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In silico and modelling experiments in design of new drugs

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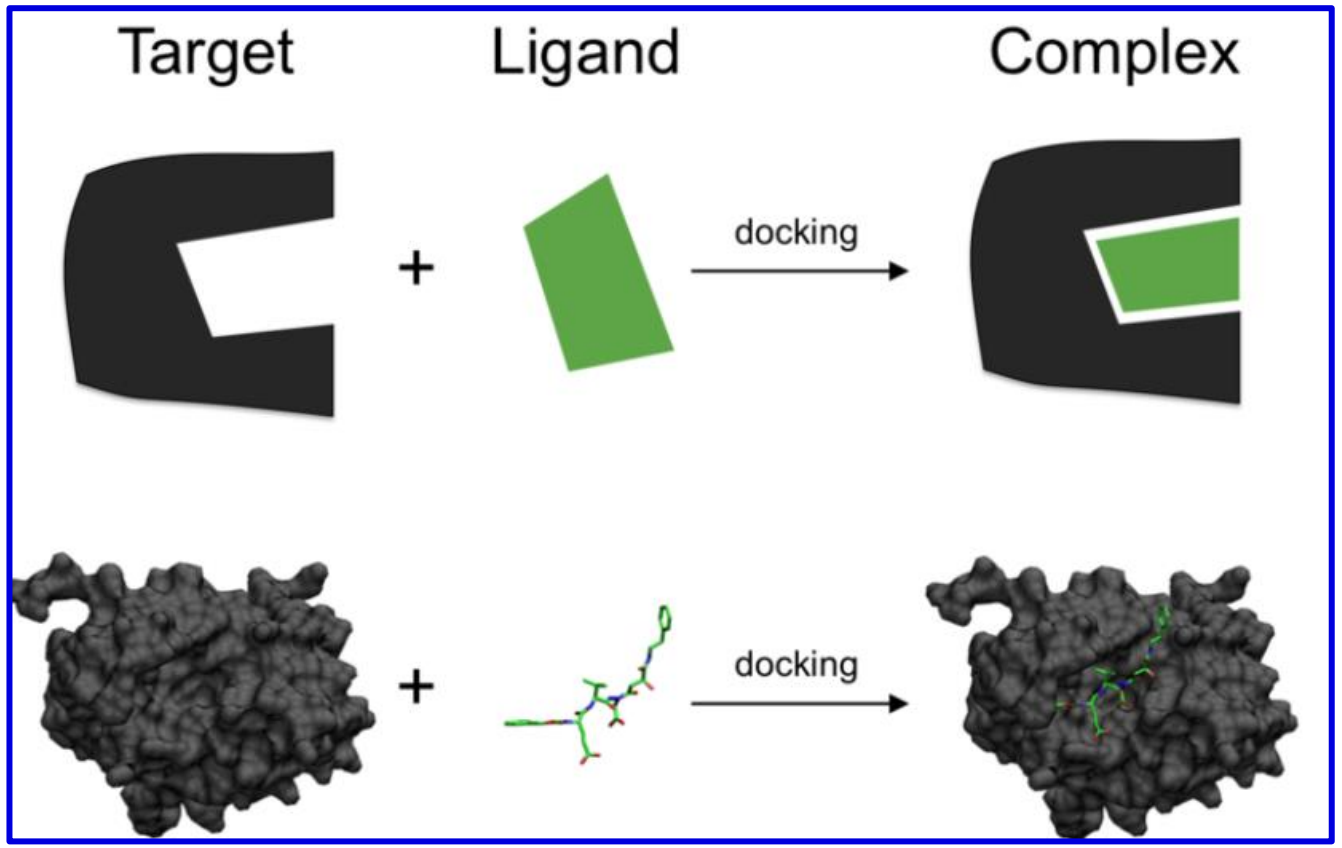
What is molecular docking?

- Molecular docking is a computational simulation of a candidate ligand binding to a receptor.
- This method predicts the preferred orientation of one molecule to another molecule when bound to each other to form a stable complex.
- The results obtained from this technique can be used to predict the strength of association or binding affinity between two molecules.

What is Molecular Docking?



https://commons.wikimedia.org/w/index.php?curid=45515965

Simple Diagram: Process of Molecular Interactions in Biological Systems

<u>Examples of target:</u>
biologically relevant molecules (proteins, peptides, nucleic acids, carbohydrates, lipids)

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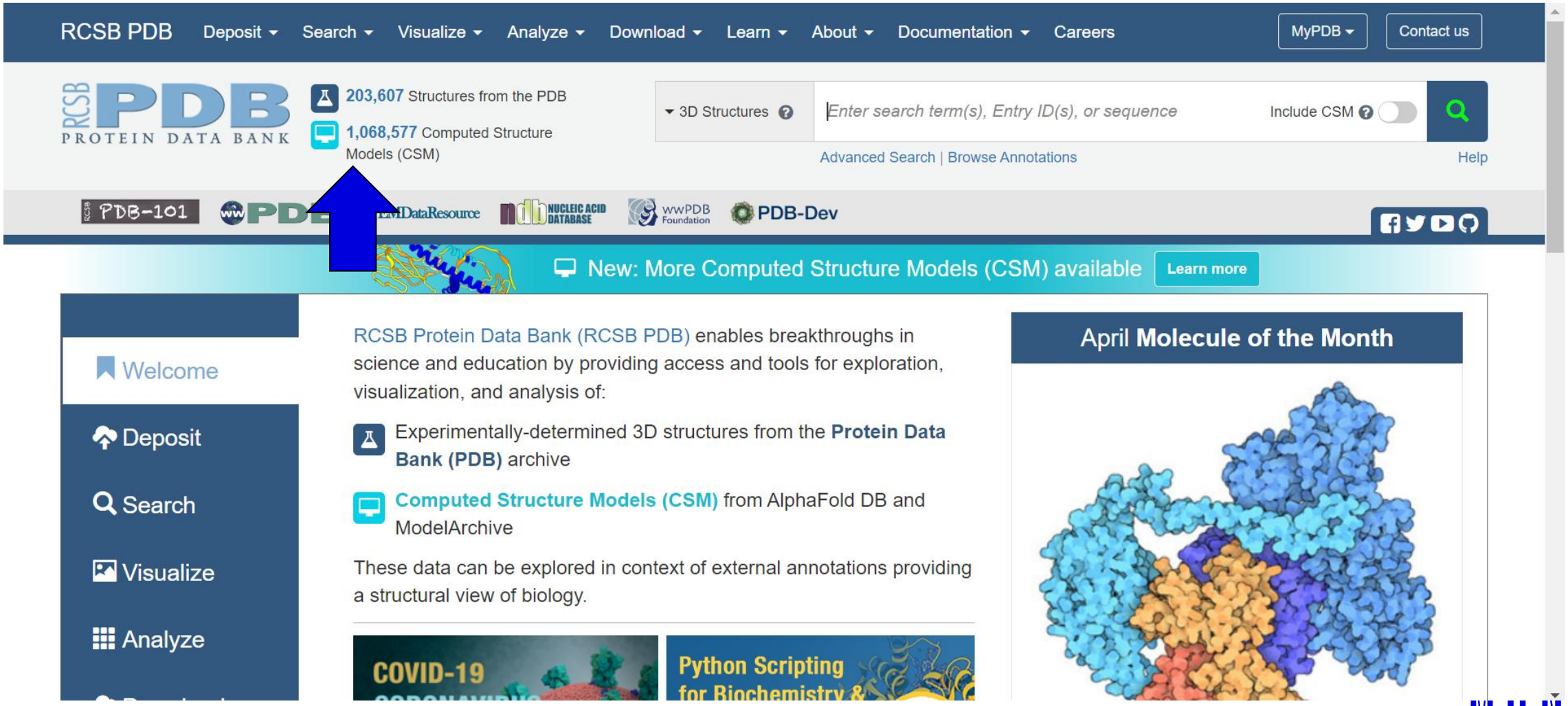
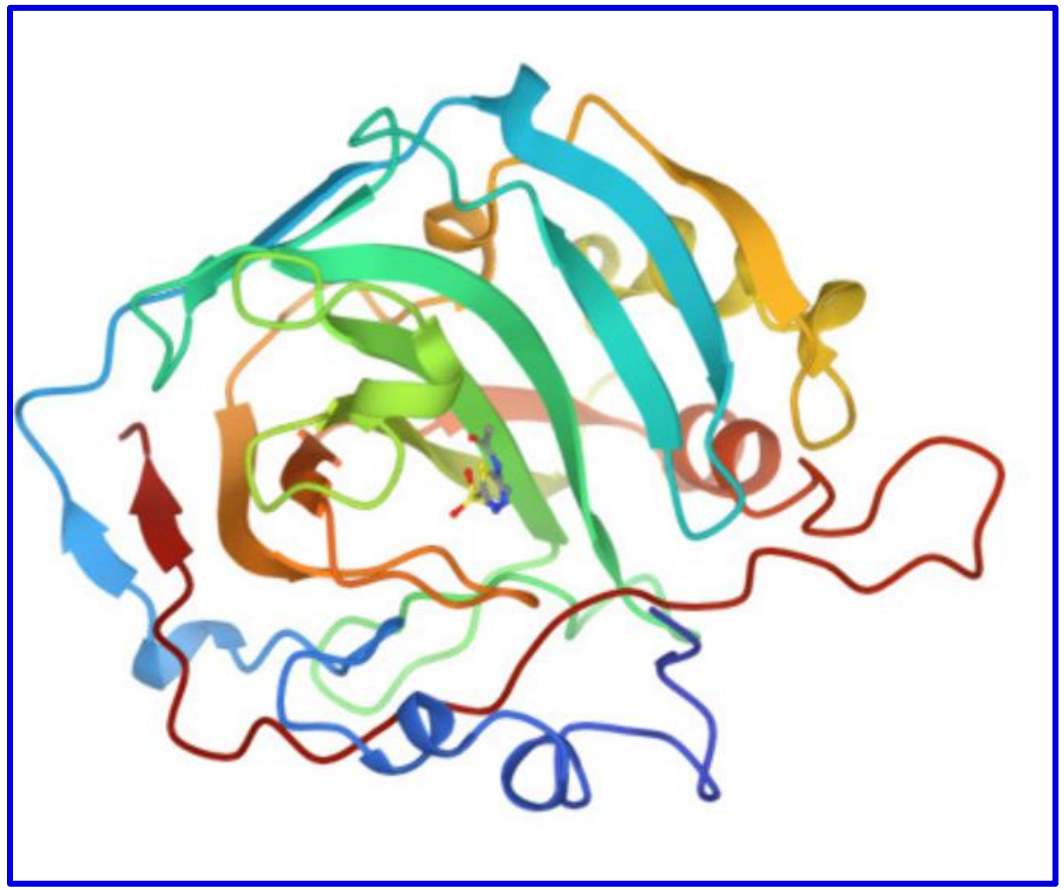
What is Molecular Docking?



What is Molecular Docking?



https://www.rcsb.org/structure/1AZM

Drug-Protein interactions: Structure of Sulfonamide drug complexed with human metaloenzyme Carbonic Anhydrase I.

RCSB Protein data bank contains **59** results for the crystal structure of the enzyme Carbonic Anhydrase I.

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Theory of docking

- The main aim of molecular docking is to give a prediction of the ligand-receptor complex structure using computation methods.

Docking can be achieved through two interrelated steps:

- 1. step - sampling conformations of the ligand in the active site of the protein (method of grid)
- 2. step - ranking these conformations via a **scoring function**

- Sampling algorithms should be able to reproduce the experimental binding mode and the scoring function should also rank it highest among all generated conformations.

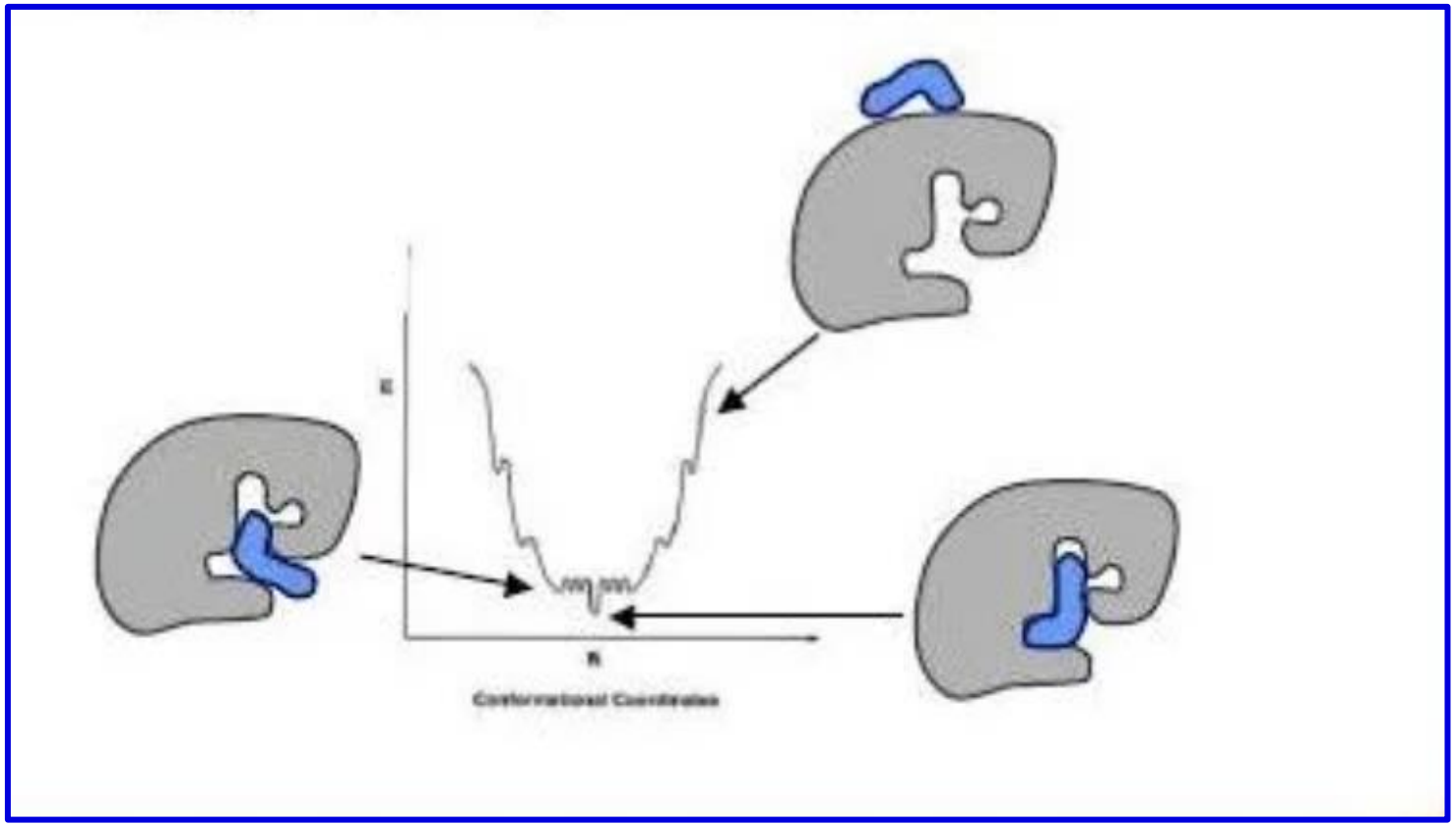
What is Molecular Scoring?

- Type of mathematic function that is useful in evaluating the progress of molecular docking
- Scoring functions are used for predicting the binding affinity between two molecules after the process of docking

The molecular scoring can be used for:

- evaluation the affinity of the drug towards the binding site (small molecule of a particle drug and biological target such as a protein)
- prediction the intermolecular interactions between two proteins or between a protein and DNA molecules

What is Molecular Scoring?



https://commons.wikimedia.org/w/index.php?curid=10888929

Simple Diagram: Molecular scoring is in the drug-designing processes

Scoring is a process of evaluating a particular pose by counting the number of favorable intermolecular interactions

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What is Molecular Scoring?

$$V = W_{vdw} \sum_{i,j} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) + W_{hbond} \sum_{i,j} E(t) \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right) + W_{elec}$$

$$\sum_{i,j} \frac{q_i q_j}{\varepsilon(r_{ij}) r_{ij}} + W_{sol} \sum_{i,j} \left(S_i V_j + S_j V_i \right) e^{\left(-r_{ij}^2 / 2\sigma^2 \right)}$$

Extended force-field-based scoring function from AutoDock.

For two atoms i, j, the pair-wise atomic energy is evaluated by the sum of van der Waals, hydrogen bond, coulomb energy
and desolvation. W are weighted factors for calibrate the empirical free energy.

$$\Delta G = \Delta G_0 + \Delta G_{rot} \times N_{rot} + \Delta G_{hb} \sum_{neutral\ H-bond} f(\Delta R, \Delta\alpha)$$
$$+ \Delta G_{io} \sum_{ion\ init.} f(\Delta R, \Delta\alpha) + \Delta G_{aro} \sum_{aro\ int.} f(\Delta R, \Delta\alpha) + \Delta G_{lipo}$$
$$\sum_{lipo\ cont.} f^*(\Delta R)$$

Empirical scoring function from FlexX.

ΔG is the estimated free energy of binding; ΔG_0 is the regression constant; ΔG_{rot}, ΔG_{hb}, ΔG_{io}, ΔG_{aro} and ΔG_{lipo} are
regression coefficients for each corresponding free energy term; $f(\Delta R,\Delta\alpha)$ is scaling function penalizing deviations from

Examples of scoring function formulae

Scoring functions can be divided in:

1. force-field-based
2. empirical
3. knowledge-based scoring functions

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Difference between Docking and Scoring

	Molecular Docking	Molecular Scoring
Definition	Computational simulation of a candidate ligand binding to a receptor	Type of mathematic function, useful in evaluating the progress of molecular docking
Goals	Predicting the orientation of molecular binding	Predicting and evaluating the affinity of molecule to bind with particular binding site
Category	Computational technique	Mathematical function
Importance	Structure-based drug designing	Virtual screening, de novo designing, lead optimalization

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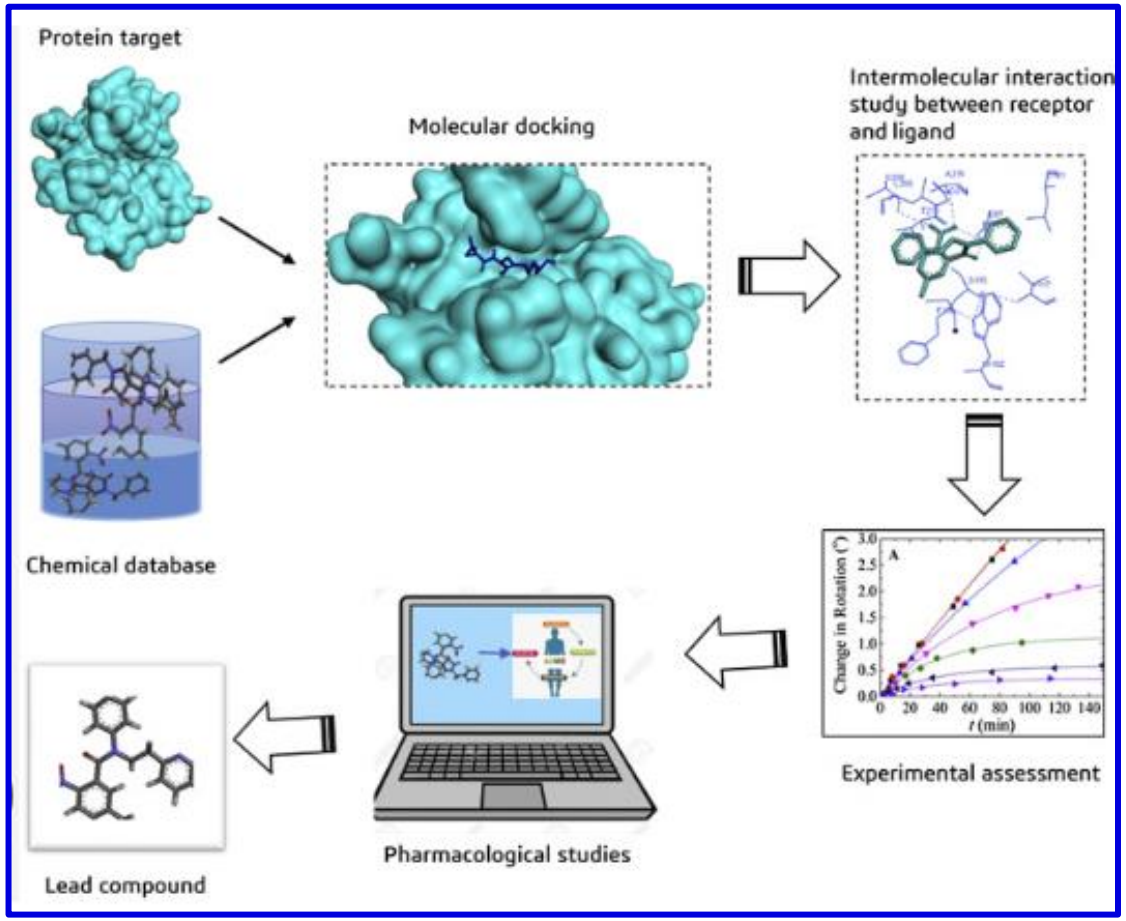
The process of molecular docking

- The molecular docking method seeks to identify the binding mode of a given ligand that best matches a target (protein).
- The process involves generating multiple possible conformations and orientations of the ligand with the binding site of the target.
- Access to the three-dimensional structure of the target is vital for this process.
- This 3D structure can be obtained via numerous methods (X-ray crystallography, NMR, or homology modeling).

The process of *In silico* experiments



https://doi.org/10.1016/B978-0-12-822312-3.00020-5

General workflow of molecular docking calculations.

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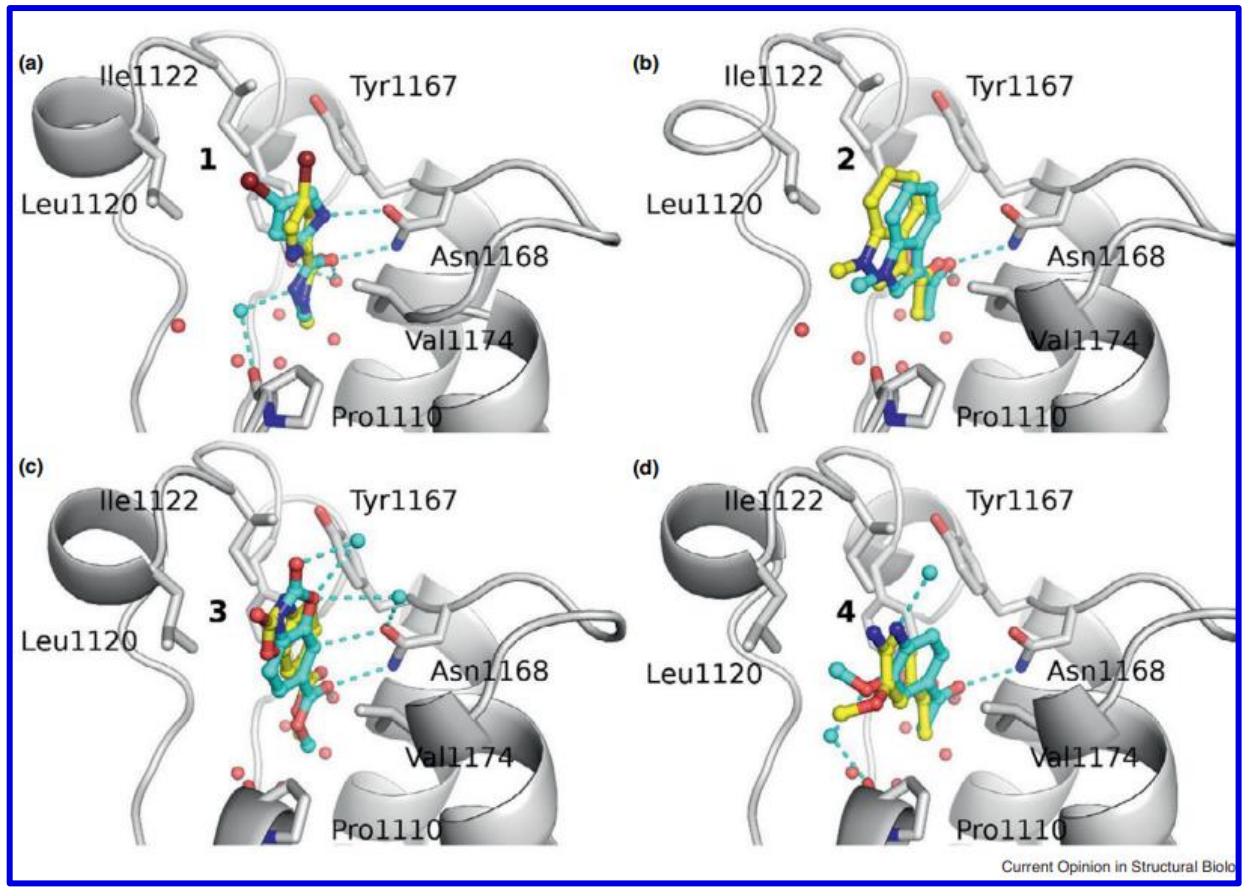
Results of molecular docking



Structural validation of the fragment-based in silico screening campaign

doi: 10.1016/j.sbi.2017.10.010

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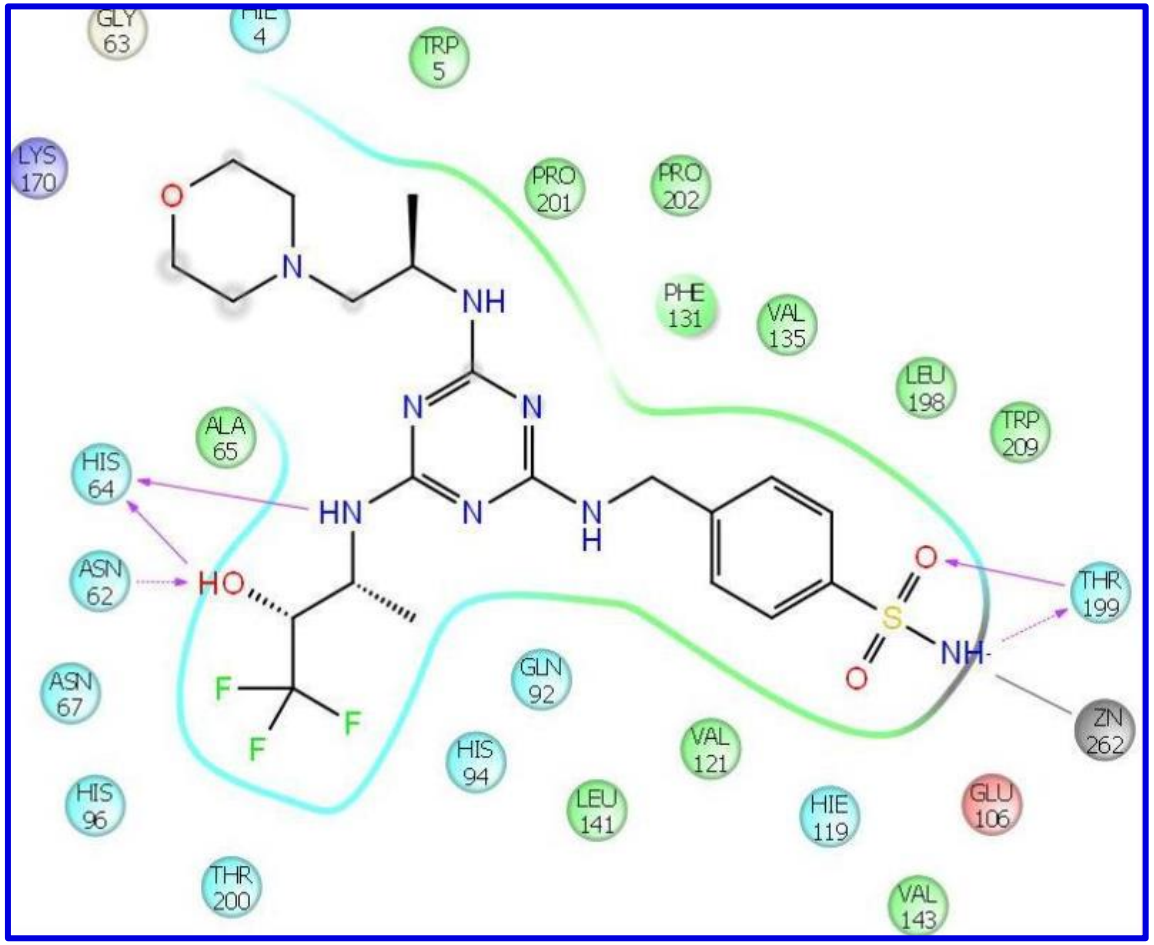
Results of *In silico* experiments



ONUŠČÁKOVÁ, Magdaléna: *Hľadanie nových inhibítorov CA IX obsahujúcich s-triazín pomocou programu CombiGlide.* [Diplomová práca].

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Classification of molecular docking methods

Docking methods are classified in terms of the degrees of flexibility of the molecules under investigation.

1. **Rigid docking (rigid ligand and rigid receptor)**
2. **Semi-flexible docking (flexible ligand and rigid receptor)**
3. **Flexible docking (flexible ligand and receptor)**

Classification of molecular docking methods

Rigid ligand and rigid receptor docking

- Rigid docking is a method where the ligand and target are classified as fixed and just three translational and rotational degrees of freedom are considered in the sampling phase.
- This model is most commonly used for protein-to-protein docking and reflects the “lock and key” model of binding.

Classification of molecular docking methods

Flexible ligands and rigid receptor docking

- The conformational degrees of freedom of the flexible molecule are sampled, and six translational and rotational degrees of freedom are also added.
- Semi-flexible methods assume that a fixed conformation of a target might correspond to the one able to recognize the docking ligands.

Classification of molecular docking methods

Flexible ligand and flexible receptor docking

- The method of flexible docking assumes that a protein does not behave passively during the binding phase and, therefore, it considers the target protein to be flexible as well as the ligand.
- There are numerous methods of flexible docking that have developed over the years with some focussing on the model of induced fit binding and others focussing on conformational selection.

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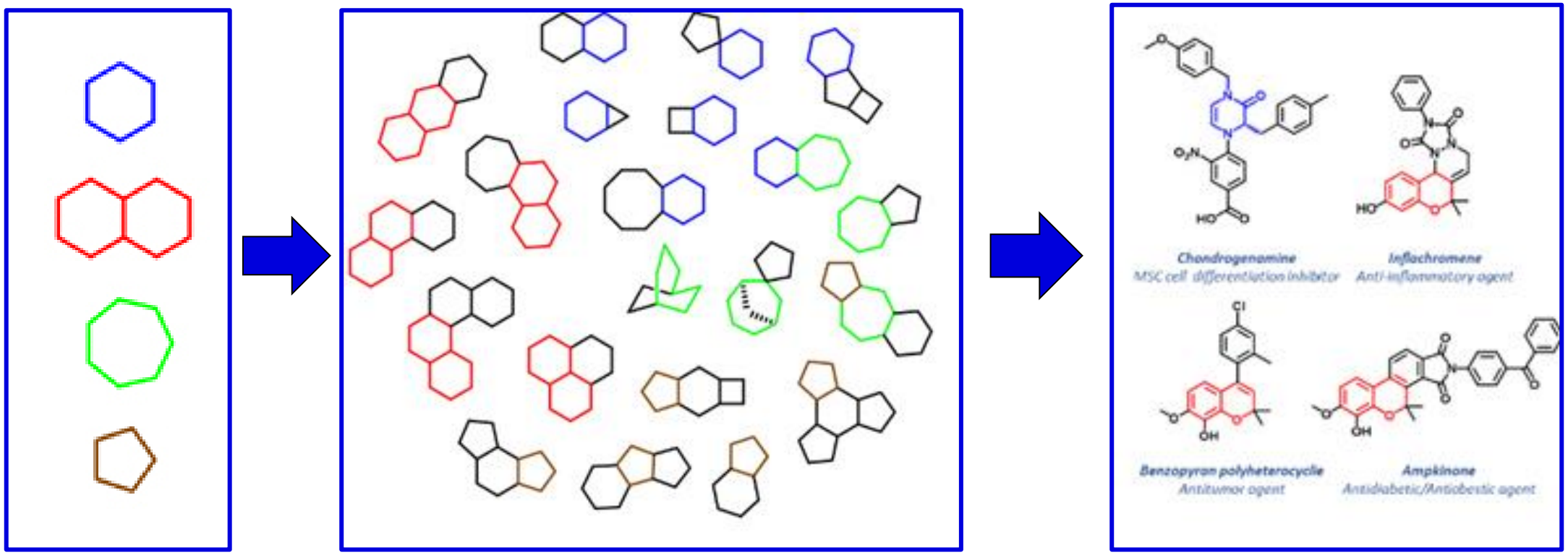
Privileged structures

What are privileged structures?

- Privileged structures are defined as molecular frameworks which are able of providing useful ligands for more than one type of receptor or enzyme target by judicious structural modifications.
- Many privileged structures have been identified simply by empirical observations.
- Privileged structures represent a viable starting point for the design of combinatorial chemistry or parallel synthesis libraries to solve drug discovery problems for GPCR, LGIC and enzyme targets.

What are privileged structures? Examples.



Privileged structures | Polycyclic small molecules | Final compounds

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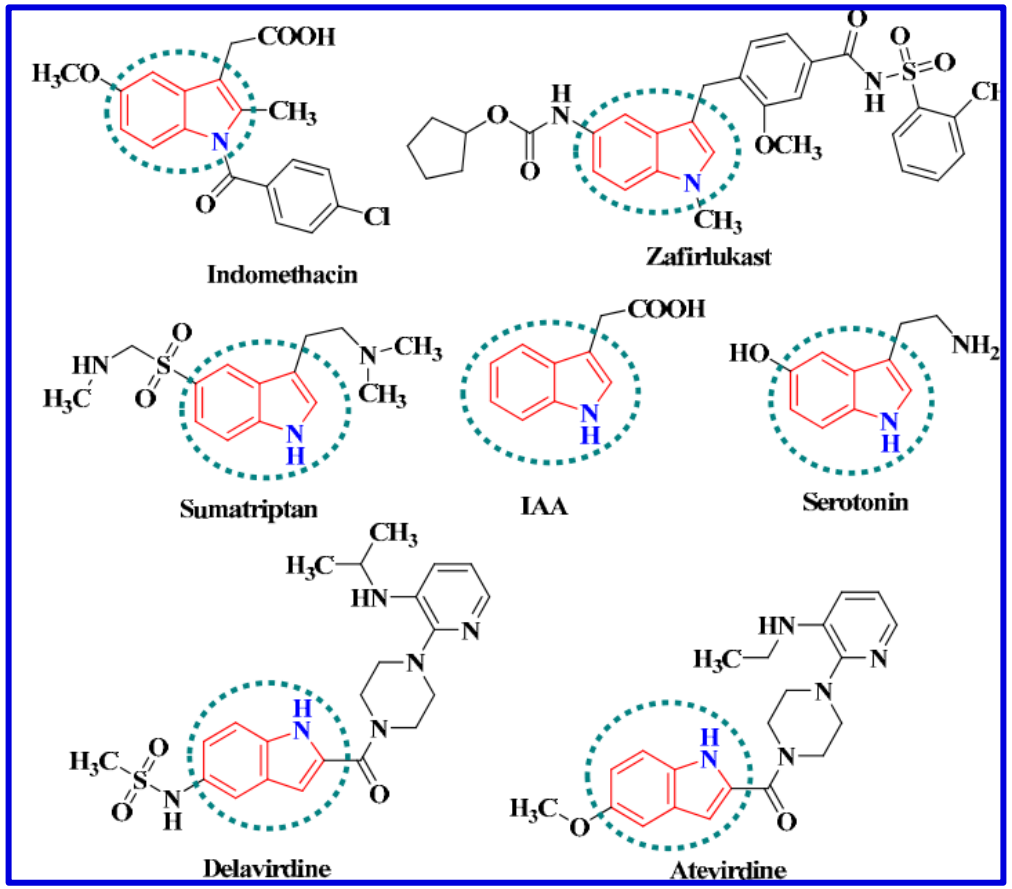
What are privileged structures? Indole



Structures of some marketed formulations and natural products containing Indole scaffold.

Naim, Mohd. Javed et al. “RECENT REVIEW ON INDOLE: A PRIVILEGED STRUCTURE SCAFFOLD.” (2016).

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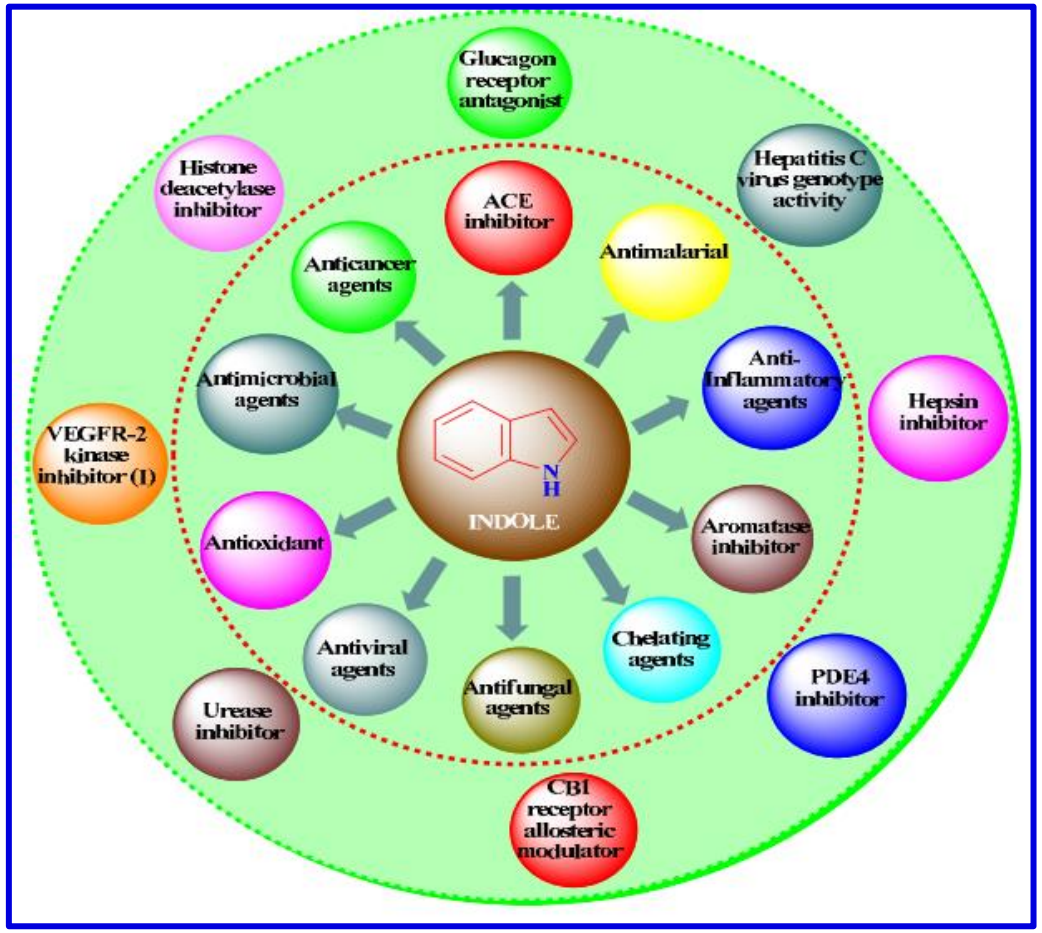
What are privileged structures? Indole



Pharmacological profile of Indole scaffold.

Naim, Mohd. Javed et al. "RECENT REVIEW ON INDOLE: A PRIVILEGED STRUCTURE SCAFFOLD." (2016).

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Thank you for your attention

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- https://www.nature.com/articles/nrd1549

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Artificial Neural Networks - ANN

RNDr. Eva Havránková, Ph.D.

Artificial Neural Networks

- ANNs are nonlinear statistical models which display a complex relationship between the inputs and outputs to discover a new pattern.

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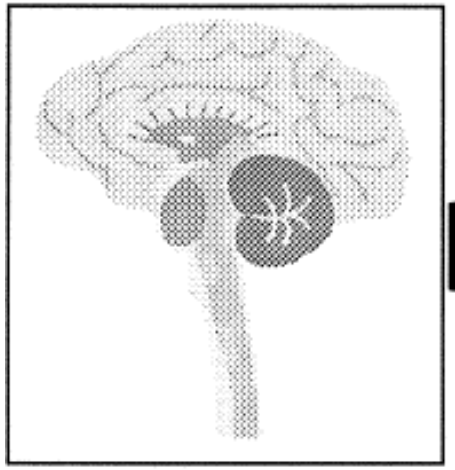
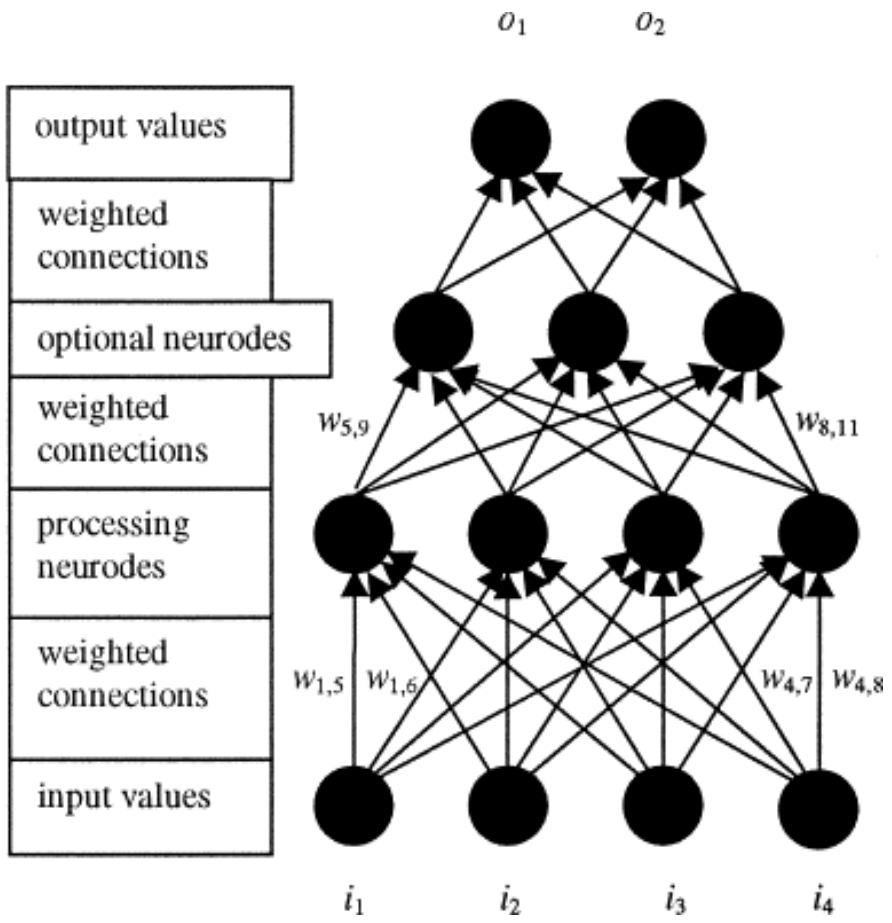
Neural Networks ?





Editor: Robert A. Meyers. Encyclopedia of Physical Science and Technology, 2001. 3rd Ed.

- ANN simulate the electrical activity of the brain and nervous system.
- Synaptic connections

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Neural Networks?

- Typically the neurodes are arranged in a layer or vector.
- The output of one layer is serving as the input to the next layer.
- Connections simulating the synaptic connections of the brain.
- It is through the adjustment of the connection strengths or weights, $w_{n,m}$, that learning is emulated in ANNs.

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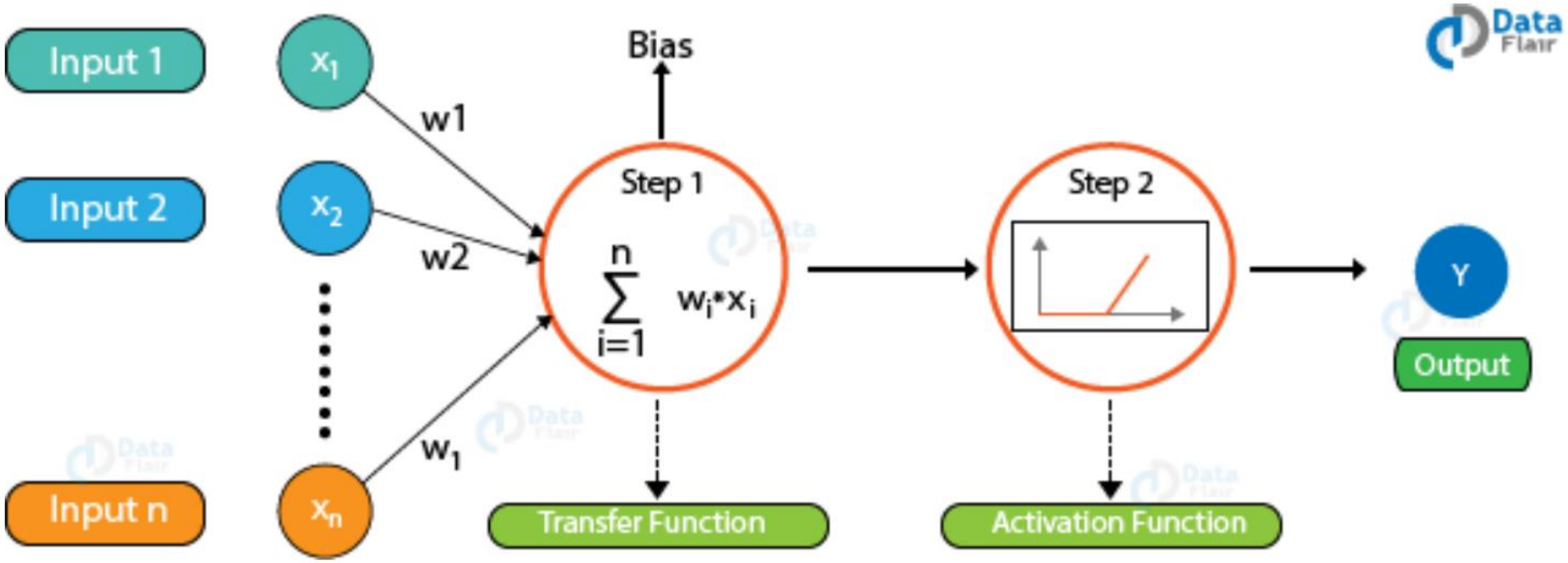
ANN – black box



https://data-flair.training/blogs/artificial-neural-networks-for-machine-learning/

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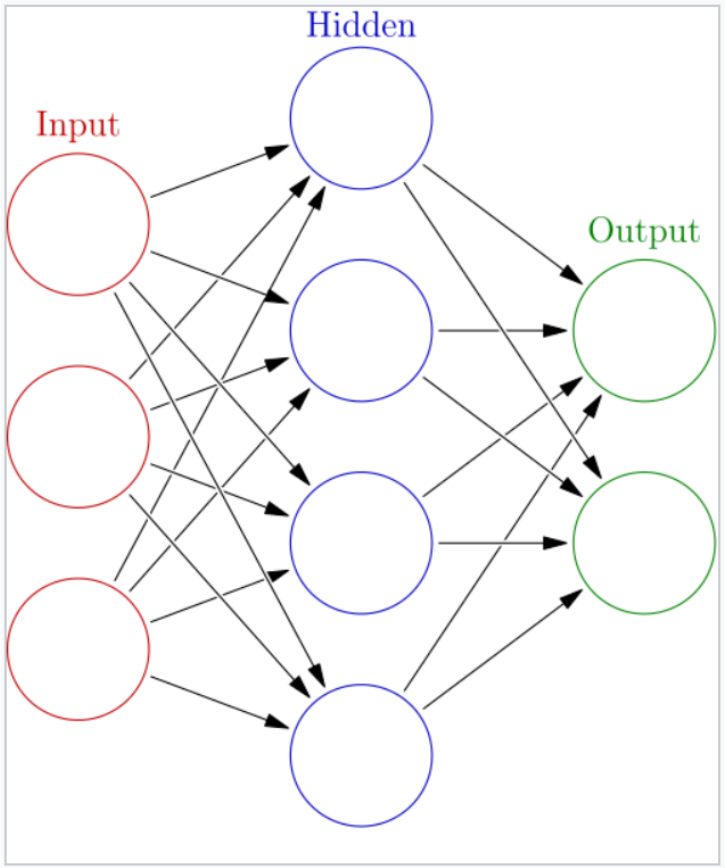
ANN – Input Layer

- The *input layer* is the first layer of an ANN that receives the input information.
- In the form of various texts, numbers, audio files, image pixels, etc.



https://en.wikipedia.org/wiki/Artificial_neural_network

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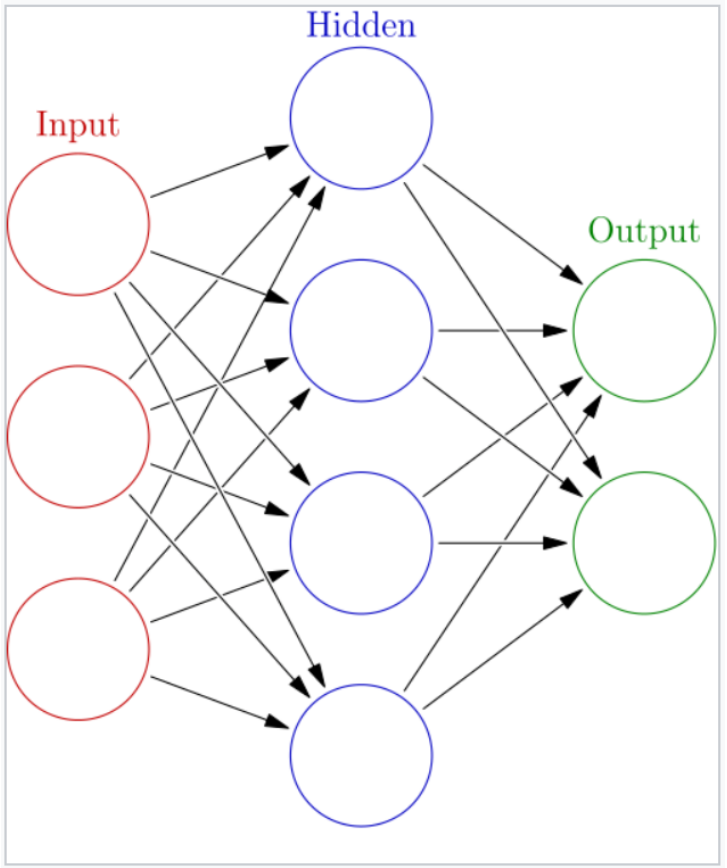
ANN – Hidden Layer

- In the middle of the ANN model are the *hidden layers*.
- There can be a single hidden layer, as in the case of a perceptron or multiple hidden layers
- These hidden layers perform various types of mathematical computation on the input data and recognize the patterns that are part of.



https://en.wikipedia.org/wiki/Artificial_neural_network

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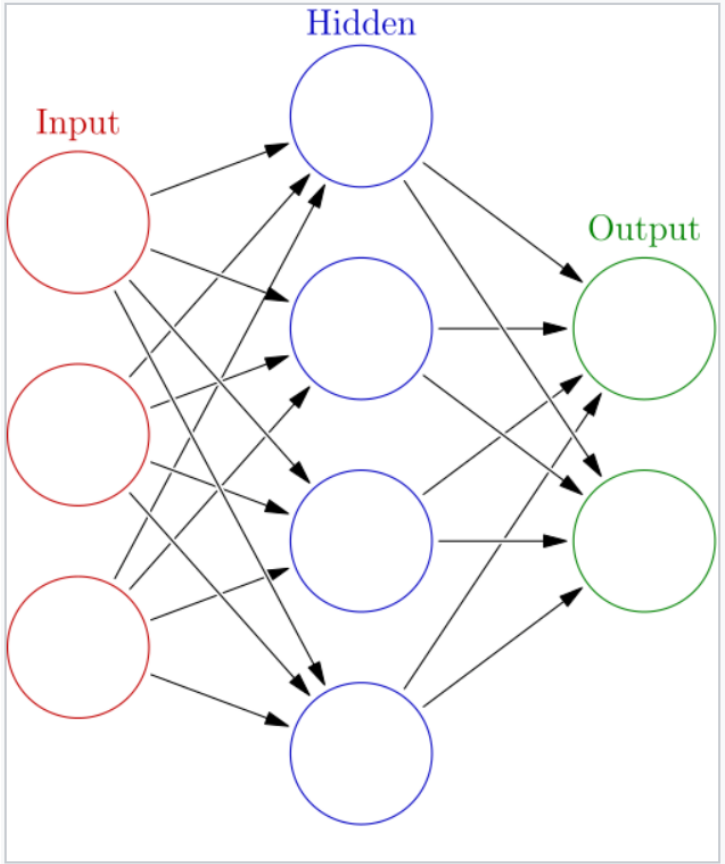
ANN – Output Layer

– In the *output layer*, we obtain the result that we obtain through rigorous computations performed by the middle layer.



https://en.wikipedia.org/wiki/Artificial_neural_network

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How we get optimized ANN model?

- Dataset – Whole set of data given to the ANN model.

- Descriptors – various texts, numbers, audio files, image pixels

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How we get optimized ANN model?

- The determination of the appropriate number of nodes in each layer and the number of hidden layers is the most critical task in designing and optimizing of ANN architecture.
- The development of the ANN optimized model has three basic steps:
  1. Training
  2. Verification
  3. Prediction

How we get optimized ANN model?

Training

$$RMS = \sqrt{\frac{\sum_{i=1}^{M}\sum_{j=1}^{N}\left(y_{ij} - out_{ij}\right)^2}{M - N}}$$

- A useful criterion indicating whether a network structure is operating correctly during the training process is to minimize the value of the root mean square (RMS)
- The training phase is considered to be complete when the neural network model achieves the required statistical accuracy for the prediction of outputs and for maintaining the required RMS for a given sequence of inputs.

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How we get optimized ANN model?

Verification

- During the verification process, the correctness and accuracy of the prediction are tested.
- Finally, the proposed optimized model of ANN can be used for the prediction of biological activity.

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How we get optimized ANN model?

Prediction

- Prediction of desired data, properties, clasification,….

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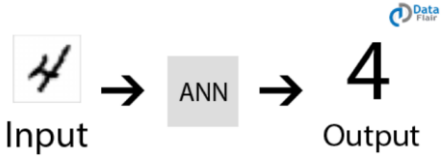
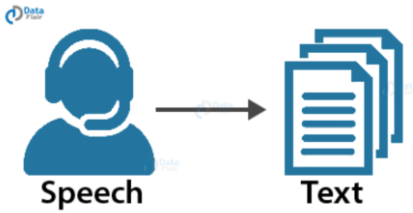
Use of ANN



- Handwritten Character Recognition
- ANNs are used for handwritten character recognition. Neural Networks are trained to recognize the handwritten characters which can be in the form of letters or digits.



- Speech recognition
- With the advent of deep learning, various types of neural networks are the absolute choice for obtaining an accurate classification.

https://data-flair.training/blogs/artificial-neural-networks-for-machine-learning/

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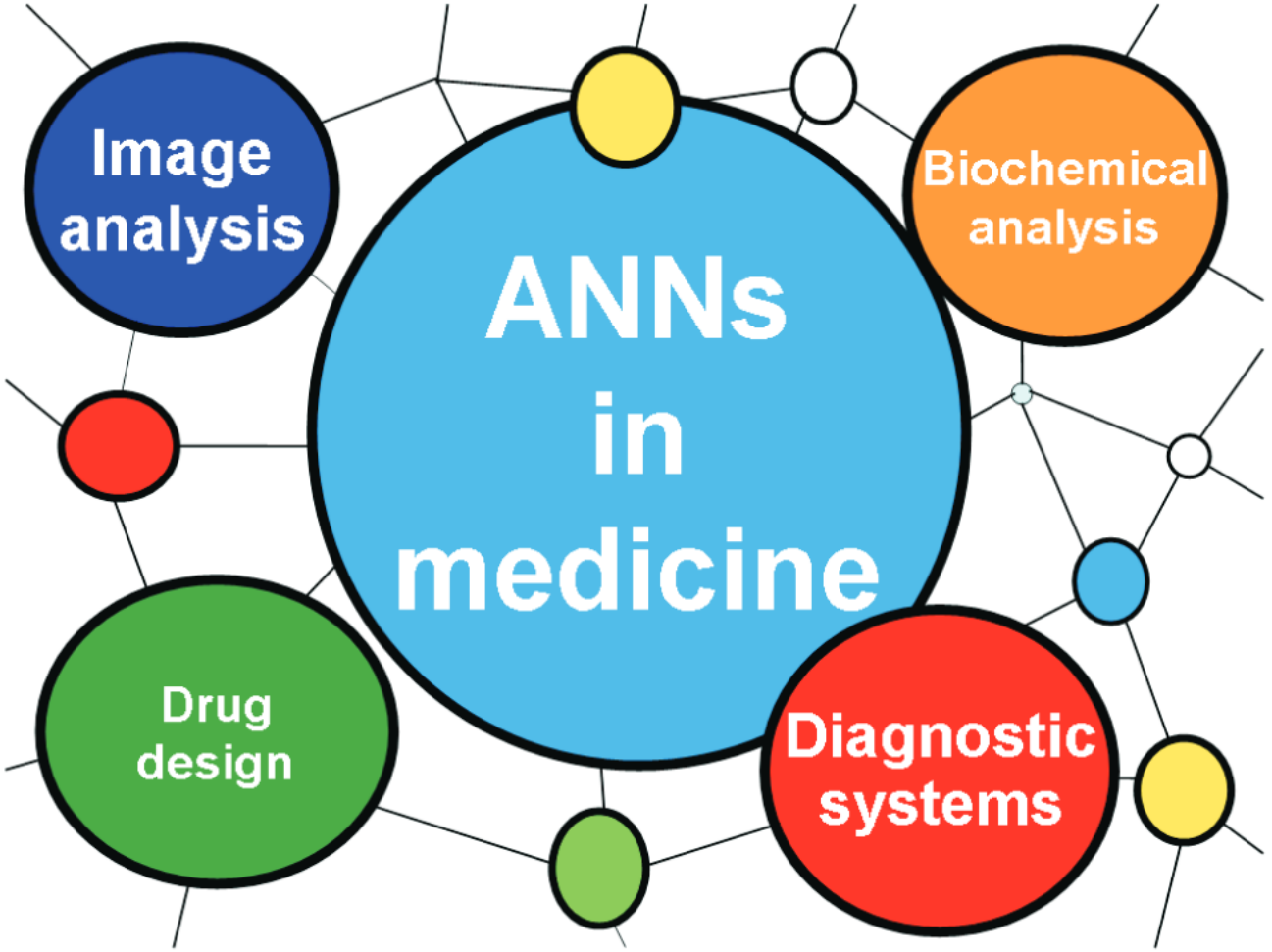
Use of ANN

- Signature Classification
- For recognizing signatures and categorizing them, for authentication. Furthermore, neural networks can also classify if the signature is fake or not.
- Facial Recognition
- In order to recognize the faces based on the identity of the person.
- They are most commonly used in areas where the users require security access.

Use of ANN

https://jab.zsf.jcu.cz/pdfs/jab/2013/02/01.pdf



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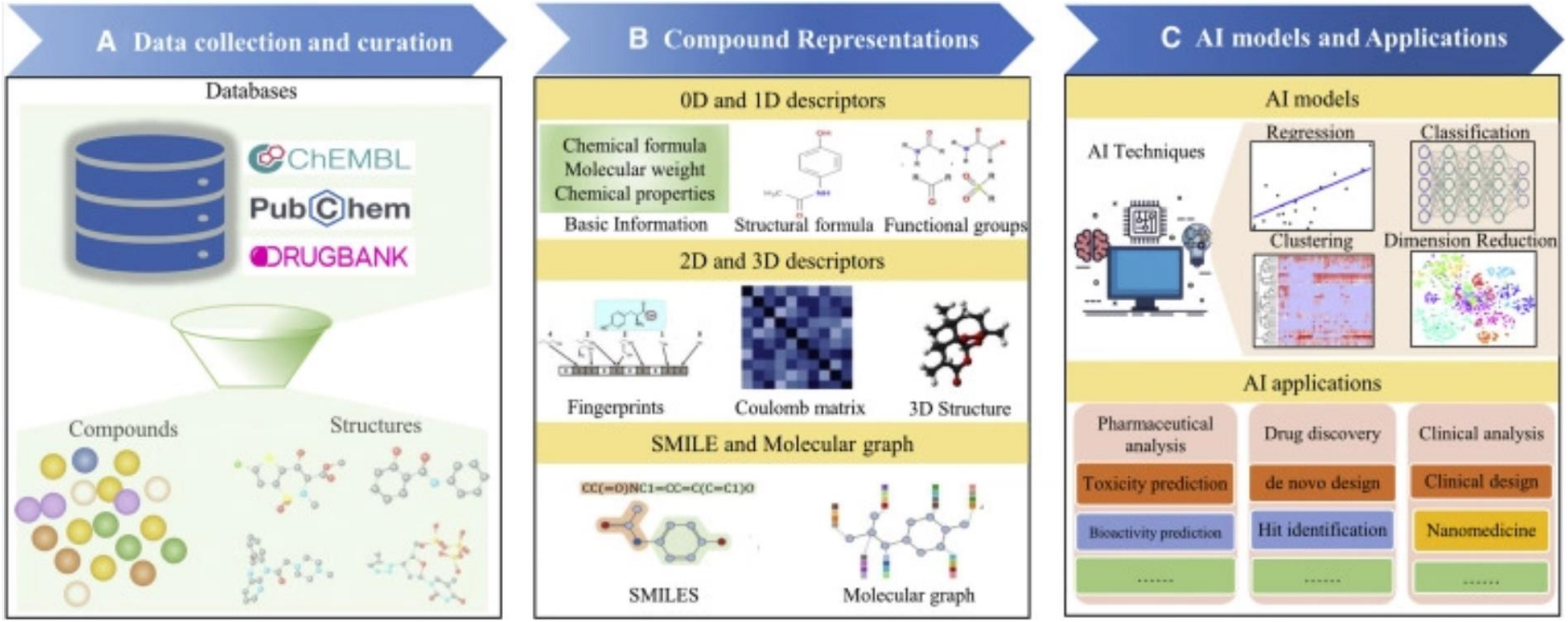
Prediction of biological activity

- Inhibitory activity
- Antibacterial activity



DOI:https://doi.org/10.1016/j.omtn.2023.02.019

Diagnosis

Input data or method	Clinical context	Output information
Age, cholesterol concentration, arterial hypertension	Coronary artery disease	Diagnosis
Heart sound	Valve stenosis	Diagnosis
Hematologic profile	Chronic myeloid leukemia	Classification of leukemia
Visual information of wireless capsule endoscopy	Small bowel tumors	Diagnosis, classification of tumor
Glucose concentration – Near-infrared spectroscopy	Diabetes	Diagnosis
Demographic and clinicopathologic data, surgical outcome	Hepatocellular carcinoma	Prediction of disease free survival
Cytology of effusion fluid	Carcinoma	Presence of malignant cells
Speech record	Oral/Oropharyngeal cancer	Detection of nasalence (hypernasality)
Electroencephalographic (EEG) recordings	Epilepsy	Prediction of seizures

https://jab.zsf.jcu.cz/pdfs/jab/2013/02/01.pdf

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Prediction of analytical properties

- Retenction time in HPLC, GC
- pH
- Concentration

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Optimalization of chemical processes

- Artificial Neural Network for Optimization of a Synthesis Process of γ-Bi_2MoO_6 Using Surface Response Methodology
- This oxide is recognized as an efficient photocatalyst for degradation of organic pollutants in aqueous media.
- The exposure time to ultrasonic radiation, calcination time and temperature.

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Thank you for your attention.

Sources

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