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APPENDIX A

Input File

```
MODEL: DRM=LPL          !Model Specification

CELL: DNA=5.667D+09 NC=46

IRAD: DSB=30 FL=0.1 LET=0.75 OER=3           !Radiation damage to DNA

CLRP: RHT=2 ETA=3.0E-04  GAM=0.25  LAM=0.35

CCKM: TCC=48 TPOT=28 GF=0.4 N0=1000000 KAP=1.0D+38 VOL=1

RBM: KX=6.0E+06 FMAX=1   !Analysis of PFGE data

SOLVER: DBLV=0 ETOL= 1.0E-09 MXSS=999999 HMAX=24

SIMCON: FSDX=1 TSAX=5 TCUT=1 FRDL=0.5 RCUT=1.09E-09

XBRT:TD4F=2 NTD=33 FDT=3 ADR=120 WDO= Y

DFDM:NBD=6 RBI=BI1 TTO= 1

BI1=  1.1 1.4 1.1 1.1 1.4 1.1
```

APPENDIX B

Description of Input file parameters

A. Biophysical parameters

1. MODEL (Model parameters)

a) CKM = QECK

Cell Kinetics Model (CKM) used for the simulation was the Quasi Exponential Cell Kinetics Model(QECK).This model is at present the only model that is implemented for Virtual cell simulations.[45]

b) DRM (Damage Repair Model) = LPL

2. CELL (Cell parameters)

c) DNA = 5.667D+09 base pairs

DNA content of the cell in G0 and G1 phase is estimated at 5.667D+09.[45]

d) NC = 46

The number of chromosomes (NC) in a cell .[45] The cell DNA content and chromosome number do not have an impact on surviving fraction quantities or the probability of neoplastic transformation.

3. CLRP (Cell Repair Parameters)

e) ETA = 2.5E-04 h^{-1}

ETA parameter specifies the pair-wise damage interaction rate per hour. Pair-wise damage interaction is also known as binary mis-repair and always produces a mutation. Sachs et al argued that almost a quarter i.e.

25% of the chromosome aberration formed are lethal for simulations in the study; ETA was set to 3.0E-04 for an α/β ratio of 1 Gy, 2.5E-04 for an α/β ratio of 1.5 Gy , and 1.0E-04 for an α/β ratio of 3 Gy.[30]

f) RHT = 2 hours

Repair Half Time (RHT) parameter specifies half time for DSB repair. Repair half time of 2 hours for double strand breaks was used.[62]

g) GAM = 0.25

GAM parameter determines the fraction of lethal DSB rejoined through the pair-wise interaction process. Sachs et al estimates that about 25% (0.25) of chromosome aberrations formed through pair-wise interaction process are lethal. GAM was thus set to 0.25.[30]

h) LAM = 0.35

LAM parameter sets the expected number of repair attempts per unit time, i.e DSB rejoining rate. Typically repair rates are on the order of 0.15 per hour to 2.77 per hour.[45] In the study LAM was set at 0.35 and kept constant.

4. IRAD (Damage formation parameters)

a) DSB (Double Strand Break)= 40 Gy cell $^{-1}$

DSB parameter specifies the number of double strand breaks expected per unit dose of ionizing radiation .DSB was set to 30 Gy cell $^{-1}$ for the 1 Gy and 1.5 Gy α/β ratios and 40 Gy cell $^{-1}$ for an α/β ratio of 3 Gy.[42]

b) FL (Fatal Lesions)= 0.1.

FL parameter specifies the expected number of fatal lesions produced directly by radiation. FL of 0.1 was adopted for use in the study. [42,45]

c) LET Linear Energy Transfer) = 0.75

X-rays are low LET radiation, hence an LET of 0.75 was used

d) OER (Oxygen Enhancement Ratio) = 3

OER is the enhancement of therapeutic or detrimental effect of ionizing radiation due to the presence of oxygen. Mammalian cells have been observed to be 2-3 times more sensitive to radiation in the presence of oxygen than in the absence of oxygen.[21]

5. CCKM (Cell Biological Parameters)

a) TCC = 48 hours.

Cell birth rate (TCC), specifies the average time for a cell to complete mitosis in hours (h).[45, 63]

b) Tpot = 28 days.

Potential doubling time (Tpot) specifies the average time for the cell population to double in size. For the prostate cells used in the simulation, Tpot = 28 days was used.[45]

c) GF = 0.25.Cell growth fraction (GF) specifies the fraction of the cell population that is actively dividing. When GF = 0 all cells are non-diving (quiescent) and the size of the cell population remains constant. Growth fraction must be set to a value greater than zero to include repopulation effects in Virtual cell calculations.[45]

d) N0 =1.0E+06(1million). The initial number of cells (N0) specifies the expected number of cells at the start of simulation (i.e. t =0).

e) KAP = 1.0E+38. Peak cell density (KAP) specifies the average cell density, measured in cells per cm^3.

f) VOL = 1. Tissue region of interest (VOL) specifies the tissue region of interest, measured in cm^3.

B. Exposure Set up Scenario

a) XBRT= External Beam Radiation Therapy.

b) TD4F = 2. TD4F parameter specifies the dose per fraction.

c) ADR = 120. ADR parameter specifies the absorbed dose rate, in Gy per hour.

d) NTD = 33

NTD sets the total number of treatment days. In conformal radiotherapy treatment of prostate tumours, 33 treatment fractions are given.

e) FDT = 3

FDT parameter sets the total time to deliver each fractional dose. From clinical practice, a time of 3 minutes was observed.

f) WDO = Y.

WDO sets a flag to indicate whether the treatment fractions are delivered over the weekend. WDO =Y means are delivered only during weekdays.[42]

g) NBD = 6.

NBD specifies the number of beams used to deliver each fraction.

h) RBI = BI 1, BI 2 and BI 3 for the three different dose delivery patterns.

RBI specifies the relative beam intensity.

i) TTO = 1.

TTO specifies the total time needed to move irradiator from one beam configuration to another. In practice, it has been observed that it takes approximately one minute to move the irradiator from one treatment field to the other treatment field.

C. Simulation conditions and Solver control

1. SOLVER

a) DBLV = 0.

DBLV specifies the debug level. Available debug level are 0 (minimal debug information), 1 (intermediate debug information) and 2 (maximum debug information).A debug level of 0 is preferred to reduce CPU time required to perform simulation.[45]

b) ETOL = 10^{-09}.

ETOL parameter specifies the error tolerance. Error tolerances in the range of 10^{-7} and 10^{-12} often yields good results.[45]

c) MXSS = 99999.

MXSS specifies the maximum number of sub-steps allowed in ISML routine. Large values are recommended because the simulation may terminate with a fatal error if MXSS is set to a small value.[45]

d) HMAX = 24 hours.

HMAX specifies the maximum step size allowed in the ISML routine. Values in the range of 1 to 24 Hours can be used; value of 24 hours is recommended.[45]

2. SIMCON

a) ACUT = 1.09E-09.

ACUT parameter terminates the simulation when the amount of residual (un-repaired) damage is less than the specified value. This parameter provides a convenient way to end the simulation as soon as all of the initial radiation damage is repaired, mis-repaired or fixed. [45]

b) FRDL = 0.

FRDL parameter specifies the fraction of residual damage at the end of the simulation that is treated as lethal. FRDL of 0 means all residual damage is non-lethal.

c) FSDX = 1.

FSDX specifies the fractional time step size taken during exposure. FSDX = 0.01 is used to observe cell and damage repair kinetics during radiation exposure. FSDX = 1 is used to speed up calculations, no cell or damage repair kinetics are output during radiation exposure. [45]

d) TSAX = 8.

TSAX parameter specifies the time step size after exposure. Small values are used when additional information on cell and damage rejoining kinetics is required. Large values are used to reduce simulation times in long radiobiological simulations. [45]

e) TCUT = 1.

TCUT parameter specifies the time allowed for repair after exposure, and is measured in hours. A TCUT = 1 h will terminate the simulation one hour after the exposure ends regardless of the duration of exposure. [45]

f) TMAX = 1000.

TMAX specifies the maximum duration of simulation, measured in hours. The simulation will terminate if the simulation exceeds the specified hours. TMAX does not control the amount of CPU time used to perform a simulation. [45]

g) NTSP = 2.

NSTP specifies the maximum number of allowed time steps after radiation exposure. Duration of simulation ends when the elapsed time after irradiation is greater than or equal to NSTP * TSAX.[45]

APPENDIX C

Output file

```
VC 2.00A (beta) 22-JAN-2005                    28-AUG-2012 10:41:43 AM

by RD Stewart (trebor@purdue.edu)


PROGRAM FILE INPUT/OUTPUT AND RUN-TIME OPTIONS:

====================================================================================
===

  CMD: vc

  FNI: tria4.inp

  FNO: tria4.out

 RADX: tria4.radx (1 exposures)

-------------------------------------------------------------------------------------



LQ TABLE: Approximate LQ parameters derived from the LPL model (1 kind of DSB)

and 2 kinds of other singly or multiply damage DNA site (other lethal mutations).

====================================================================================
=

                    ********* LETHAL MUTATIONS *********

              Lethal     Other     Double Strand Breaks     All

              damage     lesions     Simple     Complex     damage

    ALPHA (1/Gy): 1.0000E-01 + 0.0000E+00 + 0.0000E+00 + 0.0000E+00 = 1.0000E-01

   BETA (1/Gy^2):     n/a      0.0000E+00 + 9.6429E-02 + 0.0000E+00 = 9.6429E-02

  ALPHA/BETA (Gy): 1.0370E+00 + 0.0000E+00 + 0.0000E+00 + 0.0000E+00 = 1.0370E+00

-----------------------------------------------------------------------------------

Equations relating LQ parameters to kinetic-model parameters can be found in

Guerrero M,Stewart RD, Wang JZ, Li XA. Equivalence of the linear-quadratic and

two-lesion kinetic models. PMB 47(17):3197-209 (2002).
```

DFAR TABLE 1. Formation of DNA damage by ionizing radiation and endogenous processes.

Summary table is based on 1 kind of DSB (LPL or RMR model) and 2 other kinds of singly

or multiply damage DNA site. Oxygen enhancement factor (OEF) = 1.0000.

===

Effective diameter cell nucleus (um) = 5.0000

G0/G1 DNA CONTENT: 5667.000 Mbp/cell = 3.482938E+12 Da/cell

NOTE: 1 bp = 614.6 Da (amu) = 1.0205E-09 pg

	--------- ENDOGENOUS DAMAGE -----------			RESIDUAL
	per (h-Da)	per (h-Mbp)	per (h-cell)	(per cell)
SDS =	0.0000E+00	0.0000E+00	0.0000E+00	0.0000E+00
DSB =	0.0000E+00	0.0000E+00	0.0000E+00	0.0000E+00
	-------------------------------------			----------
Total (endogenous) =	0.0000E+00	0.0000E+00	0.0000E+00	0.0000E+00

	---------- RADIATION DAMAGE -----------			
	per (Gy-Da)	per (Gy-Mbp)	per (Gy-cell)	
SSB =	2.0287E-10	1.2469E-01	7.0659E+02	(32.5660%)
Other =	4.2008E-10	2.5818E-01	1.4631E+03	(67.4340%)
	--------------------------------------			----------
Total (ssb + other) =	6.2296E-10	3.8287E-01	2.1697E+03	(100.0000%)
Prompt DSB =	8.6134E-12	5.2938E-03	3.0000E+01	(100.0000%)
Enzymatic DSB =	0.0000E+00	0.0000E+00	0.0000E+00	(0.0000%)
	--------------------------------------			----------
Total DSB =	8.6134E-12	5.2938E-03	3.0000E+01	(100.0000%)

Unrepairable damage = 2.8711E-14 1.7646E-05 1.0000E-01 (0.0045% total)

Repairable damage = 6.3157E-10 3.8816E-01 2.1997E+03 (99.9955% total)

Total (all damage types) = 6.3160E-10 3.8818E-01 2.1998E+03 (100.0000% total)

DISTRIBUTION OF DNA DAMAGE (LET = 0.750 keV/um, Z1B = 6.120 mGy):

------ PROMPT DSB (FCB=0.00000) ------

	Simple	Complex	Total
DSB per cell =	3.00000E+01	0.00000E+00	3.00000E+01
DSB per track =	1.83596E-01	0.00000E+00	1.83596E-01
Over-dispersion factor (ODF) =	0.00000E+00	2.06545E-01	2.06545E-01

---- ENZYMATIC DSB (FCB=0.00000) -----

	Simple	Complex	Total
DSB per cell =	0.00000E+00	0.00000E+00	0.00000E+00
DSB per track =	0.00000E+00	0.00000E+00	0.00000E+00
Ratio enzymatic to prompt =	0.00000E+00	0.00000E+00	0.00000E+00

NOTE: OTHER = individual base damages and multiply base damaged sites. Residual damage is the number of lesions expected per cell a long time after irradiation of the cells, i.e., (residual damage)~=(formation rate)/lamda.

DFAR TABLE 2. Repair properties (rate and accuracy) for single strand breaks (SSBs) and singly and multiply base damaged sites (nsb=1, nbd=1, nsl=2).

===

PATHWAY-SPECIFIC REPAIR DATA (1 repair cycle):

- REPAIR HALF-TIME (RHT)- -- LAMDA ---

(minute) (hour) (1/hour)

Default (SLRM): 5.0000E+00 8.3333E-02 8.3178E+00

Short patch BER (SPER): 1.5000E+01 2.5000E-01 2.7726E+00

Long patch BER (LPER): 1.5000E+01 2.5000E-01 2.7726E+00

Nucleotide excision repair (NER): 1.5000E+01 2.5000E-01 2.7726E+00

------y--------------------------------

Effective (BER + NER): 5.0000E+00 8.3333E-02 8.3178E+00

SPECTRUM-AVERAGED REPAIR DATA:

----- PROBABILITY PER REPAIR EVENT -----

SSB OTHER ALL

Point mutation lethal (PHI): 0.0000E+00 0.0000E+00 0.0000E+00

Misrepaired and lethal (PHI*PM): 0.0000E+00 0.0000E+00 0.0000E+00

Misrepaired and non-lethal (1-PHI)*PM: 1.0000E-09 1.0000E-09 1.0000E-09

---------- ---------- ----------

Total point mutation (PM): 1.0000E-09 1.0000E-09 1.0000E-09

Enzymatic DSB (FCB=0.0000): SSB OTHER ALL

Simple: 0.0000E+00 0.0000E+00 0.0000E+00

Complex: 0.0000E+00 0.0000E+00 0.0000E+00

---------- ---------- ----------

Total (PB): 0.0000E+00 0.0000E+00 0.0000E+00

Correct repair (A0=1-PM-PB): 1.0000E+00 1.0000E+00 1.0000E+00

Total (A0+PM+PB): 1.0000E+00 1.0000E+00 1.0000E+00

------- NUMBER OF REPAIR CYCLES --------

	SSB	OTHER	ALL
Short patch BER (SPER):	1.0000E+00	1.0000E+00	1.0000E+00
Long patch BER (LPER):	1.0000E+00	1.0000E+00	1.0000E+00
Nucleotide excision repair (NER):	1.0000E+00	1.0000E+00	1.0000E+00
Effective (BER + NER):	1.0000E+00	1.0000E+00	1.0000E+00

------ REPAIR HALF-TIME (minutes) ------

	SSB	OTHER	ALL
Short patch BER (SPER):	1.5000E+01	1.5000E+01	1.5000E+01
Long patch BER (LPER):	1.5000E+01	1.5000E+01	1.5000E+01
Nucleotide excision repair (NER):	1.5000E+01	1.5000E+01	1.5000E+01
Effective (BER + NER):	5.0000E+00	5.0000E+00	5.0000E+00

NOTE: Repair data for the NER pathway includes LPER repair data for all categories

of lesion that cannot be completed removed by NER.

DFAR TABLE 3. Double strand break (DSB) repair properties (LPL = 1 kind of DSB, 1 lethal).

==

1ST ORDER DSB REJOINING KINETICS:

-- PROBABILITY OF CORRECT REPAIR (A0) --

	SIMPLE	COMPLEX	AVG.
Correct repair (NHEJ):	0.0000E+00	0.0000E+00	0.0000E+00
Correct repair (HREC):	1.0000E+00	1.0000E+00	1.0000E+00
	----------	----------	----------
Prompt (NHEJ+HREC):	0.0000E+00	0.0000E+00	0.0000E+00
Enzymatic:	0.0000E+00	0.0000E+00	

------------- PROMPT DSB ---------------

Incorrect repair (1-A0):	1.0000E+00	1.0000E+00	1.0000E+00
Probability lethal (PHI):	0.0000E+00	0.0000E+00	0.0000E+00
Probability non-lethal (1-PHI):	1.0000E+00	1.0000E+00	1.0000E+00
(1-A0)*PHI:	0.0000E+00	0.0000E+00	0.0000E+00
(1-A0)*(1-PHI):	1.0000E+00	1.0000E+00	1.0000E+00

------ REPAIR HALF-TIME (hour) ---------

	SIMPLE	COMPLEX	ALL
Non-homologous end-joining (NHEJ):	1.9804E+00	1.9804E+00	1.9804E+00
Homologous recombination (HREC):	0.0000E+00	0.0000E+00	0.0000E+00
	--		
Effective (NHEJ + HREC):	1.9804E+00	1.9804E+00	1.9804E+00
Enzymatic:	1.9804E+00	1.9804E+00	

------------ LAMDA (1/hour) ------------

	SIMPLE	COMPLEX	ALL
Default (CLRP):	3.5000E-01	3.5000E-01	3.5000E-01

Non-homologous end-joining (NHEJ): 3.5000E-01 3.5000E-01 3.5000E-01

Homologous recombination (HREC): 0.0000E+00 0.0000E+00 0.0000E+00

Effective (NHEJ + HREC): 3.5000E-01 3.5000E-01 3.5000E-01

Enzymatic: 3.5000E-01 3.5000E-01

FIRST- AND SECOND-ORDER DSB REJOINING KINETICS:

------ PROMPT DSB ------ ---- ENZYMATIC DSB -----

Simple Complex Simple Complex

LAMDA/ETA = 1.16667E+03 1.16667E+03 1.16667E+03 1.16667E+03

LAMDA/[ETA*(1+ODF)] = 1.16667E+03 9.66948E+02 1.16667E+03 1.16667E+03

ETA/LAMDA = 8.57143E-04 8.57143E-04 8.57143E-04 8.57143E-04

ODF*ETA/LAMDA = 0.00000E+00 1.77039E-04 0.00000E+00 0.00000E+00

DSB-DSB interaction rate (ETA or BMR): 3.00000E-04

Probability lethal (GAM): 2.50000E-01

Probability non-lethal (1-GAM): 7.50000E-01 (1/h)

NOTE: The importance of over-dispersion effects increases as ODF*ETA/LAMDA increases.

QECK TABLE 1: Cell and tissue kinetic parameters.

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Duration of cell cycle (TCC): 48.00000 h

Potential doubling time (Tpot): 672.00000 h (= 28.000 days)

Cell birth rate (AX): 3.4657E-01 cell/day (= LOG(2)/TCC)

Cell death rate (BX): 3.2182E-01 cell/day [=AX-LOG(2)/TPOT]

Net cell birth rate (AX-BX): 2.4755E-02 cell/day

Initial Number of Cells:

non-dividing: 6.00000E+05 (60.000% = 1-GF)

dividing: 4.00000E+05 (40.000% = GF)

total: 1.00000E+06 (100.000% total)

Life Support Capacity of System:

Initial system capacity utilization: 0.000000% (=F0)

Peak cell density (cells/cm^3): 1.00000E+38 (=KAP)

Tissue volume (cm^3): 1.00000E+00 (=VOL)

Maximum number of cells (cells): 1.00000E+38 (=KAP*VOL)
