Microfluidics and BioMEMS, Design task 4. 10.2.2021

**Design task instructions for the 4th design task:**

Return as a single pdf document to the return box in my courses. **Maximum length of the answer is 2 pages**. Formulae written with word or other text editor are preferred but I will accept hand-written formulas and answers. If you do not have a scanner, then if you can take a good photograph and make a good-looking pdf out of that then that is acceptable.

This task is worth **10 points** on the course. **The deadline is in 3 weeks, 3.3.2020 10:00**.

There will be a possibility to receive optional **tutoring** on this task, either **wed 17.2 15-16 or fri 19.2 9-10**. There will be a Zoom link in the lecture tab. You do not need to reserve timeslot, first come first served basis (although if there are many students I will limit time for each student).

2pt. The overall presentation of the solution is clear and it is returned on time.

2pt. There is a good drawing of the chip, explaining its channel architecture, the inlets and outlets and what is pumped in and at what flow rates.

2pt. Basic parameters, as given in the task, are calculated and presented.

4pt. The chip design and calculations would either lead to a possibly working chip OR the design, calculations and arguments show that such a chip would likely not work very well.

**The main answer that you are returning is the design of a microfluidic chip that** fits the criteria given in the task. The design means the dimensions of the microfluidic channel, and its architecture and specifications of the chip as explained in the instructions.

**There is no single correct solution.** If you cannot make a design that satisfies all criteria, then make a design that satisfies some of them and clearly identify where the design fails and why. Such a design can still be worth points as per the criteria above. **It is possible that satisfying all requirements of the chip is impossible** i.e. it is not possible to fulfill all of them. In that case, make your own best compromise and make it clear you have understood that this is the case.

In the "official" time budget, you have about 10-15 hours reserved for this task.

**NOTE: this final one is by far the most difficult.** You have seen the component parts and other tips and tricks in the previous design tasks, lectures and exercises. But to put them all together is not trivial since you can no longer independently change just one thing…at least not easily.

**If you cannot quite put it all together, you should still submit a partial solution!** Make it clear in the solution what you have achieved and what were your problems in putting the next piece together. Clearly stating your problem in getting stuck is also a sign of understanding and will be rated as such.

**Task 4:**

**The Briefing:**

Dear Mr./Ms. NN. We are a group from the University of Biosciences working together with the Capitol Area Central Hospital (CACH) in searching for new biomarkers for identifying metabolic disorders and diseases.

In recent years, more and more attention has been given to the metabolites contained in exosomes. Exosomes are small extracellular vesicles that contain proteins, peptide, DNA, RNA and metabolites. Their biological function is currently not yet fully understood. Interestingly, for example in blood, the metabolic profile in the exosomes can greatly differ from the metabolic profile of the blood itself.

We are studying exosomes in *blood samples* from both animals and patient samples. The exosomes need to be separated from both blood cells and, as much as possible, from the metabolites in blood. This way we can focus in on the metabolites contained in the exosomes only. The current method to separate the exosomes from other components in blood is ultracentrifugation. That is, however, very slow and laborious process and the recovery % of exosomes is usually only about 10%. We have been thinking, would it be possible to design a microfluidic chip based on diffusion effects?

Our **requirement** is that **all cells are removed** from the exosomes. They are very detrimental for the analysis. For the **small metabolites** in blood, we would like to **dilute them at least by a factor of 2,** the more the better!

Otherwise, the higher the throughput (volumetric flow rate) of the blood the chip can take the better. The higher the recovery (% of exosomes from the blood recovered into the exosome outlet) the better. The higher the dilution of blood metabolites, the better.

We have many syringe pumps available, 100 kPa is the maximum pressure. Any volumetric flow rate can be set with these pumps, as long as the maximum pressure is not exceeded.

**The task:**

Design a chip based on sequential H-filter structures to separate exosomes from both small metabolites and cells in blood as well as possible. See Lecture 3 and exercise 3 for background information on diffusion calculations and Lecture 1 and exercise 1 and 2 for background information on flow resistance calculations.

The parameters for these three classes of analytes are given below:

**Small metabolites in blood**. Size: 1-10 nm, Diffusion coefficient: ≈ 1000 $\mu m^2/s$

**Exosomes.** Size: ≈ 50 nm – 100 nm. Diffusion coefficient ≈ 10 $\mu m^2/s$

**Cells.** Size: ≈ 3µm-30µm. Diffusion coefficient ≈ 0.01 $\mu m^2/s$

For your design, we can use these threshold values (**these are completely invented by me for this exercise**). In a symmetrical H-filter (equal flow rate in all channels):

1. If an entity travels for >3x the channel width during its stay in the channel, then mixing is complete.

2. If an entity travels for <0.1x the channel width during its stay in the channel, then there is no mixing at all for that molecule.

3. If an entity travels for >0.1x but <3x, you can yourself make up an estimate the amount of the sample that you think could go to both sides of the channel. Your estimate needs to be consistent with rules 1 and 2 above.

**Your fabrication process** allows you to make channels with rectangular cross sections of any size between 1µm and 500 µm. You can have many different depths if you need. You can also have multilevel chips (channels that bypass each-other by going over/under each-other).

**Your answer should include your chip design that fulfills the tasks and also include answer to the following specs of your chip:**

Calculate/estimate the recovery of exosomes. Meaning of those exosome that were in the original blood, how many of them go to your exosome outlet?

What is your throughput? (The volumetric flow rate of blood at the inlet.)

What is the dilution factor of the metabolites, meaning, how much of the small metabolites there are in the exosome outlet compared to the original blood inlet?

Calculate the pressure inside your system and make sure it does not exceed 100 kPa. If analysis of the full chip is difficult, estimate it from one path with the highest flow resistance.

Estimate of the footprint your chip, meaning its physical size? Preferentially it should be few cm x few cm.

**Tips:**

You will notice that separating exosomes from cells is straightforward but separating them completely from the metabolites is not possible. Can you figure out how to dilute the metabolites?

Focus on the filters and diffusion first, worry and fix the hydraulic resistances later. The channel architecture and the H-filter designs are worth the most points.

Design a chip based on H-filters. Draw the inlets and outlets and the channels. One inlet should be for the blood sample, the other inlets are likely for pure buffer. The cells, exosomes and remaining small metabolites each go to their own outlet(s). You can have extra dummy outlets if you need them.

A H-filter is the simplest to design when both incoming channels and both outgoing samples have the same flowrate. There is a trick to achieve this without long and difficult optimization of channel dimensions and hydraulic resistances everywhere on the chip. Look at the chip that

we analyzed in exercise 4, the resistance of which component determined the whole resistance of a flow path? And how could you utilize the same concept here to simplify your design,

**Most important tip:** Do not give up. This task can be difficult or even too difficult (I do not know 😊). If you cannot do it all, do some parts and return those!