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Molecular Fluorescence, Phosphorescence, and Chemiluminescence Spectrometry

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Review Contents

This review covers the 2 year period since our last review (*1*), from January 2006 through December 2007. A computer search of *Chemical Abstracts* provided most of the references for this review. A search for documents written in English containing the terms "fluorescence or phosphorescence or chemiluminescence" published in 2006–2007 resulted in excess of 96 000 hits. An initial screening reduced this number to approximately 13 000 publications that were considered for inclusion in this review. Key word searches of this subset provided subtopics of manageable size. Other citations were found through individual searches by the various authors who wrote a particular section of this review. In an effort to more effectively accomplish this goal, we have included authors who are experts in the various subtopics of this review.

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Coverage is limited to articles that describe new developments in the theory and practice of molecular luminescence for chemical analysis in the ultraviolet, visible, and near-infrared region. In general, citations are limited to journal articles and do not include patents, proceedings, reports, and dissertations. Citations may be duplicated between sections due to articles with contents that span several topics. However, in an effort to reduce the length of this review, we have attempted to limit this kind of duplication.

We are not able to provide extensive coverage of all developments of relevance to the extremely broad field of molecular fluorescence, phosphorescence, and chemiluminescence. Instead, we have focused on important advances of general interest and relevance to the field of analytical chemistry, rather than extensions of previous advances. In addition, we have attempted to balance inclusion of a sufficient number of highly relevant, high-impact references to adequately survey the field with sufficient description of individual citations for better clarification. If you feel that we have omitted an important article published during the above referenced time period, please forward the reference to one of us and we will be certain to consider it for the next review.

BOOKS, REVIEWS, AND CHAPTERS OF GENERAL INTEREST

There were numerous review articles and book chapters discussing the use and application of luminescence techniques in the last 2 years. Of particular interest was the publication of the third edition of Lakowicz's classic reference, *Principles of Fluorescence Spectroscopy* (*2*). The full color 954 page text has been updated to include recent results from the literature and the addition of new chapters including novel fluorophores, single molecule detection, fluorescence correlation spectroscopy, and radiative decay engineering. Also appearing during the review period was the third edition of the book series *Reviews in Fluorescence* (*3*) edited by Geddes and Lakowicz. This compilation of invited reviews covered a wide range of topics and current trends. The same authors also edited the 2006 (*4*) and 2007 (*5*) editions of *Who's Who in Fluorescence* which provided the names, contact information, and a brief description of the specialties of researchers working in the field. Also appearing during the review period was Berberan-Santos's *Fluorescence of Supermolecules,*

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Polymers, and Nanosystems (*6*), the fourth volume in Springer's Series on Fluorescence. The reference emphasized fluorescence of artificial and biological nanosystems, single molecules, polymers, nanoparticles, and nanotubes and also covered fluorescence microscopy and fluorescence correlation spectroscopy. The 11th volume of the Topics in Fluorescence Spectroscopy series, *Glucose Sensing* (*7*), edited by Geddes and Lakowicz, covered the emerging area of noninvasive and continuous methods of glucose monitoring. Didenko edited *Fluorescence Energy Transfer Nucleic Acid Probes: Designs and Protocols* (*8*), the first comprehensive review of energy transfer nucleic acid probes. The *Handbook of Single Molecule Fluorescence Spectroscopy* (*9*) was also published during this review period. Emphasis was placed on the practical aspects of achieving single molecule resolution, data analysis, and applications in biophysics.

A large number of informative review articles were published during the review period. Coverage here is limited to a small number of broad reviews which are likely to be of general interest. Many reviews focusing on more narrow topics are included through the various sections of this review. In his review of new directions in single molecule imaging and analysis, Moerner noted the recent expansion of this area and summarized emerging areas such as single molecule based superresolution imaging and single molecule trapping (*10*). Tsien and colleagues reviewed the benefits and limitations of newly developed fluorescent probes used to study proteins (*11*). The application of single molecule fluorescence to the study of protein folding and conformational dynamics was also reviewed (*12*). Another review focused on the benefits and limitations of the major classes of fluorophores used in Förster or fluorescence resonance energy transfer (FRET) (*13*). A critical review, with representative examples, of fluorescent materials for chemical sensing which employ various chemical approaches in combination with a variety of materials has also appeared (*14*). The use of quantum dots in chemical and biochemical sensing (*15*) and the development of fluorescent core/shell silica nanoparticles showing promise as "lab on a particle" architectures (*16*) were also reviewed.

Useful reviews discussing chemiluminescence and phosphorescence also appeared in the literature. For example, a review with 204 references has covered the recent advances in chemiluminescence published between January 2004 and October 2006 (*17*). Diaz-Garcia et al. have noted the recent increased interest in and reviewed the emerging applications of room temperature phosphorescence in areas such as medicine, geological dating, and forensics (*18*).

GENERAL INSTRUMENTATION

Many prototype instruments as well as improvements to existing instruments were reported during this review period. Significant advances are achieved with developments of new light sources, detectors, and methods of data processing. Several prototype instruments were reported with only a small number of examples discussed below. Many interesting reports cannot be discussed due to space limitations, although several other instrumental advances may be found in other sections of this review.

In the area of sensors, Valledor et al. discussed the design and construction of a prototype fiber-optic system using low-cost optoelectronics for oxygen sensing based on dual phase-shift measurements in the frequency domain (*19*). Bromage et al. developed a real-time biosensor for detection of trace levels of trinitrotoluene in aquatic environments (*20*). A highly specific monoclonal antibody was coupled with a prototype fluorescence-based detector system. Many instrumental advances were reported in the area of chromatography, electrophoresis, and flow systems. One such example is a cam-based scanner as an alternative approach to detection in capillary array electrophoresis (*21*). A prototype instrument was reported to have a constant-velocity scanning distance similar to 10 mm, a scanning frequency of 3 Hz, and a duty cycle of similar to 70%. We also note that Casado-Terrones et al. compared the performance of a commercial capillary electrophoresis system using an argon ion laser as the excitation source with a homemade device based on an inexpensive blue-light-emitting diode (LED) and a charge-coupled device (CCD) (*22*). Several examples of portable instrumentation were found in the areas of biological, clinical, or diagnostic imaging. For example, Cottrel et al. described a portable instrument that integrated irradiation with fluorescence and reflectance spectroscopies during clinical photodynamic therapy of cutaneous disease (*23*). In another example, Jayachandran et al. reported the design and development of a hand-held optical probe for diagnostic imaging (*24*). This latter design overcame limitations such as patient comfort and instrument portability by employing a unique hand-held optical probe designed for simultaneous multiple point illumination and collection with a curved probe head that allows flexible imaging of tissue curvatures. Another area where portable instruments were reported was in the area of rapid point-of-analysis DNA typing. Mathies and co-workers report an integrated portable polymerase chain reaction−capillary electrophoresis microsystem. The feasibility of performing forensic analysis of mass disaster samples or of individuals at a security checkpoint was established through analysis of real-world oral swabs and human bone extracts from case evidence (*25*).

A continuing trend involved both researchers and instrument manufacturers adapting hardware and/or implementing commercially available instrumentation to better suit the researcher's needs. For example, Marwani et al. used a commercially available frequency domain instrument but collected data via segmentation before recombining the data sets for analysis in an effort to address photobleaching and changing fractional contributions within a multicomponent system, without the need for flow cells or relatively complex multifrequency instrumentation (*26*). As an example of hardware modifications, Dumke et al. described the reversible modification of a commercial capillary electrophoresis (CE) instrument (HP 3D-CE or Agilent G1602A) for chemiluminescence detection involving interchanging the deuterium lamp used for standard absorbance detection with a sidearm photomultiplier tube in the lamp housing (*27*). Kraikivski et al. described a complete configuration incorporating both short- and long-working distance optical trapping configurations into a single commercially available Zeiss Axiovert 200 M microscope (*28*). Manufacturers also improved their commercially available instruments in an effort to meet researchers' specific needs. As an example, the NanoLog spectrofluorometer was specially optimized for recording near-IR fluorescence from nanoparticles and is reported to offer a number of improvements over the previous versions (*29*).

Many developments in the area of detectors have been reported. A few interesting applications of camera-based and diode-based detectors are discussed below. Wohland and co-workers reported electron multiplying charge-coupled device camera-based fluorescence correlation spectroscopy (FCS) (*30*). The camera-based system allowed multiplexing of FCS measurements but had a limited time resolution of 4 ms as compared to 0.1−0.2 μs for instruments using avalanche photodiodes. Rech et al. discussed the advantages of planar epitaxial silicon single-photon avalanche diodes (SPADs) as compared to other detectors such as photomultiplier tubes (PMTs) using microchip CE with laser induced fluorescence (LIF) detection as an example (*31*). They noted that PMTs are bulky and/or costly and delicate while SPADs combined advantages such as small size, ruggedness, low power consumption, and low cost with sensitivity that was better than that of PMTs.

Detectors for single molecule fluorescence imaging and spectroscopy were recently reviewed by Weiss and co-workers, with an emphasis on the required performance of such detectors, as well as the current state of the art and future developments of single-photon counting detectors (*32*). Finkelstein et al. discussed the performance tradeoffs of single-photon avalanche diode miniaturization, noting that the performance of compact SPADs will benefit applications such as high resolution fluorescence-lifetime imaging among others (*33*).

Advances in light sources and methods to direct the light to or scan the light across a sample continue to improve analytical measurements. Zeng et al. reported that the use of a prism for simultaneous compensation of spatial and temporal dispersion from acousto-optical deflectors used in two-dimensional scanning improved the signal intensity of two-photon fluorescence microscopy by similar to 15-fold as compared to an uncompensated scanner (*34*). Temporal resolution is a challenge for scanning systems. Wolleschensky et al. reported high-speed confocal imaging with a novel line scanning microscope capable of acquisition speeds of 100 frames per second at 512 × 512 pixels (*35*). A commercial system based on this concept has been realized by Carl Zeiss (LSM 5 LIVE). The use of diode light sources to replace conventional scanning has also been reported. Ren et al. used a program controlled organic LED array as a spatial-scanning light source in a whole column fluorescence imaging application, thus allowing a PMT rather than a CCD detector to be used without the need for lenses, fibers, or other mechanical components in the system (*36*). Poher et al. described optical sectioning microscopes with no moving parts based on a microstripe array LED (*37*). Advances in the use of high power LEDs continued to be reported. For example, Moser et al. substituted ultrabright LEDs for conventional excitation sources in fluorescence microscopy using filter cubes with built-in LEDs (*38*). One benefit of the LED system was lifetime imaging without the need for image intensification. Birch and co-workers described a 265 nm pulsed LED enabling fluorescence decay of weakly emitting phenylalanine to be routinely measured in dilute solution (*39*). Lucy and co-workers observed that it is not trivial to use the greater light power provided by new high power LEDs (*40*). The large emitting area and highly divergent beam presented a classic problem in optics where one must balance light collection efficiency with the size of the focused light spot. The authors chose collection efficiency and reported low-picomolar limits of detection in a flow cell.

Another area relevant to general instrumentation which received increased attention is standardization of fluorescence measurements. Resch-Genger and co-workers developed a set of traceable fluorescence standards providing the basis for improved comparability of fluorescence measurements and eventual standardization (*41*). The Calibration Kit linked fluorescence measurements to the spectral radiance scale in the spectral range of 300−770 nm. The National Institute of Standards and Technology (NIST) responded to the need for fluorometer qualification and method validation required for quantitative measurements by reporting a method to qualify fluorescence spectrometers for measuring "true" fluorescence spectra (*42*). In related work, a multinational collection of nine laboratories using both single-photon timing and multifrequency phase and modulation fluorometry instruments reported a series of fluorophores with single-exponential fluorescence decays in liquid solution at 20 °C (*43*). Lifetimes estimated by both approaches were in agreement, and the standards were suitable for calibration or testing the resolution of both time- and frequency-domain instrumentation. Calibration of a wide-field frequency-domain fluorescence lifetime microscope (*44*), the emission light path of confocal microscopes (*45*), and the probe volume in fluorescence correlation spectroscopy (*46*) has also been reported. Comparisons of FRET measurements based on different imaging modalities (*47*) and FRET standards designed for use and exchange between laboratories (*48*) appeared during this review period. Finally, calibration standards for multicenter clinical trials of fluorescence spectroscopy for in vivo diagnosis (*49*) and instrumentation as a source of variability in detecting cervical neoplasia (*50*) has been discussed.

LASER-BASED TECHNIQUES

Of general interest to this topic is a recent review by Smith. The author described the reluctance of analytical chemists to embrace lasers and their increasing acceptance over the past 25 years. The review noted that the use of lasers in commercial analytical instrumentation was not always widespread. However, one area in which lasers have found utility is in a wide range of new spectroscopic microscopies (*51*). Laser-based techniques such as single molecule detection, optical tweezers and traps, FCS, multiphoton excitation, and fluorescence lifetime and confocal microscopies rely heavily on the high irradiance of laser sources. These techniques are becoming more routinely used and several have been commercialized and are widely applied in fields such as the life sciences. Advances continue to be reported even as the use of these techniques as tools to investigate complex problems have become increasingly more common.

Improved lasing media for dye lasers continues to be an area of interest. Ray et al. have investigated the possibility of employing the photothermal characteristics of water as a solvent for dye lasers (*52*). Their results suggest that binary solvents composed of water and about 18% to 25% *n*-propanol produced similar efficiency, better photochemical stability, and superior thermo-optic properties than ethanol alone. Garcia-Moreno et al. synthesized and studied polymerizable analogues of the borondipyrromethene (BODIPY) dye PM567 copolymerized with methyl methacrylate in search of more efficient and photostable solid-state dye lasers (*53*). They reported the highest photostability

achieved to date for solid-state lasers based on organic polymeric materials doped with laser dyes.

Several examples of supercontinuum light source based imaging systems have been reported. For example, Kano et al. obtained both vibrational and two-photon excitation fluorescence images of living cells simultaneously at different wavelength using a supercontinuum light source (*54*). The supercontinuum allowed multinonlinear optical imaging through two different nonlinear optical processes. A confocal microscope using a supercontinuum laser excitation source and a custom-built spectrometer for detection was reported by Frank et al. (*55*). The system allowed collection of fluorescence excitation and emission spectra for each location in a 3D confocal image.

Single molecule detection continued to provide valuable information. For example, Seeger and Li demonstrated the label-free detection of single protein molecules using deep UV fluorescence lifetime microscopy (*56*). A time-resolved single photon counting method and fluorescence correlation spectroscopy were employed. Intrinsic fluorescence upon one-photon excitation at 266 nm was useful for identification of biological macromolecules. The use of single molecule fluorescence to examine molecular interactions in various systems is becoming more common. Pappas et al. have reviewed recent applications of single molecule detection investigating biomolecular interactions (*57*). The focus was placed on instrumentation and tools such as anisotropy and resonance-energy transfer. Single molecule microscopy was used in conjunction with interferometric detection of single gold nanoparticles and fluorescence lifetime measurements to investigate modification of the fluorescence decay rate of single dye molecules tethered at various distances from a nanoparticle (*58*). Nanoparticle induced lifetime modification served as a nanoscopic ruler at distances beyond the upper limit of FRET. Recently, Lee et al. introduced three-color alternating-laser excitation (3c-ALEX), a FRET technique that measured up to three intramolecular distances and complex interaction stoichiometries of single molecules in solution (*59*). Widengren and co-workers recently discussed strategies to chemically retard dye photobleaching through the use of antifading compounds in ultrasensitive fluorescence measurements such as FCS, fluorescence-based confocal single molecule detection, and related techniques (*60*).

Several papers reported the development and application of optical tweezers and traps. One example applied FCS to the measurement of the local heating under laser trapping condition in the presence of a near-infrared laser beam (*61*). The relationship between the temperature rise and the incident laser power was determined. In other work, Li et al. reported single molecule fluorescence studies of multiple fluorophore-labeled antibodies in solution (*62*). Trapping was observed at laser powers below 1 mW with resonant excitation. The authors noted that selective resonance trapping may allow sorting and manipulation of biomolecules and complexes. Merenda and co-workers used an array of high numerical aperture parabolic micromirrors to generate multiple optical tweezers and trap particles in 3D within a fluidic device (*63*). The micromirrors could simultaneously collect fluorescence from the trapped particles. This approach offered a simple and efficient solution for miniaturized optical traps in laboratory-on-a-chip devices.

Many new methods continued to be reported that helped fluorescence correlation spectroscopy to meet the somewhat stringent requirements imposed by the technique (i.e., high rate of photon detection per molecule from a relatively small number of molecules). Generally, very low fluorophore concentrations are necessary. This does not pose a problem for in vitro measurements. However, micromolar concentrations are often encountered in fields such as biology. Alternatives to conventional confocal geometries are required to further confine the probe volume. Examples of FCS using a subwavelength sized aperture (*64*) in a surface plasmon coupled emission microscope (*65*) and utilizing single-mode optical fiber (*66*) were reported during the review period. Additional advances included a newly developed single-element aspheric objective lens that reduced the cost of FCS instruments and improved biomolecule quantification precision (*67*) and a prism-based multicolor instrument that offered high optical stability and no focal volume mismatch for the multicolor detection of molecular dynamics (*68*). A new distributed algorithm for multi-τ autocorrelation was also reported to reduce the memory requirements associated with accessing the large time-domain data records generated in FCS experiments (*69*). Schwille and co-workers observed that the dominant effects limiting the quality of two-photon fluorescence correlation measurements were inherent properties of the dye system such as bleaching and saturation (*70*). The authors noted that elaborate optimization of temporal and spectral laser pulse width through introduction of pulse stretchers in the beam path may be less critical than previously believed. Wiseman and co-workers extensively investigated the accuracy and precision of temporal image correlation spectroscopy as related to sampling effects, noise, and photobleaching (*71*). Photobleaching of the fluorophore was shown to cause a consistent overestimation of diffusion coefficients and flow rates and a severe underestimation of number densities. A bleaching correction equation was developed to remove these biases.

Advances in multiphoton excited fluorescence continue to be reported. Many systems that combined multiphoton imaging with other imaging modes were described. For example, Rothstein et al. reported two-photon excitation fluorescence and backscattered-second harmonic generation microscopy measurements in intact animals (*72*). Quality images were routinely collected from both the peripheral and body cavity organs. Joo et al. combined spectral-domain optical coherence phase and multiphoton microscopy (*73*). A novel multifocal multiphoton microscope was reported to provide simultaneous time- and spectrum-resolved fluorescence microscopy (*74*). Acquisition of five-dimensional data combing lifetime and spectral resolutions in biological imaging was demonstrated. Other reports included a demonstration by Bird et al. of the effectiveness of a photonic crystal fiber as a means of optimizing the temporal response in multichannel two-photon fluorescence microscopy (*75*). Their findings are pertinent to other systems that use a multimode optical fiber in lifetime measurements. Ragan and co-workers reported 3D particle tracking using a two-photon microscope (*76*). McConnell reported a greater than 3-fold increase in the penetration depth of multiphoton excitation laser scanning microscopy through the use of a passive predispersion compensation system (*77*). Systems allowing imaging at multiple focal planes were also described. Bahlmann et al. reported a high-speed multifocal multiphoton micro-

scope with a frame rate of 640 Hz (*78*). A two-photon scanning microscope capable of simultaneous imaging of three or more focal planes was described by Amir et al. (*79*). Haeberle and Simon proposed a simple technique, based on laterally interfering beams, to improve the lateral resolution in confocal fluorescence microscopy (*80*). It was shown that use of two-color two-photon excitation could permit resolution of 60 nm. The previous reference is an example of an emerging area that has seen rapid progress in recent years. The many advances in far-field fluorescence imaging techniques providing subdiffraction limit resolution cannot be adequately surveyed in the space provided. However, two recent reviews have examined this emerging field. Rice outlined developments in ultrahigh resolution far-field florescence methods with emphasis on application of these techniques to biology (*81*). Hell discussed the physical concepts that have pushed fluorescence microscopy to the nanoscale (*82*). The author avoided discussing technical aspects in great detail but instead focused on how fluorescence nanoscopy concepts to date have relied on "bright" and "dark" states of the fluorescenct molecule to break Abbe's diffraction barrier.

SENSORS

Many novel fluorescence sensors for various analytes were reported during the review period. An area continuing to receive attention was the detection of warfare agents. Simonian and co-workers described a fluorescent-based biosensor for the detection of organophosphate pesticides and chemical warfare agents (*83*) and modified an array biosensor unit developed at the Naval Research Laboratories for enzyme-based measurements with the potential for direct detection of organophosphates (*84*). Other reports included fluorescent organometallic sensors for the detection of chemical-warfare-agent mimics (*85*) and a small molecule photoinduced electron transfer (PET)-based sensor that provided an optical response to a nerve agent mimic (*86*). Anslyn and co-workers described a fast PET-based "off−on" response to chemical warfare simulants upon phosphorylation of a coumarin oximate (*87*).

Nguyen and Anslyn reviewed indicator displacement assays (IDAs), which is a popular method to convert almost any synthetic receptor into an optical sensor (*88*). Singaram and co-workers described the design and use of boronic acid appended bipyridinium salts as receptors in an IDA-based sensor array to differentiate saccharides in aqueous solution at neutral pH (*89*). The same group was also active in the area of glucose sensing including reports on the use of quantum dots with boronic acid substituted viologens to sense glucose (*90*) and the simultaneous use of multiple fluorescent reporter dyes for glucose sensing in aqueous solution (*91*). In other work, the Strongin group discussed the stereochemical and regiochemical trends in the selective detection of saccharides and presented a boronic acid-functionalized rhodamine derivative which displayed an unprecedented degree of colorimetric and fluorimetric selectivity for ribose and ribose derivatives (*92*). The same group also described the used of simple water-soluble lanthanum and europium complexes as indicators for neutral sugars and cancer biomarkers (*93*).

Detection of thiols continued to be an active area of examination. For example, Huang and co-workers were active in the area of cysteine/homocysteine sensing. Reports included a selective phosphorescence chemosensor for homocysteine based on an iridium(III) complex (*94*) and a novel Y-shaped fluorophore with potential as a two-photon excited fluorescent sensor for cysteine and homocysteine (*95*). The same group also described a turn-on sensor for cysteine/homocysteine with excitation in the visible region (*96*). Use of the sensor for the imaging of biological samples was demonstrated.

Because of its role in regulating a variety of biological processes, detection of nitric oxide (NO) is of recognized importance. Zguris and Pishko discussed a NO sensor based upon 4-amino-5-methylamino-2′,7′-difluorofluorescein entrapped in a poly(ethylene glycol) hydrogel microstructure prepared by photolithography (*97*). Sweedler and co-workers used a specific enzymatic reaction to eliminate the confounding effect of ascorbic acid on diaminofluorescein quantitation of NO and then used CE with LIF detection to distinguish the various reaction products (*98*). The simple methodology allowed NO to be measured in single cells without detectable interference from other compounds. Lim and Lippard reviewed metal-based turn-on probes developed by the Lippard laboratory for the detection of NO (*99*).

Schroder et al. described a hybrid time-resolved sensor based upon a lipophilic fluorescein derivative (lifetime similar to 5 ns) and platinum(II) mesotetrakis(pentafluorophenyl)porphyrin (lifetime similar to 70 μs in the absence of a quencher) immobilized in a hydrogel matrix for the simultaneous mapping of pH and pO_2 (*100*). Wolfbeis and co-workers reported fiber-optic microsensors for the simultaneous sensing of oxygen and pH or oxygen and temperature (*101*). The sensor utilized luminescent microbeads whose decay time and/or luminescence intensity responded to changes in the respective analytes. Valeur and co-workers reported the photophysics of a series of efficient fluorescent pH probes for dual-emission-wavelength measurements in aqueous solutions (*102*).

Many assays and sensor systems based on biological recognition elements such as antibodies, aptamers, enzymes, etc. are often expensive and unstable. Bright and co-workers reviewed the development of molecularly imprinted organic and inorganic polymers as possible replacements for biorecognition elements (*103*) and described a biomolecule-less biomolecule sensor that relied upon molecular imprinting of sol−gel-derived xerogels with the selective installation of a luminescent reporter molecule directly within the molecularly imprinted site (*104*).

Fluorescent conjugated polymers have shown great potential as signal transduction materials in chemical sensors. Swager and co-workers recently reviewed chemical sensors based on amplifying fluorescent conjugated polymers (*105*). Nesterov and co-workers described a general approach to cross-linked molecularly imprinted fluorescent conjugated polymer (MICP) materials and prepared an MICP material for the detection of 2,4,6-trinitrotoluene and related nitroaromatic compounds (*106*).

A large number of papers reporting sensors for various metal cations appeared during the review period. Only a small number of papers with an emphasis on turn-on and ratiometric modes of detection are described here. Fan and Jones prepared a highly selective and sensitive turn-on sensor for iron cations based on a transition metal derivatized conjugated polymer (*107*). Van Dongen et al. described ratiometric fluorescent sensor proteins and tuned their affinity toward Zn(II) in the pico- to femtomolar range

using a series of flexible peptide linkers (*108*). Komatsu et al. developed an iminocoumarin-based zinc sensor for ratiometric fluorescence imaging of neuronal zinc (*109*). Zeng et al. synthesized a new turn-on fluorescent chemosensor for imaging labile Cu(I) in living cells (*110*). Yang et al. synthesized a new naphthalene derivative with two urea groups for ratiometric Cu(II) detection (*111*). The Lippard laboratory described a red-emitting seminaphthofluorescein-based turn-on and single-excitation dual-emission ratiometric Hg(II) sensor for use in aqueous solution (*112*).

Compared to cations, the sensing of anions has generally been more difficult to achieve; however, research in this area has increased. Some examples reported during the review included a simple, highly selective, neutral, fluorescent sensor for fluoride anions (*113*) and the design of a fluorescence turn-on sensor array for phosphates such as AMP and ATP in blood serum (*114*). The Gunnlaugsson group has reviewed luminescent and colorimetric anion sensors developed in their laboratory based on hydrogen bonding in organic or aqueous solvents (*115*).

SAMPLE PREPARATION, QUENCHING, AND RELATED PHENOMENA

Quenching techniques continue to be an active area of research during this review period. Several reports discussed quenching in the nano regime. Cognet observed the stepwise quenching of mobile exciton fluorescence in carbon nanotubes after exposure to acid, base, or diazonium reactants using near-infrared photoluminescence microscopy (*116*). Their analysis revealed a 90 nm exciton diffusional range independent of nanotubes structure and that each exciton visited about 10 000 atomic sites during its lifetime resulting in highly efficient sensing of local physical and chemical perturbations. Schneider et al. fabricated fluorescent core/shell nanoparticles based on 13 nm gold cores and layer-by-layer assembly of fluorescently labeled polymer corona layers at various distances from the metal core (*117*). The quenching behavior of the system was strongly distance-dependent. Strouse and co-workers used fluorescent lifetime quenching of molecular dyes at discrete distances from 1.5 nm gold nanoparticles to demonstrate that the quenching behavior was constant with $1/d^4$ separation distance dependence and that energy transfer to the metal surface was the dominant quenching mechanism (*118*). Pons et al. monitored the photoluminescence quenching of CdSe−ZnS quantum dots (QDs) by gold nanoparticle acceptors at center-to-center distances in the range of 50−200 Å using steady state and time-resolved measurements (*119*). The authors indicated that the nonradiative quenching was due to long-distance dipole−metal interactions extending significantly beyond the classical Förster range. In other work, Laferriere et al. demonstrated that the quenching of QD luminescence by nitroxides was extremely nonlinear and dependent on particle size (*120*). In an effort to gain the knowledge needed to design efficient QD organic optoelectronic devices, Huang et al. investigated the bias-induced photoluminescence quenching of single QDs embedded in organic semiconductors, noting the importance of chemical compatibility between the QD and its surroundings (*121*).

A wide variety of sensing platforms based on fluorescence quenching have also been reported. Examples include a fluorescence quenching based sensor for selective detection of dopamine, levodopa, adrenaline, and catechol utilizing phosphate-modified TiO_2 nanoparticles (*122*), a protein cavity mimicking chemosensor in which the position of the fluorescent anthracene moiety modulated the Cu(II) induced emission properties from quenching to enhancement (*123*), and an optical sensor for 2,6-dinitrophenol based on fluorescence quenching of a novel functional polymer (*124*). Many high profile examples of quenching based systems employing conjugated polymers have also been reported. Examples include reports of anion-induced colorimetric response and amplified fluorescence quenching in dipyrrolylquinoxaline-containing conjugated polymers (*125*) and the use of fluorescence quenching of conjugated polymers for the detection of Diels−Alder reactions (*126*). Muller et al. have investigated the role of exciton hopping and direct energy transfer in the efficient quenching of conjugated polyelectrolytes (*127*). Liao and Swager have quantified the amplified quenching in a conjugated polymer microsphere system in response to methyl viologen and a naphthyl-functionalized viologen (*128*).

Improvements have also been reported in the area of immunoassays. Ramanavicius et al. have developed a new approach to increasing the selectivity of immunosensors by use of conducting polymer-based fluorescence quenching (*129*). Ao et al. have developed a highly specific immunoassay system for antigen detection based on fluorescence quenching of fluorescein isothiocyanate caused by gold nanoparticles coated with monoclonal antibody (*130*). Baker et al. have reported a fluorescence quenching immunoassay performed in an ionic liquid (*131*).

Advances in the use of fluorescence quenching in DNA and RNA detection schemes continue to be widely reported. Abe and Kool have described the use of quenched autoligating FRET probes in the flow cytometric detection of mRNAs in live human cells (*132*). Brennan and co-workers thoroughly investigated the quenching of fluorophore-labeled DNA oligonucleotides by divalent metal ions in an effort to develop general principles that will improve future application of signaling DNA aptamers and deoxyribozymes as biosensing probes (*133*). Bulygin and Milgrom used fluorescence quenching to investigate nucleotide binding to the catalytic sites of *Escherichia coli* βY331W-F_1-ATPase (*134*). Previous to this report, most studies had been performed in the presence of ~20 mM sulfate. This study reported that in the absence of sulfate, the nucleotide concentration dependence of fluorescence quenching induced by ADP, ATP, and MgADP was biphasic.

DATA REDUCTION

The application of various data reduction techniques involving the use of linear regression modeling such as partial least-squares (PLS), principal components regression (PCR), and multilinear regression (MLR) for fluorescence data analysis and multivariate calibration continues to be of significant interest during this review period. Consequently, several papers have reported the utility and practical application of linear regression modeling for the investigation of molecules of industrial, pharmaceutical, biomedical, clinical, and environmental interest. For example, Yang and Li reported the use of regression modeling for simultaneous detection and quantification of two species of foodborne pathogenic bacteria using quantum dots as fluorescence labels (*135*). In another study, the advantage of PLS over a multivariate curve resolution (MCR) technique for signal deconvolution in multiplexed analyses for simultaneous fluorophore detection was

demonstrated (*136*). Multivariate calibration involving the use of PLS regression analysis of fluorescence emission for the analysis and determination of enantiomeric composition of molecules of pharmaceutical interest were also reported (*137–140*).

In addition to linear PLS regression, a second-order multivariate calibration technique involving the use of unfolded-partial least-squares with residual bilinearization (U-PLS/RBL) (*141*, *142*) and a novel third-order calibration approach, multiway-partial least-squares with residual trilinearization (N-PLS/RTL) (*143*) for chemical analysis were developed. According to the authors, as compared with linear regression, the use of a second and a third order regression calibration was advantageous, with better prediction ability. Other interesting articles on the use and applications of a second- and a third-order multivariate analysis were recently reviewed by Escandar et al. (*144*).

Many research articles have also reported the use of a multilinear regression (MLR), especially in combination with other data reduction techniques for multivariate calibration. Aghamohammadi et al. have demonstrated the practical application of MLR for accurate determination of aflatoxin B-1 in pistachio samples at part per billion concentrations (*145*). In addition, the utility of MLR when combined with a genetic algorithm for a multiexponential fluorescence decay surface study (*146*) was reported. Furthermore, the use of MLR in conjunction with successive projections algorithm (MLR-SPA) for simultaneous and direct spectrophotometric determination of five phenolic compounds in seawater (*147*) was published. Compared with PLS regression, the use of MLR-SPA was reported to have better analytical performance, with potentially better resolution of complex analytical data.

The application of the fluorescence excitation−emission matrix (EEM) in combination with parallel factor analysis (PARAFAC) has become increasingly important for the characterization and qualitative analysis of complex systems. Hence, many researchers have reported the utility of EEM-PARAFAC technique for investigation of a wide range of complex mixtures during the review period. For example, Bosco et al. have investigated the photocatalytic degradation of phenol (*148*) and photodegradation kinetics of dibenz[*a*,*h*]anthracene, benz[*a*]anthracene, benz[*a*]-pyrene, and benz[*k*]fluorantene polycyclic aromatic hydrocarbons (PAHs) in aqueous suspensions using EEM-PARAFAC (*149*). With the use of this approach, the spectra of the photodegrading species were successfully resolved, affording accurate quantification of the PAHs concentration during the photodegradation process. The practical application of the EEM-PARAFAC techniques in environmental studies for characterization of dissolved organic matter in the ecosystem were also demonstrated (*150*, *151*). Other important applications involving the use of the EEM-PARAFAC approach included its use to unravel the complexation mechanism and binding mode of DNA with ternary copper(II) complexes (*152*) as well as the use of EEM-PARAFAC combined with PLS regression for qualitative and quantitative analysis of cell density evolution in biological samples (*153*).

Many research papers on the use of principal components analysis (PCA), linear discriminant analysis (LDA), artificial neutral network (AAN), K-nearest neighbor (K-NN), and soft independent model of class analogy (SIMCA) for effective classification and pattern recognition of wide range of complex fluorescence data have been reported during this review period. Zhou et al. reported the use of PCA for pattern recognition in a protein-detecting array based on porphyrins containing peripheral amino acids as protein surface receptors to distinguish between the metal and nonmetal-containing proteins (*154*). Kunnil et al. employed PCA in combination with cluster analysis of fluorescence emission to accurately differentiate between *Bacillus globigii* spores from the other species of *Bacillus* spores (*B. cereus*, *B. popilliae*, and *B. thuringiensis*) (*155*). In addition, there was a report of application of PCA in food analysis for effective monitoring of the oxidation pattern and quality of semihard cheeses (*156*). In another interesting study, Rowe and Neal developed a novel method involving the use of PCA and frequency-domain fluorescence for investigation of the photokinetic property of prodan and laurdan in large unilamellar vesicles (*157*). Application of other important classification techniques such as K-nearest (*158*, *159*), artificial neutral network (*160*, *161*), linear discriminant analysis (*162*), soft independent model of class analogy (*163*), and extended canonical variates analysis (*164*) in fluorescence studies for effective pattern recognition and accurate classification in various research studies were also demonstrated.

Various other data analysis and data reduction techniques, particularly, in fluorescence imaging and single molecule detection were also developed. Clegg and co-workers reported a method for fitting frequency-domain lifetime images in the presence of photobleaching (*165*). The method improved the speed of current numerical techniques up to 1000-fold and was fast enough to analyze images in real time. The use of multiparameter fluorescence detection (MFD) imaging for simultaneous investigation of changes in fundamental anisotropy, fluorescence lifetime, fluorescence intensity, time, excitation spectrum, fluorescence spectrum, fluorescence quantum yield, and distance between fluorophores in real time (*166*) was demonstrated. In another study, MFD was employed for the detection and quantification of labeled- oligonucleotides species in solution (*167*). Jung and Van Orden demonstrated the application of multiparameter fluorescence fluctuation spectroscopy for the investigation of folding of a dye-quencher labeled DNA hairpin molecule (*168*).

The practical applications of fluorescence correlation spectroscopy (FCS) and time-correlated single photon counting (TCSPC) also continues to be of significant analytical interest. Consequently, many research articles involving the use of FCS and TCSPC for various applications were published since the last review. For example, Werner et al. investigated the transition between acid-denatured states and the native structure of cytochrome c from *Saccharomyces cerevisiae* using FCS and TCSPC (*169*). According to the authors, compared to the use of either FCS or TCSPC alone, better results were obtained when FCS and TCSPC were used in combination. Other notable papers demonstrating the utility and practical application of FCS were those published by Burkhardt and Schwille (*170*) and Culbertson et al. (*171*).

In conclusion, it is apparent that the application and development of new data analysis and data reduction strategies in fluorescence continues to be of significant interest. It is likely that many new developments and applications of data reduction will find practical utility in analytical, biomedical, clinical, and environmental studies as well as in material analysis and in the food industry for many years to come.

ORGANIZED MEDIA

Organized media is a broad term that describes a wide variety of systems that can compartmentalize solvent or solutes and sequester them from the bulk environment. Aaron and co-workers have reviewed environmental analyses based on luminescence in organized supramolecular systems such as micellar media and cyclodextrin (CD) inclusion complexes reported between 1990 and 2005 (*172*). The Warner laboratory reviewed a selection of studies performed by the group investigating the properties of CD host−guest complexes and recent work performed by other laboratories using CDs in applications such as photochemical antennas and sensors (*173*).

Many interesting reports on a wide range of various organized media have appeared during this review period. Only a small subset of representative examples can be included in this survey. Mohanty et al. compared the complexation of neutral red (NR) with the macrocycle host molecules cucurbit[7]uril (CB[7]) and β-CD (*174*). In similar work, Liu et al. demonstrated that β-CD, calix[4]arene tetrasulfonate (C4AS), and CB[7], supramolecular hosts possessing different types of cavities, lead to different complexation-induced fluorescent behaviors of dyes including acridine red (AR), neutral red (NR), and rhodamine B (RhB) (*175*). For C4AS and CB[7] hosts, the complexation stability constants decreased in the order of NR > AR > RhB, while the order was reversed for β-CD.

Several reports using CDs in the determination of various analytes appeared during the review period. Examples included the use of hydroxypropyl-β-CD enhanced fluorescence quenching for determination of vitamin B-12 (*176*) and the determination of 3-hydroxy-2-naphthoic acid in river water by use of its ternary complex with zirconium(IV) and β-CD (*177*). Chiral recognition based upon CD complexation has also been widely reported. In one such example, Zhang et al. used γ-CD as the chiral selector in the discrimination of quinine and quinidine (*178*). Quinine and quinidine displayed strong room temperature phosphorescence (RTP) in γ-CD solution upon addition of small amounts of bromocyclohexane. Different RTP lifetimes indicated a distinct chiral discrimination for this pair of pseudoenantiomers.

Chiral molecular micelles (MMs) are another example of organized media used for chiral discrimination. The Warner laboratories have reported the use of chiral MMs combined with multivariate regression analysis of spectral data to determine the enantiomeric composition of fluorescent chiral analytes (*179*). In another example, the same group used steady-state fluorescence anisotropy, capillary electrophoresis, and NMR to investigate the mechanisms of chiral recognition displayed by four diastereomers of the chiral MM poly(sodium *N*-undecanoyl leucylvalinate) (p-SULV) for neutral and anionic chiral analytes (*180*).

Several reports of dendrimers, resorcinarenes, and calixarenes have appeared during this review period. Representative examples included the spectroscopic characterization of poly(amidoamine) dendrimers as selective uptake devices (*181*), the use of fluorescence resonance energy transfer to probe the dynamic behavior of resorcinarene capsules at nanomolar concentrations (*182*), and an investigation of atropine and cocaine host−guest interactions with a dansyl amide labeled calix[6]arene (*183*). The groups of Tucker and Atwood reported the cocrystallization and encapsulation of a fluorophore with hexameric pyrogallol[4]arene (*184*). Structural and fluorescence studies demonstrated that relatively small molecules can dramatically change the extended packing of large robust supramolecular entities.

Investigations of nonionic micellar systems continue to be reported. Because external probes may affect the property of interest, Pandey and co-workers have used steady-state and frequency domain techniques to probe the intrinsic fluorescence from the phenyl moiety of Triton X-100 in water (*185*). The concentration dependent emission and excitation were used to monitor the presence of micelles, while the decay data were used to characterize the dynamic parameters of the micelles. In other work, Pallavicini et al. reported an on−off fluorescence sensor response which could be transformed into an off−on response through a change in the lipophilicity of the receptor (*186*). When a more lipophilic long chain was used to lipophilize a ligand residing inside TritonX-100 micelles together with pyrene, an on−off sensor was obtained. An intermediate chain length resulted in an off−on response.

Ioffe et al. synthesized a new fluorescent squaraine probe for the measurement of membrane polarity (*187*). Moerner and co-workers described a class of dicyanomethylenedihydrofuran (DCDHF) fluorescent lipid analogues capable of single molecule imaging of diffusion in the cell membrane of live cells (*188*). The authors observed individual molecules of several different DCDHF lipid analogues diffusing in the plasma membrane of Chinese hamster ovary cells. In other related work, Hochstrasser and co-workers used single molecule fluorescence confocal microscopy to probe the association and dissociation reactions of single Nile Red molecules with a lipid vesicle (*189*). Nile Red was shown to be a useful probe of the structural fluctuations and heterogeneity of membrane structures.

Other related investigations employing techniques such as fluorescence lifetime imaging and other time-resolved techniques as well as fluorescence correlation spectroscopy were reported. Margineanu et al. used a perylene monoimide derivative and fluorescence lifetime imaging to visualize membrane rafts (*190*), and de Almeida et al. combined imaging with microscopic and macroscopic time-resolved fluorescence in an investigation of lipid domains and rafts in giant unilamellar vesicles (*191*). Fluorescence lifetime correlation spectroscopy was demonstrated to be a powerful technique in phospholipid bilayer research (*192*). Schwille and co-workers investigated the effects of ceramides, compounds known to influence lipid lateral organization in biological membranes, on liquid-ordered domains using simultaneous atomic force microscopy and FCS (*193*). The same group also studied slow membrane dynamics with continuous wave scanning FCS (*194*). In other work, Rhoades et al. demonstrated that FCS was a powerful tool for the quantitative characterization of α-synuclein binding to lipid vesicles (*195*).

Interesting work in the area of protein clusters was also reported. Sieber et al. used a combination of far-field optical nanoscopy, biochemistry, fluorescence recovery after photobleaching, and simulations to investigate the anatomy and dynamics of a supramolecular membrane protein cluster (*196*). The average diameter of syntaxin clusters was shown to be 50−60 nm and contain 75 densely crowded syntaxins which freely exchange with diffusing molecules.

The variety of structures and tunable properties of polymer thin films and mesoporous materials formed by cooperative self-assembly of surfactants and framework building blocks allow attractive host systems for a variety of applications. However, behavior and movement of molecules within these systems are not fully understood. Single molecule spectroscopy is a useful tool to investigate these systems. For example, Clifford et al. investigated the blinking behavior of Atto647N, an organic carborhodamine dye, in various polymer matrixes including polynorbornene (Zeonex), poly(vinyl carbazole), and poly(vinyl alcohol) (*197*). The diffusion of Nile Red in mesoporous silica thin films was studied using fluorescence imaging and single-point fluorescence time transients by Higgins and co-workers (*198*). Bein and co-workers presented the combination of electron microscopic mapping and optical single molecule tracking experiments to investigate the diffusion of single luminescent dye molecules in mesoporous materials (*199*). The combination of structural information provided by TEM and dynamic information from optical microscopy allowed an understanding of host−guest interactions not previously possible.

LOW-TEMPERATURE LUMINESCENCE

Many research articles with applications of low-temperature and related luminescence techniques have been reported during this review period. In particular, there were considerable efforts concerning the investigation of metal-enhanced phosphorescence (MEP) at low temperature. For example, Geddes and his research group have demonstrated enhancement of phosphorescence intensity when silver island films (SiFs) are in close proximity to Rose Bengal at 77 K (*200*). In a related study, an increase in S-2 emission intensity of azulene on SiFs was reported (*201*). Practical application of low-temperature luminescence for the investigation of photophysical properties of a series of 3,4-ethylenedioxythiophene oligomers (OEDOT) of many repeating units was also demonstrated (*202*). Sardar et al. also employed low-temperature phosphorescence measurements to investigate the complexation mechanism between human placental ribonuclease inhibitor (hRI) containing six tryptophan (Trp) residues and bovine pancreatic ribonuclease A (*203*).

Several papers also reported the application of low-temperature single molecule fluorescence measurements. Richter et al. have reported the use of single molecule fluorescence excitation spectra at low temperature (1.4 K) for investigations of reaction center-light-harvesting complexes from *Rhodopseudomonas palustris* and the PufX$^-$ strain of *Rhodobacter sphaeroides* (*204*). Da Como et al. have demonstrated the application of low-temperature single molecule fluorescence spectroscopy for the characterization of one-dimensional crystalline β-phase of polyfluorene nanowires (*205*). The practical utility of low-temperature luminescence in environmental studies was also demonstrated. Yu et al. determined fluoroquinolones in water samples at part per billion levels by measuring fluorescence emission and lifetime at low temperature (*206*). There was also a report of a unique screening strategy of polycyclic aromatic hydrocarbons (PAHs) in soil samples by fluorescence measurements of cryogenic probe at liquid helium temperature (*207*). In a related study, Zhang et al. developed a novel technique involving the use of low-temperature Shpol'skii effect and nonlinear variable-angle synchronous fluorescence spectrometry in combination for simultaneous identification and quantification of PAHs in mixtures (*208*). It is apparent that the use of low-temperature luminescence continues to be of significant interest since the last review. Consequently, considerable efforts were made in the development of analytical equipment and instrumentation to enhance the capability and applicability of low-temperature luminescence techniques in various research areas (*209–211*).

TOTAL LUMINESCENCE AND SYNCHRONOUS EXCITATION SPECTROSCOPIES AND RELATED TECHNIQUES

The use of total luminescence and synchronous fluorescence spectroscopy (SFS) continues to be active and exciting research areas for various applications, ranging from material and food analysis, quality assurance, DNA, protein and drug analysis to cancer diagnosis and environmental studies. For example, SFS was employed for quantitative determination of virgin olive oil adulteration with sunflower oil (*212*). According to the authors, the sunflower oil in virgin olive oil can be detected down to 3.4% (w/v) in less than 3 min. Deepa et al. used synchronous fluorescence and excitation−emission spectra to evaluate the aging and degradation of transformer oil (*213*). In a related study, analysis of petroleum products by use of SFS in conjunction with multivariate analysis has been demonstrated (*214*). The technique was reported to be sensitive, capable of detecting 1% contamination of kerosene in petrol.

SFS has also been widely used for the analysis of biological samples. Application of SFS for the detection of single-stranded and double-stranded DNA using methylene blue as a fluorescence probe has been reported (*215*). The fluorescence intensity of the methylene blue probe was observed to be quenched proportionally to the concentration of DNA in the solution. With the use of this technique, calf thymus DNA (ctDNA), thermally denatured ctDNA, and herring sperm DNA (hsDNA) were detected at low concentrations, with detection limits ranging from 0.04 to 0.11 μmol L^{-1}. In a similar study, Hou et al. demonstrated the use of SFS for the investigation of human serum albumin (HSA) using methyl blue as a fluorescence probe (*216*). Complexation between the HAS and methyl blue probe at pH 4.1 was reported to significantly increase the synchronous fluorescence intensity. In addition, the detection limit of HSA in human serum samples of 0.03 μg mL^{-1} obtained using synchronous fluorescence scan analysis was comparable when employed with clinical data. SFS was also employed for investigation of the interaction between *N*-(*p*-chlorophenyl)-*N*′-(1-naphthyl) thiourea and serum albumin (*217*), and the synchronous fluorescence of a novel functional organic nanoparticle, dodecyl benzene sulfonic acid sodium salt (DBSS)-capped nanoanthracene, for protein analysis was reported (*218*). This protein analysis technique was found to be highly reproducible, accurate, sensitive, and reliable, with potential for practical application.

Many research studies have also demonstrated the practical utility of SFS for the analysis of molecules of pharmaceutical interest. For example, Karim et al. reported the use of first derivative synchronous fluorimetry for a rapid and simultaneous determination of acetylsalicylic acid and caffeine in a pharmaceutical formulation (*219*). Pulgarin et al. developed a method using a derivative matrix isopotential SFS for direct determination of two anti-inflammatory drugs, diflunisal and salicylic acid, in human

serum (*220*). Application of SFS to tissue analysis for early cancer diagnoses also continues to be of significant biomedical and clinical interest. In particular, Diagaradjane et al. employed changes in the synchronous fluorescence property of tryptophan, collagen, and NADH during a tissue transformation process as tumor biomarkers to diagnose normal from abnormal tissues in a mouse skin tumor model (*221*). In a related study, the use of synchronous fluorescence imaging for tissue diagnosis in vivo in a mouse skin model was also developed by Liu et al. (*222*).

Total luminescence spectroscopy has also been widely used for various environmental studies during the review period. Lead et al. reported the 3D excitation−emission matrix (EEM) fluorescence and electron microscopy characterization of unfractionated and size fractionated fresh water colloids (*223*). Nahorniak and Booksh have published a paper reporting the use of EEM fluorescence for determination of benzo[*k*]fluoranthene and benzo[*a*]pyrene polycyclic aromatic hydrocarbons at part per billion (ppb) concentrations in aqueous solution (*224*). In addition to low detection limit, the technique afforded detection of PAHs in various complex matrixes, including aqueous motor oil extract and asphalt leachate. In another study, the use of synchronous-scan fluorescence for selective detection of sodium dodecylbenzene-sulfonate and pyrene in environmental samples has been reported (*225*). Application of the SFS technique for rapid and simultaneous determination of phenol, resorcinol, and hydroquinone in air samples was also demonstrated by Pistonesi et al. (*226*).

SOLID SURFACE LUMINESCENCE

The Hurtubise group continues to be active in the field of solid-matrix luminescence with reports using solid-matrix phosphorescence to characterize DNA adducts (*227*, *228*) and the investigation of several new sugar−glass systems for solid-matrix luminescence measurements (*229*). Correa and Escandar investigated the use of nylon as a novel solid matrix for inducing room-temperature phosphorescence in a report of the first analytical determination of adsorbed thiabendazole, a widely used fungicide, by nylon-induced phosphorimetry (*230*). The same group also reported the development of a new flow-injection system combined with solid-surface fluorescence detection for determination of the same analyte using nylon powder as the solid support (*231*). Previously, Garcia-Reyes et al. combined a multicommuted flow system and solid surface-fluorescence using C-18 as the solid support in the determination of thiabendazole (*232*).

Several investigations have used surface-based fluorescence imaging techniques for the investigation of molecular adsorption at various solid surfaces. For example, Yeung and co-workers used total internal reflection (TIR) fluorescence microscopy to examine the single molecule adsorption of labeled DNA at compositionally patterned self-assembled monolayers (*233*) and at glass surfaces after treatment with various chemical cleaning methods (*234*). Hollmann and Czeslik applied TIR fluorescence to study the adsorption of proteins at a planar poly(acrylic acid) brush as a function of solution ionic strength (*235*). Seeger and co-workers used a supercritical angle fluorescence biosensor to investigate the conformational reorientation of immunoglobulin G during nonspecific interaction with surfaces (*236*) and the adsorption and desorption behavior of β-lactoglobulin on a hydrophilic glass surface (*237*). Thompson and co-workers investigated the size dependence of protein diffusion near membrane surfaces using TIR-FCS and noted that the membrane surfaces slowed the local diffusion in a size-dependent manner (*238*).

In related studies, Petrou et al. described a simple glycerin treatment followed by an incubation period that effectively suppressed fluorescence self-quenching in immunoassays (*239*). The treatment dramatically increased the fluorescence signal measured directly at the solid surface. Another report provided an investigation of the potential of the fluorescence polarization immunoassay on a solid surface using dry reagent technology (*240*).

Several reports appeared during this review period which described solid surface luminescence for the analysis of agricultural and food products. Examples include the use of front-face fluorescence in the analysis of wine (*241*), cereal (*242*), and honey (*243*, *244*). Karoui and co-workers used the technique coupled with chemometric tools to characterize soft cheese (*245*), monitor ripening of a semihard cheese (*246*), and assess the freshness of eggs (*247*). Sun et al. have developed a method to screen for tetracycline residues in fish muscles utilizing CCD camera-based solid-surface fluorescence (*248*).

LUMINESCENCE IN CHROMATOGRAPHY, ELECTROPHORESIS, AND FLOW SYSTEMS

The high sensitivity of luminescence makes it an attractive approach for detection in chemical separations and flow systems. Jung et al. have presented an isotachophoresis (ITP) method integrated with microchip-based capillary electrophoresis devices and have achieved million-fold sample stacking. This high performance was the result of a single-column ITP configuration together with electroosmotic flow suppression and high leading ion concentration (*249*). When coupled with a confocal fluorescence detection system, a detection limit of 100 aM Alexa Fluor 488 was achieved (*250*). A multicolor fluorescence detection system, which uses an acousto-optic tunable filter, has been constructed for use in an electrophoretic microdevice. The system enabled detection of PCR-amplified DNA, the discrimination of multiple amplicons overlapped in time, and the identification of amplified biowarfare agents (*251*).

A microfluidic separation system has also been developed for two-dimensional differential gel electrophoretic separations of complex cellular protein mixtures to investigate protein expression in *E. coli*. Proteins were covalently labeled with Cy2 and Cy3 and detected simultaneously with a rotary confocal fluorescence scanner (*252*). The Soper group has demonstrated detection of low-abundant DNA point mutations with a microfabricated flow-through biochip. A polycarbonate (PC) chip has been used to perform primary polymerase chain reactions (PCR) followed by an allele-specific ligation detection reaction. A poly(methyl methacrylate) (PMMA) chip has been developed to monitor LDR products with fluorescence detection using a universal array platform. This rapid assay required a total analysis time of 50 min and afforded an order of magnitude reduction in reagents as compared to benchtop formats (*253*). The sequence-dependent separation of ssDNA fragments was achieved with a guanosine gel in capillary gel electrokinetic chromatography with LIF detection (*254*).

The analysis of cells with CE has been reviewed by Ewing and co-workers (*255*). CE coupled with luminescence detection has continued to expand studies of cellular function in the areas of neuroscience, oncology, enzymology, immunology, and gene

expression. The Zare research group has designed a microfluidic device to manipulate, lyse, label, separate, and quantify the protein content of a single cell using single molecule fluorescence counting (*256*). Generic labeling of proteins was achieved through fluorescent-antibody binding. The use of cylindrical optics has enabled high-efficiency (approximately 60%) counting of molecules in micrometer-sized channels. Microchip CE with laser-induced fluorescence detection (μ-chip CE-LIF) was demonstrated for rapid analysis of individual mitochondrial events in picoliter-volume samples taken from a bovine liver preparation (*257*). The Divichi group has described metabolic cytometry to analyze glycosphingolipid metabolism in single cells using CE with LIF detection. The ganglioside G(M1) has been tagged with the fluorescent dye tetramethylrhodamine, taken up by a culture of pituitary tumor (AtT-20) cells and its metabolites analyzed (*258*). Flow cytometers based on poly(dimethylsiloxane) microfluidic devices have been fabricated, with fluorescence detection accuracy comparable to that of a commercial flow cytometer and analysis speeds up to 17 000 particles/s. This high-throughput microfluidic device could be used in inexpensive stand-alone cytometers or as part of integrated microanalysis systems (*259*). An interesting development in microfabricated flow cytometers is the use of a thermoreversible gelation polymer (TGP) as a switching valve. The sol−gel transformation was locally induced by site-directed infrared laser irradiation. In the absence of fluorescence signal, the collection channel was plugged by laser-induced gelation. When a fluorescence signal was detected from the fluorescently labeled target cells, the waste channel was plugged by laser irradiation to achieve cell collection. The sorting of fluorescent microspheres and *E. coli* cells expressing fluorescent proteins was demonstrated using this system (*260*).

A notable application of fluorescence detection in two-dimensional CE is the analysis of Barrett's esophagus tissues. Rapid and highly reproducible separation has enabled the identification of 18 features from the homogenate profiles as biogenic amines and amino acids, fluorescently labeled for detection. The marked differences in concentrations of some features between squamous biopsies as compared to Barrett's and fundal biopsies from a patient with high-grade dysplasia suggested that 2D-CE may be of value for rapid characterization of endoscopic and surgical biopsies (*261*). The approach of 2D-CE coupled with ultrasensitive fluorescence detection has been used to characterize the protein and biogenic amine content of single cells from the RAW 264.7 murine macrophage cell line (*262*) and the protein expression from a single-cell mouse embryo (*263*).

Dual-color fluorescence coincidence has been reported for real-time detection of single native biomolecules and viruses in a microfluidic channel. With the use of green and red nanoparticles to simultaneously recognize two binding sites on a single target, individual molecules of genes, proteins, and intact viruses were detected and identified in complex mixtures without target amplification or probe/target separation (*264*). A novel encoding method has been devised to generate multifunctional encoded particles for high-throughput, highly multiplexed analysis of biomolecules (*265*). The probes were fabricated by use of continuous-flow lithography that combined particle synthesis and encoding and probe incorporation into a single process to generate particles bearing more than a million unique codes. With the use of fluorescence detection, DNA oligomers with encoded particle libraries were scanned rapidly in a flow-through microfluidic channel. This multiplexing approach could be extended to genetic analysis, combinatorial library, and clinical analysis. Confocal correlation spectroscopy has been used for real-time sizing of nanoparticles in microfluidic channels (*266*). This approach allowed measurement of the sizes of both fluorescent and nonfluorescent particles, including quantum dots, gold colloids, latex spheres, and fluorescent beads. Sizes were accurately measured for particles ranging in diameter from 11 to 300 nm, a size range which has previously been difficult to probe (*267*).

Luminescence spectroscopy provides a valuable technique for probing molecular interactions and flow properties in chemical separations and flow systems. In a recent review, Wirth and Legg presented a summary of single molecule studies of molecular adsorption to silica surfaces that is responsible for peak broadening and asymmetry in chromatography, an important problem in the separation of pharmaceuticals, peptides, and proteins (*268*). Using total internal reflection fluorescence microscopy (TIRFM), the Yeung research group has studied intermolecular interactions at the water/fused-silica interface, adsorption behavior and conformational dynamics of DNAs, at the single-molecule level. It was concluded that hydrophobic interactions and hydrogen bonding were the driving forces of DNA adsorption to fused-silica at pH 5 (*269*). In a separate experiment, they studied the adsorption properties of R-phycoerythrin, an autofluorescent protein, on the fused-silica surface in CE and in single-molecule experiments. The capacity factor and desorption rate were estimated from the molecular counting results (*270*). The Geng laboratory has probed the heterogeneity of a chromatographic interface using ratiometric confocal fluorescence microscopy. Spectral imaging of Nile Red revealed that the heterogeneity in environmental polarity between silica particles is of microscopic origin for band broadening in chromatography. The adsorption sites were found to be randomly distributed in the silica particles and smaller in size than the spatial resolution of confocal imaging (*271*). The pressure-driven transport of individual DNA molecules in confined fluidic channels has also been studied by use of fluorescence microscopy. Two distinct transport regimes were observed. The pressure-driven mobility of DNA increased with molecular length in channels higher than a few times the molecular radius of gyration, whereas DNA mobility was practically independent of molecular length in thin channels (*272*). Three-dimensional distribution of fluidic temperature within microchannels was mapped with high resolution using fluorescence lifetime imaging in an optically sectioning microscope (*273*). This technique has allowed optimization of the chip design for miniaturized processes, such as on-chip PCR, for which precise temperature control is important. A three-dimensional microfluidic device has been fabricated for eventual use in studying communication in an in vitro network of nerve cells (*274*). Flow profiles have been characterized with computational fluid dynamics simulations, confocal fluorescence microscopy, and carbon-fiber amperometry. This microfluidic system and incorporated cell network will ultimately show how networked neurons adapt, compensate, and recover after being exposed to different chemical compounds.

DYNAMIC LUMINESCENCE MEASUREMENTS

The ever-improving temporal and spatial resolution, the integration of multiple techniques, and progress in single molecule detection has ensured that luminescence measurements will continue to offer indispensable opportunities for deepening our insight into a host of scientific topics. Dynamic luminescence techniques in particular offer the unique potential for experimentally mapping distributions and fluctuations within heterogeneous systems, allowing researchers to unravel complex phenomena in areas ranging from biophysics and biocatalytic reactions to quantum-confined systems and even green solvent engineering, as shown by a number of examples selected from throughout this review period.

Using the lone tryptophan residue as a molecular reporter, the Zewail group studied the pH-dependence of solvation dynamics, structural integrity, and local conformational rigidity within the binding pocket surrounding Trp-214 in human serum albumin with femtosecond resolution (*275*). By replacing a native base pair located near the end of double-stranded DNA by coumarin 102, a molecular probe whose emission spectrum is sensitive to the local electric field, the Berg group observed the appearance of a rapid (~5 ps) relaxation process assigned to a "fraying" at the end of the helix (*276*). Real-time fluorescence measurements were recently used to monitor function and structural rearrangements during a dynamic reaction cycle for ribosome-associated trigger factor, a cotranslational molecular chaperone first encountered by nascent polypeptides in bacteria (*277*).

Using fluorescence autocorrelation and cross-correlation spectroscopy with photon counting histogram analysis, Jung and Van Orden investigated the folding of a dye-quencher labeled hairpin DNA. Their measurements supported a three-state mechanism for the DNA hairpin folding reaction that involved a stable intermediate form of the DNA hairpin (*278*). Brennan and co-workers have developed a novel two-point "rigid" ionic labeling approach for modifying polymeric species containing appropriately spaced amino groups with the fluorescent probe pyranine. With the use of this new strategy, pyranine-labeled poly(allylamine) and poly-D-lysine were studied in sodium silicate sol−gels, revealing a significant restriction of backbone motion in each case (*279*).

Webb and co-workers used fluorescence correlation spectroscopy (FCS) to investigate the dynamics of equilibrium structural fluctuations of the model protein apomyoglobin (*280*). The conformational fluctuations were detected by quenching of an N-terminal fluorescent label by contact with various amino acids and illustrated the complex scope of folding associated structural dynamics. Mukhopadhyay et al. recently conducted single molecule fluorescence resonance energy transfer (SM-FRET) and FCS studies to elucidate the collapsed structure, conformational fluctuations, and early folding intermediates associated with the prion-determining domain of yeast prion protein Sup35. Their results revealed a structural ensemble composed of a multitude of interconverting species rather than a small number of discrete monomeric conformers, a result likely to play a key role in the prion conversion process leading to self-perpetuating amyloidogenesis (*281*). Based largely on SM-FRET experiments probing the conformational ensemble of the collapsed unfolded state of the small cold-shock protein Csp*Tm* under near-native conditions, Hoffmann et al. have suggested that collapse in such systems can induce secondary structure in an unfolded state without interfering with long-range distance distributions characteristic of a random coil, a situation previously thought to exist only in highly expanded unfolded proteins (*282*). Eaton and co-workers also applied SM-FRET, supported by all-atom molecular dynamics calculations and Langevin simulations, to obtain quantitative information on the mean radius of gyration, end-to-end chain distribution, and dynamics (conformational averaging) of the unfolded states of the 64-residue α/β protein L in comparison to the 66-residue all-β Csp*Tm* (*283*).

Barbara and colleagues have reported a flow chamber approach which combines rapid nucleocapsid protein (NC)/nucleic acid mixing with a broad array of fluorescence single molecule luminescence tools to unravel the heterogeneous kinetics occurring during the course of NC chaperoned irreversible annealing of a model transactivation response element (TAR) DNA hairpin sequence to its complementary TAR RNA hairpin to form an extended duplex. These authors have demonstrated that the TAR hairpin reactant was predominantly a single hairpin coated by multiple NCs with a dynamic secondary structure, involving equilibrium between a "Y" shaped conformation and a closed one (*284*).

Xie and co-workers demonstrated the potential of single-molecule experiments in elucidating the workings of fundamental biological processes in living cells by probing gene expression in live cells, one protein molecule at a time (*285*). The authors found that protein molecules were produced in bursts, with each burst originating from a stochastically transcribed single mRNA molecule. The same group also probed transcription factor dynamics at the single molecule level in a living cell (*286*).

Since the recent introduction of air- and water-stable room temperature ionic liquids (RTILs), research into their potential applications has grown at an ever accelerating rate. RTILs are currently under exploration in virtually all areas of chemistry, as "green" solvents for organic and inorganic synthesis; as electrolytes in batteries, fuel cells, and solar cells; as new types of energetic materials; as stationary phases in chromatography and in a variety of other analytical applications; and in fundamental physical chemistry studies. Recent studies by Arzhantsev et al. combining results from femtosecond Kerr-gated emission spectroscopy with picosecond time-correlated single photon counting have enabled observation of the complete solvation response (dynamic Stokes shift) of the solvatochromic probe *trans*-4-dimethylamino-4′-cyanostilbene dissolved in a range of 1-alkyl-3-methylimidazolium and *n*-propyl-*n*-methylpyrrolidinium RTILs (*287*, *288*). These results highlight the fact that dielectric continuum calculations of the sort previously used to predict solvation dynamics within dipolar liquids are inadequate for predicting the response within RTILs. In subsequent work, Maroncelli and co-workers provide evidence for the presence of dynamic heterogeneity in two representative RTILs, based on the excitation wavelength dependence of several dynamical solute processes, including the rotation and solvation of coumarin 153 (C-153), the isomerization of two malononitriles, and intramolecular charge transfer in crystal violet lactone. According to the authors, the significant variation with excitation wavelength was consistent with energetically selected subpopulations relaxing at distinct rates (*289*). The Sarkar group has also studied the solvent

and rotational relaxation of C-153 in neat 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4], and has compared results to the slowed solvation resulting from confinement of the same RTIL within micelles formed using octaethylene glycol monoalkyl ethers as surfactants (*290*). Ito and Richert used time-resolved phosphorescence to study the RTIL [bmim][PF_6] in its fragile supercooled state near the glass-transition temperature, T_g. Comparing the solvation dynamics with the rotational motion of the probe (quinoxaline) and with the dielectric behavior of the neat fluid, the authors found that the dynamics in the viscous state were highly dispersive and showed a super-Arrhenius temperature dependence, as typical for glass-formers (*291*).

FLUORESCENCE POLARIZATION, MOLECULAR DYNAMICS, AND RELATED PHENOMENA

The use of fluorescence polarization continues to grow, both in terms of the breadth of application and the advancement of fundamental theory. A rather large body of work was first identified in the initial literature review and was then pared down to a representative trend of developments in fluorescence polarization and related phenomena. It should be noted that this review is not intended to be exhaustive but is a sample of developments over the time period covered by the review. For the purposes of this review we use the terms polarization and anisotropy synonymously.

Single molecule spectroscopy continues to be an evolving area of research, with experiments now reaching high levels of sophistication. Several papers have been published which involve development or application of multiparameter fluorescence detection (MFD). The method simultaneously measures eight fluorescence parameters or dimensions (anisotropy, lifetime, intensity, time, excitation spectrum, emission spectrum, quantum yield, and distance between fluorophores) following pulsed excitation and time-correlated single-photon counting detection. In 2006, the groups of Widengren and Seidel reported (*292*) two general strategies for the identification and analysis of single molecules in dilute solutions. A dye labeling scheme for oligonucleotides was demonstrated where 16 different compounds were identified in the mixture. Other applications of the technique were published in 2007 that included the investigation of dye-exchange dynamics (*293*), the investigation of structural and dynamical heterogeneity in DNA bound rhodamine dye (*294*), and the implementation of MFD imaging (*295*). The technique used MFD in a confocal apparatus that splits the fluorescence emission into its two polarization components that were then detected by avalanche photodiodes. Imaging was accomplished by scanning and storing the MFD for the three physical dimensions. Two systems involving sepharose beads and microtubule dynamics in yeast cells were used to demonstrate the ability of the technique. A study published in 2006 (*296*) detailed the use of probability distribution analysis for fluorescence resonance energy transfer. In 2007, Kalinin et al. reported an extension of this theory to apply to fluorescence anisotropy in single molecule experiments (*297*). The theory allowed prediction of the shape of anisotropy histograms for a given ensemble anisotropy and intensity distribution. The approach was well-suited for detection of biomolecular heterogeneity.

There were several other papers regarding the dynamics of single molecules using fluorescence anisotropy. Latychevskaia et al. have reported a single molecule study of polycrystalline microstructure of *n*-hexadecane at a temperature of 1.7 K, revealing a chromophore-two level system in spatially unresolved molecules (*298*). Another solid state study was reported (*299*) by Forster et al., where fluctuations of single conjugated polymer molecules were investigated in a polystyrene matrix at room temperature. The fluctuations in the degree and direction of polarization were attributed to changes in the contributions of various exciton states and selective exciton quenching by triplet states. In more biologically oriented samples, Wirth's group reported a novel study of single molecule polarization behavior of a dye-labeled peptide binding to the human δ-opiod receptor. It was reported that nonspecific binding could be differentiated from that of specific binding by analysis of the polarization and that reorientation of only a few degrees could be distinguished from the shot noise (*300*). The Vanden Bout group has published a study that examines the limitations of single molecule rotational correlation functions and the characterization of heterogeneity in molecular environments (*301*). A particular emphasis was placed on examining the effects of high numerical aperture on the correlation function and the statistical errors propagated from finite measurements. Cao et al. have also published a study detailing the monitoring of live cells by fluorescence anisotropy imaging (*302*). The technique was shown to provide an efficient method for real-time direct monitoring of the digestion of DNA in live cells. Another study that examines potential artifacts has been published by Fisz, where the problem of large excitation-detection apertures was studied in detail (*303*). It was reported that values for the emission anisotropy are affected at excitation-detection cone half angles greater than 15−20°.

DNA analysis represents an active area of research. Deng et al. have reported a novel geno-typing assay that could detect single nucleotide polymorphisms (SNPs) (*304*). The technique was based on the measurement of fluorescence anisotropy through a core/shell fluorescent nanoparticle assembly and a ligase reaction. The assay was completed in two steps, and the discrimination of a single base mutation in codon 12 of a K-ras oncogene was demonstrated as a proof-of-principle. Mestas et al. have reported the development of a new high-throughput screening assay for the detection of elongation activity in nucleic acid polymerase enzymes (*305*). The assay was demonstrated on a microtiter plate format and was shown to be a potentially efficient method for screening compounds that may inhibit nucleic acid binding.

The use of fluorescence anisotropy as a tool to examine chiral recognition continued during this review period. Xu and McCarroll have reported detailed investigations of the chiral recognition behavior of 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (*306*) and [1,1′-binaphthalene]-2,2′-diol (*307*) in the presence of various cyclodextrins. Valle et al. also reported a comprehensive study examining chiral separations in molecular micelle systems using fluorescence anisotropy, as well as capillary electrophoresis and NMR spectroscopy (*308*). Analysis of the anisotropy data indicates different separation mechanisms for the chiral selectors examined. Kimaru et al. have reported the use of fluorescence anisotropy as a general method to characterize chiral discrimination under conditions mimicking those of chromatographic separations (*309*).

Several studies were reported on the use of fluorescence polarization to study protein interactions. Bader et al. have reported the development of a time-resolved fluorescence anisotropy imaging method to study clustering in proteins (*310*). The method was based on fluorescence resonance energy transfer (FRET) as evidenced by depolarization of the fluorescence emission in a homo-FRET event. A high-throughput assay was described by Lokesh et al. for identification of small molecule inhibitors of the breast cancer gene 1 nuclear protein (*311*). Li et al. introduced a method for protein recognition and real-time quantitative analysis in homogeneous solutions (*312*). The assay was shown to be highly selective and have a detection limit of 1 nM in the case of angiogenin protein.

CHEMILUMINESCENCE

Chemiluminescence is a powerful analytical tool. This is because no excitation light is required and most samples have little or no unwanted background luminescence. However, the technique is often limited by low quantum efficiency of the chemiluminescent probe. The Geddes laboratory has made great advances in this area over the course of this review period. The interaction of chemiluminescing species with silver island films was shown to increase the signal intensity (*313*). The technique was extended to include low-power microwave heating and applied to an ultrafast and ultrasensitive clinical assay (*314*). Multicolored microwave-triggered metal-enhanced chemiluminescence using multiple chemiluminescent species emitting at different wavelengths was demonstrated (*315*). A model assay sensing platform with the potential to detect and quantify various biomolecules was demonstrated to detect femtomoles of biotinylated BSA in less than 2 min (*316*). The use of continuous aluminum metal substrates was investigated to further enhance microwave triggered chemiluminescence, and the extent of enhancement was shown to depend on the surface geometry of the film (*317*). Spatial and temporal control of the microwave triggered chemiluminescence was demonstrated and applied to a protein detection platform (*318*). After suggesting the possibility, the same group reported the observation of surface plasmon-coupled chemiluminescence on a thin continuous silver film (*319*) and observed various species emitting in different regions of the visible spectrum on other metals including aluminum and gold as well as silver (*320*). Microwave-triggered surface plasmon coupled chemiluminescence was reported as a rapid, high sensitivity technique for the detection of surface-bound proteins/enzymes and also potentially DNA/RNA (*321*).

In related work, Ou et al. have investigated the mechanism responsible for the surface-enhanced chemiluminescence of luminol at nanoscale-corrugated gold and silver films (*322*). The enhancement was found to originate from the catalytic properties induced by the corrugation. Chemiluminescence-based array imaging was reported as a new optical strategy for the rapid screening of gold catalysis (*323*). Lee et al. reported the in vivo imaging of hydrogen peroxide using chemiluminescent nanoparticles formulated from peroxalate esters and fluorescent dyes (*324*). Jie et al. reported a CdS nanocrystal-based electrochemiluminescence biosensor for the detection of low-density lipoprotein taking advantage of gold nanoparticle amplification (*325*).

Yeung and co-workers have reported the first real-time imaging of single bacterium lysis and leakage events by using an intensified CCD detector to measure chemiluminescence from an optimized bioluminescence reaction system (*326*). Rusling and co-workers have demonstrated the first electrochemiluminescent arrays for high-throughput in vitro genotoxicity screening (*327*). The Bard group continues to make advances in chemiluminescence including an immunoassay of human C-reactive protein using liposomes containing $Ru(bpy)_3^{2+}$ (bpy = 2,2′-bipyridine) as labels (*328*).

In other interesting work, Anslyn and co-workers described the "off-on" glow response of an assay to detect a chemical warfare stimulant (*329*). Detection was based on modulation of the peroxyoxalate chemiluminescence pathway through the use of an oximate super nucleophile.

NEAR-INFRARED FLUORESCENCE

During the last 2 years, advances in NIR fluorescence have basically been propelled by new chemistry of NIR fluorescing compounds rather than new instrument development. Fluorescence in vivo imaging still mostly uses animal models although a clear trend in moving to possible human use is noted. Tanaka et al. have described a real time approach to ureteral guidance (*330*). NIR imaging was used for early detection and prevention of ureteral injury vital to the health of the patient. Rats and pigs were injected with CW800-CA dye into the ureter, and the NIR fluorescence was visualized. A different approach was taken by Xu et al. (*331*) through synthesis of a lysine-based trifunctional chelate that was utilized as a complexing agent for radiometals used in medical imaging and the near-infrared dye Cy5.5 allowing for dual modality imaging. Cheng et al. (*332*) have developed a NIR fluorescent analogue of the commonly used diagnostic agent 2-deoxy-2-[18*F*]fluoro-D-glucose for tumor imaging in cell culture and living mice. Li et al. (*333*) have described the synthesis of two NIR fluorescent probes by linking a carbocyanine fluorophore and glucosamine. The probes were reported to have a high quantum yield and low cytotoxicity. In vitro NIR optical imaging indicated strong intracellular NIR fluorescence in breast epithelial cell lines.

Kalchenko et al. (*334*) have used a lipophilic dye 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide (DiR) for whole-body optical imaging to monitor normal and leukemic hematopoietic cell homing in vivo. A similar approach was used by Leevy et al. (*335*) for bacterial imaging using probes containing synthetic zinc(II) dipicolylamine (Zn-DPA) coordination complexes as affinity groups that are able to selectively bind to the surfaces of bacterial cells and apoptotic animal cells. Yang et al. (*336*) have recognized the importance of lipophilicity of NIR dyes in in vivo imaging. Highly lipophilic NIR dyes do not circulate long in the bloodstream. The authors reported the synthesis of PEG-coated, core-cross-linked polymeric micelles (CCPM) derived from an amine terminated poly(PEG-methacrylate)-*b*-poly(triethoxysilyl propylmethacrylate). A Cy-7-like NIR dye was entrapped in the core. The probe exhibited prolonged blood half-life and enhanced uptake in a tumor. Ye et al. (*337*) have used NIR fluorescence to study the molecular interactions between arginine–glycine–aspartic acid (RGD) peptides and integrins known to mediate many biological and pathological processes. The authors describe the synthesis and evaluation of a series of multimeric RGD compounds constructed on a dicarboxylic acid-containing NIR fluorescent dye (cypate) for tumor targeting.

An increasing number of applications have used probes other than conventional NIR dyes. For example, Jeng et al. (*338*) have described the optical detection of DNA hybridization on the surface of solution suspended single-walled carbon nanotubes (SWNT) for biological applications. Cherukuri et al. (*339*) have used chemically pure SWNT that were intravenously administered to rabbits and monitored by NIR fluorescence observing that the blood serum concentration decreased exponentially with a half-life of 1.0 ± 0.1 h without adverse effects. Hwang et al. (*340*) have outlined single-stranded DNA conjugated SWNT probes that can be used to locate particular sequences within DNA strands.

Zhu et al. (*341*) have prepared and structurally characterized a new expanded porphyrin which was exploited as a highly sensitive NIR fluorescent chemodosimeter selective for the detection of Hg(II) ions. The total NIR fluorescence decreased upon addition of Hg(II) due to fluorescence quenching. A selective and sensitive chemosensor for Cu(II) based on 8-hydroxyquinoline was described by Mei et al. (*342*). Kiyose et al. (*343*) described a ratiometric fluorescent zinc ion probe in NIR region, based on tricarbocyanine chromophore. Zhao and Carreira (*344*) described novel NIR fluorescent, conformationally restricted aza-dipyrromethene boron difluoride (aza-BODIPY) dyes with intense absorption, strong fluorescence, and high chemical and photostability. A different family of dyes was investigated by McDonnell and O'Shea (*345*) by using amine substituents on the BF_2-chelated tetraarylazadipyrromethene chromophore that generated a triple absorption and emission responsive sensor. Significant pH sensitivity was observed in both absorption and fluorescence in the range from pH 5 to 6 M HCl. A NIR fluorescence tricarbochlorocyanine dye (Cy.7.Cl) was synthesized by Tang et al. (*346*) and used for NIR spectrofluorimetric determination of hydrogen peroxide (H_2O_2) by flow injection analysis (FIA). Hydrogen peroxide was determined by mixing Cy.7.Cl with horseradish peroxidase. As Cy.7.Cl was oxidized, the fluorescence intensity was measured at 800 nm with excitation at 780 nm. In another study, Sunahara et al. (*347*) have systematically examined the mechanism of the solvent polarity dependence of the fluorescence of the BODIPY fluorophore and the role of photoinduced electron transfer by varying the substitution of the benzene moieties at the 8-position to measure micropolarity of biomolecule moieties and the surface polarity of living cells. Bouteiller et al. (*348*) described the preparation and properties of water soluble NIR fluorophores that can be potential substitutes of the commercially available Cy 5.5 and Cy 7.0.

Water soluble metallo-phthalocyanines (MPc) were investigated by Verdree et al. (*349*) by introducing water solubilizing moieties to minimize aggregation in aqueous environment. Basheer et al. (*350*) have investigated dialkylanthracene containing squaraine dyes possessing intense absorption and emission in the NIR region by synthesizing a novel class of tertiary arylamine derivatives by addition of squaric acid to the dimethyl aminoanthracene ring. Unsymmetrical squaraine dyes were also synthesized by the condensation of 3-[4-(*N*,*N*-dialkylamino) anthracene]-4-hydroxy-cyclobutene-1,2-dione with dialkylanilines. Fu et al. (*351*) have developed a novel NIR cyanine, 1-(ε-succinimidyl-hexanoate)-1′-methyl-3,3,3′,3′-tetramethyl-indocarbocyanine-5,5′-disulfonate potassium (MeCy5-OSu), and used it for quantification of polyamines in human erythrocytes by capillary electrophoresis with diode LIF detection achieving better than 2 nmol L^{-1} detection limits. Erythrocyte polyamines can be used as tumor markers; hence, quantifications of polyamines in human erythrocytes confirm the quantitative ability of MeCy5-OSu in complex biological samples. Ohnmacht et al. (*352*) have developed a chromatographic method for measuring free drug fractions based on an ultrafast immunoextraction/displacement assay with NIR fluorescent labels. Baek et al. (*353*) took a very different approach to achieve long wavelength absorption and fluorescence, well above 1000 nm, utilizing inert and photostable encapsulated lanthanide(III) complexes based on dendritic anthracene ligands that exhibit strong NIR emission bands via efficient energy transfer from the excited states of the peripheral antenna to Er(III), Yb(III), and Nd(III) ions.

A full synthetic and optical study of squaraine-derived rotaxanes was described by Arunkumar et al. (*354*) to avoid their inherent reactivity with nucleophiles and tendency to form nonfluorescent aggregates in water, problems normally associated with this otherwise highly fluorescent dye. Umezawa et al. (*355*) reported a squaraine dye with emission at 751 nm and a quantum yield of 0.56 in cyclohexane that exhibited linear positive solvatochromic properties near 780 nm. Thomas et al. (*356*) reported an environmentally sensitive thiol-reactive squaraine that was site-specifically coupled to various mutants of glucose/galactose binding protein containing an engineered cysteine for attachment. Strekowski et al. (*357*) have reported a detailed study evaluating NIR carbocynine dye stability in the presence of molecular oxygen under dark and light conditions finding that the heterocyclic structure has a great influence on the stability. All solutions were more stable when stored in the dark with benz[*c*,*d*]indolium dyes showing outstanding stabilities including under light conditions. Wang et al. (*358*) have developed an optical and nuclear dual labeled imaging agent by synthesizing a NIR dye containing a cyclic peptide and the nuclear reagent.

LUMINESCENCE TECHNIQUES IN BIOLOGICAL AND CLINICAL ANALYSIS

Luminescence spectroscopy continues to expand its significant impact on biological and clinical sciences. With the outstanding sensitivity of luminescence, methodologies are being developed for biosensing and bioimaging with ever increasing spatial resolution and faster time response. As a powerful tool for studying molecular structure, interactions, and environments, luminescence has been used in numerous biological applications; only representative works during the period of this review will be discussed here. An exciting advancement is the emergence of fluorescence imaging breaking the resolution limit defined by the diffraction barrier. With stimulated emission depletion (STED) fluorescence microscopy, the Hell laboratory has reported far-field fluorescence nanoscopic imaging that achieved a lateral resolution of 29−60 nm in the focal plane, corresponding to a 5- to 8-fold improvement over the diffraction barrier. The axial resolution was improved by 3.5-fold (*359*, *360*). The Zhuang group has achieved multicolor superresolution imaging by using a family of photoswitchable fluorescent probes in multicolor stochastic optical reconstruction microscopy. Spatial resolution of 20−30 nm was demonstrated in multicolor cell imaging (*361*). The Selvin laboratory monitored the transport of melanosomes, or melanin-carrying membrane organelles, and their interactions with molecular motors inside

melanophore cells with high spatial (approximately 2 nm) and temporal (approximately 1 ms) localization accuracy (*362*).

Single molecule fluorescence has been widely applied to biological systems. In vivo investigations of single molecule dynamics inside living cells have attracted considerable attention. To probe transcription factor dynamics, Xie and co-workers directly monitored the nonspecific binding of a single *lac* repressor to a DNA and its diffusion along the DNA in search of the *lac* operator. The kinetics of binding and dissociation of the repressor in response to metabolic signals was measured with single molecule spectroscopy (*363*). The assembly of telomerase, a cellular ribonucleoprotein (RNP) that maintains chromosome stability by adding telomeric DNA to the termini of linear chromosomes, was studied by use of single molecule spectroscopy. Direct observation of complex formation in real time revealed a hierarchical RNP assembly mechanism: interaction with the telomerase holoenzyme protein p65 induced structural rearrangement of telomerase RNA, which in turn directed the binding of the telomerase reverse transcriptase to form the functional ternary complex (*364*). Single molecule polarization measurements allowed detection of the orientation of a peptide with high precision and revealed that the receptors do not freely rotationally diffuse in the bilayer when they are bound by a peptide (*365*).

Luminescence techniques are also effective for the analysis of cellular components, cells, and bioaerosols. The membrane raft hypothesis postulates the existence of lipid bilayer membrane heterogeneities or domains that are important for cellular function. Using fluorescence imaging, Baumgart et al. have demonstrated that giant plasma membrane vesicles formed from the plasma membranes of cultured mammalian cells could also segregate into micrometer-scale fluid phase domains, providing an effective approach to characterization of biological membrane heterogeneities (*366*). Intravital flow cytometry was introduced to count rare circulating cancer cells (CTCs) in vivo as they flowed through the peripheral vasculature. The tumor cells were labeled with a fluorescent ligand and counted with multiphoton fluorescence imaging of superficial blood vessels. Studies in mice with metastatic tumors have provided evidence that CTCs could be quantitated weeks before metastatic disease was detected by other means (*367*). Rosch et al. have monitored and identified bioaerosols by first selecting the biotic particles with fluorescence imaging. Identification of the particles was accomplished through analysis of Raman signals of the biotic particles with support vector machine (*368*).

A number of reports have outlined the feasibility of diagnosing cancers and other diseases by use of tissue fluorescence spectroscopy. The Sevick-Muraca group has evaluated the imaging performance of a near-IR fluorescent dye in human breast cancer cells in subcutaneous xenograft models. They reported that a NIR dye provided a significantly reduced background and enhanced tumor-to-background ratio for high contrast imaging as compared to dyes excited in the visible (*369*). The same group also devised a novel noncontact fluorescence optical tomography scheme with multiple area illumination patterns. These imaging data were processed to generate the interior fluorescence distribution in tissue by implementing the fluorescence tomography algorithm. This new scheme produced significant improvements over reconstructions by use of only a single measurement (*370*). The Richards-Kortum laboratory detected cervical intraepithelial dysphasia by fitting the tissue fluorescence spectra to a mathematical model to analyze the concentrations of light scatterers, light absorbers, and fluorophores in the epithelium and the stroma. The model provided quantitative information about molecular changes during the dysplastic transformation (*371*). Calibration standards were established for in vivo fluorescence diagnosis to enable comparison of tissue data collected by multiple devices and multiple laboratories (*372*). A synchronous fluorescence imaging system with a large field of view has been developed for cancer diagnosis (*373*). The ratios of tissue tryptophan fluorescence intensity to phosphorescence intensity (*374*) and bivariate differential normalized fluorescence (*375*) have also been demonstrated to provide excellent tissue classification for cancer diagnosis. A Laguerre deconvolution technique has been reported for the analysis of time-resolved autofluorescence spectroscopy data collected from normal and atherosclerotic aortas. This technique has great potential for the diagnosis of atherosclerotic plaques, especially for the detection of macrophages infiltration in atherosclerotic lesions, a key marker of plaque vulnerability (*376*). The Feld group has introduced a novel multimodal spectroscopy method that combines intrinsic fluorescence spectroscopy, diffuse reflectance spectroscopy, and Raman spectroscopy to detect morphological markers of vulnerable atherosclerotic plaque (*377*).

An active direction of research is the development of new probes for biological sensing and imaging. Molecular imaging probes targeting specific biological molecules in sample matrices such as cells and tissue were actively pursued. A porphyrin-based molecular platform has been reported for dual functional fluorescence/magnetic resonance imaging of zinc. The molecular platform had superior physical properties as compared with earlier-generation zinc sensors including emission in the red and near-IR regions and a large Stokes shift of greater than 230 nm. The fluorescence intensity was observed to increase by more than 10-fold upon zinc binding. The manganese derivative switched the molecule to an MRI sensor. This synthetic strategy can be easily adapted to constructing other metal sensors (*378*). Nanoparticles represent an exciting alternative to conventional probes, offering the possibility of attaching multiple moieties for targeting and sensing, improved stability, and often high fluorescence intensity with low photobleaching. The Tan laboratory has devised multicolor fluorescence resonance energy transfer (FRET) silica nanoparticles by doping the particles with three fluorescent dyes. The fluorescence color output of the nanoparticle was tuned by use of the doping ratios. The nanoparticles could be excited with a single wavelength, had a large Stokes shift, and were appropriate for multiplexed analysis of nucleic acids and proteins (*379*). Aptamer-conjugated nanoparticles have been constructed to label prostate cancer cells (*380*) and leukemia cells (*381*). The aptamers were selected by cell-based SELEX strategy and target the overexpressed membrane antigens. The binding affinity and synthetic accessibility of the aptamers, in combination with the photostability of the fluorescent nanoparticles, provided a powerful and general tool for cell imaging.

REAGENTS AND PROBES

Several new fluorescent reagents and probes were developed over this review period. Only a small survey of new developments

can be presented in the limited space provided. The Lakowicz group has published extensively in the area of metal-enhanced fluorescence (MEF) in recent years. Significant changes in the photophysical properties of fluorophores in the presence of metallic nanostructures and nanoparticles have been demonstrated. Two newly developed long chain nitrobenzoxadiazol derivatives were used to investigate the polarity effect (*382*) and fluorophore distance on MEF (*383*). Single molecule spectroscopy was used to investigate fluorescence enhancements and lifetime reduction of Cy5-labeled oligonucleotides near silver island films (SiFs) (*384*). In another study, layer-by-layer assembly was used as a simple, robust, and inexpensive method to control probe distance from the surface in an investigation of sulforhodamine B assembled on SiFs (*385*). In related work, single cell fluorescence imaging was demonstrated using metal plasmon-coupled probes (*386*). Fluorescent metal plasmon-coupled probe labeled cells were 20-fold brighter than the corresponding free labeled cells. The potential of luminescent metal nanoparticles as molecule imaging agents was also explored (*387*).

Several reports of dye-doped silica nanoparticles have appeared in the literature. Geddes and co-workers have reported monodispersed core/shell nanoparticles consisting of silver nanoparticle cores coated with fluorophore doped silica shells (*388*). The potential of metal-enhanced fluorescence "nanoballs" for cellular imaging and solution based sensing was demonstrated using Rhodamine 800 within the shell. In other work, Wang and Tan described multicolor FRET silica nanoparticles with potential as barcoding tags for multiplexed signaling (*389*). Wu et al. have described a hybrid silica−nanocrystal−organic dye superstructure allowing a postencoding strategy with the potential to simplify preparation of multicolor fluorescent spheres (*390*). Saavedra and co-workers prepared and characterized poly(lipid)-coated, fluorophore-doped silica nanoparticles for biolabeling and cellular imaging (*391*). Tan and co-workers discussed the applications of silica nanoparticles doped with either magnetic materials or fluorescent dye molecules in separating and analyzing biological molecules (*392*). The same group also reported the rapid collection and detection of leukemia cells using a novel two-nanoparticle assay with aptamers as the molecular recognition element (*393*). Magnetic and fluorescent aptamer-modified nanoparticles were used for target cell extraction and sensitive cell detection, respectively. Combining two types of nanoparticles improved the performance of either particle alone. The technique was extended for the collection and detection of multiple cancer cells (*394*).

Multifunctional probes combining the benefits of fluorescent and magnetic particles in a single probe have been reported. For example, a new class of dual-function carriers for optical encoding and magnetic separation based on silica microbeads embedded with both semiconductor quantum dots and iron oxide nanocrystals were developed by Nie and co-workers (*395*). In other work, Gao et al. have synthesized core/shell nanostructures consisting of a FePt magnetic core and semiconducting chalcogenicle shells in a sequential one-pot reaction (*396*). The same group has reported the rapid detection of bacteria in human blood through the combination of fluorescent probes and biofunctional magnetic nanoparticles (*397*). Multimodal probes for combined fluorescence and magnetic resonance imaging have also been reported. In one example, Talanov et al. have synthesized a PAMAM dendrimer-based nanoprobe with Cy5.5 as the fluorescent probe (*398*). Complexation with Gd(III) did not affect the quantum yield, and the dual modality probe was used to visualize the sentinel lymph nodes in mice by both MRI and fluorescence.

Reagents for fluorescence imaging continue to be developed. Of particular interest are probes that allow for subdiffraction limit, or superresolution, far-field fluorescence imaging. Hess et al. have developed fluorescence photoactivation localization microscopy (*399*). The technique exploits the photoactivatable green fluorescent protein activated by a high-frequency (405 nm) laser and then excited at a lower frequency for imaging by a CCD. Probe molecules were either reversibly inactivated or irreversibly photobleached to remove them from the field of view. Betzig et al. have used numerous sparse subsets of photoactivatable fluorescent proteins for intracellular imaging at nanometer resolution (*400*). Bates et al. have introduced a family of photoswitchable fluorescent probes for multicolor superresolution imaging (*401*). Preparation of multiple probes with distinct colors allowed iterative, color-specific activation for multicolor imaging of biological samples with 20−30 nm resolution. Bock et al. have demonstrated two-color far-field fluorescence imaging inside whole cells with nanoscale resolution by enabling, recording, and disabling the emission of the reversible switchable fluorescent protein rsFastLime and the organic fluorophore Cy5 (*402*). Shroff and co-workers have used spectrally distinct photoactivatable fluorescent proteins for superresolution imaging of different pairs of proteins assembled in adhesion complexes (*403*).

Advances in hybridization probes continue to appear in the literature. The Turro group reviewed different approaches for design of fluorescent hybridization probes including molecular beacons (MBs) and two- and three-dye binary probes for sensitive and selective DNA and RNA detection (*404*). Moerner and co-workers have reported the bulk and single molecule characterization of an improved MB using a pair of new dicyanomethylene-dihydrofuran (DCDHF) dyes and H-dimer excitonic behavior of the fluorophores in close proximity (*405*). The doubled single molecule emission intensity of target bound self-quenched intramolecular dimer MBs ensured higher signal-to-background ratio than conventional fluorophore-quencher MBs and offered a specific means of discriminating between functional MBs and spurious fluorescence. Yeung and co-workers have presented an improved method for quantitative clinical screening of surface-hybridized human papilloma virus DNA using single molecule imaging (*406*). Single- and double-probe methods were also described. In other work, Mirkin and co-workers have demonstrated the use of novel oligonucleotide-modified gold nanoparticle probes hybridized to fluorophore-labeled complements as "nanoflares" for detecting mRNA in living cells (*407*). Nanoflares were shown to exhibit high signaling, low background fluorescence, and sensitivity to changes in the number of RNA transcripts present in cells. Geddes and co-workers have reported a fast and sensitive DNA hybridization assays using microwave-accelerated metal-enhanced fluorescence (*408*) and investigated the effects of low-power microwave heating on this new approach (*409*).

Many lanthanide-based luminescent reagents have been reported during this review period. Examples include the use of

europium tetracycline as a probe for nucleoside phosphates (*410*) and application of lanthanide-binding tags, short peptide sequences comprising 15−20 naturally occurring amino acids that bind Tb(III) with high affinity, in the investigation of protein−peptide interactions (*411*). Poupart et al. have synthesized and characterized the photophysical properties of a new terpyridine-based europium(III) chelate for peptide and protein labeling (*412*).

A large number of derivatization reagents for use in separation techniques have been developed during the review period. Examples include an intramolecular charge transfer-based fluorescent reagent that allowed rapid (15 min) staining for SDS-PAGE (*413*) and a new fluorescent derivatizing reagent that improved the HPLC analysis of amino acids which could not be determined using traditional labeling reagents (*414*).

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