protein structures; 1) a large capsid containing the viral genome, 2) a contractile tail structure connected to the capsid which generates the driving force to pierce the host membrane and conveys DNA from the capsid to the host, and 3) a baseplate equipped with fibers that recognize and bind to the host. The contractile tail consists of a rigid tail tube surrounded by an elastic six-helical-stranded sheath. During injection, the sheath undergoes a large conformational transition from a high-energy extended state to a low-energy contracted state, thereby releasing energy needed for the tail tube to penetrate the host. While the atomic structure of phage T4 is largely known, the dynamics of the injection process is not, including time scale and energetics of injection. To fill that gap, we propose a dynamic model of the entire phage T4 to simulate the dynamics of the injection process. The simulation follows in two stages; first, we employ molecular dynamic (MD) simulations to calculate the elastic stiffness constants and internal friction of the sheath strands. Second, we employ those material properties in a continuum model of the entire virus. The continuum model treats the tail sheath as a six-interacting elastic helical strands that are coupled to a massive cylinder representing the capsid and to a rigid rod representing the tail tube. The resulting model predicts that the driving energy of injection process is about 5500kT, the time scale of sheath contraction is on the order of milliseconds, and the internal friction of sheath strands is a main source of energy dissipation during sheath contraction.

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2-Photon Lithography for Nanofluidic Lab-on-Chip Devices

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The misfolding of proteins inside neuronal cells is known to be linked to neurodegenerative diseases such as Alzheimer's and Parkinson disease. Two promising approaches used by researchers in this field are: The usage of lab-on-chip devices to characterize proteins ''in vitro'' from a biophysics point of view and fluorescence microscopy to study the protein aggregation in living cells in scaffolds ''in vivo''. The length of Amyloid-β 42 (M1-42) aggregates is connected to their toxicity and integrated nanofiltration methods to separate proteins in a microfluidic process pipeline are not available in biological research laboratory without access to expensive electron beam lithography systems as in clean-room facilities. Therefore, we present a novel soft lithography method to produce nanometric structures with two-photon lithography (2PL) for nanofluidic chip fabrication. We demonstrate a system capable of producing master wafers for nanofluidic devices and use these to measure the diffusion of fluorescently labelled Amyloid-β 42 in nanochannels. [1] We also show the fabrication of 3D cell scaffolds for more realistic 3D cell cultures, to improve studies of e.g. the protein Tau in Alzheimer's and its interplay with Amyloid-β 42. [2][3] To accelerate lab-on-chip development we overcome the current microscale fabrication capabilities by combining mask whole-wafer UV-lithography with locally 2P-written nano-sized functional features and make rapid nanofluidic chip prototyping possible.

[1] Erik C. Yusko, et al., Nature Nanotechnology 6, 253260 (2011)
[2] Carla Davanzo et al., Nature 515, 274278 (13 November 2014)
[3] Clemens F. Kaminski, Gabriele S. Kaminski Schierle, Neurophoton. 3(4), 041807 (2016).

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Design of a Multiparameter Islet-on-a-Chip Device to Measure the Functional Variability of Individual Pancreatic Islets

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Type 1 diabetes results from autoimmune destruction of pancreatic islets, small micro-tissues (~150 μm) that are primarily composed of insulin secreting beta-cells. Islet transplantation is a current treatment option, but will never be universally available due to limited supply of donor tissue. Tissue engineered islets could help bridge this gap and provide an opportunity to treat many more people. However, the success will depend heavily on the quality and uniformity of the engineered tissue. To inform in the design, we are creating a microfluidic device to assay multiple readouts of function on individual islets and engineered micro-tissues. First, we aim to measure C-peptide release as a proxy for endogenous insulin. This will be done by creating an on-chip competition assay based on C-peptide conjugated to 5-TAMRA (C-peptide*) and changes in fluorescence anisotropy. Second, we aim to measure oxygen consumption rates of individual islets. Oxygen is consumed by the electron transport chain and can be used to identify perturbations in oxidative phosphorylation. We are using RuII(bpy)3 as an optical sensor to measure oxygen with excitation and emission maxima at 450 and 600 nm, respectively. Lastly, we aim to measure extracellular acidification rate as a readout of glycolytic rate and/or oxidative phosphorylation. We will use HPTS, a pH sensitive dye, in solution. Each of these sensors is spectrally and/or spatially resolved from one another. This strategy will allow us to simultaneously measure these responses to fully index the function of individual islets and engineered micro-tissues. This multiparametric characterization could inform the production of engineered islets as well as assist in the screening of tissue prior to transplantation.

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A 16384 Electrode 1024 Channel Multimodal Cmos MEA for High throughput Drug Screening

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Drug attrition is a major concern for the pharmaceutical industry. Besides the loss of the large investment needed to develop novel drugs, many lives have been lost due to lethal side effects. Cardiotoxicity accounts for more than one third of the drug withdrawals from the market. Although the Food and Drug Administration has set guidelines to tackle this issue, there is still room for improvement on the methodology of safety screening. Multi-electrode arrays (MEAs) are a candidate technology to screen in vitro cardiac parameters because of its non-invasive recording of cardiac beating rate and electrical field potential duration. Here we present a novel active MEA chip featuring 16,384 electrodes, 1024 simultaneous readout channels and 4 different electrode sizes to perform extracellular and intracellular recording from cardiomyocytes. Biocompatible TiN (height of 300nm) electrodes were processed on top of the in-house designed circuits. The circuit noise for the recording mode was 7.5 ± 0.6 μVrms and 12 ± 2.4 μVrms for extracellular and intracellular recording, respectively. Electrode impedance at 1kHz was determined using the built-in impedance circuitry and was 4.2, 2.2, 1.1 and 0.5 MΩ for electrode areas of 8.75, 10.5, 45.5 and 121μm^2, respectively. Further, we recorded extracellular signals of 1.4 mV and intracellular signals of 12.7mV on average (peak to peak) from primary rat cardiomyocytes cultured for 3 days *in vitro* on the chip. Finally, applying 1μM nifedipine, a drug to treat hypertension and angina, on the cells changed the shape and duration of intracellular action potential significantly. The novel platform thus allows for high throughput electrical activity monitoring and drug screening of cardiomyocytes, and can be used for toxicity screening or drug development.

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Effects of Hypoxia on Breast Cancer Extravasation in a 3D Microvascular Network

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Hypoxia within the tumor microenvironment plays an important role in regulating breast cancer progression and is associated with metastasis and patient mortality. Lack of oxygen in the tissue triggers changes in gene expression mediated by hypoxia-regulated proteins, i.e. hypoxia inducible factors (HIFs) that impact cancer in numerous ways: angiogenesis, metabolic reprogramming, epithelial-mesenchymal transition (EMT), invasion, and metastasis. Recent advances in microfabrication technologies have allowed for the development of in vitro platforms that recapitulate cellular components and functions relevant to cancer metastasis. Previously, we engineered 3D vascular networks with human umbilical endothelial cells (HUVECs) seeded in fibrin gels and cultured to allow signaling with human lung fibroblasts (HLFs). HUVECs spontaneously formed networks within 24 hours and the engineered perfusable vessels were mature and perfusable after 4 days. Despite the importance of hypoxia in tumour progression, as well as advances in modeling angiogenesis and vasculogenesis, these models have not previously been used to study hypoxia in metastatic tumours. Also, most pathology and gene-expression studies are performed on primary tumours, and little is known about hypoxia at the metastatic site. We, therefore, sought to investigate how hypoxia affects cancer metastasis from in vitro blood vessels. In this study, we show that three breast cancer cell lines cultured in normoxia, hypoxia, and with knock-down HIF