**Supplementary File**

**Drug Delivery through Nanoparticles in Solid Tumors: A Mechanistic Understanding**

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| **Table S1.** A summary of mathematical modeling studies on drug-loaded nanoparticles delivery to solid tumors. | | | | |
| **Authors /**  **Date** | **Main idea** | **Method** | **Results** | **Shortcomings** |
| El-Kareh and Secomb [1] / 2000 | Comparison between the efficacy of different infusion routes for both free DOX and DOX-loaded TSL | A PK/PD model | - Smaller administration duration may improve treatment efficacy;  - Cellular pharmacokinetics determines the optimum administration duration;  - Effectiveness of release rate of drug from non-TSLs. | -Spatial distribution was not taken into account. |
| Zhang et al. [2] / 2009 | Spatiotemporal investigation of drug distributions in a liposome-mediated drug delivery system. | A 2D-0D\* model & finite element method | - Free drug diffusion is an effective parameter in delivery of drug in comparison with liposomes;  - Necrosis of tumor cells can significantly affect the drug penetration. | -Normal tissue was not considered. |
| Hendricks et al. [3] / 2012 | Investigating the effects of tumor- and drug-related parameters in a liposome-mediated DOX delivery system. | A PK model | - There is a regimen in which both liposomal and traditional DOX deliver similar DOX amounts into cancerous cell;  - High variability of liposome PKs and tumor deposition. | -Spatial drug distribution was not taken into account. |
| Chauhan et al. [4] / 2012 | Impact of blood vessel normalization in improving drug delivery | A 2D-1D model & finite element method | - Smaller size of vessel-wall pores after vascular normalization decreases the tumor’s IFP values.  - NPs with smaller size show better penetration into the tumor. | - Mass transport model didn’t consider the drug binding and internalization. |
| Gasselhuber et al. [5] / 2012 | Studying drug distribution in conventional chemotherapy comparing with the results of drug delivery using thermosensitive and stealth liposomes. | A PK model | - Although compared with the free form of Dox, the stealth-DOX show high concentration profile in tumor, but the bioavailability is limited to a minor fraction;  - Release time constant’s optimal value is calculated for free and encapsulated forms of DOX. | - Spatial drug distribution was not taken into account |
| Zhan and Xu [6] / 2013 | DOX- TSL delivery | A 2D-0D model & finite element method | - Comparisons between continuous and bolus injections;  - Thermosensitive liposome encapsulated DOX delivery has better performance compared to free DOX injection in terms of reducing drug concentration in normal tissue and increasing peak intracellular drug concentration in tumor tissue. | - Just one size of nanoparticles was studied;  - Tumor shape and size were fixed. |
| Stylianopoulos et al. [7] / 2013 | Modeling of drug delivery using nanoparticles considering the electrostatic effects. | A 2D-1D model & finite element method | - Minor influence of electrostatic repulsion on the capillary exchange of nanoparticles.  - Electrostatic attraction can double the nanoparticle’s transvascular flux.  - A significant increase in trans-capillary transport for specific range of charge density of each NP’s size. | - Mass transport model didn’t consider the drug binding and internalization.  - Shape and size of tumor were fixed. |
| Stylianopoulos et al [8] / 2015 | Studying multistage drug delivery system using nanoparticles considering drug characteristics effects. | A 2D-1D tumor model &  finite element method | - Regulating the binding affinity and release rate constants of drug lead to enhanced drug transport.  - Nanoparticles with smaller size show better efficacy compared to nanoparticles with larger sizes. | - Tumor shape and size were fixed. |
| Chou et al. [9] / 2017 | Drug delivery and cumulative concentration investigation in a solid tumor. | A 2D-0D tumor model &  finite element method | - There is a limited concentration of drugs for nanoparticles and chemotherapeutic drugs in the necrotic area.  - NP as antitumor drug carrier has lower side effects and higher treatment efficiency compared with chemotherapeutic agents. | - Mass transport model didn’t consider the drug binding and internalization. Tumor shape and size were fixed. |
| Zhan and Wang [10] / 2018 | Investigating the effects of convention on the delivery of DOX using a liposome-mediated drug delivery system for the treatment of brain tumors. | A 3D-0D model & finite volume method | - Drug penetration and accumulation can be enhanced by using liposomes.  - The relation between the release-rate of drug and the effective delivery volume is nonlinear. | - Tumor shape and size were fixed. |
| Huang et al. [11] / 2019 | Spatiotemporal investigation of drug delivery using thermosensitive liposomes. | A PK/PD model | - Identification of the best parameter set is convoluted due to the intricate relationship between the associated factors (drug type, time of heating and rate of release) and the projected therapy outcome.  - Low rate of drug release in normal body temperature leads to the best treatment outcome. Also, for mild hyperthermia one hour heating post injection, moderate to high rate of drug release would have the best result. | - Spatial drug distribution was not taken into account  - Tumor shape and size were fixed. |
| Rezaeian et al. [12] / 2019 | IP administration of DOX-loaded TSL with the triggered release by HIFU. | A 2D-0D tumor model &  finite element method | - TSL-DOX transport has more effectiveness than the conventional method.  - The vessel wall permeability is a decisive factor for modifying the TSL size.  - Better treatment results using small size thermosensitive liposomes.  - TSL-DOX shows less advantages in small size tumors. | -Details of drug-related parameters were not investigated.  - Tumor shape was fixed. |
| Wirthl et al. [13] / 2020 | Investigating nanoparticle transport using a multi-phase model of tumor growth. | A 2D-0D tumor model &  finite element method | - Investigating the properties and the constraints of nanoparticle transport to solid tumors. | - Equations of drug delivery are not examined. |
| Dogra et al. [14] / 2020 | Investigating the effective parameters on low delivery of NP to tumor and high off-target accumulation of NPs using Sensitivity analysis. | Physiologically based PK model | - Kinetics of nanoparticles are related to the viscosity of blood, size of nanoparticles, tumor vascular fraction, and porosity of tumor vessels. | -Simulation was conducted ignoring the binding affinity and cellular uptake. |
| Moradi Kashkooli et al. [15] / 2021 | Influence of one-stage and two-stage delivery of drug-loaded NPs | 2D-2D & finite element method | - Continuous and low release rate of drugs from nanoparticles leads to higher therapeutic efficiency.  - In multi-stage drug delivery system, there is a different preference in release rates of the drug and secondary particle for different values of binding affinities. For the intermediate and higher binding affinities, in contrast to the lower binding affinities, higher release rate of the secondary particle, and lower release rate of the drug shows a better efficiency. | - Just two sizes of NPs and three rates of binding were studied for both one-stage and two-stage NPs.  - Tumor shape and size were fixed. |
| Soltani et al. [16] / 2021 | Influence of hypoxia and NP size on drug delivery | 2D-0D & finite element method | - NPs with smaller sizes are more effective;  - Hypoxic area in solid tumors hinders the cell killing in the tumor. | - Just three sizes of NPs were studied.  - Tumor shape and size were fixed. |
| \* 2-dimensional and 0-dimensional (avascular) tumor’s geometry and microvascular network are represented by 2D and 0D, respectively.  NP =Nanoparticle, IP=Intraperitoneal, TSL=Thermosensitive liposome, DOX= Doxorubicine | | | | |

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| **Table S2.** Parameters of interstitial fluid flow used in numerical modeling [15,17,18] | | |
| **Parameter** | **Definition** | **Value (tissue type)** |
|  | Oncotic pressure of microvessels | 20 [mmHg] (Normal tissue)  20 [mmHg] (Tumor) |
|  | Oncotic pressure of interstitial fluid | 10 [mmHg] (Normal tissue)  15 [mmHg] (Tumor) |
| *σs* | Osmotic reflection coefficient | 0.91 [-] (Normal tissue)  0.82 [-] (Tumor) |
|  | Hydraulic conductivity of microvessels wall | 0.36*×10-7* [cm/((mmHg)\*s)] (Normal tissue)  2.8*×10*-7 [cm/((mmHg)\*s)] (Tumor) |
| *L*pL(*S/V*)L | Filtration coefficient of lymph system | 1.33*×10*-5 [cm/((mmHg)\*s)] (Normal tissue)  0 [cm/((mmHg)\*s)] (Tumor) |
|  | Hydraulic conductivity of tissue interstitium | 8.53*×10*-9 [cm2/(mmHg\*s)] (Normal tissue)  4.13*×10*-8 [cm2/(mmHg\*s)] (Tumor) |
| PL | Hydrostatic pressure of lymph vessels | 0 [Pa] |

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| **Table S3.** Parameters for drug DOX used in numerical modeling [15,19-21] | | |
| **Parameter** | **Definition** | **Value (tissue type)** |
| *D* | Diffusion coefficient | 1.58*×10*-10 (Normal tissue) [m2/s]  3.40*×10*-10 (Tumor) [m2/s] |
| *P* | Permeability of microvessels | 3.75*×10*-7 (Normal tissue) [m/s]  3.00*×10*-6 (Tumor) [m/s] |
| *σf* | Filtration reflection coefficient | 0.35 [-] |
| KON | Binding coefficient | 1.5 and 15 [m3/(mole s)] |
| KOFF | Unbinding coefficient | 8*×10*-3 [1/s] |
| KINT | Internalization coefficient | 5*×10*-5 [1/s] |
| *φ* | Volume fraction of tumor accessible to drugs | 0.4 [-] |
| Crec | Cell-surface receptors’ concentration | 1*×10*-5 [M] |
| *ω* | Constant in Eq. (10) | 0.6603 [m3/mole] |

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| **Table S4.** Parameters for drug-loaded NPs (baseline state for 20 nm particles and 200 nm VWP size) [15,23-25] | | |
| **Parameters** | **Definition** | **Value** |
| *D* | Diffusion coefficient | 7*×10*-12 [m2/s] |
| Kel | Release rate of drug from carrier | 1*×10*-3 [s-1] |
| Kd | Blood circulation time | 1320 [min] |
| *α* | Number of therapeutic agents in carrier | 20 [-] |
| *φ* | Volume fraction of tumor accessible to drugs | 0.05 [-] |

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| **Table S5.** Parameters used in NP-related calculations [15, 22, 26, 27] | | |
| **Parameter** | **Definition** | **Value** |
| *L* | Thickness of microvessel wall | 5×10−6 [m] |
| *T* | Absolute temperature | 310[K] |
| *η* | Viscosity of water at 310K | 7×10−4 [Pa∙s] |
| *γ* | Fraction of vessel-wall surface area occupied by pores | 1×10−4 [-] |
| *a*1 | Coefficient for *Kt* | -73/60 [-] |
| *a*2 | Coefficient for *Kt* | 77.293/50.400 [-] |
| *a*3 | Coefficient for *Kt* | -22.5083 [-] |
| *a*4 | Coefficient for *Kt* | -5.617 [-] |
| *a*5 | Coefficient for *Kt* | -0.3363 [-] |
| *a*6 | Coefficient for *Kt* | -1.216 [-] |
| *a*7 | Coefficient for *Kt* | 1.647 [-] |
| *b*1 | Coefficient for *Ks* | 7/60 [-] |
| *b*2 | Coefficient for *Ks* | -2.227/50.400 [-] |
| *b*3 | Coefficient for *Ks* | 4.0180 [-] |
| *b*4 | Coefficient for *Ks* | -3.9788 [-] |
| *b*5 | Coefficient for *Ks* | -1.9215 [-] |
| *b*6 | Coefficient for *Ks* | 4.392 [-] |
| *b*7 | Coefficient for *Ks* | 5.006 [-] |