Acoustic Droplet Ejection (ADE): The ROI Behind Efficient Technology

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Acoustic Droplet Ejection (ADE) Devices

- Labcyte Echo
- EDC ATS-100
- Poly-Pico

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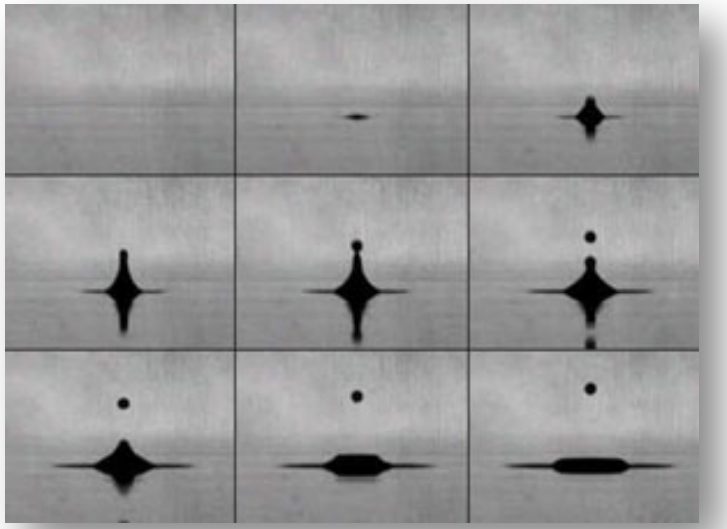
Acoustic Technology

- Moves liquids with sounds using acoustic droplet ejection (ADE)
- Low volume transfers in nano-liter increments
- Able to survey each well and report the fluid volume and the water content for samples in Dimethylsulfoxide (DMSO)
- Applications:
  - Compound Management
  - siRNA screening
  - Biochemical assays
  - Cell-based assays
  - 384- and 1536-well PCR



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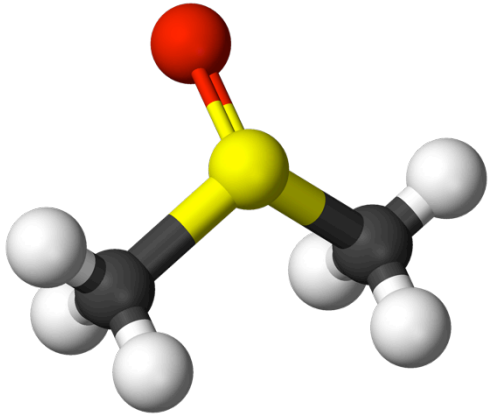
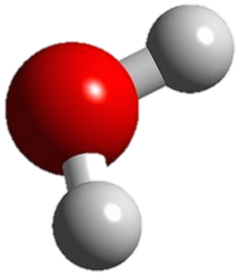
Liquid Type Transfers

- DMSO
  - 70-100%
- Aqueous
  - Buffers
  - Protein
  - DNA/RNA/Cells
- Different drop sizes
  - Echo 2.5nL and 25nL (aqueous only)
  - ATS-100 has variable drops sizes 1nL-25nL





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ADE Role in Pharmacology

- Optimize ADE in a production environment
  - Training/Certifying users
  - Enabling complex plate maps
  - Instrument maintenance
- ADE in Compound Management
  - Minimizing compound consumption
  - Cost savings
- ADE in Biological Assays
  - Increases and facilitates transfers for specific low volume ranges
  - Reduces final DMSO concentration (great advantage for cell assays)

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Disadvantages of ADE

- Can be slow when dispensing volumes greater than 250nL
- Can have limited types of source plates
- Only one source to one destination per run
- Instruments are expensive
- Service performed solely by vendor

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Justification for acquiring ADE

- Enables miniaturization
- No tips required
  - Saves cost and contamination
- Saves compound
  - Reducing dead volume
- Saves reagents
- No liquid or consumable waste locations needed
- More accurate and precise than traditional liquid handlers
- Minimal - but vital - training required

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Cost Savings

- Hamilton 50uL 384 NTR Conductive
  - $0.09 per tip (384 tip rack)
  - ADE saves $90,000 per million wells
- Agilent Axygen Robotic Tips 50uL
  - $0.13 per tip (384 tip box)
  - ADE saves $130,000 per million wells
- Ideal scenario: tip savings over 8 year period pays for instrument
  - $0.13/tip, 1,000,000 tips per year
  - Single Echo, $350,000 purchase price, $100,000 software, %15 annual service contract
  - Cost of capital = 8%
  - Saves $800K Net Present Value (NPV)
- Real world scenario: tip savings lower 8 year cost of ownership by 35%
  - $0.09/tip, 2,000,000 tips per year
  - Four Echo dispensers
  - Saves $1.1MM

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Intangible ROI

- Small volume, high concentration delivery
- Cellular assays require less/no intermediate buffer dilution
  - Simpler protocols, less chance of compound precipitation
- Enables much smaller working volumes
  - Conventional tip methods require 30-60uL or more to supply enough material for serial dilutions over several assays
  - For ADE 10 µL 10 mM stock is sufficient
  - At $20-$500/mg compound, dollar savings are less of a factor
- Library samples last much longer
  - Can use smaller scale synthesis
  - Fewer re-plates, fewer reorders/less resynthesis
- External partners and collaborators can provide much less sample

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Getting the most value from ADE

- Which devices
- What Quality Control and maintenance procedures
- Which users & what training
- Which scientific applications

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Merck Boston Echo Timeline

A decade of acoustic dispensing

2005
Echo 550

2009
Echo 520

2011
Echo 555

2014
Echo 555

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015

Echo 555
2007

Echo 555
2010

Echo 550
2011

7 Echoes deployed over 10 years

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Automation Approaches

- Stand alone workstations
  - Echo 520 2009
  - Echo 555 2011
- Integrated Echo systems
  - Single Echo System
    - Echo 550 2005
  - Dual Echo System
    - Echo 555 2007
    - Echo 555 2010
- Fully integrated assay systems
  - Echo 550 2011
  - Echo 555 2014

Stand alone Echo 520

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Merck Boston Echo Systems

Echo 550 System
- Echo 550
- Combi nL (x2)
- Staubli
- 75 Plate Positions

Echo 555 System
- Echo 555 (x2)
- 75 Plate Positions
- Staubli
- *PlateLoc*
- *Xpeel*

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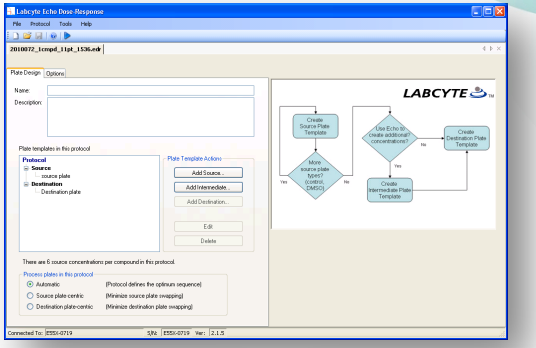
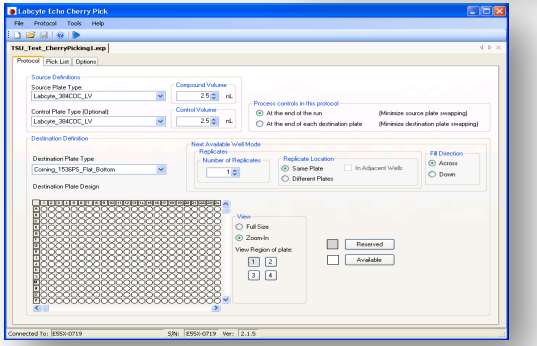
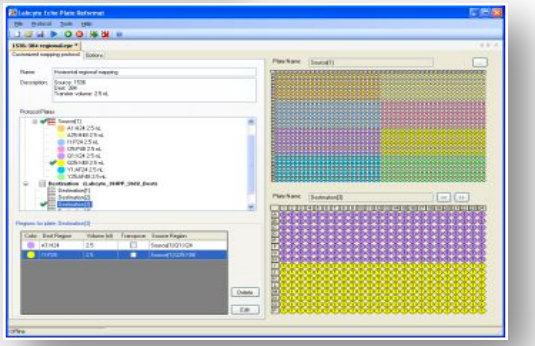
Optimizing ADE Software Applications

- Labcyte
  - Reformatting
  - Stamping
  - Dose Response
  - Cherry Pick
- HighResBio
  - Cellario
  - Echo Expansion







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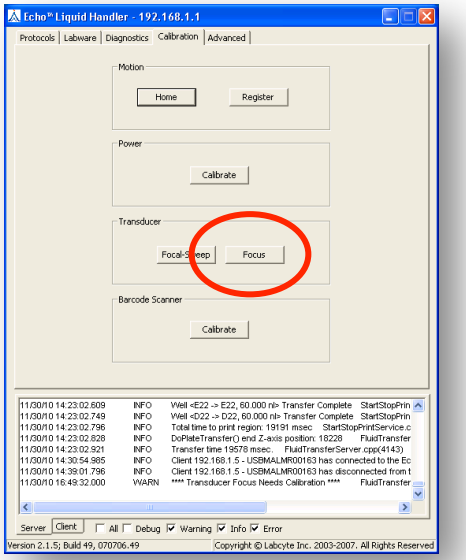
Maintenance Schedule is Key

- Focus Calibration
  - Bi-monthly
  - Follow wizard
  - No user input required
- Refilling water
  - Weekly
  - Distilled Water
  - Algaecide
- Bottle Cleaning
  - Yearly
  - Autoclaved



- Quality Control (QC)
  - Bi-monthly
  - Artel MVS
- Echo Health Check
  - Bi-yearly
  - Extensive QC
  - Checks each calibration

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Artel QC

- Routine QC
  - 3 or 4 Echoes tested each week
  - Single source dye at 100% DMSO
  - 3 destination plates per Echo, 1 source plate for each of the 3 plate types
  - ArtelWare Software keeps records over time

- Echo Health Check
  - Determine hardware failures without running a full Labcyte calibration
  - Compare Echoes against each other
  - Compare Echoes over time
  - Requires 7 dyes, one for each calibration 70-100% DMSO
  - 21 destination plates per Echo, 7 source plates for each of the 3 plate types

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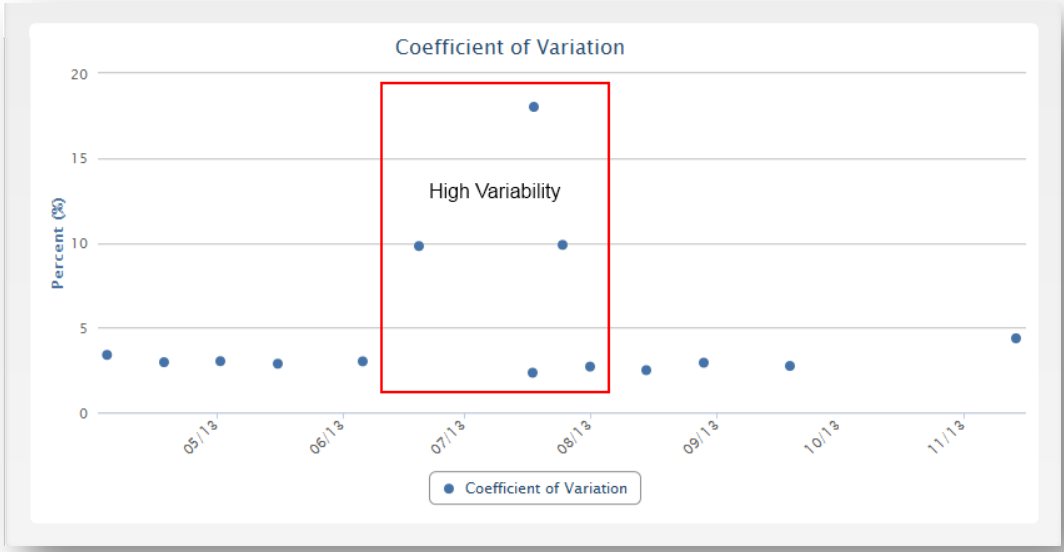
Case Study: QC Failure Prediction

- QC variability sustained over 2 months and at least 3 failed QC reports, results in a service call
- Failed QC result:
  - CV or Inaccuracy > 10% from target volume



- In June/July of 2013 there were 3 failed reports
  - Initiated service call with vendor
- Resulted in transducer replacement
  - Revealed bad manufacturing lot
  - Led to preemptive service on 3 additional instruments with same issue

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Training

- Echo training sessions
  - Every two months
  - Run by the engineering team
  - Includes live demonstration
  - Separate advance programming training available

- Approved users list
  - After training, the user is added to the list
  - List is posted by each Echo

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Training Guide

1. Users must be on the approved user list
2. Schedule time on the Outlook Calendar before using Echo
3. Do not turn off Echo unless you are filling water, refer to Echo water filling guide
4. Explain integration and stand alone anti-vibration tables
5. Maximum height of destination plates is 14.5mm and plates must be rigid to work with nests
6. Three or 4 source plates:
    a. Show physical plates
    b. Demonstrate matching inserts
    c. LV 6-9µL, LDV 2-10µL, PP 20-50µL, LVD1536 1-5µL
    d. Do not heat seal source plates before dispensing
    e. Centrifuge plates to between 1000 and 2000 RPM
    f. Hold plates on edges, do not touch bottom, prevents static
7. If doing a wet dispense, ensure that the destination plate can be help upside down
8. Show how to recover plates in case of an error or an abort
    a. Demonstrate homing the system
    b. Explain the soft and hard resets
    c. Contact engineering staff in case of any other errors or questions
9. Show how to create and perform a simple plate stamp
    a. Always use Quadrant mode
    b. Dispenses between 2.5 and 250nL, no more than 1.2 µL dispensing may be inaccurate
10. Show types of dispensing applications available: Stamp, Cherrypick, Reformat, IC-50 Dose Response
    a. Separate training on advanced application is required
11. Explain top two checkboxes on software in the advanced tab, used to save survey and print data

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Echo Quick Guide

- **Before** using the Echo:
  - Sign up on the corresponding calendar:
    - The integrated Echo 550 (Yellow Tape) calendar is "Boston Echo 550 2005 11-301".
    - The integrated Echo 555 (**Red Tape**) calendar is "Boston Echo 555 2007 11-301".
    - The integrated Echo 555 (**Green Tape**) calendar is "Boston Echo 555 2010 11-301".
    - The stand alone Echo 520 (**Blue Tape**) calendar is "Boston Echo 520 2009 11-301".
    - The stand alone Echo 550 (White Tape) calendar is "Boston Echo 550 2011 11-301".
    - The stand alone Echo 555 (**Orange Tape**) calendar is "Boston Echo 555 2011 11-301".
  - If using the Echo 550 and 555 please make sure the integrated system is not running.
  - Do not heat-seal source plate prior to dispensing.
  - Hold plates by the edges to minimize static.
  - Always centrifuge source plates.
  - Centrifuge destination plate for wet dispensing.
  - Destination plate height cannot exceed 14.5 mm.
  - If Echo requires a **Focus Calibration**, only attempt when water temperature is 22±0.5° Celsius.
  - **Bio-Rad** destination plate must be placed with A1 in the lower right corner.
  - Acceptable volume ranges for Echo source plates:
    - 384PP is 20-50µL
    - 384LV is 6-9µL
    - 384LDV is 2-10µL
    - 1536LDV is 1-5.5µL (only used on 2011 Echo 550 (White Tape) and 2011 Echo 555 (**Orange Tape**)
  - Check water level before running your protocol. If water level is below 300mL:
    - Turn off the Echo by using the power switch in the back of the Echo.
    - Remove the cap from the water bottle.
    - Using distilled water only; fill the water bottle to 900mL.
    - Add 1 drop of algaecide depending on the directions on the algaecide bottle.
    - Close the Echo water bottle and turn the Echo power back on.
    - Wait for the Echo to initialize before running your protocol.
  - If using a cherry pick list with the system in automated mode, make sure to use the following strings: Source Plate Barcode, Source Well, Destination Plate Barcode, Destination Well, Transfer Volume, Source Row, Source Column, Destination Row, Destination Column
- **After** using the Echo:
  - Close Dose Response and Cherry Pick programs.
  - Close enclosure doors.
  - Keep source adapters in the corresponding black labeled boxes.
- If you have questions or need a protocol please contact Catherine Quintero, Erik Brizzee or Kristen Tran
  - **If you have any errors, please take a screen shot and call.**

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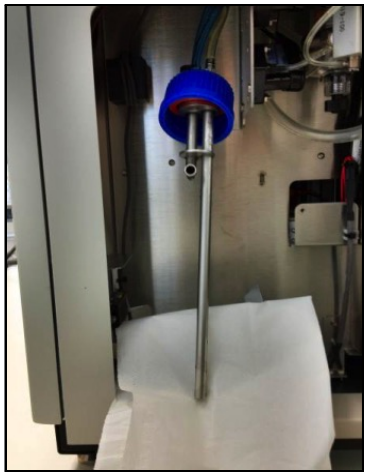
Echo Water Filling Guide

1. **Ensure the Echo is not in use.**
2. **Check to see if water is below 50%**

3. **Turn off Echo**

4. **Uncap water bottle and rest pipe on paper towel**



5. **Fill water bottle to fill line**

6. **Add 1 drop of algaecide**

7. **Cap water bottle and turn on Echo**

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Acknowledgements

- Erik Brizzee
- Labcyte
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- All our users for providing feedback

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Questions

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