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MEETING REPORT

Quantitative biology: from genes, cells to networks

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Quantitative biology is an exciting emerging field that focuses on using systematic and quantitative approaches and technologies to analyze and integrate biological systems, construct and model engineered life systems, and even manipulate biological processes and functions. The advance of high-throughput biotechnologies has shifted the paradigm of biological researches from focusing on intricacies of molecular components to understanding how biological systems function in terms of modules and networks. On October 13–17 in 2014, more than 200 participants gathered at Cold Spring Harbor Asia Conference on Quantitative Biology in Suzhou, China, to exchange and discuss recent advances in quantitatively understanding of biological systems at the scale of genes, cells, and integrated networks. The conference was led by Michael Q. Zhang (University of Texas at Dallas, USA; Tsinghua University, China), Chao Tang (Peking University, China) and Terence Hwa (University of California San Diego, USA). In this report, we highlighted a few themes among 32 oral presentations and 34 poster presentations brought by this conference.

PROCEEDING AND HIGHLIGHT TALKS

Regulatory interactions

The first lecture was given by Dr. Johan Elf (Uppsala University, Sweden). Dr. Elf demonstrated an assay for measuring the rate of dissociation for a LacI repressor from an individual chromosomal operator site at the level of individual molecules in *E. coli*. By combining with the corresponding association rate measurement [1], Dr. Elf tested the commonly used assumption that transcription factor (TF) kinetics can be considered to be at equilibrium and that the gene expression is proportional to the time the operator is free. In the second talk of this section, Dr. Gary D. Stormo (Washington University, USA) presented his recent progress in determining optimal models for transcription factor specificity by a newly developed experimental method, Spec-seq and the corresponding algorithms for data analysis [2,3]. The Spec-seq offered unprecedented accuracy for determining relative binding affinities to thousands of binding sites in parallel, which helped uncover new findings regarding the binding characteristics of Lac repressor [4]. In Dr. Hualin Shi's lecture (Institute of Theoretical Physics, Chinese Academy of Sciences, China), he quantified sequence-function relations for small RNA mediated gene silencing using the well-characterized small RNA RyhB and its target *sodB* in *E. coli* [5]. His results support the applicability of the thermodynamic model in predicting RNA-RNA interaction and suggest that both the kinetic and thermodynamic process of base-pairing between sRNA and mRNA determines the regulatory level. Dr. Xiling Shen (Cornell University, USA) discussed how miR-34a controls the asymmetric division of colon cancer stem cells by using quantitative single-cell analysis [6]. He showed that miR-34a targets Numb to form an incoherent feedforward loop (IFFL), which enhances bimodality by orders of magnitude. In addition, he demonstrated that the IFFL displays adaptive behavior to offset interference from other miR-34a target genes, and therefore buffers cell fate outcomes from fluctuations in miR-34a levels.

From molecules to cellular behavior

Systematically dissecting the molecular mechanisms how cells behave confronting changing environments is a

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daunting task. In the second section of this conference, Dr. Luhua Lai (Peking University, China) demonstrated novel attractant and antagonist molecules that bind directly with the chemoreceptor Tar in *E. coli* by using an integrated *in silio*, *in vitro* and *in vivo* screening strategy [7]. When introducing an NH group into the antagonist compound, an antagonist was converted into an attractant, suggesting a "bind-and-trigger" mechanism of Tar receptor signaling.

E. coli swims by rotating multiple flagella, which is controlled by the outputs of the bacterial chemotaxis signaling pathway. Coordination of these outputs can be induced by either the stochastic fluctuation of the intracellular level of the chemotaxis signaling protein CheY-P, and the extracellular mechanical coupling of bundled flagella. Dr. Junhua Yuan (University of Science and Technology of China, China) discussed the contribution of these two mechanisms of flagella coordination by correlating single-motor and swimming behaviors.

In the third talk of this section, Dr. Sander Tans (FOM Institute AMOLF, Netherlands) showed their recent results in elucidating the role of molecular stochasticity in cellular growth [8]. Using time-lapse microscopy, he demonstrated that expression fluctuations of catabolically active enzymes can propagate and cause growth fluctuations, with transmission depending on the limitation of the enzyme to growth. His results suggested that in addition to the molecular noise caused by regulatory proteins, cellular metabolism is inherently stochastic, and therefore a generic source of phenotypic heterogeneity. Heterogeneity in cellular responses is also essential for mammalian cells. For instance, there appears to be a direct correlation between E2F expression levels and the phenotypic responses of mammalian cells. However, there seems to exist a tremendous heterogeneity in terms of both E2F expression and cellular phenotypes. Dr. Lingchong You (Duke University, USA) discussed their efforts to dissect the regulation of stochastic dynamics of E2F and its role in cell-fate decisions by using mathematical modeling and single-cell experiments [9]. Dr. You also suggested that the stochastic dynamics of E2F might serve as a quantitative phenotype in cell line classification and drug screening.

Metabolism and cell growth

Adaptation is one of the essential cellular behaviors that enables cells to memorize, make decisions and survive in changing environments. In this section, Dr. Yuhai Tu (IBM T.J. Watson Research Cener, USA) showed that the adapted state is a nonequilibrium steady state maintained by continuous energy dissipation, adaptation speed and adaptation accuracy by studying simple biochemical networks underlying biological sensory adaptation system. This energy-speed-accuracy relation was verified in the chemosensory systems in *E. coli* and in *Dictyostelium*, which suggested a possible general principle governing cost-performance tradeoffs for accurate information processing in living systems [10,11]. In the second talk of this section, Dr. Xiongfei Fu (Yale University, USA) discussed the limits of feedback control in bacterial chemotaxis and how sensory information is best utilized by the flagellar motors to maximize drift velocity [12]. Dr. Fu showed that there is an operational regime for the signaling pathway with respect to flagellar motor that optimizes chemotactic performance by maximizing the contrast between run duration up and down signal gradients rather than maximizing contrast in the motor rotational bias.

Cell geometry is a complex trait that impacts many biological processes and thus experimentally proving causal connections between cell geometry and organismal fitness is still challenging. By systematically engineering strains with *mreB* mutations that displayed a range of function of cell width, Dr. Kerwyn C. Huang (Stanford University, USA) found that changes in cell geometry was the direct cause of fitness effects conferred by *mreB* mutations and fitness increased linearly as a function of cell width before reaching a plateau in fitness for strains with very large increases in cell width [13]. The last talk in this section was given by Terrence Hwa regarding the physiological origin of wasteful metabolism in rapidly proliferating cells. Dr. Hwa provided a quantitative phenomenological study to elucidate this seemingly wasteful phenomenon in *E. coli*, in which fermentation is used instead of the more efficient respiration process for energy production.

Population genetics and evolution

Quantitative biology became more and more important to bridge the gap between molecular biology and evolutionary biology, which helps integrate the proximate (how) and ultimate (why) mechanisms into a coherent framework. One intriguing question in this field is how bacteria utilize diverse population strategies to deal with chemotaxis trade-off problems when facing different environments. Dr. Thierry Emonet (Yale University, USA) showed that different environmental tasks required different behaviors for optimal performance by using simulations of a single-cell model of *E. coli* chemotaxis in different ecological tasks [14]. Dr. Emonet also demonstrated that clonal populations could diversify the behavior of a single biological network for a collective advantage in fluctuating environments without changing the proteins of the network or their interactions. Dr. Xiao Yi (University of Minnesota, USA) showed their recent progress on the evolutionary dynamics of the chemotaxis

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signaling network in *E. coli* during adaptation to a new environment. Evolving populations and isolated mutant strains across all stages of evolution were characterized in phenotype (growth rate and chemotactic ability) and genotype by genomic sequencing. Dr. Yi showed that intrinsic trade-off between growth rate and chemotaxis plays a critical role in shaping the realized evolutionary trajectory and ultimate phenotype of the evolved trains. In addition, Dr. Daniel Fisher (Stanford University, USA) discussed some potential approaches to caricature the complexities of organisms, environments and their interactions by using simple and abstract models of evolutionary dynamics.

Another interesting talk in this section regarding molecular population genetics is given by Dr. Boris Shraiman (University of California Santa Barbara, USA). Based on the assumption that evolution proceeds by accumulation of small effect mutations and does not required species specific input, Dr. Shraiman demonstrated that the branching pattern of reconstructed genealogical trees contains information about the relative fitness of the sampled sequences and that this information can be used to predict successful strains, by using historical data on seasonal influenza A/H3N2 virus [15].

Spatiotemporal effects from cells to organisms

Studying self-organization of biological systems in response to spatial and temporal cues has been attracting more and more attention in the field of quantitative biology. Dr. Yilin Wu (The Chinese University of Hong Kong, China) showed that biomechanical coupling between bacteria cells and the physical environment in a colony may lead to long-range self-organization, and discussed the implications of this findings on the collective behavior in active matter systems. Dr. Jian-Dong Huang (The University of Hong Kong, China) demonstrated a spatial experimental evolutionary study on the periodic patterns of high and low densities of genetic programmed *E. coli* on semi-solid agar plate [16]. Dr. Huang showed that the wavelengths of the patterns (distance between two stripes) with evolved strains displayed a linear relationship to the front propagation speed and could be controlled by tuning the migration speed without prejudice to the length of the interval. Dr. Huang's results revealed the key features of the wavelength determination of the density-suppressed motility strips formation system.

Self-organization is also ubiquitous in multi-cellular systems. Dr. Andrew C. Oates (National Institute of Medical Research / University College London, UK) presented that the time-scale of genetic oscillations that was thought to periodically trigger new segment formation in sequentially segmenting animals, was not sufficient to explain the temporal period of segmentation in zebrafish embryos [17]. In addition, Dr. Oates showed that the change of oscillation profile and the rate of tissue shortening also contributed to control the rhythm of segmentation. In the last talk of this section, Dr. Ge Yang (Carnegie Mellon University, USA) discussed how axonal transport is controlled spatially and temporally for cargo delivery by combining genetic manipulation of the molecular machinery of axonal transport with high-resolution imaging, quantitative image-based analysis, and modeling of spatiotemporal transport behavior. Dr. Yang showed that kinesin and dynein both competed and coordinated on individual cargoes, and motor-cargo interactions was modulated to control cargo loading/unloading and movement of the motor-cargo complex. At last, he also presented that regulation of motor-microtubule interactions by microtubule associated proteins produced spatial patterns of axonal cargo transport.

Intracellular networks

The rapid development of next generation sequencing technologies has been providing an unprecedented opportunity to probe intracellular networks at increasing higher resolution and depth, which facilitate the understanding of biological networks at multiple levels by using statistical models. In the first talk of this section, Dr. Michael Q. Zhang discussed the role of chromatin interactions and epigenetic regulations in mammalian development and differentiation by reviewing what we learnt through ENCODE and Epigenome Roadman projects [18]. Dr. Zhang also presented their recent progress in epigenomic analysis of multi-lineage differentiation of human embryonic stem cells, as well as in building a global chromatin map of regulatory interactions in the human genome. Dr. Jing-Dong J. Han (Chinese Academy of Sciences, CAS-MPG Partner Institute for Computational Biology, China) showed their results on predict and reconstruct regulatory networks based on heterogeneous data on gene expression, histone modification and genomic changes, which led to not only global pictures of the complex biological processes, but also developed new computational algorithms to facilitate mapping of epigenetic features from the deep sequencing data [19,20]. In the third talk of this section, Dr. Luonan Chen (Shanghai Institutes for Biological Sciences, China) presented a new method to predict the low-dimensional dynamics in a biological system from high-dimensional but short-term data, such as RNA sequencing or microarray data. Dr. Chen also showed a few benchmark examples for biological medical problems to verify the effectiveness of the theoretical result [21]. In the last talk of this section, Dr. William Bialek (Princeton University USA / City University of

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New York, USA) discussed their efforts on developing statistical physics models using simultaneous measurements on the stats of nodes in biological networks based on the maximum entropy principle. Dr. Bialek applied this model to study a few examples, such as the behavior of flock of birds [22] and neuron network in the vertebrate retina, and found that in both cases the systems seemed to be close to criticality.

Pathways and networks in action

Cells have to make various decisions in response to external and/or internal cues, such as stresses, differentiation and reprogramming triggers, and developmental inputs. Dr. Chao Tang discussed their efforts in elucidating strategies and principles in cell decision-making by combining experimental approaches and mathematical simulations. Particularly, Dr. Tang demonstrated a "see-saw model" for the induction of pluripotency in mouse somatic cells, where a balance established using pluripotency factors and/or counteracting lineage specifiers can facilitate cell reprogramming [23]. In the second talk of this section, Dr. Chin-Lin Guo ('Academia Sinica', Institute of Physics, Taiwan, China) showed that mammalian epithelial cells developed long range mechanical interactions when these cells were surrounded by 3-D extracellular matrix (ECM) in a solid phase. In contrast, these epithelial cells self-organized into centimeter-long, hundred-micrometer-wide tubules with highly organized architectures when cells were cultured in a liquid phase. Based on these results, Dr. Guo discussed how the dimensionality and complexity in cell-ECM interactions influenced the spatiotemporal coordination in the self-organization of organ-scale structures.

The rapid advance in the field of synthetic biology has enabled a forward engineering approach to study biological systems in a quantitative and predicted manner by introducing synthetic signaling components. Dr. Ping Wei (Peking University, China) developed several bacterial effector proteins to rewire kinase-mediated osmotic stress responses to periodic osmo-stimulations in yeast cells, resulting in a new pathway behavior with novel frequency-dependent input filtering. Dr. Wei also demonstrated that a minimum human NF-kappa B signaling architecture could be reconstituted in yeast cells. Dr. Xiaowo Wang (Tsinghua University, China) introduced a computational model to quantitatively describe a minimum competing endogenous RNA network. By introducing synthetic gene circuits in cultured human cells, Dr. Wang showed that the strength and effective regime of miRNA-ceRNA competition were largely determined by the relative abundance and the binding strength of miRNA and ceRNAs. In addition, Dr. Wang demonstrated that there was a non-reciprocal competition effect between partial and perfect complementary targets caused by different miRNA loss rate in these two types of regulations. In another talk, Dr. Zhen Xie (Tsinghua University, China) demonstrated a library of reversible transcription activator-like effector repressors (TALERs) that bound designed hybrid promoters and exerted transcriptional repression through steric hindrance of key transcriptional initiation elements [24]. Dr. Xie showed that the performance of modularly assembled TALER cascade and switch circuits could be quantitatively predicted by using the input-output transfer functions of individual TALER constituents, indicating that this TALER library could be a valuable toolkit to facilitate modular engineering of synthetic circuits.

Networks and diseases

Decision-making of living systems, across from bacteria in a colony to fast-growing tumor cells, relies on complex biological networks to perform complex calculations to assess the pros and cons of the different choices on selecting genetic variants. Dr. Jose N. Onuchic (Rice University, USA) discussed the molecular mechanisms controlling two-component system (TCS) in the sporula-

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tion phosphorelay. By quantifying co-evolution using direct coupling analysis based metric, Dr. Onuchic inferred the effect of mutations on the functional interaction between different TCS proteins in bacteria, which determines the decision to go into sporulation or competence stage. In the second talk of this section, Dr. Qi Ouyang suggested that to fully utilize the large amount of sequencing data on hundreds of tumor samples, it was important to study oncogenic mutations and oncogenic mechanisms from biological network perspective. In their recent studies on the oncogenic mechanisms in the p53 induced apoptosis pathway and the Rb pathway, Dr. Ouyang found that parameters that significantly affect the bifurcation point corresponded to high-frequency oncogenic mutations, indicating that the position of the bifurcation point might be a better indicator of the functionality of a biological network than gene expression levels of certain key proteins. In the third talk of this section, Dr. Hao Li (University of California San Francisco, USA) showed a microfluidic system to directly observe the aging process at the molecular level in single cells throughout the lifespan of budding yeast. Dr. Li also presented their recent progress on analyzing the cellular state and the global regulatory network that influence lifespan by a newly developed high-throughput screening method. These findings may lead to new insight into the mechanism of lifespan extension by genetic and environmental perturbations.

CONCLUSION

In summary, by highlighting a few themes in this rapid-advancing new field, the five-day Cold Spring Harbor Asia Conference on Quantitative Biology was a great success to stimulate new thoughts and concepts, and exchange ideas and knowledge among people with a diverse backgrounds, across from biology, physics to engineering disciplines. We believe that quantitative biology will continue to attract attentions of diverse researchers and audiences, and make distinguished contributions in dissecting the secret of living systems, and in searching for new solutions for real life problems.

REFERENCES

1. Hammar, P., Walldén, M., Fange, D., Persson, F., Baltekin, O., Ullman, G., Leroy, P. and Elf, J. (2014) Direct measurement of transcription factor dissociation excludes a simple operator occupancy model for gene regulation. Nat. Genet., 46, 405–408
2. Stormo, G. D. (2013) Modeling the specificity of protein-DNA interactions. Quant. Biol., 1, 115–130
3. Stormo, G.D., Zuo, Z. and Chang, Y.K. (2014). Spec-seq: determining protein-DNA-binding specificity by sequencing. Brief. Funct. Genomics, doi: 10.1093/bfgp/elu043
4. Zuo, Z. and Stormo, G. D. (2014) High-resolution specificity from DNA sequencing highlights alternative modes of Lac repressor binding. Genetics, 198, 1329–1343
5. Hao, Y., Zhang, Z. J., Erickson, D. W., Huang, M., Huang, Y., Li, J., Hwa, T. and Shi, H. (2011) Quantifying the sequence-function relation in gene silencing by bacterial small RNAs. Proc. Natl. Acad. Sci. USA, 108, 12473–12478
6. Bu, P., Chen, K. Y., Chen, J. H., Wang, L., Walters, J., Shin, Y. J., Goerger, J. P., Sun, J., Witherspoon, M., Rakhilin, N., et al. (2013) A microRNA miR-34a-regulated bimodal switch targets Notch in colon cancer stem cells. Cell Stem Cell, 12, 602–615
7. Bi, S., Yu, D., Si, G., Luo, C., Li, T., Ouyang, Q., Jakovljevic, V., Sourjik, V., Tu, Y. and Lai, L. (2013) Discovery of novel chemoeffectors and rational design of *Escherichia coli* chemoreceptor specificity. Proc. Natl. Acad. Sci. USA, 110, 16814–16819
8. Kiviet, D. J., Nghe, P., Walker, N., Boulineau, S., Sunderlikova, V. and Tans, S. J. (2014) Stochasticity of metabolism and growth at the single-cell level. Nature, 514, 376–379
9. Lee, T. J., Yao, G., Bennett, D. C., Nevins, J. R. and You, L. (2010) Stochastic E2F activation and reconciliation of phenomenological cell-cycle models. PLoS Biol., e1000488
10. Lan, G., Sartori, P., Neumann, S., Sourjik, V. and Tu, Y. (2012) The energy-speed-accuracy tradeoff in sensory adaptation. Nat. Phys., 8, 422–428
11. Lan, G., and Tu, Y. (2013). The cost of sensitive response and accurate adaptation in networks with an incoherent type-1 feed-forward loop. J. R. SOC. Interface, doi:10.1098/rsif.2013.0489
12. Dufour, Y. S., Fu, X., Hernandez-Nunez, L. and Emonet, T. (2014) Limits of feedback control in bacterial chemotaxis. PLoS Comput. Biol., 10, e1003694
13. Monds, R. D., Lee, T. K., Colavin, A., Ursell, T., Quan, S., Cooper, T. F. and Huang, K. C. (2014) Systematic perturbation of cytoskeletal function reveals a linear scaling relationship between cell geometry and fitness. Cell Reports, 9, 1528–1537
14. Frankel, N.W., Pontius, W., Dufour, Y.S., Long, J., Hernandez-Nunez, L., and Emonet, T. (2014) Adaptability of non-genetic diversity in bacterial chemotaxis. eLife, 3, e03526
15. Neher, R.A., Russell, C.A., and Shraiman, B.I. (2014). Predicting evolution from the shape of genealogical trees. eLife, 3, e03568
16. Liu, C., Fu, X. and Huang, J. D. (2013) Synthetic biology: a new approach to study biological pattern formation. Quant. Biol., 1, 246–252
17. Soroldoni, D., Jörg, D. J., Morelli, L. G., Richmond, D. L., Schindelin, J., Jülicher, F. and Oates, A. C. (2014) A Doppler effect in embryonic pattern formation. Science, 345, 222–225
18. Heidari, N., Phanstiel, D. H., He, C., Grubert, F., Jahanbani, F., Kasowski, M., Zhang, M. Q. and Snyder, M. P. (2014) Genome-wide map of regulatory interactions in the human genome. Genome Res., 24, 1905–1917
19. Chen, W., Liu, Y., Zhu, S., Green, C. D., Wei, G. and Han, J. D. (2014) Improved nucleosome-positioning algorithm iNPS for accurate nucleosome positioning from sequencing data. Nat. Commun., 5, 4909
20. Zhang, W., Liu, Y., Sun, N., Wang, D., Boyd-Kirkup, J., Dou, X. and Han, J. D. (2013) Integrating genomic, epigenomic, and transcriptomic features reveals modular signatures underlying poor prognosis in ovarian cancer. Cell Reports, 4, 542–553
21. Liu, R., Aihara, K. and Chen, L. (2013) Dynamical network biomarkers for identifying critical transitions and their driving networks of biologic

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processes. Quant. Biol., 1, 105–114

22. Bialek, W., Cavagna, A., Giardina, I., Mora, T., Pohl, O., Silvestri, E., Viale, M. and Walczak, A. M. (2014) Social interactions dominate speed control in poising natural flocks near criticality. Proc. Natl. Acad. Sci. USA, 111, 7212–7217
23. Shu, J., Wu, C., Wu, Y., Li, Z., Shao, S., Zhao, W., Tang, X., Yang, H., Shen, L., Zuo, X., et al. (2013) Induction of pluripotency in mouse somatic cells with lineage specifiers. Cell, 153, 963–975
24. Li, Y., Jiang, Y., Chen, H., Liao, W., Li, Z., Weiss, R. and Xie, Z. (2015) Modular construction of mammalian gene circuits using TALE transcriptional repressors. Nat. Chem. Biol., doi: 10.1038/nchembio.1736

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