Diffuse approximation for identification of the mechanical properties of microcapsules

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Abstract
A novel data-driven real-time procedure based on diffuse approximation is proposed to characterize the mechanical behavior of liquid-core microcapsules from their deformed shape and identify the mechanical properties of the submicron-thick membrane that protects the inner core through inverse analysis. The method first involves experimentally acquiring the deformed shape that a given microcapsule takes at steady state when it flows through a microfluidic microchannel of comparable cross-sectional size. From the mid-plane capsule profile, we deduce two characteristic geometric quantities that uniquely characterize the shape taken by the microcapsule under external hydrodynamic stresses. To identify the values of the unknown rigidity of the membrane and of the size of the capsule, we compare the geometric quantities with the values predicted numerically using a fluid-structure-interaction model by solving the three-dimensional capsule-flow interactions. The complete numerical data set is obtained off-line by systematically varying the governing parameters of the problem, i.e. the capsule-to-tube confinement ratio, and the capillary number, which is the ratio of the viscous to elastic forces. We show that diffuse approximation efficiently estimates the unknown mechanical resistance of the capsule membrane. We validate the data-driven procedure by applying it to the geometric and mechanical characterization of ovalbumin microcapsules (diameter of the order of a few tens of microns). As soon as the capsule is sufficiently deformed to exhibit a parachute shape at the rear, the capsule size and surface shear modulus are determined with an accuracy of 0.2% and 2.7%, respectively, as compared with 2–3% and 25% without it, in the best cases (Hu et al. Characterizing the membrane properties of capsules flowing in a square-section microfluidic channel: Effects of the membrane constitutive law. Phys Rev E 2013; 87(6): 063008). Diffuse approximation thus allows the capsule size...
and membrane elastic resistance to be provided quasi-instantly with very high precision. This opens interesting perspectives for industrial applications that require tight control of the capsule mechanical properties in order to secure their behavior when they transport active material.

Keywords
Identification, mechanical properties, microcapsules, data-driven method, diffuse approximation

1. Introduction
A capsule is a liquid droplet enclosed within a thin elastic membrane. Capsules are found in nature in the form of cells or eggs, but they can also be artificially synthesized for a number of industrial and clinical purposes [1, 2]. The pharmaceutical [3], textile [4], cosmetic [5], and food industries [6] make a wide use of artificial capsules to control the release of active ingredients (drugs, cells, viruses, …), aromas, or flavors. The capsule radius is typically micrometric, ranging from a few microns to a few tens of microns.

Whether natural or artificial, capsules are always in suspension in an external fluid, which subjects the capsules to hydrodynamic forces when it flows and leads to their deformation. The dynamic behavior of capsules is thus governed by three-dimensional fluid-structure interactions, in which the membrane plays a crucial role. It ensures the protection and transport of the internal content, the control of its potential release and the deformability of the capsule thanks to its thinness and elastic resistance. However, the small size and fragility of the microcapsule make the assessment of its mechanical properties a challenging task. Different experimental methods exist to deform micrometric capsules and estimate their mechanical properties. For individual cells and vesicles, micropipette aspiration is the most used technique [7]. The mechanical properties are obtained by aspirating the particle into a micropipette at different pressure conditions and measuring the resulting deformation. Atomic force microscopy can also be used to deform capsules under known forces [8]. More recently, techniques have been developed for capsule populations in suspension, based on microfluidic experiments. These techniques involve flowing the capsules through a microchannel in order to apply inverse analysis techniques to the observed deformed profiles [9–11].

In all these cases, a numerical model is needed to determine the values of the mechanical properties. For the microfluidic experiments, numerical simulations based on the resolution of complex fluid-structure interactions [12–14] provide the deformed profile of the capsules at steady state. However, identifying the mechanical properties of a capsule by comparing its deformation with that obtained in the numerical simulations remains challenging. None of the existing studies has proposed a consistent method to solve the inverse problem.

In this work, we present a fast, accurate, self-contained technique for inverse analysis using a data-driven method based on the diffuse approximation [15]. We focus on experimental data obtained by flowing a microcapsule in a microfluidic square-section channel of comparable size. The experimental data consist of the capsule velocity and mid-plane profile at steady state, from which we deduce geometric quantities (e.g. maximum extension length and axial length) that are characteristic of it. Numerical models of this exact problem exist [13, 16]. That by Hu et al. [13] is used off-line to obtain a complete numerical data set of the three-dimensional steady-state shapes adopted by the capsule inside the microchannel for a wide range of values of input parameters: the size ratio, which corresponds to the capsule-to-tube confinement ratio, and the capillary number, which represents the the ratio of the viscous friction force acting on the capsule to the restoring membrane elastic force. A database of two-dimensional capsule profiles (cross-cuts) is obtained from these numerical simulations, along with their geometric quantities. The algorithm used to identify the mechanical properties of the capsules consists of applying the diffuse approximation method to the numerical database to deduce the size ratio and capillary number that correspond to the measured values of the geometric parameters of the capsule profile.

2. Materials and methods

2.1. Problem description
We consider an initially spherical capsule of radius $a$ flowing within a long prismatic microchannel with constant square cross-section of side $2\ell$ (Figure 1). The thin membrane of the capsule is made of an impermeable hyperelastic isotropic material with surface shear modulus $G_S$. As the capsule flows, the hydrodynamic forces
inside the channel gradually deform its membrane (Figure 2). Eventually, the capsule reaches a steady-state shape that is a function of the constitutive law of the membrane and two independent parameters:

- The capillary number \( \text{Ca} \), defined as
  \[
  \text{Ca} = \frac{\mu U}{G_S},
  \]
  where \( \mu \) is the viscosity of the external liquid and \( U \) is the mean axial velocity of the undisturbed Poiseuille flow;
- The size ratio \( a/\ell \) between the capsule radius and the channel cross-dimension.

Our objective is to obtain the value of \( G_S \), which is the mechanical property that governs the capsule membrane behavior.

### 2.2. Experimental procedure

A suspension of polydisperse ovalbumin microcapsules of average diameter equal to 50 µm and of submicronic membrane thickness is prepared as described in [17] and injected into a microfluidic system at different flow rates using a syringe pump. The microfluidic system consists of a straight channel of square section, 5 mm in length and \( \ell \sim 50 \) µm. It is fabricated in polydimethylsiloxane (PDMS) following the procedure provided in [18, 19]. The motion and deformation of each capsule is observed using a microscope connected to a high-resolution high-speed camera. Two-dimensional side-view grayscale images of capsules are obtained as they flow in the microchannel (Figure 3(a)). More technical details of the experimental setup can be found in [9, 10].

The deformed profile of the capsules acquired experimentally can be characterized by geometric quantities that we normalize using the channel characteristic size \( \ell \) (Figure 4). The inverse analysis algorithm proposed here requires the measurement of only two of those quantities:

- The maximum extension of the capsule along the longitudinal axis \( L_z/\ell \);
Figure 4. Some geometric quantities that can be measured from the capsule deformed profile: the maximum extension $L_z$ along the $z$-axis, the axial length $L_a$, and the parachute depth $L_p = L_z - L_a$ (if any).

- The axial length $L_a/\ell$.

Together, they provide the information on the parachute depth, $L_p = L_z - L_a$ (Figure 4), which measures the concavity at the rear part of the capsule, and has been shown to relate well with the global deformation of the capsule [20]. It is, however, not appropriate to use it as one of the two geometric parameters, as the errors in its estimation are much larger than those for $L_z$ and $L_a$.

The other quantity obtained experimentally is the velocity of the center of mass of the capsule $v_0$. It is determined at steady state by measuring the position of a specific point on the membrane on successive time frames. Three quantities are, however, unknown:

- The membrane surface shear modulus $G_S$;
- The capsule radius $a$, which varies greatly from one capsule of the suspension to the next;
- The mean undisturbed external flow velocity $U$, which is impossible to know with precision, since the flow rate provided by a syringe pump always fluctuates a little over time.

2.3. Equations governing the forward fluid-structure interaction problem

The inertialess flow of the deformable micrometric capsule along the channel is obtained by solving the Stokes equations in the external ($\beta = 1$) and internal ($\beta = 2$) fluids, together with the membrane equilibrium equation. For the fluid problem, let $\bm{v}^{(\beta)}$, $\sigma^{(\beta)}$, and $p^{(\beta)}$ be the velocity, stress, and pressure fields in the two fluids, non-dimensionalyzed using $\ell$ as characteristic length, $\ell/U$ as characteristic time, and $G_S \ell$ as characteristic force. The Stokes equations

$$\nabla p^{(\beta)} = Ca \nabla^2 \bm{v}^{(\beta)}, \quad \nabla \cdot \bm{v}^{(\beta)} = 0, \quad \beta = 1, 2. \quad (2)$$

are solved in the domain shown in Figure 1, assuming no flow disturbance far from the capsule (i.e. the velocity field is the one in the absence of capsules at the inlet and outlet of the square channel), a no-slip boundary condition on the channel wall and capsule membrane, and the continuity of the normal load on the capsule membrane:

$$\left(\sigma^{(1)} - \sigma^{(2)}\right) \cdot \bm{n} = q, \quad (3)$$

where $\bm{n}$ is the unit normal vector pointing toward the external fluid and $q$ is the non-dimensionalyzed external load per unit area exerted by the fluids on the membrane due to viscous traction. For the solid problem, let $\tau$ be the non-dimensionalyzed Cauchy tension tensor, which corresponds to the forces per unit arclength in the plane of the membrane. The local equilibrium equation governing the inertialess membrane is then

$$\nabla_s \cdot \tau + q = 0, \quad (4)$$

where $\nabla_s \cdot$ is the surface divergence operator.

2.4. Numerical model

Equations (2) and (4), along with the boundary conditions, are solved using the numerical model described in [13]. This model, hereafter referred to as the BI–FE model, couples the boundary integral method, to solve the
Figure 5. Values of $Ca$ and $a/\ell$ included in the database. The domain where a steady-state capsule deformation exists is delimited by the black line for the case of capsules following the neo-Hookean constitutive law \[21\].

Figure 6. Values of $v_0/U$ as a function of $Ca$ and $a/\ell$.

fluid flows, with the finite-element method, to solve the membrane mechanics. It is used to obtain an extensive database of steady-state shapes of capsules in flow. The values of the parameters $Ca$ and $a/\ell$, as well as the constitutive law that governs the capsule membrane behavior, are the input parameters of the numerical model. The neo-Hookean law, whose strain-softening behavior under large deformations has proven to be appropriate to describe ovalbumin capsules \[9\], is considered here to model the membrane. The deformed profile of the capsule at steady state and the velocity ratio $v_0/U$ are some of the outputs of the model.

A database of $M = 137$ three-dimensional steady-state deformed capsules has been generated using the numerical model. The different values of $Ca$ and $a/\ell$, for which the simulations have been computed, are shown in Figure 5, and their associated values of $v_0/U$ are represented in Figure 6. We shall call $T$ the set of points $\theta^i = (\theta^i_1, \theta^i_2, \theta^i_3)$, where the superscript $i$ (for $i = 1, \ldots, M$) refers to the $i$th capsule simulation, where $\theta^i_1$, $\theta^i_2$, and $\theta^i_3$ refer to its corresponding values of $Ca$, $a/\ell$, and $v_0/U$, respectively. The representation of the points of $T$ in the $\theta$-space shows that they all lie on a surface $S_T$ (Figure 7). The profiles of all the shapes in the plane $x = 0$ have then been obtained, for comparison with the experimental profiles. For each of them, the geometric quantities of their deformed profiles have been computed and added to the database. We shall call $L$ the set of points $\lambda^i = (\lambda^i_1, \lambda^i_2)$, where the superscript $i$ (for $i = 1, \ldots, M$) identically refers to the $i$th capsule simulation, and where $\lambda^i_1$ and $\lambda^i_2$ refer to its corresponding values of $L_z/\ell$ and $L_a/\ell$, respectively (Figure 8(a)).

2.5. Inverse analysis approach

The inverse analysis method presented here characterizes the mechanical behavior of the capsule membrane by determining the value of its surface shear modulus $G_S$, as well as the capsule radius $a$ and the mean undisturbed external flow speed $U$, using two steps described further next. From the geometric quantities measured experimentally ($L_z/\ell$ and $L_a/\ell$) and with the help of the database computed using the BI–FE model, we first use a
diffuse approximation technique to obtain the unknown values of the capillary number $Ca$ and the size ratio $a/\ell$, which are the two independent parameters on which the capsule deformation depends. Knowing $Ca$ and $a/\ell$, we then determine the velocity ratio $v_0/U$ by interpolating the numerical results of Figure 7. The surface shear modulus $G_S$ is finally deduced from the values of $Ca$ and $v_0/U$ using equation (1), since the velocity of the capsule center of mass $v_o$ is estimated from the acquired images and the viscosity of the external liquid $\mu$ is measured prior to conducting the experiments.

2.6. Diffuse approximation

Only the two independent parameters of the problem, $Ca$ and $a/\ell$, are considered when applying the diffuse approximation method. We shall call $\hat{\mathcal{T}}$ the reduced set of points $\hat{\theta} = (\theta_1, \theta_2)$. From Figure 8(a), one can notice that the points of $\mathcal{L}$ are inclined. To apply the diffuse approximation more easily, a rotation of $-45^\circ$ around the axis perpendicular to the plane defined by $\mathcal{L}$ and centered on $(0,0)$ is applied. We shall call $\mathcal{L}'$ the set of points $\lambda'$ (Figure 8(b)). The points of $\hat{\mathcal{T}}$ and $\mathcal{L}'$ define, respectively, the surfaces $S_{\hat{\mathcal{T}}}$ and $S_{\mathcal{L}'}$. We deduce that any point not present in the database ($\lambda'/\ell \notin \mathcal{L}'$) but lying on the surface $S_{\mathcal{L}'}$ corresponds to admissible geometric quantities that may be obtained experimentally [22].

Using diffuse approximation techniques [15], we map an arbitrary point $\lambda' \notin \mathcal{L}'$ on the surface $S_{\mathcal{L}'}$ to a corresponding point $\hat{\theta} \notin \hat{\mathcal{T}}$ on the surface $S_{\hat{\mathcal{T}}}$. The idea is to use this mapping to estimate the unknown values of $Ca$ and $a/\ell$, knowing the values of the experimentally measured geometric quantities $L_z'/\ell$ and $L_a'/\ell$. To achieve this, diffuse approximation makes use of a local weighted least squares fitting that is valid in a small neighborhood around $\lambda'$ and is based on the points included within it (Figure 9). Within this domain centered on $\lambda'$, the coefficients $\lambda_j'$ ($j = 1, 2$) can be locally approximated by

$$\lambda_j' = p(\theta)^T a' = \begin{bmatrix} 1 & \theta_1 & \theta_2 \end{bmatrix} \begin{bmatrix} a_0' \\ a_1' \\ a_2' \end{bmatrix}, \quad (5)$$
where $\mathbf{p}$ is a vector of independent polynomial functions and $\mathbf{a}'$ are the approximation coefficient vectors. From a mathematical point of view, it is only valid to use first-order polynomial terms, since only two independent parameters are approximated.

To approximate $\lambda'$, we weight the contribution of the points $\lambda''_i (i = 1, \ldots, M)$, contained in the elliptical neighborhood, proportionally to the distance $d$ between the points $\lambda''_i$ and $\lambda'$. Distances are computed as

$$d^i = \left( \sum_{j=1}^{2} \gamma_j (\lambda''_j - \lambda'_i)^2 \right)^{1/2}.$$  

The parameters $\gamma_j$ (for $j = 1, 2$) are equal to 1 in the case of a circular neighborhood but, in the present case, we used $\gamma_1 = 1$ and $\gamma_2 = 0.05$ to suit the elongated shape of the surface $S_{L'}$ (Figure 9).

The weight assigned to each $\lambda''_i$ is chosen to be

$$w(D) = \begin{cases} 2D^3 - 3D^2 + 1, & \text{if } D \leq 1 \\ 0, & \text{otherwise} \end{cases},$$  

where the normalized distance $D = d^i / \delta$ is 0 for a point in the center of the neighborhood ($d^i = 0$) and 1 for a point located at its boundary ($d^i = \delta$). The value of $w(D)$ ranges from 1 to 0, decreasing monotonically as $D$ increases (Figure 10). To ensure that the system of equations (see next) is not overdetermined, the neighborhood must include more points $\lambda''_i \in L'$ than the number of elements in vector $\mathbf{a}'$ (i.e. $N > 3$ in this case). To meet this constraint, the neighborhood is chosen to have a variable size, but to keep its elliptical shape with fixed proportions in order to always include $N = 14$ points regardless of the position of $\lambda'$ in $S_{L'}$. This is achieved by setting $\delta$ (the distance to the boundary of the neighborhood) as the $N$th largest distance of $d^i$.

To find the vectors $\mathbf{a}'$, diffuse approximation uses least squares to minimize the following function $J$:

$$J(\mathbf{a}', \mathbf{a}^2) = \frac{1}{2} \sum_{n=1}^{N} w(d_n) \left( \sum_{j=1}^{2} (\lambda''_j - \mathbf{p}(\hat{\mathbf{a}})^T \mathbf{a})^2 \right).$$
This results in
\[
da^j = (P^T WP)^{-1} P^T WL^j,
\]
where \(P\) is an \(N \times 3\) matrix containing the vectors \(p\) of the \(N\) points included inside the neighborhood; \(L^j\), for \(j = 1, 2\), are two vectors containing the \(N\) values of \(\lambda'_j\) of the points in the neighborhood; and \(W\) is an \(N \times N\) diagonal matrix with the values of the weights associated with each point in the neighborhood:
\[
P = \begin{bmatrix} p(\theta_1) \T \\
p(\theta_2) \T \\
\vdots \\
p(\theta_N) \T \end{bmatrix}, \quad L^j = \begin{bmatrix} \lambda'_1 \\
\lambda'_2 \\
\vdots \\
\lambda'_N \end{bmatrix}, \quad W = \begin{bmatrix} w_1 & 0 & \cdots & 0 \\
0 & w_2 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & w_N \end{bmatrix}.
\]

Once the vectors \(a^1\) and \(a^2\) are known, \(\hat{\theta}\) can be computed by
\[
\hat{\theta} = A^\dagger X,
\]
where
\[
X = \begin{bmatrix} \lambda'_1 - a_0^1 \\
\lambda'_2 - a_0^2 \\
\vdots \\
\lambda'_N \
\end{bmatrix}, \quad A = \begin{bmatrix} a_1^1 & a_2^1 \\
a_1^2 & a_2^2 \end{bmatrix}
\]
and \(A^\dagger\) is the Moore–Penrose pseudoinverse of \(A\).

2.7. Interpolation

The diffuse approximation allows us to estimate the values of \(\text{Ca}\) and \(a/\ell\) for any arbitrary point \(\lambda' \not\in \mathcal{L}'\) but the quantity \(v_o/U\) remains unknown. To estimate it, we apply a Delaunay triangulation on \(\mathcal{S}'\) and identify the triangle corresponding to \(\hat{\theta}\) by projecting it onto \(\mathcal{S}'\). The velocity ratio \(v_o/U\) is obtained by calculating the weighted average of the values of \(v_o/U\) at the three vertices of the triangle [23]. The weights are the ratio between the area of the subtriangle formed by the projected point and two vertices of the triangle and the area of the entire triangle.

3. Results

3.1. Validation of the method for an ovalbumin capsule

By way of illustration, we estimate the values of \(\text{Ca}\), \(a/\ell\), and \(v_o/U\) for the ovalbumin microcapsule depicted in the middle of Figure 3(a). The input geometric quantities required by the method are the ones measured using the software \textit{ImageJ}: \(L_c/\ell = 2.14\) and \(L_a/\ell = 1.81\). The resulting output values provided by the inverse analysis method are \(\text{Ca} = 0.082\), \(a/\ell = 0.96\), and \(v_o/U = 1.29\). Since this case was not part of the database, we deduce the corresponding numerical profile by weight-averaging the profiles of the \(N = 14\) neighbors. The superposition of the experimental image with the estimated numerical profile is shown in Figure 3(b). The very good qualitative correspondence of the measured and predicted capsule profiles is consolidated by the maximum distance between both sets of points (i.e. the Hausdorff distance normalized by \(a\)), which is currently 0.066. This validates the use of the diffuse approximation method for mechanical identification.

3.2. Error estimation in the entire parameter space

An algorithm has been designed to assess the accuracy of the solutions \(\theta\) provided by the method. A series of \(M\) test sets \(\mathcal{L}'_i\), for \(i = 1, \ldots, 137\), has been generated in such a way that \(\mathcal{L}'_i = \mathcal{L} - \{\lambda'\}\). For each test set \(\mathcal{L}'_i\), we thus remove a point \(\lambda'\) that emulates an experimental result. By applying the described method, \(\theta' = (\text{Ca}, a/\ell, v_o/U)\) is obtained. It is expected to have the same value as \(\theta' \in \mathcal{T}\). The relative errors between \(\theta\) and \(\theta'\) are computed as
\[
\epsilon'_j = \frac{\left|\theta'_j - \theta^j\right|}{\theta^j},
\]
An overview of the resulting relative errors is provided for each parameter in Figure 11 by heat maps. The errors are generally higher along the borders of the domain than in the central region, especially for Ca. Previous studies showed that the identification method is only robust for sufficiently deformed capsules \cite{10, 20}. Those studies based the criterion of reliability of the method on a global capsule stretch ratio $\Lambda = P/2\pi a$, with $P$ being the perimeter of the deformed capsule profile and $2\pi a$ the capsule perimeter at rest. They choose $\Lambda > 1.04$ as a criterion (dashed black line in Figure 11).

If we only consider the cases that respect the criterion, we find mean relative errors equal to $\bar{\epsilon}_1 = 2.7\% \pm 4.1\%$ for Ca, $\bar{\epsilon}_2 = 0.2\% \pm 0.1\%$ for $a/l$, and $\bar{\epsilon}_3 = 0.2\% \pm 0.2\%$ for $v_0/U$ (despite the notation, one must note that the errors cannot be negative). We thus find that the errors are ten times smaller on $a/l$ and $v_0/U$ than on Ca.

4. Discussion

The high correspondence between the capsule profile measured experimentally and that identified from the numerical simulation using diffuse approximation (e.g. Figure 3(b)) indicates that the simulation is a very efficient technique to identify the mechanical properties of micrometric deformable capsules.

The mean error values indicate that the method is able to retrieve the unknown values of the microcapsule size $a$ (from $a/l$) and mean flow velocity $U$ (from $v_0/U$) with a precision well below 1%. As for the value of the surface shear modulus $G_S$ of the very thin microcapsule membrane, it is determined with a precision below 3%, which is remarkable for such small objects. The final precision in the determination of $G_S$ will additionally depend on the precision of the measurement of the viscosity $\mu$ of the suspending fluid, which is likely to be within a few percent \cite{20}.

The present results provide very interesting insight on the limit of the microchannel identification method. They show that the reliability criterion based on the global capsule stretch ratio $\Lambda$ is very relevant. The advantage is that $\Lambda$ is a quantity that can be determined from images acquired experimentally and can thus provide an indication of the level of deformation of the microcapsule membrane. The limiting value was defined as $\Lambda = 1.03$ for Hu et al. \cite{10}, which was corrected to $\Lambda = 1.04$ by Gubspun et al. \cite{20}. Figure 11, on which the lines $\Lambda = 1.04$ have been added for indication, shows that a good accuracy is reached, even for confinement ratios $0.70 \leq a/l \leq 0.85$. No such results were obtained in the previous studies, because the microcapsules are too little deformed in the range. The diffuse approximation method thus allows the domain of the validity of identification to be greatly extended.

There is only one zone where the identification method leads to high errors even though the criterion is satisfied: $a/l \geq 1.1$ and $Ca \leq 0.03$. It is firstly caused by the intrinsic very low value of the capillary number in this region: small variations in the estimation of Ca lead to greater relative errors, especially in the Ca range $[0.005, 0.04]$. Another cause is the abrupt changes in deformed capsule shapes that may happen for small increments of Ca when it is smaller than 0.02. Indeed, the capsule may not have a parachute shape ($L_p = 0$) for very small values of Ca. The large elliptical neighborhood (with $\mathcal{N} = 14$) thus contains the two kinds of deformed capsule profiles, some with a parachute and others without, which greatly impairs the identification precision.

**Figure 11.** Heat maps of the relative errors $\epsilon$, as a function of $Ca$ and $a/l$, when estimating (a) $Ca$, (b) $a/l$, and (c) $v_0/U$. The region to the left of the dashed black line indicates capsule stretch ratios $\Lambda \leq 1.04$. 

with $j = 1, 2, 3$. 

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When compared with previously developed inverse analysis procedures based on microfluidics [9, 10], much lower errors are currently found with the diffuse approximation technique. As soon as the capsule is sufficiently deformed, the capsule size and surface shear modulus are determined with an accuracy of 0.2% and 2.7%, respectively. Hu et al. [10] determined these quantities with an accuracy of 2–3% and 25% in the best cases. Similar precision in the determination of mechanical properties was found using micropipette aspiration. Zhelev et al. [24], for instance, estimated the accuracy to be within 25%. Using diffuse approximation for identification thus improves both the accuracy and the reliability of the results.

The present results have been obtained for the neo-Hookean law, since we were interested in applying the technique to characterize the mechanical properties of ovalbumin capsules. The method is, however, valid regardless of the constitutive law used and could be applied to any artificial or natural (micro)capsule. The only challenge to use it on cells, such as red blood cells, is purely experimental: the cells will indeed have to be flowed in a microchannel of about 10 \( \mu \text{m} \). The results will have to be analyzed using the numerical database obtained for the Skalak’s law [10], which has been shown to model well the membrane deformation of red blood cells [25].

5. Conclusion

We have presented a novel inverse analysis procedure that uses a data-driven diffuse approximation technique to identify the mechanical properties of microcapsule populations. This procedure is applied to the flow of a capsule through a long prismatic microfluidic channel of comparable size. The hydrodynamic forces inside the channel lead to the deformation of the membrane of the capsule, which eventually reaches a steady-state shape. The latter depends on the constitutive law of the membrane and two independent parameters: the capillary number \( \text{Ca} \) and the size ratio \( a/\ell \). Geometric quantities characterizing the deformed profiles of the capsules at steady state are determined from images acquired experimentally using a rapid camera mounted on a microscope.

The identification method is based on the results of numerical simulations of the fluid-structure interactions between the capsule wall and the fluid flows, obtained off-line. A comprehensive database of microcapsule deformed profiles and velocity ratios \( v_0/\text{U} \) has been generated using the BI–FE numerical model described in [13] for different values of \( \text{Ca} \) and \( a/\ell \). Diffuse approximation uses this database to efficiently estimate the unknown values of \( \text{Ca} \), \( a/\ell \), and \( v_0/\text{U} \) of each capsule from its characteristic geometric quantities, measured experimentally. Low errors are achieved over a wide range of values of the estimated parameters, which indicates that the method allows the surface shear modulus \( G_S \) of the microcapsule membrane to be determined with a precision below 3%. It opens interesting perspectives for industrial applications that rely on microcapsules to transport active material, and require a tight control of the capsule mechanical properties to secure the targeted delivery.

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References

[1] Barthès-Biesel, D. Motion and deformation of elastic capsules and vesicles in flow. Annu Rev Fluid Mech 2016; 48: 25–52.
[2] Ma, G, and Su, Z. Microspheres and microcapsules in biotechnology: Design, preparation and applications. Boca Raton, FL: CRC Press, 2013.
[3] Yih, TC, and Al-Fandi, M. Engineered nanoparticles as precise drug delivery systems. J Cell Biochem 2006; 97(6): 1184–1190.
[4] Nelson, G. Application of microencapsulation in textiles. Int J Pharm 2002; 242(1): 55–62.
[5] Miyazawa, K, Yajima, I, Kaneda, I, et al. Preparation of a new soft capsule for cosmetics. J Soc Cosmet Chem 2000; 51(4): 239–252.
[6] Gibbs, BF, Kermasha, S, Alli, I, et al. Encapsulation in the food industry: A review. Int J Food Sci Nutr 1999; 50(3): 213–224.
[7] Needham, D, and Zhelev, DV. The mechanochemistry of lipid vesicles examined by micropipet manipulation techniques. *Surfactant Sci Ser* 1996; 62: 373–444.

[8] Fery, A, and Weinkamer, R. Mechanical properties of micro-and nanocapsules: Single-capsule measurements. *Polymer* 2007; 48(25): 7221–7235.

[9] Chu, TX, Salsac, AV, Leclerc, E, et al. Comparison between measurements of elasticity and free amino group content of ovalbumin microcapsule membranes: Discrimination of the cross-linking degree. *J Colloid Interface Sci* 2011; 355(1): 81–88.

[10] Hu, XQ, Sévénié, B, Salsac, AV, et al. Characterizing the membrane properties of capsules flowing in a square-section microfluidic channel: Effects of the membrane constitutive law. *Phys Rev E* 2013; 87(6): 063008.

[11] De Loubens, C, Deschamps, J, Georgelin, M, et al. Mechanical characterization of cross-linked serum albumin microcapsules. *Soft Matter* 2014; 10: 4561–4568.

[12] Lefebvre, Y, and Barthès-Biesel, D. Motion of a capsule in a cylindrical tube: effect of membrane pre-stress. *J Fluid Mech* 2007; 589: 157–181.

[13] Hu, XQ, Salsac, AV, and Barthès-Biesel, D. Flow of a spherical capsule in a pore with circular or square cross-section. *J Fluid Mech* 2012; 705: 176–194.

[14] Lac, E, Barthès-Biesel, D, Pelekasis, NA, et al. Spherical capsules in three-dimensional unbounded Stokes flows: Effect of the membrane constitutive law and onset of buckling. *J Fluid Mech* 2004; 516: 303–334.

[15] Nayroles, B, Touzot, G, and Villon, P. Generalizing the finite element method: diffuse approximation and diffuse elements. *Comput Mech* 1992; 10(5): 307–318.

[16] Kuriakose, S, and Dimitrakopoulos, P. Motion of an elastic capsule in a square microfluidic channel. *Phys Rev E* 2011; 84(1): 011906.

[17] Edwards-Lévy, F, Andry, MC, and Lévy, MC. Determination of free amino group content of serum albumin microcapsules using trinitrobenzenesulfonic acid: Effect of variations in polycondensation pH. *Int J Pharm* 1993; 96(1–3): 85–90.

[18] McDonald, JC, and Whitesides, GM. Poly(dimethylsiloxane) as a material for fabricating microfluidic devices. *Acc Chem Res* 2002; 35(7): 491–499.

[19] Fiorini, G, and Chiu, D. Disposable microfluidic devices: Fabrication, function, and application. *BioTechniques* 2005; 38(3): 429–450.

[20] Gubspun, J, Gires, PY, De Loubens, C, et al. Characterization of the mechanical properties of cross-linked serum albumin microcapsules: Effect of size and protein concentration. *Colloid Polym Sci* 2016; 294(8): 1381–1389.

[21] Barthès-Biesel, D. Modeling the motion of capsules in flow. *Curr Opin Colloid Interface Sci* 2011; 16(1): 3–12.

[22] Meng, L, Breitkopf, P, Le Quilliec, G, et al. Nonlinear shape-manifold learning approach: Concepts, tools and applications. *Arch Comput Method Eng* 2018; 25: 1–21.

[23] Amidror, I. Scattered data interpolation methods for electronic imaging systems: A survey. *Journal of Electronic Imaging* 2002; 11(2): 157–176.

[24] Zhelev, DV, Needham, D, and Hochmuth, RM. A novel micropipet method for measuring the bending modulus of vesicle membranes. *Biophys J* 1994; 67: 720–727.

[25] Skalak, R, Tozeren, A, Zarda, RP, et al. Strain energy function of red blood cell membranes. *Biophys J* 1973; 13(3): 245–264.