The multi-channel cell force analyser CFA_{ref} for quantifying bi-axially, drug induced forces in cell monolayers and co-cultures

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INTRODUCTION

The routine analysis of intrinsic and drug-induced tensile forces in cultured cell layers based on CellDrum™ technology is a promising tool for reliable toxicological biomechanical studies. Adherent cell cultures can be measured over a long time in a sterile, heated environment. Both low and high velocity contraction cultures are measurable and allow absolute value comparisons.

APPLICATION AND RESULTS

"Static" measurements of tensile stress in cell monolayers

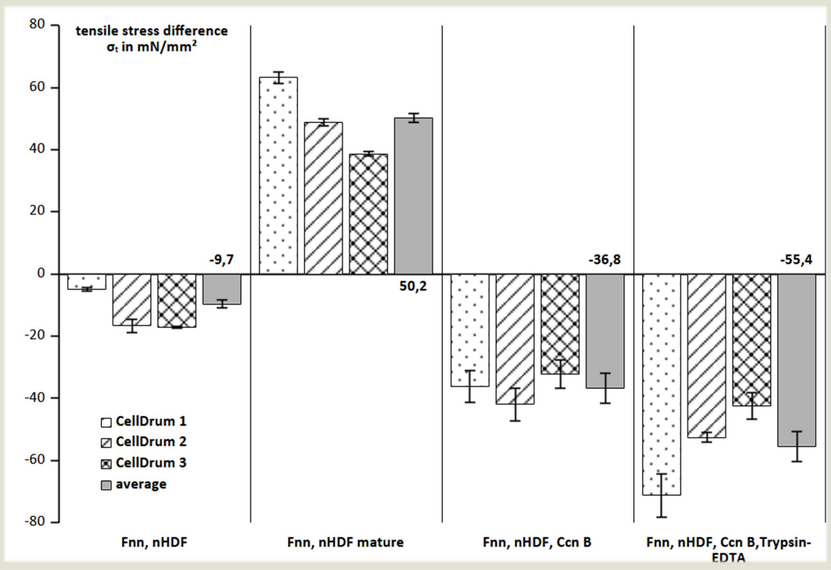
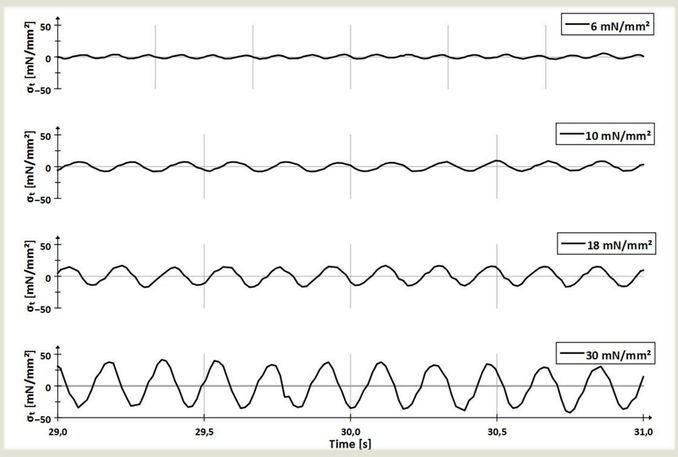


Figure 1:
Tensile stress (mN/mm²) of N=3 CellDrum™ units seeded with **fibroblast monolayers**.
Fnn: Fibronectin coating
nHDF: normal human dermal fibroblasts
Ccn B: Cytochalasin B (10 µg/ml)



"Dynamic" measurements of self beating cells

Figure 2:
Tensile stress time course of **murine cardiomyocyte** and **fibroblast co-culture** on a **CellDrum™**; This experiment aimed to demonstrate the **Frank-Starling effect** by subjecting the same heart muscle cell layer to **stepwise increased preload**. A **rising amplitude** with increased preload is congruent with FS-effect theory and an impressive proof of viability for the presented **in-vitro heart model**.

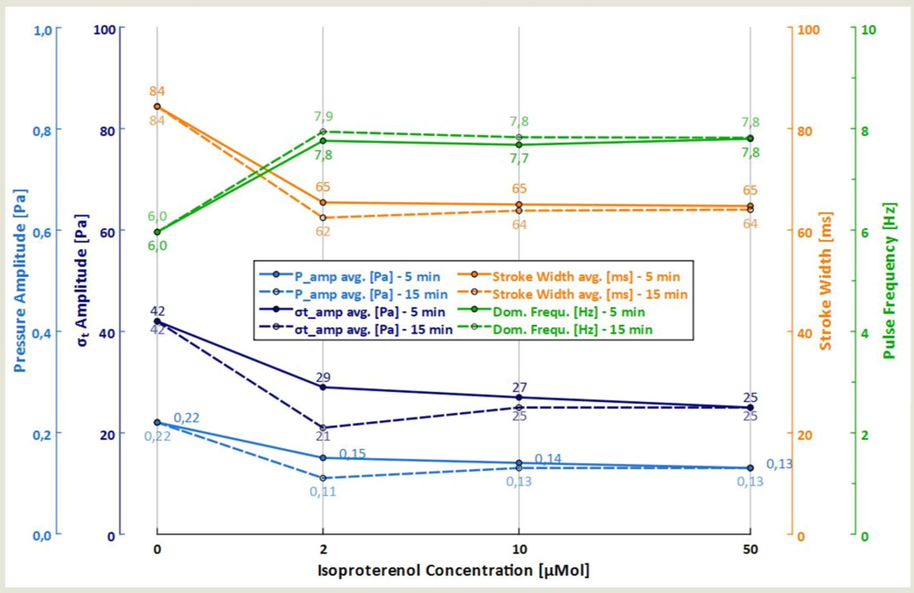
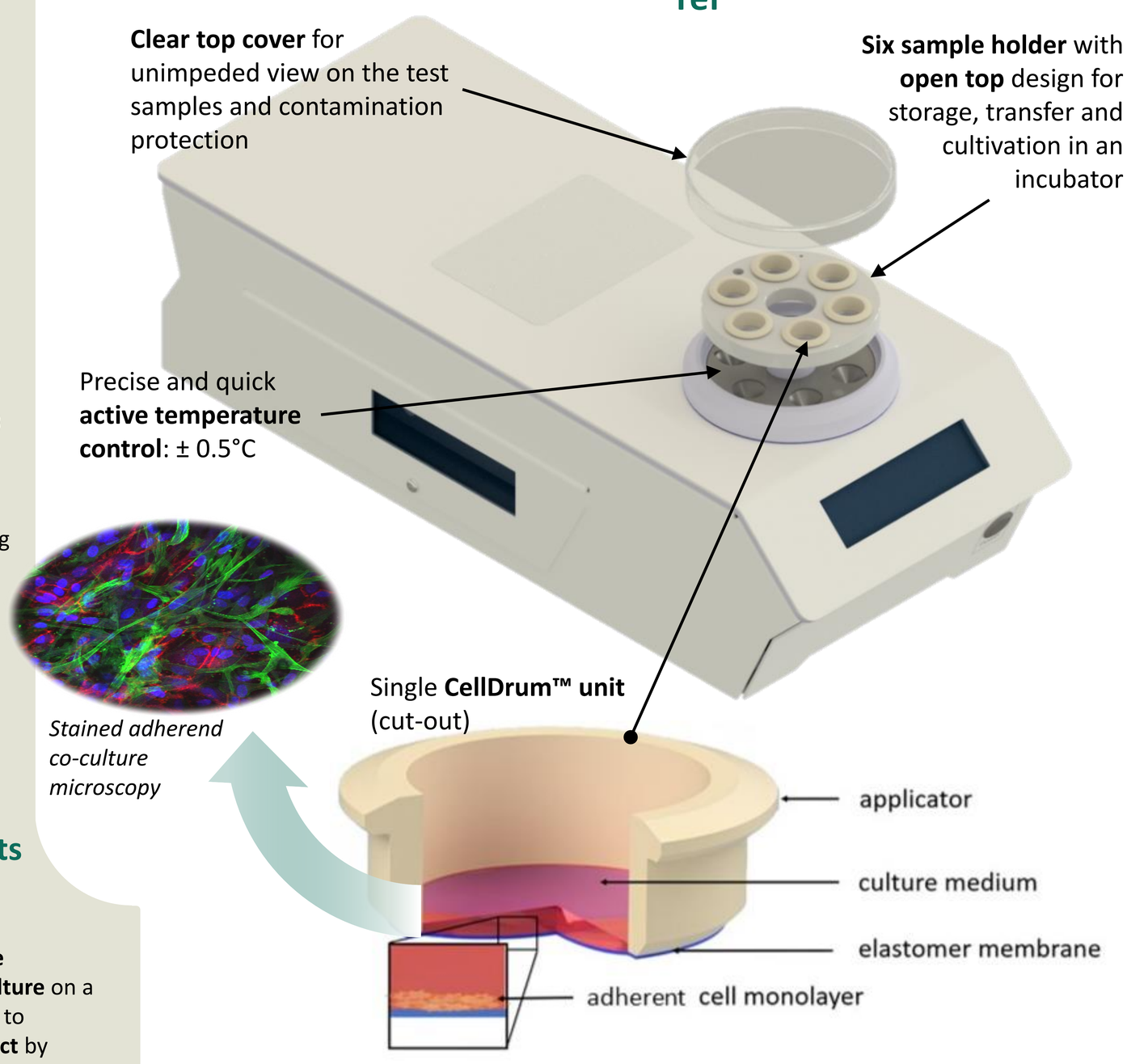


Figure 3:
Summary sheet of self beating cardiomyocyte co-culture subjected to **increasing cardioactive agent concentrations** (Isoproterenol). Shown metrics are **tension amplitude** (in Pa), **pulse frequency** (in Hz) and **pulse width** (in ms).

The CFA_{ref} device



CFA_{ref} allows consecutive tensile stress measuremts of up to 6 CellDrum™ units. The cell cultures within can have contractions with "high" or "low" velocity. For both cases different program functions are used. The adherent cells are **cultured on exeptionally thin PDMS membranes** (3.4-4 µm) as cell culture substrate over several days, allowing cell culture **approaches closer to in-vivo environments**.

The membranes show a **reproducibility of the mechanical tension** with less than 1% deviation. Prevailing and induced forces of fibroblast monolayers were found to be accurate within 2-7%.
Self beating murine cardiomyocyte co-cultures reacting to increasing doses of Isoproterenol, show a peak increase in **pulse frequency** and decrease in **tension amplitude** at 2 µMol concentration.
When subjecting an equal culture to changing loads, tension amplitude and pulse frequency rise, verifying a **Frank-Starling effect** and the measurability of the metrics of interest.

CONCLUSION AND OUTLOOK

We present
a) the CellDrum™ technology principle
b) evaluation experiments with fibroblast monolayers
c) dose response of beating murine cardiomyocyte co-cultures to a cardioactive substance
and d) we demonstrate the Frank-Starling effect quantitatively.

CFAref offers a broad potential for varius biomechanical measurement approaches at the bulk cell-layer level. We seek to constantly widen the capabilities of the device and software as well as the portfolio of possible measurement setups.
Future developments aim to add even more functionality and value to the device. By integrating further advanced sensors, optimizing production and integrating user feedback we are convinced we can make it possible.

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