From Specific to Universal: One Biomedical Image Segmentation Model To Rule Them All

by

Seyed Alireza Vaezi

(Under the Direction of Shannon Quinn)

Abstract

This section of the page is where your abstract will go. Fill in this spot in the dissertation.tex file with your abstract. Doctoral 350 words max, 150 max for masters.

Index words: [PUT YOUR LIST OF INDEX WORDS HERE SEPERATED BY COMMAS]

From Specific to Universal: One Biomedical Image Segmentation Model To Rule Them All

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Seyed Alireza Vaezi

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Major Professor:	Major Prof
Committee:	Prof 1 Prof 2 Prof 3

Electronic Version Approved:

Ron Walcott
Dean of the Graduate School
The University of Georgia
Month Year

Dedication

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Chapter 1

Introduction

Image segmentation started with traditional methods and algorithms such as thresholding, watershed, and optical flow, which rely on pixel intensity. Traditional rule-based methods like Thresholding and Watershed analyze pixel values to identify borders and boundaries within areas of interest. Machine learning-based methods - such as Support Vector Machines (SVM), random forests, and contrastive learning - involve the use of statistical machine learning models and increased the popularity and applicability of segmentation. Finally, deep learning-based methods leverage neural networks to learn hierarchical feature representation from raw images without requiring manual feature engineering. This process saw significant improvement with the introduction of Convolutional Neural Networks (CNN). CNNs are trained to detect features in regions of interest, enabling them to perform similarly on new images. Segmentation techniques can be divided into three categories: supervised, semi-supervised, and unsupervised.

U-Net and its variants are extensively adopted in biomedical image segmentation for their capability to automatically extract features from images without manual intervention or preprocessing. They can learn high-level semantic information and low-level spatial information from large-scale data. U-Net architectures are categorized based on their design and functionality. Basic U-Nets, like the original U-Net and 3D U-Net, are foundational, with the latter extending to 3D data for volumetric segmentation useful in CT and MRI scans. Advanced U-Nets include Attention U-Net, which uses attention mechanisms for precision; Inception U-Net, capturing multi-scale information through varied kernel sizes; Residual U-Net, which incorporates residual connections to aid deep network training; and Dense U-Net, promoting feature reuse via dense connections. Currently, CNNs represent the state-of-the-art in image segmentation, with U-Net being the predominant architecture, especially in the field of biomedical image segmentation. These advancements have greatly improved the accuracy and efficiency of biomedical image analysis, making it an essential tool in various fields of research.

Biomedical images come in a vast variety of formats, types, and modalities. The modalities in medical imaging include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound, while microscopy modalities include fluorescent microscopy, brightfield, lens-free microscopy, light microscopy, volume electron microscopy, and phase contrast microscopy, just to name a few. Similarly, due to the variety of biological structures, segmentation targets can vary from nuclei and cell membranes to organelles such as mitochondria, cilia, tumors, and lesions, as well as blood vessels, bone, and brain structures. This diversity in imaging techniques and segmentation targets highlights the need for specialized and customizable deep learning models in biomedical applications.

The Segment Anything Model (SAM) can segment an object within an image using user inputs, including a single point, multiple points, an entire mask, a bounding box, or textual descriptions. This functionality is based on the model's inherent ability to recognize objects, which enables it to segment unfamiliar object types without further training, effectively supporting zero-shot learning. Furthermore, the effectiveness of SAM is enhanced by its specialized architecture and the use of a significantly large dataset.

1.1 Challenges

Despite their success, CNN methods face challenges including poor generalizability, limited transferability, and the complexity of model development as well as fine-tuning pre-trained models in biomedical applications. This is due to the fact that manual labeling of data in biomedicine requires expert knowledge and is a costly and time-consuming task, making large and quality annotated datasets scarce. As a result, there exists a vast variety of deep learning models, each tailored to a specific modality and target structure. Unsupervised methods, on the other hand, do not require pre-training or an existing dataset and rely on domain-specific rules and heuristics. Although these methods exhibit less accuracy than CNN methods, they excel in reproducibility and generalizability as they do not depend on prior data knowledge. These different approaches to image segmentation provide a range of options for researchers to choose from, depending on their specific needs and resources.

In the biomedical field, where labeled data is often scarce and costly to obtain, several solutions have been proposed to augment and utilize available data effectively. These include semi-supervised learning, which utilizes both labeled and unlabeled data to enhance learning accuracy by leveraging the data's underlying distribution. Active learning focuses on selectively querying the most informative data points for expert labeling, optimizing the training process by using the most valuable examples. Data augmentation techniques, such as image transformations and synthetic data generation through Generative Adversarial Networks, increase the diversity and volume of training data, enhancing model robustness and reducing overfitting. Transfer learning transfers knowledge from one task to another, minimizing the need for extensive labeled data in new tasks. Self-supervised learning creates its labels by defining a pretext task, like predicting the position of a randomly cropped image patch, aiding in the learning of useful data representations. Additionally, few-shot, one-shot, and zero-shot learning techniques are designed to operate with minimal or no labeled examples, relying on generalization capabilities or metadata for making predictions about unseen classes.

Generalizability refers to the trained model's ability to perform well on unseen data outside of the training set. It is a crucial aspect of machine learning, particularly in biomedical applications, where variations in image acquisition conditions, tissue types, and other factors can be substantial. Data augmentation techniques and transfer learning are two excellent methods to overcome overfitting and improve generalizability where the training data is small. While transfer learning is a powerful technique for leveraging pre-trained models to boost performance, especially in scenarios with limited data, it does come with its own set of challenges and limitations such as domain mismatch, risk of overfitting, computational demands, and potential biases from the source dataset.

Reproducibility refers to obtaining consistent results using the same input data, computational steps, methods, and conditions of analysis. This concept is key in scientific research to ensure that outcomes can be reliably replicated under the same conditions, fostering trust and confidence in the findings. Reproducibility is influenced by various factors including dataset variability, model architecture specifics, optimization procedures, and computational infrastructure. Apart from the loss of validity of a scientific method, non-reproducibility can lead to wasted resources, stalled scientific progress, erroneous conclusions, and significant ethical concerns. To ensure reproducibility in deep learning for medical image segmentation, Renard et al. advocate for comprehensive documentation, standardized practices, fixed random seeds, cross-validation, multiple evaluation metrics, and sharing of source code and dependencies.

Deep learning models are effective across various applications but their usability depends on several factors such as the complexity of the task at hand, data availability, and the extent of necessary model customization. For users who prefer straightforward applications, ease of use is crucial. They benefit from methods that do not require extensive modifications or tuning to achieve optimal results. Incorporating an intuitive graphical user interface (GUI) and ensuring interactivity can enhance the usability of these tools, making them more accessible to non-expert users, such as biologists, who need practical, ready-to-use solutions without the intricacies of model adjustments.

Chapter 2

All about Citations and BibTex

Before diving into BibTex and how it all works, citing a figure or table that does not exist in the same subpage is also possible. Figure **??** is on page **??**.

2.1 The Bibliography

In this section, we are going to dive into how LaTeX automates your citations and generates your bibliography on the fly. That way if you make any additions or deletions, LaTeX will handle all of that.

2.1.1 BibTex File Formatting

All of the citations will live in one file, in this case is called dissertation.bib. This file will have to follow a specific format. Each entry will start with an @ and following the type of entry. If it is a book, then it will start with @book{...}. Inside the brackets will contain all of the information about this entry. Fisrt it will have an ID that you will use to cite inside the tex files. Not sure of a convention, but each ID must be unique so something that pertains to the entry should suffice. There is a lot you can put with each entry, so here is a link to all the different types and the different attributes each entry can have. Each attribute inside the curly brackets needs to be separated by a comma, but each entry just needs to be on its own line and not separated by a comma.

2.1.2 Loading BibTex File

If you look at the main file, *disseration.tex*, there are two places that involve the bibliography. First is at the top where the command is `\usepackage[backend=biber,style=apa,sorting=nyt]{biblatex}`. This lets you change the style and how the bibliography is sorted. Don't touch the *backend=biber*. The next command is `\addbibresource{dissertation.bib}` further down before the actual document begins. This does not neet to be touched because it also needs to be called the same as the main file, besides the extention. This is how the compiler knows which file to grab.

Then lets take a look at the very bottom of *dissertation.tex*, there will be two commands that are very important.

```
\addcontentsline{toc}{chapter}{Bibliography}
\printbibliography[title={Bibliography}]
```

Unless you want to change the title of the bibliography or sort the bibliography, then you may want to touch this. Other than that, there is no need to mess with these two lines of the file.

2.2 Inline Citations

There are two commands that you will need to know. `\cite & \parencite`. The way these are used is when you use these commands, you need to have provide the ID of the specific entry in the bib file. `\cite{article1}` produces **article1** where as the other command adds parentheses around it. These will change when you change the style of the Bibliography from apa to mla or any other format. (**article1**) (**article2**)

Chapter 3

Footnotes and Sidenotes

Dissertations will most likely include numerous side comments that are tangential to the main text. Generally, these are included in the document as footnotes or endnotes. With this template, you have the option to include them as *sidenotes*, meaning they appear in the margin of your page rather than at the bottom.[1] In this "chapter", we'll[2] weigh the benefits and drawbacks of sidenotes and show you how you can toggle between them in your document.

3.1 Turning sidenotes on

The way to turn sidenotes on in this template is pretty straightforward. In the `dissertation.tex` file, you should find a command called `sidenotetrue`. All you need to do is delete that line of code and type `sidenotefalse`.

3.2 List of changes

If you do choose to turn the sidenotes on, be aware that it makes a couple other changes to your document. This section lists those changes.

3.2.1 Changes to the footnote command

The biggest change to your code is that the `\footnote` command has been recoded to now produce sidenotes. Specifically, the code that accomplishes this rewriting:

```
\renewcommand{\footnote}[1]{
    \sidenote{\RaggedRight\footnotesize #1}
```

[1]Prior to 2020, this layout had not been used in a UGA dissertation. However, because of this LaTeX template, the Graduate School and the format checkers approved the use of sidenotes specifically for us!

[2]I'll mention that this chapter was written primarily by Joey Stanley, so you'll know who's talking when I express my typographical opinions.

```
}
```

This code essentially turns the `\footnote` function into a wrapper around the `\sidenote` function from the `sidenote` package. It also changes the default fully-justified behavior to "ragged right."[3] Finally, it ensures the font size is footnote size.

The reason for redefining `\footnote` rather than using `\sidenote` is becaue I wanted to make toggling between them as simple as possible. If you're three chapters into your dissertation and you decide you want to switch to the other layout, all you need to do is change one line of code. Had I required you to use `\sidenote`, you would have to change the one command *and* change all the `\footnote` commands to `\sidenote`. I think doing it this way makes sense.

3.2.2 Changes to the page layout

If you have footnotes, the margins of your paper will be 1 inch on all sides, except for the bottom which is 1.25 inches.[4]. The body of the text is therefore centered, and there is no difference between even- and odd-sided pages.

If you turn on the sidenotes though, we needed to make some extra room to accomodate them in the margin.[5] To accomplish this, we had to reformat the layout on the page.

The biggest change is that the body of the text is now off-center. For odd-sided pages (meaning it would appear on the right side when you lay the book open), it's shifted towards the left and for even-sided pages (the left side of a two-page spread), it's shifted towards the right. In other words, the text is shifted towards the spine of the book. This leaves some room for the margins, which are towards the edges of the book. Here are the default dimensions:

- The top margin is 1 inch and the bottom margin is 1.25 inches.
- Starting from the edge of the page (on an odd-sided page), the outer margin is 0.75 inches. This is the distance from the page to the edge of your sidenotes.
- The sidenotes themselves are 1.5 inches wide.
- There is a one-eighth inch space between the sidenotes and the body text.
- The body text itself is 4.375 inches wide.
- The inner margin is 1 inch.

[3]With a sidenote margin so small, it's basically impossible to have good-looking text if it's forced to align to the left and right margins. Using `RaggedRight` from the `ragged2e` package does a nice job at making a narrow column of text look nice.

[4]This extra space is typograhpically recommended to give the page a more balanced appearance.

[5]Ideally, we'd make the paper wider so that it's slightly more square. Most books that use sidenotes today are like that. It gives a little extra width to the margins so the sidenotes aren't so narrow. Alas, we are constrained by UGA and Print & Copy in Tate since they can only bind specific paper sizes.

- There is an additional "binding offset" of a quarter inch added to the inside margin to accomodate for printing. This basically just means that the inside margin is 1.25 inches.

The outer margin has to be a little bit narrower than the typical 1 inch to give the body text enough room. Because footnotes are left-justified, this is not as noticeable on odd-sided pages, though on even-sided pages it's a little more obvious.

3.3 Details about how sidenote behavior

You should be aware of how the sidenotes behave, as they are implemented in this document. Sidenotes will be placed on the outer marin, but its their vertical positioning that may shift around.

By default, sidenotes will start on the same line as the sidenote *marker* (that is, the small superscripted number within the body of your text). If you use relatively few sidenotes, or if they're generally short, this is what you'll typicaly find.

The question then is what happens if a sidenote runs up against the bottom of the page. Like if the sidenote marker is on the bottom line of a page and the sidenote itself is several lines long. As expected, the position of the sidenote itself will simply shift up so that it doens't spill into the bottom margin. Under the hood, while it is important that a sidenote be near its marker, is is *more* important for the sidenote to not spill into the bottom margin, so that takes priority.

Similarly, if you have multiple sidenotes that are near each other, the notes themselves will not overlap. They'll reposition themselves vertically along the margin so that they're as close to their markers as possible without overlapping with eaach other or with a top/bottom margin.

For very long sidenotes,[6] or for pages with many sidenotes such that they fill the margin completely, LaTeX will do what it can to put it on the same page as the marker, but if it cannot, it will push it to the next page. For long footnotes, you may have seen them start on the correct page but spill over onto the next page—that behavior is unfortunately not possible with the current implementation of sidenotes in this template. For the most part this behavior is fine and readers typically are aware enough to look on the next page. However, be aware that should this next page be, say, the start of a new chapter, you'll get some unexpected sidenote placements.

For sidenotes that are so long that they cannot fit on a single page, it will cause an error in LaTeX and your document will not compile. If you typically have many very long sidenotes, it may be better to switch to a footnote layout.

[6] Here is a very long sidenote so you can get a feel for what it looks like. Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum.

3.4 Pros and Cons

With this information in mind, it's important to consider the pros and cons of using sidenotes.

3.4.1 Why I love sidenotes

There are lots of reasons why I love sidenotes. First off, since they were popularized by statisticiaon Edward Tufte[7] in his books on data visualization, they've been used widely and are adopted by many typographers. The reason is simple: they just look nice. Rather than your eye having to dart to the bottom of the page and back, sidenotes are *in situ*, and they do a nice job at making it easier for the reader to find them.

In addition to making the sidenotes themselves easier to find and read, increasing the margin on one side makes the body text a little narrower. The typical 6.5 inch body text with 10- or 12-point font is a little too wide. The narrower layout, together with an appropriate line spacing, makes for a sophisticated layout that's easier to read than what you might be used to in a dissertation.

Sidenotes are nice for putting some kinds of additional, non-textual information that are very vertical. It's possible to put a very narrow table, a very narrow image, or even a smaller image,[8] icon, or plot in a sidenote.

3.4.2 Why you may not love sidenotes

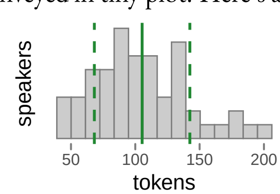
First, as just mentioned, they're not ideal if you often use many long footnotes. If that's the case, you would probably be better off with the footnotes option.

Another small issue relates to how this particular template is structured. You can work on each chapter and compile each chapter individually. However, because the command that reorganizes the layout on the page is on the `dissertation.tex` file, when you compile just a single chapter, you don't get the right layout. This can be kind of annoying.

For certain things that may go in footnotes but are inherently wider, like formulas, computer code, extended quotations, data, numbered examples, or images, sidenotes are just too narrow. You're better off switching to footnotes if you make use of many of these. You may find a way to hack a one-off footnote if you need it for just one case.

[7] Note that there is a `tufte` package that creates sidenotes. Because we did not necessarily want to use the other changes that package makes to the document, we chose not to use it here.

[8] There's no need for an image to take up half a page when the information can be conveyed in tiny plot. Here's an actual image I included in my dissertation, showing the distribution of a particular variable.



It was handy to be able to have several of these little guys scattered around in the margins rather than taking up a huge chunk of the page.

Finally, because I've redefined `\footnote` to do sidenotes, it's not possible to include both footnotes and sidenotes within your document. I have seen some books do this, but I'm not sure why you would need both. Fortunately, this is an easy fix: you would just remove the code in `dissertation.tex` that redefines footnotes, and now you're free to use `\footnote` and `\sidenote` independently of each other. This behavior has not been tested so you're on your own as far as debugging goes.

3.5 Hacking some less common cases

3.5.1 Putting a plot in a sidenote

The code for the little plot I have in the sidenote above is this:

```
\includegraphics[width = 1.5in]{figures/tiny.pdf}
```

Note that because these are so small, there is no figure number assigned to them and there's no caption. Consequently, they will not appear in the "List of Figures" in your frontmatter if you have one.

3.5.2 Others?

TODO.

Chapter 4

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Chapter 5

Conclusion

This is where your Conclusion will go

Appendix A

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