Enhanced multielectrode configurations in miniaturized 3D electrical impedance spectroscopy and tomography – monitoring the overall process of tissue engineering with spatial sensing for future challenges in microfluidics

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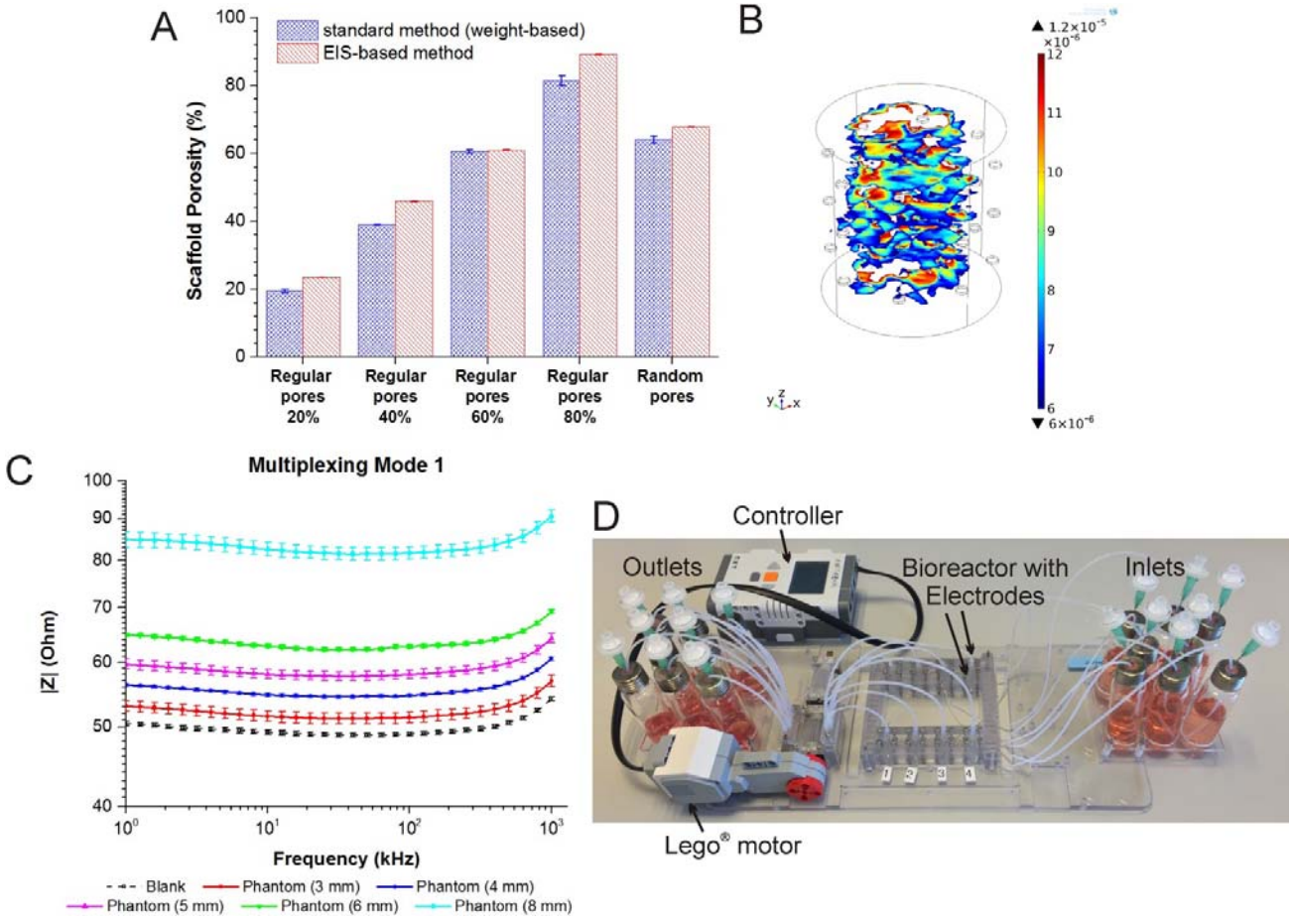
Over the past two decades, 3D cell culture models have attracted considerable attention to achieve in vivo-like structural organization, gene and protein expression, response to stimuli, drug metabolism, etc. A significant challenge in this regard is gaining spatial distributed information when monitoring cell proliferation on a biocompatible scaffold displaying well defined physico-chemical properties. Electrical impedance spectroscopy (EIS) have been shown to be a non-invasive method for biomaterial characterization and monitoring microfluidic cell cultures, gaining an insight on cell activity and proliferation over time.

We have developed and validated planar and needle-based multielectrode systems which offer the advantage of switching among different two-, three- and four-electrode configurations to focus impedance-based sensing on specific sub-volumes in a 3D cell culture. Information about scaffold architecture supporting cell organization (e.g. porosity, Fig. 1A), medium conductivity, and cell 3D spatial distribution can be obtained. Furthermore, four-electrode configurations can be also used for electrical impedance tomography (EIT)-based imaging to map the conductivity distribution within a miniaturized 3D cell culture system (Fig. 1B). Finite element simulations were used to optimize electrodes number, spacing and orientation with respect to the bioreactor geometry, by maximizing the deriving sensitivity field distribution for measurements. Validation with phantom experiments mimicking cell clusters (Fig. 1C) and cell-based experiments was performed aiming to incorporate spatial-enhanced 3D sensing into a 8-channel bioreactor array with integrated microfluidics for real-time monitoring of cell proliferation in porous scaffolds (Fig. 1D). The integration of the non-invasive sensing methods developed enable monitoring of tissue development within otherwise inaccessible areas of a 3D tissue construct, overcoming limitations of more traditional optical techniques.


A
standard method (weight-based)
EIS-based method
Scaffold Porosity (%)
100
80
60
40
20
0
Regular pores 20%
Regular pores 40%
Regular pores 60%
Regular pores 80%
Random pores
B
▲ 1.2×10⁻⁵
×10⁻⁶
12
11
10
9
8
7
6
▼ 6×10⁻⁶
C
Multiplexing Mode 1
|Z| (Ohm)
100
90
80
70
60
50
40
10⁰
10¹
10²
10³
Frequency (kHz)
Blank
Phantom (3 mm)
Phantom (4 mm)
Phantom (5 mm)
Phantom (6 mm)
Phantom (8 mm)
D
Controller
Outlets
Bioreactor with Electrodes
Inlets
Lego® motor