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Original Research Article

Neuro-Bioelectronics Retina Leaky and Integrate Neuronal Models With/Without Refractory Period Simulations Plus Neurophysiology Studies. Third Part.

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Abstract

To continue with these publications series, Structural Retina models are 2D-3D digitally simulated. The selected models are firstly Leaky Integrate and Fire model (LIAF), with/without refractory period. Innovation here is the 3D multidigital simulation for LIAF model. Additionally, a review of constrained evolutionary 3D-2D optimization algorithms for classical Integrate and Fire (IAF) is presented with 3D-spatial Pareto-Multiobjective Optimization, details are shown. All the programming software is made with realistic neurophysiological literature-datasets, with/without refractory period. The software was carried out with two systems, Matlab and GNU-Octave, comparing both. Results comprise all these 2D-3D graphical series and numerical-optimal datasets. Based on previous contributions, deduced/elaborated/reviewed pre-hypotheses for rational-conscious human-thinking, general visual system, and neurology-neuropsychiatry networks are presented. The paper is both an advance with software engineering 2D-3D imaging/multiple-imaging process and mathematical methods/formulations improvements in a review of previous publications.

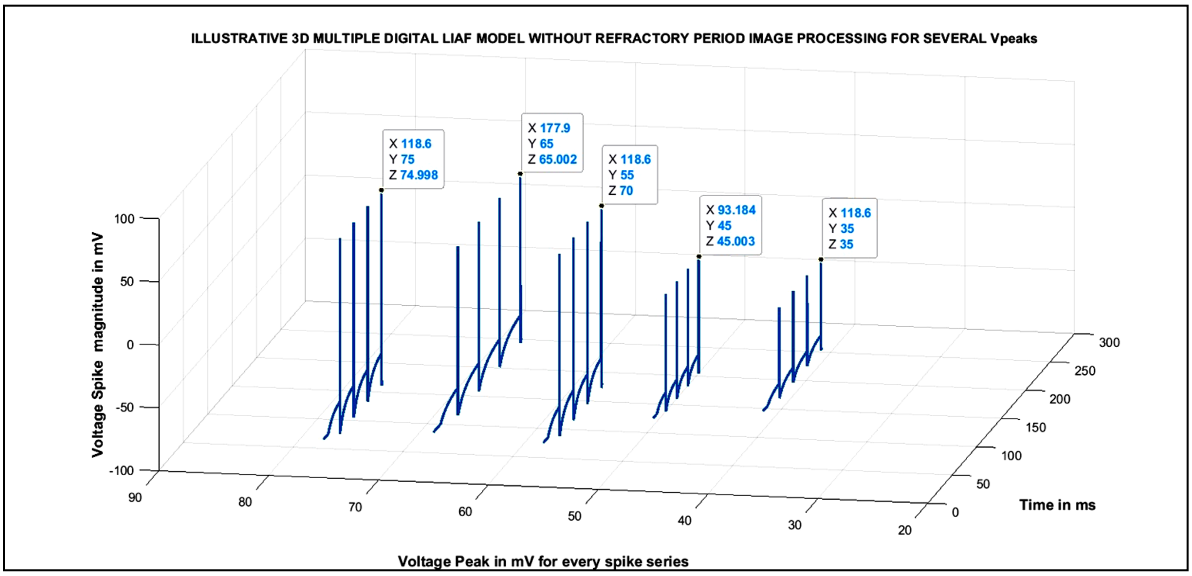
Keywords: *Mathematical Methods (MM), Biological Models (BM), Integral Equation (IE), Nonlinear Optimization, Artificial Intelligence (AI), Pareto-Multiobjective Optimization (PMO), Genetic Algorithms (GA), Leaking IAF Model (LIAF).*

1. Introduction And Objectives

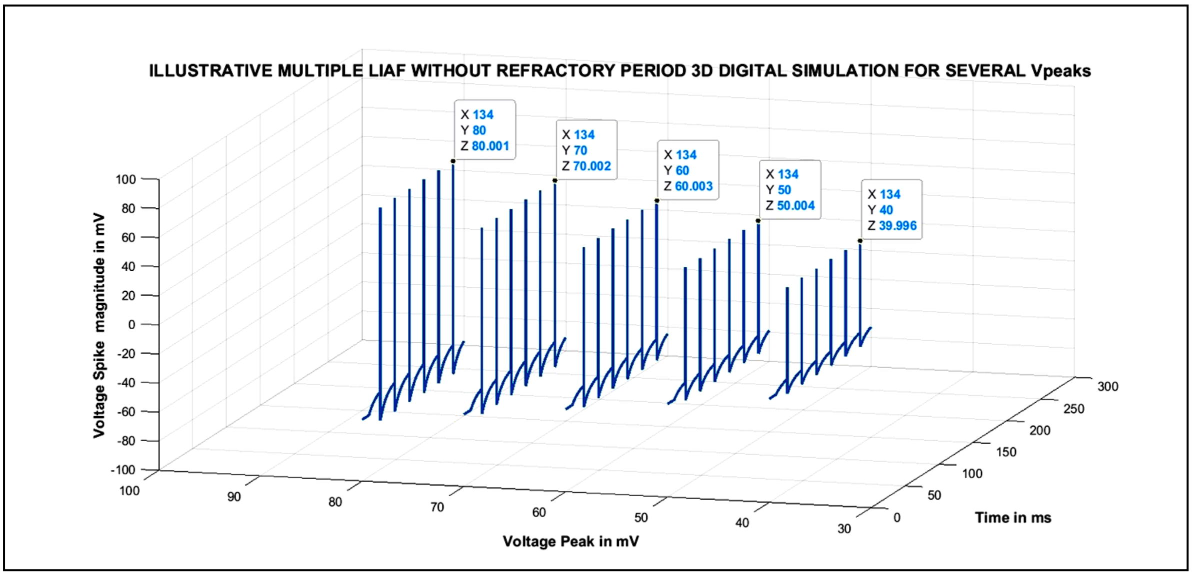
Following with Structural Retina models are 2D-3D digitally simulated. Namely, Leaky Integrate and Fire model (LIAF), with/without refractory period. Innovation here is the 3D multidigital simulation for LIAF model. The utility of 3D multidigital simulation can offer several aspects. Firstly, rapid information and numerical-functional database can be got from the system image directly. Secondly, it gives a fast overview of the neural spike trains and shapes, almost all the parameters visually can be checked/catched up.

The review of constrained evolutionary 3D-2D optimization algorithms for classical Integrate and Fire (IAF) includes further details. It is simulated with 3D-spatial Pareto-Multiobjective Optimization is shown. Database for programming software is implemented with realistic neurophysiological literature-datasets, with/without refractory period. Programming series are done with two systems, Matlab and GNU-Octave. Quality of images, precision, running time, and tools are compared, their advantages/inconvenients are commented. Reviewing previous contributions, deduced/elaborated/reviewed pre-hypotheses for reasoning, visual systems, rational-conscious human-thinking, general-biological visual system, and neurology-neuropsychiatry neural-networks are presented.

Generally/briefly speaking, Compilation 1, neuronal retinal models can be included/classified into two main groups. Namely, the broad neural networks classification and the retina specific category. Within the first are the Rate-Code, and the Time-Code (this later related to spike trains and the former data can be guessed from this one). Secondly, and specifically for retina, according to retina internal structure, there are Structural and Functional models. Structural models are classically set mostly by Differential and Integral equations, Compilation 2. Neural retina models, e. g., IAF and LIAF are not exclusive for retina neurobiology. Instead, they are implemented for several brain structures. Previously, [26], Integrate and Fire (IAF) classical retina model was optimized for several parameters with PMO. That model constitutes a base for more improved ones, such as LIAF Model (Leaking IAF Model, LIAF) [1-7]. Its mathematical algorithms are based on ordinary differential and integral equations of First Class (usually integral equations are the analytic solutions from differential equations), Compilation 2. Both IAF and LIAF can be simulated with/without refractory period. More largely, the visual system, can be seen as a part of the Fundamental Barrier Model, previously developed/improved, (Casesnoves, 2023, [Casesnoves Bioengineering Laboratory Algorithms 23.11] Instance Figure 1). Additionally for further clarification-introduction, one LIAF example in Instance Figure 2 [Casesnoves Bioengineering Laboratory Software 16.23] is shown.



Instance Figure 1.- 3D LIAF multisimulation, with four different spike series with several Vpeaks. The software design was rather complicated. Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: Is = 1 nA, Cm = 1 nF, Rm = 10 MΩ, τ =10 ; (Vth = -51 mV, Vreset = -75 mV, Vspikes = 35, 45, 65, ≈75, 70 mV simulation time 120 ms). [Casesnoves Bioengineering Laboratory Software 17.23]. The utility of 3D multidigital simulation can offer several aspects. Firstly, rapid information and numerical-functional database can be got from the system image directly. Secondly, it gives a fast overview of the neural spike trains and shapes, almost all the parameters visually can be checked/catched up.



Instance Figure 2.- 3D LIAF multisimulation, with four different spike series with several Vpeaks. The software design was rather complicated. Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: Is = 1 nA, Cm = 1 nF, Rm = 10 MΩ, τ =10; (Vth = -52.5 mV, Vreset = -75 mV, Vspikes = ≈ 40, 50, 60, 70, 80 mV simulation time 120 ms). [Casesnoves Bioengineering Laboratory Software 17.24].

RETINA NEURONAL MODELS BRIEFING			
MODEL GROUP	**TYPES**	**CHARACTERISTICS**	**COMMENTS**
Structural for Retina	For example, IAF, LIAF	Use Differential Equations Generally	Not difficult programming
Functional for Retina	Deterministic and Stochastic models	**Deterministic:** rate-code type, output response is homogeneous and steady for a given input stimulus **Stochastic:** simulate stochastic variability of the retinal response adding noise functions/parameters	Could be difficult programming, Deterministic models use Kernels. A variant of Stochastic is White-Noise models
General Neural Models	Rate-code	Related to the Retina Ganglia Cells output for given the light stimulus,	Common models Applied in Neurophysiology and Neurobiology
	Time-Code	for a time-code model its output corresponds to the spike train related to the encoding of the gathered image.	

Compilation 1.- Briefing of Retina and General Neuronal models. This is an introduction. Today, that research modelling area is continuously improving. [Casesnoves Bioengineering Laboratory 19.01].

BRIEFING OF MATHEMATICAL METHODS FOR RETINA AND GENERAL NEURONAL MODELS			
GENERIC METHOD	**VARIANT(S)**	**ALGORITHMS**	**COMMENTS**
Integral Equation	Simple, Double or Multiple, with one or several variables	The multiple Integral equations are	For IAF LIAF and early Structural Models
Ordinary Differential Equation	First order and First Order with Convolutions	Analytic and Numerical methods or mixed	There are many programming options, both directly for the equation and numerical/analytical or mixed, very frequently exponentials
Convolution Methods and Kernels, laplace Transforms	Several types of use in Integral equations combined or not	These algorithms seem difficult, but analytic solution can be dealt	Necessary to understand these methods, very frequently exponentials combinations
Statistical Methods, Correlation, Regression, Probability	Poisson methods,	Several variants included in simple or several variables multiple integrals	Poisson integrals are not difficult, Correlation either
Special Functions	Dirac-Delta (for spike-firing settings in models or integrals), Heaviside	Those are set in integrands, and usually combined with convolutions	Necessary to understand these methods

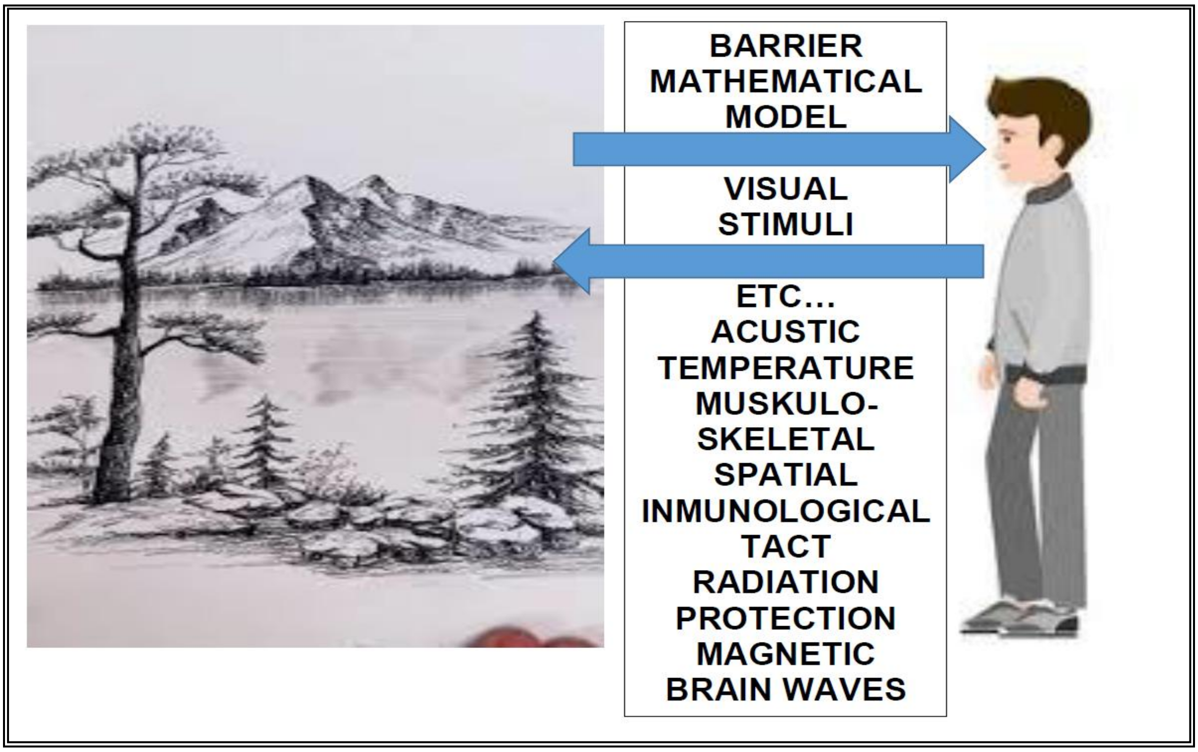
Compilation 2.- Briefing of mathematical methods used for Retina and General Neuronal models. [Casesnoves Bioengineering Laboratory 19.02].

The visual pathway resembles in some way to the modern artificial intelligence advances. However, nature had designed its proper 'artificial intelligence' millions of years ago. In other words, the conversion of photons energy and spectrum-parts into an image takes several 'human computational' steps to create a 3D image in brain, and compared to other living beings, complemented with colors, contrast, bright, movements-dynamic, and what is more, spatial resolution of distances, superpositions, angles and spatial-memory coordination/comparison with previous images. Modelling in computational neuroscience implies the evoked potentials encode information, and, [1], 'given a spike train, how the stimulus that originated it can be reconstructed'. Namely, neurobiological coding and decoding, and their possible applicable mathematical models. Generally speaking, from [1], the rather high difficulty is how the visual image is encoded into the spike trains that are sent to the brain, through the optic nerve. Therefore, according to Author's proposal, there are questions of importance, [1-7], such as,

1. The conversion of light into a spike pattern. That is, make over the photon spectrum and energy with its wavelengths, wave frequency into transmitting neuronal spikes. This interaction is external-to-internal, and is a key factor for getting vision accuracy, Instance Figure 1. Without photon-spikes mechanism, the faculty of this crucial sense would be impossible. Modern electronics sensors are inspired in these natural neural photoreceptors (around 120 million). Once gathered the information, it is compressed-filtered and transmitted by the optical nerve with about 1 million fibers.
2. There are number of factors, such as, approximated nonlinearity (the functions that link stimuli at ganglia and firing rate), and scarcely linear for some ganglion cells. Moreover, spatial resolution and increasing/decreasing contrast stimuli is computed by neural ganglion cells. There might possibly non-discovered additional factors.
3. However, in this topic several rather important questions remain. Such as, for instance [directly from 1], 'whether the neural code is a rate code or a time code or whether the neural code of the retina can be viewed as an individual process, or where each individual neuron cell acts independently, or as a population process'.

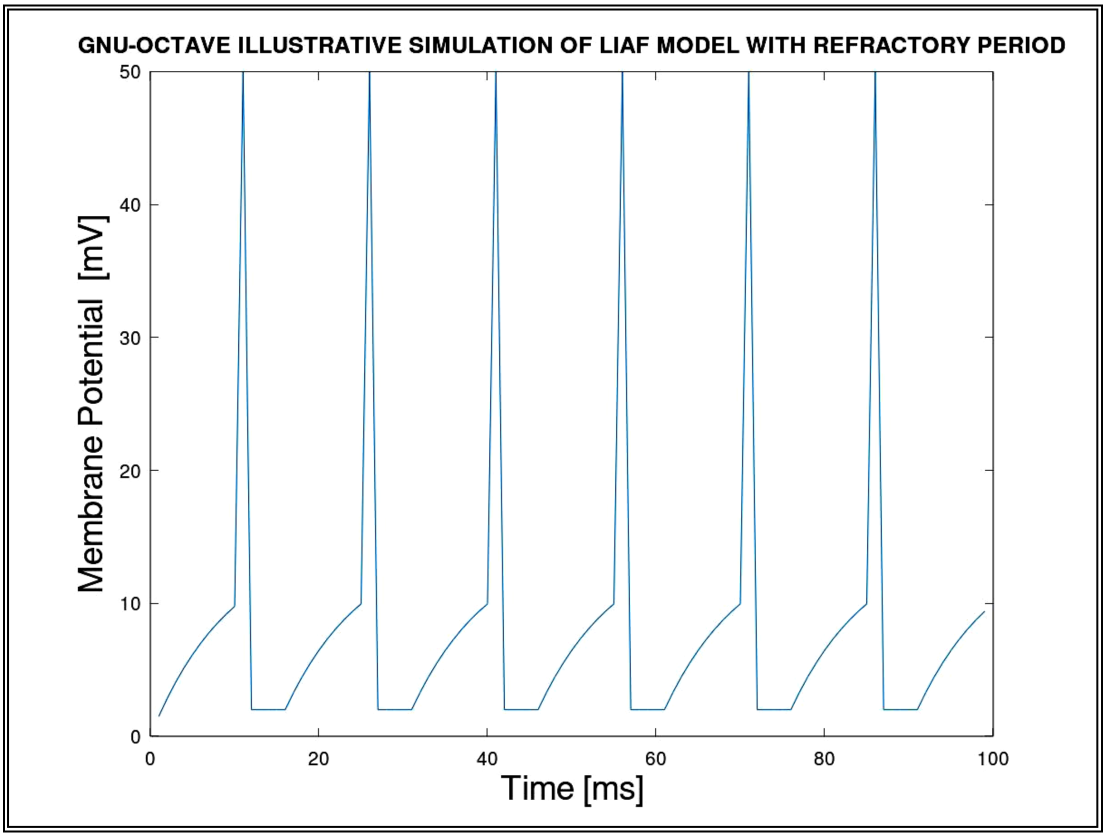
Given all these neurophysiological hurdles, and general neurobiological ones, Author's proposal is,

External-Internal Mathematical Barrier Model. *'The barrier between the external and internal media is crucial for survival because of multiple and different physiological and anatomical factors, which defines the essentiality of human life endurance'*. That is, Instance Figure 1, the vision, the neurophysiological functions, temperature control, humidity and sweat controls related to temperature, mechanical and musculoskeletal factors, immunology, and many others, Instance Figure 1. Important remark: those mathematical models are interrelated, that is, when an individual integrates the image of some obstacles at the floor, then through brain networks, the musculoskeletal model-system is activated to sort those hurdles.

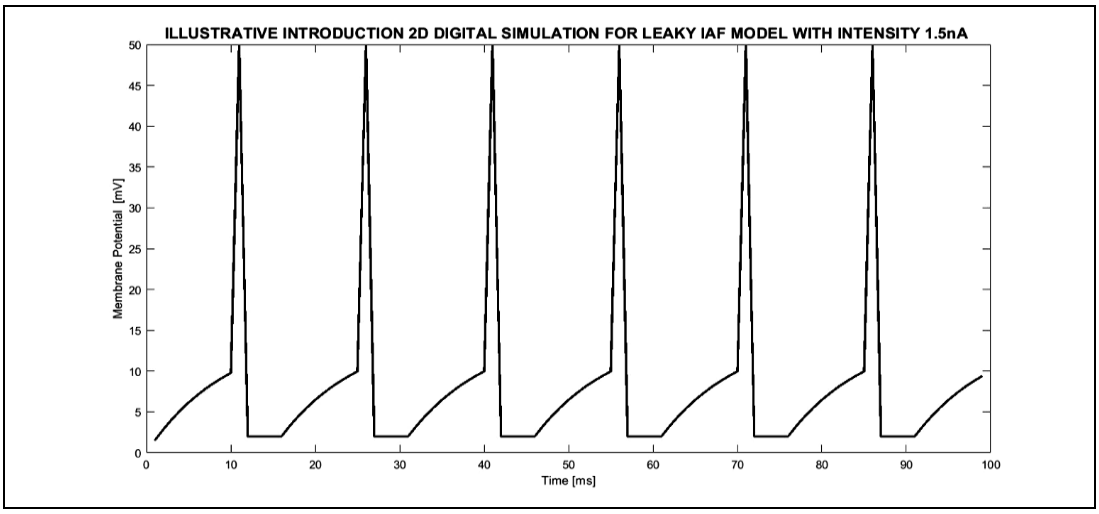


Instance Figure 1.-Sketch of Fundamental Barrier Mathematical Model, [Casesnoves Bioengineering Laboratory 2.11]. Almost all interactions through the biological barrier can be modelled mathematically. The Fundamental barrier Model is crucial to keep the homeostasis during all lifetime.

Important remark: those mathematical models are interrelated, that is, when a person integrates the image of some obstacle at the floor, through brain networks, the musculoskeletal model-system is activated to sort that hurdle. The Fundamental Barrier Model defines the existence and biological boundaries of any being, not exclusively the animals or humans.



Instance Figure 2.- (First with GNU-Octave, second with Matlab in Figure 2.1) 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: Is = 1.5 nA, Cm = 1 nF, Rm = 10 M, and Tref = ≈ 5 ms; (Vth = 10 mV, Vthreshold = 50 mV, simulation time 100 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude. [Casesnoves Bioengineering Laboratory Software 16.23].



Instance Figure 2.1.- (First with GNU-Octave, second with Matlab here) 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: Is = 1.5 nA, Cm = 1 nF, Rm = 10 M, and Tref = ≈ 5 ms; (Vth = 10 mV, Vthreshold = 50 mV, simulation time 100 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude. [Casesnoves Bioengineering Laboratory Software 16.23].

The Leaky Integrate-and-Fire Model was the first succeeding advancement of IAF. Both IAF and LIAF models constitute the initial powerful ones before advancing to more complicated retina and neuronal networks models in general. Those ones show exponentials, derivatives, and complementary integrals [1-7]. Mathematically, is simple. In functional terms, it is still useful as an initial research step.

The objectives of this study are various. Initially, to optimize a number of parameters for a series of published values of IAF and LIAF models, with/without refractory period. In this Third Part, emphasis is on LIAF without refractory period. Innovation is the 3D multidigital imaging processing of LIAF model without refractory period. Additionally, a number of equations and their numerical and analytical solutions are explained based on literature [1-7]. For IAF model, the methods use computational intelligence programming with Genetic Algorithms (GA) Pareto-Multiobjective software, this is a review of 3D Pareto-Simple new-included programs. Further innovation of this article includes 2D imaging processing results for LIAF Model series without refractory period, numerical data included. The second part objectives are defined and justify a number of pre-hypothesis paradigms related to brain intelligence developments in humans. That part is based on Darwin evolutionary biological theory and fundamental neurobiology [25,26], .

This second part of the study involves a number of pre-hypotheses for brain cognitive thinking, optical system biologically evolved, and neuropsychiatry extrapolated notes. All of them grounded on Evolutionary Theory and its up-to-present consequent improvements.

Grosso modo, LIAF and IAF models were optimized with 2D and 3D computational intelligence techniques. 3D-2D PMO algorithms with/without refractory period. Innovation is the 3D multidigital imaging processing of LIAF model without refractory period. Additional review of mathematical background for retina-general neuronal models is explained, Compilations 1-2. Results comprise acceptable numerical values, 2D-3D graphs, and numerical dataset in each and every chart. A number of neurophysiology extrapolations pre-hypothesis are complemented.

2. Review Of Mathematical and Computational Methods

From previous publications and extended, mathematical model's equations are set in this section. The first model for simulations is Leaky IAF, it is explained and detailed firstly. The second list of more explained reviewed formulas corresponds to the IAF model described in previous contributions. Numerical and analytic solutions are discussed.

Leaky IAF Basic Differential Equation Model

The first variant of the basic LIAF is an ordinary differential equation of first order. This model takes into account that the previous stimulus do not get influence over the following ones, which is an approximation. Its formulation, [1-7,26], [Casesnoves Bioengineering Laboratory Algorithms 23.11], reads,

$$V_m(t) = R_m \left[I_S - C_m \times \frac{dV_m}{dt} \right];$$

$$\text{for } t \text{ continuous variable or, } t_i \geq t \leq t_{i+1} \text{ if}$$

$$\text{taken } dV_m \cong \Delta V_m; \text{ and } dt \cong \Delta t; \text{ for numerical;}$$

$$\text{the product } C_m R_m \text{ is usually set as,}$$

$$C_m R_m = \tau_m$$

(1)

where, provided that units magnitudes are changed for software implementation,

C_m (F) : Neuron membrane capacity.

I_s (t) (A) : Input current.

T_{REF} (s) : Refractary time.

V_m (V) : Membrane potential.

R_m (Ω) : Membrane resistance.

dt (s) : Differential of time.

This model, Equation 1, can be programmed numerically, but a number of mixed numerical-analytic solutions are also feasible. For example, the complete analytic solution is an integral equation that can be resolved numerically. Usually in software ΔV_m is set 0.1 ms.

LIAF Analytical Solution without/with Functional Series

The analytic option for programming the LIAF model could set the equation as direct analytic solution within the program patterns. The analytic solutions go from simple exponentials to integral equations with Heaviside functions and convolutions [1-7]. The exponentials of the analytic solutions can also be approximated by series. So, for simplicity it is not included the analytic solution that involves Heaviside functions. One quite simple analytical solution is,

$$V_m(t) = V_r \times e^{-\left[\frac{t-t_i}{\tau_m}\right]} + R_m \times I_S \times \left[1 - e^{-\left[\frac{t-t_i}{\tau_m}\right]}\right];$$

$$\text{for} \quad t \text{ continuous variable or,} \quad t_i \geq t \leq t_{i+1}$$

$$\text{it can be taken } \operatorname{abs}[t - t_i] \cong \Delta t \text{; for numerical programming;}$$

$$\text{the product } C_m R_m \text{ is usually set as,}$$

$$C_m R_m = \tau_m;$$

(1.1)

where all parameters can be read from Equation (1). This solution yields an integral equation rather more complicated. Note that a series approximations for exponentials are feasible. This equation is implemented computationally here with/without refractory period.

LIAF Numerical Solution

From Equation 1, the numerical programming of LIAF has to be rearranged to set a for loop at least. That software can be performed by several programming systems. Therefore, the resulting algorithm is as follows,

$$V_m(t) = V_m(t) + dt \times (V_l - V_m(t) + Im \times Rm)/\tau;$$

$$\text{for} \quad t_i \geq t \leq t_{i+1} \quad ;$$

(2)

where,

R_m (F) : Neuron membrane resistance.

I_m (t) (A) : Intensity membrane current.

V_m (V) : Membrane Voltage potential.

V_l (V) : Force Potential

Dt (s) : Differential of time.

τ (s) : Firing rate (Tau).

IAF Basic Model

The simplest Integrate retina model, IAF, and for neuron models in general, without exponentials, is based on [1-7,26]. Its standard formulation begins with a first order integral equation. The integral equation is usually simulated with numerical methods. It reads,

$$V_m(t) = V_r + \frac{1}{C_m} \times \int_{t_i}^{t_{i+1}} I_S(t)\, dt;$$

$$\text{for} \quad t_i \geq t \leq t_{i+1} \quad ;$$

(3)

where,

C_m (F): neuron membrane capacity.

I_s (t) (A): Input current.

V_r (V): Reset potential.

(t_{i+1} is the time instant of the next generated spike after the spike in t_i) .

If I_S is constant, [1-7, 26], the integral equation solution reads,

$$\text{If} \quad I_S(t) = I_S \text{ , constant,}$$
$$\text{Integral Equation Analytic Solution,}$$
$$V_m(t) = V_r + \frac{1}{C_m} \times \quad I_S(t - t_i),$$
$$\text{for} \quad t_i \quad \leq t \leq t_{i+1} \quad ;$$

(4)

where parameters are the same as detailed in Algorithm (1)

This Equation 4 is simulated in 3D PMO programs. Firing rate is essential as it means the frequency of spikes during the spikes train. Vision accuracy and precision depend on it. To build the objective function, the algorithm, provided I_s be constant, and getting firing rate as parameter also, r , from [1-7, 26], is software-engineered and applied,

$$\text{firing} \quad \text{rate} \quad r,$$
$$r = \frac{I_S}{C_m \times V_\theta + T_{REF} \times I_S} ;$$

(5)

where,

C_m (F): neuron membrane capacity.
I_s (t) (A): Input current.
T_{REF} (s): Refractory time.
V_r (V): Reset potential.
V_θ (V): Threshold potential
r (s): Firing rate

In such simple-model way, the objective function applied for computational intelligence genetic algorithms, [1-7, 8-16,23-24,26] based on IAF model is shown in next subsection.

LIAF Numerical Optimization Objective Functions

The optimization objective function can be set related to one important parameter, I_S . For inverse implementation in software as follows,

$$\text{minimize Chevyshev } L_1$$
$$\text{objective function,}$$
$$\left\| I_S \quad - \quad \frac{r\,C_m \times (V_\theta - V_r)}{1 - r\,T_{ref}} \right\| ;$$
$$\text{subject} \quad \text{to,}$$
$$\text{Table 1 constraints;}$$

where,

C_m (mF): neuron membrane capacity.
I_s (t) (mA): Input current.
T_{REF} (ms) : Refractary time.
V_r (mV) : Reset potential.
V_θ (mV) : Threshold Potential.
r (ms) : Firing rate.

(Algorithm 6, Casesnoves 2022)

The IAF input computational data for 3D Pareto Multiobjective Optimization, Figures 10-13, is presented at Table 1. All figures belong to standard values [1-7,26,27]. Note at program: parameters are not given in 'V, A', it is usual to implement units in 'mV, mA, ms, etc'. Are set in program as detailed in the rest of Algorithms. Table 1 shows optimization dataset intervals applied for optimization intervals in this and previous publications.

PMO NUMERICAL PROGRAMMING DATASET	
PARAMETER	OPTIMIZATION VALUE/INTERVAL
C_m F	1e-9
I_s (t) A	[1e-3 , 1.8e-3]
T_{REF} s	5e-3
V_r v	[20e-3 , 60e-3]
V_θ v	[20e-3 , 80e-3]
r s	[0.001 , 0.007]

Table 1.- From [26] and for Figures 6-10, parameters setting for the IAF previous study [1-7,26], to get 3D-2D PMO-GA optimal results.

3. 3D-2D Gnu-Octave and Matlab LIAF Without Refractory Period Graphical and Numerical Optimization Results

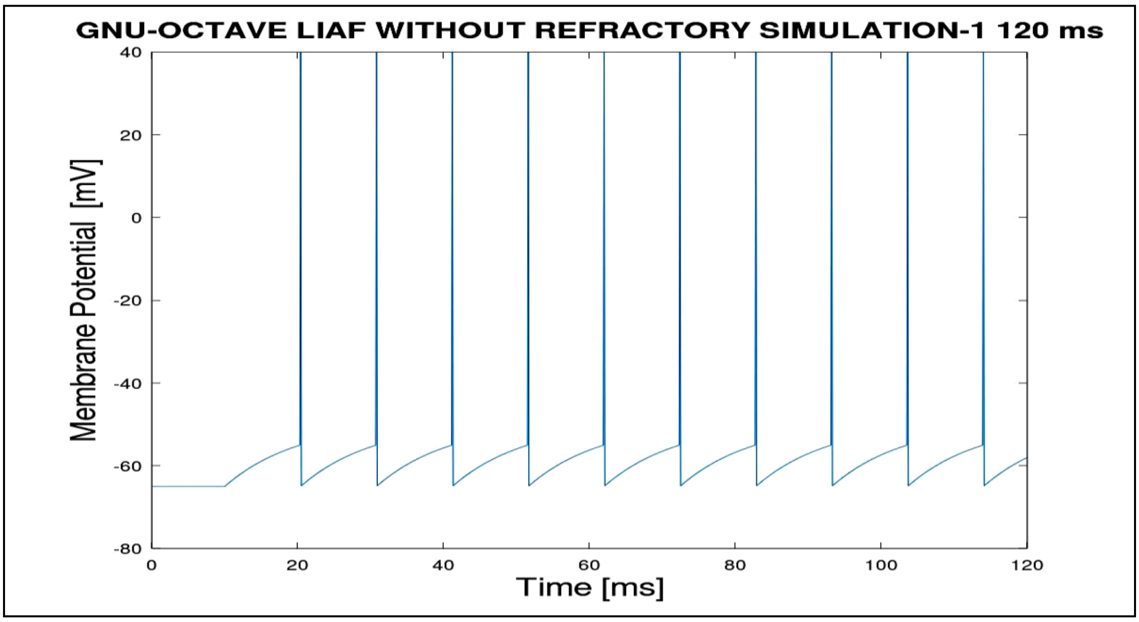
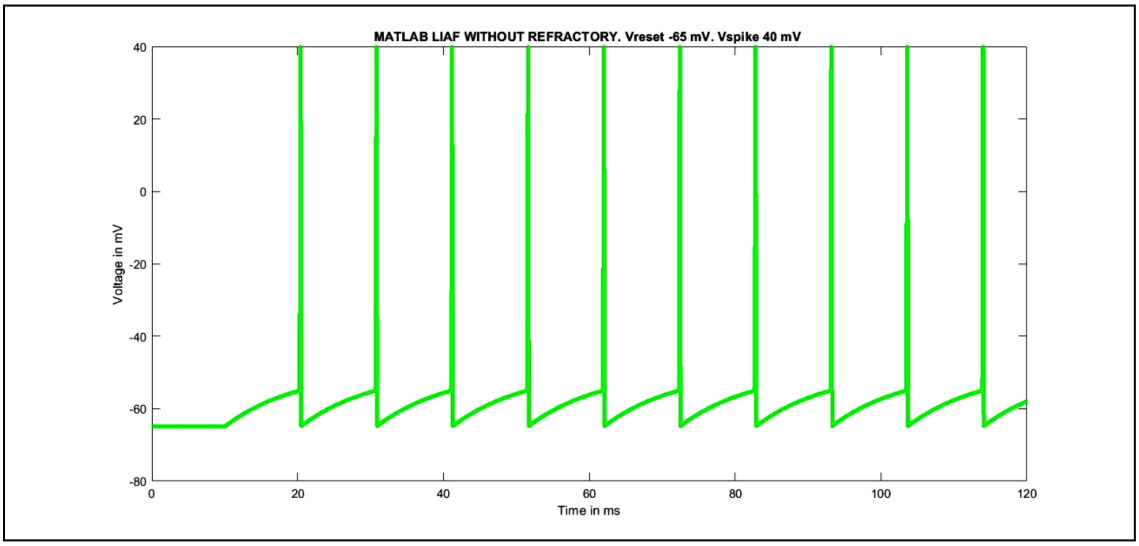


Figure 1.- GNU-Octave 2D digital simulation for LIAF model without refractory period, absolute values. : (Is = 1.55 nA, Rm = 10 MΩ, and (Vspike = 40 mV, Vreset = 55 mV, simulation time 120 ms)). [Casesnoves Bioengineering Laboratory Software 16.33].



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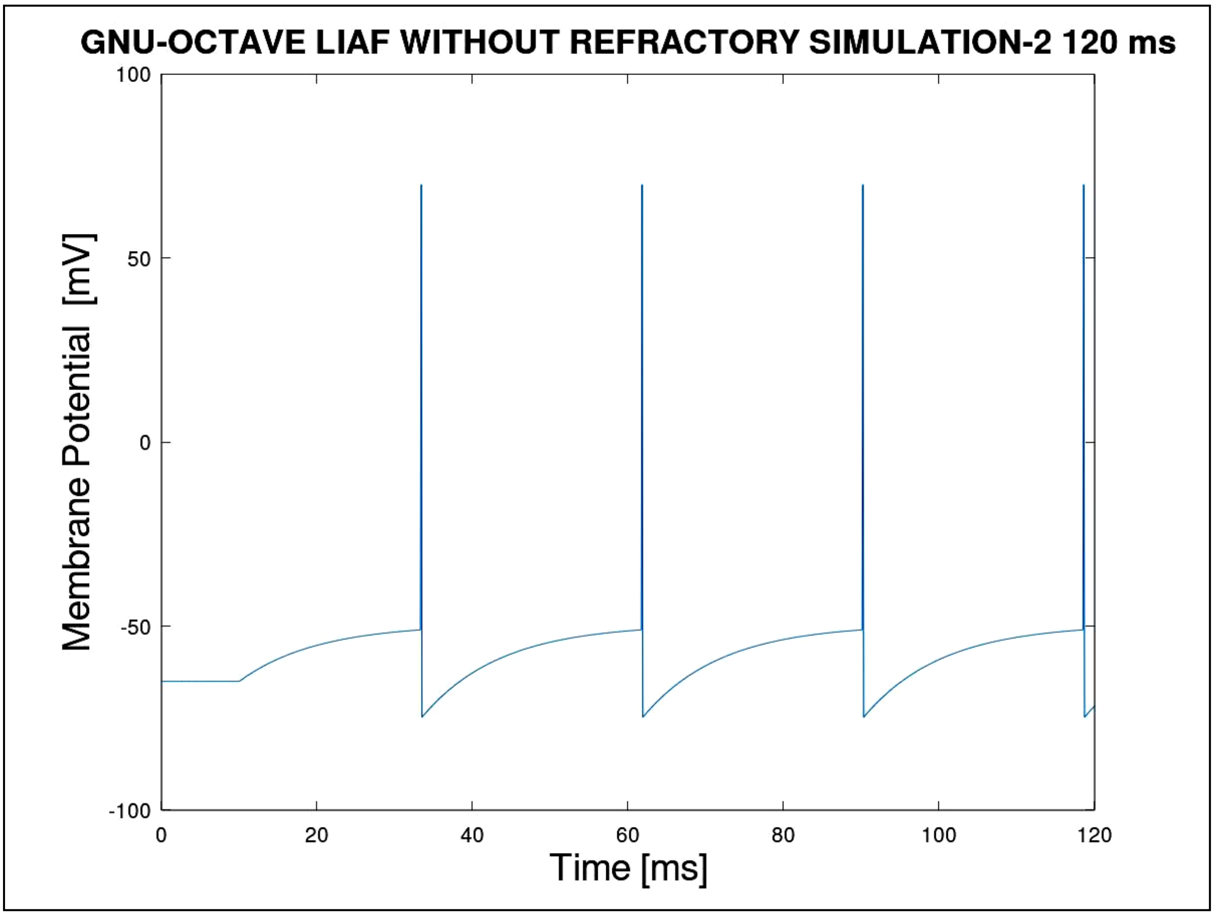
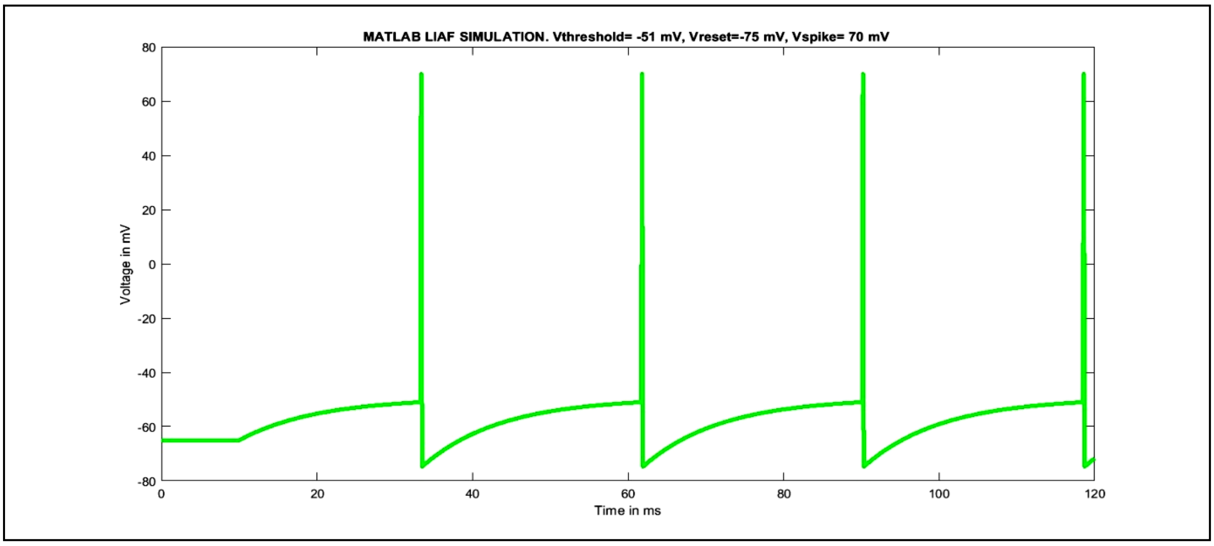


Figure 2.- 2D digital simulation for LIAF model without refractory period refractory period, absolute values. : (Is = 1.55 nA, Rm = 10 MΩ, and (Vspike = 75 mV, Vreset = 65 mV, simulation time 120 ms)). [Casesnoves Bioengineering Laboratory Software 16.36].



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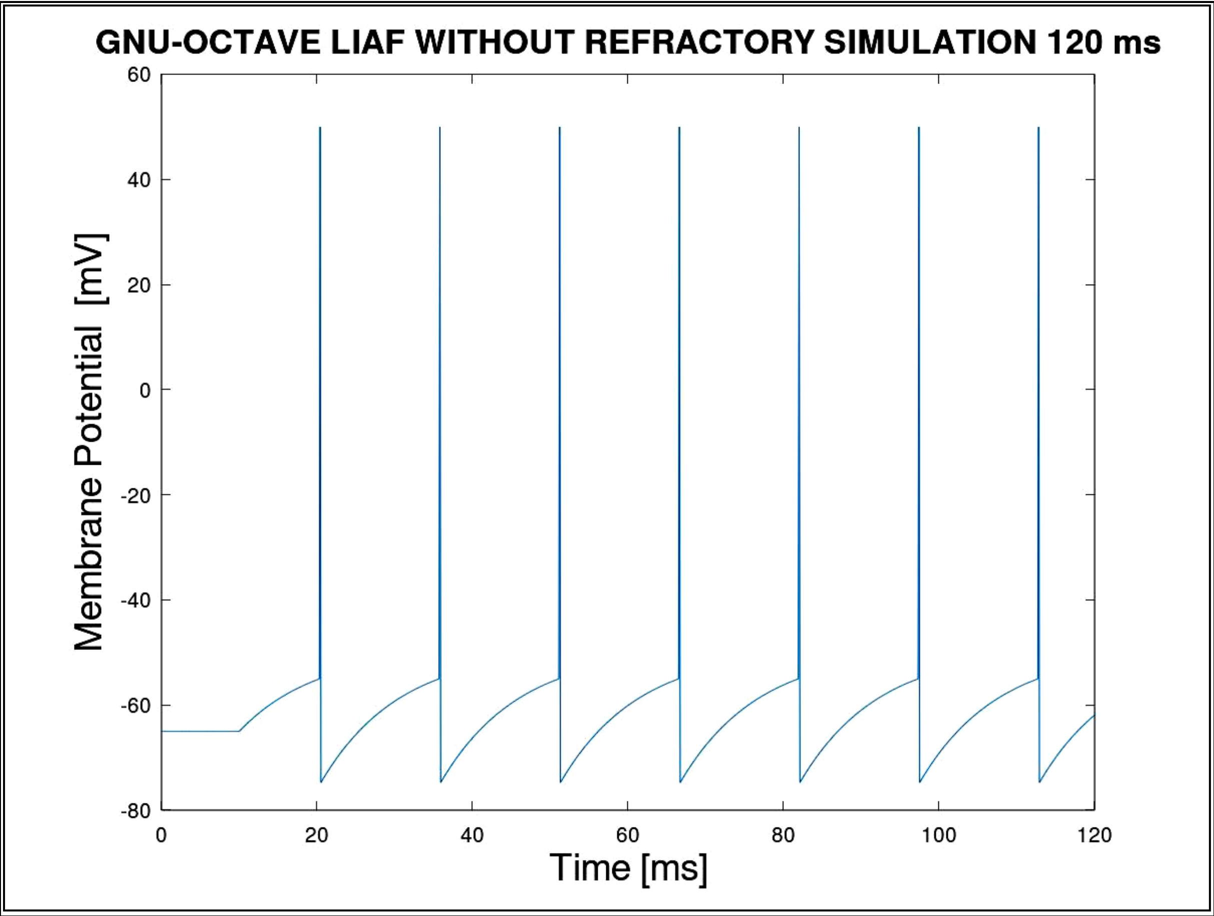


Figure 3.- 2D digital simulation for LIAF model without refractory period, absolute values: (Is = 1.55 nA, Rm = 10 MΩ, and (Vth = 10 mV, Vspike = 55 mV, Vreset = 55 mV, simulation time 120 ms)). [Casesnoves Bioengineering Laboratory Software 16.38].

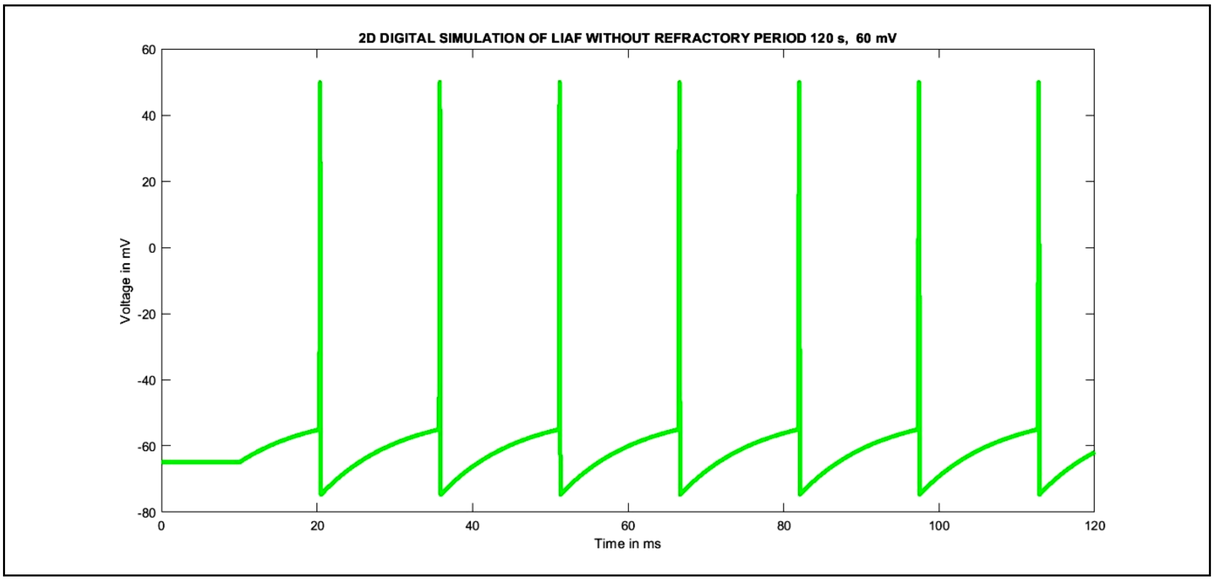


Figure 3.1.- 2D digital simulation for LIAF model without refractory period, absolute values : (Is = 1.55 nA, Rm = 10 MΩ, and (Vspike = ≈ 60 mV, Vreset = 75 mV, simulation time 120 ms)). [Casesnoves Bioengineering Laboratory Software 16.33].

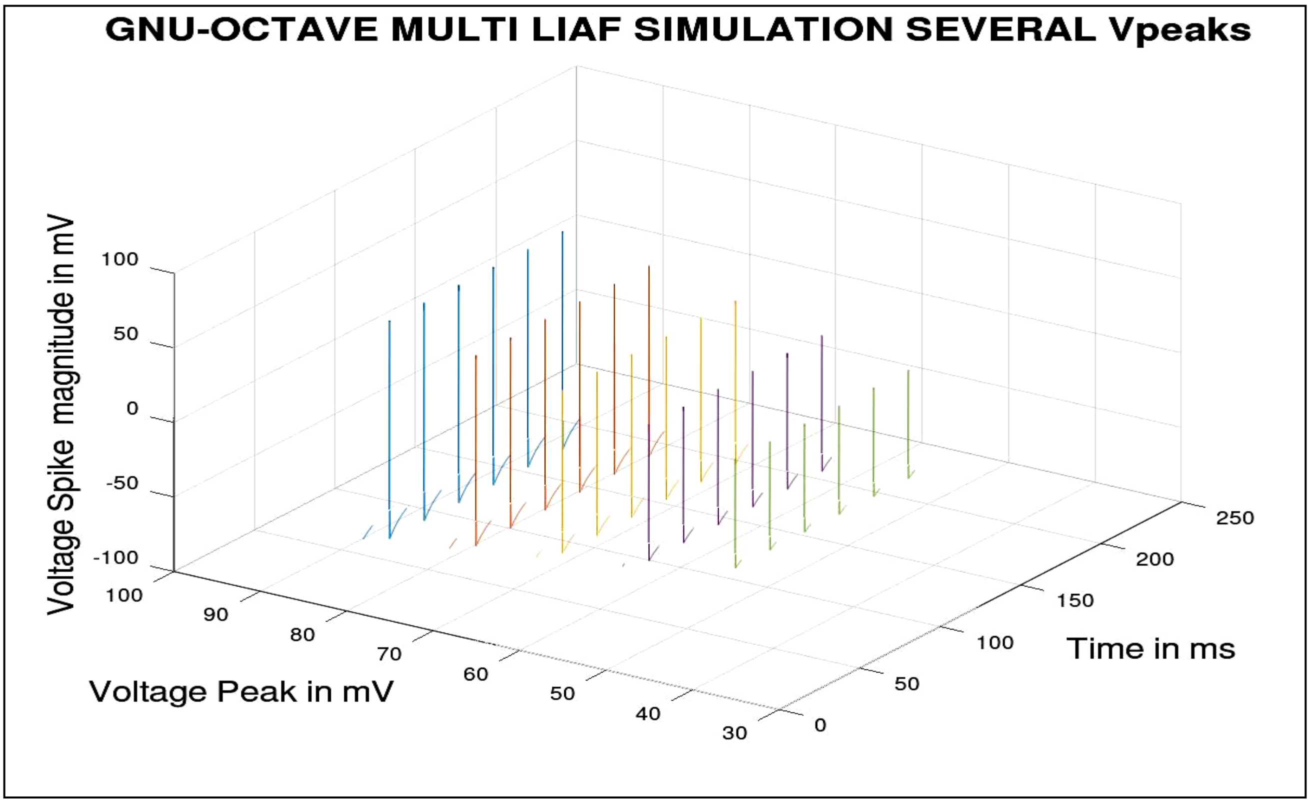


Figure 4.- GNU-Octave 3D LIAF multisimulation, with four different spike series with several Vpeaks. The software design was rather complicated. Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: Is = 1 nA, Cm = 1 nF, Rm = 10 MΩ, τ =10; (Vth = -52.5 mV, Vreset = -75 mV, Vspikes = ≈ 40, 50, 60, 70, 80 mV simulation time 120 ms)). [Casesnoves Bioengineering Laboratory Software 17.25]. Note that GNU-Octave image quality is rather poorer that Matlab in this case.

4. 2D DIGITAL MATLAB AND GNU-OCTAVE SIMULATIONS FOR LIAF MODEL WITH REFRACTORY PERIOD. GRAPHICAL AND NUMERICAL RESULTS

Matlab and GNU-Octave LIAF simulation series. The LIAF input computational data is presented at Figures 5-9. All figures belong to standard literature values [1-7,26,27]. Parameters dataset is set in program-graphs as detailed in the rest of Algorithms. A number of values for digital simulations are detailed at every figure, Figures 5-9. Note the differences without refractory period.

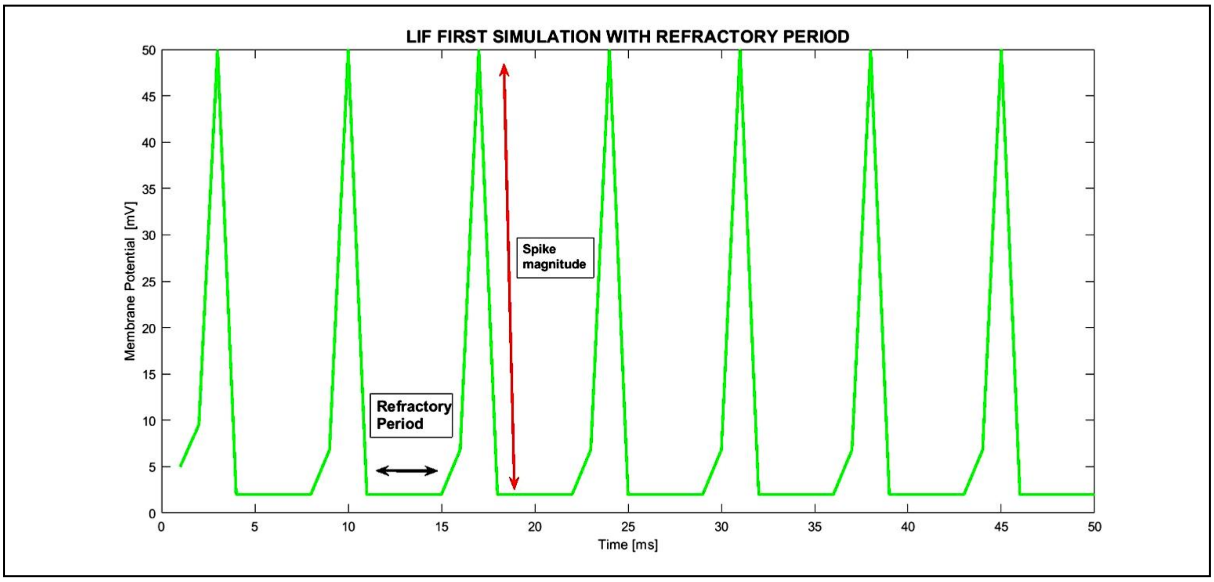


Figure 5.-2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 5 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 5 ms; (Vth ≈ 10 mV, Vspike = 50 mV, simulation time 50 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude. [Casesnoves Bioengineering Laboratory Software 16.24].

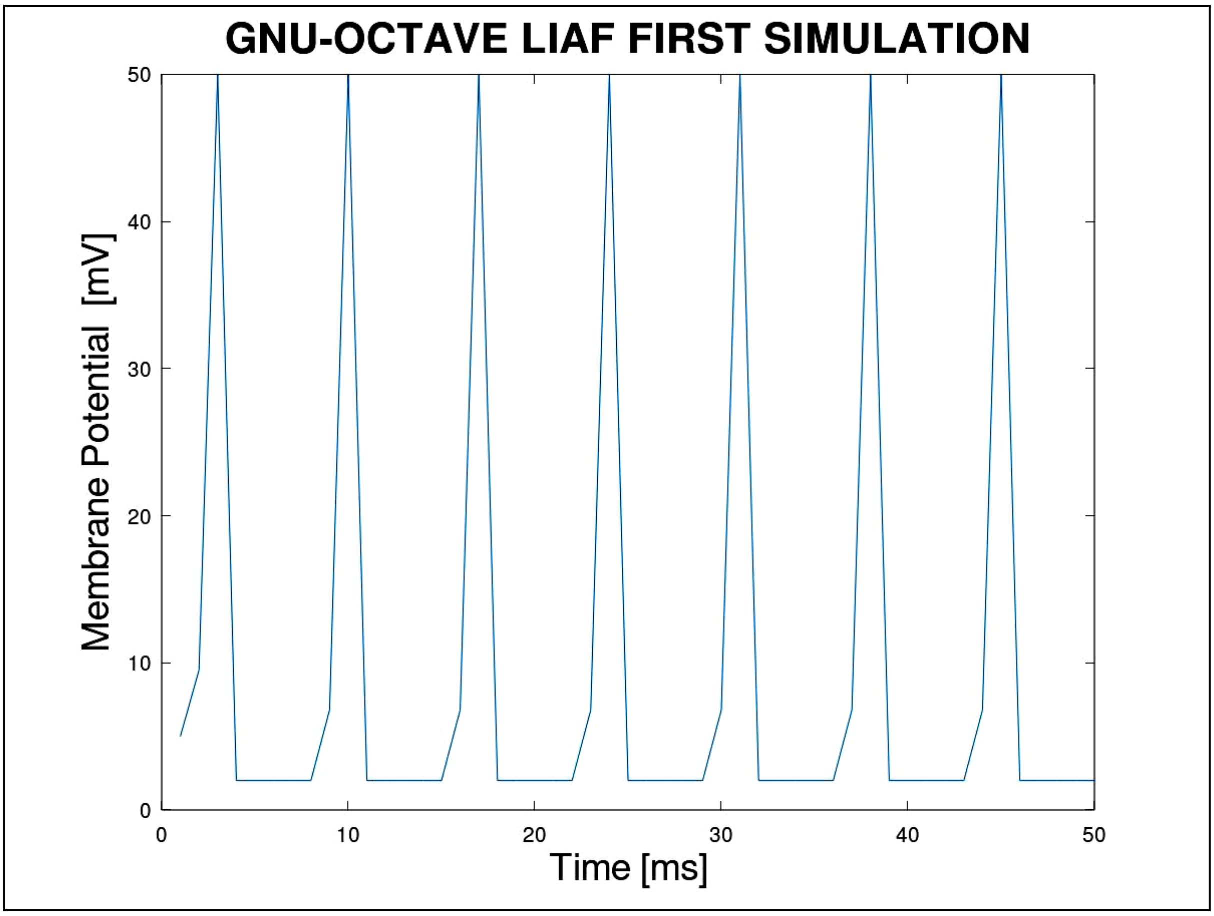


Figure 6.-GNU-Octave 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 5 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 5 ms; (Vth = 10 mV, Vspike = 50 mV, simulation time 50 ms)). Note: the program is designed in splines, and that makes some small image precision bias. [Casesnoves Bioengineering Laboratory Software 16.25.1].

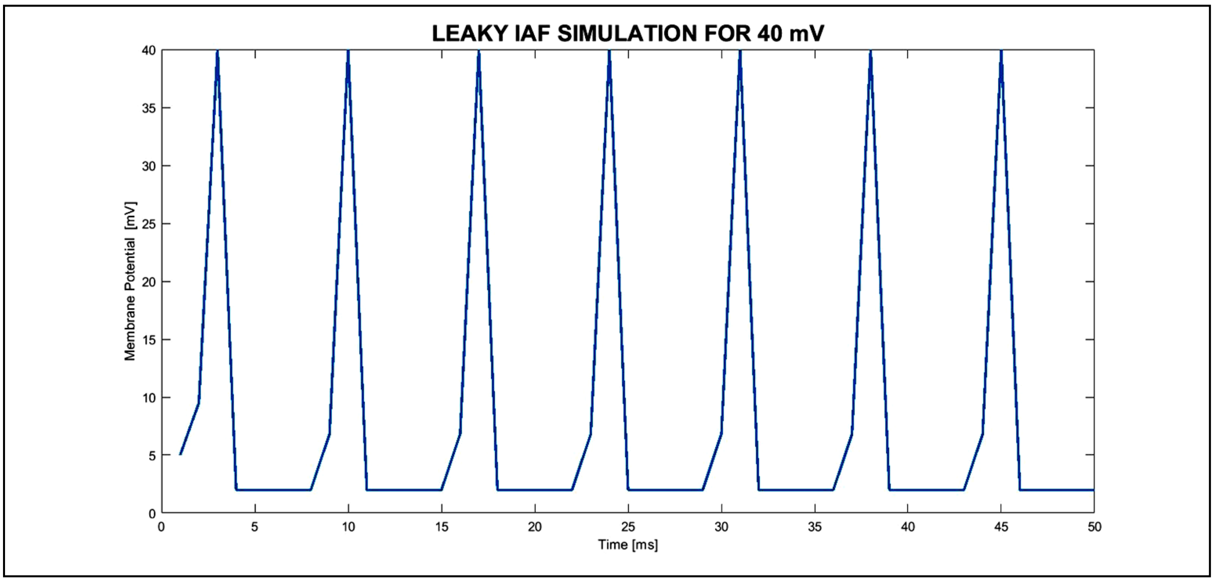


Figure 6.1.- 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 5 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 4 ms; (Vth = 10 mV, Vspike = 40 mV, simulation time 50 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude. [Casesnoves Bioengineering Laboratory Software 16.25].

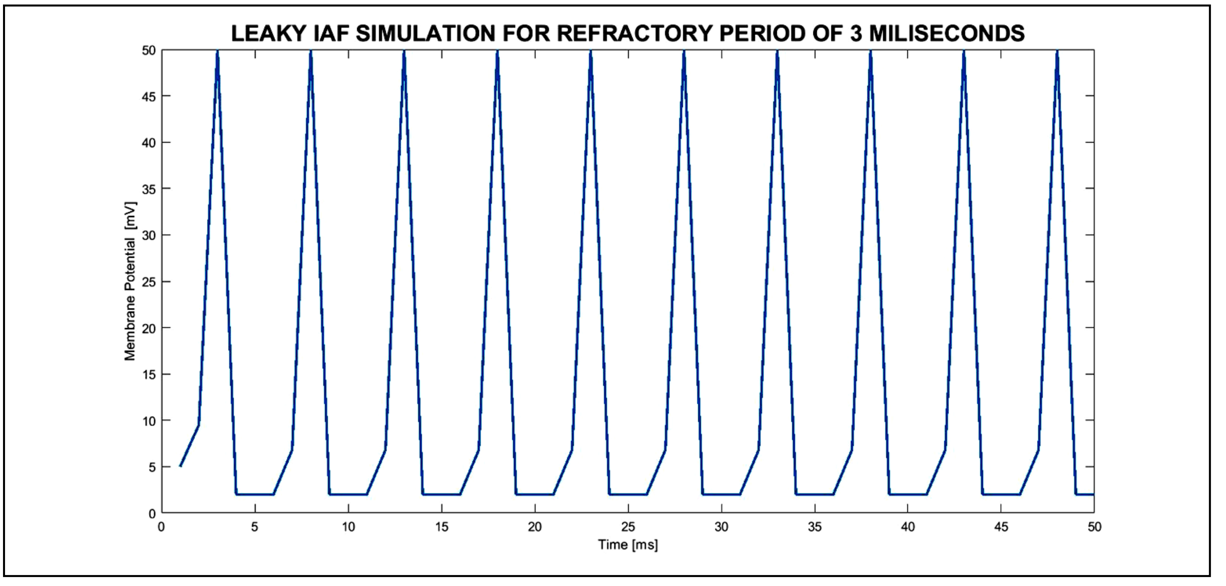


Figure 7.- 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 5 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 3 ms; (Vth = 10 mV, Vspike = 50 mV, simulation time 50 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude. [Casesnoves Bioengineering Laboratory Software 16.26].

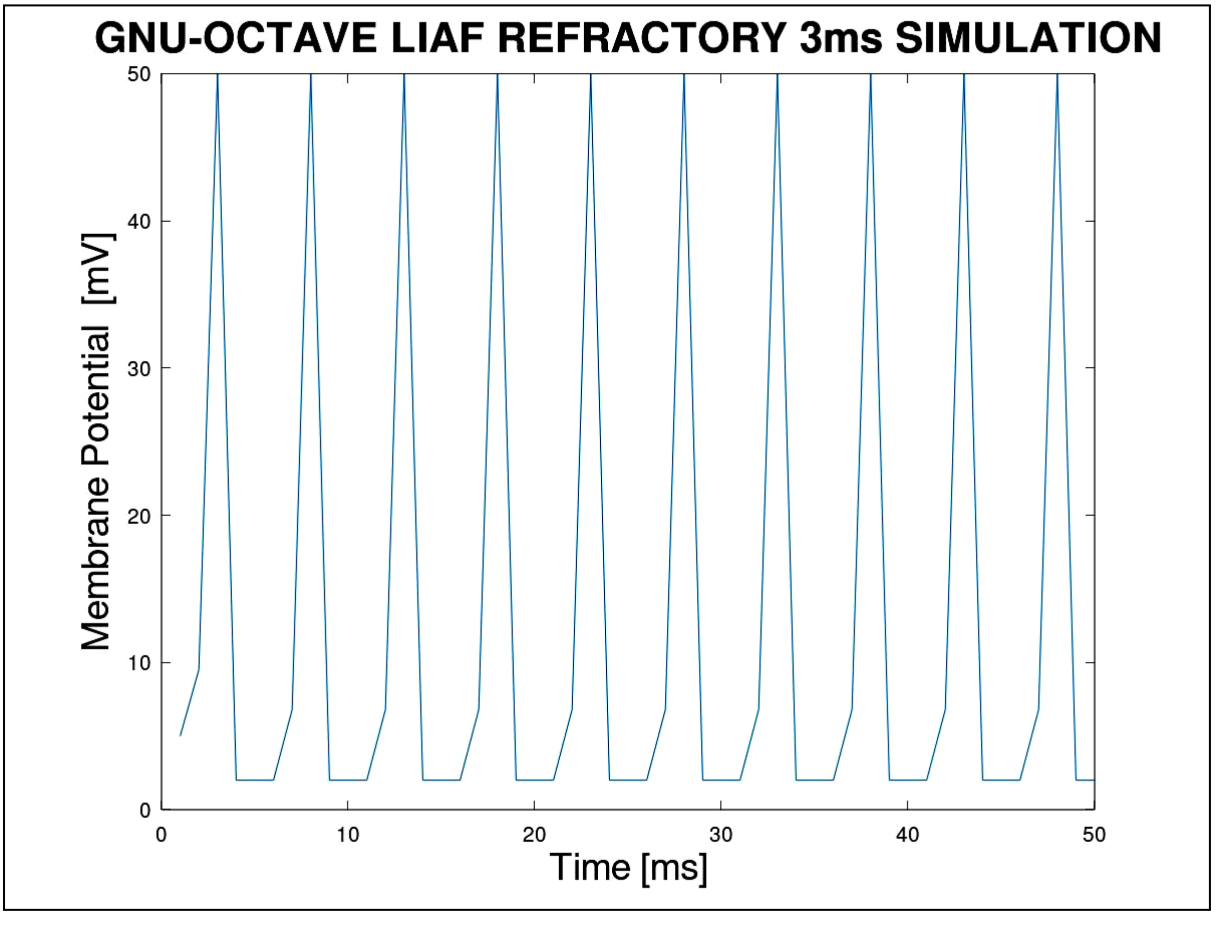


Figure 7.1.- GNU-Octave 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 5 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 3 ms; (Vth = 10 mV, Vspike = 50 mV, simulation time 50 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude. [Casesnoves Bioengineering Laboratory Software 16.26].

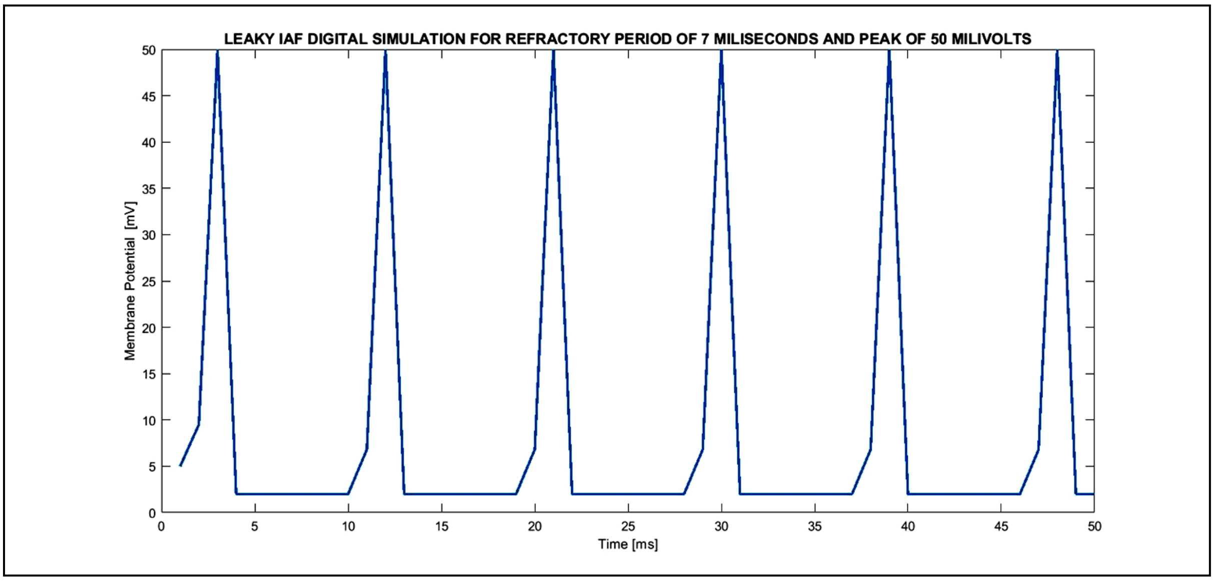


Figure 8.- 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 5 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 7 ms; (Vth = 10 mV, Vspike = 50 mV, simulation time 50 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude. [Casesnoves Bioengineering Laboratory Software 16.27].

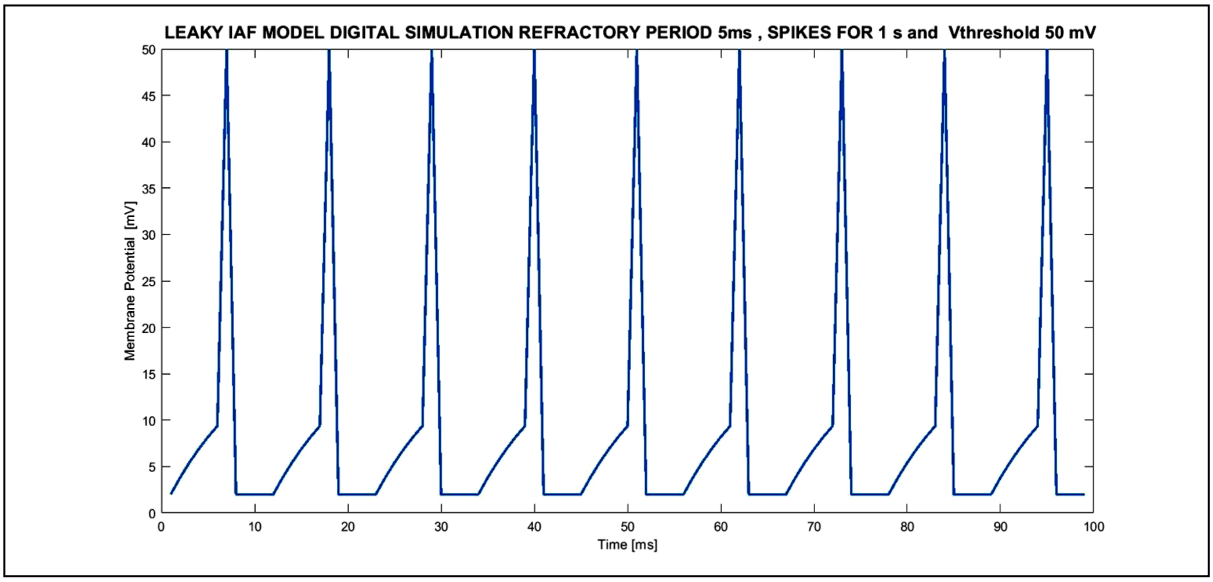


Figure 9.- 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 2 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 4 ms; (Vth = 10 mV, Vspike = 40 mV, simulation time 100 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude, but with Is = 2 nA it is almost exact. [Casesnoves Bioengineering Laboratory Software 16.28].

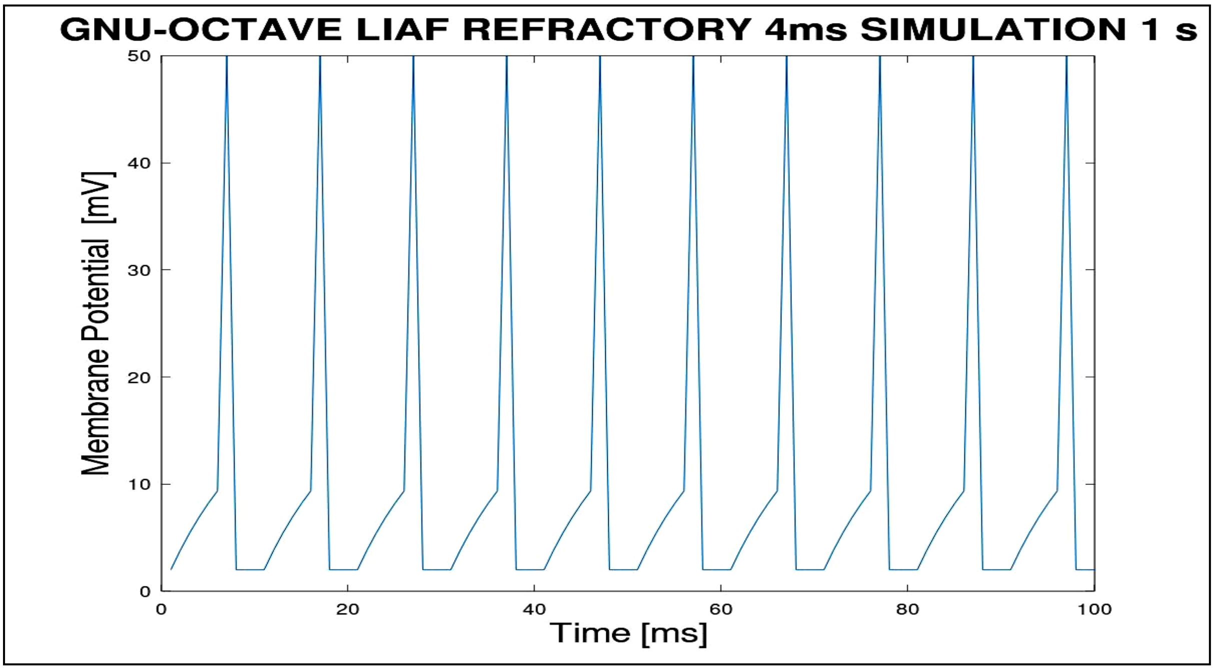


Figure 9.1.- GNU-Octave 2D LIAF simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact simulation. Dataset for programming patterns: (Is = 2 nA, Cm = 1 nF, Rm = 10 MΩ, and Tref = ≈ 4 ms; (Vth = 10 mV, Vspike = 40 mV, simulation time 100 ms)). Note: the program is designed in splines, so the totally exact points at graph differ something in magnitude, but with Is = 2 nA it is almost exact. [Casesnoves Bioengineering Laboratory Software 16.28].

5. REVIEW OF 3D IAF WITHOUT REFRACTORY PERIOD GRAPHICAL AND NUMERICAL PARETO OPTIMIZATION RESULTS

It is included for clarification a review of previous articles results in 3D PMO-GA optimization for IAF model without refractory period. New 3D PMO charts are supplemented. Results are presented in 3D-2D GA graphics, Figures 10-13 and numerically, Table 3. These are 3D-2D Graphical and Numerical predictions. Complete graphical results for 3D-2D evolutionary PMO optimization are shown in Figures 10-13. [Casesnoves Bioengineering Laboratory Software]. These numerical results are shown at Table 2.

3D-2D Pareto-Optimization Software Results

From [26], graphics at Figures 6-9 show results for a number of parameters whose determination is detailed in Table 3. All of them get acceptable results for pareto 1, pareto 2, and pareto 3 functions. Remark: it is not usual getting one optimal 3D pareto point, rather a points cloud, and in this case that indicates the precision of the program designed.

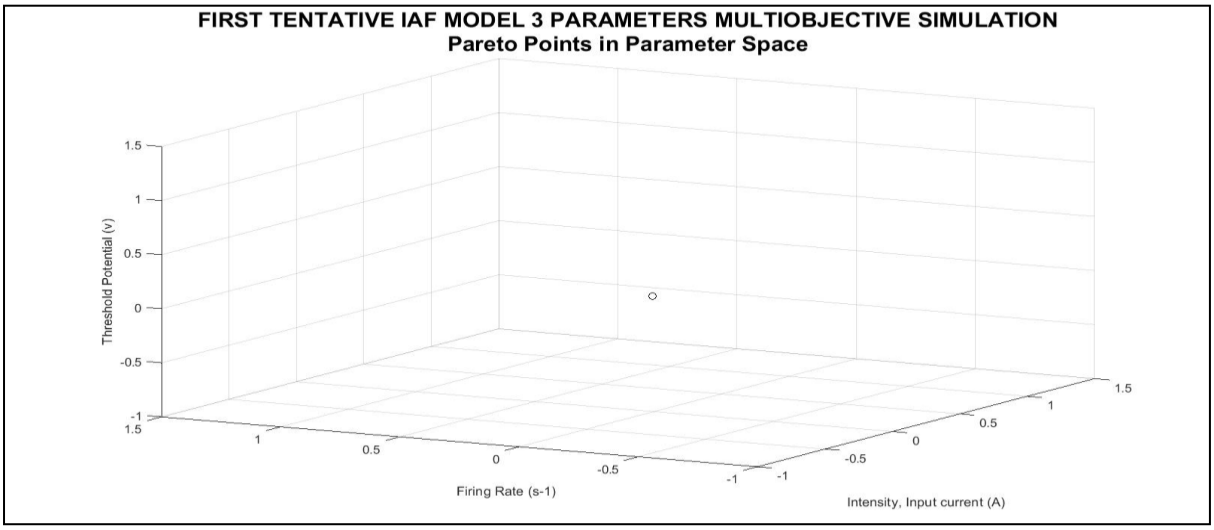


Figure 10.-First tentative 3D simulation to try further clearer/improved graphs. Input Intensity, Firing rate, and Threshold Potential. Almost exact. Numerical results in Table 2. [Casesnoves Bioengineering Laboratory Software 16.29].

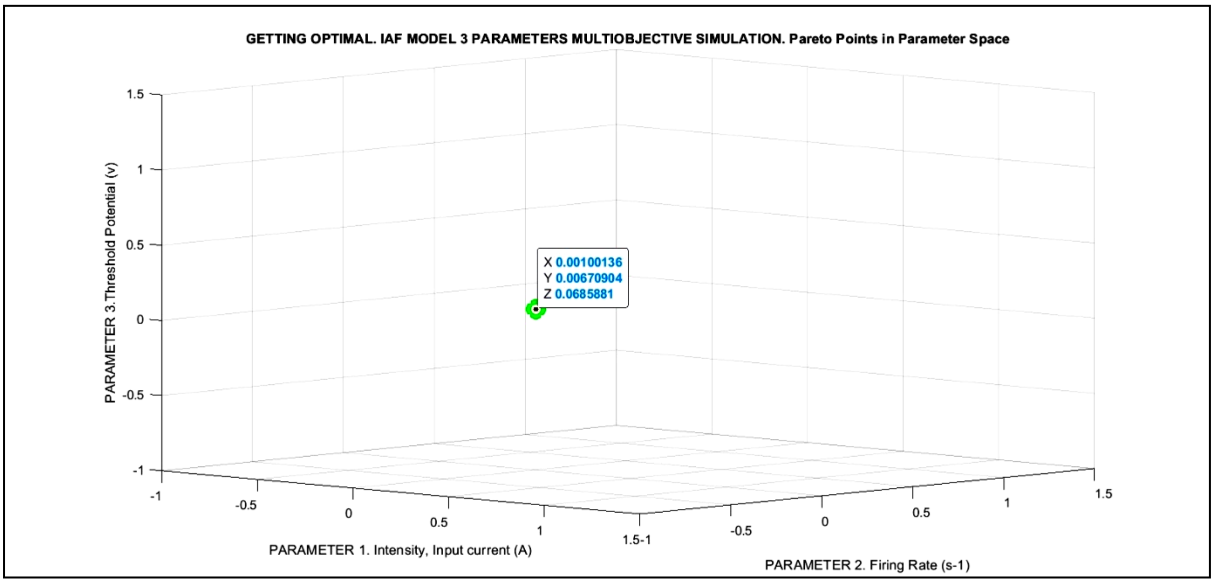


Figure 10.1.-Searching optimal values yet. 3D simulation to try further clearer/improved graphs. Input Intensity, Firing rate, and Threshold Potential. Almost exact. Numerical detailed results can be found at Table 2. [Casesnoves Bioengineering Laboratory Software 16.291].

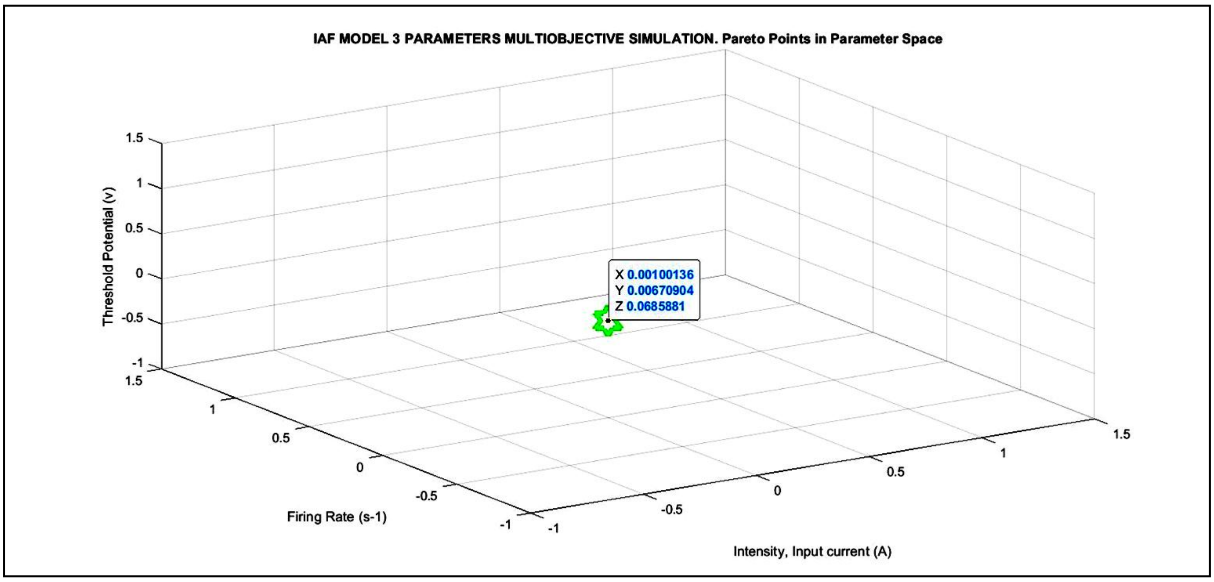


Figure 11.-3D simulation, Input Intensity, Firing rate, and Threshold Potential. Almost exact. Numerical results in Table 2. [Casesnoves Bioengineering Laboratory Software 16.30].

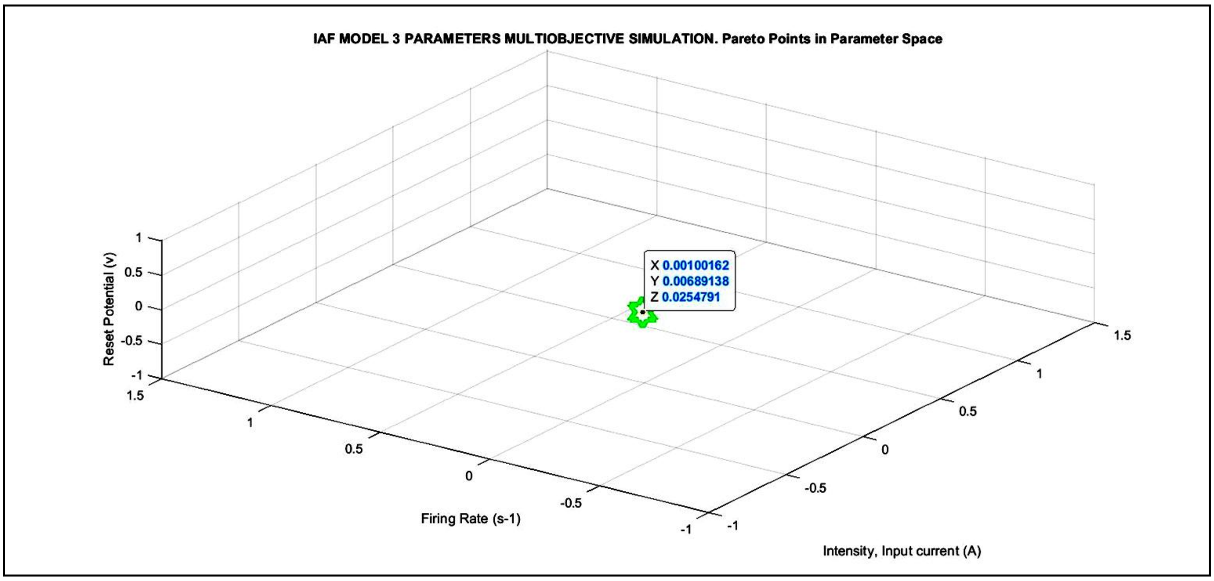


Figure 12.-3D simulation, Input Intensity, Firing rate, and Reset Potential. Almost exact. Numerical results in Table 2. [Casesnoves Bioengineering Laboratory Software 16.31].

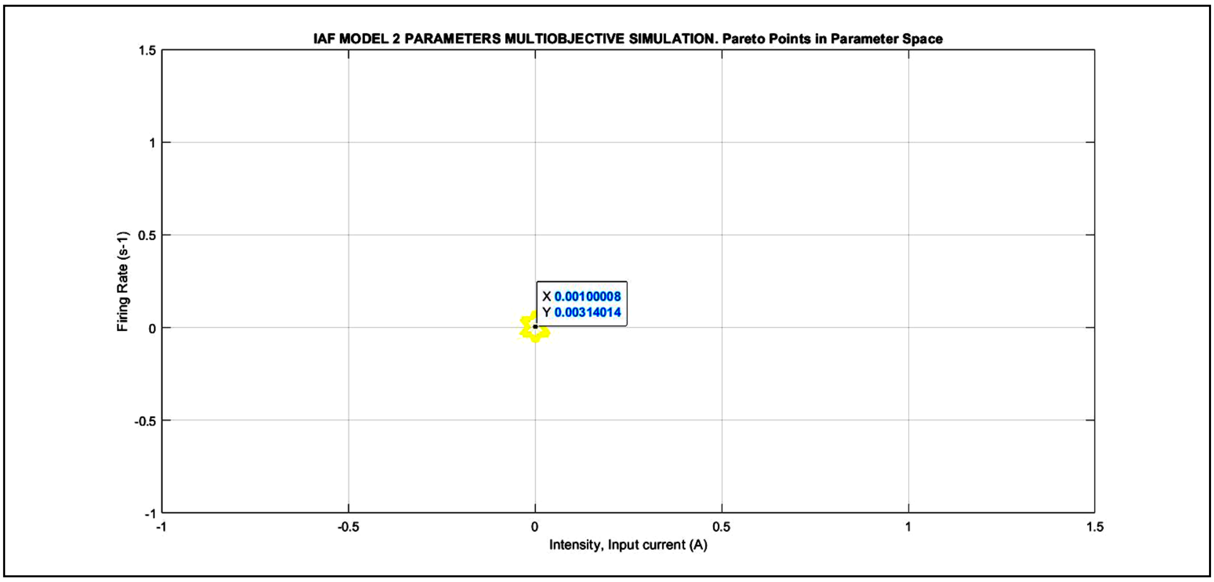


Figure 13.-2D simulation, Input Intensity and Firing rate. Almost exact. Numerical results in Table 2. [Casesnoves Bioengineering Laboratory Software 16.32].

6. 3D PMO IAF Numerical Results and Review

Numerical results for LIAF are set along Figures 10-13. IAF 3D PMO numerical results are included in Table 2. Optimal intervals are detailed. Residuals are acceptable, almost null, Figures 10-13.

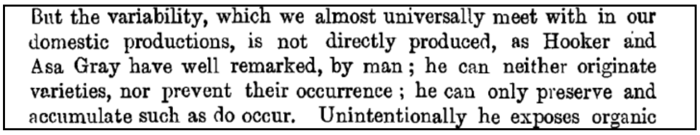
PMO NUMERICAL PROGRAMMING RESULTS	
PARAMETER	**OPTIMAL VALUE**
OPTIMIZATION RESIDUALS FOR ALL PROGRAMS	≈ 0
I_s (t) A	0.0010
V_r v	0.0255
V_θ v	0.0686
r s	0.00341

Table 2.-Dataset from programming software results in 3D PMO for IAF without refractory period. Figures 10-13

7. Review And Extension. Neuro-Bioelectronics Modelling Applications and Neurophysiology of Human Brain-Thinking Pre-Hypotheses

This section reviews and develops the previous extrapolation of brain and retine neurophysiology to human thinking pre-hypotheses [25,26]. The previously published, [26], pre-hypothesis points in brief are as follows,

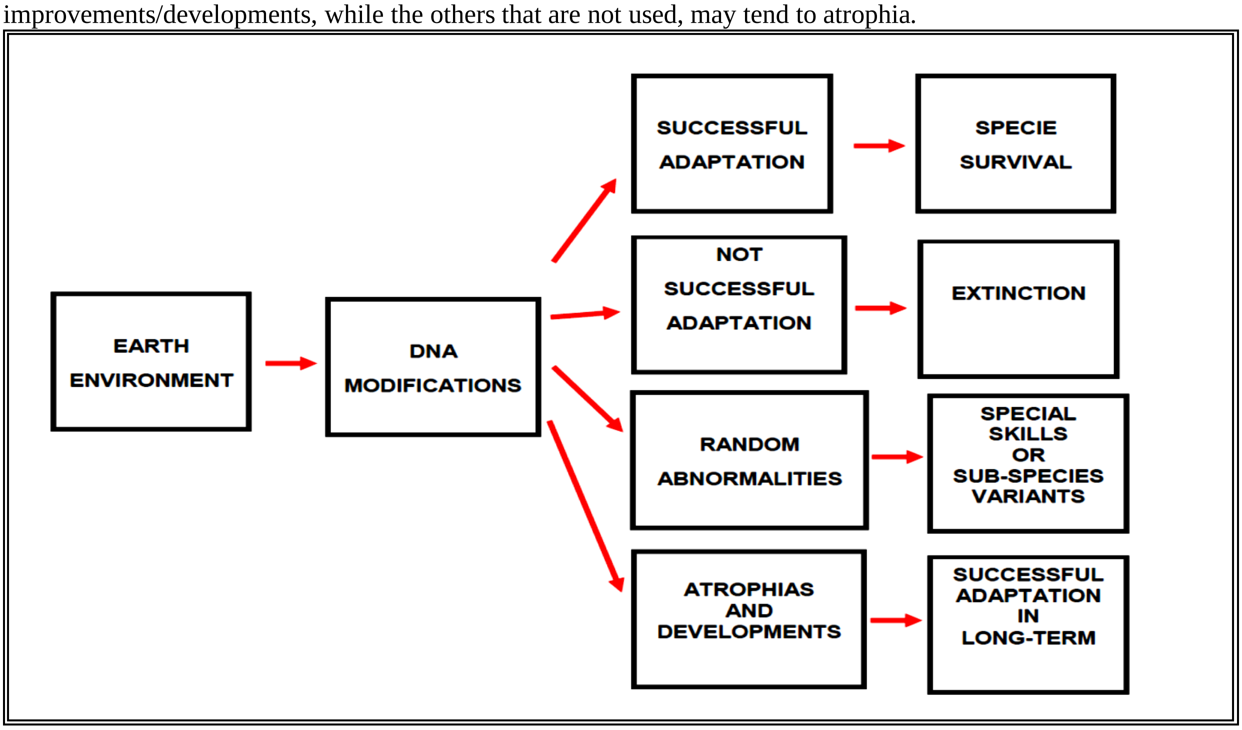
1. why, because of which, for what humans think, and why humans have survival instinct?. For survival mainly.
2. The Central Questioning is: why humans ignore almost all about human brain operation and at the same time humans are using it for rational thinking and reasoning?. That is, why humans use a 'thinking-computer-machine' and ignore its operation?. It seems be a nonsense paradigm/situation.
3. why humans beings think?: primary hypothesis: For survival mainly. However, the nature laws might have made human brain, and humans actually ignore the key of those knowledge almost at all.
4. Fundamental interrogate: For what we think?: For specie survival within the biological earth environment.
5. The cognitive-thinking might also have surged after millions of random trials, (nature-optimization: Trial and Error), during millions of years to improve the survival capacity of humans.
6. Remark literally from [26]: mathematical stochastic optimization idea for evolutionary biology does not belong to author. It was discovered long time ago. However, without any mathematical background. Example [25, page 62].


But the variability, which we almost universally meet with in our domestic productions, is not directly produced, as Hooker and Asa Gray have well remarked, by man; he can neither originate varieties, nor prevent their occurrence; he can only preserve and accumulate such as do occur. Unintentionally he exposes organic

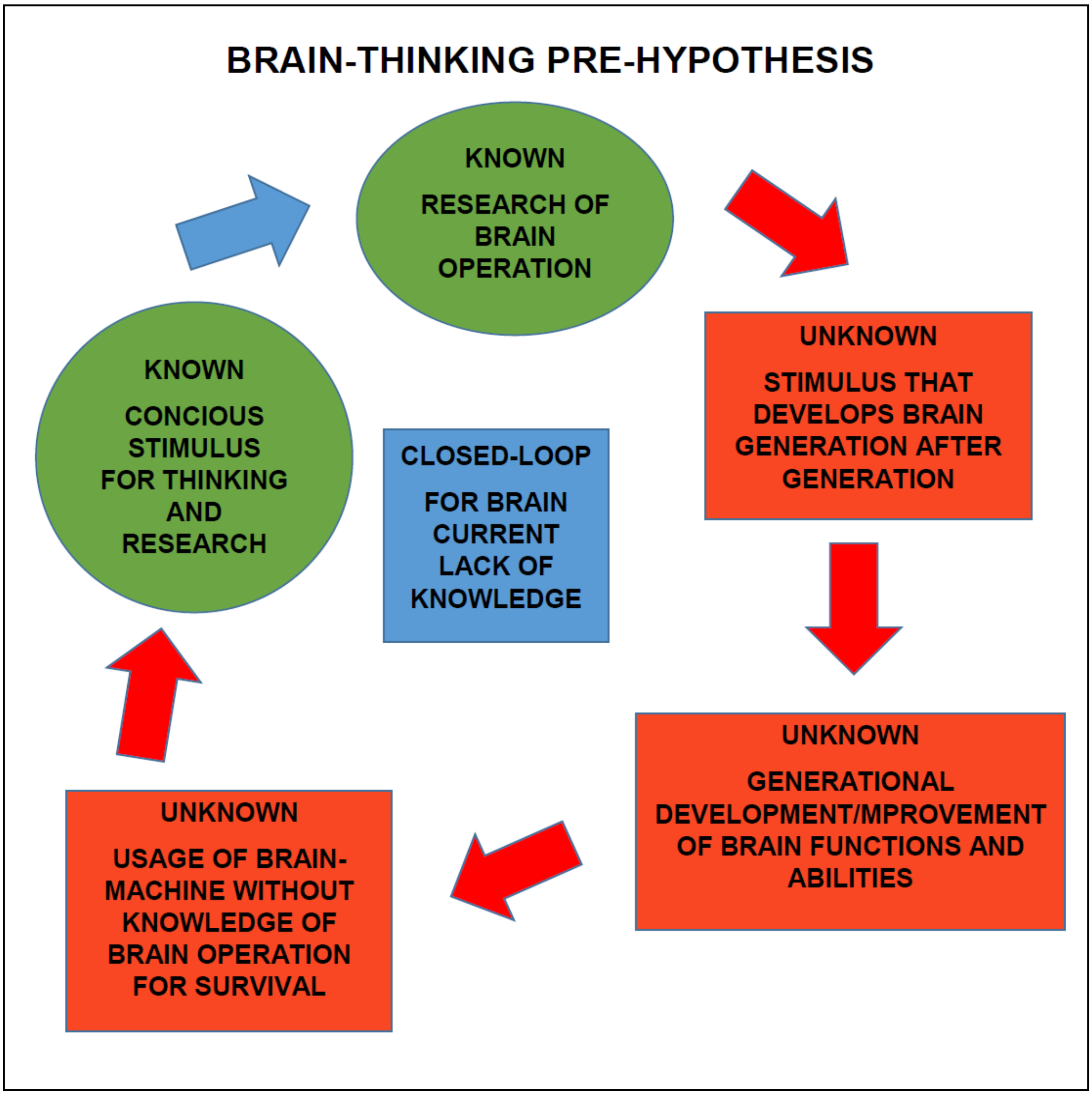
7. Generation after generation, for what humans think?: Perhaps the cell differentiation of neurons goes forward changes, improves along successive generations, in the same way than the body structure, bones dimensions, and anatomical-physiological attributes change from generation to next generation.
8. Why humans have to study/think to guess-understand-discover their proper reasoning-cognitive system?: that might be a subsequent growing step after the surge of thinking capability.
9. The random matter organization could take many different ways. Therefore, biological animal life, developed initially by presence of water, might not be considered exclusive, and at universe might exists possible different forms of 'life' as it is named by science.
10. The emotions, playful sensations, emotional pleasure feelings, brain pleasure stimuli (music, visual, for example), might constitute a survival method as a catalyzer for further usage of exclusive rational thinking in survival tasks.

Further Deductions with Previous Review

Continuing with previous publications, a number of guessed deductions are shown related to Sketchs 1-2. Sketch 1 displays the DNA evolution consequences along probably million years. Between complete adaptation and extinction, some intermediate stages could happen. Namely, random positive for adaptation abnormalities could yield specie variants and/or kind of like new surviving skills for individuals. Those functions that are most used for survival get improvements/developments, while the others that are not used, may tend to atrophia.



Sketch 1.-Guessed from previous publications, Pre-Hypothesis extrapolations. The DNA modifications could yield several outcomes along millions of years.



Sketch 2.-From previous publications, resume of Pre-Hypothesis. Human beings might obey almost totally unknown natural laws that make them think/reason for survival. In that sense, human thinking might be a part of an automatic-unknown survival chain driven by superior/ignored laws of nature at present. Currently, it is possible to get research results for 'the how', 'the where', 'the when', and something about 'the for what', but not too many responses for 'the because of' or 'the from that/where'.

These further concepts (pre-hypothesis) related to [26], are set in Sketchs 1-2, with improved pre-hypothesis details. To add some extrapolation comments, it is necessary to take a realistic overview of planet earth life proportions related to universe—provided the comfirmed dimensions of universe as those are known at the present stages. That is, the earth life and dimensions compared to universe ones can be considered almost null. If the earth magnitude size is divided by the approximated universe dimensions, the quotient is almost null. This implies that the earth planet significance/existence is almost irrelevant within the universe. Mathematically speaking, earth can be considered one point within the 3D universe mathematical infinite points set (closed or open, unknown at the moment). However, the subjective unrealistic perception of human beings, in a kind of like relativistic physics sense, is that the earth constitutes a center of essential importance in the universe. That is, reasoning in the same way than at Middle Ages, when it was believed that the solar system orbits were rotating around the earth. Nevertheless, those concepts do not mean that investigation/progress could be unpractical/unuseful or a nonsense task.

8. Review and Extension. Derived Pre-Hypotheses Extrapolations for Neurophysiology-Neurobiology Examples

Following the previous section extrapolations, this one deals with further extrapolations of neuronal physiology network for some pre-consideration additional evidences about the biological optical neurosystem rapid evolution/adaptation, and reflection for malfunctioning of some neuronal systems in psychiatric disorders. Namely, the example of the visual adaptation of the squirrels optics, exterior and interior, and the pre-hypothesis about the neurophysiological-neurobiology interferences, for instance, in the retina-optical neurobiological-system or auditive one at some psychiatric disorders. This second extrapolation should be seen as a cautious pre-hypothesis [26,27].

For observation of the optical neurobiological system internal and external of the squirrels, as a choice among the nature for plain catching up the idea, basic natural evidence is shown. First, the squirrels spherical eyes are big and almost totally spherical-shaped, just like the current common type of surveillance cameras. So, they can cover all the angles for its spherical geometry. At the same time, the eyes are separated at cranial anatomical semisphere or ellipsoid by about 180 degrees. This is the optimal anatomical position selected by evolution to cover almost all the possible vision angles. What is more, the darkness of the eyes, kind of black, permits to catch up all the wavelengths and do not reflect any light spectrum, saving all the visual signals (just to remind the physics black body theory). The survival-evolution at trees, as a pre-hypothesis, 'built' this impressive system for squirrels survival within a predators environment and at the same time to avoid risks of any movement at the branches of the trees and those high spots over the ground.

However, [28, pages 571-572, for example], scientific controversy remains about the Evolution Theory applied on the nature design of the optical systems, and particularly the eye for different species. It might be seen as a difficult discussion, and *ex aequo*, it might be possible to maintain that nature evolution is not perfect. Specially with those parts/systems of animals or humans that do not depend exclusively on the internal medium. In fact, they depend of multiple external variables determined by nature. The evidence is that the percentage of humans whose eyes do not have any defect is not high, and the proving evidence to continue with the controversy is that symmetry and perfection in natural parts of anatomy and physiology fails in a high percentage of humans. For instance, the congenital chardiophaties are not unfrequent because of the difficulties to develop embriologically a perfect heart. That happens with the musculoskeletal system and other essential parts of the body. All things considered, Evolution Theory and its improvements is realistically what is available at the moment. Further, some unpredictable abnormalities might suppose kind of advantages for special skills.

The second extrapolations comes from the retina neuronal models and clinical neurobiology at this and previous publication series [26,27,28]. It is extensively proven by MRI, [27], histology and anatomical-pathology studies that metal disorders show alteration in neuronal activations and neurotransmitters, among several others [27,28]. Given the fact, for example, that some psychiatric patients suffer visual hallucinations, those disorder-symptoms could be interpreted as a biased stimulus for the retina-brain neuronal-neurobiological vias. That is, stimulus for the wrong neurons and at the wrong time, and possibly with the wrong neurotransmitters both in type and quantity. That implies that mental disorders symptoms, no matter detected experimentally with evidence or not, might have a determined neurobiological-physiological cause. Therefore, the rather great difficulties to cure/treat mental disorders symptoms with pharmacological drugs might come from the fact that it is extremely difficult to modify a neurophysiological network just exactly and ideal-exclusively for avoiding those biased stimulus that might produce the referred problem. Following the idea, the actually unavoidable side effects of those psychiatric drugs might come form that current impossibility. In such hurdle, the modern pharmacology finds enormous difficulties to activate exclusively the affected pathologically neuronal-neurobiological systems, avoiding the inmense number of other neuronal networks and mutual connections at brain.

All things considered, the pre-hypothesis from the disease is extrapolated to normality. In other words, if neurobiological alterations are found in brain disorders, [27-28], the normal differences in behaviour, emotional characteristics, reasoning and other multiple neurology functions might have a tangible neuro-transmission differences, and other neurophysiology ones. Therefore, here is the pre-hypothesis:

Author's proposal (1)

'Any normal, special, or pathological phenomena in human capabilities and behavior possibly might have always a tangible neurophysiological base at the neuronal system networks'.

Provided the former, some Author's extrapolations for normality, developed from [26-28], might include some examples:

Author's proposal (2)

1. The emotions. They might depend on every individual neural connection and proper neural networks of its brain. There might be also, for instance, tangible neurophysiological difference in emotional brain neural networks and possibly neuron connections according to different races. For example, north-europeans are more reluctant to show emotional behavior and reactions, while south europeans get an emotionally clearly different conduct. Same extrapolations might be found for other continent races.
2. The personality. It might have a tangible neurophysiological base for each and every individual, and the differences among them might be difficult to detect given the complicated neural networks. The same examples as point 1.
3. The intelligence. As a rule, located mainly at pre-frontal zone, reasoning and intelligence capabilities might also get a neuronal tangible difference among different races or sub-races. Also, for example, the talent and skills for music or language abilities could present neuronal differences, as, for example, the history of musical geniuses demonstrates.
4. The races personality. For example, extrovert races, introvert ones, races with tendency to depressive behavior, might have neurobiological differences.
5. The special capabilities. There might be neurobiological differences among the different individuals. In the same way than there are not, in general, two identical persons in look and, therefore, might exist differences among the individual neurobiological characteristics. Furthermore, the evolution of generations might cause atrophia or greater development of capabilities that are not used or improved more.
6. The sex behaviour and preferences. There might be neurobiological tangible differences for sex behavior, preferences, special conducts or other related factors.

Discussion and Conclusions

The innovations of this article are mainly two. First and foremost is the LIAF 2D digital simulations series. Secondly, the software engineered creation of 3D multidigital simulations for LIAF model with Vpeak parameters sequences. This second strand was rather complicated and required special programming patterns and several 3D imaging processing fittings. Both Matlab and GNU-Octave were proven as suitable systems for these simulations. The utility of 3D multidigital simulations for getting fast datasets of different neuronal spike trains, parameters, and optimization numerical data can be checked at Instace Figures 1-2, and Figure 4.

Therefore, the objectives of the study were to continue/improve previous advances in this subject. Firstly, the LIAF 2D digital simulations series. Secondly, to digitally 3D multisimulate with Matlab and GNU-octave the LIAF model without refractory period. To make all that in clear and illustrative 2-3D imaging-processing series. Additionaly, to review the IAF model optimization in 3D with several parameters using Tikhonov and Chevyshev objective function algorithms. Along the review-formulation section, more explanations and details of usual equations for LIAF and IAF models were included. Specifically, differences for numerical and analytic solutions were described.

The second part of the paper reviews/supplements the neurobiology-neurophysiological extrapolations that were presented in pervious contributions. Those are extended towards visual neurophysiology and neuropsychiatry applications, provided all of them kept/considered as a cautious pre-hypotheses.

It was intended to show differences/advantages/disadvantages between image processing in Matlab and GNU-Octave. The programming techniques for 3D multidigital simulations is complicated, rather difficult, and needs special procedures for getting precision. Running time for 3D multidigital simulation increases related to 2D simple ones. The programming methods for the first 2D LIAF digital programming series were based on for/if/elseif loops, and complementary elseif patterns blocks. Parameters and units had to be carefully checked. The IAF and LIAF parameters at the charts were set with parameters and significance details. The method for second-review part was 3D-2D PMO optimization and the software was designed especially for that model based on previous radiotherapy computational intelligence PMO programs. Just to mark that to design programs in 3D for pareto-multiobjective optimization is rather difficult, because the Genetic Algorithms patterns in 3D are not simple.

Results mean advances related o previous articles. They give clear 2D-3D multidigital imaging-processing graphics for LIAF without refractory period and LIAF review with refractory period models. All of them with extensive numerical details. The second improved 3D PMO simulations review/show a number of charts derived from previous publications. Programming precision gets almost null residual for all pareto functions. Running time for all simulations is adequate, sometimes several seconds, and 3D-2D graphics show about 100% numerical-criteria matched. When using GNU-octave, the running time is higher. Apart from that, the time for 2D-3D multidigital imaging-processing graphics is rather longer.

In brief, series of extended/improved Matlab and GNU-Octave simulations for LIAF and IAF neuronal models were obtained with perfected software-engineering. Firstly, is the LIAF 2D digital simulations series. Secondly, the software engineered creation of 3D multidigital simulations for LIAF model with Vpeak parameters sequences. Numerical dataset and 2D-3D charts are sharp and meaningful. A review and extension of several neurophysiological pre-hypotheses for neuroscience of brain thinking, visual neurophysiology and neuropsychiatry extrapolations were explained in in short.

10. Scientific Ethics Standards

The article contains reviews of the previous publications essential for complete understanding. The 3D multidigital simulations are original from the Author, software, design, patterns and 3D image processing. The 2D LIAF without refractory period software-programs were developed by Author, based on literature and Radiotherapy publications, [8-15, 23,24], and previous experience. Author's Proposals are completely deductions from the author based on literature. Article has parts of review to make all more sharp/perceptive. Number of Author's references is large due to computational-software evolved programs applied. New software-programs are developed by Author from literature and systems, always improved, changed patterns, values, and modified. No artificial intelligence (AI) tools were used for programming anyway. Radiotherapy references are included as they are the programming base. Model is a slight modification from several authors [1-7,26], based also on [8-16,26] techniques. Methods in software for these publications were created by Dr Casesnoves in 2021-2. This article has previous papers information, from [8-16,26], whose inclusion is essential to make the contribution understandable. This study was carried out, and their contents are done according to the International Scientific Community and European Union Technology and Science Ethics [16-19]. References [16-19]: 'European Textbook on Ethics in Research'. European Commission, Directorate-General for Research. Unit L3. Governance and Ethics. European Research Area. Science and Society. EUR 24452 EN. And based on 'The European Code of Conduct for Research Integrity'. Revised Edition. ALLEA. 2017.

This research was completely done by the author, the computational-software, calculations, images, mathematical propositions and statements, reference citations, and text is original for the author. When a mathematical statement, algorithm, proposition or theorem is presented, demonstration is always included. When a formula is presented, all parameters are detailed or referred. If any results inconsistency is found after publication, it is clarified in subsequent. When a citation such as [Casesnoves, 'year'] is set, it is exclusively to clarify intellectual property at current times, without intention to brag. The article is exclusively scientific, without any commercial, institutional, academic, religious or religious influences, religious-similar, non-scientific theories, personal opinions, political ideas, or economical influences. When anything is taken from a source, it is adequately recognized. Ideas and some text expressions/sentences from previous publications were emphasized due to a clarification aim.

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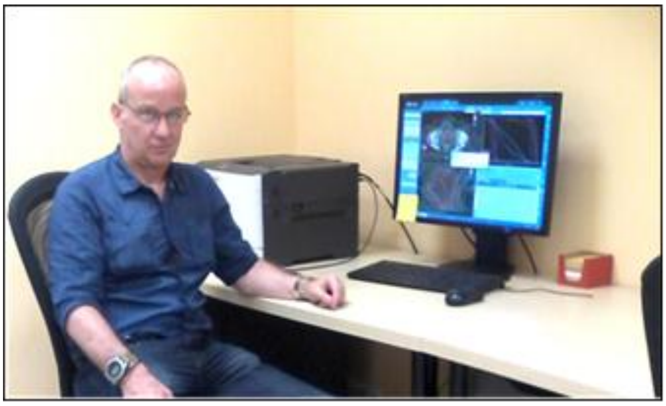

Dr Francisco Casesnoves earned the Engineering and Natural Sciences PhD by Talllinn University of Technology (started thesis in 2016, thesis Defence/PhD earned in December 2018, official graduate Diploma 2019). He works as independent research scientist in computational-engineering/physics. Dr Casesnoves earned MSc-BSc, Physics/Applied-Mathematics (Public Eastern-Finland-University, MSc Thesis in Radiotherapy Treatment Planning Optimization, which was developed after graduation in a series of Radiation Therapy Optimization-Modelling publications [2007-present]). Dr Casesnoves earned Graduate-with-MPhil, in Medicine and Surgery [1983] (Madrid University Medicine School, MPhil in Radioprotection Low Energies Dosimetry [1985]). Casesnoves resigned definitely to his original nationality in 2020 for ideological reasons, anti-monarchy-corruption, democratic-republican ideology, and ethical-professional reasons, and does not belong to Spain Kingdom anymore. Besides, for his anti-corruption ethical ideas, has no any collaboration-links in research for that country. His constant service to the International Scientific Community and Estonia Republic technological progress involves about 80 articles, more than 100 total publications, and about 4 books. Recent advances published are in Superconductors Mathematical Modelling and Radiotherapy Brain Neurobiological Models, 3D-AI Isodosezones and Isodoselines. Among Dr Casesnoves inventions and scientific creations are:

Radiotherapy Comformal Wedge design and formulation

Numerical Reuleaux Method

Radiotherapy Omega Factor correction for AAA model wedge filters dose delivery

Integral-Differential materials erosion model

Graphical Optimization

Interior Optimization

Superconductors Molecular Effect Model

Superconductors Multifunctional Transmission Line

BED radiotherapy model GA optimization

RT Isodoselines and Isodosezones.

Artificial-Intelligence applications with GA for Treatment Planning Optimization in applied Nuclear Physics.