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NanoTek® LF

Advion
Accelerated Chemistry

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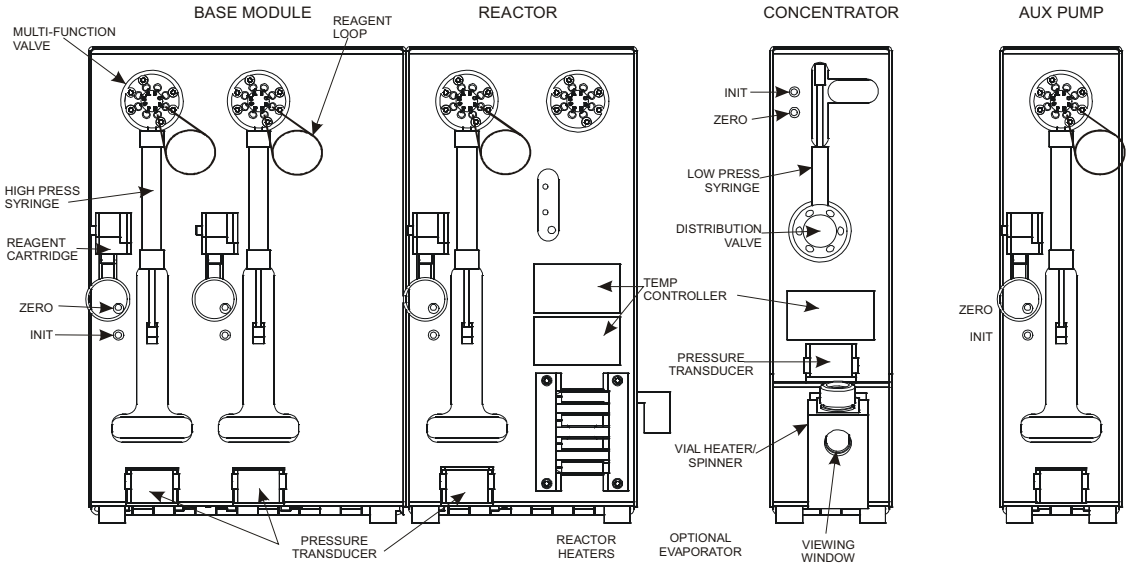
System Overview



The standard module consists of three main modules:

- A Base Module which consists of two syringe pumps with multi-function valves per syringe pump
  - this unit delivers metered amounts of precursors, activity and reagents to the reactor module in accurate volumes down to 5 µl

- A Reactor Module which contains a syringe pump, two mutifunction valves and a heated zone which possesses four independently heated zones for the reactor cartridges
  - The Reactor Module stages isotope in a loop that is isolated from the Base Module. This allows users to safely and rapidly change chemistries without having radioactivity, thereby productivity from a single supply of isotope. This configuration allows multiple syntheses using different tracers and/or doses in a single day.
  - During synthesis, the activity which is either ^{18}F, ^{11}C or other isotopes being tested and precursor are pumped into the glass microfluidic reactor cartridge located in Reactor Module. Each of the four reactor cartridges can be operated at pressures up to 500 psi and temperatures to 200 °C. With four reactor cartridges, multistep or parallel syntheses are possible, as well as final product or isocratic HPLC in-line. If gradient elution is required, the module can send reaction products to an external HPLC system. It is also able to combine and evaporate larger volumes of precursor and isotope for clinical scale synthesis. The reactor cartridges are available in a range of diameters and lengths to ensure optimum synthesis.

- A Concentrator which possesses a syringe pump, multiport valve, and a vessel heater
  - The Concentrator/Evaporator Module automatically concentrates and prepares either ^{18}F or other isotopes being tested. In addition, it can evaporate and purify intermediates.

- Software control
  - The NanoTek Microfluidic Synthesis System and its modules are controlled by a software program on a standard laptop computer. The software allows total control of reactions and optimization of methods. A visual interface displays real-time system conditions.

- Additionally, auxilliary pumps or additional concentrators can be added to the Standard system if additional flexibility is required

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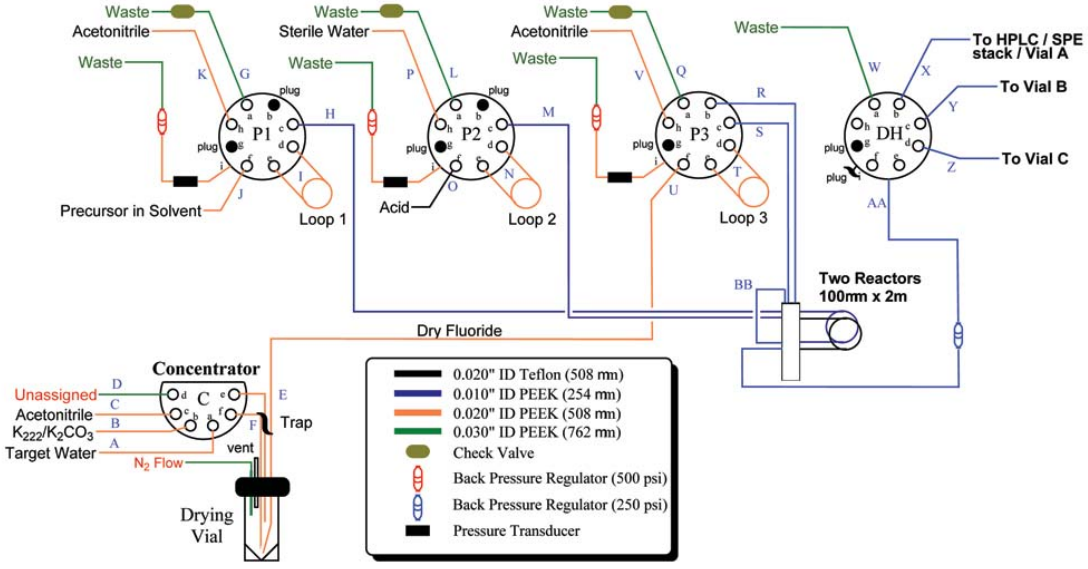
Operating Modes for NanoTek LF

The system and control software can be configured to operate in Discovery, Batch, or Parallel modes:

1) Discovery Mode



Schematic diagram of system in Discovery Mode

a) The NanoTek LF software and hardware has been developed to aid in the rapid research of discovering new or optimizing existing chemistry reactions. The software automatically calculates flow rates and volume deliveries based on inputs from the user. It also provides feedback to the user if an error will occur during the process such as low solvent volume or incorrect system setup.

b) The Discovery Tool operates in two different modes; Volume or Activity.
   i) In Volume Mode the discovery calculations are based on a known volume of fluoride.
   ii) In Activity Mode, the discovery calculations are based on delivering a requested amount of activity determined from a starting concentration value.

c) The tool was developed using pump 1 to deliver the precursor and pump 3 to deliver the activity. A second step reaction can be exercised by using pump 2 to introduce a second reagent. The first reaction between the precursor and the activity is reacted in Reactor 1 while the optional second reaction takes place in Reactor 2. Pump 3 is used to sweep the reacted bolus of activity and precursor through the system to the collection vial.

d) In Discovery Mode the user is able to try 10-15 reaction conditions from a single vial of precursor and activity.
   i) Reaction temperature
   ii) Flow rates/residence times
   iii) Ratios of precursor to activity (this can be used to determine the optimum or minimum precursor concentration)

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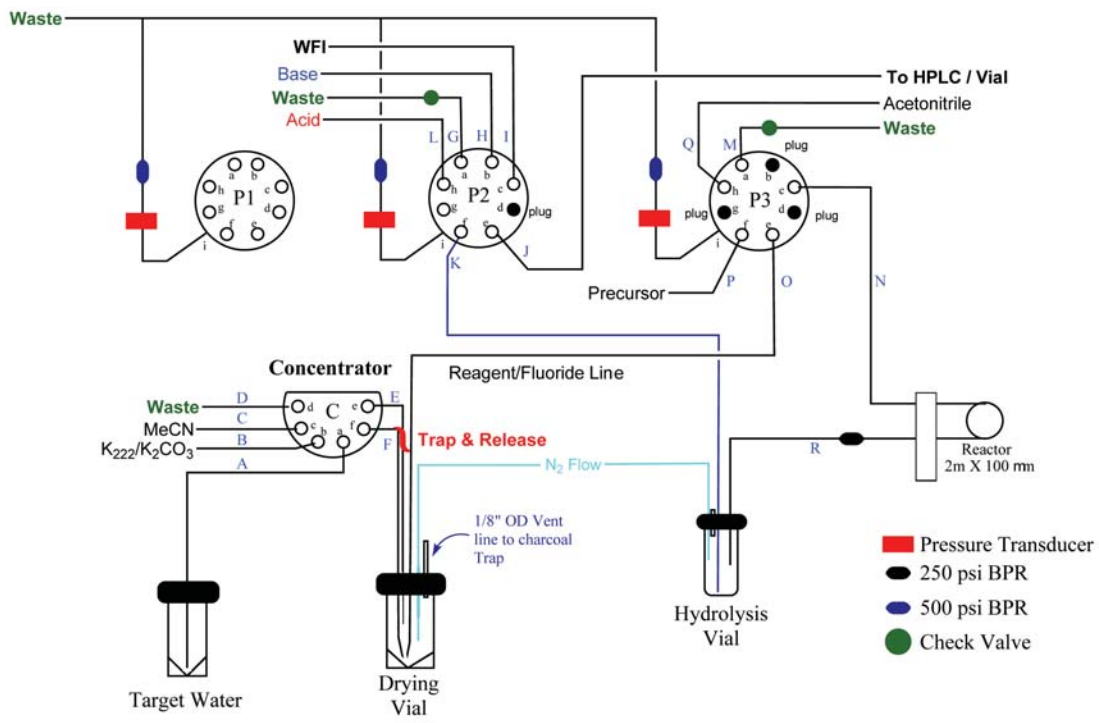
Operating Modes for NanoTek LF, continued

2) Batch Mode



Schematic diagram of system in Batch Mode
for a system using one reactor and post reactor hydrolysis

a) The NanoTek LF software and hardware has been developed to allow for the rapid conversion of the optimized methods developed in Discovery Mode to be converted to Batch Mode for preparation of larger amounts of material.

b) In Batch Mode, the system can perform multiple reactions in both reactor-based systems, or a mix of reactor- and vial-based chemistry. In the schematic above, the first incorporation of fluoride is performed in the reactor and the subsequent hydrolysis is performed in a vial-based process. The choice of reactor versus vial reaction is dependent upon the chemistry of the particular tracer being prepared and the system offers the user the flexibility to choose which is more appropriate for the radiotracer being synthesized.

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Operating Modes for NanoTek LF, continued

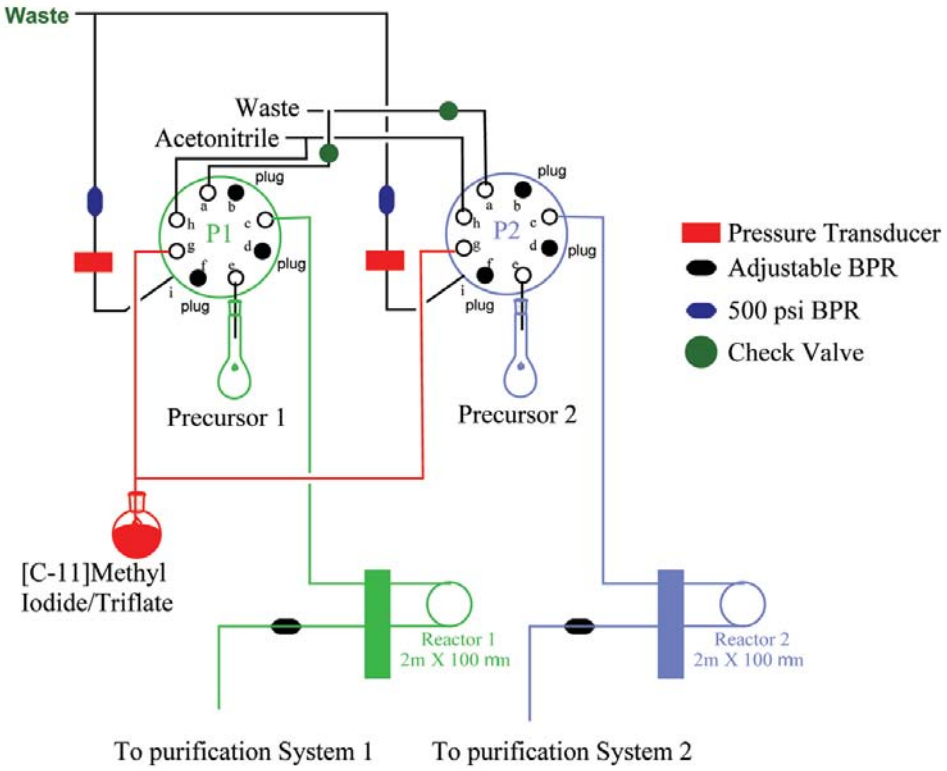
3) Parallel Mode

a) The NanoTek LF software and hardware can be configured to operate in a Parallel Mode.

b) The optimized method is programmed as a batch method using the conditions derived from the optimization which was performed in a Discovery Mode for each individual radiotracer.

c) An example of the parallel synthesis is shown in the schematic diagram below. In this example:

i) the isotope used is [C-11] methyl iodide or triflate
ii) Each reaction is a simple one step reaction with no deprotection
iii) The source of the radioisotope could be replaced with fluoride or another isotope from a vial or from the concentrator



Schematic diagram of system in Parallel Mode for a system using two independent reactors and the source isotope is [C-11] methyl iodide. The activity may also be isotope, such as fluoride obtained from the concentrator module.

d) Each reaction may have its own:

i) Reactor temperature
ii) Reaction flow rate
iii) May use different isotopes if necessary

e) The basic operation involves the following steps:

i) Collection or preparation of the radioisotope to be used for radiolabelling
ii) Thoroughly mix radioisotope with precursor
iii) Draw up the radioisotope into each syringe and push through the reactor at each reactions appropriate flow rate
iv) As each reaction finishes, it will need to be passed onto a purification system