Physics-based models and simulations of cancer drug response in solid tumors

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2020 National Cancer Institute statistics:
- Almost 40% of men and women in the United States end up developing cancer in their lifetime.
- 57% of new cancer cases and 65% cancer-related deaths are in less developed parts of Africa, Asia, and Central America.
- Underrepresented?
- National expenditure on cancer was $147.3 Billion in 2017.

The effect of transport on efficacy
- Known since the 80’s that ethanol kills solid tumor cells.
- Also kills healthy cells.
- Mohard et al. \([1]\) mixed ethyl-cellulose with ethanol to change the fluidic properties of the drug.
- Ethyl-cellulose mixture achieved similar efficacy as previous studies while injecting a quarter of the volume.

The model can perform two layer optimization:
- Use the mechanistic model’s performance on par with its data-driven counterparts.
- Can be used as an alternative to the ubiquitous Hill and sigmoidal data-driven models.
- Using only two free parameters, the mechanistic model performs better than twelve parameter data-driven models.

Can the inhomogeneous-anisotropic model predict treatment strategies that outperform the intuitive choice?
- For a nearly homogeneous-isotropic tumor, the intuitive choice of injecting into the center would work well.
- For highly inhomogeneous-anisotropic regions such as the brain, injecting into the center is not necessarily the best.
- Oncologists have more advanced intuition due to heristic knowledge of the blood-brain barrier, blood-brain-tumor barrier, and location of blood vessels.
- This supplements an oncologists expertise with more information about the expected transport in the tumor.

Brain tumors are different
- The brain is highly inhomogeneous and anisotropic.
- Tumors also become inhomogeneous and anisotropic.
- Diffusion tensor magnetic resonance imaging (DTI) is employed to map the inhomogeneities and anisotropies in the brain.

Current and future work
- Mechanistic - Statistics hybrid models.
- Stochastic population models.
- Asymptotic analysis on weak inhomogeneities/anisotropies.
- Collaborate with clinicians for better MRI data and test the theory through experiments.

References
[4] E.K. and E.A. gratefully acknowledge support from the Department of Mathematics and Statistics at TTU. S.G. acknowledges support from the National Science Foundation.

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Figure: Simulated dose-response curves of efficacy (blue), in vitro toxicity (red) and empirical observation (blue stan).

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Figure: Visualizations of DTI volume, mean diffusivity, and fractional anisotropy constructed from the eigenvalues of diffusion tensor, D(x).

Figure: Left: DTI image of a brain. Right: Plot of diffusion tensor from three intersecting slices.

Figure: Left: Performance of various injection points. Right: Dose-response curves from four representative points.

Challenges for simplest model
- Can the mechanistic model’s performance be on par with its data-driven counterparts?
- Both efficacy and toxicity is necessary to develop a treatment strategy.
- Real-world tumor population dynamics is more complex.
- Initial mechanistic model required calibration, which would be too clumsy for real world implementation.
- Initial mechanistic model assumed homogeneous-isotropic spherical tumors.

Efficacy-toxicity model
- Similar set up to simplest model.
- Only cancerous cells in the inner sphere.
- Only healthy cells outside of the sphere.
- Piecewise-constant diffusivity between healthy and cancerous cells.
- Natural cell death negates cell growth.

Simple transport-population model
Developed by A.R. \([2]\) to build a transport-population modeling framework with predictive performance on par with data-driven models.

Transport model
- Assumptions:
  - Spherical solid tumor.
  - Constant diffusivity.
  - Leaky boundary.
  - Injection into the center.
  - Diffusion begins after injection ends.

Population model
- Assumptions:
  - Minimum drug concentration, \(cT\) required to kill a cell.
  - Once apoptosis is triggered in a cell it cannot be stopped.
  - Initial mechanistic model intersecting slices.

What is cancer?
Step 1: Mutation
- Original sequence
- Point mutation

Step 2: Abnormal Growth
- Step 3: Invasion
- Normal
- Hyperplasia
- Dysplasia
- Cancer

Step 4: Metastasis
Source: https://www.cancer.gov/about-cancer/understanding/what-is-cancer

Source: [In this section, there are diagrams and images that are not fully visible or may require further description to understand clearly.]

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Inhomogeneous - anisotropic model
Developed by E.K. et al. \([4]\) to model drug response in the brain from injection therapies such as convection enhanced delivery.

\[
\frac{\partial u}{\partial t} = \nabla \cdot (D(x) \nabla u(x,t)) - u(x,t) \gamma(x,t) \nabla u(x,t) \quad \text{for} \quad x \in \Omega; \quad u(x,t) = 0, \quad \nabla \cdot D(x) \nabla u(x,t) = 0 \quad \text{at} \quad \partial \Omega.
\]

Can be used as an alternative to the ubiquitous Hill and sigmoidal data-driven models.
- Using only two free parameters, the mechanistic model performs better than twelve parameter data-driven models.
- Can be used as an alternative to the ubiquitous Hill equation (state-of-the-art for over 100 years) to fit dose-response curves.
- The model can perform two layer optimization: biochemistry and biophysics.

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