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MEETING REPORT

Integrating the -omics*

Towards the end of 20th century, newer high-throughput technologies made the study of biological phenomena on a large scale possible. An era of '-omics' emerged: genomics – determining entire DNA sequence; transcriptomics – measuring expression of all genes; metabolomics – identification and quantification of various metabolites; proteomics – studying structures and functions of all proteins, and several others like lipidomics, glycomics, epigenomics, interactomics, miRnomics, etc. Bioinformatics played an unequivocal role in analysing and making biological sense of this huge information. In the 21st century, the stage is set to integrate multidimensional and complex information from large-scale experiments and create mathematical models for simulation and prediction[1]. In this respect, establishment of UNESCO training-centre for BIOmics and the organization of the First BIOmics hands-on workshop and conference was timely.

Modelling protein structures. The conformation of a protein is important for its functionality, and is determined largely by the sequence of amino acids. However, it is difficult to predict the precise structure of a protein from its sequence. Solving 3D structures of proteins is vital for understanding protein-folding problem, determining the structure–function relationships and eventually in rational drug-design[2,3].

Proteins with multiple transmembrane helices comprise about 25% of all open-reading-frames, and are targets of most drugs. Ilan Samish (University of Pennsylvania, PA, USA) expressed concern over the limited number of membrane protein structures in the Protein Data Bank (PDB)[4]. Limited raw structural data hinders understanding of structure–function relationships, prediction of related protein structures and designing new proteins[5]. To address this, Ilan's group identified all such proteins from PDB, using appropriate filters and created a dataset. This was used to formulate motifs and create tools useful for designing novel proteins.

Structures of macromolecular complexes, though crucial for understanding cellular processes, represent only a minority fraction in PDB. Structural data for these assemblies comes from cryo-EM, FRET, SAXS, etc., which generate very low resolution data[6]. Haim Wolfson (Tel Aviv University, Israel) presented work on modelling macromolecular assemblies at high resolution, by integrating information from X-ray data of monomers or dimers and low-resolution cryo-EM data of bigger assemblies having these units. This is indeed a unique way of getting past the experimental constraints of solving structures of macromolecular complexes at high resolution.

Understanding protein–protein and protein–ligand interactions. Experiments to find interacting partners for all proteins encoded in an organism's genome fuelled growth of databases enlisting such interactions[7]. This provides opportunity to mine this data and determine underlying themes of protein–protein and protein–ligand interactions.

Hanah Margalit (The Hebrew University of Jerusalem, Israel) described domain-pair based modular structure of protein–protein interaction networks. To find features other than domains that affect protein interactions, she used guanylate kinase sequences from different organisms. Comparison of homomultimers with monomers, those include the same interaction-promoting domains, helped to identify intra-domain features that could be classified into 'enabling-loops' or 'disabling-loops', depending on whether they promoted or inhibited such interactions. When both enabling and disabling-loops were present in protein, the disabling-loop was usually dominant[8].

Gideon Schreiber (Weizmann Institute of Science (WIS), Israel) used available data on protein–protein interactions to understand the architecture of protein–protein binding sites and to design interface with better binding potential. PARE, an algorithm from his lab, was used to engineer β-lactamase with increased charge around substrate-binding site, leading to enhanced association-rate. Protein interface usually has a modular architecture. Gideon's group searched PDB to find a module structurally similar to that present in TEM-BLIP and replaced it. This resulted in TEM1-BLIP interface with new specificity[9,10]. In another example, where RAS normally binds RAF, when the electrostatic potential at the interface of RAL was changed to mimic RAF, it led to binding of RAS to RAL[11]. He also demonstrated that engineering of binding affinity of interferon to its receptor led to alteration in its biological activity[12]. These studies could eventually be used for engineering proteins for therapeutic uses.

Piotr Zielenkiewicz (Institute of Biochemistry and Biophysics, Poland) demonstrated use of small molecule inhibitors of protein–protein interaction as new line of treatment for cystic

*A report on the 'First BIOmics Workshop and Conference' held at the Weizmann Institute of Science, Rehovot, Israel during 30 August–4 September 2009.

fibrosis[13]. ΔF508 mutation in CFTR protein is the most common cause of cystic fibrosis. Piotr, using molecular dynamics simulations, demonstrated that mutant protein exposes more hydrophobic surface, allowing its detection by housekeeping proteins for degradation. Candidates from small compound database were tested for inhibition of CFTR interactions with housekeeping genes. Four of these small molecules efficiently allowed CFTR mutant to escape ER quality control system and appearance of functional CFTR on the cell membrane.

High throughput sequencing. The human genome project initiated in 1990 took nearly 10 years for publication of its first draft[14,15] and the final traces were published only by 2008 (ref. 16). With evolution of technology, many new generation sequencing platforms have come up, which considerably reduced the time and cost required for sequencing[17]. A new project initiated with three-year deadline, for sequencing genomes of 1000 individuals, aims at creating a detailed catalogue of sequence variation[18]. Daron Lancet (WIS) used this data to study variation in 'olfactory sub-genome', the largest gene superfamily in humans, responsible for the sense of smell. His findings indicate that there are huge differences in copy numbers of different genes in this subfamily along with other genetic-variants like SNPs, etc. which contribute to wide variation in olfactory abilities of different individuals.

Modelling metabolic networks. The post-genomics era has spawned databases like GeneDB[19], KEGG[20], etc. with a challenging aim to generate complete computer representation of a cell, an organism and its biosphere. These provide information on genes, metabolites and various biological pathways, represented in the context of metabolic networks in a cell/organism.

Ron Milo (WIS) presented work on *in silico* representation of metabolic pathways. His database B10NUMB3R5 is a collection of numerical information regarding metabolites, biomolecules, macromolecular complexes, cells, etc.[21]. In the context of carbon metabolism, he identified 12 core precursor metabolites that form basis for biomass. Using a computational approach, he generated all possible paths between any two metabolites, such that they were connected by minimal number of enzymatic steps. Analysing this hypothetical network showed similarities with naturally occurring central metabolism, suggesting that it operates on an optimality principle. Potential alternatives to the natural pathway of carbon fixation were suggested, which could be used to construct artificial pathways.

Yitzhak Pilpel (WIS) described of his work on regulatory networks that control cellular processes. Different species show a codon bias, which could be an adaptation to the organism's tRNA pool. Presence of a codon with lesser number of tRNA molecules results in slow-down of translation and vice-versa[22]. He analysed gene sequences from several species, and, correlation with respective tRNA pools showed the same underlined theme. Translation of a gene starts with low-efficiency segment followed by longer high-efficiency segments. Pilpel suggested that this design is repeatedly selected through evolution as it optimizes the process of translation and minimizes cost of expression.

Modelling metabolic and regulatory networks also helps to understand the functioning of cellular machinery and eventually to design better drugs[23]. Luhua Lai (Peking University, China) pointed out that currently structure-based drug design, used widely for compound identification and optimization, is based on wrong assumption that one compound binds only one target. It is important to consider the action of the drug with respect to all proteins where the drug can bind. Using arachidonic acid metabolic network, she introduced the multi-target optimum intervention (MTOI) method for identification of key targets and discovery of optimal intervention strategies, which would shift the biological network from diseased-state to normal-state[24]. This study shifts focus from unique single targets to systems-based drug discovery.

Rewiring of biological networks is often used for functional genomics or to produce novel phenotypes[25]. Ploidy level changes and hybrids have since long been used to produce novel characteristics[26]. Avraham Levy (WIS) revisited hybrids and polyploids to assess the genetic and epigenetic basis of large scale rewiring happening in these systems. In hybrid of *Saccharomyces cerevisiae* and *S. paradoxus*, differences in expression profile of F1, when compared to the parents, were mostly results of divergence in *cis*-regulatory sites. Expression of profile changes due to *trans*-acting factors was mostly condition-specific and reflected environmental sensing[27]. In another example, using experimentally created wheat polyploids, Avraham showed that changes in the epigenome play a key role in altering characteristics of the polyploid[28].

Asaph Aharoni (WIS) is interested in understanding control-circuits that regulate production and accumulation of secondary metabolites in plants. These metabolites often accumulate in considerable concentrations either constitutively during growth or in response to environmental stresses. Asaph demonstrated that activation of sulphur-assimilation and massive changes in primary metabolism were required to increase levels of defence compounds like glucosinolates. These changes occur right from basic pathways like TCA-cycle to committed steps of methionine biosynthesis pathways, highlighting intricate balance in the components of biological networks[29].

Bharat Chattoo (M.S. University, India) demonstrated the use of genetic rewiring for creating broad-spectrum disease-resistance in rice. In *Arabidopsis*, Constitutive Disease Resistance (CDR1), encodes an aspartate-protease, which is an essential component of systemically acquired resistance (SAR)[30]. Overexpression of rice homologue (OsCDR1) in *Oryza sativa* and *Arabidopsis* led to enhanced resistance against phytopathogens, due to oxidative burst along with accumulation of salicylic acid and several fold induction of defence-related genes *PR1* and *PR2* (ref. 31). As a complementary approach, Bharat identified pathogenecity related genes in rice-blast fungus *Magnaporthe oryzae*. Using insertion mutagenesis screen, he identified a gene *MGA1*, required for development of 'appressoria' and essential for causing root infection[32]. *ABC4* encoding a transporter was also found essential for pathogenesis[33]. His group developed a comprehensive database, GROMO[34], which integrates information from several sources and presents a platform for analysis of rice–*M. oryzae* pathosystem. This study helps to understand metabolic crosstalk in host–pathogen interaction.

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MEETING REPORT

Consensus on prior informed consent and conservation of biodiversity based traditional knowledge systems*

People who have been conserving and adding value to indigenous biodiversity should be formally recognized but unfortunately a majority of them have not reaped the benefits of their efforts even after the implementation of the Convention on Biological Diversity Agreement 1992. In the broadest aspect of intellectual property rights (IPR) and prior informed consent (PIC) of traditional knowledge holders (TKHs), their moral rights are said to have been fully taken into account which has helped tremendously in conserving the biological resources.

To educate the indigenous communities of northeast India about traditional knowledge (TK) and exercising PIC at grassroots level, a series of seven workshops were organized on PIC and traditional knowledge systems (TKS), its use and promoting conservation in northeast India.

The objective of these workshops was to seek the opinion of multi-stakeholders about benefit sharing (tangible and non-tangible), arising from bioresources of the region. The knowledge holders of the Monpa community of Dirang and Tawang (West Kameng and Tawang districts; 72.12%) have emphasized that due recognition and reward must be given to the conservator of indigenous biodiversity. There was a consensus among Monpa TKH (97.68%) that a fair and equitable benefit sharing must be assured on any economic benefits that accrue from TK and indigenous biodiversity.

A majority (>85%) of them have opined that before publishing any research work on TK and related biodiversity, it must be circulated back to the TKHs in the regional language of the community so that a social validation could be made to avoid cases of misappropriation. Every TK based on local biodiversity (whether it is in the public domain or the property of individual) must be processed before use in R&D through a written PIC.

More or less a similar opinion was received from the Khasi community of Meghalaya (87.90%). They also responded (89.13%) that the share of benefits – if it is monetary, must be exercised either through indigenous institutions or through a trust. Village panchayats may be networked with indigenous institutions in an indirect way. Common practices (used in solving day-to-day problems) based on indigenous biodiver-

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