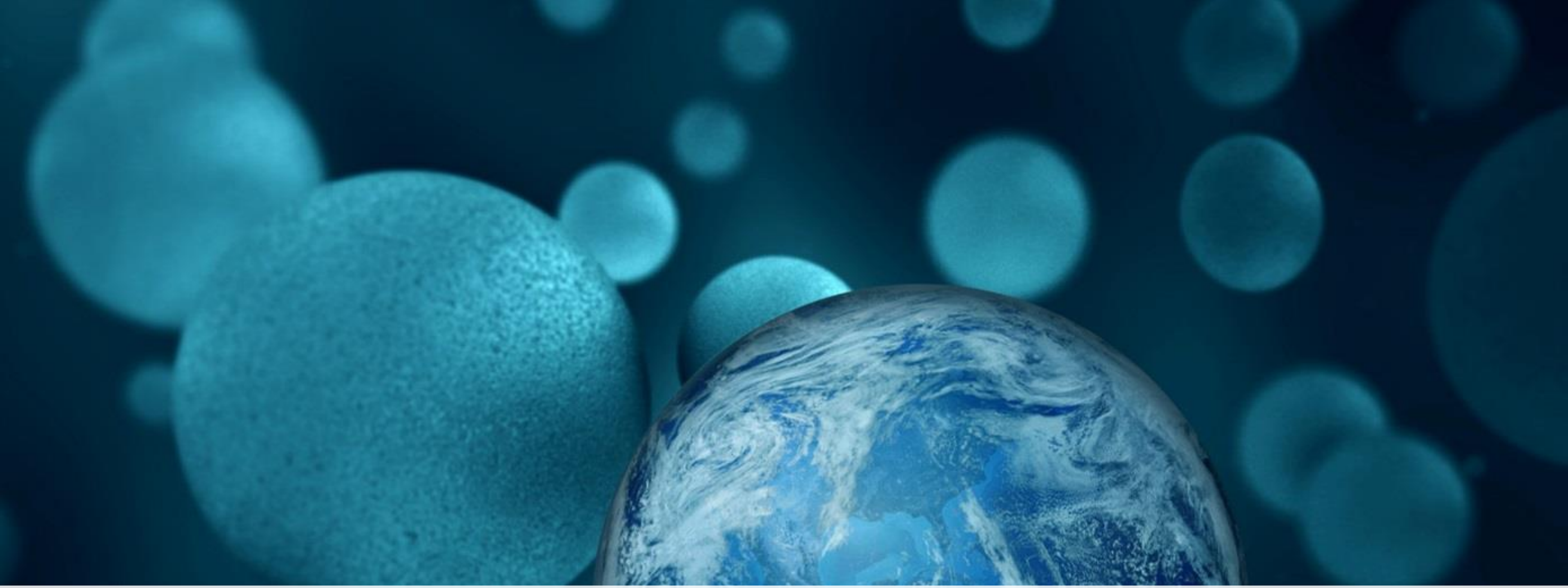


ThermoFisher SCIENTIFIC

Mass spectrometry assay optimization using functional programming patterns in Lua

Bennett Kalafut

Outline

1. Mass Spectrometry and Lua
   a) Mass spectrometry basics (what, why, and how?)
   b) Lua as a control language

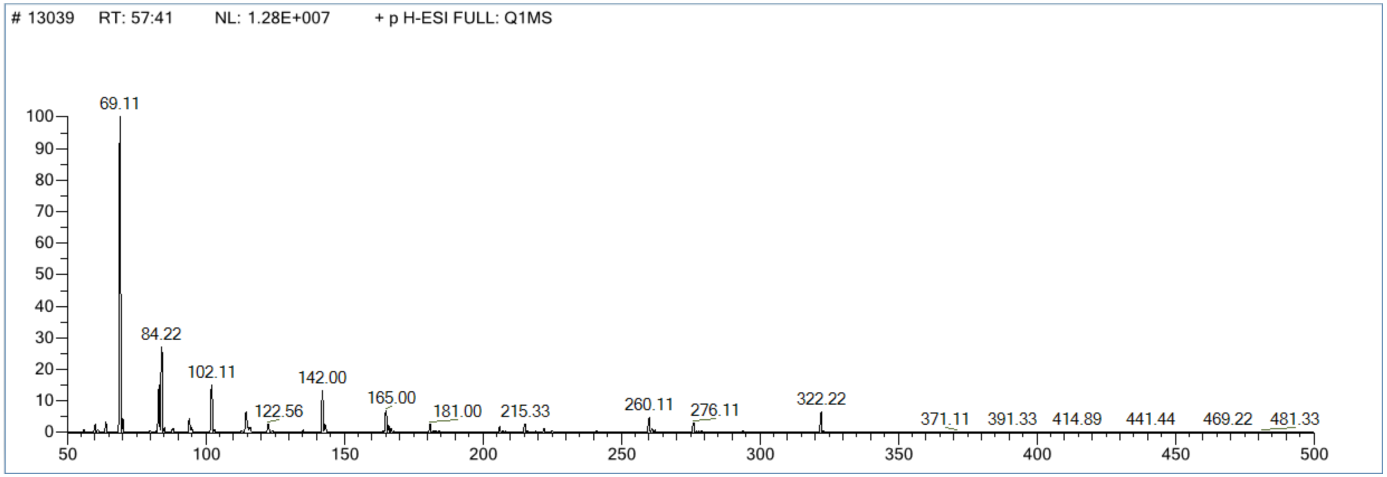
2. Iterator pipelines and higher-order table functions
   a) Core functionals: Map, filter, and reduce
   b) Lua-specific patterns
   c) Warm-up 1: Tuning up an ion source
   d) Warm-up 2: Check some electronics

3. Automated assay optimization
   a) Why per-assay optimization?
   b) Optimizations as composable functions
   c) How to hide/handle state
   d) Putting it all together

What is mass spectrometry?

Separation and quantification of ions in a mixture, by mass.

- An electrical or electromagnetic technique. Separation by m/z, not m.



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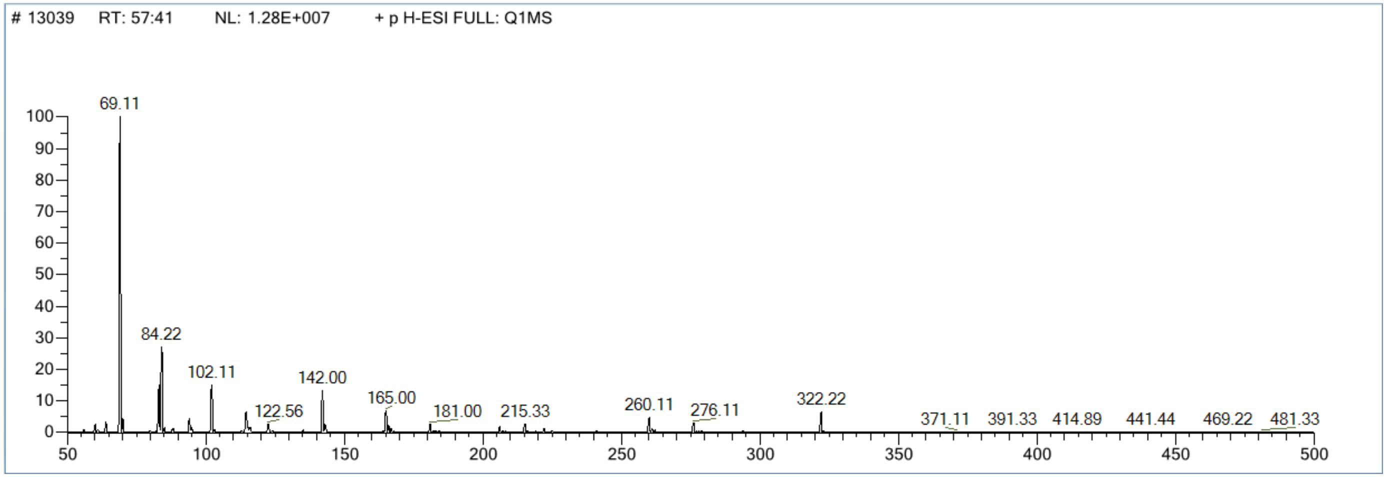

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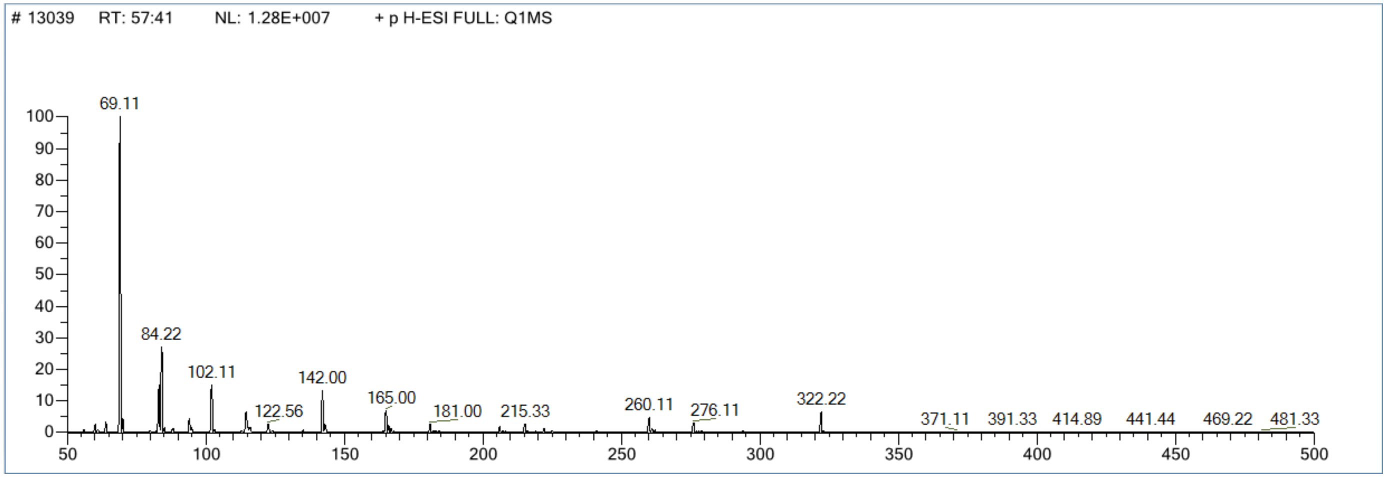

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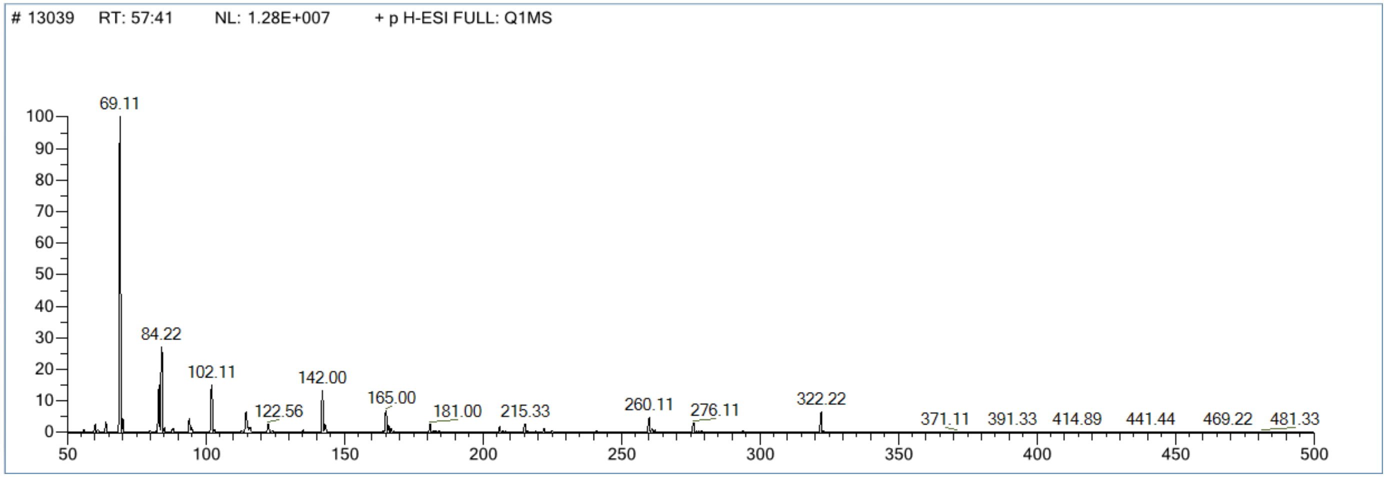
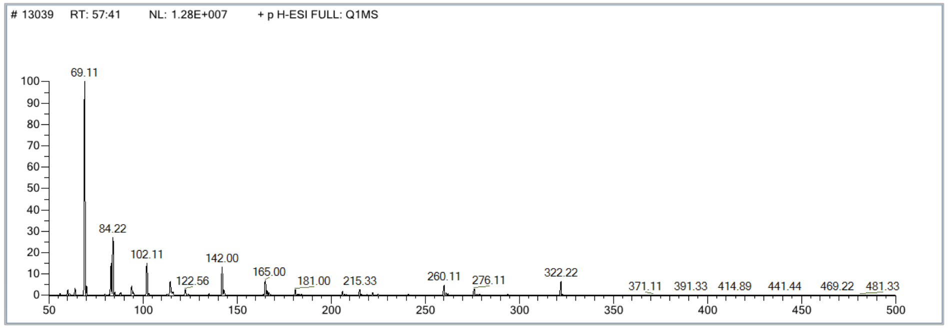
- Future: Surgery, personalized medicine.



The modern standard technique: Tandem MS

- MS/MS: Separate, fragment, separate again



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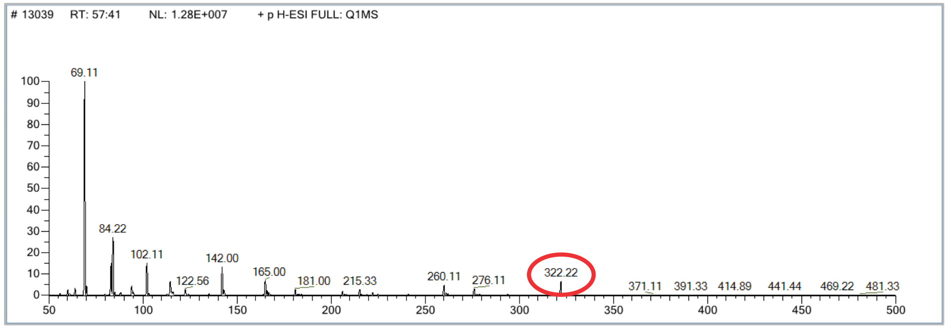

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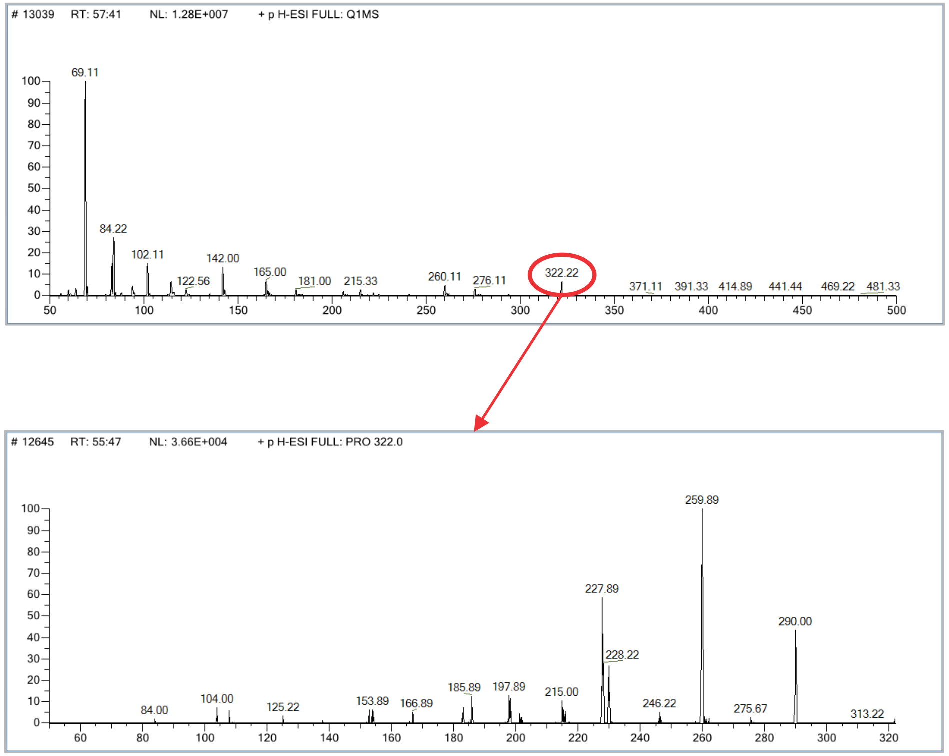

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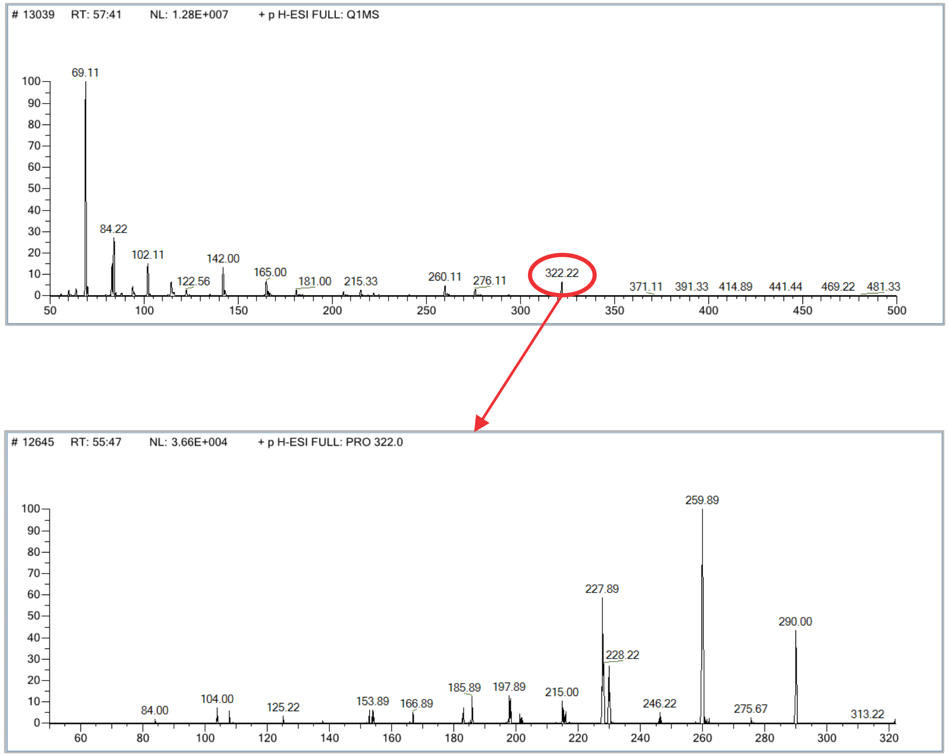

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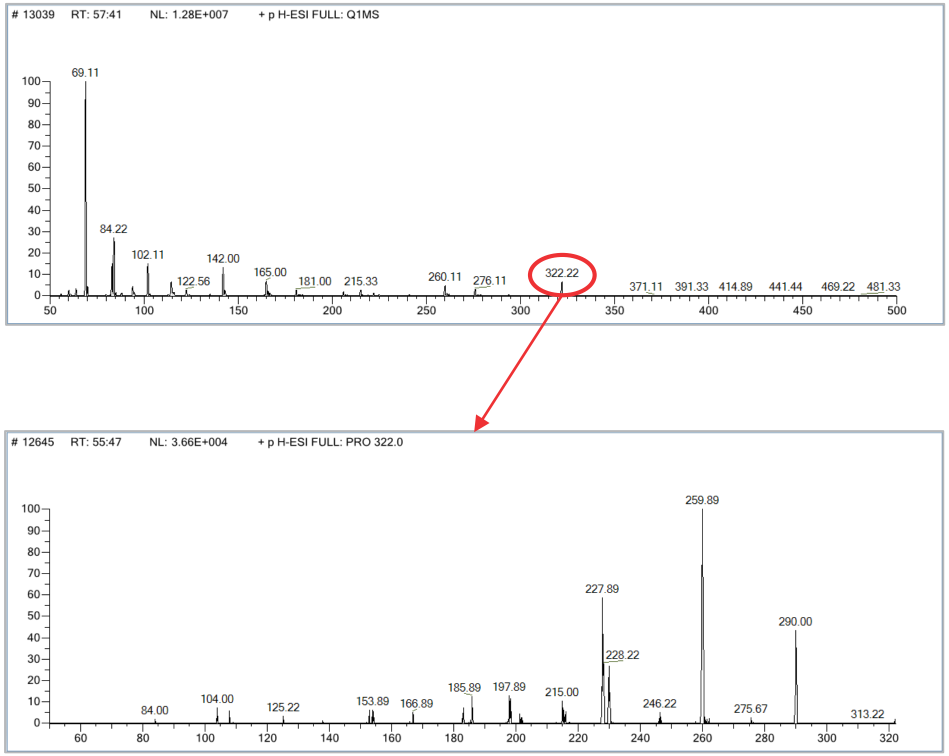

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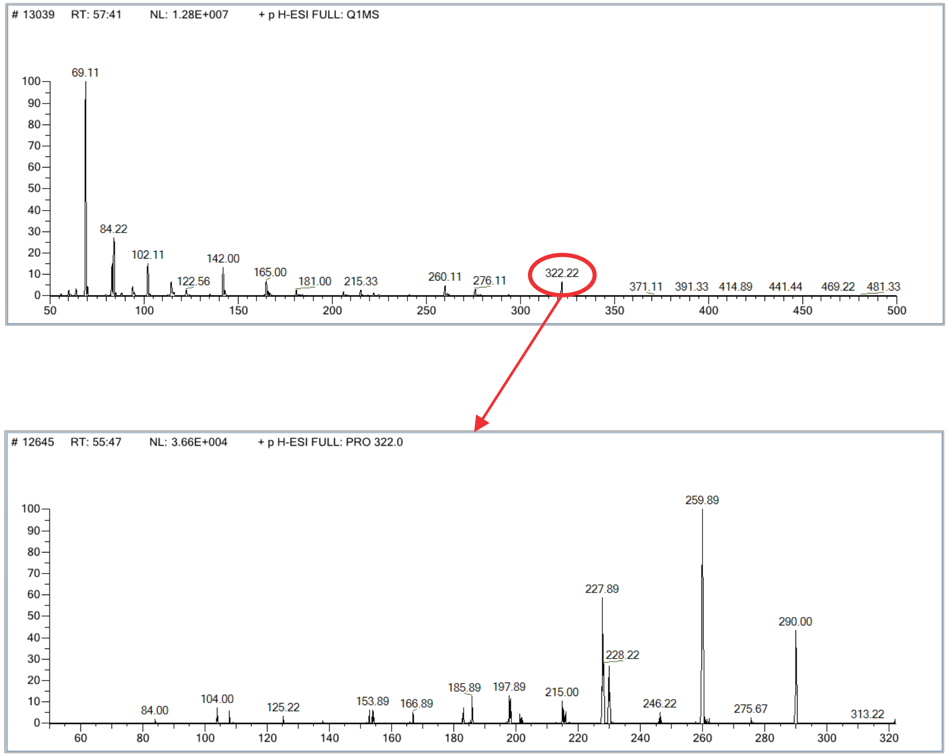

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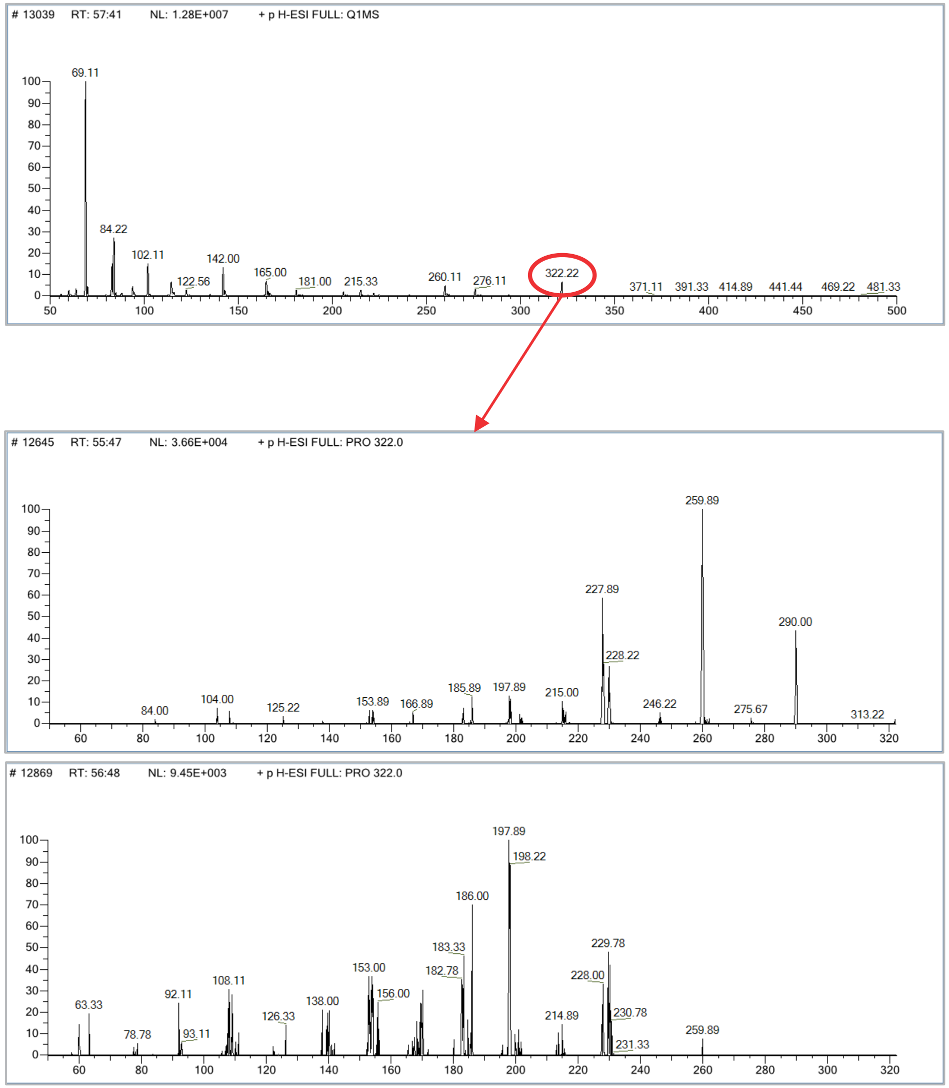

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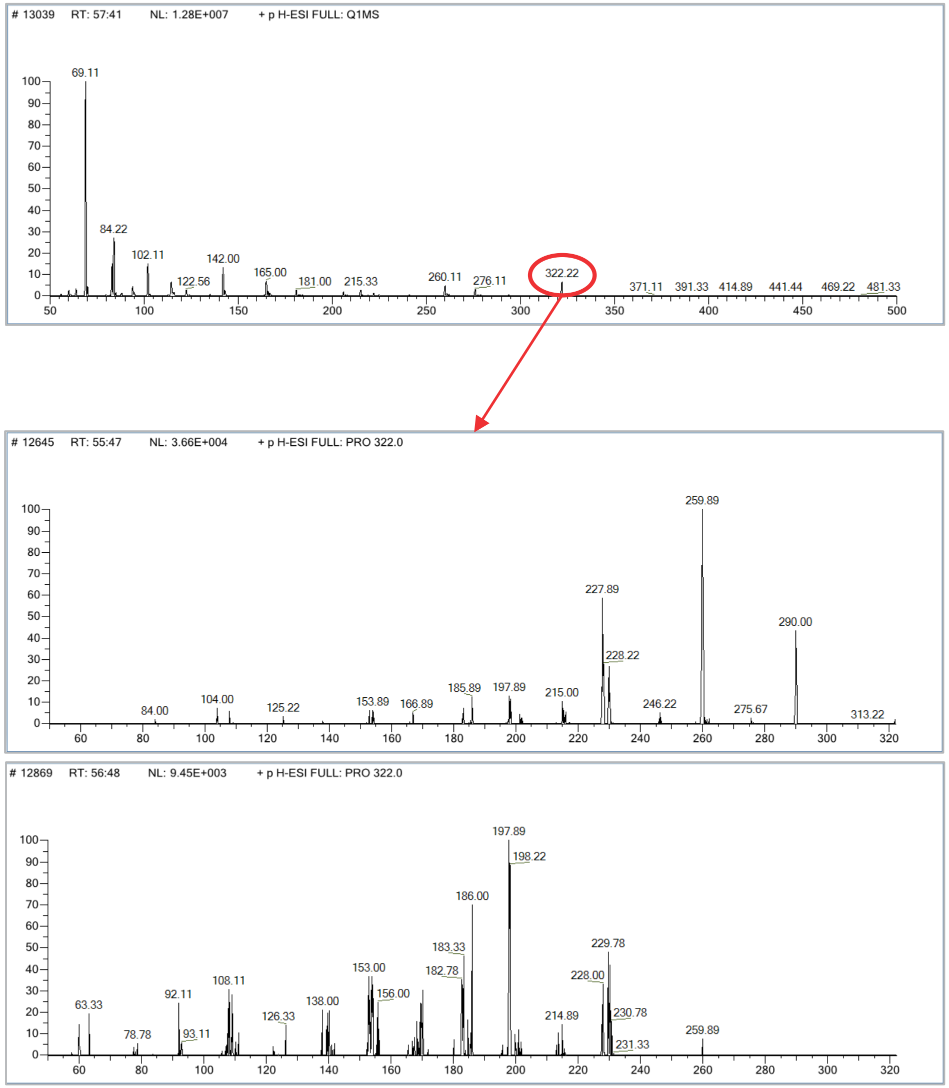
- Often coupled with other separation techniques:
  - Liquid chromatography
  - Gas chromatography
  - Ion mobility
  - FAIMS



Thermo Fisher Scientific Lua-Controlled Mass Spectrometers

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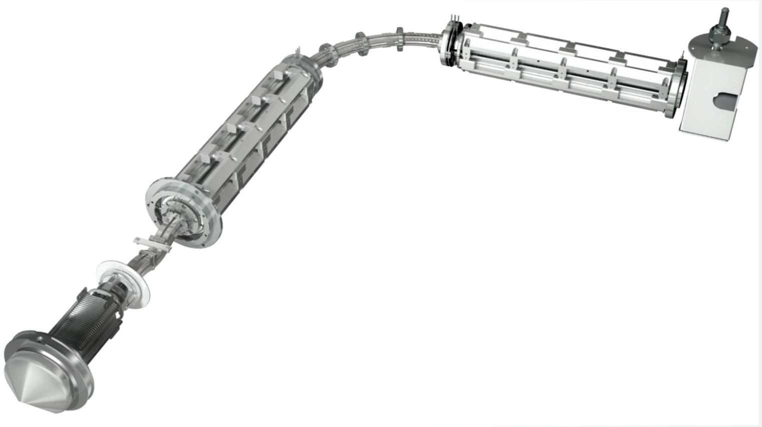

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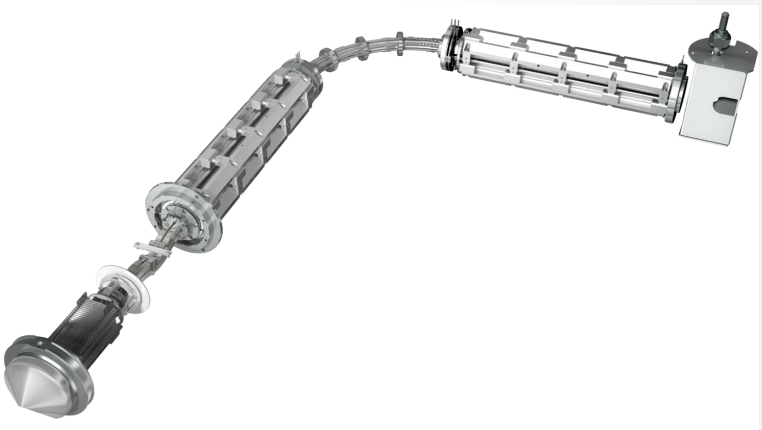

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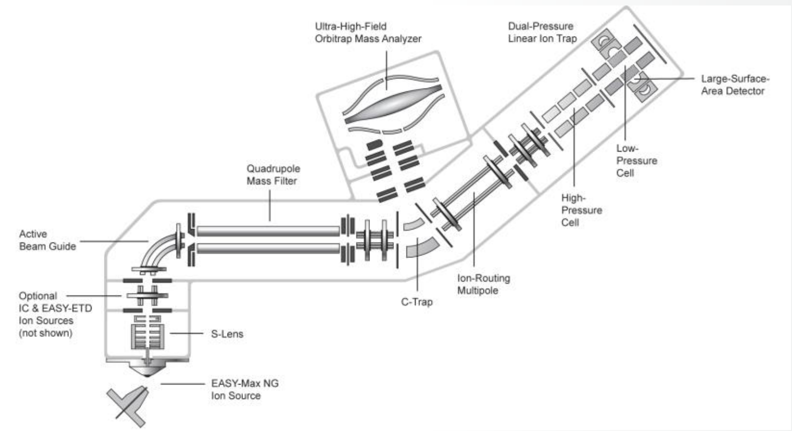

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Lua for instrument control: how Thermo does it.

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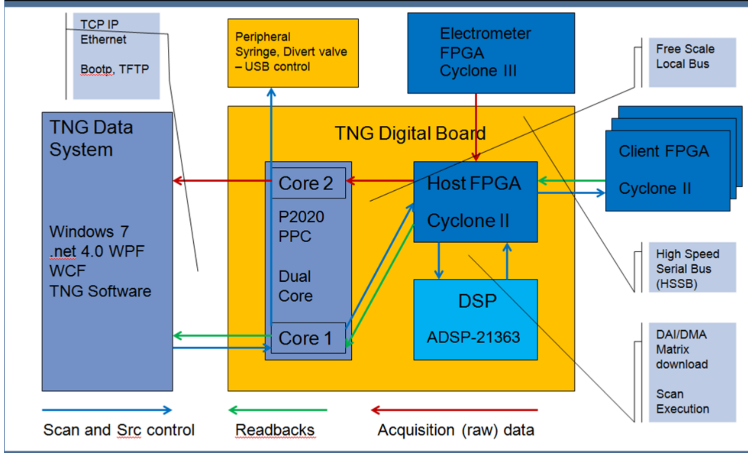
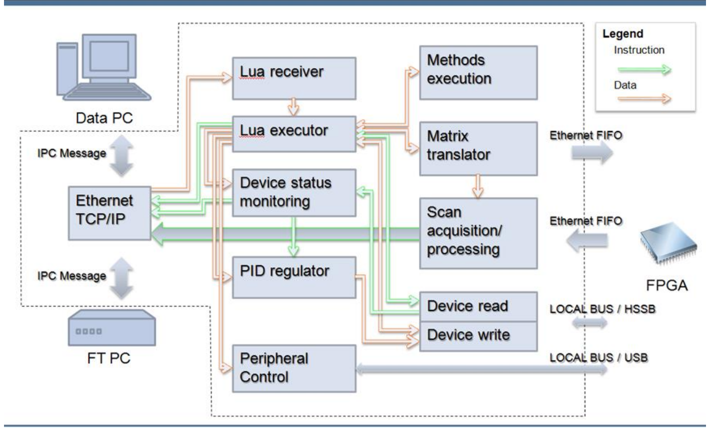
TNG Firmware View



Firmware Interfaces view



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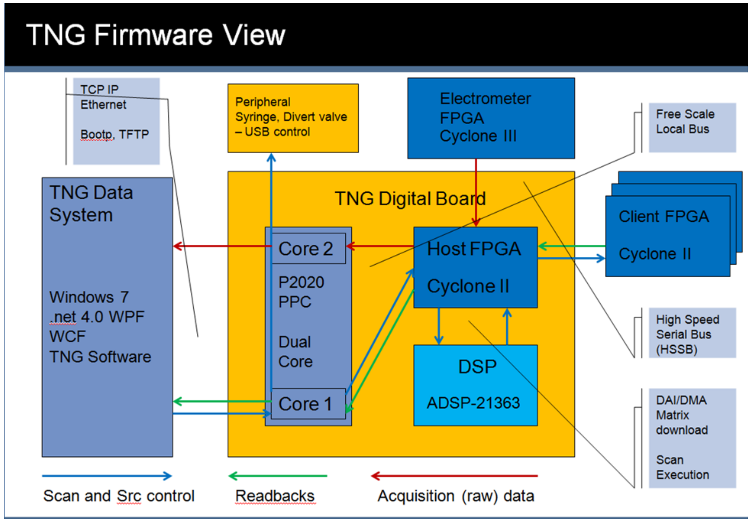

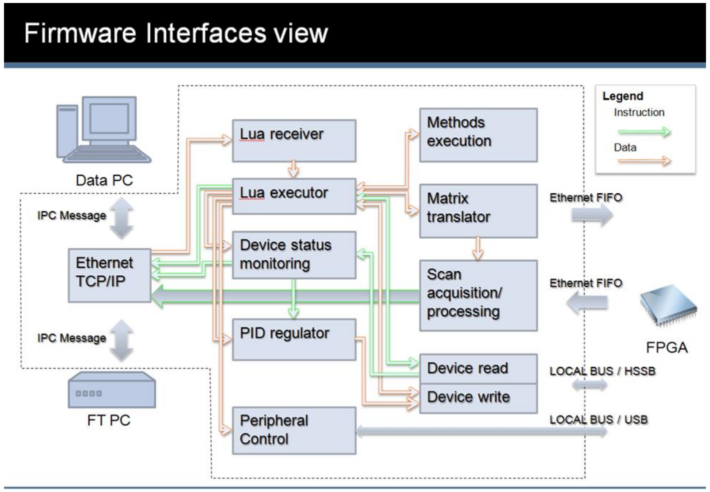

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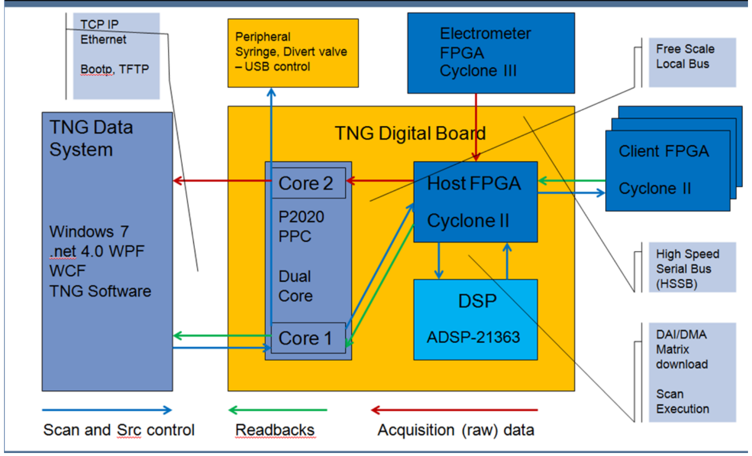

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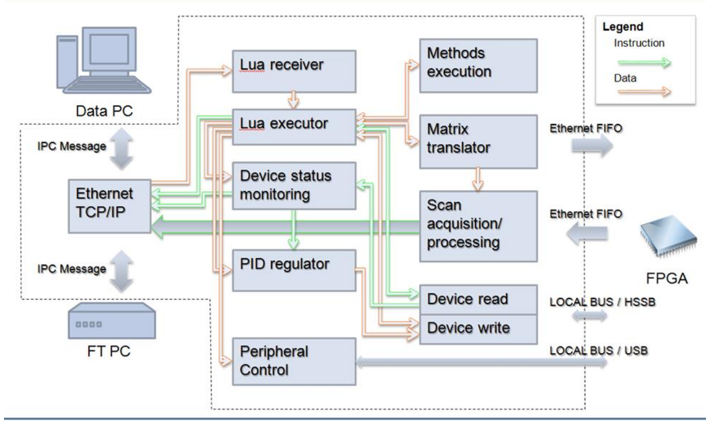

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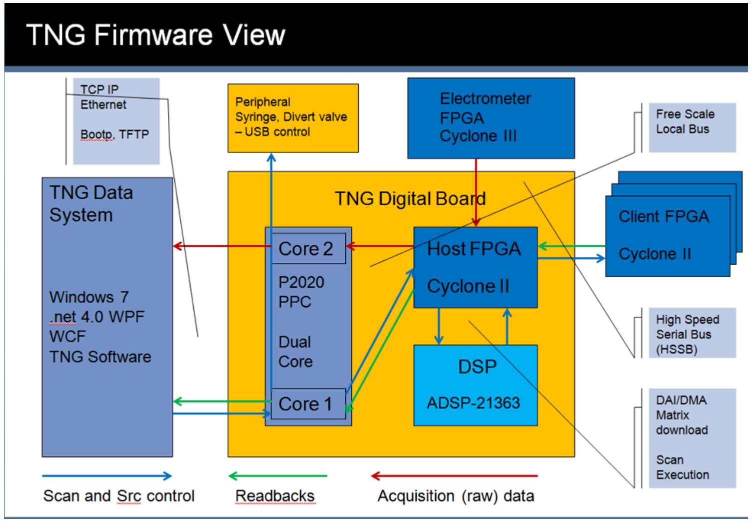

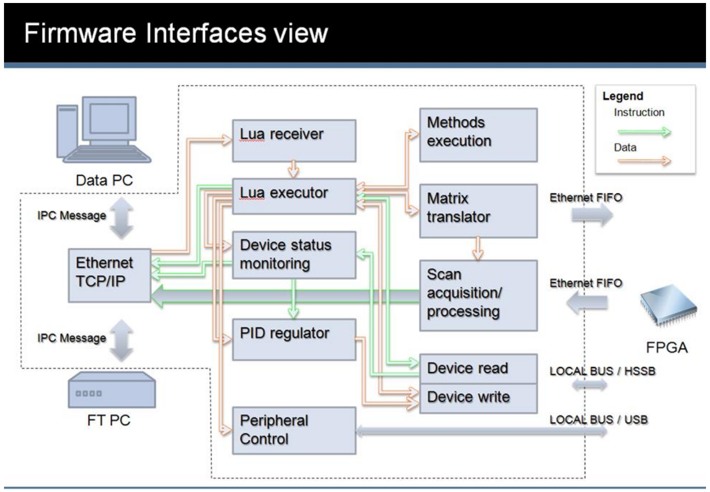

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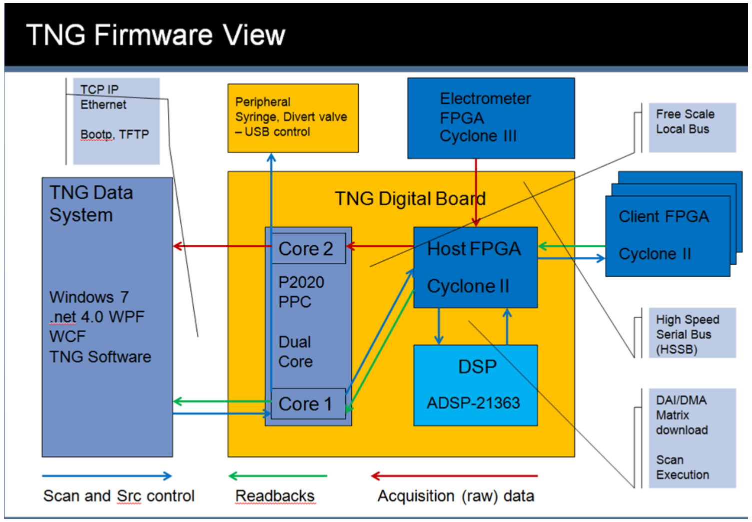
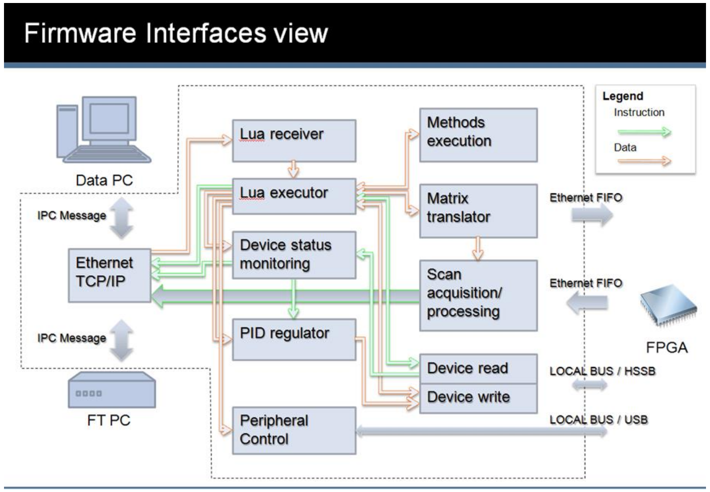
5. Data query primitives provide information about the buffered spectrum to Lua.





Lua in the mass spectrometer: first example

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  for i = 1, totalScans do
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    if Sys.Abort()==true then
      RestoreDragCellVoltages()
      print("Aborted by user.")
      error(Diag.exceptions.ABORT)
    end
    xvalues[i]=i
    CF2:SetAndUpdate(100, DRAG_1)
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    Sys.TakeAScan()   -- take one scan to warm up the MS
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Not shown:

- Scan matrix builder
- Direct voltage control

Core higher-order functions: map, filter, and reduce

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  - Reduce (left fold)
    Applies a function pairwise from left to right, reducing the set to a single value. Sums, products, projections, and multi-function composition are some examples.
    `Reduce(f,{a,b,c,…})→f(…(f(f(a,b),c),…)`

Composable iterators (iterator pipelines)

Iterator pipelines allow the series of operations to be applied one element at a time.

- Map:

```
function Map(fun,first,second,third)
    local itercoroutine=function ()
        for value in (function () return first,second,third end)() do
            coroutine.yield(fun(value))
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    end
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- Filter:

```
function Filter(condition,first,second,third)
    local itercoroutine=function ()
        for value in (function () return first,second,third end)() do
            if condition(value) then coroutine.yield(value) end
        end
    end
    return coroutine.wrap(itercoroutine),nil,nil
end
```

Composable iterators (iterator pipelines)

Iterator pipelines allow the series of operations to be applied one element at a time.

- Map:

```
function Map(fun,first,second,third)
    local itercoroutine=function ()
        for value in (function () return first,second,third end)() do
            coroutine.yield(fun(value))
        end
    end
    return coroutine.wrap(itercoroutine),nil,nil
end
```

- Filter:

```
function Filter(condition,first,second,third)
    local itercoroutine=function ()
        for value in (function () return first,second,third end)() do
            if condition(value) then coroutine.yield(value) end
        end
    end
    return coroutine.wrap(itercoroutine),nil,nil
end
```

- Reduce:

```
function Reduce(func,first,second,third)
    local initialized=false
    local accumulator
    for value in (function () return first,second,third end)() do
        if not initialized then
            accumulator=value
            initialized=true
        else
        accumulator=func(accumulator,value)
    end
    return accumulator
end
```

Lua-specific considerations (or: Lua is not Lisp.)

- Operations should support unordered hashtables, where applicable.
- Map and Filter iterate using pairs, keeping input table keys:

```
Map(f,{[foo]=a,[bar]=b,[baz]=c})
→ {[foo]=f(a),[bar]=f(b),[baz]=f(c)}
```

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- KeyValueMapping operation is very useful: define a table as a function of the keys. *E.g:*

```
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→ {[2]="even", [10]="even", [11]="odd"}
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- Keyed Zip and Unzip: Zip into keyed tables, unzip from keyed tables:

```
KeyedZip({"pants","size"},{"corduroy","gabardine"},{32,36})
→ {{pants="corduroy",size=32},{pants="gabardine",size=36}
```

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```

(Keyedunzip is inverse of keyed zip)

Example 1: Ion source tuning (with complications)

```
local setpoints,sprayCurrents,intensities=
           table.KeyedUnzip(
             fun.IteratorToArray(
               fun.Map(AcquireResponse,
                 fun.TerminateIf(APCIIsOutOfControl,
                   fun.Map(SetAndReadback,
                     fun.Values(grid))))),
          {"setting","readback","ionIntensity"})
```

- Motivation: current is limited by spray chemistry, and true value can lag setpoint

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```

```
local AcquireResponse=
    function (sourceStatus)
        Sys.TakeAveragedScan(nScans)
        return {setting=sourceStatus.setting,
                readback=sourceStatus.readback,
                ionIntensity=DQ:TIC()}
    end
```

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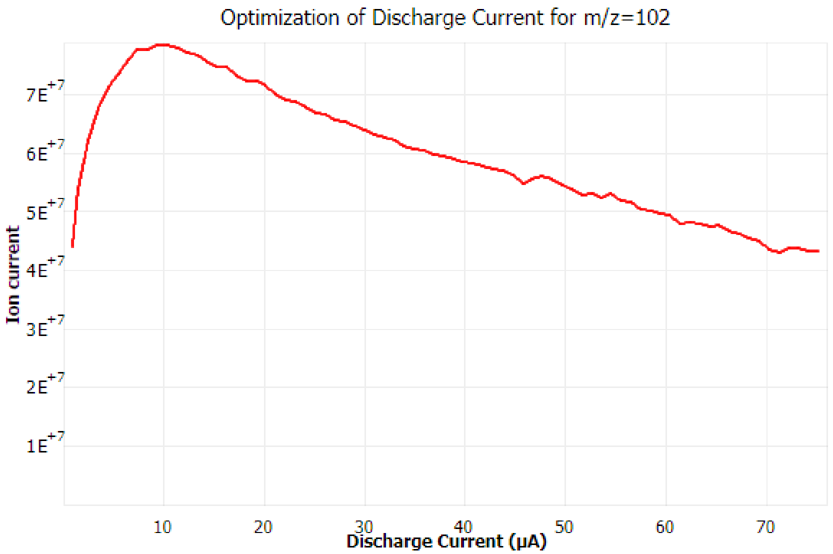
  5. We pack it all into an array, then unzip for further processing.

Example 1 continued: Function decoration for output and more.

```
function
utils.AutoPlotOneParameterFunction(f,Plotter)
    return function(x)
        local y=f(x)
        Plotter(x,y)
        return y
    end
end
```



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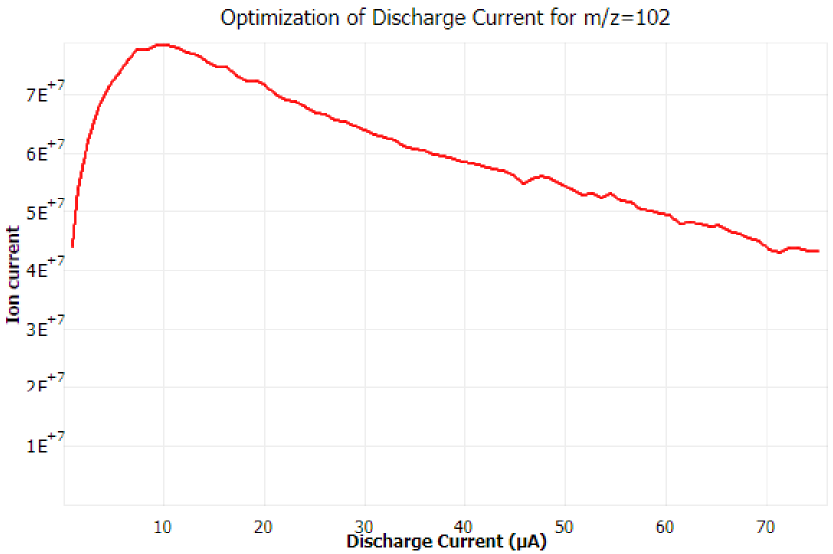
```

```
AcquireResponse=
utils.AutoPlotOneParameterFunction(
    AcquireResponse,
    function (x,y)
        graph:Plot(x.readback,y.ionIntensity,2)
    end)
```



Example 1 continued: Function decoration for output and more.

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    end)
```
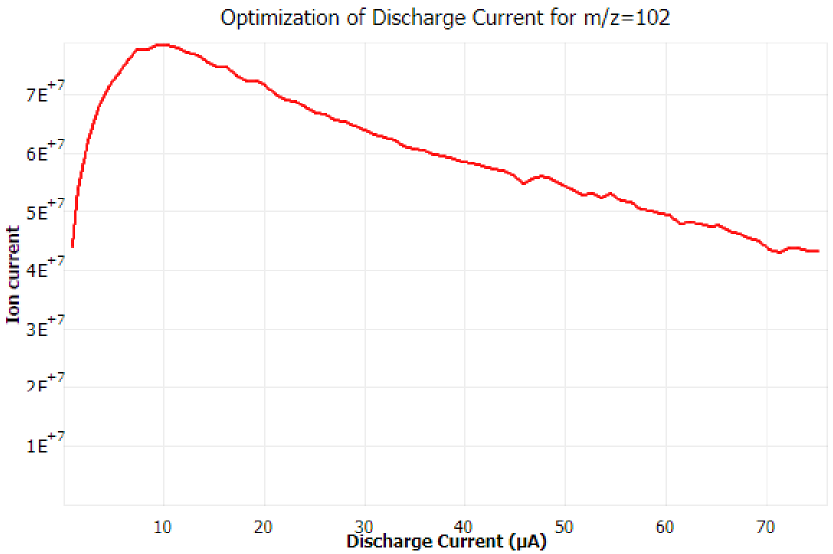

```
AcquireResponse=
CO.ErrorHandlerDecorator(
    AcquireResponse,
    Cal.CommonErrorHandler())
```



Example 2: Electronics ramp test

```
local pCallStatus,result=
          pcall(function ()
                    return fun.IteratorToArray(
                       fun.Map(utils.AutoPlotOneParameterFunction(ReadDevices(readbackDevices),Plotter),
                           fun.Map(SetDeviceAndSleep(rampDevice,sleepTime),
                               fun.iValues(table.Range(rampStart,rampStop,stepSize)))))
                end)
```

Example 2: Electronics ramp test

Creates a function of setpoint that returns a table:
{setpoint=setpoint,
responses=a table of device readbacks, keyed by device)}

```
local pCallStatus,result=
          pcall(function ()
                    return fun.IteratorToArray(
                       fun.Map(utils.AutoPlotOneParameterFunction(ReadDevices(readbackDevices),Plotter),
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                           fun.Map(SetDeviceAndSleep(rampDevice,sleepTime),
                               fun.iValues(table.Range(rampStart,rampStop,stepSize)))))
               end)
(Restore system state, process pcall, omitted from example)

local setpoints,responses=table.KeyedUnzip(result,{"setpoint","readbacks"})
local selfResponse,crossResponses=table.KeyedUnzip(responses,{selfReadback}),
                                  table.KeyedTranspose(responses,otherReadDevices)
responses=table.KeyedTranspose(responses,readbackDevices)
```

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```
local pCallStatus,result=
          pcall(function ()
                    return fun.IteratorToArray(
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local setpoints,responses=table.KeyedUnzip(result,{"setpoint","readbacks"})
local selfResponse,crossResponses=table.KeyedUnzip(responses,{selfReadback}),
                                  table.KeyedTranspose(responses,otherReadDevices)
responses=table.KeyedTranspose(responses,readbackDevices)
(Evaluate device setpoint-readback correspondence, omitted from example)

--Now check the cross responses:
local impedances=
    table.KeyValueMapping(function (dev) return MutualImpedance(selfResponse,crossResponses[dev]) end,
                          otherReadDevices)
local shortedDevices=
    fun.Filter(function (dev) return impedances[dev]<minMutualImpedance end,otherReadDevices)

(Plotting of suspected shorts, return table formatting omitted)
```
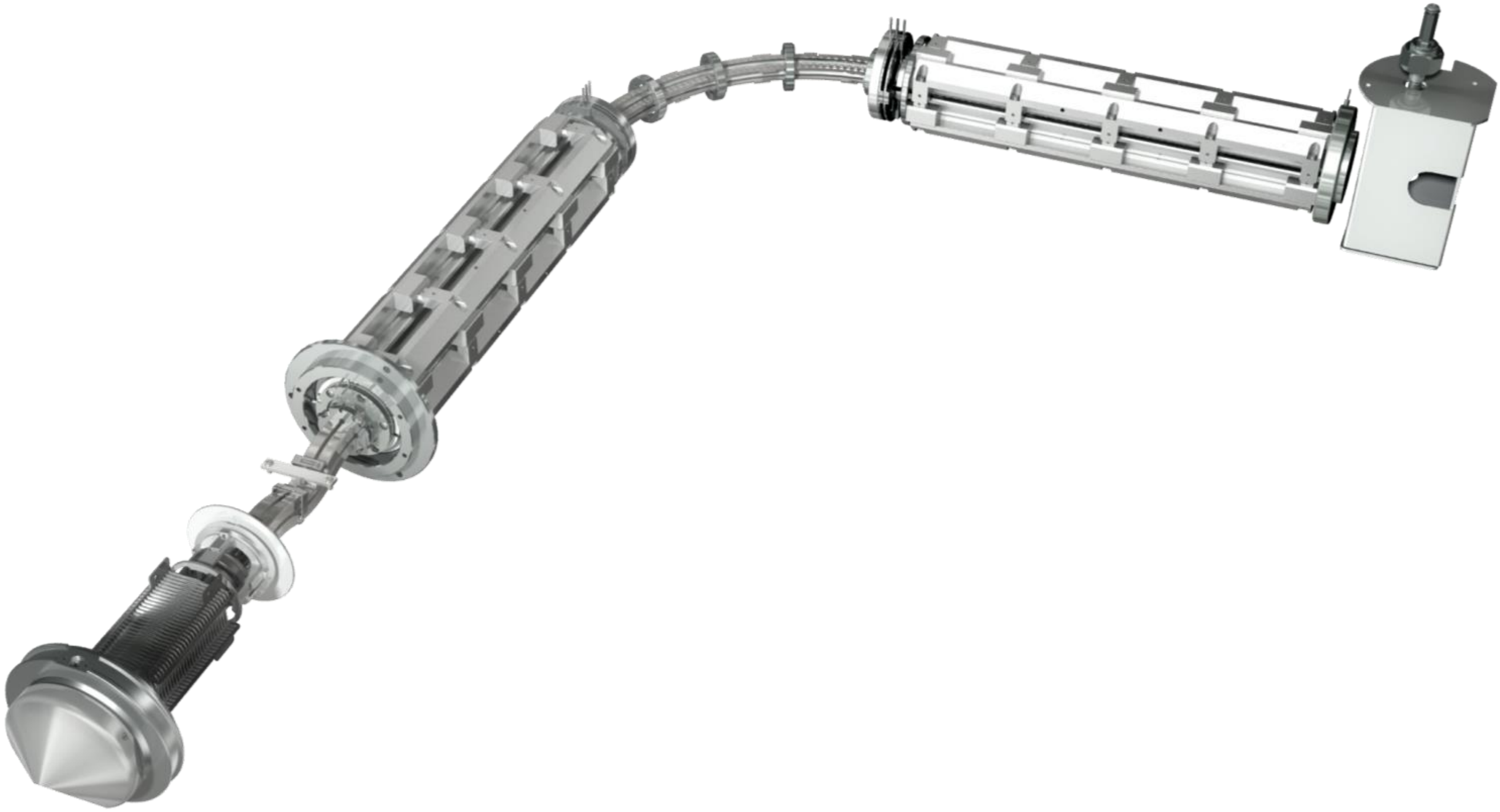
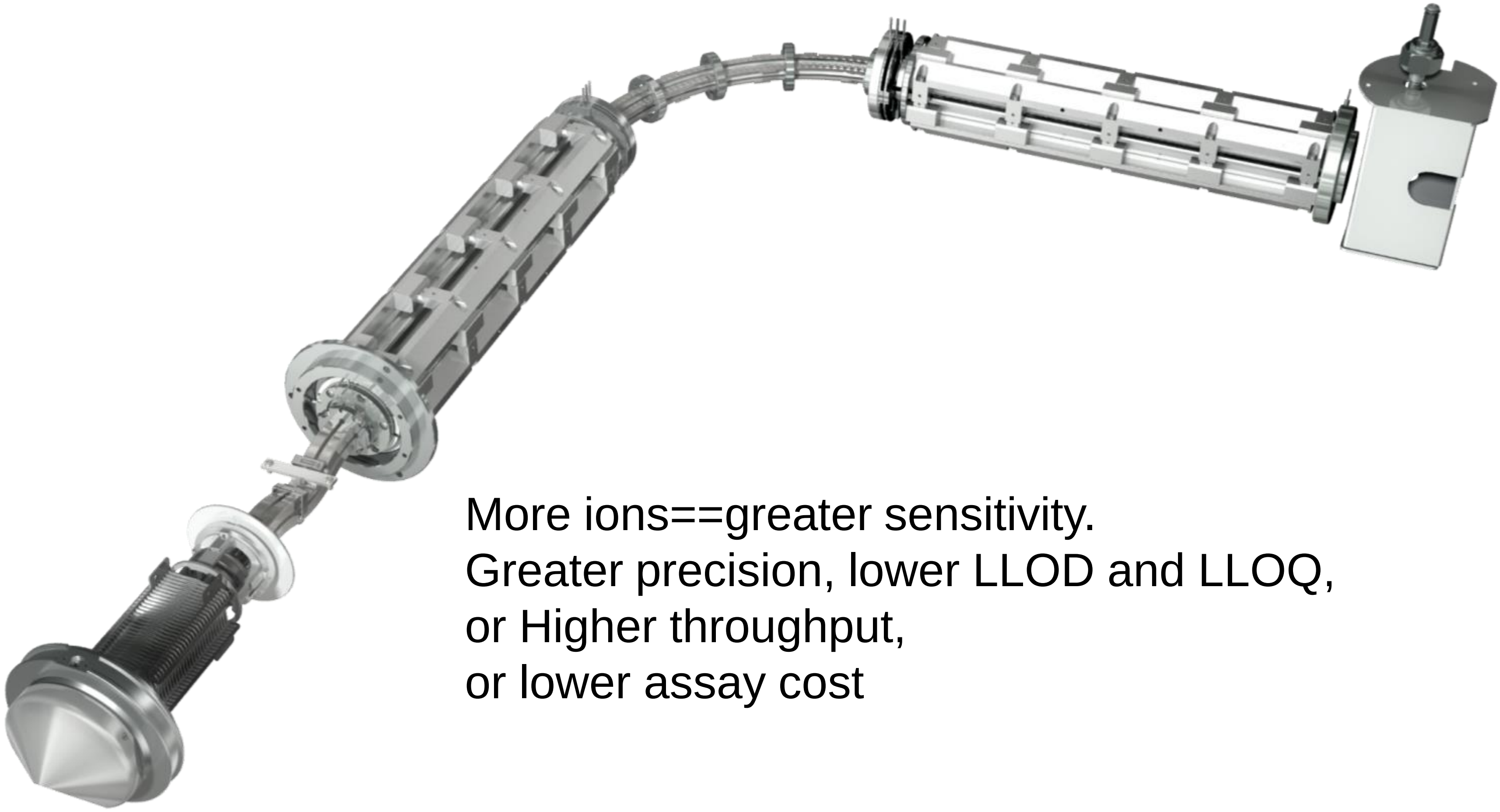

Compound-dependent tuning of a TSQ mass spectrometer



Compound-dependent tuning of a TSQ mass spectrometer



More ions==greater sensitivity.
Greater precision, lower LLOD and LLOQ,
or Higher throughput,
or lower assay cost

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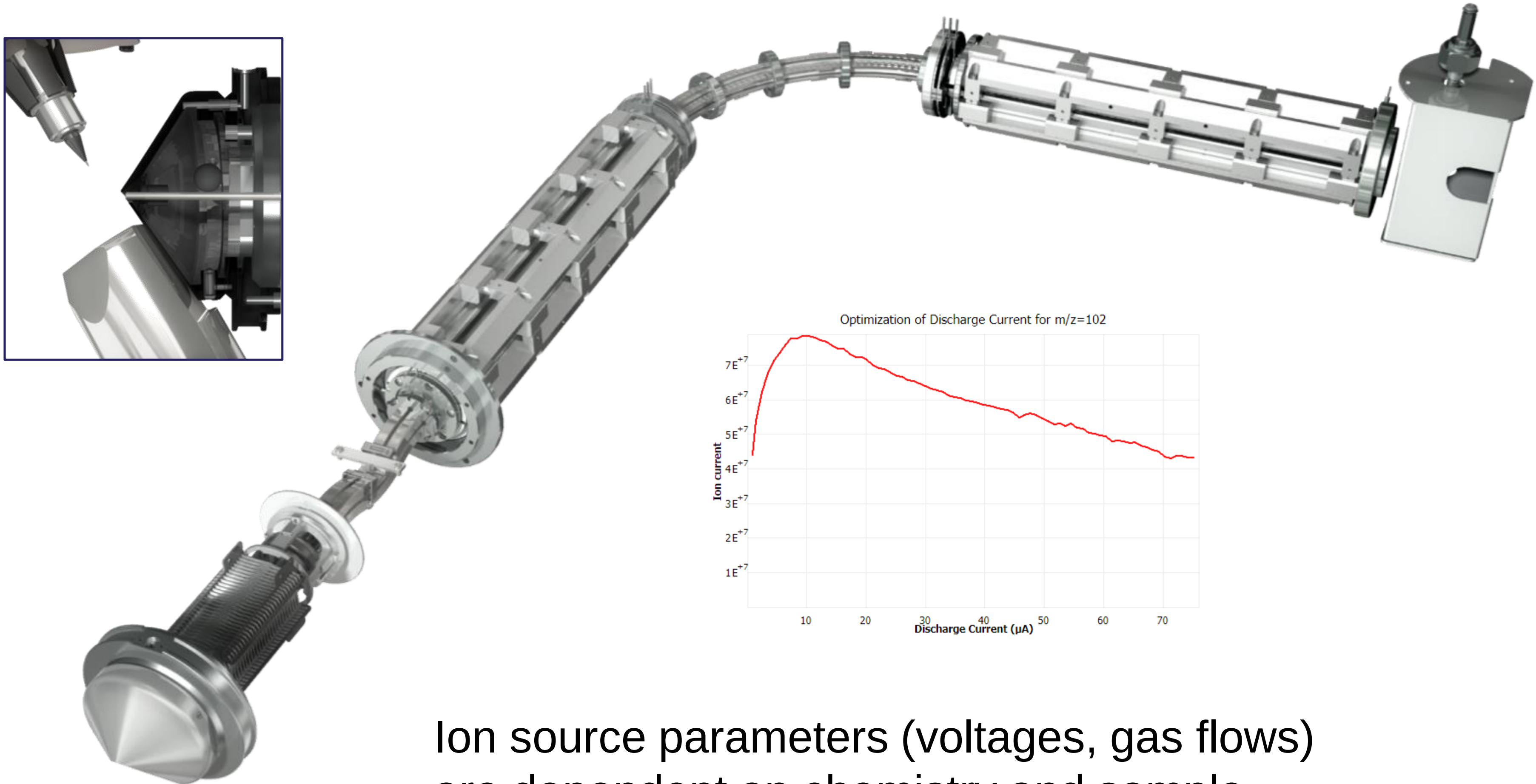
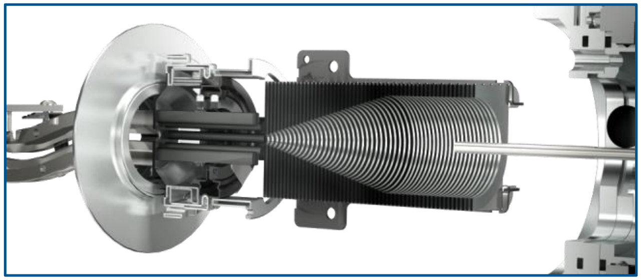
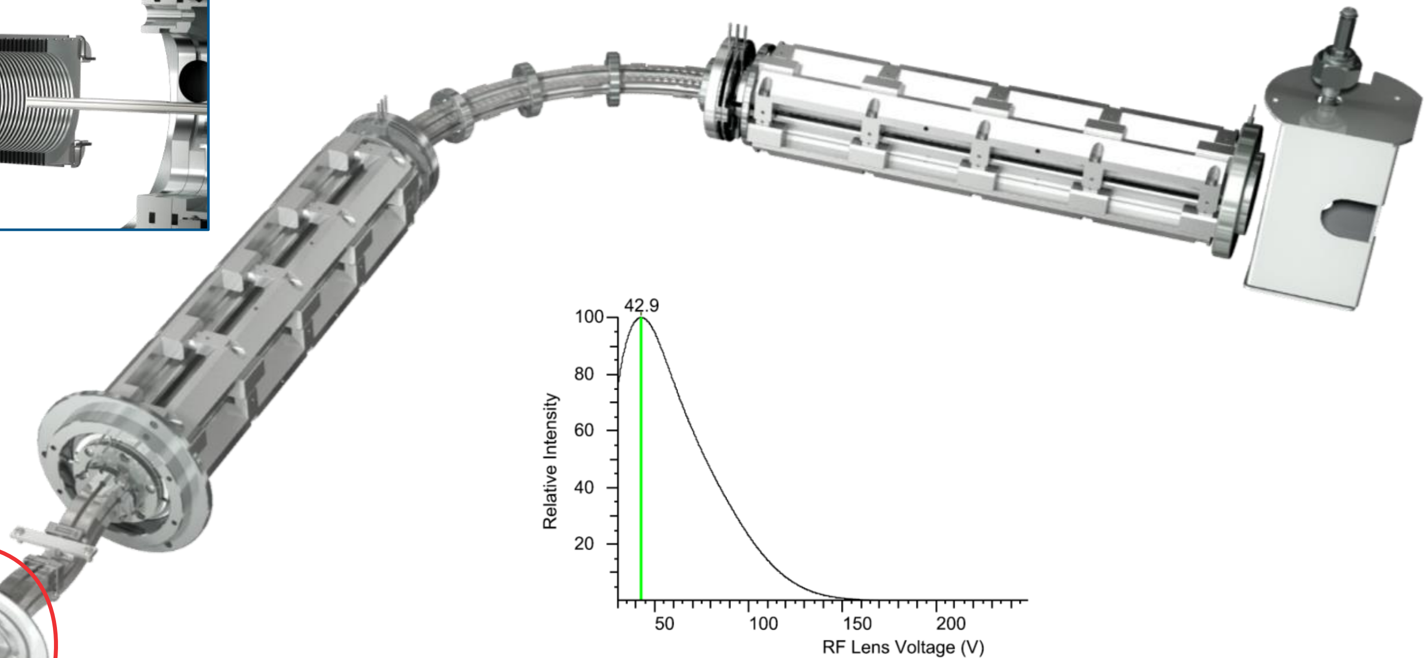
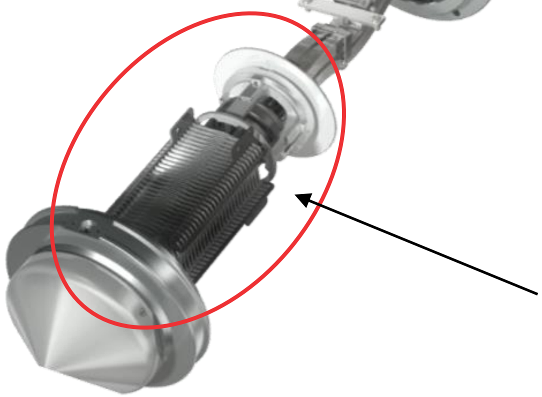


Ion source parameters (voltages, gas flows) are dependent on chemistry and sample delivery rate.

Compound-dependent tuning of a TSQ mass spectrometer







Ion funnel: RF tuning trades off several effects; DC offset used for declustering or fragmentation.

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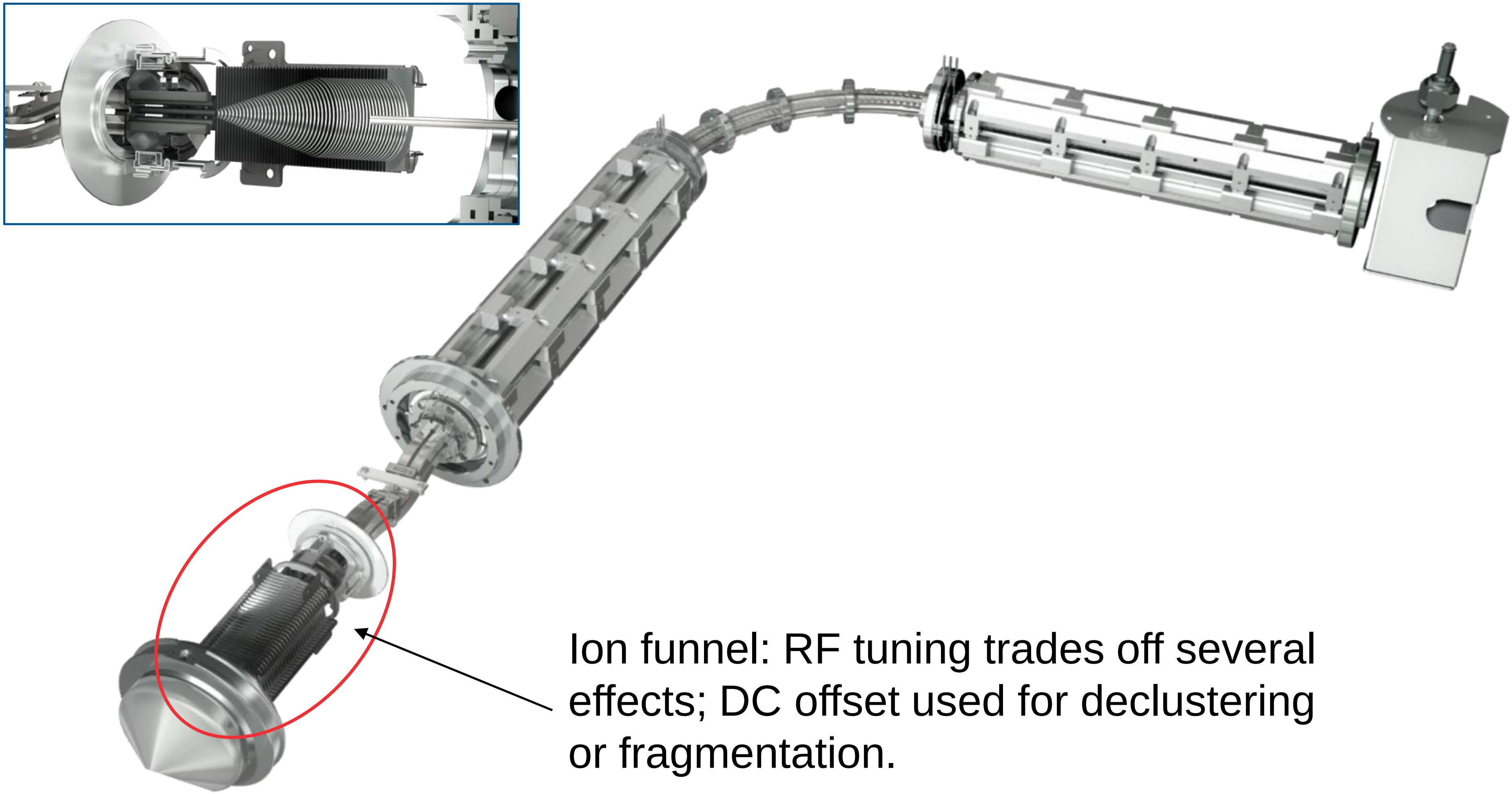

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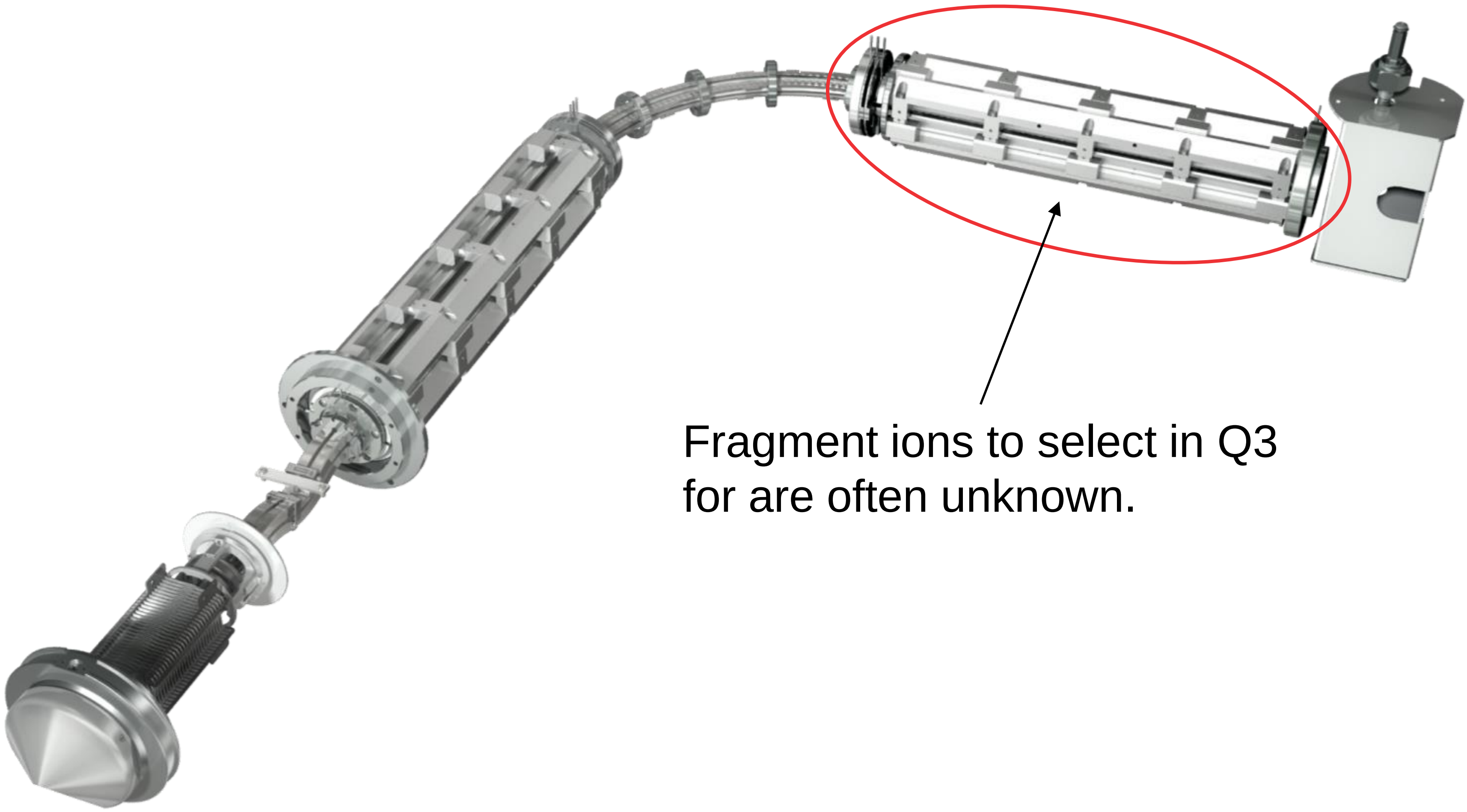

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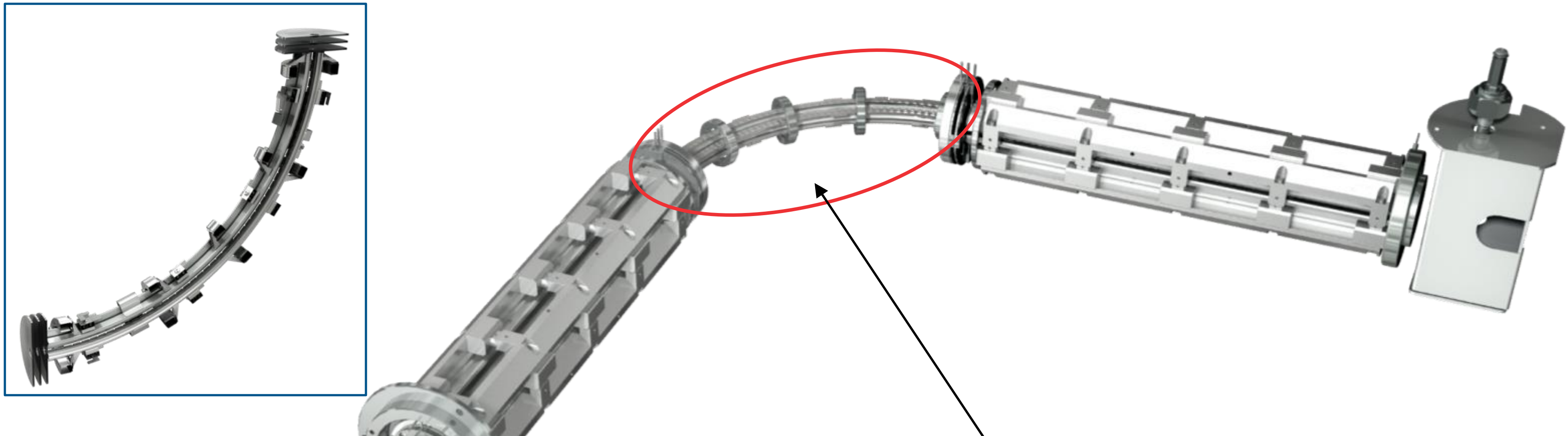
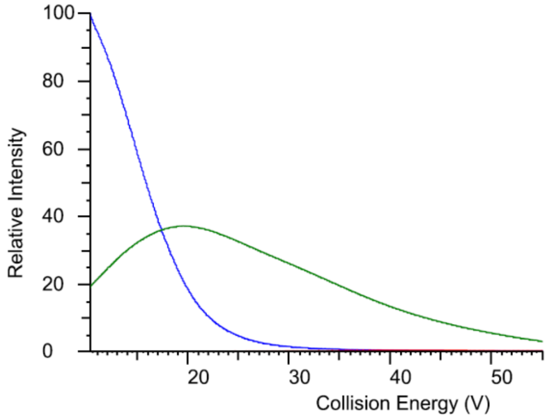


Collision energy optimizing any CID transition must be determined empirically.



Optimizations as pure and composable functions

- We want to be able to insert or remove optimizations at (customer) will.
- Future compatibility is also desired.
- Optimizations should use previous results in a clean way.
- Design:
  - Precursor and product data structures: attributes name, mass, tunings, etc.
  - Precursor ion optimizations take a precursor as input and yield a precursor as output, with updated tunings or updated mass.
  - Product ion optimizations are similar
  - Optimizations are composed/put into sequence by function composition.
  - Optimization internals may be procedural code, but no persistent side effects or communication at a distance through instrument state allowed. (Either clean up state changes or be indifferent.)

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Assay optimization: Handling state using decorators

- Decorator sets system according to previous tunings; optimizer functions concerned only with their proper optimization operation:

```
local function PrecursorStateSetter(precursor)
    local doWait=false
    if Sys.Polarity()~=precursor.polarity then
        DS:SetSystemPolarity(precursor.polarity)
        doWait=true
    end
    --Set ion source devices
    for _,dev in pairs(Sys.IonSourceDevices()) do
        if precursor.tunings[dev.name] and (precursor.tunings[dev.name]~=dev.value) then
            CF2:SetAndUpdate(precursor.tunings[dev.name],dev)
            doWait=true
        end
    end
    --Now set everything else:
    (…)
    if doWait then SleepSec(SOURCE_WAIT) end
    return
end

function CO.StateManipulationDecoratorPrecursor(f)
    return function (precursor)
        if precursor then PrecursorStateSetter(precursor) end
        return f(precursor)
    end
end
```

Sample delivery request and detection by sample delivery decorator:

```
function CO.GetSampleDecorator(f,timeout)
    return function (ion)
        local monitoredMZ= ion.precursor and ion.precursor.mz or ion.mz
         --This construction makes this precursor or product compatible
        local monitoredPolarity=ion.precursor and ion.precursor.polarity or ion.polarity
        if firstInjectionReceived then --Don't do this for first injection of a series.
            Signal(DS.SIG_REQUEST_SAMPLE)
            if not MethodControl.WaitCC()
                error(CO.exceptions.ABORTED_WAITING)
            end
        end
       local result=Sys.GetSample({mass parameters: omitted details},timeout,false)
       if result==0 then
           Signal(DS.SIG_SAMPLE_NOT_RECEIVED)
             (…)
           error(CO.exceptions.SAMPLE_NOT_RECEIVED)
       elseif result==1 then
           Signal(DS.SIG_RECEIVED_SAMPLE)
            (…)
       end
       SleepSec(0.5)
      return f(ion)
    end
end
```

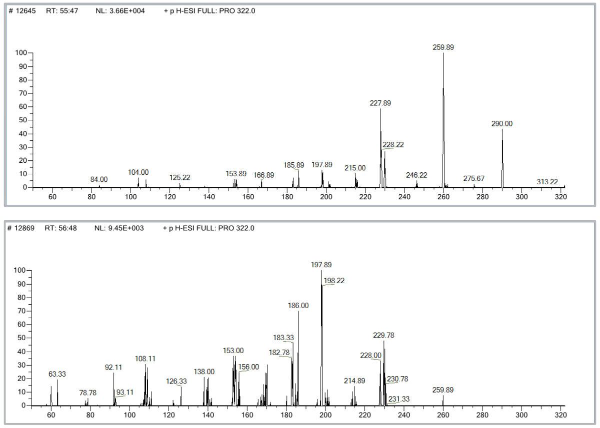
Assay optimization: Use of Reduce() in product search

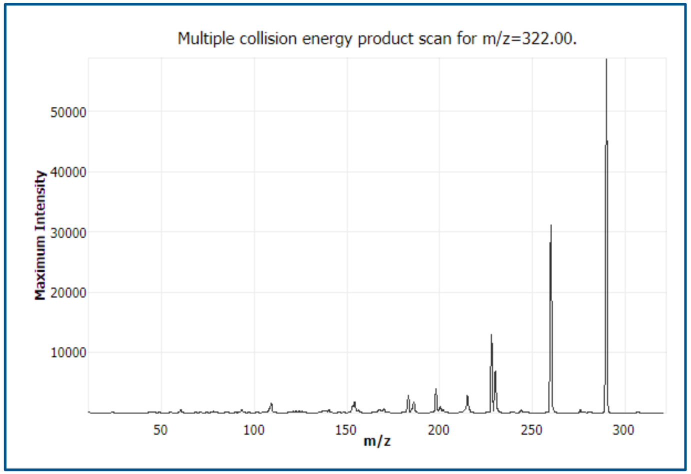
Composite spectrum generated by

```
fun.Reduce(function (a,b) return CO.MergeSpectra(a,b,false) end,
           fun.Map(SingleRampScan,fun.Values(CEs)))
```

where MergeSpectra is a pointwise max intensity selector

```
function CO.MergeSpectra(a,b)
    local retstructure=a
    (…)
    for index=1,#a.y do
        retstructure.y[index]=math.max(a.y[index],b.y[index])
    end
    return retstructure
end
```





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Assay optimization: putting it all together

Optimize precursor list:

```
local runSucceeded, result=
    pcall(function ()
              return ProductOptimization(
                         PrecursorOptimization(
                            fun.Map(SourceOptimization,
                                GetInjection(experiment.precursors)))) end)
```

Optimize product list:

```
ProductOptimization=
  function (precursor)
    if precursor then
        precursor.products=
            fun.IteratorToArray(
                fun.Map(function (x) return GraphProductPoint(x) end,
                        fun.TakeFirstN(experiment.nProducts,
                        CheckProductExistencesAndCountFailures(
                             fun.Filter(ProductMassFilterCondition,
                                        fun.Map(OptimizeProduct,
                                        GetProducts(precursor).ProductsIterator))))))
    (…)
    end
    return precursor
end
```

OptimizeProduct is a composition of optimizer functions (tuning mass, collision energy). A binary compose operation is reduced across a list to make it.