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An Algorithm for Optimizing Anticancer Treatment

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***Abstract*—*In the past few decades, many anticancer drugs were discovered and developed, nowadays, the newer chemotherapeutic agents were being continually introduced. This is good news for cancer patients, but it puts a much burden on the physician. It is difficult for physicians to recommend drugs with the best efficacy for cancer patients with long experience. Therefore, an algorithm that recommends optimal drugs is needed. It is the best drug to have good sensitivity and low resistance to cancer patients. Algorithm should be designed based on Big Data about sensitivity correlation coefficient and resistance correlation coefficient. For optimal drug prediction, it is necessary to go through several complex layers. The DBN model is more suitable than the ANN model*.

***Keywords*—** *Chemotherapy, Chemical Drug, Anticancer Drugs, Artificial Neural Networks(ANN), Deep Belief Networks (DBN), Correlation Coefficient*.

I. INTRODUCTION

Drug development currently remains an expensive and time-consuming process with extremely low success rate, it typically takes 10–15 years and $800 million–1 billion to bring a new drug to market[1]. This is one of the reasons for the need for effective drug use in cancer treatment. Today, there are many treatment options available to doctors. Chemotherapy is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer, which is called medical oncology. There are the first-generation, chemical drugs, second-generation, target anti-cancer drugs, and third-generation, Immune-cancer drugs in chemotherapy. Advances in cancer immunotherapy are the result of several decades of basic research. Now, many clinical trials are performing in attempts to treat cancer with wild-type or naturally attenuated viruses[2]. Due to too many anticancer drugs, it is difficult to find which drug is the most effective treatment. The optimal treatment options will play a pivotal role in saving lives. The time given to cancer patients is very short. It is the role of the physician to prescribe optimal therapeutic drugs. The physician has to find the optimal drugs on the many therapeutic drugs, the clinical experience alone is not enough. Now, we are in the age of artificial intelligence processing big data to provide useful information. The medical field is no exception. Artificial intelligence physician, Watson, offers drug prescription solutions in addition to cancer diagnosis. It needs an algorithm to recommend the optimal drug for type and stage of each cancer.

II. BASIC ARCHITECTURE FOR OPTIMIZING TREATMENT

During oncogenesis, gene mutations or expression changes accumulate in some pathways regulating specific aspects of cell proliferation. Cancer-related pathways allow cells to grow and divide unchecked including apoptosis, cell cycle, DNA damage repair, and growth factor responses[3]. These pathways play important roles in cell response to chemotherapy drugs.

TABLE 1. List of Chemotherapy Drugs[4,5,6].

Family	Drugs	Target	Remark
Nitrogen Mustard	Chlorambucil,	Interstrand cross-link.	DNA adducts
	Melphalan,	Interstrand cross-link.	DNA adducts
	Cyclophosphamide.	Interstrand cross-link.	DNA adducts
	Ifosfamide	Interstrand cross-link.	DNA adducts
Aziridines,	Triethylenemelamine,	Interstrand cross-links, Monofunctional adducts	DNA adducts (A-G, G-G)
	Triethylenethiophosphoramide (thio-tepa)	Interstrand cross-links, Monofunctional adducts	DNA adducts (A-G, G-G)
	Mitomycin C	Interstrand cross-links, Monofunctional adducts	DNA adducts
	Hexamethylmelamine (Altretamine)	Interstrand cross-links, Monofunctional adducts	DNA adducts
Alkyl Sulphonates	Busulphan	Interstrand cross-links	DNA adducts
Nitrosoureas	CENUs (2chloroethylnitrosoureas).	Interstrand cross-links	DNA adducts
	BCNU (carmustine).	Interstrand cross-links	DNA adducts
	CCNU (lomustine),	Interstrand cross-links	DNA adducts
	Methyl-CCNU (semustine)	Interstrand cross-links	DNA adducts
	Chlorozotocin	Interstrand cross-links	DNA adducts
PLATINUM-BASED AGENTS	Cisplatin	monofunctional DNA adducts	DNA adducts
	Carboplatin	monofunctional DNA adducts	DNA adducts
	Oxaliplatin	monofunctional DNA adducts	DNA adducts
	Pyriplatin	monofunctional DNA adducts	DNA adducts

Chemical drugs are the first line in cancer treatment. Chemotherapy is accompanied by many side effects, but it has

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the advantage of directly attacking cancer cells. Cancer patients want the most effective drug among various chemical drugs.

Many genes are overexpressed in cancer cells. When an anticancer drug is administered, cancer cells react in two forms. One is Sensitivity. The other is resistance[4]. Sensitivity means that growth of cancer cells is inhibited. Resistance means promoting the growth of cancer cells.

When radiation or ROS (Reactive Oxygen Species) attacks normal cells, DNA in the nuclear membrane is damaged. Likewise, cancer cells are also attacked by chemicals, damaging DNA in the nuclear envelope. In Table 1, we can see the type of chemical attack of cancer cells. There are two main ways in which chemicals can attack cancer cells. One is to prevent replication by the bases linking complementary base pairs with drugs, the other is that the drug binds to one side of the base to prevent replication[7]. From the perspective of cancer cells, chemical drugs are enemies that destroy their DNA. Currently, about 130 chemical drugs are applied in clinical hospitals. In practice, there are at least five to twenty chemical agents corresponding to one cancer. However, for the algorithm design, it is assumed that there are 120 chemical drugs as shown in Table 2, and 5 chemicals are prescribed for each cancer in the progress stage.

TABLE 2. Anticancer Drugs Lists on Cancer Types.

Stage/Type	Breast Cancer	Colon Cancer	Lung Cancer	Liver Cancer	Blood Cancer	Brain Cancer
Stage 1	1-5	6-10	11-15	16-20	21-25	26-30
Stage 2	31-35	36-40	41-45	46-50	51-55	56-60
Stage 3	61-65	66-70	71-75	76-80	81-85	86-90
Stage 4	91-95	96-100	101-105	106-110	111-115	116-120

* Chemical drugs: No.1 - No.120

At this time, if a patient is stage 2 breast cancer, the physician prescribes one of five chemical drugs. In practice, two or more drugs are prescribed. However, the physician cannot know in advance the sensitivity and resistance of each drug to the patient. A life-threatening patient must take his fate into the physician's experience. This is why we need prescription algorithms for patients. If the physician knows in advance the sensitivity and resistance of the chemical to the patient, the physician can prescribe the optimal treatment. Chemical drugs do not always remove 100% cancer cells. Chemical drugs damage DNA of cancer cells. This is because chemical drugs attack DNA directly. Cancer cells react the same way as normal cells if DNA gets damaged. The DNA repair pathway is activated by recognizing DNA damage. Also, the cell cycle is stopped[8]. By the activity of DNA repair proteins, DNA can restore the original double helix structure. If the recovery failed, it enters the cell death pathway. If the activity of the cell apoptosis pathway is strong, it can be judged that the drug is sensitive to the chemical. Conversely, if the activity of the cell proliferation pathway remains the same despite the injection of the chemical, it can be judged that the drug is resistant. There is a criterion for judging the sensitivity of chemical drugs. In other words, Drug sensitivities are evaluated by the half maximal inhibitory concentration (IC_{50}) relative to the control[9]. Drug sensitivity is judged by whether the growth of cancer cells is reduced. Compared to before and after injecting the drug, if the size of the cancer cells is reduced, it is sensitive. If the size of the cancer cells is the same, it is resistant. The sensitivity of cancer cells to chemicals means that they are smaller than the size of cancer cells before drug treatment. It needs to know the genes that are involved in drug sensitivity. These include cell cycle arrest genes and cell apoptosis genes, respectively. p21, p53, and RB are the cell cycle arrest genes[10]. MGMT, MSH2, and TDP1 are genes involved in DNA repair. Caspase-3 and p53 are genes involved in apoptosis[10]. It is assumed to be gene group 1 in Table 3, the genes responsible for DNA damage, gene group 2 in Table 3, genes for repairing DNA damage, and gene group 3 in Table 3, genes involved in cell apoptosis. Based on the sensitivity test results for chemical drugs administered to patients with stage 2 breast cancer, Table 3 below was established with the binary algorithm. Cancer cells can be extracted through histological examination of cancer patients. When the cancer cells are administered in vitro, drug sensitivity of the gene group in Table 3 can be determined. For example, when the drug 34 in Table 3 was administered, Compared to the control group, the expression levels of gene group 1 and gene group 3 were 30% or more and the expression level of gene group 2 were 10% or more. On the other hand, when the drug 31 was administered, the gene group 1 involved in the cell cycle arrest showed no response. In the end, the doctor should administer drug 34, which is sensitive to breast cancer stage 2 patients.

TABLE 3. Anticancer Drugs Sensitivity on Stage 2 Breast cancer.

Sensitivity	Drug 31	Drug 32	Drug 33	Drug 34	Drug 35
Gene Group 1	1000	1000	0100	0001	0001
Gene Group 2	0100	1000	0100	0010	0010
Gene Group 3	0100	0100	0010	0001	0010

* There is no difference to control group: 1000
* the gene expression level was increased by less than 10% to the control group: 0100
*The gene expression was increased by 10% or more but less than 30% to the control group: 0010
* The gene expression was increased by more than 30% to the control group: 0001

On the other hand, cancer cells are also resistant to bacteria. Cancer cells have many options to defend against chemical attacks. Cancer cells have a gene to export drugs to the extracellular matrix[11]. When one proliferation pathway is blocked, it expresses a gene that activates a bypass pathway or expresses a gene that induces the activity of another pathway, thereby maintaining its survival[11]. Cancer often results when normal cellular growth goes away due to alterations in critical signal transduction cascades. Complex interactions between the TGF-β, Wnt, Hedgehog (Hh), Notch, mitogen-activated protein kinase (MAPK), Ras, and signal transducers and activators of transcription (STAT) signaling pathways play key roles in the transmission of proliferation, differentiation, migration, and survival signals (Table 4)[12]. Dysregulation of these pathways in the form of driver mutations is often found in the cancer cell. When cancer cells are attacked by chemicals, cancer cells become resistant by switching on

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special survival genes when they sense danger. They express various genes involved in natural resistance. The following genes, genes that prevent DNA damage by chemical drugs, genes that repair DNA damage by chemical drugs, and genes that induce cell apoptosis inhibition are expressed. Genes involved in the release of chemical drugs, genes involved in the degradation of chemical drugs, and genes that induce changes in the proliferative pathway are genes that make acquisition resistance. Acquired resistance is said to occur when a cancer cell obtains the ability to resist the activity of chemical drugs to which it was previously sensitive. When a chemical is administered to a cancer cell, the cancer cell promotes the expression of various genes for survival. Resistance is the biggest barrier to drug therapy[13]. The process of finding the lowest resistance among the various drugs for cancer patients is essential as a process for finding highly sensitive drugs. Each drug has a different resistance pattern. Resistance is negative variables expressed as a Pearson correlation coefficient, positive variables to the chemical drugs indicate sensitivity[14]. Conversely, the negative variable is a measure of resistance[14]. Table 4 shows several pathways in which cancer cells proliferate. The genes that are active for each path are different. Cancer cells are active in at least one of the seven pathways in Table 4. At this time, the chemical agent impacts the proliferation pathway in the active state. Cancer cells make a bypass path to maintain the active state of the proliferation pathway. If this is not possible, it induces the activity of other proliferation pathways. All of the genes shown in Table 4 synthesize adapter proteins involved in cancer cell proliferation.

TABLE 4. Cancer Pathways and Driver Genes[15,16].

Pathway	Gene 1	Gene 2	Gene 3	Gene 4
[1] MAPK	RAS	BRAF	MEK	ERK
[2] NF-kappa B	TRAF	IRAK	TAB	IKK
[3] TGF-beta	TAB	PI3K	SMAD	AKT
[4] NOTCH	PSE2	PSEN	CSL	APH1
[5] WNT	PIP5K1	GSK3	APC	Rac
[6] JAK-STAT	TYK	JAK	STAT3	STAT3
[7] HEDGEHOG	GSK3	SUFU	GLI1	GLI2

* Gene 1-5: Adapter Proteins. * Driver gene encodes adaptor proteins

The resistance correlation coefficient of the cancer cells to the drug can be known from drug experiments in vitro. Using a cDNA microarray kit and real-time RT-PCR, the expression level of genes involved in resistance can be measured. The resistance correlation coefficient is denoted by -(minus value) since it means a negative variable[17].

TABLE 5. Anticancer Drugs Acquired Resistance to Stage 2 Breast cancer[15,16].

Resistance	Gene 1	Gene 2	Gene 3	Gene 4
Drug 31	GSK3[001]	SUFU[001]	GLI1[001]	GLI2[001]
Drug 32	TAB[010]	PI3K[001]	SMAD[001]	AKT[001]
Drug 33	PIP5K1[100]	GSK3[010]	APC[001]	Rac[001]
Drug 34	RAS[100]	BRAF[010]	MEK[100]	ERK[100]
Drug 35	TYK[010]	JAK[001]	STAT3[001]	STAT3[001]
The resistivity correlation coefficients -0.2 or less: 100 The resistivity correlation coefficients -0.4 or less: 010 The resistivity correlation coefficients -0.5 or above: 001				

The results of the chemical resistance test for stage 2 breast cancer patients are shown in Table 5. Drugs 31, 32, 33, and 35 show that the resistivity correlation coefficients are all above -0.5. On the other hand, Drug 34 has the highest resistance correlation coefficient of -0.4 and the remainder of all -0.2 or less. Drug 34 is relatively less resistant than other drugs. Drug 34 is optimal given the resistance correlation coefficient. Many clinical cases are needed to know precisely the resistivity correlation coefficient for chemical drugs. Through this, the accumulation of the big data enables to know the resistance correlation coefficient for each chemical agent in advance. Experiments with sensitivity and resistance to cancer cells from tumors can find the optimal chemical drug. However, the longer the frequency and duration of the same drug, the greater the acquisition resistance that was not initially present in cancer tissue[18]. Repeated administration of the same antibiotic is equivalent to antibiotic resistance. Acquired drug resistance is a major limitation for the successful treatment of cancer**.** Acquired resistance may arise readily after short periods of treatment, or gradually as a result of treatment over prolonged periods. Table 6 shows the time to appear acquisition resistance for the five drugs that can be used in patients with stage 2 breast cancer. Table 6 shows the algorithm binary on the duration of acquisition resistance after administration of the chemical. Of course, this is not the result of actual experiments. The mean variables can be counted if the big data on the acquisition time of resistance can be obtained through the experiment of acquisition resistance. Based on this, an optimal treatment strategy can be developed.

TABLE 6. Optimizing Treatment Strategy to Minimize Acquired Resistance to Stage 2 Breast cancer.

Acquisition period	Drug 31	Drug 32	Drug 33	Drug 34	Drug 35
[1] within 8 weeks					
[2] within 16 weeks	01000		01000		
[3] within 32 weeks				00100	
[4] within 48weeks		00010			
[5] within 60 weeks					00001
* When resistance appears within 8 weeks: 10000 *When resistance appears within 16 weeks: 01000 *When resistance appears within 32 weeks: 00100 *When resistance appears within 48weeks: 00010 *When resistance appears within 60weeks: 00001					

If physicians know in advance the acquisition period of drug resistance, they will get another treatment option. Currently, drug therapy for cancer patients is going beyond the chemical drugs to targeted cancer therapy. December 2017, the target chemotherapeutic agent is in charge of the second treatment[19]. Even if cancer cells have high sensitivity to chemical drugs, cancer cells themselves do not die 100%. Thus, a molecular target anti-cancer drug is necessary to remove cancer cells with acquisition resistance. Molecular targeted anti-cancer drugs are an essential option in cancer patients. The molecule-targeted anticancer drug needs gene mutation testing. Table 7 shows the options for prescribing Molecule-targeted anticancer drugs according to the results of

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gene mutation tests in breast cancer patients. In particular, when there are two or more mutations in the genes, big data are needed for building a therapeutic combination of targeted anticancer drugs. Molecule-targeted anticancer drugs are drugs that attack receptor, domain, and adapter proteins, respectively, in the growth pathway of cancer cells. Genes that participate in the growth pathway of cancer cells are called driver genes, Genes that are independent of the proliferation pathway are called passenger genes[20].

TABLE 7. Molecular Targeted Anticancer Drug Option on Stage 2 Breast cancer.

Target Gene	BRCA1 Wild-type(11)	BRCA1 Mutation(10)
HER 2 Wild-type(00)	0011	0010
HER 2 Mutation(01)	0111	0110
*Trastuzumab(Herceptin) : 0011 * Olaparib(Lynparza) : 0010 *Neratinib. : 0111		

Genetic mutation testing for cancer patients is helpful in treatment strategies, but it also hints at new drug development. Among breast cancer patients with the same genetic mutation (BRCA1 mutation), there are a group of patients A group

who respond to targeted chemotherapy, and patients B group who don't respond to targeted chemotherapy. If most of the B group of patients have mutations in the MEK gene, it is possible that the MEK gene is a driver gene that leads to the proliferation of cancer cells. This is a hint to try the development of a targeted anticancer agent corresponding to the MEK mutation.

III. An Algorithm for Optimizing Treatment

Artificial Neural Networks (ANN) and Deep Belief Networks (DBN): The more chemical drugs, the more doctor's choice. Clinical experience alone can't provide optimal treatment for cancer patients. Deep learning is needed to analyze big data on chemical sensitivity and resistance in real time[21]. The most common deep-running model is ANN (Artificial Neural Network). To analyze big data, it is necessary to construct Data Warehousing Software which stores and manages big data. The ANN model is an auto-encoder deep running. Auto-Encoder is a tool that improves accuracy through pre-training, the deep learning method to use the weight in the auto-encoder is a back-propagation (BP) algorithm[22]. The BP algorithm principle is simple. It is calculated the value by assigning a weight between the input layer(unit) and the hidden layer(unit), put the value into the sigmoid function. Again, based on the median value, give weights between the hidden unit and output unit to obtain the estimated values[23]. This output value is continuously compared with the initial data value to update the error[23]. Recently, DBN (Deep Belief Network) model has improved the disadvantages of Auto-Encoder[24]. DBN is a deep running of a stacked auto-encoder method. DBNs are formed by stacked RBM (Restricted Boltzmann Machines)[24]. Deep belief network consists of multiple layers of RBMs trained in a greedy, layer-by-layer way. Recently DBN with RBM models are successfully applied to a wide range of classification tasks[24]. RBMs, which are used as important learning modules for constructing deep belief nets, have been successfully applied in many fields, such as classification[25]. An RBM is a two-layer graphical model that can be used to learn a probability distribution over input data[25]. An RBM consists of a layer of visible units and a layer of hidden units[25]. Each visible unit is connected to all hidden units, and no intra-layer connection exists between any pair of visible units or any pair of hidden units[26]. There is evidence that adding more layers helps in classification tasks. RBMs are stochastic generative neural networks that can learn probability distributions over a set of their input vectors[26]. The main consequence of this definition is that such a neural network learns p(data) instead of p(label | data) – essentially these models are modeling data, not labels[26]. This allows us to deal with unlabelled or partially labeled data[26]. The AE learns the weight by using BP, but the more the layer is, the larger the weight learning and the less accurate. DBN is the model to improve this. DBN is a useful model when the amount of data is large or complex[26]. The idea was to cleverly train RBM on a training vector, then after finishing the training process to use the first RBM hidden layer neuron activations as input for a visible layer of the second stacked RBM to train it and continue this procedure for all subsequent layers[27]. When overall training is performed, the found network weights can be fine-tuned with a regular Error Back Propagation algorithm[25]. The ANN model requires a hidden layer, where X = data and Y = label, However, in DBN model, label (correct answer) can be created in layer even if only X = data[27]. In other words, since Input and Output are not required in Training Data, it is optimal for Unsupervised Learning. The DBN model is an algorithm for calculating the joint probability of several random variables[27]. Assuming that there are two variables X1 and X2, the conditional probability can be obtained by using an X1 variable as the change value and X2 as the fixed value. The condition value can then be obtained in reverse order. By repeating this process, we can obtain the joint probability. To analyze and predict complex variables, one layer is insufficient, and several layers are needed. It is DBM (Deep Boltzmann Machine) to apply RBM model to each layer. In other words, DBM is a multilayer neural network constructed by superimposing RBMs[28]. If there are multiple layers, the bottom layer is the input layer, and the final layer is the output layer. The middle layers are the hidden layers. Data is injected into the input layer. The value obtained by applying RBM to the input layer enters the hidden layer again. The value obtained by applying RBM to the hidden layer is a medium value. Finally, the values from each layer are probability values. DBM is a model for pre-learning in the Unsupervised Learning method with no label[28]. Then, fine-tuning is done by BP-based supervised Learning[29]. RBM model can be used as a highly powerful tool for predicting optimizing drug with high accuracy[30].

Applications of Deep Belief Networks (DBN): There are some steps involved in administering the optimal drug for cancer patients. First, Physician should make a list of approved drugs for each type of cancer. Here, he needs to find drug options that can be administered according to the cancer stage (Table 1). For example, to find the optimal drug for stage 2 breast cancer, it needs to select the drugs with the highest sensitivity

among drugs 31, 32, 33, 34, and 35. It is assumed that there are 21 genes involved in sensitivity. In detail, it is assumed that the number of genes involved in cell cycle arrest (gene group A), DNA repair (gene group B), and cell death (gene group C) are 7 each. Candidate drugs are administered to cancer cells extracted from cancer tissues of stage 2 breast cancer patients, and mRNA expression levels of the sensitivity genes are measured. And the sensitivity correlation coefficient is measured based on this. Gene group A and B, rather than gene group C, are key determinants of the sensitivity of candidate drugs. Gene group C is directly involved in the cell death of cancer cells. When the RBM model is applied to determine the optimal candidate drug for stage 2 breast cancer patients, first, it enters each gene into 21 units of the input layer (layer 1) as below Table 8. The genes involved in DNA repair do not have a positive impact on the sensitivity. DNA repair helps cancer cells survive. Genes involved in DNA repair are not factors that directly affect the sensitivity.

TABLE 8. Gene Group List: Layer 1.

Gene Group A	Gene Group B	Gene Group C
Gene A1	Gene B1	Gene C1
Gene A2	Gene B2	Gene C2
Gene A3	Gene B3	Gene C3
Gene A4	Gene B4	Gene C4
Gene A5	Gene B5	Gene C5
Gene A6	Gene B6	Gene C6
Gene A7	Gene B7	Gene C7

Among the gene groups A, B, and C, When the candidate drug is administered to cancer cells, the mRNA expression level expressed in each gene group is measured. Table 9 assumes measured values. Table 9 below shows the comparison with the control group.

TABLE 9. Quantification of Transcriptome on Each drug: Layer 2.

	Gene Group A	Gene Group B	Gene Group C
Drug 31	1.2	1.3	1.2
Drug 32	1.2	1.3	1.2
Drug 33	1.2	1.4	1.1
Drug 34	1.2	1.3	1.5
Drug 35	1.2	1.2	1.1

In Table 9, Drug 34 has the highest expression level of genes involved in apoptosis. Here, it is possible to test the gene that has the greatest influence on the sensitivity among the seven genes involved in apoptosis. Seven candidate genes are knocked out in turn, and the size of cancer cells following drug 34 administration is measured. (Table 7). Gene 7 has the greatest effect on cell death, followed by gene 6 (Table 7). Therefore, the expression level of genes 6 and 7 should be carefully observed in determining the sensitivity of the candidate drug. It is not always correct to administer candidate drug 34 for patients with stage 2 breast cancer. If the expression level of genes 6 and 7 is too low in some stage 2 breast cancer patients, the effect of apoptosis is less than expected. When the RBM model is applied to the sensitivity test results of the candidate drug, the accuracy of sensitivity determination is increased by weighting the results of the genes 6 and 7.

TABLE 10. Quantification of Apoptosis Gene Transcriptome on Drug 34: Layer 3.

Drug 34	Knockout Gene	Before(Tumor Size)	After((Tumor Size)
K-100	Control	1.00	0.40
K-101	Gene 1	1.00	0.80
K-102	Gene 2	1.00	0.75
K-103	Gene 3	1.00	0.90
K-104	Gene 4	1.00	0.70
K-105	Gene 5	1.00	0.85
K-106	Gene 6	1.00	0.65
K-107	Gene 7	1.00	0.55

* Cancer cell lines from K-100 to K-107 were extracted from cancer tissues of stage 2 breast cancer patient.
* It is assumed that the size of the control cell line is 1.0.

Now, we can apply the RBM model to the fourth layer (Layer 4) based on the resistance correlation coefficient. The resistance referred to here is not acquisition resistance but natural resistance. Genes that protect DNA damage and genes that inhibit cell apoptosis are important factors for resistance. The resistance correlation coefficient can be obtained by measuring the expression levels of the resistance genes for each candidate drug. In particular, the attention must be paid to the expression levels of genes involved in cell apoptosis. The fifth layer (Layer 5) is the application of the RBM model based on the acquisition resistance that the cancer cells will have after the candidate drug has been administered. Chemical drugs to cancer cells is very strong stress. Cancer cells repel very strongly against chemicals. This appears to be an acquisition resistance. Understanding at what time cancer cells have acquired resistance to chemical drugs is a very important factor in cancer treatment. Administration of the targeted anticancer drugs should be initiated before achieving acquisition resistance. Or simultaneous administration should be considered. Even with the same drug, the timing of acquisition resistance differs among cancer patients. It needs Big data about the timing of acquired resistance in cancer patients. This is to know when to stop chemical drugs. Finally, after the administration of candidate drug 34 for stage 2 breast cancer patients, a feedback check is needed to see if the sensitivity and resistance are as predicted. The BP method of the ANN model is applied here. Based on an arithmetic way, a sensitivity score and a resistance score is calculated for each cell line-drug pair. The final score for each cell line-drug pair is obtained by subtracting the sensitivity score from the resistance score. The final score is used to assess the likelihood that the cell line is sensitive to the drug. The final score differs from patient to patient on the same drug. For Drug 34, when predicted value differs from the actual value, we should find out another reason. Verify the main factor that causes the difference and modifies the potential value of each layer based on that factor. This is a weight change process. Using the DBN and ANN algorithms, the more stage 2 breast cancer patients receiving drug 34, the higher the accuracy of the drug prescription.

IV. Conclusion

On above, the algorithm has been tested on direct and indirect drug-DNA relationships, it is general and can be easily extended to integrate other types. The current version of

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our prediction algorithm only considers connections between drugs and DNA. In the future, we will extend our approach to exploit the connections between drugs and proteins.

Additional Information

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