Zeptomole-Level Detection by Multi-Photon Nonlinear Laser Wave-Mixing Spectroscopy for Biomedical and Environmental Applications

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Multi-photon nonlinear laser wave-mixing methods with zeptomole (10^{-21} mole) or sub-parts-per-quadrillion detection sensitivity levels are presented for biomedical and environmental applications. Laser wave mixing offers better detection sensitivity levels as compared to laser fluorescence-based methods, and yet our wave-mixing methods can detect both fluorescing and nonfluorescing molecules, i.e., labeled or native label-free biomolecules without using tags or labels. The detector probe volume is very small (nanoliter to picoliter), and hence, it offers high spatial resolution for 2D or 3D mapping of single cells. Nanoliter-level probe volumes also offer effective interfacing to microarrays, lab-on-a-chip, chip-based electrophoresis systems, and microfluidics. Unlike fluorescence methods, our laser wave mixing creates a strong coherent laser-like signal beam with its own propagation direction, and hence, it is easy to detect with excellent signal-to-noise ratios with minimum optical background. Our patented laser wave-mixing methods can distinguish not only large biomolecules but also small isotopes. Our laser-based detectors are more portable and less expensive than isotope-capable high-resolution mass spectrometers. Wave-mixing laser methods yield hyperfine profiles (atomic fingerprints), and hence, unambiguous isotope information from both stable and radioisotopes. Hence, one could use stable isotopes as biotracers instead of radioactive biotracer isotopes. We have also studied fast laser-induced diagnostic real-time monitoring of reaction rates, intermediate species, and mechanisms of semiconductor materials. We use a wide range of lasers with wavelengths from UV (solid-state lasers) and visible (tunable external cavity diode lasers) to mid-IR (tunable quantum cascade lasers). Potential applications include earlier detection of diseases (Parkinson's, Alzheimer's, Multiple Sclerosis, CTE), more sensitive detection of biomarkers, cancer cells, heart-failure biomarkers, and viruses (HPV, HIV), more sensitive detection of pollutants and chemicals both inside the human body and in the environment, remote standoff detection of chem/bio agents, and even authentication of paintings and art objects.

About the Speaker:

Bill Tong joined San Diego State University in 1985 as an associate professor after his postdoctoral research at the Oak Ridge National Laboratory, U.S. Department of Energy. In 1989, five years after receiving his Ph.D., he was promoted to full professor. He has supervised more than 50 Ph.D. (University of California San Diego and San Diego State) and Masters students and many postdoctoral students and visiting scientists/professors from many countries. He has been awarded major grants by the U.S. National Science Foundation, U.S. National Institutes of Health (R01), U.S. National Institute of General Medical Sciences, U.S. Department of Defense, U.S. Department of Homeland Security, U.S. Army Research Office, Beckman, Johnson and Johnson, Lockheed Martin and other funding agencies. He holds various patents on nonlinear multi-photon laser methods. He regularly serves on NIH, NSF, DoD, NASA, and ACS panels, and reviews for peer-reviewed research journals. He founded a laser technology company in La Jolla, California, for U.S. security and defense projects. He has served as Provost and Vice Provost since 2020.

He was named the 2003 Distinguished Scientist (San Diego Region) by the American Chemical Society (2 of the 22 winners of this award later won the Nobel Prize in Chemistry). He was named Distinguished Professor of Chemistry and Biochemistry in 2005. He received the Albert Johnson University Research Award, SDSU's top research award, in 2005, the 2017 SDSU Faculty Diversity Award, and the 2005 Distinguished Achievement Award from the Sigma Xi Research Society. He also received the 2008 SDSU President Leadership Award. He was awarded Outstanding SDSU Faculty Awards in 1990, 1991 and 2000, and the SDSU Technology Innovation Award in 2002. His research projects have been reported and highlighted by *Analytical Chemistry, Applied Spectroscopy* (cover story), San Diego Union-Tribune (front page), and San Diego TV stations (ABC, CBS, NBC, Fox, KUSI, KPBS, UCSD-TV and University of California-TV). He served on the SDSU Campanile Board of Directors and other boards at different U.S. universities and institutions. He was a leader in building international programs in different countries.