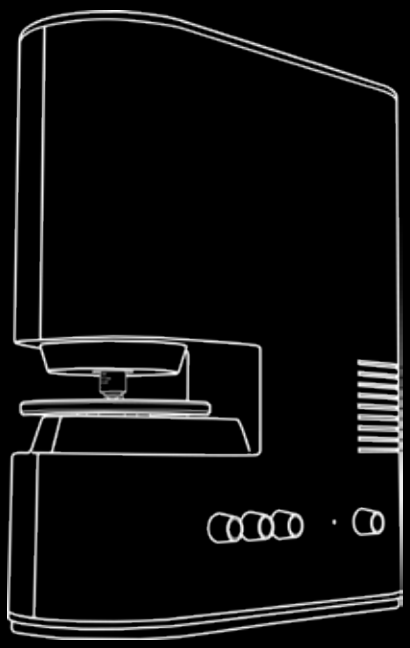
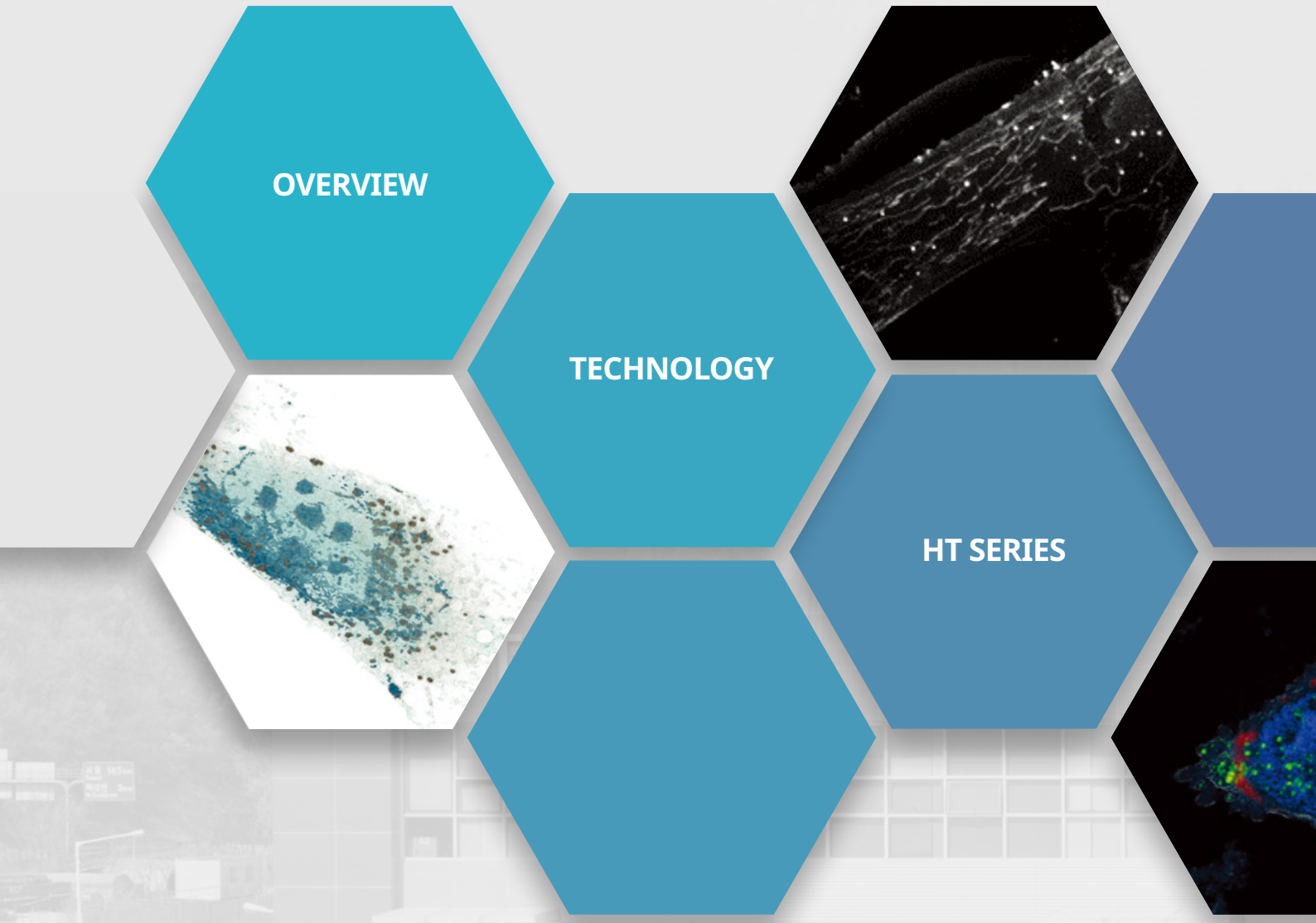
IMAGE DIFFERENT



Tomocube

CONTENTS



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www.facebook.com/tomocubeinc

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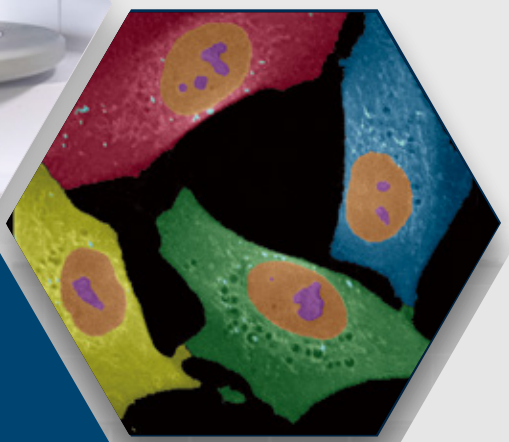
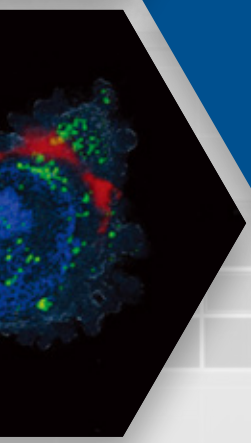




SOFTWARE

APPLICATIONS

SPECIFICATION

Revolutionary Holotomography (3D holographic microscopy) opens a new era for label-free live cell imaging

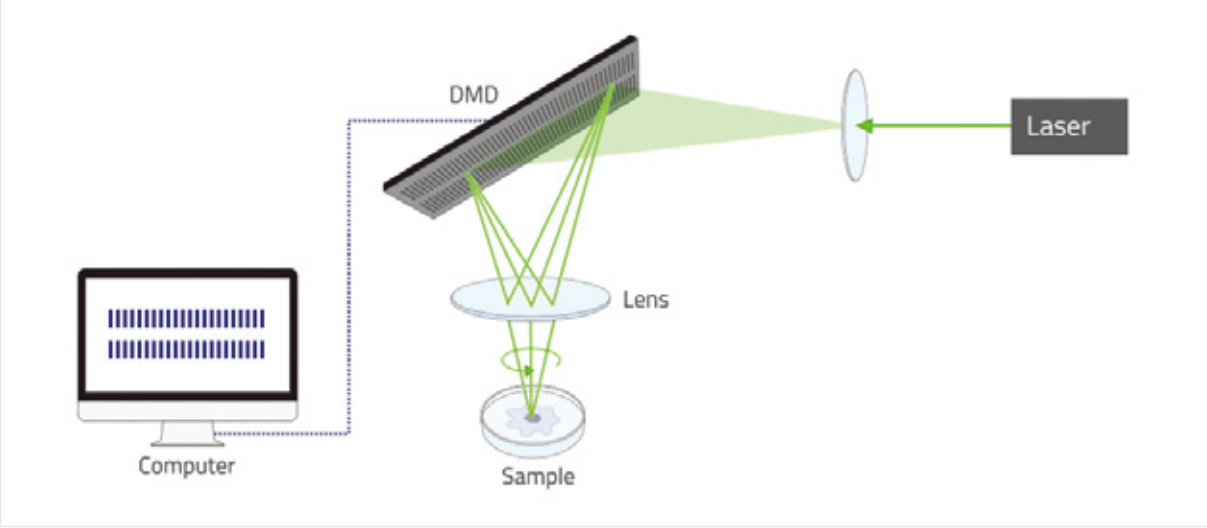
Cellular analysis plays a crucial role in a wide variety of research fields and diagnostic activities in the life sciences and medicine. However, the information available to researchers and clinicians is limited by the current microscopy techniques. An innovative new tool – holotomography – can overcome many of these limitations and open new vistas for researchers and clinicians to understand, diagnose and treat human diseases.

What is Holotomography (HT)?

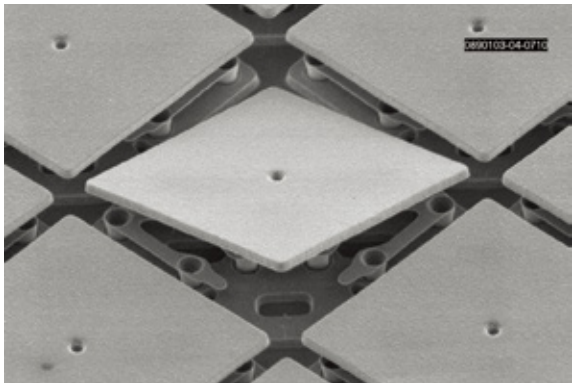
Tomocube's HT technology enable users to quantitatively and noninvasively investigate live biological cells and thin tissues in 3D. HT reconstructs the 3D refractive index (RI) distribution of live cells and provides structural and chemical information about the cell, including dry mass, morphology and dynamics of the cellular membrane. This can be done very easily and quickly, because RI is an intrinsic optical parameter of a material and thus HT does not require any sample preparation.

Holotomography (HT) is optically analogous to X-ray CT

Refractive index (RI) is an intrinsic optical parameter that describes the speed of light passing through a specific material. Light passing through a cell is slower than light passing through the surrounding medium. Analogous to X-ray CT (computed tomography), HT uses a laser beam to measure 3D RI distribution of cells. The system measures multiple 2D holograms of a sample in various illumination angles, from which a 3D RI tomogram is reconstructed via an inverse scattering algorithm. Tomocube presents unprecedentedly precise laser beam control, powered by Texas Instruments™ digital micromirror device (DMD) technology.



Digital Micromirror Device (DMD)



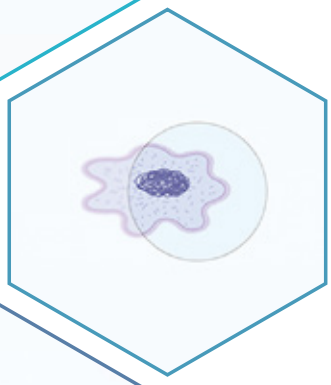
Texas Instruments™

The DMD consists of several hundred thousand micromirrors arranged in a rectangular array. Each individual mirror can be rapidly tilted electronically to create a mirror pattern which can rotate the beam through 360° around the optical axis at a desired angle.

Advantage of HT

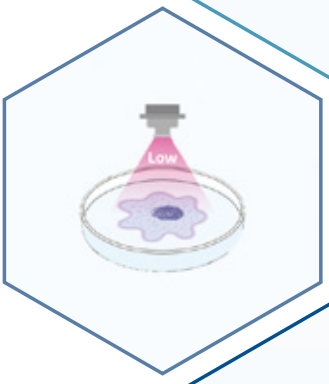
No labeling

RI distributions of cells are utilized as an intrinsic imaging contrast. No labeling, fixation, staining, or transfection is required for high-resolution imaging of cells.



High resolution

Exploiting synthetic aperture effects in tomographic reconstruction, the spatial resolution is 110 nm (lateral) and 356 nm (axial).

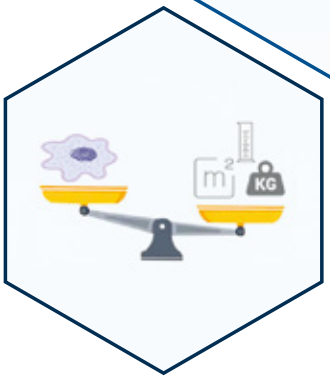


Low phototoxicity

The principle of HT is based on the inverse of light diffraction. Because of negligible light absorption, there is almost no phototoxicity.

Fast imaging

It only takes 0.4 sec to acquire the three-dimensional imaging with the field-of-view of 80 μm x 80 μm x 40 μm.

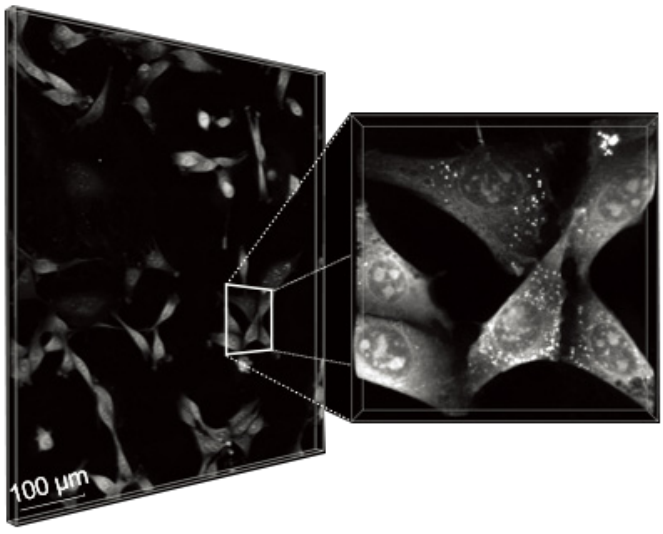


Quantification

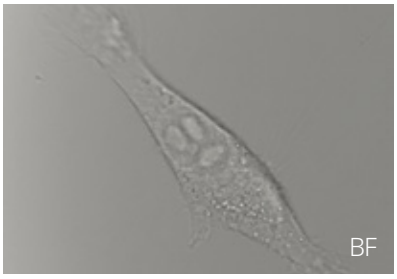
The RI value can be directly translated into the molecular concentration. By multiplying with the measured volume information, dry mass information can also be retrieved.

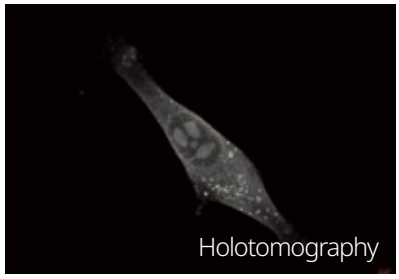
HT-1

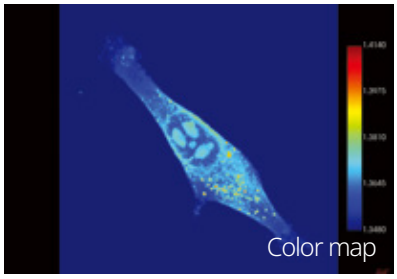
Tomocube's HT series utilizes optical diffraction tomography (ODT) to non-invasively and quantitatively image live biological samples. Using HT technology, researchers can visualize 3D reconstructions of their live samples based on RI distributions and in long-term time-lapse imaging.



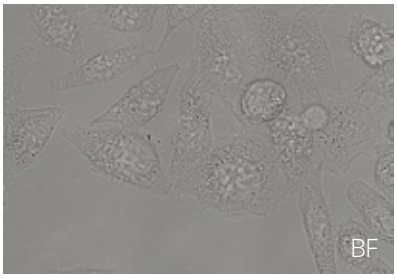
What you can see using HT

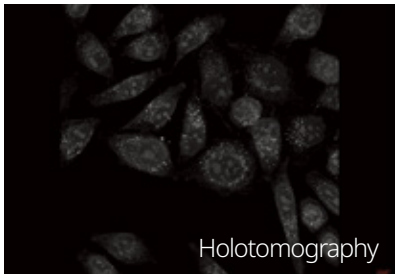


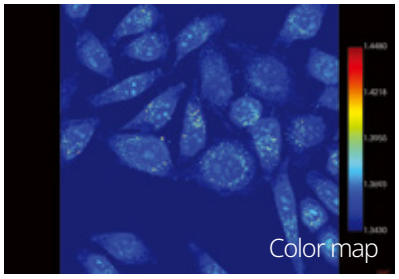




NIH/3T3 (Mouse fibroblast)



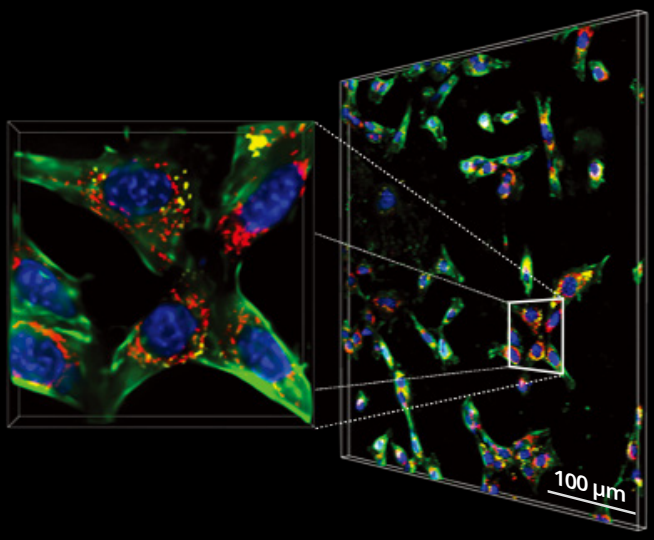




HeLa (Human cervical cancer cells)

HT-2
(HT with 3D Fluorescence)

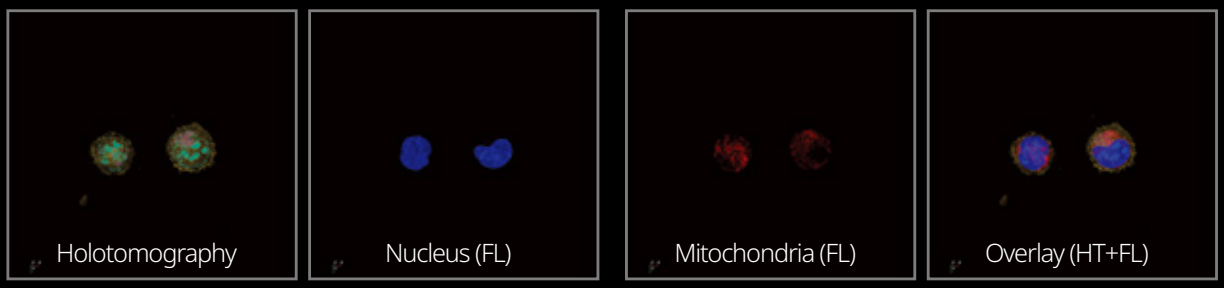
Tomocube's HT-2 offers all the functionality of HT-1, but with the added advantage of correlative 3D fluorescence and embedded deconvolution for confocal like images.



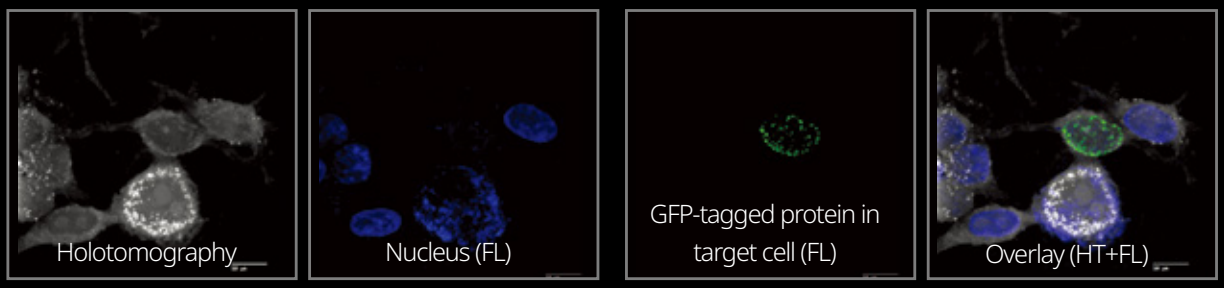
While HT enables quantitative analysis (volume, surface area, mean RI, concentration and dry mass) and label-free visualization of live cell samples, fluorescence microscopy provides the sometimes-essential molecular specificity.

Combining the two technologies together provides the best of both worlds — imaging longer with minimal phototoxicity and photobleaching using HT and intermittent fluorescence.

Correlative images of HT and FL



THP-1 (Human monocyte)



HeLa (Human cervical cancer cells)

TomoStudio | HT series operating software

SET-UP

- Control of fluorescence (up to 3 channels) and HT in various time scales (Hetero time-lapse e.g. 1 FL in every 10 tomograms)
- 'Mark' and 'Find' function for recording the positions of multiple cells

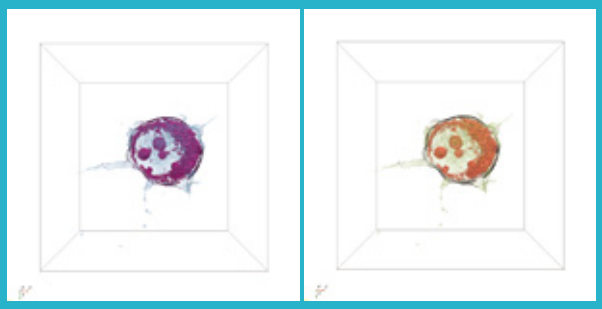
ACQUISITION

- Imaging in multiple modalities including holotomography, phase, brightfield, and fluorescence.
- Multi-point acquisition allows imaging of multiple areas and in timelapse.
- Tile-scanning and stitching function allows imaging of larger areas than the field of view.

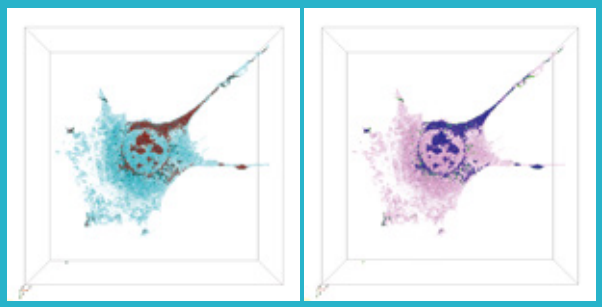
PROCE

- Fast processing o
- Background da parallel with ir process.

3D digital coloring

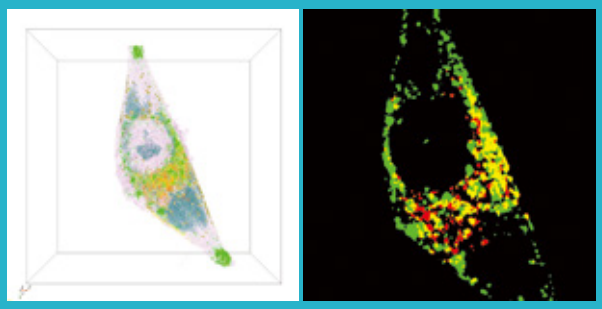


HL-60 (Human leukocyte)

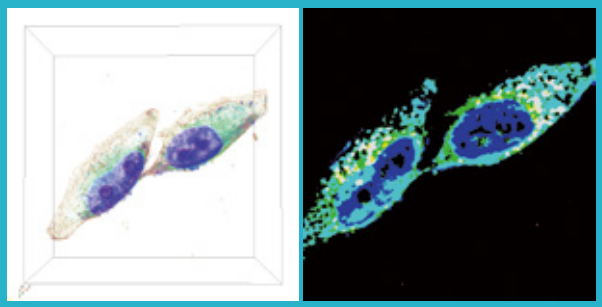


NIH/3T3 (Mouse fibroblast)

Overlay (HT+FL)



HeLa (Human cervical cancer cells)



HeLa (Human cervical cancer cells)

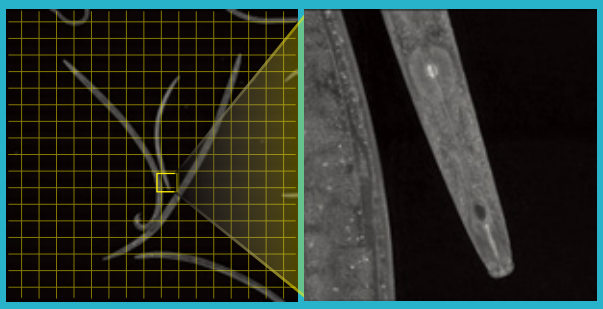
ESSING | VISUALIZATION | QUANTIFICATION

f acquired images.
ata processing in
mage acquisition

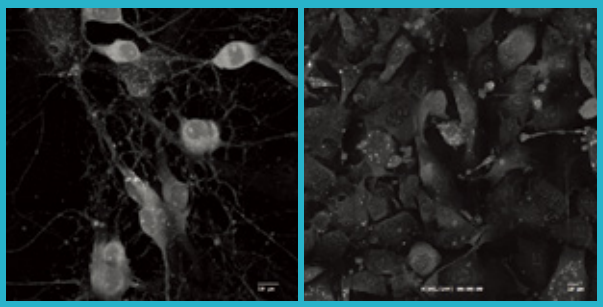
- 3D digital coloring controller (transfer function) GUI stains the sample digitally based on RI distribution.
- Samples can be visualized intuitively in 3D and in 2D maximum intensity projection (MIP), RI heatmaps in multiple color schemes.

- TomoStudio provides quantitative information about morphological and biophysical properties of the sample (volume, surface area, projected area, mean RI, concentration and dry mass).

Stitching (tile-scanning)

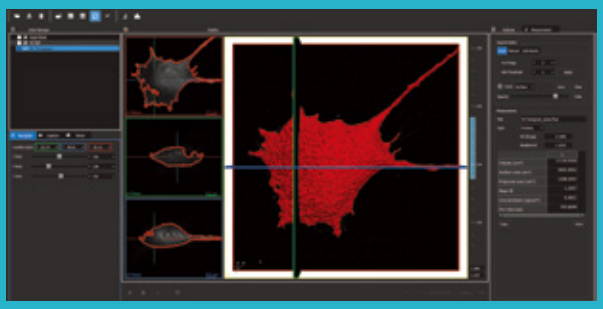


Nematode, 17x17 tile-scanning



Mouse neuron

Analysis

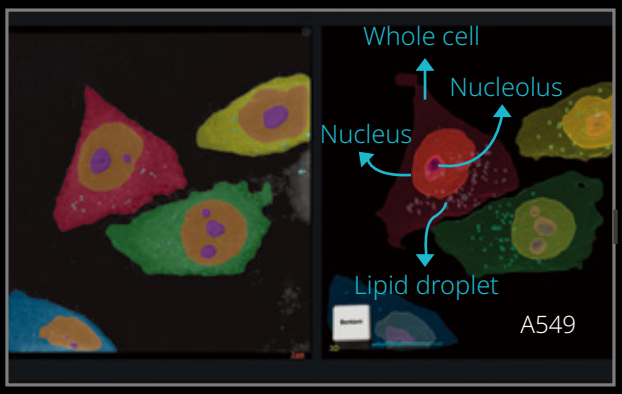


NIH/3T3 (Mouse fibroblast)

Quantitative Data	Result
Volume (μm^3)	11,129
Surface area (μm^2)	5,694
Projected area (μm^2)	1,337
Mean RI	1.35
Concentration ($pg/\mu m^3$)	0.06
Dry mass (pg)	702.65

TomoAnalysis | New insights into single cell analysis

TomoAnalysis functions as a platform for HT data analysis, and various analysis functions will be installed in the future. The TomoAnalysis enables comparative studies between groups and analysis of cells and organelles through several analyzing tools.



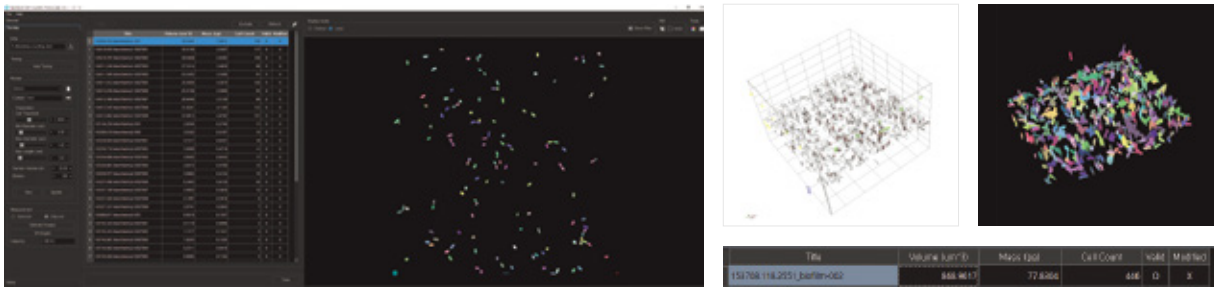
Features

- **AI-enhanced automatic single cell analysis**
  Including cells, nuclei, nucleoli and lipid droplets
- **Quantification of subcellular organelles**
  Including cell volume, surface area, protein concentration, dry mass

Functions

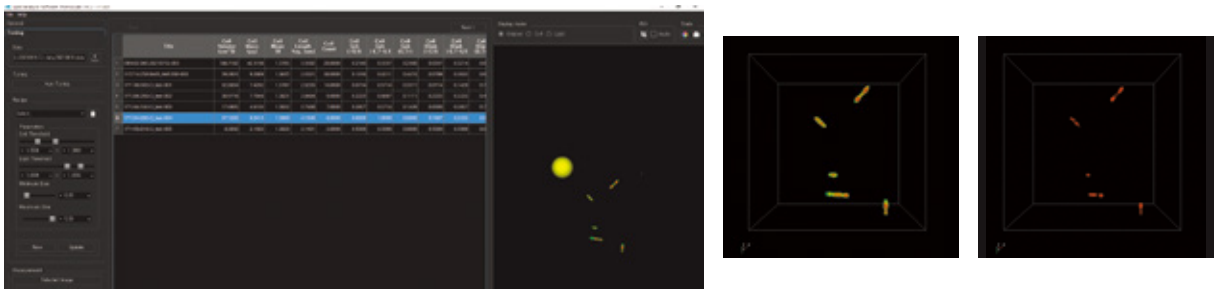
- **Quantitative analysis**
  AI segmentation can separate single cells and their organelles from images and perform quantitative analysis
- **Thumbnail view**
  Compare multiple datasets simultaneously
- **Batch analysis**
  Categorize multiple data into control and experimental group
- **Report Generation**
  Provide quantification results of snapshot data and time-lapse data including tables and graphs

Bacteria Cell Counter



- Program that counts the number of individual bacteria through threshold analysis of RI
- Measurement of the volume, dry mass, and number of all bacteria including spores
- Visualization of recognized objects with different colors

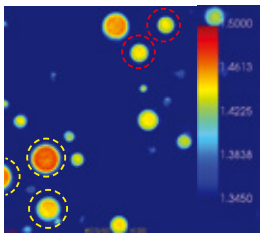
Lipid Analyzer



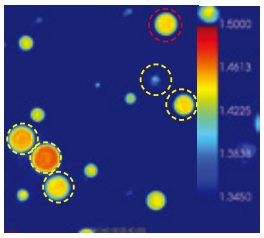
- Program that isolates and recognizes lipids in individual cells, and performs quantitative analysis of recognized cells and lipids
- Measurement of volume, dry mass, and number of lipids within a whole group and individual cells
- ROI (Region Of Interest) 3D area crop function

Liquid-liquid phase separation

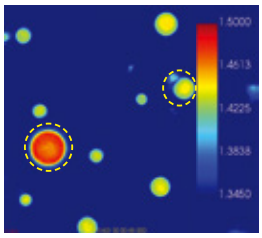
Time-lapse observation of protein condensates



15 s



30 s



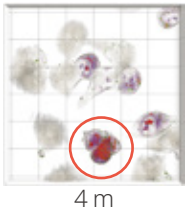
45 s

Hong et al., ***Advanced Optical Materials*** 2100697 (2021)

Cell growth and death

Label-free observation of cell death and differentiation

0 m



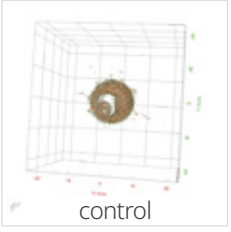
4 m

6 m

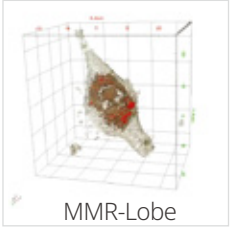
Lee et al., ***eLife 6***, 36815 (2020)

Lipid droplet analysis

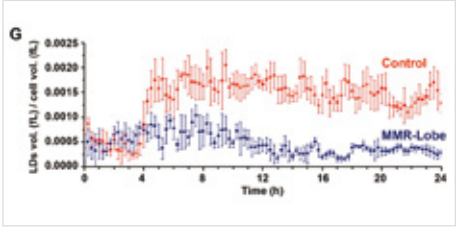
Real-time volume quantification of lipid droplets in foam cells



control



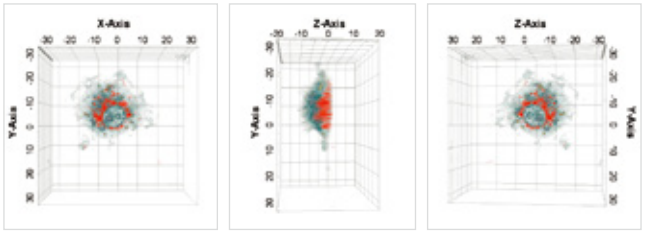
MMR-Lobe



Park et al., ***ACS Nano*** 14(2), 1856-1865 (2020)

Nanomaterial delivery

AuNP(Gold nanoparticle)-loaded mouse macrophage



Kim et al., ***Electronics***. 9(7), 1105, 9071105 (2020)

- Gold nanoparticle
- Nanoplastic
- Nanodiamond
- Nano-biofilament
- Urate crystal
- Structural proteins

Cellular dynamics

Quantitative cell biology

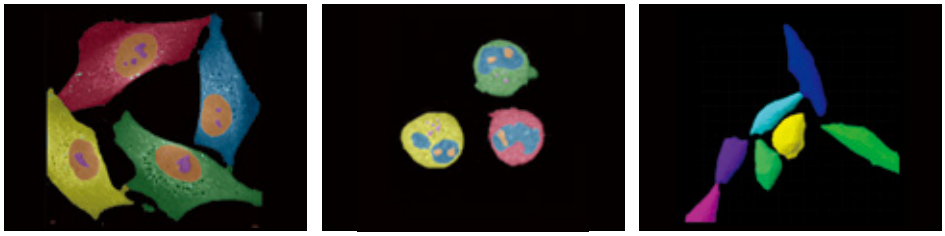
Quantification of subcellular metabolites

Image-based cell classification

Research for new biomarker discovery

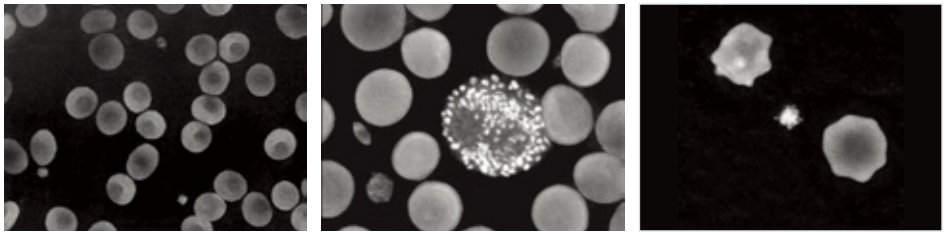
Microbiology

Cell and organelle segmentation



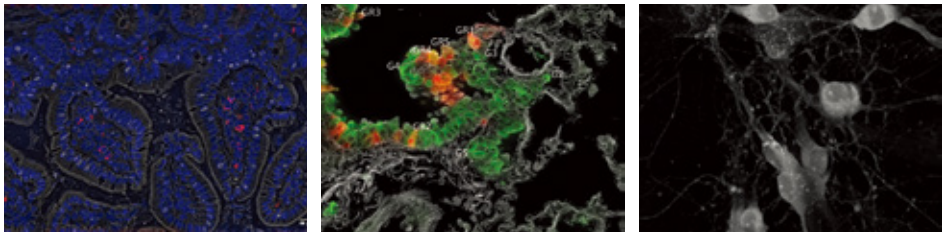
A549 K562 HeLa

Blood cell



Red blood cell White blood cell Platelet

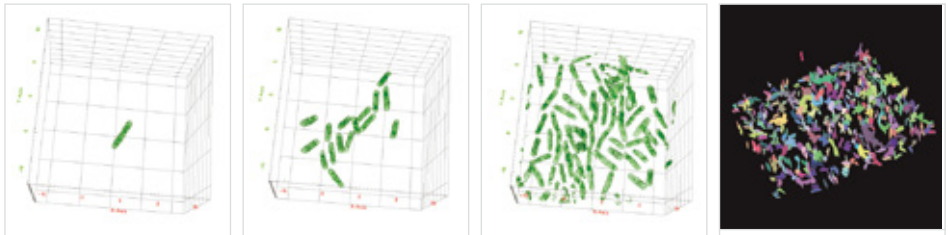
Tissue



Mouse intestine tissue Mouse lung tissue Mouse neuron

Bacterial growth analysis

Bacillus Subtilis growth monitoring and quantification of individual bacteria



0 h 2 h 3 h 40 m Auto segmentation

Oh et al., ***Biomedical Optics Express*** 11(3):1257-1267 (2020)

Selected Publications

nature COMMUNICATIONS

Enhanced succinic acid production by Mannheim employing optimal malate dehydrogenase

DOI 10.1038/s41467-020-15839-z

nature COMMUNICATIONS

PRMT6-mediated H3R2me2a guides Aurora B to chromosome arms for proper chromosome segregation

DOI 10.1038/s41467-020-14511-w

nature COMMUNICATIONS

Large-scale simulation of biomembranes incorporating realistic kinetics into coarse-grained models

DOI 10.1364/OL.41.000934

Science Advances

Self-luminescent photodynamic therapy using breast cancer targeted proteins

DOI 10.1126/sciadv.aba3009

SCIENTIFIC REPORTS

Super-resolution imaging of platelet-activation process and its quantitative analysis

DOI 10.1038/s41598-021-89799-9

ISSCR

A Scalable Suspension Platform for Generating High-Density Cultures of Universal Red Blood Cells from Human Induced Pluripotent Stem Cells

DOI 10.1016/j.stemcr.2020.11.008

NANO LETTERS

Surface Charge-Dependent Cytotoxicity of Plastic Nanopaticles in Alveolar Cells under Cyclic Stretches

DOI 10.1021/acs.nanolett.0c02463

ADVANCED OPTICAL MATERIALS

Label-Free Quantitative Analysis of Coacervates via 3D Phase Imaging

DOI 10.1002/adom.202100697

ACSNANO

Label-Free Tomographic Imaging of Lipid Droplets in Foam Cells for Machine-Learning-Assisted Therapeutic Evaluation of Targeted Nanodrugs

DOI 10.1021/acsnano.9b07993

PNAS

Three-dimensional label-free visualization and quantification of polyhydroxylkanoates in individual bacterial cell in its native state

DOI 10.1073/pnas.2103956118

nature cell biology

TGF-β-induced DACT1 biomolecular condensates repress Wnt signalling to promote bone metastasis

DOI 10.1038/s41556-021-00641-w

nature COMMUNICATIONS

CD45 pre-exclusion from the tips of T cell microvilli prior to antigen recognition

DOI 10.1038/s41467-021-23792-8

01 **HT series**

Microscope body, Fluorescence LEDs for triple channels

02 **TomoStudio and TomoAnalysis**

Operating and analysis software for HT series

03 **TomoChamber**

The incubator chamber for HT series consists of stage top incubator, humidifier, temperature controller and gas mixer (CO_2 and Hypoxia)

04 **TomoPlate**

Active anti-vibration plate for HT series

05 **3D controller**

X/Y/Z axes jog controller

Technical Specifications

Model		HT-1	HT-2
Objective Lens		60x NA 1.2 (water immersion)	
Light source		532 nm diode laser	LED for fluorescence excitation
Resolution (optical/ reconstructed voxel)	Lateral resolution	~ 110 nm / 110 nm	
	Axial resolution	~ 356 nm / 220 nm	
Field of view		80 μm x 80 μm	
Depth of field		Max. 40 μm	
Imaging dimension		2D/3D/4D HT	
Imaging speed		2D HT: 150 frame per second (0.4 sec/ image)	
		3D HT: 2.5 frame per second (0.007 sec/ image)	
Maximum exposure		1 sec	
Sample stage		Fully motorized	
Size (W x D x H, mm)		445 x 180 x 500	
Weight		29 kg / 63 lbs.	
Power requirement		100~240 V, 50/60 Hz, 1.5 A, 100 W	
Laser lifetime		> 10,000 hrs	
Temperature		18°C - 25°C	
Humidity		< 65%, non-condensing	

Tomocube, Inc.

4th Floor, 155, Sinseong-ro,
Yuseong-gu, Daejeon, 34109, Republic of Korea

Tel +82-42-863-1100
info@tomocube.com
www.tomocube.com