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Design and evaluation of a Deep Learning approach to quantify synthetic volumetric autofluorescence data of immune cell infiltrate

Master’s Thesis

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*Submitted by*

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Zusammenfassung

**Design und Evaluierung eines Deep-Learning-Ansatzes zur Quantifizierung synthetischer volumetrischer Autofluoreszenzdaten von Immunzellinfiltraten**

Da die Biologie eine quantitative Disziplin ist, sind viele Beweise erforderlich, um eine Hypothese zu stützen. Bilder von Zellen und Geweben sind eine hervorragende Datenquelle, aber um aussagekräftige Erkenntnisse zu erhalten, müssen sie verarbeitet, analysiert und quantifiziert werden. Deep Neural Networks sind eine der Techniken, die im Datenanalyseprozess verwendet werden. Diese Netzwerke können bei Aufgaben wie der Bildsegmentierung und -klassifizierung bemerkenswerte Leistungen erbringen, benötigen dafür jedoch viele Trainingsdaten. Wenn Bilder dreidimensional sind, wird die Kennzeichnung von Trainingsdaten erheblich schwieriger. Um dieses Problem anzugehen, ist ein Simulator für synthetische Daten erforderlich, um dieses Problem zu lösen. Es kann unbegrenzt kommentierte Daten für neuronale Netze erstellen, um deren Leistung zu testen. Diese Arbeit entwickelt einen Simulationsrahmen, vergleicht seine Ergebnisse mit tatsächlichen Stapeln, die mit einem Multiphotonenmikroskop aufgenommen wurden, und trainiert ein tiefes Faltungsnetzwerk, das diese künstlichen Daten verwendet, um Immunzellen zu zählen und zu klassifizieren.

Abstract **Design and evaluation of a Deep Learning approach to quantify synthetic volumetric autofluorescence data of immune cell infiltrate**

As biology is a quantitative discipline, it requires a lot of evidence to support a hypothesis. Images of cells and tissues are an excellent source of data, but to get meaningful insights, they must be processed, analyzed, and quantified. Deep Neural Networks are one of the techniques used in the data analysis process. These networks may perform remarkably in tasks like picture segmentation and classification, but they need a lot of training data to do so. When images are three-dimensional, labeling training data becomes considerably more difficult. To address this issue, a synthetic data simulator is necessary to solve this problem. It can create unlimited annotated data for neural networks to test their performance. This thesis develops a simulation framework, compares its results to actual stacks acquired with a multiphoton microscope, and trains a deep convolutional network using this artificial data to count and classify immune cells.

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Abbreviations

|  |  |
| --- | --- |
| MPM | Multiphoton Microscope |
| CNN | Convolutional Neural Network |
| H&E | Hematoxylin and Eosin |
| RF | Random Forest |
| DTC | Decision Tree Classifier |
| FAD | Flavin Adenine Dinucleotide |
|  |  |
|  |  |

# Introduction

In contemporary drug, therapy, or disease research, researchers not only need to develop a method, but they also need to be able to see what is going on, whether it be with a patient or with a test subject. First comes the hypotheses, then it must be tested via experiment, and this experiment must be somehow observed. The observation of experiment can be done via imaging modalities, such as conventional microscope, cell-counter, computed tomography or by naked eye. For investigation of small cells usually microscopy is a good modality. There is a plethora of different microscopic modalities, and in the scope of this project, a multiphoton microscope was used. It can establish three-dimensional image acquisition and utilize fluorescence for morphological sample understanding.

Acquired images themselves are useful at a first glance. The images can be examined by knowledgeable pathologists or biologists, and then a conclusion can be drawn from those observations. Because biology is a quantitative field of study, the significance of statistical analysis is something that must not be overlooked. To gain a deeper understanding of it, analysis is required to find more insights. Images need to be processed and analyzed before they can provide a better understanding of the experiment.

The problem of image processing and analysis can be solved using a variety of mathematical and software techniques. These techniques can either be traditional, such as thresholding, watershed, or region growing algorithms, or they can be addressed to more sophisticated techniques, such as decision tree, random forest, and support vector machines. All these methods are still in use today, but recent developments in deep learning have made it possible to perform image processing that is both more general and more concise.

The way these networks are working is not the same as for the traditional approaches. For Neural Networks no particular algorithm is being developed to perform image processing and classification, but network is being “trained” on datasets that consist of original images and the output that is required to get from the network given that image. The output is usually created manually, by hand, and this time-consuming process is named labeling. Network “learns” mapping between input and output, and hence can be used on unseen data to do the same. This makes it possible to process a great variety of images, which makes it superior to any of the traditional methods.

These networks may demonstrate remarkable performance in tasks such as image segmentation and classification, but they require a substantial amount of training data to do so. When images contain a third dimension, labeling the training data becomes considerably more difficult. A data simulation tool is required to find a solution to this issue. It is able to generate an unlimited amount of annotated data for use in testing the performance of neural networks. This simulator must generate images that resemble real ones and a random assortment based on parameter settings. The advantage of using a simulator instead of manually annotated data is data with flawless annotations and unlimited dataset capacity. Any experiment of image annotation and augmentation can be done in a matter of minutes, but not weeks.

In this dissertation, a simulation framework for FAD cytoplasm fluorescence in volumetric data is developed, its results are compared to actual stacks acquired with a multiphoton microscope, and a deep convolutional network is trained to count and classify immune cells using the simulated data.

# State of the Art

The human body is a highly complex system with a multitude of organs composed of tissues composed of billions of grouped cells. These cells interact with one another to maintain life in the body. As with any complex system, this one has a potential to fail; any disease can make life difficult or impossible. The initial step in treating any illness is diagnosis. In modern medicine, there are numerous imaging modalities, including X-ray, Ultrasound, Computed tomography, Optical coherence tomography, Magnetic resonance imaging, and Microscopy.

The purpose of microscopy is to visualize single cells and tissue. Typically, tissue samples must be fixed (with a substance such as formaldehyde) and stained prior to image acquisition. Hematoxylin and Eosin are the most common stains for brightfield imaging. The most common stains for fluorescence microscopy are DAPI, Hoechst, FITC, and TRITC. These are utilized to make tissue or cellular structures visible and distinguishable from other structures. Different microscopic modalities can deliver fluorescent volumetric data such as Multiphoton Microscopy or Confocal laser Microscopy.

Typically, cells are nonplanar and live in three dimensions. The examination under the coverslip is insufficiently precise and can conceal some cellular behavior. In addition, 2D in vivo imaging is not always possible, particularly when underlying cell cultures are concealed beneath the surface. To obtain more information from the tissue, volumetric images, also known as Z-stacks or stacks, must be captured. Multiple color channels are present in this three-dimensional image.

Graphical user interface, application

Description automatically generated

**Figure 1**. Representation of volumetric data. A: The montage of images acquired at different depths Z. B: Zoomed in a single image. C: 3D representation of a stack.

Stack allows seeing the cells in volume, which is oftentimes necessary, for example, direct observation of skin cells together with immune cells lying under skin layer [1]. Volumetric data is more difficult to work with, due to the high memory consumption and visualization tradeoffs that we must do to observe the data.

## Motivation

Any experiment in biological research consists of multiple steps, including hypothesis, subject preparation, acquisition, and analysis. In this section, the concepts of experiment subject, data acquisition method, and general data analysis will be explained.

### Human immune cells in colon tissue

To a large extent, immune cells can be found everywhere; however, if inflammation takes place in a particular region, immune cells will congregate there, causing a shift in both the concentration and composition of immune cells in that region. The doctor can learn a lot about the inflammation process by looking at the different types of cells that are present in the affected area as well as the relative concentration of those cells.

It is undeniable proof that inflammation exists in the human colon tissue when there is a high number of immune cells present. However, information about the inflammatory process can be gleaned not only from the presence of immune cells, but also from the cell types present, the concentration of those cells, and the locations of those cells. After the fluorescence signal has been produced, it is essential to avoid conflating it with signals that are produced by other objects in observation volume that are not of interest. These other signals come from different objects. As a result, the location of immune cells is an essential component in the measurement of the immune infiltrate.

Imaging techniques such as multiphoton microscopy may be useful for determining the presence, quality, and quantity of immune cells in tissue.

### Multiphoton Microscope

Multi-photon microscopy (MPM) is an efficient method that enables three-dimensional mapping of materials having a detectable nonlinear optical response, such as second harmonic generation (SHG), third harmonic generation (THG), or fluorescence caused by multiphoton absorption. MPM allows for the 3D observation of stained tissue and single cells with high resolution. By only exciting the focal plane, it reduces scattering from non-focal planes.

Fluorescence is the process that occurs when the fluorophore's electron absorbs the excitation photon and settles on a higher energy level within the molecule. The atom then returns to its ground state by emitting a photon of a different wavelength (**Figure 2A**). Two-photon excitation operates in the same manner as single-photon excitation but requires two incident photons with half the energy of the required photon. For this effect to occur, these photons must simultaneously strike the same atom. To achieve this infrequent occurrence, the photon density must be high. This condition is exploited to achieve a very small excitation volume without scattering from non-focal planes, which results in accurate volumetric data.

The principle of this modality differs from the fluorescent microscope. In a fluorescence microscope, the excitation response of the fluorophore is linear, more excitation light - more fluorescence response. But with the two-photon excitation, it is different (**Figure 2B**). Excitation is visible only at the focal point – the place where the photon density will be the highest.

A picture containing diagram

Description automatically generated

**Figure 2 A**: S. Schürmann, Department MBT, Multiphoton fluorescence energy diagram comparison of a single-photon (1 PE) fluorescence and two-photon (2 PE) fluorescence. In two-photon fluorescence, 2 photons of the energy twice lower than required are exciting electrons together. This is achieved by higher energy density which results in a higher probability of excitation events happening. B: The comparison of the excited volumes – 1 PE ­­­has a lot of exciting molecules out of the focal plane which results in worse image quality, compared to 2 PE.

MPM has been shown to have useful applications in areas such as the characterization of nonlinear materials, biological research, and the diagnosis of medical conditions.

### Aims of Image Analysis

For the experiment conduction, the data is acquired by any given sensor (photo-multiplier tube in our case). This raw information provides a good view on the processes, structure, intensity, but to reveal a full potential and extract more information from them some analysis is required. To prove the hypothesis this information must be cleaned, distilled, and processed. All these tasks are faced by image analysis – the field of science and the mathematical toolset. Image analysis involves processing images into fundamental components to extract important information. It may involve tasks such as finding shapes, detecting edges, removing noise, counting objects, texture analysis, etc. achieved by means of mathematical operations, or dynamically, using machine learning approaches. In this Thesis, only the segmentation procedure for human immune cells in three-dimensional data will be explained.

### Machine learning in image processing

Machine learning is a set of sophisticated mathematical operations performed on data to receive an expressive result from it. These algorithms are conventionally generalized in form of a pattern recognition pipeline (**Figure 3**). An electronic device, such as a camera, microphone, or microscope, is initially used to collect the data. The data is then saved and preprocessed. In the preprocessing step, data is filtered, improved, and prepared for subsequent processing. Next is a feature extraction, which uses a series of mathematical operations to extract representative features from the data. These characteristics may represent a streamlined version of the original data or generate new data, enabling algorithms to locate intra-data correspondences. For image processing these characteristics could be obtained using convolutional filters such as Gaussian, Laplacian, and Gradient, among others. Later, these characteristics are utilized for the so-called learning or training step. During training, the Algorithm attempts to identify the optimal split for classifying data with minimal error, based on extracted features.

Graphical user interface, diagram

Description automatically generated

**Figure** **3** Typical pattern recognition pipeline [3]. It is divided into two parts: The test phase and the Training phase. Sensor, preprocessing, and feature extraction steps are common for both phases.

These algorithms in image processing are conventionally divided into two groups: Classical and Deep Learning approaches. Differences between those groups can be compared using the pattern recognition pipeline (**Figure** **3**):

* Classical machine learning approaches follow this pipeline. They require a small amount of data and small computational costs. Lack of generalization and precision.
* Deep Learning approaches bypass part of this pipeline by combining feature extraction with classification. There are no predefined feature extraction procedures in neural networks, and these procedures are estimated, during the training process. They require a substantial amount of labeled data, high computational costs, and time. They are good at generalization and most of the state-of-the-art methods now are using neural networks.

Using machine learning (ML), a subset of artificial intelligence (AI), software programs can more accurately predict outcomes without being explicitly programmed to do so. In order to forecast new output values, machine learning algorithms using previous data as input. There are concepts like Decision Tree and Random Forest that allow to map several values from one domain to another by classifying them with simple rules, based on few annotated examples. Those can be used for image processing for automated pixel-wise classification, which is also known as segmentation task.

These procedures are lacking in a few areas. The first is that the user must design and select the feature extraction stage based on their own experience. Secondly, inefficient computation. Using traditional machine learning algorithms for three-dimensional stacks becomes very slow. Thirdly, these methods cannot be applied effectively to unknown data.

Neural networks are developed to provide solutions for all three of these issues.

## Neural Networks

Artificial neural networks are a subfield of machine learning that is partly based on how neurons in the human brain function. In the last decade, neural networks have had a tremendous rebirth because to the immense availability of data and the great growth in computing power, mainly due to use of Graphical Processing Units (GPU) availability. There are a variety of neural network types (Feedforward, Convolutional, Recurrent, etc.). A neural network is not an algorithm, rather it is a computational structure that approximates an algorithm by being built on learnt mapping and being calculated via the process of training. Algorithms use is commonly referred to the simplest formula:

An algorithm, is a sequence of computations, that is defined by human, and usually algorithm is not a self-improving system. Neural network on another hand is being trained by following this formula:

By displaying the network's input and output, it is feasible to educate it to produce a new output given a new input.

### Feed forward network

Diagram, shape

Description automatically generated

Figure 4: Schematic representation of feed forward network; A. Forward pass from neuron x1; B. Forward pass from neuron x2; C. Forward pass from all input neurons.

Feed forward network is one of the earliest forms of neural networks. It allows to approximate mapping of complex domains and solve problems like, classification, regression. On Figure 4 as an example illustrated a feed forward network with one input layer one hidden layer and output layer, that consists of one neuron . Every node or “neuron” is considered as a variable for or as linear combination of weights and inputs. Considering the first case on Figure 4A the so called forward pass is performed from input layer to hidden one. It is represented by lines. Each input neuron has “connection” with all neurons in the next layer. Each connection has a weight assigned to it. It can be written as:

This operation is repeated for all input neurons, Figure 4B:

All neurons in hidden layer A represent nothing more than a linear combination. Linear combination cannot approximate mappings more complex than linear ones. To solve this issue every layer output has a non-linearity function , that allows to approximate more complex distributions.

There are multiple functions that are used: Rectified linear unit, Sigmoid, Softmax etc. Once the non-linearity is added to every layer’s output, it can be forwarded to next layer until the end.

For computational efficiency and simplicity computation from one layer to another can be rewritten in matrix form:

And because values were computed the same way as via matrix multiplication:

But how exactly do neural networks compare their output to the training samples? It is done by loss functions. They compare the network’s output with ground truth and measure how different they are. Once a loss is calculated, it is backpropagated. Backpropagation is the process of sequential gradient computation from the loss value back to the input layer. A gradient of loss with respect to input and with respect to weights is computed and used for gradient descent weight optimization. This method force weights change to minimize loss or difference between output and target values.

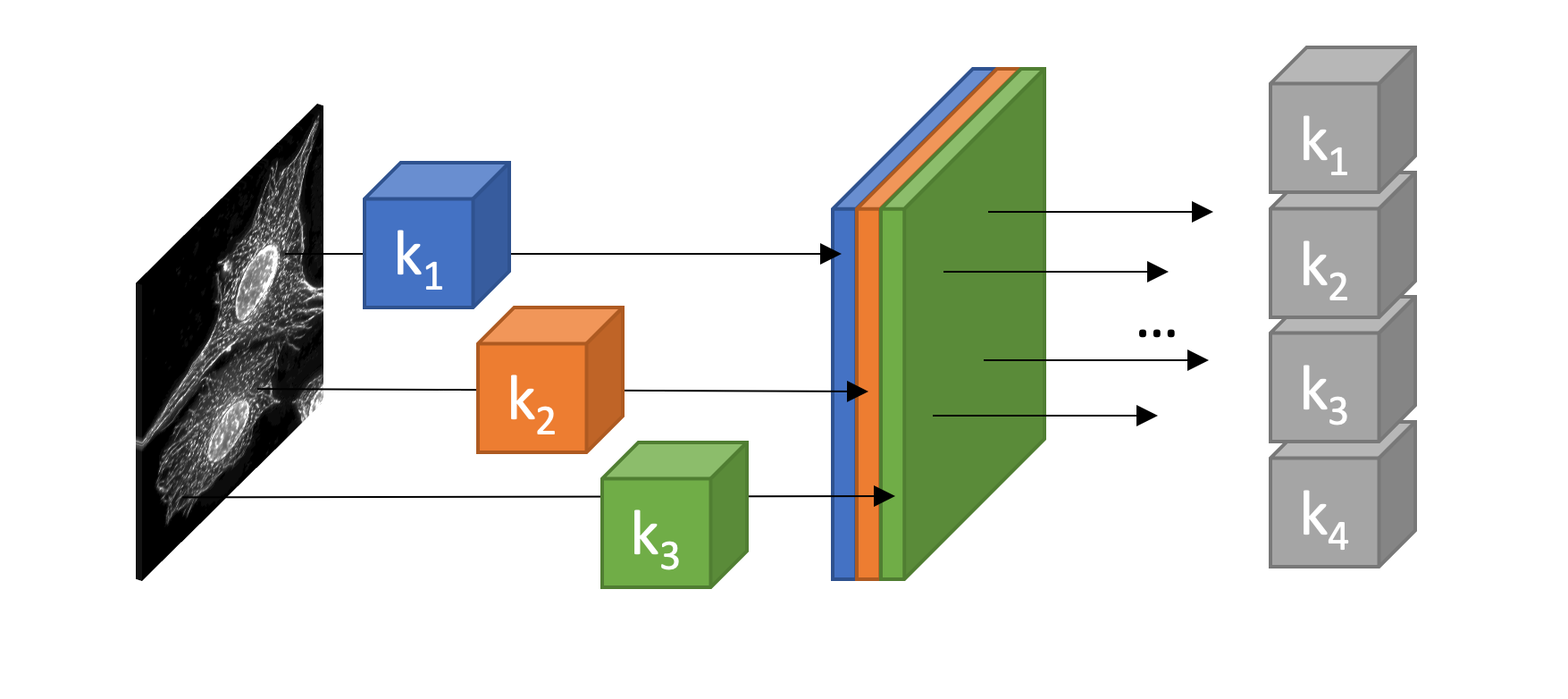
### Convolutional neural networks

Feed forward networks operate well but have limitations that prevent them from working with large data such as photos, video, and audio. There are two primary reasons for considering an alternative to feed-forward networks.

Firstly, feed-forward networks are not scalable. Mainly, because they are computed by matrix multiplication which has a complexity of . Imagine the example with a 512-by-512-pixel picture. For a single hidden layer with 8 neurons, it results in trainable weights. Memory consumption for a single operation is very high, it is not feasible to train a network with so many weights on average personal computer.

Second, pixels are a poor representation from the standpoint of machine learning. They are highly correlated, scale dependent and vary in intensity. Hence pixels on their own do does not carry any spatial information about object, it is just a floating-point value.

For images, feed forward networks become computationally difficult and worthless. Convolutional neural networks (CNN) were constructed as a result. They address both issues simultaneously. The size of a convolutional kernel is typically between 1 and 81 pixels, and kernel values are trainable weights. This provides for significant memory savings, while the convolutional kernel enables the manipulation of spatial features through image convolution. Instead of forwarding the whole image, CNN convolves it using kernels and only transmits the output of the convolution **Figure 5**.



**Figure 5:** Representation of CNN work. Image is convolved with three kernels k1, k2, k3, to produce a tensor with three channels. Convolution is repeated with a new set of kernels, using the output feature maps from the previous stage as inputs.

CNNs are very powerful networks, and they can solve problems with different approaches. To satisfy the requirements of this project it is necessary to detect, classify and count cells from three dimensional images. Two common approaches are used to accomplish that task: object detection and image segmentation.

## Object detection vs. Image Segmentation

Image classification is one of the most prevalent applications of CNNs; it takes an image as input and predicts the probability of object existence. State of the art networks like in [3] can define presence of object on the image. For an image containing 100 cells it would predict that “cell” is there, but it does not provide information about cells number. For predicting cell number, first those cells must be localized on the image and then, it is possible by postprocessing means to determine their number and class. One of the approaches is called object detection.

A picture containing text, different, mammal

Description automatically generated

**Figure 6:** Example of algorithm output difference. From left to right: Classification – allows to predict content on image; Detection – allows to localize objects on image with bounding boxes and to predict their class; Segmentation – allows to assign every pixel on image to class.

Object detection enables the prediction of an object's position using a bounding box — a rectangular frame that encompasses the object's perimeter. There is multiple of models, that exploit different architectures to solve this problem. One of the most popular networks YOLOv3 [4] sort of divided image in grid and predicted bounding boxes coordinates and class probability for every image chunk. And then by using non-maximal suppression technique leave only boxes high class probability. There are other good alternatives like SSD – Single Shot MultiBox Detector [5], Faster R-CNN [6], or RetinaNet [7]. These networks might be utilized for cell detection, however for three-dimensional data they have not yet been implemented.

In contrast, there are algorithms designed for segmentation purposes. They enable class assignment for each pixel in an image. When morphological examination of cell shape is necessary, this capability is used. Commonly used networks are U-net [8] an encoder-decoder shaped network with residual connections, usually it has output of the same shape as input, that allows to map pixels directly without rescaling back on input. Mask R-CNN [9] is another network design, that augments Faster R-CNN architecture with a segmentation branch, it basically takes each predicted boundary box and performs segmentation inside it.

Both network design branches are efficient and functioning well, but research articles consistently overlook a challenge that is seldom considered: labeling. For boundary box labeling, it is required to label 2 points on image and for segmentation it is 1 contour. When pictures are three-dimensional instead of two-dimensional, however, boundary boxes need three points and segmentation requires contours multiplied by image depth in pixels. For cellular data both boundary box labeling and segmentation become tedious time consuming.

What if it is not necessary to label whole cells with contours or boundary boxes, but only their centers with a single point? That would make labeling easier. That’s what we are going to investigate in results section.

# Methods

## Cell simulator

Deep Learning approaches require a lot of labeled data like hundreds or even thousands of images. Due to that, it is always preferable to find a way to minimize the labeling time because it is tedious and expensive. Therefore, it is essential to either simplify labeling or synthesize datasets.

## MBT-net

## Cell Counting and post processing

# Results

## Cell counting performance

## Images and distances

# Discussion

## Model selection

Why have I selected this network

## Problems faced

## Failed approaches

## What can be done better

# Conclusion

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# Appendix

Curriculum vitae

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Erklärung

Ich versichere, dass ich diese Arbeit selbständig verfasst und keine anderen als die angegeben Quellen und Hilfsmittel verwendet habe. Die Arbeit hat in dieser oder ähnlicher Form noch keiner anderen Prüfungsbehörde vorgelegen.

Declaration

I confirm that I have written this thesis without any external help and

not using sources other than those I have listed in the thesis. I confirm also

that this thesis or a similar version of it has not been submitted to any

other examination board and has not been previously accepted as part of a

exam for a qualification.

Erlangen, den 19.09.2022

(sign here)

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