Radiosynthesis in Microfluidic Devices

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April 17, 2013

Outline

- Brief recap
  - PET probe production
  - Centralized vs Decentralized production
- Motivation for microfluidic synthesizers
- Microfluidic synthesis examples
  - Continuous flow synthesizers
  - [^{18}F]fluoride drying methods compatible with continuous flow
  - Batch mode synthesizers
  - Optimization of reaction conditions (antibody labeling)
  - Visualization of microfluidic chips

Production of PET Tracers

Radioisotope Production → Radiolabeling, Purification, and Formulation → Quality Control Testing

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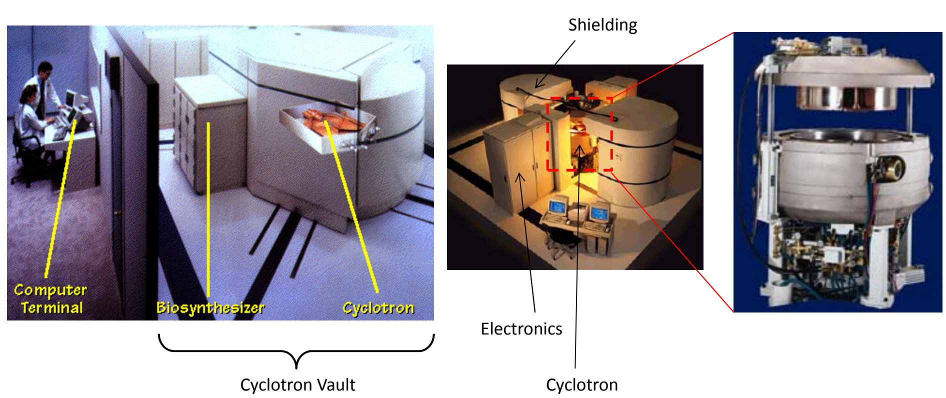
Radioisotope Production → Radiolabeling, Purification, and Formulation → Quality Control Testing

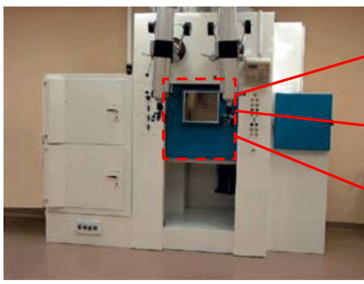
Nuclear reaction



Production of PET Tracers

Radioisotope Production → **Radiolabeling, Purification, and Formulation** → Quality Control Testing

Chemical reaction, chromatography, solvent exchange


Hot cell


Radiosynthesizer


Rotary evaporator


Semi-prep HPLC

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Production of PET Tracers

Radioisotope Production → Radiolabeling, Purification, and Formulation → **Quality Control Testing**

Analytical chemistry


Gas chromatograph (measure residual solvents)


Radio-TLC (measure purity)


Analytical radio-HPLC (measure purity)


Dose calibrator (measure radioactivity)

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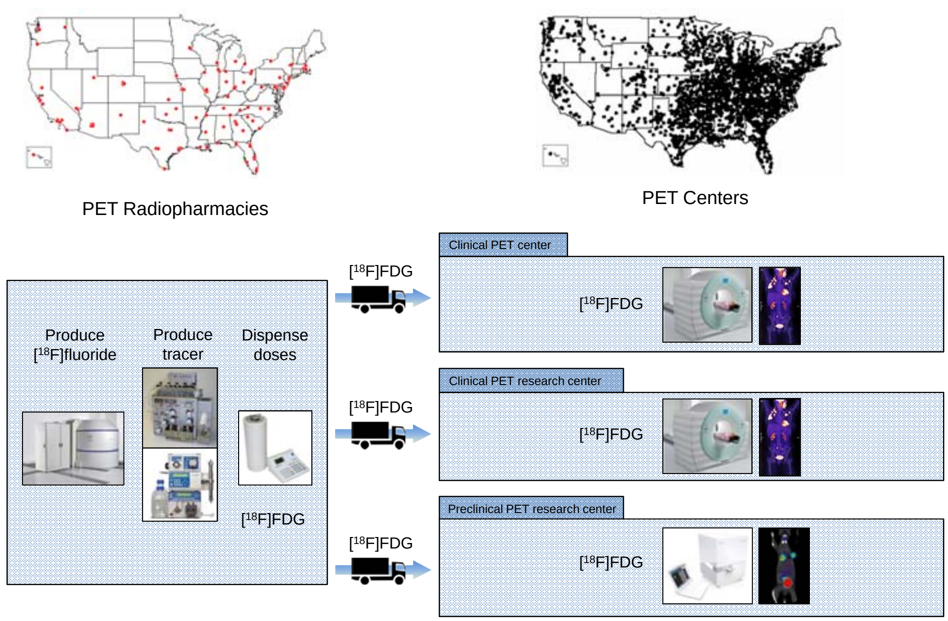
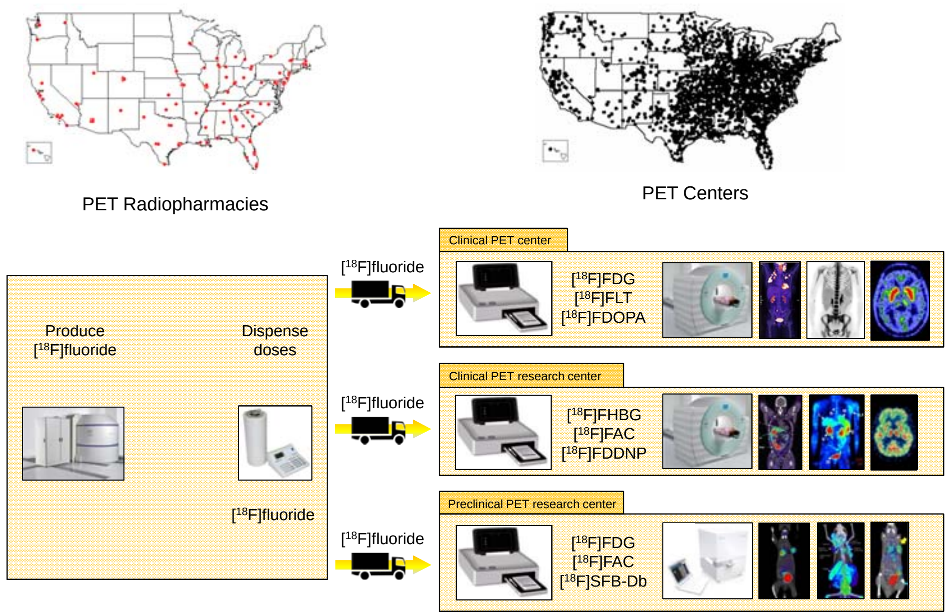
Production is currently very expensive

- Equipment costs
  - Radiosynthesizer and HPLC purification
  - Dedicated synthesizer for each tracer
  - Analytical equipment for QC
- Infrastructure costs
  - Radiation hazard requires use of expensive hot cells
  - Size/weight of hot cells requires site planning
- Operating costs
  - Maintenance and repairs for each equipment
  - Personnel with specialized expertise
    - Synthesizer setup and operation
    - Quality control testing
  - Reagents and consumables

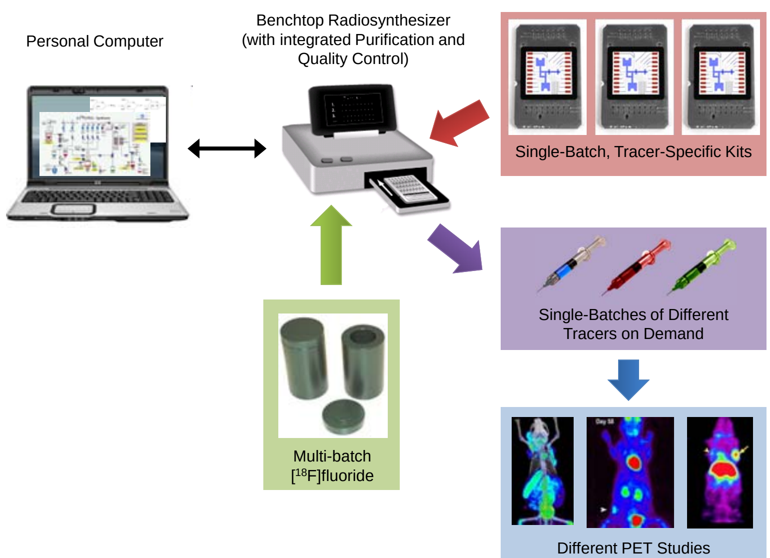
PET probe production now: centralized



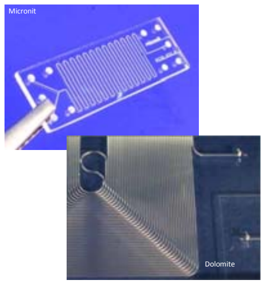
Paradigm shift: Decentralize production



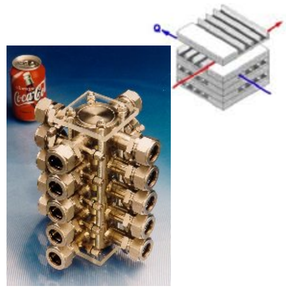
Need a technology that PET tracer production affordable and enables decentralization

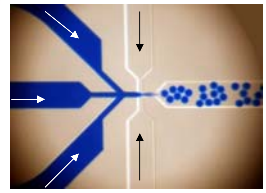


Microfluidics – an ideal platform for PET?

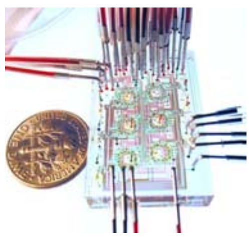


Glass microreactors

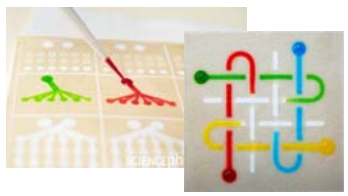

Metal microreactors


Continuous droplet microfluidics

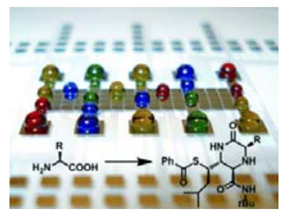
PDMS (silicone) microfluidics



Paper microfluidics



Digital microfluidics



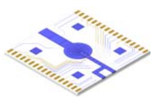
Importance of Microfluidics in Radiochemistry?

Compact size

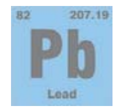
- During production of PET probes, shielding is needed to protect operator from gamma radiation
- Minimum size can be considered a “shell” around the synthesizer
- Thus mass of shielding scales as R^2

If synthesizer is size of a hot cell:
50” x 37” x 47” rectangular interior, 3” thick
Mass of Pb = 7600 kg

If size of mini cell:
27” x 20” x 24” rectangular interior, 3” thick
Mass of Pb = 2400 kg



Hypothetical future microfluidic system:
2” x 2” x 2” rectangular interior, 3” thick
Mass of Pb = 90 kg (BENCHTOP!)



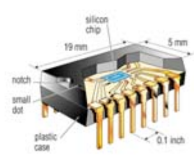
11.34 g/cm^3
T_H(Pb): 4.1mm

$$I = I_0 \left(\frac{1}{2} \right)^{\frac{T}{T_H}}$$

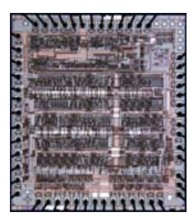
Low Cost Systems

- Many components can be integrated onto a single microfluidic chip, decreasing overall system cost
- Microfluidic chips can be mass-produced which drives cost of the consumables down

Microelectronics Revolution

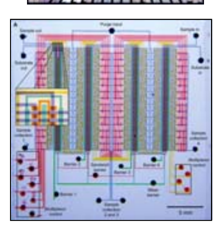


Parallel fabrication of many transistors



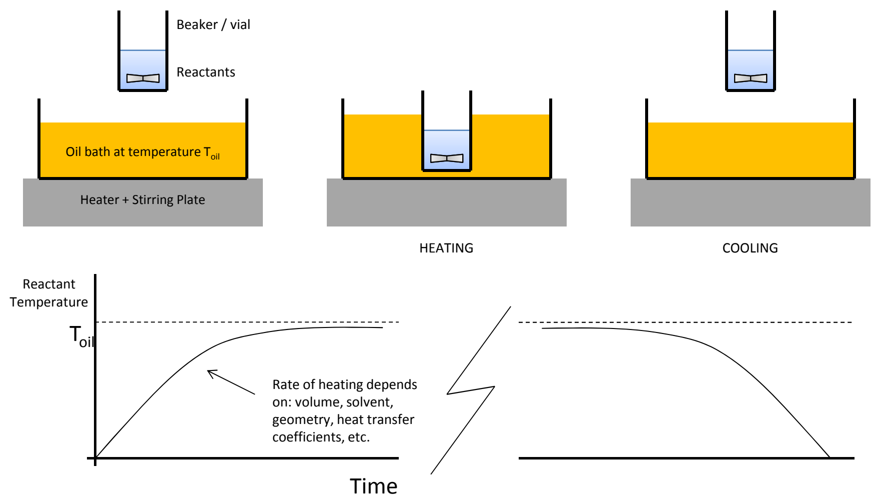
Microfluidics Revolution (Lab on a chip)

Parallel fabrication of many microvalves



Precise control of reaction conditions

Macroscale heating



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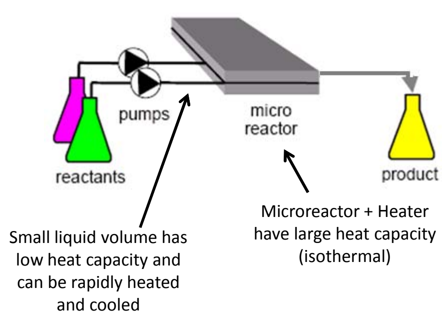
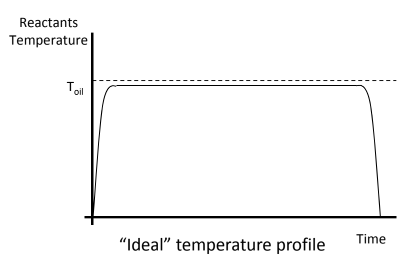
Microscale heating





"Ideal" temperature profile

Reactions
Alkylation and acylation
Oxidation
Nitration
Halogenation with fluorine, chlorine and bromine
Lithiation and Grignard reactions
Hydrogenation
Dehydration
Glycosylations
Diels–Alder
Wittig
Diazotisation and diazo coupling
Enamine synthesis
Aldol condensation
Michael addition
β-peptide synthesis
Chiral resolutions of epoxides
Free-radical, RAFT and ATRP polymerisations
Heck, Suzuki, Kumada, Sonogashira and Stille reactions
Nanoparticle and colloid synthesis – Au, CdSe, silica, polymers

Source: David Brown, Synthetic Chemistry in Microreactors

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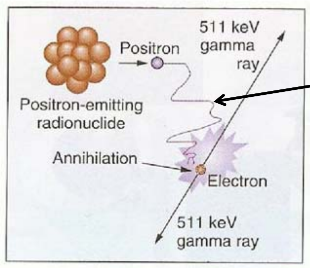
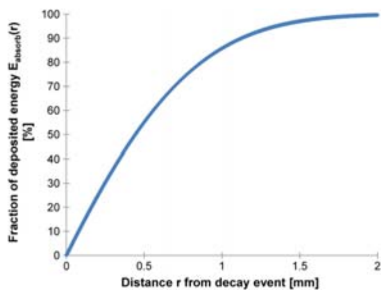
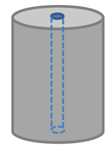
Reduced radiolysis



Energy deposited by scattering positron forms radicals in solvent and leads to radiolysis (radiation damage to the PET tracer)

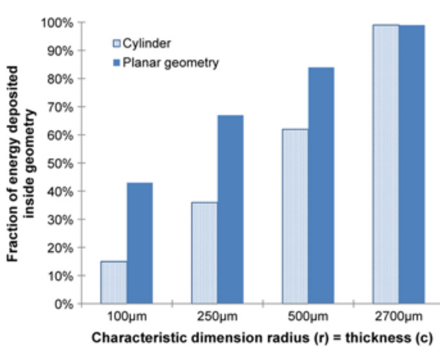


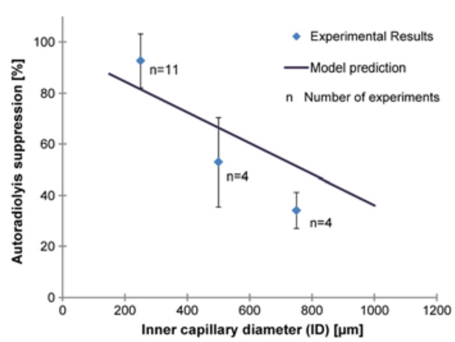


Cylinder, radius r

Planar droplet, thickness c

If characteristic dimension << positron range, positrons deposit very little energy in liquid



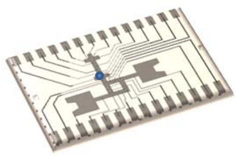


Rensch *et al.* Microfluidic reactor geometries for radiolysis reduction. Applied Radiation and Isotopes 70: 1691-1697 (2012)

Reduced reagent cost / consumption

Macroscale synthesizer

Typical reaction volume: 1.0 mL
Typical reagent cost: up to several hundred $



Microscale synthesizer

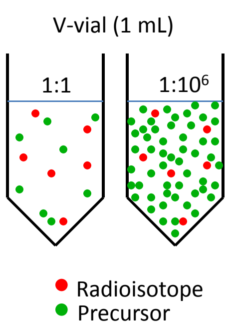
Demonstrated microscale volume: 10 µL = 0.01 * 1.0 mL
Reagent savings: 100X *

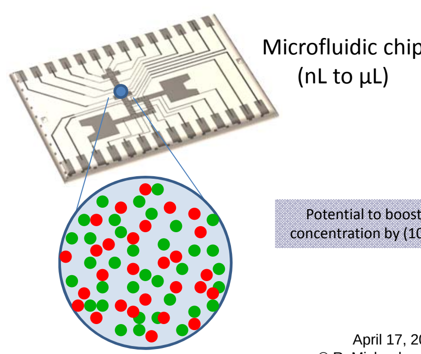
* Sometimes slightly less if higher reagent concentration needed

Boost concentrations for reactions

- Example: F-18

Theor. Max. Specific activity:	1710 Ci/µmol
Number of F-18 in 1 Ci	0.6 nmol
Concentration (1 mL):	0.6 µM
Human image needs ~10 mCi:	6 nM
Mouse image needs ~100 µCi:	60 pM



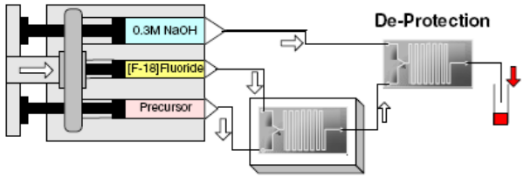


Potential to boost F-18 concentration by (10^3-10^6 x)

Additional advantages

- Increased specific activity? (Currently being investigated)
- Faster overall synthesis process

Continuous-flow Radiochemistry

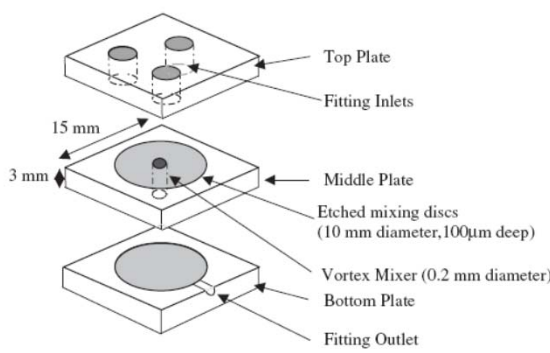


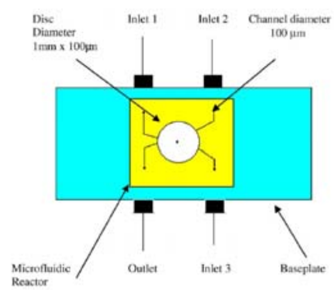
Steel et al. J Label Compd Radiopharm (2007)

Fluoride drying omitted

Volumes: 500 µL
Flow rate: 50 µL/min
Residence time: 9sec
(6 sec fluorination, 3 sec deprotection)
Total reaction time: 10 min

Polymer (polycarbonate and SU8)
microfluidic chip with vortex mixer

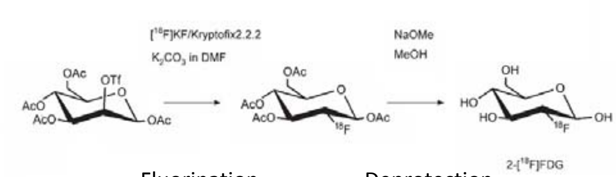




500 µL volumes
250 µL/sec flow rate
2 sec residence time
6 sec ***total*** reaction
No on-chip F-18 drying

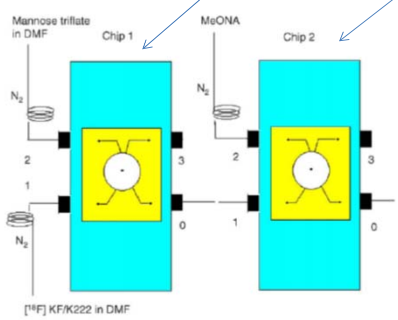
Gillies et al. Applied Rad. and Isotopes 64: 333-336 (2006).
Gillies et al. Applied Rad. and Isotopes 64: 325-332 (2006).

2-step synthesis of [18F]FDG



Fluorination

Deprotection



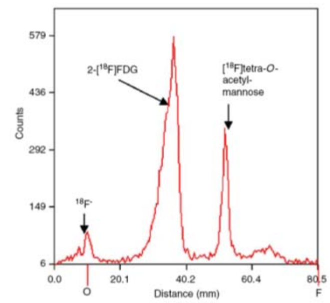


Fig. 8. Radio-TLC analysis of 2-[18F]FDG at 4s synthesised on-chip at ambient temperature.

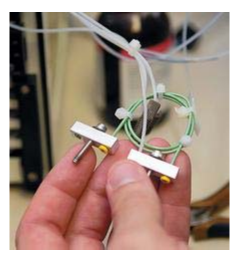
Commercial flow-through synthesizer: Advion NanoTek

Syringe pump module

Capillary reactor module

Evaporation module

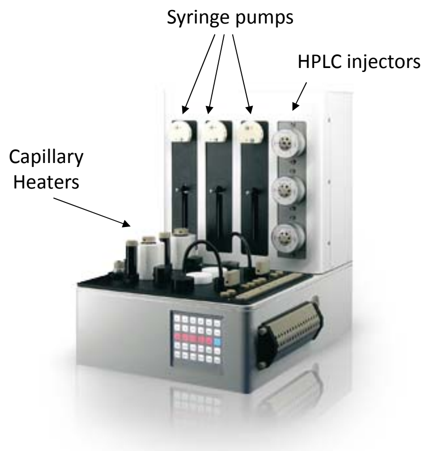
May need several of these

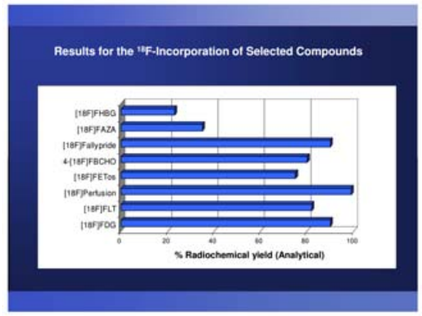


4 parallel mixers and reactors for up to 4-step reactions

Key abilities:
- High temperature
- High pressure
- Multiple back-to-back runs, optimization
- Volumes 100s of µL

Another commercial flow-through synthesizer: Scintomics µ-ICR





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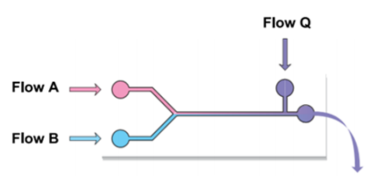
Another commercial flow-through synthesizer: Veenstra / Future Chemistry D-500



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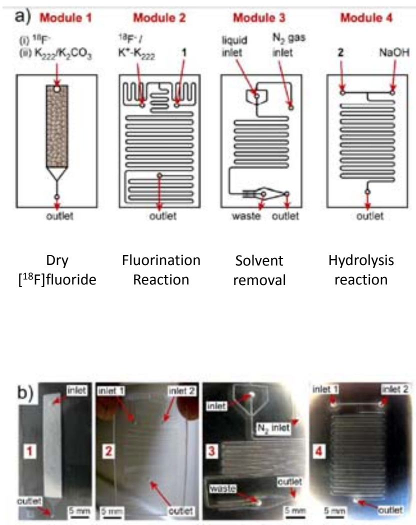
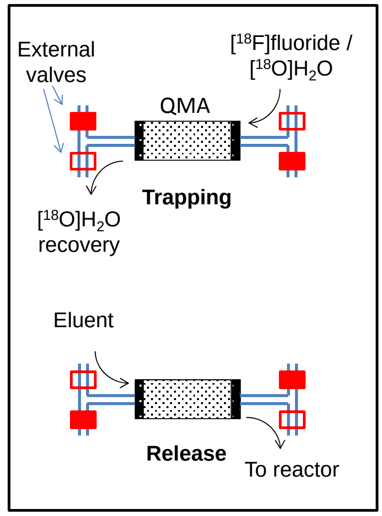
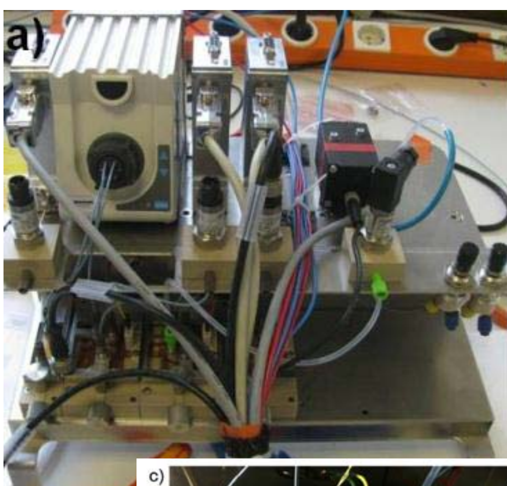
Radiochemistry-on-chip (ROC) project

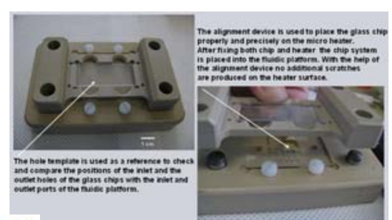


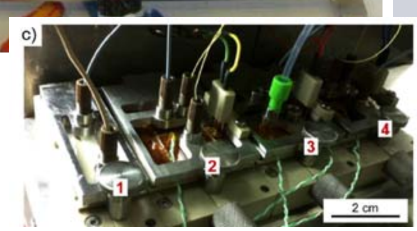
Module 1 traps in "batch" mode, then releases in continuous mode



Arima *et al.* 2013. Lab on a Chip. DOI: 10.1039/C3LC00055A







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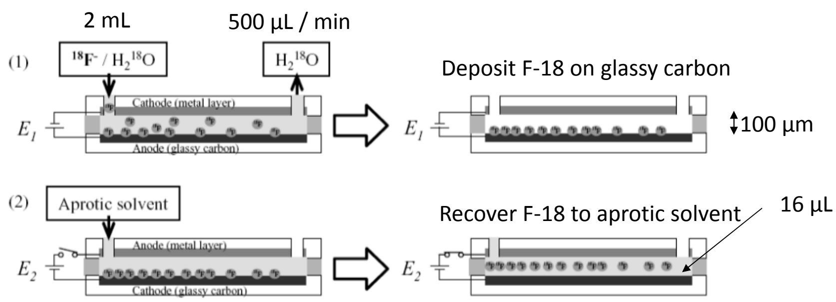
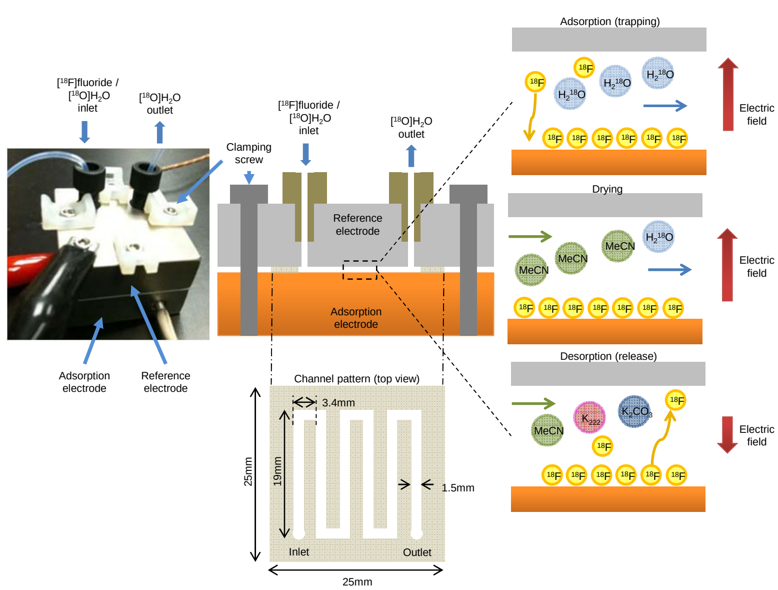
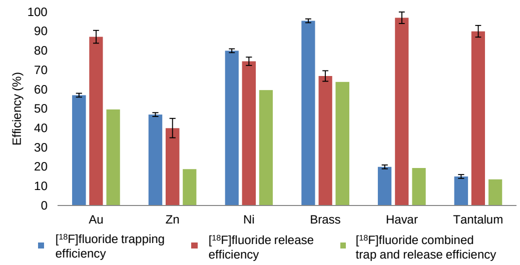
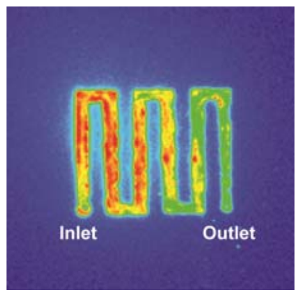
Microfluidic electrochemical trapping
(Traps in batch mode, releases in continuous mode)



Yamahara *et al.* Proc. MicroTAS 2007: 856-858
Saiki *et al.* Applied Radiation and Isotopes 68: 1703-1708 (2010)







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Batch Radiochemistry

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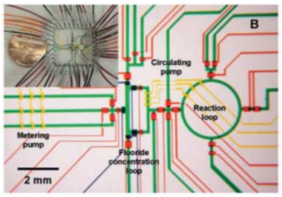
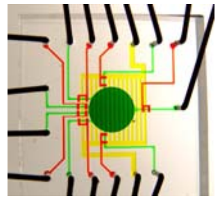
Batch-mode microsynthesis

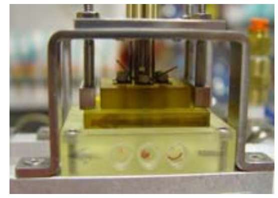


Lee *et al.* *Science* **310:** 1793 (2005)

40 nL reaction volume

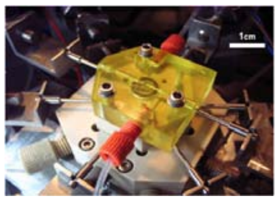


Elizarov *et al.*
J. Nucl Med **51(2):** 282 (2010)



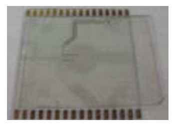
van Dam *et al.*
Proc Nanotech 2007 **3: 300** (2007)

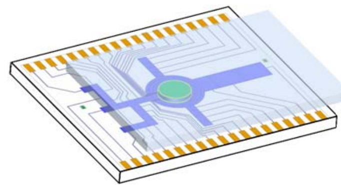
5 µL reaction volume



Bejot *et al.* *J. Label Compd. Radiopharm* **54:** 117-122 (2011)

60 µL reaction volume



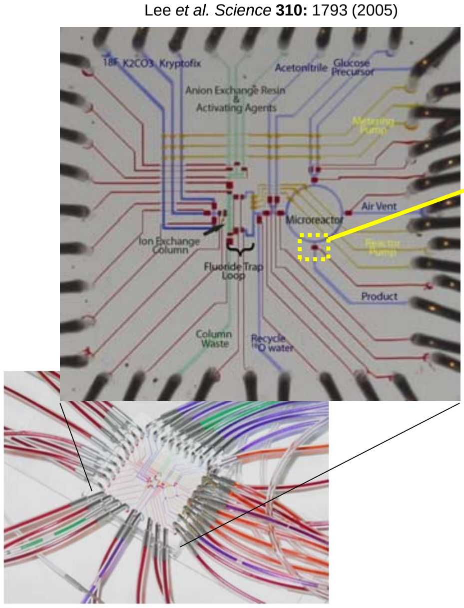


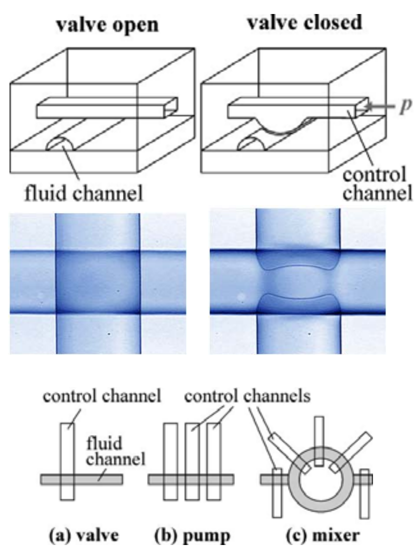
Keng *et al.* *PNAS* **109(3):** 690 (2012)

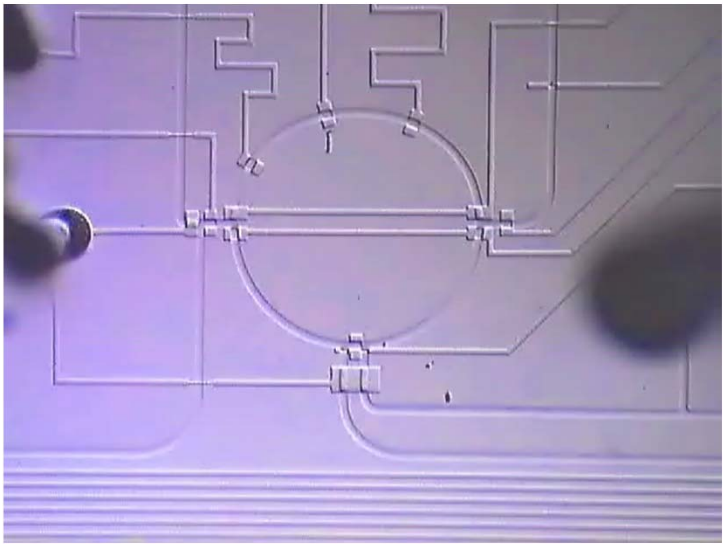
~1-16 µL reaction volume

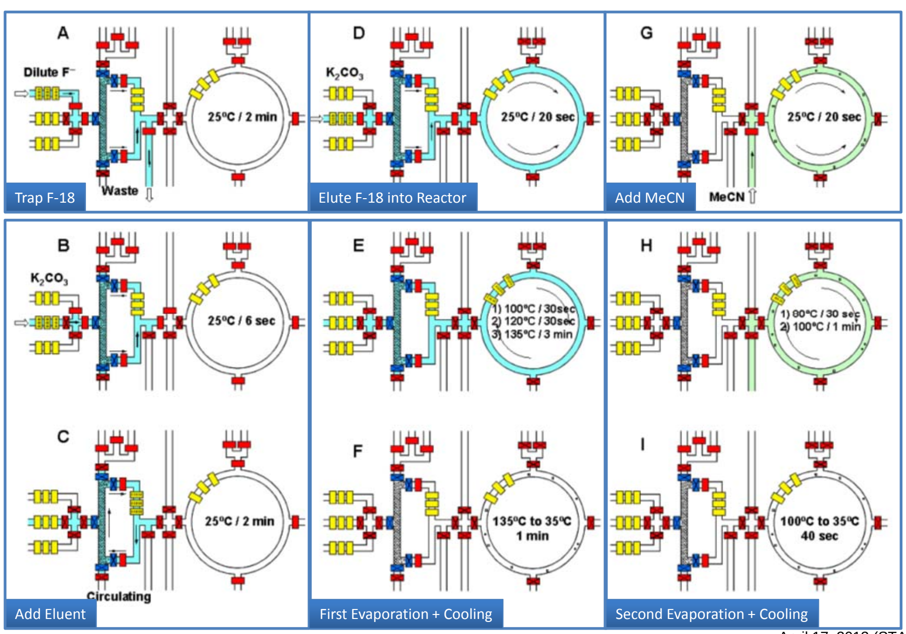
PDMS Microfluidics

Lee *et al.* *Science* **310:** 1793 (2005)

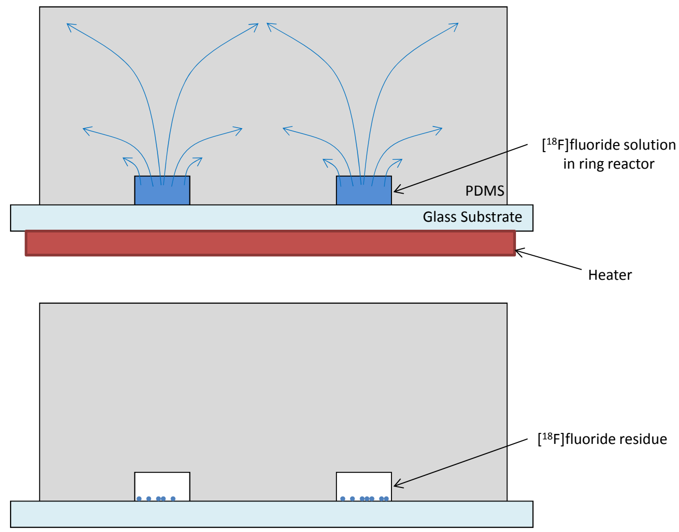




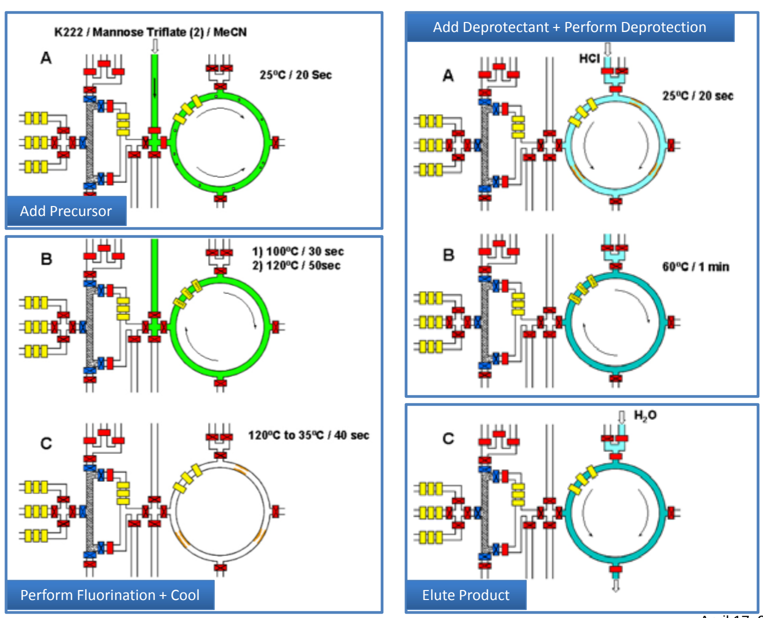



A
Dilute F⁻
25ºC / 2 min
Waste
Trap F-18
D
K_2CO_3
25ºC / 20 sec
Elute F-18 into Reactor
G
25ºC / 20 sec
Add MeCN
MeCN
B
K_2CO_3
25ºC / 6 sec
E
1) 100ºC / 30sec
2) 120ºC / 30sec
3) 135ºC / 3 min
H
2) 100ºC / 1 min
C
25ºC / 2 min
Circulating
Add Eluent
F
135ºC to 35ºC
1 min
First Evaporation + Cooling
I
100ºC to 35ºC
40 sec
Second Evaporation + Cooling

Solvent removal in PDMS microfluidics



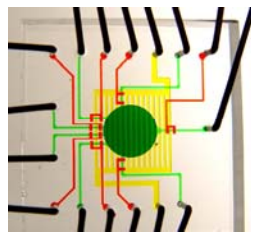
April 17, 2013 (START)



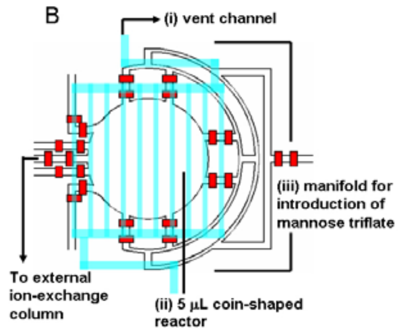
April 17, 2013 (START)

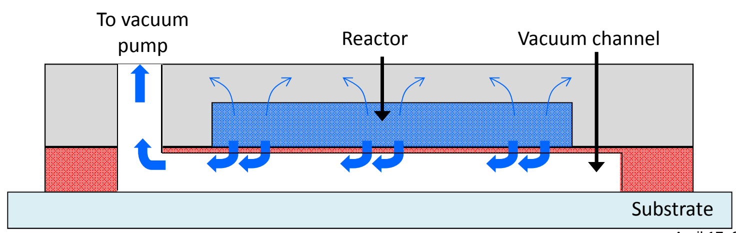
Scaled-up PDMS chip

Scaled-up chip for human dose
5 µL "coin-shaped" reaction volume

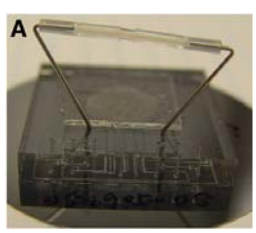


Elizarov, van Dam, et al. JNM 2010

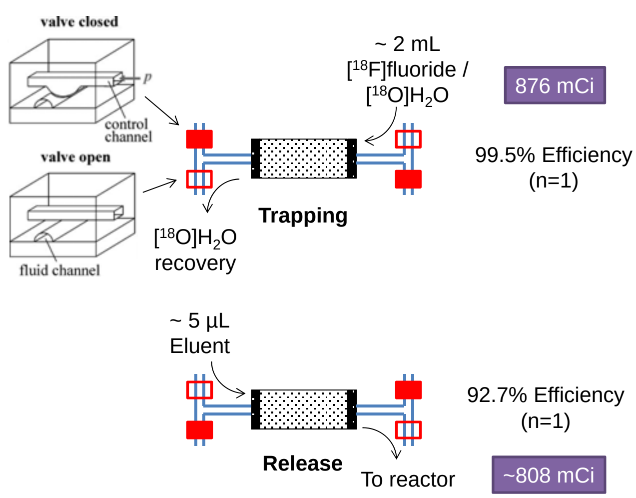




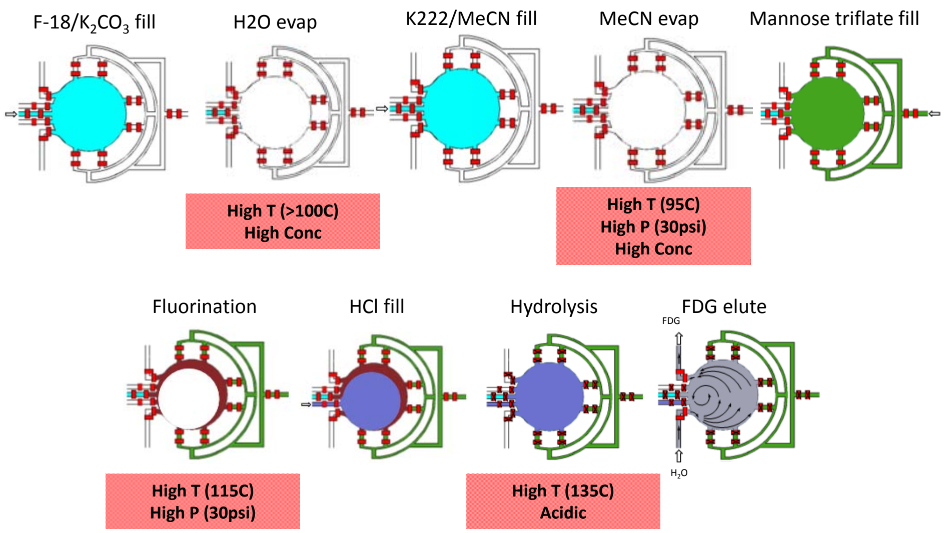
2 µL volume resin bed
(AG1-X8, BioRad)



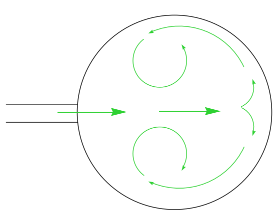
Elizarov *et al.*
J. Nucl Med **51(2):** 282 (2010)



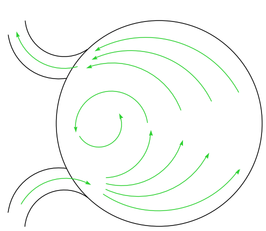
Synthesis process

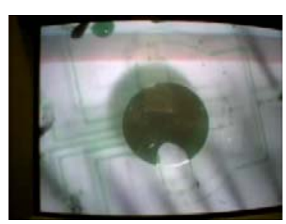


- Mixing



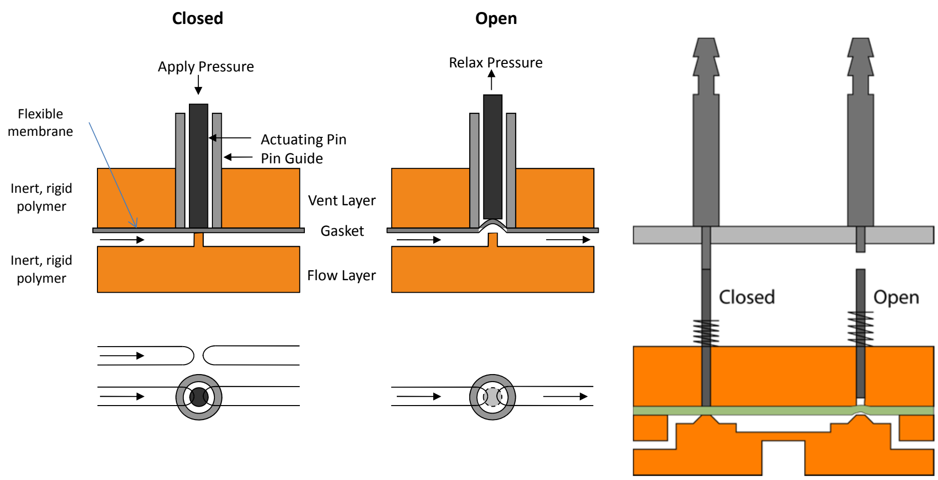
- Elution





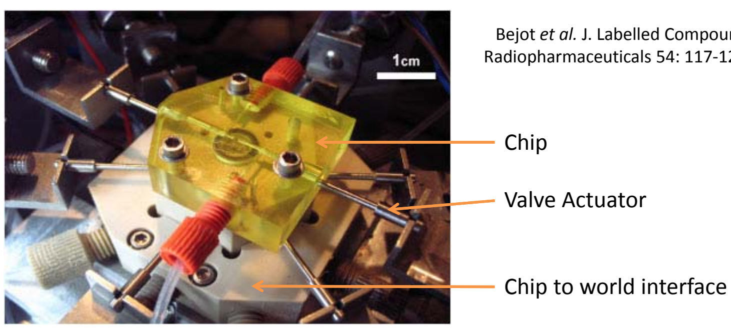
Elizarov *et al.* Biomed Microdevices 13(1): 231-242 (2010)

Alternative architecture for coin-shaped chip

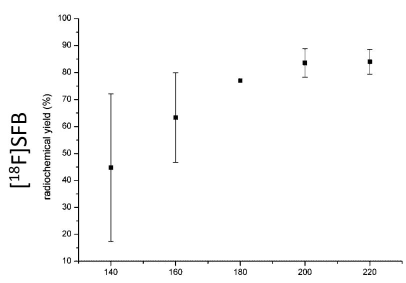


van Dam *et al.* Proc. Nanotech 2007

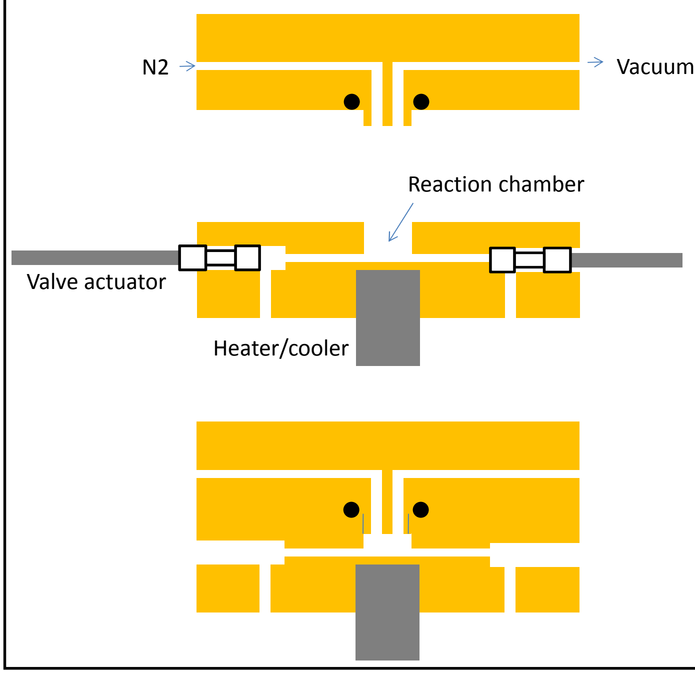
April 17, 2013 (START)

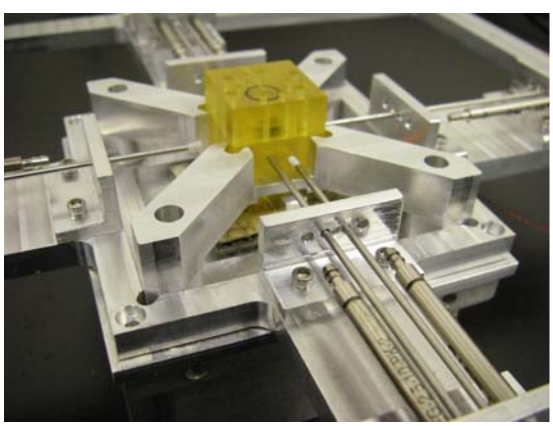


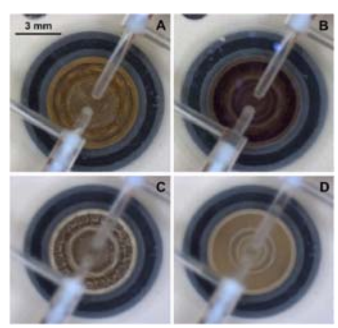
Bejot *et al.* J. Labelled Compounds and Radiopharmaceuticals 54: 117-122 (2011)



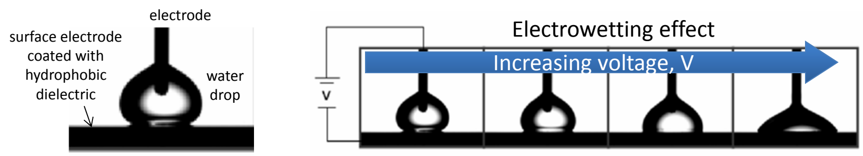
April 17, 2013 (START)

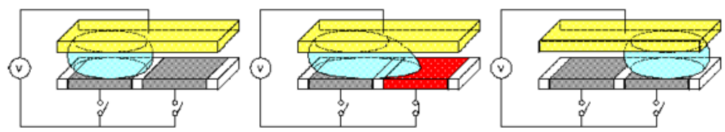

N2
Vacuum
Reaction chamber
Valve actuator
Heater/cooler



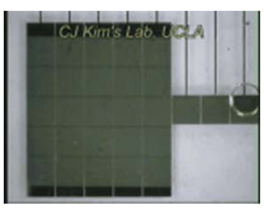

3 mm
A
B
C
D

Digital microfluidics: Electronic control of chemical reactions

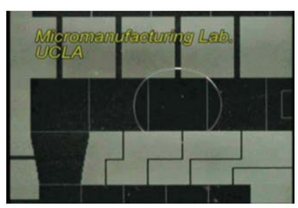




Unlike chips with internal or external valves and pumps, liquid movement is controlled *electronically*



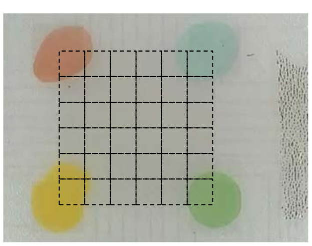
Droplet moving



Splitting Droplets

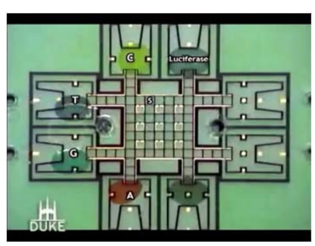
EWOD Concentration Video

Separations

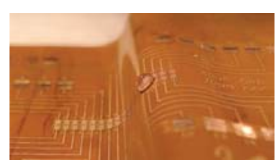


Droplet dispensing, moving, merging, splitting, mixing

Hyejin Moon Lab, UT Arlington

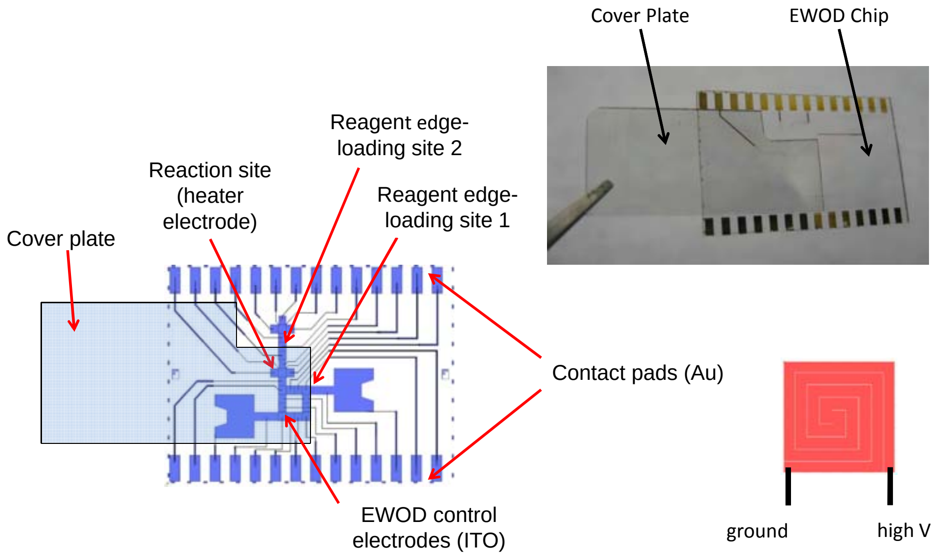


Richard Fair, Duke University



Aaron Wheeler, Univ. Toronto

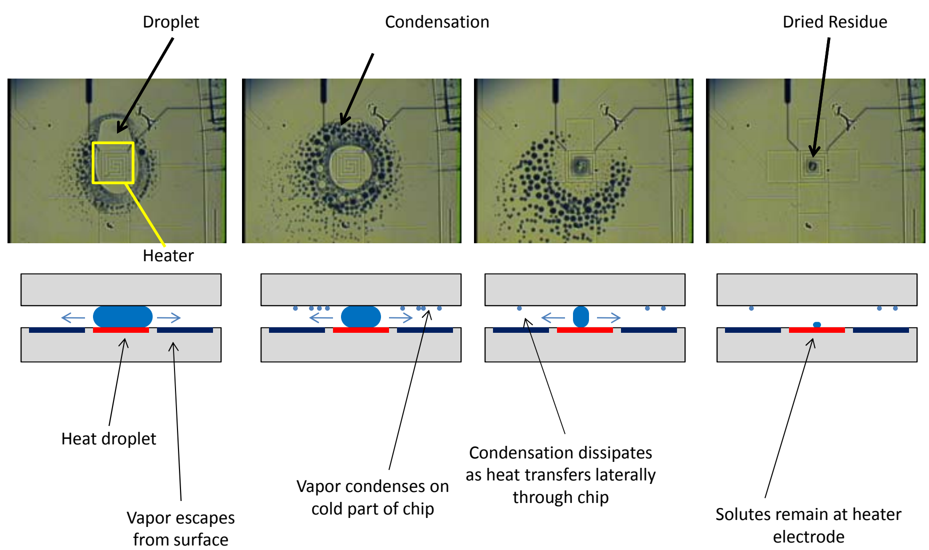
Radiosynthesis on digital microfluidics



Keng, van Dam, et al. PNAS 2012

April 17, 2013 (START)

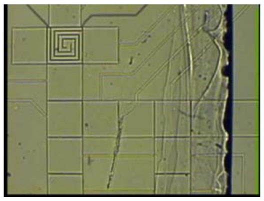
Open structure permits faster evaporations



April 17, 2013 (START)

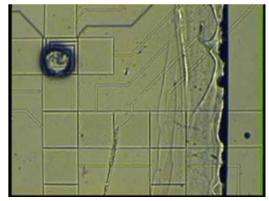
^{18}F-Radiosynthesis in EWOD chip

^{18}F Drying



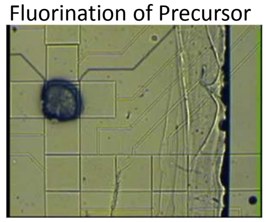
Add F-18 solution

Azeotropic Distillation



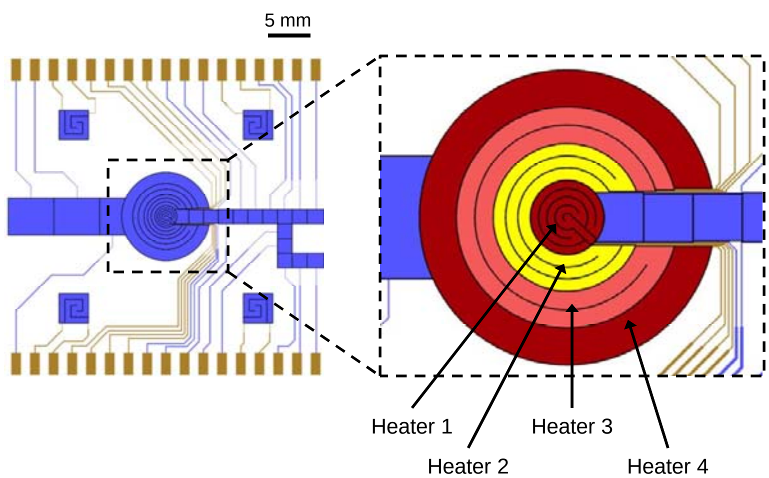
Add MeCN

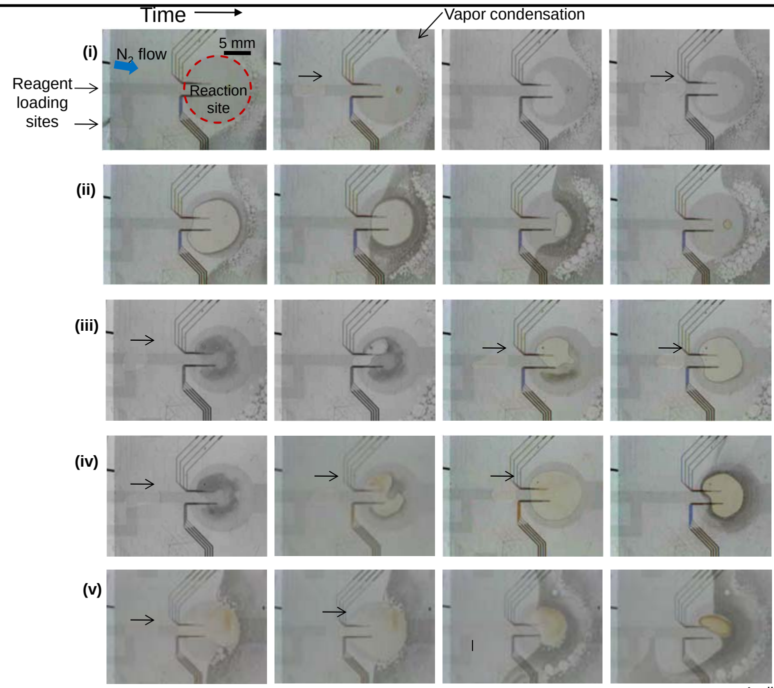
Fluorination of Precursor



Add Precsursor

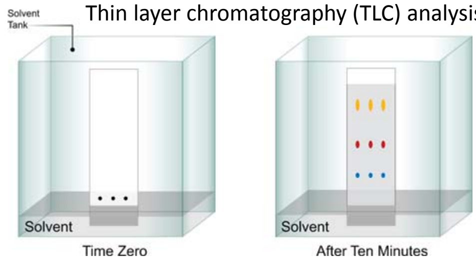
Scaled-up chip for larger doses





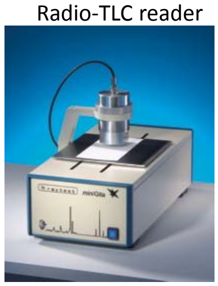
Demonstrated repeatable synthesis of [^{18}F]FDG

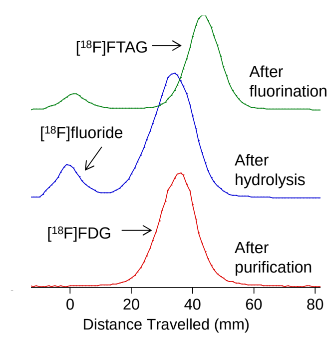
Thin layer chromatography (TLC) analysis



Source: Waters Corporation

Radio-TLC reader



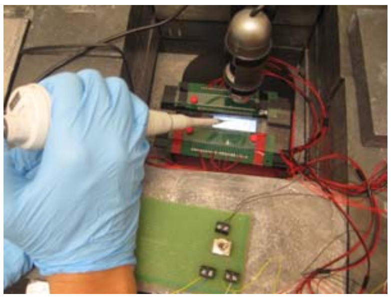


- Avg. fluorination efficiency: 88±7% (n=11)
- Avg. hydrolysis efficiency: >95% (n=9)
- Miniature off-chip purification: >99% pure
- Scale of synthesis: several mCi

Reagent loading

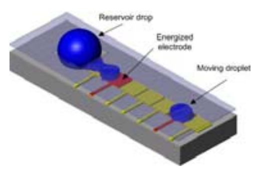
Proof-of-concept approach:

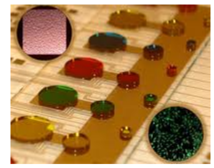
Manual reagent loading, product extraction, purification



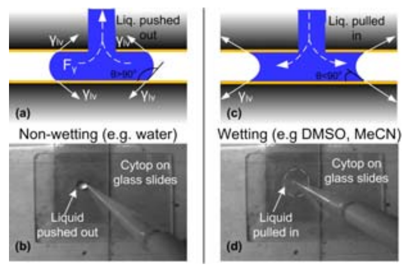
Need to store volatile reagents OFF chip, and introduce on chip on-demand

Typical EWOD approaches:





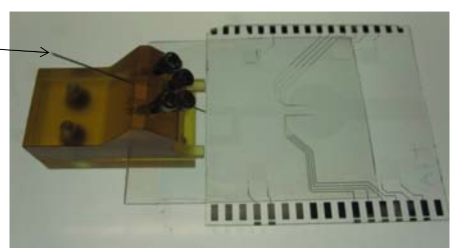
Reagents stored IN the chip

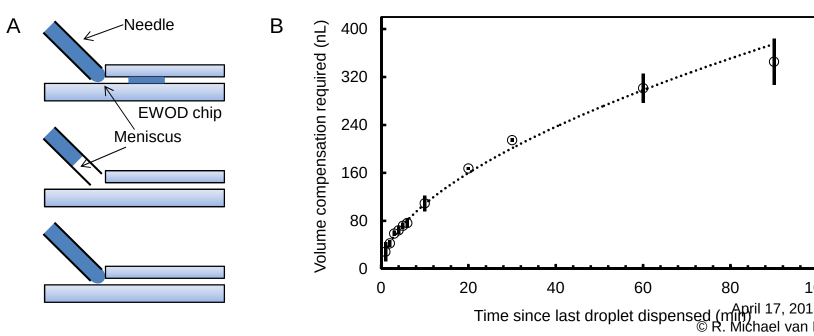


Reagents stored
ON TOP of the chip

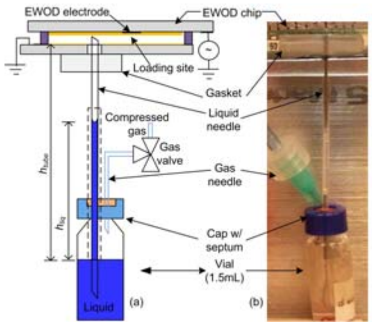
Simple reagent loading system

Syringe pump

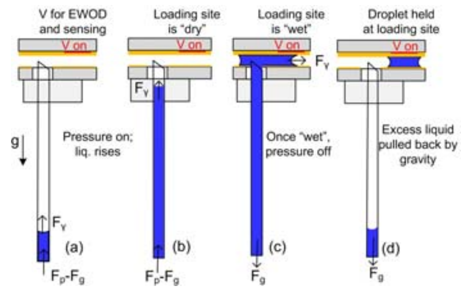


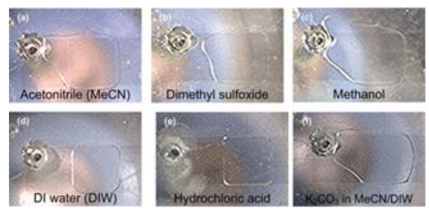


2nd-generation reagent loading



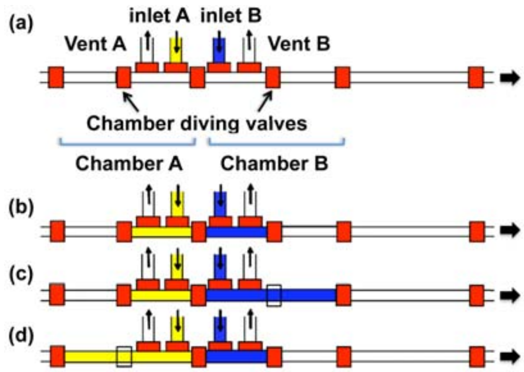
Reagents pushed with gas pressure; no syringe pumps

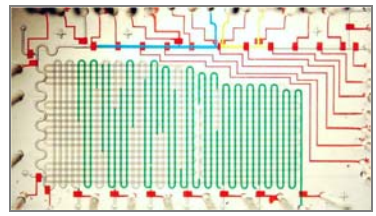




On-chip radiochemistry optimization

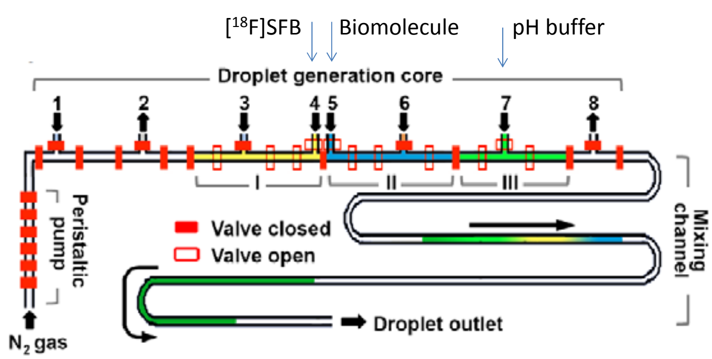
PDMS chip for generation of programmable droplet composition



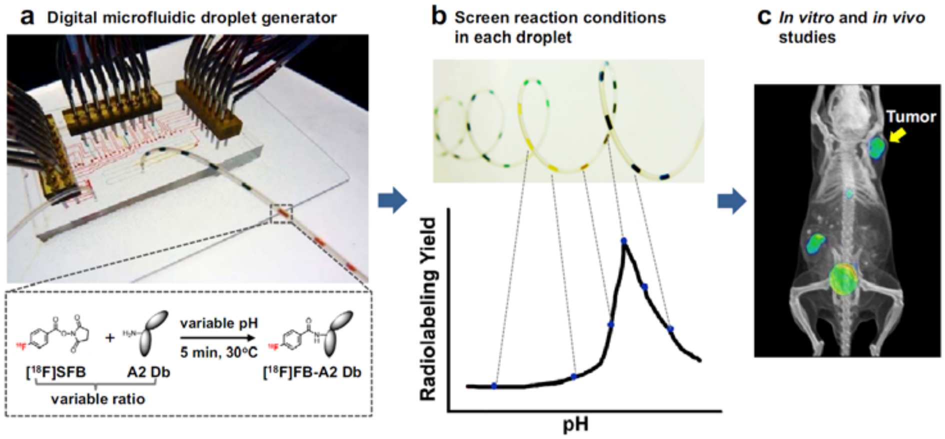


- Can perform analytical scale optimization to deal with batch-to-batch variations
  - Mix droplets with different ratios
  - Analyze
  - Pick best conditions for labeling a larger batch

April 17, 2013 (START)



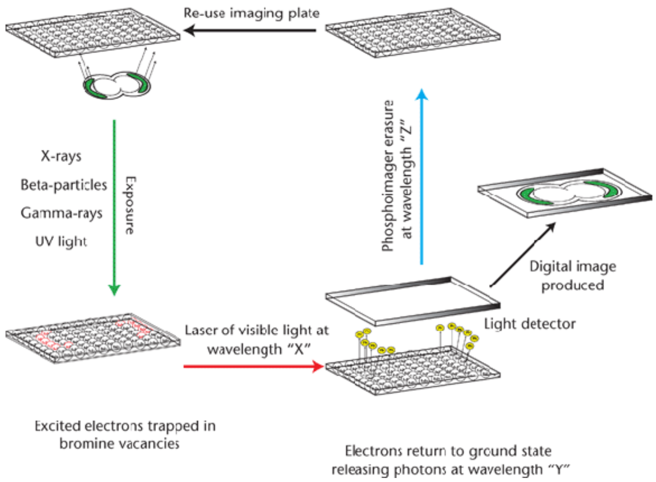
April 17, 2013 (START)

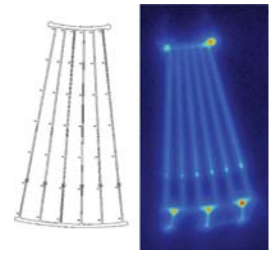


Liu *et al.* Molecular Imaging 10(3): 168-176 (2011)

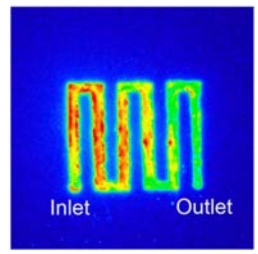
Tools for visualizing microfluidic radiochemistry

Phophorimager



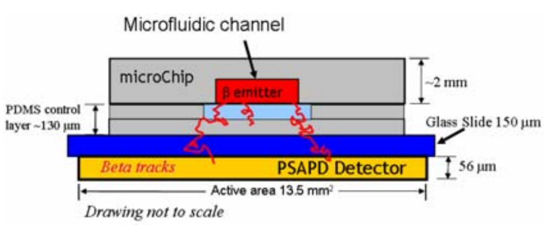


Ga-68
Lavén *et al.* Lab on a Chip 5: 756-763 (2005)



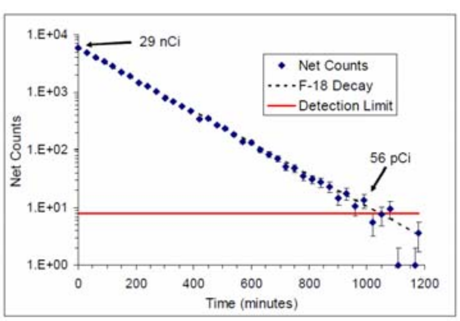
F-18
Sadeghi *et al.* Applied Radiation and Isotopes 75: 85-94 (2013)

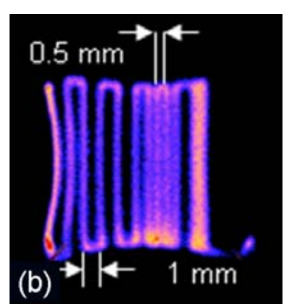
Direct positron detection with PSAPD



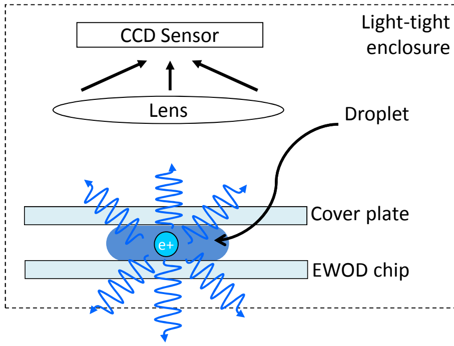
Vu *et al.* Proc. IEEE Nucl. Science Symposium 2006, pg 3536-3539

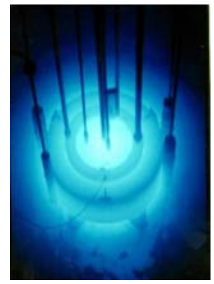
Vu *et al.* J Nucl. Med 52: 815-821 (2011)

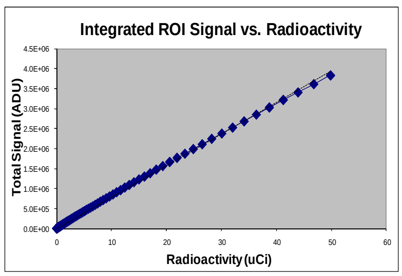


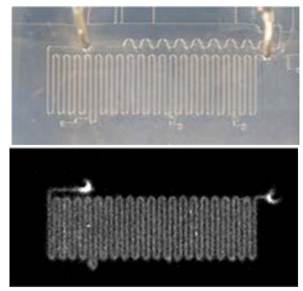


Čerenkov Imaging



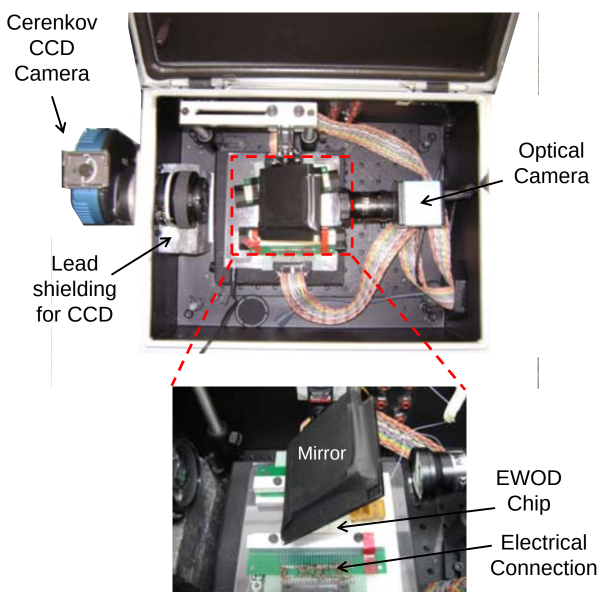




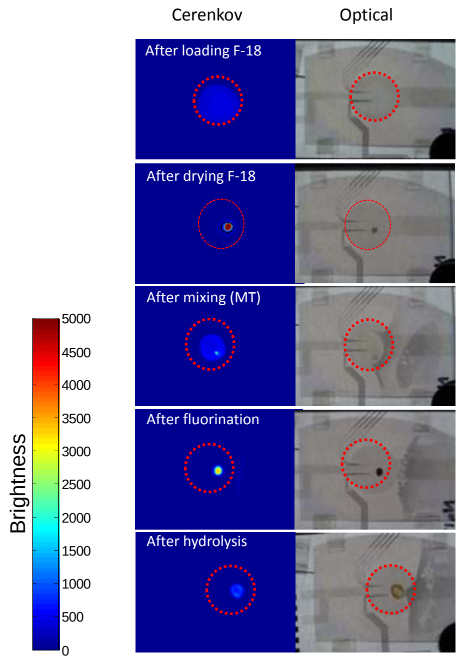


Cho *et al.* Phys. Med. Biol. **54** (2009) 6757–6771

2nd generation Cerenkov imaging setup



April 17, 2013 (START)



April 17, 2013 (START)

Summary

- Recap of PET tracer production
- Importance of microfluidics in radiochemistry
- Examples of microfluidic radiochemistry
  - Continuous flow synthesis
  - [18F]fluoride drying methods compatible with continuous flow
  - Batch mode synthesis
  - Reaction optimization
  - Visualization of microfluidic chips
- Next couple of weeks:
  - Microfluidic chip fabrication and cleanroom tour
  - Microfluidic chip lab / demonstration

April 17, 2013 (START)

Resources

- S. Y. Lu and V. W. Pike, "Micro-reactors for PET Tracer Labeling," in PET Chemistry: The Driving Force in Molecular Imaging, P. Schubinger, Ed. Springer, 2007, pp. 271–287.
- H. Audrain, "Positron Emission Tomography (PET) and Microfluidic Devices: A Breakthrough on the Microscale?," Angewandte Chemie International Edition, vol. 46, no. 11, pp. 1772–1775, 2007.
- P. W. Miller, "Radiolabelling with short-lived PET (positron emission tomography) isotopes using microfluidic reactors," Journal of Chemical Technology & Biotechnology, vol. 84, no. 3, pp. 309–315, 2009.
- A. M. Elizarov, "Microreactors for radiopharmaceutical synthesis," Lab Chip, vol. 9, no. 10, pp. 1326–1333, 2009.
- P. Y. Keng, M. Esterby, and R. M. van Dam, "Emerging Technologies for Decentralized Production of PET Tracers," in Positron Emission Tomography - Current Clinical and Research Aspects, C.-H. Hsieh, Ed. InTech, 2012, pp. 153–182.
- Watts et al. Positron emission tomography radiosynthesis in microreactors. J. Flow Chemistry 2(2): 37-42 (2012).

April 17, 2013 (START)