
# IFB, Programmed Droplet Desolvation And Occam's Razor.

A Decade + of IBF Apps.

Induction vs Conduction. Directed Droplets vs Sprays.

IBF Apps: Making nL/pL Droplets; Crystals; Electrets and MS Sample Input

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# Introduction

In 2019 we presented a summary of work conducted over more than a decade on Induction Based Fluidics (IBF) at the November ASMS meeting in Philadelphia. This work showed applications including MALDI and SIMS sample placement, ESI sample introduction for both rapid infusion and UPLC MS where major increases in sensitivity were observed.

For MALDI the excellent crystals made via nanoLiter droplets presumably caused the major sensitivity increase, typically > 10 for MALDI of bradykinin  and 10-100x increase by SIMS for cocaine and RDX, as published by NIST. Also for complex mixtures of proteins and peptides at Genentech the 50 nL volume as shown to approach the sensitivity of a 1.0 uL aliquot of the same sample acquired identically.

For ESI, the 100% sample input with the pulsed nature of the device was shown to readily detect fg for all elements of the entire Lanthanide series as observed for +eV and –eV chelates. Excellent sensitivity was also shown for nucleosides acquired at the University of Cincinnati, as well.

The presentation also showed accurate nanoLiter dispensing reported by the US Army for application to “special” liquids. We also addressed in part fundamentals as to explaining why these enhanced sensitivity observations were made.

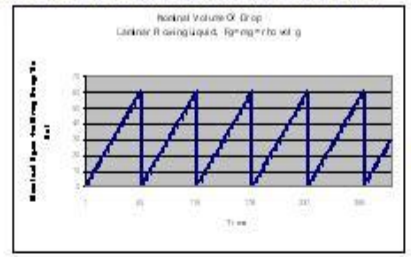
Here we further address IBF empirically and via fundamentals showing jpgs and videos of dispensing, drying  and related IBF processes in an attempt to come to an understanding of input and on-put as well as dispensing for MS and related applications of induction based fluidics as allowed by issues due to the covid-19 pandemic.

# IBF Theory

One IBF device, a flowing or stop flow system. There are many IBF embodiments

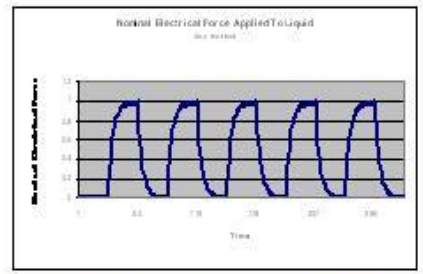
The liquid volume passing through a tube is given by the Hagen Poiseuille equation. The volume of fluid ($V$) that flows down a small-diameter capillary tube per unit of time ($t$) is proportional to the radius of the rube ($r$), the pressure pushing the fluid down the tube ($P$), the length of the tube ($l$), and the viscosity of the fluid n. Note v is linear in t.

$$V = ((\pi r^4 P)/8nl)t$$



Since electric fields can be rapidly toggled on and off, with great accuracy and precision, and since F= qE, the forces on liquid drops can be changed rapidly. Because F is a vector, we can direct the drop as well.

$$F = qE$$



For a charged drop with initial value, q0, with th e relaxation time, λ, where λ = (ε0εr / κ)
where ε0 is the dielectric constant of free space, εr is the relative permittivity and κ is the solution conductivity and t is time, we have q defined.

$$q = q_0 e^{(-t/\lambda)}$$

Now, a charged liquid drop in an electric field, cannot only experience the qE force, but of course it experiences, different forces as well in the atmosphere in x, y and z space depending on the specifics of the system. Using standard, well known physics, Newton's 2nd Law, we can equate the forces (electric, drag, buoyant, gravity and coulombic) acting on a drop to those acting in the direction x as,

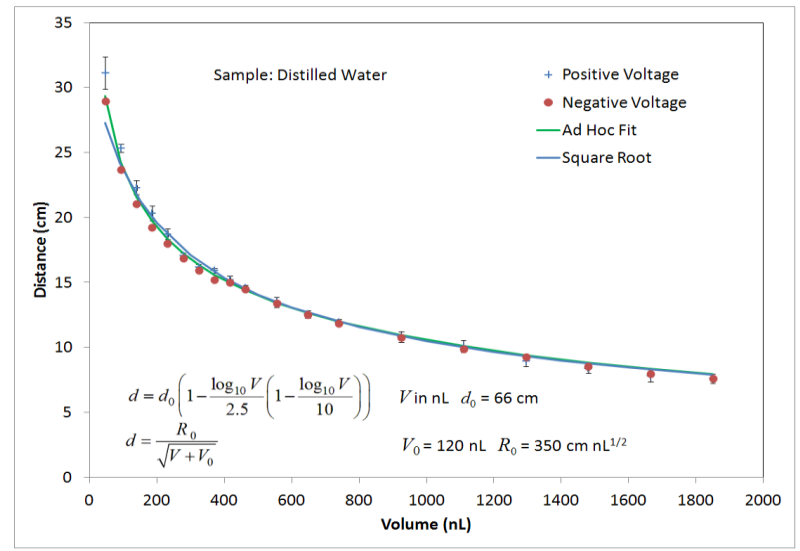
$$F_x = m\,(a_x) = m\,(dv_x/dt) = F_{elec\,x} + F_{drag\,x} + F_{buoyant\,x} + F_{grav\,x} + F_{coul\,x}$$

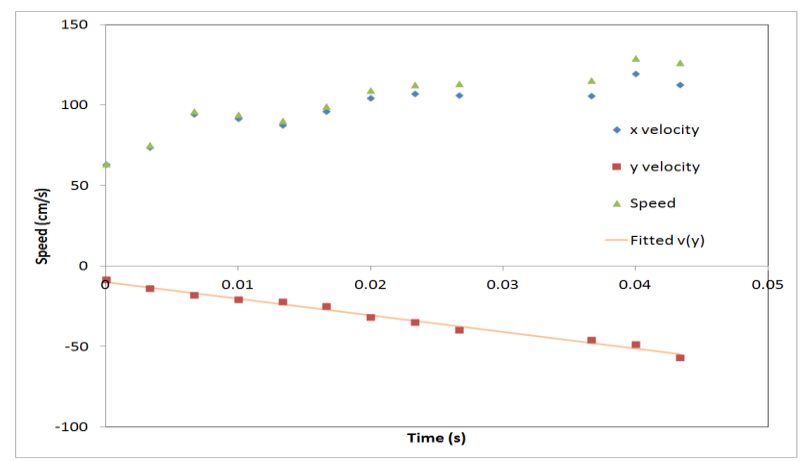
The same can be written for the y and z coordinates. Then with accurate model equations for Fy and Fz, we can actually **calculate the trajectories** of the drops (distances of travel, d) of the drops at any time t, knowing the initial position of the drop and that

$$V_x = dx/dt,\ V_y = dy/dt,\ V_z = dz/dt$$

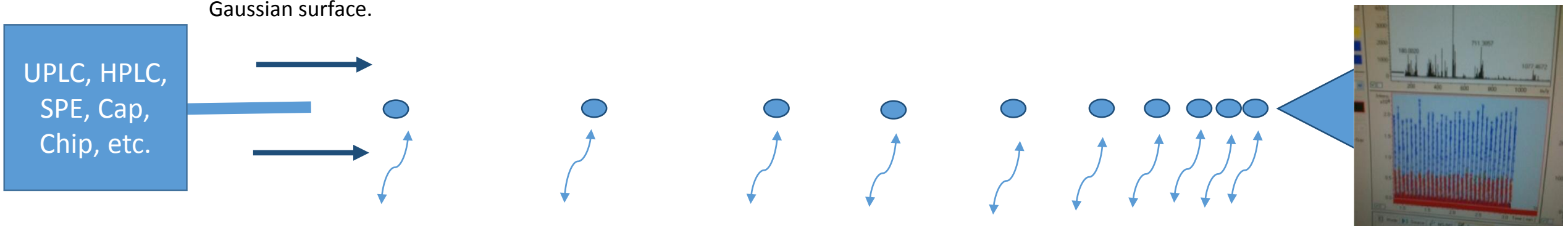
$$V^2 = V_x^2 + V_y^2 + V_z^2.$$

+/- Droplets follow the same trajectories,17.



IBF is analogous to printing into an ESI. Or shooting the drop down to a surface produces excellent MALDI crystals. All examples or APPS reported here consist of a fluidic path, a Gaussian surface, an inductor and energy source.




Programmed inductive energy from the Programmable nanoLiter Wave. One configuration.

## Example Ink Jet Calculations. IBF is NOT an Ink Jet, but it's analogous.

Below we ignore all but electrical and drag forces as they are the largest forces inside printers.

$F = ma = Fe + Fd$

$mdu(z)/dt = qE(t) - K u$

$Uz = qEo/K (1\text{-}exp\text{-}t/tm) = velocity$

$Z = qEo/K (t\text{-}tm(1\text{-}exp\text{-}t/tm)) = displacement$

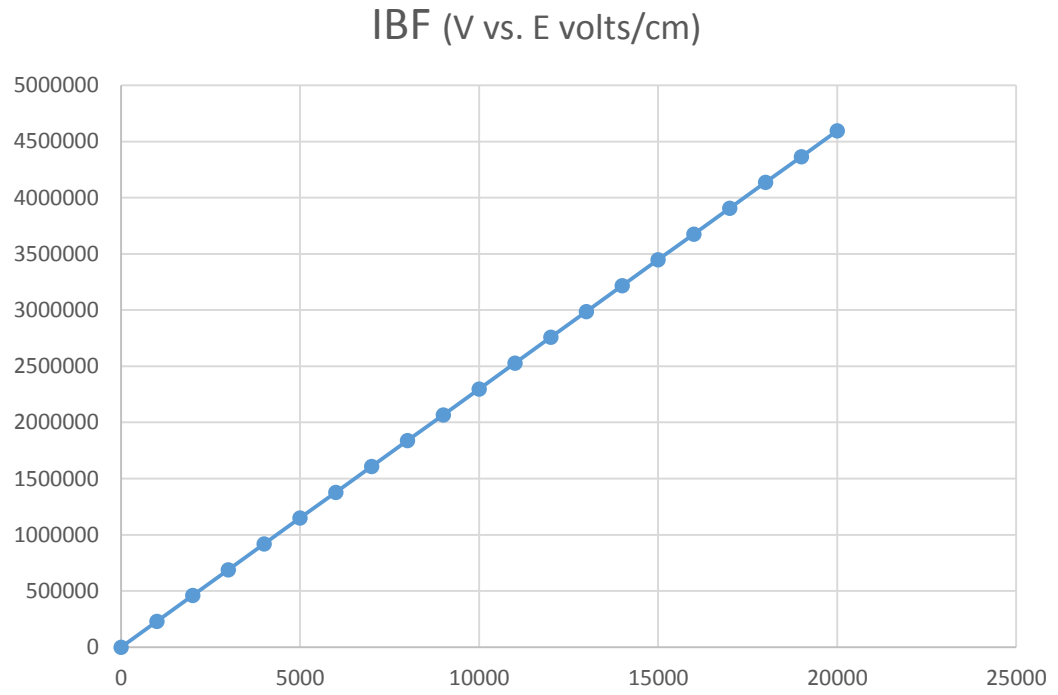
$tm = m/K = m/6pina = (2/9)(ya\text{^}2/n) = 2.5\ ms$

$Zm = ((q/m)Et\text{^}2)/z = 16\ mm$

Fe = external field, qEo.
Fd = drag force = 6pinau = Ku
U = velocity

n = dynamic viscosity.
a = drop radius ca. 15 um.
Y = density of ink, 10^3kg/m^3

After Kiser ,Sauter and Kaley



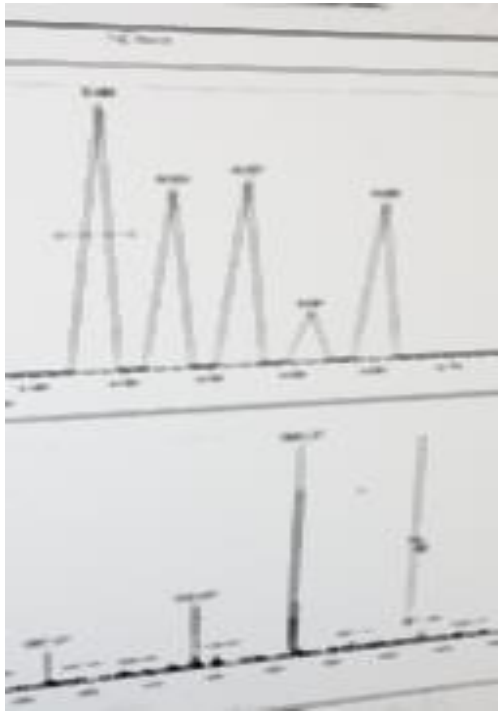
# For Droplets, nL Peak Shapes, Very SHARP and Similar On Very Different Systems. Helps Standardize Input.

## Also, rate of programmed sample input can be 100-1000 x that of continuous spray. (Best Results = Energy Programmed.)

Precision can approach, ca. 5% RSD. ESI MS systems can handle much larger nL volumes quite easily. **Note nLs > fLs ,rapidly for desolvattion!**

Penicillin, +eV, TIC

Analogue Device

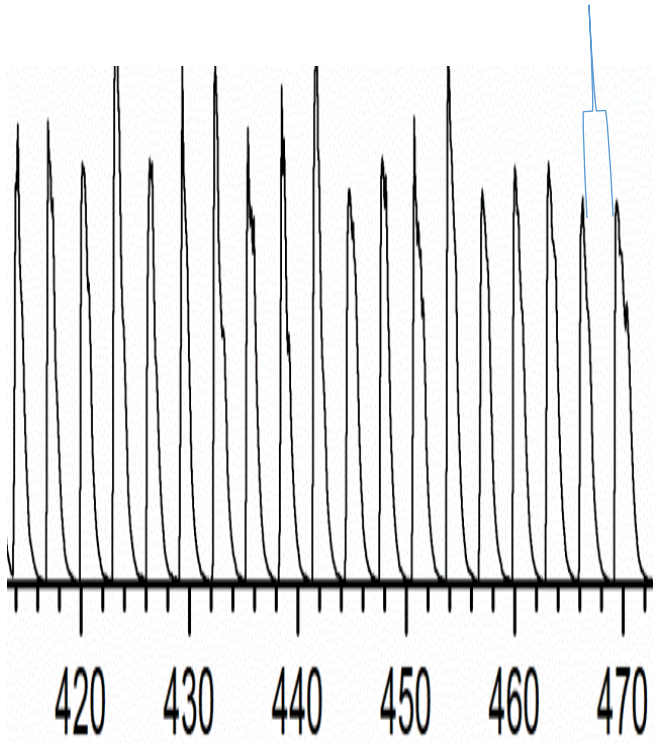


Manual infusion TIC. under-sampled, with poor ca. 3 s. injections. Unipolar, +eV. LTQ, TIC, NSC

Lanthanide tetra nitrate –eV ion

Digitral Device

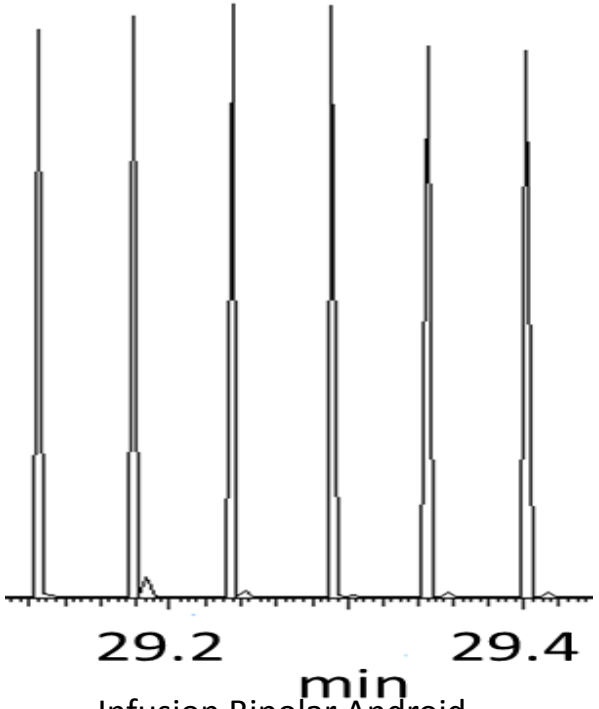
**m/z 422.9, $[Lu(NO_3)_4]^-$ from 400 to 470, 3 sec/scan.**




Digital bipolar 3 second shots. Bruker u-ToF. INL
http://www.youtube.com/watch?v=mzMDdFul6hE

MS/MS, 5 Nucleoside mix.

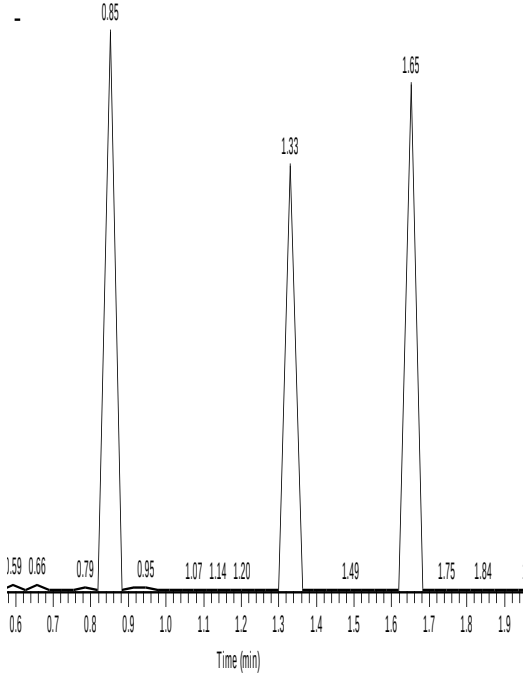
Digital Device




Infusion Bipolar Android Programmable Source, 2s. +eV, LTQ, TIC, U Cin.

25 Pesticide Screen ca. 1 Hz

Digital Device




+ eV, TIC, LCQ MS via nL Prog Wave 75% fs, 50 nL, droplets. Ca. 1 % formic, Caltech, 8/18

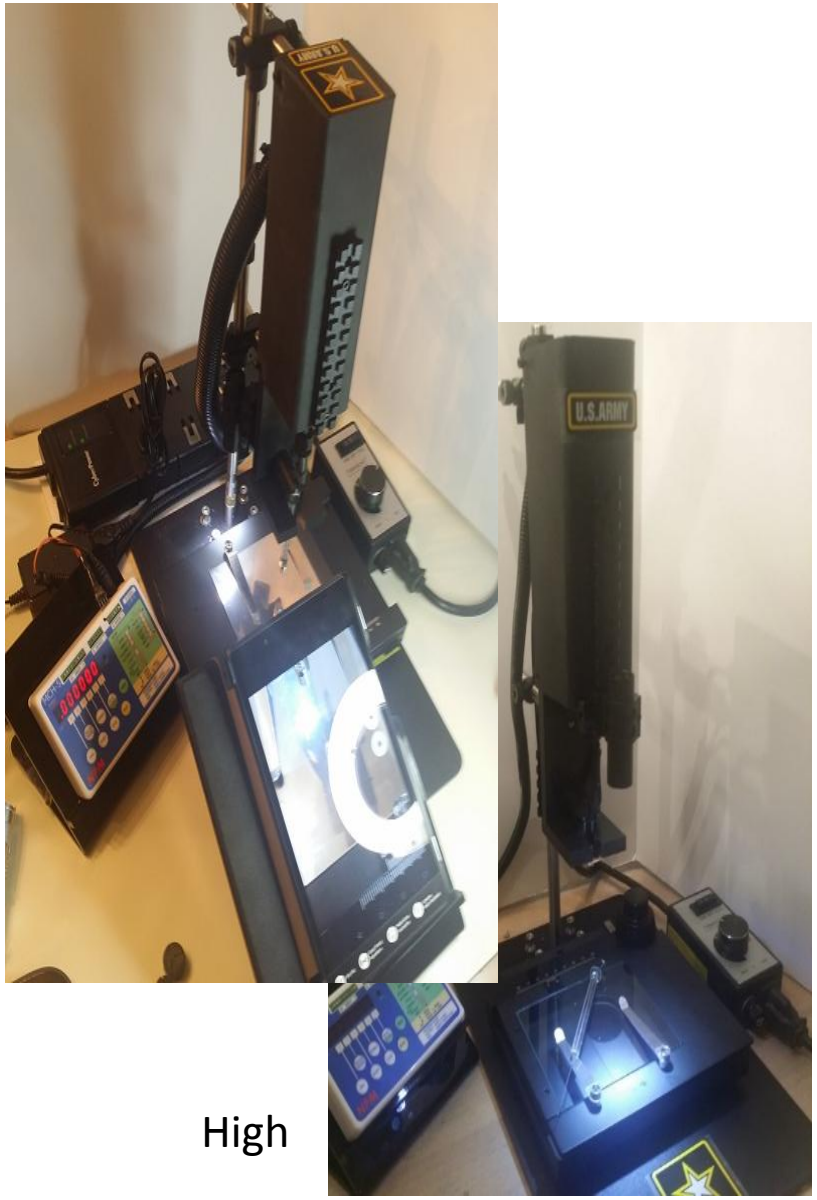
In all of the above examples a droplet, ca. 50/100 nL was shot at ca. 1 m/s yielding the sharp ion current peaks from the droplets.

# Example IBF Embodiments For ESI, MALDI and DOD,DOE, USDA & Other nanoLiter Dispensing.

Use of inductive electric fields allows for the placement of energy into fluids from devices of many forms and shapes.

Low

Med

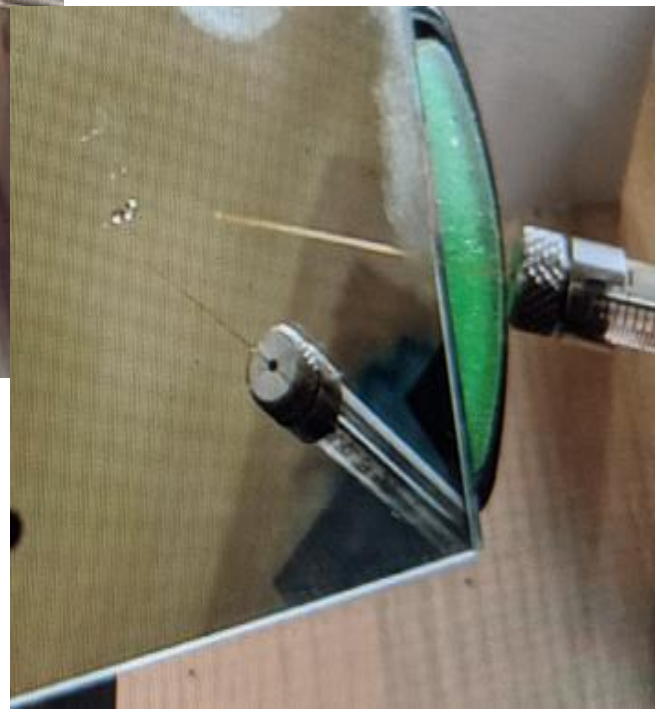


High

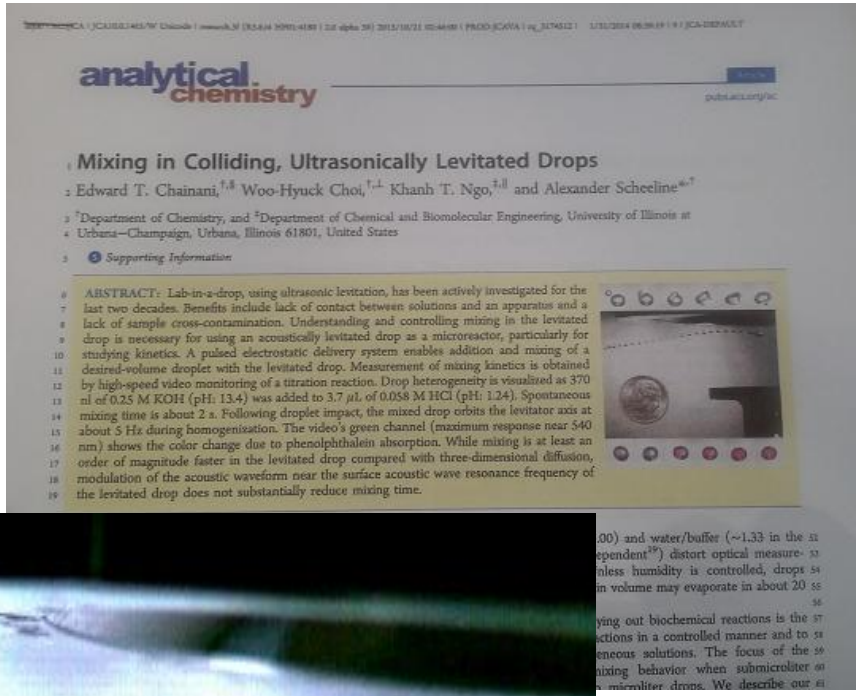
# Droplets: Shooting Entire nL Droplets To Targets. Two Examples

150 nL Droplet on Tip

150 nL Droplet  Shot to target.



300 nLs
shot into a
Levitated 3.0 uL
Scheeline, et al,
U Illinois,



analytical chemistry

Mixing in Colliding, Ultrasonically Levitated Drops

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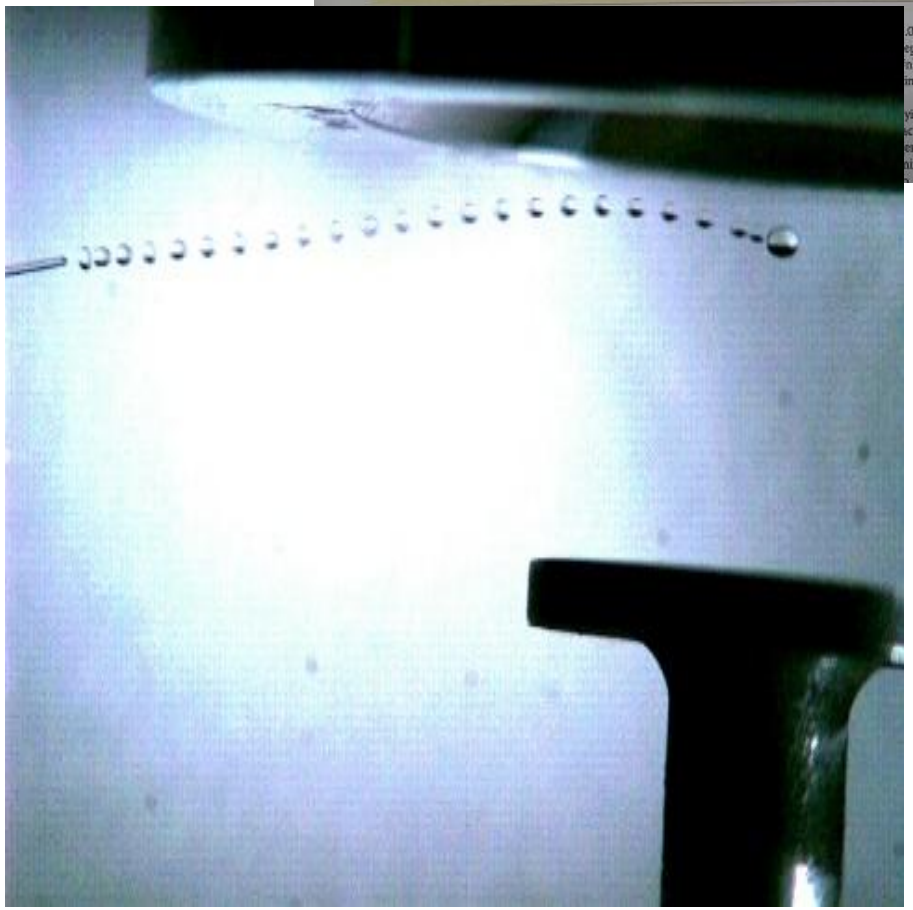
[†]Department of Chemistry, and [‡]Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801, United States

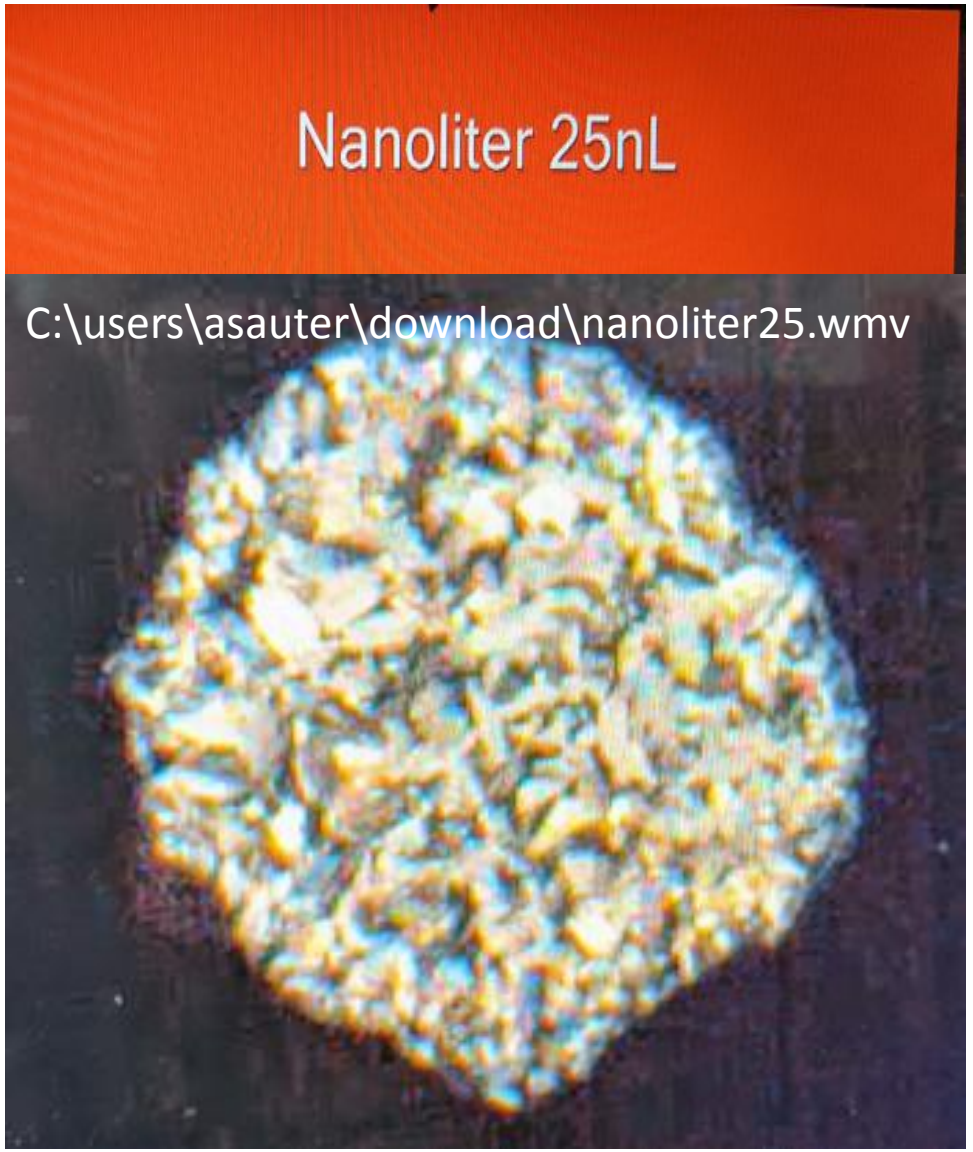
Supporting Information

ABSTRACT: Lab-in-a-drop, using ultrasonic levitation, has been actively investigated for the last two decades. Benefits include lack of contact between solutions and an apparatus and a lack of sample cross-contamination. Understanding and controlling mixing in the levitated drop is necessary for using an acoustically levitated drop as a microreactor, particularly for studying kinetics. A pulsed electrostatic delivery system enables addition and mixing of a desired-volume droplet with the levitated drop. Measurement of mixing kinetics is obtained by high-speed video monitoring of a titration reaction. Drop heterogeneity is visualized as 370 nl of 0.25 M KOH (pH: 13.4) was added to 3.7 μl, of 0.058 M HCl (pH: 1.24). Spontaneous mixing time is about 2 s. Following droplet impact, the mixed drop orbits the levitator axis at about 5 Hz during homogenization. The video's green channel (maximum response near 540 nm) shows the color change due to phenolphthalein absorption. While mixing is at least an order of magnitude faster in the levitated drop compared with three-dimensional diffusion, modulation of the acoustic waveform near the surface acoustic wave resonance frequency of the levitated drop does not substantially reduce mixing time.



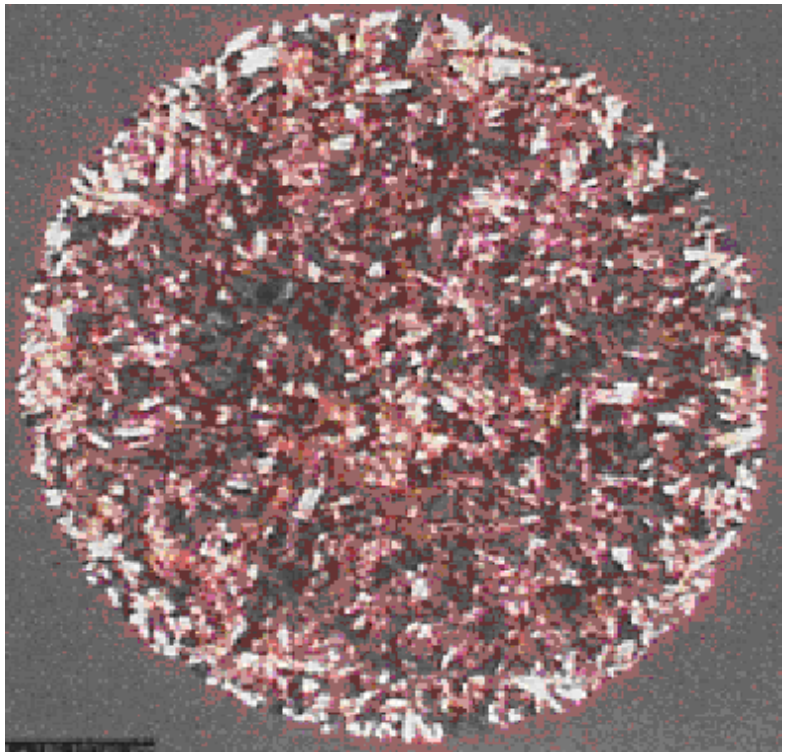
Drying nL Droplets Produces Excellent Crystals, J. Harmon, et al. USF.

PMMA
DROPLET JPG

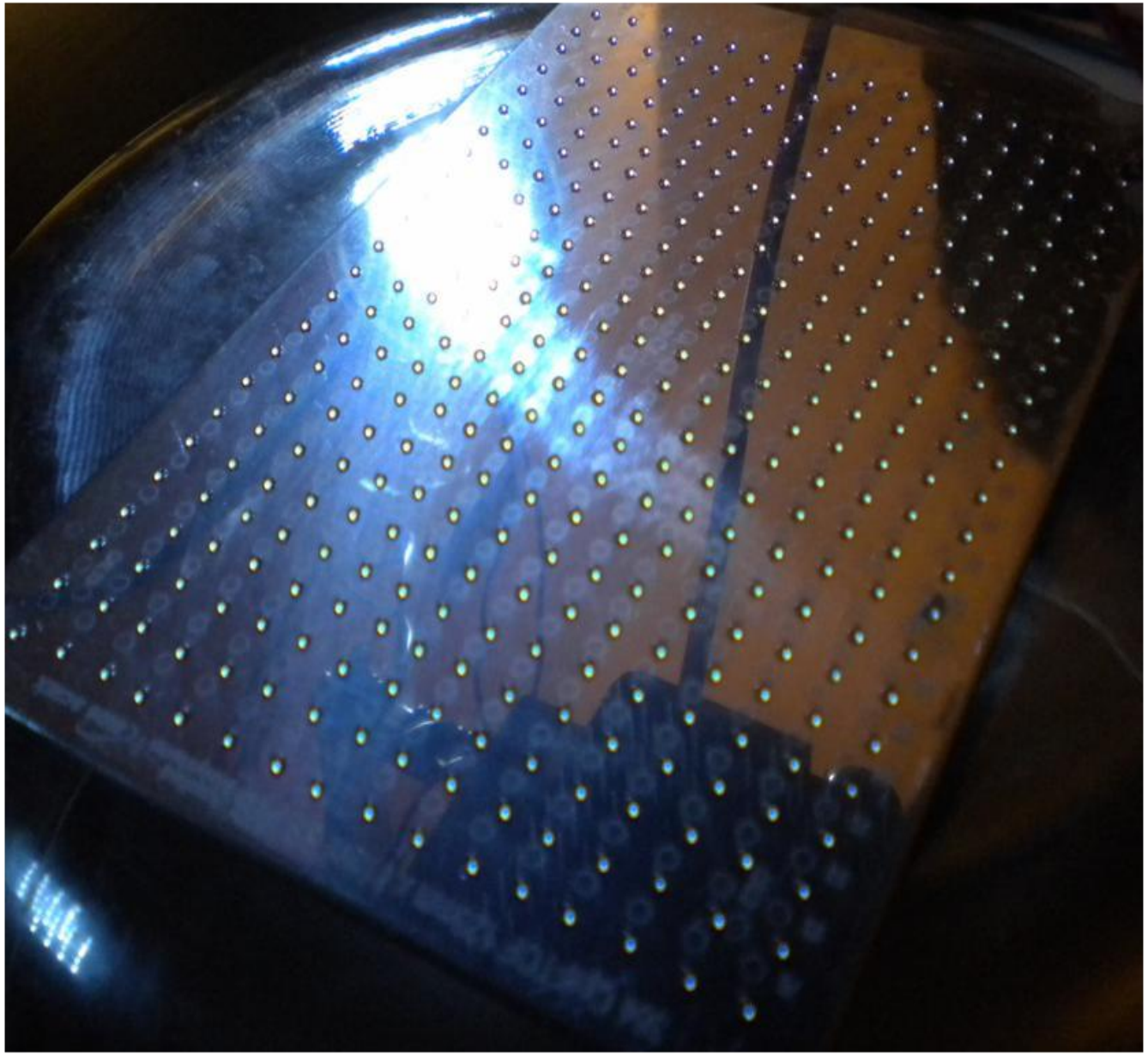



← PMMA DROPLET DRYING VIDEO.

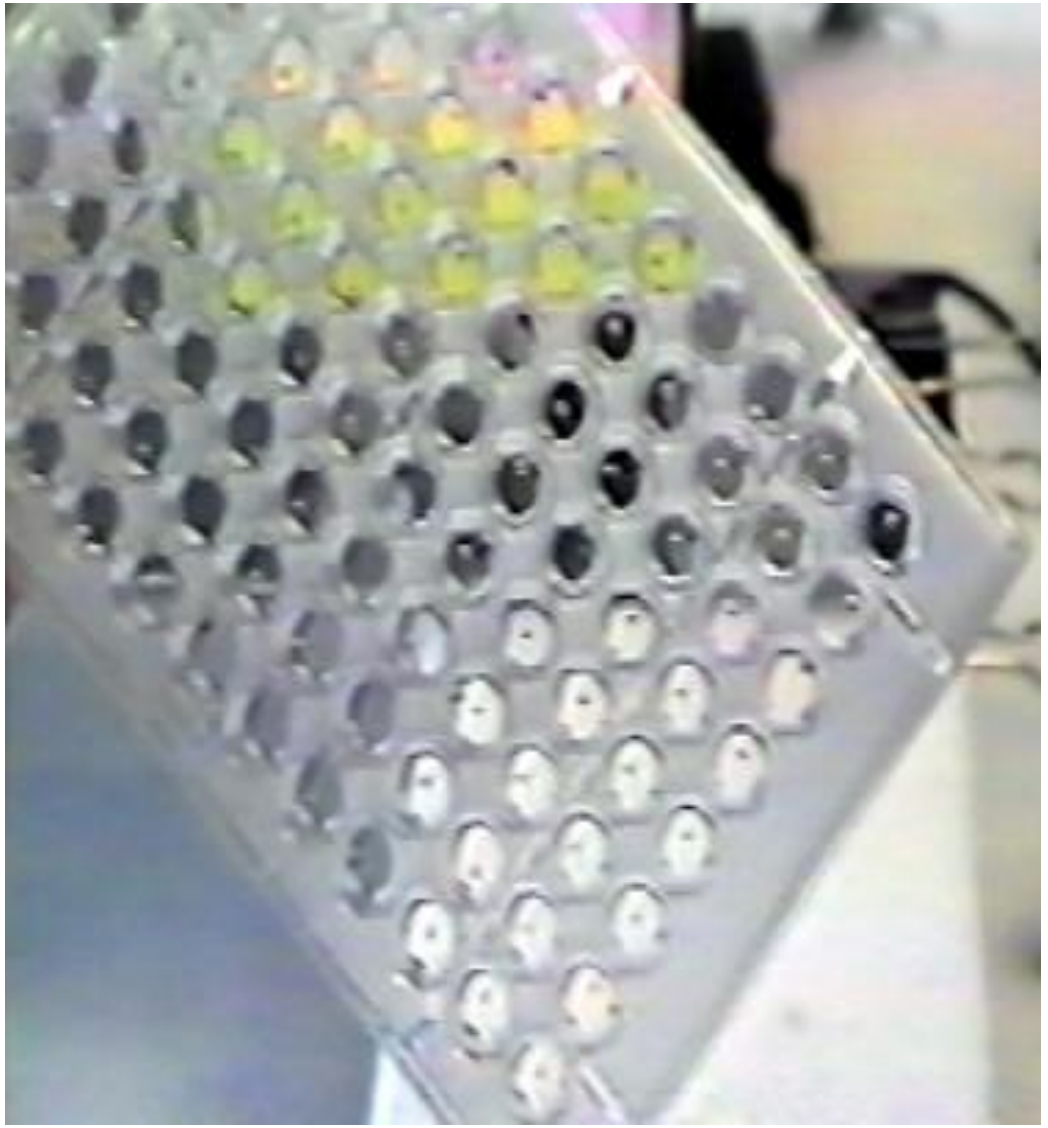
100 nL PMMA



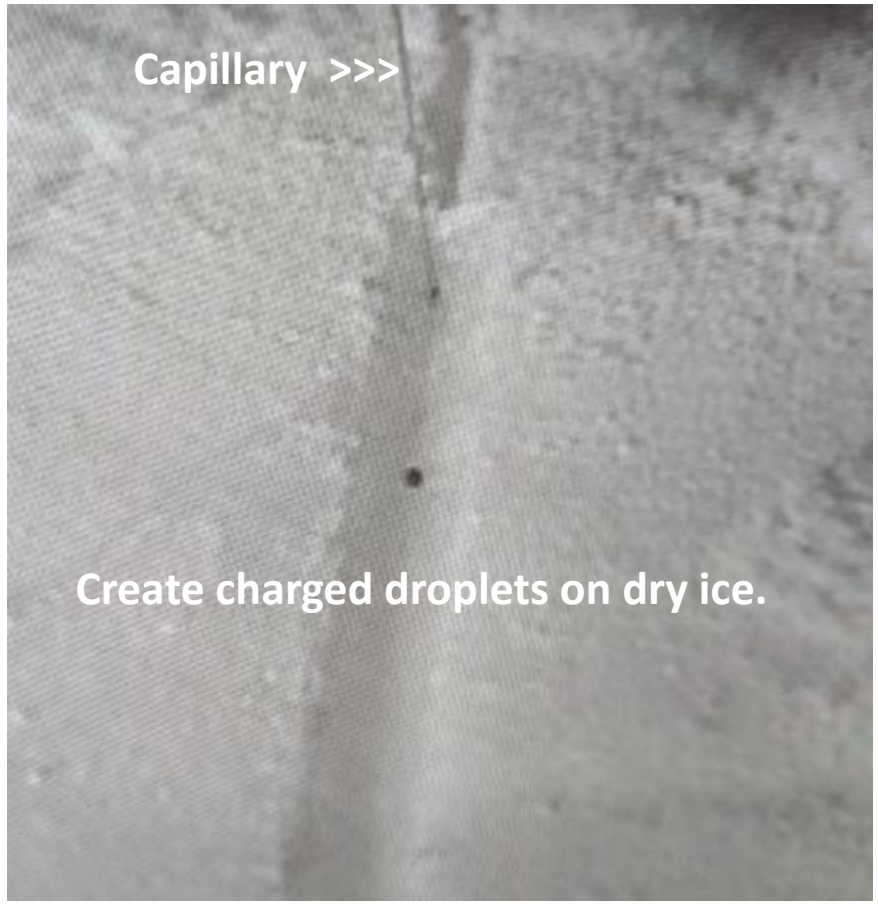
**Droplets: Parallel 384 Channel *Robotic* Dispensing in 1 millisecond, 150 nL normal tips.**

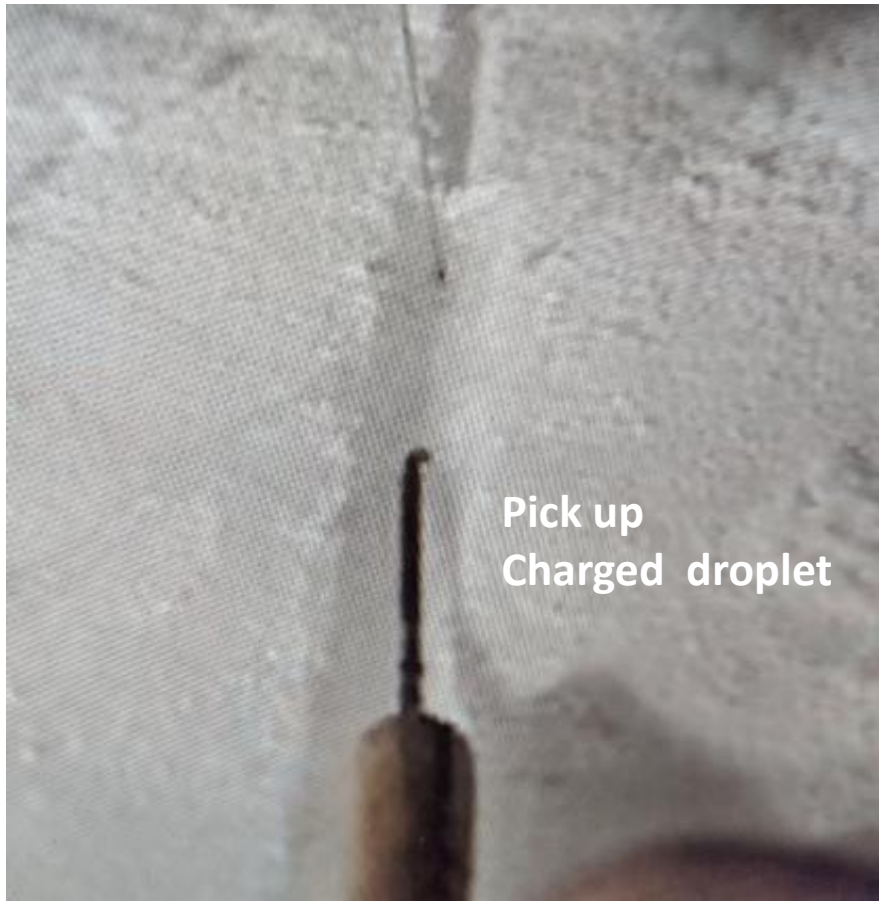


**8 Channel, 50 nL Robotic Dispensing to a MT plate.**



## Droplets: Make Charged Solid Droplets, Electrets, i.e., Nanolitersicles in DROPLET MODE.



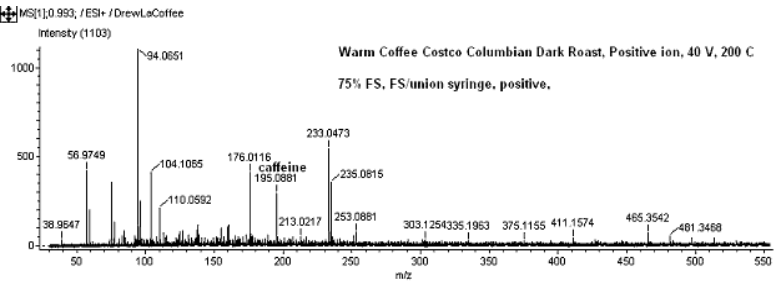

Ask for video link.

# Type 1 & Type 2 nL “manual” E droplet dispensers with 3x 50 nL shown dispenses + tip 1.



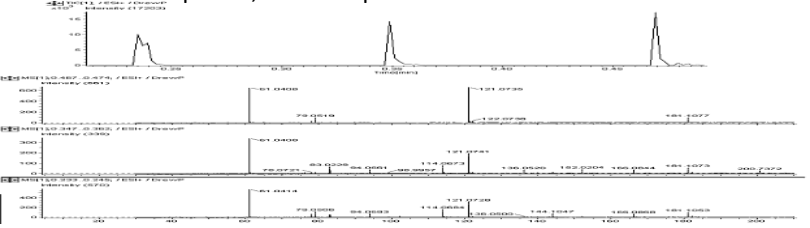
# “All In” IBF Analysis of Coffee, Urine, Drugs of Abuse and Caffeine/Nicotine std, Oral Liquids and DOD Liquids.

## IBF, ESI Coffee

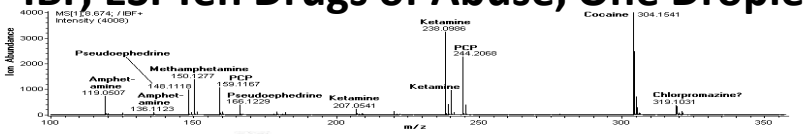


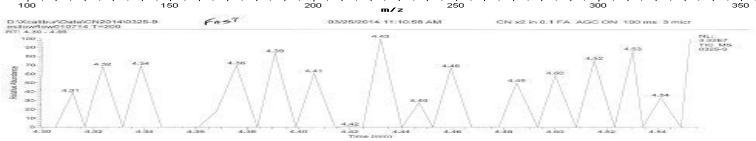

## IBF, ESI Urine, Urea & Aspirin

+ TIC and 3x spectra, urea + aspirin.

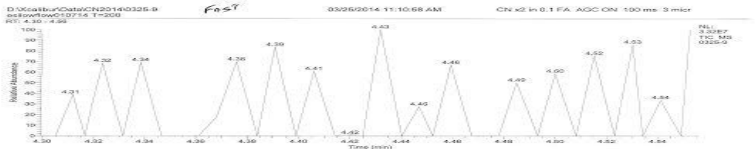


## IBF, ESI Ten Drugs of Abuse, One Droplet.+MS



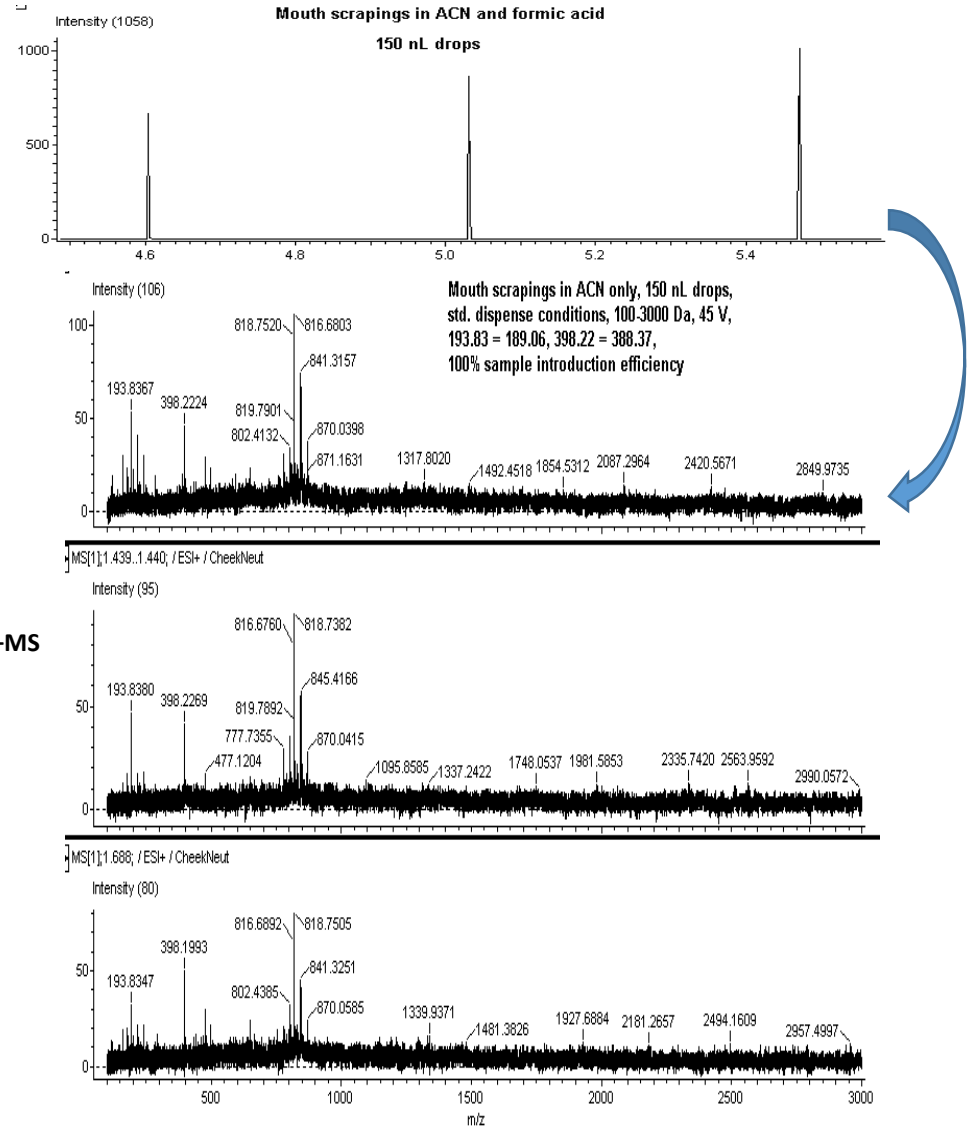



## IBF, ESI Caffeine & Nicotine Std.



## Oral Cellular Liquid Mix,

n=3 TIC, + 3 MS, Dr. Grange, EPA LV.



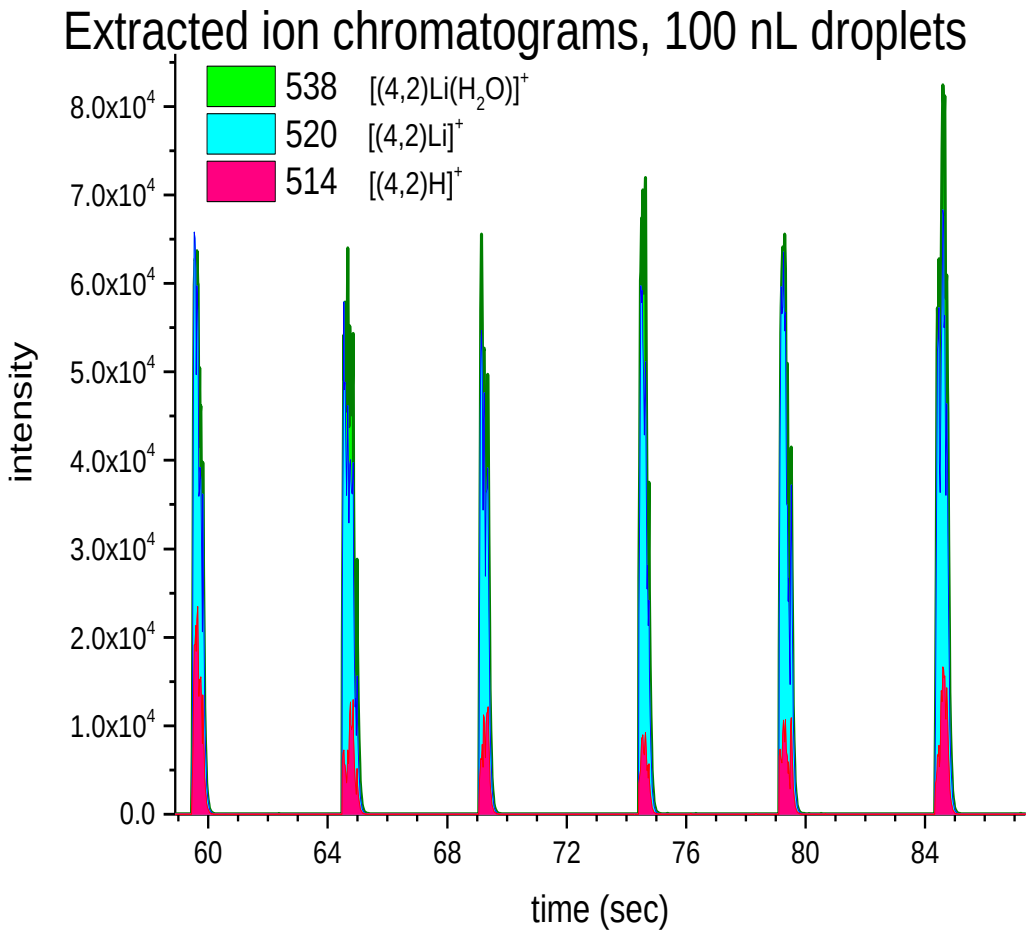

## New 2019 DOD Dispenser.

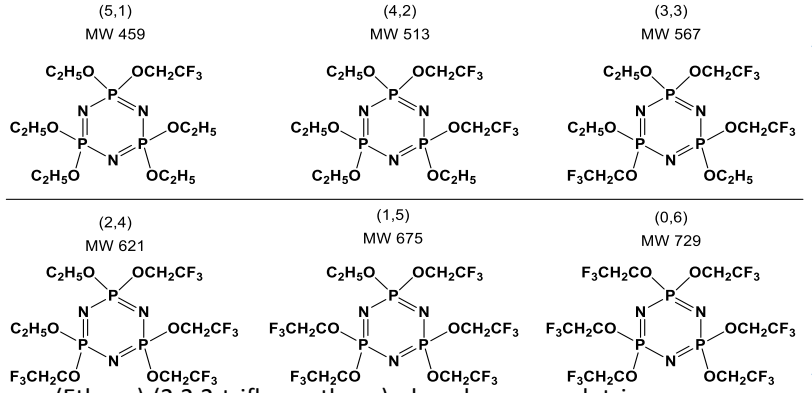
nLs Shot Onto Various Materials.

# Droplets: nanoLiters of a Lithium battery electrolyte w/fire retardants shot directly into a HRMS @ INL.

Work of G. Groenewold, et al @ Idaho Nat'l Lab.

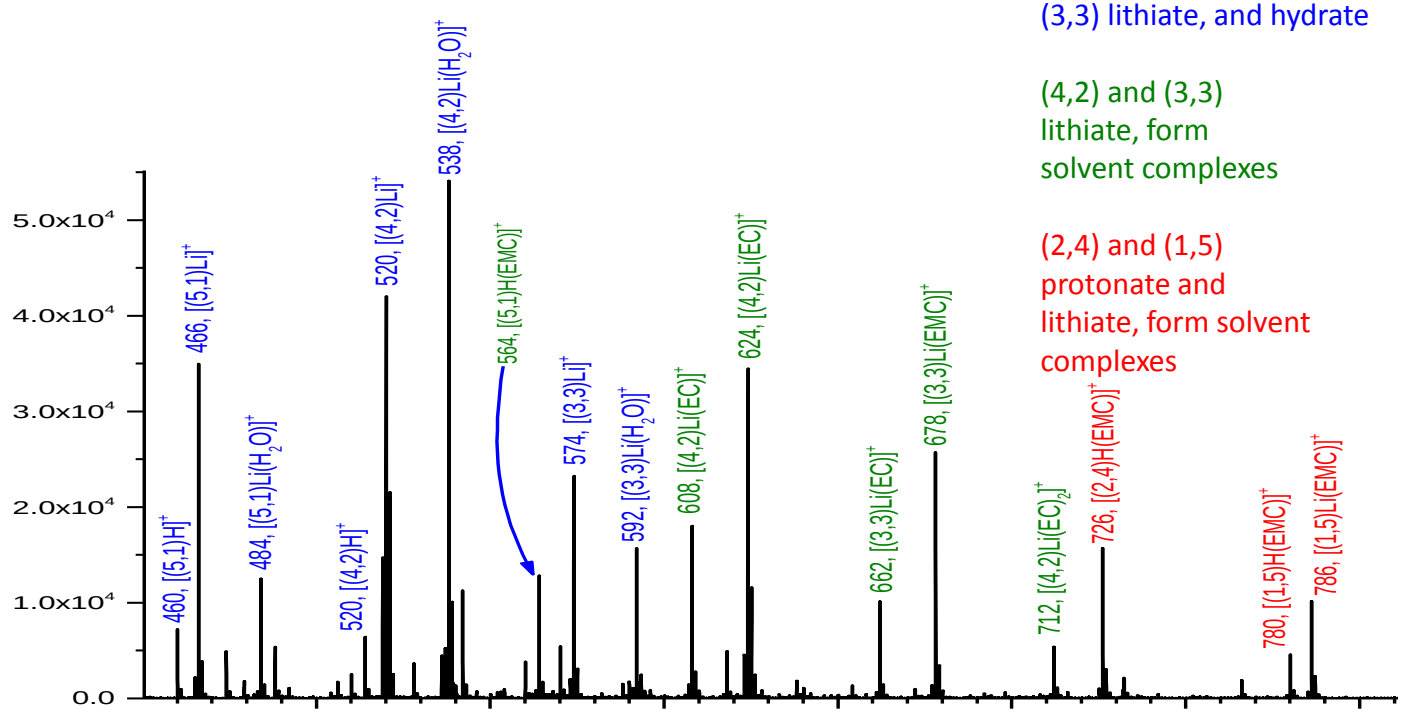
- Temporal profiles
  - 100 nL, manually launched, below.
  - 35 nL, field induced, @ 0.5 Hz, not shown




(Ethoxy)$_x$(2,2,2-trifluorethoxy)$_y$phosphazene cyclotrimers
(x,y) short hand nomenclature

← Fire retardants.




More ethoxylated congeners (5,1), (4,2), and (3,3) lithiate, and hydrate

(4,2) and (3,3) lithiate, form solvent complexes

(2,4) and (1,5) protonate and lithiate, form solvent complexes

# IBF BASED "ESI" UPLC MS & INFUSION.

The Department of Chemistry
McMicken College of Arts & Sciences

UNIVERSITY OF Cincinnati

## Droplet Based Sampling of RNA Hydrolysates by Induction Based Fluidics

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[1]University of Cincinnati, Cincinnati, OH;
[2]nanoLiter, LLC, Henderson, NV

### Overview

The goal of this study was to couple an inductive charging device to a liquid chromatography separation with a focus of lowering the LOD for standard RNA nucleoside analysis. As such, a synthetic test mix comprised of cytidine, uridine, 5-methylcytidine, adenosine and 2'-O-methyladenosine were separated by means of capillary chromatography and delivered into the mass spectrometer by using a modified inductive charging source powered by a modified inductor coupled to a digital programmed energy and polarity pulsed DC source[1].

### Introduction

Post-transcriptional chemical covalent modification of adenosine, guanosine, uridine and cytidine occurs frequently in all types of ribonucleic acids (RNAs). In ribosomal RNA (rRNA) and transfer RNA (tRNA) these modifications make important contributions to RNA structure and stability and to the accuracy and efficiency of protein translation. These modifications can be present at very low levels and their analysis can be challenging. This work builds on previous work where the utility of Inductive Based Fluidics (IBF) as a sample introduction method is examined while coupled to an LC platform. Because IBF creates inductively charged droplets instead of an electrospray, theoretically, a droplet sampling method would allow for greater sensitivity as more sample would enter the mass spectrometer.

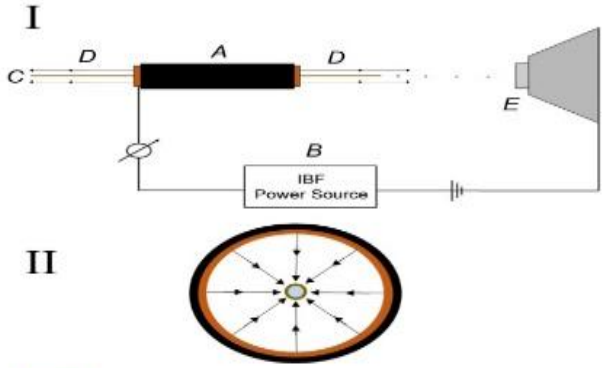


**Figure 1.** Schematic of inductor employed in this work, inspired by R.W. Kiser[2]
I A: Insulated copper tube (90 x 6 mm) B: Inductive charging device C: Capillary tubing (360 X 50 µm) with flow from column D: Field lines E: Inlet to mass spectrometer.
II Forward view of IBF charging tube showing nexus of field lines onto the sampling capillary

### Methods

An equimolar RNA hydrolysate mixture was separated on a porous graphitic carbon packed capillary column inserted into an in-house inductive charging tube with capillary positioned 2-4 mm from inlet orifice. Mass spectra were recorded in positive polarity on a Thermo Fisher LTQ-XL. A capillary temperature of 275 °C, spray voltage of 0 kV, capillary voltage of 0 kV, and tube lens at 0 kV. IBF device was set to −2000V and pulsed + and - with 2 s intervals over a 40 min acquisition. Data acquisition was through the Thermo Fisher Xcalibur software.

### Results and Discussion

Five RNA nucleoside standards, cytidine, uridine, 5-methyluridine, adenosine, and 2'-O-methyladenosine were separated and sampled using the IBF device. Extracted ion chromatograms of the analytes are shown in Figure 2.

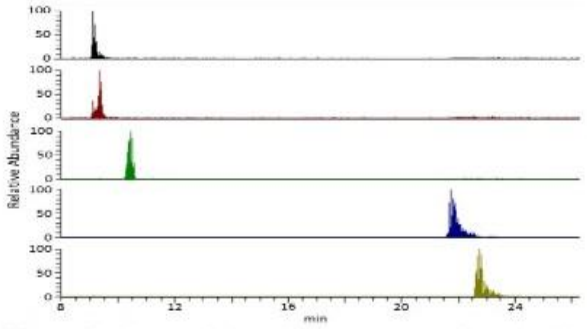


**Figure 2.** Extracted ion chromatograms of nucleosides cytidine, uridine, 5-methyluridine, adenosine, and 2'-O-methyladenosine separated on a PGC capillary column and introduced into the mass spectrometer by inductive charging.

Droplets were delivered with a 2 s interval over a total run time of 40 min. The total ion chromatogram (TIC) showed steady reproducible droplet peaks throughout the gradient. Each peak in the TIC corresponds to a single droplet delivered via IBF, Figure 3.

XICs of individual nucleosides were generated, with a signal response generated over a single droplet peak in the analyte elution or across the entire set of droplet peaks generated from each analyte. The mass spectrum obtained when summing across the entire acquisition window illustrates one advantage of pulsed operation wherein the background is significantly reduced as illustrated in Figure 4.

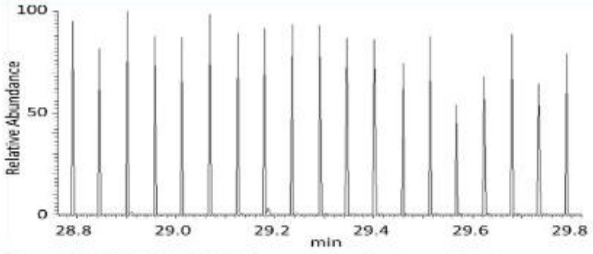


**Figure 3.** IBF-LC-MS/MS data of droplet introduction over a one minute acquisition window.

The intervals between droplet arrival in the mass analyzer are characterized by no background, which can be reflected in the summed mass spectral data. More Importantly, the ion abundances present within a single droplet are similar to the integrated peak values as previously shown by Groenwold, et al.[3]

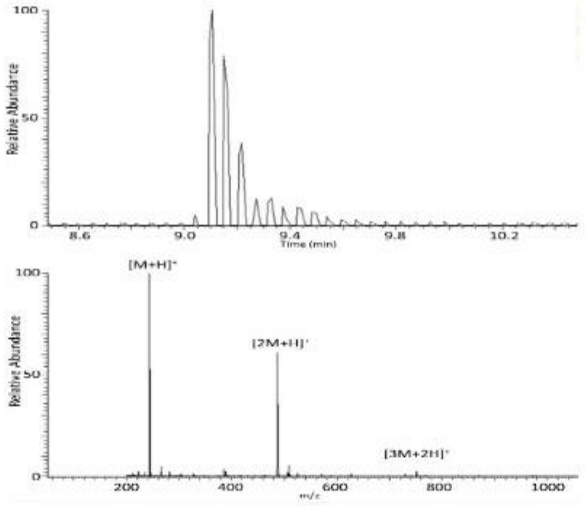


**Figure 4.** IBF-MS data of the nucleoside cytidine introduced dropwise by inductive charging. (a) Total ion chromatogram showing droplet introduction. (b) Mass spectrum of cytidine obtained by averaging over one peak in the acquisition window.

Droplet desolvation may be more efficient than nESI. This could limit sampling bias for mixtures if ion generation is influenced more by the kinetics of desolvation rather than the thermodynamic partitioning of the analytes with different hydrophobicities at the droplet surface. Figure 5 shows XICs of the equimolar nucleoside mixture with the relative abundances listed. This data aligns with previous work[4] suggesting that kinetics may better represent ion generation with droplet sampling. More experiments are planned to strengthen this argument

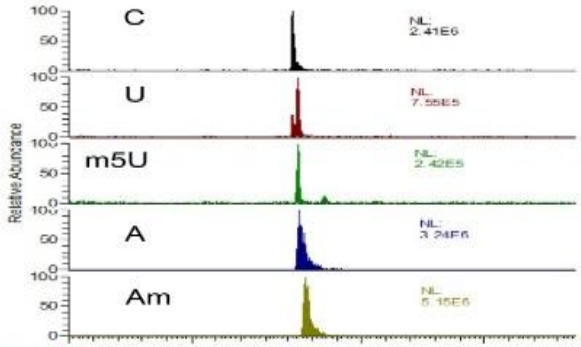


**Figure 5.** Mass spectra of nucleosides (5 ng/µl), cytidine, uridine, 5-methyluridine, adenosine, and 2'-O-methyladenosine. Droplet introduction could minimizes the sampling bias related to nucleobase hydrophobicity

### Conclusions

A programmable IBF droplet source appears suited for nucleoside UPLC sample introduction and mass spectrometric analysis. Preliminary results show this droplet based approach is equivalent to or may exceed nESI. Work to determine LOD's and more is continuing.

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### Acknowledgments

The presenting author would like to thank the members of the Limbach Research Group for their assistance. Financial support of this work was provided by the National Science Foundation (CHE1212625). The nanoLiter Programmable Wave device was acquired under license from nanoLiter LLC

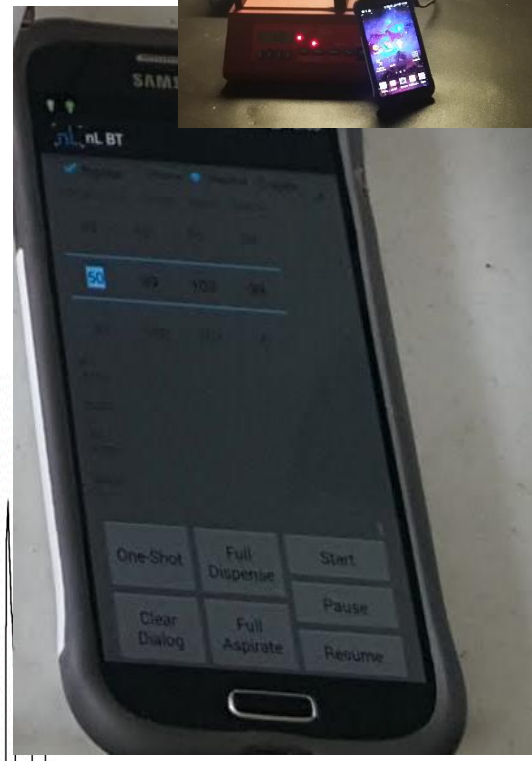
# Greater Sensitivity, “All in” + Pulsed Sample Input !

1. Shooting **all of the sample** into the ion inlet tube, gets, ca. 100x more moles into the MS.

2. Pulsing the sample input **gets another ca. 100-1000x** in d(moles)/dt into the ion inlet tube!

3. Video shows…….nLs/pLs  produced … then morph to fL …. onto bare ions! (Some References)



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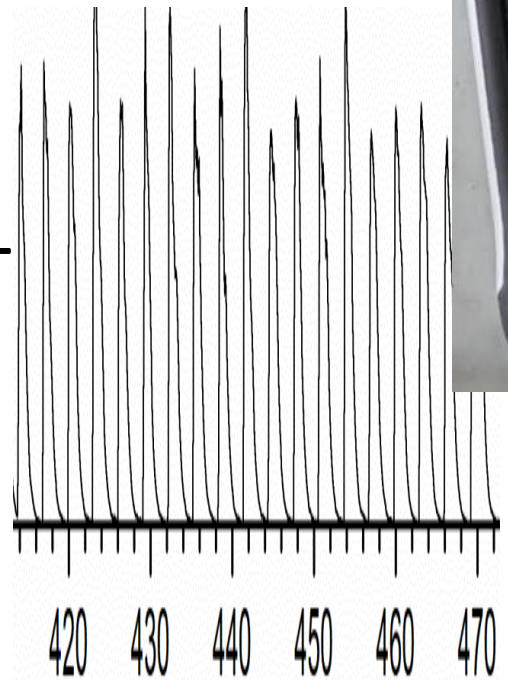



**Sprays**: Internet ESI Pic Data (Click on link). Note Traditional sprays are continuously dispersive without Droplet level control. Also, condensed droplets from traditional approaches makes desolvation difficult at best. Wide Spraying reduces sample input.

Digital bipolar 3 second shots. Bruker u-ToF. INL
http://www.youtube.com/watch?v=mzMDdFul6hE

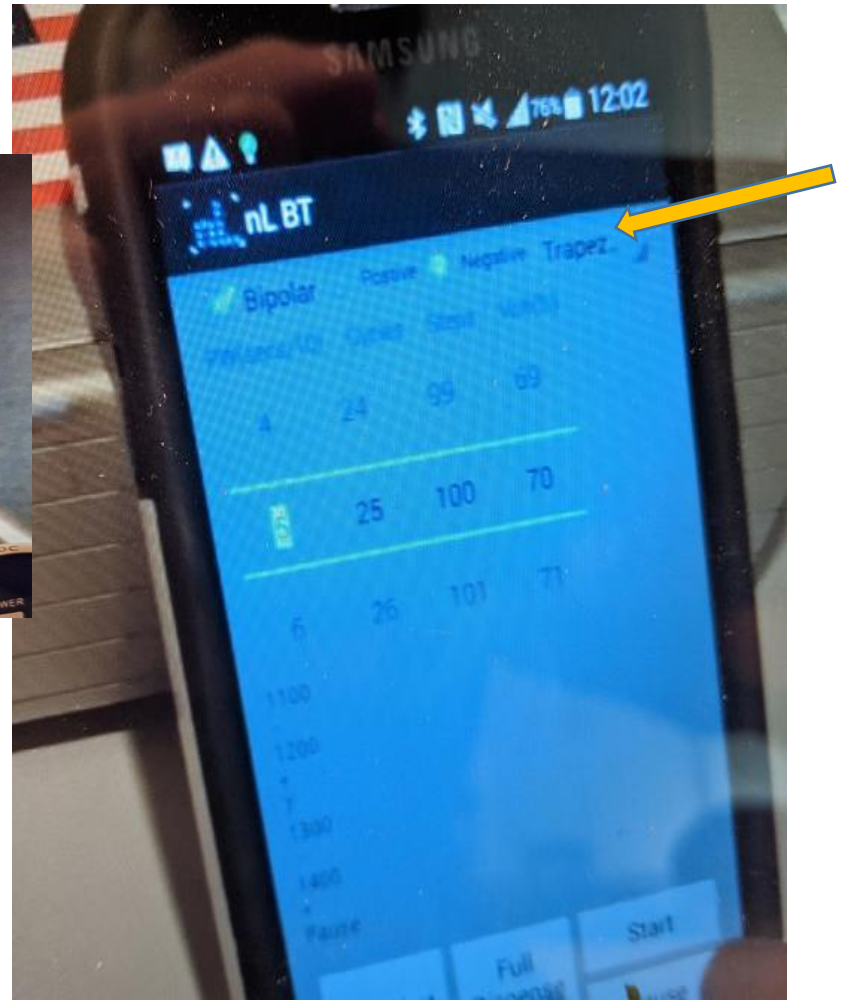
# Is An Increase In ESI Sensitivity of 4-5 Order of Magnitude Possible?

**"All In!" = ca. 100x More Molar Input Compared To A ESI Spray! Also, Pulsing Yields 100-1000 Increase In d(Moles)/dt, as well. Find Optimum Desolvation Conditions.**

**The Best Inductive Energy Program & Other Conditions Will Yield Highest Sensitivity , (i.e., I/P or I/w). More Observations/Data Coming After Covid-19. Seeking Collaborators.**

Energy Functions vs. Time.






Four wave functions are selectable.
Trapezoidal selected here.

Other variables include
- Position
- Energy
- Polarity,
- Mode thereof

Acquisition Parameters
- PW,
- Cycles,
- Steps,
- Applied Energy

Also
- Solvents, Flow, Temp, arrangements, etc.

# Previous IBF User Successes. (Overview of IBF)



IBF marijuana, very rapid FIA ( 1 sec/sample pesticide,(potency) screening R&D) ongoing with **Caltech and Adaptas.**

IBF has been used by 4 **US Army** and 1 Air Force groups for special nanoliter dispensing projects..

IBF being used for MS Analysis of oligonucleotides. JMS paper w/ **U of Cincinnati** yields most sensitive analysis for oligonucleotides!

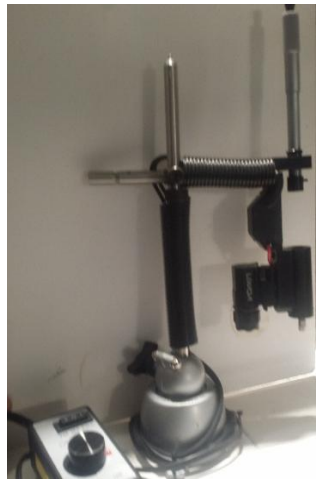

**US Department of Energy** is using IBF in the field to analyze Lanthanide elements at fg levels WITHOUT an ICP (Radio-active elements!)

IBF is being used to introduce samples into a MS from an **OPERATING** battery at INL lab. App for TESLA here in Nevada?

**USF, NIH, NIST & JEOL**. publish that by using nLs for MALDI, SIMS, LDI & DART that MS sensitivity increases by 10-100x LITERALLY!

***University of Wisconsin*** has used IBF for single cell MALDI identifying six new ocular proteins. We shot cells into an ESI at gov't lab.

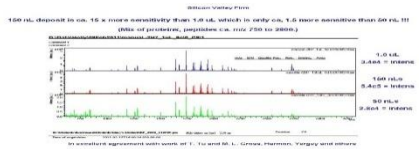
**University of Illinois** published that IBF can fly nanoLiters of liquids into levitated microliters to study wall-less reaction kinetics.



For **Abbott,** nanoLiter LLC used IBF to dispenses PVA, w/ave. MW of 300,000 in pseudo 3D "printing." app.


**At Genentech,** nanoLiter demonstrates 20 x improvement in MALDI sensitivity for proteins, peptides.

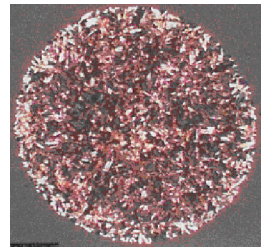
For **Spark Holland** we demoed a form of LC/MALDI. Ask to see video.



384 channel parallel nL dispensing in a millisecond.

**USF** used IBF to make electrets USF.

**NIH,** in it's first application of IBF, PTM's of tublin (glycosylation) were first ided, in actual brain cancer samples given a 100x sensitivity increase claims NIH!



**Sciex** offered to license IBF for ESI LCMS and for LC/MALDI. Parallel 8 channel IBF LC demoed with dyes.

**nanoLiter** morphed Roche polypipettor for **Douglas** and **Spark Holland's** systems for parallel or single channel millisecond nL dispensing, SPE, LC.

**See references.,** We can rapidly fly **droplets, in 5 sec, 0.5 sec or in 1 sec into ESI's & onto surfaces,**

**Example customers/clients/collaborators: U's of Ill, WI, CA, Cinn., MUSC, Wash. U. St. L, UCSD, USF, USU, US Army (APG, ECBC, Dugway PG and Natick),Tyndall AFB, Abbott, Biogen Idec, Genentech, Amgen, Hitachi, Allergan, Merck, Sciex, Spark, Douglas, NIH, NIST, USDOE INL, Ga Tech, UNH, Duquesne, Adaptas (SIS), Caltech and more.**

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# ASMS 2020 Submission

Title.

Programmed Droplet Desolvation And Occam's Razor.

Introduction

Traditional ESI can result in wasting a major amount of the sample because the E fields from the cone jet are inherently, spatially dispersive, plus as the droplets are liked charged, they also repel each other. This, of course, minimizes sample input.

We've used induction based fluidics (IBF) to overcome adverse impact of traditional ESI charging/desolvation approaches. Essentially, we use an inductive approach to launch 100% of the sample into the ion inlet tube, and now, also to assist with desolvation.

This work addresses inductive IBF droplet launching, desolvation of nL/pL droplets and Occams Razor.

Methods

Inductive droplet generators were used to produce charged droplets inductively. A newly modified unipolar analogue nL dispenser was used to inductively apply charge to nL sample droplets. Also, a digital, bipolar, programmable Android embodiment was also used in this work. Using these tools, inductively applied field could be programmed to increase the field strength using one of four energy programmed functions for the digital tool, effecting shredded droplets to aid desolvation on directed droplets. Energy and polarity pulsing were applied using the digital device. Parameters were adjusted in an attempt to direct the droplets into the ion inlet tube, initially with subsequent droplet shredding to decease the volume of the directed droplet cloud.

Preliminary Data

Previously reviewed and new inductive data were acquired at typical nL/sec flow rates and observations were made to study results. Also, applied inductive data were acquired, frequently pulsed at approximately 1 Hz or faster with the selected applied energy function.

Additional photographic, video and IBF/ESI MS data were acquired to help characterize said sample input which is shown to be unlike traditional conductive dispersive ESI sprays. Observations of droplet sample introduction show that at the sample input point, the droplets begin as fine apparent condensed, directed droplets with volumes obviously smaller than the nanoliter droplet creation rate. Said droplets are shown to be shredded after they are initially directed to the targeted ion inlet tube. This work aims to further characterize droplet creation/desolvation, as these parameters appear to directly impact analyte sensitivity.

We continue to study the energy and applied energy function to impact sensitivity including the device, its' physical arrangement, and its functional energy form, as we consider other (temperature, flow) variables.

Novel Aspect

Programmed inductive electric fields are shown to fragment and direct nL droplets using simple analogue or a programmable IBF Android device.