INDIANA UNIVERSITY
BLOOMINGTON

Fall25 Introduction to Computational Bioengineering

METABOLISM IN CANCER CELLS

A Modeling Approach

By
Varalakshmi Perumal

INDIANA UNIVERSITY
BLOOMINGTON

This project is about:

“ Modeling the dynamics of genotypically equivalent cancer cell proliferation through glycolytic and oxidative pathways ”

“how the uptake dynamics of glucose and lactate, together with substrate availability, govern the metabolic balance between glycolysis and oxidative phosphorylation and thereby influence the growth of an in vitro tumor cell population?”

“ In addition, oxygen dynamics are introduced to examine whether the system responds in a biologically consistent manner under varying oxygen conditions ”

Why this study ?

1. Modeling tumor growth provides enhanced predictive capability and enables in silico exploration of tumor behavior under varying metabolic and environmental conditions.
2. By capturing metabolic heterogeneity, nutrient-driven phenotypic switching, and oxygen-dependent regulation, these models support the rational design of conceptually novel combination therapies.
3. Moreover, they complement standard clinical trials by reducing experimental burden, providing mechanistic insight into therapy-induced metabolic adaptation, and facilitating the integration of multi-scale biological data.

INDIANA UNIVERSITY
BLOOMINGTON

Key Cell Metabolisms

Aerobic +O2

Oxidative (Glucose)

Glucose + 6 O2 → 6 CO2 + 6 H2O + ATP (30-32 numbers)

Highly efficient energy production. Dominant in normal differentiated cells.

Aerobic +O2

Oxidative (Lactate)

2 Lactate + 6 O2 → 6 CO2 + 6 H2O + ATP (30 – 32 numbers)

Lactate is imported via MCT transporters and used as fuel.

Anaerobic without O2

Glycolysis

Glucose → 2 Lactate + 2 ATP

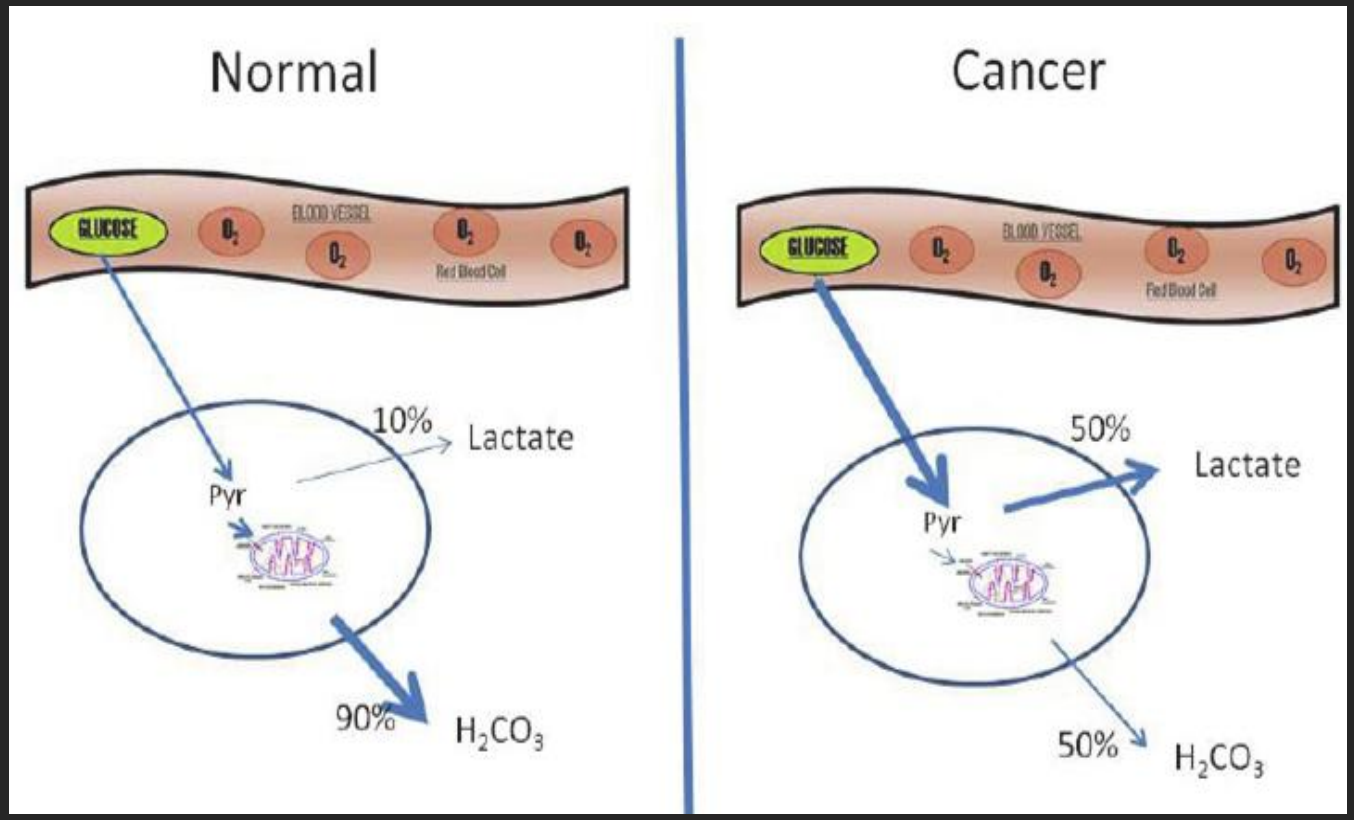
Inefficient ATP yield but rapid turnover. Produces biomass precursors.

INDIANA UNIVERSITY
BLOOMINGTON

The Warburg Effect

Metabolic Reprogramming

- Unlike normal cells, cancer cells exhibit a distinct metabolic phenotype known as the **Warburg Effect**.
- Even in the presence of sufficient oxygen (aerobic conditions), cancer cells preferentially utilize glycolysis for energy production rather than the more efficient oxidative phosphorylation.



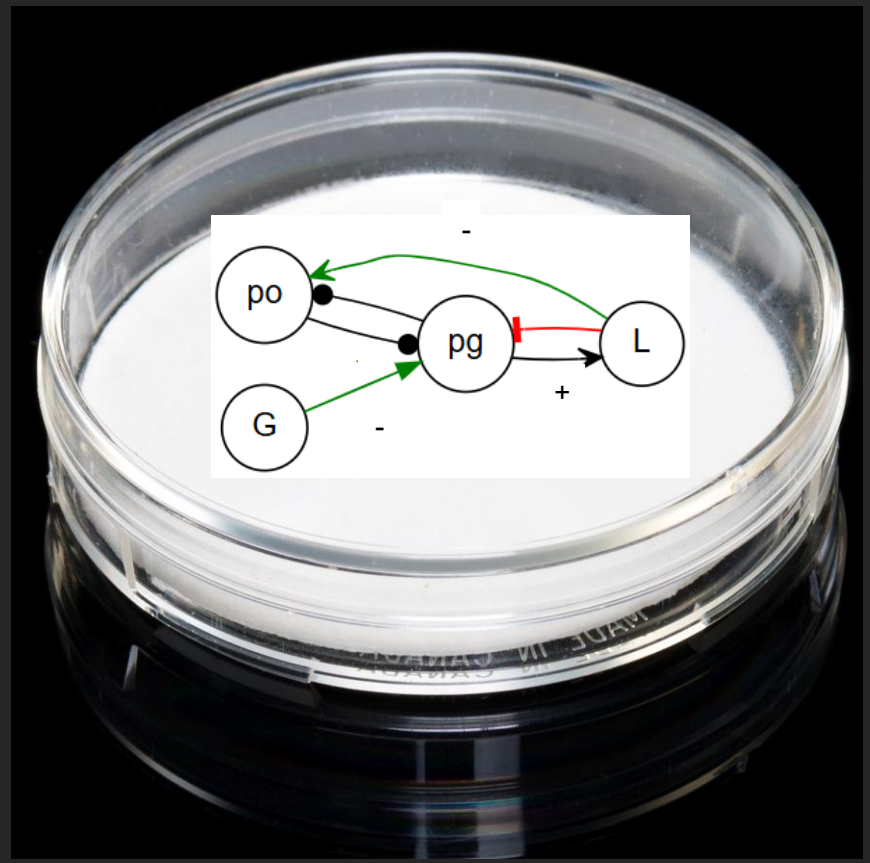
Source: researchgate.com DOI:10.1002/nbm.3509

INDIANA UNIVERSITY
BLOOMINGTON

Reaction in the Medium

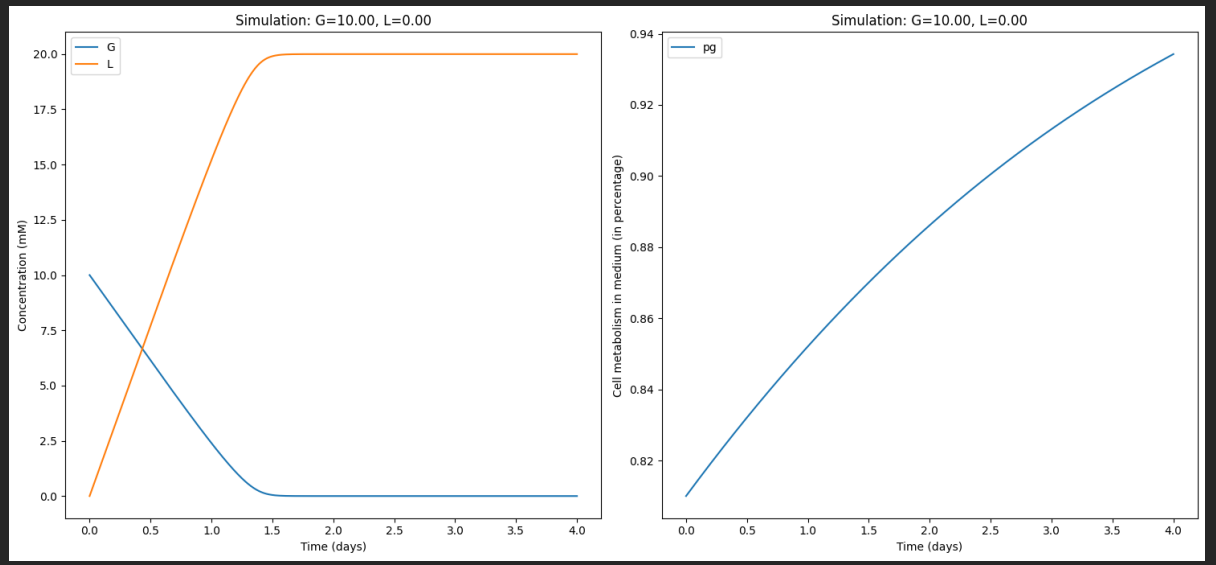
po, pg - Population of cell in medium undergoes oxidation and glycolysis

G, L - Glucose and Lactate substrate in the medium

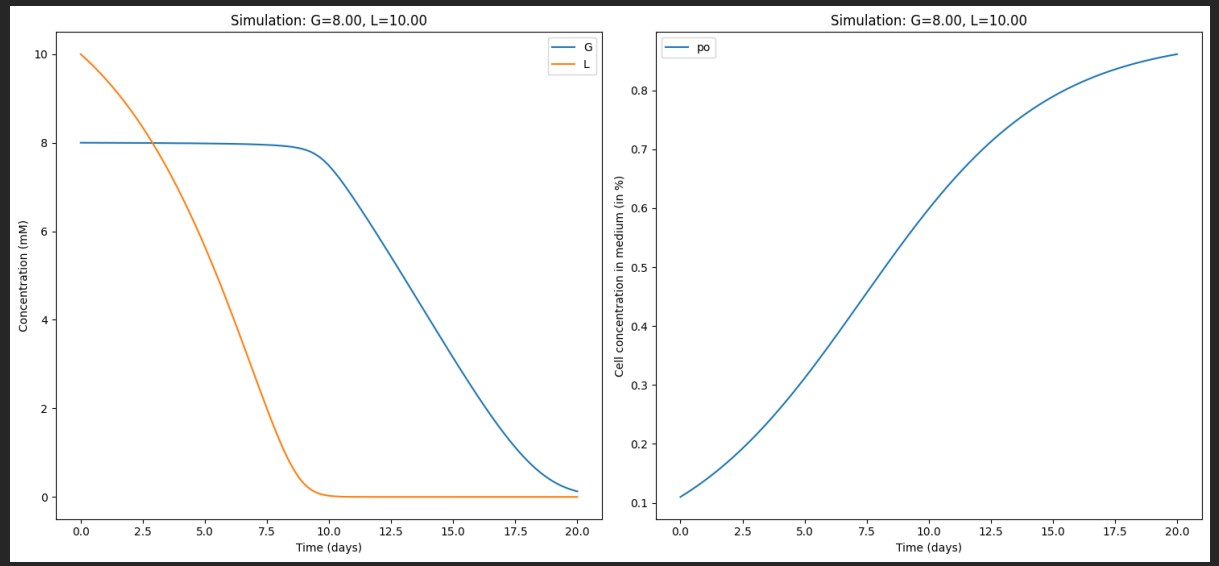


INDIANA UNIVERSITY
BLOOMINGTON

System with only Glycolysis metabolism

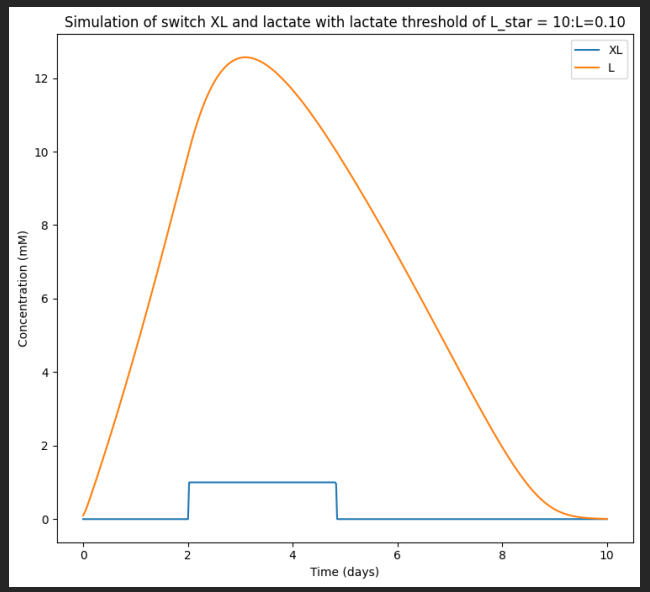


System with only oxidative metabolism



INDIANA UNIVERSITY
BLOOMINGTON

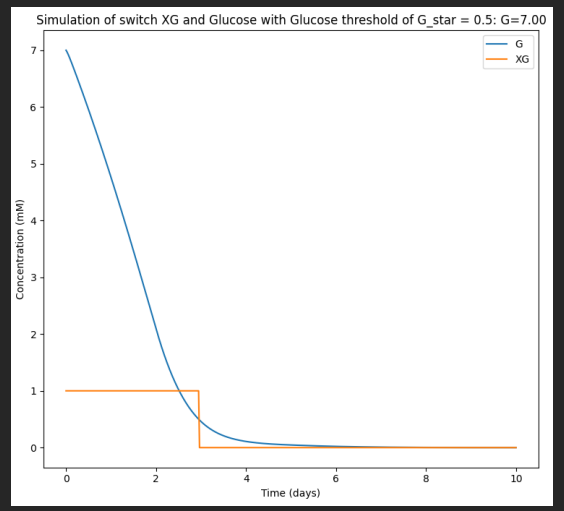
Switches



$$\chi_L(L) = \frac{1}{2}[1 + \tanh(\gamma(L - L_*))],$$

1. This switch depends on the levels of lactate(L) and the Lactate threshold(L*) that cells can support and on the medium's acidity (gamma).
2. Switch XL is an increasing function, close to zero for low Lactate, and XL_star is decreasing function, close to one for High lactate.
3. The glycolysis is PH dependent which mean parameter (gamma) is a measure of cell sensitivity to change in lactate.

$$\chi_G(G) = \begin{cases} 0, & \text{if } G \leq G_{\min}, \\ 1, & \text{if } G > G_{\min}, \end{cases}$$

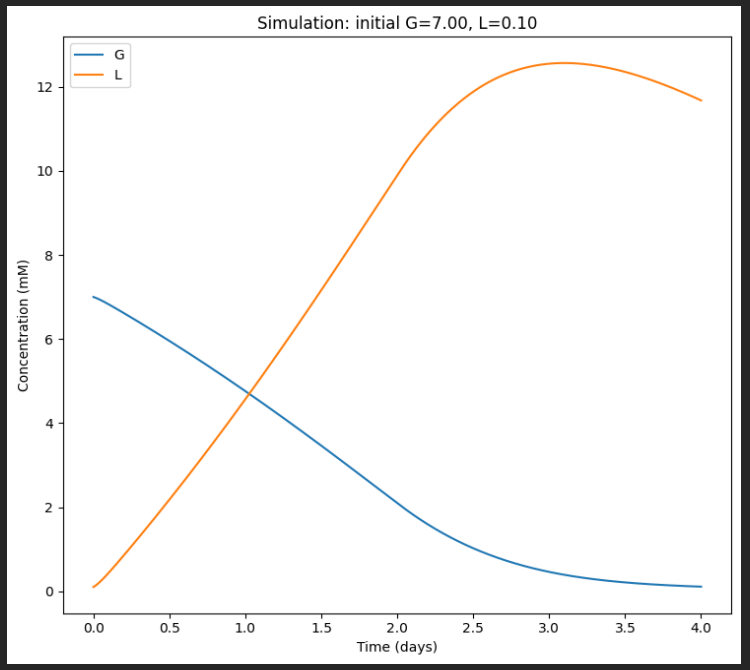


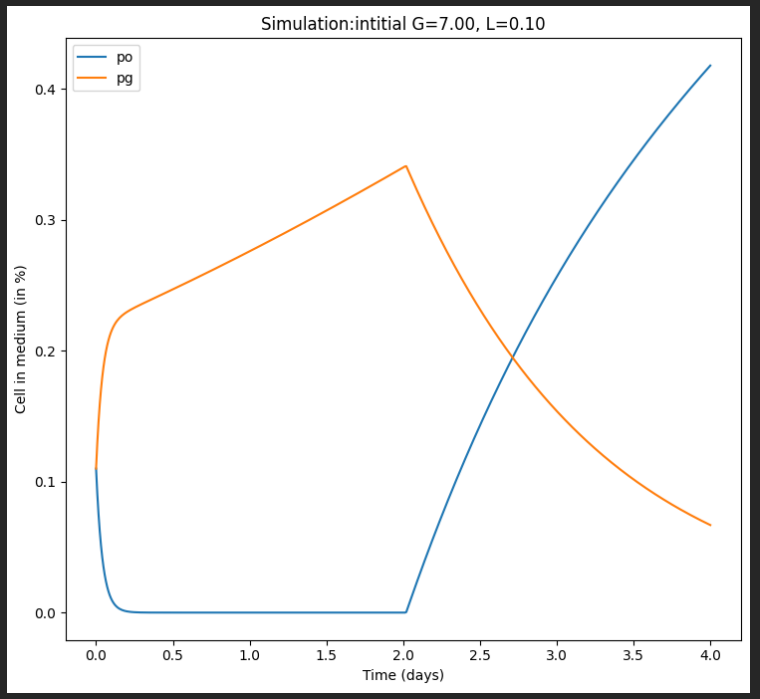
1. In the absence of glucose, cells do not switch to a glycolytic metabolism.
2. Without this function, in absence of glucose, and with lactate concentration lower than the acidosis threshold but sufficient to survive, cells would become glycolytic but could not consume any nutrients.

INDIANA UNIVERSITY
BLOOMINGTON

Both Glycolysis and Oxidation together

1. The cancer cell proliferation first starts with glycolysis exhibiting warburg effect.
2. As the result in increasing in the lactate in the medium due to glycolysis, Cells switches to oxidative metabolism consuming Lactate from the medium for the survival.
3. In the graph in the right, you can see the cell proliferation due to oxidation increases consuming lactate when availability of glucose decreases.

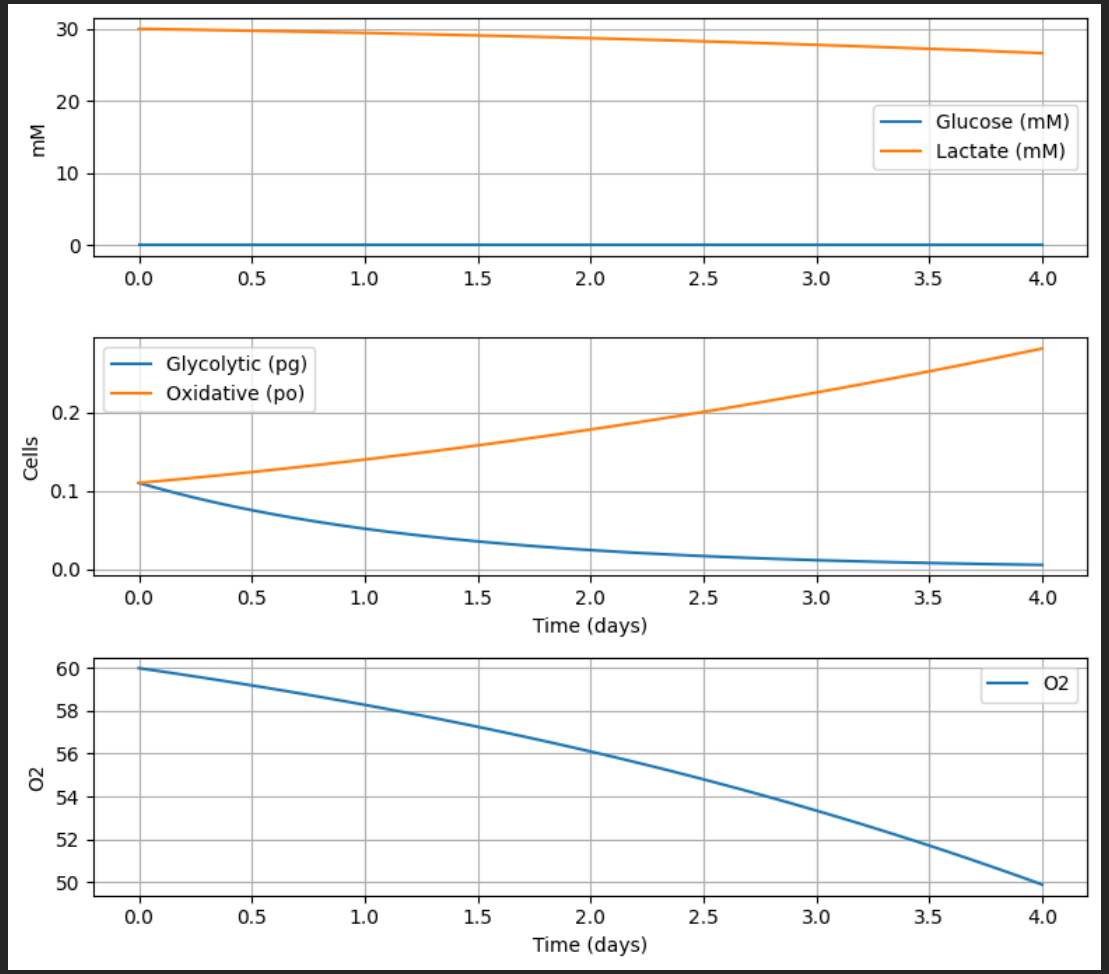




INDIANA UNIVERSITY
BLOOMINGTON

Introducing O2 track to the system

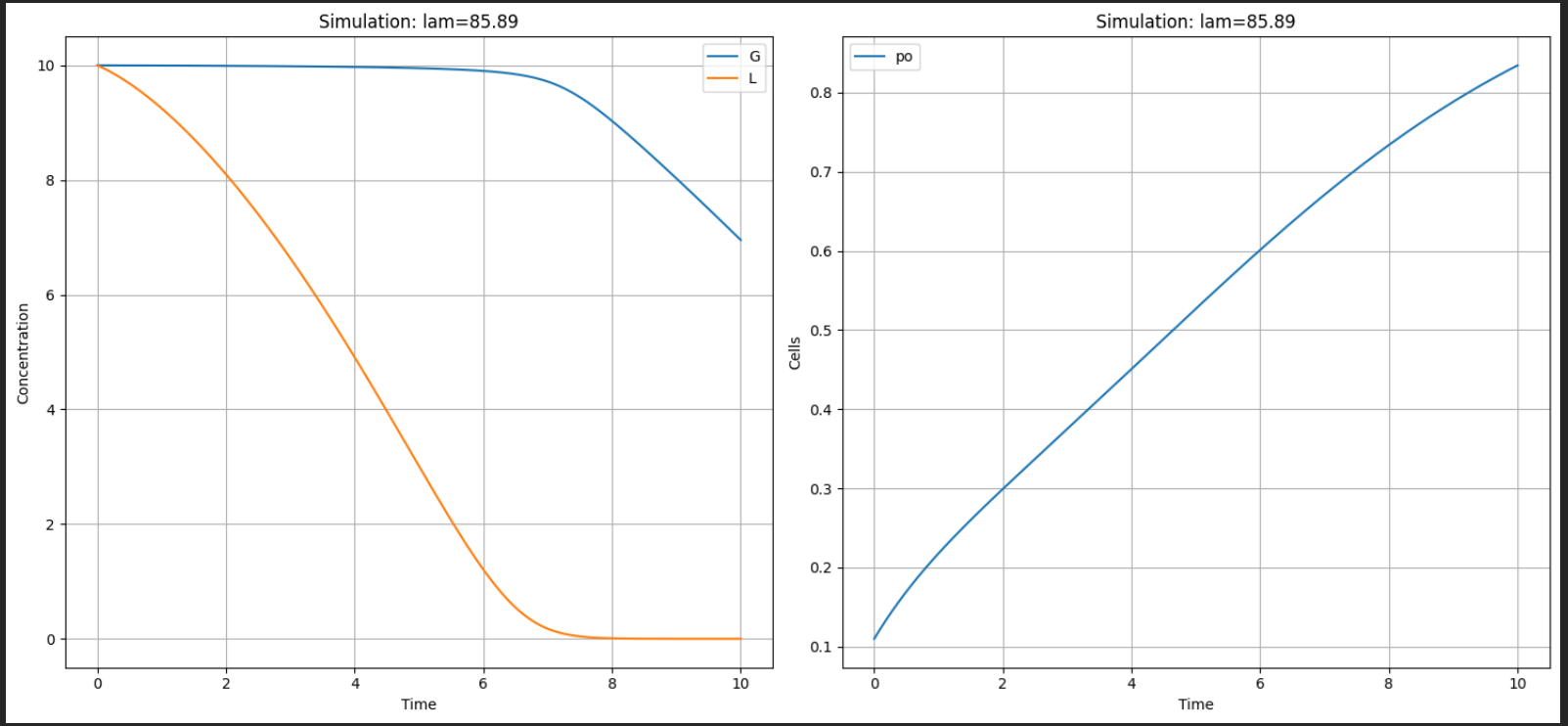
1. Adding O_2 dynamics allows the model to explain metabolic flexibility rather than fixed glycolysis.
2. So, the model can now predict- When cells oxidize glucose, When cells oxidize lactate, When they revert to glycolysis.
3. Also, availability of oxygen and nutrients is an important part for a model to determine the cells necrotic behavior.



INDIANA UNIVERSITY
BLOOMINGTON

Exercise 1: How do cells decide whether to consume oxygen and lactate instead or glucose as during aerobic phosphorylation?

Varying the MCT1 factors and analyzing the aerobic metabolism using glucose and lactate how the preference changes as we change lambda.



INDIANA UNIVERSITY
BLOOMINGTON

Exercise 2: How does the change in the PH of the medium affect the oxidative and glycolysis metabolism.

Tumor cells constantly produce acidic metabolites—especially lactic acid—as a result of high glycolytic flux. In an in-vitro culture dish, this acid accumulates in the medium, lowering the extracellular pH (pH). Cancer cells are very sensitive to these pH changes.

[Medium pH drops]

↓

[Cells sense acidity]

↓

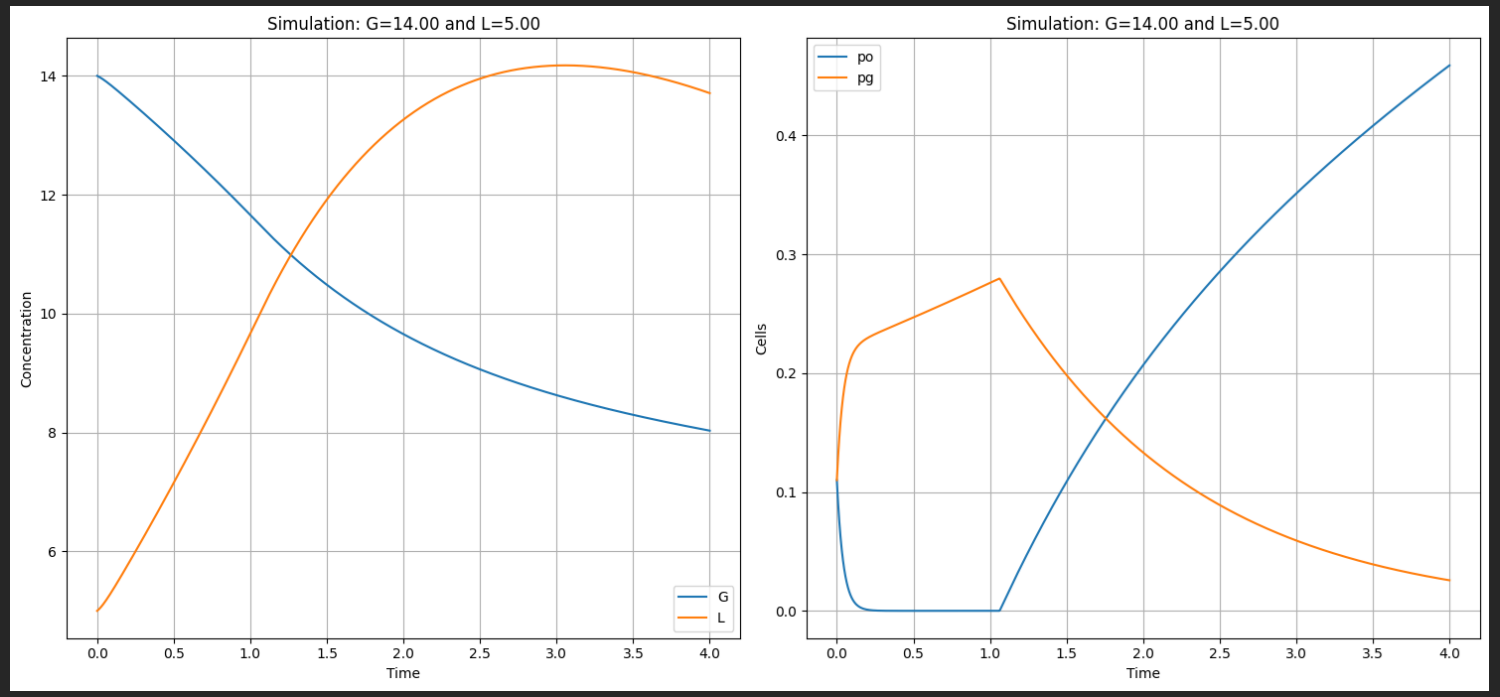
[Glucose uptake ↓] [less cell glycolysis]

↓

[Oxidative ↑ → less lactate/H^+] [Lactate uptake ↑]

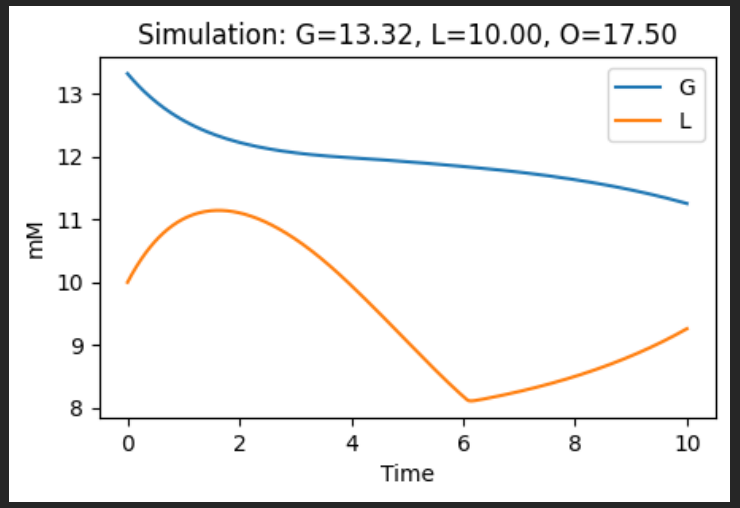
↓

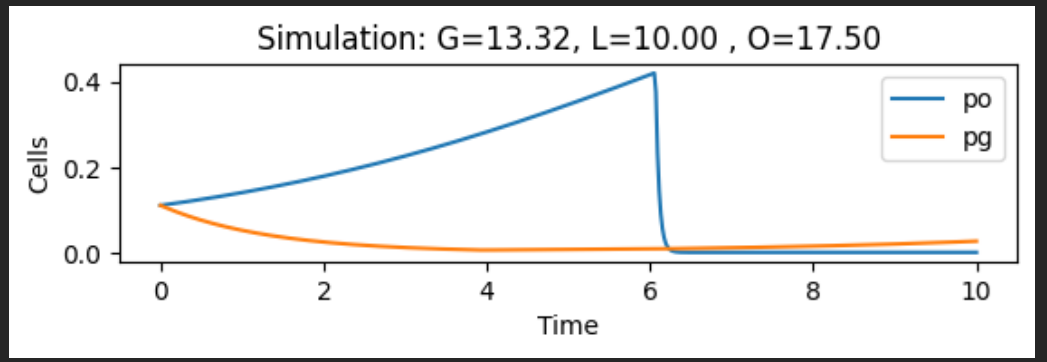
[Medium pH improves further]

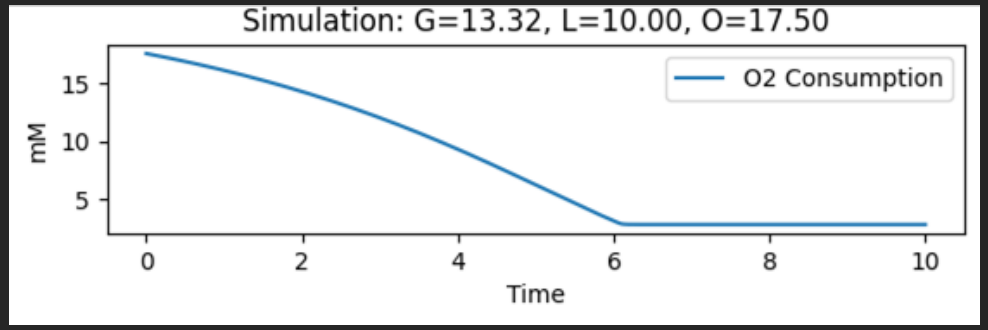


INDIANA UNIVERSITY
BLOOMINGTON

Exercise_3: What will happen if the glucose and O2 supply cut down completely to the medium?







INDIANA UNIVERSITY
BLOOMINGTON

Conclusions and Future Work

Key Findings:

Characterized metabolic interplay (Glucose, Lactate, O2) using a systems-biology approach.

Model successfully reproduced cancer metabolism: elevated consumption, lactate production, and lactate reutilization.

Differential-equation models captured dynamic switching between glycolysis and oxidative phosphorylation.

Provided a quantitative framework to predict metabolic behaviors and guide hypothesis generation.

Future Extensions:

Can extend the model to include cell necrosis, pH regulation, and detailed transporter kinetics.

Incorporate cell-cell metabolic interactions for more physiologically realistic tumor microenvironment simulations.

INDIANA UNIVERSITY
BLOOMINGTON

Reference:

1. Mendoza-Juez B, Martínez-González A, Calvo GF, Pérez-García VM. A mathematical model for the glucose-lactate metabolism of in vitro cancer cells. Bull Math Biol. 2012 May;74(5):1125-42. doi: 10.1007/s11538-011-9711-z. Epub 2011 Dec 22. PMID: 22190043.

Thank you