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Computational Modeling of Signal Transduction Pathways in Breast Cancerous Cell and Target Therapy

Prasanna Priya Golagani, Shaik Khasim Beebi, Tummala Sita Mahalakshmi

Abstract: ***In this paper we identify the mutated signal transduction pathways in a breast cancerous cell. A simulated model is developed for these pathways. To reduce cancer some drugs are suggested that are helpful in correcting the pathways. Some of the pathways like PKB (Protein Kinase B), MAPK (Mitogen Activated Protein Kinase), MTOR (Mammalian Target Of Rapamycin), Fas Ligand (Type-II Tran membrane Protein), Notch (Single Pass Transmembrane Receptor), SHH (Sonic Hedgehog), Tnf (Tumor Necrosis Factor), Wnt (Wingless/Integrated) Pathways are simulated. Converting these biological pathways into a computable model helps in analyzing it rapidly. For Computational modeling of signal transduction pathways, SBML (Systems Biology Markup Language) is used. Programming is done in SBML and executed in Cell Designer. In this paper simulated models of PKB, MAPK, MTOR, FasL, Notch, SHH, Tnf, Wnt pathways are developed and shown in the results. Target Therapy can be implemented to these pathways. Drugs like Wortmannin, Perifosine and Rapamycin are suggested. These drugs help in modifying the pathways in such a way that, their metabolism is converted into the metabolism of a normal breast cell. This helps in reducing breast cancer.***

Index Terms**: *Cancer, Benign Cancer, Malignant Cancer, Breast Cancer, PKB, MTOR, MAPK, SBML, Cell Designer.***

I. INTRODUCTION

Cancer causes severe metabolic changes in the cell [1].In cancer, the cells do not die when they have to die and new cells are born when they are not required. Cancer cell divides uncontrollably and produce numerous new cells. Cancer is of two types benign and malignant. Malignant tumors are cancerous and can invade to the surrounding tissues, benign tumors do not spread to other tissues they are local to their site and sometimes they can be quite large.

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Cancer Statistics: Cancer stands second worldwide to cause death. In 2015 8.8 million people died out of cancer [2]. In 2017 the estimated no. of new cancer cases are 16, 88,780.Nearly 6, 00,920 people are estimated to die with cancer in 2017[3].For every 8 minutes one woman dies with cervical cancer. In India an estimated number of 2.5million people are suffering from cancer. Every year an estimated number of 7 lakh cases are registered in India. Nearly 5, 56,400 people are dying with cancer every year in India [4].Based on the primary site of origin cancer can be divided into different types like 1) Breast Cancer2)Lung Cancer3) Prostrate Cancer4) Liver Cancer5)Renal Cell Carcinoma6)Oral Cancer and 7)Brain Cancer.

Breast Cancer: A malignant growth in the breast is known as Breast Cancer [5].Breast Cancer can be classified based on Histopathology, Stage (TNM), Grade, Receptor status and the presence or absence of genes in the DNA [6].

Breast Cancer Statistics: There is an estimation that in 2017, 2, 52,710 new cases of invasive Breast Cancer will be detected in females and 2,470 in males. Along with it 63,410 new cases of in situ breast carcinoma will be detected in females. Nearly 40,610 female and 460 male deaths from breast cancer are estimated in 2017.More than 3.5 million women were alive with a history of breast cancer on January 01 2017. [7]

1.1 Signal Transduction Pathways: In the Breast Cancerous cell, the cell signaling is affected. Apoptosis in inhibited and new cells are produced continuously this is due to the changes in some of the signal transduction pathways. In this paper we studied some of these signal transduction pathways like PKB, MAPK, MTOR, FasL, Notch, SHH, Tnf and Wnt.

1.2Computational Modeling of the Pathways Using SBML and Cell Designer: Converting the biological pathway into a computable model helps in analyzing it rapidly using simulation and other mathematical methods. We used SBML for computational modeling of signal transduction pathways. The programs written in SBML for each Pathway are executed in Cell Designer.

1.3 Drug therapy and Target therapy: In this paper we studied 3 pathways in depth that is PBK, MAPK and MTOR pathways we suggested 3 drugs that are for these pathways (Wortmannin, Perifosine and Rapamycin) and specified the exact targets in the pathway where these drugs can be used to make the pathway function as it is functioning in a normal breast cell and reduce cancer.

1. Literature Review:

Ezio Bartocci and Pietro Lio discussed the most important computational tools currently available to systems biologists in 2016 [15]. Maria and John focused on the use of Computational modeling to the analysis of biochemical systems in 2011[16]. Liviqni A and O Hara developed a graphical model scheme which facilitates construction of detailed network diagrams, summarizing the components of the biological pathways and illustrating how they interact in 2017[17]. Koh Yeow and Geoffrey used Petri Net to model an AKT pathway and its interaction with ERK cascade53. Haijun and Paolo developed a model for HMGB1 pathway using BioNetGen language in 2010[18]. Ji-Young Hong and Geun-Hong Kim proposed inducing cell death with the help of cisplatin [19]. Yosef and Sekar proposed a plan to model the whole cell [20]. Walter Koch and Melinda Halasz discussed how signaling of the networks are regulated and how they cause cancer [21]. Gendelman and Xing constructed a model for networks caused by inhibition of MEK ½. Through simulation of a reverse engineered Bayesian network model, they generated predictions for G1-S transition[22]. Donya and Schmitt presented a model for the dynamics of calcium-induced CAMP/PKA in dendritic spines[23]. Leon and Paul demonstrate how computational multi-scale brain modeling links phenomena of different scales and therefore identifies potential disease mechanisms leading the way to improved diagnostics and treatment [24]. Aravind and Garegin have simulated Abelson murine lymphosarcoma kinase signaling pathway using MEDYAN software to monitor the growth [25].

Proposed Work

Breast Cancerous Cell has changes in signal transduction pathways when compared to a normal breast cell. In this paper we are studying some of these pathways like PKB, MAPK, MTOR, Fas Ligand, Notch, SHH, Tnf and Wnt Pathways. Converting these biological pathways into a computable model helps in analyzing it rapidly.We are using SBML for computational modeling of signal transduction pathways. The programs written in SBML for each Pathway are executed in Cell Designer. In this paper we have simulated models for PKB, MAPK, mTOR, FasL, Notch, SHH, Tnf, Wnt pathways which are shown in the results. Target Therapy can be implemented to these pathways.In this paper we are suggesting drugs to the pathways such as Wortmannin, Perifosine and Rapamycin which can be extracted from microorganisms. These drugs are useful in converting the pathways into normal.

2.1Architectural Diagram of our work:

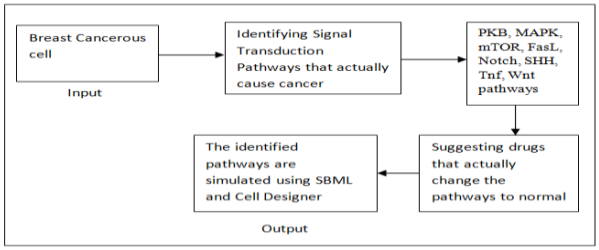

Figure: Architectural Diagram of our work

2.2.Methods

Target Pathways for Breast Cancer treatment:

PKB/Akt–Pathway: Akt signaling pathway is actuated by coupling of extracellular Growth factors such as Epidermal Growth Factor to the Receptor tyrosine kinases,on the cell membrane. This causes dimerization of the monomers and heterologous auto phosphorylation of the monomers of the tyrosine kinase. The p85 subunit binds to the Tyrosine kinase and p110 attaches to the p85 and forms the fully activated PI3K(PhosphoInositide 3 Kinase).PI3K catalyzes the formation of PIP3 by adding a phosphate group to PIP2 (Phosphoinositol 3, 4 biphosphate) to produce PIP3 Phosphoinositol 3, 4, 5 triphosphate.PIP3 activates AKT (Protein Kinase B).AKT is involved in mechanisms such as stopping cell apoptosis and causing cell proliferation [8].

Akt Pathway Causing Cancer:Over production of Akt due to mutations leads to cancer.Akt stops apoptosis or programmed cell death by binding with BAX (Bcl-2-like protein 4) and making it to lose the power to make cavities in the outer mitochondrial membrane.In the dearth of Akt, these cavities cause cell death or apoptosis.Akt also plays a major role in,protein synthesis or translation.Akt activates protein Rheb which triggers MTOR. MTOR interacts and actuates the translation factor S6K.By binding to the big subunit of the ribosome, S6K triggers the translation of mRNA into protein synthesis[9].

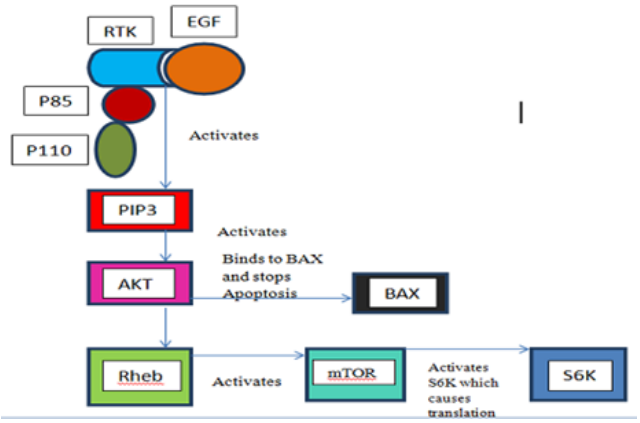

Figure 1:PKB/AKT Pathway.

The Table 1: An Activation Percentage of Akt and MTOR pathways in different types of Human Cancers

Tumor Type	% Of Tumors with active Akt pathway	% Of Tumors with active MTOR pathway
Glioma	55	40-50
Thyroid Carcinoma	80-100	61
Breast Carcinoma	20-55	26
Small Cell Lung Carcinoma	60	28
Non - Small Cell Carcinoma	30-75	36
Gastric Carcinoma	80	60-80
Pancreatic Carcinoma	30-70	20
Bile Duct Carcinoma	85	40
Ovarian Carcinoma	40-70	42
Endometrial Carcinoma	35	50
Prostate Carcinoma	45-55	40

Renal Cell Carcinoma	40	59
Anaplastic Large Cell Lymphoma	100	85
Acute Myeloid Leukemia	70	55
Multiple Myeloma	90	58
Malignant Mesothelioma	65	50
Malignant Melanoma	43-67	23

2.3. MTOR Pathway: The mechanistic target of rapamycin or the mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that monitors cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy and transcription. The pathway starts with the active Akt which is an end product of Akt pathway.

The active Akt inhibits TSC1 (Tuberous Sclerosis protein 1)and TSC2 (Tuberous Sclerosis protein 2)complex by phosphorylation. This TSC1 and TSC2 complex inhibits Rheb (Ras homolog enriched in the brain) TSC2 is GTPase activating protein(GAP).This TSC2 interacts with the Rheb-GTP complex diversifying it into idle Rheb- GDP complex. When the Akt is inhibiting the TSC1 and TSC2 complex, Rheb-GTP is free to activate MTORC1. MTOR exists in 2 complex forms,MTORC1 and MTORC2,MTORC1 contains MTOR protein, RAPTOR (it allows the mTORC1 to bind to its substrate),mLST8(It allows MTORC1 to phosphorylate its target), it also has 2 inhibitory proteins PRAS40 and DEPTOR. Activated MTOR interacts and triggers translation factor S6K.By linking to the big subunit of the ribosome,S6K actuates the translation of mRNA into protein synthesis. [10]

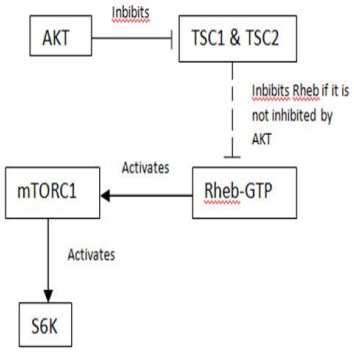

Figure 2: MTOR Pathway

2.4. The MAPK Pathway

In this pathway MAPK/ ERK (Mitogen activated protein the kinase/Extracellular signal regulated kinase)is the final product. It causes transcription and translation to occur in the cell. If it is over produced due to mutated genes then more cells are produced which causes cancer. The MAPK pathway also familiar as Ras – Raf – MEK-ERK pathway. A series of proteins in the cell communicate through a receptor on the surface of the cell to the DNA in the nucleus of the cell. Binding of the growth factor causes activation of receptor tyrosine kinase.It causes the phosphorylation of RTK.The GRB2 protein gets attached to the RTK and SOS is attached to the GRB2.The activated SOS catalysis the conversion of RAS GDP to RAS GTP. This activated RAS GTP actuates RAF.RAF actuates MEK. MEK actuates the ERK.ERK activates FOS.FOS enters the nucleus and binds to the CCND1 and causes the transcription to produce CyclinD1.Cyclin D1 plays a major role in cellgrowth,cellproliferation,cellmotility,cellsurvival,proteins ynthesis,autophagy and transcription [11].

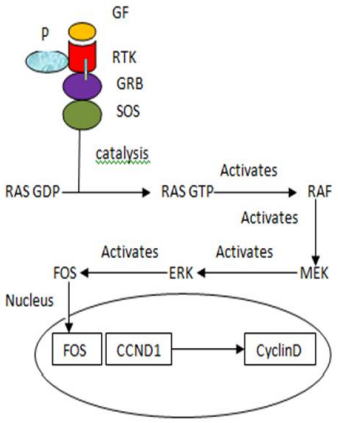

Figure 3:MAPK pathway

3. Proposed Method

Using target therapy we can apply drugs that are specified below to the exact location of the pathway (target) where it is altered. Thus they can be made to function as they function in a normal breast cell. This helps in reducing cancer. The main modification in the pathways is generally the excess production of proteins which are causing continuous cell division and in turn cancer. This excess production of these proteins can be stopped by using these drugs.

Wortmannin: Wortmannin presents antitumor activity. Wortmannin is a steroid metabolite of the fungi Penicillium funiculosum, Talaromyces wortmannii. It is a non-specific, covalent inhibitor of PI3K. It has an invitro inhibitory concentration of around 5nM; making it more powerful than any other routinely used PI3K inhibitor LY294002. It shows homogeneous potential in vitro for class I, II and III PI3K members. It can also retard other enzymes such as MTOR, DNA-PKcs, some phosphatidyl inositol 4-kinases, myosin light chain kinase (MLCK) and mitogen activated protein kinase (MAPK) at high concentrations.

Perifosine: Akt inhibitor Perifosine was used in several preclinical and clinical trials for diverse cancer types for example, prostate cancer. This drug scatters the interaction between the PIP3 and pleckstrin homology PH domain of Akt. So it avoids membrane delimitization of Akt which is very crucial for its actuation [12].

Rapamycin: It is a drug originally found in Easter Island bacteria. Rapamycin is also known as sirolimus. Rapamycin is a definite inhibitor of mTOR and functions downstream of Akt. This drug has the characteristic feature of suppressing the immune system. Because of this ability it is used in transplant rejection. Streptomyces hygroscopicus which is a soil bacterium produces Rapamycin.

4. Computational Modeling of Signal Transduction Pathways: Converting the biological pathway into a computable model helps in analyzing it rapidly using simulation and other mathematical methods. At the software level a different format is required for quantifying a model to the point where it can be simulated and analyzed.

SBML (Systems Biology Markup Language) is a programming language that can be used for this purpose. Using SBML offers many benefits such as: A) multiple tools can be used on the same model without building a different model for every tool. B) These models can be used by other researchers in a different software environment. C)
The models survive beyond the lifetime of the software used to develop them. SBML files can be run using many software environments such as Jarnac, J Designer, Cell Designer and Gepasi [13]. We used Cell Designer for running our SBML programs.

Cell Designer : Apart from SBML Cell Designer also supports other standard formats like BioPax and SBGN. Cell Designer sustains graphical notations, mathematical simulations and database connections [14].

5. Results and Discussions

Ezio Bartocci and Pietro Lio discussed the most important computational tools currently available to systems biologists in 2016[15]. They just specified the important computational tools available for systems biologists, they did not study any of the cell physiology nor did they use any of the tools for simulating any of the physiology. Whereas in this paper apart from specifying some of the computational tools that can be used we also studied the breast cancerous cell physiology in depth and identified some physiological aspects that can be modeled using computational tools we identified 2 tools that can be used that are SBML and Cell Designer and we used them effectively. Maria and John focused on the use of Computational modeling to the analysis of biochemical systems [16]. Maria and John used computational modeling to study the pathways in detail but they did not specify the deviations caused in them due to cancer. They did not specify the targets in the pathway where drugs can be used to convert them into normal pathways.

Whereas in this paper we are not only doing computational modeling of the pathways, but we also specified the deviations in the pathways and explained how they are becoming the root cause for cancer. We are specifying targets in the pathway where the drugs can be used to convert them into normal and reduce cancer. Liviqni A and O Hara developed a graphical model scheme which facilitates building of comprehensive network diagrams, abridging the constituents of the biological pathways and illustrating how they interact [17]. Liviqni A and O Hara concentrated only on the molecules involved in the pathway. They wanted to clearly show all the molecules that are involved in the pathway and clearly show their interaction using the graphical model but there is no further work on the pathway. This is exactly what we are doing in our paper studying the deviations of the pathway in a breast cancerous cell and identifying how it can be modified. Koh Yeow and Geoffrey used Petri Net to model the AKT pathway and its interactivity with ERK cascade [18]. Petri nets are used to represent the chemical reactions in the cells in the form of places, transitions and arcs. This forms a graphical representation of the chemical reaction and they developed a mathematical notation from it. But they used only one single pathway, whereas in our paper we described 3 pathways in detail and we modeled totally 8 pathways.We studied the pathways that are altered in the breast cancer cell and we developed computational models for them using SBML and Cell Designer.In figure 5, the simulated PKB pathway in cell designer was presented. The PKB pathway program written in SBML is executed in cell designer and it can be observed in figure 5.

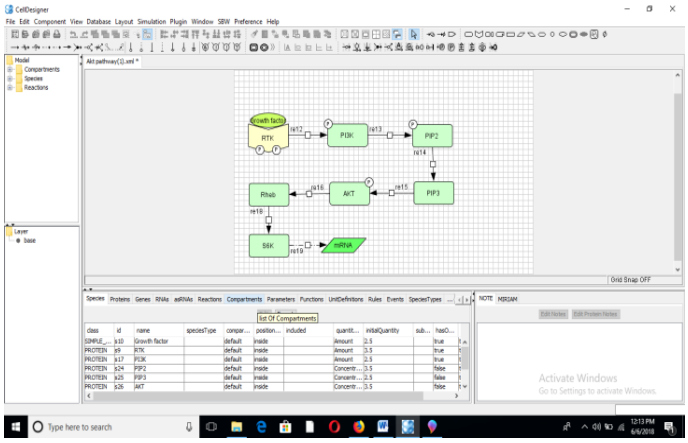

Figure 5: PKB/AKT Pathway in Cell Designer: The Simulated PKB/AKT pathway in cell designer. The PKB/AKT pathway program written in SBML is executed in cell designer.

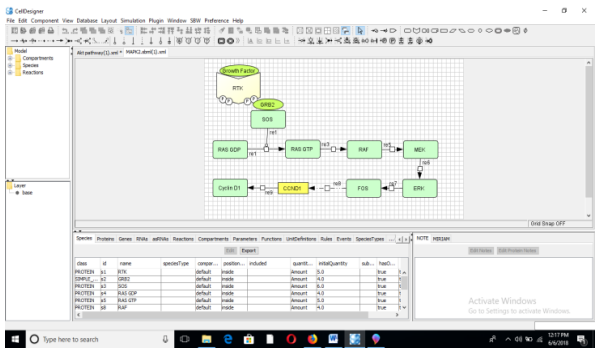

Figure 6: MAPK Pathway in Cell Designer: The Simulated MAPK pathway in cell designer. The MAPK pathway program written in SBML is executed in cell designer.

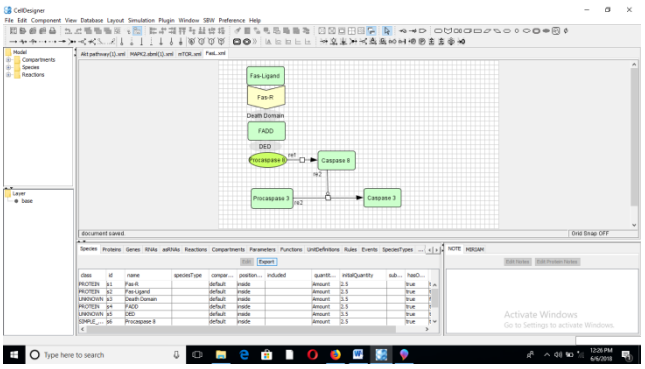

Figure 7: FasL Pathway in Cell Designer: The Simulated FasL pathway in cell designer. The FasL pathway program written in SBML is executed in cell designer.

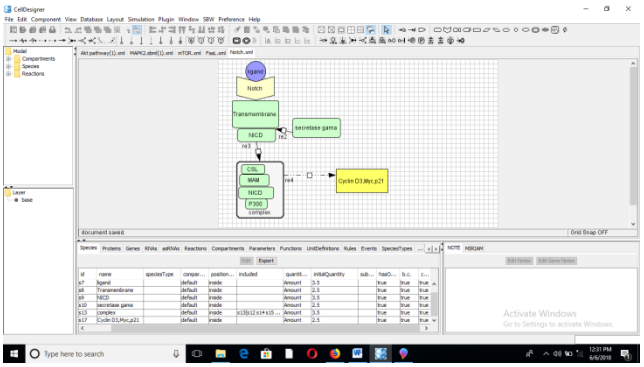

Figure 8: Notch Pathway in Cell Designer: The Simulated Notch pathway in cell designer. The Notch pathway program written in SBML is executed in cell designer.

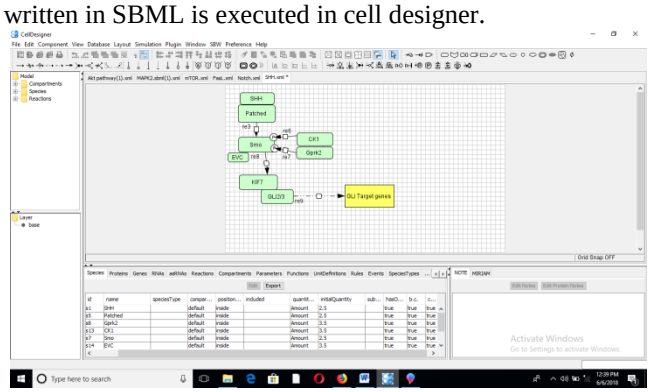

Figure 9: SHHPathway in Cell Designer: The Simulated SHH pathway in cell designer. TheSHH pathway program written in SBML is executed in cell designer.

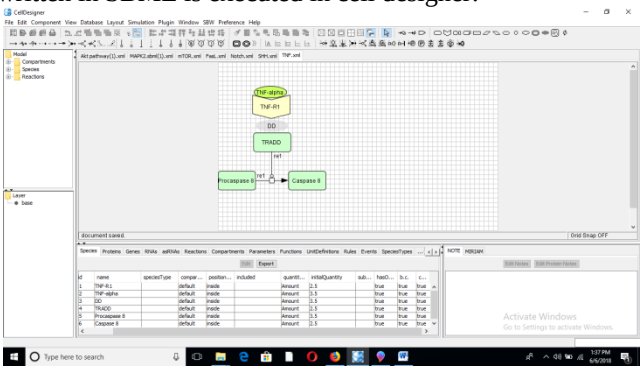

Figure 10: Tnf Pathway in Cell Designer: The Simulated Tnf pathway in cell designer. The Tnf pathway program written in SBML is executed in cell designer.

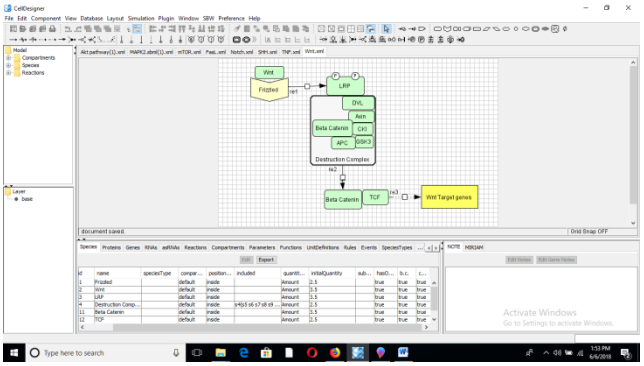

Figure 11: Wnt Pathway in Cell Designer: The Simulated Wnt pathway in cell designer. The Wnt pathway program written in SBML is executed in cell designer.

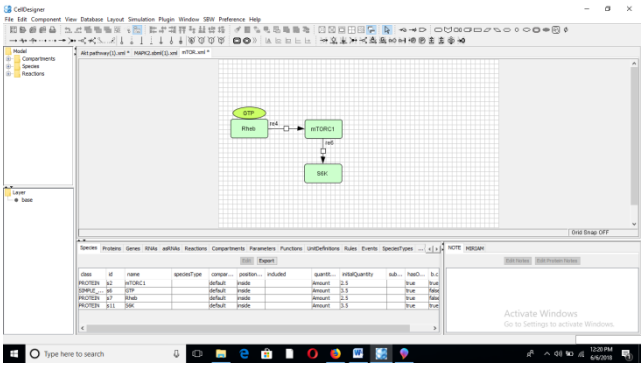

Figure 12: MTOR Pathway in Cell Designer: The Simulated MTOR pathway in cell designer. The MTOR pathway program written in SBML is executed in cell designer.

6. The Conclusion:

The complete study of the signal transduction pathways which are mutated because of breast cancer helps researchers to study the morphology of the breast cancerous cell better and they can start to work to change the morphology of the breast cancerous cell into a normal breast cell, in spite of starting from the beginning of how the pathway actually works and what is the deviation. Computational modeling of these pathways helps in making this data readily available to them in a format where the exact locations where the pathways are deviated are specified. The drugs specified in this paper helps in reducing cancer.

7. Future Work: We are aiming at creating a database of all the transformed breast cancer cell pathways. We are further going to form a bio grid with all the pathways. We are also looking forward to use data mining techniques to store and retrieve the XML files.

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