Universal collective fluctuations in gene expression dynamics from yeast to human

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Abstract

In this work, the dynamics of fluctuations in gene expression time series is investigated. By using collected data of gene expression from yeast and human organisms, we found that the fluctuations of gene expression level and its average value over time are strongly correlated and obey a scaling law. As this feature is found in yeast and human organisms, it suggests that probably this coupling is a common dynamical organizing property of all living systems. To understand these observations, we propose a stochastic model which can explain these collective fluctuations, and predict the scaling exponent. Interestingly, our results indicate that the observed scaling law emerges from the self-similarity symmetry embedded in gene expression fluctuations.

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1 Introduction

Latest advances and discoveries in network science [1, 2] has made it possible to obtain a huge understanding of the topology of biological complex systems. However, the acquired knowledge is restricted by time, as far as the studies focussed mainly on topological–spatial properties of the networks. More recently, some studies have dealt with this issue by unifying the study of spatial- and time-dependent observables in networks (systems) in order to simultaneously investigate the collective behaviour of tens thousand nodes (elements of the systems). In particular, some works studied the fluctuations dynamics in natural and technological transport networks [3, 4], and described the relationship among the flux fluctuations and the average of flux as a scaling-law. On the biological side, experimental and theoretical works have also shown that some macroscopic phenomena, as the scale-free distribution, observed in gene expression systems (i.e., abundance of mRNA of a gene) emerges as a consequence of dynamical and collective self-organizing properties of the system [5, 6].

In our post-genomic era, DNA microarrays, also known as BioChips and GeneChips, have become the latest and most efficient method to simultaneously analyze thousands of genes [7, 8]. By using these technologies, the amount of mRNA contained in cells from different tissues and organisms can be collected at different time points. Moreover, the abundance of mRNA of a gene (i.e., gene expression) fluctuates in time, and it reveals correlations among many genes. Although there are currently many efforts to understand the gene regulation and transcriptional control, we have only a limited knowledge of these processes due to the huge quantity of genes involved and their intrinsic complexity. In order to obtain a better description on the collective behaviour of thousands of genes, we search for dynamical organizing principles in gene expression fluctuations, which are common for all living organisms. In particular, we analyse the coupling between the average on time of gene expression value $m$ and fluctuation $\sigma$ (i.e., standard deviation) of individual genes, from yeast [9] and human [10] organisms. Our results indicate that these magnitudes of gene expression system are related each other and depend on a scaling law $\sigma \propto m^\alpha$ with exponent one $\alpha = 1$. Intriguingly, the same scaling-law was found in [3] for natural and transport systems as rivers, WWW or highways.

To explain this observation found in gene expression systems, we developed a theoretical model based on stochastic processes. The general strategy
is as follows. First, we classified the genes from yeast [9] and human [10] organisms by the average value of expression level \( m \). All the genes which expression level fluctuates around a given \( m \) value will belong to the same group. Simultaneously, we assume that the gene expression dynamics of each group obeys the Markov property [6, 11]. Secondly, by using the short time transition probability (properly defined later), we construct the stochastic model for gene expression level. Lastly, we solve the model and obtain the same scaling-law observed experimentally. In addition, the relevant scaling-exponent is predicted successfully. The crucial point is that our stochastic approach reveals the existence of the self-similar symmetry embedded in the gene expression fluctuations, and the observed scaling-law emerges from this symmetry [12].

2 Gene expression time series data

We used experimental data from two well-known experiments on absolute gene expression from yeast [9] and human [10] organisms. The first experiment analysed cell cycle of the budding yeast \( S. Cerevisiae \), where around 6220 genes were monitored. Data of absolute value of gene expression fluctuations were collected at 17 time points every 10 min intervals. Data was obtained from WWW site http://genomics.stanford.edu.

The second experiment identifies cell-cycle-regulated transcripts in human cells using high-density oligonucleotide arrays. Data are collected every 2 hours for 24 hours, what is equivalent to almost 2 full cell cycles. The number of genes monitored was around 35000, and data for absolute value of gene expression fluctuations was obtained from WWW site http://www.salk.edu/docs/labs/chipdata. Further details about the experimental set up can be found in [9] and [10], respectively.

In Fig. 1, we show the experimental absolute value of gene expression level (vertical axis) vs. time (horizontal axis) of a selected group of genes which belong to human organism [10]. We see that the gene expression value of the selected genes fluctuates around the mean value \( m=6000 \) and \( m=1000 \).
3 Fluctuation observables: average and standard deviation of gene expression

By using the yeast and human data on gene expression time series, we proceed as follows. First, we calculate the average expression value of each gene of yeast datasets [9] and human datasets [10]. This expression reads as:

\[ m = \frac{\sum_{t=1}^{T} g_t}{T}, \]  

(1)

where \( g_t \) means the absolute expression level of gene at time step \( t \), and \( T \) is the total number of time steps. Secondly, we calculate the standard deviation (i.e., dispersion) of each gene by using the following expression:

\[ \sigma = \sqrt{\frac{1}{T} \sum_{t=1}^{T} (g_t - m)^2}. \]  

(2)

Therefore, for the yeast organism, we obtain 6220 dataset of coupled pairs \((\sigma, m)\), and 35120 for the human organism.

4 Experimental observations

By plotting the pairs \((\sigma, m)\) of yeast and human after some binning of the data, we find that the following scaling law between fluctuations and average of expression level over time:

\[ \sigma \propto m^\alpha, \]  

(3)

where the scaling exponent is one \( (\alpha = 1) \).

We show these results in Fig. 2(left) (human) and Fig. 2(right) (yeast). Both organisms (human and yeast) obeys the same scaling-law \( \sigma \propto m^\alpha \) with exponent \( \alpha = 1 \). The scaling-law indicates that genes with higher expression level fluctuate more, and in addition, the fluctuation size depends linearly on the mean expression value \( m \). Therefore, this scaling-law is a macroscopic and collective effect of the fluctuations shown in Fig. 1.

It is worth noticing that recent works have reported about this type of scaling law between the average of flux and fluctuations in non-biological
systems \[3, 4\]. In particular, similar observations were found in natural transportation systems as river network, and artificial ones as WWW and highways \[3\]. Intriguingly, these systems show the same scaling exponent \((\alpha = 1)\) that we have also found for gene expression fluctuation in yeast and human organisms. In contrast, more technological systems as Internet routers and Microchips, revealed a scaling law with exponent \(1/2\).

In order to understand the origin of this self-organizing principle of gene dynamical systems, we have developed a model based on a stochastic approach. This model reveals that the self-similarity symmetry (i.e., surprisingly, the gene expression short-time fluctuations contain a repeating pattern of smaller and smaller parts that are like the whole, but different in size) in the short-time transition probability reported in our companion paper \[12\], re-builds the observed scaling law \(\sigma \propto m^\alpha\) with exponent \(\alpha = 1\). We will explain the model in detail in next section.

Finally, it important to remark that while the scaling exponent \((\alpha = 1)\) seems to be universal, since as we will explain later, the self-similarity symmetry strongly constrains the possible exponents to only \(\alpha = 1\), the universal nature of the exponent \((\alpha = 1/2)\) is not clear enough as it is also discussed in \[3\].

5 The model

5.1 Stochastic process

A stochastic process is one in which only the probability distribution for future states can be specified, even given the exact knowledge of the present state. Although there are many complex non-biological and biological systems which are not stochastic, for our gene expression problem a probabilistic approach seems plausible and natural. For example, the number of molecules which are involved in signal transduction pathways fluctuates from \(10^2 - 10^4\) and concurrently, the physical volumes of cells are small. Furthermore, an additional source of randomness comes from instrumental noise, which exceeds 30% from chip to chip (GeneChips arrays).

Moreover, experimental and theoretical studies on stochastic noise and fluctuations of gene expression in cells have recently been carried out by revealing an inherent (intrinsic noise) and external (extrinsic noise) stochasticity \[13, 14\], and by providing a huge knowledge of the mechanisms involved
5.2 Stochastic differential equation

Let \( \{X(t), 0 \leq t < \infty\} \) be a stochastic process. For \( (s > t) \), the conditional probability density function \( p(y, s|x, t) = p(X(s) = y|X(t) = x) \) is defined as usual manner. For the matter of convenience, we often write \( p(y, s) \) for \( p(y, s|x, t) \).

We make use of Ito Stochastic process in order to construct our model. First, we assume the following Stochastic Differential Equation (SDE) (see also [12, 19, 20] for further details):

\[
dX^m(t) = \alpha^m(X^m(t))dt + \beta^m(X^m(t))dW(t),
\]

where stochastic variable \( X^m(t) \) denotes the gene expression level of genes fluctuating around mean value \( m \), \( \alpha^m(x) \) denotes the drift (i.e. the average of the instantaneous transition of the expression level per unit of time) defined by

\[
\alpha^m(x) = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \int (y - x)T^m_\epsilon(y, x)dy,
\]

(5)

\( \beta^m(x) \) denotes the diffusion (i.e., the variance of the instantaneous transition the gene expression level per unit of time) defined by

\[
\beta^m(x) = \left( \lim_{\epsilon \to 0} \frac{1}{\epsilon} \int (y - x)^2T^m_\epsilon(y, x)dy \right)^{\frac{1}{2}},
\]

(6)

and \( W(t) \) denotes the Wiener process [11]. Here, \( T^m_\epsilon(y, x) \) is an Instantaneous Transition Probability (ITP) defined by \( T^m_\epsilon(y, x) = p^m(y,t+\epsilon|x,t) \) for sufficient small \( \epsilon \). Details of the proof can be found in [11].

5.3 Experimental Input Data

From the data of \( T^m_\epsilon(y, x) \), we can obtain \( \alpha^m(x) \) and \( \beta^m(x) \). We evaluate these two magnitudes by using experimental data [9, 10] and Eqs. (5-6), and we observed that behaviour of \( \alpha^m(x) \) and \( \beta^m(x) \) can be expressed by using the following functions:

\[
\alpha^m(x) = \mu(m - x),
\]

(7)
\[ \beta^m(x) = m((x/m - 1)^2 + b). \]  

(8)

Readers interested in details of derivation of Eqs. (7-8) are referred to our companion manuscript [12]. These results obtained by using experimental data are interesting since expression level of genes follows the same tendency independently of the scale of the gene expression value (i.e., exhibiting a self-similar dynamics). In addition, same feature has been found in a simple organism as yeast and in a complex one as human.

By substituting Eqs. (7-8) into Eq. (4), we obtain:

\[ dX^m(t) = \mu(m - X^m(t))dt + m((X^m(t)/m - 1)^2 + b)dW(t), \]  

(9)

This equation is scale-invariant, since if we take different \( m' \), we recover the original Eq. (9) by substituting \( X^{m'}(t) \rightarrow X^m(t)m'/m. \)

5.4 Solution of Stochastic Equation

The solution of Eq. (9) is given by the following equation:

\[ \rho^m(x) = \frac{K}{m((x/m - 1)^2 + b)^2} \exp\left(\frac{\mu}{(x/m - 1)^2 + b}\right), \]  

(10)

where \( m \) is the mean value of gene expression for each gene, \( b \approx 0.2 - 0.3 \), and \( \mu = 1 \). \( \rho^m(x) \) indicates the probability distribution of genes with expression level \( x \) which fluctuates around mean value \( m \). In [12], we find that Eq. (10) shows a good agreement with experimental data from yeast [9] and human [10] organisms. Furthermore, the formula \( \rho^{cm}(x) = \frac{1}{c}\rho^m(x/c) \) holds for arbitrary real number \( c. \)

5.5 Fluctuation observables obtained by the model.

Average value of gene expression  By using Eq. (10), we can calculate the average expression value as follows:

\[ E[x] = \int x\rho(x)dx = m. \]  

(11)
Standard deviation of gene expression  By using the formula $\rho'^m(x) = \frac{1}{c} \rho^m(x/c)$ in previous section, we obtain the variance $V[x] \equiv \sigma^2$ as follows:

$$V[x] = \int (x - m)^2 \rho^m(x) dx \propto m^2. \quad (12)$$

Then, by using Eqs. (11) and (12), we find the observed scaling law in gene expression systems as:

$$\sigma \propto m^\alpha, \quad (13)$$

with exponent $\alpha = 1$.

6 Conclusions

In summary, we have analysed datasets of gene expression time series from yeast and human organisms and we have found that the coupling between the average expression level and fluctuations follows a scaling-law with exponent one $\alpha = 1$. Therefore, as we have found the same scaling-law for organisms as yeast and human, we believe that it probably indicates that this is a universal feature of the gene expression dynamics in all the living organisms.

Furthermore, in order to explain this observation in gene expression fluctuations, we have proposed a stochastic model, which is able to reproduce the observed scaling-law and it also generates the relevant scaling exponent. Precisely, we show that this scaling law with mysterious exponent one emerges from one generic mechanism: self-similarity symmetry [12].

Interestingly, the same scaling-law and the same exponent $\alpha = 1$ were recently found in natural transport systems as rivers and highways [3]. Although in our model the scaling-law and the exponent one is re-built from the self-similarity symmetry embedded in the gene expression fluctuations, we believe that this self-similar property is not only a feature of gene expression systems and it could also be found in natural transport systems and technical and artificial dynamical networks. Therefore, our stochastic approach and this symmetry could explain the origin of scaling law of fluctuation dynamics in biological and nonbiological systems in a broader scope.

Moreover, as this model has been used successfully to uncover other scaling properties of gene expression dynamics [6, 12] and to analyze the gene correlation dynamics [21], it indicates that it contains valuable information
about the gene expression dynamics and it is a useful tool for studying it. Therefore, further advances towards this direction, and in particular, about the study of specific biological processes in gene regulatory architectures by using these stochastic concepts and techniques are encouraged.

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Figure 1: We show the experimental absolute value of gene expression level (vertical axis) vs. time (horizontal axis) of a selected group of genes which belong to human organism [10]. We see that the gene expression value fluctuates around the mean value $m=6000$ and $m=1000$. By observing this figure, we see that genes with high expression level fluctuates more (i.e., jump size is large, which in the end is the origin of the scaling-law $\sigma \propto n^\alpha$ with $\alpha = 1$. In Fig. 2, we show more clearly this phenomena by using the appropriate observables.
We show the experimental results of the coupling of the fluctuations $\sigma$ and the average of gene expression level $m$. Horizontal axis denotes the average of gene expression level $m$ and vertical axis denotes the fluctuations $\sigma$ for each gene expression data. Left) The analyzed data corresponds to human organism. Right) The analyzed data corresponds to yeast organism. Figures are in log-log scale. We see that both organisms (human and yeast) obeys the same scaling-law $\sigma \propto m^\alpha$ with exponent $\alpha = 1$. The scaling-law indicates that genes with high expression level fluctuate more, and in addition, the fluctuation size (i.e., jump size) depends linearly on the mean value of gene expression $m$. Therefore, this scaling-law is a macroscopic and collective effect of the fluctuations shown in Fig. 1. It is worth noticing that this scaling-law was also found in non-biological systems as for example, rivers, highways and World Wide Web [3], with the same exponent $\alpha = 1$. 