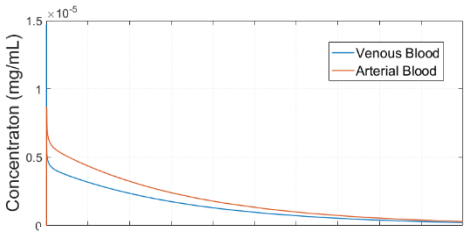
Whole-Body Mathematical Models of Synthetic Biosensing Liposomes: An Application for the Prevention of Metastasis

Tanishq Abraham[1] and Cheemeng Tan[1]
[1]University of California, Davis, Davis, CA

Introduction: Circulating tumor cells (CTCs) cause metastasis, which is responsible for over 90% of cancer deaths. To prevent metastasis, it is proposed that liposomes could be used for drug delivery to the CTCs. To maximize the efficiency of drug delivery, it is important to tune the physicochemical parameters of liposomes to optimize the bioavailability of the encapsulated drug. Along this line, mathematical models are commonly used in *a priori* modeling and design of liposomes, focusing primarily on transport of drugs within a single organ. However, whole-body pharmacokinetic models for liposomes are currently lacking. Here, we formulate three universal whole-body physiologically-based pharmacokinetic models (WPBPK) for various liposome sizes and transport processes and validate them with experimental data. Based on the WPBPK model, we further investigate a unique approach to prevent metastasis using liposome-based multifunctional artificial cells, and establish the feasibility and efficacy of the artificial-cell-based approach when compared to state-of-the-art approaches.

Materials and Methods: We implement three WPBPK models, to describe the liposome bioavailability. All models are mass-balance ODEs of liposome concentration in organ compartments. The first two models are blood-flow limited models of small unilamellar liposomes (SUVs), and large unilamellar liposomes (LUVs), respectively. The third model simulates dynamics of SUVs by incorporating transvascular transport. A mathematical whole-body model for circulating tumor cells are developed using similar principles as the WPBPK models. Literature data are used to fit CTC-specific parameters. The two models are combined, and a binding reaction between the CTCs and the liposomes are incorporated with a simple kinetic rate constant. It is assumed that the liposomes have an anti-EpCAM antibody on their surface that binds to the CTCs.

a) b) c)



Sensitivities

RES Clearance	Liver Clearance
-3.61E-3	-3.54E-3

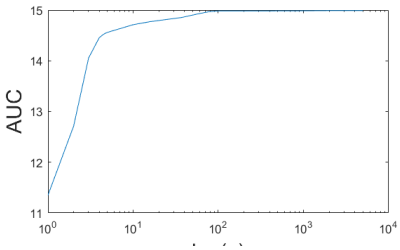


Figure 1: a) Concentration profiles of liposome in Venous and Arterial Blood for the SUV model. b) Sensitivity Analysis of liposome concentration in Venous Blood, with clearances as inputs. c) Log plot of area-under-the-curve (AUC) vs liposome size for complex SUV model ("a" represents radius of liposome).

Results and Discussion: The concentration profiles of the liposomes in venous and arterial blood show that the circulation time of the liposomes is about 10 hours (Fig 1a). The liposome concentration in venous blood is slightly more sensitive to reticuloendothelial (RES) clearance than liver clearance (Fig. 1b). In addition, the SUV model with transvascular and lymphatic transport shows that larger liposome size increases the bioavailability of liposomes (reported as area-under-the-curve, Fig. 3). The combined CTC-liposome model shows efficient capture of the liposomes with the CTCs. Artificial cells could therefore be used to capture and destroy circulating tumor cells.

Conclusion: This work is important for whole-body mathematical modeling of liposomes *a priori*, especially for other applications of liposomes apart from tumor drug delivery. This work also provides a platform to develop a model for liposomes and CTCs from experimental data. The results of this work provide an analysis of the effect of the liposome size and the vascular physiology of the tissues on biodistribution of liposomes. The CTC-liposome model shows that liposomes can bind to many of the CTCs in circulation. The engineering design establishes a foundation toward the implementation of multi-functional artificial cells that attack and provide therapeutics to the primary tumor, as well as prevent metastasis by destroying circulating tumor cells.