Abstracts – BMT 2020 – Leipzig, September 29 – October 1 • DOI 10.1515/bmt-2020-6051
Biomed. Eng.-Biomed. Tech. 2020; 65(s1): S296–S300 • © by Walter de Gruyter • Berlin • Boston

Evaluation of semi-supervised learning using sparse labeling to segment cell nuclei

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Introduction

The analysis of microscopic images from cell cultures plays an important role in the development of drugs. The segmentation of such images is a basic step to extract the viable information on which further evaluation steps are build. Classical image processing pipelines often fail under heterogeneous conditions. In the recent years deep neuronal networks gained attention due to their great potentials in image segmentation. One main pitfall of deep learning is often seen in the amount of labeled data required for training such models. Especially for 3D images the process to generate such data is tedious and time consuming and thus seen as a possible reason for the lack of establishment of deep learning models for 3D data.

Methods

We present a new semi-supervised training method for image segmentation of microscopic cell recordings based on an iterative approach utilizing unlabelled data during training. First, sparsely labelled data is used to train a U-Net which is then used to segment unlabelled data. After a post-processing step new labels are extracted from the segmented image which are then used in the next training step.

Results

By labeling less than one percent of the training data, a performance of 90% compared to a full annotation with 342 nuclei can be achieved. Over subsequent iterations the method can reduce the amount of falsely segmented background.

Conclusion

The proposed method reduces the amount of labels and thus the time needed for labelling to train deep learning models for image segmentation. An annotation time of 45 minutes can be reduced to half a minute while maintaining 90% of the performance. The method will be applied to 3D data, where a single image stack can easily contain 2000 nuclei requiring 75 hours of annotation time.

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Rapid development of tailored micro-physiological systems using novel modular plug&play construction kit

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Introduction

Micro-physiological platforms (MPS) - often referred as organ-on-chip or multi-organ-chip - have an enormous potential to strengthen research in drug development, toxicological screening, personalized medicine and disease modeling. The design of such MPS is an interdisciplinary challenge. At the beginning of development, many parameters and boundary conditions (geometries, volumes, flow rates, interfaces, and coatings) are often still unknown. The probability that the first draft will work is therefore very low. A large number of design cycles are necessary to develop a miniaturized MPS with a high functional density.

Methods

However, we have identified the key elements and designed a modular plug&play construction kit for the development of tailored MPS. The modular system provides a large number of functional, miniaturized modules such as pneumatic driven micro-pumps, oxygenators, reservoirs, sensors and cell culture compartments whose fluidic interfaces comply with the Luer-Lock standard. This allows a quick and easy combination of modules with each other, according to the intended application.

Results

By using the modular plug&play construction kit, the successful creation of different MPS setups has achieved in the shortest time and with minimal effort. As an example, we show tailored Kidney-MPS with perfused tubular or glomerular barrier. A quick and easy integration of microfluidic components, pumps and sensors from third party suppliers is possible.

Conclusion

Thus, with the help of the modular plug&play construction kit, a drastically reduction of financial and time expenditure of an MPS development is possible. Once an application-specific design has been successfully determined, it is possible to derive a compact MPS by following certain design rules.

High-Current Neutral Electrodes

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Introduction

In electrosurgery tissue is cut and coagulated by means of electrical current. The surgeon's active electrode takes the current to the site of operation from where it needs to be returned via a return electrode - the neutral electrode (NE) – to the electrosurgical generator. During this surgical process, the heating of the skin under the NE must not exceed 6°C according to Standard IEC 60601-2-2, 6th Ed, 2016.
Modern surgical techniques (ablation) use higher energies with high currents and long-activation times, which increases the load (heating) on the neutral electrode.

Conventional NE versus high-current NE

For **conventional** NEs the Standard stipulates energy limits (heating factor $30A^2s$) and measurement procedures for quality testing (700mA during 60s). For surgery with **high-current**, however, the only parameter stipulated in the Standard so far is a heating factor $>30A^2s$. And there is no upper limit nor any recommendation for testing.
The definition for high-current as „maximum output current" leaves room for misinterpretations, since this "maximum output current" is neither displayed anywhere nor is it readily measurable.
Instead of the "maximum output current" the characteristic features for high-current NEs should be the "**activation time**" that is foreseeable for the scheduled surgery.

Suitability assessment of high-current NEs

Testing of NEs of adequate area (active surface ~$250cm^2$) as to their load capacity in high-current mode by means of an electronic test device yielded the following results for the allowable activation times and respective load currents: 5 min with 1A, 15 min with 700 mA and 2 times higher load currents if 2 NEs are used in parallel.
The results also showed that testing at 1,4A during 60s (heating factor $120A^2s$) could constitute a quality test for high-current NEs.

Conclusion

This paper aims at finding a **workable differentiation** between conventional NEs and high-current NEs and suggesting a recommendation for quality testing.

Parallel online monitoring of substance transport processes in a micro-physiological tubular barrier

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Introduction

Animal experiments are, despite their disadvantages, like high costs, and their poor predictive value, still the state of the art for pharmaceutical substance testing. One reason for this problem is the incapacity of modern *in vitro* models, like micro-physiological systems, to perform parallel online-monitoring of transport processes over membrane barriers, such as the kidney tubular barrier. Nevertheless, the investigation of those transport processes proves to be crucial for artificial organ models. Thus the aim of this work is to develop and evaluate a compact setup for the parallel quantification of substance transport above artificial cellular membranes.

Methods

The tubular barrier was created by seeding a monolayer of immortalized human renal proximal tubule epithelial cells (RPTEC/TERT1) on 24-well transwell cell culture inserts (ThinCert™). Rhodamine 123 was chosen as substrate for transport assays, due to its fluorescence and biochemical characteristics. The fluorescence measurements were performed by a miniaturized fluorescence measurement device (Fluo Sens Integrated). Two sets of LEDs and detectors were used for simultaneous measurement of fluorescence signals with excitation and emission wavelengths at λ_{ex}=470/625 nm and λ_{em}=520/680 nm.

Results

The setup used for online-monitoring of Rhodamine 123 transport comprises a miniaturized fluorescence measurement device in a sealed housing suitable for handling in cell culture incubators. Reliable, parallel detection of Rhodamine 123 and fluorescence labeled human serum albumin was confirmed by comparison with an established fluorescence detection method.

Conclusion

Here, we present a setup which allows parallel online measurement of two substrates during transport assays over a micro-physiological tubular barrier. This could be a useful tool to investigate the reabsorption and secretion capability of artificial, cell-based model systems for both, glomerular as well as tubular barriers.

pH- and oxygen sensors based on fluorescent nanoparticles for Lab-on-Chip applications

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Introduction

We present the synthesis of silica (SiO_2)-nanoparticles functionalized with fluorescent dyes. These nanoparticles were developed for multi-sensor spots directly inkjet-printed on microfluidic sytems such as Lab-on-Chip (LoC). The nanoparticle-based sensor spots have well-defined fluorescent properties and can be modified for sensing different environmental parameters. This was demonstrated by developing fluorescent nanoparticles whose fluorescent intensity strongly depends on the pH-value of the solution.

Methods

We used the Stöber method (sol-gel process) to synthezise SiO_2-nanoparticles. The nanoparticles were functionalized by either a pH-sensitive (Fluorescein isothiocyanate (FITC)) or a dissolved oxygen (DO)-sensitive (Tris(2,2-bipyridyl)dichlororuthenium(II)hexahydrate ($[Ru(bpy)_3]^{2+}$)) dye. The distribution of nanoparticle size was evaluated by scanning electron microscope (SEM) and dynamic light scattering. The fluorescenct properties (excitation and emission spectrum) of nanoparticles and the pH/oxygen-dependency of the fluorescent intensity were measured using a microplate reader.

Results

We obtained spherical SiO_2 nanoparticles with a high monodispersity (typical geometric standard deviation of 1.1). Using the Stöber process it is possible to synthesize SiO_2 nanoparticles with adjustable diameters between 40 nm and 3.6 µm. Fluorescence measurements showed that the functionalization was successful with both the pH- and the oxygen-sensitive dye. The nanoparticles functionalized with FITC showed a linear dependence of fluorescence intensity in the pH range from 4.7 to 8.8 with increasing pH values. The relative increase in intensity was 22 % per pH change relative to the maximum intensity value.

Conclusion

We successfully established a procedure for synthetizing and functionalizing SiO_2-nanoparticles of defined size. The nanoparticles can be functionalized by dyes whose fluorescent properties change with altered environmental conditions such as temperature, pH, DO, Ca_2^+ etc. Such nanoparticles are of particular interest as an ink for printing fluorescent multi-sensor spots in lab-on-chip applications.