MERCK MILLIPORE

The CellASIC® ONIX2 Microfluidic System

Precision control of your cell culture environment for advanced live cell imaging & microscopy

Merck Millipore is a business of MERCK

Leading the way in science and technology

Merck KGaA, Darmstadt, Germany is a leading science and technology company in healthcare, life science and performance materials. Around 50,000 employees work to further develop technologies that improve and enhance life – from biopharmaceutical therapies to treat cancer or multiple sclerosis, cutting-edge systems for scientific research and production, to liquid crystals for smartphones and LCD televisions. Founded in 1668, we are the world's oldest pharmaceutical and chemical company.

Our Life Science team is dedicated to providing scientists and engineers with best-in-class technologies, lab materials and services with the intention of making research and production simpler, faster and more successful.

Our solutions enable scientists to spend more time advancing the promise of science through technologies that help detect the previously undetectable, and products that make it possible to monitor live cells in intricate detail.

Cleanroom for CellASIC® ONIX2 Microfluidic System, Hayward, California, USA.

Quality, reliability and a growing array of publications.

Introducing the CellASIC® ONIX2 Microfluidic System

With a history of success, dedication to innovation and expertise in life science, Merck KGaA, Darmstadt, Germany, is committed to providing the highest quality, most reliable and relevant products for life science research and production.

The CellASIC® ONIX2 System incorporates extraordinary improvements to traditional live cell observation and experimentation, using advanced microfluidics technology with computer automation to manipulate the culture environment under controlled conditions while allowing you to monitor the cells as they react in real-time.

This second generation CellASIC® ONIX2 Microfluidic System is backed by a strong history of distinctive publications, stringent, globally-certified manufacturing and quality processes, and a multinational organization committed to delivering the utmost in local service and support.

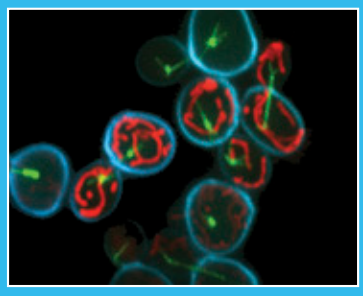
Life is Dynamic

Why study living processes by killing your cells?

Scientists recognize that live cell analysis yields necessary and unique insight into living processes that are rapidly changing. While collecting data from a moment in time with classical endpoint analyses has value, the increasingly common practice of observing and measuring cellular changes over extended periods of time reveals more about the true behavior of biological systems. The challenge has been in creating a dynamic cell culture environment that is controllable, manipulatable, and reproducible.

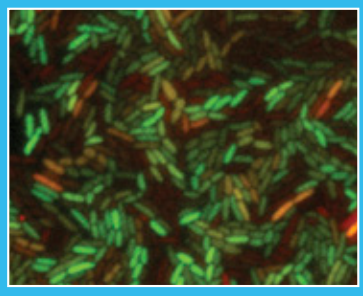
Live cell imaging to transform your research

Move beyond the status quo and gain unprecedented insight into live cells using advanced microfluidics technology. With the CellASIC® ONIX2 Microfluidic System, you too can easily and efficiently create a stable, reproducible environment for imaging. See how it can transform your research.

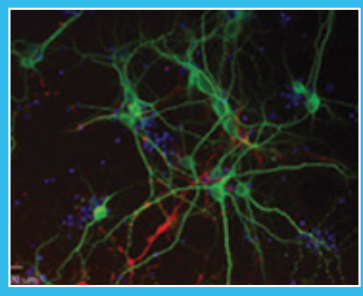


S. cerevisiae yeast cells with labeled mitochondria (red), cell wall (cyan), and tubulin (green), imaged in CellASIC® ONIX yeast haploid plate.

Image credit: Maja Bialecka-Fornal, University of California, Irvine, Rafelski Lab.



Measuring a gene circuit in *E. coli* in a time-lapse experiment with the CellASIC® ONIX B04 bacterial microfluidic plate. Images were acquired at 100x magnification.



Culturing primary rat cortical neurons (GFP) cultured in the CellASIC® ONIX M04S mammalian microfluidic plate.

> “Microfluidic technology is changing the way we perform live cell analysis. The CellASIC ONIX Microfluidic System is **amazingly easy to use yet highly adaptable**, which greatly reduces the barrier to adopting this emerging technology.”
>
> *- Dr. Jintao Liu, Ph.D., UCSD*

The CellASIC® ONIX2 Microfluidic System

Precision control of your cell culture environment for advanced live cell imaging and microscopy.

The ability to grow, observe and manipulate complex cultures requires precision control over the cell culture environment. The second generation CellASIC® ONIX2 Microfluidic System is a refined, yet powerful, automated platform for precise manipulation of multiple key cell culture parameters, enabling measurement of cellular responses to pre-programmed media, temperature, and gas environment changes.

The CellASIC® ONIX2 Microfludic System uses high quality, optically clear microfluidic plates and intuitive software, while integrating with a broad range of inverted microscopes to allow continuous, high magnification observation of live cells—as they react to their environment in time.

1

Controller System: Small footprint, integrated microincubator controller maintains fluid movement, reagent additions, temperature, and gas conditions.

2

Microfluidic Plates: Application specific plates bring new cell culture capabilities for live cell imaging.

3

Manifold: Low-profile, high quality, high optical clarity culture chambers and manifold, mount easily on an inverted microscope—without the need for a bulky environmental chamber.

4

Software: Intuitive software enables quick and easy set-up of detailed protocols for truly automated hands-free cell culture.

Nikon
139-Eclipse
Ti-E System.
Image Courtesy
of Nikon, Inc.

The boost your microscope needs for advanced live cell imaging.

The CellASIC® ONIX2 System turns your microscope into a powerful live cell culture and imaging system that works in conjunction with your capture and analysis software.

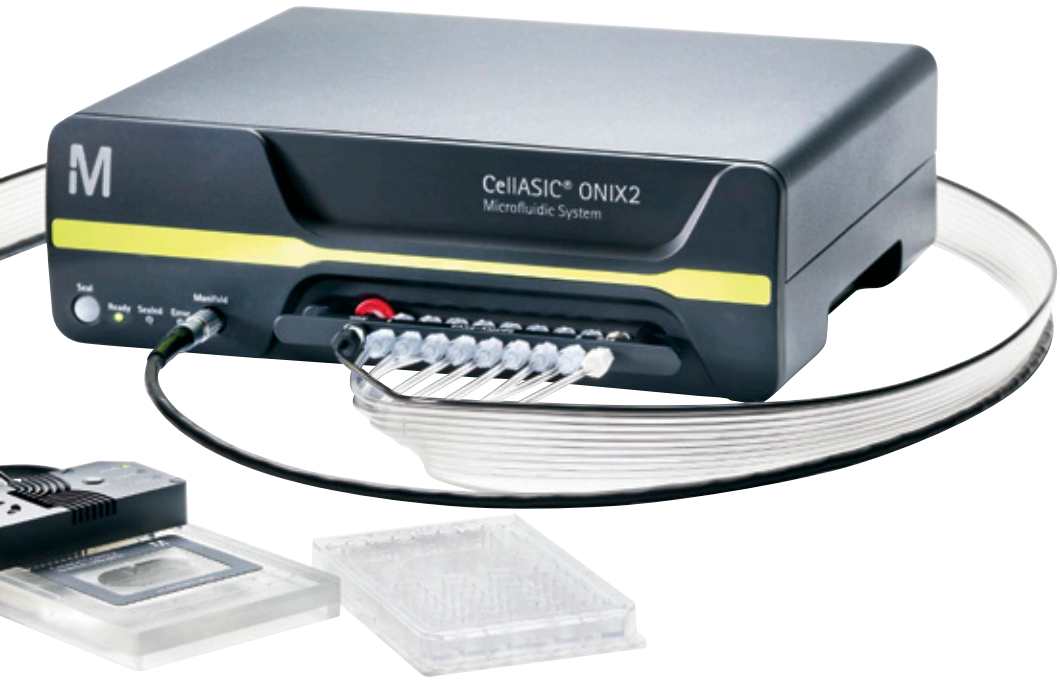
You've invested in a powerful microscope; don't limit its use to observing live cells in a static fashion. Enhance your return on investment and obtain more meaningful data using the CellASIC® ONIX2 Microfluidic System as your live cell imaging platform. The low-profile manifold and plate assembly are easily positioned and removed from the microscope stage providing maximum ease of use and flexibility.

> "... the key advantage of live cell imaging is that you get to actually watch things unfold before your eyes. It's very powerful to see, visually what the cells are doing and how they change in space and as a function of time, because biology is a dynamic process...**and watching the cells do what they do is something that really appeals to us and is driving our science.**"
>
> *- Dr. Gurol Suel, UCSD*

There is simply no better way to conduct live cell analysis.

Watch cells change through time and space, all with the precision of the CellASIC® ONIX2 System. Automatically control flow rates, gas and temperature shifts, standing gradients, nutrient/drug additions, and media changes. With uninterrupted high resolution microscopic culture observation and truly consistent, controlled cell culture, you'll answer the questions that set your research apart.

1 Small footprint, integrated microincubator controller maintains fluid movement, reagent additions, temperature, and gas mixture.



Eight critical cell culture parameters can be controlled by the CellASIC® ONIX2 Microfluidic System:

Parameter	If too low, can cause:	If too high, can cause:
Temperature	Decreased cell response	Increased respiration / protein damage
Oxygen Level	Decreased pH / increased glycolysis	Increased ROS, membrane damage
Growth Factors	Increased apoptosis / decreased protein synthesis	Increased angiogenesis and cell division
Humidity	Increased osmolarity / cell metabolism / oxidative stress	Could damage imaging equipment
pH	Protein and membrane denaturation	Increased alkalosis and dehydration
Osmolality	Decreased cell division / increased autophagic proteolysis and cell rupture	Increased oxidative stress, DNA breakage, and nutrient digestion
Glucose	Decreased autophagy and metabolism	Increased apoptosis and ROS
ECM and Adhesion	Decreased angiogenesis / aberrant differentiation	Increased cell adhesion, chemotaxis, proliferation

Application-specific microfluidic plates for optimized, bio-inspired cell culture.

2

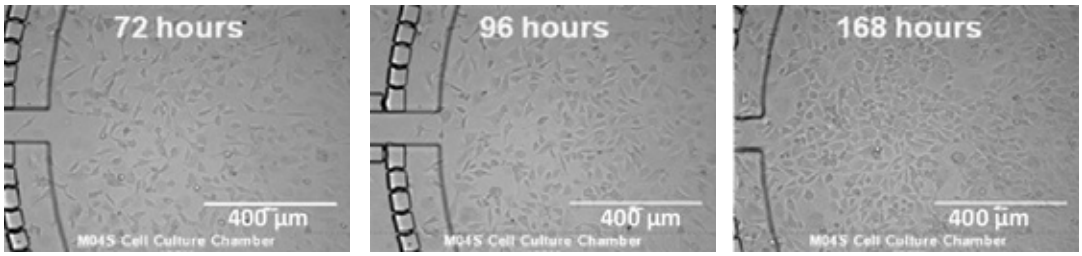
Application-specific plates bring new cell culture capabilities for live cell imaging.

The key to microenvironment control using the CellASIC® ONIX2 System is in coupling precision manufactured microfluidic cell culture plates with an automated perfusion system to provide a controlled environment optimized for high resolution live cell imaging.

Optimized, bioinspired cell culture

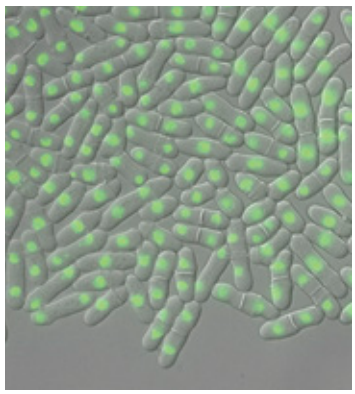
Different cells need different environments. CellASIC® ONIX Microfluidic Plates are designed to optimize cell health during dynamic live cell experiments. Various application specific plate designs give you the flexibility to probe the questions that interest you most.

Healthy long-term cultures outside the incubator.
NIH 3T3 cells were cultured in the CellASIC® ONIX Microfluidic System (M04S plate) with continuous perfusion and monitored using bright field microscopy for 168 hours.



Key advantages of the CellASIC® ONIX2 microfluidic plates:

- Rapid perturbations of environmental parameters due to the tiny microfluidic volumes involved
- Perfusion microbarriers allow continuous reagent transport without shearing stress
- High resolution imaging through optical glass bottom and chamber structures that keep cells in a single focal plane
- Ability to run multiple independent experiments simultaneously
- Continuous access of nutrients and ongoing removal of waste, promoting optimal cell health.



Fission yeast, cultured and imaged in the CellASIC® Y04D microfluidic plate.
Image courtesy of Prof. Hironori Niki, National Institute of Genetics, Japan.

Merck Millipore's strength in engineering and quality systems are ideally suited to meet the challenges for consistent and scalable microfluidic plate manufacturing:

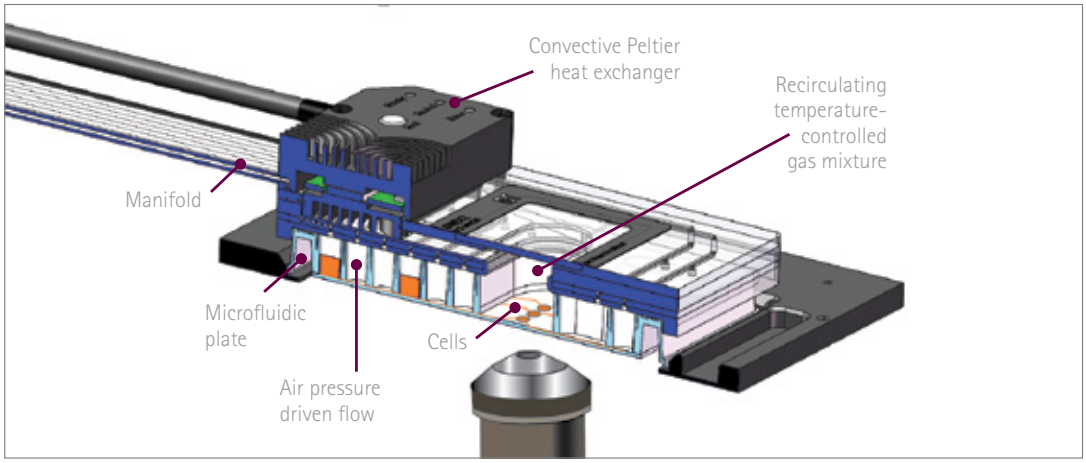
- Patented microfluidic manufacturing method
- Multi-layer molding capability from 0.5-150 microns
- Commitment to continuous improvement of product quality

Low-profile manifold replaces bulky environmental chambers.

The key to high-resolution, long-term cell imaging is being able to control the culture environment without impeding optical access to the cells. This is complicated by the proximity of microscope elements (objective lens, condenser, stage), and the need for an unobstructed light path through the sample without hindering stage or objective movement. The miniaturization provided by the CellASIC® ONIX2 Microfluidic System is not only valuable for easily controlling temperature and fluids but also maintains a small footprint for use directly on the microscope stage for optimal clarity and ease of use.

3

Low profile, high quality, high optical clarity culture chambers and manifold, mount easily on an inverted microscope—without the need for a bulky environmental chamber.



A low-profile manifold connects the control system with the microfluidic plates. Various manifold layouts are available to address different plate formats and application types.

Manifold Advantages:

- Manifold seals to the microfluidic plate via "one-touch" vacuum mechanism.
- Pressure-driven flow of liquids to the cell chamber provides high precision even at very small volumes.
- No contact between the flow system and the biological solutions (on the plate) prevents contamination.
- Low-profile manifold is easy to adapt to any inverted microscope stage.

> "What the CellASIC® system lets us do is very rapidly turn on and off conditions or insults while following single cells."
>
> *- Dr. Ethan Garner, Harvard University*

Intuitive software adds the power of automation to your experiment.

4

Intuitive software enables quick and easy set-up of detailed protocols for truly automated hands-free cell culture.

Set your parameters, time your changes and the system does the rest. Simple and straightforward, the intuitive interface makes it possible for experts or novice users to get started quickly and easily, while ensuring consistency throughout the experiment.

In addition, the software offers:

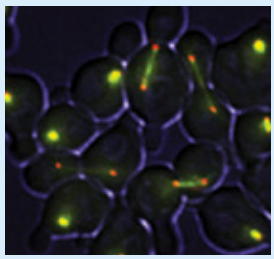
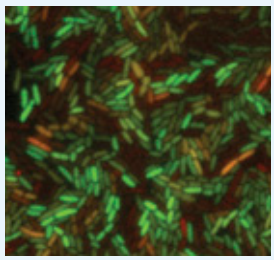
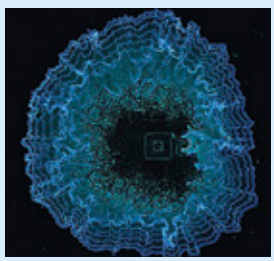
- Clearly defined protocols with all experimental parameters saved in one file
- Convenience and reproducibility - to repeat an experiment, just put in a new plate, and click 'run'.
- Consistency and reliability - Better portability and control of software protocols means more consistent experimentation.
- Error checking, self test, and data logging all make for better troubleshooting and serviceability.
- The ability to use together with your microscopy software - synchronize imaging with cell experiment control, and connect your experiment data with your image data.

> "...We've been able to quickly and **easily perform novel and technologically demanding experiments without any prior microfluidic experience.** I've been able to focus on the fundamental biological questions while letting CellASIC® provide me with the tools I need to answer them."
>
> *- Maheshri Lab, MIT*

Discover new insights to dynamic cellular processes.

The CellASIC® ONIX2 Microfluidic System provides detailed information about live cell processes with ultra-high quality images and complete environment control.

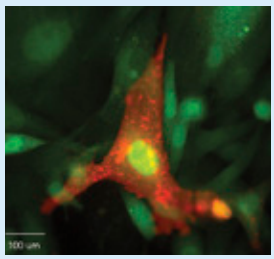
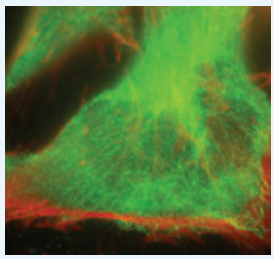
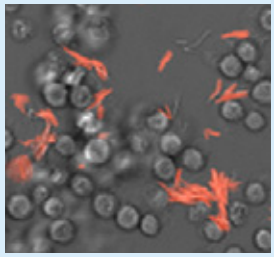
Dynamic assays on adherent and non-adherent cells

CellASIC® ONIX2 Advantage:	Application		
High resolution imaging in single focal plane with controlled nutrient flow for tracking single cells over time	Yeast single cell response		*S. cerevisiae* cells expressing GFP-tubulin and SPC42-mCherry during alpha-factor exposure and arrest. Images were acquired at 60x magnification. Courtesy of S. Lacefield, U. Indiana
Measure multi-generational responses to live bacteria while maintaining cells in a single focal plane for days	Bacterial single cell response		A gene circuit in *E. coli* was induced and visualized for a time-lapse experiment in the CellASIC® ONIX B04 microfluidic plate. Images were acquired at 100x magnification.
Continuous monitoring of community dynamics and precise control of growth environment	Bacterial biofilm dynamics		Time lapse, composite image of bacterial biofilm growth. Courtesy of the Suel lab, UCSD.

The CellASIC® ONIX2 Microfluidic System works with your inverted microscope to enable long-term cell perfusion experiments and dynamic time-lapse analysis. (Shown with Lionheart™ FX automated Live Cell Imager from BioTek® Instruments)

Control cell culture conditions to induce and observe reactions in real-time.

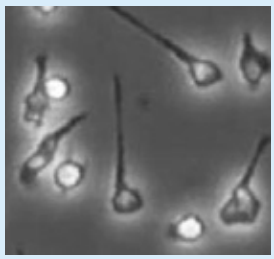
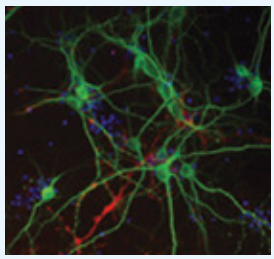
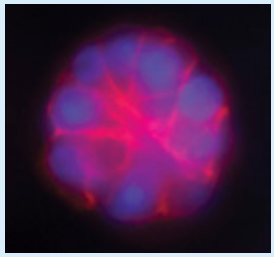
Rapid gas and media switching capabilities

CellASIC® ONIX2 Advantage:	Application		
Fast and precise control over culture conditions to induce hypoxic, starvation, or toxic microenvironments	Cell response to hypoxic environments		LAMP1-RFP/ LC3-GFP CHO reporter cells cultured on the CellASIC® ONIX system showing autophagosomes (green) and lysosomes (red) during a hypoxia-induced autophagy assay over 24 hours.
Microfluidic control of nutrient additions during continuous observation	Cell response to changing media conditions, drugs, and other stimulants		Long-term live cell microscopy of cellular cytoskeletal changes in HeLa cells with precise microenvironment control. Cells were stained for tubuliin (green) and actin (red) using "in-plate" immunostaining with multi-solution, automated washing and exposure programs,in the CellASIC® ONIX M04S Microfluidic Plate. Image was acquired at 100X magnification.
High resolution imaging of dynamic cellular interactions	Host-pathogen interactions		Host-pathogen assay monitoring of M. tuberculosis-RFPinfection in macrophages

> "Since I aim to quantify mitochondrial morphology, I require constant, stable imaging conditions that maintain the health of the cells, which the CellASIC® ONIX System does very well."
>
> *- Marshall Lab, UCSF*

Enhance live cell imaging with stable, optimized culture conditions.

Maintenance of constant environment for optimal cell culture

CellASIC® ONIX2 Advantage:	Application		
Microfluidic control creates stable standing chemical gradients	Chemotaxis/migration in response to chemogradient		Chemotaxis/migration in response to chemogradient HL-60 neutrophil migration in response to a chemokine. This frame from a live cell analysis video shows cells concentrating toward the chemokine in one chamber of a CellASIC® ONIX M04G Microfluidic Gradient Plate. Courtesy of Jason Park, Wendell Lim Lab, UCSF.
Microfluidics and computer control allow quick adjustments to microenvironment parameters and media changes, all while recording cell behavior	Setting optimal culture parameters for difficult cell types or long term experiments		Primary rat cortical neurons cultured in the CellASIC® ONIX M04S Microfluidic Plate to Day 15 and immunostained in-plate for MAP2 (Green GFP, neurons) and GFAP (Red RFP, astrocytes; 40X).
Control and perfusion dynamics create more *in vivo*-like environment for complex cultures	Microscopy of 3D cell culture		Observation of multi-day morphology changes of 3D cancer spheroids cultured in extracellular matrix. MCF-10A breast cancer cells were suspended in Matrigel® substrate and grown in the CellASIC® ONIX M04S Microfluidic Plate. Cells were stained for actin (red) and nuclei (blue). Image was acquired at 40X magnification.

A Growing Array of Distinguished Publications

The CellASIC® ONIX2 Microfluidic System is the next generation of a well- established and highly published technology. Here is a sampling of recent publications.

Find more by visiting our website at: **www.merckmillipore.com/cellasic-publications**

Yeast

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Peroza EA, Ewald JC, Parakkal G, Skotheim JM, Zamboni N; A genetically encoded FRET sensor for monitoring in vivo trehalose-6-phosphate dynamics; Analytical Biochemistry 2015, Apr 1; 474:1-7. doi:10.1016/j. ab.2014.12.019
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Kabeche R, Madrid M, Cansado J, Moseley JB. Eisosomes Regulate Phosphatidylinositol 4,5-Bisphosphate (PI(4,5)P2) Cortical Clusters and Mitogen-activated Protein (MAP) Kinase Signaling upon Osmotic Stress. J. Biol. Chem., Oct 2015; 290: 25960 - 25973.
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A Growing Array of Distinguished Publications

Bacteria

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Mammalian

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Technical Specifications

General	
Dimensions	System: 330 mm wide × 306 mm deep × 108 mm high (13 in. × 12 in. × 4.25 in.)
Weight	System: 6.7 kg (14.75 lb)
Power consumption	100–240 VAC, 50/60 Hz 40 W
Cooling mode	Air cooled (natural convection)
Environmental conditions	For indoor laboratory use
Operating temperature	20 °C to 30 °C
Storage temperature	5 °C to 35 °C
Stability of sample chamber temperature	± 0.2 °C
Rise time (25 °C to 37 °C)	< 30 minutes
Cooling time (37 °C to 25 °C)	< 30 minutes
Flow Control	
Number of outputs	8 (each addressable by either of two pressure controllers)
Pressure range	-50 to 70 kPa (-7.25–10.2 psi)
Pressure accuracy	± 1.5 kPa (0.22 psi)
Pressure stabilization time	within ± 5 kPa (0.73 psi) in < 5 seconds
Gas Environment Control	
Control capabilities	Option to electronically select between two premixed gasses and set flow rate to slow or fast.
Gas input requirements	Clean, dry, premixed gas mixtures containing air, CO2, N2, and oxygen (up to 25%), regulated to between 100 kPa and 700 kPa (15 psi and 100 psi)
Gas consumption	Slow flow: 5 mL/min ± 2 mL/min
	Fast flow: 50 mL/min ± 20 mL/min
Cell culture region gas environment accuracy	For gas flow at 3 mL/min: < 10% deviation from delivered gas concentration
	For gas flow at 30 mL/min: < 2% deviation from delivered gas concentration
Temperature Control	
Temperature control range	Room temperature to 40 °C
Control method	Bi-directional PID
Accuracy of sample chamber temperature	± 1 °C (using the CAX2-ACT20 ONIX2 Temperature Calibration Plate can result in accuracy as high as ± 0.2 °C)
Computer Requirements	
Operating system	Windows® 7, or Windows® 10 (32 or 64 bit)
Random access memory (RAM)	4 GB or higher
Monitor	1920x1080 resolution or higher
Hard drive	200 MB or higher
Hardware interface	USB 2.0 or higher
Microscope Requirements	
Type	Inverted microscope
Stage weight capacity	For CAX2-MXT20 CellASIC® ONIX2 Manifold XT and filled plate: 325 g (11.1 oz)
	For CAX2-MBC20 CellASIC® ONIX2 Manifold Basic and filled plate: 150 g (5.3 oz)
Minimum condenser working distance	For CAX2-MXT20 CellASIC® ONIX2 Manifold XT: 28 mm (0.9 in)
	For CAX2-MBC20 CellASIC® ONIX2 Manifold Basic: 28 mm (0.9 in)
Maximum condenser diameter	For CAX2-MXT20 CellASIC® ONIX2 Manifold XT: 70 mm (2.8 in)
	For CAX2-MBC20 CellASIC® ONIX2 Manifold Basic: no limit

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