CSE 397 Introduction to Computational Oncology
Homework 3 Part 1- Modeling Metabolism

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Problem 1: Describe the equations of the cancer cell metabolism model. Ignoring the logistic growth and diffusion terms, what to the remaining terms represent biologically?

The paper uses the subscript "o" to refer to cells that metabolize properly by oxidative phosphorylation, and the subscript "g" for the less efficient glycolysis that results in large glucose consumption and lactate production.

$k_{go}N_g\chi_L(L)$: tumor cells switching from glycolytic to oxidative at a rate of k_{go} as long as there is sufficient lactate present (χ_L is a step-like function) for the switch to occur.

-$k_{og}N_o\chi_L^*(L)\chi_G(G)$: tumor cells switching from oxidative to glycolytic at a rate of k_{og} as long as there is not much lactate present (one minus the step-like function) and as long as there is sufficient glucose present (χ_G)

-$k_{og}N_{ng}\chi_L(L)$: same as above but negative since it is in the equation for glycolytic cells

$k_{og}N_o\chi_L^*(L)\chi_g(G)$ same as above but positive since it is in the equation for glycolytic cells

$-\beta_o\dfrac{\alpha_G G}{\alpha_G G+\alpha_L L+N^*}N_o$: glucose decreases as it is consumed by oxidative cells

$-\beta_g\dfrac{G}{G+G^*}N_g$: glucose decreases as it is consumed by glycolytic cells

$-\beta_L\dfrac{\alpha_L L}{\alpha_G G+\alpha_L L+M^*}N_o$: lactate decreases as it is oxidized by oxidative cells

$2\beta_g\dfrac{G}{G+G^*}N_g$: lactate increases by 2 as a product of glycolytic cells

$\chi_L(L)$: similar to a step function, it is zero when lactate is close to a lower threshold and 1 when it is higher.

$\chi_L^*(L)$: 1 - (step-like function)

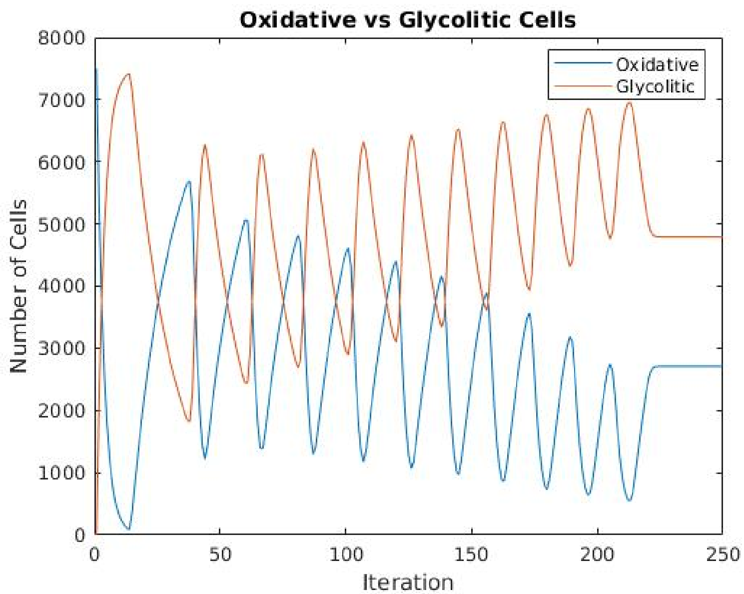
$\chi_G(G)$: on/off switch determined by whether sufficient glucose is available

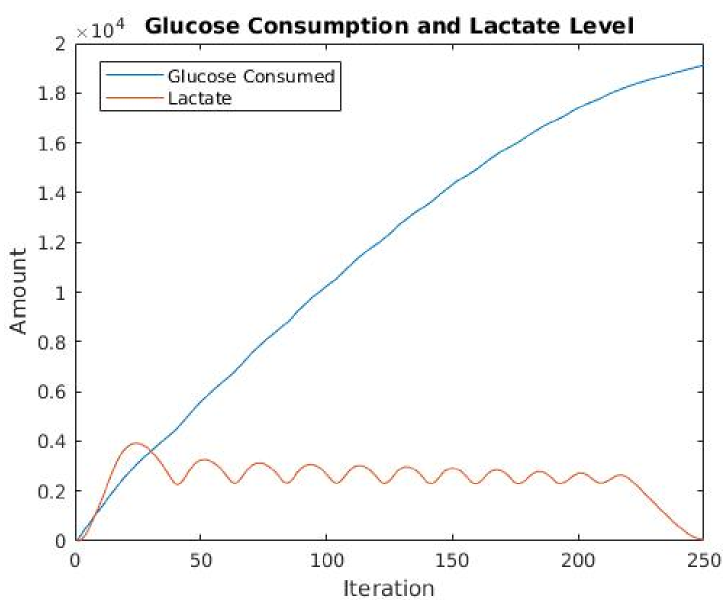
Problem 2: Implement the cancer cell metabolism model

(2a) In this first simulation, there is no diffusion or growth terms and a uniform amount of cells over the grid. The only terms left in the equations for cell rates are for switching back and forth between oxidative and glycolytic. This is exactly what happens for the most part - initially low lactate levels lead to a switch of almost all cells from initially oxidative to glycolytic. As the glycolytic numbers increase, lactate increases too, and so the cells start switching back.

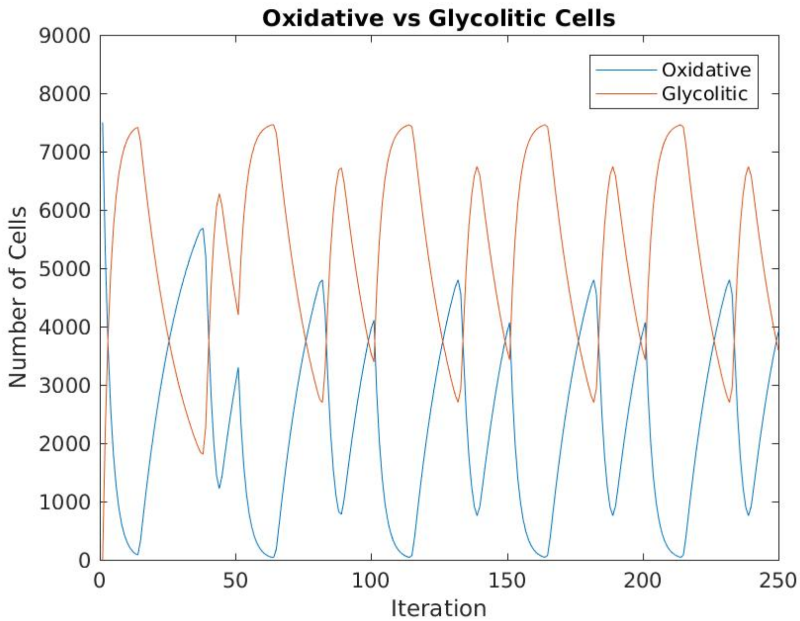
This cycle is repeated several times, with lactate slightly decreasing as some oxidative cells oxidize the lactate, thus decreasing the amount. Glucose continues to be consumed.

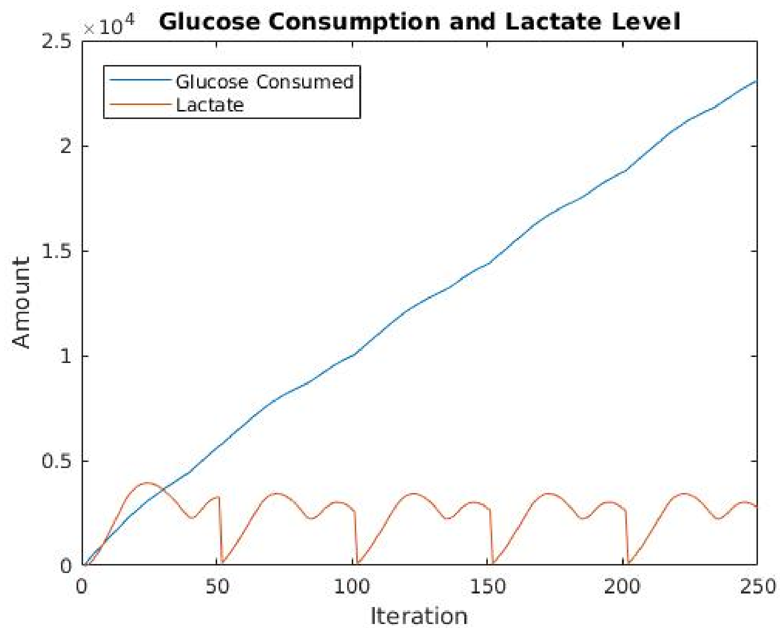
Towards the end, we reach a change when both glucose and lactate levels are too low, and so the cells stop switching.





(2b) Resetting the medium allows glycolysis to continue when it otherwise wouldn't. Thus the initial cycle repeats. Glucose continues to be consumed at a nearly steady rate as it is replenished, and lactate, instead of oscillating about L^*, is flushed out so that the cells are not limited in their glycolysis.





(2c) Run the simulation with non-zero diffusion and proliferation terms. Display what happens to N_{ng} and N_o over time.

Note: an additional change that has been made in this file is that $\beta_g = 10$, much greater than it's previous value of 1.15. This increases glucose consumption by the glycolytic cells but also increases the lactate production, which will cause glycolytic cells to switch to oxidative.

Summary of simulation:

1. We see somewhat similar behavior to (2a) except it is damped.
2. The oscillations are seen to occur in space as the cells proliferate and diffuse outward, but the larger β_g factor means that the glycolytic cells return to oxidative much faster.
3. As the cells diffuse, high glucose concentrations and low lactate concentrations make for a wave of glycolytic cells expanding slowly outward before converting back to oxidative
4. Periodic switches from oxidative to glycolytic occur when the oxidative cells have processed enough lactate, but this is quickly reversed

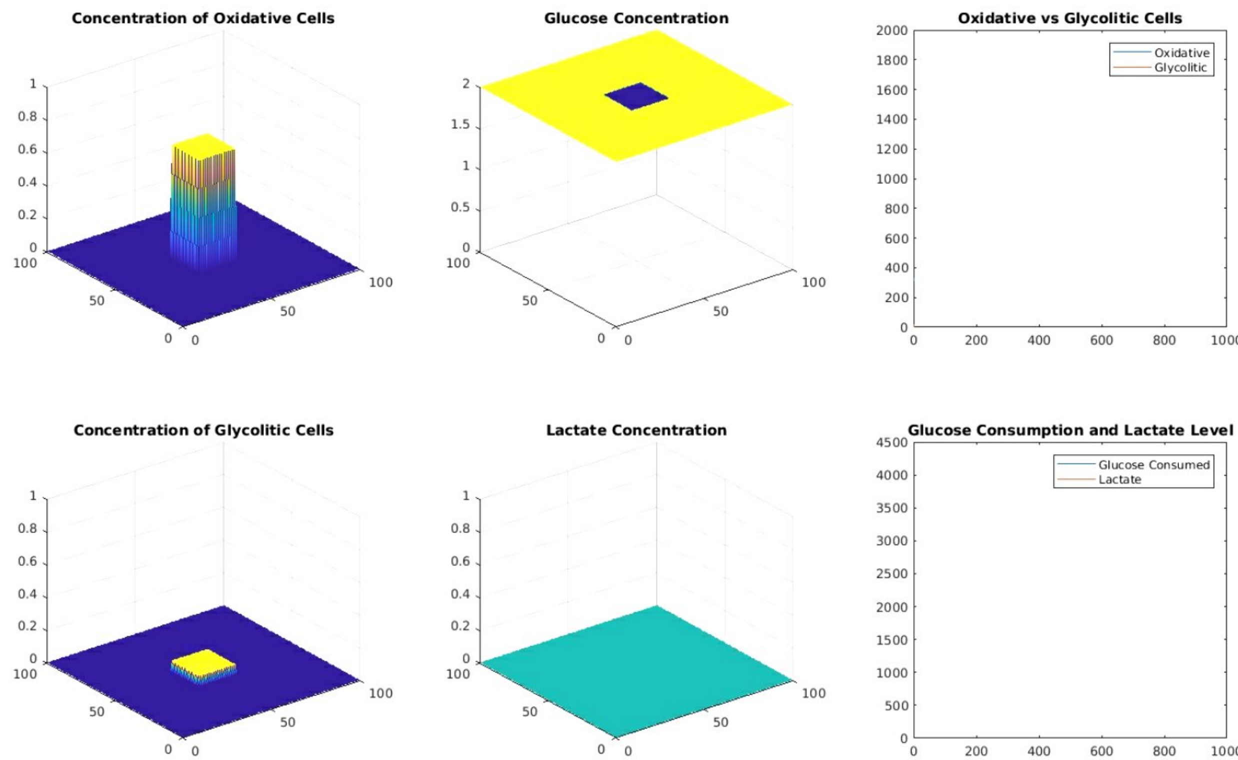


Figure 1: Oxidative cells begin switching to glycolytic.

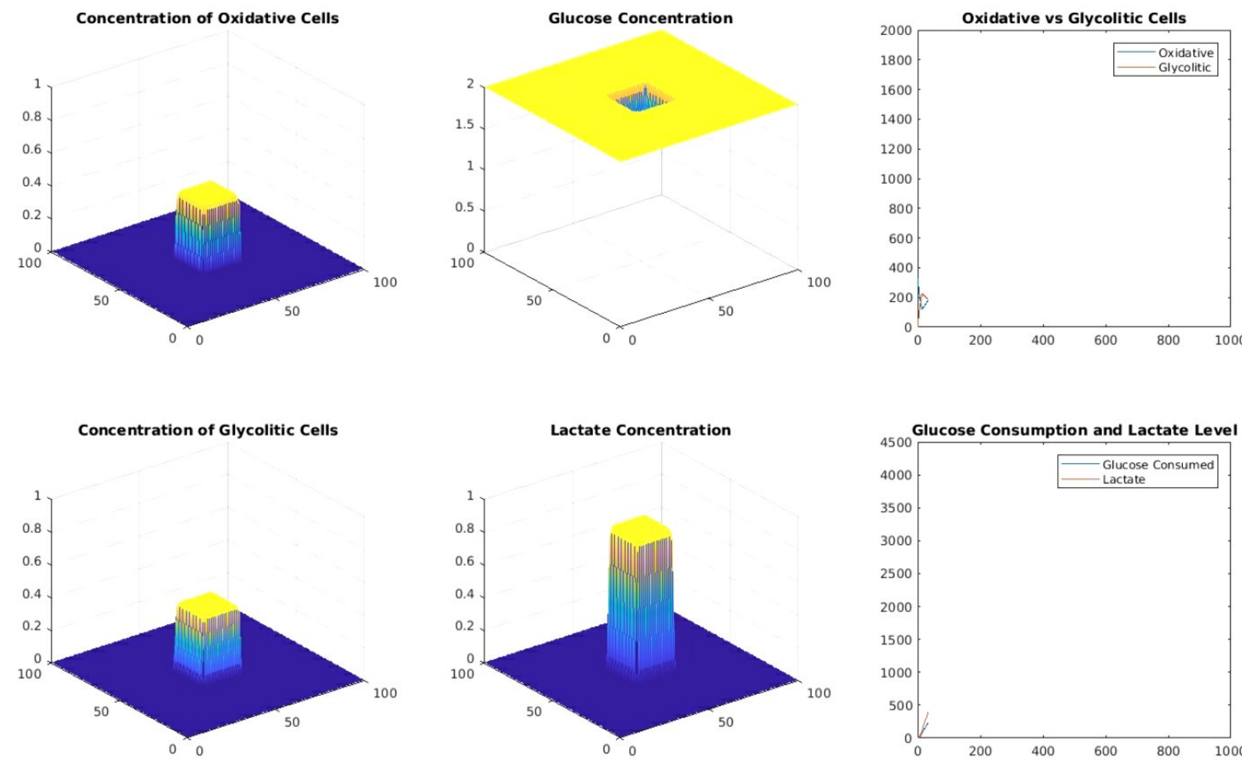


Figure 2: Lactate increases as a product of glycolytic cells.

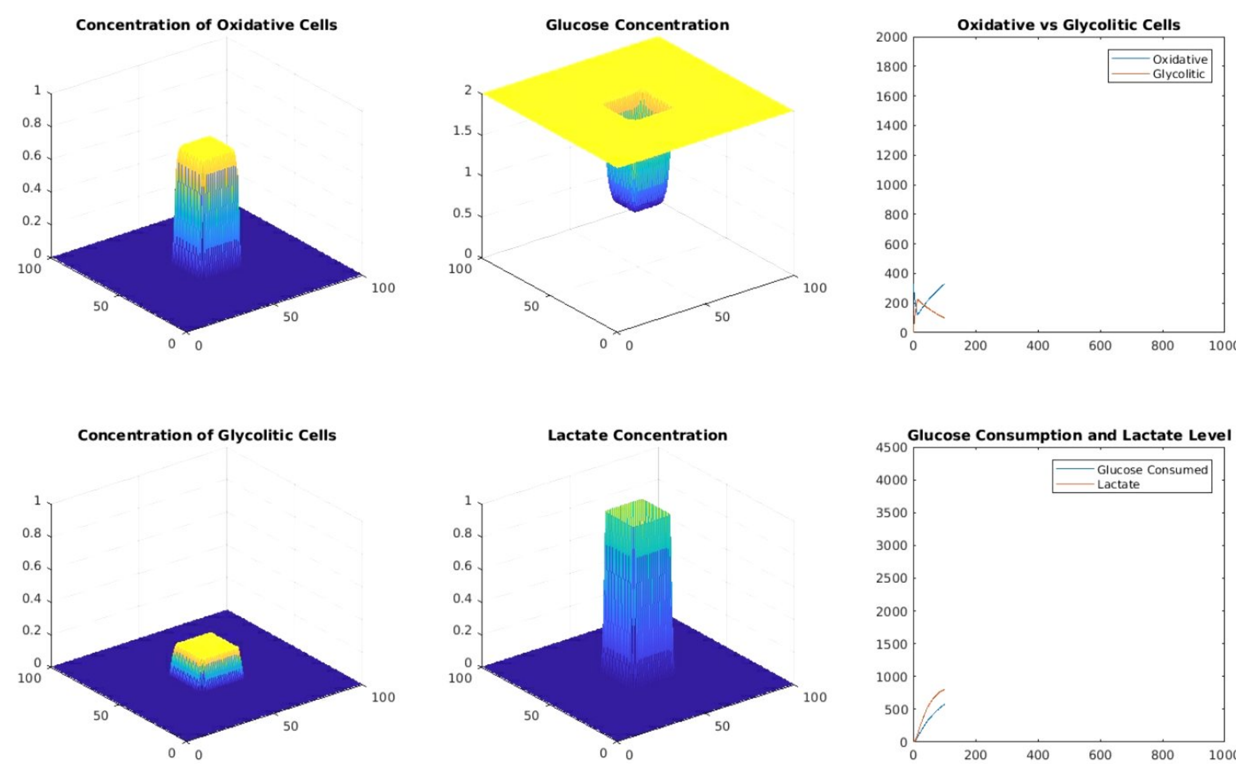


Figure 3: Central glycolytic cells revert to oxidative, which oxidize lactate.

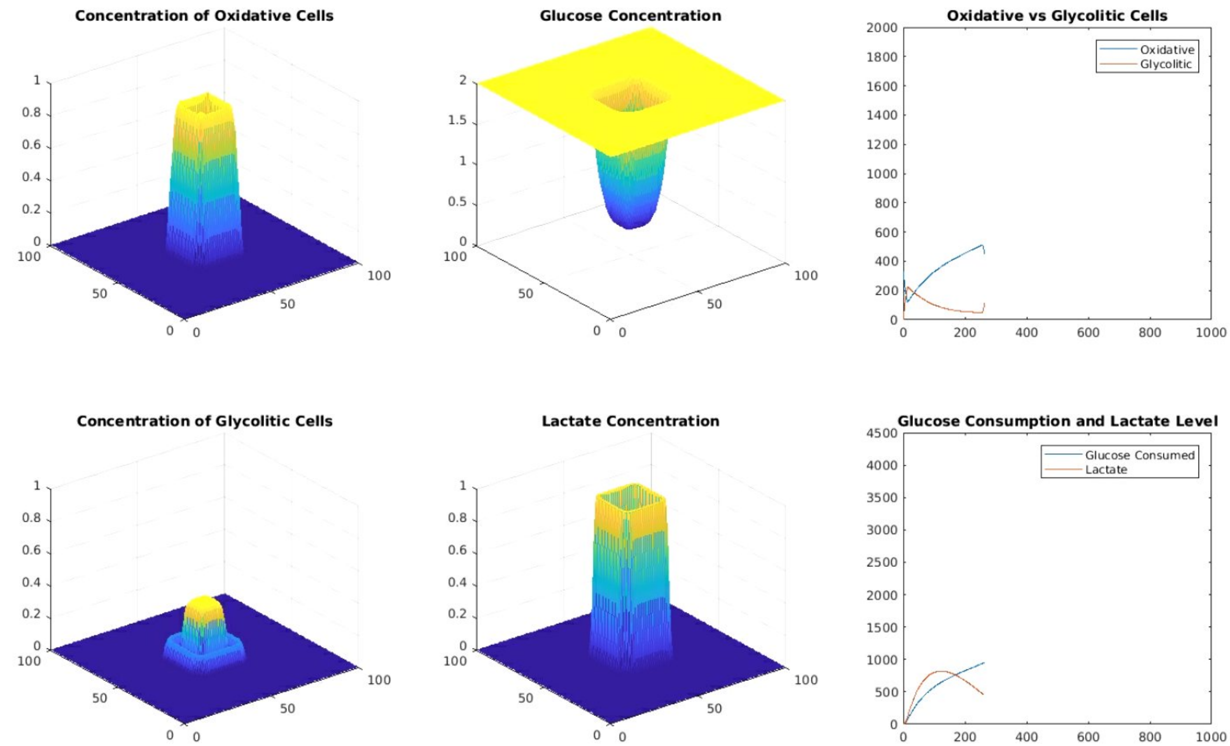


Figure 4: Oxidation of lactate allows central cells to convert back to glycolytic.

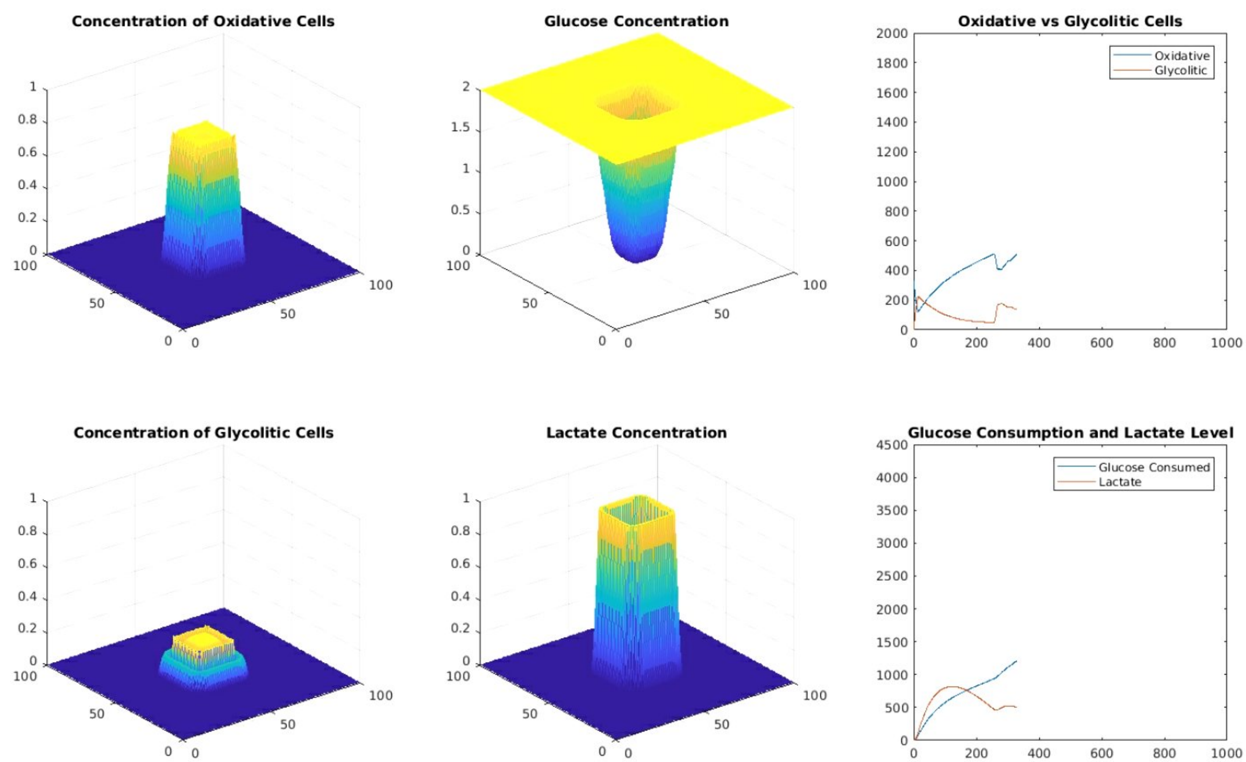


Figure 5: Oscillations between glycolytic/oxidative occur spatially based on lactate.

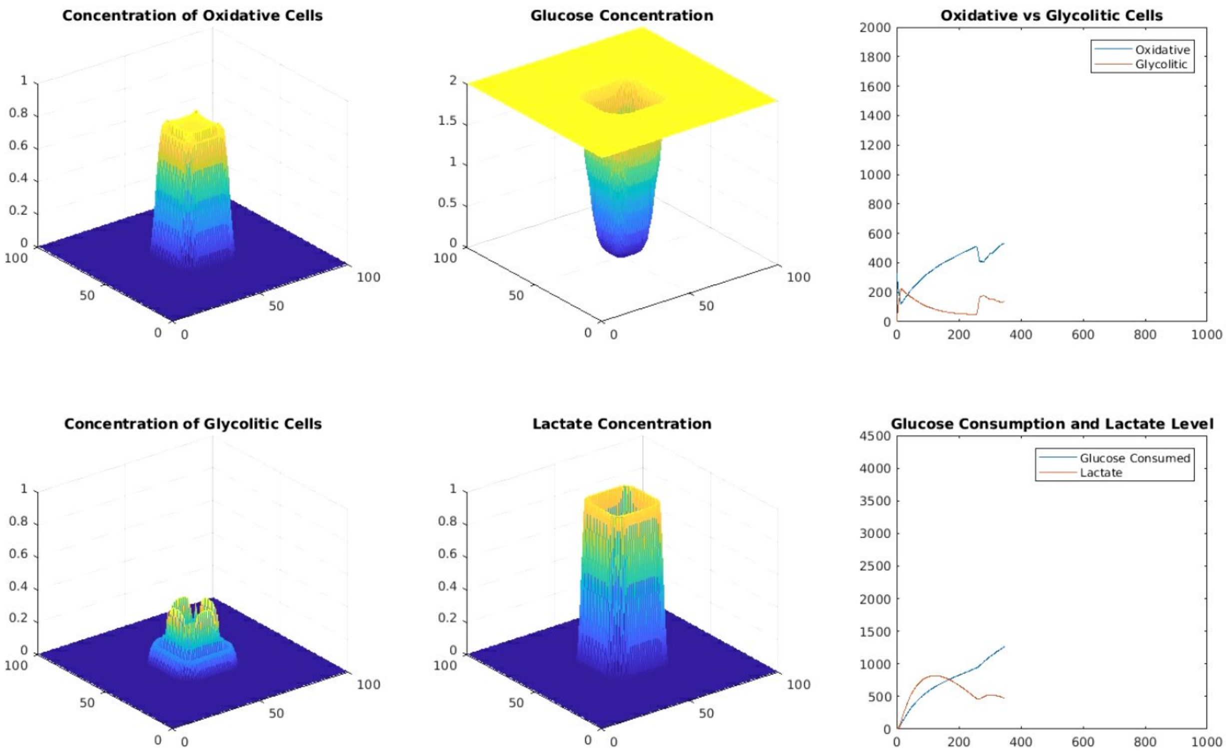


Figure 6: Glucose is limited in the center, so only oxidative cells remain.

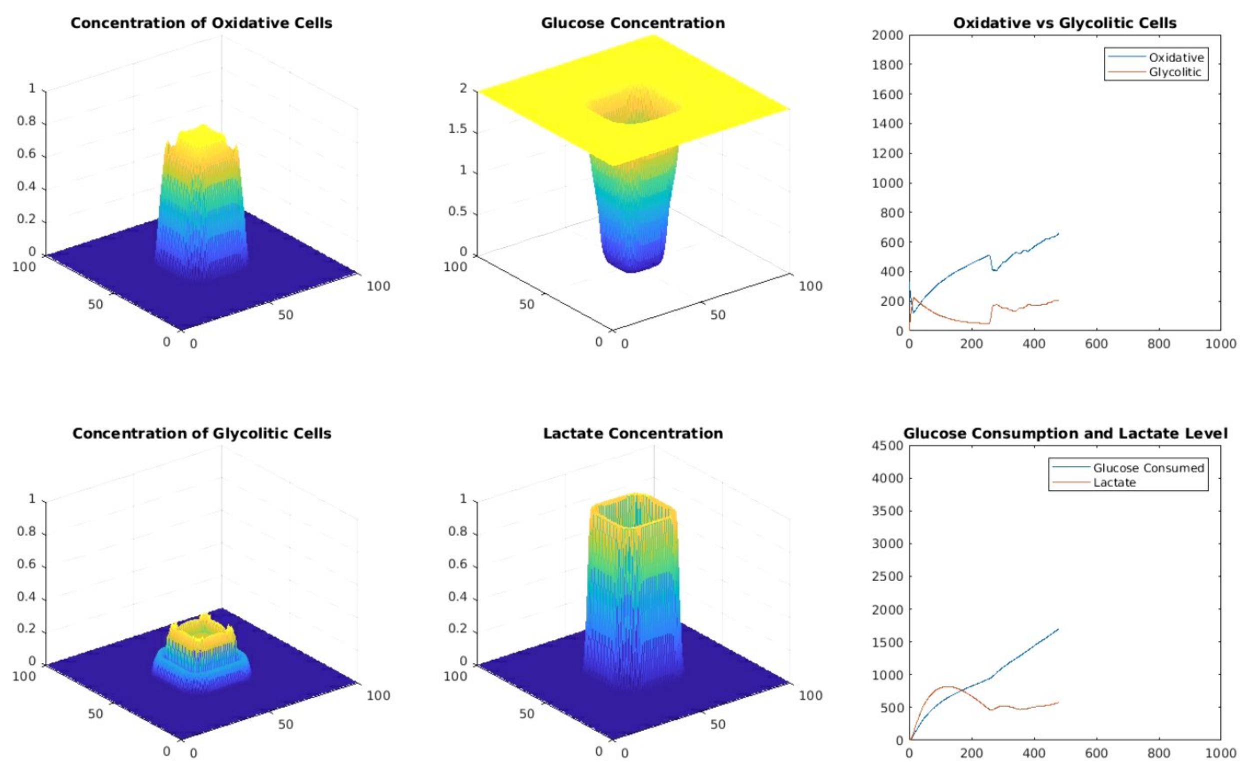


Figure 7: Outer "wave" continues production of lactate during interior oscillations

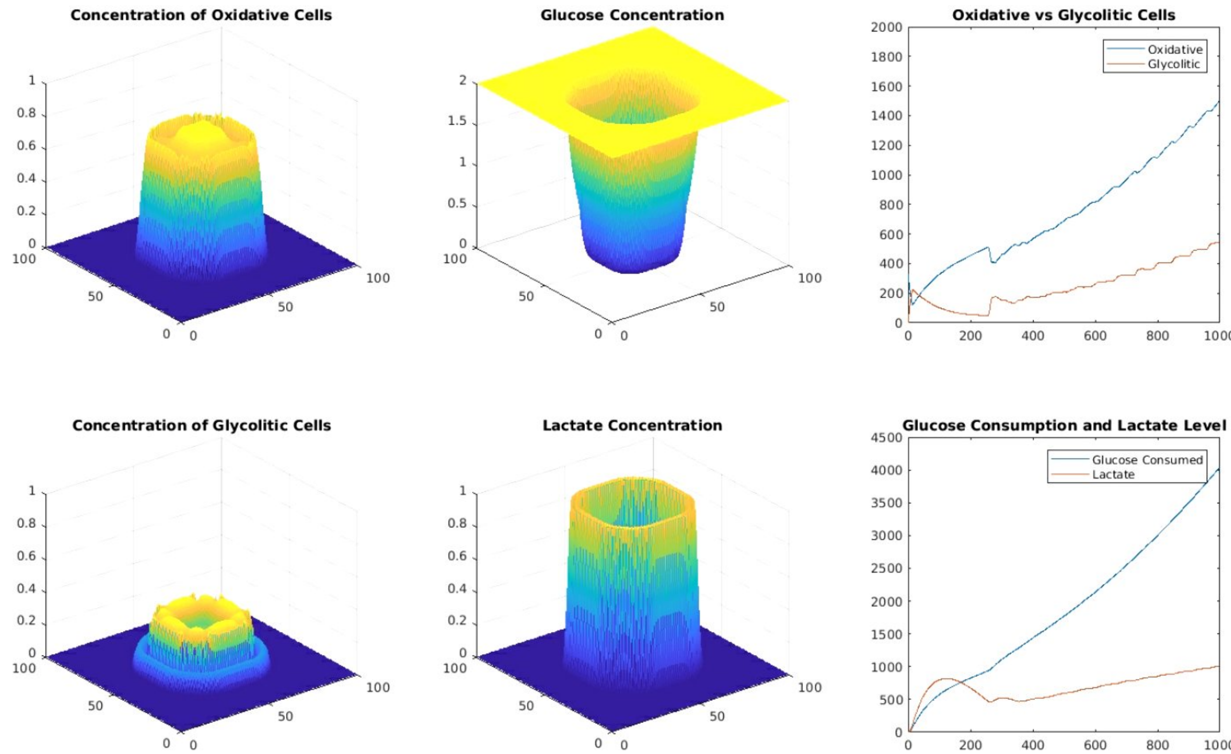


Figure 8: At the end of our simulation, there is an oxidative core surrounded by two "waves" of glycolytic cells responding to high glucose and low lactate in some regions. However, high production of lactate causes a rapid switch back to oxidative, with glucose being rapidly depleted after that.