# Why Microfluidic Synthesis?


**NanoTek: A Microfluidic Flow-Chemistry System by Advion**

SNM

San Antonio 2011

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# References


- Quantitative Spatial Mapping of Mixing in Microfluidic Systems.
  Steven W. Magennis, Emmelyn M. Graham, and Anita C. Jones
  Angew. Chem. Int. Ed. 2005, 44, 6512 –6516

- Greener Approaches to Organic Synthesis Using Microreactor Technology
  Brian P. Mason, Kristin E. Price, Jeremy L. Steinbacher, Andrew R. Bogdan,
  and D. Tyler McQuade*
  Published on Web 03/21/2007 American Chemical Society

- Miniaturized continuous flow reaction vessels: influence on chemical reactions
  Monica Brivio, Willem Verboom and David N. Reinhoudt
  Lab Chip, 2006, 6, 329–344


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# Key Microfluidic Differences

- Mixing is by diffusion
  - A reproducible and rapid process under laminar flow.
  - Vial based mixing is turbulent and stochastic.
- Precise temperature control
  - High surface area to volume eliminates temperature gradients
  - Vial based systems exhibit considerable temperature variations within the vial.
- Short residence times
  - Incorporation typically undertaken in seconds.

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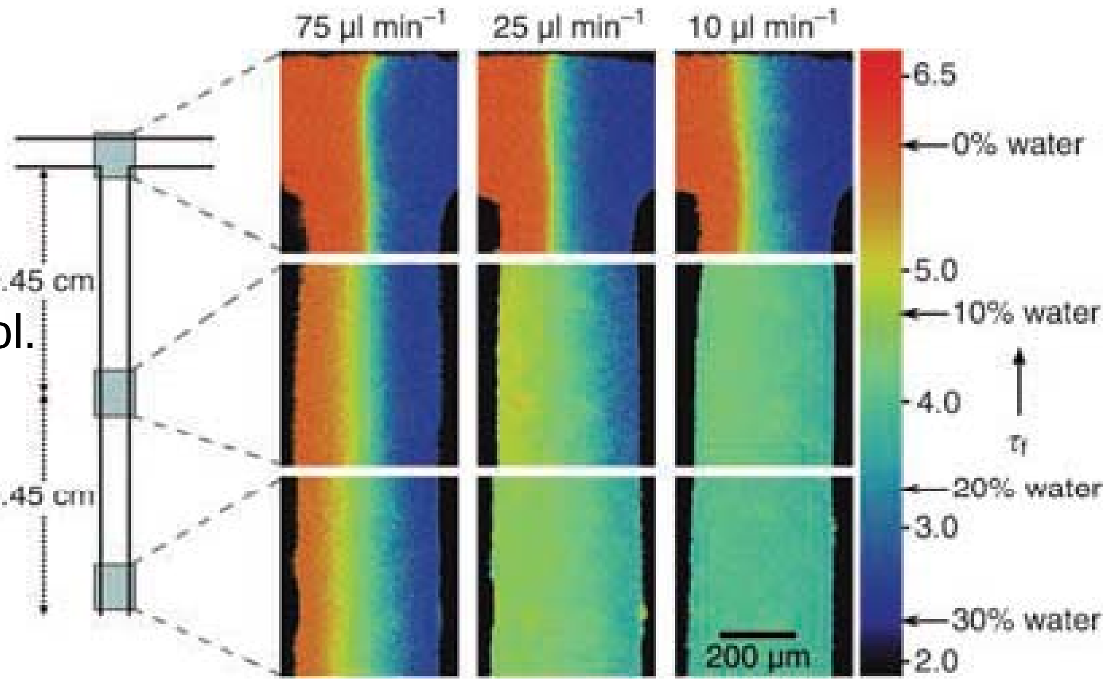
# Laminar Flow and Diffusion

## Fluorescence Lifetime Imaging Microscopy (FLIM)

Red = Fluorescent dye 1,8-anilinonaphthalene sulfonate (ANS) in pure methanol.

Blue = ANS in water/methanol mixture (1:1 molar ratio, which corresponds to water at 30.8% v/v)




- The compositional variation observed is indicative of two fluids under laminar flow there is no sign of turbulent mixing.
- The input streams are well-behaved. The two streams stay completely separate, except for the mixing region that results from diffusion as the fluids move further downstream.

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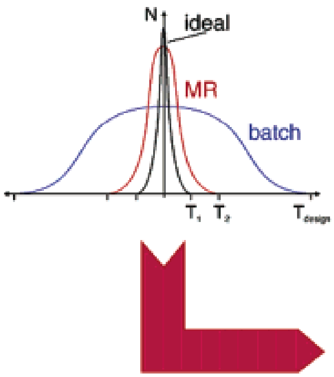
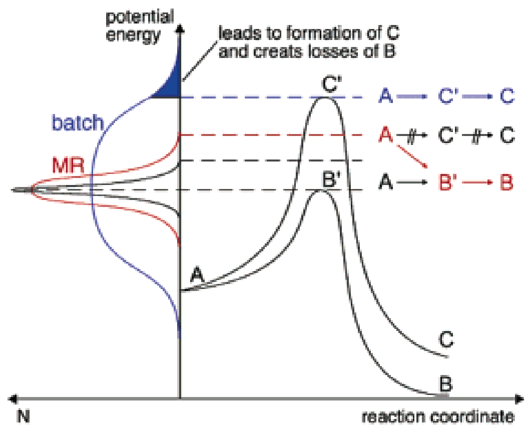
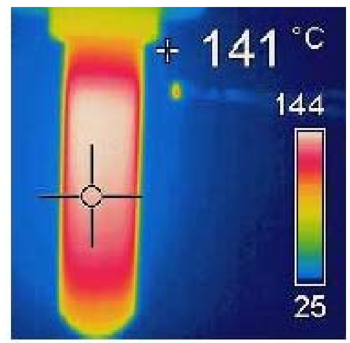
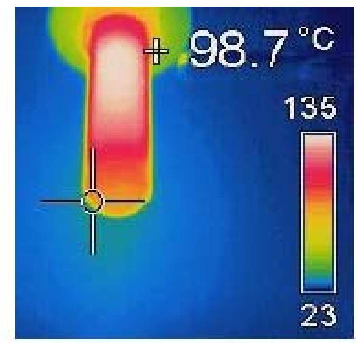
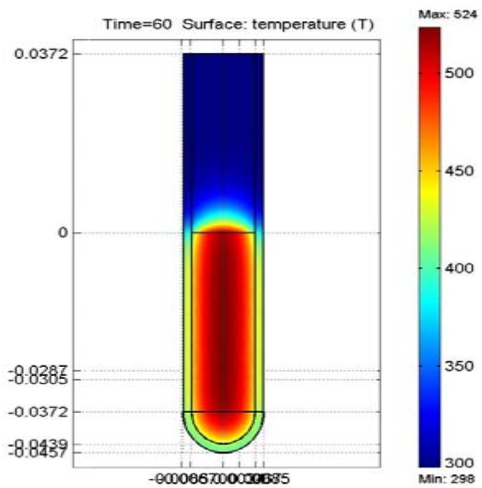
# Precise Temperature Control

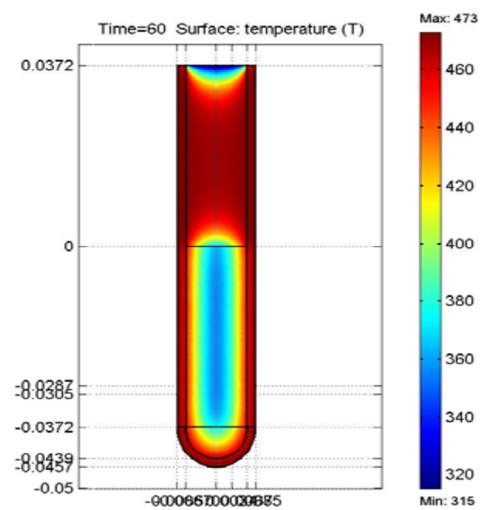


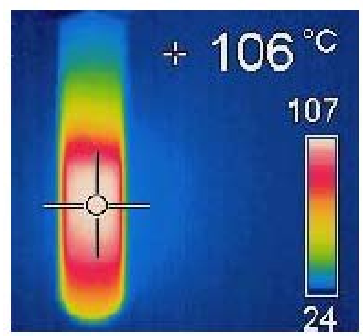



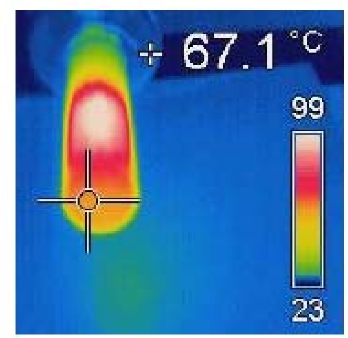

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# Potential Improvements Utilizing Microfluidics

- Speed
- Reproducibility
- Yield
- Purity
- Versatility
- Conservation of reagents

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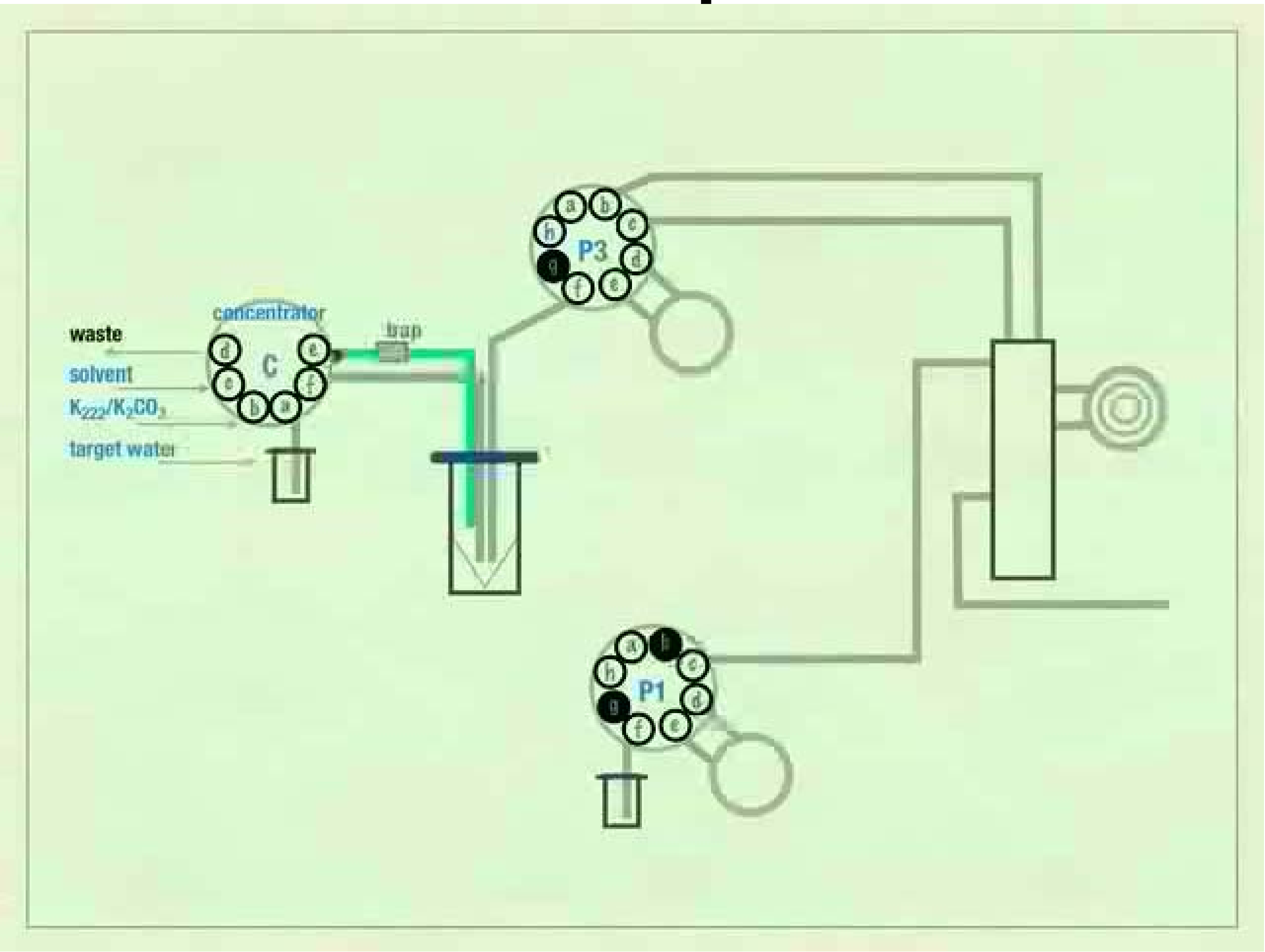
# Mode of Operation




E-mail info@advion.com to request a copy of the animation.

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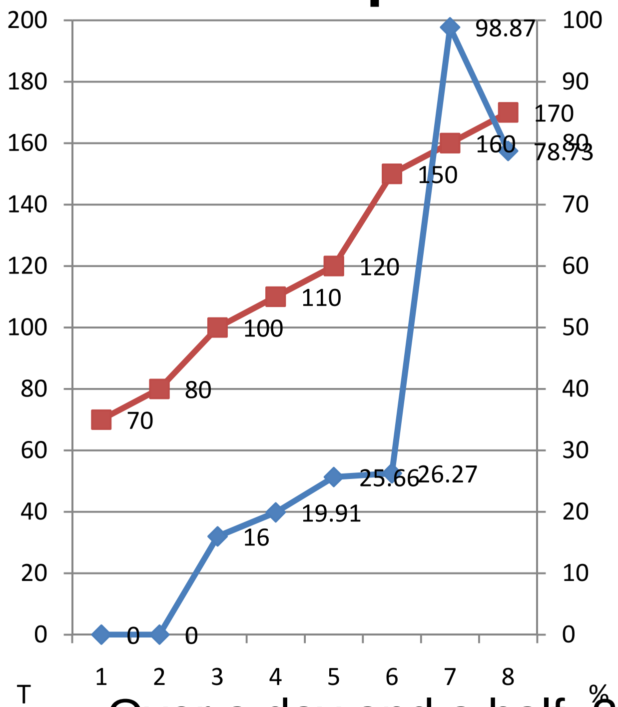
# Short Reaction Times: Proprietary Precursor Optimization

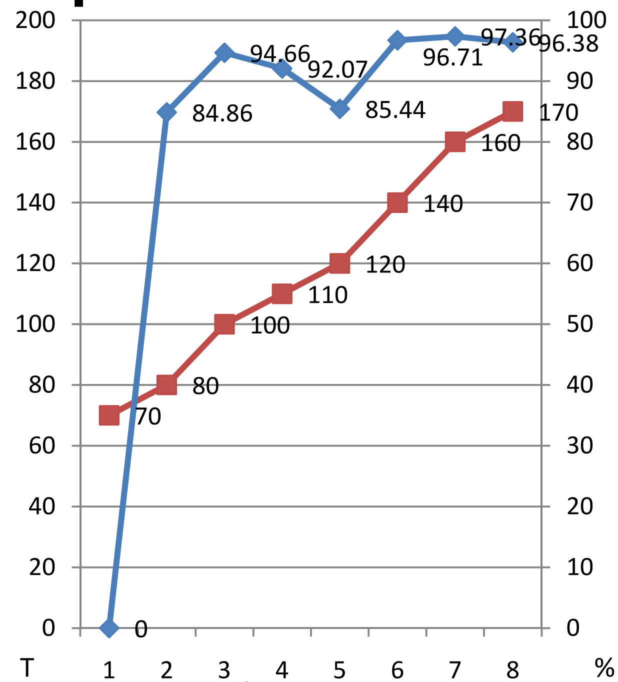



% RCY Radio TLC

DMSO

DMF

Reaction times 45 sec




- Over a day and a half, 20 experiments were conducted along with Radio TLC and HPLC analysis.
- Three solvents were evaluated at temperatures ranging from 700C to 1700C along with an initial evaluation of precursor concentration and reaction time.
- Reducing precursor concentration to 20% of initial experiments had little effect on overall labeling efficiency .

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# Reproducibility

- Intra-system example
  - UT, FLT the yield (uncorrected) starting with up to 1 Ci of [18F]fluoride was 22 ± 3% (n=20).
- Inter-system examples: Fallypride

| Temp | Reactor | %Yield | Activity | |
|---|---|---|---|---|
| 170 | 2 x 2M | 88 | 15.4mCi | NIH |
| 160 | 4M | 88 | NA | Wolfson |
| 170 | 4M | 93 | 4mci | Yale |

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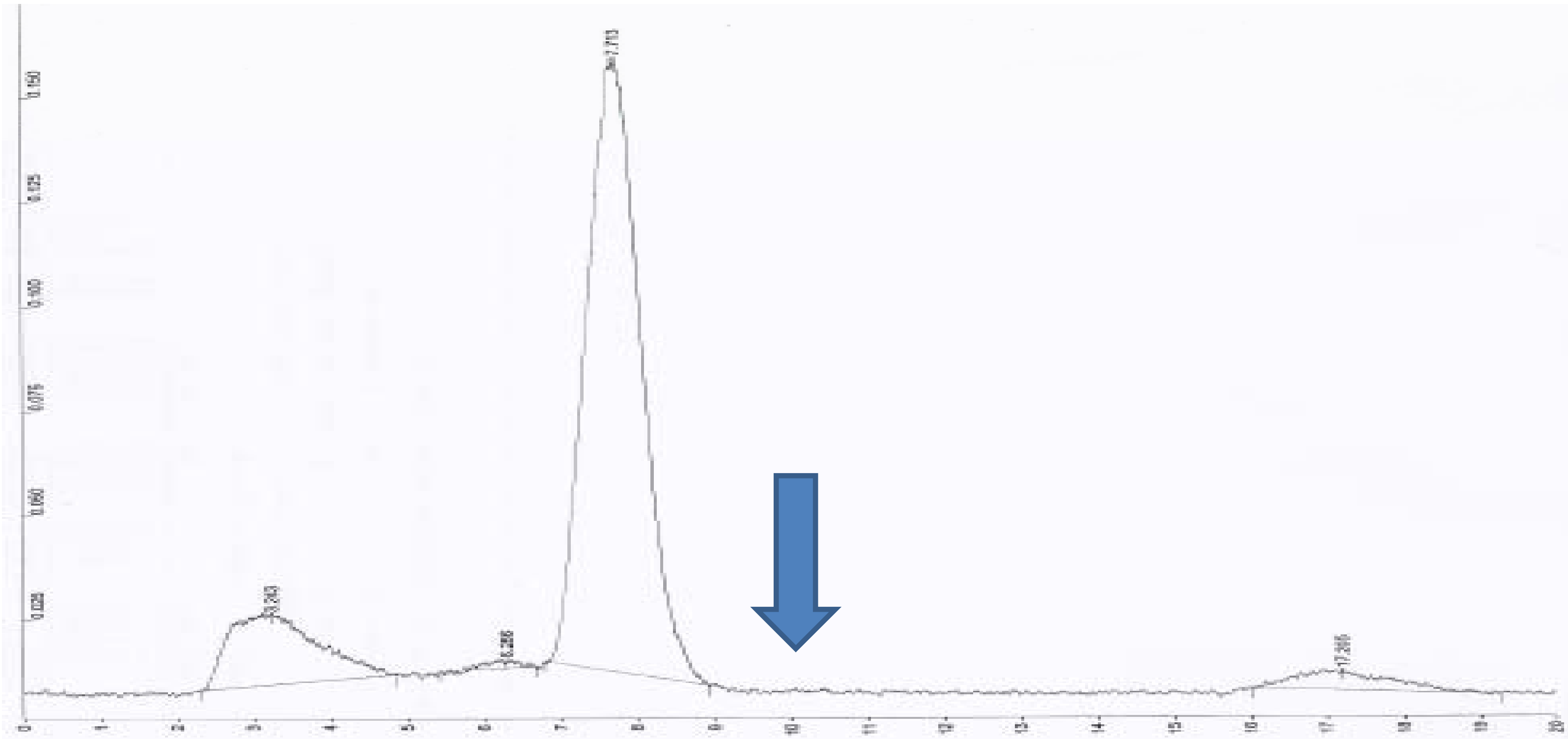
# Examples of Incorporation Yield

| 18F Tracers | % Incorporation | % RCP | % TCY | Source | Reference |
|---|---|---|---|---|---|
| FDG | | >95 | 62.5±3(n=12) | Advion System Validation project | NA |
| Fallypride | 88 | | | NIH, V Pike, Shuiyu Lu | Current Radiopharmaceuticals, 2009, 2, 49-55 |
| FLT | 89 | >99 | 18 - 25 (n=30) | UT | J Nucl Med. 2010; 51 (Supplement 2):1473 |
| FMISO | 91 | >97 | 42±3 (n=8) | UT | J Nucl Med. 2010; 51 (Supplement 2):1462 |
| **FIAU** | | | **10±6 (n=18)** | Harry Anderson, MSKCC | Nuclear Medicine and Biology 37 (2010) 439-442 |
| Altanserin | | | >50 | Advion App Note | Preparation of [F-18]Altanserin using the NanoTek® LF |
| **2FA** | | 100 | **8** | Internal communication | |
| **PBR 06** | >95 | | **>50** | Evaluation at UT | |
| **DPA 714** | >95 | | | Evaluation at UT | |
| CB-102 | 90 | 96±5 (n=8) | | Pascali at Pisa | Nuclear Medicine and Biology 37 (2010) 547–555 |
| EtDT | 67±3 (n=8) | | | Pascali at Pisa | Nuclear Medicine and Biology 37 (2010) 547–556 |
| PrDT | 78±3 (n=5) | | | Pascali at Pisa | Nuclear Medicine and Biology 37 (2010) 547–557 |
| **FTHA** | 74 | | **>40** | UT | |
| FE@SUPPY | 79.2±10.9 (n=6) | | | Vienna | Comparison of "conventional" radiosynthesis and microfluidic preparation of [18F]FE@SUPPY EANM 2010-Vienna |
| FE@SUPPY 2 | 95.3±1.9 | | | Vienna | RAPID RADIOSYNTHESIS OF [18F]FE@SUPPY:2 USING THE NANOTEK® MICROFLUIDIC DEVICE www.radiopharmaceutical-sciences.net |
| FEPPA | 95 | >99 | >50 | GSK | User group presentation Edmonton 2009 |
| FAZA | 80 | >95 | >20(n=3) | Elsinga Groningen | Optimizing Radio Synthesis of Hypoxia Tracer [18F]FAZA using Microfluidic Chemistry EANM 2010 - Vienna |
| FBA | >85 | >95 | | GSK and UC Davis with Lee | |
| FDG Peptide | 87 | | | Alberta | 2-[$^{18}$F]-2-DEOXY-D-GLUCOSE ([$^{18}$F]-FDG) LABELING OF PEPTIDES USING A MICRO-FLUIDIC REACTOR |

# Flow Synthesis Incorporation Experiment 170C No By-product Formation



| Peak No. | Peak Name | Result () | Ret. Time (min) | Time Offset (min) | Area (counts) | Sep. Code | Width 1/2 (sec) | Status Codes |
|---|---|---|---|---|---|---|---|---|
| 1 | | 15.1816 | 3.243 | 0.000 | 1376169 | BB | 86.7 | |
| 2 | | 0.4872 | 6.286 | 0.000 | 44162 | BB | 13.1 | |
| 3 | | 80.1477 | 7.713 | 0.000 | 7265166 | BB | 47.1 | |
| 4 | | 4.1835 | 17.205 | 0.000 | 379222 | BB | 50.0 | |
| | Totals: | 100.0000 | | 0.000 | 9064719 | | | |

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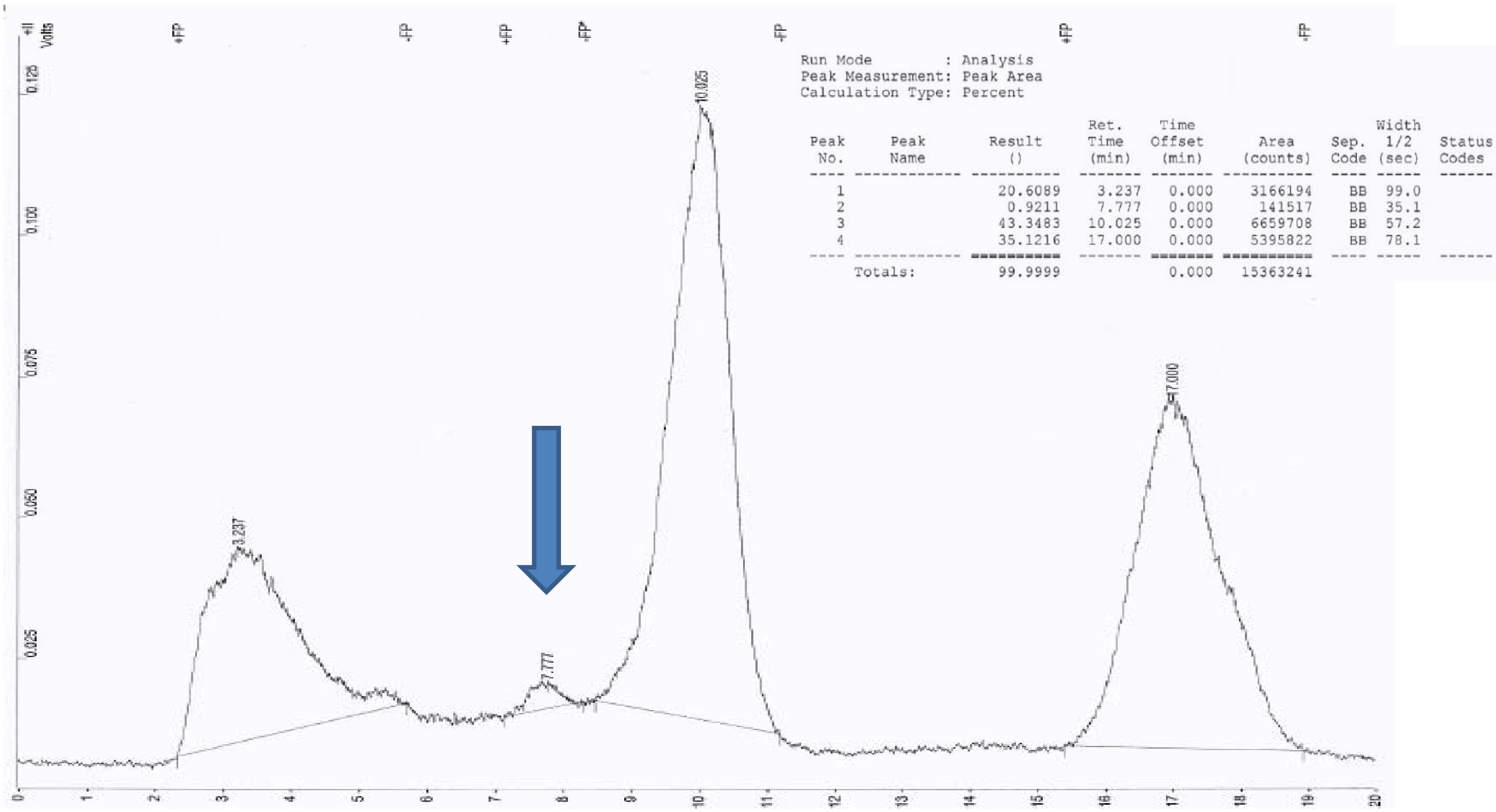
# Reaction at 180C vs. 170C
# By-product Formed and Desired Product Yield Drops from 80% to 1%




Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

| Peak No. | Peak Name | Result () | Ret. Time (min) | Time Offset (min) | Area (counts) | Sep. Code | Width 1/2 (sec) | Status Codes |
|---|---|---|---|---|---|---|---|---|
| 1 | | 20.6089 | 3.237 | 0.000 | 3166194 | BB | 99.0 | |
| 2 | | 0.9211 | 7.777 | 0.000 | 141517 | BB | 35.1 | |
| 3 | | 43.3483 | 10.025 | 0.000 | 6659708 | BB | 57.2 | |
| 4 | | 35.1216 | 17.000 | 0.000 | 5395822 | BB | 78.1 | |
| | Totals: | 99.9999 | | 0.000 | 15363241 | | | |

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# Temperature, Solvent, Pressure

- Calculated variation of boiling point of common solvents with pressure

  – Acceleration of reaction rates in flow vs. batch reactors may be achieved by routinely operating at elevated pressures and temperatures.

| | *Boiling point °C @* | | |
|---|---|---|---|
| | 1 bar | 6.9 bar | 17.0 bar |
| $CH_2Cl_2$ | 41 | 109 | 153 |
| MeOH | 65 | 138 | 185 |
| THF | 66 | 140 | 186 |
| $^{i}$PrOH | 82 | 159 | 207 |
| MeCN | 82 | 159 | 207 |
| $H_2O$ | 100 | 181 | 231 |
| Dioxane | 101 | 182 | 234 |
| DMF | 153 | 244 | 301 |
| DMA | 165 | 259 | 318 |

Useful solvents for flow with bp exceeding 150°C @ 7 bar

•NanoTek back-pressure upper operating limit is 400 psi (28 bar).
•Reactor upper temperature limit is 220$^{0}$C.

gsk GlaxoSmithKline

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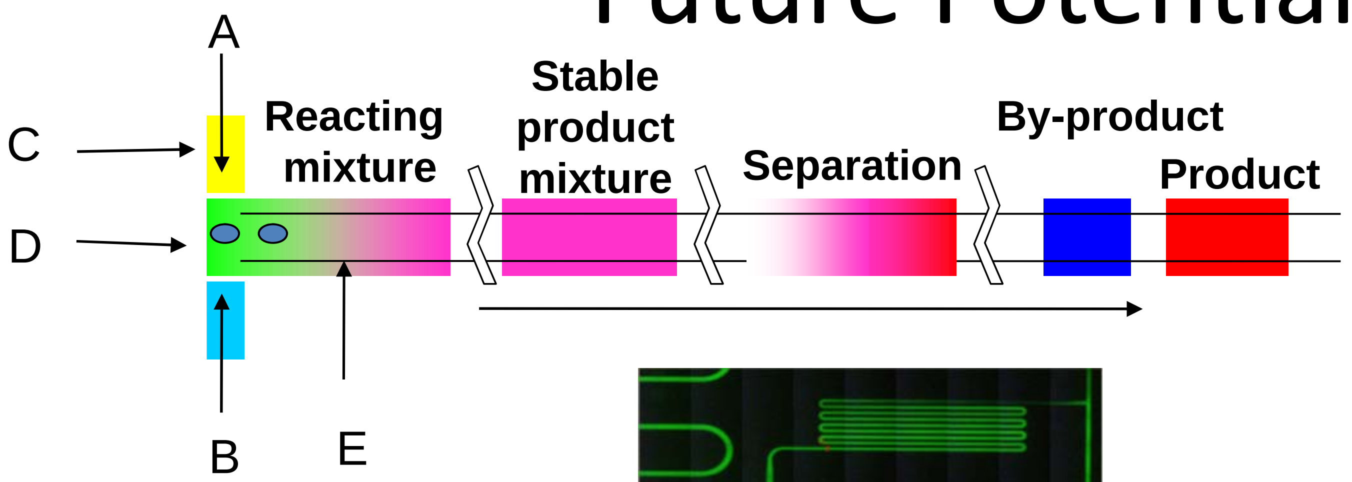
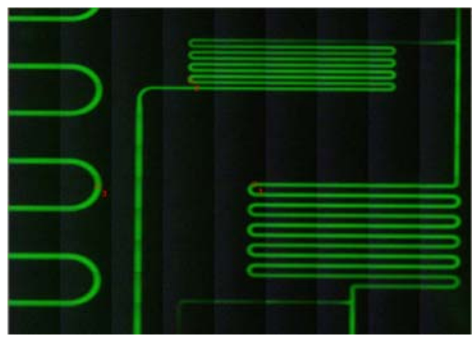
# Future Potential



Dilute (~$10^3$)

**Assays**

Conditions ← Chemistry

**Decision software**

Reagents ← Biology

**Flow**

**Well-based**

- Single
- Multiplex

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# Versatilty

- 40+ optimization reactions possible in one day.
- Operating range of activities µCi to Ci.
  - No observed changes is yield as scale increases.
    SNM 2010 Poster :

***Microfluidic Synthesis of [18F]FLT***

Murthy R. Akula1, Thomas L. Collier4, George W.Kabalka2, Jonathan S. Wall3, Steve Kennel4, Alan Stuckey3 and Amy K. LeBlanc2

[1]Department of Radiology, University of Tennessee, Knoxville, TN, United States.

[2]Departments of Radiology and Chemistry, University of Tennessee, Knoxville, TN, United States.

[3] Department of Medicine, University of Tennessee, Knoxville, TN, United States.

[4]Advion BioSystems, Inc., Ithaca, NY, United States

- Dose-on-demand capability published

***Dose-on-demand of diverse 18F-fluorocholine derivatives through a two-step microfluidic approach***

Giancarlo Pascalia,!, Giovanni Nannavecchiaa,b, Sabrina Pitziantia,c, Piero A. Salvadoria
*Nuclear Medicine and Biology* (March 2011) doi:10.1016/j.nucmedbio.2011.01.005

- Back to back production

Tuesday morning presentation 8:48 AM to 9:00 AM
Location: 213AB Publication number: 289

***Sequential preparation of two different PET radiotracers employing the Advion NanoTek synthesis system***

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***Sequential preparation of two different PET radiotracers employing the Advion NanoTek synthesis system***

Authors shown: Murthy R. Akula and T. Lee Collier

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