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ChronoRepair: Agent-Based Modelling of Charged Particle Survival Curves from Double-Strand Break Repair Kinetics

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INTRODUCTION

ChronoRepair is a computational mechanistic toolkit to create models that simulate how radiation-induced double-strand breaks (DSBs) are repaired over time and how this repair affects cell survival. It explicitly includes repair kinetics, cell cycle progression and arrest, DSB misrepair and cell death.

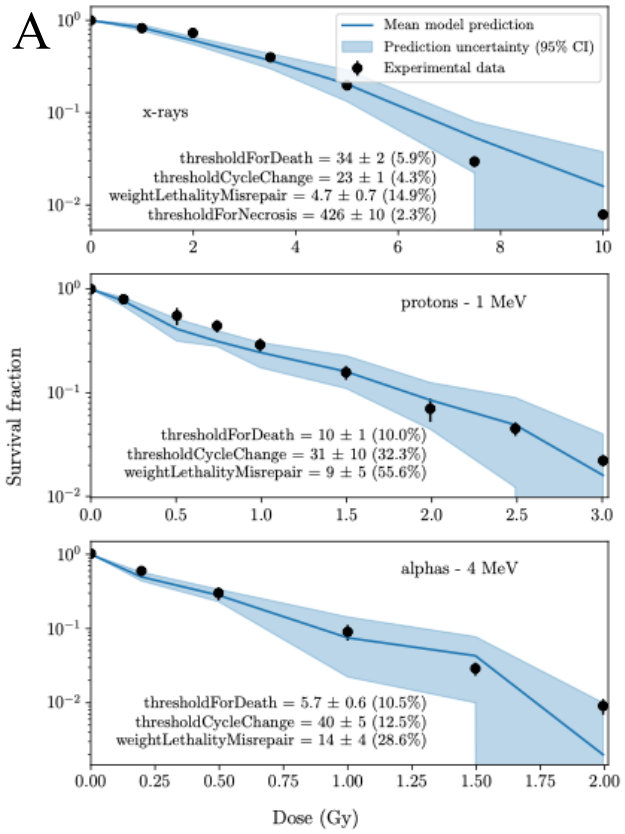
In this work, one ChronoRepair model, the basicModel, was applied to A549 cells exposed to different radiation qualities. We focused on studying clonogenic survival after x-ray, proton, and alpha irradiation, and on how sensitive these predictions are to the model parameters.

MATERIALS AND METHODS

DSBs were calculated with TOPAS-nBio simulations [1]. The basicModel parameters controlling repair kinetics (repairDetectionRate and repairSpeedRate) were obtained from experimental x-ray-induced γ-H2AX foci kinetics [2]. Then, survival-related parameters (thresholdForDeath, thresholdCycleChange, thresholdForNecrosis and weightLethalityMisrepair) were fitted to experimental survival data for x-rays, 1-MeV protons, and 4-MeV alpha particles [3,4]. Figure A shows the resulting survival curves and obtained fitted parameters.

To evaluate the model sensitivity, repairDetectionRate and repairSpeedRate were perturbated around their fitted values. The effect of these variations on survival predictions was quantified using the root mean square error (RMSE) in Figure B.

A

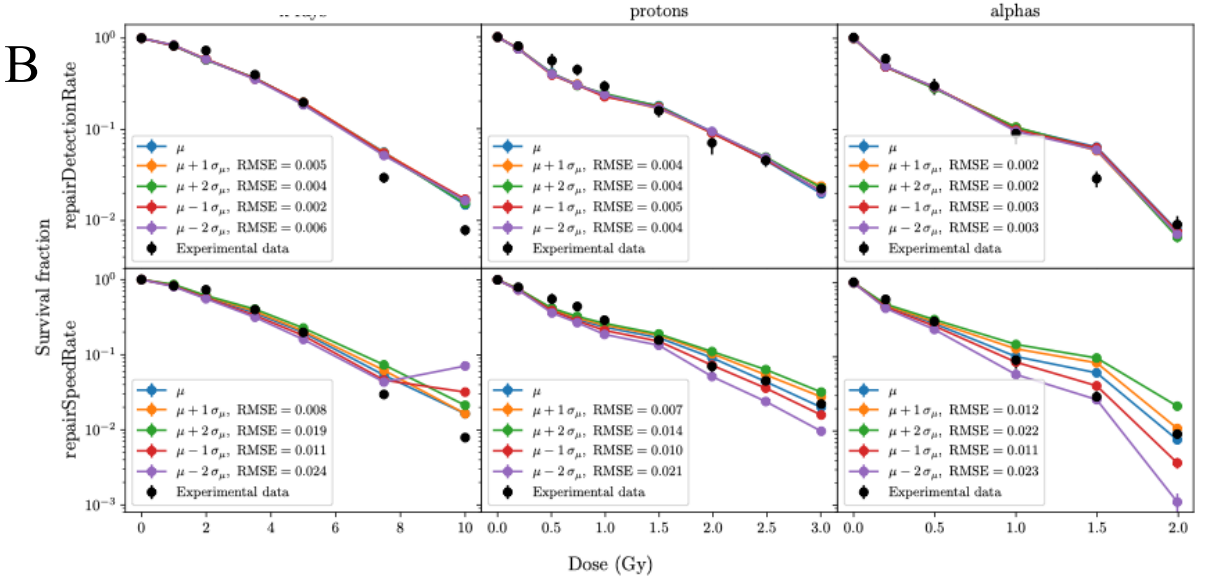


RESULTS AND DISCUSSION

Figure A shows that ChronoRepair reproduced the survival trends for x-rays, protons, and alpha particles. The fitted thresholdForDeath decreased with LET, suggesting that fewer unrepaired DSBs are needed for cell death after proton and alpha irradiation. In contrast, weightLethalityMisrepair increased with LET, indicating that misrepair becomes more lethal for more complex and/or clustered damage.

Figure B shows that survival predictions were more sensitive to repairSpeedRate than to repairDetectionRate.

B



Similar sensitivity patterns were observed for all radiation types, supporting the use of common repair kinetics.

CONCLUSIONS

The resulting ChronoRepair basicModel fitted parameters suggest that radiation quality affects both the amount of unrepaired damage required for cell death and the lethality of misrepair. Survival predictions were found to be especially sensitive to repair completion kinetics.