Reduction in the Biomedical Sciences

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Abstract: This chapter discusses several kinds of reduction that are often found in the biomedical sciences, in contrast to reduction in fields such as physics. This includes reduction as a methodological assumption for how to investigate phenomena like complex diseases, and reduction as a conceptual tool for relating distinct models of the same phenomenon. The case of Parkinson's disease illustrates a wide variety of ways in which reductionism is an important tool in medicine.

1. Introduction

Reductionism has a long history in philosophical and scientific thought, and is an intuitively appealing view about how the world works. It its simplest form, reduction involves taking something larger, more complex, or more specific, and 'reducing' it to smaller, simpler, or more universal components. Reduction can be understood as a relationship between parts of the world, in which case it involves the view that larger objects, like physical bodies that we can see and hold, just are lots of very small bodies like atoms and molecules, organized by similarly microscopic forces. Reductionism can

also be understood as a relationship between theoretical structures like theories, laws, or models. In that context, reductionism involves commitment to the goal of taking multiple distinct and possibly conflicting models of one phenomenon and reducing those to a single, overarching or unifying model of that phenomenon.

In a medical context, reduction often takes three forms. One is the reduction of a system to its component parts and their organization. A second is reduction from a set of models to a single model that incorporates or unifies them. A third form of reduction involves a simplification in the overall complexity required to explain a particular disease, for example, by 'reducing' it to a few primary causal factors with a simplified causal path along which it unfolds and into which interventions can be attempted to alleviate or prevent the disease. Reduction understood as simplification of complexity is an especially useful tool in biology, medicine, and related sciences that study target systems that are characteristically complex.

Reduction is a process of moving 'downward', to less complexity, smaller sizes, and fewer models. It has a converse process, that of integration, which involves moving 'upward', to complex interacting causal structure, to larger size scales or higher levels, and to navigation among multiple overlapping models. Like integration and differentiation in calculus, these directions in which one can move are not in competition – they each have a use and must often be deployed together in the overall process of solving a problem (Mitchell 2002).

Reduction is a useful tool both conceptually and methodologically. Methodologically, it is often helpful to think of a disease in terms of a series of smaller, less complex, interlocked submechanisms, each of which could potentially be intervened on independently. Many diseases stem from dysfunctions at subcellular levels, yet have wide-ranging symptom effects at a variety of size scales in the body. Reduction as a guiding methodological assumption can assist researchers in isolating the earliest causal stages of such diseases, and in isolating the main drivers of a disease in a population where there may be a huge variety of causes, but a few causes or causal pathways that are common to most cases. Reduction is also methodologically useful for guiding interventions: targeting dysfunction earlier in a causal chain of cascading problems is, when possible, optimal for preventing or treating disease. Smaller size scales also tend to

be (although do note, they are not always) easier to intervene on than are later stages that are higher level or more complicated in terms of how far-reaching the effects become.

Conceptually, reduction can assist us in understanding how different models of the same or closely related phenomena relate to one another, so that we can use these distinct models under appropriate circumstances. Different methods of studying something like protein folding may yield very different models of a target phenomenon like a quaternary protein structure. The differences in the models reflect differences in the kinds of environments in which each method studies the same proteins, and in the ways those environments distort the target to be studied (Mitchell and Gronenborn forthcoming). The structure might be studied using X-ray crystallography, ab initio predictions based on amino acid sequence, or nuclear magnetic resonance spectroscopy. Even though it is the 'same' protein studied each way, each method produces different models without being false, since model differences reflect differences in how the experimental method and environment affects the protein being studied. Understanding how different research methods shape the models those methods can produce of their target systems may help us reduce those different models into one overarching or unified model of the target phenomenon. Or, reduction may turn out to not be possible, and instead of reduction, integration of the models is required, to guide researchers in knowing which model(s) to deploy under a variety of circumstances. It can still be conceptually fruitful to pursue reduction until we are clear on the details of why reduction fails.

Biomedical sciences are arguably the setting in which we can find the most striking gaps between what we can call the locus of explanation and the locus of control. The locus of explanation is the mechanism or mechanisms, at their characteristic size scale, that are primarily responsible for a given effect. In the case of a mis-folded protein, the characteristic mechanisms will involve subcellular machinery, the chemical environment, the base pairs in the protein, and more. These are all at a characteristic and similar size scale, yet the effects of mis-folding might cascade up the size scale to produce symptoms at a variety of physical size levels. The locus at which we identify the primary source or origin of a particular causal chain or disease is the locus of explanation for it. This might differ, sometimes dramatically, from the loci available for interventions

to prevent or alleviate the disease. The locus of intervention is the mechanism or mechanisms on which we actually intervene in clinical practice. This is constrained by a host of factors beyond the locus of explanation. We might simply not have developed any intervention that could target the locus of explanation; it might not be feasible for logistical or ethical reasons. Instead, knowledge gained through reduction downwards and integration upwards might yield a different target for intervention, a locus for control that is not the main causal driver but nevertheless is pragmatically accessible to us.

The way in which reduction figures in characteristically medical examples will be illustrated by considering Parkinson's disease. This disease is now known to have several variants. One variant is monogenic; another involves the interaction of several genes. One is environmental, involving exposure to known toxins. And one involves the combination of multiple genes that render a patient more susceptible, coupled with subsequent exposure to environmental toxins. Originally defined as an idiopathic disease, with no known origin, researchers have used reductionist methodological tools and conceptual frameworks to isolate the genes and environmental factors that drive this disease, and to work towards unification of the various causal etiologies into a common pathway by which to identify and distinguish Parkinson's from other diseases. This yields a variety of potential targets for intervention. A locus of control might involve eliminating use of the pesticides known to trigger it; another locus might involve targeting pharmaceutical interventions that prevent or slow genetically triggered deterioration; or a locus might focus on lessening symptoms directly.

Parkinson's helps illustrate the power of reduction as a guiding assumption, and the ways in which reduction can fail in the face of certain kinds of complexities. Ultimately, the success or failure of reduction in the biomedical sciences depends on the particular phenomenon in question. Some causal structures yield great insights when reduction is applied as a methodological and conceptual tool; some causal structures, because of details related to their internal complexity and the difficulty in controlling messy complexity in experimental settings, resist reduction indefinitely.

2. Reduction: Sweeping Physics and Creeping Biomedicine

Physics is a field where reductionism has a long history of leading to useful scientific breakthroughs, and for which most accounts of reduction were originally developed. Many, or arguably all, accounts of reductionism that were developed to apply in physics foundered when they were applied to other sciences such as biology and medicine. The systems being studied in physics versus the biomedical sciences differ in so many relevant ways, and the tools available to study them differ so dramatically, that it is illuminating to first see what reductionism looks like in fields such as physics, and then see how this picture gets complicated in the case of the biomedical sciences.

The most traditional account of reduction can be seen in Oppenheim and Putnam's classic paper, "The Unity of Science as a Working Hypothesis" (1958). They present reduction as key to the unification of different areas of science. The world is divided up into levels of physical size and organization, each of which is associated with a characteristic field of study. Physics is the most fundamental. The next, chemistry, is taken to be nothing more than complicated physics that could in principle be eliminated with sufficient knowledge of the relevant physics. Biology is above and reduces to chemistry, and psychology to biology. This hierarchy embeds strong commitments about the 'real' objects and the most fundamental fields of study. Molecules just are compounded particles; organisms just are complicated arrangements of chemicals, and so on. Following on these levels relationships in the world, the theories of chemistry should be reducible to the theories of physics, and those of biology to chemistry, etc.

On this way of thinking, reduction is the path by which to unify the disparate sciences together. Oppenheim and Putnam take the unity of science to be, first, an ideal future state of science, in which the vocabulary used in one science can be fully translated into the vocabulary of another. The concept of a genetic disease, for instance, would be entirely translatable into chemical terminology, and then into the terminology of particle physics. Oppenheim and Putnam take the unity of science to be, second, a trend in science, such that unification of apparently disparate phenomena is an ongoing process, and we can continue to unify even if we never reach the ideal end state of total unity. In that regard, reduction as traditionally conceived is somewhat closer to what can be found in medicine in terms of unification of distinct models at distinct levels into a more

comprehensive view of the whole, but without the end goal of a single, molecule by molecule and moment by moment map of everything in the body.

There are some systems studied by physics that undermine such strong reduction. For instance, in phase transitions for gasses, there are behaviors that are almost completely independent of the microphysical details of the system in question. That would mean that reduction of such systems would yield less rather than more explanation of the target phenomenon (Batterman 2000). Nevertheless, there is a strong tendency towards successful breakthroughs following the method of reducing complex systems to smaller and simpler parts that are studied separately and then re-assembled, and a track record of making new discoveries by connecting via attempted but failed reduction the theories for higher-level behaviors such as boxes of gas to theories for lower-level behaviors such as energy and momentum of atoms.

Such reductions in physics are examples of what Schaffner (2006, 2011) has called "sweeping reductions." They take a broad swath of phenomena and demonstrate how they are completely explainable with reference to their smaller scale components, or as specific instances of a more universal phenomenon. Sweeping reductionism is strong: it commits to the idea that, ontologically, there *is* nothing at the higher levels in a metaphysically strong sense. That which is reduced is thereby ontologically dependent on or secondary to that by which it is reduced.

Schaffner contrasts this with "creeping reductions," which are small reductions between specific phenomena at different levels, such that the higher level is not eliminated but rather connected in an explanatory way to the lower level. Creeping reductions lack the synoptic scope and grand unificatory power of sweeping reductions. These are much less dramatic, as least from a philosopher's perspective, than a sweeping reduction. As rare as sweeping reductions are in physics, they are completely absent from fields like medicine, where creeping reductions are considered successes.

Creeping reductions are not thereby less valuable or easy to achieve in biology and related sciences. Schaffner notes that creeping reductions "…are fragmentary patchy explanations, and though patchy and fragmentary, they are *very important*, potentially Nobel-prize winning advances" (2011, 139). The systems studied in physics lend themselves to decomposition as a technique for study. The systems in biology and

medicine, on the other hand, cannot be so simply decomposed while still retaining the features that make them of interest to us. Reducing a sample organism to component atomic elements might be possible, certainly, but sorting an organism into piles of atomic elements is not a way to figure out what the organism is like when it is intact, what it can do in various environments, and how to intervene on it in medically illuminating ways. Creeping reductions accomplish important explanatory work that lack the universal character of sweeping reductions but which nevertheless yield incredibly useful information when they are found.

Levels and mechanisms are a useful way of understanding the compositional and organizational structure of systems, especially in biology, medicine, and related fields. There are many, many ways to individuate levels in organisms, including humans, but there are some that tend to be robust across populations and across species. Cells are often a useful level on which to focus. Picking out the cell level can be thought of as analogous to focusing a mental microscope at that magnification, or zooming in to a map to the street level but not the house by house or city by city level. Certain kinds of physical processes, recognizable types of entities (including non-cellular ones), identifiable patterns of activity, and common temporal scales, can be characterized at the cellular level. Moving 'downward', or zooming in on the map, subcellular machinery pops into focus, with a somewhat different set of characteristic processes, on a slightly different time scale, that together constitute the cell at the next level up. Further down we find the genetic level with complex molecular biology, where macromolecules with potentially incredibly complex physical organizations and time scales play key roles. These, taken together in their totality of interactions, constitute the subcellular machinery of another level up.

Going in the other direction from cells, tissues are a frequently used individuation of levels in the human body. Tissues involve cells as components, but not in the simplistic way that a house made of blocks involves those blocks as small pieces. To count as a tissue, there have to be special kinds of interactions between the cells, and similarities in terms of their type, or common function, or some other parameter. There are many important mechanisms, and many medical issues, that can be best described in terms of tissues. Further up, organs are another common level at which to find a

distinctive set of processes, entities, activities, and time scales. Systems, such as the endocrine system or the nervous system, are arguably the highest sub-organism level.

Zooming yet further out, though, the human body can also be understood as one distinctive entity, engaging in certain kinds of processes and activities at characteristic time scales. The social environment of a person may be invoked to explain certain kinds of anxiety or stress reactions, and it might be at the larger social or physical environment levels to which more effective interventions might be targeted.

Mechanisms offer another way to keep track of reduction between levels. Mechanisms are causal chains of entities and activities that are connected in such a way that, once triggered, they proceed reliably enough through the causal pathway to a termination state, which may involve a cycle that is maintained (where the termination state is the triggering conditions again for the same mechanism) (Andersen 2014 a and b). Mechanisms involve some degree of regularity, in that the same causal pathways retain their stability so that they perform similarly over time and in different instances. (Andersen 2012a). For instance, the transcription of DNA by RNA to form various proteins involves mechanisms that work consistently, and about which we can make stable generalizations that might not satisfy a strong reductionist but which do provide weakly reductive characterizations of the relevant upper level phenomena. Mechanisms in medicine are often ones that involve hidden causal relationships, however, to maintain certain kinds of stable parameters in the body (Andersen 2012b). This makes mechanisms a difficult way to construe reduction in medicine, by providing less experimental guidance for effective intervention even when reduction is in principle possible.

As this discussion illustrates, there are some robust ways to individuate levels in the human body. However, there need not be any 'one right set' of levels by which to break down such a complex system. Some mechanisms might cross levels, some phenomena might involves cascades upwards from the molecular level to effects that are macroscopic and phenotypical in size scale. Some phenomena, such as the folding of complex protein structures, might sit awkwardly between the molecular and subcellular levels, and a different way of individuating levels would be required when researching those phenomena. There is no single level individuation built into the world itself; such divisions always involve an element of pragmatic interest and attention on our part as

researchers, clinicians, and patients. Levels should instead be thought of as handy divisions in order to keep track of where the action is, so to speak.

Reduction in the biomedical sciences is thus unique compared to sciences like physics in terms of the complexity of systems to which reduction is applied, the extent to which it is illuminating to reduce systems to component parts, and the extent of the resulting unification from successful reductions – sweeping in physics, creeping in biomedicine.

3. Reduction as a methodological approach in biomedicine

There are many ways in which reduction can manifest in the collection of sciences that are grouped under the heading biomedicine. These sciences share a focus on the human body, at all relevant levels from the subcellular through to the social/environmental, from earliest development through old age. Informally, this goal of understanding is oriented towards *explanation*, in terms of explaining how things work when they work well and what goes wrong when things go wrong; and towards *intervention*, in terms of finding ways to keep things working normally and to restore as much normal function as possible when they are not.

Linus Pauling used the notion of a "molecular disease" to show how mutation involved in the gene for one protein was sufficient to explain sickle cell anemia. This involved a conceptual orientation, namely, commitment to the idea that there was a single or very few primary causal drivers of the disease to which other complexities in the manifestation of the symptoms could be reduced. It also involved a methodological orientation, namely, commitment to such a causal driver being at the molecular level, rather than at a higher level of organization. "Thus, a single molecular change is fundamental to understanding the patient's pathology, symptoms, and prognosis" (Kandel et al 2000, 867). This encapsulates the potential for reduction in the biomedical sciences – when it works, it works well.

Being able to successfully take a disease as complex as sickle cell anemia or Parkinson's and reduce it to a single genetic error that cascades through various systems, even if that reduction holds for only a proper subset of cases, illustrates that reduction can be a powerful tool for research and explanation in medicine. It cannot be the only tool in

the toolkit, since there will be diseases or dysfunctions that may be only partially reducible, or for which only some cases are reducible. But it is a good working assumption, as Oppenheim and Putnam put it, in tackling a problem with an unknown etiology, to look for ways to reduce it to a few or even a single causal driver at a molecular level.

Consider the case of Parkinson's disease. Parkinson's is a disorder affecting the nervous system, resulting in characteristic tremors and slowed and difficult movements. In the monogenic variant, a single allele results in a mis-folded version of a key protein in the brain, alpha-synuclein. The triggering condition is the genetic component, which leads to a mis-shaped protein that then clumps in characteristic ways to form Lewy bodies that accumulate, especially in the substantia nigra. This part of the mid-brain in involved in, for instance, controlling movements, and the accumulation of Lewy bodies inside of the nerve cells in this area lead to the characteristic tremors and other issues with motor control seen at the human level in Parkinson's patients.

The mechanisms by which Parkinson's affects those with the disease involve small molecular changes that cascade up through different level boundaries, per Pauling's description. This holds even though distinct factors such as single genes, gene combinations, and environmental factors can be involved in the onset of Parkinson's. In monogenic cases, though, Parkinson's disease is like sickle cell anemia, in that it is the result of a very localized genetic mutation.

Thus, considering the monogenic case, there are several senses of reduction by which a complex, multi-level phenomenon like Parkinson's might be reduced. The mechanisms involved may be at a lower level of organization than that of downstream causal effects. The locus of causal explanation of the dysfunction might be at a very small size scale, such a subcellular level, rather than at a higher level such as organs. And there may be a great deal of complexity and noise in the patient population, such that it is very difficult to discern for many patients what caused the onset of the disease, that can be reduced away by identifying a clear genetic component for some variants. There is thus no single way but rather a nexus of ways in which research has reduced Parkinson's: causal complexity must be reduced to a few initial transcription errors; mechanisms for control of movement at the mid-brain level are reduced to mechanisms at the subcellular

level; and physical size scale is reduced further along the chain, from organism-level symptoms to mid-brain structures like the substantia nigra to protein aggregates inside nerve cells to allele-sized triggering conditions. Nevertheless, this nexus of ways all point 'downward' in a reductive fashion, such that the locus of explanation for Parkinson's is illuminated by reduction, and options for targeting interventions appear because of the reduction.

There are several examples here of a creeping reduction in Schaffner's sense, a patchy and fragmentary connection between partial explanations. This is highlighted by the fact that this explanation as given only applies to the rare monogenic case; additional factors must be introduced for multi-genic cases, and yet more for the environmental cases. Nevertheless, a key insight into Parkinson's came out of the methodological constraints imposed by the reductive assumption that it might be a molecular disease, in Pauling's term, by which possible avenues for intervention were revealed.

4. A conceptual guide to navigating a plurality of models

In its traditional understanding from physics, reduction ultimately involves relationships between theories, laws, models, or other representational content being reduced via translation into the terminology of another theory. By extension to medicine, if Parkinson's involves genetic causes, then on this understanding of reduction as a relationship between theoretical structures like models, we should be able to assemble a single overarching or unified model from the concatenated models of various stages of the diseases, of the distorted protein shape through to how this protein clumps into Lewy bodies, through how these accumulate in the substantia nigra cells, through to the disruption on motor control that is a consequence. This is something of an ideal, like the perfectly unified science that Oppenheim and Putnam envisioned, that we may never reach, but towards which researchers do often aim.

There are reasons to think we may never be able to reach such a unification of all the different stages of such a complex mechanism as that involved in the cascading effects of the monogenic variant of Parkinson's. Mitchell and Gronenborn (2015) show how different techniques for modeling the quaternary structure of a protein result in differences in the modeled shape. These different shapes can be incorporated into a

fusion model that uses them to triangulate somewhat on the actual shape of the protein. But a reduction in this case would involve being able to eliminate the prior models, either because they are redundant given the new one, or because one is found to be more accurate than the other. In the case of protein folding, it would be a mistake to say that one model is more accurate than another: they are different, because they are generated using different techniques that place the protein in different environments and systematically deform it in different ways. These techniques for modeling the same quaternary protein structure have, in an important sense, different objects that they model.

Such protein modeling techniques are involved in studying the protein structures that go awry in genetic variants of Parkinson's (both monogenic and those involving multiple genes). Yet in the simplest case, we should not expect a reduction in models in the sense of ending up with fewer of them, but rather an integration of models that must be retained in a pluralistic way. Even the simplest monogenic case appears to resist model-reduction to a single overarching and exhaustive representation of the mechanisms by which symptoms are produced. Instead of aiming for an idealized but probably unreachable unification via reduction of the models, we can look for ways to integrate without reducing. This means finding techniques for navigating the pluralism of models with knowledge about how each model was produced that can inform when we should rely on model or another model based on our pragmatic interests in using it.

Parkinson's disease has yet more complexity in this regard as well, because there are variants that involve environmental components. There are other ways to construe how Parkinson's can involve a reduction in causal complexity that does not require idealized model simplification. There are distinct causal mechanisms that lead to four variants of Parkinson's: the monogenic variant, as we saw; a multi-gene variant; an environmentally caused variant; and a variant involving both genetic susceptibility and environmental causes. Thus, in the general population of patients with Parkinson's, there are multiple causal etiologies for patients with Parkinson's, at different size scales. Furthermore, some patients may individually have a variety of causal factors involved in their case of Parkinson's, such as the interaction between several gene sites that contribute to susceptibility, and environmental factors that trigger Parkinson's in the

presence of that genetic susceptibility. Modeling the variants of Parkinson's will thus require the integration of multiple models that may each involve multiple levels of organization. For the variant involving both environmental exposure combined with genetic susceptibility, these models cannot be reduced in the sense of being combined into one overarching model. Rather, they must be integrated so that researchers can navigate the complex causal pathways at each characteristic level of organization and those that cascade up or down levels as well.

Even in the case of Parkinson's with multiple sites for genetic susceptibility in combination with environmental exposure, though, there can be other goals served by intertheoretic or inter-model reduction. For a single patient with a causally complex etiology for Parkinson's, reduction can highlight a few key causal drivers, and leave out those that are not the primary causal factors. Even though some of the key causal factors are not available as loci for control (the exposure to chemicals has already occurred for a given individual, for instance), reducing the number of causal factors under consideration in the models to just a few key drivers still may be illuminating as loci of explanation. Parkinson's disease is an excellent example of a complex disease where several different kinds of reductions have yielded insight into variation across patient populations and in variation across the etiological factors for individual patients.

5. Conclusion

Reduction is a powerful tool for investigating phenomena in the biomedical sciences. It can guide methodological inquiry in useful ways, and provide conceptual frameworks that bring clarity to complexity and enable researchers, clinicians, and others to navigate among relevant models and to test and implement various intervention strategies. Reduction can involve 'zooming in', to smaller size scales or levels of organization. It can involve the reduction of many models to one inclusive model for a phenomenon. And, it can involve a reduction in the degree of complexity required to explain or control. Cases like Parkinson's show how many different kinds of reduction applied to the same phenomenon can nevertheless robustly point in the same direction.

Reduction cannot serve alone as such a tool, however, in the biomedical sciences. In physics, the integration of components back into a cohesive system is vastly simpler

than it is in biological systems. Here, reduction needs to be paired with integration as a strategy to focus in on the right level: one zooms in and the other zooms out, and with both tools the right level at which to describe and explain, as well as to control and intervene, can be found. Reduction can also yield explanations that are not themselves suitable as direct targets for interventions. But finding the locus on explanation via reduction opens up downstream pathways that might serve as useful loci of control for preventing or alleviating symptoms.

Recommendations for further reading:

Brigandt, Ingo and Love, Alan, "Reductionism in Biology", *The Stanford Encyclopedia of Philosophy* (Winter 2014 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/win2014/entries/reduction-biology/>. (An excellent overview of issues particular to reduction in biology)

Schaffner, K. F. (2011). Reduction in Biology and Medicine. *Philosophy of Medicine*, *16*, 137. (An extended look at the creeping versus sweeping distinction)

Oppenheim, P., & Putnam, H. (1958). Unity of science as a working hypothesis. In Herbert Feigl, Michael Scriven & Grover Maxwell (eds.). University of Minnesota Press (3), 3-36. (A classic text for discussions of reduction)

Waters, Ken, "Molecular Genetics", *The Stanford Encyclopedia of Philosophy* (Fall 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2013/entries/molecular-genetics/>. (A detailed look at reduction and anti-reduction as it relates to molecular genetics)

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