Using GEANT4-dna-chemistry to Estimate DNA Damage from Radiation: Summary and Challenges

- DNA-Chemistry basics
- Our micro geometry
- Looping structure basics
- Difficulties encountered
- Solutions

GEANT4-dna-chemistry

- Interfaces with GEANT4-dna processes.
- Must be included/activated
- Physics stage: Energy deposition -> free radical precursors
  - H2O+
  - Excited H2O
  - Solvated electrons

Chemical Stage

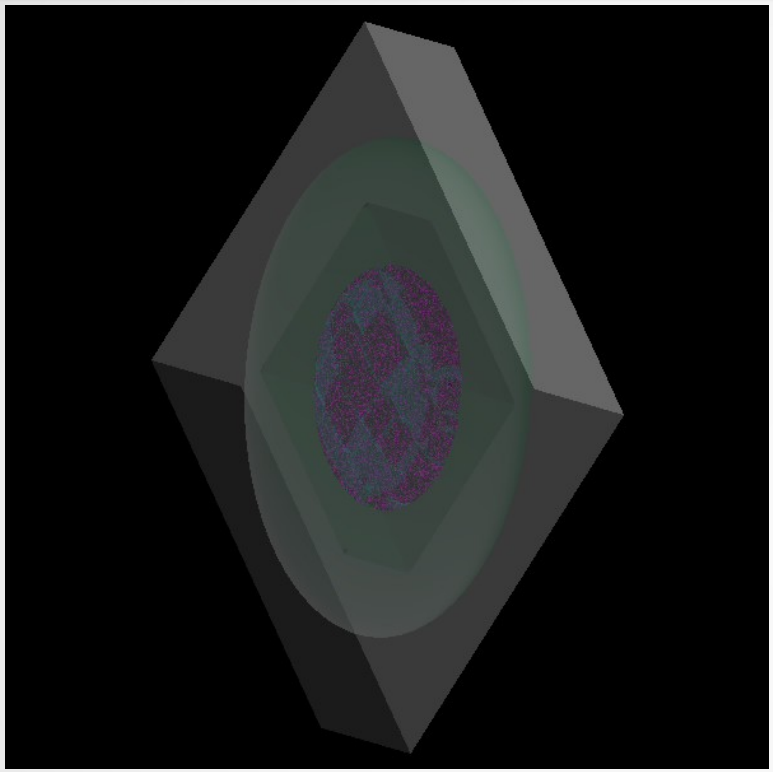
- Pre-processing: Precursors to free radicals
  - OH variants
  - H2O2
  - Solvated electrons
  - Some less significant ones
- Processing
  - By time step
  - Uses a KDTree system to iteratively calculate reactions
  - Advance time step
- Includes reactions with water.
- Make sure doesn’t generate in DNA pieces

Chemical Stage: Inherent Limitations

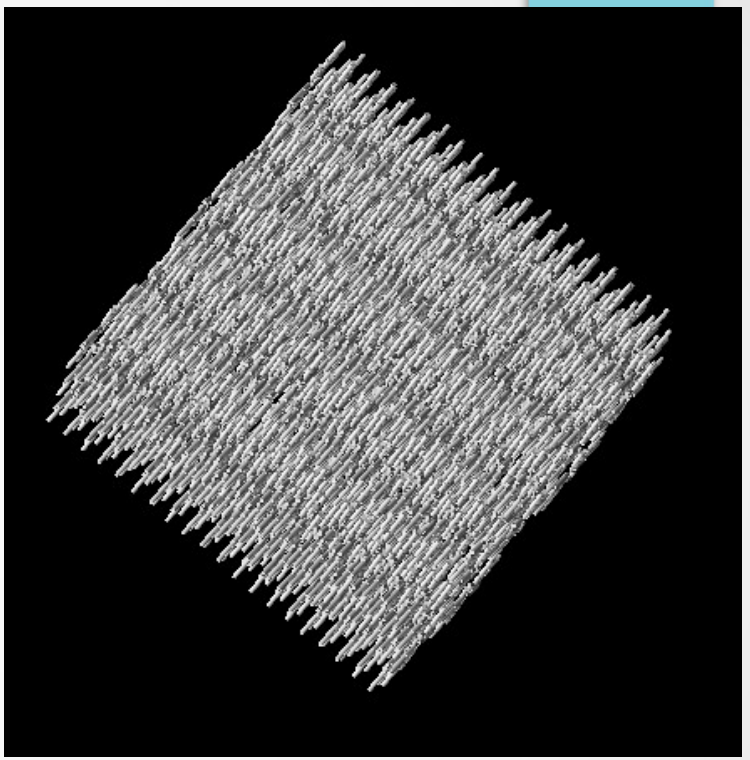
- Almost always consumes more resources than physical stage.
- Deals with 1 primary's products
- A large cascade consumes excessive resources
- A large geometry results in same as they have to be tracked too far
- Doesn't (presently) work with anything but water.
  - Hence, need to figure out DNA breaks on the user end
- We will deal with these as they come up

Geometry

- Need to know where the DNA is to know when it breaks
- Some simulations deal with this statistically
- Advances in geometric modeling have led to sophisticated and adaptable models of cellular DNA [Friedland et al 2003, Bernal et al 2013, GEANT4 wholenucleardna example].
- We have adapted these models into a single GEANT4 model.
- Additional adaptations allow this model to be applied to macroscopic structure.



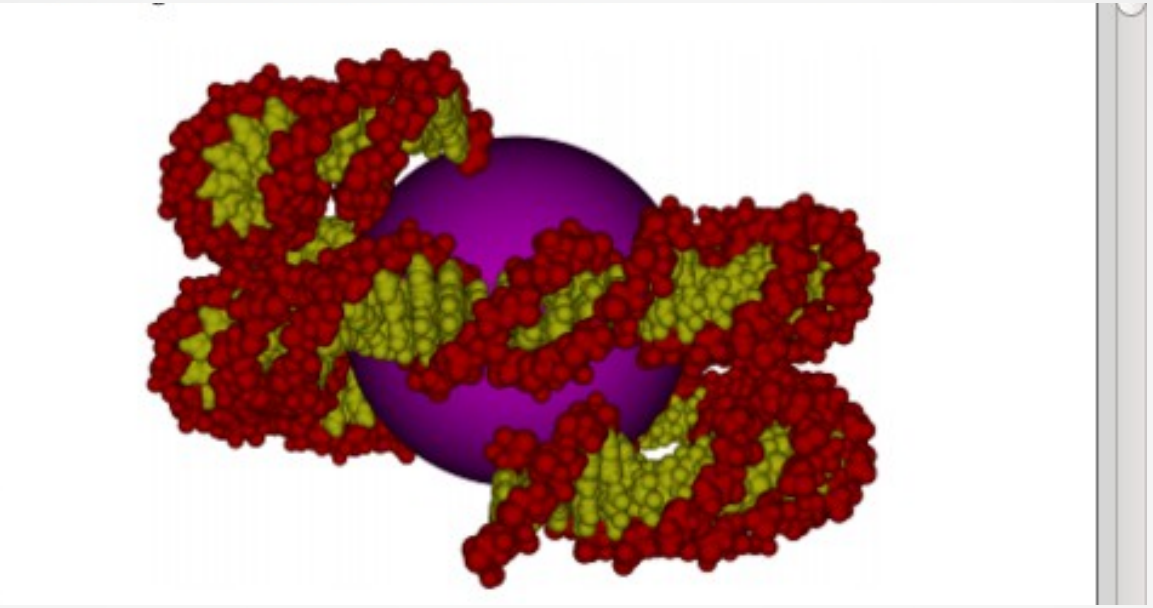
- Cell (outer box is for ease of display)



- Chromosome made of rosette stacks

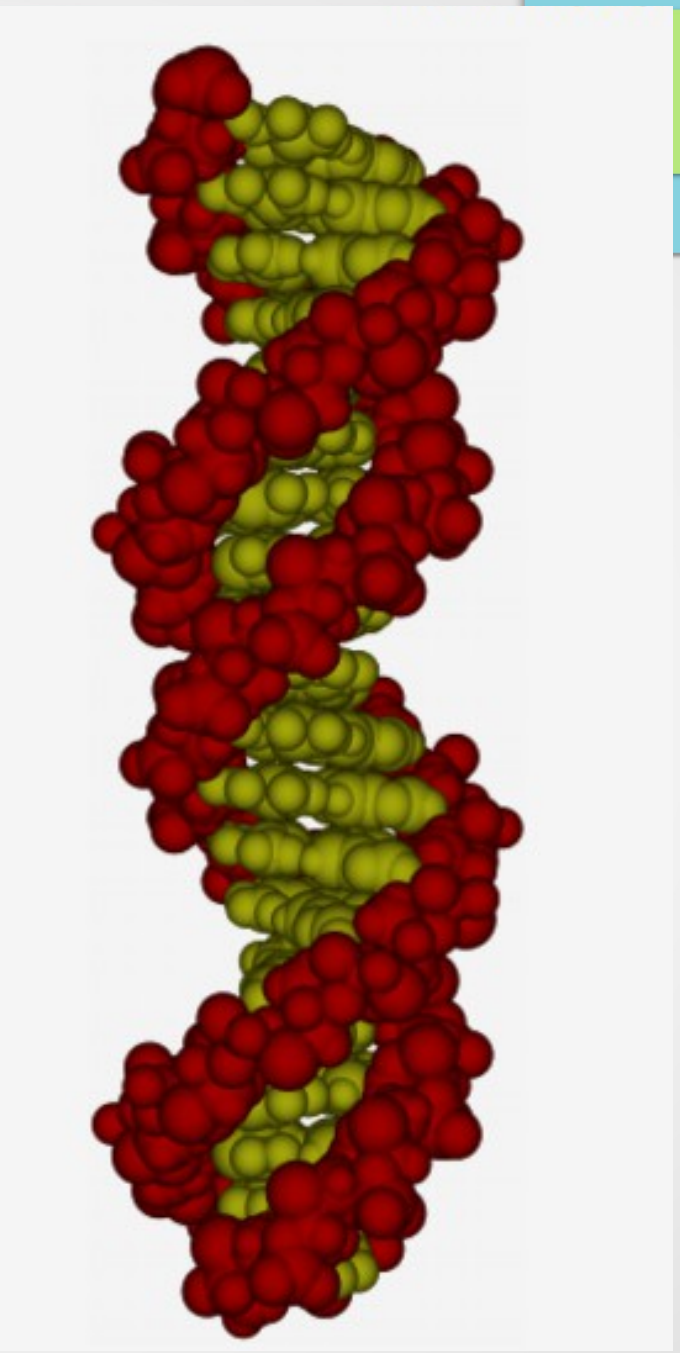
DNA Structure

- The sub-rosette structure is adapted from Bernal et al 2013, available here.
- This consists of a few additional levels:
  - Repeating 6-nucleosome single helix unit filling out the rosette segments
  - Nucleosomes consisting of double helix DNA strands wrapped 2.5 times around a histone
  - DNA double helix consisting of repeated guanine-cytosine pairs.
  - The guanine and cytosine are modeled as a union of overlapping atoms.
    - The atoms are modeled as spheres with radius twice their van der Waals radius.



- Nucleosome (taken from Bernal et al 2013).

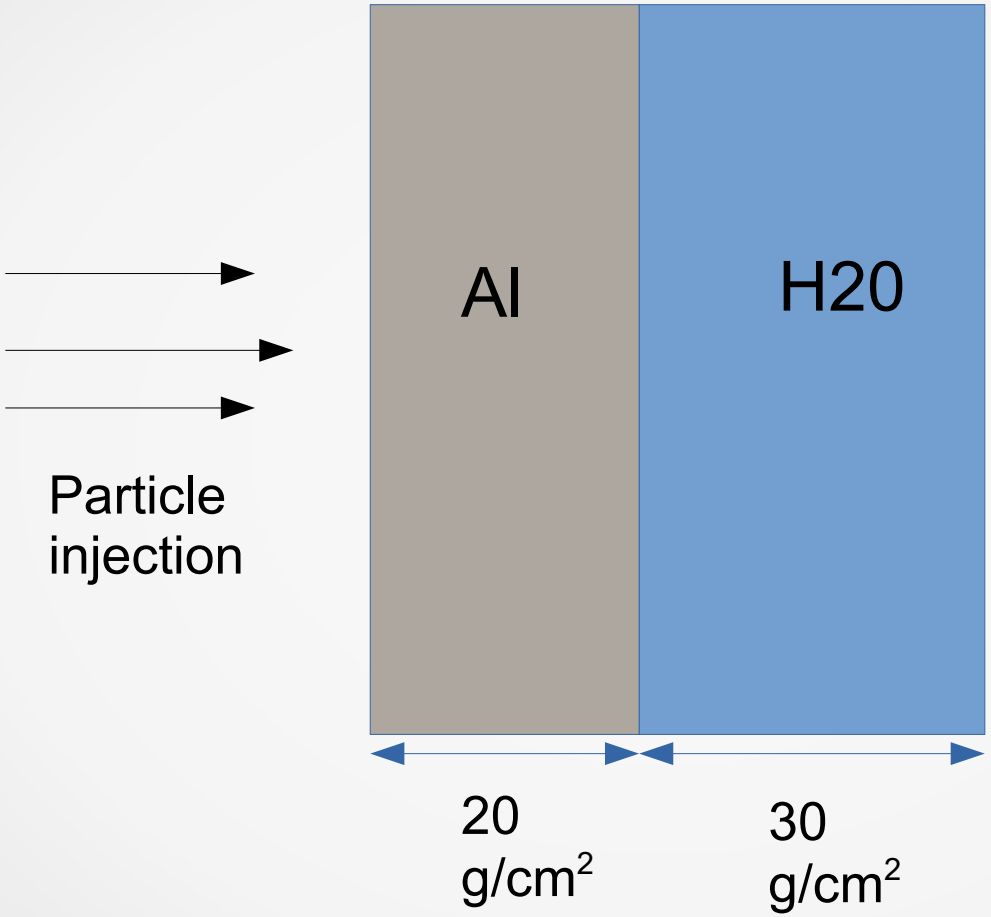
- Double Helix Structure
- Taken from Bernal et al 2013.



Macro Geometry

- For an arbitrary macroscopic geometry, particles are captured before they reach the DNA energy limit.
  - 100 MeV for protons and heavy ions, 1 MeV or lower for everything else.
- Particle information is then passed to the micro level.
- A single cell is looped on the physical stage, with attached indices
- Clusters of DNA damage can thus be tracked by position within a body.
- Slabs and spheres have been tested, and a proof-of-concept GEANT4-CAD interface has been written.

Macro Geometry Example



- Simple Slab Phantom

Working with dna-chemistry limitations

- By iterating a single cell we mitigate the large geometry issue.
- Using an appropriate energy cut-off reduces secondaries from what is considered a ‘primary’.
  - Chemistry uses 1 MeV cut-off
  - Some DNA processes use a higher cut-off.
  - We take the highest transition energy by particle type
- By splitting up the original primary, we can more easily spread the load among processors.

Other Problems

- IT and ITFinder have errors that will not come up much.
- But with enough small geometries and/or particles they sometimes do.
- Had to modify the classes: It appears that functionality was changed but one ‘catch’ in each was not updated.
- [ ] operator in IT
- FindNearest in ITFinder
- It’s now possible to create an empty node: presumably this used to be checked for earlier.
- Latter already has a fail-safe but as-is it never triggers as it falls after an uncommented exception throw.
- Latter is a .icc, so have to change in library.

New Problems We Created

- The looping structure in the physics stage means chemistry may now get precursors in different cells.
- As-is, it has no way of knowing that.
- Ordinarily use UserTrackInformation to pass this info, but chemistry is already using this.
- Have to thus use AuxiliaryTrackInformation
  - Can still use UserTrackInformation at the physical stage.
- Now we need to let Chemistry know the ‘real’ positions without it moving the particles out into the void.

Using AuxiliaryTrackInformation

- To pass it correctly, need our own DNAChemistryManager and MollecularDissociation classes.
  - User functions provided kick in too late
  - Track is either already destroyed or isn't passed to the user function as-is.
- Ultimately wwant the 'position shift' to be read from here when building/reading the KDTree
- But the local position still must be readable.

Implementing

- The reaction list propogates the KDTree, but then a different function/class reads it.
- Each read separately off of the Track, which is linked to the nodes.
  - The tree is built based on positions.
- Hence, we had to add the shift in 2 places.
- In SmoluchowskiReactionModel to build tree properly.
- In IT's [ ] function to read from the tree properly.
- Side note: The KDTree system is set up with a lot of redundancy atm.
  - Probably for future expansion.

Strand Breaks

- Lastly, Strand Breaks
- Methodology worked from Friedland et al 2017 and back-tracking their sources.
- Physical stage: Energy depositions w/in 2 van der Waals radii of sugar-posphate backbone
  - Scaled probability: 0 at 5 eV, 1 at 32.5 eV
- Chemical stage: Only consider OH as causing breaks
- Look for passing w/in reaction radii of bases and backbone.
- Apply simple probability multiplier of 0.65
  - Milligan et al 1993
  - Gets ~ 0.32, but doesn't consider histones

Double Strand Breaks

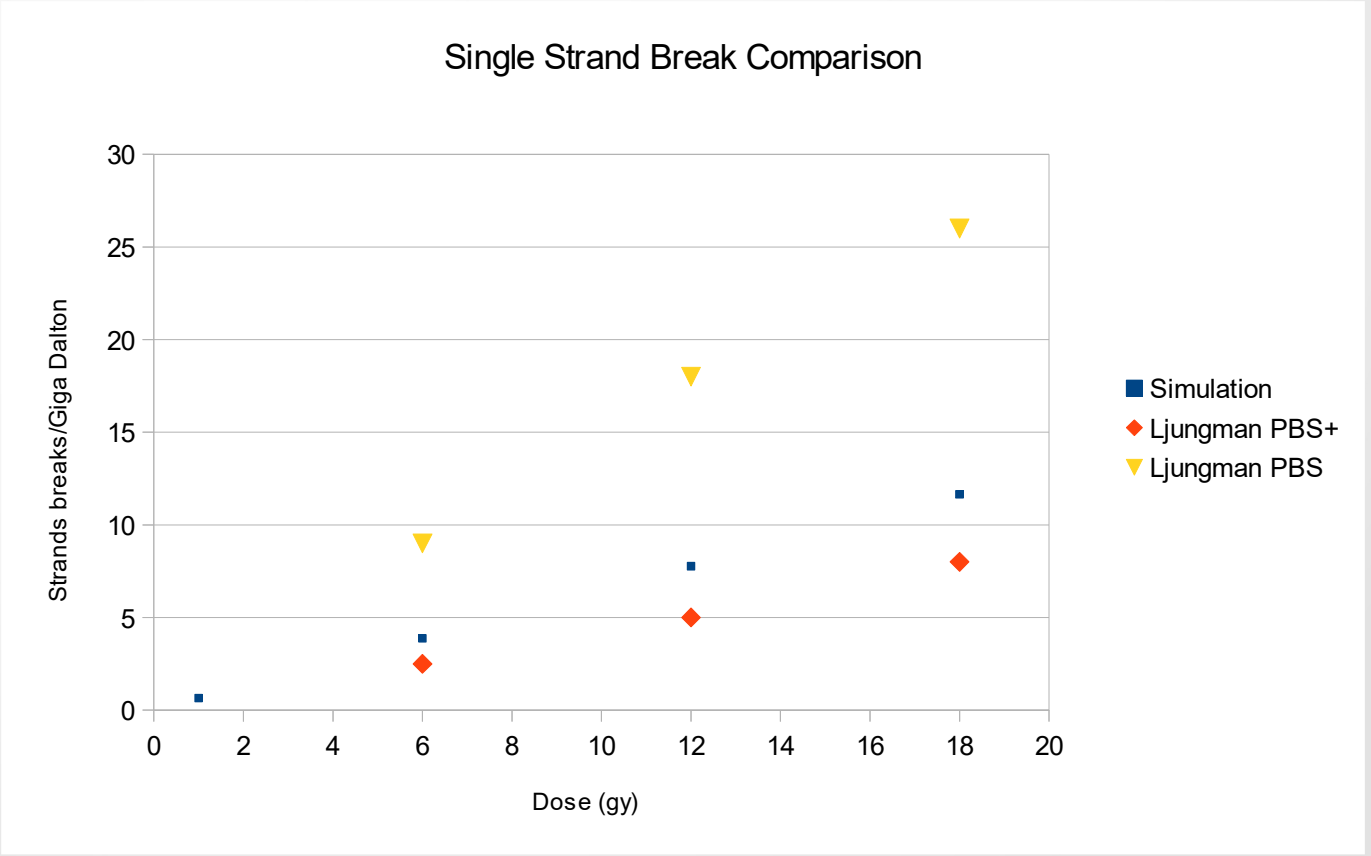
- Track exactly what cell and which of the 6.4 GBP w/in the cell is hit.
- Count a DSB if on opposite strands w/in 10.
  - In actuality, would have a diminishing probability peaking at some point greater than 5 and going to zero at or past 12
  - Chaudhry and Weinfeld 1995
  - Considered too small a difference to deal with at this stage.
- Subtract that from total strand breaks, add 1% of the remainder to DSBs
  - A chain reaction effect: empirical estimate

Validation

- We have done 2 experimental comparisons
- Ljungman et al involved irradiation of cell nuclei.
- Birnboim and Jevcak irradiated blood

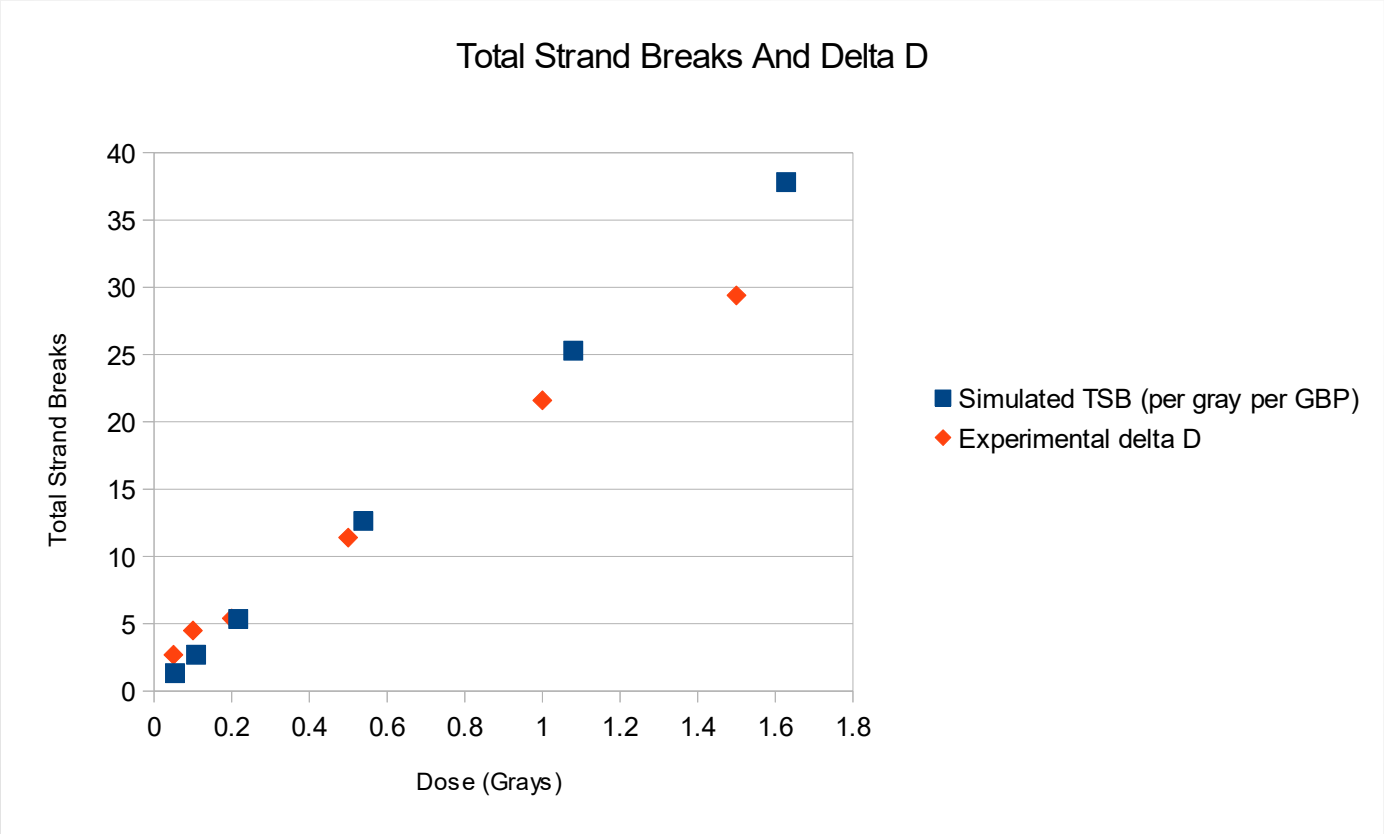
Ljungman et al

- Our results are systematically higher.
- The expected reason is repair mechanisms, which we do not attempt to simulate.



Birnboim and Jevcak 1981

- Requires a macroscopic simulation.
- They tracked difference in unspooled DNA, which should scale with strand breaks



Works Cited (1)

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- **Chaudhry, M. A. and Weinfeld, M. 1995. The Action of Escherichia coli Endonuclease III on Multiply Damaged Sites in DNA. Journal of Molecular Biology, vol. 249 pp. 914-922.**

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- **Milligan, J. R., Aguilera, J. A., and Ward, J. F. February 1993. Variation of Single-Strand Break Yield with Scavenger Concentration for Plasmid DNA Irradiated in Aqueous Solution. Radiation Research, Vol. 133, No. 2 pp. 151-157.**