KinetixPredict

in silico Prediction of binding kinetics by MD simulations and machine-learning

Samia Aci-Sèche
Structural Bioinformatic & Chemoinformatic team

Binding kinetics

Drug discovery

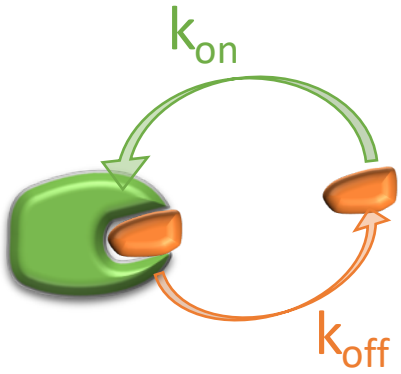
Choice of drug candidate: based on equilibrium constants such as
K_i, K_D, IC_{50}, EC_{50}

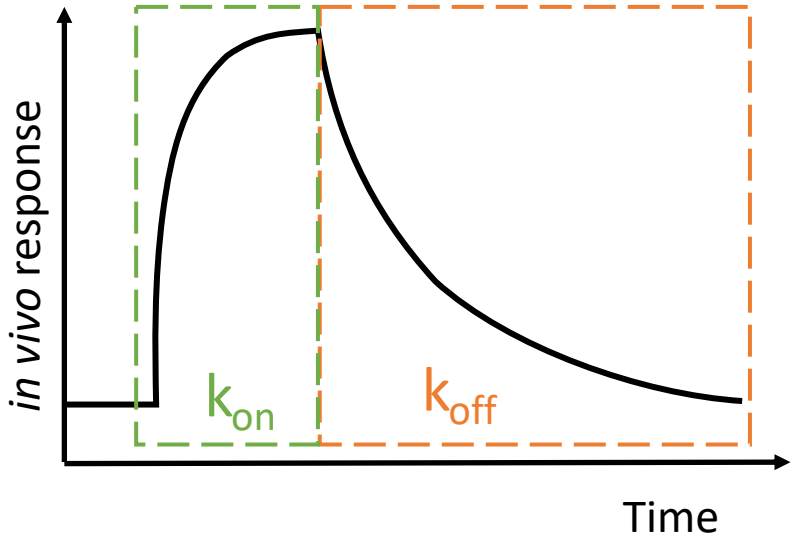
Clinical trials

Phase II: highest failure rate 68%

Due to poor efficacy

⟹ binding kinetics





k_{on}: association constant ($M^{-1}\,s^{-1}$)

k_{off}: dissociation constant (s^{-1})

Affinity: $K_D = k_{on}/k_{off}$

Residence time: RT = $1/k_{off}$

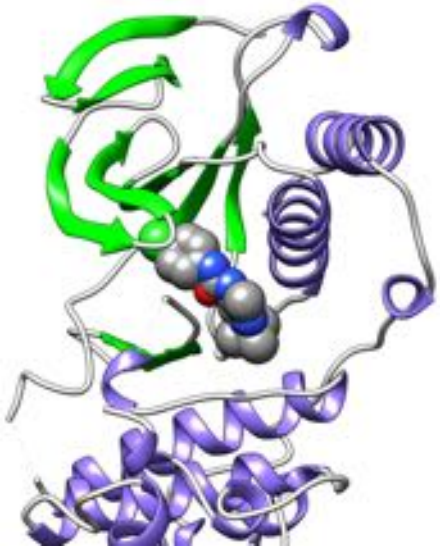
Previous work

ANR JCJC 2013 ChADock

***C**inétique des in**h**ibiteurs de protéines kinases et **A**ffinité par **Dock**ing flexible*

Abdennour Braka

- 48 month project funded by ANR (09/2014 ➔ 09/2018)
- Involved Modelers, Chemists (ICOA) and Biologists (CBM)
- PhD student for modeling tasks



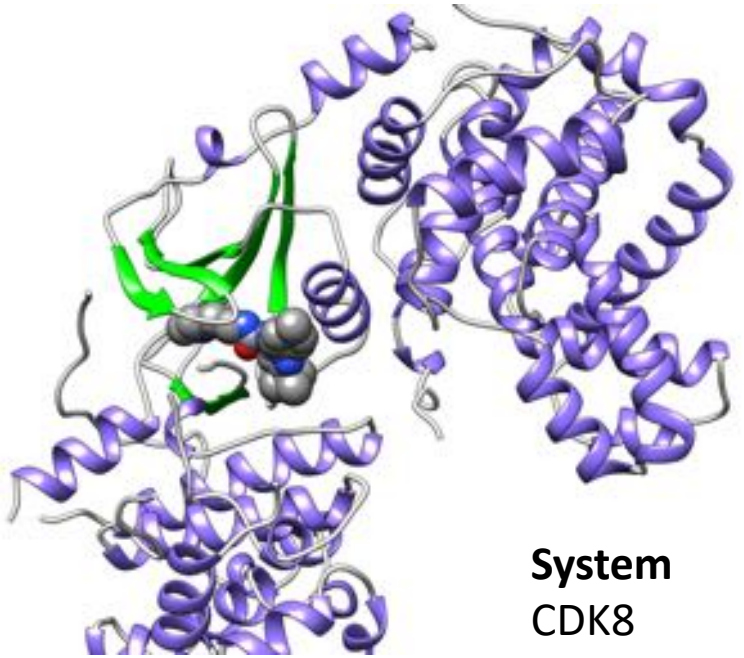
System
p38α MAPK

Kinetix4PKi project

Prediction of binding kinetics data of protein/ligand complexes using bioinformatics tools

Sonia Ziada

- Collaborative project with Servier Institute
- PhD student for modeling tasks



System
CDK8

Previous work

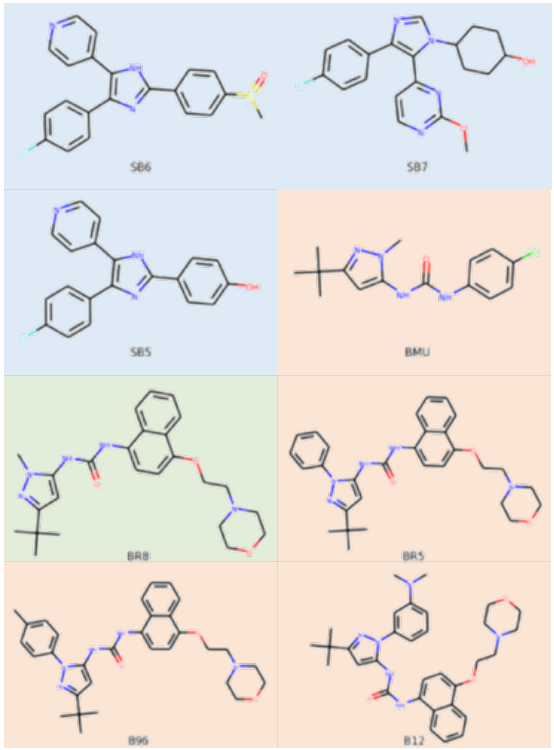
ANR JCJC 2013 ChADock

Abdennour Braka

Dataset

long RT (LRT)
medium RT (MRT)
short RT (SRT)

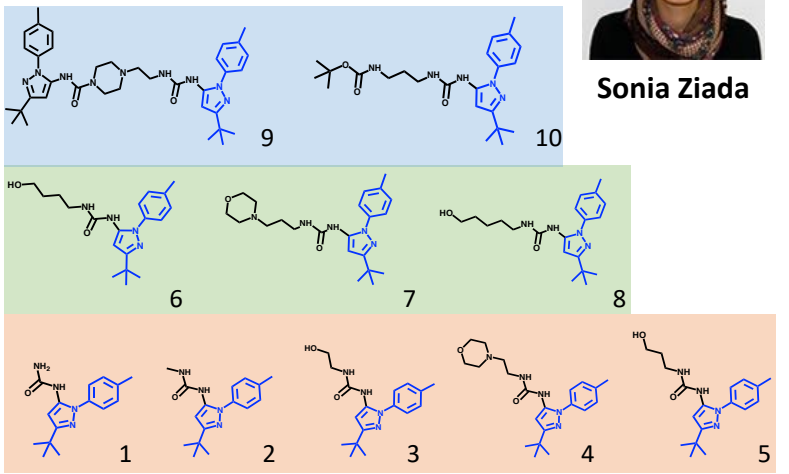
Ligand	RT (Exp)
BR5	18.5 h
B12	10.6 h
B96	5.3 h
BR8	5 min
BMU	35.7 s
SB5	37 s
SB7	14.9 s
SB6	7.7 s



Kinetix4PKi project

Sonia Ziada

Dataset



Ligand	RT (Exp)
10	1944 min
9	1626 min
8	57 min
7	14 min
6	7 min
1, 2, 3, 4, 5	< 1.4 min

Schneider E.V. *et al.* (2013). Proceedings of the National Academy of Sciences *110*, 8081–8086.

Previous work

ANR JCJC 2013 ChADock

Method

Steered molecular dynamics (SMD)

Potential of Mean Force

Abdennour Braka

Kinetix4PKi project

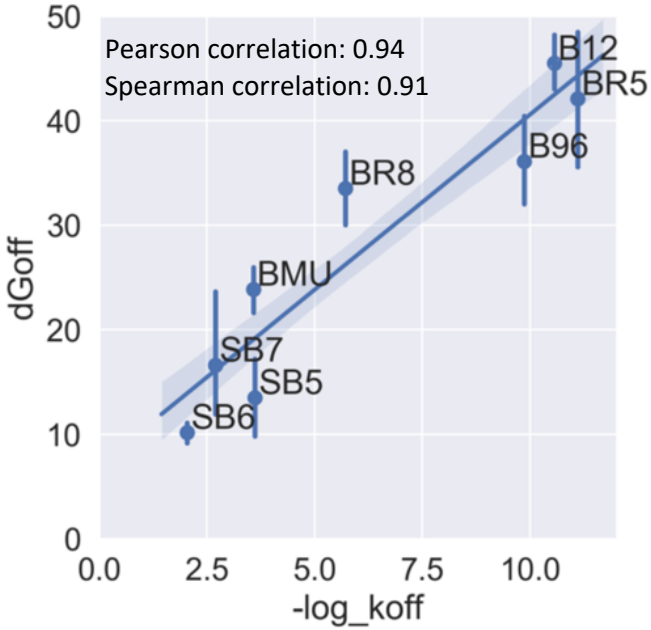
Method

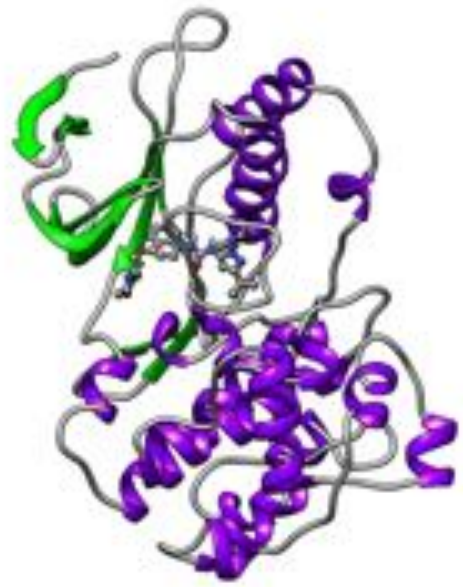
Targeted molecular dynamics (TMD)

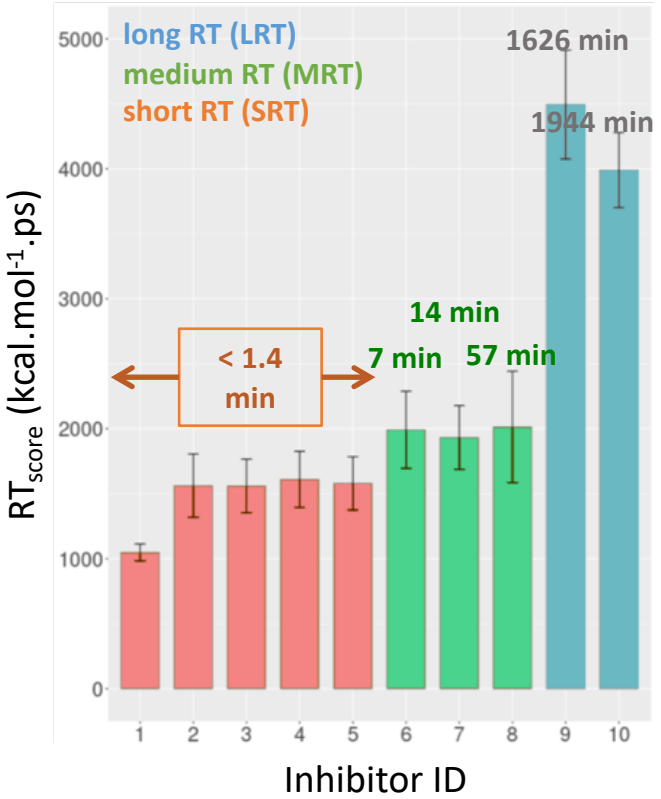
RT score evaluation

Sonia Ziada

$$RT = \frac{1}{k_{off}}$$







Previous work

Naïm Husain

M2 Internship

Development of Quantitative Structure-Kinetics Relationship (QSKR) models

Objective : Develop QSKR models to predict kinetics properties

Gather data from literature

Train an estimator

Obtain a predictive model

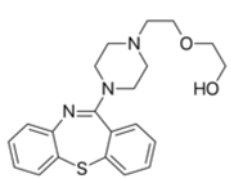
Previous work

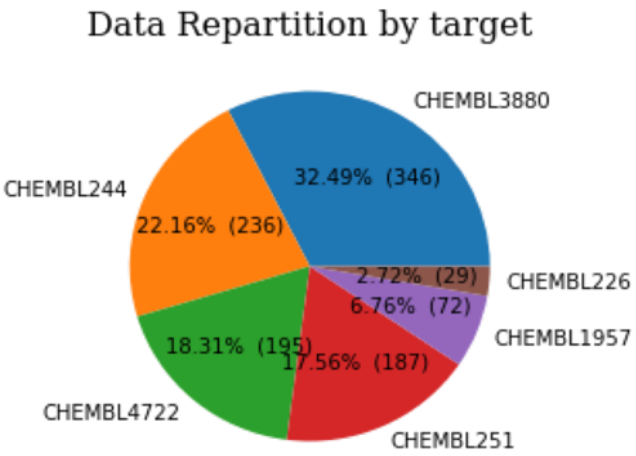
Naïm Husain

M2 Internship

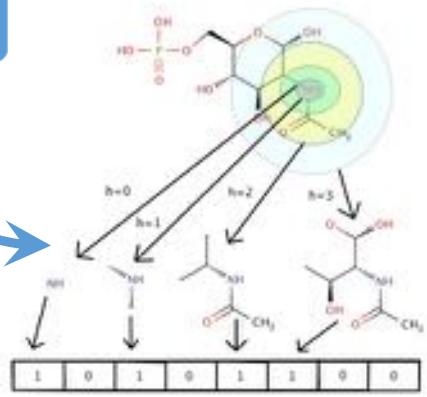
Datasets

ChEMBL





181 Molecular descriptors



1024 Circular fingerprints

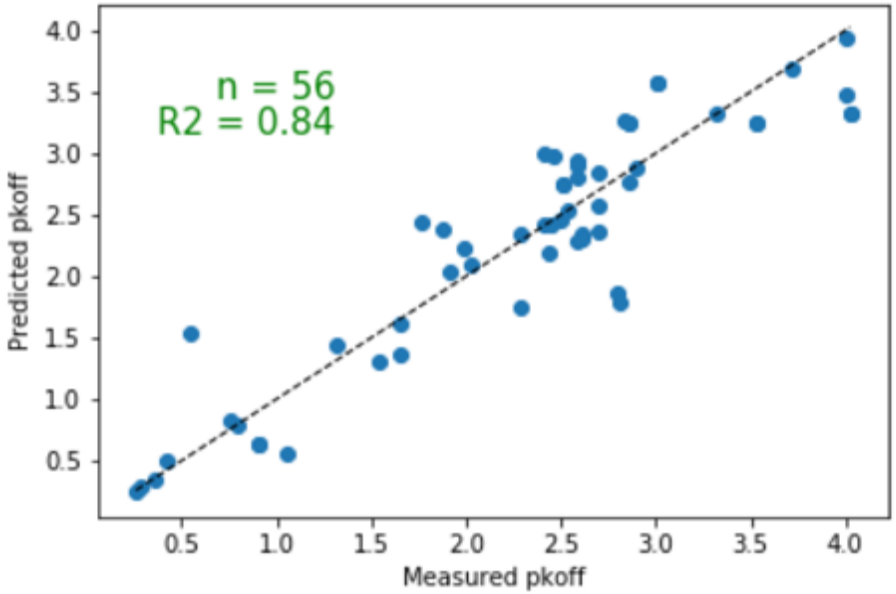
Previous work

Naïm Husain

M2 Internship

Some results

Regression model of k_{off} on HSP90-alpha



- partition coefficient (slogP)
- Number of rings
- Electrostatic interaction (peoe)
- Topological Polar Surface (Area TPSA)
- Molecular Quantum Numbers (MQN)
- Fraction CSP3
- Polarizability (SMR)

Application of the model to a test set

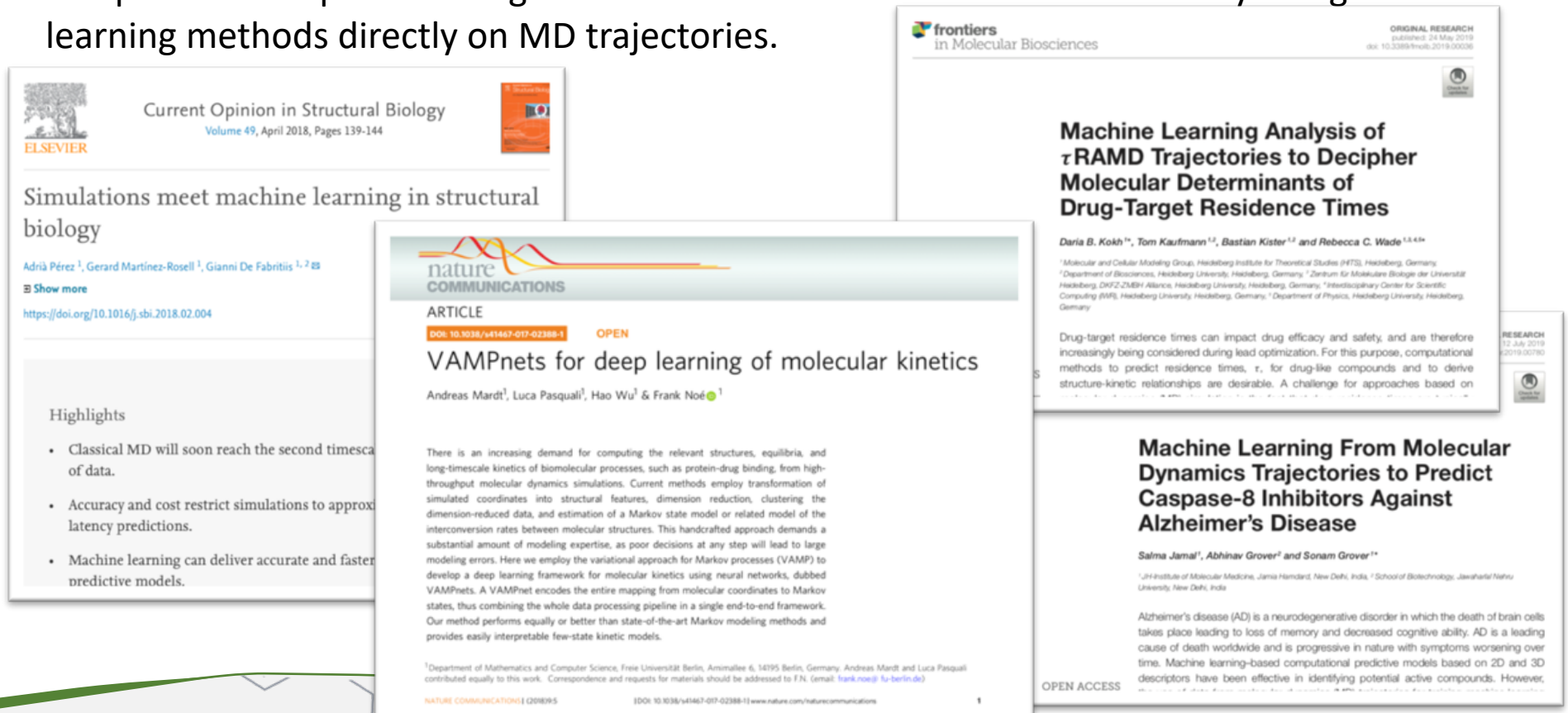
Features identification

KinetixPredict

in silico Prediction of binding kinetics by MD simulations and machine-learning

Objective

Develop an innovative and performing method to predict the binding kinetics of compounds and provide insight to the structural determinant involved by using machine learning methods directly on MD trajectories.



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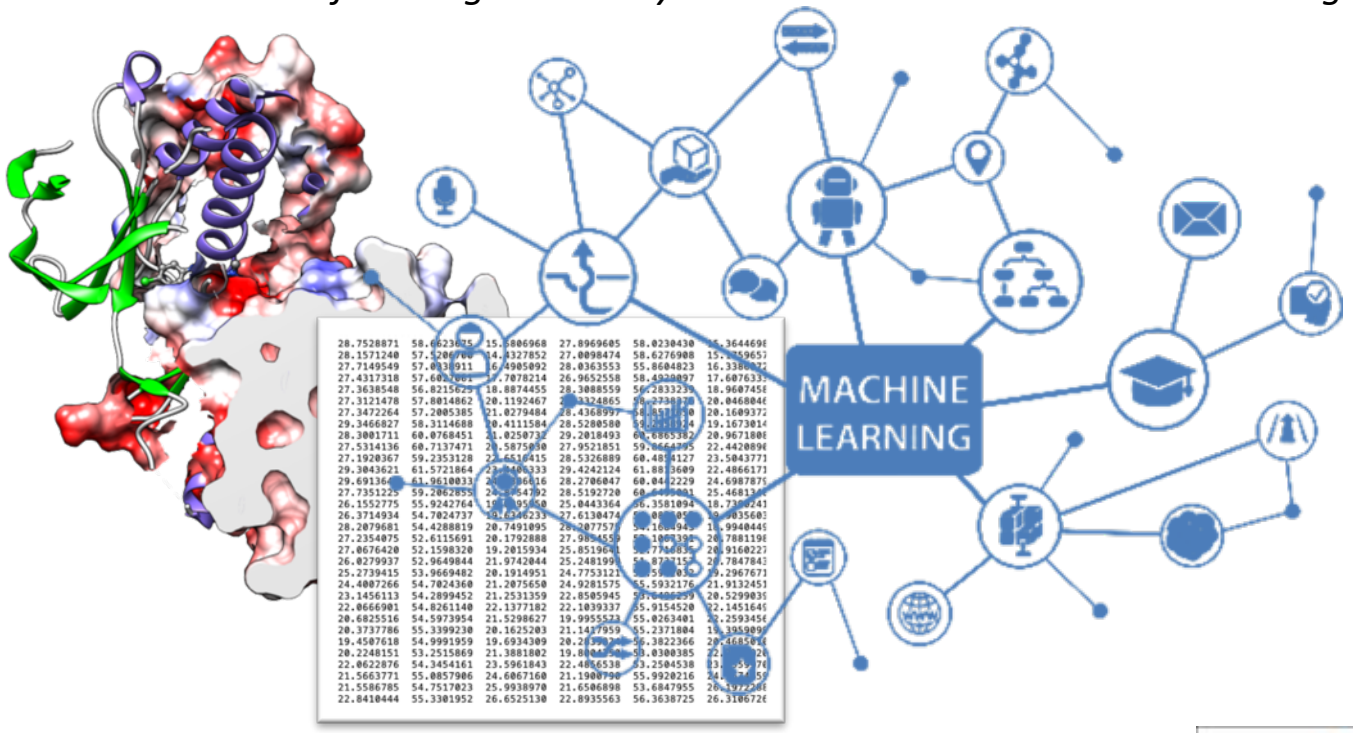

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