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Review

Can a systems approach produce a better understanding of mood disorders?

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ABSTRACT

Background: One in twenty-five people suffer from a mood disorder. Current treatments are sub-optimal with poor patient response and uncertain modes-of-action. There is thus a need to better understand underlying mechanisms that determine mood, and how these go wrong in affective disorders. Systems biology approaches have yielded important biological discoveries for other complex diseases such as cancer, and their potential in affective disorders will be reviewed.
Scope of review: This review will provide a general background to affective disorders, plus an outline of experimental and computational systems biology. The current application of these approaches in understanding affective disorders will be considered, and future recommendations made.
Major conclusions: Experimental systems biology has been applied to the study of affective disorders, especially at the genome and transcriptomic levels. However, data generation has been slowed by a lack of human tissue or suitable animal models. At present, computational systems biology has only be applied to understanding affective disorders on a few occasions. These studies provide sufficient novel biological insight to motivate further use of computational biology in this field.
General significance: In common with many complex diseases much time and money has been spent on the generation of large-scale experimental datasets. The next step is to use the emerging computational approaches, predominantly developed in the field of oncology, to leverage the most biological insight from these datasets. This will lead to the critical breakthroughs required for more effective diagnosis, stratification and treatment of affective disorders.

1. General introduction

The post-genomic era promised much with respect to a greater understanding of human biology, and the development of new, more effective medicines [1]. While this has been achieved to some degree, it can be argued that the genomics era actually produced as many questions as it solved, if not more. This is particularly true with regard to the human brain, which has one of the most complex transcriptomes in the human body [2–4].

There is a pressing need to develop effective treatments, or management strategies, for many complex diseases, including cancer, fatty liver disease and mental disorders [5]. This review will consider one aspect of mental disorders: mood, or affective, disorders. The spectrum of affective disorders afflicts an estimated 14 million sufferers in the USA alone, representing 4.4% of the adult population [6].

1.1. The potential of systems biology

At it's broadest definition, systems biology is, quite literally, the biology of complete systems [7]. The aim of systems biology is to predict the emergent biological phenotype from the interactions that occur within a system [8]. Emergent properties are those that cannot be easily divined by study of the individual components of the system. For example, all life can be seen as an emergent property of the interaction between the proteins, lipids and other chemicals that make up an organism. While it is obvious that the human phenotype emerges from these interactions, it is not possible to define what a person will look like by studying the phosphorylation of MAP kinase. It is only through the systems approach, where the study of these individual components are connected, that higher-scale properties emerge. Systems approaches are now standard practice to understand the complex interactions that occur within biological systems. In addition, they are increasingly used to the understand aberrant behaviour of these systems (i.e. disease states), helping identify novel therapeutic options [7,8]. It could be argued that this approach is of particular importance for the examination of complex biological phenomenon such as mood. This is an area where much knowledge has been gained at the molecular level, but it is still

Abbreviations: 5HTT, serotonin transporter; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase; GEM, genome-scale model of metabolism; MAO-A, monoamine oxidase A; UD, unipolar disorder.

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not fully understood how such interactions link together to produce a particular mood phenotype. This review will cover three questions:

(i) Can a systems biology approach determine how the phenotype 'mood' emerges from multiple biological interactions?
(ii) Can a systems biology approach determine how common errors to this system result in affective disorders?
(iii) Can a systems biology approach be used to develop effective treatments, pushing the affective phenotype back toward normal?

To fully understand the potential for systems biology to benefit the understanding of affective disorders, it is important to unpick the definition of systems biology further. This will clarify both what we can hope to achieve using a systems approach, and what tools are available to achieve this.

1.1.1. What is systems biology?

If systems biology can be defined as a means of studying the biology of an entire system then we must first define what we mean by system. At one end of the biological spectrum we ultimately wish to understand the biology of an entire organism. The recreation of an entire organism in silico can be achieved with simple, single-celled organisms such as bacteria. However, the reconstruction of an in silico human is currently beyond our technical and biological understanding. In these cases, we usually define a system as a lower level of organisation, such as an organ or cell, or even an individual sub-compartment of the cell. Robustly reconstructing these individual components, will allow their merging to create larger structures, eventually leading to the in silico human [8].

Once we have decided on which biological system to study, there are two major flavours of systems biology that can be explored: *Experimental systems biology* undertakes measurements of the system at the global-scale., while *computational systems biology* involves the integration of experimental data in silico in an attempt to improve biological understanding [8]. Consideration of these two sub-disciplines leads to the realisation that they are highly dependent upon each other. For example, computational modelling is a logical way to attempt to interpret the large experimental datasets produced through omic approaches [9–11]. Conversely, computational models require experimental data to both inform their construction and to validate the final model. This leads to the conclusion that computational and experimental systems biology must be envisaged as an iterative cycle, rather than a linear pathway [12].

1.1.2. Tools to study experimental systems biology

Biological systems may be viewed as series of interconnected levels. The most obvious interconnection is the central dogma, the flow of information from DNA to RNA to Protein [13]. Experimental systems biology was initially concerned with the capture of the total information at each of these levels. For example, transcriptomic studies utilise microarray or RNASeq technology to examine all the transcripts within a system [14,15]. Analogous measurements can be made at the level of the genome and proteome [16,17]; in addition, study of the chemical complement of a system, the metabolome, is becoming increasing common [18]. As shown in Fig. 1, these technologies provide a comprehensive snapshot of the vertical information flow from blueprint (i.e. DNA) to phenotype (i.e. chemical composition).

Consideration of this vertical information flow has yielded significant insights into a wide range of biological questions, plus an impressive legacy of experimental data [19]. However, to examine the vertical flow of information alone ignores the control that exists within each vertical level. For example, the importance of post-translational modifications in setting the biological activity of proteins is well established [20,21]. The post-translational modification status of proteins will be captured in a standard proteome analysis, but its significance may be lost in the deluge of data: a case of not being able to see

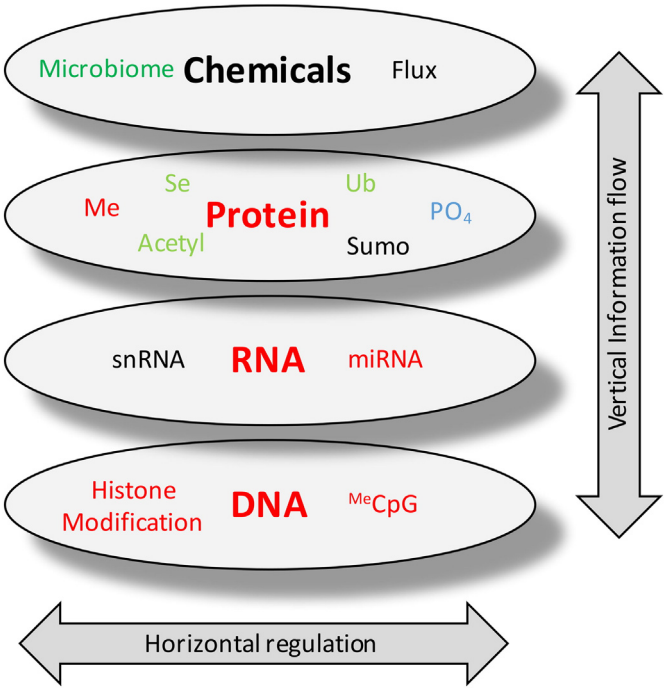

Fig. 1. The omic levels of organisation and affective disorders. Information flow within the cell can be envisaged as being a vertical continuum from DNA, through transcript and protein, to metabolites. Within each of these levels exits horizontal regulatory levels, controlling the vertical flow of information. For each 'ome', the extent of experimental systems biology devoted to the understanding of mood and affective disorders is indicated. Black text indicates no major studies reported to date; Green indicates some evidence for a role in affective disorders, but limited and/or sub-omic level analyses. More robust experimental systems biology approaches are required to further investigate; BLUE indicated that omic level studies have been undertaken, but only in animal models or in vitro. Extrapolation to human situation therefore complicates their interpretation; red indicated a good number of omic level studies have been undertaken, including in human studies, providing a solid legacy knowledgebase.

the trees for the wood. Targeted analyses must be used to focus on specific sub-populations of the proteome, such as the phosphoproteome, methylome or acetylome [21–23]. Likewise, analysis of the horizontal control within the genome (i.e. epigenome), transcriptome (i.e. small non-coding RNAome) and metabolome (i.e. fluxome) can be undertaken. Considerable work is also now focussed on the interaction of human biology with our symbiotic bacteria, mostly through study of the microbiome.

Experimental systems biology is focussed on the capture of comprehensive information on biological systems. These high-density data are ideal for identifying novel biological features, as they provide increased analytical power. They provide the building blocks for computational models, hypothesis generation and targeted follow-up experiments. Fig. 1 presents a cartoon of the omic levels of investigation, and highlights those that have been utilised to date in the study of the biology of affective disorders.

1.1.3. Tools to study computational systems biology

Computational models can, essentially, be categorised by two important factors: the size of network, and the level of parameterisation. The reconstruction of large molecular networks, often utilising omic level datasets, aims to integrate large amounts of data, either automatically or through manual curation. In contrast, 'bottom-up' approaches create highly detailed models of small biological networks, which may later be combined to create larger models, if desired [12].

The desired degree of parameterisation within a model is often a deciding factor for many decisions within computational systems biology, including the size of the generated network. To fully represent a biological system in the most accurate manner possible requires complete

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