Modeling the transport of molecules in the liver: application to dynamic MRI

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Hepatocarcinogenesis: liver cancer

► HepatoCellular Carcinoma (HCC): one of the most common malignant tumors worldwide (3/100000 in Europe and North America, \(\approx 30\times\) more in parts of Asia and Africa)

► Despite scientific advances in measurements for early HCC detection, patient survival has not improved significantly during the last three decades:

  ▶ Advanced stage of the disease at the time of diagnosis

  ▶ Limited therapeutic options: surgical interventions, percutaneous interventions, transarterial interventions, radiation therapy

► Earliest possible detection and characterization of the pathology: a crucial issue

► Need for an noninvasive tool able to detect small nodules and to characterize HCC
The need for a noninvasive imaging technique

Magnetic resonance imaging:
- Noninvasive (compared to a biopsy)
- Good spatial resolution
- High signal to noise ratio

Liver MRI:
- Lesion detection and characterization for diagnosis, chirurgical planning, treatment evaluation
- Improvement of detection and characterization by the use of contrast agents
The need for contrast agents

- After venous injection, MRI contrast agents increase or decrease the signal depending on:
  - Their nature
  - Their concentration
  - Their distribution
  - The applied sequence
  - The injection profile

Biomedical context
Clinical context

Modeling the transport of molecules in the liver: application to dynamic MRI
Physiological interpretation of MRI of the liver

- Clinical examinations ⇒ macroscopic detection and characterization of pathology
  - Image markers integrate lower level physiological parameters

- Interpretation depends on sets of parameters:
  - Physiological “parameters”
  - Physical parameters
  - Image features

Organ
Liver

Acquisition Modality
MRI

2D / 3D / t images

Characterization shape / function

Gd-BOPTA-enhanced T1W-GRE sequence
Arterial phase

Hepatobiliary phase

Dysplastic nodule DN

Poorly-differentiated HepatoCellular Carcinoma HCCp

Therapy ?

Detection / characterization of the pathological processes ?

Modeling the transport of molecules in the liver: application to dynamic MRI
Proposed approach: model-based approach

Modeling the transport of molecules in the liver: application to dynamic MRI
Macroscopic model of the liver

2 main components:

► **Tissue:**
Macro-functional units (MFUs) distributed in the 3D liver envelope

► 1 MFU:
∈ a class → physiological characteristics
(birth/death probability, blood flow, pressure…)

► Possibility to define several regions (with different vascular properties) → ≠ classes of MFUs

► **Blood:** 3D vascular network which consists of 3 trees:

► hepatic artery
► portal vein
► hepatic vein

Supplying vessels
The distribution of molecules in the liver model is described by its concentration, at each time:

- In all vessels
- In all MFUs

The terminal branches of each vascular tree are connected at the level of a MFU:

- **inputs** = concentrations $C$ and flows $F$ in hepatic arteriole and portal venule
- **outputs** = concentration $C$ and flow $F$ in hepatic venule
Propagatin in the vessels

- Concentration computation in each vessel of the vascular trees:
  - arterial-like tree
    \[ C_B(t) = C_{O1}(t + \Delta t_1) = C_{O2}(t + \Delta t_2) \]
  - venous-like tree
    \[ C_B(t) = \frac{F_1 C_{I1}(t - \Delta t_1) + F_2 C_{I1}(t - \Delta t_2)}{F_1 + F_2} \]

- Crossing time:
  \[ \Delta t = \frac{\pi r^2 l}{F} \]
  \( l \) radius
  \( l \) length
  \( F \) vessel geometrical characteristics
  Blood flow

Modeling the transport of molecules in the liver: application to dynamic MRI
Multiscale model of dynamic MRI of the liver

Model of the propagation of extracellular MRI contrast agents

Propagation in the tissue (MFU)

► MFU: structurally considered as a hepatic lobule

► Lobule = functional unit of the liver

► Portal tracts (triades) = a portal venule + a hepatic arteriole + a bile duct

► Capillary network (sinusoids): exchange between the portal triades and the centro-lobular vein (hepatic vein)
Propagation in the tissue (MFU)

Compartmental description

- Hepatic arteriole
- Portale venule
- Plasma (Sinusoids)
- Space of Disse (Extracellular extravascular space)
- Hepatocyte (hepatic cell)
- Bile canaliculus

Modeling the transport of molecules in the liver: application to dynamic MRI
Propagatin in the tissue (MFU)

- Transport of extracellular molecules

- No cellular uptake \(\Rightarrow\) no biliary excretion

- Model \(\Leftrightarrow\) 2-compartment model
  - Dual arterio-portal input and hepatic venous output
  - Two exchanging regions: sinusoids and space of Disse
Multi-scale model of dynamic MRI of the liver: Application to dynamic MRI

Propagation in the tissue (MFU)

- Model parametrization

- Each compartment is characterized by:
  - its concentration \( C \)
  - its volume \( V \)
  - its dispersion coefficient \( D \) (axial diffusion)

- Transcapillary fluid flux, \( J_v \), and solute flux, \( J_s \), exchanges occur through the fenestrated endothelium (sinusoidal wall)
Model of transcapillary exchange: coupled solute-solvant exchange

- **Fluid exchange:** Starling hypothesis
  Filtration through a vessel wall depends on an equilibrium between hydrostatic $\Delta p$ and osmotic $\Delta \pi$ pressure gradients through the membrane.

- **Solute exchange:** Patlak equation
  Combination of a diffusive term which depends on a concentration gradient through the membrane, and a convective one.

- **Pore model for transcapillary exchange**
  - Endothelial membrane of liver sinusoids = porous membrane

- **Pore $k$ (small pore, large pore, fenestration):** defined by transport parameters:
  \[
  \begin{align*}
  &\text{Hydraulic conductivity} \\
  &\text{Permeability} \\
  &\text{Reflection coefficient}
  \end{align*}
  \Rightarrow PS
  \]

Membrane

Diagram: Pore, Molecule, Membrane.
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Multiscale model of dynamic MRI of the liver

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Propagatin in the tissue (MFU)

► Pore model for transcapillary exchange
  ► Endothelial membrane of liver sinusoids = porous membrane

► Pore \( k \) (\textit{small pore, large pore, fenestration}): defined by transport parameters:

\[
\begin{align*}
L_k &= \left( \frac{A_k}{S_p \Delta r} \right) \frac{r_k^2}{8 \eta} \\
P_k &= \left( \frac{A_k}{S_p \Delta r} \right) D \phi F(\alpha_k) \left[ 1 + 9 \alpha^{5.5} (1 - \alpha^5)^{0.02} \right] \\
\sigma_k &= 1 - \left[ 1 - (1 - \phi)^2 \right] G(\alpha_k) + 2\alpha^2 \phi F(\alpha_k)
\end{align*}
\]

\[\Rightarrow PS\]
Model equations: 2 approaches

- Compartmental approach*:
  - Compartments = well-stirred tanks
  - Instantaneously filled

  \[
  \begin{align*}
  V_p \frac{dC_p(t)}{dt} &= (F_{ha} + F_{pv})(C_{in}(t) - C_p(t)) - S_p J_s(t) \\
  V_d \frac{dC_d(t)}{dt} &= S_p J_s(t)
  \end{align*}
  \]

  \[
  C_{in}(t) = \frac{F_{ha} C_{ha}(t) + F_{pv} C_{pv}(t)}{F_{ha} + F_{pv}}
  \]

- Distributed approach:
  - Axially distributed (along the capillary length)
  ⇒ allows for concentration gradients

  \[
  \begin{align*}
  V_p \frac{\partial C_p(t, x)}{\partial t} &= -(F_{ha} + F_{pv}) L \frac{\partial C_p(t, x)}{\partial x} - S_p J_s(t, x) + V_p D_p \frac{\partial^2 C_p(t, x)}{\partial x^2} \\
  V_d \frac{\partial C_d(t, x)}{\partial t} &= S_p J_s(t, x) + V_d D_d \frac{\partial^2 C_d(t, x)}{\partial x^2}
  \end{align*}
  \]

* Mescam et al. *Contrast Media & Molecular Imaging* 2007
Multiscale model of dynamic MRI of the liver

Model of the propagation of extracellular MRI contrast agents

Propagation in the tissue (MFU)

Mean concentration (in each MFU)

- Compartmental approach:

\[ C_{tissue}(t) = \frac{V_p C_p(t) + V_d C_d(t)}{V_p + V_d} \]

- Distributed approach:

\[ C_{tissue}(t) = \frac{V_p \int_0^L C_p(t, x) \, dx + V_d \int_0^L C_d(t, x) \, dx}{L(V_p + V_d)} \]

Reasonable inflows and dispersion

Better fit of the real physiology with the distributed model

Modeling the transport of molecules in the liver: application to dynamic MRI
MRI Simulator

▶ MRI simulator: SIMRI

H. Benoit-Cattin, G. Collewet, B. Belaroussi, H. Saint-Jalmes and C. Odet
The SIMRI project: a versatile and interactive MRI simulator.

- Virtual object: \(N(H), T1, T2\)
- Magnetization computation kernel
- \(k\) space (RF signals)
- MRI Sequence
  - RF pulse
  - Gradient
  - Precession
  - Acquisition
- Noise filtering
- Reconstruction algorithm
- MR Image
3D input object

- Intrinsic $T1$ and $T2$ relaxation times and proton density $N(H)$ for each MFU and each vessel
- Post-injection $T1$, $T2$ and $N(H)$:
  \[ R1, 2_{post} = R1, 2_{pre} + r_{1,2}C(t) \]
  \[ T1, 2 = 1/R1, 2 \]

- Voxel sampling → blood and tissue proportions $\alpha$ and $\beta$
- Post-injection $T1$, $T2$ and $N(H)$ 3D maps

\[ T1, 2_{voxel} = \frac{\alpha T1, 2_{blood} + \beta T1, 2_{liver}}{\alpha + \beta} \]
\[ N(H)_{voxel} = \frac{\alpha N(H)_{blood} + \beta N(H)_{liver}}{\alpha + \beta} \]

Modeling the transport of molecules in the liver: application to dynamic MRI
Analysis of simulated MR Images of the liver

Biomedical context

Clinical context
Problematic
Proposed approach

Multiscale model of dynamic MRI of the liver

Macroscopic model of the hepatic vascular network
Model of the propagation of extracellular MRI contrast agents
Model of MRI acquisition

Analysis of simulated MR images of the liver

Visual analysis
Sensitivity analysis
Texture analysis

Conclusion and future prospects
Simulation of MR images

- Simulation of tumor generation
  - at the macroscopic scale: hypervascularized region
    \textit{Exp: growth of new arterial vessels (neoangiogenesis)}
  - at the microscopic scale:
    - modification of $F_{ha}$ and $F_{pv}$
    - modification of PS (by changing the size and density of pores)
    \textit{Ex: inhibition of the portal inflow}

- Simulation of the propagation of a contrast agent
  - Model of a particular contrast agent, defined by its size and molecular diffusion
    \textit{Ex: Gd-DOTA (Dotarem\textsuperscript{®}, Guerbet, France)}

- Simulation of an MRI sequence
  \textit{Ex: T1-weighted fast gradient echo ($T_E$=1.36 ms, $T_R$=2.75 ms, $\theta$=10°)}
Comparison simulated/real images

► HCCp
(poorly-differentiated HCC)

► No portal supply
► High arterial supply
► Weak permeability
(no fenestrations on capillaries)

► Coherent contrast
tumor/normal tissue

► Arterial phase
  → hyperintense tumor
► Portal phase
  → ≈ isointense tumor

Simulated
Real
(CHU Pontchaillou)

Arterial Phase (24 sec)
Portal Phase (50 sec)
Sensitivity analysis method

- **Modification of pathological markers**
  - Arterial inflow $F_{ha}$
    - $F_{ha} \downarrow$
    - $F_{pv} = 0$
  - Hypervascularized “pseudo-tumor”

- **Vascular permeability: permeability-surface area product PS**
  - Variation of small, large pores and fenestrations density on capillary membrane
  - Estimation of the corresponding PS

- **Sensitivity of the mean signal**
  - ROI in the *tumoral* and in the *normal* tissues
  - Analysis of the mean signal
Study of pathological markers

- Study of the influence of the arterial inflow
  - at arterial phase:

\[
R_C = \frac{C_{tumoral}}{C_{normal}}
\]

\[
R_S = \frac{S_{tumoral}}{S_{normal}}
\]

\[\text{Isointensity threshold} \]

Modeling the transport of molecules in the liver: application to dynamic MRI
**Application to the hepatocarcinogenesis**

► HCC development: simultaneous modifications of several physiological parameters:

- Fha
- Fpv
- PS

Arterialization phenomena

Capillarization phenomena

► Simulation results

- Linear relationship intensity-Fha
- Increased arterialization if Fpv diminishes
- Linear relationship intensity-PS

**Fha:** paramount influence on the contrast at arterial phase
Texture analysis procedure

- Same acquisition parameters and simulation conditions as for the sensitivity analysis

- Increasing arterial inflow $F_{ha}$

- ROI on tumor

- Texture analysis (statistical methods) with MaZda software

M. Strzelecki, A. Materka, and P. Szczypinski

MaZda.

Analysis of simulated MR Images of the liver

Evolution of statistical features with the arterial inflow

- Co-occurrence matrix-based features
- Run-length matrix-based features

- Co-occurrence matrix-based features
- Run-length matrix-based features

\[ Fha \xrightarrow{ \Rightarrow } \text{Heterogeneity} \]
Conclusion

- Multiscale model of hepatic perfusion
  - Coupling of an existing macroscopic model with an axially distributed PBPK model of hepatic microvascularization
  - Simulation of pathological situations related to hepatocarcinogenesis
  - Simulation of MRI contrast agents propagation

- Model of dynamic MRI
  - Coupling of the multiscale model of contrast agent propagation to an MRI simulator
  - Simulation of MR images of HCC-liver at typical enhancement phases after media injection
  - Analysis of the multiscale model through a sensitivity analysis to pathological indicators

- A step towards a better understanding of MRI of the HCC
  - Underlying the existence of relationships between structural features in arterial-phase MR images and physiological parameters such as the arterial flow

- New model of hepatobiliary transport → MRI contrast agents diversity
Perspectives

► Improvement of the model at all levels, especially at the microscopic scale:
  ► Addition of new compartments to the PBPK model → simulation of other transport mechanisms
  ► Metabolism
  ► MRI simulation: integration of flux-related phenomena

► Deepening of texture analysis
  ► More samples
  ► Dynamic texture analysis: evolution of textural features with time
  ► Exploration of other methods (wavelet-based, fractals…)

► Coupling of the hepatobiliary transport model to the macroscopic model
  ► Possibility to simulate Gd-BOPTA-enhanced MRI
  ► Possibility to simulate a wide range of contrast agents and to a larger extent, therapeutic molecules
  ► Promising advances in pharmaceutical sciences (molecular design, etc)

► Important identification step at all levels
  ► By mathematical methods
  ► Through *in vivo* and experimental studies