Monte Carlo Simulation of the Effects of Oxygen on Clustered DNA Lesions Formed by Ionizing Radiation

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Stochastic Track Models
Monday September 22, 2008
2:30 to 4:30 pm
Monte Carlo Damage Simulation (MCDS)

MCDS (Semenenko and Stewart 2004, 2006) developed as a byproduct of our effort to develop a Monte Carlo model to simulate the excision repair of clustered DNA lesions (Semenenko et al. 2005, Semenenko and Stewart 2005)

Needed nucleotide-level maps of clustered DNA lesions to simulate the outcome from base excision repair

Monte Carlo simulations were and still are the only way to generate plausible spatial arrangements of the DNA lesions forming a cluster.

MCDS Overview

Three step procedure used to simulate cluster formation

1. Determine number lesions formed in the DNA
2. Place lesions within the DNA
3. Classify clusters according to properties and complexity

Step 1 consistent with track structure simulations and available experimental data (~216.67 strand breaks Gy\(^{-1}\) Gbp\(^{-1}\) and 3 bases damaged per strand break)

Step 3 is not specific to the MCDS algorithm (i.e., same methods can be used in track structure simulations to categorize groups of lesions as SSB, SSB++, DSB, DSB++, …)

Step 2 is a radical departure from track structure simulations

http://rh.healthsciences.purdue.edu/mcds/
Placement (clustering) of lesions in DNA

Define a DNA segment of length $n_{seg}$

$n_{seg} \leq 149,200$ bp

Insert strand breaks and base damage at random locations (1300 strand breaks and 3900 damaged bases in a cell with 6 Gbp of DNA) – about 1 in 28.6 bp damaged when $n_{seg} = 149,200$ bp. Fraction of bp damaged increases (i.e., more clustering) as $n_{seg}$ decreases.

$N_{min} = 9$ bp

Cluster 1

Cluster 2
\( N_{\text{seg}} \) as function of radiation quality

**Found** (Semenenko and Stewart 2006) that damage yields from track structure simulations could be reproduced within the apparent precision of the published data using

\[
n_{\text{seg}}(x) = 149,200 - \frac{123,600x}{x + 267} \text{ bp Gy}^{-1}, \quad 1 \leq x \equiv \frac{Z_{\text{eff}}^2}{\beta^2} \leq 3200
\]

\( \beta = \sqrt{1 - \frac{1}{\left(1 + \frac{T}{m_0c^2}\right)^2}} \)

\( Z_{\text{eff}} = Z \left[1 - \exp\left(-125\beta Z^{-2/3}\right)\right] \)

Effective charge (Barkas 1963)

Speed of particle (relative to \( c \)) with kinetic energy \( T \)
Why does it seem to work so well?

Spatial distribution of lesions within individual clusters (~few tens of bp) dominated by random processes such that nucleotides are about equally likely to be damaged.

Average diffusion distance of an •OH in a cellular milieu is about 4-6 nm (Roots and Okada 1975)

Original MCDS – Brief Recap

- Has three adjustable parameters
  - Number of strand breaks per bp (216.67 Gbp Gy⁻¹)
  - Number of damaged bases per bp (650 Gbp Gy⁻¹)
  - DNA segment length ($n_{seg}$) determined from fits to track structure simulations

- Produces nucleotide-level maps of clusters comparable to track structure simulations
  - Electrons, protons and alpha particles up to 1 GeV
  - Photons with energies greater than about 100 eV

- Very fast (for a Monte Carlo simulation)
  - Useable results in < 1 minute on a fast PC

- Can download and use for free

http://rh.healthsciences.purdue.edu/mcfs/
Effects of oxygen on DNA damage induction

Long been known that oxygen is a powerful modulator of DNA damage induction and closely related endpoints, such as clonogenic death and mutation.

- Cells irradiated under reduced oxygen sustain less damage and are much more likely to survive (factor ~ 2-4)

Models to predict the effects of oxygen on cluster induction could be used to help test hypotheses such as

Reduced oxygen levels at the time of irradiation decreases cluster complexity (number of DNA lesions per cluster) and reduces the overall cluster yield per cell and per unit dose.

The rate and fidelity (efficiency) of cluster repair increases as cluster complexity decreases. Enhanced repair of clusters increases cell survival.
Chemical Basis of the Oxygen Effect

Competition between oxygen fixation and chemical repair is the prevailing hypothesis (von Sonntag 2006)

(1) DNA + ionizing radiation $\rightarrow$ DNA lesion (biochemical repair required)

(2) DNA + ionizing radiation $\rightarrow$ DNA$\cdot$ (various)

(3) DNA$\cdot$ + O$_2$ $\rightarrow$ DNA-O$_2$· ("oxygen fixation" – biochemical repair required)

(4) DNA$\cdot$ + RSH $\rightarrow$ DNA ("chemical repair" – restoration of the DNA$^*$)

(5) DNA$\cdot$ $\rightarrow$ DNA lesion (biochemical repair required)

* Von Sonntag notes that donation of a proton to a DNA radical may or may not restore the original chemical structure of the DNA. But, the chemical repair process evidently converts the DNA radical (or cluster of radicals?) into a form that is more amenable to biochemical repair…

MCDS Modification – Step 1

Use the original MCDS to simulate the location of DNA radicals

At this stage of the simulation...

All lesions formed in the original MCDS treated as a radical that may undergo fixation or chemical repair

No distinction made between radicals formed through direct and indirect mechanisms

Preserves the ability of the MCDS to simulate lesion (radical) clustering effects without introducing any additional parameters into the modeling process.
**MCDS Modification – Step 2 (conceptual basis)**

Oxygen is uniformly distributed near the DNA and able to interact with all DNA radicals with equal probability.

![Diagram of DNA radicals with oxygen molecules]

If *oxygen fixation* occurs (DNA· + O₂ → DNA-O₂·), radical converted to a strand break or damaged base *as in the original MCDS* – cluster yields for normoxic conditions same as original MCDS.

“Fixation” implicitly includes other processes that convert DNA radicals to a form requiring biochemical repair.

\[
\text{DNA·} \rightarrow \text{DNA lesion (biochemical repair)}
\]

If *chemical repair* occurs (DNA· + RSH → DNA), DNA is restored to its original *(undamaged)* state – *lesion not created*.
Chemical repair or fixation?

Define $f$ as the fraction of the DNA radicals that undergo chemical repair

\[
 f ([O_2]) = 1 - \frac{[O_2] + K}{[O_2] + M \cdot K}
\]

$[O_2] = \text{oxygen concentration at time of irradiation}$

Formula is derived from *(related to) oxygen-effect formula of Alper and Howard-Flanders (1956)*

Introduces two adjustable parameters ($M$ and $K$) into the modeling process.

Effect of $O_2$ on fixation and chemical repair

\[ f([O_2]) = 1 - \frac{[O_2] + K}{[O_2] + M \cdot K} \]

$M$ determines maximum fraction of radicals fixed at 0% $O_2$

$K = \text{oxygen concentration at which } f \text{ equals } 1/M$
OER for Damage Induction (low LET)

Trends and estimates of OER for DSB induction and cell survival comparable to values predicted by MCDS ($K = 0.5209$, $M = 1.6574$).

Interplay between oxygen and LET

(1) DNA + ionizing radiation → DNA lesion
(2) DNA + ionizing radiation → DNA·

(3) DNA· + O₂ → DNA-O₂· (“oxygen fixation” – biochemical repair required)
(4) DNA· + RSH → DNA (“chemical repair” – restoration of the DNA*)
(5) DNA· → DNA lesion

If ionization does not substantially alter the local cellular environment (e.g., “oxygen-in-track hypothesis”), might expect reactions (3)–(5) to be same for low and high LET radiation.

\[ f \left( [O_2] \right) = 1 - \frac{[O_2] + K}{[O_2] + M \cdot K} \]

Assume \( M \) and \( K \) are independent of radiation quality.
OER with $f$ independent of LET

Model cannot easily explain the decrease in the OER as LET increases

### Table: DSB Yield (%)

<table>
<thead>
<tr>
<th>Number of Lesions</th>
<th>Anoxic</th>
<th>Normoxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.033</td>
<td>5.148</td>
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<tr>
<td>2</td>
<td>21.070</td>
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<td>3</td>
<td>18.900</td>
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<td>4</td>
<td>14.523</td>
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<td>14</td>
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<td>1.939</td>
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<tr>
<td>&gt; 16</td>
<td>0.214</td>
<td>18.207</td>
</tr>
</tbody>
</table>

Avg per DSB: 4.711 7.859

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**LET (keV/μm)**

- $10^{-1}$
- $10^0$
- $10^1$
- $10^2$

**OER**

- 4.0
- 3.5
- 3.0
- 2.5
- 2.0
- 1.5
- 1.0
- 0.5

**Number of Lesions**

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- > 16

**DSB Yield (%)**

- Anoxic
- Normoxic

**Legend**

- Cell survival (Carlson et al. 2006)
- Frankenberg-Schwager et al. (1991)
- Prise et al. (1989)
- Prise et al. (1990)
- Hirayama et al. (2005)

---

2 MeV $\alpha$

(162.5 keV/μm)

$f = 39.6\%$
Possible explanation for LET effect?

(1) DNA + ionizing radiation $\rightarrow$ DNA lesion (biochemical repair required)
(2) DNA + ionizing radiation $\rightarrow$ DNA· (various)
(3) DNA· + O$_2$ $\rightarrow$ DNA-O$_2$· (“oxygen fixation” – biochemical repair required)
(4) DNA· + RSH $\rightarrow$ DNA (“chemical repair” – restoration of the DNA*)
(5) DNA· $\rightarrow$ DNA lesion (biochemical repair required)

Ionization does not substantially alter the local cellular environment (reactions 3-5 same for low and high LET radiation), but reaction 1 is enhanced relative to reaction 2

$$f ([O_2]) = 1 - \frac{[O_2] + K}{[O_2] + [M(I)] \cdot K}$$

$K$ is independent of radiation quality and $M$ becomes function of radiation quality (convenient way to implement effect into model)
OER with $f$ a function of radiation quality

\[
f([O_2]) = 1 - \frac{[O_2] + K}{[O_2] + M(l) \cdot K}
\]

\[
M(l) = M_0 - \frac{(M_0 - 1)}{1 + q / l}
\]

where \( l \equiv \left( \frac{Z_{eff}}{\beta} \right)^2 \)

\[
Z_{eff} = Z \left[ 1 - \exp\left(-125 \beta Z^{-2/3}\right) \right]
\]

\[
\beta = \sqrt{1 - \frac{1}{\left(1 + T / m_0 c^2\right)^2}}
\]

\[M_0 = 1.658326, \; q = 817.2638, \; K = 0.5209\]
# Effect of Oxygen on Cluster Complexity

<table>
<thead>
<tr>
<th>Number of Lesions</th>
<th>Anoxic</th>
<th>Normoxic</th>
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Avg per DSB 6.856 7.994

OER 1.217

**2 MeV α (162.5 keV/μm)**

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<thead>
<tr>
<th>Number of Lesions</th>
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<th>Normoxic</th>
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Avg per DSB 2.473 2.813

OER 2.585

**1 MeV e⁻ (0.186 keV/μm)**
OER for SSB and DSB induction

\[ \text{OER}_{\text{DSB}} \approx (\text{OER}_{\text{SSB}})^2 \approx M(l)^2 \]
Summary

- Predicted trends in the OER for DSB induction consistent with estimates derived from measured data for DSB induction and cell survival (OER ~ 2 to 3)
  - Three new parameters introduced into the modeling process to account for oxygen concentration ($M$ and $K$) and to correct for the effects of radiation quality ($q$)
  - As LET increases, the probability chemical repair occurs per initial DNA radical may decrease (oxygen fixation increases and/or lesions are directly created)
- Predicted OER for SSB induction approximately equal to the square root of the OER for DSB induction (OER ~ 1.4 to 1.7)
  - Most of the measured data suggest a higher OER for SSB induction
- Average cluster complexity increases as the oxygen concentration increases
  - 1 MeV $e^-$ (2.5 lesions/DSB 0% $O_2$ and 2.8 lesions/DSB 21% $O_2$)
  - 2 MeV $\alpha$ (6.8 lesions/DSB 0% $O_2$ and 8.0 lesions/DSB 21% $O_2$)
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