**Supplementary File**

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

Farshad Moradi Kashkooli, Mohsen Rezaeian, M. Soltani

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| (a) Tumor shapes | (b) BCs |
| **Fig. S1.** Different shapes of tumor considered in the present study along with BCs | |

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| (a) IFV and IFP distribution |
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| (b) Concentration-time distribution |
| **Fig. S2.** Distribution of (a) IFV and IFP (b) Concentration-time |

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| **Fig. S3.** FKCs over time for different sizes of tumor for NSDDS |

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| **Fig. S4.** FKCs over time for different shapes of tumor for NSDDS |

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| **Fig. S5.** Effect of NP size on FKCs |

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| **Fig. S6.** Effect of binding affinity on FKCs |

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| **Fig. S7.** Effect of release rate of drug on FKCs |

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| (a) ψ = 0.1 | (b) ψ = 0.2 | (c) ψ =0.5 | (d) ψ =1 |
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| (e) ψ = 2 | (f) ψ = 5 | (g) ψ = 10 | |
| **Fig. S8.** 2D maps of IFP for the different tumor shapes | | | |

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| (a) ψ = 0.1 | (b) ψ = 0.2 | (c) ψ =0.5 | (d) ψ =1 |
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| (e) ψ = 2 | (f) ψ = 5 | (g) ψ = 10 | |
| **Fig. S9.** 2D maps of IFV for the different tumor shapes | | | |

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| (a) ψ = 0.1 | (b) ψ = 0.2 | (c) ψ =0.5 | (d) ψ =1 |
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| (e) ψ = 2 | (f) ψ = 5 | (g) ψ = 10 | |
| **Fig. S10.** 2D maps of drug concentration for the different tumor shapes | | | |

**References**

[1] El-Kareh AW, Secomb TW. A Mathematical Model for comparison of bolus injection, continuous infusion, and liposomal delivery of doxorubicin to tumor cells. *Neoplasia* 2, 325 (2000).

[2] Zhang A, Mi X, Yang G, Xu LX. Numerical study of thermally targeted liposomal drug delivery in tumor. *J. heat transfer* 131(4), 043209 (2009).

[3] Hendriks BS, Reynolds JG, Klinz SG, Geretti E, Lee H, Leonard SC, et al. Multiscale kinetic modeling of liposomal doxorubicin delivery quantifies the role of tumor and drug-specific parameters in local delivery to tumors. *CPT Pharmacometrics Syst. Pharmacol.* 1(11), e15 (2012).

[4] Chauhan VP, Stylianopoulos T, Martin JD, Popović Z, Chen O, Kamoun WS, et al. Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner. *Nat. Nanotechnol.* 7, 383–388 (2012).

[5] Gasselhuber A, Dreher MR, Rattay F, Wood BJ, Haemmerich D. Comparison of conventional chemotherapy, stealth liposomes and temperature-sensitive liposomes in a mathematical model. *PlOS One* 7(10), e47453 (2012).

[6] Zhan W, Xu XY. A Mathematical model for thermosensitive liposomal delivery of doxorubicin to solid tumour. *J. Drug Deliv.*  172529 (2013).

[7] Stylianopoulos T, Soteriou K, Fukumura D, Jain RK. Cationic nanoparticles have superior transvascular flux into solid tumors: Insights from a mathematical model. *Ann. Biomed. Eng.* 41, 68–77 (2013).

[8] Stylianopoulos T, Economides E-A, Baish JW, Fukumura D, Jain RK. Towards optimal design of cancer nanomedicines: Multi-stage nanoparticles for the treatment of solid tumors. *Ann. Biomed. Eng*. 43, 2291–300 (2015).

[9] Chou C-Y, Chang W-I, Horng T-L, Lin W-L. Numerical modeling of nanodrug distribution in tumors with heterogeneous vasculature. *PlOS One* 12, e0189802 (2017).

[10] Zhan W, Wang C-H. Convection enhanced delivery of liposome encapsulated doxorubicin for brain tumour therapy. *J. Controlled Release* (2018) 285:212–29.

[11] Huang Y, Gu B, Liu C, Stebbing J, Gedroyc W, Thanou M, et al. Thermosensitive liposome-mediated drug delivery in chemotherapy: Mathematical modelling for spatio-temporal drug distribution and model-based optimisation. *Pharmaceutics* 11(12), 637 (2019).

[12] Rezaeian M, Sedaghatkish A, Soltani M. Numerical modeling of high-intensity focused ultrasound-mediated intraperitoneal delivery of thermosensitive liposomal doxorubicin for cancer chemotherapy. *Drug Delivery* 26, 898–917 (2019).

[13] Wirthl B, Kremheller J, Schrefler BA, Wall WA. Extension of a multiphase tumour growth model to Study Nanoparticle Delivery to Solid Tumours. *PlOS One* 15(2), e0228443 (2020).

[14] Dogra P, Butner JD, Ramírez JR, Chuang Y-L, Noureddine A, Brinker CJ, et al. A mathematical model for nanomedicine pharmacokinetics and tumor delivery. *Comput. Struct. Biotechnol. J.*  18, 518–531 (2020).

[15] Moradi Kashkooli F, Soltani M., Momeni M.M., Rahmim A. Enhanced drug delivery to solid tumors via drug-loaded nanocarriers: An image-based computational framework. Front. Oncol. 11, 655781 (2021).

[16] Soltani M, Souri M, Moradi Kashkooli F. Effects of hypoxia and nanocarrier size on pH-responsive nano-delivery system to solid tumors. Sci. Rep. 11, 19350 (2021).

[17] Soltani M, Chen P. Numerical modeling of fluid flow in solid tumors. PLoS ONE 6, 1-15 (2011).

[18] Mpekris F, Baish JW, Stylianopoulos T et al. Role of vascular normalization in benefit from metronomic chemotherapy. PNAS 114, 1994–1999 (2017).

[19] Chou CY, Chang WI, Horng TL et al. Numerical modeling of nanodrug distribution in tumors with heterogeneous vasculature. PLoS ONE 12, e0189802 (2017).

[20] Eikenberry S. A tumor cord model for Doxorubicin delivery and dose optimization in solid tumors. Theor. Biol. Med. Model. 6, 16 (2009).

[21] Moradi Kashkooli F, Soltani M, Hamedi MH. Drug delivery to solid tumors with heterogeneous microvascular networks: Novel insights from image-based numerical modeling. Eur. J. Pharm. Sci. 151, 105399 (2020).

[22] Mpekris F, Angeli S, Pirentis AP et al. Stress-mediated progression of solid tumors: effect of mechanical stress on tissue oxygenation, cancer cell proliferation, and drug delivery. Biomech Model Mechanobiol. 14, 1391–1402 (2015).

[23] Chauhan VP, Stylianopoulos T, Martin JD et al. Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner. Nat. Nanotechnol. 7, 383–388 (2012).

[24] Stylianopoulos T, Economides EA, Baish JW et al. Towards optimal design of cancer nanomedicines: multi-stage nanoparticles for the treatment of solid tumors. Ann. Biomed. Eng. 43, 2291–2300 (2015).

[25] Stylianopoulos T, Jain RK. Combining two strategies to improve perfusion and drug delivery in solid tumors. PNAS 110, 18632–18637 (2013).

[26] Stylianopoulos T, Soteriou K, Fukumura D et al. Cationic nanoparticles have superior transvascular flux into solid tumors: insights from a mathematical model. Ann. Biomed. Eng. 41, 68–77 (2013).

[27] Deen WM. Hindered transport of large molecules in liquid-filled pores. AIChE J. 33, 1409–1425 (1987).