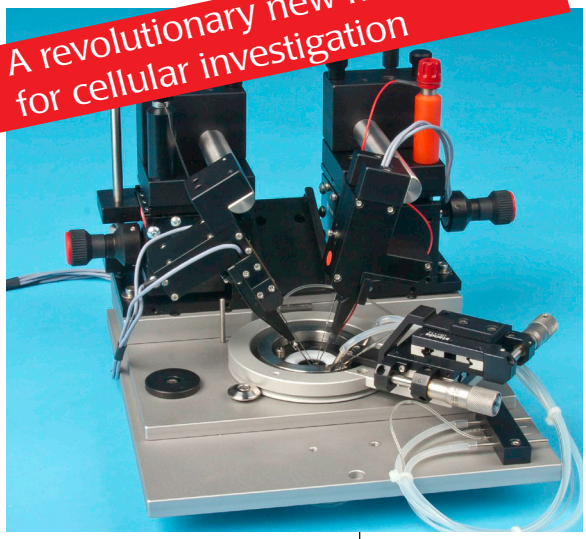
SI-CTS100A/B/C

Characterize and investigate functional physiological properties of single living cells



Overview

The **Cell Tester** is the product of three years of design and field testing. It represents a blending of state-of-the-art technologies, including electronics, mechanics and optics. The end result is a revolutionary new research tool for cellular investigation.

All living systems can be studied from several perspectives. We can examine the entire organism or a specific organ system. We can characterize a single organ in a system or a type of tissue in an organ or the cells that make up that tissue. To completely understand any system, all of these perspectives must be considered. Often, entirely different systems are needed in a parallel experimental paradigm. The **Cell Tester** accomplishes this on one platform.

The **Cell Tester** can, without any changes, be used for one single living cell, for a small multi-cellular preparation and for single or larger skinned muscle strip preparations. Translational experiments from the single living cells to the intact multi-cellular level can be accomplished. For example, using the **Cell Tester**, the influence of the connective tissue on muscle function can be distinguished from the clean muscle work for the first time. Conversely, skinning allows a direct comparison between the living cell response and a cell, whereby the subcellular contractile proteins are studied with full experimental access to cell signalling and cellular biochemistry.

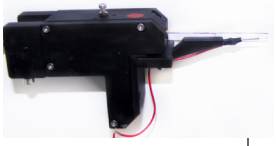
The **Cell Tester** provides researchers with the comprehensive ability to investigate and characterize the physiological, bio-mechanical and bio-physical properties of single isolated living cells and extend these findings to the sub- and multi-cellular level.

- Integral microtweezer apparatus facilitates cellular attachment
- Bio-compatible adhesive included
- Unique rotational stage–easy cellular alignment, improved experimental throughput
- Ultra-quiet force transducer included
- Linear displacement motor stretches or compresses cells with 25nm precision

System Organization

The **Cell Tester** is designed to sit on top of the stage of a standard inverted research microscope. The optical path of the microscope is left intact for simultaneous fluorescence or confocal imaging.

Nanomotor



The heart of the system is a tuned and paired combination of a linear actuator offering nanometer (nm) precision and a force transducer with nano Newton nN) sensitivity. Each element (actuator and sensor) is equipped with a remote controlled micro grabber that allows tissues to be held firmly. In addition, a critically important, non-cytotoxic adhesive (MyoTAK) facilitates the bonding of tissue to the measuring device where needed.

Force Transducer

KG-series force transducers measure a large range of detectable forces. The transducer with the highest sensitivity (20nN) is sufficient to measure the force of a single heart cell. Because all transducers are extraordinarily rugged, withstanding even overload forces, they come with a lifetime warranty on the optical transducer heads.

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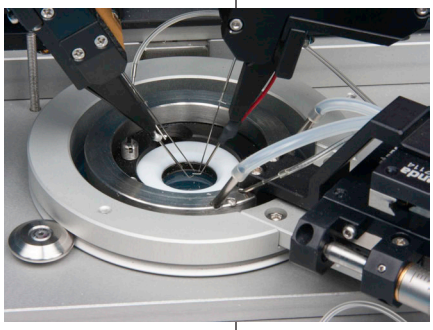
Rotating Cuvette



The complete system utilizes a unique rotating bath to dramatically improve experimental throughput. The rotating bath is designed to orient cells in the XY plane so that no physical manipulation of the position of the cell itself is required prior to capture by the grabbing devices attached to the force sensor and linear actuator.

Electronics

WPI's **Signal Conditioning Amplifier System** is a customizable electronic platform. It consists of an 8-channel, rack-mountable frame with an ultra quiet, shielded power supply. For the **Cell Tester**, it includes the Nanomotor controller, the **SI-BAM21LCB** amplifier and the **SI-AOSU** anti-oscillation unit.

The **SI-BAM21-LCB** KG Optical Force Transducer Amplifier powers the force transducer and outputs an analog voltage proportional to the force applied to the force transducer. The force feedback signal can be multiplied by a factor of 1, 2, 5 or 10 to provide better resolution for a minimal change in applied force.

The anti-oscillation option eliminates the native resonance frequency of the transducer and mounting support for unparalleled low noise recording and fidelity.

Data Acquisition

The data from the **Cell Tester** can be recorded by any generic data acquisition system.

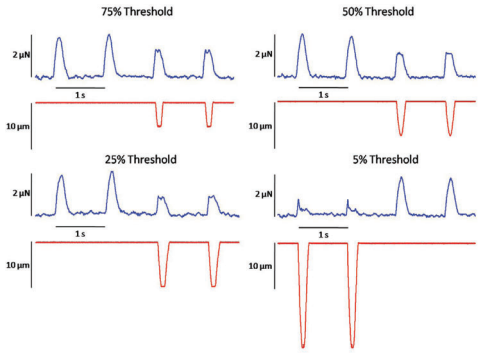
Research

Classic Cross-Bridge Cycling Studies

Afterloaded Contractions in Single Cardiac Muscle Cells - Part I

Above–A single FDB skeletal muscle cell is held by two microtweezers in the **Cell Tester** *unit.*

To understand the capabilities of the **Cell Tester**, consider this experiment that looks at the work loop in a cell.



A cell was allowed to develop force after an electrical field stimulation. At 5%, 25%, 50% or 75% of maximal developed force (taken from the average of the previous 10 isometric twitches), the cell is actively shortened by the system so that force is held constant. At the moment the force transient would again reach that force level while relaxing, the actuator re-lengthens the cell to complete the transient. This simulates, at the cellular muscle level, the contraction of the ventricle, ejection phase, and finally, refilling and relaxation of the left ventricle at different levels of afterload. Plotting and analysis of length versus force allows analysis of work under the different levels of simulated afterload.

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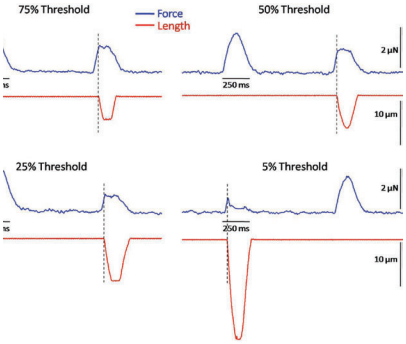
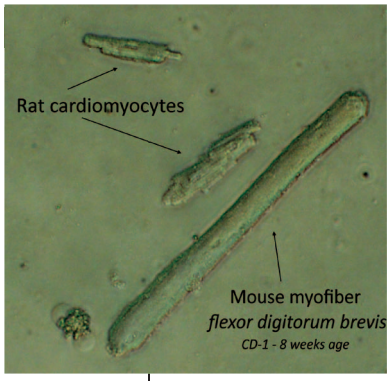
Afterloaded Contractions in Single Cardiac Muscle Cells - Part II

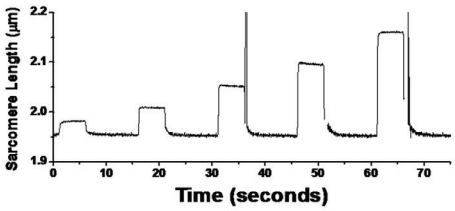


This experiment demonstrates the speed with which the **Cell Tester** can work. Two isometric contractions (twitches) are immediately followed by afterloaded contractions at different levels (5%, 25%, 50% and 75%). In a largely unattended, automated manner or under twitch by twitch control, different protocols can be executed according to the experimenters' requirements.



Above–Cells used in the preliminary experiments include single rat cardiac myocytes next to a single mouse muscle cell from the FDB skeletal muscle.

Precise Stretching of Single Skeletal Muscle Cells to Preset Sarcomere Lengths



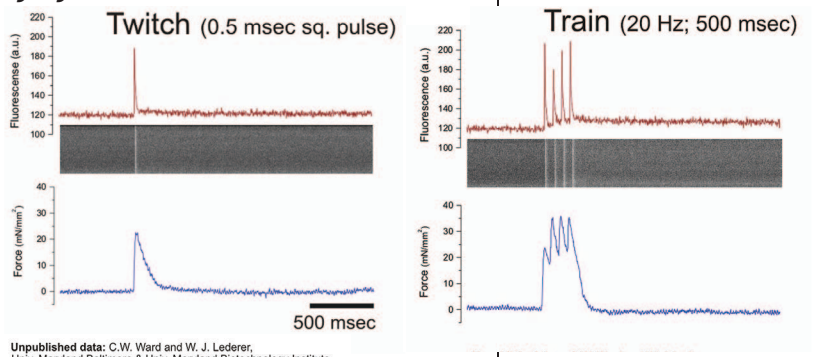
Sarcomere length can be set by discrete steps of the actuator with 20nm precision.

Something Very Different

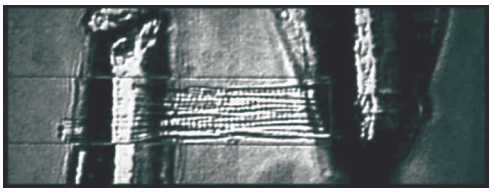
Axial Stretch of Rat Single Ventricular Cardiomyocytes Causes an Acute and Transient Increase in Ca2+Spark Rate

When examining single cell mechanisms, results were surprising. When a rat cardiomyocyte was stretched acutely and transiently, the sarcoplasmic reticulum Ca^{2+} spark rate increased by means of a mechanism independent of sarcolemmal stretch-activated ion channels, nitric oxide synthesis, or availability of extracellular calcium. These data suggest another mechanism for the release of calcium in cardiomyocytes.

Gentaro Iribe, Christopher W. Ward, Patrizia Camelliti, Christian Bollensdorff, Fleur Mason, Rebecca A.B. Burton, Alan Garny, Mary K. Morphew, Andreas Hoenger, W. Jonathan Lederer, Peter Kohl "Axial Stretch of Rat Single Ventricular Cardiomyocytes Causes an Acute and Transient Increase in Ca^{2+}Spark Rate" *Circulation Research (circres.ahajournals.org)*. 2009: 104;787-795.



Unpublished data: C.W. Ward and W. J. Lederer, Univ. Maryland Baltimore & Univ. Maryland Biotechnology Institute



Left–A single rat cardiac myocyte is held by MyoTAK coated glass rods on the Cell Tester.

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SYSTEM CONFIGURATIONS

SI-CTS100A

System includes: Nanomotor with microtweezer, SI-KG Force transducer with microtweezer, Signal Conditioning Amplifier System with SI-BAM21LCB, SI-AOSU, Nanomotor position controller (piezo motor driver).

SI-CTS100B

System includes: SI-CTS100A components plus base unit with rotating cuvette, two manual micromanipulators.

SI-CTS100C

System includes: SI-CTS100A components plus base unit with rotating cuvette, two remote control stepper motors. Available mid-year 2011.

CELL TESTER SPECIFICATIONS

Base Dimensions ..... 8.25x9" (21x23cm)

Nanomotor

Total Travel ..... ±90µm
Resolution 20nm
Smallest Step 60nm
Input ..... ±10V (calibrated at 10µm/V)

SI-KG7TWE Force Transducer

Range 0–5mN (0–0.5g)
Noise ..... 20nN at 10X gain
Compliance 10µm/mN
Resonance Frequency 250Hz
(This is eliminated from the measurement by the AOSU)

SI-BAM21LCB Optical Force Transducer Amplifier

Input Configuration ..... Current to voltage converter
Gain ..... 1X, 2X, 5X, 10X - Switch selectable*
Offset (with a 1X gain) 10mV
Output Impedance 470Ω
Power Requirements ..... 12V DC at 3A (wall adaptor included)
Output Range ..... ±10V DC
*An optional factory setting increases the multiplier by a factor of 10, allowing to signal to be multiplied by 10, 20, 50 and 100.

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