

KinetixPredict

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

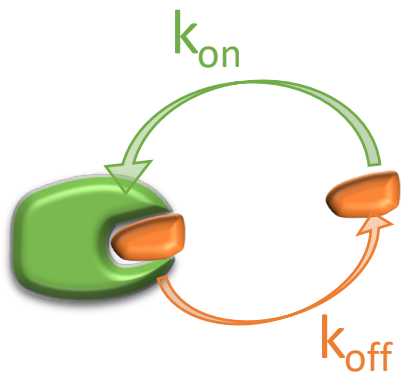


Samia Aci-Sèche
Structural Bioinformatic & Chemoinformatic team

Binding kinetics

Drug discovery

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

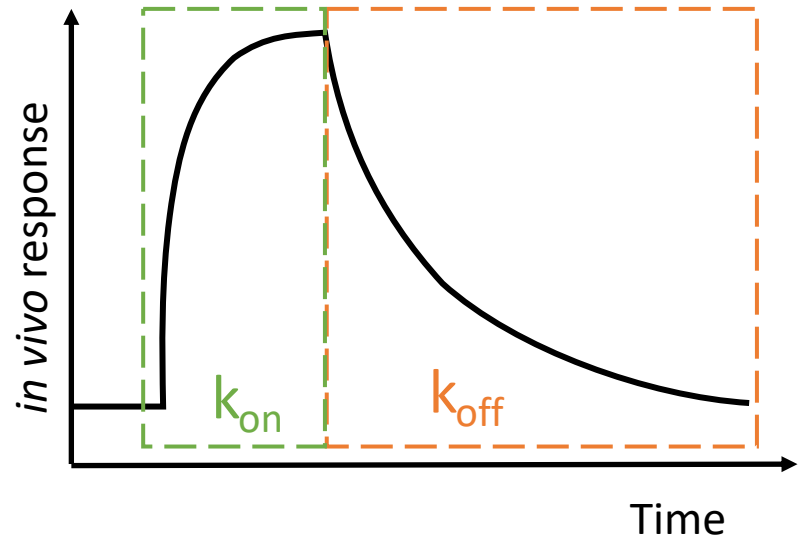


Clinical trials

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

Cinétique des inhibiteurs de protéines kinases et Affinité par Docking flexible



Abdenmour Braka

Kinetix4PKi project

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



Sonia Ziada



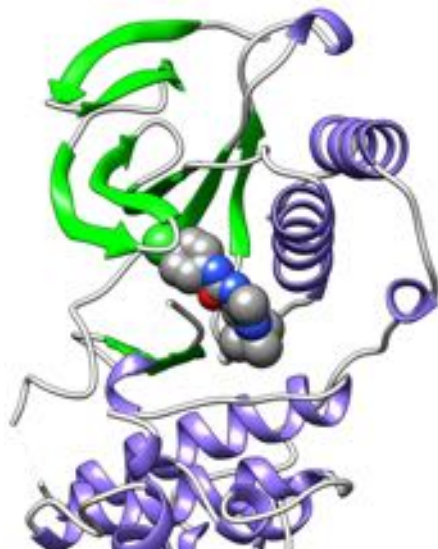
- 48 month project funded by ANR (09/2014 → 09/2018)
- Involved Modelers, Chemists (ICOA) and Biologists (CBM)



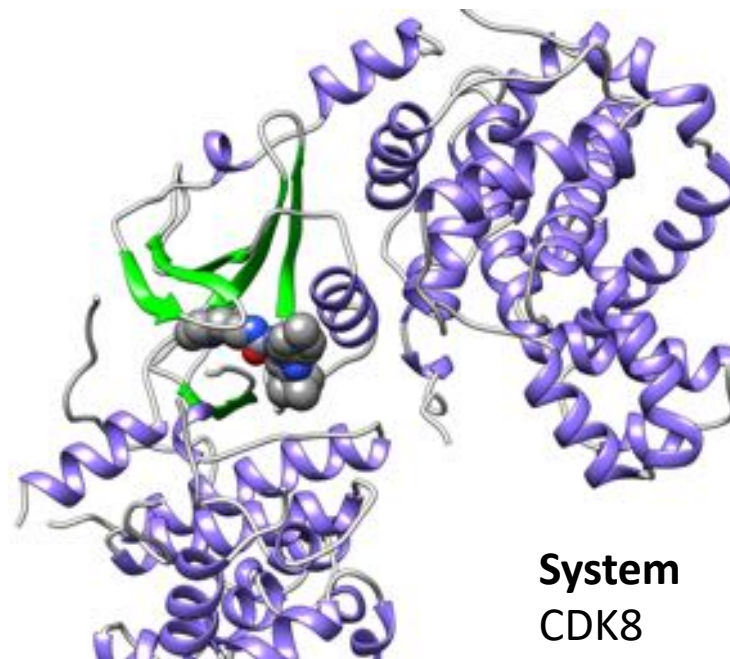
- Collaborative project with Servier Institute

- PhD student for modeling tasks

- PhD student for modeling tasks



System
p38 α MAPK



System
CDK8

Previous work

ANR JCJC 2013 ChADock

Dataset

long RT (LRT)

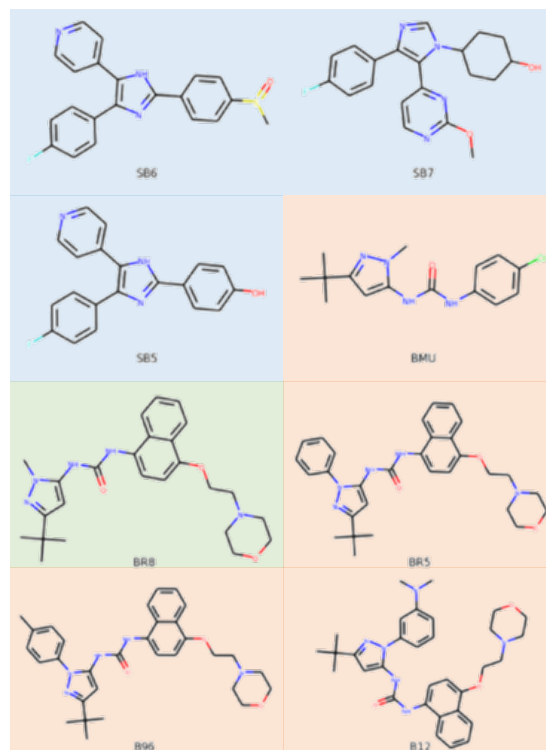
medium RT (MRT)

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 |



Abdenmour Braka

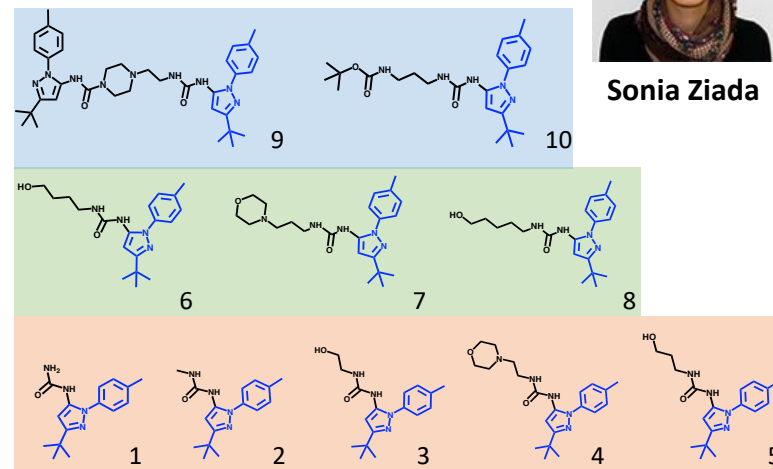


Kinetix4PKi project

Dataset



Sonia Ziada



| 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



Abdenmour Braka

Kinetix4PKi project

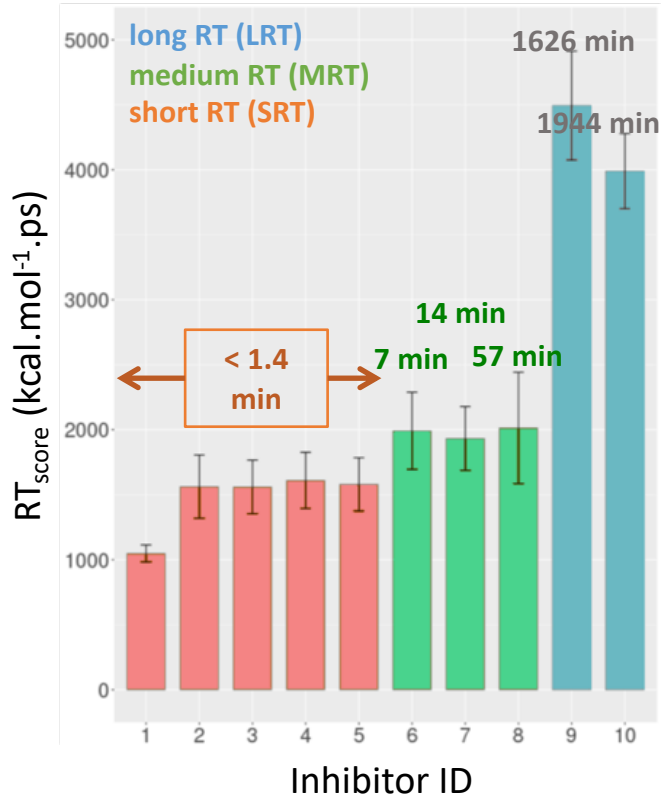
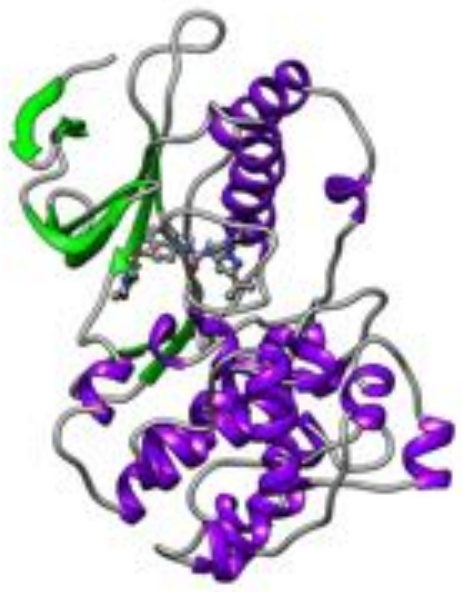
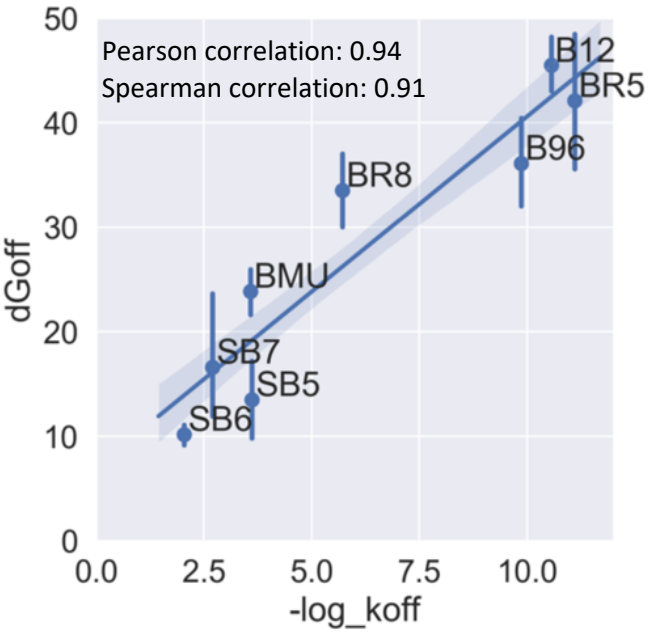
Method

Targeted molecular dynamics (TMD)
RT score evaluation



Sonia Ziada

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





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

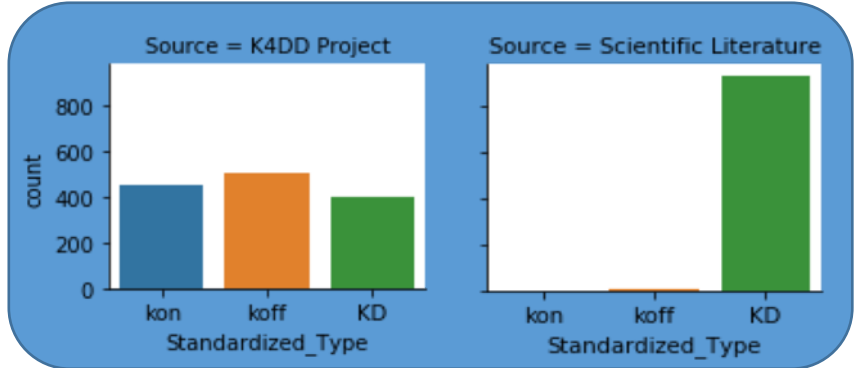
Previous work



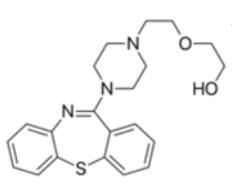
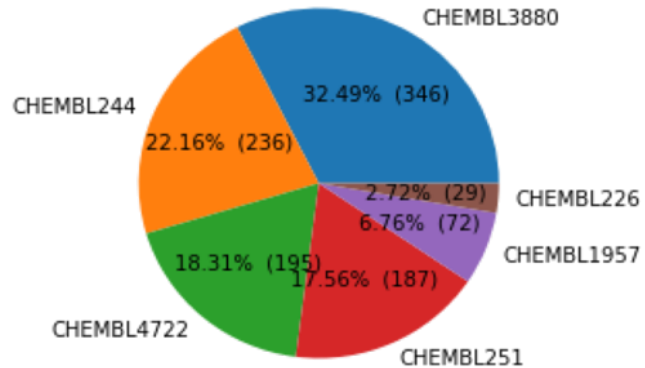
Naïm Husain

M2 Internship

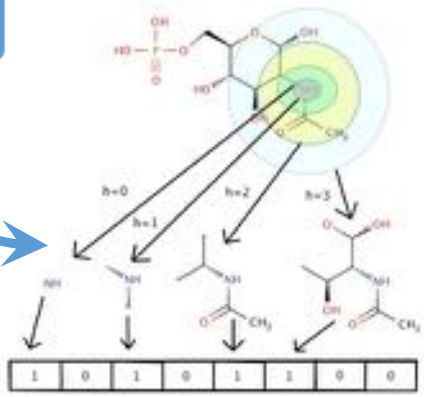
Datasets



Data Repartition by target



181 Molecular descriptors



1024 Circular fingerprints

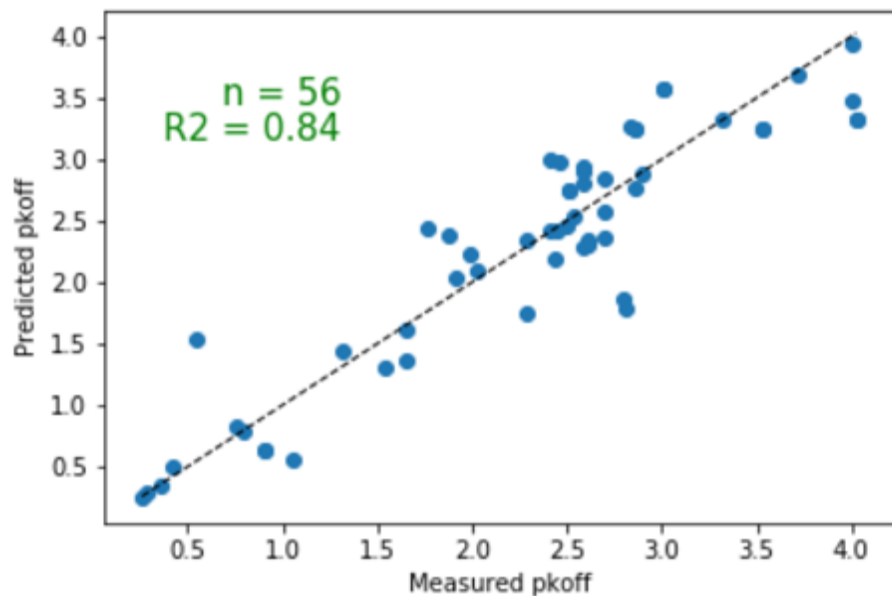


Naïm Husain

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

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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.

Current Opinion in Structural Biology
Volume 49, April 2018, Pages 139-144

ELSEVIER

Simulations meet machine learning in structural biology

Adrià Pérez¹, Gerard Martínez-Rosell¹, Gianni De Fabritius^{1, 2}

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<https://doi.org/10.1016/j.sbi.2018.02.004>

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-02388-1 OPEN

VAMPnets for deep learning of molecular kinetics

Andreas Mardt¹, Luca Pasquali¹, Hao Wu¹ & Frank Noé¹

There is an increasing demand for computing the relevant structures, equilibria, and long-timescale kinetics of biomolecular processes, such as protein-drug binding, from high-throughput molecular dynamics simulations. Current methods employ transformation of simulated coordinates into structural features, dimension reduction, clustering the dimension-reduced data, and estimation of a Markov state model or related model of the interconversion rates between molecular structures. This handcrafted approach demands a substantial amount of modeling expertise, as poor decisions at any step will lead to large modeling errors. Here we employ the variational approach for Markov processes (VAMP) to develop a deep learning framework for molecular kinetics using neural networks, dubbed VAMPnets. A VAMPnet encodes the entire mapping from molecular coordinates to Markov states, thus combining the whole data processing pipeline in a single end-to-end framework. Our method performs equally or better than state-of-the-art Markov modeling methods and provides easily interpretable few-state kinetic models.

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frontiers in Molecular Biosciences

ORIGINAL RESEARCH
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Machine Learning Analysis of τ RAMD Trajectories to Decipher Molecular Determinants of Drug-Target Residence Times

Daria B. Koth^{1*}, Tom Kaufmann^{1,2}, Bastian Kister^{1,2} and Rebecca C. Wade^{1,3,4,5*}

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Drug-target residence times can impact drug efficacy and safety, and are therefore increasingly being considered during lead optimization. For this purpose, computational methods to predict residence times, τ , for drug-like compounds and to derive structure-kinetic relationships are desirable. A challenge for approaches based on

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ORIGINAL RESEARCH
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Machine Learning From Molecular Dynamics Trajectories to Predict Caspase-8 Inhibitors Against Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disorder in which the death of brain cells takes place leading to loss of memory and decreased cognitive ability. AD is a leading cause of death worldwide and is progressive in nature with symptoms worsening over time. Machine learning-based computational predictive models based on 2D and 3D descriptors have been effective in identifying potential active compounds. However,

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

| | | | | | |
|------------|------------|------------|------------|------------|------------|
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