Precision Imaging: more descriptive, predictive and integrative imaging

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Abstract

Medical image analysis has grown into a matured field challenged by progress made across all medical imaging technologies and more recent breakthroughs in biological imaging. The cross-fertilisation between medical image analysis, biomedical imaging physics and technology, and domain knowledge from medicine and biology has spurred a truly interdisciplinary effort that stretched outside the original boundaries of the disciplines that gave birth to this field and created stimulating and enriching synergies. Consideration on how the field has evolved and the experience of the work carried out over the last 15 years in our centre, has led us to envision a future emphasis of medical imaging in *Precision Imaging*. Precision Imaging is not a new discipline but rather a distinct emphasis in medical imaging borne at the cross-roads between, and unifying the efforts behind mechanistic and phenomenological model-based imaging. It captures three main directions in the effort to deal with the information deluge in imaging sciences, and thus achieve wisdom from data, information, and knowledge. Precision Imaging is finally characterised by being descriptive, predictive and integrative about the imaged object. This paper provides a brief and personal perspective on how the field has evolved, summarises and formalises our vision of Precision Imaging for Precision Medicine, and highlights some connections with past research and current trends in the field.

Keywords: Precision Imaging, Precision Medicine, image-based modelling, model-based imaging, phenomenological modeling, mechanistic modeling

1. The state of play and how we came to it

Medical image analysis has evolved over the past 40 years from being practically a sub-discipline at the cross-roads of image processing, computer vision, and pattern recognition, to become a distinct discipline of its own. Medical image analysis addresses exciting new challenges that emerged from close and creative dialogue with healthcare practitioners and biomedical researchers. This dialogue has generated novel and fundamental ideas that have been adopted back by its parent disciplines and has created a vibrant interdisciplinary community involving specialized meetings, tutorials and summer schools, and journals that top journal rankings in engineering, computer science, and mathematics in terms of impact factor. The introduction of the Medical Image Analysis journal in 1996 was not, correspondingly, an instance of "yet another journal". It was only in 1987, that the Medical Subject Heading (MeSH) concept 'Image Processing, Computer-Assisted was first adopted by the National Library of Medicine as a preferred concept. Also, 'Image Analysis, Computer-Assisted was then categorized as a narrow concept in MeSH terms. A PubMed query on Mar 30th 2016 by this term returns a total of 19,342 entries in this category in 1976-1995, and 161,948 entries in 1996-2015. These numbers show that the expansion of the field has been enormous, yet this evolution has been qualitative as much as quantitative (cf. Fig. 1).

In comparison with 20 years ago, the field of medical image analysis has made terrific progress both in terms of depth and breadth of the research carried out. Both the emerging methods and applications have been affected as much as the way in which we do research in medical image analysis. The first two decades (1976-1995) were dominated by what we know today as *image processing* and paralleled breakthrough developments in *image acquisition*. Scientific questions that marked this period tackled, for instance, image reconstruction, restoration, enhancement, filtering, visualization, and detection problems. The last two decades, however,

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have placed a greater stress on *image analysis* and *image understanding* thus addressing higher-level computational vision tasks connected with image interpretation. Key challenges addressed have been pattern and shape analysis, non-rigid registration and tissue deformation analysis, high-dimensional (e.g. vector, tensor) image analysis and registration, multi-scale and multi-resolution modeling and analysis, to name just a few. This period witnessed also important developments in machine learning (e.g. graphical models, deep learning, transfer learning) and new computing hardware (e.g. distributed computing and graphical processing units) that enabled complex data-driven approaches to flourish. Computational imaging emerged as an ever more intimate cross-fertilization between electrical engineering, computer science, and mathematics to which additional disciplines like mechanical engineering, physics, medicine and biology helped further by providing inspiration or priors from domain knowledge. This confluence of disciplines spurred a host of new methodological developments but also a new way to think and work together across disciplines, an aspect that has also radically changed over the past 40 years. Up to the 90s, it was common to illustrate newly proposed methods working on a handful of medical images; it was then rare to find medical image analysis groups within healthcare institutions. Consequently, the dialogue between people doing image processing at the time and those eventually being the recipients of the technology was not as fluid as nowadays. A number of groups around the world led a major transformation in this regard (e.g. the Wolfson Image Analysis Unit at the Medical School of the University of Manchester, the Surgical Planning Lab at the Harvard Medical School, the Imaging Sciences Institute in University Medical Centre Utrecht at Utrecht University, the Medical Imaging Research Center at KU Leuven, the Computational Imaging Science Group based at Guy's Hospital in London, the Image Processing and Analysis group at Yale University, or various groups at the interface between image acquisition, medical robotics and image analysis at Johns Hopkins University, to name a few). These groups spearheaded a different approach to medical image analysis that highlighted the understanding and focus on clinical translation without compromising the scientific rigor and methodological underpinnings of the proposed solution. The unmet clinical needs became a stimulus for new methodological and system developments. This new focus had a progressive influence on a number of aspects: 1) research questions gradually moved away from mere illustration of what was technically feasible towards addressing questions that were clinically relevant, 2) peer-reviewing in top scientific journals increasingly requested more extensive and exhaustive evaluation of image analysis methodologies, 3) the importance placed on open image databases and benchmarking protocols developed to the current "challenges" (www.grand-challenge.org), 4) influential papers usually combined engineering and scientific rigor with clinical or biological insights, and 5) leading institutions developed creative ways to foster ever stronger multi-disciplinary teams to maximize knowledge permeation and collaboration, etc. These are just some of the trends that have become stronger in the past decades. Interestingly, when the cross-fertilization has worked at its best with the medical and biological disciplines, it has not diluted core methodological rigor but rather served to stimulate new scientific challenges leading to the current distinctiveness and impact in medical image computing and computer assisted interventions. Fig 2, for instance, shows that in spite of the staggering increase in absolute number of journal papers, our community continues to publish largely in Engineering, Computer Science and Mathematics journals.

2. The Trend: From Data to Wisdom and Back

What is next in medical image analysis? In our view, medical image analysis, is moving like other disciplines in the direction "from data to wisdom". The DIKW Hierarchy (cf. Fig. 3) articulated by Ackoff (1989), and reviewed by Rowley (2007), provides an interesting construct to elaborate on this. Most of the early research in medical image processing and analysis, and more broadly in computer vision, image processing and analysis was focused on acquiring, reconstructing, enhancing, and detecting data. The former methodologies opened up the way to more recent efforts of information processing and knowledge extraction and focused on understanding relationships between data and the patterns behind information. The transformation from data to information seeks answers to the questions of 'who?', 'what?', 'when?' and 'where?', and hence delivers useful, organised and structured information. Knowledge extraction from information, in turn, addresses the question of 'how?' information is organized. It focuses on contextualizing, synthesizing and learning information. It focuses on retrospective analyses of the data and, hence, reveals the patterns hidden in past experience. Ultimately, however, we would like to understand the 'why?' behind fundamental processes in health and disease and, hence, acquire the ability to make predictions about or take decisions that affect the future healthcare or biomedical principles. "Wisdom" is that phase

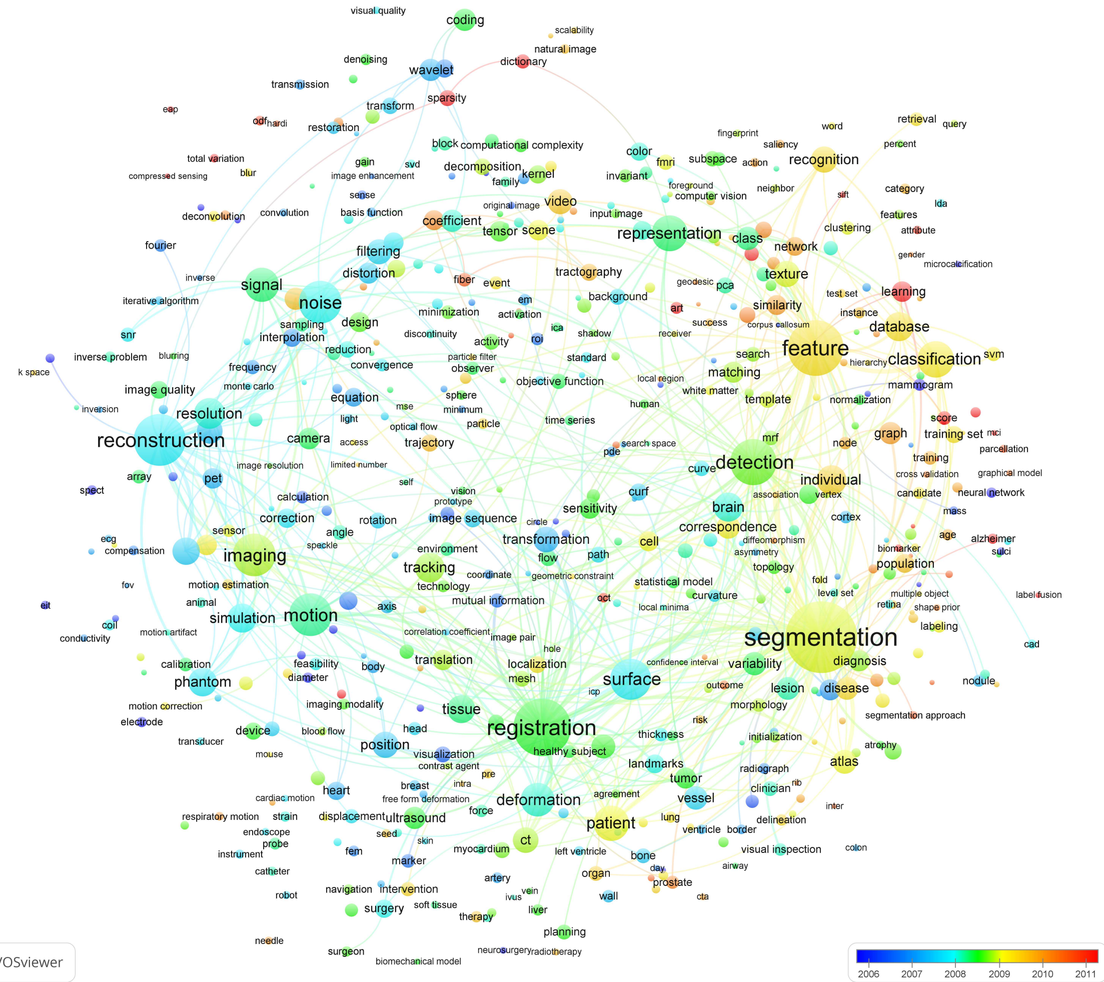

Figure 1: Network visualization based on clusters of key-phrases in titles and abstracts of the top ranking journals and conferences in our field corresponding to the MeSH term 'Image Processing, Computer-Assisted'. Circles represent concepts, radii are proportional to their frequency, and links encode the top 200 strongest normalized co-occurrences. Colour coding relates to the average publication date of the associated articles. The results correspond to the period 1996-2015 and include ca. 10,012 publications from PubMed on Mar 30th 2016.

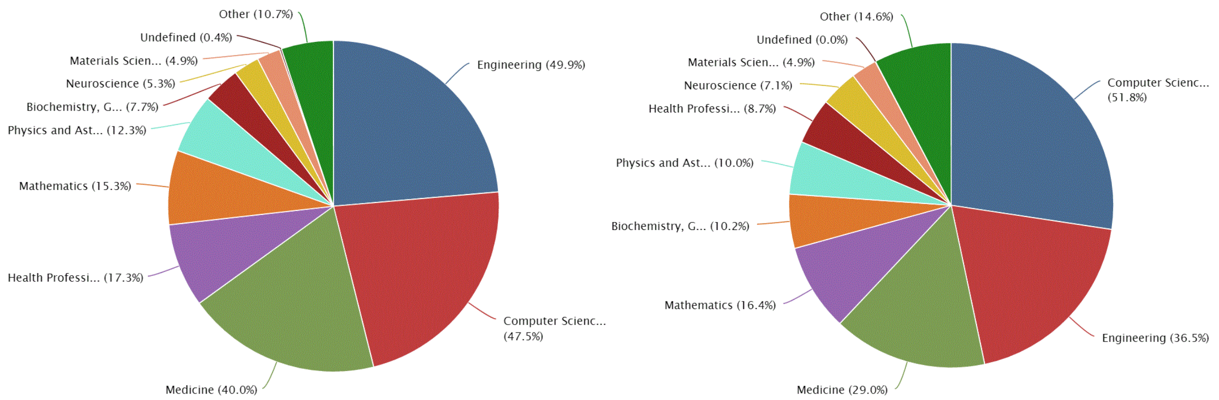

Figure 2: Distribution of the disciplines associated with the journals publications published in the period 1976-1995 (left) and 1996-2015 (right) with keywords "medical image AND (analysis OR processing OR computing)". The total number of publications has grown enormously from 1,771 (left) to 56,707 (right).

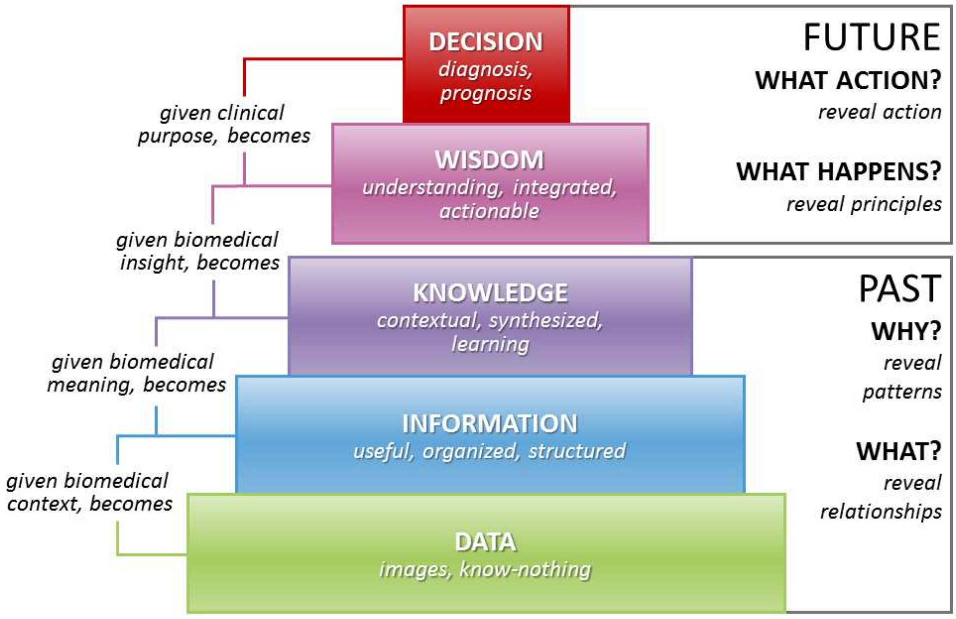

Figure 3: The DIKW Hierarchy: the journey from data to wisdom in the context of medical imaging (and more widely, clinical data). The diagram is an adaptation of the one available from www.pursuant.com.

of understanding, integrated and actionable knowledge that enables us to choose a suitable course of action, or to abstract fundamental principles in biomedicine. Moving forward, we believe image analysis will be ever more focused on "computational imaging", i.e. on technologies for which computation plays an integral role in image formation (data), image processing (information), and image modelling (knowledge). Concomitantly, these technologies will help us to unravel the underlying principles that determine health and disease (wisdom), and thus enable us to take better healthcare decisions about individuals and populations. Computational imaging will thus aim at providing the theoretical frameworks, the operational methods, and the practical infrastructure to enable the seamless transition from data all the way up to wisdom. Considering the information flows in the DIKW Hierarchy, we distinguish three directions that put in harmonic perspective most trends in medical image computing.

Bottom-up: Image-based phenomenological modeling. On the one side, there is a bottom-up, data-driven direction which we like to refer to as "image-based modelling" or more broadly, "phenomenological modelling". Perhaps starting with the success of statistical shape modelling (Young and Frangi, 2009; Castro-Mateos et al., 2014), and successive developments leading to computational atlasing, computational anatomy (Miller et al., 2015) and disease state fingerprinting (Kumar et al., 2012; Mattila et al., 2011), these and other developments accelerated by machine learning emphasize learning and inference of knowledge directly from vast amounts of imaging data (Kansagra et al., 2016; Medrano-Gracia et al., 2015; Margolies et al., 2016). This confluence of image-based computational modelling with developments on population imaging (Volzke et al., 2012) will increasingly underpin computational models and phenotypes of health and disease. Well developed theories from machine learning applied to image computing provide natural metrics to relate individual phenotypes to those within a population (e.g. Duchateau et al., 2012; Schmidt-Richberg et al., 2016). These developments can play a profound role in supporting stratified medicine (e.g. Mattila et al., 2011) or, more widely, to revise current disease taxonomies themselves, which are under debate (Committee on a Framework for Development a New Taxonomy of Disease; Board on Life Sciences; Division on Earth and Life Studies; National Research Council, 2011) in the wider context of Precision Medicine (Collins and Varmus, 2015).

Middle-out: Image-based mechanistic modelling. Alternatively, fundamental principles (wisdom) from biomechanics, biophysics, biochemistry, etc. may flow top-down and be invoked in personalised in personalised computational models built bottom-up from subject-specific data (e.g. medical imagery (Frangi et al., 2013) but also omics data, physiological measurements, lifestyle and environmental variables (Frangi et al., 2011), etc.). Imaging in this context is used as part of the model personalization either of the computational domain, its boundary/initial conditions, or its tissue distribution and properties (Frangi et al., 2013). Unlike phenomenological approaches, this strategy to analyze population imaging data is not purely data-driven as it incorporates explicit insights from known mechanisms in health and disease (Sharpe, 2011; Villa-Uriol et al., 2010, 2011; Smith et al., 2011). Combined with virtual interventions (e.g. Larrabide et al., 2012; Morales et al., 2013), this approach enables execution of *in silico* clinical trials (Viceconti et al., 2016) or supporting of regulatory processes (Center for Devices and Radiological Health, 2014) especially in scenarios that could be impractical, costly or unethical (e.g. Larrabide et al., 2013; Morales et al., 2011) to carry out in animals or humans as a first line of choice.

Top-down: Model-based computational imaging. Finally, knowledge of the physical principles governing specific image scenarios (e.g. biomechanics and biophysics of tissues and fluids, physiology of disease processes, physics of imaging processes, etc.) can be used to regularise the processes of image formation, transformation and interpretation (Sarvazyan et al., 1991). Examples can be found in the use of biomechanics to drive image registration (e.g. Hu et al., 2012), use of structural models to infer tissue micro-structure (e.g. Lekadir et al., 2014, 2015; Clayden et al., 2016), use of computational models to produce virtual images of unobservable features (e.g. Nørgaard et al., 2016; Lekadir et al., 2016), or *computational imaging* approaches that incorporate prior knowledge into image acquisition or reconstruction leading, for instance, to agile or portable imaging/sensing systems (York et al., 2011; Coskun and Ozcan, 2014). Such models provide a framework for interpolating between, and extrapolating from the sparse observational states (spatially, temporally, and functionally) afforded by images. In like manner, they enable systematic integration of disparate observations, for example from distinct modalities. So-called model-based imaging, in other words, constitutes a top-down flow through the DIKW hierarchy.

3. Precision Imaging for Precision Medicine

In the future, we envision an even stronger emphasis on quantitative imaging methods targeted at optimizing diagnosis and treatment selection, which we term "Precision Imaging". Precision Imaging is distinct from, but complementary to "Precision Medicine" (Collins and Varmus, 2015). The concept of Precision Medicine –viz. holistic prevention and treatment strategies that take individual variability into account– is not new but has so far lacked practical methods and systems that translate into tangible clinical impact. Precision Medicine emphasizes accounting for personalized genetic, environmental and lifestyle profiles (and variability thereof) in healthcare, while diagnosis and stratification has traditionally considered only individual phenotypes derived from various medical examinations, including imaging. The latter still offers a relevant component in accounting for the individual presentation of disease: the challenge is to harmonise these two views through quantitative approaches that are underpinned by understanding of disease mechanisms, account for individual phenotypic uncertainty, and rigorously and accurately propagate that uncertainty down the diagnostic and prognostic inference chain. Precision Imaging provides a descriptive, predictive, and integrative approach to disease diagnosis and stratification that maps disease-specific pathophysiology mechanisms onto quantitative imaging phenotypes with an estimate of their confidence. This approach also exploits the growing and complex nature of large population databases, particularly those which are imaging-rich (e.g. UK Biobank (Petersen et al., 2013), The German National Cohort (Bamberg et al., 2015), The Rotterdam Scan Study (Ikram et al., 2015), etc.). From automated analysis of those databases, population disease models have been derived. Current progress on machine learning and image computing allows such models to be endowed with individual-to-group distances (or disease state fingerprints or scores), which can account for uncertainty in the image-derived estimates and can be further extended to incorporate non-imaging variables (available, e.g., from omics, lifestyle, demographics, etc.). Precision Imaging is, in principle, well positioned to contribute to the objectives of personalised medicine and establish a quantitative approach to disease classification and patient stratification. In summary, Precision Imaging is a mechanism-driven, model-based approach to acquiring quantitative imaging phenotypes possessing the following three key attributes:

- *Descriptive*: it probes quantitatively living systems based on mechanistic first principles underlying health and disease and interprets image-based biological, biochemical, physical and physiological information that is optimised for patient management.
- *Predictive*: it estimates not only the quantity of interest, but also the confidence with which we

believe the estimate to reflect the quantities' true value and/or how the quantity in an individual relates to that in a reference population. It is therefore well suited to handling uncertainty in subsequent inference steps.

- *Integrative*: it fuses multi-modal information sources not only from a spatial and/or temporal stand-point but where appropriate from a mechanistic perspective by integrating image acquisition and image interpretation via underlying models of physiological processes in health and disease, growth, ageing, etc. Consequently, Precision Imaging exploits the most appropriate imaging modality in a mechanism-driven manner to underpin disease stratification.

The models used to encode physiological and disease mechanisms effectively introduce domain knowledge into Precision Imaging (model-based imaging), which regularises image acquisition and/or reconstruction with the best available mechanistic understanding or phenomenological insights. Therefore, the derived image quantities probe tissue properties at a spatial, temporal or functional scale (image-based modelling) that would otherwise be beyond the limits of the data directly measured with the imaging system (super resolution). It is the simultaneous pursuit of these three attributes that is a key distinction from current imaging technology; they mark a focus on developing imaging techniques not only as proxies of clinical end-points, but designed specifically for their role within the image-based modelling pipeline at the heart of this programme. We focus here on mapping properties of organ tissue that key disease processes commonly disrupt, exploiting the sensitivity of various imaging contrasts. Precision Imaging, one can argue, is not necessarily a new imaging paradigm in the same way that Precision Medicine is not a new form of medicine. Precision Imaging, rather, reminds us to seek beyond ever higher image resolution merely as a byproduct of technological progress in image acquisition. Precision Imaging achieves more sensitivity and specificity in medical imaging through the cooperation of mechanistic and phenomenological model-based imaging. While subtle, this distinction is crucial as it is the view of the authors that it fundamentally departs from mainstream current use of imaging, which attempts diagnostic and prognostic decision-making primarily through phenomenological associations between imaging biomarkers and clinical outcomes.

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References

Ackoff, R., 1989. From data to wisdom. Journal of Applied Systems Analysis 16, 3–9.

Bamberg, F., Kauczor, H. U., Weckbach, S., Schlett, C. L., Forsting, M., Ladd, S. C., Greiser, K. H., Weber, M. A., Schulz-Menger, J., Niendorf, T., Pischon, T., Caspers, S., Amunts, K., Berger, K., Bulow, R., Hosten, N., Hegenscheid, K., Kroncke, T., Linseisen, J., Gunther, M., Hirsch, J. G., Kohn, A., Hendel, T., Wichmann, H. E., Schmidt, B., Jockel, K. H., Hoffmann, W., Kaaks, R., Reiser, M. F., Vlzke, H., German National Cohort MRI Study Investigators, 2015. Whole-Body MR Imaging in the German National Cohort: Rationale, Design, and Technical Background. Radiology 277 (1), 206–220.

Castro-Mateos, I., Pozo, J. M., Cootes, T. F., Wilkinson, J. M., Eastell, R., Frangi, A. F., 2014. Statistical shape and appearance models in osteoporosis. Curr Osteoporos Rep 12 (2), 163–73.

Center for Devices and Radiological Health, 2014. Reporting of computational modeling studies in medical device submissions. Draft Guidance Federal Register Number 2014-00874, Food and Drug Administration.

Clayden, J. D., Nagy, Z., Weiskopf, N., Alexander, D. C., Clark, C. A., 2016. Microstructural parameter estimation in vivo using diffusion mri and structured prior information. Magn Reson Med 75 (4), 1787–96.

Collins, F. S., Varmus, H., 2015. A new initiative on precision medicine. New England Journal of Medicine 372 (9), 793–795.

Committee on a Framework for Development a New Taxonomy of Disease; Board on Life Sciences; Division on Earth and Life Studies; National Research Council, 2011. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. The National Academies Press.

Coskun, A. F., Ozcan, A., 2014. Computational imaging, sensing and diagnostics for global health applications. Curr Opin Biotechnol 25, 8–16.

Duchateau, N., De Craene, M., Piella, G., Frangi, A. F., 2012. Constrained manifold learning for the characterization of pathological deviations from normality. Med Image Anal 16 (8), 1532–49.

Frangi, A. F., Coatrieux, J. L., Peng, G. C., D'Argenio, D. Z., Marmarelis, V. Z., Michailova, A., 2011. Multiscale modeling and analysis in computational biology and medicine. IEEE Trans Biomed Eng 58 (10), 2936–42.

Frangi, A. F., Hose, D., Hunter, P., Ayache, N., Brooks, D., 2013. Medical imaging and image computing in computational physiology. IEEE Trans Med Imaging 32 (1), 1–7.

Hu, Y., Ahmed, H. U., Taylor, Z. A., Allen, C., Emberton, M., Hawkes, D., Barratt, D., 2012. Mr to ultrasound registration for image-guided prostate interventions. Medical Image Analysis 16 (3), 687–703.

Ikram, M. A., van der Lugt, A., Niessen, W. J., Koudstaal, P. J., Krestin, G. P., Hofman, A., Bos, D., Vernooij, M. W., 2015. The Rotterdam Scan Study: design update 2016 and main findings. Eur J Epidemiol 30 (12), 1299–315.

Kansagra, A. P., Yu, J. P., Chatterjee, A., Lenchik, L., Chow, D. S., Prater, A., Yeh, J., Doshi, A., Hawkins, C. M., Heilbrun, M., Smith, S., Oselkin, M., Gupta, P. amd Ali, S., 2016. Big data and the future of radiology informatics. Acad Radiol 23 (1), 30–4249.

Kumar, V., Gu, Y., Basu, S., Berglund, A., Eschrich, S. A., Schabath, M. B., Forster, K., Aerts, H. J., Dekker, A., Fenstermacher, D., Goldgof, D. B., Hall, L. O., Lambin, P., Balagurunathan, Y., Gatenby, R. A., Gillies, R. J., 2012. Radiomics: the process and the challenges. Magn Reson Imaging 30 (9), 1234–48.

Larrabide, I., Aguilar, M. L., Morales, H. G., Geers, A. J., Kulcsar, Z., Rüfenacht, D., Frangi, A. F., 2013. Intra-aneurysmal pressure and flow changes induced by flow diverters: relation to aneurysm size and shape. AJNR Am J Neuroradiol 34 (4), 816–22.

Larrabide, I., Kim, M., Augsburger, L., Villa-Uriol, M. C., Rüfenacht, D., Frangi, A. F., 2012. Fast virtual deployment of self-expandable stents: method and in vitro evaluation for intracranial aneurysmal stenting. Med Image Anal 16 (3), 721–30.

Lekadir, K., Hazrati-Marangalou, J., Hoogendoorn, C., Taylor, Z. A., van Rietbergen, B., Frangi, A. F., 2015. Statistical estimation of femur micro-architecture using optimal shape and density predictors. J Biomech 48 (4), 598–603.

Lekadir, K., Noble, C., Hazrati-Marangalou, J., Hoogendoorn, C., van Rietbergen, B., Taylor, Z. A., Frangi, A. F., 2016. Patient-specific biomechanical modeling of bone strength using statistically-derived fabric tensors. Ann Biomed Eng 44 (1), 234–46.

Lekadir, K., Pashaei, A., Hoogendoorn, C., Pereanez, M., Alba, X., Frangi, A. F., 2014. Effect of statistically derived fiber models on the estimation of cardiac electrical activation. IEEE Trans Biomed Eng 61 (11), 2740–8.

Margolies, L. R., Pandey, G., Horowitz, E. R., Mendelson, D. S., 2016. Breast imaging in the era of big data: Structured reporting and data mining. AJR Am J Roentgenol 206 (2), 259–64.

Mattila, J., Koikkalainen, J., Virkki, A., Simonsen, A., van Gils, M., Waldemar, G., Soininen, H., Ltjnen, J., Alzheimers Disease Neuroimaging Initiative, 2011. A disease state fingerprint for evaluation of Alzheimer's disease. J Alzheimers Dis 27 (1), 163–76.

Medrano-Gracia, P., Cowan, B. R., Suinesiaputra, A., Young, A. A., 2015. Challenges of cardiac image analysis in large-scale population-based studies. Curr Cardiol Rep 17 (3), 563.

Miller, M. I., Trouv, A., Younes, L., 2015. Hamiltonian systems and optimal control in computational anatomy: 100 years since d'arcy thompson. Annu Rev Biomed Eng 17, 447–509.

Morales, H. G., Kim, M., Vivas, E. E., Villa-Uriol, M. C., Larrabide, I., Sola, T., Guimaraens, L., Frangi, A. F., 2011. How do coil configuration and packing density influence intra-aneurysmal hemodynamics? AJNR Am J Neuroradiol 32 (10), 1935–41.

Morales, H. G., Larrabide, I., Geers, A. J., San Romn, L., Blasco, J., Macho, J. M., Frangi, A. F., 2013. A virtual coiling technique for image-based aneurysm models by dynamic path planning. IEEE Trans Med Imaging 32 (1), 119–29.

Nørgaard, B. L., Leipsic, J., Koo, B. K., Zarins, C. K., Jensen, J. M., Sand, N. P., Taylor, C., 2016. Coronary computed tomography angiography derived fractional flow reserve and plaque stress. Curr Cardiovasc Imaging Rep 9 (2), in press.

Petersen, S. E., Matthews, P. M., Bamberg, F., Bluemke, D. A. ., Francis, J. M., Friedrich, M. G., Leeson, P., Nagel, E., Plein, S., Rademakers, F. E., Young, A. A., Garratt, S., Peakman, T., Sellors, J., Collins, R., Neubauer, S., 2013. Imaging in population science: cardiovascular magnetic resonance in 100,000 participants of UK Biobank - rationale, challenges and approaches. J Cardiovasc Magn Reson 28, 15–46.

Rowley, J., 2007. The wisdom hierarchy: representations of the DIKW hierarchy. Journal of Information Science 33 (2), 163–180.

Sarvazyan, A. P., Lizzi, F. L., Wells, P. N., 1991. A new philosophy of medical imaging. Med Hypotheses 36 (4), 327–35.

Schmidt-Richberg, A., Ledig, C., Guerrero, R., Molina-Abril, H., Frangi, A. F., Rueckert, D., Alzheimers Disease Neuroimaging Initiative., 2016. Learning biomarker models for progression estimation of alzheimer's disease. PLoS One 11 (4), e0153040.

Sharpe, J., 2011. Two ways to use imaging: focusing directly on mechanism, or indirectly via behaviour? Curr Opin Genet Dev 21 (5), 523–29.

Smith, N., de Vecchi, A., McCormick, M., Nordsletten, D., Camara, O., Frangi, A. F., Delingette, H., Sermesant, M., Relan, J., Ayache, N., Krueger, M. W., Schulze, W., Hose, R. D., Valverde, I., Beerbaum, P., Staicu, C., Siebes, M., Spaan, J., Hunter, P. J., Weese, J., Lehmann, H., Chapelle, D., Rezavi, R., 2011. euHeart: personalized and integrated cardiac care using patient-specific cardiovascular modelling. Interface Focus 1 (3), 349–64.

Viceconti, M., Henney, A., Morley-Fletcher, E., 2016. in silico Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. Research and Technological Development Roadmap, Avicenna Consortium, http://avicenna-isct.org/roadmap.

Villa-Uriol, M. C., Berti, G., Hose, D. R., Marzo, A., Chiarini, A., Penrose, J., Pozo, J. M., Schmidt, J. G. Singh, P., Lycett, R., Larrabide, I., Frangi, A. F., 2011. @neurIST complex information processing toolchain for the integrated management of cerebral aneurysms. Interface Focus 1 (3), 308–19.

Villa-Uriol, M. C., Larrabide, I., Pozo, J., Kim, M., Camara, O., De Craene, M., Zhang, C., Geers, A., Morales, H., Bogunovi, H., Cardenes, R., Frangi, A. F., 2010. Toward integrated management of cerebral aneurysms. Philos Trans A Math Phys Eng Sci 368 (1921), 2961–82.

Volzke, H., Schmidt, C. O., Hegenscheid, K., Kuhn, J.-P., Bamberg, F., Lieb, W., Kroemer, H. K., Hosten, N., Puls, R., 2012. Population imaging as valuable tool for personalized medicine. Clinical Pharmacology & Therapeutics 92 (4), 422–424.

York, T., McCann, H., Ozanyan, K. B., 2011. Agile sensing systems for tomography. IEEE Sensors Journal 11 (12), 3086–105.

Young, A. A., Frangi, A. F., 2009. Computational cardiac atlases: from patient to population and back. Exp Physiol 94 (5), 578–96.