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Mathematical Modeling of Drug Delivery via Nanoparticles in Cancer Treatment

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Cancer is a complex and heterogeneous disease. Despite all efforts to fight cancer, it continues to impact every segment of society. For example, many patients fail conventional cancer therapies, including chemotherapy, radiation, and surgery; and it is still difficult for physicians to predict a treatment outcome with certainty. Indeed, cancer treatment efficacy depends on the concentration of the drug that reaches the tumor and the particular effectiveness of the drug against the tumor. Once drugs are delivered into the blood stream, they encounter diffusion barriers, which are physiological obstructions that prevent drugs from reaching the tumor. If adequate amounts of drug reached the tumor mass, the goal of successfully delivering chemotherapy to kill enough cells to shrink or eradicate a tumor would likely be realized. We thus hypothesize that if drugs can be delivered to the site of the tumor in sufficient concentration (e.g., through nanoparticles that can temporarily stay in the tumor vasculature), then the drugs should perform as expected, as is the case in monolayers where diffusion barriers do not exist. Here, we introduce and discuss a combined mathematical modeling and experimental approach to understand drug delivery and predict chemotherapeutic outcomes based on physical parameters.

Physical transport barriers in cancer treatment

In treating cancer with different forms of therapies based on drugs, including chemotherapy, targeted therapy, as well as immunotherapy, a critical problem that oncologists face is the dissimilar results of tests performed in laboratories on monolayers of cancer cells in petri dishes versus treatments performed in live patients or on laboratory animals. Various cancer-fighting drugs exhibit highly effective results when delivered to monolayers, but they underperform *in vivo* as well as in patients. We believe accurately describing and modeling drug transport across diffusion barriers will lead to breakthroughs for chemotherapy, even on so-called resistant cell lines, which show far less resistance when diffusions barriers are minimized.

The physical properties of a tumor's microenvironment influence a drug's ability to penetrate and kill tumor cells. Some of these properties can be potential obstructions to drug diffusion, increasing the tumor's resistance to chemotherapy. As previously reported, these barriers include overexpression of protein efflux pumps, cell growth cycles, acidosis, hypoxia, tissue density, high interstitial fluid pressure, and electrostatic

charge. We argue that diffusion barriers may be another main cause for a tumor's ability to be drug resistant, and while all of the above factors contribute to resistance, the drug's primary challenge is reaching the tumor microenvironment. Thus, diffusion barriers are our primary target in understanding why drugs prove less effective in patients. Whether a drug can be ultimately delivered to the tumor, past the diffusion barriers, depends primarily on the vasculature in the surrounding area and its influence in creating a static environment that prevents perfusion of blood. In particular, it has been hypothesized and experimentally proven that tumor kill would be significantly enhanced through the elution of drug from a nanoparticle that deposits in the tumor (Ferrari, Trends Biotechnol 2010, PMC2843761).

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We developed a mathematical model that accounts for both spatial and temporal heterogeneities of drug dosing to help explain, examine, and prove the concept of using nanoparticles as the drug delivery method for enhancing treatment efficacy. This integrated mathematical modeling and experimental work lays the groundwork for further human clinical studies, as well as further research into the contribution of other factors in the microenvironment on drug resistance.

Development of a spatio-temporal mathematical model

We extended a previously developed time-dependent drug-cell interaction model (Pascal *et al.,* ACS Nano 2013, PMC3891887) by incorporating spatial dependence to describe perfusion and diffusion heterogeneities. The governing equations for drug concentration $\sigma(\mathbf{x}, t)$ and the volume fraction of tumor cells $\varphi(\mathbf{x}, t)$ are

$$\frac{\partial \sigma}{\partial t} = D\nabla^2\sigma - \lambda_u \varphi\sigma, \qquad (1)$$

$$\frac{\partial \varphi}{\partial t} = -\lambda_u\lambda_k\varphi(\mathbf{x}, t)\int_0^t \sigma(\mathbf{x}, \tau)\varphi(\mathbf{x}, \tau)\mathrm{d}\tau, \qquad (2)$$

where D is the diffusivity of the drug, λ_u the per-volume cellular uptake rate of drug, and λ_k the death rate of tumor cells per unit cumulative drug concentration. Because drug diffusion time and the plasma half-life of drug are both much shorter than the time scale for cell death (on the order of minutes vs. hours or days), and also because the model will be examined on time scales of days to weeks, rather than minutes, Eq. 1 can be solved at the steady state, i.e., $\partial\sigma / \partial t \cong 0$. Note that this is actually a quasi-steady state, meaning that $\sigma(\mathbf{x}, t)$ quickly relaxes to the instant steady state defined by $\varphi(\mathbf{x}, t)$). Thus, without the time derivative in Eq. 1, the solution $\sigma(\mathbf{x}, t)$ is independent of initial conditions. For boundary conditions, we set a drug concentration σ_0 at the blood vessel wall.

We further assumed that a drug administered as bolus at a certain dose level has the same effect as the same total amount of drug administered over several months at a constant, smaller dose level; see our prior work (Pascal *et al.,* Proc Natl Acad Sci U S A 2013, PMC3761643; Koay *et al.,* J Clin Invest 2014, PMC3973100) for validation of this assumption (with patient data) on the use of a constant boundary condition. Accordingly, for a cylindrically symmetric domain surrounding a blood vessel, the boundary conditions can be set to

$$\sigma(r = r_b, t) = \sigma_0, \text{ and} \qquad (3)$$

$$\mathbf{n}\cdot\nabla\sigma\big|_{\mathbf{x}\to\infty} \to 0, \qquad (4)$$

where r denotes the radial position from the center of the cylinder, and r_b represents the

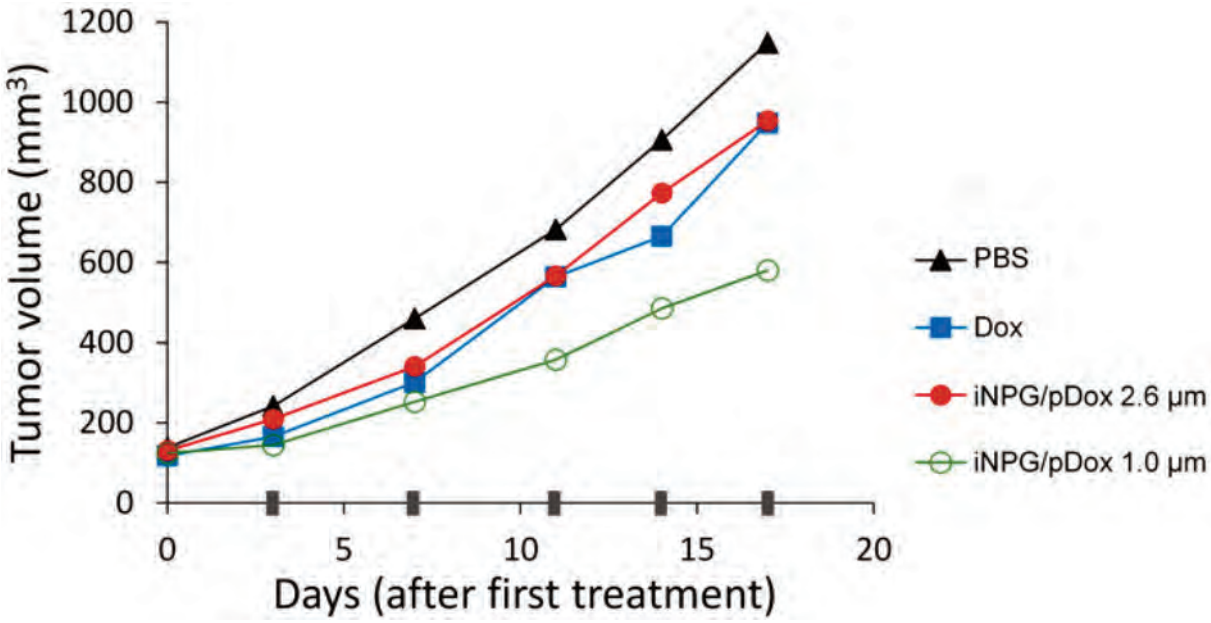

Figure 1. Measurements of tumor volume. Four treatment groups: PBS (control), free doxorubicin, 1.0 μm porous silicon particle loaded with chemotherapy drug (iNPG/pDox 1.0), and 2.6 μm porous silicon particle loaded with chemotherapy drug (iNPG/pDox 2.6). Data were measured on days 0, 3, 7, 11, 14, and 17 after first treatment. Figure reproduced from (Wang *et al.,* PLoS Comput Biol 2016, PMC4902302).

blood vessel radius; the second boundary condition reflects that the far-field drug concentration flattens out. Furthermore, Eq. 2 has no spatial derivatives, and thus only requires the initial conditions for $\varphi(\mathbf{x}, t)$, which we set to

$$\varphi(\mathbf{x}, t = 0) = \varphi_0, \qquad (5)$$

i.e., a homogeneous initial tumor volume fraction. As detailed below, this model allows us to examine drug release through loaded nanoparticles where drugs are released at a nearly constant rate over a certain time interval, approximated here by a constant σ_0.

Prediction of treatment outcome for time-course measurements

Histology data are not always available for determining parameter values for the models presented in (Pascal *et al.,* Proc Natl Acad Sci U S A 2013, PMC3761643; Koay *et al.,* J Clin Invest 2014, PMC3973100). Thus, we derived an alternative form of treatment outcome (denoted by f_{kill}) as a function of another set of experimental parameters, the values of which can be obtained from *in vivo* cytotocixity experiments. The reader may refer to (Wang *et al.,* PLoS Comput Biol 2016, PMC4902302) for further details on model derivation. The final mathematical formula for calculating the amount of f_{kill} through the delivery method of loaded nanoparticles is as follows:

$$f_{\text{kill}} = \frac{F \lambda_k}{2 V_{T,0}} t^2. \qquad (6)$$

Note that there is a quadratic increase in f_{kill} with time, which is consistent as previously observed *in vitro* (Pascal *et al.,* ACS Nano 2013, PMC3891887).

Experimental validation of model predictions

We validated our model results with a set of published cytotoxicity experimental data on comparison of free and nano-particle-based drug delivery *in vivo* (Xu *et al.,* Nat Biotechnol 2016, PMID: 26974511). In this experiment, mice were randomly placed into four groups (10 mice per group) and administered intravenously beginning on day 14 according to a predefined protocol. The four groups were: i) control: phosphate buffered saline (PBS), administered twice a week; ii) free doxorubicin (3 mg/kg, i.v.), administered twice a week; iii) 1.0 μm porous silicon particle loaded with chemotherapy drug (iNPG/pDox 1.0, 6 mg/kg, i.v.) (Xu *et al.,* Nat Biotechnol 2016, PMID: 26974511), administered once a week; and iv) 2.6 μm porous silicon particle loaded with chemotherapy drug (iNPG/pDox 2.6, 6 mg/kg, i.v.), administered once a week. Tumor volume was measured for each mouse on days 14, 17, 21, 25, 28, and 31 after tumor cell injection (see **Fig. 1**). Mice were sacrificed on day 31, and tumors were removed. For comparison with model predictions (i.e., Eq. 6), the tumor volume measurements were normalized across the four treatment groups to the measurements from the PBS control group and to the initial tumor volume, and for each tumor, f_{kill} was calculated as 1 minus the normalized tumor volume.

From the time-evolution of f_{kill} for the three groups of BALB/c mice (**Fig. 2**), it is evident that, after roughly three days of first treatment with rapid growth, f_{kill} remains approximately constant until the end of the experiments ($f_{kill} = 0$ at the onset of the treatment on day zero). This rapid growth of the fraction of dead cells is consistent with the quadratic time-dependence predicted by model Eq. 6. The measured tumor kill from nanoparticles is about 0.5, and roughly 3 times that from free drug, in excellent agreement with the model predictions of a 2-4 fold increase in kill depending on the parameter values. From the experimental protocol, we know that the total amount of drug released by the particles is $F \cdot t \approx 1.2 \cdot 10^{-4}$ g for a typical mouse weight of 20 g. We then analyzed the time-course tumor growth and estimated the approximate (linear) growth rates. For example, the controls were found to grow at an average rate of $\Lambda \approx 70\text{mm}^3$ (proliferation only; no death), while the tumors in mice treated with iNPG/pDox 1.0 μm grow at a rate of $\approx 35\text{mm}^3$ (net outcome of proliferation minus death rates). The latter result produces a net death rate for the iNPG/pDox 1.0 μm treated tumors of $\Lambda_k \approx 35\text{mm}^3$ / day, which, since the specific rate of kill (per molecule of drug) is $\lambda_k = \Lambda_k / (Ft)$, gives, together with Eq. 6, an estimate for $t_{kill} = \frac{2V_0}{\Lambda_k} \cdot f_{kill} \approx 4$ days (corresponding to $f_{kill} \approx 0.5$ and $V_0 = 130\ \text{mm}^3$), in excellent agreement with the observed time to plateau of the cell kill reported in the experiments (**Fig. 2**).

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Challenges and future directions

We have developed a mathematical model that accounts for spatial dependence in predicting tumor response to systemic agents. This model allows us to consider a variety of treatment strategies, and helps to predict the tumor response to different forms of drug delivery methods before the start of treatment. Furthermore, we found that the pathological response to cancer treatment is heterogeneous within a given tumor and that the local physical properties of the tumor describe this response. This is significant in understanding therapeutic resistance, suggesting that the physical microenvironment naturally selects cancer cells that reside in areas with poor drug penetration. This observation of heterogeneous response inspired a concept for improving drug delivery,

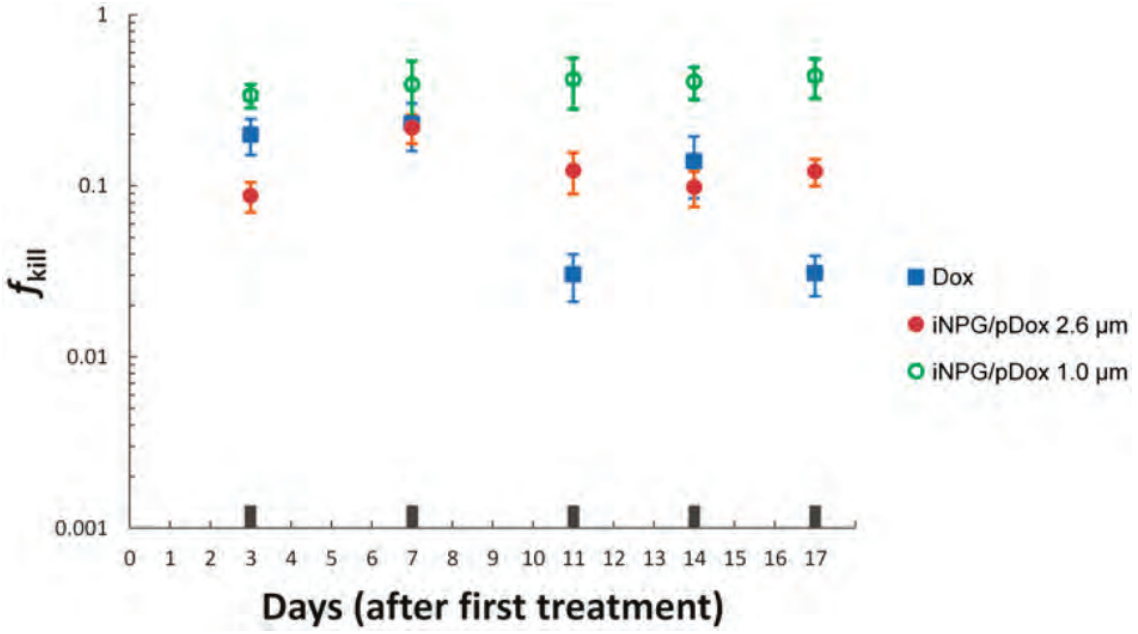
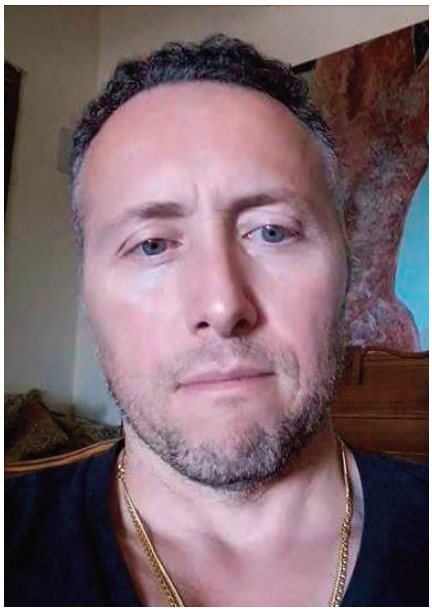


Figure 2. Testing the efficacy of drug-loaded nanoparticles in mice. Comparison of fraction of tumor killed measured across three different treatment BALB/c mice groups (n=10 per group) over a period of 17 days (from day 14 to day 31 after 4T1 tumor cell inoculation) showing a roughly 3-fold increase in kill from nanoparticle-based drug vs. free drug. At each time point, tumor volume measurements from the three drug treatment groups were first normalized to the measurement from the control (PBS) group (no drug treatment), and then to the initial tumor volume for each group; f_{kill} was then calculated as (1 – normalized tumor volume). Figure reproduced from (Wang *et al.,* PLoS Comput Biol 2016, PMC4902302).

e.g., through the use of nanoparticles that can accumulate within the tumor, delivering sustained local release of drug to the cancer cells. In this study, we found that the delivery of systemic chemotherapy using these nanoparticles would have enhanced cell kill by a factor of 2 to 4 over the standard therapy that the patients actually received. However, this strategy may not be feasible in practice due to the constraint of tolerable cytotoxicity to healthy cells. Further investigation into tumor-targeted nanoparticles may be necessary to realize the results in patients that our model predicts.

In the future, we will add other factors or physiological barriers to the model in an effort to improve the accuracy of model predictions. For example, tumor cell regrowth or proliferation that repopulates the killed region, effect of cell to cell contact, and effect of chemotherapy on the tumor vasculature can be implemented in the model. This model may be generalized even more to account for cancer cell kill by the immune system, accounting for the physical barriers to immune cell infiltration into the cancer. Moreover, through the use of non-invasive characterization of transport prior to therapy using diagnostic CT or MRI imaging, as well as the biological characterization of molecular targets for an individual tumor, one could optimize both drug delivery and therapeutic selection for a given patient. This biophysical characterization and prediction strategy would complement genetically-based, patient-specific cancer therapy methods by individualizing drug administration regimens.



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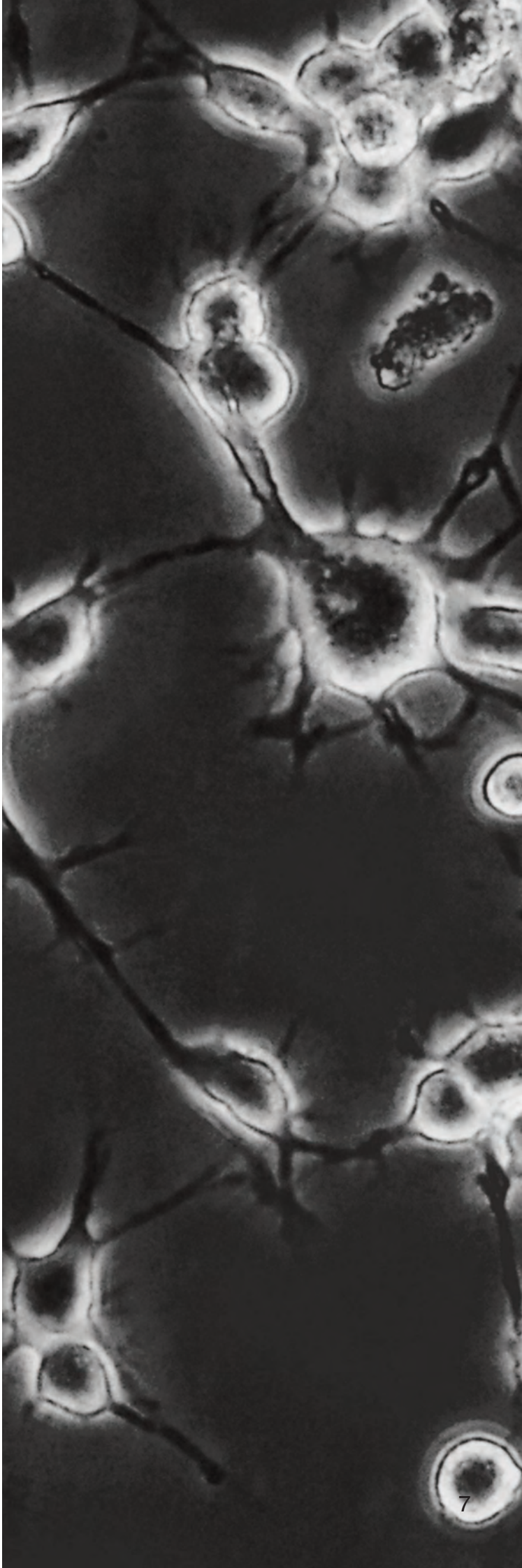

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