Reductionism and Proxy Failure:
From Neuroscience to Target-Based Drug Discovery

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Abstract:

Reductionist methodologies reduce phenomena to some of their lower-level components. Researchers gradually shift their focus away from observing the actual object of study toward investigating and optimizing such lower-level proxies. Following reductionism, these proxies progressively diverge further from the original object of study. We vividly illustrate this in the evolution of target-based drug discovery from rational and phenotypic drug discovery.

Main Text:

We want to add reductionist methodologies to John et al.'s valuable list of the various contexts where proxy failure can be observed. Reductionist methodologies primarily focus on a lower-level component of their phenomena of interest with this presumption that understanding or manipulating that component is sufficient for understanding or manipulating their phenomenon of interest. In other words, they presume that their phenomenon of interest can be reduced to some of its lower-level components. We believe that extending the conceptualization of John et al. to reductionist methodologies and using the insights it might offer can be of great value since currently, despite considerable criticism, reductionism dominates diverse scientific fields; from psychology and neuroscience to biomedical sciences and drug discovery.

To align these methodologies with the conceptualization and terminology of John et al., researchers can be considered *regulators*, with the *goal* of understanding or manipulating some complex phenomenon manifested by their objects of study (*agent*). These objects of study "possess multiple ways of producing or expressing a proxy, which can be influenced by feedback from the regulator." Finally, the *proxy* is a lower-level component of the phenomenon under study that the researchers prioritize. The "pressure which tends to make the proxy a worse approximation of the goal" has been provided and amplified by the deep-seated reductionist mindset of the scientific community and the incessant technological progress that has enabled the dissection and reduction of many phenomena to their lower levels.

Consider the example of target-based drug discovery which has been the dominant paradigm of drug discovery for about four decades. While the *goal* of researchers in the field of drug discovery (*regulators*) is to discover molecules that can suitably alter the phenotypes of humans, based on reductionist target-based drug discovery, the lower-level *proxy* of binding affinity to a target protein is prioritized. Instead of selecting and optimizing molecules based on their effects on phenotypes, candidate molecules are primarily selected and optimized based on their binding affinity to a target protein whose manipulation is supposed to counteract the disorder; for example, candidate antipsychotics are selected and optimized based on their binding affinity to specific dopamine receptors. This selection and optimization is the *regulatory feedback* mentioned by John et al where the agents are selected based on the proxy and "which induces optimization of the proxy."

For years, binding affinity to a target has been criticized as an overly simplistic proxy (Horrobin, 2003). Our recent analysis of the real-world efficiency of target-based drug discovery further substantiates these criticisms and reveals, based on significant evidence, the failure of this proxy (Sadri, 2023). The data reveals that, despite decades of utter dominance, only 9.4% of small-molecule approved drugs have originated from target-based drug discovery.

Moreover, the analysis demonstrates that even this minor portion cannot be entirely attributed to target-based drug discovery, as their therapeutic effects are mediated by numerous mechanisms that are independent of the targets they have been discovered for (Sadri, 2023). This aligns perfectly with one of the factors identified by John et al. to drive proxy failure: The human body and the therapeutic effects of molecules are highly complex and there are "numerous proxy-independent actions that lead to the goal."

Another match is between the evolution of drug discovery methodologies and the statement of John et al. that "whenever incentivization or selection is based on an imperfect proxy measure of the underlying goal, a pressure arises which tends to make the proxy a worse approximation of the goal." Target-based drug discovery was born out of rational drug discovery (Al-Ali, 2016; Sadri, 2023). Rational drug discovery

used the available scientific knowledge, from molecular biology and physiology to pathology and pharmacology, to guide and focus the random screening of substances. This approach was immensely successful and culminated in the discovery of tens of approved drugs and Nobel Prizes for several of its pioneers: Paul Ehrlich, Gertrude Elion, George Hitchings, and James Black. Assessing the activity of molecules at the protein level and their binding affinity toward specific proteins was an important proxy and source of information in rational drug discovery; however, in the end, it relied on phenotypic observations for selecting and optimizing molecules. This is evident in the discoveries of the abovementioned pioneers and many other examples (Sadri, 2023). Gradually, the proxy of binding affinity to targets got excessively prioritized to the point that it even replaced the use of phenotypic observations in selecting and optimizing molecules.

Similar cases of proxy failure can be recognized in other reductionist methodologies across different fields. For example, in neuroscience, while the *goal* is to understand the behaviors of organisms (*agents*), researchers (*regulators*) excessively prioritize various *proxies* and observations at lower levels like neurons and neural circuits (Frangou, 2020; Gazzaniga, 2010; Krakauer et al., 2017; Parker, 2022; Uttal, 2003). This conceptualization can be extended to the reductionist methodologies that are currently dominant across various fields, including molecular biology (Lazebnik, 2002) and medical sciences (Ahn et al., 2006).

However, it must be noted that although John et al.'s conceptualization perfectly fits the reductionist methodology of target-based drug discovery, extending it to other reductionist methodologies may require a more general account of proxy failure. The challenge is generalizing to these methodologies the key concept of the pressure "which tends to make the proxy a worse approximation of the goal." Alternatively, it can be proposed that another approach toward generalizing the conceptualization of John et al. to reductionist methodologies might mitigate this challenge. For example, reductionism and the reductionist methodologies themselves can be considered as the regulator, the researchers as the agents, investigating the object of study as the goal, and the lower-level observations as the proxies.

Anyhow, we believe that the concept of proxy failure is a valuable asset for recognizing and addressing the limitations of reductionism, which is in absolute reign across diverse fields. Lest these limitations are addressed, huge resources would be expended on research with marginal contact with the real world.

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