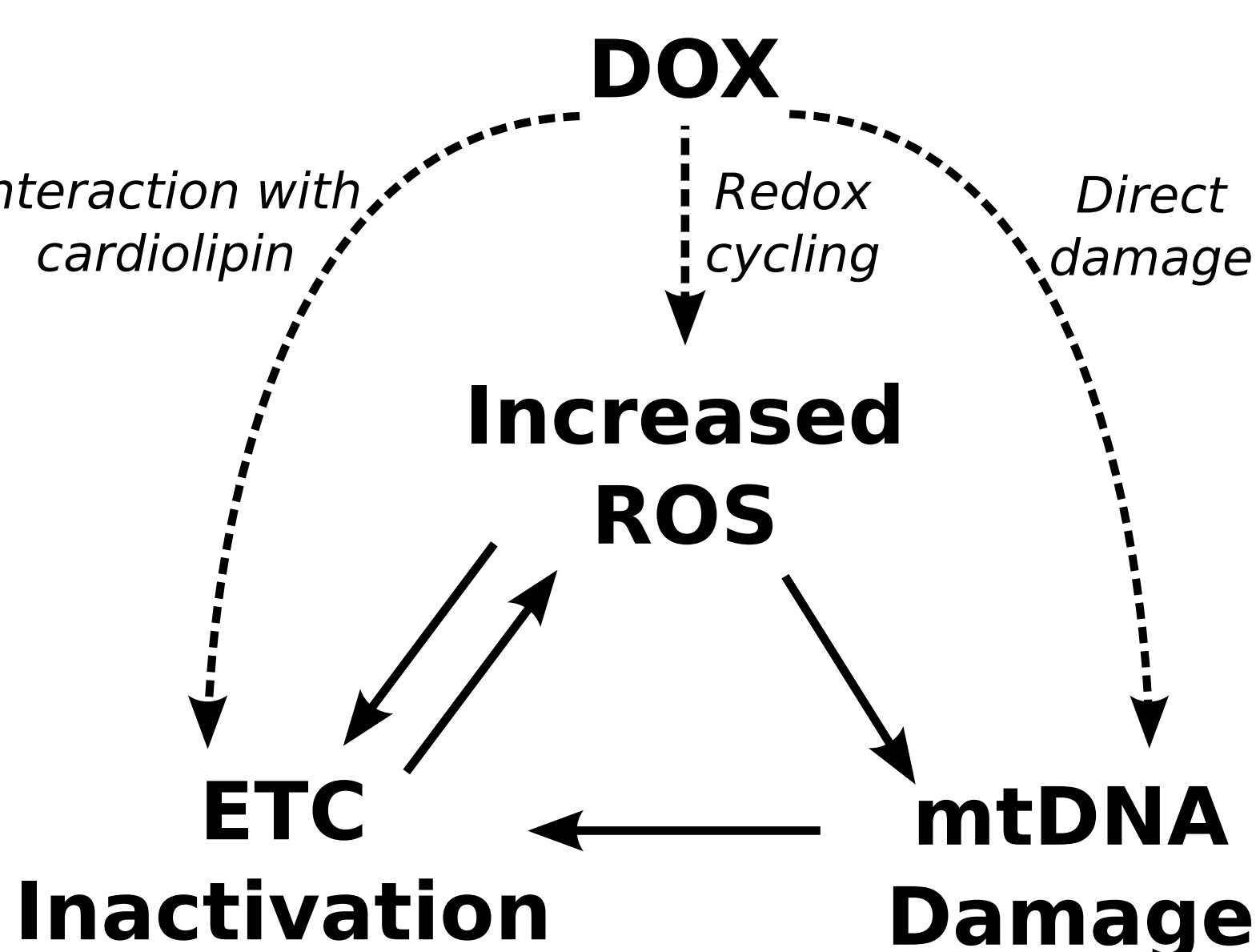


## Motivation

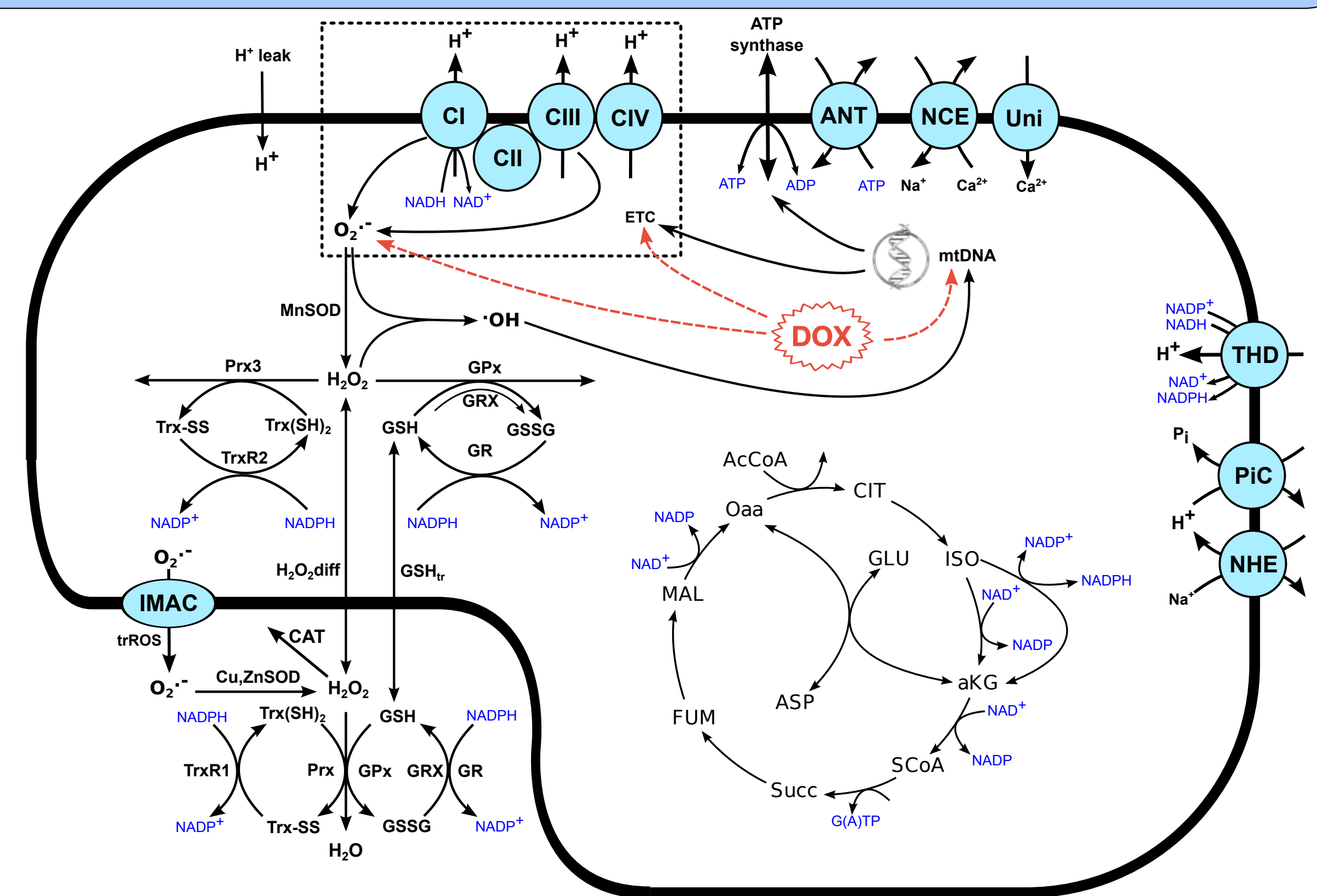
Doxorubicin (DOX) is a potent antineoplastic anthracycline, however, its clinical usage is limited by its cardiotoxicity. Patients exposed to high doses of this drug can develop a cumulative, dose-dependent cardiomyopathy that can manifest years or even decades after the termination of the treatment. Doxorubicin cardiotoxicity is strongly associated with mitochondrial dysfunction, leading to an increase in ROS production and cardiac oxidative stress [1]. The aim of this study is to develop computational models and tools to study the mechanisms of doxorubicin cardiotoxicity and quantify the contribution of different components to the mitochondrial dysfunction associated to it.



**Figure 1.** It has been suggested that DOX can trigger a vicious cycle where increased ROS levels lead to mtDNA damage which exacerbate the mitochondrial dysfunction and further increase ROS production [1].

## Model

A biophysical computational model of the mitochondria based on ordinary differential equations was implemented [2]. This model includes the TCA cycle, transporters, the electron transport chain, ROS production and ROS scavenging systems. To simulate the acute effects of doxorubicin, the activities of Complexes I to IV were inhibited to match experimental data [3] and ROS production was increased to represent redox cycling. The chronic effects were represented by reducing the expression of mtDNA encoded proteins as a result of damage.

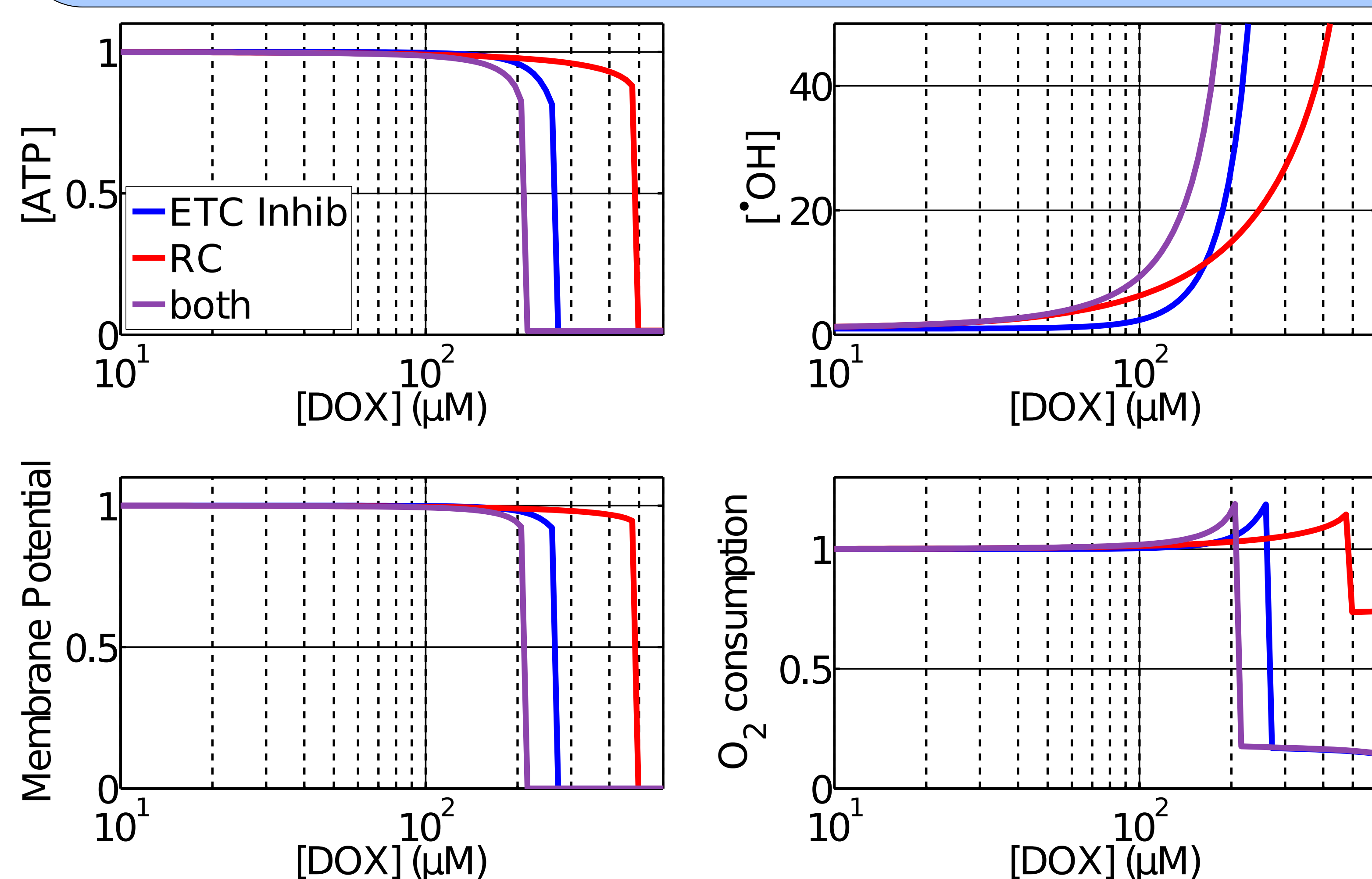


**Figure 2.** A schematic of the biophysical mitochondrial computational model that was adapted to simulate the effects of DOX

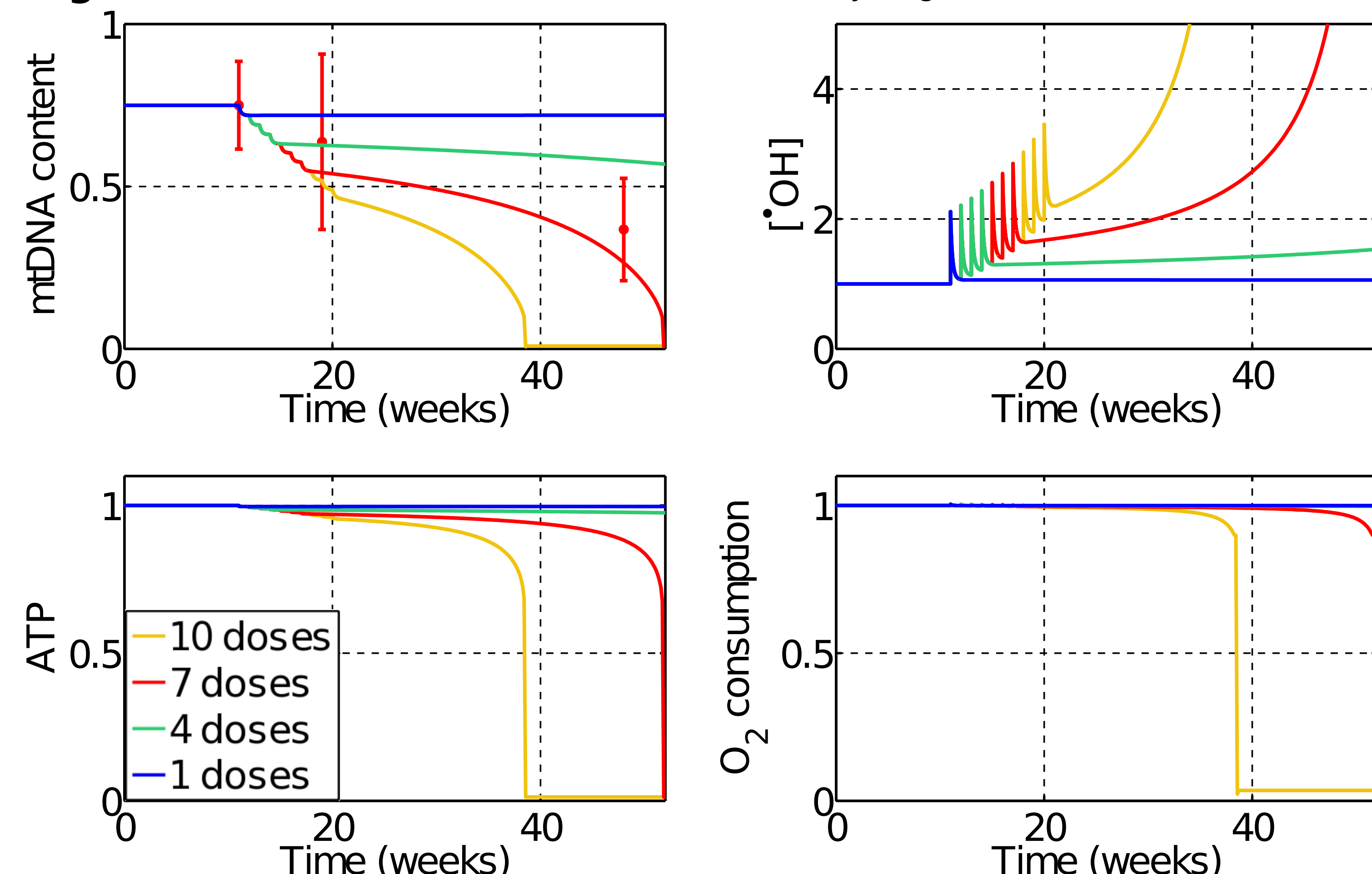
## Results

When the acute and chronic effects of DOX were incorporated into the model, a dose dependent drug response could be investigated. Different quantities were used to quantify mitochondrial dysfunction and multiple features associated with DOX toxicity were reproduced. By quantitatively comparing the effect of multiple toxicity mechanisms, we could identify that direct damage to the mtDNA is the principal pathway of chronic cardiotoxicity by altering mitochondrial function from a stable to an unstable state.

$$\frac{d(\text{mtDNA})}{dt} = \alpha \cdot \frac{(1 - \text{mtDNA})}{(1 - \text{mtDNA}) + \kappa} - \beta \cdot [\cdot\text{OH}]_n \cdot \text{mtDNA} - \gamma[\text{DOX}] \cdot \text{mtDNA}$$



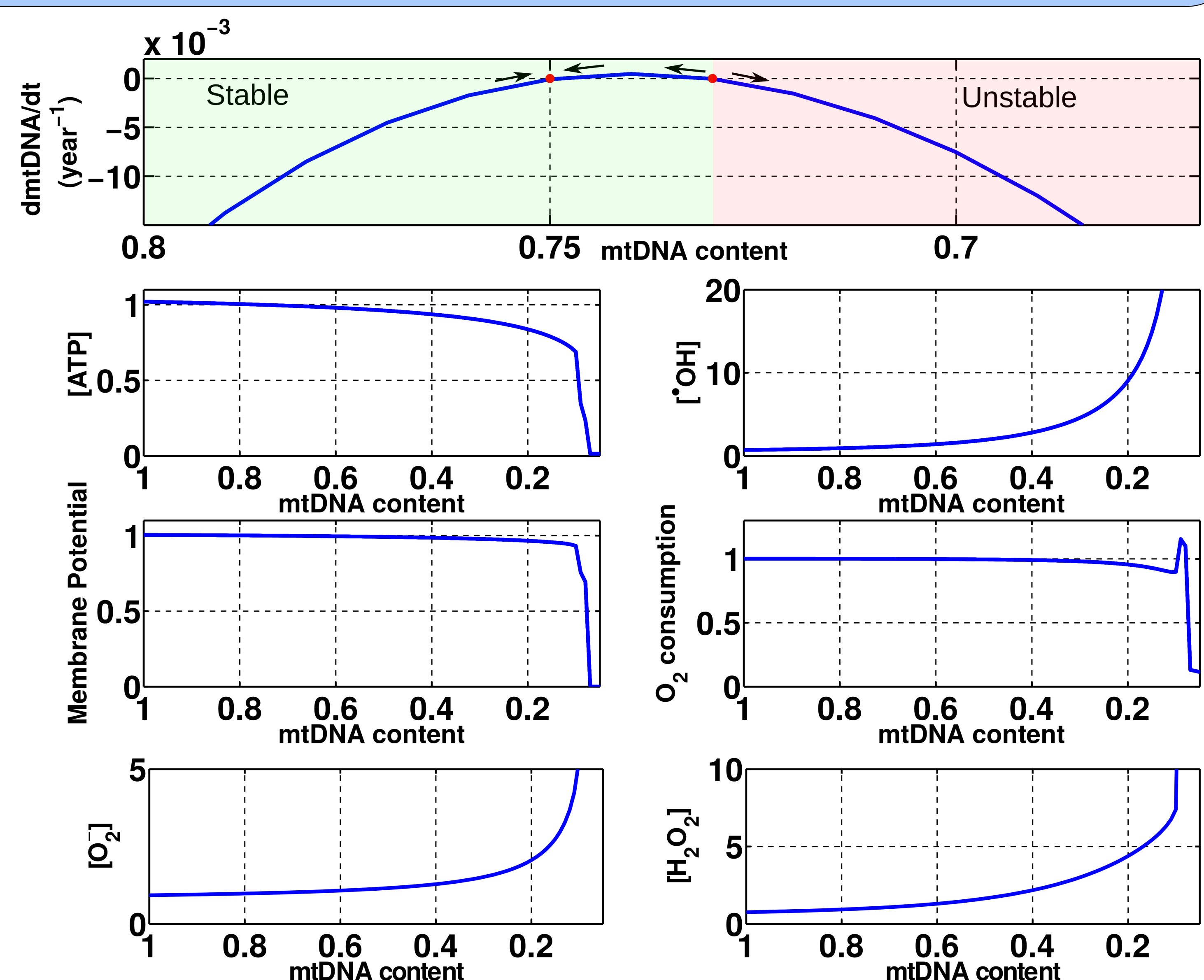
**Figure 3.** Acute effects of ETC Inhibition and redox cycling at different DOX concentrations.



**Figure 5.** The predicted effect of the treatment with weekly doses DOX matches reported experimental data [1]. After consecutive doses a vicious cycle is triggered.

## References

- [1] Dirk Lebrecht, et al. Time-dependent and tissue-specific accumulation of mtDNA and respiratory chain defects in chronic doxorubicin cardiomyopathy. *Circulation*, 108(19):2423–9, Nov 2003.
- [2] Laura D. Gauthier, et al. An integrated mitochondrial ROS production and scavenging model: Implications for heart failure. *Biophysical Journal*, 105(12):2832 – 2842, 2013.
- [3] K. Nicolay and B. de Kruijff. Effects of adriamycin on respiratory chain activities in mitochondria from rat liver, rat heart and bovine heart. evidence for a preferential inhibition of Complex III and IV. *Biochimica et Biophysica Acta*, 892:320–330, 1987.



**Figure 4.** Effects of the variation of the mtDNA content in mitochondrial function. A bifurcation point is observed when the mtDNA content is equal to 0.73.

## Future Work

The methods and tools presented in this work can serve as a framework for the development of a computer assisted protocol for the prediction of cardiotoxicity of new compounds. Using *in vitro* experiments, it is possible to acquire data for the IC<sub>50</sub> values and effects of the drugs on the proteomic profiling. By incorporating this information in detailed biophysical computational models, it is possible to estimate the effects of the drugs *in vivo* in a fast and economical way, with no ethical implications. Future work involve extending our models to include even more proteins that can be drug targets, generate results for more compounds and develop a fully automated method that can allow for fast and standardized testing of multiple compounds.