Toward a testable statistical model for radiation effects in DNA

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with
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Motivation

- Understanding the physical basis for
  - Differences in biological effects between: photons, electrons, protons, carbon…
- Model to predict:
  - Prompt damage to DNA, RNA, etc:
    - Direct, indirect
  - Experimental correlations to
    - Strand breaks, Clustered lesions, free radical activation …
      - biological consequences, short- & long-term: cell death, apoptosis, carcinogenesis
- Improve understanding radiation effects in biological systems

Apply concepts from theory of radiation interactions with matter, applied to particle detectors that involve chemical sensitization (etchable track detectors, nuclear emulsion)

What is radiation damage?

Transfer of energy to (mostly) electrons in matter, causing

- Physics
  - Ionization: electrons "escape" from atoms/molecules
- Chemistry
  - Ionized/excited atoms/molecules lead to (bio)chemical reactions -> molecular reconfiguration
- Biology
  - Effects on biological processes: cellular response(s) to DNA damage, replication/reproduction

How is radiation damage measured?

- Radiation Dose – deposited energy/mass
  - Source carries **energy**, which is transferred to target material
- Chemical/Biological effects depend on
  - **Numbers** of electrons released/excited (holes)
    - 1 Gray = 10^4 erg/g ~1.0×10^{-1} holes/Mbp
  - Nanoscale **clustering** of holes, time evolution
    - lethal damage, e.g. double strand breaks result from multiple holes within a few nm

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  - Nanoscale **clustering** of holes, time evolution
    - **Clustering differences between different forms of radiation [photons, electrons, protons, ions, neutrons, …] are thought to explain differences in biological effect**

What more is there to physics besides dose?

- Chemical/Biological effects depend on
  - **Numbers** of electrons released/excited (holes)
  - Position and timing of holes
  - Clustering of holes
    - Lethal damage, e.g. double-strand breaks, require >1 hole, within ~10 base prs, ~3 nm
    - Clustering is a **statistical** process
- Primary (direct) ionization is well understood
  - Many (in some cases most) holes are from **secondary** ionization (e.g. when primary electrons cause additional ionization) – biological response depends on numbers and clustering of all holes

Patterns of ionization

- Electrically neutral particles (photons, neutrons)
  - few and spatially random, large energy transfer
- Electrically charged particles (electrons, protons, ions)
  - peripheral (distant) collisions near trajectory (few nm) violent (close) collisions (delta rays); in energy. distant/close ~ 1, in numbers distant>> close [see, e.g., S.P.Ahlen, Rev. Mod. Phys. 52, 121 (1980)]

⇒ Model(s) ("spherical cow")

- Ionization patterns
  - 2 primitive models, "photon", "proton"
- Target material (DNA)
- Lethality criteria

Patterns of ionization

⇒ Construct 2 primitive models

- **Primitive photon** – ionization (holes) distributed uniformly in 3-d
- **Primitive proton** – holes distributed on ***tracks***: straight lines, ≈3.2 holes/μm, lines distributed randomly in 3-d

- define cluster: = 2 holes separated by <3 nm
- find probabilities, rates

primitive photon

- **Primitive photon** – holes distributed uniformly in 3-d
  - Pair density = hole density x probability of nearest neighbor (NN) @<3nm
  - Mean # pair clusters per molecule = pair density x volume of molecule
- Nearest neighbor probability distribution: (same as NN in ideal gas, a standard calculation of statistical mechanics/thermodynamics; see, e.g.,

  https://en.wikipedia.org/wiki/Mean_inter-particle_distance

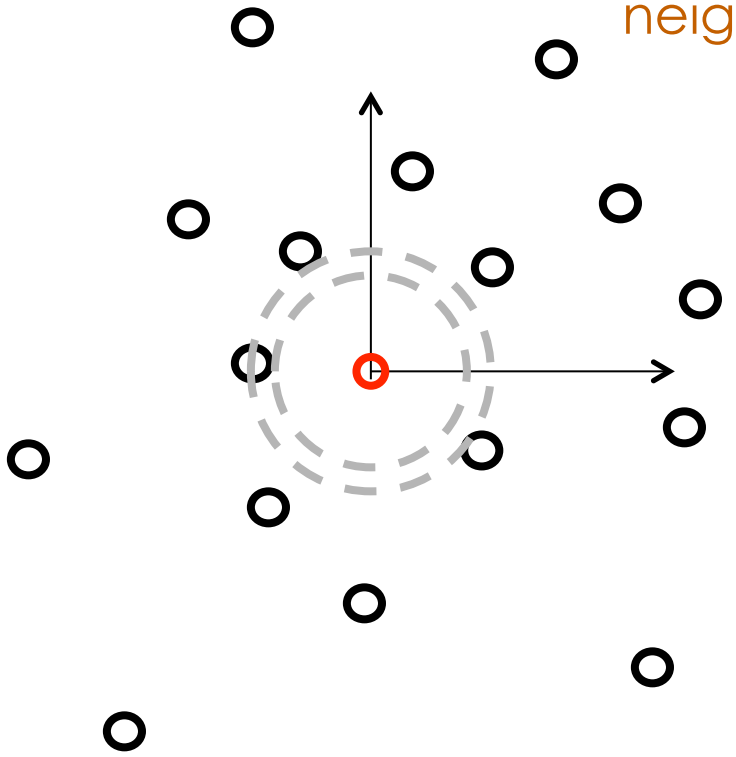
primitive photon

- **Primitive photon**

  Nearest neighbor probability distribution

  place a random hole at the origin

  what is the probability that the distance to its **nearest** neighbor (NN) is between r and dr?



- Uniform density *n* in 3-d (n holes/μm^3)
  =3-d probability density
- Number N_0 within radius r_0

$$N_0 = \int_{r<r_0} n\, d^3r = \int_0^{r_0} \overbrace{n \times 4\pi r^2 dr}^{\text{prob. of neighbor between r and r+dr}}$$

- Probability P that no NN for 0< r <r_0
  is reduced by P x prob. of neighbor between r_0 and r_0+dr

$$dP = -P \times 4\pi r^2 n dr$$

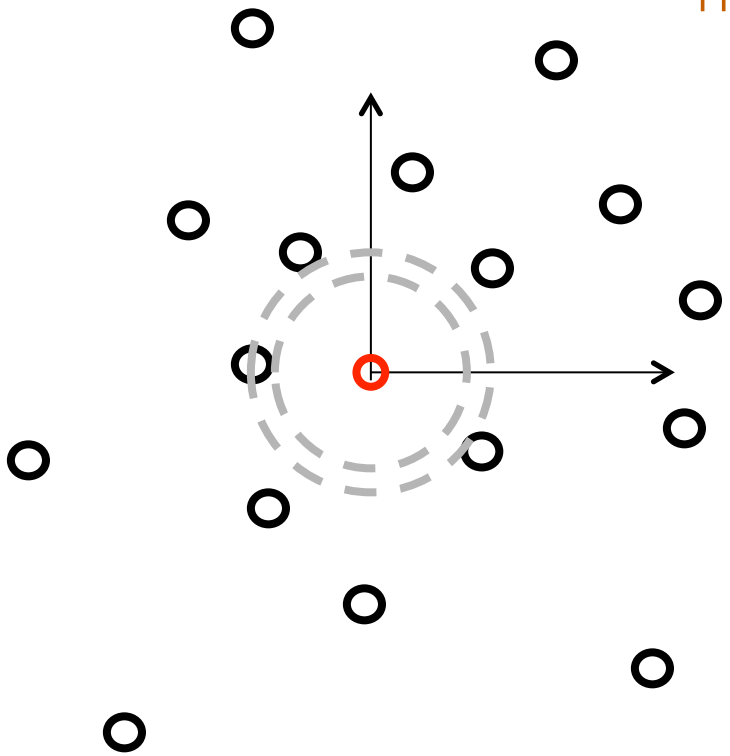
primitive photon

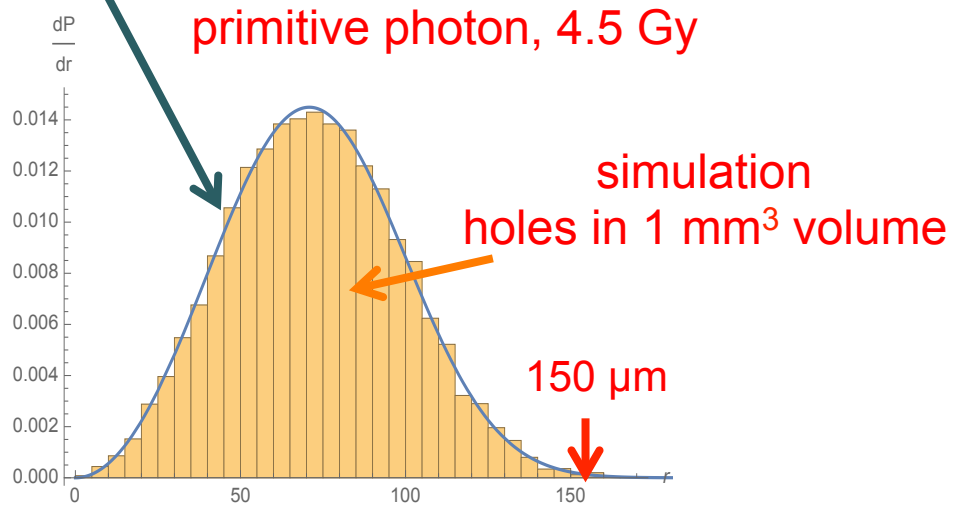
- Probability P that no NN for 0< r <r_0
  is reduced by P x prob. of neighbor between r_0 and r_0+dr

$$dP = -P \times 4\pi r^2 n dr \quad \Rightarrow P = e^{-n \times \frac{4}{3}\pi r^3}$$

  - probability that the distance to the **nearest** neighbor (NN) is between r and dr

$$= \frac{dP}{dr} = n \times 4\pi r^2 \times e^{-n \times \frac{4}{3}\pi r^3}$$





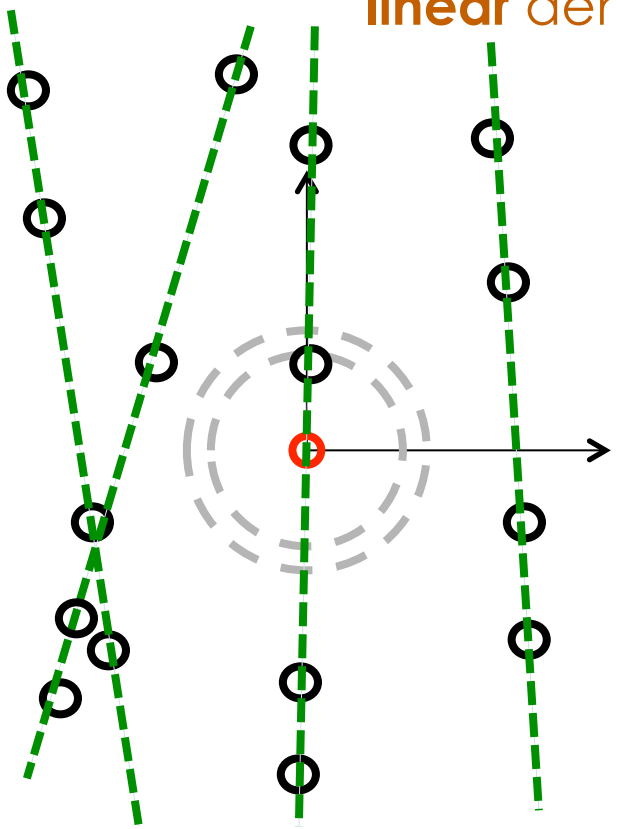
primitive proton

- **Primitive proton**

  Nearest neighbor probability distribution

  place random hole at the origin on particle trajectory

  linear density λ holes/μm overall density n in 3-d



- Density $n_\lambda = \lambda\ \delta(x)\ \delta(y) + n$

$$N_0 = \int_{r<r_0} n_\lambda d^3r$$

$$= n \times 4\pi \int_0^{r_0} r^2 dr + 2\int_0^{r_0} \lambda dz$$

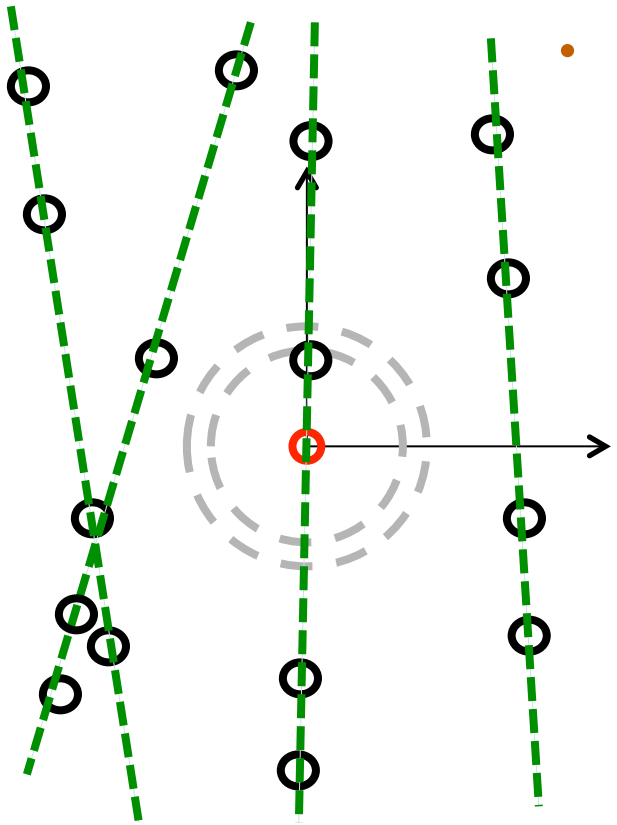
- Change in probability P that no NN for $0< r <r_0$ between r_0 and r_0+dr

$$dP = -P \times [4\pi r_0^2 n + 2\lambda r_0]$$

primitive proton

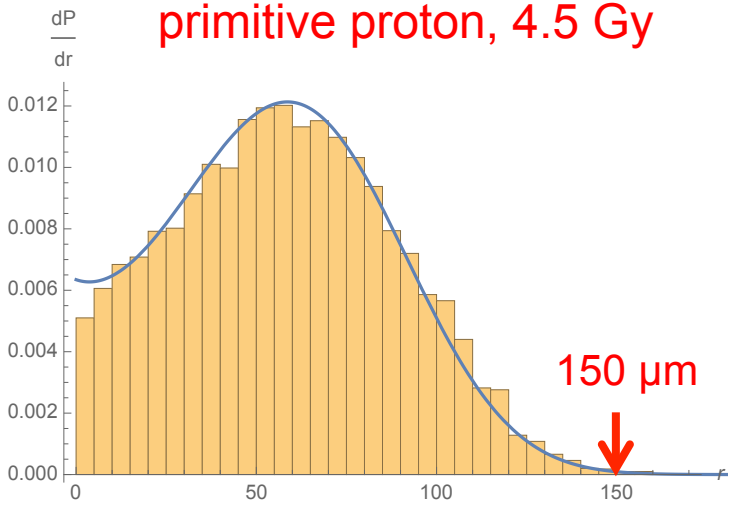
- Probability P that no NN for 0< r <r_0
  is reduced by P x prob. of neighbor between r_0 and r_0+dr

$$dP = -P \times [4\pi r_0^2 n + 2\lambda r_0] \Rightarrow P = e^{-(\frac{4}{3}\pi r^3 n + 2\lambda r)}$$



- probability that the distance to the **nearest** neighbor (NN) is between r and dr

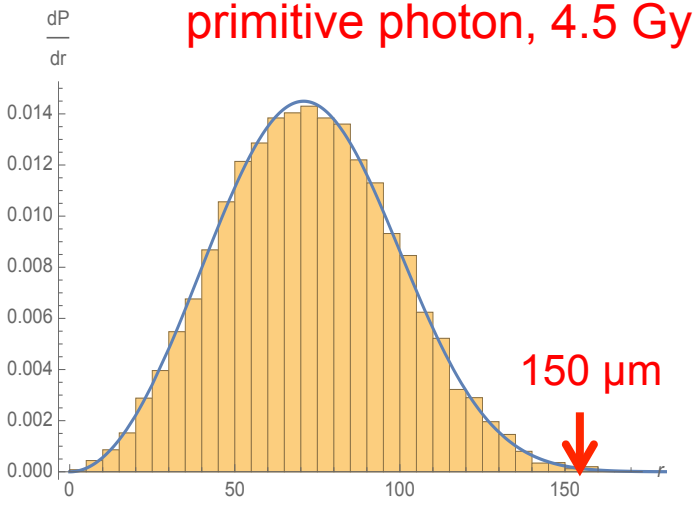
$$= \frac{dP}{dr} = (4\pi r^2 n + 2\lambda) \times e^{-(\frac{4}{3}\pi r^3 n + 2\lambda r)}$$

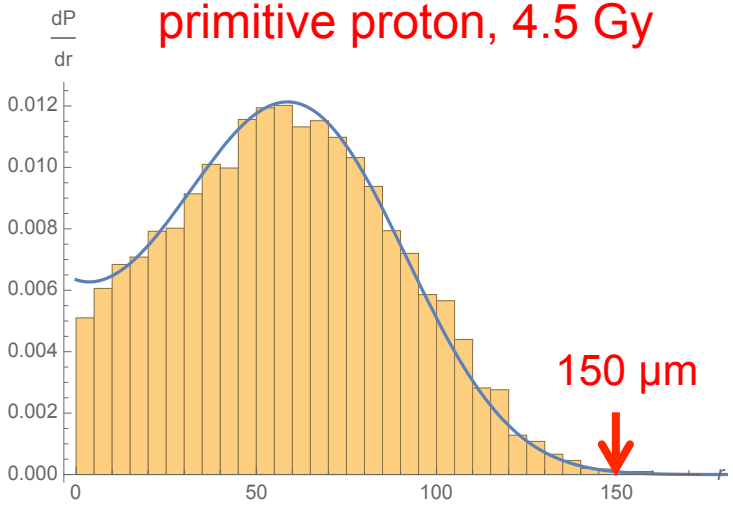


primitive models: comparison

- Cluster rate is proportional to the distribution integrated
  - 0 < r < 3 nm

Charged particle tracks produce clusters at a higher rate





primitive models

- probability that nearest neighbor @<3nm

$$P_{cluster} = \int_0^{r_0=0.003\mu m} \frac{dP}{dr} dr$$

- For primitive photon

$$P_{cluster} = 1 - e^{-\frac{4}{3}\pi r_0^3 n}$$

- For primitive proton

$$P_{cluster} = 1 - e^{-(\frac{4}{3}\pi r_0^3 n + 2\lambda r_0)}$$

Target material

- Energy loss theory (Bohr, Bethe, Bloch)
  - Charged particles, v >> v(atomic electron: ~0.01c)
  - Target is ≈ sea of free stationary electrons, number density = n_e
  - Fast proton LET=1.99 x 10^6 eV-$g^{-1}cm^{-2}$ in H_2O
- Target = DNA molecule
  - Base pairs A-T/G-C: ~ same elemental composition vis-à-vis energy loss – ≈3.13 x 10^{23} electrons/g
  - Mean ionization energy (log average over all electrons) ≈ 69 eV (H_2O)
  - 1 Gy dose = 6.25 x 10^{15} eV/g → ~91 holes/pg
    Assume a mass density ρ = 1.4 g cm^{-3}
    → 1 Gy = 127 holes/μm^3 (primary ionization) ≡ n_0

Numerical evaluation

- probability that nearest neighbor @<3nm

$$P_{cluster} = \int_0^{r_0=0.003\mu m} \frac{dP}{dr} dr$$

- For primitive photon

n=n_0 x (dose D in Gy)

1.4 x 10^{-5}D

$$P_{cluster} = 1 - e^{-\frac{4}{3}\pi r_0^3 n}$$

$$\approx \frac{4}{3}\pi r_0^3 n_0 D \text{ for D<<}10^5 \text{ Gy}$$

λ ~4.0 holes/μm

- For primitive proton

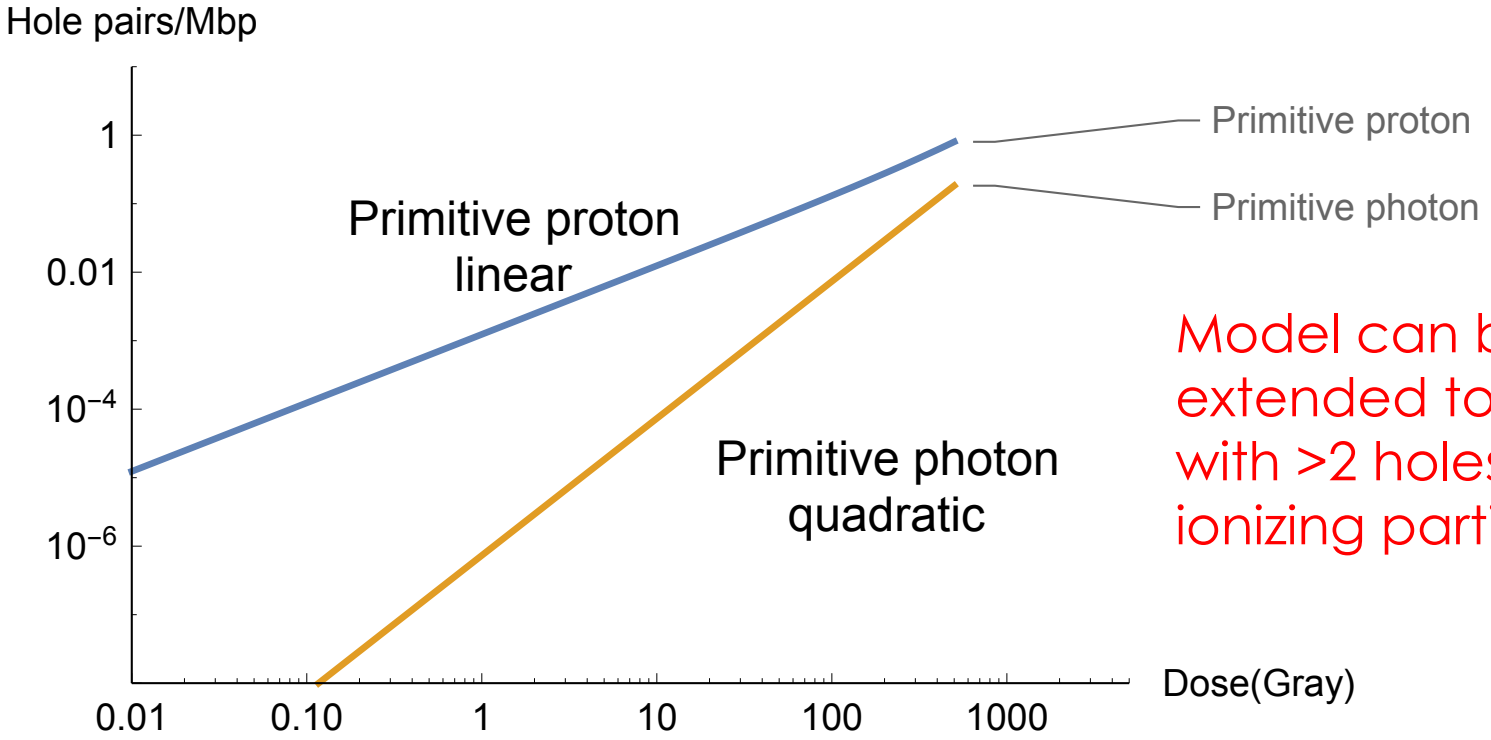
2.4 x 10^{-2}

$$P_{cluster} = 1 - e^{-(\frac{4}{3}\pi r_0^3 n + 2\lambda r_0)}$$

$$\approx 2\lambda r_0 \quad \text{for D<<}10^3 \text{ Gy}$$

Cluster density

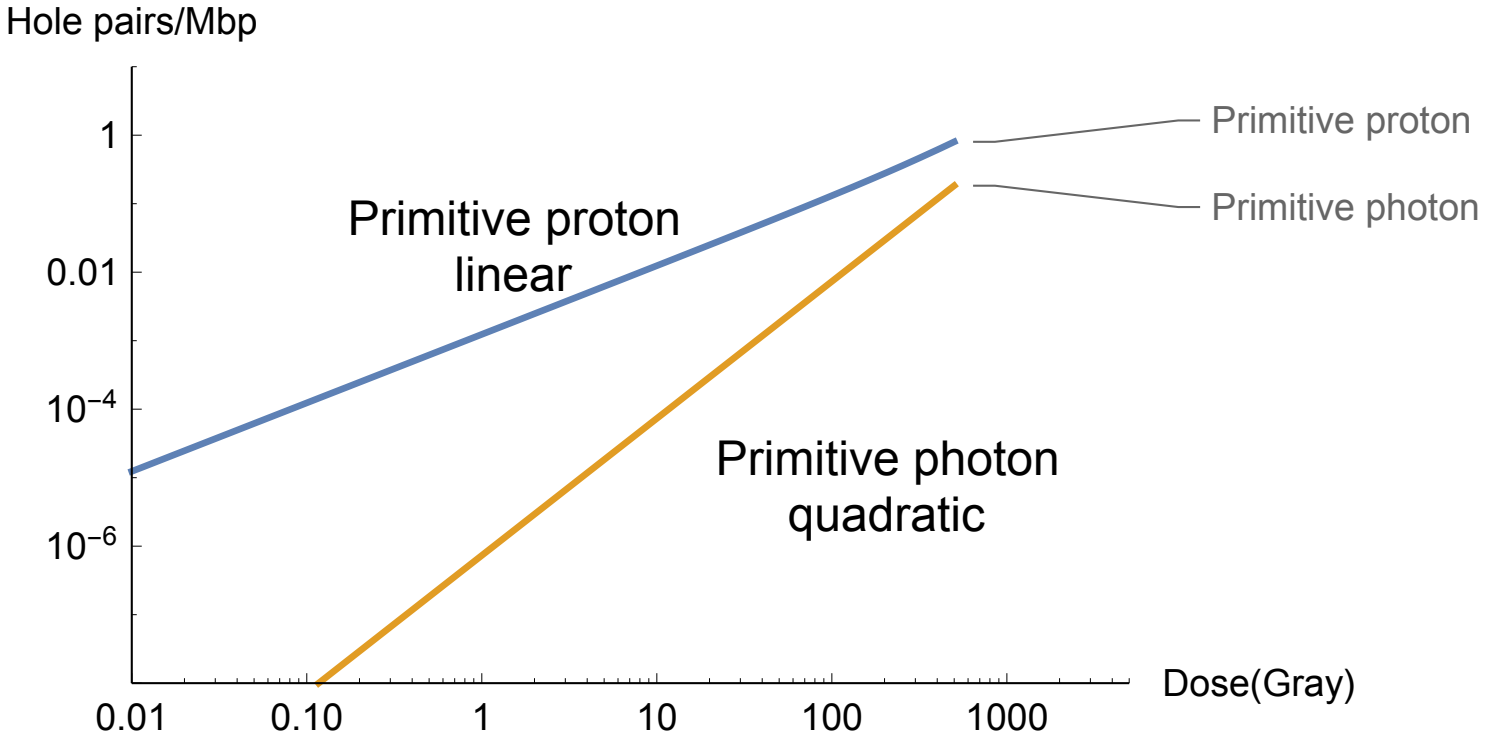
- Pair density = ½ x hole density x cluster probability
  - "photon" $\approx \frac{2}{3}\pi r_0^3 n_0^2 D^2$
  - "proton" $\approx \lambda r_0 n_0 D$
- Mean # pair clusters per Mbp = pair density x volume/Mbp



Model can be readily extended to clusters with >2 holes, heavily ionizing particles

primitive models: interpretation

- Human DNA consists of ~3Gbp →
  - ~3.7 pairs/Gy "proton" model
  - ~2.2 x 10^{-3}/Gy^2 "photon" model
- "proton" appears to be a better fit for IR used in cancer therapy: gamma, electron, proton, ions



primitive models: interpretation

- Human DNA consists of ~3Gbp →
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- "proton" appears to be a better fit for IR used in cancer therapy: gamma, electron, proton, ions
  - Electron ionization is similar to "protons" (no Bragg peak due to low mass)
  - MeV γ's ionize primarily by Compton scattering, producing energetic secondary electrons that behave as tracks (⇒RBE for electrons=1)
  - Ions may be modeled as a mix of high-LET tracks and low-LET δ-rays
  - Some scenarios may be best modeled as a mix of tracks & random (e.g. low-energy photons)

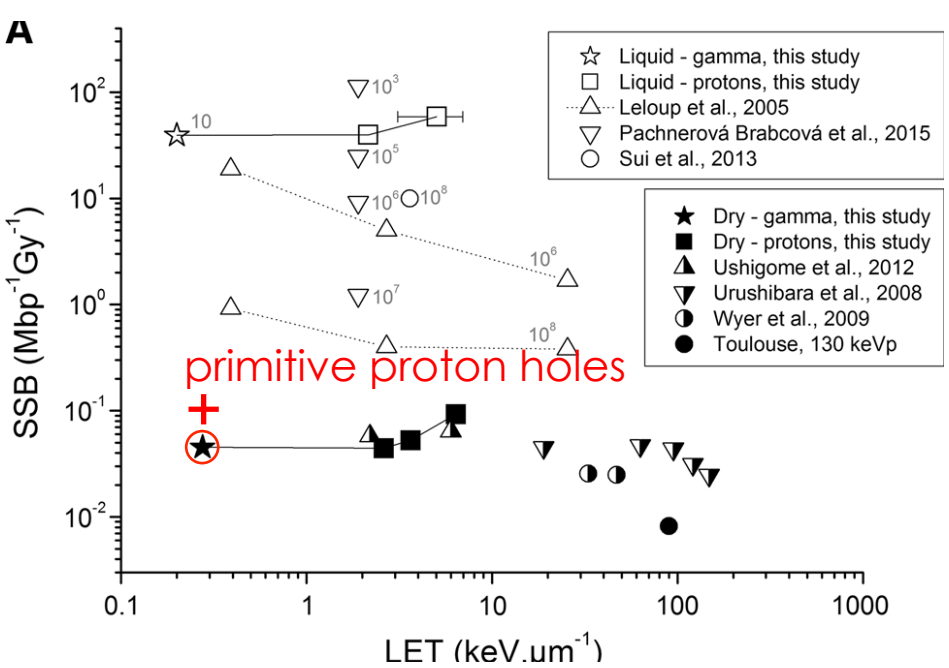
Model testing

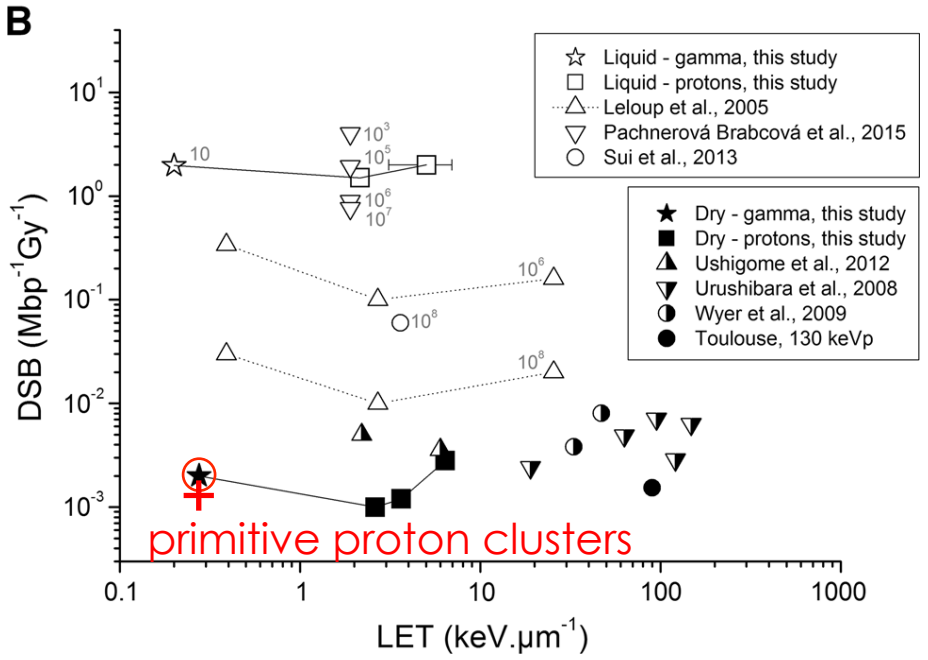
- Translation to experimental measurement
  - Measurements: rates vs Dose of SSB, DSB, other complex lesions
  - Model calculation (so far) applies to *direct* ionization, not indirect → test on dry DNA
  - Effective ionization energy needs tuning
  - Not every hole/cluster may produce SSB/DSB – what's the "efficiency"?
  - Different types of lesions have different energy thresholds → different rates – can these be extracted from experimental rates?

Model testing

- Model calculation vs measurements on dry DNA

Recent publication:
Vyšín et al, "Proton-induced direct and indirect damage of plasmid DNA," Radiat Environ Biophys (2015) 54:343–352





Model testing

- Model calculation vs measurements on dry DNA
  - Need clean measurements with protons
    - degree of dryness may matter
    - Clean beam: energy definition, minimal fragmentation products
    - Insignificant slowing of beam in sample/container (i.e, range > 1 cm)
  - First beam tests proposed at Cincinnati Children's Proton Therapy Center
    https://www.cincinnatichildrens.org/service/p/proton-therapy/research
    - Dedicated research gantry to begin operations May 2017

Future plans

- Dry DNA
  - Model testing/tuning:
    - Photons, protons @250 MeV, 70 MeV
    - Plasmid DNA: SSB, DSB, other damage markers
    - Geometric factors?
- DNA in cells is not dry
  - Indirect damage stemming from ionization/ excitation in surrounding fluid may mimic "primitive photon"
  - Magnitude of effects depend on ability of fluid to quench excitations, concentration of DNA – to be explored
- Pursue funding with NSF

Thank you