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Invited Review

Systems biology of complex symptom profiles: Capturing interactivity across behavior, brain and immune regulation

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ABSTRACT

As our thinking about the basic principles of biology and medicine continue to evolve, the importance of context and regulatory interaction is becoming increasingly obvious. Biochemical and physiological components do not exist in isolation but instead are part of a tightly integrated network of interacting elements that ensure robustness and support the emergence of complex behavior. This integration permeates all levels of biology from gene regulation, to immune cell signaling, to coordinated patterns of neuronal activity and the resulting psychosocial interaction. Systems biology is an emerging branch of science that sits as a translational catalyst at the interface of the life and computational sciences. While there is no universally accepted definition of systems biology, we attempt to provide an overview of some the basic unifying concepts and current efforts in the field as they apply to illnesses where brain and subsequent behavior are a chief component, for example autism, schizophrenia, depression, and others. Methods in this field currently constitute a broad mosaic that stretches across multiple scales of biology and physiological compartments. While this work by no means constitutes an exhaustive list of all these methods, this work highlights the principal sub-disciplines presently driving the field as well as future directions of progress.

1. Introduction

The prevalence of behavioral and psychiatric disorders is increasing, and with it the cost to society. Currently, 5.4 million Americans have Alzheimer's disease requiring $200 billion in care, with the prevalence of this disease expected to double by 2050 (Alzheimer's Association, 2012). Autism now affects 1 in 88 children (Wingate et al., 2012) at an estimated annual cost of $60 billion (Järbrink and Knapp, 2001). An even more poorly understood illness, Chronic Fatigue Syndrome/myalgic encephalopathy (CFS/ME), is estimated to affect 800,000 Americans and cost the US economy approximately $9.1 billion in lost productivity and up to $24 billion dollars in health care expenditures annually (Jason et al., 2008). Clearly, the individual suffering, loss of social function, and economic cost caused by these conditions present a significant societal burden, however resolution of these illnesses is anything but simple. In a clinical setting, the classification of behavioral and psychiatric disorders remains one of the foremost challenges (Bousman and Everall, 2011). Individuals with the same disorder often present with a broad constellation of symptoms. Likewise individuals presenting with the same symptom profile may be suffering from disparate diseases. This biological complexity creates significant challenges for standard illness classification frameworks such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Assoc., 1994) and the International Classification of Diseases (ICD-10) (World Health Org., 1992). Discovery of the molecular features that underlie these pathologies is desperately needed however in many if not most cases no single marker or identifiable lesion has been found that reliably supports screening and diagnosis of these conditions.

Reductionist approaches have and continue to serve us well on several fronts however the very breadth of symptoms and their inter-dependency pose significant challenges to this piece-wise approach. In illnesses where dysfunction spans across several of the body's main systems the issue of breadth of coverage is critical if we are to examine markers in the proper biological context. The rise of "omic" research (genomic, proteomic, metabolomic etc.) has lead to a rapid increase in our ability to collect and store much more comprehensive snapshots of biological processes. Indeed more data can now be collected on a single process in a year, than has been gathered over the course of scientific history (Chuang et al., 2010). Yet despite the growing mass of data describing genotypic variation, transcription, translation, and enzymatic biochem-

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istry, little is known of how these elements give rise to disease and their behavioral symptoms. Clearly breadth is not sufficient and it may well be perceived as overwhelming by most, leaving us data rich and knowledge poor. However is omic data as high-dimensional as it appears? Biological markers are not expressed independently but instead manifest according to patterns that arise at least in part from the critical property of robust design.

A first contributor to biological robustness is partial redundancy of the components themselves. For example genes with overlapping functions will be able to compensate for one another. A second source of robustness has its origin in the interactions linking components with distinct but complementary functions. These interactions are dictated by the structure of the overarching regulatory network (Barabási et al., 2011). At a given point in time, the end result is that the number of fundamental processes regulating the changes observed in broad sets of markers will typically be much smaller than the list of parts. Feala et al., 2012 estimate that the number of controllers in a typical biological network will be less than 10% of the total regulatory targets. Importantly, this active subset in a much larger network will change over time giving rise to complex dynamic behavior (Hanel et al., 2012). Understanding these system-wide relationships, how they evolve over time and the emergent behaviors they support is essential if we are to formulate and test clinical hypotheses in any but the simplest of pathologies. This is the aim of systems biology as we define it in this work. With this in mind, our aim in this review was not to be inclusive, but rather to provide a representative overview of the various dimensions of systems biology and the challenges faced with an emphasis on applications in the realm of behavioral medicine.

2. Interaction: the connective fabric of biology and emergent behavior

The nature of biology is that of a holistic system. Like words in a language, the actions and effects of biological components are dependent on the context within which they occur. Systems biology in its simplest form can be described as an integrative science. Fundamentally it is directed at the identification of organizing principles that govern the context-specific emergence of function from the interactions that occur between constituent parts (Broderick and Rubin, 2006; Chuang et al., 2010). Our current understanding suggests that many of these principles appear to be conserved across scales of biology. An important and popular example is the small-world or scale-free topology of biological networks whereby the number of highly connected nodes decreases according to a power law. This typically results in sparsely connected networks that are governed by a small number of highly influential nodes. This pattern of interactivity is a defining feature of network architecture; one that reaches from the regulation of genes within a cell to the social interaction between individuals (Barabási, 2009). Indeed this applies broadly to network nodes representing the concentration of an individual mRNA species to the activity an individual cell phone subscriber and where associations between nodes can represent a chemical bond or a telephone conversation. This pattern of interactivity is a defining feature of network architecture; one that reaches from the regulation of genes within a cell to the social interaction between individuals (Barabási, 2009). It is important at this point to distinguish clearly between scale-free topology of anatomical and biochemical association networks and scale invariance with respect to temporal dynamics. These are essentially independent properties that must not be mutually confused. Interestingly it is now well established that intrinsic brain activity is arrhythmic and manifests scale-free temporal dynamics, where the contribution or power at a specific frequency decreases according to a power law at rest (Ciuciu et al., 2012). Deviation from this bias towards persistent long-term associations occurs during certain tasks but has also been observed at rest in conditions such as Alzheimer's disease (Maxim et al., 2005).

With interactivity being so pervasive in biology it follows that a physiological disturbance cannot be fully understood in terms of localized components alone, but must also be realized in the context of the entire system. The vast majority of research in the area of behavioral and psychiatric disorders has focused on the brain. However, to effectively address the growing epidemic of "brain diseases" the metabolic, nutritional, and environmental influences that exert effects on the brain must also be considered (Hyman, 2007). It is from this very interactivity and its fluidity in biology that complex behavior emerges. The first obvious examples of this phenomenon can be found in the generation of organ structure and function from cell interaction during embryological development (Setty et al., 2011). This is not limited to the emergence of structure but extends to complex dynamic behavior. Indeed it can be shown mathematically that interactivity between even a small number of components can lead to the existence of multiple regulatory modes. Examples of complex dynamic behavior include the emergent and context-dependent selection of cell fate (Hanel et al., 2012), immune cell population dynamics (Almeida et al., 2012) and bifurcation in immune response (Reynolds et al., 2006). Perhaps more complex still is the concept of emergence of consciousness from the large-scale interaction of neurons (Greenfield and Collins, 2005). Though we are increasingly aware of the relevance of these properties of biological systems to illness pathology their use in practice remains limited and focused primarily on the integration of elements that co-exist at the same scale, within specific physiological compartments and systems.

3. Linking parts within scales and compartments of biology

A natural consequence of interactivity and regulation is that biological markers will present in specific patterns of expression that reflect the underlying recruitment and instantiation of an active regulatory structure. Examining the structure of these co-expression patterns has the potential to enhance our diagnostic resolution by enforcing context (de la Fuente, 2010). This was recognized early in the social and behavioral sciences where extensions of classical statistics were applied to identify symptom constructs. For example Schröder et al. (1992) applied common factor analysis (CFA) to isolate and describe patterns of symptom association and their relation to neuro-imaging results in the establishment of sub-types of schizophrenia. More recently similar statistical methods have been used to identify constructs that distinguish patient sub-groups based on clinical presentation in a complex and poorly understood illness: chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) (Aslakson et al., 2006). Methods such as these that are based on singular value decomposition (SVD) essentially capture patterns of linear correlation between markers that exist at distinct levels of resolution and that can be superimposed to reconstruct the original data. Another related method, independent component analysis (ICA), was applied recently to construct inter-regional networks of brain activity serving as cerebral correlates of cognitive deficits in schizophrenia (Nygård et al., 2012). Association networks can also be constructed using more sophisticated and sensitive measures of similarity. For example information theoretic measures such as mutual information (MI) have been used to map non-linear associations between transcription factors and their mediators in the context of oncogenesis (Sumazin et al., 2011) and schizophrenia (Torkamani et al., 2010). An important caveat to this remains the multiplicity