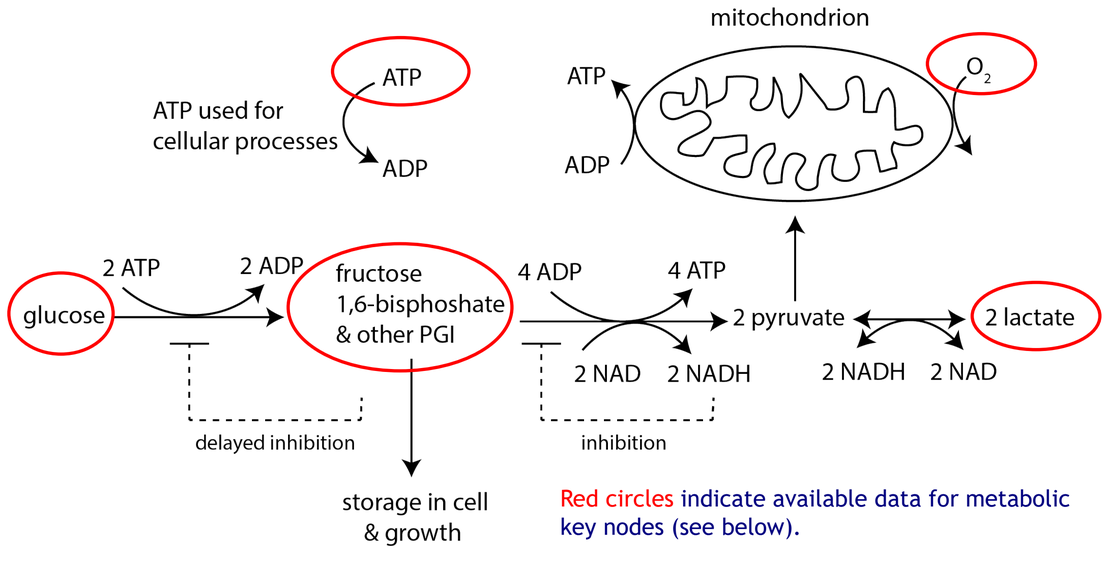
Metabolic competition for glucose between tumor cells and host cells

Johannes van Beek Amsterdam University Medical Centers, location AMC, Amsterdam, the Netherlands

Background

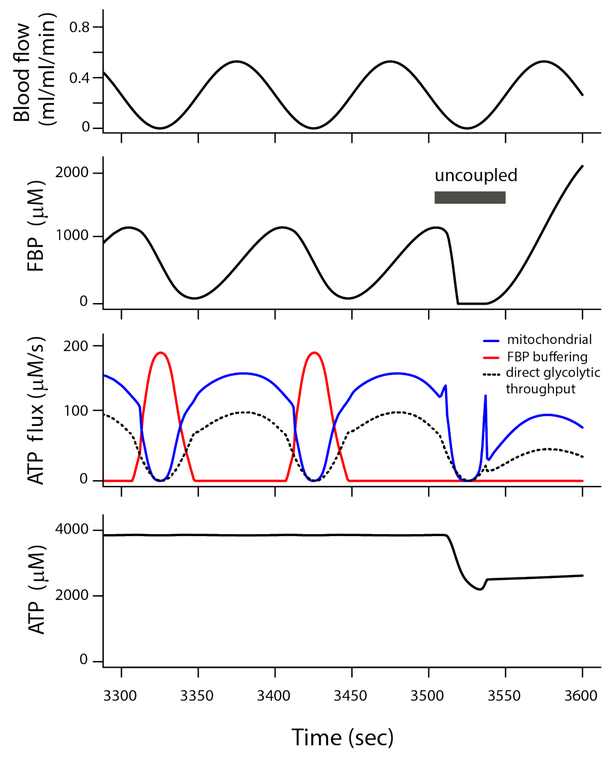
Tumor cells show high glucose uptake and lactate production, even when there is sufficient oxygen. Transient glucose uptake is especially high when glucose arrives after a period of starvation.
I developed a computational model which quantitatively describes data on a broad range of experiments by Warburg (1952) and others.

Scheme Computational Model



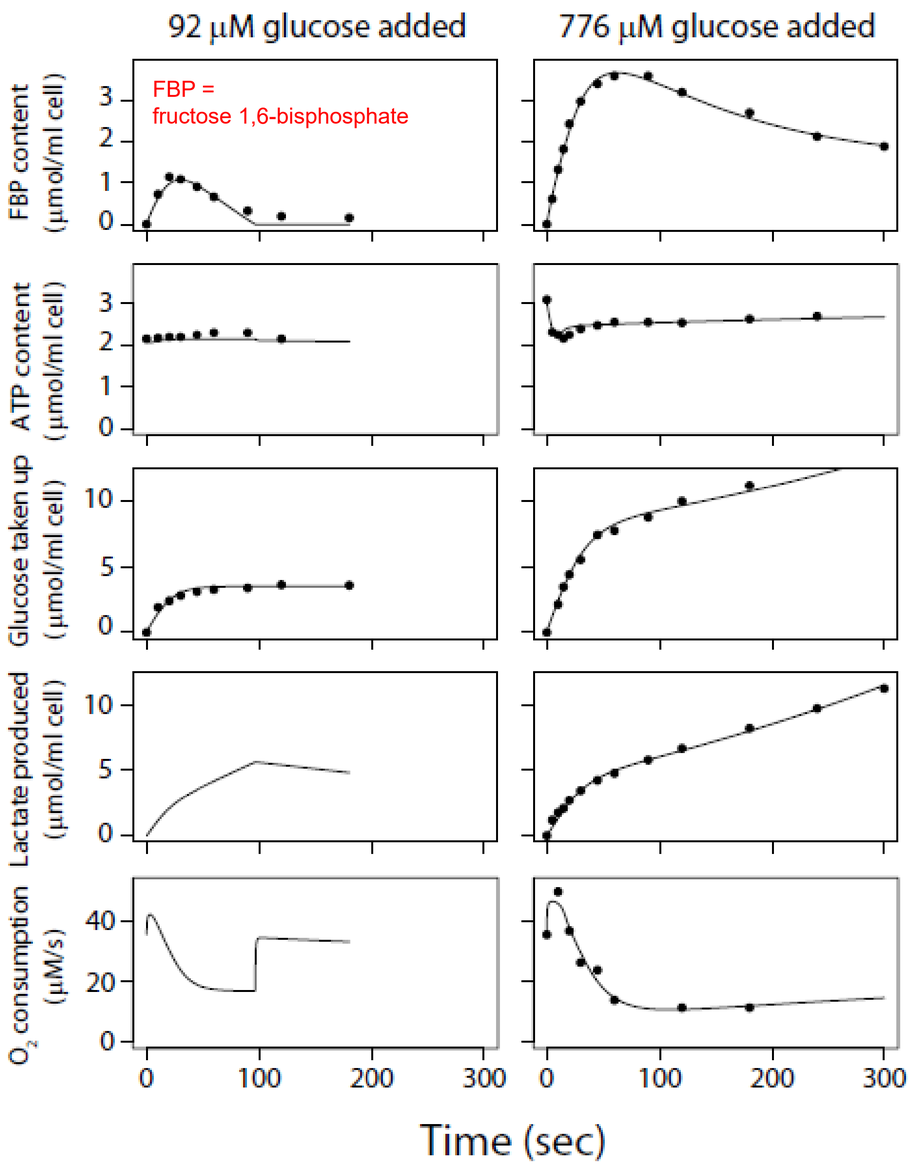
Model predictions for tumor cells

Tumor tissue often has fluctuating low blood flow, leading to oscillating O_2 and glucose concentrations in the tumor tissue. The glucose metabolism of tumor cells was simulated under these conditions.



During the high blood phase glucose is stored as fructose 1,6-bisphosphate (FBP). When blood flow is low, O_2 concentration and mitochondrial ATP synthesis (blue), and also glucose concentration and direct glycolytic ATP synthesis (black) quickly approach zero. The stored FBP is then used in the second part of glycolysis for ATP synthesis (red). If the FBP buffering mechanism is uncoupled, ATP levels fall immediately.

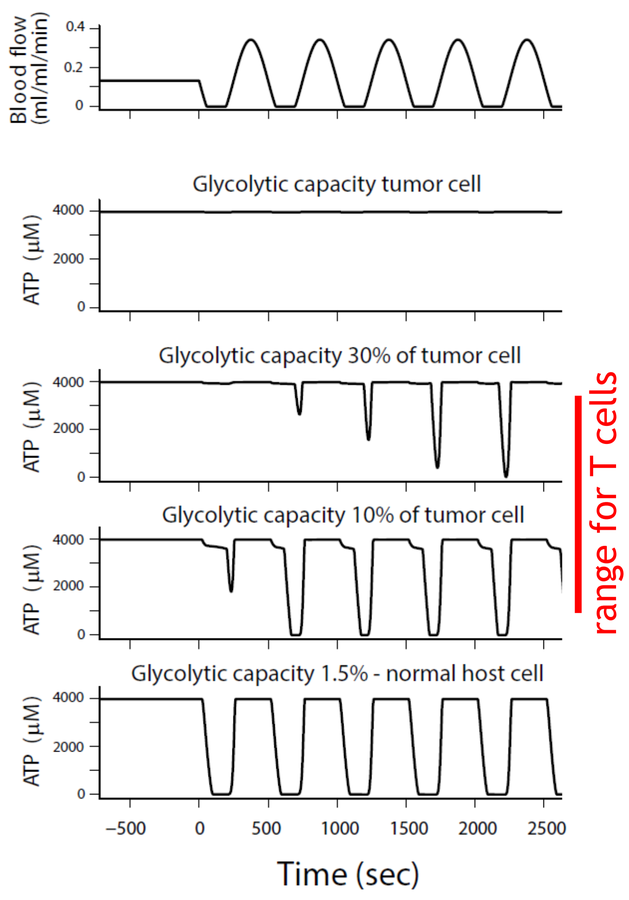
Model fits kinetic data



Dots: experimental data (Coe et al., 1966-1967)
Line: model (Van Beek, 2018)
Ehrlich ascites tumor cells in vitro. Glucose had been depleted and was reintroduced at t=0.
Low concentrations of glucose in the medium are efficiently accumulated in the cells as phosphorylated carbohydrates (up to ~5 mM fructose 1,6-bisphosphate, good for synthesis of ~20 mM ATP).

Predictions for tissue with tumor and host cells

The glucose uptake and FBP buffering mechanism is much stronger in tumor cells than normal host cells in the same tissue.



A hypothetical transition from constant blood flow to a state of intermittent blood flow is simulated. The glucose uptake during flow resumption and the FBP buffering is much stronger in tumor cells than in normal host cells (bottom row) in the same tissue.
T lymphocytes tend to have a stronger glycolytic system than normal cells, although probably not as strong as tumor cells. As a consequence their ATP levels are less affected by flow interruption.

Conclusions

After a period of glucose starvation, tumor cells take up glucose much more avidly than before and store it as phosphorylated carbohydrates. This glucose uptake mechanism has a considerably higher capacity in tumor cells than in normal host cells, with T lymphocytes in an intermediate position.
As a consequence the metabolic resilience of tumor cells in tissue with low blood flow is higher than for host cells, although T lymphocytes are better off than some other types of host cells.