder, whilst Enc-Dec USE-Net has 9 SE blocks integrated after every encoder/decoder (represented with red/blue contours, respectively).

in Fig. 2. As pointed out before, U-Net allows for a multi-resolution decomposition/composition technique [62], by combining encoders/decoders with skip connections between them [63]; in our implementation, encoders and decoders consist of four pooling operators that capture the context and up-sampling operators that conduct precise localization, respectively.

We introduce SE blocks to enhance image segmentation, expecting an increased representational power from modeling the channel-wise dependencies of convolutional features [21]. These blocks were originally envisioned for image classification using adaptive feature recalibration to boost informative

features and suppress the weak ones at minimal computational burden.

Enc USE-Net and Enc-Dec USE-Net are investigated to evaluate the effect
 275 of strengthened feature recalibration. Since the template of the SE blocks is
 generic, they can be exploited at any depth of any architecture. Considering
 that SE blocks should be placed after output feature maps for feature recal-
 ibration, we have three possible places to integrate them for U-Net, namely:
 (i) after encoders; (ii) after decoders; (iii) after a classifier. SE blocks are
 280 more powerful in the encoding path than in the decoding path and more pow-
 erful in the decoding path than after a classifier, as they affect lower-level
 features in the U-Net architecture and thus increase the overall performance
 significantly; consequently, instead of placing only a single SE block after
 the first encoder/decoder, we place SE blocks after each encoder/decoder for
 285 both coarse-grained context detection in the earlier layers and fine-grained
 localization in the deeper layers for the best segmentation performance.

The SE blocks can be formally described as follows:

Squeeze. Let $\mathbf{U} = [\mathbf{u}_1, \mathbf{u}_2, \dots, \mathbf{u}_F]$ be an input feature map, where $\mathbf{u}_f \in \mathbb{R}^{H \times W}$ is a single channel with size $H \times W$. Through spatial dimensions $H \times W$, a global average pooling layer generates channel-wise statistics $\mathbf{z} \in \mathbb{R}^F$, whose f -th element is given by:

$$z_f = \frac{1}{H \times W} \sum_{h=1}^H \sum_{w=1}^W [\mathbf{u}_f]_{i,j}. \quad (3)$$

Excitation. To limit the model complexity and boost generalization, two fully-connected layers and the Rectified Linear Unit (ReLU) [64] function δ transform \mathbf{z} with a sigmoid activation function $\sigma(\cdot)$:

$$\mathbf{s} = \sigma(g(\mathbf{z}, \mathbf{W})) = \sigma(\mathbf{W}_2 \delta(\mathbf{W}_1 \mathbf{z})), \quad (4)$$

where $\mathbf{W}_1 \in \mathbb{R}^{\frac{F}{r} \times F}$, $\mathbf{W}_2 \in \mathbb{R}^{F \times \frac{F}{r}}$, and r is the reduction ratio controlling the capacity and computational cost of the SE blocks. Hu *et al.* [21] showed that the SE blocks can overfit to the channel inter-dependencies of the training set despite a lower number of weights with respect to the original architecture; they found the best compromise of $r = 8$, which guarantees the lowest overall error (in terms of top-1 and top-5 errors) with ResNet-50 [23] for the ImageNet Large Scale Visual Recognition Challenge (ILSVRC) 2017 classification competition [65]. Therefore, we also selected $r = 8$ for the USE-Net. In order to obtain an adaptive recalibration that ignores less important channels and emphasizes important ones (allowing for non-mutual exclusivity among multiple channels, differently from one-hot encoding), \mathbf{U} is rescaled into $\tilde{\mathbf{X}} = [\tilde{\mathbf{x}}_1, \tilde{\mathbf{x}}_2, \dots, \tilde{\mathbf{x}}_F]$ by applying Eq. (5):

$$\tilde{\mathbf{x}}_f = \mathbf{F}_{\text{scale}}(\mathbf{u}_f, s_f) = s_f \cdot \mathbf{u}_f, \text{ for } f = 1, 2, \dots, F, \quad (5)$$

where $\mathbf{F}_{\text{scale}}(\mathbf{u}_f, s_f)$ represents the channel-wise multiplication between the feature map $\mathbf{u}_f \in \mathbb{R}^{H \times W}$ and the scalar $s_f \in [0, 1]$.

290 3.2.2. Pre-processing

To fit the image resolution of dataset #1, we either center-cropped or zero-padded the images of datasets #2 and #3 to resize them to 288×288 pixels. Afterwards, all images in the three datasets were masked using the corresponding prostate binary masks to omit the background and only focus
 295 on extracting the CG and PZ from the WG. This operation can be performed either by an automated method [17] or previously provided manual WG segmentation [2]. As a simple form of data augmentation, we randomly cropped the input images from 288×288 to 256×256 pixels and horizontally

flipped them.

300 *3.2.3. Post-processing*

Two efficient morphological operations were applied on the obtained \mathcal{R}_{CG} binary masks to smooth boundaries and deal with disconnected regions:

- a hole filling algorithm on the segmented \mathcal{R}_{CG} to remove possible holes in a predicted map;
- 305 • a small area removal operation dealing with connected components smaller than $\lfloor |\mathcal{R}_{WG}|/8 \rfloor$ pixels, where $|\mathcal{R}_{WG}|$ denotes the number of pixels contained in WG segmentation. This adaptive criterion takes into account the different sizes of \mathcal{R}_{WG} (ranging from the apical to the basal prostate slices).

310 *3.2.4. Comparison against the State-of-the-Art Methods*

We compare USE-Net against three supervised CNN-based architectures (i.e., U-Net, pix2pix, and Mixed-Scale Dense Network) and the unsupervised continuous max-flow model [25]. All the investigated CNN-based architectures were trained using the \mathcal{L}_{DSC} loss function (i.e., a continuous version of the *DSC*) [34] through the N pixels to classify:

$$\mathcal{L}_{DSC} = -\frac{2 \sum_{i=1}^N s_i \cdot r_i}{\sum_{i=1}^N s_i + \sum_{i=1}^N r_i}, \quad (6)$$

where s_i and r_i refer to the continuous values in $[0, 1]$ of the prediction map and the Boolean ground truth annotated by experienced radiologists at the i -th pixel, respectively. The \mathcal{L}_{DSC} loss function was designed by Milletari *et al.* [34] to deal with the imbalance of the foreground labels in medical image
315 segmentation tasks.

USE-Net and U-Net. Using four scaling operations, U-Net and USE-Net were implemented on Keras with TensorFlow backend. We used the Stochastic Gradient Descent (SGD) method [66] with a learning rate of 0.01, momentum of 0.9, weight decay of 5×10^{-4} , and batch size of 4. Training was executed
320 for 50 epochs, multiplying the learning rate by 0.2 at the 20-th and 40-th epochs.

pix2pix. This image-to-image translation method with conditional adversarial networks was used to translate the original image into the segmented one [52]. The generator and discriminator (both U-Nets in our implemen-
325 tation) include eight and five scaling operations, respectively. We developed pix2pix on PyTorch. Adam [67] was used as an optimizer with a learning rate of 0.01 for the generator—which was multiplied by 0.1 every 20 epochs—and 2×10^{-4} for the discriminator. Training was executed for 50 epochs with a batch size of 12.

330 *MS-D Net.* This dilated convolution-based method, characterized by densely connected feature maps, is designed to capture features at various image scales [24]. It was implemented on PyTorch with a depth of 100 and width of 1. We used Adam [67] with a learning rate of 1×10^{-3} and trained it for 100 epochs with a batch size of 12.

335 *Continuous Max-flow Model.* This model [25] exploits duality-based convex relaxed optimization [39] to achieve better numerical stability (i.e., convergence) than classic graph cut-based methods [68]. This semi-automatic approach simultaneously segments both \mathcal{R}_{WG} and \mathcal{R}_{CG} under the constraints given in Eq. (2), relying on user intervention. The initialization procedure

340 consists in two closed surfaces defined by a thin-plate spline interpolating
 10-12 control points interactively selected by the user (considering both the
 axial and sagittal views). These 3D partitions estimate the intensity proba-
 bility density functions associated with three sub-regions of background, CG,
 and PZ. This allows for defining the region appearance models for global
 345 optimization-based multi-region segmentation [39].

Since the supervised CNN-based architectures rely on the gold standard
 \mathcal{R}_{WG} for zonal segmentation, we apply the continuous max-flow method on
 CG for single-region segmentation for a fair comparison. Moreover, in our
 tests, a very accurate slice-by-slice \mathcal{R}_{CG} initialization is provided by eroding
 350 the gold standard CG with a circular structuring element (radius = 6 pixels).

The continuous max-flow model [25] was implemented in MatLab[®]
 R2017a 64-bit (The Mathworks, Natick, MA, USA).

3.3. Evaluation Metrics

We evaluate the segmentation methods by comparing the segmented MR
 355 images (\mathcal{S}) to the corresponding gold standard manual segmentation (\mathcal{G})
 using spatial overlap- and distance-based metrics [69, 70, 71]. Those metrics
 are calculated using a slice-wise comparison and then averaged per patient;
 thus, each single result regarding a patient represents an aggregate value.

Overlap-based metrics. These metrics quantify the spatially-overlapping seg-
 360 mented Region of Interest (ROI). Let true positives be $TP = \mathcal{S} \cap \mathcal{G}$, false
 negatives be $FN = \mathcal{G} - \mathcal{S}$, false positives be $FP = \mathcal{S} - \mathcal{G}$, and true negatives
 be $TN = \mathcal{I}_\Omega - \mathcal{G} - \mathcal{S}$. In what follows, we denote the cardinality of the pixels
 belonging to a region \mathcal{A} as $|\mathcal{A}|$.

- *Dice similarity coefficient* [72] is the most used measure in medical image segmentation to compare the overlap of two regions:

$$DSC = \frac{2 \cdot |TP|}{|S| + |G|} \cdot 100. \quad (7)$$

- *Sensitivity* measures the correct detection ratio of true positives:

$$SEN = \frac{|TP|}{|TP| + |FN|} \cdot 100. \quad (8)$$

- *Specificity* measures the correct detection ratio of true negatives:

$$TNR = \frac{|TN|}{|TN| + |FP|} \cdot 100. \quad (9)$$

However, this formulation is ineffective when data are unbalanced (i.e., the ROI is much smaller than the whole image). Consequently, we use the following definition:

$$SPC = \left(1 - \frac{|FP|}{|S|}\right) \cdot 100. \quad (10)$$

Distance-based metrics. As precise boundary tracing plays an important role in clinical practice, overlap-based metrics have limitations in evaluating segmented images. In order to measure the distance between the two ROI boundaries, distance-based metrics can be considered. Let the manual contour G consist in a set of vertices $\{\mathbf{g}_a : a = 1, 2, \dots, A\}$ and the automatically-generated contour S consist in a set of vertices $\{\mathbf{s}_b : b = 1, 2, \dots, B\}$. We calculate the absolute distance between an arbitrary element $\mathbf{s}_b \in S$ and all the vertices in G as follows:

$$d(\mathbf{s}_b, G) = \min_{a \in \{1, 2, \dots, A\}} \|\mathbf{s}_b - \mathbf{g}_a\|. \quad (11)$$

- *Average absolute distance* measures the average difference between the ROI boundaries of \mathcal{S} and \mathcal{G} :

$$AvgD = \frac{1}{B} \sum_{b=1}^B d(\mathbf{s}_b, G). \quad (12)$$

- *Maximum absolute distance* represents the maximum difference between the ROI boundaries of \mathcal{S} and \mathcal{G} :

$$MaxD = \max_{b \in \{1, 2, \dots, B\}} d(\mathbf{s}_b, G). \quad (13)$$

4. Experimental Results

365 This section shows how the CNN-based architectures and the continuous max-flow model segmented the prostate zones, through the evaluation of their cross-dataset generalization ability. Aiming at showing the performance boost achieved by integrating the SE blocks into U-Net, we performed a fair comparison against the state-of-the-art architectures under the same
370 training/testing conditions. In particular, due to the lack of annotated MR images for prostate zonal segmentation, we used three different datasets by composing a multi-institutional dataset. This allowed us to show the SE blocks' cross-dataset adaptive feature recalibration effect, better capturing each dataset's peculiar characteristics. Therefore, we exploited all possible
375 training/testing conditions involving the three analyzed datasets (for a total of 21 configurations) on each dataset to overcome the limitation from the small sample size, confirming the intra- and cross-dataset generalization ability of the CNN-based architectures.

Table 1 shows the 4-fold cross-validation results, as assessed by the *DSC*
380 metrics, obtained under different training/testing conditions (the values of

the other metrics are given in Supplementary Material, Tables S1-S4). For visual and comprehensive comparison, the Kiviati diagrams (also known as radar or cobweb charts) [73, 59] for each CNN-based architecture are also displayed in Fig. 3. Here, we can observe the impact of leaving dataset #3
 385 out of the training set and, at the same time, using it as test set: the corresponding spokes III, VI, and XII generally show lower performance, probably due to the peculiar image characteristics of dataset #3 (comprising the highest number of patients) that are not learned during the training phase on datasets #1/#2. In general, Enc USE-Net performs similarly to U-Net,
 390 which stably yields satisfactory results. More interestingly, Enc USE-Net obtains considerably better results when trained/tested on multiple datasets. Enc-Dec USE-Net (characterized by a higher number of SE blocks with respect to Enc USE-Net) consistently and remarkably outperforms the other methods on both CG and PZ segmentation when trained on all the investigated datasets, also performing well when trained and tested on the same
 395 datasets.

We executed the Friedman’s test to quantitatively investigate any statistical performance differences among the tested approaches. Regarding the three-dataset condition: $p = 0.0009$ and $p = 1.3 \cdot 10^{-6}$ for the CG and
 400 PZ, respectively. Considering all training/testing combinations: $p = 0.01$ and $p = 1.7 \cdot 10^{-10}$ for the CG and PZ, respectively. Since the p -values allowed us to reject the null hypothesis, we performed the Bonferroni-Dunn’s *post hoc* test for both the three-dataset condition and all training/testing combinations [74]. In order to visualize the achieved results, example images segmented by each method are compared in Fig. 4 under the three-
 405

Table 1: Prostate zonal segmentation results of the CNN-based architectures and the unsupervised continuous max-flow model (proposed by Qiu *et al.* [25]) in 4-fold cross-validation assessed by DSC (presented as the mean value \pm standard deviation). The supervised experimental results are calculated under the different seven conditions described in Section 3.1. Numbers in bold indicate the best DSC values (the higher the better) for each prostate region (i.e., \mathcal{R}_{CG} and \mathcal{R}_{PZ}) among all architectures.

	Method	Testing on dataset #1		Testing on dataset #2		Testing on dataset #3	
		CG	PZ	CG	PZ	CG	PZ
Training on dataset #1	MS-D Net	84.3 \pm 1.6	86.7 \pm 1.6	77.3 \pm 4.1	65.6 \pm 11.2	66.2 \pm 3.7	50.9 \pm 1.2
	pix2pix	81.9 \pm 2.2	85.9 \pm 5.0	77.2 \pm 2.9	73.7 \pm 4.3	52.5 \pm 3.2	47.1 \pm 1.3
	U-Net	78.6 \pm 4.1	78.3 \pm 7.6	77.4 \pm 5.4	75.3 \pm 1.4	73.6 \pm 6.2	50.9 \pm 1.5
	Enc USE-Net	79.3 \pm 3.5	77.7 \pm 2.7	81.3 \pm 1.5	74.7 \pm 1.8	75.0 \pm 4.2	50.3 \pm 1.2
	Enc-Dec USE-Net	78.8 \pm 2.9	79.4 \pm 7.9	76.9 \pm 5.5	72.7 \pm 1.7	63.7 \pm 14.6	46.3 \pm 1.8
Training on dataset #2	MS-D Net	78.7 \pm 1.1	70.0 \pm 4.4	86.8 \pm 3.7	81.1 \pm 0.5	83.2 \pm 1.0	54.6 \pm 0.8
	pix2pix	78.3 \pm 0.9	67.3 \pm 3.2	87.1 \pm 2.9	81.8 \pm 1.0	80.0 \pm 2.5	51.1 \pm 1.5
	U-Net	78.6 \pm 1.0	70.9 \pm 3.2	87.7 \pm 2.0	82.4 \pm 2.4	83.8 \pm 1.8	54.9 \pm 1.8
	Enc USE-Net	78.8 \pm 1.4	72.3 \pm 5.6	87.4 \pm 2.5	82.6 \pm 2.1	82.9 \pm 2.5	54.5 \pm 2.0
	Enc-Dec USE-Net	77.5 \pm 2.1	70.6 \pm 5.5	87.8 \pm 2.7	82.8 \pm 1.9	82.7 \pm 1.5	53.6 \pm 1.0
Training on dataset #3	MS-D Net	81.2 \pm 1.3	73.3 \pm 3.7	82.5 \pm 1.9	74.7 \pm 2.0	91.6 \pm 1.1	71.4 \pm 5.6
	pix2pix	79.1 \pm 5.6	64.6 \pm 22.1	81.2 \pm 4.2	66.6 \pm 19.1	89.4 \pm 4.8	62.8 \pm 10.0
	U-Net	75.9 \pm 3.4	63.3 \pm 5.0	82.1 \pm 2.9	66.6 \pm 8.4	91.7 \pm 2.4	76.1 \pm 4.1
	Enc USE-Net	77.3 \pm 3.6	64.7 \pm 6.4	82.7 \pm 4.3	66.7 \pm 15.9	91.5 \pm 3.2	74.0 \pm 7.8
	Enc-Dec USE-Net	76.1 \pm 4.2	58.9 \pm 13.7	81.8 \pm 4.8	67.6 \pm 13.2	90.7 \pm 3.1	76.6 \pm 7.8
Training on datasets #1/#2	MS-D Net	84.4 \pm 3.1	86.5 \pm 2.7	86.4 \pm 2.8	81.2 \pm 1.3	81.7 \pm 2.3	54.9 \pm 2.5
	pix2pix	83.8 \pm 2.6	84.8 \pm 3.1	87.1 \pm 2.7	81.0 \pm 0.4	82.1 \pm 2.5	54.0 \pm 1.8
	U-Net	82.6 \pm 3.3	90.0 \pm 2.7	86.4 \pm 2.0	82.2 \pm 2.7	81.8 \pm 2.1	55.3 \pm 2.5
	Enc USE-Net	81.7 \pm 5.4	90.0 \pm 2.1	87.0 \pm 2.1	82.2 \pm 1.8	80.8 \pm 2.7	55.8 \pm 1.7
	Enc-Dec USE-Net	82.9 \pm 3.4	90.6 \pm 1.8	85.9 \pm 2.1	82.9 \pm 1.4	81.1 \pm 2.7	55.1 \pm 2.1
Training on datasets #1/#3	MS-D Net	85.4 \pm 1.8	87.7 \pm 2.5	80.9 \pm 2.7	72.6 \pm 3.7	91.0 \pm 2.9	72.2 \pm 1.9
	pix2pix	85.2 \pm 1.6	86.8 \pm 2.4	82.7 \pm 1.9	75.7 \pm 3.6	91.5 \pm 1.9	71.0 \pm 3.6
	U-Net	84.8 \pm 0.4	90.4 \pm 2.8	82.1 \pm 2.9	72.5 \pm 4.5	92.6 \pm 1.5	78.9 \pm 4.0
	Enc USE-Net	83.8 \pm 1.4	91.1 \pm 1.4	81.6 \pm 3.7	71.9 \pm 8.1	92.5 \pm 1.9	79.6 \pm 2.1
	Enc-Dec USE-Net	83.3 \pm 3.2	90.4 \pm 2.1	81.5 \pm 4.6	71.8 \pm 6.7	92.2 \pm 2.4	80.8 \pm 1.8
Training on datasets #2/#3	MS-D Net	81.0 \pm 1.3	72.5 \pm 5.6	86.2 \pm 2.5	77.4 \pm 4.7	91.7 \pm 0.9	69.8 \pm 3.6
	pix2pix	81.1 \pm 1.1	73.4 \pm 3.3	87.4 \pm 2.2	79.6 \pm 5.7	92.0 \pm 1.3	71.3 \pm 3.4
	U-Net	79.2 \pm 2.0	65.7 \pm 6.3	88.1 \pm 2.9	81.4 \pm 2.6	92.9 \pm 1.1	77.6 \pm 3.0
	Enc USE-Net	79.8 \pm 1.8	70.3 \pm 7.6	88.5 \pm 2.4	82.0 \pm 3.2	92.8 \pm 1.0	76.3 \pm 2.7
	Enc-Dec USE-Net	79.4 \pm 2.5	67.4 \pm 8.9	88.2 \pm 2.9	82.0 \pm 4.1	93.7 \pm 0.6	76.1 \pm 3.4
Training on datasets #1/#2/#3	MS-D Net	84.8 \pm 4.5	83.6 \pm 6.9	86.8 \pm 2.6	78.6 \pm 5.1	91.1 \pm 1.0	69.4 \pm 4.5
	pix2pix	85.5 \pm 2.6	87.6 \pm 3.5	87.5 \pm 2.0	80.9 \pm 5.3	91.8 \pm 1.3	69.7 \pm 4.8
	U-Net	84.6 \pm 1.9	90.5 \pm 3.0	86.6 \pm 2.0	80.9 \pm 3.3	92.9 \pm 1.1	77.2 \pm 2.0
	Enc USE-Net	84.8 \pm 2.3	91.1 \pm 2.5	87.4 \pm 1.8	81.4 \pm 4.4	93.2 \pm 0.7	79.1 \pm 3.5
	Enc-Dec USE-Net	87.1 \pm 3.6	91.9 \pm 2.1	88.6 \pm 1.5	83.1 \pm 2.9	93.7 \pm 1.0	80.1 \pm 5.5
None	Qiu <i>et al.</i> [25]	78.0 \pm 4.9	75.3 \pm 6.4	71.0 \pm 7.0	77.3 \pm 2.6	82.1 \pm 1.5	61.9 \pm 4.6

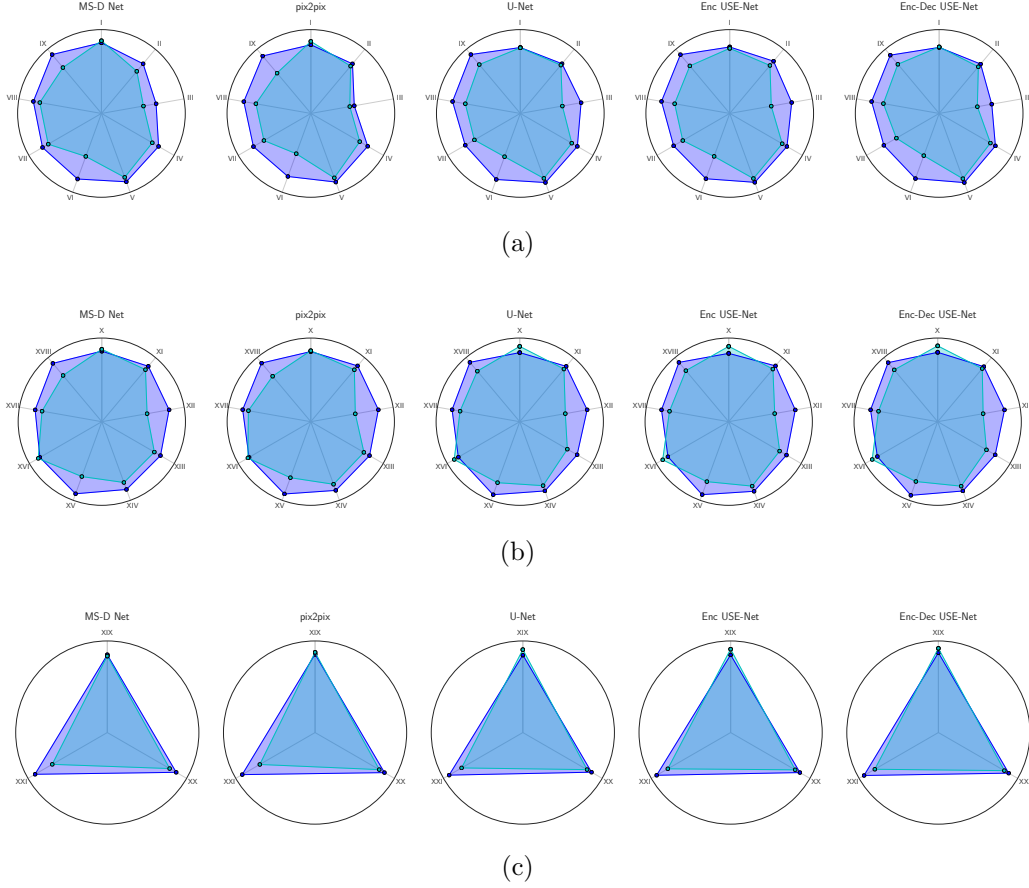


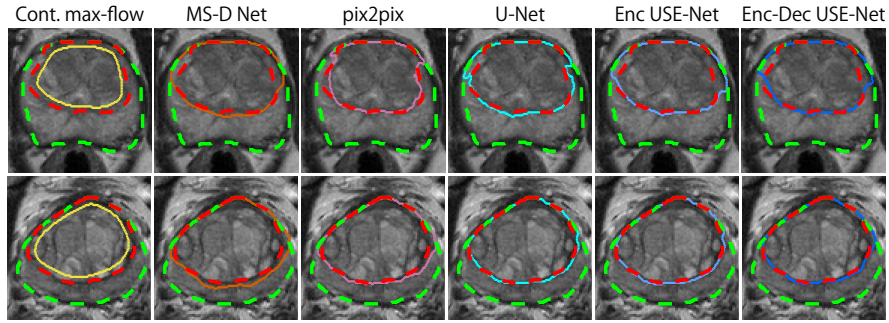
Figure 3: Kiviati diagrams showing the DSC values achieved by each method under different conditions. \mathcal{R}_{CG} and \mathcal{R}_{PZ} results are denoted by blue and cyan colors, respectively.

Each variable represents a “training-set \rightarrow test-set” condition as follows:

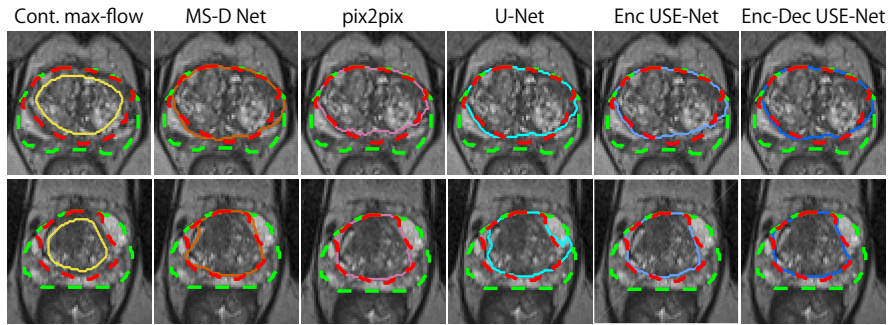
(a) one-dataset training: I) #1 \rightarrow #1; II) #1 \rightarrow #2; III) #1 \rightarrow #3; IV) #2 \rightarrow #1; V) #2 \rightarrow #2; VI) #2 \rightarrow #3; VII) #3 \rightarrow #1; VIII) #3 \rightarrow #2; IX) #3 \rightarrow #3.

(b) two-dataset training: X) #1/#2 \rightarrow #1; XI) #1/#2 \rightarrow #2; XII) #1/#2 \rightarrow #3; XIII) #1/#3 \rightarrow #1; XIV) #1/#3 \rightarrow #2; XV) #1/#3 \rightarrow #3; XVI) #2/#3 \rightarrow #1; XVII) #2/#3 \rightarrow #2; XVIII) #2/#3 \rightarrow #3.

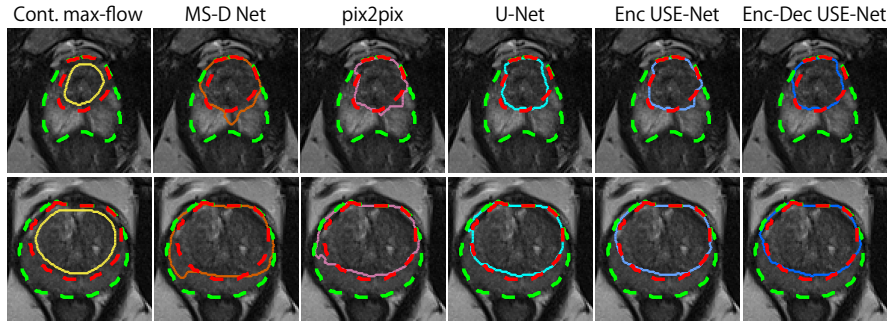
(c) three-dataset training: XIX) #1/#2/#3 \rightarrow #1; XX) #1/#2/#3 \rightarrow #2; XXI) #1/#2/#3 \rightarrow #3.



(a)



(b)



(c)

Figure 4: Segmentation results obtained by the six investigated methods (under the three-dataset training condition) on two different images for each dataset: (a) #1; (b) #2; (c) #3. Automatic \mathcal{R}_{CG} segmentations (solid lines) are compared against the corresponding gold standards (dashed red line). \mathcal{R}_{PZ} segmentations can be obtained from \mathcal{R}_{CG} and \mathcal{R}_{WG} (dashed green line) according to the constraints in Eq. (2).

dataset training condition. The critical difference diagram (Fig. 5) using the Bonferroni-Dunn’s *post hoc* test also confirms this trend, considering *DSC* values for every round of the 4-fold cross-validation.

However, as shown in Fig. 6, Enc-Dec USE-Net shows less powerful
410 cross-dataset generalization when trained and tested on different datasets, achieving slightly lower average performance than Enc USE-Net (considering all training/testing combinations). This implies that the SE blocks’ adaptive feature recalibration—boosting informative features and suppressing weak ones—provides excellent intra-dataset generalization in the case
415 of testing performed on multiple datasets used during training (i.e., when training samples from every testing dataset are fed to the model).

On the contrary, pix2pix achieves good generalization when trained and tested on different datasets, especially under mixed-dataset training conditions, thanks to its internal generative model. MS-D Net generally works better in single dataset scenarios, using a limited amount of training samples,
420 according to [24]. The unsupervised continuous max-flow model achieves comparable results to the supervised ones only when trained and tested on different datasets. However, this semi-automatic approach is outperformed by the supervised methods when trained and tested on the same datasets, as
425 it underestimates \mathcal{R}_{CG} .

The results also reveal that training on multi-institutional datasets generally outperforms training on each dataset during testing on any dataset/zone, realizing both intra-/cross-dataset generalization. For instance, training on datasets #1 and #2 generally outperforms training on dataset #1 during
430 testing on all datasets #1, #2, and #3, without losing accuracy.

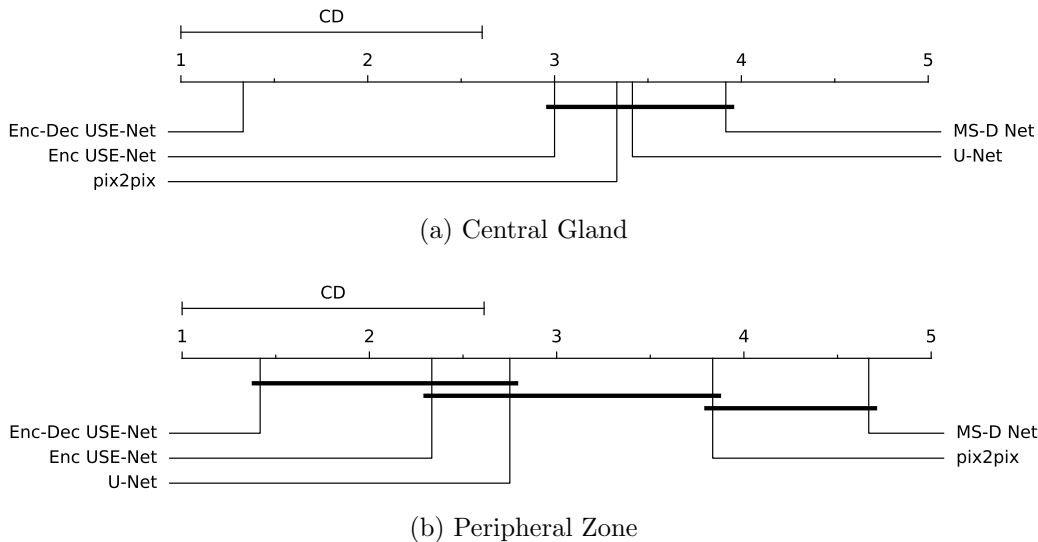


Figure 5: Critical Difference (CD) diagram comparing the DSC values achieved by all the investigated CNN-based architectures using the Bonferroni-Dunn’s *post hoc* test [74] with 95% confidence level for the three-dataset training conditions. Bold lines indicate groups of methods whose performance difference was not statistically significant.

Therefore, training schemes with mixed MRI datasets can achieve reliable and excellent performance, potentially useful for other clinical applications. Comparing the CG and PZ segmentation, the results on the CG are generally more accurate, except when trained and tested on dataset #1; this could be
 435 due to intra- and cross-scanner generalization, since dataset #1’s scanner is different from those of datasets #2 and #3.

The trend characterizing the best DSC accuracy performance, especially in the case of three-dataset training/testing conditions, is reflected by both the SEN and SPC values (Tables S1 and S2). As shown in Tables S3 and S4,
 440 the achieved spatial distance-based indices are consistent with overlap-based metrics. Hence, Enc-Dec USE-Net obtained high performance also in terms

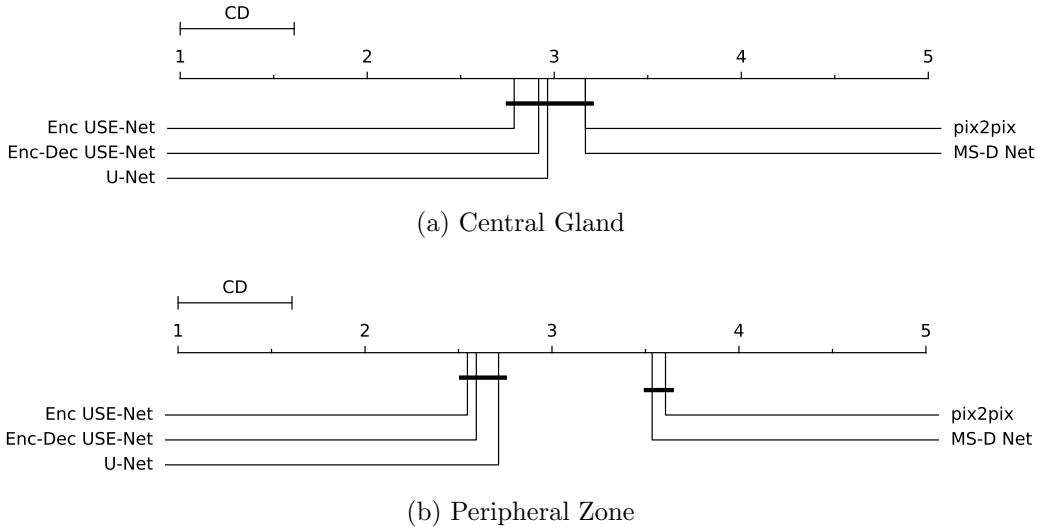


Figure 6: Critical Difference (CD) diagram comparing the DSC values achieved by all the investigated CNN-based architectures using the Bonferroni-Dunn’s *post hoc* test [74] with 95% confidence level considering all training/testing combinations. Bold lines indicate groups of methods whose performance difference was not statistically significant.

of difference between the automated and the manual boundaries.

Considering more permutations in the random partitioning and running multiple 4-fold cross-validation instances may increase the robustness of the results, by evaluating the combination of the multiple executions. However, with particular reference to the three-dataset training/testing condition, where the feature recalibration can effectively capture the dataset characteristics with the most available samples, the Bonferroni-Dunns *post hoc* test showed significant differences in the multiple comparisons among the competing architectures (Fig. 5). On the contrary, no significant statistical difference was detected when considering all training/testing conditions (Fig. 6). The achieved results suggest that cross-validation with a single random permutation is methodologically sound. In addition, we can state

that the patterns arising from the 4-fold cross-validation experiments are
455 not just by chance or biased by the increased training samples, so USE-Net
significantly outperforms the other techniques.

To conclude, the comparison of U-Net and USE-Nets shows the individ-
ual contribution of SE blocks under each of the 21 dataset combinations.
Interestingly, USE-Net is not always superior on one- or two-dataset cases,
460 but consistently outperforms U-Net on three-dataset training/testing. This
arises from USE-Net’s higher number of parameters than U-Net, generally
requiring more samples for proper tuning.

5. Discussion and Conclusions

The novel CNN architecture introduced in this work, Enc-Dec USE-Net,
465 achieved accurate prostate zonal segmentation results when trained on the
union of the available datasets in the case of multi-institutional studies—
significantly outperforming the competitor CNN-based architectures, thanks
to the integration of SE blocks [21] into U-Net [44]. This also derives from
the presented cross-dataset generalization approach among three prostate
470 MRI datasets, collected by three different institutions, aiming at segmenting
 \mathcal{R}_{CG} and \mathcal{R}_{PZ} ; Enc-Dec USE-Net’s segmentation performance considerably
improved when trained on multiple datasets with respect to individual train-
ing conditions. Since the training on multi-institutional datasets analyzed in
this work achieved good intra-/cross-dataset generalization, CNNs could be
475 trained on multiple datasets with different devices/protocols to obtain bet-
ter outcomes in clinically feasible applications. Moreover, our research also
implies that state-of-the-art CNN architectures properly combined with inno-

vative concepts, such as feature recalibration provided by the SE blocks [21], allow for excellent intra-dataset generalization when tested on samples coming from the datasets used for the training phase. Therefore, we may argue that multi-dataset training and SE blocks represent not just individual options but mutually indispensable strategies to draw out each other’s full potential. In conclusion, such adaptive mechanisms may be a valuable solution in medical imaging applications involving multi-institutional settings.

As future developments, we will refine the output images considering the 3D spatial information among the prostate MR slices. Finally, for better cross-dataset generalization, we plan to use domain adaptation *via* transfer learning by maximizing the distribution similarity [20]. In this context, Generative Adversarial Networks (GANs) [75, 76] and Variational Auto-Encoders (VAEs) [77] represent useful solutions.

Acknowledgment

This work was partially supported by the Graduate Program for Social ICT Global Creative Leaders of The University of Tokyo by JSPS.

We thank the Cannizzaro Hospital, Catania, Italy, for providing one of the imaging datasets analyzed in this study.

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