**Artemisinin Optimization based on Malaria Therapy: Algorithm and Applications to Medical Image Segmentation**

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**Inspiration from the malaria treatment**

One of the most dreaded illness is one caused by a species of parasitic protozoa known to man as Malaria caused by the Plasmodium falciparum and others in the Plasmodium family. [1]. Malaria is now a global pandemic and is a major public health problem in tropical and subtropical areas of the world such as Asia, Africa and Central and South America [2]. Among the many steps to control malaria epidemic, in the area of malaria drug treatment, under the leadership of Youyou Tu, in 2015 several Chinese scientists were able to make an important contribution in malaria treatment when they isolated and extracted a compound artemisinin from a plant artemisia annua. They purified and performed crystallographic analysis of artemisinin. This is just the first time Artemisinin was extracted by Chinese in early 1970s. Artemisinin has exceptional abilities to quickly clear the parasite load from the patient's blood, rapidly reduce clinical manifestations of malaria and give relief to the malaria patient [1, 3].

Artemisinin medications travel throughout different parts of the body and cells once they enter the human bloodstream. It's worth mentioning that red blood cells carry a significant amount of ferrous ions (Fe2+), especially in those infected by malaria parasites [4]. The artemisinin molecule has certain active groups that react chemically when they come into contact with ferrous ions. This interaction harms the biological membrane of the malaria parasite and internal biomolecules, leading to the disruption of cellular membrane integrity and causing the membrane to rupture. At the same time, artemisinin messes with the internal biochemical workings of the malaria parasite, messing up its ability to survive. When someone gets malaria, the journey from getting infected to finally finding relief with artemisinin follows a certain path [2, 5, 6]:

1. Infection: Malaria generally starts when the parasite is passed on by a mosquito's bite. After entering the bloodstream, the malaria parasite moves to liver cells, goes through various stages of development, and then invades red blood cells.

2. Malaria symptoms onset: After the malaria parasite enters red blood cells, there is a quick growth that results in the release of toxins and the start of malaria symptoms in the infected person. These signs frequently consist of elevated body temperature, shivering, head pain, and muscle soreness, indicating the start of the illness presentation.

3. Medical consultation and diagnosis: When individuals show symptoms of malaria, they usually go to a doctor for diagnosis and treatment. Healthcare providers use blood tests to verify the existence of malaria parasites in the blood.

4. Initial treatment (Attack phase): Treatment begins with the initial phase of attack, where medical professionals give artemisinin medications in higher amounts to promptly relieve malaria symptoms.

5. Subsequent medication: Patients have regular appointments for blood tests to track the advancement of the illness and guarantee successful therapy, ultimately lowering the chances of a recurrence.

6. Mid-to-Late treatment (Maintenance phase): After the initial phase of treatment, patients move on to the maintenance phase, during which they receive reduced amounts of artemisinin in order to ensure full elimination of the malaria parasites. The length of this stage changes based on the specific situations of each patient and medical advice given.

7. Complete recovery: Malaria is deemed completely healed once all malaria parasites have been eliminated from the patient’s system, and all symptoms have disappeared. This marks the end of the malaria life cycle in the host, with no parasites left.

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| **Figure 1.** Malarial parasites parasitize human body cells. |

The outlined process incorporates nuanced details: initially, upon invasion into the human body, parasites do not immediately trigger symptoms; rather, they infiltrate hepatocytes, undergoing continuous replication (the incubation period). Following a series of lifecycle stages, a substantial population of parasites enters the bloodstream, rampant infection of red blood cells, further replication, and toxin release (the active period), as shown in Figure 1. Upon seeking medical attention and receiving a confirmed diagnosis of malaria, patients commence artemisinin treatment. Prior to diagnosis, during the period of parasitization until symptomatic manifestation, malaria parasites persistently replicate and invade additional red blood cells, potentially concealing themselves at any location within the intricate spatial confines of the human body—a "complex space." Within this realm, each "unraveling" of symptoms signifies an unfolding chapter in the intricate narrative of the malaria parasite's presence. Given the dispersion of malaria parasites throughout diverse bodily regions, the purpose of employing artemisinin is to seek out and eliminate all malaria parasites, serving as a comprehensive strategy to address the complexity of their concealment within the human body.

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| **Figure 2**. Artemisinin cures malaria |

In Figure 2, in the initial treatment phase, higher doses of artemisinin medicines are employed to control malaria symptoms and reduce the parasite count swiftly. A substantial amount of the medication diffuses rapidly through the bloodstream, permeating the entire space (human body) to search for the ultimate solution (parasite). Subsequently, the treatment progresses gradually into the maintenance phase. During this stage, the medicine dosage is decreased, aiming to persist in clearing any remaining malaria parasites within the body until reaching the most concealed "solution." The ultimate objective is the complete eradication and cure of malaria. Through an analysis of the entire process and leveraging its intricate details, this study proposes the Artemisinin Optimization (AO).

**The Artemisinin optimization algorithm**

Drawing upon the analysis presented earlier, three distinct strategies have been devised based on the various stages of artemisinin treatment for malaria. The amalgamation of these three strategies forms the foundation of the AO. This section comprehensively explains the inspirations behind the design and the mathematical model.

* 1. **Initialization phase**

A patient introduces artemisinin medicines into the body through oral ingestion or injection. Drawing inspiration from this reality, this paper conceptualizes medicine microparticles as search agents for the algorithm, with the entire ensemble of these search agents constituting the algorithm's solution set. Initially, the entire population, denoted as , is initialized. As described by Eq. (1), the complete population comprises search agents, where signifies multiple-dimensional components within a search agent. This abstraction mirrors the decomposition and absorption of drugs in the human body, dispersing through the bloodstream to various locations throughout the body.

|  |  |
| --- | --- |
|  | (1) |

In the equation, and represent the boundaries of the solution space, while denotes a set of random number sequences, with values ranging between . AO employs a common approach found in metaheuristic algorithms by utilizing random number sequences to generate initial solutions.

* 1. **Comprehensive elimination phase**

During the initial phase of malaria treatment, patients are administered larger doses of medication to control the progression of the disease swiftly. Artemisinin, once absorbed, diffuses throughout the human body as blood is transported to various regions. The distribution of the drug within the body is influenced by factors such as blood flow, vascular permeability, and the drug's binding affinity to proteins. Moreover, the intricate structure of the human body poses a labyrinthine challenge for artemisinin medicines. Considering these considerations, this section introduces a unique search model to simulate the process of drug diffusion, as depicted in Eq. (2):

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|  | (2) |

In this strategy, search agents exhibit characteristics of large-scale dispersion, serving as guides to explore the intricate solution space. Here, ​ and respectively represent the search agent before and after the update, and is the current optimal. Simultaneously, the diffusion of artemisinin drugs in the human body adheres to the principles of pharmacokinetics. This strategy considers the fact that drug concentration diminishes over time. In Eq. (2), represents the decay exponent of drug concentration in the human body. The decay of artemisinin drug concentration can be described using a one-compartment model, as follows:

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|  | (3) |
|  | (4) |

In Eq. (3), the variable represents the concentration of the drug, and denotes the rate constant. Solving this differential equation yields Eq. (4): signifies the drug concentration at time . Within this model, as time progresses, the drug concentration undergoes exponential decay. Consequently, the exponent of the artemisinin drug concentration can be calculated using Eq. (5):

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|  | (5) |

In this strategy, assuming the initial drug concentration of 1 and the drug decay rate of 4, the algorithm's evaluation process is utilized to simulate the progression of time in the model. Here, and represent the current and maximum evaluation iterations of the algorithm. Acknowledging variations in the severity of patients' conditions and differences in physiological factors, which lead to distinct dosages and durations of medication, patients may spend varying durations in this phase. To encapsulate this inherent variability, a probabilistic coefficient is introduced, as depicted in Eq. (6):

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|  | (6) |

In this equation, serves as a probabilistic coefficient, incorporating the algorithm's evaluation progress to simulate the objective scenario where patients exhibit diverse responses and durations during this stage based on individual conditions. This section provides a brief simulation of the motion process for each particle, as illustrated in Figure 3. Ultimately, the comprehensive elimination phase strategy can be expressed by Eq. (7):

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|  | (7) |

where is a random number with a range of . Following the initial phase of treatment, as the disease is under control, the treatment transitions into the maintenance phase to ensure the complete cure of malaria.

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| Figure 3. Comprehensive elimination phase of particle motion. |

* 1. **Local clearance phase**

The objective of the maintenance phase is to eliminate any remaining malaria parasites in the body, preventing their reproduction and the recurrence of malaria symptoms. While early-stage treatment typically swiftly alleviates symptoms, a small number of malaria parasites may persist in the body, especially in cases of severe infection. During this phase, patients continue to receive treatment with lower doses of artemisinin and its derivatives to ensure the complete eradication of malaria parasites, minimizing the risk of adverse reactions in the human body. Inspired by this, the paper has designed a Local clearance phase strategy. In this strategy, the particle's movement process is depicted in Figure 4, calculated using Eq. (8) to determine the particle's position.

|  |  |
| --- | --- |
|  | (8) |
|  | (9) |
|  | (10) |



**Figure 4**. Local clearance phase of particle motion.

In this equation, represents the normalized fitness value, transforming the fitness values into a probability distribution to serve as relative weights among individuals. This ensures that individuals with higher fitness have a larger corresponding probability. This aids in retaining excellent individuals to a certain extent while providing lesser-performing individuals with a chance, adjusting the algorithm's focus on different individuals. The represents the coefficient, taking a random value between. This strategy simulates the process of a small amount of artemisinin clearing potential malaria parasites in the human body. The maintenance phase strategy allows the algorithm to exploit and exchange local information. In MAs, information exchange among individuals occurs during the iterative process. If an algorithm's information exchange is thorough, its performance might be notably enhanced [7, 8].

* 1. **Post-consolidation phase**

Indifference to the severity of the illness and laxity during treatment represent perilous detrimental factors. Due to the improvement of their condition, patients might gradually become less vigilant against malaria, reducing medication frequency, dosage, or even discontinuing treatment, potentially leading to a recurrence of the disease. Despite having passed through the attack and maintenance phases, where most malaria parasites in the body have been eradicated, there remains a possibility that a small fraction of parasites may gradually develop resistance to artemisinin. They may even enter a dormant phase, referred to as the "dormant form," significantly diminishing their biological activity and making it challenging for drugs to exert an effective killing effect. If treatment is discontinued, malaria parasites, after passing through the dormant form, may cause a relapse of the disease. Patients should strictly follow to the plan to have a chance to get ride of malaria.

This part presents the post-consolidation, recognizing the chance of unexpected situations and simulating this particular circumstance. It is hypothesized in this strategy that inactive parasite forms remain in the human body. Unfortunately, some patients may suffer a reappearance of malaria despite the continued presence of these dormant parasites. The model for this strategy is expressed by Eq. (11):

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| --- | --- |
|  | (11) |



**Figure 5**. Post-consolidation of particle motion.

In this equation, represents a sub-vector of the current best solution in the th dimension. Eq. (11) representing malaria parasites that have not been eliminated due to entering the dormant phase. As depicted in Figure 5, this strategy enhances the ability of search agents to escape from local optima.

* 1. **The proposed algorithm**

The entire process of treating malaria patients with artemisinin inspires the introduction of the AO. Through an examination of the treatment process for malaria and the integration of metaheuristic algorithm principles, this paper analyzes different stages, drawing inspiration to propose distinct strategies of the AO. These strategies include the comprehensive elimination phase strategy, encouraging the algorithm to perform global exploration; the local clearance phase strategy, promoting local exploitation, and the post-consolidation phase strategy, enhancing the algorithm's ability to escape local optima.

Specifically, the inspiration behind AO and the algorithm's operational flow can be outlined as follows: Initially, drawing inspiration from the parasitic nature of malaria parasites in the human body, the human body is metaphorically considered a 'space' with constraints. The invading malaria parasites are viewed as 'solutions' to be explored, and artemisinin drugs are regarded as search agents in the algorithm. Inspired by the process of controlling the disease with higher doses of medication in the initial stages of treatment, the comprehensive elimination phase strategy is introduced. Under this strategy, the AO gains global search capabilities, rapidly exploring the entire space and discovering potential regions of optimal solutions. Drawing inspiration from the gradual control of the disease in the later stages of treatment and the reduction in medication dosage, the local clearance phase strategy is proposed. This strategy allows the algorithm to explore potential local optimal solutions. Lastly, anticipating the possibility of symptom recurrence due to the awakening of dormant malaria parasites during treatment, the post-consolidation phase strategy is introduced, reinforcing the algorithm's ability to escape local optima. The pseudocode in Algorithm 1 provides a clearer understanding of the AO's operational process. The flowchart in Figure 6 visually illustrates the structure of the algorithm.

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| **Algorithm 1** Artemisinin Optimization pseudo-code |
| /\* Starting phase \*/  Parameters initializing: Fitness evaluation , Max fitness evaluation , Population size , Dimension .  Randomly initialize the agent population and evaluate their fitness ,  Find the current optimal .  /\* Main loop\*/  **While**  Calculate the probability , exponent .  **For** each agent  **For** each dimension  /\* Comprehensive elimination phase \*/  **If** rand<  Update search agent using Eq. (7).  End If  /\* Local clearance phase \*/  Update search agent using Eq. (8)  /\* Post-consolidation phase \*/  Search agent information crossover by Eq. (11)  End For  End For  Calculate the fitness .  Update the population and find the optimal.  End While  Return the optimal solution |



**Figure 6**. Flowchart of the AO

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