Estimation of Tumor Tracer Kinetics Employing a Novel Cross-Voxel Exchange Model

N. Sinno [1,2], E. Taylor [2], M. Milosevic [2,3], D. Jaffray [4], and C. Coolens [1,2,3]

1 The Institute of Biomaterials & Biomedical Engineering (IBBME), University of Toronto, Toronto, Canada

2 Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

3 Department of Radiation Oncology, University of Toronto, Toronto, Canada

4 University of Texas, MD Anderson Cancer Centre, Texas, USA

Institute of Biomaterials & Biomedical Engineering UNIVERSITY OF TORONTO

UHN Princess Margaret Cancer Centre

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EASTERN TIME [GMT-4]

INTRODUCTION

- Pharmacokinetic models, in conjunction with DCE-MRI, allow the estimation of transport properties of drugs in tumor tissue.

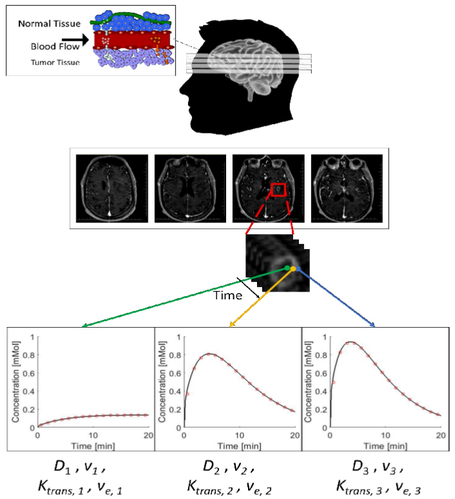

Figure 1: DCE-MRI and DCE-CT images are time-sequenced scans that record the extravasation of a CA from the intravascular network into the extravascular space. The change of tracer concentration over time is captured in an array of discrete elements, voxels.

- Drugs are transported to the tumor tissue via 3 mechanisms: diffusion, convection and extravasation.

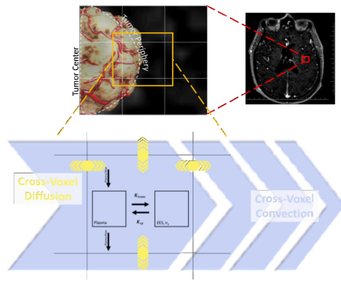

Figure 2: The variation of concentration in each voxel illustrates the exchange of tracer within a voxel (extravasation) as well as a cross-voxel exchange (convection and diffusion) in tumor tissue. The fitting of transport models to these time-concentration curves allows the quantification of transport parameters.

- Tofts Model (TM), most commonly used pharmacokinetic model. The application of TM assumes no cross-voxel transport of tracer leading to the misinterpretation of tracer perfusion in tumors[1,2].

AIM

- Develop the Cross-Voxel Exchange Model (CVXM) to describe extravascular diffusion and convection, in addition to the exchange of tracer between the blood vessels and tumor tissue.
- Investigate the impact of cross-voxel transport on the interpretation of Tofts' perfusion parameters using *in*-silico datasets.
- Test the feasibility of using CVXM in a practical setting. Derive transport parameters from DCE-MRI of a TS-415 human cervical carcinoma xenograft by using TM and CVXM.

MATHEMATICAL MODELLING

Development of the Cross-Voxel Exchange Model (CVXM)

$$\frac{\partial c(\boldsymbol{r},t)}{\partial t} + \nabla . \boldsymbol{j}(\boldsymbol{r},t) = \Lambda(\boldsymbol{r},t)$$

$$\boldsymbol{j}(\boldsymbol{r},t) = c(\boldsymbol{r},t)\boldsymbol{v}(\boldsymbol{r}) - \boldsymbol{D}\nabla c(\boldsymbol{r},t) \qquad \Lambda(\boldsymbol{r},t) = \boldsymbol{K_{ext}}(C_p(t) - c(\boldsymbol{r},t))$$

Convection Diffusion — Exchange blood vessels-tissue

c	local concentration of tracer in the extracellular extravascular space
C_p	concentration of the tracer in plasma
v	velocity of fluid flow in the tumor tissue
D	diffusivity of the tracer in the tumor tissue
K_{ext}	extravasation parameter function of the capillary permeability in at the boundary of capillaries (0 otherwise)

ABBREVIATIONS

CVXM	Cross-Voxel Exchange Model
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging
TM	Tofts Model

CONTACT INFORMATION

E-mail: noha.sinno@mail.utoronto.ca

IN-SILICO TESTING

- Simulations: Data generated using CVXM with varying diffusion, convection and extravasation parameters.

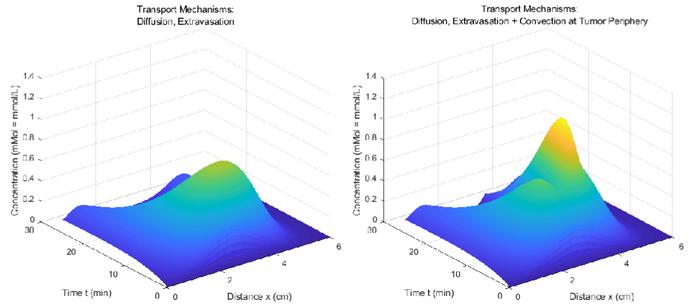

Figure 3: Numerical solutions of tissue concentration for Tissue Models.

- Fitting: TM fitted to the simulated data to produce an estimate of Tofts' perfusion parameters K_{trans} and v_e.

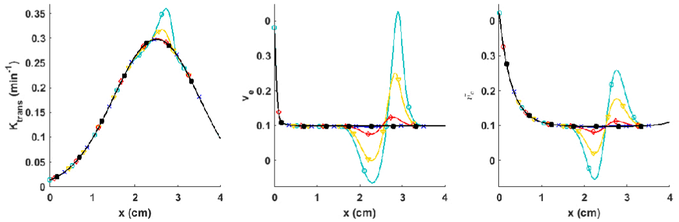

Figure 4: Results of fitting TM to the simulated data. Left: plots comparing the fitted K_{trans} profiles to the input parameters Kext (black line). Middle: corresponding plots of the fitted v_e profiles. Right: $\bar{v}_e$ plots generated using equation developed to predict the impact of cross-voxel transport on Tofts' v_e. Colors correspond to the fitting results of data simulated with varying velocity profiles with peak v = 0 (●), 0.1 (■), 1 (◊), 5 (△) and 10 (○) µm/s.

CONCLUSIONS

CVXM, paired with DCE-MRI, allows for a more accurate understanding of physical mechanisms driving tracer transport in the tumor microenvironment
»»» Better informed and more personalized treatment choices.

Tofts' extravasation parameters reflect the effects of inter-voxel diffusion and convection, even though TM does not include these effects (in-silico testing).

Fitting TM and CVXM to DCE-MRI data of TS-415 cervical carcinoma xenografts reveals that CVXM parameters are a more accurate representation of transport parameters in tumors.

PRE-CLINICAL TESTING

- Tumor Model: TS-415 human cervical carcinoma[3].
- Data Acquisition: DCE-MRI recorded using a 1.5-T whole body scanner (Signa, General Electric) over a period of 15 min[3].
- Model fitting: TM and CVXM fitted to DCE-MRI data to produce an estimate of TM and CVXM parameters.

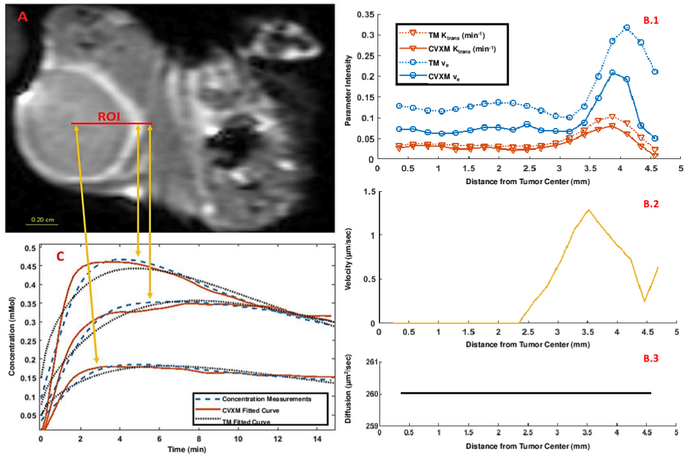

Figure 5: Transport parameters derived from DCE-MRI of a TS-415 human cervical carcinoma xenograft by using TM and CVXM.

ACKNOWLEDGEMENTS

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