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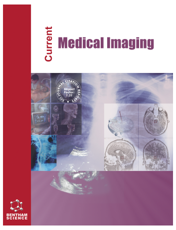

PERSPECTIVE

# Recent Applications of Deconvolution Microscopy in Medicine

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**Abstract:**

Deconvolution microscopy is a computational image-processing technique used in conjunction with fluorescence microscopy to increase the resolution and contrast of three-dimensional images. Fluorescence microscopy is a widely used technique in biology and medicine that involves labeling specific molecules or structures within a sample with fluorescent dyes and then electronically photographing the sample through a microscope. However, the resolution of conventional fluorescence microscopy is limited by diffraction within the microscope's optical path, which causes blurring of the image and reduces the ability to resolve structures in close proximity with one another. Deconvolution microscopy overcomes this limitation by means of computer-based image processing whereby mathematical algorithms are used to eliminate the blurring caused by the microscope's optics and thus obtain a higher-resolution image that reveals the fine details of the sample with greater accuracy. Deconvolution microscopy, which can be applied to a range of image acquisition modalities, including widefield, confocal, and super-resolution microscopy, has become an essential tool for studying the structure and function of biological systems at the cellular and molecular levels. In this perspective, the latest deconvolution techniques have been introduced and image-processing methods for medical purposes have been presented.

**Keywords:** Deconvolution microscopy, Medical imaging, Fluorescent microscopy, Cell biology, Confocal, Diffraction.

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## 1. INTRODUCTION

Deconvolution is a specialized technique used in microscopy to produce much sharper and more detailed images. This article will cover what needs to be known about deconvolution microscopy in terms of its application to medicine, including how it works and what its advantages and disadvantages are. The article will also explore some of the ways this kind of microscopy is being used today and where it may be heading in the field of medical science.

Deconvolution microscopy is a modern image-processing technique that has revolutionized cell biology, developmental biology, immunology, neuroscience, and other fields of medicine in which microscopy is indispensable [1, 2]. The technique makes it possible to restore images that have been distorted by the diffraction limit of optical microscopy, producing higher resolution and clearer images. Richardson *et al.* [3] reported the first demonstration of deconvolution microscopy in the field of medicine by describing an image-processing method for removing the out-of-focus light that typically blurs fluorescence microscopy images. The algorithm they used involved iteratively estimating the point spread function (PSF) and the original image from a set of observed degraded images. The authors achieved this by computationally reconstructing the image using a mathematical model that considered the point spread function of the microscope and other optical factors [4, 5]. This improved the contrast and resolution, thereby revealing greater detail in samples. The authors described this method as a means of achieving rapid and clearer imaging of cellular structures; however, it is now commonly known as deconvolution microscopy. The principle it embodies is the mathematical removal of the blur introduced by the PSF of the optical system, which is a measure of how the system responds to a point source of light. By removing the blur, the resolution of the image is improved, and fine details that were previously hidden can be revealed.

Deconvolution microscopy has three distinct advantages over traditional microscopy. First, because it effectively removes the blurring that is inherent in traditional microscopy, it provides significantly higher-resolution images of cells and cellular structures. Consequently, these objects can be observed in greater detail, allowing more accurate analysis and identification [6]. Second, because it can separate different features of cells and cellular structures that would otherwise merge into a blur, it produces images with greater contrast.

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Consequently, different features can be distinguished more easily, again allowing more accurate analysis. Third, it is much less expensive than confocal laser scanning microscopy or total internal fluorescent microscopy [7]. This is because it does not require the use of expensive equipment, such as a laser scanning unit or a laser unit that generates an evanescent wave along the glass surface. Consequently, it is an ideal tool for use in research laboratories or by clinicians who need to rapidly and accurately identify cells or cellular structures.

## 2. RECENT APPLICATIONS OF DECONVOLUTION MICROSCOPY

### 2.1. Deconvolution and Super-resolution Microscopy for Higher-resolution Imaging

Optically, there is a limit to the degree to which two objects can be resolved. This is called the diffraction limit and is dependent on the wavelength of the light used for illumination and the numerical aperture of the microscope lens. By means of deconvolution, the diffraction limit can be exceeded to obtain a higher resolution. This method is based on the acquired point spread function (PSF) and improves the sharpness and clarity of an acquired image by effectively repositioning photons mispositioned above and below the focal plane to their original positions, with the mispositioning being the cause of noise detected from outside the focal plane. Resolution can also be improved by such super-resolution microscopy techniques as stimulated emission depletion (STED) and structured illumination microscopy (SIM), and deconvolution can be used in conjunction with these techniques [8].

STED microscopy relies on the principle of stimulated emission, which occurs when a molecule is excited by a laser and then immediately returns to its ground state by emitting a photon. In STED microscopy, two laser beams are used: a donut-shaped excitation beam that excites a fluorophore and a second beam that is overlaid on the first beam to deactivate or “quench” the fluorophores at the periphery of the excitation spot. This results in a sharper, smaller excitation spot, allowing for higher-resolution imaging.

SIM is another super-resolution microscopy technique that uses patterned illumination to generate high-resolution images. In SIM, a patterned illumination is projected onto the sample and multiple images are taken with different patterns of illumination. The images are then combined to create a high-resolution image that exceeds the diffraction limit of conventional light microscopy.

More recently, sparse illumination theta microscopy with fourier interpolation reconstruction (SPITFIR), which is a deconvolution microscopy technique used to improve the resolution of fluorescence microscopy images, has been introduced [9]. It involves illuminating a sample with a sparse set of laser beams at varying angles, thereby generating a set of 2D images. SPITFIR is a flexible method designed to accurately and quickly restore 2D-3D fluorescence microscopy images and videos (4D images).

Both STED and SIM are techniques that can be used in conjunction with deconvolution microscopy to achieve even higher-resolution images. By combining these techniques, researchers can obtain detailed information about the structure and function of biological molecules, such as proteins and DNA, at the nanoscale level.

### 2.2. Deconvolution Microscopy Technique Using Open-source Software

It also offers an inexpensive microscopy solution when used with a simple grazing fluorescence microscopy system by using commercial or open-source software to process acquired images. Recently, it has also seen as a method that will contribute to simple on-site measurements to assist in the definitive diagnosis of cytology tests [10].

Because the deconvolution technique requires multiple images with different focal planes, increased computational cost due to the large volume of data involved is an issue. Accordingly, ways for improving the processing algorithm are being investigated. For example, when mapping from an image containing noise to a target image, it is common to use elements called forward operators ($f$) and backward operators ($b$) for calculation, where ($f$) is the PSF and $b$ is the transposed PSF. Thus, by causing $f * b$ to approach a delta function by setting $b$ appropriately, it has been found that the image processing time can be cut to 1/10 or less [11]. The challenges inherent in handling an increased volume of data will become greater as a result of the recent surge in 3D measurement.

One reason for this surge is increased software availability. For example, an open-source MATLAB toolbox called DVDeconv, which includes an algorithm that takes depth asymmetry into account by calculating and employing asymmetric PSFs, has been released [12], making it possible to use 3D deconvolution without special equipment or technology. The deconvolution technique needs to be changed depending on the measurement device and technique. Over the past decade, there has been increasing interest in light-sheet microscopy, which by allowing faster measurement than conventional microscopy, causes less optical damage. However, it has been difficult to measure PSF with this method, and only limited software is available for the purpose. Accordingly, to solve this problem, algorithms and software that employ PSF theoretically calculated from the optical model of light-sheet microscope image formation have been developed [13]. Other methods have been proposed to reconstruct multi-view measurements of light-sheet microscopy by extending to the autocorrelation space the blind deconvolution in autocorrelation inversion for the multi-view approach of the Richardson-Lucy deconvolution method. This is made possible even if the PSF is unknown by iteratively performing calculations to find objects with a fixed PSF [14].

### 2.3. Performing Deconvolution Microscopy with Open-source Software

Deconvolution microscopy can be performed by using NIH ImageJ software and installing an appropriate deconvolution plugin. ImageJ is a widely used open-source image analysis software developed by the National Institutes of Health [15] that provides a range of tools and functionalities allowing users to manipulate and analyze digital images. These include image enhancement techniques, such as filtering, segmentation, and thresholding, as well as more advanced image analysis techniques, such as particle tracking, colocalization analysis, and 3D reconstruction. ImageJ can be used in conjunction with MicroManager, which is a free, open-source software platform that allows microscope hardware to be controlled and images to be acquired. Originally developed at the University of California, San Francisco, it works with microscopes, CCD or CMOS cameras, and microscopy peripherals [16].

The following is an overview of the features and capabilities of the ImageJ deconvolution software and also describes the several open-source plugins that expand its functionality. These plugins, such as DeconvolutionLab2 [17], Ops deconvolution (Richardson-Lucy Deconvolution), and Iterative Deconvolve 3D [18], are available online. To use any of them, one opens the microscopy image in ImageJ (serial optical sections are needed for image analysis, and measured or calculated PSF are needed) and applies any necessary pre-processing steps, such as background and contrast adjustment or image filtering, to improve the quality of the original image. Next, one opens the deconvolution plugin installed in ImageJ. With some plugins, serial optical sections of the microbeads that allow the PSF to be calculated are also obtained (the PSF should vary according to the individual optical lenses). If a real (measured) PSF image is not available, the parameters for the deconvolution algorithm must be set [19]. These include the PSF of the microscope, the number of iterations, and the type of algorithm (*e.g.*, iterative, maximum likelihood, or blind deconvolution) [20 - 23]. These parameters will vary depending on the type of deconvolution microscopy being performed. Finally, one executes the software to perform deconvolution, causing the deconvolved image to be displayed in a new window. It may be necessary, after evaluating the quality of the image, to adjust the parameters, experimenting with different values to achieve the best results. Examples of deconvolution microscopy images using the Iterative Deconvolve 3D plugin are shown in Fig. (**1**).

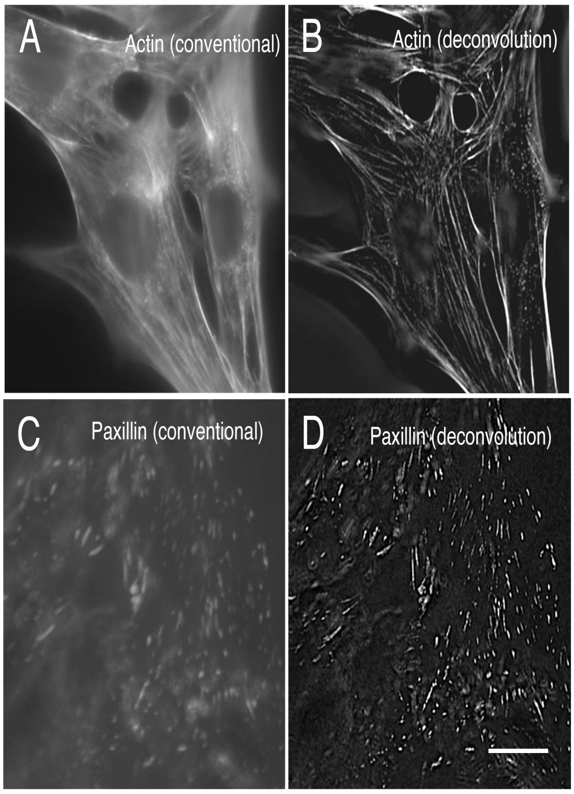

**Fig. (1).** Comparison of cellular observation with conventional fluorescence microscopy (**A** and **C**) and deconvolution fluorescence microscopy (**B** and **D**).

Observation of actin filaments, stained with rhodamine-labeled phalloidin, by means of conventional fluorescence microscopy (**A**) and deconvolution fluorescence microscopy (**B**) is illustrated. The staining of the rhodamine-labeled phalloidin, as a marker of actin filaments, is shown in A and B. When using a conventional fluorescence microscope, extraneous fluorescence occurring outside the focal plane can overlap the actual fluorescence, leading to the blurring of the convolution image (**A**). The images (41 sections having 0.5-μm intervals) acquired in (**A**) were deconvoluted using a PSF image (Iterative Deconvolve 3D software for ImageJ) [18]. (**B**). Out-of-focus fluorescence arising from regions other than the focal plane is eliminated (**B**). Bundles of actin filaments located in the basal part of the cell (stress fibers) are clearly observable. Figs. **C** and **D** show staining with an anti-paxillin antibody, as a focal adhesion marker, in myoblast cells. The cells, having been stained with anti-paxillin antibody, were observed by means of conventional fluorescence microscopy (**C**). Extraneous out-of-focus fluorescence prevents observation of the actual fluorescence, and the shape of the focal adhesion is not well-defined. Out-of-focus fluorescence from the upper surface layer overlaps the fluorescence on the basal plane, which is unclear when the cells are observed by means of conventional fluorescence microscopy (**C**). Deconvolution was performed using the image sequence obtained in (**C**) (Iterative Deconvolve 3D software for ImageJ) and is shown in (**D**). Out-of-focus fluorescence is eliminated, especially with respect to the focal adhesions localized on the basal plane of the cell, after deconvolution microscopy (B: basal); Bar: 20 μm [7].

Alternatively, several commercial software packages are also available. These are AutoQuant X3 Deconvolution Software, developed by Mayer Instruments (Houston, Texas); Huygens Deconvolution Software, developed by Scientific Volume Imaging (Hilversum, Netherlands); Imaris Clearview-GPU Deconvolution, developed by Oxford Instruments (Oxfordshire, UK); and Zen Deconvolution, developed by Carl Zeiss Microscopy (Baden-Württemberg, Germany). Each package has its own unique features and capabilities.

### 2.4. Application of Deconvolution Microscopy in Medical Imaging

Deconvolution microscopy has a wide range of applications in various fields, such as cell biology, neurobiology, immunology, and the field of medical imaging. Deconvolution microscopy is a type of computational microscopy that aims to improve the resolution of images captured by a microscope. There are several types of deconvolution microscopy techniques. Richardson-Lucy deconvolution method is a specific implementation of iterative deconvolution, and it is widely used in microscopy [3]. It iteratively estimates the original image by convolving the current estimate with the PSF and then scaling the result to match the observed image. The iterative deconvolution method involves iteratively estimating a PSF and deconvolving the image with the estimated PSF [4]. This process is repeated until the image is sufficiently deconvolved. Maximum likelihood deconvolution involves modeling the image formation process as a statistical problem, and then using maximum likelihood estimation to obtain the best estimate of the original image [24]. Blind deconvolution involves estimating both the PSF and the original image without any prior knowledge of either [25]. This is a challenging problem, and blind deconvolution methods typically require a large number of images to obtain a reliable estimate. The selection of the deconvolution method depends on the specific imaging observation and the properties of the image being analyzed.

Recent advancements in deconvolution microscopy have led to the development of new applications that have the potential to transform imaging in the field of medicine. Deconvolution microscopy has been applied to a wide range of research in the fields of biology and medical science, and new applications are constantly being developed. Live-cell imaging [16], super-resolution imaging [17], multicolor imaging [24], and three-dimensional deconvolution microscopy [25, 26] are examples of such applications. Light sheet microscopy provides optical sectioning even with objectives of very low magnifications at the threshold between microscopy and macro-photography [13].

The three-dimensional measurement deconvolution techniques have been used in a study on *in vivo* imaging of neural activity in the whole brain of a zebrafish [27]. This ability to measure brain activity three-dimensionally at high resolution makes it possible to study neural activity in its entirety. To enable *in vivo* time-varying measurements, the study used neural networks to reduce the computational time of deconvolution. Neural networks have also been used for SIM deconvolution. SIM typically uses a known structural illumination pattern, but there is also a blind SIM technique that uses an unknown structural illumination pattern. This image analysis requires complex and computationally expensive deconvolution algorithms, but it has been reported that deconvolutional neural networks can be utilized to achieve higher resolution at higher speeds than conventional blind SIM deconvolution algorithms. In the future, neural-network-based deconvolution methods, such as these, are expected to be used widely [28].

Deconvolution microscopy has been used in many cutting-edge studies in medical biology. For example, one study has reported the results of using the method to assess the percentage expression of E-cadherin [26], which is one of the core proteins regulating intercellular adhesion and is an important target in tumorigenesis and tumor progression. By means of deconvolution microscopy, the study has shown that, at the tissue level, lysosome-associated membrane glycoprotein 1 (LAMP1)-positive exosomes/polyhedrosomes are transported across the membrane of tumor epithelial cells. In another study, observation of autophagosome formation by means of deconvolution microscopy clarified the mechanisms underlying autophagy in nucleated platelets and so revealed that platelet autophagy was partially induced *via* the AMPK-MTOR pathway [29, 30]. Deconvolution microscopy is a software-based microscopy technique that uses a conventional fluorescence microscope, focal plane control equipment along the z-axis, and software to obtain high-resolution images.

### 2.5. Limitation of Deconvolution Microscopy

While deconvolution microscopy can significantly improve image quality, it has a number of limitations that need to be taken into consideration [18]. Software deconvolution requires a detailed knowledge of the microscope’s PSF, which is a mathematical representation of the light distribution as it is transmitted through the microscope’s optical system. Since the PSF varies depending on the microscope’s optics (such as the objective lens) and the characteristics of the sample whose image is being acquired, accurate determination of the PSF is critical for successful deconvolution. However, in practice, this can be difficult to achieve. Furthermore, deconvolution microscopy can eliminate only the out-of-focus blur that is present in the image. Other sources of image degradation, such as electrical noise, uneven illumination, and non-specific fluorescence elements, may still be present in the deconvoluted image and may limit the ultimate resolution achievable. In addition, deconvolution microscopy can be computationally intensive, and the processing time required for deconvolution can be significant, especially where the dataset representing the image is large. This can limit the practical use of deconvolution microscopy, particularly in time-sensitive applications. Accordingly, although deconvolution microscopy can be a powerful tool for improving image quality, its limitations need to be carefully considered in order to ensure accurate and reliable results.

## CONCLUSION

Deconvolution microscopy is an image-acquisition technique that offers numerous advantages over traditional, purely optical microscopy. The technique is based on the principle of deconvolution, whereby an image is reconstructed by correcting distortions due to diffraction in a microscope's optical system. By enhancing the spatial resolution of fluorescence microscopy images, deconvolution microscopy reveals the finer details that would normally be obscured by the microscope's point spread function. The advantages of deconvolution microscopy are as follows:

1. Enhanced contrast: Deconvolution microscopy is able to increase the contrast of fluorescence microscopy images, making it easier to distinguish different objects and structures in the images [2].

2. Improved signal-to-noise ratio: By helping reduce noise, deconvolution microscopy is able to improve the signal-to-noise ratio of fluorescence microscopy images. This becomes important when the images are of low intensity or their fluorescence is weak.

3. Fast image acquisition: Deconvolution microscopy is able to acquire images relatively quickly [9].

4. Wide-ranging compatibility with various types of microscopy: Technically, deconvolution microscopy can be applied to a wide variety of fluorescence microscopy modalities, such as conventional fluorescence microscopy, confocal microscopy [29, 30], and total internal reflection fluorescence microscopy (TIRFM).

5. Cost-effective equipment configuration: Deconvolution microscopy is achievable by pairing an existing microscope with conventional computer hardware running open-source software [7].

Deconvolution microscopy is a powerful tool that greatly improves the quality of fluorescence microscopy images, helping researchers better understand biological structures and processes. Open-source deconvolution microscopy software provides a cost-effective and flexible solution for researchers who want to acquire superior microscopy images. Because running such software on conventional computer hardware allows deconvolution microscopy to be achieved relatively cheaply with existing microscopes, the technique promises to be of great utility in the field of medical research.

## LIST OF ABBREVIATIONS

**LAMP1** = Lysosomal associated membrane protein 1
**CCD** = Charge-coupled device
**CMOS** = Complementary metal-oxide semiconductor
**STED** = Stimulated emission depletion

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## CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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