Solving Biomedical Challenges with the bigRing Problem-Solving Platform

An example of causal examination of potential mechanisms of metformin's impact on C9orf72-mediated ALS using tools of advanced knowledge management platform

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Technology background - Causal-based approach applied to problem solving in biomedicine

The BIGRING product represents an innovative approach to Amyotrophic Lateral Sclerosis (ALS) research, specifically targeting the mutation in the C9orf72 gene. It surpasses current methodologies by employing a network medicine approach, focusing on causal analysis of well-structured multi-omics data. The product utilizes cutting-edge techniques such as Meta Graphs, Knowledge Graphs, and graph-based analysis, aiming to enhance ALS diagnostics and treatment.

The state-of-the-art methods include leveraging the network medicine approach, integrating multi-omics data, emphasizing causal inference, and utilizing graph-based analysis methods like Directed Acyclic Graphs and Directed Cyclic Graphs. Beyond the state of the art, BIGRING incorporates Meta Graphs, Knowledge Graphs, contrafactual reasoning, community detection, and similarity assessment in causal graphs for a comprehensive understanding of C9orf72 ALS.

The product justifies the use of Meta Graphs and Knowledge Graphs for data integration, directed cyclic graphs for capturing complex dependencies, directed acyclic graphs for causal inference, graph computing for algorithm development, and graph databases for efficient data storage. Metamodeling, data mapping, and data extraction and transformation are highlighted for their roles in creating a unified and structured graph dataset.

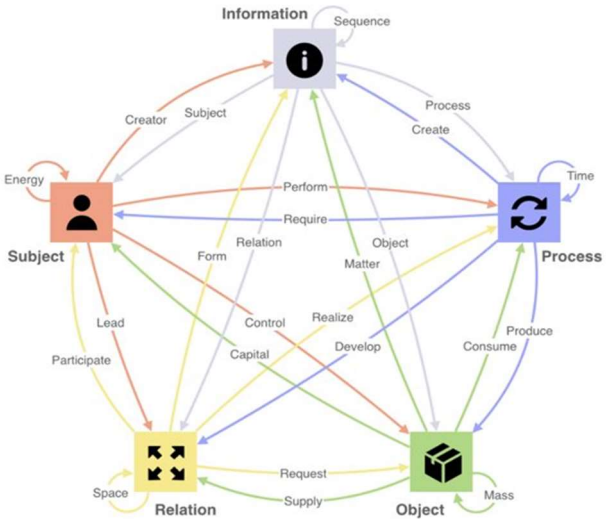
The importance of graphic query languages, pathfinding algorithms, and causal inference methods is emphasized for efficient retrieval of information, uncovering relationships within the dataset, and identifying cause-and-effect relationships. Causal reasoning, root cause analysis, and visualization of causality are deemed integral for drawing conclusions about causality and understanding the complex causal relationships within C9orf72 ALS.

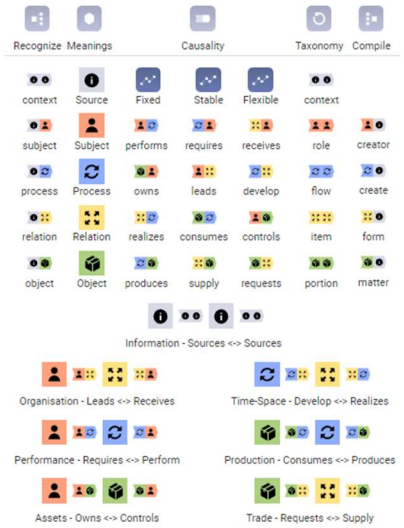
The methods of community detection and centrality and assessing similarities in causal graphs, and contrafactual reasoning are justified for uncovering patterns, identifying key factors, and exploring hypothetical scenarios, respectively. In conclusion, BIGRING's comprehensive and advanced methodologies have the potential to significantly impact ALS research, ushering in a new era of precision medicine.

Data from networks are processed in two consecutive transformations:

A) first transformation is ontological, from a network-based to a causal-based structure. It defines 4 types of nodes and 7 types of edges.

B) the second semantic transformation defines 5 types of meanings of reality-elements, each of which has 5 types of properties and 25 different transits between types of meanings of reality-elements.





The result is creation of a framework for effective problem solving in a low number of finite elements and complexity reduction without losing any meanings, while all aspects of knowledge representation are present, and thus it is ensured that every element of the transformed original network is placed in an ontologically and semantically coordinated model of reality.

1. Introduction to use case study

Amyotrophic lateral sclerosis (ALS), commonly referred to as motor neuron disease, represents a severe neurodegenerative condition characterized by the gradual deterioration of upper motor neurons in the motor cortex and lower motor neurons in the brainstem and spinal cord, leading to the progressive loss of voluntary muscle control. Pathologically, ALS is characterized by the absence of upper and lower motor neuron cell bodies and the degeneration of the corticobulbar/corticospinal tracts as well as the axons of lower motor neurons, resulting in denervation changes within the muscle tissues. The estimated incidence of ALS is approximately 2 cases per 100,000 person-years (Mead et al., 2023). ALS is a complex disease, with most affected individuals influenced by a combination of various genetic and environmental risk factors. Over 30 genes have been identified that either directly contribute to the development of ALS or elevate the risk of its occurrence. In European populations, four genes, C9orf72, SOD1, TARDBP, and FUS, are accountable for the ailment in up to 70% of familial ALS cases.

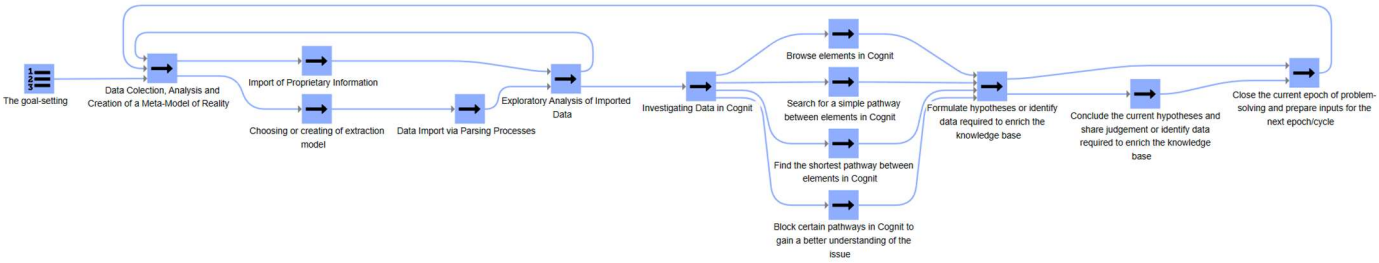
The identified risk genes converge on several key biological pathways including oxidative stress; dysregulation of mitochondrial function, protein homeostasis, RNA processing, axonal transport, and nucleocytoplasmic transport (NCT); neuroinflammation; excitotoxicity; and DNA damage. These pathways should be subjected to rigorous investigation to discover novel targets for therapy (Mead et al., 2023). Metformin, a widely used biguanide drug known for its safety and cost-effectiveness, has been a staple in treating early-stage type 2 diabetes for over six decades due to its remarkable capacity to reduce plasma glucose levels.

Furthermore, its versatile applications have expanded over time, with its use extending to a variety of conditions, including cancer, obesity, liver diseases, cardiovascular diseases, renal diseases, and autoimmune diseases. Metformin's mechanism of action is linked to its inhibition of mitochondrial NADH: ubiquinone oxidoreductase (Complex I), resulting in the activation of AMPK. Complex I plays a crucial role in electron transport, consequently leading to reduced ATP production and increased intracellular ADP and AMP levels. This elevation in AMP levels ultimately triggers AMPK activation, a central regulator of various metabolic pathways encompassing glucose metabolism, lipid metabolism, and energy balance. Metformin exerts different effects through different signaling pathways (Lv & Guo, 2020). The regulation of protein synthesis is critically important for the normal development and function of the brain. Protein synthesis misregulation accompanies and in some cases underlies a diverse set of developmental and neurodegenerative diseases including ALS. For C9orf72 ALS/FTD and other expansion diseases, these mutations result in a variety of downstream consequences, including the expression and accumulation of sense and antisense expansion transcripts.

These RNAs can cause RNA toxicity as well as the sequestration of RNA binding proteins and also serve as templates for the production of toxic proteins expressed from both sense and antisense transcripts. The latter phenomenon results from repeat associated non-AUG translation results in the expression of toxic repetitive RAN proteins in all reading frames without the requirement for AUG or AUG-close cognate codons (Rosbash, 2020). Study Zu et al. showed that, that RAN proteins translation is highly regulated by the double-stranded RNA-dependent protein kinase (PKR), moreover the drug metformin inhibits PKR and reduces the levels of several RAN proteins in mammalian cells. The effect of this drug was tested in vivo by using C9-BAC mice, a C9orf72-based pre-clinical model of ALS. Administration of metformin at the pre-symptomatic stage resulted in lowered RAN proteins aggregates and p-PKR levels. Treatment of C9-BAC mice with the drug up until the advanced stage led to substantially reduced astrogliosis in the motor cortex, decreased motor neuron degeneration in the spinal cord, and improved locomotive and behavioral parameters, compared to non-treated animals (Zu et al., 2020).

Building on the established pathways influenced by metformin and the disrupted pathways in Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disease, our introductory section initiated the use case study of the bigRing tool to explore new connections between metformin and ALS. This initiative, conducted not by a scientific research organization but as a practical demonstration, leveraged the KEGG database, a repository of known cellular pathways, including those involving metformin. Crucially, bigRing's capacity extends beyond the KEGG database, allowing for the modeling and analysis of yet-to-be-added data, which can be imported by researchers or medical professionals as needed. This approach facilitated the prediction of metformin's effects based on its interactions with the causal factors in ALS pathogenesis. Our study, therefore, serves to demonstrate bigRing's effectiveness in efficiently addressing complex biomedical topics, focusing on practical applications rather than direct contributions to scientific research.

2. Our workflow for solving biomedical problems



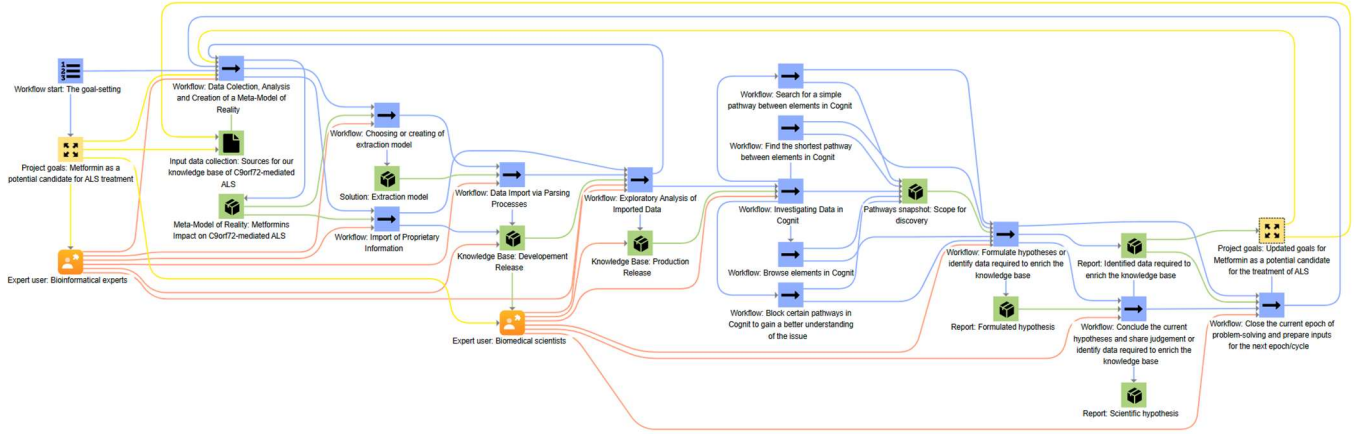
Our methodology for solving biomedical problems, as demonstrated by the study of Metformin's influence on ALS, begins with goal setting. We aim to comprehend Metformin's role in ALS caused by the C9orf72 gene mutation, understanding which is crucial for devising more effective therapeutic strategies. We then proceed to construct a progressive knowledge base, which includes the systematic collection, analysis, and interpretation of data, encompassing both proprietary and publicly available datasets. Our data is analyzed and integrated using advanced tools, enabling us to delve deeper into the data and uncover new biological pathways.

The process of enhancing our knowledge base is iterative. Each epoch concludes with the synthesis of current findings, guiding future data collection. This methodology also enhances our understanding of complex problems by utilizing structured processes and meta-models that help us systematically analyze and comprehend complex relationships in biomedical data. Finally, our work supports cognitive understanding by providing clear, structured, and actionable insights. The continuous development of our knowledge base helps unravel the mysteries of complex biomedical phenomena, opening doors to new discoveries and deepening our understanding of how to combat diseases.

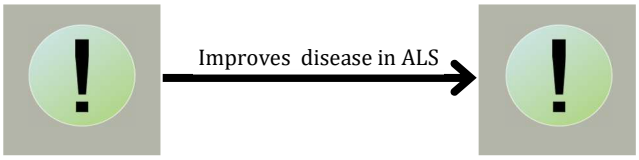
This use case study serves as a prototype example of the initial epoch in investigating ALS, underscoring that our role is not as a research institution but as an IT enterprise offering a platform for problem-solving within the biomedical sector.

Key Points:

- Case Study Example: Metformin's Impact on ALS
- Demonstrating workflow through practical examples in biomedical problem-solving.
- Goal Setting: Understanding Metformin's role in C9orf72-mediated ALS.
- Progressive Knowledge Base Development: Building a foundation through sequential data collection and analysis, incorporating proprietary and public datasets.
- Data Analysis and Integration: Using our tools for investigative analysis and pathway exploration.
- Iterative Improvement Across Epochs: Refining the knowledge base through multiple iterations, each ending with a synthesis of findings.
- Enhanced Understanding of Complex Problems: Using structured workflows and meta-models for systematic analysis.
- Facilitating Cognitive Comprehension: Providing insights for the continuous evolution of the knowledge base to demystify biomedical complexities.



3. Goal setting: Metformin's Impact on C9orf72-mediated ALS



Compound
Metformin

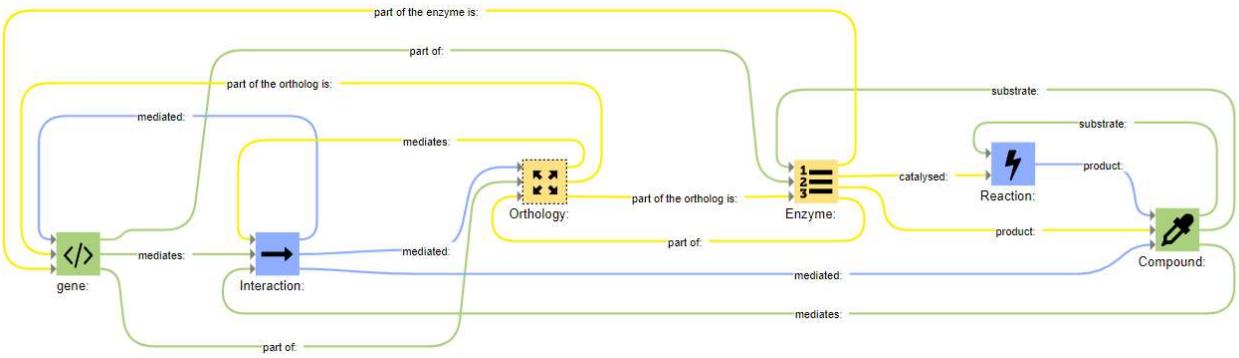
Disease
Amyotrophic Lateral Sclerosis
(ALS)

In line with the objectives set at the beginning of our case study, we have selected Metformin as a potential candidate for ALS treatment based on the information, we gathered from studying the subject matter, as indicated by various publications. However, the details regarding its mechanisms of action in ALS are not yet fully understood and articulated. This gap in comprehensive knowledge has led us to select the impact of Metformin on ALS as our inaugural case study. We will leverage published findings and metabolic pathways to gain a deeper insight into Metformin's influence on ALS. In the forthcoming section of this study, we will detail our approach, utilizing our bigRing platform. Our aim is to illustrate how bigRing can be instrumental in addressing complex biomedical challenges, potentially contributing to your own research endeavors. Join us as we delve into the intricacies of ALS treatment possibilities and explore how collaboration with our platform can augment your problem-solving capabilities.

4. Data collection, analysis, and creation of a meta-model of reality

Continuing from our previous discussion on our approach to the impact of Metformin on ALS, we delve deeper into the foundational steps of data collection, analysis, and meta-model creation within the context of our bigRing platform. We initiate by studying and analyzing the issue at hand, which involves an in-depth review of the biomedical topic and identification of critical factors and variables that inform our understanding. This is followed by the careful selection of datasets for our knowledge base. We determine which datasets are relevant and should be integrated into our analysis, prioritizing them based on their significance and the quality of the data they provide.

Next, we scrutinize the sources of our data, assessing their reliability and validity to ensure we base our conclusions on solid grounds. We examine the integrity and applicability of the data, as these are paramount for accurate analysis. The subsequent phase is the creation of a meta-model. We develop a framework that mirrors the complex reality of biomedical data, ensuring that our model can accommodate the diverse types of data and the relationships they entail. Finally, we structure the data according to the specifications of our meta-model, implementing a systematic approach to data integration and harmonization. This step is critical in aligning disparate data points and making sense of the extensive information. The schematic diagram of meta-model at the bottom of the slide illustrates the interaction between various biological processes and elements, such as genes, orthologs, and enzymes. Understanding and simulating these biological and chemical interactions is key to our case study of Metformin's influence on ALS.

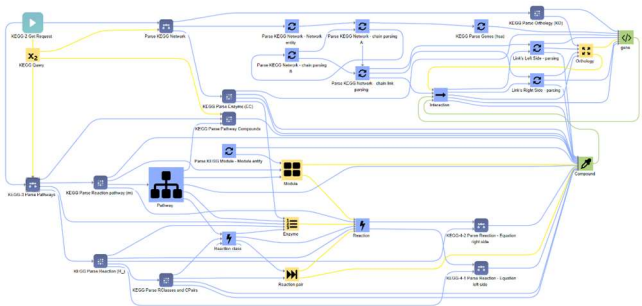


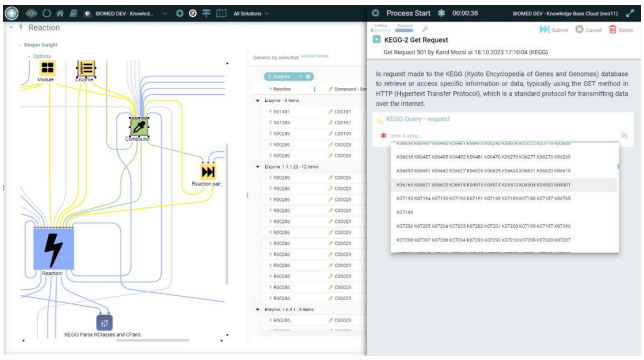
5. Data import via parsing processes

Building upon the foundational aspects of data collection and meta-model creation, this chapter focuses on the data import process utilizing parsing processes within the bigRing platform.

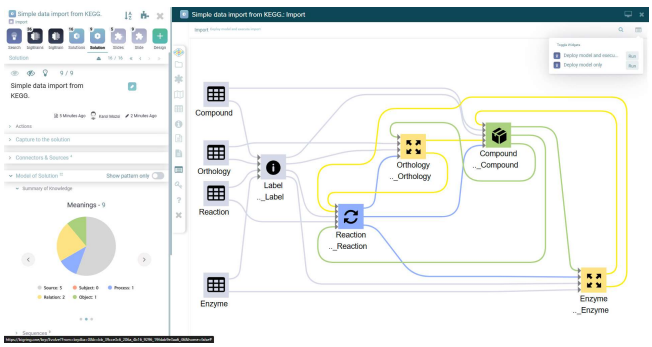
Starting with data import efficiency and smoothness, our platform offers tools that facilitate the comfortable and seamless import of extensive datasets into your metamodel's structure. We acknowledge the diversity of data sources and have designed our tools to handle data from various origins, ensuring flexibility in data integration. Our advanced parsing solutions bring simplicity to data integration, making the process accessible and manageable. In the context of our study, these parsing tools have been instrumental in importing data from the KEGG database. Specifically, we have utilized them to integrate pathways pertinent to our research on Amyotrophic Lateral Sclerosis in Homo sapiens, including the Adipocytokine signaling pathway, Insulin signaling pathway, and AMPK signaling pathway within the human context. This tailored data import is a testament to the versatility and precision of our parsing tools.

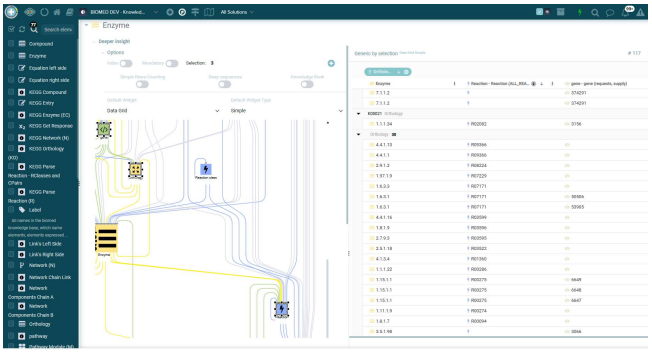
Structured data can be directly fed into your metamodel using our efficient parsing technologies, which not only streamline the structure of the metamodel but also significantly save time. These tools are capable of quickly parsing and integrating data into your existing systems, optimizing your data management processes. Further enriching your knowledge base, our comprehensive parsing tools enhance your analytical capabilities. With customizable parsing options, you can tailor the parsing process to fit your specific requirements, ensuring that the tools you use are perfectly aligned with your needs. Lastly, we offer full support in the purchase, setup, and integration of these parsing tools into your workflow. With our assistance, the data integration process will be smooth and worry-free, allowing you to focus on the insights and knowledge gained from your enriched data.





Alternatively, import directly from spreadsheet:





6. Import of proprietary information

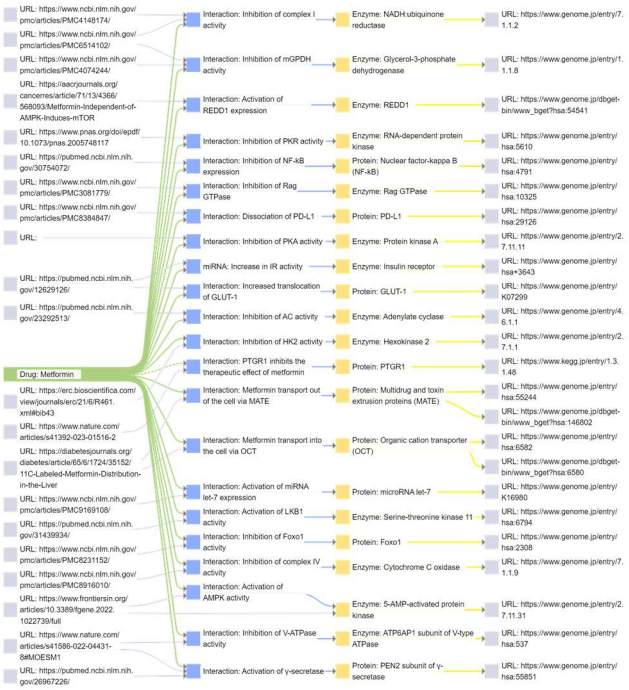
Extending the capabilities of our bigRing platform, the chapter demonstrates how it enables the importation and efficient utilization of proprietary information:

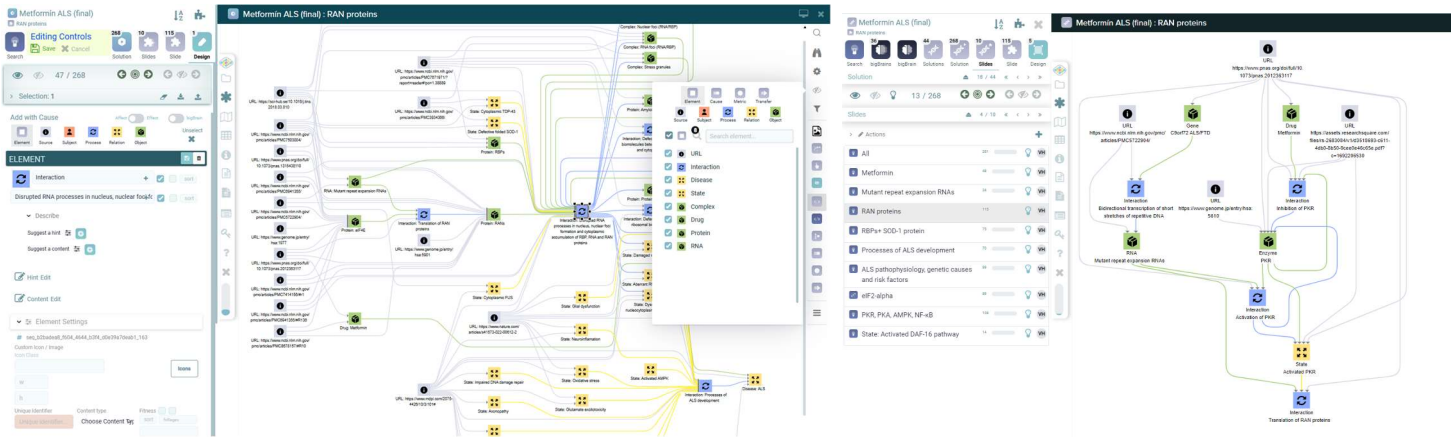
The bigRing platform provides personalized data organization tools, allowing experts to tailor and arrange their data within the metamodel framework as needed. Using our sophisticated editing tools, experts can transform their unique data into the structured format of the metamodel. For our study, this has included enriching our knowledge base with insights from fifty publications pertinent to the theme of ALS and Metformin. The relevance of these publications was curated by Vladimir Heger, a graduate of the Faculty of Natural Sciences at Comenius University in Bratislava, whose expertise guided the publication selection

process. The comprehensive list of these publications is provided in the appendix of this use case study. From these publications, we extracted critical information on the interactions caused by Metformin in metabolism, which has been instrumental in shaping our metamodel concept.

Once the data is organized, it can be effortlessly integrated into the knowledge base, ensuring efficient linkage with existing information. This approach simplifies synthesis and amplifies the value of your data. The platform also fosters a collaborative environment, meaning multiple experts can work on various datasets simultaneously, utilizing the advantages of the metamodel's structured coherence. Furthermore, the unified data structure ensures all expert perspectives are interconnected within the knowledge base, enabling the synthesis and mutual enrichment of this information. Knowledge synergy is another key element—the platform facilitates the merging of individual expertise, resulting in a comprehensive and enriched knowledge base. Updates are dynamic. As experts contribute, the knowledge base evolves in real time, reflecting the latest information and research findings. The platform also allows for cross-disciplinary collaboration. The flexibility of the metamodel permits the integration of data from various disciplines, thereby broadening the depth and scope of the knowledge base.

Lastly, real-time data sharing. Experts have immediate access to each other's curated data, promoting an environment of true collaboration and knowledge sharing in real time. By adopting this approach, the bigRing platform transforms how experts' access and utilize data, enabling a better understanding and application of information in their work.





7. Exploratory analysis of imported data

As we progress with our bigRing platform, the importance of scrutinizing the quality of imported data is paramount. The network visualizations here illustrate the complexities of data interrelations and serve as a tool for experts to ensure the integrity and validity of our knowledge base.

Starting with assessing data consistency, experts can scrutinize the network's overall structure, comparing it against the expected patterns within the knowledge domain. Should there be any discrepancies, such as unexpected connections or missing relationships, this may prompt a suggestion for meta-model adjustments, ensuring the data structure accurately reflects the conceptual framework of our study.

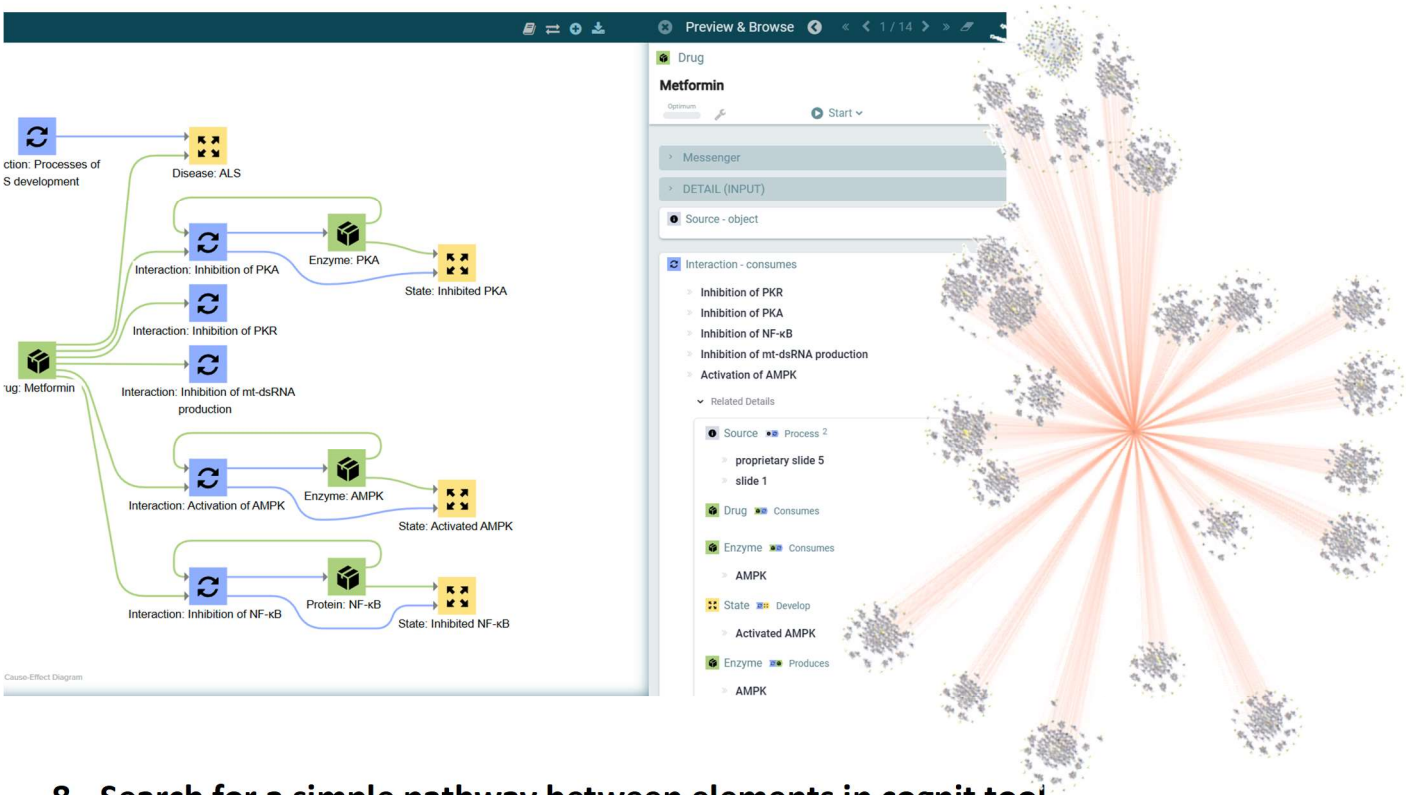
Identifying data gaps is another critical step. By examining the network, experts can pinpoint areas that require further data collection, highlighting entities or relationships that are currently underrepresented. This ensures that our model is robust and comprehensive,

capturing all relevant aspects of the ALS and Metformin interactions.

Verifying data integrity is essential before diving into in-depth analysis. By using the network graph, experts can confirm that the imported data aligns with the initial expectations, ensuring no inconsistencies would skew the analytical outcomes.

Moreover, this process significantly saves time by allowing quick identification and rectification of errors or inconsistencies within the imported data. This preemptive measure avoids the costly expense of time that would be wasted on analyzing flawed information.

Through this meticulous approach, we elevate the efficiency and accuracy of our research, ensuring that our findings are both precise and reliable. The network graphs serve as both a map and a filter, guiding us to a thorough understanding while keeping our data free from errors and omissions, thereby solidifying the trustworthiness of our analytical results.



8. Search for a simple pathway between elements in cognit tool

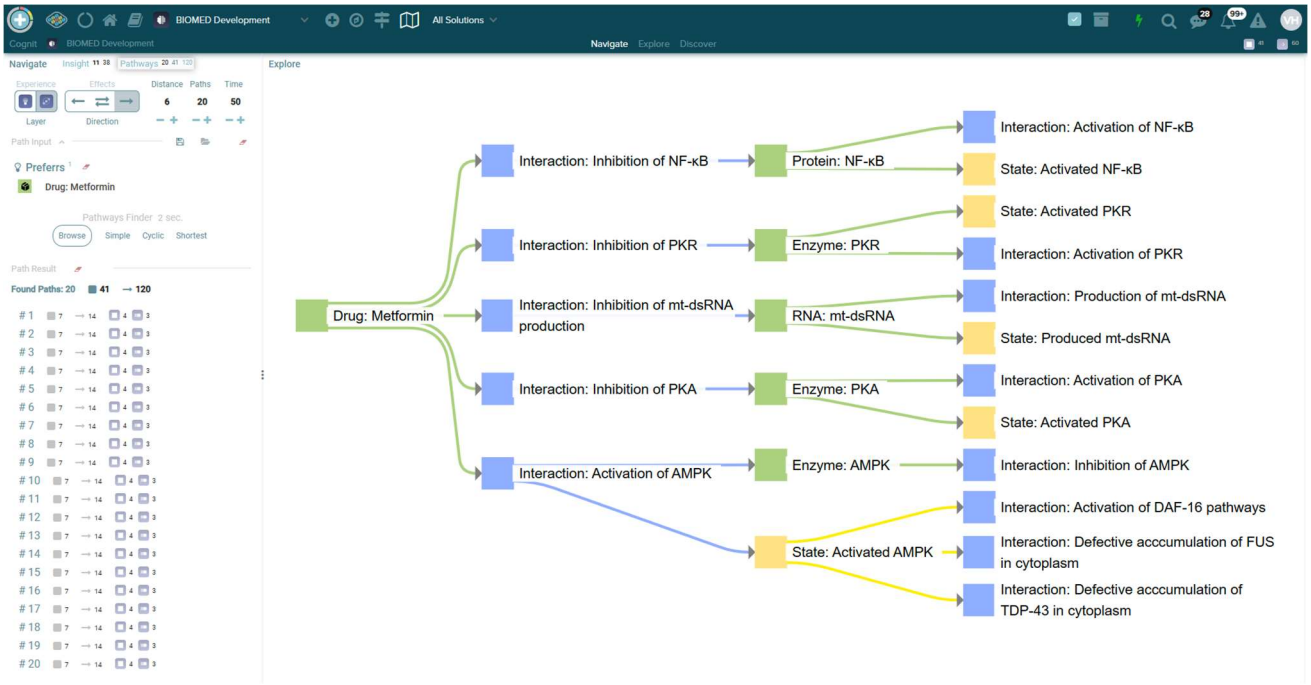
Leveraging the sophisticated features of our bigRing platform, the interface presented in the chapter above enables an intuitive and interactive exploration of complex knowledge bases. This empowers experts to seamlessly navigate and manipulate vast data networks, uncovering mechanisms through which Metformin interacts within the ALS disease progression.

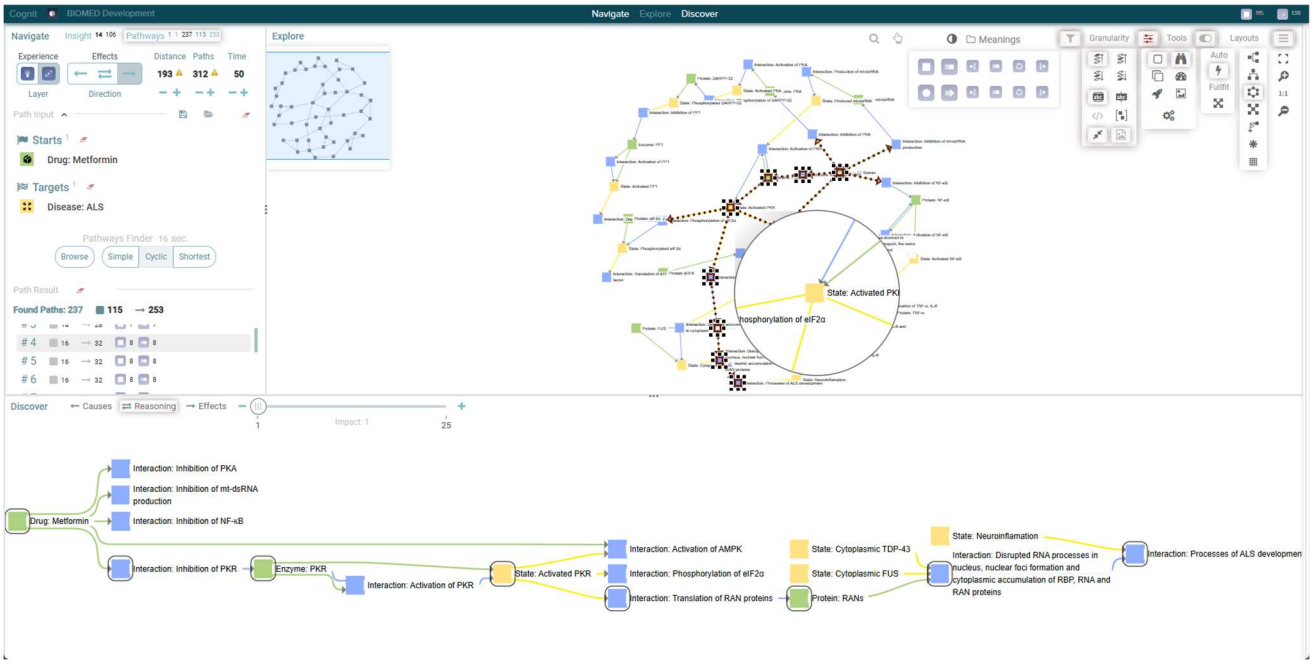
In our focused use case study, we have pinpointed four distinct mechanisms by which Metformin impacts ALS development. These mechanisms, derived from a targeted yet small set of data from scholarly publications and KEGG in the initial epoch, are:

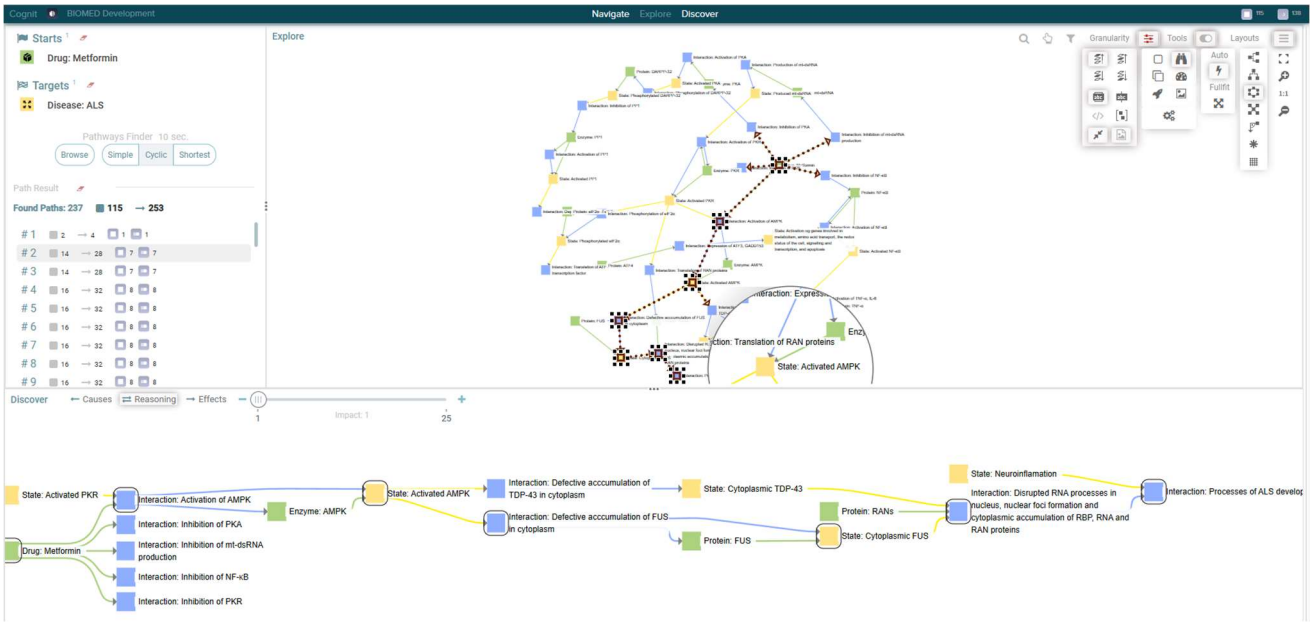
- Inhibition of Protein Kinase A (PKA)
- Inhibition of Protein Kinase R (PKR)
- Inhibition of mitochondrial double-stranded RNA (mt-dsRNA) production
- Activation of AMP-activated protein kinase (AMPK)

With features like 'Shortest pathway' and 'Simple pathway', our experts efficiently traced the most direct connections between pathway elements, leading to the elucidation of these mechanisms. The 'Browse' feature further allowed for the exploration of adjacent elements and the discovery of related components, crucial for hypothesis testing and revealing new patterns. Element and cause blocking focused our search, allowing us to refine our exploration and concentrate on pathways leading to significant insights into Metformin's role in ALS. This targeted approach has streamlined our investigative process, identifying the most probable mechanisms influencing disease progression. Our dynamic visualization tools have beautifully depicted these mechanisms, providing real-time updates as new data are incorporated or hypotheses are tested. This has been invaluable for formulating agile hypotheses about disease mechanics and the effects of drugs.

Moreover, the platform's grouping feature for spatial relevance has ensured that the interactions modeled are biologically plausible, reflecting pathways that are feasible within the cellular context. The collaborative features of the platform have enabled experts from various disciplines to engage in collective hypothesis testing and knowledge exchange, fostering a truly multidisciplinary scientific inquiry. As we continue to expand our knowledge base in future epochs, we anticipate uncovering currently unknown mechanisms that have not been directly described in scientific literature. Nevertheless, the bigRing platform has already been instrumental in visualizing and enhancing our understanding of the potential mechanisms through which Metformin may influence ALS progression, even within the scope of a small-scale study.






Navigate Explore Discover
Starts
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Targets
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Explore
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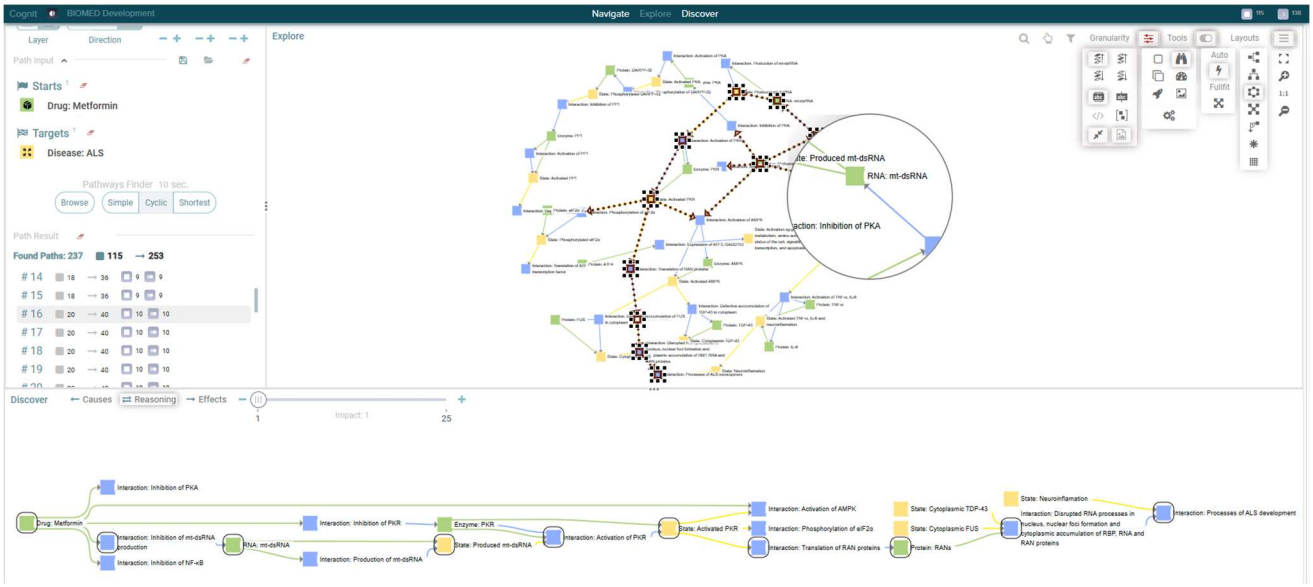
Interaction: Activation of AMPK
Interaction: Inhibition of PKA
Interaction: Inhibition of mt-dsRNA production
Interaction: Inhibition of NF-κB
Interaction: Inhibition of PKR
Drug: Metformin
Enzyme: AMPK
State: Activated AMPK
Interaction: Defective acccumulation of TDP-43 in cytoplasm
Interaction: Defective acccumulation of FUS in cytoplasm
State: Cytoplasmic TDP-43
Protein: FUS
Protein: RANs
State: Cytoplasmic FUS
State: Neuroinflamation
Interaction: Disrupted RNA processes in nucleus, nuclear foci formation and cytoplasmic accumulation of RBP, RNA and RAN proteins
Interaction: Processes of ALS develop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Interaction: Inhibition of NF-κB
RNA: mt-dsRNA
Interaction: Inhibition of PKR
Interaction: Production of mt-dsRNA
Enzyme: PKR
State: Produced mt-dsRNA
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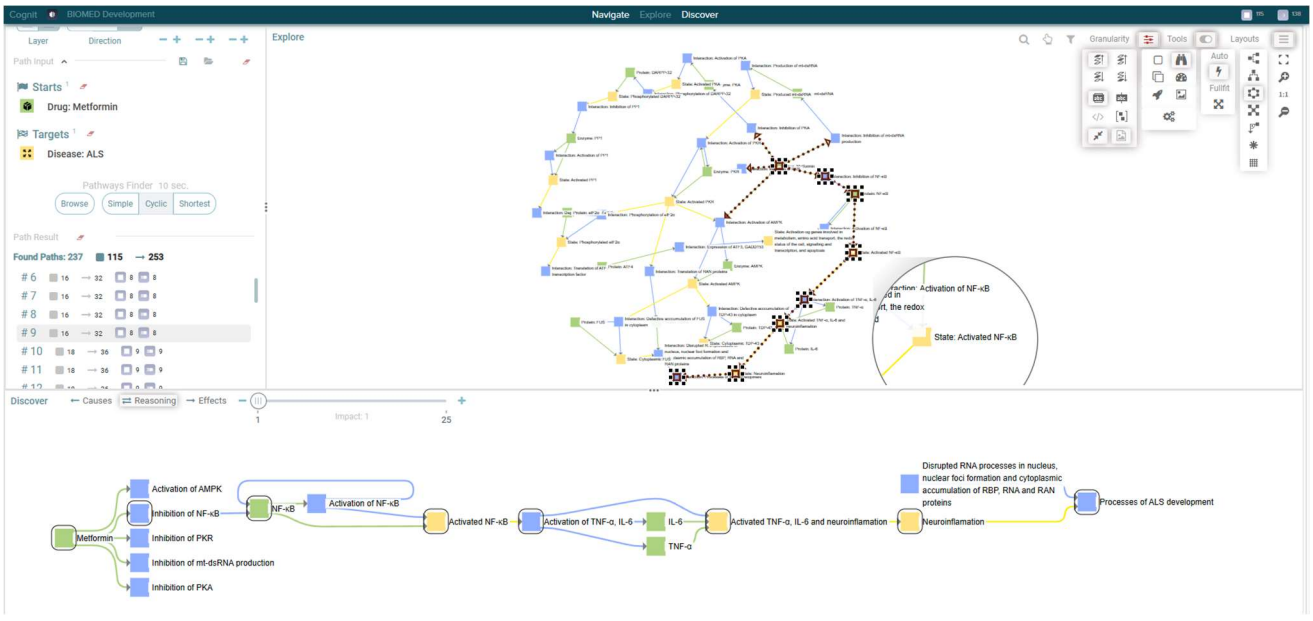
Interaction: Processes of ALS development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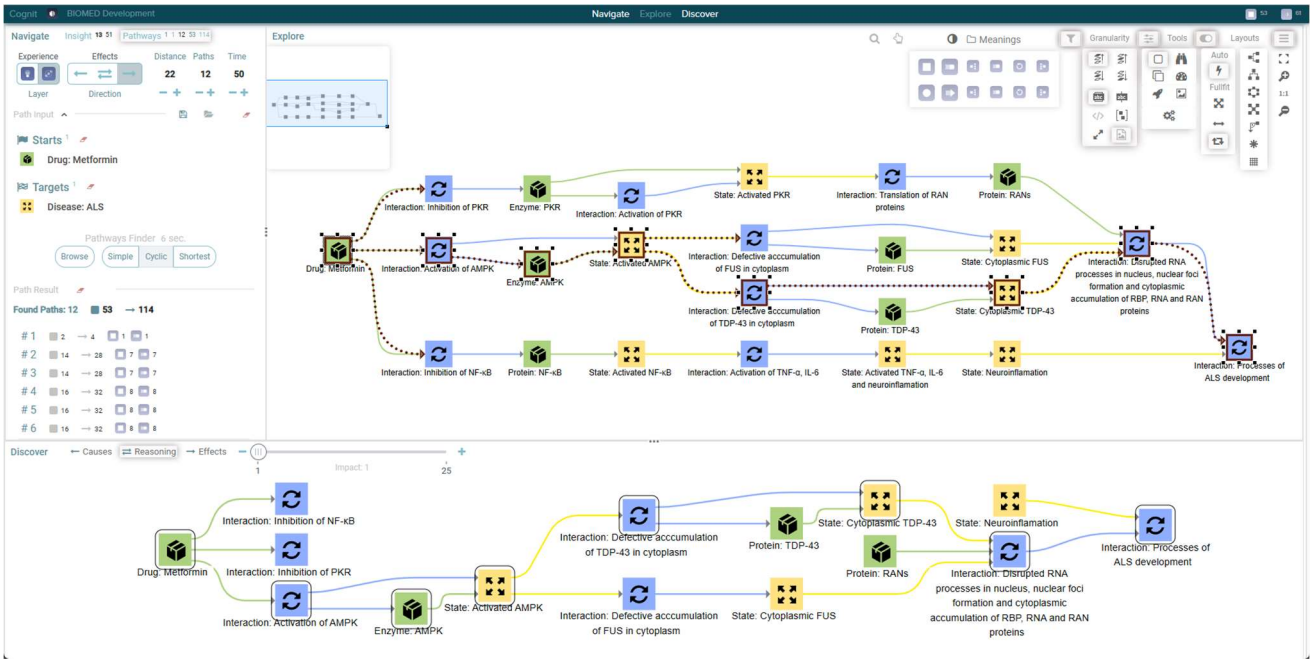
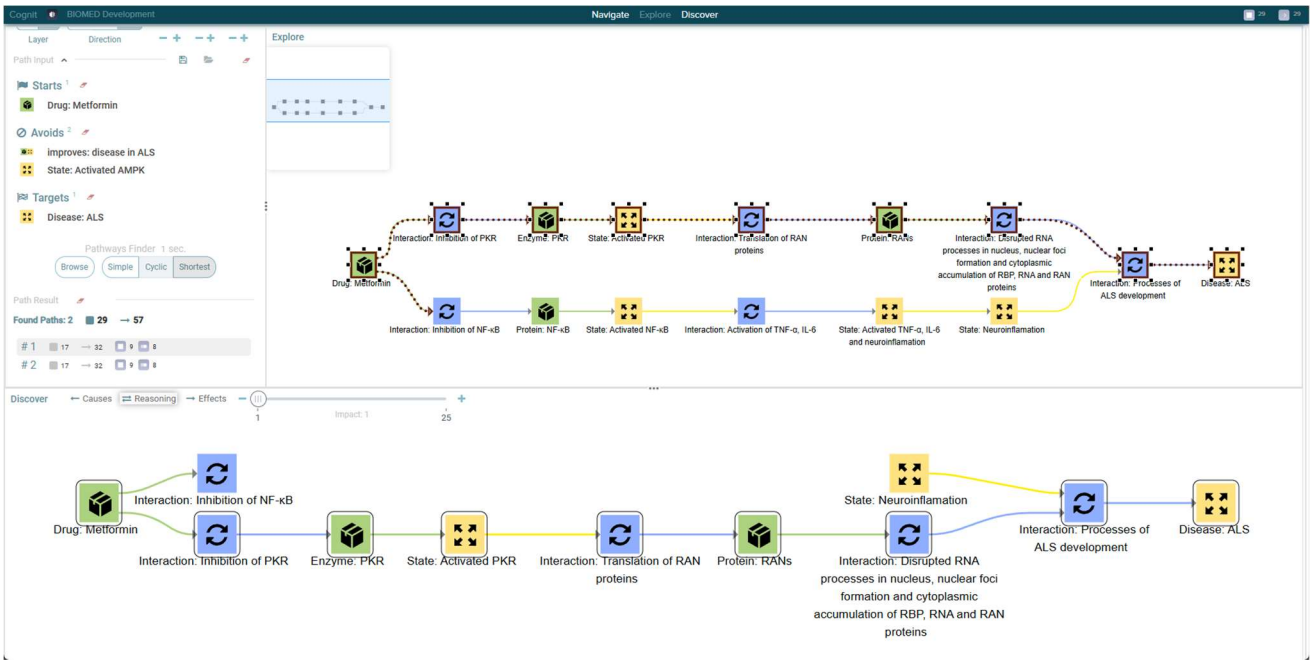
Inhibition of NF-κB
Metformin
Inhibition of PKR
Inhibition of mt-dsRNA production
Inhibition of PKA
NF-κB
Activation of NF-κB
Activated NF-κB
Activation of TNF-α, IL-6
IL-6
TNF-α
Activated TNF-α, IL-6 and neuroinflamation
Disrupted RNA processes in nucleus, nuclear foci formation and cytoplasmic accumulation of RBP, RNA and RAN proteins
Neuroinflamation
Processes of ALS development





9. Formulate hypotheses and identify data required to enrich the knowledge base.

Continuing from our previous discussion on utilizing bigRing platform capabilities, this chapter represents a practical application of our methodical approach to hypothesis generation and data enrichment within the knowledge base. In the process of building hypotheses, we've visualized the mechanisms by which Metformin may influence the development of ALS, though thus far on a relatively small data sample. From the first epoch, it's become clear that our platform is well-suited to addressing biomedical topics. From the analysis of the first epoch, we are gradually proposing the composition of a potential second epoch, where we could augment data from databases such as Reactome, Gene Ontology, WikiPathways, Malacard, protein-protein interaction via STRING, PharmGKB, and ClinVar. Furthermore, we see room for further enhancement of the meta-model, as each new epoch allows us to adjust not only the data sources but also the meta-model itself, enabling its continual refinement.

We begin with a gap analysis, where the expert examines the existing knowledge base to identify any missing elements or areas ripe for the addition of new data. This meticulous review is crucial in pinpointing the areas that require further information to complete our understanding of Metformin's impact on ALS. Following this, we proceed to the data integration phase. Here, we determine whether to incorporate new information, such as pertinent biological pathways, data from

supplementary databases, or the latest scientific research findings. The insights gained from these new data integrations may lead to the development of new hypotheses regarding biological processes or the efficacy of treatments, such as the inhibition of PKA and PKR, the inhibition of mt-dsRNA production, and the activation of AMPK, as identified in our study.

Armed with these hypotheses, the expert can design experiments to test and further expand the knowledge base, potentially involving in vitro studies, clinical trials, or computational simulations, all aimed at validating our predictions and exploring new avenues. Interactive visualization plays a critical role in this process. By mapping specific data points or pathways within the editor, the expert can interact with the data, fostering a more profound understanding and the emergence of new insights. This manipulation of the data within the editor can reveal new patterns and connections, inspiring further investigations, and research directions. These steps enable us to continually enrich and expand our knowledge base, thereby contributing to scientific advancement. Our platform transforms the way we access, analyse, and apply data, facilitating a dynamic and evolving understanding of complex biomedical information. Through this process, we ensure that our findings are not only accurate but also reflective of the latest scientific insights, allowing us to push the boundaries of what is known and explore the untapped potential of emerging data.

10.Conclude the current epoch and prepare inputs for the next epoch.

As we advance to the next stage of our research, the emphasis shifts to leveraging the initial successes to further deepen our understanding of Metformin's role in ALS. The previous epoch laid the foundation, identifying four key mechanisms of Metformin's interaction with the disease process. Looking forward, the goal is to expand our dataset beyond the initial scope. This expansion aims to not just fill the gaps identified but also to introduce a spectrum of new hypotheses into our knowledge base. The next phase of development is set to include a collaborative effort to refine the meta-model. This will involve a detailed analysis by experts across disciplines to ensure the model accurately reflects the complex interactions within ALS pathology and the effects of Metformin. We anticipate making structural enhancements to the meta-model, which will involve incorporating new data relationships that capture the nuanced dynamics of the disease more effectively.

Quality control remains a cornerstone of our data integration strategy, where rigorous criteria will be applied to the selection of new data. This ensures that only the most relevant and reliable information bolsters our knowledge base, thereby increasing the potency of our research outputs. We conceptualize our progress as a continuous cycle of improvement, where each epoch builds upon the insights gained from the last. This progression is not linear but rather a recursive process that allows us to refine our approaches and hypotheses iteratively. In closing, we set our sights on the horizon of discovery, with the expectation that the next epoch will bring breakthroughs in identifying as yet unknown pathways through which Metformin interacts with ALS. We are in the process of mapping out a timeline that will guide us through these upcoming milestones, heralding a new era of exploration and understanding in our scientific journey. We trust that the insights shared have been both informative and thought-provoking. Should our Metformin ALS use case pique your interest, we warmly encourage you to reach out to us, to explore the possibilities our platform offers in greater detail.

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