# IGEM team SIAT-SCIE Modelling part - an intuitive summary

## Dsup - the key protein that protects tardigrades from lethal dosage of radiation

## Part 0 - Kinetic based model 1st edition backup

### The primary focus - Survival rate

The survival rate is a key variable in our model, as it is the most easy one to be accurately quantified (via standarised protocols of flow cytometer), and directly reflects the DSB break, robustness of our cell thus the degree of protection offered by Dsup.
Survival rate (s)
Factor 1: DSB contribution (Q1)
Factor 2: Protein denature distribution (Q2)
Factor 3: Membrane damage distribution (Q3)

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S = Q1 * Q2 * Q3
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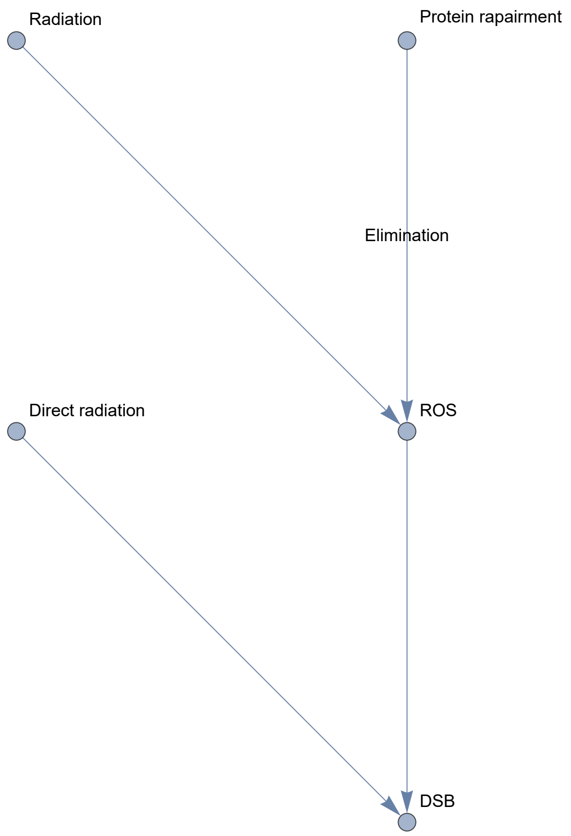
When radiation dosage (D) = 0, Q1 = Q2 = Q3 = 1

# Reaction mechanism




# The very underlying assumptions

1. ROS, DSB & Radiation are all 1st order reaction
2. Since ROS transfer charges to DNA, causing DSB, ROS itself is lost in this process.
3. As ROS damage the proteins in the cell, both ROS and protein repairing functionality are lost.
4. Super-oxide Dismutase (SoD) are not considered in this model.

# ODEs

$$\frac{d\,DSB}{d\,t} == C_1\,R + C_2\,ROS$$

$$\frac{d\,ROS}{d\,t} == C_3\,R - C_2\,ROS - C_4\,ROS * PR$$

$$\frac{d\,PR}{d\,t} == -C_4\,ROS * PR$$

And therefore, our goal is to combine the equations into non-linear ODE system, and estimate the constants given initial conditions.
Thus, via substitution, compute numerical solution for DSB.

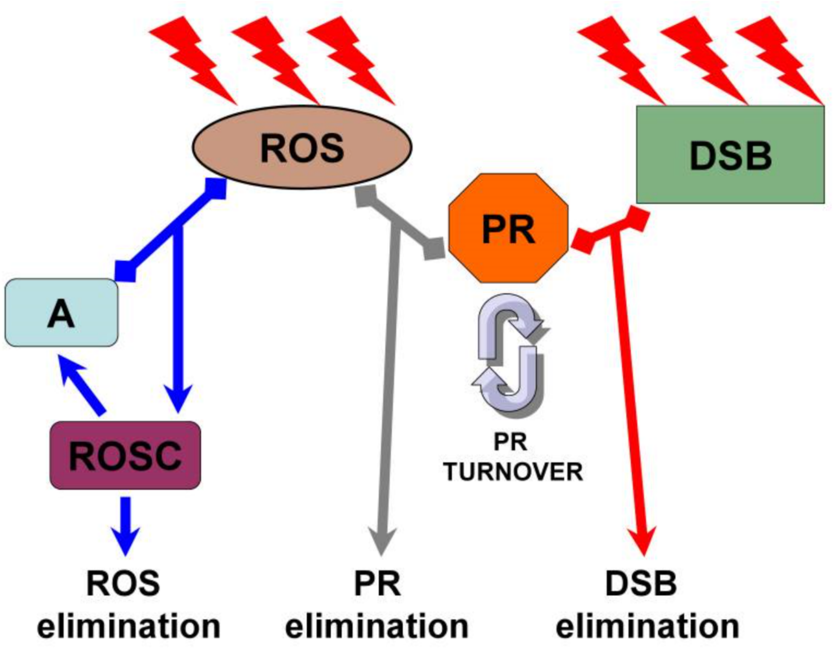
## Limitations

- Reliable direct measurement of DSB unavailable
- Estimation may not have a high accuracy or confidence
- Other factors we failed to take into account may affect the model

# Part I - Kinetic based model

## Reference: "A model of interactions between radiation-induced oxidative stress, protein and DNA damage in Deinococcus radiodurans" I. Shuryak et al, 2009

## Schematic diagram




From "A model of interactions between radiation-induced oxidative stress, protein and DNA damage in Deinococcus radiodurans"
We will explain the notations in math modelling parts below.

## Reactions

ROS + A -> ROSC
ROSC -> A (ROS elimination)

ROS + PR -> $\phi$ (Protein repair)
PR + DSB -> PR
ROS = reactive oxygen species
PR = proteins needed for DNA repair
A = antioxidants

# Modelling

## Protein oxidation (differential equations):

Assume ROS react with A and PR via 1st order equation, then

$$\frac{d\,ROS[t]}{dt} = c_1 * D_2 - c_2 * ROS[t] * A[t] - c_3 * ROS[t]$$

In the reaction above:

$$D_2 = \frac{d\,D}{d\,t}$$

That is, ROS induced by radiation dosage

ROS[t] * A[t]

ROS + A -> ROSC (antioxidants elimination)

The last term refers to natural ROS elimination, we assume that it is a 1st order equation

Then, we have

$$\frac{d\,A[t]}{d\,t} = -c_2 * ROS[t] * A[t] + c_4 * ROSC[t]$$

The 1st term refers to reaction ROS + A -> ROSC
The 2nd term means that ROSC -> A

Intuitively,

$$\frac{d\,ROSC[t]}{d\,t} = c_2 * ROS[t] * A[t] - c_4 * ROSC[t]$$

Finally we have

$$\frac{d\,PR[t]}{d\,t} = c_5 - c_6 * PR + G * ROS[t] * PR[t] \quad (* \text{ equations 1 } *)$$

Where $c_5$ is the synthesis rate of protein, $c_6$ term refers to natural protein degradation, last term represents ROS + PR -> $\phi$

## Protein oxidation modelling:

Under background condition, at equilibrium,

$$\frac{dPR[t]}{dt} == 0$$

$$c_5 - c_6 * PR[t] == 0$$

$$PR[t] = \frac{c_5}{c_6}$$

Assume antioxidants and ROSC always exists in equilibrium, sum of A, $A_{total}$ is considered to be constant, hence, from equation1, we have

$$\frac{dROS[t]}{dt} = c_1 * D_2 - \frac{c_2 * c_4 * ROS[t] * A_{total}}{c_4 + c_2 * ROS[t]} - c_3 * ROS[t]$$

$$\frac{dPR[t]}{dt} = c_5 - (c_6 + c_7 * ROS[t]) * PR[t] \quad (* \text{ equations 2 } *)$$

Assume the kinetics of ROS production and removal are faster than those of protein turnover, have ROS always exist as an equilibrium concentration $ROS_{eq}$

$$\frac{dROS[t]}{dt} == 0$$

$$ROS_{eq} = \frac{\left(c_2 * x_1 - c_3 * c_4 + x_3^{\frac{1}{2}}\right)}{2\, c_2 * c_3}$$

$$x_1 = c_1 * D_2 - c_4 * A_{total}$$

$$x_2 = c_1 * D_2 + c_4 * A_{total}$$

$$x_3 = c_2^2 * x_1^2 + 2\, c_2 * c_3 * c_4 * x_2 + (c_3 * c_4)^2 \quad (* \text{ equations 3 } *)$$

Substitute $ROS_{eq}$ in equations 3 in equations e, yield $PR_{eq}$ :

$$PR_{eq} = (2\, c_2 * c_3 * c_5) \Big/ \left(c_2\, (c_7 * x_1 + 2\, c_3 * c_6) - c_7 \left(c_3 * c_4 - x_3^{\frac{1}{2}}\right)\right) \quad (* \text{ equation 4 } *)$$

## DNA damage:

Assume DSB is only induced by radiation dosage, rather than ROS

$$\frac{dDSB[t]}{dt} = c_8 * D_2 - c_9 * PR[t] * DSB[t] \quad (* \text{ equation 5 } *)$$

This equation represents DSB induced by radiation dosage, and protein repair (PR + DSB -> PR)

Substitute $PR_{eq}$ in equation 4 to equation 5

$$DSB_{eq} = \frac{c_8 * D_2}{c_9 * PR_{eq}}$$

## Acute radiation exposure (high-dosage rate)

By the time radiation is over, for example t = $\frac{D_2}{D}$, the concentration of active protein $PR_d$ can be calculated from eqns (2), (3) and assume that PR[t=0] = $\frac{c_5}{c_6}$

$$PR_d = \left( c_5 \left( \frac{2\, c_2 * c_3 * c_6}{y_2} + c_7 \left( y_1^{\frac{1}{2}} + c_2 * x_1 - c_3 * c_4 \right) \right) * y_2 \right) \Big/ \left( c_6 \left( c_7 * y_1^{\frac{1}{2}} + c_7\, (c_2 * x_1 - c_3 * c_4) + 2 * c_2 * c_3 * c_6 \right) \right)$$

$$PR_d = c_5\, [2\, c_2\, c_3\, c_6 / Y_2 + c_7\, (Y_1^{1/2} + c_2\, X_1 - c_3\, c_4)] Y_2 / [c_6\, (c_7\, Y_1^{1/2} + c_7\, (c_2\, X_1 - c_3\, c_4) + 2\, c_2\, c_3\, c_6)], \text{ where } X_1 = c_1\, R - c_4\, A_{tot},$$
$$Y_1 = c_4^2\, (c_2\, A_{tot} + c_3)^2 + 2\, c_1\, c_2\, c_4\, R\, (c_3 - c_2\, A_{tot}) + (c_1\, c_2\, R)^2,$$
$$Y_2 = \exp[-Dose\, (c_7\, Y_1^{1/2} + c_2\, (2\, c_3\, c_6 + c_7\, X_1) - c_3\, c_4\, c_7) / (2\, c_2\, c_3\, R)]$$

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(* equations 7 *)
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Assuming radiation is acute, no DSB can be repaired during exposure, the number of DSB's just after exposure is $DSB_d = c_8 * D$

$PR_d$ is given by equations 7, over the time after exposure,

$$\frac{dDSB[t]}{dt} = -c_9 * PR[t] * DSB[t]$$
$$\frac{dPR[t]}{dt} = c_5 - c_6 * PR[t] \quad \text{(* equations 8 *)}$$

Solve equations 8 analytically

$$DSB(t) = c_8\, Dose\, \exp[-c_9\, (c_6\, (c_5\, t + PR_d) + (c_5 - c_6\, PR_d) \exp[-c_6\, t] - c_5) / c_6^2]$$
$$PR(t) = [(c_6\, PR_d - c_5) \exp[-c_6\, t] + c_5] / c_6$$

Define $t_{rep}$ : the time that all repair is completed

Survival rate $S = e^{-DSB[t_{rep}]}$

# Part II - Model based on fitting

## Reference: 'A discrete cell survival model including repair after high dose-rate of ionising radiation', W. Santag