

GC-MS: The yin to LC-MS's yang

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It's no secret that [mass spectrometry](#)'s star is on the rise in the life sciences. From proteomics to metabolomics, clinical analysis to biomarker discovery, mass spectrometers have transitioned from niche tools for analytical chemists to standard equipment in biology labs.

For the most part, the mass specs used in those labs tend to be coupled to some sort of liquid-chromatographic separation, a configuration called [LC-MS](#). LC-MS is broadly compatible with both polar and nonpolar compounds, which is one reason the technology is so popular, explains Gary Siuzdak, director of the Center for Metabolomics and Mass Spectrometry at the Scripps Research Institute in La Jolla, Calif. Another reason is that LC-MS's liquid separations naturally fit with some liquid-phase soft-ionization technologies, such as electrospray ionization, that can ionize and transfer into the MS biopolymers like proteins without shattering them.

But there is another option. [GC-MS](#), or gas chromatography-coupled mass spectrometry, is the yin to LC-MS's yang. Where LC-MS is solvent-based, GC-MS is a gas-phase technique. LC-MS essentially coddles analytes in solvents; it's limited only by a molecule's ability to be resolved by LC and ionized by a coupled ionization source, making it ideal for peptides, drugs, and most metabolites. In contrast, GC-MS separations occur at high temperature and typically are used to look at volatile compounds as well as small metabolites such as steroids or more polar compounds such as amino acids and organic acids after simple derivatization.

In fact, LC-MS and GC-MS are highly complementary, says Corey Broeckling, facility manager for metabolomics at the Proteomics and Metabolomics Facility at Colorado State University in Fort Collins, which houses a single [Thermo Fisher Scientific](#) Trace DSQ single-quadrupole GC-MS plus three LC-MS instruments from [Waters](#).

The DSQ is used mostly for nontargeted profiling of small, polar organic molecules in everything from serum and urine to

plant and soil samples, Broeckling says. (Because these molecules are polar, they are first “derivatized” by silylation with trimethyl silane to make them nonpolar and volatile.) “Most LC is reverse-phase, and you don’t retain most compounds on LC that we see well by GC. So they are very complementary approaches.”

Upsides and downsides

Siuzdak has 20 LC-MS instruments in his facility and only three GC-MSs—two older single quadrupoles and one brand new quadrupole time-of-flight (GC-qTOF) hybrid, all from [Agilent Technologies](#).

GC-MS, Siuzdak explains, is immensely powerful—it offers exquisite separation, for instance, “far beyond what you would achieve with LC”—but it is often incompatible with life-science research. For one thing, he says, many biological molecules are relatively labile and break down at the high temperature (300°C) often used prior to GC separation to vaporize them.

Still, “certain molecules just don’t ionize particularly well by electrospray ionization,” Siuzdak says. “The most extreme example would be a hydrocarbon, where there’s nothing to put a proton on. But you can ionize them with [the] electron-ionization beams commonly used as an ionization source in a GC-MS.”

But that presents another problem, Siuzdak says. Electron ionization (EI) is much harsher than the soft-ionization methods often associated with LC-MS. The molecules very often fragment during the ionization process itself, making it difficult to know which ion (if any) is the intact molecular ion, a deficiency that can complicate molecular identification. (Soft-ionization techniques like electrospray ionization and matrix-assisted laser desorption/ionization (MALDI), in contrast, largely retain those ions.) On the other hand, because EI-based fragmentation is also very reproducible, researchers have compiled libraries of hundreds of thousands of fragmentation patterns to simplify the problem.

The other popular form of ionization in GC-MS is chemical ionization (CI). Some new instruments, including Siuzdak’s Agilent 7200 GC-qTOF, can perform APCI, or atmospheric pressure chemical ionization, which is gentler than EI, he says.

According to Siuzdak, GC-MS technology has undergone something of a resurgence recently, thanks largely to the development of new GC-MS configurations. Most GC-MSs are single-quad instruments; Terry Sheehan, director of GC-MS marketing at Agilent Technologies, estimates that as many as 4,500 such instruments are sold annually. But now, researchers can also purchase GC-triple quads, which are highly sensitive and quantitative, and GC-qTOFs, which offer high mass accuracy and resolution. (Sheehan estimates about a thousand GC-triple quads are sold each year, making it the fastest-growing segment of the GC-MS market.)

Both triple quads and qTOFs enable so-called tandem mass spectrometry, or MS/MS, applications (as does a third configuration, the GC-ion trap). The advantage of such a system, says Sheehan, is that it enables the user to specifically focus on select ions in complex ion backgrounds while rejecting extraneous “matrix ions” that might otherwise obscure the signal. As a result, tandem mass spec instruments, though more complex and expensive, are also in a sense easier to use than single quads.

“If you can get more selectivity in your mass spectrometer, you can do less work elsewhere, like sample preparation,

which is quite labor intensive and often prone to errors," Sheehan explains.

In fact, Sheehan says one researcher told him that the triple quad required such lower operating costs in terms of sample prep that the workflow savings balanced out the higher purchase price of the triple-quad over the single-quad (about \$175,000 vs. \$75,000) after just six months of use.

GC-qTOFs offer an additional advantage in terms of higher resolution and mass accuracy, enabling users to differentiate, say, mass-to-charge ratios of 200.0001 from 199.9998. That equates to molecular formula information that greatly enhances the qualitative information provided by the GC/MS, Sheehan says.

Buying advice

When it comes to selecting a GC-MS system, budget is obviously one key consideration. Agilent's GC-qTOF has a list price of about \$375,000, Sheehan says, which is four-to-five times more than a single-quad system.

But think also about application, he says. What kind of samples will you be working with, for instance? "If I have an exceedingly simple matrix like drinking water, then I don't need all the selectivity of a triple-quad or qTOF system," he says. "As sample complexity increases, I must rethink the MS performance even though the analytes are the same."

Another consideration is whether you will be quantifying known compounds or looking for unknowns. A triple quad is highly sensitive and quantitative, but it is blind to ions it's not programmed to find. In that case, Sheehan says, consider either a single quad (such as Agilent's new 5977A system) or a qTOF system, both of which collect full ion spectra for the analytes.

Broeckling suggests a few practical considerations, as well. "Don't be swayed by the sales pitch," he says. Consider, for instance, the control and analysis software and especially the availability of local service representatives. A local or regional tech-support team can service an instrument faster than someone who must travel to visit your lab; plus, you may be on the hook for travel and hotel expenses.

Long story short, Broeckling says, a GC-MS purchase is about more than just hardware. "You're buying the whole package."

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