(Working Paper) Illustrated Numerical Reviews: DNA Repair

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Mathematical Learning Space Research Portfolio Summer Semester 2021

Working Papers in this series of Illustrated Numerical Reviews are designed for scientific collaboration, communication and classroom examples with a revision update before modified for publication.

Abstract

DNA damage is considered to be related to cancer. In the human cell with endogenous cellular processes , over fifty thousand new and natural DNA damages are generated per day. In Nucleotide excision repair, the Thymine dimer and photolyase relationship with the frequency of light are part of the repair mechanism for DNA. In order to control the DNA damage and its repair mechanism, a protein interaction network for DNA damage based on UV wavelengths is presented with the following four networks of genetic material such as (1) UV - ATR - DNA Damage - RPA and ATRp and (2) p21 - DDB2 -RBp - CYCe - RB - EF21 as two networks within the cell cycle for handing DNA damage. The third network (3) P53 Mdm2n Mdm2cp - Aktp - p53p - Pten - Mdm2c - Akt - PIP2 - PIP3 and (4) BAX - CytoC - Apops - CASP -Procasp3 -Apaf-1 -Procasp9 - casp3 -APTX -PARP1 -PARP3 - Apoptosis. Each of these networks are examined with a frequency of ultraviolet light as an external stimulus for the endogenous network and observations made.

Introduction

Damage to DNA can be caused by exposure to (a) radiation, (b) chemicals, and (c) environmental sources. DNA damage is an abnormal chemical structure in DNA and causes changes in the structure of the genetic material and inhibits replication. [1] Figure 1 has the steps in Nucleotide Excision Repair.[2]

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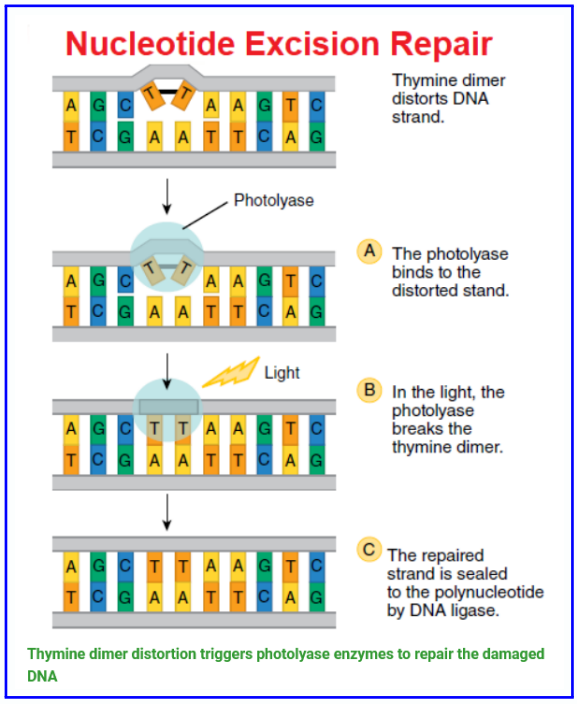


Figure 1: General Steps in Nucleotide Excision Repair

energy from light is absorbed by proteins called reaction where light-dependent reactions, some energy removes electrons from water and produces oxygen gas. The hydrogen released by water separation creates 2 compounds for short-term stores of energy that drive other reaction: (a) nicotinamide adenine dinucleotide phosphate (NADPH) and (b) adenosine triphosphate (ATP), the "energy currency" of cells. [5]

Figure 1A has the steps in Nucleotide Excision Repair.[401]

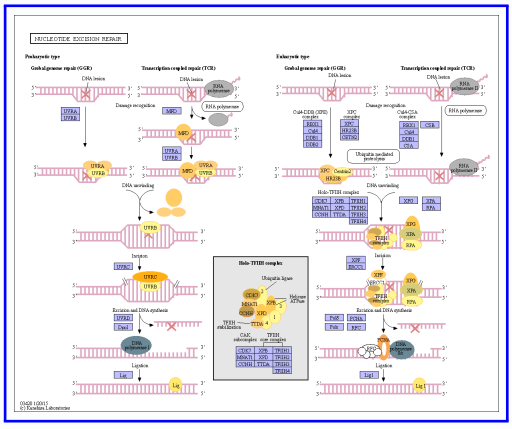


Figure 2: Detailed Genetic Material Steps in Nucleotide Excision Repair

In the chemical reactions, Activation of cyclin-dependent kinases requires an enzyme relationship with a regulatory subunit(i.e. cyclin) with sequential activation and inactivation of cyclin-dependent kinases by periodic synthesis and destruction of cyclins in cell-cycle regulation. The reaction is ATP + a protein = ADP + a phosphoprotein or by RNA polymerase (EC 2.7.7.6) the enzyme does not phosphorylate casein, phosvitin or histone with ATP + [DNA-directed RNA polymerase] = ADP + phospho-[DNA-directed RNA polymerase]. Here 2 H2O + 2 NADP+ + 3 ADP + 3 Pi + light → 2 NADPH + 2 H+ + 3 ATP + O2 is the light-dependent reactions under the conditions of non-cyclic electron flow in green plants. [5]

For ATP, the Chemical reactions (1219), KEGG ENZYME (517) , KEGG REACTION (702) and involved with KEGG GENES (1033802) [401] Figure 1B has the ATP + a protein SMILE notation. [470]

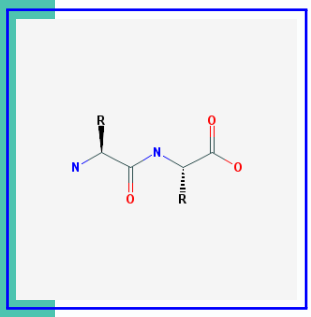


Figure 3: A protein C2H4NO2R(C2H2NOR)n in reaction is ATP + a protein = ADP + a phosphoprotein

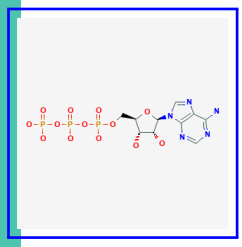


Figure 4: ATP Adenosine 5'-triphosphate C10H16N5O13P3

Most DNA damages can undergo DNA repair, however not 100 percent efficient. Un-repaired DNA damages accumulate in non-replicating cells and in replicating cells, errors generated upon replication with past damages in the template strand of DNA or during repair of DNA damages. These errors can give rise to mutations or epigenetic alterations where the change gene function or regulation of gene expression that can lead to cancer. [1] Figure 2 has an example of the relationship between Ultraviolet Light and DNA.[3]

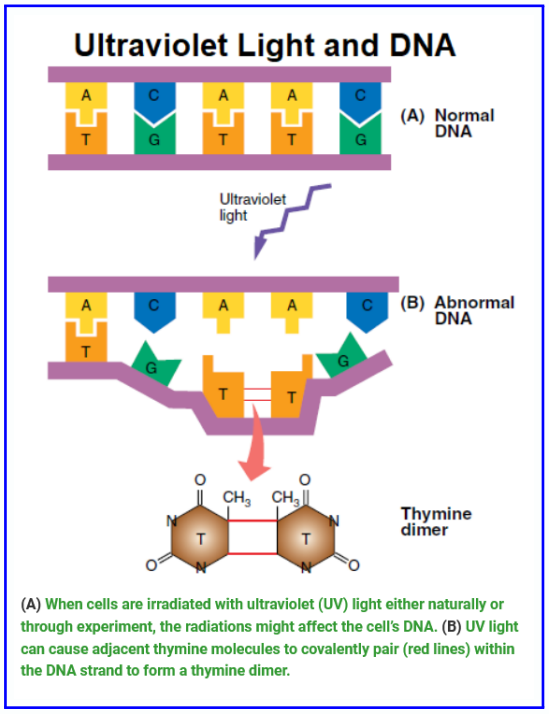
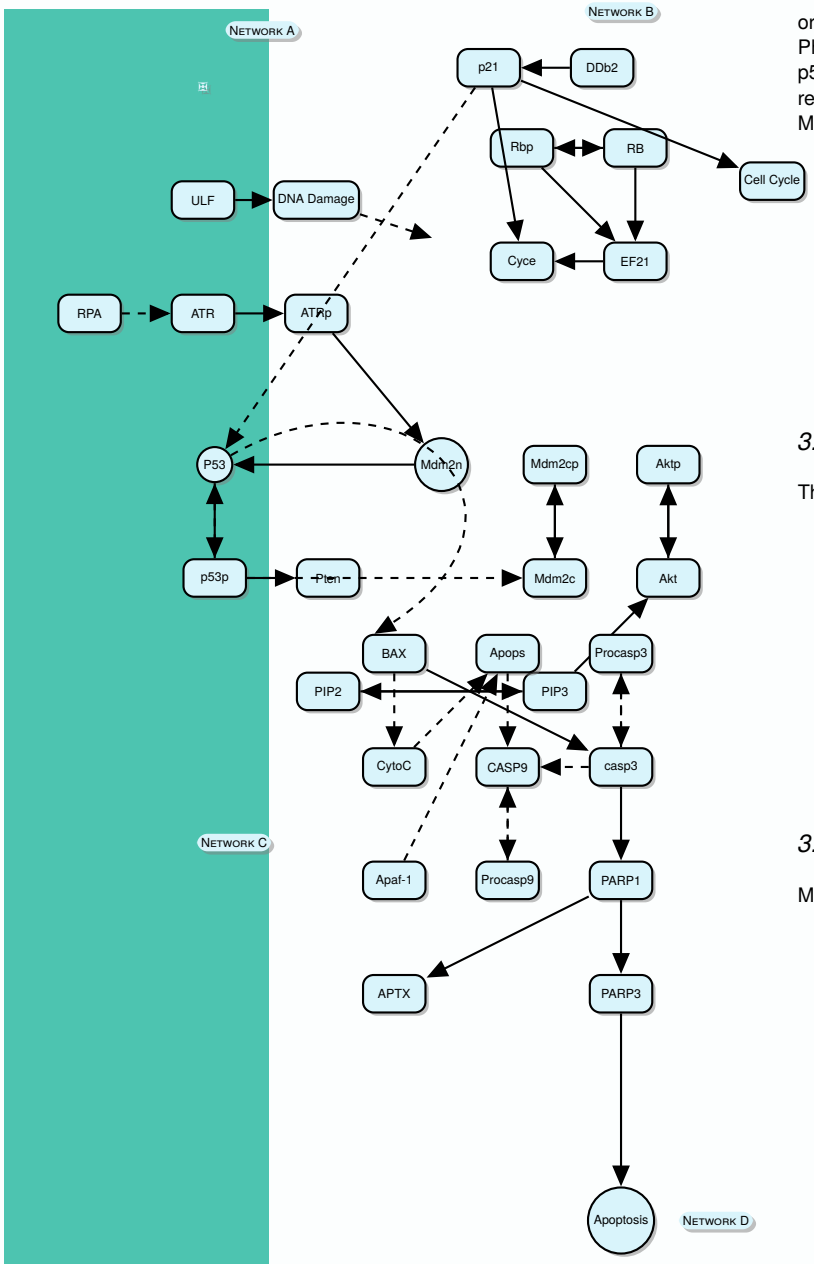


Figure 5: Ultraviolet Light and DNA

Equation System

Consider the following set of proteins with a external change agent ULF and ATRp, p53, p53p ,Mdm2c ,Mdm2cp ,Mdm2n, Aktp, PIP3, PTEN, DDB2, p21tot, p21CE, CycEtot, E2F1, Rbp, Bax, CytoC, Apaf1, Apops, Casp9, and Casp3. [1]

Figure 1 has the interaction model for the list of proteins.



Consider the treatment model with the krepair parameter, a stochastic noise and a transformation H(*) of the external agent for system interaction.[1A] [10][11][12][13][14][15][16][17] [18] The three ranges of UV light is (a) UVA (315-400 nm) (b) UVB (280-315 nm) and (c) UVC (100-280 nm) Here the change in UV light is given by the following equations with the parameter k.noise.1=k.noise.*. The value noise.test is set to zero. The photon energy (eV, aJ) for Ultraviolet A is UV-A 3.10–3.94, 0.497–0.631, Ultraviolet B UV-B 3.94–4.43, 0.631–0.710 and Ultraviolet C UV-C 4.43–12.4, 0.710–1.987. The lowest energy light that can break the bond in ozone has a wavelength of 330 nm.

$$\begin{aligned} \mathrm{d.1.ULF.dt.1} &= -\mathrm{krepair} * \mathrm{H(ULF)} \\ &\quad + \mathrm{k.noise.1} * \mathrm{noise.test}[1] whiteleft[1] \end{aligned} \quad (1)$$

where $\mathrm{H}(*) = \mathrm{if}(\mathrm{x} >= 0)1\mathrm{else}0$.

3.1. ATR

Serine/threonine protein kinase activates checkpoint signaling upon genotoxic stresses such as (a) ionizing radiation (IR), (b) ultraviolet light (UV), or (c) DNA replication stalling and serves as a DNA damage sensor. Phosphorylates BRCA1, CHEK1, MCM2, RAD17, RPA2, SMC1 and p53/TP53, all together inhibit DNA replication, mitosis and promote DNA repair, recombination and apoptosis. [500]. The equations for the ATR Model are given by: .[1A]

$$\begin{aligned} \mathrm{d.1.ATRp.dt.1} &= (\alpha_a \mathrm{catr0} \\ &\quad + \alpha_a \mathrm{catr} * (\mathrm{ULF}/(\mathrm{ULF} + \gamma_d)) * \mathrm{ATRp}) \\ &\quad * (\mathrm{ATR}/(\mathrm{ATR} + \gamma_a \mathrm{catr})) \\ &\quad - \alpha_d \mathrm{eatr} * (\mathrm{ATRp}/(\mathrm{ATRp} + \gamma_d \mathrm{eatr})) \\ &\quad + \mathrm{k.noise.2} * \mathrm{noise.test} \\ \mathrm{ATR} &= \mathrm{ATRtot} - \mathrm{ATRp} \\ \alpha_a \mathrm{cp53} &= \alpha_a \mathrm{cp530} * (\mathrm{ATRp}/(\mathrm{ATRp} + \gamma_a \mathrm{tr})) \end{aligned} \quad (2)$$

3.2. p53

The p53 model equations are:

$$\begin{aligned} \mathrm{d.1.p53.dt.1} &= \alpha_s \mathrm{p53} - \alpha_d \mathrm{p530} * \mathrm{p53} \\ &\quad - \alpha_d \mathrm{p53} * \mathrm{Mdm2n} * (\mathrm{p53}/(\mathrm{p53} + \gamma_d \mathrm{p53})) \\ &\quad - \alpha_a \mathrm{cp53} * \mathrm{p53} + \alpha_d \mathrm{ep53} * \mathrm{p53p} \\ &\quad + \mathrm{k.noise.3} * \mathrm{noise.test} \\ \mathrm{d.1.p53p.dt.1} &= \alpha_a \mathrm{cp53} * \mathrm{p53} - \alpha_d \mathrm{ep53} * \mathrm{p53p} \\ &\quad - \alpha_d \mathrm{p53p} \\ &\quad * \mathrm{Mdm2n} * (\mathrm{p53p}/(\mathrm{p53p} + \gamma_d \mathrm{p53p})) \\ &\quad + \mathrm{k.noise.4} * \mathrm{noise.test} \end{aligned} \quad (3)$$

3.3. MDM2

MDM2 equations are given as: .[1A]

$$\begin{aligned} \mathrm{d.1.Mdm2c.dt.1} &= \alpha_s \mathrm{mdm20} \\ &\quad + \alpha_s \mathrm{mdm2} \\ &\quad * (\mathrm{p53p}^{\mathrm{alpha.1}}/(\mathrm{p53p}^{\mathrm{alpha.1}} \\ &\quad + \gamma_s \mathrm{mdm2}^{\mathrm{alpha.1}})) \\ &\quad - \alpha_d \mathrm{mdm2} * \mathrm{Mdm2c} \\ &\quad + \alpha_d \mathrm{pmdm2} \\ &\quad * (\mathrm{Mdm2cp}/(\mathrm{Mdm2cp} + \gamma_d \mathrm{pmdm2})) \\ &\quad - \alpha_p \mathrm{mdm2} * (\mathrm{Aktp}) \\ &\quad * (\mathrm{Mdm2c}/(\mathrm{Mdm2c} + \gamma_p \mathrm{mdm2})) \\ &\quad + \mathrm{k.noise.5} * \mathrm{knoise.test} \\ \mathrm{d.1.Mdm2cp.dt.1} &= \alpha_p \mathrm{mdm2} * \mathrm{Aktp} \\ &\quad * (\mathrm{Mdm2c}/(\mathrm{Mdm2c} + \gamma_p \mathrm{mdm2})) \\ &\quad - \alpha_d \mathrm{pmdm2} \\ &\quad * (\mathrm{Mdm2cp}/(\mathrm{Mdm2cp} + \gamma_d \mathrm{pmdm2})) \\ &\quad - \mathrm{kinmdm2c} * \mathrm{Mdm2cp} \\ &\quad + \mathrm{koutmdm2n} * \mathrm{Mdm2n} \\ &\quad - \alpha_d \mathrm{mdm2} * \mathrm{Mdm2cp} \\ &\quad + \mathrm{k.noise.6} * \mathrm{noise.test} \\ \mathrm{d.1.Mdm2n.dt.1} &= \mathrm{kinmdm2c} * \mathrm{Mdm2cp} \\ &\quad - \mathrm{koutmdm2n} * \mathrm{Mdm2n} \\ &\quad - (\alpha_d \mathrm{mdm2} + \alpha_d \mathrm{mdm2n}) * \mathrm{Mdm2n} \\ &\quad + \mathrm{k.noise.7} * \mathrm{noise.test} \\ \alpha_d \mathrm{mdm2n} &= \alpha_d \mathrm{mdm2n0} * (\mathrm{ATRp}/(\mathrm{ATRp} + \gamma_a \mathrm{tr})) \end{aligned} \quad (4)$$

3.4. AKT

The AKT model equations are: .[1A]

$$\begin{aligned} \mathrm{d.1.Aktp.dt.1} &= \alpha_p akt * PIP3 * (Akt/(Akt + \gamma_p akt)) \\ &\quad - \alpha_d pakt * (Aktp/(Aktp + \gamma_d pakt)) \\ &\quad + k.noise.8 * noise.test \\ Akt &= Akttot - Aktp \end{aligned} \tag{5}$$

3.5. PIP3

The PIP3 model equations are:

$$\begin{aligned} \mathrm{d.1.PIP3.dt.1} &= \alpha_p 2 * (PIP2/(PIP2 + \gamma_p 2)) \\ &\quad - \alpha_p 3 * PTEN * (PIP3/(PIP3 + \gamma_p 3)) \\ &\quad + k.noise.9 * noise.test \\ PIP2 &= PIPtot - PIP3 \end{aligned} \tag{6}$$

3.6. PTEN and DDB2

The equations for PTEN and DDB2 models are: .[1A]

$$\begin{aligned} \mathrm{d.1.PTEN.dt.1} &= \alpha_s PTEN0 \\ &\quad + \alpha_s PTEN \\ &\quad * (p53p^{alpha.1}/(p53p^{alpha.1} \\ &\quad + \gamma_s PTEN^{alpha.1})) - \alpha_d PTEN * PTEN \\ &\quad + k.noise.10 * noise.test \\ \mathrm{d.1.DDB2.dt.1} &= \alpha_s DDB20 \\ &\quad + \alpha_s DDB2 * (p53p^{alpha.1}/(p53p^{alpha.1} \\ &\quad + \gamma_s DDB2^{alpha.1})) - \alpha_d DDB2 * DDB2 \\ &\quad + k.noise.11 * noise.test \end{aligned} \tag{7}$$

3.7. p21

The p21 model equations are: .[1A]

$$\begin{aligned} \mathrm{d.1.p21tot.dt.1} &= \alpha_s p210 \\ &\quad + \alpha_s p21 * (p53p^{alpha.1}/(p53p^{alpha.1} \\ &\quad + \gamma_s p21^{alpha.1})) \\ &\quad - \alpha_d p210 * p21tot \\ &\quad - \alpha_d p21 * DDB2 * p21tot \\ &\quad + k.noise.12 * noise.test \\ \mathrm{d.1.p21CE.dt.1} &= \alpha_a sp21ce * p21 * CycE \\ &\quad - \alpha_d sp21ce * p21CE \\ &\quad + k.noise.13 * noise.test \\ p21 &= p21tot - p21CE \end{aligned} \tag{8}$$

3.8. Cyc

The Cyc model equations are: .[1A]

$$\begin{aligned} \mathrm{d.1.CycEtot.dt.1} &= \alpha_s cyce0 \\ &\quad + \alpha_s cyce * (E2F1^{alpha.2}/(E2F1^{alpha.2} \\ &\quad + \gamma_s cyce^{alpha.2})) - \alpha_d cyce * CycEtot \\ &\quad + k.noise.14 * noise.test \\ CycE &= CycEtot - p21CE \\ \mathrm{d.1.E2F1.dt.1} &= -\alpha_a sre * Rb * E2F1 \\ &\quad + \alpha_d sre * RE \\ &\quad + k.noise.15 * noise.test \end{aligned} \tag{9}$$

3.9. RE-rbp-rb

The RBPt model is given as:

$$\begin{aligned} RE &= E2F1tot - E2F1 \\ \mathrm{d.1.Rbp.dt.1} &= \alpha_p rb * CycE * (Rb/(Rb + \gamma_p rb)) \\ &\quad - \alpha_d prb * (Rbp/(Rbp + \gamma_d prb)) \\ &\quad + k.noise.16 * noise.test \\ Rb &= Rbtot - Rbp - RE \end{aligned} \tag{10}$$

3.10. BAX

The BAX equations are: .[1A]

$$\begin{aligned} \mathrm{d.1.Bax.dt.1} &= \alpha_s bax0 \\ &\quad + \alpha_s bax * (p53p^{alpha.1}/(p53p^{alpha.1} \\ &\quad + \gamma_s bax^{alpha.1})) - \alpha_d bax * Bax \\ &\quad + k.noise.17 * noise.test \end{aligned} \tag{11}$$

3.11. Cytoc-Apaf1-Apops

The equations for Cytoc, Apaf1 and Apops are: .[1A]

$$\begin{aligned} \mathrm{d.1.CytoC.dt.1} &= \alpha_a ccytoc0 \\ &\quad + \alpha_a ccytoc * (Bax^{alpha.1}/(Bax^{alpha.1} \\ &\quad + jbax^{alpha.1})) * (CytoCtot - CytoC) \\ &\quad - \alpha_d ecytoc * CytoC + k.noise.18 * noise.test \\ \mathrm{d.1.Apaf1.dt.1} &= \alpha_s apaf10 \\ &\quad + \alpha_s apaf1 * (E2F1^{alpha.2}/(E2F1^{alpha.2} \\ &\quad + \gamma_s apaf1^{alpha.2})) - \alpha_d apaf1 * Apaf1 \\ &\quad + k.noise.19 * noise.test \\ \mathrm{d.1.Apops.dt.1} &= \alpha_a capops \\ &\quad * ((CytoC - (alpha.3) * Apops) \\ &\quad * (Apaf1 - (alpha.3) * Apops))^{alpha.3} \\ &\quad - \alpha_d eapops * Apops \\ &\quad + k.noise.20 * noise.test \end{aligned} \tag{12}$$

3.12. CASP

The equations for the CASP model are: .[1A]

$$\begin{aligned} \mathrm{d.1.Casp9.dt.1} &= (\alpha_a ccasp90 \\ &\quad + \alpha_a ccasp9 \\ &\quad * (Casp3^{alpha.1}/(Casp3^{alpha.1} \\ &\quad + jcasp3^{alpha.1}))) * (Casp9tot - Casp9) \\ &\quad - \alpha_d ecasp9 * Casp9 \\ &\quad + k.noise.21 * noise.test \\ \mathrm{d.1.Casp3.dt.1} &= (\alpha_a ccasp30 \\ &\quad + \alpha_a ccasp3 \\ &\quad * (Casp9^{alpha.1}/(Casp9^{alpha.1} \\ &\quad + jcasp9^{alpha.1})) * (Casp3tot - Casp3) \\ &\quad - \alpha_d ecasp3 * Casp3 \\ &\quad + k.noise.22 * noise.test \end{aligned} \tag{13}$$

Table 1 shows the list of Gene/Protein/Enzymes Description and References.

Table 1: Gene/Protein/Enzymes Description and References

Gene/Protein	Description	Reference
ULF	UVA(315–380 nm), UVB (280–315 nm), and UVC (190–280 nm)	[4]
ATRp	phosphorylated ATR serine/threonine kinase	[601]
p53	tumor protein p53	[601]
p53p	phosphorylated tumor protein p53 binding protein 1	[601]
Mdm2c	MDM2 proto-oncogene, E3 ubiquitin protein ligase	[601]
Mdm2cp	phosphorylated MDM2 proto-oncogene, E3 ubiquitin protein ligase	[601]
Mdm2n	MDM2 proto-oncogene, E3 ubiquitin protein ligase	[601]
Aktp	phosphorylated AKT serine/threonine kinase 1	[601]
PTEN	phosphatase and tensin homolog	[601]
DDB2	damage-specific DNA binding protein 2, 48kDa	[601]
p21tot	total levels of p21	[601]
p21CE	p21 incomplex with CDK2-cyclin E)	[601]
p21	free p21	[601]
CycEtot	total levels of cyclin E	[601]
E2F1	E2F transcription factor 1	[601]
E2F1tot	total levels of E2Ftot	[601]
Rb	(free, non-phosphorylated Rb	[601]
Rbp	phosphorylated (free,hyperphosphorylated Rb	[601]
Rbtot	total levels of Rb	[601]
RE	Rb in complex with E2F1	[601]
Bax	BCL2-associated X protein	[601]
CytoC	cytochrome c-1	[601]
Apaf1	apoptotic peptidase activating factor 1	[601]
Apops	apoptogenic 1, mitochondrial	[601]
Casp9	caspase 9, apoptosis-related cysteine peptidase	[601]
Casp3	caspase 3, apoptosis-related cysteine peptidase	[601]

Parameter Specifications

Table 2 has the parameter values for the equation system. [1A]

krepair	0.01								
k.noise.1	0								
$\alpha_a catr0$	0.001	$\alpha_a catr$	2.0	$\gamma_a catr$	1.0	$\alpha_d eatr$	1.5	$\gamma_d eatr$	2.5
γ_d	2.0	$\gamma_a tr$	1.0	ATRtot	5.0	$\alpha_s p53$	0.04	$\alpha_d p530$	0.03
$\alpha_d p53$	0.2	$\gamma_d p53$	0.1	$\alpha_d p53p$	0.01	$\gamma_d p53p$	0.1	$\alpha_a cp530$	0.2
$\alpha_d ep53$	0.1	$\alpha_d mdm2$	0.009	$\alpha_s mdm20$	0.002	$\alpha_s mdm2$	0.01	$\gamma_s mdm2$	1.0
$\alpha_p mdm2$	4.0	$\gamma_p mdm2$	0.3	$\alpha_d pmdm2$	0.3	$\gamma_d pmdm2$	0.1	kinmdm2c	0.06
koutmdm2n	0.09	$\alpha_d mdm2n0$	0.05	$\alpha_p akt$	0.25	$\alpha_d pakt$	0.1	$\gamma_p akt$	0.1
$\gamma_d pakt$	0.2	Akttot	1.0	PIPtot	1.0	$\alpha_p 2$	0.1	$\alpha_p 3$	0.45
$\gamma_p 2$	0.2	$\gamma_p 3$	0.4	$\alpha_s PTEN0$	0.001	$\alpha_s PTEN$	0.05	$\gamma_s PTEN$	2.0
$\alpha_d PTEN$	0.01	$\alpha_s DDB20$	0.01	$\alpha_s DDB2$	0.6	$\gamma_s DDB2$	2.0	$\alpha_d DDB2$	0.15
$\alpha_s p210$	0.01	$\alpha_s p21$	0.4	$\gamma_s p21$	0.7	$\alpha_d p210$	0.1	$\alpha_d p21$	0.2
$\alpha_s cyce0$	0.0005	$\alpha_s cyce$	0.0275	$\gamma_s cyce$	0.2	$\alpha_d cyce$	0.005	$\alpha_a sre$	0.5
$\alpha_d sre$	0.05	$\alpha_p rb$	0.05	$\gamma_p rb$	0.1	$\alpha_d prb$	0.025	$\gamma_d prb$	0.1
$\alpha_a sp21ce$	0.5	$\alpha_d sp21ce$	0.05	Rbtot	2.0	E2F1tot	1.0	$\alpha_s bax0$	0.01
$\alpha_s bax$	0.8	$\gamma_s bax$	2.0	$\alpha_d bax$	0.1	jbax	3.0	$\alpha_a cytoc0$	0.01
$\alpha_a cytoc$	1.0	$\alpha_d ecytoc$	0.1	$\alpha_s apaf10$	0.001	$\alpha_s apaf1$	0.6	$\gamma_s apaf1$	0.6
$\alpha_d apaf1$	0.1	$\alpha_a capops$	5.0	$\alpha_d eapops$	0.5	$\alpha_a ccasp900$	.001	$\alpha_a ccasp9$	3.0
jcasp3	0.5	$\alpha_d ecasp9$	0.05	$\alpha_a ccasp300$	.001	$\alpha_a ccasp3$	0.1	jcasp9	0.5
$\alpha_d ecasp3$	0.07	CytoCtot	5.0	Casp9tot	3.0	Casp3tot	3.0		

Results

Computation for the system with parameters was performed with the following R API [1000], [1001], [1002], [1003], [1004], [1005], [1006], [1007], [1008], [2000], [2001], [2002], [2003], [2004],

For the initial conditions of ULF=5, ATRp=0.1, p53=0.1, p53p=0.1, Mdm2c=0.1, Mdm2cp=0.1, Mdm2n=0.1, Aktp=0.1, PIP3=0.1, PTEN=0.1, DDB2=0.1, p21tot=0.1, p21CE=0.1, CycEtot=0.1, E2F1=0.1, Rbp=0.1, Bax=0.1, CytoC=0.1, Apaf1=0.1, Apops=0.1, Casp9=0.1, and Casp3=0.1. The hill response coefficients are given by alpha.1=4; alpha.2=2; alpha.3=7. Figure 1 has the correlation structure for the first group of proteins from Figure 1.

A protein interaction network for DNA damage based on UV wavelengths with the following list of genetic material such as (1)ULF - ATR - DNA Damage - RPA and ATRp and (2) p21 - DDB2 -RBp - CYCe - RB - EF21 as two networks within the cell cycle for handing DNA damage. The third network (3) P53 Mdm2n Mdm2cp - Aktp - p53p - Pten - Mdm2c - Akt - PIP2 - PIP3 and (4) BAX - CytoC - Apops - CASP -Procasp3 -Apaf-1 -Procasp9 -casp3 -APTX -PARP1 -PARP3 - Apoptosis. Table 2 has the summary moments for the solution of equation system with the parameters of Table 3 and initial conditions.

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	N	sd
LD	4.80	4.85	4.90	4.90	4.95	5.00	52.00	0.06
ATR	-0.56	3.89	7.34	8.65	12.94	21.67	52.00	6.19
ATRp	0.08	0.57	1.60	4.47	5.68	25.13	52.00	6.14
p21	0.00	0.13	0.51	0.68	1.13	2.05	52.00	0.63
p21CE	0.00	0.00	0.00	0.01	0.01	0.01	52.00	0.00
p21tot	0.00	0.05	0.10	0.11	0.16	0.23	52.00	0.07
DDB2	0.00	0.04	0.05	0.05	0.06	0.06	52.00	0.02
Rb	0.00	5.12	10.22	10.22	15.33	20.39	52.00	6.07
Rbp	-0.00	-0.00	0.00	0.00	0.00	0.00	52.00	0.00
CycE	-0.00	0.00	0.00	0.00	0.01	0.01	52.00	0.00
CycEtot	0.00	0.00	0.01	0.00	0.01	0.01	52.00	0.00
E2F1	0.00	0.00	0.00	0.00	0.00	0.01	52.00	0.00
p53	0.00	0.15	0.25	0.22	0.30	0.36	52.00	0.10
p53p	0.00	0.04	0.11	0.12	0.18	0.26	52.00	0.08
kacp53	0.00	0.66	1.26	1.25	1.82	2.40	52.00	0.68
Mdm2n	0.00	0.00	0.01	0.05	0.05	0.30	52.00	0.08
Mdm2c	0.00	0.01	0.02	0.02	0.03	0.04	52.00	0.01
Mdm2cp	0.00	0.01	0.08	0.74	0.89	4.75	52.00	1.24
kdmdm2n	0.00	0.17	0.32	0.31	0.45	0.60	52.00	0.17
Akt	-0.10	3.09	5.83	5.20	7.60	8.25	52.00	2.64
Aktp	-0.90	0.14	0.63	0.94	1.61	3.10	52.00	0.97
PIP2	0.00	2.94	4.47	4.01	5.40	5.72	52.00	1.59
PIP3	0.00	0.44	0.92	0.91	1.39	1.84	52.00	0.56
PTEN	0.00	0.00	0.01	0.01	0.01	0.02	52.00	0.01
Bax	0.00	0.04	0.06	0.06	0.08	0.09	52.00	0.03
CytoC	0.00	0.04	0.06	0.06	0.08	0.09	52.00	0.03
Apaf1	0.00	0.00	0.01	0.01	0.01	0.01	52.00	0.00
Apops	0.00	0.00	0.00	0.00	0.00	0.00	52.00	0.00
Casp9	0.00	0.01	0.02	0.02	0.03	0.04	52.00	0.01
Casp3	0.00	0.01	0.02	0.02	0.03	0.03	52.00	0.01

Figure 3 has the results for (a)ULF - ATR - DNA Damage - RPA and ATRp and Figure 2 for the second network (b) p21 - DDB2 -RBp - CYCe - RB - EF21 as two networks within the cell cycle for handing DNA damage. The third network in Figure 3 (c) P53 Mdm2n Mdm2cp - Aktp - p53p - Pten - Mdm2c - Akt - PIP2 - PIP3 and (d) BAX - CytoC - Apops - CASP -Procasp3 -Apaf-1 -Procasp9 -casp3 -APTX -PARP1 -PARP3 - Apoptosis is shown in Figure 4.

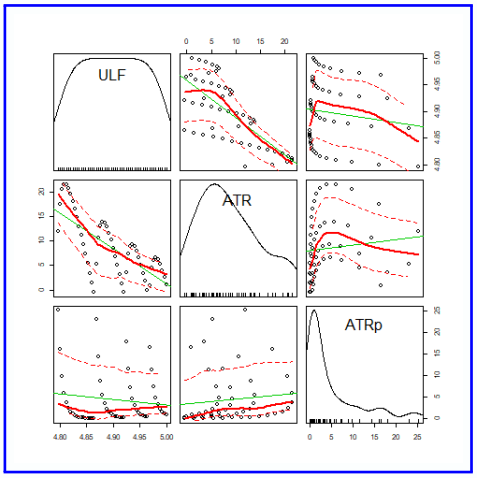


Figure 6: (a)UV - ATR - DNA Damage - RPA and ATRp.

Table 4 has the increase decrease duration and time for network A.For the first order or 1 hour difference in the protein , the Increase.A is the ratio of the number of positive values divided by the total hours. Decrease.B is 1-Increase.A. The duration is the total number of consective positive values and time is the hour of change

	Increase.A	Decrease.B	Duration	Time
UV	0	1	0.00	0.00
ATR	0.706	0.294	14.00	49.00
ATRp	0.902	0.098	12.00	34.00

Table 2: For the first order or 1 hour difference in the protein , the Increase.A is the ratio of the number of positive values divided by the total hours. Decrease.B is 1-Increase.A. The duration is the total number of consective positive values and time is the hour of change.

Figure 4 has the correlation structure for the first group of proteins from Figure 1. (b) p21 - DDB2 -RBp - CYCe - RB - EF21 as two networks within the cell cycle for handing DNA damage.

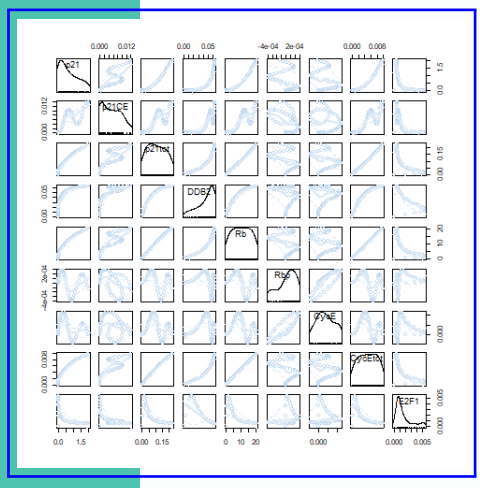


Figure 7: (b) p21 - DDB2 -RBp - CYCe - RB - EF21 as two networks within the cell cycle for handing DNA damage.

Table 5 has the summary moments for the solution of equation system with the parameters of Table 1 and initial conditions.

	V1	V2	V3	average	variance	skewness	kurtosis	kurtosis.variance.1	variance.2	theta.2
1	p21	0	0	0.68	0.38	0.69	2.2	2	2.8	0.31
2	p21CE	0	0	0.005	1.9e-05	0.37	1.9	0.0084	1e-04	0.19
3	DDb2	0	0	0.11	0.0042	0.13	1.9	0.036	0.018	0.068
4	Rb	0	0	0.046	0.00031	-1	2.9	-0.1	0.0042	-0.35
5	Rbp	0	0	10	36	-0.002	1.8	-0.06	139	-0.0011
6	Cyclin E	0.0	0.0	2.1e-05	4e-08	-0.68	2.4	-0.00063	3e-07	-0.28
7	EF21	-0.00	-0.00	0.0038	2.2e-05	0.11	2	0.0013	1e-04	0.055

Table 6 has the increase decrease duration and time for network B.

	Increase.A	Decrease.B	Duration	Time
p21	1	0	0.00	0.00
p21CE	0.784	0.216	30.00	32.00
DDb2	1	0	0.00	0.00
Rb	1	0	0.00	0.00
Rbp	1	0	0.00	0.00
Cyclin E	0.549	0.451	17.00	19.00
EF21	0.627	0.373	21.00	23.00

Table 3: For the first order or 1 hour difference in the protein , the Increase.A is the ratio of the number of positive values divided by the total hours. Decrease.B is 1-Increase.A. The duration is the total number of consective positive values and time is the hour of change.

Figure 5 has the correlation structure for the first group of proteins from Figure 1. The third network (c) P53 Mdm2n Mdm2cp - Aktp - p53p - Pten - Mdm2c - Akt - PIP2 - PIP3.

Figure 8: The third network (c) P53 Mdm2n Mdm2cp - Aktp - p53p - Pten - Mdm2c - Akt - PIP2 - PIP3.

Table 7 has V1, V2, and V3 with average variance skewness kurtosis kutosis variance 1 and kurtosis variance 2 and theta.

1	p53	0	0	0.22	0.01	-0.46	2.1	-0.22	0.065	-0.22
2	p53p	0	0	0.12	0.0058	-0.022	1.8	0.013	0.023	-0.012
3	Pten	0	0	1.2	0.46	-0.21	1.9	-0.57	2	-0.11
4	Mdm2n	0	0	0.047	0.0062	1.9	5.3	1.2	0.27	0.35
5	Mdm2c	0	0	0.02	0.00014	0.0033	1.8	0.00015	0.00056	0.0018
6	Mdm2cp	0	0	0.74	1.5	1.8	5.3	18	66	0.34
7	Akt	0	0	0.31	0.029	-0.21	1.9	-0.14	0.13	-0.11
8	Aktp	-0.09	-0.09	5.2	6.9	-0.53	2	-6	37	-0.27
9	PIP2	-0.09	-0.897468256442197	0.94	0.93	0.66	2.4	2.9	7.8	0.28
10	PIP3	0	0	4	2.5	-0.8	2.6	-7.2	28	-0.31

Table 8 has the increase decrease duration and time for network C.

	Increase.A	Decrease.B	Duration	Time
p53	0.784	0.216	29.00	31.00
p53p	0.843	0.157	19.00	21.00
Pten	1	0	0.00	0.00
Mdm2n	1	0	0.00	0.00
Mdm2c	1	0	0.00	0.00
Mdm2cp	1	0	0.00	0.00
Akt	1	0	0.00	0.00
Aktp	0.588	0.412	29.00	31.00
PIP2	0.98	0.0196	49.00	51.00
PIP3	0.549	0.451	27.00	29.00

Table 4: For the first order or 1 hour difference in the protein , the Increase.A is the ratio of the number of positive values divided by the total hours. Decrease.B is 1-Increase.A. The duration is the total number of consective positive values and time is the hour of change

Figure 6 has the correlation structure for the first group of proteins from Figure 1. and (d) BAX - CytoC - Apops - CASP -Procasp3 -Apaf-1 -Procasp9 -casp3 -APTX -PARP1 -PARP3 - Apoptosis.

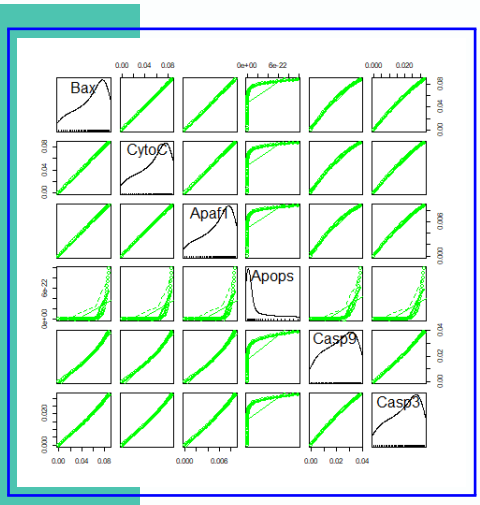


Figure 9: (d) BAX - CytoC - Apops - CASP -Procasp3 -Apaf-1 -Procasp9 -casp3 -APTX -PARP1 -PARP3 - Apoptosis.

Table 9 has V1, V2, and V3 with average variance skewness kurtosis kutosis variance 1 and kurtosis variance 2 and theta.

	V1	V2	V3	average	variance	skewness	kurtosis	kurtosis.variance.1	kurtosis.variance.2	theta
1	BAX	0	0	0.057	0.00062	-0.69	2.3	-0.085	0.005	-0.3
2	CytoC	0	0	0.057	0.00062	-0.7	2.3	-0.085	0.005	-0.3
3	Apops	0	0	0.0058	6.2e-06	-0.73	2.4	-0.009	5.3e-05	-0.3
4	Apaf-1	0	0	1.5e-22	6.6e-44	1.8	5.2	3.6e-21	2.7e-42	0.35
5	CASP9	0	0	0.022	0.00013	-0.34	1.9	-0.017	0.00061	-0.17
6	Procasp90		0	0.02	8.8e-05	-0.5	2.1	-0.022	0.00052	-0.24

Table 10 has the increase decrease duration and time for network D.

	Increase.A	Decrease.B	Duration	Time
BAX	1	0	0.00	0.00
CytoC	1	0	0.00	0.00
Apops	1	0	0.00	0.00
Apaf-1	1	0	0.00	0.00
CASP9	1	0	0.00	0.00
Procasp9	1	0	0.00	0.00

Table 5: For the first order or 1 hour difference in the protein , the Increase.A is the ratio of the number of positive values divided by the total hours. Decrease.B is 1-Increase.A. The duration is the total number of consective positive values and time is the hour of change.

Conclusions

In this illustrated numerical example for DNA repair the following set of proteins ATRp, p53, p53p ,Mdm2c ,Mdm2cp ,Mdm2n, Aktp, PIP3, PTEN, DDB2, p21tot, p21CE, CycEtot, E2F1, Rbp, Bax, CytoC, Apaf1, Apops, Casp9, and Casp3 with a protein-protein interaction model was specified and solved for a 48 hour time period. A treatment model with ULF (Ultraviolet light frequency) was specified and the results examined with 4 density and correlation illustrations dervived from the numerical computation. The model can be used for other types of DNA repairs.

For the four networks, (a) UV - ATR - DNA Damage - RPA and ATRp and Figure 2 for the second network (b) p21 - DDB2 -RBp - CYCe - RB - EF21 as two networks within the cell cycle for handing DNA damage. The third network in Figure 3 (c) P53 Mdm2n Mdm2cp - Aktp - p53p - Pten - Mdm2c - Akt - PIP2 - PIP3 and (d) BAX - CytoC - Apops - CASP -Procasp3 -Apaf-1 -Procasp9 -casp3 -APTX -PARP1 -PARP3 - Apoptosis

For each of the networks, Increase.A Decrease.B Duration and Time and V1 V2 V3 average variance skewness kurtosis kurtosis.variance.1 kurtosis.variance.2 and theta. For the totals of p21 and Cyce the relationship is given by Figure 7.

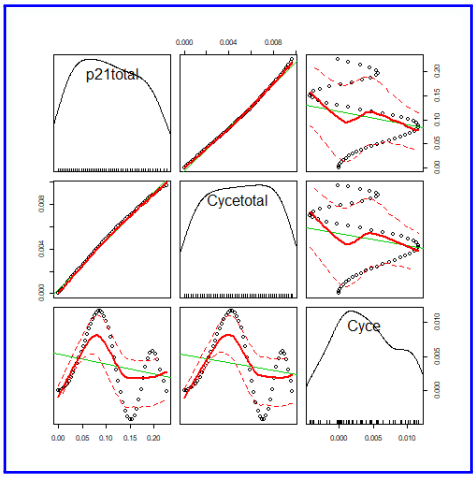


Figure 10: p21 totals and CycE totals relationship from the Equation System with p21tot=total levels of p21[601], p21CE=p21 incomplex with CDK2-cyclin E [601] p21=free p21 [601] CycEtot=total levels of cyclin E [601]

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