Attribute Exploration with Proper Premises and Incomplete Knowledge Applied to the Free Radical Theory of Ageing

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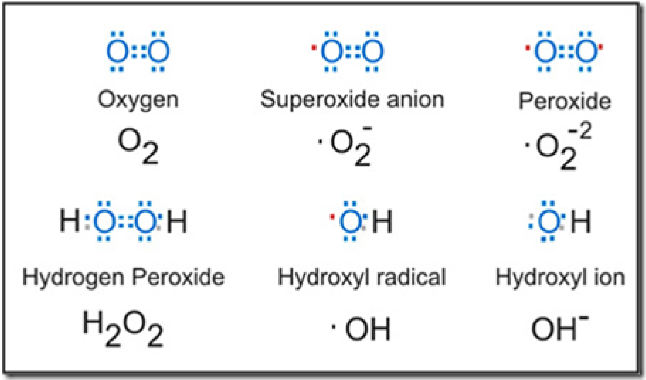
Outline

Free radicals

- Free radicals have unpaired electrons.
- One subclass of reactive oxygen species (ROS), highly oxidative small molecules capable of damaging organic molecules.



ROS generation in the mitochondrial respiratory chain

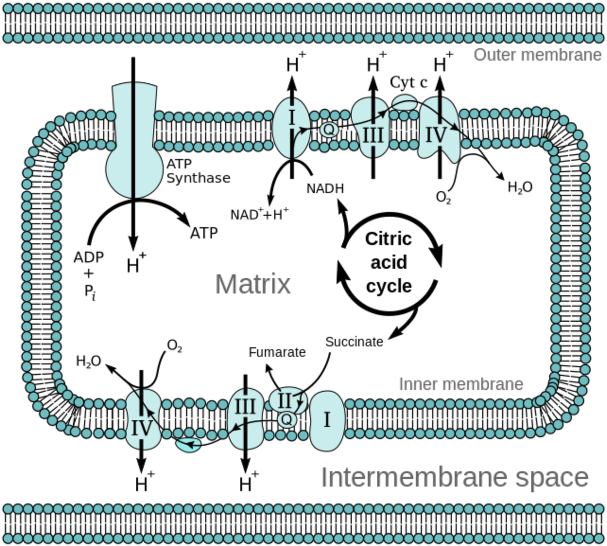


Figure: [*Tim Vickers. In: en.wikipedia.org, Electron transport chain.*]

Mitochondria get damaged with age.

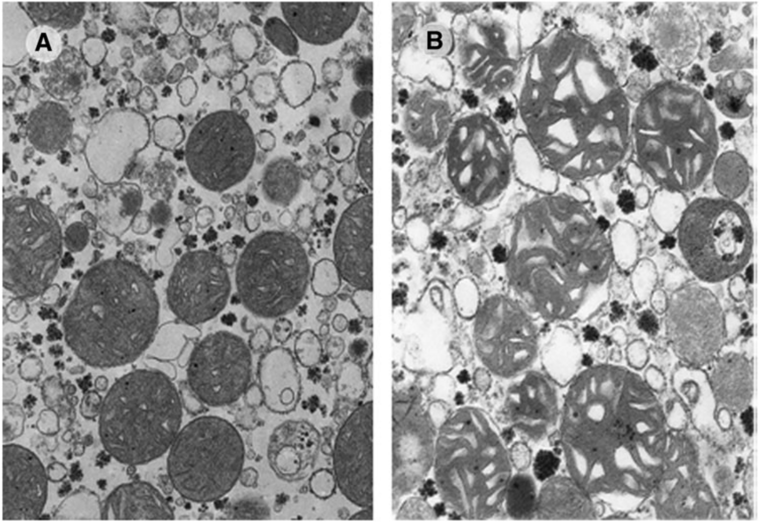
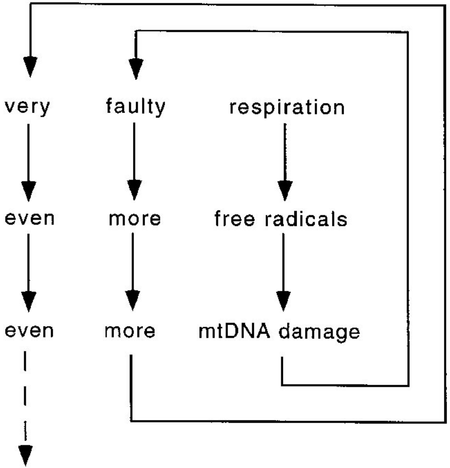


Figure: Liver mitochondria from young and old rats. [*Jose Vina. Antioxidant & Redox Signaling, 19 (8), 2013, Figure 2*]

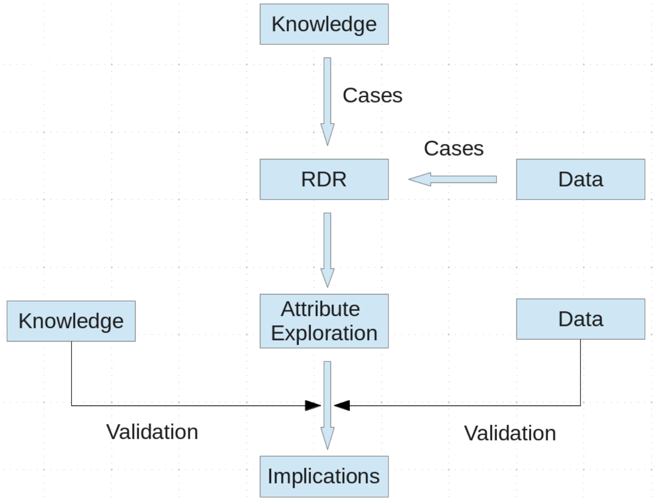
Vicious cycle of ROS generation and molecular damage



[*Aubrey de Grey. The Mitochondrial Free Radical Theory of Aging, 1999, Fig. 6.1*]

Outline

The workflow



A collection of Ripple Down Rules (RDR) and cornerstone cases is converted to a complete knowledge base of implications.

Rules from literature

Knowledge[1] is collected in a tree of general and exceptional rules (*Ripple Down Rules, RDR*).

Observed cases, defined by attributes $m \in M \setminus C$, are classified by classes $C \subseteq \{ROS.old.+, ROS.old.-, Lifespan.+, Lifespan.-\} \subseteq M$.

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    - 1.1. AntiOx1.+ $\rightarrow$ ROS.old.–, Lifespan.+
        - 1.1.1. AntiOx1.+, AntiOx2.– $\rightarrow$ ROS.old.+
    - 1.3. AntiOx2.–, Mouse $\rightarrow$ ROS.old.+
    - 1.3. AntiOx2.–, CElegans $\rightarrow$ ROS.old.+

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   - 1.3. AntiOx2.–, Mouse $\rightarrow$ ROS.old.+
   - 1.3. AntiOx2.–, CElegans $\rightarrow$ ROS.old.+

Background knowledge for later exploration:

$$\text{AntiOx2.–} \rightarrow \text{ROS.old.+}$$

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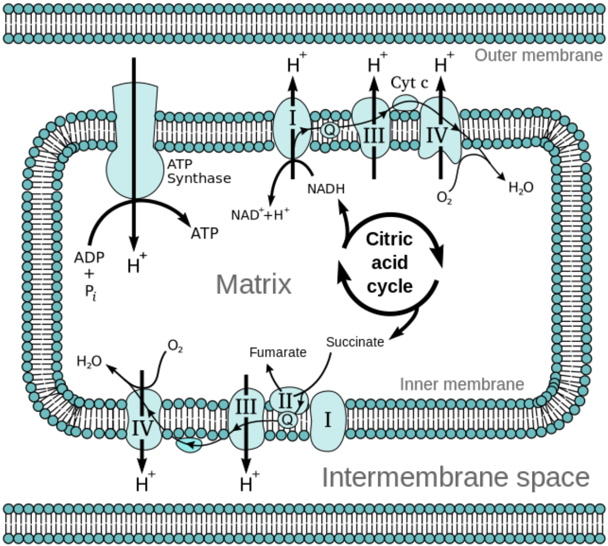
Mutations of respiratory chain molecules are studied in the ROSAge project



A rule derived from ROSAge data

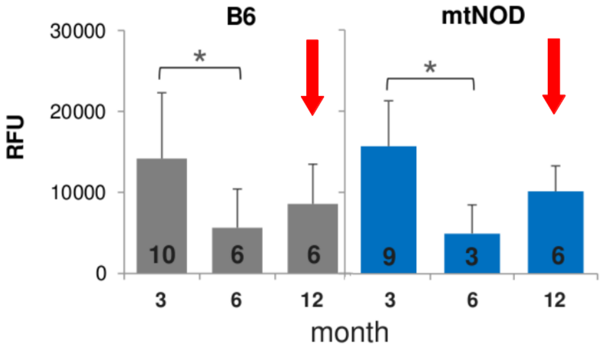


Figure: Basal ROS measurements by Dept. of Hematology Rostock.

Mouse, Mut-ETC, $\rightarrow \emptyset$

A conflicting rule derived from ROSAge data

Figure: Basal ROS measurements by Institute of Physiology Rostock for the mouse strain NOD (mutation in complex IV of the respiratory chain). A significant increase of free radicals in 24 month old mice is measured, compared to 3 month.

$$\text{Mouse, Mut-ETC} \rightarrow \text{ROS.old.+}$$

$\Rightarrow$ Mut-ETC, Mouse $\rightarrow \emptyset$ not accepted as background knowledge.
Both cases are stored in the formal context of cornerstone cases.

The tree of rules and exceptions

1. $\top \rightarrow$ ROS.old.+, Lifespan.–
    1.1. AntiOx1.+ $\rightarrow$ ROS.old.–, Lifespan.+
        1.1.1. AntiOx1.+, AntiOx2.– $\rightarrow$ ROS.old.+
    1.2. Mouse, AntiOx2.– $\rightarrow$ ROS.old.+
    1.3. CElegans, AntiOx2.– $\rightarrow$ ROS.old.+
    1.4. Mouse, Mut-ETC $\rightarrow \bot$

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1. $\top \rightarrow$ ROS.old.+, Lifespan.–
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2. OxStress $\rightarrow$ ...
   2.1. ...

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   1.4. Mouse, Mut-ETC $\rightarrow \bot$
2. OxStress $\rightarrow$ ...
   2.1. ...
3. ATP.old.– $\rightarrow$ ...
   3.1. ...

The incomplete formal context of cornerstone cases

	AntiOx1.+	AntiOx1.−	AntiOx2.+	AntiOx2.−	CElegans	Mouse	Mut-ETC	ROS.old.+	ROS.old.−	Lifespan.+	Lifespan.−
1.	?	?	?	?	×	×	?	×			×
1.1.	×		?	?	×	×			×	×	
1.1.1.	×			×	×	×		×		?	?
1.2.-1.3.	?	?		×	×	×		×		?	?
1.4a	?	?	?	?	?	×	×			?	?
1.4b	?	?	?	?	?	×	×	×		?	?

Table: Examples (cornerstone cases) related to the RDR knowledge base: Certain context $\mathbb{K}_+$ and possible context $\mathbb{K}_?$.

Outline

Confirmed rules (some logical juggling)

AntiOx1.– $\longrightarrow$ ROS.old.+

AntiOx1.–, AntiOx2.+ $\longrightarrow \perp$ (background) implies that AntiOx2.+ does not hold.
As RDR, we had already the stronger rule AntiOx1.+, AntiOx2.– $\longrightarrow$ ROS.old.+.

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AntiOx2.+ $\longrightarrow$ ROS.old.–

AntiOx1.–, AntiOx2.+ $\rightarrow \bot$ (background) implies that AntiOx1.– does not hold.
Hence, AntiOx2.+, AntiOx1.– $\rightarrow$ ROS.old.+ (parallel to RDR 1.1.1) is the only exception.

Confirmed rules

AntiOx1.+, AntiOx2.+, CElegans $\longrightarrow$ Lifespan.+

The strong conclusion can be assumed for the short living worm C. elegans.[2]

[3]Sohal R., Orr, W. *Free Radical Biology and Medicine* 52(3), 539-555 (2012)
[3]Kirkwood TBL, Kowald A. *BioEssays* 2012, p. 6

Confirmed rules

AntiOx1.+, AntiOx2.+, CElegans $\longrightarrow$ Lifespan.+

The strong conclusion can be assumed for the short living worm C. elegans.[2]

AntiOx1.–, Mouse, Mut-ETC $\longrightarrow$ Lifespan.–

Mutations (deletions) of the mitochondrial DNA can cause lifespan reducing damage for long-lived animals like mice.[3]

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[3] Sohal R., Orr, W. *Free Radical Biology and Medicine* 52(3), 539-555 (2012)

[3] Kirkwood TBL, Kowald A. *BioEssays* 2012, p. 6

Counterexamples

Mouse, CElegans, Mut-ETC, AntiOx1.$+ \to$ ROS.old.–

Counterexample:

AntiOx2.$+ \to$ ROS.old.– was accepted, but here AntiOx2.– is possible.

[3] Fitzenberger E, Boll M, Wenzel U. Impairment of the proteasome is crucial for glucose-induced lifespan reduction in the mev-1 mutant of Caenorhabditis elegans. *Biochim Biophys Acta*, 2013 Apr, 1832(4), p. 565-73.

Counterexamples

Mouse, CElegans, Mut-ETC, AntiOx1.+ $\longrightarrow$ ROS.old.–

Counterexample:

AntiOx2.+ $\longrightarrow$ ROS.old.– was accepted, but here AntiOx2.– is possible.

AntiOx2.+ $\longrightarrow$ Lifespan.+

ROS are reduced, but this is not sufficient to extend lifespan.
Counterexample:

(AntiOx1.+,) AntiOx2.+, (Mouse,) ROS.old.–, NOT Lifespan.+

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Implications with proper premises

Definition

For a given formal context (G, M, I) and a set of attributes $P \subseteq M$, define $P^\bullet$ to be the set of those attributes in $M \setminus P$ that follow from P but not from a strict subset of P, i.e.

$$P^\bullet = P'' \setminus \left(P \cup \bigcup_{S \subsetneq P} S''\right)$$

P is called a *proper premise* if $P^\bullet$ is not empty. It is called a *proper premise for m* if $m \in P^\bullet$.

Exploration with incomplete counterexamples

PP-Implications are suited for disjoint basic sets for the premises and conclusions:

- Decision of an implication $P \to C$ by closure under all implications of the base: $C \subseteq \mathcal{L}(P)$?
- PP base is iteration free: Closure is reached in one step.
- For disjoint implications, no iteration is possible.

$\Rightarrow$ Standard algorithm for the base construction of the whole context can be used, with iteration through the interesting $m \in C \subsetneq M$.

Implications have to be valid for any *realizer* of $\mathbb{K}_+$ and $\mathbb{K}_?$.

Proposition (Proposition 30 from Ganter/Obiedkov 2013[4])

A set $P \subseteq M$ possibly entails $m \in M$ if and only if $m \in P^{+?}$.

[4] Ganter, B., Obiedkov, S.: Conceptual Exploration. Preprint, Dresden (2013)

A new algorithm

define `algorithm-2` $(\mathbb{K}_+ = (G,M,I_+), \mathbb{K}_? = (G,M,I_?), C \subsetneq M,$
$\mathcal{B} \subseteq \mathrm{Th}_C(\mathbb{K}_+))$
  $\mathcal{L} := \mathcal{B}$
  forall $m \in C$ **do**
    $\mathcal{P} := \{P \subseteq M \setminus C \mid P$ possible proper premise for m in $(\mathbb{K}_+, \mathbb{K}_?)\}$
    while there exists $P \in \mathcal{P}$ with $\mathcal{L} \not\models (P \longrightarrow \{m\})$ **do**
      if expert confirms $P \longrightarrow \{m\}$ **then**
        $\mathcal{L} := \mathcal{L} \cup \{P \longrightarrow \{m\}\}$
        forall $g \in G$ **do**
          $g^+ := \mathcal{L}(g^+)$
          forall $m \in g^? \setminus g^+$ **where** $\mathcal{L}(g^+ \cup \{m\}) \not\subseteq g^?$ **do**
            remove m from $g^?$
          end
        end
      else
        ask expert for valid counterexample and augment $\mathbb{K}_+$ and $\mathbb{K}_?$
        $\mathcal{P} := \{P \subseteq M \setminus C \mid P$ possible proper premise for m in $(\mathbb{K}_+, \mathbb{K}_?)\}$
      end
    end
  end
  return $\mathcal{L} \setminus \mathcal{B}$
end

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- Integration of insecure data - Fuzzy FCA?
- Larger, biologically more relevant application.

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