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Optimization of Cdx Transcription Factors Characteristics

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Abstract. This study presents a new application of TOPSIS for the optimization of transcription factors characteristics. This application is essential as it can help compare the characteristics of these proteins and determine the optimized output of their comparison with this decision-making method. The hypothesis in this article was that according to the previous study of the Cdx transcription factors, as the Cdx2 transcription factor showed more robust characteristics than Cdx1 and Cdx4, the TOPSIS method would show a better rank position of these first proteins in comparison with the two other ones. Moreover, the engrailed repressor domain EnRCdx1 used in the plasmid showed the reduction of the pax3 gene expression in comparison with the induced regulation of the gene expression with the production of the Cdx1, Cdx2, and Cdx4 transcription factors using the corresponding plasmids, the worst rank position with TOPSIS was expected for this repressor domain. The results obtained with this ranking method showed that the rank positions of the transcription factors and the repressor domain corresponded to their compared properties. Moreover, the change in the weight values of the candidates showed the modification of their distances from the best and worst alternatives and closeness coefficients. However, as expected, the candidates' rank positions were unchanged, and the Cdx2 transcription factor was still the best candidate. The results of this article can be used in computer engineering to improve biological applications of these proteins.

Keywords: decision-making process, TOPSIS, algorithm, transcription factor, optimization.

1 Introduction

Optimization methods have been applied in different research fields in recent years. These methods are essential for predicting and improving the materials' properties.

The Technique for Order of Preference by Similarity to the Ideal Solution (TOPSIS) is among the decision-making methods with various applications in science and engineering [1–4]. Decision-making algorithms such as TOPSIS can predict, optimize, and detect the candidates according to their properties, which are considered criteria [5–8].

In the TOPSIS method, the candidates are ranked according to the values of their closeness coefficients, which in turn depends on their distances from their positive and negative ideal solutions. These solutions are obtained by considering the maximal values of the profit criteria and the minimal values of the cost criteria for the candidates.

Transcription factors are the proteins that regulate the expression of genes, an essential biological process that

occurs in cells [9–11]. These proteins bind to the gene's promoter region and regulate its expression [12–16]. The study of these proteins has shown their importance in molecular biology for determining various gene expression regulation pathways [17–20].

2 Literature Review

The Cdx transcription factors regulate the pax3 gene expression [21, 22]. This gene forms neural tubes and migrates neural crest cells in vertebrates [23–25].

It has been shown previously that the Cdx transcription factors could regulate the expression of the pax3 gene via the Wnt pathway [21]. The activity of Tead2 and Brn1/2 transcription factors has been considered in this pathway [21].

Studying the transcription factors characteristics that have crucial roles in gene expression regulation is essential to compare them for further applications in science and engineering.

The advantage of the TOPSIS method over the others is that the algorithm in this first technique considers the profit and cost criteria differently. These criteria positively and negatively affect the candidates' rank positions, respectively.

Considering the types of criteria as profit or cost criteria and their weights are essential as they can impact the output of TOPSIS. However, it can sometimes happen that the modification of these elements of this method does not affect its output, as the change in the weight values in the current study has not affected the candidates' ranks.

Although TOPSIS has been used to optimize, predict, and analyze different materials characteristics, the characteristics of transcription factors have not been compared and optimized with this technique.

This study aims to perform a novel optimization of transcription factors characteristics with TOPSIS. The current investigation could help determine which transcription factor, according to its characteristics, would be ranked in the best position and which other transcription factors would take other positions. Moreover, this study could help analyze the role of the weight values on the ranks of transcription factors.

The optimization of transcription factors according to their characteristics has not been investigated with this method yet.

The novel application of the decision-making method with TOPSIS presented in the current work can open new insights into investigating these proteins and improving their application in computer engineering.

3 Research Methodology

3.1 Plasmids preparation

The plasmids allowing the expression induction of the pax3 gene by the overexpression of the Cdx1, Cdx2, and Cdx4 transcription factors and the expression reduction of this gene by the overexpression of the negative dominant EnRCdx1 were prepared. Moreover, the corresponding transcription factors' characteristics were previously studied [21, 22].

Figure 1 shows the Cdx-dependent transactivation of a Pax3p1.6kb-luciferase construct for Cdx1, Cdx2, and Cdx4 dose dependencies of this transactivation. Lanes 2–4 repressed with the increase of EnRCdx1 (lanes 5–7).

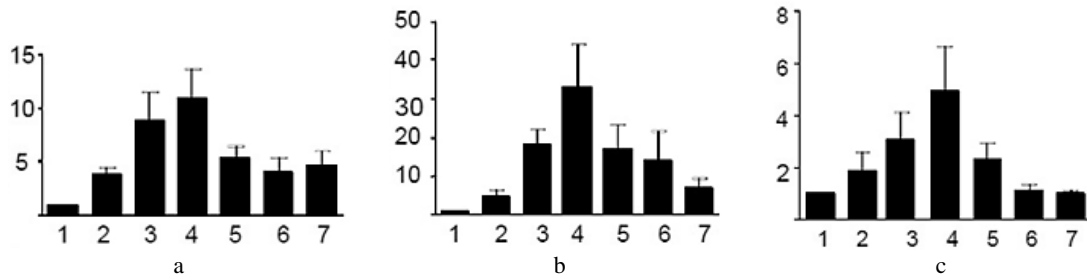


Figure 1 – The Cdx-dependent transactivation of a Pax3p1.6kb-luciferase construct: a – Cdx1; b – Cdx2; c – Cdx4

In each case, fold induction was compared to the reporter vector alone [21].

It is important to note that Luciferase reporter constructs consisting of the Pax3 150 bp minimal promoter (min) with or without regions of the Pax3 promoter were assayed for Cdx2 transactivation [21].

Figure 2 shows the Wnt-Cdx pathway that was previously proposed for the induction of the Pax3 expression in the posterior neural plate.

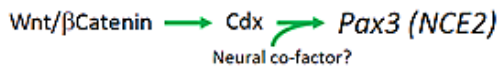


Figure 2 – The Wnt-Cdx pathway that was previously proposed for the induction of the Pax3 expression in the posterior neural plate

It was suggested that the expression in the closed neural tube would be maintained by the activity of Tead2 and Brn1/2 transcription factors [21].

3.2 TOPSIS method

A version of TOPSIS in Python was used to optimize the properties of the transcription factors. The distances from the best and worst alternatives (d_i^* and d_i^-) and closeness coefficients (CC_i) were determined for each

candidate [26, 27]. First, the evaluation matrix was created, including the entry data. Then, its values were normalized with the vector normalization using the formula below:

$$r_{ij} = \frac{x_{ij}}{\sqrt{\sum_{i=1}^m x_{ij}^2}} \quad (1)$$

The next step was to create the weighted normalized decision matrix by multiplying the weight values by the normalized data. The formula below was used in this step:

$$v_{ij} = w_j \cdot r_{ij} \quad (2)$$

The ideal solutions were determined according to the maximum values for the profit criteria and the minimum values for the cost criterion.

The separation distances from these solutions were calculated, and then the similarity coefficients were obtained with TOPSIS. The formulas below were used in this step:

$$D_j^* = \sqrt{\sum_{i=1}^m (v_{ij} - v_i^*)^2}, \quad j = \overline{1, J} \quad (3)$$

$$D_j^- = \sqrt{\sum_{i=1}^m (v_{ij} - v_i^-)^2}, \quad j = \overline{1, J} \quad (4)$$

The rank inversion was not a problem in the current study as ranking, and its inversion were presented and used in the Python code of the version of TOPSIS. This article presents the candidates' ranking according to the first rank.

4 Results

We analyzed four candidates: Cdx1 (1st candidate, C1), Cdx2 (2nd candidate, C2), Cdx4 (3rd candidate, C3), and EnRCdx1 (4th candidate, C4).

Relative expression of mRNA and expression regulation of pax3-luciferase were considered profit criteria, whereas labor for plasmid preparation and analysis was considered cost criterion. The expression levels were divided by 10 to get the values between 0.10 and 1.00. The first results are summarized in Tables 1–8.

Table 1 – The crisp values of the candidates' properties

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3- luciferase	Labor for plasmid preparation and analysis
C1	0.33	0.90	1.00
C2	0.44	1.00	1.00
C3	0.37	0.40	1.00
C4	0.01	0.20	1.00

Table 2 – The weights applied for each criterion of Cdx transcription factors

Alternatives/ Values	Relative expression for mRNA	Expression regulation of pax3- luciferase	Labor for plasmid preparation and analysis
C1–C4	0.50	0.50	0.50

Table 3 – The criteria matrix

Alternatives/ Values	Relative expression for mRNA	Expression regulation of pax3- luciferase	Labor for plasmid preparation and analysis
C1–C4	True	True	False

Table 4 – The normalized decision matrix

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3- luciferase	Labor for plasmid preparation and analysis
C1	0.4978	0.6348	0.50
C2	0.6637	0.7053	0.50
C3	0.5581	0.2821	0.50
C4	0.0151	0.1411	0.50

Table 5 – The weighted normalized decision matrix

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3- luciferase	Labor for plasmid preparation and analysis
C1	0.1659	0.2116	0.1667
C2	0.2212	0.2351	0.1667
C3	0.1860	0.0940	0.1667
C4	0.0050	0.0470	0.1667

Table 6 – The best and the worst alternatives for Cdx transcription factors

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3- luciferase	Labor for plasmid preparation and analysis
A*	0.2212	0.2351	0.1667
A ⁻	0.0050	0.0470	0.1667

Table 7 – The distances from the best alternative and the worst alternative

Candidates	d_i^*	d_i^-
C1	0.0600	0.2302
C2	0.0000	0.2866
C3	0.1454	0.1870
C4	0.2866	0.0000

Table 8 – The similarity coefficients and rankings for Cdx transcription factors

Candidates	CC_i	Ranking
C1	0.7930	2
C2	1.0000	1
C3	0.5626	3
C4	0.0000	4

Figure 3 shows the distances from the best and worst alternatives and the similarity coefficients of the Cdx transcription factors.

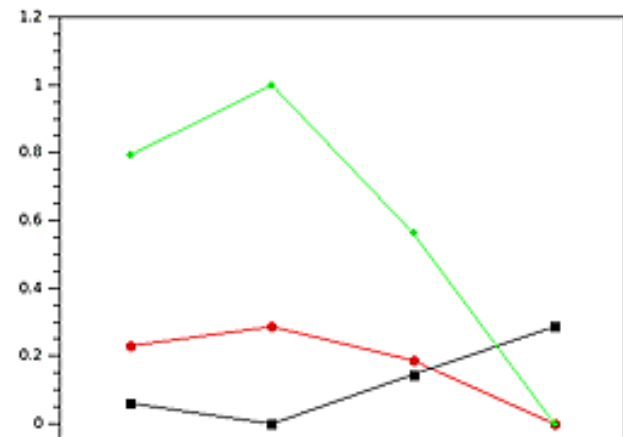


Figure 3 – The distances from the best and worst alternatives and the similarity coefficients of the Cdx transcription factors with the black (C1), red (C2), and green (C3) lines, respectively

As shown in Figure 3, the second candidate (Cdx2) has the best rank position, whereas the other candidates (Cdx1 and Cdx4) have the 2nd and third rank positions, respectively. The repressor domain EnRCdx1 has the last rank position.

In the second series of our analysis on transcription factors, we reduced the cost criterion (labor). Tables 9–16 show the corresponding results after the second analysis series.

Ass the characteristics of candidate 2, the Cdx2 transcription factor was more robust than the other transcription factors, and the weight value of the first protein was considered more than those of the other ones.

Table 9 – The crisp values of the candidates' properties with the reduced labor values

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3-luciferase	Labor for plasmid preparation and analysis
C1	0.33	0.90	0.50
C2	0.44	1.00	0.50
C3	0.37	0.40	0.50
C4	0.01	0.20	0.50

Table 10 – The weights applied for each criterion of transcription factors

Alternatives/ Values	Relative expression for mRNA	Expression regulation of pax3-luciferase	Labor for plasmid preparation and analysis
C1–C4	0.50	0.80	0.50

Table 11 – The criteria matrix

Alternatives/ Values	Relative expression for mRNA	Expression regulation of pax3-luciferase	Labor for plasmid preparation and analysis
C1–C4	True	True	False

Table 12 – The normalized decision matrix

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3-luciferase	Labor for plasmid preparation and analysis
C1	0.4978	0.6348	0.50
C2	0.6637	0.7053	0.50
C3	0.5581	0.2821	0.50
C4	0.0151	0.1411	0.50

Table 13 – The weighted normalized decision matrix

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3-luciferase	Labor for plasmid preparation and analysis
C1	0.1383	0.2821	0.1389
C2	0.1843	0.3135	0.1389
C3	0.1550	0.1254	0.1389
C4	0.0042	0.0627	0.1389

Table 14 – The best and the worst alternatives for Cdx transcription factors

Candidates/ Criteria	Relative expression for mRNA	Expression regulation of pax3-luciferase	Labor for plasmid preparation and analysis
A*	0.1843	0.3135	0.1389
A-	0.0042	0.0627	0.1389

Table 15 – The distances from the best alternative and the worst alternative

Candidates	d_i^*	d_i^-
C1	0.0557	0.2572
C2	0.0000	0.3088
C3	0.1904	0.1634
C4	0.3088	0.0000

Table 16 – The similarity coefficients and rankings for Cdx transcription factors

Candidates	CC_i	Ranking
C1	0.8219	2
C2	1.0000	1
C3	0.4618	3
C4	0.0000	4

Figure 4 shows the distances from the best and worst alternatives and the similarity coefficients of the Cdx transcription factors.

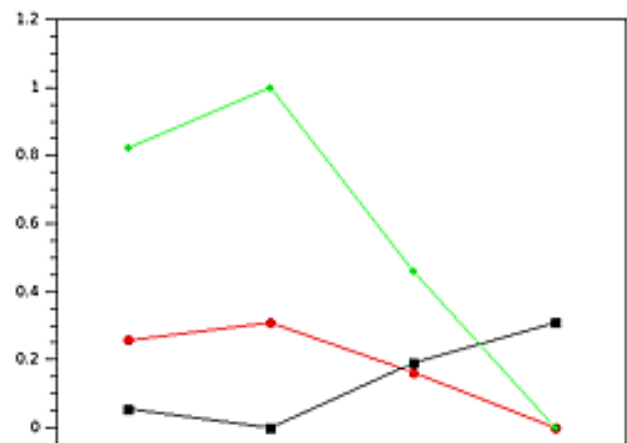


Figure 4 – The distances from the best and worst alternatives and the similarity coefficients of the Cdx transcription factors with the black (C1), red (C2), and green (C3) lines, respectively

As shown in Figure 4, the second candidate (Cdx2) has the best rank position, whereas the other candidates (Cdx1 and Cdx4) have the second and third rank positions, respectively. The repressor domain (EnRCdx1) has the last rank position.

Thus, the second analysis series does not change the rank positions of the candidates.

5 Discussion

The comparison of the ranks in the two analysis series in the current study showed the same ranking for the candidates. In other words, no effect was observed due to the weights of their characteristics on their ranking. Therefore, although the criteria weights can affect the evaluation results, no effect was obtained for the cases in which the same or different weights were considered for the candidates in this study.

Previous studies have shown the Cdx and Brn1 transcription factors' synergic effects in regulating the pax3 gene expression [21, 22].

Modified TOPIS, including Łukasiewicz fuzzy disjunction, was used previously to adjust the maximum of the membership degrees of candidates. This version of TOPSIS helped perform an automated decision-making process to control the algorithm's output [28, 29]. The modified TOPSIS can be used to determine the rank positions of the Cdx transcription factors when their synergic effect with other transcription factors can be considered to regulate the pax3 gene expression. The same approach can be used to investigate the synergic effects of other transcription factors on the expression regulation of other genes.

The properties of some materials with diverse applications have also been investigated [30–34]. Some of these materials have been studied in science and engineering [35–39]. More investigations are required to investigate the automated decision-making process for optimizing these materials with the TOPSIS method.

Another critical issue to investigate would be predicting different gene expression pathways with TOPSIS. This can help to classify different biomolecules related to the pathway information [40] and gene expression [41–45] that have crucial impacts on the output of these pathways [46–51]. Recently, this technique has been used to predict the properties of some biomolecules [52–54]. The investigations on optimizing different materials, such as water and machine learning algorithms for proteomic analysis, have been done with TOPSIS [55, 56].

The novelty of the current work is that this is a new optimization of the transcription factors as biological

materials with this technique that has not been done previously. Moreover, the modified TOPSIS with fuzzy disjunction was used in these works, which can also be used to optimize these proteins in further work.

Automated decision-making with modified TOPSIS was used previously [29], which can help compare the properties of these materials with this technique.

6 Conclusions

This article presented a new insight into the application of TOPSIS to optimize the characteristics of the Cdx transcription factors and revealed their position ranks with this method. The current study aimed to determine the best candidate and the rank of other candidates as well as the effect of the weights of their characteristics on their ranks.

As expected, a better output for the Cdx2 transcription factor than the other proteins was observed. The repressor domain showed the worst rank position. This result coincided with the fact that this domain showed the weakest characteristics in the previous studies. Moreover, the current study showed that the weights of the characteristics of the transcription factors did not affect their ranks.

The synergic effects of these transcription factors with other proteins in regulating various gene expressions can be optimized with this decision-making method, as presented in this article.

The novel application of TOPSIS for optimizing the Cdx transcription factors properties can open new insights into improving gene expression regulation and its applications in computer engineering in the future.

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