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Compendium Model of AkT for Cell Survival/Death and its Equivalent Bio-Circuit

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Abstract*—This paper demonstrates the compendium model of AkT (protein kinase B) for cell survival/ death. AkT is a central signaling molecule in the Tumor Necrosis factor-α (TNF), Epidermal Necrosis Factor (EGF) and Insulin pathway. Model demonstrates how AkT promotes cell survival by inactivating several targets, including forkhead transcription factors, p53, GSK-3B and caspase-9 and activating Bad, NF-κB and mTOR. On the basis of model for AkT we have made the truth tables, Boolean equations and then implement the equations using logic circuits and Bio-circuits showing cell survival and death. Heat map of 13 time points at 0, 5, 15, 30, 60, and 90 min and 2, 4, 8, 12, 16, 20, and 24 hr for ten cytokine treatments of TNF, EGF and Insulin has been taken for AkT signal. We have plotted their corresponding graph of time-dependent signals. The results obtain will give information on how the input signals inducing cell survival/ death should be modulated to achieve desire outputs

***Index Terms*— AkT, Pro-Apoptotic, Anti-Apoptotic**

I. INTRODUCTION

In recent years, there has been considerable interest in the development of small cell-permeable inhibitors of protein kinases. Many such compounds are now undergoing human clinical trials for the treatment of cancer, chronic inflammatory diseases and other indications, and a few have already been approved for clinical use [1]. There is also considerable interest in the exploitation of specific protein-kinase inhibitors for the study of cell signaling. Akt, also referred to as PKB or Rac, plays a critical role in controlling survival and apoptosis [2, 3, 4, 5]. Translocation of Akt to the plasma membrane through its pleckstrin homology domain is likely required for its activity [6, 7, 8, 9], and constitutive targeting of Akt to the plasma membrane is sufficient to promote its activation [10, 11, 12, 13]. Both the upstream activating kinases and the recruitment of Akt to the plasma membrane are dependent upon the products of PI3K [14]. Some evidence suggests, however, that Akt isoforms are differentially activated in different insulin-responsive tissues following insulin stimulation [15]. Akt is activated in response to many different growth factors, including insulin and IGF-1 [10]. Akt is important for mediating the effects of these growth factors on the control of mammalian cell cycle progression and cell survival, as well as on the regulation of processes that influence growth, including protein synthesis and glucose metabolism. Akt plays a key role in the coordinated regulation of growth, apoptosis and metabolism by the TNF, EGF and insulin/IGF–signaling pathway.

Akt promotes cell survival by inactivating several targets, including forkhead transcription factors, p53, GSK-3B and caspase-9 and activating Bad, NF-κB, and mTOR Phosphatase and tensin homolog (PTEN) phosphatase is a major negative regulator of the PI3 kinase/Akt signaling pathway.

In this paper we will discuss the compendium model of AkT which consists of different pathways. Each pathway is expressed in truth table and Boolean equations and then implemented those equations using logic circuits and bio-circuits.

II. COMPENDIUM MODEL

The prediction model for cell survival/ death heading by AkT has been implemented. The block diagram of the signaling system that was modeled is shown in Figure 1.

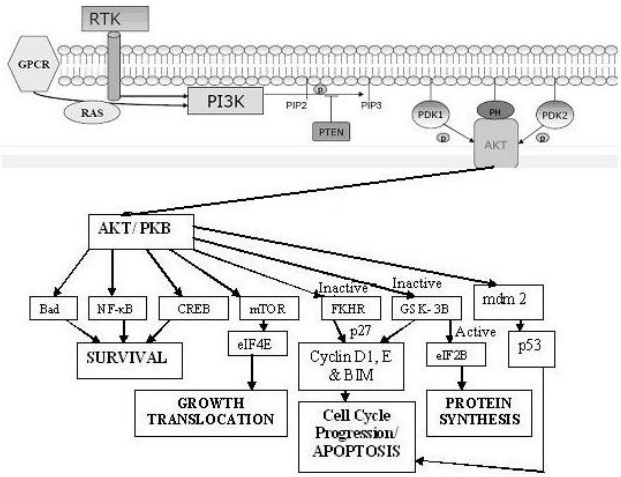

Fig 1: Compendium model of cell signaling regulated by AkT

TNF, EGF and Insulin activate the PI3-Akt signaling cascade through corresponding receptor tyrosine kinases After receptor dimerization, PI3K is recruited to the plasma membrane where its catalytic subunit generates lipid second messengers, phosphoinositide phosphates (PIP_2, PIP_3) [16], at the inner surface of the plasma membrane. Phosphoinositide-dependent protein kinase-1 (PDK1) then acts in concert with PIP_2 and PIP_3 to phosphorylate and activate Akt. Dominant-negative and constitutively active forms of Ras [17], PI3K [18, 19], and Akt [20] have been used to study signaling through the PI3K-Akt pathway. These

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and other studies have demonstrated downstream signaling effects that regulate cellular survival, proliferation, and metabolism. For example, Akt phosphorylates and inactivates FKHR1, a member of the family of Forkhead transcriptional regulators [21]. Inactivated FKHR1 is unable to induce the expression of death genes. Akt activates the cAMP-responsive element binding protein (CREB) and nuclear factor-κB (NF-κB)[22, 23], additional transcriptional regulators that may promote neuronal survival. In addition, Akt can directly inhibit the apoptotic machinery by phosphorylation at sites both upstream (BAD) [24] and downstream (Caspase-9) of mitochondrial cytochrome c release. Finally, there is evidence to support the role of Akt in promoting neuronal survival through metabolic effects, by regulating glucose metabolism in neurons. [25]

Activated Akt has the capacity to phosphorylate a wide variety of substrate proteins in order to perform its various functions in the cell. A most important discovery in the Akt function was made using synthetic peptides with sequences that are related to the phosphorylation site of GSK-3 as substrates for Akt kinase activity. As a result, the consensus site for Akt phosphorylation, the subsequent searches for apoptosis-related proteins that contain this sequence led to the identification of numerous proteins that are involved in apoptosis as targets of Akt.

III. RESULTS AND DISCUSSION

On the basis of the compendium model we have made truth tables of every possible path culminate in cell death/ survival of individual inputs i.e. TNF, EGF and Insulin. Than we realize the truth tables by Karnaugh Map (K-Map) and get the expression for each input and its individual possible paths. With the help of Boolean equations we have implemented circuits using Logic gates. Logic gates are the basic building blocks in electronic circuits that perform logical operations. These have input and output signals in the form of 0's and 1's; '0' signifies the absence of signal while '1' signifies its presence. Similar to the electronic logic gates, cellular components can serve as logic gates. There are three steps in a simple gate:i) Translation of the input mRNA signal, ii) cooperative binding of the protein (repressor) to the DNA (operator) and iii) regulated gene expression to generate the output signal [27, 28].

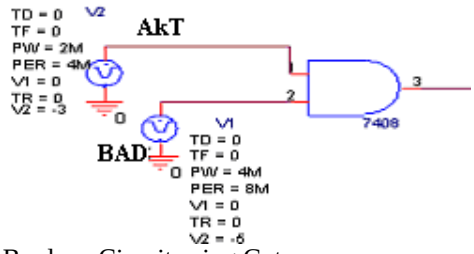
The NOT Gate: The NOT gate is the simplest biochemical circuit. The gate has a single input signal. The NOT gate 'inverts' the input signal, hence known as the inverter gate. The NOT gate is built using two promoter/repressor pairs. The inducer input is applied to the first promoter/ repressor pair (P1/R1). The output protein produced by the first repressor/promoter pair acts as the repressor (R2) to the second promoter (P2). Hence, whenever the inducer input is introduced, the second promoter is repressed and no output is produced. When no inducer input is present, then the second promoter will produce the output protein..

The AND Gate: The AND gate has two input signals and only when both the signals are present, an output signal is generated. The AND gate can be built using a single repressor/ promoter pair which is activated using two inducers. Both the inducers have to be present to activate the output protein production.

Following are the various proteins which helps in Cell survival/ Death using AkT .

A. Bad : Bad was the first protein that is directly involved in apoptosis to be identified as a target of Akt. Bad is a member of the Bcl-2 family, which converges on the mitochondrial outer membrane to regulate cell death. In the absence of Akt activity, Bad binds with another pro-survival member of the Bcl-2 family, Bcl-XL, and induces cell death, most likely by inhibiting the function of Bcl-XL to block the release of cytochrome *c* from mitochondria to the cytoplasm . Fig 2 shows the truth table, logical circuit and bio circuit for cell death/ survival for AkT/ BAD pathway. In output '1' means survival and '0' means death.

AkT	BAD	Output
0	0	0
0	1	0
1	0	0
1	1	1



Boolean Circuit using Gates

Bio Circuit

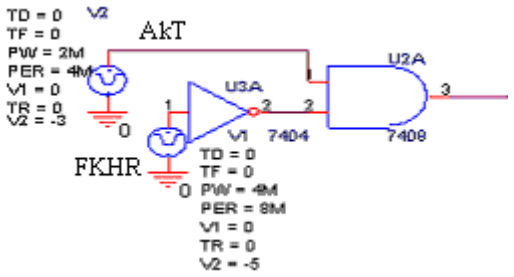
Fig 2: The truth table, logical circuit and bio circuit for cell death/ survival for AkT/ BAD pathway.

B. Caspase 9: During apoptosis, cytochrome c that is released into the cytoplasm binds the CED-4 homologue, Apaf-1. This causes it to bind, cleave, and activate the cysteine protease procaspase-9, which propagates the apoptotic caspase cascade that results in the activation of the 'executioner' caspases, caspase 3 and caspase 7. Interestingly, Akt phosphorylates procaspase-9 at Ser-196 rendering it resistant to processing and activation. Although it may appear redundant for Akt to act both upstream and downstream of cytochrome c in preventing apoptosis, the phosphorylation of procaspase-9 by Akt must have a physiological significance, as the cells that express caspase-9 with the Ser-196 mutated to alanine and underwent apoptosis that was resistant to Akt activity

C. FKHR1: Akt phosphorylates and inactivates the Forkhead transcriptional factors. In the absence of survival signalings (i.e. phosphorylation by Akt), the Forkhead proteins enter the nucleus and are thought to induce the transcription of various cell-death related genes, such as FasL (Fas ligand) However,

active Akt induces the phosphorylation of a specific site on the FKHR1 molecule that causes it to be excluded from the nucleus, therefore losing its transcriptional activity. Fig 3 shows the truth table, logical circuit and bio circuit for cell death/ survival for AkT/ FKHR pathway.

AkT	FKHR	Output
0	0	0
0	1	0
1	0	1
1	1	0



Boolean Circuit using Gates

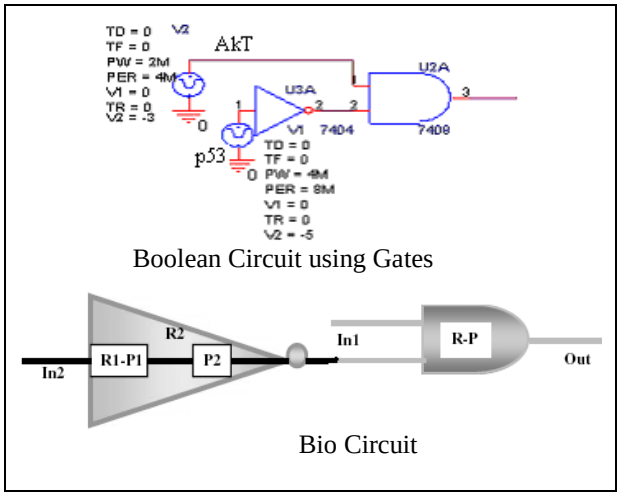
Bio Circuit

Fig 3: The truth table, logical circuit and bio circuit for cell death/ survival for AkT/ FKHR pathway.

D. p53: The Bcl2 family member, Bax, is involved in p53-mediated neuronal death. Bax-deficient neurons are protected from cell death induced by DNA-damaging agents and adenovirus-mediated p53 overexpression. Moreover, various forms of neuronal injury are associated with Bax translocation from the cytosol to the mitochondria. The redistribution of Bax to the mitochondria has been associated with a reduction in mitochondrial membrane potential, mitochondrial release of cytochrome c, and activation of caspases, suggesting that caspases may also be a component of a p53-induced cell death pathway.

In this regard it is interesting to note that the important survival-promoting protein, Akt, can protect neurons from cell death by inhibiting p53-dependent transcriptional activity. These results demonstrate the interconnection that exists between pathways that govern cell death and viability and serve to remind us that the response and the outcome of neurons to stress are exceedingly complex. Fig 4 shows the truth table, logical circuit and bio circuit for cell death/ survival for AkT/ p53 pathway.

AkT	p53	Output
0	0	0
0	1	0
1	0	1
1	1	0



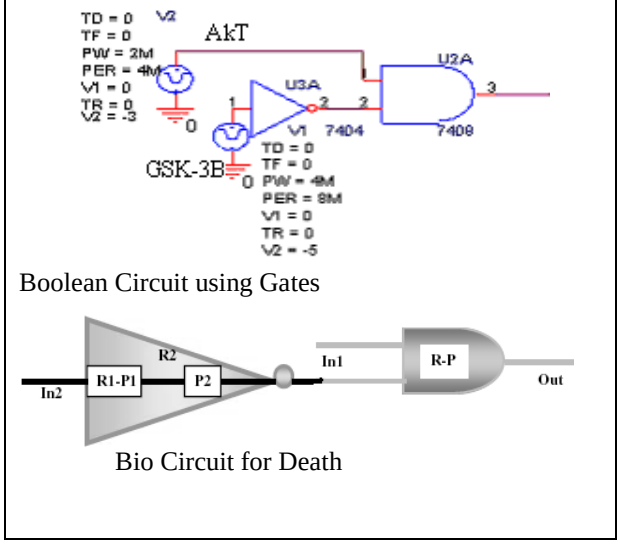
Boolean Circuit using Gates

Bio Circuit

Fig 4: The truth table, logical circuit and bio circuit for cell death/ survival for AkT/ p53 pathway.

E. GSK-3B: Another emerging kinase that has been implicated in neuronal cell death is glycogen synthase kinase-3β (GSK-3β). Activation of AKT also requires the protein kinase 3-phosphoinositide-dependent protein kinase-1 (PDK1), which in combination with a yet unidentified kinase leads to the phosphorylation of AKT [30]. Once active, AKT enters the cytoplasm where it leads to the phosphorylation and inactivation of glycogen synthase kinase 3 (GSK3). A major substrate of GSK3 is glycogen synthase, an enzyme that catalyses the final step in glycogen synthesis. Phosphorylation of glycogen synthase by GSK3 inhibits glycogen synthesis; therefore, the inactivation of GSK3 by AKT promotes glucose storage as glycogen [31]. Insulin directly controls the activities of a set of metabolic enzymes by phosphorylation and dephosphorylation events and also regulates the expression of genes encoding hepatic enzymes involved in gluconeogenesis. The truth table, logical circuit and bio circuit for cell death/ survival for AkT/ GSK-3B pathway.

AkT	GSK-3B	Output
0	0	0
0	1	0
1	0	1
1	1	0



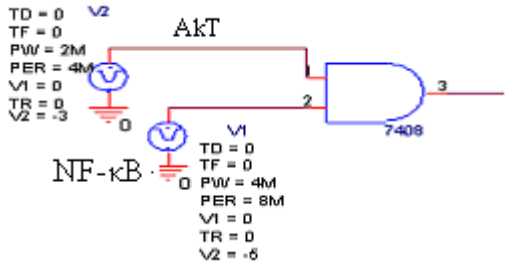
Boolean Circuit using Gates

Bio Circuit for Death

Fig 5 The truth table, logical circuit and bio circuit for cell death/ survival for AkT/ GSK-3B pathway.

F. NF-κB : NF-κB is a factor that is involved in cell survival. It has been identified as a functional target of Akt. NF-κB is a family of transcription factors, which induce the expression of a wide variety of genes, especially those involved in survival, such as the Bcl-2 family member Bfl-1, and the caspase inhibitors c-IAP1 and c-IAP2. Binding with IκB sequesters it to the cytoplasm. Upon phosphorylation of IκB by IKKalpha and IKKbeta, IkB is degraded and NF-κB can enter the nucleus to induce transcription. It must be noted that NF-κB does not appear to be directly phosphorylated by Akt, but indirectly activated.

AkT	NF-kB	Output
0	0	0
0	1	0
1	0	0
1	1	1



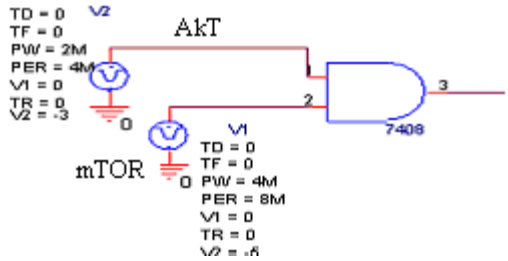
Boolean Circuit using Gates

Bio Circuit

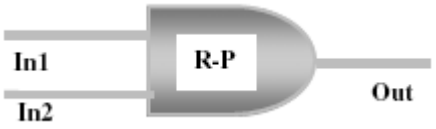
Fig 6 The truth table, logical circuit and bio circuit for cell death/ survival for AkT/ NF-kB pathway.

G. mTOR : Using cell biological, biochemical, genomic, and proteomic approaches, we are uncovering the complex molecular understanding of a signaling network centered around a G protein switch involving the tuberous sclerosis complex (TSC) tumor suppressors (TSC1 and TSC2) and the Ras-related small G protein Rheb. A complex between TSC1 and TSC2 is regulated by multi-site phosphorylation and acts as a point of integration for a diverse array of cellular signals, including those arising from growth factors, nutrients, and a variety of stress conditions. When active, the TSC1-TSC2 complex acts as a GTPase activating protein (GAP) for Rheb, thereby turning Rheb off by stimulating its intrinsic GTPase activity. In the presence of growth factors and nutrients, this complex is turned off, allowing the GTP-bound active version of Rheb to accumulate and turn on downstream pathways. The best-characterized downstream effectors of Rheb is the mammalian target of rapamycin complex 1 (mTORC1), a critical regulator of cell growth and proliferation.

AkT	mTOR	Output
0	0	0
0	1	0
1	0	0
1	1	1



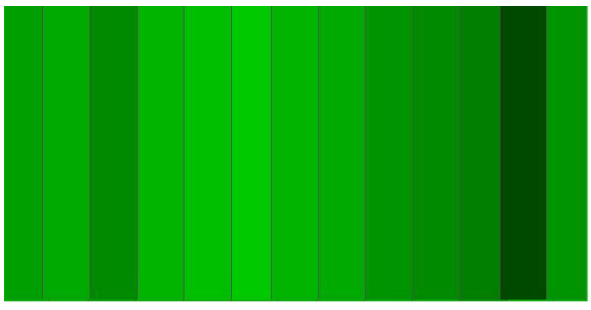
Boolean Circuit using Gates

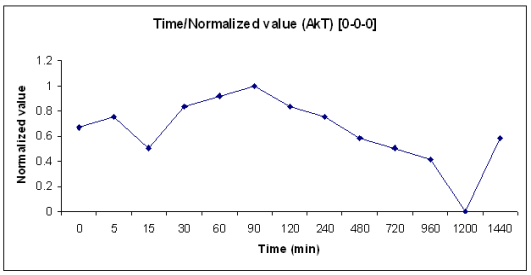


Bio Circuit

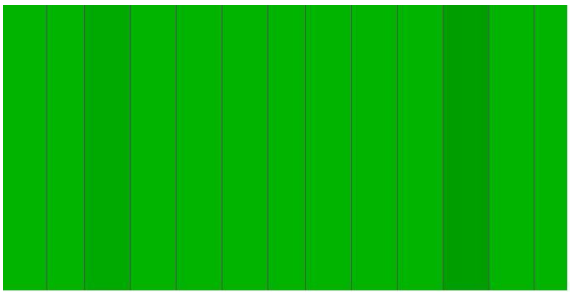
Fig 7 The truth table, logical circuit and bio circuit for cell death/ survival for AkT/ mTOR pathway.

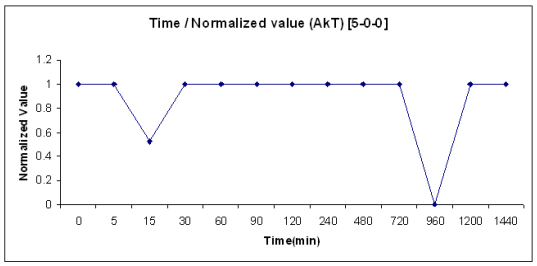
The cultures were stimulated 24 hr later by adding the stimulus diluted in 1/20 of the culture volume of serum-free medium, for final concentrations of 0, 0.2, 5, or 100 ng/ml TNF, 0, 1, or 100 ng/ml EGF, and 0, 1, 5, or 500 ng/ml insulin. Heat map of 13 time points at 0, 5, 15, 30, 60, and 90 min and 2, 4, 8, 12, 16, 20, and 24 hr been taken from Gaudet et.al for ten cytokine treatments (shown in table 1) of TNF, EGF and Insulin has been examined for AkT signal. We have plotted their corresponding graph of time-dependent signals in cells treated with 10 cytokine combinations are shown in Fig 8(*a*) to (*j*). Fig.8 (*a*) shows the heat map and corresponding graph of time-dependent signals for AkT using TNF/ EGF/ Insulin combination of 0/0/0 ng/ml with (0, 5, 15, 30, 60, 90, 120 min) and then (4, 8, 12, 16, 20, 24 hr).



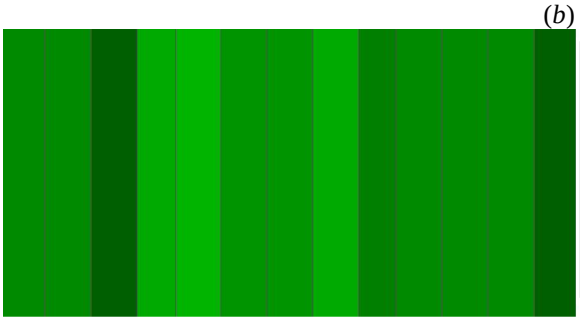


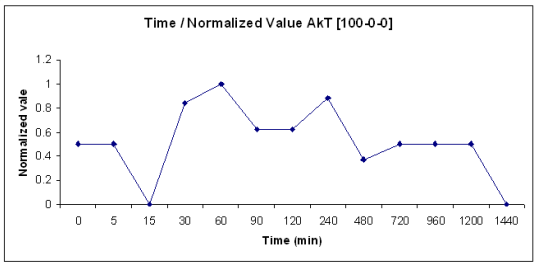
(*a*)



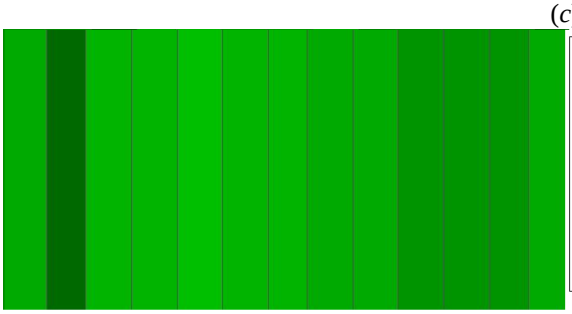

Time / Normalized value (AkT) [5-0-0]
Normalized Value
Time(min)

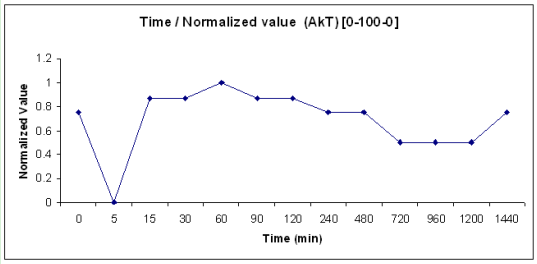
(*b*)



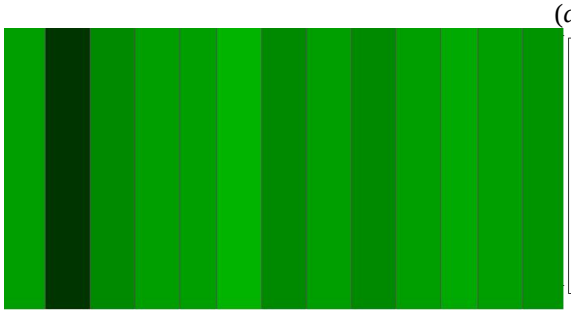

Time / Normalized Value AkT [100-0-0]
Normalized vale
Time (min)

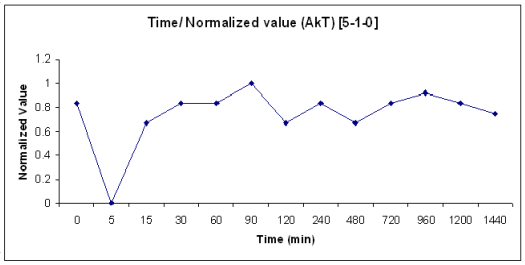
(*c*)



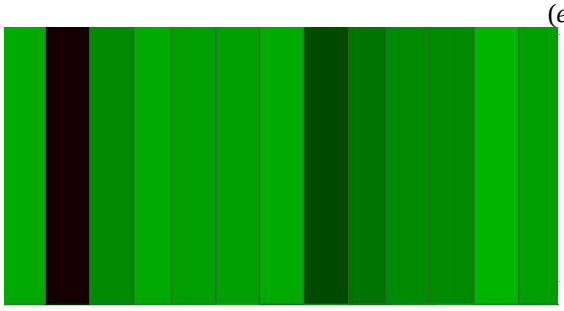

Time / Normalized value (AkT) [0-100-0]
Normalized Value
Time (min)

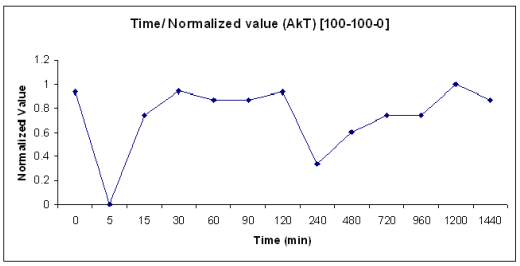
(*d*)



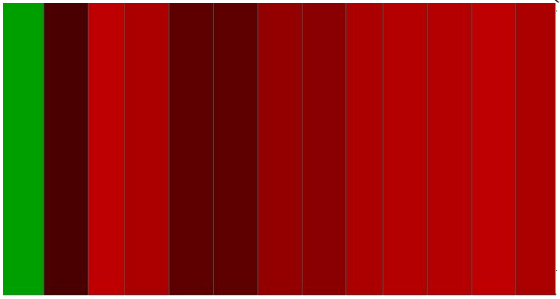

Time/ Normalized value (AkT) [5-1-0]
Normalized Value
Time (min)

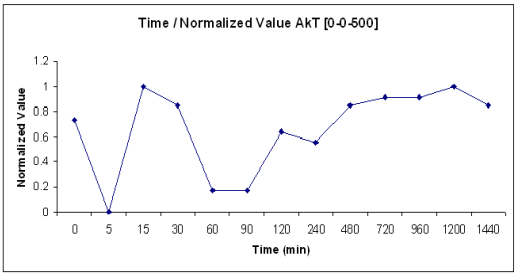
(*e*)




Time/ Normalized value (AkT) [100-100-0]
Normalized Value
Time (min)

(*f*)




Time / Normalized Value AkT [0-0-500]
Normalized Value
Time (min)

(*g*)

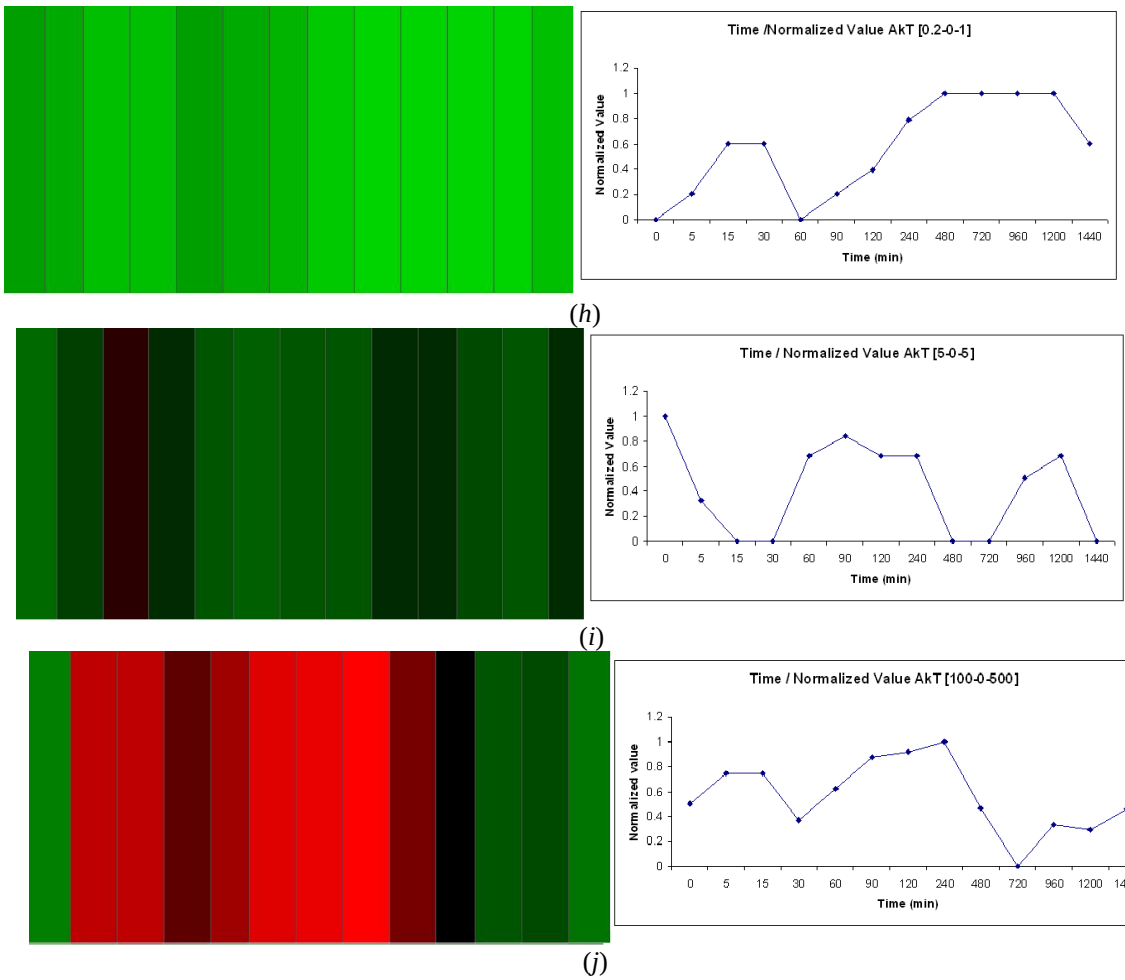


Fig 8 : Heat map and corresponding graph of time-dependent signals in cells treated with 10 cytokine combinations. For each treatment, the average signal intensities were normalized to the maximal value obtained for that signal (1: green; 0: red) and are plotted for the 13 time points.

Similarly Fig. 8 (b) to (j) shows the heat map and corresponding graph for rest nine cytokine combinations. For each treatment, the average signal intensities were normalized to the maximal value obtained for that signal (1: green; 0: red).

Table 1 : Ten cytokine treatments

	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*f*)	(*g*)	(*h*)	(*i*)	(*j*)
TNF(ng/ml)	-	5	100	-	5	100	-	0.2	5	100
EGF(ng/ml)	-	-	-	100	1	100	-	-	-	-
Insulin(ng/ml)	-	-	-	-	-	-	500	1	5	500

IV. CONCLUSION

We have demonstrated that the logic circuits and bio-circuits that can be applied to predict the cell survival/ death with a high level of accuracy for AkT signal with different marker proteins. The signaling pathway has reproduced experimental data with accurate. We come to know that AkT promotes cell survival by inactivating several targets, including forkhead transcription factors, p53, GSK-3B and caspase-9 and activating Bad, NF-κB and mTOR.Heat map and corresponding graph were plotted for 10 cytokine combinations. Understanding the nature of signaling networks that control the cell survival/ death is very significant and theoretical calculations seen to be a proper tool for gaining such understanding. The results obtain will give information on how the input signals inducing cell survival/ death should be modulated to achieve desire outputs. It thus helps the experimentalists to design proposals regarding possible improvements to cell survival/ cell death.

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ABBREVAITIONS

AP-1, Activation Protein 1; ASK1, Apoptosis signal-regulating kinase 1; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular-regulated kinase; FKHR, Forkhead transcription factor; Grb2, growth factor receptor-bound 2; GSK 3, Glycogen synthase kinase 3; IR, insulin receptor; IRS1, insulin receptor substrate 1; JNK1, c-jun NH_2 terminal kinase 1; MAP kinases, mitogen-activated protein kinases; MEK, mitogen-activated protein kinase and extracellular-regulated kinase kinase; MK2, mitogen-activated protein kinase-activated protein kinase 2; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PDK, Phi Delta Kappa; PI3K, phosphatidylinositol 3-kinase; p38, P38 mitogen-activated protein kinases**;** Rac, Ras-related C3 botulinum toxin substrate; SAPK/JNK , Stress-activated protein kinase/Jun-amino-terminal kinase; SH2, Src homolgy 2; SODD, Silencer of death domains; SOS, Son of Sevenless; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; TNFR2, tumor necrosis factor receptor 2; TRADD, TNFR associated via death domain; TRAF2, TNF receptor associated factor 2.

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