Computing Life: Blue-print modelling and domino approach in design principle studies of Reactive Oxygen Species management

Dr. Alexey Kolodkin

Or:

Designing strategies to visualize Life


Seattle, USA
Knowledge Transfer in Systems Biomedicine
Irkutsk, Russia
Physiology at Irkutsk State University (Diploma)
Tarragona, Spain
Chemical Engineering
(M.Sc)
Amsterdam, the Netherlands
Systems Biology (M.Sc and Ph.D)
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Arctic Ocean
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North America
Baffin Island
Greenland
Norway
Amsterdam
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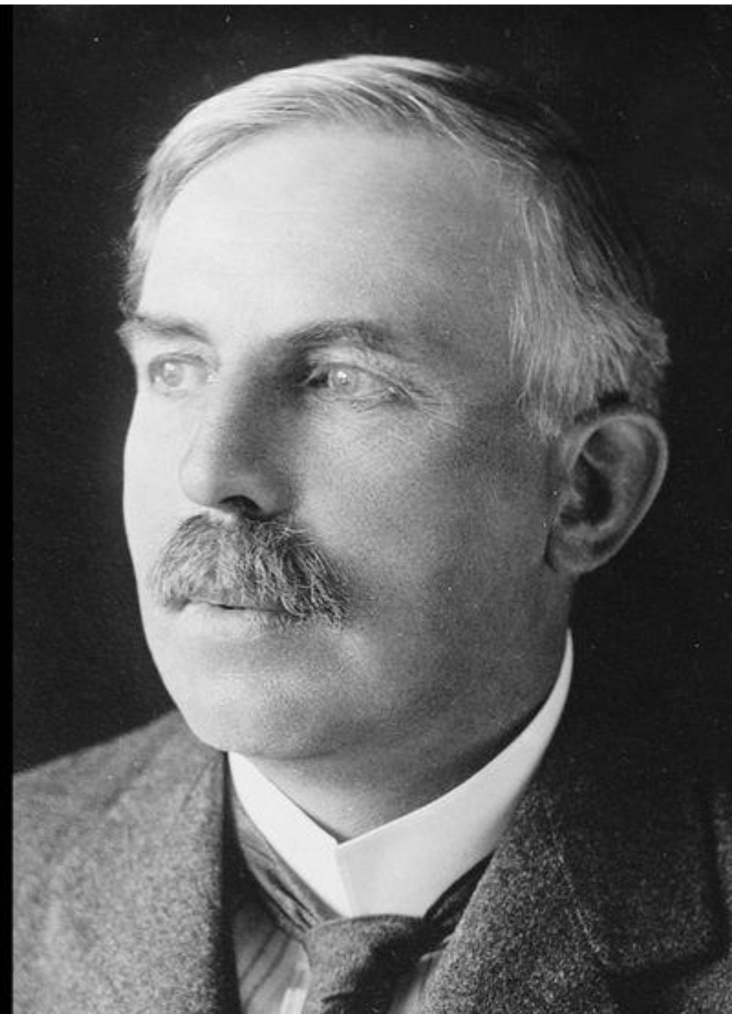
“All science is either physics or stamp collecting.”

Ernest Rutherford, *physicist, born August 30, 1871*

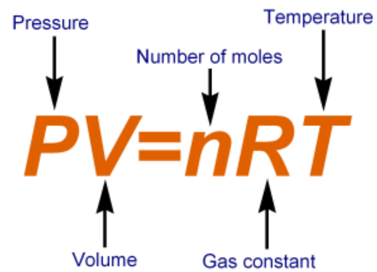


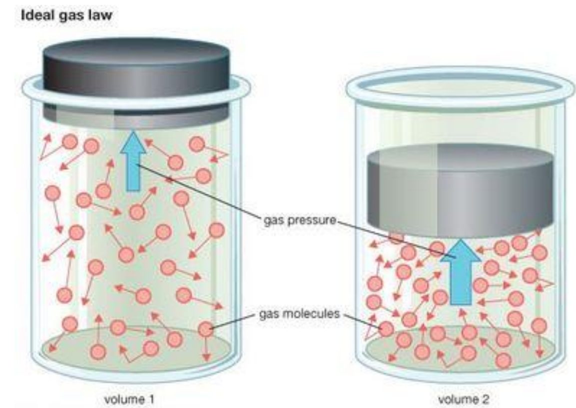
Dobson's Improbable Quote of the Day

Physics

Stamp collecting

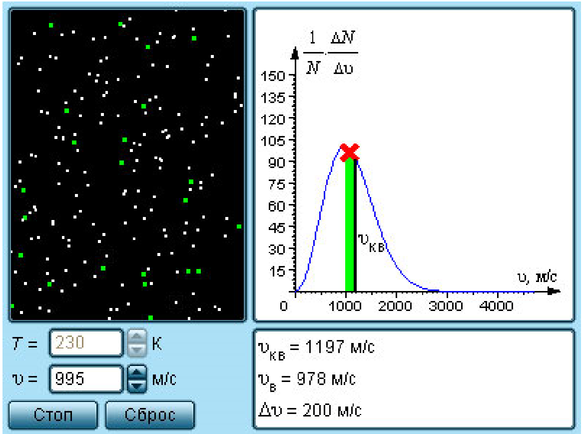
How emergent properties of system relate to each other:



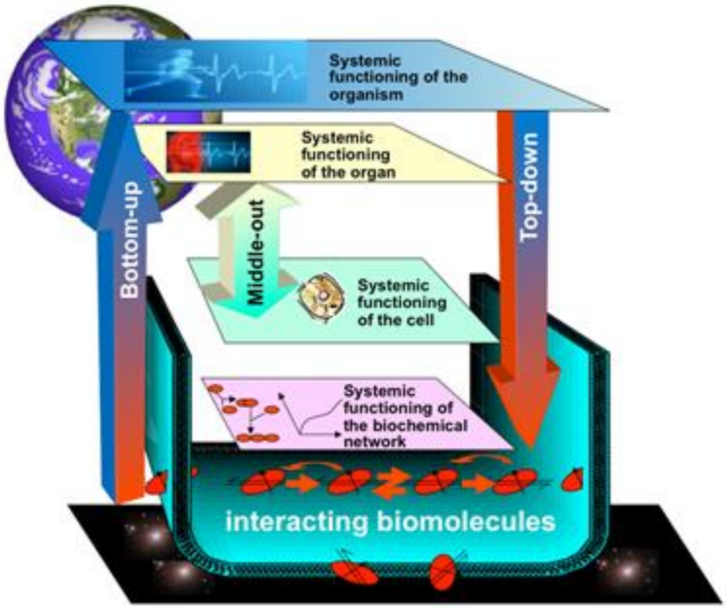


How properties of system emerge:

$$E_k=3/2k*T$$



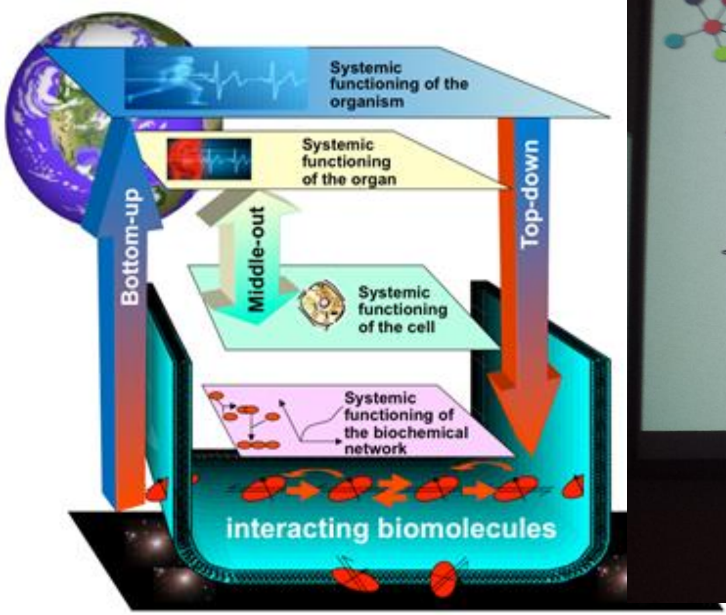
“Stamp collecting” in biology

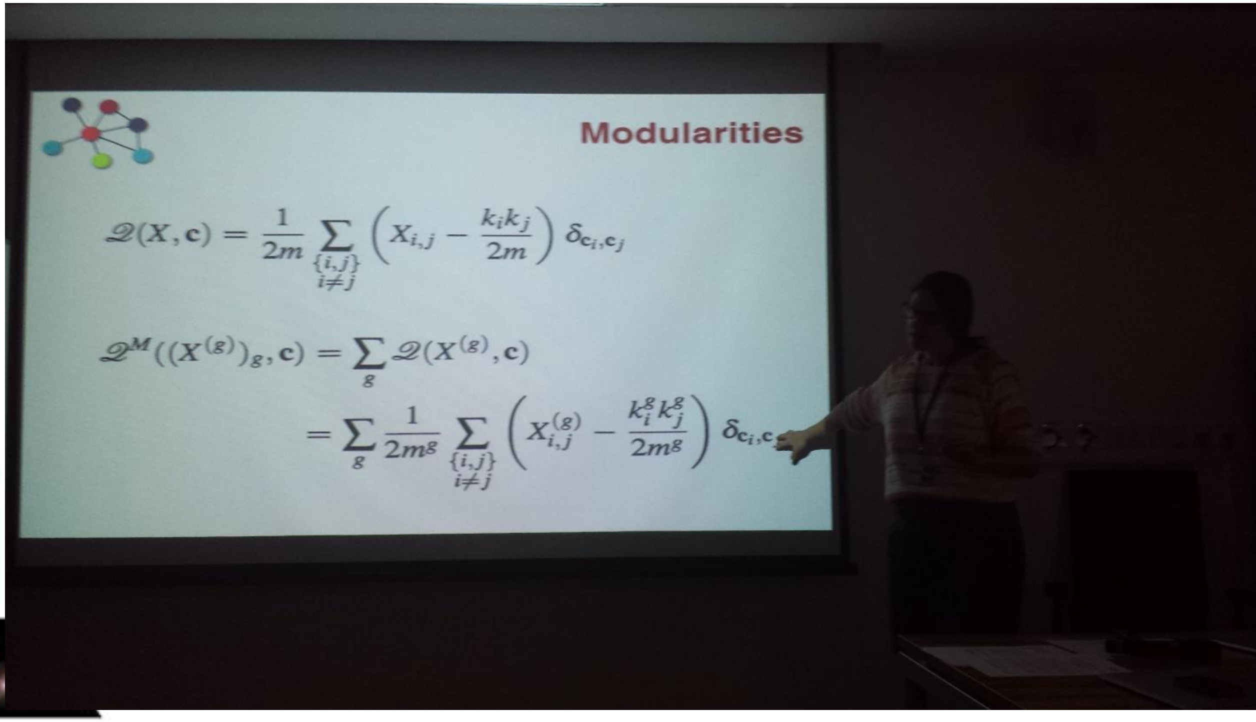


List of genes associated with 6000 genetic diseases:

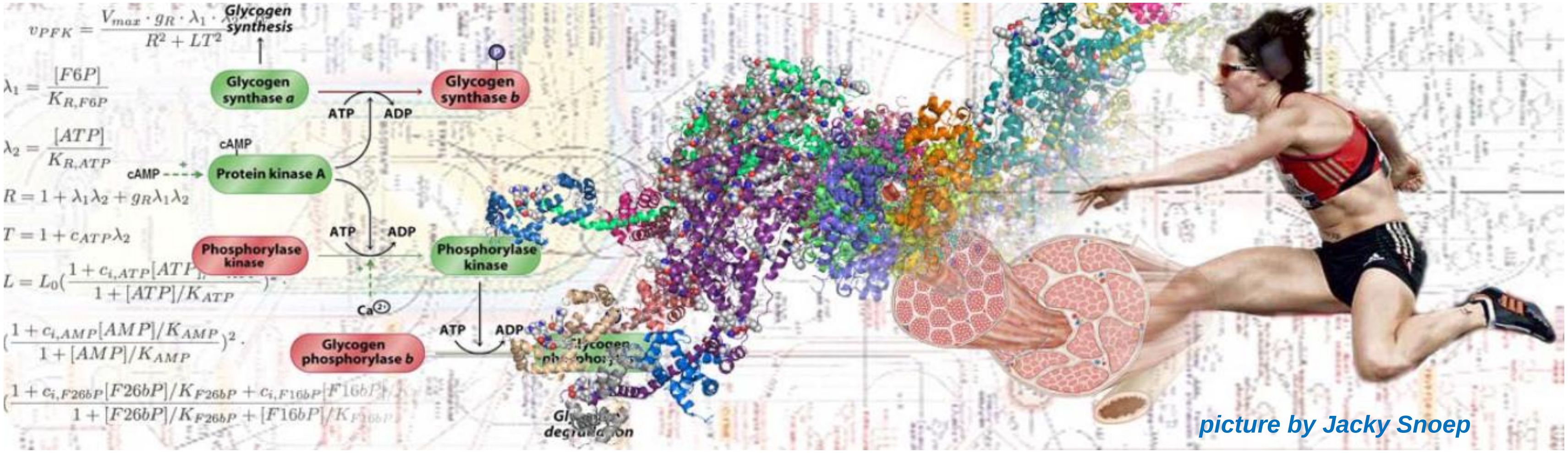
Disease	Type of Inheritance	Gene Responsible
Phenylketonuria (PKU)	Autosomal recessive	Phenylalanine hydroxylase (*PAH*)
Cystic fibrosis	Autosomal recessive	Cystic fibrosis conductance transmembrane regulator (*CFTR*)
Sickle-cell anemia	Autosomal recessive	Beta hemoglobin (*HBB*)
Albinism, oculocutaneous, type II	Autosomal recessive	Oculocutaneous albinism II (*OCA2*)
Huntington's disease	Autosomal dominant	Huntingtin (*HTT*)
Myotonic dystrophy type 1	Autosomal dominant	Dystrophia myotonica-protein kinase (*DMPK*)
Hypercholesterolemia, autosomal dominant, type B	Autosomal dominant	Low-density lipoprotein receptor (*LDLR*); apolipoprotein B (*APOB*)
Neurofibromatosis, type 1	Autosomal dominant	Neurofibromin 1 (NF1)

“Physics” in Biology





System of many equations, or, perhaps, one very complex equation?

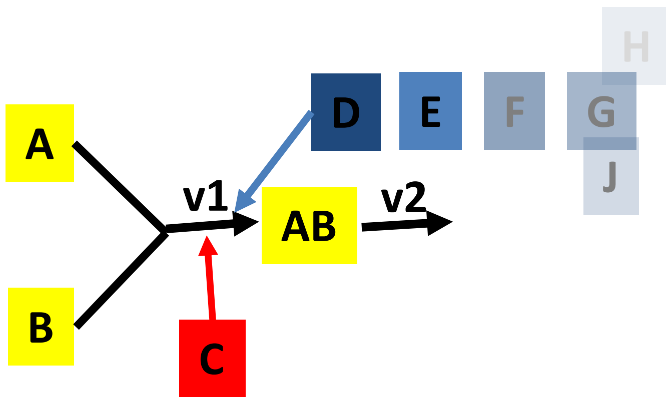


picture by Jacky Snoep

Problems in computing the Life

High state-dependency of component properties E.g. interactions between proteins A and B depends on

- **Other components (C,D,E,F…)**
- **Hysteresis**
- **Flow of mass and energy through the system**
- **Initial and boundary conditions, etc.**



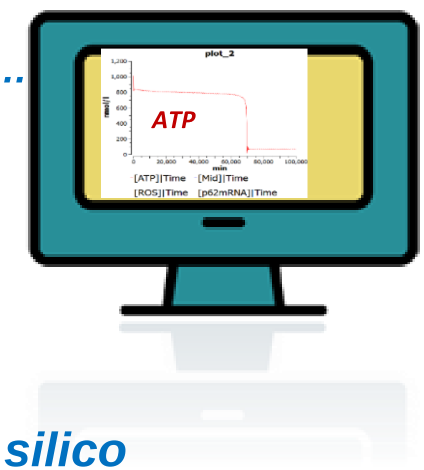
Solution through the systems biological approach:

Protein A + Protein B = Complex AB

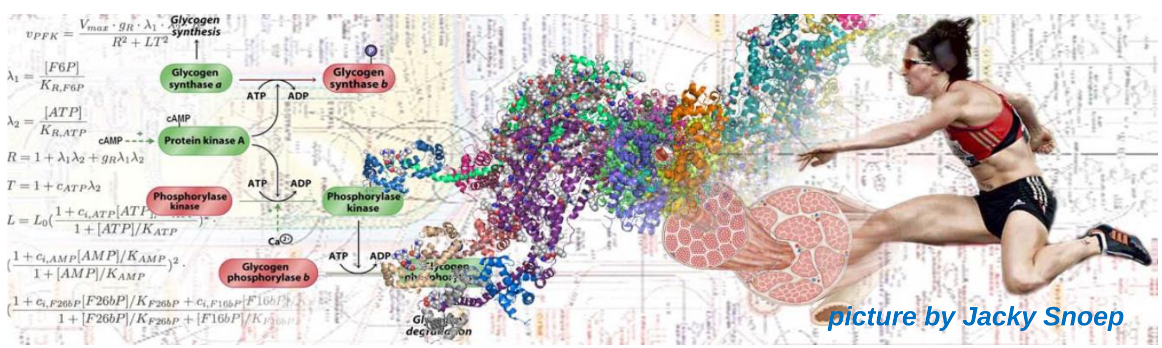
v1= kf*[A]*[B]*[C] – kb*[AB]

v2=…..

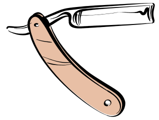
d[AB]/dt=v1-v2….



Systems Biology – reconstruction of biological emergence *in silico*



picture by Jacky Snoep



Occam's razor

William of Occam (1285-1349):
"One should not postulate (pose) more things without necessity" (*Pluralitas non est ponenda sine necessitate*)

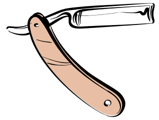
Which model is more likely to be correct?

more complicated model

A B C D

simpler model

A B C



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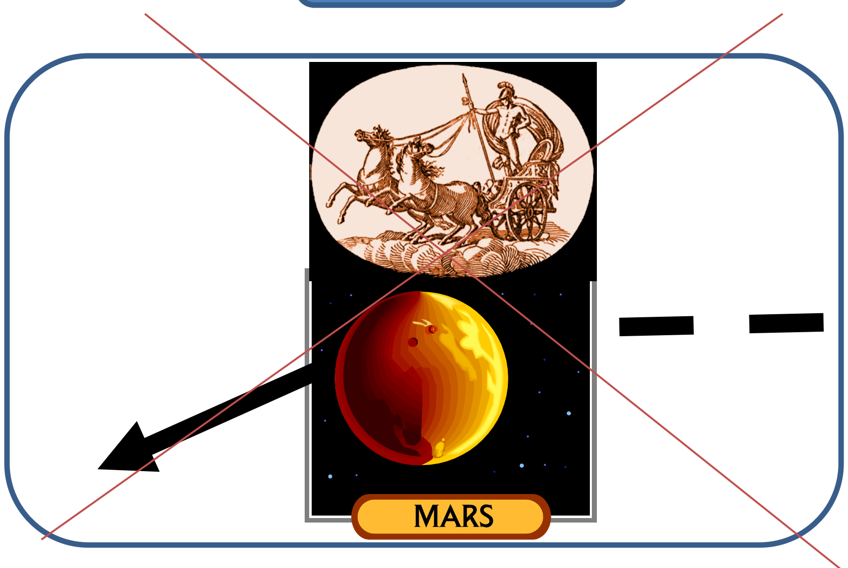


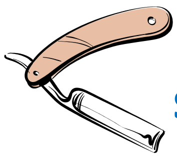
simpler model

A B C

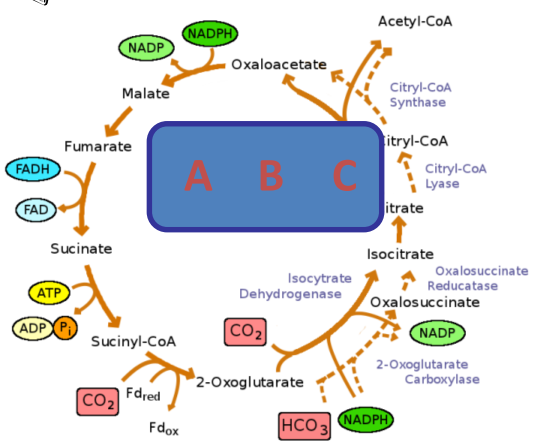
Systems Biology

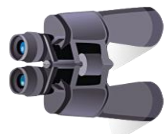
Hans V. Westerhoff (at the begging of XXI century):
One should not remove things without necessity
(*Pluralitas non est eliminanda sine necessitate*)

More likely to be correct

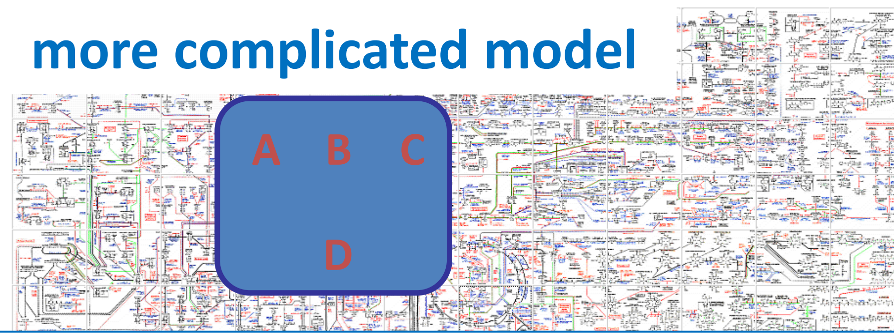


simpler model





more complicated model



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journal homepage: www.elsevier.com/locate/pbiomolbio

ELSEVIER

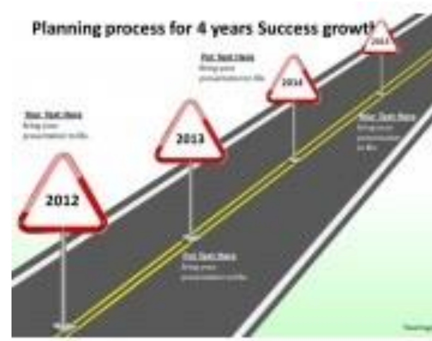
Orginal research

Computing life: Add *logos* to biology and *bios* to physics

Alexey Kolodkin [a,b,*], Evangelos Simeonidis [a,b], Hans V. Westerhoff [c,d,e]

Vision and Strategy with flexible plans

Stiff plan



Move forward:

2000
Craig Venter's genome

Step by step:

1957

1957

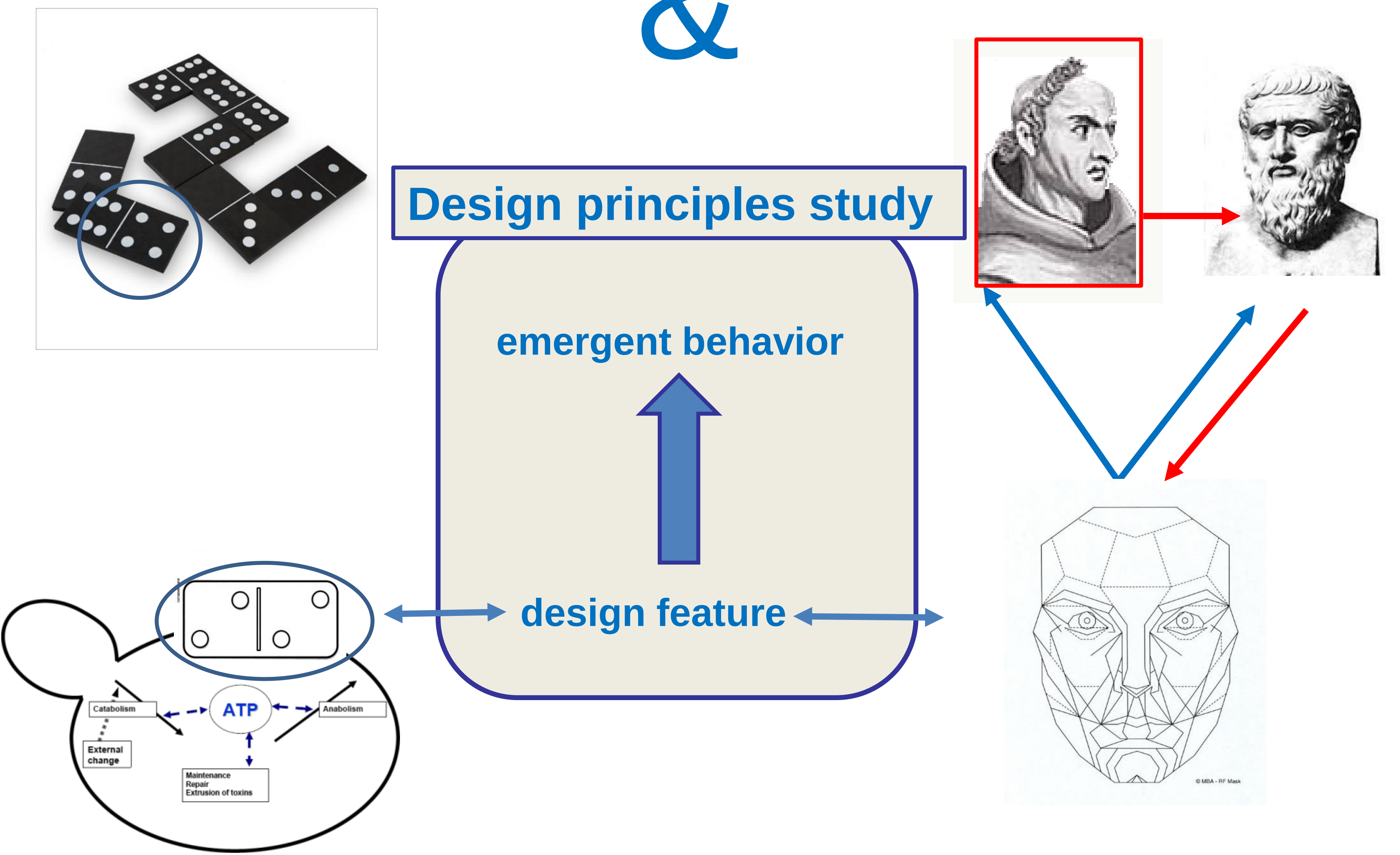
1961

1965

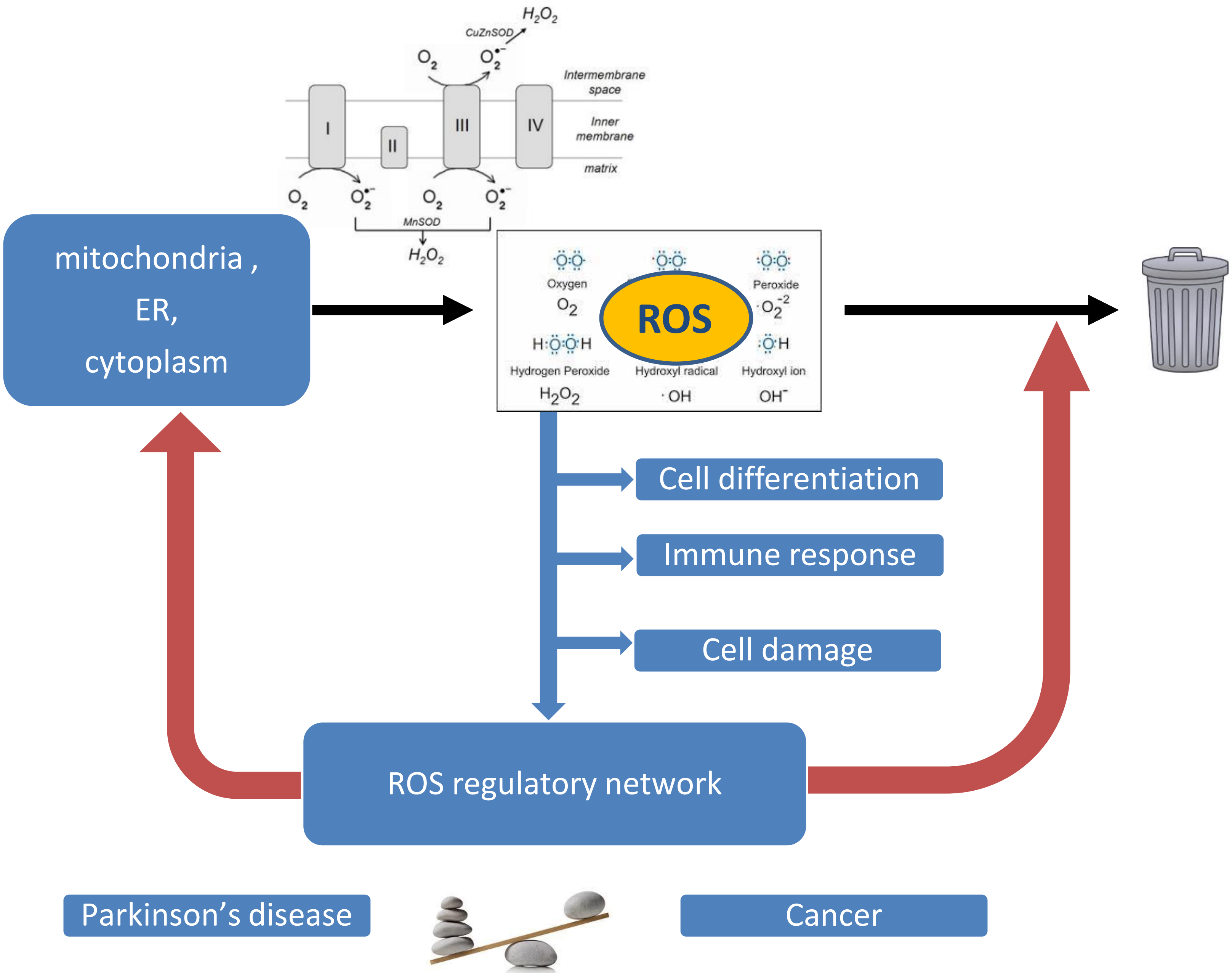
1969

2015

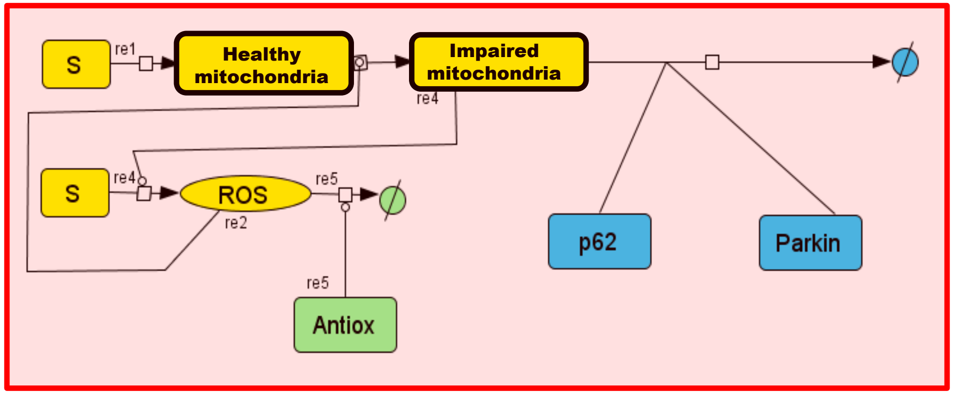
“Domino” approach & “Blue-print” modelling



Reactive Oxygen Species (ROS) management

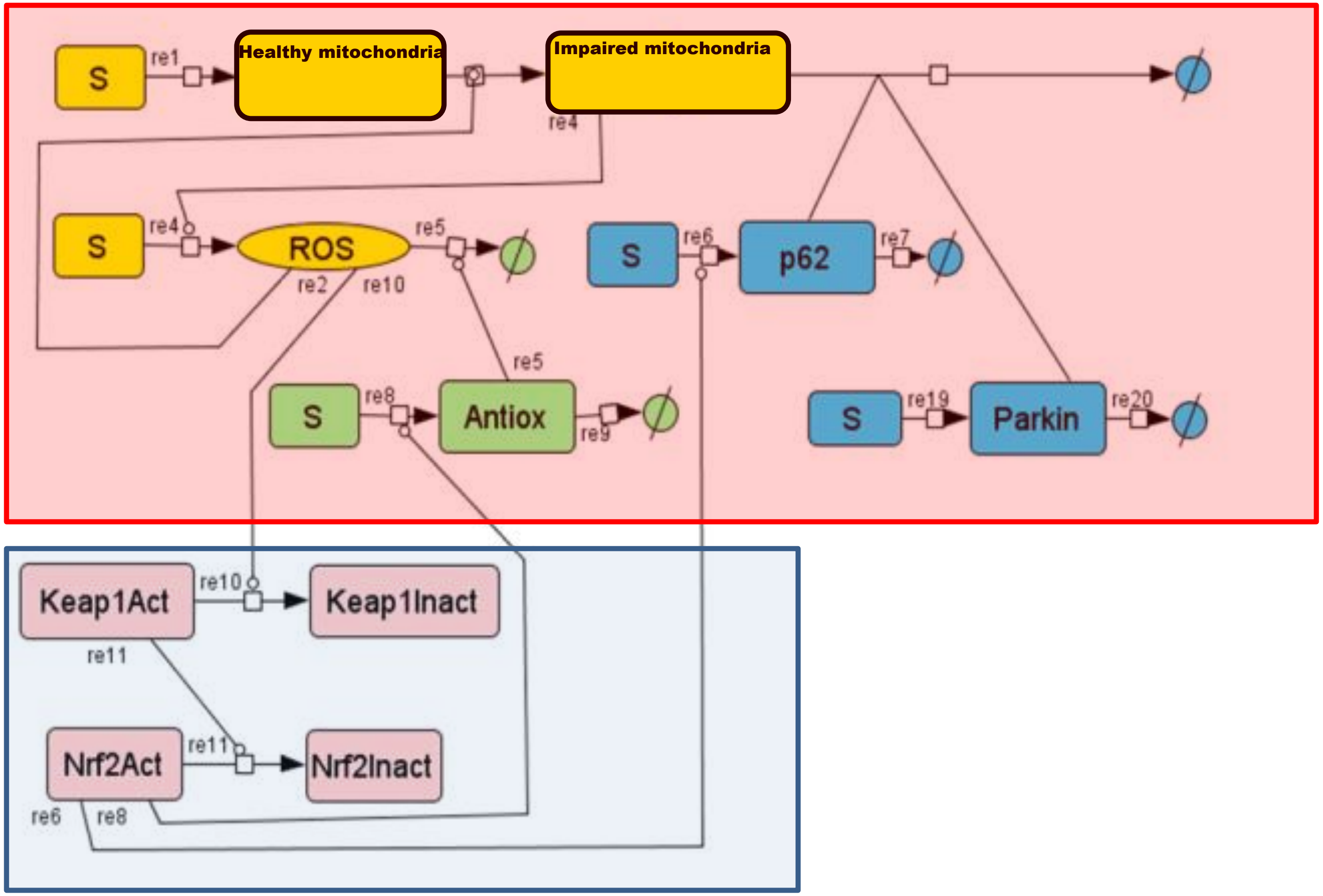


Model 1


S
re1
Healthy mitochondria
Impaired mitochondria
re4
S
re4
ROS
re5
re2
re5
Antiox
p62
Parkin

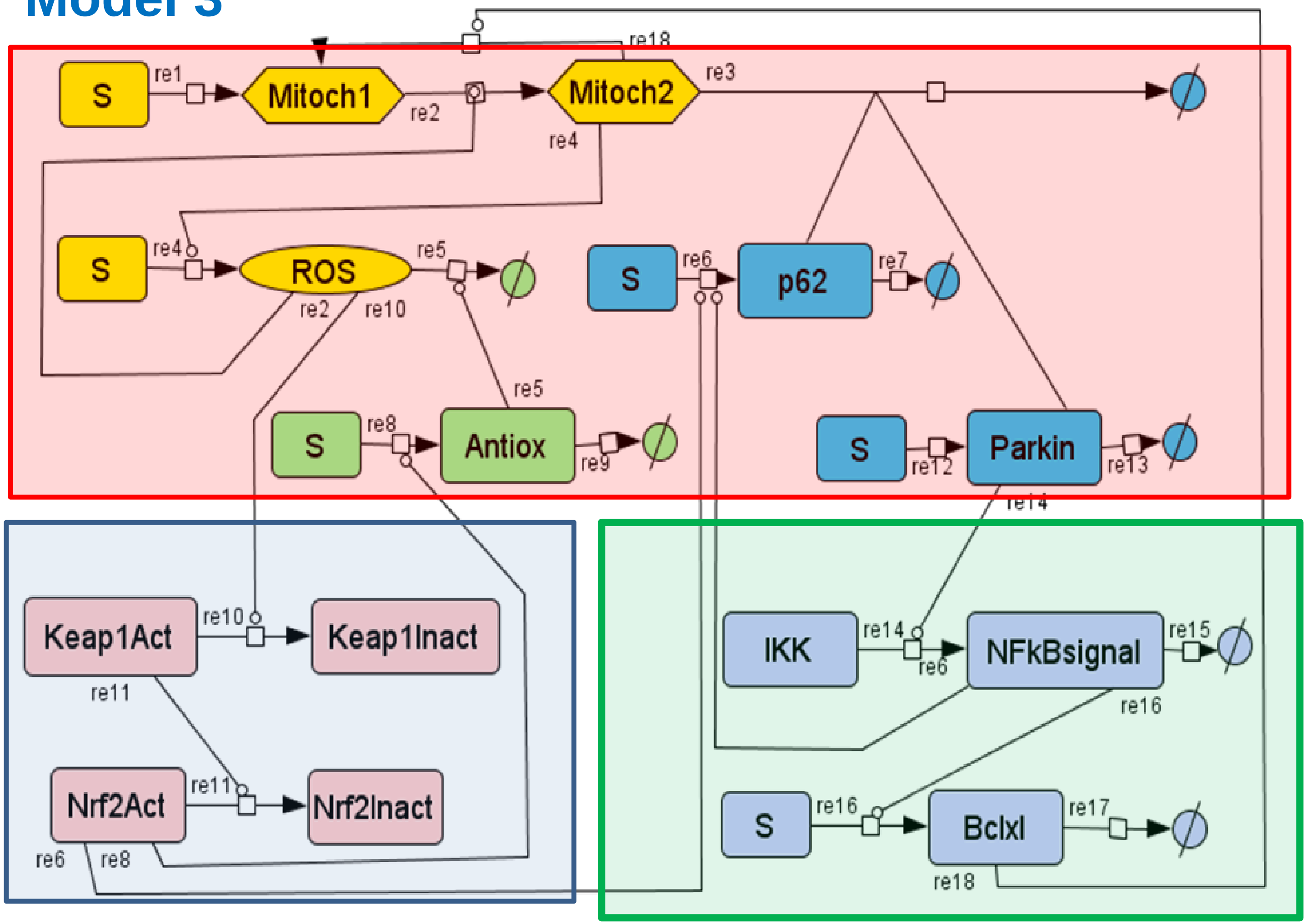
We add nrf2-keap1 system (regulation of p62 and antioxidants)

Model 2



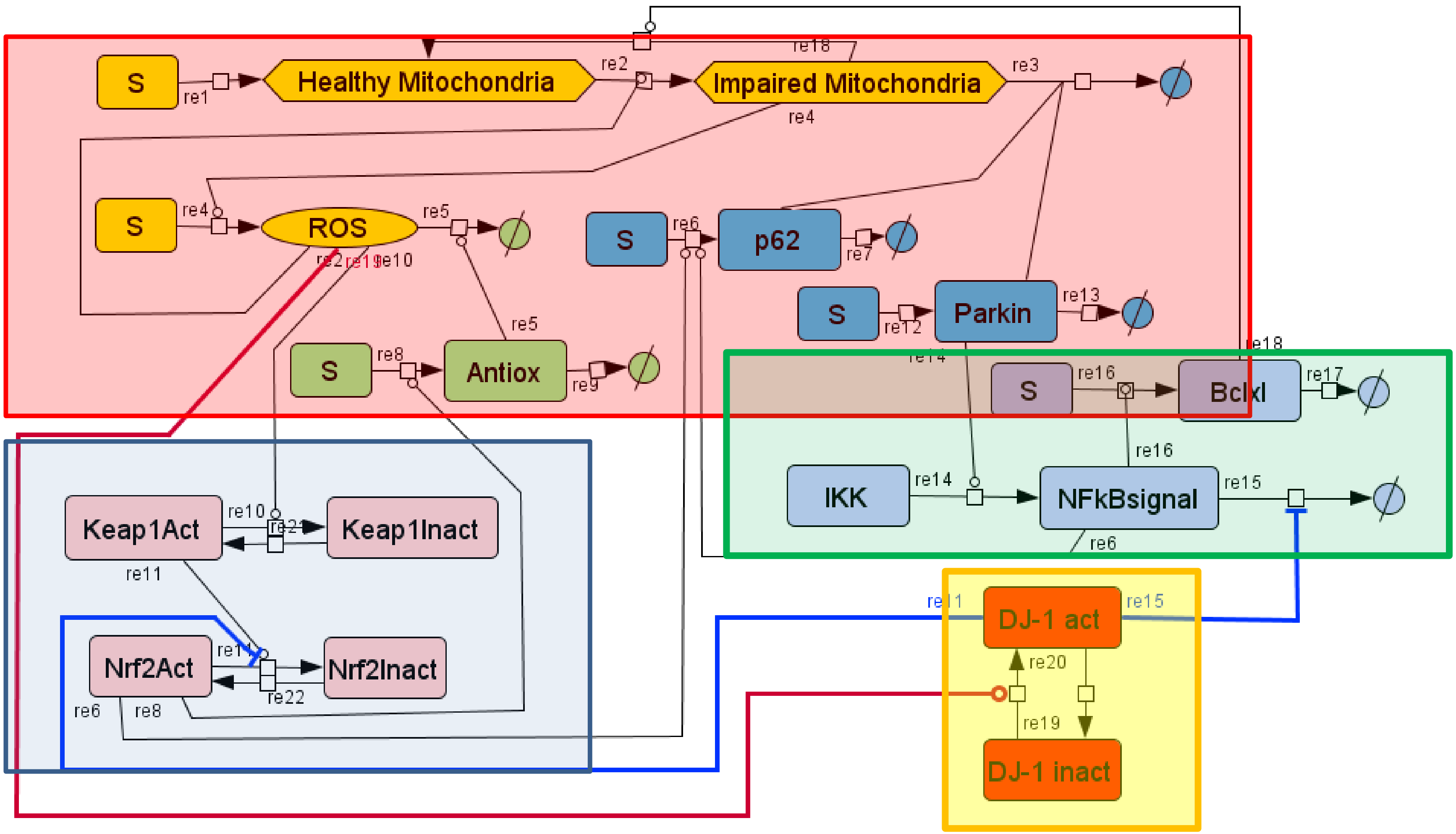
We add NFkB signalling (“recovery” of mitochondria)

Model 3

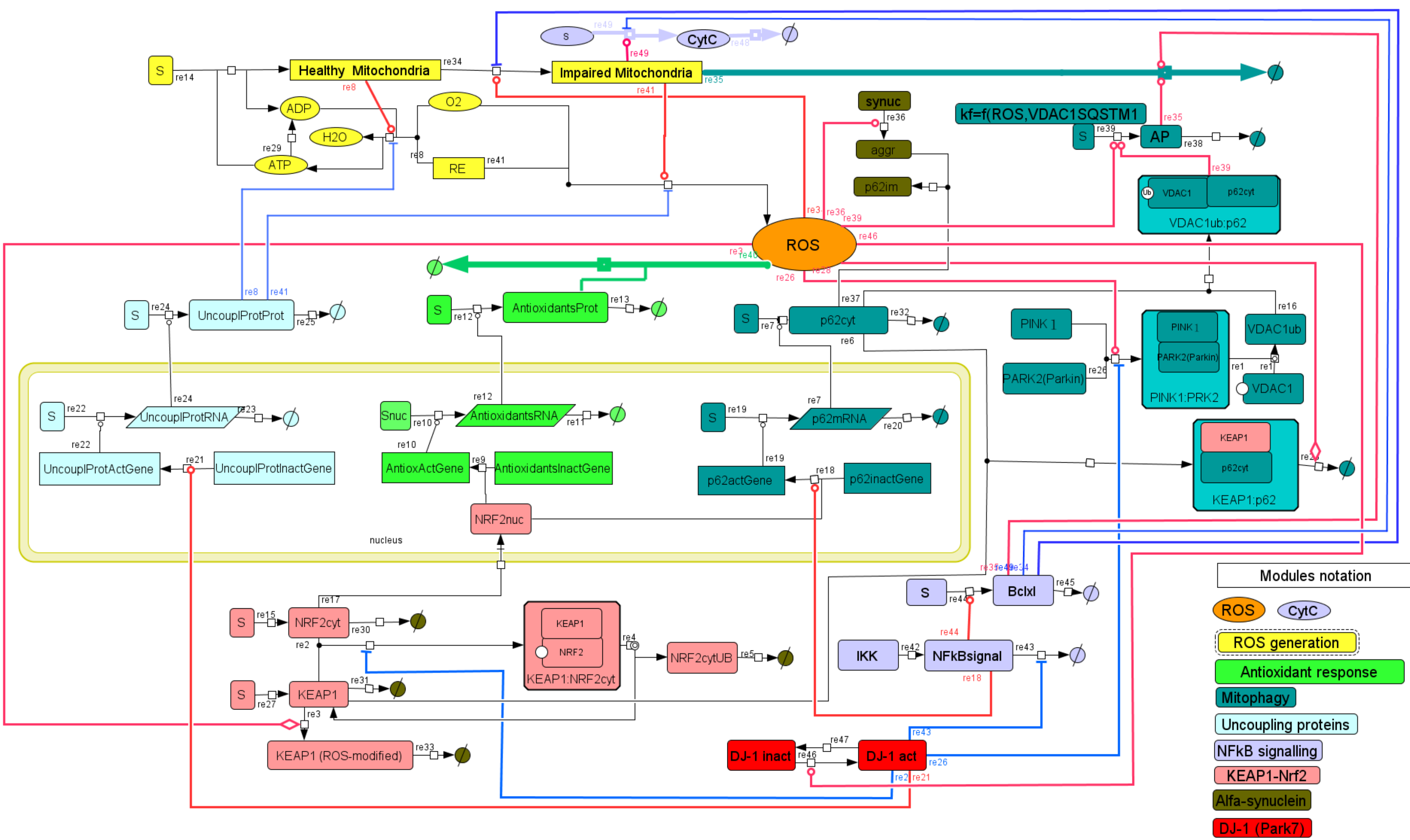


DJ-1 is a regulator of regulators

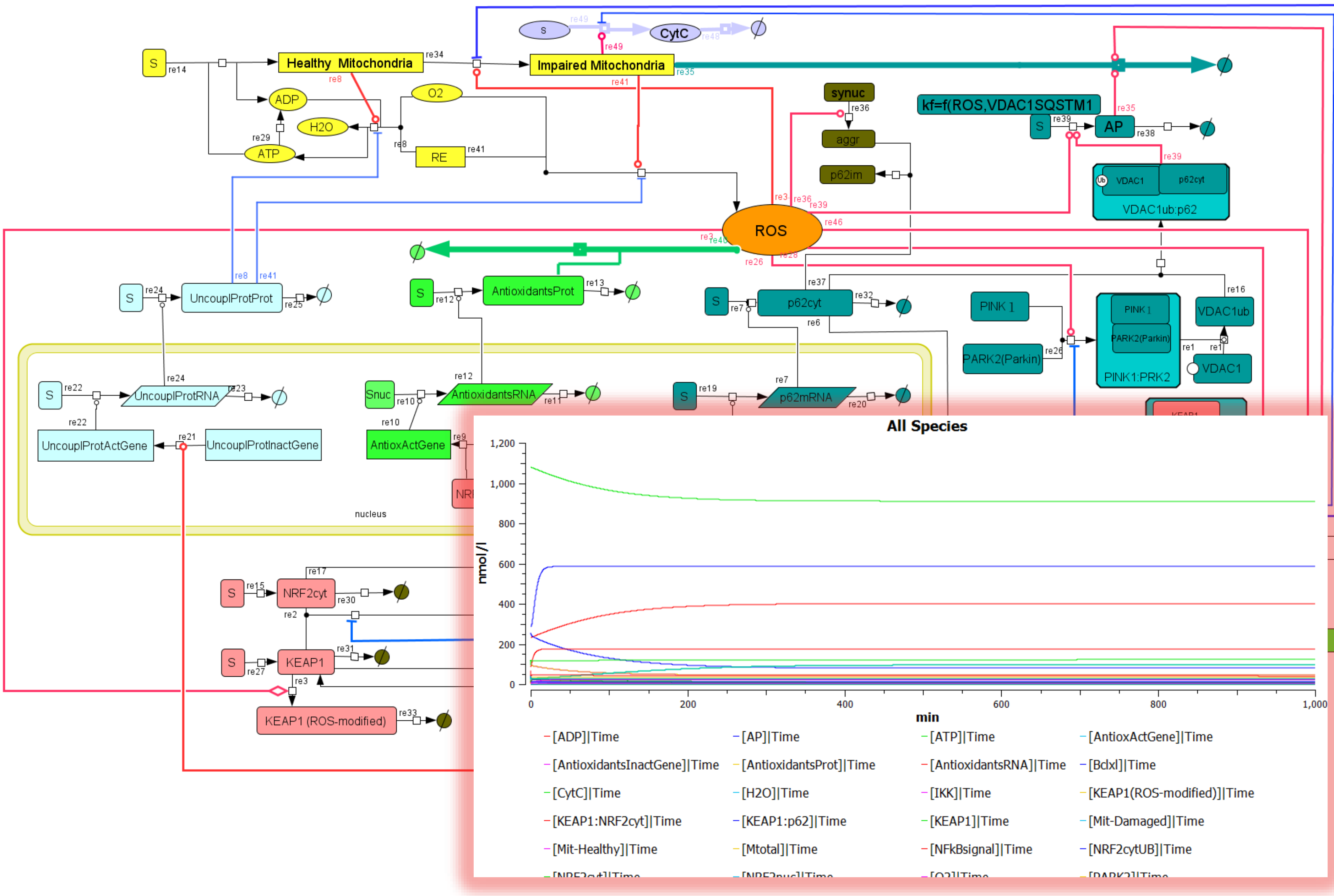
Model 4



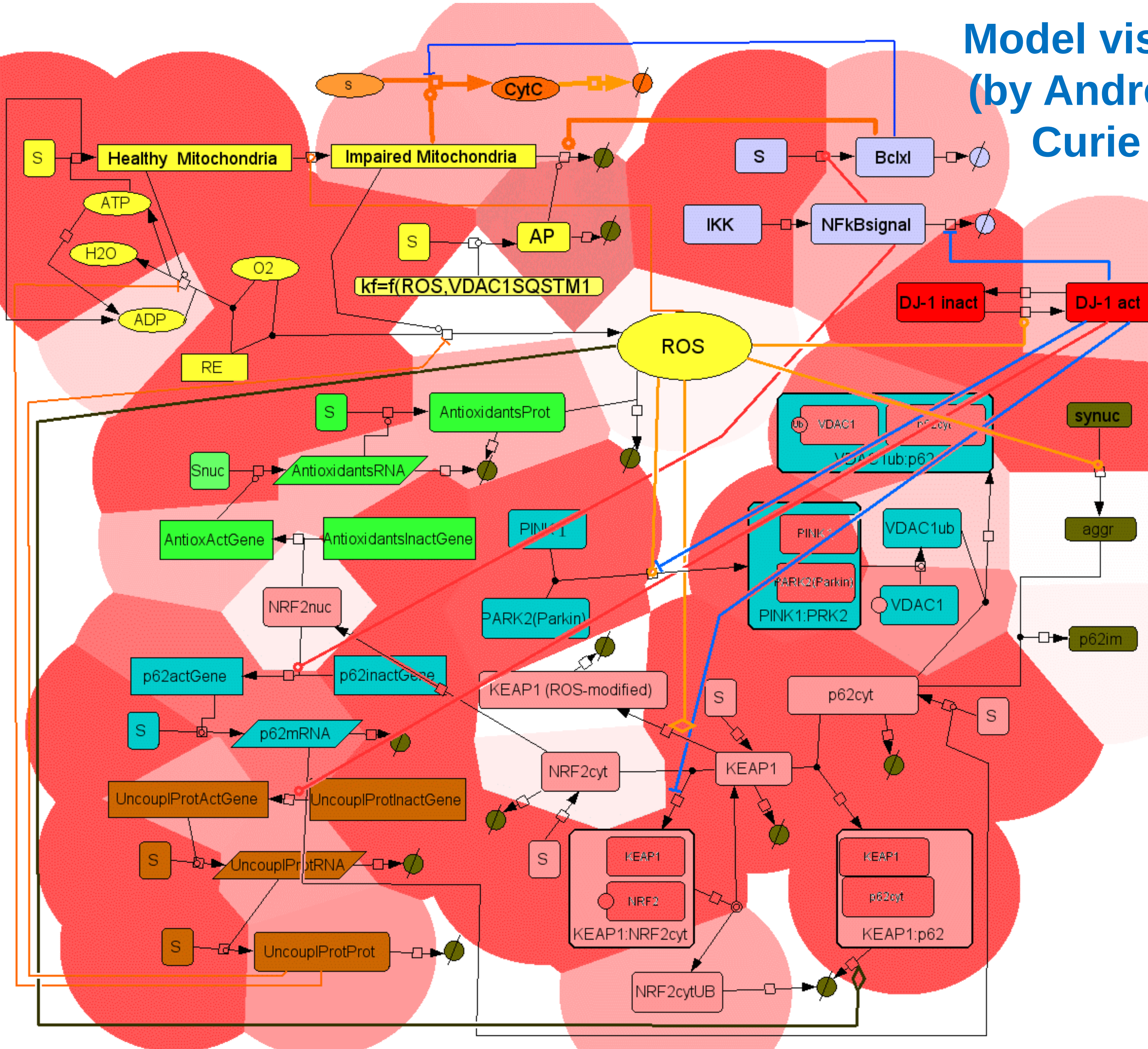
Detailed model of ROS management



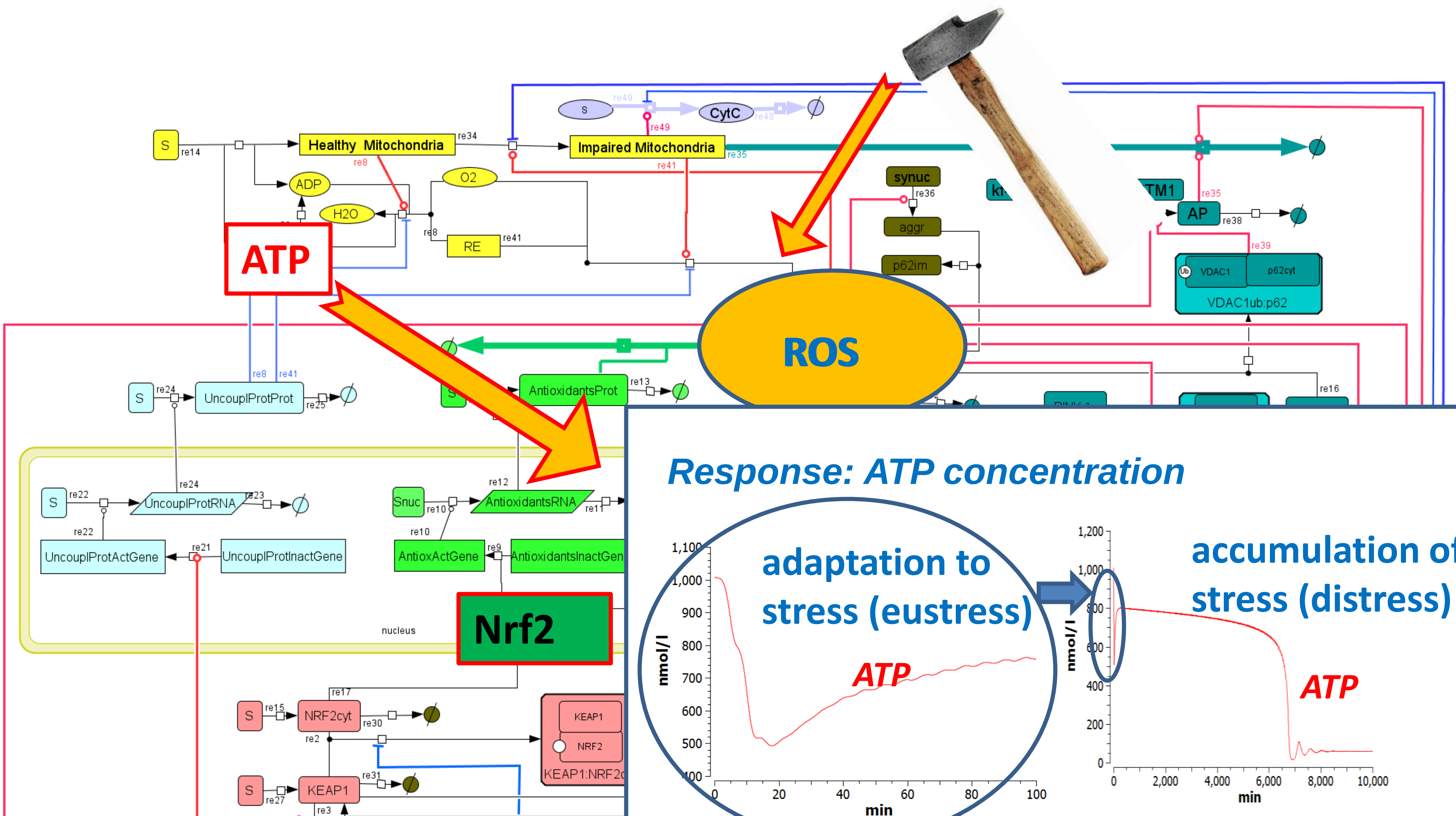
Model visualizes Life



Model visualizes Life (by Andrei Zinovyev, Curie Insttute)



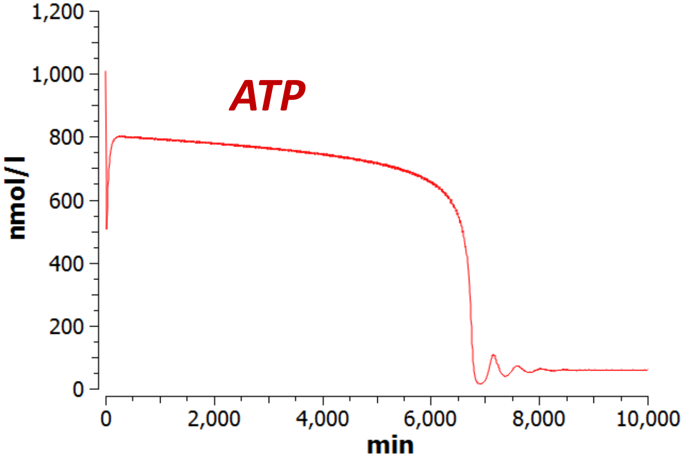
Simulation of emergent behavior: stress and distress



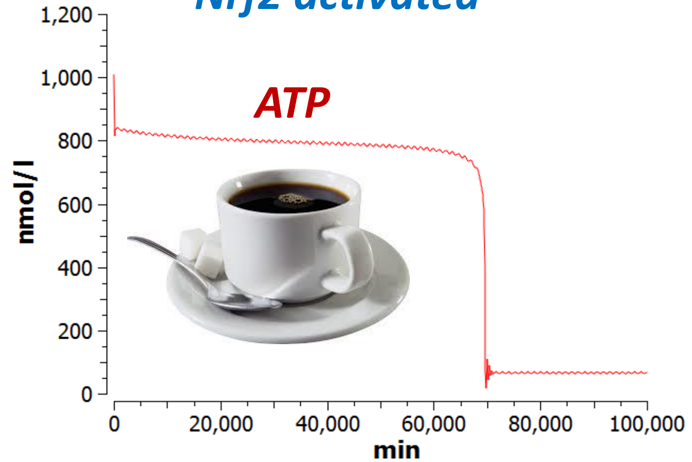
Design principle 1: strong adaptation runs out with ageing.

Simulation of treatment
Nrf2 may be activated by many drugs and biologically active compounds, e.g. caffeine and save neurons.

Without treatment

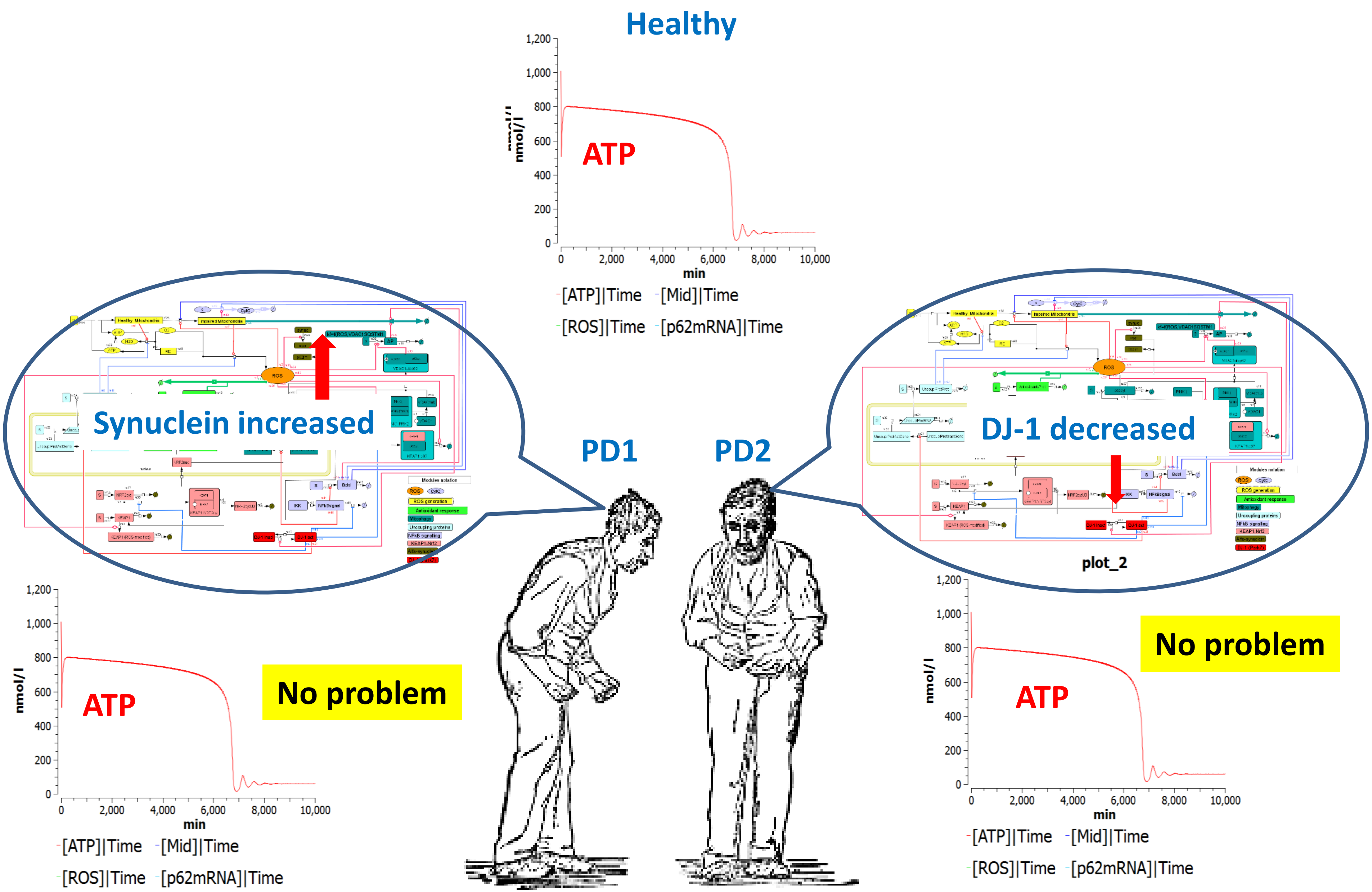


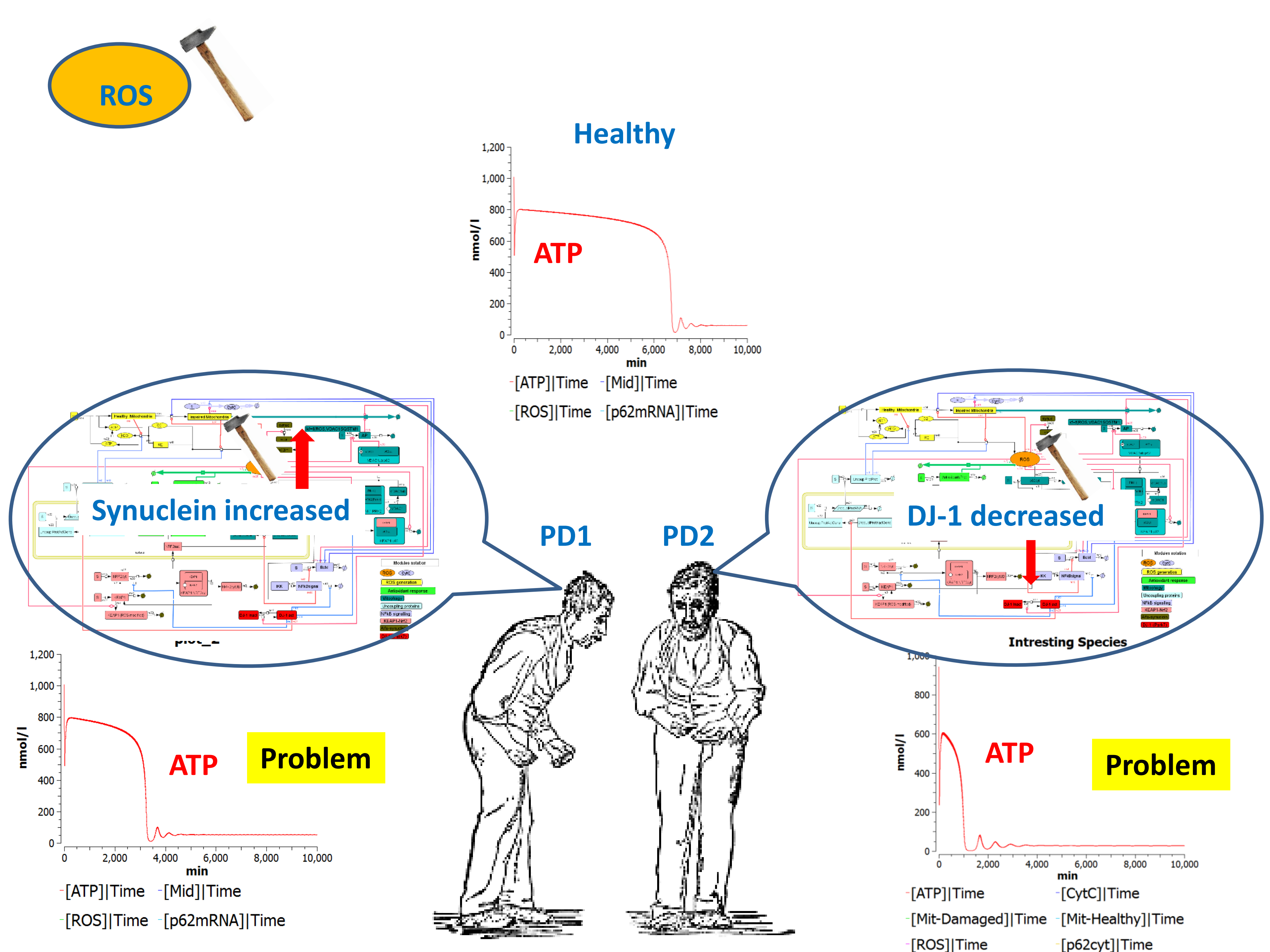
Nrf2 activated



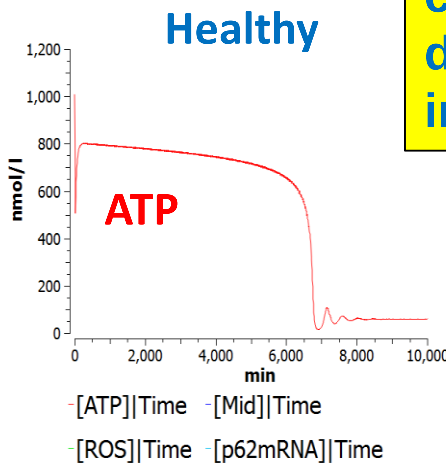
Design principle 2: Nrf2 activation might help.

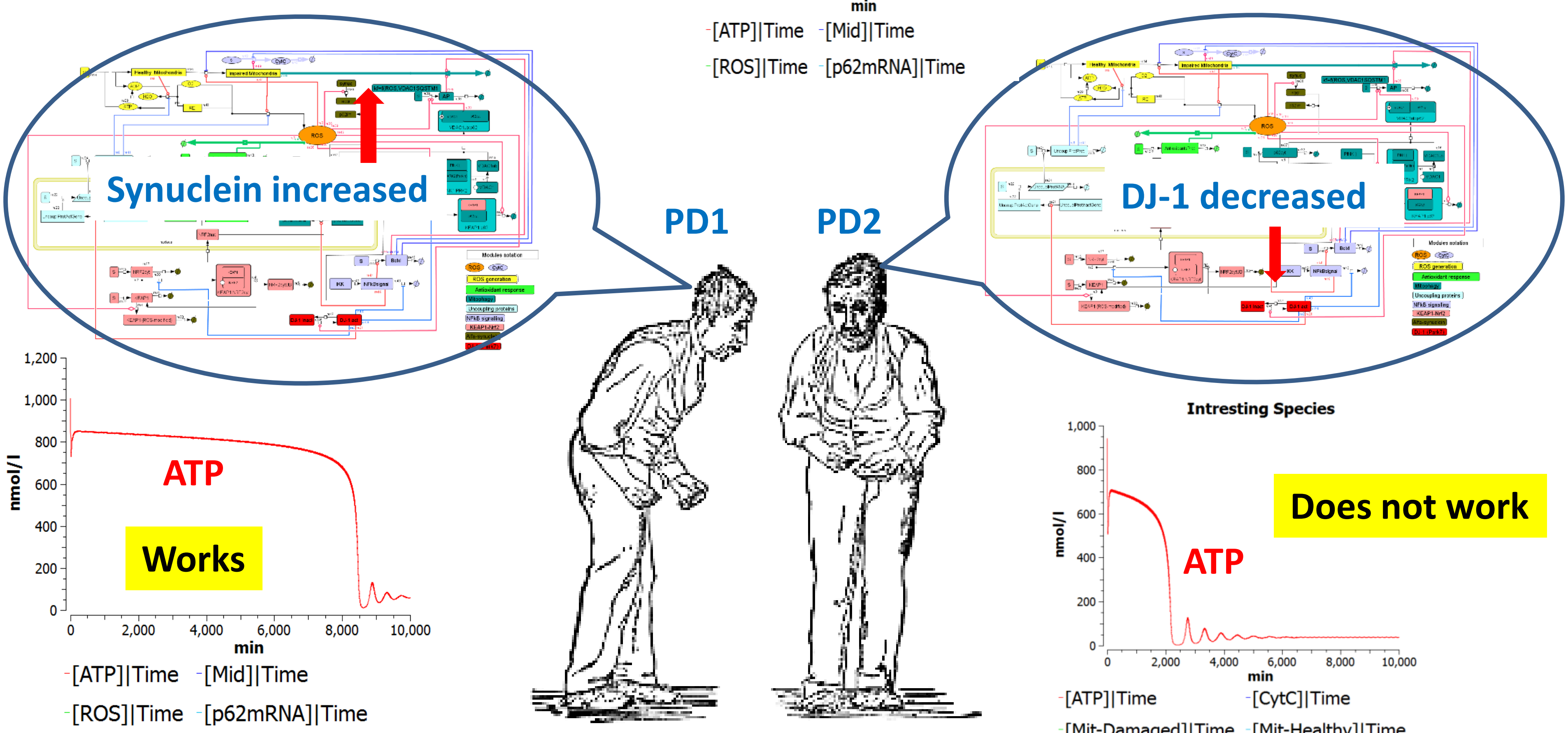
Two mutations of Parkinson's Disease. No stress:




ROS
Healthy
ATP
nmol/l
min
[ATP]|Time
[Mid]|Time
[ROS]|Time
[p62mRNA]|Time
Synuclein increased
PD1
PD2
DJ-1 decreased
Intresting Species
ATP
Problem
nmol/l
min
[ATP]|Time
[Mid]|Time
[ROS]|Time
[p62mRNA]|Time
ATP
Problem
nmol/l
min
[ATP]|Time
[CytC]|Time
[Mit-Damaged]|Time
[Mit-Healthy]|Time
[ROS]|Time
[p62cyt]|Time

Design principle 3: inter - individual variation in controllers may well cause disease variability between individuals.





Conclusions

- **A detailed, mechanistic, dynamic model of ROS management recapitulates ROS homeostasis and enlightens the functionality of this system in health and in Parkinson's disease**
- **PD-related increase of α-synuclein might be compensated by increased Nrf2 activation due to the individual's genome or behaviour (caffeine). However, Nrf2 activation does not help if PD is caused by various genetic deficiencies or mutations of DJ-1**
- **Inter-individual variation in controllers may well cause disease variability between individuals**

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