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System Biology of Plant-Microbe Interactions: Understanding Biology at Systems level

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Abstract

Over the last two decades, we have seen a shift of focus in the biomolecular sciences, from the desire to understand how a single gene functions, to understanding how all genes and gene products of a cell work together. This new paradigm for understanding interrelationships between networks of biological processes is termed systems biology, and when applied to the cell biology, it is primarily about the network of genes, mRNA and proteins. This approach to scientific analysis rests on a new way of looking at processes: understanding them within a much broader context than ever before. Consequently, this approach rests on recent technological progress that allows data to be analyzed in much larger amounts. As plants have to sustain the varied habitats due to their sedentary lifestyle, they have evolved and developed different mechanisms to overcome the constraints. Due to this co-evolution, the intricate interactions are existing between the host and microbe interactions. Therefore, we need to apply the system biology approaches to understand the dynamic nature of interactions at the molecular level. The present chapter deals with the introduction of system biology, the two approaches to systems biology, and how these approaches are applied in plant-microbe interactions at systems level, as well as related tools of system biology briefly.

Keywords: System biology, Top-Down approach, Bottom-Up approach, Interactome network analysis, Bioinformatic tools

Introduction

The abiotic environment and its biotic inhabitants, such as several kinds of microbes like bacteria, oomycetes, fungi, archaea, and a little understood universe of viruses, interact in complicated, multilateral ways to influence the composition of the plant microbiome (Agler *et al*., 2016; Berendsen *et al*., 2012; Bue´e *et al*., 2009; Swanson *et al*., 2009). It is predicted that all facets of eukaryote life would be impacted by the intricate and deep-rooted interactions between microorganisms and hosts. Henceforth, traditional as well as

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systems biological "omics" and quantitative modelling approaches will be needed to understand the interactions between microbes and their hosts. As Denis Noble states "systems biology is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programs, but different. It means changing our philosophy, in the full sense of the term." So**,** to better understand complex biological processes, they will first look at how all of a system's components interact, whether at the level of a population, organism, tissue, or cell. Specifically, they will look at how and why systems exhibit properties that cannot be deduced from looking at the individual components. Hence, systems biologists take a reverse approach compared to majority of researchers who continue to break disease down into smaller and smaller pieces in an effort to understand how they work (Bruggeman *et al*., 2007).

A recently emerging field of biology titled “systems biology” endeavors to comprehend biological systems at the system level. By elucidating, modelling, and forecasting the behavior of all parts and interactions (gene, proteins, and metabolites) with respect to external stimuli, systems biology recognizes and comprehends entire biological system (Singh and Shukla, 2011, 2015; Karthik and Shukla, 2012; Baweja *et al*., 2015, 2016; Singh *et al*., 2016). It is the collaboration between numerous fields, such as Cell Biology, Proteomics, and Genomics, is common in systems biology. Some consider it to be bioinformatics because it involves processing a tremendous amount of data. "Some others view it as computational biology, computing the operation of the systems. But you require both of these components. It is based on physiology for its special interest in adaptive states of the cell and organism, on developmental biology for the significance of defining a succession of physiological states in that process, and on evolutionary biology and ecology for the understanding that all aspects of the organism are products of selection, a selection we rarely understand on a molecular level. Molecular biology is a foundational field because of its special concern for information transfer. Recently, the phrase "systems biology" has emerged to describe the cutting edge of interdisciplinary study in the biological sciences (Westerhoff and Palsson, 2004; Alberghina and Westerhoff, 2007)

In order to decode the complexity of biological systems, researchers are now using two system-based approaches: a "Top-down" approach and a "Bottom-up" approach. Researchers use a "top-down" method to decipher links between various levels of transcripts and proteins by analyzing massive datasets. This method begins with high-throughput experimental "omics" data and uses bioinformatics and systems biology tools to analyze the data and identify qualities that are significant for agriculture. The bottom-up approach is an integrative method in which properties of genes and proteins are combined with quantitative data, such as transcription rates and kinetics data, to build a model of thoroughly characterised components (genes and proteins, etc.), which can then be computationally simulated to identify and predict the behaviour of the system under various conditions. Systems biology makes an effort to understand living systems by identifying all of its constituent parts and the relationships that exist between them (Bruggeman *et al*., 2007)

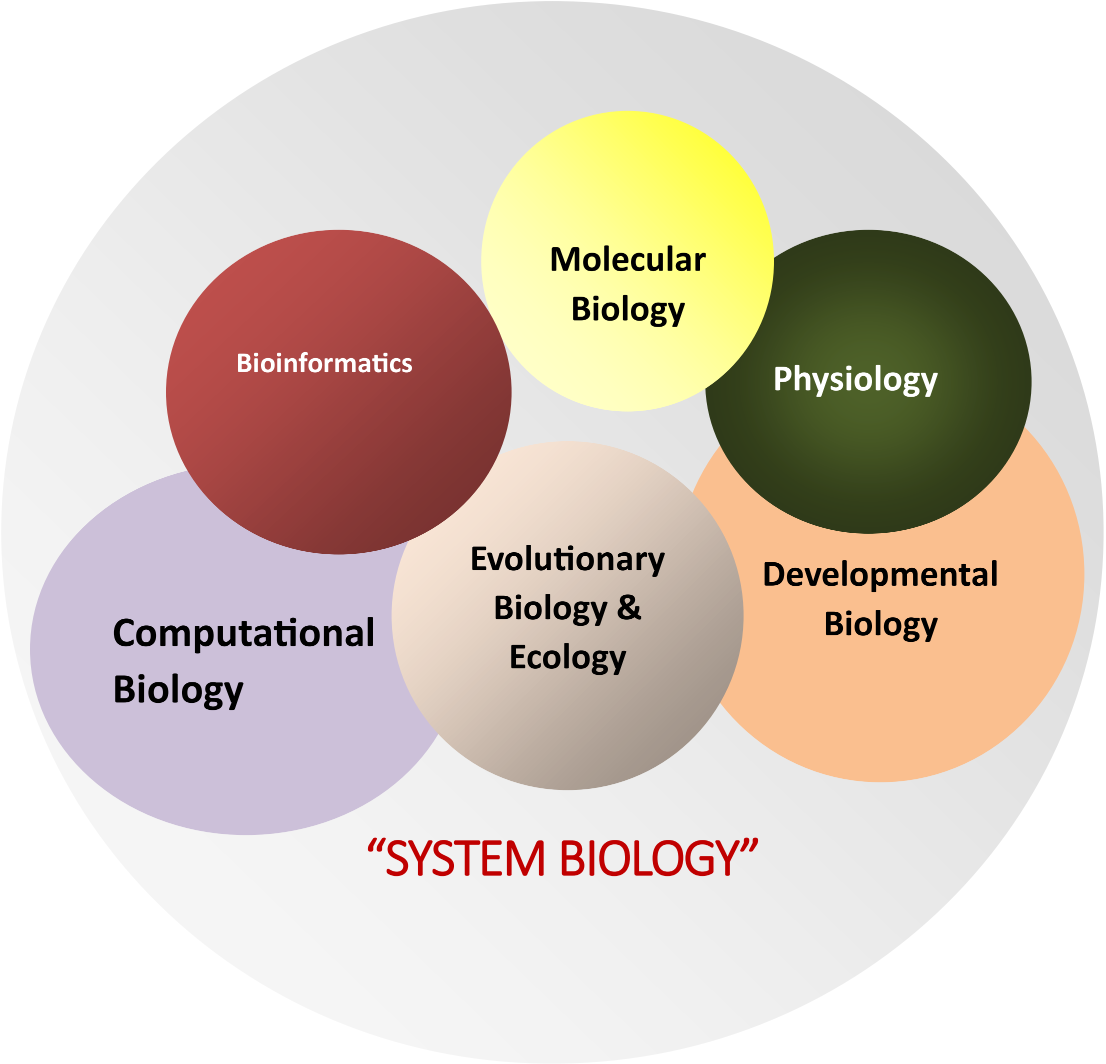

Fig 1. Illustrating of cross disciplines of research included in System Biology

System Biological Approaches to Molecular Microbe-Host Interactions:

Plants must adapt to their habitats to the greatest extent possible given their static lifestyle as they cannot escape physically from attack. Microbes that are pathogenic and mutualistic have a significant impact on plant fitness and exploit host plants as a source of reproduction. According to Jones and Dangl (2006) and

Oldroyd (2013), host plants and microorganisms have coevolved and developed a variety of mechanisms that affect the results of their interactions. Abiotic environmental elements like temperature and light also have an impact on how plants react to bacteria (Hua, 2013). As a result, interactions between plants and microbes are intricate and dynamic biological processes. Systems biology methods are therefore necessary to comprehend the true nature of plant-microbe interactions.

System biological techniques are used to comprehend the following elements in plant-microbe interactions:

1. PRRs for Plant Perception of Microbes
2. Bacterial Signaling: Quorum Sensing and Symbiosis Factors
3. The role of Hormone Signaling in Microbe–Host Interactions
4. Interactome Network Analysis
5. Metabolic Exchanges and Nutrient Competition in the Soil
6. Integrated Multi-omics Modeling
7. Transcriptional Regulatory Networks

I. Plant Perception of Microbes – PRRs

The extensive research on model PRRs and LysM-RLK suggests that the specificity and integration of signals depend on combinatorial physical interactions between receptors and co-receptors. In nature, an abundance of signaling molecules and a multitude of MAMPs are simultaneously in contact with plant roots. Because of this, it is feasible, if not likely, that a network of interacting receptors mounts a customized response to particular microbial assemblages that are recognized via combinatorial and quantitative perception of the varied signaling chemicals. Consequently, PRR signaling will require integrated global systems techniques.

II. Bacterial Signaling: Quorum Sensing and Symbiosis Factors

Plants detect bacterial communication using metabolites, volatiles, symbiosis signals, and quorum sensing (QS) molecules in addition to monitoring conserved microbial patterns (Jourdan *et al*., 2009; Chowdhury *et al*., 2015). The essential building blocks of bacterial communication that are also detectable by plants are N-acyl homoserine lactones (AHL). It's possible that the QS molecules' combinations and concentrations point to an unbalanced microbial mix. Although the physiological consequences of AHLs have been somewhat characterised, it is still unclear how plants perceive these bacterial compounds L (Cha *et al*., 1998; von Bodman *et al*., 2003).

III. Hormone Signaling in Microbe–Host Interactions

Signaling by phytohormones is fundamental to almost all plant functions. The traditional mediators of defense responses are ethylene (ET), jasmonic acid (JA), and salicylic acid (SA). JA and ET mediate ISR and defense against necrotrophs and insects, whereas SA mediates SAR and defense against biotrophic and hemi biotrophic pathogen attacks (Glazebrook, 2005; Pieterse *et al*., 2014). Other hormones, such as auxin, gibberellins, BR, or cytokinin's, as well as abiotic stress responses like abscisic acid (ABA), primarily regulate developmental processes. Beyond these orderly divisions, it is evident that hormone signaling is extremely interconnected and that several hormones have an impact on every function of interest. Consequently, phytohormones are important for the two-way exchange of information between plants and microorganisms. All hormone signaling pathways are interrelated, with the exception of the individual ones, and very few biological reactions are regulated by a single hormone (Vos *et al*., 2015; Nguyen *et al*., 2016).

IV. Interactome Network Analysis

Molecular interaction network techniques can be effective in identifying modules, routes, parts, and system-level patterns of molecular host-microbe interactions in the absence of quantitative dynamic models (Marin-de la Rosa and Falter-Braun, 2015). A reference protein network is necessary to put host-microbe interaction data in the context of host biology. A first comprehensive organizational picture of plant molecular connection was provided with the publishing of the *Arabidopsis* Interactome-1 (AI-1) map, which was the first experimental map of physical protein-protein interactions among thousands of proteins in plants (*Arabidopsis* Interactome Mapping Consortium, 2011). Since then, more and more specialized maps have been created, which make it easier to analyze particular processes. Interolog mapping, or the transfer of interaction annotations between conserved protein pairs between organisms, recently generated a protein-protein interaction network for the fungus *Phomopsis longicolla*, which causes *Phomopsis* seed decay in soybeans. This allowed the detection of disease-associated subnetworks (Yu *et al*., 2004; Li *et al*., 2018).

V. Metabolic Exchanges and Nutrient Competition in the Soil

Metabolic exchanges are one of the underlying tenets of microbiome-host interactions. Plants feed the microbiome by releasing up to 40% of the complex carbons generated during photosynthesis through their roots into the rhizosphere (Whipps, 1990). In contrast, fungi and bacteria help the plant absorb vital elements like phosphorus, nitrogen, and iron by assisting in their solubilization (Rashid *et al*., 2016; Jacoby *et al*., 2017). An key objective of plant reprogramming by pathogens through effectors and hormone signaling is the re-localization of nutrients. Individual organism metabolism has been studied using genome-scale

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metabolic modelling, and although community level response modelling is complex, it is making progress (Kruger and Ratcliffe, 2015; Topfer *et al*., 2015).

Table 1: Interactome Network Datasets for Plant–Microbe Interactions Studies

Study	Organism 1	Organism 2	Year	Reference
Arabidopsis thaliana interactome	*Arabidopsis thaliana*		2011	*Arabidopsis* Interactome Mapping Consortium, 2011
Convergent targeting of hubs in a plant–pathogen interactome network	*Hyaloperonospora arabidopsidis* and *Pseudomonas syringae* effectors	*Arabidops isthaliana*	2011	Mukhtar *et al*., 2011
Convergent targeting of a conserved host–microbe interface	*Golovinomyces orontii* effectors	*Arabidops isthaliana*	2014	Wessling *et al*., 2014
Pathogenicity genes in *Ustilaginoidea virens*	*Ustilaginoidea virens*		2017	Zhang *et al*., 2017
Extracellular network of *A. thaliana* LRR-RKs	*Arabidopsis thaliana*		2018	Smakowska-Luzan*et al*., 2018
Pathogenic protein networks in *Phomopsis longicolla*	*Phomopsis longicolla*		2018	Li *et al*., 2018

VI. Integrated Multi-omics Modeling

Although there is a demonstrable reciprocal benefit between plants and their microbiome and a "cry for aid" can attract microorganisms to the host to sustain it, it is still not known how the plant integrates detection of microbes with nutrient-related signals. Although phosphorus is typically present in high proportions, soil contains little orthophosphate that plants can absorb. The relationship between diet and defense was clarified by Castrillo *et al*. (2017) in a stunning multi-omics, systems biology experiment. They demonstrated that the plant phosphate starvation response (PSR) plays a significant role in regulating the root microbiome by combining 16S rRNA sequencing, genome-wide expression analysis, analysis and modelling of SynComs, and functional experiments.

VII. Transcriptional Regulatory Networks

Contrary to comparative transcriptomics, which is often used, causal regulatory networks and co-expression correlation networks are less frequently used. Based on the idea that transcript profiles of time series may be suggestive of causal links between transcripts, co-expression networks have been developed. An approach that is frequently used to classify genes by hierarchical clustering into co-expression modules is called weighted gene correlation network analysis (WGCNA) (Langfelder and Horvath, 2008). These modules are contrasted with metabolic pathways, phenotypic features, or the connectedness of signaling networks. The identified modules offer a preliminary understanding of genes with similar capabilities and can aid in improving our comprehension of processes important for infection or commensalism (Vella *et al*., 2017).

Systems Biology to Crop Protection

Understanding interactions between crops and microbes is becoming more and more aided by conceptual and molecular developments in microbe-host biology. The secretome of the newly discovered foliar fungal barley pathogen *Ramularia collo-cygni* that causes *Ramularia* leaf spot was predicted by McGrann *et al*. (2016) using a draught genome assembly. They hypothesised that *R. collo-cygni* initially behaves as an endophyte without causing disease symptoms and then shifts to a necrotrophic phase based on the decreased amount of plant cell-wall-degrading enzymes and the presence of genes related to chitin recognition avoidance. An essential component of systems biology analysis will be comprehending such dynamics and the underlying molecular mechanisms and signals.

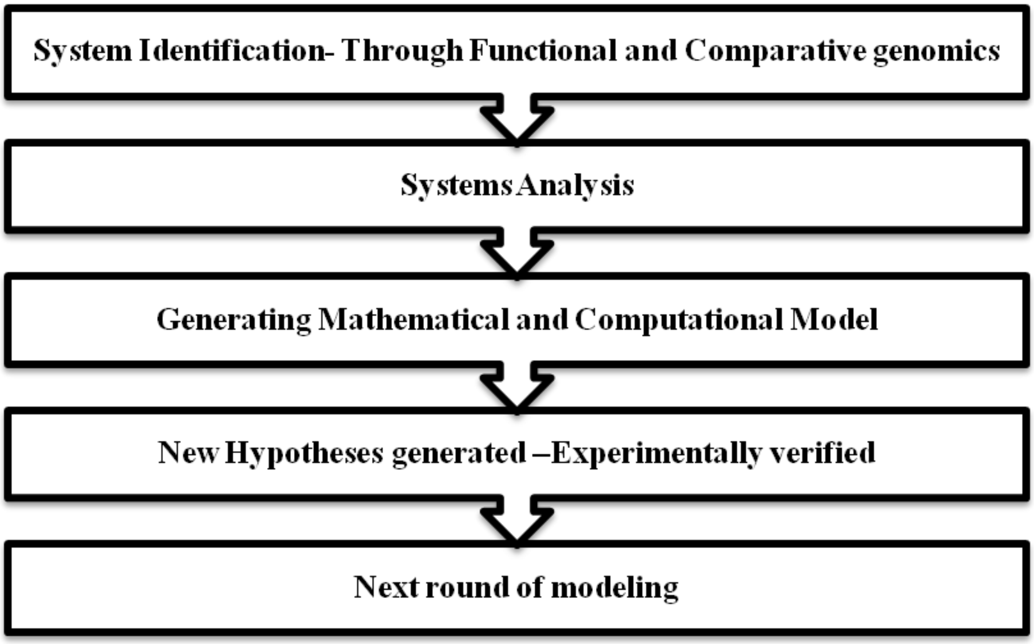

Fig 2. Concept of System Biology (Kitano, 2002; Ukai and Ueda, 2010)

Table 2: Application of Tools related to System Biology

Name	Description	Operating system	License	Reference
Biotapestryy	An interactive tool for building, visualizing and simulating genetic regulatory networks	Mulitplatform (Java-Based)	LGPL	https://biotapestry.systemsbiology.net/
Cytoscape	Data integration, network visualization and analysis	Mulitplatform (Iava-Based)	LGPL	https://cytoscape.org/
MEGA	Free, online, open-source, phylogenetic analysis, drawing dendrograms, etc.,	Windows/DOS-Win/Mac/Linux	Shareware	https://megasoftware.net/
Pathvisio	Tool for displaying and editing biological pathways	Multiplatform (Java-based)	Apache License	https://pathvisio.org/
InCroMAP	Integration of omics data and joint visualization of experimental data in pathways	Mulitplatform (Iava-Based)	LGPL	https://uni-tuebingen.de/fakultaeten/mathematisch-naturwissenschaftliche-fakultaet/fachbereiche/informatik/lehrstuehle/kognitive-systeme/software/
Pathview	Pathway-based data integration and visualization, user friendly and integrate into pathway analysis	Multiplatform (R/Bio-conductor)	GPL	https://pathview.uncc.edu/
Cell Designer	Structured diagram editor for gene-regulatory networks	Windows/Linux	The Systems Biology Institute	https://celldesigner.org/
SBML toolbox	Analysis of SBML models in MATLAB	Windows/Linux	California Institute of Technology, Pasadena, CA, USA,	https://sbml.org/software/sbmltoolbox/

Conclusion

The new approaches, such as whole genome comparisons and genomic sequencing, have developed as a result, allowing us to alter the way we study living cells. These advancements herald a new way of thinking about and in biology rather than merely new directions along the well-traveled path. After all, up until this point, the only way to comprehend biological complexity was to study each component separately. There have always been more qualitative questions in molecular biology and biochemistry, such whether or not we have cloned the relevant gene. Does it exist and is it active? Where in the cells? Systems biology is certain to relieve that load, become significantly more quantitative, and provide a more comprehensive perspective on a cell's internal workings without having to resort to ambiguity. This makes systems biology a challenging but precise field of study.

References

Available on request

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