Two different modes of oscillation in a gene transcription regulatory network with interlinked positive and negative feedback loops

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Abstract

We study the oscillatory behaviour of a gene regulatory network with interlinked positive and negative feedback loop. Frequency and amplitude are two important properties of oscillation. Studied network produces two different modes of oscillation. In one mode (mode 1) frequency remains constant over a wide range amplitude and in other mode (mode 2) the amplitude of oscillation remains constant over a wide range of frequency. Our study reproduces both features of oscillations in a single gene regulatory network and show that the negative plus positive feedback loops in gene regulatory network offer additional advantage. We identified the key parameters/variables responsible for different modes of oscillation. The network is flexible in switching between different modes by choosing appropriately the required parameters/variables.

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1 Introduction

The fundamental unit of life is the cell. Organisms may consist of just one cell or they may be multicellular. The multicellular organisms organized into tissues which are groups of similar cells arranged so as to perform a specific function. One may view cell life as a collection of networks interacting through proteins, RNA, DNA and small molecules involved in signaling and energy transfer. These networks process environmental signals, induce cellular responses and execute internal events such as gene expression, thus allowing cells and entire organisms to perform their basic functions. These control and communication networks can be relatively simple (in bacteria) or they may be incredibly sophisticated (in higher organisms). In addition to their own needs for survival and reproduction, cells in multicellular organisms need additional levels of complexity in order to enable communication among cells and overall regulations. In living organism, proteins are the functional molecules. They are synthesized in a regulated processes known as Gene Expression (GE). So, gene expression and regulation are of fundamental importance in cell. Again, proteins from one gene regulate the expression from other. In this way, gene regulatory networks have grown inside the cell. There can be other type of networks like metabolic networks, protein-protein interaction networks etc. In general, the structure or architecture of the networks determines the function of the networks. It is observed that positive and negative feedback loops are very common motifs in biological networks. They occur frequently in different gene regulatory and cell signaling circuits. In general, it is known that positive feedback loop induces a switch like behaviour and bistability and that negative feedback loop produces oscillations, suppresses noise/fluctuation effects etc. The loops are often coupled to perform various functions in the networks acting as bistable switches, oscillators, excitable devices etc.

Rhythmic phenomena represent one of the most striking manifestations of dynamic behaviour in biological systems. Cellular rhythms are generated by complex interactions among genes, proteins and metabolites. They are used to control signaling, motility, growth, division and death. These
rhythms appear in many regulatory mechanisms that control the dynamics of living system. For example, neural and cardiac rhythms are associated with the regulation of voltage dependent ion-channels, metabolic oscillations originate from the regulation of enzyme activity and intracellular calcium oscillations involve the control of transport process while regulation of gene expression underlies circadian rhythms at the cellular level. There are some essential requirements for biochemical oscillations\textsuperscript{14–15}. In the course of time, open systems that exchange matter and energy with their environment generally reach a stable steady state. However, once the system operates sufficiently far from equilibrium and when its kinetics acquires a sufficient nonlinearity, the steady state may become unstable. Feedback processes and cooperativity are two main sources of nonlinearity that favour the occurrence of instabilities in biological systems. When the steady state becomes unstable, the system moves away from it, often bursting into sustained oscillations around the unstable steady state. Theoretical analysis shows that a negative feedback networks with sufficient amount of time delay and nonlinearity produces oscillations\textsuperscript{4,11,13}. The time delay in the networks can be created by a long chain of intermediate reactions or by an extra positive feedback loop. Different types of interlinked positive and negative feedback loops are observed in cellular systems with different number of nodes and links (Fig. 1). Such coupled loops play a variety of roles, acting as bistable switches, oscillators etc., although a single positive and negative feedback loop can also perform these functions under certain conditions. It is demonstrated that coupled or interlinked feedback loops are superior to single feedback loops as oscillators\textsuperscript{16}. A superior oscillator has the property of constant amplitude over a wide range of frequency. There may be another type of oscillation in which frequency remains constant though amplitude of oscillations may varied. Constant amplitude oscillations are important in heart beat, cell cycle etc. For circadian oscillations frequency should remain constant in different environmental conditions. Here we study a gene regulatory network which show both type oscillations depending on the variation of appropriate parameter.
2 Interlinked gene transcription regulatory network: The model

We consider a gene regulatory network consist of three genes X, Y and Z which synthesizes three proteins $x$, $y$ and $z$ respectively. Three genes form a closed loop structure and the product of each gene represses the synthesis process from other in a cyclic way starting from X to Y to Z. In addition to that there is a autocatalytic positive feedback loop in X. The network architecture is identical to the module considered by Tsai et al.\textsuperscript{16}. Only difference is that, the network module considered by Tsai et al. is regulated at the degradation level but in our network the regulation is achieved at the synthesis level. The network is shown in Fig. 1. The dynamics of the network is driven by the following coupled nonlinear differential equation.

$$\frac{dx}{dt} = -k_2 x + \frac{k_1}{K_{n1}^{n1} + x^{n1}} + \frac{k_7 x^{n4}}{K_{n4}^{n4} + x^{n4}}$$  \hspace{1cm} (1)$$

$$\frac{dy}{dt} = -k_4 y + \frac{k_3}{K_{n2}^{n2} + x^{n2}}$$  \hspace{1cm} (2)$$

$$\frac{dz}{dt} = -k_6 z + \frac{k_5}{K_{n3}^{n3} + y^{n3}}$$  \hspace{1cm} (3)$$

The equations contain basically three different kinds of terms, viz., degradation, negative transcription or repression and autocatalysis. The oscillatory behaviour (Figs. 2 and 3) of the interlinked gene transcription regulatory network is studied by varying the different rate constants. We solve the coupled nonlinear equations to observe oscillation numerically by Runge-Kutta 4 technique. To verify the stability of the network, we consider the random parameter values in the range given in Table 1. We observe that 500 out of 8404 parameter sets (5.94\%) yielded the oscillations in presence of positive feedback loop. But in absence of autocatalytic positive feedback loop we observe that 500 out of 7937 parameter sets (6.3\%) yielded the oscillations. The last result (network without autocatalytic feedback loop) is completely different from the result of Tsai et al.\textsuperscript{16}. To study the role of positive feedback
loop in the network we measure frequency and amplitude of oscillations from the 500 oscillatory data sets with different rate constants as variable. Then we take a particular set of rate constant chosen from the 500 sets of parameter values for which oscillations are observed. When we vary the repression strength \((k_1)\) on \(X\), we observe that frequency remains constant over a wide range of amplitude. As the positive feedback strength increases the range of amplitude of oscillation over which the frequency remains constant increases (Fig. 4). But if we vary the degradation rate constant \((k_2)\), we observe that amplitude remains constant over a wide range of frequency. The autocatalytic loop in \(X\) increases that behaviour further (Fig. 5). Same behaviour is observed when both \(k_1\) and \(k_2\) varies simultaneously (Fig. 6). This observation shows that the degradation rate has more impact on the oscillatory behaviour of the network. Fig. 7 shows that amplitude remains constant over a wide range of frequency when varied the autocatalytic positive feedback strength \(k_7\).

Fig. 1. Gene transcription regulatory network with interlinked positive and negative feedback loop.
Fig. 2. Time dependent Oscillatory behaviour of X, Y and Z for the parameter values $k_1=266.152$, $k_2=5.730$, $k_3=331.660$, $k_4=3.681$, $k_5=494.232$, $k_7=9.168$, $K_1=1.280$, $K_2=0.982$, $K_3=0.959$, $K_4=18.882$, $n_1=2.658$, $n_2=2.048$, $n_3=2.512$, $n_4=3.940$.

Fig. 3. Different Phase plots corresponding to the oscillatory behaviour in Fig. 2

Fig. 4. Amplitude versus Frequency plot when varied $k_1$ with different values of positive feedback strength shown in the graph. The other rate constants are fixed at $k_2=5.730$, $k_3=331.660$, $k_4=3.681$, $k_5=494.232$, $k_7=9.168$, $K_1=1.280$, $K_2=0.982$, $K_3=0.959$, $K_4=18.882$, $n_1=2.658$, $n_2=2.048$, $n_3=2.512$, $n_4=3.940$. 
Fig. 5. Frequency versus Amplitude plot with $k_2$ variation for different values of positive feedback strength shown in the graph. The other rate constants are fixed at $k_1=266.152$, $k_3=331.660$, $k_4=3.681$, $k_5=494.232$, $k_7=9.168$, $K_1=1.280$, $K_2=0.982$, $K_3=0.959$, $K_4=18.882$, $n_1=2.658$, $n_2=2.048$, $n_3=2.512$, $n_4=3.940$.

Fig. 6. Frequency versus Amplitude plot with $k_2$ and $k_1$ (both) variation for different values of positive feedback strength shown in the graph. The other rate constants are fixed at $k_3=331.660$, $k_4=3.681$, $k_5=494.232$, $k_7=9.168$, $K_1=1.280$, $K_2=0.982$, $K_3=0.959$, $K_4=18.882$, $n_1=2.658$, $n_2=2.048$, $n_3=2.512$, $n_4=3.940$. 
Fig. 7. Frequency versus Amplitude plot with $k_7$ variation. The other rate constants are fixed at $k_1=266.152$, $k_2=5.730$, $k_3=331.660$, $k_4=3.681$, $k_5=494.232$, $k_7=9.168$, $K_1=1.280$, $K_2=0.982$, $K_3=0.959$, $K_4=18.882$, $n_1=2.658$, $n_2=2.048$, $n_3=2.512$, $n_4=3.940$.

Table 1: Different rate constants with their ranges used to solve the coupled equation numerically.

| Rate Constant | Value/Range | Description                                      |
|---------------|-------------|--------------------------------------------------|
| $k_2$         | 0-20        | Degradation rate constant                        |
| $k_4$         | 0-20        | Degradation rate constant                        |
| $k_6$         | 0-20        | Degradation rate constant                        |
| $k_1$         | 0-500       | Negative feedback/repression Strength            |
| $k_3$         | 0-500       | Negative feedback/repression Strength            |
| $k_5$         | 0-500       | Negative feedback/repression Strength            |
| $k_7$         | 0-100       | Autocatalytic Positive feedback strength         |
| $n_1$         | 2-4         | Hill coefficient of repression                   |
| $n_2$         | 2-4         | Hill coefficient of repression                   |
| $n_3$         | 2-4         | Hill coefficient of repression                   |
| $n_4$         | 2-4         | Hill coefficient of auto-activation              |
| $K_1$         | 0-2         | Half maximum value of repressive Hill function at $z=K_1$ |
| $K_2$         | 0-2         | Half maximum value of repressive Hill function at $x=K_2$ |
| $K_3$         | 0-2         | Half maximum value of repressive Hill function at $y=K_3$ |
| $K_4$         | 0-20        | Half maximum value of repressive Hill function at $x=K_4$ |

3 Conclusion

We study a gene regulatory network with interlinked positive and negative feedback loop. The loop produces two different modes of oscillation. In
one mode (mode 1) frequency remains constant over a wide range amplitude and in other mode (mode 2) the amplitude of oscillation remains constant over a wide range of frequency. For circadian rhythm, mode 1 oscillation is very important because organisms try to maintain a constant frequency of their daily clocks in spite of the variation of the environmental condition. Mode 2 oscillation is important for heart beat or cell cycle for which fixed amplitude of oscillations is very much crucial in different frequency region. Our study reproduces both features of oscillations in a single gene regulatory network and show that the negative plus positive feedback loops in gene regulatory network offer additional advantage. We identified the key parameters/variables responsible for different modes of oscillation. The network is flexible in switching between different modes by choosing appropriately the required parameters/variables. Therefore, gene regulatory networks with interlinked positive and negative feedback loops work as more superior oscillator rather than the signaling networks.

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