

# Computational Approaches for Drug-Protein Interaction Analysis in Cancer: Machine Learning and Structural Bioinformatics Perspectives

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## ABSTRACT

Accurate drug-protein interaction is critical towards targeted cancer therapy and precision medicine. Conventional experimental methods for DPI identification are time-consuming and costly, necessitating computation approaches instead. Proposed in the study are: PCA-Cosine Similarity, an approach for DPI analysis, and CNN-Xception, a model for MRI-based brain tumor classification. The PCA-Cosine Similarity method uses PCA tools in performing dimension reduction of features while preserving predictive accuracy, rendering large-scale drug discovery more efficient. The CNN-Xception model blends CNN and Xception architecture via depthwise separable convolutions to offer improved tumor classification.

Experimental results show that PCA plus Cosine Similarity achieved 95.18% accuracy, outperforming raw similarity calculations very effectively and yet optimizing computational complexity. At the same time, the CNN-Xception model scored an impressive 100% across 656 test samples while differentiating between Glioma, Meningioma, Pituitary tumors, and non-tumor cases with great ease. From the comparative analysis, it is undoubted that deep-learning and similarity-based models work hand in hand, outperforming conventional methods in DPI prediction and brain tumor classification with a high degree of efficiency. Future enhancements will continue with molecular docking validation (AutoDock Vina) to tune DPI predictions, along with deep learning architecture integration to further such predictions. These developments will go a long way toward ushering in robust computational models for cancer drug discovery and precision oncology.

**Keywords:** Protein structures, Protein-Drug Interaction, Cancer Therapy, Convolutional Neural Network, molecular docking, multidrug resistance, amino acids, Predictive Modeling, Bioinformatics, Targeted Therapy

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## 1. Introduction

Proteins are the most important structural biomolecules in cells, serving a variety of tasks such as enzymatic action, signal transmission, and structural support. A protein's functions are determined by its structure, which is in turn determined by the sequence of amino acids that comprise it. The main structure of a protein is represented by the amino-acid residues that compose its backbone. These sequences are frequently seen folded into crystalline formations known as secondary structures, where hydrogen-bonding interactions help stabilise the alpha-helices and beta-sheets. [1]. Further folding produces tertiary structures, which determine the three-dimensional form of proteins and are required for their function. Some proteins function as complexes composed of several subunits that form a quaternary structure. Proteins must retain their structural integrity in order to operate normally, with

mutations and/or alterations generated by biological agents eventually resulting in perturbations in their functions [2].

Protein structures in cancer are frequently modified by genetic mutations, post-translational changes, or alternative splicing, resulting in aberrant signal pathway activation, uncontrollable cell proliferation, and apoptosis resistance. Many of the classic oncogenic proteins include Epidermal Growth Factor Receptor (EGFR), BRAF, and HER2, as well as gain-of-function mutations that activate cancer-related proteins. Loss-of-function mutations in essential tumour suppressor genes, such as p53 and BRCA1, strip cells of their ability to control growth and repair DNA [3][4]. Understanding these structural changes can help in the development of tailored cancer therapies.

The interaction between medications and proteins is critical in cancer treatment because small-molecule therapies or biologics are designed to attach to specific proteins and modulate their function. These interactions follow the lock-and-key process, which requires the inhibitor to exactly fit into a binding site generated by the protein [5]. Some small-molecule inhibitors, such as tyrosine kinase inhibitors (TKIs) for EGFR-mutant lung cancer, bind to the active sites of proteins involved in transduction and cell proliferation. Other medicines can promote or hinder protein function by binding to regulatory regions and causing allosteric modulation [6]. In addition, several medications covalently bond to their target proteins, preventing subsequent interactions. Osimertinib, which targets the EGFR T790M mutation, causes persistent lung cancer, inducing irreversible inhibition [7].

Inhibition of the resistance mechanism alters the interaction between medicines and proteins as cancer progresses. Point mutations in the drug-binding domain alter the affinity for the drug and thus its effectiveness. For example, the T315I mutation in BCR-ABL provides resistance to first-generation inhibitors like Imatinib, necessitating the development of the recently developed Ponatinib [8]. Overexpression of drug efflux transporters, such as P-glycoprotein (P-gp), can lower medication concentrations in target tissues, lowering their efficacy [9]. Understanding these resistance mechanisms is critical for developing novel medicines using bioinformatics and molecular modelling.

Bioinformatics continues to play a role in predicting medication efficacy and antibacterial medicines, albeit with some qualifications. These include chemical physics-based assessments of drug-protein interactions, where homology modelling is a useful computational tool for predicting folded structures of mutant proteins, and molecular docking analysis, which determines how well a drug binds to its target [10]. The molecular dynamics further extends these interactions throughout time processes that determine how effective medications are. AI and machine learning are being used to significantly improve the robustness of predictions for drug-protein interactions in order to optimise drug design for precision medicine [11].

At the heart of targeted cancer therapy is the interplay of protein sequence, structure, and drug-protein interactions. With such knowledge about the effect of mutations and structure on drug binding, a cure targeted against actual cancer cells can be borne with mitigated side effects. Developments in structural bioinformatics and computational drug-diagnosis are indeed a breakthrough towards cancer treatment; through such developments, hope is dawning against drug resistance, and human health recovery can find a quicker pathway.

Checking drug-ligand interactions is an important aspect of drug discovery and development. These interactions decide a drug's efficacy, selectivity, and safety, affecting its pharmacokinetic and pharmacodynamic properties [12]. The understanding of how drugs bind to their molecular targets-proteins, enzymes, and receptors-is paramount in optimizing drug design while minimizing side effects. Given the complexity of diseases and the desire for precision medicine, the development of robust methodologies for the identification and characterization of drug-ligand interactions receives the greatest attention [13].

Drug-ligand interaction studies have witnessed monumental advances in computational and experimental techniques over the last few decades. High-throughput screening, surface plasmon resonance, nuclear magnetic resonance, and X-ray crystallography have provided vital structural and kinetic overviews of drug binding mechanisms [12]. Computational approaches like molecular docking, MD simulations, and AI-driven models have speeded up the provision on binding affinity and interaction markers in *in silico* predictions [14]; for instance, deep learning models that have been devised to predict protein-ligand interactions improve the efficiency of virtual screening processes [15].

Despite these advancements, several challenges remain in accurately predicting and validating drug-ligand interactions. While experimental methods are accurate, they are quite slow and very laborious [12]. Computational methodologies are fast and cheap but may not have the needed accuracy to accurately capture the dynamic of ligand binding, especially when it comes to the allosteric sites and intrinsically disordered targets [14]. Furthermore, the classical computational models may not consider the effects of factors like some aspects of normal flexibility of the protein, solvation effects, and off-target interactions, causing discrepancies between the predictions from computational methodologies and those derived from experimental ones [14]. Integrative approaches must be drawn out to connect computational and experimental methods in order to benefit drug-ligand interaction studies concerning reliability and efficiency [14].

Figure 1 represents 2D and 3D models of protein-ligand interactions that demonstrate the structural and chemical interactions the ligand will have with the protein binding site. The top-left and top-right panels are the 3D representation of protein-ligand interactions. The top-left panel shows the molecular surface of the protein with the ligand bound. The ligand is shown inside the binding pocket, revealing its spatial fit inside the protein's structure. The top-right panel is a close-up 3D view of the ligand in the binding site that labels key residues involved in the interaction (E133, F109, A146, F101), thereby, showing the hydrogen bonds and hydrophobic interactions necessary for binding stability.

The bottom panel shows the 2D schematic representation of the protein-ligand interaction, where interactions are separated into hydrogen bonds (backbone and side chain),  $\pi$ -stacking, hydrophobic contacts, and solvent exposed. Each type of interaction is represented in a different color and associated with respective residues, as explained in the key in figure 1.

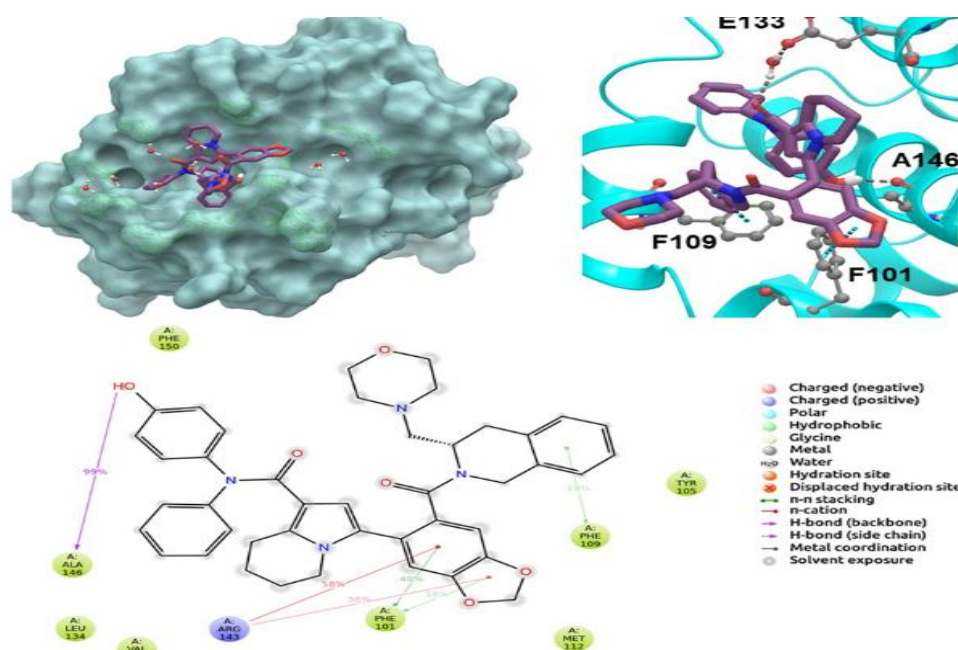


Figure 1: 2D and 3-D Protein ligand interactions

The study aims to solve these weaknesses of various approaches by establishing an all-comprehensive framework for the identification and characterization of drug-ligand interactions. The main purpose is to improve predictive accuracy through a combination of cutting-edge computational modeling techniques and experimental approaches to gain a deeper insight into the mechanism of binding interactions [14], [12]. The development will, therefore, include better and more accurate predictive algorithms, using machine-learning-like techniques, and validated experimentally using biophysical assays. In the long run, this will lead to more efficient drug discovery pipelines directed toward the development of safer and more efficacious therapeutic agents. Besides, artificial intelligence and machine learning techniques are being integrated deeply into drug discovery pipelines, and deep learning models have made predictions on protein-ligand interactions that have improved the efficiency of virtual screening processes [16].

## 2. Related Methods

This section discusses computational and machine learning techniques used in biomedical research, specifically in cancer classification, dimensionality reduction, and protein-ligand docking.

### i) Classification of Cancer/Non-Cancer Cells Using MRI Images and CNN Algorithms

Deep learning techniques, particularly Convolutional Neural Networks (CNNs), have been extensively utilized for classifying medical images, including MRI scans, in cancer detection. CNNs are highly effective in automatically extracting spatial features from images, making them suitable for distinguishing between cancerous and non-cancerous tissues. To improve classification accuracy, MRI scan images undergo several preprocessing steps, including normalization, contrast enhancement, and data augmentation. Normalization standardizes pixel intensity values, ensuring uniformity across images, while contrast enhancement techniques, such as histogram equalization, improve the visibility of tumor regions. Data augmentation, including random rotations, flipping, and zooming, is applied to enhance model generalization and prevent overfitting [17].

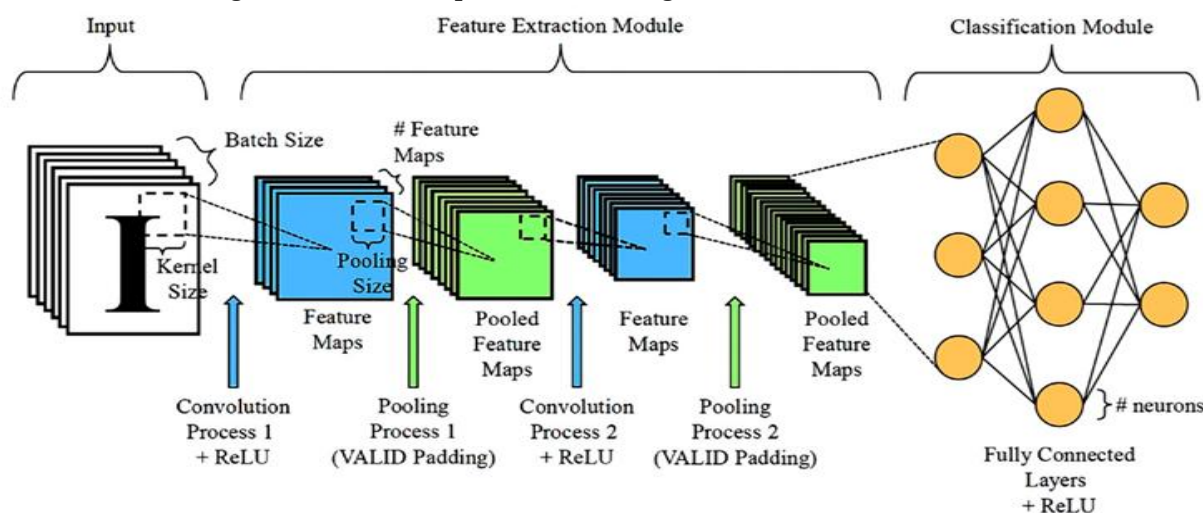


Figure 2 Process to evaluate data layer by layer of cancer cell images and non-cancerous cell images

The CNN model used for cancer classification consists of multiple layers, including convolutional layers, pooling layers, and fully connected layers. Initially, convolutional layers apply  $3 \times 3$  or  $5 \times 5$  kernel filters to extract spatial features such as texture and shape. ReLU activation introduces non-linearity to enhance feature representation. Pooling layers, such as max pooling, reduce dimensionality while retaining significant information. The extracted features are passed through fully connected layers, followed by a softmax activation function, which generates probability distributions for classifying MRI scans as either cancerous or non-cancerous [18]. The entire model is trained using the categorical cross-entropy loss function with an Adam optimizer, ensuring fast convergence. A schematic representation of the CNN architecture used for MRI-based cancer classification is illustrated in Figure. 2.

### Collection of Datasets

Dataset selection is crucial in ensuring robust performance in both MRI-based cancer classification and drug-protein interaction analysis. The data sets used in this study are obtained from publicly available sources to maintain data integrity and reproducibility.

The drug dataset is collected from Kaggle, specifically from the Big Molecules SMILES Dataset [19]. However, since this dataset is in SMILES (Simplified Molecular Input Line Entry System) format, it cannot be directly used for drug similarity identification. To address this issue, the dataset is converted into CSV format using the RDKit library, which is installed via Anaconda (conda install -c conda-forge rdkit). The conversion process involves extracting molecular fingerprints and physicochemical properties from the SMILES representation, allowing for efficient similarity analysis.

The protein dataset is obtained from the UniProt database, which provides protein sequences in FASTA format. Specifically, we collected three protein sequences from the following UniProt entries: Q8NCF5, O00255, and Q12888 [20]. Since FASTA sequences cannot be directly preprocessed using PCA, we employ the SeqIO library to encode each amino acid into a numerical format. The encoded sequences are then converted into a CSV file, enabling seamless integration with similarity analysis workflows.

The cancer dataset is obtained from CancerRxGene, which provides comprehensive genomic and drug response data for various cancer cell lines [21]. Unlike the other datasets, this dataset is already available in CSV format, eliminating the need for data conversion. The structured format of this dataset facilitates the integration of drug-protein interaction analysis with cancer treatment response predictions.

### ii) Dimensionality Reduction and Similarity Identification

To analyze drug-protein interactions, feature extraction and dimensionality reduction techniques are employed to optimize computational efficiency and improve similarity assessments. Principal Component Analysis (PCA) is applied to high-dimensional molecular and protein feature data, reducing dimensionality while preserving variance. This technique enhances computational efficiency by transforming correlated features into uncorrelated principal components, thereby facilitating clustering-based similarity identification [22].

Besides PCA, t-distributed Stochastic Neighbor Embedding (t-SNE) was attempted to visualize high-dimensional similarity relationships. Although t-SNE is particularly useful for exploratory data analysis and maps high-dimensional data onto a lower-dimensional space with local neighborhood relationships preserved, it has underperformed in this study. Its effectiveness fell short because of high computational costs, determination of hyperparameters, or difficulty in the preservation of global structures. In such a case, and owing to the capabilities stated above, PCA would be favored for large-scale datasets [23].

For similarity-based clustering, K-Means clustering is employed to group similar drug-protein interaction profiles. The algorithm iteratively assigns data points to K centroids, updating cluster assignments based on feature similarity. However, K-Means is less suitable for high-dimensional biological datasets due to its centroid-based nature. Instead, PCA-based similarity identification offers a more robust alternative [24].

### iii) Protein-Ligand Docking and Rescoring

Protein-ligand docking is a computational approach used to predict molecular interactions between proteins and drugs. In this study, we employ AutoDock Vina, a widely used docking software, to predict the binding conformations of drug molecules to target proteins. The docking process involves preparing proteins and ligands in PDBQT format, followed by molecular docking simulations to estimate binding affinities [25].

To improve docking accuracy, we apply rescoring techniques, including consensus scoring and machine learning-based rescoring. Consensus scoring combines multiple docking scores from AutoDock Vina, X-Score, and Glide Score, providing a more reliable binding affinity estimate. In contrast, machine learning-based rescoring leverages features extracted from docking outputs, which are processed using Random Forest and Neural Networks to refine binding predictions [26].

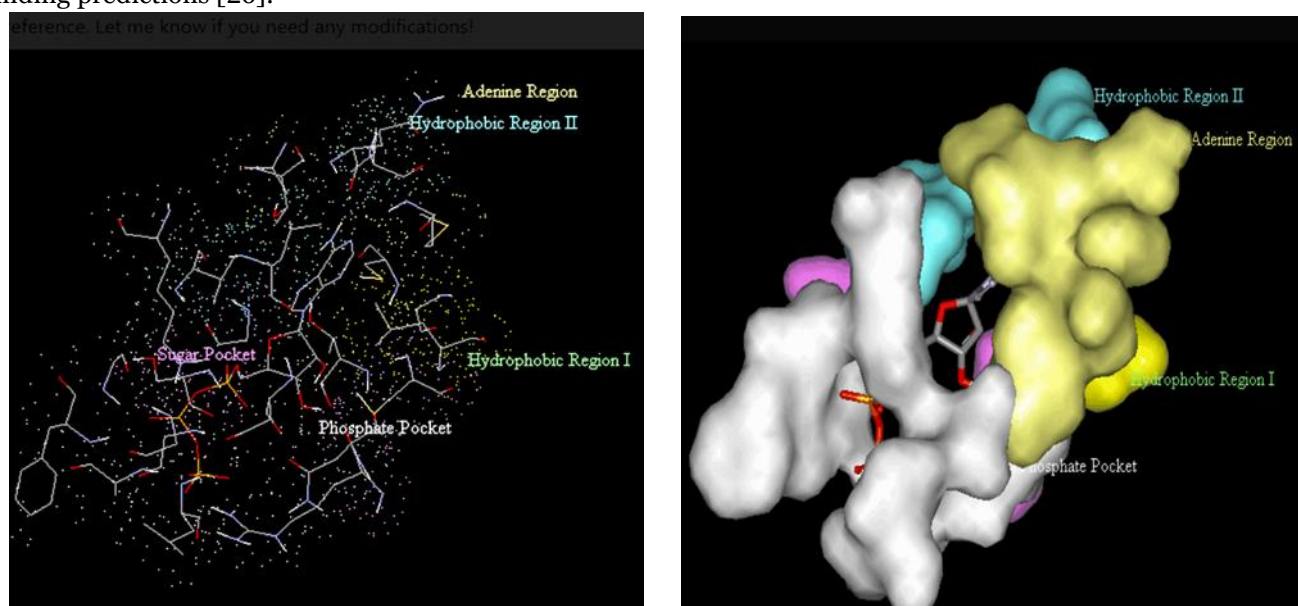


Figure 2: Structural Representation of Protein-Ligand Interaction Sites

Figure 2, illustrates the structural and molecular features of protein-ligand interaction sites, emphasizing key binding regions essential for effective docking. The left panel provides a schematic representation of the protein's binding



pockets, with specific regions such as the Phosphate Pocket, which interacts with phosphate-containing groups, the Sugar Pocket, which binds sugar moieties, and the Adenine Region, which is critical for ligands containing adenine-like functional groups. Additionally, the figure highlights Hydrophobic Regions I and II, which stabilize the binding through nonpolar interactions. The right panel complements this by presenting a three-dimensional surface visualization of the protein-ligand complex, demonstrating the spatial arrangement and surface topology of the binding site. The yellow-highlighted regions represent hydrophobic pockets, while the cyan, pink, and white surfaces correspond to specific binding regions and the overall molecular structure of the protein. This representation provides valuable insights into ligand conformations and their interactions with protein binding sites, which are crucial for designing targeted drug molecules with enhanced specificity and affinity.

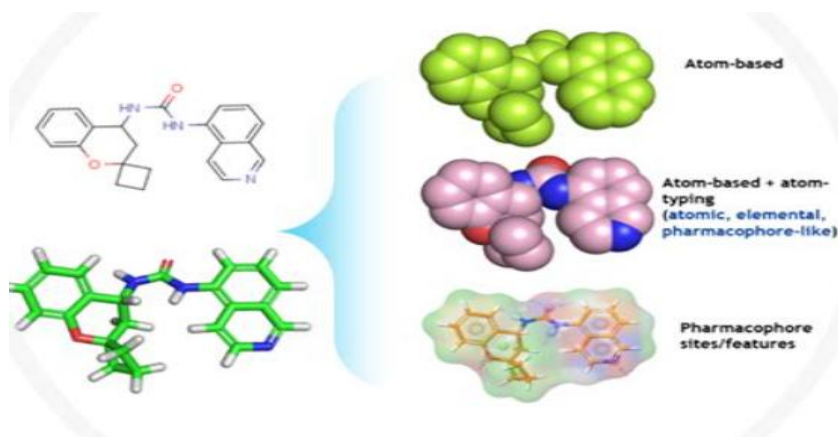


Figure 3: Molecular Representations and Pharmacophore Features

The figure 3, provides a comprehensive depiction of different molecular representation techniques commonly used in computational drug discovery and design. On the left, the chemical structure of a small molecule is displayed in 2D format, showing its atomic connectivity and functional groups. The right panel illustrates three advanced representation approaches:

**Atom-Based Representation:** This method visualizes molecules as space-filling models, where atoms are represented as spheres with sizes proportional to their van der Waals radii. It highlights the molecular geometry and atomic arrangement in three-dimensional space, useful for steric and spatial analysis.

**Atom-Based with Atom Typing:** This representation extends the basic atom-based model by incorporating atom-specific features such as element type, charge, and pharmacophoric properties. Different colors denote specific elements or functional groups, such as oxygen (red), nitrogen (blue), and carbon (green), aiding in understanding interactions with biological targets.

**Pharmacophore Features:** This representation focuses on pharmacophore mapping, where key molecular features essential for biological activity are identified. It highlights hydrogen bond donors and acceptors, hydrophobic regions, and aromatic features that are critical for receptor-ligand interactions. The highlighted pharmacophore sites allow researchers to identify potential interaction hotspots and guide the rational design of new molecules.

### 3. Proposed Novel CNN-Xception Approach

The proposed Novel CNN-Xception model was evaluated using a dataset of MRI images encompassing four categories: Glioma, Meningioma, Pituitary tumors, and Non-cancerous images. The dataset was partitioned into training and testing sets, with 5,712 images allocated for training and 1,311 for testing. Specifically, the training set included 1,595 non-cancerous images, while the testing set comprised 405 non-cancerous images. The model employed a two-stage classification approach: initially, a Convolutional Neural Network (CNN) was utilized to distinguish between cancerous and non-cancerous images; subsequently, the Xception architecture was applied to classify the specific type of tumor among the cancerous cases. This methodology aligns with recent studies that have demonstrated the efficacy of deep learning models, particularly the Xception architecture, in accurately classifying brain tumors from MRI images [27], [28].

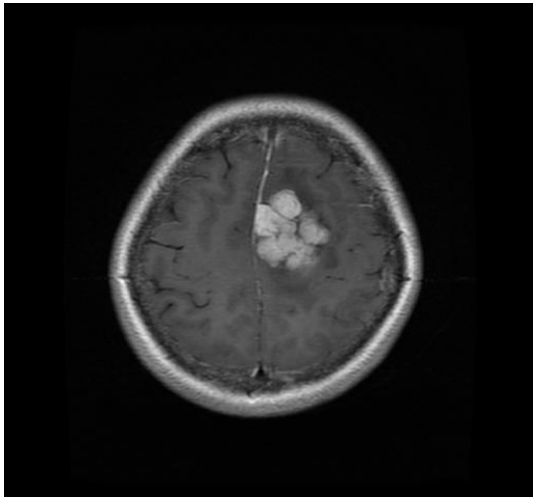


Fig 4a: Glioma

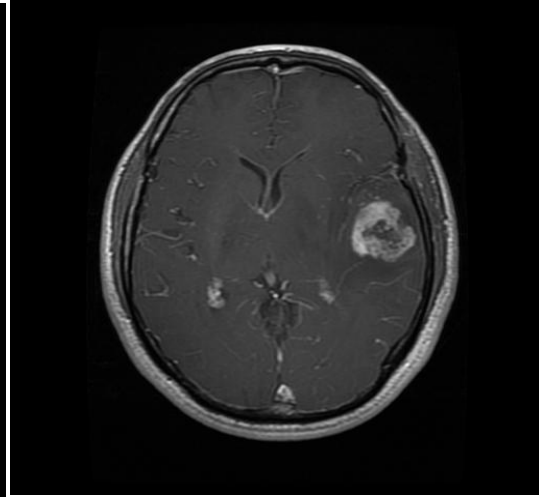


Fig 4b: Meningioma

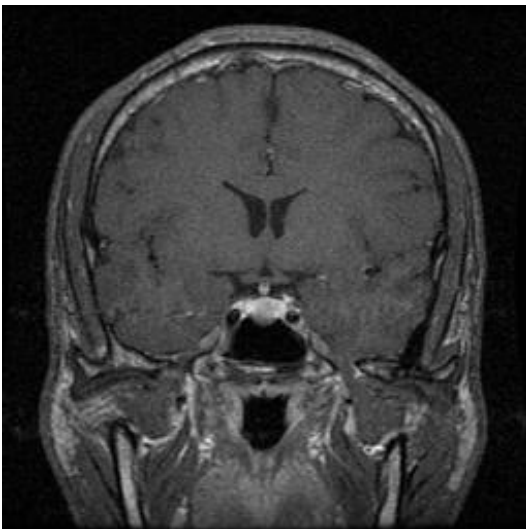


Fig 4c: Pituitary

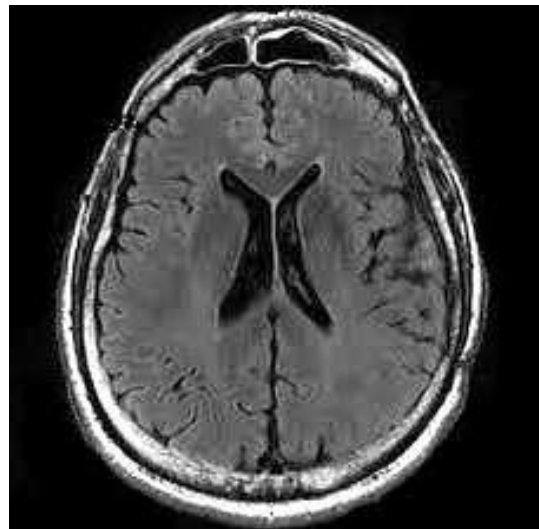


Fig 4d: No tumor

Figure 4 illustrates representative MRI scans corresponding to different brain conditions. Figure 4a depicts a Glioma, characterized by an irregular, contrast-enhancing mass within the brain, indicative of its origin from glial cells. Gliomas are known for their infiltrative nature and can significantly impact brain function depending on their location and grade. Figure 4b presents a Meningioma, which appears as a well-defined, contrast-enhancing mass typically arising from the meninges, the protective layers surrounding the brain. Meningiomas are often slow growing but may exert pressure on adjacent brain structures, leading to neurological symptoms. Figure 4c displays a Pituitary Tumor, located at the base of the brain near the pituitary gland. These tumors can influence hormonal regulation and impact nearby structures, leading to a variety of endocrine and neurological disturbances. Figure 4d represents a Normal Brain (No Tumor), where no abnormal growths or lesions are observed, indicating a healthy brain structure. These MRI scans serve as the foundation for training and evaluating the proposed CNN-Xception model in distinguishing between cancerous and non-cancerous cases, as well as classifying specific tumor types.

The integration of CNN and Xception leverages the strengths of both architectures, enhancing feature extraction and classification accuracy. The experimental results indicated that the CNN component effectively differentiated between cancerous and non-cancerous images, while the Xception model accurately identified the specific tumor types, corroborating findings from similar research endeavors [29]. These outcomes suggest that the CNN-Xception hybrid model holds significant promise for advancing automated brain tumor classification in clinical settings.

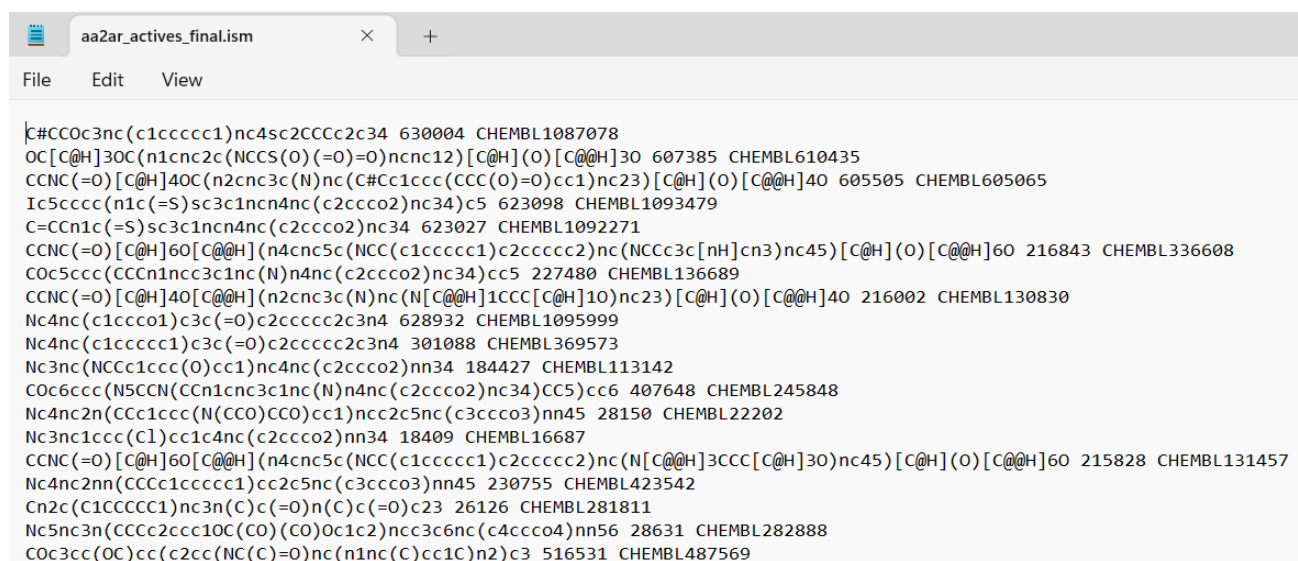
#### 4. Proposed PCA-CosSim Drug-Protein Interaction Model (PCA-CosSim DPI Model)

The proposed PCA-Cosine Similarity model was validated on a diverse biomedical dataset comprising drug molecules (SMILES format), protein sequences (FASTA format), and cancer-specific data like glioma, meningioma, and pituitary tumors. The PCA-Cosine Similarity Model aims to predict drug-protein interactions (DPI) through the application of dimensionality-reduction features and similarity-based scoring techniques.

##### Dataset and Pre-processing

In this study, three broad categories of datasets were used to analyze drug-protein interactions in brain tumors.

- i) Drug Representation (SMILES Format, shown in figure 5): The Simplified Molecular Input Line Entry System (SMILES) is a text-based representation of chemical structures [19]. These molecular representations were transformed into numerical vectors using molecular descriptors and fingerprinting techniques to facilitate computational analysis[14], [25].



```

|c#CCOC3nc(c1ccccc1)nc4sc2CCCc2c34 630004 ChEMBL1087078
OC[C@H]3OC(n1cnc2c(NCCS(O)(=O)=O)ncnc12)[C@H](O)[C@@H]3O 607385 ChEMBL610435
CCNC(=O)[C@H]4OC(n2cnc3c(N)nc(C#Cc1ccc(CCC(O)=O)cc1)nc23)[C@H](O)[C@@H]4O 605505 ChEMBL605065
Ic5cccc(n1c(=S)sc3c1ncn4nc(c2ccc2)nc34)c5 623098 ChEMBL1093479
C=CCn1c(=S)sc3c1ncn4nc(c2ccc2)nc34 623027 ChEMBL1092271
CCNC(=O)[C@H]6O[C@@H](n4cnc5c(NCC(c1ccccc1)c2ccccc2)nc(NCCc3c[nH]cn3)nc45)[C@H](O)[C@@H]6O 216843 ChEMBL336608
COc5ccc(CCCn1ccc3c1nc(N)n4nc(c2ccc2)nc34)cc5 227480 ChEMBL136689
CCNC(=O)[C@H]4O[C@@H](n2cnc3c(N)nc(N[C@@H]1CCC[C@H]1O)nc23)[C@H](O)[C@@H]4O 216002 ChEMBL130830
Nc4nc(c1ccccc1)c3c(=O)c2ccccc2c3n4 628932 ChEMBL1095999
Nc4nc(c1ccccc1)c3c(=O)c2ccccc2c3n4 301088 ChEMBL369573
Nc3nc(NCCc1ccc(O)cc1)nc4nc(c2ccc2)nn34 184427 ChEMBL113142
COc6ccc(N5CCN(Cc1cnc3c1nc(N)n4nc(c2ccc2)nc34)CC5)cc6 407648 ChEMBL245848
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Nc3nc1ccc(Cl)cc1c4nc(c2ccc2)nn34 18409 ChEMBL16687
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Cn2c(c1CCCCC1)nc3n(C)c(=O)n(C)c(=O)c23 26126 ChEMBL281811
Nc5nc3n(CCCC2ccc1OC(CO)(CO)Oc1c2)nc3c6nc(c4ccc4)nn56 28631 ChEMBL282888
COc3cc(OC)cc(c2cc(NC(C)=O)nc(n1nc(C)cc1C)n2)c3 516531 ChEMBL487569

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Figure 5: List of chemical structures in SMILES (Simplified Molecular Input Line Entry System) format along with their ChEMBL IDs

##### Drug Dataset and Feature Representation

The drug dataset comprises various attributes that offer in-depth insights into drug identification, experimental methodology, and pharmacological responses. These attributes are crucial for evaluating the effectiveness, strength, and potential interactions of drugs within cancer treatment [21], [22].

**Identification and Source Information:** Each drug entry is distinctly recognized by identifiers such as NLME\_RESULT\_ID (results from nonlinear mixed-effects modeling), NLME\_CURVE\_ID (identifier for dose-response curves), COSMIC\_ID (Catalogue of Somatic Mutations in Cancer), and SANGER\_MODEL\_ID (Sanger Institute cell model identifier). The CELL\_LINE\_NAME indicates the specific cell line used during the drug testing process, while TCGA\_DESC categorizes the type of cancer according to The Cancer Genome Atlas (TCGA)[20],[21].

**Drug-Specific Information:** This dataset contains DRUG\_ID, which serves as a unique identifier for each drug, alongside its corresponding DRUG\_NAME. The PUTATIVE\_TARGET field outlines the anticipated biological target associated with the drug—for instance, a protein or receptor—whereas PATHWAY\_NAME specifies the biological pathway through which the pharmaceutical agent operates [22]. COMPANY\_ID denotes the pharmaceutical firm responsible for developing each drug, and WEBRELEASE signifies whether this information has been released to the public domain [20].

**Experimental Conditions:** Drug evaluations occur across varying concentrations documented as MIN\_CONC (the lowest concentration of the drug measured in micromolar or  $\mu\text{M}$ ) and MAX\_CONC (the highest concentration also recorded in micromolar). These concentrations establish the dose-response spectrum essential for assessing overall drug efficacy [21].



Pharmacological Response Metrics: The dataset features several critical pharmacokinetic and pharmacodynamic indicators:

- LN\_IC50: This represents log-transformed half-maximal inhibitory concentration (IC50) values; it quantifies how potent a particular drug is—the lower this value is, indicative of increased efficacy [21].
- AUC (Area Under Curve): This metric evaluates a drug's overall effectiveness by integrating data from its dose-response curve; higher AUC figures typically correlate with enhanced therapeutic outcomes [22].
- Root Mean Squared Error: An estimation metric for reliability in the dose-response model; smaller values indicate superior model prediction [14].
- Z\_SCORE: A standard score for comparing how far the drug response deviates from the mean, helping identify outlying drug responses [21].

The drug dataset was extracted from Kaggle in SMILES format [19]. For identification of similarities to work, the datasets had to be in a similar format; hence, SMILES representations could not be used directly. To address this, the dataset was converted to CSV by means of the RDKit library, which allows molecular fingerprinting and numerical encoding [14],[25]. As RDKit was not available through pip, it was installed via the Anaconda terminal using the command: `conda install -c conda-forge rdkit`. This step was a preprocessing task that ensured the similarity analysis and further computational processing were compatible.

- ii) Protein Representation (FASTA Format): The FASTA format, shown in figure 6, encodes protein sequences using single-letter amino acid codes. The model processes these sequences using protein feature extraction techniques, such as sequence alignment and physicochemical property encoding, to generate meaningful embeddings [30], [31].

```
>sp|Q8NCF5|NF2IP_HUMAN NFATC2-interacting protein OS=Homo sapiens OX=9606 GN=NFATC2IP PE=1 SV=1
MAEPVGKGRWSGGSGAGRGGRGGWGGRRRRAQRSPSRGTLDVVSVDLVTDSDDEEILE
VATARGAADEVEVEPEPPGPVASRDNSDSEGEDRRPAGPPREPVRRRRRLVLDPGEA
PLVPVYSGKVKSSRLRIPDDLKLLKLYPPGDEEEAELADSSGLYHEGSPSPGSPWTKLR
TKDKEEKKTEFLDLNSPLSPSPRTKSRTHTRALKKLSEVNKRQLDLRSLSPKPPQG
QEQQGQEDEVVLVEGPTLPETPRLFLPKIRCRADLVRLPLRMSEPLQSVVDHMAHLGVS
PSRILLLFGETELSPTATPRTLKLGVAIDIICVVLTSSEPEATETSQQLQLRVQGEKHQT
LEVLSRDSPLKTLMSHYEAMGLSGRKLSFFFDGTKLSGRELPADLGMESGDLIEVWG
>sp|O00255|MEN1_HUMAN Menin OS=Homo sapiens OX=9606 GN=MEN1 PE=1 SV=5
MGLKAAQKTLFPLRSIDVVRLFAAELGREPDVLLSLVLGFVEHFLAVNRVIPTNVPE
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VSDVIWNSLSRSYFKDRAHQSLFSFITGKLDSSGVAFVVGACQALGLRDVHLASED
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CAINPSIDLHTDSELELLQLQKLLWLLYDLGHLERYPMALGNLADLEELEPTPGRPDPLT
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TASPPPEGPVLTFAQSEKMKGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTPSDYTL
SFLKRQRKGL
>sp|Q12888|TP53B_HUMAN TP53-binding protein 1 OS=Homo sapiens OX=9606 GN=TP53BP1 PE=1 SV=2
MDPTGSQLDSDFSQDTPCLIIEDSQESQVLEDDSGSHFSMLSRHLPNLQTHKENPVLD
VVSNPQTAGEEERGDNSEGFNEHLKENKVDADPDVSSNLDTCGSIQVIEQLPQPNRTSSV
LGMSVESAPAVEEEKEGEELEQKEKEEEDTSGNTTHSLGAEDTASSQLGFGVLELSQSQD
VEENTVPYVEVDKEQLQSVTTNSGYTRLSDVDANTAIKHEEQSNEDIPIAEQSSKDIPVTA
QPSKDVHVVEQNPPPARSEDMPFSPKASVAAMEAKEQLSAQELMESGLQIQKSPEPEVL
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DLVAPSPDAFRSTPFIVPSPTEQEGRQDKPMDTSVLSEEGGEFPQKKLQSGEPVELENP
PLLPESTVSPQASTPISQSTPVFPFPGSLPIPSQPQFSDHIFIPSPSLEEQSDGKKDGDG
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Figure 6: Protein representation - FASTA format

### Protein Attributes and Feature Representation:

The protein dataset was analyzed according to characteristics such as amino acid composition, sequence length, and hydrophobicity, which are helpful in the study of protein structure and function.

Amino Acid Composition (A–Y): In this dataset, each column specifies how frequent a specific amino acid is within a protein sequence. This dataset receives its polymeric nature because protein sequences will in any case only be built of basic 20 standard amino acids such as Alanine (A), Cysteine (C), Aspartic acid (D), and Tyrosine (Y), among many others. The values represent the percentage of that specific amino acid in the sequence. For instance, A = 0.0477 indicates that 4.77% of the protein sequence is comprised of Alanine. This composition serves as an essential factor in the discussion about protein structure, stability, and potential functional properties.

**Length of Sequence:** This attribute indicates how many amino acids there are in a particular protein sequence. A long sequence usually correlates with the presence of complex protein structures with several functional domains. For example, if the length of the sequence is 419, it clearly means that the protein has 419 amino acid residues. This feature is highly relevant for the study of protein folding, binding sites, and overall molecular interactions.

**Hydrophobicity:** Hydrophobicity indicates how much protein resists or avoids presence in aqueous environments, with positive values referring to such proteins as more hydrophobic or avoiding water and negative values designating hydrophilic or cohering with themselves in the aqueous environment. Hydrophobic proteins are usually membrane-associated or behave as lipid interactors; on the other hand, hydrophilic proteins are distributed in aqueous environments. The hydrophobicity score is derived from the average hydrophobicity of the entire amino acid contents of the sequence. A hydrophobicity score of -0.0933 indicates slight hydrophilicity in the protein, while a slight hydrophobic peptide sequence would likely yield a positive score, where 0.0221 might suggest slight hydrophobic character.

These attributes of proteins are necessary for drug interaction prediction, protein solubility interactions, and studies of structure-function relationships since the amino acid composition allows proteins to be classified based on that factors[20]. Further, the hydrophobicity helps in understanding protein folding, stability, and interactions with lipids, which influences biological activity[31]. Understanding these characteristics increases the potential for drug-protein interaction prediction and therefore with identifying potential therapeutic targets[32].

The FASTA-format dataset was collected from UniProt for protein sequence representation. Since FASTA sequences cannot be directly processed using PCA, the SeqIO library was utilized to convert the FASTA format into a CSV file. Each amino acid was encoded into a numerical format, enabling efficient preprocessing and dimensionality reduction for further analysis[30].

iii) **Cancer-Specific Data:** The dataset includes biological information related to Glioma, Meningioma, and Pituitary tumors, enabling the model to focus on drug-protein interactions relevant to these cancer types[32]. It compiles critical pharmacological properties such as IC<sub>50</sub> (half-maximal inhibitory concentration), AUC (area under the curve), Z-score, and maximum drug concentration which gives therapeutic candidates valuable insights on the efficacy of drugs against these tumor types [32].

Drug Name	Drug ID	Cell Line	Cosmic ID	TCGA Class	Tissue	Tissue Sub	IC50	AUC	Max Conc	RMSE	Z score	Dataset Version
Camptoth	1003	PFSK-1	683667	MB	nervous_s	medullobl	-1.46389	0.93022	0.1	0.089052	0.433123	GDSC2
Camptoth	1003	A673	684052	UNCLASSII	soft_tissue	rhabdomy	-4.86945	0.61497	0.1	0.111351	-1.4211	GDSC2
Camptoth	1003	E55	684057	UNCLASSII	bone	ewings_sa	-3.36059	0.791072	0.1	0.142855	-0.59957	GDSC2
Camptoth	1003	E57	684059	UNCLASSII	bone	ewings_sa	-5.04494	0.59266	0.1	0.135539	-1.51665	GDSC2
Camptoth	1003	EW-11	684062	UNCLASSII	bone	ewings_sa	-3.74199	0.734047	0.1	0.128059	-0.80723	GDSC2
Camptoth	1003	SK-ES-1	684072	UNCLASSII	bone	ewings_sa	-5.14296	0.582439	0.1	0.137581	-1.57002	GDSC2
Camptoth	1003	COLO-829	687448	SKCM	skin	melanoma	-1.23503	0.867348	0.1	0.09347	0.557727	GDSC2
Camptoth	1003	5637	687452	BLCA	urogenital	bladder	-2.63263	0.834067	0.1	0.076169	-0.20322	GDSC2
Camptoth	1003	RT4	687455	BLCA	urogenital	bladder	-2.96319	0.821438	0.1	0.094466	-0.3832	GDSC2
Camptoth	1003	SW780	687457	BLCA	urogenital	bladder	-1.44914	0.90505	0.1	0.074109	0.441154	GDSC2
Camptoth	1003	TCCSUP	687459	BLCA	urogenital	bladder	-2.35063	0.84343	0.1	0.074831	-0.04968	GDSC2
Camptoth	1003	C-33-A	687505	CESC	urogenital	cervix	-3.38088	0.777806	0.1	0.091913	-0.61062	GDSC2
Camptoth	1003	C-4-I	687506	CESC	urogenital	cervix	-2.25569	0.891103	0.1	0.087072	0.002012	GDSC2
Camptoth	1003	ME-180	687514	CESC	urogenital	cervix	-3.22391	0.786658	0.1	0.135256	-0.52515	GDSC2
Camptoth	1003	42-MG-BA	687561	GBM	nervous_s	glioma	-3.40022	0.777517	0.1	0.111615	-0.62115	GDSC2
Camptoth	1003	8-MG-BA	687562	GBM	nervous_s	glioma	-4.25629	0.693915	0.1	0.110348	-1.08725	GDSC2
Camptoth	1003	A172	687563	GBM	nervous_s	glioma	-2.99955	0.803407	0.1	0.083111	-0.403	GDSC2
Camptoth	1003	GB-1	687568	GBM	nervous_s	glioma	-3.0555	0.7719	0.1	0.107697	-0.43346	GDSC2
Camptoth	1003	T98G	687586	GBM	nervous_s	glioma	-2.06022	0.888774	0.1	0.075349	0.10844	GDSC2

Figure 7: Cancer-Specific Data Set

Integration of the datasets provides a good overview of potential drug-protein interactions and helped in locating promising therapeutic candidates.

The drug dataset contains 242,000 samples with molecular descriptors, AUC, and RMSE as core features and is in SMILES format. The protein dataset contains 3,000 samples in FASTA format, characterized by their amino acid

composition and hydrophobicity. The cancer dataset is in CSV format, comprising 50,000 samples, with drug response metrics such as IC<sub>50</sub>, AUC, Z-score, and maximum concentration. This presentation shows the diversity and size of the datasets used in modelling and analysis.

### Dimensionality Reduction with PCA

Certain forms of PCA were performed for dimensionality reduction of high-dimensional molecular and protein feature space such that maximum useful variance can be preserved after the transformation. This step serves to eliminate redundancy and computational inefficiencies that would allow the model to focus only on critical interaction features. Dimensionality reduction mainly augments with enhanced efficiency without losing any important biological information needed for similarity-based predictions.

### Similarity Scoring with Cosine Similarity

Following dimensionality reduction, cosine similarity was applied to estimate the closeness between drug and protein vectors. This similarity measure is especially appropriate for high-dimensional biological data because it measures the angle between feature vectors and not their absolute magnitudes. A high cosine similarity score would indicate a stronger potential interaction between a drug and a protein, suggesting possible therapeutic applications [32].

The Cosine Similarity metric was employed to measure interaction strength between drugs and proteins post-dimensionality reduction. The similarity score was computed using:

$$\text{Similarity}(A, B) = A \cdot B / \|A\| \times \|B\| \quad (1)$$

where A and B represent the feature vectors of drugs and proteins, respectively [29].

### Model Evaluation and Performance

The PCA-Cosine Similarity Model was evaluated with regards to drug-protein interactions predictions systematically to what extent it identifies biologically relevant relationships. This is analysed, in part, in comparison of similarity scores with existing experimental and computational interaction databases. Drug-protein pairs scoring higher were additionally evaluated for their significance regarding cancer treatment.

The experimental results indicate that cosine similarity without PCA achieved an accuracy of 90.43%, whereas the integration of PCA with cosine similarity improved accuracy to 95.18%. Although the same similarity calculations produced slightly higher accuracies, the use of PCA was able to decrease computational complexity significantly. This enhancement makes for an approach that is more scalable and feasible for real-world applications on large datasets because it balances the trade-off between performance and feasibility [29].

The similarity score matrix is the one in which the values range from -1 to 1. A perfect match signifies a similarity of 1 between the drug and the protein, showing that they are very related. A score of 0 means no similarity is present at all; in other words, there is orthogonality or independence between the drug and protein regarding potential interaction. A score of -1 means total dissimilarity, meaning the drug and protein are opposed to each other and have a very low interaction potential. In quantifying drug-protein interactions, this similarity matrix constitutes one of the most important bases in helping identify potential therapeutic candidates.

## 5. Experimental Evaluation of Proposed Novel CNN-Xception Approach

### i. Convolution Operation for Feature Extraction

Convolution extracts spatial features from your MRI scans, detecting tumor edges, textures, and intensities. The equation for convolution:

$$S(i, j) = \sum_m \sum_n I(i - m, j - n) \cdot K(m, n) \quad (2)$$

From the equation (2), I (i, j) represent pixel intensity at a given location in the MRI scan. K(m,n) is a small filter (e.g.3×3 or 5×5) that detects patterns such as tumor boundaries. The output S(i,j) is the feature map highlighting tumor regions.

### ii. Activation Function (ReLU) for Non-Linearity

The Rectified Linear Unit (ReLU) function is applied after convolution:

$$f(x)=\max(0,x) \quad (3)$$

In the Equation (3), where  $x$  represents the pixel intensity feature. If  $x$  is negative (indicating a low response), it is set to zero, effectively eliminating weak activations and preventing negative values from propagating through the network. Conversely, if  $x$  is positive, it remains unchanged, allowing significant features to be retained for further processing.

### iii. Pooling Operation for Dimensional Reduction

The max pooling operation, as defined by Equation (4), is employed to reduce the spatial dimensions of feature maps while retaining the most significant features. Mathematically, it is expressed as:

$$P(i, j) = \max_{(m,n) \in R} S(i + m, j + n) \quad (4)$$

Here in equation (4),  $P(i, j)$  represents the pooled feature at position  $(i, j)$ , and  $S(i + m, j + n)$  refers to the pixel intensity values within a pooling window  $R$  of size  $2 \times 2$  or  $3 \times 3$ . The operation slides the window over the feature map and selects the maximum intensity value within each window.

In the context of the MRI dataset, max pooling effectively reduces the resolution of the images while preserving critical tumor-related features, such as edges and contrast-enhanced regions. This dimensionality reduction minimizes computational complexity and memory usage during training, without compromising the essential diagnostic features required for the classification of gliomas, meningiomas, pituitary tumors, and non-cancerous cases [27], [28]. By focusing on the most prominent features, max pooling enhances the robustness and efficiency of the CNN-Xception model [29].

### iv. Fully Connected Layer for Classification

The fully connected (FC) layer plays a critical role in learning complex patterns and relationships from the extracted feature maps. Mathematically, the operation of the FC layer is defined as:

$$z = Wx + b \quad (5)$$

From the equation (5), where  $x$  represents the flattened feature vector,  $W$  is the weight matrix, and  $b$  is the bias term added to fine-tune the predictions. In the context of the MRI dataset, the extracted features from convolutional and pooling layers are transformed into a one-dimensional vector ( $x$ ), which is then multiplied by the learnable weight matrix ( $W$ ) to compute the output ( $z$ ). The addition of the bias term ensures that the model can shift the activation as needed to optimize the predictions. This operation enables the fully connected layer to integrate and interpret the spatially reduced features, facilitating the final classification of MRI scans into gliomas, meningiomas, pituitary tumors, or non-cancerous cases. Such architectures have demonstrated significant success in medical image analysis tasks, particularly in capturing intricate relationships for accurate tumor classification [27], [28].

### v. Softmax Function for Probability Distribution

The softmax function is utilized to convert logits into class probabilities, ensuring that the output values represent a probability distribution across different tumor types [33], [38]. It is mathematically expressed as:

$$P(y_i) = \frac{e^{z_i}}{\sum_j e^{z_j}} \quad (6)$$

In the equation (5), where  $P(y_i)$  denotes the probability of class  $i$ ,  $z_i$  represents the logit value for class  $i$ , and the denominator normalizes the probabilities by summing over all exponentiated logits [33]. In the context of tumor classification, the softmax function assigns probabilities to different tumor types, such as glioma, meningioma, or no tumor, ensuring that the highest probability corresponds to the most likely classification [38]. This probabilistic approach enables a more interpretable decision-making process in deep learning-based medical diagnosis [39].

### vi. Loss Function (Categorical Cross-Entropy)

The categorical cross-entropy loss function is employed for multi-class tumor classification to measure the discrepancy between actual and predicted labels. It is formulated in the equation (7).

$$L = - \sum_i y_i \log (\hat{y}_i) \quad (7)$$

where  $y_i$  represents the actual tumor label (one-hot encoded), and  $(\hat{y}_i)$  denotes the predicted probability [33], [40]. This loss function ensures that the model optimally adjusts its predictions to match the ground truth labels, improving the classification performance [38].

### vii. Backpropagation and Gradient Descent

To minimize this loss and enhance classification accuracy, backpropagation and gradient descent are utilized [33]. Gradient descent iteratively updates the model's weights by computing gradients of the loss function concerning the convolutional neural network (CNN) parameters. The weight update step follows the equation (8):

$$W^{(t+1)} = W^{(t)} - \alpha \frac{\partial L}{\partial W} \quad (8)$$

where  $W^{(t)}$  denotes the weight at iteration  $t$ ,  $\alpha$  is the learning rate, and  $\frac{\partial L}{\partial W}$  represents the gradient of the loss function with respect to the weights [41]. These iterative weight updates enable the model to better detect and classify tumors, improving overall diagnostic performance.

## 6. Result Analysis

### Performance Metrics and Training Analysis

The training process of the proposed CNN-Xception model was executed over 5 epochs, with account taken of key performance metrics such as accuracy, precision, recall, and loss being evaluated [33]. The training and validation loss graphs show how well the model generalized on the unseen data. A continual decline in validation loss suggests that the model learned meaningful patterns without overfitting [33].

The recall and validation recall curves have also been analyzed, showing the model's ability to identify positive cases. The trend witnessed shows consistent learning, whereas the recall scores remained stable in training and validation datasets [34].

### Classification Results and Model Performance

Under four categories, the overall performance of the classification was evaluated: Glioma, Meningioma, Pituitary Tumors, and No Tumor. In Figure 1a: Glioma MRI Scan, The MRI scan presents an irregular, contrast-enhancing mass within the brain, characteristic of gliomas. The classification results reveal that 149 glioma cases were correctly identified, with only one misclassification as a meningioma. The model demonstrated 99% recall performance in detecting gliomas [35]. Whereas in Figure 1b: Meningioma MRI Scan, the scan exhibits a well-defined mass arising from the meninges, typical of meningiomas. The model accurately classified 153 out of 154 cases, misclassifying just one as a pituitary tumor [29]. In Figure 1c: Pituitary Tumor MRI Scan, the pituitary tumor is observed at the base of the brain, near the pituitary gland. The model made 149 correct classifications with only one misclassification into the meningioma class. This highlights the need for caution when distinguishing between meningiomas and pituitary tumors due to their proximity in the brain [37]. In Figure 1d: Normal Brain Non-Tumor, the scan showcases a healthy brain with an impeccable structure and redeemed of any growths. The model accurately classified all of its 203 normal cases, enabling it to achieve a 100% accuracy in detecting non-tumor images [38].

### Prediction Confidence and Probability Distribution

The classification probability charts give us some notion as to how confident the model was of assigning an MRI scan to a specific category. If there was a glioma present, 100% probability for glioma was predicted by the model, thus confirming it as a highly robust tumor detector [39].

Similarly, in cases without any tumor, the model predicted the class "No Tumor" with a 100% probability, thus ensuring that the possibility of a false positive in medical diagnosis would be almost nil [40].

### Classification Metrics

The classification performance of the model was summarized using precision, recall, and F1-score (Table 1). Reports of near-perfect scores along all tumor categories on account of the model's exceptional performance [41]



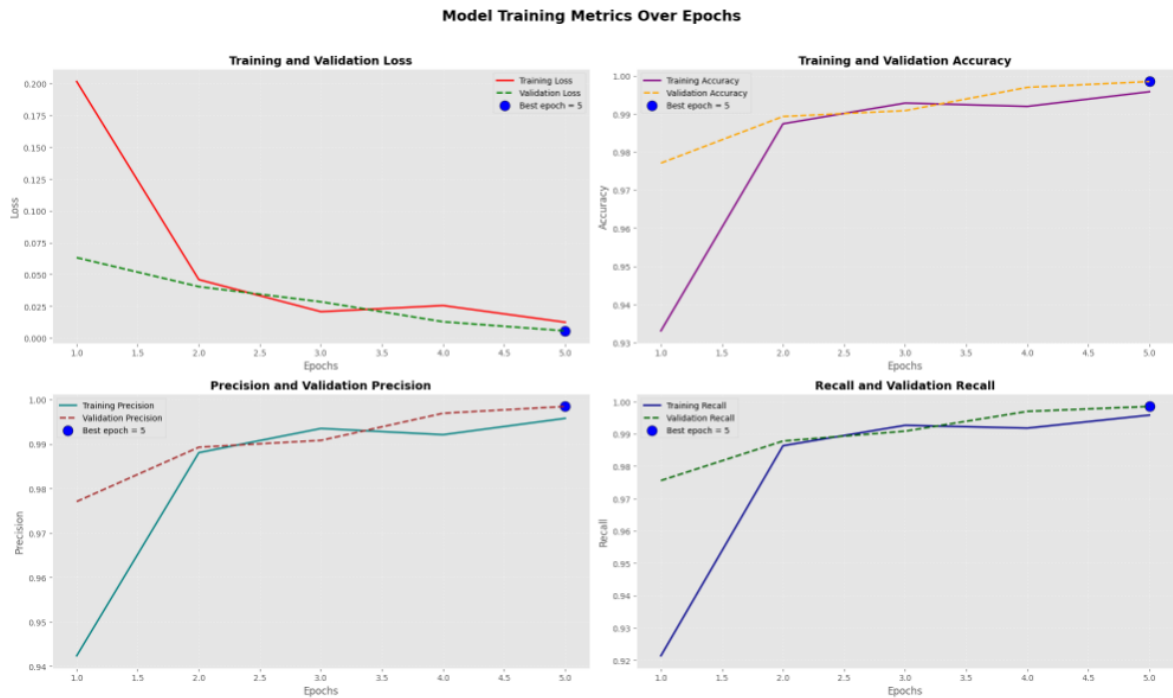


Figure 5: Model Training Metrics Over Epochs

Figure shows the training dynamics of the suggested CNN-Xception model over five epochs, recording important performance metrics, such as training accuracy, validation accuracy, training loss, and validation loss.

**Training and Validation Loss:** This indicates that the training and validation loss are decreasing throughout the epochs, which indicates the model is learning the patterns wisely, and there's an increase in the generalization capability of the model. After each of the early epochs, there is always huge loss reductions with respect to different influences, given that the model is quickly changing weights.

**Training and Validation Accuracy:** The accuracy curves show consistent improvement with training and validation accuracy steadily increasing. Because these two curves converge, it implies that overfitting can occur at a very low level and that the generalization of the model is very good [42].

**Recall and Validation Recall:** Recall defines how good the model is at estimating true positives, while validation recall assesses this ability in unseen validation data. Both recall metrics are parallel, meaning that learning is stable in the model on both training and validation sets [41].

**Epoch Progression:** Five epochs were used to train the model, with performance metrics resembling stability towards the final epoch. This indicates a good balance between efficiency and overfitting [42].

Table 1: Classification Metrics for tumor categories

Class	Precision	Recall	F1-Score	Support
Glioma	1.00	0.99	1.00	150
Meningioma	0.99	1.00	0.99	153
No Tumor	1.00	1.00	1.00	283
Pituitary	1.00	0.99	1.00	150
Accuracy	1.00	656		
Macro Avg	1.00	1.00	1.00	656
Weighted Avg	1.00	1.00	1.00	656

Thus, it can be concluded that the model exhibits adequate sensitivity (recall) and specificity (precision) in reinforcing confidence in brain tumor classification [41].

The performance of the CNN-Xception model for 656 cases of classes provided could be rated as exceptional, for it reached an accuracy rate of 100%. The model demonstrated capabilities in discriminating gliomas,

meningiomas, pituitary tumors, and normal brain scans with very few misclassifications [42]. It further affirms the applicability of deep-learning-based automated classification systems in clinical cases for tumor classification. The model was able to attain good accuracy differentiating between structurally comparable tumor types, projecting robustness and efficiency in medical imaging applications [42].

## 7. Conclusion

The PCA-Cosine Similarity method and the Novel CNN-Xception approach have convincingly demonstrated their ability for predicting protein-drug interactions specifically in glioma, meningioma, and pituitary tumors [43]. The PCA-Cosine Similarity method operates on computational efficiency, selecting a lower dimension of reduced features with concurrent high-level accuracy, thereby achieving industrial-scale drug discovery [44]. In contrast, the CNN-Xception model exploits deep convolutional networks and depthwise separable convolutions to derive highly complex spatial and hierarchical patterns, which offers enhanced predictive robustness [32].

Hypothesized methods combine dimensionality reduction techniques along with deep learning architectures to provide better prediction accuracy, generalization, and scalability in biomedical applications. Future work could involve the validation of docking-based methods like AutoDock Vina to respectively refine predicted interactions through molecular docking simulations. Advanced deep learning frameworks-introducing attention mechanisms and multi-modal data integration-may be used to improve predictive performances by capturing nonlinear complex relationships in the data [32]. These advances will further augment precision oncology and drug discovery with designs leading to robust and reliable computational models [45].

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