Cellular Interactions Networking in Interactive Models of Diseases

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Abstract

Integromics is necessitated as the complex diseases require to collate the integrated analysis expression, variation, and regulation of genes involved in trigger, prognosis, and establishment of factors creating the complete disease paradigm. The further involvement of the non-genetic and environmental exogenous factors are also designated to formulate the multitude of data for furthering the "integromic" approaches. Identification and validation of interaction networks and network biomarkers have become more critical and important in the development of disease models, which are functionally changed during disease development, progression, or treatment. We represent the requirement of the multi-node analyses that goes beyond the binary relationships to enterprise the structured interactions at the interface of genotype to phenotype correlations in disease biology. The prevalence and sporadic occurrence of endemic and pandemic infectious diseases, as well as the unmanageable burden of the non-communicable diseases, have emerged as the most burgeoning task of scientific investigations. Disease-specific interaction networks, network biomarkers, or Dynamic network biomarkers have great significance in the understanding of molecular pathogenesis, risk assessment, disease classification and monitoring, or evaluations of therapeutic responses and toxicities. The systems level studies have indicated biomolecule to cellular organization requires communication and cross-talk possibilities at the organism levels. Designing newer theranostic regimes, thus is required to focus on disease heterogeneity integrating the knowledge base of dynamic physical or functional interactions of network of networks. The chapter is targeted toward the identification, characterization, and a follow through of the experimental and computational tools for evincing the futuristic plan for modular endeavors in disease biology.

Keywords

Disease network · Interectomics · Network Biomarkers

Chapter Learning

- Disease Biology – Categories, characterization, and challenges of complex diseases
- Physical and Functional Networks – Multi-omics analyses
- Disease Networks and pathways – Expression, variation, and regulatory factors for identifying dysregulation
- Integromics – Constructing network modules on multifactorial data types and integrating non-genetic components modelling genotype to phenotype correlations
- Applications of networks inferring precision and accuracy in disease biology and management

Introduction

"Disease" aka malaise is a result of combination of genetic and non-genetic factors that have varied stages of acquisitions, activation, advancement and institution. The fact that most of the events of cellular welfare is pertaining to its inherent capacity to repair and regenerate the archetypical state. The perturbations in this capacity is mounted through a scheme of dysregulation involving genes, small molecules, proteins, RNA species propagated through the various stages of disease. Thus, disease biology contemplates the role of such networks, conditioned to the nodes of inter-connected genetic modules or sub-networks (Ghadie and Xia 2022). The emergence of diseases is with shared symptomatic patterns are also pinning that the focal causal factors are co-evolved, with cross-talk between interactive networks. A plethora of diseases fall in the category of such complex disorders that relay the importance of creating the niche of network of networks in concerted efforts toward clinical translation of the mega-initiatives toward precision medicine. The chapter is designated to provide the reader facts behind the pathobiology of complex diseases with focus toward curating the types of tools for functional theranostic designs.

Disease Biology: Noncommunicable/Communicable/Metabolic Syndromes

Diseases are complex network involving interactions between genes, environment, and lifestyle associated with self-limiting to life-threatening entities in all underlying classified diseases, e.g., tumors, infectious diseases, and cardiovascular diseases (Chan and Loscalzo 2012a). These diseases are complex, multifactorial diseases with varied outcome. Multiple physiological systems interact throughout the development of a complex disease. Life sciences research has been revolutionized in past decades by a series of technologies, starting with the Human Genome Project in 1990. The speed and scale of genomics analysis increased exponentially and is classified as discovery science, along with other omics such as transcriptomics, miRNAomics, epigenomics, cistromics, proteomics, metabolomics, and microbiomics. The goal of all these sciences is to collect and store data based on all the molecules involved (Manzoni et al. 2018). This helped in generation of enormous amount of biological data, leading to emergence of challenges in term of analysis and interpretation of data. This led to the discovery of the Network science which is involved with the analysis of interactions occurring between biomolecules (proteins, RNA, gene sequences), pathways, cells, organs. Hence, through network analysis, it is possible to identify complex patterns among different components to generate scientific hypotheses regarding the interactions present in health and disease events (Li et al. 2015). Gaining knowledge of the dynamics interactions across physiological systems facilitate the prevention or mitigation of biological damage in term of loss of functions in complex diseases, many of which are used to add on information or targets in developing new interventions (e.g., hypertension) (Abbas

et al. 2019; Zhou et al. 2016). There is a probability that complex biological pathway have low abundant molecular entities (genes and proteins) which interact with other molecules involved in similar pathways. Hence each pathway represents a specific region of an extended network in a given biological system. This led to thought that there is dire need of network analysis methods that can be elucidated to provide an add on biological insights that cannot be obtained from pathway analyses alone in vivo (Joshi et al. 2021).

Biological networks comprise nodes that correspond to genes, proteins, metabolites, or other biological entities, and edges that correspond to molecular interactions and other functional relationships between the biological molecules. In general, biological networks of the same size and connectivity exhibit significant differences in aspects such as: wiring type or presence of topological motifs (groups of interconnected nodes with a given structure). This affects (1) modularity, i.e., the degree of division of the network into subnetworks that comprise densely connected nodes but share few edges outside the module, (2) dissortativity, i.e., the tendency of nodes to connect to other nodes in the network that are associated with different characteristics (e.g., nodes with many connections link to nodes with few connections), and (3) robustness, i.e., the resilience of the network to the removal of nodes or edges. For example, COPD will be one of the top five chronic diseases in terms of global mortality and morbidity by 2030. The present chapter highlight network biomarkers, interaction networks, dynamical network biomarkers in diseases, with an emphasis to integrate bioinformatics-based screening of biomarkers, network biomarker, dynamic network biomarkers with clinical informatics and phenotypes, and establish a systems biomedicine-evidenced dynamic network specific disease models (Barabasi et al. 2011).

Causative Analysis; Etiology of Disease Immunopathogenesis, Molecular Events, Cellular Events

Complex disease conditions characterized by co-morbidities involve pathological dysregulation that evolves across multiple systems over time. Thus, a holistic approach is required to deconvolve the spatiotemporally distributed mechanisms of multifactorial disease pathogenesis at the tissue, cellular, and molecular levels of analysis. A disease's etiology, or cause, generally falls into three main categories; intrinsic, extrinsic, and idiopathic. The intrinsic etiologies are part of internal system, e.g., inherited disease, metabolic and endocrine disorders, neoplastic disorders and immunity, while the extrinsic etiologies are associated with infectious agents, animal bites, chemical agents. There are certain unknown etiologies are also called idiopathic (Fig. 1).

The development and progression of the disease involves complex etiology associated with interplay of a group of correlated molecules or a network, rather than from the malfunction of the individual gene, protein, or cell. Traditionally, molecular pathology analyzed well-characterized individual genes, proteins, or other molecules. Subsequently, this strategy was expanded to more elaborately

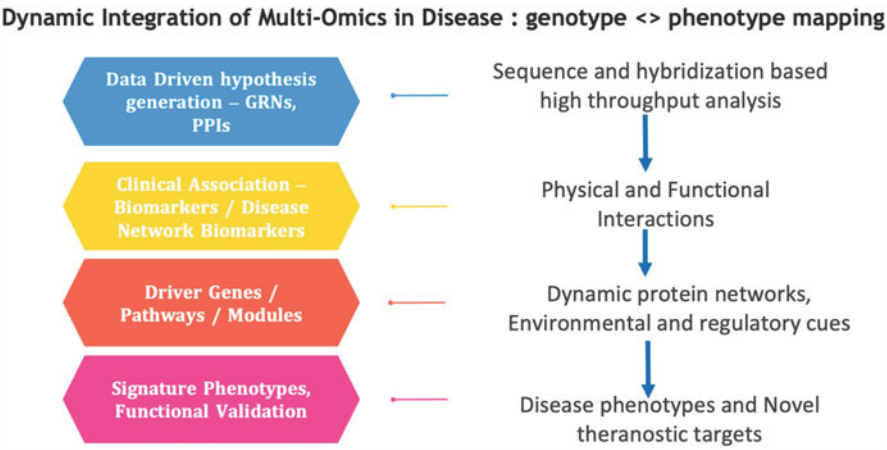

Fig. 1 Hierarchical generation of clinical interventions related to disease pathobiology and structured disease phenotype analyses – Contributions of the biomolecular interactions that modulate the cellular/tissue behavior and the studies conducted to unravel disease progression and establishment

deciphering the systematic alterations in the expression of mRNA using gene expression microarrays. Further, this technology has been advanced with full-genome, deep- and transcriptome-sequencing platforms, for example, mRNA or non-coding RNA quantitation, detection of gene copy-numbers, and genomic sequencing. Similarly, recent advances in mass spectrometry-based analysis now enable detection and quantitation of selected small compounds, proteins, and other biomolecules. Hence, identify and assess individual molecular entities (proteins, in particular) to ongoing molecular pathology toward higher-throughput and clinical applications, using technologies such as serum mass spectrometry. Cell signaling molecules are highly dynamic, potent, and specific in both structure and utilization and in both cell- and tissue-specific manner (Wang 2011) (Fig. 2). In the last decade, network-based approaches have been successfully applied to a broad range of diseases, with examples ranging from rare Mendelian disorders, cancer or metabolic diseases, to identifying basic strategies by which viruses hijack the host interactome, to name but a few. The important aspects of molecular networks such as simultaneous input cues should be processed and integrated to determine alterations in cellular behavior such as migration, proliferation, apoptosis, differentiation, etc. in order to design biomarker-based assays. An important aspect of cellular signaling networks is that at any given time in a given state impacts directly on the cellular response to an environmental stimulation. This multivariate nature enables cells to respond to multiple input events in an integrative and quantitative manner (Winslow et al. 2012) (Fig. 2). Hence there is a probability that failing to describe network states and biological context for molecular biomarkers can have potentially damaging consequences for the patient. It is believed that these potent alternations of complexes will represent and influence the responses of cells or organs to real-time changed microenvironment. Therefore,

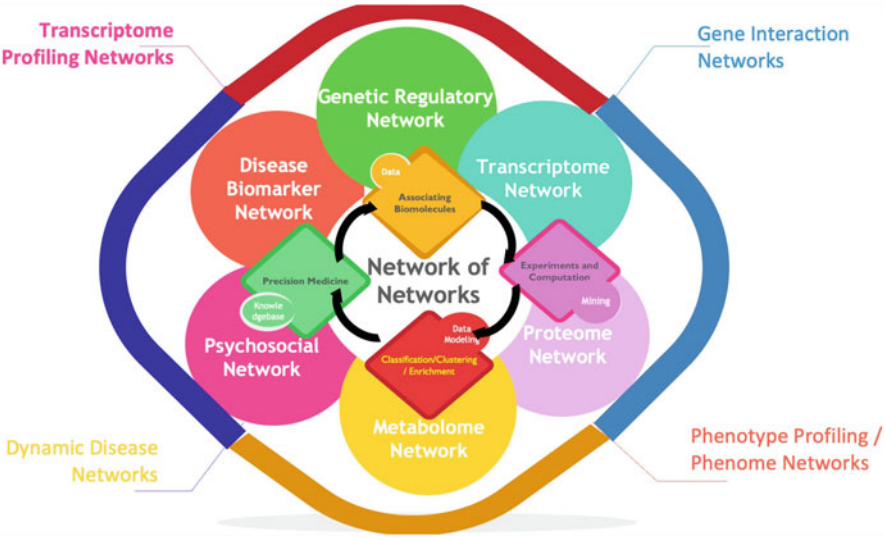

Fig. 2 Biological Networks – Disease biology profiling and the control networks which are integrated to allow dynamic programming and information processing through multitude of interaction networks. The interplay of these integrative models layered and connected to generate the network of networks as the focal high throughput disease models, converging disease states, phenotypes and regulatory patterns in disease biology

identification and validation of interaction networks and network biomarkers, especially at the protein level, become critical to develop disease-specific biomarkers for monitoring disease occurrence, progression, or treatment efficacy. In order to study clinical manifestations, interaction networks between immunologic, molecular, and cellular events should be envisioned. The new insights generated by extracting information from biological events depending on varied patterns of interconnections between these events during the initiation, progression, and extension of disease should be analyzed to understand the clinical sequalae and development of target specific therapies to treat the disease.

One of the major challenges in the medicine is the lack of disease-specific biomarkers for disease diagnosis, illness monitoring, therapy evaluation, and prognosis prediction. Hence, there is a dire need to identify biomarkers that should be a measurable indicator of normal physiological and pathological events. The disease specific biomarkers should be a guiding element in clinical manifestations, intervention, risk assessment, early diagnosis, and prognosis of disease. Disease-specific biomarkers are also expected to demonstrate the disease-associated specificity, sensitivity, traceability, stability, repeatability, and reliability. For example, somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor was shown to be a predictive marker in many lung cancer. However, only a few have been found to be useful clinically, although numbers of discovered and identified biomarkers are generated from preclinical research.

Profiling and Diagnostic Approaches in Disease Biology: Experimental/Computational/Mathematical

The culmination of the high-throughput studies of live images at cellular, and molecular levels have created stimulating possibilities for systematically investigating disease biology. The cataloguing of the diagnostic approaches followed by traditional toward integration of both in vitro and in vivo investigations with molecular basis will allow the clinical decisions based on such exploratory understanding of the disease. A perspective futuristic diagnostic and therapy regimen would thus be mapping functional details of disease progression and hence profiling in depth clinico-molecular aspects. The varied targets of disease biology includes the Experimental analyses, computational simulations, and mathematical modeling (Miles Macleod 2021; Scholl et al. 2018; Trapotsi et al. 2021). Here, we present the profiling approaches based on all these aspects.

Experimental Profiling

Disease research had extensive work performed in creating the experimental niche for demarcating the live cell imaging, cellular and tissue analyses, followed with molecular analysis. These studies have enabled us to update, improve, and facilitate empirical designs of disease biology. The results of experimental profiling is incorporated in the corresponding computational models. The computational studies including drug efficacy mechanistic studies, simulations of the genetic variants, predictive analyses, and dynamic profiling further makes the mathematical models that perceives to theranostic analysis. Together, these convey how experimental standardization, improvized parametric optimization in simulations, model refinements, inverse engineering can lead to inculcation of futuristic use of deep learning and machine learning while designing AI-based disease management strategies.

Computational Profiling

The recent years have seen a heightened interest in generating computational models for predictive and potential disease pathophysiology and drug targets. The computational models mostly range from score-function-based, network algorithm-based, machine learning-based, and experimental analysis-based models (Saiker 2021).

Multifactorial/Combinatorial Designs in Disease Diagnostics/Prognosis and Interventions

Disease biology involves the layered biological components that include the genes, regulatory components, proteins, metabolites, and epigenomes. Singular level omics approaches have been prevalent to be undertaken in disease pathobiological analysis

interrogating pools of genomes, trancriptomes, epigenomes, proteomes, metabolomes, and microbiomes using the ever diversifying workflows of high-throughput technologies. The mechanistic details of each such work-pipelines have paved way from hypothesis driven targeted approach to discovery driven untargeted analyses in disease biology. The data derived from the single level omics is enormous, though still not sufficing the need to resolve the causal relationships between molecular alterations at each level to the phenotypic manifestations in totality. This directs the systems level integration that allows multi-disciplinary data information to be processed through studying physical and functional interactions holistically. Integration of such systematic studies would also require adding up the regulatory window of information that is suitable to dissect the aberrant cellular functions behind complex diseases (Hood et al. 2004).

Multi-omics data generates the clusters of biologically relevant groups, enabling aspects of genetic variants and environment and interaction parameters between them. Thus, predictive models of prognostic and therapy have been devised, that now needs to be processed into integrative disease models to assist clinical translation of the research findings.

Interactome: Molecular Niche

Interactome refers to the inter-connected networks housing the physical and functional interactions, with physical interactions involving direct contact between participating biomolecules while functional interactions catering to biologically relevant relationships. In expression networks where genes are co-expressed and regulated, there are expression patterns that maybe connected, while functional interactions provide for genetic interactions, where genes are linked if simultaneous changes occur in genes involved. The functional and physical interaction networks provide for important insights into disease mechanisms. We process some details of these interaction networks for further analysis.

Physical and Functional Interactions

Diversifications and adaptations in the fields of chemistry, physics, mathematics, biology, critically engineering, the field of diagnostics, and therapy of diseases have paved its way from immunotherapies, radiotherapies, chemotherapies, tissue engineering, and realms of personalized medicine (Krzyszczyk et al. 2018). The genera of innovative technologies have seen the clinical translation and varying levels of success with a research stronghold that involves novel interventions using the "omics" toolkit, mathematical modelling, pharmacokinetics (PK)/pharmacodynamics (PD), and computational simulations and models [Docking and molecular dynamics (MD)] (Kitano 2002).

Cellular activities governed by physical and functional interactions to create biological pathways, with interactions between biomolecules or gene products.

Identification of the systems level cellular process description as a pre-requisite of meaningful derivations of biological state. Disease biology is similarly being addressed, where the advent of high throughput data and sequence details pave way toward elucidation of diverging descriptions of interactomes. The meaningful and accurate procedures deriving binary interactions and gauging their influence in disease development require convergence and comparative assessment of interactome descriptions. These include the core genomic, transcriptomic, and proteomic data inputs deepening the efficacy of theranostics obtained through the comprehensive interplay of bio-interactions.

Network biology scores in coordinating the conserved relations between the immune pathways, effects of pathogens on immunity, diversity and heterogeneity of immune cellular responses, mechanistic details of bio-interactions at the system's level. The integrative networks are being explored to provide for innovative information using a tri-partite approach that involves experimental data, advanced mathematical and computational modelling with validations to ensure the generation of high throughput reliable data (Lim et al. 2013; Voit 2000).

Network of Networks

Human disease is a constant aspect of life and consistently being studied using latest techniques, increasing our knowledge dramatically, through molecular basis, taxonomic and phenotypic screening, and creating therapeutic screens. The associations between diseases using these aspects has further helped in re-categorization and structuring of existing knowledge through the data driven analyses. This is a strong indication of the complex biological and cellular networks underlying the genotype to phenotype correlations. The demarcation of the network biology discussing the relevant types of interactome networks, their mapping, and integration into interactome network models is important for functional theranostic designs in most of communicable and non-communicable diseases.

The interactome networks are suggesting unique inter-connected nodes which represent the biomolecules that are possibly perturbed in disease conditions. These are sometimes referred to as modules or sub-networks that comprehensively depict the coordinated role of the molecular players at the cellular system. The genetic factors that are responsible or modulated can be caused by different genetic directives but have many overlapping factors involved (Vidal et al. 2011). Scientific deliberations are now focusing increasingly on the study of the patterns of interaction networks to comprehend the underlying causal effects in disease development. The complex diseases have inherent heterogeneity that spices up the utmost need of generating the discreet data that relays quantitative details as per the patient based phenotypic characteristics (Vidal et al. 2011).

The complex disease investigations have fundamental difficulties in ascertaining the details of the factors, their levels and role due to the shared combinatorial effects of the genetic and non-genetic influences. The demarcation and discovery of such elements and also the broad spectrum impact of the findings have led to altering the

specified complex disorders mostly to be grouped under the "group of – or spectrum disorders or part of syndrome." Examples of such exist in genetically inherited diseases (e.g., autism); infectious diseases (e.g., Leishmaniases); non-communicable diseases (Cancer) (Pujana et al. 2007). The individual contributions of genetic changes, rare mutations, expression level modulations are challenging to be deciphered for such complex disease settings, making the need of network of networks, more pertinent and prominent in near future.

The identification, characterization, and validation of the interaction networks and network based biomarkers is critical to organize the disease-specific functional biomarker details that modulate during the progression, development, or treatment of the disease. Precision medicine tethers to the concept of network medicine that is crucial to extricate the interplay and cross-talk between clinico-molecular features associated with disease utilizing the multiplexed network of genetic and non-genetic factors.

Drafting Interactome Networks

The dissection of the cellular interactomes is a bottom up approach which simplify the complex systems as components or nodes and interactions as edges. This is how the usual interaction networks are structured, where nodes as mostly biomolecules like proteins, RNA, gene sequences, or metabolites, while the edges are the physical, biochemical, or functional interactions between them that have been demarcated either through experimental means or by prediction algorithms (Allore and Murphy 2008). The "interactome networks" are prepared through systematic, empirical, and standardized assays, serving as scaffold information to create graph theory property or neural networks scaled at either local or global levels between the interacting components or nodes. The unbiased and statistically different outputs from randomized networks have led to potential true estimations of biological processes, though powerful details of dynamic and logical features that connect the structural alterations with functional outputs of the gene products, e.g., alternate splice variants, allosteric changes, and post-translational modifications are mostly not included in the simplified models (Licatalosi and Darnell 2010). To create the modelling details that can scale at the level of complete cells, such molecular transitions also need to be added to the layered interactome networks that might overcome the lacunae of individual interactome networks.

Network Biomarkers

Biomarkers are quantifiable indicators of differential aspects of normal biological processes in comparison to the pathological conditions and therapeutic responses that allow for early diagnosis, predicting, and monitoring outcomes. The disease-related biomarkers are critically important for demonstrating specificity, sensitivity, stability, reliability, repeatability, traceability, as well as levels of treatment efficacy

that can be conferred while banking on their application in disease biology (Simon 2005; Liu et al. 2012). It has been well established that the physiological alterations in the cellular systems is conveyed by mechanistic changes of varied players and their interactions at different stages of disease progression and establishment is critical to estimate dynamical networks and the associated network biomarkers that have inherent all types of interaction networks including the experimental, computation, or bioinformatics based, mathematical model based clinically relevant modules.

The high throughput data mining from the various omics technologies at the level of genome, transcriptome, proteome, epigenomes, and metabolomes all contribute toward the multi-dimensional data that form the systems clinical medicine exploring the untangled realms of functional modules in complex diseases. The categorical heterogeneity of such complex diseases, that confers the severity and progression differences and also the drug responses of being sensitive to resistance, have been deciphered for cardiovascular-related network and respiratory networks. These networks are widely used in studying the complex interactions, InSyBio BioNets, which is a cloud-based web platform offering a unique biomarker discovery pipeline, which combines differential expression analysis and a method for comparing biological networks to identify biomarkers efficiently. As a case study, InSyBio BioNets was applied to a Parkinson dataset of gene expression measurements and outperformed a standard statistical approach by recovering a more compact and informative set Biological of biomarkers (Theofilatos et al. 2016).

The sensitive detections of such network biomarkers have led to categorization of the clinical details in terms of patient stratification in terms of their biological molecular interaction, perturbed under specific therapeutic conditions leading to improved outcomes of patients. The candidate network biomarkers have been intensively utilized in cancer diagnostics, prognosis, efficacy prediction studies that includes microarray analysis as well as protein-protein interaction networks as layered information that were combined to reach accurate molecular interpretations and classification of tumors (Wu et al. 2012; Liu et al. 2013). The network biomarker studies have provided details of disease-related molecular interactions that are altered under the dysfunctional processes triggered under specific conditions relaying diseased phenotypes, e.g., expression profiling studies in combination with functional genomics and proteomics data found potential functional associations in breast cancer studies (Marcotte et al. 2016). Similarly, network biomarkers have been utilized in other complex disorders that target both non communicable as well as infectious diseases.

Interaction Networks and Dynamic Network Biomarkers

Interaction networks embrace the biomolecular factors creating gene regulatory networks (GRNs), RNA network that includes mRNA – miRNA networks, signaling networks, protein-protein interactions (PPI), and metabolite networks. The high-throughput collections of the large heterogenous datasets build using such

interaction networks have been collated for various cancer studies that include breast cancer, prostate cancer, bladder cancer, colorectal cancers, hepatocellular carcinoma (Nibbe et al. 2010; Chan et al. 2012b; Debmalya et al. 2020; Green et al. 2018).

The experimental scale interactome network mapping has been created using proteome scale analysis (Loscalzo et al. 2017; Finley and Brent 1994; Bartel et al. 1996; Fromont-Racine et al. 1997; Vidal 1997), while metabolic pathways at cellular scales and signaling pathways have given detailed cross-talk between biomolecules involving physical as well as functional web of interactions (Leiserson et al. 2015). Similarly, identification of interactions between transcription factors and DNA regulatory sequences are being captured to estimate the expression regulation and its global organization within the cells (Chen et al. 2008). The interactome networks have been compiled using three major strategies, i.e., (i) curating the data from literature studies or text mining, usually obtained from few types of physical and biochemical interactions (Roberts 2006); (ii) Computational simulations and predictions that is structured on "orthogonal" information in addition to the physical and functional interactions that involves sequence, gene order conservations, co-occurrence of genes, as well as protein structural information (Marcotte and Date 2001); and (iii) experimental mapping using high throughput systematic data using the whole genome or proteome analyses (Walhout and Vidal 2001). The interactome networks thus created are complimentary but still have different possible interpretations. Thus, network of networks could probably bridge the gap that exists between the varied literature-based interactome data that lacks systematic analysis, to the efficiency of computational predictions, that handle large data sets though on indirect information to the detailed experimental interactomics describing unbiased, systematic, and controlled data. Such a thorough interactome studies have been conducted on model organisms that have proven a milestone of information and provided support to the conceptual integration through pioneering technologies and improvement in the algorithms thereby.

The largely incomplete and sometimes overrepresented networks that may confer missing nodes, i.e., biomolecules, complexes, or phenotypes and edges, e.g., associations due to co-localization, reactions, or influences; sometime false positives that have any conclusive contextual information in cellular processes. The dynamic structures of the networks also represent changes that necessitate the development of scale free networks (Albert 2005) that allows node connectivity distribution to follow a power-law, having small world networks such that the distance between nodes have proportional increment to the logarithm of the network size (Albert 2005). This leads to few nodes as highly "connected hubs" with majority of these nodes having low degree of connectivity. These dynamical networks have also proven to be valuable in representing the complex biological processes. The dynamic interactions of disease biology is also linked to designing these dynamic interactome networks, as the gene co-expression data, stoichiometry, and kinetic parameters are required to have accurate characterization for knowledge of the underlying mechanisms in disease progression. These are to be further integrated with drug and phenotype networks that could correlate the dysfunctional biological perturbations in disease, to provide comprehensive and concise details for effectual

medical interventions (Pichlmair et al. 2012). Identification of disease micro-biomarkers requires effective computational and statistical methods for determiningfrom a very large number of candidate biomarkers a minimal subset of biomarkers that can accurately discriminate between two or more phenotypes. The various resources, e.g., SparCC: Sparse Correlations for Compositional data (SparCC) infers a network of associations between the microbial species based on the linear Pearson correlations between the log-transformed components (e.g., OTUs). SparCC makes two main underlying assumptions: (i) the number of nodes (e.g., OTUs) is large; and (ii) the underlying network is sparse. Implementation of SparCC included as part of the SPIEC-EASI tool is recommended (Hood et al. 2004). The Meinshausen and Bühlmann (MB) method is another technique for estimating sparse networks based on estimation of the conditional independence restrictions of each individual node in the graph and can also be implemented in SPICE EASI tool (Manazalwy et al. 2019).

Interactome Network Types

Gene Regulatory Networks

The gene regulatory networks (GRNs) or the transcriptional networks involve the transcription factor or putative regulatory biomolecules that act as nodes, and edges represent the physical interaction of these transcriptional factors (TFs) with DNA regulatory elements. The edges are considered as incoming (TFs binding to regulatory DNA) or outgoing (regulatory DNA bound by TFs), that have been deciphered using either in vivo yeast one hybrid or in vitro ChIP approaches for large scale mapping. The yeast one hybrid, utilizes a cis-regulatory DNA element as bait that uses genes and captures associated proteins (gene-centric), while in chromatin immunoprecipitation antibodies are raised against TFs, or against peptide tags fused with TFs, making it as protein centric approach. The techniques can unravel novel regulatory motifs if accurate predictions of TFs are made for applying either of these to demarcate gene regulatory interactions (Zhang and Horvath 2005; Reece-Hoyes et al. 2005; Vaquerizas et al. 2009). Model organisms including yeast, C. elegans, as well as cultured mammalian cells have been used for creating interactome networks using Y1H and ChIP (Vermeirssen et al. 2007; Grove et al. 2009; Lee et al. 2002; Cawley et al. 2004).

The regulatory RNAs including miRNAs or short non-coding RNAs that also sometimes part of the GRNs as they bind to complementary cis-regulatory RNA elements located in 3′ UTRs of target mRNAs. miRNAs form complex networks, interactions with its targets, where nodes are either these miRNAs or target 3′ UTRs, with similar incoming and outgoing interactions possible as edges. The non-coding RNAs are not master regulatory molecules, as they mostly attune to post-transcriptional regulation of gene expression, while mostly computational predictions of miRNA interactions as well as experimental methods are now focusing toward these miRNAs/3′ UTRs as part of GRNs as studies performed as large-scale

miRNA network in C. elegans. These studies need to be also appended in the other known genomes for a comprehensive look into the interactome networks.

Metabolic or Protein: Protein Interactome Networks

The functional protein-protein interaction networks represent the physical association between proteins, its signature peptides, or motifs/domains of the complete proteins as nodes while edges that are non-directed as the interaction module itself. There are various in vitro and in vivo technologies that have been utilized to create the experimental PPI maps as binary interactions, e.g., yeast two hybrid, or as indirect associations using TAP-Tags or Affinity or immune-precipitation for mapping multitude of interacting proteins in a complex, or directly using affinity associated MS analysis for the same (Rolland et al. 2014; Bonder et al. 2017). These interactions create differential maps of interactions due to their direct or indirect analyses patterns, serving as gene essentiality relationships with the number of interacting proteins. The interaction maps have been prepared using the comprehensive Y2H technologies with model organisms (S.cerevisiae, D.melanogaster and C.elegans), and also mapping of co-complex high throughput protein interactions using the AP/MS efforts (Sun et al. 2016).

The cumulative efforts of protein-protein interactions require accurate and sensitive mapping utilizing the empirical framework favoring critical parameters of completeness (most or all of protein physical interactions allowed in given search space), precision (true biophysical interactors), and assay or sampling sensitivity (number of interactions detected by particular assay or fraction of all detectable interactions in a single assay) (van Leeuwen et al. 2016). The interactome proteome maps could pave way for a roadmap toward comprehensive functional maps addressing the biological processes (Srivas et al. 2016). NetworkAnalyst 3.0 its key need for interpreting gene expression data within the context of protein-protein interaction (PPI) networks.

Metabolic Networks

Networks comprising all plausible biochemical reactions, in particular, cellular system or organism, where metabolites act as nodes and reactions or enzyme catalyzing these reactions occur as edges. Like the PPIs, the edges here are non-directions either directed or undirected, depending upon whether reactions is reversible or not (Motter et al. 2008). In some metabolic network models, the opposite situation can also be true, as per the representation of the nodes and edges, with enzyme as nodes and edges belonging to “adjacent” enzyme pairs with interdependent substrate and products among them. Classically metabolic networks have been represented as large metabolic pathways that have been completed with additional gene annotation data from the sequenced genomes. The metabolic networks have been constructed manually with computation prowess

added through a thorough curation of literature or text mining of published reports describing experimental evidences of metabolic reactions characterized from reconstituted or purified enzymes. There is also additionally compilation of orthologous enzyme reactions as part of the computational layer added that are experimentally characterized and show sequence conservation across species. Metabolic reconstructions involve the base of these elaborate proteome scale metabolic network maps demarcated for many prokaryotes and unicellular eukaryotes, as these are the most comprehensive maps of all biological processes occurring inside a cell and representing validated experimental evidences. The gaps that exists in such maps need also direct experimental analysis to generate more robust metabolic network systems or reconstructions simulated on existing networks (Ghiassian et al. 2015).

Designing Interactome Networks with Cellular Networks

The three major types of interactome networks discussed so far based on both physical and biochemical interactions need to be extrapolated to design the "scaffold" that could be used to overlay complete information of cellular systems, with additional "functional" layers to be appended to fine tune representation of biological processes and actual quantitative estimations. These networks that have the functional links represent the conceptual interactions where links between genes and gene products are reported based on functional interactome integrations taking cues from the existing interactome networks, though not requiring always the physical macromolecular interactions (Dezs et al. 2009; Greene et al. 2015). These designs are possible due to the complementary data made available genome scale analyses and predictions that interrogate the complexities or heterogeneities of the genotype to phenotype relationships. This has been mainly branched from the realization of the dysbiotic physiological modulations that affect the functional aspects on the existing interactome network maps (Menche et al. 2015; Corradin et al. 2016; Greene et al. 2015; Xenarios et al. 2002).

These have been further grouped as discussed in brief here so that these accrue the graph properties of interactome networks that can be simulated to generate the most, unbiased profile of cellular status and its correlation to the physiological conditions. These include

(i) Transcriptome – Interactome Profiling Networks
(ii) Phenotypic Profiling Networks
(iii) Genetic Interactions Networks

Transcriptome: Interactome Profiling Networks

Macromolecules or biomolecules are known to coordinate and act together in a biological process, not just individual entities. This cooperativity is tended to be captured at varied interaction networks including the Protein – DNA/RNA/protein

interactions, conveniently represented as networks or graphs with the molecules addressed as nodes or vertices and links or edges denoting the interactions between them. These networks have topological characteristics that include scale free property in a network, that confers in highly connected nodes, called "hubs" have a sub-network of sparsely connected nodes. The contextual application of these networks in disease biology refers to the topological properties of the interacting networks using connectivity or modularity of the participating genes or gene products that rely on generating both the physical and functional correlation. The gene products and complexes in common signaling cascades or similarly in disease biology are expected to show patterns of expression with higher similarities, and such a situation from either using transcriptome or proteome data need to be correlated globally with interactome networks. The vast majority of the transcriptome profiles generated from microarray, RNAseq data, that have been detailed for different species residing across multitude of diverse genetic and environmental conditions (Vidal 2001, 2011). The genes may be co-localized, co-regulated, co-expressed punched in matrices of genes of an organism against all conditions that the organism is exposed toward to generate the expression compendium. Discriminant and correlation analysis are statistically tested on the nodes and edges in the co-expression networks above a set threshold (Kim et al. 2001; Stuart et al. 2003) so as to agree to titration procedures applied thereof in such transcriptome interaction networks. The transcriptome co-expression network profiles created have higher degree of confidentiality about the regulatory network operations (Amit et al. 2009). The profiling networks have been combined using similarly co-expression profiles with the protein interaction maps in yeast revealing the significant overlaps between the interaction edges in interactome networks with the one found in transcription profiling networks. These studies have to be additionally linked to biologically relevant protein interactions who are not a part of such co-expressed systems or are rather segregated as never correlated, to generate a true functional transcriptome interaction profile.

Phenomics: Phenotype Profiling Networks

The need for linking gene modulations that relay functionally or phenotypic detectable changes is quite pertinent to disease biology. Genes encoding functionally related products are linked in networks contributing to similar phenotypic alterations. In the transcriptional profiling networks these are the genes that are grouped under the matrices with all genes of an organism and the phenotypes that are profiled in a same phenotypic compendium. Studies in model organisms (yeast, C. *elegan*, Drosophila) and even in humans (Giaever et al. 2002; Mohr et al. 2010) using gene knock-out/down techniques have shown all genes amenable to perturbations leading to variety of standardized phenotypes. The phenomics or "phenome" networks that are investigated through systematic gene-phenotype analyses is targeted to show these linked genes as nodes, and edges linking pair of genes depicting correlated

phenotypes tested above a set threshold. These efforts require titrations and decisions for the threshold properties of the phenotypic similarity or dissimilarity.

The phenome profiling networks have been shown to be associated with protein-protein interactome networks where overlapping and integrating the binary interactions, co -expression, or transcriptional networks and protein-protein interactions are overlayed to create very robust integrated networks with precise prediction patterns and power (Piano et al. 2002; Walhout et al. 2002; Gunsalus et al. 2005; Grove et al. 2009). The efforts to design these genome-wide phenome networks are underway in most of the model organisms after the proof of concept detailing in yeast model.

Gene Interaction Networks

The systematic mapping of the functionally related genes also points toward them exhibiting genetic interactions through gene mutations studies. The studies include comparison of phenotypes generated by double mutants (mutations in pair of genes) to single mutants (mutation in either pair of genes). These are also termed as synthetic lethals or negative, when phenotype conferred by the double mutant is aggressively worse than single mutant, or as positive or alleviating/suppressive if the phenotype of double mutant is significantly better compared to single mutant (Mani et al. 2008). These gene interaction or linkage studies have been utilized traditionally by genetics, while their inclusion in the functional genome analyses using systematic high throughput mapping has given rise to large-scale gene interaction networks (Boone et al. 2007). The pattern of genetic interactions here would confer similar details as the transcriptional and phenotypic profiling networks, with the gene or the nodes in genetic interaction networks representing the matrices of genes exhibiting the positive or negative features in the interaction and the edges functionally linking such genes based on their high similarities. The genetic interaction networks here provide an additive layer of predictive models of biological processes for its power and robustness along with the other interactome networks. The nature of the genetic interaction maps, derived using various methodologies like high density arrays or synthetic genetic arrays, barcoding microarray using deletion mutants in yeast clearly depicts that these interactions may not correspond to physical interaction of the corresponding gene products (Boone et al. 2007; Mani et al. 2008; Costanzo et al. 2010). This leads to detailing of unique patterns of the interactions from the different datasets, as these increase probability to reveal pair of genes in parallel pathways or in different molecular machines. The negative mode of interactions here would not correlate with the protein-protein interactions in either binary or multi-complex protein modes, while the positive mode genetic interactions provide more probable physical interactions between these genes (Beltrao et al. 2010; Costanzo et al. 2010). These details of positive interactions is studied as loss of either one or two gene products coordinating to provide similar effects in a molecular complex.

Conclusion and Perspectives

The interactome networks confer that discreet detailing and inter-connection of the normal biological processes as well as the disease-specific insights would have a greater impact in understanding and establishing the molecular transitions that are related to the mechanistic details, early diagnosis, risk assessment, classification of the stage or grade, as well as monitoring and therapy regimes. These intricate details would step up the efforts toward targeted directive or combinatorial therapeutics, with highest degrees of sensitivities and specificities. The disease networks could point toward the differential states of normal or pre-disease analyses, optimization of the effectiveness of direct assessment many-fold to allow designing theranostics with impactful effectiveness and finesse. We hope to usher into the era of utilizing and optimizing the upcoming machine learning and artificial intelligence approaches (Sniecinski et al. 2018; Moingeon et al. 2021) further to swiftly turn from reactive to preventive medicine strategies and designs.

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