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EDITORIAL

Photon mayhem: new directions in diagnostic and therapeutic photomedicine

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A photon is a quantum of electromagnetic radiation. Photons possess intrinsic properties that can be exploited in biomedicine to both analyze and treat tissue: sterile, non-contact and non-invasive, high-resolution and precise localization, wavelength tunability and polarization selectivity, and a variety of highly selective and specific photon-tissue interactions. In the optical portion of the electromagnetic spectrum, the photon energies (~ eV) couple nicely to the *molecular* energy levels of most biomolecules (unlike for example X-rays, whose energy levels are in tune with *atomic* binding energies). Further, the wavelength scale of optical photons (~ µm) corresponds well to the length scale of relevant tissue microstructures (e.g., cells and sub-cellular organelles). For these and other reasons, biophotonics is well poised to play a significant role in enabling the emerging clinical paradigm of *molecular medicine*.

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Photomedicine is thus a burgeoning area in the life sciences (biology and medicine) that involves optical imaging of target molecules, cells, or tissues as well as optical interventions to treat/alter the course of the disease. An absolutely essential step to fully exploit the photon's potential for improving current clinical practice in interdisciplinary communication and collaboration—thus close linkages between physicists, engineers, biologists, chemists, mathematicians, and physicians are needed. Towards the goals of inter-/cross-disciplinary communication and exploration of new collaborative directions in photonic diagnosis and therapy in biomedicine, this *Special Issue* on *Emerging Optical Technologies for Biomedical Engineering Applications* comprised of six reviews and one research article is presented.

To highlight the featured *Special Issue* articles, one of the emerging optical advances that may impact the human histopathological examination in the clinic is light sheet microscopy (LSM). Combined with optical tissue clearing, LSM has the potential to significantly augment conventional histopathology from two-dimensional tissue sections to optical sectioning with a three-dimensional assessment of biopsy specimens. Poola et al. review the rapid progress of LSM technology covering its history, comparisons with other microscopic modalities, and currently available commercial LSMs along with various human histology applications [1].

Utilizing in vivo optical microscopy for "deep" tissue imaging has been pioneered by the development of nonlinear microscopy, especially its two-photon variant, since the early 1990s [2]. However, as most fluorescence imaging techniques, the signal depends on the spatially- and temporally-heterogeneous fluorophore concentration, with the added complexity of photobleaching that can further distort the quantitation. Recent advances in two-photon lifetime imaging obviate some of these difficulties, and allow 3D quantitative imaging of fluorescence lifetime—the average time of a fluorophore spends in the excited state before returning to the ground state. Not only is the lifetime independent of fluorophore concentration and photobleaching, but it also provides the local microenvironmental information including the alterations in a metabolic state via fluorescence lifetime imaging (FLIM). Ranawat et al. thus review the principle of two-photon FLIM, its various exciting applications in biological research, and possible clinical translation routes [3].

An example of biophotonic imaging technology that has been widely adopted in the clinic is optical coherence tomography (OCT), a low coherence interferometry imaging method that provides micron-scale depth-resolved information based on scattering of light within tissue [4]. Prof. Choi reviews an emerging OCT angiography (OCTA) for preclinical neuroimaging [5]. Utilizing clever scanning and signal processing techniques without the need of potentially toxic exogenous contrast agents, OCTA can visualize 3D functional microvascular blood networks in the brain of laboratory animals. In addition to covering the principle of OCTA algorithms, the review also discusses preclinical applications of OCTA for traumatic brain injury, cerebral stroke, and brain aging.

Light propagation within scattering and absorbing media such as tissue has been studied extensively over the last several decades, as a necessary enabling step for understanding and optimizing light-tissue interactions and applications. Along with advanced analytical models based on radiative transfer theory and diffusion approximations, Monte Carlo (MC) simulation approaches have also proven very useful and robust in many practical and complex biomedical scenarios. Krasnikov et al. review the recent advances in the MC simulation methods of light-tissue interaction encompassing realistic tissue parameters as well as diverse MC applications in OCT, Raman spectroscopy, optogenetics, and polarimetry/Mueller matrix techniques in biomedical optics and spectroscopy [6]. Related to the latter application area, a quantitative polarized light imaging modality based on Mueller polarimetry has been explored by Gribble et al. for label-free visualization of tissue pathology, utilizing a simple modular design that can couple easily into most commercial stereo zoom microscopes [7].

Biophonics is not limited to tissue imaging or diagnosis. The photon energy can be used to alter/treat tissue, often is a highly selective and sensitive manner. For example, laser eye surgery such as LASIK (laser assisted in situ keratomileuses) is now routinely performed in ophthalmology clinics; and photodynamic therapy (PDT) is clinically used for treating cancer and various non-oncologic pathologies with a photosensitizer activated by a specific wavelength of light. The final two articles of this *Special Issue* are phototherapeutic in nature, covering a growing interest in the field of photo-bio-modulation (PBM), an emerging therapeutic/treatment augmentation modality in clinical scenarios where current (e.g., pharmacological) treatments are of limited efficacy or yield debilitating side effects. Lee et al. describe the spectrum of PBM from the preclinical to the clinical applications in hearing research [8]. The efforts to use PBM to non-invasively improve hearing (including tinnitus) are reviewed, driven by the absence of currently accepted therapeutic modality for properly managing sensorineural hearing loss. In addition, Hong reviews the use of PBM to treat neurodegenerative disorders in preclinical settings [9] as an alternative therapeutic approach to slow down neuronal degeneration and achieve neuroprotection in serious brain disorders including Alzheimer's and Parkinson's diseases. To achieve the full potential of PBM in managing these significant irreversible pathologies, PBM is suggested at an early stage of disease progression, and/or as an adjunctive augmentation to standard treatment.

While we introduce selected emerging areas of biophotonics for biomedical engineers in this *Special Issue*, these are far from exhaustive but rather represent only illustrative examples. The future of photonics in photomedicine will also rely on, and will integrate the advances from several related disciplines, including (but not limited to) non-photonic imaging, biomaterials, nanotechnology, theranostics, various "omics" and machine learning/data analytics, and genetic engineering. It is our hope that the BMEL readers of this *Special Issue* will find (1) the illustrative articles interesting, (2) overall field of biophotonics exciting, and (3) the inter-disciplinary nature of the field "actionable" in their own research. Finally, we would like to thank all the participating authors for their valuable contributions, and BMEL's editor-in-chief, Prof. Jae S. Lee, for inviting us to put together this *Special Issue* and encouraging us throughout the process of its completion.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

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