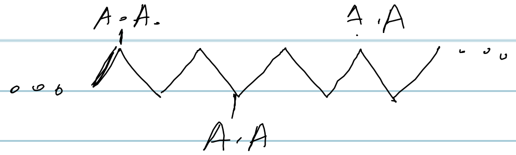
Applications in Molecular Biology

Fundamental dogma:

$$\text{DNA} \to \text{RNA} \to \text{Protein}$$

ATP

A protein is a chain of amino acids:



Glycolytic Oscillations:

Food ⟶ Glucose in blood ⟶ ATP in cells

ATP is adenosine triphosphate, the energy molecule.

Glucose metabolism:

Glucose ($C_6H_{12}O_6$) — Transported from blood into cell

↓ glycolysis

(within cytoplasm) → Pyruvate ($2C_3H_4O_3$) — Enzyme that catalyzes transfer of a phosphate group from phosphoenolpyruvate or PEP to ATP.

↓ citric acid cycle

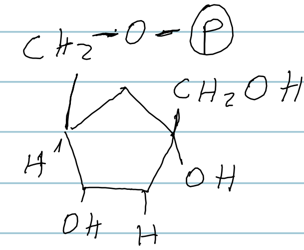
(in mitochondria) → $FADH_2$ NADH ← coenzymes

↓ oxidative phosphorylation

(in mitochondria) → ATP

Our focus is glycolisis, which has 10 enzymat steps converting glucose to pyruvate. One of these enzymes, phosphofructokinase (PFK) converts fructose-6-phosphate to fructose-1, 6-biphosphate.

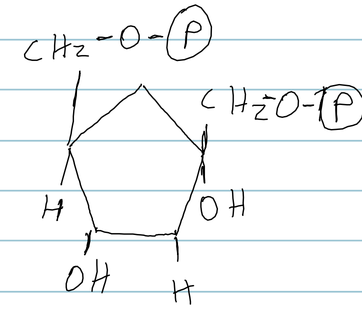
Fructose-6-phosphate (F6P)



ATP → ADP

$\downarrow$ PFK

Fructose-1, 6-biphosphate (FBP)



P = phosphate group

On a larger scale,

glycolysis $\left\{ \begin{array}{l} \text{Glucose} \\ \downarrow \\ \text{F6P} \\ \downarrow \text{PFK} \\ \text{FBP} \\ \downarrow \\ \text{pyruvate} \\ \downarrow \\ \text{ATP} \end{array} \right.$

PFK is an <u>allosteric</u> <u>enzyme</u>; its catalysis depends on several factors:

e.g. <u>yeast:</u> ADP increases reaction rate of PFK

<u>Muscle or β-cells:</u> ATP <u>decreases</u> reaction rate of PFK, FBP <u>increases</u> reaction rate of PFK

Feedback can lead to oscillations. One of the first models of glycolytic oscillations was by Goldbeter and Lefever in 1972; it describes oscillations in yeast.

$$\xrightarrow{\nu} \boxed{ATP} \xrightarrow{\overset{(PFK)}{f}} \boxed{ADP} \xrightarrow{\xi_{ADP}}$$

where

ν = constant influx of ATP
ξ = ADP removal rate
f = PFK reaction

$$\begin{cases} \dot{ATP} = \nu - f(ATP, ADP) \\ \dot{ADP} = f(ATP, ADP) - \xi\, ADP \end{cases}$$

Note that ATP and ADP are measures of concentration. The correct notation would be [ATP] and [ADP]

The PFK function defined by Goldbeter and Lefever was:

$$f(ATP, ADP) = ATP\,(1 + ADP)^2$$

Positive feedback of ADP onto PFK occurs via $(1 + ADP)^2$. Oscillations can occur due to depletion or substrate. ATP and ADP concentrations will oscillate out of phase.

<u>Analysis:</u> <u>ATP nullcline:</u> $\dot{ATP} = 0$

$$\Rightarrow f = \nu$$

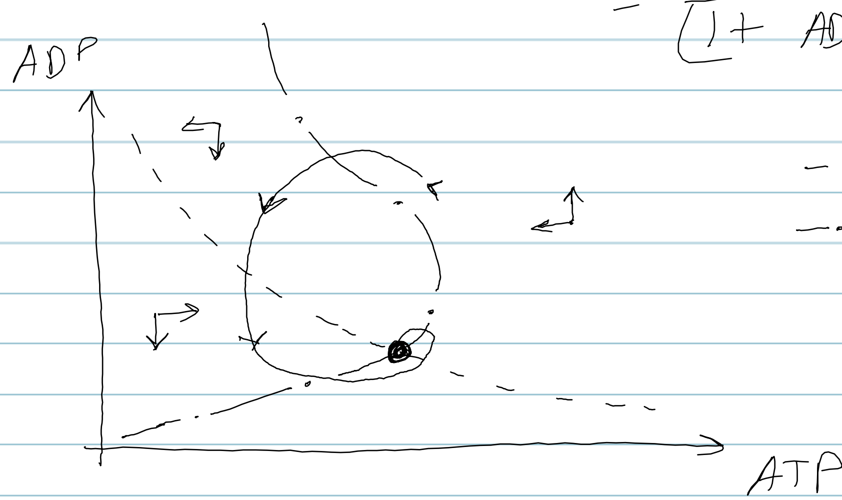
solve for ATP:

$$ATP = \frac{\nu}{(1 + ADP)^2}$$

ADP nullcline: $\dot{ADP} = 0$

$$\Rightarrow ATP(1+ADP)^2 = \xi \, ADP$$

$$ATP = \frac{\xi \, ADP}{(1+ADP)^2}$$



--- ATP nullcline

-·-· ADP nullcline

● stable spiral

with $\nu = 100$

$\xi = 120$

Oscillations occur via supercritical Hopf bifurcations. This model is studied in detail in the homework assignment.