KSBi-BIML 2024

Bioinformatics & Machine Learning(BIML)
Workshop for Life and Medical Scientists

생명정보학 & 머신러닝 워크샵 (오프라인)

인공지능 신약개발
AI Drug Design

김동섭 _ KAIST

KSBI KOREAN SOCIETY FOR BIOINFORMATICS | 한국생명정보학회

본 강의 자료는 한국생명정보학회가 주관하는 BIML 2024 워크샵 오프라인 수업을 목적으로 제작된 것으로 해당 목적 이외의 다른 용도로 사용할 수 없음을 분명하게 알립니다.

이를 다른 사람과 공유하거나 복제, 배포, 전송할 수 없으며 만약 이러한 사항을 위반할 경우 발생하는 **모든 법적 책임은 전적으로 불법 행위자 본인에게 있음을 경고**합니다.

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안녕하십니까?

한국생명정보학회가 개최하는 동계 교육 워크샵인 BIML-2024에 여러분을 초대합니다. 생명정보학 분야의 연구자들에게 최신 동향의 데이터 분석기술을 이론과 실습을 겸비해 전달하고자 도입한 전문 교육 프로그램인 BIML 워크샵은 2015년에 시작하여 올해로 벌써 10년 차를 맞이하게 되었습니다. BIML 워크샵은 국내 생명정보학 분야의 최초이자 최고 수준의 교육프로그램으로 크게 인공지능과 생명정보분석 두 개의 분야로 구성되어 있습니다. 올해 인공지능 분야에서는 최근 생명정보 분석에서도 응용이 확대되고 있는 다양한 인공지능 기반 자료모델링 기법들에 대한 현장 강의가 진행될 예정이며, 관련하여 심층학습을 이용한 단백질구조예측, 유전체분석, 신약개발에 대한 이론과 실습 강의가 함께 제공될 예정입니다. 또한 단일세포오믹스, 공간오믹스, 메타오믹스, 그리고 롱리드염기서열 자료 분석에 대한 현장 강의는 많은 연구자의 연구 수월성 확보에 큰 도움을 줄 것으로 기대하고 있습니다.

올해 BIML의 가장 큰 변화는 최근 연구 수요가 급증하고 있는 의료정보자료 분석에 대한 현장 강의를 추가하였다는 것입니다. 특히 의료정보자료 분석을 많이 수행하시는 의과학자 및 의료정보 연구자들께서 본 강좌를 통해 많은 도움을 받으실 수 있기를 기대하고 있습니다. 또한 다양한 생명정보학 분야에 대한 온라인 강좌 프로그램도 점차 증가하고 있는 생명정보 분석기술의 다양화에 발맞추기 위해 작년과 비교해 5강좌 이상을 신규로 추가했습니다. 올해는 무료 강좌 5개를 포함하여 35개 이상의 온라인 강좌가 개설되어 제공되며, 연구 주제에 따른 연관된 강좌 추천 및 강연료 할인 프로그램도 제공되며, 온라인을 통한 Q&A 세션도 마련될 예정입니다. BIML-2024는 국내 주요 연구 중심 대학의 전임 교원이자 각 분야 최고 전문가들의 강의로 구성되었기에 해당 분야의 기초부터 최신 연구 동향까지 포함하는 수준 높은 내용의 강의가 될 것이라 확신합니다.

BIML-2024을 준비하기까지 너무나 많은 수고를 해주신 운영위원회의 정성원, 우현구, 백대현, 김태민, 김준일, 김상우, 장혜식, 박종은 교수님과 KOBIC 이병욱 박사님께 커다란 감사를 드립니다. 마지막으로 부족한 시간에도 불구하고 강의 부탁을 흔쾌히 허락하시고 훌륭한 현장 강의와 온라인 강의를 준비하시는데 노고를 아끼지 않으신 모든 강사분들께 깊은 감사를 드립니다.

2024년 2월

한국생명정보학회장 이 인 석

강의 시간표

DAY1 : 2월 24일 (토)

시간	강 의 (자연과학대학 28동 101호)
12:30-12:50	등록
12:50-13:00	공지사항 전달
13:00-14:30	**의료빅데이터/인공지능 총론** 김헌성 교수(가톨릭대학교)
14:30-14:45	휴식
14:45-16:15	**의료영상 인공지능의 이해 및 의료영상 레이블링 실습** 백서연 교수(연석대학교)
16:15-16:30	휴식
16:30-18:00	**의료 정보처리 자동화 실습 / 독자적인 어플리케이션 만들기** 김선근 대표(원닥 주식회사), 서사도 조교

시간	강 의 (자연과학대학 28동 102호)
12:30-12:50	등록
12:50-13:00	공지사항 전달
13:00-14:20	**EMR 데이터를 활용한 머신러닝 기반 예후예측:** **Decision Tree-based Models + EMR 샘플 데이터 실습 (MIMIC sample dataset)** 고태훈 교수(가톨릭대학교)
14:20-14:40	휴식
14:40-16:00	**Chest X-ray 영상을 활용한 딥러닝 기반 폐질환 진단:** **Convolutional Neural Network + 의료영상 샘플 데이터 실습 (NIH Chest X-ray14)** 고태훈 교수(가톨릭대학교)
16:00-16:20	휴식
16:20-17:40	**심전도 데이터를 활용한 딥러닝 기반 부정맥 탐지: Recurrent Neural Network + Transformer + 심전도 샘플 데이터 실습 (MIT-BIH Arrhythmia Database)** 고태훈 교수(가톨릭대학교)

DAY1 : 2월 26일 (월)

시간	강 의 (자연과학대학 28동 101호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-10:50	**DNN (이론)** 이상근 교수(고려대학교)
10:50-11:00	휴식
11:00-12:10	**CNN (이론)** 이상근 교수(고려대학교)
12:10-13:40	점심
13:40-15:10	**RNN, ChatGPT, XAI (이론)** 이상근 교수(고려대학교)
15:10-15:20	휴식
15:20-16:50	**CNN/RNN 모델 구조 정의, 학습 알고리즘 적용, 성능 평가, 시각화 방법 (Tensorflow 실습)** 이정현 조교, 한성민 조교

시간	강 의 (자연과학대학 28동 102호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-11:00	**Best practice for single-cell data analysis** 박종은 교수(KAIST)
11:00-11:10	휴식
11:10-12:40	**Practice1: Scanpy basic workflow** 정성민 조교, 고용준 조교
12:40-14:10	점심
14:10-15:30	**Public database, data integration, reference mapping, multiomics** 박종은 교수(KAIST)
15:30-15:40	휴식
15:40-16:50	**Practice2: Advanced single-cell analysis (siVI universe)** 정성민 조교, 고용준 조교

DAY1 : 2월 27일 (화)

시간	강 의 (자연과학대학 28동 101호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-10:50	**AI-based protein structure prediction** **- Intro to protein structure prediction** **- Early AI-based approaches** **- AlphaFold and RoseTTAFold** 백민경 교수(서울대학교)
10:50-11:00	휴식
11:00-12:10	**단백질 구조 예측 실습** **- ColabFold를 활용한 단백질 구조 및 상호작용 예측** **- Tips &Tricks for better structure modeling** 백민경 교수(서울대학교)
12:10-13:40	점심
13:40-15:10	**AI-based protein design** **- Intro to protein design** **- Protein backbone design using RFdiffusion** **- Protein sequence design using ProteinMPNN** 백민경 교수(서울대학교)
15:10-15:20	휴식
15:20-16:50	**단백질 디자인 실습** **- RFdiffusion 및 ProteinMPNN의 활용법 실습** 백민경 교수(서울대학교)

시간	강 의 (자연과학대학 28동 102호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-11:00	**Introduction to Single-cell biology** 최정민 교수(고려대학교)
11:00-11:10	휴식
11:10-12:40	**i. Unsupervised Spatial transcriptome analysis** **ii. Tumor Boundary Determination in Spatial Transcriptomics** 유광민 조교, 이문영 조교
12:40-14:10	점심
14:10-15:30	**i. Deconvolution Analysis Using Single-cell RNA Sequencing and Spatial Transcriptomics** **ii. Cell-Cell Interaction Analysis in Spatial Transcriptomics** 김지현 조교, 최승지 조교
15:30-15:40	휴식
15:40-16:50	**i. Open Chromatin Region Analysis and Biological Interpretation of Using scATAC-seq Dataset** **ii. Construction of Gene Regulatory Networks Based on Integrated Analysis of scATAC-seq and scRNA-seq Datasets** 천하림 조교, 이호진 조교

DAY1 : 2월 28일 (수)

시간	강 의 (자연과학대학 28동 101호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-11:00	**Introduction to Transformers (이론)** 전민지 교수 (고려대학교)
11:00-11:10	휴식
11:10-12:40	**Introduction to Transformers (실습)** 봉현수 조교, 임우택 조교
12:40-14:10	점심
14:10-15:40	**Deep learning in Bioinformatics** 노미나 교수(한양대학교)
15:40-15:50	휴식
15:50-17:20	**Deep learning model을 이용한 실습** 박예솔 조교

시간	강 의 (자연과학대학 28동 102호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-10:50	**마이크로바이옴 기본 이론** 이선재 교수(GIST)
10:50-11:00	휴식
11:00-12:10	**16S rRNA amplicon seq. - DADA2** 조준우 조교, 백재우 조교
12:10-13:40	점심
13:40-14:40	**최신 메타지놈 분석 기법의 현황** 이선재 교수(GIST)
14:40-14:50	휴식
14:50-16:50	**Shotgun metagenome 분석 (Linux)** 조준우 조교, 백재우 조교

DAY1 : 2월 29일 (목)

시간	강 의 (자연과학대학 28동 101호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-10:50	**화학정보학 기초(Cheminformatics) / 약물특성 및 약물다움(druglikeness)** **Molecular Notations &Descriptors / AI 신약개발을 위한 Databases** **AI 신약개발을 위한 Programming 기초** 김동섭 교수(KAIST)
10:50-11:00	휴식
11:00-12:10	**Google Colab에 RDKit 설치 / 화합물 정보 읽기 실습** **Bioactivity database 검색 및 정보 읽기 실습** **Molecular descriptor (fingerprint) 생성 및 similarity 계산 실습** 정수재 조교, 나민주 조교
12:10-13:40	점심
13:40-15:10	**AI 신약개발을 위한 기계학습법 기초 / QSAR 모델링 기초 / AI 신약개발을 위한 딥러닝 모델** **Virtual screening (ligand-based, structure-based) 및 de novo design** 김동섭 교수(KAIST)
15:10-15:20	휴식
15:20-16:50	**QSAR modeling 전체 과정 실습/ 화합물의 Bioactivity 예측 모델 개발** **Virtual screening 과정을 통한 신약후보물질 발굴 실습** 정수재 조교, 나민주 조교

시간	강 의 (자연과학대학 28동 102호)
09:00-09:20	등록
09:20-09:30	공지사항 전달
09:30-11:00	**Single cell multiomics 이론 / Gene regulatory network 이론** 김준일 교수(숭실대학교)
11:00-11:10	휴식
11:10-12:40	**Seurat/Signac, ArchR, TENET+ 실습** 김현규 조교, 정회빈 조교
12:40-14:10	점심
14:10-15:40	**롱리드 시퀀싱 소개 및 유전체 조립 실습** 김준 교수(충남대학교)
15:40-15:50	휴식
15:50-17:20	**변이 분석 및 시각화 실습** 김준 교수(충남대학교)

강의개요

인공지능 신약개발
AI Drug Design

신약개발에 소요되는 시간과 비용이 급속도로 증대됨에도 불구하고 신약 개발의 성공 사례는 그에 반해 날로 감소하고 있다. 이를 극복하기 위한 노력의 일환으로 다양한 종류의 인공지능 (AI) 신약개발 모델이 개발되고 있으며, 이 모델들을 활용하여 신약개발의 효율을 획기적으로 증대하고자 하는 노력들이 계속되고 있다. 이 강의에서는 이 과정에 필수적인 기초 지식인 화학정보학 (Cheminformatics) 및 기초 프로그래밍(RDKit)에 대해서 학습한 후, 인공지능 분야에서 널리 사용되는 다양한 모델들을 이용하여 신약개발에 사용되는 다양한 예측 모델 개발 방법에 대해 실습한다. 특히, 최근 그 중요성이 대두되고 있는 Deep learning 기술을 이용한 AI 신약개발 모델 개발에 대해 학습한다.

강의는 다음의 내용을 포함한다:

- 화학정보학 기초 (Introduction to cheminformatics)
- AI 신약개발을 위한 Databases
- AI 신약개발을 위한 Programming (RDKit)
- AI 신약개발을 위한 기계학습법 및 QSAR 모델링 기초
- AI 신약개발을 위한 딥러닝 모델

* 참고 강의교재: 강의자료

* 교육생 준비물: 노트북

* 선수 지식: 기초 수준의 python programming

* 강의 난이도: 초급

* 강의: 김동섭 교수 (카이스트 바이오및뇌공학과)

Curriculum Vitae

Speaker Name: Dongsup Kim, Ph.D.

▶ Personal Info

Name	Dongsup Kim
Title	Professor
Affiliation	KAIST

▶ Contact Information

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Research Interest

Structural bioinformatics and computational drug development

Educational Experience

1989	B.S., Seoul National University
1991	M.S., Seoul National University
1998	Ph.D., Brown University, USA

Professional Experience

1998-2000	Post-doc research fellow, University of Pennsylvania
2001-2002	Post-doc research fellow, Oak Ridge National Lab
2003-	Professor, Department of Bio and Brain Engineering, KAIST

Selected Publications (5 maximum)

1. D. Yang, T. Chung, D. Kim, "DeepLUCIA: predicting tissue-specific chromatin loops using Deep Learning-based Universal Chromatin Interaction Annotator", Bioinformatics, 38:3501-3512 (2022)
2. H.Y. Kim, W. Jeon, D. Kim, "An enhanced variant effect predictor based on a deep generative model and the Born-Again Networks", Scientific Reports, 19127(2021)
3. H. Kim, D. Kim, "Prediction of mutation effects using a deep temporal convolutional network", Bioinformatics, 36:2047-2052 (2020)
4. A. Lee, D. Kim, "CRDS: Consensus Reverse Docking System for target fishing", Bioinformatics, 36:959-960 (2020)
5. W. Jeon, D. Kim, "FP2VEC: a new molecular featurizer for learning molecular properties", Bioinformatics, 35:4979-4985 (2019)

KSBi-BIML 2024

인공지능 신약설계

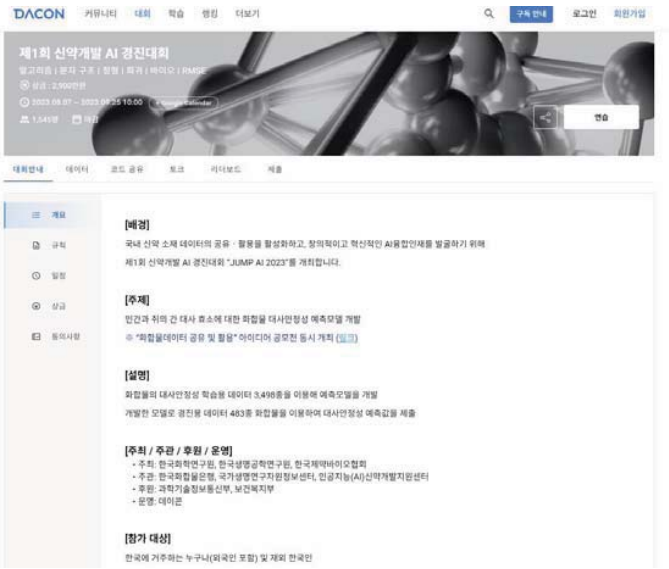
AI Drug Design

Google Classroom

- BiML: AI 신약개발
- https://classroom.google.com/u/0/c/NjYxMDE1NTMyMTI0
- 강의자료 및 실습용 코드 다운로드를 위해 모두 가입!

After this lecture, you can win

- https://dacon.io/competitions/official/236127/overview/description



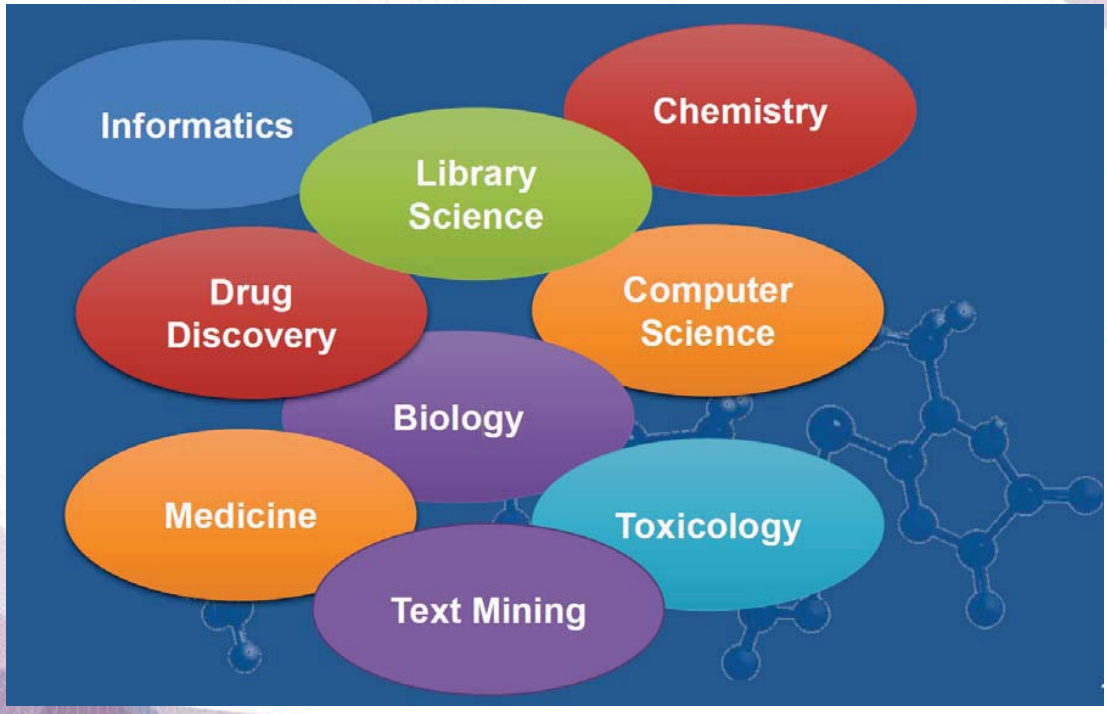
개요

- 강의
  - 화학정보학 기초(Cheminformatics)
  - 약물특성 및 약물다움(druglikeness)
  - Molecular Notations & Descriptors
  - AI 신약개발을 위한 Databases
  - AI 신약개발을 위한 Programming 기초
- 실습
  - Google Colab에 RDKit 설치
  - RDKit 실습: 화합물 정보 읽기 등
  - Bioactivity database 검색 및 정보 읽기 실습
  - Molecular descriptor (fingerprint) 생성 및 similarity 계산 실습

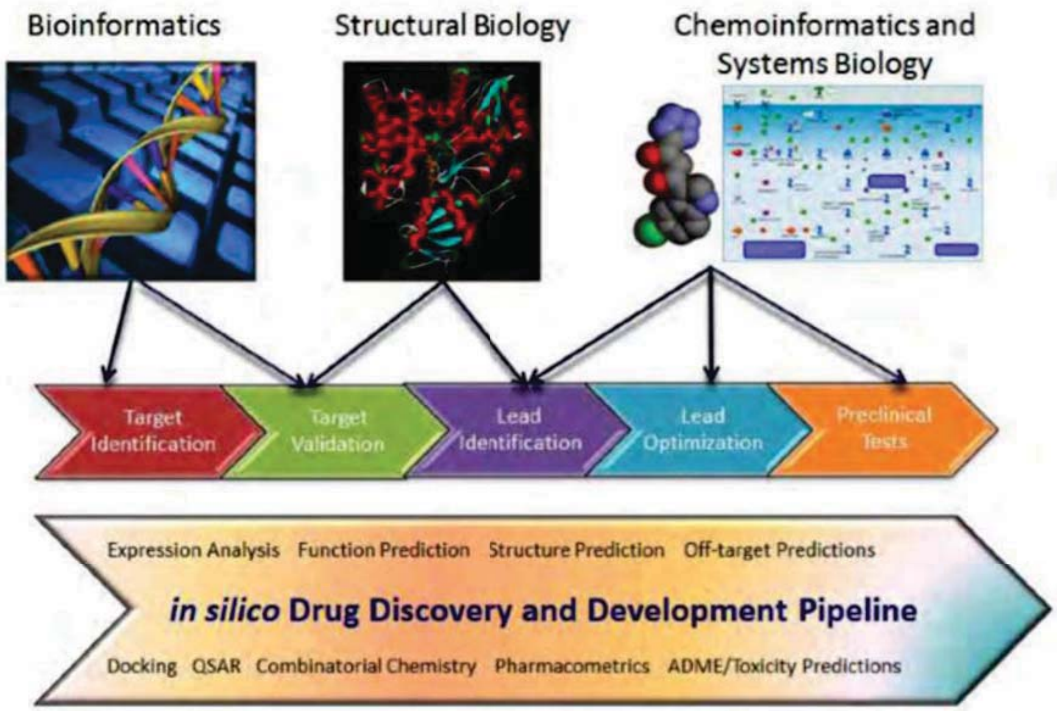
화학정보학이란

- Field of **information technology** that uses computers and computer programs to facilitate the collection, storage, analysis, and manipulation of large quantities of **chemical data**
- 여러 이름
  - Cheminformatics
  - Chemoinformatics
  - Chemical informatics
- Bioinformatics vs. Chemiformaics
  - Biological data: Bioinformatics
  - Chemical data: Cheminformatics
- 응용분야: 신약개발, 독성학, …

Interdisciplinary

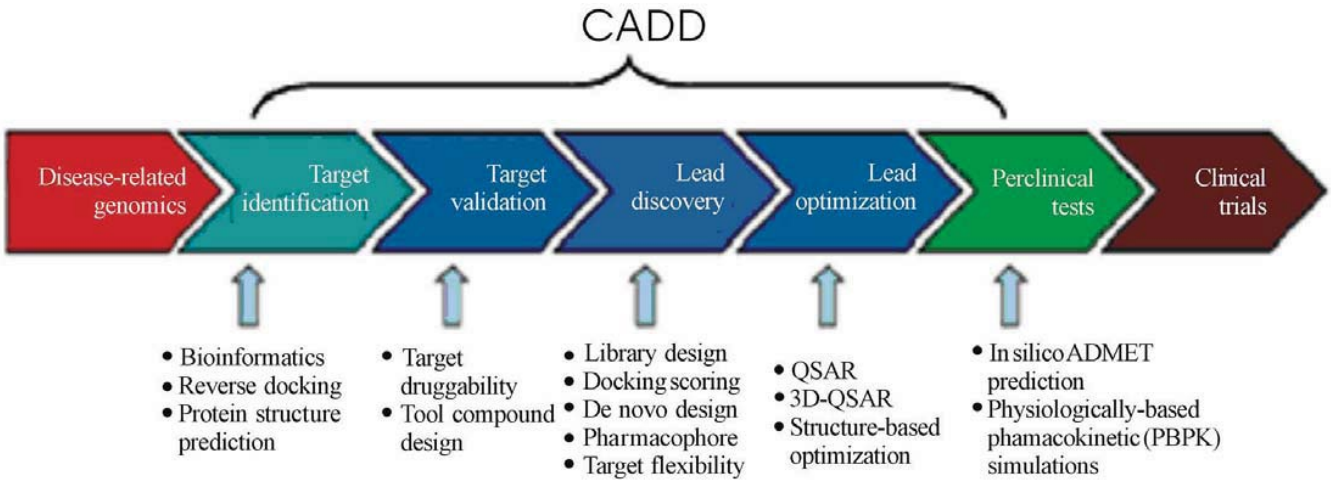


바이오정보학 vs 화학정보학



신약개발과 화학정보학

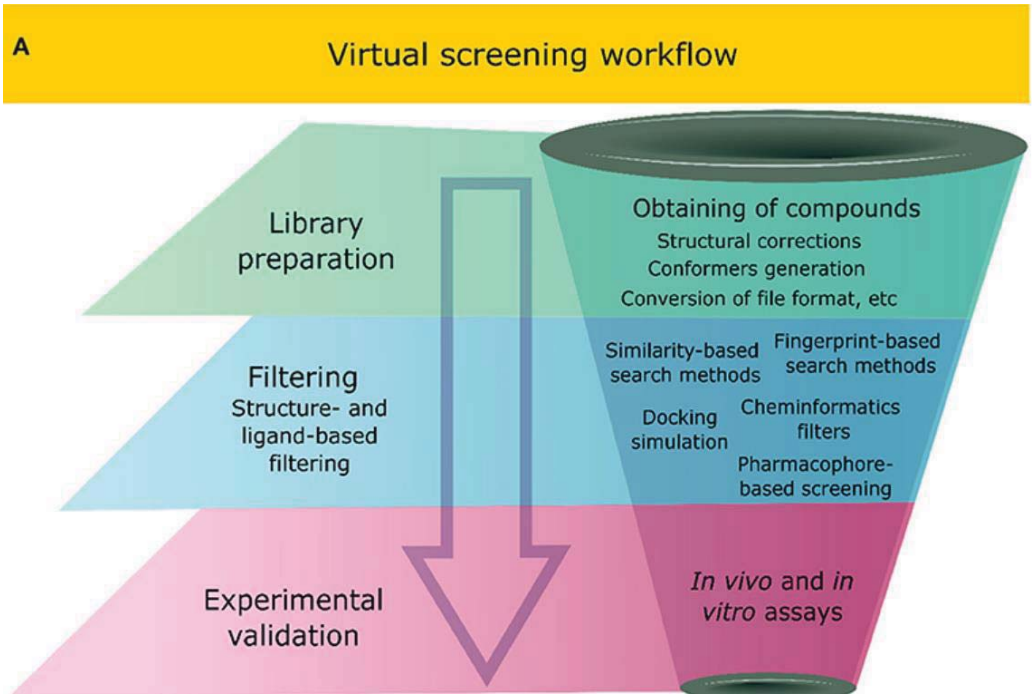
- Computer-Aided Drug Design (CADD)



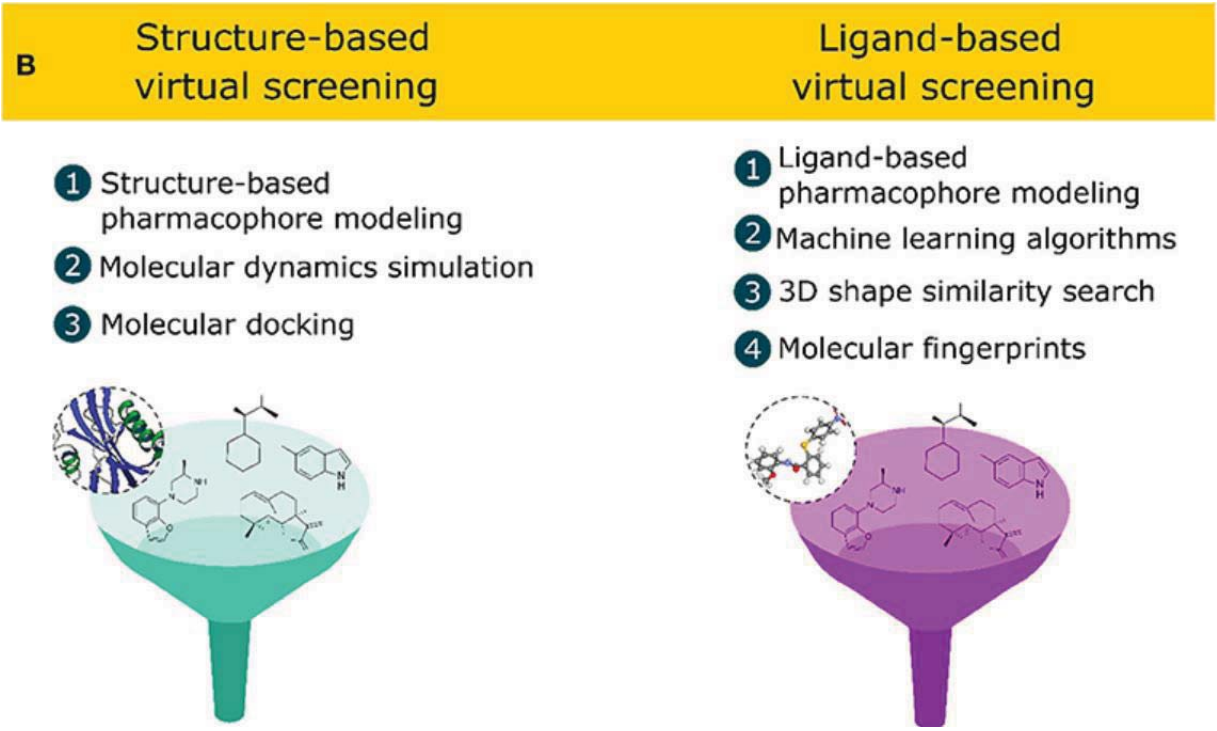
Lead Discovery & Optimization

- Compound library design
- Virtual screening
- Docking
- Pharmacophore modeling
- QSAR (Quantitative Structure Activity Relationship)
- De novo design

가상 스크리닝



방법



Molecular structures

- Linear notation
  - SMILES
  - InChI, InChIKey
- Connection table method
  - Molfile
  - SDF
  - MOL2

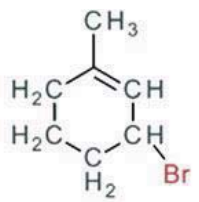
https://www.ebi.ac.uk/chembldb/compound/inspect/CHEMBL413
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5284616&loc=ec_rcs

Linear Notation

- Line notations represent structures as a linear string of alphanumeric symbols.
- Their compactness was an advantage in the early days of cheminformatics when storage space was at a premium.
- Even nowadays, it can be faster to enter a structure as a notation instead of using a chemical structure drawing program.

SMILES

- Simplified Molecular Input Line Entry System
- A given chemical structure can have many valid and unambiguous representations (e.g., it is possible to start with any atom to derive a SMILES string).
- But for comparison purposes it is desirable to have a unique representation known as the 'canonical' one.
  - Morgan algorithm: iterative calculation of connectivity value of each atom
- http://www.daylight.com/dayhtml/doc/theory/theory.smiles.html



CC1=CC(Br)CCC1

Atoms

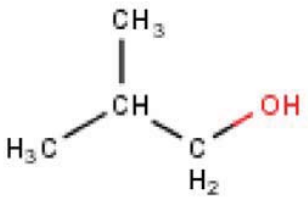
- Represented by their atomic symbols: C, N, O, and P
- The second letter of two-character atomic symbols must be in lower case: Cl (not CL), Br (not BR)
- Each non-hydrogen atom is enclosed in square brackets: [Au] or [Fe]
- Square brackets can be omitted for elements in the organic subset (B, C, N, O, P, S, F, Cl, Br, and I), if the proper number of "implicit" hydrogen atoms is assumed: BH_3 → B, CH_4 → C, NH_3 → N, H_2O → O

Bonds

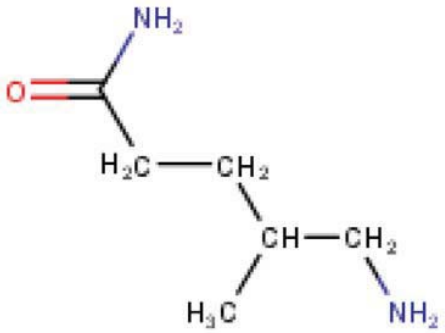
- Single bond → "-" (can be omitted)
- Double bond → "="
- Triple bond → "#"
- Aromatic bond → ":" (can be omitted)
- Examples
  - CH_4 → C
  - CH_3-CH_3 → CC (or C-C)
  - CH_2=CH_2 → C=C
  - CH ≡ CH → C#C
  - CH_3OCH_3 → COC
  - CH_3CH_2OH → CCO
  - CH_3CH=O → CC=O
  - HC≡N → C#N

Branches

- Specified by enclosures in parentheses
- Can be nested or stacked



CC(C)CO

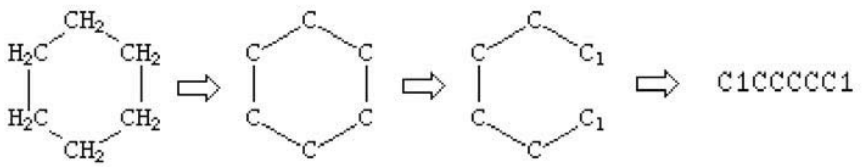


CC(CCC(=O)N)CN

Rings

- Represented by breaking one single or aromatic bond in each ring, designating this ring-closure point with a digit

Cyclohexane

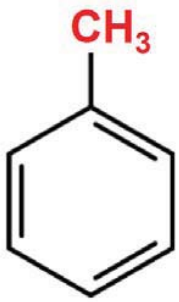


Benzene → C1=C-C=C-C=C1 OR c1ccccc1

<u>Note: Lower-case letters represent aromaticity.</u>

Canonical SMILES

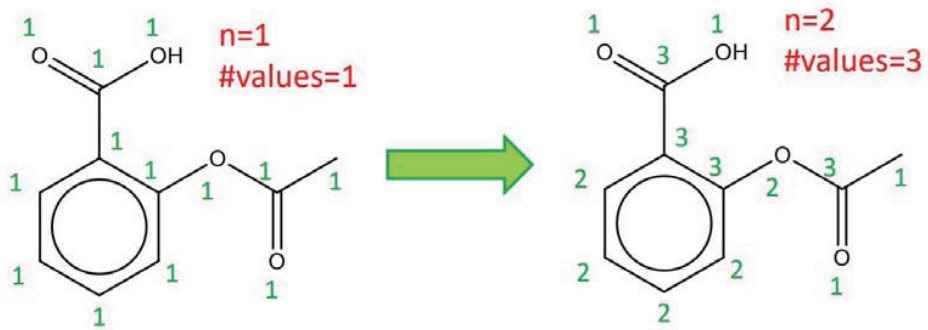
- Multiple SMILES representations exist for a given molecule.
- One “canonical” SMILES is selected among them: Morgan algorithm



Cc1ccccc1
c1(C)ccccc1
c1c(C)cccc1
c1cc(C)ccc1
c1ccc(C)cc1
c1cccc(C)c1
c1ccccc1C

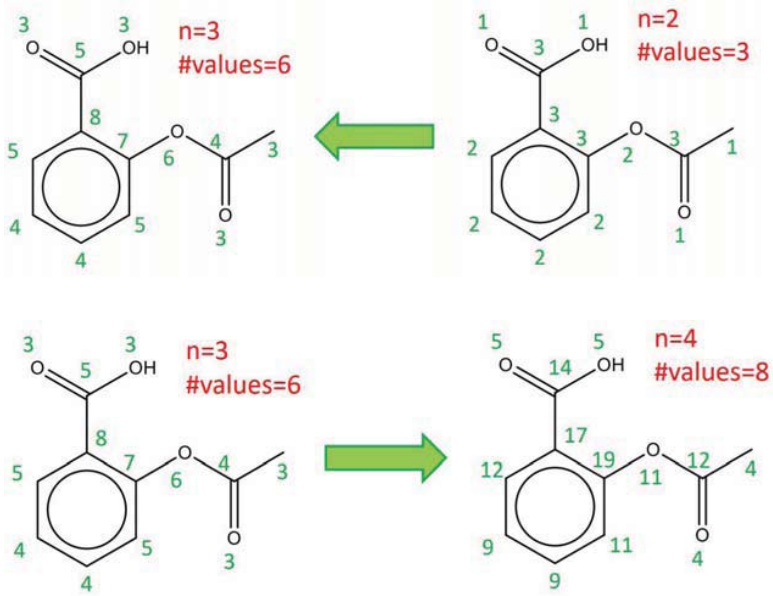
Morgan Algorithm

1. Assign initial invariant of 1
2. New invariant: Sum of neighboring values
3. Determine number of values



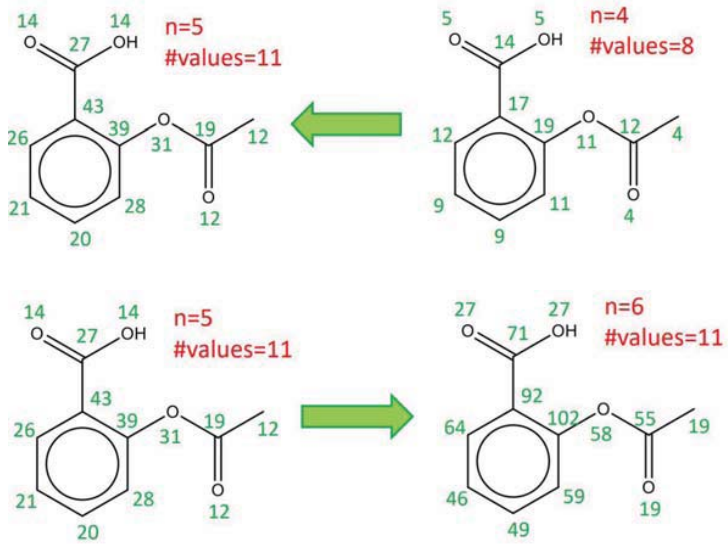
Morgan Algorithm

- Repeat summing of neighboring values



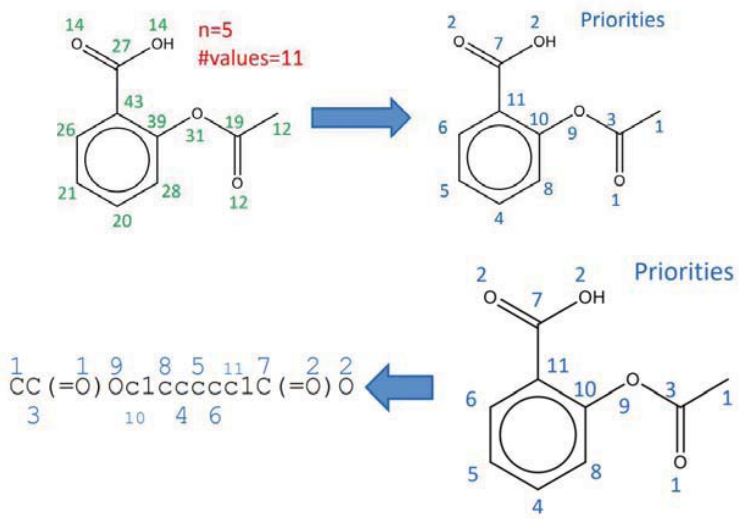
Morgan Algorithm

- Repeat summing of neighboring values
- Until number of values does not increase anymore



Morgan Algorithm

- Assign priorities according to invariants
- Disambiguate ties by atom type and bond order
- Construct Smiles according to invariants



Isomeric SMILES

- Isotope: the integral atomic mass preceding the atomic symbol: $^{13}CH_4$ → [13CH4]
- Stereochemistry
  - Atom stereo centers [(R/S)-configurations for a chiral center]
    - C[C@@H](C(=O)O)N L-Alanine
    - C[C@H](C(=O)O)N D-Alanine
  - Bond stereo centers [cis/trans-isomerism]
    - F/C=C/F or F\C=C\F (E)-1,2-difluoroethene (trans isomer)
    - F/C=C\F or F\C=C/F (Z)-1,2-difluoroethene (cis isomer)

Limitation of SMILES

- Most SMILES encoders/decoders are proprietary.
  - Different groups implemented (slightly) different SMILES generation algorithms.
  - Not interchangeable between databases (or research groups) unless the same software is used.
- Doesn't have 2d and 3d coordinates retained, so need to changes to other formats like MOL, SDF, etc.
- Multiple smiles for one compound

InCHI

- International Chemical Identifier
- The goal of InChI is to provide a unique string representing a chemical substance of known structure.
- InChI is freely available and extensible.

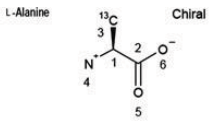
InChI = 1S/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3
InChIKey = RYYVLZVUVIJVGH-UHFFFAOYSA-N

InChIKey

- The length of an InChI string increases with the size of the corresponding chemical structure.
- Not appropriate to use in internet search engines.
  - These search engines do not care case sensitivity nor special characters used in InChI.
- InChIKey was introduced for internet and database searching/indexing.
- A 27-character string derived from InChI, using a hashing algorithm.

Connection Tables

- The MDL (now Symyx) connection table or CTfile, has become the *de facto* standard for exchange of datasets.
- It separates atoms and bonds into separate blocks.
- A molecule file, or ‘molfile,’ describes a single molecular structure that can contain disjoint fragments.
- A molfile consists of a header block and a connection table.
- Structure–data files (SDFiles) contain structures and data for any number of molecules.




```
  6  5  0  0  1  0              3 V2000
   -0.6622    0.5342    0.0000 C   0  0  2  0  0  0
    0.6622   -0.3000    0.0000 C   0  0  0  0  0  0
   -0.7207    2.0817    0.0000 C   1  0  0  0  0  0
   -1.8622   -0.3695    0.0000 N   0  3  0  0  0  0
    0.6220   -1.8037    0.0000 O   0  0  0  0  0  0
    1.9464    0.4244    0.0000 O   0  5  0  0  0  0
  1  2  1  0  0  0
  1  3  1  1  0  0
  1  4  1  0  0  0
  2  5  2  0  0  0
  2  6  1  0  0  0
M  CHG  2   4   1   6  -1
M  ISO  1   3  13
M  END
```

Counts line

Atom block

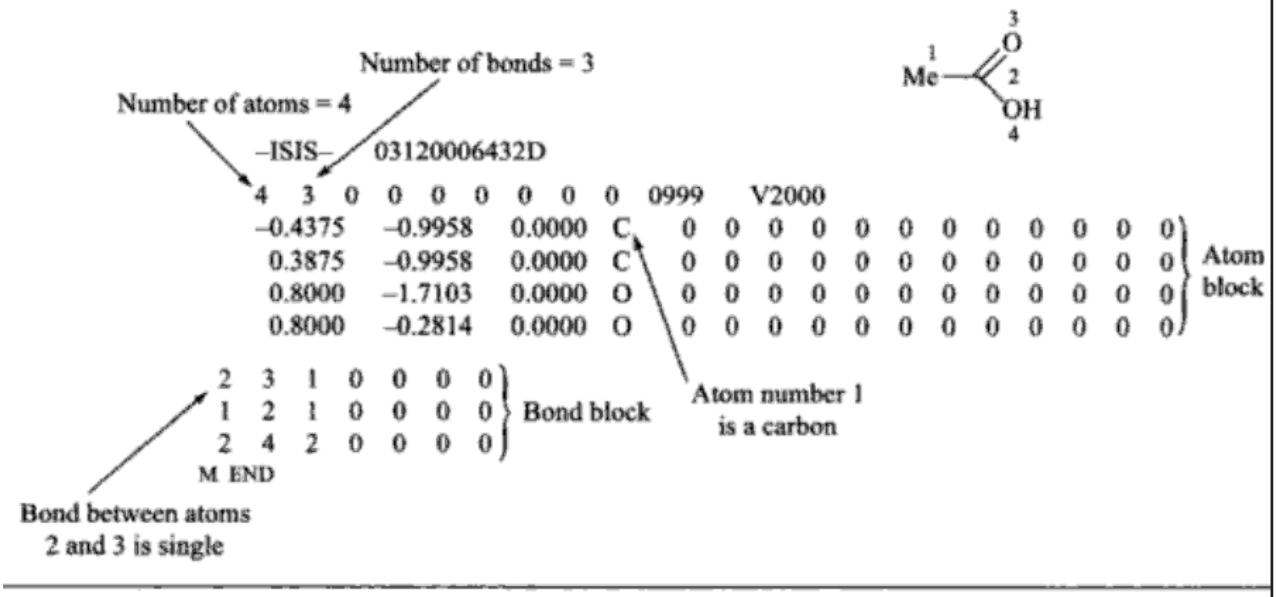
Bond block

Blocks not used in this Ctab: Atom list, Stext

Properties block

Connection Table (Ctab)

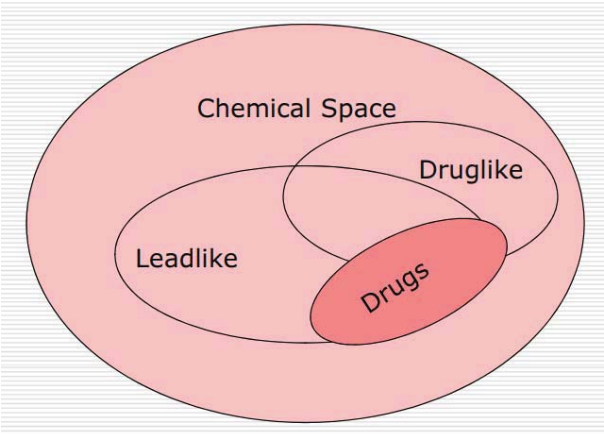
Mol file



12.3: *MDL mol file for acetic acid, in the hydrogen-suppressed form.*

Chemical Space

- Chemical space can be viewed as being analogous to the cosmological universe.
- The total number of possible small organic molecules that populate 'chemical space' has been estimated to exceed 10^{60}
- Drug-like & Lead-like



Drug & Drug-likeness

- Drugs are an ill-defined entity from a chemical standpoint.
- Drug-like compound is defined as those compounds that have acceptable ADME/Tox properties to survive through the completion of human Phase 1 trials

Lipinski's Rule-of-5

- The rule of five states that poor absorption or permeability are more likely when
  - cLogP (the calculated 1-octanol–water partition coefficient, a measure of lipophilicity) is >5
  - molecular mass is >500 Da
  - the number of hydrogen-bond donors (OH plus NH count) is >5
  - the number of hydrogen-bond acceptors (O plus N atoms) is >10
- Its conceptual simplicity and ease of calculation has made it the leading measure of drug-likeness.

QED

- Quantitative Estimate of Drug-likeness

ARTICLES
PUBLISHED ONLINE: 24 JANUARY 2012 | DOI: 10.1038/NCHEM.1243
nature chemistry

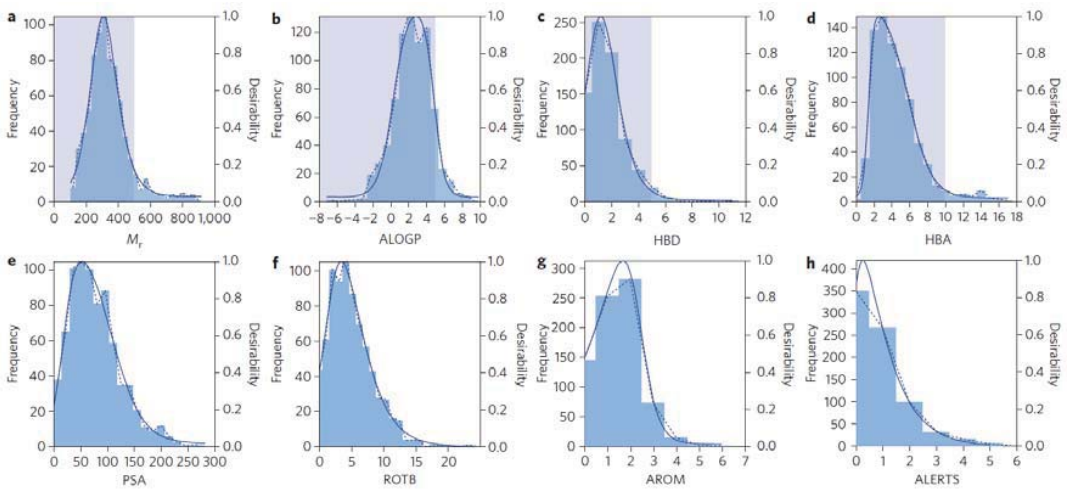
Quantifying the chemical beauty of drugs

G. Richard Bickerton[1], Gaia V. Paolini[2], Jérémy Besnard[1], Sorel Muresan[3] and Andrew L. Hopkins[1]*

Drug-likeness is a key consideration when selecting compounds during the early stages of drug discovery. However, evaluation of drug-likeness in absolute terms does not reflect adequately the whole spectrum of compound quality. More worryingly, widely used rules may inadvertently foster undesirable molecular property inflation as they permit the encroachment of rule-compliant compounds towards their boundaries. We propose a measure of drug-likeness based on the concept of desirability called the quantitative estimate of drug-likeness (QED). The empirical rationale of QED reflects the underlying distribution of molecular properties. QED is intuitive, transparent, straightforward to implement in many practical settings and allows compounds to be ranked by their relative merit. We extended the utility of QED by applying it to the problem of molecular target druggability assessment by prioritizing a large set of published bioactive compounds. The measure may also capture the abstract notion of aesthetics in medicinal chemistry.

Histograms of molecular properties

- Eight selected molecular properties for a set of 771 orally absorbed small molecule drugs



Quantitative Estimate of Drug-likeness (QED)

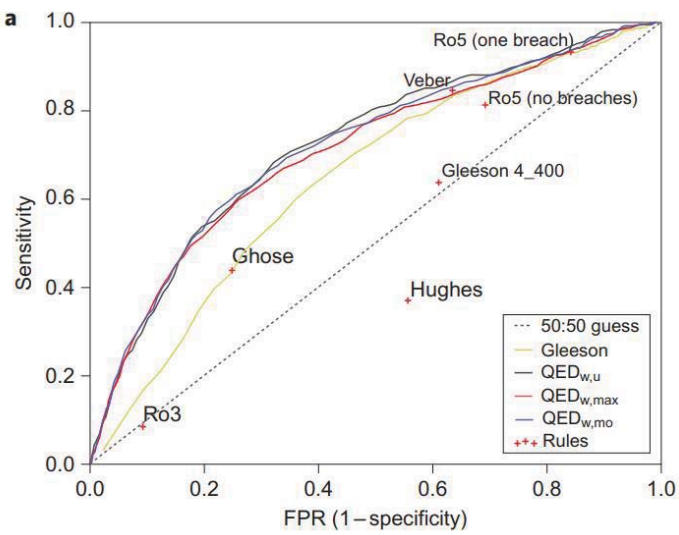
- Combining the individual desirability functions into the QED,

$$\mathrm{QED}_{\mathrm{w}} = \exp\left[\frac{W_{\mathrm{MW}}\ln d_{\mathrm{MW}} + W_{\mathrm{ALOGP}}\ln d_{\mathrm{ALOGP}} + W_{\mathrm{HBA}}\ln d_{\mathrm{HBA}} + W_{\mathrm{HBD}}\ln d_{\mathrm{HBD}} + W_{\mathrm{PSA}}\ln d_{\mathrm{PSA}} + W_{\mathrm{ROTB}}\ln d_{\mathrm{ROTB}} + W_{\mathrm{AROM}}\ln d_{\mathrm{AROM}} + W_{\mathrm{ALERTS}}\ln d_{\mathrm{ALERTS}}}{W_{\mathrm{MW}} + W_{\mathrm{ALOGP}} + W_{\mathrm{HBA}} + W_{\mathrm{HBD}} + W_{\mathrm{PSA}} + W_{\mathrm{ROTB}} + W_{\mathrm{AROM}} + W_{\mathrm{ALERTS}}}\right]$$

$$d(x) = a + \frac{b}{\left[1+\exp\left(-\frac{x-c+\frac{d}{2}}{e}\right)\right]}\left[1-\frac{1}{\left[1+\exp\left(-\frac{x-c-\frac{d}{2}}{f}\right)\right]}\right]$$

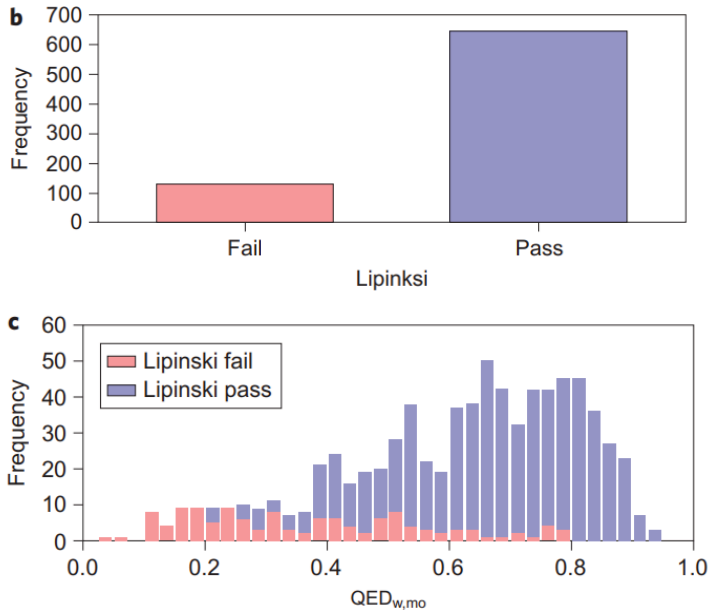
Performance

- A receiver operating characteristic plot in classifying compounds as drug-like or otherwise



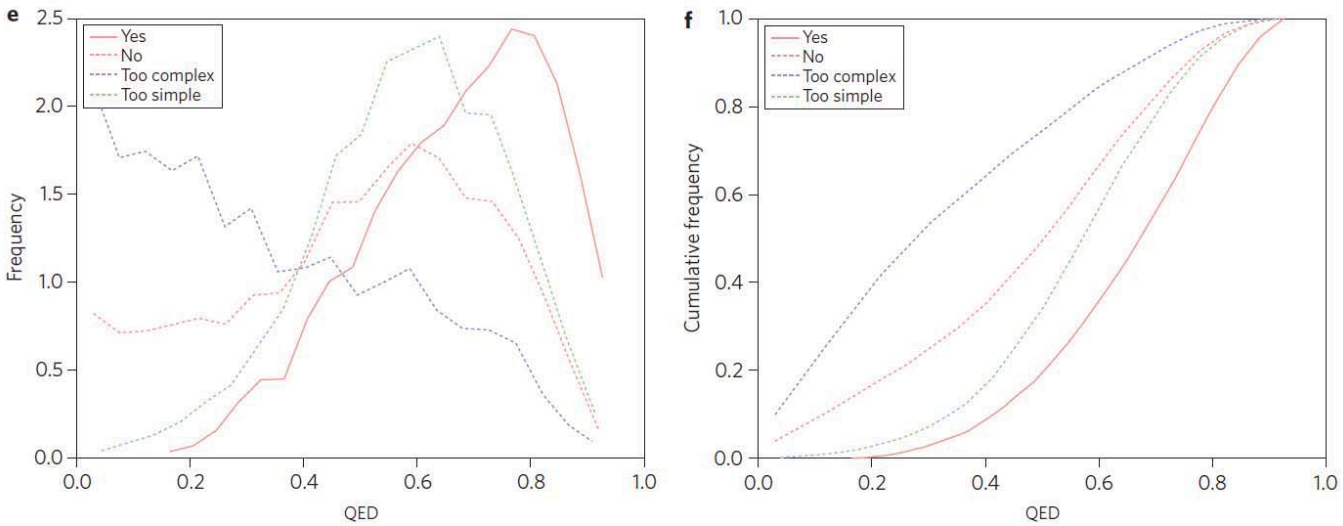
Rule-of-5 Comparison

- Direct comparison of the Ro5 and QED shows the drugs failing (red) and passing (blue) Lipinski's Ro5



Chemical aesthetics

- Question: "Would you undertake chemistry on this compound if it were a hit?"



Synthetic Accessibility Score (SAS)

- Ertl et al., "Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions", J. Cheminformatics, 1:8 (2009)

Journal of Cheminformatics

ChemistryCentral

Research article

Open Access

Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions

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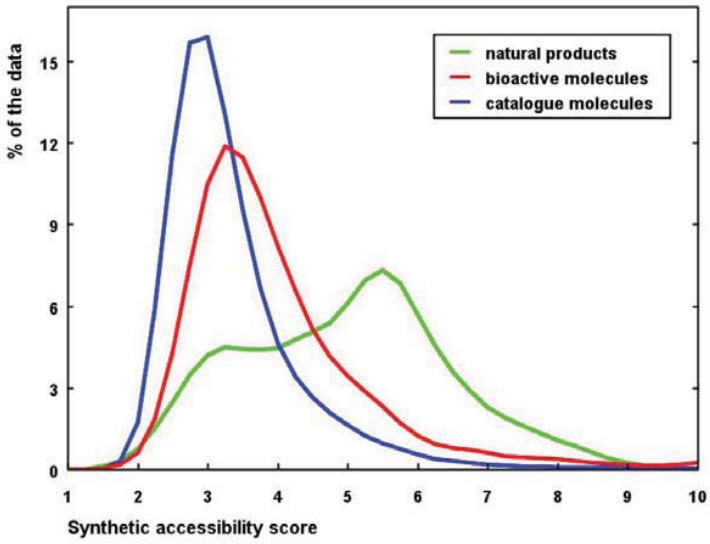
Accepted: 10 June 2009

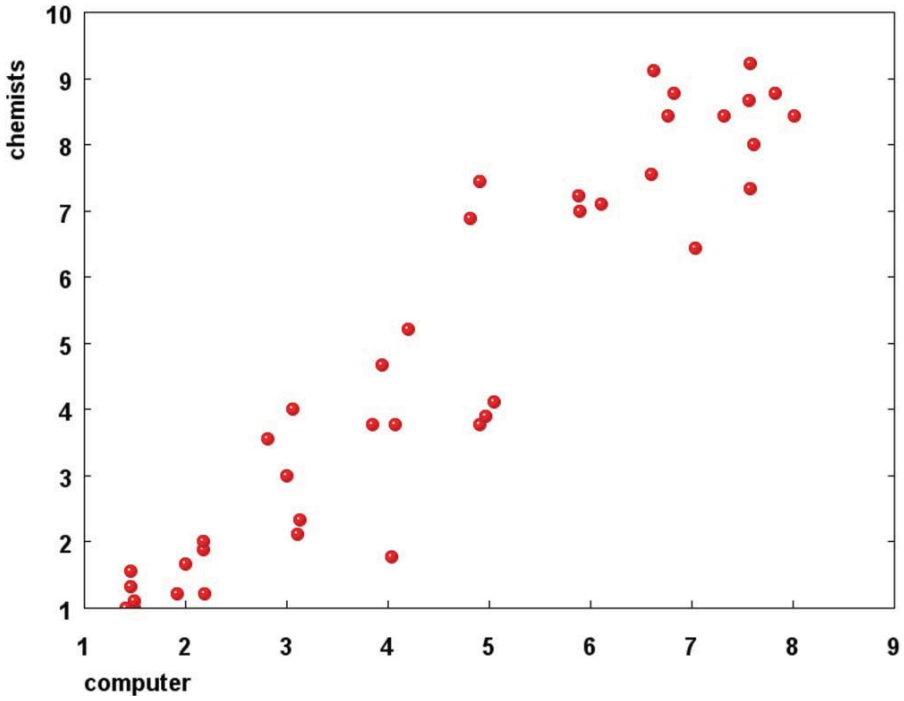
This article is available from: http://www.jcheminf.com/content/1/1/8

Score Distribution

- Ease of synthesis of compounds
- SAscore = fragmentScore - complexityPenalty



Synthetic Accessibility Score (SAS)



RDKit

- https://www.rdkit.org/

RDKit: Open-Source Cheminformatics Software

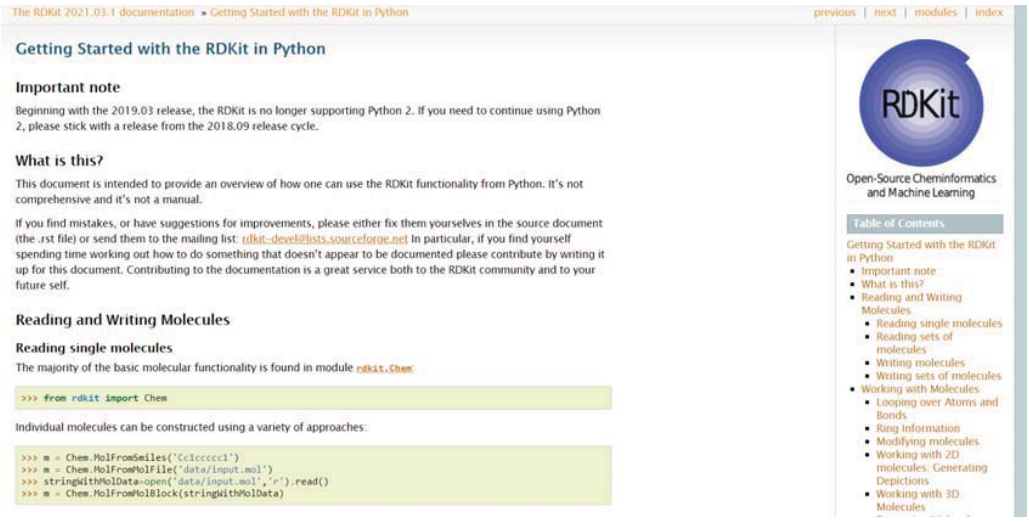
Useful Links

- GitHub page
  - Git source code repository
  - The bug tracker
  - The releases (downloads)
- Sourceforge page
  - The mailing lists
  - Searchable archive of rdkit-discuss
  - Searchable archive of rdkit-devel
- RDKit at LinkedIn
- The RDKit Blog
- Online Documentation

RDKit
Open-Source Cheminformatics and Machine Learning

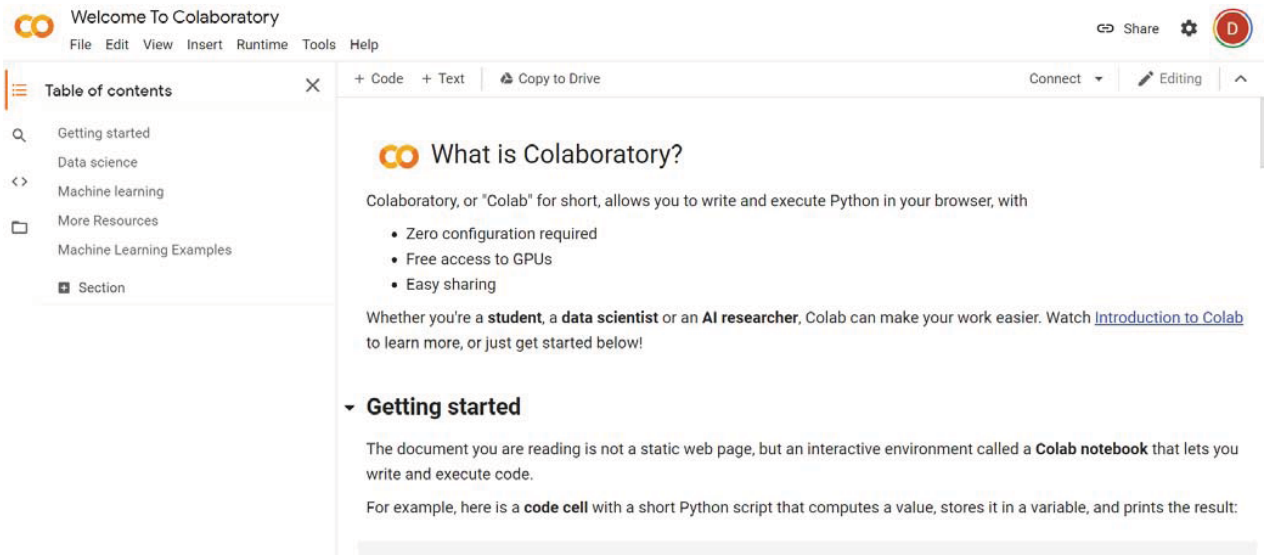
Tutorial

- https://www.rdkit.org/docs/GettingStartedInPython.html



Colab

- https://colab.research.google.com/notebooks/intro.ipynb



Installing RDKit

- !pip install rdkit

QED

- `from rdkit import Chem`
- `m = Chem.MolFromSmiles('Cc1ccccc1')`

- `from rdkit.Chem import QED`
- `qed=QED.qed(m)`
- `print(qed)`

SAS

- https://mattermodeling.stackexchange.com/questions/8541/how-to-compute-the-synthetic-accessibility-score-in-python

Databases

Chemical Databases

Database	Content	Size (no. of compounds)	URL
Bioactivity data			
ChEMBL	Bioactivity data from the medicinal chemistry literature	1 360 000	https://www.ebi.ac.uk/chembldb
PubChem	Biological screening results on small molecules	49 000 000	https://pubchem.ncbi.nlm.nih.gov/
Patents			
IBM	Chemicals from full text patents	2 500 000	http://www-935.ibm.com/services/us/gbs/bao/siip/
SureChEMBL	Chemicals from full text patents	12 400 000	https://www.surechembl.org
Drugs			
DRUGBANK	Drug data and drug target information	7700	http://www.drugbank.ca
FDA/USP SRS	Substances present in FDA regulated products	34 000	http://fdasis.nlm.nih.gov/srs/srs.jsp
Availability			
ZINC	Commercially available compounds	22 700 000	http://zinc.docking.org
emolecules	Commercially available compounds	5 900 000	http://www.emolecules.com
Other			
ChEBI	Database and ontology of Chemical Entities of Biological Interest	27 000	https://www.ebi.ac.uk/chebi/
PDB	Data on biological macromolecular structures	16 000	https://www.ebi.ac.uk/pdbe/

Note: All numbers from Apr 2014.

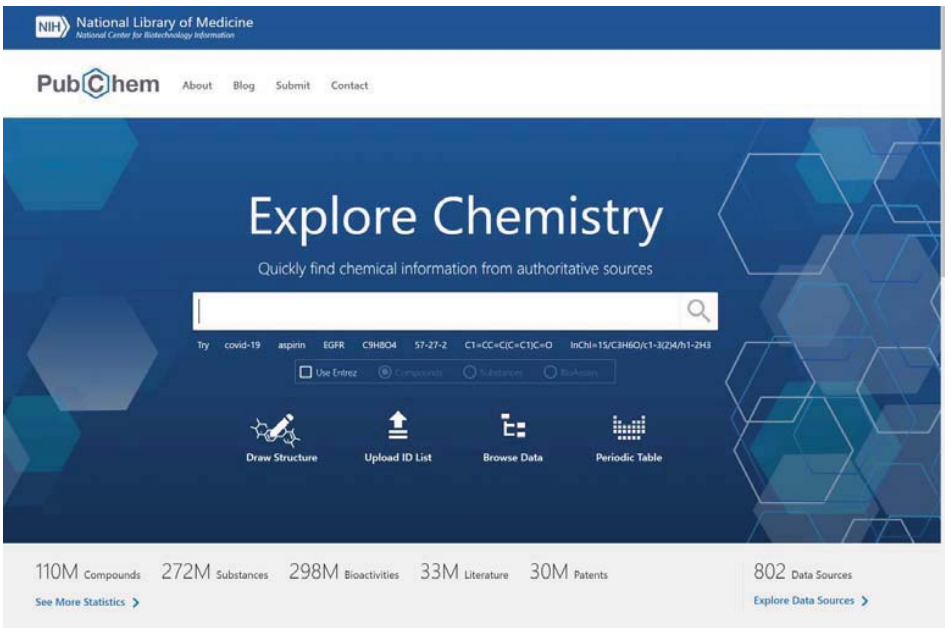
http://dx.doi.org/10.1016/j.ddtec.2015.01.005

Databases

Database	Coverage (Number of entities)		
	Compounds	Proteins	Interactions
PubChem	111 m	99 k	273 m
ChEMBL	1,961,462	13,382	16,066,124
DUD-E	22,886	102	22.8 k*
DrugBank	13,791	5,696	27,954
STITCH	0.5 m	9.6 m	1.6b
TTD	2,251	3,473***	43,875
PharmGKB	708	–	–
Matador	801	2,901	15,843
DrugCentral	2,529	2,003	17,390
SuperTarget	195,770	6,219	332,828
Metz	3,858	172	258,094
MUV	93 k	17	–
ZINC	750 m**	2,864 (for eukaryotes)	638,174

PubChem

- https://pubchem.ncbi.nlm.nih.gov/



Components

- Compounds: Unique chemical structures
- Substances: Information about chemical entities
  - any combination of chemical structures, synonyms, registration IDs, descriptions, patent identifiers, protein 3D structures, and biological screening results, etc.
- Bioassay: Biological experiments
- Bioactivities

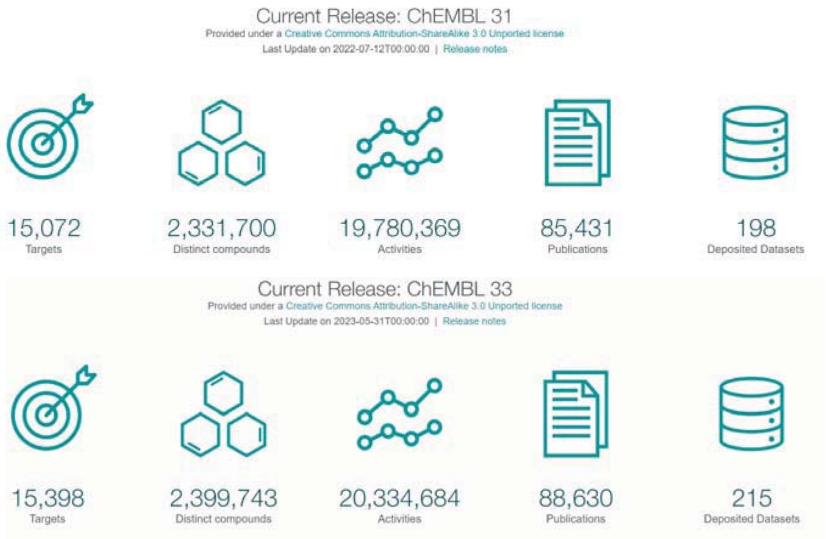
Statistics

PubChem Data Counts

Data Collection	Live Count	Description
Compounds	110,040,027	Unique chemical structures extracted from contributed PubChem Substance records
Substances	271,907,539	Information about chemical entities provided by PubChem contributors
BioAssays	1,366,296	Biological experiments provided by PubChem contributors
Bioactivities	298,299,306	Biological activity data points reported in PubChem BioAssays
Genes	103,715	Gene targets tested in PubChem BioAssays and those involved in PubChem Pathways
Proteins	96,561	Protein targets tested in PubChem BioAssays and those involved in PubChem Pathways
Taxonomy	112,763	Organisms of targets tested in PubChem BioAssays and those involved in PubChem Pathways
Pathways	237,925	Interactions between chemicals, genes, and proteins
Literature	32,849,900	Scientific publications with links in PubChem
Patents	29,940,379	Patents with links in PubChem
Data Sources	805	Organizations contributing data to PubChem

ChEMBL

- https://www.ebi.ac.uk/chembl/
- A manually curated database of bioactive molecules with drug-like properties



ChEMBL Assays – Binding, Functional, ADMET

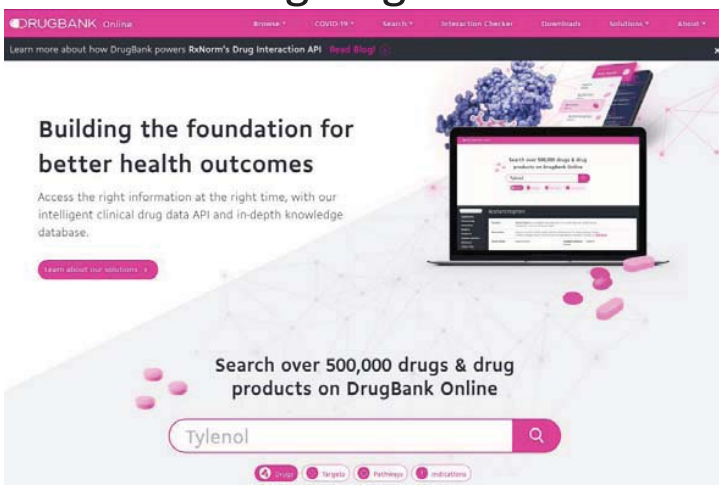
- Binding Assays
  - Assays which directly measure the binding of a compound to a particular target
    - E.g., competition binding assays with a radioligand
- Various endpoints measured, but most commonly reported are:
  - IC50 (half maximal inhibitory concentration)
  - Ki (binding affinity)
  - MIC (minimum inhibitory concentration)
  - % Inhibition (of activity)

Protein Targets

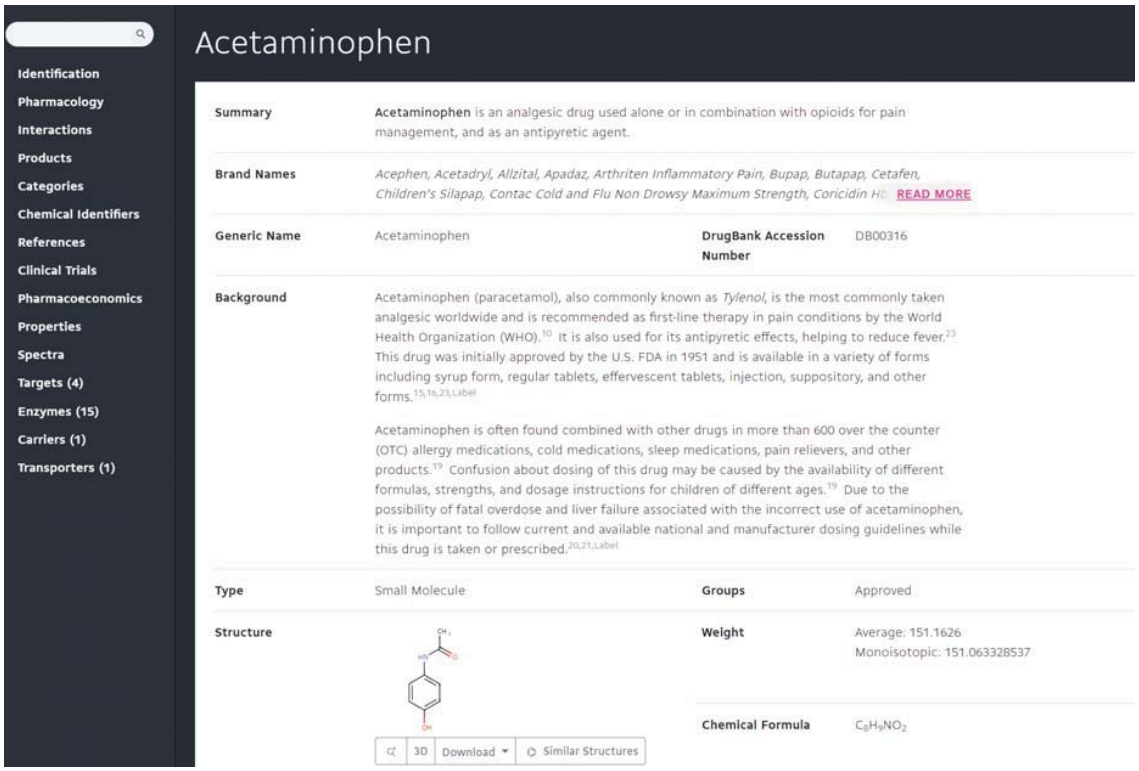
- Each protein target linked to a sequence in UniProt
- Information from UniProt used in ChEMBL to allow searching:
  - Protein name/description
  - Synonyms and gene names
  - Organism (and NCBI Tax ID)
- Proteins in ChEMBL also classified according to family (e.g., Receptor, Kinase, Protease, Transporter etc).
  - Used for searching by target tree (Browse Targets)

DrugBank

- https://go.drugbank.com/
- Detailed drug (i.e. chemical) data with comprehensive drug target



DrugBank example



Targets

1. Prostaglandin E synthase 3 — Details

Kind	Protein	**General Function**	Unfolded protein binding
Organism	Humans	**Specific Function**	Cytosolic prostaglandin synthase that catalyzes the oxidoreduction of prostaglandin endoperoxide H2 (PGH2) to prostaglandin E2 (PGE2) (PubMed:10922363). Molecular chaperone that localizes to genomi...
Pharmacological action	Unknown		
Actions	Inhibitor		
		Gene Name	PTGES3
		Uniprot ID	Q15185
		Uniprot Name	Prostaglandin E synthase 3
		Molecular Weight	18697.195 Da

References

1. Botting R, Ayoub SS: COX-3 and the mechanism of action of paracetamol/acetaminophen. Prostaglandins Leukot Essent Fatty Acids. 2005 Feb;72(2):85-7. [Article]
2. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, Simmons DL: COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci U S A. 2002 Oct 15;99(21):13926-31. Epub 2002 Sep 19. [Article]
3. Data sheet, Acetaminophen, ebi.ac.uk [File]

2. Prostaglandin G/H synthase 2 — ··· Binding Properties — Details

Kind	Protein	**General Function**	Prostaglandin-endoperoxide synthase activity

ZINC

- http://zinc.docking.org/
- ZINC was originally designed for target based virtual screening (docking)
- Now, zinc20

(Old) ZINC subsets

	Lead-Like	Fragment-Like	Drug-Like	All	Shards
Standard Size Updated	**Lead-Like** 6,053,287 2014-09-29	**Fragment-Like** 847,909 2015-02-04	**Drug-Like** 17,900,742 2014-11-24	**All Purchasable** 22,724,825 2014-11-28	**Shards** 635,159 2014-05-16
Clean Size Updated	**Clean Leads** 4,591,276 2014-09-25	**Clean Fragments** 1,611,889 2014-09-24	**Clean Drug-Like** 13,195,609 2013-11-05	**All Clean** 16,403,865 2013-12-18	**Clean Shards** 325,950 2014-11-24
In Stock Size Updated	**Leads Now** 3,687,621 2014-06-25	**Frags Now** 704,041 2015-02-04	**Drugs Now** 10,639,555 2014-11-24	**All Now** 12,782,590 2014-05-01	**Shards Now** 424,775 2014-09-24
Boutique Size Updated	**Boutique Leads** 5,114,169 2012-12-24	**Boutique Frags** 2,755,555 2013-11-08	**Boutique Drugs** 10,292,210 2012-11-27	**All Boutique** 12,217,845 2012-11-27	**Boutique Shards** 80,698 2013-11-08
Comments/Citation	Teague, Davis, Leeson, Oprea, Angew Chem Int Ed Engl. 1999 Dec 16;38(24):3743-3748.	Carr RA, Congreve M, Murray CW, Rees DC, Drug Discov Today. 2005 Jul 15;10(14):987	Lipinski, J Pharmacol Toxicol Methods. 2000 Jul-Aug;44(1):235-49.	Purchasable chemical space	Type I binding sites
Filtering Critieria	p.mwt <= 350 and p.mwt >= 250 and p.xlogp <= 3.5 and p.rb <= 7	p.xlogp <=3.5 and p.mwt <=250 and p.rb <= 5	p.mwt <= 500 and p.mwt >= 150 and p.xlogp <= 5 and p.rb <=7 and p.psa < 150 and p.n_h_donors <= 5 and p.n_h_acceptors <= 10		p.mwt < 190

Rep. 2D 3D React. Standard Purch. Wait OK pH N/A Charge N/A

Molecular Weight (up to, Daltons)

LogP (up to)	200	250	300	325	350	375	400	425	450	500	>500	Totals, by LogP
-1	27,791	172,563	710,795	1,072,978	2,241,498	786,738	276,834	116,066	92,417	77,790	7,310	5,582,780
0	139,434	934,776	3,655,384	5,126,157	10,608,025	3,498,214	1,663,579	708,919	570,546	507,344	4,734	27,417,112
1	362,437	2,884,636	12,030,074	16,154,544	33,650,249	11,885,957	6,807,876	3,178,487	2,648,581	2,412,998	9,940	92,025,779
2	467,220	4,584,223	22,941,208	30,908,513	65,047,385	26,752,849	17,839,254	9,349,272	8,099,970	7,686,687	24,554	193,701,135
2.5	167,513	2,136,113	12,849,121	17,977,157	38,682,058	18,584,223	13,812,274	8,111,104	7,197,414	6,979,014	24,126	126,520,117
3	90,548	1,570,772	11,037,383	16,282,627	34,831,558	19,940,391	16,037,132	10,339,743	9,362,233	9,118,717	37,422	128,648,526
3.5	36,748	929,872	7,920,574	12,490,662	27,380,104	18,703,024	16,485,194	11,784,160	10,774,472	10,693,411	58,791	117,257,012
4	9,017	369,565	4,332,131	6,472,808	10,487,856	13,034,155	14,329,253	11,683,208	10,891,465	11,003,975	86,262	82,699,695
4.5	993	86,613	1,814,492	3,457,942	6,367,225	8,853,064	10,320,054	9,945,353	9,486,869	9,825,079	117,980	60,275,664
5	150	13,393	536,018	1,405,708	3,168,584	4,995,850	6,471,525	7,025,034	6,976,742	7,325,833	144,297	38,063,134
>5	39	1,097	22,854	103,521	376,905	927,395	1,670,856	2,195,160	2,588,702	3,052,048	767,762	11,706,339
Totals, by Weight	1,301,890	13,683,623	77,850,034	111,452,617	232,841,447	127,961,860	105,713,831	74,436,506	68,689,411	68,682,896	1,283,178	884M Substances 1.9K Tranches

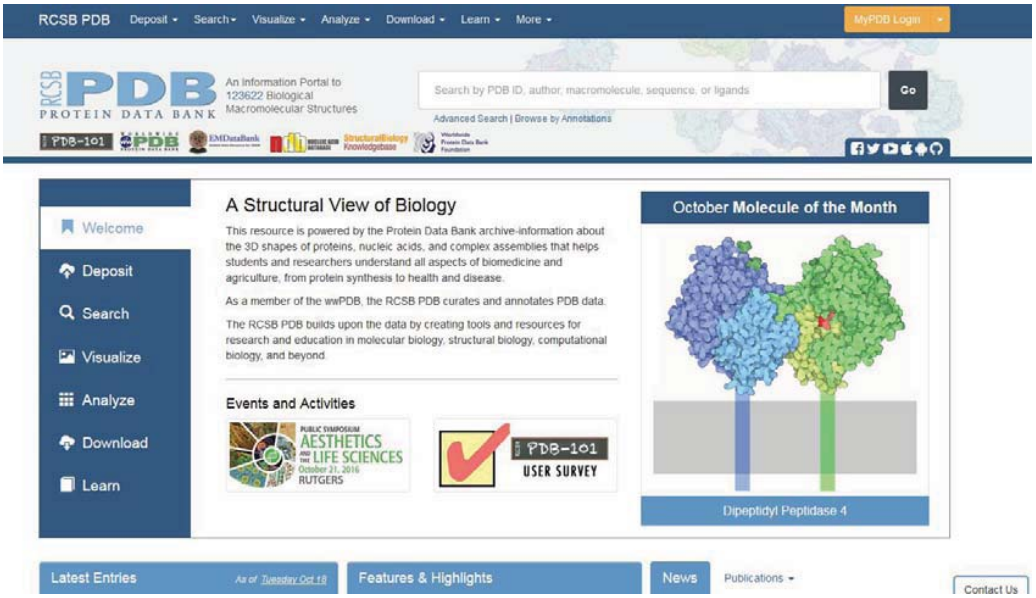
Targets

- https://zinc.docking.org/majorclasses/

Name	# Sub Classes	# Genes	# Orthologs	# Observations	# Substances	# Purchasable	# Predictions
adhesion	1	7	11	534	292	32	79415
auxiliary transport protein	3	8	14	643	458	182	497749
cytosolic other	1	39	58	5664	4162	461	2859674
enzyme	13	1942	2819	412921	205504	23889	107386614
epigenetic regulator	3	97	103	6250	2856	510	7743379
ion channel	3	152	246	34563	22500	2638	34121578
membrane other	1	6	12	301	271	30	166343
membrane receptor	7	289	670	307365	143352	13445	79804362
Nuclear-other	1	6	8	1053	784	68	176523
Secreted	1	41	52	913	757	175	3733709
Structural	1	7	9	482	417	161	310275
surface antigen	1	14	25	444	383	74	4370725
Transcription factor	2	53	108	45550	18111	1687	5537528
Transporter	4	110	186	47632	19622	2889	12273240
Unclassified	1	540	611	11256	8680	1942	21021371

Protein Data Bank(PDB)

- https://www.rcsb.org/

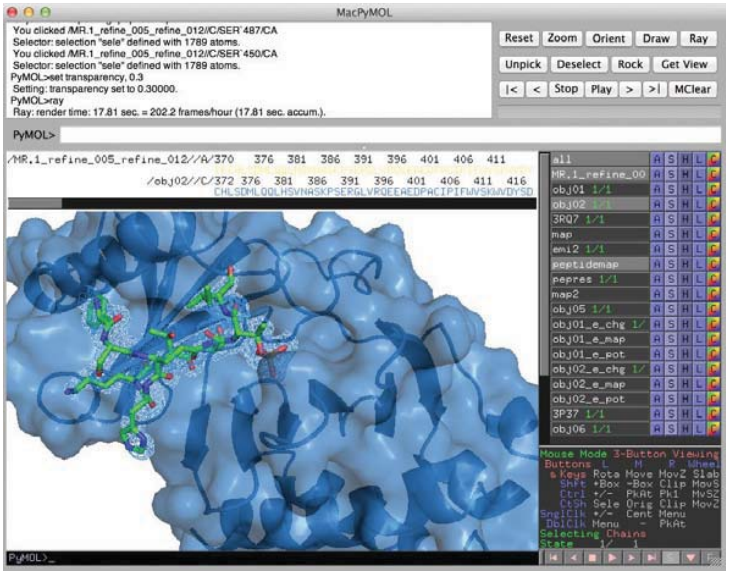


PDB ID

- 4-letter code
  - e.g) 12AS, 3INS
- Chain ID concatenated form
  - e.g) 12ASA

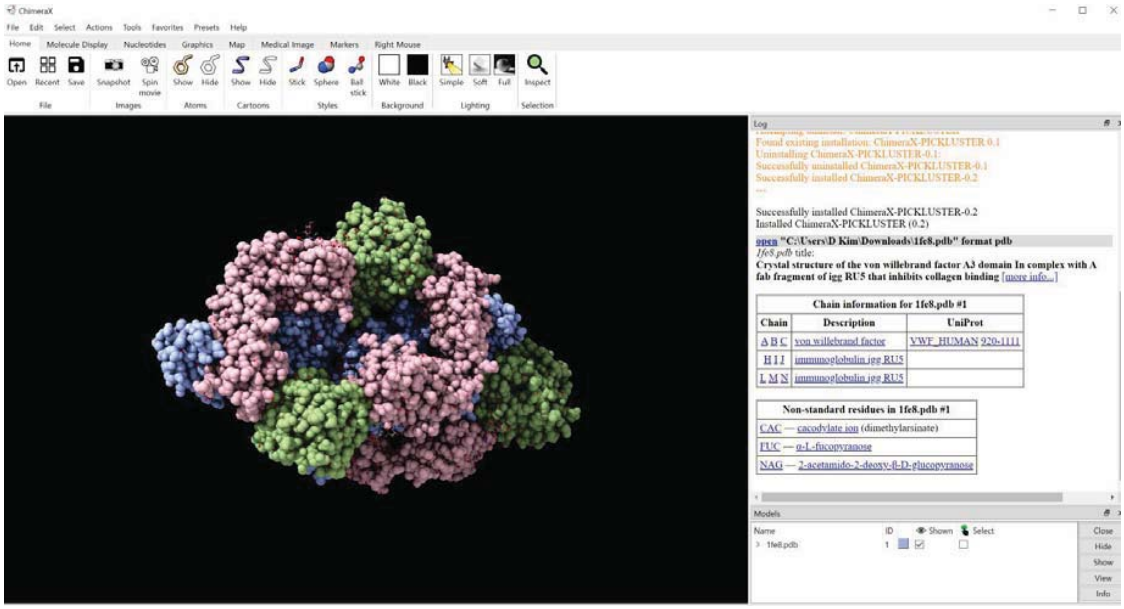
PyMOL: structure viewer

- Free software (http://pymol.org)
- https://pymolwiki.org/index.php/Windows_Install

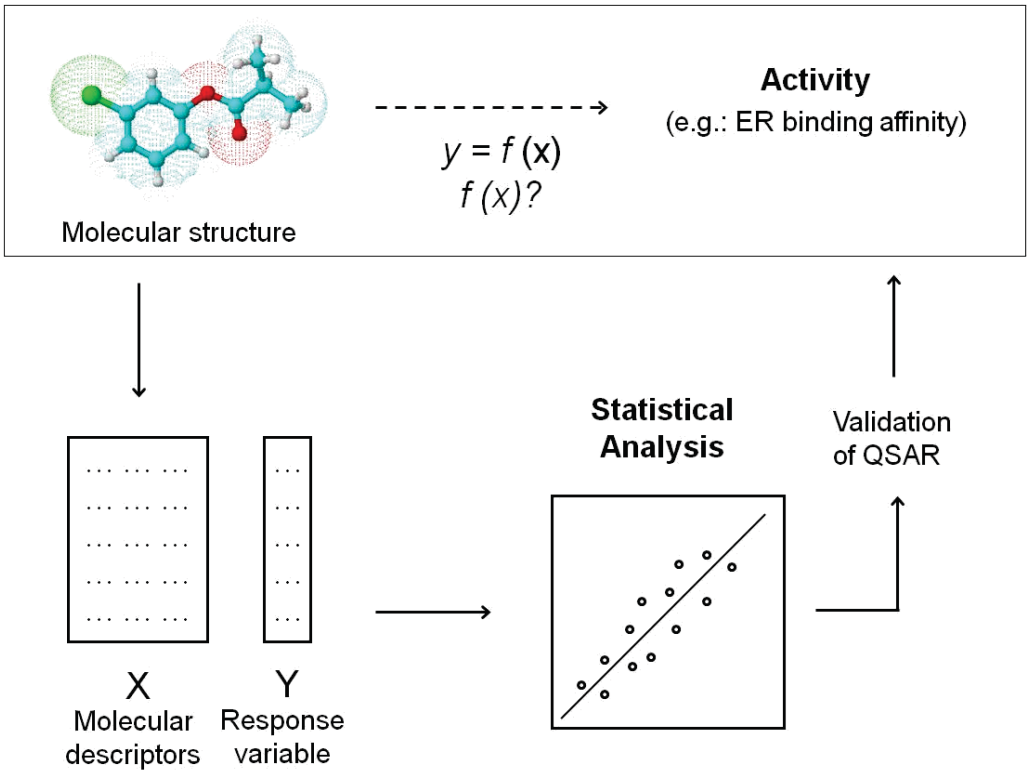


UCSF ChimerX

- https://www.rbvi.ucsf.edu/chimerax/



QSAR 모델링 과정



Molecular Descriptors

- Constitutional descriptors
  - molecular weight, number of chemical elements, number of H-bonds or double bonds, …
- Physicochemical descriptors
  - lipophilicity, polarizability, …
- Topological descriptors
  - atomic branching, …
- Electronic, geometrical and quantum-chemical descriptors
- Fragmental/Structural keys
  - MACCS keys, ECFP

1D, 2D, 3D

- 1D descriptors encode numerically generic properties
  - Molecular weight, molar refractivity, and octanol/water partition coefficient, etc.
- 2D descriptors: topological representations of molecules.
  - 2D-QSAR
- 3D descriptors: obtained directly from the 3D structure of molecules
  - 3D-QSAR methods
  - Dependent on the molecular conformation

PaDEL descriptor

- http://www.yapcwsoft.com/dd/padeldescriptor/
- 1875 descriptors (1444 2D_descriptors + 431 3D_descriptors)

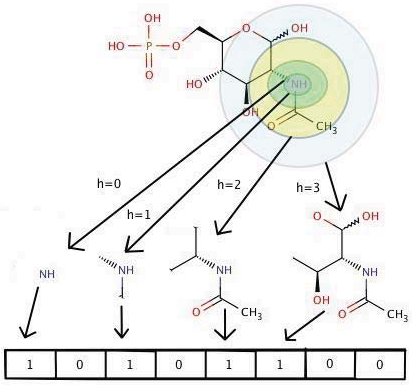
Descriptor Java Class	Descriptor	Description	Class
AcidicGroupCountDescriptor	nAcid	Number of acidic groups. The list of acidic groups is defined by these SMARTS "$([O;H1]-[C,S,P]=O)", "$([*;-;!$(*~[*;+])])"	2D
ALOGPDescriptor	ALogP	Ghose-Crippen LogKow	2D
	ALogP2	Square of ALogP	2D
	AMR	Molar refractivity	2D
APolDescriptor	apol	Sum of the atomic polarizabilities (including implicit hydrogens)	2D
AromaticAtomsCountDescriptor	naAromAtom	Number of aromatic atoms	2D
AromaticBondsCountDescriptor	nAromBond	Number of aromatic bonds	2D
AtomCountDescriptor	nAtom	Number of atoms	2D
	nHeavyAtom	Number of heavy atoms (i.e. not hydrogen)	2D
	nH	Number of hydrogen atoms	2D
	nB	Number of boron atoms	2D
	nC	Number of carbon atoms	2D
	nN	Number of nitrogen atoms	2D
	nO	Number of oxygen atoms	2D
	nS	Number of sulphur atoms	2D
	nP	Number of phosphorus atoms	2D
	nF	Number of fluorine atoms	2D
	nCl	Number of chlorine atoms	2D
	nBr	Number of bromine atoms	2D
	nI	Number of iodine atoms	2D
	nX	Number of halogen atoms (F, Cl, Br, I, At, Uus)	2D
AutocorrelationDescriptor	ATS0m	Broto-Moreau autocorrelation - lag 0 / weighted by mass	2D
	ATS1m	Broto-Moreau autocorrelation - lag 1 / weighted by mass	2D
	ATS2m	Broto-Moreau autocorrelation - lag 2 / weighted by mass	2D
	ATS3m	Broto-Moreau autocorrelation - lag 3 / weighted by mass	2D
	ATS4m	Broto-Moreau autocorrelation - lag 4 / weighted by mass	2D
	ATS5m	Broto-Moreau autocorrelation - lag 5 / weighted by mass	2D
	ATS6m	Broto-Moreau autocorrelation - lag 6 / weighted by mass	2D
	ATS7m	Broto-Moreau autocorrelation - lag 7 / weighted by mass	2D

Fragment Codes

- A fragment coding system is based on a collection of small substructures or features in a closed list.
- Sub structural 'keys' from a fragment dictionary are usually recorded as a binary bit string, or fingerprint.
  - MACCS Keys
  - Comparing fingerprint bit strings is very fast.
- The alternative to structural keys is a 'hashed fingerprint.'
  - ECFPs (Extended Connectivity FingerPrints)
  - Morgan fingerprint

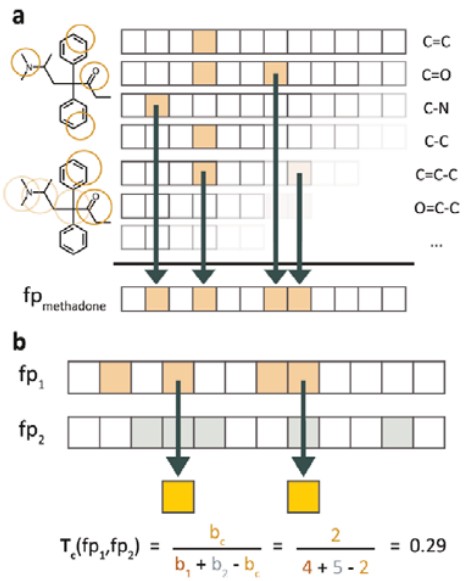
Molecular Fingerprint

- Bit string representations of molecular structure and properties
- 2D structure features typically encoded as a vector of binary values
- ECFPs, Morgan
- Reasons for popularity in similarity searching:
  - computational efficiency
  - surprising effectiveness in detecting active compounds



Similarity

- Tanimoto coefficient



ECFP

- Extended Connectivity FingerPrint
- https://docs.chemaxon.com/display/docs/extended-connectivity-fingerprint-ecfp.md

742 J. Chem. Inf. Model. 2010, 50, 742–754

Extended-Connectivity Fingerprints

David Rogers*,† and Mathew Hahn‡

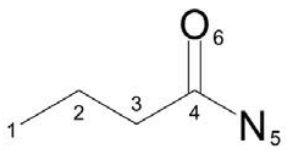
3429 North Mountain View Drive, San Diego, California 92116 and Accelrys, Incorporated, 10188 Telesis Court, Suite 100, San Diego, California 92121

Received February 4, 2010

Extended-connectivity fingerprints (ECFPs) are a novel class of topological fingerprints for molecular characterization. Historically, topological fingerprints were developed for substructure and similarity searching. ECFPs were developed specifically for structure−activity modeling. ECFPs are circular fingerprints with a number of useful qualities: they can be very rapidly calculated; they are not predefined and can represent an essentially infinite number of different molecular features (including stereochemical information); their features represent the presence of particular substructures, allowing easier interpretation of analysis results; and the ECFP algorithm can be tailored to generate different types of circular fingerprints, optimized for different uses. While the use of ECFPs has been widely adopted and validated, a description of their implementation has not previously been presented in the literature.

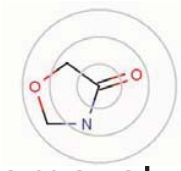
생성 과정

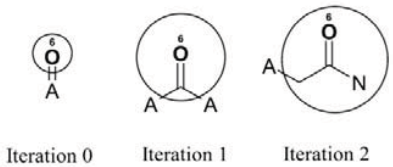
- Initial assignment of atom identifier



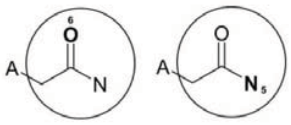
1: 734603939
2: 1559650422
3: 1559650422
4: -1100000244
5: 1572579716
6: -1074141656

- Iterative updating of identifiers



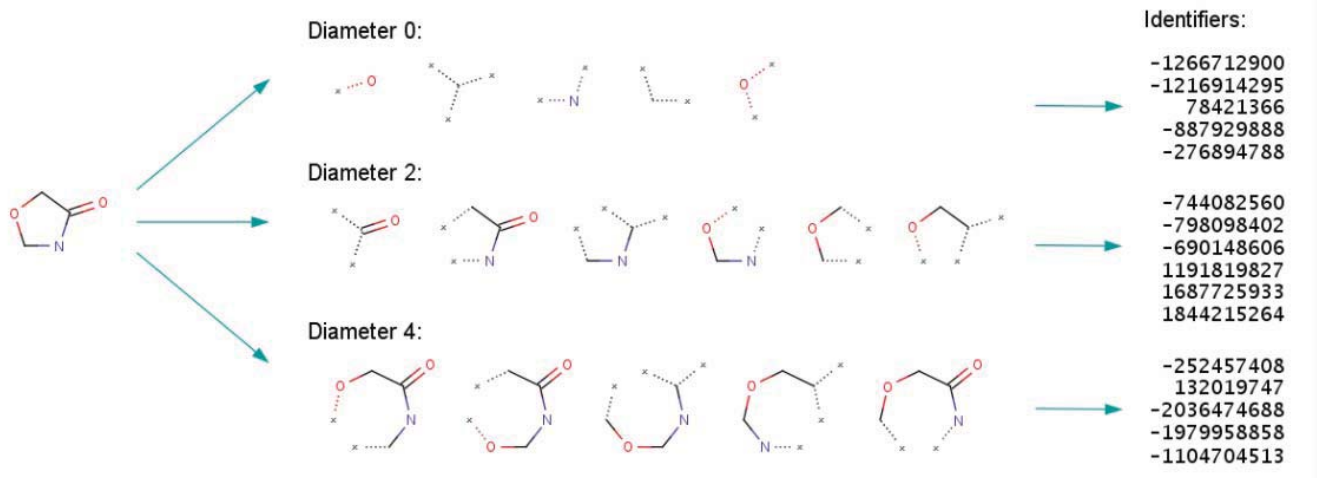


- Duplication removal



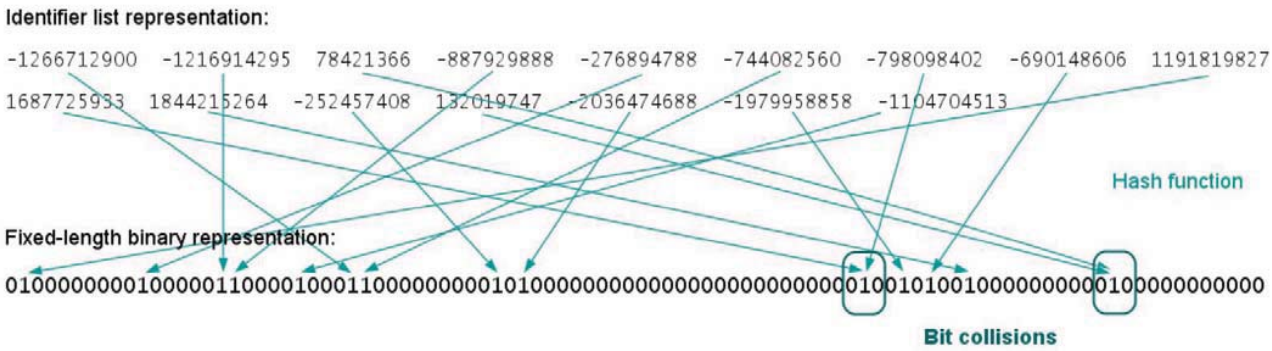
ECFP generation process

- Diameter (0, 2, 4, …) or Radius (0, 1, 2, …)



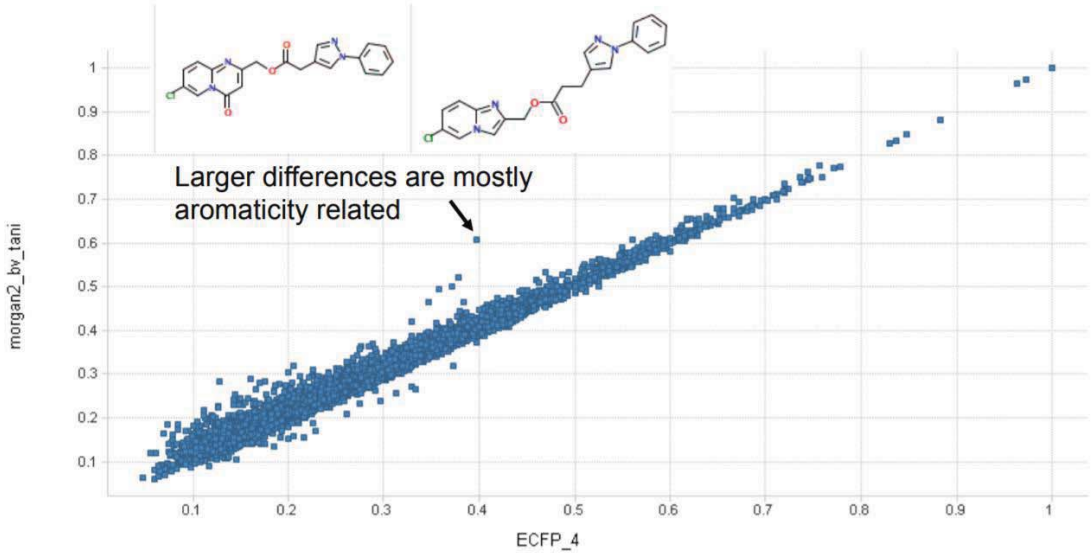
Generation of the fixed-length bit string

- "Folding" process
- length: 1024, 2048, …
- Bit collisions can happen.



ECFP vs. RDKit Morgan FP

- RDKit Morgan2 vs PP ECFP4



- RDKit Morgan3 vs PP ECFP6 is similar

Morgan/Circular FP

- Rdkit implementation of ECFP

```
>>> from rdkit.Chem import AllChem
>>> m1 = Chem.MolFromSmiles('Cc1ccccc1')
>>> fp1 = AllChem.GetMorganFingerprint(m1,2)
>>> fp1
<rdkit.DataStructs.cDataStructs.UIntSparseIntVect object at 0x...>
>>> m2 = Chem.MolFromSmiles('Cc1nccccc1')
>>> fp2 = AllChem.GetMorganFingerprint(m2,2)
>>> DataStructs.DiceSimilarity(fp1,fp2)
0.55...
```

```
>>> fp1 = AllChem.GetMorganFingerprintAsBitVect(m1,2,nBits=1024)
>>> fp1
<rdkit.DataStructs.cDataStructs.ExplicitBitVect object at 0x...>
>>> fp2 = AllChem.GetMorganFingerprintAsBitVect(m2,2,nBits=1024)
>>> DataStructs.DiceSimilarity(fp1,fp2)
0.51...
```

KSBi | 한국생명정보학회

KSBi-BIML 2024

인공지능 신약설계

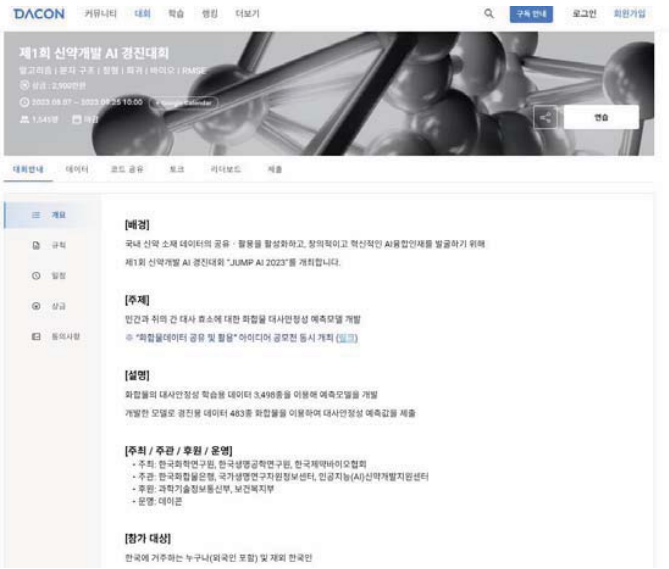
AI Drug Design

개요

- 강의
  - QSAR 모델링 기초
  - AI 신약개발을 위한 기계학습법 기초
  - AI 신약개발을 위한 딥러닝 모델
  - Virtual screening (ligand-based, structure-based) 및 de novo design
- 실습
  - QSAR modeling 전체 과정 실습
  - 화합물의 Bioactivity 예측 모델 개발
  - Virtual screening 과정을 통한 신약후보물질 발굴 실습

신약개발 AI 경진대회

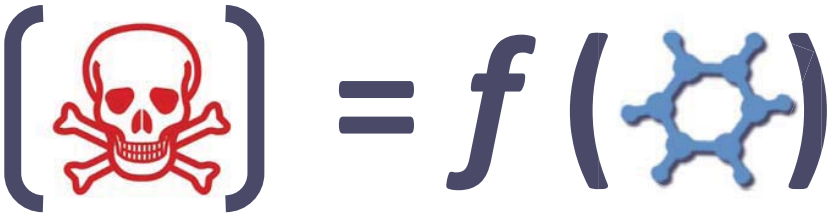
- https://dacon.io/competitions/official/236127/overview/description



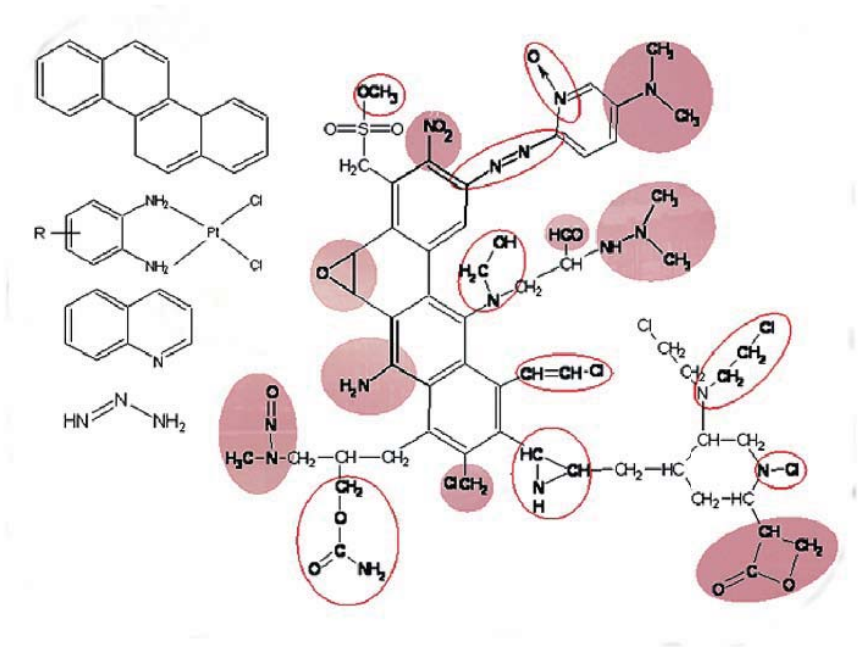
QSAR 모델링

QSAR

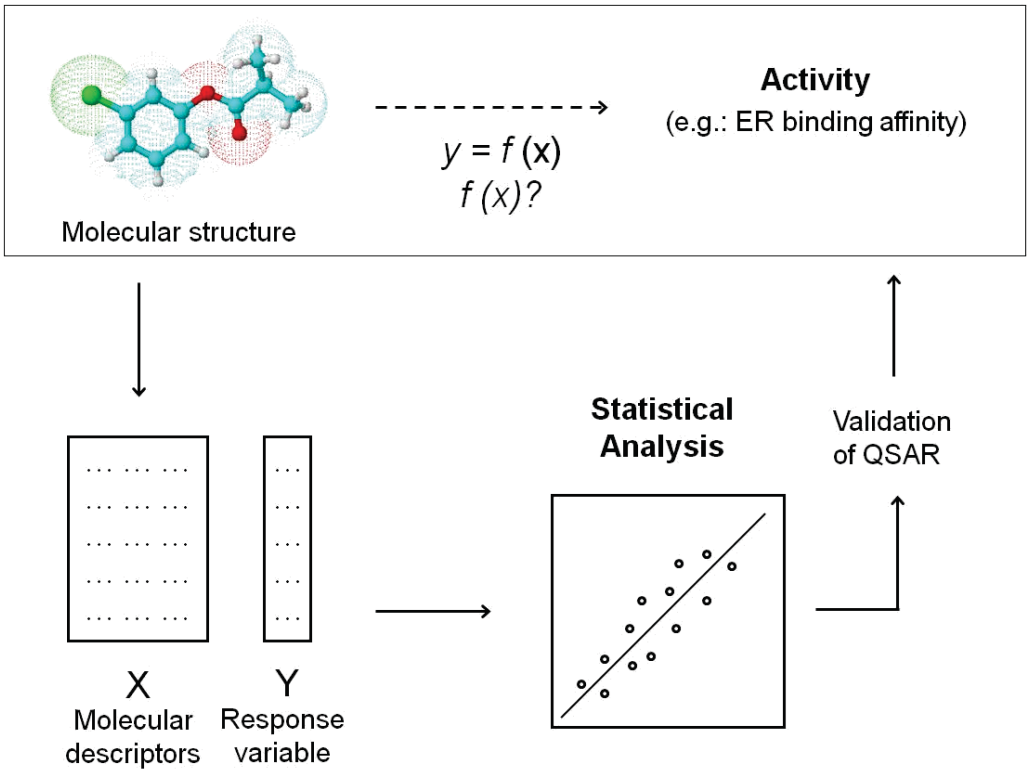
- Quantitative structure–activity relationships
- Construction of a mathematical model relating a molecular structure to a chemical property or biological effect by means of statistical techniques



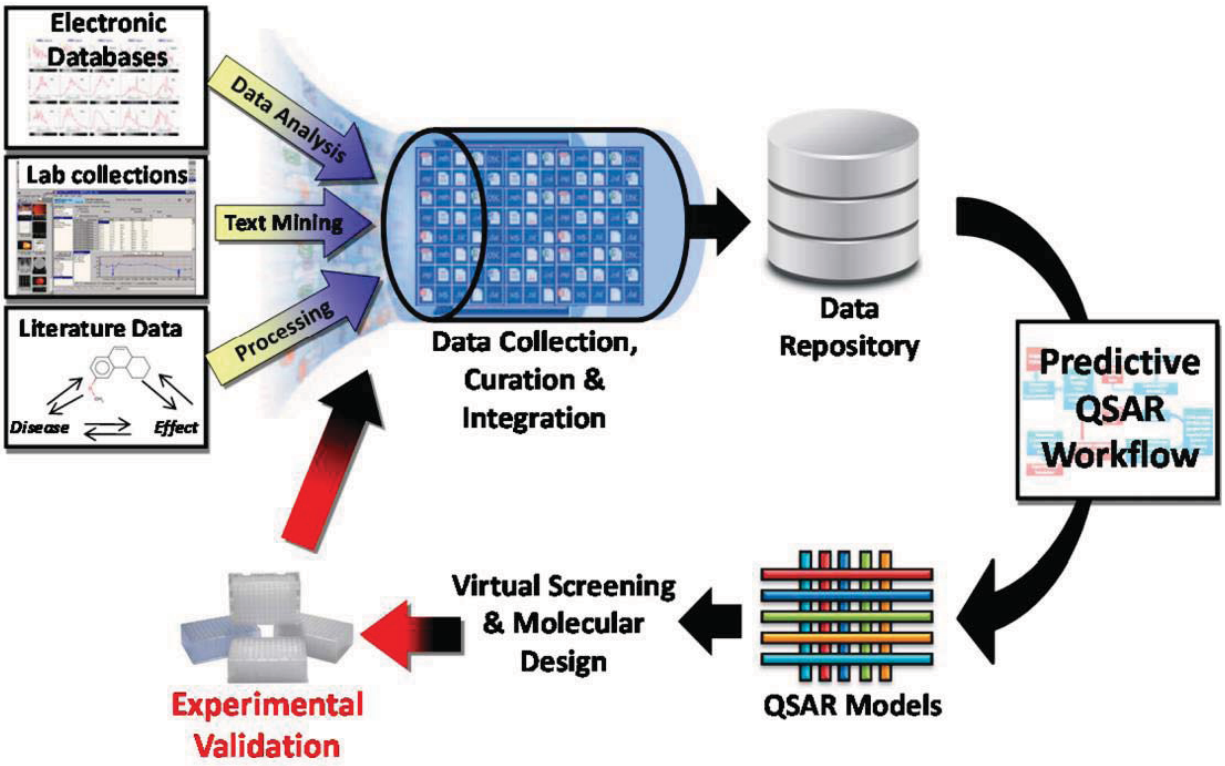
Link between toxicity and structures



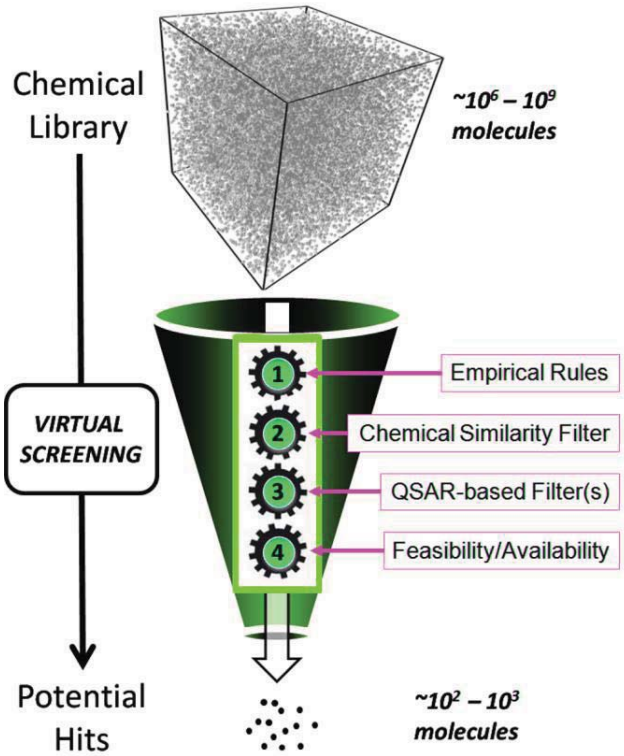
QSAR 모델링 과정



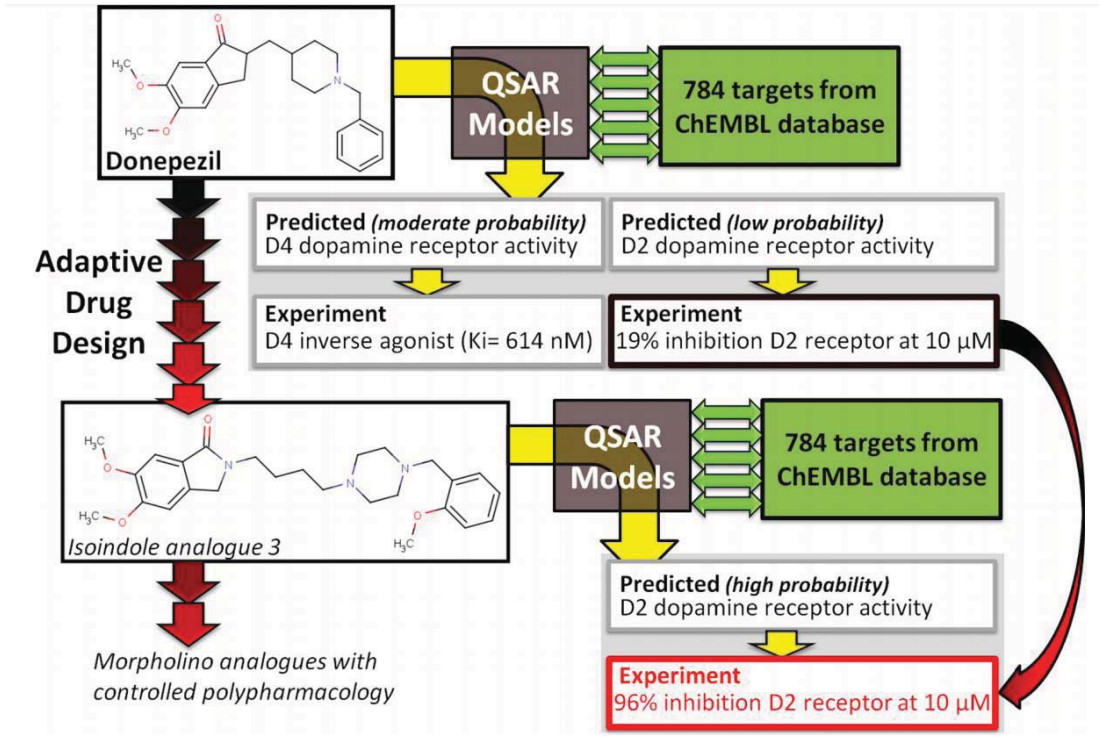
QSAR-guided drug discovery



QSAR-based virtual screening



Target prediction and optimization



Components

- 화합물 데이터: a set of chemical structures that are represented by molecular descriptors
- Activity 데이터: a set of observed 'activities' associated with the structures.
  - Any form of experimental observation, not limited to biological activities
  - Numerical (IC_{50}, K_i, or K_d) or
  - Categorical labels (active/inactive; soluble/insoluble)
- A statistical modeling method to identify the key relationships between the molecular descriptors and the activities
  - Linear regression, SVM, Random forest, Deep learning

Binding Affinity

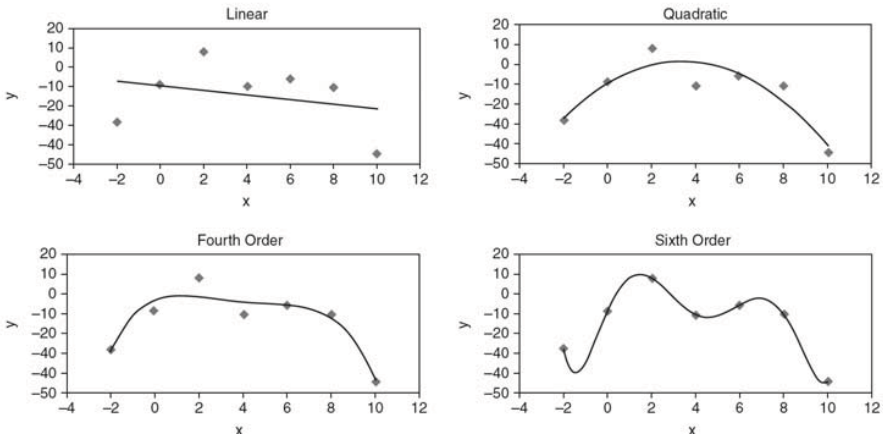
- **IC50** - The half maximal (50%) inhibitory concentration, a measure of the potency of a substance in inhibiting a specific biological or biochemical function.
- **EC50** - Half maximal effective concentration, the concentration of compound that generates a half-maximal response in a given assay.
- **KD** – dissociation constant; the concentration of ligand that gives even odds that a given protein molecule has a ligand bound.
- **KI** - For enzyme inhibitors, this is the inhibition constant, essentially the dissociation constant KD
- **ΔG** – Gibbs free energy change associated with a chemical reaction, here a binding reaction

PREPARATION

- ‘Garbage-in, garbage-out’ principle
- There are many ways in which erroneous or misleading models can be produced.
  - Data and/or Statistical method
- Check that the observations are consistent, preferably obtained from a single experimental source.
- Data taken from different assays should not be combined into a single model where possible.
- It is better to have the data points evenly spread.
- We cannot be sure that what is not reported is indeed negative.

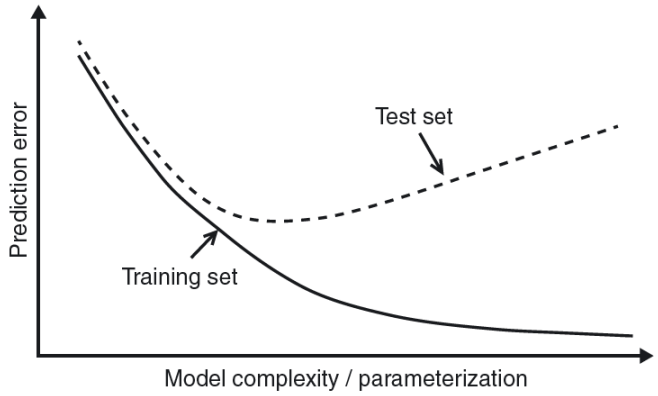
Model validation

- Once the model is fully optimized, it is important to determine the level of prediction accuracy that can be expected when the model is applied to new compounds.
- The fit of a model to its training data is *not* a good indicator of its predictive performance for new compounds.



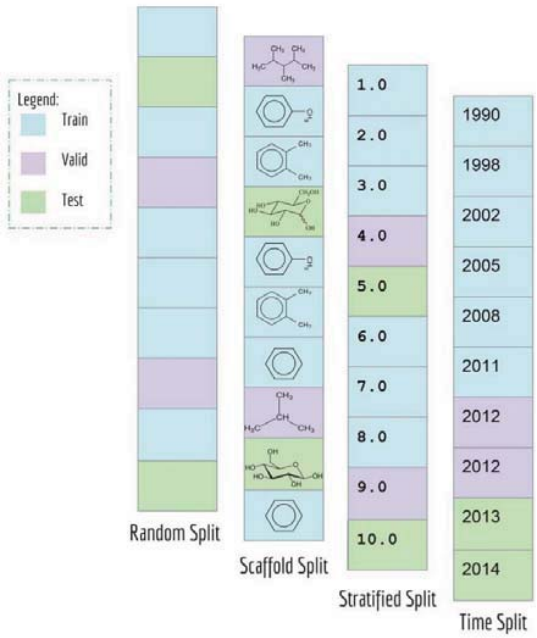
External Test Sets and Cross Validation

- The most basic approach for assessing models involves splitting a dataset into a training set and a test set (or validation set).
- Train your model until prediction error is minimized on a test set.
- Finally test the model accuracy on an independent test set



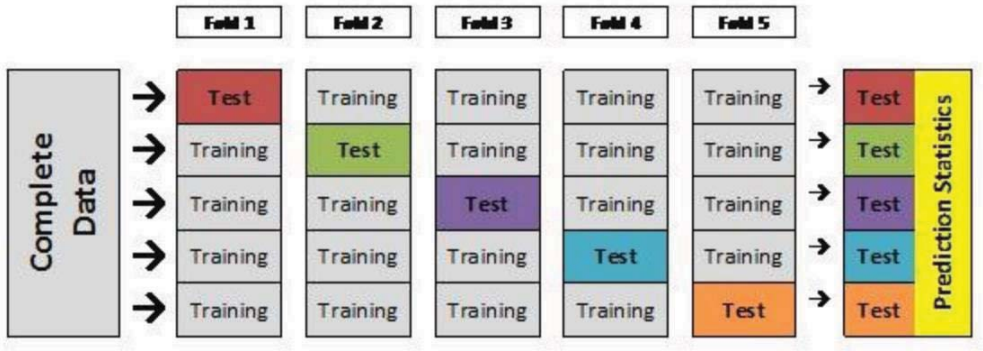
Data Splitting

- A number of different methods for splitting datasets
  - Random
  - Stratified
  - Cluster-based (scaffold split)
  - Temporal:
    - Chembl20 (training), Chembl21 (test)



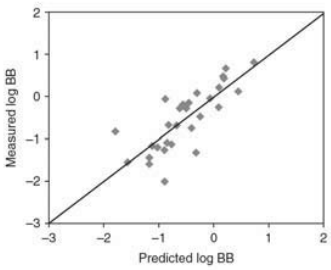
Cross Validation

- Cross- validation
  - Leave-one-out, leave-cluster-out, *n*-fold cross validation
- Additional validation set

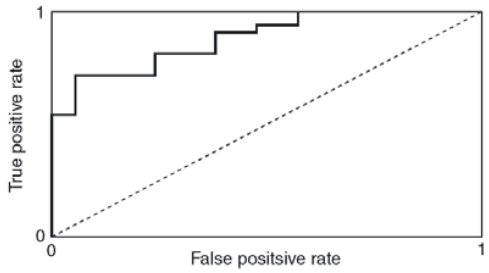


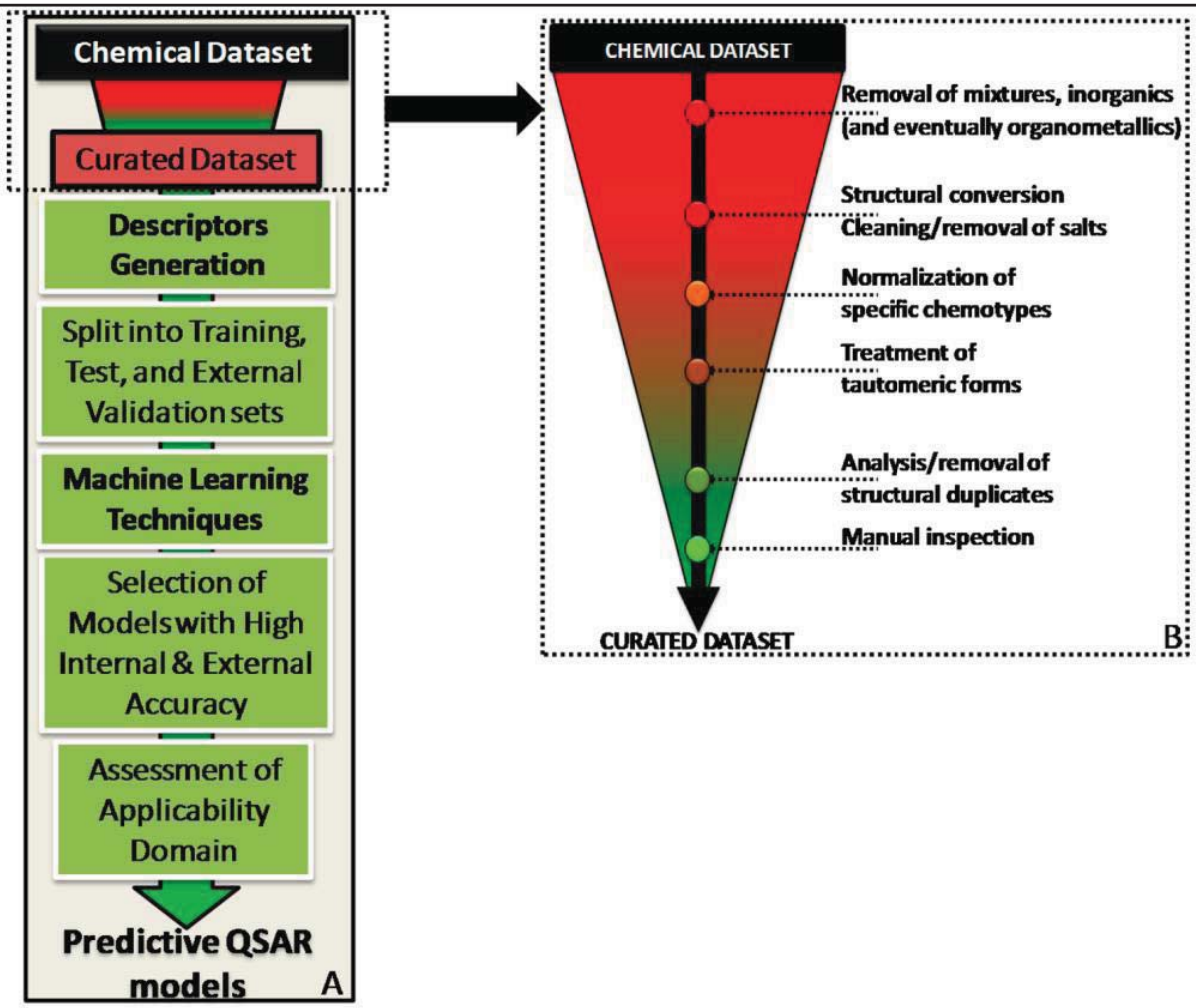
Assessing Model Performance

- https://towardsdatascience.com/metrics-to-evaluate-your-machine-learning-algorithm-f10ba6e38234
- Regression Problems
  - MAE, MSE, RMSE, Pearson correlation coefficient, Spearman Rank Correlation
- Classification Problems
  - Classification Accuracy, Precision, Recall, F1 score, AUC, PRC



Statistic	Value
N	29
$Stdev_y$	0.73
RMSE	0.44
r_2	0.63
q_2	0.55

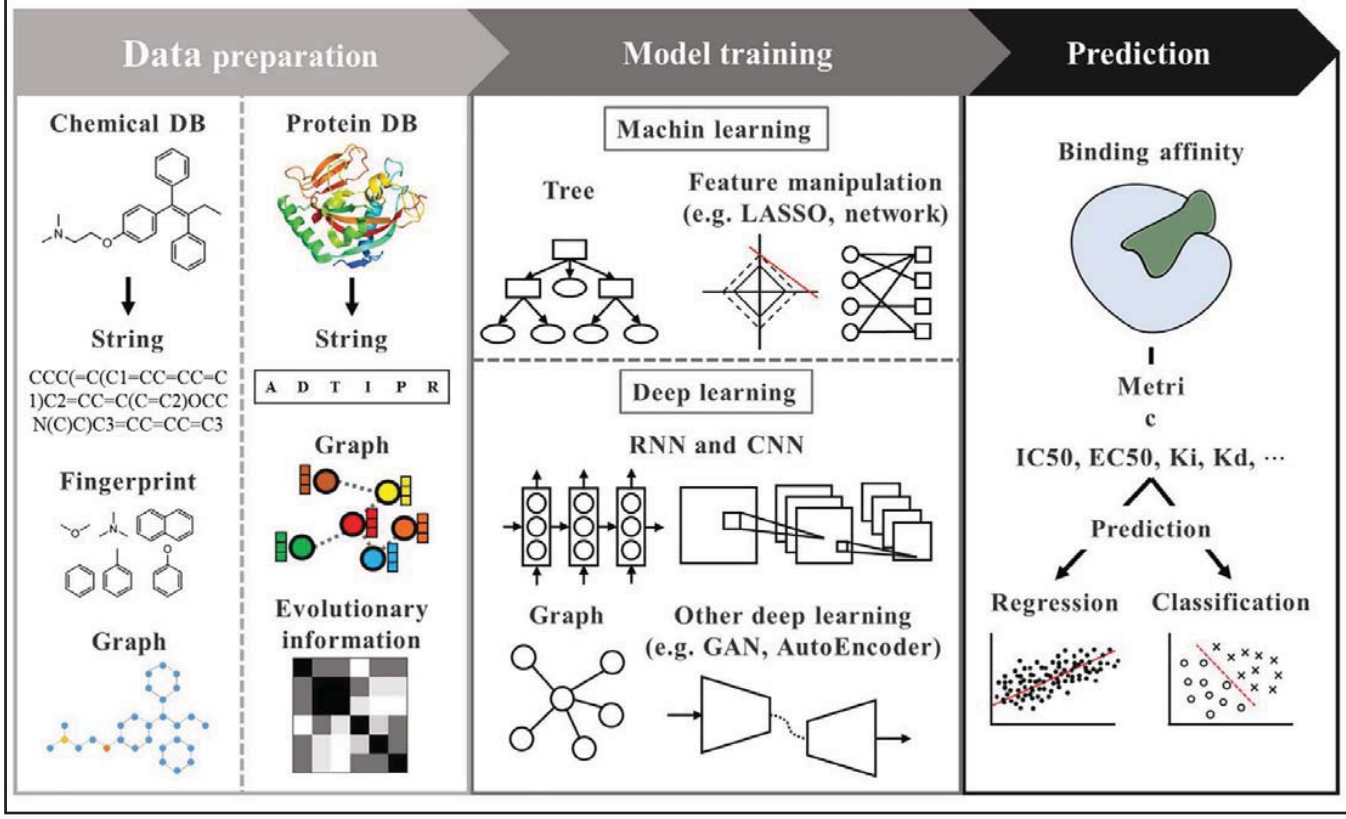




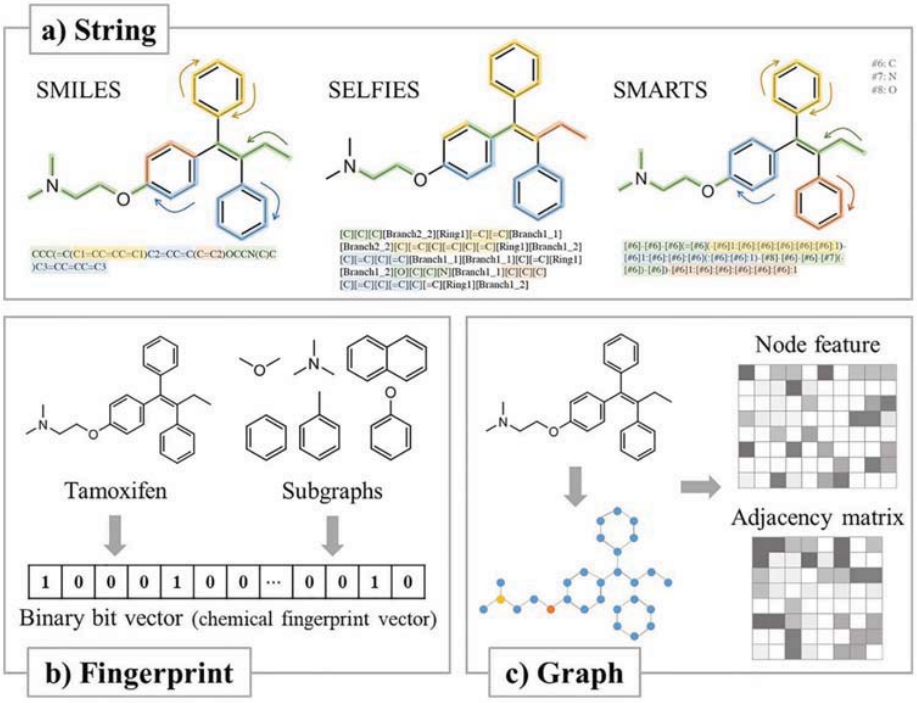
Lower limit

- If training sets are too small, correlation and over-fitting problem.
- Continuous response variable (activity),
  - the number of compounds in the training set should be at least 20
  - about 10 compounds should be in each of the test and external evaluation sets.
- Classification or category response variable
  - training set should contain at least about 10 compounds of each class
  - test and external evaluation sets should contain no less than five compounds for each class.

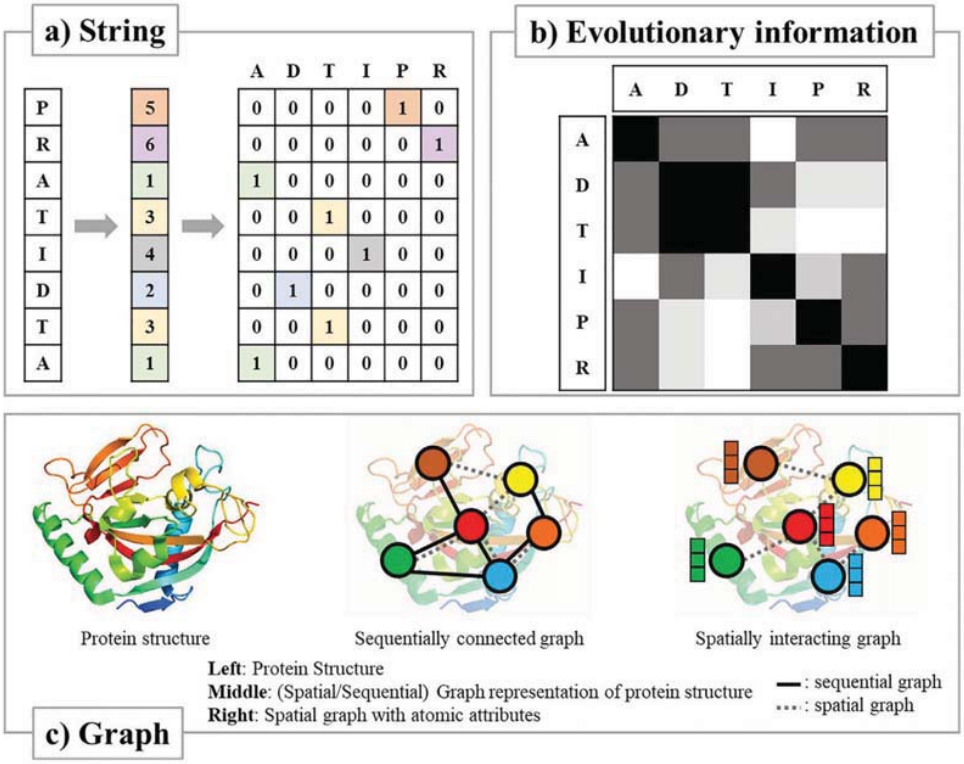
ML Approaches: Overall Process



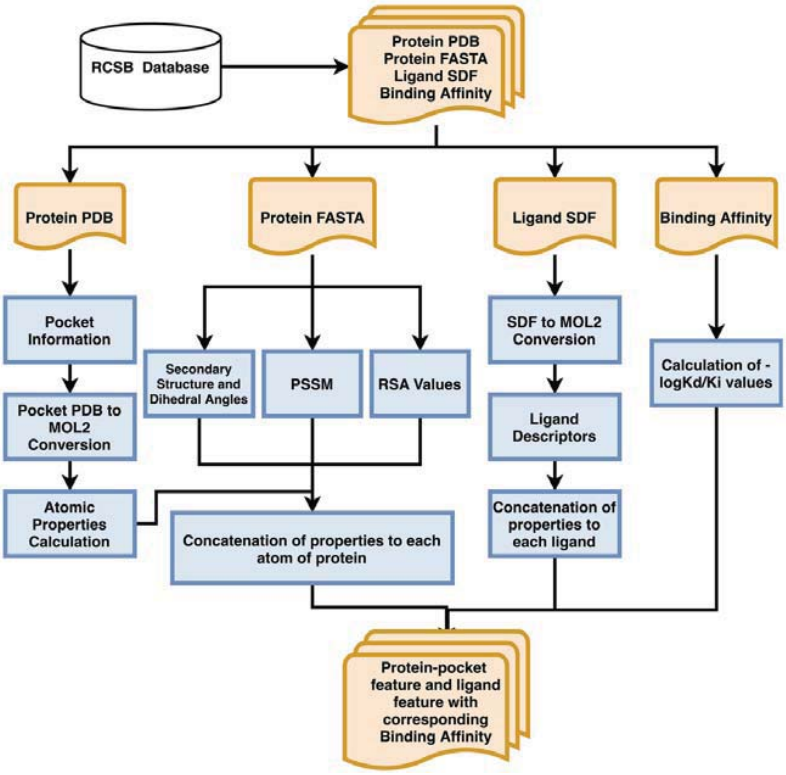
Ligand Featurization



Protein Featurization



Feature extraction pipeline

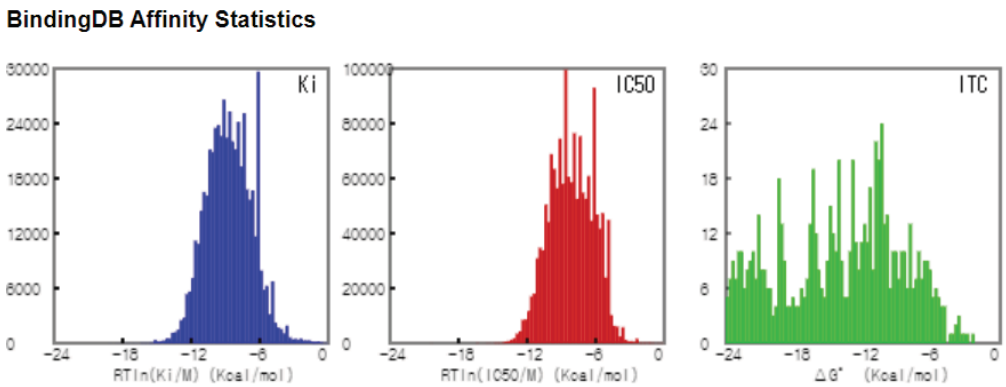


Database

Protein-centric databases	Compounds	Proteins	Interactions
UniProt	–	20,385	–
Protein Data Bank	–	170,597	–
PDBbind	11,762	3,566	17,679*
Pfam	–	18,259	–
BRENDA	46	8083**	500 k
Integrated databases			
	Compounds	Proteins	Interactions
KEGG	18,749***	31,224,482****	–
BindingDB	910,479	8,161	2.1 m
Davis	72	442	30 k
K KIBA	229	211	118 k
IUPHAR/BPS	10,053	2,943	48,902

BindingDB

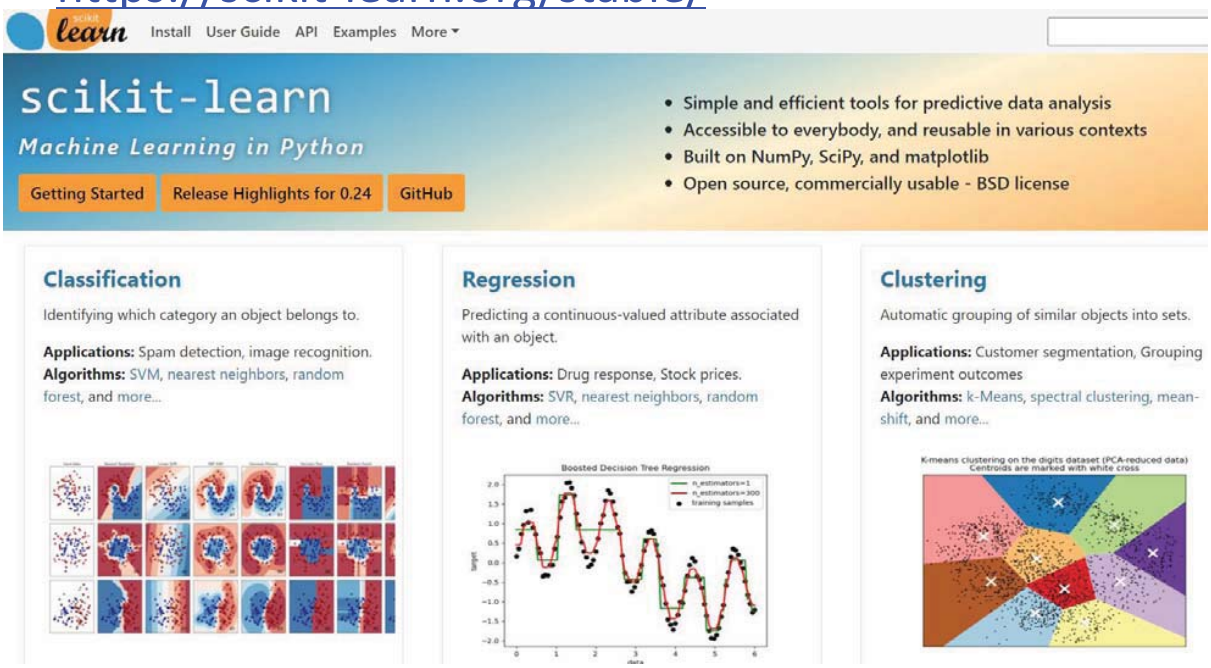
- https://www.bindingdb.org/rwd/bind/
- As of July 24, 2022, 2,546,129 binding data for 8,821 protein targets and 1,093,579 small molecules
- https://www.bindingdb.org/bind/glossary.jsp



QSAR를 위한 기계학습법

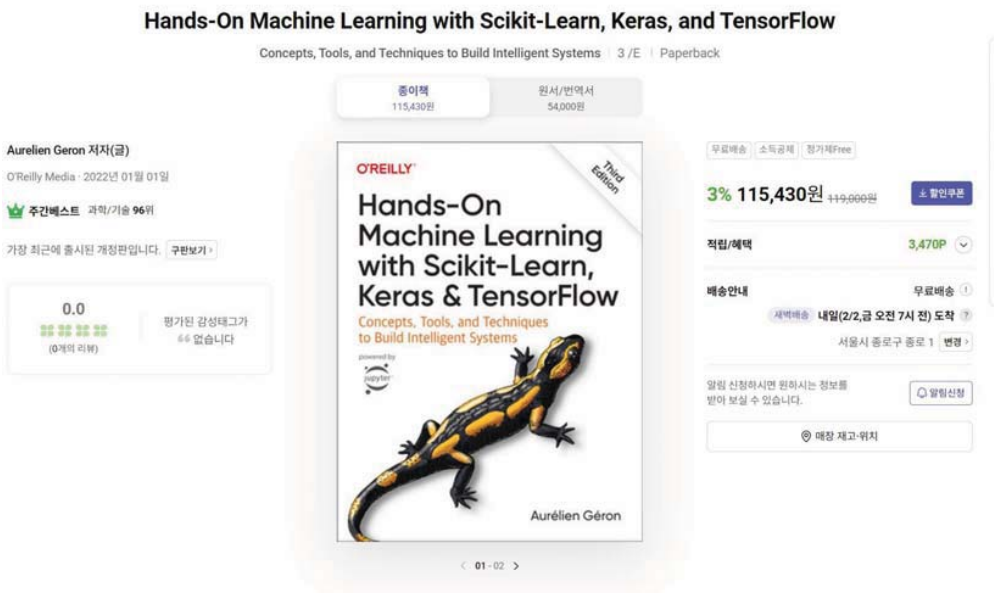
Scikit-learn

- https://scikit-learn.org/stable/



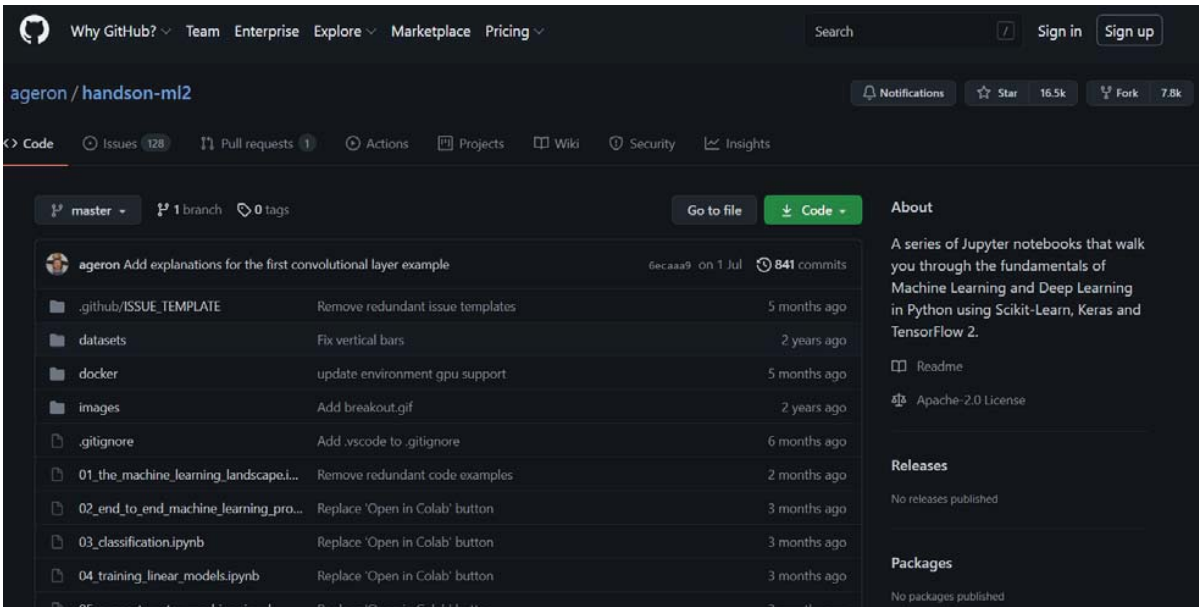
Machine learning book

- https://product.kyobobook.co.kr/detail/S000200135401



Codes

- https://github.com/ageron/handson-ml3

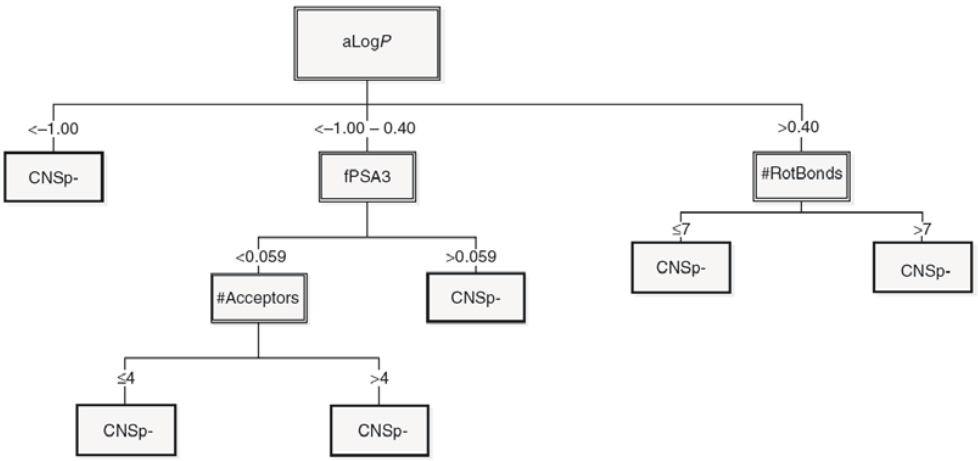


기계학습법 (Machine learning)

- Simple methods
  - Linear regression-based methods
  - Decision tree
  - k-nearest neighbor (kNN)
- Nonlinear methods
  - Random Forest
  - XGboost
  - Support vector machine (SVM)
- Deep learning methods
  - Deep neural network
  - Convolutional neural network
  - Recurrent neural network
  - Graph neural network

Decision Tree

- Decision trees are another interpretable approach to QSAR modeling that produce predictions by applying a series of descriptor-based rules to a compound.



Example

```
from sklearn.datasets import load_iris
from sklearn.tree import DecisionTreeClassifier

iris = load_iris()
X = iris.data[:, 2:] # petal length and width
y = iris.target

tree_clf = DecisionTreeClassifier(max_depth=2)
tree_clf.fit(X, y)
```

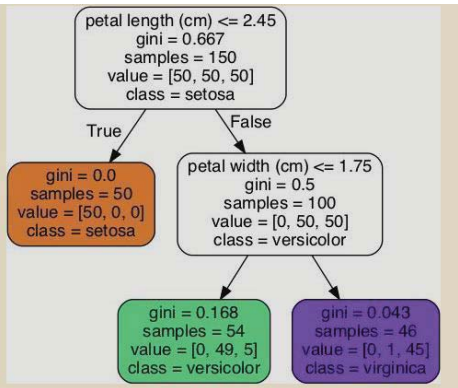


Figure 6-1. Iris Decision Tree

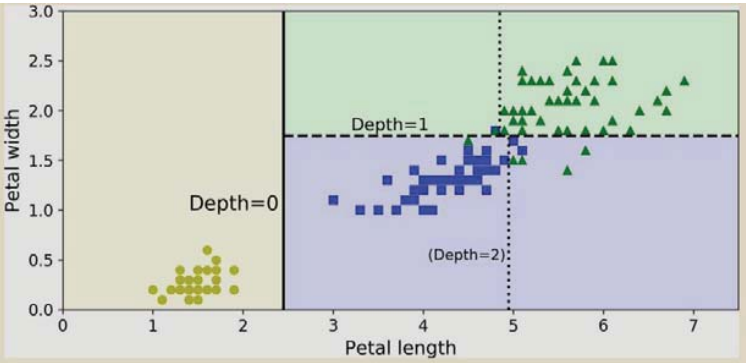


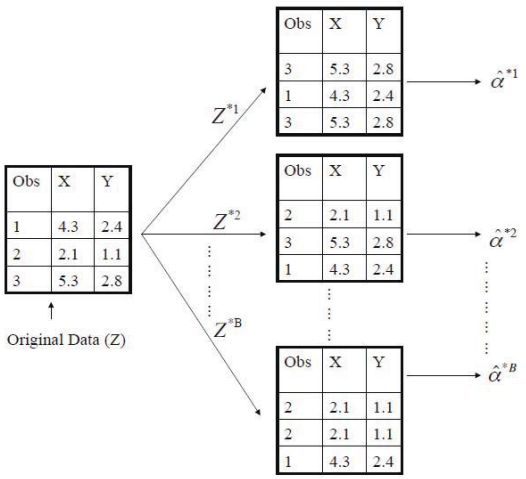
Figure 6-2. Decision Tree decision boundaries

Pros and Cons

- Tree-based methods are simple and useful for interpretation.
- However, they typically are not competitive with the best supervised learning approaches in terms of prediction accuracy.
- Bagging, random forests, and boosting methods grow multiple trees which are then combined to yield a single consensus prediction.
- Combining a large number of trees can often result in dramatic improvements in prediction accuracy, at the expense of some loss interpretation.

Bootstrapping

- Obtain distinct data sets by repeatedly sampling observations from the original data set with *replacement*.
- Each of the “bootstrap data sets" is the same size as our original dataset.



Bagging

- ***B**ootstrap **agg**regation*, or *bagging*

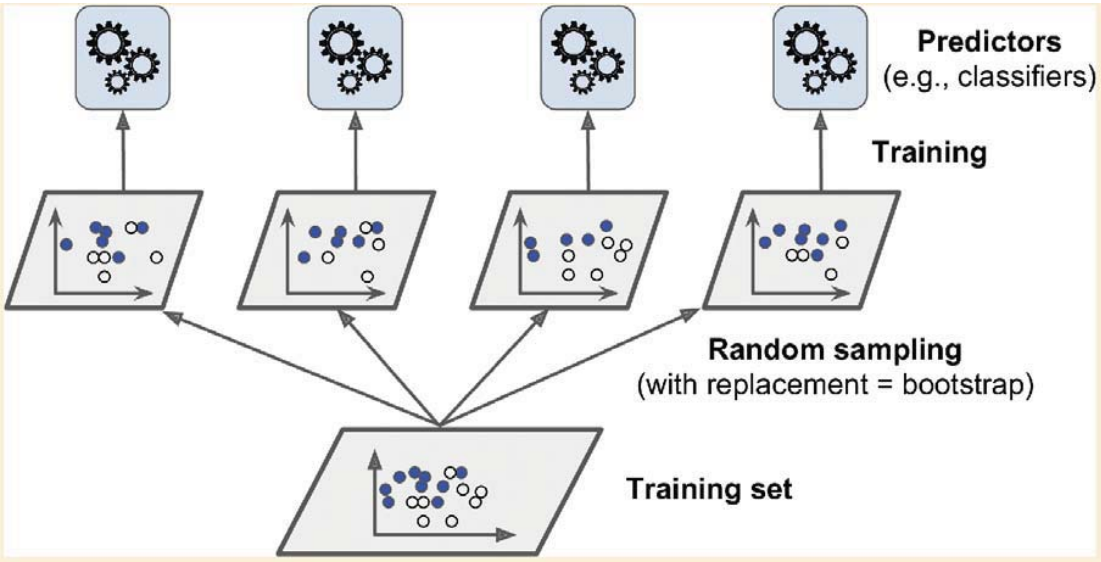
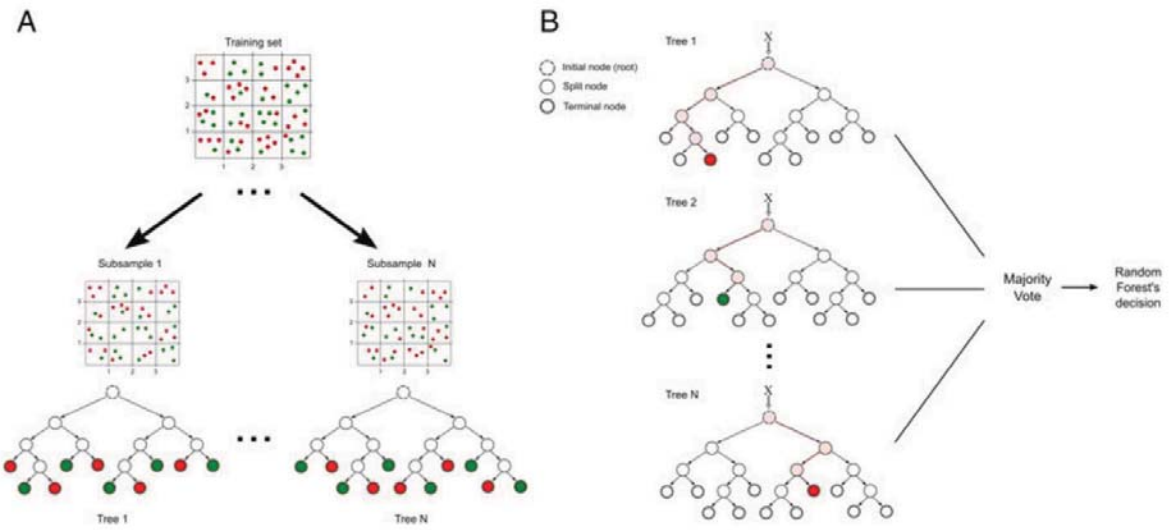


Figure 7-4. Bagging and pasting involves training several predictors on different random samples of the training set

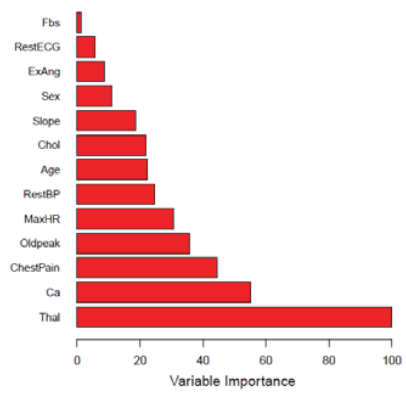
Random Forest

- Become the industry standard method for generating global QSAR models.



Variable importance measure

- For bagged/RF regression trees, we record the total amount that the RSS is decreased due to splits over a given predictor, averaged over all *B* trees.
- A large value indicates an important predictor.
- Similarly, for bagged/RF classification trees, we add up the total amount that the Gini index is decreased by splits over a given predictor, averaged over all *B* trees.



Variable importance plot for the Heart data

RF Codes

```
from sklearn.ensemble import RandomForestClassifier

rnd_clf = RandomForestClassifier(n_estimators=500, max_leaf_nodes=16,
n_jobs=-1)
rnd_clf.fit(X_train, y_train)

y_pred_rf = rnd_clf.predict(X_test)
```

```
>>> from sklearn.datasets import load_iris
>>> iris = load_iris()
>>> rnd_clf = RandomForestClassifier(n_estimators=500, n_jobs=-1)
>>> rnd_clf.fit(iris["data"], iris["target"])
>>> for name, score in zip(iris["feature_names"],
rnd_clf.feature_importances_):
...     print(name, score)
...
sepal length (cm) 0.112492250999
sepal width (cm) 0.0231192882825
petal length (cm) 0.441030464364
petal width (cm) 0.423357996355
```

Boosting

- Bagging involves creating multiple copies of the original training data set using the bootstrap, fitting a separate decision tree to each copy, and then combining all of the trees in order to create a single predictive model.
- Notably, each tree is built on a bootstrap data set, independent of the other trees.
- Boosting works in a similar way, except that the trees are grown sequentially: each tree is grown using information from previously grown trees.

AdaBoost

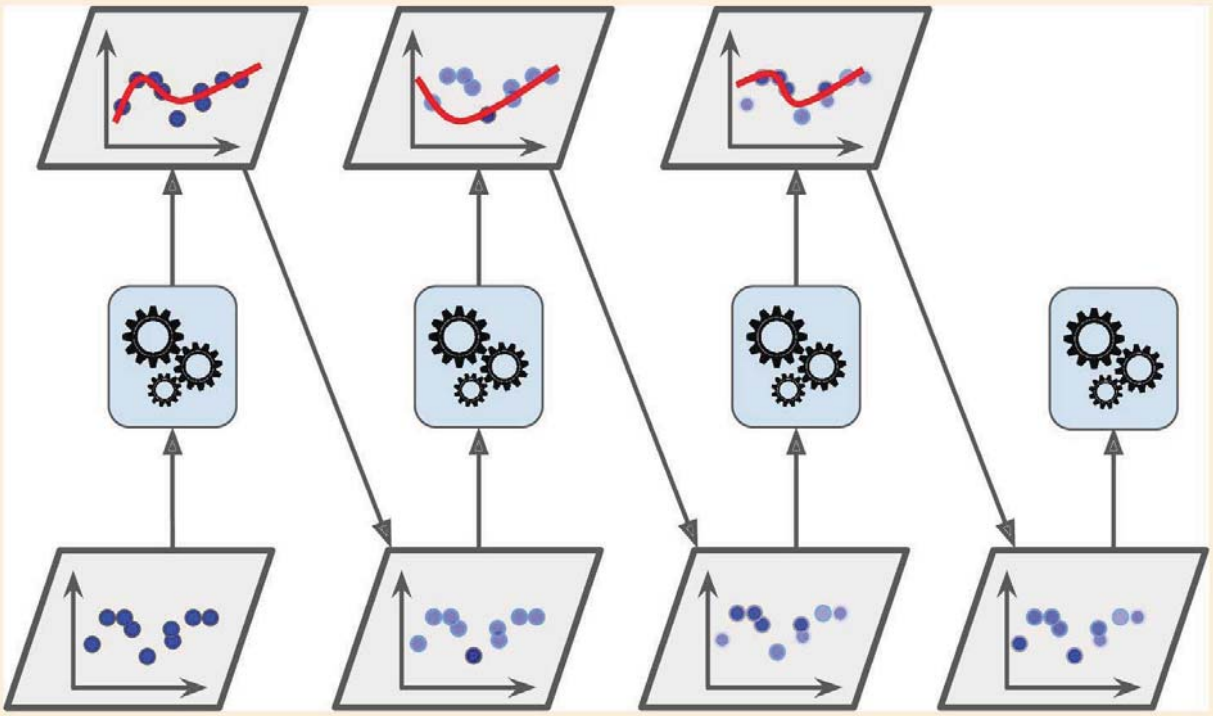
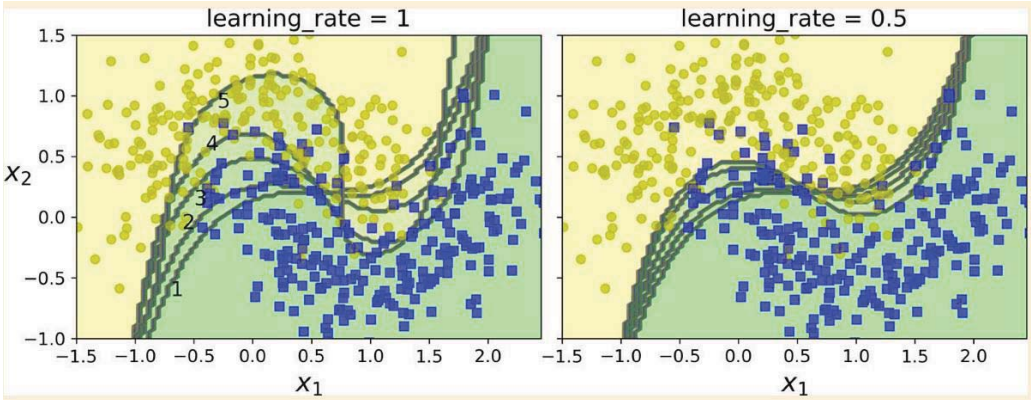


Figure 7-7. AdaBoost sequential training with instance weight updates

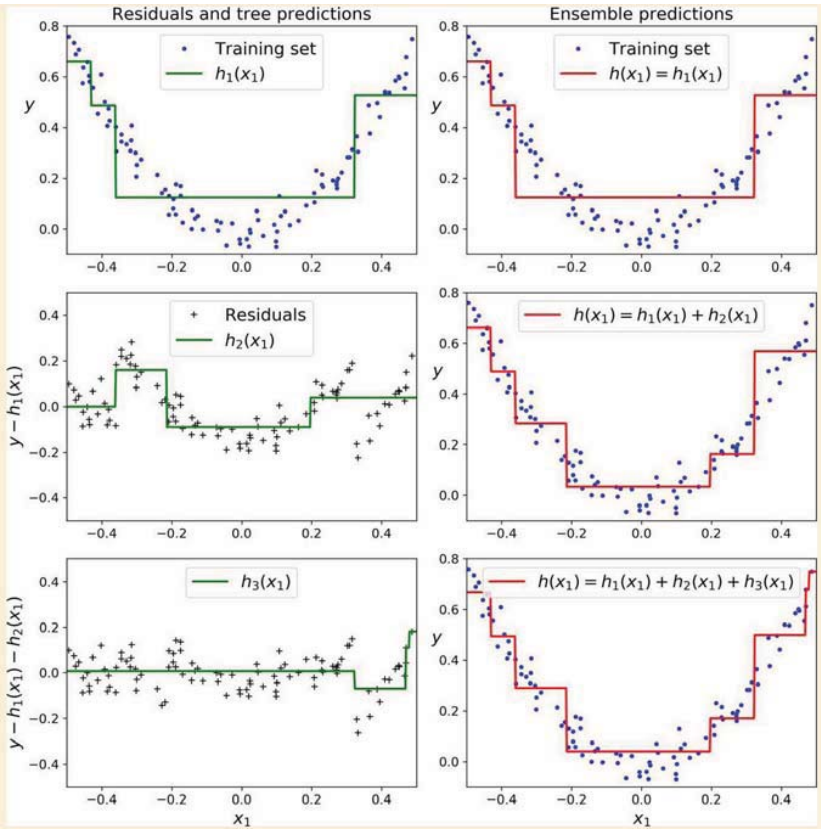
AdaBoost Code

```
from sklearn.ensemble import AdaBoostClassifier

ada_clf = AdaBoostClassifier(
    DecisionTreeClassifier(max_depth=1), n_estimators=200,
    algorithm="SAMME.R", learning_rate=0.5)
ada_clf.fit(X_train, y_train)
```



Gradient Boosting

- Just like AdaBoost, Gradient Boosting works by sequentially adding predictors to an ensemble, each one correcting its predecessor.
- However, instead of tweaking the instance weights at every iteration like AdaBoost does, this method tries to fit the new predictor to the residual errors made by the previous predictor.




```
from sklearn.ensemble import GradientBoostingRegressor

gbrt = GradientBoostingRegressor(max_depth=2, n_estimators=3, learning_rate=1.0)
gbrt.fit(X, y)
```

XGBoost

- Extreme Gradient Boosting
- Very popular, and known to be accurate

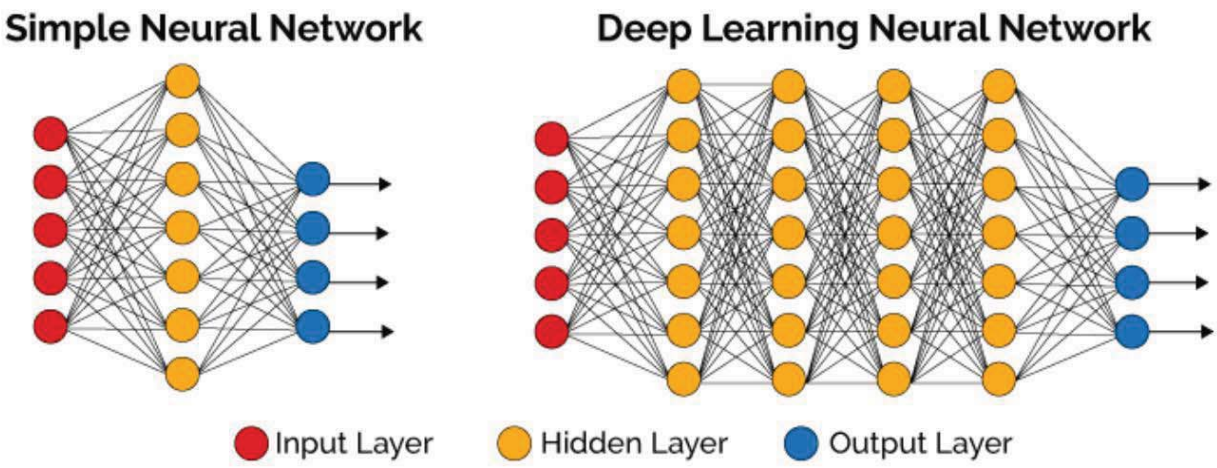
```
import xgboost

xgb_reg = xgboost.XGBRegressor()
xgb_reg.fit(X_train, y_train)
y_pred = xgb_reg.predict(X_val)
```

- XGBoost also offers several nice features, such as automatically taking care of early stopping:

```
xgb_reg.fit(X_train, y_train,
            eval_set=[(X_val, y_val)], early_stopping_rounds=2)
y_pred = xgb_reg.predict(X_val)
```

- https://www.kaggle.com/stuarthallows/using-xgboost-with-scikit-learn

Deep learning methods



Drug Discovery

The rise of deep learning in drug discovery

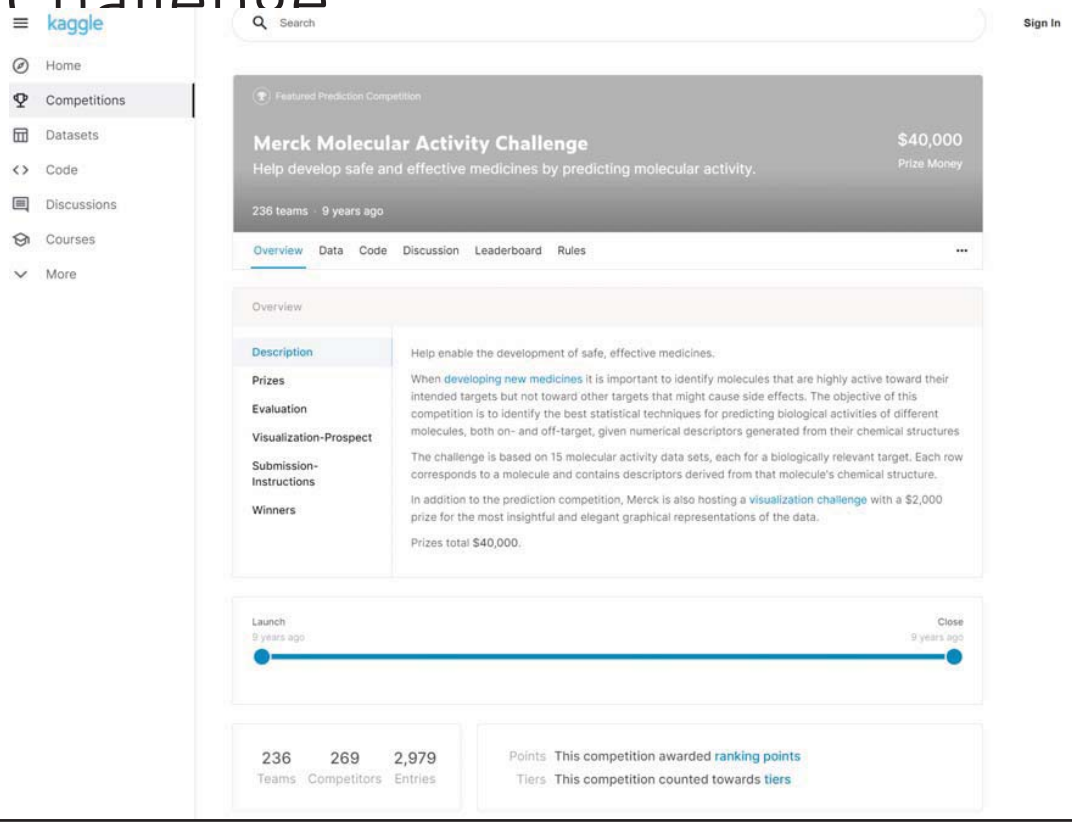
Hongming Chen[1], Ola Engkvist[1], Yinhai Wang[2], Marcus Olivecrona[1] and Thomas Blaschke[1]

[1] Hit Discovery, Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca R&D Gothenburg, Mölndal 43183, Sweden
[2] Quantitative Biology, Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Unit 310, Cambridge Science Park, Milton Road, Cambridge CB4 0WG, UK

Over the past decade, deep learning has achieved remarkable success in various artificial intelligence research areas. Evolved from the previous research on artificial neural networks, this technology has shown superior performance to other machine learning algorithms in areas such as image and voice recognition, natural language processing, among others. The first wave of applications of deep learning in pharmaceutical research has emerged in recent years, and its utility has gone beyond bioactivity predictions and has shown promise in addressing diverse problems in drug discovery. Examples will be discussed covering bioactivity prediction, *de novo* molecular design, synthesis prediction and biological image analysis.

Drug Discovery Today, 23:1241 (2018)

Merck Molecular Activity Challenge



Winner

essentially creating 15 difficult prediction tasks in one.

An In-the-Wild Test of Deep Learning

Competition was intense, with more than 2900 entries in just 60 days. The winners, a group of Kaggle newcomers led by graduate student George Dahl, used a deep learning model originally developed for speech recognition. The winners demonstrated that deep learning—a powerful form of artificial neural network, based on the way that the human brain learns and represents information — could provide accurate predictions with no domain specific expertise or data preprocessing. The winning result represented a 17% improvement over an industry standard benchmark and was the first time that deep learning won a Kaggle competition, opening exciting new avenues for computer-aided pharmaceutical research.

Further reading—

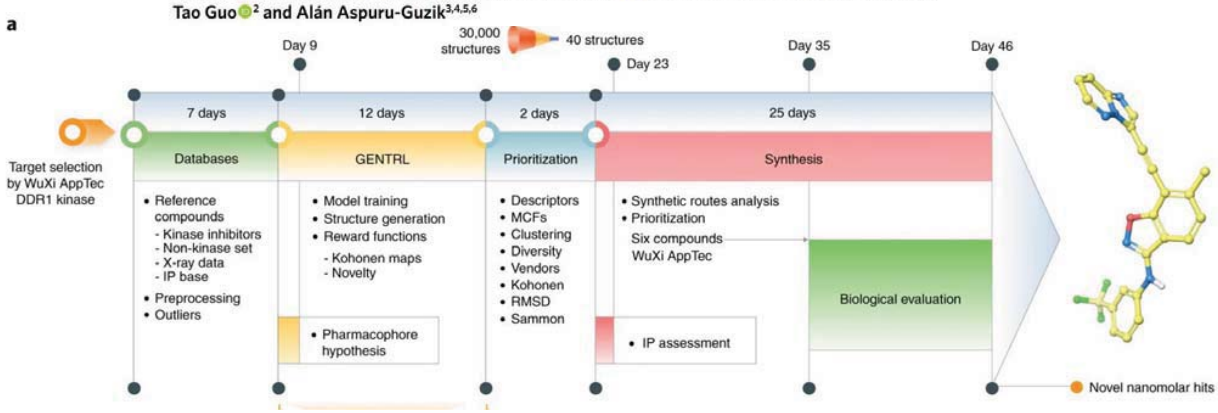
Industry domain	Pharmacology
Data Type	Anonymized molecular structure and activity data
Task	Predict activity levels between molecules and biologically relevant targets
Participants	269 participants on 236 teams
No. of entries	2979
Length of competition	60 days
Winning Method	Deep learning neural networks
Prizes	$40,000

AI 신약개발 (Deep Learning 모델)

BRIEF COMMUNICATION
https://doi.org/10.1038/s41587-019-0224-x
nature biotechnology

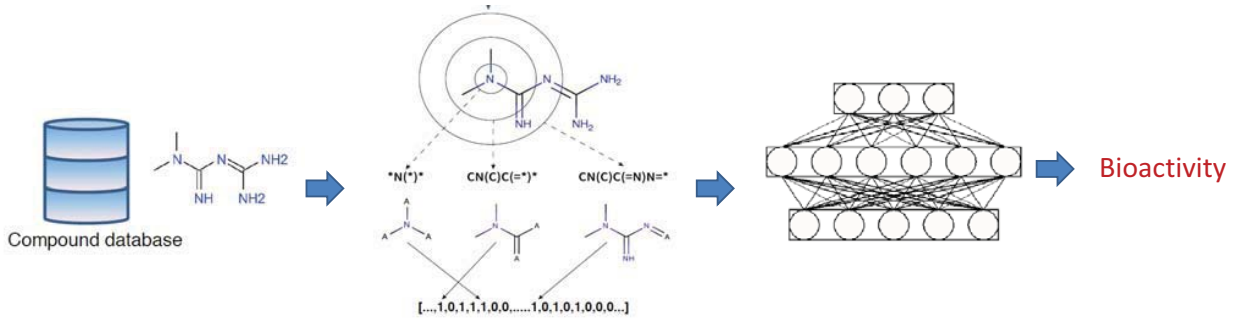
Deep learning enables rapid identification of potent DDR1 kinase inhibitors

Alex Zhavoronkov[1*], Yan A. Ivanenkov[1], Alex Aliper[1], Mark S. Veselov[1], Vladimir A. Aladinskiy[1], Anastasiya V. Aladinskaya[1], Victor A. Terentiev[1], Daniil A. Polykovskiy[1], Maksim D. Kuznetsov[1], Arip Asadulaev[1], Yury Volkov[1], Artem Zholus[1], Rim R. Shayakhmetov[1], Alexander Zhebrak[1], Lidiya I. Minaeva[1], Bogdan A. Zagribelnyy[1], Lennart H. Lee[2], Richard Soll[2], David Madge[2], Li Xing[2], Tao Guo[2] and Alán Aspuru-Guzik[3,4,5,6]



Simple Deep learning model

- QSAR Procedure



Molecular Structures

Features

Deep learning model

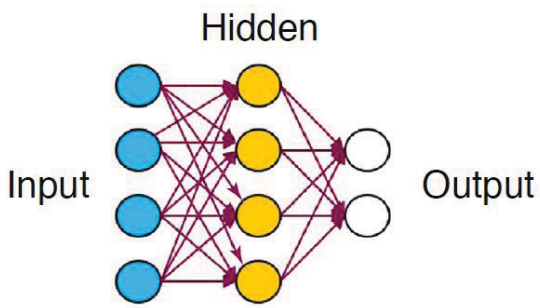
- Issues
  - Featurization 방법
  - DL 모델

Deep Learning

- Conventional machine learning methods for drug discovery.
  - SVM, neural networks, and random forest (RF)
- A difference between most other machine learning methods and DL is the flexibility of the NN architecture in DL.
  - fully connected feed-forward networks (FNN)
  - convolutional neural networks (CNN)
  - recurrent neural networks (RNN)
  - graph convolutional network (GCN)

Principles of deep learning

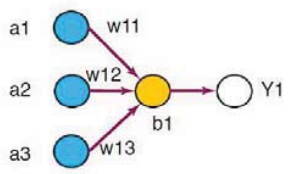
- DL uses artificial neural networks (ANNs) with many layers of nonlinear processing units for learning data representations.
- Three basic layers
  - input layer, hidden layer and output layer



Principles of deep learning

- The interrelationship between input and output values of a hidden unit. Y_i:

$$Y_i = g\left(\sum_j W_{ij} * a_j\right)$$



  - a_j: the input variables
  - W_{ij}: weight of input node j on node i
  - g: activation function, which is normally a nonlinear function (e.g., sigmoid or relu)
- The training of an ANN is done by iterative modification of the weight values through the back-propagation methods.

Principles of deep learning

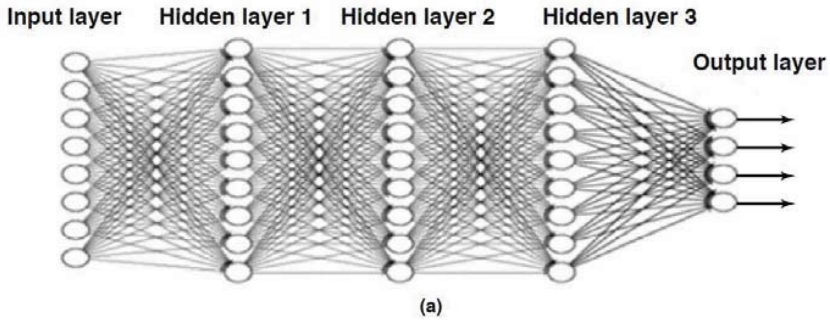
- Problems of traditional ANN
  - Overfitting
  - Vanishing gradients
- Algorithmic improvements in DL:
  - Dropout to address overfitting problem
  - Rectified linear unit (ReLU) to avoid vanishing gradients
  - Many novel network architectures
- Most of the DL software packages are open-sourced
  - TensorFlow, PyTorch
- Hardware: GPU, TPU
- Data, Data, Data

Popular Architectures

- Fully connected deep neural network (FCN)
- Convolutional neural network (CNN)
- Recurrent neural network (RNN)
- Graph convolutional network (GCN)
- Autoencoder (AE)

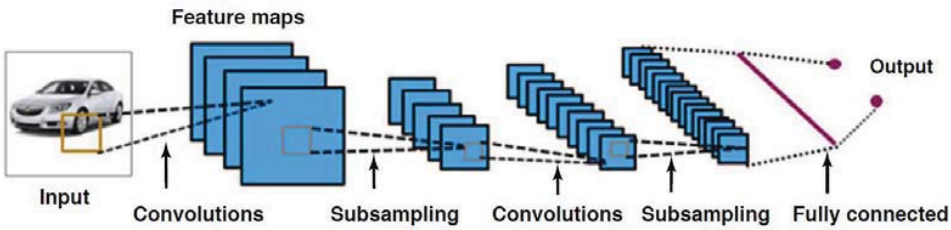
Fully connected deep neural network (FCN)

- Contains multiple hidden layers and each layer comprises hundreds of nonlinear process units
- FCNs can take large numbers of input features.
- Molecular Features: Fingerprint



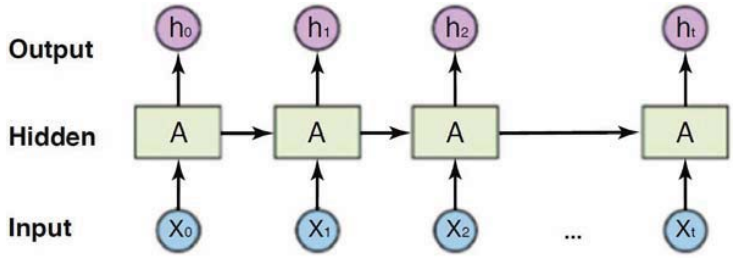
Convolutional neural network (CNN)

- Contains several convolution layers and subsampling layers
- The convolution layer consists of a set of filters (or kernels).
- Each filter is convoluted across the width and height of the input volume.
- The subsampling layer is used to reduce the size of feature maps.
- Owing to sharing the same parameters for each filter, a CNN largely reduces the number of free parameters learned.
- It has outperformed other types of machine learning algorithms in image recognition
- Molecular feature: 2D connection table, SMILES



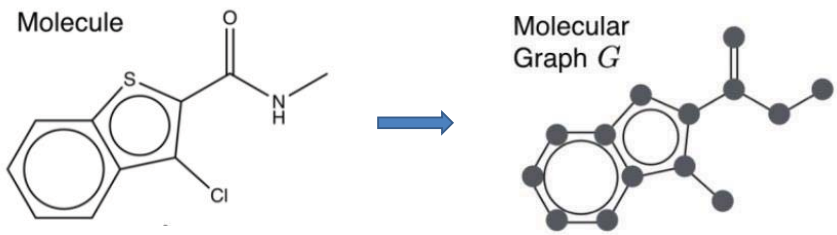
Recurrent neural network (RNN)

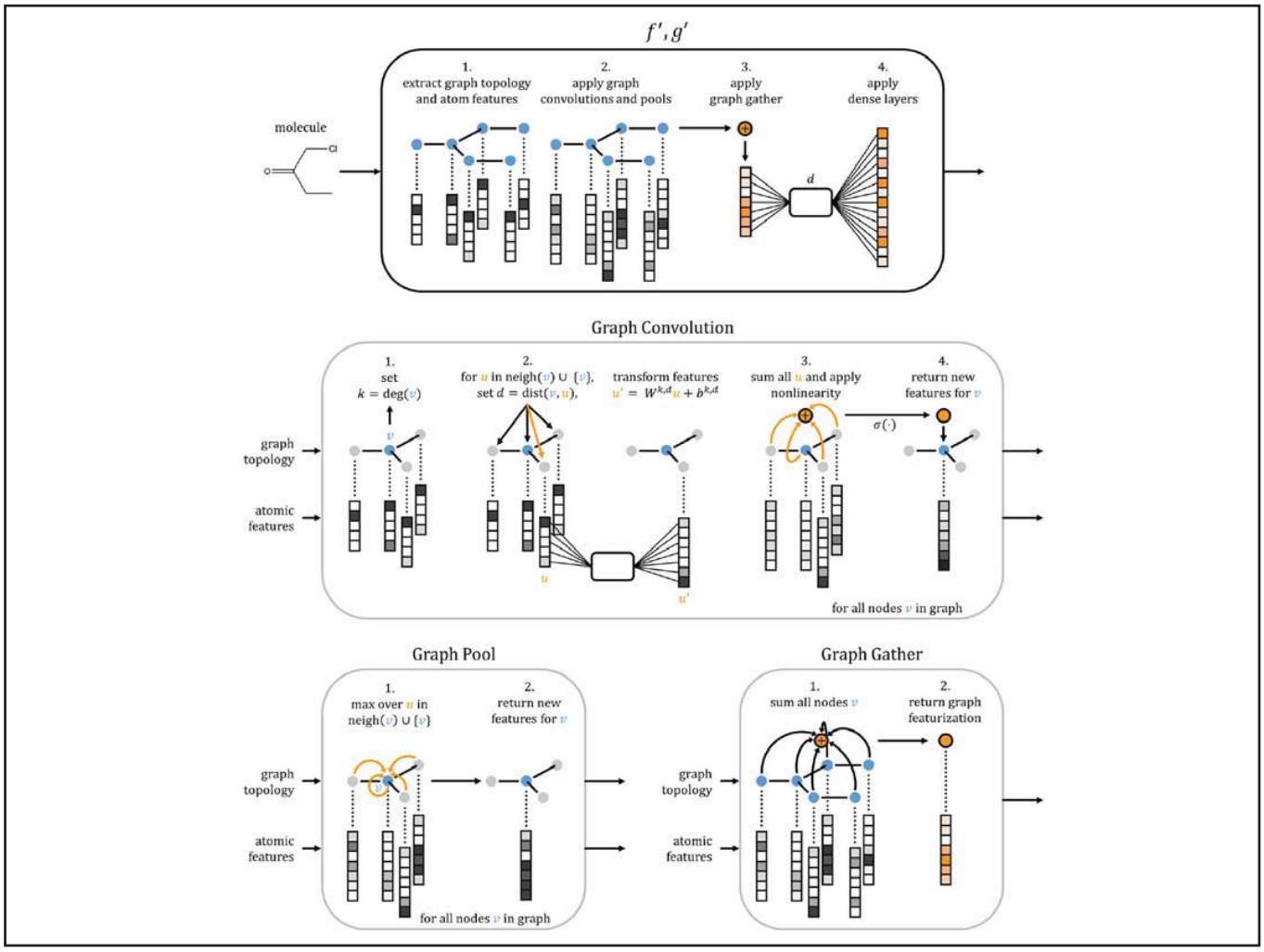
- RNNs can take sequential data as input features, which is very suitable for time-dependent tasks like language modeling.
- Using a technology called long short term memory (LSTM), RNNs can reduce the vanishing gradient problem.
- Molecular feature: SMILES



Graph convolution

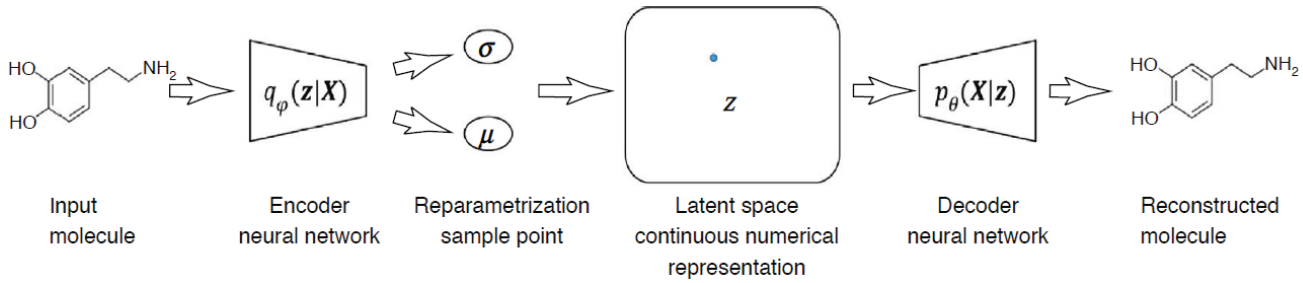
- Inspired by the Morgan circular fingerprint method
- First, the 2D molecular structure is read to form a state matrix, containing atom and bond information for each atom (Graph)
- The state matrix then goes through a convolution operation to generate a fixed length vector as the molecular representation.
- Molecular feature: Graph

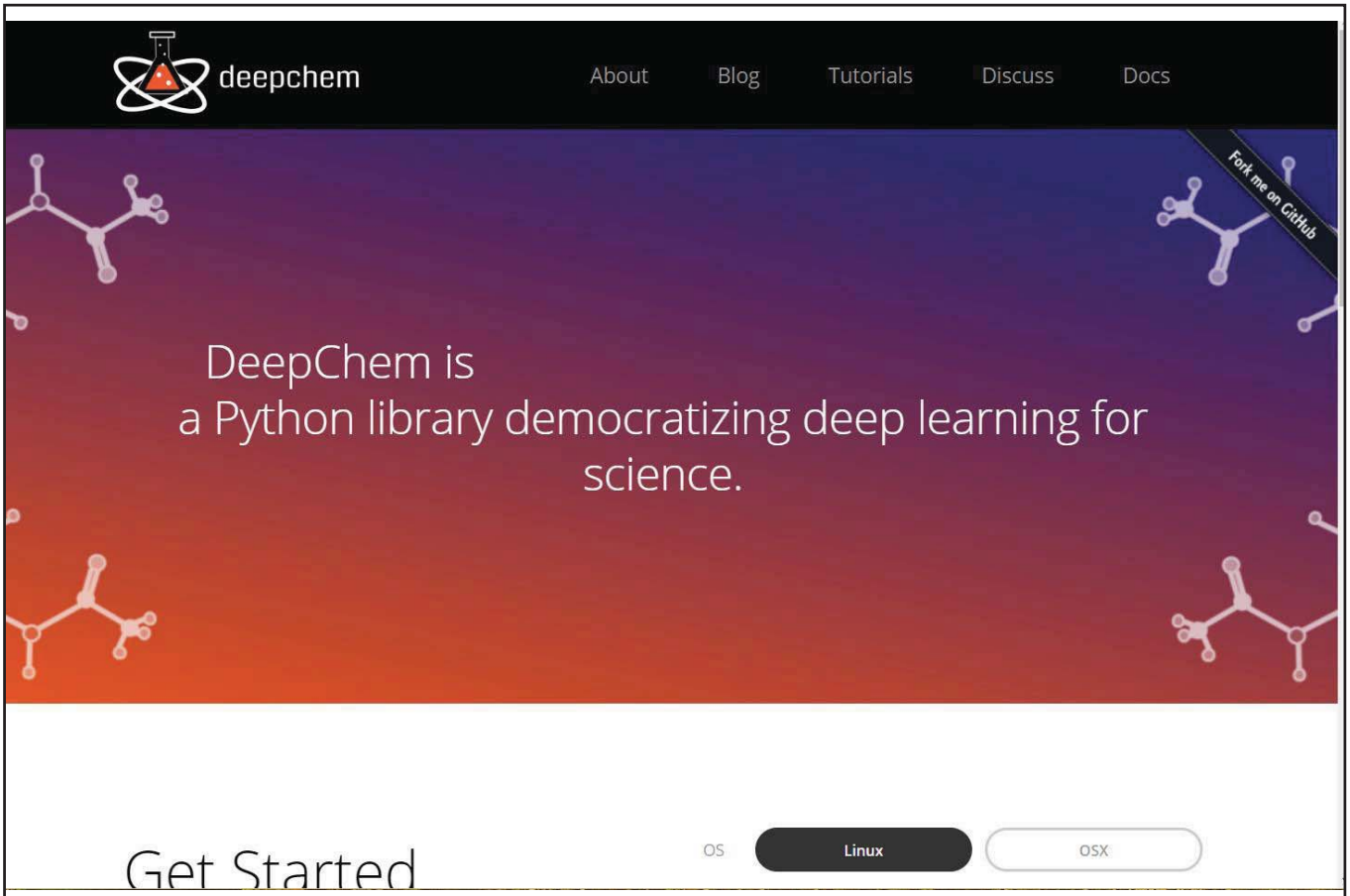




De novo design

- Generation of new chemical structures
- Variational autoencoder (VAE) to generate chemical structures
  - Use VAE to do unsupervised learning to map chemical structures (SMILES strings) in the ZINC database into latent space
  - Latent vector in the latent space becomes a continuous representation of molecular structure
  - and can be reversibly transformed to a SMILES string through the trained VAE
  - Generation of a new structure with desirable properties

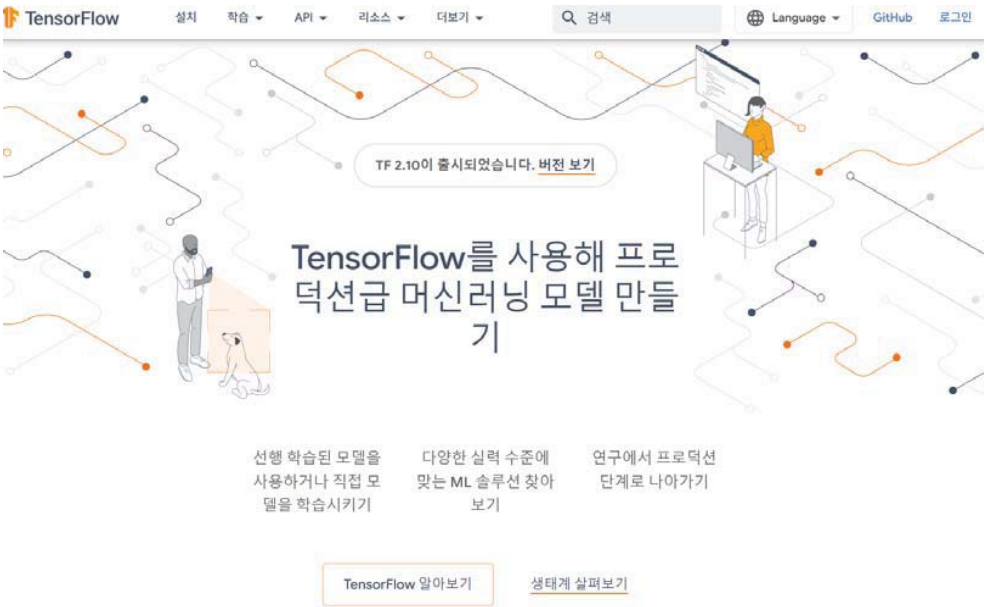




https://deepchem.io/

Tensorflow

- https://www.tensorflow.org



QSAR example: HIV datasets

- The HIV dataset:
  - Ability to inhibit HIV replication for over 40,000 compounds.
- Classification task between inactive (CI) and active (CA and CM)
- The raw data csv file contains columns below:
  - “smiles”: SMILES representation of the molecular structure
  - “HIV_active”: Binary labels for screening results: 1 (CA/CM) and 0 (CI)
- Total 41913, #pos = 1487: highly imbalanced dataset
- https://colab.research.google.com/drive/1r4qF7DAw56_9umrsV3k

smiles	activity	HIV_active
CCC1=[O+][Cu-3]2([O+]=C(CC)C1)[O+]=C(C	CI	0
C(=Cc1ccccc1)C1=[O+][Cu-3]2([O+]=C(C=C	CI	0
CC(=O)N1c2ccccc2Sc2c1ccc1ccccc21	CI	0
Nc1ccc(C=Cc2ccc(N)cc2S(=O)(=O)O)c(S(=O)	CI	0
O=S(=O)(O)CCS(=O)(=O)O	CI	0
CCOP(=O)(Nc1cccc(Cl)c1)OCC	CI	0

Virtual Screening

Virtual Screening

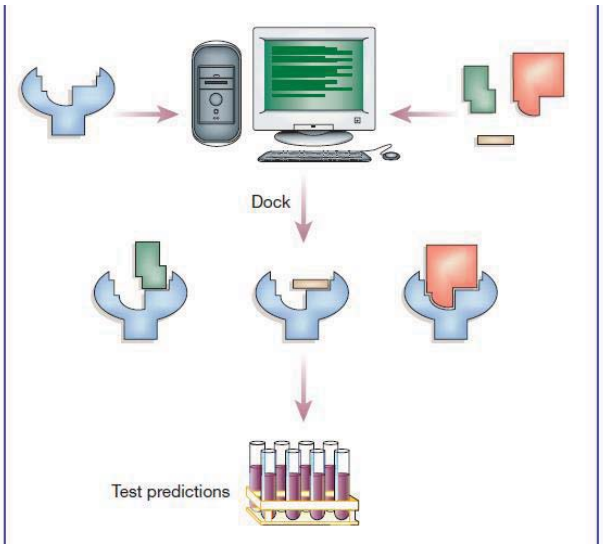


Table 1 **Hit rates and drug-like properties for inhibitors discovered with high-throughput and virtual screening against the enzyme PTP-1B** (ref.19)

Technique	Compounds tested	Hits with $IC_{50} < 100\mu M$	Hits with $IC_{50} < 10\mu M$	Lipinski compliant hits*	Hit rate†
HTS	400,000	85	6	23	0.021%
Docking	365‡	127	18	57	34.8%

*Number of 100 μM or better inhibitors that passed all four of the drug-like criteria identified in Lipinski's 'rule of five'[25]; †The number of compounds experimentally tested divided by the number of compounds with IC_{50} values of 100 μM or less; ‡The number of top-scoring docking hits that were experimentally tested; IC_{50}, The concentration of inhibitor at which the enzyme is 50% inhibited.

리간드 기반 신약 발굴

- Ligand-based Virtual Screening
- Procedure
  - 타겟 선정
  - 타겟 단백질에 관한 정보 수집
  - ChEMBL (or BindingDB) 에서 화합물 데이터 수집
  - Binding affinity 예측 모델 개발 (QSAR)
  - ZINC에서 화합물 라이브러리 구축
  - Virtual screening으로 후보물질 선정
  - Docking 계산, Visual inspection 등을 거쳐 최종 후보물질 발굴

타겟

LAIDD-Practice3-Predicting_pIC50_of_JAK2_inhibitors.ipynb

File Edit View Insert Runtime Tools Help Changes will not be saved

+ Code + Text Copy to Drive

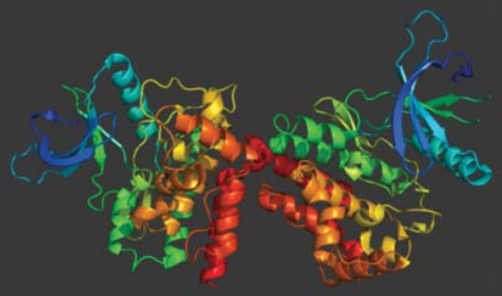
Predicting activity of JAK2 inhibitors

Goal of the class

- Practice the **regression model** using biological data

Janus kinase

Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway. They were initially named "just another kinase" 1 and 2 (since they were just two of many discoveries in a PCR-based screen of kinases),[1] but were ultimately published as "Janus kinase". The name is taken from the two-faced Roman god of beginnings, endings and duality, Janus, because the JAKs possess two near-identical phosphate-transferring domains. One domain exhibits the kinase activity, while the other negatively regulates the kinase activity of the first.



타겟 단백질에 관한 정보

- UniProt: https://www.uniprot.org/uniprotkb/O60674/entry

UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB Advanced | List Search Help

Function
Names & Taxonomy
Subcellular Location
Disease & Variants
PTM/Processing
Expression
Interaction
Structure
Family & Domains
Sequence
Similar Proteins

O60674 · JAK2_HUMAN

Tyrosine-protein kinase JAK2 · **Homo sapiens (Human)** · EC:2.7.10.2 · **Gene:** JAK2 · 1132 amino acids · Evidence at protein level · **Annotation score:** 5/5

Entry Feature viewer Publications External links History

BLAST Align Download Add Add a publication Entry feedback

Function

Non-receptor tyrosine kinase involved in various processes such as cell growth, development, differentiation or histone modifications. Mediates essential signaling events in both innate and adaptive immunity. In the cytoplasm, plays a pivotal role in signal transduction via its association with type I receptors such as growth hormone (GHR), prolactin (PRLR), leptin (LEPR), erythropoietin (EPOR), thrombopoietin (THPO); or type II receptors including IFN-alpha, IFN-beta, IFN-gamma and multiple interleukins (PubMed:7615558).
Following ligand-binding to cell surface receptors, phosphorylates specific tyrosine residues on the cytoplasmic tails of the receptor, creating docking sites for STATs proteins (PubMed:9618263).
Subsequently, phosphorylates the STATs proteins once they are recruited to the receptor. Phosphorylated STATs then form homodimer or heterodimers and translocate to the nucleus to activate gene transcription. For example, cell stimulation with erythropoietin (EPO) during erythropoiesis leads to JAK2 autophosphorylation, activation, and its association with erythropoietin receptor (EPOR) that becomes phosphorylated in its cytoplasmic domain. Then, STAT5 (STAT5A or STAT5B) is recruited, phosphorylated and activated by JAK2. Once activated, dimerized STAT5 translocates into the nucleus and promotes the transcription of several essential genes involved in the modulation of erythropoiesis. Part of a signaling cascade that is activated by increased cellular retinol and that leads to the activation of STAT5 (STAT5A or STAT5B) (PubMed:21368206).
In addition, JAK2 mediates angiotensin-2-induced ARHGEF1 phosphorylation (PubMed:20098430).
Plays a role in cell cycle by phosphorylating CDKN1B (PubMed:21423214).
Cooperates with TEC through reciprocal phosphorylation to mediate cytokine-driven activation of FOS transcription. In the nucleus, plays a key role in chromatin by specifically mediating phosphorylation of 'Tyr-41' of histone H3 (H3Y41ph), a specific tag that promotes exclusion of CBX5 (HP1 alpha) from chromatin (PubMed:19783980). 7 Publications

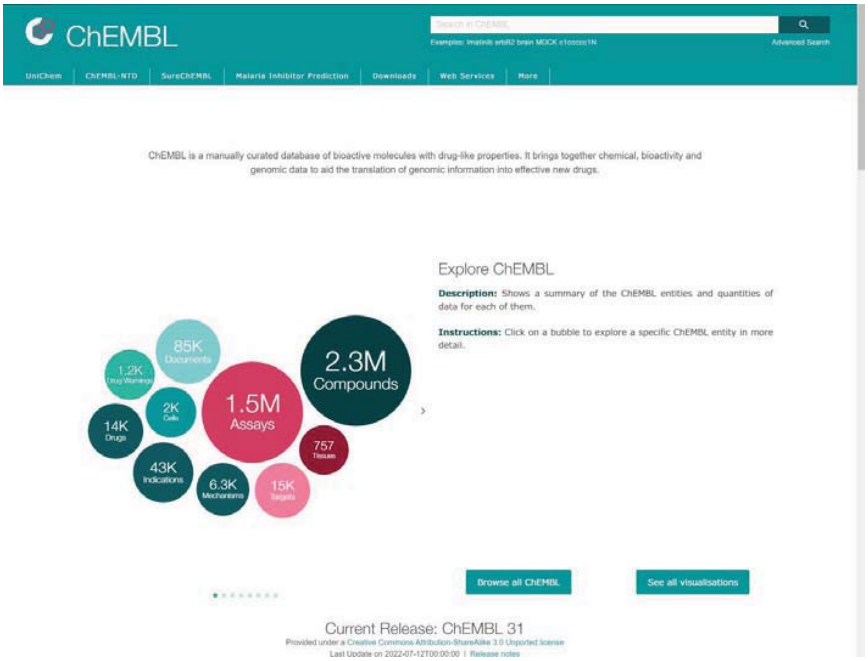
Catalytic Activity

ATP + L-tyrosyl-[protein] = ADP + H$^+$ + O-phospho-L-tyrosyl-[protein] 1 Automatic Annotation 2 Publications
EC:2.7.10.2 (UniProtKB | ENZYME | Rhea)
Source: Rhea 10596

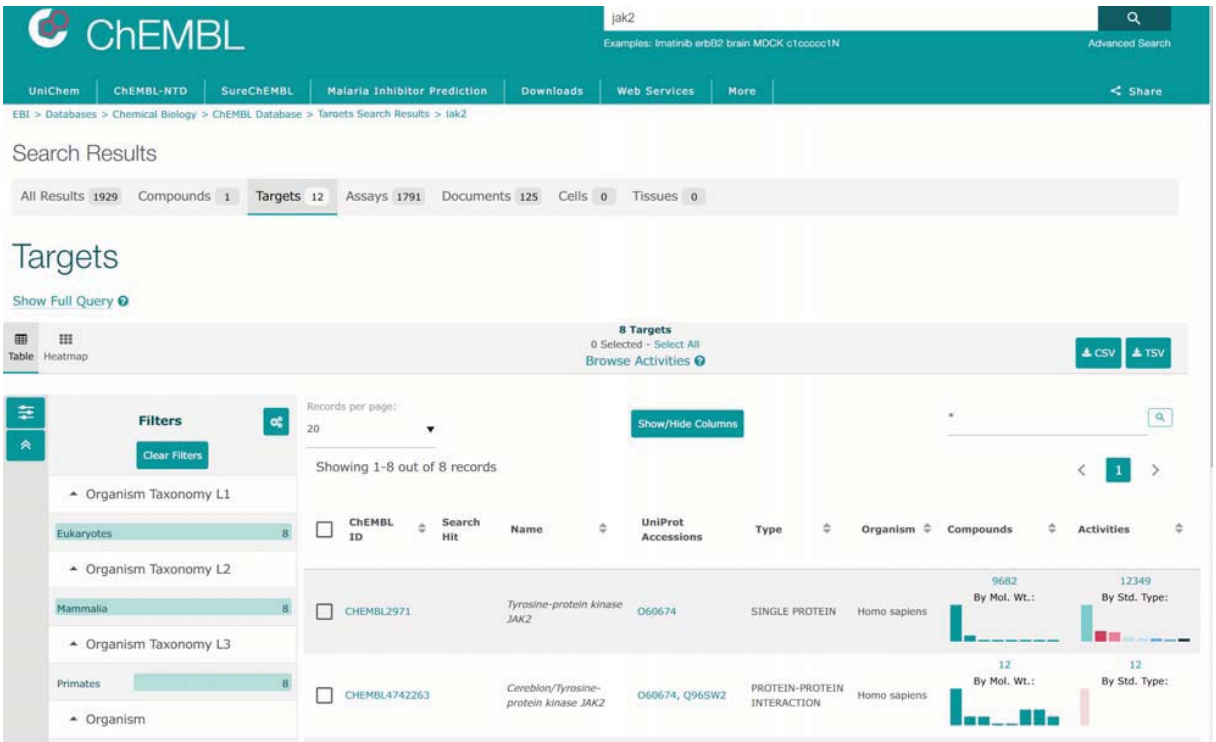
Feedback Help

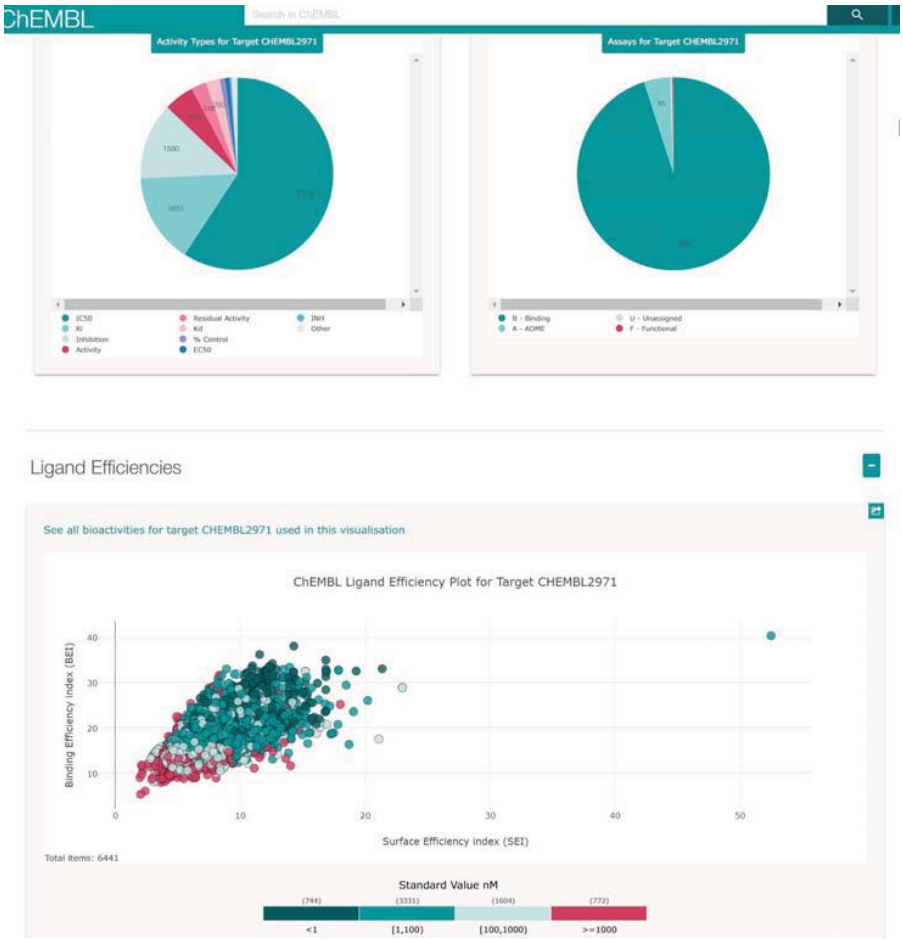
ChEMBL

- https://www.ebi.ac.uk/chembl/



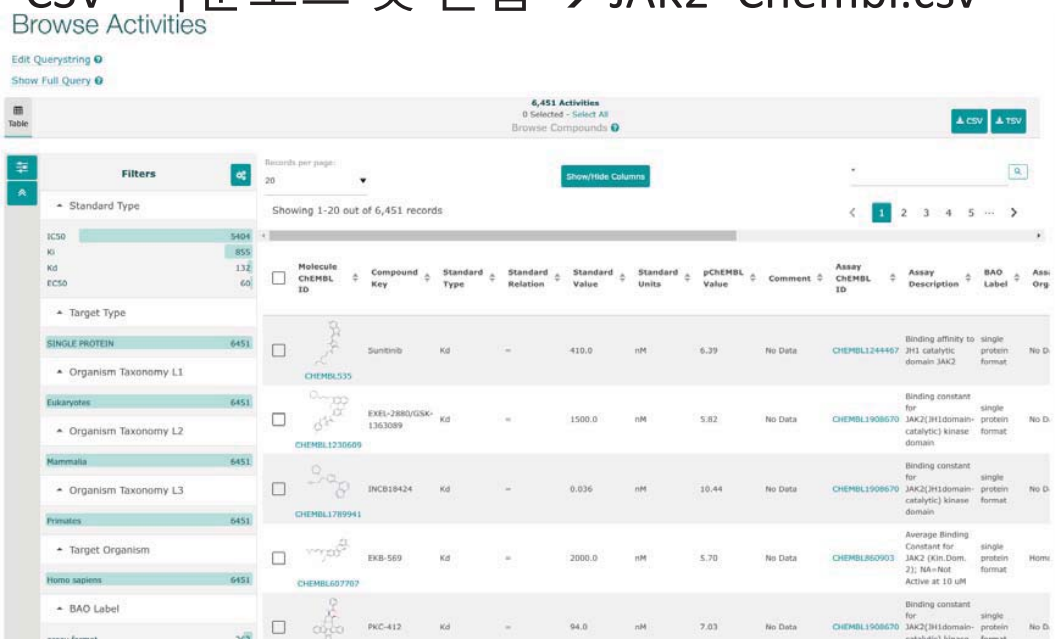
JAK2





Activity Data

- "CSV" 다운로드 및 편집 → JAK2 Chembl.csv

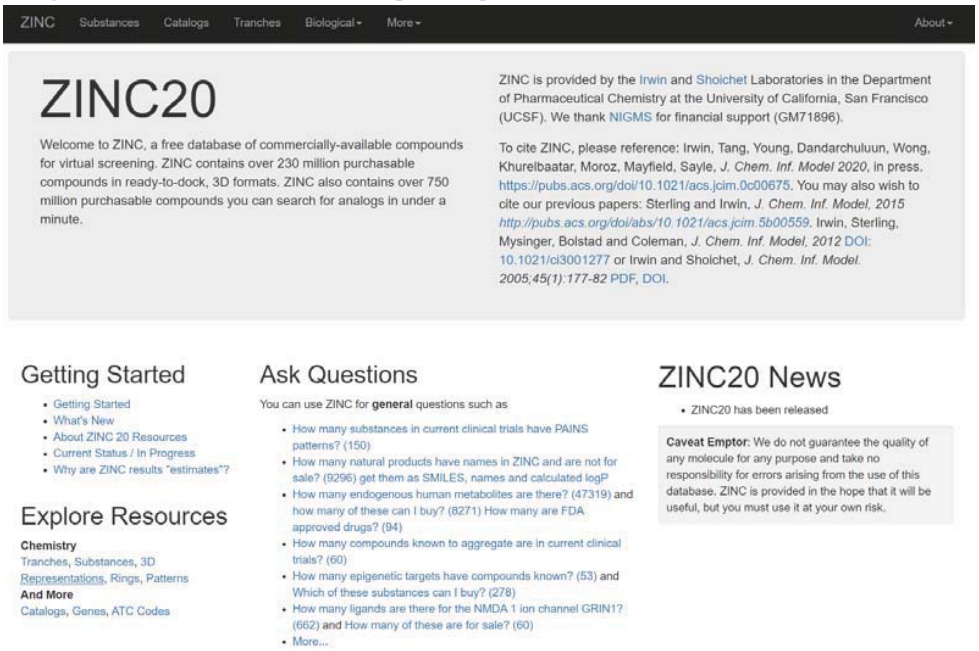


QSAR Model 개발

- Input: Smiles
- Feature: ECFP
- Target values: pChEMBL Value
- Models: Regression model
  - Random Forest regression (Scikit-learn: RandomForestRegressor)
  - FNN (Tensorflow.keras, Deepchem)
  - Loss: Mean square error (MSE)
- Model selection:
  - Validation set

ZINC

- https://zinc.docking.org/



Compound Library

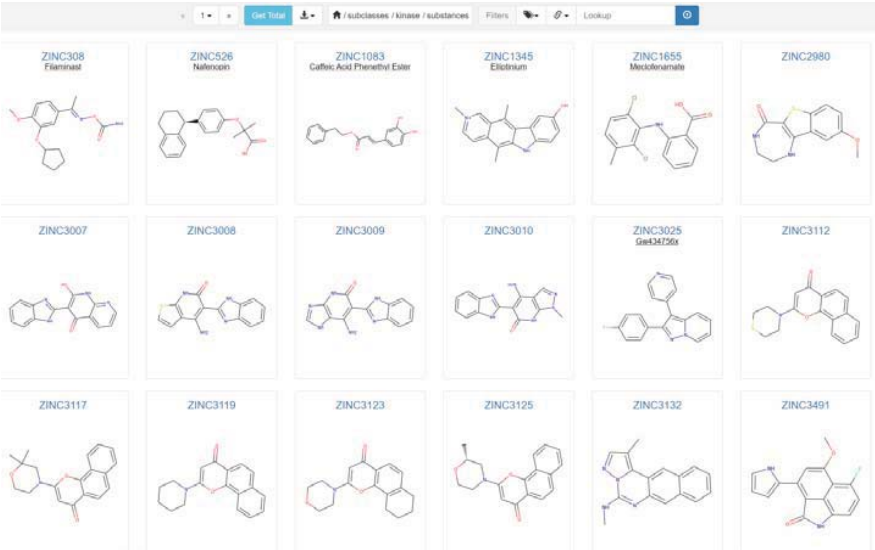
- https://zinc.docking.org/tranches/home/

Rep. 2D 3D React. Standard Purch. Wait OK pH N/A Charge N/A

LogP (up to) \ Molecular Weight (up to, Daltons)	200	250	300	325	350	375	400	425	450	500	>500	Totals, by LogP
-1	27,791	172,563	710,795	1,072,978	2,241,498	786,738	276,834	116,066	92,417	77,790	7,310	5,582,780
0	139,434	934,776	3,655,384	5,126,157	10,608,025	3,498,214	1,663,579	708,919	570,546	507,344	4,734	27,417,112
1	362,437	2,884,636	12,030,074	16,154,544	33,650,249	11,885,957	6,807,876	3,178,487	2,648,581	2,412,998	9,940	92,025,779
2	467,220	4,584,223	22,941,208	30,908,513	65,047,385	26,752,849	17,839,254	9,349,272	8,099,970	7,686,687	24,554	193,701,135
2.5	167,513	2,136,113	12,849,121	17,977,157	38,682,058	18,584,223	13,812,274	8,111,104	7,197,414	6,979,014	24,126	126,520,117
3	90,548	1,570,772	11,037,383	16,282,627	34,831,558	19,940,391	16,037,132	10,339,743	9,362,233	9,118,717	37,422	128,648,526
3.5	36,748	929,872	7,920,574	12,490,662	27,380,104	18,703,024	16,485,194	11,784,160	10,774,472	10,693,411	58,791	117,257,012
4	9,017	369,565	4,332,131	6,472,808	10,487,856	13,034,155	14,329,253	11,683,208	10,891,465	11,003,975	86,262	82,699,695
4.5	993	86,613	1,814,492	3,457,942	6,367,225	8,853,064	10,320,054	9,945,353	9,486,869	9,825,079	117,980	60,275,664
5	150	13,393	536,018	1,405,708	3,168,584	4,995,850	6,471,525	7,025,034	6,976,742	7,325,833	144,297	38,063,134
>5	39	1,097	22,854	103,521	376,905	927,395	1,670,856	2,195,160	2,588,702	3,052,048	767,762	11,706,339
Totals, by Weight	1,301,890	13,683,623	77,850,034	111,452,617	232,841,447	127,961,860	105,713,831	74,436,506	68,689,411	68,682,896	1,283,178	884M Substances 1.9K Tranches

Compound Library

- Biological → Major target classes → enzyme → kinase → substances
- “csv” file 다운로드 및 변환

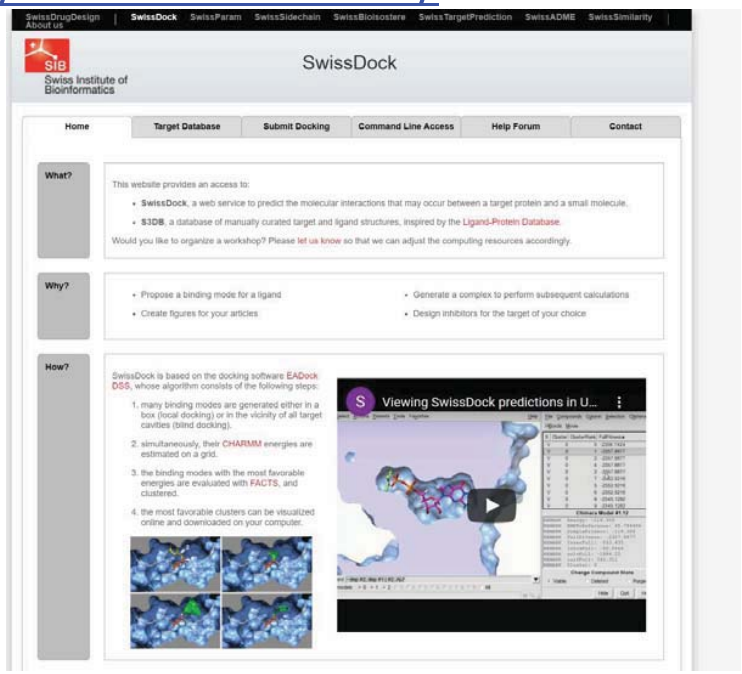


Virtual Screening

- 개발한 QSAR regression model을 구축한 화합물 라이브러리에 적용
- Sorting
  - Prediction values
- Screening
  - 동일한 or 매우 유사 화합물 제거
  - Training data에 있는 화합물들 과의 유사성 계산 (Tanimoto Coefficient or Dice Coefficient)

Docking

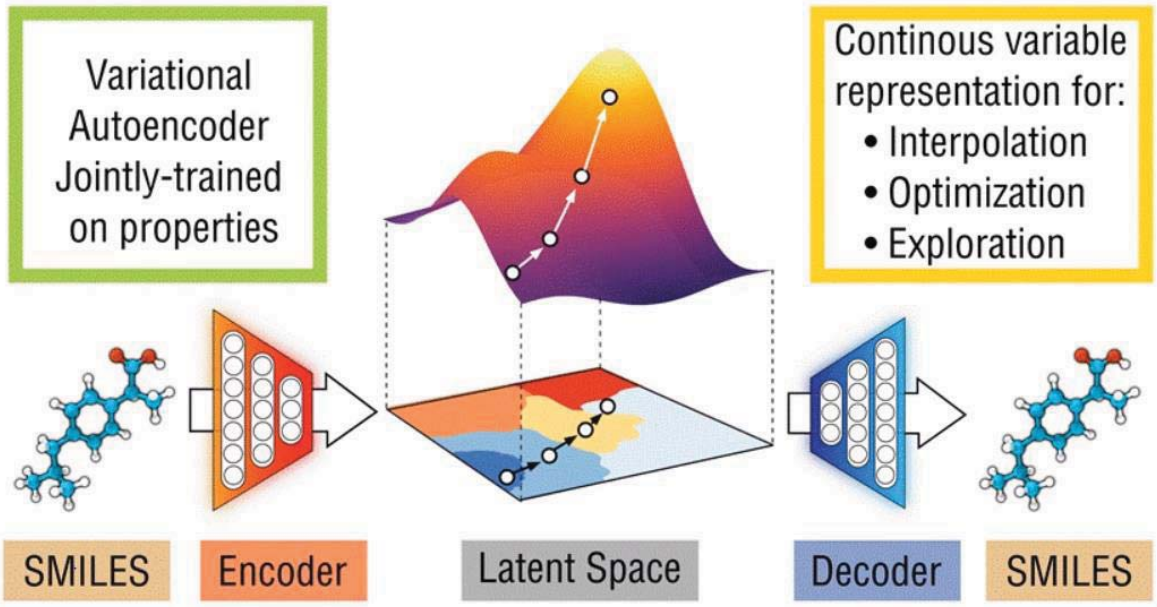
- http://www.swissdock.ch/



And, more

- ADME
- Toxicity 예측
- MD simulation (예, RMDS)
- Free energy ($\Delta\Delta G$) 계산
- Optimization 등

De Novo Design



Optimization

- MORLD
- http://morld.kaist.ac.kr/

- Questions?