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Mathematical Modelling of Gene Regulatory Networks

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Abstract:

This research includes the use of artificial intelligence algorithm, which is one of the algorithms of biological systems which is the algorithm of genetic regulatory networks (GRNs), which is a dynamic system for a group of variables representing space within time. To construct this biological system, we use (ODEs) and to analyze the stationarity of the model we use Euler's method. And through the factors that affect the process of gene expression in terms of inhibition and activation of the transcription process on DNA, we will use TF transcription factors. The current research aims to use the latest methods of the artificial intelligence algorithm. To apply Gene Regulation Networks (GRNs), we used program (MATLAB2020), which provides facilitation to the most important biological concepts for building this biological interactions.

Keywords:

Ordinary Differential Equations (ODEs), Gene-Regulation Networks (GRNs), Runge-Kutta method (RK), Time-Discretization, Central Dogma of Biology, Gene-expression, Transcription, Translation.

1- Introduction:

All living systems, form unicellular to multicellar plants and animals, store and replicate information and pass it on to the next offspring. Knowledge of genetics cannot be obtained with a real understanding of biology or its appreciation. The cell, which is the smallest building unit of life, contains many basic molecules that regulate and coordinate all interaction. The cell generally consists of water, deoxyribonucleic acid (DNA), proteins, polysaccharides, and small organic compounds such as acids and sugars.

Some macromolecules, in addition to being a store of vital information, have important vital properties such as controlling all biological activities, and this is done by the DNA molecule, which is the main controller of this complex structure because it stores information about the structure and function of basic molecules and helps in the production of the needs of the cell, constitutes a molecule (DNA) (a blueprint) for the organism by means of the biochemical information stored in it. The DNA strands consist of basic bases called nucleotides, which carry the genetic information of living organisms and the sequence consists of four different bases (A) adenine, (G) guanine, (T) thymine and (C) cytosine, and they determine the type and timing of protein synthesis. These base pairs are connected in the form of opposite (A-T) and (G-C) in its double helical structure to bind the two DNA strands it derived J.D.Watson and F.H.C.Crick in 1953, see Figure (1).

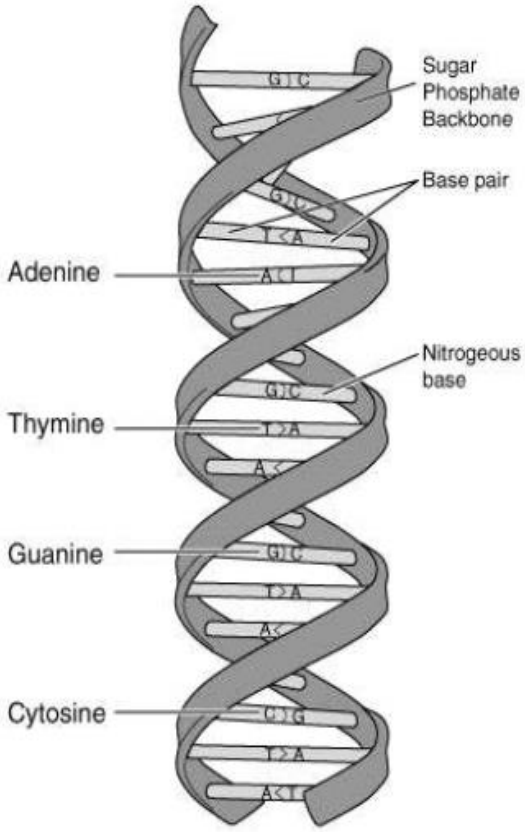

Figure (1): The structure of DNA and its nitrogenous bases.

An important feature of the DNA model is that the two strands are held together by non-covalent hydrogen bonds, a weak electrostatic bond between two atoms that can be easily broken and reshaped. The number of bonds in base pairs varies so that there are two between (A) and (T), and there are three bonds between (G) and (C). target segments representing unite of the DNA sequence are genes that control specific genetic triatic of an organism, and a gene can be defined as a portion of DNA that determines the formula for RNA, because only specific parts of the DNA and genes are expressed as in Figure (2), and this region is less than 5% of the human DNA for protein production.

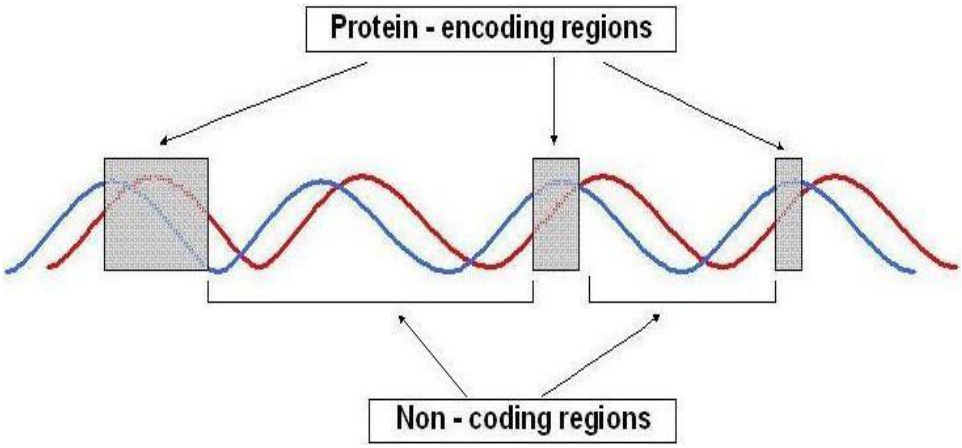

Figure (2): The non-coding regions in the DNA strand and the regions that do not carry the code, which are genes.

2- Central Dogma of Biology

The flow of information from DNA through RNA to form proteins, by the intermediate element represented by (RNA) which consists of a similar structure to the DNA molecules, but the difference is first, in the sugar element and instead of Deoxyribose RNA consists of the sugar ribose, and secondly, in the base pairs of nucleotides so that it contains RNA instead of T (thymine) containing U (uracil), and thirdly, in the property of the double strand, the (RNA) consists of a single strand, and determines above, the central doctrine of biology, which includes the transfer of genetic information from DNA to RNA and this process is called (transcription) and then pass the information from this process is called translation (translation) as shown in Figure (3), and the idea that comes from the central dogma, which states that one gene is responsible for one protein molecule has recently changed; we are facing more dynamics more complex than we thought, one gene may interact with many molecules C cells in the cell and can lead to the production of more protein molecules, with all this complexity, the map of relationships between genes still seems buildable due to the limited interaction of genes stemming from their limited topological structures.

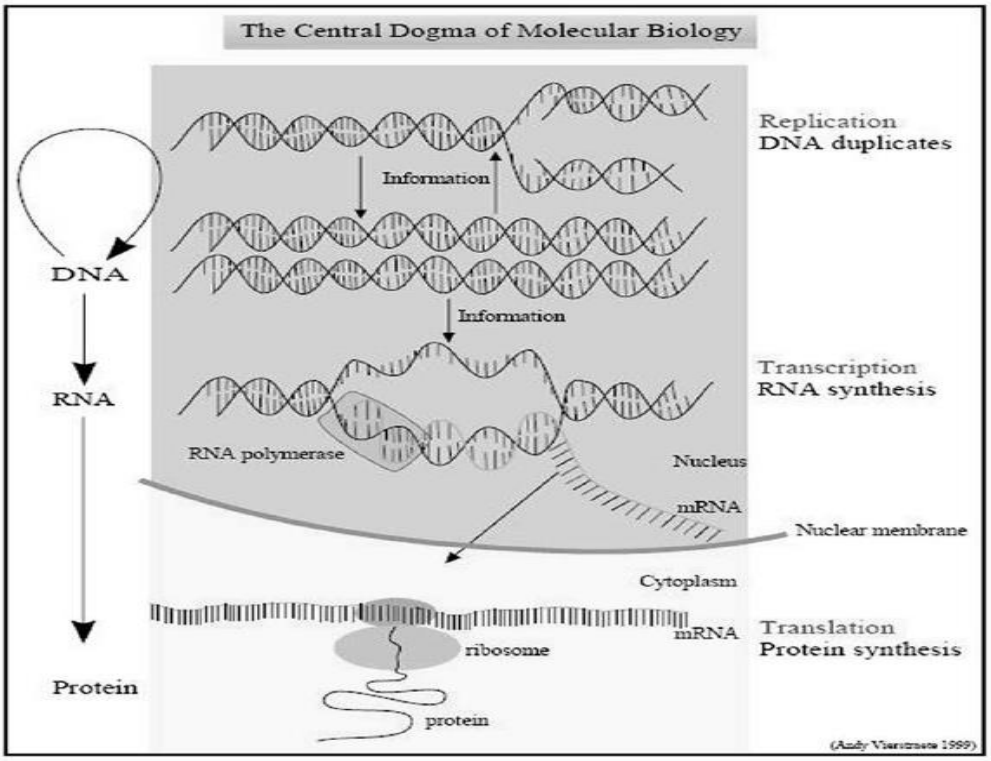

Figure (3): An illustrative scheme of the steps of the central doctrine in biology.

3 - Modelling gene networks with ODEs from gene expression data

In general, continuous models that indicate the differential relationship between variants of gene regulatory networks are presented from systems of (ODEs) [1], [2], [3],

$$\dot{E}_i = F_i(E) \qquad (i = 1, 2, \dots, n) \quad \dots \quad (1)$$

Where n represents the number of gene in the model, and $E = (E_1, E_2, \dots, E_n)^T$ this vector represents the positive concentrations of proteins produced from transcription and translation and $(mRNA)$ produced from transcription and small components involved. $F_i : R^n \to R$ are nonlinear functions [4],[5], [6], [7], [8], [3], [9]. It was suggested by Chen et al. of ODEs to represent the dynamic and sequential biochemical reactions, and in our case the transcription and translation reactions, so that the results of these reactions are the concentration of $(mRNA)$ and the continuous equation $\dot{E} = ME$, in which the matrix M, it was a constant matrix ,depend on E, [5], the vector E is the expression level of the genes, then De Hoon and lmoto used this linear model on $(mRNA)$ data from to estimate M with the method of maximum likelihood estimation [4], [7]. In 2001, suggest [7] a mathematical model as follows :

$$\dot{E}_i = F_i(E_1, E_2, \dots, E_n) \quad \dots \quad (2)$$

With F_i being fun of $E = (E_1, E_2, \dots, E_n)^T$ which is determined by mathematical programming of GP and LS methods.

Through generalization of the on top form, a following form was reached [9], [2], [8], [7], [3].

$$(\mathcal{CE}) \qquad \dot{E} = M(E)E \qquad (3)$$

Where M was a matrix, it was a constant matrix, depend on E, for optimization problem we use least squares method of finding a mathematical model and an approximate network, the gene length (DNA) will be determined to be an initial value to finally constrain the solution by imposing limits on the number of regulating factors for each gene depending on the combined environmental impact of the genes, the initial values $E(t^0) = E^0$ in $(\mathcal{CE})$ especially to $E^0 = \bar{E}^0$ which was the first vector from the computed experimental data [10], [11], [12], [13], [14].

4 -Gene Regulatory

The matrix formula $M(E)$ can deriving by using the following system of (ODEs) [15], [1], [16], [2]:

$$\dot{E}_i = c_i - \delta_i E_i + \sum_{j=1}^{j_i} regf_{i,j}^{+} + \sum_{k=1}^{k_i} regf_{i,k}^{-} \quad (i = 1, 2, \dots, n) \ \dots \ (4)$$

Where, parameters $c_i \geq 0$ and $\delta_i \geq 0$ were coefficients representing basal structure or basal dissolution, and the amounts match to activation and inhibition. It have been shown that the activation and inhibition functions $regf_{i,j}^{+}$, $regf_{i,k}^{-}$ have been show to possess a sigmoid shape [17]. And these results are in the form of an array containing the entries for the array system.

$$m_{ii} = (c_i/E_i) - \delta_i + \alpha_{ii}\left(E_i^{m_{ii}-1}/\left(E_i^{m_{ii}} + \theta_{ii}^{m_{ii}}\right)\right), (i = 1, 2, \dots, n) \ \dots \ (5)$$

$$m_{ij} = \alpha_{ij}\left(E_j^{m_{ij}-1}/\left(E_j^{m_{ij}} + \theta_{ij}^{m_{ij}}\right)\right), \qquad (i, j = 1, 2, \dots, n; i \neq j) \quad \dots (6)$$

With $\alpha_{ij} \in \mathbb{R}$ and $\theta_{ij}, m_{ij} \in \mathbb{R}_0^+$. The parameters were collecting in a vector y and can estimate by data from laboratory experiments DNAmicroarray [18], [10], [19]. These represents of m_{ii} and m_{ij} discover the discontinuity of poles.

Note the x-axis can be theoretically derived, taking into account the TF_j binding reaction of transcription factor j ,for the founder gene region i, i.e. the B_{ij} binding site and as a Reverse Chemical Reaction $(\mathcal{RCR})$ [18], [20] :

$$(\mathcal{RCR}) \qquad m_{ij} \cdot FT_j + B_{ij} \underset{}{\overset{K}{\rightleftarrows}} C$$

The factor m_{ij} match to the collaboration between single transcription factors and often referred to as the Hill-coefficient. In $(\mathcal{RCR})$ [21], [22], [23], where a number of transcription factors represent an activation complex. m_{ij} indicates the number of transcription factors in this complex. In terms, m_{ij} can interpret as a relationship among transcription factors and dose not being an integer, given that the chronometry of our system that measures changes in the process of gene expression was much slower than the binding of a transcription factor to DNA, we assume that the $(\mathcal{RCR})$ was always in equilibrium, so the reaction constant K uniquely determines the relationship between the

concentrations of products and according to the law-mass action [24], [25], and K was the relationship between the reaction rate constants k_1 for complex formation and k_2 foe dissociation, it depends on the temperature and binding energy of the compound, as shown in [26], [27].

5 -Time-Discretization and the Stability Analysis

An estimate concerned with the approximation of continuous mathematical models by transforming the continuous model into a discrete model and the numerical solution resulting from simulating the behavior of the dynamic system through (ODEs) which starts with the initial value t_0 with the given value E_0 which is an approximation of the solution in a separate set of points; we follow the paths with approximate values of the solution, so choosing an appropriate numerical method to be applied to the continuous model of time is Euler's method, which is one of the simplest for estimating time for gene expression patterns [28], but for a more accurate method, we use the RK estimation method.

6 -RK method

When using (ODEs) as a numerical method for solving models, one of the most important numerical methods for measuring errors is Euler's Method, and to measure the error of the curve $E(t)$ it is approximated by a straight line. The line between the points t_k and t_{k+1}, and also Euler's method compares the derivative at the beginning of the time interval t_k and its endt_{k+1}. This reduces the accuracy by ignoring the estimation of the distance between the two points. (RK) which takes into account the points within the time period in the system of continuous equations($\mathcal{CE}$), and (Runge-Kutte) (RK) method is characterized by the stability that increases the stability of the time-continuous model.

RK methods use information at time t_k only, which makes it self-operating at the beginning of integration and becomes easy to program. This accounts in part for their popularity [29].

Use a central idea of (RK) method to model gene-expression patterns [3], [30], [2], [8] applying a different method (RK). It is the Heun method, a modifier novel of Euler's Method, which is a more straightforward simpler case of the RK path. It is formulated as follows:

$$E_{k+1} = E_k + \frac{h_k}{2}(k_1 + k_2) \ , \qquad \dots \ (7)$$

Where

$$k_1 = M(E_k)E_k \ , \quad and \quad k_2 = M(E_k + h_k k_1)(E_k + h_k k_1) \ \dots \ (8)$$

More explicitly, we write

$$E_{k+1} = E_k + \frac{h_k}{2}M(E_k)E_k + \frac{h_k}{2}M(E_k + h_k M(E_k)E_k)(E_k + h_k M(E_k)E_k) \ , \dots (9)$$

$$E_{k+1} = \left[I + \frac{h_k}{2}M(E_k) + \frac{h_k}{2}M(E_k + h_k M(E_k)E_k)\big(I + h_k M(E_k)\big)\right]E_k . \dots (10)$$

Defining

$$M_k := I + \frac{h_k}{2}M(E_k) + \frac{h_k}{2}M(E_k + h_k M(E_k)E_k)\big(I + h_k M(E_k)\big) \ , \dots . (11)$$

We get the following discrete time equation:

$$(\mathcal{CD})_{ext} \qquad E_{k+1} = M_k E_k \ . \quad \dots \ (12)$$

Thus, the experimental results can be represented as $\overline{E}_0, \overline{E}_1, \dots, \overline{E}_{l-1}$ and we can represent the estimates as follows $\widehat{E}_1, \widehat{E}_2, \dots, \widehat{E}_{l-1}$ and in the following way: setting $\widehat{E}_0 = \overline{E}_0$, the $k^{th}$is calculated from the approximate values

$$\widehat{E}_k = M_{k-1}\left(M_{k-2} \dots \left(M_1(M_0\overline{E}_0)\right)\right), \qquad (k \in \overline{E}_0). \qquad \dots(13)$$

The formula $(\mathcal{CD})_{ext}$ was the perfect way to understand how to obtain genetic environment networks from the discrete time dynamics, if the input m_{ij}^k for the matrix are M_k and i^{th} rows and j^{th} columns, m_{ij}^k is the coefficient proportionality (i.e. E_j factorial) such that i^{th} gene(or environmental factor). The variable became j^{th} gene (or environmental factor) at the $k+1$ time point.

While, genes and environmental factors are represented by the nodes (vertices) of our dynamic network and the interactions between them and weighted by those parameters.

7 -Model a Gene-Regulation Networks in MATLAB For Biology Systems

The method (ODEs) used in building a set of equations to represent a set of reactions in the modeling of biochemical pathways, through two steps that represent the two processes that make up gene expression First, the pathway analysis for a set of primary reactions whose information was encoded in three matrices, related to the measurement of elements and rate coefficients of the Biochemical system. This information is used to create and solve equations (ODE), and it was assuming that the path can be decomposed into one-way elementary reactions, then the law of mass action can be apply to each initial reaction to get the following differential equations and to build the complex system of equations we use flexible (MATLAB) files that allow us to construct biological and dynamic systems more precisely and in the form of matrices.

We can a systems biology model with different levels of differentiation. This model is an example of simple genetic regulation, in which a protein product controls from transcription to translation. We can create a more complex model by adding enzymes, coenzymes, cofactors, nucleotides and amino acids not included in this model. This example simplifies the mechanisms of gene regulation by assuming an initial value of $E = 50$.

By the way the interactions are listed in a model and the processes they represent:

Transcription: $DNA \rightarrow DNA + mRNA$
Translation: $mRNA \rightarrow mRNA + protein$
Binding: $DNA + protein \rightarrow DNAproteinComplex$
Unbinding: $DNAproteinComplex \rightarrow DNA + protien$
Degradation: $mRNA \rightarrow null$
Degradation: $protien \rightarrow null$.

Drawing reaction pathways helps visualize the relationships between reactions and species as in Figure (4). In the gene regulation example, as the amount of protein increases, the protein forms a complex with the gene responsible for its gene expression, and protein production slows down.

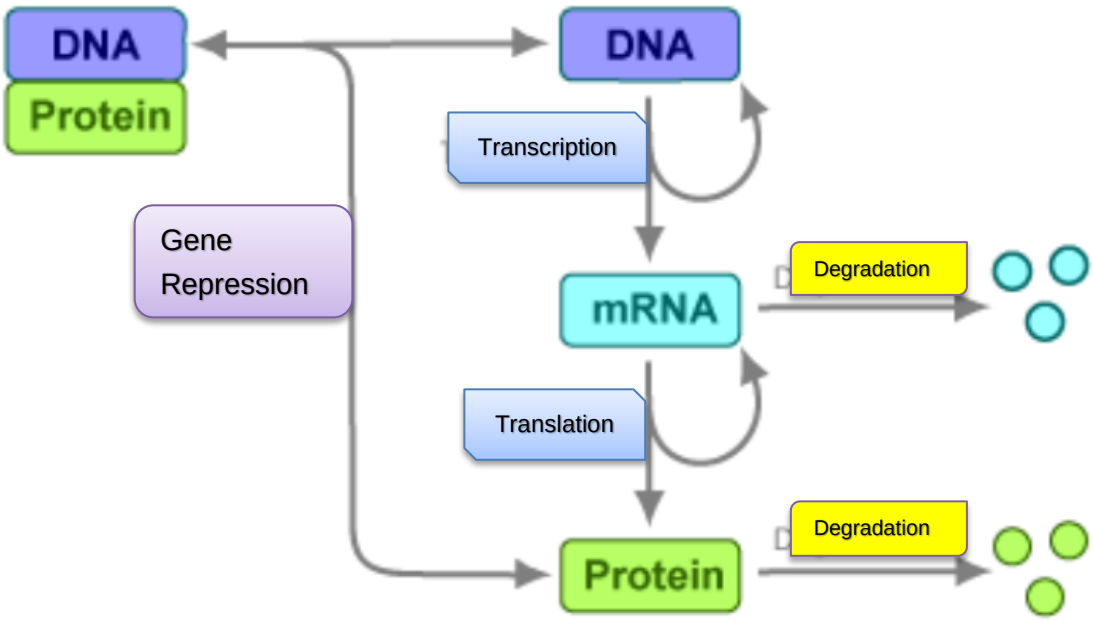

Figure (4): Scheme of the regulatory gene expression process, model interactions.

Table (1): Results matrix for a dynamic gene expression model.

DNA	mRNA	protein	DNAprotein Complex	Time	DNA	mRNA	protein	DNAprotein Complex
50	0	0	0	0.15429533	49.2383438	1.37127505	1.36146673	0.76165624
50	6.32E-05	6.75E-09	3.60E-13	0.18199529	48.8433609	1.58162075	1.74197986	1.15663913
50	0.000126489	2.13E-08	1.55E-12	0.20969526	48.3598637	1.7810193	2.13673414	1.64013626
50	0.000173443	3.67E-08	3.15E-12	0.23739522	47.7901248	1.96944077	2.5415986	2.20987523
50	0.000220396	5.66E-08	5.64E-12	0.26509518	47.1377978	2.14687386	2.95389823	2.8622022
50	0.000258714	7.59E-08	8.41E-12	0.29279515	46.4075509	2.31333058	3.37203043	3.59244913
50	0.000297031	9.81E-08	1.20E-11	0.3478888	44.7448613	2.61196025	4.21780905	5.25513867
50	0.000335348	1.23E-07	1.66E-11	0.40298246	42.8425053	2.86799172	5.08232819	7.15749473
50	0.000407312	1.77E-07	2.77E-11	0.45807611	40.7504725	3.08252895	5.9681383	9.24952753
50	0.000479274	2.41E-07	4.29E-11	0.51316977	38.5180749	3.25712312	6.87837374	11.4819251
50	0.000551236	3.15E-07	6.30E-11	0.56826343	36.192831	3.39371979	7.81611745	13.807169
50	0.000623197	4.00E-07	8.88E-11	0.62335708	33.8199961	3.49459861	8.78437259	16.1800039
50	0.000778047	6.17E-07	1.67E-10	0.76735248	27.6841551	3.60844006	11.4713839	22.3158449
50	0.000932894	8.82E-07	2.82E-10	0.91134787	22.1089014	3.54723809	14.3803897	27.8910986
50	0.001087738	1.19E-06	4.43E-10	1.05534327	17.4776569	3.3654996	17.4386177	32.5223431
50	0.001242577	1.56E-06	6.55E-10	1.19933866	13.9253264	3.11376512	20.494718	36.0746736
50	0.001397413	1.96E-06	9.27E-10	1.34333406	11.3863332	2.83321441	23.3575396	38.6136668
50	0.001933116	3.75E-06	2.43E-09	1.48732945	9.67127974	2.55327651	25.8430634	40.3287203
50	0.002468775	6.10E-06	5.04E-09	1.62331098	8.60752579	2.30563079	27.7300721	41.3924742
50	0.00300439	9.03E-06	9.07E-09	1.75929251	7.91863668	2.08237042	29.1290498	42.0813633
50	0.003539963	1.25E-05	1.48E-08	1.89527404	7.48609867	1.88683006	30.0571021	42.5139013
50	0.004075493	1.66E-05	2.26E-08	2.03125557	7.22842718	1.71920149	30.5686227	42.7715728
49.9999999	0.00728604	5.30E-05	1.29E-07	2.1672371	7.09117296	1.57787261	30.7352623	42.908827

49.9999996	0.010495039	0.00010985	3.85E-07	2.31246164	7.03692525	1.45320825	30.6158853	42.9630747
49.9999991	0.013702493	0.00018709	8.56E-07	2.45768617	7.04967815	1.35249901	30.2719393	42.9503219
49.9999984	0.0169084	0.00028462	1.61E-06	2.60291071	7.11050985	1.27252324	29.7766882	42.8894902
49.9999973	0.020112763	0.00040238	2.71E-06	2.74813525	7.20504531	1.21026653	29.1889937	42.7949547
49.9999958	0.023315582	0.00054026	4.21E-06	2.89335978	7.32229241	1.16298595	28.555059	42.6777076
49.999981	0.03851213	0.00146809	1.90E-05	3.1549433	7.56713085	1.10819982	27.3967678	42.4328691
49.9999488	0.053673909	0.00284012	5.12E-05	3.41652682	7.82394195	1.08221169	26.3362725	42.1760581
49.9998923	0.068800993	0.00464792	0.0001077	3.67811033	8.06750515	1.07545815	25.4427075	41.9324948
49.999805	0.083893452	0.00688324	0.000195	3.93969385	8.28201297	1.08072967	24.7331874	41.717987
49.9996806	0.098951356	0.00953796	0.0003194	4.20127736	8.45935618	1.09269524	24.1977101	41.5406438
49.9995127	0.113974771	0.01260412	0.0004873	4.54041392	8.63165776	1.11227991	23.7251826	41.3683422
49.9984151	0.169200885	0.02737911	0.0015849	4.87955047	8.74317387	1.13138648	23.4513765	41.2568261
49.9963459	0.223959791	0.04729051	0.0036541	5.21868703	8.80578727	1.14721541	23.3177714	41.1942127
49.993032	0.278254184	0.07198447	0.006968	5.55782359	8.83378424	1.15890748	23.273019	41.1662158
49.988221	0.332086431	0.10113039	0.011779	5.89696014	8.84059838	1.16671636	23.2784396	41.1594016
49.9816801	0.385458612	0.13441929	0.0183199	6.40650395	8.8301127	1.17284565	23.3284548	41.1698873
49.9731951	0.438372537	0.17156243	0.0268049	6.91604775	8.81368899	1.17455087	23.3811285	41.186311
49.9437531	0.56349066	0.27483669	0.0562469	7.42559156	8.80106885	1.17422747	23.4164593	41.1989312
49.8996543	0.685995077	0.39546357	0.1003457	7.93513537	8.79396773	1.17341348	23.4344147	41.2060323
49.8390081	0.805896318	0.53063131	0.1609919	8.44467917	8.79079307	1.17275634	23.4414586	41.2092069
49.7603198	0.923200212	0.67796121	0.2396802	9.31310209	8.78899898	1.17211896	23.4446828	41.211001
49.662434	1.037908999	0.83544407	0.337566	10	8.78938113	1.17195145	23.442985	41.2106189

8 -Conclusions

To use the Gene Regulatory Networks (GRNs) algorithm, which is a dynamic system, to solve dynamic programming problems. It also integrates the problem with system of (ODEs) dynamically and uses Runge-Kutta method to estimate and analyze stability.

To use the Gene Regulatory Networks (GRNs) algorithm in processing time series data, because the algorithm factors process translation and transcription data during the time factor to complete the interaction.

To use the Gene Regulatory Networks (GRNs) algorithm to process bag data. Using the Gene Regulatory Networks (GRNs) algorithm in processing time series data, because the transcription data during the time factor to complete the interaction.

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النمـــــذجـــــة الرياضـــــيـة لشـــــبكات التنظـــــيم الجـــينية

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مستخلص البحث:

يتضـــمن هـــذا البحـــث اســـتعمال خوارزميـــة الـــذكاء الصـــناعي, احـــد خوارزميـــات الـــنظم البايلوجيـــة وهـــي خوارزميـــة الشـــبكات التنظيميـــة الجينيـــة (GRNs), وهـــي عبـــارة عـــن نظـــام دينـــاميكي لمجموعـــة مـــن المتغيـــرات تمثـــل الفضـــاء ضـــمن الـــزمن. ولبنـــاء هـــذا النظـــام البـــايلوجي نســـتعمل المعـــادلات التفاضـــلية العاديـــة (ODEs) ولتحليـــل اســـتقرار الانمـــوذج نســـتعمل طريقـــة (Euler) . ومـــن خـــلال العوامـــل التـــي تـــؤثر فـــي عمليـــة التعبيـــر الجينـــي مـــن حيـــث التثبـــيط والتنشـــيط فـــي عمليـــة النســـخ علـــى الحمـــض النـــووي (DNA) سنســـتعمل عوامـــل النســـخ (TF). يهـــدف البحـــث الـــى اســـتخدام أحـــدث أســـاليب خوارزميـــات الـــذكاء الاصـــطناعي. لتطبيـــق شـــبكات تنظـــيم الجينـــات (GRNs) ، اســـتخدمنا برنـــامج المـــاتلاب (MATLAB2020) ، والـــذي يـــوفر التســـهيلات لأهـــم المفـــاهيم البيولوجيـــة لبنـــاء هـــذه التفاعلات البيلوجية.

المصطلحات الرئيسة للبحث: المعادلات التفاضلية العادية (ODEs) , الشبكات التنظيمية الجينية (GRNs) , طريقة Runge-Kutta , تقدير الوقت , العقيدة المركزية في علم الاحياء , التعبير الجيني , النسخ , الترجمة .

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