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Flexible electro-osmotic systems for healthcare

Neural engineering devices interact directly with the nervous system. They can be used to deliver drugs with neural targets to treat neurological disorders. Interfacing with the brain directly circumvents the blood brain barrier, but implanting a device results in tissue inflammation, which can affect the function and decrease the lifespan of the devices, as well as potentially damaging the brain. Smaller devices produce smaller inflammatory response and also allow precise spatial targeting of treatments. For instance, microfluidics-based neurally-implanted devices can deliver antiepileptic drugs automatically in response to early signs of a seizure, in precise amounts to the correct brain region. This allows the drugs to act faster and with fewer side effects than systemically administered drugs can.
To deliver precise amounts of drugs in response to brain activity or external inputs, we need a way to drive flow through these devices with high spatial and temporal resolution. Electroosmosis can be used to drive flow of drugs on a micro scale in a tightly controlled manner, without requiring any moving parts which would wear down over time.

Applying an electrical current produces electrokinetic flow through a channel, with a plug-like velocity profile that makes it suitable for driving flow though channels of small dimensions. Electroosmosis is the movement of a bulk solution in a microchannel in response to an externally applied voltage. When a voltage is applied across the ends of the channel, it generates an electric field parallel to the channel walls. The channel walls become charged, which leads to the formation of an electrical double layer at the interface between the channel wall and the electrolyte: ionic solutes are adsorbed onto the walls, forming a fixed-charge layer at the surface of the membrane. Adjacent to this 'rigid' layer, there forms a corresponding layer of opposite charge in the electrolyte solution, composed of a mobile diffuse layer of ions, the 'diffuse double' layer. When a potential difference is applied, this mobile layer of ions is attracted to the oppositely charged electrode and the ions move and forcing the bulk liquid along with them due to shear viscosity and the cohesive nature of water. This movement of the bulk liquid is the electroosmotic flow.
An electroosmotic device would be subject to a number of constraints. To drive flow with classical electroosmosis, using a direct current, the voltage required is high enough that it produces unwanted reactions such as electrolysis of water, which can be dangerous in vivo. The fixed charge layer also becomes increasingly thick over time, which reduces the effectiveness of the electrodes. Additionally, as the final application is going to be in vivo, the materials all need to be biocompatible, and made from materials that allow minimally invasive implantation.

So in my project, I've fabricated a flexible AC electroosmotic pump, that works at low voltages. I have also optimised it to maximise the speed of the flow it produces while staying within the limitations.
My device design is based on Yang et al.'s 2009 paper, which has a periodic array of symmetric electrodes connected in an asymmetric fashion.
My design has four main components: the microfluidic channel, the electrodes, the electrical connections from the electrodes to the function generator, and the fluidic connections from the ends of the pump to the input and output.

For the channel, I designed a mould in SolidWorks and 3D printed it in a biocompatible resin. After cleaning, UV-crosslinking and parylene coating of this mould, I poured PDMS, a flexible biocompatible polymer, into the resin mould, and cured it in the oven. The channel is removed from the mould immediately before attaching it to the substrate that holds the electrodes. The substrate is subjected to ozone plasma treatment, which improves the bonding integrity by creating highly reactive -OH groups on the surface of the substrate. After testing, the initial mould was adapted twice, firstly allow simultaneous casting of multiple channels and so the device could fit under the higher-powered objective lenses of the microscope, then again to accommodate the fluidic connections with greater integrity. For the electrodes, I designed a mask in AutoCAD, for five separate pumps on the same substrate. The mask is used to deposit gold electrodes onto the surface of the substrate. In this first design, each pump has a 152-electrode array in the middle. The electrodes are periodically offset, to allow two electrodes in each period to connect to the AC signal, one to ground, with the remaining one floating to act as a spacer. This asymmetry in electrical connections allows the otherwise symmetrical electrodes to generate net flow along the channel under AC stimulation.

I then created a second design that would allow greater versatility in changing the electrical connections. In the second design, the geometry and the arrangement of the electrodes are the same, but the connection of each electrode can be changed individually so linear arrangement of electrode connections is possible. This also allows control over the number of electrodes across which current is applied.

I bonded the tabs on the electrodes to an FPC cable. The pins on the FPC cable are too closely spaced to allow direct connection to the function generator, so the other end of the cable is attached to a circuit board, and pins soldered to the circuit board allow attachment of crocodile clips in the first case, and connection to a breadboard in the second case.
The two ends of the channel are connected to flexible polymer tubing using the modified tips of dispensing needles. This allows fluid to enter and leave the channel, which in the final device would mean a drug solution entering from a reservoir and exiting into the target region in the brain. A syringe can be used to test the integrity of the bonding and the connections, as well as to replace the fluid in the channel.

Alongside the design and fabrication, I also developed techniques to characterise flow through the device. The imaging equipment available in the lab meant I couldn't rely on tracking fluorescent particles, which is what is used in the majority of the literature. I found that polystyrene beads of 1 or 2 micron diameter were visible under the optical microscope I used the Manual Tracking plugin on ImageJ to characterise flow rates of particles along the channel. Videos taken of the channel during application of the signal are processed then uploaded to ImageJ, then the trajectory of individual particles tracked. The x-component of their velocities can then be taken and averaged or plotted. (show videos) This allowed me to determine the flow rate through the channel in different trials, produced by the application of different signals, and with different solutions.

As well as my fabrication and experimental work, I also created models of the device in COMSOL Multiphysics and ran studies to visualise the electrical and fluidic changes, and to simulate how these are affected by different changes to the channels. These models were 2D simplifications from two different views, one capturing variations with height above the

substrate, and another capturing variation with width across the channel. The base model had the same setup as my first design, with the periodically offset electrodes. I modified aspects of the model, for instance the channel width or the number of electrodes, and computed a study of each model to determine the flow rate produced by the device.

Both the experimental and simulation data showed the same shape of profile for flow rates in the channel. There is a non-linear increase in velocity from a minimum directly next to the channel wall, where the fixed charge layer is. As the velocity increases away from this, it reaches a plateau maximum at which the majority of the solution is moving. This is the uniform flow profile of electroosmotic flow described in the literature, that makes electroosmosis preferable over hydrodynamic flow.

Using the results across many trials, I determined the changes to the parameters that would maximise flow rate within the constraints, and produced a model of an optimised pump. This pump produced flow at 360 times the rate of the initial design.

The agreement of the experimental and simulation results with each other and with the literature suggests that the fabrication, characterisation, experimentation and simulation work have all been successful. The techniques, guidelines and models developed in the course of this project can also be used for other microfluidic and electroosmotic devices.