Subject Section

Global Transformer U-Nets for Label-Free Prediction of Fluorescence Images

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Abstract

Visualizing the details of different cellular structures is of great importance to elucidate cellular functions. However, it is challenging to obtain high-quality images of different structures directly due to complex cellular environments. Fluorescence microscopy is a popular technique to label different structures but has several drawbacks. In particular, labeling is time consuming and may affect cell morphology, and simultaneous labels are inherently limited. This raises the need of building computational models to learn relationships between unlabeled and labeled fluorescence images, and to infer fluorescent labels of other unlabeled fluorescence images. We propose to develop a novel deep model for fluorescence image prediction. We first propose a novel network layer, known as the global transformer layer, that fuses global information from our proposed global transformer layers and dense blocks to build an U-Net like network. We believe such a design can promote feature reusing between layers. In addition, we propose a multi-scale input strategy to encourage networks to capture features at different scales. We conduct evaluations across various label-free prediction tasks to demonstrate the effectiveness of our approach. Both quantitative and qualitative results show that our method outperforms the state-of-the-art approach significantly. It is also shown that our proposed global transformer layer is useful to improve the fluorescence image prediction results.

1 Introduction

Capturing and visualizing the details of different sub-cellular structures is an important but challenging problem in cellular biology. Detailed information on the shapes and locations of cellular structures plays an important role in investigating cellular functions. One popular technique to overcome these limitations is fluorescence microscopy, which labels different structures with dyes or dye-conjugated antibodies. One important consideration is that cell nuclei can be labeled and visualized after stained by DAPI (Ounkomol et al., 2018). However, fluorescence labeling is time consuming, especially when cell structures are complex. In addition, due to the overlap of spectrum, there is a limit on the number of fluorescent labels to be applied simultaneously on the same microscopy image (Bray et al., 2001). Furthermore, labeling may interfere with regular physiological processes in live cells, resulting in changes in cell morphology (Jo et al., 2014; Ounkomol et al., 2018). These limitations raise the need of advanced methods to label cellular structures more effectively and efficiently.

With the rapid development of deep learning methods, recent studies (Ounkomol et al., 2018; Christiansen et al., 2018; Yuan et al., 2018) propose to formulate such problems as image dense prediction tasks using deep neural networks. In such a dense prediction task, we wish to predict if each pixel on the input transmitted light image belongs to a fluorescent label or not. Given transmitted light images and corresponding fluorescence labeled images, the models are trained to capture the relationship between them. Then for any newly obtained transmitted light image, the fluorescence image can be predicted by the models based on the learned relationships. When considering multiple fluorescent labels for the same image, a multi-task image dense prediction problem can be used. In these cases, the models are trained to learn the underlying relationships between the raw images and multiple fluorescent labels. In the prediction phase, the models produce a prediction map for each fluorescent label. Such a problem formulation allows us to obtain multiple fluorescent labels simultaneously from transmitted light images without labeling.
The recent study in Christiansen et al. (2018) proposes to use convolutional neural networks (CNNs) for such a task and obtains promising results for prediction of fluorescence images. It stacks multiple convolutional layers to enlarge the receptive field and employs inception modules to facilitate the training. However, only local operators, such as convolution, pooling, and deconvolution, are used in their model. Hence, the global information cannot be captured effectively and efficiently, while such information may be important to determine certain fluorescent labels. Meanwhile, another work Ounkomol et al. (2018) employs a vanilla U-Net framework for prediction of fluorescence images. For each type of fluorescent label, it builds a model to learn the relationships between transmitted light images and the corresponding fluorescent label. However, such a design learns different fluorescent types separately, thereby ignoring important relationships among different fluorescent labels. In addition, it only employs local operators so that the global information cannot be effectively captured. Other studies on image missing modality prediction tasks employ similar network architectures (Cui et al. 2018; Zhang et al. 2019; Liu et al. 2018; Chen et al. 2019).

In this work, we propose a novel deep learning model, known as the global transformer (GT) U-Nets, for fluorescent label predictions. As a radical departure from previous studies that invariably employ local operators, we develop a novel network layer, known as the global transformer layer, to fuse global information efficiently and effectively. The global transformer layer is inspired by the attention operators Vinaswami et al. (2017); Wang et al. (2018), and each position of the output in the global transformer layer fuses information from all input positions. Particularly, our proposed layer can be flexibly generalized to produce outputs of any dimensions. We build an U-Net like architecture based on our proposed global transformer layer. We further develop dense blocks in our network to promote feature reuse between layers in the network. To capture both global contextual and local subtle features, we propose a multi-scale input strategy in our model to incorporate information at different scales. Importantly, our model is designed in a multi-task manner to predict several target fluorescent labels simultaneously. We conduct extensive experiments to evaluate our proposed approach across various fluorescent label prediction tasks. Both quantitative and qualitative results show that our model outperforms the existing approach Christiansen et al. (2018) significantly. Our ablation analysis shows that the proposed global transformer layer is useful to improve model performance.

### 2 Background and Related Work

We describe the attention operator in this section. The inputs to an attention operator include three matrices; those are, a query matrix $Q = [q_1, q_2, \ldots, q_m] \in \mathbb{R}^m$ with each query vector $q_k \in \mathbb{R}^n$, a key matrix $K = [k_1, k_2, \ldots, k_n] \in \mathbb{R}^{n \times m}$ with each key vector $k_i \in \mathbb{R}^n$, and a value matrix $V = [v_1, v_2, \ldots, v_n] \in \mathbb{R}^{d \times m}$ with each value vector $v_i \in \mathbb{R}^d$. An attention operator computes output at each position by performing a weighted sum over all value vectors in $V$, where the weights are acquired by attending the corresponding query vector to all key vectors in $K$. Formally, to compute a response at a position $i$, the attention operator first computes the weight vector as

$$a_i = \text{Softmax}(K^T q_i) \in \mathbb{R}^n,$$

where $\text{Softmax}()$ ensures the sum of all the elements in $a_i$ to be 1. Each element in $a_i$ measures the importance of the corresponding vector in $K$ by performing the inner product between it and $q_i$. The response at position $i$ is then computed by using the weight vector $a_i$ to perform a weighted sum over all vectors in $V$ as

$$o_i = V a_i \in \mathbb{R}^d.$$

In this way, the response at position $i$ fuses the global information in $V$ by assigning an importance to each value vector referring to $q_i$. For response at each position, we follow the same procedure and obtain outputs as

$$O = [o_1, o_2, \ldots, o_m] \in \mathbb{R}^{d \times m}.$$

We rewrite outputs of an attention operator as

$$O = V \times \text{Softmax}(K^T Q) \in \mathbb{R}^{d \times m},$$

where $\text{Softmax}()$ denotes a column-wise softmax operator to ensure every column sum to 1. We can easily see the number of vectors in output...
matrix $O$ is determined by the number of vectors in query matrix $Q$. In self-attention operators, we set $Q = K = V$. Thus, response of a position is computed by the weighted average of features at all positions, thereby fusing global information from input feature maps. Note that a fully connected (FC) layer also fuses global information from whole receptive fields. However, the self-attention operator computes responses based on similarities between feature vectors at different positions, whereas a FC layer connects every neuron to compute responses using learnable weights. Moreover, a self-attention operator deals with inputs with variable sizes, whereas a FC layer needs sizes of input to be fixed.

3 Global Transformer U-Nets

In this section, we introduce a novel model for prediction of fluorescence images, known as the multi-scale global transformer U-Nets with dense blocks.

3.1 Global Transformers

Traditional deep learning models for dense prediction tasks contain several key operators, such as convolution, pooling, and deconvolution. These operators are all performed within a local neighborhood, restricting the capacity of networks to fuse global context information. To overcome this limitation, we propose a novel network layer, known as the global transformer (GT), which is based on the attention operator and captures dependencies between each position on outputs and all positions on inputs, thereby fusing global information from input feature maps. Unlike the self-attention operator that generates outputs with the same dimensions as the inputs, our proposed GT layer can generate output feature maps with arbitrary dimensions, and can be employed for both regular, down-sampling, and up-sampling operators. Specifically, we investigate three types of global transformers, namely global down transformer (GDT), global up transformer (GUT), and global same transformer (GST). The three types of global transformers are halved in GDT, while those are doubled in GUT and kept the same in GST.

Although the three types of global transformers generate outputs of different sizes, they share similar structure and computational pipeline. An illustration of our proposed GT is provided in Figure 2. Let $Z \in \mathbb{R}^{H \times W \times C}$ denote the input of the GT layer, the first step is to compute the query tensor $Q$, key tensor $K$ and value tensor $V$ based on $Z$. We employ a generator layer to obtain the query tensor, and two $1 \times 1$ convolution layers to obtain the key and value tensors as

$$Q = \text{Generator}(Z) \in \mathbb{R}^{H_Q \times W_Q \times C_Q} ,$$
$$K = \text{Conv}1_{C_K}(Z) \in \mathbb{R}^{H_K \times W_K \times C_K} ,$$
$$V = \text{Conv}1_{C_V}(Z) \in \mathbb{R}^{H_V \times W_V \times C_V}$$

where Generator denotes a query generator layer, and Conv1 denotes a $1 \times 1$ convolution layer with stride 1 and M output feature maps. Hence, $H_K$ is equal to $H_V$ and $W_K$ is equal to $W_V$. The choice of the query generator depends on the types of global transformers. For GDT, we employ a $3 \times 3$ convolutional layer with stride $= 2$ to generate $Q$. For GUT, we employ a $3 \times 3$ deconvolutional layer with stride $= 2$ to generate $Q$. For GST, we employ a $3 \times 3$ convolutional layer with stride $= 1$ to generate $Q$.

We then extract the each of the third-order tensors into a matrix by unfolding along mode-3 (Kolda and Bader, 2009). In this way, tensor $Q \in \mathbb{R}^{H_Q \times W_Q \times C_Q}$ is converted into a matrix $Q \in \mathbb{R}^{C_Q \times H_Q \times W_Q}$. Similarly, $K \in \mathbb{R}^{H_K \times W_K \times C_K}$ is converted into a matrix $K \in \mathbb{R}^{C_K \times H_K \times W_K}$.

![Overall pipeline of our method for prediction of fluorescence images. The network produces predictions for a cropped $H \times W$ patch, two other patches centered at the same pixel with sizes $2H \times 2W$ and $H/2 \times W/2$ are also cropped and re-scaled to $H \times W$. The input to the network is the concatenation of these three patches. The U-like architecture includes an encoder part and decoder part. In the encoder part, each dense block is followed by a GDT layer. Sizes of feature maps are reduced by the GDT layer, and numbers of feature maps are increased by the dense block. In the bottom block of the U-like architecture, a GST layer following a dense block to transmit information from the encoder to the decoder. A detailed diagram of a dense block with 3 layers is also shown. Each layer includes convolution, batch normalization, ReLU activation, and dropout. A $1 \times 1$ convolution layer is added at the end to adjust the number of feature maps.](image)
value matrices in Eq. 4. To ensure the attention operator to be valid, we set $C_{Q} = C_{Q}^{'}$. The output of the attention operator is computed as

$$O = V \times \text{Softmax}(K^T Q) \in \mathbb{R}^{V \times H \times W \times C}.$$  

Finally, the output matrix $O \in \mathbb{R}^{V \times H \times W \times C}$ is converted back to a third-order tensor $O \in \mathbb{R}^{H/2 \times (W/2) \times C}$, as output of the GT layer. To this end, each position feature in the output tensor $O$ is computed as a weighted sum of all feature vectors in $V$, which is obtained directly from the input tensor $I$. Apparently, global information from input features is captured and fused to generate the output through our GT layers. In addition, the spatial sizes $(H/2, W/2)$ of output feature maps are determined by spatial sizes of the query tensor $Q$, while the number of output feature maps $C_{V}$ depends on the value tensor $V$. Theoretically, our proposed GT layer can generate feature maps of arbitrary dimensions. In practice, the commonly used local operators either keep the spatial sizes of feature maps, or double the spatial sizes for up-sampling, or halve the spatial sizes for down-sampling. Hence, in this work, we propose to substitute these local operators by three types of global transformers.

The traditional local operators, such as $2 \times 2$ max pooling and convolution with stride 2, may also capture global information by stacking the same operator many times. However, such stacking is not efficient. For example, when trying to capture the global information in an $L \times L$ area, the $2 \times 2$ max pooling needs to be repeated $\lceil \log_{2} L \rceil$ times. However, our proposed GT layers can capture global relationships among any two positions using only one layer. Therefore, our proposed methods are more efficient and effective compared to traditional local operators.

### 3.2 Global Transformer U-Nets

It is well-known that encoder-decoder architectures like U-Nets [Ronneberger et al., 2015] have achieved the state-of-the-art performance in various dense prediction tasks. However, these networks employ local operators like convolution, pooling and deconvolution, which cannot efficiently capture global information. Based on our GT layer, we propose a novel network for dense prediction tasks, known as the global transformer U-Nets (GT U-Nets).

In U-Nets, down-sampling layers are employed to reduce spatial sizes and obtain high-level features, while up-sampling layers are used to recover spatial dimensions. The commonly used convolution, pooling, and deconvolution operators are performed in local neighborhood on feature maps. We propose to substitute these local operators with our proposed GT layers. By setting different sizes for the query tensor $Q$, our proposed GT layers can be employed for both down-sampling and up-sampling, while considering global information to build output features. Suppose an input feature map has spatial size of $H \times W$. For the down-sampling operator, a GT layer halves the spatial sizes of input feature maps, which can be achieved by setting the sizes of query tensor as $H_{Q} = H/2$ and $W_{Q} = W/2$. For the up-sampling operator, the spatial sizes of feature maps are doubled by setting $H_{Q} = 2H$ and $W_{Q} = 2W$ in a GT layer. In addition, the GST layers are employed to transmit information from the encoder to the decoder in the bottom block of U-Nets.

In addition, due to the multiple down-sampling and up-sampling operators in U-Nets, the spatial information, such as the shapes and locations of cellular structures, is largely lost in its information flow. Since the decoder recovers the spatial sizes from high-level features, the prediction may not fully incorporate all spatial information while such spatial information is important to perform dense prediction. Hence, we adapt the idea to build skip connections between the encoder and the decoder in U-Nets. Such connections are expected to enable the sharing of spatial information and high-level features between the encoder and decoder, and hence improve the performance of dense prediction.

### 3.3 Global Transformer U-Nets with Dense Blocks

To perform dense prediction on images, deep networks are usually required to extract high-level features. However, a known problem for training very deep CNNs is that gradient flow in deep networks is sometimes saturated. Residual connections have been shown to be effective to solve such a problem in various popular networks, such as ResNets [He et al., 2016] and DenseNets [Huang et al., 2017]. In ResNets, residual connections are employed in residual blocks to share the different levels of features between the non-linear transformation of the input and the identity mapping. They benefit the convergence of very deep neural networks by providing a highway for the gradients to back propagate. Recently, residual U-Nets [Quan et al., 2016; Eslahi et al., 2017] is proposed to inherit the benefits of both long-range skip connections and short-range residual connections. It is shown to obtain more precise results on dense prediction tasks without increasing parameters. Since DenseNets employ extreme residual connections, also known as dense connections, to build dense blocks and achieve state-of-the-art performance on image classification tasks, we follow a similar idea to use dense blocks in our proposed global transformer U-Nets.

The general structure of our model is shown in Figure 2. We combine the dense block and the GT layer to better incorporate dense connections. For the encoder part, each dense block is followed by a GTD layer, since the dense block retains the spatial sizes of the input while the GTD layer performs down-sampling. The reduction of spatial sizes is compensated by the growth in feature map number generated by the dense block. Correspondingly, each GUT layer in the decoder is followed by a dense block, and the GUT layer recovers the spatial sizes and reduces the number of feature maps.

For each dense block in our model, residual connections are employed to connect every layer and its subsequent layers. A typical $L$-layer dense block can be defined as

$$x_{L} = H_{L}([x_{0}, x_{1}, \ldots, x_{L-2}, x_{L-1}]),$$

where $x_{0}$ is the input to the dense block, $x_{i} \in \{[\ldots, [x_{0}], \ldots]\}$ is the output of the $i^{th}$ layer, and $\ldots$ represents the concatenation operator. $H_{i}(\cdot)$ denotes a series of operators, including convolution, batch normalization (BN) [Ioffe and Szegedy, 2015], ReLU activation, and dropout [Srivastava et al., 2014]. Each layer in a dense block generates $k$ new feature maps and they are concatenated with previously generated feature maps. Note that $k$ is also called the growth rate of dense block. Hence, the output of the dense block contains information regarding both the input feature maps $x_{0}$ and $k \times L$ newly generated feature maps. A general illustration of our employed dense block is shown in Figure 3.

Note that we add a $1 \times 1$ convolution layer before the output to make the dense block more flexible so that the number of output feature maps can be controlled. Intuitively, a dense block encourages feature reuse between layers. In addition, compared with traditional networks of the same capacity, it can significantly reduce the number of parameters since each layer in dense block only contains $k$ new feature maps.

### 3.4 Multi-Scale Input Strategy

One training strategy for dense prediction tasks is to feed the whole image as input and produce predictions for all input pixels. However, such a strategy requires excessive memory on training hardware. On modern hardware like GPUs, memory resource is always limited. This data feeding strategy becomes inefficient for large inputs, which is quite common for biological image processing tasks. One common solution is to crop small
4 Experimental Studies

We use both quantitative and qualitative evaluations to demonstrate the effectiveness of our proposed model. The dataset used for evaluation and the experimental settings are presented in Section 4.1. We compare our experimental results with the existing approaches in Section 4.2. Finally, we provide an ablation analysis in Section 4.3.

4.1 Dataset

We use the dataset in the existing work of Christiansen et al. [2018]. The dataset contains 2D high-resolution microscopy images from five different laboratories. Note that a set of such 2D microscopy images are originally z-stacks of transmitted-light images collected from one 3D biomedical sample. Christiansen et al. [2018] specifically, the z-stack 2D images are collected from several planes at equidistant intervals along the z axis of a 3D sample. They collected 13 2D images from a sample. Thus, for all the 13 2D images from the same set, they share the same fluorescence image for each fluorescent label. Different laboratories obtained the microscopy images under different conditions using different methods. Two imaging modalities, namely confocal and wide-field are used during microscopy photon imaging. In addition, three different types of cells are collected by different laboratories, including human motor neurons from induced pluripotent stem cells (iPSCs), primary rat cortical cultures, and human breast cancer line. Detailed information of this dataset is given in Table 1.

### Table 1. A description of the datasets used in our experiments. The datasets are created by Christiansen et al. [2018] under five conditions from three laboratories.

| Condition | Cell Type | Fluorescent Label 1 and Modality | Fluorescent Label 2 and Modality | Fluorescent Label 3 and Modality | Training Data (2D) | Testing Data (2D) | Spatial Sizes | Laboratory |
|-----------|-----------|---------------------------------|---------------------------------|---------------------------------|--------------------|-----------------|--------------|------------|
| A | Human motor neurons | DAPI (Confocal) | MAP2 (Confocal) | NFH (Confocal) | 273 | 273 | 2400x2400 | Finkbeiner |
| B | Human motor neurons | DAPI (Confocal) | DEAD (Confocal) | - | 273 | 273 | 2400x2400 | Finkbeiner |
| C | Primary rat cortical cultures | DAPI (Confocal) | MAP2 (Confocal) | NFH (Confocal) | 26 | 13 | 4600x3500 | Google |
| D | Primary rat cortical cultures | DAPI (Confocal) | CellMask (Confocal) | - | 13 | 13 | 3500x3500 | Google |

4.2 Experimental Setup

The architecture of our model is shown in Figure 2. It shows the changes of feature maps through the information flow in our networks. The growth rate of our dense blocks is set to 16. We employ three GDT layers with dense blocks in our encoder to perform down-sampling and extract high-level features. Correspondingly, there are three GUT layers with dense blocks to recover the spatial sizes. For the bottom block connecting the encoder and the decoder, we employ one GST layer and one dense block. The depth of different dense blocks are different. Note that the depths of different dense blocks are different.

Training examples are obtained by randomly cropping from the raw images. Since we employ the multi-scale input strategy, we crop images at three different scales; namely 64 × 64, 128 × 128, and 256 × 256. The network predicts fluorescence maps with sizes equal to 128 × 128. We train our proposed model across all target-related training examples in a multi-task learning manner. Number of output fluorescence maps equals to number of target fluorescent labels. In addition, for each pixel in the predicted maps, the network outputs a probability distribution over 256 pixel values, so c = 256 in Table 2. Cross-entropy loss is employed for network training. Note that there are at most three fluorescent labels available for a given input. The loss is calculated by only considering target labels while irrelevant labels are ignored. During training, we employ the dropout with a rate of 0.5 in our dense blocks to avoid over-fitting. To optimize the model, we employ the Adam optimizer [Kingma and Ba, 2014] with a learning rate of 1 × e−3 and a batch size of 4. During the prediction stage, test patches are cropped in a sliding-window fashion. We...
extract patches from test images with the same sizes as those in training ($128 \times 128$) by sliding a window with a constant step size. The step size is set to 64 in our experiments. Then we build predictions for the original test images based on predictions of small patches.

4.3 Comparison with the Baseline

We compare our approach with the existing model [Christiansen et al., 2018] as it achieves the state-of-the-art performance on the dataset we are using. To demonstrate the effectiveness of our proposed approach, we conduct comparisons with the baseline method for three different tasks:
Table 4. Ablation analysis on prediction of cell nuclei by comparing Pearson’s correlations between different models. DB denotes dense block. All models are trained across all training samples and evaluated on one specific task. Details of the models are provided in Section 3.

|                      | Condition A | Condition B | Condition C | Condition D |
|----------------------|-------------|-------------|-------------|-------------|
| Baseline             | 0.928 ± 0.0026 | 0.913 ± 0.0018 | 0.902 ± 0.0029 | 0.896 ± 0.0032 |
| Ours                 | 0.948 ± 0.0027 | 0.933 ± 0.0019 | 0.915 ± 0.0031 | 0.909 ± 0.0022 |

**Prediction of Cell Viability:** Given an image, the task is to predict the viability of live cells. The nuclei of live cells are labeled using DAPI on both confocal and wild field modalities. Samples created under condition A, B, C, D have fluorescent labels to investigate the cell nuclei.

**Prediction of Cell Type:** Given an image, this task predicts the neurons with cell nuclei as visual background. Dead cells on images are labeled with propidium iodide (PI) on confocal modality. These images are obtained under condition C.

**Prediction of Cell Nuclei:** Given an image, this task predicts the dead cells with cell nuclei as visual background. Dead cells on images are labeled using DAPI on both confocal and wild field modalities. Samples created under condition A, B, C, D have fluorescent labels to investigate the cell nuclei.

**Prediction of Cell Viability:** Given an image, this task predicts the viability of live cells. The nuclei of live cells are labeled using DAPI on both confocal and wild field modalities. Samples created under condition A, B, C, D have fluorescent labels to investigate the cell nuclei.

5 Conclusions

Visualizing cellular structure is important to understand cellular functions. Fluorescence microscopy is a popular technique but has key limitations. Here, we develop a novel deep learning model to directly predict labeled fluorescence images from unlabeled images. To fuse global information effectively and efficiently, we propose a novel global transformer layer and build an U-Net like network by incorporating our proposed global transformer layer and dense blocks. A novel multi-scale input strategy is also proposed to combine both global and local features for more accurate predictions. Experimental results on various fluorescence image prediction tasks indicate that our model outperforms the baseline model significantly. In addition, ablation study shows that all of our proposed modules are effective to improve predictive performance.

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