Neurological Disease: Are Systems Approaches the Way Forward?

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Abstract

Most neurological diseases are multifactorial diseases, where environmental conditions combine with genetic background or somatic mutations to trigger a pathological state. In the case of Parkinson's Disease and Schizophrenia, recent research revealed that susceptibility genes coded for proteins involved at different steps of specific metabolic networks and cellular processes. Comprehension of the pathology of those diseases is therefore very likely to benefit from Systems approaches. This is also true of their symptomatology, affecting neurological systems at molecular, cellular, and microcircuit levels.

Most neurological disorders have initially be identified as syndromes, that is a set of symptoms or features clinically recognizable. Later on, when the pathogenic process is elucidated and a specific cause identified, some of them acquired the status of disease. However, even in the latter case, the pathology can often be caused by several different elementary defects, acting alone or in synergy. In addition, endogenous predispositions and environmental conditions are often involved together in the onset of the disease. Therefore, most neurospychiatric disorders are multifactorial diseases. Both the aetiology and the symptomatology of those diseases are complex, and so far understanding and treatment have resisted the traditional divide and conquer approach. It is maybe time to take a Systems Biology approach, and using the analytic power of reductionist approaches, try to reconstruct an integrated image of those diseases. Here we will use the example of Parkinson's Disease and of Schizophrenia to propose some possible applications of Systems Biology that could open some doors.

Understanding the aetiology

The genesis of Parkinson's disease symptomatology begins to be reasonably well-understood. The neurodegeneration in the substantia nigra of the dopaminergic neurons projecting to the striatum causes an hypodopaminergic state responsible for the bradykinesia, rigidity and tremors [29, 32]. Two main cellular mechanisms have been involved in PD-related celldeath. Sporadic forms are most often associated with mitochondrial dysfunction and oxidative stress, for instance caused by environmental factors, while familial forms would involve impairment of the ubiquitin-proteasome system. However, the division is not that clear-cut since accumulation of protein aggregates seems to be the outcome of mitochondrial defects, and some susceptibility genes affect mitochondrial function. What is far less understood is the mechanisms by which susceptibility genes affect the survival of neurons. 13 susceptibility loci have been identified so far, named PARK1 to PARK13, plus the gene encoding synphilin [9, 25]. This complexity is increased by the fact that different susceptibility loci were associated with different onsets of the disease. Interestingly, most of the proteins encoded by the genes located at the susceptibility loci are involved in the mechanisms quoted above. α-synuclein (PARK1/4), parkin (PARK2), and UCHL1 (PARK5) are involved in the ubiquitin-proteasome system while PINK1 (PARK6), DJ-1 (PARK7) and HtrA2 (PARK13) are involved in mitochondrial function [28]. However, HtrA2 being a protease, it is not impossible that both pathways are linked. And indeed interactions between parkin and Pink1 have recently been shown [12, 37]. Therefore, we have now an integrated picture of

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a complex pathway, where perturbations of almost each node can increase the risk of a dysfunction. This complexity is further increased by the fact that several mutations have been identified in some of those genes. They were shown either to affect different functions (ubiquitinylation of alpha-synuclein or binding to proteasome's lid for Parkin) or even to have opposite effects on the disease onset [34].

The wealth of information available, and in particular the correlation between biochemical knowledge and genetic insights makes Parkinson's Disease aetiology one of the most promising candidate for a Systems Biology approach applied to a medical problem. Central to such an approach would be the development of quantitative models of the pathways involved. Unfortunately, up to now most of the efforts have been focused on dopamine metabolism (e. g. [18, 19, 26]).

As Parkinson's Disease, Schizophrenia has been mainly characterized by its symptoms. However, contrary to Parkinson's Disease, where the symptomatology is consistent, the symptoms of Schizophrenia are heterogenous. There are positive symptoms, such as hallucinations, disorganised speech and behaviours etc. and negative symptoms such as poverty of speech, loss of interest in social interactions, impairment of attention etc. The ability of neuroleptic, inhibiting dopamine function, to relieve positive symptoms led to the dopamine hypothesis of schizophrenia, that postulate an hyperdopaminergy [7]. More recently, a glutamate hypothesis of schizophrenia emerged, based on an hypofunction of NMDA receptors [10]. New glutamatergic treatments seem to counteract positive and negative symptoms [27]. However, despite all the information accumulated about those two alternative hypothesis, it emerged recently that schizophrenia would a neuro-developmental disease rather than a neurotransmission one. And that both the hyper-dopaminergy and hypo-glutamatergy would be consequences of anomalous neuronal differentiation and migration. That theory would be in line with the fact that the symptoms appear in the young adult, coinciding with the end of the synaptogenesis. Genetic analysis found several susceptibility genes involved in the migration of neurons, the transport of proteins and the formation of synapses, thus supporting the developmental hypothesis. Although many plausible genes have been located in regions linked to a susceptibility to schizophrenia [30], the most promising candidate is DISC1 [23]. DISC1 is a putative scaffolding protein. It has been shown to interact with protein thought to be involved in neurogenesis (FEZ1) and neuronal migration (LIS1, NDEL1). The complete human interactome of DISC1 has been determined [6], and unravelled other interactors involved in synapse development. Interestingly, DISC1 has been shown to interact with other susceptibility genes, directly, such as phosphodiesterase 4 (PDE4B) or indirectly via one intermediate, such as dysbinding (DTNBP1). As with Parkinson's Disease we are in the presence of an interaction network where the perturbation of several nodes increases the susceptibility to the disease. While the former was mainly made up of metabolic interactions, DISC1 network is rather involved in structural and signalling functions.

Many models have been developed in computational neurosciences, in order to explain the symptomatology of schizophrenia (e. g. [1, 16, 31]). However, the level of abstraction of those models is rather high and the process they are describing are mostly unrelated to what we know of the aetiology. Now that we have a list of susceptibility genes, the interactome of the protein they code for, there is a strong case to move toward quantitative models at molecular and cellular levels.

Since the biochemistry of the pathways involved in PD and schizophrenia are being uncovered as genetic analysis progress, full quantitative reconstructions, including dynamical descriptions of all processes, are still out of reach. A first step would be to list all the identified molecular partners, whether identified or not by genetic screens, and their interactions. In order to lead to quantitative models, mechanistic descriptions of the biochemical processes are needed, rather than just phenomenological descriptions of the type "X inhibits Y". Such mechanistic pathways can already lead to structural analysis, potentially pointing experimentalists toward new hypothesis [5]. In particular, the effect of removing a partner or strengthening a control system can often be understood by inspecting the network structure. Of course, most of the molecular causes of PD or schizophrenia are more nuanced. The next step is therefore to add two kinds of quantitative information to the models. The most frequently quoted as problematic are the kinetic and equilibrium constants. We do not fully agree with that judgement. First of all, many of those missing parameters can be inferred either from orthologous systems (the "same" systems in other species), or from close paralogs (proteins encoded by duplicated genes) having kept the same function. Table 1 of Fernandez et al. [12] shows that complex models can be constructed where the majority of the kinetic parameters are estimated. Furthermore changing kinetic constant often leads to homothetic transformations. Few changes actually modify qualitatively the result. And arguably those are the most interesting, and will have to be studied by sensitivity analysis anyway (**Fig. 1**).

The real challenge lies elsewhere, in the initial quantities of the molecular partners, and their precise location However, while many groups are measuring functional parameters, the experimental difficulties are such that very few try to measure protein quantities and subcellular locations in neurons. Quantitative proteomic will therefore be an absolute pre-requisite in developing models of neurological disease, as well-understood by the HUPO Brain Proteome Project (http://www.hbpp.org/). The difficulties are such [3] that in the foreseeable future modellers will still have to rely on non-standardised measurements of single molecular components, or on rough estimations.

Improving the treatments

Most treatments of Parkinson's disease rely on alleviating dopamine related symptoms. While this approach remains successful in the earliest stages of the disease, it faces several severe problems [33, 35]. 1) Chronic administration of dopamino-mimetic or precursors of dopamine do not reflect endogenous dopamine dynamic, causing secondary effects such as dyskinesia; Phenomens of dopa-resistance appears after some time; 2) the supply of dopamino-mimetic or precursors of dopamine to counteract the striatal hypo-dopaminergy causes dopamine unbalance in other regions, for instance the neocortex, and triggers psychosis. 3) although dopaminergic neurons are among the first to die, they are not the only ones. Note that these problems are by no means restricted to the dopa treatments. Part of Parkinson's Disease symptomatology has been explained by a dopamine-acetylcholine imbalance [4] and treatments based on anti-cholinergics have been used very early. However, they triggered adverse cognitive effects. Conversely, PD dementias have been treated with cholinesterase inhibitors, that sometimes triggered tremors.

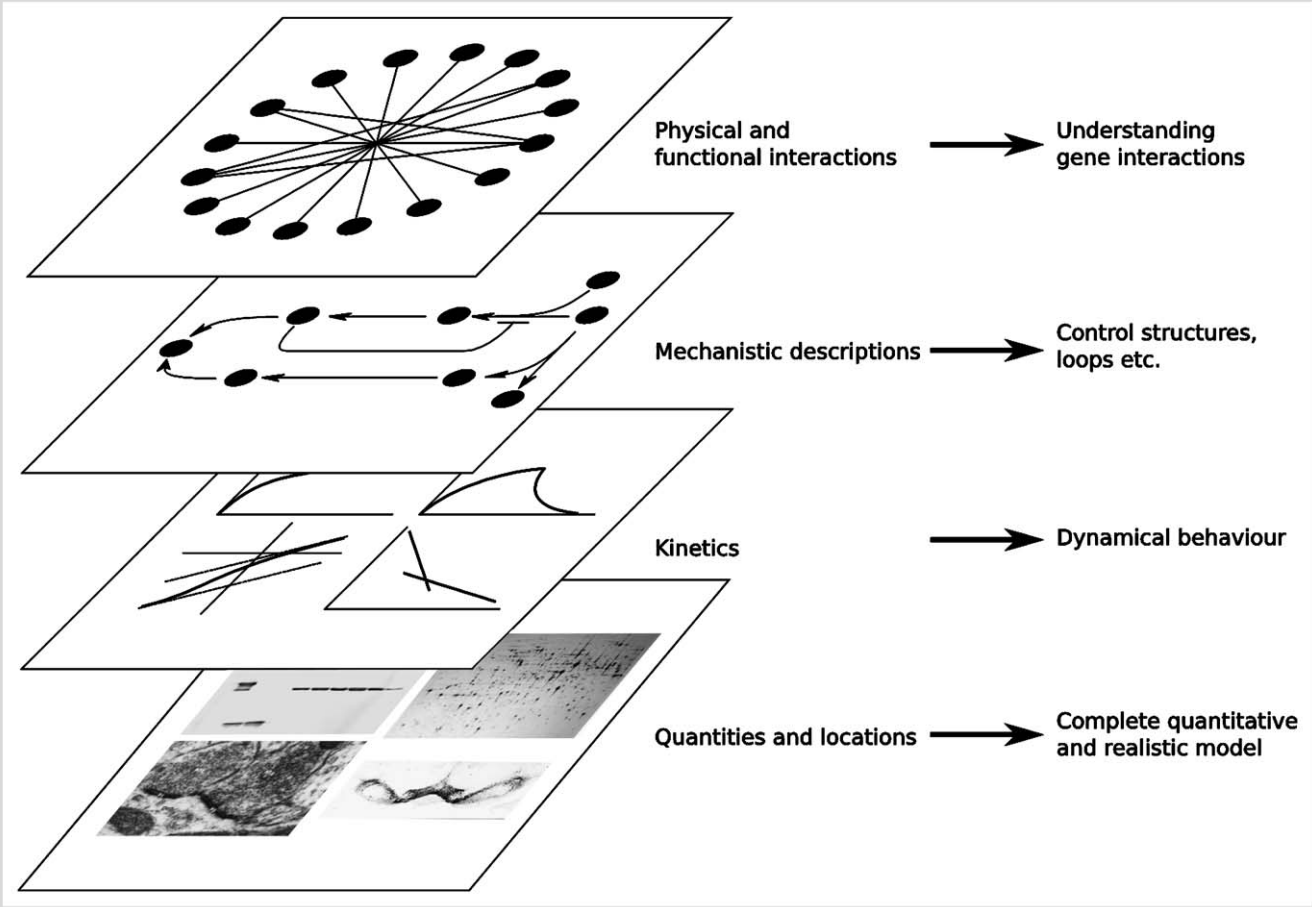

Fig. 1 Description of the layered approach to modelling biochemical basis of neurological diseases, and the informations one can gain at each level. Note that this does not encompass the spatial and multicellular levels, that are necessary to comprehend and tackle the symptomatology.

A systems-centred approach would likely provide new avenues to think the treatment of Parkinson's Disease. Contrarily to the aetiology, the systems considered are now multicellular, and involve the circuitry of basal ganglia, or even the brain in its entirety. First of all, multi-drug protocols have to be designed, that will target the locomotor symptoms, while blocking the onset of cognitive sideeffects. Although pharma companies are reluctant to take this avenue because of the burden associated with risk assessment, the dream of the miracle-pill definitively over. But actions at a system level do not need to stay only pharmacological. A precursor of a systems approach was the deepbrain stimulation [21]. In this approach, high frequency stimulation is continously applied, generally to the subthalamic nucleus, to alleviate the motor symptoms. Although the exact mechanism is still debated [14], this stimulation results in a longlasting improvement of patient conditions, without noticeable secondary effects.

Considering the complexity and diversity of of Parkinson's disease symptomatology, it is unlikely that the best possible treatment comes from simplistic conceptual models and treatments. Modelling in neuroscience now reached a state where true systems approaches are possible [20]. Several tentatives were performed to model some facets of PD using formal neural networks [2, 8, 11, 17]. However, the level of abstraction required by the formal neural networks makes difficult to capture the complexity of signal integration at the level of dopaminergic and striatal medium-spiny neurons, as well as the effect of neuromodulators. A more realistic approach should be attempted. As demonstrated on other cerebral systems [24, 37] systems, models comprising a large number of neurons, each modelled with many compartments containing various channels can now be envisioned. Such an approach would permit to take into account the precise cytoarchitectony of the systems (for instance acetylcholine and GABA inputs on medium-spiny neurons are not located on the same potion of neuron than glutamate and dopamine inputs), but would also permit to integrate electrical and biochemical descriptions.

Although temporary relief is obtained with pharmacological treatment such as L-dopa, and deepbrain frequency allows to treat patients who would not respond to pharmacological treatments any more, they are still only ways to temporarily alleviate locomotor symptoms. They are not cures for the disease and the neurons, not only dopaminergic, keep degenerating. If one wants to stop the evolution of the disease, it has to be tackled at the cellular level. Possibilities would be to block the formation of synuclein/synphilin or dj-1 aggregates, or to increase their clearance. Considering the number of proteins revealed by the familial forms of Parkinson's disease, it is very unlikely that one will be able to find a single molecular partner or a reaction on which a perturbation would suffice.Quantitative models will have to be developed that reproduce the effects of the various mutations observed, and then used to predict the best action or combination of actions to perform in order to slow down the pathogenesis, on a personal basis.

Application of Systems Biology to treat Schizophrenia is a more challenging question. Because of the neuro-developmental

nature of the disease, it is quite illusory to expect a cure any time soon. Therefore, one can only try to alleviate the symptoms. The heterogeneity of schizophrenic symptoms is then a blessing and a curse. One has to tackle both positive and negative symptoms,without side-effects. That has been shown in the past a very difficult task for a single compound. Here, quantitative models at the level of microcircuits, incorporating a certain level of molecular information, in relation to dopamine and glutamate receptors may prove useful. Complex models of neurons involved in schizophrenic symptomatology exists (e.g. [39]), and multi-cellular models can be easily built as it was done to study other disorders such as epilepsy [36, 37]. The intra-cellular pathways involved in dopamine and glutamate signalling have also been modelled [13, 15, 22]. One needs to be done is to make the two levels interoperate in order to have an integrative view of the systems involved and test in silico possible new way of perturbing them, electrophysiologicaly or pharmacologically.

Conclusion

Systems Biology approaches may not be the Graal, and answer all the questions or provide suitable treatments for every disorders. However, the reductionist methods consistently failed when it comes to multi-factorial neuropsychiatric diseases. They failed to properly explained the aetiology of the diseases, and they failed to provide efficient treatments devoid of side-effect almost as severe as the diseases's symptoms. Now that genome-wide screens and functional genomics brings us comprehensive data-set about the genes, proteins, and interactions involved in those diseases, it is worth tempting to go upward and try to reconstruct an integrated view of the disease process, and their systemic effect, in order to understand and treat.

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