Modelling Krebs Cycle as an Electrical Circuit

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Abstract: We propose an electrical circuit analogue for the well known Krebs cycle, which can be useful in the kinetic studies for various components. Electrical circuits are easier to analyse and study, as several useful tools are already available for this purpose. It is possible to study theoretically the stability conditions for the cycle as a whole. The Krebs cycle is essentially modelled as a blackbox equivalent to an electrical circuit.

Krebs Cycle at a glance:

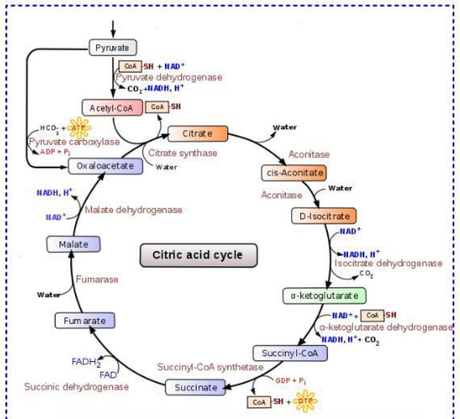
Acetyl-CoA formed by the oxidation of pyruvate enters the Krebs cycle to combine with oxaloacetate to form citrate. This is followed by seven sequential reactions to regenerate oxaloacetate with the release of two CO_2 molecules. In one complete cycle one acetyl-CoA is oxidized and the energy is trapped by the reduction of three molecules of NAD^+ to NADH, one molecule of FAD to $FADH_2$ and formation of one molecule of nucleoside triphosphate (ATP or GTP).

Reaction Step	Enzyme	Input	Output	Inhibitor	Activator
Citrate formation	citrate synthase	Oxaloacetate, Acetyl CoA, H_2O	Citrate, CoA-SH	NADH, succinyl-CoA, citrate, ATP	ADP
Isocitrate formation	Aconitase	Citrate	Isocitrate		
α-Ketoglutarate formation	Isocitrate dehydrogenase	Isocitrate, NAD^+	α-Ketoglutarate, $NADH^+ +H^+$, CO_2	ATP	Ca^{2+}, ADP
Succinyl-CoA formation	α-Ketoglutarate dehydrogenase complex	α-Ketoglutarate, CoA-SH and NAD+	Succinyl-CoA, $NADH^+ +H^+$, CO_2	Succinyl-CoA, NADH	Ca^{2+}
Succinate formation	Succinyl-CoA synthetase	Succinyl-CoA, GDP+Pi	Succinate, GTP, CoA-SH		
Fumarate formation	Succinate dehydrogenase	Succinate, FAD	Fumarate, $FADH_2$		
Malate formation	Fumarase	Fumarate, H_2O	Malate		
Oxaloacetate formation	Malate dehydrogenase	Malate	Oxaloacetate, $NADH^+ +H^+$		

The enzymes of the Krebs cycle with their reactants, products, inhibitors and activators.

The birth of an idea:

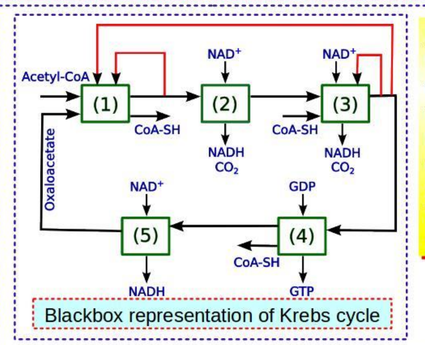
We have modified this cycle so that enzymes appear at the nodes and the substrates appear along the edges. The substrates appear as fluxes in/out of the enzymes which is easier to understand in kinetics studies. Several consecutive reactions can be combined to get one reaction, if the intermediate reactions do not have any regulatory sites.



The Krebs cycle adapted from wikipedia

$$Acetyl-CoA + Oxaloacetate + H_2O \rightarrow Citrate + CoA-SH$$
$$Citrate \rightarrow Isocitrate$$
$$Isocitrate + NAD^+ \rightarrow \alpha-Ketoglutarate + NADH + H^+ + CO_2$$
$$\alpha-Ketoglutarate + CoA-SH + NAD^+ \rightarrow Succinyl-CoA + NADH + H^+ + CO_2$$
$$Succinyl-CoA + GDP + P_i \rightarrow Succinate + GTP + CoA-SH$$
$$Succinate + FAD \rightarrow Fumarate + FADH_2$$
$$Fumarate + H_2O \rightarrow Malate$$
$$Malate + NAD^+ \rightarrow Oxaloacetate + NADH + H^+$$
$$Acetyl-CoA + 2H_2O + 3NAD^+ + GDP + P_i + FAD \rightarrow 3NADH + 3H^+ + FADH_2 + GTP + CoA-SH + 2CO_2$$

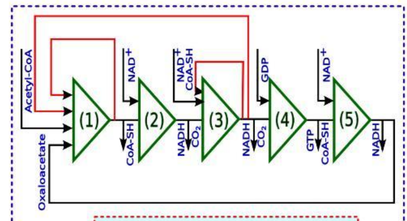
The details of the reactions involved in the Krebs cycle. The intermediates of the Krebs cycle do not appear in the overall reaction and the overall reaction (last line) consist of oxidation of Acetyl-CoA to Carbon dioxide.



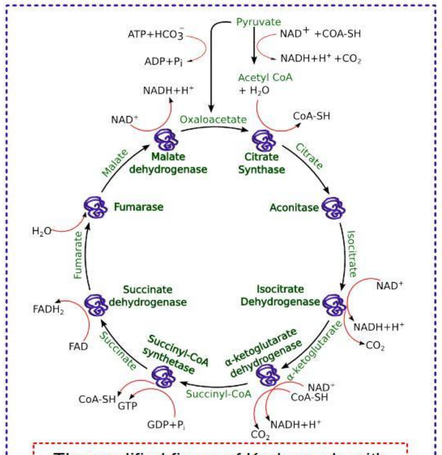
Blackbox representation of Krebs cycle

An enzyme with a regulatory site can be modelled as an amplifier with negative feedback. The negative feedback causes the output to stay stable in spite of changes in the input signal and ensures the role of the amplifier (the specific activity of the enzyme) is minimal. The feedback elements contribute to the overall performance of the circuit.

The Krebs cycle is modelled as a series of five amplifiers that are connected in a cyclic manner. In a biochemical reaction, unit input flux always gives rise to unit output flux and the operational amplifiers in the above scheme have gains very close to unity.



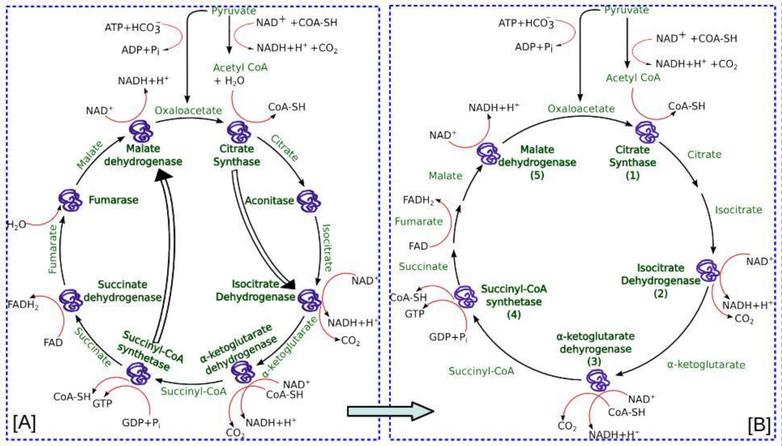
Operational amplifier blocks



The modified figure of Krebs cycle with enzymes drawn at the nodes.

Feeding the idea:

Within a cell, connection between different nodes is established by products and reactants. Connection between different pathways can also occur via nodes, i.e., enzymes, that may be shared between two different circuits. In an electrical circuit this connection is made by physical metallic wire that are responsible for electron conduction. A regulatory enzyme acts more like an amplifier, whose gain can be controlled by another molecule. Such a system is best represented with an amplifier with a feedback network.



[A] : The Krebs cycle shown with enzymes that can be eliminated in the modelling.
[B] : The final diagram suitable for modelling.

The red lines represent feedback path. The degree of feedback depends on the sensitivity of the particular enzyme and need to be explicitly modelled in to the operational amplifiers.

The electrical analogue:

In electrical circuit, potentials and currents hold the central space.

Potential: Analogue of potential in the metabolic pathway is concentration, or more accurately, log[concentration], which corresponds to the thermodynamic potential.

Current: Analogue of current in the metabolic pathway is the flux, more accurately the local rate of change of concentration, that depends on the enzyme concerned.

Concluding the Idea:

This is a very good overall simplification of the Krebs cycle, that can be used in actual kinetic modelling if sufficient detailed parameters of the enzymes are available.