Preprint 141: A Mathematical Model of F-box-like/WD repeat-containing Protein-Protein Interaction and Proteasomal Degradation of Transcription Repressor Complexes with TP53

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Work currently in review with revision updates.

1 Abstract

A Three Group Eight member network was specified with molecules NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1 with a set of nonlinear difference equations with parameters sampled from a three set distribution and examined for similarity with the results from expression scores from carcinomic cell lines. Two experiments are conducted with solution to a set of differential equations and the before and after treatments are compared as well as a proposition developed with $\Theta = a11/a21 > 1$ where a11/a21=1.85 then Equation system A has positive eigenvalues for J(0.1 ,0.1, 0.1 , 0.1, 0.1 , 0.1, 10, 0.1).

2 Introduction

TP53 is a Cellular tumor antigen p53 tumor suppressor in many tumor types and induces growth arrest or apoptosis depending on the physiological circumstances and cell type. It is involved in cell cycle regulation as a trans-activator and acts to negatively regulate cell division byt control. One of the activated genes is an inhibitor of cyclin-dependent kinases and the apoptosis induction is mediated either by stimulation of BAX and FAS antigen expression, or by repression of Bcl-2 expression. [601]

Consider the vector X=[NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1] with the protein interaction network given by Figure 1

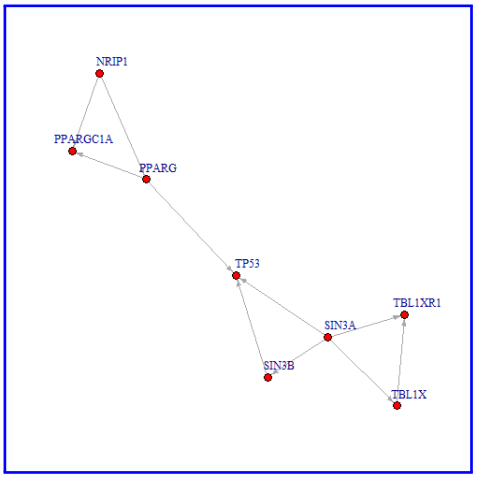

Figure 1: Protein Interaction Network for NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1

Figure 2 has the three communities for the eight node network.

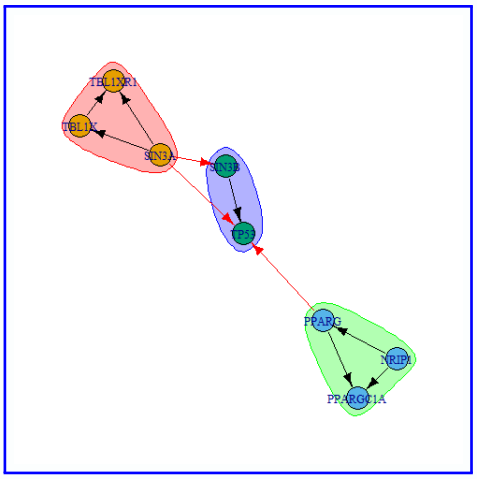

Figure 2: Protein Interaction Network for NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1

Here in Figure 1 amd 2, the following descriptions are :

TBL1X is a F-box-like/WD repeat-containing protein TBL1X; F-box-like protein that has an essential role in transcription activation mediated by nuclear receptors with involvement in the recruitment of the ubiquitin/19S proteasome complex to nuclear receptor-regulated transcription units with molecular function as an integral component of corepressor complexes that mediates the recruitment of the 19S proteasome complex with subsequent proteasomal degradation of transcription repressor complexes with permitted cofactor exchange in the WD repeat domain. [601] Figure 3 has the secondary structure of 2XTD with repression complex involves the recruitment of three proteins, HDAC3, GPS2 and TBL1, to a highly conserved repression domain within SMRT and NCoR.

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Figure 3: Eukaryotic transcriptional repressors function by recruiting large coregulatory complexes that target histone deacetylase enzymes to gene promoters and enhancers. Transcriptional repression complexes, assembled by the corepressor NCoR and its homolog SMRT, are crucial in many processes, i.e. development and metabolic physiology. The core repression complex involves the recruitment of three proteins, (1) HDAC3, (2) GPS2 and (3) TBL1, to a highly conserved repression domain within SMRT and NCoR.[401]

TBL1XR1 is a F-box-like/WD repeat-containing protein TBL1XR1; F-box-like protein involved in the recruitment of the ubiquitin/19S proteasome complex to nuclear receptor-regulated transcription units. [601]

NRIP1 is a Nuclear receptor-interacting protein 1 that modulates transcriptional activation by steroid receptors such as (a) NR3C1, (b) NR3C2 and (c) ESR1. Also modulates transcriptional repression by nuclear hormone receptors and is a positive regulator of the circadian clock gene expression: stimulates transcription of (a) ARNTL/BMAL1, (b) CLOCK and (c) CRY1 by acting as a coactivator for (1) RORA and (2) RORC. [601]

SIN3A is a Paired amphipathic helix protein Sin3a and serves as a transcriptional repressor. Corepressor for REST and interacts with MXI1 to repress MYC responsive genes and antagonize MYC oncogenic activities. MXD1-MAX heterodimer interaction inhibits transcription by tethering SIN3A to DNA and cooperatively interacts with OGT to repress transcription in parallel with histone deacetylation with involvement in control of the circadian rhythms necessary for the transcriptional repression of circadian target genes, PER1, mediated by the large PER complex through histone deacetylation. [601]

Figure 4 has the transcriptional misregulation in cancer for

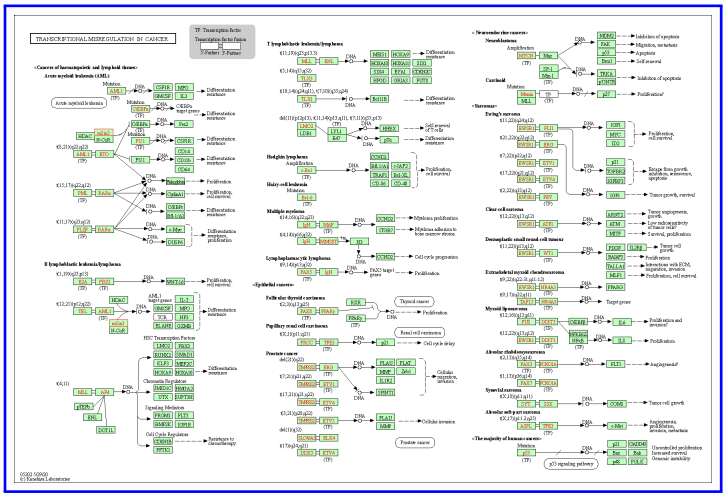

Figure 4: In tumor cells, genes encoding transcription factors (TFs) are often (a) amplified, (b) deleted, and (c) rearranged by chromosomal translocation and inversion, or subjected to point mutations that result in a (1) gain- or (2) loss-of- function. In hematopoietic cancers and solid tumors, the translocations and inversions increase or deregulate transcription of the oncogene.[401]

SIN3B is a Paired amphipathic helix protein Sin3b; Acts as a transcriptional repressor and interacts with MXI1 to repress MYC responsive genes and antagonize MYC oncogenic activities. This Interaction with MAD-MAX heterodimers by binding to MAD where the heterodimer then represses transcription by tethering SIN3B to DNA. The protein forms a complex with FOXK1 inhibits transcription and combined with FOXK1, regulates cell cycle progression probably by inhibiting cell cycle inhibitor genes expression. [601]

PPARG is a Peroxisome proliferator-activated receptor gamma; Nuclear receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Upon activation by a ligand, the nuclear receptor binds to DNA specific PPAR response elements (PPRE) and modulates the transcription of its target genes (a) acyl-CoA oxidase. This controls the peroxisomal beta-oxidation pathway of fatty acids and is a key regulator of adipocyte differentiation and glucose homeostasis. ARF6 acts as a key regulator of the tissue-specific adipocyte P2 (aP2) enhancer and is a critical regulator of gut homeostasis. [601]

PPARGC1A is a Peroxisome proliferator-activated receptor gamma coactivator 1-alpha and a transcriptional coactivator for steroid receptors and nuclear receptors that greatly increases the transcriptional activity of PPARG and thyroid hormone receptor on the uncoupling protein promoter. It can regulate key mitochondrial genes that contribute to the program of adaptive thermogenesis and has an essential role in metabolic reprogramming in response to dietary availability through coordination of the gene expressions involved in both glucose and fatty acid metabolism. [601]

Consider the following observations from titles with A Three Group Eight member network was specified with molecules NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1 from

1. (2018) Unscheduled HDAC4 repressive activity in human fibroblasts triggers TP53-dependent senescence and favors cell transformation. [2056].
2. (2019) Common genetic variants in the TP53 pathway and their impact on cancer. [2982].
3. (2020) Phase I studies of vorinostat with ixazomib or pazopanib imply a role of antiangiogenesis-based therapy for TP53 mutant malignancies. [5230].
4. (2014) Promyelocytic leukemia zinc finger-retinoic acid receptor alpha (PLZF-RARalpha), an oncogenic transcriptional repressor of cyclin-dependent kinase inhibitor 1A (p21WAFCDKN1A) and tumor protein p53 (TP53) genes. [5302].

5. (2012) Potential tumorigenic programs associated with TP53 mutation status reveal role of VEGF pathway. [6235].
6. (2018) The clinicopathological and prognostic significance of TP53 alteration in K27M mutated gliomas: an individual-participant data meta-analysis. [9042].
7. (2016) TP53 and Histone H3.3 Mutations in Triple-Negative Lower-Grade Gliomas. [9178].
8. (2019) Central Hypothyroidism and Novel Clinical Phenotypes in Hemizygous Truncation of TBL1X. [131].
9. (2015) TBL1XR1 in physiological and pathological states. [784].
10. (2017) The mutational landscape of ocular marginal zone lymphoma identifies frequent alterations in TNFAIP3 followed by mutations in TBL1XR1 and CREBBP. [960].
11. (2017) De novo non-synonymous TBL1XR1 mutation alters Wnt signaling activity. [1988].
12. (2016) Mutations in TBL1X Are Associated With Central Hypothyroidism. [3305].
13. (2008) The complex genomic profile of ETV6-RUNX1 positive acute lymphoblastic leukemia highlights a recurrent deletion of TBL1XR1. [5356].
14. TBL1XR1 Is Highly Expressed in Gastric Cancer and Predicts Poor Prognosis. [6151].
15. (2017) Correlations between TBL1XR1 and recurrence of colorectal cancer. [7561].
16. (2019) TBL1XR1 as a potential therapeutic target that promotes epithelial-mesenchymal transition in lung squamous cell carcinoma. [8580].
17. (2018) Expanding the spectrum of TBL1XR1 deletion: Report of a patient with brain and cardiac malformations. [9026].
18. (2016) A specific mutation in TBL1XR1 causes Pierpont syndrome. [9138].
19. (2015) A new syndrome of intellectual disability with dysmorphism due to TBL1XR1 deletion. [9185].

3 Equation System

Table 1 has the adjacency matrix for the network in Figure 1.

	NRIP1	PPARGC1A	TP53	TBL1X	TBL1XR1	SIN3A	PPARG	SIN3B
NRIP1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PPARGC1A	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00
TP53	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00
TBL1X	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
TBL1XR1	0.00	0.00	0.00	1.00	0.00	1.00	0.00	0.00
SIN3A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PPARG	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SIN3B	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00

3.1. System A

For system A, NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1 is given by

$$\begin{aligned}
dNRIP1 &= a11 * f.1(PPARGC1A, n) \\
&+ a12 * f.1(PPARG, n) && (1)\\
dSIN3A &= a21 * f.1(TP53, n) \\
&+ a22 * f.1(TBL1X, n) \\
&+ a23 * f.1(TBL1XR1, n) \\
&+ a24 * f.1(SIN3B, n) && (2)\\
dSIN3B &= a31 * f.1(TP53, n) && (3)\\
dPPARG &= a41 * f.1(PPARGC1A, n) \\
&+ a42 * f.1(TP53, n) && (4)\\
dPPARGC1A &= a51 * runif(1, 0, 1) && (5)\\
dTP53 &= a61 * runif(1, 0, 1) && (6)\\
dTBL1X &= a71 * f.1(TBL1XR1, n) && (7)\\
dTBL1XR1 &= a81 * runif(1, 0, 1) && (8)
\end{aligned}$$

where Let n=2 (a) $f.1 = x^n/(1+x)^n$ (b) $f.2 = z = lag(x)z^n/(1+z)^n$, (c) $f.3 = z = diff(x)z^n/(1+z)^n$ and (d) $f.4 = z = x + noise.5.4[1]; z^n/(1+z)^n$

3.2. System B

For system B, NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1 is given by

$$\begin{aligned}
dNRIP1 &= a11 * f.1(PPARGC1A, n) \\
&+ a12 * f.1(PPARG, n) && (9)\\
dSIN3A &= a21 * f.1(TP53, n) \\
&+ a22 * f.1(TBL1X, n) \\
&+ a23 * f.1(TBL1XR1, n) \\
&+ a24 * f.1(SIN3B, n) && (10)\\
dSIN3B &= a31 * f.1(TP53, n) && (11)\\
dPPARG &= a41 * f.1(PPARGC1A, n) \\
&+ a42 * f.1(TP53, n) && (12)\\
dPPARGC1A &= a51 * runif(1, 0, 1) && (13)\\
dTP53 &= a61 * rnorm(1, 0, 1) && (14)\\
dTBL1X &= a71 * f.1(TBL1XR1, n) && (15)\\
dTBL1XR1 &= a81 * runif(1, 0, 1) && (16)
\end{aligned}$$

Here the treatment equation is a change in the cdf specification of dTP53.

4 Parameter Specifications

Consider $\Pr[a \le X \le b] = \int_a^b f_X(x)\,dx$ where $f_X(x)$

$$\frac{2}{d+c-a-b}\frac{x-a}{b-a} \quad a \le x < b \qquad (17)$$

$$\frac{2}{d+c-a-b} \quad b \le x < c \qquad (18)$$

$$\frac{2}{d+c-a-b}\frac{d-x}{d-c} \quad c \le x \le d \qquad (19)$$

Powers on the $E[X^k]$ is given by three components

$$\frac{2}{d+c-b-a}\frac{1}{(k+1)(k+2)}\left(\frac{d^{k+1}-c^{k+2}}{d-c}-\frac{b^{k+1}-a^{k+2}}{b-a}\right) \quad (20)$$

If a=b and c=d, then the uniform distribution. This requires that the four parameter distribution is two and this reduction is based on the choice between the two. Table 1 has the Parameter Description, Value, Sampling Interval and Distribution for Parameter Matrix 1 for equation system A.

Table 1: Parameter Description, Value, Sampling Interval and Distribution

Parameter	Value	Interval	CDF
a11	0.53	[0:1]	Generalized Trapezoid
a12	0.54	[0:1]	Generalized Trapezoid
a21	0.29	[0:1]	Generalized Trapezoid
a22	0.38	[0:1]	Generalized Trapezoid
a23	0.8	[0:1]	Generalized Trapezoid
a24	0.52	[0:1]	Generalized Trapezoid
a31	0.13	[0:1]	Generalized Trapezoid
a41	0.43	[0:1]	Generalized Trapezoid
a42	0.25	[0:1]	Generalized Trapezoid
a51	0.29	[0:1]	Generalized Trapezoid
a61	0.37	[0:1]	Generalized Trapezoid
a71	0.4	[0:1]	Generalized Trapezoid
a81	0.24	[0:1]	Generalized Trapezoid

Table 2 has the Parameter Description, Value, Sampling Interval and Distribution for Parameter Matrix 2 for Equation System 2.

Table 2: Parameter Description, Value, Sampling Interval and Distribution

Parameter	Value	Interval	CDF
a11	0.7	[0:1]	Generalized Trapezoid
a12	0.08	[0:1]	Generalized Trapezoid
a21	0.51	[0:1]	Generalized Trapezoid
a22	0.67	[0:1]	Generalized Trapezoid
a23	0.02	[0:1]	Generalized Trapezoid
a24	0.47	[0:1]	Generalized Trapezoid
a31	0.34	[0:1]	Generalized Trapezoid
a41	0.86	[0:1]	Generalized Trapezoid
a42	0.24	[0:1]	Generalized Trapezoid
a43	0.57	[0:1]	Generalized Trapezoid
a51	0.82	[0:1]	Generalized Trapezoid
a61	0.96	[0:1]	Generalized Trapezoid
a71	0.43	[0:1]	Generalized Trapezoid
a81	0.64	[0:1]	Generalized Trapezoid

In the following two tables, the genes and proteins in Figure 1 have QSAR properties grouped by similar molecular function. The following three groups of (a) NRIP1, PPARG and PPARGC1A, (b) TP53 and SIN3B and (c) SIN3A, TBL1X, and TBL1XR1. Based on the following properties, they all have the same attributes when viewed from this dimension except for changes in charge at pH7. Table 1 has Protein Stability Index, Binding Potential, ALiphatic, f.1, CpH5, CpH7 and CpH9.

	Protein	Stability Index	Binding Potential	ALiphatic	f.1	CpH5	CpH7	CpH9
46	NRIP1	8.855	0.3785	11.975	-0.12496	51.43	13.821	-8.311
49	PPARG	3.408	0.1115	5.860	-0.02092	7.17	-9.915	-23.207
50	PPARGC1A	8.413	0.3525	5.980	-0.12333	12.19	-11.695	-33.746
70	TP53	3.830	0.1164	3.075	-0.03936	12.49	-1.404	-13.257
59	SIN3B	9.478	0.3785	12.694	-0.10889	40.26	-1.300	-28.138
58	SIN3A	9.784	0.4160	14.338	-0.13098	49.81	4.286	-20.842
62	TBL1X	3.162	0.1316	5.777	-0.02614	16.78	-5.878	-23.308
63	TBL1XR1	2.277	0.1056	5.386	-0.02030	2.55	-15.232	-29.044

Table 3: For the stability index the threshold value is less than 40 for stability. For positive binding potential greater than the threshold 2.48. ALiphatic is relative volume of aliphatic side chains (Alanine, Valine, Isoleucine, and Leucine) and is a positive factor for the increase of thermostability of globular proteins, f.1 is based on hydrophobicity,CpH5 is the charge at pH 5, CpH7 at 7 and CpH9 at 9.[1003]

5 Results

Consider the results from the cell lines for NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1 with Table 2. [1006]

	NRIP1	SIN3A	SIN3B	PPARG	PPARGC1A	TP53	TBL1X	TBL1XR1
BR:MCF7	0.01	1.63	-0.15	-0.44	-0.56	1.22	0.48	-0.43
BR:MDA_MB_231	-0.94	-0.29	0.43	0.20	-0.46	0.87	0.46	-0.68
BR:HS578T	-0.35	-1.82	0.44	-0.23	-0.61	0.79	1.10	0.19
BR:BT_549	-1.01	-0.96	-0.42	0.09	-0.56	1.70	-0.02	-0.43
BR:T47D	0.25	-0.26	-1.49	-0.74	0.03	0.63	-0.12	1.28
LC:A549	0.70	1.00	-1.43	0.63	-0.21	0.81	1.00	-1.52
LC:EKVX	0.06	0.83	-0.17	-0.60	1.02	-1.86	0.69	-1.42
LC:HOP_62	0.42	-0.63	-0.55	1.16	-0.30	-1.70	-0.36	-0.31
LC:HOP_92	0.39	-1.46	0.05	0.46	-0.26	-0.65	-0.44	0.08
LC:NCI_H226	0.71	0.96	0.76	-0.48	-0.55	0.90	-0.52	-1.38
LC:NCI_H23	-1.58	2.02	0.17	-0.54	-0.15	0.30	0.80	-0.58
LC:NCI_H322M	0.13	0.43	-0.03	0.10	-0.48	0.81	-0.70	-0.20
LC:NCI_H460	0.29	0.26	-1.26	0.20	0.49	0.27	1.11	-0.48
LC:NCI_H522	-1.68	0.14	-0.37	-0.72	-0.48	-2.02	1.33	-0.91

Table 4: Expression Values based on NCI Cell Lines [1006]

Table 3 has the moments based on all the cell lines for NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1.

	NRIP1	SIN3A	SIN3B	PPARG	PPARGC1A	TP53	TBL1X	TBL1XR1
vars	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00
n	60.00	60.00	60.00	60.00	60.00	60.00	60.00	59.00
mean	-0.00	-0.00	0.02	-0.01	-0.01	-0.01	-0.00	-0.00
sd	0.91	0.88	0.88	0.89	0.88	0.97	0.85	0.83
median	0.06	-0.04	0.18	-0.38	-0.40	0.29	-0.06	-0.03
trimmed	0.05	-0.00	0.01	-0.16	-0.20	0.08	-0.03	0.01
mad	0.96	0.85	0.79	0.54	0.23	0.76	0.95	0.96
min	-2.19	-2.13	-1.86	-0.88	-0.71	-2.43	-1.75	-1.66
max	1.97	2.02	2.05	2.81	4.11	1.70	1.99	1.62
range	4.16	4.15	3.91	3.69	4.82	4.13	3.74	3.28
skew	-0.43	0.01	0.03	1.45	2.51	-0.80	0.24	-0.13
kurtosis	-0.13	-0.29	-0.35	1.54	7.27	-0.23	-0.56	-0.83
se	0.12	0.11	0.11	0.12	0.11	0.12	0.11	0.11

Figure 5 has the difference between the Model A without treatment and Model B with treatment.

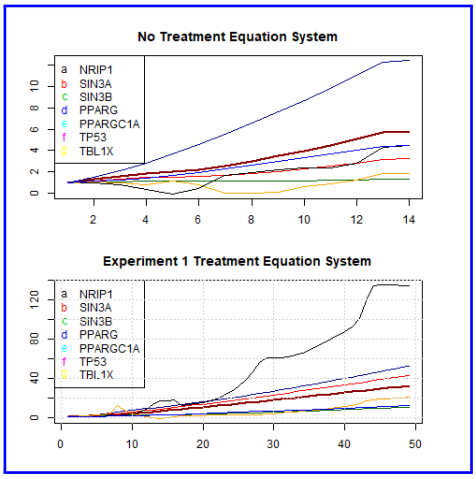

Figure 5: Protein Interaction Network with and without treatment

The next four figures has the matrix relationships between and among the proteins in the subset of the interaction network. Figure 6 has the result of the first of four experiments with Equation System 1 with Parameter Matrix 1 (7) Equation System 1 with Parameter Matrix 2 (8) Equation System 2 with Parameter Matrix 1 and (9) Equation System 2 with Parameter Matrix 2

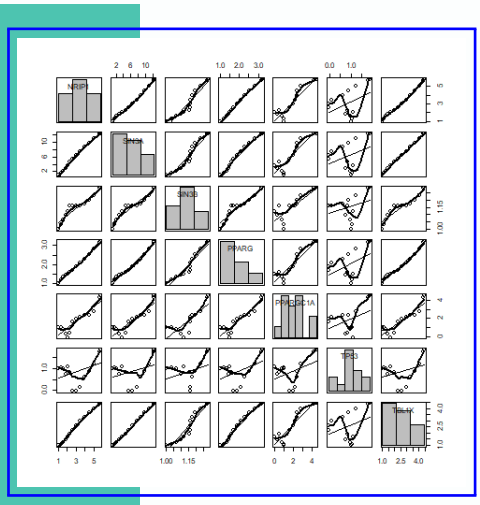

Figure 6: Protein Interaction Network No Treatment Equation System 1 and Parameter Matrix 1

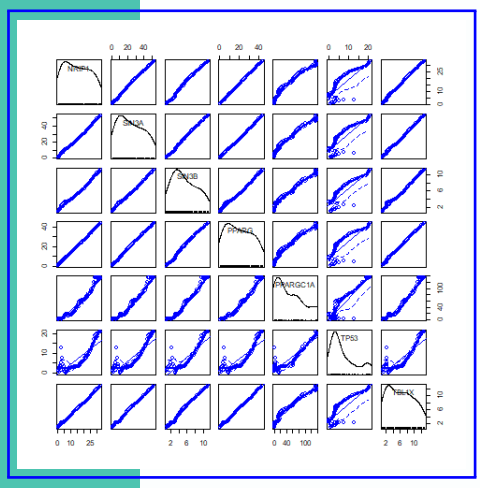

Figure 7: Protein Interaction Network No Treatment Parameter Matrix 2

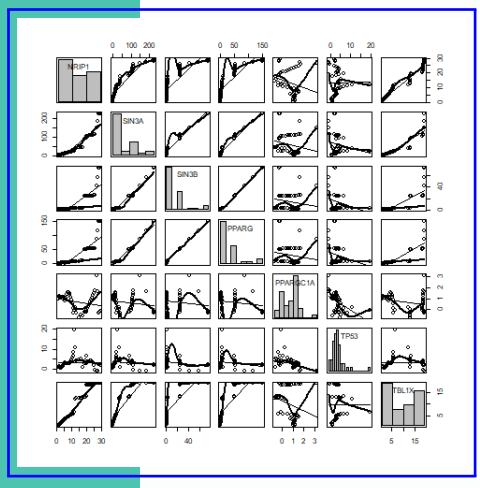

Figure 8: Protein Interaction Network Treatment A Equation 2 Parameter 1

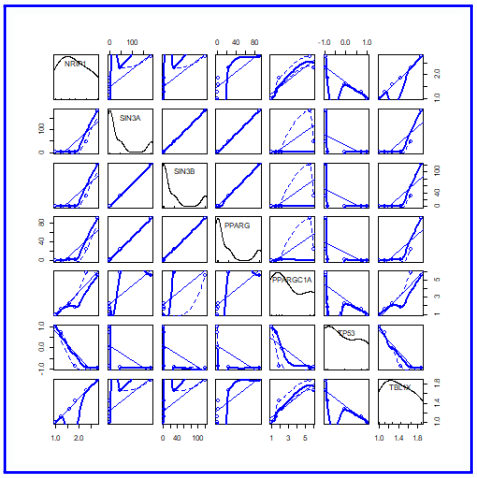

Figure 9: Protein Interaction Network Treatment B Equation 2 Parameter 2

Table 4 has the descriptive results from the solution of Equation System A.

	time	NRIP1	SIN3A	SIN3B	PPARG	PPARGC1A	TP53	TBL1X	TBL1XR1
vars	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00
n	14.00	14.00	14.00	14.00	14.00	14.00	14.00	14.00	14.00
mean	6.44	3.14	6.41	1.15	1.98	1.83	0.87	2.58	12.01
sd	4.08	1.63	3.99	0.08	0.73	1.39	0.58	1.23	9.78
median	6.50	2.77	6.04	1.16	1.77	1.80	0.93	2.43	13.89
trimmed	6.50	3.10	6.36	1.15	1.95	1.76	0.86	2.55	11.39
mad	5.19	1.78	5.21	0.08	0.70	1.34	0.34	1.61	13.45
min	0.00	1.00	1.00	1.00	1.00	-0.06	-0.04	1.00	1.00
max	12.11	5.76	12.42	1.28	3.21	4.51	1.88	4.43	30.55
range	12.11	4.76	11.42	0.28	2.21	4.57	1.92	3.43	29.55
skew	-0.06	0.34	0.17	-0.12	0.44	0.53	-0.01	0.20	0.48
kurtosis	-1.51	-1.46	-1.55	-0.96	-1.29	-0.86	-0.83	-1.60	-1.04
se	1.09	0.43	1.07	0.02	0.19	0.37	0.16	0.33	2.61

Table 5 has the descriptive results from the solution of Equation System B.

	time	NRIP1	SIN3A	SIN3B	PPARG	PPARGC1A	TP53	TBL1X	TBL1XR1
vars	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00
n	49.00	49.00	49.00	49.00	49.00	49.00	49.00	49.00	49.00
mean	24.00	13.44	59.10	14.30	30.06	0.69	3.43	9.83	1.42
sd	14.29	8.80	63.15	20.21	40.84	0.79	3.20	6.81	1.66
median	24.00	11.84	25.37	2.57	6.81	0.97	3.03	6.53	1.02
trimmed	24.00	13.17	49.56	10.16	22.05	0.68	3.03	9.80	1.34
mad	17.79	11.44	29.54	2.04	6.99	0.78	1.80	8.08	1.88
min	0.00	1.00	1.00	1.00	1.00	-0.71	-0.92	1.00	-0.81
max	48.00	29.05	224.84	74.40	149.40	3.13	19.67	18.77	4.73
range	48.00	28.05	223.84	73.40	148.40	3.84	20.58	17.77	5.54
skew	0.00	0.24	1.18	1.74	1.65	0.22	2.82	0.16	0.38
kurtosis	-1.27	-1.36	0.50	2.36	2.04	0.02	11.51	-1.70	-1.37
se	2.04	1.26	9.02	2.89	5.83	0.11	0.46	0.97	0.24

5.1. Propositions

If the polynomial has a multiple root, then its discriminant is zero, and that if all the roots are real and simple, then the discriminant is positive based on the Fundamental theorem of Galois theory. [1] If (discriminant (A) > 0) if (trace(A) < 0) classification ="Stable expression" if (trace(A) > 0) classification= "Unstable expression". However if (discriminant(A) < 0) then (a) if (trace(A) < 0) classification="Stable focus expression if (trace(A) > 0) classification=Unstable focus expression if (trace(A) == 0) classification=Centre expression. Here A is the Jacobian $n \times n$ matrix J of complex numbers with eigenvalues $\lambda_1, \ldots, \lambda_n$. Each eigenvalue appears $\mu_A(\lambda_i)$ times in this list, where $\mu_A(\lambda_i)$ is the eigenvalue's algebraic multiplicity. The following are properties of this matrix and its eigenvalues: The trace(A) is the sum of all eigenvalues, $\mathrm{tr}(A) = \sum_{i=1}^{n} a_{ii} = \sum_{i=1}^{n} \lambda_i = \lambda_1 + \lambda_2 + \cdots + \lambda_n$. The determinant(A) is the product of all its eigenvalues,

Proposition 1.1 Let $\Theta = a11/a21 > 1$ where a11/a21=1.85 then Equation system A has positive eigenvalues for J(0.1 ,0.1, 0.1 , 0.1, 0.1 , 0.1, 10, 0.1). [2]

Proof: Based on the specification of Equation System 1 with the relationship of $\Theta = \alpha 11/\alpha 21 > 1$ where a11/a21=1.85 , the Jacobian at J(0.1 ,0.1, 0.1 , 0.1, 0.1 , 0.1, 10, 0.1) is given by

$$J(0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 10, 0.1) = \begin{pmatrix} 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.00 & 0.08 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.08 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.08 & 0.00 & 0.00 & 0.06 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.00 & 0.00 & 0.00 & 0.01 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.00 & 0.08 & 0.00 & 0.00 & 0.00 & 0.00 & 0.06 & 0.00 \\ 0.00 & 0.08 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \end{pmatrix} \quad (21)$$

with characteristic polynomial for the evaluated Jacobian is $1*\lambda^8 + -0.13* \lambda^7 + 0 * \lambda^6 + 0 * \lambda^5 + 0 * \lambda^4 + 0 * \lambda^3 + 0 * \lambda^2 + 0 * \lambda^1 + 0$. the eigenvalues are 0.13 and 0 and 0 and 0 and 0 and 0 and 0 and 0 for this vector (0.1,0.1,0.1,0.1,0.1,10,0.1,0.1). The trace(A) = -0.13 and determinant(A)=0. QED

6 Conclusions

A Three Group Eight member network was specified with molecules NRIP1 SIN3A SIN3B PPARG PPARGC1A TP53 TBLIX TBL1XR1 with a set of nonlinear difference equations with parameter sampled from a three set distribution and examined for similarity with the results from expression scores from carcinomic cell lines. For $\Theta = \alpha 11/\alpha 21 > 1$ where a11/a21=1.85 then Equation system A has positive eigenvalues for J(0.1 ,0.1, 0.1 , 0.1, 0.1 , 0.1, 10, 0.1) and the system is considered stable.

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