BRIGHAM AND WOMEN'S HOSPITAL

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Channing Network Science Seminar

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Principles of dynamical modularity in biological regulatory networks

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"Modularity is the human mind's lever against complexity"(Victor Bret). It is also nature's. Biological systems, from our bodies to cellular regulatory networks, are built of modules, and modules of modules, organized as a hierarchy. This appears to be great news, as it means reductionism is "in", as long as we carefully chop the biological system at its joints. We may study these modules in isolation, then put them together to figure out how the whole system works. The problem is, when these modules are wired together they create a system which is strongly dependent on its microenvironment and history. A registry of modules (and their behaviors) is not sufficient to decipher their coordinated response. Indeed, the most intractable complex diseases affect more than one facet of cellular function, the dynamical behavior of more than one module. Even if mechanistic insight into individual functions (modules) is available, deciphering how their coordination is altered by disease remains problematic (e.g., in cancer). Here we ask: are there general principles that govern healthy coordination between distinct cellular functions? We propose that 1) the cellular regulatory system is built as a hierarchy of multi-stable phenotype switches, or dynamical modules, 2) complex phenotypes are discrete combinations of the phenotypic arsenal of these switches, and 3) every phenotype switch at every hierarchical level is relevant to the global phenotype, in certain contexts. We show that the mammalian cell cycle is dynamically modular, composed of a two-state restriction-point switch and a three-state phase switch. With the aid of three novel measures that test these principles in discrete-state network models, we show that random non-biological networks often violate at least one principle, or satisfy all three more weakly that the cell cycle model. Finally, we propose a computational method able to distill the coarse-grained dynamics of dynamically modular networks. The method collapses the biochemical interactions within individual modules into discrete-state nodes. Inter-module links are reduced to phenotype-level combinatorial influences, revealing their higher-level coordination. A future, dynamically modular model uniting the regulatory switches critical to proliferation, apoptosis, migration and inflammation could provide insight into how breakdown in these core processes leads to cell- and tissue- specific disease.

Hosted by Yang-Yu Liu