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M. Kokkolaras

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GERAD HEC Montréal
3000, chemin de la Côte-Sainte-Catherine
Montréal (Québec) Canada H3T 2A7

Tél. : 514 340-6053
Téléc. : 514 340-5665
info@gerad.ca
www.gerad.ca

A dual nanoparticle delivery strategy for enhancing drug distribution in cancerous tissue

Ibrahim M. Chamseddine [a, b]
Michael Kokkolaras [a, c]

[a] *Systems Optimization Lab, Department of Mechanical Engineering, McGill University, Montréal (Québec) Canada, H3A 0C3*

[b] *H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA*

[c] *GERAD, Montréal (Québec), Canada, H3T 2A7*

michael.kokkolaras@mcgill.ca

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Abstract: Nanoparticle-mediated drug delivery may be a promising alternative to traditional chemotherapy of high systemic toxicity. Tumor tissue architecture poses a challenge to delivery of nanoparticles. Small and spherical nanoparticles have poor adherence to the tumor vasculature, while larger and more eccentric ones create high heterogeneity in tissue-to-drug exposure. In previous work, we quantified these tradeoffs using numerical optimization. In this study, we demonstrate that simultaneous delivery of multiple nanoparticle designs can enhance drug distribution in the cancerous tissue without compromising nanoparticle tumoral accumulation. We formulate and solve optimization problems to find the optimal constituent of the heterogenous injection in terms of nanoparticle design diversity that increases drug distribution by 14%.

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Nomenclature	
a	Nanoparticle major axis
AR	Nanoparticle aspect ratio
$c(\mathbf{x})$	Spatial distribution of drug concentration in tumor
D_d	Effective diffusion coefficient of drug in tumor
$\delta_e q$	Equilibrium separation distance between a nanoparticle and vessel wall
η	Nanoparticle delivery efficiency
$\mathbf{J}_{NP}$	Flux of nanoparticles entering the tissue from the blood
K_a^0	Ligand receptor affinity under zero external force
ℓ	Vector of vessels' lengths
λ_p	Area fraction of tumor regions that receive drug greater than or equal to the effective dose (this quantity is used as surrogate to the negative of tissue proliferation rate)
M	Molar mass of drug
m_l	Surface density of ligands
m_r	Surface density of receptors
m_{10}	Mass of drug encapsulated in 10 billion nanoparticles
$\dot{N}_{in}$	Nanoparticles inlet flow rate
R	Vector of vessels' radii
σ	Oxygen and nutrients concentration
τ	Wall shear stress in blood vessels
U_∞	Blood speed in parent vessel
$\%wt$	Nanoparticle drug-loading capacity
Quantities with a star superscript denote optimal values	

1 Introduction

Nanoparticle drug delivery can improve pharmacokinetic measurements of anticancer agents as compared to intravenous free drug injection [1]. The biodistribution of nanoparticles and their adherence to tumors are related to their structural design [2]. For this reason, experimental and computational studies to understand the effect of nanoparticle size and shape have preceded clinical applications in an attempt to find the optimal nanoparticle biophysical properties. Many nanomedicines have been approved to treat subtypes of breast, ovarian, blood, bone-marrow, lymphatic, pancreatic, and lung cancers; and others are currently under clinical trails to treat a wider range of tumors [3].

It has been shown that nanoparticle accumulation and distribution has a competing effect [4, 5]. Large oblate nanoparticles accumulate in high percentages at the tumor margin. In contrast, small spherical nanoparticles have better spatial distribution but weaker adherence properties. In previous work [4], we have quantified the tradeoff between maximizing nanoparticle accumulation and spatial distribution by means of numerical optimization. The obtained Pareto set motivated us to examine strategies that consider multiple nanoparticle designs.

While nanoparticle accumulation could be maximized drug distribution was limited. Therefore, the objective in this work is to develop a nanoparticle delivery protocol that increases drug distribution (λ_p). Simply injecting higher doses of nanoparticles designed to maximizes λ_p may not be optimal as i) it increases toxicity caused by the nanoparticles that escape the tumor and ii) reduces nanoparticle accerss to certain vasculature regions (less area is available for new nanoparticles to bound).

The combination of multiple drugs is a common practice in chemotherapy. An increase in therapeutic potential can result from combining two or more drugs in the same injection. For example, doxorubicin is combined with cyclophosphamide to treat breast cancer in what is known clinically as the AC regimen [6]. The synergy resulted from cocktail chemotherapy has also been benefiting the field of nanotherapy; nanoparticles encapsulating many types of drugs showed enhanced therapeutic performance in treating solid tumors [7, 8, 9, 10, 11, 12]. However, combining multiple nanoparticle sizes and shapes in the same injection has not been investigated. In this paper, we propose injecting a mixture of nanoparticles with different designs as a new protocol with the potential of outperforming homogeneous nanoparticle injections.

2 Computational model

A computational model is used to evaluate the flow and accumulation of nanoparticles in the tumor vessels as well as drug transport in the tumor tissue. The model was developed in previous work [4] and was validated by comparing its results against experimental results reported in [13, 14]. It is composed of 4 submodels as shown in Figure 1.

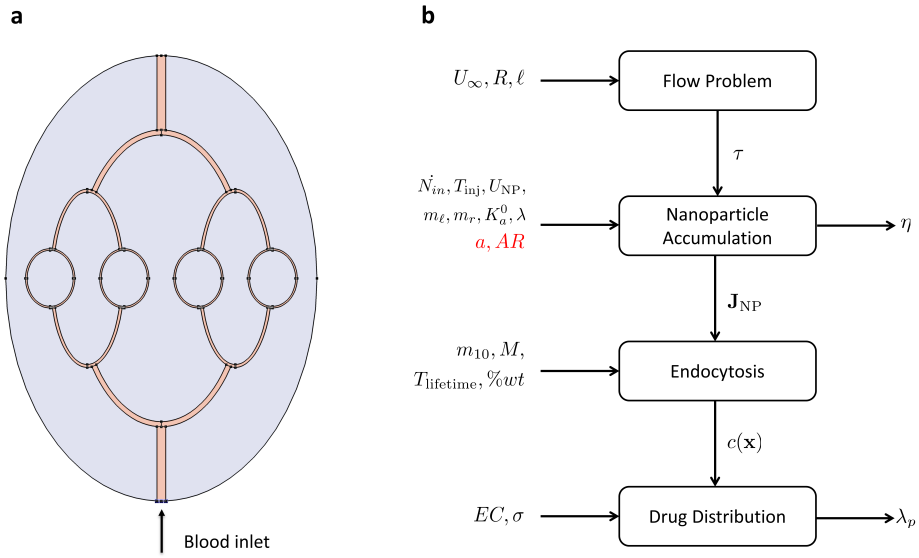

Figure 1: Tumor analysis model. (a) Tumor tissue represented as a 2D vascularized ellipsoid. Epithelial cells and extracellular matrix are shown in grey and blood vessels in red. Nanoparticles are injected at the blood inlet at the bottom of the tumor. (b) Interactions among different submodels as described in [4].

The *Flow Problem* solves the Navier-Stokes equations and the continuity equation with constant inlet speed boundary condition taking into consideration non-Newtonian fluid properties. The submodel parameters were calibrated to physiological values reported in [15].

The obtained wall shear stress is then fed as an input together with other quantities including nanoparticle geometry (e.g., size and aspect ratio) and chemical properties (e.g., ligand density and receptor-ligand affinity) into the *Nanoparticle Accumulation* subproblem that estimates the number of nanoparticles adhering to each tumor vessel.

Nanoparticles at the endothelium release drugs that internalize to the tumor cells through the process of *Endocytosis*. A reaction-diffusion equation is solved using Neumann boundary conditions modeling the flux of drugs leaving the blood stream to compute the temporal-spatial distribution of drugs in the cancerous tissue.

Lastly, in the *Drug Distribution* subproblem, we determine regions where apoptosis starts when drug concentration exceeds a certain value that depends on the drug potency. We then evaluate λ_p as the ratio of the tumor dead area to the total tumor area. More details on the modeling process and its parameter values can be found in [4].

3 Multiobjective optimization approach

The model output η and λ_p quantifies toxicological and therapeutic performance of the nanotherapy, respectively. In [4], we formulated the bi-objective optimization problem

$$\begin{array}{ll} \max\limits_{a,AR} & [\eta, \lambda_p] \\ \text{subject to} & 10 \leq a \leq 1000 \text{ (nm)} \\ & 1 \leq AR \leq 10 \end{array} \tag{1}$$

to determine the set of Pareto-optimal solutions (nanoparticle size and aspect ratio) that quantify the tradeoff between the two competing objectives. Only one of these Pareto-optimal solutions ($a = 553$ nm and $AR = 5$) maximizes λ_p, and the corresponding maximum value is 54.7%.

In what follows, we attempt to further increase λ_p through a heterogeneous injection of nanoparticles that differ in their design. We first investigate a mixture of two types of nanoparticles, and then increase the diversity of the dose until we reach a plateau in maximizing λ_p.

4 Dual nanoparticle delivery

We consider a 1:1 regimen of two types of nanoparticles: NP1 and NP2 with the designs $x_1 = [a_1, AR_1]^T$ and $x_2 = [a_2, AR_2]^T$ respectively. Nanoparticles of different designs flow in the blood at different speeds, and thus may adhere to tumor vessels subsequently. We define the sequential optimization framework of Figure 2 to explore whether the distribution of faster nanoparticles affects the optimal design of the successor; and if so, to determine the optimal design of both nanoparticles in an integrated fashion. The first optimization problem determines the optimal distribution of NP1 by computing $x_1^\star$ that maximizes λ_p. Then, information about the distribution of NP1 (i.e., the optimal design of NP1, the number N_1 of NP1 bounding to the endothelium, and the area A_{occ_1} of tumor vessels occupied by NP1), is used by the second optimization problem to determine the optimal design of NP2. If the solution of the sequential optimization framework yields $x_1^\star \neq x_2^\star$, then dual delivery enhances λ_p. Otherwise, the optimization problem converges to the homogeneous injection; i.e., $x_1^\star = x_2^\star$.

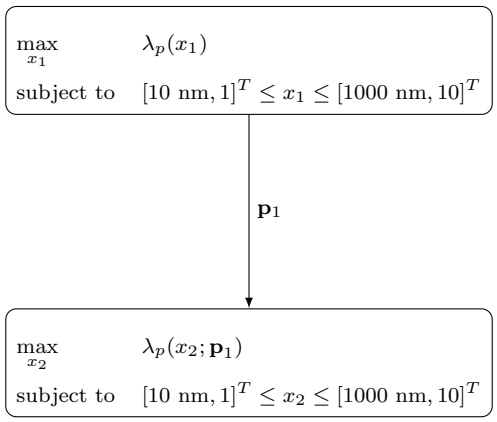

Figure 2: Sequential optimization framework developed for the design of dual nanoparticle delivery. The parameter $\mathbf{p}_1$ is a set that combines x_1, N_1, and A_{occ_1}, which is used in the second optimization problem.

Both optimization problems in Figure 2 are solved using the derivative-free Mesh Adaptive Direct Search (MADS) algorithm [16], which is implemented in the NOMAD software package [17]. Results show that $x_1^\star = [553nm, 5]^T$ (confirming the λ_p maximizer of the previously obtained set of Pareto-optimal solutions) and $x_2^\star = [37 \text{ nm}, 9.31]^T$, indicating that injecting a heterogeneous mixture of 1:1 large ellipsoidal nanoparticles and small more eccentric ones yields higher λ_p than the homogeneous injection. The performance of dual delivery is benchmarked against homogeneous injection to quantify the increment in λ_p. We define:

- **Reg1:** a homogeneous injection formed of the maximizer of λ_p.
- **Reg2:** a dual injection formed of the optimal solutions of the sequential problem in Figure 2.

The values of λ_p referring to both regimens are shown in Figure 3. In the homogeneous injection, the second segment of nanoparticles distributes in the same fashion as the first segment because they have identical designs. The result is a small increase in λ_p. In dual delivery, the second segment is designed to complement the existing distribution of NP1, and thus yields higher increase in λ_p. The tumor areas subject to apoptosis using Reg1 and Reg2 are shown in Figure 3a and 3b, respectively. The enhancement in dead area is shaded in red in 3c.

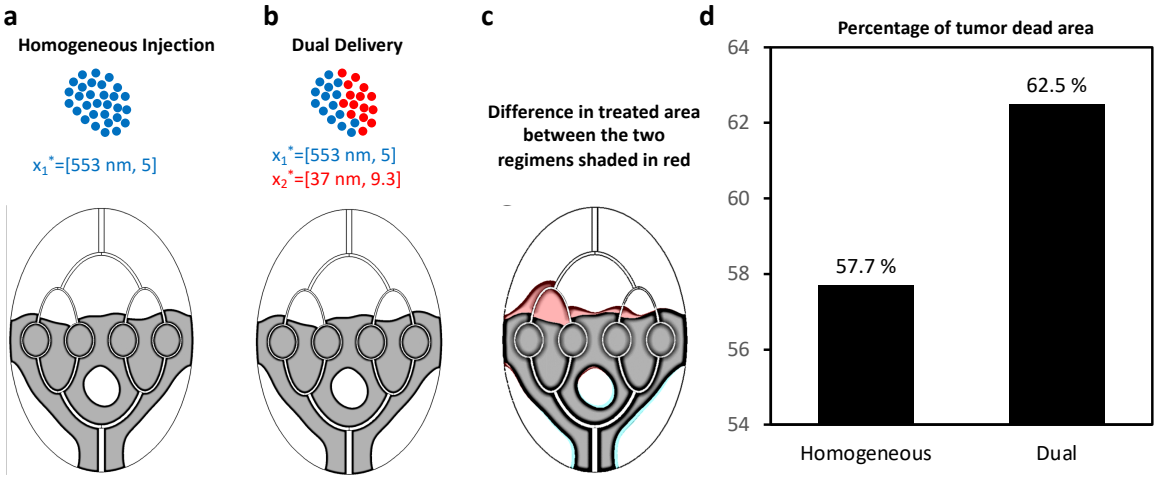

Figure 3: Effect of dual nanoparticle delivery on λ_p. Illustration of the regimen, optimal designs of nanoparticles and tumor dead area (in gray) of (a) homogenous injection, (b) dual delivery. (c) Increase in tumor dead area resulting from dual delivery is shaded in red. (d) values of λ_p using the two types of regimens.

5 Multifarious nanoparticle delivery

The increase in drug distribution caused by dual nanoparticle delivery motivated us to explore more diversified treatment protocols. We formulated a set of optimization problems to quantify the increase in λ_p as the function of the number of nanoparticle types considered in the regimen. Algorithm 1 represents as a recursive implementation of the flowchart in Figure 2. We used it to determine the regimen that maximizes λ_p.

Algorithm 1 Optimizing a cocktail injection of nanoparticles

$L_b = [10 \text{ nm}, 1]^T$ {specify the lower bound of all nanoparticle designs}
$U_b = [1000 \text{ nm}, 10]^T$ {specify the upper bound of all nanoparticle designs}
$A_{occ} = \mathbf{0}$ {initialize the area of tumor vessels occupied by NPs as zero vector}
$N_{avb} = \mathbf{0}$ {initialize the number of NPs available at tumor vessels as zero vector}
$x_1^\star = [553, 5]^T$ {computed in section 3}
$i = \mathbf{2}$ {dummy variable representing the number of nanoparticle types}
while λ_p is increasing by more than 1% **do**
  $x_i^\star \in argmax\left(\lambda_p\left(x_i; A_{occ}, N_{avb}, x_1^\star, \cdots, x_{i-1}^\star\right)\right)$
  $A_{occ} = A_{occ} + A_{occ_i}$
  $N_{avb} = N_{avb} + N_{avb_i}$
  $i = i + 1$
end while
return λ_p

Algorithm 1 terminates after the third iteration when the increase in λ_p becomes less than 1%. The change in λ_p as the function of number of nanoparticle designs considered is shown in Figure 4d. The dead tumor area is demonstrated in Figure 4a-c.

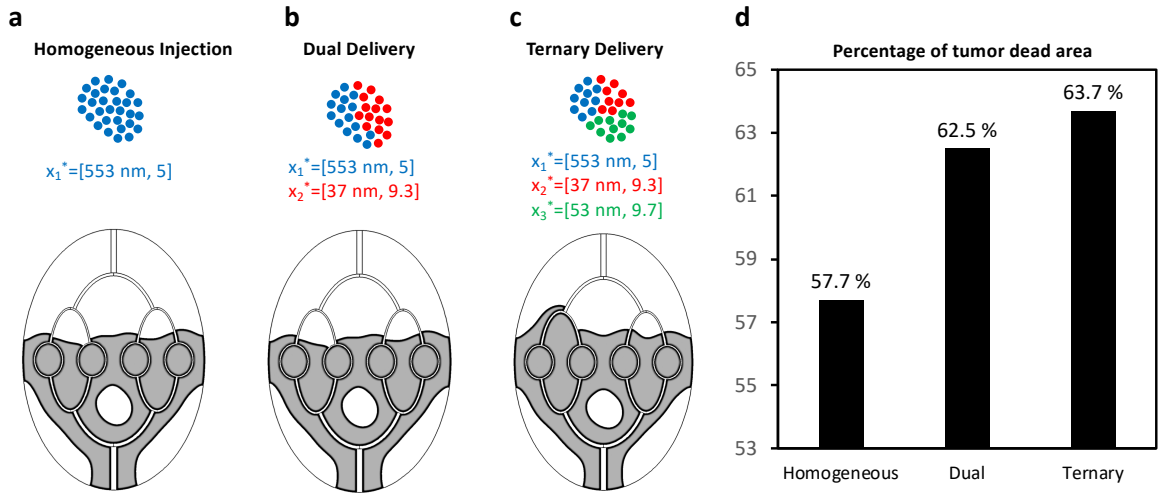

Figure 4: Effect of cocktail nanoparticle delivery on λ_p. Illustration of the regimen, optimal designs of nanoparticles and tumor dead area (in gray) of (a) homogenous injection, (b) dual delivery (c) ternary delivery. (d) values of λ_p using the three types of regimens.

6 Homogeneous versus heterogeneous injections

In this section, we determine how many homogeneous segments of nanoparticles are needed to reach the value of λ_p that corresponds to the cocktail nanoparticles delivery. In other words, we want to plot λ_p as a function of homogeneous segments and heterogeneous segments, and investigate if the two curves intersect. This analysis provides an insight on the saving in total drug usage caused by heterogeneous nanoparticle injection. To compute this savings, we implement Algorithm 1 with the following modifications: refer to the returned λ_p as λ_{p_2}, compute $\lambda_{p_1} = f\left(A_{occ}, N_{avb}, x_1^\star\right)$ at each iteration, and set the termination criteria to $\lambda_{p_1} = \lambda_{p_2}$.

The value of λ_{p_1} stayed below λ_{p_2} even after 10 iterations (Figure 5). Therefore, the homogeneous injection does not provide the same antitumor activity as heterogeneous injection unless a very large number of nanoparticles are used, which creates a toxicological risk. This solidifies our recommendation of using heterogeneous nanoparticle delivery as new nanotherapy protocol. The values of the optimal nanoparticle designs in each iteration as well as λ_{p_1} and λ_{p_2} are listed in Table 1. The objective function λ_{p_2} reaches its maximum value after 4 iterations.

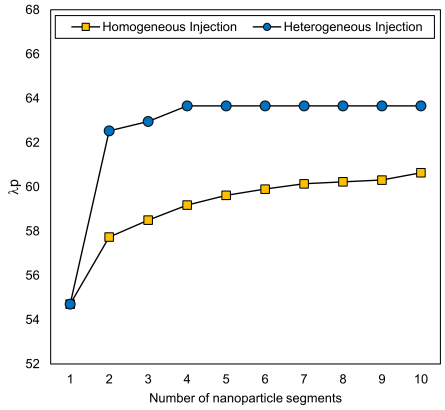

Figure 5: Comparison of homogeneous and heterogeneous injections in increasing λ_p

Table 1: Solution of the modified version of Algorithm 1 as described in section 6

Iteration	$\lambda_{p_1}(x_1^\star)$	$x_i^\star$	λ_{p_2}
1	54.7%	$[553\text{ nm}, 5]^T$	54.7%
2	57.73%	$[37\text{ nm}, 9.31]^T$	62.5%
3	58.5%	$[53\text{ nm}, 9.96]^T$	63%
4	59.2%	$[10\text{ nm}, 10]^T$	63.7%
5	59.6%	$[10\text{ nm}, 10]^T$	63.7%
6	59.9%	$[10\text{ nm}, 10]^T$	63.7%
7	60.1%	$[10\text{ nm}, 10]^T$	63.7%
8	60.2%	$[10\text{ nm}, 10]^T$	63.7%
9	60.3%	$[10\text{ nm}, 10]^T$	63.7%
10	60.6%	$[10\text{ nm}, 10]^T$	63.7%

7 Summary and conclusion

This study suggests a new nanoparticle delivery method that shows enhancement of drug distribution in cancerous tissues. It uses a heterogenous injection of nanoparticle designs as opposed to one nanoparticle design per injection of previous methods. We used numerical optimization to find nanoparticle sizes and aspect ratios that maximize the exposure of cells to cytotoxic drugs. We first considered an injection formed of two nanoparticle designs (dual delivery). We assumed that nanoparticle designs are equally present; i.e. the dual nanoparticle delivery is a 1:1 injection of two nanoparticle designs. The obtained optimal sizes and aspect ratios of the two nanoparticles were [553 nm, 5] and [37 nm, 9.31], leading to a 14.26% increase in the area exposed to anticancer drugs as compared to the homogenous injection.

We then expanded the optimization problem to consider an injection composed of 3 nanoparticle designs. The increase in drug distribution was only 0.5% from dual delivery. We further investigated more heterogenous mixtures consisting of up to 10 designs but a plateau in the drug distribution was noticed after two nanoparticles were considered, recommending the use of dual delivery. We also tried to compute the number of homogenous injections needed to cause the same drug distribution as dual delivery. Drug distribution reached only 60.6% even after 10 injections as opposed to 63.7% in dual delivery.

The multiple nanoparticle design drug delivery may have an important impact. The enhancement in drug distribution means that the same antitumor activity can be provided with lower drug dosages. Therefore, neoadjuvant therapies would require less treatment cycles to reduce tumor size before radical interventions. In addition, the proposed injection method may be suitable for aggressive tumors. Due to the increase in treatment efficacy from the enhanced drug distribution, tumors would undergo faster regression and possibly avoid invasion to nearby tissues and lymph nodes. Moreover, the results suggest that dual nanoparticle delivery would promote metronomic schedules as an alternative to MTD (Maximal Tolerate Dose) due to the enhanced drug distribution, thus slowing down the evolution of resistant cells.

This paper provides a proof of concept that using a heterogeneous injection composed of multiple nanoparticles designs would lead to a better drug distribution than limiting the injection to a single nanoparticle design. The dual nanoparticle delivery provided the largest increase in tumor area exposed to drugs. It should be noted that the tumor under consideration is small, and nanoparticles with high dosage might have aggregated in some vessels in large amounts. For larger more realistic tumors, a high drug distribution may be induced by regimens that involve more than two types of nanoparticles. Nevertheless, our optimization approach can be easily adapted to consider larger tumors that could benefit from more diversified protocols. In addition, the optimization approach presented here could benefit the design of multiple therapeutic and diagnostic nanosystems that have proven to enhance tumor targeting.

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