Utilizing Self-Supervised Graph Neural Networks in De Novo Drug Discovery

# Introduction and Background

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The advent of artificial intelligence (AI) in medicinal chemistry has revolutionized the field of drug discovery, providing novel methodologies to address long-standing challenges associated with molecular representation and property prediction. Among the various AI-driven techniques, Graph Neural Networks (GNNs) have emerged as a powerful tool for representing molecular data due to their ability to capture intricate relationships within molecular structures [2][6]. However, despite their advantages, the effective learning of molecular representations remains a critical challenge, particularly in scenarios where labeled molecular data is scarce [3][4].  
  
The concept of self-supervised learning has garnered significant attention in recent years as a potential solution to the limitations inherent in traditional supervised learning approaches. Self-supervised frameworks can leverage vast amounts of unlabeled data to pre-train models, thereby enhancing their ability to generalize to downstream tasks such as molecular property prediction and drug-target interaction [1][2]. For instance, recent work has proposed a bi-branch masked graph transformer autoencoder, termed BatmanNet, which simultaneously learns local and global information about molecules through a straightforward self-supervised strategy [1]. This model has achieved state-of-the-art results across multiple drug discovery tasks, indicating its efficacy in molecular representation learning.  
  
The need for robust molecular representations is underscored by the challenges faced in de novo drug discovery, where computational methods are employed to generate novel chemical entities with promising biological activity. Traditional experimental methods for identifying potential drug candidates are labor-intensive and slow, prompting a shift towards computational models that can efficiently screen and design new molecules [8][11]. The integration of GNNs into the drug discovery pipeline allows for the modeling of complex molecular interactions, which is essential for predicting drug-target binding affinities and optimizing lead compounds [11][12].  
  
In the context of de novo drug design, several frameworks have been developed that utilize GNNs for generating novel molecules. For example, the Molecular Pre-training Graph-based (MPG) framework incorporates a self-supervised learning strategy to produce expressive molecular representations from large-scale unlabeled datasets [2][3]. The MolGNet model, as part of this framework, demonstrates the capacity to capture significant chemical insights, further facilitating the fine-tuning of models for various drug discovery tasks [2][5].  
  
Moreover, hybrid neural network architectures have been proposed to enhance the generation of hit-like molecules by considering biological responses alongside chemical properties. The HNN2Mol framework, for instance, utilizes gene expression profiles to guide the generation of molecular structures with desirable phenotypes, thereby bridging the gap between molecular design and biological activity [8]. This hybrid approach exemplifies the potential of integrating biological data into machine learning models to enrich the drug discovery process.  
  
Despite the promising advancements in GNNs and self-supervised learning, challenges remain in the interpretability of these models. As the complexity of GNN architectures increases, understanding the specific contributions of molecular substructures to biological activity becomes increasingly difficult. Recent studies have highlighted the importance of explainable AI (XAI) techniques to elucidate the decision-making processes of GNNs, thereby improving their acceptance in the drug discovery domain [10][12]. For instance, the Hierarchical Grad-CAM graph Explainer (HGE) framework has been implemented to provide detailed insights into molecular moieties that influence protein-ligand interactions, facilitating better rational drug design [10].  
  
Furthermore, the integration of reinforcement learning (RL) with GNNs has shown promise in optimizing the design of drug candidates. The 3D-MolGNN$\_{RL}$ framework, which employs RL to guide the generation of molecules in three-dimensional space, addresses the challenges of optimizing multiple molecular properties simultaneously [14]. This approach not only enhances the efficiency of the drug design process but also ensures the generated molecules exhibit desirable characteristics such as binding affinity and synthetic accessibility.  
  
In summary, the utilization of self-supervised GNNs in de novo drug discovery represents a significant advancement in the field of medicinal chemistry. The ability to learn robust molecular representations from unlabeled data, coupled with the integration of biological insights and explainable methods, positions these frameworks as pivotal tools in accelerating the discovery of novel therapeutic candidates. As ongoing research continues to refine these methodologies, the potential to overcome traditional barriers in drug design and discovery becomes increasingly attainable.  
  
### References  
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## Overview of Drug Discovery

### Traditional Drug Discovery Process and the Role of Computational Methods  
  
The traditional drug discovery process is a complex, resource-intensive endeavor that typically spans several years and involves multiple stages, including target identification, hit discovery, lead optimization, and preclinical testing. Historically, the identification of drug candidates relied heavily on empirical methods, which often incorporated high-throughput screening of vast libraries of compounds against biological targets. However, this approach is not only labor-intensive and time-consuming but also often results in low success rates due to the inherent complexity of biological systems and the need for specific interactions between drug molecules and their targets [5], [12].  
  
The initial phase of drug discovery typically begins with the identification of a biological target, often a protein or nucleic acid implicated in a specific disease pathway. Following target identification, researchers engage in hit discovery, wherein they seek small molecules that can bind to the target with sufficient affinity and specificity. This is often achieved through high-throughput screening (HTS), where thousands of compounds are tested in parallel. However, the HTS process is limited by its ability to explore only a fraction of the chemical space [4], [14]. Consequently, many potential drug candidates are overlooked, and the pipeline becomes constrained by the inefficiencies of empirical methodologies.  
  
To address the limitations of traditional drug discovery, computational methods have increasingly been integrated into the process. These techniques, collectively referred to as computer-aided drug design (CADD), leverage computational power to predict the interactions between small molecules and biological targets, thereby enhancing the efficiency of drug discovery [3], [4]. In particular, the advent of artificial intelligence (AI) and machine learning has revolutionized the field by enabling the analysis of vast datasets to uncover structure-activity relationships that are not readily apparent through experimental methods alone [2], [11].  
  
One of the most promising computational strategies in drug discovery is de novo drug design, which involves the generation of novel molecular structures from scratch. This approach utilizes algorithms to navigate chemical space efficiently and identify compounds that meet specific biological criteria. Recent advancements in deep learning, particularly through the use of graph neural networks (GNNs), have enabled more sophisticated modeling of molecular interactions and properties. GNNs are well-suited for this task as they can represent molecular structures as graphs, capturing the relationships between atoms and their connectivity in a way that traditional methods cannot [6], [8].  
  
Self-supervised learning has emerged as a particularly effective approach within GNNs, mitigating the challenges associated with labeled data scarcity. For instance, the Molecular Pre-training Graph-based deep learning framework, known as MPG, utilizes large-scale unlabeled datasets to learn molecular representations that can then be fine-tuned for specific downstream tasks, such as predicting drug-target interactions or molecular properties [7], [11]. This capability enhances the interpretability of molecular representations and enables more effective generation of drug candidates.  
  
Moreover, the integration of self-supervised techniques within GNNs allows for the extraction of valuable insights from unlabeled molecular data, which is abundant but often underutilized in traditional drug discovery. Studies have demonstrated that pre-trained GNN models can achieve state-of-the-art results across various drug discovery tasks, including molecular properties prediction and drug-drug interaction assessments [10], [13]. By leveraging these models, researchers can explore a broader chemical space and identify novel compounds that possess the desired pharmacological profiles.  
  
The role of computational methods extends beyond de novo design; they also play a critical role in lead optimization, where existing compounds are refined to enhance their efficacy and reduce side effects. Lead optimization often involves iterative cycles of design, synthesis, and testing, which can be accelerated through predictive modeling. For example, machine learning algorithms can predict the impact of structural modifications on biological activity, thus guiding chemists in their experiments and reducing the number of compounds that need to be synthesized and tested [4], [10]. This synergy between computational predictions and experimental validation facilitates a more targeted approach to drug development.  
  
Despite the advantages of computational methods in drug discovery, challenges remain regarding the interpretability and reliability of these models. While GNNs and other AI-driven techniques can provide insightful predictions, the complexity of biological systems means that these predictions must be validated through rigorous experimental work. Furthermore, the integration of explainable artificial intelligence (XAI) techniques is crucial for elucidating the contributions of specific molecular features to biological activity, thus enhancing the interpretability of models used in drug design [8], [12].  
  
In summary, the traditional drug discovery process is evolving through the incorporation of computational methods, particularly self-supervised learning and GNNs, which enhance the efficiency and effectiveness of de novo drug design and lead optimization. These advancements allow researchers to explore larger chemical spaces and generate novel compounds with improved properties while addressing the limitations of empirical approaches. As the field continues to advance, the integration of computational techniques will likely play an increasingly vital role in expediting drug discovery and improving the success rates of clinical candidates.  
  
In conclusion, the intersection of traditional methodologies and computational innovations represents a promising frontier in drug discovery, one that holds the potential to revolutionize how new therapeutics are developed and brought to market. The future of drug discovery may very well hinge on our capacity to harness computational power effectively, creating a more streamlined and productive pathway to uncovering novel therapeutics that can address unmet medical needs.

## Introduction to Graph Neural Networks

### Fundamentals of Graph Neural Networks and Their Advantages in Modeling Molecular Structures  
  
Graph Neural Networks (GNNs) have emerged as a transformative computational paradigm for processing graph-structured data, particularly in the field of molecular modeling. Unlike traditional neural networks that operate on fixed-size data structures, GNNs leverage the inherent relational structures present in graphs, allowing for effective representation and manipulation of complex data such as molecular structures. This section delves into the fundamentals of GNNs, their operational mechanics, and the distinct advantages they offer in modeling molecular structures relevant to de novo drug discovery.  
  
#### 1. Understanding Graph Neural Networks  
  
GNNs are designed to capture the dependencies between nodes and edges in graph data by employing a message-passing mechanism [2]. In the context of molecular structures, atoms can be represented as nodes, while chemical bonds serve as edges, thus forming a graph representation of a molecule. The GNN architecture operates by iteratively updating the representation of each node based on information from its neighbors, effectively allowing the network to learn localized features pertinent to the molecular graph [3].  
  
The learning process within GNNs typically involves two key phases: aggregation and update. During the aggregation phase, each node collects messages from its neighbors, which are then combined to form a new representation for the node. The update phase modifies the node's features based on the aggregated information and its current state. This iterative process can be continued for several layers, enabling the GNN to capture both local and global graph structures [4].   
  
#### 2. Advantages of GNNs in Molecular Modeling  
  
The application of GNNs in molecular modeling offers several advantages over traditional methods, particularly in the context of de novo drug discovery:  
  
##### 2.1 Expressive Representation Learning  
  
One of the primary challenges in AI-driven drug discovery is the generation of expressive molecular representations that can accurately capture chemical properties [5]. GNNs excel in this regard due to their ability to model complex relationships and interactions within molecular graphs. For instance, the Molecular Pre-training Graph-based model (MPG) has demonstrated that pre-training GNNs on large unlabeled datasets can yield rich molecular representations that are interpretable and effective for downstream tasks such as molecular property prediction and drug-target interaction modeling [2].  
  
##### 2.2 Robustness to Data Scarcity  
  
Traditional supervised learning methods often suffer from limitations associated with labeled data scarcity, which is a significant hurdle in drug discovery [3]. GNNs leverage self-supervised learning techniques that allow them to learn from large-scale unlabeled molecular datasets. For instance, MolGNet, a GNN architecture, effectively captures valuable chemical insights from 11 million unlabeled molecules, enhancing its adaptability and generalization capabilities [2]. This is particularly advantageous in de novo drug discovery, where generating labeled data can be labor-intensive and costly.  
  
##### 2.3 Enhanced Interpretability  
  
Despite the complexity of GNNs, recent advancements have introduced explainable artificial intelligence (XAI) techniques to elucidate the contributions of specific molecular substructures to biological activity. For example, the Hierarchical Grad-CAM graph Explainer (HGE) framework has been successfully employed to analyze molecular moieties that drive protein-ligand binding stabilization, thereby enhancing the interpretability of GNN models [4]. This interpretability is crucial for computational chemists aiming to rationally design novel therapeutics and optimize molecular structures.  
  
##### 2.4 Integration with Other Computational Techniques  
  
GNNs can also be integrated with other computational methodologies to enhance their performance in molecular modeling. For instance, recent studies have combined GNNs with reinforcement learning models to optimize molecular generation processes, demonstrating that such hybrid approaches can yield high-quality drug candidates [11]. Moreover, GNNs have been utilized in conjunction with geometric deep learning techniques, which further enhances their applicability in structure-based drug design by allowing the model to incorporate 3D geometric information of macromolecules [7].  
  
#### 3. Applications in De Novo Drug Discovery  
  
The application of GNNs in de novo drug discovery has shown promising results across various tasks, including molecular generation, property prediction, and drug-target interaction modeling. The ability of GNNs to effectively explore chemical space and generate novel molecular structures addresses the long-standing challenges associated with traditional drug discovery methods, which often rely on a limited subset of known compounds [1].  
  
For instance, the implementation of a GNN framework for virtual screening tasks has resulted in high accuracy and robustness across different protein targets, showcasing the potential of GNNs to enhance the drug discovery pipeline by rapidly identifying bioactive molecules [4]. Additionally, GNNs have been employed to predict binding affinities of drug-target interactions, facilitating the identification of promising drug candidates for further experimental validation [14].  
  
#### 4. Challenges and Future Directions  
  
Despite the numerous advantages that GNNs offer, several challenges remain. The computational demands associated with training large GNN models on extensive datasets can be resource-intensive, necessitating advancements in optimization and scalability techniques [10]. Furthermore, while GNNs have improved interpretability through XAI frameworks, the subjective nature of “ground truth” in explainability assessments poses a challenge for quantitative evaluation [12].  
  
Future research in GNN-based molecular modeling should focus on enhancing model interpretability, improving data efficiency, and integrating emerging techniques such as transfer learning to leverage existing knowledge across different tasks and domains [9]. Moreover, exploring novel architectures that balance expressiveness and computational efficiency will be crucial for advancing GNN applications in drug discovery.  
  
### Conclusion  
  
In summary, Graph Neural Networks represent a significant advancement in the modeling of molecular structures, offering robust, expressive, and interpretable representations that are particularly beneficial for de novo drug discovery. Their ability to operate effectively on graph-structured data positions them as an essential tool in the computational chemist's toolkit, enabling the exploration of vast chemical spaces and the generation of innovative drug candidates. While challenges remain, ongoing research and technological advancements are likely to further enhance the capabilities and applications of GNNs in drug discovery.

## Self-Supervised Learning in GNNs

### Self-Supervised Learning and Its Relevance for Enhancing Graph Neural Networks in Drug Discovery  
  
#### Introduction to Self-Supervised Learning  
  
Self-supervised learning (SSL) is a paradigm of machine learning where the model learns to predict parts of the input data from other parts, thus generating supervisory signals from the data itself without the need for explicit labels. This approach has gained significant traction in various domains, particularly in natural language processing and computer vision, and is now making inroads into drug discovery, particularly through the enhancement of Graph Neural Networks (GNNs) [1][2]. In the context of drug discovery, SSL facilitates the learning of rich molecular representations from vast quantities of unlabeled molecular data, which is especially crucial given the scarcity of labeled datasets in this field [3].  
  
#### Significance of Self-Supervised Learning in Drug Discovery  
  
The application of SSL in drug discovery is particularly relevant due to the inherent challenges associated with traditional supervised learning approaches, which often require extensive labeled datasets that are not readily available in the domain of molecular data. The reliance on labeled data not only limits the generalizability of model predictions but also increases the dependency on domain expertise for annotation [4]. The integration of SSL allows GNNs to leverage large-scale unlabeled molecular datasets, which can lead to more robust and transferable molecular representations [5].  
  
For instance, a novel framework called Molecular Pre-training Graph-based deep learning framework (MPG) has been proposed to utilize SSL for pre-training the MolGNet model on a dataset comprising 11 million unlabeled molecules. This framework demonstrated that the self-supervised pre-training enhances the model's ability to capture meaningful chemical insights, thus improving interpretability and performance across various drug discovery tasks, including molecular property prediction and drug-target interaction [6]. Such advancements underscore the transformative potential of self-supervised methodologies in overcoming the limitations of current supervised learning approaches.  
  
#### Enhancing Graph Neural Networks with Self-Supervised Learning  
  
Graph Neural Networks, which excel in modeling molecular structures due to their ability to capture the relationships between atoms and bonds, benefit significantly from self-supervised learning techniques. The underlying structure of molecules can be represented as graphs, where nodes correspond to atoms and edges represent chemical bonds. By employing self-supervised strategies, GNNs can effectively learn both local and global features of molecular graphs [7].  
  
One innovative approach involves the bi-branch masked graph transformer autoencoder (BatmanNet), which utilizes a self-supervised strategy to reconstruct missing nodes and edges in a molecular graph. This model not only facilitates the learning of local interactions but also captures global structural features, thereby enhancing the quality of the learned molecular representations [8]. The performance of BatmanNet across multiple drug discovery tasks illustrates the efficacy of combining self-supervised learning with GNNs, achieving state-of-the-art results on benchmark datasets [7][8].  
  
Moreover, the exploration of hierarchical informative graph neural networks (HiGNN) has shown that integrating hierarchical information into GNN architectures can further refine molecular representation learning. This framework employs co-representation learning of molecular graphs and chemically synthesizable fragments, demonstrating significant improvements in predictive performance for drug discovery tasks [9]. The incorporation of attention mechanisms within HiGNN enhances the model’s ability to recalibrate atomic features, ultimately leading to better interpretability and accuracy in predicting molecular properties.  
  
#### Challenges and Future Directions  
  
While the integration of self-supervised learning into GNNs presents substantial advantages, several challenges remain. The complexity and computational demands of developing effective self-supervised tasks can hinder the scalability of these approaches. Many existing methods require intricate architectures and vast computational resources, which can be prohibitive for practical applications in drug discovery [10]. Consequently, there is a pressing need for more streamlined and efficient self-supervised strategies that can operate effectively even with limited computational resources.  
  
Furthermore, the interpretability of GNN models remains a critical concern. Despite advances in explainable artificial intelligence (XAI) techniques, the subjective nature of interpretability metrics complicates the evaluation of model outputs [11]. Future research should focus on developing robust frameworks that not only address the interpretability of GNNs but also enhance their reliability and applicability in real-world drug discovery scenarios.  
  
#### Conclusion  
  
In conclusion, self-supervised learning represents a pivotal advancement in enhancing Graph Neural Networks for drug discovery applications. By leveraging large-scale unlabeled datasets, SSL facilitates the creation of expressive molecular representations that can significantly improve the performance of GNNs across various drug discovery tasks. As the field continues to evolve, addressing the computational challenges and enhancing interpretability through innovative frameworks will be essential for translating these technological advancements into practical applications. The integration of self-supervised learning within GNN architectures holds great promise for revolutionizing the drug discovery process, ultimately leading to more efficient identification and optimization of therapeutic candidates.  
  
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# Data and Preprocessing

### Data and Preprocessing  
  
The utilization of Self-Supervised Graph Neural Networks (GNNs) in de novo drug discovery necessitates a comprehensive understanding of data sourcing, preprocessing, and representation learning. This section elucidates the methodologies employed in data acquisition, preprocessing techniques, and the intricacies of molecular representation that are pivotal for effective drug discovery outcomes.  
  
#### Data Acquisition  
  
In the context of drug discovery, data availability is paramount. The challenge of acquiring labeled molecular data is well-documented; traditional supervised learning techniques often falter due to the scarcity of annotated datasets, which limits their generalization capabilities [1][2]. To counteract this limitation, recent advancements have embraced large-scale unlabeled datasets. For instance, the Molecular Pre-training Graph-based deep learning framework (MPG) leveraged a dataset comprising 11 million unlabeled molecules, facilitating the learning of molecular representations through self-supervised strategies [1][3]. Such expansive datasets are essential for training robust models capable of capturing the intricate chemical features that define molecular behavior.  
  
#### Preprocessing Techniques  
  
Preprocessing is a critical step in preparing molecular data for GNNs. The transformation of raw molecular structures into a format suitable for GNNs typically involves the generation of graph representations where atoms are treated as nodes and chemical bonds as edges. This graph-based representation allows GNNs to naturally encode the structural characteristics of molecules, thus enhancing their predictive capabilities [4][5].   
  
One innovative approach to preprocessing is the bi-branch masked graph transformer autoencoder (BatmanNet), designed to reconstruct missing nodes and edges from a masked molecular graph. This technique simultaneously captures local and global information about the molecular structure, thereby enriching the molecular representation [3][6]. Additionally, the incorporation of hierarchical informative graph neural networks (HiGNN) has further refined the preprocessing stage by effectively integrating co-representation learning of molecular graphs with chemically synthesizable fragments [7]. This hierarchical approach not only preserves the intricate relationships among molecular features but also improves the interpretability of the resulting models.  
  
#### Molecular Representation Learning  
  
The crux of leveraging GNNs in drug discovery lies in their ability to learn expressive molecular representations. Previous methodologies often relied on complex self-supervised tasks that were computationally intensive and time-consuming [3][8]. In contrast, the MPG framework proposes a simplified yet effective self-supervised learning strategy that focuses on pre-training at both the node and graph levels. This dual-level approach has been shown to yield representations that encapsulate valuable chemistry insights, facilitating subsequent fine-tuning for various drug discovery tasks, such as molecular property prediction and drug-target interaction [1][9].  
  
Furthermore, the integration of gene expression profiles into the molecular generation process has been explored in hybrid neural network architectures like HNN2Mol. This model utilizes variational autoencoders to learn latent distributions from gene expression data, thereby generating molecular structures that satisfy specific biological criteria [8]. Such integration signifies a shift towards more biologically relevant models that can produce compounds with desirable phenotypes.  
  
#### Challenges and Future Directions  
  
Despite these advancements, several challenges persist in the realm of molecular representation learning. For instance, the need for interpretability in GNNs remains a significant barrier to their widespread adoption in drug discovery [10][11]. As the field progresses, developing explainable artificial intelligence (XAI) methodologies to elucidate the contributions of specific molecular substructures to biological activity will be crucial [12]. Recent studies have highlighted the efficacy of XAI techniques, such as the Hierarchical Grad-CAM graph Explainer (HGE), which provides insights into the molecular moieties driving protein-ligand interactions [12].  
  
Moreover, the optimization of molecular characteristics for specific therapeutic targets continues to pose a challenge. Approaches like NovoMol, which employs recurrent neural networks to generate drug candidates optimized for oral bioavailability, exemplify innovative strategies to address this issue [13]. By refining generated molecules based on established pharmacokinetic parameters, such methods can significantly enhance the efficiency of clinical trial processes.  
  
#### Conclusion  
  
In summary, the integration of self-supervised GNNs in de novo drug discovery offers a transformative approach to molecular representation learning. By leveraging large-scale unlabeled datasets and advanced preprocessing techniques, these frameworks are poised to overcome traditional limitations associated with supervised learning. As the field continues to evolve, addressing challenges related to interpretability and the optimization of molecular characteristics will be essential for realizing the full potential of GNNs in drug discovery. Future research should focus on enhancing the efficiency of model training and validating the predictive power of generated molecular candidates against real-world biological systems.  
  
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## Data Sources

### Key Datasets for Small-Molecule Structures and Protein Targets  
  
#### Introduction  
The identification of small-molecule structures and their corresponding protein targets is a fundamental aspect of drug discovery. This task is often hampered by the complexity of biological systems and the sheer volume of available chemical and biological data. Recent advancements in computational methodologies, particularly those leveraging graph neural networks (GNNs) and self-supervised learning, have paved the way for more efficient identification and optimization of drug candidates. This section discusses key datasets relevant to small-molecule structures and protein targets, alongside the computational approaches utilized in de novo drug discovery.  
  
#### Datasets for Small-Molecule Structures  
Several databases have been established to facilitate the accessibility of small-molecule structures, which are crucial for computational drug discovery. Prominent among these are the ChEMBL and PubChem databases, which contain extensive information on bioactive compounds and their corresponding biological activities. ChEMBL, for instance, houses over 2 million compounds with associated bioactivity data against a variety of protein targets, making it a significant resource for drug discovery researchers [1].  
  
Another notable dataset is the ZINC database, which provides a collection of commercially available compounds for virtual screening [2]. It contains over 230 million purchasable molecules, including diverse chemical classes, thus enabling researchers to identify novel drug candidates through high-throughput virtual screening techniques.  
  
In addition to these databases, specialized datasets such as the Davis and KIBA datasets are instrumental in training machine learning models to predict drug-target binding affinities. The Davis dataset includes 442 drug-target pairs, while the KIBA dataset contains over 1,000 drug-target interactions, both of which have been extensively used for benchmarking predictive models in drug discovery [3].  
  
#### Datasets for Protein Targets  
The study of protein targets is equally critical in drug discovery, with several databases providing comprehensive information on protein structures and functions. The Protein Data Bank (PDB) is the primary repository for three-dimensional structural data of biological macromolecules. It includes over 180,000 structures, enabling researchers to visualize molecular interactions and understand the binding sites relevant for drug design [4].  
  
Another significant resource is UniProt, which offers a comprehensive protein sequence and functional information database. UniProt provides detailed annotations of protein sequences, including functional domains, post-translational modifications, and interaction partners, which are vital for understanding the biological context of drug-target interactions [5].  
  
#### Computational Approaches in De Novo Drug Discovery  
The integration of datasets into computational models enhances the efficiency of drug discovery processes. Recent advancements in deep learning frameworks, particularly GNNs, have demonstrated substantial promise in modeling molecular interactions and predicting their properties. For instance, the Molecular Pre-training Graph-based deep learning framework (MPG) has been shown to learn molecular representations effectively from large-scale unlabeled datasets, significantly improving the predictive performance of drug-target interactions [6].  
  
In the context of de novo drug design, methodologies utilizing recurrent neural networks (RNNs) have been employed to generate novel molecular structures. These generative models have been trained on existing chemical libraries, allowing them to produce compounds with desirable properties, such as high binding affinity to specific biological targets [7]. For example, one study demonstrated that an RNN-based model could reproduce a significant percentage of drug-like molecules designed by medicinal chemists [8].  
  
Moreover, self-supervised learning techniques have emerged as a powerful approach to enhance molecular representation learning. For instance, the BatmanNet architecture leverages a bi-branch masked graph transformer autoencoder to learn both local and global features of molecular graphs. This model has been shown to improve performance across various drug discovery tasks, including drug-drug interactions and drug-target interactions, by capturing essential structural and semantic information [9].  
  
#### Challenges and Future Directions  
Despite the advancements in datasets and computational models, challenges remain, particularly in addressing the scarcity of labeled data. Traditional supervised approaches often struggle with generalization due to the limited number of experimentally validated examples [10]. Self-supervised learning offers a potential solution by enabling models to learn from unlabeled data, although it requires substantial computational resources and sophisticated methodologies [11].  
  
Furthermore, the integration of hierarchical information and attention mechanisms in GNNs has been shown to enhance interpretability and predictive performance. The HiGNN framework, for example, incorporates a feature-wise attention block to recalibrate atomic features, thereby improving the model's ability to predict molecular properties [12]. Such innovations could provide deeper insights into the structure-activity relationships of drug candidates.  
  
#### Conclusion  
In summary, the identification of key datasets for small-molecule structures and protein targets is crucial in facilitating efficient drug discovery processes. The integration of comprehensive databases such as ChEMBL, PubChem, and PDB with advanced computational techniques, particularly GNNs and self-supervised learning, has enhanced the capabilities of researchers in predicting drug-target interactions and optimizing small-molecule drug candidates. While challenges regarding data scarcity and model generalization persist, ongoing advancements in computational methodologies and the development of innovative frameworks hold great promise for the future of de novo drug discovery. Continued exploration in these areas is essential for accelerating drug development and improving therapeutic outcomes.  
  
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## Data Representation

### Methods for Representing Molecules and Proteins as Graphs for GNN Input  
  
The representation of molecular structures and proteins in a format amenable to analysis by Graph Neural Networks (GNNs) poses a fundamental challenge in the field of de novo drug discovery. GNNs leverage the inherent graph-based nature of molecular structures, enabling the modeling of complex relationships between atoms and their connectivity within molecules. Thus, understanding how to effectively represent these molecular entities as graphs is critical for enhancing the performance of GNNs in various drug discovery tasks, including molecular property prediction, drug-target interaction, and virtual screening.  
  
#### Graph Representation of Molecules  
  
Molecules can be naturally represented as graphs, where nodes correspond to atoms and edges represent chemical bonds. The choice of graph representation significantly influences the performance of GNNs. A typical molecular graph consists of various node and edge features that encode valuable information about the molecular structure. For instance, node features may include atomic properties such as atomic number, hybridization state, or partial charges, while edge features can encode bond types (single, double, aromatic) and bond lengths [1][2].   
  
In recent advancements, frameworks like the Molecular Pre-training Graph-based deep learning framework (MPG) have demonstrated the efficacy of using extensive unlabeled datasets to pre-train GNNs on molecular representations. The MolGNet model, a key component of MPG, is designed to capture both node-level and graph-level representations, thereby facilitating the extraction of meaningful chemical insights from the data [1][2].  
  
#### Self-Supervised Learning Techniques  
  
The integration of self-supervised learning (SSL) methodologies has emerged as a promising approach to enhance the representation learning of molecular graphs. Traditional supervised learning techniques often struggle due to the scarcity of labeled molecular data, which can lead to overfitting and poor generalization [3]. Self-supervised techniques enable models to learn from large-scale unlabeled molecular datasets, effectively addressing the data scarcity issue.  
  
For instance, BatmanNet, a bi-branch masked graph transformer autoencoder, utilizes a self-supervised strategy to simultaneously learn local and global information about molecules. By reconstructing masked nodes and edges, BatmanNet captures the underlying structure and semantic information of molecules, thus enhancing the quality of molecular representations [4]. This approach has shown state-of-the-art performance across various drug discovery tasks, reinforcing the importance of SSL in molecular representation learning.  
  
#### Hierarchical Graph Neural Networks  
  
Hierarchical Graph Neural Networks (HiGNN) have been proposed to better capture the hierarchical and relational information inherent in molecular structures. HiGNN utilizes co-representation learning of molecular graphs alongside chemically synthesizable fragments to improve predictive performance in drug discovery tasks [5]. This model design incorporates a feature-wise attention mechanism, allowing for adaptive recalibration of atomic features, thereby enhancing the interpretability of molecular representations at the subgraph level [5].  
  
The ability to capture hierarchical information is vital, as it allows GNNs to understand not just the individual components of a molecule but also their interactions and overall structural context. This capability is particularly beneficial in applications such as drug-target interaction predictions, where understanding the nuances of molecular interactions is crucial [6].  
  
#### Incorporation of Biological Context  
  
While molecular graphs serve as a robust representation for chemical compounds, incorporating biological context—such as gene expression profiles and protein structures—can further enrich these representations. The hybrid neural network HNN2Mol exemplifies this approach by integrating gene expression data to guide the generation of molecular structures with desired phenotypic outcomes [7]. This fusion of biological data with molecular representations facilitates the generation of compounds that are not only chemically viable but also biologically relevant.  
  
Moreover, the incorporation of protein structure data into GNN frameworks allows for the exploration of drug-target interactions in a more integrated and holistic manner. For instance, methods that utilize 3D structural information alongside graph representations can mitigate the challenges posed by traditional 2D representations of molecular data, ultimately leading to better performance in predicting binding affinities [8].  
  
#### Challenges and Future Directions  
  
Despite the advancements in graph-based representations of molecules and proteins, several challenges remain. The computational demands associated with processing large-scale graph data can be prohibitive, particularly in the context of training GNNs on extensive datasets [9]. Additionally, the interpretability of GNN models, while improving, still presents challenges, particularly regarding the subjective nature of "ground truth" assessments in explainable artificial intelligence (XAI) applications [10].   
  
Future research should aim to develop more efficient algorithms and architectures that can handle large-scale molecular graphs while maintaining interpretability. Approaches like explainable GNNs, which utilize XAI techniques to elucidate the contributions of specific molecular substructures to predictive outcomes, are crucial for enhancing the transparency and reliability of GNN models in drug discovery [11].   
  
#### Summary  
  
In summary, representing molecules and proteins as graphs for GNN input is a multifaceted challenge that encompasses the effective encoding of atomic and molecular features, the integration of self-supervised learning methodologies, and the incorporation of biological context. By leveraging advanced graph-based techniques such as hierarchical GNNs and hybrid models, researchers can enhance the interpretability and predictive performance of GNNs in drug discovery applications. Continued advancements in computational efficiency, interpretability, and the integration of diverse biological data will further propel the capabilities of GNNs in elucidating the complexities of molecular interactions and facilitating the drug discovery process.  
  
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## Preprocessing Techniques

### Preprocessing Methods in Self-Supervised Graph Neural Networks for De Novo Drug Discovery  
  
In the realm of de novo drug discovery, the preprocessing of molecular data is a critical step that influences the efficacy of machine learning models, particularly Graph Neural Networks (GNNs). This section outlines key preprocessing methods including normalization, augmentation, and feature extraction, which are integral to the development of robust and interpretable models capable of predicting molecular properties and interactions.  
  
#### 1. Normalization  
  
Normalization is a fundamental preprocessing step aimed at standardizing the range of independent variables, thereby improving the convergence of learning algorithms. In the context of molecular data, normalization techniques can be applied to the features extracted from molecular graphs to ensure that all input features contribute equally to the model training process. Common normalization techniques include Min-Max scaling and Z-score normalization, which adjust the data to a common scale without distorting differences in the ranges of values.   
  
For instance, the use of normalization has been shown to enhance the performance of GNNs by mitigating the impact of outliers and varying distributions of molecular features [1][2]. In particular, when training GNNs on large-scale unlabeled datasets, the inclusion of normalized features can facilitate better representation learning, leading to improved transfer performance in downstream tasks such as molecular property prediction and drug-target interaction assessments [3][4].  
  
#### 2. Data Augmentation  
  
Data augmentation refers to techniques that artificially increase the size and diversity of training datasets by creating modified versions of existing data points. In drug discovery, where labeled data is often scarce, augmentation techniques are particularly valuable. Augmentation methods for molecular data can include structural perturbations, such as adding noise to molecular representations, or generating new molecular graphs through transformations like rotation, translation, and scaling.  
  
One innovative approach involves the use of self-supervised learning paradigms, where models learn to predict certain properties of the data from its augmented versions. For example, the MolGNet framework employs self-supervised strategies that allow the model to generalize better from the augmented data by learning both local and global molecular features [5][6]. This is particularly beneficial in complex molecular environments, where traditional data augmentation may not capture the intricate relationships present within molecular graphs.  
  
In addition, augmentation techniques can facilitate the exploration of chemical space, allowing models to generate diverse molecular candidates that can subsequently be screened for bioactivity. This is exemplified in the work of [7], where augmented training data contributed to improved model performance in predicting drug-like properties, thus enhancing the overall drug discovery pipeline.  
  
#### 3. Feature Extraction  
  
Feature extraction is a critical preprocessing step that involves transforming raw molecular data into a set of representative features that can be effectively utilized by machine learning algorithms. In GNNs, feature extraction typically focuses on transforming molecular graphs into structured embeddings that encapsulate relevant chemical properties and structural characteristics.  
  
Recent advancements have highlighted the efficacy of graph-based convolutional layers that operate directly on molecular graphs, allowing for the extraction of features that reflect the local connectivity and chemical environment of each atom within a molecule. The BatmanNet architecture, for instance, employs a bi-branch masked graph transformer autoencoder that learns to reconstruct missing nodes and edges from a masked molecular graph, thereby capturing essential structural and semantic information [8].  
  
Moreover, feature extraction can be enhanced by integrating hierarchical information, as demonstrated in the HiGNN framework, which utilizes co-representation learning of molecular graphs alongside chemically synthesizable fragments. This dual approach not only improves predictive performance but also aids in the interpretability of the models by allowing chemists to identify key components responsible for desired molecular properties [9][10].  
  
The selection of features can significantly influence the model's ability to generalize across different molecular tasks, such as predicting drug-drug interactions or estimating binding affinities. Techniques such as attention mechanisms can further refine feature extraction by dynamically recalibrating the importance of different molecular features during the training process, as evidenced by the work on ViDTA, which incorporates global memory nodes to enhance feature representation [11][12].  
  
#### Conclusion  
  
In summary, effective preprocessing methods, including normalization, data augmentation, and feature extraction, play an essential role in the application of self-supervised GNNs for de novo drug discovery. These techniques not only enhance model performance but also facilitate the interpretation of molecular representations, thereby contributing to the overall success of AI-driven drug discovery efforts. By employing a combination of these preprocessing strategies, researchers can improve the robustness and accuracy of predictive models, paving the way for the identification of novel drug candidates with desirable biological activities.  
  
The integration of these preprocessing methods into the drug discovery workflow exemplifies the potential of advanced machine learning techniques to address the challenges posed by the complexity of molecular data, ultimately leading to more efficient and effective drug development processes [13][14].

# Model Architecture and Optimization

## Model Architecture and Optimization  
  
The application of Self-Supervised Graph Neural Networks (GNNs) in de novo drug discovery represents a significant advancement in the field of computational drug design. The inherent ability of GNNs to model complex molecular structures via graph-based representations addresses many challenges associated with traditional molecular representation methods, particularly in the context of insufficient labeled data. This section discusses the architectures of the proposed models, their optimization processes, and the implications of self-supervised learning techniques in enhancing molecular representation learning.  
  
### 1. Overview of Graph Neural Networks in Drug Discovery  
  
Graph Neural Networks have emerged as a leading paradigm for modeling molecular data due to their capability to capture intricate relationships within molecular graphs. Traditional supervised learning approaches in drug discovery often struggle with the scarcity of labeled data, which adversely affects generalization capabilities of the models [2], [3]. In contrast, GNNs can exploit structural information from large-scale unlabeled datasets, facilitating better molecular representation learning. Recent studies have demonstrated that pre-training GNNs via self-supervised learning on extensive unlabeled datasets can significantly improve their performance in downstream tasks such as molecular property prediction and drug-target interaction [6], [11].  
  
### 2. Self-Supervised Learning Strategies  
  
Self-supervised learning (SSL) serves as a vital component in the optimization of GNN architectures for drug discovery. The self-supervised strategies enable the model to learn useful representations from the intrinsic properties of the data without requiring explicit labels. For instance, the bi-branch masked graph transformer autoencoder (BatmanNet) employs a dual approach to reconstruct missing nodes and edges from masked molecular graphs, thereby enriching the model's understanding of both local and global molecular structures [4]. This architecture has shown state-of-the-art results across multiple drug discovery tasks, including molecular properties prediction, drug-drug interaction, and drug-target interaction [5].  
  
Furthermore, the Molecular Pre-training Graph-based deep learning framework, named MPG, leverages a self-supervised strategy that operates at both node and graph levels. This approach allows for the effective capture of valuable chemical insights from a vast corpus of unlabeled molecular data, ultimately leading to interpretable molecular representations [3]. The MPG framework demonstrates the potential for fine-tuning with minimal additional layers, thus facilitating efficient adaptation to various drug discovery tasks.  
  
### 3. Model Architectures  
  
The architectural design of GNNs used in drug discovery varies considerably, incorporating several innovative features aimed at enhancing model performance. For example, the use of hierarchical informative GNNs (HiGNN) incorporates co-representation learning of molecular graphs and chemically synthesizable fragments to better predict molecular properties [7]. The introduction of feature-wise attention blocks further refines the model's ability to recalibrate atomic features post-message passing, resulting in superior predictive performance on benchmark datasets [8].  
  
Additionally, the 3D-MolGNN$\_{RL}$ framework integrates reinforcement learning with a deep generative model built upon 3D scaffolds. This model enables the atom-by-atom construction of target candidates while optimizing key molecular features based on multi-objective reward functions [9]. Such architectures not only enhance the design process but also contribute to the interpretability of the model, allowing for insights into the activity and binding affinities of generated molecules.  
  
### 4. Optimization Techniques  
  
The optimization of GNNs for drug discovery is a multifaceted process, involving both architectural refinements and training strategies. One significant aspect of this optimization involves the incorporation of domain-specific knowledge, such as drug-like properties and synthetic accessibility. For instance, NovoMol employs recurrent neural networks to generate drug candidates optimized for oral bioavailability, demonstrating a rigorous training cycle that incorporates quantitative estimates of drug-likeness (QED) [5]. This approach led to a substantial improvement in the number of generated molecules meeting stringent bioavailability thresholds.  
  
Moreover, the integration of multi-objective optimization strategies allows for the simultaneous targeting of multiple desirable molecular characteristics. For example, the molecular graph conditional variational autoencoder (MGCVAE) has been shown to effectively generate molecules that satisfy dual optimization criteria, leading to a marked increase in the production of drug-like compounds [15]. Such strategies highlight the importance of balancing various molecular features during the optimization process, which is critical for successful drug development.  
  
### 5. Challenges and Future Directions  
  
Despite the advancements in GNN architectures and optimization techniques, several challenges remain. The effective integration of hierarchical information and the relationships between molecular features continue to present obstacles [6], [12]. Moreover, there exists a need for improved interpretability of GNN models, particularly in the context of explainable artificial intelligence (XAI) methods, which can elucidate the contributions of specific molecular substructures to biological activity [11].   
  
Future research should focus on developing more sophisticated self-supervised learning methodologies that require fewer computational resources while improving model efficiency. Additionally, enhancing the interpretability of GNN-driven models will be paramount, allowing researchers to derive actionable insights from the predictions made by these complex architectures [14]. Furthermore, as the field of de novo drug discovery continues to evolve, the integration of hybrid models that combine various AI techniques, such as the utilization of gene expression profiles alongside molecular structures, may provide a pathway to generating molecules with desirable phenotypes [9].  
  
### Conclusion  
  
The utilization of Self-Supervised Graph Neural Networks in de novo drug discovery represents a transformative approach to molecular design. By employing innovative architectures and optimization strategies, these models can effectively navigate the complexities of molecular representations and improve predictive accuracy across various drug discovery tasks. While challenges remain in the areas of interpretability and data efficiency, ongoing advancements in self-supervised learning and GNN frameworks hold great promise for accelerating the drug discovery process and enhancing the identification of viable drug candidates. The synthesis of these techniques not only facilitates the exploration of vast chemical spaces but also paves the way for future innovations in computational drug design.

## GNN Architectures for Drug Discovery

### Review of Existing GNN Architectures Suitable for Predicting Properties and Binding Affinities  
  
The application of Graph Neural Networks (GNNs) in the domain of drug discovery has emerged as a transformative approach, particularly for predicting molecular properties and binding affinities. This review synthesizes the advancements in GNN architectures tailored for such predictive tasks, emphasizing the evolution and efficacy of self-supervised learning strategies within this context.  
  
#### 1. Importance of Molecular Representation Learning  
  
A pivotal challenge in drug discovery is the effective representation of molecular structures to enhance predictive accuracy. Traditional methods often rely on handcrafted features, which can be insufficient in capturing the intricate relationships inherent in molecular graphs. GNNs have been developed to address this limitation by leveraging the graph-based nature of molecular data, allowing for the extraction of richer feature representations from the structural information encoded in molecular graphs [1][2].   
  
Recent advancements have demonstrated that multi-layer GNN architectures can model complex interactions between atoms and their connections, ultimately improving the performance of various downstream tasks including property prediction and binding affinity estimation. For instance, the hierarchical informative graph neural network (HiGNN) has been proposed to integrate co-representation learning of molecular graphs with chemically relevant fragments, thereby achieving state-of-the-art results on benchmark datasets [1].   
  
#### 2. Self-Supervised Learning in GNNs  
  
Self-supervised learning (SSL) has gained traction as a method to enhance the training of GNNs, particularly when labeled data is scarce. Recent studies indicate that SSL can significantly boost the transferability of learned representations to various molecular property prediction tasks [3]. The BatmanNet architecture exemplifies this trend, employing a bi-branch masked graph transformer autoencoder that reconstructs missing nodes and edges in molecular graphs. This dual approach allows the model to capture both local and global molecular characteristics, resulting in improved predictive performance across a spectrum of drug discovery tasks [3].  
  
Moreover, the Molecular Pre-training Graph (MPG) framework illustrates the utility of SSL by leveraging large-scale unlabeled datasets to pre-train GNNs, which can subsequently be fine-tuned for specific tasks. This methodology optimally positions GNNs to learn valuable chemical insights and produce interpretable representations of molecules, thereby facilitating the design of effective drug candidates [4][5].  
  
#### 3. Predicting Drug-Target Binding Affinities  
  
The prediction of drug-target binding affinities is crucial in the drug discovery pipeline, as it directly influences the selection of viable drug candidates. Recent advancements in GNN-based models have demonstrated promising results in this area. For example, a modified gated recurrent unit (GRU) combined with GNN architectures has been proposed to extract features from both drug-target protein sequences and molecular representations, effectively yielding high accuracy in binding affinity predictions [2].  
  
Further explorations into GNN architectures have revealed the potential of integrating explainable artificial intelligence (XAI) techniques to enhance interpretability in binding predictions. The Hierarchical Grad-CAM graph Explainer (HGE) framework, for instance, elucidates the molecular moieties contributing to binding affinities, thus enabling computational chemists to optimize molecular structures based on empirical observations [8].   
  
#### 4. Challenges and Future Directions  
  
Despite the significant strides made in GNN architectures for drug discovery, challenges remain, particularly regarding the interpretability and scalability of these models. While several GNN approaches have been shown to outperform traditional methods, their acceptance in the pharmaceutical industry is often impeded by a lack of transparency in model decisions [7]. To address this, the combination of GNNs with XAI methods has emerged as a viable strategy to enhance interpretability without compromising performance.  
  
Furthermore, the integration of geometric deep learning techniques presents an exciting avenue for future research. By incorporating three-dimensional structural information into GNN models, researchers can enhance the predictive capabilities concerning binding affinities and molecular interactions [14][15]. The development of frameworks like 3D-MolGNN$\_{RL}$, which utilizes reinforcement learning to generate target-specific molecules, exemplifies the innovative potential of combining GNNs with advanced computational strategies [15].  
  
#### 5. Summary  
  
In conclusion, the evolution of GNN architectures has significantly enhanced the predictive capabilities in drug discovery, particularly in the context of molecular property prediction and drug-target binding affinity assessments. The application of self-supervised learning has proven to be a critical factor in improving model performance, allowing for richer molecular representations derived from unlabeled datasets. While challenges in interpretability and scalability persist, the integration of novel computational techniques and frameworks offers promising avenues for future exploration. Continued research in this field is essential for advancing drug discovery methodologies, ultimately leading to the identification of more effective therapeutic agents.  
  
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## Training Strategies

### Self-Supervised Training Approaches and Optimization Techniques  
  
The advent of self-supervised learning has significantly transformed the landscape of drug discovery, particularly in the utilization of Graph Neural Networks (GNNs) for molecular representation learning. This section discusses the current self-supervised training approaches and optimization techniques that leverage the unique properties of GNNs to facilitate de novo drug discovery.  
  
#### Self-Supervised Learning Frameworks  
  
Self-supervised learning (SSL) enables models to learn from vast amounts of unlabeled data, addressing the critical challenge of data scarcity commonly encountered in supervised learning paradigms. SSL frameworks extract meaningful features from input data by creating surrogate tasks that help the model learn representations without explicit labels. In the context of molecular data, GNNs have emerged as a powerful tool due to their ability to model complex relationships inherent in molecular structures.  
  
One notable self-supervised approach is the Molecular Pre-training Graph-based framework (MPG), which employs a novel MolGNet model. This model is pre-trained on extensive datasets of unlabeled molecules—specifically, 11 million compounds. The pre-training process captures both local and global molecular features through an effective self-supervised strategy, allowing for the generation of interpretable molecular representations that are subsequently fine-tuned for various downstream tasks, including molecular property prediction and drug-target interaction modeling [1][2].   
  
Another innovative architecture, the BatmanNet, utilizes a bi-branch masked graph transformer autoencoder to learn molecular representations by reconstructing masked nodes and edges from molecular graphs. This architecture improves the model's capacity to capture underlying molecular semantics, thereby enhancing its performance across multiple drug discovery tasks [3]. Such approaches illustrate the potential of self-supervised learning to generate robust molecular representations that extend beyond traditional supervised methods.  
  
#### Optimization Techniques in Self-Supervised Learning  
  
Optimization techniques play a crucial role in enhancing the efficacy of self-supervised models. The performance of GNNs, particularly in drug discovery applications, can be significantly influenced by the choice of optimization algorithms and hyperparameter tuning. The self-supervised tasks employed in training must be carefully designed to balance model complexity and computational efficiency.   
  
For instance, while many existing methodologies involve multiple complex self-supervised tasks, recent developments advocate for simpler strategies that simultaneously capture local and global molecular information without incurring excessive computational costs. This balance is vital, as complex tasks may lead to longer training times and require substantial computational resources, which are not always feasible in drug discovery settings [3][4].  
  
In addition to task design, incorporating advanced optimization techniques such as reinforcement learning (RL) has shown promise in refining generated molecular candidates. The 3D-MolGNN$\_{RL}$ framework couples RL with GNNs to optimize molecular design in a three-dimensional space, effectively generating target-specific candidates while ensuring that key features such as binding affinity and synthetic accessibility are prioritized. This multi-objective reward function approach facilitates efficient exploration of chemical space, thereby expediting the drug discovery process [13][14].  
  
#### Transfer Learning and Fine-Tuning Approaches  
  
Transfer learning plays a pivotal role in leveraging pre-trained GNNs for specific drug discovery tasks. By fine-tuning models that have been pre-trained on large unlabeled datasets, researchers can efficiently adapt these models to new tasks with relatively small labeled datasets. This strategy significantly mitigates the challenges posed by data scarcity and enhances the model's generalization capabilities [1][2].  
  
For example, the MolGNet model, after its pre-training phase, can be fine-tuned by adding a minimal output layer to perform various predictive tasks related to drug properties. This adaptability demonstrates the versatility of self-supervised learning in facilitating a broad range of applications within drug discovery, encompassing molecular property prediction, drug-drug interaction assessments, and drug-target interaction evaluations [1].  
  
Similarly, the hybrid neural network approach, HNN2Mol, integrates gene expression profiles to guide the generation of molecular structures with desirable phenotypes. By employing a variational autoencoder coupled with a long short-term memory network, this model effectively learns latent features from biological data, allowing for the generation of novel molecules that demonstrate potential bioactivity [9]. Such integration of biological data into the self-supervised learning pipeline exemplifies the innovative approaches being employed to enhance molecular representation and discovery.  
  
#### Interpretability and Explainability in GNNs  
  
Interpretability remains a significant challenge in the application of GNNs for drug discovery. Despite the advancements made in self-supervised learning, the ability to elucidate the contributions of specific molecular substructures to biological activity is crucial for rational drug design. Recent efforts to integrate explainable artificial intelligence (XAI) techniques with GNNs have made strides in addressing this issue. The Hierarchical Grad-CAM graph Explainer (HGE) framework, for instance, provides insights into molecular moieties that drive protein-ligand binding stabilization by leveraging various levels of model output explanations [11][12].  
  
The implementation of such explainability frameworks not only enhances the interpretability of GNN models but also empowers computational chemists to make informed decisions during the drug design process. Understanding the molecular patterns that contribute to binding affinities can guide the optimization of molecular structures and the repurposing of existing drugs, thus accelerating the discovery of new therapeutics [11][12].  
  
#### Summary and Conclusion  
  
In summary, self-supervised training approaches, particularly those harnessing the capabilities of GNNs, are revolutionizing the domain of de novo drug discovery. The ability to learn from unlabeled data, coupled with innovative optimization techniques and transfer learning strategies, is paving the way for the efficient generation of novel molecular candidates. Furthermore, the integration of interpretability and explainability frameworks is essential for ensuring that these advanced models can be utilized effectively in practical drug discovery scenarios. As research in this area continues to evolve, it will be imperative to develop robust methodologies that combine the strengths of self-supervised learning with domain-specific insights to enhance the efficiency and success rates of drug discovery initiatives.   
  
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## Uncertainty Calibration

### Methods for Calibrating Uncertainty in Predictions to Support Active Learning  
  
#### Introduction  
  
The integration of Artificial Intelligence (AI) and machine learning techniques, particularly Graph Neural Networks (GNNs), has revolutionized de novo drug discovery by facilitating the generation and evaluation of novel molecular structures. However, the inherent uncertainties associated with predictions made by these models pose significant challenges, particularly in active learning contexts where iterative model improvement relies on the reliability of predictive outputs. Active learning aims to optimize the learning process by selectively querying the most informative samples from a pool, thus necessitating robust mechanisms for uncertainty quantification and calibration. This section discusses various methods for calibrating uncertainty in predictions derived from GNNs and other deep learning paradigms, emphasizing their relevance to enhancing active learning strategies in drug discovery.  
  
#### Uncertainty Calibration Techniques  
  
1. \*\*Bayesian Approaches\*\*: One of the foundational techniques for uncertainty quantification in machine learning, including GNNs, is the application of Bayesian inference. Bayesian Neural Networks (BNNs) provide a probabilistic framework to model uncertainty by treating weights as distributions rather than fixed values. This approach facilitates the estimation of uncertainty in predictions through a posterior distribution of the model parameters. Recent advancements in variational inference methods have made it feasible to apply BNNs to GNNs, thus enabling the calibration of uncertainty in molecular property predictions [5][8]. By quantifying uncertainty, researchers can prioritize experiments and focus resources on the most promising molecular candidates.  
  
2. \*\*Ensemble Learning\*\*: Another effective strategy for uncertainty calibration is the use of ensemble methods, where multiple models are trained on the same task and their predictions are aggregated. Ensembles can provide an estimate of uncertainty by evaluating the variance in predictions across different models. This method has been successfully implemented in GNN frameworks, where diverse architectures or training subsets can capture varying aspects of molecular representations [6][10]. The ensemble predictions can also improve robustness against overfitting, thereby enhancing the reliability of active learning cycles.  
  
3. \*\*Dropout as a Bayesian Approximation\*\*: A more straightforward approach for uncertainty estimation involves the use of dropout during inference, initially proposed by Gal and Ghahramani [2]. By randomly dropping units from the network, this technique simulates a Bayesian approximation, allowing for the generation of uncertainty estimates during model predictions. This approach has been integrated into GNNs to measure model confidence in predicting molecular properties, thereby providing valuable insights for active learning scenarios where uncertain predictions may warrant additional exploration [3][7].  
  
4. \*\*Prediction Interval Estimation\*\*: A novel approach to uncertainty quantification involves the construction of prediction intervals, which provide a range within which the true output is expected to fall with a certain confidence level. This method can be particularly beneficial in active learning as it allows practitioners to establish thresholds for data selection based on the reliability of predictions [9]. Techniques such as quantile regression have been used to generate these intervals, enabling a more nuanced selection process that can prioritize samples with higher uncertainty.  
  
5. \*\*Calibration Methods\*\*: Beyond the initial uncertainty estimation, calibration techniques such as Platt Scaling and Isotonic Regression can be employed to adjust the predicted probabilities to better reflect true outcomes. These methods involve fitting a secondary model to the outputs of the primary model to align predicted probabilities with empirical frequencies [4]. In drug discovery, where the stakes of false positives and negatives are inherently high, calibrated probabilities can significantly enhance decision-making processes in active learning frameworks.  
  
#### Active Learning Integration  
  
To leverage the calibrated uncertainty in predictions effectively, several strategies can be employed within active learning paradigms:  
  
1. \*\*Uncertainty Sampling\*\*: This strategy focuses on selecting the samples for which the model exhibits the highest uncertainty. By incorporating uncertainty estimates from the aforementioned methods, researchers can identify molecular candidates that are not only novel but also critical for refining the model. This approach is particularly valuable in scenarios characterized by limited labeled data, allowing for efficient resource allocation towards the most informative samples [1][12].  
  
2. \*\*Expected Model Change\*\*: Another approach is to select samples that are predicted to induce the greatest change in the model upon inclusion. This method utilizes uncertainty estimates to evaluate the potential impact of adding specific samples to the training set, thus guiding the active learning process towards the most influential candidates [11][14].  
  
3. \*\*Diversity-Based Sampling\*\*: In addition to uncertainty, incorporating diversity into the selection process ensures a broad exploration of the chemical space. This can be achieved by integrating diversity measures into the uncertainty framework, allowing for the identification of molecular candidates that are not only uncertain but also diverse in terms of their chemical properties. This dual approach can enhance the exploration-exploitation balance critical to effective active learning [13][15].  
  
4. \*\*Iterative Feedback Loops\*\*: The calibration of uncertainty should be an iterative process, where predictions are continually assessed and refined based on experimental feedback. By establishing a closed-loop system, researchers can adaptively improve the model's performance, thereby enhancing the predictive power and applicability of GNNs in drug discovery [6][9]. This iterative refinement process is crucial for maintaining the relevance of the model in dynamic research environments.  
  
#### Conclusion  
  
The calibration of uncertainty in predictions plays a pivotal role in supporting active learning in de novo drug discovery, particularly with the integration of self-supervised GNNs. Through various techniques such as Bayesian approaches, ensemble learning, and dropout methods, researchers can enhance the reliability of predictive models, thereby improving the selection of molecular candidates for further investigation. By implementing strategies that combine uncertainty with diversity and iterative feedback, the active learning process can be optimized, ultimately leading to more efficient and effective drug discovery outcomes. As the field continues to evolve, the development of robust uncertainty calibration methods will remain essential for advancing AI-driven drug discovery methodologies.

# Implementation and Deployment

# Implementation and Deployment  
  
## Introduction to Self-Supervised Graph Neural Networks in Drug Discovery  
  
The implementation of self-supervised graph neural networks (GNNs) in de novo drug discovery represents an innovative approach to addressing the challenges associated with molecular representation learning. Traditional supervised learning methods often struggle with the scarcity of labeled data, which is particularly problematic in the field of drug discovery. In this context, self-supervised learning emerges as a compelling alternative, enabling models to learn from vast amounts of unlabeled molecular data [1][2]. This section discusses the implementation and deployment strategies for self-supervised GNNs in the context of drug discovery, focusing on the methodologies employed, the frameworks developed, and the anticipated impact on the drug discovery pipeline.  
  
## Methodological Framework  
  
### Molecular Pre-training Graph-based Deep Learning Framework (MPG)  
  
One pioneering framework is the Molecular Pre-training Graph-based deep learning framework (MPG), which employs a self-supervised strategy to learn molecular representations from large-scale unlabeled datasets. The MPG framework utilizes the MolGNet model, pre-trained on an extensive dataset of 11 million unlabeled molecules. This pre-training allows the model to capture essential chemical insights and produce interpretable molecular representations, which can then be fine-tuned for various drug discovery tasks, such as predicting molecular properties and drug-target interactions [3][4]. The adaptability of the MPG framework facilitates the development of state-of-the-art models with minimal additional training requirements, thereby streamlining the drug discovery process and enhancing its efficiency.  
  
### BatmanNet: A Bi-Branch Masked Graph Transformer Autoencoder  
  
Another notable approach is the BatmanNet, a bi-branch masked graph transformer autoencoder designed to learn molecular representations by reconstructing masked molecular graphs. This model effectively captures both local and global information within molecular structures, addressing the limitations of previous GNN architectures that often failed to integrate hierarchical information [5][6]. BatmanNet utilizes complementary graph autoencoders to reconstruct missing nodes and edges, thus improving the representation of molecular data. The successful implementation of BatmanNet across multiple drug discovery tasks highlights its superior performance in molecular representation learning, particularly in the context of drug-drug and drug-target interactions [7].  
  
### Integration of Gene Expression Profiles  
  
Recent advancements have also introduced hybrid approaches that leverage gene expression profiles to enhance molecular generation. The HNN2Mol model, for instance, utilizes a variational autoencoder to extract latent features from gene expression data, which are then combined with chemical generators to produce molecular structures aligned with desired phenotypes [8]. This innovative integration allows for the generation of molecules that not only exhibit favorable bioactivity but also align with the specific biological contexts, thereby optimizing the drug design process.  
  
## Deployment Strategies  
  
### Reinforcement Learning in Drug Discovery  
  
The use of reinforcement learning (RL) within the framework of GNNs has shown promise in optimizing molecular design. The 3D-MolGNN$\_{RL}$ framework couples RL with a deep generative model to create target-specific molecules by iteratively optimizing key molecular features [9]. This approach not only addresses the challenges of traditional design-test cycles but also leverages multi-objective reward functions to enhance the activity, binding affinity, and synthetic accessibility of generated candidates. Such methodologies are particularly relevant for infectious disease targets and could potentially revolutionize lead optimization strategies.  
  
### Hierarchical Informative Graph Neural Networks (HiGNN)  
  
The implementation of hierarchical informative GNNs, such as HiGNN, represents a significant advancement in molecular property prediction. By utilizing co-representation learning of molecular graphs and chemically synthesizable BRICS fragments, HiGNN enhances the interpretability and predictive performance of GNN models [10]. The inclusion of a feature-wise attention block allows for adaptive recalibration of atomic features, further improving the model's capability to identify key molecular components crucial for the design of new therapeutic agents.  
  
### Explainable Artificial Intelligence (XAI)  
  
The integration of explainable artificial intelligence (XAI) methods within the drug discovery pipeline is critical for enhancing model interpretability. The application of techniques such as Grad-CAM and hierarchical Grad-CAM graph explainers offers insights into the contributions of molecular substructures to biological activity [11][12]. These advancements not only improve the transparency of GNN models but also empower computational chemists to refine molecular designs based on a deeper understanding of the underlying biology.  
  
## Challenges in Implementation  
  
Despite the promising advancements in self-supervised GNNs for drug discovery, several challenges remain. The computational demands of training large-scale GNN models can be prohibitive, particularly in resource-limited settings [13]. Moreover, the integration of diverse data types, such as molecular structures and biological profiles, necessitates robust data management and preprocessing strategies to ensure effective model performance.  
  
Furthermore, the interpretability of GNNs continues to be a significant concern. While recent innovations in XAI have made strides in addressing this issue, the subjective nature of model interpretation still poses challenges for quantitative assessments [14]. As such, ongoing research is needed to develop standardized evaluation metrics that can objectively assess the interpretability of GNN models in drug discovery contexts.  
  
## Future Directions  
  
The future of self-supervised GNNs in de novo drug discovery holds significant promise. Continued advancements in computational capabilities and model architectures are likely to enhance the efficiency and effectiveness of drug design processes. The integration of multi-modal data sources, including genomic, proteomic, and chemical data, will be instrumental in refining molecular representations and improving predictive accuracy [15]. Additionally, the development of user-friendly software tools and frameworks will facilitate the adoption of these advanced methodologies by researchers and practitioners in the pharmaceutical industry.  
  
## Conclusion  
  
In conclusion, the implementation and deployment of self-supervised GNNs in de novo drug discovery represent a transformative shift in the methodologies employed within the field. By leveraging large-scale unlabeled datasets and advanced machine learning techniques, frameworks such as MPG and BatmanNet have demonstrated significant potential in optimizing molecular representation and enhancing drug discovery outcomes. As the field progresses, addressing the challenges of computational demands and model interpretability will be essential for realizing the full potential of self-supervised learning in drug discovery. The integration of these methodologies promises to streamline the drug design process, ultimately yielding novel therapeutic agents with enhanced efficacy and safety profiles.  
  
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## Integration into Drug Discovery Workflows

### Integration of Self-Supervised Graph Neural Networks into Drug Discovery Pipelines  
  
The integration of Graph Neural Networks (GNNs) into drug discovery pipelines has emerged as a promising approach to enhance the efficiency and accuracy of molecular representation and prediction tasks. Particularly, self-supervised learning strategies have been developed to address the challenges associated with the scarcity of labeled data in traditional supervised learning frameworks. This section explores the potential of self-supervised GNN models in de novo drug discovery, focusing on their mechanisms, applications, and the advantages they offer in existing drug discovery workflows.  
  
#### The Role of GNNs in Drug Discovery  
  
Graph Neural Networks have garnered attention for their ability to capture complex relationships within molecular structures by representing them as graphs, where atoms are nodes and bonds are edges. This representation allows GNNs to effectively model molecular properties and interactions, which are crucial for drug discovery applications, including molecular property prediction, drug-drug interactions, and drug-target interactions [1], [3]. Traditional approaches often rely on handcrafted features, which may fail to encapsulate the underlying chemical insights, whereas GNNs can learn these features directly from the molecular graph representations [4], [5].  
  
Despite their advantages, the adoption of GNNs in drug discovery has been hampered by the limitations of supervised learning, particularly the need for large labeled datasets. Self-supervised learning (SSL) has emerged as a viable alternative, enabling the pre-training of models on large unlabeled datasets to learn rich molecular representations. For instance, the Molecular Pre-training Graph-based framework (MPG) showcases how GNNs can be pre-trained on 11 million unlabeled molecules, demonstrating a significant improvement in performance across various downstream tasks [1], [2].  
  
#### Self-Supervised Learning Mechanisms  
  
Self-supervised learning mechanisms in GNNs typically involve the generation of pseudo-labels or representations from unlabeled data, allowing the model to learn without the need for extensive labeled datasets. For example, the MolGNet model proposed in the MPG framework employs self-supervised strategies at both the node and graph levels, capturing valuable chemistry insights that lead to interpretable representations [1]. Similarly, BatmanNet utilizes a bi-branch masked graph transformer autoencoder to reconstruct missing nodes and edges, thereby learning local and global molecular information effectively [4].  
  
These self-supervised strategies not only enhance the models' understanding of molecular structures but also enable them to generalize better to unseen data, addressing the challenge of poor transfer performance that often plagues supervised models [1], [4]. The ability to fine-tune these pre-trained models with minimal additional data further facilitates their integration into drug discovery pipelines, making them adaptable to a wide range of tasks such as predicting molecular properties and elucidating drug-target interactions [2], [4].  
  
#### Enhancing Interpretability in GNN Models  
  
One of the significant challenges in the application of GNNs to drug discovery is the interpretability of the models. Traditional GNN approaches have faced criticism for their "black box" nature, which complicates the understanding of how specific molecular features contribute to predictive outcomes. Recent advancements in explainable artificial intelligence (XAI) techniques have sought to mitigate this issue by providing frameworks that elucidate the contributions of various molecular substructures to biological activity [3], [6].   
  
For instance, the Hierarchical Grad-CAM graph Explainer (HGE) allows for detailed analyses of molecular moieties driving protein-ligand binding, highlighting the relevance of specific chemical structures in the context of drug-target interactions [6]. Furthermore, integrating XAI techniques with GNNs has been shown to improve the interpretability of models without compromising their predictive performance, thus facilitating the rational design of novel therapeutics [3], [6].  
  
#### Applications in De Novo Drug Discovery  
  
The application of self-supervised GNNs is particularly relevant in de novo drug discovery, where the objective is to generate novel molecular structures with desirable properties. Approaches such as NovoMol and HNN2Mol leverage GNNs to synthesize new molecules by exploring the chemical space more efficiently than traditional methods [9], [11]. These models can be fine-tuned using small sets of known active compounds against specific targets, enhancing their ability to generate hit-like molecules with high affinity and bioactivity [9], [11].  
  
Moreover, GNNs have been employed in virtual screening tasks, where they demonstrate state-of-the-art performance in predicting the activity of small molecules against various biological targets [6], [10]. The ability to efficiently identify potential drug candidates accelerates the drug discovery process and reduces the time and costs associated with experimental validation.  
  
#### Challenges and Future Directions  
  
Despite the promising potential of self-supervised GNNs in drug discovery, several challenges remain. The computational intensity of training large models on extensive datasets poses practical limitations, as does the need for sophisticated architectures that can balance local and global molecular information [4], [5]. Furthermore, while self-supervised learning addresses some limitations of traditional supervised methods, it is essential to ensure that the learned representations are robust and generalizable across diverse chemical spaces.  
  
Future research should focus on optimizing the architectures of GNNs for specific drug discovery tasks, enhancing the interpretability of models, and exploring hybrid approaches that combine GNNs with other machine learning techniques. Additionally, developing standardized benchmarks for evaluating GNN performance in drug discovery contexts will be crucial to advancing the field [3], [6].  
  
#### Conclusion  
  
In conclusion, the integration of self-supervised Graph Neural Networks into drug discovery pipelines represents a significant advancement in the field of computational drug design. By leveraging large unlabeled datasets and innovative self-supervised strategies, GNNs can produce expressive molecular representations that facilitate various drug discovery tasks. As the challenges of interpretability and computational demands are addressed, self-supervised GNNs are poised to play a pivotal role in the future of drug discovery, ultimately leading to more efficient and effective therapeutic development processes. The ongoing exploration of these models will undoubtedly yield new insights and methodologies that could revolutionize how drug discovery is approached in the coming years.

## Deployment Considerations

### Challenges Related to Deploying GNN Models in Real-World Scenarios  
  
Graph Neural Networks (GNNs) have shown significant promise in the realm of de novo drug discovery, particularly in their capability to model complex molecular structures and predict molecular properties. However, the deployment of GNN models in real-world scenarios is fraught with several challenges that hinder their widespread acceptance and practical application. This section discusses these challenges in detail, drawing from a range of studies and insights from the current literature.  
  
#### Data Scarcity and Quality  
  
One of the most pressing challenges in deploying GNN models is the scarcity of labeled data, which is essential for supervised learning approaches. Most GNNs rely heavily on labeled datasets for training; however, in drug discovery, obtaining high-quality labeled data is both expensive and time-consuming. This scarcity leads to models that may exhibit poor generalization capabilities when applied to unseen data [1][3]. The introduction of self-supervised learning strategies, such as the Molecular Pre-training Graph-based deep learning framework (MPG) and the BatmanNet model, highlights attempts to mitigate this issue by leveraging large-scale unlabeled datasets [1][4]. These methods are designed to learn molecular representations from vast amounts of unlabeled data, yet they still require substantial computational resources and time to pre-train effectively, thus posing a barrier for rapid deployment in real-world settings [4].  
  
#### Interpretability and Explainability  
  
The interpretability of GNN models remains a significant challenge, which is critical for their acceptance in the pharmaceutical industry. While advances in explainable artificial intelligence (XAI) techniques have been made, many GNN models still lack the transparency required for clinicians and researchers to trust their outputs [2][5]. For instance, while GradInput and Integrated Gradients have been identified as effective methods to enhance model interpretability, the subjective nature of "ground truth" assignments complicates the evaluation of these interpretations [3][6]. As a result, the lack of clear insights into the decision-making processes of these models can hinder their adoption in critical applications such as drug design and optimization, where understanding the rationale behind predictions is vital for further development and regulatory approval.  
  
#### Computational Resources and Scalability  
  
Deploying GNN models in real-world drug discovery contexts often demands extensive computational resources, which can be a limiting factor for many research institutions and pharmaceutical companies. The complexity of GNN architectures, coupled with the need for large-scale pre-training on extensive datasets, requires high-performance computing environments that may not be readily available [4][12]. Moreover, the inherent scalability issues in training GNNs on large graphs can lead to significant delays in model deployment, especially when rapid iterations are necessary to adapt to evolving research demands [4][13]. Consequently, balancing the computational demands of GNNs with practical deployment considerations is crucial for their real-world application.  
  
#### Integration with Existing Workflows  
  
Integrating GNN models into existing drug discovery workflows presents another layer of complexity. Many pharmaceutical companies have established traditional methodologies that may not easily accommodate the novel approaches introduced by GNNs. The incorporation of GNNs requires not only the adaptation of computational frameworks but also a cultural shift within research teams to embrace data-driven methodologies [5][6]. This integration challenge is exacerbated by the need for collaboration between computational chemists, biologists, and data scientists to ensure that GNN models are effectively utilized in the drug discovery pipeline [1][9]. The fragmented nature of interdisciplinary collaboration can hinder the seamless adoption of GNN technologies in practical settings.  
  
#### Ethical Considerations and Bias  
  
Ethical implications surrounding the use of GNNs in drug discovery also warrant careful examination. The potential for biased predictions arising from the data used to train these models can lead to disparities in drug development, particularly if certain populations are underrepresented in the training datasets [2][6]. Ensuring that models are trained on diverse and representative data is critical to mitigate these biases and promote equitable outcomes in drug discovery. Furthermore, the ethical considerations surrounding data privacy, especially with patient data, necessitate stringent guidelines and practices to protect sensitive information while leveraging machine learning techniques in drug research [12][13].  
  
#### Future Directions and Solutions  
  
To address these challenges, several future directions can be proposed. Firstly, enhancing self-supervised learning techniques could alleviate data scarcity by enabling models to learn from unlabeled data more effectively. For example, hybrid models that combine the strengths of GNNs with other machine learning approaches, such as reinforcement learning, may provide a pathway to generate more robust and interpretable drug candidates [11][15]. Additionally, ongoing research into developing more interpretable GNN architectures will be crucial for building trust among stakeholders in the drug discovery process [2][6].   
  
Moreover, investing in computational infrastructure and fostering interdisciplinary collaboration will be essential to facilitate the integration of GNNs into existing workflows. Finally, implementing ethical guidelines to ensure the equitable use of AI in drug discovery will be vital for addressing biases and promoting inclusivity within this rapidly evolving field [12][13].  
  
### Conclusion  
  
In summary, while GNNs present a transformative opportunity for de novo drug discovery, their deployment in real-world scenarios is challenged by issues such as data scarcity, interpretability, computational demands, integration complexities, and ethical considerations. Addressing these obstacles through innovative methodologies, interdisciplinary collaboration, and ethical practices will be essential for harnessing the full potential of GNNs in drug discovery and advancing the development of novel therapeutics.

# Evaluation and Validation

### Evaluation and Validation  
  
The integration of Self-Supervised Graph Neural Networks (GNNs) in de novo drug discovery represents a significant advancement in computational methodologies aimed at addressing the challenges associated with molecular representation learning. Traditional supervised learning approaches have faced limitations due to the scarcity of labeled datasets, which negatively impacts their generalization capabilities and overall predictive performance [1][2]. In contrast, the advent of self-supervised strategies has allowed for the utilization of vast amounts of unlabeled molecular data, thereby enhancing model robustness and interpretability.  
  
One prominent framework that embodies this paradigm shift is the Molecular Pre-training Graph-based deep learning framework, referred to as MPG. This framework employs a novel MolGNet model that leverages self-supervised learning techniques for both node and graph-level pre-training. The efficacy of MPG was demonstrated through extensive pre-training on a dataset comprising 11 million unlabeled molecules, resulting in the generation of molecular representations that not only encapsulate intricate chemical insights but also enable the creation of state-of-the-art models for diverse drug discovery tasks, including molecular property prediction and drug-target interaction analysis [1][3]. The ability to fine-tune the pre-trained MolGNet with minimal adjustments facilitates its application across various drug discovery scenarios, underscoring the versatility of self-supervised learning in this domain.  
  
In addition to MPG, other innovative architectures such as BatmanNet have emerged, which employ bi-branch masked graph transformer autoencoders to enhance molecular representation learning further. BatmanNet's design incorporates two asymmetrically structured graph autoencoders, tasked with reconstructing missing nodes and edges from masked molecular graphs. This dual approach effectively captures both local and global molecular features, thereby improving predictive accuracy across multiple drug discovery benchmarks [3]. The success of BatmanNet and similar models emphasizes the potential of self-supervised learning in refining molecular representations and advancing drug discovery efforts.  
  
The challenges of data scarcity in drug discovery have led to the exploration of generative models, such as the recurrent neural networks (RNNs) employed for de novo molecular design. These models facilitate the generation of novel molecular structures by learning from existing datasets, akin to language models in natural language processing. The utility of RNNs was demonstrated through their ability to reproduce a substantial percentage of drug-like molecules, indicating their effectiveness in generating compounds with desirable bioactivity profiles [4][5]. Furthermore, the incorporation of scoring functions and fine-tuning methods enhances the generation process, allowing for the optimization of drug-like characteristics in generated molecules [5].  
  
Recent advancements in reinforcement learning (RL) have also shown promise in addressing the challenges associated with de novo drug design. Models such as 3D-MolGNN$\_{RL}$ leverage RL to optimize molecule generation based on specific target characteristics, enabling the design of compounds with tailored bioactivities and properties [11]. The ability to navigate complex chemical spaces while maintaining a focus on target-specific interactions represents a significant advancement in the field, potentially streamlining the drug discovery process.  
  
Despite these advancements, challenges remain in ensuring the interpretability and generalizability of GNN-based models in drug discovery. The integration of explainable artificial intelligence (XAI) techniques has emerged as a crucial avenue for enhancing the interpretability of graph-based models. Approaches like the Hierarchical Grad-CAM graph Explainer (HGE) have been developed to elucidate the contributions of molecular substructures to biological activity, thus providing insights that are essential for rational drug design [10]. By analyzing molecular moieties at various levels, HGE facilitates a deeper understanding of the binding interactions between drugs and their targets, which is pivotal for optimizing drug candidates in silico.  
  
Moreover, the hierarchical informative graph neural networks (HiGNN) framework has been proposed to address the limitations of existing GNN architectures by incorporating hierarchical information and feature-wise attention mechanisms. HiGNN not only enhances predictive performance on benchmark datasets but also offers interpretability at the subgraph level, enabling researchers to identify key molecular components relevant to desired properties [9]. This dual focus on performance and interpretability is essential for advancing the practical application of GNNs in drug discovery.  
  
The role of data quality and diversity in model performance cannot be overstated. Studies have indicated that the selection of training data significantly influences the predictive capabilities of GNN models. For instance, the integration of multiplex heterogeneous functional networks with mutual attention mechanisms has been shown to improve drug-target interaction predictions, underscoring the importance of leveraging rich, diverse datasets in model training [14]. Furthermore, the exploration of data-driven methodologies for feature extraction and representation learning emphasizes the necessity of robust data pipelines to support high-performing models.  
  
In conclusion, the application of self-supervised GNNs in de novo drug discovery represents a transformative approach that addresses key challenges in molecular representation learning. The integration of innovative architectures, generative models, and explainable AI techniques has the potential to enhance the efficiency and effectiveness of drug discovery pipelines. As research continues to evolve in this area, ongoing evaluations and validations of these models will be critical for ensuring their reliability and applicability in real-world drug development scenarios. Future directions should focus on refining GNN architectures, enhancing interpretability, and exploring the synergy between generative models and reinforcement learning to further accelerate the discovery of novel therapeutic agents.

## Model Performance Metrics

### Metrics for Evaluating Model Accuracy, Precision, and Recall in Predictions  
  
In the realm of de novo drug discovery, the utilization of self-supervised graph neural networks (GNNs) has become increasingly significant due to their capability to model complex molecular structures and predict molecular properties effectively. However, the performance of these models hinges on robust evaluation metrics that quantify their accuracy, precision, and recall. This section delineates these metrics, contextualizing their importance within the application of GNNs in drug discovery.  
  
#### 1. Accuracy  
  
Accuracy is a fundamental metric that represents the ratio of correctly predicted instances to the total instances in the dataset. Formally, it can be expressed as:  
  
\[  
\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}  
\]  
  
where TP (True Positives) and TN (True Negatives) denote the number of correctly predicted positive and negative instances, respectively, while FP (False Positives) and FN (False Negatives) represent the incorrectly predicted instances. In the drug discovery context, high accuracy signifies that the model can reliably predict active compounds that interact effectively with intended biological targets, as demonstrated by GNN methodologies that achieved state-of-the-art performance in molecular property prediction tasks across various benchmarks [2][10].  
  
#### 2. Precision  
  
Precision, also known as positive predictive value, assesses the ratio of true positive predictions to all positive predictions made by the model. It is particularly crucial in scenarios where the cost of false positives is high, such as in drug discovery, where predicting a non-active compound as active could lead to wasted resources in further development stages. Precision is mathematically defined as:  
  
\[  
\text{Precision} = \frac{TP}{TP + FP}  
\]  
  
In the context of GNNs applied to drug-target interaction prediction, high precision indicates that the model is effective in identifying compounds that are genuinely active against specific targets, thereby enhancing the efficiency of the virtual screening process [8][12]. This metric is indispensable when fine-tuning models like Molecular Pre-training Graph-based deep learning frameworks (MPG), which utilize small sets of active compounds to improve their predictions [5].  
  
#### 3. Recall  
  
Recall, or sensitivity, measures the ability of a model to identify all relevant instances within a dataset, defined mathematically as:  
  
\[  
\text{Recall} = \frac{TP}{TP + FN}  
\]  
  
In drug discovery, recall is vital for ensuring that the model does not miss potential active compounds, which could lead to overlooked therapeutic opportunities. High recall in GNN models indicates that a significant proportion of actual positive instances (active compounds) are correctly identified, thereby facilitating a more comprehensive exploration of the chemical space [7][11]. For instance, the MPG model demonstrated a remarkable capacity for capturing valuable chemistry insights, leading to high recall rates in predicting molecular properties and drug-drug interactions [4][5].  
  
#### 4. F1 Score  
  
To balance precision and recall, the F1 Score is often employed as a single metric that reflects both aspects. It is calculated as the harmonic mean of precision and recall:  
  
\[  
F1 = 2 \times \frac{\text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}}  
\]  
  
The F1 Score is particularly useful in scenarios where there is an uneven class distribution, which is a common challenge in drug discovery datasets [3]. For instance, in the application of GNNs for predicting drug-target interactions, the F1 Score provides a more nuanced evaluation of model performance, especially when the number of active compounds is significantly lower than inactive ones [9].  
  
#### 5. Receiver Operating Characteristic (ROC) and Area Under the Curve (AUC)  
  
The ROC curve is a graphical representation of a model's diagnostic ability across various threshold settings, plotting the true positive rate (sensitivity) against the false positive rate (1-specificity). The AUC quantifies the overall ability of the model to discriminate between positive and negative classes, with a value of 1 indicating perfect discrimination and 0.5 representing random chance [6]. In drug discovery, ROC and AUC metrics are vital in comparing different models and selecting the most appropriate one for further development, particularly in applications involving large datasets with varying thresholds for activity prediction [13].  
  
#### 6. Application of Metrics in Self-Supervised Learning  
  
Self-supervised learning frameworks, such as those utilizing GNNs, benefit significantly from these evaluation metrics. For instance, the BatmanNet model, which employs a bi-branch masked graph transformer autoencoder, has shown exceptional performance in molecular representation learning, achieving state-of-the-art results across multiple drug discovery tasks [5]. The use of precision, recall, and F1 Score, alongside ROC and AUC analyses, enables researchers to rigorously evaluate and refine such models, ultimately leading to more reliable predictions of drug-target interactions and molecular properties.  
  
#### Conclusion  
  
In summary, the evaluation of model accuracy, precision, recall, and their integrated metrics such as the F1 Score and AUC is essential for assessing the performance of self-supervised GNNs in de novo drug discovery. These metrics not only facilitate the identification of effective predictive models but also enhance the interpretability and reliability of the generated molecular representations. As the field advances, the adoption of these metrics will continue to play a pivotal role in optimizing drug discovery pipelines, ultimately contributing to the successful identification of novel therapeutic compounds. Future research should focus on refining these metrics and exploring additional evaluation strategies to address the inherent challenges associated with drug discovery tasks.

## Case Studies and Benchmarking

### Section Title: Analyze case studies that demonstrate the effectiveness of GNNs in drug discovery  
  
The application of Graph Neural Networks (GNNs) in drug discovery has gained significant traction, particularly with the advent of self-supervised learning techniques that enhance molecular representation learning. This section analyzes multiple case studies that highlight the effectiveness of GNNs in various stages of drug discovery, including molecular property prediction, drug-target interaction, and de novo drug design.  
  
#### 1. Molecular Representation Learning  
  
A fundamental challenge in drug discovery is generating expressive molecular representations that accurately capture the underlying chemical properties and biological activities. Traditional supervised learning methods often struggle due to the scarcity of labeled data, which limits their generalization capabilities. Recent advancements, such as the Molecular Pre-training Graph-based deep learning framework (MPG), leverage large-scale unlabeled datasets to develop more robust molecular representations [2], [5]. The MPG framework incorporates a MolGNet model and employs self-supervised strategies for pre-training at both the node and graph levels. After training on over 11 million unlabeled molecules, MolGNet demonstrated its ability to produce interpretable representations that can be fine-tuned for specific drug discovery tasks, achieving state-of-the-art performance across 13 benchmark datasets [2], [3].  
  
Similarly, the BatmanNet model employs a bi-branch masked graph transformer autoencoder to learn molecular representations by reconstructing missing nodes and edges from masked molecular graphs. This dual approach effectively captures both local and global molecular information, resulting in improved predictive performance for drug discovery tasks, including drug-drug interactions and molecular property predictions [5]. The effectiveness of these models underscores the potential of GNNs to address the critical challenge of molecular representation learning in drug discovery.  
  
#### 2. Predicting Molecular Properties and Drug-Target Interactions  
  
The ability to predict molecular properties and drug-target interactions accurately is pivotal in drug discovery. Recent studies have shown that GNNs can achieve remarkable advancements in this area. For instance, the HiGNN framework utilizes a hierarchical informative GNN architecture that integrates co-representation learning of molecular graphs and chemically synthesizable fragments. This approach enables the model to adaptively recalibrate atomic features, leading to state-of-the-art performance in predicting molecular properties across various benchmark datasets [4].  
  
Moreover, a study involving the training of 20 GNN models on small molecules aimed at predicting their activity against different protein targets demonstrated the robustness and accuracy of GNNs in virtual screening tasks. The implementation of the Hierarchical Grad-CAM graph Explainer (HGE) framework provided insights into the molecular moieties responsible for protein-ligand binding, enhancing the interpretability of GNN models and facilitating the rational design of novel therapeutics [6]. The combination of high predictive performance and enhanced interpretability positions GNNs as indispensable tools in drug-target interaction studies.  
  
#### 3. De Novo Drug Design  
  
De novo drug design involves generating novel molecules with desirable biological activities. GNNs have shown promising capabilities in this area, particularly through the integration of reinforcement learning and generative models. For example, the 3D-MolGNN$\_{RL}$ framework combines a deep generative model with reinforcement learning to generate target-specific drug candidates atom by atom. This model optimizes key molecular features while considering the binding affinity and synthetic accessibility of the generated candidates, thereby addressing significant challenges in lead optimization [12].  
  
Furthermore, the application of a hybrid neural network, HNN2Mol, integrates gene expression profiles to generate molecular structures with targeted phenotypes for specific proteins. This approach not only enhances the relevance of generated molecules but also demonstrates the capacity of GNNs to incorporate biological system responses into molecular design [9]. The ability of GNNs to bridge the gap between molecular design and biological activity significantly enhances their utility in de novo drug discovery.  
  
#### 4. Challenges and Future Directions  
  
Despite the progress made, challenges remain in the application of GNNs in drug discovery. One major limitation is the interpretability of GNN models, which is crucial for understanding the structure-activity relationships. Although recent advancements in explainable artificial intelligence (XAI) techniques have mitigated some interpretability issues, the reliance on subjective human judgment for "ground truth" assignments complicates the evaluation of model interpretations [1]. Future research should focus on developing more quantitative interpretability metrics and methodologies that can objectively assess the quality of model explanations.  
  
Additionally, the computational cost associated with training large-scale GNN models and the necessity of extensive unlabeled datasets poses significant barriers to widespread adoption. Simplifying self-supervised learning strategies, as exemplified by BatmanNet’s approach, may alleviate some of these challenges, enabling more efficient pre-training processes [5]. The exploration of hybrid models that integrate GNNs with other machine learning paradigms could also enhance performance and reduce computational demands.  
  
#### Conclusion  
  
The application of GNNs in drug discovery, particularly through self-supervised learning approaches, has demonstrated significant potential in enhancing molecular representation learning, predicting molecular properties, and facilitating de novo drug design. Case studies reveal that models like MPG, HiGNN, and BatmanNet not only achieve state-of-the-art performance across various drug discovery tasks but also contribute to the interpretability of GNN outputs. However, challenges related to model interpretability and computational efficiency remain. Addressing these challenges through the development of more robust methodologies and frameworks will be essential for the continued advancement of GNNs in drug discovery, ultimately leading to more effective therapeutic candidates and streamlined drug development processes.   
  
In summary, GNNs represent a promising frontier in the ongoing evolution of drug discovery, with the potential to transform how medicinal chemists approach molecular design and optimization in the quest for novel therapeutics.

## Validation Techniques

### Section Title: Methods for Validating Predictions and Ensuring Model Reliability  
  
In the realm of de novo drug discovery, the integration of self-supervised Graph Neural Networks (GNNs) presents novel opportunities for enhancing molecular design and optimizing drug candidates. However, with these advancements comes the imperative to establish robust methodologies for validating predictions and ensuring model reliability. This section discusses various strategies that can be employed to assess the predictive performance of models based on GNNs in drug discovery, focusing on validation techniques, interpretability, and the integration of explainable artificial intelligence (XAI).  
  
#### 1. Validation Techniques  
  
The validation of predictions generated by GNNs is vital, particularly in the context of de novo drug design where the stakes are high. A common approach involves the use of hold-out test datasets, which enable the assessment of model generalization capabilities. For example, a study utilizing recurrent neural networks demonstrated that fine-tuning the model on small sets of active molecules resulted in significant correlations between generated structures and known active compounds, achieving 14% and 28% reproduction rates against Staphylococcus aureus and Plasmodium falciparum, respectively [1].  
  
Moreover, cross-validation techniques are essential for ensuring the reliability of predictive models. By partitioning the available data into training and validation sets, researchers can mitigate overfitting, thereby enhancing the generalizability of the model to unseen data. This approach has been effectively implemented in multiple studies employing GNNs to predict molecular properties across various tasks, including drug-drug interactions and drug-target interactions [2][6].  
  
#### 2. Benchmarking and Performance Metrics  
  
Establishing standardized benchmarks is critical for assessing the performance of GNN models in drug discovery. The creation of benchmark datasets allows for quantitative comparisons between different modeling approaches. Recent research has introduced three levels of benchmark datasets to quantitatively evaluate the interpretability of state-of-the-art GNN models, facilitating a deeper understanding of their predictive capabilities [4].  
  
Performance metrics such as accuracy, precision, recall, and F1-score provide insights into the effectiveness of the models in real-world applications. For instance, GNNs trained on extensive datasets have shown state-of-the-art performance in virtual screening tasks, achieving high accuracy on various protein targets [9]. Furthermore, the use of receiver operating characteristic (ROC) curves and area under the curve (AUC) metrics can further elucidate the trade-offs between true positive rates and false positive rates, offering a comprehensive view of model performance [10].  
  
#### 3. Interpretability and Explainability  
  
Although GNNs have shown promise in drug discovery, their interpretability remains a significant challenge. The integration of XAI techniques can enhance understanding of the models' decision-making processes. For instance, Gradient-weighted Class Activation Mapping (Grad-CAM) has been applied to GNNs to identify critical molecular substructures contributing to the predicted bioactivity. This method enables researchers to visualize which parts of the molecular graph are most influential in driving predictions, thus fostering a deeper understanding of molecular interactions [4][9].  
  
Moreover, employing hierarchical attention mechanisms within GNN architectures can improve interpretability by recalibrating atomic features during the message-passing phase. This allows for a more nuanced understanding of how different features influence the model’s predictions, particularly in the context of molecular property prediction [8]. The development of model-agnostic explainability frameworks can also facilitate the evaluation of multiple GNN architectures, providing insights into their strengths and weaknesses [4].  
  
#### 4. Self-Supervised Learning and Pre-Training Strategies  
  
Self-supervised learning has emerged as a powerful paradigm for improving the robustness of GNNs, particularly in scenarios where labeled data is scarce. By leveraging large-scale unlabeled datasets, models can capture valuable chemical insights and produce interpretable representations. For instance, the Molecular Pre-training Graph-based deep learning framework (MPG) has shown that GNNs can effectively learn molecular representations from extensive unlabeled datasets, enabling fine-tuning for specific drug discovery tasks with minimal labeled data [2][6].  
  
The application of bi-branch masked graph transformers, such as BatmanNet, represents another innovative approach to enhancing molecular representation learning. This architecture simultaneously learns local and global information about molecules by reconstructing missing nodes and edges from masked graphs, thereby improving the model's predictive capabilities across diverse drug discovery tasks [6]. The performance gains achieved through these pre-training strategies highlight the importance of effective validation methods in ensuring model reliability.  
  
#### 5. Addressing Data Scarcity and Transferability  
  
Data scarcity poses a significant challenge in drug discovery, particularly in training predictive models. GNNs trained on large, diverse datasets can facilitate improved transferability to related tasks, thereby enhancing model reliability. For instance, models pre-trained on extensive unlabeled datasets have exhibited superior performance in downstream tasks, such as predicting molecular properties and drug-target interactions [6].   
  
Additionally, the implementation of semi-supervised learning techniques can help address data limitations by integrating both labeled and unlabeled data, further enhancing the robustness and reliability of predictions. As demonstrated in several studies, semi-supervised approaches have provided valuable insights into structure-property relationships, yielding models that can effectively predict molecular behavior while being resilient to data limitations [5][11].  
  
#### 6. Continuous Monitoring and Re-Evaluation  
  
To maintain model reliability over time, continuous monitoring and re-evaluation of model performance are essential. This involves updating models with new data, re-training them as necessary, and validating their predictions against experimental results. The iterative nature of model training and validation allows researchers to refine their predictive capabilities and adapt to new insights and findings in the rapidly evolving field of drug discovery [12].  
  
Implementing robust feedback loops that incorporate experimental validation of predicted outcomes can significantly enhance the reliability of GNN models. For instance, the application of reinforcement learning techniques in generative models allows for the incorporation of real-world feedback, further improving the alignment between model predictions and biological realities [12].  
  
### Conclusion  
  
In conclusion, the validation of predictions and ensuring model reliability in self-supervised GNNs for de novo drug discovery necessitates a multifaceted approach. Key strategies include implementing rigorous validation techniques, establishing benchmark datasets, enhancing model interpretability through XAI, and leveraging self-supervised learning to address data scarcity. Continuous monitoring and adaptive model management further bolster the reliability of these models in a dynamic research environment. The integration of these methodologies not only enhances the predictive performance of GNNs but also facilitates the rational design of novel therapeutics, ultimately advancing the field of drug discovery.

# Applications and Future Directions

### Applications and Future Directions  
  
The integration of self-supervised graph neural networks (GNNs) in de novo drug discovery represents a transformative advancement in the pharmaceutical sciences, promoting the development of molecular representations that can significantly enhance drug design processes. The current landscape of drug discovery is characterized by a reliance on labeled molecular datasets, which are often limited in scope and can lead to overfitting and poor generalization in predictive models [2], [4]. Self-supervised learning methods, particularly those utilizing GNNs, have emerged as promising solutions to these challenges by enabling the extraction of meaningful representations from vast amounts of unlabeled data [1], [3].  
  
One notable approach is the development of the bi-branch masked graph transformer autoencoder, termed BatmanNet, which simultaneously learns local and global molecular information. This model employs complementary graph autoencoders to reconstruct missing nodes and edges from masked molecular graphs, thereby capturing the underlying structural and semantic features of molecules more effectively than traditional methods [1]. The success of BatmanNet in achieving state-of-the-art results across multiple drug discovery tasks—including molecular property prediction and drug-target interactions—highlights the potential of such self-supervised architectures to address critical challenges in molecular representation learning [1].  
  
In parallel, the Molecular Pre-training Graph-based framework (MPG) has been proposed to overcome the limitations associated with labeled data scarcity. By leveraging self-supervised strategies to pre-train models like MolGNet on large-scale unlabeled molecular datasets, researchers have demonstrated that these models can uncover valuable chemistry insights, yielding interpretable representations that can be fine-tuned for various drug discovery applications [2], [3]. The ability of MPG to adapt to different downstream tasks with minimal additional training positions it as a viable candidate for incorporation into the drug discovery pipeline.  
  
Furthermore, the application of self-supervised GNNs extends beyond mere representation learning; they also facilitate a deeper understanding of molecular interactions. For instance, hierarchical models that incorporate attention mechanisms can provide insights into the relationships between molecular features and biological activities, addressing the interpretability concerns that have historically hindered the acceptance of GNNs in drug discovery [4], [6]. The development of explainable artificial intelligence (XAI) techniques in conjunction with GNNs enhances the interpretability of these models, allowing researchers to elucidate how specific molecular substructures influence biological activity [4], [10].  
  
While the potential of GNNs in drug discovery is substantial, future research must address several key challenges to further enhance their applicability. First, the integration of multi-modal data—such as biological, chemical, and structural information—into GNN frameworks could significantly improve predictive accuracy and model robustness [5], [8]. Additionally, the exploration of richer molecular representations that account for hierarchical and contextual information will be crucial for optimizing molecular design and lead optimization processes [6], [9].  
  
Another promising direction involves the application of GNNs in lead optimization, where deep generative models can refine existing molecules to enhance their drug-like properties. While traditional methods have focused predominantly on de novo design, recent advancements in lead optimization utilizing GNNs illustrate the dual potential of these models to facilitate both the generation of novel compounds and the refinement of existing drug candidates [11], [12]. By employing hybrid neural networks that integrate biological data, researchers can generate molecules with specific bioactivities tailored to desired targets, thereby streamlining the drug discovery process [9].  
  
Moreover, the advent of reinforcement learning (RL) techniques in conjunction with GNNs has the potential to revolutionize the drug design landscape. The introduction of models such as 3D-MolGNN$\_{RL}$ allows for the generation of target-specific candidates by optimizing molecular features within protein binding pockets, thereby enhancing the efficacy and specificity of drug candidates [13]. Such approaches not only expedite the discovery of viable drug candidates but also improve their biophysical properties, addressing the pressing need for more effective therapeutic agents [13].  
  
The ability to predict drug-target interactions through advanced deep learning models has also gained traction, with frameworks like DrugMAN illustrating the power of integrating heterogeneous biological networks to enhance prediction accuracy [15]. This model's success in capturing interaction information underscores the necessity of leveraging large-scale biological datasets for improved drug discovery outcomes, paving the way for more robust drug repurposing strategies [15].  
  
In summary, the application of self-supervised GNNs in de novo drug discovery holds significant promise for enhancing molecular representation learning and optimizing drug design processes. Future research should continue to explore multi-modal data integration, hierarchical representations, and the synergy between generative models and reinforcement learning to address existing challenges in drug discovery. The ultimate goal is to create a more efficient and effective pipeline for drug development that leverages the full potential of artificial intelligence and machine learning, facilitating the discovery of novel therapeutics that can meet the complex needs of modern medicine. With ongoing advancements in these areas, the landscape of drug discovery is poised for a radical transformation, characterized by increased efficiency, improved accuracy, and a deeper understanding of the molecular underpinnings of drug action.  
  
### References  
1. Reference for BatmanNet  
2. Reference for MPG framework  
3. Reference for self-supervised learning methods  
4. Reference for explainable AI techniques  
5. Reference for multi-modal data integration  
6. Reference for hierarchical models and attention mechanisms  
7. Reference for generative models in lead optimization  
8. Reference for drug-target interactions  
9. Reference for reinforcement learning in drug design  
10. Reference for molecular property prediction  
11. Reference for the dual potential of GNNs  
12. Reference for hybrid neural networks  
13. Reference for 3D-MolGNN$\_{RL}$ framework  
14. Reference for DrugMAN model  
15. Reference for integration of biological datasets in drug discovery.

## Potential Benefits

## Advantages of Using Graph Neural Networks for Property Prediction and Compound Prioritization  
  
The application of Graph Neural Networks (GNNs) in drug discovery has emerged as a pivotal advancement, particularly in the context of property prediction and compound prioritization. GNNs leverage the structural information inherent in molecular graphs, thereby providing a framework capable of capturing complex relationships within molecular data. This section elucidates several key advantages of employing GNNs for these tasks, supported by insights from recent studies.  
  
### 1. Enhanced Expressiveness of Molecular Representations  
  
One of the primary advantages of GNNs is their ability to produce expressive molecular representations. Traditional machine learning approaches often struggle with the intricacies of molecular data, particularly when it comes to capturing the relationships between atoms and their connectivity. GNNs, by virtue of their architecture, can model these relationships effectively, allowing for a more nuanced understanding of molecular properties. For instance, the MolGNet model, as detailed in the Molecular Pre-training Graph-based deep learning framework (MPG), demonstrated that GNNs could yield interpretable representations by capturing valuable insights from large-scale unlabeled molecular datasets [2][3]. This capability is crucial for accurately predicting molecular properties such as bioactivity and druggability, which are essential in the drug discovery pipeline.  
  
### 2. Robustness Against Data Scarcity  
  
The scarcity of labeled data in drug discovery poses a significant challenge for machine learning models. GNNs, particularly when combined with self-supervised learning strategies, have shown remarkable resilience in this context. For example, the MPG framework utilizes self-supervised learning to pre-train the MolGNet model on a vast dataset consisting of 11 million unlabeled molecules, allowing it to generalize effectively across various downstream tasks [3][5]. This approach not only alleviates the data scarcity issue but also enhances the model's generalization capabilities across different molecular property prediction tasks, thus streamlining the drug discovery process.  
  
### 3. Improved Predictive Performance  
  
The predictive performance of GNNs has been validated across numerous benchmark datasets, showcasing their superiority over traditional models. Recent experiments indicate that GNN-based methodologies, such as HiGNN and BatmanNet, achieve state-of-the-art results in tasks including molecular property prediction, drug-drug interaction, and drug-target interaction [1][4][6]. These improvements in predictive performance can be attributed to the GNNs' ability to integrate both local and global information from molecular structures, thus enabling a comprehensive analysis of the underlying chemical properties.  
  
### 4. Interpretability of Predictions  
  
Despite the complexities of deep learning models, GNNs have made strides toward improving the interpretability of predictions. The integration of explainable artificial intelligence (XAI) techniques with GNNs has facilitated the elucidation of molecular substructures contributing to biological activity. For instance, the Hierarchical Grad-CAM graph Explainer (HGE) framework highlights the significance of specific molecular moieties in binding interactions, thereby enhancing the interpretability of predictive models [7]. This interpretability is critical for chemists and pharmacologists who require insight into the rational design of novel therapeutics.  
  
### 5. Facilitating Multi-Task Learning  
  
The versatility of GNNs allows for multi-task learning, which is particularly advantageous in drug discovery where multiple molecular properties may need to be predicted simultaneously. The SGNN-EBM framework demonstrates this capability by effectively modeling task relationships within a structured graph [11]. This approach not only optimizes resource utilization but also enhances the performance of predictive models by leveraging shared information across related tasks. As a result, GNNs can facilitate the simultaneous prediction of various molecular properties, thus expediting the drug discovery process.  
  
### 6. Integration of Hierarchical and Structural Information  
  
GNNs can seamlessly integrate hierarchical and structural information, leading to more accurate molecular representations. For instance, the HiGNN architecture incorporates a hierarchical informative mechanism that leverages co-representation learning between molecular graphs and chemically synthesizable fragments, thereby enhancing predictive accuracy in property prediction tasks [1]. This ability to capture hierarchical relationships is crucial for understanding complex molecular behaviors and optimizing compound prioritization.  
  
### 7. Reduction of Computational Costs  
  
The efficiency of GNNs in learning from large datasets can significantly reduce computational costs associated with drug discovery. Traditional methods often require extensive computational resources and time for feature extraction and model training. However, GNNs, particularly those utilizing self-supervised learning, can streamline this process by extracting relevant features directly from the graph structures, as exemplified by the BatmanNet model [5][6]. This efficiency not only accelerates the discovery process but also allows researchers to allocate resources more effectively.  
  
### 8. Robustness to Noise and Variability in Molecular Data  
  
Molecular data can often be noisy or exhibit variability due to experimental conditions. GNNs demonstrate robustness in handling such inconsistencies through their ability to aggregate information from neighboring nodes and edges within molecular graphs. This characteristic allows GNNs to mitigate the impact of noise, ensuring that predictions remain reliable even in the presence of data variability [4][9]. Consequently, GNNs provide a more stable framework for property prediction and compound prioritization.  
  
### Conclusion  
  
In summary, the utilization of Graph Neural Networks in de novo drug discovery presents several significant advantages, including enhanced expressiveness of molecular representations, robustness against data scarcity, improved predictive performance, and increased interpretability of predictions. Furthermore, GNNs facilitate multi-task learning, integrate hierarchical and structural information, reduce computational costs, and demonstrate resilience to noise. Collectively, these benefits position GNNs as a transformative tool in the drug discovery landscape, promising to accelerate the identification of novel therapeutics and optimize the drug development process. Future research should continue to explore the potential of GNNs and their integration with other advanced techniques to further enhance their efficacy and applicability in drug discovery.

## Challenges and Limitations

### Section Title: Challenges in Implementation and Areas for Future Research  
  
The integration of Self-Supervised Graph Neural Networks (GNNs) into de novo drug discovery represents a significant advance in the application of artificial intelligence (AI) to medicinal chemistry. Despite promising results, the implementation of these methodologies encounters several challenges, necessitating a comprehensive examination of both current limitations and future research avenues.  
  
#### Challenges in Implementation  
  
1. \*\*Data Scarcity and Quality\*\*: A critical challenge in the application of GNNs for molecular representation learning is the scarcity of labeled data. Most supervised learning approaches falter in their performance due to the limited availability of high-quality labeled datasets, which are essential for training robust predictive models. As noted by several studies, self-supervised learning methods, while beneficial, demand large-scale unlabeled datasets for effective pre-training [1][3]. The complexity and computational expense associated with generating these datasets can hinder their practical application in drug discovery pipelines.  
  
2. \*\*Computational Complexity\*\*: The computational demands of training large GNN models are non-trivial. For instance, the bi-branch masked graph transformer autoencoder, BatmanNet, proposed for simultaneous local and global molecular representation learning, requires substantial computational resources for pre-training and fine-tuning [1]. This computational burden can limit accessibility for smaller research institutions and impede widespread adoption.  
  
3. \*\*Interpretability of Models\*\*: Although GNNs are powerful tools for molecular modeling, their inherent lack of interpretability remains a significant barrier to their application in drug discovery. The difficulty in elucidating how molecular features contribute to predictive outcomes complicates the validation of results and the rational design of new therapeutic agents [6][11]. Recent advancements in explainable AI (XAI) techniques, such as the Hierarchical Grad-CAM graph Explainer, have attempted to address this issue; however, the subjective nature of "ground truth" assignment for interpretability assessments poses challenges for quantitative evaluation [6][11].  
  
4. \*\*Integration of Biological Context\*\*: Current GNN frameworks often neglect the complex biological context within which molecular interactions occur. For example, models that solely focus on molecular structures may fail to account for the dynamic responses of biological systems, such as those involving gene expression profiles [9]. This oversight can result in the generation of compounds that theoretically exhibit desirable properties but perform poorly in biological assays.  
  
5. \*\*Transferability Across Diverse Tasks\*\*: The generalization capability of GNNs, particularly when transitioning from one drug discovery task to another, is variable. While some models, such as MolGNet, show promise in capturing valuable chemistry insights through extensive pre-training, their performance can diminish when applied to tasks with different contextual requirements [3][4]. This challenge underscores the need for adaptable models that can seamlessly transition across various stages of the drug discovery process.  
  
#### Areas for Future Research  
  
1. \*\*Development of Hybrid Models\*\*: Future research should focus on creating hybrid models that integrate GNNs with other machine learning techniques to improve predictive accuracy and interpretability. For instance, the combination of GNNs with recurrent neural networks (RNNs) could enhance the generation of drug-like molecules by incorporating temporal dependencies inherent in biological systems [9][10]. Such hybrid approaches can leverage the strengths of different algorithms to address specific challenges in drug design and optimization.  
  
2. \*\*Advancements in Self-Supervised Learning\*\*: Given the challenges associated with labeled data, further exploration into self-supervised learning strategies is warranted. This includes designing innovative self-supervised tasks that require fewer labeled examples while still yielding robust molecular representations [1]. Additionally, research into more efficient algorithms that can utilize smaller datasets effectively is essential to facilitate the practical application of GNNs in drug discovery.  
  
3. \*\*Enhanced Interpretability Techniques\*\*: Continued efforts in developing interpretability frameworks for GNNs are crucial. As highlighted in recent studies, the establishment of standardized benchmarks for evaluating model interpretability can guide the development of more transparent AI systems in drug discovery [6][11]. Enhancing interpretability not only aids in model validation but also fosters trust among researchers and practitioners in the pharmaceutical industry.  
  
4. \*\*Incorporating Biological Knowledge\*\*: Future research should emphasize the incorporation of biological knowledge into GNN frameworks. This could include the integration of biological pathways, chemical interactions, and pharmacokinetic properties into the model architecture, resulting in a more holistic representation of drug-target interactions [5][9]. Such integration can also facilitate the identification of key molecular features that contribute to activity across diverse biological contexts.  
  
5. \*\*Exploring Multi-Task Learning Frameworks\*\*: The adoption of multi-task learning frameworks could yield significant benefits in drug discovery. By training models on related tasks simultaneously, researchers can enhance the transferability of learned features and improve the robustness of predictions across various applications, such as drug design and lead optimization [10][12]. This approach could streamline the drug discovery process by allowing for more efficient exploration of chemical space.  
  
6. \*\*Addressing Ethical and Regulatory Considerations\*\*: As AI-driven methodologies become more integrated into drug discovery, addressing ethical and regulatory considerations is paramount. Future research should explore the implications of deploying GNN-based models in clinical settings, including the need for transparent reporting and validation of AI-generated drug candidates [10][12]. Engaging with regulatory bodies early in the research process can help establish guidelines that ensure safety and efficacy.  
  
#### Conclusion  
  
In summary, while the application of Self-Supervised Graph Neural Networks in de novo drug discovery holds great promise, several challenges remain that must be addressed to facilitate their widespread adoption. Future research should focus on the development of hybrid models, advancements in self-supervised learning, enhanced interpretability techniques, incorporation of biological knowledge, exploration of multi-task learning frameworks, and addressing ethical considerations. By overcoming these challenges, researchers can harness the full potential of GNNs to accelerate drug discovery and improve therapeutic outcomes.

## Future Trends in Drug Discovery

### Future Developments in Graph Neural Networks and Their Impact on Drug Discovery  
  
The advent of Graph Neural Networks (GNNs) has revolutionized the field of drug discovery, particularly in the generation and optimization of molecular structures. As research progresses, the integration of self-supervised learning techniques within GNN architectures is anticipated to significantly enhance the capabilities of drug discovery processes. This section discusses potential future developments in GNNs, emphasizing the implications for de novo drug discovery.  
  
#### Enhanced Molecular Representation Learning  
  
One of the primary challenges in drug discovery is the generation of robust and expressive molecular representations. Traditional supervised learning approaches are often hindered by the scarcity of labeled data, which diminishes their generalization capabilities [2]. Recent advancements suggest that self-supervised learning frameworks, such as the Molecular Pre-training Graph-based deep learning framework (MPG), could address these limitations. MPG utilizes a large corpus of unlabeled molecular data to pre-train models that capture valuable chemistry insights, thus enabling effective fine-tuning for various drug discovery tasks [2], [5].   
  
Moreover, the proposed bi-branch masked graph transformer autoencoder (BatmanNet) exemplifies a novel self-supervised strategy that can learn both local and global molecular information simultaneously. This approach effectively reconstructs masked molecular graphs, thereby improving the performance of molecular representation learning [5]. Such innovative methods are likely to become standard practices in upcoming GNN architectures, leading to improvements in predictive accuracy across multiple drug discovery applications.  
  
#### Interpretability and Explainability  
  
Despite the promising capabilities of GNNs, interpretability remains a significant barrier to their widespread adoption in drug discovery. The complexity of GNN models often leads to challenges in elucidating the rationale behind predictions, which is critical in therapeutic development [1]. Recent efforts to incorporate explainable artificial intelligence (XAI) techniques, such as GradInput and Integrated Gradients (IG), have shown potential in enhancing interpretability [1]. The development of integrated XAI packages can facilitate model training across various drug discovery tasks, ultimately providing practitioners with tools to better understand model decisions [1].  
  
The establishment of benchmark datasets to quantitatively assess model interpretability is also vital. Such datasets enable a systematic evaluation of different GNN models and their explainability, fostering advancements in model design that prioritize both predictive performance and interpretability [1], [4]. Future GNN frameworks will likely incorporate these considerations as integral components, facilitating a more transparent decision-making process in drug design.  
  
#### Addressing Hierarchical Information  
  
Current GNN methodologies often neglect the hierarchical structure inherent in molecular data. The introduction of hierarchical informative GNNs (HiGNN), which incorporate co-representation learning of molecular graphs and chemically synthesizable fragments, represents a significant step towards overcoming this limitation [4]. HiGNN's utilization of attention mechanisms to recalibrate atomic features post-message passing enhances the model's ability to capture complex molecular interactions, thereby improving predictive accuracy [4].  
  
Future GNN developments may continue to explore hierarchical representations, further refining models to account for the intricate relationships between molecular components. This could lead to more accurate predictions of molecular properties and druggability, streamlining the drug discovery process [4].  
  
#### Integration with Reinforcement Learning  
  
The coupling of GNNs with reinforcement learning (RL) paradigms presents a promising avenue for future research. By employing RL to optimize molecular generation, frameworks like 3D-MolGNN$\_{RL}$ can efficiently design target-specific molecules while addressing multiple objectives such as activity, potency, and synthetic accessibility [12]. This integration could facilitate the rapid generation of drug candidates tailored for specific therapeutic targets, significantly reducing the time and cost associated with traditional drug discovery methods [12].  
  
As reinforcement learning techniques mature, their integration with GNNs is likely to yield sophisticated models capable of navigating vast chemical spaces and generating novel compounds with desirable properties. Such advancements will be crucial for enhancing the efficiency and success rates of clinical trials, ultimately leading to better therapeutic outcomes.  
  
#### Utilization of Large-scale Biological Data  
  
The incorporation of large-scale biological and pharmacological data into GNN frameworks represents another critical development horizon. Models like DrugMAN, which leverage multiplex heterogeneous functional networks, are designed to improve drug-target interaction predictions by capturing complex relationships across diverse datasets [15]. This integration not only enhances predictive performance but also allows for the mining of interaction information that can inform drug repurposing efforts.  
  
Future GNN architectures will likely expand their focus on integrating multi-modal biological data, enabling the development of more comprehensive models that can accurately predict drug-target interactions and guide lead optimization strategies. As data availability continues to grow, the potential for GNNs to harness this information will be pivotal in accelerating drug discovery.  
  
#### Ethical Considerations and Regulatory Frameworks  
  
As GNNs become increasingly integrated into drug discovery workflows, ethical considerations and regulatory frameworks will play an essential role in shaping their application. The need for transparency in model predictions, particularly in areas impacting patient health, underscores the necessity for robust governance structures [6]. The adoption of ethical guidelines will ensure that GNN applications in drug discovery maintain high standards of safety, efficacy, and fairness.  
  
Future research must address these ethical implications, developing frameworks that promote responsible AI usage in pharmaceutical contexts. Such frameworks will guide researchers and practitioners in navigating the complexities of deploying GNNs in real-world scenarios, facilitating the responsible advancement of drug discovery technologies.  
  
#### Conclusion  
  
The future of Graph Neural Networks in drug discovery promises to be transformative, driven by advancements in self-supervised learning, interpretability, hierarchical modeling, reinforcement learning integration, and the utilization of extensive biological data. As these technologies evolve, they will likely enhance the efficiency and effectiveness of drug discovery processes, enabling the rapid development of novel therapeutics. The incorporation of ethical considerations and regulatory guidelines will further ensure that these advancements contribute positively to public health and safety. Collectively, these developments signify a paradigm shift in how drug discovery is approached, with GNNs at the forefront of this evolution.  
  
In summary, the ongoing research and development within GNN frameworks are set to redefine the landscape of drug discovery, providing powerful tools that can facilitate the identification and optimization of new therapeutic candidates. As the field progresses, it will be essential to balance innovation with ethical responsibility, ensuring that the benefits of GNNs in drug discovery are realized in a manner that prioritizes human health and well-being.

# Glossary

### Extracted Technical Terms and Jargon: \*\*Extracted Technical Terms and Jargon\*\*: A collection of specialized vocabulary and phrases drawn from a specific field or context, often used to convey precise meanings and concepts that may not be easily understood by those outside the discipline.

1. \*\*Artificial Intelligence (AI)\*\*: \*\*Artificial Intelligence (AI)\*\*: A branch of computer science focused on creating systems and software that can perform tasks typically requiring human intelligence, such as learning, reasoning, problem-solving, perception, and language understanding.

1. \*\*De novo drug discovery\*\*: \*\*De novo drug discovery\*\* refers to the process of designing and developing new pharmaceutical compounds from scratch, using computational methods, molecular modeling, and biological data to identify potential drug candidates, rather than modifying existing drugs or compounds.

1. \*\*Graph Neural Networks (GNNs)\*\*: \*\*Graph Neural Networks (GNNs)\*\*: A class of neural networks designed to operate on graph-structured data, GNNs leverage the connectivity and relationships between nodes (vertices) and edges to learn representations and perform tasks such as node classification, link prediction, and graph classification. They aggregate information from a node's neighbors to update its representation, enabling effective modeling of complex relational data.

1. \*\*Self-Supervised Graph Neural Networks (GNNs)\*\*: \*\*Self-Supervised Graph Neural Networks (GNNs)\*\*: A type of machine learning model designed to operate on graph-structured data, where the network learns to generate useful representations of nodes and edges without relying on labeled data. Instead, it generates supervisory signals from the graph's inherent structure or attributes, enabling the model to perform tasks such as node classification or link prediction by leveraging the relationships and features present in the graph.

1. \*\*Self-supervised graph neural networks (GNNs)\*\*: \*\*Self-supervised graph neural networks (GNNs)\*\*: A type of machine learning model that processes graph-structured data by leveraging self-supervised learning techniques, allowing the network to generate supervisory signals from the data itself without requiring labeled examples. This approach enables the model to learn representations and patterns in the graph through tasks such as node prediction, link prediction, or graph reconstruction, enhancing its performance in various applications like social network analysis, recommendation systems, and molecular property prediction.

1. \*\*Small-molecule structures\*\*: \*\*Small-molecule structures\*\* refer to the chemical configurations of low molecular weight compounds, typically consisting of fewer than 900 daltons. These structures are characterized by their discrete, well-defined compositions and are often used in pharmaceuticals, agrochemicals, and as biological probes due to their ability to easily penetrate cells and interact with biological macromolecules.

1. Drug discovery process: The drug discovery process is a systematic series of steps and methodologies used to identify, develop, and bring new pharmaceutical compounds to market, typically involving target identification, lead compound discovery, optimization, preclinical testing, and clinical trials to evaluate safety and efficacy.

1. Graph Neural Networks (GNNs): Graph Neural Networks (GNNs) are a class of neural networks designed to process data structured as graphs, where nodes represent entities and edges represent relationships between them. GNNs leverage the connectivity and topology of the graph to learn representations that capture the interactions and features of the nodes, enabling tasks such as node classification, link prediction, and graph classification.

1. Self-Supervised Graph Neural Networks (GNNs): Self-Supervised Graph Neural Networks (GNNs) are a type of machine learning model designed to operate on graph-structured data without the need for labeled training examples. They leverage self-supervised learning techniques to extract features and learn representations from the graph's topology and node attributes by generating pseudo-labels or tasks from the data itself, enabling the model to discover patterns and relationships in an unsupervised manner.

1. Self-Supervised Learning (SSL): Self-Supervised Learning (SSL) is a machine learning approach where a model is trained on unlabeled data by creating its own supervisory signals from the data itself. This is typically achieved by setting up tasks that require the model to predict part of the input from other parts, enabling it to learn useful representations without the need for manual labeling.

1. Self-supervised graph neural networks (GNNs): Self-supervised graph neural networks (GNNs) are a type of machine learning model that learn to represent graph-structured data without requiring labeled examples. Instead, they utilize self-supervised learning techniques, such as predicting missing parts of the graph or creating auxiliary tasks from the graph's structure, to automatically generate training signals from the data itself. This allows GNNs to capture complex relationships and patterns within the graph while improving generalization to downstream tasks.

10. \*\*BatmanNet model\*\*: \*\*BatmanNet model\*\*: A deep learning architecture designed for processing and analyzing image data, particularly in the context of computer vision tasks. It incorporates advanced techniques such as convolutional neural networks (CNNs) and attention mechanisms to improve performance in image classification, segmentation, or object detection tasks.

10. \*\*BatmanNet\*\*: \*\*BatmanNet\*\*: A decentralized and privacy-focused peer-to-peer network designed for secure communication and data sharing, utilizing a combination of encryption and routing protocols to ensure user anonymity and data integrity.

10. \*\*Bayesian Inference\*\*: \*\*Bayesian Inference\*\*: A statistical method that uses Bayes' theorem to update the probability of a hypothesis as more evidence or information becomes available. It incorporates prior beliefs and combines them with new data to refine predictions or inferences about uncertain parameters.

10. \*\*ChEMBL database\*\*: \*\*ChEMBL database\*\*: A large, publicly available database that contains curated information on bioactive molecules with drug-like properties, including their chemical structures, biological activities, and pharmacological data. It is primarily used for drug discovery and research in medicinal chemistry.

10. \*\*False Negatives (FN)\*\*: \*\*False Negatives (FN)\*\*: Instances in which a test or diagnostic method incorrectly indicates that a condition is absent when it is actually present. In other words, a false negative occurs when the test fails to detect a positive case, leading to an erroneous conclusion that the disease or condition does not exist.

10. \*\*Hybridization state\*\*: \*\*Hybridization state\*\* refers to the specific arrangement and mixing of atomic orbitals within an atom to form new, equivalent hybrid orbitals that facilitate the bonding of atoms in a molecule. This concept is commonly used in chemistry to explain the geometry and bonding properties of molecular structures, such as sp, sp², and sp³ hybridization, which correspond to different angles and shapes of molecular bonds.

10. \*\*Min-Max scaling\*\*: \*\*Min-Max scaling\*\*: A normalization technique used to rescale features of a dataset to a specified range, typically [0, 1]. It transforms each feature by subtracting the minimum value and dividing by the range (maximum - minimum), ensuring that the smallest value corresponds to 0 and the largest value corresponds to 1. This method is commonly used in machine learning to improve model performance by standardizing input features.

10. \*\*Model generalization capabilities\*\*: \*\*Model generalization capabilities\*\* refer to a model's ability to perform well on unseen data that it has not encountered during training. This indicates the model's effectiveness in capturing underlying patterns and relationships within the training data, allowing it to make accurate predictions or classifications in diverse scenarios beyond the specific examples it was trained on.

10. \*\*MolGNet model\*\*: \*\*MolGNet model\*\*: A machine learning framework designed for predicting molecular properties and interactions by leveraging graph neural networks (GNNs). It represents molecules as graphs where atoms are nodes and bonds are edges, facilitating the analysis of molecular structures and their effects on chemical behavior.

10. \*\*Pre-train Models\*\*: \*\*Pre-train Models\*\*: Pre-train models refer to machine learning models that have been trained on a large dataset before being fine-tuned for a specific task. This initial training phase helps the models learn general features and patterns in the data, which can improve performance and reduce training time when adapting to particular applications or domains.

10. \*\*Pseudo-labels\*\*: \*\*Pseudo-labels\*\*: In machine learning, pseudo-labels are labels generated for unlabeled data using a model's predictions. These labels are created to enhance the training dataset, allowing semi-supervised learning techniques to leverage both labeled and unlabeled data, potentially improving model performance.

10. \*\*Unlabeled Molecular Data\*\*: \*\*Unlabeled Molecular Data\*\*: A type of molecular dataset that contains information about the properties or structures of molecules without any accompanying labels or annotations that indicate specific categories, classifications, or outcomes for the molecules. This data is often used in unsupervised learning or exploratory analysis in cheminformatics and drug discovery.

10. \*\*Unlabeled datasets\*\*: \*\*Unlabeled datasets\*\*: Collections of data points that do not have associated output labels or target values, often used in machine learning and data analysis for tasks such as clustering or unsupervised learning, where the objective is to discover patterns or structures within the data without predefined categories.

10. Computer-aided drug design (CADD): Computer-aided drug design (CADD) is a set of computational techniques used in the drug discovery process to identify, design, and optimize new pharmaceutical compounds by simulating and predicting their interactions with biological targets, such as proteins or enzymes.

10. Hierarchical informative graph neural network (HiGNN): A Hierarchical Informative Graph Neural Network (HiGNN) is a type of neural network designed to process graph-structured data by leveraging hierarchical relationships and informative features. HiGNNs enhance traditional graph neural networks (GNNs) by incorporating multiple levels of abstraction, allowing for improved representation learning and more effective information propagation across nodes in complex graph structures. This approach is particularly useful in tasks such as social network analysis, recommendation systems, and knowledge graph completion.

10. Labeled datasets: Labeled datasets are collections of data that have been annotated with labels or tags, which provide information about the data's characteristics or categories. These labels are used in supervised machine learning to train models by allowing them to learn the relationship between input data and the corresponding output labels.

10. Large-scale unlabeled datasets: Large-scale unlabeled datasets refer to extensive collections of data that do not have associated labels or annotations. These datasets are typically used in machine learning and artificial intelligence to train models, particularly in unsupervised learning scenarios, where the goal is to identify patterns or structures within the data without predefined categories.

10. Molecular Pre-training Graph-based deep learning framework (MPG): Molecular Pre-training Graph-based deep learning framework (MPG) is a computational approach that leverages graph neural networks to model molecular structures and properties. It involves pre-training on large datasets of molecular graphs to capture the relationships and interactions between atoms and bonds, enabling improved performance in tasks such as molecular property prediction and drug discovery.

10. Molecular graph: A molecular graph is a representation of a chemical molecule where atoms are depicted as vertices (nodes) and chemical bonds are represented as edges (lines) connecting the vertices. This graphical representation helps in visualizing the structure and relationships within the molecule, aiding in analysis and computational chemistry.

10. Molecular property prediction: Molecular property prediction refers to the computational techniques and methodologies used to estimate the physical, chemical, and biological properties of molecules based on their structure and composition. This process often employs machine learning algorithms, quantitative structure-activity relationship (QSAR) models, and molecular simulations to forecast properties such as solubility, reactivity, toxicity, and spectral characteristics.

10. Unlabeled molecular data: Unlabeled molecular data refers to chemical or biological datasets that contain information about molecular structures, properties, or interactions without any accompanying annotations or classifications that specify the identity or function of the molecules. This type of data is often used in machine learning and computational modeling to discover patterns or make predictions without prior knowledge of the samples.

10. supervised learning approaches: Supervised learning approaches are a type of machine learning where an algorithm is trained on a labeled dataset, meaning that each training example is paired with an output label. The model learns to map inputs to the correct outputs by identifying patterns in the data, and it is then evaluated based on its ability to predict the labels of unseen data.

11. \*\*Active compounds\*\*: \*\*Active compounds\*\*: Chemical substances that exert a biological effect on living organisms, often used in pharmaceuticals, agriculture, and biochemistry to induce a specific response or action.

11. \*\*Bayesian Neural Networks (BNNs)\*\*: \*\*Bayesian Neural Networks (BNNs)\*\*: A type of neural network that incorporates Bayesian inference to estimate uncertainty in model parameters and predictions. BNNs treat weights as probability distributions rather than fixed values, allowing for the quantification of uncertainty in the model's outputs, which can improve generalization and robustness in uncertain environments.

11. \*\*Computational complexity\*\*: \*\*Computational complexity\*\* refers to the study of the resources required for an algorithm to solve a computational problem, primarily focusing on time complexity (the amount of time taken to complete) and space complexity (the amount of memory used). It classifies problems based on their inherent difficulty and the efficiency of algorithms in solving them, often using Big O notation to express upper bounds on resource usage.

11. \*\*Downstream Tasks\*\*: \*\*Downstream Tasks\*\*: Activities or processes that occur after an initial phase, particularly in data processing or machine learning, where the output from earlier stages is used as input for subsequent analyses, applications, or operations. These tasks often involve applying the results of prior work to real-world scenarios or further refining and utilizing the data.

11. \*\*Fine-tuning\*\*: \*\*Fine-tuning\*\*: The process of making small adjustments to a pre-trained model's parameters or hyperparameters to improve its performance on a specific task or dataset, often involving additional training on a smaller, task-specific dataset.

11. \*\*Local and global molecular information\*\*: \*\*Local and global molecular information\*\* refers to the data and characteristics that describe the properties and behavior of molecules at two distinct levels:   
  
- \*\*Local molecular information\*\* pertains to the specific interactions and arrangements of atoms within a molecule, such as bond lengths, angles, and electronic configurations. This information is crucial for understanding the molecule's stability and reactivity.  
  
- \*\*Global molecular information\*\* encompasses broader properties of molecules within a system, including their spatial arrangements, interactions with other molecules, and overall behavior in

11. \*\*MolGNet model\*\*: \*\*MolGNet model\*\*: A machine learning framework specifically designed for predicting molecular properties and interactions using graph neural networks, where molecules are represented as graphs with atoms as nodes and bonds as edges, enabling the modeling of complex chemical structures and relationships.

11. \*\*Molecular representations\*\*: \*\*Molecular representations\*\* refer to various methods and visual formats used to depict the structure, composition, and connectivity of molecules. These representations include two-dimensional structural formulas, three-dimensional models, and simplified notations such as Lewis structures or ball-and-stick models, allowing chemists to analyze and communicate molecular information effectively.

11. \*\*Partial charges\*\*: \*\*Partial charges\*\* refer to the unequal distribution of electric charge within a molecule, resulting from differences in electronegativity between atoms. This creates regions of slight positive and negative charge, typically denoted as δ+ (delta plus) for partial positive charge and δ- (delta minus) for partial negative charge, influencing molecular interactions and properties such as polarity and hydrogen bonding.

11. \*\*PubChem database\*\*: \*\*PubChem database\*\*: A publicly accessible online database maintained by the National Center for Biotechnology Information (NCBI) that provides detailed information on the biological activities of small molecules, including chemical properties, structure, and experimental data, serving as a key resource for researchers in chemistry and life sciences.

11. \*\*Recurrent neural networks\*\*: \*\*Recurrent Neural Networks (RNNs)\*\*: A class of artificial neural networks designed for processing sequential data by utilizing internal memory to maintain information about previous inputs. This architecture allows RNNs to recognize patterns and dependencies in sequences, making them suitable for tasks such as language modeling, time series prediction, and speech recognition.

11. \*\*Self-supervised strategies\*\*: \*\*Self-supervised strategies\*\* refer to machine learning techniques where a model learns to predict part of its input from other parts, effectively generating its own supervisory signals from the data itself. This approach allows models to leverage large amounts of unlabeled data for training by creating tasks that do not require manual annotation, enabling better feature extraction and representation learning.

11. \*\*Z-score normalization\*\*: \*\*Z-score normalization\*\*: A statistical technique used to standardize data by transforming values to have a mean of zero and a standard deviation of one. This is achieved by subtracting the mean of the dataset from each data point and dividing the result by the standard deviation, resulting in a Z-score that indicates how many standard deviations a data point is from the mean.

11. Aggregation phase: \*\*Aggregation Phase\*\*: In data processing and analysis, the aggregation phase refers to the stage where individual data points are combined or summarized into a single representation, such as a total, average, or other statistical measure, to simplify analysis and reveal trends or patterns in the dataset.

11. Artificial intelligence (AI): Artificial intelligence (AI) refers to the simulation of human intelligence processes by computer systems, enabling them to perform tasks such as learning, reasoning, problem-solving, perception, and language understanding. AI can be categorized into narrow AI, which is designed for specific tasks, and general AI, which possesses the ability to understand and perform any intellectual task that a human can do.

11. Bioactivity: \*\*Bioactivity\*\*: The effect that a substance or compound has on living organisms or biological systems, often measured in terms of its ability to elicit a specific biological response, such as antimicrobial, anti-inflammatory, or therapeutic effects.

11. Co-representation learning: Co-representation learning is a machine learning approach that involves training models to simultaneously learn multiple representations of data, often across different modalities or tasks. This technique aims to enhance the model's ability to capture complementary information, improve generalization, and facilitate knowledge transfer by leveraging shared features or relationships among the different representations.

11. Drug-target interaction modeling: Drug-target interaction modeling refers to the computational and experimental techniques used to predict and analyze the interactions between drug molecules and their biological targets, typically proteins. This modeling aims to understand binding affinities, mechanisms of action, and the potential effects of drugs on specific targets, facilitating drug discovery and development processes.

11. Generalizability: \*\*Generalizability\*\*: The extent to which findings or conclusions from a study or experiment can be applied to broader populations or different contexts beyond the specific conditions of the original research.

11. Model robustness: Model robustness refers to the ability of a predictive model to maintain its performance and accuracy when exposed to varying conditions, such as changes in data distribution, noise, or different input features. A robust model can generalize well to unseen data and is less sensitive to outliers and small perturbations in the input.

11. MolGNet model: MolGNet model: A machine learning framework designed for predicting molecular properties by leveraging graph neural networks, which represent molecules as graphs of atoms and bonds, enabling the capture of complex structural information and interactions within chemical compounds.

11. Molecular Pre-training Graph-based deep learning framework (MPG): Molecular Pre-training Graph-based deep learning framework (MPG) is a computational model designed for molecular property prediction that utilizes graph-based neural networks. It leverages pre-training techniques to enhance the learning of molecular representations by capturing relational and structural information from molecular graphs, thereby improving performance on downstream tasks such as drug discovery and material science.

11. generalization capabilities: Generalization capabilities refer to the ability of a machine learning model to apply learned patterns from training data to new, unseen data effectively. This involves making accurate predictions or classifications based on examples that were not part of the training set, ensuring the model is not just memorizing the training data but rather understanding underlying trends and relationships.

12. \*\*Bi-branch masked graph transformer autoencoder\*\*: \*\*Bi-branch masked graph transformer autoencoder\*\*: A neural network architecture designed for processing graph-structured data, which utilizes a bi-branch approach to simultaneously encode and decode graph information. It employs masked learning techniques to improve the model's ability to understand complex relationships within the graph while preserving important structural features.

12. \*\*Bioactive compounds\*\*: \*\*Bioactive compounds\*\*: Naturally occurring substances in food and plants that have biological activity in the body, potentially influencing health and disease prevention by interacting with cellular processes. Examples include polyphenols, flavonoids, and certain vitamins.

12. \*\*Biological targets\*\*: \*\*Biological targets\*\*: Specific molecules, such as proteins, nucleic acids, or cell structures, in living organisms that are intended to be affected by drugs or therapeutic agents in order to elicit a biological response or effect.

12. \*\*Bond types\*\*: \*\*Bond types\*\* refer to the various classifications of bonds based on their characteristics and features, including but not limited to government bonds, corporate bonds, municipal bonds, and convertible bonds. Each type differs in terms of issuer, risk level, interest rates, and tax implications.

12. \*\*Computational resources\*\*: \*\*Computational resources\*\* refer to the hardware and software components necessary for performing computations, including processing power (CPU, GPU), memory (RAM), storage (disk space), and networking capabilities. These resources are essential for executing algorithms, processing data, and running applications in computing environments.

12. \*\*De novo Drug Discovery\*\*: \*\*De novo Drug Discovery\*\*: A process of developing new pharmaceutical compounds from scratch, utilizing computational methods, biological data, and chemical synthesis to identify novel drug candidates, rather than modifying existing drugs.

12. \*\*Fine-tuning\*\*: \*\*Fine-tuning\*\*: The process of making small adjustments to a pre-trained machine learning model to improve its performance on a specific task or dataset. This involves retraining the model on a smaller, task-specific dataset while retaining the knowledge gained from the larger dataset used during initial training.

12. \*\*Graph autoencoders\*\*: \*\*Graph autoencoders\*\* are neural network architectures designed to learn low-dimensional representations of graph-structured data. They consist of an encoder that maps input graphs to latent representations and a decoder that reconstructs the original graph from these representations, facilitating tasks such as node classification, link prediction, and graph generation.

12. \*\*Molecular Property Prediction\*\*: \*\*Molecular Property Prediction\*\*: The process of using computational methods and models to estimate the physical and chemical properties of molecules based on their structure and composition, often employing techniques such as machine learning, quantum chemistry, or molecular dynamics simulations.

12. \*\*Node and graph levels\*\*: \*\*Node and Graph Levels\*\*: In graph theory, "node levels" refer to the hierarchical depth or position of individual nodes within a graph, often used to indicate their distance from a designated root node. "Graph levels" typically describe the overall structure and organization of the graph based on the arrangement of its nodes and edges, particularly in hierarchical or layered representations. Levels can help analyze relationships and paths within the graph.

12. \*\*Outliers\*\*: \*\*Outliers\*\*: Data points that differ significantly from other observations in a dataset, often falling outside the expected range or distribution. Outliers can indicate variability in measurement, experimental errors, or novel phenomena and may influence statistical analyses if not addressed properly.

12. \*\*Probabilistic Framework\*\*: \*\*Probabilistic Framework\*\*: A structured approach for modeling and analyzing uncertain systems or processes using probability theory, where outcomes are represented as probability distributions, enabling the incorporation of uncertainty into decision-making and predictions.

12. BatmanNet: \*\*BatmanNet\*\*: A decentralized, peer-to-peer network protocol designed for efficient and secure communication between devices, often used in the context of privacy-focused applications and technologies. It enables users to exchange data without reliance on central servers, enhancing anonymity and resilience against censorship.

12. Benchmark datasets: \*\*Benchmark datasets\*\*: Standardized collections of data used to evaluate and compare the performance of algorithms, models, or systems in a consistent manner. They provide a reference point for measuring improvements and establishing best practices within a specific domain, such as machine learning or data analysis.

12. Domain expertise: \*\*Domain Expertise\*\*: Specialized knowledge and skills in a specific field or industry, allowing an individual to understand complex concepts, solve problems, and make informed decisions related to that area.

12. Druggability: Druggability refers to the likelihood that a biological target, such as a protein or enzyme, can be effectively modulated by a drug to produce a therapeutic effect. It encompasses factors such as the target's accessibility, binding affinity for potential drug candidates, and the potential for achieving a desirable pharmacological response without significant toxicity.

12. Interpretability: \*\*Interpretability\*\*: The degree to which a human can understand the cause of a decision made by a machine learning model. It involves the ability to explain how inputs are transformed into outputs, enabling users to comprehend and trust the model's predictions.

12. Machine learning: Machine learning is a subset of artificial intelligence that involves the development of algorithms and statistical models that enable computers to learn from and make predictions or decisions based on data, without being explicitly programmed for specific tasks.

12. Molecular representations: Molecular representations are graphical depictions of chemical structures that illustrate the arrangement of atoms and the connectivity between them in a molecule. These representations can take various forms, including Lewis structures, ball-and-stick models, space-filling models, and skeletal formulas, each providing different levels of detail regarding molecular geometry and bonding.

12. Pre-training: Pre-training is the process of training a machine learning model on a large dataset to learn general features and patterns before fine-tuning it on a smaller, task-specific dataset. This approach enhances the model's performance by leveraging previously acquired knowledge.

12. Update phase: \*\*Update Phase\*\*: The stage in a process, often within software development or project management, where changes, enhancements, or corrections are implemented to improve functionality, performance, or user experience based on feedback or new requirements.

12. structural information: \*\*Structural Information\*\*: Data that describes the arrangement and organization of components within a system or object, often detailing relationships, hierarchies, and spatial configurations that influence functionality and behavior.

13. \*\*Active molecules\*\*: \*\*Active molecules\*\*: Chemical compounds that exhibit biological activity, influencing physiological processes or biochemical reactions within living organisms. These molecules can act as drugs, hormones, or signaling agents, often interacting with specific biological targets, such as proteins or enzymes.

13. \*\*BatmanNet\*\*: \*\*BatmanNet\*\*: A decentralized network protocol designed for establishing secure and efficient communication between devices in a mesh network, primarily used in scenarios where traditional internet connectivity is unavailable, such as disaster recovery or remote areas. It enables nodes to relay information between each other, ensuring data transmission even when some nodes are offline.

13. \*\*Bi-branch Masked Graph Transformer Autoencoder (BatmanNet)\*\*: \*\*Bi-branch Masked Graph Transformer Autoencoder (BatmanNet)\*\*: A neural network architecture designed for learning representations of graph-structured data. It employs a dual-branch structure to process input graphs, utilizing masked input techniques to enhance feature extraction and robustness. The autoencoder framework allows for unsupervised learning, enabling the model to capture complex relationships and patterns within the graph data while preserving essential information during encoding and decoding processes.

13. \*\*Bioactivity data\*\*: \*\*Bioactivity data\*\* refers to quantitative or qualitative information that describes the effects of a substance, such as a drug or chemical compound, on living organisms or biological systems. This data helps in assessing the efficacy, potency, and mechanism of action of the substance in relation to biological targets.

13. \*\*Drug-Target Interaction\*\*: \*\*Drug-Target Interaction\*\*: The specific binding or interaction between a drug (a chemical compound or therapeutic agent) and a biological target (such as a protein, enzyme, or receptor) that mediates the drug's therapeutic effects or biological activity. This interaction is crucial for the drug's mechanism of action and influences its efficacy and safety.

13. \*\*Interpretability\*\*: \*\*Interpretability\*\*: The degree to which a human can understand the reasoning and decisions made by a machine learning model or algorithm, often involving the clarity of the model's outputs and the transparency of its internal processes.

13. \*\*Interpretable representations\*\*: \*\*Interpretable representations\*\* refer to data representations or models that enable humans to understand the underlying relationships and patterns within the data. These representations are designed to be transparent and provide insights into how decisions are made, making it easier for users to analyze and trust the outcomes produced by machine learning algorithms or statistical models.

13. \*\*Local and global molecular information\*\*: \*\*Local and global molecular information\*\* refers to the distinct types of data derived from molecular structures and interactions. Local molecular information pertains to the specific characteristics and behaviors of individual molecules or local regions within a molecule, such as bond lengths, angles, and functional groups. In contrast, global molecular information encompasses broader insights that consider the overall structure, dynamics, and interactions of the entire molecular system, including properties like stability, reactivity, and conformational changes.

13. \*\*Missing nodes and edges\*\*: \*\*Missing nodes and edges\*\*: In graph theory and network analysis, this term refers to the absence of certain vertices (nodes) or connections (edges) that are expected to be present in a complete or fully connected graph. Missing nodes can indicate unrepresented entities, while missing edges signify unrepresented relationships between existing nodes, potentially leading to incomplete data representation or analysis inconsistencies.

13. \*\*Posterior Distribution\*\*: \*\*Posterior Distribution\*\*: In Bayesian statistics, the posterior distribution is the probability distribution that represents the updated beliefs about a parameter after observing new evidence or data. It is calculated by applying Bayes' theorem, combining the prior distribution (the initial beliefs about the parameter) with the likelihood of the observed data.

13. \*\*Precision\*\*: \*\*Precision\*\*: The degree to which repeated measurements or calculations yield consistent results, indicating the reliability and reproducibility of the data, regardless of its accuracy relative to the true value.

13. \*\*Representation learning\*\*: \*\*Representation learning\*\* is a type of machine learning focused on automatically discovering and learning useful representations of data, often in a lower-dimensional space, to facilitate tasks such as classification, clustering, or regression. This approach enables models to identify patterns and features in the data without extensive manual feature engineering.

13. \*\*Single, double, aromatic bonds\*\*: \*\*Single, double, aromatic bonds\*\*: Types of chemical bonds between atoms in molecules. A \*\*single bond\*\* consists of one pair of shared electrons, allowing for free rotation around the bond axis. A \*\*double bond\*\* involves two pairs of shared electrons, resulting in a stronger bond that restricts rotation. \*\*Aromatic bonds\*\* refer to cyclic structures with alternating single and double bonds, characterized by electron delocalization that provides stability and unique chemical properties, typically found in aromatic compounds like benzene

13. BatmanNet architecture: \*\*BatmanNet Architecture\*\*: A routing protocol designed for ad hoc networks that enables efficient and decentralized communication by allowing nodes to discover and maintain routes dynamically. It uses a mesh network topology to facilitate peer-to-peer connectivity, optimizing data transmission through broadcast and multi-hop techniques.

13. Bi-branch masked graph transformer autoencoder: A bi-branch masked graph transformer autoencoder is a neural network architecture designed for processing graph-structured data. It consists of two parallel branches: one for encoding the input graph while masking certain nodes or edges to learn robust representations, and another for decoding, which reconstructs the original graph from the encoded representations. This approach leverages attention mechanisms typical of transformers to capture complex relationships in the graph, enhancing tasks such as graph reconstruction, anomaly detection, or node classification.

13. Chemical insights: \*\*Chemical Insights\*\*: The understanding and interpretation of chemical phenomena, reactions, and properties based on experimental data and theoretical models. This encompasses knowledge gained from analyzing chemical behaviors, mechanisms, and interactions at the molecular or atomic level to inform research, product development, or industrial applications.

13. Localized features: Localized features refer to specific attributes or characteristics within a particular region of a dataset or a model, often used in the context of machine learning and computer vision. These features are typically relevant to the local context and can help improve the accuracy and efficiency of algorithms by focusing on small, distinct areas rather than the dataset as a whole.

13. Molecular Pre-training Graph-based deep learning framework (MPG): Molecular Pre-training Graph-based deep learning framework (MPG) is a computational approach that leverages graph-based representations of molecular structures to enhance the performance of deep learning models in cheminformatics. MPG utilizes pre-training on large datasets of molecular graphs to capture complex relationships and features, enabling improved predictions for tasks such as molecular property prediction, drug discovery, and chemical synthesis.

13. Self-supervised learning: Self-supervised learning is a type of machine learning where the model is trained on unlabeled data by generating its own supervisory signals from the input data itself. It typically involves creating auxiliary tasks or predictions based on the data, allowing the model to learn representations and features without the need for manually labeled examples.

13. Self-supervised strategies: Self-supervised strategies are machine learning techniques that leverage unlabeled data to automatically generate supervisory signals, enabling models to learn representations or features without requiring explicit human-annotated labels. These strategies often involve predicting parts of the input data from other parts, thereby allowing the model to learn useful patterns and structures in the data.

13. Structure-activity relationships: Structure-activity relationships (SAR) are analyses that explore the relationship between the chemical or three-dimensional structure of a molecule and its biological activity. SAR studies aim to identify how specific structural features influence the efficacy, potency, and safety of compounds, often guiding the design of new drugs in medicinal chemistry.

13. unlabeled datasets: Unlabeled datasets refer to collections of data points that do not have associated labels or annotations indicating their categories or classes. These datasets are often used in machine learning for unsupervised learning tasks, where the goal is to identify patterns or structures without prior knowledge of the outcomes.

14. \*\*Benchmark datasets\*\*: \*\*Benchmark datasets\*\*: Standardized collections of data used to evaluate and compare the performance of algorithms, models, or systems in a consistent manner across different research studies or applications.

14. \*\*Bi-branch Masked Graph Transformer Autoencoder (BatmanNet)\*\*: \*\*Bi-branch Masked Graph Transformer Autoencoder (BatmanNet)\*\*: A neural network architecture designed for graph-based data processing, which utilizes a bi-branch approach to simultaneously encode and reconstruct graph structures while applying masking techniques. This allows for enhanced representation learning by focusing on relevant substructures within the graph, making it suitable for tasks such as node classification and graph generation.

14. \*\*Explainability\*\*: \*\*Explainability\*\* refers to the degree to which the internal mechanisms of a machine learning model or algorithm can be understood and interpreted by humans. It encompasses the clarity and transparency of how the model makes decisions, allowing users to comprehend the reasoning behind its outputs and predictions.

14. \*\*Masked Molecular Graphs\*\*: \*\*Masked Molecular Graphs\*\*: A representation of molecular structures where specific atoms or bonds are hidden (masked) to focus on particular features or substructures. This technique is often used in cheminformatics and machine learning to simplify the analysis of complex molecules by reducing the graph's complexity while retaining essential information for tasks such as property prediction or molecular similarity assessment.

14. \*\*Masked molecular graphs\*\*: \*\*Masked molecular graphs\*\*: A representation of molecular structures where certain atoms or bonds are obscured or "masked" to focus on specific features or interactions within the molecule. This technique is often used in cheminformatics and molecular modeling to simplify complex molecular representations for analysis or comparison.

14. \*\*Molecular Pre-training Graph-based deep learning framework (MPG)\*\*: \*\*Molecular Pre-training Graph-based deep learning framework (MPG)\*\*: A computational framework designed for drug discovery and molecular analysis that utilizes graph-based deep learning techniques. It pre-trains models on molecular structures represented as graphs, capturing complex relationships and features, which are then fine-tuned for specific tasks such as predicting molecular properties or interactions.

14. \*\*Positive predictive value\*\*: \*\*Positive Predictive Value (PPV)\*\*: A statistical measure that indicates the probability that subjects with a positive test result truly have the condition being tested for. It is calculated as the ratio of true positive results to the total number of positive results (true positives plus false positives).

14. \*\*Pre-training and fine-tuning\*\*: \*\*Pre-training and fine-tuning\*\*: A two-step process in machine learning, particularly in natural language processing, where a model is first trained on a large dataset (pre-training) to learn general patterns and representations, and then subsequently refined (fine-tuning) on a smaller, task-specific dataset to improve performance on that particular task.

14. \*\*Reproduction rates\*\*: \*\*Reproduction rates\*\* refer to the frequency at which a specific population or species produces offspring within a given time period, often expressed as the number of offspring per individual or per unit of population. This metric is crucial for understanding population dynamics, growth potential, and ecological balance.

14. \*\*Transfer performance\*\*: \*\*Transfer performance\*\* refers to the efficiency and effectiveness with which data, information, or tasks are moved or transitioned from one system, location, or format to another. It is often assessed in terms of speed, accuracy, and reliability during the transfer process.

14. \*\*Variational Inference\*\*: \*\*Variational Inference\*\*: A Bayesian inference technique that approximates complex posterior distributions by transforming the inference problem into an optimization problem, where a simpler, tractable distribution is fitted to the true posterior by minimizing the distance between them, often using Kullback-Leibler divergence.

14. \*\*ZINC database\*\*: \*\*ZINC database\*\*: A publicly accessible online resource that provides a comprehensive collection of commercially available chemical compounds, primarily focused on drug-like molecules. It is used by researchers for virtual screening, chemical informatics, and drug discovery, offering tools for searching and retrieving compounds based on various chemical properties and structural features.

14. Bi-branch masked graph transformer autoencoder: A bi-branch masked graph transformer autoencoder is a neural network architecture designed for processing graph-structured data. It features two parallel branches that encode and decode graph information while incorporating masking techniques to handle missing or incomplete data. The model utilizes transformer mechanisms to capture relationships between graph nodes, enhancing its ability to learn representations that are robust to noise and variation in graph topology.

14. De novo drug design: De novo drug design is a computational approach in pharmaceutical chemistry where novel drug candidates are created from scratch, utilizing knowledge of biological targets and molecular interactions, rather than modifying existing drugs. This method often employs algorithms and simulations to predict the structure and activity of potential compounds before synthesis and testing.

14. Downstream tasks: Downstream tasks refer to subsequent activities or processes that occur after an initial operation or analysis, often utilizing the outputs or results from that initial step. In machine learning, for example, downstream tasks involve specific applications such as classification, regression, or prediction that rely on features extracted from earlier stages, like data preprocessing or model training.

14. Global graph structures: \*\*Global Graph Structures\*\*: These are data structures that represent relationships between a set of entities (nodes) and the connections or interactions (edges) between them on a global scale, facilitating analysis and exploration of complex networks across various domains, such as social networks, transportation systems, or biological systems.

14. Graph representations: Graph representations refer to the various ways of visualizing or encoding the structure of a graph, which consists of vertices (nodes) connected by edges (links). Common representations include adjacency lists, adjacency matrices, and edge lists, each offering different advantages for storage, manipulation, and analysis of graph data.

14. Interpretable molecular representations: Interpretable molecular representations refer to formats or models used to describe molecular structures and properties in a way that is understandable and can be analyzed by humans. These representations facilitate the interpretation of chemical information, often highlighting key features or relationships within the molecular data that can be linked to biological, chemical, or physical phenomena.

14. MolGNet model: The MolGNet model is a deep learning framework designed for molecular property prediction, leveraging graph neural networks (GNNs) to represent molecular structures as graphs. It captures the relationships between atoms and bonds, enabling the analysis and prediction of various chemical properties based on molecular topology and features.

14. Molecular semantics: Molecular semantics is a subfield of semantics in linguistics that analyzes the meaning of expressions based on the molecular structure of the concepts they represent, often focusing on how complex meanings arise from the combination of simpler components. It examines the relationship between language and the molecular-level representation of meaning, considering how various elements interact to form coherent semantic interpretations.

14. molecular property prediction: Molecular property prediction refers to the use of computational methods and algorithms to estimate the physical, chemical, or biological properties of molecules based on their structure and composition. This process often involves machine learning, quantum chemistry, or molecular modeling techniques to forecast characteristics such as solubility, reactivity, or toxicity, facilitating the design of new compounds in fields like drug discovery and materials science.

15. \*\*BatmanNet model\*\*: \*\*BatmanNet model\*\*: A deep learning architecture designed for image segmentation tasks, particularly in medical imaging, which leverages a combination of convolutional neural networks (CNNs) and attention mechanisms to improve performance in identifying and delineating structures within images.

15. \*\*Downstream tasks\*\*: \*\*Downstream tasks\*\* refer to specific activities or processes that occur after an initial operation or analysis, typically involving the application of the results from earlier stages in a workflow. In machine learning, for example, downstream tasks may include classification, regression, or other applications that utilize features or models developed during earlier phases of data processing or training.

15. \*\*Ensemble Learning\*\*: \*\*Ensemble Learning\*\*: A machine learning technique that combines multiple models, often referred to as "weak learners," to improve overall performance and accuracy. By aggregating the predictions of these individual models, ensemble methods can reduce variance, bias, and improve robustness compared to any single model. Common techniques include bagging, boosting, and stacking.

15. \*\*Explainable artificial intelligence (XAI)\*\*: \*\*Explainable Artificial Intelligence (XAI)\*\*: A field of AI focused on developing models and systems that provide transparent and understandable explanations for their decisions and actions, enabling users to comprehend how and why specific outcomes were reached. This enhances trust, accountability, and usability in AI applications.

15. \*\*MolGNet model\*\*: \*\*MolGNet model\*\*: A machine learning framework specifically designed for predicting molecular properties and interactions by leveraging graph neural networks. It represents molecules as graphs, where atoms are nodes and bonds are edges, allowing for the extraction of complex structural information and facilitating tasks such as drug discovery and material science.

15. \*\*Molecular modeling\*\*: \*\*Molecular modeling\*\*: A computational technique used to represent and simulate the structures, properties, and behaviors of molecular systems. It involves the use of mathematical models and computer algorithms to visualize and predict molecular interactions, conformations, and dynamics, aiding in fields such as drug design, materials science, and biochemistry.

15. \*\*Predictive Accuracy\*\*: \*\*Predictive Accuracy\*\*: A measure of how correctly a predictive model or algorithm forecasts outcomes, typically expressed as the ratio of correct predictions to the total number of predictions made, often represented as a percentage.

15. \*\*Staphylococcus aureus\*\*: \*\*Staphylococcus aureus\*\*: A type of bacteria commonly found on the skin and in the respiratory tract of humans and animals. It is known for causing a range of infections, from minor skin conditions to more serious illnesses such as pneumonia, bloodstream infections, and food poisoning. Some strains of S. aureus are resistant to antibiotics, notably methicillin-resistant Staphylococcus aureus (MRSA).

15. \*\*State-of-the-Art Results\*\*: \*\*State-of-the-Art Results\*\*: The highest level of performance or achievement currently attainable in a particular field or technology, often established through leading research or innovative practices, and serving as a benchmark for future developments.

15. \*\*Structural and semantic features\*\*: \*\*Structural and Semantic Features\*\*: Characteristics of a system or dataset that define its organization (structural features) and meaning (semantic features). Structural features pertain to the arrangement and relationships of components, while semantic features relate to the interpretation and significance of the data or elements within the structure.

15. \*\*Virtual screening process\*\*: \*\*Virtual screening process\*\*: A computational technique used in drug discovery to evaluate and prioritize large libraries of compounds by predicting their interactions with specific biological targets, typically through molecular docking or similarity searching, thus identifying potential drug candidates more efficiently than traditional experimental methods.

15. \*\*Virtual screening\*\*: \*\*Virtual screening\*\*: A computational technique used in drug discovery to evaluate and prioritize large libraries of compounds by predicting their potential interactions with biological targets, typically proteins. This process helps identify promising candidates for further experimental testing, thereby streamlining the drug development process.

15. Atoms (nodes): Atoms (nodes): In the context of graph theory and network analysis, atoms (or nodes) refer to the fundamental units or individual entities within a graph or network. Each atom represents a point of interest, such as an object, person, or concept, and can be connected to other atoms through edges (links) to form relationships or interactions.

15. Chemical insights: \*\*Chemical Insights\*\*: Analytical interpretations or understandings derived from the study of chemical properties, reactions, and behaviors of substances, often used to inform research, development, and practical applications in chemistry and related fields.

15. Drug discovery tasks: \*\*Drug Discovery Tasks\*\*: A series of systematic processes in pharmaceutical research aimed at identifying, designing, and developing new therapeutic compounds. These tasks typically include target identification, lead compound discovery, optimization, preclinical testing, and clinical trials to evaluate the safety and efficacy of potential drugs.

15. Expressive Representation Learning: \*\*Expressive Representation Learning\*\*: A subfield of machine learning focused on developing models that can capture and encode complex patterns and relationships in data into high-dimensional representations, allowing for improved performance in tasks such as classification, generation, and reinforcement learning. It emphasizes the ability to represent intricate structures and semantics inherent in the data.

15. Local and global molecular characteristics: \*\*Local and Global Molecular Characteristics:\*\* Local molecular characteristics refer to the properties and behaviors of specific regions within a molecule, such as bond lengths, angles, and electronic environments. Global molecular characteristics encompass the overall structure, shape, and behavior of the entire molecule as a whole, including its spatial arrangement and interactions with other molecules.

15. Molecular structures: \*\*Molecular Structures\*\*: The three-dimensional arrangement of atoms within a molecule, including the types of bonds, angles between bonds, and the overall shape of the molecule, which determines its chemical properties and reactivity.

15. Node-level pre-training: Node-level pre-training refers to a machine learning technique where individual nodes (or vertices) in a graph or network are trained on their own features and local neighborhood information before being fine-tuned for specific tasks. This approach enhances the model's ability to understand the structure and relationships within the data, facilitating improved performance in downstream tasks such as node classification, link prediction, or graph classification.

15. Optimization techniques: Optimization techniques refer to mathematical and computational methods used to find the best solution or outcome from a set of available options, often under specific constraints. These techniques aim to maximize or minimize a particular objective function, such as cost, efficiency, or performance, by systematically adjusting variables and parameters. Common examples include linear programming, gradient descent, genetic algorithms, and simulated annealing.

15. Predictive performance: Predictive performance refers to the ability of a model or algorithm to accurately forecast outcomes or trends based on input data. It is typically assessed using metrics such as accuracy, precision, recall, and F1-score, which evaluate how well the model can generalize to unseen data.

15. drug-target interaction: \*\*Drug-target interaction\*\*: The specific biochemical interaction between a drug molecule and its biological target, typically a protein, enzyme, or receptor, which results in a therapeutic effect or biological response.

16. \*\*Bi-branch masked graph transformer autoencoder\*\*: \*\*Bi-branch masked graph transformer autoencoder\*\*: A neural network architecture designed for processing graph-structured data, which consists of two parallel branches that simultaneously encode and decode graph representations. The "masked" component indicates that certain parts of the input data are intentionally obscured during training to improve the model's ability to learn useful features and representations. This type of autoencoder is particularly useful for tasks such as graph reconstruction and node classification in scenarios where incomplete information is common.

16. \*\*De Novo Drug Discovery\*\*: \*\*De Novo Drug Discovery\*\*: A process of identifying and developing new pharmaceutical compounds from scratch, rather than modifying existing drugs. This approach involves the use of computational methods, high-throughput screening, and biological assays to discover novel molecules that can potentially become effective therapeutic agents.

16. \*\*Ensemble Methods\*\*: \*\*Ensemble Methods\*\*: A set of machine learning techniques that combine multiple models (often referred to as "base learners") to improve overall predictive performance. By aggregating the predictions of various models, ensemble methods aim to reduce errors and increase robustness compared to individual models. Common examples include bagging, boosting, and stacking.

16. \*\*Explainable AI (XAI)\*\*: \*\*Explainable AI (XAI)\*\*: A subset of artificial intelligence that focuses on creating models and systems that provide transparent and understandable explanations for their decisions and behaviors, enabling users to comprehend how outcomes are derived and fostering trust in AI applications.

16. \*\*GradInput\*\*: \*\*GradInput\*\*: A term commonly used in machine learning and neural networks, referring to the gradient of the input data with respect to a loss function. It represents how changes in the input affect the loss, and is used during backpropagation to update model parameters effectively.

16. \*\*Hierarchical Grad-CAM graph Explainer (HGE)\*\*: \*\*Hierarchical Grad-CAM graph Explainer (HGE)\*\*: A visualization technique that extends the Grad-CAM (Gradient-weighted Class Activation Mapping) method by organizing the activation maps of neural network features in a hierarchical structure. HGE provides insights into the decision-making process of complex models by illustrating how different levels of abstraction contribute to the final classification, enabling a clearer understanding of model behavior and feature importance across various layers.

16. \*\*High-throughput virtual screening\*\*: \*\*High-throughput virtual screening\*\*: A computational method used in drug discovery that allows for the rapid evaluation of large libraries of compounds against specific biological targets, using algorithms and simulations to predict the binding affinity and activity of the compounds without the need for physical testing.

16. \*\*Interpretability\*\*: \*\*Interpretability\*\*: The degree to which a human can understand the cause of a decision made by a machine learning model or system. It involves the clarity of the model's processes and outputs, allowing users to comprehend how input data is transformed into predictions or decisions.

16. \*\*Molecular Pre-training Graph-based deep learning frameworks (MPG)\*\*: \*\*Molecular Pre-training Graph-based Deep Learning Frameworks (MPG)\*\*: A class of machine learning models specifically designed for processing molecular data, utilizing graph-based representations to capture the relationships between atoms and bonds. These frameworks leverage pre-training techniques to enhance the model's understanding of molecular structures and properties, improving performance in tasks such as molecular property prediction, drug discovery, and material science.

16. \*\*Molecular property prediction\*\*: \*\*Molecular property prediction\*\* refers to the computational process of estimating the physical, chemical, or biological properties of molecules based on their structure and composition. This involves using algorithms and models, often derived from machine learning or quantum chemistry, to predict characteristics such as solubility, reactivity, stability, and biological activity, aiding in fields like drug discovery and materials science.

16. \*\*Node-level and graph-level representations\*\*: \*\*Node-level and graph-level representations\*\* refer to two approaches in graph-based data analysis and machine learning. Node-level representations focus on encoding the features and relationships of individual nodes (vertices) within a graph, typically used for tasks like node classification or link prediction. In contrast, graph-level representations aggregate information across the entire graph, capturing the overall structure and properties, and are often used for tasks such as graph classification or regression.

16. \*\*Plasmodium falciparum\*\*: \*\*Plasmodium falciparum\*\*: A protozoan parasite and the most deadly species of the genus Plasmodium, responsible for the majority of malaria cases and deaths worldwide. It is transmitted to humans through the bite of infected Anopheles mosquitoes and is characterized by its ability to rapidly replicate and invade red blood cells, leading to severe disease.

16. \*\*State-of-the-art results\*\*: \*\*State-of-the-art results\*\*: The highest level of performance or achievement currently recognized in a particular field or domain, typically reflecting the most advanced techniques, methodologies, or technologies available at a given time.

16. AI-driven drug discovery: AI-driven drug discovery is the use of artificial intelligence technologies and algorithms to identify, design, and optimize new pharmaceuticals more efficiently and effectively, often by analyzing biological data, predicting molecular interactions, and accelerating the drug development process.

16. Algorithms: Algorithms are step-by-step procedures or formulas for solving problems or performing tasks, typically defined in a precise manner to ensure repeatability and efficiency in processing data or executing computations.

16. Benchmark datasets: Benchmark datasets are standardized collections of data used to evaluate and compare the performance of algorithms, models, or systems in a specific domain, ensuring consistency and reproducibility in research and development.

16. Chemical bonds (edges): Chemical bonds (edges) refer to the connections between atoms in a molecule or compound, represented as edges in a molecular graph. These bonds can be covalent (shared electrons), ionic (electrical attraction between charged atoms), or metallic (delocalized electrons), and they determine the structure and properties of the substance.

16. Graph-level pre-training: Graph-level pre-training is a machine learning technique where a model is initially trained on graph-structured data to learn general representations and patterns before being fine-tuned for specific tasks. This process enhances the model's ability to understand the underlying relationships and features within graph data, improving its performance on downstream applications such as node classification, link prediction, or graph classification.

16. Hyperparameter tuning: Hyperparameter tuning is the process of optimizing the settings or configuration parameters of a machine learning model that are not learned from the training data. These parameters, known as hyperparameters, influence the model's performance and training process, and tuning them involves selecting the best combination through methods such as grid search, random search, or Bayesian optimization.

16. Interpretability: Interpretability refers to the degree to which a human can understand the cause of a decision made by a machine learning model. It involves the clarity of the model's processes and the ability to explain how inputs are transformed into outputs, enabling users to trust and verify the model's predictions or classifications.

16. Molecular Pre-training Graph (MPG) framework: The Molecular Pre-training Graph (MPG) framework is a computational approach designed for enhancing the performance of machine learning models in drug discovery and molecular biology. It leverages graph-based representations of molecular structures to pre-train models on large datasets, capturing complex relationships and features within molecular data, which can then be fine-tuned for specific tasks such as predicting molecular properties or interactions.

16. Predicting molecular properties: Predicting molecular properties refers to the use of computational methods and models to estimate the physical and chemical characteristics of molecules, such as reactivity, stability, solubility, and spectroscopic behavior, based on their molecular structure and composition.

16. Self-Supervised Learning (SSL): Self-Supervised Learning (SSL) is a machine learning approach where a model learns to predict parts of the input data from other parts, using the data itself as a source of supervision, without relying on manually labeled datasets. It often involves generating pseudo-labels from the data, enabling the model to learn useful representations and features automatically.

17. \*\*Computational Methods\*\*: \*\*Computational Methods\*\*: A set of numerical techniques and algorithms used to solve mathematical problems and simulate complex systems through computer-based calculations, often employed in fields such as engineering, physics, finance, and data analysis.

17. \*\*Cross-validation techniques\*\*: \*\*Cross-validation techniques\*\* refer to a set of statistical methods used to assess the performance and generalizability of machine learning models by partitioning the dataset into subsets. These techniques involve training the model on a portion of the data and validating it on the remaining data, often using multiple iterations to ensure robustness. Common methods include k-fold cross-validation, leave-one-out cross-validation, and stratified cross-validation.

17. \*\*Drug-target interaction assessments\*\*: \*\*Drug-target interaction assessments\*\* refer to the systematic evaluation of the binding and activity between a drug and its biological target, typically a protein or receptor, to understand the pharmacological effects, efficacy, and potential side effects of the drug. These assessments often utilize various biochemical, biophysical, and computational methods to characterize the interaction at a molecular level.

17. \*\*Explainability\*\*: \*\*Explainability\*\*: The degree to which an artificial intelligence model's decision-making process can be understood by humans, allowing users to comprehend how and why specific outcomes are reached, facilitating trust and accountability in AI systems.

17. \*\*Hierarchical Grad-CAM graph Explainer\*\*: \*\*Hierarchical Grad-CAM Graph Explainer\*\*: A visualization tool that extends the Grad-CAM (Gradient-weighted Class Activation Mapping) technique by organizing and displaying the contributions of different layers in a neural network in a hierarchical manner. It helps in understanding how various levels of features influence the final model predictions, allowing for more interpretable insights into complex deep learning models.

17. \*\*Integrated Gradients\*\*: \*\*Integrated Gradients\*\*: A method for attributing the prediction of a machine learning model to its input features by calculating the integral of the gradients of the model's output with respect to the input, along a straight line from a baseline input to the actual input. This technique helps to provide insights into the importance of each feature in the model's decision-making process.

17. \*\*Machine learning models\*\*: \*\*Machine learning models\*\*: Algorithms or mathematical frameworks that enable computers to learn patterns and make predictions or decisions based on data, without being explicitly programmed for specific tasks. These models are trained on datasets to improve their accuracy and performance over time.

17. \*\*Masked molecular graphs\*\*: \*\*Masked Molecular Graphs\*\*: A representation of molecular structures in which certain atoms, bonds, or substructures are deliberately obscured or "masked" to focus on specific features or properties of the molecule. This technique is often used in computational chemistry and machine learning to simplify the analysis of molecular interactions, facilitate the training of predictive models, or enhance the interpretability of molecular data.

17. \*\*Molecular moieties\*\*: \*\*Molecular moieties\*\*: Distinct structural units or functional groups within a molecule that contribute to its chemical behavior and properties. These can include specific arrangements of atoms or specific groups of atoms that influence the molecule's reactivity and interactions.

17. \*\*Molecular property prediction\*\*: \*\*Molecular property prediction\*\* refers to the process of using computational methods and models to estimate the physical, chemical, or biological properties of molecules based on their structure and composition. This includes predicting attributes such as solubility, reactivity, stability, and biological activity, often utilizing techniques like machine learning, quantum mechanics, and cheminformatics.

17. \*\*Recall\*\*: \*\*Recall\*\*: In the context of information retrieval and machine learning, recall is a metric that measures the ability of a model to identify all relevant instances within a dataset. It is defined as the ratio of true positive results to the sum of true positives and false negatives, indicating the proportion of actual positives that were correctly identified. A higher recall value signifies better performance in capturing all relevant cases.

17. \*\*Self-supervised learning (SSL)\*\*: \*\*Self-supervised learning (SSL)\*\* is a machine learning paradigm where a model is trained on a dataset without explicit labels by generating supervisory signals from the data itself. It typically involves creating tasks from the input data, such as predicting parts of the data from other parts, enabling the model to learn useful representations without human-annotated labels.

17. \*\*Variance in Predictions\*\*: \*\*Variance in Predictions\*\*: A statistical measure that quantifies the extent to which predicted values differ from each other across multiple instances or models. It reflects the model's sensitivity to fluctuations in the training data; high variance indicates that small changes in the input data can lead to large changes in predictions, often resulting in overfitting.

17. Drug-target binding affinities: Drug-target binding affinities refer to the strength of the interaction between a drug molecule and its biological target, typically a protein or enzyme. This affinity is often quantified by the dissociation constant (Kd), with lower values indicating stronger binding. High binding affinity can enhance a drug's effectiveness, as it suggests that the drug is more likely to remain bound to its target and produce a therapeutic effect.

17. Drug-target interactions: Drug-target interactions refer to the specific biochemical interactions between a drug and its intended molecular target, typically a protein, enzyme, or receptor, that lead to a therapeutic effect. These interactions are crucial for the drug's efficacy and safety, influencing its mechanism of action, pharmacodynamics, and overall therapeutic outcomes.

17. Graph neural networks (GNNs): Graph Neural Networks (GNNs) are a class of neural networks designed to process data structured as graphs, where nodes represent entities and edges represent relationships between them. GNNs leverage the graph's topology to learn representations for nodes, edges, or entire graphs by iteratively aggregating and transforming features from neighboring nodes, enabling effective modeling of complex relational data in applications like social networks, molecular chemistry, and recommendation systems.

17. HiGNN: HiGNN (Heterogeneous Graph Neural Network) refers to a type of neural network designed to operate on heterogeneous graphs, which contain different types of nodes and edges. HiGNNs leverage the diverse information present in these graphs to perform tasks such as node classification, link prediction, and graph classification, effectively capturing the complex relationships and interactions among varied entities.

17. Molecular property prediction: Molecular property prediction refers to the computational methods and techniques used to estimate the physical, chemical, or biological properties of molecules based on their structure and composition, often employing machine learning, quantum chemistry, or molecular simulations to facilitate the analysis and understanding of molecular behavior and interactions.

17. Molecular representations: Molecular representations refer to various ways of depicting the structure and composition of molecules, including two-dimensional diagrams (like Lewis structures), three-dimensional models, and computer-generated visualizations. These representations help convey information about the arrangement of atoms, bonds, and functional groups within a molecule.

17. Predictive capabilities: Predictive capabilities refer to the ability of a system or model to forecast future events or outcomes based on historical data and patterns. This often involves the use of algorithms, statistical techniques, and machine learning to analyze data and generate predictions about trends, behaviors, or potential scenarios.

17. Reinforcement learning (RL): Reinforcement learning (RL) is a type of machine learning where an agent learns to make decisions by taking actions in an environment to maximize cumulative rewards. The agent receives feedback in the form of rewards or penalties based on its actions, allowing it to optimize its behavior over time through trial and error.

17. bi-branch masked graph transformer autoencoder (BatmanNet): A bi-branch masked graph transformer autoencoder (BatmanNet) is a neural network architecture designed for processing graph-structured data. It features two parallel branches: one for encoding the input graph with masked nodes to learn meaningful representations, and another for decoding the learned representations back into a graph format. This architecture leverages transformer mechanisms to capture complex relationships within the graph while enhancing the model's ability to handle missing or incomplete information effectively.

18. \*\*Biological context\*\*: \*\*Biological context\*\*: The specific environmental, ecological, and social factors that influence the behavior, interactions, and development of organisms within a biological system. This includes the relationships among species, their habitats, and the physiological and genetic factors that affect their survival and reproduction.

18. \*\*Chemical Entities\*\*: \*\*Chemical Entities\*\*: Distinct substances or compounds with defined chemical compositions that can be identified and characterized by their molecular structure, properties, and reactivity. These entities may include elements, molecules, ions, and complexes involved in chemical reactions or processes.

18. \*\*Data augmentation\*\*: \*\*Data augmentation\*\*: A technique used in machine learning and computer vision that involves creating additional training data by applying various transformations to existing data samples, such as rotation, scaling, flipping, or adding noise, to improve model generalization and performance.

18. \*\*Drug-target binding affinities\*\*: \*\*Drug-target binding affinities\*\* refer to the strength of the interaction between a drug molecule and its biological target (such as a protein or receptor). It is typically quantified by the dissociation constant (Kd), where a lower Kd indicates a higher affinity, meaning the drug binds more tightly to the target, potentially enhancing its efficacy in therapeutic applications.

18. \*\*Drug-target interactions\*\*: \*\*Drug-target interactions\*\* refer to the specific biochemical interactions between a pharmaceutical compound (drug) and its biological target, typically a protein such as an enzyme or receptor. These interactions are critical for the drug's efficacy, as they determine how the drug alters the target's function, influencing therapeutic outcomes and side effects.

18. \*\*Explainable Artificial Intelligence (XAI)\*\*: \*\*Explainable Artificial Intelligence (XAI)\*\* refers to methods and techniques in artificial intelligence that make the decision-making processes of AI systems understandable to humans. XAI aims to provide insights into how AI models arrive at conclusions, enabling users to trust, interpret, and effectively manage AI outcomes while ensuring compliance with ethical standards and regulations.

18. \*\*Ground truth\*\*: \*\*Ground truth\*\*: The actual, verified data or information used as a benchmark for assessing the accuracy of models, algorithms, or predictions in various fields such as remote sensing, machine learning, and data analysis. It represents the real-world conditions or outcomes against which computational results are compared.

18. \*\*Overfitting\*\*: \*\*Overfitting\*\*: A modeling error that occurs when a machine learning algorithm captures noise or random fluctuations in the training data rather than the underlying pattern, resulting in poor generalization to new, unseen data.

18. \*\*Predictive performance\*\*: \*\*Predictive performance\*\* refers to the effectiveness of a model or algorithm in making accurate predictions based on input data. It is typically evaluated using metrics such as accuracy, precision, recall, or the area under the ROC curve (AUC), and indicates how well the model generalizes to unseen data.

18. \*\*Protein-ligand binding\*\*: \*\*Protein-ligand binding\*\* refers to the interaction between a protein and a ligand, where the ligand (which can be a small molecule, ion, or another protein) binds to a specific site on the protein, often resulting in a conformational change that affects the protein's function. This interaction is fundamental in biological processes, including enzyme activity, signal transduction, and molecular recognition.

18. \*\*Sensitivity\*\*: \*\*Sensitivity\*\*: In statistics and signal processing, sensitivity refers to the ability of a system or test to correctly identify true positive results. It is the proportion of actual positives that are correctly identified, often expressed as a percentage. In medical testing, for example, high sensitivity indicates that the test can accurately detect the presence of a condition.

18. \*\*Supervised learning techniques\*\*: \*\*Supervised learning techniques\*\* refer to a category of machine learning algorithms that learn a mapping from input data to output labels by utilizing a dataset containing input-output pairs. In this approach, the model is trained on a labeled dataset, where the correct output is provided for each input during the training process, enabling the model to make predictions on new, unseen data based on learned patterns.

18. 3D-MolGNN$\_{RL}$ framework: The 3D-MolGNN$\_{RL}$ framework is a computational model that integrates three-dimensional molecular graph neural networks (GNNs) with reinforcement learning (RL) techniques to predict molecular properties and optimize molecular structures. It leverages the spatial representation of molecules to enhance the learning process, allowing the model to effectively navigate the chemical space for tasks such as drug discovery and material design.

18. BatmanNet: \*\*BatmanNet\*\*: A decentralized network protocol designed for enhancing the privacy and security of peer-to-peer communications over the internet, often associated with anonymity and untraceable transactions. It utilizes techniques such as routing through multiple nodes to obscure user identities and data origins.

18. Bi-branch masked graph transformer autoencoder (BatmanNet): Bi-branch masked graph transformer autoencoder (BatmanNet) is a neural network architecture designed for processing graph-structured data. It utilizes a bi-branch structure to simultaneously capture both local and global features of the graph while employing masked autoencoding techniques to reconstruct missing or corrupted parts of the input graph. This approach leverages transformer mechanisms to enhance the model's ability to understand complex relationships and patterns within the graph, making it effective for tasks such as graph representation learning and node classification.

18. Chemical properties: \*\*Chemical properties\*\*: Characteristics of a substance that determine how it interacts with other substances during a chemical reaction. These properties include reactivity, acidity, flammability, and oxidation states, and are essential for understanding the substance's behavior in different chemical contexts.

18. Drug-target interaction: \*\*Drug-target interaction\*\*: The specific binding or interaction between a drug molecule and its biological target, such as a protein, enzyme, or receptor, which results in a pharmacological effect. This interaction is crucial for the drug's mechanism of action and efficacy in treating a disease.

18. Gated recurrent unit (GRU): A Gated Recurrent Unit (GRU) is a type of recurrent neural network (RNN) architecture designed to handle sequential data. It uses gating mechanisms to control the flow of information, allowing it to maintain long-term dependencies and mitigate the vanishing gradient problem. GRUs combine the input and forget gates into a single update gate and include a reset gate, making them simpler and often more efficient than traditional RNNs or Long Short-Term Memory (LSTM) networks.

18. Molecular property prediction: Molecular property prediction refers to the use of computational methods and algorithms to estimate the physical, chemical, and biological properties of molecules based on their structure and composition. This process often employs machine learning, quantum mechanics, or other modeling techniques to forecast behaviors such as solubility, reactivity, and toxicity, aiding in fields like drug discovery and materials science.

18. Self-supervised learning: Self-supervised learning is a machine learning paradigm where a model is trained on unlabeled data by generating its own supervisory signals from the data itself. This approach involves creating tasks or labels from the input data, allowing the model to learn representations without requiring external annotations.

18. dual approach: \*\*Dual Approach\*\*: A strategy that combines two different methods or perspectives to address a problem or achieve a goal, often integrating qualitative and quantitative analysis to enhance decision-making and outcomes.

19. \*\*Biological Activity\*\*: \*\*Biological Activity\*\*: The effect or influence that a substance, such as a drug or chemical, has on living organisms or biological systems, often measured by its ability to induce a specific biological response, such as enzyme activity, cell proliferation, or changes in physiological functions.

19. \*\*Chemical space\*\*: \*\*Chemical space\*\* refers to the vast theoretical multidimensional space that represents all possible chemical compounds based on their molecular structures, properties, and compositions. It encompasses the diversity of chemical structures, including variations in atoms, bonds, and functional groups, and is often used in fields like drug discovery and materials science to explore and identify potential candidates for new substances.

19. \*\*Computational frameworks\*\*: \*\*Computational frameworks\*\*: Structured sets of tools, libraries, and conventions that provide a foundation for developing, testing, and deploying computational models and algorithms, often facilitating tasks in areas such as data analysis, machine learning, and simulation.

19. \*\*Data scarcity\*\*: \*\*Data scarcity\*\* refers to a situation where there is insufficient data available for analysis, model training, or decision-making processes. This lack of data can hinder the development of accurate models, limit insights, and affect the performance of machine learning algorithms.

19. \*\*Davis dataset\*\*: \*\*Davis dataset\*\*: A benchmark dataset commonly used in machine learning and statistical analysis, particularly for evaluating regression algorithms. It consists of a collection of observations with multiple features and a target variable, often employed to demonstrate the performance of models in predicting outcomes based on input attributes.

19. \*\*Dropout as a Bayesian Approximation\*\*: \*\*Dropout as a Bayesian Approximation\*\*: A technique used in neural networks where dropout layers randomly deactivate a portion of neurons during training to prevent overfitting. This method can be interpreted as a Bayesian approximation by modeling uncertainty in the network's weights, effectively averaging over multiple models with different subsets of active neurons, thus providing a form of regularization that approximates a posterior distribution over the model's parameters.

19. \*\*Drug-drug interactions\*\*: \*\*Drug-drug interactions\*\* refer to the effects that occur when two or more medications are taken together, potentially altering the efficacy or safety of one or both drugs. These interactions can lead to increased side effects, reduced therapeutic effects, or unexpected outcomes due to changes in drug metabolism, absorption, or excretion.

19. \*\*Gene expression profiles\*\*: \*\*Gene expression profiles\*\* refer to the patterns of gene activity in a cell or tissue, indicating which genes are actively being expressed (transcribed and translated) at a given time. These profiles are often analyzed using techniques such as microarrays or RNA sequencing to understand cellular functions, developmental stages, or responses to environmental changes.

19. \*\*Generalizability\*\*: \*\*Generalizability\*\*: The extent to which findings from a study or experiment can be applied or extended to a broader population or context beyond the specific conditions or subjects involved in the research.

19. \*\*GradInput\*\*: \*\*GradInput\*\*: A parameter in machine learning frameworks, particularly in deep learning, that specifies whether the gradients should be calculated for the input tensors during backpropagation. When set to true, the gradients of the input with respect to the loss are computed, allowing for optimization of the input itself, which can be useful in certain applications like adversarial training or input perturbation analysis.

19. \*\*Molecular Pre-training Graph-based framework (MPG)\*\*: \*\*Molecular Pre-training Graph-based framework (MPG)\*\*: A computational model designed for the pre-training of molecular representations using graph-based structures, which captures the relationships and properties of molecular components. It leverages graph neural networks to enhance the understanding of molecular interactions and features, enabling improved performance in tasks such as drug discovery and molecular property prediction.

19. \*\*NovoMol\*\*: \*\*NovoMol\*\*: A computational platform designed for the simulation and modeling of molecular dynamics, facilitating the analysis of molecular interactions, structural properties, and dynamic behavior of biological and chemical systems.

19. \*\*Training datasets\*\*: \*\*Training datasets\*\*: Collections of data used to train machine learning models, consisting of input features and corresponding target outputs. These datasets help the model learn patterns and improve its performance on specific tasks by providing examples from which it can generalize.

19. Bi-branch masked graph transformer autoencoder: A Bi-branch Masked Graph Transformer Autoencoder is a neural network architecture designed for processing graph-structured data. It consists of two parallel branches that encode input graphs while masking certain elements to enhance learning. The transformer component utilizes self-attention mechanisms to capture relationships and dependencies in the graph, while the autoencoder structure enables effective representation learning and reconstruction of the original graph data.

19. Drug-target interaction analysis: Drug-target interaction analysis refers to the systematic study of the binding and effects of a pharmaceutical compound (drug) on a specific biological molecule (target), typically a protein or enzyme. This analysis helps in understanding the mechanism of action, efficacy, and potential side effects of the drug, and is crucial for drug development and optimization.

19. Explainable artificial intelligence (XAI): Explainable Artificial Intelligence (XAI) refers to methods and techniques in artificial intelligence that make the outputs of AI systems understandable to humans. XAI aims to provide insights into how AI models make decisions, ensuring transparency, accountability, and trustworthiness in their operations, particularly in critical applications such as healthcare, finance, and autonomous systems.

19. Local and global features: \*\*Local and Global Features\*\*: In data analysis and machine learning, local features refer to specific, detailed characteristics of a data point or a small region within a dataset, while global features represent broader, overarching characteristics that summarize or capture patterns across the entire dataset. Local features can vary significantly within a dataset, whereas global features provide an aggregate view, often used for tasks like classification or clustering.

19. Missing nodes and edges: \*\*Missing Nodes and Edges\*\*: In graph theory, missing nodes refer to vertices that are expected to exist within a graph but are not present, while missing edges are the connections between nodes that should exist but are absent. These omissions can affect the graph's structure and the analysis of its properties, leading to incomplete or inaccurate representations of the underlying data or relationships.

19. Molecular Pre-training Graph-based deep learning framework (MPG): Molecular Pre-training Graph-based deep learning framework (MPG) is a computational architecture designed for predictive modeling in chemistry and biology, which utilizes graph neural networks to represent molecular structures. It involves pre-training on large datasets to capture molecular properties and relationships, enabling the model to refine its understanding and improve performance on specific tasks, such as drug discovery or molecular property prediction.

19. Molecular Pre-training Graph-based model (MPG): Molecular Pre-training Graph-based model (MPG) is a machine learning approach that utilizes graph structures to represent molecular data, enabling the model to learn molecular properties and interactions through pre-training on large datasets. It enhances the understanding of molecular relationships by leveraging graph neural networks to capture the intricate connections and features inherent in molecular structures.

19. Molecular property prediction: Molecular property prediction is the process of using computational models and algorithms to estimate the physical, chemical, or biological properties of molecules based on their structure and composition. This technique often employs machine learning, quantum chemistry, or molecular simulations to forecast behaviors such as solubility, reactivity, stability, and biological activity, aiding in drug discovery and materials science.

19. Multi-objective reward function: A multi-objective reward function is a mathematical framework used in optimization and reinforcement learning that evaluates multiple conflicting objectives simultaneously. It assigns rewards based on the performance of an agent across different criteria, allowing for the balancing of trade-offs among these objectives to achieve a more comprehensive assessment of the agent's effectiveness.

19. local and global molecular structures: \*\*Local and Global Molecular Structures\*\*: Local molecular structures refer to the arrangement and interactions of atoms within a small, defined region of a molecule, often focusing on functional groups or specific bonding patterns. Global molecular structures, on the other hand, encompass the overall three-dimensional arrangement of all atoms within a molecule, including how different local structures interact and contribute to the molecule's overall shape and properties.

2. \*\*De novo drug discovery\*\*: \*\*De novo drug discovery\*\* refers to the process of designing and developing new pharmaceutical compounds from scratch, rather than modifying existing drugs. This approach typically involves the use of computational methods, biological insights, and various screening techniques to identify novel chemical entities that can effectively interact with specific biological targets.

2. \*\*Drug Discovery\*\*: \*\*Drug Discovery\*\*: The process of identifying and developing new medications, which involves the stages of target identification, compound screening, lead optimization, and preclinical and clinical testing to evaluate efficacy and safety before regulatory approval.

2. \*\*Machine Learning\*\*: \*\*Machine Learning\*\*: A subset of artificial intelligence that involves the use of algorithms and statistical models to enable computers to improve their performance on tasks through experience and data, without being explicitly programmed for specific outcomes.

2. \*\*Medicinal Chemistry\*\*: \*\*Medicinal Chemistry\*\*: A multidisciplinary field focused on the design, development, and optimization of pharmaceutical compounds, combining principles of chemistry, biology, and pharmacology to create effective medications for treating diseases.

2. \*\*Preprocessing\*\*: \*\*Preprocessing\*\*: The set of operations performed on raw data to clean, transform, and organize it into a suitable format for analysis or modeling. This may include tasks such as normalization, handling missing values, and feature extraction.

2. \*\*Protein targets\*\*: \*\*Protein targets\*\*: Specific proteins in biological systems that are the focus of drug development or therapeutic interventions. These proteins typically play crucial roles in disease processes, and targeting them can alter their function to achieve a desired therapeutic effect.

2. \*\*Self-supervised Graph Neural Networks (GNNs)\*\*: \*\*Self-supervised Graph Neural Networks (GNNs)\*\*: A class of graph neural networks that leverage self-supervised learning techniques to automatically generate labels or representations from the graph data itself, without requiring labeled examples. These networks utilize intrinsic properties of the graph, such as node relationships and structural features, to learn useful embeddings for tasks like node classification or link prediction.

2. \*\*Self-supervised graph neural networks (GNNs)\*\*: \*\*Self-supervised graph neural networks (GNNs)\*\*: A type of machine learning model that learns to represent graph-structured data by utilizing self-supervised learning techniques, which generate supervisory signals from the data itself rather than relying on labeled datasets. These networks capture the relationships and features of nodes and edges in a graph, enabling tasks such as node classification, link prediction, and graph classification without extensive human-annotated labels.

2. \*\*Self-supervised learning (SSL)\*\*: \*\*Self-supervised learning (SSL)\*\*: A machine learning paradigm where a model is trained on unlabeled data by generating its own supervisory signals, often through predicting parts of the data from other parts, enabling it to learn representations without explicit labels.

2. \*\*Self-supervised learning\*\*: \*\*Self-supervised learning\*\*: A machine learning paradigm where a model is trained on unlabeled data by generating its own supervision signals. This is typically achieved by creating auxiliary tasks from the data itself, allowing the model to learn useful representations without the need for annotated labels.

2. Computational paradigm: A computational paradigm is a fundamental model or approach for solving problems using computational methods, which defines the types of abstractions, structures, and techniques that can be employed to process information and execute algorithms. Common examples include procedural, object-oriented, functional, and parallel paradigms.

2. De novo drug discovery: De novo drug discovery refers to the process of designing and developing new pharmaceutical compounds from scratch, utilizing computational methods, biological data, and synthetic chemistry, rather than modifying existing drugs or compounds. This approach often involves screening large chemical libraries and predicting the interaction of potential drug candidates with target proteins to identify novel therapeutic agents.

2. Drug discovery: \*\*Drug Discovery\*\*: The process of identifying and developing new medications, involving the stages of target identification, compound screening, lead optimization, and preclinical testing, ultimately aimed at bringing a safe and effective drug to market.

2. Graph Neural Networks (GNNs): Graph Neural Networks (GNNs) are a class of neural networks designed to process and analyze data represented as graphs, where nodes represent entities and edges represent relationships between them. GNNs leverage the connectivity and structure of the graph to learn and propagate node features, enabling tasks such as node classification, link prediction, and graph classification.

2. Machine Learning: Machine Learning is a subset of artificial intelligence that involves the development of algorithms and statistical models that enable computers to learn from and make predictions or decisions based on data, without being explicitly programmed for specific tasks.

2. Target identification: \*\*Target Identification\*\*: The process of determining specific biological molecules, such as proteins or genes, that are involved in a disease or biological pathway, which can be targeted for therapeutic intervention or drug development.

2. de novo drug discovery: De novo drug discovery refers to the process of identifying and developing new pharmaceutical compounds from scratch, rather than modifying existing drugs. This approach typically involves using computational methods, high-throughput screening, and experimental techniques to design and synthesize novel molecules that have the potential to be effective treatments for specific diseases.

20. \*\*BatmanNet\*\*: \*\*BatmanNet\*\*: A decentralized network protocol designed for secure and efficient communication between nodes in peer-to-peer applications, often utilized in the context of blockchain and cryptocurrency systems to enhance privacy and scalability.

20. \*\*Computational Models\*\*: \*\*Computational Models\*\*: Mathematical and algorithmic frameworks used to simulate and analyze complex systems or processes, enabling the study of their behavior under various conditions through computation.

20. \*\*Data-driven methodologies\*\*: \*\*Data-driven methodologies\*\* refer to approaches and techniques that prioritize the use of data collection, analysis, and interpretation to inform decision-making, improve processes, and enhance outcomes in various fields, including business, science, and technology. These methodologies rely on empirical evidence and statistical analysis to guide actions and strategies, rather than intuition or anecdotal evidence.

20. \*\*Drug-drug interactions\*\*: \*\*Drug-drug interactions\*\* refer to the effects that occur when two or more drugs are administered together, potentially altering the pharmacokinetics (absorption, distribution, metabolism, and excretion) or pharmacodynamics (effects and mechanisms of action) of one or more of the involved substances, which can lead to reduced efficacy or increased toxicity.

20. \*\*F1 Score\*\*: \*\*F1 Score\*\*: A statistical measure used to evaluate the accuracy of a binary classification model, calculated as the harmonic mean of precision and recall. It ranges from 0 to 1, with 1 indicating perfect precision and recall. It is particularly useful in scenarios where there is an uneven class distribution.

20. \*\*HNN2Mol\*\*: \*\*HNN2Mol\*\*: A computational tool or software package used in cheminformatics for converting molecular structures represented in the HNN (Hierarchical Network Notation) format into standard molecular file formats, facilitating the analysis and visualization of chemical compounds.

20. \*\*Hierarchical informative GNN architecture\*\*: \*\*Hierarchical Informative GNN Architecture\*\*: A type of Graph Neural Network (GNN) structure that organizes information in a multi-layered hierarchy, allowing the model to capture and propagate features at different levels of granularity. This architecture enhances the representation of complex graph data by integrating local and global contextual information through a systematic layering process, improving performance on tasks such as node classification, link prediction, and graph classification.

20. \*\*Integrated Gradients (IG)\*\*: \*\*Integrated Gradients (IG)\*\*: A method for attributing the output of a neural network to its input features by calculating the integral of the gradients of the output with respect to the input along a straight path from a baseline input to the actual input. This technique helps in understanding which features most influence the model's predictions, providing insights into model interpretability.

20. \*\*KIBA dataset\*\*: \*\*KIBA dataset\*\*: A dataset used in computational biology and cheminformatics, specifically designed for drug discovery, that contains information on the binding affinities of various compounds to a set of protein targets. The KIBA dataset combines data from multiple sources to provide a comprehensive resource for training and evaluating machine learning models in predicting molecular interactions.

20. \*\*Large-scale unlabeled molecular datasets\*\*: \*\*Large-scale unlabeled molecular datasets\*\*: Collections of molecular data, such as chemical structures or biological sequences, that consist of a significant number of entries but lack corresponding labels or annotations that provide specific information about the molecules' properties, functions, or classifications. These datasets are often used in machine learning and computational biology for tasks like pattern recognition and feature extraction.

20. \*\*Structural perturbations\*\*: \*\*Structural perturbations\*\* refer to alterations or disruptions in the arrangement or organization of components within a system, often leading to changes in its physical properties or behavior. This term is commonly used in fields such as materials science, biology, and physics to describe the effects of external forces, environmental changes, or intrinsic fluctuations on the stability and functionality of structures.

20. \*\*Transferability\*\*: \*\*Transferability\*\*: The ability to apply knowledge, skills, or competencies acquired in one context to different settings or situations. In various fields, such as education and employment, it refers to the extent to which skills or qualifications can be recognized and utilized across different roles or environments.

20. \*\*Uncertainty Estimates\*\*: \*\*Uncertainty Estimates\*\*: Quantitative assessments of the potential variation or error in a measurement or prediction, reflecting the degree of confidence in the results. These estimates account for factors such as measurement precision, variability in data, and inherent limitations of the modeling process.

20. Chemical space: Chemical space refers to the multidimensional continuum that encompasses all possible chemical compounds and their variations, defined by their molecular structures, properties, and interactions. It is used in fields such as chemistry, drug discovery, and materials science to explore and analyze the vast array of potential chemical entities.

20. Drug-drug interaction: \*\*Drug-drug interaction\*\*: A pharmacological phenomenon that occurs when the effects of one drug are altered by the presence of another drug, potentially leading to increased side effects, reduced efficacy, or unexpected therapeutic outcomes.

20. Fine-tune: Fine-tune: The process of making small adjustments or optimizations to a model, system, or process to improve performance or accuracy based on specific data or requirements.

20. Hierarchical Grad-CAM graph Explainer (HGE): Hierarchical Grad-CAM Graph Explainer (HGE) is a method used in machine learning and computer vision to provide interpretable visual explanations of model predictions by generating hierarchical visualizations of feature importance. It builds upon the Grad-CAM (Gradient-weighted Class Activation Mapping) technique, enhancing it by organizing the activation maps in a graph structure that reflects the relationships between different features and layers of a neural network, thus enabling a deeper understanding of how input data influences model decisions at multiple levels of abstraction.

20. Local and global information: \*\*Local and Global Information\*\*: In data analysis and computing, local information refers to data or insights that are specific to a particular context, location, or subset of the data. In contrast, global information encompasses data or insights that are relevant across the entire dataset or system, providing a broader perspective that integrates multiple local contexts.

20. Molecular graphs: Molecular graphs are graphical representations of the molecular structure of compounds, where atoms are represented as vertices (nodes) and chemical bonds as edges (links) connecting these vertices. They are used in cheminformatics to analyze and visualize molecular properties, relationships, and reactions.

20. Molecular representations: Molecular representations are graphical depictions of molecules that illustrate their structure, composition, and spatial arrangement of atoms. These representations can include 2D drawings, 3D models, or symbolic formulas, and are used to convey information about molecular connectivity, geometry, and chemical properties.

20. Molecular structures: Molecular structures refer to the three-dimensional arrangement of atoms within a molecule, including the types of atoms present, the bonds connecting them, and the spatial orientation of these atoms, which ultimately determine the molecule's chemical properties and behavior.

20. Self-supervised learning techniques: Self-supervised learning techniques are a category of machine learning methods that leverage unlabeled data to create supervisory signals. These techniques generate labels from the data itself, enabling models to learn representations and features without the need for extensive manual labeling. This approach often involves predicting parts of the input data from other parts, such as in contrastive learning or predicting masked inputs in a sequence.

20. state-of-the-art results: State-of-the-art results refer to the highest level of performance or achievement currently available in a particular field, often representing the latest advancements in technology, methods, or techniques that set the benchmark for excellence.

21. \*\*Benchmark Datasets\*\*: \*\*Benchmark Datasets\*\*: Standardized collections of data used for evaluating and comparing the performance of algorithms, models, or systems in a specific domain. They provide a common reference point to assess improvements and ensure reproducibility in research and development.

21. \*\*Bi-branch masked graph transformer autoencoder\*\*: \*\*Bi-branch Masked Graph Transformer Autoencoder\*\*: A neural network architecture that processes graph-structured data by utilizing a bi-branch design to capture both local and global dependencies, while employing a masked learning strategy to reconstruct missing information in the graph. This enables effective representation learning and feature extraction for tasks such as node classification and link prediction in graph data.

21. \*\*Chemical: \*\*Chemical\*\*: A substance composed of atoms or molecules that has a defined composition and distinct properties; can be an element, compound, or mixture used in various scientific and industrial applications.

21. \*\*Co-representation learning\*\*: \*\*Co-representation learning\*\*: A machine learning approach that simultaneously learns multiple representations of data to capture different aspects or features, often through joint training processes. This method aims to improve model performance by leveraging the complementary information from various representations.

21. \*\*Computational chemists\*\*: \*\*Computational Chemists\*\*: Scientists who use computer simulations and modeling techniques to study chemical systems, predict molecular behavior, and understand chemical properties. They apply principles of chemistry, physics, and mathematics to analyze and visualize complex chemical interactions and reactions.

21. \*\*Drug-Target Binding Affinities\*\*: \*\*Drug-Target Binding Affinities\*\*: A measure of the strength of interaction between a drug and its biological target, typically a protein, reflecting how tightly the drug binds to the target. Higher affinities indicate stronger binding, which can enhance the drug's efficacy in modulating the target's activity.

21. \*\*Drug-target interactions\*\*: \*\*Drug-target interactions\*\* refer to the specific binding and biochemical interactions between a drug and its molecular target, typically a protein or enzyme, that mediate the drug's therapeutic effects or side effects. These interactions are crucial for understanding the mechanism of action of drugs and for optimizing their efficacy and safety in medical treatments.

21. \*\*Generalization capability\*\*: \*\*Generalization capability\*\* refers to the ability of a machine learning model to perform well on unseen data, beyond the specific examples it was trained on. It indicates how effectively the model can apply learned patterns to new instances, ensuring that its predictions remain accurate and relevant in diverse scenarios.

21. \*\*Harmonic mean\*\*: \*\*Harmonic Mean\*\*: The harmonic mean is a measure of central tendency calculated as the reciprocal of the arithmetic mean of the reciprocals of a set of values. It is particularly useful for sets of numbers that are defined in relation to some unit, such as rates or ratios, and is given by the formula: \( H = \frac{n}{\sum\_{i=1}^{n} \frac{1}{x\_i}} \), where \( n \) is the number of

21. \*\*Interpretable representations\*\*: \*\*Interpretable representations\*\* refer to data embeddings or models that provide insights into the underlying features or decision-making processes, allowing users to understand and interpret the relationships and significance of the represented information. These representations are designed to make complex data more accessible and meaningful, facilitating analysis and communication of results.

21. \*\*Molecular representations\*\*: \*\*Molecular representations\*\* refer to various ways of depicting the structure and composition of molecules, including two-dimensional drawings (like Lewis structures), three-dimensional models, and symbolic formulas (such as molecular formulas). These representations help visualize molecular geometry, connectivity, and functional groups, facilitating understanding and communication about chemical compounds.

21. \*\*Prediction Interval Estimation\*\*: \*\*Prediction Interval Estimation\*\*: A statistical method used to calculate a range of values within which future observations are expected to fall, with a specified probability. It accounts for both the uncertainty in the estimated mean of the data and the variability of individual observations, providing a more comprehensive understanding of potential outcomes than a simple point estimate.

21. \*\*Predictive models\*\*: \*\*Predictive models\*\*: Statistical or machine learning algorithms used to analyze historical data and identify patterns, enabling the forecast of future outcomes or behaviors based on new input data.

21. BatmanNet: \*\*BatmanNet\*\*: A decentralized network protocol designed to facilitate the efficient routing of data in low-bandwidth environments, particularly in scenarios where traditional internet infrastructure is unavailable or unreliable. It uses a mesh networking approach to enable peer-to-peer communication among devices.

21. Drug-target interaction: \*\*Drug-target interaction\*\*: The specific biochemical interaction between a drug molecule and its biological target, typically a protein, enzyme, or receptor, that results in a therapeutic effect or biological response. This interaction is crucial for the drug's efficacy and can influence its pharmacodynamics and pharmacokinetics.

21. Graph representation: Graph representation refers to the method of depicting a graph's structure and its components, such as vertices (nodes) and edges (connections), using various formats, such as adjacency lists, adjacency matrices, or edge lists. This representation allows for efficient storage, manipulation, and analysis of graph data in computer science and mathematics.

21. Hierarchical informative graph neural networks (HiGNN): Hierarchical Informative Graph Neural Networks (HiGNN) are a type of neural network architecture designed to process graph-structured data by leveraging hierarchical representations. They enhance the extraction of relevant features and relationships at multiple levels of granularity, enabling more effective learning and inference in tasks such as node classification, link prediction, and graph classification. HiGNNs achieve this by incorporating both local and global information through layers that progressively aggregate and refine node embeddings.

21. Local and global information: \*\*Local and Global Information\*\*: In the context of data analysis and networking, local information refers to data or insights that are specific to a particular area, system, or context, often limited in scope. Global information, on the other hand, encompasses a broader perspective, integrating data and insights from multiple areas or systems, allowing for a comprehensive understanding of trends or patterns across a wider context.

21. MolGNet: MolGNet is a machine learning framework specifically designed for molecular graph representation and property prediction, leveraging graph neural networks to capture the structural and chemical features of molecules for tasks such as drug discovery and materials science.

21. Molecular moieties: Molecular moieties refer to distinct parts or functional groups within a molecule that contribute to its chemical properties and reactivity. These can include specific atoms, functional groups, or structural elements that define the molecule's behavior in chemical reactions.

21. Predicting drug-target interactions: Predicting drug-target interactions refers to the computational and experimental methods used to identify and forecast the relationships between pharmaceutical compounds (drugs) and their biological targets (typically proteins or enzymes), which can inform drug discovery and development processes.

21. Transfer learning: Transfer learning is a machine learning technique where a model developed for a specific task is reused as the starting point for a model on a different but related task. This approach leverages knowledge gained from the initial task to improve learning efficiency and performance in the new task, often requiring less data and training time.

21. drug-drug interaction: A drug-drug interaction refers to a situation where one drug affects the pharmacological effect of another drug when both are administered together, potentially leading to reduced effectiveness, increased side effects, or unexpected adverse reactions.

22. \*\*Atomic features\*\*: \*\*Atomic features\*\*: The smallest indivisible components of a system or product that represent specific functionality or attributes, often used in modular design and development to enhance reusability and maintainability.

22. \*\*Biologists\*\*: \*\*Biologists\*\*: Scientists who study living organisms, their structure, function, growth, evolution, and interactions with their environment. They may specialize in various fields such as ecology, genetics, microbiology, and zoology.

22. \*\*Confidence Level\*\*: \*\*Confidence Level\*\*: A statistical measure that quantifies the degree of certainty in an estimate, typically expressed as a percentage. It indicates the likelihood that a parameter lies within a specified interval, commonly used in the context of confidence intervals in inferential statistics. For example, a 95% confidence level suggests that if the same sampling procedure were repeated multiple times, approximately 95% of the calculated intervals would contain the true population parameter.

22. \*\*Downstream: \*\*Downstream\*\*: In a supply chain or production process, "downstream" refers to the stages that occur after the initial production or processing of goods. This includes activities such as distribution, marketing, sales, and delivery to the end consumer. It contrasts with "upstream," which involves the sourcing of raw materials and initial production stages.

22. \*\*Hier: \*\*Hier\*\*: A prefix used in various contexts, often indicating a relationship to a specific hierarchy or level within a structure, such as in hierarchical databases or organizational hierarchies. It can also refer to "hierarchical" in contexts like file systems or data structures, where elements are arranged in a tree-like structure with parent-child relationships.

22. \*\*Lead Compounds\*\*: \*\*Lead Compounds\*\*: Chemical substances that contain lead and are often used in research and development, particularly in pharmacology and material science, to study their biological effects or as precursors for synthesizing other compounds.

22. \*\*Local and global information\*\*: \*\*Local and global information\*\* refers to data that is relevant to a specific context or area (local information) versus data that encompasses a broader perspective or overall context (global information). Local information provides detailed insights into particular events or conditions, while global information offers a comprehensive view that can include trends, patterns, or relationships across multiple contexts or areas.

22. \*\*MolGNet\*\*: \*\*MolGNet\*\*: A machine learning framework specifically designed for predicting molecular properties and behaviors by leveraging graph neural networks (GNNs). It represents molecules as graphs, where atoms are nodes and bonds are edges, enabling the model to capture complex relationships and interactions within the molecular structure for tasks such as property prediction, activity classification, and molecular generation.

22. \*\*Protein Data Bank (PDB)\*\*: \*\*Protein Data Bank (PDB)\*\*: A global repository for three-dimensional structural data of large biological molecules, primarily proteins and nucleic acids. It provides information on the atomic coordinates, chemical properties, and experimental techniques used to determine the structures, facilitating research in fields such as molecular biology, biochemistry, and drug design.

22. \*\*Receiver Operating Characteristic (ROC)\*\*: \*\*Receiver Operating Characteristic (ROC)\*\*: A graphical plot that illustrates the diagnostic ability of a binary classifier system by displaying the trade-off between true positive rate (sensitivity) and false positive rate (1-specificity) across various threshold settings. The ROC curve helps assess the performance of the classifier, with the area under the curve (AUC) quantifying its overall accuracy.

22. \*\*Standardized benchmarks\*\*: \*\*Standardized benchmarks\*\* are predefined criteria or measurements used to evaluate and compare the performance, quality, or effectiveness of products, services, or processes against a consistent standard across different contexts or organizations.

22. \*\*Transformations\*\*: \*\*Transformations\*\*: In mathematics and computer science, transformations refer to operations that change the position, size, or shape of an object or dataset. This can include geometric transformations (such as translation, rotation, and scaling) in graphics, and data transformations (such as normalization or encoding) in data processing and analysis.

22. Bi-branch masked graph transformer autoencoders: \*\*Bi-branch Masked Graph Transformer Autoencoders\*\*: A type of neural network architecture designed for processing graph-structured data, which utilizes a bi-branch approach to encode information from two distinct pathways. It incorporates masked learning techniques to allow the model to predict missing or masked elements within the graph, enhancing its ability to capture complex relationships and dependencies in the data while leveraging transformer mechanisms for improved representation learning.

22. Co-representation learning: Co-representation learning is a machine learning technique that involves simultaneously learning multiple representations of data that capture different aspects or features. This approach aims to enhance model performance by leveraging the complementary information from various representations to improve tasks such as classification, clustering, or regression.

22. Data scarcity: \*\*Data Scarcity\*\*: A condition in which insufficient data is available for analysis or model training, often hindering the development of accurate predictions or insights in machine learning, statistics, and research.

22. Drug-drug interaction assessments: Drug-drug interaction assessments are systematic evaluations conducted to determine how two or more medications may affect each other's pharmacokinetics or pharmacodynamics, potentially altering their efficacy or causing adverse effects. These assessments help inform prescribing practices and ensure patient safety.

22. Fine-tuning: Fine-tuning refers to the process of making small adjustments to a pre-trained machine learning model to improve its performance on a specific task or dataset. This involves retraining the model on a smaller, task-specific dataset while typically keeping most of the model's original parameters fixed.

22. Hierarchical information: Hierarchical information refers to data organized in a structured format where elements are ranked or classified according to levels of importance or authority, typically resembling a tree-like structure. Each level represents a different degree of detail, with higher levels encompassing broader categories and lower levels containing more specific subcategories.

22. Interpretability: Interpretability refers to the degree to which a human can understand the cause of a decision or prediction made by a model, particularly in the context of machine learning and artificial intelligence. It involves the ability to explain how inputs are transformed into outputs, allowing users to grasp the underlying mechanisms and rationale behind the model's behavior.

22. Local and global information: \*\*Local and Global Information:\*\*   
  
Local information refers to data or knowledge relevant to a specific, confined area or context, often reflecting immediate conditions or characteristics. Global information, on the other hand, encompasses broader, more comprehensive data that spans larger areas or contexts, allowing for comparisons and trends across multiple locales or systems.

22. Molecular Pre-training Graph-based deep learning framework (MPG): Molecular Pre-training Graph-based deep learning framework (MPG) is a specialized machine learning approach designed to analyze molecular structures using graph neural networks. It leverages pre-trained models on molecular graph data to improve predictions related to chemical properties, interactions, and behaviors, enabling enhanced performance in tasks such as drug discovery and materials science.

22. Nodes (atoms): Nodes (atoms): In the context of network theory and computer science, nodes (or atoms) refer to individual units or elements within a system or graph that can represent data points, entities, or components. Each node can have connections (edges) to one or more other nodes, facilitating the representation of relationships and interactions within the network.

23: In mathematics, "23" is a prime number that follows 22 and precedes 24. It is an integer that is only divisible by 1 and itself, making it a fundamental element in number theory.

23.: The term "23" typically refers to the number twenty-three, which is a natural number following twenty-two and preceding twenty-four. In various contexts, it can represent a quantity, an identifier, or a component within a larger framework, such as a chromosome count in humans (23 pairs of chromosomes).

23. \*\*Area Under the Curve (: \*\*Area Under the Curve (AUC)\*\*: A quantitative measure used in statistics and machine learning to evaluate the performance of a classifier. It represents the probability that a randomly chosen positive instance is ranked higher than a randomly chosen negative instance. The AUC value ranges from 0 to 1, with 1 indicating a perfect classifier and 0.5 suggesting no discriminative power.

23. \*\*Benchmark datasets\*\*: \*\*Benchmark datasets\*\*: Standardized collections of data used to evaluate and compare the performance of algorithms, models, or systems in machine learning and data science. These datasets provide a common reference point, allowing researchers and practitioners to assess improvements and validate results across different approaches.

23. \*\*Data scientists\*\*: \*\*Data scientists\*\*: Professionals who utilize statistical analysis, machine learning, programming, and data visualization techniques to extract insights and knowledge from structured and unstructured data, enabling informed decision-making and predictive modeling in various fields.

23. \*\*Masked nodes and edges\*\*: \*\*Masked nodes and edges\*\*: In graph theory and network analysis, masked nodes and edges refer to certain nodes and connections within a graph that are intentionally obscured or hidden from view or analysis. This can be done for privacy, security, or simplification purposes, allowing researchers or analysts to focus on specific aspects of the graph while excluding sensitive or irrelevant information.

23. \*\*Molecular Pre-training: \*\*Molecular Pre-training\*\*: A machine learning technique that involves training models on large datasets of molecular structures and properties to enhance their ability to predict chemical behaviors and interactions. This process typically uses unsupervised learning methods to capture the underlying patterns in molecular data before fine-tuning the model on specific tasks, such as drug discovery or material design.

23. \*\*Quantile Regression\*\*: \*\*Quantile Regression\*\*: A statistical technique that estimates the relationship between independent and dependent variables at specific percentiles (quantiles) of the dependent variable's distribution, rather than focusing solely on the mean. This allows for a more comprehensive analysis of how predictors influence different points of the outcome distribution, providing insights into variability and heterogeneity in the data.

23. \*\*Self-supervised learning paradigms\*\*: \*\*Self-supervised learning paradigms\*\*: A category of machine learning approaches where models are trained without explicit labeled data, using the data itself to generate supervisory signals. In these paradigms, the model learns to predict parts of the input from other parts, effectively creating its own labels from the structure or patterns within the data.

23. \*\*Three-dimensional structural data\*\*: \*\*Three-dimensional structural data\*\* refers to spatial information that describes the shape, orientation, and arrangement of objects or structures in a three-dimensional space. This data is often represented using coordinates (x, y, z) and can be utilized in various fields such as computer graphics, architecture, and molecular biology to visualize and analyze complex structures.

23. Asymmetrically structured graph autoencoders: Asymmetrically structured graph autoencoders are a type of neural network architecture designed to learn representations of graph-structured data. Unlike traditional autoencoders, which typically use symmetric encoding and decoding processes, these models employ different structures for encoding and decoding, allowing them to capture complex relationships and features within the graph more effectively. They are commonly used in tasks such as link prediction and node classification in graph-based machine learning applications.

23. Chemically synthesizable fragments: Chemically synthesizable fragments are small organic or inorganic molecules or molecular structures that can be created through established chemical reactions and techniques, allowing them to be assembled into larger, more complex compounds or materials in a laboratory setting.

23. Complementary graph autoencoders: Complementary graph autoencoders are a type of neural network architecture designed for graph data, which simultaneously learn to encode and decode information from two complementary graph structures. They utilize two distinct graphs that represent different aspects or relationships of the same underlying data, enabling the model to capture richer representations and improve tasks such as link prediction, graph classification, and node embedding by leveraging the complementary information present in both graphs.

23. Edges (chemical bonds): Edges, in the context of chemical bonds, refer to the connections between atoms in a molecular structure, representing the interactions that hold the atoms together. These bonds can be covalent, ionic, or metallic, and they determine the molecule's shape, stability, and reactivity.

23. Explainable artificial intelligence (XAI): Explainable Artificial Intelligence (XAI) refers to methods and techniques in the field of artificial intelligence that make the outputs and decision-making processes of AI systems understandable and interpretable to humans. The aim of XAI is to provide transparency, allowing users to comprehend how and why AI models arrive at specific conclusions, which is crucial for trust, accountability, and ethical considerations in AI applications.

23. Lead optimization: Lead optimization is the process in drug discovery and development that involves refining and enhancing chemical compounds (leads) to improve their efficacy, selectivity, and safety while minimizing undesirable properties, ultimately resulting in a viable candidate for further development and clinical trials.

23. Predictive tasks: Predictive tasks refer to analytical processes that involve forecasting future outcomes or trends based on historical data and statistical models. These tasks utilize algorithms and machine learning techniques to identify patterns and make informed predictions about variables of interest.

23. Scalability: Scalability is the ability of a system, network, or process to handle a growing amount of work or to be easily expanded to accommodate increased demand without compromising performance or efficiency.

23. node and graph levels: \*\*Node and Graph Levels\*\*: In graph theory, "nodes" (or vertices) represent individual elements or data points within a graph, while "graph levels" refer to the hierarchical layers or stages that organize nodes based on their relationships or distances from a starting node. Levels can indicate the shortest path or traversal order in a directed or undirected graph, facilitating analysis of connectivity and structure.

24. \*\*Calibration Methods: \*\*Calibration Methods\*\*: Techniques used to adjust and verify the accuracy of measuring instruments or devices by comparing their output against a known standard or reference to ensure precise and reliable measurements.

24. \*\*Hierarchical Graph Neural Networks (HiGNN): \*\*Hierarchical Graph Neural Networks (HiGNN)\*\*: A type of neural network designed to process graph-structured data by utilizing a hierarchical approach, where nodes are grouped into layers or clusters. HiGNNs capture multi-level relationships and dependencies within the graph, enabling more efficient learning and representation of complex structures by propagating information through these hierarchical levels.

24. \*\*Interdisciplinary collaboration\*\*: \*\*Interdisciplinary collaboration\*\* refers to the process where individuals or teams from different academic, professional, or disciplinary backgrounds work together to achieve a common goal, integrate diverse perspectives, and address complex problems that cannot be effectively solved by one discipline alone.

24. \*\*MolGNet framework\*\*: \*\*MolGNet framework\*\*: A computational framework designed for molecular graph neural networks, which facilitates the prediction of molecular properties by leveraging graph-based representations of molecular structures. It integrates deep learning techniques to analyze molecular data, enhancing the accuracy of property predictions and enabling efficient modeling of complex molecular interactions.

24. \*\*Molecular interactions\*\*: \*\*Molecular interactions\*\* refer to the various forces that occur between molecules, influencing their behavior and properties. These interactions include van der Waals forces, hydrogen bonds, ionic bonds, and covalent bonds, and play a crucial role in chemical reactions, biological processes, and the physical state of substances.

24. \*\*Quantitative comparisons\*\*: \*\*Quantitative comparisons\*\* refer to the evaluation and analysis of numerical data to determine the differences or similarities between two or more variables, typically expressed in terms of measurement, amounts, or ratios. These comparisons often involve statistical methods to derive insights or make decisions based on the data.

24. Bi-branch masked graph transformer autoencoder (BatmanNet): A Bi-branch Masked Graph Transformer Autoencoder (BatmanNet) is a neural network architecture designed for processing graph-structured data. It utilizes a bi-branch approach to separately encode and decode features, leveraging masked graph transformer mechanisms to capture complex relationships within graphs. This model is particularly effective in tasks such as graph representation learning and semi-supervised learning, where it can learn meaningful embeddings while handling missing or incomplete data.

24. Drug-drug interaction assessments: Drug-drug interaction assessments are systematic evaluations conducted to identify and analyze the potential effects that different medications may have on each other when administered together, including alterations in efficacy, toxicity, or metabolism, to ensure safe and effective pharmacotherapy.

24. Hierarchical Grad-CAM graph Explainer (HGE): Hierarchical Grad-CAM Graph Explainer (HGE) is a visualization technique that combines Gradient-weighted Class Activation Mapping (Grad-CAM) with a hierarchical structure to provide insights into the decision-making process of deep learning models. It generates a graph-based representation that highlights the importance of different features or regions in the input data, allowing users to understand how various levels of abstraction contribute to the model's predictions.

24. Interpretability: \*\*Interpretability\*\*: The extent to which a human can understand the cause of a decision made by a model, especially in the context of machine learning and artificial intelligence. It involves the clarity of the model's processes and the ability to explain its predictions in a meaningful way to users.

24. Masked molecular graphs: Masked molecular graphs are a representation of molecular structures in which certain atoms or bonds are obscured or marked as "masked" to focus on specific substructures or features. This approach is commonly used in cheminformatics and machine learning to enhance the learning of molecular properties by directing attention to relevant parts of the molecule while ignoring others.

24. Molecular representation learning: Molecular representation learning is a computational technique used in cheminformatics and drug discovery that involves the use of machine learning algorithms to create numerical or graphical representations of molecular structures. These representations capture important features and relationships of the molecules, enabling models to predict properties, interactions, or behaviors of chemical compounds based on their structural characteristics.

24. Predictive modeling: Predictive modeling is a statistical technique used to forecast future outcomes based on historical data. It involves creating a mathematical model that identifies patterns and relationships in the data, which can then be used to make predictions about unseen events or behaviors.

24. Reinforcement learning: Reinforcement learning is a type of machine learning where an agent learns to make decisions by taking actions in an environment to maximize cumulative rewards. It involves exploring actions and receiving feedback in the form of rewards or penalties, allowing the agent to improve its performance over time through trial and error.

24. chemical insights: \*\*Chemical Insights\*\*: Chemical insights refer to the understanding and interpretation of chemical data and phenomena, often derived from experimental results, computational models, or theoretical frameworks. These insights can inform the development of new materials, the optimization of chemical processes, and the elucidation of reaction mechanisms, ultimately enhancing knowledge in fields such as chemistry, materials science, and pharmacology.

25: The term "25" typically refers to the numerical value that comes after 24 and before 26 in the sequence of natural numbers. It is an integer and can represent quantity, order, or a specific measurement in various contexts such as mathematics, counting, and data representation.

25. \*\*Binding sites\*\*: \*\*Binding sites\*\*: Specific regions on a molecule, such as a protein or nucleic acid, where other molecules, such as ligands, substrates, or inhibitors, can attach through non-covalent interactions, influencing the molecule's function or activity.

25. \*\*Interpretability: \*\*Interpretability\*\*: The degree to which a human can understand the reasons behind the predictions or decisions made by a machine learning model, enabling insights into how the model operates and the factors influencing its outputs.

25. \*\*Local and global molecular features\*\*: \*\*Local and global molecular features\*\* refer to the characteristics of a molecular structure that can be analyzed at different scales. Local molecular features pertain to the properties and interactions of atoms and bonds within a small, specific region of a molecule, such as bond angles, bond lengths, and functional groups. Global molecular features, on the other hand, describe the overall properties and behaviors of the entire molecule, including its three-dimensional conformation, molecular weight, and polarity. Together, these features help in understanding the

25. Explainable artificial intelligence (XAI): Explainable Artificial Intelligence (XAI) refers to methods and techniques in artificial intelligence that make the outputs and decision-making processes of AI systems understandable to humans. XAI aims to provide transparency, allowing users to comprehend how and why AI systems arrive at specific conclusions or recommendations, thereby building trust and facilitating accountability in AI applications.

25. Expressive molecular representations: \*\*Expressive Molecular Representations\*\*: Advanced graphical or mathematical models that effectively capture and convey the complex structural and functional characteristics of molecules, enabling better interpretation, analysis, and prediction of chemical behavior and properties. These representations often include features like 3D coordinates, electronic configurations, and functional groups to enhance understanding and communication in fields such as chemistry and bioinformatics.

25. Gene expression profiles: Gene expression profiles refer to the measurement and analysis of the activity levels of multiple genes within a cell or tissue at a given time. This profiling helps to identify which genes are active, their expression levels, and how they vary under different conditions, providing insights into cellular functions and responses.

25. Hybrid neural network approach (HNN: \*\*Hybrid Neural Network Approach (HNN)\*\*: A computational model that combines different types of neural networks or integrates neural networks with other machine learning techniques to enhance performance, improve learning efficiency, and leverage the strengths of various algorithms for tasks such as classification, regression, or feature extraction.

25. Local and global molecular features: \*\*Local and Global Molecular Features\*\*: Local molecular features refer to specific structural or chemical properties of a small region within a molecule, such as functional groups or atom connectivity. In contrast, global molecular features encompass the overall characteristics of the entire molecule, including its shape, size, and overall electronic distribution. These features are essential for understanding molecular behavior and interactions in various chemical and biological contexts.

25. Local interactions: Local interactions refer to the interactions or relationships that occur between entities or components within a limited, confined area or proximity, often influencing their behavior or outcomes in a specific context. These interactions typically emphasize the immediate environment and direct influences rather than global or long-range effects.

25. Molecular moieties: \*\*Molecular moieties\*\*: Distinct structural units or functional groups within a molecule that contribute to its chemical properties and reactivity. These can include specific atoms, groups of atoms, or substructures that characterize the behavior of the molecule in chemical reactions.

25. interpretable molecular representations: Interpretable molecular representations are structured ways of encoding molecular information that allow for human understanding and analysis of the underlying chemical properties, relationships, and behaviors of molecules. These representations facilitate the interpretation of complex data by providing insights into molecular structure, function, and interactions, often used in fields like cheminformatics and machine learning to enhance model transparency and decision-making.

26: The term "26" typically refers to the integer that comes after 25 and before 27. It can represent a numerical value used in various contexts, such as counting, mathematics, or coding systems. In specific fields, it may also denote a particular item, category, or identifier, depending on the context in which it is used.

26.: It seems like "26." is not a recognized technical term. If you meant to ask for a definition of a specific term or concept, please provide the term, and I'll be happy to help!

26. \*\*Chemical space\*\*: \*\*Chemical space\*\* refers to the vast theoretical multidimensional space that encompasses all possible chemical compounds and their structural, electronic, and physical properties. It is used to describe the diversity and relationships among molecules based on variations in molecular composition and configuration.

26. Experimental validation: Experimental validation is the process of verifying the accuracy and reliability of a model, hypothesis, or system by conducting controlled experiments and comparing the results to theoretical predictions or expected outcomes.

26. Global structural features: Global structural features refer to the overarching characteristics and elements that define the organization, framework, and interconnections within a system or model on a large scale. These features provide insight into how different components interact and contribute to the overall functionality and behavior of the system.

26. HNN2: HNN2, or 1-hydroxy-2-nitro-4-(trifluoromethyl)benzene, is a chemical compound commonly used in organic synthesis and research, particularly in the study of reactive intermediates and in the development of pharmaceutical compounds. It is characterized by its nitro and trifluoromethyl substituents, which influence its reactivity and properties.

26. Multi-task learning: Multi-task learning is a machine learning approach where a model is trained to perform multiple related tasks simultaneously, leveraging shared representations and knowledge across tasks to improve overall performance and efficiency.

26. Protein-ligand binding stabilization: Protein-ligand binding stabilization refers to the molecular interactions and conformational changes that enhance the affinity and durability of the binding between a protein and its ligand, resulting in a more stable complex. This stabilization can occur through various forces, including hydrogen bonds, hydrophobic interactions, and electrostatic attractions, which collectively contribute to the overall stability and functionality of the protein-ligand complex.

26. hierarchical informative GNNs: Hierarchical Informative Graph Neural Networks (GNNs) are a class of graph-based models designed to learn representations of data structured in a hierarchical manner. They leverage the relationships between nodes at different levels of the hierarchy to capture and propagate informative features, enabling improved performance in tasks such as node classification, link prediction, and graph classification by effectively utilizing both local and global structural information within the graph.

27. Computational techniques: Computational techniques refer to a set of mathematical and algorithmic methods used to solve complex problems through computer simulations and calculations, often applied in fields such as data analysis, modeling, optimization, and artificial intelligence.

27. Hierarchical informative graph neural: Hierarchical Informative Graph Neural Networks (HIGNN) refer to a class of neural network architectures designed to process graph-structured data by leveraging hierarchical relationships and informative features within the graph. These networks typically use multiple layers to capture varying levels of abstraction and dependencies in the graph, enabling them to enhance tasks such as node classification, link prediction, and graph classification by incorporating both local and global structural information.

27. Pharmacological profiles: Pharmacological profiles refer to the comprehensive characterization of a drug's effects, mechanisms of action, therapeutic uses, side effects, and interactions with other substances. This profile encompasses both the efficacy (how well a drug works) and the safety (potential adverse effects) in various biological systems and conditions.

27. SGNN-EBM framework: SGNN-EBM framework refers to a machine learning architecture that combines Stochastic Graph Neural Networks (SGNN) with Energy-Based Models (EBM). This framework leverages the strengths of SGNN for processing graph-structured data and EBMs for learning complex distributions, enabling robust inference and generation tasks in various applications such as social network analysis and recommender systems.

28. Hier: \*\*Hier\*\*: A term commonly used in computing and data structures, short for "hierarchical," referring to a system of organization where elements are ranked or arranged in levels or layers, typically resembling a tree structure. In this context, each level can contain nodes that represent entities, with parent-child relationships defining the structure.

28. Reinforcement learning models: Reinforcement learning models are a type of machine learning algorithms that enable an agent to learn optimal behaviors through interactions with an environment. They operate on the principle of receiving feedback in the form of rewards or penalties based on the actions taken, allowing the agent to improve its decision-making over time by maximizing cumulative rewards.

28. Therapeutics: Therapeutics refers to the branch of medicine that focuses on the treatment and management of diseases and medical conditions through various methods, including medications, surgeries, physical therapies, and other interventions aimed at improving health outcomes.

29. Hybrid approaches: Hybrid approaches refer to methodologies that combine elements from different frameworks, techniques, or paradigms to leverage the strengths of each. In various fields such as machine learning, project management, and software development, hybrid approaches aim to optimize performance, enhance flexibility, and address complex problems by integrating diverse strategies and tools.

3. \*\*Artificial Intelligence (AI)\*\*: \*\*Artificial Intelligence (AI)\*\*: A branch of computer science focused on creating systems or machines that can perform tasks typically requiring human intelligence, such as learning, reasoning, problem-solving, perception, and language understanding.

3. \*\*Drug Discovery\*\*: \*\*Drug Discovery\*\*: The process of identifying and developing new medications, which involves the discovery of potential drug candidates, the optimization of their chemical properties, and the evaluation of their safety and efficacy through preclinical and clinical trials.

3. \*\*Drug discovery\*\*: \*\*Drug discovery\*\*: The process of identifying and developing new medications, which involves the stages of target identification, compound screening, optimization, and preclinical and clinical testing to evaluate safety and efficacy before potential market approval.

3. \*\*Graph Neural Networks (GNNs)\*\*: \*\*Graph Neural Networks (GNNs)\*\*: A class of neural network architectures specifically designed to operate on graph-structured data. GNNs leverage the relationships and connectivity between nodes (vertices) and edges in a graph to perform tasks such as node classification, link prediction, and graph classification, by aggregating and propagating information across the graph's structure.

3. \*\*Molecular data\*\*: \*\*Molecular data\*\* refers to information derived from the molecular composition of biological samples, including DNA, RNA, and proteins. It is used in various fields such as genetics, genomics, and bioinformatics to analyze genetic relationships, evolutionary processes, and biological functions.

3. \*\*Molecular design\*\*: \*\*Molecular design\*\*: The process of creating and optimizing molecular structures with specific properties and functions, often utilizing computational methods and simulations to predict the behavior of molecules in various environments, aimed at applications in fields such as pharmaceuticals, materials science, and nanotechnology.

3. \*\*Molecular representation learning\*\*: \*\*Molecular representation learning\*\* is a subfield of machine learning that focuses on creating effective numerical representations of molecular structures. These representations capture the essential features and properties of molecules, enabling algorithms to perform tasks such as predicting chemical properties, analyzing molecular interactions, and facilitating drug discovery.

3. \*\*Molecular representation\*\*: \*\*Molecular representation\*\*: A graphical or textual depiction of the structure of a molecule, illustrating the arrangement of atoms, bonds, and functional groups. It can take various forms, including Lewis structures, ball-and-stick models, space-filling models, and molecular formulas, used to convey information about the molecule's composition and geometry.

3. \*\*Molecular representations\*\*: \*\*Molecular representations\*\* refer to various ways of depicting the structure and composition of molecules, including their atoms, bonds, and spatial arrangements. Common forms include two-dimensional structural formulas, three-dimensional models, and simplified drawings like line-angle formulas, which convey information about molecular connectivity and geometry.

3. \*\*Molecular structures\*\*: \*\*Molecular structures\*\* refer to the specific arrangement of atoms within a molecule, including the types of atoms present, the bonds connecting them, and the overall three-dimensional shape. This arrangement determines the molecule's properties and behavior in chemical reactions.

3. \*\*Self-supervised Learning\*\*: \*\*Self-supervised Learning\*\*: A machine learning approach where a model is trained on unlabeled data by generating its own supervisory signals from the data itself, typically by predicting parts of the input from other parts. This method allows the model to learn useful representations without requiring manual labeling of data.

3. Computational methodologies: Computational methodologies refer to systematic approaches and techniques used to solve complex problems through computational processes, often involving algorithms, simulations, and mathematical models. These methodologies are employed in various fields such as computer science, engineering, and data analysis to analyze data, optimize solutions, and conduct research effectively.

3. Data sourcing: Data sourcing refers to the process of identifying, acquiring, and collecting data from various sources to be used for analysis, decision-making, or application development. This can involve accessing data from databases, APIs, web scraping, or external datasets.

3. Graph-structured data: Graph-structured data refers to a type of data representation that organizes information as nodes (entities) and edges (relationships) in a graph format. This structure allows for the modeling of complex relationships and interactions between data points, making it suitable for applications such as social networks, recommendation systems, and knowledge graphs.

3. Hit discovery: Hit discovery refers to the process of identifying potential lead compounds or drug candidates in drug development that exhibit desired biological activity against a specific target or disease. This phase typically involves screening large libraries of chemical compounds to find those that effectively interact with the target, leading to the identification of "hits" that warrant further investigation and optimization.

3. Molecular properties: Molecular properties refer to the characteristics and behaviors of molecules, including their structure, size, shape, polarity, and interactions with other molecules. These properties influence physical and chemical behavior, such as boiling and melting points, solubility, and reactivity.

3. Molecular representation learning: Molecular representation learning is a machine learning approach that focuses on creating efficient and informative representations of molecular structures and properties. These representations, often in the form of vectors, enable computational models to better understand and predict molecular behavior, interactions, and biological activity, facilitating tasks such as drug discovery and material design.

3. Predictive modeling: Predictive modeling is a statistical technique that uses historical data and algorithms to forecast future outcomes or behaviors by identifying patterns and relationships within the data.

3. Property prediction: Property prediction refers to the process of estimating the characteristics or behaviors of a chemical compound, material, or biological system based on its structural information or other relevant data, often using computational models and machine learning techniques. This is commonly applied in fields such as cheminformatics, materials science, and drug discovery to facilitate the identification of promising candidates for further study or development.

3. computational drug design: Computational drug design is a scientific approach that utilizes computer algorithms and simulations to identify, develop, and optimize potential pharmaceutical compounds. It involves modeling molecular interactions, predicting the biological activity of drug candidates, and facilitating the drug discovery process by analyzing the structure and properties of molecules.

30. Geometric deep learning techniques: Geometric deep learning techniques refer to a set of methods in machine learning that extend deep learning principles to non-Euclidean domains, such as graphs and manifolds. These techniques leverage the geometric properties of data structures to improve learning tasks, enabling the analysis of complex relationships and spatial structures that traditional deep learning approaches may not effectively handle.

4. \*\*Biological systems\*\*: \*\*Biological systems\*\*: Complex networks of biologically relevant entities, including cells, tissues, organisms, and ecosystems, that interact with each other and their environment to sustain life processes and maintain homeostasis.

4. \*\*De Novo Drug Discovery\*\*: \*\*De Novo Drug Discovery\*\*: A process of designing and developing new pharmaceutical compounds from scratch, utilizing computational methods, biological data, and chemical insights, rather than modifying existing drugs. This approach aims to identify novel drug candidates that have not been previously known or studied.

4. \*\*De novo drug discovery\*\*: \*\*De novo drug discovery\*\* refers to the process of designing and developing new pharmaceutical compounds from scratch, using computational methods, biological insights, and chemical synthesis, rather than modifying existing drugs. This approach aims to identify novel molecules that can effectively target specific biological pathways related to diseases.

4. \*\*Drug candidates\*\*: \*\*Drug candidates\*\*: Compounds that have been identified and evaluated for their potential therapeutic effects and are undergoing testing to determine their efficacy, safety, and suitability for further development into a pharmaceutical drug.

4. \*\*Drug design processes\*\*: \*\*Drug design processes\*\* refer to the systematic approach of discovering and developing new pharmaceutical compounds. This involves identifying biological targets, optimizing chemical structures for efficacy and safety, and using computational models and experimental techniques to predict how compounds interact with these targets. The overall goal is to create effective and safe drugs for therapeutic use.

4. \*\*Graph representation\*\*: \*\*Graph representation\*\*: A method of illustrating a graph's structure using mathematical notation or visual formats, which includes vertices (nodes) and edges (connections) to depict relationships and properties of the graph, commonly represented in forms such as adjacency lists, adjacency matrices, or edge lists.

4. \*\*Machine learning models\*\*: \*\*Machine learning models\*\*: Computational algorithms that learn patterns and make predictions or decisions based on input data, improving their performance over time through experience without being explicitly programmed for specific tasks.

4. \*\*Medicinal chemistry\*\*: \*\*Medicinal Chemistry\*\*: A multidisciplinary field that involves the design, development, and optimization of pharmaceutical compounds. It combines principles of chemistry, biology, and pharmacology to create new medications and improve existing ones, focusing on their chemical properties, biological activity, and therapeutic efficacy.

4. \*\*Molecular Representation\*\*: \*\*Molecular Representation\*\*: A graphical or symbolic depiction of the structure of a molecule, illustrating the arrangement of atoms, their connectivity, and the spatial orientation of bonds. It can include various formats such as Lewis structures, ball-and-stick models, or space-filling models, providing insight into the molecule's chemical properties and behavior.

4. \*\*Molecular Structures\*\*: \*\*Molecular Structures\*\*: The three-dimensional arrangement of atoms within a molecule, including the types of atoms, their bonding patterns, and spatial orientation, which collectively determine the molecule's properties and reactivity.

4. \*\*Molecular properties\*\*: \*\*Molecular properties\*\* refer to the characteristics and behaviors of molecules, including their structure, size, shape, polarity, reactivity, and interactions with other molecules. These properties influence how molecules behave in chemical reactions and their physical properties, such as boiling and melting points, solubility, and viscosity.

4. \*\*Molecular property prediction\*\*: \*\*Molecular property prediction\*\* refers to the computational or experimental methods used to estimate the physical, chemical, or biological properties of molecules based on their structure and composition. This process often employs techniques such as machine learning, quantum chemistry, or molecular modeling to forecast characteristics like solubility, reactivity, and stability, aiding in drug discovery, materials science, and chemical engineering.

4. Binding affinities: Binding affinities refer to the strength of the interaction between a ligand (such as a drug or hormone) and a specific target molecule (such as a protein or receptor). It is quantitatively expressed as the equilibrium constant (Kd), where a lower Kd value indicates a higher affinity, meaning the ligand binds more tightly to the target.

4. Compound prioritization: \*\*Compound Prioritization\*\*: The process of ranking chemical compounds based on specific criteria, such as biological activity, safety, cost, and feasibility, to identify the most promising candidates for further development in drug discovery or research.

4. Lead optimization: Lead optimization is the process in drug discovery and development that involves refining and enhancing the chemical properties and biological activity of lead compounds to improve their efficacy, safety, and pharmacokinetic profiles before advancing to clinical trials.

4. Molecular modeling: Molecular modeling is a computational technique used to represent and analyze the structures, properties, and behaviors of molecules. It utilizes mathematical models and simulations to predict molecular interactions, conformations, and reactions, often employing software tools to visualize and manipulate molecular systems.

4. Molecular representation learning: Molecular representation learning is a subfield of machine learning focused on creating numerical representations (or embeddings) of molecular structures that capture their chemical properties and behaviors. This technique enables the application of machine learning algorithms to predict molecular characteristics, optimize drug discovery, and facilitate the understanding of chemical interactions by encoding molecular information in a format suitable for computational analysis.

4. Preprocessing: Preprocessing refers to the series of data transformation steps applied to raw data before it is analyzed or used in machine learning models. This includes activities such as cleaning, normalization, transformation, and feature extraction to improve data quality and enhance model performance.

4. Supervised learning methods: Supervised learning methods are a category of machine learning techniques where a model is trained on a labeled dataset, meaning that each training example is paired with an output label. The model learns to map input features to the correct output by minimizing the difference between its predictions and the actual labels during training. This approach is commonly used for classification and regression tasks.

4. Supervisory signals: \*\*Supervisory Signals\*\*: Control signals used in electronic and communication systems to manage and coordinate the operation of devices or processes, ensuring proper timing, synchronization, and data flow between components.

4. Surrogate tasks: Surrogate tasks are simplified or alternative tasks used in research or machine learning to approximate the complexity of a real-world problem. They serve as proxies to evaluate algorithms or models in a more controlled setting, allowing for easier analysis and understanding of their performance before applying them to more complex, real-world scenarios.

4. molecular representation methods: Molecular representation methods are techniques used to depict the structure and properties of molecules in a standardized format, enabling visualization, analysis, and computational modeling. These methods include various graphical representations, such as ball-and-stick models, space-filling models, and two-dimensional structural formulas, as well as computational formats like SMILES (Simplified Molecular Input Line Entry System) and InChI (International Chemical Identifier).

5. \*\*Chemical and biological data\*\*: \*\*Chemical and biological data\*\*: Information that encompasses the properties, behaviors, and interactions of chemical substances and biological organisms. This data can include molecular structures, reaction mechanisms, genetic sequences, metabolic pathways, and ecological interactions, and is often used in research, development, and regulatory contexts in fields like chemistry, biology, and environmental science.

5. \*\*Drug-target interaction\*\*: \*\*Drug-target interaction\*\*: The specific binding or interaction between a drug molecule and a biological target, typically a protein or receptor, that leads to a pharmacological effect. This interaction is crucial for the drug's mechanism of action and efficacy in treating a disease.

5. \*\*Evaluation metrics\*\*: \*\*Evaluation metrics\*\*: Quantitative measures used to assess the performance of a model or algorithm, typically in the context of machine learning or data analysis. These metrics help determine how well a model predicts outcomes compared to actual results, guiding improvements and comparisons between different models. Common examples include accuracy, precision, recall, F1 score, and area under the ROC curve (AUC-ROC).

5. \*\*Graph Neural Networks (GNNs)\*\*: \*\*Graph Neural Networks (GNNs)\*\*: A class of neural networks designed to operate on graph-structured data, enabling the processing and learning of node and edge features by leveraging the relationships and connectivity between nodes in a graph. GNNs are used for tasks such as node classification, link prediction, and graph classification in various domains, including social networks, molecular biology, and recommendation systems.

5. \*\*Labeled molecular datasets\*\*: \*\*Labeled molecular datasets\*\* are collections of molecular data where each entry is accompanied by annotations or labels that provide specific information about the molecular structure, properties, or biological activity. These datasets are often used in machine learning and computational biology to train models for tasks such as molecular classification, prediction of chemical properties, or drug discovery.

5. \*\*Molecular Representation Learning\*\*: \*\*Molecular Representation Learning\*\*: A computational method in machine learning that focuses on creating numerical representations of molecular structures, enabling algorithms to understand and predict molecular properties and behaviors. This approach typically involves encoding molecular graphs or features into vector spaces, facilitating tasks such as drug discovery, material science, and bioinformatics.

5. \*\*Molecular properties\*\*: \*\*Molecular properties\*\* refer to the characteristics and behaviors of molecules that arise from their structure, composition, and interactions. These properties include aspects such as molecular weight, polarity, reactivity, and spectral characteristics, which influence how molecules behave in different chemical and physical environments.

5. \*\*Molecular representation learning\*\*: \*\*Molecular representation learning\*\* refers to the process of using machine learning techniques to create numerical representations (embeddings) of molecular structures, allowing for the analysis and prediction of chemical properties and behaviors. This approach typically involves transforming molecular data into a format suitable for computational models, enabling applications in drug discovery, materials science, and cheminformatics.

5. \*\*Nodes and edges\*\*: \*\*Nodes and Edges\*\*: In graph theory, nodes (or vertices) are the fundamental units that represent entities, while edges (or links) are the connections or relationships between these nodes. Together, they form a graph, which is a mathematical representation used to model pairwise relations in various fields such as computer science, network analysis, and social sciences.

5. \*\*Property Prediction\*\*: \*\*Property Prediction\*\*: A computational technique used in materials science and chemistry to forecast the physical, chemical, or mechanical properties of substances based on their molecular structure or composition, often utilizing machine learning algorithms and databases of known material properties.

5. \*\*Robust methodologies\*\*: \*\*Robust methodologies\*\* refer to systematic approaches or frameworks that are designed to produce reliable and valid results across various conditions and contexts. These methodologies are characterized by their ability to withstand variability, adapt to different datasets, and maintain their effectiveness despite changes in underlying assumptions or external factors.

5. \*\*Supervised learning\*\*: \*\*Supervised learning\*\* is a type of machine learning where a model is trained on a labeled dataset, meaning that each training example is paired with an output label. The model learns to map inputs to the correct outputs by identifying patterns in the data, allowing it to make predictions on new, unseen data.

5. \*\*Uncertainty Quantification\*\*: \*\*Uncertainty Quantification\*\*: A systematic process used to assess and communicate the uncertainties in mathematical models and simulations, including the identification, characterization, and propagation of uncertainty through analysis to improve decision-making and risk assessment.

5. Molecular Pre-training Graph-based framework (MPG): Molecular Pre-training Graph-based framework (MPG) is a machine learning approach designed for molecular property prediction that leverages graph-based representations of molecular structures. It involves pre-training models on large datasets of molecular graphs to capture complex relationships and features, which can then be fine-tuned for specific tasks such as drug discovery or material science applications, improving prediction accuracy and efficiency.

5. Molecular graphs: Molecular graphs are graphical representations of chemical structures where atoms are represented as vertices (nodes) and chemical bonds are represented as edges (lines connecting the nodes). This representation allows for the visualization and analysis of molecular connectivity and properties in a structured format, facilitating computational chemistry and cheminformatics applications.

5. Natural Language Processing (NLP): Natural Language Processing (NLP) is a subfield of artificial intelligence that focuses on the interaction between computers and humans through natural language. It involves the development of algorithms and models that enable machines to understand, interpret, generate, and respond to human language in a meaningful way, facilitating tasks such as translation, sentiment analysis, and conversational agents.

5. Neural networks: Neural networks are computational models inspired by the human brain, consisting of interconnected layers of nodes (neurons) that process and learn from data. They are used in machine learning to recognize patterns, make predictions, and solve complex problems across various domains such as image recognition, natural language processing, and autonomous systems.

5. Preclinical testing: Preclinical testing refers to the phase of research that evaluates the safety, efficacy, and pharmacokinetics of a drug candidate using in vitro (test tube) and in vivo (animal) models before it is tested in humans. This stage is crucial for identifying potential adverse effects and determining appropriate dosages prior to clinical trials.

5. Representation learning: Representation learning is a subset of machine learning focused on automatically discovering and learning the representations or features of data that are most useful for specific tasks, such as classification or regression, without needing manual feature engineering. It aims to transform raw data into a format that enhances the performance of machine learning algorithms.

5. Scarcity of labeled data: Scarcity of labeled data refers to the insufficient availability of annotated datasets where input data is paired with corresponding output labels, which is often a challenge in machine learning and data analysis. This limitation can hinder the development and performance of models, as they rely on sufficient labeled examples for training and validation.

5. Self-supervised learning (SSL): Self-supervised learning (SSL) is a machine learning approach where a model is trained on unlabeled data by generating its own supervisory signals from the data itself, typically by predicting parts of the input from other parts. This method leverages the inherent structure within the data to learn useful representations without requiring explicit labels.

5. Supervised learning approaches: Supervised learning approaches are a type of machine learning where a model is trained on a labeled dataset, meaning that each training example is paired with an output label. The model learns to map inputs to the correct outputs by minimizing the difference between its predictions and the actual labels, enabling it to make accurate predictions on new, unseen data.

5. labeled data: Labeled data refers to a dataset in which each input sample is paired with a corresponding output label or category, used to train machine learning models. This data helps algorithms learn to make predictions or classifications based on the provided examples.

6. \*\*Accuracy\*\*: \*\*Accuracy\*\*: The degree to which a measured or calculated value aligns with the true or accepted value, indicating the correctness of a result in relation to a standard or benchmark.

6. \*\*Active Learning\*\*: \*\*Active Learning\*\*: A machine learning approach where the algorithm selectively queries a user or an oracle to obtain labels for specific data points, thereby improving its learning efficiency and performance by focusing on the most informative examples.

6. \*\*Computational methodologies\*\*: \*\*Computational methodologies\*\* refer to systematic approaches and techniques employed to solve complex problems using computational tools and algorithms. These methodologies encompass various disciplines, including computer science, mathematics, and engineering, and are used to analyze data, simulate processes, and optimize solutions across diverse applications.

6. \*\*De novo drug design\*\*: \*\*De novo drug design\*\*: A computational approach in drug discovery where new drug candidates are created from scratch using structural information about biological targets, rather than modifying existing drugs. This method employs algorithms and molecular modeling to predict the interactions and efficacy of novel compounds against specific biological pathways or diseases.

6. \*\*Drug-drug interactions\*\*: \*\*Drug-drug interactions\*\* refer to the effects that occur when two or more medications are taken together, potentially altering the effectiveness or safety of one or more of the drugs involved. These interactions can lead to increased side effects, reduced therapeutic effects, or unexpected reactions, and can occur through various mechanisms including pharmacokinetic and pharmacodynamic changes.

6. \*\*Graph Neural Networks (GNNs)\*\*: \*\*Graph Neural Networks (GNNs)\*\*: A class of neural networks designed to process data represented as graphs. GNNs leverage the relationships and structures within graph data, allowing them to learn features from nodes and edges, making them effective for tasks such as node classification, link prediction, and graph classification in domains such as social networks, biological networks, and recommendation systems.

6. \*\*Labeled data\*\*: \*\*Labeled data\*\* refers to a dataset where each data point is associated with a corresponding label or annotation that indicates its category or value. This is commonly used in supervised machine learning tasks, where the labels help algorithms learn to make predictions or classifications based on the features of the data.

6. \*\*Node features\*\*: \*\*Node features\*\*: Attributes or characteristics associated with a specific node in a graph or network, used to describe its properties or behavior. In machine learning and graph analysis, these features can include numerical values, categorical data, or any relevant information that helps in modeling or understanding the relationships within the graph.

6. \*\*Normalization\*\*: \*\*Normalization\*\*: A process in database design and data management that organizes data to minimize redundancy and dependency by dividing large tables into smaller, related tables and defining relationships between them, thereby ensuring data integrity and efficiency in data retrieval.

6. \*\*Overfitting\*\*: \*\*Overfitting\*\*: A modeling error that occurs when a statistical model or machine learning algorithm captures noise or random fluctuations in the training data rather than the underlying distribution, resulting in poor generalization to new, unseen data.

6. \*\*Supervised Learning\*\*: \*\*Supervised Learning\*\*: A type of machine learning where a model is trained on a labeled dataset, meaning that each training example is paired with an output label. The model learns to map input data to the correct output by minimizing the difference between its predictions and the actual labels during training. This approach is commonly used for classification and regression tasks.

6. \*\*Validation techniques\*\*: \*\*Validation techniques\*\* refer to methods and processes used to ensure that a system, product, or model meets specified requirements and performs its intended functions accurately and reliably. These techniques help verify the correctness, completeness, and quality of the data, design, or implementation, often involving testing, reviews, and assessments to confirm that outcomes align with expectations.

6. Computer Vision: Computer Vision is a field of artificial intelligence that enables computers and systems to interpret and understand visual information from the world, such as images and videos, by simulating human vision processes.

6. Data acquisition: Data acquisition is the process of collecting, measuring, and analyzing data from various sources, including sensors, instruments, or databases, to support research, monitoring, and decision-making.

6. Empirical methods: Empirical methods refer to research and analytical approaches that rely on observation, experimentation, and real-world data collection to test hypotheses and develop knowledge, rather than solely on theoretical or conceptual frameworks.

6. Labeled datasets: Labeled datasets are collections of data points that have been annotated with specific labels or tags, indicating the desired output or category for each data point. These labels help machine learning models learn to make predictions or classifications based on the input data.

6. MolGNet model: MolGNet model: A machine learning framework specifically designed for predicting molecular properties and interactions by leveraging graph neural networks (GNNs) to represent molecules as graphs, where atoms are nodes and bonds are edges, thereby capturing complex structural information in a computationally efficient manner.

6. Molecular data: Molecular data refers to information derived from the molecular composition of biological entities, such as DNA, RNA, and proteins. It is used in various fields, including genetics, molecular biology, and bioinformatics, to analyze genetic variations, evolutionary relationships, and biochemical processes.

6. Molecular representation learning: Molecular representation learning is a subfield of machine learning focused on creating numerical representations of chemical compounds and molecular structures. These representations, often in the form of vectors or embeddings, capture the essential features and relationships of molecules, enabling algorithms to perform tasks such as prediction of chemical properties, drug discovery, and molecular classification.

6. Relational structures: Relational structures refer to mathematical or logical frameworks that consist of a set of objects along with a collection of relations that define how those objects interact or relate to each other. These structures are foundational in fields such as relational databases, graph theory, and formal logic, where the focus is on the relationships among entities rather than the entities themselves.

6. Self-supervised learning: Self-supervised learning is a type of machine learning where a model is trained on unlabeled data by creating its own supervisory signals from the data itself. This approach typically involves generating labels from the input data through predefined tasks, enabling the model to learn representations and features without the need for manually annotated datasets.

6. architectures: Architectures refer to the structured frameworks or designs that define the organization, components, and relationships within a system, application, or technology. This term is commonly used in various fields, including software engineering, network design, and information systems, to describe how elements are arranged and how they interact to achieve specific functions or goals.

7. \*\*Drug-target interactions\*\*: \*\*Drug-target interactions\*\* refer to the specific biochemical interactions between a drug molecule and its biological target, typically a protein, enzyme, or receptor, which lead to a therapeutic effect or biological response. Understanding these interactions is crucial for drug design and development, as they influence the efficacy and safety of the medication.

7. \*\*Edge features\*\*: \*\*Edge features\*\* refer to distinctive characteristics or attributes that highlight the boundaries or outlines of objects within a dataset, particularly in image processing and computer vision. These features are often used in algorithms to detect shapes, contours, and transitions in visual data, aiding in tasks such as object recognition and scene understanding.

7. \*\*Generalization capabilities\*\*: \*\*Generalization capabilities\*\* refer to the ability of a model or algorithm to apply learned knowledge from training data to new, unseen data effectively. This involves recognizing patterns and making predictions or decisions based on previously encountered information, ensuring that the model performs well outside the specific examples it was trained on.

7. \*\*Generalization\*\*: \*\*Generalization\*\*: The process of formulating general concepts by extracting common properties or patterns from specific examples or instances, often used in fields like machine learning, statistics, and logic to apply learned knowledge to new, unseen situations.

7. \*\*Graph neural networks (GNNs)\*\*: \*\*Graph Neural Networks (GNNs)\*\*: A class of neural networks specifically designed to process and analyze data structured as graphs. GNNs operate by capturing the relationships and dependencies between nodes (vertices) and edges in a graph, enabling the model to learn representations that can be used for tasks such as node classification, link prediction, and graph classification.

7. \*\*Independent variables\*\*: \*\*Independent variables\*\*: Factors or conditions in an experiment or study that are manipulated or controlled by the researcher to observe their effect on dependent variables. They are not influenced by other variables in the context of the experiment.

7. \*\*Iterative Model Improvement\*\*: \*\*Iterative Model Improvement\*\*: A systematic approach in machine learning and software development where models are repeatedly refined and enhanced through cycles of testing, evaluation, and feedback. This method allows for incremental adjustments based on performance metrics, leading to progressively better results over time.

7. \*\*Labeled Data\*\*: \*\*Labeled Data\*\*: Data that has been annotated with specific tags or labels that provide context or meaning, allowing it to be used for training machine learning models. Each data point in a labeled dataset is associated with a corresponding output or category, facilitating supervised learning tasks.

7. \*\*Molecular Data\*\*: \*\*Molecular Data\*\*: Information derived from the analysis of molecular structures, sequences, and interactions, often used in fields such as genetics, bioinformatics, and molecular biology to understand biological processes, relationships, and functions at the molecular level.

7. \*\*Predictive performance\*\*: \*\*Predictive performance\*\* refers to the effectiveness of a model or algorithm in accurately forecasting outcomes based on input data. It is typically evaluated using metrics such as accuracy, precision, recall, and F1 score, which assess how well the model's predictions align with actual results.

7. \*\*Supervised learning approaches\*\*: \*\*Supervised learning approaches\*\*: A category of machine learning techniques where a model is trained on labeled data, meaning that the input data is paired with the correct output. The model learns to map inputs to the desired outputs by minimizing the error between its predictions and the actual labels during training. Common applications include classification and regression tasks.

8. \*\*Predictive models\*\*: \*\*Predictive models\*\*: Statistical or machine learning algorithms used to forecast future outcomes based on historical data and patterns. These models analyze trends, relationships, and variables to make informed predictions about events, behaviors, or trends in various domains, such as finance, healthcare, and marketing.

8. \*\*Self-Supervised Learning\*\*: \*\*Self-Supervised Learning\*\*: A machine learning paradigm where a model is trained on unlabeled data by generating its own supervisory signals from the data itself, often through tasks like predicting parts of the input from other parts, enabling the model to learn useful representations without the need for manual annotations.

8. \*\*Self-supervised learning methods\*\*: \*\*Self-supervised learning methods\*\*: A class of machine learning techniques where a model learns to predict part of the input data from other parts, using the data itself as a source of supervision without requiring labeled datasets. This approach often involves generating pseudo-labels from the data, enabling the model to learn useful representations and features autonomously.

8. \*\*Self-supervised learning\*\*: \*\*Self-supervised learning\*\* is a machine learning paradigm where a model is trained on unlabeled data by generating its own supervisory signals from the data itself. This approach allows the model to learn useful representations or features without the need for manually annotated labels, typically by predicting parts of the input from other parts or by solving auxiliary tasks derived from the input data.

8. \*\*True Negatives (TN)\*\*: \*\*True Negatives (TN)\*\*: In a binary classification context, true negatives refer to the instances where the model correctly predicts the absence of a condition or class. In other words, TN represents the number of negative samples that are accurately identified as negative by the classifier.

8. Biological targets: \*\*Biological Targets\*\*: Specific molecules, such as proteins, enzymes, or nucleic acids, within living organisms that are intended to be interacted with or modulated by drugs, therapies, or other biological agents to achieve a therapeutic effect.

8. Implementation and deployment strategies: \*\*Implementation and Deployment Strategies\*\*: A set of planned approaches and methodologies used to execute a project or application in a live environment, ensuring that it operates effectively and meets user requirements. This includes the processes for configuring, testing, and rolling out software or systems, as well as managing updates and addressing any issues that arise post-deployment.

8. Local and global molecular features: \*\*Local and Global Molecular Features\*\*: Local molecular features refer to specific structural or chemical characteristics of a molecule that are confined to a small region, such as functional groups or bond angles. Global molecular features encompass the overall structure and properties of the entire molecule, including its three-dimensional shape, molecular weight, and interactions with other molecules. Together, these features play a crucial role in determining the behavior and reactivity of chemical compounds.

8. Machine learning: Machine learning is a subset of artificial intelligence that enables systems to automatically learn from data, identify patterns, and make decisions or predictions without being explicitly programmed for each specific task.

8. Molecular graphs: Molecular graphs are graphical representations of the structure of molecules, where atoms are depicted as vertices (nodes) and chemical bonds are represented as edges (connections) between these vertices. They are used in cheminformatics to analyze molecular properties, relationships, and interactions.

8. Molecular representations: Molecular representations refer to various visual or symbolic methods used to depict the structure, composition, and arrangement of atoms within a molecule. These representations can include structural formulas, ball-and-stick models, space-filling models, and 2D or 3D diagrams, each providing insights into the molecule's geometry, bonding, and functional groups.

8. Nodes: \*\*Nodes\*\*: In computing and networking, nodes refer to individual devices or points within a network that can send, receive, or forward data. Each node can be a computer, printer, router, or any other device that connects to the network and participates in its operations. In data structures, nodes are elements that contain data and may link to other nodes, forming structures like trees or linked lists.

8. Predictive performance: Predictive performance refers to the effectiveness of a model or algorithm in accurately forecasting outcomes or behaviors based on input data. It is typically assessed using metrics such as accuracy, precision, recall, F1 score, or area under the receiver operating characteristic curve (AUC-ROC) to evaluate how well the model generalizes to unseen data.

8. Supervised learning techniques: Supervised learning techniques are a category of machine learning methods where a model is trained on labeled data, meaning the input data is paired with the correct output. The model learns to map inputs to outputs by identifying patterns in the training data, allowing it to make predictions or classifications on new, unseen data.

8. self-supervised learning techniques: Self-supervised learning techniques are a subset of machine learning methods where models learn representations from unlabeled data by generating supervisory signals from the data itself. This approach typically involves the model predicting parts of the input from other parts, allowing it to capture underlying patterns and features without the need for explicit labels or annotations.

9. \*\*Atomic number\*\*: \*\*Atomic number\*\*: The number of protons in the nucleus of an atom, which determines the element's identity and its position in the periodic table. It is typically represented by the symbol \( Z \).

9. \*\*Bayesian Approaches\*\*: \*\*Bayesian Approaches\*\*: A statistical methodology that applies Bayes' theorem to update the probability of a hypothesis as more evidence or information becomes available. This approach incorporates prior knowledge (prior probability) and combines it with new data (likelihood) to produce a revised probability (posterior probability), allowing for a flexible framework in statistical inference and decision-making.

9. \*\*Bi-branch masked graph transformer autoencoder\*\*: \*\*Bi-branch masked graph transformer autoencoder\*\*: A neural network architecture designed for processing graph-structured data, which employs a bi-branch framework to simultaneously encode information from two different perspectives. It utilizes masked graph transformers to selectively obscure portions of the input, facilitating representation learning and enabling the model to reconstruct the original graph by capturing essential structural and relational features.

9. \*\*De novo drug discovery\*\*: \*\*De novo drug discovery\*\* refers to the process of designing and developing new pharmaceutical compounds from scratch, rather than modifying existing drugs. This approach involves using computational methods, high-throughput screening, and various experimental techniques to identify novel molecular structures that have the potential to become effective medications.

9. \*\*False Positives (FP)\*\*: \*\*False Positives (FP)\*\*: Instances in which a test or system incorrectly indicates the presence of a condition or characteristic when it is not actually present, leading to a positive result that is misleading.

9. \*\*Hold-out test datasets\*\*: \*\*Hold-out test datasets\*\*: A subset of data that is separated from the training data during the model development process, used exclusively to evaluate the performance of a predictive model. This approach helps to assess how well the model generalizes to unseen data and reduces the risk of overfitting.

9. \*\*Molecular Pre-training Graph-based deep learning framework (MPG)\*\*: \*\*Molecular Pre-training Graph-based Deep Learning Framework (MPG)\*\*: A specialized machine learning architecture designed to analyze molecular structures by leveraging graph-based representations. MPG utilizes pre-training techniques to enhance the model's understanding of molecular properties and relationships, enabling improved predictions and insights in fields such as drug discovery and material science.

9. \*\*Molecular Pre-training Graph-based framework (MPG)\*\*: \*\*Molecular Pre-training Graph-based framework (MPG)\*\*: A machine learning approach that utilizes graph-based representations of molecular structures to pre-train models on large datasets, facilitating enhanced understanding and prediction of molecular properties and interactions through the incorporation of graph neural networks and transfer learning techniques.

9. \*\*Molecular graphs\*\*: \*\*Molecular graphs\*\* are mathematical representations of molecules, where vertices (nodes) represent atoms and edges (lines) represent chemical bonds between those atoms. These graphs are used in cheminformatics and computational chemistry to analyze molecular structures, predict properties, and model molecular interactions.

9. \*\*Self-supervised learning methods\*\*: \*\*Self-supervised learning methods\*\*: A type of machine learning approach in which a model learns to predict part of its input data from other parts, using the data itself as a source of supervision. This technique eliminates the need for labeled datasets by generating labels from the input data, enabling the model to learn useful representations without explicit external annotations.

9. \*\*Supervised Learning\*\*: \*\*Supervised Learning\*\*: A type of machine learning where a model is trained on labeled data, meaning that each training example is paired with an output label. The model learns to map inputs to the correct outputs, allowing it to make predictions on new, unseen data.

9. Annotated datasets: Annotated datasets refer to collections of data that have been enhanced with additional information or labels, which provide context or meaning to the raw data. This can include tags, classifications, or descriptions that help in training machine learning models or conducting analysis, facilitating better understanding and interpretation of the data.

9. Chemical space: Chemical space refers to the multidimensional space that represents all possible chemical compounds and their properties, encompassing various molecular structures, configurations, and compositions. It is used in fields such as drug discovery and materials science to explore and identify new compounds with desired characteristics.

9. Downstream tasks: Downstream tasks refer to specific applications or processes that utilize the outputs of a preceding system, model, or stage in a workflow. In the context of machine learning and data processing, these tasks often involve specific objectives such as classification, regression, or prediction that build upon the features or representations generated by earlier phases.

9. Edges: Edges refer to the boundaries or lines where two surfaces meet in a geometric shape or object. In computer graphics, edges are the lines that define the shape and outline of a 3D model, connecting vertices to form polygons. In graph theory, edges represent the connections between nodes in a graph structure.

9. Methodological framework: \*\*Methodological Framework\*\*: A structured set of guidelines and principles that outline the research methods, processes, and approaches to be used in a study. It serves as a blueprint for designing, conducting, and analyzing research, ensuring consistency and rigor in the investigation of a specific problem or phenomenon.

9. MolGNet model: MolGNet is a machine learning model specifically designed for molecular property prediction. It utilizes graph neural network (GNN) architectures to represent molecular structures as graphs, where atoms are nodes and bonds are edges. This approach allows the model to effectively capture the complex relationships and interactions within molecules, enabling accurate predictions of various chemical properties and activities.

9. Multi-layer GNN architectures: \*\*Multi-layer GNN architectures\*\*: These are graph neural network (GNN) models that consist of multiple layers of graph convolutional operations, allowing them to learn hierarchical representations of graph-structured data. Each layer aggregates information from neighboring nodes, enabling the network to capture complex relationships and features across the graph over multiple iterations.

9. Self-supervised strategies: Self-supervised strategies refer to a class of machine learning techniques where a model learns representations or features from unlabeled data by generating its own supervisory signals. This approach typically involves tasks where the model predicts parts of the input from other parts, enabling it to learn useful patterns and structures without the need for labeled datasets.

9. Unlabeled molecular data: Unlabeled molecular data refers to chemical or biological data that consists of molecular structures or properties without any associated labels or classifications. This type of data is often used in machine learning and data analysis to identify patterns or relationships among molecules without predefined categories.

9. molecular graphs: Molecular graphs are graphical representations of the structure of molecules, where vertices (nodes) represent atoms and edges (lines) represent chemical bonds between those atoms. These graphs facilitate the visualization and analysis of molecular connectivity, properties, and relationships in cheminformatics and computational chemistry.

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# References

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[8] NovoMol: Recurrent Neural Network for Orally Bioavailable Drug Design and Validation on PDGFRα Receptor. [n.d.].

[8] Here is the formatted reference information extracted from the citation text:  
  
Title: Semi-Supervised GCN for Learning Molecular Structure-Activity Relationships   
Authors: [Author information not provided]   
Year: [Year not provided]   
Publication: [Publication information not provided]   
DOI: [DOI not provided]   
  
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[8] Author(s). (Year). Title of the paper. Journal/Conference Name. Volume(Issue), Page range. DOI/Publisher information (if available).  
  
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[9] Here is the formatted reference information based on the provided citation text:  
  
Title: Structure-based drug design with geometric deep learning   
Authors: [Information not provided]   
Journal/Conference: [Information not provided]   
Year: [Information not provided]   
Volume: [Information not provided]   
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Here is the formatted reference:  
  
\*\*Author(s).\*\* (Year). \*De novo design of protein target specific scaffold-based inhibitors via reinforcement learning\*. Journal Name, Volume(Issue), Page range. DOI/URL (if available)  
  
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[9] Author(s): Not specified   
Title: De Novo Generation of Hit-like Molecules from Gene Expression Profiles via Deep Learning   
Journal/Source: Not specified   
Year: Not specified   
Volume: Not specified   
Issue: Not specified   
Pages: Not specified   
DOI/URL: Not specified   
  
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[9] Author(s): Not specified   
Title: Generating Focussed Molecule Libraries for Drug Discovery with Recurrent Neural Networks   
Year: Not specified   
Journal/Publisher: Not specified   
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[10] Author(s): Not specified   
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Source: Not specified   
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[10] Author(s): Unknown   
Title: BatmanNet: Bi-branch Masked Graph Transformer Autoencoder for Molecular Representation   
Year: Unknown   
Journal/Conference: Unknown   
Volume: Unknown   
Issue: Unknown   
Pages: Unknown   
DOI: Unknown   
  
(Note: The citation does not provide complete information such as authors, year, or publication details, so they are marked as unknown.)

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Journal: [Not provided]   
Year: [Not provided]   
Volume: [Not provided]   
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