Automated Radiosynthesizers for PET Probes

R. Michael van Dam

March 6, 2013

Outline

- Recap: Synthesis of FDG on robotic synthesis module
- Remote control vs automation
- Basic architecture and elements of radiosynthesizers
- Examples of commercial radiosynthesizers of different types
  - Fixed systems
  - Flexible/modular systems
  - Disposable cassette systems
- In-depth example of ELIXYS radiosynthesizer
- In-depth example of ELIXYS software

Recap: FDG synthesis on robotic synthesis module

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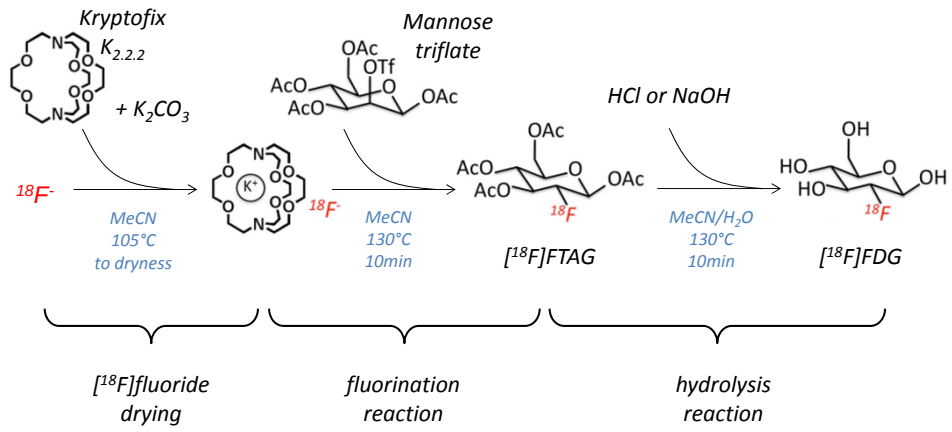
[^{18}F]FDG Synthesis



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Viewing the synthesis from a system/engineering perspective

- How many reaction vessels are needed?
  - Is purification required between steps?
- How does the synthesis translate into the following typical synthesizer operations?
  - Adding reagents to the vessel
  - Mixing vessel contents
  - Heat vessel to perform evaporation
  - Heat vessel to perform reaction
  - Transfer from vessel
  - Purification

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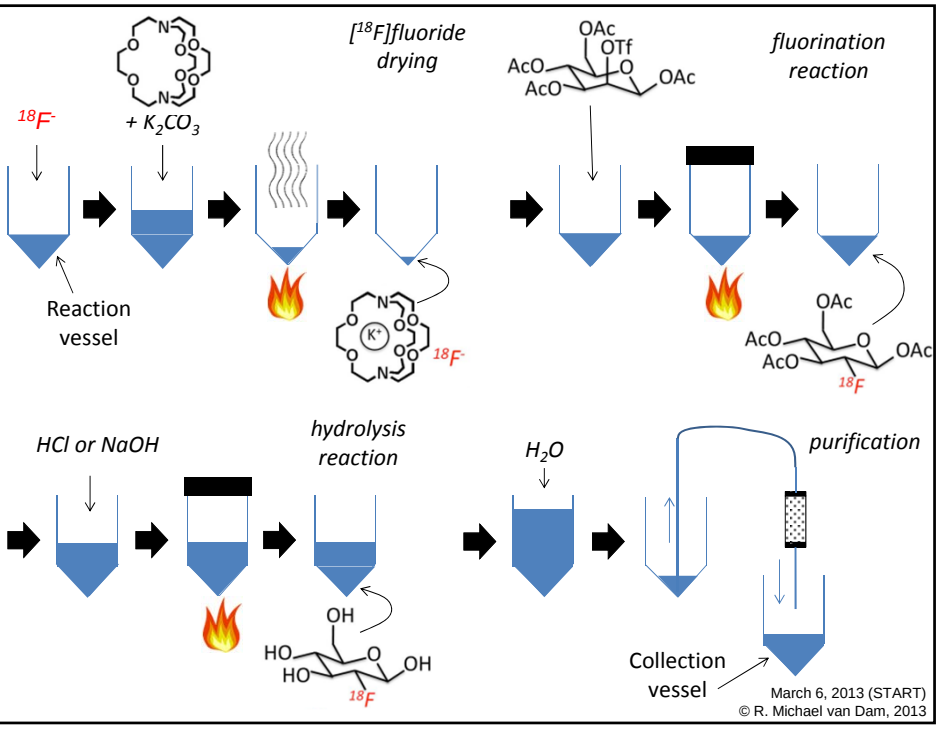

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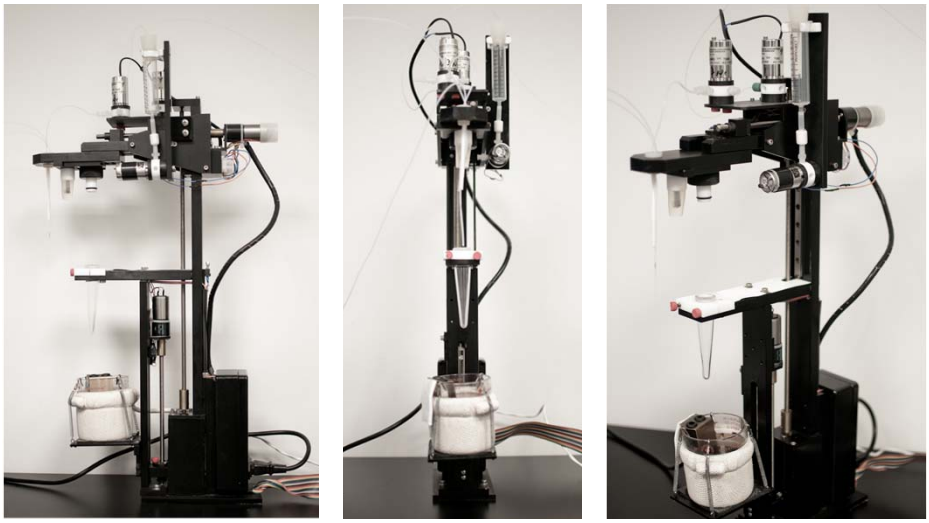

B. Amarasekera, N. Satyamurthy

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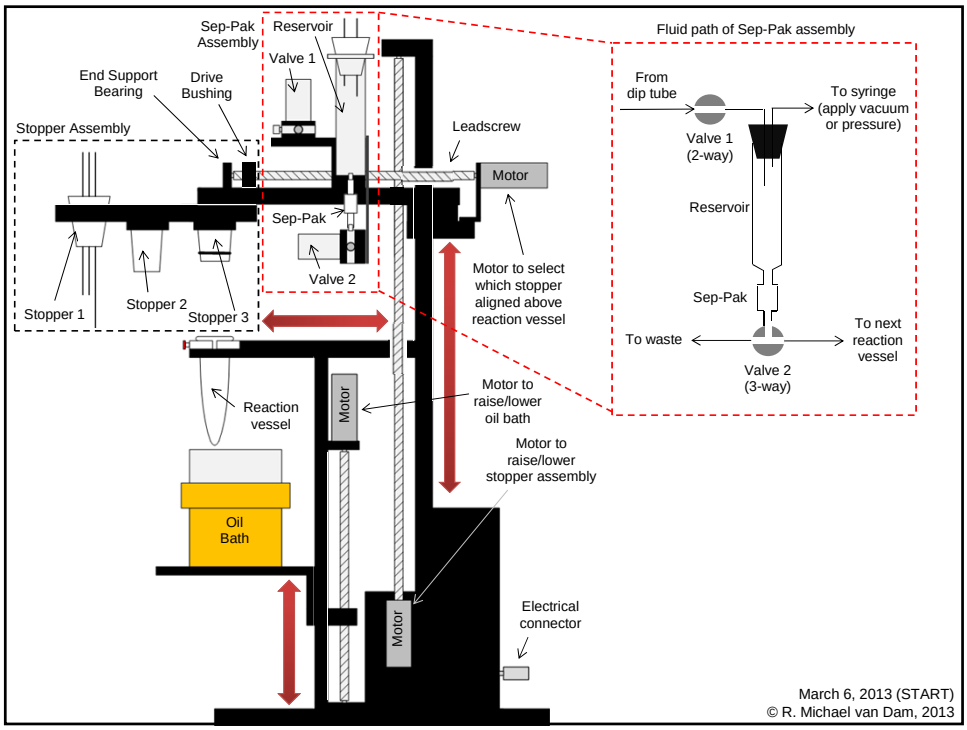

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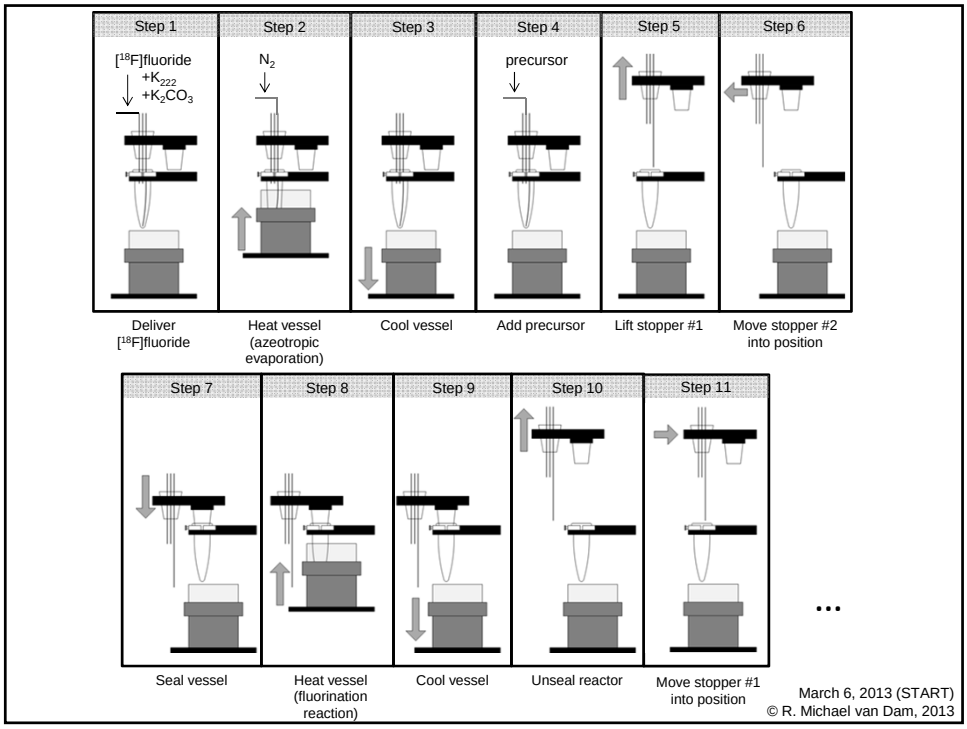
Step 1
[18F]fluoride
+K222
+K2CO3
Deliver [18F]fluoride
Step 2
N2
Heat vessel (azeotropic evaporation)
Step 3
Cool vessel
Step 4
precursor
Add precursor
Step 5
Lift stopper #1
Step 6
Move stopper #2 into position
Step 7
Seal vessel
Step 8
Heat vessel (fluorination reaction)
Step 9
Cool vessel
Step 10
Unseal reactor
Step 11
Move stopper #1 into position
...
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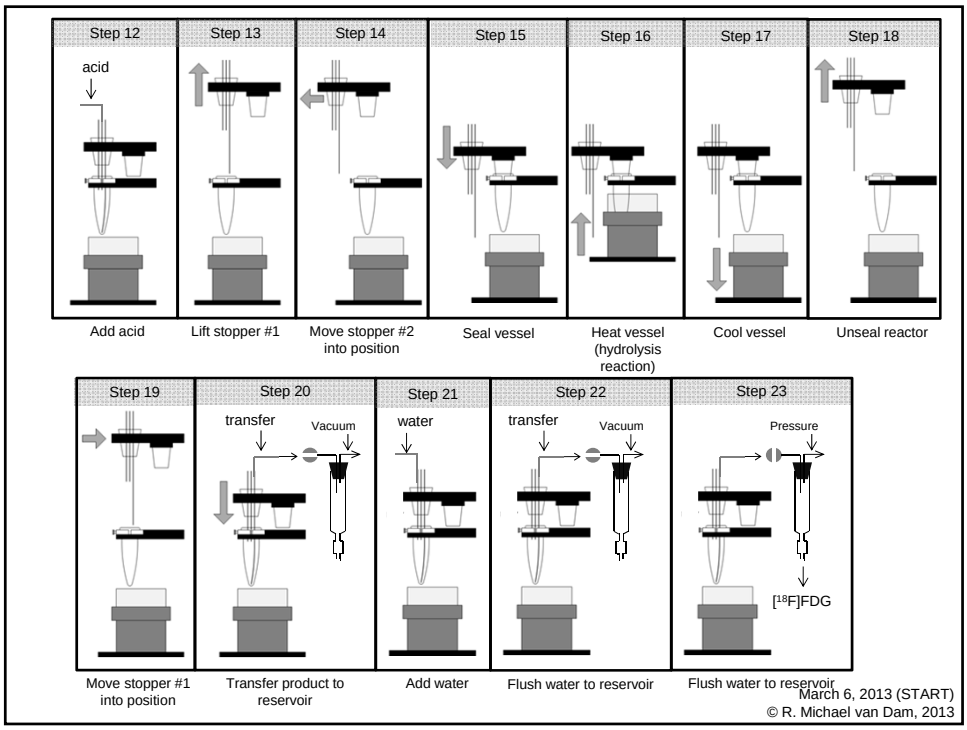
Step 12
acid
Add acid
Step 13
Lift stopper #1
Step 14
Move stopper #2 into position
Step 15
Seal vessel
Step 16
Heat vessel (hydrolysis reaction)
Step 17
Cool vessel
Step 18
Unseal reactor
Step 19
Move stopper #1 into position
Step 20
transfer
Vacuum
Transfer product to reservoir
Step 21
water
Add water
Step 22
transfer
Vacuum
Flush water to reservoir
Step 23
Pressure
[18F]FDG
Flush water to reservoir
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Remote controlled chemistry is not automation

- Remote control provides protection from radiation exposure

- But many steps require intervention:
  - Motion – manually start, manually stop
  - Oil bath – turning on/off and setting temperature
  - Using syringes to add reagents
  - Judging when evaporation complete and removing heat
  - Judging when liquid has flowed through purification cartridge (when to open/close valves)
  - Etc.

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What is Automation?

- Definition
  - Making an apparatus, process, or system operate without outside intervention (generally under computer control)
- General Goals
  - Increased throughput or productivity.
  - Improved robustness (consistency), of processes or product.
- Advantages:
  - Reduced process/synthesis time (higher synthesis yield)
  - Reduced cost of PET probe (reduced personnel effort)
  - Increased repeatability (make probe consistently from day to day and at different sites)
  - Safety (avoid radiation exposure)
  - Eliminate monotonous work and free up radiochemists to develop new probes

Adapted from http://en.wikipedia.org/wiki/Automation

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General architecture of automated radiosynthesizers

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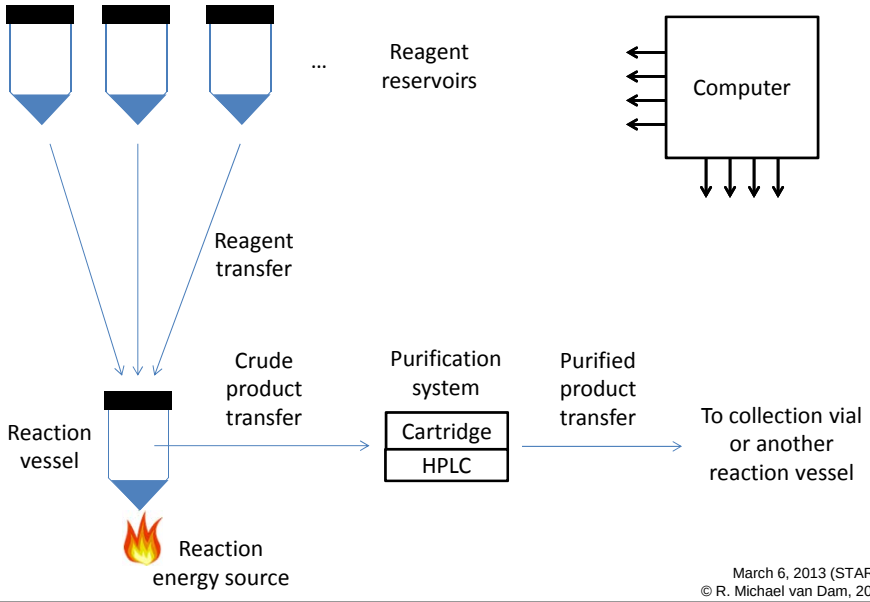
General elements of a radiosynthesizer



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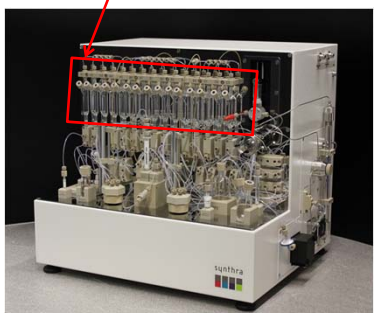
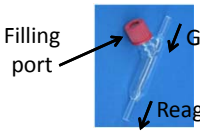
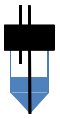
Types of reagent reservoirs

Fixed reservoirs



Filled by user at the start of the synthesis process

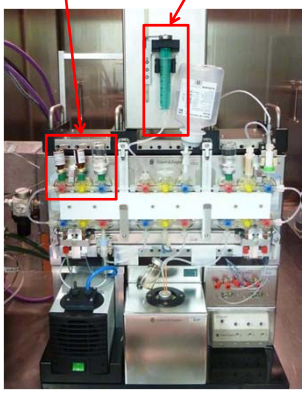




Disposable, pre-filled vial

Disposable, pre-filled syringe

Vial spike



User must install/connect reagent reservoir, but no other handling required

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Automated transfer of liquids

- Requires a liquid path between the source (e.g. reagent reservoir) and destination (e.g. reaction vessel)
- Electronically-controlled pump provides force to move the liquid
- Electronically-controlled valves control opening and closing of fluid path

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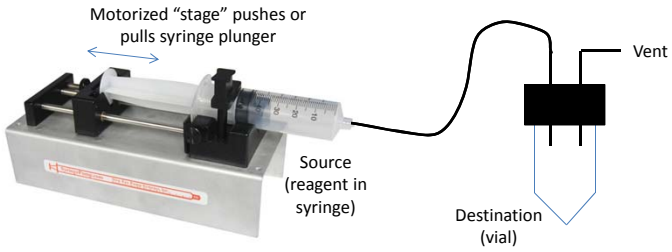
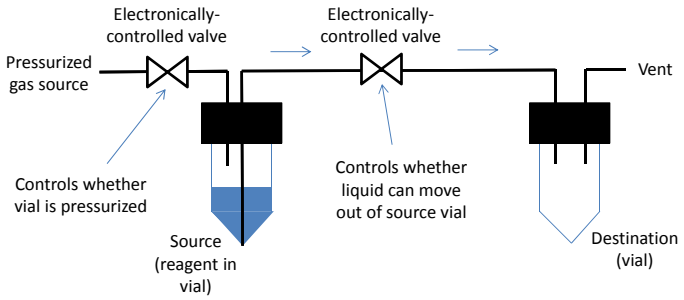
Common methods to pump liquids

Syringe pump



Pressure-driven flow



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Comparison of pump approaches

	Syringe pump	Pressure-driven
Control of volume?	Yes, can accurately dispense arbitrary volume	Difficult to control volume. Generally all or nothing
Feedback signal	Motor position feedback reflects how much volume dispensed	No feedback. Measurement of "mass flow" of gas may enable feedback
Safety	Pressure can build up (if there is a clog) and can leak if it exceeds pressure limits of tubing/fittings	Intrinsic pressure limit (driving pressure)
Cost	Expensive	Inexpensive
Physical size	Bulky	Compact
Disposable?	Yes (syringe)	Yes (vial)

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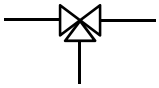
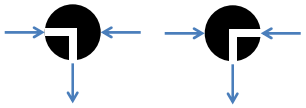
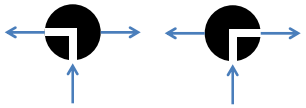
Common types of valves

Type	Symbol	Applications
2-way (shutoff)		Open or close a fluid path 
3-way (selector)		Connect one of two inlets to a common outlet  Connect a common inlet to one of two outlets 

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Solenoid valves (2-way or 3-way)

Electrical signal controls valve state

Expensive. Non-disposable. Must be cleaned.

Small dead volumes (10s of µL)

Max. operating pressure is low (30-50 psig typ)

Stopcock valves (2-way or 3-way)

Must be actuated by a rotary motion system (electric or pneumatic)

Inexpensive. Disposable.

Significant dead volume (~100 µL). Some commercial systems use "zero-dead-volume" stopcocks

Somehwat higher operating pressure

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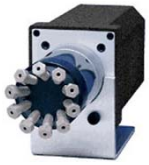
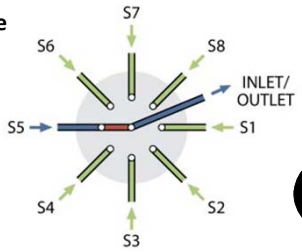
Rotary valves

Stream selection valve





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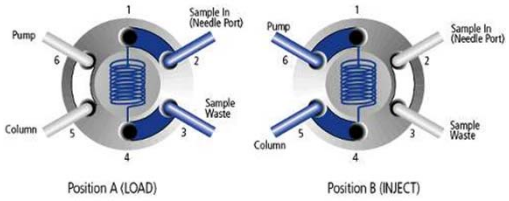
Rotary valves are expensive and non-disposable, but can operate at very high pressures

Injection valve (e.g. for HPLC)



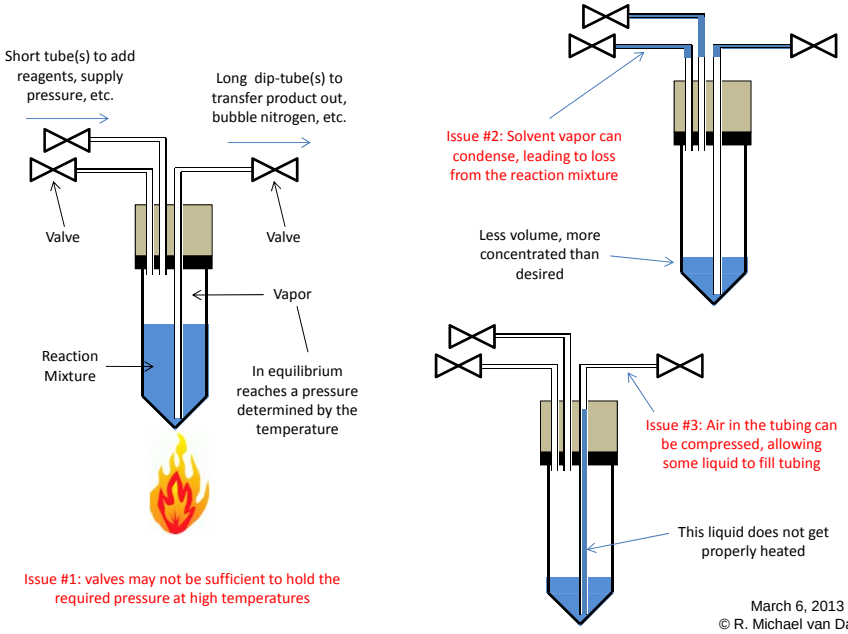
Flow path of Medium Pressure Injection Valve
(highlighting flow through sample loop in each position)

Motor for electronic control

Reaction vessels

- General characteristics:
  - Inert material: glass or glassy-carbon
  - Often have a V-shaped bottom to avoid residual liquid
  - Volume commonly 5-20 mL
- Types:
  - Fixed – all tubing is always connected to reaction vessel
  - Semi-fixed – most tubing is connected to reaction vessel but dip tube is retractable (motorized or pneumatic)
  - Needles/septum sealed – Needles are inserted through a septum
  - Reconfigurable

Fixed reaction vessel



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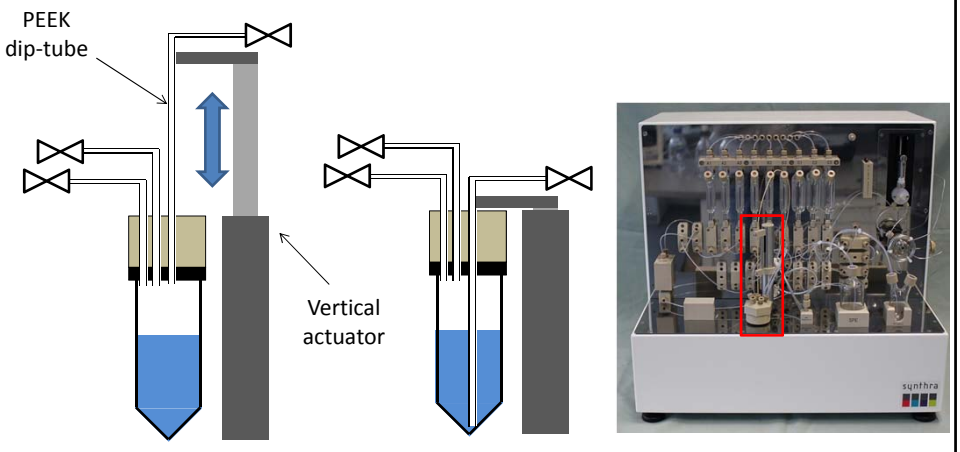
Retractable dip tube vessel



Start with dip-tube in retracted position

Lower dip-tube at end of synthesis

Resolves Issue #3

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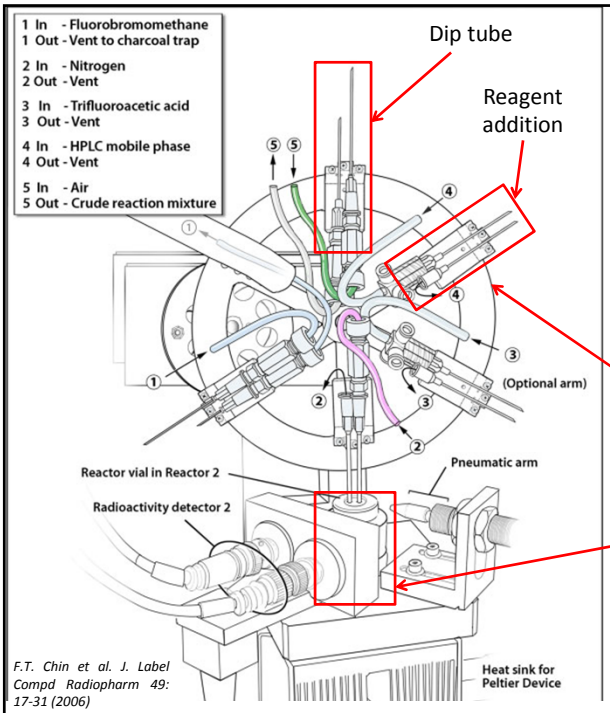

F.T. Chin et al. J. Label Compd Radiopharm 49: 17-31 (2006)

Septum-sealed vessel

Resolves Issues #1,2,3
(removes tubing from vessel)

NOTE: pierced septum has limited pressure-holding ability.

Wheel of needle pairs that can be inserted into septum

Reaction vial

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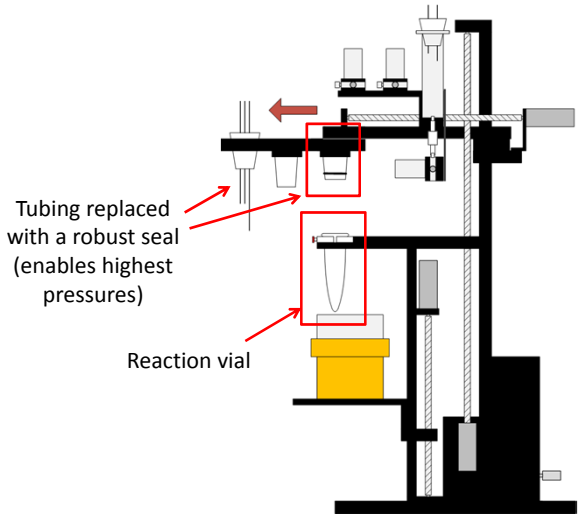
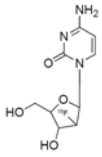
Reconfigurable reaction vessel

Resolves Issues #1,2,3
(removes tubing from vessel)



Tubing replaced with a robust seal (enables highest pressures)

Reaction vial



[^{18}F]FAC

Radu et al. Nature medicine 14(7): 783-788 (2008)

Fluorination reaction:
MeCN
T = 165°C
P = 121 psi [834 kPa]

Base coupling reaction:
1,2-dichloroethane
T = 160°C
P = 101 psi [695 kPa]

[^{18}F]FMAU,
[^{18}F]FIAU,
[^{18}F]BMAU

Mangner et al. Nuclear Medicine and Biology 30: 215–224 (2003)

Base coupling reaction:
chloroform
T = 150°C
P = 139 psi [957 kPa]

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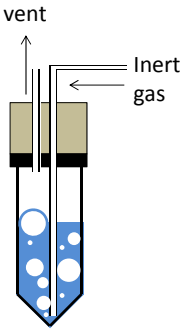
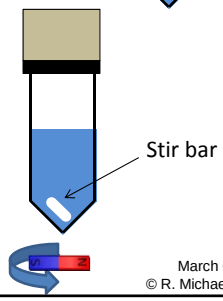
Mixing methods

- Inert gas bubbling
  - Bubbling gas up from the bottom of the vessel agitates liquid
  - Can only mix while a dip tube is in the vessel



- Magnetic stirring
  - A rotating magnet below the vessel causes a magnetic stirbar inside the vessel to rotate
  - Can mix at any time



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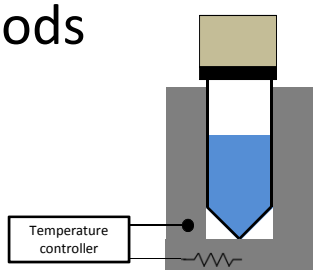
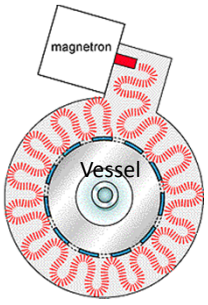
Heating methods

- Oil bath
  - Control temperature of oil
  - Lower vessel into oil



- Metal jacket
  - Control temperature of a metal jacket around the vessel (resistive heater; thermoelectric)
  - Heat conducts from metal to vessel
  - Advantages: easier to switch temperatures; less messy
- Microwave
  - Feedback control of glass temperature (IR sensor); or apply constant power



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Motion in radiochemistry system – some examples

- Syringe drives
- Raise and lower a dip-tube
- Rotate a stopcock valve

- Robotic synthesis module
  - Raise/lower oil bath
  - Select “stopper”
  - Raise/lower stopper

- Septum-sealed vessel module
  - Rotate needle wheel
  - Raise/lower needles

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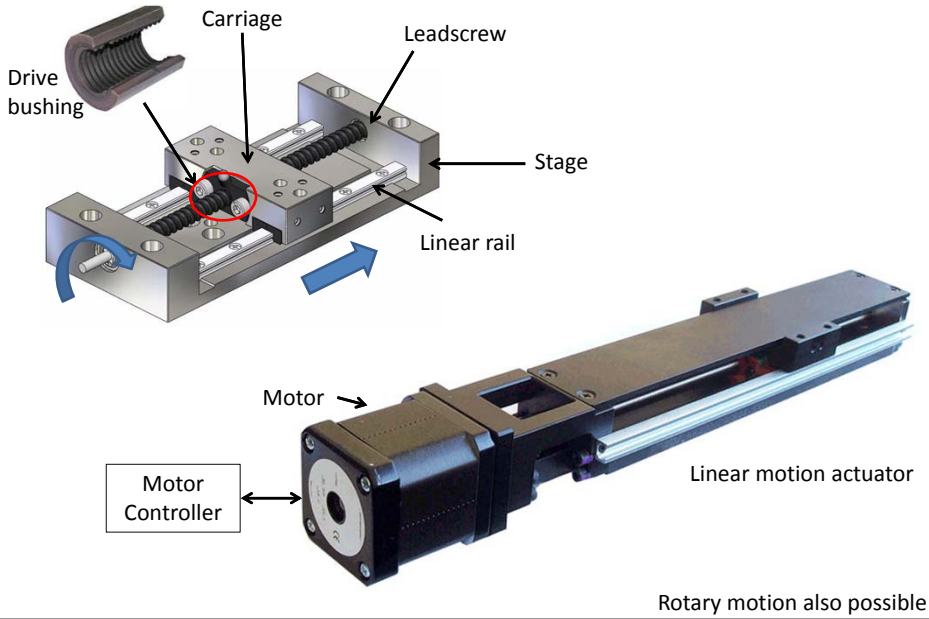
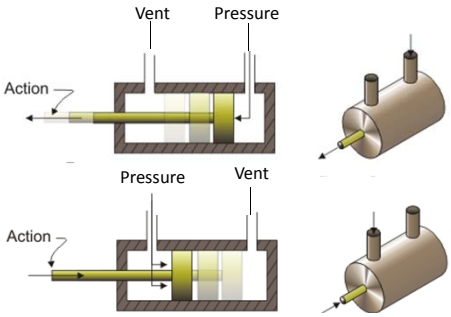
Motion actuation - electric

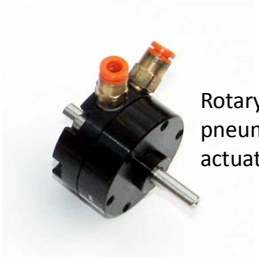


Rotary motion also possible

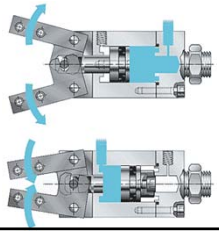
Motion actuation - pneumatic



Straightforward control. Use valves to control opening of pressure/vent



Rotary pneumatic actuator



Pneumatic Gripper

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Comparison of motion actuation

	Leadscrew actuator	Pneumatic actuator
Available positions	Can move to arbitrary positions with high accuracy	Can move to one end of travel or the other
Detectable positions	Can detect "home" and end-points with switches. Can detect intermediate positions with "encoder"	Can detect end-points with switches
Cost	Expensive actuator plus expensive controller	Low-cost actuator. No controller (only requires 2 valves)
Setting amount of force	Difficult	Choose operating pressure (and cylinder bore size)
Actuator size (for a given force)	Large	Small

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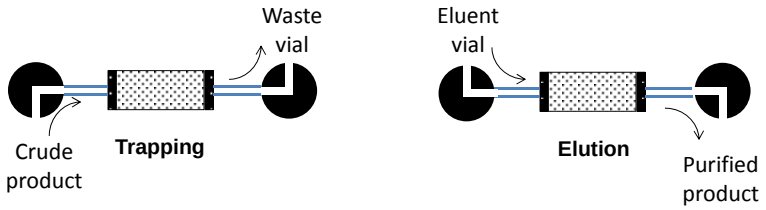
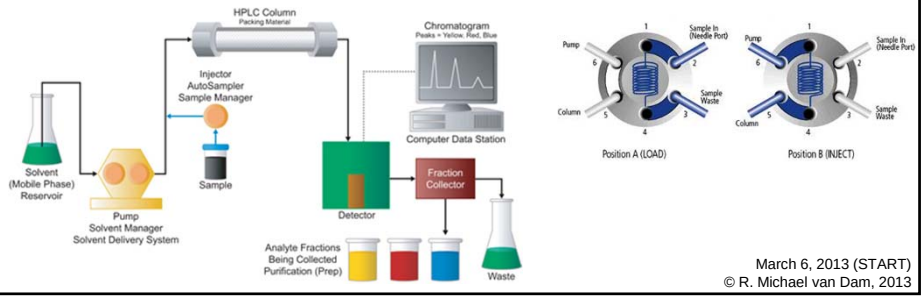
Purification

Cartridge (Solid-Phase Extraction, SPE)



High-Performance Liquid Chromatography (HPLC)



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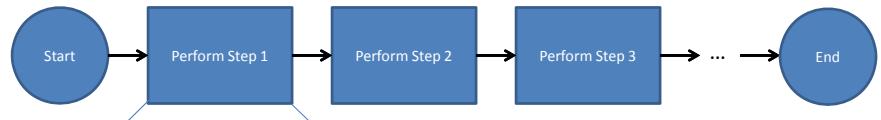
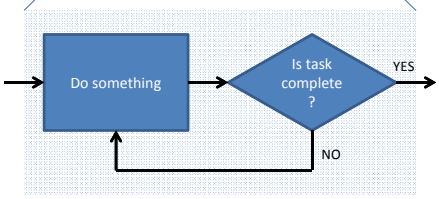
Automation can be achieved by having a computer execute steps in sequence





Deciding when to move on to the next Step is an important part of automation

How does the computer decide when to move forward?

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Sensors provide information about the system in an electronic format

- Desired temperature reached?
  - Thermocouple, thermistor, infra-red sensor, etc.
- Desired pressure reached?
  - Pressure transducer
- Certain amount of time elapsed?
  - Timer
- Moving part arrived at correct position?
  - Position sensors (optical, magnetic, electronic, etc…)
- Has all of liquid flowed from A to B?
  - Liquid detector can monitor contents of transparent tubing
- Other types of sensors:
  - Radiation
    - Can estimate amount of radioactivity in parts of system (e.g. in vials, trapped on cartridges, etc…)
    - Clever combinations of sensors can estimate reaction yield
  - Camera
    - Provide visual image of part of system (e.g. reaction vial)
    - Can verify completion of liquid transfers, completion of evaporation, etc.
    - Difficult for a computer to interpret images

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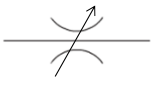
Additional system components that may be found on system diagrams

Filter

Pressure gauge



Pressure regulator

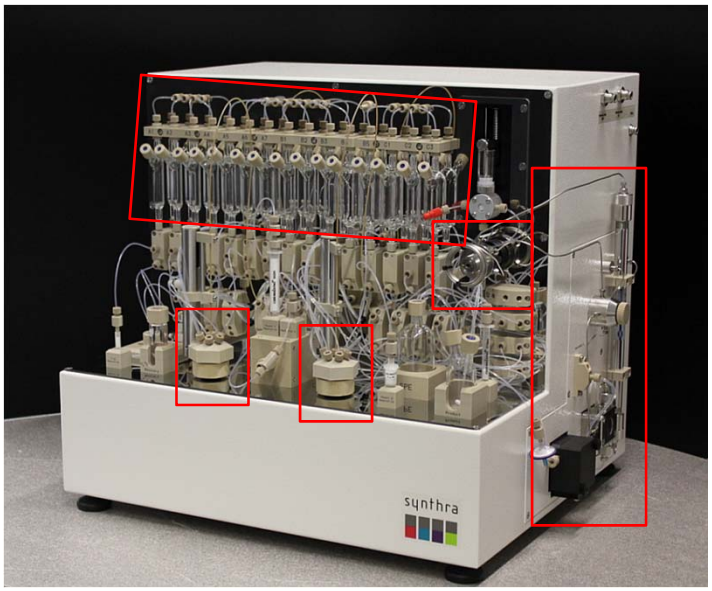
March 6, 2013 (START)

Examples of commercial radiosynthesizers

General types of synthesizers

- Fixed
  - System components and plumbing are fixed
  - Can make one probe, or other probes with similar synthesis protocols
  - Replumbing may enable other probes to be made
  - System must be cleaned between syntheses
- Modular
  - System can be expanded with additional hardware (e.g. additional reaction vessels, valves, reagent vials, etc.)
  - Replumbing is essential to incorporate additional elements. Every system is custom.
  - System must be cleaned between syntheses
- Disposable cassette
  - Fluid path designed as a self-contained "cassette" that can be discarded after each synthesis
  - Different cassettes may enable other probes to be made
  - Some systems allow users to reconfigure cassettes (by replumbing)
  - Cleaning is **not** required
  - Sometimes limitations due to materials (polymers) used

Fixed systems



Synthra RNplus

Tracera TS-1

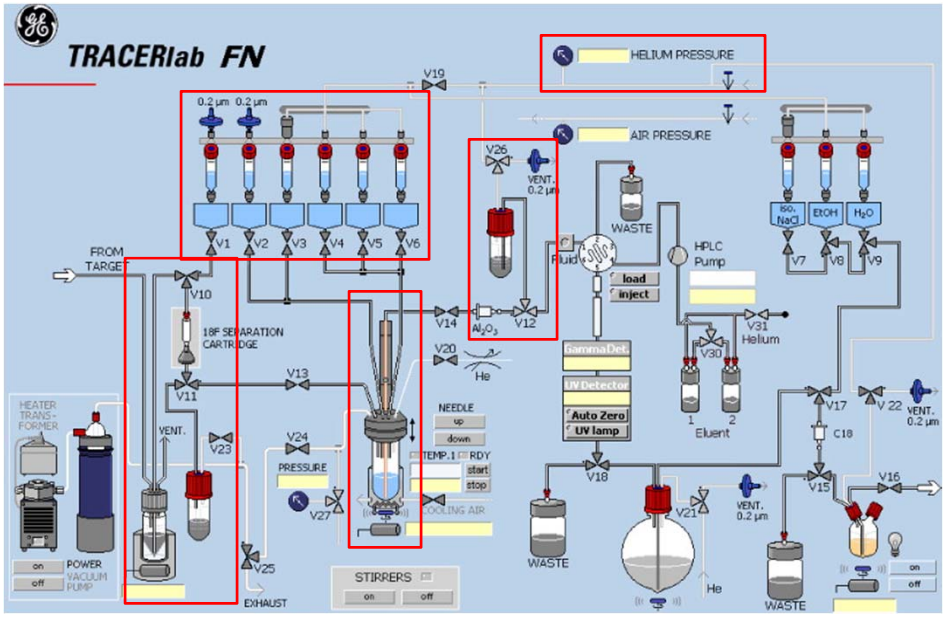
Siemens Explora FDG4

Raytest SynChrom

Scintomics hotbox^2

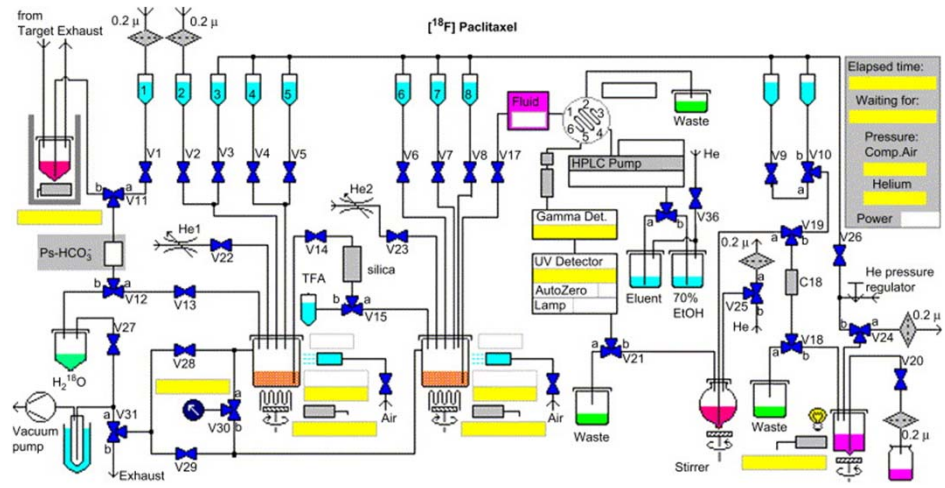
GE TRACERlab FX F-N

GE TRACERlab FX N Pro



A. Schildan, M. Patt, O. Sabri, 2007. Synthesis procedure for routine production of 2-[18F]fluoro-3-(2(S)-azetidinylmethoxy)pyridine (2-[18F]F-A-85380), Applied Radiation and Isotopes 65(11): 1244-1248.

March 6, 2013 (START)



Tracerlab FX F-N Dual Reactor system

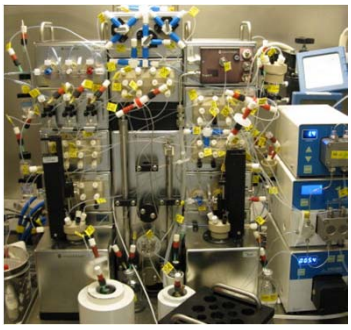
J.D. Kalen et al. 2007. Automated synthesis of 18F analogue of paclitaxel (PAC): [18F]Paclitaxel (FPAC), Applied Radiation and Isotopes 65(6): 696-700

March 6, 2013 (START)

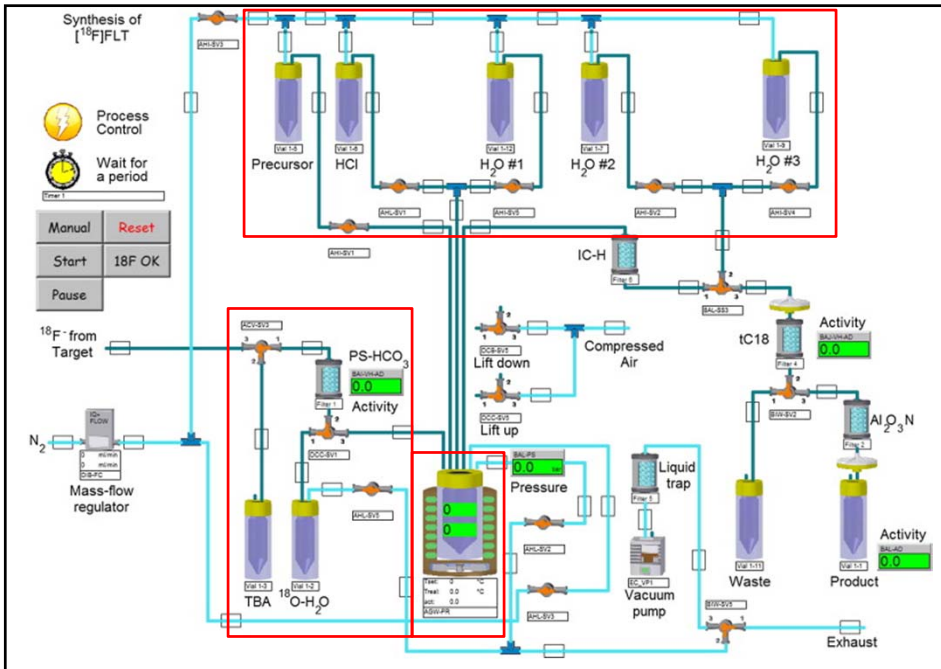
Modular systems

Eckert&Ziegler
Modular-Lab

T. Läppchen *et al.*, 2012. Applied Radiation and Isotopes 70(1): 205-209.

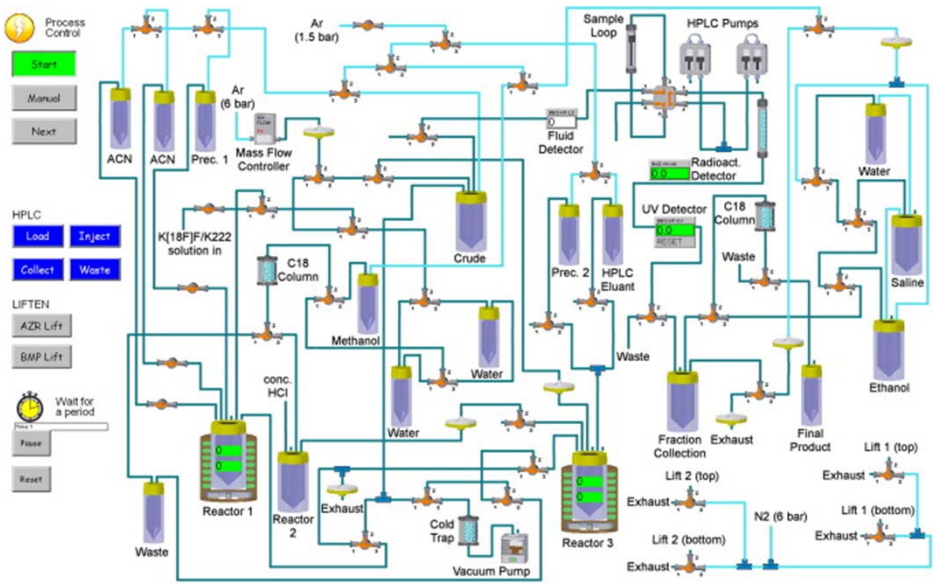


March 6, 2013 (START)



C. Pascali *et al.* 2012. Simple preparation and purification of ethanol-free solutions of 3′-deoxy-3′-[18F]fluorothymidine by means of disposable solid-phase extraction cartridges, Nuclear Medicine and Biology 39(4): 540-550.

March 6, 2013 (START)



T. Läppchen *et al.*, 2012. Automated synthesis of [18F]gefitinib on a modular system, Applied Radiation and Isotopes 70(1): 205-209.

March 6, 2013 (START)

Disposable-cassette-based systems

Bioscan F-18 Plus

GE TRACERlab MX

- Currently most widely used kit-based system
- 15 3-way stopcocks
- several syringe drives

March 6, 2013 (START)

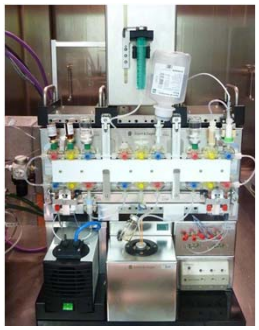
Comecer Taddeo
***Universal* Synthesis Module**

Scintomics GRP

GE FASTlab

Cassettes come pre-loaded with reagents

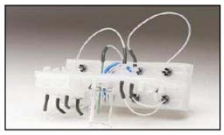
Eckert & Zigler
PharmTracer



Modular, cassette-based system.
Cassettes can be expanded
(more valves, syringes, etc…)

March 6, 2013 (START)

IBA Synthera



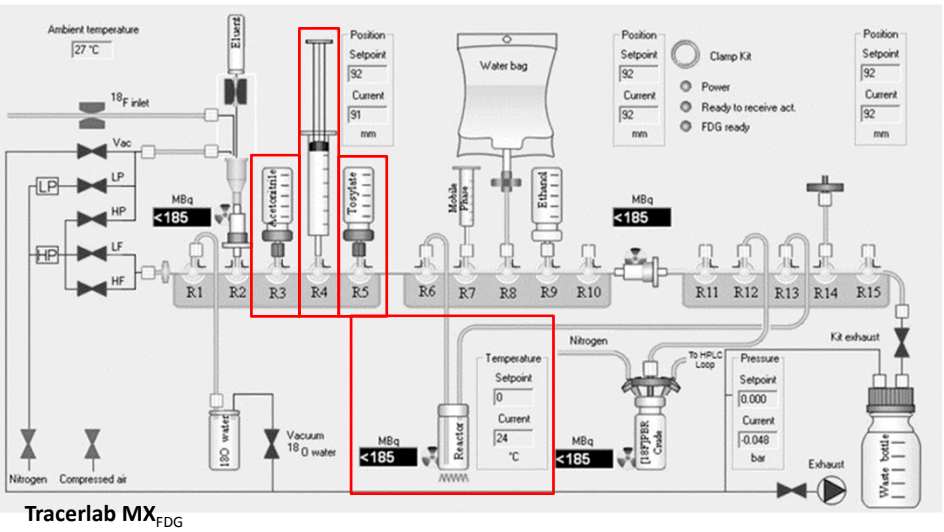
IFP™ Nucleophilic

FDG reagents set

FDG ancilliaries

-Very compact
-HPLC module available

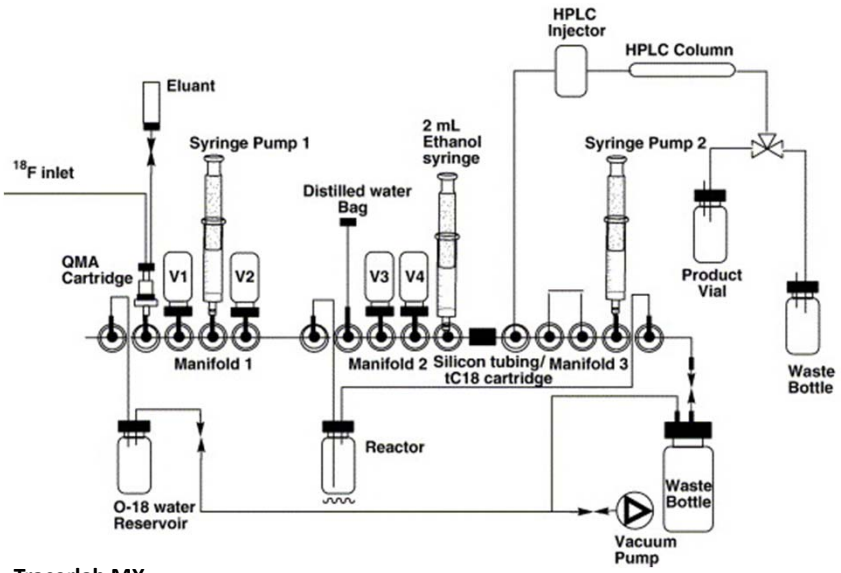
March 6, 2013 (START)



Tracerlab MX$_{FDG}$

T. Bourdier *et al.* 2012. Automated radiosynthesis of [18F]PBR111 and [18F]PBR102 using the Tracerlab FXFN and Tracerlab MXFDG module for imaging the peripheral benzodiazepine receptor with PET, Applied Radiation and Isotopes 70(1): 176-183

March 6, 2013 (START)



Tracerlab MX$_{FDG}$

S.J. Oh *et al.* 2005. Fully automated synthesis of [18F]fluoromisonidazole using a conventional [18F]FDG module, Nuclear Medicine and Biology 32(8): 899-905.

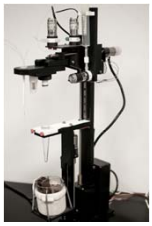
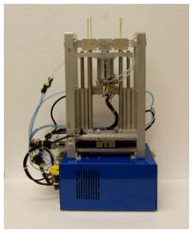
March 6, 2013 (START)

ELIXYS radiosynthesizer (cassette-based)

Sofie Biosciences ELIXYS

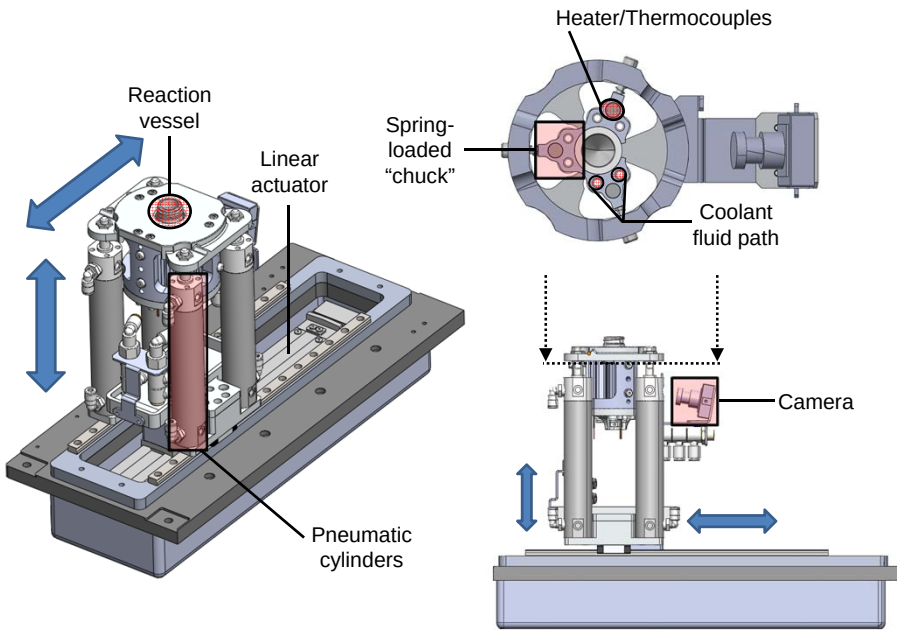
March 6, 2013 (START)

Progression to automation

Remote-controlled	Semi-automated	Fully automated
		
Robotic synthesis module	ARC-P	ELIXYS
• Visual feedback for completion of step • Manual addition of reagents • Manual control of all components	• Visual feedback for completion of step • Automated addition of some reagents • Automated control of movement and temperature.	• Integration of three reactors in one system • Automated control of all components

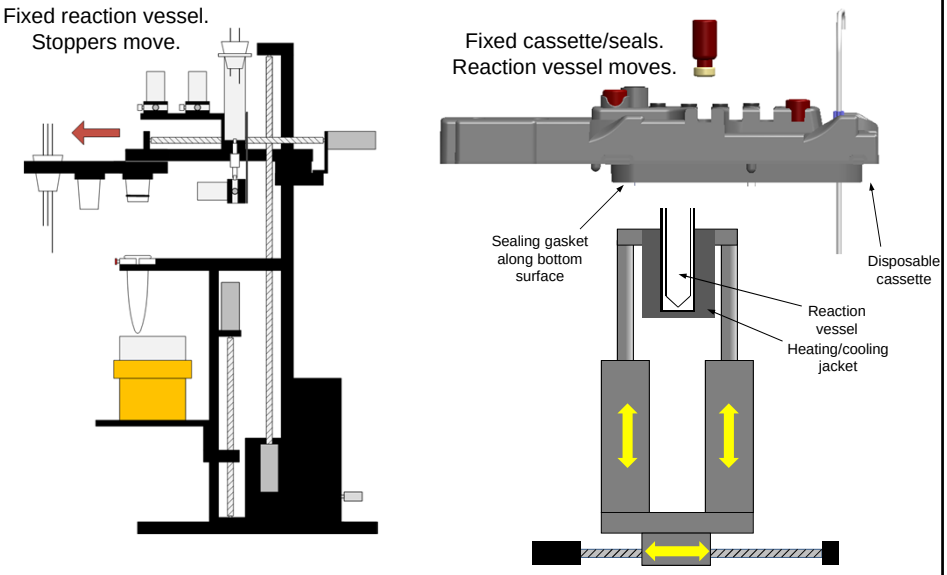
March 6, 2013 (START)

March 6, 2013 (START)



March 6, 2013 (START)

Reactor design of ELIXYS radiosynthesizer



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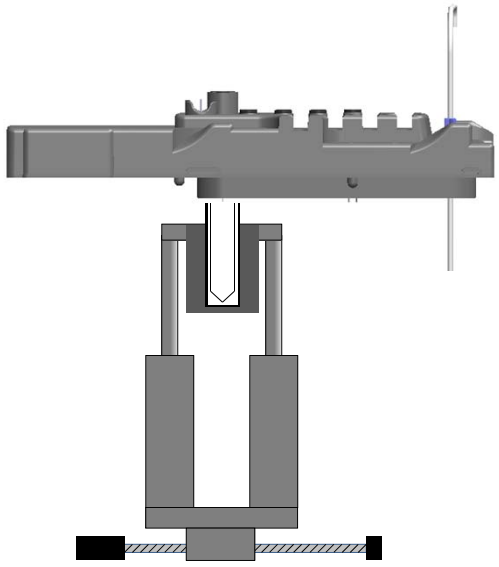

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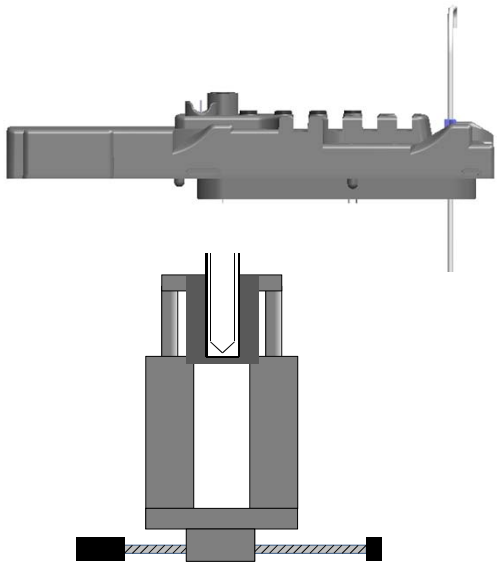

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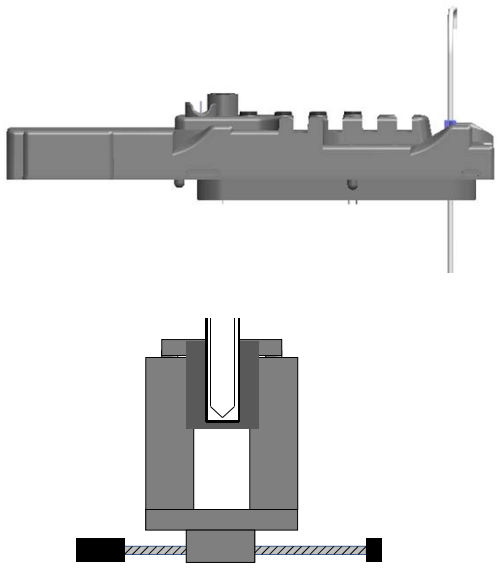

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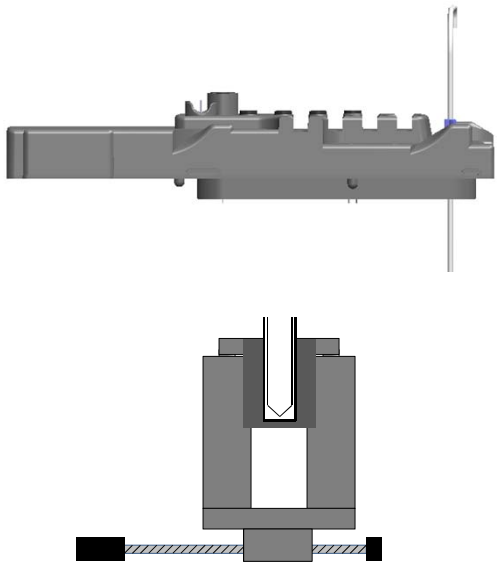

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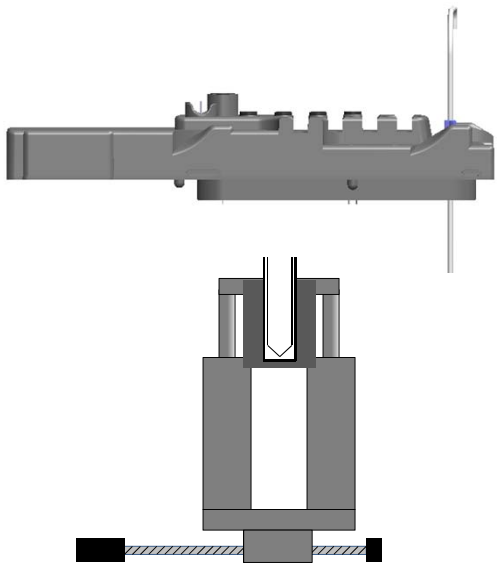

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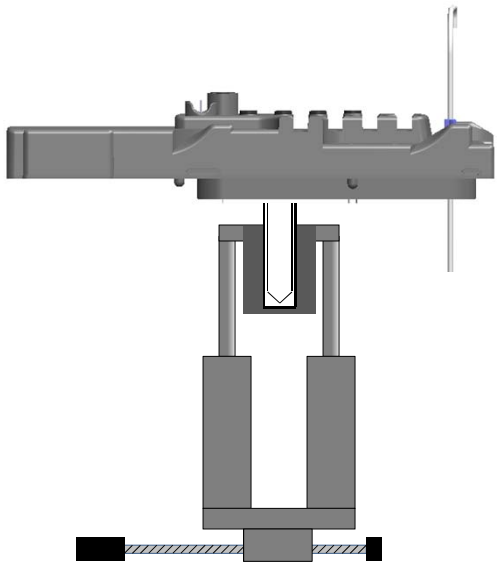

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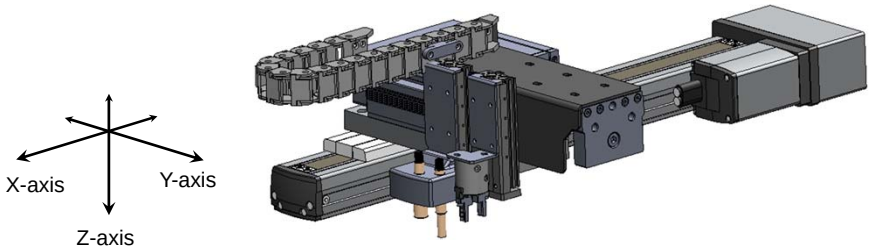
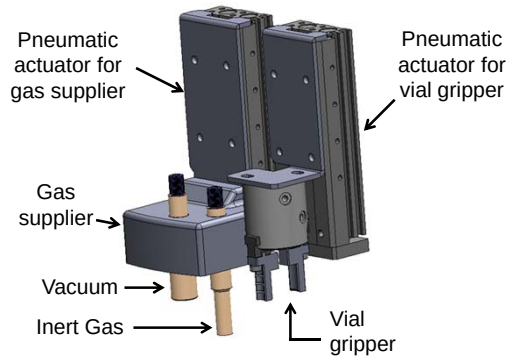




March 6, 2013 (START)

Disposable Cassettes

Top

Bottom

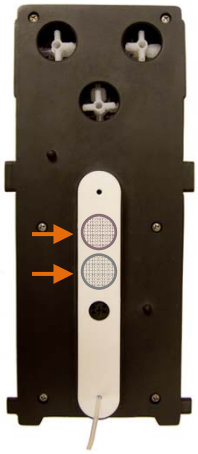
Reagent addition

March 6, 2013 (START)

Disposable Cassettes

Top

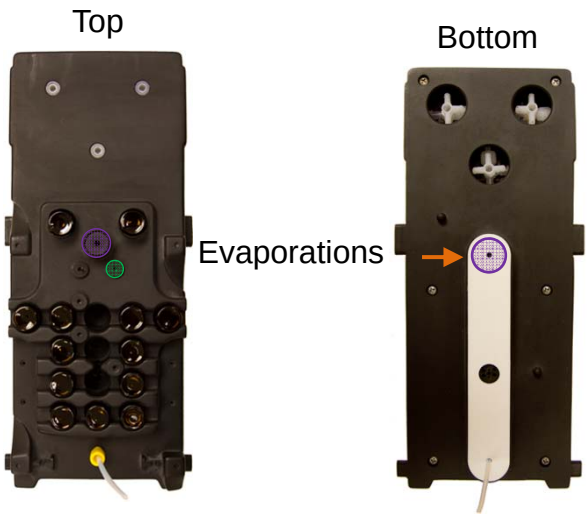
Bottom



Chemical reactions

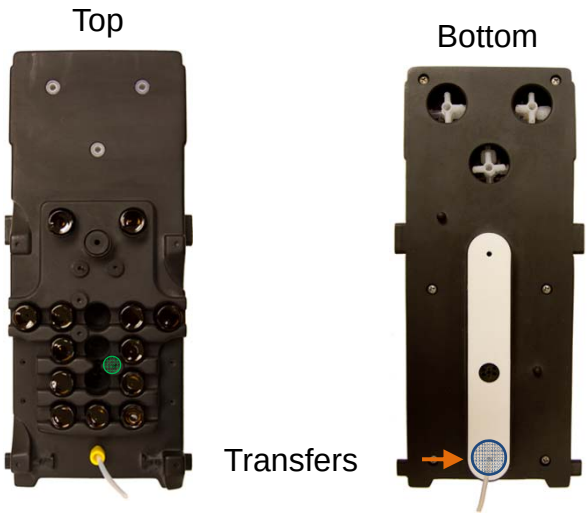
March 6, 2013 (START)

Disposable Cassettes

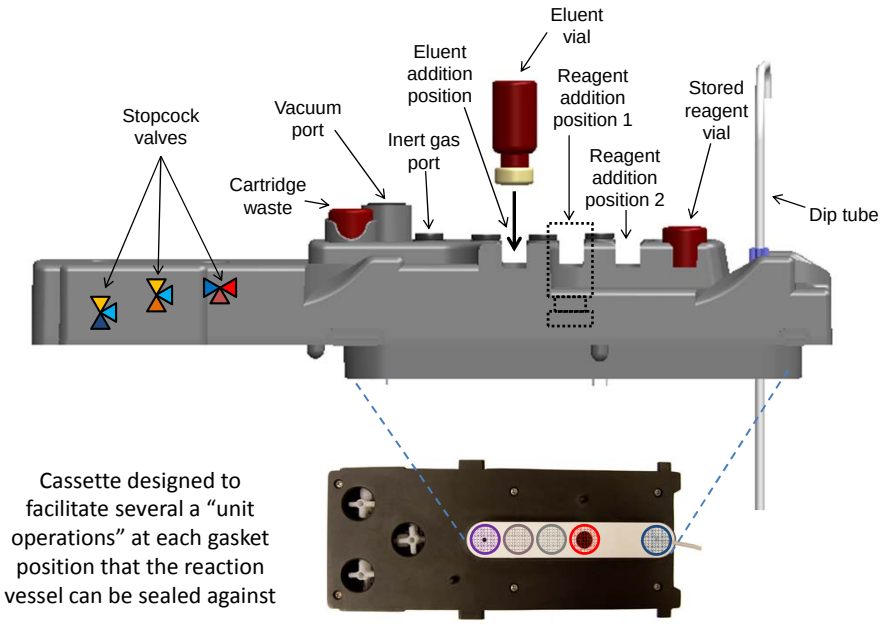


March 6, 2013 (START)

Disposable Cassettes



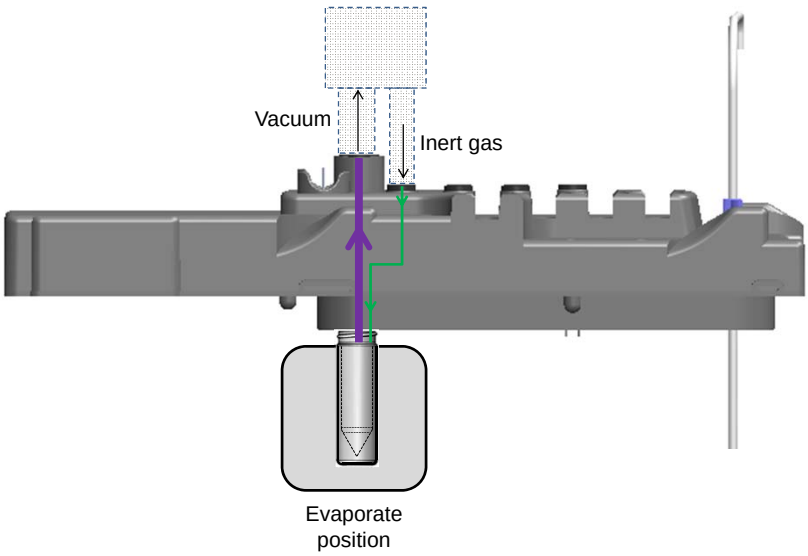
March 6, 2013 (START)



Cassette designed to facilitate several a "unit operations" at each gasket position that the reaction vessel can be sealed against

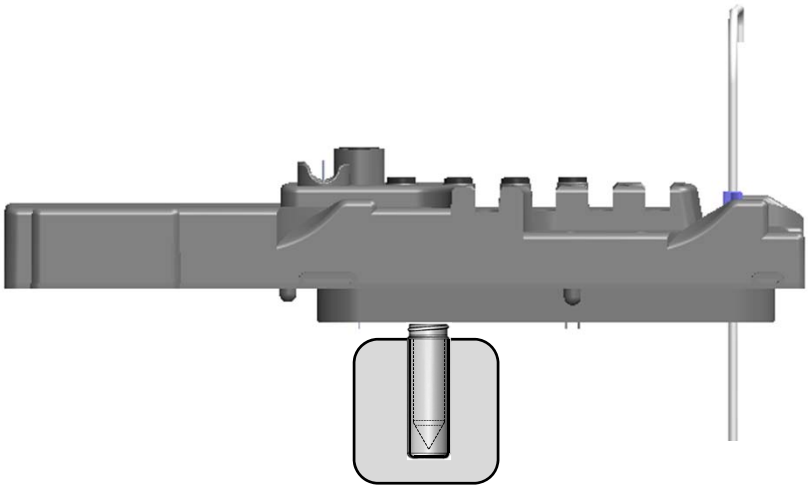
March 6, 2013 (START)

Evaporation



March 6, 2013 (START)

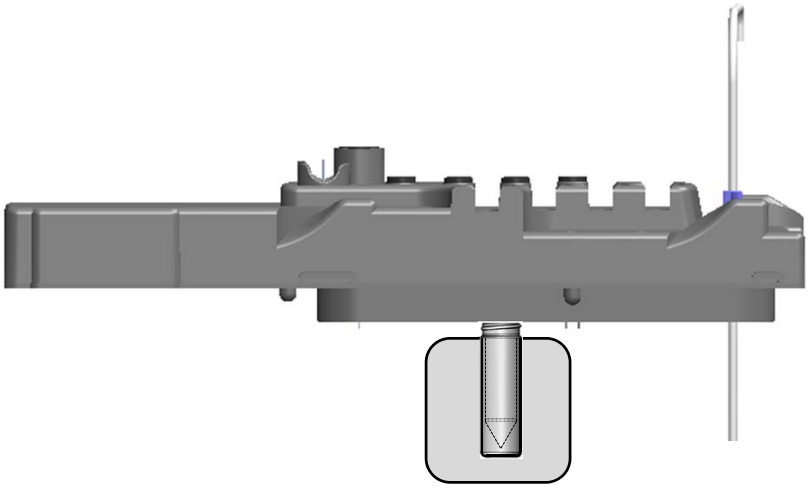
Sealed Reaction



React
position 2

March 6, 2013 (START)

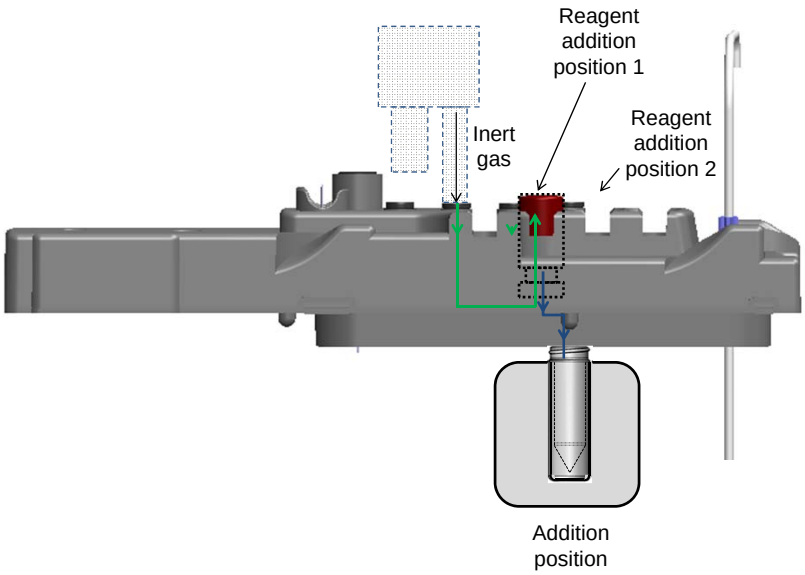
Sealed Reaction



React
position 1

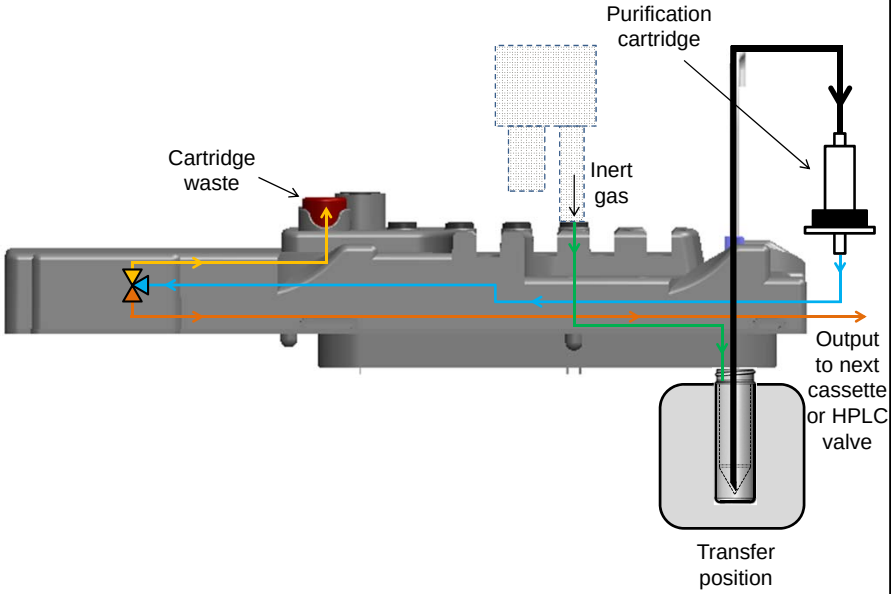
March 6, 2013 (START)

Reagent Addition



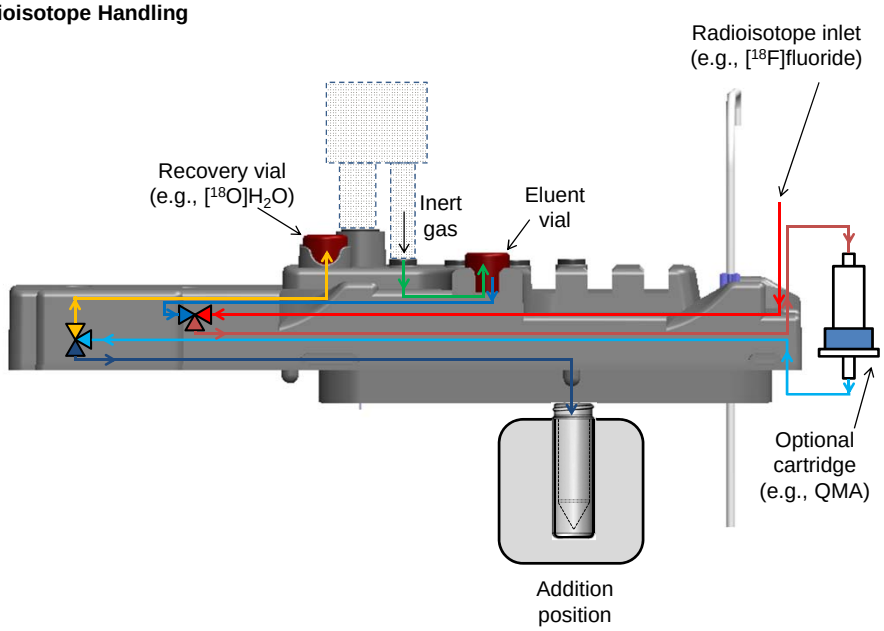
March 6, 2013 (START)

Transfer



March 6, 2013 (START)

Radioisotope Handling

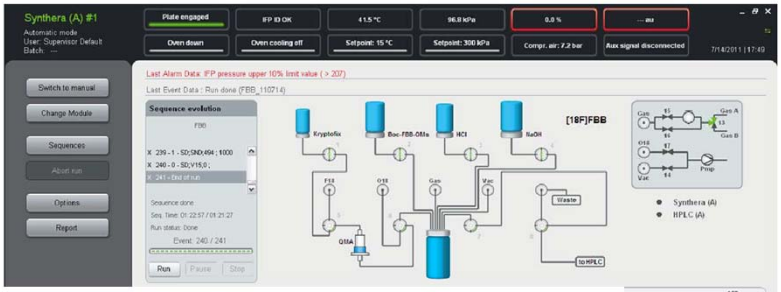


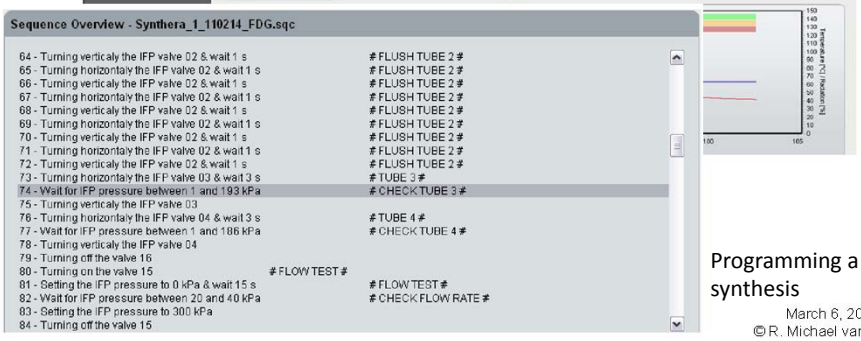
March 6, 2013 (START)

ELIXYS Radiosynthesizer software

March 6, 2013 (START)

Simplifying software for radiochemists





Programming a synthesis

Unit operations to hide complexity from users

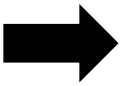
```
# Adjust pressure
- Set regulator 1 to delivery pressure

# Move reactor to add position
- Lower reactor
- Move reactor robot to add position
- Raise reactor

# Move reagent vial to delivery position
- Open gripper
- Raise gripper
- Raise gas transfer
- Move reagent robot to reagent position
- Lower gripper
- Close gripper
- Raise gripper
- Move reagent robot to delivery position
- Lower gas transfer
- Open gas transfer valve
- Lower gripper

# Deliver reagent
- Wait for delivery time to elapse

# Return vial to reagent position
- Raise gripper
- Close gas transfer valve
- Raise gas transfer
- Move reagent robot to reagent position
- Lower gripper
- Open gripper
- Raise gripper
- Move reagent robot to home
```



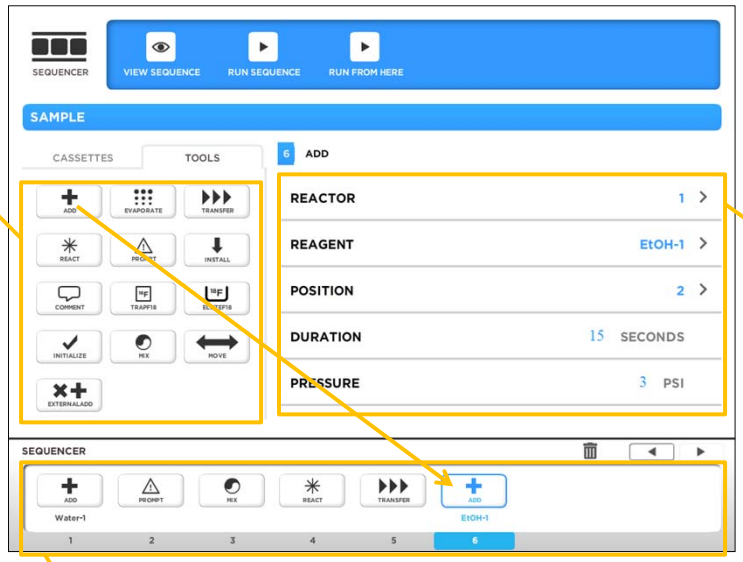
"ADD REAGENT" unit operation

Parameters:

- Reactor
- Reagent
- delivery position
- delivery pressure
- delivery time

Other unit operations:

- REACT (temperature, time)
- EVAPORATE (temperature, time)
- TRANSFER (from, to, pressure)
- PROMPT (message)
- etc…



Toolbox of unit operations

Parameters for selected unit operation

"Filmstrip" view of synthesis process

March 6, 2013 (START)

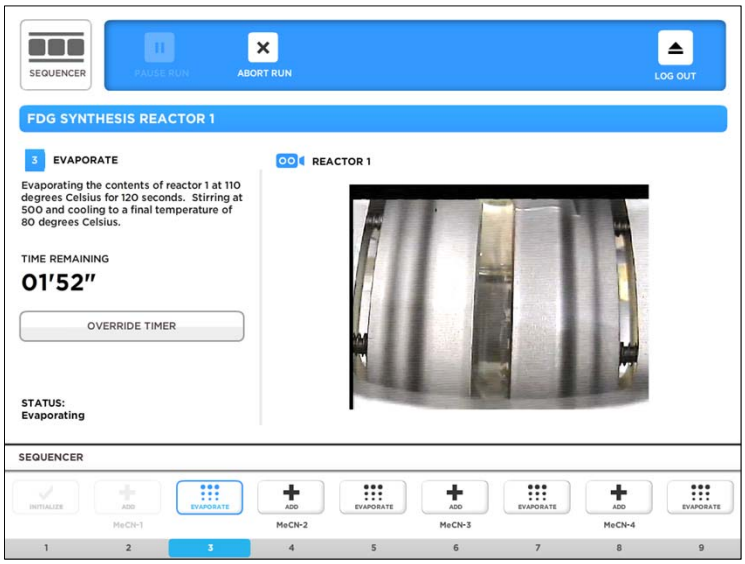
How to choose parameter values?

- For some processes, there are no sensors built into ELIXYS to detect completion. A timer approach is used instead.
- Example: How to determine desired duration of applying gas pressure for reagent addition
  - Load reagent vial with desired volume of desired reagent
  - Deliver at desired pressure to reaction vessel
  - Monitor completion with camera
  - Repeat many times, take maximum time, multiply by safety factor (e.g. 1.3 – 1.5)
  - Set this as the desired time

March 6, 2013 (START)

System	Probe	Operation count
ELIXYS	[^{18}F]FDG	17 unit operations
ELIXYS	D-[^{18}F]FAC	42 unit operations
ELIXYS	L-[^{18}F]FMAU	42 unit operations
ELIXYS	[^{18}F]SFB	15 unit operations
ELIXYS	[^{18}F]FLT	15 unit operations
ELIXYS	[^{18}F]Fallypride	12 unit operations
IBA SYNTHERA	[^{18}F]FDG	227 program steps
IBA SYNTHERA	[^{18}F]FLT	241 program steps
IBA SYNTHERA	[^{18}F]SFB	206 program steps
GE FASTLAB	[^{18}F]FDG	335 program steps

March 6, 2013 (START)



March 6, 2013 (START)

Summary

Advantages of ELIXYS

- Flexibility for diverse PET probes
  - Up to 3 reaction vessels
  - Movable reactor can withstand high reaction temperatures and pressures
  - Most fluid paths (e.g. connection between a reagent vial and reaction vessel) are created on the fly
    - Allows most reconfiguration to be done in software
    - No need to customize / replumb system
    - Improves standardization of hardware so a custom system isn't used for each probe
- Very few valves and fittings (improves reliability)
- Intuitive software interface, requires no knowledge of hardware architecture of the system
- Cassettes enable rapid shift from probe development to routine production

Summary

- Recapped synthesis of FDG on robotic synthesis module
- Remote control vs automation
- Basic architecture and elements of radiosynthesizers
- Examples of commercial radiosynthesizers of different types
- ELIXYS radiosynthesizer
- ELIXYS software

- Next week: automated radiosynthesizer lab (ELIXYS)

Resources

- R. Krasikova. 2007. "Synthesis Modules and Automation in F-18 Labeling". In *PET Chemistry: The Driving Force in Molecular Imaging*, Schubiger, P.A., Lehmann, L., Friebe, M. (Eds.). 62: 289-316. Springer-Verlag Berlin Heidelberg.

- D.L. Alexoff. 2003. "Automation for the Synthesis and Application of PET Radiopharmaceuticals." In *Handbook of Radiopharmaceuticals: Radiochemistry and Applications*, Welch, M.J. and Redvanly, C.S. (Eds.). 283-305. John Wiley & Sons, Ltd.

- P.Y. Keng, M. Esterby, R.M. van Dam. 2012. "Emerging Technologies for Decentralized Production of PET Tracers". In *Positron Emission Tomography: Current Clinical and Research Aspects*. 153-182. InTech.

- J.I. Sachinidis , S. Poniger, H.J. Tochon-Danguy. 2010. "Automation for Optimised Production of Fluorine-18-Labelled Radiopharmaceuticals." Current Radiopharmaceuticals 3: 248-253.

- H.C. Padgett, D.G. Schmidt, A. Luxen, G.T. Bida, N. Satyamurthy, J.R. Barrio. 1989. "Computer-controlled radiochemical synthesis: A chemistry process control unit for the automated production of radiochemicals". Applied Radiation and Isotopes 40(5): 433-445. [Historical paper]