A Survey on U-shaped networks in Medical Image Segmentations

Article *in* Neurocomputing · June 2020

DOI: 10.1016/j.neucom.2020.05.070

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Neurocomputing 409 (2020) 244–258

Contents lists available at ScienceDirect

Neurocomputing

journal homepage: www.elsevier.com/locate/neucom

A survey on U-shaped networks in medical image segmentations

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ARTICLE INFO

Article history:
Received 14 January 2020
Revised 14 April 2020
Accepted 26 May 2020
Available online 1 June 2020
Communicated by Xiaofeng Zhu

Keywords:
U-shaped network
Convolutional neural networks
Medical image segmentation
Extended mechanism

ABSTRACT

The U-shaped network is one of the end-to-end convolutional neural networks (CNNs). In electron microscope segmentation of ISBI challenge 2012, the concise architecture and outstanding performance of the U-shaped network are impressive. Then, a variety of segmentation models based on this architecture have been proposed for medical image segmentations. We present a comprehensive literature review of U-shaped networks applied to medical image segmentation tasks, focusing on the architectures, extended mechanisms and application areas in these studies. The aim of this survey is twofold. First, we report the different extended U-shaped networks, discuss main state-of-the-art extended mechanisms, including residual mechanism, dense mechanism, dilated mechanism, attention mechanism, multi-module mechanism, and ensemble mechanism, analyze their pros and cons. Second, this survey provides the overview of studies in main application areas of U-shaped networks, including brain tumor, stroke, white matter hyperintensities (WMHs), eye, cardiac, liver, musculoskeletal, skin cancer, and neuronal pathology. Finally, we summarize the current U-shaped networks, point out the open challenges and directions for future research.

1. Introduction

Medical imaging play an important role in clinical diagnosis, especially in treatment planning, surgery and prognosis evaluation. Medical images are used to collect potential life-saving information by non-invasive peering at human organs [1]. Rapid and accurate identifications and segmentations of lesions tissues are the basis of diagnosis. With the rapid development and popularization of medical imaging equipments, medical imaging information is provided by magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), digital pathology and microscopy. These medical images can provide exceptional anatomical views of organs. However, it is not easy for radiologists to quantify organs or lesions from these medical images. For instance, CT and MRI images are 2 important diagnostic basis in clinical diagnosis. Both images are frequently in the 3D format, and segmentation of lesions tissues need to be done slice by slice on 2D images. If all medical images are hand-marked by radiologists, it will take up to 15 min per image [2], which is a time-consuming task with low inter-rater agreement [3]. Therefore, it is necessary to develop automated methods which can locate, segment, and quantify the lesion tissues. The segmentation methods are expected to have a broad impact by supporting clinician decisions.

In adjuvant treatment decision, an automatic segmentation method can provide reliable diagnostic evidence for radiologists. It will not only help radiologists examine lesion tissues and make treatment plans for predicting potential treatment risks and benefits, but will also qualitatively and quantitatively analyze damaged tissues, which makes medical trials more reliable and repeatable [4,5]. Another beneficiary is the patients as automatic segmentations can reduce trauma and help them intuitively understand the condition [6,7].

However, there are 3 challenges in medical segmentation tasks. First, the limited number of image samples for specific disease is one of the challenges to segmentation methods. Second, the similar intensity and the changeable position shape and the size of interest lesions case the difficulty in segmentation methods. Third, many factors of capturing images, such as sampling artifacts, spatial aliasing and noise factors may cause the boundary of structures to be indistinct and disconnected. In fact, many researchers have proposed a variety of segmentation methods. In particular, in recent years the developments of deep learning methods have made remarkable achievements in medical image segmentation field.

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https://doi.org/10.1016/j.neucom.2020.05.070
0925-2312/

Deep learning in medical applications have aroused great interest in past few years. These methods attempt to use multiple non-linear transformations to abstract input data at multiple levels and map predicted results. These methods not only learn the non-linear mapping between input data and predicted results, but also learn the hidden features [8]. So far, the most successful image analysis methods are convolution neural networks (CNNs) [9–14]. The breakthrough of CNNs is very important for the development of the medical image segmentations [15]. In these CNN methods, U-shaped networks have made outstanding achievements and thus become the popular technology for medical image segmentations.

Some reviews and researchs on the applications of deep learning to medical image analysis were published by Liu et al. [16], Litjens et al. [17], Shen et al. [18], Suzuki et al. [19], Yu et al. [20], and Chang et al. [21]. They covered a lot of research work. However, the contribution of U-shaped networks in the medical image segmentation field was not reflected in these existing reviews. Since the U-shaped network (U-Net) was made public in 2015, in less than 4 years, it has received more than 5400 references. Most medical image segmentation methods have chosen U-shaped architecture as the basic segmentation framework or chosen the U-Net as the basic comparison method. The motivation of our review is to provide a comprehensive analysis of medical image segmentation methods which are related U-Net/ U-shaped networks. This also include overview tables of most publications, so readers can use to quickly assess the method. Finally, we leverage our own experience with the applications of related U-shaped methods and public datasets in medical image segmentations. We also provide readers with a dedicated discussion on the state-of-the-art methods, and research directions.

To identify relevant papers, we used the Google scholar search engine to query papers with titles or abstracts containing (‘‘U-Net”, ‘‘V-Net”, ‘‘U shape” or ‘‘U-shaped”). The start time of the included articles is 2015, and the deadline is May 1, 2019. This survey comes from more than 100 papers related to medical image segmentation tasks in the search results. Some papers come from academic journals, such as PNAS, IEEE Transactions on Image Processing, Neuroimage and IEEE Transactions on Medical Imaging and some are from related conferences, such as CVPR, ICCV, MICCAI and ISBI, while others are from ArXiv. We re-checked all papers and excluded the papers that had nothing to do with medical images or U-shaped networks. If overlapping work were reported in multiple publications, only the papers with the highest citation rate were included.

With this survey we aim to:

1. Summarize the advancement of U-shaped networks in the field of medical image segmentations.
2. Highlight specific contributions of extended mechanisms based on U-shaped architectures.
3. Present some public datasets and demonstrate the achievements of these extended networks in medical image segmentation application areas.

The rest of this survey is structured as followed. Section 2 reviews the history and architecture of U-shaped networks. Section 3 describes the extended mechanisms based on U-shaped architectures. Section 4 introduces the public datasets used in medical image segmentations. Section 5 provides the main applications. We end with a summary, a critical discussion and an outlook for future research in Section 6.

2. U-net neural network

In 2006, Hinton et al. proposed a classic architecture: encoder-decoder [22]. The initial encoder-decoder architecture was not used for the segmentation task, but for compressing images and denoising functions. For example, encoder is a down-sampling process, and obtains smaller features from input image in the down-sampling process. This process is equivalent to image compression. Decoder is an up-sampling process. During this process, the compressed image is restored to the original image.

In 2015, Ronneberger et al. [23] and Long et al. [24] introduced an encoder-decoder architecture into image segmentation, and proposed a U-Net and a Fully Convolutional Network (FCN), respectively. U-Net was proposed later than FCN, and both network architectures are similar: there are 2 main differences between these 2 networks. The first difference is that U-Net is a symmetric architecture, which consists of 2 parts (encoder and decoder). However, the decoder of FCN is relatively simple. There is only one deconvolution operation in the decoder process, and does not keep up with the convolution architecture. The second difference is the manner of skip connections: FCN uses *add*() as the skip connection to connect encoder and decoder, while U-Net uses *concat*() as the skip connection to connect encoder and decoder. Compared with *add*() method, *conat*() method can help U-Net model to obtain more feature information. This is a key to improve the performance of segmentation methods.

U-Net is a neat end-to-end neural network architecture which is known for its ‘‘U” shape. Meanwhile, U-Net achieved a remarkable success in cell segmentation with the light microscope images. U-Net won the championship with great advantage in neuronal structures segmentation at ISBI challenge 2012. In addition, U-Net got the top ranked in ISBI 2014 challenge for segmentation of Glioblastoma-astrocytoma U373 cells.[1] It achieved an average intersection over union (IOU) of 92%, as opposed to the second best algorithm with an IOU of 83%. Besides, U-Net won the Grand Challenge for Computer-Automated Detection of Caries in Bitewing Radiography at ISBI 2015.[2] It outperformed the second best method by a large margin. Furthermore, U-Net also won the HeLa Cells Tracking Challenge at ISBI 2015.[3] It achieved an average IOU of 77.5% which is better than the second best method with an IOU of 46%. In 2016, Ronneberger et al. further extended the previous U-Net from 2-dimensional (2D) space to 3-dimensional (3D) space and utilized the proposed 3D U-Net to segment dense volumetric images from a sparse annotation in MICCAI 2016 [25]. Moreover, another volumetric convolutional neural network called V-Net was proposed by Milletari et al. in 2016. This network was used to segment prostate volumes [26]. Based on 2D U-Net architecture, Isensee et al. improved the 3D U-Net to segment brain tumors with multi-subregion architectures and achieved competitive results in BraTS 2017 and 2018 challenges [27,28], respectively. A recent study showed that the methods based on the U-shaped architecture achieved the best performance on 6 publicly available segmentation tasks and can automatically adapt to any given dataset [29]. Due to its excellent performance and elegant architecture, the U-shaped networks have shown the best performance in segmentations of medical images [30], and quickly become a benchmark in medical image segmentations.

2.1. Network architecture

A classical architecture of U-Net is shown in Fig. 1. U-Net is composed of a contracting path and an expanding path, which correspond to an encoder and a decoder, respectively. The contracting path consists of a series of down-sampling operations, which is used to reduce the scale of images and obtain context information.

[1] https://cs.adelaide.edu.au/c~arneiro/isbi14_challenge/.
[2] www-o.ntust.edu.tw/c~weiwang/ISBI2015/challenge2/index.html.
[3] https://cs.adelaide.edu.au/z~hi/isbi15_challenge/index.html.

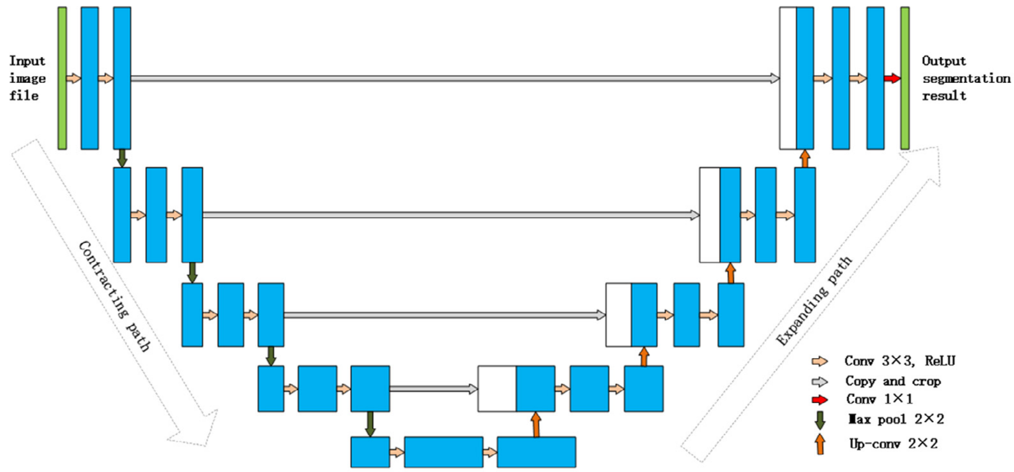

Fig. 1. The architecture of a U-Net.

The expanding path consists of a series of up-sampling operations, which is used to precisely locate pixels/ voxels and restore images.

Specifically, as an encoder-decoder network, U-Net architecture can be divided into 4 parts: a) convolution operations, b) down-sampling operations, c) up-sampling operations and d) concatenation operation. The contracting path consists of repeated operations of convolution and down-sampling layers. Symmetrically, the expanding path is made up of convolution and up-sampling layers. In order to fuse more context information, concatenation operations are adopted between contracting and expanding paths at the same depth level.

2.1.1. Convolution operation

Convolution is the most important operation in deep learning methods. It is mainly used to extract features from input data. However, a simple convolution is not enough in medical image segmentation. Because a simple convolution is insufficient for extracting abstract features information from input images, since a lot of image features are lost in the convolution process. In order to alleviate this problem, a convolution is frequently combined with several normalization methods such as Batch Normalization [31], Layer Normalization [32], Instance Normalization [33] and Group Normalization [34]. In addition, activation function is also an important part of a neural network. Activation function is used to realize nonlinearity between input and output of neurons. Common activation functions include: ReLU [35], LReLU [36], PReLU [37] and RReLU [38]. Some of them not only speed up the convergence, but also avoid the gradient vanishing problem. In the classical architecture of the U-Net, each convolutional operation is usually followed by a normalization and an activation function, which constitutes a high-performance convolutional block [27].

2.1.2. Down-sampling operation

In image segmentations, down-sampling operation reduces the resolution of feature maps while retaining the significant information. Max pooling and average pooling are 2 common strategies used in down-sampling operation. The pooling strategy uses higher level abstraction to represent image features. Neural networks use pooling strategy to integrate feature points within small neighborhoods after several convolution layers to get new features. The max pooling is beneficial for extracting the extreme features such as edges, while the average pooling makes features smoother. The max pooling was used in original U-Net. Although pooling can be positive to have invariance and to remove irrelevant details, it also has a negative impact on removing important information. To address this drawback, Milletari et al. [26] and Isensee et al. [27] used convolutional blocks with a stride of 2 instead of the pooling operations. The advantages of this strategy is that it not only retains the image details but also reduces the image resolution to be suitable for understanding and learning.

2.1.3. Up-sampling operation

Up-sampling aims to magnify the original image and display it at a higher resolution. Compared with down-sampling operation, up-sampling operation mainly increases the resolution of feature maps in neural networks. That is to say, it allows network to transfer context information from the low spatial resolution layer to the higher spatial resolution layer in the up-sampling stage. The commonly used up-sampling methods are: bilinear, deconvolution and unpooling. Almost all image segmentation methods use an interpolation algorithm (one of bilinear algorithms) in the up-sampling operation [39], and so is the U-Net. The interpolation algorithm inserts new elements between the pixels in image matrix. This algorithm is mainly used to repair the uneven lines in images. Compared with other methods, the interpolation algorithm is more suitable for image segmentations.

2.1.4. Concatenation operation

Concatenation is one essential operation in U-Net network. It is used to pinpoint pixel locations. In U-Net network, the high resolution feature maps from the contracting path are combined with that from the expanding path in the same depth layers. Some researchers extended the concatenation operation in U-Net. For instance, the studies of Milletari et al. have shown that the extended concatenation operations not only improve the quality of the final result, but also shorten the convergence time of the training [26]. In addition, the attention concatenation is the latest and efficient way of concatenation operations [40].

2.2. Advantage

There are usually 2 challenges for CNNs in medical image segmentations: One is the limited number of samples for training. Another is that increase of the depth and width of CNNs is likely to cause the problem of gradient vanishing problem or gradient exploding problem. Most researchers tried to change the network architectures to alleviate these 2 challenges. The appearance of U-Net alleviates those 2 challenges. Compared with other CNN models, U-Net has the following advantages: 1. Supporting a limited number of samples to train network. 2. Realizing image features with a multi-scale recognition and fusion. 3. Having a simple and flexible structure. 4. Obtaining high quality pixel level segmentation results.

The original U-Net not only shows a good performance in medical segmentation applications, but also provides a flexible and extensible structure. So the improved model can adapt to new tasks. In the next section, we introduce some U-Net-related models.

3. Improved mechanisms

Despite the original U-Net network has shown outstanding performance in segmenting medical images, the classical U-Net architecture also have some defects in certain aspects. Therefore, based on the U-shaped architecture, researchers have proposed various improved mechanisms to improve the performance of the model, such as: residual mechanism, dense mechanism, dilated mechanism, attention mechanism, multi-module mechanism, and ensemble mechanism. The segmentation models built on these extension mechanisms are the potential successors of the U-Net architecture. In the following section, we introduce these improved mechanisms based on U-shaped architecture since 2015. This survey includes over 100 papers, and the pie chart of various improvement mechanisms in the literature is shown in Fig. 2. It is easy to observe that the residual and ensemble mechanisms are mostly used in these papers.

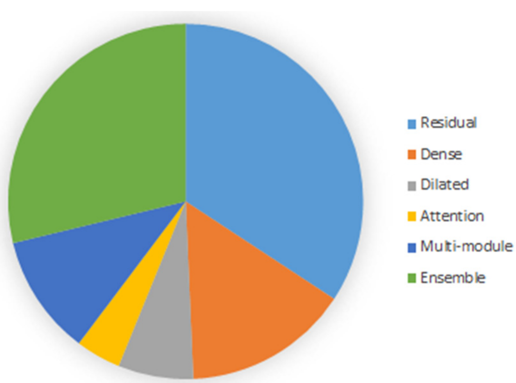

Fig. 2. The pie chart of various improvement mechanisms in these literatures.

3.1. Residual mechanism

He et al. proposed a residual deep convolution network (ResNet) in 2015 [41]. ResNet won the championship of image classification, detection and location in ImageNet challenge. ResNet used residual convolutions to improve feature utilization and thus increase the performance of networks. In addition, residual mechanism adds the depth of the network while ensuring good performance. With the increase of network depth, this mechanism also alleviates the gradient vanishing problem in deep networks.

ResNet was originally used for image classification [41]. After that, many researchers introduced the essence of ResNets into the field of medical image segmentations by combining residual blocks and U-shaped architectures. As shown in Table 1, Fakhry et al. proposed a residual deconvolutional network (RDN) based on U-Net [42]. RDN consists of 2 information pathways that capture full-resolution features and contextual information, respectively. Residual convolution not only deepens RDN network, but also contains enough context information and provides multi-scale full resolution features. Furthermore, Chen et al. embedded residual blocks into a U-shaped segmentation network for obtaining more contextual information [43]. Residual blocks consist of different size kernels which can aggregate feature mappings from different branches. Similarly, Alom et al. also embedded residual blocks into the U-shaped architecture for training a deep network and ensuring better feature representation for medical image segmentation tasks [44]. Chen et al. proposed a VoxResNet basis on the U-shaped architecture [45]. They took advantage of the characteristics of residual networks to alleviate the degradation of training deep networks, and increased the network depth to improve segmentation performance. Likewise, in order to alleviate the gradient vanishing problem of the back-propagation flow and improve the convergence speed, Guerrero et al. also applied the residual structure to WMH lesion segmentations [46]. In addition, Drozdzal et al. [47], Clèrigues et al. [48], Ibtehaz et al. [49] and Liu et al. [50] also used the residual mechanisms in their studies.

3.2. Dense mechanism

Huang et al. published the best paper on CVPR conference in 2017 [61]. They proposed a deep network, named DenseNet, which breaks away the traditional idea of the ResNet and expands reception to improve network performance. Compared with ResNet,

Table 1
Overview of papers using residual mechanism techniques in U-shaped networks.

Model name	Image type	Target
FCNs [51] (2016)	EM images	Neural structures
RDN [42] (2017)	EM images	Neural structures
DRINet [43] (2018)	CT, MRI	CSF, Multi-organ, Brain tumor
FC-ResNet [47] (2018)	CT, MRI	Liver, Prostate
R2U-Net [52] (2018)	Nuclei images	Nuclei
RA-UNet [53] (2018)	CT	Liver tumor
R2U-Net [52] (2018)	Retina image, Photograph, CT	Blood vessel, Skin cancer, Lung
SUNet [48] (2018)	MRI	Stroke lesion
VoxResNet [45] (2018)	MRI	Brain structures
ResU-Net [54] (2018)	MRI	WMH
uResNet [46] (2018)	MRI	WMH
MultiResUNet [49] (2019)	Microscopy, dermoscopy, endoscopy imageS, MRI	Neural structures, Electron microscopy, Skin lesions, Colonoscopy, Brain tumor
CNN [55] (2019)	MRI	Brain tumor
DRUNet [56] (2019)	MRI	Brain tumor
CE-Net [57] (2019)	Retina image, CT, Endoscopy Image, Retina image	Optic disc, Lung, Cell contour, Retinal OCT layer
CNN [58] (2019)	MRI	Brain tumor
Res-CNN [50] (2019)	MRI	Stroke
STRAINet [59] (2019)	MRI	Prostate
AnatomyNet [60] (2019)	CT	Head and Neck

DenseNet was embedded a more radical dense connection strategy: interconnecting all layers, specifically each layer accepts all the layers in front of it as its additional input. From feature point of view, by feature reusing and bypass settings, DenseNet not only greatly reduces the amount of network parameters, but also alleviates the gradient vanishing problem when the back-propagation flows in deep networks.

DenseNet is a convolutional neural network with dense connections. Dense mechanism is the essence of this network. Dense mechanism allows a network to obtain the maximum information flow and the gradient flow. At the same time, this mechanism can inhibit the problem of gradient vanishing in the process of iteration and reduce the number of parameters when training networks. Dense block is the presentation of the dense mechanism. In a dense block, there is a direct connection between any 2 layers, this means that input of each layer of network is the union of the output of all the previous layers, and feature maps learned by this layer are passed directly to all layers behind it as input.

Embedding dense blocks into a network not only alleviates the gradient vanishing problem, but also makes segmentation networks much wider and deeper. In many studies of lesion segmentations, dense blocks were embedded into U-shaped networks to improve the segmentation performance. As shown in Table 2, Li et al. proposed a hybrid densely connected U-Net (H-DenseUNet) for liver and tumor segmentation [62]. H-DenseUNet inherits the advantages of both densely connected paths [61] and U-shaped network [23]. H-DenseUNet realizes hierarchical aggregation volume contexts by combining 2D and 3D DenseUNets. In addition, Liu et al. embedded dense blocks into 2 symmetrical U-shaped networks [63]. They used multi-kernels to extract effective features from sparse pixels, and verified the performance of the proposed network on 2 open challenges: sub-acute ischemic stroke lesion segmentation (SISS) and acute stroke outcome/penumbra estimation (SPES). Similarly, Zhang et al. proposed a gland segmentation network, which consists of 3 different multi-scale dense connections with U-shaped architectures [64]. Likewise, some researchers also embedded dense blocks and residual blocks into U-shaped architectures for medical image segmentations. For instance, Chen et al. proposed a DRINet for 3 different segmentation tasks [43]. DRINet inherits the architecture of U-Net, and has an analysis path and a synthesis path. The analysis path is composed of the stack dense blocks rather than the traditional convolution layers. The synthesis path consists of residual blocks and unpooling blocks. In addition to the above extended models, the other models in Table 2 also show good performance in different organ segmentation tasks.

3.3. Dilated mechanism

Dilated convolution was first introduced into the field of semantic image segmentation by Yu et al. in 2015 [71]. Traditional CNNs perform convolution and pooling operations on the input images, which can reduce input image size and increase the receptive field in the down-sampling process. However, image segmentation prediction is the output of pixel-wise (voxel-wise), it is necessary to restore small-sized images to the size of input image by up-sampling process. In the process of image size reduction and enlargement, some feature information is lost. The advantage of dilated convolution is without pooling operations, which can alleviate the loss of feature information in down-sampling and up-sampling processes. Dilated convolution also enlarges the receptive field size, so that the output of each convolution contains a larger range of feature information.

Compared with an ordinary convolution, there is an additional parameter named dilation rate in dilated convolution. Dilated rate is mainly used to represent the size of expansion. The similarity between dilated convolution and ordinary convolution is that the size of convolution core is the same. In a neural network that uses dilated convolution instead of ordinary convolution, a number of training parameters do not increase. However, dilated convolution can make the model obtain larger receptive field size and reduce the loss of feature information, it will help to improve the performance of the model.

Dilated convolution first comes from semantic image segmentations [71]. Dilated convolution not only has a simple and elegant structure, but also helps to improve the performance of segmentation models. As shown in Table 3, Nie et al. applied dilated convolution in a novel deep network (STRAINet) to segment of pelvic organs from MRI images [59]. Dilated convolution helps STRAINet to gain a larger receptive field at the lowest cost of memory. In addition, Dolz et al. embedded 2 different scale dilated blocks into a dense network for ischemic stroke lesion segmentations [70], they used multiple dilated convolutions to handle the variability size of lesions and prevent them from losing during training. Likewise, Tureckova et al. proposed a 3D U-shaped segmentation model that was derived from the model presented by Isensee et al. [27]. Tureckova et al. used dilated convolution as input convolution of the network, which outperforms the original architecture in nearly all used evaluation metrics [72]. Furthermore, Vesal et al. [73] and Li et al. [56] also used the dilated convolution to segment left atrial and brain tumors, respectively.

Attention mechanism in deep learning originates from the attention mechanism of human brain [75]. When human brain receives external information, such as visual information and auditory information. Brain does not processes and understand all information, but only focuses on some significant or interesting information, which helps to filter out the unimportant information and improve the efficiency of information processing. In deep learning methods, attention mechanism was first used to improve the distinguish ability on the recurrent neural network (RNN). Then it was widely used in many fields such as machine translation, speech recognition, image segmentation and so on [76–79]. In 2014, a recurrent model of visual attention (RAM) was proposed by the Google Mind team, which attracted the attention from a large number of researchers [75]. Subsequently, Bahdanau et al. introduced attention mechanism into NLP field [76]. Then RNN models consisting of the attention mechanism are applied to various NLP tasks [80].

Recently, how to use attention mechanism in medical image segmentations has became a hot research topic. As shown in Table 4, Jin et al. were the first researchers to introduce attention mechanism into medical image segmentations [40]. They proposed a 3D hybrid residual attention-aware segmentation method (RA-UNet). Attention mechanism was used in RA-UNet to extract contextual information by combining low-level feature maps with high-level ones, which helps models to compensate the missing feature information. Similarly, Oktay et al. proposed a novel attention gate (AG) model for segmenting abdominal organs from 2

Table 2
Overview of papers using dense mechanism techniques in U-shaped networks.

Model name	Image type	Target
Dense-CRFs [65] (2017)	MRI	Stroke
DFCN [66] (2017)	MRI	Cardiac
DRINet [43] (2018)	CT, MRI	CSF, Multi-organ, Brain tumor
DenseNet [67] (2018)	MRI	Brain tumor
3D-SkipDenseSeg [68] (2018)	MRI	Brain tumor
DenseNet [69] (2018)	MRI	Brain tumor
H-DenseUNet [62] (2018)	MRI	Intervertebral disc (IVD)
MDU-Net [64] (2018)	EM images	Neural structures
MK-DCNN [63] (2019)	MRI	Stroke and penumbra
CNN [70] (2018)	MRI	Stroke and penumbra

Table 3
Overview of papers using dilated mechanism techniques in U-shaped networks.

Model name	Image type	Target
CNN [72] (2019)	CT	Stroke
CSAU [74] (2019)	Eye-fundus image	Retinal vessel
RA-UNet [53] (2018)	CT	Liver tumor

Table 4
Overview of papers using attention mechanism techniques in U-shaped networks.

Model name	Image type	Target
Attention U-Net [81] (2018)	CT	Liver and pancreas
DRUnet [56] (2019)	MRI	Brain tumor
3D CNN [73] (2018)	LGE-MRI	Left atrial chamber
RA-UNet [53] (2018)	CT	Liver tumor
STRAINet [59] (2019)	MRI	Prostate

large CT medical datasets [81]. AG model can automatically learn to focus on target of varying shapes and sizes. In addition, Li et al. developed a connection sensitive attention U-Net (CSAU) for retinal vessel segmentation [74]. Before outputting predicted result, CSAU integrated connection sensitive loss and AG concatenated attention weights to features. Experiments illustrated that this strategy can improve the accuracy on detailed vessels.

3.4. Multi-module mechanism

Multi-module mechanism is a general term for a class of methods, which uses multiple neural networks to improve segmentation performance. It is widely used in many deep learning methods [63,64,82–86]. These methods are usually structured in containing multi-scale or multi-kernel formats, which contain encode informative and discriminative features covering multiple granularity levels. The internal representations of these methods have different regions of interest, and allow the construction of multi-grained feature information.

Table 5 shows some multi-module U-shaped networks which were used in medical image segmentation field. Multi-module networks can process high and low resolution images at the same time, which helps networks to obtain complementary feature information. These segmentation networks are usually used to conjunct with other mechanisms. For example, Zhang et al. proposed a multi-scale U-shaped network for gland segmentations [64], which also consists of some dense convolutions. The proposed network can directly fuse the neighboring different scale feature maps from both higher layers and lower layers, which can strengthen the feature propagation in current layer and reduce over-fitting problem. Similarly, an end-to-end multi-kernel deep convolution neural network (MK-DCNN) was proposed for stroke MRI segmentation [63]. MK-DCNN consists of 2 sub-densenets that with different convolution kernels. MK-DCNN can extract more image features than that of the single DCNN, which helps improve the performance of the model. In addition, 2 cascade of 3D U-Nets and a multi-scale 3D U-Net were used for brain tumor segmentations [84,86,87], respectively.

Table 5
Overview of papers using Multi-module mechanism techniques in U-shaped networks.

Model name	Image type	Target
CNNs [70] (2018)	MRI	Stroke and penumbra
CNNs [84] (2019)	MRI	Brain tumor
V-Net [87] (2019)	MRI	Brain tumor
MS-DCNN [88] (2018)	CT	Stroke
MK-DCNN [63] (2019)	MRI	Stroke and penumbra
Multi-scale Masked U-Net [86] (2018)	MRI	Brain tumor

3.5. Ensemble mechanism

In deep CNNs, ensemble mechanisms are also used to reduce the over-fitting problem in the training process [89]. An ensemble module consists of a set of parallel neural networks, which can process the same input data in parallel and finally their outputs are combined to complete the segmentations [89]. It consists of a main segmentation network and a pre-processing module or a post-processing module. The pre-processing module is used to roughly process input images, the main segmentation network is used to segment target lesions, and the post-processing module is used to refine segmentation results. Most times, the performance of ensemble modules is better than that of a single subnet. In an ensemble network, subnets can learn different attributes from the training data during the batch learning processing [90].

As shown in Table 6, there are various ensembles models which consist of U-shaped networks and other models. For example, Kamnitsas et al. constructed an ensemble of multiple models and architectures (EMMA) for brain tumor segmentations [92]. EMMA won the brain tumor segmentation challenge (BraTs) 2016. Similarly, Li et al. presented a study using deep neural networks and n U-shaped models to automatically detect WMH from multi-modality MRI images [90]. In order to further study the segmentation performance of ensemble models, Han et al. investigated 2 types of novel U-shaped architectures for medical image segmentations [96]. One is a dual frame U-shaped architectures that can get residual signals in the low-resolution path. Other is a tight frame U-shaped architecture with the orthogonal wavelet frame. Both architectures exhibited better performance than that of a standard U-Net [95]. In addition, Jin et al. proposed an end-to-end Deformable U-Net (DUNet) for retinal vessel segmentations [40], which exploited the local features of retinal vessels with a U-shaped architecture. DUNet captures the retinal vessels at various shapes and scales by adaptively adjusting the receptive fields according to the scales and shapes of vessels. Likewise, Fu et al. proposed an ensemble deep learning system for the cup of glaucoma segmentation [99]. They introduced the polar transformation technology to the ensemble system, and combined with a multi-scale U-shaped convolutional network.

4. Public datasets

There are lots of medical image segmentation methods proposed during last years. However, some datasets used in these methods are not available. In order to get a deeper understanding, we discuss some of the most widely used public datasets on medical image segmentations, which are summarised in Table 7 (Medical datasets correspond to websites are shown in Appendix A). All datasets listed in Table 7 and each dataset provides the ground truth. These datasets can be divided into 2 parts according to the nature of the data: 2D or 3D. X-ray images are in 2D from and most CT and MRI images are in 3D form.

The traditional segmentation methods frequently use 2D images as inputs, such as threshold method [103–105], fuzzy technique [106], modified context-sensitive gaussian mixture model [107], adaptive outlier detection method [108], morphological segmentation method [109], and region-growing technique [110]. These segmentation methods only consider the information in a single image and treat each 2D images as a separate sample. Most deep learning segmentation methods also used 2D medical images as inputs [23,42,43,47,57,111]. This is a simple way to segment medical images. With the advent of computer hardware and GPU

Table 6
Overview of papers using Ensemble mechanism techniques in U-shaped networks.

Model name	Image type	Target
M-net [91] (2017)	MRI	CSF
EMMA [92] (2017)	MRI	Brain tumors
UNet++ [93] (2018)	CT	Liver, lung nodule
Two-stream U-Net [94] (2018)	EM images	Neural structures
DUNet [40] (2018)	Photographs	Retinal vessel
3D U-Nets [95] (2019)	MRI	Gliomas brain tumors
Dual and tight U-Nets [96] (2018)	CT	Abdomen
Ensemble FCNs [90] (2018)	MRI	WMH
InfiNet [97] (2018)	MRI	CSF
Multi-stream 3D U-Net [98] (2018)	MRI	Prostate
M-Net [99] (2019)	Images	Glaucoma
3D-ESPNet [100,101] (2019)	MRI	Brain tumors
MHL [102] (2019)	DCE-MRI	Breast tumor

Table 7
Overview of medical datasets used in U-shaped networks.

Dataset	Sample number, Image types	Target
BraTS 2015	274/110, MRI (3D)	Brain tumor
BraTS 2016	200/191, MRI (3D)	Brain tumor
BraTS 2017	285/146, MRI (3D)	Brain tumor
BRATS 2018	285/191, MRI (3D)	Brain tumor
MRBrainS13	36/15, MRI (3D)	WM, GM and CSF
MRBrainS18	7/23, MRI (3D)	WM, GM and CSF
SPES 2015	30/20, MRI (3D)	Acute stroke lesion
SISS 2015	28/36, MRI (3D)	Ischemic stroke lesion
ISLES2016	35/40, MRI(3D)	Ischemic stroke lesion
ISLES2017	43/32, MRI(3D)	Ischemic stroke lesion
ISLES2018	63/40, CT(3D)	Ischemic stroke lesion
iSeg 2017	10/13, MRI (3D)	WM, GM and CSF
WMH 2017	60/110, MRI(3D)	WMH
IBSR	18, MRI (2D)	NITRC
Head&Neck	25/15, CT (2D)	Head and Neck
ACDC 2017	100/50, MRI (3D)	Cardiac
DSB 2015	191612/171920, MRI (2D)	Cardiac
LIDC-IDRI	244527, CT (2D)	Lung
LowDoseCT	10/20, CT (2D)	Low dose abdomen
PROMISE 2012	50/30, MRI (3D)	Prostate
LiTS 2017	130/70, CT (2D)	Liver tumor
ISIC 2017	2000/600, Dermoscopic image (2D)	Skin
ISIC 2018	2594/1000, Dermoscopic image (2D)	Skin
GlaS	85/80, Histology image (2D)	Gland
NIH-TCIA	19328, CT (3D)	Pancreas
IVD 2018	8/6, MRI (3D)	Intervertebral disc
STARE	400, Photograph (2D)	Retina
HRF	45, Photograph (2D)	Retina
IDRiD	516, Fundus images (2D)	Retinal
ORIGA	650, Fundus images (2D)	Glaucoma
ISBI 2012	30/30, Microscopy images (2D)	Neuronal
DRIVE	20/20, Photograph (2D)	Blood vessels

servers, more and more researchers use 3D medical images as input of segmentation methods. There are 2 main ideas for using 3D medical images as deep learning methods inputs: (1) Conversing the 3D image into 2D image slices, then using 2D slices as inputs of segmentation methods [46,50,63,88,112–115]. Finally the predicted 2D results are stitched into 3D form. This approach has a drawback is that although 2D slice makes full use of the information in the entire 2D slice, it ignores the relationship between several adjacent slices and loses the correlation between global slice sequences. (2) Using 3D images as inputs [26,73,116–120]. Compared with using 2D images, using 3D images as input can obtain more semantic information, which helps improve the performance of segmentation models. However, the number of parameters for training 3D network is much more than that for training 2D networks, which leads to the large amount of time required for training models. In addition, processing 3D images requires high-performance GPU and larger video memory server, which are also the challenge of 3D image segmentations. Therefore, it is necessary to cut 3D images into 3D patches, then apply 3D CNNs on each patch [121–126]. The advantage is that the global slice sequence information can be taken into account, while the disadvantage is that they lack the pre-trained model parameters for 3D CNNs.

2D images and 3D images have their own advantages in segmentation tasks. In the same segmentation task, using 3D images as input can result in slightly better segmentation than using 2D images, but it takes longer training time, and needs much powerful hardware devices. In the study, whether to use 2D images or 3D images as the input of the segmentation models depends on the nature of images and the condition of the hardware devices.

5. Application areas

Based on these datasets introduced in the previous section, in this section, we present an overview of the U-shaped networks applications to the various areas in medical imaging. We highlight some key contributions and discuss the performance in different application areas. The main application areas are shown in Fig. 3.

5.1. Brain

As shown in Tables 1–6, U-shaped networks have been extensively used for brain image segmentations in several different application domains, such as: brain tumors, stroke lesions and WMH lesions. The challenges for brain tissue segmentations in medical images are twofold: 1. Segmentation methods cannot precisely segment the boundaries of different lesions. 2. Patients often have other diseases, which have similar intensities to target lesions. However, the U-shaped segmentation networks have achieved remarkable results in brain tissue segmentations.

5.1.1. Brain tumor

Brain tumor is one of the most dreadful types of cancer. The noninvasive evaluation of brain tumors can provide valuable information for diagnosis and prognosis. Due to unpredictable appearance and shape of brain tumors, accurate segmentation of brain tumors from multi-modality medical images is one of the most challenging tasks in medical image studies.

From 2012 to 2018, Medical Image Computing and Computer Assisted Intervention (MICCAI) provides a series of available datasets about brain tumor in MRI scans (BraTS 2012–2018). Many researchers have devoted themselves to this research. For instance, Dong et al. proposed a 3D U-shaped network on BraTS 2015 challenge [127], which obtained the outstanding segmentation performance. Similarly, Isensee et al. developed a 3D network that was also inspired by the U-shaped network. The proposed network not only achieved the stat-of-the-art on BraTS 2015, but also was one of the top ranked methods on BraTS 2017 [27]. In addition, in 2017, Kamnitsas et al. proposed a dual pathway 3D CNN for brain tumor segmentations in BraTS 2015 challenge [122]. They employed the dual-pathway architecture to obtain multiple scales feature information and used fully connected conditional random field to remove false positives. The proposed network was the top ranked methods on BraTS 2015. Likewise, Hussain et al. proposed a 3D DCNN segmentation network and evaluated it on BraTS 2013 and BraTS 2015 challenge [128]. In all above studies, the input MRI images are in 3D. As far as we know, there is no 2D segmentation network for these brain tumor segmentation challenges.

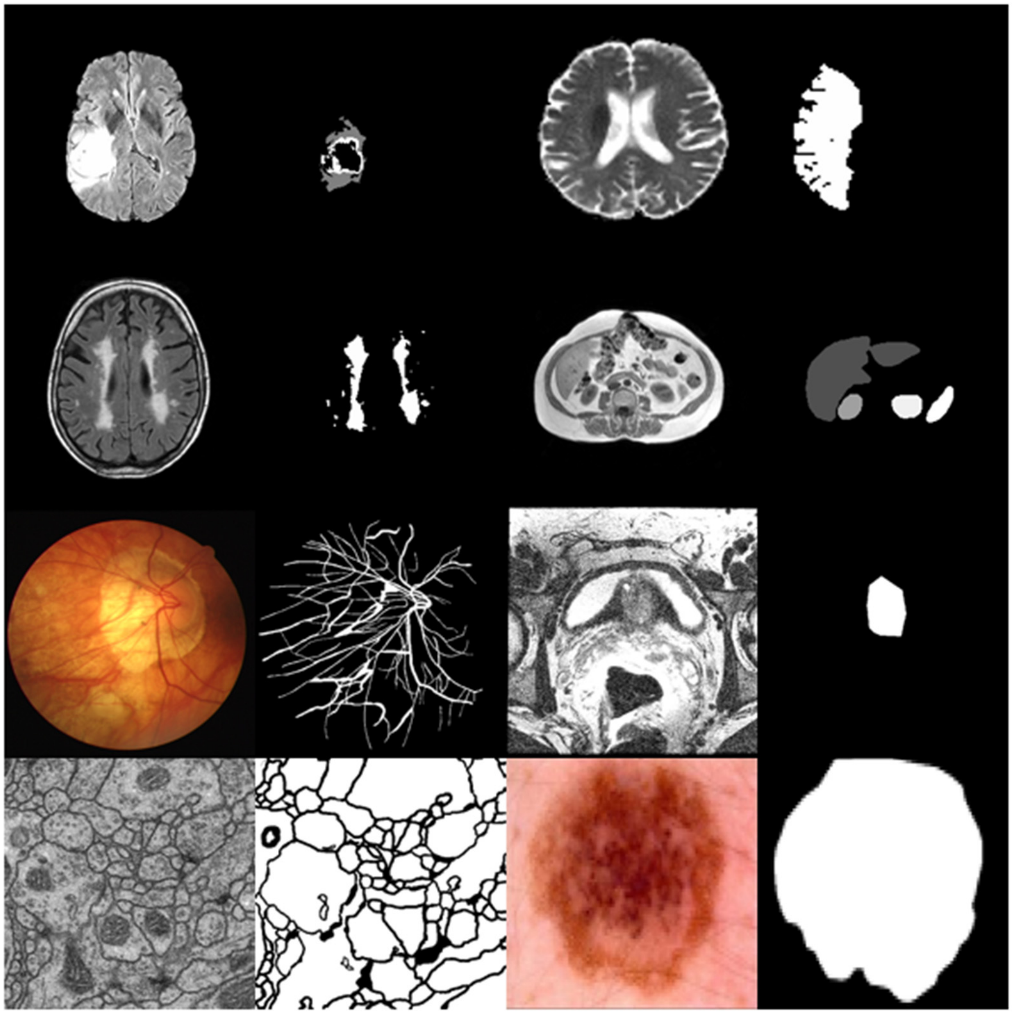

Fig. 3. Collage of several medical imaging applications with U-shaped networks. The first and third columns are original images, and the second and fourth columns are ground truths.

5.1.2. Stroke and penumbra

Stroke is the second cause of death and disability worldwide. Ischemic stroke is the main sub-type of stroke diseases. It is often caused by local thrombosis or embolic causes. Penumbra is a lesion tissue that surrounds stroke lesion. Correct assessment of the presence, location, extent and evolution of stroke and penumbra lesions is great significance for treatment and prognosis. As shown in Table 7, Ischemic Stroke Lesion Segmentation (ISLES) challenge provides 5 public stroke image datasets for researchers and a fair and direct platform for segmentation methods.

ISLES 2015 provides 2 sub-challenges (SPES and SISS). SPES is a challenge that aims to segment penumbra lesion of the acute stroke, while SISS is a challenge that aims to segment stroke lesion of the ischemic stroke. CH-Insel (the team of McKinley et al.) and UK-Imp2 (the team of Konstantinos et al.) are the top ranked methods on 2 sub-challenges [129], respectively. In addition, the networks proposed by participating teams lianl1 and clera1 showed the best robustness on both sub-challenges [63]. In 2016, Choi et al. proposed an ensemble segmentation model that consisted of 2 deep convolutional neural networks. The ensemble model inherited the advantages of FCN and U-Net [130], which was the top ranked method in ISLES 2015 challenge. Furthermore, Choi et al. proposed another ensemble segmentation model that consists of residual U-Net [130] and spatial pyramid pooling [131], this model was the top ranked method in ISLES 2017 challenge. Song et al. proposed a 3D multi-scale U-Net that obtained the top ranked in ISLES 2018 challenge [132]. Although these challenges were very successful, but the best performance segmentation methods was unsatisfactory in these challenges. For example, the presence of similar lesions in the limited number of images the performance of the models [129]. How to cross this gap is still one of the challenges we should focus on.

5.1.3. WMH

White matter hyperintensities (WMH) is one of the main small vessel disease in brain [133]. A dedicated review about automated WMH segmentation techniques on medical image analysis [134] has noted that segmentation and quantification of WMH volume plays an importance role in clinical studies and practices. Correct assessment of WMH also is a way to support diagnosis, prognosis, and monitor of treatment for dementia and other neurovegetative diseases.

As show in Table 7, there are a limited number of public datasets about WMH segmentations. Where WMH challenge 2017 provides a prominent WMH segmentation platform. In 2017, an extended U-shaped network was used to automatically detect and segment WMH from Flair and T1 MRI images [90]. This model was evaluated and ranked the first in the WMH segmentation challenge. Similarly, Zhang et al. used an extended U-shaped network to accomplish WMH segmentation in the same challenge [135]. They used randomly initialized weights to improve the segmentation performance. In order to study WMH deeply, Guerrero et al. proposed an uResNet to segmentation and differentiation between WMH and stroke lesions [46]. The extracted WMH volumes were found to correlate with the Fazekas visual rating score, which is very meaningful work for clinicians to study these 2 kinds of lesions. In addition, Liu et al. [136] also used the deep CNN model to segment WMH tissue from stroke MRI images. Although these studies yielded good results in WMH segmentations, but they ignored to distinguish the similar lesions from WMH, such as stroke lesions and multiple sclerosis lesions.

5.1.4. Other

Segmentation of normal brain structures is also an important research direction. Some studies focus on the segmentation of white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF), which is critical to study the early brain development in infants or neurodevelopmental or neuropsychiatric disorders, such as schizophrenia and autism. More and more attention has been paid to these 3 brain tissues.

MICCAI have provided 3 relevant challenges: MRBrainS13, iSeg2017 and MRBrainS18. The U-shape-related segmentation methods perform well on these 3 segmentation challenges. For example, Chen et al. proposed a segmentation model (VoxResNet) for the brain segmentation on 3D MRI images [45]. VoxResNet achieved the first place in the challenge out of 37 competitors including several state-of-the-art brain segmentation methods. Moreover, Li et al. adopted deep dilated a residual U-shaped network to segment brain tissues from multi-modality MRI images in MRBrainS18 [56]. Similarly, Luna et al. also provided a 3D patch-wise U-shaped network in MRBrainS18 [137]. In addition to public datasets, Chen et al. used DRINet method to segment the CSF tissues on 2D CT images from an in-house dataset [43]. Moreover, multiple sclerosis [138], diencephalon [91] and others are also the subjects of brain imaging research.

5.2. Eye

Fundus image is a specialized form of medical images. It is taken by fundus camera operated. Retinal fundus images are mostly stored in the form of 2D images. Ophthalmologists can diagnose eye diseases with retinal fundus images such as: glaucoma, optic disc, blood vessel and retina. Diagnosis of eye diseases is not only time-consuming but also inefficient. Therefore, using computer technologies to segment eye tissues for early screening and detection of eye diseases is critical to maintain healthy vision and quality of life.

U-shaped networks have shown its excellence in medical image segmentation tasks, it also attracts more attention compared with the traditional CNN due to its ability to obtain a coarse-to-fine representation. For example, Fu et al. [99] proposed a deep U-shaped network (M-Net) for segmenting optic disc (OD) and optic cup (OC) on ORIGA dataset [139]. The experiments showed that M-Net not only achieved the state-of-the-art segmentation result, but also could diagnose glaucoma. Similarly, Alom et al. developed 2 recurrent convolutional neural networks based on the U-shaped architecture [44] and applied them to blood vessel segmentations in retina images. In addition, Li et al. developed a connection sensitive attention U-shaped network (CSAU) for vessel segmentations from retinal fundus images [74]. CSAU achieved the leading position on all 3 public fundus image datasets (DRIVE, STARE and HRF). Likewise, Jin et al. also confirmed the good performance of their proposed segmentation model on these 3 fundus image datasets [40].

5.3. Cardiac

In medical image analysis, accurate location and segmentation of abdominal organs has always been one of the themes of medical image segmentations. The high mortality rate of cardiovascular diseases has always been one of the hot research topics, especially segmentation of left ventricle (LV) organ.

In all cardiovascular segmentation methods, U-shaped architectures were used by all top performing models. In automated cardiac diagnosis challenge (ACDC) 2017, the most of top-ranking segmentation methods are related to U-shaped networks [66,119,120,140–142]. For example, Poudel et al. proposed an U-shaped network that segmented LV from full stack of 2D slices in MICCAI 2009 LV Segmentation Challenge [143]. Similarly, Veasl et al. proposed a 3D U-shaped CNN for volumetric segmentation of the LV chamber in STACOM MICCAI 2018 challenge[73]. In addition, Isensee et al. introduced an nnU-Net (‘‘no-new-Net”), which is a robust and self-adapting framework on basis of 2D and 3D vanilla U-Nets [28]. Compared with the state-of-the-art methods, nnU-Net achieved the highest mean dice scores in a heart disease in–house dataset.

5.4. Liver

Liver cancer is a disease with a high incidence and the relevant medical images are readily available. There are massive amounts of data available for the demand of deep learning model. Deep learning methods have shown output performance on liver and tumor segmentation tasks. Among these models, U-shaped network is the most used one.

LiTS 2017 is a public challenge that about liver and tumor in CT scans. It provides a fair competition platform for many medical image segmentation methods. Deep learning segmentation methods perform well in this challenge. Especially H-DenseUNet [62] and RA-UNet [53] segmentation methods outperformed other state-of-the-art segmentation methods. These 2 methods achieved very competitive performance on liver segmentations. In addition, a novel UNet++ segmentation model was proposed in LiTS 2018 challenge [93]. UNet++ was also used in nuclei and polyp segmentation tasks. Results showed that UNet++ could achieve better performance than U-Net.

5.5. Prostate

Prostate images most come from radiography or computed tomography. It is an easily accessible medical kind of diagnosis images. There are a large number of unlabeled prostate images that need to be processed by clinicians [144]. It is a tedious task for clinicians to locate and mark the shape of target tissues in images. With the development of deep learning in the field of image analysis, more and more researchers try to use deep learning methods to assist in localization and segmentation of prostate lesions. U-shaped segmentation models is one of them.

PROMISE12 is a well know challenge that is used to compare interactive and (semi)-automatic segmentation algorithms of prostate from MRI images. In this challenge, top ranked methods taken by a 3D U-shaped segmentation method fCNN, which was proposed by Yu et al. [118]. The fCNN model is a hybrid network which consists of ResNet and U-net architecture. In addition, by using the volumetric convolutional strategy, a 3D segmentation method (V-Net) also achieved good performances in PROMISE12 challenge [26]. Furthermore, Drozdzal et al. proposed a 3D FC-ResNet network for liver lesions and prostate segmentations on in–house dataset and PROMISE12, respectively [47]. Different from above studies, Chen et al. proposed a bridge U-shaped network for prostate segmentation which is based on 2D images [111]. In

PROMISE12 challenge, they converted 3D prostate MRIs to 2D slices. This proposed network not only got the highest score among 2D methods, but also performed better than the contrastive 3D methods in 2 metrics.

5.6. Musculoskeletal (intervertebral disc)

Accurate localization and segmentation of musculoskeletal are crucial for the assessment of bone diseases. Deep learning methods have been extensively used for musculoskeletal image analysis in several different application domains: bone, spinal and intervertebral discs. These images always show in X-ray or MRI images. Table 7 shows some public datasets.

The latest public musculoskeletal dataset is IVDM3Seg, which is published in MICCAI 2018. The goal of IVDM3Seg is to provides a standard evaluation framework for investigating (semi-) automatic intervertebral discs (IVDs) localization and segmentation algorithms. Dolz et al. extended the U-Net architecture and proposed IVD-Net for localization and segmentation of IVDs from multi MRI images in IVDM3Seg [145]. They demonstrated that naive feature fusion strategies in IVD-Net can improve the representation power and boost discriminative performance. Similarly, on the same dataset, Li et al. also proposed a segmentation network for IVDs from multi-scale and modality MRI images [124], the proposed method achieved the first place in the IVDM3Seg 2018 challenge.

5.7. Neuronal

Neuronal segmentation is an important part of medical image segmentations. U-Net was firstly evaluated on neuronal dataset (ISBI 2012) [23]. ISBI challenge 2012 is the first challenge that aims to segment neurons on 2D EM images. Since then, a wide variety of depth learning segmentation methods used this challenge as the benchmark.

In ISBI 2012 challenge, a residual deconvolutional U-shaped network (RDN) was proposed for 2D EM image segmentations [42], which consisted of 2 information pathways that captured full-resolution features and contextual information, respectively. RDN achieved one of the top results on this challenge. Furthermore, Drozdzal et al. provided a pipeline which was combined FCNs with FC-ResNets for medical image segmentations [47]. Compared with other 2D methods, the proposed method exhibited the state-of-the-art performance on EM images challenging. In addition, R2U-Net [52], MultiResUNet [49] and CE-Net [57] and so on also showed outstanding performance in ISBI 2012 challenge.

5.8. Skin cancer

Skin cancer is the most common malignant tumour in human beings. The degree of skin lesions in dermatoscopy images varies greatly. At present, diagnosis of benign and malignant skin diseases is mainly performed by doctors on dermatoscopy images. This is a time-consuming and error-prone process. In 2017, the researchers in Stanford University showed that deep neural networks could analyze skin cancer, which has greatly inspired the research in this field [146]. More and more deep learning methods are applied to this field.

In the field of skin lesion segmentations, ISIC 2017 and 2018 are 2 public challenges which concern skin cancer. Alom et al. proposed a recurrent residual convolutional neural network (R2U-Net) for skin image segmentations. R2U-Net have made an impressive achievement in ISIC 2017 challenge. Similarly, Ibtehaz et al. developed a novel architecture MultiResUNet as the potential successor to successful U-Net architecture [49]. Compared with the U-Net, MultiResUNet obtained a remarkable performance in ISIC 2018 challenge. Furthermore, Kawahara et al. also made outstanding achievement in an in-house dataset of skin cancer [147]. In addition, Codella et al. provided a review of the ISIC challenge [148]. They affirmed that the advance of deep learning methods on skin segmentation tasks, at the same time, they also pointed out that these methods generate little interpretable evidence of disease diagnosis.

5.9. Other

In addition to above studies, this final section briefly describes the application of U-shaped networks in other diseases. It is remarkable that U-Nets or U-shaped networks can be applied in different medical images segmentation tasks, which marks the versatility and applicability of U-shaped networks.

In GlaS challenge of MICCAI 2015, Li et al. proposed a bi-directional recurrent U-Net based on probabilistic map guidance (PBR-UNet) and used the proposed method to segment pancreatic cancer [149]. Zhang et al. proposed an ensemble U-shaped network for pancreatic cancer segmentation [64]. The proposed network consisted of 3 different multi-scale dense connections. In addition, Chen et al. proposed a U-SEG-NET segmentation network for hippocampus segmentations [150]. U-SEG-NET combined U-net with multiple decision maps. The performance of U-SEG-NET was validated by the brain dataset of ADNI project. Furthermore, Zhu et al. applied an improved 3D U-Net (AnatomyNet) to the segmentation of head and neck (HAN) cancer organs in MICCAI challenge 2015 [60]. AnatomyNet was able to process whole-volume CT images and delineate all organs-at-risks in one pass, which only need a few pre- or post-processing operations. In addition, U-shaped networks were also used in polyp and cell nuclei segmentation task [93], kidney segmentation task [151], lung segmentation task[44], and breast tumor segmentation task [102] and so on.

6. Discussion

From more than 100 papers reviewed in this survey, it can be clearly seen that U-shaped networks have played a significant role in the study of medical image segmentations. U-shaped networks have made a profound impact on current medical image segmentation research. As shown in Fig. 1, the number of related papers has grown very rapidly. Among them, combination of U-shaped networks with residual, dense and dilated mechanisms not only delivered a variety of deep networks, but also promoted the performance of medical image segmentation. It can be found that in the past 3 years, the end-to-end CNN networks with U-shaped architectures have become the preferred method for medical image segmentations.

After reviewing of these papers, we hope to provide the comprehensive information for developing better U-shaped segmentation methods for each individual lesion or organ segmentation. The derived U-shaped networks are outstanding in many medical image segmentation challenges, 2 significant conclusions we can draw are: 1. The same network is difficult to apply to the segmentation of multiple tasks, and the generalization performance of the segmentation methods needs to be improved. For example, embedding residual mechanism into U-Net network is an effective way to segment the individual lesion, but the results are quite different in other segmentation tasks with the same architecture and parameters. 2. Increasing the depth of network structures can improve network performance, but the precise structure is not the most important determinant. The prior knowledge of doctors on medical images is one of the important keys. These prior knowledge can provide advantages to improve the performance of segmentation methods. In addition, data augmentation methods are also an aid way to improve the performance of segmentation networks, such as increasing the number of medical images and enhancing image quality by image pre-processing methods.

Of course, data augmentation and preprocessing are not the only key factors for a good solution. More and more researchers are using hybrid architectures instead of single architecture to achieve better segmentation results. For example, multi-scale, multi-modality and multi-model are integrated into segmentation methods. More contextual information can be obtained by controlling the size or modality of input images, or the same image information can be processed by multiple models and then be merged to obtain better feature maps. It is also an effective way to improve model performance by using 3D images instead of 2D images as data source.

In addition, most researchers proposed U-shaped methods which retains the architecture of the original U-Net with 4 levels of down-sampling and 4 levels of up-sampling. The improvements on original U-Net architecture have also been made. For example, Zhou et al. [93] used redesigned skip paths and deep supervision [152] to improve segmentation performance. The proposed method was validated on 4 different medical segmentation tasks. The experiments illustrated that the design of network architectures need to consider specific situation of segmentation tasks. For most simple segmentation tasks, a segment network does not need to be very deep or complex, and a very wide network can achieve good performance. However, more complex segmentation tasks require deeper and more complex networks to achieve satisfactory results.

Finally, U-shaped networks and other deep learning methods lack the interpretability of the "black box" problem. Although the performance of some segmentation methods have reached or exceeded that of radiologists in some areas, radiologists and patients do not intuitively understand the operating mechanisms of models, which makes them suspicious to deep learning methods. In order to solve this problem, some researchers have developed strategies to interpret the operating mechanism of the inner layers of neural networks, such as deconvolution networks [153], guided back-propagation [154]. Some researchers combined images with electronic medical records, and they tried to use textual information in electronic medical records to explain the internal mechanisms of networks [155,156]. Other researchers have tried to visualize the hidden layers of neural networks, and they used visual intermediate layer images to explain image processing in neural networks [157]. These methods allow radiologists to assess the reliability of network and accelerate the acceptance of deep learning applications in the process of clinical auxiliary diagnosis. The interpretability of deep learning networks in medical image segmentation field is unexplored and needs to be further improved in future.

Due to the complexity of medical image segmentation tasks and the variety of target tissues, current segmentation methods are difficult to be fully used for clinical diagnosis. It is not feasible to use fully automatic, reliable and accurate segmentation methods to completely replace the work of physicians and clinical researchers. Instead, according to different segmentation tasks, physicians and clinical researchers can choose appropriate segmentation method to assist diagnosis: In particular, clearly outlined, large lesions are already segmented with good results, which are usually tedious to outline by hand. For smaller and less pronounced lesions the manual approach is still recommended.

CRediT authorship contribution statement

Liangliang Liu: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Jianhong Cheng:** Investigation. **Quan Quan:** Investigation. **Fang-Xiang Wu:** Writing - review & editing. **Yu-Ping Wang:** Writing - review & editing. **Jianxin Wang:** Conceptualization, Funding acquisition, Writing - review & editing.

Acknowledgment

The work described in this paper was supported by the National Natural Science Foundation of China under Grant Nos. U1909208, 61772552; the 111 Project (No.B18059); the Hunan Provincial Science and Technology Program (2018WK4001); the Natural Science Foundation of Hunan Province in China (2018JJ2534).

Appendix A

Overview of medical datasets and websites.

Dataset	Website
BraTS 2015	https://www.med.upenn.edu/sbia/brats2015.html
BraTS 2016	https://www.med.upenn.edu/sbia/brats2016.html
BraTS 2017	https://www.med.upenn.edu/sbia/brats2017.html
BRATS 2018	https://www.med.upenn.edu/sbia/brats2018.html
MRBrainS13	https://mrbrains13.isi.uu.nl/index.php
MRBrainS18	https://mrbrains18.isi.uu.nl/
SPES 2015	http://www.isles-challenge.org/ISLES2015/
SISS 2015	http://www.isles-challenge.org/ISLES2015/
ISLES2016	http://www.isles-challenge.org/ISLES2016/
ISLES2017	http://www.isles-challenge.org/ISLES2017/
ISLES2018	http://www.isles-challenge.org/
iSeg 2017	http://iseg2017.web.unc.edu/
WMH 2017	http://wmh.isi.uu.nl/
IBSR	https://www.nitrc.org/projects/ibsr/
Head&Neck	http://www.imagenglab.com/newsite/pddca/
ACDC 2017	https://www.creatis.insa-lyon.fr/Challenge/acdc/index.html
DSB 2015	https://www.kaggle.com/c/s-annual-data-science-bowl/overview
LIDC-IDRI	https://wiki.cancerimagingarchive.net/display/Public/LIDC-IDRI
LowDoseCT	https://www.aapm.org/grandchallenge/lowdosect/
PROMISE 2012	https://promise12.grand-challenge.org/
LiTS 2017	https://competitions.codalab.org/competitions/15595
ISIC 2017	http://challenge2017.isic-archive.com/
ISIC 2018	https://challenge2018.isic-archive.com/task1/
GlaS	https://warwick.ac.uk/fac/sci/dcs/research/tia/glascontest
NIH-TCIA	https://www.cancerimagingarchive.net/
IVD 2018	https://ivdm3seg.weebly.com/
STARE	http://cecas.clemson.edu/ ahoover/stare/
HRF	http://www5.cs.fau.de/research/data/fundus-images/
IDRiD	https://idrid.grand-challenge.org/
ORIGA	http://www.moh.gov.sg/mohcorp/publications.aspx?id = 16320
ISBI 2012	http://brainiac2.mit.edu/isbi_challenge/
DRIVE	http://www.isi.uu.nl/Research/Databases/DRIVE/

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