Modelling of Patient-Specific Liver Vasculature and Sorafenib Pharmacokinetics in Hepatocellular Carcinoma

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Introduction

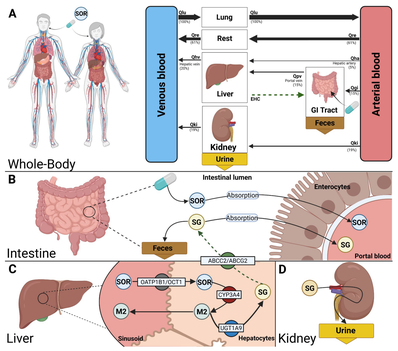
Liver cancer is the second leading cause of cancer-related deaths. Despite the various therapeutic options for hepatocellular carcinoma (HCC) treatment, selecting patient-specific therapy remains challenging. A major challenge is **predicting the distribution and heterogeneity of anti-cancer medication** in the liver due to factors such as liver anatomy, vascular topology, perfusion and tumour location.

Aim & Methods

To apply a recently published algorithm [1] to generate vessel trees within a defined liver volume and to model the **spatio-temporal pharmacokinetics** of the multi-kinase inhibitor sorafenib (NEXAVAR®) within the liver.

Steps:

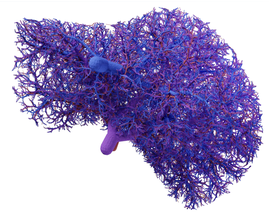
- Generation of **physiologically realistic** arterial, portal, venous, and biliary vessel trees in a given liver volume.
- Development of a mechanistic **pharmacokinetic model** for substance transport in these trees.
- Accessing **computational performance** of the model.
- **Coupling** of this model with a physiologically based pharmacokinetic (PBPK) model of sorafenib.
- Simulation of **drug concentration dynamics** within the whole body model



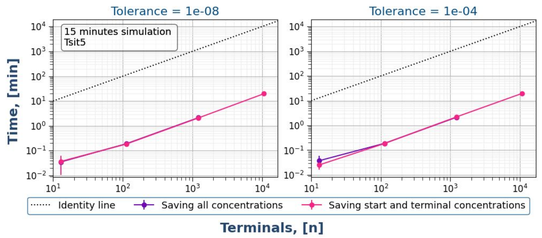
PBPK model of sorafenib. *SOR - sorafenib, M2 - sorafenib N-oxide M2, SG - sorafenib N-oxide glucuronide, EHC - enterohepatic circulation [2].*

Results

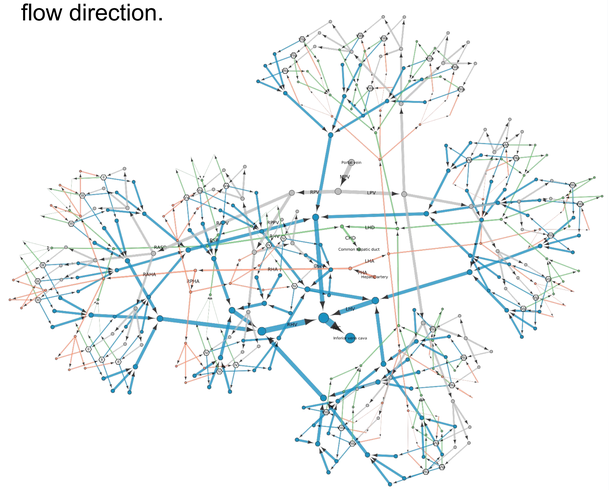
- Generated system of three vascular trees (arterial, portal, and venous) in the liver volume with the **fixed positions of their main branches.**



- Time needed to simulate pharmacokinetics of the drug along one vessel tree depending on the size of the tree.
- It takes less than 2 minutes to simulate 15-minutes pharmacokinetics along the tree with more than 100 bifurcations.



- Representation of the arterial, portal, venous vascular, and biliary duct trees as a **system of interconnected nodes**, where each node represents a bifurcation and their connections - vessels/ducts. Arrows show the flow direction.



Simulations of drug transport along arterial, portal, venous vascular, and biliary duct trees in a given liver volume.

- Simulations show small **topological heterogeneity** of the drug concentration in the liver tissue and the difference in it's half-life in bile and venous plasma (Fig. 1A).
- Decrease in total liver blood flow leads to the significantly **increased exposure** of the drug, while increase in its value does not have such an influence, possible because the model tends to **overpredict** the velocity of drug pharmacokinetics (Fig. 1B).

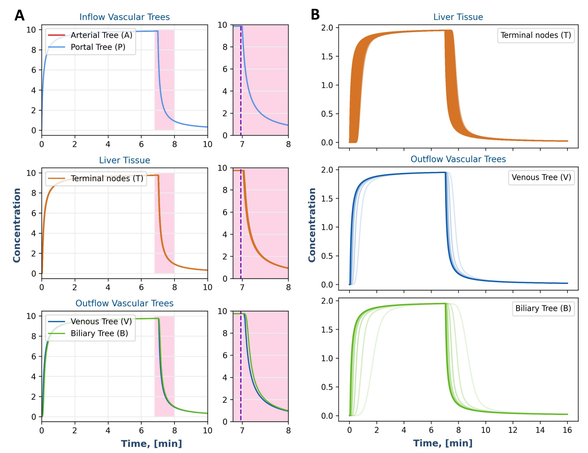


Fig.1 A) *Comparison of the drug concentration and its half-life in the hepatic artery (arterial tree), portal vein (portal tree), liver tissue (terminal nodes), hepatic vein (venous tree) and common bile duct (biliary tree). Administration of the drug was simulated so its pharmacokinetic profiles in the inflow vascular trees were the same.* ***B)*** *Dependence of the drug concentration on the value of total liver flow, where increase in transparency of the color indicate decrease in value. The flow was changed between the 6% and 400% from the normal value. Drug was simulated only in hepatic artery, in portal vein its concentration was fixed on zero. Simulations were done in the system with 1000 terminal nodes.*

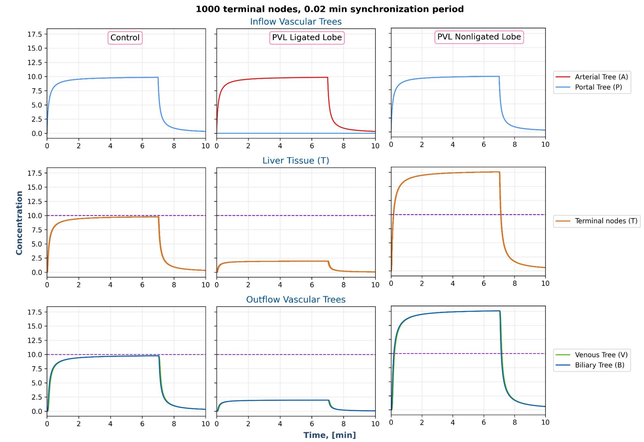


Fig. 2 *Comparison of the concentration of the drug in the hepatic artery (arterial tree), portal vein (portal tree), liver tissue (terminal nodes), hepatic vein (venous tree) and common bile duct (biliary tree) in control system and after portal vein ligation (PVL). Administration of the drug was simulated so its pharmacokinetic profiles in the inflow vascular trees in control system were the same. Synchronization period - period over which concentrations in all trees were synchronized.*

- Simulations confirm the relative significant decrease in concentration of the drug after portal vein ligation in the ligated lobe and increase in it in the non-ligated lobe (Fig. 2).
- The following is explained by the changes in the liver blood flow in the corresponding lobes.

Outlook

- Coupling of this model with a physiologically based pharmacokinetic (PBPK) model of sorafenib.
- Simulation of drug concentration dynamics within the whole body model.

Conclusions

The established workflow for simulating the spatial distribution and heterogeneity of anti-cancer medication provides a basis for the following research, including coupling with sorafenib PBPK model and can provide important information for **individual HCC treatment planning**.

References

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[2] Okibedi Frances, & König, Matthias. (2023). Physiologically based pharmacokinetic (PBPK) model of sorafenib. Zenodo. https://doi.org/10.5281/zenodo.10432855

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