Dimensioning of a new micro-needle for the dispense of drugs in tumors and cell clusters

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ABSTRACT

In medical treatment, there is a constant need to deliver active molecules into targeted cells, but this dispense is often difficult and time consuming. In order to improve the rapidity of dispense and its efficiency, a special injection needle has been designed. This micro-needle has a central channel and presents side exits uniformly distributed on the sides. The advantages of this type of needle is that drug delivery starts from all side exits disposed along the needle tip. For the best possible efficiency of the micro-needle, all side exits should have the same flow rate. Eventually, the needle may be used as an electrode to increase the uptake rate.

An inverse algorithm for the dimensioning of such a needle has been set up; this algorithm is based on a lumped model approach. We verify that it is numerically consistent with SABER direct calculation. Moreover the approach has been proved to be correct after micro-fabrication of such needles and verification that drug delivery requirements are met.

Keywords: microfluidics, needle, micro-channels, algorithm, lumped model

INTRODUCTION

Drug delivery of active molecules into targeted cells is often difficult and time consuming. For example, in cancerology, it has been shown that active molecules (iRNA or antisens) delivery to tumoral cells takes more than 48 hours for a 1 cm wide tumor and that an incomplete delivery leads to the regrowth of the tumor in a few days [1]. It is thus extremely important that all cells in a tumor are concerned by the diffusion and subsequent uptake of the injected molecules.

The standard procedure consists in injecting a small drop of buffer liquid containing the active molecules at the tip of a needle. After the injection, the active molecules diffuse inside the tumor. In fact, molecular diffusion takes place inside the small liquid gap separating the cells, which is called the extracellular space (ECS). At the same time, the ECS is very narrow - less than 5 µm - and presents an important tortuosity (fig 1) [2].

Thus the diffusion time from the injection point to the targeted cells is long [3]. An apparent diffusion coefficient can be derived from the cluster topology and is shown to be more than two times smaller than the real (free space) diffusion coefficient [4] and frequently even far much smaller [5].

In order to improve the speed of dispense and its efficiency, a special injection needle has been designed and patented [6]. This micro-needle has a central channel and presents side exits uniformly distributed on the sides. The advantages of this type of needle is that the drug delivery starts from all the side exits disposed along the needle tip. If we want the best possible efficiency of the micro-needle, all side exits should have the same flow rate, i.e. upon injection all the micro-drops located at exits should be the same as schematized in figures 2 and 3.
As it has been observed that an electric field increases the uptake rate [7], the needle can be electrically actuated [8]. However, in the present paper, we discuss only the microfluidic aspects.

**ALGORITHM**

In this problem, the number of unknowns - the $N$ widths $\{a_i, i = 1, N\}$ of the $2N$ side channels - is important and it would have been very difficult to determine these unknowns by an optimization method based on direct calculation. We have rather considered an inverse problem. Using a lumped element model for modeling all the different microfluidic segments in the needle, and imposing the constraint that the flow rate at all exits is identical, we derive a recurrence relation for the pressure at the nodes that we solve to obtain the desired channel widths.

**Step 1: Velocities in the axial (central) channel**

Let the letters $P_1$, $Q_1$, $V_1$, $V_1^*$ stand respectively for the pressure, flow rate, fluid velocity in the central channel, and in a side channel. The density of the liquid is $\rho$. Because of the process of fabrication of the needle, the vertical dimension of the micro-channels $b$ is the same for all the channels. For most efficient drug dispersion, the spacing $L$ (axial distance) between the side channels is constant, and for simplicity during fabrication, the width $a_0$ of the main channel is a given constant; as a consequence, the length of the side channels is also a constant $L_s$. A schematic view of the flow channels is indicated in figure 4.

Because there are $2N$ exits, the total mass conservation equation gives

$$Q_i = (2N)Q_2,$$  

(1)

where indices 1 and 2 refer respectively to the inlet and outlet. By a recurrence approach, starting from the far end of the needle and progressing to the front end, we obtain

$$V_i = \frac{2Q_2}{\rho a_0 b} (N - i), \quad i = 0, \ldots, N - 1$$  

(2)

**Step 2: Pressure at the axial nodes**

The pressure drop for a cylindrical channel is given by Washburn’s law. In a capillary of length $L$ and hydraulic radius $R_h$ in which a fluid of viscosity $\eta$ flows with an average velocity $V$, the pressure drop is given by

$$P_e = P_s + \frac{8\eta L V}{R_h^2}$$  

(3)

For a rectangular capillary of cross dimensions $a$ and $b$, the pressure drop has a similar form as (3) with some corrections depending on the value of $\lambda = b/a$

$$\Delta P = \frac{8\eta L V}{a^2} g(\lambda)$$

where the function $g(\lambda)$ is defined by using the Heaviside function $H$

$$g(\lambda) = \left(\frac{1 + \lambda^2}{\lambda}\right) H(4.45 - \lambda) + \frac{3}{2} H(\lambda - 4.45)$$

At an intersection, there is a distortion of the laminar flow lines. This problem is complex in a rectangular geometry [9,10] and we simplify by

$$\Delta P \text{int,cr} = \frac{8 \eta (13a) V}{a^2} g(\lambda)$$

and in a side branch, the linear pressure drop is reduced to

$$\Delta P \text{linear} = \frac{8 \eta (L - 4a) V}{a^2} g(\lambda)$$

So that the pressure drop of a side branch is

$$\Delta P = \Delta P \text{linear} + \Delta P \text{int,cr}$$

$$= \frac{8 \eta (L + 9a) V}{a^2} g(\lambda)$$  

(4)

Again, we start from the last node in the axial channel and apply the equation (4) to obtain the pressure at this last node.
\[ P_N = P_o + \frac{8\eta (L_s + 9a_s)}{a_s^N} V_N^* g(\lambda_N) \]

where \( V_N^* \) is the velocity in the \( N \)th side branch and \( P_o \) the pressure at the outlets (atmospheric pressure). By replacing the flow velocity by the flow rate in the \( N \)th side branch, the pressure can be cast into the form

\[ P_N = P_o + \frac{8\eta (L_s + 9a_s)}{b a_s^3} Q_s g(\lambda_N) \]

Now, we progress towards the front end of the axial channel, and deduce the recurrence relation

\[ P_i = P_o + \frac{8\eta (L_s + 9a_s)}{b a_s^3} Q_s g(\lambda_N) \]

\[ + \frac{8\eta LQ_s}{b a_o^3} g(\lambda_o)(N-i)(N-i+1) \]  

We have found a recurrence relation for the pressure at the nodes versus the widths of the side channels; this relation has been obtained by considering the velocities in the axial main channel only (to the exception of the last side channel). The pressures at the nodes are now calculated using the side channels.

**Step 3: Pressure at the nodes (from side channels)**

The pressure at a node is directly related to the outside pressure by the relation

\[ P_i = P_o + \frac{8\eta (L_s + 9a_s)}{b a_i^3} Q_s g(\lambda_i) \]  

At this stage, if the widths \( \{a_i, \ i = 1, N\} \) were known, the hydrodynamic behavior of the micro-system would be totally determined.

**Step 4: Solution**

The next step is to find an inverse solution for the \( a_i \). The solution is obtained by equating the values of the pressure at the nodes from (5) and (6)

\[ \frac{(L_s + 9a_s)}{a_i^3} g(\lambda_i) = \frac{(L_s + 9a_s)}{a_N^3} g(\lambda_N) \]

\[ + \frac{L}{a_o^3} g(\lambda_o)(N-i)(N-i+1) \]  

For any given value of the width of the last side channel \( a_N \), the right hand side of the previous relation is known, and we find the implicit relation for the \( a_i \) of the type

\[ \frac{(L_s + 9a_s)}{a_i^3} g(\lambda_i) = B_i \]  

where \( B_i \) is the value of the right hand side (which depends only of the width of the last side channel). The inverse solution is then reduced to an implicit solution of an analytical function, and this is tractable. Depending on the value of the \( \lambda_i \) one has to solve either one of these two third-order polynomials

For \( \lambda_i > 4.45 \)

\[ \frac{2}{3}B_i a_i^3 - 9a_i - L_s = 0 \]

For \( \lambda_i < 4.45 \)

\[ (B_i a_i^3 - (L_s + 18b) a_i^2 - b(2L_s + 9b)a_i = L_s b^2 \]

It can be shown that these two polynomials have one real root and 2 imaginary roots, so that the real root is the desired solution. It is interesting to note that the fluid viscosity \( \eta \) does not appear in equation (7) nor the value of the total flow rate \( (Q_s) \), so that the calculated dimensions of the micro-system will satisfy the constraint of delivering the same flow rate at the outlets for different fluids and different inlet flow rates. That shows a generality in the system. Another advantage of this method is that it is straightforward to change the angle between the main and side channels by changing the pressure drop expression at an intersection, and replacing (4) by

\[ \Delta P = \frac{8\eta (L + 9 a \sin^2 \alpha)V}{a^2} g(\lambda) \]

For \( \alpha = 90^\circ \), formula (10) is the same as (4). Figure 5 shows that the distribution of the \( a_i \) in the case of 2 x 10 side channels, for a value of \( a_{10} = 30 \mu m \).

**NUMERICAL VERIFICATION**

Before starting the fabrication step, we have used the SABER code from the COVENTOR package to numerically verify the accuracy of the algorithm. The verification approach is the following: the different widths of the side channels are produced by the preceding algorithm. They are then used as inputs for the SABER calculation. If the algorithm is valid, the results should agree. It is checked in the figure 6 that the SABER results agree well with the algorithm results.
REALIZATION AND VERIFICATION

Micro-needles based on the results of the dimensioning algorithm have been realized in silicon using microtechnologies for silicon etching and assembling (fig 7). Needles of different sizes (from 500µm to 300 µm) and with different side channel angles have been fabricated (fig. 8).

Fig 7. Top: View of the needle; bottom: detailed view of an axial cut

Fig. 8. Microscope views of an axial cut of the needle

Using methyl blue colored water and disposing the needle on a flat blotter, it is checked that all the flow at all exits are identical (fig 9).

Fig 9. Visualization of equal flow rates at all exits

CONCLUSION

A new micro-needle with many side exits - instead of one unique at the tip - has been developed for in vivo applications. Such a needle facilitates the dispersion of active molecules in cell clusters and tumors and increases the efficiency of electric methods for cellular uptake. The dimensioning of the needle has been performed by developing an inverse algorithm based on a lumped model for the hydrodynamics inside the micro-channels. This algorithm has been numerically checked against SABER numerical results and has proved to give very satisfactory experimental results. On an applicative standpoint, our next task is to test this micro device in living tissue and assess the benefit of this micro needle in the context of drug delivery to targeted cells.

REFERENCES