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MODELLING GAIT SYNDROME IN HUNTINGTON'S DISEASE: THE GENETIC ALGORITHM APPROACH

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ABSTRACT
Huntington's disease (HD) which usually affects the patients at middle age results from malfunctioning of the basal ganglia. It is characterized by cognitive impairment, involuntary movements, neuropsychiatric and psychological disturbances. Early motor signs of Huntington's disease typically include the gradual onset of clumsiness, balance difficulties, and brief, random, fidgeting movements. A popular approach to solving symptoms arising from HD has been through the administration of drugs. But drugs debase human activities, thus the application of electroconvulsive therapy. This work proposes a genetic algorithmic (GA) simulation of chorea in HD patient as a pedestal for the design of a therapeutic device aimed at managing the phenomenon. Earlier efforts have led us to the formulation of such models in recent past. We also compared the GA model with our foremost effort: the electromechanical model, and we observe that the GA model adequately capture the physiological presentation of gait phenomenon in Huntington's disease.

Keywords: *basal ganglia; chorea; genetic algorithm; Huntington's disease; mutant allele*

1. INTRODUCTION
Huntington's disease is an autosomal dominant neurodegenerative disorder that results from mutant alleles which codes a long span of trinucleotide repeats. Trinucleotide repeat disorders are a set of genetic disorders characterized by the expansion of certain genes of a segment of deoxyribonucleic acid (DNA) that contains a repeat of three nucleotides, thus exceeding the normal stable threshold: usually, there exists an increase in the number of triplet repeats as the gene is passed from generation to generation which results in abnormalities in gene expression and function [1]. Other such diseases caused by triplet repeat expansion are Fragile X syndrome, Myotonic dystrophy and Friedreich ataxia [1]. One of the basal ganglia disorders, HD is caused by dysfunction of the subcortical circuits which responsibility is to regulate movement and posture. The motivation to unveil the mystery behind HD is due to its inheritance pattern. As an autosomal dominant disorder, a 50% chance of inheritance translates to huge population of HD sufferers; it is a matter of time. Fundamentally, the study of biological cellular behavior depends on the understanding of how biological activities are governed by the connectivity of genes and proteins [2]. A way of representing such a connectivity is usually in the form of genetic regulatory networks. A gene network consists of a group of genes that interact among themselves to synthesize proteins. The types and amount of proteins produced by a gene network have a fundamental effect on the development of the gene network itself and on the biological systems with which the network interacts [2, 3].

Huntington's disease (HD) is characterized by midlife onset and a triad of symptoms, including progressive involuntary movements, neuropsychiatric disturbances, and cognitive impairment [4]. HD is caused by an enlarged CAG repeat expansion in the huntingtin protein gene on the short arm of chromosome 4, which results in a diffuse neuronal degeneration preferentially involving striatum and cortex [4, 5]. As the disease progresses, motor disability develops, especially stereotypic involuntary movements (Huntington's chorea). There is no provided treatment for delaying the development of the disease or to stop the progression of HD. Disturbances in gait are symptomatic in HD. Gait abnormalities in HD include reduced walking, widened stance width, reduced stride length and sway; gait variability has been shown to be significantly higher in HD compared to control subjects, [6]. The work in [6] revealed that a common mouse model of HD is obtained by repeated administration of the mitochondrial toxin 3-nitropropionic acid (3NP) which causes striatal neurodegeneration that results in mild dystonia and

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bradykinesia comparable to the manifestation of HD in people.

Chorea is a hallmark of Huntington disease (HD). Other attributes of the disease are cognitive decline and psychiatric impairment. It often develops early, gradually worsening and plateauing in late stages [7]. Motor dysfunction, including chorea, decrease in functional capacity, particularly in early HD. Chorea worsens with weight loss and can compromise safety with attendant increase in fall risk. Treating chorea is most probably the important part of HD management. The pathophysiology and neurochemical bases of HD are complex and incompletely understood. Dopamine and glutamate transmission and interactions are affected, contributing to striatal and cortical vulnerability featuring such presentations as chorea, [1, 7, 8]. Most agents investigated for HD chorea target the neuro transmitters and receptors, [9, 10, 11]. The current management of HD is focused on symptom reduction, because there is no treatment capable of halting the progressive global deterioration and eventual death occurring within 10–20 years of disease onset. To this end, efforts are only targeted at symptomatic management of the disease: the goals of managing HD are to reduce the impact of the disease on individuals' abilities, primarily improving motor function, in order to obtain a favorable impact on sufferers' quality of life[4, 12]. Electroconvulsive therapy has been shown to resuscitate dead brain tissues in Parkinson's disease[4]. For a proper application of the electroconvulsive therapy, a clear understanding of the gait mechanism must be sort. It is in line with this domain that this work is targeted to define the behavior of Huntington's chorea in a simulation model based on genetic algorithm simulation technique.

Huntington's disease (HD) has been studied for decades now. A presentation that makes the study of HD an important one to neuroscientists of mathematics and physical sciences origin is the rhythmic choreitheosis otherwise known as the gait syndrome that accompanies the disease. Our earlier attempts at capturing the gait phenomenon have produced positive results by way of mathematical modelling: electromechanical, artificial neural network (ANN) simulation, fuzzy set and fuzzy logic modelling techniques. One outstanding result described by [13] is the biometry of gait models based on artificial neural network simulation and the electromechanical techniques the graphical representation of which is presented in Figure 1. Figure 1 relates in some details the dynamic behaviour of the arm of HD patients in an electromechanical equation described in Cartesian coordinates with the ANN simulation of the same movement.

The two curves ably captured the phenomenon between time $T = 0$ and time $T = 28.5$ representing a steady build-up of excitatory post synaptic potentiation (EPSP) that culminates in the potentiation threshold at $T = 28$ milliseconds which explains the fact that they both approach threshold at approximately the same rate. This is the point in time when the inhibitory post synaptic potentiation (IPSP) completely failed to match the EPSP thereby resulting in a jerk [9]. Since the etiology of HD has been traced to a mutation in chromosome 4p15, and the pathogenesis of the disease is well known: it is practicable to deploy the genetic algorithm in the modelling of gait syndrome in HD for its probabilistic properties since the precipitation of action potential is not a sufficient but only a necessary condition for the production of chorea in an HD patient.

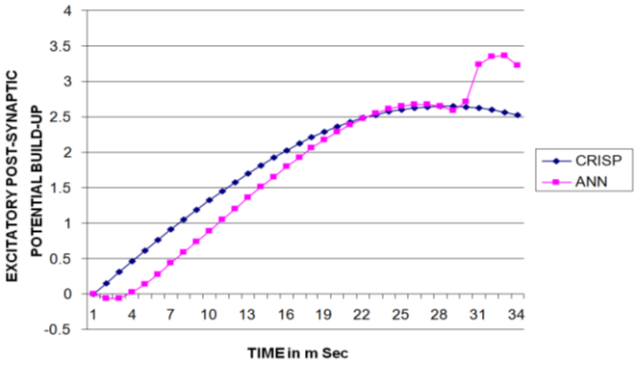

Figure 1: The ANN Analysis of Arm gait of HD Patient using sigmoid function.

A popular strategy to optimize non-linear systems with a large number of variables, Genetic Algorithm (GA) is a class of stochastic search strategies modeled after evolutionary mechanisms involving evolution of offspring from chromosomes through crossover with allowance for possibility of genetic mutation. GA is a random search optimization technique that mimics the natural selection process in that it randomly generates a new set of solutions from existing ones in order that it may improve on the quality of the solutions through all the generations [14]. In Genetic Algorithm, the crossover operation and the mutation operation are the two commonly used reproduction operators. They are user-defined guided by experience and principle, although their values (rates) may also be tuned to work for a specific problem setting. It is however possible to use other operators such as regrouping, colonization-extinction, or migration in genetic algorithms [15]. Crossover is a genetic operator used to vary the programming of a chromosome or chromosomes from one generation to the next. It is the major reproduction operator in GA that is analogous to reproduction and biological crossover, upon which genetic algorithms are based. Cross over is a process of taking more than one parent solutions and producing a child solution from them. A crossover probability (rate) that is too high may lead to premature convergence of the genetic algorithm: the crossover probabilities of between 0.60 and 0.85 are in common use in GAs.

On the other hand, mutation is a genetic operator used to maintain genetic diversity from one generation of a population of genetic algorithm chromosomes to the next. It is analogous to biological mutation. Mutation alters one or more gene values in a chromosome from its initial state. In mutation, the solution may change entirely from the previous solution. Hence GA can come to better solution by using mutation. Mutation occurs during evolution according to a user-definable mutation probability. This probability should be set low. If it is set too high, the search will turn into a primitive random search. A very small mutation rate may lead to genetic drift , i.e. change in the frequency of a gene variant in a population due to random sampling, (which is non-ergodic in nature). A mutation rate that is too high may lead to loss of good solutions unless there is elitist selection. Mutation probabilities of between 0.1 and 0.25 are in common use. The purpose of mutation in GAs is preserving and introducing diversity. Mutation should allow the algorithm to avoid local minima by preventing the population of chromosomes from becoming too similar to each other, thus slowing or even stopping evolution. In this work, we have made an attempt to advance the understanding of HD phenomenon by capturing the gait syndrome in a simulation model based on GA prowess.

2. METHODOLOGY

The procedure enunciated below elucidates the methods used in simulating chorea excitation using Genetic Algorithm. The procedure is premised on availability of real time data for such diseases as the Huntington's disease. It is premised on using any nth order polynomial,

$$F(X) = \sum_{I=0}^{N} a_i x^i \quad (1)$$

where $a_i$is the ith parameter and x^i, the ith power of the predicting variable x, to fit real life chorea excitation distribution with time using Genetic Algorithm. The GA procedure simulates values of the polynomial parameters, a_i, i $= 0, 1, \ldots, n$, and uses the Root Mean Square Error (RMSE), a statistical error measures defined as:

$$RMSE = \sqrt{\frac{\sum_{J=1}^{N}(y_j - \hat{y}_j)}{N}} \quad (2)$$

where: y_j = the data ordinate point j, j $= 1, 2, \ldots, N$
$\hat{y}_j$ is the predicted ordinate for data point j, j=1, 2,…,N
to determine the best fit polynomial parameters for the chorea distribution.

2.1 Encoding and Decoding

Various techniques of continuous distribution representation using the Genetic Algorithm for simulation are available. However, the current approach to this simulation uses denary entries (0, 1, . . . 9) into strings of byte lengths L, representing each parameter and concatenated to form the chromosomal representation of a possible parameter set simulated. The chromosomal solution set representations are then decoded by simply converting the entries to decimal values within predetermined but viable bounds $[\underline{a}_i, \overline{a}_i]$, for parameter $i = 0, 1, \ldots, n$ as,

$$a_i = a_i + (\overline{a}_i - \underline{a}_i) \sum_{k=1}^{L} \frac{d_k}{10^k} \quad (3)$$

In (3), $\overline{a}_i$, is the upper bound of parameter value and $\underline{a}_i$ is the lower bound of parameter value while d_k = denary entry of byte position in the parameter string, k = $1, 2, \ldots, L$

2.2 Crossover

One-point crossover was adopted for the evolution of chromosomal solutions. A crossover probability of 0.85 was adopted. This high crossover probability was informed by the vast and enormous combinations of possible solution representations that are possible for denary representation as against lower u-nary representations. Primarily, possibilities of crossover are determined for pairs of possible parent-chromosomes. For selected parent-chromosomes, secondary possibilities of crossing on one parameter string or the other are also determined using the same weight of probability.

2.3 Mutation

Byte-wise mutation operation was done at a probability of 0.25. Again this high mutation probability was informed by the large number of exhaustive representation combinations that were expected for denary encoding. Parent chromosomes were selected into the mating pool based on mutation probability, while the string on which mutation operation was carried out was also determined by the same probability before determining which byte position to mutate on.

2.4 Selection

Selection operation was conducted using the classical Roulette wheel mechanism. Before selection, candidate chromosomes were ranked in ascending order of statistical measure of fitness (in this case, RMSE). The selection procedure allowed some elite top-ranked chromosomes byte into the next generation.

2.5 Evaluation

The Root Mean Square Error (RMSE) as explained above was used as a measure of fitness of the chromosomes and a basis for ranking them. The different evaluation of RSME was based on calculating the ordinates $\hat{y}_j = f(x_j)$

for each epoch $j = 1, 2, \ldots, N$ in order to obtain deviation (error), $(y_j - \hat{y}_j)$, squaring each, summing over all epochs and obtaining the square root of the result. The parameters a_i's are the decoded values for each chromosome at any evaluation point. The lesser the RMSE, the better the chromosome solution and the more the chance of being selected into the ensuing generation of chromosomal solutions. The step-wise procedure for executing the Genetic Algorithm simulation is as captured in the GA-Huntington-Chorea pseudo-code below.

2.6 Programme: *GA-Huntington-Chorea*

Read GA parameters, Crossover probability, p_c, Mutation probability, p_m, String length, L, Population Size, s_p, No of Generations , G, No of batches, B (runs).
Read Problem Parameters, Number of chorea data points N, Number of parameters n, Upper parameter bound $\overline{a}_i$ for each i ,Lower parameter bound, $\underline{a}_i$, for each I, C_data (Chorea Data).

$b = 1$
Do While $b \leq B$
$g = 0$
Generate Initial Population: g = 0, for g = 0, 1, 2, . . . , G and b = 1, for b = 1, 2, 3,. . . , B
Evaluate: Population P_0
Select: Population P_1 from P_0
Do While $g \leq G$

$$g = g + 1 \quad (4)$$

Crossover: string-wise based on p_c
Mutate: *byte-wise operation based on* p_m
Evaluate: Population P_g; *evaluate fitness based on RMSE; record best solutions if* $g = G$
Select P_{g+1} from P_g
Loop

2.7 Features of Huntington's chorea

A scaled-down version of the above algorithm was used to simulate a Huntington disease chorea data with 34 epochs. The following are the GA and the problem parameters used.

3. RESULTS AND DISCUSSION

The code for executing the GA was written in Visual Basic 11 and run on an All-in-One DEL 1.67GHz Intel Core Duo CPU T2300 with 512MB memory. Results were obtained for each generation but recorded at the end of each batch-run. In all, a total of 500,000 candidate-chromosomal-solutions were generated and evaluated. The results for 20 batch-runs for a quadratic of the Huntington chorea data are as depicted in Figure 2.
The comparative analyses of results for the 20 data batch-runs for the aforementioned quadratic interpolation of the chorea syndrome in HD of Figure 3 above were based on the Root Mean Squared Error (RMSE). Figure 4 is the graphical interpretation of the pattern of distribution of the RMSE of Figure 3 showing decreasing optimal RMSE over 20 batch-runs of the GA.

Table 1: Problem parameters for GA Simulation Model

GA Parameter	Assigned Value
Crossover Probability, p_c	0.85
Mutation Probability, p_m	0.25
Population Size, P_g	500
No of generations, G	50
Number of Batches, B	20
Parameter String length, L	7
All parameter upper bounds, $\overline{a}_i$	0.1
All parameter lower bounds, $\underline{a}_i$	1×10^{-9}

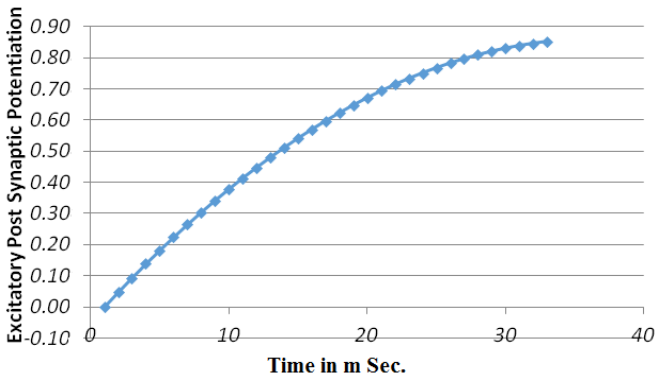

Figure 2: Graph of GA Simulation Model for Arm Gait in HD Patient.

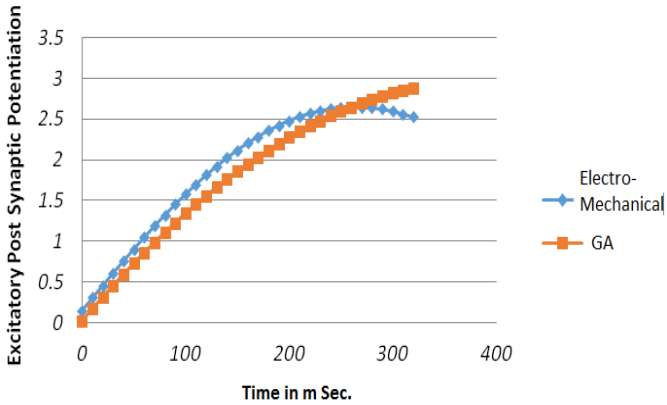

Figure 3: Comparing GA Model with Electromechanical Model for Arm gait in HD Patient.

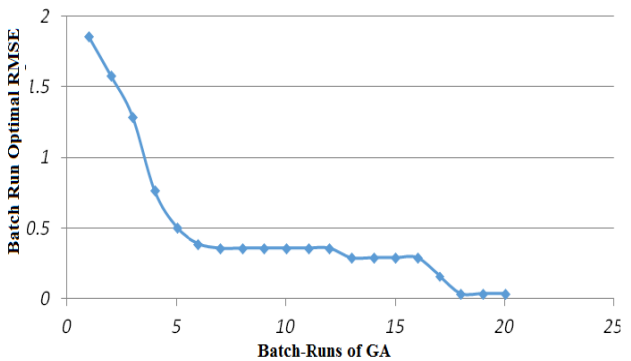

Figure 4: Optimal RMSE Distribution Over 20 Batch-Runs of GA Simulation of Gait Syndrome in HD

Figure 4 captures the distribution of the decreasing RMSE of the GA simulated for the Gait Syndrome in HD

over 20 batch-runs of the GA with 50 generations per run in which the chromosome with the best RMSE in every generation and by implication from one batch-run to the next was selected as an elite chromosome into the following generation or batch-run. The figure shows that a near-zero RMSE was obtained at the 20th batch-run eliciting the efficacy of the GA Simulation for this problem.

This paper investigates the chorea phenomenon in HD: some jerky spasmodic movements usually of facial muscles, the limbs and trunks resulting from annihilation of key nerve cells in the caudal region especially those of the medium spiny strata neurons of the basal ganglia [12, 16]. Attempts at managing Parkinsonism, a similar presentation associated with Parkinson's disease (PD) has yielded encouraging results. One of such results is the Metrode Incorporated device; a nano-robot that manages the choreiform movements associated with PD with the additional quality that it rejuvenates the central nervous system (CNS) [4]. However, electroconvulsive based therapies for other prime diseases such as seizures and muscular contractions experienced during child birth have not yielded positive results. Unlike Parkinsonism, symptomatic treatment of Huntington's chorea is chiefly done by drug administration [7, 17]. The ultimate goal of our study is to achieve the simulation model for the phenomenon which precipitates the gait syndrome in HD. Figure 1 is the outcome of our effort in this endeavour and it is in agreement with previous works in literature. The outcome of our research effort is in agreement with the existing literature [1, 5, 9, 13]. Figure 3 is a comparative analysis of the electromechanical model of gait phenomenon of [12] and the GA simulation model.

According to literature, the threshold for the precipitation of chorea in any HD patient is largely dynamic depending on the potentiality of the physiological information in the neuronal circuit of the HD sufferer, [18, 19]. Important functions of the biochemical pathways can be responsible for chorea if one of two of such functions occur simultaneously. These functions usually culminate in the boosting of weak signals and the ability to suppress over-activity. The processes that culminate in action potential and consequently a jerk where the IPSP is in short supply relative to the EPSP include: convergence phenomena where signals from different parts of the CNS may serve as input into a single motor neuron; divergence phenomena when a single neuron sends out collateral which serve as input to few or very many other neurons; temporal facilitation whereby increase in excitability brought about by successive excitatory post-synaptic potential (EPSP), earlier EPSP may facilitate effects of later EPSP in triggering nerve impulse and the effect of several such stimuli occurring in rapid succession is greater than the sum of the effect of individual stimulus while spatial facilitation occur when the effect of several simultaneous stimuli is greater than the sum of the effect of individual stimulus; synaptic facilitation involving repeated use of synapse results in considerable increase in synaptic potentials and a way of facilitating repetition of neuronal activities; occlusion is said to exist where the effect of many stimuli produced in rapid succession or simultaneously is less than the sum effect of individual stimuli [8, 20]. One or more of the aforementioned processes may have been responsible for distinct threshold levels in Figure 2 and Figure 3 [4, 21, 22, 23].

The paper investigates the chorea; a physiological attribute of HD, and presents in some detail the dynamic behaviour of HD in the arm of patients using genetic algorithm. It is often said that the etiology of HD is not yet fully understood but increasing evidence suggests that the steady progression of motor dysfunction which takes place in Huntington's disease cannot be isolated from the role of altered gene transcription, mitochondrial dysfunction and excito-toxicity consequent upon which is the distortion of smooth motion especially of the arms and this is considered as a major indicator of pre-symptomatic HD progression [24]. The analysis of these movements of the arm, which has been found to be in agreement with existing literatures in that regard, led to the generation of the model. The work is a consolidation on our previous exploration in the modeling of the chorea syndrome that characterizes the Huntington's disease. Figure 3 is only a confirmation of the convergence of the GA phenomenon [25].The results provide a springboard for further promotion of the understanding of HD with a view to proffer a management mechanism to a physiological presentation of the disease. The paper considered the global case without recourse to the stage of the disease.

4. CONCLUSION

In this paper, we have harmonized various works on choreic disorders to propose a uniquely formulated simulation model of the chorea phenomenon in Huntington's disease based on genetic algorithm. Our earlier research efforts on gait syndrome in HD have produced various models for the physiological presentation of choreiform movements in HD. The genetic algorithm being an evolutionary programming approach searches from one population of points to another with focus on the best solution while sampling the total parameter space on continuous basis[23]. One feature of GA algorithm that made it captivating for this process is the number of sub-processes such as crossover, mutation to mention but a few, that brought the procedure intimately connected to the etiological agent of HD. It is our believe that with this work we have been able to promote a better understanding of the

disorder once describe by George Huntington as an heirloom in the dim past generation.

In the nearest future we hope to capture the physiological presentation with neuro-fuzzy simulation and Markov chain procedures. It is believed that this work will provide the necessary pedestal for future work in this area of academic endeavour.

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