

# Novel Nonlinear Laser Methods for Chemical Analysis: Approaching Single-Atom Detection With Isotope Resolution

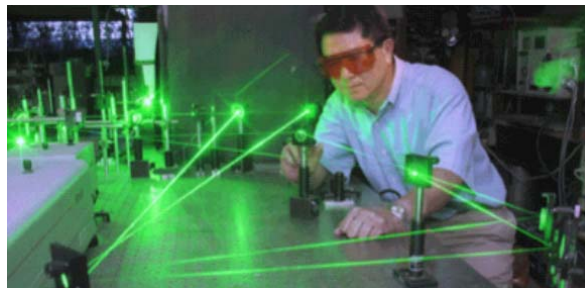
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Novel multi-photon optical methods based on laser wave mixing and dynamic laser gratings offer many advantages compared to conventional optical methods. These simple, compact and robust systems offer excellent detection sensitivity and high chemical selectivity.

Chemical and isotope analyses at trace-concentration levels with Doppler-free spectral resolution have been demonstrated using various atomizers, including flames, discharge plasmas, graphite furnace, and inductively coupled plasma atomizers. Since the signal is a coherent laser beam (unlike fluorescence signal), virtually 100% of the generated signal can be collected and directed into a detector.

The nonlinear signal has a cubic dependence on excitation intensity, and hence, laser power requirements are low, and mW-level continuous-wave lasers and nJ-level pulsed dye lasers can be used for this multi-photon spectroscopic setup. The optical alignment and beam quality requirements are relatively less demanding, and hence, compact inexpensive lasers, including laser diodes, can be used. Since the coherence time and coherence length requirements are also relatively low, many types of laser sources can be used conveniently in this nonlinear spectroscopic setup.

In addition to isotope and hyperfine analyses for gas-phase analytes, sensitive on-column absorbance measurements can be made also for liquid analytes with sensitivity levels comparable to those of fluorescence-based methods, and yet both fluorescing and non-fluorescing analytes can be detected without tedious labeling processes. The small (pL range) probe volume (laser beam overlap zone) allows convenient interfacing of this detection method to capillary-based electrophoresis or chromatography separation systems. Hence, it offers many potential applications.



## Advantages

- Coherent laser-like signal
- Highly efficient signal collection and detection
- Positive signal measured against dark background
- Easily interfaced to other analytical instruments
- Comparable or better sensitivity than fluorescence
- Approaching single-atom detection in flow cells
- Orders of magnitude better detection sensitivity
- Both fluorescing and non-fluorescing samples OK
- Measurement of biomolecules without labels/tags
- Native biosample analysis
- Quadratic dependence on analyte concentration
- More dramatic monitoring of smaller changes
- Small probe volume (pL)
- Better spatial resolution (small probe)
- Sub-Doppler spectral resolution for isotopes
- Analyte linewidth limited by laser only
- No monochromators
- No mass analyzers
- Unambiguous isotope-ratio information
- Unique hyperfine structure-based isotope ratio
- Cubic dependence on laser power

## Potential Applications

- Biomedical, biotechnology
- Chemical sensors on a chip
- Microarrays and microfluidic devices
- Thin-film chemical and biosensors
- Native DNA and protein detection without labels
- Sensitive studies of bio mechanisms & dynamics
- Sensitive monitoring of enzyme activity
- Circular dichroism spectroscopy
- On-column detection of capillary electrophoresis
- Sensitive absorption detection for chromatography
- Doppler-free nonlinear laser spectroscopy
- Non-radioactive, safe isotopes as biotracers
- High-temperature ICP absorption spectroscopy
- Atmospheric and environmental chemistry
- Geochemistry
- Surface deposition processes