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Full Length Article

AI-driven Q-learning for personalized acne genetics: Innovative approaches and potential genetic markers

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ABSTRACT

Genetic markers for acne are being studied to create personalized treatments based on an individual's genes, and the field is benefiting from the application of artificial intelligence (AI) techniques. One such AI tool, the Q-learning algorithm, is increasingly being utilized by medical researchers to delve into the genetics of acne. In contrast to previous methods, our research introduces a Q-learning model that is adaptable to diverse sample groups. This innovative approach involves preprocessing data by identifying differentially expressed genes and constructing gene-gene connectivity networks. The key advantage of using the Q-learning model lies in its ability to transform acne gene data into Markovian domains, which are essential for selecting relevant genetic markers. Performance evaluations of our Q-learning model have shown high accuracy and specificity, although there may be some sensitivity variations. Notably, this research has identified specific genes, such as CD86, AGPAT3, TMPRSS11D, DSG3, TNFRSF1B, PI3, C5AR1, and KRT16, as being acne-related through biological verification and text data mining. These findings underscore the potential of AI-driven Q-learning models to revolutionize the study of acne genetics. In conclusion, our Q-learning model offers a promising approach for the selection of acne-related genetic markers, despite minor sensitivity fluctuations. This research highlights the transformative potential of Q-learning in advancing our understanding of the genetics underlying acne, paving the way for more personalized and effective treatments in the future.

1. Introduction

Acne, a common skin problem affecting people of all ages, has emerged as a significant public health challenge. It boasts a global prevalence rate of 9.38 %, as reported by the Global Burden of Disease Study 2010 [33]. The comedones, papules, pustules, and, in severe cases, cysts and nodules characterize this multifaceted skin condition.

The European Union (EU) has been actively engaged in developing regulations and guidelines to govern the implementation of AI in healthcare to ensure patient safety, data privacy, and ethical considerations are upheld [31]. By adhering to these regulations and ethical guidelines, stakeholders in the medical field can harness the potential of AI technology while upholding legal and ethical standards. AI has had a significant impact on the field of dermatology, particularly in addressing acne and skin health concerns. By utilizing AI-powered image recognition and analysis tools, dermatologists can efficiently identify various acne lesions, assess their severity, and monitor their progression over time [11]. These AI systems process extensive visual data from patient images and clinical studies, aiding in early diagnosis and personalized treatment planning for individuals affected by acne.

Genetics has emerged as a crucial factor in determining an individual's predisposition to acne [1,37,10,29]. AI and machine learning algorithms are instrumental in analyzing large-scale genetic data to identify potential genetic markers associated with acne susceptibility.

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Through the use of AI, researchers can navigate through vast genomic information more effectively, revealing valuable insights into the genetic foundations of acne.

Discovering these genetic markers through AI-driven research can enhance our understanding of acne's origins and open doors to personalized treatment approaches. With AI's assistance, dermatologists can potentially tailor acne treatment plans based on an individual's genetic predisposition, optimizing therapeutic outcomes, and minimizing adverse effects. This intersection of dermatology, genetics, and AI holds promise for advancing our ability to manage and treat skin conditions like acne effectively.

Scientists studying acne have looked for genetic markers, without considering how diverse people can be. In the past, more studies focused on identifying genetic markers related to acne by examining DEGs via the weighted gene co-expression network analysis (WGCNA) [5,18]. However, these methods have limitations because they rely on co-expression for gene functional inference. Genes with similar expression profiles have different functions or inconsistencies that arise from regulation and post-transcription, so this approach may not be useful.

The core issue lies in the rigidity of these methods, which approach genetic marker identification and may overlook significant heterogeneity. To address this, some researchers have proposed a more dynamic approach by leveraging reinforcement learning models, such as Q-learning. This dynamic approach considers the sequential nature of Markov Decision Processes (MDPs) to optimise active feature selection policies [13,14,30].

This research confronts the primary challenge of elucidating the interaction between genes and the actions of reinforcement learning agents without biological traits. These traits encompass various aspects, such as acne progression, mutations, copy number variations, and mRNA levels. The reinforcement learning model aims to optimise policies based on states reflecting action quality. Since a Markov decision process involves sequential actions with consequences unfolding over subsequent steps, immediate outcomes remain elusive. Moreover, gene expression data comprises numerous genes, including irrelevant ones that can negatively impact classification accuracy. The demand for biomarker testing, especially in cancer treatment and drug discovery, is increasing. Unfortunately, methodologies for processing acne gene expression data for reinforcement learning models remain limited. Therefore, this research addresses the lack of standardised data preprocessing when applying the Q-learning model to acne gene expression data. This method aims the model to learn from gene expression data and select informative genetic markers linked to acne. Furthermore, the ethical considerations surrounding medical AI emphasise the need for transparency in AI algorithms, accountability for decision-making processes, and the importance of human oversight in healthcare settings [31]. Ethical guidelines such as those outlined in the EU's Ethics Guidelines for Trustworthy AI are essential for ensuring that AI in

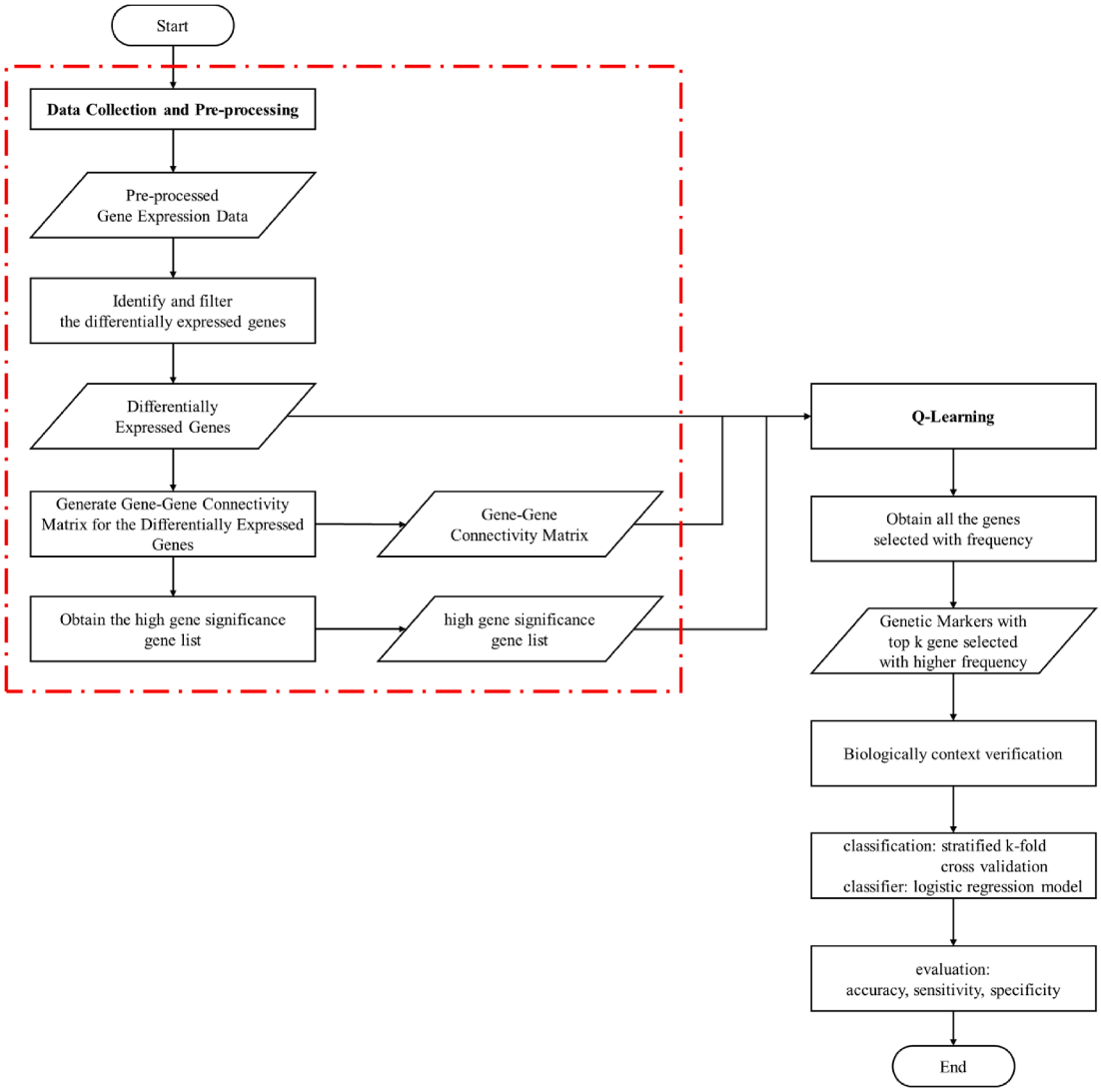

Fig. 1. Framework of the proposed method.

medicine upholds fundamental rights and values.

This study aims to show how Q-learning can improve the selection of genetic markers linked to acne. By harnessing the adaptability of this algorithm, the research aims to enhance the precision and specificity of marker identification while considering the subtle variations among different patient groups. This research aims to improve acne treatment by personalising it, leading to a breakthrough in acne genetics research.

2. Materials and methods

Fig. 1 presents the framework of the proposed method including data pre-processing and Q-learning.

2.1. Data collection and pre-processing

In our quest for knowledge about acne genetics, we delve into GSE108110, GSE53795, and GSE6475 as input data sourced from gene expression datasets through the Gene Expression Omnibus (GEO) [19]. It's worth noting that GSE53795 and GSE6475 have been instrumental in prior investigations [18]. However, their usage in these previous studies involved a comprehensive analysis of datasets and pathways via weighted gene co-expression network analysis (WGCNA). GSE108110 and GSE53795 are investigated by Yang et al. [38] for the inflammatory acne-related key biomarkers, signalling pathways, and immune infiltration in the acne lesion. These datasets are built upon gene expression data and securely stored in quantified Affymetrix image (CEL) files. Thus, the data undergoes rigorous preprocessing, a vital step to ensure accuracy and reliability, as the missing or redundant data can significantly sway survival analysis and the interpretation of pivotal factors like diagnosis stages [25,21,24]. Hence, the datasets were profiled into probe set as the raw data. Then, the raw data was carried out the background correction and quantile normalization of the probe level for gene expression data by using the robust multichip average (RAM) algorithm [24]. Next, the gene Entrez IDs were extracted to be the row name for the gene expression data by using the R software package of *hgu133plus2.db*. Therefore, the conversion of the row from the probe identifiers to Gene Entrez IDs has been performed. Furthermore, the values of the columns for the data have been converted into the gene expression value for the Gene Entrez ID [34–35]. Nevertheless, the missing data and repeated data can cause the ineffective on the analysis result [25]. Based on the previous studies, the record of the missing gene Entrez IDs were removed, whereas the repeated record with the same Gene Entrez IDs were took the average gene expression value from all sample [24,21]. Table 1 summarises the details of the data before and after data preprocessing. All the datasets that have been cleaning the data rows with missing values and the repeated value of the Gene Entrez ID are further carried out for the identification of the differentially expressed genes, which is summarized in Fig. 2.

Table 1
Summary of the data on handling missing data and repeated rows for Gene Entrez ID.

Characteristics of the Data	GSE108110	GSE53795	GSE6475
Number of **Samples**	54 18: non-lesional, 18: lesional (papules persisting for less than 48 h), 18: lesional (papules for 21 days)	24 12: lesional, 12: non-lesional	18 6: lesional, 6: non-lesional, 6: normal
Number of rows of **Raw Data** (probes)	54,675	54,675	22,277
Number of rows of data with **missing values** for Gene Entrez ID (genes)	11,537	12,753	2466
Number of rows of data **BEFORE** handling the **duplicated** Gene Entrez ID (genes)	43,138	41,922	19,811
Number of rows of data **AFTER** handling the **duplicated** Gene Entrez ID (genes)	20,857	20,174	12,402

2.2. Q-learning reinforcement model

Fig. 3 shows how Q-learning model to learn about the gene expression data. We denote the gene expression matrix as $X = [x_1, x_2, \cdots, x_m]^T \in \mathbb{R}^{m \times k}$, where m is the number of samples; k is the number of differentially expressed genes. Nevertheless, the differentially expressed gene data is further processed by generating the weighted co-expression network to obtain a gene-gene connectivity matrix [6]. Furthermore, the differentially expressed gene data is correlated to the acne trait by using Pearson correlation in order to obtain a gene list with high gene significance. Hence, the Q-learning agent is learning from the acne sample, and the Q-learning agent's reward function corresponds to the valid connection between genes based on the sample, and provides the rewards based on the gene-gene connectivity matrix.

The Q-learning reinforcement model consists of an environment, agent, and Q-learning module. The role of the environment module is to provide a learnable gene co-expression environment for a Q-learning agent. Furthermore, in the environment module, the generated environment is based on the gene expression of the expressed genes in the acne samples. Thus, for the environment module, there are eight

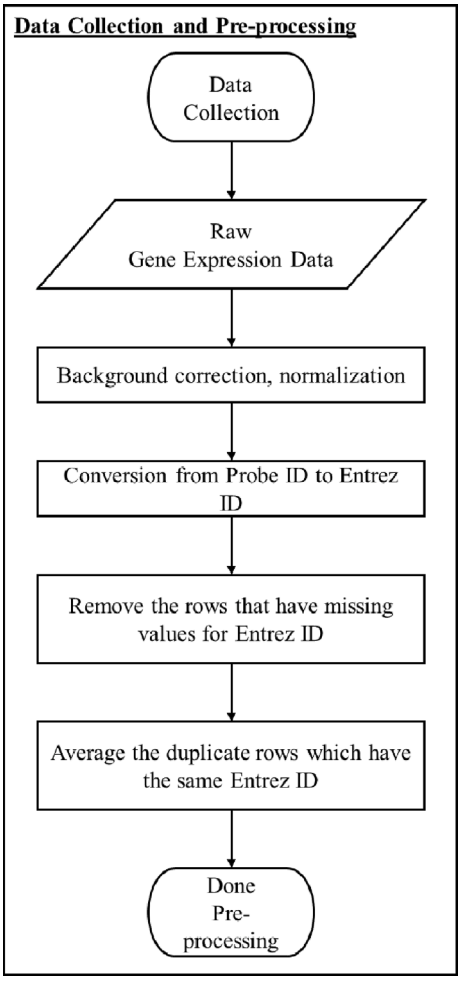

Fig. 2. Data collection and pre-processing before identifying and filtering the differentially expressed genes.

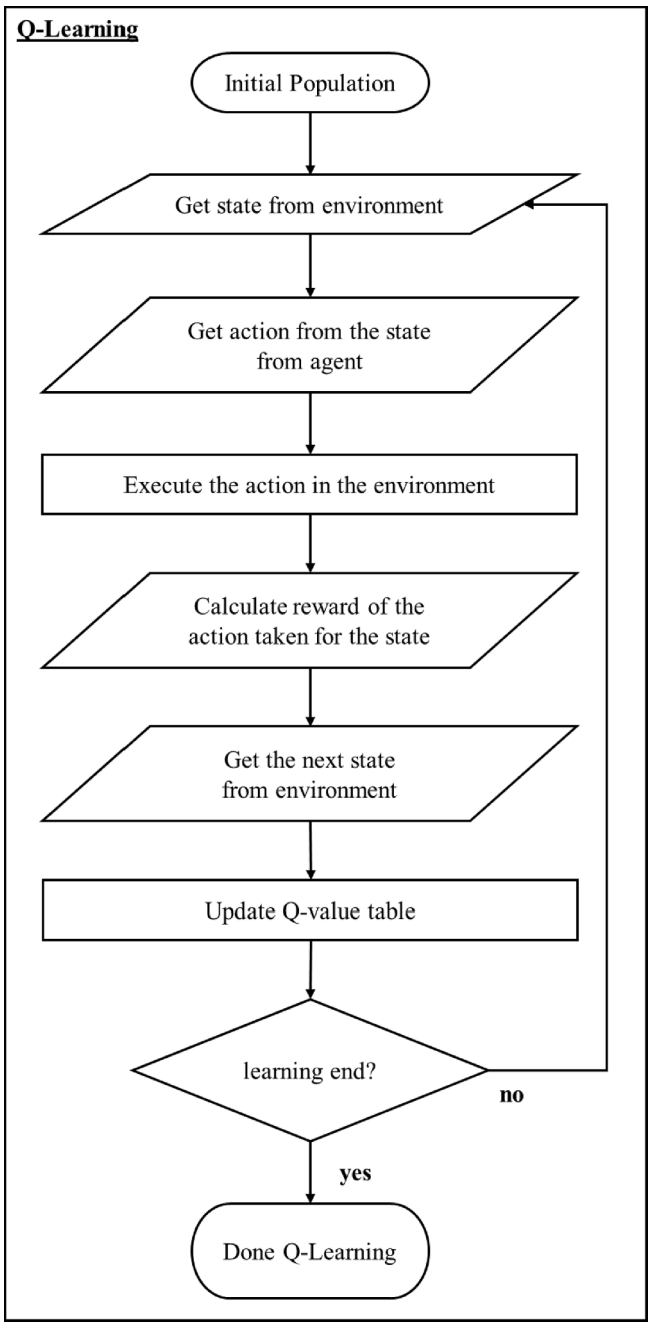

Fig. 3. How Q-learning works in the proposed method.

variables and four functions. The first variable is "ggc", which stores the gene-gene connectivity matrix. Besides, the "top_gene_list" variable stores the genes Entrez ID which have high gene significance, and the "index_top_genes" variable stores the index for the genes Entrez ID which have high gene significance. Furthermore, the "selection" variable is to store the selected gene in an array. The "expression" variable is to store the actively expressed gene from the acne sample in an array. The "terminated" variable is a boolean variable for checking the terminated index has been selected. Nonetheless, the "gene_num" is the variable to stores the number of genes in the acne sample. The last variable of the "gene_id" is a list of gene Entrez ID that exists in the acne sample. Nevertheless, the function of the "reset()" is used to reset the environment when the agent has selected the terminated index as an action. The "play_step()" function is used to make the selection of genes, whereas the "get_index_top_genes()" function is to obtain the index for every gene Entrez ID that has high gene significance. The last function is "is_connective()", which is used to check the selected genes whether the gene-gene connectivity is greater than a small threshold for an agent to distinguish the value of the state.

Next, the role of the Q-learning module is to provide the Q-learning model to the agent for calculating and storing the Q-value for pairs of state and action, $Q(s, a)$. Thus, the agent aims to identify the optimal action from the Q-value table and to choose the best action in a given state. In the Q-learning module, there are three variables and two functions. The first variable in the Q-learning module is the "Q" variable in array form, which is used to behave as a Q-value table for storing the Q-value for the states and actions. Besides, the "gamma" variable is used as the discount factor, whereas the "learning_rate" variable is used as the learning rate for updating the Q-value table with the Bellman equation. The values of "gamma" and "learning_rate" variables set to 0.9, due to the convergence speed of which is much faster than that of other values [39]. Since when the value of the discount factor is low, the agents are more eager for the short-term benefits than future return, resulting eventually in getting stuck in a local optimum and following a long-path strategy. Moreover, the area of variance for different values of discount factor is presented with a huge difference: the larger the value of the discount factor, the smaller the variance area. The two functions of the Q-learning module are "update_Q_value()" and "get_Q_table()". The function of "update_Q_value()" is used to update the Q-value table by using the Bellman equation, while the function of "get_Q_table()" is used to retrieve the Q-value table.

Lastly, the agent module is to behave as a decision-maker. Hence, the agent retrieves a state from the environment and responds with an action which is the gene to be selected based on the exploration and exploitation approach, with a probability of the execution of a random action. The objective of the agent is to select the genes based on the gene co-expression pattern for a list of the potential genetic markers that have high gene significance value among the genes. Nevertheless, an agent with the Q-learning aims to maximize the expected rewards. Hence, the penalty-reward function for the gene correlation is applied to the gene expression environment to provide a reward for the agent in order to identify genetic markers from the correlation pattern by referring to a list of potential genetic markers [9,26]. Therefore, the agent module consists of 9 variables and 6 functions. In the agent module, the "epsilon" variable is used as the probability of the agent executing the random action or executing the action based on the Q-value table. The "model" variable is the variable used to initiate the Q-learning model in the agent class. Furthermore, the "num_action" indicates the size of the space in which random action can be executed. The "selected_gene" variable is used to store the selected gene index when the selection of the gene is executed. Besides, the "previous_selected_gene" variable is used to store the selected gene index for the previous round of the gene selection. The "state" variable is initiated as an array for storing the state extracted from the environment. Next, the variable "state_index" is used to store the index of the state for the particular state and used to update the Q-value table. The "action" variable is used to store the gene index which decides the action from the agent and is also used to update the Q_value table. The last variable in the agent module is the "reward", it is used to store the value of the reward which has been calculated from the function of "get_rewards()" and also used to update the Q-value table. Nevertheless, the "get_action()" function is used to obtain the gene index which represents the action for the agent based on the probability of the agent executing the random action or executing the action based on the Q-value table. The "get_state()" function is used to obtain the state value from the environment, whereas the "get_state_index()" function is to convert the given state into an index for storing in and retrieving from the Q-value table. The function of "get_rewards()" is to calculate the gene-gene connectivity as a reward for the particular state and action with the application of the reward-penalty function. The "get_selected_gene()" function is used to obtain the selected gene while the selection of the gene. The last function of the agent module is the

"update_Q_table()" function, which is used to call the "update_Q_value ()" function from the Q-learning module.

2.3. Markov decision process

Markov Decision Process is a control process for modeling sequential decision-making in a stochastic situation with a discrete stage [36]. In this process, a set of states, S, actions, A, and rewards, R, will be involved with the interaction between agent and environment. Thus, in this Q-learning model, the agent retrieves a state from the environment and uses a Q-value table to determine the action that will be executed for the current state. After executing an action, the agent will gain a reward as feedback from the environment and move on to the next state to carry out the learning process again. Therefore, an optimal Q-value table will be obtained, and the Q-value table will provide the optimal solution for discrete stages. The Q-value table consists of a set of states, S, actions, A, and the accumulated value of rewards, R.

The Q-learning agent conducts the selection of the different genes across different samples. Hence, the state of the agent represents the degree of the gene-gene connectivity of the selected genes with the genes that have high gene significance, considering the gene-gene connectivity is greater than a threshold. This can help the agent to distinguish which genes in the list of high gene significance genes are connective to the selected gene. The state, s_i is indicated by the gene-gene connectivity of selected genes and genes in the list of high gene significance genes, if it is greater than the threshold used, then the indicator vector e_i is set to one, otherwise is set to be zero. Hence, this shows that state, $s_i = e_i \in \{0,1\}^{m \times 1}$, where i is the time step, and m is the size of the list of high gene significance genes. In this research, the threshold used is 0.1, whereas the m used is 10.

For the selection of genes for identifying genetic markers, the action space consists of all the possible actions which are the differentially expressed genes. In the Q-learning agent, the action space includes the index of differentially expressed genes, $A \in \{a_1, a_2, \ldots, a_L\}$, where A is the action space, a is the index of differentially expressed genes and L is the number of differentially expressed genes. In this research, the value of action, a consists of {0, 1, …, L, L + 1}, where L + 1 represents the stop action.

$$\text{Reward, } R \begin{cases} -w \cdot \sum C_{jk}, C_{jk} < \epsilon \\ \sum C_{jk}, otherwise \end{cases}, \text{where} j \in J,\ k \in K,\ J \subset K \quad (1)$$

From the function above, j is the genes in the list of high gene significance genes, whereas J is the list of genes that have high gene significance. Furthermore, the k is the selected gene and K is the list of differentially expressed genes. Nonetheless, C_{jk} is the gene-gene connectivity of j and k. Hence, the reward-penalty function above shows that the reward depends on the gene-gene connectivity between the gene selected and the gene in the list of high gene significance genes. This is because gene significance value can be used to identify potential genetic markers, as gene significance is a measurement of the correlation for the gene expression with an external trait [17]. Furthermore, in this reward-penalty function, the used value of w is 1.5 and the purpose of the w in this reward-penalty function is to enlarge the sparsity of the penalty for the genes that have the gene-gene connectivity is less the ϵ value [26]. For this reward-penalty function, the value of ϵ used is 0.01, to quantify the contribution of the gene as a genetic marker by considering the gene-gene connectivity is greater than a small threshold [26].

$$Q_{new}(s_t, a_t) = Q(s_t, a_t) + \alpha(R + \gamma \cdot \max Q(s_{t+1}, a) - Q(s_t, a_t) \quad (2)$$

The Q-value function above shows that $Q(s_t, a_t)$ is the Q-value for the current state, s_t and action was taken for the current state, a_t; α is the learning rate; R is the reward for the current state, s_t and action was taken for the current state, a_t; γ is the discounted factor; $\max Q(s_{t+1}, a)$ is the maximum Q-value for the new state from all the possible actions. Lastly, the Q-value function which is based on the Bellman equation is used to update the Q-value table.

The objective of the agent is to select the genes based on the gene co-expression pattern for a list of the potential genetic markers that have high gene significance value among the genes. Nevertheless, an agent with the Q-learning aims to maximize the expected rewards. Hence, the penalty-reward function for the gene correlation is applied to the gene expression environment to provide a reward for the agent in order to identify genetic markers from the correlation pattern by referring to a list of potential genetic markers [26].

2.4. Differentially expressed genes

The genetic markers are defined from the differentially expressed genes [26]. Hence, the differentially expressed genes are identified, and removed the no or low changes in expression in different samples for the datasets [12,3,34–35]. Firstly, the information of the sample is obtained by using the library of "GEOquery" [7]. Next, the boxplot and hierarchical tree are used to check the distribution of the gene expression data and detect the sample outliers respectively. Furthermore, in the process of identification of differentially expressed genes, the value of the median of gene expression level is used for filtering the low expressed genes across samples when the particular gene is not being expressed by at least 2 samples. Next, the gene expression data is compared by two conditions, such as in non-acne condition and acne condition, for identifying the differentially expressed genes by using the function of "makeContrasts()" in the limma library [27]. Lastly, the differentially expressed genes are identified from the conditions, such as adjusted P value <0.05 and absolute value of log 2 based on the fold change >1.5 [4,15]. Eventually, all the differentially expressed genes which included up-regulated genes and down-regulated genes are filtered out for further analysis. Thus, the data of differentially expressed gene expression level is passed to the Q-learning agent to obtain the differentially expressed genes as the action for the Q-learning agent. Nevertheless, the data of differentially expressed gene expression levels is also used for generating the gene-gene connectivity matrix and gene list of high genes for the Q-learning model.

2.5. Gene-gene connectivity matrix

Furthermore, in order to represent the dependency between genes, a gene-gene connectivity matrix is generated by using the function of "TOMsimilarity()" [12,17]. In this process, the Pearson correlation matrix is calculated from the differentially expressed genes and gives a high topological overlap for two genes that have common neighborhoods with a soft threshold. Hence, a weighted gene co-expression network is constructed, representing the gene-gene connectivity [12].

Fig. 4 shows the scale independence and the mean connectivity for the list of soft threshold for the dataset of GSE108110. Thus, 20th power is picked as the soft threshold for generating the cluster for the differentially expressed genes. This is because the soft threshold is selected when it have the scale-free fit index is higher and the mean connectivity is remained lower. After picking the soft threshold, a topological overlap network construction and module detection in the approach of average linkage hierarchical clustering are performed for the differentially expressed genes by using the function of blockwiseModules() with the picked soft threshold and Pearson correlation.

Fig. 5 illustrates a list of soft thresholds into two plots which are according by the scale independence and the mean connectivity for the dataset of GSE53795. Hence, the 20th of the soft threshold was picked for the construction of the topology overlap network for the dataset of GSE53795. This is because the 20th soft threshold has a high scale independence power which is nearly to 0.8 and a low mean connectivity. Then, the differentially expressed genes are performed topological overlap network construction and average linkage hierarchical clustering for gene module clustering by using the function of blockwiseModules() with the picked soft threshold and Pearson correlation.

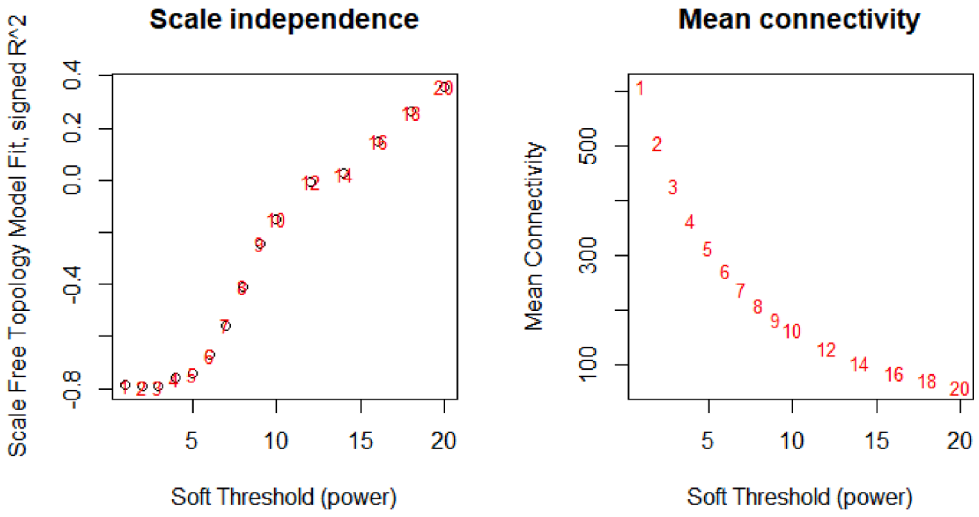

Fig. 4. The selection of soft threshold of GSE108110.

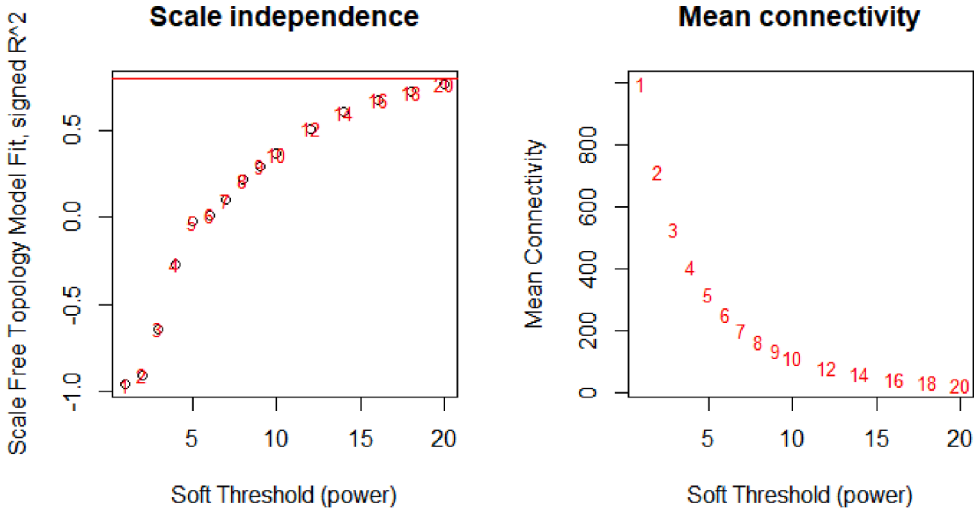

Fig. 5. The selection of soft threshold of GSE53795.

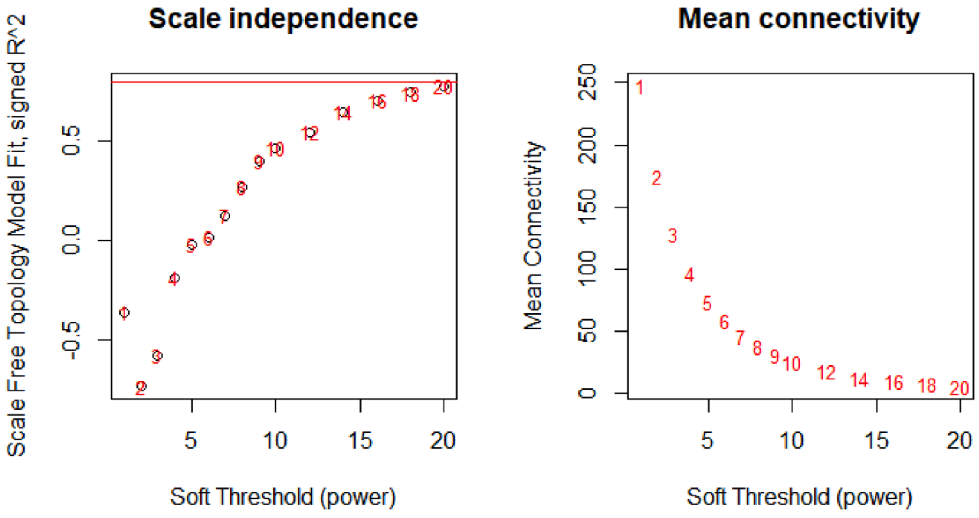

Fig. 6. The selection of soft threshold of GSE6475.

Fig. 6 shows the soft thresholds of GSE6475 dataset by their scale independence and the mean connectivity. Thus, the 20th power was selected as the soft threshold for the differentially expressed genes to generate a topology overlap network. The selection for the picked soft threshold is due to the soft threshold selected soft threshold has a nearly to 0.8, high scale independence power and a low mean connectivity. After the selection of the soft threshold, the network construction and module detection are performed by using blockwiseModules() with the picked soft threshold and Pearson correlation. In this process, a topological overlap network is constructed and gene module is identified in the approach of average linkage hierarchical clustering.

Nevertheless, the differentially expressed genes data is correlated with acne trait in order to generate the correlation for genes and acne trait. Then, the correlation of the differentially expressed genes and acne trait is further processed with the function of "corPvalueStudent()" for generating the gene significance for the differentially expressed genes [17]. In this process, the P-value for correlation is calculated for the differentially expressed genes and acne traits. In order to obtain a gene list of high gene significance, the values of the P-value for correlation of the differentially expressed genes and acne trait are sorted in acceding order and the top 10 genes which have the lowest value of P-value are extracted. Hence, the gene list of high gene significance is passed and used for the reward-penalty function in the Q-learning agent.

For the GSE108110 dataset, the gene list of the high gene significance used included the genes with the gene Entrez ID of 4321, 55509, 1000506776, 4826, 4329, 158830, 64761, 555619, 355, and 1200. Nevertheless, the high gene significance genes used for the GSE53795 dataset are the genes with the gene Entrez ID of 1786, 7264, 2769, 6283, 387695, 57016, 5266, 79155, 7378, and 338324. Furthermore, for the GSE6475 dataset, the gene list of the high gene significance consists of the genes that have the gene Entrez ID of 2210, 4312, 10288, 3002, 5552, 57016, 5265, 1890, 3868, and 6702.

The higher the topological overlap for two genes, the higher the similarity for two particular genes as they have common neighborhoods. Therefore, the data pre-processing reduces the redundancy of the dataset and prepares the data for configuring and inputting to the Q-learning algorithm.

2.6. Q-learning algorithm

Firstly, the differentially expressed genes matrix is passed into the environment module to generate a learnable environment for the Q-learning agent. The differentially expressed genes matrix has been converted into the "actively expressed" pattern with the value of the median of the gene expression level. In other words, the genes in the matrix are expressed in active, "1", when the expression level is over the value of median of expression level, otherwise the gene is not expressed, "0". In the Q-learning, the data have to be Markovian domain in order to learn the data as the Markov Decision Process. Therefore, the data input needs to be configured as a Markovian domain. Hence, this configuration process includes the configuration of data to the environment for the Q-learning agent to retrieve a learnable state from the environment and the configuration of action for the Q-learning agent to be able to execute an action in the environment. Furthermore, the actively expressed gene expression data is then configured as an environment. Then, the agent retrieves the state from the environment by comparing the gene-gene connectivity of the selected gene and the gene in the high gene significance gene list with a value of ϵ used. If the value of the gene-gene connectivity of the selected and the gene in the high gene significance gene list is greater than the value of ϵ used, then the value of the digit returns as 1. Hence, the number of digits for the state is 10 due to there are 10 genes in the high gene significance gene list. Nevertheless, the configuration of the action also is carried out. In this process, the number of genes is calculated from the gene list that has been read from the gene expression data. Then, the agent generates an action space that contains the gene to be selected and evaluated by the Q-learning agent. Next, the agent executed an action with epsilon to generate a probability for an agent to execute the random action or execute the action based on the Q-value table. In this process, the agent carries out an exploration, if the agent executes a random action; otherwise agent carries out exploitation for the execution of an action that has the highest Q-value from the Q-value table.

After that, the agent calculates the reward based on the action taken, which means the gene-gene connectivity of the gene selected and genes from the gene list of the high gene signature is calculated as a reward for an agent by the reward-penalty function that has been applied in an agent. Then, the next state is retrieved from the environment based on the action taken. Next, the agent updates the Q-value table. In this research, for the Q-learning agent, the number of learning episodes for every sample is 200.

The Q-function will be updated with an optimized Q-value until the iteration of the learning is stopped. Hence, the output of the model is the genes selected with its frequency of selected. Then, the top 10 genes selected are considered as the genetic markers.

2.7. Performance evaluation

For the evaluation of the performance of the Q-learning model, the genetic markers obtained from the Q-learning model have carried out performance evaluation by classification with the model of logistic regression and stratified five-fold cross-validation. In the classification, the ratio of 0.8: 0.2 is used for splitting the data into the training set and test set. The used ratio follows the ratio used in the literature review in the research of using reinforcement learning to select the active gene signatures for identification in renal cell carcinoma [12]. Moreover, when the ratio is closer to 0.8, it provides empirically best splitting for the training set and test set [8]. Thus, the genetic marker is evaluated by classification using the genetic marker as features for accuracy, sensitivity, specificity, and AUC. K-fold cross-validation divides the data into k groups and carries out the validation by using one of the folds as a test fold, the rest are train folds [16,23]. In this evaluation, the datasets are split into five-fold and the stratified five-fold cross-validation. In the stratified five-fold cross-validation, the different datasets use different ratios five-fold for the group of acne. For dataset, GSE108110, the ratio used for the acne sample to the non-acne sample is 0.33:0.67, because there are 18 acne-lesional samples and 36 non-acne lesional samples. For dataset GSE53795, there are 12 ance-lesional samples and 12 non-acne-lesional samples, hence, the ratio used for acne sample to non-acne sample is 0.5:0.5. Lastly, for the dataset GSE6475, the ratio used for acne sample to non-acne sample is 0.33:0.67 because there are 6 acne-lesional samples and 18 non-acne lesional samples.

Nevertheless, PubMed text data mining is used to provide the biological context verification of the gene selected by the Q-learning agent. In the PubMed text data mining, the gene symbol of the gene selected by the Q-learning agent, which has been converted from the gene Entrez ID, is used to find the relationship of the particular gene symbol with acne. Furthermore, This process is carried out by the function of get_pubmed_ids() to find out whether the particular gene symbol has been involved in the publication from PubMed. In this process, the keyword used for finding the genetic markers that have a relationship with acne from the publication in PubMed is "acne". Thus, the result of the PubMed text data mining shows the direct relationship between the genetic markers to acne.

3. Results

Table 2 shows the gene Entrez ID of the gene selected with its frequency of being selected for three datasets, which are GSE108110, GSE53795, and GSE6475. In this process, all the genes are recorded in their gene Entrez ID. For the dataset of GSE108110, the top 10 genes selected are "21", "100506779", "942", "5160", "199", "54440", "56894", "91010", "3109" and "128346", and the gene with gene Entrez

Table 2
The frequency of the genes selected.

GSE108110		GSE53795		GSE6475	
Gene Entrez ID	**Frequency**	**Gene Entrez ID**	**Frequency**	**Gene Entrez ID**	**Frequency**
21	1274	12	1364	120	523
100,506,779	181	3587	196	5266	389
942	148	9407	196	728	210
5160	147	7029	171	3868	193
199	139	5495	167	5552	165
54,440	113	1830	163	6699	158
56,894	85	6372	120	10,261	156
91,010	76	2237	114	11,151	135
3109	69	2752	98	224	128
128,346	59	7133	91	5320	115

ID of "21" is selected with the highest frequency which is 1274. Nevertheless, The top 10 genes selected for the dataset of GSE53795 are "12", "3587", "9407", "7029", "5495", "1830", "6372", "2237", "2752" and "7133". The gene with the gene Entrez ID of "12" has the highest frequency which is 1364. Nonetheless, for the dataset of GSE6475, the top 10 of the genes selected are the genes with the gene Entrez ID of "120", "5266", "728", "3868", "5552", "6699", "10261", "11151", "224" and "5320". The gene with the gene Entrez ID of 120 has the highest frequency of selection which is 523. Lastly, the genes selected which have been listed above are used for performance validation by using as the features for the classification of the acne samples and non-acne samples.

Table 3 illustrates the accuracy, sensitivity, and specificity of the stratified 5-fold cross-validation. Gene set variation analysis (GSVA) has been identified genetic markers in acne vulgaris that are validated toward personalized diagnostic and therapeutic strategies [20]. The GSE108110 achieved 81.80 % accuracy, specificity is 100 %, and sensitivity is reached 75 %. For GSE53795 and GSE6475, both datasets achieved 100 % accuracy, specificity, and sensitivity. However, this research has been outperformed than GSVA in GSE53795 and GSE6475.

Table 4 presents the comparative analysis of Q-learning and GSVA for the GSE108110, GSE53795, and GSE6475 datasets. The tables also state the differences in AUC values between the methods in term of percentages. There were statistically significant differences between the methods, as supported by *p*-values and the 95 % confidence interval. Additionally, the Q-learning demonstrated consistent and significant improvement over other methods with a minimum average difference of 0.70 %.

For biological verification, the genes Entrez ID of the high selected frequency of the genes selected by the Q-learning model are converted into a gene symbol. Table 5 shows the gene symbol for the high frequency of genes selected. In the biological validation, the gene symbols are used in PubMed text data mining to find which gene is related to acne. Table 6 shows the gene symbols with the acne publication record on PubMed. Therefore, 8 gene symbols show the relationship with acne, as 8 gene symbols have publication records about acne on PubMed. Hence, for the GSE108110, the gene symbols CD86 and AGPAT3 have a relationship with acne. For the dataset of GSE53795, gene symbols of TMPRSS11D, DSG3, and TNFRSF1B are the genes that have a relationship with acne. For the GSE6475 dataset, the gene symbols PI3, C5AR1, and KRT16 have a relationship with acne.

Table 3
Summary of the accuracy, specificity, and sensitivity of the datasets.

Datasets	Q-Learning				GSVA [20]
	Accuracy	**Specificity**	**Sensitivity**	**AUC**	**AUC**
GSE108110	81.80 %	100 %	75 %	75 %	94.35 %
GSE53795	100 %	100 %	100 %	100 %	96.68 %
GSE6475	100 %	100 %	100 %	100 %	99.30 %

Table 4
Comparative analysis of Q-learning and GSVA for the studied datasets in terms of AUC.

	p-values	95 % Confidence Interval	Differences
GSE108110	4.06×10^{-8}	(18.14, 20.56)	19.35
GSE53795	0.04	(−0.62, 5.94)	3.32
GSE6475	0.36	(−0.99, 2.11)	0.70

Table 5
Table of the conversion of Gene Entrez ID to Gene Symbol.

GSE108110		GSE53795		GSE6475	
Gene Entrez ID	**Gene Symbol**	**Gene Entrez ID**	**Gene Symbol**	**Gene Entrez ID**	**Gene Symbol**
21	ABCA3	12	SERPINA3	120	ADD3
100,506,779	BZRAP1-AS1	3587	IL10RA	5266	PI3
942	CD86	9407	TMPRSS11D	728	C5AR1
5160	PDHA1	7029	TFDP2	3868	KRT16
199	AIF1	5495	PPM1B	5552	SRGN
54,440	SASH3	1830	DSG3	6699	SPRR1B
56,894	AGPAT3	6372	CXCL6	10,261	IGSF6
91,010	FMNL3	2237	FEN1	11,151	CORO1A
3109	HLA-DMB	2752	GLUL	224	ALDH3A2
128,346	C1orf162	7133	TNFRSF1B	5320	PLA2G2A

Table 6
Table of the gene symbols related to the acne publication record.

Datasets	Gene Symbol	PubMed Publication record ID
GSE108110	CD86	26495013
	AGPAT3	32031713
GSE53795	TMPRSS11D	31838778
	DSG3	31337387
	TNFRSF1B	20556591
GSE6475	PI3	31838778
	C5AR1	31688984
	KRT16	36291580

4. Discussion

The limitation of the proposed method is that the features that have been used to identify the differentially expressed genes for the datasets are "patient_id" and "sample_type". This is because the datasets used, which are GSE108110, GSE53795, and GSE6475 do not include more features such as the age of the patient, and background of the patient. Due to the lack of more information for the patient, factors other than "type of sample" are lacking to consider for analysis on identifying differentially expressed genes. For example, acne is a symptom of many endocrine disorders [22]. Furthermore, the side effects of medication treatment such as intake the medicine that contains lithium also is a factor that causes the acne problem [2]. Hence, it is hard to distinguish the patients who have acne problems due to endocrine disorders and the patients who have acne problems due to the side effects of medication treatment by only using the gene expression level data. Therefore, a lack of more information about the patient may lead to a limited analysis of it.

The proposed method can select the genes that are associated with acne from an action space that consists of plenty of genes. For instance, the action space for GSE108110 consists of 749 gene candidates, the action space for GSE53795 consists of 1482 gene candidates and the

action space for GSE6475 consists of 370 genes. The gene symbol of the gene selected for the GSE108110 are ABCA3, BZRAP1-AS1, CD86, PDHA1, AIF1, SASH3, AGPAT3, FMNL3, HLA-DMB and C1orf162. For the GSE53795, the genes selected are SERPINA3, IL10RA, TMPRSS11D, TFDP2, PPM1B, DSG3, CXCL6, FEN1, GLUL, and TNFRSF1B. Furthermore, for the GSE6475, the genes selected are ADD3, PI3, C5AR1, KRT16, SRGN, SPRR1B, IGSF6, CORO1A, ALDH3A2 and PLA2G2A. For the dataset of GSE108110, the genes that have been biologically verified for having a relationship with acne are CD86 and AGPAT3. Besides, for the GSE53795, the genes that have biologically verified for having a relationship with acne are TMPRSS11D, DSG3, and TNFRSF1B, whereas for the dataset of GSE6475, the genes that have biologically verified for having a relationship with acne are PI3, C5AR1, and KRT16.

According to the list of genes validated by PubMed text data mining, type-1 macrophage marker (Gene Symbol: CD86) with PubMed ID: 26495013, shows that it is highly phagocytic and play critical roles in infections and cancers to protect the host [28]. Hence, liquiritigenin and isoliquiritin activated human monocytes by increasing CD86 expression and phagocytosis. By enhancing macrophage functions, it may be beneficial in a therapeutic strategy for skin inflammation disorders including acne. TNF receptor superfamily member 1B (Gene Symbol: TNFRSF1B) with PubMed ID: 20556591, has been presented with the high frequency of 196R allele in the functional M196R polymorphism of TNFR2 is a risk factor for acne vulgaris in Han Chinese [32]. Transmembrane serine protease 11D and peptidase inhibitor 3 (Gene Symbols: TMPRSS11D and PI3) with PubMed ID: 31838778, shows these two genes and KRT16 (keratin 16) were found to characterize hidradenitis suppurativa/acne inversa (HS) from a molecular standpoint [40]. TMPRSS11D is released in the host defence system from the submucosal serous glands onto mucous membrane. PI3 was detected to be differentially regulated in HS perfomed by Quantitative real-time PCR. PI3 functions as an antimicrobial peptide against Gram-positive and Gram-negative bacteria and fungal pathogens. It modulates a wide range of parameters that are critical for the inflammation process, such as NFκB pathway modulation, cytokine secretion and cell recruitment.

Fig. 7 shows the cumulative rewards by the number of episodes for the Q-learning agent. The purpose of the graph of the cumulative reward and number of episodes is to show the learning trend of the Q-learning model. The inclining trend shows the Q-learning model is gaining positive feedback as a reward for selecting genes that are more connective to the high gene significance gene list; whereas the declining trend shows the Q-learning model is experiencing negative feedback as a penalty for selecting genes that are less connective to the high gene significance gene list. Therefore, reinforcement learning for selecting genes that are associated with acne is being carried out.

The proposed Q-learning model has a high accuracy, and high specificity but is unstable for sensitivity. Hence, the proposed method is a model with high accuracy and specificity. Therefore, the proposed method can correctly classify the non-acne sample as the non-acne sample and is less likely to predict the non-acne sample as an acne sample. However, the proposed method performed unstable for the sensitivity, because the proposed method has a low sensitivity for GSE108110 but remained a high sensitivity for the other two datasets. Therefore, the proposed method is unstable for correctly classifying acne samples as acne samples and may produce false negative predictions.

5. Conclusion

The introduction of a Q-learning model for the selection of genetic markers associated with acne represents a significant advancement in the field of medical research. Q-learning, an AI-driven approach, allows the system to autonomously identify and select genes that play a crucial role in the development of acne. To achieve this, various data preprocessing techniques are applied, including handling missing data, deduplication of Gene Entrez IDs, and identification of differentially expressed genes. These processes help streamline the input data for the Q-learning model, making it more effective in identifying relevant genetic markers.

One of the key innovations in this research is the construction of a gene-gene connectivity matrix, which measures the relationships between different genes. This matrix, coupled with gene significance calculations, transforms the raw acne gene expression data into a format suitable for the Q-learning model to understand and learn from. Consequently, the Q-learning agent can efficiently pinpoint genetic markers associated with acne after this data preprocessing.

The study incorporates three different acne gene expression datasets from Gene Expression Omnibus (GEO), providing a comprehensive analysis. Notably, the results reveal specific genes associated with acne for each dataset, shedding light on the genetic factors contributing to this skin condition. For instance, genes like CD86 and AGPAT3 are linked to acne in one dataset, while TMPRSS11D, DSG3, and TNFRSF1B are implicated in another. These findings demonstrate the power of the proposed Q-learning model in uncovering genetic markers associated with acne across diverse datasets.

Moreover, the study employs logistic regression with five-fold cross-validation to classify the datasets, showcasing the practicality and robustness of the proposed model. It achieves high accuracy and specificity in identifying genetic markers selected by the Q-learning agent. However, it's important to note that the model exhibits some variability in sensitivity, indicating an area for potential improvement.

In summary, this research leverages AI-driven Q-learning to effectively identify genetic markers associated with acne. The model's ability to autonomously select relevant genes, its innovative data preprocessing techniques, and its success in classifying acne gene expression datasets highlight its potential in advancing genetic marker identification not only for acne but potentially for other diseases as well. This work represents a significant step toward personalized treatments and a deeper understanding of the genetic basis of skin conditions.

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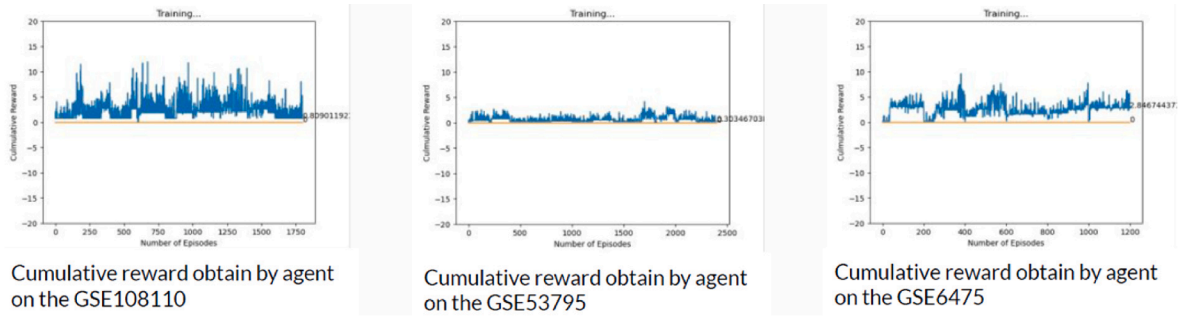

Fig. 7. The cumulative reward obtained by the agent.

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References

[1] Bungau AF, Radu AF, Bungau SG, Vesa CM, Tit DM, Endres LM. Oxidative stress and metabolic syndrome in acne vulgaris: pathogenetic connections and potential role of dietary supplements and phytochemicals. Biomed Pharmacother 2023;164:115003.
[2] Chaudhari D, Vohra RR, Ali MA, Nadeem H, Tarimci B, Garg T, et al. A Rare phenomenon of lithium-associated acne inversa: A case series and literature review. Cureus 2023;15(3).
[3] Chen B, Zheng Y, Liang Y. Analysis of potential genes and pathways involved in the pathogenesis of acne by bioinformatics. BioMed Res Int; 2019.
[4] Chen Y, Lun AT, Smyth GK. From reads to genes to pathways: differential expression analysis of RNA-Seq experiments using rsubread and the edgeR quasi-likelihood pipeline. F1000Research 2016:5.
[5] Cheng Y, Chen T, Hu J. Genetic analysis of potential biomarkers and therapeutic targets in neuroinflammation from sporadic Creutzfeldt-Jakob disease. Sci Rep 2023;13(1):14122.
[6] Darvish Z, Ghanbari S, Afshar S, Tapak L, Amini P. Psoriasis associated hub genes revealed by weighted gene co-expression network analysis. Cell Journal (yakhteh) 2023;25(6):418.
[7] Davis S, Meltzer PS. GEOquery: a bridge between the Gene Expression Omnibus (GEO) and BioConductor. Bioinformatics 2007;23(14):1846–7.
[8] Gholamy A, Kreinovich V, Kosheleva O. Why 70/30 or 80/20 relation between training and testing sets: A pedagogical explanation; 2018.
[9] Guttà C. Prognostication and prediction of cancer patient outcomes using AI-based classifiers; 2023.
[10] Heng AHS, Say YH, Sio YY, Ng YT, Chew FT. Gene variants associated with acne vulgaris presentation and severity: a systematic review and meta-analysis. BMC Med Genomics 2021;14(1):1–42.
[11] Holzinger A, Haibe-Kains B, Jurisica I. Why imaging data alone is not enough: AI-based integration of imaging, omics, and clinical data. Eur J Nucl Med Mol Imaging 2019;46(13):2722–30.
[12] Huang M, Ye X, Imakura A, Sakurai T. Sequential reinforcement active feature learning for gene signature identification in renal cell carcinoma. J Biomed Inform 2022;128:104049.
[13] Iftikhar A, Ghazanfar MA, Ayub M, Alahmari SA, Qazi N, Wall J. A Reinforcement learning recommender system using bi-clustering and Markov decision process. Expert Syst Appl 2023;121541.
[14] Janisch J, Pevný T, Lisý V. (2019, July). Classification with costly features using deep reinforcement learning. In Proceedings of the AAAI Conference on Artificial Intelligence (Vol. 33, No. 01, pp. 3959-3966).
[15] Jia K, Wu Y, Ju J, Wang L, Shi L, Wu H, et al. The identification of gene signature and critical pathway associated with childhood-onset type 2 diabetes. PeerJ 2019;7:e6343.
[16] Karasiak N, Dejoux JF, Monteil C, Sheeren D. Spatial dependence between training and test sets: another pitfall of classification accuracy assessment in remote sensing. Mach Learn 2022;111(7):2715–40.
[17] Langfelder P, Horvath S. WGCNA: an R package for weighted correlation network analysis. BMC Bioinf 2008;9(1):1–13.
[18] Li X, Jia Y, Wang S, Meng T, Zhu M. Identification of genes and pathways associated with acne using integrated bioinformatics methods. Dermatology 2019;235(6):445–55.
[19] Liang J, Chen Y, Wang Z, Wang Y, Mu S, Zhang D, et al. Exploring the association between rosacea and acne by integrated bioinformatics analysis; 2023.
[20] Lin Q, Cai B, Ke R, Chen L, Ni X, Liu H, et al. Integrative bioinformatics and experimental validation of hub genetic markers in acne vulgaris: Toward personalized diagnostic and therapeutic strategies. J Cosmet Dermatol 2024.
[21] Liu W, Wang W, Tian G, Xie W, Lei L, Liu J, et al. Topologically inferring pathway activity for precise survival outcome prediction: breast cancer as a case. Mol Biosyst 2017;13(3):537–48.
[22] Lolis MS, Bowe WP, Shalita AR. Acne and systemic disease. *Medical.* Clinics 2009;93(6):1161–81.
[23] Lyu Z, Yu Y, Samali B, Rashidi M, Mohammadi M, Nguyen TN, et al. Back-propagation neural network optimized by K-fold cross-validation for prediction of torsional strength of reinforced Concrete beam. Materials 2022;15(4):1477.
[24] Mohammed A, Biegert G, Adamec J, Helikar T. Identification of potential tissue-specific cancer biomarkers and development of cancer versus normal genomic classifiers. Oncotarget 2017;8(49):85692.
[25] Nies HW, Mohamad MS, Zakaria Z, Chan WH, Remli MA, Nies YH. Enhanced directed random walk for the identification of breast cancer prognostic markers from multiclass expression data. Entropy 2021;23(9):1232.
[26] Qiu Y, Wang J, Lei J, Roeder K. Identification of cell-type-specific marker genes from co-expression patterns in tissue samples. Bioinformatics 2021;37(19):3228–34.
[27] Ritchie ME, Phipson B, Wu DI, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 2015;43(7). e47–e47.
[28] Sekiguchi K, Koseki J, Tsuchiya K, Matsubara Y, Iizuka S, Imamura S, et al. Suppression of Propionibacterium acnes-induced dermatitis by a traditional Japanese medicine, jumihaidokuto, modifying macrophage functions. Evid-Based Complement Altern Med 2015;2015.
[29] Shen C, Wang QZ, Shen ZY, Yuan HY, Yu WJ, Chen XD, et al. Genetic association between the NLRP3 gene and acne vulgaris in a Chinese population. Clin Exp Dermatol 2019;44(2):184–9.
[30] Shim H, Hwang SJ, Yang E. Joint active feature acquisition and classification with variable-size set encoding. Adv Neural Information Process Syst 2018:31.
[31] Stöger K, Schneeberger D, Holzinger A. Medical artificial intelligence: the European legal perspective. Commun ACM 2021;64(11):34–6.
[32] Tian L, Xie H, Yang T, Hu Y, Li J, Wang W. TNFR 2 M196R polymorphism and acne vulgaris in Han Chinese: a case-control study. J Huazhong Univ Sci Technol [medical Sciences] 2010;30(3):408–11.
[33] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2163–96.
[34] Wang CC, Li CY, Cai JH, Sheu PCY, Tsai JJ, Wu MY, et al. Identification of prognostic candidate genes in breast cancer by integrated bioinformatic analysis. J Clin Med 2019;8(8):1160.
[35] Wang T, Bao X, Clavera I, Hoang J, Wen Y, Langlois E, et al. Benchmarking model-based reinforcement learning. arXiv preprint arXiv:1907.02057; 2019.
[36] White III CC, White DJ. Markov decision processes. Eur J Oper Res 1989;39(1):1–16.
[37] Wu C, Xu H, Bai D, Chen X, Gao J, Jiang X. Public perceptions on the application of artificial intelligence in healthcare: a qualitative meta-synthesis. BMJ Open 2023;13(1):e066322.
[38] Yang L, Shou YH, Yang YS, Xu JH. Elucidating the key biomarkers and immune infiltration in acne by integrated bioinformatics analysis; 2021.
[39] Zhou X. Optimal values selection of Q-learning Parameters in Stochastic Mazes. In *Journal of Physics: Conference Series* (Vol. 2386, No. 1, p. 012037). IOP Publishing; 2022.
[40] Zouboulis CC, Nogueira da Costa A, Makrantonaki E, Hou XX, Almansouri D, Dudley JT, et al. Alterations in innate immunity and epithelial cell differentiation are the molecular pillars of hidradenitis suppurativa. J Eur Acad Dermatol Venereol 2020;34(4):846–61.