ROS homeostasis in a dynamic model: How to save PD neuron?

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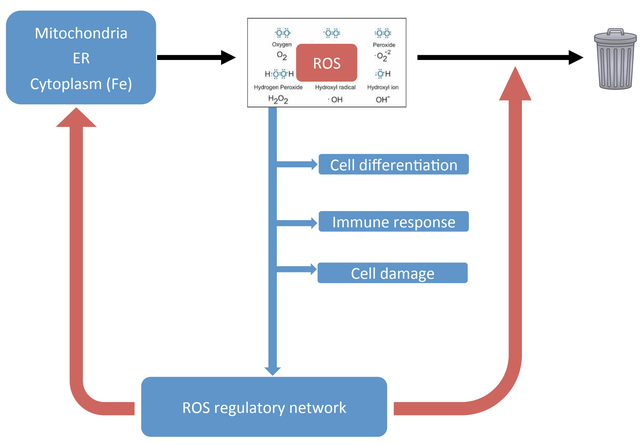
Introduction



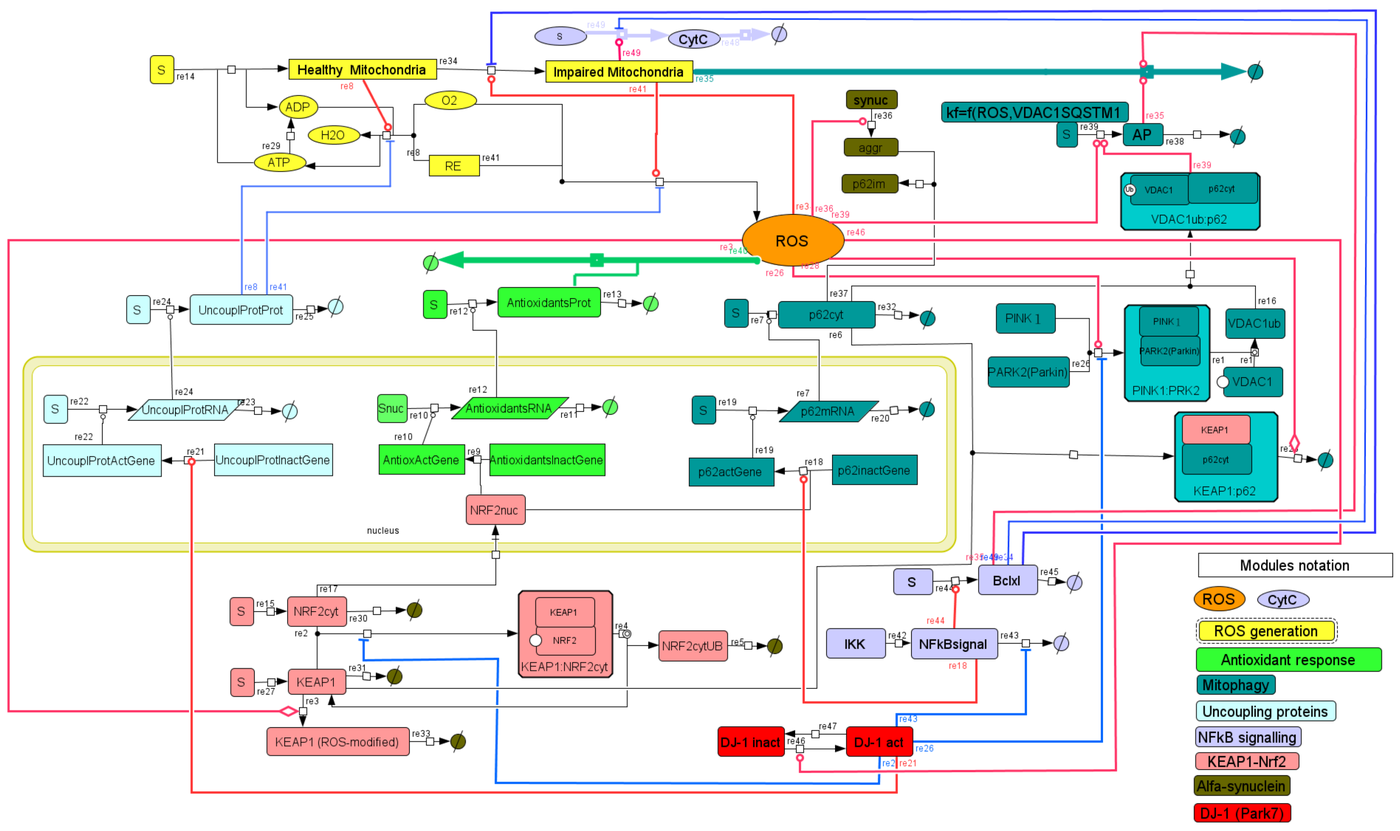
ROS plays three main roles in the cell: it is a (i) signalling molecule in cell differentiation, (ii) "killing" ingredient in immune response, and (iii) damaging component leading to undesired cell death. The precise tuning of ROS management is crucial in cell functioning.

Parkinson's disease (PD) is an example of ROS-related neurodegenerative disorders, affecting 1–3% of the population over 65 years of age. PD is characterised by motoric disorders and is caused by the death of dopaminergic neurons in the *substantia nigra* - a brain structure located in the mesencephalon (midbrain). Dopaminergic neurons need a lot of energy to secrete dopamine. Thus, dopaminergic neurons have a higher level of oxidative phosphorylation and produce more ROS.

ROS management network is a good example of a non-linear multi-component system which is too complex for intuitive understanding and needs more advanced systems biological approaches.

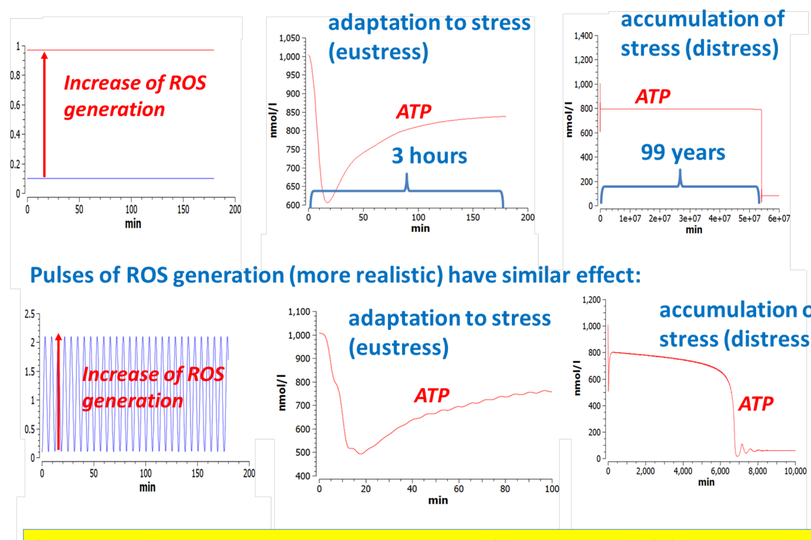
We propose a detailed, mechanistic, dynamic model of ROS management. Our model offers insight into the design principles underlying the functionality of ROS homeostasis and enlightens the functionality of this system in health and Parkinson's disease.

Detailed model of ROS management

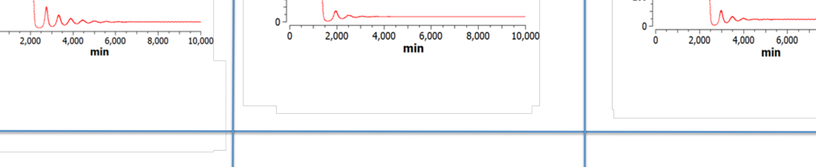


An emergent behaviour: Response to the increased ROS generation

System responds to the step increase of ROS generation:

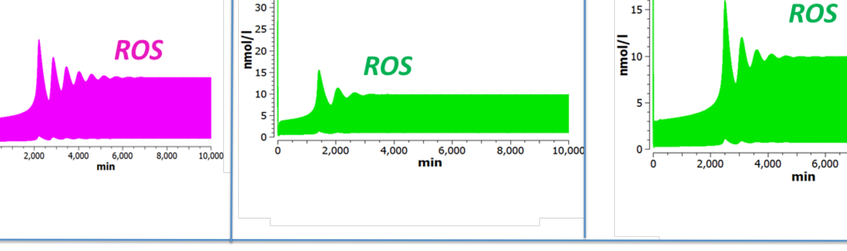


Pulses of ROS generation (more realistic) have similar effect:



System allows to compensate stress (increased ROS generation) in the short term. However, in the long term, system collapses.

Mechanism explaining why does it happen:



Parkinson's disease: How to save a neuron

Activation of Nrf2 synthesis (e.g. by caffeine) might help

Activation of Nrf2 synthesis (e.g. by caffeine) does not help

Proposed example of personalised medicine: PD-related increase of α-synuclein might be compensated by Nrf2 activation. However, Nrf2 activation does not help if PD is caused by DJ1 knockdown or other mutations.