Modeling Liver Cancer with Yes-Associated Protein (YAP) Hyperactivation

Emma Slack[1], Darsh Gandhi[2], Souvik Roy[1], Hristo V. Kojouharov[1], Benito Chen-Charpentier[1]

[1]University of Texas at Arlington, [2]University of Maryland

Background

- 3rd leading cause of cancer-related deaths
- Treatment includes partial hepatectomy where up to 70% of the liver is removed
  - Liver regrows to its original size, but can lead to tumor growth
- Hyperactivation of YAP shown to reduce speed of tumor growth and limit tumor size by 87.5%
- We are interested in how hyperactivation of YAP impacts tumor growth after partial hepatectomy.

Mathematical Model

We make the following assumptions when constructing out model:

1. "Healthy cells" consist primarily of hepatocytes
2. Healthy cells start reproducing after hepatectomy
3. Resource competition between healthy and cancerous cells
4. Healthy cells have YAP
   - But only hyperactivation can clear tumor
5. Logistic growth in isolation
6. Always a marginal amount of the healthy liver
7. No external carcinogenic factors or reverse mutation

We construct a system of ODEs modeling liver and cancer cell dynamics with YAP hyperactivation based on these assumptions.

$$\frac{dL}{dt} = \lambda_L\left(1 - \frac{L+\gamma_C C}{K_L}\right)L,\ L(0) = L_0$$

$$\frac{dC}{dt} = \lambda_C(1-\mu)\left(1 - \frac{\gamma_L L + C}{K_C(1-\mu)}\right)C,\ C(0) = C_0,$$

Descriptions of the state variables and parameters in our model are listed in the table below.

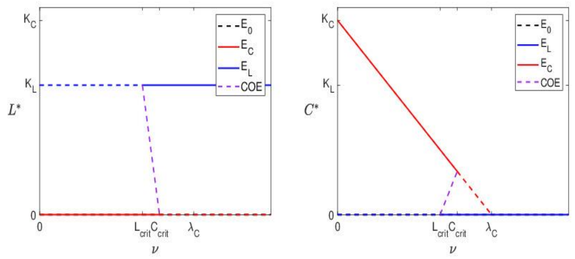
Variables	Description	Units
L	Healthy liver cells	mm^3
C	Cancer cells	mm^3
t	Time	weeks
Parameters	**Description**	**Units**
λ_L	Healthy cell proliferation rate	$week^{-1}$
λ_C	Cancer proliferation rate	$week^{-1}$
γ_L	Influence of healthy liver cells on cancer cells	dimensionless
γ_C	Influence of cancer cells on healthy liver cells	dimensionless
ν	Drug efficacy	$week^{-1}$
K_L	Carrying capacity of healthy cells	mm^3
K_C	Carrying capacity of cancer cells	mm^3

Qualitative Analysis

There are four equilibrium points to the system of equations, described in the table below:

	(L^*, C^*)	Existence	Stability
E_0	$(0,0)$	always	unstable
E_L	$(K_L, 0)$	always	stable iff $\frac{K_C}{K_L} < \gamma_L$
E_C	$(0, K_C)$	always	stable iff $\frac{K_L}{K_C} < \gamma_C$
COE	$(\frac{K_L - \gamma_C K_C}{1-\gamma_L\gamma_C}, \frac{K_C - \gamma_L K_L}{1-\gamma_L\gamma_C})$	$\gamma_C > \frac{K_L}{K_C}, \gamma_L > \frac{K_C}{K_L}$ or $\gamma_C < \frac{K_L}{K_C}, \gamma_L < \frac{K_C}{K_L}$	stable iff $\gamma_L\gamma_C < 1$

Global stability analysis says that all solutions are bounded and must approach an equilibrium point. Stability of solutions as treatment efficacy increases is depicted in the bifurcation diagrams below. This reveals a minimum efficacy level needed.

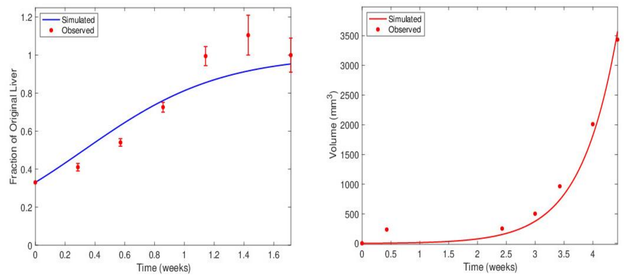


Parameter Estimation

Least squares minimization problem to determine value of parameters based on data (performed on two data sets to fit both liver and cancer-specific parameters):

$$\min_{\boldsymbol{\theta}\in T_{ad}} J(\vec{y}, \boldsymbol{\theta}) := \frac{\alpha}{2}\sum_{i=1}^{N_t}(\vec{y}(t_i) - \vec{y}_i)^2 + \frac{\beta}{2}\|\boldsymbol{\theta}\|_2^2$$

Results from minimization problem show that errors are within acceptable industry standards (i.e. <10%).

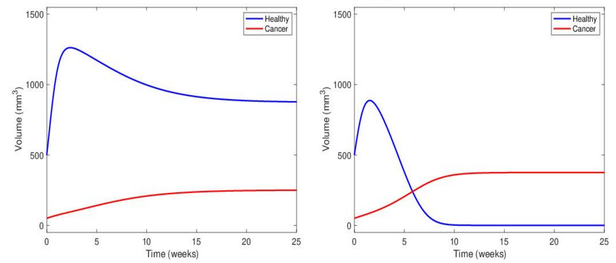


We are unable to estimate γ_C because no data exists which measures tumors size at various stages of liver regeneration.

Numerical Simulations

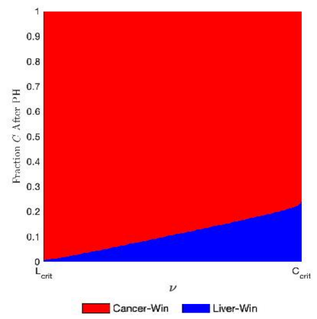
Simulations of healthy and cancerous liver populations at various values of γ_C give a notion of ***tumor aggression***.

Non-Aggressive $(\gamma_C = 2.5)$ **Aggressive** $(\gamma_C = 7.1)$



Varying the value of γ_C also shows

- Value of γ_C mainly impact healthy cells populations
- Longer recuperation for aggressive tumors
- End behavior in coexistence region depends on treatment and initial tumor size
  - Mostly ends with cancer overtaking the liver



Conclusions and Future Work

- Literature and simulations confirm $\gamma_L < \gamma_C$
- Fitted parameters need "high" effect of treatment ($\mu > 0.9$)
- Value of γ_C significant in a patient's outcome
- For "normal" tumor aggression, $1 < \gamma_C < 1/n$, physicians may prescribe slightly lower dose to support immune system
- Future Work: Model YAP hyperactivation in combination with other treatments

References

Slack, E., Gandhi, D., Roy, S., Kojouharov, H. V., & Chen-Charpentier, B. (2025). Modeling Competitive Dynamics Between Healthy and Cancerous Liver Cells with Yes-Associated Protein (YAP) Hyperactivation. *Mathematics*, *13*(21), 3479.

Grant No.
DMS- 510 2230790