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Rationality in discovery

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Chapter 3

Neuropharmacology

3.1 Introduction

What is the rational use of theory and experiment in drug research for Parkinson's disease? In this Chapter I discuss this problem from a bird's eye perspective, providing an introduction to the more detailed analysis of discovery in neuropharmacology in Part III of this thesis.

The approach of this thesis is that the best way to understand the process of discovery in empirical science is to see it at work. This opinion is endorsed by both psychologists, studying how people actually make discoveries in scientific practice (*e.g.* Dunbar, 1995), and computer scientists, who want to make programs that aid discovery, no matter how people actually make discoveries (*e.g.* Valdés-pérez, 1998).

I took a similar approach, in conducting my case study of drug research for Parkinson's disease at the Groningen University Center for Pharmacy. It turned out that fundamental research into the biological mechanisms of the brain and new drug experiments go hand in hand in the search for new drugs. Theories and models of biochemical and neurophysiological mechanisms guide the search for a new drug and drug treatment, and newly designed highly selective drugs are used to empirically test those models and further explore those mechanisms in the laboratories.

This chapter globally surveys my analysis of the reasoning involved in using theoretical diagram models in neuropharmaceutical research. These describe relations between variables of a biological system. The use of such diagram models has some limitations in practice, due to their complexity. A formal way to understand these models is to represent a model as a qualitative differential equation. An explication of the reasoning task can help to understand the search for drugs led by suggestions originating from such models, and possibly aid that task by computational techniques.

The next section briefly describes the field of neuropharmacology and the case of Parkinson's disease. In section 3.3, I will compare the reasoning in the search for an explanation with reasoning in the search of a drug treatment. In section 3.4 I outline a method of making predictions from knowledge in neurobiology by using qualitative differential equations. Section 3.5 defines and discusses the process of rational drug discovery. This chapter ends with some general conclusions.

3.2 Description

In this section I globally describe the field of neuropharmacology. One aim of drug research in neuropharmacology is to find a way to intervene in neurophysiological and neurochemical processes such that pathological properties or symptoms are suppressed, or desired properties are induced, (Vos 1991). Those unwanted properties are determined and discovered in numerous ways. The history of pharmacology and medicine is rich with serendipitous cases where a patient with a particular disease comes into contact with a compound that enhances his condition, hence providing a clue about the disease mechanism. A systematic study involves comparison of properties of pathological processes of patients with those of control subjects. In some cases, such as in Parkinson's disease, a cause of disease symptoms can be traced back to different concentrations of a single neurotransmitter compound.

Neural disorders have their origin in shifts in delicate balances of neurochemicals, which can be caused by *e.g.* cell damage or degeneration. The plasticity of the brain is large enough to restore imbalances, *e.g.* by increasing the sensitivity for a particular neurotransmitter. But when it fails, *e.g.* when a substance is depleted almost completely as in the case of Parkinson's disease, a severe neurological disorder results.

The aim of a therapeutic strategy is to find or design chemicals that selectively influence neurotransmission. The goal is to restore balances by administering those chemicals, to nudge derailed processes back on the track. This kind of research has a top-down and bottom-up strategy. In the latter case, one tries to discover and understand structures and processes in the brain by influencing them selectively, and seeing what happens. This is done both locally and globally. How does a new drug influence local neurological processes, and how does it influence behavior? In the top-down case, one uses all knowledge available about the pathology of a disease to discover new therapeutic targets, leading to a so-called *drug lead*. This is a description of the functional properties a potential drug should have to influence that target. In practice, top-down and bottom-up go often hand-in-hand.

Using knowledge to build models of neurochemical structures and processes to guide drug research is dubbed rational drug design. Computational models of complex receptor structures are made to infer what chemicals might interact with them. Yet, in contrast to such rational methods, currently a very successful strategy is to generate chemicals massively and to test them *in vitro* on their potency for influencing receptors. This strategy will end up with a nice set of chemicals to influence the biological machinery in a highly selective way. On the other hand, it is not always obvious how to employ those chemical tools optimally. For example, it may turn out that a particular combination of drugs is needed to properly influence several mechanisms involved in a disease. This can be discovered by first rationally understanding those mechanisms.

Hence, fundamental research into the workings of the mechanisms of the brain is also pursued in neuropharmacology. One research tool employed is building models of neurochemical and neurophysiological processes that aim to fit data acquired by lab-studies on animal models. This is conducted in the Pharmacy Department of the Groningen University by employing electrophysiological methods and microdialysis to track nerve signals.

A nerve propagates a signal by conducting an electric pulse called an action potential. This signal initiates the release of transmitter chemicals at the terminals of the cell, that affect receptors of nearby nerve cells that may further propagate a signal. Placing an electrode in the brain can monitor the electrical activity. The release of transmitter is measurable by means of a microdialysis probe. This probe can also be used to release chemicals locally and measure the effect *in vivo*. At the Pharmacy Department of the Groningen University the function of neurophysiological pathways is studied by using these two techniques.

Specific studies of the functional relation between several variables together contribute to understanding the function of a brain area, or cell groups called nuclei. To describe these neural circuits, box and arrow models are drawn showing positive and negative influence relations (Timmerman, 1992). These models are further tested for their correctness and used to explain and predict the functioning of the system. Newly developed drug compounds play a bootstrap role in this research: they are used to revise and refine the model and experiments conducted, while on its turn the model is used to understand their effect. A drug that works very selectively for one particular type of pathway can be used to further explore the function of that pathway. The acquired data may then serve to refine the model, so that the effects of the new drug can be explained and predicted.

A group of subcortical nuclei called the basal ganglia are studied in Groningen (Timmerman *et al.*, 1998). These nuclei play an important role in the control of voluntary behavior. In the case of Parkinson's disease a part of them, called the *substantia nigra pars compacta* (SNC), decays due to an unknown cause. The SNC is a supplier of an important neurotransmitter called dopamine, which is postulated to serve a modulating function. It is thought to maintain a delicate balance in influencing signals from the cortex. To understand this balance a schematic model is used to represent neural activity in the basal ganglia in Parkinson's disease, see Figure 3.1.

Figure 3.1 presents a schematic representation of neural activity in the basal ganglia in Parkinson's disease, as postulated in studies by Timmerman (1992, p. 18). An arrow in the diagram is a neural pathway, consisting of a bundle of individual nerve cells. A box is a nucleus, or clustering of nerve cells. Increased inhibition induced by receptors sensitive to the transmitter GABA of the external segment of the *globus pallidus* (GPe) leads *e.g.* to disinhibition of the subthalamic nucleus (STN). In turn, this provides increased excitatory drive to the internal segment of the globus pallidus (GPi) and *substantia nigra reticulata* (SNR), therefore leading to increased thalamic inhibition. This is reinforced by reduced inhibitory input to the SNR/GPi. These effects are postulated to result in a strong inhibition of brainstem neurons. D1 and D2 are two different types of receptors, postulated to react excitatory and inhibitory, respectively, to dopamine (DA). (This model is explained in more detail in part III)

In the model dopamine has a dual function. It enforces the direct path from the striatum to the SNR/GPi while it inhibits the indirect path, via the GPe and STN. This balance maintains an inhibition of both the brainstem and the thalamus. Yet when dopamine is nearly depleted, the balance becomes disrupted, resulting in a strong increase of the activation of an area called the SNR/GPi, see Figure 3.1. This hyper-activation causes strong inhibition of brainstem neurons and is correlated with some of the major symptoms of Parkinson's disease.

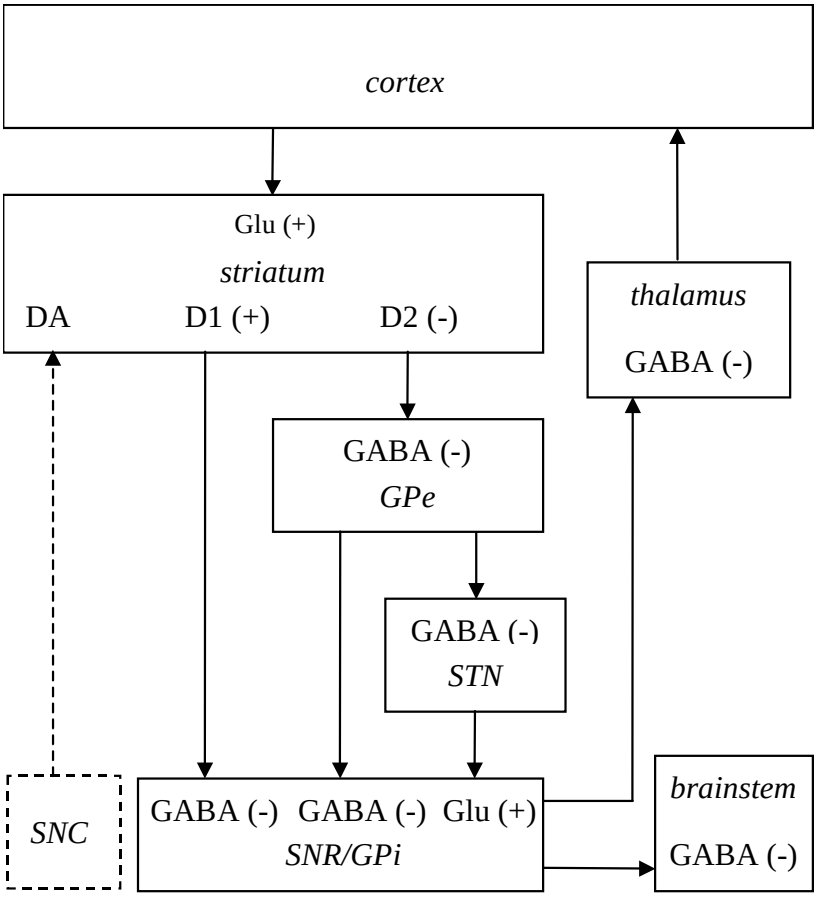

Figure 3.1: Diagram model of the basal ganglia

Most of the traditional research on Parkinson's disease is focused on restoring levels of dopamine. This compound cannot be administered as a drug that can be swallowed because it does not pass the so-called blood-brain barrier. Yet it was discovered that L-dopa, which metabolizes in the brain to dopamine, can pass this barrier. Administering doses of L-dopa regularly is to date the most successful therapy to deal with Parkinson symptoms.

Yet administering L-dopa also causes dopamine levels in other parts of the body to increase. This higher concentration of dopamine in the blood causes nausea as a side effect due to stimulation of dopamine-receptors elsewhere in the body. And after three to five years of use the therapeutic effect wears off drastically. Further research investigates the use of highly selective dopamine receptor agonists, compounds that interact only with particular dopamine receptors. The dopamine receptors on the direct route from the striatum to the SNR/GPi were discovered to be mainly of another type (D1) than that of the indirect route (D2) via the GPe. Both receptors can be stimulated by dopamine, but with different effects. D1-receptor stimulation with dopamine has an excitating effect on a cell, while stimulation of the D2-receptor with dopamine inhibites the cell. Clinical studies are conducted to investigate the therapeutic effects of using different compounds that differ in selectivity to both the D1 and D2-receptor. These studies show that using only a selective D1-agonist, a compound that stimulates D1 but not D2-receptors, is not successful.

The model in Figure 3.1 is used to understand the effect of selective compounds. However, in the literature opinions about these kinds of models are rather diverse. Some people use them to understand and theorize about physiological phenomena extensively, while others are wary of using them because they are too simple, not respecting the subtlety of the data, and therefore not realistic. In a recent article in the movement disorder literature it is said:

> "On the one hand, efficient models have to be simple, but simple models can provide only part of the reality and are thus bound to be wrong (for example, current basal ganglia model) ... On the other hand, an elaborated model that would embody all the complexities of a given reality ... is doomed to be useless" (Parent and Cicchetti, 1998)

The practical problem of the diagram model is that it is informally represented. Its consequences are inferred by tracking the boxes and arrows. The general basal ganglia model is already fairly elaborate. A more realistic picture would have to be substantially larger, including more transmitters, peptides, small interactions and feedback loops. Including these would cloud the overview, drowning it in the complexity of all the consequences of the model.

The following sections generally describe a part of the reasoning involved with such models, introducing the use of qualitative differential equations to represent them. These allow for systematic and computational exploration of their consequences and have the potential to aid with both the understanding and the testing of the models, but also to explore them for new drug lead suggestions. But first we will look at the kind of reasoning that is involved.

3.3 Explanation

In the literature on scientific discovery, a lot of attention is paid to understanding and explicating the process of explaining surprising or anomalous observations. The generation of potential explanations is often dubbed *abduction* after the work of C. S. Peirce, whereas their evaluation is known as *inference to the best explanation*. The starting point in those analyses is in most cases a new phenomenon or observation that comes as a surprise, because it cannot be explained by current knowledge, or because a contradictory outcome was predicted. From then on, new explanations are sought, evaluated, and incorporated in the known theories and background (Th. Kuipers, 1999). How an anomalous or surprising observation comes about is often the result of casual observation, serendipity, or devised laboratory experiments that aim to test explanations on their correctness.

In pharmacology, the research aims have a strong pragmatic component. The goal in rational drug design research is to understand a particular biological structure or mechanism and to use this knowledge to devise chemicals to influence it. A research problem aiming at a new drug treatment for a particular disease starts with phenomena or symptoms that do occur but that we do not want to happen, or with properties or symptoms that do not occur, but that we *do* want to see. Now the goal is to find a drug inducible condition that causes the wanted properties to occur and the unwanted

symptoms to disappear. Superficially this reasoning task does not differ in structure from abduction and inference to the best explanation. Only the status of the initial condition and the observation is different. In the explanation task, the observation to be explained occurs, needing an as yet unknown initial condition or theory to explain it. In the other case, the wanted property does not occur, needing an as yet absent initial condition that can cause it to occur.

The search involved is structurally similar to that of abduction and inference to the best explanation, but it has a different goal. Instead of finding a simple explanation of an observed effect, the task is to infer a simple (drug) intervention that causes a desired effect. So we could call this reasoning task: *inference to the best intervention*. Note that this task differs from diagnostic reasoning. Inferring what causes a disease symptom is not the same as to infer how to remedy it. That may often be as simple as removing the found cause, *e.g.* by killing a germ. But, as the case of Parkinson's disease shows, that is not always possible.

3.4 Prediction

To understand inference to the best intervention based on the schematic diagrams about the dynamics of the brain we employ the formalisms of qualitative reasoning to deduce predictions from those diagrams (*cf.* B. Kuipers, 1994). In qualitative reasoning research, the structure of a dynamical system is described by a qualitative differential equation (QDE), that defines the relations between the variables of the system. The exact nature of a relation may not be known, as is the case in many investigated relations in the model in Figure 3.1. Yet it may be known what the *sign* of the relation is. It may be known that a function describing the relation between two or more variables, that change in time, belongs to the class of monotonically increasing (M^+), or decreasing (M^-) functions.

Furthermore, any variable can be ascribed a qualitative landmark value such as *high*, *low*, or *normal*, and a direction of change over time: *increasing*, *steady*, or *decreasing*. Several variables can influence one other variables such that the differentials of all variables together determine the resulting value. There is a calculus defined to determine these values. For example, if the value of variable p_1 is a differential function over time of p_2 plus p_3 and the function belongs to the class of monotonically increasing functions, then the value of p_1 will increase if both p_2 and p_3 increase, but remains unknown if p_2 increases and p_3 decreases. The lack of knowledge in the last case is a necessary consequence of the qualitative and incomplete character of a QDE.

A qualitative state of a system described by a QDE is an attribution of variable values to all variables of the system, consistent with the constraints in the QDE. Given a QDE and a set of known initial variable values, a set of all consistent system states can be deduced, together with their possible transitions. When a calculated value is unknown, all possible states are included in the set. This set is complete, but is proved to be not always correct since spurious states may be included as well.

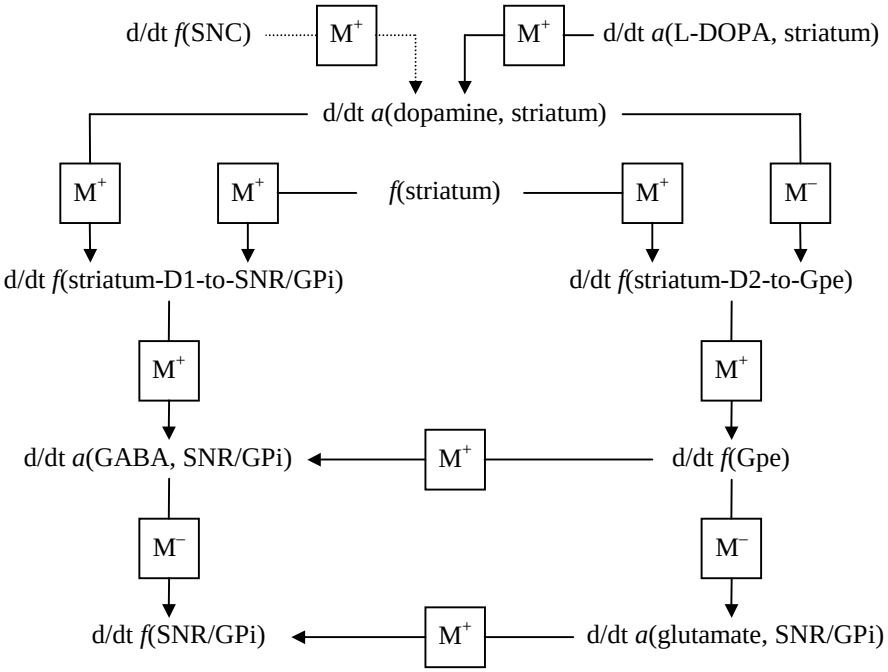

Figure 3.2: QDE fragment of the basal ganglia

Figure 3.2 displays a QDE fragment including a part of the basal ganglia model in Figure 1, and the metabolism of dopamine. It relates variables such as the firing rate (*f*) of nuclei and neural pathways, and amounts (*a*) of neurotransmitters in nuclei. For example, the increase of the firing rate of the SNC causes an increase in the amount of dopamine in the striatum, while this latter increase causes a decrease in activation of the neural pathway that signals to the GPe, etc.

3.5 Intervention

In medical practice, a disease is characterized by a profile, which is a set of characteristics with certain qualitative values. Given a profile, it is a goal in neuropharmacology to discover a drug lead, which is a set of wished-for functional drug characteristics (Vos, 1991). This search can be based on qualitative knowledge if the profiles include comparative values of variables of a normal and a pathological state of a system. This is the case when values of variables are known to be higher or lower in a pathological condition, compared to controls.

The search goal is to find those variables by which one can intervene in the profile in such a way that the pathological values of the variables associated with a disease are reversed. The goal set is defined to consist of the variables of the disease profile with an inverted direction of change, *i.e.* if a variable value is lower in the pathological profile, it is included in the goal to increase that variable value. We can now define the ideal goal of this search task: find a minimal set of variables such that a manipulation of the variable values propagates a change in direction of the values of the variables in the goal set.

However, there may not exist a set of variable influences that causes all desired changes of values of the goal set. So we have to moderate our goal to find that set of variables for which an influence causes the largest number of desired goal variable values, while minimally affecting the other variables of the system. This intuition can be explicated by an approximation criterion analogous to a criterion used in explicating design research and truth-approximation, (T. Kuipers, 1999; Van den Bosch, 1997, 1998, see part III).

The defined task can now be carried out as a search in a solution space of conceptually possible interventions. We start with a QDE model and known initial values of its variables. A goal of desired variable values is set. Reasoning backward from the goal values one can explore possible manipulations of the variables. The approximation criterion is used to measure the difference between the goal values and the values caused by a particular manipulation, implementing a means-end analysis.

In Parkinson's disease, the goal set includes a lower activation frequency of the SNR/GPi than in the pathological case, *cf.* Figure 3.1. A search through possible manipulations will not only find an increase of the amount of L-dopa in the striatum. It will also find that a decrease of the firing rate of the indirect pathway between the striatum and the GPe results in a decrease of the firing rate of the SNR/GPi. Administering a selective D2 agonist can cause such a decrease, with a lesser effect on other dopaminergic pathways than dopamine.

This reconstruction tells us nothing new about what to do about Parkinson's disease. Yet by making the knowledge and reasoning explicit (by describing it formally) it is possible to increase the complexity of the basal ganglia model without rendering such a model useless in the manner that was argued in the movement disorder literature. Via a computer program as a modeling tool it is still possible to keep track of, and further investigate, all the consequences of such a model.

However, because of the incompleteness of the data, numerous and possibly spurious suggestions will be made. So, drug lead suggestions can best be seen as proposals for experiments. A manipulation derived from current knowledge is an excellent basis for a new experiment design serving both a practical and epistemic goal: testing a manipulation for its therapeutic appropriateness and testing the models used to derive the manipulation for their correctness.

If a large enough domain of data is included, it also has the benefit of connecting results, in the way the ARROWSMITH program does, based on text analysis of titles in the MEDLINE-abstract database (Swanson and Smalheiser, 1997). ARROWSMITH discovers the missing link between literature that describes relations between subjects, compounds or functions A and B and literature that did the same for B and C, but in ignorance of each other. In this way the relation between magnesium deficiency and migraine was discovered, via eleven intermediate effects linking them together. In principle, inference to the best intervention can do the same, given qualitative models of results in MEDLINE. Initiatives to collect results in biology in qualitative formalisms on a grand scale are already undertaken; see, for instance, the EcoCyc and MetaCyc projects on the web by Karp and Riley (1993).

3.6 Conclusion

The rational use of neurophysiological models can be modeled as goal directed reasoning about qualitative differential equations. Applying effective search techniques to such models could potentially aid drug lead discovery for complex biological systems with a large set of variables and constraints. However, this is a claim only warranted by theoretical considerations. Whether novel results can thus be produced still has to be seen, because there are problems as well. When a large-scale QDE model is compiled it can be severely inconsistent because the empirical results are not always mutually consistent. Yet by using the best intervention suggestions to devise new experiments, qualitative reasoning about neurophysiological models as part of a computer supported discovery system could still aid in using, understanding and testing models about larger biological systems.

This also concludes the introduction part of this thesis. Part II will go further into rationality in discovery in more detail, while Part III will, in detail, further address discovery in neuropharmacology.

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