ON THE FEASABILITY OF FOR USING A MULTI-PARAMETER SENSOR FOR THE INLINE CHARACTERISATION OF MEDICINE MIXTURES

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ABSTRACT

Initial investigations into the use of a MEMS based multi-parameter sensor for the characterization of medicine mixtures are presented. The current results show good results for density and mediocre results for heat capacity. Viscosity measurements have not yet produced any usable results. However there are clear flaws in the setup which could be the cause of this and which will not be present in the final integrated chip design.

KEYWORDS

Medical analysis, multi-parameter sensor, infusion, mass flow, density, heat capacity, viscosity, temperature.

INTRODUCTION

In hospitals medicine containing fluids fluids are commonly administered intravenously (IV), often combining multiple fluid lines into one single IV line. It is particularly important for prematurely born babies to keep the the number of access points to a minimum is as these neonates are very fragile and the risk of inflammation at the access site is high. IV therapy in this special patient group is associated with extreme low total flow rates and relatively high concentrations of medicines contained therein [1].

Although the combining of multiple single medicine IV lines through a manifold (multi-infusion) might seem relatively straight forward, the underlying physics can actually be quite complex. Multi-infusion can lead to undesired medication flow rates or even serious dosage errors. To understand these complex mixture flows and prevent adverse effects during therapy, a verification of the exact composition of the medicine mixture as well as the flow rate just before entering the patient is required [2].

The system requirements to measure a composed medicine flow are multiple: the measurement should be fast, accurate, real time, close to the admission site without affecting the medicines or medicine flow. Most of the current solutions for identifying components in a mixture fail at least one of these requirements (e.g. chromatography). Here we propose to utilize a MEMS based multi-parameter sensor, developed at the University of Twente, for checking the mixture on a set of specific physical parameters [3].

If the separate flows and the effects of the different medicines on the physical properties of the total flow are known, the properties of the total flow at the admission site can be predicted and compared against the actual measurements by using the multi-parameter sensor. Any deviation between measured and predicted values means the mixture is not as expected and could be reason for alarm.

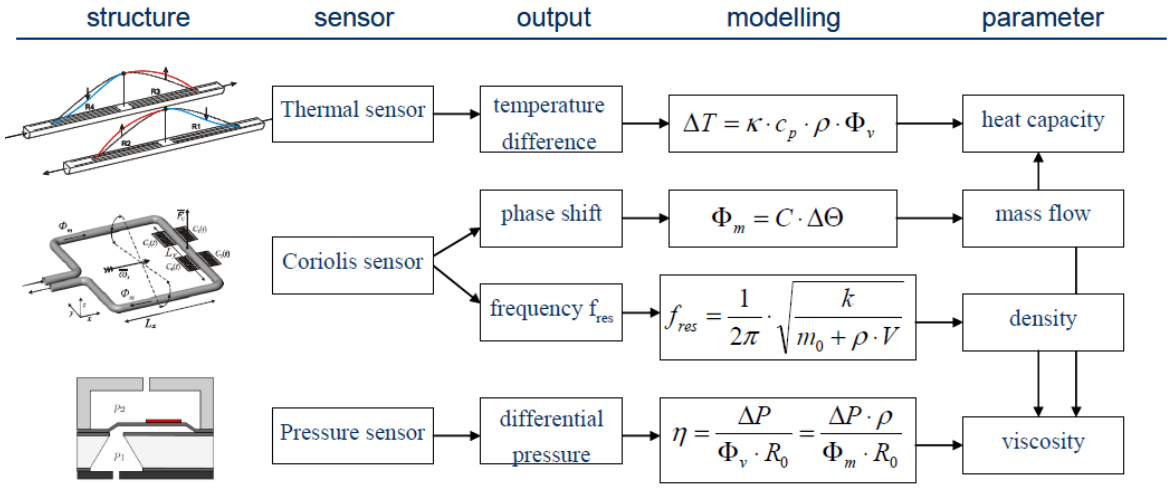

Figure 1 : Schemtic showing the different sensors and how the data combines to obtain the different physical parameters. Obtained from [3].

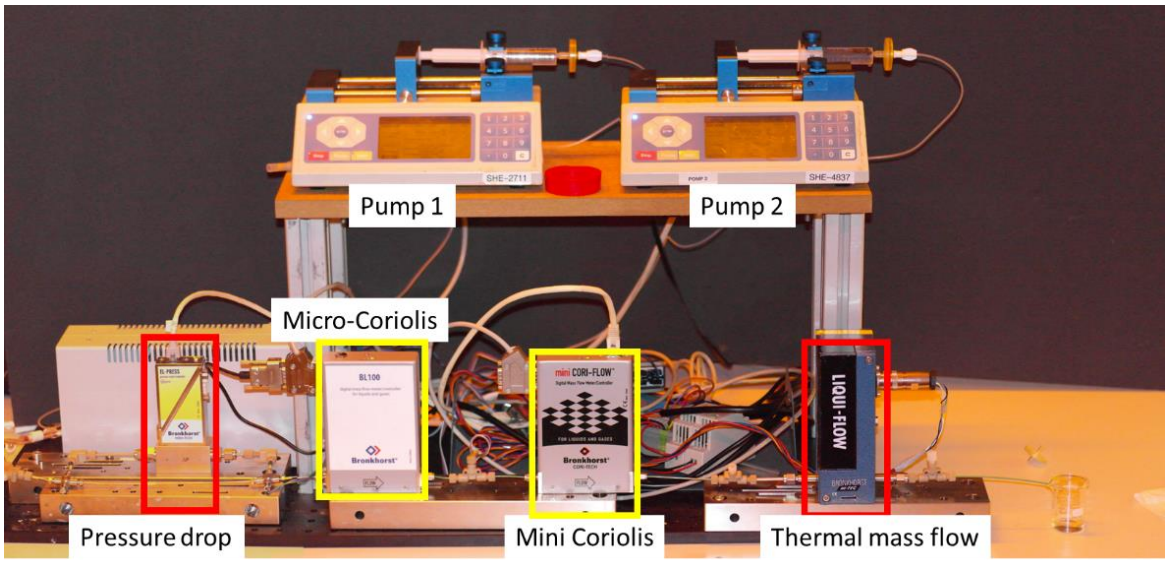

Figure 2: Overview of the multi parameter setup with two syringe pumps allowing the concentrations of binary mixtures to be changed during a measurement run. The measurement section of the setup contains a differential pressure sensor, a thermal mass flow sensor and two Coriolis sensors. The micro-Coriolis is a prototype MEMS sensor similar to the multi parameter chip being developed. All sensors were supplied by Bronkhorst HighTech BV [5].

THEORY

The chosen approach is to track medicine concentrations through their effect on the physical properties, such as density and heat capacity, of the fluid mixture. These effects are undocumented for medicines and first need to be determined for each separate medicine before mixtures can be characterized.

The density and mass-flow of a liquid can be measured directly using a Coriolis sensor, but for the other parameters of the multi-parameter sensor multiple measurement signals need to be combined (see Figure 1). The heat capacity is obtained from combining the thermal mass-flow and Coriolis mass-flow sensor and for the viscosity even three signals are used, namely differential pressure, Coriolis mass-flow and Coriolis density.

Because we are dealing with low mass fraction solutions it is expected that a linear mixing model can be used. A linear mixing model implies a linear relation between concentration and a change in physical properties as well as an adding of effects when multiple medicines are combined. Taking the density of water as the base density the total density can then be defined as follows [4]:

$$\rho_{mix} = \rho_w \left(1 + \sum_i c_{\rho i} \cdot w\%_i\right)$$

Here ρ_{mix} is the total density of the mixture, ρ_w is the density of water, $w\%_i$ are the mass fractions of the different dissolved medicines and $c_{\rho i}$ are the effects of these medicines on the density of the mixture. Similar equations exist for the heat capacity and the viscosity of the mixture.

METHODS

The current prototype of the MEMS multiparameter chip (BL100, [5]), containing only the Coriolis mass-flow and density sensor, is combined with a separate thermal mass flow sensor (LiquiFlow, [5]), and a differential pressure sensor (EL-Press, [5]), to simulate the final design of the multi-parameter sensor[1]. The medicine mixture is created by combining two separate medicine flows from two syringe-pumps [6] whose mixing ratio can be changed during the experiment (see Figure 2).

RESULTS

Initial experiments are aimed at verifying the linear behavior of the physical properties as a function of medicine concentration and to characterize the slopes of these relations. As an example Figure 3 shows the change in heat capacity as the weight

[1] The focus of this research is not the chip itself but an investigation into the feasibility of using the MEMS-chip to detect the required medicine concentrations. For further information on the workings of the chip and its ongoing development the reader is directed to other talks and posters at this conference.

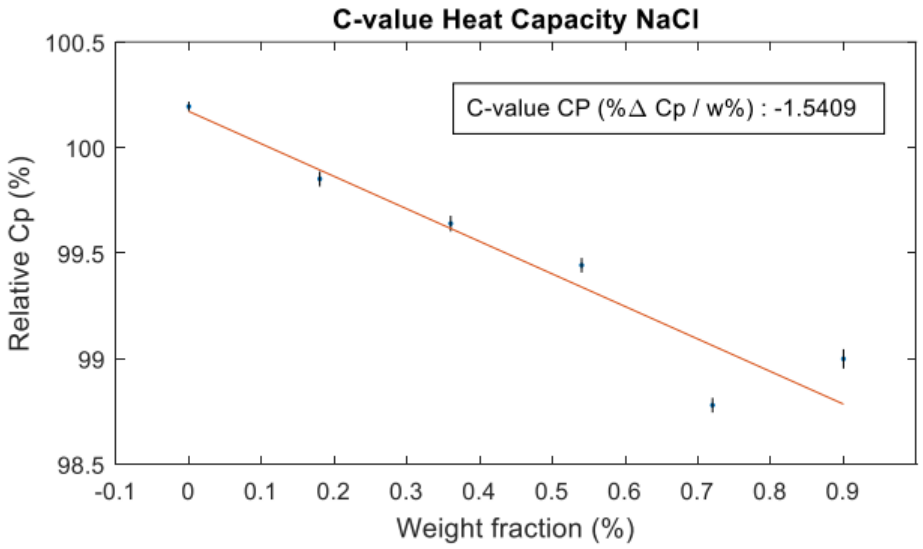

Figure 3: a measurement series showing the dependence of the relative heat capacity (with respect to pure water) as a function of the weight fraction of a medical salt solution.

fraction of NaCl in solution increases. Though the data does seem to indicate a linear effect, the scatter in the data for weight fractions higher than 0.5% is still too high. A possible reason is that heat capacity is based on the signal of two different sensors which are still situated some distance apart in our current setup. Similar measurements were performed for viscosity but the results are as of yet unsatisfactory and are thus not shown here.

In contrast, Density does show a linear relation to the mass concentration. This can be seen in Figure 4 where a 1.25% Dobutamine solution is phased out in exchange for a 4% Dopamine solution. The two pure solutions and the intermediate mixed steps show a linear trend in density indicating that the linear model holds for mixtures.

DISCUSSION

Relative heat capacity seems a useful measurement parameter as it showed a nice linear relation with weight fraction of a salt solution for fractions smaller than 0.5%. Density also has a linear relation to the mass concentration. However, similar measurements on viscosity are still unsatisfactory, probably caused by the strong temperature dependence of fluid viscosity. This effect may be reduced by integrating the pressure difference sensor into the multi-parameter sensor in order to minimize temperature gradients within the measurement section .

A second source of measurement errors is the physical distance between the three sensors from

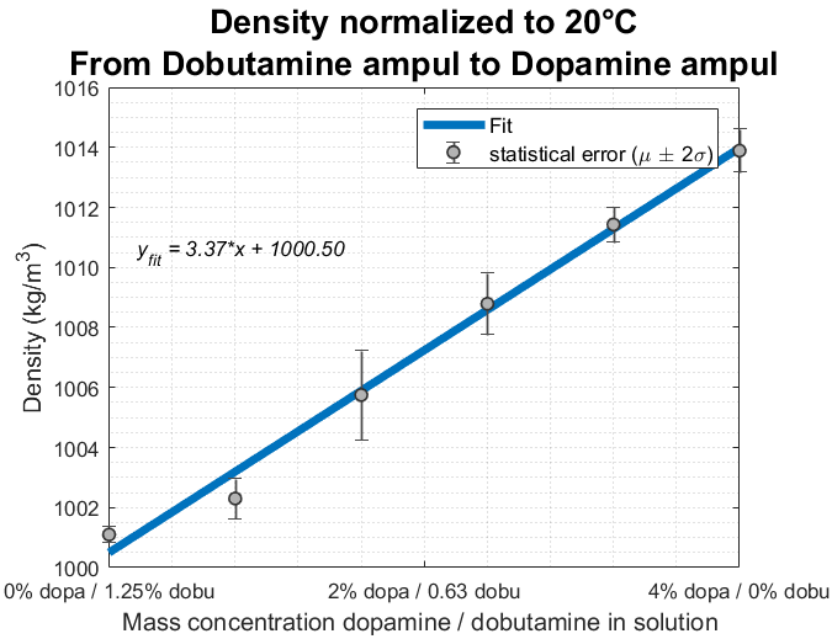

Figure 4: a measurement series showing density as a function of the concentration of Dopamine and Dobutamine. On the far left the mixture contains only Dobutamine which is linearly blended out in favor of Dopamine when moving to the right along the horizontal axis. It can be seen that in this two medicine mixture the density dependence is indeed linear. The total flow is kept constant during this measurement.

which the viscosity is calculated. Fluctuations in the composition of the flow will pass through the different sensors at different moments in time. This same effect is also present in the heat capacity measurement. Like the thermal gradient this phase shift between sensors is also expected to be significantly reduced when all sensors are combined on a single chip.

CONCLUSIONS

The linear mixing model has been shown to applicable in the medical range of medicine concentrations, both for single and binary solutions. The density and heat capacity have shown good and promising results respectively. Viscosity has been unreliable so far, probably due to temperature gradients within the setup. It is expected that on-chip integration will improve these results are gradients and delay effects will be strongly reduced.

REFERENCES

[1] A.C. van der Eijk, R.M.F.P.T. van Rens, J. Dankelman, B.J. Smit, “A literature review on flow-rate variability in neonatal IV therapy”, Pediatric Anesthesia, Vol. 23, pp. 9–21, 2013.

[2] A.M.D.E. Timmerman, B. Riphagen, J.H.G.M Klaessens, R.M. Verdaasdonk, “Confirmation of uncontrolled flow dynamics in clinical simulated multi-infusion setups using absorption spectral photometry”, Proc. of SPIE, Vol. 7556, pp. 75560U1-9

[3] J.C. Lötters, E. van der Wouden, J. Groenesteijn, W. Sparreboom, T.S.J. Lammerink and R.J. Wiegerink, “Integrated multi-parameter flow measurement system”, MEMS 2014, San Francisco, CA, USA, January 26 - 30, 2014, pp. 975-978.

[4] E. van der Wouden, J. Groenesteijn, R.J. Wiegerink, J.C. Lötters, “Multi Parameter Flow Meter for On-Line Measurement of Gas Mixture Composition”, Micromachines, Vol. 6, pp. 452-461, 2015.

[5] Bronkhorst High-Tech, Ruurlo, NL.

[6] Fusion 200, Chemyx Inc., USA.