Article

Stability analysis of a biological network

Q. Din
Department of Mathematics, University of Poonch Rawalakot, Pakistan
Email: qamar.sms@gmail.com

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Abstract
In this paper, we study qualitative behavior of a network of two genes repressing each other. More precisely, we investigate the boundedness character and persistence, existence and uniqueness of positive steady-state, local asymptotic stability and global behavior of unique positive equilibrium point of this model.

Keywords biological network; stability analysis; local asymptotic stability; global behavior.

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1 Introduction

In case of systems biology it is very crucial impression of modeling the qualitative behavior of biological and biochemical networks where molecules are represented as nodes and the molecular interactions are so called edges. Due to scope and complicated behavior of these networks it is very important to discuss and study their dynamical behavior. An interaction dynamics can be used instead of an explicit mathematical description of these biological networks and computer simulations can be used to study the dynamical behavior of these complex biological networks. It is well known fact that dynamics is related to the study of changes with respect to time. For example in case of classical mechanics an apple falling to the ground, or the growth of the human population. Particularly, in case of systems biology dynamics is related to the changes in concentrations of molecules (or numbers) within a cell. Differential equations and difference equations are main tools for modeling these biological networks.

A dynamical system is defined by a set of variables describing the state of the system and the laws for which the values of these variables change with respect to time. Variables can be regarded as discrete-time variables where the state of the variable can be described by a distinct set of values, or continuous variables in which any real value can be used. The option of differential equations or difference equations depends upon the time and on the state of all variables. Furthermore, it can be deterministic where the time and variable states uniquely defines the state at next time point, or it can be stochastic where the time and variable state defines the probability of how the variable values changes over time. The goal when dealing with a dynamical system is to describe and analyze the behavior of the individual variables and also of the complete system, and to be able to make predictions. A dynamical system can be in equilibrium where variables do not change, it can oscillate in a repeating fashion, or it can be more complicated and even chaotic.

In this paper, we study the qualitative behavior of construction of a genetic toggles witch in *Escherichia coli*. The dynamical behavior of the toggle switch can be described by using the following planar system of nonlinear differential equations:

$$\frac{dx}{dt}=\frac{a}{1+y^{\alpha}}-x,\ \frac{dy}{dt}=\frac{b}{1+x^{\beta}}-y, \tag{1.1}$$

where x,y are concentrations of the two repressors, a,b are the rates of synthesis of repressors, respectively. Moreover, α,β are cooperativity factors. For further detail of system (1.1) we refer interested readers to (Gardner et al., 2000). As it is pointed out in (Zhou and Zou, 2003; Liu, 2010) the discrete time models governed by difference equations are more appropriate than the continuous ones when the populations are of non-overlapping generations. The study of discrete-time models described by difference equations has now been paid great attention since these models are more reasonable than the continuous time models when populations have non-overlapping generations. Discrete-time models give rise to more efficient computational models for numerical simulations and also show rich dynamics compared to the continuous ones (Ahmad, 1993; Tang and Zou, 2006). It is very interesting mathematical problem to discuss qualitative behavior of discrete dynamical systems. For more results for the qualitative behavior of discrete dynamical systems, we refer the reader to (Papaschinopoulos et al., 2011; Din, 2013, 2014; Din and Donchev, 2013).

Using the Euler's method the discretization of (1.1) can be obtained, where the discretization preserves the property of convergence to the equilibrium, regardless of the step size.

Let $t_n=nh$, where h is step size. Applying Euler's method, we obtain

$$x_{n+1}=\frac{ah}{1+(y_n)^{\alpha}}+(1-h)x_n,\ y_{n+1}=\frac{bh}{1+(x_n)^{\beta}}+(1-h)y_n. \tag{1.2}$$

Re-scaling the parameters in (1.2)by$ah\to A, bh\to B, 1-h\to C$, we obtain the following discrete dynamical system:

$$x_{n+1}=\frac{A}{1+(y_n)^{\alpha}}+Cx_n,\ y_{n+1}=\frac{B}{1+(x_n)^{\beta}}+Cy_n. \tag{1.3}$$

In this paper, our aim is to study the boundedness and persistence, existence and uniqueness of positive equilibrium point, local asymptotic stability and global asymptotic behavior of unique positive equilibrium point of discrete dynamical system (1.3).

2 Main Results

Theorem 2.1: Assume that $C<1$, then every positive solution of (1.3) is bounded and persists.

Proof: Let $\{(x_n,y_n)\}$ be any arbitrary positive solution of (1.3), then one has

$$x_{n+1}\leq A+Cx_n,\qquad y_{n+1}\leq B+Cy_n$$

for all $n=0,1,2,\cdots$. Furthermore, consider the following system of linear difference equations:

$$u_{n+1}=A+Cu_n,\qquad v_{n+1}=B+Cv_n$$

for all $n=0,1,2,\cdots$. Then solution of this linear system is given by

$$u_n=\frac{A(1-C^n)}{1-C}+C^nu_0, v_n=\frac{B(1-C^n)}{1-C}+C^nv_0$$

for all $n=1,2,\cdots$, and where u_0,v_0 are initial conditions. Assume that $C<1$, then it follows that

$$u_n\leq\frac{A}{1-C}+u_0, v_n\leq\frac{B}{1-C}+v_0$$

for all $n = 1,2,\cdots$. Taking $u_0 = x_0, v_0 = y_0$, then it follows by comparison that

$$x_n \le \frac{A}{1-C}, y_n \le \frac{B}{1-C}$$

for all $n = 1,2,\cdots$. Furthermore, it follows from (1.3) that

$x_{n+1} \ge \frac{A}{1+(y_n)^\alpha} \ge \frac{A}{1+\left(\frac{B}{1-C}\right)^\alpha} = K_1,$

$$y_{n+1} \ge \frac{B}{1+(x_n)^\alpha} \ge \frac{B}{1+\left(\frac{A}{1-C}\right)^\alpha} = K_2.$$

Hence, we obtain

$$K_1 \le x_n \le \frac{A}{1-C}, K_2 \le y_n \le \frac{B}{1-C}$$

for all $n = 1,2,\cdots$. This completes the proof.■

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Theorem 2.2: Assume that $C < 1$, then for every positive solution of (1.3) the set $\left[K_1, \frac{A}{1-C}\right] \times \left[K_2, \frac{B}{1-C}\right]$ is an invariant set.

Proof: Let $\{(x_n, y_n)\}$ be any arbitrary positive solution of (1.3) such that the initial conditions $(x_0, y_0) \in \left[K_1, \frac{A}{1-C}\right] \times \left[K_2, \frac{B}{1-C}\right]$Then it follows from system (1.3) that

$K_1 \le x_1 = \frac{A}{1+(y_0)^\alpha} + Cx_0 \le \frac{A}{1-C},\ K_2 \le y_1 = \frac{B}{1+(x_0)^\beta} + Cy_0 \le \frac{B}{1-C}.$

From mathematical induction, we obtain that

$$(x_n, y_n) \in \left[K_1, \frac{A}{1-C}\right] \times \left[K_2, \frac{B}{1-C}\right]$$

for all $n = 1,2,\cdots$.■

Theorem 2.3: Suppose that $C < 1$, then (1.3) has unique positive equilibrium point $(\bar{x}, \bar{y}) \in \left[K_1, \frac{A}{1-C}\right] \times \left[K_2, \frac{B}{1-C}\right]$, if the following conditions are satisfied:

$K_1 < \frac{B}{(1-C)\left[1+\left(f(K_1)\right)^\alpha\right]},$

$\alpha\beta\left(\frac{A}{1-C}\right)^\beta [A-(1-C)K_1] < A\left(1+K_1^\beta\right),$

where $K_1 = \frac{A}{1+\left(\frac{B}{1-C}\right)^\alpha}$ and $f(\mathrm{x}) = \frac{B}{(1-C)(1+x^\beta)}$.

Proof: Consider the following system of algebraic equations

$x = \frac{A}{1+(y)^\alpha} + Cx,\ y = \frac{B}{1+(x)^\beta} + Cy.$ (2.1)

Then, it follows from (2.1) that $x = \frac{A}{(1-C)(1+y^\alpha)}$ and $y = \frac{B}{(1-C)(1+x^\beta)}$. Assume that

$(x, y) \in \left[K_1, \frac{A}{1-C}\right] \times \left[K_2, \frac{B}{1-C}\right].$

Set

$F(\mathrm{x}) = \frac{A}{(1-C)\left[1+(f(x))^{\alpha}\right]} - x,$

where $f(\mathrm{x}) = \frac{B}{(1-C)(1+x^{\beta})}$. Then it follows that $F(K_1) = \frac{B}{(1-C)\left[1+(f(K_1))^{\alpha}\right]} - K_1 > 0$ for all $C < 1$. Furthermore, $F\left(\frac{A}{1-C}\right) = \frac{A}{(1-C)\left[1+\left(\frac{B}{\left(1+\left(\frac{A}{1-C}\right)^{\beta}\right)(1-C)}\right)^{\alpha}\right]} - \frac{A}{1-C} < 0$ if and only if

$\frac{1}{1+\left(\frac{B}{\left(1+\left(\frac{A}{1-C}\right)^{\beta}\right)(1-C)}\right)^{\alpha}} < 1$, that is, $\left(\frac{B}{\left(1+\left(\frac{A}{1-C}\right)^{\beta}\right)(1-C)}\right)^{\alpha} > 0$. Hence, $F\left(\frac{A}{1-C}\right) < 0$ for all $C < 1$.

Thus $F(\mathrm{x})$ has a root in $\left[K_1, \frac{A}{1-C}\right]$. Furthermore, we have

$$F'(x) = -1 - \frac{A\alpha f(x)^{-1+\alpha} f'(x)}{(1-C)(1+f(x)^{\alpha})^2},$$

$$f'(x) = -\frac{Bx^{-1+\beta}\beta}{(1-C)(1+x^{\beta})^2}.$$

Let z be a solution of $F(x) = 0$, then $z = \frac{A}{(1-C)\left[1+(f(z))^{\alpha}\right]}$. Hence it follows that

$$F'(z) = -1 + \frac{Az^{-1+\beta}\left(\frac{B}{(1-C)(1+z^{\beta})}\right)^{1+\alpha}\alpha\beta}{B\left(1+\left(\frac{B}{(1-C)(1+z^{\beta})}\right)^{\alpha}\right)^2}$$

$$= -1 + \frac{\alpha\beta z^{\beta}(A-(1-C)z)}{A(1+z^{\beta})}$$

$$< -1 + \frac{\alpha\beta\left(\frac{A}{1-C}\right)^{\beta}[A-(1-C)K_1]}{A\left(1+K_1^{\beta}\right)} < 0,$$

which completes the proof.■

Lemma 2.1 (Sedaghat, 2003): Assume that $X_{n+1} = F(X_n)$, $n = 0,1,\ldots$ be a system of difference equations and $\bar{X}$ is an equilibrium point of F. If all eigenvalues of the Jacobian matrix J_F about the fixed point $\bar{X}$ lie inside the open unit disk $|\lambda| < 1$, then $\bar{X}$ is locally asymptotically stable. If one of them has absolute value greater than one, then $\bar{X}$ is unstable.

Lemma 2.2 (Grove and Ladas, 2004): Consider the following equation

$$\lambda^2 + a\lambda + b = 0, \qquad (2.2)$$

where a and b are real numbers. Then, the necessary and sufficient condition for both roots of the equation (2.2) to lie inside the open disk $|\lambda| < 1$ is

$|a| < 1 + b < 2.$

Theorem 2.4: The unique positive equilibrium point of system (1.3) is locally asymptotically stable, if the following condition is satisfied:

$2C + C^2 + \frac{\alpha\beta A^{\beta}B^{\alpha}}{(1-C)^{\alpha+\beta-2}} < 1.$

Proof. The Jacobian matrix of linearized system of (1.3) about the fixed point $(\bar{x}, \bar{y})$ is given by

$$F_J(\bar{x},\bar{y}) = \begin{bmatrix} C & -\frac{A\alpha\bar{y}^{\alpha-1}}{(1+\bar{y}^{\alpha})^2} \\ -\frac{B\beta\bar{x}^{\beta-1}}{(1+\bar{x}^{\beta})^2} & C \end{bmatrix}.$$

The characteristic polynomial of $F_J(\bar{x},\bar{y})$ is given by

$$P(\lambda) = \lambda^2 - 2C\lambda + C^2 - \frac{AB\bar{x}^{\beta-1}\bar{y}^{\alpha-1}\alpha\beta}{(1+\bar{x}^{\beta})^2(1+\bar{y}^{\alpha})^2}. \quad (2.3)$$

From (2.1) it follows that

$$\bar{x} = \frac{A}{(1-C)(1+\bar{y}^{\alpha})}, \ \bar{y} = \frac{B}{(1-C)(1+\bar{x}^{\beta})}. \quad (2.4)$$

Using relations (2.4) in (2.3), the characteristic polynomial of $F_J(\bar{x},\bar{y})$ can be written as

$$P(\lambda) = \lambda^2 - 2C\lambda + C^2 - \frac{\alpha\beta(1-C)^4\bar{x}^{\beta+1}\bar{y}^{\alpha+1}}{\mathrm{AB}}. \quad (2.5)$$

Let $\phi(\lambda) = \lambda^2$ and $\psi(\lambda) = 2C\lambda - C^2 + \frac{\alpha\beta(1-C)^4\bar{x}^{\beta+1}\bar{y}^{\alpha+1}}{\mathrm{AB}}$. Furthermore, assume that $|\lambda| = 1$, then it follows that

$$|\psi(\lambda)| < 2C + C^2 + \frac{\alpha\beta(1-C)^4\bar{x}^{\beta+1}\bar{y}^{\alpha+1}}{\mathrm{AB}}$$

$$< 2C + C^2 + \frac{\alpha\beta A^{\beta}B^{\alpha}}{(1-C)^{\alpha+\beta-2}} < 1.$$

Lemma 2.3 (Grove and Ladas, 2004): Supposes that$I_1 = [\alpha,\beta]$ and $I_2 = [\gamma,\delta]$ be intervals of real numbers, and assume that $f_1: I_1 \times I_2 \longrightarrow I_1$ and $f_2: I_1 \times I_2 \longrightarrow I_2$ are continuous functions. Assume the following system

$$x_{n+1} = f_1(x_n, y_n), y_{n+1} = f_2(x_n, y_n) \quad (2.6)$$

where initial conditions $(x_0, y_0) \in I_1 \times I_2$.Let the following conditions are true:

(i) $f_1(x,y)$ is non-decreasing in x and non-increasing in y.

(ii) $f_2(x,y)$ is non-increasing in x and non-decreasing in y.

(iii) If $(m_1, M_1, m_2, M_2) \in I_1{}^2 \times I_2{}^2$ be a solution of the system:

$$m_1 = f_1(m_1, M_2), \quad M_1 = f_1(M_1, m_2)$$
$$m_2 = f_2(M_1, m_2), \quad M_2 = f_2(m_1, M_2)$$

such that $m_1 = M_1$ and $m_2 = M_2$. Then, there exists exactly one fixed point $(\bar{x},\bar{y})$ of the system (2.6) such that $\lim_{n\to\infty}(x_n, y_n) = (\bar{x},\bar{y})$.

Theorem 2.5: The unique positive equilibrium point of the system (1.3) is a global attractor, if the following condition is satisfied:

$$(1-C)^{2\alpha}(1+L_1{}^{\alpha})(1+L_2{}^{\alpha})^2 > \alpha^2(AB)^{\alpha}, \quad (2.7)$$

where $L_1 = \frac{A}{1-C}\left(\frac{1}{1+\left(\frac{B}{1-C}\right)^{\alpha}}\right)$ and $L_2 = \frac{B}{1-C}\left(\frac{1}{1+\left(\frac{A}{1-C}\right)^{\beta}}\right)$.

Proof: Let $f_1(x,y) = \frac{A}{1+y^{\alpha}} + Cx$, and $f_2(x,y) = \frac{B}{1+x^{\beta}} + Cy$. Then it is simple to see that $f_1(x,y)$ is non-decreasing in x and non-increasing in y .Moreover, $f_2(x,y)$is non-increasing in x and non-decreasing in y. Let (m_1, M_1, m_2, M_2) be a positive solution of the system

$$m_1 = f_1(m_1, M_2), \quad M_1 = f_1(M_1, m_2)$$
$$m_2 = f_2(M_1, m_2), \quad M_2 = f_2(m_1, M_2)$$

Then,

$$m_1 = \frac{A}{1+{M_2}^{\alpha}} + Cm_1, \quad M_1 = \frac{A}{1+{m_2}^{\alpha}} + CM_1, \tag{2.8}$$

and

$$m_2 = \frac{B}{1+{M_1}^{\beta}} + Cm_2, \quad M_2 = \frac{B}{1+{m_1}^{\beta}} + CM_2. \tag{2.9}$$

Then it follows from (2.8) and (2.9) that

$$L_1 = \frac{A}{1-C}\left(\frac{1}{1+\left(\frac{B}{1-C}\right)^{\alpha}}\right) \le m_1 \le M_1 \le \frac{A}{1-C}, \tag{2.10}$$

$$L_2 = \frac{B}{1-C}\left(\frac{1}{1+\left(\frac{A}{1-C}\right)^{\beta}}\right) \le m_2 \le M_2 \le \frac{B}{1-C}. \tag{2.11}$$

On subtracting (2.8), we obtain

$$(1-C)(M_1 - m_1) = A\left(\frac{{M_2}^{\alpha} - {m_2}^{\alpha}}{(1+{m_2}^{\alpha})(1+{M_2}^{\alpha})}\right)$$

$$= A\alpha\theta^{\alpha-1}\frac{(M_2 - m_2)}{(1+{m_2}^{\alpha})(1+{M_2}^{\alpha})}, \tag{2.12}$$

where $m_2 \le \theta \le M_2$. From (2.11) and (2.12), it follows that

$$M_1 - m_1 \le \frac{\alpha AB^{\alpha-1}}{(1-C)^{\alpha}(1+{L_2}^{\alpha})^2}(M_2 - m_2). \tag{2.13}$$

Similarly subtracting (2.9) and using (2.10), we have

$$M_2 - m_2 \le \frac{\alpha BA^{\alpha-1}}{(1-C)^{\alpha}(1+{L_1}^{\alpha})^2}(M_1 - m_1). \tag{2.14}$$

Finally, from (2.13) and (2.14), one has

$$[(1-C)^{2\alpha}(1+{L_1}^{\alpha})(1+{L_2}^{\alpha})^2 - \alpha^2(AB)^{\alpha}](M_1 - m_1) \le 0. \tag{2.15}$$

Under the condition (2.7), it follows from (2.15) that $M_1 = m_1$. Similarly, one has $M_2 = m_2$.

Lemma 2.4: Under the conditions of Theorem 2.4 and Theorem 2.5 the unique positive equilibrium point of system (1.3) is globally asymptotically stable.

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