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A SCILAB BASED SIMULATION SOFTWARE FOR GENETIC PROBLEM

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Abstract: In this paper, we discussed on the development of a simulation software with graphical interfaces to simulate the interaction in genetic problem using Scilab. However we only focus on problems such as Genetic Toggle Switch , Biological Clock of Neurospora Crassa , and Biological Circuit of the Repressilator. This simulation software may overcome the destructive DNA experiment. We apply numerical analysis approaches to construct the algorithm in the software. Fourth order Runge Kutta (RK4) and Runge Kutta Fehlberg (RKF) were used to approximate the result. Results show that the Scilab based simulation software via RK4 and RKF was superb in simulating the genetic problem.

Keywords: Genetic simulation software, Fourth order Runge-Kutta , Runge-Kutta Fehlberg, Scilab

1. Introduction

Simulation system aim to mimic a phenomenon in physical environment. Thus, the simulation require the presentation of object behaviour as real as possible. The system have the ability to solve real-world problem safely and efficiently. The system provides clear insights into a real-world problem. Therefore, simulation system gives benefit to student, researcher, and practitioner to perform certain tasks or to understand certain situation especially dangerous or hazardous problem in healthy and safe condition.

Teaching student using a simulator give flexibility to student to manage their study time. This will accomodate weaker and gifted student learning phase. Increase their understanding the application of some theory in an applications. For researcher and practitioner, the simulation software aided them with early prediction of an experiment. This help them to speed up their research and development activity and reduce cost. Simulations also allow exploring situations too complex to be solved analytically. Simulations also permit us to validate inferences drawn from empirical studies. They can be run with different estimated parameters and compared to the original dataset. In addition, simulated data can be very useful for educational purposes. Various datasets can be generated and provided to student to train their skills.

Interaction and interrelationships in system biology is a complex interaction to understand. Lab experiment often need to be conducted to understand their behaviour, In DNA research as an instance, DNA often need to be bought with high price. After the research, the DNA protein cannot be recycle to be used in other research (Atkinson et al., 2003; Yihai, 2004; Gardner et al., 2000; Csicsery & O'Laughin, 2013). This was called as destructable items. Simulation research in DNA provides better solution to help the research

process. The system act as a predictors in research before we conduct a real lab experiment to confirm the behaviour.

In this research, we develop an simulation software for Genetic Toggle Switch , Biological Clock of Neurospora Crassa, and Biological Circuit of the Repressilator. Gardner et al. (2000), Atkinson et al. (2003) and Csicsery & O'Laughin(2013) have done research in Genetic Toggle Switch problem mathematically. Merciful of Allah (s.w.t.) let us understand his creation using mathematics. Its complex creation shows its power, its grace and its vast knowledge. Figure 1 shows the Genetic Toggle Switch architecture.

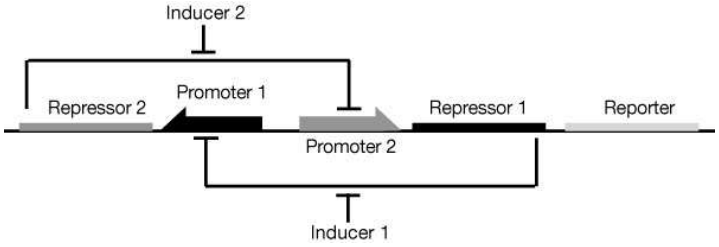


Figure 1. Architecture of the Genetic Toggle Switch. (Gardner et al., 2000)

According to Atkinson et al. (2003), the Genetic Toggle Switch is a genetic network constructed by referring to Escherichia coli bacteria. The differential equation for the Genetic Toggle Switch problem system of equations can be refer in Hasan et al. (2016) are given in equation (1) and (2).

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^{\beta}} - u, \qquad (1)$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^{\gamma}} - v, \qquad (2)$$

where u represent concentration of repressor 1, v represent concentration of repressor 2, α represent repressor synthesis rate and β, γ represent the cooperativity of the repressor.

A more complex DNA interaction is the Biological Clock of Neurospora Crassa. Yihai et al. (2004) develop a system of stiff differential equations from an architecture for the Biological Clock of Neurospora Crassa interactions proposed by Yu et al. (2004). The interactions of RNAs, proteins, biomolecules and its offsprings is given in Figure 2.

The systems of stiff differential equations can be refer in Hasan et al. (2016) are given in equations (3)-(9).

$$f'_1 = A(f_C - f_1)\, w^n - A' f_1 \qquad (3)$$

$$f'_r = S_3(f_C - f_1) + S_4 f_1 - D_3 f_r \qquad (4)$$

$$f'_p - L_3 f_r - D_6 f_p \qquad (5)$$

$$w' = E_2 u_p - D_8 w - nA(f_C - f_1)\, w^n + nA'^{f_1} - P w f_p^{\,m} \qquad (6)$$

$$u'_p = L_1 u_{r1} - D_4 u_p - E_2 u_p \qquad (7)$$

$$u'_{r1} = C_1 u_{r0} f_p - D_7 u_{r1} \qquad (8)$$

$$u'_{r0} = V_1 + D_1 u_{r0} - C_1 u_{r0} f_n \qquad (9)$$

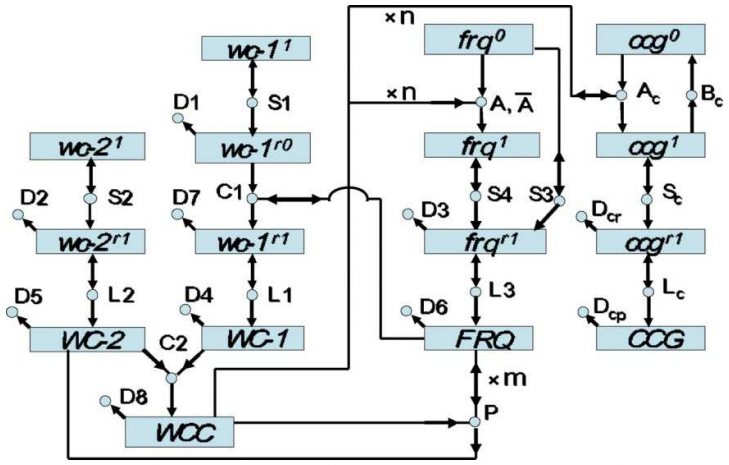


Figure 2. Biological Clock of Neurospora Crassa (Yu et al., 2004)

Another stiff differential equations develop by Yihai (2004) was the Biological Circuit of the Repressilator. The architecture of the Biological Circuit of the Repressilator is given in Figure 3.

The systems of stiff differential equations are given in equations (10) and (11).

$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{1+p_j^n} + \alpha_o \qquad (10)$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_i), \qquad (11)$$

where α_o is the protein in each cell when a promoter saturated with repressor, $\alpha+\alpha_o$ is the protein in each cell when a repressor was not exist, and β is the ratio of protein and decay rate of mRNA.

2. Simulation System

The simulation System for solving genetic problem developed using SCILAB open source software. The development architecture of the proposed simulation software is given in Figure 4. The simulation software have three module, which refer to cases. Case 1 is for Genetic Toggle Switch, Case 2 is for Biological Clock of Neurospora Crassa and Case 3 is for Biological Circuit of Repressilator. User may select "CASE A" for *Genetic toggle switch,* "CASE B" for Biological clock of neurospora crassa or "CASE C" for Biological circuit of repressilator to run a simulation. The interface design is given in Figure 5.

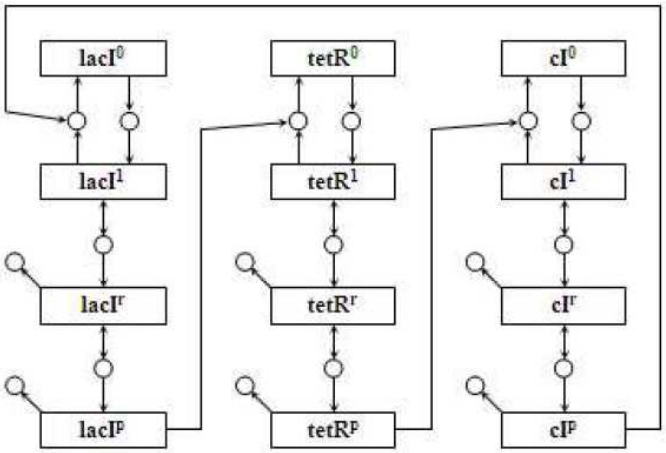


Figure 3. Architecture of Biological Circuit of the Repressilator (Yihai, 2004)

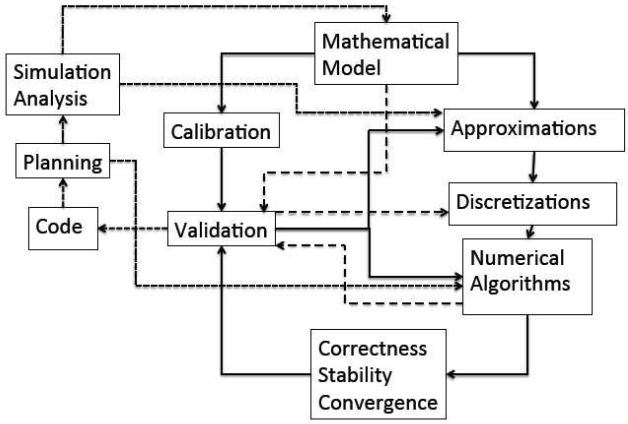
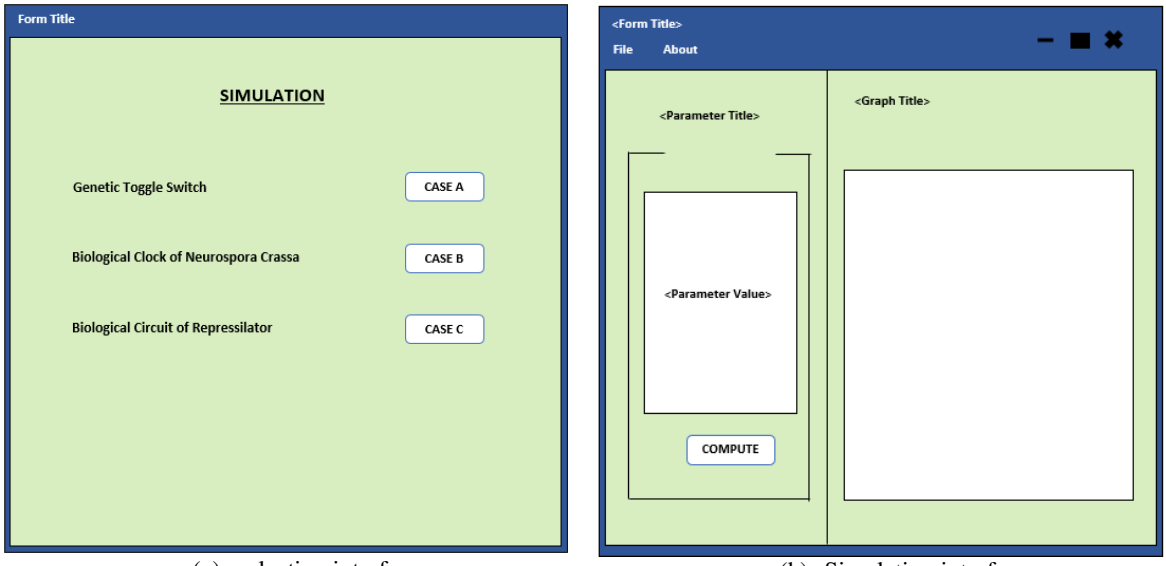


Figure 4. Architecture of development process of the proposed simulation software.



(a) selection interface (b) Simulation interface

Figure 5. Interfaces design.

3. Numerical formulation

Two numerical method will be applied in the simulation software, i.e. fourth order Runge-Kutta (RK4) and Runge-Kutta-Fehlberg (RKF). The RK4 schemes is given by equation (12).

$$y_{i+1} - y_i + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4), \tag{12}$$

where

$k_1 = f(t_i, y_i), k_2 = f\left(t_i + \frac{h}{2}, y_i + \frac{h}{2}k_1\right),$

$k_3 = f\left(t_i + \frac{h}{2}, y_i + \frac{h}{2}k_2\right)$ and $k_4 = f(t_i + h_i y_i + hk_3)$ for $i = 0,1,2,\ldots,n.$

The RKF schemes is given in equation (13).

$$y_{k+1} = y_k + \frac{25}{216}k_1 + \frac{1408}{2565}k_3 + \frac{2197}{4101}k_4 - \frac{1}{5}k_5$$
$$z_{k+1} = y_k + \frac{16}{135}k_1 + \frac{6656}{12825}k_3 + \frac{28561}{56430}k_4 - \frac{9}{50}k_5 + \frac{2}{55}k_6 \tag{13}$$

where

$k_1 = hf(t_k, y_k), k_2 = hf\left(t_k + \frac{1}{4}h, y_k + \frac{1}{4}k_1\right),$

$k_3 = hf\left(t_k + \frac{3}{8}h, y_k + \frac{3}{32}k_1 + \frac{9}{32}k_2\right)$,

$k_4 = hf\left(t_k + \frac{12}{13}h, y_k + \frac{1932}{2197}k_1 + \frac{7200}{2197}k_2 + \frac{7296}{2197}k_3\right)$,

$k_5 = hf\left(t_k + h, y_k + \frac{439}{216}k_1 - 8k_2 + \frac{3680}{513}k_3 - \frac{845}{4104}k_4\right)$, and

$k_6 = hf\left(t_k + \frac{1}{2}h, y_k + \frac{8}{27}k_1 - 2k_2 + \frac{3544}{2565}k_3 - \frac{1859}{4104}k_4 - \frac{11}{40}k_5\right)$, for $i = 0,1,2,\ldots,n.$

4. Numerical Experiment

To analyze the functionalability of the system of the simulation system, we create several cases following Yihai (2004). The cases are

i. Assume repressor is excluded at t = 0

$$K = \frac{K_{transcription[DNA]}}{1 \mid \left(\frac{[Repressor]}{\left(1 + \left(\frac{[Inducer]}{K_s}\right)^{n2}\right)K_d}\right)^{n1}}$$

$$[mRNA] = \frac{K}{Ym} - \frac{K}{Ym}\, e^{-Ymt}$$

$$[Protein] = \frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm}\, e^{-Ymt} - \left(\frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm}\right) e^{-Ypt}$$

ii. Assume repressor is added at t = 0

$$K = \frac{K_{transcription[DNA]}}{1 + \left(\frac{[Repressor]}{\left(1 + \left(\frac{[Inducer]}{K_s}\right)^{n2}\right) K_d}\right)^{n1}}$$

$$[mRNA] = \frac{K}{Ym} + \left(2.5 \times 10^3 - \frac{K}{Ym}\right) e^{-Ymt} \qquad (17)$$

$$[Protein] = \frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm}\, e^{-Ymt} - \left(3.34 \times 10^5 - \left(\frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm}\right)\right) e^{-Ypt}$$

$$K = \frac{K_{transcription[DNA]}}{1 + \left(\frac{[Repressor]}{\left(1 + \left(\frac{[Inducer]}{K_s}\right)^{n2}\right) K_d}\right)^{n1}}$$

$$[Protein] = K_{translation}\, \frac{\left(\frac{K}{Ym}\right)}{Yp}$$

iii. Reanalyzed case where *repressor* is excluded at t = 0

$$K = \frac{K_{transcription[DNA]}}{1 + \left(\frac{[Repressor]}{\left(1 + \left(\frac{[Inducer]}{K_s}\right)^{n2}\right) K_d}\right)^{n1}}$$

$$[mRNA] = \frac{K}{Ym} - \frac{K}{Ym}\, e^{-Ymt}$$

$$[Protein] = \frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm}\, e^{-Ymt} - \left(\frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm}\right) e^{-Ypt}$$

iv. Reanalyzed case where repressor is added at t = 0

$$K = \frac{K_{transcription[DNA]}}{1 + \left(\frac{[Repressor]}{\left(1 + \left(\frac{[Inducer]}{K_s}\right)^{n2}\right) K_d} \right)^{n1}}$$

$$[mRNA] = \frac{K}{Ym} + \left(2.5 \times 10^3 - \frac{K}{Ym}\right) e^{-Ymt}$$

$$[Protein] = \frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm} e^{-Ymt} - \left(3.34 \times 10^5 - \left(\frac{Kk_{translation}}{YpYm} + \frac{Kk_{translation}}{Ym^2 - YpYm}\right)\right) e^{-Ypt}$$

Table 1. Parameter values for Genetic Toggle Switch

Parameter	**explaination**	value
[DNA]	DNA concentration	150 cell
$k_{transiation}$	Protein synthesis rate	2.85 min^{-1}
$k_{transcription}$	RNA synthesis rate	3.17 min^{-1}
γp	Protein degradation rate	2.13*10^{-2} min^{-1}
γm	mRNA degradation rate	0.19 min^{-1}
Ks	Inducer constant	1000 molecule/cell
Kd	Repressor constant	0.05 molecule/cell
n1	Cooperation of repressor bind to promoter	2
n2	Cooperation of inducer bind to repressor	2

Biological Clock of Neurospora Crassa

Table 2. Initial value for of Biological Clock Neurospora Crassa

Species	**Initial value**
f_1	0.00400782
f_r	0.181388
f_v	1.37307
w	0.0000663227
u_v	0.0000362815
u_{r1}	0.212505
u_{r0}	0.0000000252030

Table 3. Parameter value for of Biological Clock Neurospora Crassa

Parameter	Nilai	Parameter	Nilai
A	0.0000462010	D_8	0.00285475
A'	0.566108	C_2	1.66501
S_1	9.22739	P	3.55829
S_2	0.00353803	A_o	5.57336
S_3	0.000000136553	B_o	1.82043
S_4	9.07295	S_o	0.0149985
D_1	1.35911	L_o	0.0111332
D_2	2.77832	D_{or}	0.268920
D_3	0.223231	D_{op}	0.269409
C_1	0.0545178	v_v	0.120699
L_1	59.7062	u_1	0.0124268
L_2	35.3755	f_0	0.692213
L_3	0.798222	n	4
D_4	0.00000947792	m	4
D_5	0.00000179706	E_2	$v_v * C_2$
D_6	0.159737	f_C	$f_0 + f_1$
D_7	0.192918	V_1	$S_1 * u_1$

Biological Circuit of Repressilator

Table 4. Parameter value for Biological Circuit of Repressilator

Parameter	value
alpha0	1
Alpha	1000
N	2.0
Beta	5

5. Experiment results

Simulation results for Genetic Toggle Switch are displayed in Figure 7 to Figure 10. Figure 7 represent graph for three different γ_v; i.e. $2.13 \times 10^{-2}\ min^{-1}$, $4.26 \times 10^{-2} min^{-1}$ and $2.13 \times 10^{-1}\ min^{-1}$. Initial value for protein is 0 and Repressor value is also 0. Figure 8 represent graph for similar value of parameter in Figure 7 but with Repressor 3.5^5. Figure 9 represent a protein 3D plot for Repressor value $R = 0{:}10000{:}3.5 \times 10^5$ and Inducer value $I = 0{:}10000{:}5 \times 10^5$. Figure 10 represent mRNA expression level versus time with three different γ_m; i.e. 0.19 min^{-1}, 0.38 min^{-1} and 1.9 min^{-1}. Initial value for protein is 0 and Repressor value is also 0.

Simulation results for Biological Clock of Neurospora Crassa are displayed in Figure 11 to Figure 16. Figure 11 represent graph f_1 with initial value 0.0040078. Figure 12 represent graph f_v with initial value 1.37307. Figure 13 represent graph w with initial value 0.0000663227. Figure 14 represent graph u_v with initial value 0.0000362815. Figure 15 represent graph ur_1 with initial value 0.212505. Figure 16 represent graph ur_0 with initial value 0.0000000252030.

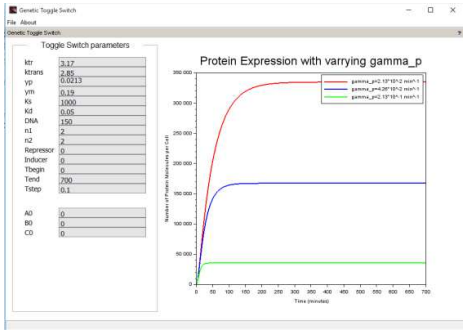


Figure 7. Repressor excluded at $t = 0$.

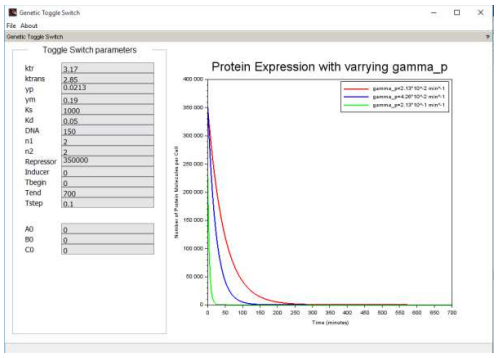


Figure 8. Repressor added at $t = 0$.

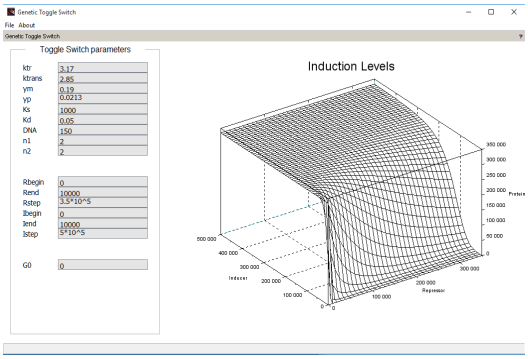


Figure 9. Plot 3D of the result.

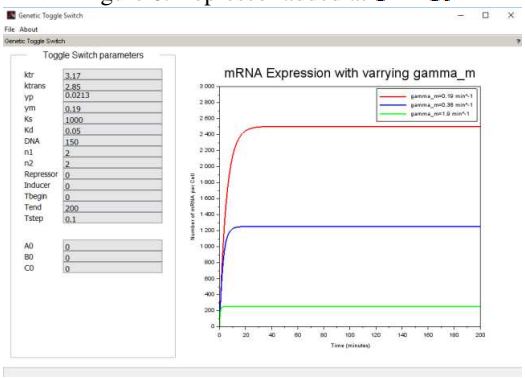


Figure 10. Different initial value at $t = 0$.

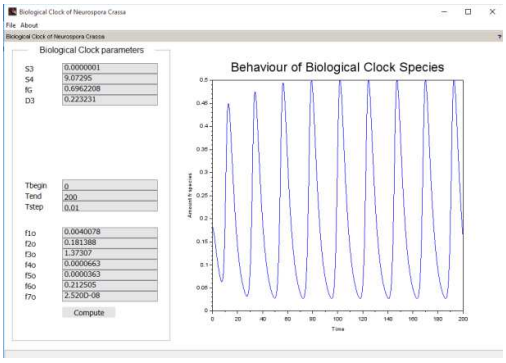


Figure 11. Species f_1 behaviour.

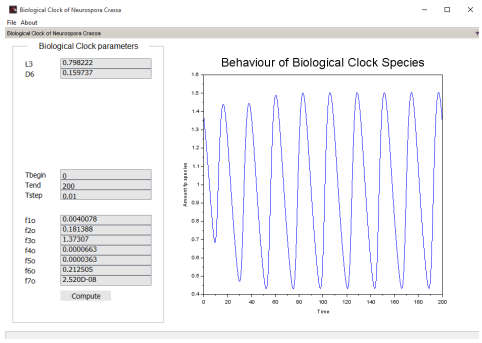


Figure 12. Behaviour of species f_2.

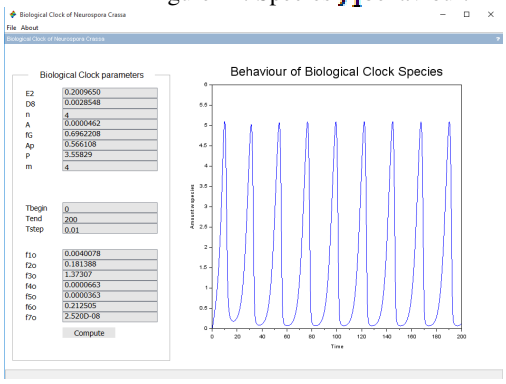


Figure 13. Behaviour of species w.

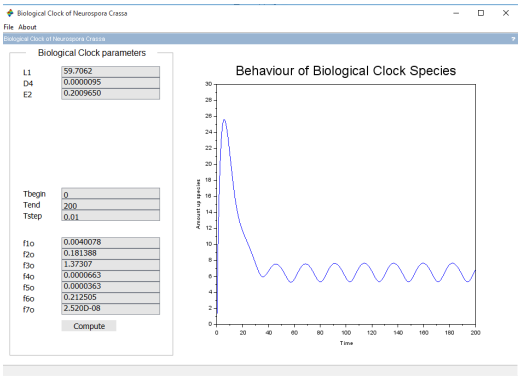


Figure 14. Behaviour of species u_p.

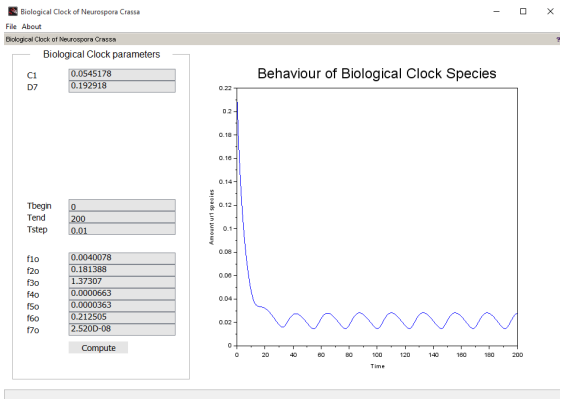


Figure 15. Behaviour of species m_1.

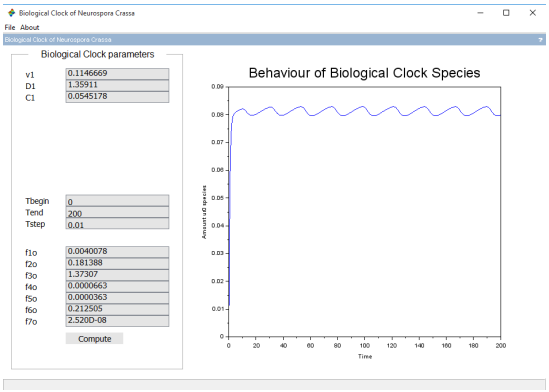


Figure 16. Behaviour of species m_0.

For Biological Circuit of Repressilator, we examine three condition; i.e. stable steady state solution, oscillatory solution and changes in behaviour of repressilator solutions. Simulation results displayed in Figure 17 to Figure 28. For the first condition, the results are displayed in Figure 17 till Figure 20. Figure 17 represent graph for species m1, p1, m2, p2, m3, p3 behaviour with initial value 0, 1, 0, 1, 0, 1, respectively. Figure 18 represent graph of interaction between species m1 and p1 with initial value of m1 is 0 and p1 is 1. Figure 19 represent graph of interaction between species m2 and p2 with initial value of m2 is 0 and p2 is 1 while Figure 20 represent graph of interaction between species m3 and p3 with initial value of m2 is 0 and p2 is 1.

For the second condition, the results are displayed in Figure 21 till Figure 24. Figure 21 represent graph for species m1, p1, m2, p2, m3, p3 behaviour with initial value 0, 1, 0, 2, 0, 5, respectively. Figure 22 represent graph of interaction between species m1 and p1 with initial value of m1 is 0 and p1 is 1.

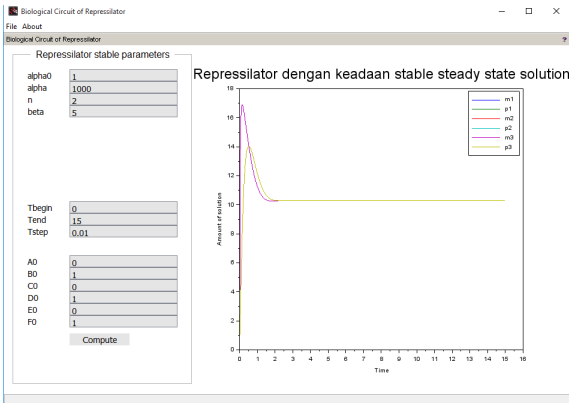


Figure 17. Stable steady state solution of species m1, p1, m2, p2, m3, p3

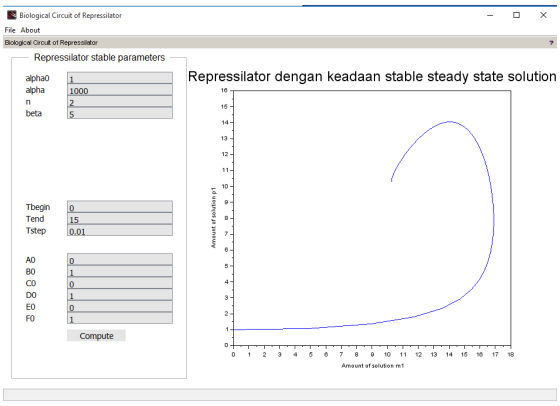


Figure 18. Interaction of species m1 and p1

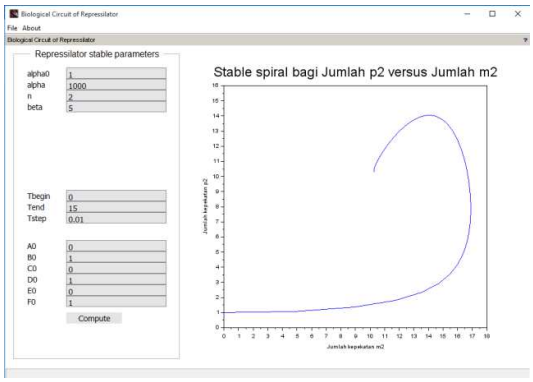


Figure 19. Interaction between species m2 dan p2

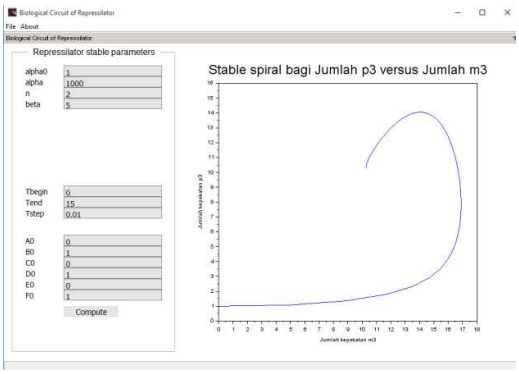


Figure 20. Interaction between species m3 dan p3

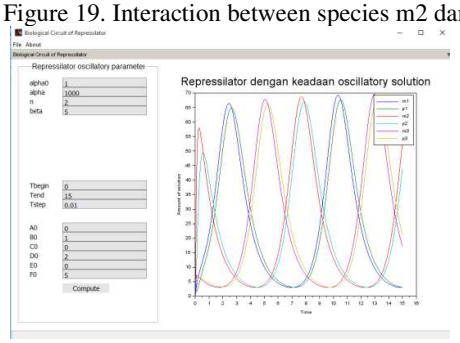


Figure 21. Oscilatory solution of species m1, p1, m2, p2, m3, p3

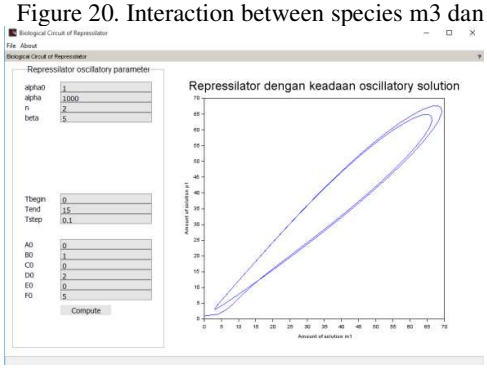


Figure 22. Interaction of species m1 and p1

Figure 23 represent graph of interaction between species m2 and p2 with initial value of m2 is 0 and p2 is 2 while Figure 24 represent graph of interaction between species m3 and p3 with initial value of m3 is 0 and p3 is 5.

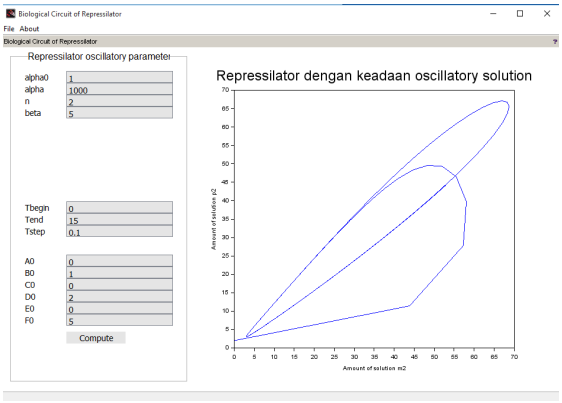


Figure 23. Interaction of species m2 and p2

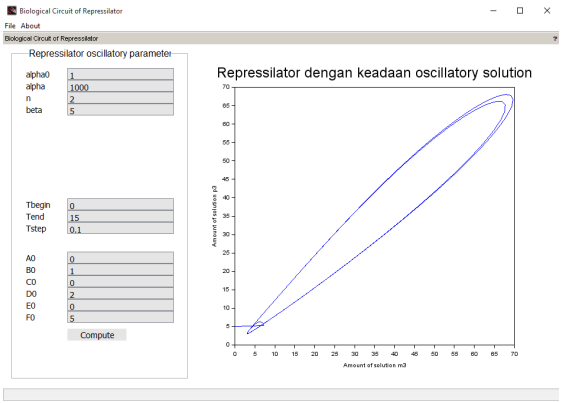


Figure 24. Interaction of species m3 and p3

For the third condition, the simulated results are displayed in Figure 25 to Figure 28. Figure 25 shows the behaviour of repressilator for species m1, p1, m2, p2, m3, p3 with parameter value for the first graph for alpha0, n, beta, alpha are 1, 1.75, 5, 5, respectively. Parameter value for the second graph for alpha0, n, beta, alpha are 1, 1.75, 5, 28, respectively. Parameter value for the third graph for alpha0, n, beta, alpha are 1, 1.75, 5, 1000, respectively. Initial value for species m1, p1, m2, p2, m3, p3 are 0, 1, 0, 2, 0, 3, respectively.

Figure 26 shows the interaction of species m1 and p1. Parameter value for the first graph for alpha0, n, beta, alpha are 1, 1.75, 5, 5, respectively. Parameter value for the second graph for alpha0, n, beta, alpha are 1, 1.75, 5, 28, respectively. Parameter value for the third graph for alpha0, n, beta, alpha are 1, 1.75, 5, 1000, respectively. The initial condition for species m1 and p1 are 0 and 1, respectively.

Figure 27 shows the interaction of species m2 and p2. Parameter value for the first graph for alpha0, n, beta, alpha are 1, 1.75, 5, 5, respectively. Parameter value for the second graph for alpha0, n, beta, alpha are 1, 1.75, 5, 28, respectively. Parameter value for the third graph for alpha0, n, beta, alpha are 1, 1.75, 5, 1000, respectively. The initial condition for species m2 and p2 are 0 and 2, respectively.

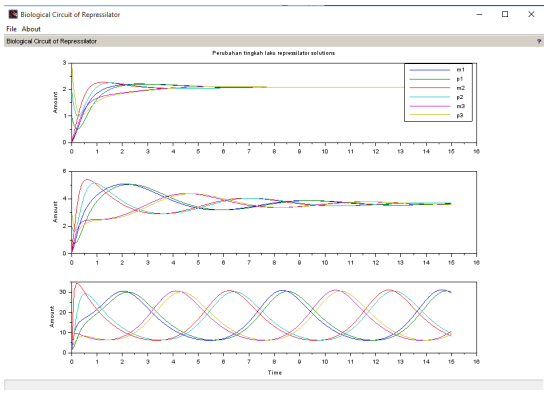


Figure 25. Behaviour of repressilator for species m1, p1, m2, p2, m3, p3.

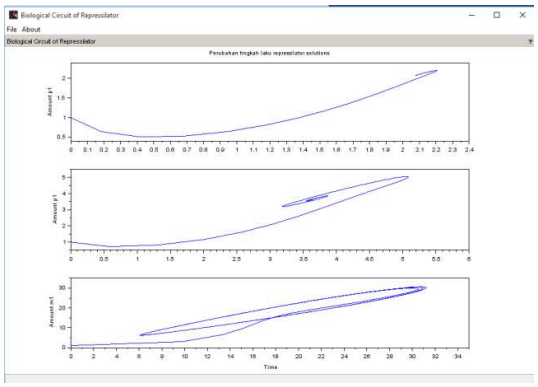


Figure 26. Interaction between m1 and p1

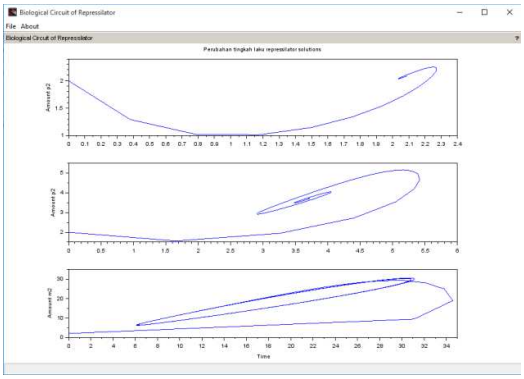


Figure 27. Interaction between m2 and p2

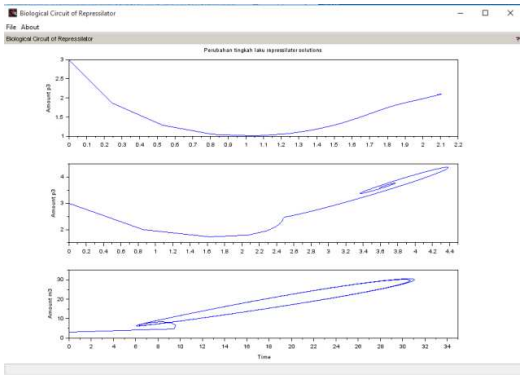


Figure 28. Interaction between m3 and p3

Figure 28 shows the interaction of species m3 and p3. Parameter value for the first graph for alpha0, n, beta, alpha are 1, 1.75, 5, 5, respectively. Parameter value for the second graph for alpha0, n, beta, alpha are 1, 1.75, 5, 28, respectively. Parameter value for the third graph for alpha0, n, beta, alpha are 1, 1.75, 5, 1000, respectively. The initial condition for species m3 and p3 are 0 and 3, respectively.

6. Conclusions

A simulation system for 3 selected genetic problem were developed using Scilab software. The engine for the simulation were developed based on numerical method approach. We apply fourth order Runge-Kutta (RK4) and Runge-Kutta-Fehlberg (RKF) method. The

genetic problem selected are *Genetic Toggle Switch, Biological Clock of Neurospora Crassa,* and *Biological Circuit of Repressilator.* The system we tested using several parameter setup. Result shows that the system succeed to simulate the behaviour of protein, mRNA, species cell molecule with satisfied user interface.

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