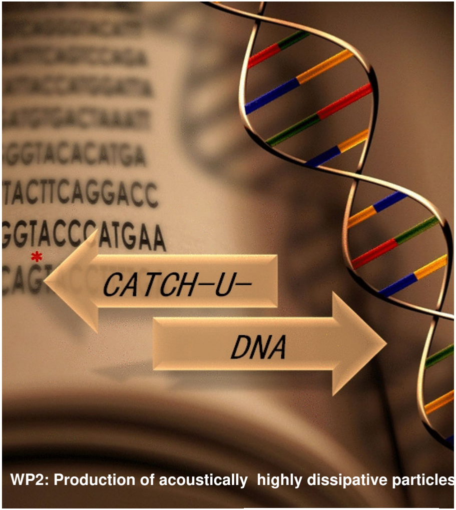


Partner involved →

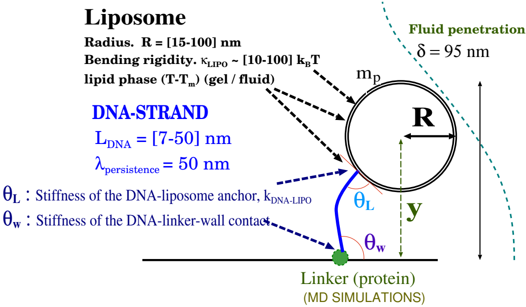
UNIVERSIDAD AUTONOMA DE MADRID

Rafael Delgado Buscalioni

Outline

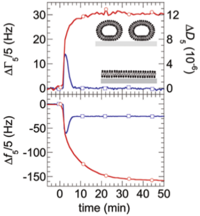
- M20. Molecular dynamics simulations QCM for streptavidin under GHz flow.
- M30. QCM analysis of liposome-DNA complex

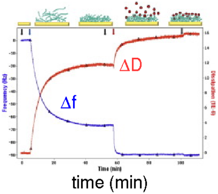
- Suspended dissipative particles
- Methods
- Comparison with experiments
- Analysis: ways to dissipate
  - Liposome
  - DNA
  - Coverage
- Conclusions and futher work



Adsorbed analytes.

Δf related to deposited mass and ΔD related to viscoelasticity.





Suspended analytes

How Δf and ΔD relate to "mass" and "dissipation" when then analyte is **NOT adsorbed**?.

# bp	L_{DNA} (nm)	ΔD/ΔF (10^{-6} Hz^{-1}) (L)	ΔD/ΔF (10^{-6} Hz^{-1}) (D_1)	ΔD/ΔF (10^{-6} Hz^{-1}) (D_2)	ΔD/ΔF (10^{-6} Hz^{-1}) (D_3)
157	53,4	0.0317	0.061	0.088	0.143
50	17,0	0.0181	0.044	0.062	0.113
21	7,1	0.0137	0.038	0.051	0.111

Table 1: ΔD/ΔF data for the specific binding of biotin-DNA of various lengths (L_{DNA}) to neutravidin (red), followed by liposomes (D_{1-3} = 50, 100, 200 nm) occurring through cholesterol-DNA (cholesterol placed at the opposite site of biotin). Ratios are averages of over 10 exp.; signal variation 10-15%. Device: QCM-D, 35 MHz. ΔD/ΔF data refer to low surface coverages.

Ring-down

$$x(t) = \Delta x e^{-2\pi\Gamma t}\cos(\omega t + \phi)$$

$$\omega = 2\pi f$$

$$D = \frac{2\Gamma}{f}$$

Impedance

$$Z = \frac{\text{wall stress}}{\text{wall velocity}}$$

$$Z = -\frac{\overline{\sigma}}{v_{wall}}$$

$$[Z] = \frac{\text{Mass}}{\text{Area} \times \text{time}}$$

Phasor

$$x(t) = x_R\cos(\omega t) + x_I\sin(\omega t)$$

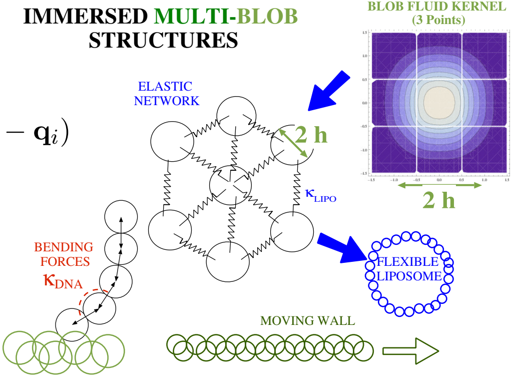
$$x(t) = \Re[\hat{x}\exp[-\mathrm{i}\omega t]]$$

$$\hat{x} \equiv x_R + \mathrm{i}x_I$$

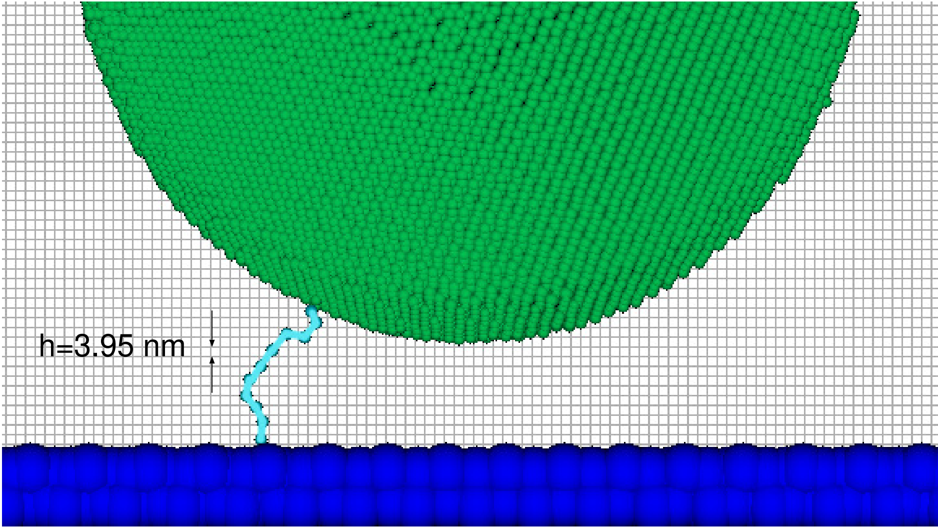
FLUAM: *Fluid And Matter*. GPU CODE
https://github.com/fbusabiaga/fluam

Fluid $\rho \frac{\mathrm{d}\mathbf{v}}{\mathrm{d}t} = -\nabla \cdot \mathbf{P} - \sum_i \boldsymbol{\lambda}_i \, \mathbb{S}(\mathbf{r} - \mathbf{q}_i)$

Blob $m_e \frac{\mathrm{d}\mathbf{u}}{\mathrm{d}t} = \boldsymbol{\lambda}_i + \mathbf{F}_i$



Excess-mass: $m_e = m - \rho \mathbb{V}$ (Archimedes)


h=3.95 nm

Unit-mapping with experiments

Unit length simulation: $\ell = 7.917\mathrm{nm}$

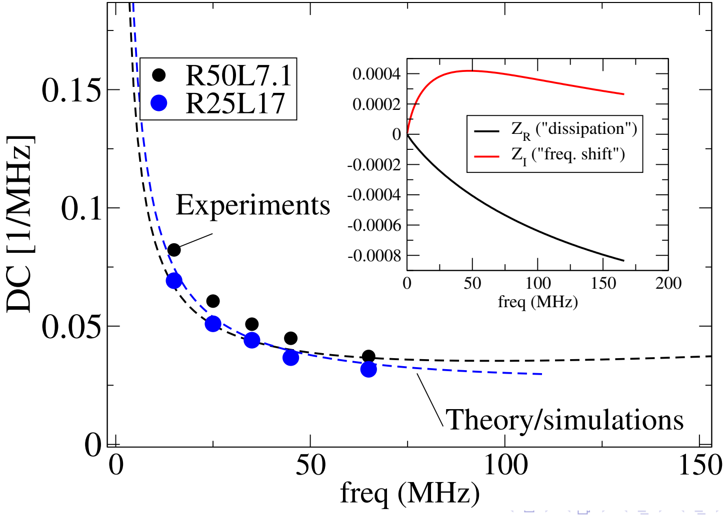
Magnitude	Simulation	International Units
ℓ	1	$7.917\mathrm{nm}$
Resolution	h	$\ell/2 = 3.95\mathrm{nm}$
Kin. viscosity	0.226	$10^{-6}\mathrm{m}^2/\mathrm{s}$
fluid density	1	$10^3\mathrm{kg}/\mathrm{m}^3$
sound velocity	2.68	$1.5 \times 10^3\mathrm{m/s}$
QCM frequency	$\mathbf{0.0005}$	$35\mathrm{MHz}$
$k_B T$	6.6×10^{-5}	$4 \times 10^{-21}\mathrm{J}$

Comparison with experiments: Acoustic Ratio.

- Experiments: POPC lipids with dsDNA at $T = 24^oC$.
- Simulations: impedance-velocity, $k_{lipo} = 100$, $h = 0.5$.

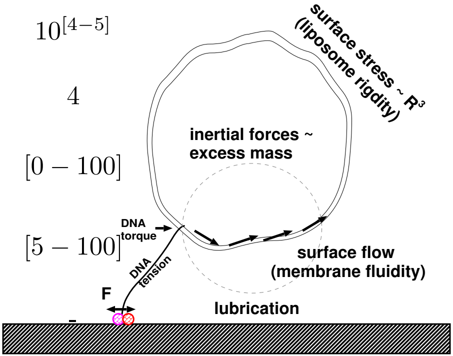
AR= [35MHz] x DC from SIMULATIONS			
Liposome Radius [nm]	DNA length= 50 nm	L_{DNA} = 17 nm	L_{DNA} = 7.1 nm
25	1.5 ± 0.5	1.3 ± 0.1	0.95 ± 0.01
50	3.0 ± 0.5	2.54 ± 0.05	1.68 ± 0.01
100	7 ± 1	5.6 ± 0.4	3.27 ± 0.07
AR= [35MHz] x DC from EXPERIMENTS			
25	2.2 ± 0.4	1.54 ± 0.05	1.33±0.05
50	3.2 ± 0.5	2.5 ± 0.2	1.78±0.05
100	6.0 ± 0.5	3.95± 0.05	3.85±0.05

- Experiments: POPC lipids with dsDNA at $T = 24^o C$.
- Simulations: impedance-velocity, $k_{lipo} = 100$, $h = 0.5$.



Impedances due different dissipation mechanisms

	element	Impedance	$kg/(m^2\ s)$
Wall-stress	Fluid	η/δ	$10^{[4-5]}$
Wall-Force	DNA	$\frac{50 k_B T x_0}{(L_{DNA}^2 L^2)}$	4
Inertia	Liposome	$m_e \omega / L^2$	$[0-100]$
Surface Stress	Liposome	$\frac{\eta R^3}{\delta^2 L^2}$	$[5-100]$
Surface flow	Liposome	-	-
Lubrication	Liposome	$\frac{1}{d}$	> 100

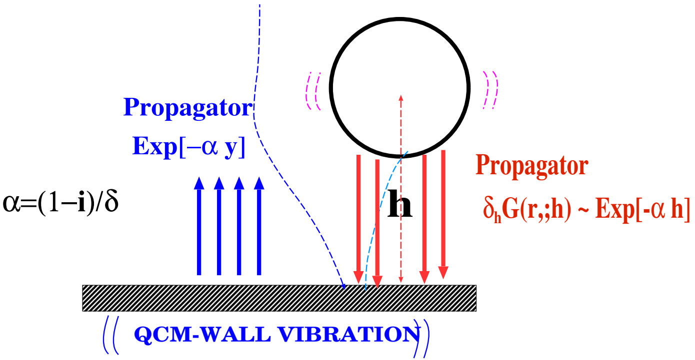


Liposome's perturbative flow

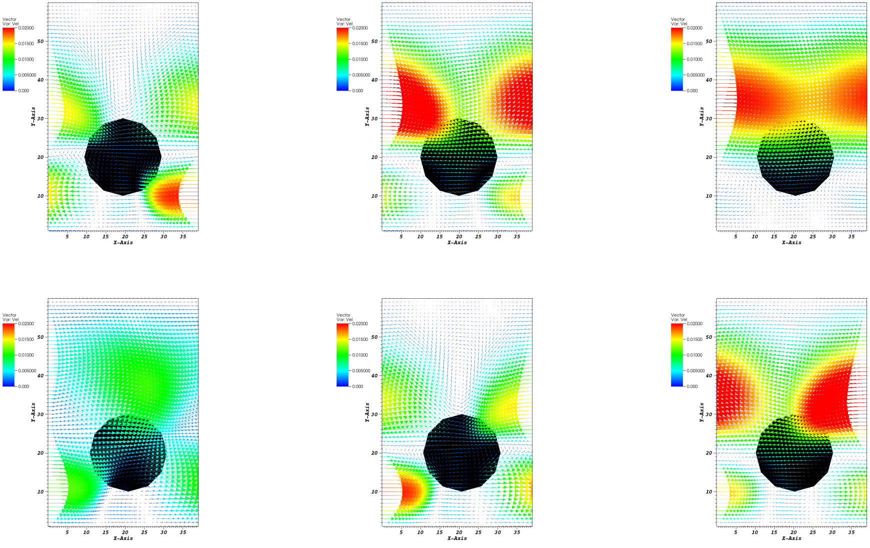
IMPEDANCE ~ $Z_S\, f(R/\delta)\, \mathrm{Exp}[-2\,\alpha\, h]$

Response-flow(r) = $[f_{LIPO}\, \delta_h G(r;h)]$ Base flow(h)

Base flow(y) = $e^{-\alpha y}$ wall-velocity



Liposome's perturbative flow



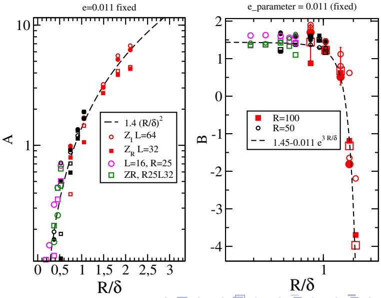
- Unsteady stresslet bounded flow: work against deformation

$$S_{xy}(y) = \frac{20\pi\eta R^3}{3}\,[B + \mathrm{i}A]\exp[-\mathrm{i}\alpha y]$$

- **Impedance**

$$Z^{(free)}(y) = Z_S\,[A + \mathrm{i}B]\exp[-2\mathrm{i}\alpha y]$$

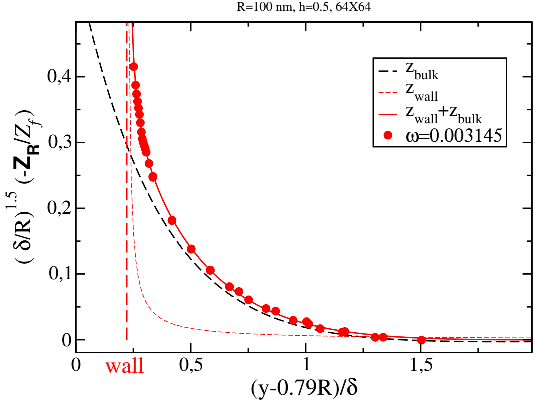
$$\begin{aligned} Z_S &= \frac{20\pi\eta R^3}{3\delta^2 L^2} = \frac{m_f}{\tau_\nu} \\ A &\approx 1.40\frac{R^2}{\delta^2} \\ B &\approx 1.45 - 0.01\exp[3.0R/\delta] \end{aligned}$$



Free liposomes (without DNA)

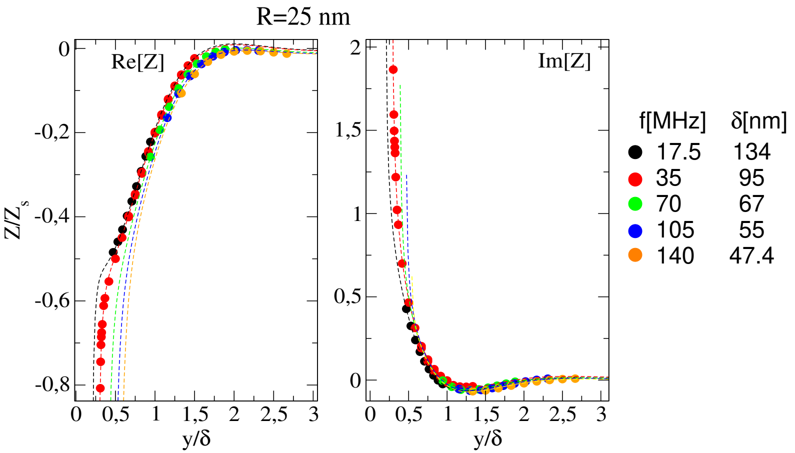
$$Z^{(free)} = \frac{20\pi\eta R^3}{3\delta^2 L^2}\left[(A+\mathrm{i}B)\exp[-2\alpha y] + \frac{C\delta}{(y-R)}\right]$$

Lubrication



Free liposomes (without DNA)

$$Z^{(free)} = Z_S \left[(A + \mathrm{i}B)\exp[-2\alpha y] + \frac{C\delta}{(y-R)} \right]$$



Free liposomes (without DNA)

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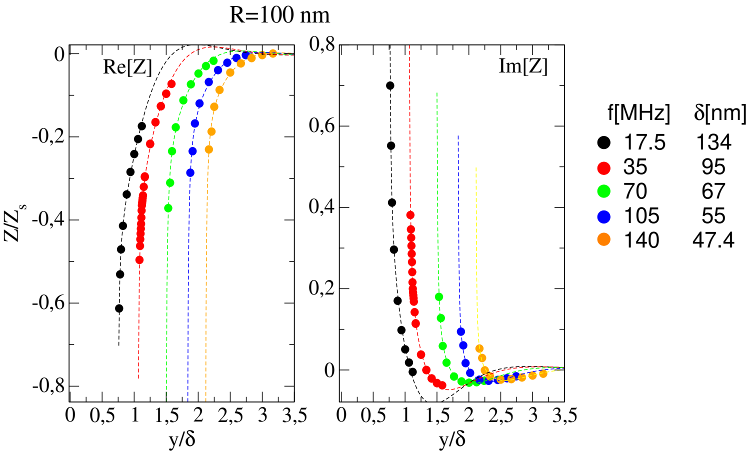


- Liposome elastic network: spring between neighbour beads κ_{LIPO}
- The liposome deforms more easily as $\downarrow \kappa_{\mathrm{LIPO}}$

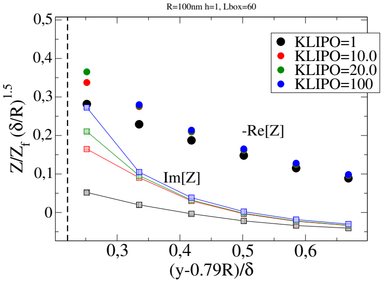
$$\downarrow \kappa_{\mathrm{LIPO}} \implies \downarrow \mathrm{impedance}(Z)$$

.

- But freq. shift $Im[Z]$ decreases more than dissipation $-Re[Z]$.

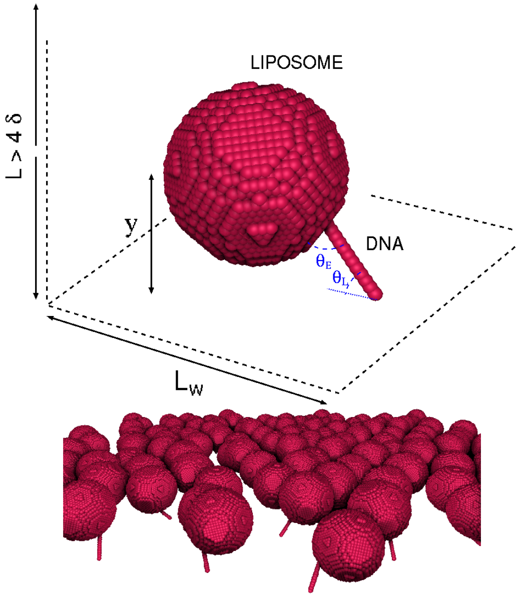
Thus, $\downarrow \kappa_{\mathrm{LIPO}} \implies \uparrow \mathrm{AR}$

- Theory and experiments in qualitative agreement



DNA effects

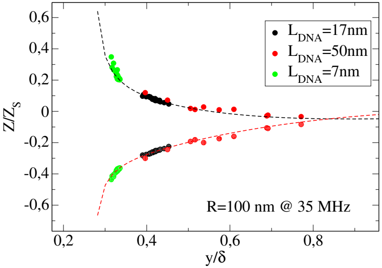
- **DNA contribution to impedance**: $Z^{(lipo-DNA)} - Z^{(free-lipo)}$
- **Neck**: DNA-liposome-cholesterol linker, DNA-tilt angle
- **Linker**: DNA-wall (protein); tilt angle



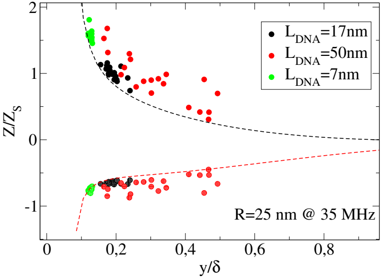
DNA contribution to impedance

- $\delta Z^{(DNA)} \equiv Z^{(Lipo-DNA)} - Z^{(free-Lipo)}$
- $\delta Z^{(DNA)} \sim RL_{dna}$
- $Z^{(A)}(y; R, L_{DNA}) = Z^{(free)}(y; R) + \delta Z^{(DNA)}(R, L_{DNA})$

$R = 100\text{nm}$



$R = 25\text{nm}$

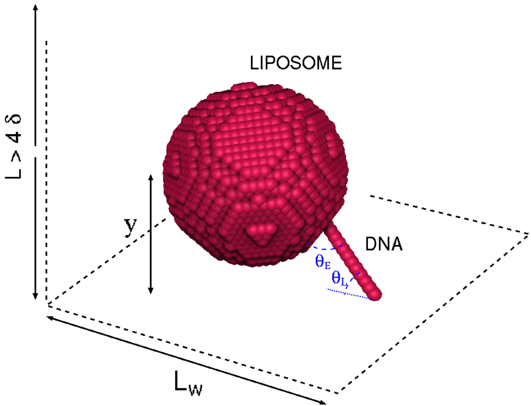


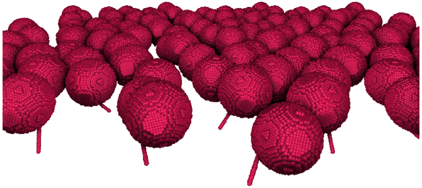
Many liposome-DNA's

$$\rho_L = \frac{N}{L^2}$$

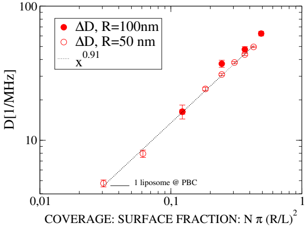
$$\phi \equiv \frac{N\pi R^2}{L^2}$$

- Δf and ΔD versus ϕ
- **Predict decrease of $\Delta D/\Delta f$ versus ϕ** (remains an open question in the literature)

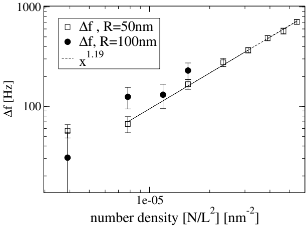




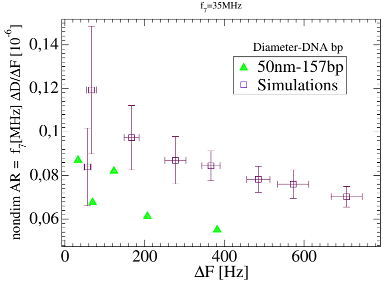
ΔD



$-\Delta f$



$-\Delta D/\Delta f$



Conclusions

- Hydrodynamics controls the dissipation and frequency shift of suspended particles
- Acoustic ratio is a complex quantity, not always indicating larger dissipation
- Dissipation ΔD is better suited for Limit of Detection (LOD) analyses
- Surface stress is the dominant hydrodynamic QCM-sensing effect of liposomes: increases like R^3
- Larger dissipation for shorter DNA strands (closer to surface)