Giving grayscale microscopy images a colourful world by using artificial intelligence technology.
Nanoscale Microscopy Images Colourisation Using Neural Networks

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ABSTRACT

Microscopy images are powerful tools and widely used in the majority of research areas, such as biology, chemistry, physics and materials fields by various microscopies (Scanning Electron Microscope (SEM), Atomic Force Microscope (AFM) and the optical microscope, et al.). However, most of the microscopy images are colourless due to the unique imaging mechanism. Though investigating on some popular solutions proposed recently about colourizing microscopy images, we notice the process of those methods are usually tedious, complicated, and time-consuming. In this paper, inspired by the achievement of machine learning algorithms on different
science fields, we introduce two artificial neural networks for grey microscopy image colourization: An end-to-end convolutional neural network (CNN) with a pre-trained model for feature extraction and a pixel-to-pixel Neural Style Transfer convolutional neural network (NST-CNN) which can colourize grey microscopy images with semantic information learned from a user-provided colour image at inference time.

Our results show that our algorithm not only could able to colour the microscopy images under complex circumstances precisely but also make the colour naturally according to a massive number of nature images training with proper hue and saturation.

Keywords: Colourisation, Deep learning, Microscopy images, Neural networks
1. Introduction

Nanotechnology is the art and science of manipulating matter at nanoscale to create new and unique materials and products[1-4]. Electron microscopes like the scanning electron microscope (SEM)[5, 6] and transmission electron microscope (TEM)[7], near-field microscopes like atomic force microscope (AFM)[8, 9] and scanning tunnelling microscope (STM)[10, 11] are widely used in various scientific fields. As they are versatile imaging and measurement sources, they help researchers and scientists visualize structures from nanoscale or microscale level, providing observations required for nanoscience and nanotechnology experiments[12]. These imaging techniques are strongly essential to various types of researchers.

Since some of these microscope devices, form images with physical parameters instead of photons of visible light. For example, SEM produces images by scanning the surface of the sample with a focused beam of electrons, while AFM measures the forces between the probe and the sample as a function of their mutual separation. Hence, the resulting images are grayscale, and these single-channel images contain less information than the coloured version of the same image. Despite the many advantages of imaging results by these devices, we do not see the full colour micro-world. For example, most of the micro images contain multi-components structures, however, there are only grey image obtained by SEM /TEM/AFM, and so on. As a result, using the grayscale images out-of-the-box may result in limited observation between the experimenter and their audience. To prevent these limitations and to help bridge the gap, researchers have developed different tools, and authors spend money
and time to redraw or to colour their experimental images as colourful, while faithfully representing the precise 3D appearance of the samples.

Colourisation of grayscale SEM images is a common task among researchers working with microscopy images. In most images, the signal intensity at each pixel corresponds to a single number that represents the proportion number of electrons emitted, and these numbers are usually described as a grayscale image. Perhaps the most common approach is to use software like Mountains-Map, Adobe Photoshop, Fiji, Image J, or even by-hand. This is time-consuming and requires distinctive knowledge. Some methods come with different tools for automatic colourisation[13], but they still require massive user inputs. This process requires extensive background researches and inputs, just to colour one single image. The process might start from reading or researching about what is in the image and how to represent the colour, ending with restoring the original content and colourising the arrangement. In some scenarios, a picture can take up to several days to colourise, and it requires extensive research if the structures in the image are complicated. Some objects might need multi-layers and different colour shades to get it just right; it requires specialised knowledge of software or manual skills. Furthermore, gradient ramp and fusion between two colours are extensively common in micro-world images, and it is a huge obstacle for ordinary software and hand drawing.

To solve these problems, previously, abundant colourization methods were developed and worked well. Some methods given an input grayscale image, first define one or more colour reference images (provided by a user or retrieved automatically)
to be used as source data. Then, following the Image Analogies framework, colour is transferred onto the input image from analogous regions of the reference image[14,15]. Parametric methods, on the other hand, learn prediction functions from large datasets of colour images at training time, posing the problem as either regression onto continuous colour space [16,17] or classification of quantized colour values[18]. Researchers proposed a multi-modal scheme, where each pixel was given a probability for each possible colour[19]. A recent method introduced a model which combines a deep convolutional neural network (D-CNN) trained from scratch with high-level features extracted from a pre-trained model[20]. There are also methods, which leverage large-scale data and CNNs[21]. In terms of loss function of the methods, classification loss was used with rebalanced rare classes[19], other works use an un-rebalanced classification loss and a regression loss[22]. However, these methods are for general-purpose image colourisation and are not explicitly designed for nano/micro-structural microscopy images. To our knowledge, most colourisation works on microscopy images, and their image colourisation used graphics software and human hand drawing, not deep learning methods.

In this paper, we proposed two approaches to colourise the grayscale microscopy images by using artificial neural networks. These algorithms learn multiple levels of colour representations corresponding to different levels of abstraction in microscopy images. To improve the relationship between the samples under the microscopes and their real-world representative, and to answer what will help our algorithm understand what is in the image and their relations to one another? we use pre-trained inception
ResNetV3 model [23, 24] as a feature extractor. This pre-trained model was trained on existed dataset ImageNet[25]. Microscopy images might not have one exact colour or ground truth to compare with the output. Instead, colouring these images must look realistic and represent their desired appearance. By our designed models, the results demonstrated a good colourization ability on most microscopy images with/without substrate.

**Experimental and Methods**

CIELAB colour space was used which colour-opponent space with dimension L for luminance and “a” and “b” for the red-green colour spectrum and blue-yellow colour-opponent dimensions respectively[26]. For each given image X, it has a brightness channel “L”. The model learns to predict “a” and “b” colour and contrast values. Grayscale images can be considered pixel values with the only L in the LAB colour space, and by using LAB colour space, our model will only learn how to colour the images, not how to maintain light intensities. Predicting the “ab” in LAB colour space can be either trained using colourful microscopy images or informed by a colourful reference photo. Finally, the output images are converted into red, green and blue in RGB colour spaces to use them in general application. The full system architecture has pre-process and post-process steps to handle all the input and output images before and after colourisation. The pre-processing mainly takes the resizing and reshaping task, while the post-processing deals with colour balancing and converting to the best colour space. Sometimes where there are un-necessary colour shadows on
the image, this step removes them using image processing techniques like
thresholding[27]. For better accuracy, the algorithm divides the colours into the same
grey same value, which leads to categorising the pixels in the same content for two
identical objects in different positions.

Dataset

“SEMCOLOURFUL” dataset (https://isrugeek.github.io/semcolour/), the first
colourful SEM images dataset collected was contributed in this paper. The dataset
was a collection of ~1000 colourful SEM images (each image in this dataset is an
RGB image), and it was divided as 90% for TrainSET and 10% for TestSET. The images have different shapes and sizes due to varying resolution of the images; for simplicity, all images in the dataset were resized to 300 × 300 pixels. During training time, these images can be an input for the encoder and scale up again to 299 × 299 for feature extraction in the network. Here each image will be stretched or shrunken during the resizing process. To keep their aspect ratio, white pad was added if needed.

Model development

Two methods were used in this paper. These methods learned multiple levels of
colour representations corresponding to different levels of abstraction in microscopy
images. The methods called end-to-end convolutional neural network (EE-CNN) and
NST-convolutional neural networks models (NST-CNN). Convolutional neural
networks are a type of neural network made to process image data[28].

EE-CNN model
The first model EE-CNN was fully trained on a colourful microscopy images from our dataset. To improve the relationship between microscopy samples and their real-world colourful representative, we used a pre-trained model Inception ResNet V3 [23, 24, 29] as a feature extractor. The pre-trained model was trained on ImageNet[25] with over 1.2 million images. The proposed model has an encoder-decoder structure.

Assuming an input image $X$ with height $H$ and width $W$ in $LAB^*$ colour space.

The encoder network layer takes $H \times W \times L$ channel images and outputs $\frac{1}{8} (H \times W) \times 512$ unique features. It has eight convolutional layers, each with $4 \times 4$ kernels. Padding method was used to the layer’s input size.

While working with colourful microscopy images, there are only limited number of images. Instead of training a feature extractor from scratch, a pre-trained classifier model Inception-V3[24] was used. By using this classifier, it is possible to retrieve the grayscale image from the final layer and discover the relation between what is in the object (input) and the real-world example which the pre-trained model trained on. The loss function on ImageNet[30]. A fusion method from Iizuka, S.et.al[22], which takes a feature vector from the encoder and reproduces it $\frac{H}{8} \times \frac{H}{8}$ times and binds it to the feature extraction in the next layer.

The decoder takes the output from the fusion layer and applies convolutional up-sampling layers. This can provide the model with a final image of size $H \times W \times 2$. Our up-sampling function adopts a nearest neighbour approach. Skip connections [29] were used in 3 layers of the encoder to transmit outputs directly to the decoder.
Mean squared error (MSE) computed between the estimated \( a, b \) colour in pixel and their real value for training loss.

\[
L(Y_{ab}, Y) = \frac{1}{2} \sum_{h,w} |Y_{h,w} - Y_{ab(h,w)}|^2
\]

Where \( Y_{ab} \) and \( Y \) are the predicted and the real values of \( ab \) respectively in each pixel, and \( h \) and \( w \) are the height and width of the images. The Adam optimizer[31] back propagates the loss method. To allow batch processing, the input image size was fixed during the training time.

Our first model was shown in Fig. 1(a). The model has four components:

- **Encoder:** Takes the input image and middle-level features like the colour values.
- **Inception module (Feature extractor):** Obtains high-level features.
- **Fusion layer:** Merge the encoder and feature extractor.
- **Decoder:** Gives us the output.

**Encoder:** The encoder process is taking \( H \times W \) only L channel images and outputs \( \frac{1}{8} (H \times W) \times 512 \) unique feature. It has 8 convolutional layers each \( 4 \times 4 \) kernels. Padding was used to the layer’s input size. Stride has applied on each odd numbered layers. Here it is important to reduce their size for computations.

**Feature Extractor:** A pre-trained model is a model that was trained on a large benchmark dataset to solve a problem of image detection or classification. These pre-trained models can be used as feature extractor. Accordingly, due to the computational cost of training such models and lack of dataset, in this paper, instead
of training feature extraction from scratch by using transfer learning we have applied existed classifier trained on ImageNet with over 1.2 millions of images.

**Fusion**: The fusion method states as follows by taking a feature vectors from encoder and reproduce $\frac{H}{8} \times \frac{W}{8}$ times and then it will bind it to the feature extraction one and give it to the next layer[23]. This approach obtains a single volume with the encoded image and the mid-level features of shape $\frac{H}{8} \times \frac{W}{8} \times 1000$. By mirroring the feature vector and concatenating the vector several times it will help to ensure that the semantic information conveyed by the feature vector is uniformly distributed among all spatial regions of the image.

**Decoder**: The decoder takes the output from the fusion and apply convolutional up-sampling layers to get the final image with $H \times W \times 2$. Our up-sampling function was performed using basic nearest neighbour approach, rather than calculate an average value by some weighting criteria we simply determine the “nearest” neighbouring pixel for up sampling. So that the output’s height and width are twice the input.

The summarised flow of this method is by providing the image's luminance component ($L$); the model estimates the remaining $ab$ components and combines the input $L$ with the predicted $a$ and $b$. Finally, the output image is converted to RGB colour space.

**NST-CNN Model**

Some microscopy images, like red blood cells, plants leave images have known colours. To solve this colouring problem, our EE-CNN model was redesigned to accept grayscale microscopy image and colourful real-world images as input from the
user. In this method, our model was inspired by neural style transfer (NST)[32]. The input grayscale microscopy image treated as content and the colourful real-world image as reference style; unlike traditional style transfer, the microscopy image only receives colour information. Therefore, the model can transfer precise colour tones from reference to content. For different colour distribution and when the image has different objects with different orientations, our algorithm classifies and categorises the same grey pixels under the same group and then matches the same grey values with the reference image to make their content colourful. The model uses one image as a reference and learns all the colours from the reference image content wisely, and the learned colour will be transfer into the content image to colourize. As any pre-trained haven’t been used as feature extractor in this method, an approach by using the same $L$ and $AB$ is used to categorise same colour channel and their values. In this approach, we take the value of L in the input image and find the similar pixels in the image to give them same $AB$ value. This method (NST-CNN) model is for pixel-to-pixel colour transfer as shown in Fig. 1 (b). The model takes one content ($X_c$) and one reference image ($X_r$) as input from the user and resize them to $H \times W$ in LAB colour space. The CIE LAB components values:

$$f(X) = \bigcup_{0}^{100} L + \bigcup_{-128}^{128} (a + b)$$

By taking the $L$ value from both images, $X_L = H \times W \times 1$ as input the model learns the colour from the reference image and predicts $Y_{ab} = R^{(H \times W \times 2)}$ for the content image and finally, generates fully coloured versions on the style image $I_{LAB} = R^{(H \times W \times 3)}$. Our target function $F$ maps our input $X$ to output $Y \in R^{(H \times W \times 2)}$, that is, $Y = F(X_L)$. For proper learning and feature extracting as a pre-training step,
the input needs to be scaled and centralized in accordance with the range of the pixel values of all LAB components in LAB colour space. \( L \) is a grayscale layer from input \( X \) which has a value from 0 to 100, the \( a \) layer have a value -128 to 128 and the \( b \) layer is from -128 to 128, all in LAB colour space.

To summarize the process, our NST-CNN model takes two images as input one for the reference and one as content image, after the CNN model is trained on the reference image it will apply the colour as style transfer to the content image. In addition, this method is also can accept two reference images, with proper pre-processing the input image can be divided and colourized from two reference images.

**Figure 1.** The overview of proposed mode: (a) End-to-end CNN (EE-CNN) model with encoder-decoder structure. The model has encoder to obtain important features, inception module to extract features from real-world image and finally the decoder uses the features from encoder and inception module to predict the output. (b) Pixel-to-Pixel style transfer-based CNN (NST-CNN) model. The model architecture takes
two inputs: one image as reference and grayscale microscopy image as a style image. The model has same CNN structure as EE-CNN model, but the full network architecture is like Neural style transfer. The model train on one image then it saves the weights at the inference time. Finally, transfer of the trained weight colour to the microscopy images as shown in the figure.

**Experiments**

From the dataset’s TrainSET was divided to 90% for training and 10% for validation during training. The network trained and tested on MILA’s cluster node, leveraging the NVIDIA CUDA 10 Toolkit, and the 3 NVIDIA Tesla K80 GPU for training. The full training took around 6.5 hours with the batch size of 16 to avoid overflowing of the GPU memory. Adam optimizer [31] is used during the training process; the initial learning rate is 0.0001. The loss function is mean squared error (MSE) calculated in equation. The model was trained for 300 epochs and stop to avoid the overfitting problem[33]. The whole program was written using the python programming language, and we used Tensorflow [34] and Keras[35] deep learning framework libraries. The pre-processing uses OpenCV and Scikit-image[36].

**Results and discussion**

Different microscopy images scenarios were checked and then presented the approach on SEM micrograph of human cell, plant tissues, pollen grains, fab-nanostructure,
insects, or shells and other commonly used specimen microscopy samples. The results from the colouring model vary in the different samples under microscope scenarios. In various situations, our algorithm performed well in colourisation task. The main categories of these samples and their colourisation results scenarios discussed below.

**Colourization by EE-CNN model**

Our end-to-end convolutional neural network (EE-CNN) approach was designed to identify an input microscopy images and colourise them independently and correctly. Most microscopy images are different and might not have ground truth or one true colour therefore we need to identify them accurately. To determine the objects and their relation with the real-world objects, we used the pre-trained model to find the patterns and give them the colour. Fig. 2 illustrates the results from our EE-CNN model. Several grayscale microscopies images (bacillus, cilia, wood surface, nuclear membrane, stamens, leaf surface) were selected as the research samples (the web links of images are shown in Table S1). It is obviously that the colourization results display a beauty of multi-colour with soft colour gradient (Fig. ((h)-(m))). For example, the detailed components in Fig. 2(c) could be easily distinguished in our colourized image (Fig. 2(j)). In addition, the combination of luminosity and colour in colourized images dramatically improve the quality of images (Fig. 2(k), (m)). Significantly, the images of leaf surface can be recognized precisely as the pre-trained dataset contain huge number of nature images.
**Figure 2.** Results from EE-CNN model and colour analysis of EE-CNN model results in HSV colour space. Input greyscale images of bacillus (a), cilia(b), wood surface(c), nuclear membrane(d), stamens(e), leaf surface(f). Together with their colourized results ((h)-(m)), respectively. 3D intensity distribution of saturation value from Fig. 2(I) (Fig. 2(n)) and Fig. 2(h) (Fig. 2(o)). The grey surface in top side of each Fig. represent the saturation intensity distribution of greyscale image from Fig. 2(e) and Fig. 2(a).
To check the colourized results of our EE-CNN model, the distribution of each
colour composition is analysed. HSV (hue, saturation, value) are alternative
representations of the RGB colour model[37]. The selected saturation value in Fig.
2(n)) and Fig. 2(o) were obtained from Fig. 2(l) and Fig. 2(h), respectively. The
colourized results show a relatively uniform saturation intensity distribution in main
objects (bacillus, stamens). Furthermore, another two type of images were colourized
by our algorithm. Pollen granule image without substrate in Fig. S2(a) and barium
carbonate crystals grow on substrate in Fig. S2(d). The EE-CNN model painted the
green colour to the pollen granule, while giving gold colour to barium carbonate
crystals. Form the separation of L and ab channels in output images, it clearly shows
that the colour matches to the pollen particles well (Fig. S2(b)). In terms of barium
carbonate crystals with substrate, the crystals could be colourized properly (Fig.
S2(e)). However, the substrate was also coloured by gold value, together with the
influence of the shadows.

A pre-processing strategy was applied for the keeping of uniform colour on one
kind of object in an image to improve the quality of colourization. Holistically nested
edge detection[38] was uses to obtain the edge from input images Fig. 3((b), (e))
before the colourization. Based on those boundary condition, the model colour the
bounded area with a same colour, this process was shown in Fig. 3(c, f). However,
this pre-processing strategy is successfully used in the strong contrast images but
failed (not well) in some soft edge images, such as the image exhibited in Fig. 3(d).
**Fig. 3.** Holistically nested edge detection-based colourisation. Our input images ((a), (d)) and the detected edge from edge detection algorithm ((b), (e)) and finally the coloured results ((c), (f)).

**Colourization by NST-CNN model**

To solve the background problem that we met in EE-CNN model, a new pixel-to-pixel Neural Style Transfer convolutional neural network (NST-CNN) model based on the EE-CNN model was developed. Firstly, some observation results by microscopy images, especially obtained by transmission electron microscopy, only have the main objects with black/white background. This is due to the use of mesh grid to support the samples. In this case, the NST-CNN algorithm will only colour the main objects and the background remains black, compared with EE-CNN result in Fig. S2(c). In addition, it might have the requirements that give a specific colour to the main objects. Therefore, a reference picture was selected as the guiding colour. For example, the input SEM image of virus (Fig. 4(a)) was coloured beautifully with its reference image of bread (Fig. 4(b)) as demonstrated in Fig. 4(c). The flower anthers image presented in Fig. 4(d) was designed for getting the colour from another
colourful brain neuron image which also has black background (Fig. 4(e)). The final colourized result revealed the same uniform colour as the reference image (Fig. 4(f)). Furthermore, it is obvious to know that some objects must represent their real-world representation such as red blood cell which need to have a red colour. As a result, red colour reference image (Fig. 4(h)) was selected and got a beautiful result image that exhibit the desired red colour. Compared with the results made by EE-CNN, a clear black background colourized picture was obtained, together with specified reference colour on main objects (Fig. 4(c, f, i)).
Figure 4. Colouring results for the images with a black background and Colour analysis of our NST-CNN model results in HSV colour space. (a) input greyscale virus SEM image, reference image of bread (b) and coloured result accordingly (c). (d) input greyscale anthers SEM image (d), reference image of blue coloured neuron cell (e), and the result image (f). (g) input sample SEM image of red blood cells, red
tablet picture as a reference, and red colourization result (i). 3D intensity distribution of saturation value (j) and hue value (k) from Fig. 4(f).

To check the quality of colourization results by our NST-CNN model, the saturation value and hue value from HSV colour space was also analyzed. The colourized sample in Fig. 4(f) was selected as the sample. 3D intensity distribution of saturation reveals a rich saturation value in anther structures (Fig. 4(j)), but with the value of 255 (black) in background. Hue value can be typically represented the properties of color. The hue intensity distribution from our colourized sample (Fig. 4(k)) exhibits an uniform value of one color, with only some tiny color noise inside. Furthermore, we made a comparison with previous general proposed model[19]. For the first row of greyscale images (Fig. S3 (a-d)), the second row and third row represent the results of previous approaches (Fig. S3 (a1-d1)) and our methods (Fig. S3 (a2-d2)), respectively. It is clear show that some of the background is coloured with colour print which do not have necessary (Fig. S3 (a1)). In addition, the same object was coloured by the unnecessary multi-colour (Fig. S3 (b1, c1, d1)), since they are the same object have the same properties.

In another case, the majority of samples might have a substrate under the primary object. These substrates can be the surface on which the material deposed or the wafer or the specially fabricated micro/nano structures on substrates. During the imaging stage, the microscopy images will cover both objects and substrates, for example, the chromosome deposed in the surface of substrates (Fig. 5(a, b)). When colouring these images, the algorithm divides the primary object (orange arrows in Fig. 5(a, b)) as
foreground and the substrate (blue arrows) on the image as background. By our NST-CNN method, by providing a reference picture (randomly selected), the coloured results exhibited a distinguishable double colour images in Fig. 5(c, d), which is not skilled by our EE-CNN model.

![Figure 5](image)

**Figure 5.** Colouring results of greyscale images with main objects and substrates. (a) grayscale image of chromosome on substrate and (b) double helix DNA on substrate. colourization results by NST-CNN algorithm with pink DNA (c) and green DNA fiber (d).

Our NST-CNN model can also show improvement if we manually pre-process the image. Fig. 6(c) is a microscopy image result from the SEM microscope which have two visible objects (bedbug in the fibre) in the input image. Adaptive-thresholding was done in the input image so that it can separate the two objects in the image, after the thresholding two reference images were applied (Fig. 6(a, b)) for each separated
content to get a colourful result (Fig. 6(d)). The Hue value analyzed result exhibits a balanced colourization (Fig. S4). However, the method shows improvement on limited images. This is because the adaptive thresholding cannot be well enough to identify and group objects in an image. However, the successful colourized images display a beautiful colourisation result.

![Figure 6](image)

**Figure 6.** Colouring results with manual pre-processing for an image with two contents (c). We applied adaptive thresholding and use two reference images (a,b) to get a colourful results (d).

Finally, a quantitative metric was proposed to measure the performance of general colourization task which based on survey mechanism. First, 16 images were randomly selected from our dataset and 16 images from the predictions of our model. Then, the 32 images mixed randomly and upload on a website (https://github.com/isrugeek/semcolour/tree/master/semcolor-survey). Participants were invited to select 16 images which they consider as the predictions from our model. After submitting the result, the accuracy of \( Y_i \) of the selection of participant \( i \) was calculated. The higher of \( Y_i \) means, the better performance of our model. The results show in Table S1. As we can see that the NST-CNN method is slightly better
than the EE-CNN method since we give a specific reference image for each input SEM-image. And the accuracies of two methods are both closed to 0.5, which means a human cannot distinguish which one is select from human-print and which one is the prediction from our model.

**Conclusion**

To summarise, in this work, we have shown that fully implemented two deep learning architectures can able to colourise nanoscale microscopy images with the natural colour. With the help of pre-trained Inception ResNetV2 model, most greyscale images without substrate could be successfully colourised with proper colours by our EE-CNN algorithm. Besides, holistically nested edge detection was developed to optimise the approach to high contrast images. In order to colourise the images with a black background or substrate, we further developed the NST-CNN model based on EE-CNN. By giving reference images, our methods perform well colourisation ability with the separation of the substrate. Furthermore, multi-objects images could also be well colourised with different colours by giving a corresponding number of reference images. By using generative models and extending our dataset, we believed that it can improve the precision of colourisation in the future. Overall, we have shown that colourisation with neural networks can precisely give colourful and attractive images without sacrificing their original appearance, which provides superior help to scientists or even other fields such as arts.
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Electronic Supplementary Material: Supplementary material (grayscale images links from websites; Results from EE-CNN model; Comparison results with Zhang et al.; The Hue value analysed results from Fig. 6.) is available in the online version of this article at

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