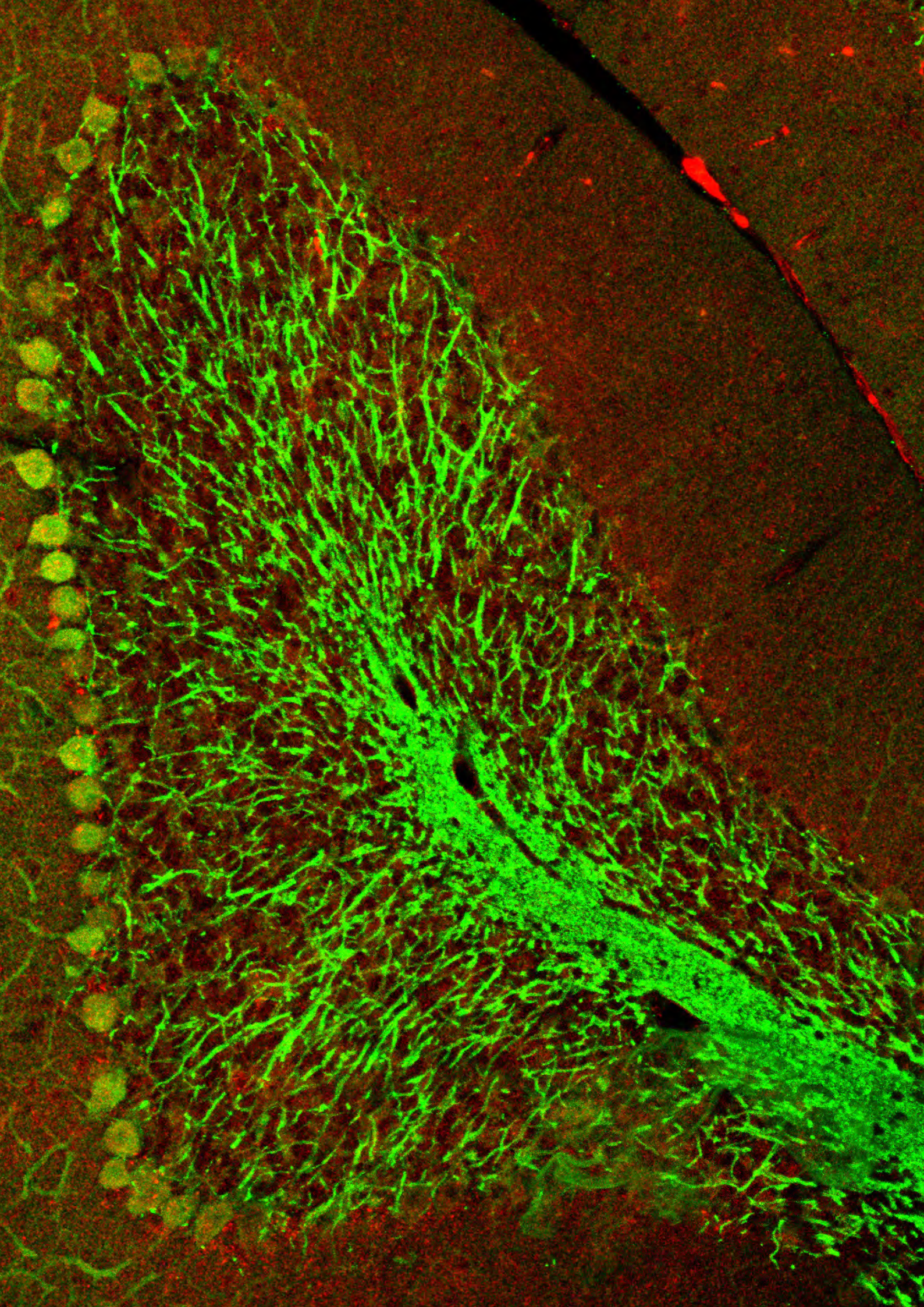


Life Science & Light Microscopy



Life Science & Light Microscopy

In both, light microscopy and the even more spread field of life sciences, precise and reliable sample handling is mandatory. To address the varying requirements of such a protean environment, SmarAct has formed a dedicated team of scientists, engineers and modeling experts with specific know-how in life sciences and light microscopy.

(Light-)Microscopy

SmarAct has developed microscope stages that allow the specimens to be positioned in multiple dimensions and can be combined with micro-manipulation systems for in situ sample manipulation. Our microscope stages are based on compact linear positioners and allow long travel ranges with nanometer precision in highest closed-loop repeatability. In addition to the standard universal object slide holder, unified well plate holders, standard bread board adapters and petri dish holders are available. The optional micro-manipulation systems are very versatile devices when it comes to the handling of pipettes, micro-knives, micro-grippers, micro-injectors or other mechanical or electrical probes. Our portfolio includes several different manipulators with three and four degrees of freedom for the most common tasks.

Super Resolution Microscopy

With the advancements in super resolution microscopy, the demand for highly precise, multi-dimensional sample manipulation has increased together with the need for affordable solutions. SmarAct offers several plug-and-play kits for different open-source microscopes (e.g., NanoPro 1.0, MiCube, K2 TIRF a.o.) and our team of experts will support you all the way to realize your specific setup.

Assisting 3D Printing with High Precision Microscopy Stages

3D printing in life sciences holds immense potential for creating complex biological structures, from tissue engineering scaffolds to fully functional organ models. Today, microscopic bracket scaffolds can be placed directly on open wounds, where they retain larger quantities of healing cells transported in the blood stream, helping to accelerate the healing process. However, printing real functioning organs for medical applications requires overcoming substantial obstacles. While it is possible to print the biological structures of an organ with cell scaffolds, it remains challenging to imbue the function of an organ into the printed structure. In both previous applications, 3D printers rely on strict requirements for precision and control, paired with an in-depth analyses to minimize vibrational coupling and achieve outstanding stability during the process.

Key challenges for 3D printing at the nanoscale:

Sub-Micron Precision and Complex Material Handling

Many biological applications, such as cell-laden hydrogels or microfluidic devices, require structures with nanoscale features. To achieve the necessary accuracy, precise handling of the printed constructs and layers is necessary. Additionally, 3D printing in the life sciences involves delicate biomaterials, such as live cells and bioinks, that are highly sensitive to mechanical forces. Precise control over

deposition, layering, and curing is critical to maintaining cell viability and structural integrity.

Environmental Sensitivity

Biological printing often requires tightly controlled conditions, including sterility, humidity, and temperature regulation. Small deviations can significantly affect print quality and the viability of biological constructs.

These challenges require positioning equipment for the sample stage, laser manipulation, optics and printing components that support the operation of 3D printing on the nanoscale.

SmarAct's products are designed to accommodate various applications that require nanometer resolution, vibration sensitivity, high stability and material flexibility. The user can choose the technological drive principle that is best matches their requirements. Our MLS series of electromagnetic (EM) drives allows for smooth and frictionless motion at high positioning velocities to enhance the printing speed. In contrast, our piezo based systems can achieve low drift and environmental stability for challenging environmental requirements that include temperature gradients and thermal expansion. The piezo and EM technologies can be combined to form a cutting-edge system ready to tackle the biggest challenges nanoscale 3D printing is currently facing.



UpNano, a high-tech company specializing in the development and manufacturing of two-photon polymerization (2PP) 3D printing systems, has demonstrated its cutting-edge capabilities using SmarAct's microscopy piezo stage series and complementary positioning systems. Their proprietary 2PP technology enables rapid and precise microfabrication, allowing them to produce complex structures such as advanced microfluidic

devices for revolutionizing IVF treatments or the famous castle on a pencil tip. This breakthrough technology is unlocking new possibilities for applications in biomechanics, tissue engineering, microfluidics, photonics, and optics.

Cutting-Edge Technology in TIRF Microscopy: Overcoming Motion System Challenges

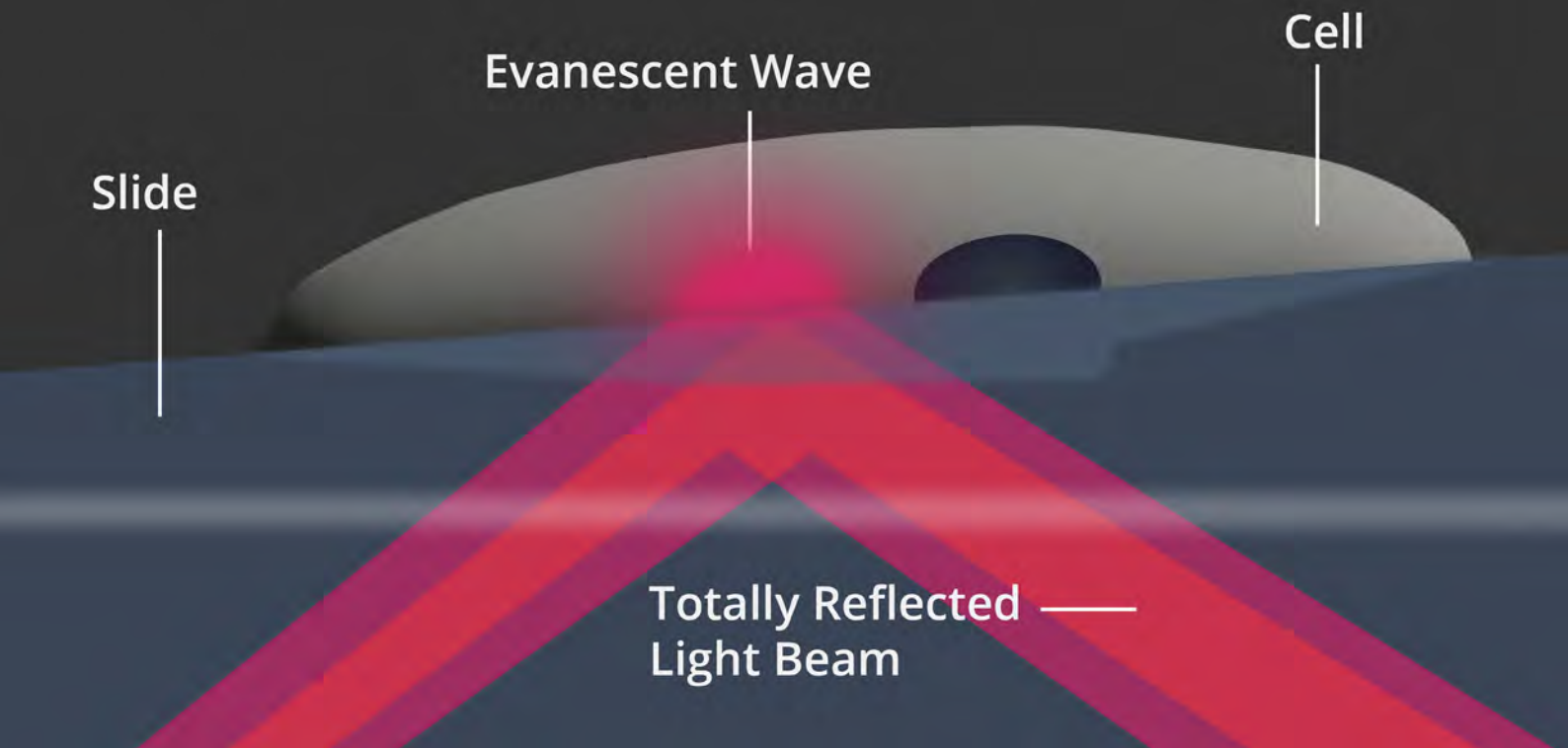
Total Internal Reflection Fluorescence (TIRF) Microscopy is a powerful imaging technique for visualizing single-molecule events near the glass-water interface with exceptional axial resolution. However, achieving the full potential of TIRF microscopy requires ultraprecise motion control, particularly in positioning the sample and optics. The high demands for stability, repeatability, and dynamic performance present significant challenges that modern motion systems must overcome.

Precision Challenges in TIRF Microscopy

One of the primary technical difficulties in TIRF microscopy is the need for nanometer-scale positioning and stability over extended imaging sessions. The excitation evanescent field, responsible for illuminating fluorophores within a few hundred nanometers of the coverslip, is highly sensitive to deviations in sample position and angle. Any drift, vibration, or thermal expansion in the positioning system can lead to intensity fluctuations, reducing image fidelity.

Another critical requirement is the ability to precisely adjust the excitation laser's angle of incidence. Small angular changes can significantly alter the penetration depth of the evanescent field, affecting the contrast and specificity of the image. This necessitates ultra-stable goniometer or piezo-driven tilting mechanisms capable of sub-microradian adjustments.

TIRF (TOTAL INTERNAL REFLECTION)



SmarAct Motion Systems: Addressing the Challenges

SmarAct offers high-precision motion control solutions that are ideally suited for the demanding requirements of TIRF microscopy. SmarAct's **XY and XYZ positioning solutions** provide nanometer resolution and repeatability, ensuring sample stability over long acquisition times. Their compact and tailor-made design makes them compatible with advanced microscopy setups.

The **Opto-Mechanics solutions** from SmarAct are particularly advantageous for controlling the incident angle of the excitation beam. With angular resolutions down to $< 5 \mu\text{rad}$, these stages enable precise tuning of the evanescent wave penetration depth, ensuring optimal signal-to-noise ratios.

Additionally, SmarAct's closed-loop **piezo positioners** integrate seamlessly with TIRF setups, offering sub-nanometer resolution

without introducing electronic noise that could interfere with sensitive fluorescence detection.

TIRF microscopy requires a motion control system that is not only precise but also stable and resistant to thermal drift and vibrations. SmarAct's advanced positioning solutions, including its high-resolution XYZ stages and precision opto-mechanics, provide the necessary tools to enhance TIRF imaging performance. By addressing key motion system challenges, SmarAct empowers researchers to push the boundaries of single-molecule fluorescence microscopy and unlock new insights in life sciences.



Light Microscopy and Lab Automation

Modern laboratories in medical research and biotech industries are no longer just spaces to conduct experiments – they have transformed into high-tech hubs that leverage automation and high-throughput processes to generate vast amounts of data. Traditional methods relied heavily on manual work, but today's advancements demand a shift toward smarter, more efficient solutions.

A key improvement in this regard has been the automation of laboratory instrumentation for precise, fast, and reliable sample handling. Automated systems ensure that samples are processed consistently and efficiently, minimizing variability and contamination risks. These benefits apply to both sample preparation and data acquisition, which in a best-case scenario can be combined for walk-away solutions that minimize

human interaction and boost the yield and quality of data. Autosamplers, one example of an automated system, ensure that critical samples are handled with care, reducing the risk of failure, downtime, and maintenance. This not only protects valuable research materials but also enhances the overall reliability of experimental outcomes.

At the same time, such systems provide scalability for high-throughput screening and manufacturing processes that do not compromise data integrity. Minimized hands-on time and unsupervised processes allow for continued operation beyond working hours, increasing productivity and efficient use of resources.

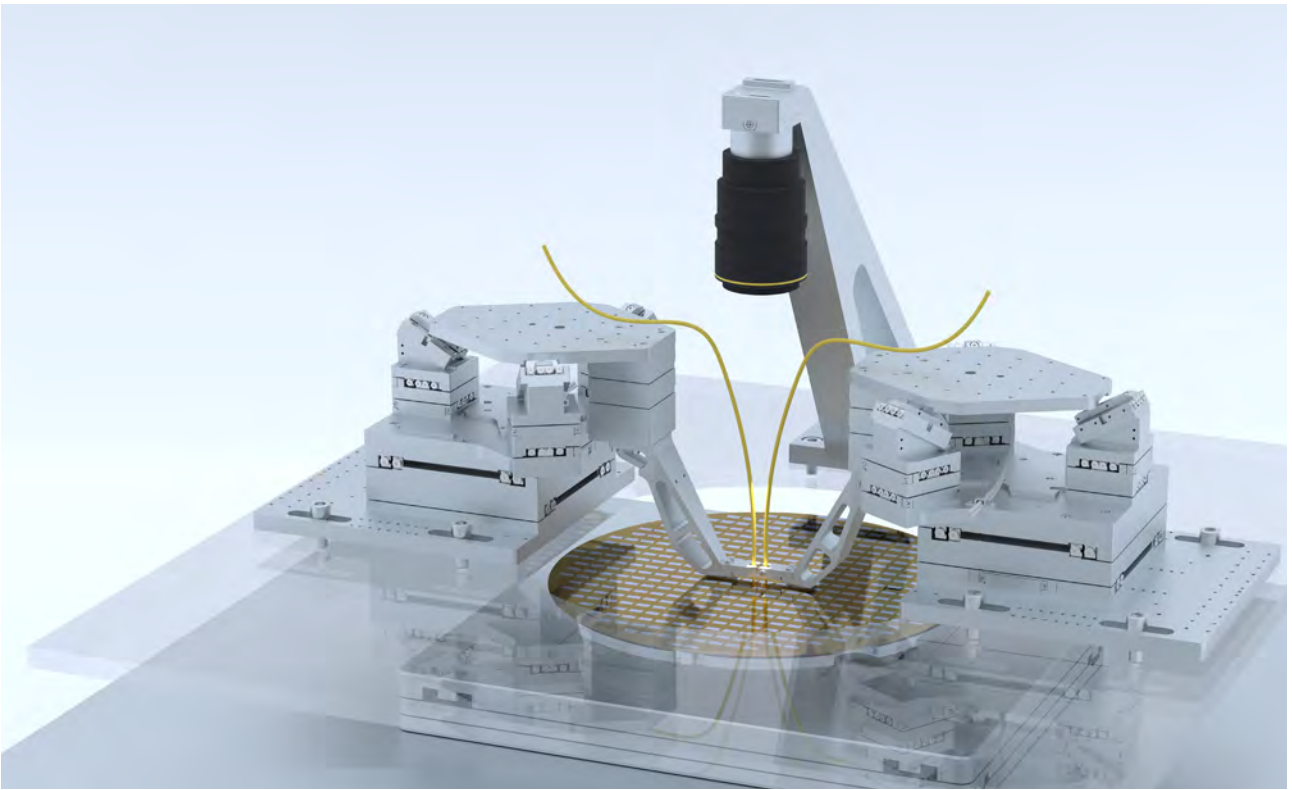
In the field of microscopy, automation has been long established. Modern research microscopes are fully motorized turn-key



systems which allow for remote operation and streamlined image acquisition. In combination with advanced imaging software, microscopes have evolved into high-throughput screening systems for large field of view stitching, time lapse imaging and rare event detection. These applications demand high precision positioning and focusing stages that do not compromise on performance but rather increase accuracy, repeatability, and stability. In recent years, the rise of super-resolution microscopy techniques has set the bar even higher for these requirements.

SmarAct nanopositioning systems are the ideal solution for device automation in the laboratory. Our diverse portfolio of microscopy stages covers travel ranges up to the size of a typical microtiter plate, and all three dimensions can be controlled

with nanometer precision by combining our XY tables with focusing stages. In addition, optical systems benefit from our automated optomechanical solutions that boast sub-microrad precision. Our large portfolio of modular positioning stages can be easily combined into complete positioning systems for the precise operation of custom-built research equipment or OEM systems.



Overcoming Challenges in Optical Wafer Inspection with Nanopositioning Technology

The semiconductor industry relies on optical inspection and microscopy to detect defects in wafers at nanometer scales. As feature sizes shrink and process nodes advance, traditional inspection methods face increasing challenges. High-resolution imaging, precise defect localization, and automation are essential to maintaining yield and performance and have much in common with current demands in life sciences applications. Nanopositioning systems play a critical role in overcoming these obstacles by providing sub-nanometer precision, stability, and adaptability to demanding inspection environments. Some key challenges in today's techniques involving optical inspection are described in the following sections:

Resolution and Stability at the Nanoscale

Optical inspection demands extreme precision, including the ability to detect defects at sub-10 nm nodes. Traditional motorized stages often suffer from vibrations and thermal drift, limiting their effectiveness. Piezo-driven nanopositioning systems provide nanometer-level stability with minimal drift, ensuring clear, high-resolution imaging. To keep up with semiconductor production demands, optical inspection tools must scan large areas quickly while maintaining precision. High-speed nanopositioning solutions, such as SmarAct's closed-loop piezo stages, deliver fast scanning without compromising resolution. Hybrid piezoelectric and direct-drive technologies

enable increased speeds while maintaining nanometer repeatability.

Compensation for Environmental Disturbances

Vibrations, thermal expansion, and mechanical drift can affect wafer inspection accuracy. Active compensation strategies using the SmarAct Metirio optical encoder or even the Picoscale interferometer can actively correct for positioning errors in real-time. This ensures that imaging remains stable even in fluctuating environmental conditions.

Automation and Process Integration

Wafer inspection systems require seamless integration into automated semiconductor fabrication environments. SmarAct's modular automation solutions, such as customizable XYZ stages and precision alignment modules, support fully automated workflows with real-time feedback control, reducing operator intervention and enhancing repeatability.

As semiconductor technology advances, the challenges of optical wafer inspection become more complex. Precision positioning is critical to achieving the required resolution, stability, and speed. Combining knowledge from diverse fields of applications such as light microscopy allows for cutting edge solutions to similar problems. SmarAct's nanopositioning solutions offer the sub-nanometer precision, multi-axis control, and real-time feedback necessary to enhance optical inspection processes, ensuring the detection of even the smallest defects while maintaining high throughput and automation efficiency. By integrating these advanced positioning technologies, semiconductor manufacturers can improve yield, reduce costs, and push the boundaries of next-generation chip production.





Medical Research

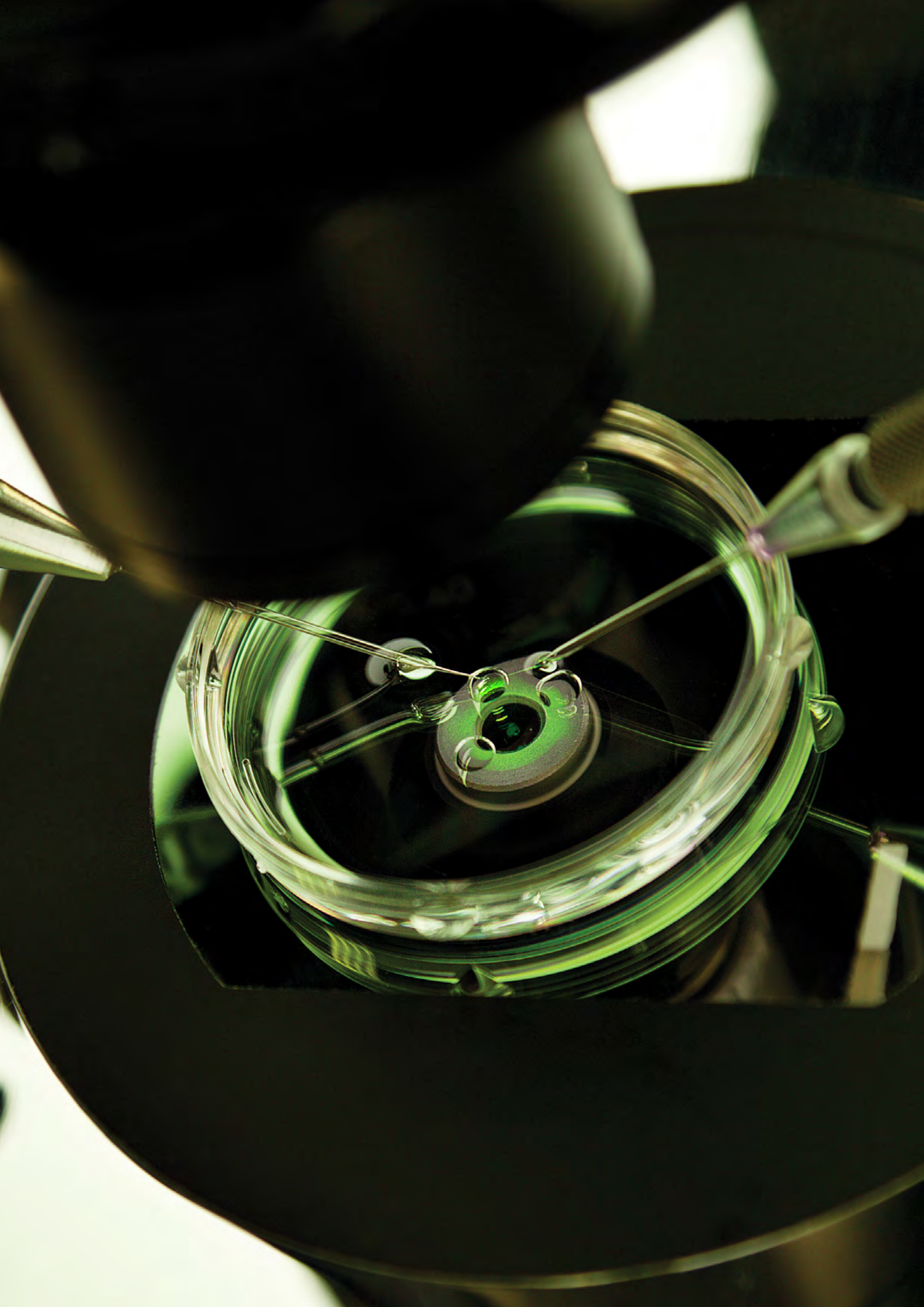
Samples used in medical research are an indispensable and costly resource. Oftentimes, the preparation of a suitable sample takes days, weeks, or even months. This process occupies labor, high-end equipment and expensive consumables. In the field of pathology, samples are irreplaceable as they originate from actual patients and cannot be requested on demand. These circumstances require that samples are handled with the highest care in order to avoid costly mistakes that cannot be corrected. At the same time, as much insight as possible should be obtained from the individual specimens to increase efficiency and maximize the cost-benefit ratio per sample.

These requirements call for optimized methods and protocols which minimize chances of failure and maximize data quality. In the field of robotic surgery, for example, this guideline means that prototype development should be based on the best and most precise actuators to reduce mechanical uncertainties and tolerances. On a smaller scale, tissue engineering requires accurate positioning systems during any manipulation, including 3D tissue printing, force measurements, and microsurgery of delicate in vitro samples. Methods such

as in vitro fertilization, cell manipulation, or laser dissection demand even stricter performance standards since they operate on a cellular level.

All methods listed have demanding requirements for any instrumentation involved, as accuracy, stability and repeatability directly translate into quality of both research and data output. In addition, for every example mentioned, complex positioning of effectors is needed, at times with a high number of degrees of freedoms (DoF).

SmarAct's nanopositioning devices are designed to overcome such positioning challenges and are accurate down to the nanometer scale. From individual positioning of effectors in a single dimension to compact 6 DoF positioning systems from our SmarBotic product line, SmarAct's portfolio can handle nanoscale positioning tasks with the highest accuracy and repeatability.



Nanopositioning in Super-Resolution Microscopy

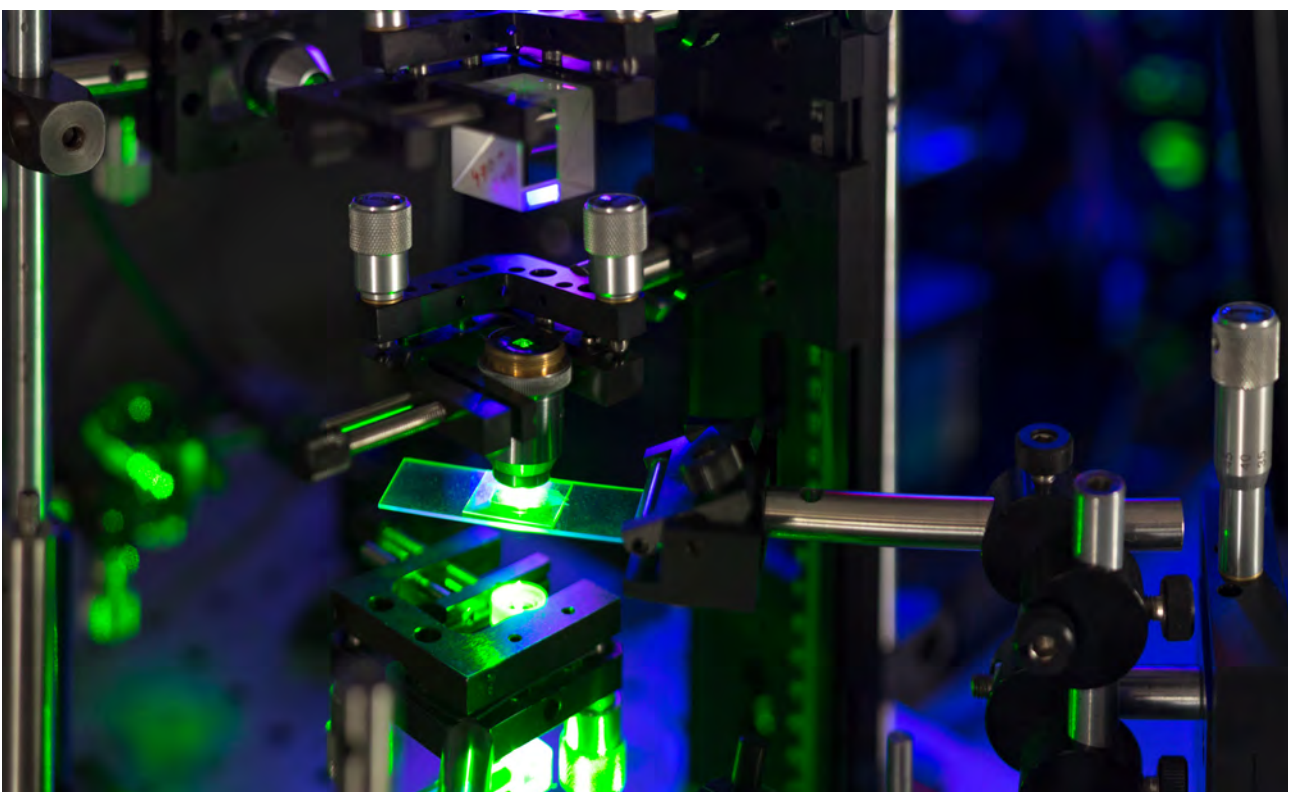
Light microscopy has long been constrained by the diffraction limit, a fundamental barrier restricting the resolution of optical systems. Breakthroughs in imaging technology have successfully overcome this limitation through super-resolution microscopy techniques, enabling researchers to achieve resolution even at the single-digit nanometer scale. The field has now become well-established, and scientists can visualize structures and molecular interactions in unprecedented detail.

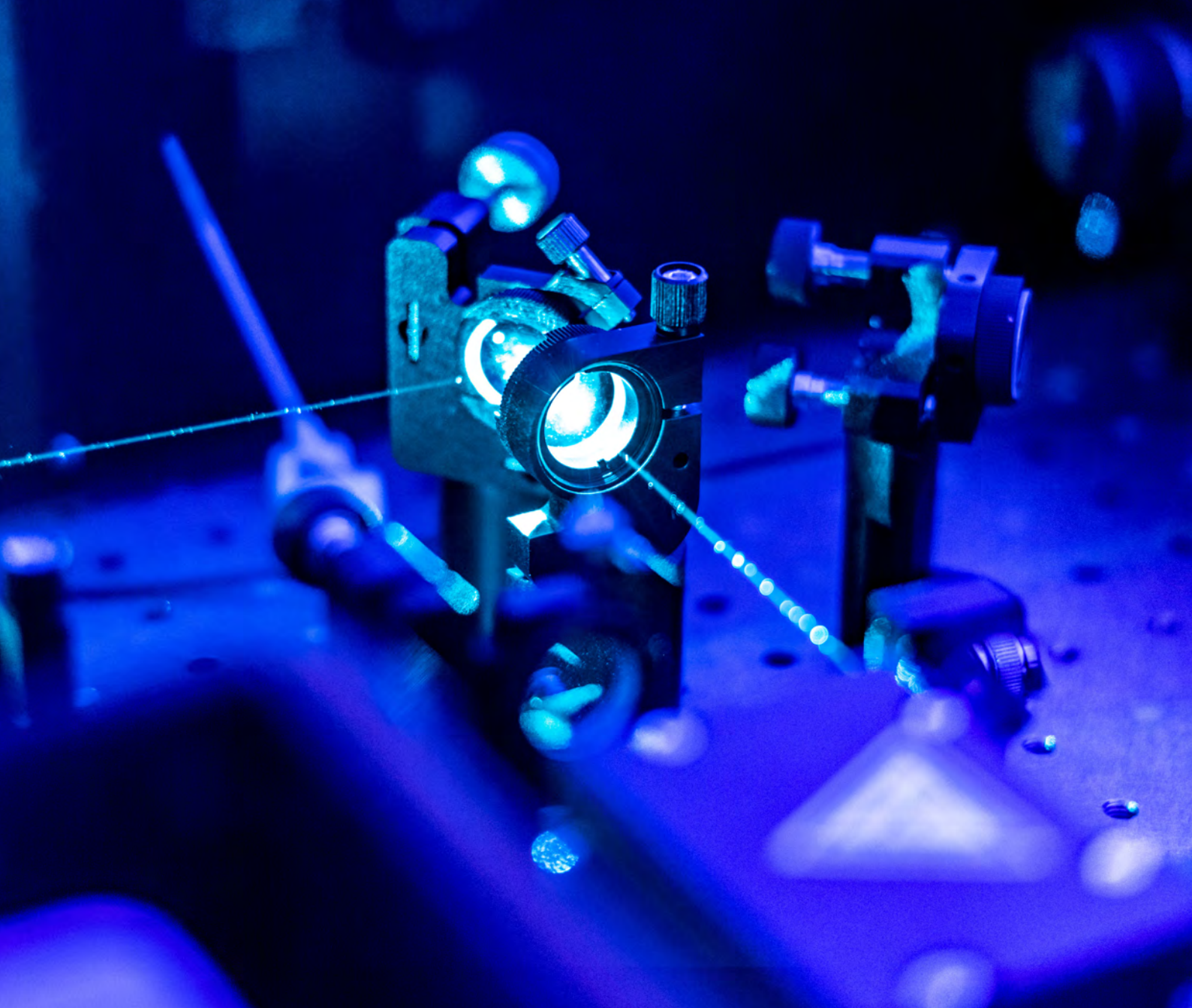
For super-resolution imaging to be effective, precise and repeatable alignment of optical components is crucial. Inaccuracies can introduce errors, affecting the quality and reliability of results. On the sample side, such systems require exceptional positioning accuracy and repeatability. In particular, high precision in the Z-dimension is critical for

3D imaging applications. Precise control of the focus unit ensures that the focal plane is well-defined across multiple layers, producing accurate reconstructions of biological structures or materials.

Since image acquisition takes place on a longer timescale than typical light microscopy imaging techniques, drift compensation is another essential aspect of high-precision imaging. Due to environmental factors and mechanical instabilities, sample drift can occur over time and negatively impact the image resolution. Systems with small step sizes and fast feedback loops enable continuous drift compensation, ensuring that imaging remains stable even during extended acquisition periods.

As super-resolution microscopy moves beyond proof-of-concept research and into routine imaging applications, the



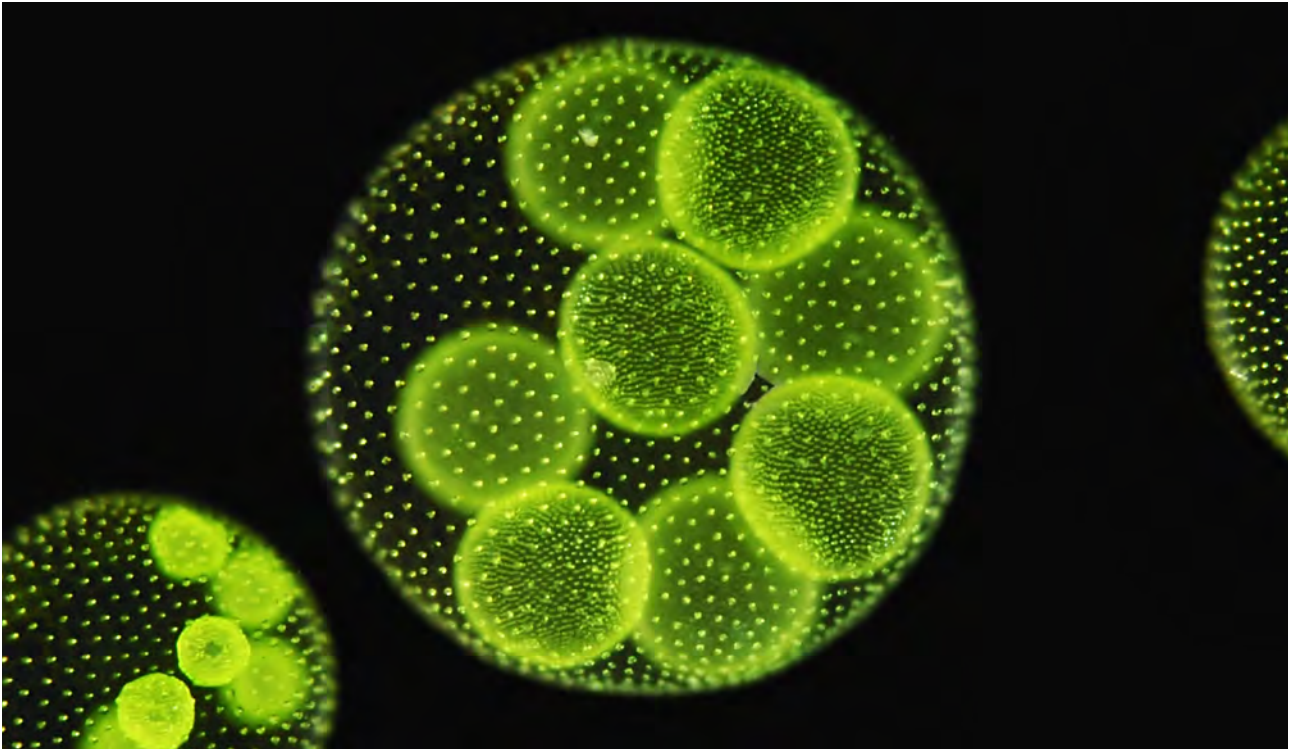


need for high-precision positioning systems becomes even more apparent. Long travel ranges with nanometer-level accuracy are necessary to screen samples and scale data acquisition. Ensuring these capabilities enables microscopists to fully harness the power of super-resolution imaging for practical, high-impact research with robust statistics.

The future of super-resolution microscopy relies heavily on the advancement of precise positioning systems. From automated optical alignment to high-precision focus control, these technologies are essential for maintaining the stability, accuracy, and repeatability required for cutting-edge

imaging. As research continues to evolve, laboratories that integrate advanced positioning solutions will be at the forefront of scientific discovery.

From optomechanics to our microscopy and focus stages, SmarAct is well positioned to overcome the challenges that arise during the conception of a super-resolution microscope. Our wide range of modular positioning devices and microgrippers is ideal for further expansion of imaging applications to include other techniques like micromanipulation, microsurgery, or cell picking.



Light Sheet Fluorescence Microscopy

Life sciences research demands advanced imaging technologies to achieve precise and reliable results. In light sheet fluorescence microscopy, a sample is illuminated from the side with a thin, focused sheet of light. This allows fluorophores within the focal volume of the sample to be excited. The emitted fluorescence is then captured by a second objective, typically positioned orthogonally to the light sheet.

By restricting the illumination to the focal volume of the light sheet, this technique significantly reduces photobleaching and phototoxicity. The result of rastering the light sheet across the sample is a series of optical sections. In addition to its minimal impact on specimens, light sheet microscopy is characterized by shorter acquisition times and high spatial and temporal resolution. These microscopes are widely used for analyzing fixed or

cleared samples as well as for observing living biological systems with high resolution.

High-precision motion is essential for ensuring the accurate positioning of key components in any advanced microscope. SmarAct provides high-performance solutions for sample positioning and scanning in all translational and rotational degrees of freedom, and also has options for objective and optic positioning. SmarAct's products achieve nanometer precise resolution and high stability. Their compact and modular design allows for easy integration into highly specialized setups, even in space-constrained environments. Thanks to the adaptable drive technology of SmarAct's stages, these positioners can be used in a wide range of environmental conditions including cryogenic and ultra-high vacuum applications.

The Role of Nanopositioners in Ophthalmology, Endoscopy and Ultrasonic Surgical Devices

Precision in Surgical Devices

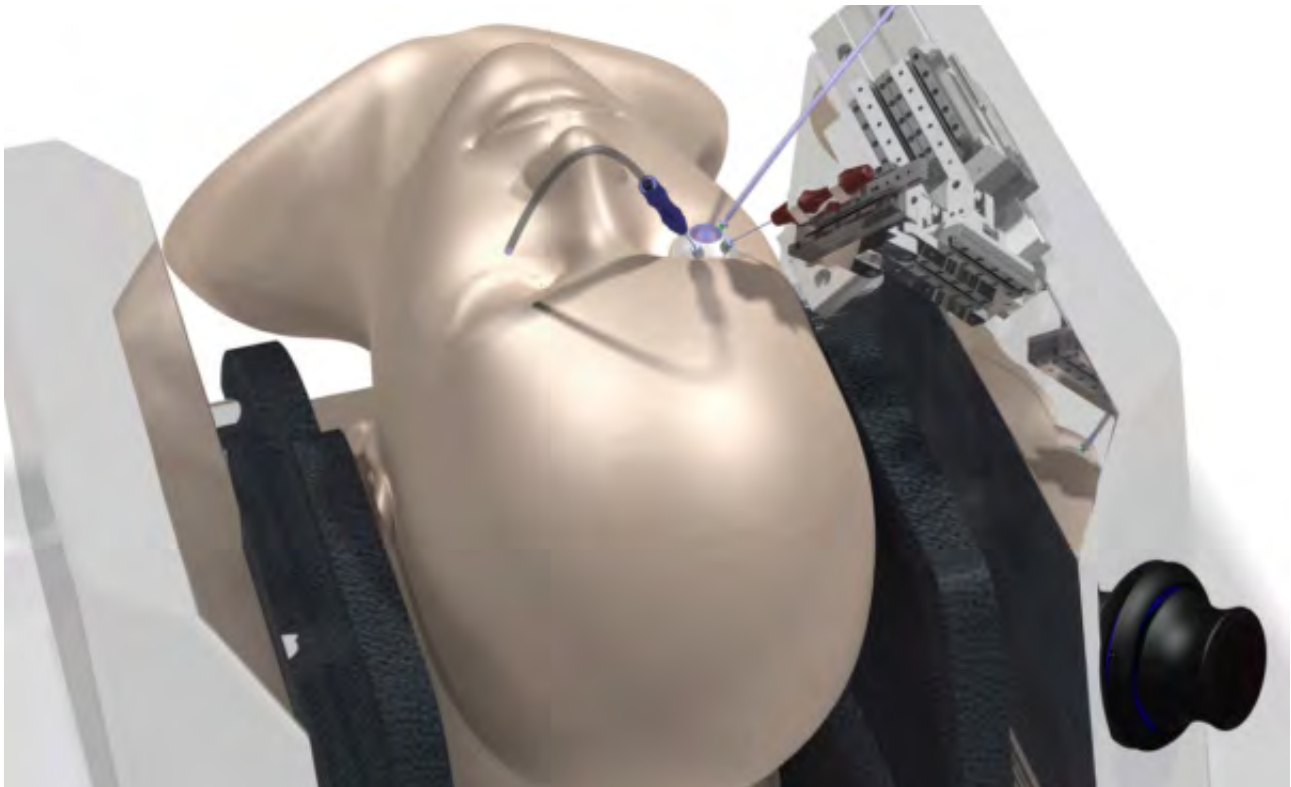
Advancements in medical technology have revolutionized surgical devices used for ophthalmology, endoscopy and ultrasonic methods, allowing for minimally invasive procedures with exceptional precision. In all three fields, the need for highly accurate positioning of instruments and imaging components is critical.

Ophthalmology: Enhancing Eye Surgery and Treatment

In ophthalmology, precision is paramount, especially in delicate procedures such as retinal surgery and targeted drug delivery. SmarAct's piezo-driven nanopositioners, such as the SLC-1750 stages, have been integrated into ophthalmic research at

TU Munich (Augenlinik und Poliklinik, Klinikum Rechts der Isar, Dr.-Ing. M. Ali Nasser) for improving the administration of drugs and stem cells to specific locations beneath the retina.¹ The compact design of the stages and high-accuracy movement, ensures that surgeons can operate with minimal invasiveness while maximizing the effectiveness of the treatment.

Additionally, high-precision positioning systems facilitate laser eye surgery by enabling controlled movements of laser systems and optical elements. This ensures that corrective procedures, such as LASIK or femtosecond laser treatments, achieve the desired outcomes with sub-micron accuracy.



¹A targeted drug delivery platform for assisting retinal surgeons for treating Age-related Macular Degeneration (AMD), M. A. Nasser et al., 2017 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), doi: 10.1109/EMBC.2017.8037815

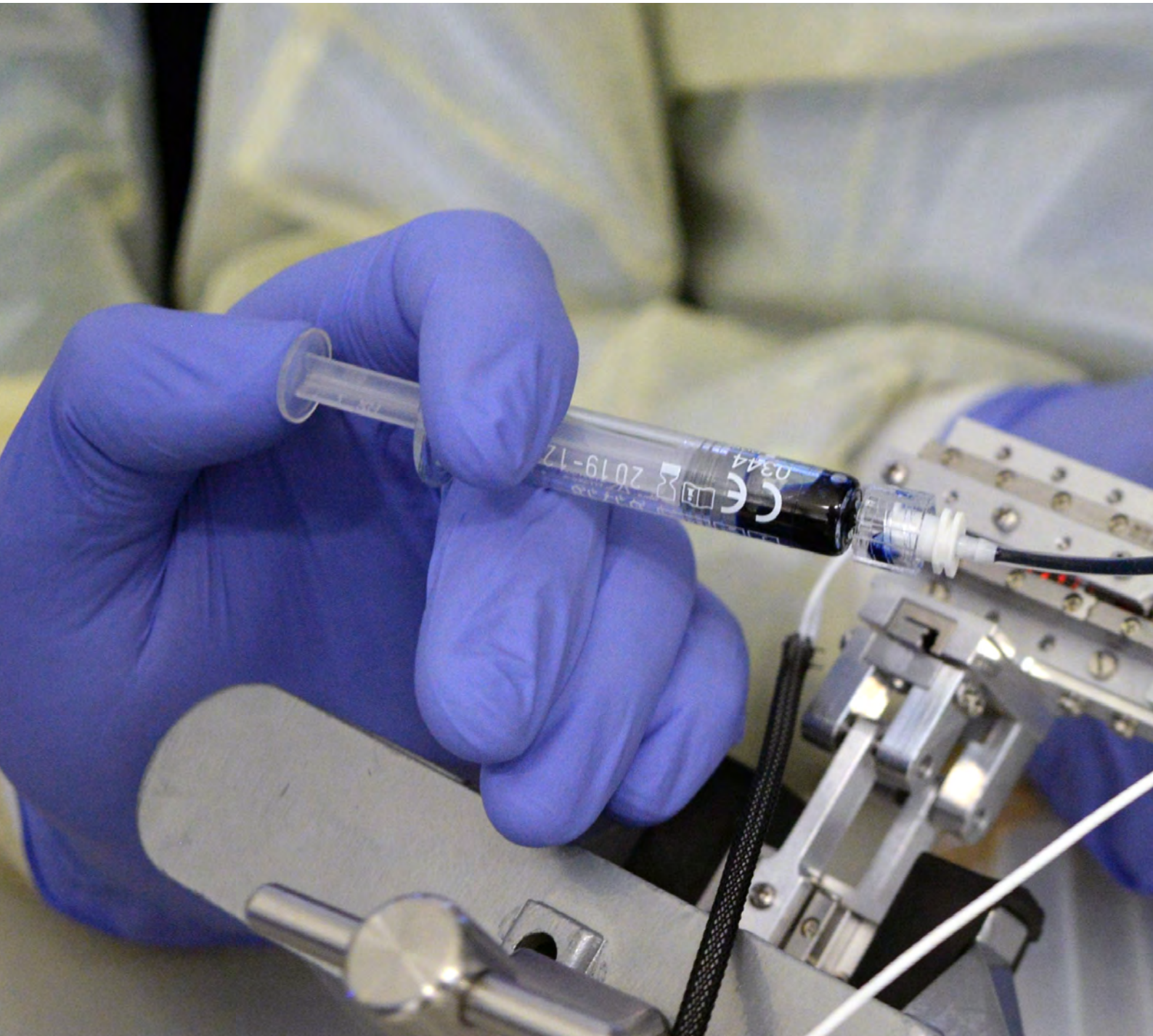
Endoscopy: Improving Imaging and Instrumentation Control

Endoscopic procedures require real-time imaging and the ability to maneuver surgical tools within the body's narrow pathways. Nanopositioners enhance these procedures by providing ultra-precise control over integrated endoscope lenses, biopsy tools, and laser-based instruments.

Ultrasonic Imaging Techniques for Surgical Devices and Research

Technologies based on ultrasonic imaging, such as Multispectral Optoacoustic Tomography (MSOT) and brain scans rely

on precisely emitted ultrasonic waves that allow clear images of affected organs to be obtained *in vivo*. Iconeus uses multi-plane-wave pulses of ultrasound to provide information on blood flow, which can be used to gain insights on brain activity.² The ultrasonic probes need to be accurately positioned during the scanning process, to optimize the field of view (and resolution) of the final 2D or 3D brain image. The current challenges these research fields are facing concern accelerating the development of clinical applications in humans. Therefore, there now is increasing interest in using the equipment with primates. However,



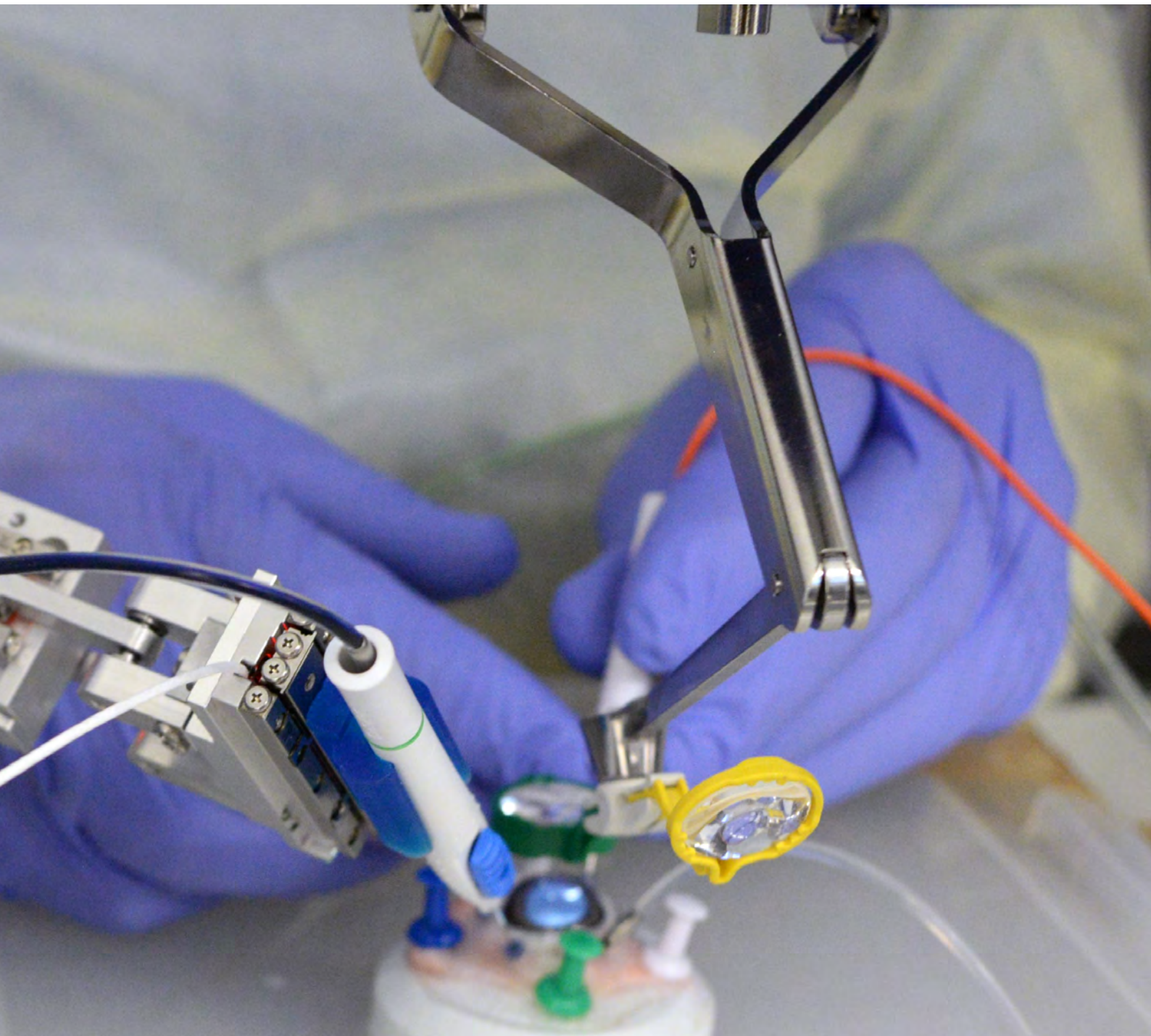
this requires a lighter probe positioning system than the four-axis motorized scanning platforms that are commonly utilized. With a weight of just 26 g, the SLC-1740 is far less cumbersome than the existing head-fixed platform, providing greater comfort for the subjects, while retaining the single axis of movement that is needed to accurately position the probe.

The Future of Nanopositioning in Surgery

As medical procedures continue to evolve, their optics and laser units require high-precision nanopositioning solutions for

stable operation. SmarAct's expertise in automation and precision engineering ensures that ophthalmology, endoscopic and ultrasonic technologies remain at the cutting edge, enabling safer, more efficient, and highly targeted interventions.

²Functional ultrasound imaging of the brain reveals propagation of task-related brain activity in behaving primates. Dizeux A, Gesnik M, Ahnine H, Blaize K, Arcizet F, Picoud S, Sahel JA, Deffieux T, Pouget P, Tanter M. *Nat Commun*, 2019. doi: 10.1038/s41467-019-09349-w



With the development and production of market-leading solutions in the field of high-precision positioning, automation and metrology, the SmarAct Group reliably accompanies their customers in achieving their goals. The broad product portfolio – from single positioning stages to complex parallel kinematics, miniaturized robots, control systems and measurement technology – is complemented by automated microassembly solutions. Even the most challenging customer requirements can be met by maximum adaptability and complete in-house production.

Since its founding in 2005, SmarAct has steadily grown from a small team of engineers to a group of companies with three independent business units and over 270 highly skilled members. Today, SmarAct relies on years of experience and, above all, on a very passionate team with unconditional customer focus.

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