(Revised 07/09)

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(please insert ref. above)

NSFC/RGC Joint Research Scheme
Joint Completion Report

(Please attach a copy of the completion report submitted to the NSFC by the Mainland researcher)

Part A: The Project and Investigator(s)

1. Project Title

Noise and transient dynamics in intracellular biochemical networks（细胞内生化网络的噪声和暂态动力学研究）

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	TANG, Leihan 汤雷翰	MA, Yuqiang 马余强
Post	Professor	Professor
Unit / Department / Institution	Department of Physics/HKBU 香港浸会大学物理系	Department of Physics/Nanjing University 南京大学物理系
Co-investigator(s) *(with title)*	SHI, Jue 史珏 Assistant Professor Dept of Physics, HKBU 助理教授， 香港浸会大学物理系	JIN, Guojun 金国钧 Professor Dept of Physics, Nanjing University 教授，南京大学物理系

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted)*
Project Start date	1/1/2011		
Project Completion date	31/12/2013		
Duration *(in month)*	36 months		

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. Develop a statistical mechanical formalism for quantitative characterization of copy number fluctuations in intracellular biochemical networks.
2. Develop analytical and computational methodologies for interpretation of single cell kinetic measurements and for extracting parameters in quantitative modeling.
3. Consolidate experimental and computational approaches to study pulsed transport and transient response based on selected intracellular biochemical pathways.

5.2 Revised Objectives: N/A.

Date of approval from the RGC: _____

Reasons for the change: _____

6. Research Outcome

Major findings and research outcome
(maximum 1 page; please make reference to Part C where necessary)

1) *A theoretical scheme to study propagation of noise in biochemical networks (papers 1, 2 and thesis by Miss Ao Xue)*

We have completed the formulation of a theoretical scheme to study noise propagation in large biochemical networks. The scheme focuses on the transformation process of individual molecules and study the temporal clustering of molecular events which are at the heart of fluctuations in the copy numbers of molecules. This allows for a clear separation of noise due to upstream events (random arrivals) and noise due to stochasticity in the reaction at a particular node of the network. For transport and metabolic processes that conserves the number of molecules, we show that only the second noise will be transmitted in the network, and its intensity will continue to weaken and gradually disappear down a pathway. On the other hand, in signal transduction and gene expression, the two types of noise are both transmitted to the downstream nodes. The noise strength may also be enhanced in the propagation process. Our formalism allows us to treat non-Markovian processes as well, which can be used as effective descriptions for multi-step reactions. We found that multi-step reactions can be quite effectively in reducing noise at a particular network node, but is not so effective in buffering upstream noise that can be passed to the downstream. We have computed the protein copy number fluctuations using realistic models of gene expression in prokaryotes and eukaryotes. Our results suggest that, in both cases, the downstream protein noise is reduced, but the strategies used are different in the two cases. This is an interesting new finding.

Negative feedback regulation is a common noise reduction mechanism. It is generally believed that the feedback is able to weaken the noise. However, we found that when non-Markov effects and negative feedback are combined, instabilities and oscillatory behavior emerges in certain parameter regimes. After introduction of the non-Markovian effect, fluctuations in the time interval between successive molecular events are reduced. This leads to stronger amplification of noise in a certain frequency range.

2) *Single-cell p53 dynamics (thesis by Miss Li Mengyao, to be published)*

The p53 protein plays a pivotal role in the cell fate decision upon DNA damage, caused by irradiation or drug. The level of damage, which is naturally involved in the decision process, affects the temporal response pattern. Since different cells may sustain different levels of damage, and may also differ in their internal states, measurement and characterization of the p53 temporal pattern at the single-cell level is essential for quantitative understanding of the cell-fate decision process.

From the time-lapse fluorescence microscope images collected in Dr. Shi's lab, time traces of the nuclear p53 intensity for tens of cells were collected. Statistical analysis is performed on the p53 pulse shape, including its peak height and duration of the high and low phases etc. Theoretical study of the circuit involving four essential molecular components is carried out. Conditions for the appearance of an oscillating state are identified. Furthermore, various characteristics of the oscillating state are investigated in detail. Comparison of these dynamical features with the model led to suggestions on the possible origin of the pulse-to-pulse and cell-to-cell variations.

Potential for further development of the research and the proposed course of action *(maximum half a page)*

We believe the theoretical framework developed in this project can be applied to many specific biochemical networks for better characterization of fluctuation effects. Therefore it should become a useful experimental tool. We will actively search for such examples and to promote its usage.

The research has prompted us to look more generally into fluctuation effects in molecule processes and molecular devices in biology. One example is the analysis of the switching time series of the bacterial flagellar motor. The switching process is highly cooperative, and affected by the noise in the binding-unbinding of the signaling molecule CheY-P. We have carried out a study of the "conformational spread model" by Duke et al and identified nontrivial memory effects in the time series. We are in the process of comparing the theoretical findings with experimental data collected by Dr. Fan Bai at PKU. Another project is the analysis of the time series for the F1-ATPase motor. Here interesting results are expected on features of the motor design that controls its energy conversion efficiency, in particular the comparison with the less efficient V1-motor. These projects will be completed in the near future.

We have plans to extend the auto-correlation-based approach to networks that contain feedback interactions. At this point there are some conceptual difficulties that need to be resolved before progress can be made.

7. The Layman's Summary

(describe in layman's language the nature, significance and value of the research project, in no more than 200 words)

How can genetically identical cells exhibit a broad range of phenotypes and responses? The search for answers to this question, which appears to violate some of the long-held believes in textbook biology, prompted active experimental and theoretical investigation of noise in molecular networks in recent years. The research is aided by recent advances in GFP fluorescent microscopy that tracks the copy number of selected proteins in a single cell. In this project, we develop effective and robust methodologies to analyze the rapidly accumulating experimental data to extract underlying molecular mechanisms of noise generation and propagation. Through close collaboration between the participating theoretical and experimental groups, we develop theoretical tools to integrate molecular level knowledge and data for systems level modeling and analysis, and test the general framework in specific cases of interest. Although the focus of the current project is on quantitative description of basic biological processes in a network setting, the capabilities developed will enable us to tackle problems related to complex dynamics in human disease such as cancer, thus gaining a broader impact. The project will also benefit the collaborating institutions in their respective research developments in this burgeoning interdisciplinary field.

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project

(Please attach a copy of each publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.))

The Latest Status of Publications				Author(s) *(bold the authors belonging to the project teams and denote the corresponding author with an asterisk*)*	Title and Journal/Book *(with the volume, pages and other necessary publishing details specified)*	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*
Year of publication	Year of Acceptance *(For paper accepted but not yet published)*	Under Review	Under Preparation *(optional)*					
2014				Liang Luo, **Lei-Han Tang**	Subdiffusive scaling with power-law trapping times, Chinese Physics B **23**:070514		Yes	Yes
			2014	Li-Ping Xiong, **Yuqiang Ma, Lei-Han Tang**	Temporal clustering of molecular reactions and its propagation in biochemical networks*		Yes	Yes
			2014	Mengyao Li, Xuefei Li, **Jue Shi, Lei-Han Tang**	p53 dynamics: single-cell imaging data analysis and modeling**		No	Yes
			2014	Ao Xue, Liping Xiong, Xuefei Li, **Lei-Han Tang**	Study of fluctuations in gene regulation circuits with memory**		No	Yes

* The draft manuscript was completed for some time. It was felt that incorporation of a realistic biological example would significantly enhance the impact of the work. In view of the time constraint, we will submit the paper before end of October 2014 to a high impact journal and keep the Research Office informed about progress.

** Both work have been completed and the relevant part of the thesis will be converted to publishable form. This will be done before the end of 2014.

9. Recognized International conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each delivered paper)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*
Nov, 2010 Kolkata, India	Noise propagation in biochemical networks	StatPhys Kolkata VII	Yes (mid-term report)		During presentation.

July, 2013, Seoul, Korea	Noise propagation in biochemical networks: beyond the master equation	StatPhys 25		Yes	Yes
Sept, 2014 Harbin, China	p53 dynamics: what can we learn from single-cell imaging	Chinese Physical Society Fall Meeting		Yes	During presentation.

10. Student(s) trained *(Please attach a copy of the title page of the thesis.)*

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Xue AO	MPhil	1 September, 2009	March, 2012
Xuefei LI	PhD	1 August, 2008	July, 2012
Mengyao LI	MPhil	1 August, 2012	August, 2014

11. Other impact *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

Together with Prof. Yuqiang Ma, we organized the First East-Asia Joint Seminars on Statistical Physics in March 2012, with generous support from Suzhou University and the Beijing Computational Science Research Center. The focus of the meeting was on nonequilibrium statistical physics. Many active researchers in statistical physics from China, Japan and South Korea attended the meeting. The meeting now becomes a series with the second one took place at the Yukawa Institute in Kyoto in Oct 2013, and the third one scheduled to take place in Seoul in 2015.

In 2012 and 2013, together with Haijun Zhou from ITP/CAS, Professor Tang Leihan organized two consecutive Statistical Physics Summer Schools at the CCAST, Beijing. A major topic in these schools is the fluctuation phenomena in small systems. The schools were well-received by students and postdocs, and helped to strengthen collaborations in the statistical physics community in China. He also organized a biological network dynamics and control workshop held in Hong Kong in December 2012, participated by people from Nanjing U and also several other institutions in Europe and Korea.