EBioMedicine 2 (2015) 1304–1305

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

In vivo X-Ray Phase Imaging

Erik L. Ritman

Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN 55905 USA

In this issue of *EBioMedicine*, the article by Velroyen et al. (2015) is a most recent presentation of the evolving x-ray imaging technology that is based on use of x-ray photons that deviate from the straight line described by the "ballistic" photons due to changes of the phase of the wave front that the x-rays undergo when passing through tissue. "Ballistic" photons are assumed to follow a straight path linking the x-ray source and detector pixel and form the basis of the attenuation based shadow graph imaging method that is used in essentially all routine x-ray imaging methods since its initial development by Roentgen and subsequent application to medical computed tomographic imaging by Hounsfield. This article by Velroyen et al. involves the measurement of the miniscule deviation of x-ray photons from the "ballistic" path caused by the refraction of the x-ray by tissue (Velroyen et al., 2015). Their study used microscopic venetian blind-like metal grids that predictably diffract the x-ray photons so that any deviation from that known diffraction deviation can be quantitatively related to the cumulative refraction as the x-ray photons pass through tissue.

The Velroyen scans did not use 'gated' scans, i.e., piecewise accumulation of the necessary multi-angular scan data synchronized with a biological signal such as a selected phase of the respiratory cycle. Gating of CT scan acquisition is not novel in micro-CT (Badea et al., 2004), but because of the need for very high spatial precision and reproducibility of the image data acquisition at each angle of view, its demonstration of its feasibility in a living mouse would be a considerable contribution. Without gating and 5-second duration exposures at each angle of view, the role of image blurring is not clear. The study highlights that structural information at a scale smaller than the detector pixel size can be obtained. The detection of sub-pixel structural information is particularly important for several reasons. In conventional shadow-graph x-ray imaging a sub-pixel structure cannot be unambiguously quantified (Vercnocke et al., 2014). The importance of this issue is well demonstrated by the desire to quantify structural aspects of lung alveoli. These alveoli consist of little spherical air sacks 100–250 μm in diameter and enclosed by a spherical shell consisting of a layer of cells a few micrometer thick (Bachofen et al., 1987). Alveolar wall thickness, as well as alveolar air space's partial replacement with fluid or cells, are critically important factors affecting the efficacy of gas exchange to, and from, inhaled air to blood. Hence, the detector pixels being of the order of 58 μm in the micro-CT scanner used in this study would not be able to quantify that information if conventional, attenuation-based, CT was used. This particular property of the method used is important in that it could significantly extend the repertoire of pre-clinical evaluation of disease processes and therapeutic interventions using mice.

Despite all the encouraging results of this and other similar studies, as pointed out by the authors, many issues need resolution before this methodology can be translated to more general use at the micro-CT and ultimately the clinical levels of application. The following is an outline of some aspects of the methodology that need to be addressed in greater depth:

1) How does the method, as applied to lung, compare to Magnetic Resonance Imaging (MRI) using hyperpolarized Helium 3 (Yablonskiy et al., 2002) or Optical Coherence Tomography (OCT) (Hou et al., 2011) or x-ray scatter (Cui et al., 2010; Norton, 1994) based methods which already exist?
2) The duration of the phase-based scan can still be an issue in that the spontaneous respiratory cycle is often not reproducible over an extended period of time so that the gated scan may still not capture the same phase of the sequential respiratory cycles.
3) Longitudinal studies involve repeat scans of each subject and thereby increase cumulative radiation exposure and this could increase the risk of collateral tissue damage or even interfere with the disease, or therapeutic, process itself. Hence, minimization of radiation exposure per scan will be a priority. It will be of interest to see to what extent algorithms for CT image noise reduction (Chen et al., 2010) and reduced number of angles of view (Sidky et al., 2006) can be implemented in phase-based imaging beyond the implementation used in this study.
4) The results of the presented study of two mice is encouraging, but "a single sparrow not a spring make". For instance:

   (a) Experiments of a sufficient number of mice need to be designed so that sensitivity and specificity of the approach can be quantified.
   (b) Use of phantoms that have microscopic structures with a range of dimensions of the order of alveoli (e.g., precision foam materials) so that the limits of the image data can be quantified.
   (c) The use of suitable phantoms to establish the technical requirements for applying the methodology to larger diameter objects (ultimately the adult torso – although the breast and peripheral limb would be a very good start) to address questions such as (i) what is the role of x-ray photon energy and

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.08.014.
E-mail address: elran@mayo.edu.

http://dx.doi.org/10.1016/j.ebiom.2015.09.008

spectral bandwidth?, (ii) what is the impact of tissue heterogeneity on the number of different phase shifts along the x-ray photon path?

Disclosure

The author is supported by National Institutes of Health grants (EB016966, HL83231, DK73608).

References

Bachofen, H., Schurch, S., Urbinell, M., Weibel, E.R., 1987. Relations among alveolar surface tension, surface area, volume, and recoil pressure. J. Appl. Physiol. 62 (5), 1878–1887.

Badea, C., Hedlund, L.V., Johnson, G.A., 2004. Micro-CT with respiratory and cardiac gating. Med. Phys. 31 (12), 3324–3329.

Chen, G.-H., Tang, J., Nett, B., Qi, Z.-H., Leng, S., Szczykutowicz, T., 2010. Prior image constrained compressed sensing (PICCS) and applications in x-ray computed tomography. Curr. Med. Imag. Rev. 6 (2), 119–134 (16).

Cui, C., Jorgensen, S.M., Eaker, D.R., Ritman, E.L., 2010. Direct three-dimensional coherent scattered x-ray micro-tomography. Med. Phys. 37 (12), 6317–6322.

Hou, R., Le, T., Murgu, S.D., Chen, Z., Brenner, M., 2011. Recent advances in optical coherence tomography for the diagnosis of lung disorders. Expert Rev. Respir. Med. 5 (5), 711–724.

Norton, S.J., 1994. Compton-scattering tomography. J. Appl. Phys. 76, 2007–2015.

Sidky, E.Y., Kao, C.-M., Pan, X., 2006. Accurate image reconstruction from few-views and limited-angle data in divergent-beam CT. J. X-Ray Sci. Technol. 14, 119–139.

Velroyen, et al., 2015. Grating-based X-ray dark-field computed tomography of living mice. EBioMedicine 2, 1500–1506.

Vercnocke, A.J., Anderson, J.L., Jorgensen, S.M., Ritman, E.L., 2014. CT Image-based Quantification of Sub-pixel Diameter Microparticle Accumulations in Tissues Using á Priori Biological Information. Proc SPIE Developments in X-ray Tomogr IX ((9212): 92121C-1–6).

Yablonskiy, D.A., Sukstanskii, A.L., Leawoods, J.C., Gierada, D.S., Bretthorst, G.L., Lefrak, S.S., Cooper, J.D., Conradi, M.S., 2002. Quantitative in vivo assessment of lung microstructure at the alveolar level with hyperpolarized ^{3}He diffusion MRI. PNAS 99 (5), 3111–3116.