Bioimpedance monitoring of 3D cell culturing—Complementary electrode configurations for enhanced spatial sensitivity

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A bioimpedance platform is presented as a promising tool for non-invasive real-time monitoring of the entire process of three-dimensional (3D) cell culturing in a hydrogel scaffold. In this study, the dynamics involved in the whole process of 3D cell culturing, starting from polymerisation of a bare 3D gelatin scaffold, to human mesenchymal stem cell (MSC) encapsulation and proliferation, was monitored over time. The platform consists of a large rectangular culture chamber with four embedded vertical gold plate electrodes that were exploited in two- and three terminal (2T and 3T) measurement configurations. Computational finite element (FE) analysis and electrochemical impedance spectroscopic (EIS) characterisation were used to determine the configurations’ sensitivity field localisation. The 2T setup gives insight into the interfacial phenomena at both electrode surfaces and covers the central part of the 3D cell culture volume, while the four 3T modes provide focus on the dynamics at the corners of the 3D culture chamber. By combining a number of electrode configurations, complementary spatially distributed information on a large 3D cell culture can be obtained with maximised sensitivity in the entire 3D space. The experimental results show that cell proliferation can be monitored within the tested biomimetic environment, paving the way to further developments in bioimpedance tracking of 3D cell cultures and tissue engineering.

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1. Introduction

The current challenge in systems biology is to explore the intricate dynamics that orchestrate the cellular microenvironment where complex signalling pathways spatially and temporally direct cellular phenotype towards tissues formation, function and pathophysiology (Huh et al., 2011). The physico-chemical phenomena that take place in the extracellular three dimensional (3D) environment significantly contribute to tissue organisation, but may be hidden by compensating mechanisms when operated in two dimensional (2D) cell culture models (Tibbitt and Anseth, 2009). Therefore, 3D cell cultures are believed to enable, in a more physiologically true manner, the formation of dynamic spatial gradients of soluble factors that influence cell migration, cell-cell communication and differentiation (Watt and Huck, 2013). To reach this goal new scientific advances in the fields of biomimetic materials (Lu et al., 2013), molecular biochemistry (Baker and Chen, 2012) and microfluidic perfusion techniques (Buchanan and Rylander, 2013) are being explored to mimic biomechanical stability and more complex cell functionality.

Any sensing technique for real-time monitoring of 3D cell cultures must be able to collect real-time information of the time course of the biological processes at strictly controlled physiological-like conditions without damaging the cells. However, the advances so far are still some way off from providing fully robust, quick and user-friendly on-line detection solutions to follow biological dynamics throughout the 3D organisational complexity. Confocal imaging microscopy is widely used for monitoring cell culture evolution in terms of cell viability and differentiation with high subcellular resolution. Nevertheless, this approach still needs to be optimised for tissue engineering purposes. At this point it can be implemented only as an endpoint analysis since a large 3D scaffold has to be sectioned in thin slices (200–300 μm) to allow
light penetration (Smith et al., 2010). Furthermore, the scaffold should be optically transparent and composed of materials with low autofluorescence.

Electrical impedance measurements, including electrochemical impedance spectroscopy (EIS), are used to describe material properties as resistance to electrical current flow and ability to store electrical charge. Impedance measurements have been demonstrated as a powerful tool for the real-time study of complex biological systems both in vivo (Weijenborg et al., 2013) and in vitro (Giaever and Keese, 1984; Daza et al., 2013; Lei et al., 2012, 2014) by establishing a correlation between the electrical measurements and the biological phenomena in a non-destructive way. Physiological impedance measurements on tissues and organs have been extensively described by Grimnes and Martinsen (2008) and defined as bioimpedance. These measurements give an insight of biological 3D systems, reflecting cell dimensions, density and integrity as well as the extracellular matrix composition, in vitro applications of impedance measurements may encompass 2D and 3D cell cultures. However, the methodology originally proposed by Giaever and Keese (1993) for monitoring 2D cultures (electric cell–substrate impedance sensing, ECIS) is still the main focus of such applications. The measurements reflect the electrode interface impedance (polarisation impedance, $Z_p$) modulated by adhering cells. Lei et al. (2012) and (2014) have applied 2-electrode impedance measurements on 3D cell cultures using thin agarose layers. However, the emergence of 3D culturing and tissue engineering warrant significant development of bioimpedance monitoring strategies to map spatial distribution of cells in larger scaffolds.

![Fig. 1](image_url)

Fig. 1. (A) Schematics of the 2T and 3T (modes 1–4) configurations tested. In bioimpedance measurements (a) CC1 and CC2 form the current-carrying couple. PU1 and PU2 form the pick-up couple. Red (CC) and blue (PU) arrows represent a top view of the equipotential surface directions. In EIS analysis (b): WE = working electrode, CE = counter-electrode, RE = reference electrode. (B) Design of the overall bioimpedance platform. (a) The system consists of 3 layers: bottom plate accommodating the electrodes, culture chamber and lid. (b) Photograph of the system embedding four electrodes for 3T measurements. (c) Experimental setup for the 2T configuration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
To maximise the biophysical information obtained through in vitro bioimpedance measurements on tissue engineering scaffolds and 3D cell cultures, it is crucial to tailor parameters like electrode number, geometry, orientation and spacing. Furthermore, the sensitivity field in such bioimpedance measurements largely depends on the used configurations between electrode couples (current carrying, CC, and picking up, PU). The same electrode pair can have a dualistic role serving both as CC and PU, as in the case of a more conventional two-terminal (2T) configuration (Fig. 1Aa, 2T), which typically includes \( Z_p \) and the entire sample volume between the two electrodes. The measurement sensitivity is proportional to the square of the current density (Grimnes and Martinsen, 2008). Alternatively, three- and four-terminal (3T or 4T) configurations, as conventionally used in physiological bioimpedance, are also possible. 4T measurements are commonly used when there is a need to reduce the sensitivity close to both PU electrodes, either to avoid contribution from \( Z_p \) or to focus the measurements on a specific volume inside the sample. In this case, separate electrodes are used as CC and PU, none of them with a dualistic role. In 3T configurations, one electrode is common for the CC and PU couple with a dualistic role (Fig. 1Aa, 3T modes). The impedance of that electrode is the only one having a contribution from \( Z_p \) and reflecting the sample volume in its close proximity (Grimnes and Martinsen, 2007).

To our knowledge, bioimpedance monitoring has not been previously established for large 3D cultures applicable in tissue engineering. To fill this gap, we present here bioimpedance monitoring of 3D cultures, including the different stages from gelatin scaffold polymerisation and cell encapsulation to cell proliferation in the 3D environment. A number of alternative and complementary 2T and 3T electrode configurations (Fig. 1A) were applied between vertical gold plate electrodes (Fig. 1B) in a multiplexing-like approach to maximise the sensitivity in a 2-ml gelatin matrix with embedded human mesenchymal stem cells (MSCs). The difference and complementarity between 2T and 3T configurations were described by finite element (FE) analysis and EIS characterisation.

2. Material and methods

2.1. Design and fabrication of bioimpedance platform

The bioimpedance platform (Fig. 1B) was designed for static cell cultures and consists of a bottom plate with rectangular slits for mounting up to four electrodes adjacent to each sidewall of the culture chamber (\( 19 \times 16 \times 10 \text{mm}^3 \)). The two parts were sealed together using a PDMS O-ring. The chamber is closed with an optically transparent lid having an opening (2-mm diameter) to enable culture medium removal and replenishment. The system components were fabricated of polycarbonate using micromilling. Vertical electrodes (\( 10 \times 25 \times 0.525 \text{mm}^3 \)) were fabricated by thermally evaporating a 200-nm thick layer of gold onto an oxidised (650 nm) silicon wafer coated with a 20-nm titanium adhesion layer.

2.2. FE analysis

FE simulations were carried out using Comsol Multiphysics v4.3b to study the sensitivity field distribution within the bioimpedance platform with the different electrode configurations. The method for calculating the sensitivity field has been previously described by Pettersen and Høgetveit (2011). 3D models of the chamber containing four electrodes and a gelatin scaffold (5% w/v, 2 mL) were created in the AC–DC module. Gelatin parameters were set as 0.3 S/m for conductivity \( (\sigma) \) (Marchal et al., 1989) and 60 for relative permittivity \( (\varepsilon_r) \) (Ferguson et al., 1934). The electrode parameters were set as 45.6 \( \times 10^6 \text{S/m} \) for \( \sigma \) and 1.5 for \( \varepsilon_r \). The mesh consisted of 33,772 tetrahedral elements with an average element quality of 0.77.

For simulating the 2T configuration, 10 mV were applied to one electrode while the other was grounded. Electrical insulation was applied to the chamber chassis. The sensitivity field \( (S) \) was computed as \( S=J^2 / \varepsilon \) (Heyum et al., 2010) where \( J \) is the relative surface density of the injected current. For the 3T configurations, 10 mV were applied between two opposing electrodes, and \( S \) was evaluated in relation to the adjacent PU couple at the corner of the chamber (Fig. 1Aa). In this case, \( S \) was calculated as \( S=J_{\text{pu}}^2 / \varepsilon \) (Marchal et al., 1989) where \( J_{\text{pu}} \) is the current density vector for the PU couple and \( J_{\text{cc}} \) is the current density for the CC couple.

2.3. EIS analysis of \( Z_p \) distribution in 2T and 3T configurations

Prior to any measurements, gold electrodes were cleaned by a 10-min treatment using a mixture of \( \text{H}_2\text{O}_2 \) (25% v/v) and KOH (50 mM) followed by a potential sweep from \(-200 \text{ mV} \text{ to } -1200 \text{ mV} \text{ in } 50 \text{ mV} \text{ KOH} \) (Heiskanen et al., 2008). EIS analysis was performed using an equimolar solution of \( \text{K}_3[\text{Fe(CN)}_6]_3 \) and \( \text{K}_4[\text{Fe(CN)}_6]_4 \) (10 mM) dissolved in 1 M KOH. Electrode modification with sodium 3-mercaptop-1-propanesulfonate (MPS, 63765 Fluka) was performed for EIS analysis of \( Z_p \) distribution. A sinusoidal perturbation of 10 mV (rms) with respect to the open circuit potential was applied in the frequency range between 10 mHz and 1 MHz using a Reference 600 potentiostat/galvanostat/ZRA (Gamry Instruments). 2T and 3T measurements were performed on conductivity standard solutions (Hanna Instruments) with \( \sigma \) values (25 °C): 84 \( \times 10^{-4} \text{ (cat. 663-5054, 0.14 \text{ (cat. 663-5048, 1.29 \text{ (cat. 663-5047 and 11.18 S/m (cat. 663-5008) using an SI1260 impedance analyser and a 1294 impedance interface (Solartron Instruments) based on the protocol described above. Due to the platform symmetry and solution homogeneity, only one side is reported for the 3T configuration. Fig. 1Ab shows the assignment of electrodes for EIS (see also Section S1 in Supplementary material).

2.4. Bioimpedance experiments

Experiments were carried out using 5% w/v gelatin (Fluka 48723). The hydrogel was covalently cross-linked using the microbial enzyme transglutaminase (Activa\textsuperscript{®}, RM, Ajinomoto) dissolved in 1× PBS (Sigma D8537). Bioimpedance was used to monitor: (1) polymerisation of the bare gelatin matrix, (2) encapsulation of MSCs (Gibco A15652) within the scaffold, and (3) MSCs growth over time. The used measurement volume was in all cases 2 mL. Bioimpedance measurements using Solartron SI1260/SI1294 were performed by applying a 10 mV AC in the frequency range between 100 Hz and 1 MHz. Two densities of MSCs (1.5 \( \times 10^5 \text{ and } 1.5 \times 10^5 \text{ cells/mL} \)) were encapsulated within the hydrogel by directly mixing the cell suspension with gelatin. Prior to measurements, the mixture was allowed to polymerise in the chamber for 2 h at room temperature. Separate measurements were conducted on the bare gelatin scaffold (also 10% w/v for comparison) during the process of polymerisation without any cells present.

To investigate the capability of the system to monitor cell growth, 5 \( \times 10^5 \text{ cells/mL} \) MSCs were loaded into the gelatin scaffold and measurements were performed over time. In this case, cross-linking of 5% gelatin was carried out in cell culture medium (RPMI 1640 with 10% fetal bovine serum and 1% penicillin/streptomycin). Scaffolding polymerisation was allowed for 45 min (37 °C, 5% CO\textsubscript{2} in a humidified incubator) and then the culture chamber was filled with cell culture medium. Cells were grown for 48 h in the incubator. At the end of each growth experiment, cells...
were recovered from gelatin to estimate the cell number and viability. Gelatin scaffolds were digested at 37 °C with a 250 µg/mL thermolysin (Sigma T7902) solution in 50 mM Tris and 10 mM CaCl₂. Cells were counted with a MOXI Z automated cell counter (Orflo Technologies) and viability was estimated using Trypan blue (Sigma T8158).

3. Results and discussion

3.1. FE analysis

Fig. 2 shows the solutions of the mathematical models for the spatial distribution of the sensitivity field of 2T (a) and 3T (b) configuration. The 3T setup allows several combinations of CC and PU electrode couples and four of them were chosen with the aim to focus on the dynamics occurring at the corners of the 3D culture chamber. Due to the platform symmetry and bulk homogeneity, only the FE model for 3T mode 1 (Fig. 1Aa) is shown here, while the complete FE analysis for all the 3T setups (modes 1–4) is reported in Fig. S1.

As expected, the 2T configuration senses the dynamics occurring in the whole volume between the two electrodes with significant contribution from $Z_p$ at both interfaces (Fig. 2a). The 3T configuration mainly focuses on the volume between the PU couple at the corner of the respective culture chamber (Fig. 2b). Hence, by switching between modes 1–4 it is possible to build a multiplexing-like approach that provides an insight of the 3D space at the corners. A minor influence of the electrode edge on conduction was emphasised in these models. This localised charge density is related to the used electrode structure with conductive spaces at the corners. A minor influence on 2T and 3T configurations are shown in Fig. S4 and further discussed in Section S3 in Supplementary material.

3.2. EIS analysis of $Z_p$ distribution in 2T and 3T configurations

As discussed in the introduction and theoretically illustrated in the FE simulations (Fig. 2), $Z_p$ has a different influence on 2T and 3T configuration. To experimentally validate this, we used EIS characterisation with the redoxactive probe $[\text{Fe(CN)}_6]^{3–/4–}$ combined with a self-assembled monolayer (SAM) of MPS, modifying each electrode one-by-one (see the defined roles of the different electrodes in Fig. 1Ab). MPS renders a modified electrode with a negative net charge, which repels $[\text{Fe(CN)}_6]^{3–/4–}$. When using a redoxactive probe, the $Z_p$ in acquired impedance spectra shows both a Faradaic (electron transfer: charge transfer resistance, $R_{ct}$, and mass transfer: Warburg impedance, $Z_w$) and non-Faradaic (double layer capacitance, $C_{dl}$) contribution. Due to repulsion by the negatively charged MPS SAM, especially the $R_{ct}$ should increase on electrodes, whose $Z_p$ is a part of the sensitivity field of the electrode configuration. Since the electrodes in the system are equal in size, in 2T configuration the contribution of $Z_p$ at both electrodes should be equal, whereas in 3T configuration the contribution of $Z_p$ should be eliminated at one of the PU electrodes. Fig. 3a shows two Nyquist plots, one for an unmodified WE and another for the same WE after MPS modification, the latter indicating a significant increase in $R_{ct}$. If the electrode assignment is reversed, i.e. the MPS-modified electrode is used as the CE, the acquired Nyquist plot is superimposable with the one in Fig. 3a. A corresponding set of Nyquist plots for mode 1 of 3T configuration (Fig. 1Ab) is shown in Fig. 3b. In this case, the MPS-modified electrode is the RE, the PU at which the $Z_p$ is expected to be eliminated. This is verified by the fact that the Nyquist plots before and after MPS modification are superimposable. When a corresponding test is performed modifying the other PU, i.e. the WE in Fig. 1Ab, an increase in $R_{ct}$ is observed (result not shown).

All together, these results demonstrate that the 2T configuration allows gathering of information about the interfacial phenomena at both electrode surfaces in addition to those occurring at the centre of the 3D sample. By combining the 2T information with the one acquired using the 3T configuration when switching between the four modes (Fig. 1A), it is possible to collect spatially distributed information that focuses on the culture chamber corners in a multiplexing-like approach. Additional EIS-based verification regarding the differences between the 2T and 3T configuration are shown in Fig. S4 and further discussed in Section S3 in Supplementary material.

3.3. EIS conductivity measurements

The system needs to account for changes in the cell-scaffold conductivity during cellular growth. For instance, a decrease in pH within the cell culture leads to an increase in conductivity, thus influencing the sensed impedance. Such changes may be correlated to different biochemical phenomena, e.g. hypoxia and cell death, bacterial contamination, aging of the culture. To ensure system reproducibility, the intra- and inter assay reproducibility were first determined and found to be excellent for the 2T and 3T measurement modes (Figs. S2 and S3). Impedance spectra were then acquired for different conductivity standard solutions using

![Figure 2](image_url)

**Fig. 2.** FE analysis: Sensitivity field [m⁻¹] distribution (slice view) and current density vectors for (a) 2T configuration and (b) 3T configuration (mode 1).
the 2T and 3T (mode 1) configurations. As shown in Fig. 3c, the spectra (presented as Bode plots) provide a clear discrimination between standards of medium low (1.29 S/m) and high (11.18 S/m) conductivity. Due to the system isotropy, the acquired Bode plots are characterised by bulk resistance at high frequencies and superimposability (Fig. S5).

The impedance spectra acquired using conductivity standard solutions are characterised by bulk resistance at high frequencies and as expected is more pronounced for 10% cross-linked gel (Fig. 4a). In our further study, 5% scaffold was employed since it displays a Young’s modulus of approximately 3.6 kPa (data not shown), which is the stiffness common to many soft tissues (e.g. liver, kidney and some blood vessels) (Janmey and Miller, 2011).

Fig. 4 shows Bode plots for the 2T (b) and 3T (c) configuration acquired during polymerisation of 5% gelatin scaffold during 2-h period. At the beginning of the polymerisation (0 h), the standard deviation among acquired triplicate spectra was higher, especially for the 2T configuration (Fig. 4b). This may be explained by the higher ionic mobility at the beginning in comparison with the fully cross-linked polymer. Since each spectrum acquisition took 7 min, it is plausible to correlate the higher impedance variation with the higher ionic mobility. Moreover, the 2T configuration reflects a more significant contribution from both the gelatin bulk resistance (cf. conductivity standards, Fig. 4c) and \( Z_p \) at both electrodes, which may also explain the higher standard deviation in comparison with the 3T configuration, where the contribution of \( Z_p \) on one PU electrode is negligible. After the first hour of polymerisation, a 1.05 (± 0.02)-fold increase in \( |Z| \) was detected with both 2T and 3T (mode 1) configurations, related to the differential mapping of the 3D space as also illustrated in Fig. 2, can be seen in the high-frequency behaviour of \( |Z| \), being systematically higher in comparison with the average of the four 3T modes (further details shown in S4).

3.4. Bioimpedance of gelatin scaffold polymerisation and cell encapsulation

Gelatin is a well-known biodegradable and biocompatible material often exploited as scaffold for tissue engineering, either alone or in combination with other molecules, such as chitosan (Kang et al., 1999; Huang et al., 2005). Engler et al. (2006) showed that MSCs were able to specify lineage and commit to phenotypes that MSCs were able to specify lineage and commit to phenotypes, which may also explain the higher standard deviation in comparison with the 3T configuration (Fig. 3c) and \( Z_p \) on both electrodes.

Between resistive and capacitive behaviour is roughly the same although a sharper transition is observed for the 2T configuration. Low-conductivity solutions (84 × 10\(^{-4}\) and 0.14 S/m) were also tested to evaluate the functionality of the setup under conditions, which often lead to artefacts especially at high frequencies due to the formation of parasitic conduction paths (Scully and Silverman, 1993; Stewart et al., 1993). Even under these conditions, the platform facilitated stable measurements, which were negligibly affected by noise (Fig. S6). A characteristic difference between the 2T and 3T configuration, related to the differential mapping of the 3D space as also illustrated in Fig. 2, can be seen in the high-frequency behaviour of \( |Z| \).
with the one found for the conductivity standard of 1.29 S/m (Fig. 3c) since gelatin was prepared in PBS at physiological concentration.

The two configurations were further characterised in terms of their ability to discriminate between different cell loadings within the 5% gelatin scaffold. This was achieved by directly mixing different MSCs densities (1.5 × 10^5 and 1.5 × 10^6 cells/mL) with a gelatin solution in PBS, which was poured into the culture chamber and let polymerise for 2 h at room temperature. Fig. 5 shows clearly that the 2T configuration (solid lines, solid symbols) can discriminate between the bare gelatin scaffold (solid line) and the scaffold loaded with both cell densities, whereas the 3T configuration could only discriminate the higher cell density (solid lines, open symbols) from the bare gelatin scaffold (dashed line). This difference in sensitivity may be partially explained by the larger number of cells in the central volume of the culture chamber in comparison with the restricted zones at the corners where the 3T configuration modes are focused. Analogously to this, the lower detection limit of the 2T configuration is also related to the findings of Kalvøy et al. (2009) as well as the FE simulations and EIS characterisation presented above, i.e., in 2T configuration the highest sensitivity field is located around the entire width of the two electrodes (pronounced \( Z_p \) contribution for the 2T configuration).

3.5. Bioimpedance of 3D cell growth

As a proof of concept on the capability of the system to monitor cell proliferation and distribution over time, based on the above results, 5 × 10^5 cells/mL was chosen as a starting cell density. MSCs were encapsulated in a 5% gelatin scaffold and cultured in the chamber for 48 h. In this experiment, the gelatin scaffold was polymerised in cell culture medium to provide a proper environment for cell growth. The cell culture was performed under static conditions (37 °C, 5% CO2 in a humidified incubator) while bioimpedance monitoring was performed in triplicate every 24 h. Fig. 6 shows the increase in \(|Z|\) (at 4 kHz) for the 2T (a) and 3T (modes 1–4, b) configuration. This frequency was chosen based on spectral analysis (see Section S5 in Supplementary material), which indicates that the discrimination between time points was the highest for both configurations.

The two different configurations showed consistent results in terms of the increase in \(|Z|\), albeit with different trends over time. For the 3T measurements, which respond to the dynamics occurring at the corners of the 3D culture chamber, the growth curve is still rising after 48 h (Fig. 6b), whereas the growth curve for the 2T measurements is approaching a saturation limit after 48 h (Fig. 6a), which may correspond to differences in cell distribution inside the gelatin matrix during the culture period. Corresponding results were obtained in bioimpedance monitoring of the growth of HeLa and HepG2 cells as well as neural stem cells (results not
Due to the hydrogel scaffold thickness, the visualisation of the 3D culture over time with optical microscopy was not possible. Furthermore, the softness of 5% gelatin hampered the possibility of slicing the scaffold. At the end of the experiment, the MSCs were therefore recovered from gelatin by incubating the scaffolds with a thermolysin solution at 37 °C to estimate the cell number and viability using the Trypan blue endpoint assay. Based on this assay, the average cell number was almost doubled from the initial value shown). In separate tests, the initial cell distribution in gelatin has been found to be homogeneous (results not shown). Based on this, the bioimpedance results support the hypothesis that the cells tend to proliferate more in the centre of the culture chamber than in the corners close to the chamber walls. Indirectly, this is also supported by the findings of Rao et al. (2012) showing differential behaviour glioblastoma cells (morphology and motility) in the bulk of 3D Matrigel in comparison with regions in the proximity of the scaffold space, whereas the 3T configurations focus on the corners. The differential spatial distribution of the sensitivity fields were exploited in multiplexed bioimpedance monitoring of MSC proliferation inside the gelatin scaffolds maximising the obtained spatial information. This approach constitutes a first attempt of generating a flexible bioimpedance based method for monitoring large 3D cell cultures with spatial resolution, hence, bridging the gap between conventional impedance monitoring of 2D cultures and future electrical impedance tomography of 3D cultures.

4. Conclusions

A bioimpedance based platform has been developed for real-time monitoring of the dynamics involved in the whole process of 3D cell culturing in large gelatin scaffolds, comprising enzymatic polymerisation, mesenchymal stem cell (MSC) encapsulation and proliferation. Using finite element (FE) simulations and electrochemical impedance spectroscopic characterisation, we demonstrate the distribution of the sensitivity fields and behaviour of impedance measurements when employing 2 terminal (2T) and 3 terminal (3T) electrode configurations. The 2T configuration maps the central part of the scaffold space, whereas the 3T configurations focus on the corners. The differential spatial distribution of the sensitivity fields were exploited in multiplexed bioimpedance monitoring of MSC proliferation inside the gelatin scaffolds maximising the obtained spatial information. This approach constitutes a first attempt of generating a flexible bioimpedance based method for monitoring large 3D cell cultures with spatial resolution, hence, bridging the gap between conventional impedance monitoring of 2D cultures and future electrical impedance tomography of 3D cultures.

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Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bios.2014.07.020.

References