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Editorial

Corresponding author
Mario Sansone, PhD
Assistant Professor
Department of Electrical Engineering and Information Technologies
University of Naples Federico II
Via Claudio 21, Naples 8013, Italy
E-mail: msansone@unina.it

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Bio-Mathematical Modelling in Tumor Evaluation *Via* Magnetic Resonance Imaging

Mario Sansone, PhD*

Department of Electrical Engineering and Information Technologies, University of Naples Federico II, Via Claudio 21, Naples 8013, Italy

In the last 25 years, within the field of tumor evaluation using magnetic resonance imaging (MRI), 2 main promising applications have emerged that can provide useful *functional* information beyond the morphological images: dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted imaging (DWI or DW-MRI). DCE-MRI involves the administration of a contrast medium that, flowing into the vascular network feeding the tumor, might give information on tissue vascular perfusion which is related to the *angiogenesis* phenomenon, in turn associated to tumor growth. DWI exploits the water brownian motion that is affected by tissue cellularity and vascularization. The successful application of both DCE-MRI and DWI lays strongly on both technical MRI improvements achieved in the last decades and on adequate bio-mathematical modelling of tissues. In this editorial, I will briefly discuss a few main issues of both applications focussing on bio-mathematical modelling.

DCE-MRI

The main technical issues in DCE-MRI concern the trade-off between time-space resolution and accurate quantification of contrast medium concentration. They both affect the accuracy of bio-mathematical modelling typically used in DCE assessment of the tumor.

In the early years of DCE, radiologists mainly looked at the *shape* of the time-intensity curve of a single voxel or averaged regions of interest (ROIs); in fact, it had been observed that, after contrast medium administration, a typical aggressive (malignant) tumor showed a wash-in (absorption) and a wash-out (excretion) phase while a benign lesion showed a slow absorption rate. However, this type of analysis was strongly reader-dependent and did not allow to easily and quantitatively compare subsequent studies of the same subject or studies from different subjects. It was clear that a more quantitative approach was needed.

Several groups (Tofts et al[1], Larsson et al[2], Brix et al[3]) proposed to use bio-mathematical models to analyze DCE data. These early models are based mainly on tissue compartmentalization (plasma and extracellular compartments) and the interesting parameters are the kinetics constants of exchange across compartments that are related to the permeability of the vessel walls: in fact, immature, leaky vessels (quickly grown stimulated with the vascular endothelial growing factor (VEGF) by the tumor) should show a higher permeability.[4] However, these models are a strong simplification of reality because of limitation of the technical equipments available at that time. In fact, the need for high resolution images prevented fast acquisition of multiple series.

Today, a number of fast pulse sequences of acquisition give the possibility to use more realistic bio-mathematical models: different groups Koh et al[5], Schabel et al[6], Sourbron[7] have proposed more sophisticated models including some aspects not considered by the first generation models: the rough approximation of only 2 compartments within a voxel has been abandoned and a more realistic distribution of compartments is considered instead: moreover, capillary transit-time (the time required for a contrast medium particle to travel across a capillary) and vascular permeability are considered random variables with a certain distribution

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within the voxel (region) of interest.

The complexity of the model and the measurement uncertainty pose some limits in the evaluation of the kinetics parameters (permeability, vascular fraction, transit time, etc.): the accuracy (repeatability) with which these parameters can be evaluated is intrinsically limited by mathematical constraints.[8] Moreover, accurate measurement of the contrast medium concentration within the voxel is still an issue because fast pulse sequences can overcome the time-space resolution trade-off but typically introduce some additional uncertainty in the measurement.[9]

Therefore, it is important for the radiologists evaluating the parametric maps to be supported by specialised professionals (such as biomedical engineers) in the interpretation of these maps in order to take into account the quality of the map reconstruction.

DWI

DWI was born for brain perfusion assessment[10] (and has quickly evolved leading to the tractography[11] that is not considered further here) and has been quickly becoming an important tool for the evaluation of tumors in other body parts such as prostate[12] and breast.[13] The diffusion of water (brownian motion) has been studied by many physicists among which Einstein gave an important contribution: in fact, considering the diffusion as a random process he established the relation between the *diffusion constant*, the time of observation and the path of a water particle. Diffusion within biological tissues depends on tissue organization: in order to evaluate whether there are some preferred directions of motion, the concept of *diffusion tensor imaging* (roughly, diffusion constants along 3 orthogonal directions) has been introduced.[14]

During DWI acquisition random moving spins are affected by magnetic gradients in such a way that fast diffusing water molecules contribute to attenuate the signal from a specific voxel. The magnetic gradients parameters are called b-values. In this way, qualitative maps can be obtained in which voxels with fast diffusing water are represented by darker colors.[15] However, this type of images give information on the apparent diffusion coefficient (ADC) because true molecular water diffusion is restricted and hindered by vascular tortuosity.

To overcome this issue, the first bio-mathematical model of water diffusion within biological tissues has been developed by Le Bihan et al[16] in the late 1980's. This model, called intra-voxel-incoherent-motion (IVIM), again considered the tissues within a voxel as organized in compartments (capillaries and extracellular space). In this model the interesting quantities are the vascular fraction, the water diffusion constant and the pseudo-diffusion constant. This latter has been introduced to account for the *random* orientation of vessels in tissues.

As in the case of DCE-MRI, also in the case of DW-MRI the quantitative analysis is limited by mathematical constraints. Specifically, the b-values used in DW acquisition strongly affect the accuracy of parameters estimation. Very sophisticated solutions have been proposed in the field of tractography[14]; moreover, some studies have been performed in the field of tumor evaluation[17]; however, this issue is still under debate and no definitive solution is currently available.

Finally, a very interesting issue is the link between the different models. As the mentioned models describe different measurements of related quantities (liquid flow and diffusion across compartments within tissues) it seems not unreasonable that model parameters should be related across different models. A link between perfusion and IVIM models was first suggested theoretically by Le Bihan et al.[18] This link, if definitively shown, might be used to cross-validate DCE and DW studies and possibly to improve the accuracy of parametric maps. However, in the field of tumor studies, it seems that this issue has not been yet addressed specifically: a very small number of studies has been performed in this direction[13,19] but they did not show this link in a conclusive manner.

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