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

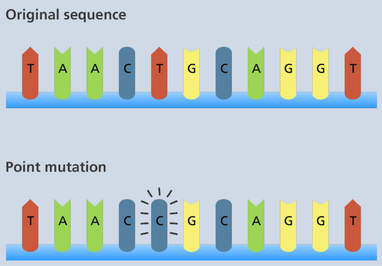
Aminur Rahman[1], Souparno Ghosh[2], Erdi Kara[3], Eugenio Aulisa[3];
[1]Department of Applied Mathematics, University of Washington; [2]Department of Statistics, University of Nebraska - Lincoln; [3]Department of Mathematics and Statistics, Texas Tech University;
[1]✉ arahman2@uw.edu, [1] http://faculty.washington.edu/arahman2

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.
- Good news: cancer death rate in US fell by 26% from 1991 to 2015.

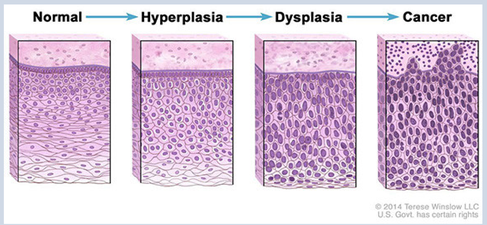
What is cancer?

Step 1: Mutation



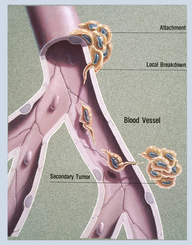
Source: https://www.yourgenome.org/facts/what-is-a-mutation

Step 2: Abnormal Growth
Step 3: Invasion



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

Step 4: Metastisis



Source: https://en.wikipedia.org/wiki/Metastasis

The effect of transport on efficacy

- Known since the 80's that ethanol kills solid tumor cells.
- Also kills healthy cells.
- Morhard *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.

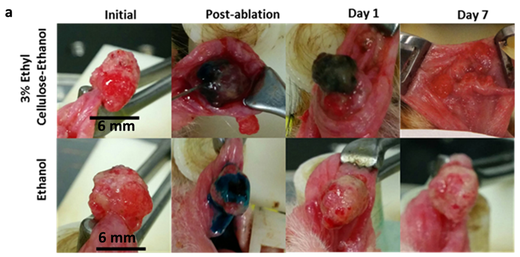
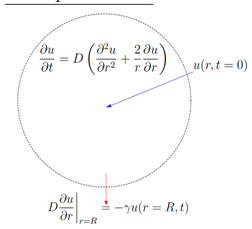


Figure: Morhard *et al.* [1]

Simple transport-population model

Developed by A.R. *et al.* [2] to build a transport-population modeling framework with predictive performance on par with data-driven models.

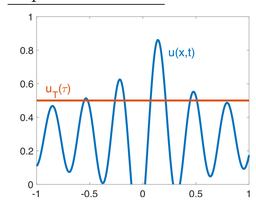
Transport model



Assumptions:

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

Population model



Assumptions:

- Minimum drug concentration, u_T, required to kill a cell.
- Once apoptosis is triggered in a cell it cannot be stopped [3].
- Natural cell death negates cell growth.

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

Assumptions:

- 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.

$$\frac{\partial u}{\partial t} = D'(r)\frac{\partial u}{\partial r} + \frac{2}{r}D(r)\frac{\partial u}{\partial r} + D(r)\frac{\partial^2 u}{\partial r^2};$$
$$D = 1 \text{ for } r \le 1,\ D = D_h/D_c \text{ for } r > 1;$$
$$u(r=0,t) < \infty,\ u(r=\infty,t) = 0;$$
$$u(r, t=0) = \begin{cases} \frac{U_0}{V_b}\exp\left(1 - \frac{1}{1-r^2}\right) & \text{for } r < 1, \\ 0 & \text{for } r \ge 1; \end{cases}$$

- 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.

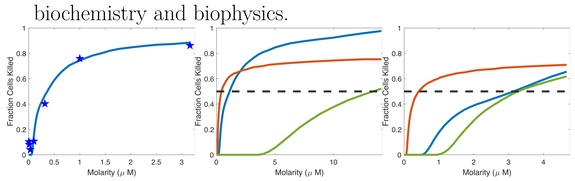


Figure: Simulated dose-response curves of efficacy (blue), *in vitro* toxicity (red), *in vivo* toxicity (green), and empirical observation (blue stars).

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.

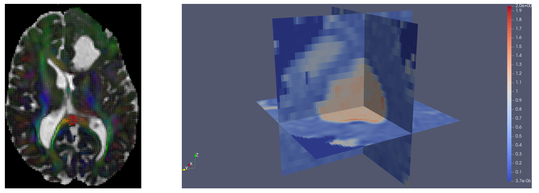


Figure: Left: DTI image of a brain. Right: Plot of diffusion tensor from three intersecting slices.

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*.

$$\frac{\partial u(\mathbf{x};t)}{\partial t} = \nabla\cdot(\mathbf{D}(\mathbf{x})\nabla u(\mathbf{x};t)), \quad \mathbf{x}\in\Omega;$$
$$\mathbf{D}(\mathbf{x})\nabla u(\mathbf{x};t)\cdot n = -\gamma u(\mathbf{x};t), \quad \mathbf{x}\in\partial\Omega; \qquad u(\mathbf{x};t=0) = \bar{u}(\mathbf{x}),$$

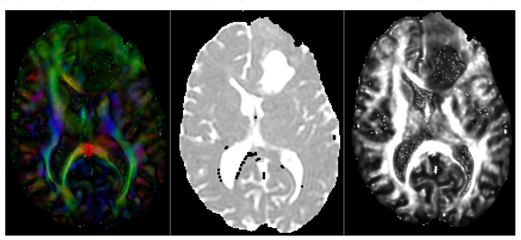


Figure: Visualizations of DTI volume, mean diffusivity, and fractional anisotropy constructed from the eigenvalues of diffusion tensor, $\mathbf{D}(\mathbf{x})$.

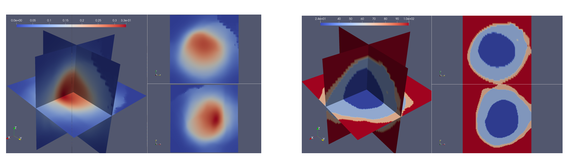
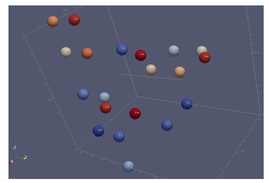


Figure: Left: Concentration profile $u(\mathbf{x};t)$. Right: Region of cell death before 24 (blue), 48 (light blue), 72 (light red) hours, and after 72 hours (red).

Can the inhomogeneous-anisotropic model predict treatment strategies that outperform the intuitive choice?

Yes.



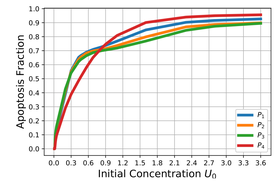


Figure: Left: Performance of various injection points. Right: Dose-response curves from four representative points.

- 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 heuristic 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.

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

[1] R. Morhard, C. Nief, C.B. Castedo, F. Hu, M. Madonna, J.L. Mueller, M.W. Dewhirst, D.F. Katz, and N. Ramanujam. Development of enhanced ethanol ablation as an alternative to surgery in treatment of superficial solid tumors. *Scientific Reports*, 7:8750, 2017.

[2] A. Rahman, S. Ghosh, and R. Pal. Modeling of drug diffusion in a solid tumor leading to tumor cell death. *Phys. Rev. E*, 98:062408, 2018.

[3] X. Cheng and J. E. Ferrell. Apoptosis propagates through the cytoplasm as trigger waves. *Science*, 361(6402):607–612, 2018.

[4] E. Kara, A. Rahman, E. Aulisa, and S. Ghosh. Tumor ablation due to inhomogeneous anisotropic diffusion in generic three-dimensional topologies. *Phys. Rev. E*, 102:062425, 2020.

Acknowledgements

E.K. and E.A. are grateful to NSF (grant # DMS-1912902) for partial support of their contributions to this investigation, and they appreciate the support of the Department of Mathematics and Statistics at TTU. S.G. appreciates the support of the Department of Statistics at UNL. A.R. appreciates the support of the Department of Applied Mathematics at UW.