Chaotic Inertia Weight Particle Swarm Optimization for PCR Primer Design

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ABSTRACT

In order to provide feasible primer sets for performing a polymerase chain reaction (PCR) experiment, many primer design methods have been proposed. However, the majority of these methods require a long time to obtain an optimal solution since large quantities of template DNA need to be analyzed, and the designed primer sets usually do not provide a specific PCR product size. In recent years, particle swarm optimization (PSO) has been applied to solve many problems and yielded good results. In this paper, a logistic map is proposed to determine the value of inertia weight of PSO (CIWPSO) to design feasible primers. Accuracies for the primer design of the Homo sapiens RNA binding motif protein 11 (RBM11), mRNA (NM_144770), and the Homo sapiens G protein-coupled receptor 78 (GPR78), mRNA (NM_080819) were calculated. Five hundred runs of PSO and the CIWPSO primer design method were performed on different PCR product lengths and the different methods of calculating the melting temperature. A comparison of the accuracy results for PSO and CIWPSO primer design showed that CIWPSO is superior to the PSO for primer design. The proposed method could effectively find optimal or near-optimal primer sets.

Keywords: Polymerase chain reaction (PCR), primer design, particle swarm optimization (PSO), chaos

1. INTRODUCTION

A feasible primer set is required before performing polymerase chain reactions (PCR). The PCR method is used for fast mass duplication of DNA sequences [1] and is a common technology applied in the biomedical and biotechnology field. Before a PCR experiment can be successfully performed, a primer set has to be designed. In primer design numerous constraints, such as the length, length difference, GC content, melting temperature (T_m), difference of melting temperature ($T_{m\text{-}diff}$), GC clamp, dimer, hairpin and specificity of a primer pair need to be considered, and large quantities of template DNA need to be analyzed. Manually designing primers is unsuitable due to the complexity of the processes involved. Consequently, design of feasible primer sets using automatic computation is preferable.

Many primer design methods have been proposed to date for the design of feasible primer sets. Kämpke *et al.* design primers using dynamic programming [2]. This allows for designing multiple primers for multiple target DNA sequences. However, the method requires a relatively long time to obtain a suitable primer set. Chen *et al.* used thermodynamic theory to evaluate the fitness of primers to develop the web-based tool PDA for primer design [3] and Wu *et al.* proposed a genetic algorithm (GA) imitating nature's process of evolution and genetic operations on chromosomes in order to achieve optimal solutions [4]. Hsieh *et al.* developed an efficient algorithm using automatic variable fixing and automatic redundant constraint elimination to tackle the binary integer programming problem associated with the minimal primer set (MPS) selection problem [5]. Wang *et al.* employed a greedy algorithm to generate a MPS specifically annealed to all open reading frames (ORFs) in a given microbial genome, thus improving the

hybridization signals of microarray experiments [6]. Miura *et al.* developed an algorithm that identifies the specificity-determining subsequence (SDSS) of each primer and examines its uniqueness in the target genome [7]. We have previously presented a memetic algorithm (MA) [8] and particle swarm optimization (PSO) method [9] to search for feasible primers.

During the past decade, PSO has been applied to all kinds of problems and yielded promising results. PSO, developed by Kennedy and Eberhart in 1995 [10], is a population-based stochastic optimization technique that simulates the social behavior of organisms, such as birds in a flock, and describes an automatically evolving system. However, many studies in the literature report the premature convergence of PSO and that the process may get trapped in a local optimum easily when handling complex multimodal problems [11-14]. Chaos has ergodic and stochastic properties, and contains elements of certainty. By following chaotic orbits, a global optimum or a good approximation may eventually be reached with high probability in a dynamic system. In this paper, we use a logistic map to determine the value of inertia weight of PSO named (CIWPSO) to improve the performance of the primer design. Different PCR product lengths and melting temperature calculations are used to compare the performances of PSO and CIWPSO.

2. PROBLEM DEFINITION

The primer design problem is defined in this section. Let T_D be the template DNA sequence, which is made up of base-nucleic acid codes of the DNA, i.e., 'A', 'T', 'C', or 'G'. T_D can then be defined as follows:

$$T_D = \{B_i \mid \forall B_i \in \text{'A' or 'T' or 'C' or 'G'}, i \in Z^+\} \quad (1)$$

where, B represents the base-nucleic acid sequence made up of the base-nucleic acid codes of the DNA; i is the index of the position on T_D, and Z^+ represents the region of positive integers.

The primer design problem now consists of finding a pair of sub-sequences in T_D for corresponding constraints. One sub-sequence is called the forward primer and the other is called the reverse primer. The forward primer and the reverse primer are defined as follows:

$$P_f = \{B_i \mid \forall B_i \in \{\text{'A','T','C','G'}\}, F_s \le i \le F_e \le T_D, i \in Z^+\} \quad (2)$$

$$P_r = \{\overline{B_i} \mid \forall B_i \in \{\text{'A','T','C','G'}\}, R_s \le i \le R_e \le T_D, i \in Z^+\} \quad (3)$$

where, P_f is the forward primer, and F_s and F_e denote the start index and the end index of P_f in T_D. P_r is the reverse primer, and R_s and R_e denote the start index and the end index of P_r in T_D. Together, P_f and P_r are called a primer pair. The anti-sense sequence of B is called $\overline{B}$. This anti-sense sequence $\overline{B}$ is the reverse of the complementing sequence of B.

In Fig. 1, the length of the template DNA is T_l, the minimum PCR product length is P_{min}, the maximum PCR product length is P_{max}, the start position of the forward primer is F_s, the length of the forward primer is F_l, the PCR product length between the forward primer and the reverse primer is P_l, the length of the reverse primer is R_l, the random range of F_s is F_{s_Range}, and the length from F_s to the template DNA end is P_{Range}. Now, a vector given by F_s, F_l, P_l and R_l can determine a primer pair. We define this vector P_v as:

$$P_v = (F_s, F_l, P_l, R_l) \quad (4)$$

In order to determine the reverse primer start index, we use the following equation:

$$R_s = F_s + P_l - R_l \quad (5)$$

The forward primer (P_f) and the reverse primer (P_r) can both be obtained through P_v. This vector P_v is the prototype of a particle in the PSO, and later sections will use P_v to perform PSO primer design. Table 1 summarizes the parameters used in Fig. 1.

3. PRIMER DESIGN METHOD

The flowchart of the proposed method is shown in Fig. 2. The separate processes of 1) initialization of particle swarm, 2) determination of initial inertia weight, 3) evaluation of fitness value, 4) judgment of termination condition, 5) finding *pbest* and *gbest*, 6) updating of inertia weight using chaos, and 7) updating of velocity and position of each particle, are described below.

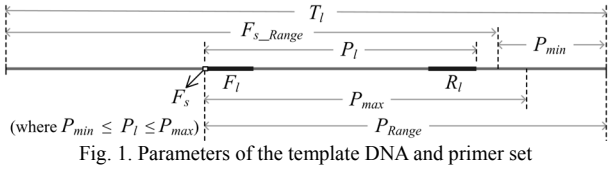

Fig. 1. Parameters of the template DNA and primer set

TABLE I. PARAMETERS USED IN FIGURE1.

Parameter	Description
F_s	Start position of the forward primer
F_l	Length of the forward primer
P_l	PCR product length between forward primer and reverse primer
R_l	Length of the reverse primer
F_{s_Range}	Random range of F_s
P_{min}	Minimum PCR product length
P_{max}	Maximum PCR product length
P_{Range}	Length from F_s to the template DNA end
T_l	Length of template DNA

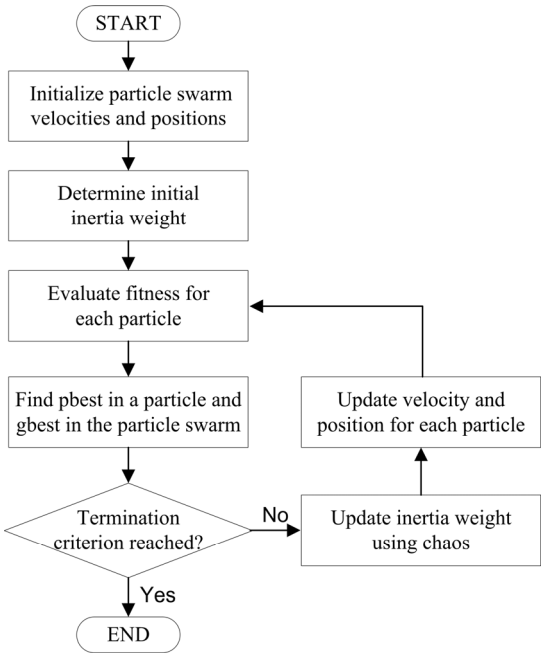

Fig. 2. Flowchart of the proposed algorithm for PCR primer design.

1) Initialization of particle swarm

Initially, ten particles $P_v = (F_s, F_l, P_l, R_l)$ are randomly generated as an initial particle swarm without duplicates. F_s is randomly generated between 1 and $(T_l - P_{min} + 1)$. F_l is randomly generated between the minimum length of the primer and the maximum length of the primer. In the present study, the minimum length of the primer was set to 16 bps and the maximum length of the primer was set to 28 bps. In order to limit the PCR product length, we did not select $P_l = R_e - F_s + 1$, but instead randomly generated P_l between P_{min} and P_{max}. R_l was randomly generated in the same way as F_l. Each particle is given a velocity (v). This velocity is randomly generated within 0~1.

2) Determination of initial inertia weight

Chaos is highly sensitive to its initial conditions. Small differences in the initial conditions yield widely diverging outcomes and can make long-term prediction impossible [15]. This inertia weight is subsequently updated and fine tuned by a chaotic map. In this paper, we initialize an inertia weight equal to 0.8 which is commonly used in other studies, to test the performance of CIWPSO.

3) Evaluation of fitness value

A fitness function is used to evaluate the fitness value of each particle in order to check whether the candidate primers satisfy the design constraints or not. The primer design constraints are used as estimated values for the fitness function, and the produced fitness value is minimized.

A primer length between 16 bps and 28 bps is considered feasible for a PCR experiment [4]. If a primer is longer, its specificity may be higher, and a relatively high T_m is required. On the other hand, a relatively short primer may have a decreased specificity. Hence, neither a primer that is too long nor too short is suitable. We did not include the length constraint in the fitness function, because F_l and R_l are always limited between the minimum length and the maximum length of the primer under the constraints. The fitness value is provided by the following fitness functions, which are made up of $Len_{diff}(P_v)$, $T_m(P_v)$, $T_{mdiff}(P_v)$, $GC_{proportion}(P_v)$, $GC_{clamp}(P_v)$, $dimer(P_v)$, $hairpin(P_v)$ and $specificity(P_v)$, each of which is described below:

$$\begin{aligned} Fitness(P_v) = 3 * (&Len_{diff}(P_v) + GC_{proportion}(P_v) + GC_{clamp}(P_v)) \\ &+ 10 * (Tm(P_v) + Tm_{diff}(P_v) + dimer(P_v) \\ &+ hairpin(P_v)) + 50 * specificity(P_v) \end{aligned} \quad (6)$$

The weights of components in the fitness function are 3, 10 and 50 based on their importance. A larger weight indicates that the constraint is more importance. The weights are can be adapted freely by users to different conditions.

A primer length of 16 to 28 bps is considered feasible for a PCR experiment is considered between 16 and 28 bps [4]. If a primer is longer, its specificity may be higher, and a relatively high T_m is required. On the other hand, a relatively short length decreases the specificity. Hence, neither a primer that is too long nor too short is suitable. In this study, the primer length is not considered in the fitness function since the random values of F_l and R_l always satisfy the constraints.

A primer length difference less than or equal to 3 bps of difference for the forward primer and the reverse primer is considered optimal [4]. The $Len_{diff}(P_v)$ function is used to check this condition. The $Tm(P_v)$ function is used to check whether the melting temperature of a primer pair is between 50°C and 62°C. The $Tm_{diff}(P_v)$ function checks whether the T_m difference between the forward and reverse primer exceeds 5°C, as a lower T_m difference indicates a better primer pair. In this study, the melting temperatures (T_m) of primers are calculated by the Wallace formula [16]. The computational formula for T_m is:

$$Tm_W(P) = (\#G + \#C) * 4 + (\#A + \#T) * 2 \quad (7)$$

where, P represents the forward primer or reverse primer, #G represents the number of 'G', #C represents the number of 'C', #A represents the number of 'A' and # T represents the number of 'T'. The suffix W represents the

formula which was proposed by Wallace.

Furthermore, a more elaborate equation proposed by Bolton and McCarthy [17] that takes the ionic strength, G and C content and the length of the primer into account was is also used in this study.

$$Tm_{BM}(P) = 81.5 + 16.6(\log_{10}[Na^+]) + 0.41 * (\text{GC content}) - 675/|P| \quad (8)$$

where, P represents a primer and $|P|$ represents the length of primer P; $[Na^+]$ is the molar salt concentration. The suffix BM represents the formula which was proposed by Bolton and McCarthy.

The $GC_{proportion}(P_v)$ function is applied to evaluate the GC proportion in a primer. It calculates the ratio of nucleotide G and C that appear in a primer. An appropriate GC proportion in a primer should be in the range of 40-60%. The $GC_{clamp}(P_v)$ function is used to check whether the 3' terminal end of a primer is G or C. It ensures that the primer has a tightly localized hybridization bond. Furthermore, the *dimer*(P_v) function is used to check whether the forward primer and the reverse primer anneal to each other or anneal to themselves. The *hairpin*(P_v) function is used to check if a primer anneal to itself. The annealing of primers is detrimental to the PCR experiment. Finally, the *specificity*(P_v) function is used to judge whether the primer reappears itself in the template DNA sequence, and thus it ensures the specificity of the primer. The PCR experiment is more easily successful if the primer is specific which means it is annealed to specific position of the template sequence.

4) Judgment of termination condition

The proposed method is terminated when *gbest* has achieved the best position, i.e., its fitness value is 0, or when a maximum number of generations have been reached. When the termination condition is reached, *gbest* is the optimal solution for the primer design in the respective run.

5) Finding *pbest* and *gbest*

One of the characteristics of PSO is that each particle has a memory of its own best experience. This is true for CIWPSO as well. Each particle needs to find its personal best position and velocity (called *pbest*), and all particles must determine the global best position and velocity (called *gbest*). If the fitness of a particle P_v is better than the fitness of *pbest* in the previous generation, *pbest* will be updated to P_v in the current generation. If the fitness of a particle P_v is in turn better than *gbest* in the previous generation and is the best one in the current generation, *gbest* will be updated to P_v. Based on *pbest* and *gbest*, each particle adjusts its direction in the next generation.

6) Updating of inertia weight using chaos

In PSO, the inertia weight is used to balance the global and local search ability. A large inertia weight facilitates a global search while a small inertia weight facilitates a local search [18]. In order to adjust the search ability, the inertia weight is changed dynamically using a chaotic system. In this paper, we propose a logistic map to generate chaotic sequence for updating inertia weight. The logistic map used to determine the value of inertia weight is described by:

$$w(t+1) = 4.0 \times w(t) \times (1 - w(t)), \quad w(t) \in (0,1) \quad (9)$$

where the value of w at (t+1)th iteration is represented by w(t+1).

7) Updating of velocity and position of each particle

In each generation, the particles will change their position and velocity. Equations (20) and (21) give the updating formulas for each particle.

$$v_i^{next} = w \times v_i^{current} + c_1 \times r_1 \times (s_i^p - s_i^{current}) + c_2 \times r_2 \times (s_i^g - s_i^{current}) \quad (10)$$

$$s_i^{next} = s_i^{current} + v_i^{next} \quad (11)$$

In equations (10) and (11), v_i^{next} is the updated velocity of the ith particle; $v_i^{current}$ is the current velocity of the ith particle; c_1 and c_2 are the acceleration coefficients; w is the inertia weight; r_1 and r_2 is a number which is randomly generated within 0~1; s_i^p is the personal best position of the ith particle; s_i^g is the global best position of the particles; $s_i^{current}$ is the current position of the ith particle; s_i^{next} is the updated position of the ith particle. In order to avoid a particle overshooting the limits of F_s, F_l, P_l and R_l when being updated, we use a random process to reset the position of an unavailable particle based on the primer constraints.

4. RESULTS AND DISCUSSIONS

Data sets and environment

The template sequence of the Homo sapiens RNA binding motif protein 11 (RBM11), mRNA (NM_144770), and the Homo sapiens G protein-coupled receptor 78 (GPR78), mRNA (NM_080819) were tested with PSO and the proposed method CIWPSO for primer design. Five main parameters, namely the number of iterations (generations), the number of particles, the inertia weight w, and the acceleration coefficient c_1 and c_2 were set in the PSO and CIWPSO primer design methods for the computational simulations. These values were set

to 100, 10, 0.8, 2 and 2, respectively. Five hundred runs were performed with the PSO and CIWPSO primer design methods, with PCR product lengths in 150~300 bps, 500~800 bps and 800~1000 bps, and a T_m calculated by the Wallace formula and the Bolton and McCarthy formula. The simulated environment used a Pentium 4 CPU 3.4 GHz and 1GB of RAM under Microsoft Windows XP SP3.

Comparison of the primer design results

The results of the PSO and CIWPSO primer design methods for the Homo sapiens RNA binding motif protein 11 (RBM11), mRNA (NM_144770), and the Homo sapiens G protein-coupled receptor 78 (GPR78), mRNA (NM_080819) with different product lengths are shown in Table II and Table III, respectively.

Average accuracies of 79.8 % and 84.3% were reached when the CIWPSO primer design method with the Wallace formula was used to design NM_144770 and NM_080819 for different product lengths. However, the average accuracies only got up to 68.0% and 64.6% when PSO was used under the same circumstances. The accuracies of the CIWPSO primer design method are thus 12.3% and 23.2% higher than for PSO primer design method for the two template sequences. Furthermore, the average accuracies reached 75.3% and 73.3% when CIWPSO was used with T_m calculation by the Bolton and McCarthy formula. The average accuracies only got up to 57.3% and 39.8% when PSO was used under these conditions. The accuracies of the CIWPSO primer design method were thus 18.0% and 33.5% higher than the accuracies of the PSO primer design method for the two template sequences.

The CIWPSO primer design method also outperformed the PSO primer design method in terms of the average running time with different T_m calculations. The computationally simulated results show that the performance of the proposed CIWPSO method is superior to the performance of PSO for the primer design problem.

The proposed chaos effect for inertia weight

Chaos is a deterministic, random process found in non-linear system. It is greatly sensitive to its initial conditions. Small differences in initial conditions yield widely diverging outcomes making long-term prediction impossible [15]. Mathematically, chaos may be considered a source of randomness since its simple deterministic dynamical behavior. In this study, we propose a logistic map to generate chaotic sequences for updating the inertia weight. The proposed chaotic map behaves chaotically in (0, 1). Since chaos possesses elements of certainty, ergodicity, and stochastic properties, it was introduced to control the movement of the particles. This allowed us to eventually reach a good approximation of optimal results with high probability.

TABLE II. ACCURACY AND RUNNING TIME FOR THE PSO AND CIWPSO PRIMER DESIGN METHODS. COMPUTATIONALLY SIMULATED RESULTS FOR THE HOMO SAPIENS RNA BINDING MOTIF PROTEIN 11 (RBM11), MRNA (NM_144770) USING THE WALLACE FORMULA AND BOLTON AND MCCARTHY FORMULA WITH PCR PRODUCT LENGTHS IN 150 ~ 300 BPS, 500~800 BPS AND 800~1000 BPS. A, ACCURACY (%); T, RUNNING TIME (MS). BOLDFACE INDICATES HIGHEST VALUES.

T_m formula and primer design methods	Wallace's formula				Bolton and McCarthy formula			
	PSO		CIWPSO		PSO		CIWPSO	
PCR product length	a (%)	t (ms)	a (%)	t (ms)	a (%)	t (ms)	a (%)	t (ms)
150~300 bps	68.0	371562	**81.6**	308766	56.0	435235	**73.6**	352735
500~800 bps	69.6	387406	**76.2**	368141	58.4	424687	**73.6**	352297
800~1000bps	65.0	395454	**81.6**	308703	57.4	425094	**78.6**	325531
average	67.5	384807	**79.8**	328537	57.3	428339	**75.3**	343521

TABLE III. ACCURACY AND RUNNING TIME FOR THE PSO AND CIWPSO PRIMER DESIGN METHODS. COMPUTATIONALLY SIMULATED RESULTS FOR THE HOMO SAPIENS G PROTEIN-COUPLED RECEPTOR 78 (GPR78), MRNA (NM_080819) USING THE WALLACE FORMULA AND BOLTON AND MCCARTHY FORMULA WITH PCR PRODUCT LENGTHS IN 150 ~ 300 BPS, 500~800 BPS AND 800~1000 BPS. A, ACCURACY (%); T, RUNNING TIME (MS). BOLDFACE INDICATES HIGHEST VALUES.

T_m formula and primer design methods	Wallace's formula				Bolton and McCarthy formula			
	PSO		CIWPSO		PSO		CIWPSO	
PCR product length	a (%)	t (ms)	a (%)	t (ms)	a (%)	t (ms)	a (%)	t (ms)
150~300 bps	64.6	370812	**92.2**	236453	45.0	463844	**78.8**	333032
500~800 bps	66.8	362219	**83.4**	321438	45.2	489078	**78.0**	344079
800~1000bps	52.0	454219	**77.4**	328016	29.2	544641	**63.0**	416453
average	61.1	395750	**84.3**	295302	39.8	488188	**73.3**	364521

5. CONCLUSION

Primer design has become an important issue over the last decade. The quality of primers always influences whether a PCR experiment is successful or not. To date, many primer design methods and tools have been developed, but most of these are inefficient or fall short of designing optimal primers pairs for PCR experiments. PSO is considered an efficient algorithm widely applied to solve various optimization problems. However, PSO tends to get trapped in a local optimum easily when applied to complex problems. In this study, we propose a logistic map embedded in PSO to improve the performance of the primer design.

The proposed CIWPSO designs optimal primers with primer constraints, such as primer length, primer length difference, GC proportion, PCR product length, melting temperature (T_m), melting temperature difference ($T_{m\text{-}diff}$), GC clamp, dimers (including cross-dimer and self-dimer), hairpin and specificity used to appraise the fitness values. Each constraint was given a suitable weight based on its significance. Through the evolution of a fitness function, feasible primer sets could always be obtained using the CIWPSO method. The primer design results show that different methods of T_m calculation affect the size of the primer length and the melting temperature. A shorter primer length and lower temperature value were obtained when Wallace formula was used to calculate Tm, whereas a longer primer length and a higher temperature value were obtained when the Bolton and McCarthy formula was used to calculate Tm. The computationally simulated results indicate that the proposed method can design optimal or near-optimal primer sets. The CIWPSO primer design method could be a valuable tool for biologists and researchers involved in related research fields.

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REFERENCES

[1] K. B. Mullis and F. A. Faloona, "Specific synthesis of DNA in vitro via a polymerase-catalyzed chain reaction," *Methods Enzymol,* vol. 155, pp. 335-350, 1987.

[2] T. Kämpke, M. Kieninger, and M. Mecklenburg, "Efficient primer design algorithms," *Bioinformatics,* vol. 17, pp. 214-225, Mar 2001.

[3] S. H. Chen, C. Y. Lin, C. S. Cho, C. Z. Lo, and C. A. Hsiung, "Primer Design Assistant (PDA): A web-based primer design tool," *Nucleic Acids Res,* vol. 31, pp. 3751-3754, Jul 2003.

[4] J. S. Wu, C. Lee, C. C. Wu, and Y. L. Shiue, "Primer design using genetic algorithm," *Bioinformatics,* vol. 20, pp. 1710-1717, Jul 2004.

[5] M. H. Hsieh, W. C. Hsu, S. K. Chiu, and C. M. Tzeng, "An efficient algorithm for minimal primer set selection," *Bioinformatics,* vol. 19, pp. 285-286, Jan 2003.

[6] J. Wang, K. B. Li, and W. K. Sung, "G-PRIMER: greedy algorithm for selecting minimal primer set," *Bioinformatics,* vol. 20, pp. 2473-2475, Oct 2004.

[7] F. Miura, C. Uematsu, Y. Sakaki, and T. Ito, "A novel strategy to design highly specific PCR primers based on the stability and uniqueness of 3'-end subsequences," *Bioinformatics,* vol. 21, pp. 4363-4370, Dec 2005.

[8] C. H. Yang, Y. H. Cheng, L. Y. Chuang, and H. W. Chang, "Specific PCR product primer design using memetic algorithm," *Biotechnology progress,* vol. 25, pp. 745-753, 2009.

[9] C. H. Yang, Y. H. Cheng, H. W. Chang, and L. Y. Chuang, "Primer Design with Specific PCR Product using Particle Swarm Optimization," *International Journal of Chemical and Biomolecular Engineering,* vol. 3, pp. 18-23, 2010.

[10] J. Kennedy and R. Eberhart, "Particle swarm optimization," *IEEE International Conference on Neural Networks,* vol. 4, pp. 1942-1948, 1995.

[11] F. Van den Bergh and A. P. Engelbrecht, "A cooperative approach to particle swarm optimization," *IEEE Transactions on Evolutionary Computation,* vol. 8, pp. 225-239, 2004.

[12] J. J. Liang, A. K. Qin, P. N. Suganthan, and S. Baskar, "Comprehensive learning particle swarm optimizer for global optimization of multimodal functions," *IEEE Transactions on Evolutionary Computation,* vol. 10, pp. 281-295, 2006.

[13] X. Yang, J. Yuan, J. Yuan, and H. Mao, "A modified particle swarm optimizer with dynamic adaptation," *Applied Mathematics and Computation,* vol. 189, pp. 1205-1213, 2007.

[14] S. T. Hsieh, T. Y. Sun, C. C. Liu, and S. J. Tsai, "Efficient population utilization strategy for particle swarm optimizer," *IEEE Trans Syst Man Cybern B Cybern,* vol. 39, pp. 444-56, Apr 2009.

[15] S. H. Kellert, *In the wake of chaos: Unpredictable order in dynamical systems*: University of Chicago Press, 1993.

[16] R. B. Wallace, J. Shaffer, R. F. Murphy, J. Bonner, T. Hirose, and K. Itakura, "Hybridization of synthetic oligodeoxyribonucleotides to phi chi 174 DNA: the effect of single base pair mismatch," *Nucleic Acids Res,* vol. 6, pp. 3543-57, Aug 10 1979.

[17] J. Sambrook, E. F. Fritsch, and T. Maniatis, *Molecular cloning*: Cold Spring Harbor Laboratory Press Cold Spring Harbor, NY, 1989.

[18] Y. Shi, R. C. Eberhart, E. Team, and I. N. Kokomo, "Fuzzy adaptive particle swarm optimization," *Proceedings of IEEE International Conference on Evolutionary Computation,* vol. 1, pp. 101-106, May 2001.