Light Sheet Microscopy Across Scales: From Single Cells to Whole Organs

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Abstract: Light sheet fluorescence microscopy (LSFM), or selective plane illumination microscopy (SPIM), has revolutionized biological imaging by enabling rapid, high-resolution 3D visualization of living and fixed specimens with minimal photodamage. Since its introduction in 2004, LSFM has diversified into modalities suited for single-cell dynamics, small to medium tissues, and large, cleared specimens. This article explores how different LSFM platforms are optimized for specific sample size ranges. We compare their design features, strengths, and limitations while highlighting practical considerations for sample preparation, data handling, and system selection. Ultimately, matching LSFM modality to biological scale enhances imaging outcomes, guiding researchers in choosing the most appropriate system for their experimental needs.

Keywords: SPIM, LSFM, light sheet fluorescence microscopy, tissue clearing, lattice light sheet

Introduction

Light sheet fluorescence microscopy (LSFM), also known as selective plane illumination microscopy (SPIM), is a powerful optical technique that enables rapid, high-resolution three-dimensional (3D) imaging of biological specimens with significantly reduced photodamage compared to traditional point-scanning methods. Originally described in 2004 by Jan Huisken and Ernst Stelzer, the first SPIM system was developed to image *Drosophila* embryos, enabling researchers to capture entire developmental processes *in vivo* with extraordinary clarity and temporal resolution [1]. The key innovation of SPIM was the use of a thin sheet of laser light to illuminate only a single optical plane at a time, reducing light exposure and photobleaching in out-of-focus regions. Fluorescence emitted from this plane is collected by a camera placed perpendicular to the illumination path, allowing for fast planar imaging without the need for raster scanning (Figure 1).

Since its introduction, SPIM has undergone rapid evolution, spawning a diverse array of variants tailored for different applications, ranging from lattice light sheet (LLS) microscopy for live single-cell dynamics to mesoscopic light sheet systems for whole-organ imaging in cleared tissue [2]. This flexibility has made SPIM an important tool in fields such as developmental biology, neuroscience, organoid modeling, and tissue engineering [3,4]. One of its greatest strengths is scalability, that is, the same optical principle can be adapted to image a single cell, an organoid, or an entire mouse or rat brain, simply by modifying beam geometry, objective lenses, and sample handling. As such, understanding the different "scales" of LSFM (that is, single-cell, small tissue, and large tissue) is essential for selecting the right approach for a given biological question. Building on *The Alphabet Soup of Microscopy: Part III*, which introduced the core components of light sheet microscopy systems [5], this article delves into how different LSFM platforms are tailored to specific sample size regimes (Table 1). Emphasis is placed on the practical strengths and limitations of each approach. While the discussion will focus primarily on the 3i Lattice LightSheet, ZEISS Lightsheet 7, and Miltenyi Blaze as representative examples (Table 2), it is important to note that many other systems exist, each with unique capabilities that may better suit the needs of different users.

Anatomy of a Light Sheet Fluorescence Microscope

At the heart of any LSFM is a dual-axis configuration that separates illumination and detection. As mentioned above and in Figure 1, a thin sheet of excitation light is projected into the sample, typically in the xy plane, while fluorescence is collected along the orthogonal z-axis. This selective plane illumination limits excitation to the focal plane, dramatically reducing phototoxic effects and bleaching compared to confocal or multiphoton systems that illuminate through the same objective used for detection [2,6]. The light sheet itself can be generated in several ways. A basic method involves using a cylindrical lens to focus a Gaussian beam—a type of laser beam whose intensity profile follows a bell-shaped (Gaussian) distribution, with the highest intensity at the center that gradually decreases toward the edges—into a sheet. However, more advanced methods scan a Gaussian beam rapidly (digital scanned light sheet) or use non-diffracting beams like Bessel or Airy patterns to increase the uniformity and depth of field. LLS systems, for example, use structured interference patterns to further suppress out-of-focus excitation while maintaining subcellular resolution [7] (Figure 2).

The detection path typically consists of a high numerical aperture (NA) objective placed perpendicular to the light sheet, which focuses emitted fluorescence on a sensitive camera, often a sCMOS or EMCCD sensor. This setup allows entire planes to be imaged in parallel, resulting in far faster acquisition rates than point-scanning methods [6]. To generate a full 3D volume, either the sample or the light sheet is moved incrementally along the z-axis using a high-precision motorized stage. Environmental enclosures, including temperature and gas controls, are often

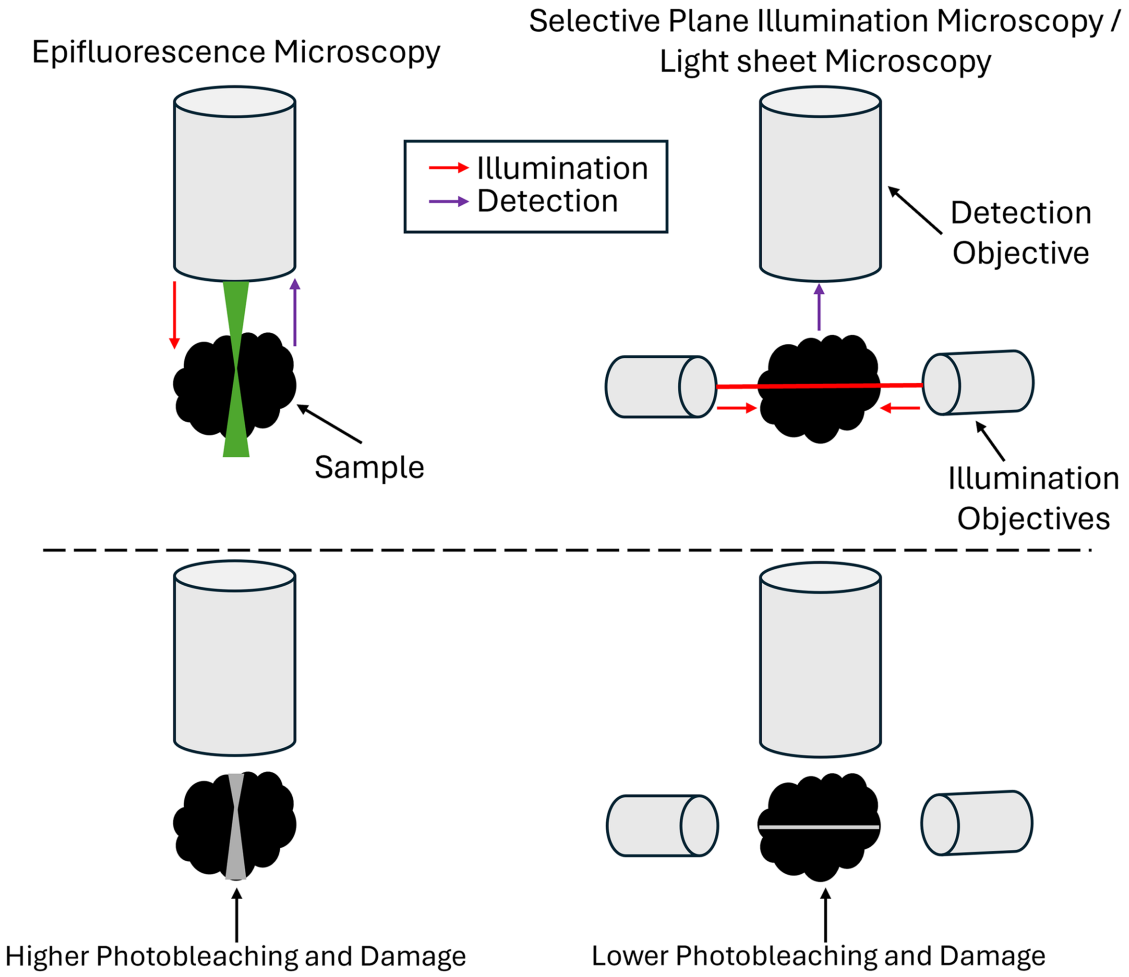


Figure 1: Selective plane illumination microscopy (SPIM). SPIM, or LS microscopy, illuminates biological samples with a thin sheet of light, which excites fluorescence in only a single plane of the sample at a time, minimizing light exposure and reducing photodamage. A camera positioned perpendicular to the LS captures the fluorescent signals, enabling rapid, high-resolution three-dimensional imaging by scanning the LS through the sample or vice versa. From Worden et al., 2024 [5].

Table 1: General comparison of different LSFM scales.

Parameter	Single-Cell LSFM	Small/Medium-Tissue LSFM	Large-Tissue LSFM
Sample Size	<100nm (for example, mammalian cell, yeast)	~100nm–2cm (for example, organoids, embryos, tissue blocks)	> 2cm (for example, whole mouse organs, cleared tissues)
Resolution	~250–400nm lateral, ~400–600nm axial	~500–800nm lateral, ~1–2µm axial	~2–5µm lateral, ~5–10µm axial
Light Sheet Type	Lattice, Bessel, Gaussian scanned	Gaussian (dual-sided), Bessel, structured sheets	Swept Gaussian, Airy, Bessel (low NA)
Objective Lenses	High NA (1.1–1.4 NA water/oil)	Medium to long working distance (0.3–0.8 NA)	Low NA, long working distance
Imaging Medium	Live-cell buffer	Aqueous buffer or mild clearing agents	Clearing agents (for example, CUBIC, iDISCO, MACS)
Mounting Method	Coverslips, agarose, microfluidics	Capillaries, holders, agarose, immersion chambers	RI-matched holders, baskets, mesh cradles
Live Imaging	Yes	Yes (with environmental control)	No (fixed only)
Data Volume	MB to GB	GB to TB	100s of GB to TB
Applications	Organelle dynamics, cytoskeleton, mitosis	Development, organoids, tissue morphology	Connectomics, anatomical mapping, pathology

Table 2: Comparison of the 3i Lattice LightSheet, ZEISS Lightsheet 7, and Miltenyi Blaze.

Feature	3i Lattice LightSheet	ZEISS Lightsheet 7	Miltenyi Blaze
Illumination Type	Lattice LS (structured Bessel beams)	Gaussian LS (dual-sided)	Swept or dynamic digitally scanned LS
Resolution (XYZ)	Sub-300nm lateral, sub-400nm axial (near isotropic)	~350–500nm lateral, ~1μm axial	~1.1μm lateral, ~3–5μm axial
Objective Type	High NA (for example, 1.1NA water immersion)	Low to medium NA (0.5–0.8), long WD objectives	Low NA, long working distance objectives
Sample Compatibility	Live cells, organelles, thin tissue (~<100μm)	Cleared tissues, embryos, organoids	Large, cleared tissues (whole mouse brain, organs)
Live Imaging?	Yes (optimized for subcellular dynamics)	Limited; more suited for fixed tissues	No; designed for fixed and cleared tissues
Sample Mounting	Coverslip or custom microchamber	Glass capillaries, agarose in tubes	Special sample holders, mesh baskets, immersion holders
Clearing Compatibility	Not required; live samples	Compatible with clearing (for example, CUBIC, CLARITY)	Optimized for Miltenyi clearing protocols (for example, MACS Clearing)
Speed (Volume Imaging)	Moderate (high-resolution = more time per plane)	Fast (for meso-scale volumes)	Ultra-fast (terabyte-scale datasets in hours)
Data Output	GB–TB per experiment	100s of GB–TB	TB-scale (multi-TB per sample possible)
Strengths	Subcellular imaging, live dynamics	Flexible sample handling, balanced resolution/speed	High-throughput atlas-level imaging
Limitations	Small FoV, low depth penetration	Resolution limited for deep tissue structures	Lower resolution, no live imaging
Link	https://www.intelligent-imaging.com/lattice	https://www.zeiss.com/microscopy/us/products/light-microscopes/light-sheet-microscopes/lightsheet-7.html	https://www.miltenyibiotec.com/US-en/products/ultramicroscope-blaze.html

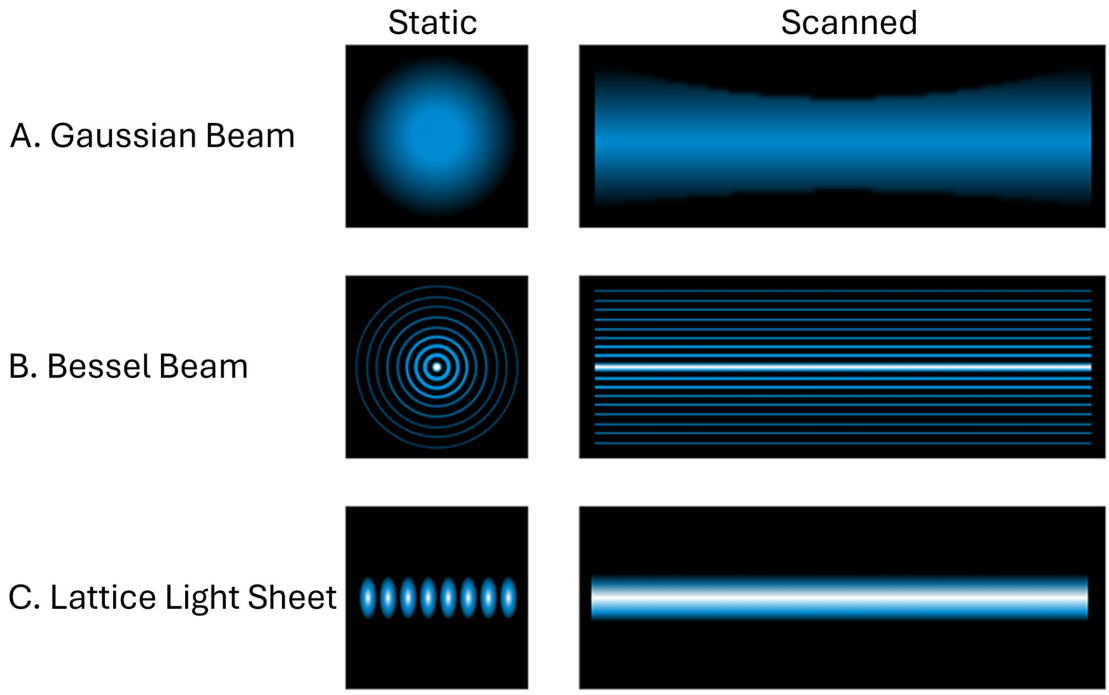


Figure 2: Comparison of illumination profiles in LS microscopy. Schematic representation of three beam types used for generating LSs: (A) Gaussian beam, which produces a narrow waist but suffers from rapid divergence, limiting the FoV; (B) Bessel beam, which offers extended axial propagation with a thinner core but introduces significant side lobes that can cause out-of-focus excitation; and (C) lattice LS, which combines structured interference patterns to create a thin, extended light sheet with minimal side lobes, enabling high-resolution, low-phototoxicity imaging over large volumes. Adapted from [16].

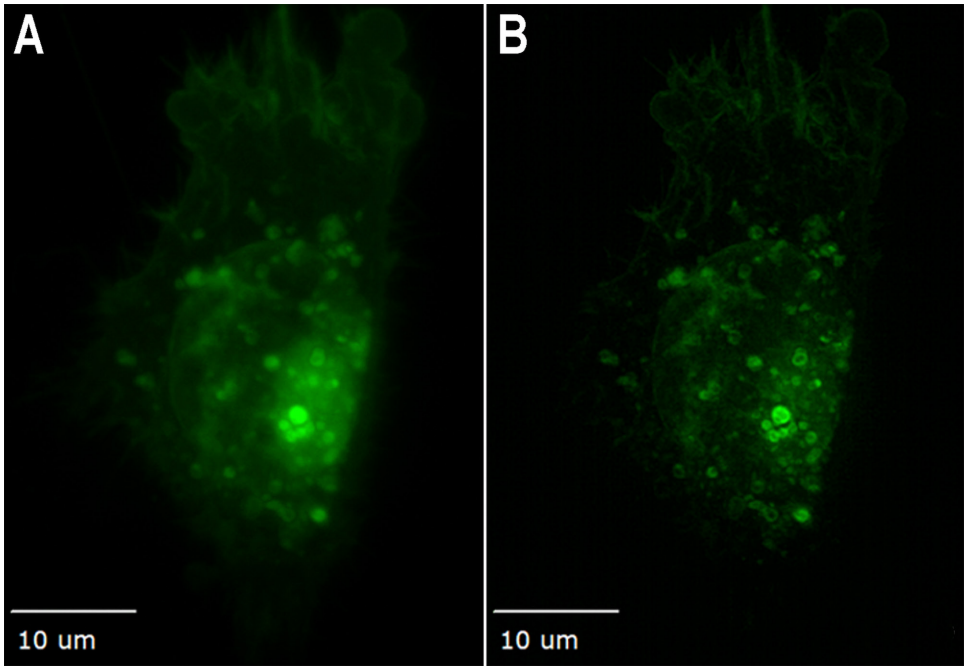


Figure 3: Representative image from Intelligent Imaging Innovations (3i) LLS. The sample shows mammalian cells expressing GFP-tagged lysosomes. A) Raw captured data, and B) the same dataset with the 3i deconvolution module in their SlideBook software. Adapted from [17].

incorporated for live imaging, particularly in long-term studies of embryos or organoids. Sample mounting varies widely depending on the scale and condition of the specimen, for example, single cells may be grown on coverslips or embedded in microfluidic chambers, while cleared tissues are suspended in refractive index–matched media within large sample holders [2,8].

Different LSFM modalities optimize these components for specific imaging needs. For example, systems designed for live-cell imaging often prioritize high NA detection and ultrathin light sheets, whereas large-volume tissue imagers trade off resolution for field-of-view (FoV) and depth penetration. The modularity of LSFM makes it an incredibly adaptable tool, but it also means users must carefully match the system design to the sample size, optical clarity, and biological dynamics under investigation [2,4].

LSFM Modalities by Scale

Single-cell LSFM. Single-cell light sheet microscopy operates at the scale of a few microns, capable of capturing several cells and limited structures. Utilizing a LLS microscope reduces sheet thickness compared to larger light sheets (LS) and increases the temporal resolution using a dithering apparatus. The 3i LLS can produce an LS on the order of 400nm and capture a volume with a temporal resolution on the order of a second or less. The captured volume will be correspondingly small, but the LLS allows researchers to capture the kinetics both inside and outside cells (Table 2, Figure 3).

LLS microscopes utilize light interference to generate very thin LSs. The 3i LLS uses an "annular mask" with different-sized annuli to create sheets with different properties. These changes alter the thickness of the LS as well as how "long" it is. Optimizing the LS parameters provides an additional field of control to image live cell structures and dynamics. Single-cell light sheet microscopy allows for high physical and temporal resolution utilizing LS imaging. LS thickness for the 3i LLS microscope is approximately 400nm, with the microscope allowing for changes to the thickness in order to optimize imaging parameters [9]. In short, the thickness of the LLS combined with the high temporal resolution means that optically the samples are exposed to much less laser light, leading to less bleaching and phototoxicity compared to point scanning confocal fluorescence microscopy [9,10] (Figure 1).

Drawbacks for this technique include a limited FoV, specialized mounting and sample preparation techniques, and limited imaging depth [11]. Sample size is constrained by the limited FoV. The 3i system, for example, allows only a 4μm² translation range, and only the central 4μm² area of the coverslip is accessible for high-quality imaging. This presents a significant limitation for larger specimens, such as organoids, which can easily exceed this size. Additionally, samples embedded in gel are subject to optical diffraction and scattering, which restricts effective imaging to the uppermost layers of the specimen, reducing resolution and signal quality at greater depths.

Likewise, standard mounting slides and wells are not compatible with the 3i system. More complex samples like organoids require post-growth attachments to an LLS coverslip or else must be grown on the coverslip itself. This is required for cellular imaging, as the cells must be affixed to the coverslip strongly enough not to detach during immersion.

Lastly, samples imaged with the 3i LLS system must be immersed in a carefully selected cellular medium that supports viability and optical compatibility. Cells or specimens should be mounted directly onto a coverslip that has been appropriately treated to promote stable adhesion. It is also essential to use a medium free of unbound fluorophores to minimize background fluorescence and ensure optimal signal-to-noise during imaging.

Small to medium tissue LSFM. Small to medium tissue LSFM spans a biologically rich and technically diverse imaging range, from ~100µm specimens (such as individual organoids or early embryos) to tissue blocks and small organs approaching 2cm in size. This imaging scale is especially valuable for applications in developmental biology, stem cell research, organoid modeling, neuroanatomy, and small animal histology, where researchers must capture both cellular-level detail and the three-dimensional context of complex biological systems [2,8]. LS systems optimized for this size range offer a powerful compromise between resolution, imaging depth, and acquisition speed, thus allowing dynamic processes, multicellular interactions, and tissue architecture to be visualized in full volumetric form.

To achieve this, most small to medium tissue systems utilize dual-sided Gaussian illumination, which improves uniformity across thick or irregular specimens while reducing shadow artifacts. For example, the ZEISS Lightsheet 7 and Bruker Luxendo MuVi SPIM integrate long working-distance objectives with moderate NA (typically 0.3–0.8 NA), striking a balance between resolution and FoV. These platforms often support multiview acquisition, in which images are collected from multiple angles and computationally fused to reconstruct isotropic volumes and to correct for light scattering or occlusion.

Systems like the Leica Viventis Deep are optimized specifically for long-term live imaging, with integrated temperature, CO_2, and humidity control to maintain physiological conditions during extended time-lapse studies of organoids, embryos, or tissue explants. In contrast, the Leica Stellaris DLS brings digital LS imaging into a confocal architecture, enabling flexible integration with inverted microscope workflows, ideal for imaging spheroids, adherent cell layers, or 3D cultures using familiar sample preparation formats. While the Viventis and Stellaris systems excel in live imaging applications, platforms like ZEISS and Luxendo are equally effective for fixed and optically cleared tissues, offering high-throughput volumetric imaging of thick sections, embryonic structures, organoids (Figure 4), or small organs (Table 3).

Sample preparation and mounting methods vary with imaging mode. Live samples are typically embedded in low-melt agarose or held in perfusion-compatible chambers that regulate pH and temperature to sustain viability. For cleared tissues, samples are immersed in refractive index–matched media and supported by mesh baskets, glass holders, or custom mounting systems to minimize drift and distortion during long imaging sessions. Imaging workflows may range from high-resolution 3D reconstructions for developmental studies to fast mesoscopic scans optimized for throughput and coverage.

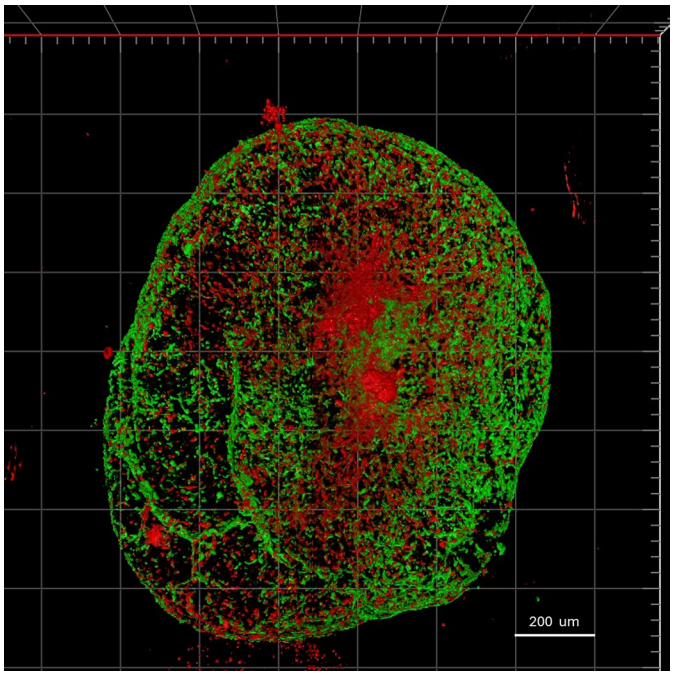


Figure 4: Representative image from sample on ZEISS Lightsheet 7. Image of a 30 × 33µm iPSC-derived vascular organoid stained for CDH5 (green) and αSMA (red).

Table 3: Comparison of additionally mentioned commercial LSFMs.

System	Best For	Sample Size Range	Fixed/Cleared Imaging	Mounting Format	Website
Bruker Luxendo MuVi SPIM	Live/fixed multiview imaging of embryos, explants	100µm–1.5cm	Yes (optimized for multiview cleared imaging)	Capillaries, embedded gels, sample holders	https://www.bruker.com/en/products-and-solutions/fluorescence-microscopy/light-sheet-microscopes/muvi-spim-family.html
Leica Viventis Deep	Long-term live imaging of 3D samples (organoids, embryos)	200µm–1cm	Limited (primarily live samples)	Agarose, custom chambers for live samples	https://www.leica-microsystems.com/products/p/viventis-deep/#
Leica Stellaris Digitally Scanned LSFM	Flexible light sheet + confocal for 3D cultures, spheroids	100µm– 5mm	Yes (via digital LS in confocal format)	Standard confocal slide/chamber formats	https://www.leica-microsystems.com/products/confocal-microscopes/p/leica-tcs-sp8-dls/
mesoSPIM	Whole cleared organs, brain mapping, connectomics	1mm–3cm	Yes (requires clearing with iDISCO/CUBIC/etc.)	RI-matched media, custom holders	https://mesospim.org/

The greatest strength of small to medium tissue LSFM lies in its versatility. It can accommodate a broad spectrum of sample types (that is, live or fixed, transparent or cleared) while offering a scalable balance between resolution, depth, and volume. Limitations do persist where imaging depth is constrained in uncleared samples, and subcellular resolution may not reach the level achieved by LLS systems designed for single-cell work [2,6]. However, for most biological questions involving coordinated cell behavior, tissue organization, or developmental dynamics, small to medium LSFM platforms provide an ideal window into 3D biology, offering gentle illumination, efficient acquisition, and comprehensive spatial insight.

Large-tissue LSFM. This section will focus on large-tissue (>1mm) LSFM as well as its advantages and disadvantages over small-tissue techniques. Large-tissue LS imaging can be achieved through several methods, including:

- *Digitally scanned LSFM*: A blanket term referring to the scanned illumination of individual planes of tissue perpendicular to a camera by use of a high-concentration laser light source. Rather than illuminating and imaging entire planes at once, a single laser line penetrates the sample, then scans through the plane perpendicular to the camera view. The advantage of this is that the full power of the laser is concentrated into a single line, increasing illumination and penetration into large tissue samples [12] (Table 3).
- *mesoSPIM*: This features a rolling camera shutter to remove edge-blurring artifacts produced by imaging the entire plane at once, a rotating sample mount that allows for 360° manipulation, and a scanned Gaussian light source to remove shadowing artifacts. These features paired with high working distance objectives provide a microscope intended for high-throughput large-tissue imaging (Table 3).
- *Miltenyi Blaze*: This dual-laser microscope increases penetration depth by illuminating from both sides of a sample at once. Variable NA light sources allow the illumination plane to be flattened for subcellular resolution or widened for increased FoV. This grants a degree of versatility when dealing with samples of different sizes. Like the mesoSPIM, the Blaze uses scanning image collection and stitching to remove edge-blurring artifacts from the final images. This increased focus on penetration depth and resolution makes this microscope a better fit for versatility in resolution and detail (Table 2, Figure 5).

Given that light must penetrate more deeply into larger samples, samples must be fixed and cleared, thus no live-sample imaging is possible when imaging through large-tissue samples. Common clearing methods for large-tissue LSFM include CUBIC [13], iDISCO [14], and MACS [15]. Once cleared, samples are mounted on a stand or similar holder and submerged in a liquid medium that matches the refractive index of the cleared tissue. This minimizes diffraction and increases image quality. After clearing and mounting, samples are ready to be imaged.

Illuminating and collecting light over a larger area allows for rapid acquisition of large sections of tissue. As is the case in more traditional microscopy, however, spreading illumination over a larger area limits the collection of finer details on the sample surface. Put simply, taking in the whole forest at once limits one's ability to see a single leaf up close. While the loss of detail is notable, this trade-off is appropriate in many circumstances. For example, if the goal is to count the islets of Langerhans in a pancreas sample, a sample can be cleared and stained for beta and alpha cells. Given that islets need to be counted, and not the individual cells, a broader and faster scan of the whole tissue is appropriate. However, if visualization of more specific intracellular protein interactions is required, the broader scan would preclude this. These advantages and limitations apply to many different experimental scenarios, including atlas construction, whole organ pathology, and screening for abnormal tissue. Generally, when trying to draw a map of *in vivo* cellular processes, the aforementioned small tissue LS techniques are probably more applicable.

Choosing the Right LSFM

The correct LSFM for an experiment will meet the desired resolution and sample prep conditions. For example, live cell imaging is not compatible with the Miltenyi Blaze because it requires tissues to be cleared. The decision flowchart (Figure 6) provides a high-level overview of how to choose the correct microscope.

Crucially, the first choice is to decide whether clearing is needed, such as with a tissue/organ sample, or if the interest is in live cell dynamics. This is the biggest limiter on the machine use, as LLS systems are not utilized for cleared samples due to their operation at a high magnification and small FoV to interrogate cellular dynamics. The opposite is true for larger samples or whole tissues where a high-resolution session on a system designed for imaging small samples would take prohibitively longer and require stitching of multiple volumes.

The included radar plot (Figure 7) shows which systems operate better in which areas. This is meant as an overview, and the specific experimental needs should always guide machine

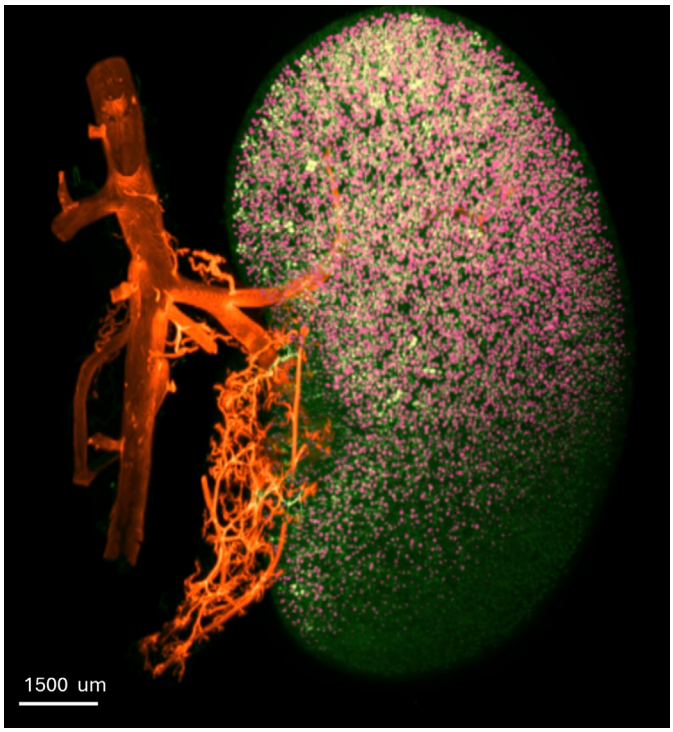


Figure 5: Representative image from sample on Miltenyi Blaze. Healthy mouse kidney cleared with iDISCO and imaged. Pseudo-coloring and 3D composition were performed with Imaris software.

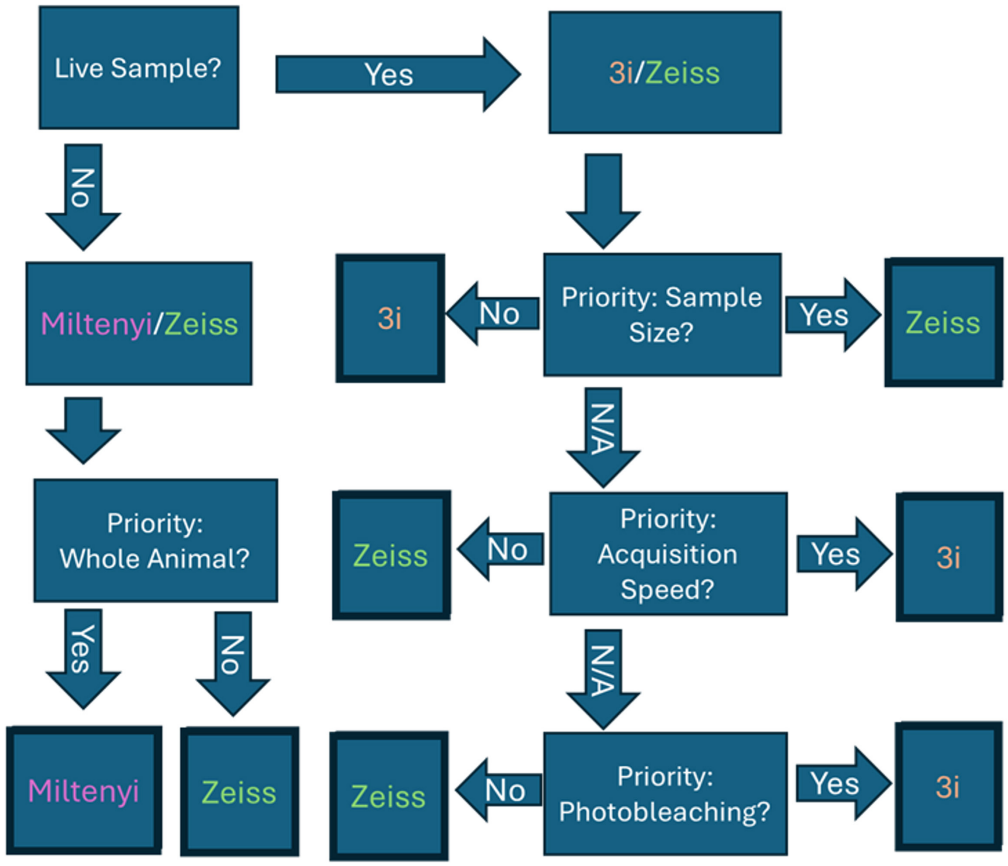


Figure 6: Flowchart for selecting the appropriate LS system. This diagram serves as a general guide for choosing between available platforms. In most cases, there is flexibility at decision points, allowing one system to substitute for another based on specific needs or constraints. The primary exceptions are the Miltenyi Blaze, which does not support live-cell imaging, and the 3i Lattice LightSheet, which is designed exclusively for live-cell applications.

choice, assuming availability. It should be noted that LLS microscopes are relatively more rare than confocal or widefield fluorescence microscopes. As such the "ideal" system for an experiment may not be available. Consult the local microscopy core to ask for advice, as the systems mentioned here are described for their ideal performance and sample. Ideal reality seldom exists.

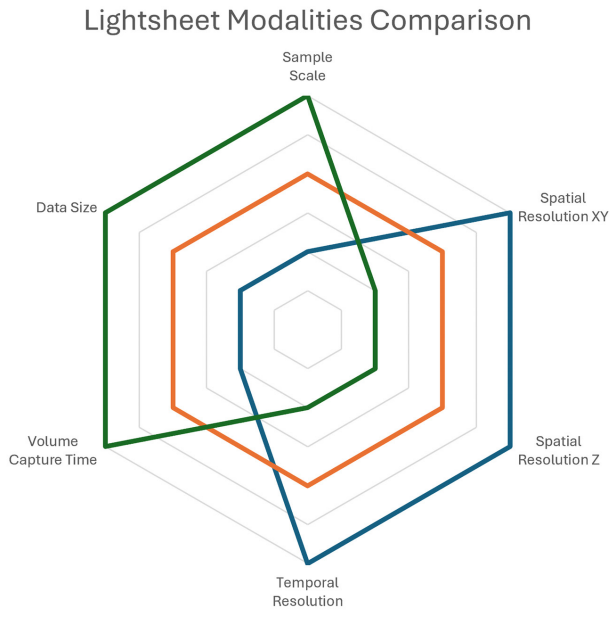
Data Concerns and Further Reading

LSFM is incredibly powerful and versatile, allowing for highly detailed imaging of internal cell kinetics and large/whole tissues (including whole cleared animals). The caveat to these benefits is the commensurately larger datasets produced by LSFM. Sizes can range from tens of gigabytes to many terabytes of image data depending on acquisition requirements. This often presents challenges in terms of storing such massive datasets for extended periods of time and frequently complicates the use of analytical software.

Datasets on the scale of hundreds of gigabytes, particularly those representing single, contiguous 3D volumes, require robust and specialized analysis infrastructure. Workstations must support advanced volumetric analysis software such as Imaris, arivis Vision4D, or AMIRA and be equipped with sufficient computational resources to efficiently manage large data loads. Key hardware considerations include high-performance CPUs or GPUs, ample RAM, and fast storage solutions capable of supporting real-time rendering, surface reconstruction, segmentation, and quantitative analysis without bottlenecks. Beyond raw storage capacity, performance is heavily influenced by drive speed (for example, SSDs versus HDDs), memory bandwidth and size, and processing power, including the number of CPU cores and dedicated GPU memory. For example, Imaris recommends at least 64GB of RAM, 12–16 CPU cores at 3.3GHz, an 8GB graphics card, and multiple high-speed SSDs to support smooth data handling. As such, it is strongly advised that data storage and analysis needs are discussed and planned prior to imaging, ensuring the infrastructure is ready to accommodate large-scale datasets without compromising downstream analysis.

It is possible during acquisition to optimize imaging parameters, storage parameters, and even qualities like image "bit-depth," all of which can affect the final size of the data files. This is less of an issue for exploratory one-off projects, but repeated imaging sessions should consider the data footprint. It's much cheaper today to store data, but the size of datasets is increasing even more quickly than storage options, and costs may balloon if imaging is done to "get everything."

For those interested in exploring advanced techniques and analyses in LS microscopy, key resources include an overview of deconvolution methods for LS datasets, offering insight into post-acquisition resolution enhancement [11]; the foundational work on LLS microscopy, detailing its applications from molecular to embryonic imaging [10]; and a



System	Sample Scale	Spatial Resolution XY	Spatial Resolution Z	Temporal Resolution	Volume Capture Time	Data Size
LLS	1	3	3	3	1	1
Small Tissue	2	2	2	2	2	2
Large Tissue	3	1	1	1	3	3

Figure 7: Radar plot of LS modalities. The three imaging modalities presented in this article are arranged according to a scale 1–3, with a rating of 3 meaning "best fit" for that specific criterion. While the modalities are compared to each other, these ratings should be considered alongside the decision flowchart in Figure 6.

quantitative evaluation of lattice illumination patterns, which provides a deeper understanding of performance trade-offs in structured LS designs [9].

Conclusion

LSFM offers an unmatched combination of gentle illumination, volumetric speed, and spatial resolution, making it a transformative tool across the biological sciences. Its scalability, from probing intracellular dynamics to surveying entire organs, depends on selecting the right system for the size, condition, and biological context of the sample. As shown through comparison of platforms like the 3i Lattice LightSheet, ZEISS Lightsheet 7, and Miltenyi Blaze, each system excels in a particular imaging niche. Understanding these distinctions helps researchers make informed decisions, balancing optical performance with sample compatibility, throughput, and downstream data analysis needs. With the continued growth of LS technology and data infrastructure, LSFM will remain central to high-resolution, high-content imaging across diverse biological applications.

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