A Differential Evolution for Operon Prediction

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***Abstract*—An operon is the basic unit of transcription. The structural gene in the operon is co-transcribed into single-stranded mRNA sequence, and thus operons contribute to the understanding of transcription rules. However, experimental methods for detecting operons are extremely difficult and time-consuming to execute, thus using operon prediction as pre-treatment can greatly reduce the cost of performing an experimental assay. Scholars used different algorithms with biological properties to predict genome operons distributions. In this study, we employ a differential evolution algorithm with three biological properties to predict the operons of bacterial genomes. Three biological properties of the *Escherichia coli* genome are used: the intergenic distance, the metabolic pathway and the cluster of orthologous groups (COG); these properties are used to train the evaluation standards of the fitness function of gene pairs. Then the accuracy (ACC), sensitivity (SN) and specificity (SP) of four b acterial genomes are calculated to evaluate the prediction method. The experimental results show that the accurauy values for the four genomes were 0.923, 0.954, 0.963 and 0.963, respectively. A comparison with other methods in the other literature is proves that our method can effectively be used for operon prediction.**

***Index Terms*—operon prediction, Differential Evolution, intergenic distance, metabolic pathway, cluster of orthologous groups.**

I. Introduction

In prokaryotic organisms operons of bacterial genomes contain valuable information, for drug design and protein functions. An operon contains a promoter, an operator, one or more continuously-structural gene, and a terminator. The structural gene is co-transcribed into a single strand of mRNA, which provides information that is translated into proteins. However, experimental methods for detecting operons are extremely difficult and time-consuming [1] thus raising the urgency of developing an effective prediction method. This research focuses on using machine learning and biological properties for operon prediction. Since the co-transcribed genes have the same biological properties, machine learning can be applied to these biological properties for operon prediction. The prediction results of an assay can be used as reference data, thus greatly reducing costs and improving the effectiveness of experimental detection.

In recent years, several properties have been proposed in studies to infer prokaryote operon structures, namely intergenic distance, conserved gene clusters, functional relations, genome sequence-based, and experimental evidence [2]. Genome sequence-based promoters and terminators are most commonly used for operon prediction for these five properties [3], with intergenic distance being the simplest to predict. It is widely used in operon prediction because the distance between operon pairs (i.e., adjacent genes within a single operon) is significantly less than the distance between non-operon pairs (i.e., adjacent genes within different operons), thus intergenic distance on its own can yield good operon prediction results [2]. Since genes in the same operon often show similar functional relations, this property also provide good prediction results. Metabolic pathways [4], clusters of orthologous groups [5], and gene ontologies [3] are also often used for operon prediction.

Operon prediction methods proposed in recent years include hidden Markov models [6], support vector machines [7], probabilistic learning [8], Bayesian networks [9], fuzzy guided genetic algorithms [1], and genetic algorithms. This study uses the differential evolution of an optimization algorithm to predict operons. The *Escherichia coli* (NC_000913) genome was used to train the fitness value of a gene pair, and accuracy testing was conducted using four test data sets. The fitness function evaluation standard was based on the intergenic distance, the metabolic pathway and the cluster of orthologous groups (COG) of the *E. coli* genome, and the log-likelihood [10] was used to assess the scores of three biological properties.

We propose a simple and highly accurate computational method for operon prediction. We used the direction and distance between adjacent genes to encode chromosomes during the initialization process, and considered the relationship of adjacent and nearby genes in the iterative process. Continuous iterations can results in a operon combination We tested our method on the *B. subtilis* (NC_000964), *P. aeruginosa PA01* (NC_002516), *S. aureus* (NC_002952) and *M. tuberculosis* (NC_000962) genomes. Experimental results on the four test data sets indicate that the proposed method obtained higher levels of accuracy, sensitivity, and specificity than can be obtained from other methods from the literature.

II. Methodology

A. Training score based on biological properties

In this study, the *E. coli* genome is used to train various property scores. Accuracy tests are then conducted on the

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testing data genomes by further dividing the training data set to estimate prediction accuracy during the search. Predictors are easier to build for large data sets like the *E. coli* genome. We applied three biological properties for operon prediction: the intergenic distance, the metabolic pathway and the cluster of orthologous groups (COG). These three properties for the *E. coli* genome were used to assess the possibility of an assumed operon, with assessment scores calculated by the log-likelihood method. The properties and score assessment method are introduced below.

1) Intergenic Distance

Adjacent genes within the same operon are usually characterized by short distances, and adjacent genes may sometimes even overlap. Hence a short intergenic distance indicates that genes are more likely to be located in the same operon. [11]. Yan and Moult [12] further proposed that the distance distribution frequency of non-operon pairs increases with distance, and gradually becomes higher than the frequency of operon pairs. We chose this feature as an evaluation criterion. The log-likelihood method for the scores is given in Eq.1:

$$\mathrm{LL}_{\mathrm{Property}}\left(gene_i, gene_j\right) = \ln\left(\frac{N_{WO}(distance)/TN_{WO}}{N_{TUB}(distance)/TN_{TUB}}\right) \quad (1)$$

where $N_{WO}(distance)$ and $N_{TUB}(distance)$ respectively correspond to genes with the same characteristics on the number of WO and TUB pairs. TN_{WO} and TN_{TUB} are the total pair numbers of WO and TUB, respectively. Table I shows the score of each interval of the *E. coli* genome, each of which is based on 10bps [13]. The table shows that, if the distance between a gene pair is -4 bps, the score of the gene pair is 2.22656. It also shows that the short distances between gene pairs often obtain higher scores.

2) Metabolic Pathway

Genes within an operon often participate in the same biological process [7] and co-transcribed genes often share the same properties and functional relations. Therefore, this property can also be used to predict whether a gene pair is located in the same operon. Using Eq.1 to calculate the gene pair score of metabolic pathways based on the *E. coli* genome shows that, if the adjacent gene has the same metabolic pathway, the gene pair has a score of 2.671; otherwise the score is 0.

3) Cluster of Orthologous Groups

The Cluster of Orthologous Groups (COG) contains three levels biological functions; each level can be subdivided into several functional categories. The first level is divided into four main categories, namely (1) information storage and processing, (2) cellular processing and signaling, (3) metabolism and (4) different COG categories. We use Eq.1 to calculate the scores of categories (1), (2) and (3) of the first level. Gene pairs have a score for one of these three categories when the gene pair shares the same categories. If the gene pair belongs to different COG categories, the score of this category is calculated with Eq.2. Table 2 shows the training scores of this property.

$$\mathrm{LL}_{\mathrm{Property}}\left(gene_i, gene_j\right) = \ln\left(\frac{1-N_{WO}(COG)/TN_{WO}}{1-N_{TUB}(COG)/TN_{TUB}}\right) \quad (2)$$

B. Differential Evolution

The differential evolution algorithm (DE) was proposed by Storn and Price in 1995 [14] and has been shown to have superior solving ability. The DE algorithm is similar to the genetic algorithm (GA) and particle swarm optimization (PSO); all are optimized algorithms. The differential evolution

TABLE I
INTERVALS OF INTERGENIC DISTANCE USING THE LOGARITHMIC LIKELIHOOD METHOD FOR E. COLI GENOME

Interval	Score	Interval	Score	Interval	Score
[$-\infty$, -99]	-0.82457	[30, 39]	0.568643	[170, 179]	-1.83357
[-100, -91]	0.00000	[40, 49]	-0.67375	[180, 189]	-1.98772
[-90, -81]	1.478014	[50, 59]	-0.52852	[190, 199]	-1.51772
[-80, -71]	0.00000	[60, 69]	-0.43437	[200, 209]	-2.35497
[-70, -61]	-0.31375	[70, 79]	-0.6435	[210, 219]	-1.98772
[-60, -51]	0.00000	[80, 89]	-0.6322	[220, 229]	-3.4918
[-50, -41]	0.533552	[90, 99]	-0.55887	[230, 239]	-2.23556
[-40, -31]	-0.22673	[100, 109]	-1.48787	[240, 249]	-2.25966
[-30, -21]	0.379401	[110, 119]	-1.15683	[250, 259]	-2.79865
[-20, -11]	2.019145	[120, 129]	-1.43768	[260, 269]	0.00000
[-10, -1]	2.22656	[130, 139]	-1.84221	[270, 279]	-3.33417
[0, 9]	2.2105	[140, 149]	-2.66512	[280, 289]	-2.1329
[10, 19]	2.340637	[150, 159]	-1.80384	[290, 299]	-2.83947
[20, 29]	1.564274	[160, 169]	-1.78965	[300, ∞]	-2.96611

TABLE II
FREQUENCIES OF ADJACENT PAIRS FOR DIFFERENT COG FUNCTIONAL CATEGORIES AND THEIR SCORES IN THE E. COLI GENOME

COG main categories of the first level	OP pairs frequency	NOP pairs frequency	Score
Information storage and processing	0.046	0.018	0.9360
Cellular processing and signaling	0.105	0.023	1.4996
Metabolism	0.271	0.085	1.1543
Different COG categories	0.579	0.873	-0.4112

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algorithm (GA) and particle swarm optimization (PSO); all are optimized algorithms. The differential evolution algorithm includes three steps: mutation, recombination and selection. In selection, DE uses a one-to-one elimination mechanism to update the chromosome, which is similar to the recording of the best experience in PSO. DE considers the correlation between multiple variables; this coupling has an advantage over PSO. The differential evolution algorithm has superior random searching performance and simple parameter settings, leading it to be widely used in various fields including data mining, electronic engineering and decision support. Below, the several DE processes are introduced, including (1) Chromosome encoding, (2) Initialization, (3) Fitness evaluation, (4) Mutation, (5) Recombination and (6) selection.

1) Chromosome encoding

To evaluate prediction accuracy, we must first define the adjacent gene pair for operon prediction. Adjacent genes in the same operon are called operon pairs (OP) and are positive. If an operon contains only a single gene or if it contains an adjacent gene within a different operon is called a non-operon pair (NOP) and the gene pair is negative. If we assume an adjacent gene within the same operon, then the upstream gene of the adjacent gene will be coded 1. On the other hand, if the gene is coded 0, the gene and downstream gene are assumed to be NOP. For example, coding the chromosome x_i = (1, 1, 0, 0, 1, 0) indicates the assumption that $gene_1$, $Gene_2$ and $Gene_3$ are located in the same operon; $Gene_4$ is a single-gene operon; $Gene_5$ and $Gene_6$ belong to a single operon.

2) Initialization

The initialization process is divided into two steps. In the first step the preferred initial solution is obtained and, in the second step the execution of the DE algorithm is facilitated. As shown in Fig. 1, in the first step we use the direction and distance of adjacent genes to generate a binary coding and randomly generate a threshold for each chromosome between from 0-600bps [1]. The distance is calculated by Eq.3 [15]. If the distance of the adjacent gene is greater than the random threshold value and the adjacent gene has the same direction, the upstream gene is encoded as 1 (such as $Gene_1$); $Gene_2$ is encoded as 0 because the distance between $Gene_2$ and $Gene_3$ is exceeds the threshold. $Gene_n$ is encoded 0 because it is the last gene in the genome. In the second step, we divide the binary sequence into a plurality of 8-bit snippets, and convert these 8-bit binary sequences into decimal sequences to finish encoding the chromosome.

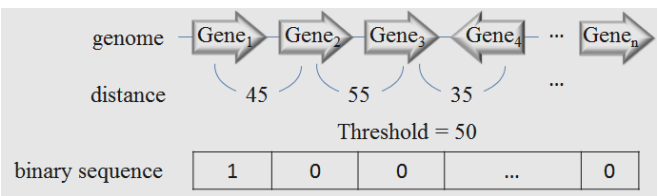

Fig 1. Diagram of binary sequence

$$\text{distance} = Gene_2\_start - (Gene_1\_finish + 1) \quad (3)$$

where $Gene_1\_finish$ is the base end position of the upstream gene, and $Gene_2\_start$ is the base start position of the downstream gene.

3) Fitness evaluation

In this study, we converted the decimal chromosome encoding of DE into binary encoding for assessment, and used intergenic distance, metabolic pathway and COG gene properties to calculate the fitness value. By using the training scores of the *E. coli* genome to obtain the overall pair-score of the adjacent genes, Eq. 4 is used to calculate the fitness value of the c^{th} putative operon.

$$fitness(operon_{th}) = \sum_{i=1}^{m-1}(d_i) - d_m + \frac{\sum_{i=1}^{m-1}\sum_{j=i+1}^{m}(S_{path}(gene_i, gene_j) + S_{COG}(gene_i, gene_j))}{n} \times m \quad (4)$$

where m and n are the total number of genes and gene pairs in the $operon_{th}$, respectively. Finally, the fitness value of a chromosome is calculated as the sum of the fitness values from all putative operons in the chromosome as follows:

$$fitness_{c^{th}} = \sum_{i=1}^{c} fitness(operon_i) \quad (5)$$

where c is the number of operons in the particle.

4) Mutation

In DE, each chromosome (Target vector, $X_{i,G}$) randomly selects three variable vectors ($X_{r1,G}$, $X_{r2,G}$ and $X_{r3,G}$) from the chromosome group, and uses Eq. 6 to combine the three variable vectors into a donor vector ($V_{i,G+1}$). In Eq.6, F is a scale factor which controls the length of the exploration vector ($X_{r2,G} - X_{r3,G}$).

$$V_{i,G+1} = X_{r1,G} + F(X_{r2,G} - X_{r3,G}) \quad (6)$$

where i is the target chromosome; G is the number of generations**.**

5) Recombination

When the donor vector has been generated by mutation, the target vector ($X_{j,i,G}$) and donor vector ($V_{j,i,G}$) is exchanged by crossover rate (CR), and thus generated $u_{i,G+1}$ (trial vector or final offspring) by Eq.7.

$$u_{j,i,G+1} = \begin{cases} V_{j,i,G} & ,if\ rand \le CR \\ X_{j,i,G} & ,if\ rand > CR \end{cases} \quad (7)$$

where *rand* is a random number between 0 and 1; j is the dimension of the chromosome i under examination.

6) Selection

The resulting $u_{i,G+1}$ is evaluated following a one-by-one spawning strategy, such as Eq. 8. $u_{i,G+1}$ replaces x_i when $f(u_{i,G+1}) \le f(X_{i,G})$; otherwise, replacement does not occur.

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$$X_{i,G+1} = \begin{cases} u_{i,G} & ,if\ F(u_{i,G}) \geq F(X_{i,G}) \\ X_{i,G} & ,otherwise \end{cases} \quad (8)$$

C. Parameter settings

In this study, the parameter value for the population number *P* is 20, the iteration number *G* is 100, the scale factor (*F*) is 0.5, the crossover rate (*CR*) is 0.5, and the initialization thresholds are between 0 and 600 bps.

III. Experimental results and discussions

A. Data sets

In the study, experimental data sets consisted of the *E. coli*, *B. subtilis*, *P. aeruginosa PA01, S. aureus* and *M. tuberculosis* genomes; the data sets respectively contain 4430, 4160, 5566, 2656 and 3988 genes, respectively. All experimental data and annotated genes can be downloaded from the GenBank database (http://www.ncbi.nlm.nih.gov/). The data records the definition, name, number, start position, end position, direction, and product names of each gene. We obrained the experimental operon data of the *E. coli* and *B. subtilis* genome form the OperonDB [15] and DBTBS (http://dbtbs.hgc.jp/) [16] databases; and the operon data of the *P. aeruginosa PA01* genome, *S. aureus* and *M. tuberculosis* genome from the ODB (http://odb.kuicr.kyoto-u.ac.jp/) [17]. The genome's metabolic pathway and COG were obtained from KEGG (http://www.genome.ad.jp/kegg/pathway.html) and NCBI (http://www.ncbi. nlm.nih.gov/COG/).

B. Performance measurement

Tables III and IV show the medical diagnostics assessment methods. TP and FP represent true and false positives, and TN and FN represent true and false negatives. Table III is used to calculate the sensitivity (SN), specificity (SP) and accuracy (ACC) [16]. If, for example, a gene sequence is encoded as 111010, our prediction result is 110110. $Gene_1$, $Gene_2$ and $Gene_5$ are TP, $Gene_3$ is FN, $Gene_4$ is FP, and $Gene_6$ is TN. Finally, the sensitivity, specificity and accuracy are calculated using the equations in Table VI and are compared with results obtained by the other methods. It should be noted that the proposed method achieved a good balance between sensitivity and specificity.

TABLE III
THE POSITIVE AND NEGATIVE EVALUATION

Prediction \ True	Positive	Negative
Positive	TP	FP
Negative	FN	TN

TABLE VI
EVALUATION METHOD FOR OPERON PREDICTION

Value to be estimated	Equation for estimation
Sensitivity	TP/(TP+FN)
Specificity	TN/(FP+TN)
Accuracy	(TP+TN)/(TP+FP+TN+FN)

C. Prediction results

We use the DE algorithm to identify the highest probability of operon combinations in a gene sequence, and compare the result with the experimentally verified operons to calculate TP, FN, TN, and FP and evaluate accuracy, sensitivity, and specificity. The results, shown in Table V, are compared to those of the other methods. The proposed method obtains accuracy values of 0.907, 0.954, 0.954 and 0.954, respectively, for the *B. subtilis*, *P. aeruginosa PA01*, *S. aureus* and *M. tuberculosis* genomes. Although we only used three features for prediction (fewer than are used in other operon prediction methods), our method achieved a good balance between sensitivity and specificity. Since the resulting prediction accuracy compares well with that achieved by other methods, the proposed method can be used to solve operon prediction problems.

TABLE V
ACCURACY, SENSITIVITY, SPECIFICITY OF THREE GENOMES

Genome	Methodology	Accuracy	Sensitivity	Specificity
B. subtilis (NC_000964)	DE	**0.923**	**0.910**	0.934
	BPSO[18]	0.921	0.887	0.945
	UNIPOP [20]	0.792	0.782	0.821
	GA [11]	0.883	0.873	0.897
	Using both genome-specific and general genomic information [21]	0.902	N/A	N/A
	SVM [7]	0.889	0.900	0.860
	ODB [22]	0.632	0.499	**0.992**
	FGA [1]	0.882	N/A	N/A
	JPOP [23]]	0.746	0.720	0.900
P. aeruginosa PA01 (NC_002516)	DE	**0.954**	**0.967**	0.935
	BPSO[18]	0.933	0.930	**0.939**
	GA [11]	0.813	0.870	0.763
S. aureus (NC_002952)	DE	**0.963**	**0.972**	0.945
	BPSO[18]	0.959	0.959	**0.959**
	Genome-wide operon prediction in *Staphylococcus aureus* [24]	0.920	N/A	N/A
M. tuberculosis (NC_000962)	DE	**0.963**	**0.963**	**0.963**
	BPSO[18]	0.951	0.944	**0.963**
	A Predicted Operon map for Mycobacterium tuberculosis [25]	0.908	N/A	N/A

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D. Discussion

The DE algorithm is similar to a genetic algorithm and particle swarm optimization, but the DE also considers the multivariate correlation, and hence has an advantage over PSO in solving problems where variables are coupled. DE uses a one-on-one elimination mechanism to update the population, which makes it easier for it to find the global optima.

Since the genome contains many genes (i.e., the solution space is very large), the initialization step is very important for operon prediction. To enhance DE prediction performance, we use the direction and distance to generate the initial population instead of a random method. This improves the fitness value of the population of chromosomes in the initialization step, and updating the population effectively improves operon prediction accuracy through multiple iterations. The direction of the adjacent gene is important for operon prediction because adjacent genes having different directions must belong to different operons, and can thus effectively predict NOP to enhance prediction accuracy and specificity. And the port of threshold of intergenic distance, adjusting the initial threshold to 600 bps raises the sensitivity and specificity of the gap [18]. Therefore, we used these two conditions for initialization.

Most methods use the properties of adjacent genes to determine whether a gene pair is OP or NOP, while ignoring the importance of the relationship between a gene and its neighbors. To increase the likelihood of finding an optimal solution, the DE fitness functions must consider the properties of nearby genes. The log-likelihood method is used to design the fitness function and to assess the scores of each property. In this study, we selected the *E. coli* genome as the training data since the *E. coli* genome has been extensively studied in experiments, and the majority of its operons has been experimentally confirmed, thus increasing the credibility of *E. coli* as a training data set. Theoretically, the use of additional properties for operon prediction should yield prediction results with a degree of higher confidence.

In operon prediction, selecting biological properties and designing a fitness function both directly affect the prediction results. Even though adjacent genes have related features, they could possibly belong to different operons, and hence the two factors above are the key to successful operon prediction. We select the metabolic pathway and cluster of orthologous groups to predict operons because DVDA [19] only used homologous genes for prediction, yielding unsatisfactory results. ODB [17] used the intergenic distance, metabolic pathway, microarray and Gene order conservation as properties, but failed to achieve a good balance between sensitivity and specificity. Therefore, we chose features based on feature utilization and prediction results. The three features used in this study are the same in those used in the GA study. However, even though GA also used microarray expression data, the proposed method achieved a higher accuracy level, indicating that the three features used in DE are effective for operon prediction.

IV. Conclusions

An effective operon prediction method with improved differential evolution is proposed. The direction and intergenic distance of adjacent genes are considered in the initialization step, and the log-likelihood method is used to design the fitness function to further improve evaluation accuracy. Experimental results show that DE, using only three kinds of biological properties, can obtain excellent prediction results. Future research will use a greater variety of biological properties to predict operons and provide related prediction results to provide a better understanding of the impact of other features on the operon prediction problem.

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