Biophysics and data science approaches towards Central Nervous System translational medicine

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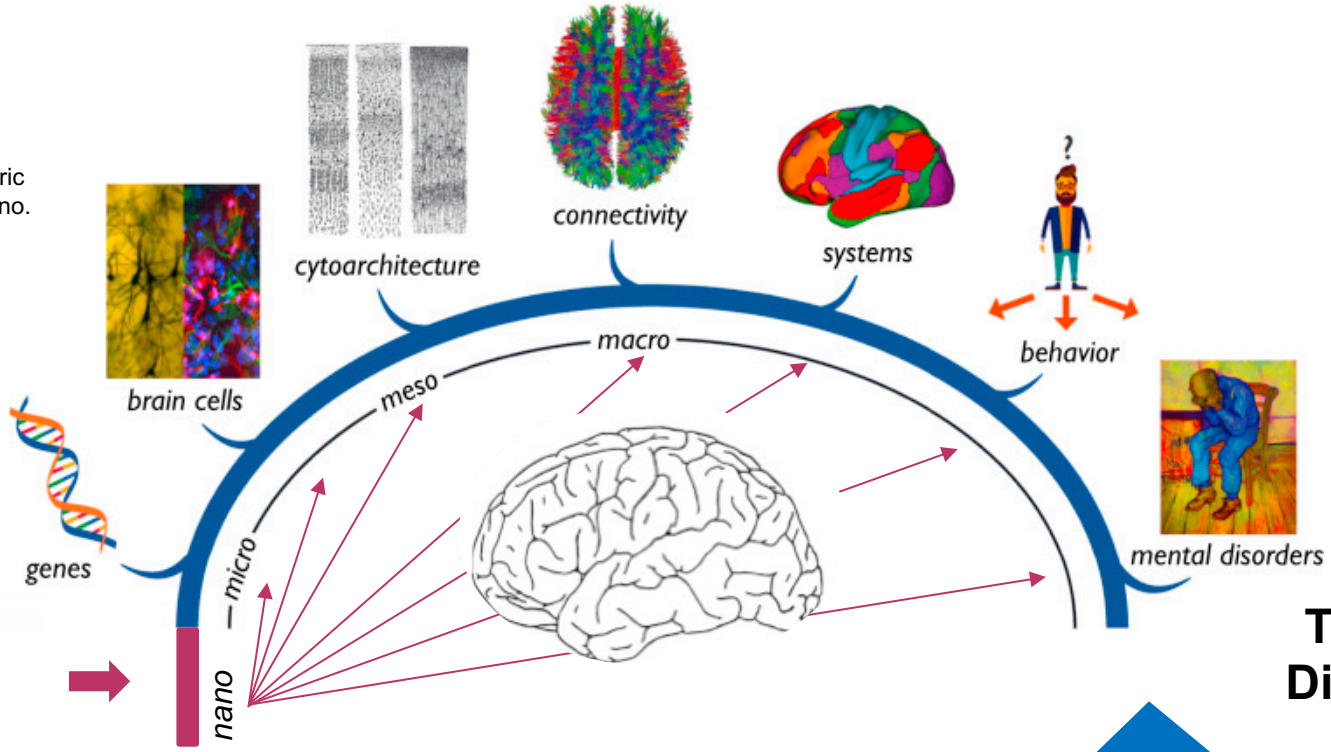
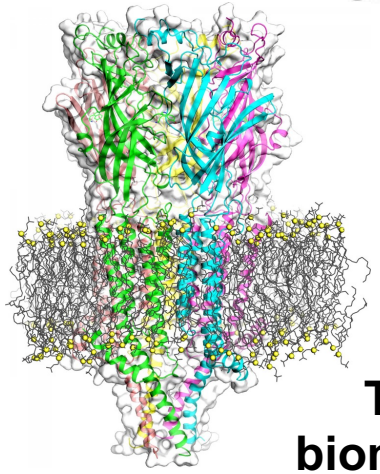
BrainComp, Cetraro, Sep 2022

Computational Molecular Medicine

How small?

van den Heuvel, Martijn P, Lianne H Scholtens, and René S Kahn. "Multiscale Neuroscience of Psychiatric Disorders." *Biological Psychiatry* 86, no. 7 (October 1, 2019): 512–22.





Target biomolecule

Drugs are prescribed and taken at the **organism level** but exert their effects by interacting with their target at the **molecular level**

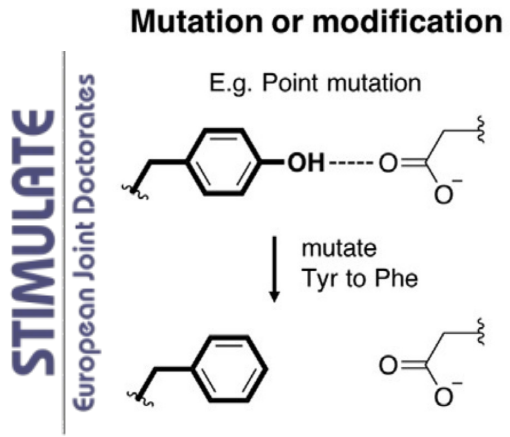
Target Disease

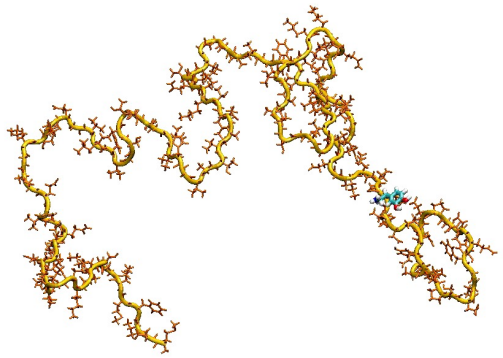
- **Physics-based approaches** *(*molecular simulations)*
- **Bioinformatics**
- **Chemoinformatic**
- **Artificial Intelligence**
- **System Biology**

Experiments

What can we do with computational molecular approaches?

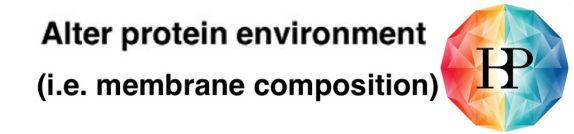
Replica Exchange MD

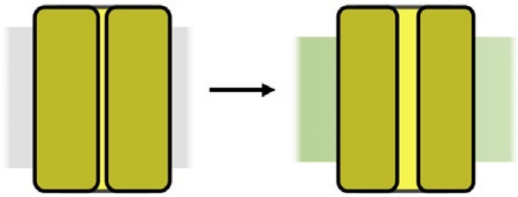


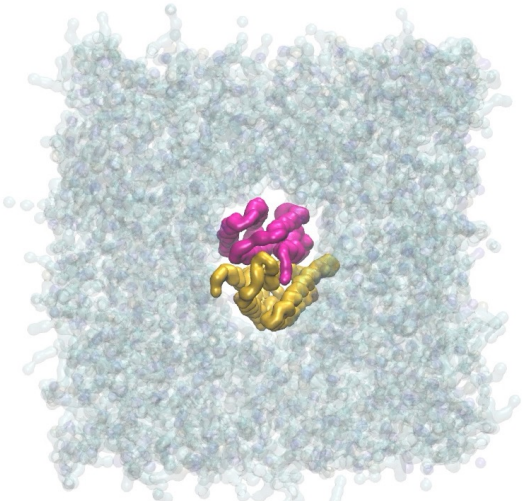


- Hernandez, O. *et al. IJMS* (2020).
- Villar-Piqué, A. *et al. PNAS* (2016).
- Rossetti, G. *et al. Phys. Chem. Chem. Phys.* (2016).

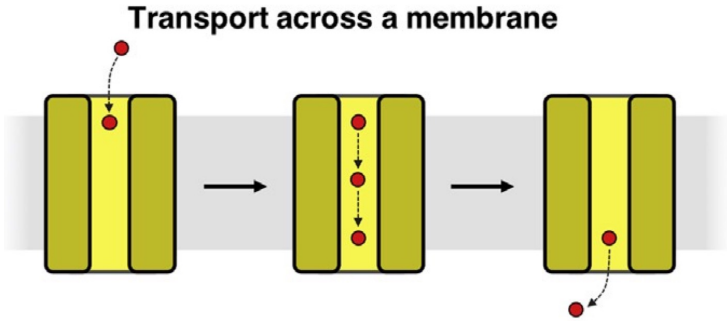
Free-Energy + Coarse Grain MD







- Chaib, Z. *et al. Molecules* (2020).
- Rossetti, G. *et al. Biochem Soc Trans* (2019)
- Maggi L. et al. *Scient. Rep.* 2020

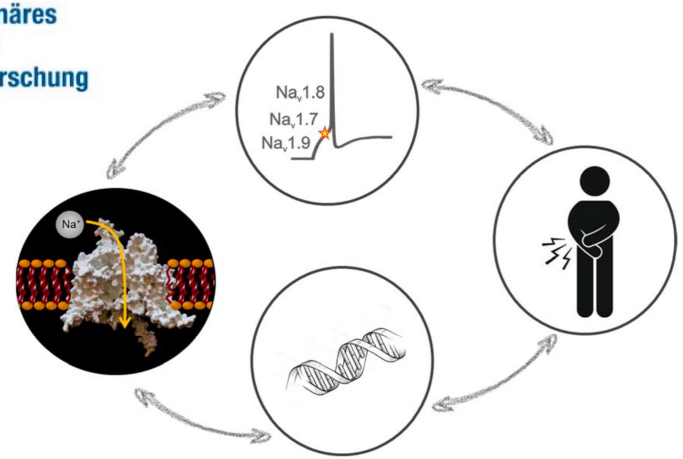


„Sodium channel-related pain disorders: From molecular mechanisms towards personalized treatment"

IZKF Interdisziplinäres Zentrum für Klinische Forschung

UNIKLINIK RWTH AACHEN

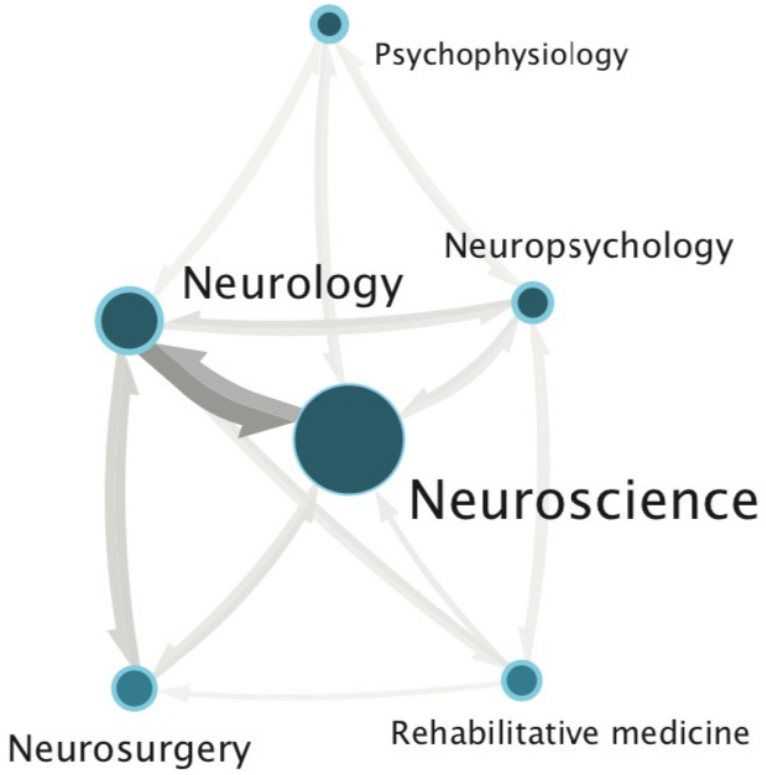
RWTH AACHEN UNIVERSITY



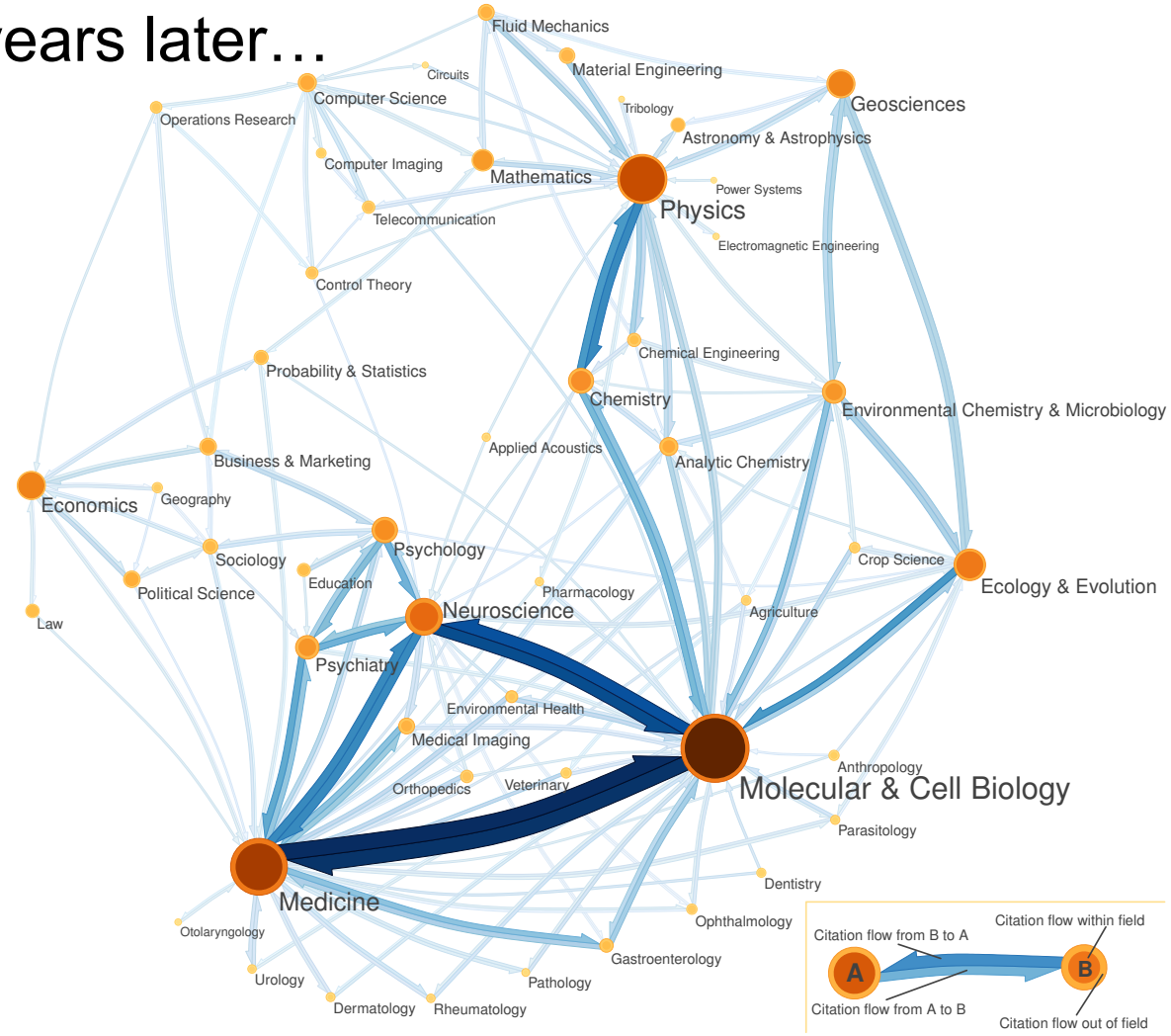
Neuroscience and computations

Map of (Neuro)science: Toward interdisciplinarity

1997



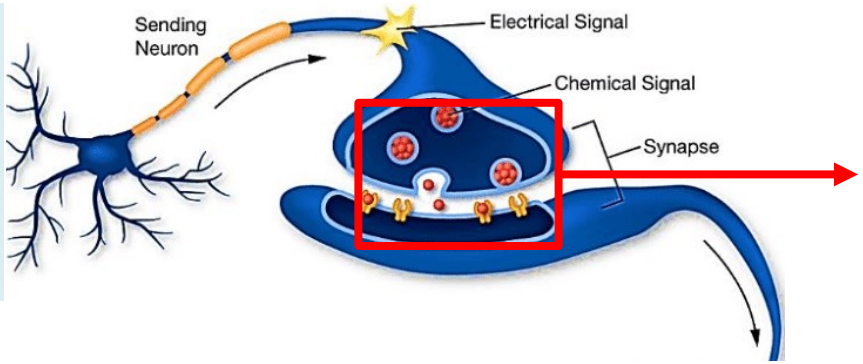
Ten years later…



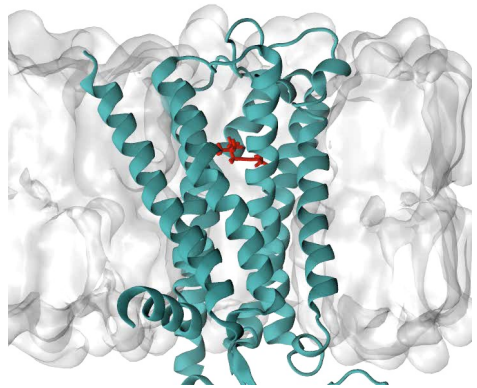
http://www.eigenfactor.org/map/maps.php

Molecular aspects of Neurotransmission and Translational Neuroscience

Challenges



Synaptic transmission is a finely regulated mechanism of neuronal communication



Approaches

Physics-based

Chem-/Bioinformatics-based

Artificial Intelligence-based

SUBCELLULAR models

MOLECULAR models

Perspectives

Molecular Mechanisms

New Drugs

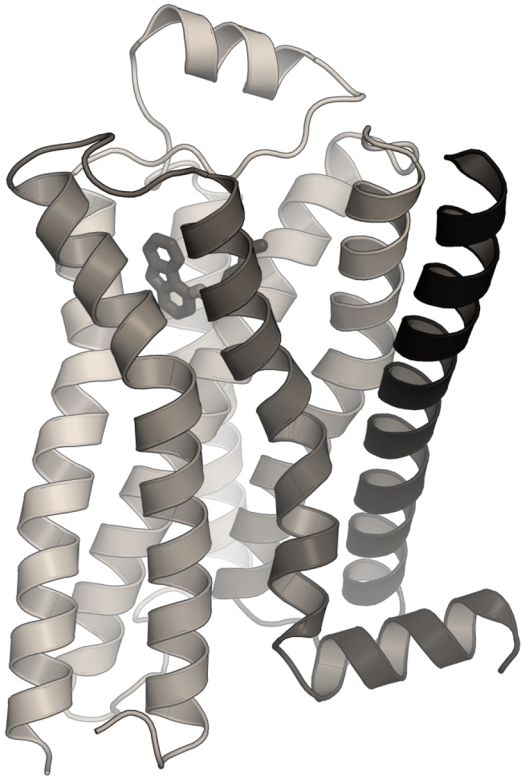
Novel Targets

New Biomarkers

- **Precision Therapeutics**
- **Precision Diagnostics**
- **Precision Medicine**

Lets focus on GPCRs: essential nodes of communication

Extending the concept of druggability



Fruitful source of drug targets constituting over **~35%** of all FDA-approved drugs

- Encephalitis (GABA, $mGluR_5$, D_2R)
- Cerebellar Ataxia ($mGluR_1$)
- Schizophrenia (M1, M2 mAChRs)
- Alzheimer's Disease (a_1AR)
- Parkinson's Disease ($A_{2A}R$)

GPCR-based drug discovery largely treated these receptors as black boxes

→ main focus being on discovering molecules that mimic or inhibit the actions of endogenous hormones or neurotransmitters

- Failure to substantially expand the number of truly 'druggable' GPCR targets
- Lack of new ligand classes
- key GPCRs' aspect overlooked: ***allosterism**

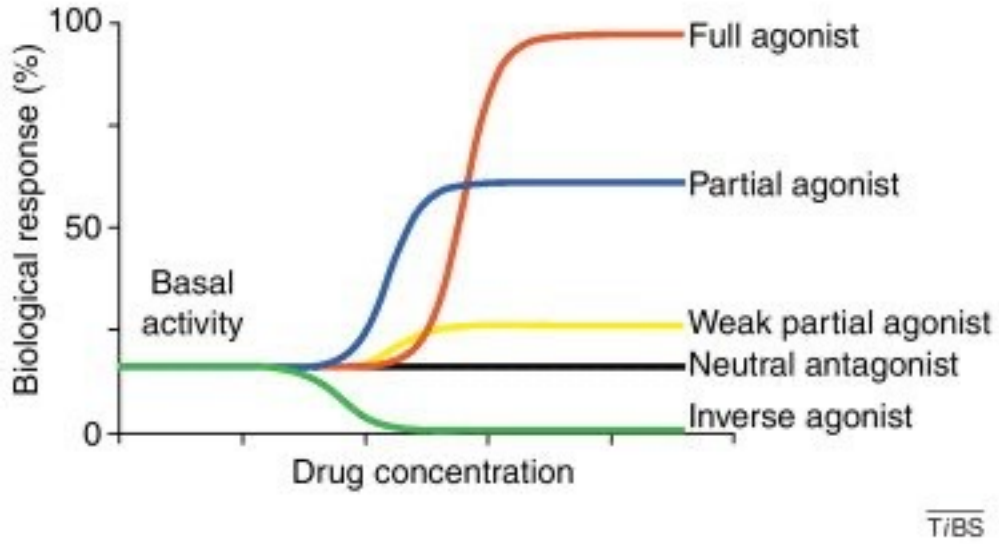
*A change in the shape and activity of a protein due to the interaction with a molecule at a point other than the chemically active site

Bioactive Molecules and GPCRs

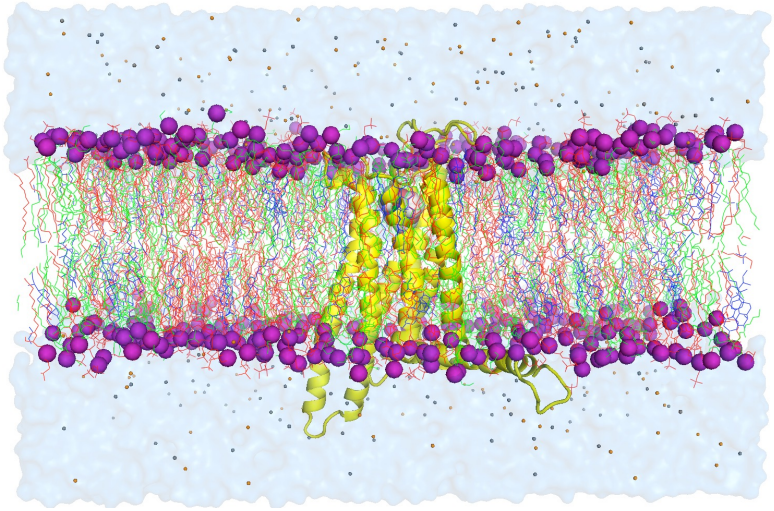
What is the ‘Biological activity’? Simple Agonism/Antagonism is not enough

***Biological activity**
/noun

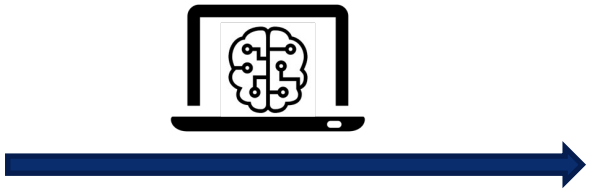
{ *the capacity of a specific molecular entity to achieve a defined biological effect” }



What makes a GPCR agonist an agonist and antagonist an antagonist?

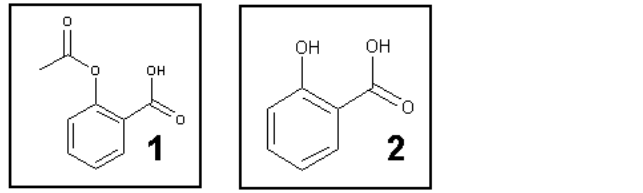


Adenosine Receptor A_{2A}



Molecular fingerprints

→ Identify fingerprints that properly describe a wide chemical space and allows resolution among molecules

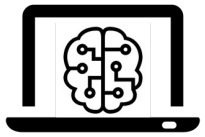


1	1	1	0	1	1	0	1	0
2	1	1	0	1	0	0	0	0

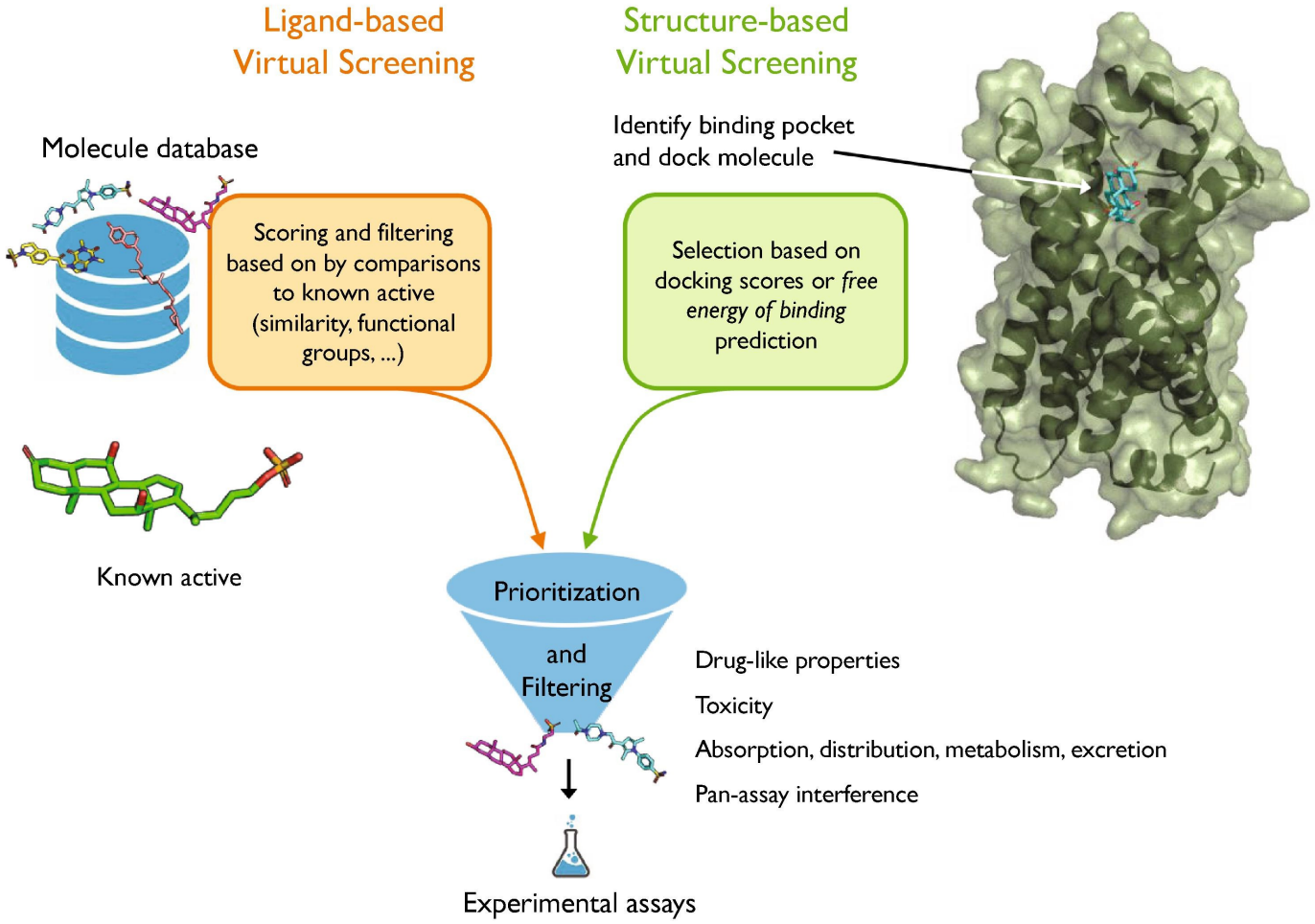
input

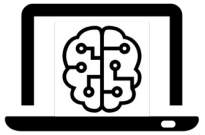
What makes a GPCR agonist an agonist and antagonist an antagonist?

Jonas Gossen



Ligand-based classifier



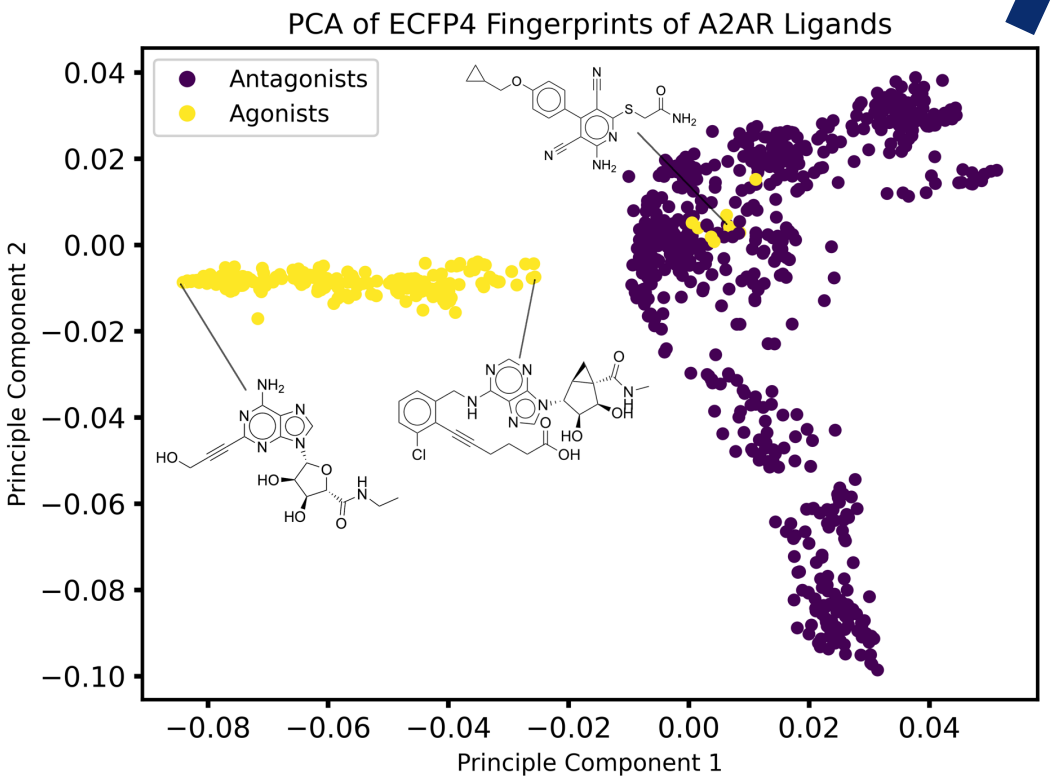


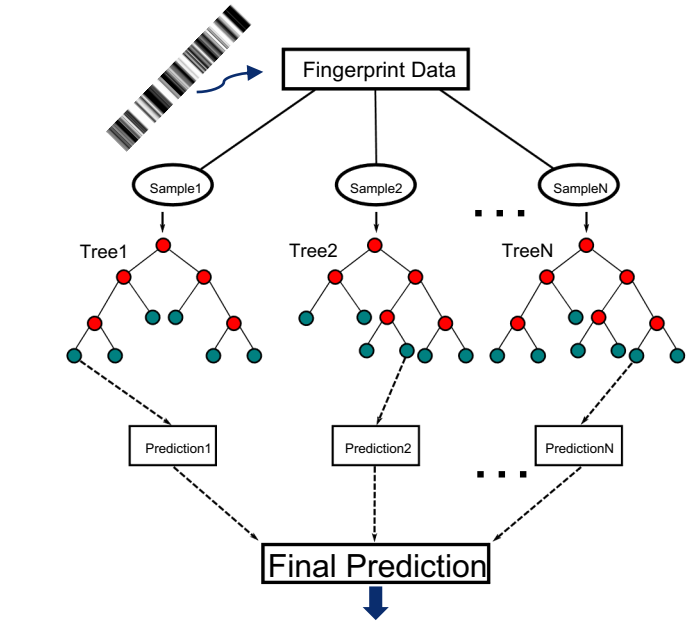
Structure-based classifier

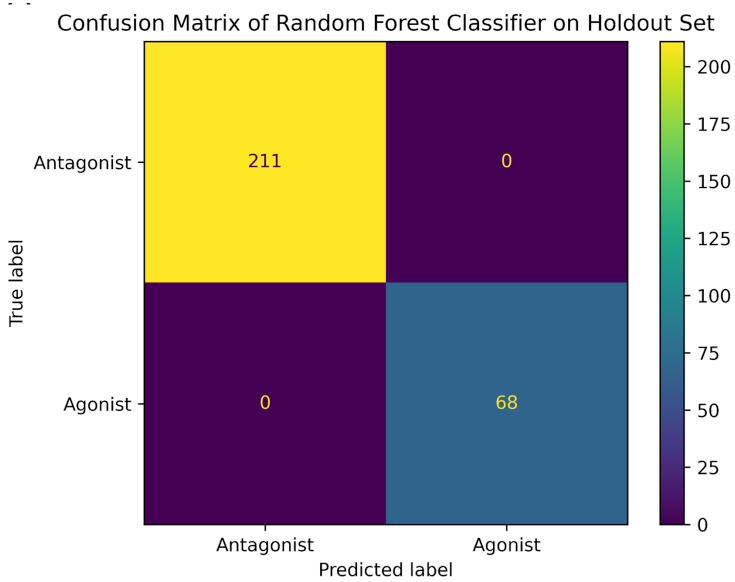
Raschka, S. & Kaufman, B. *METHODS* **180,** 89–110 (2020).

Ligand-based approach

Molecular fingerprints



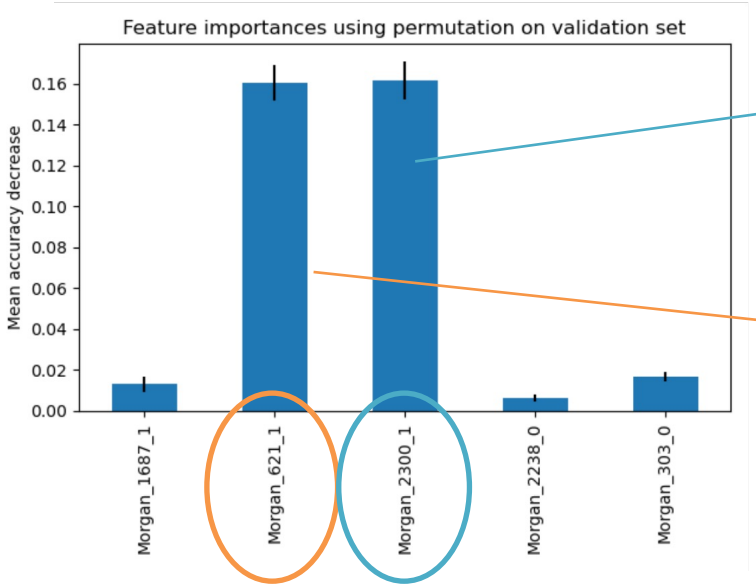


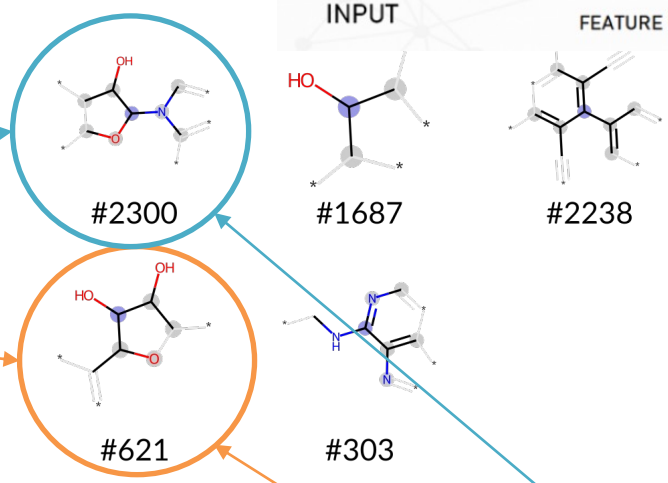


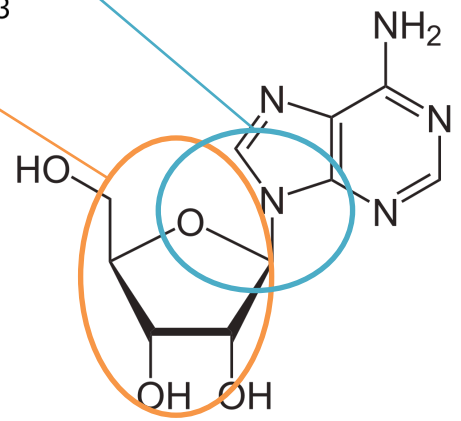
- classifier lead to ‘perfect’ classification of the holdout set

Agonist/antagonist classification

Results







Adenosine ($A_{2a}R$ agonist)

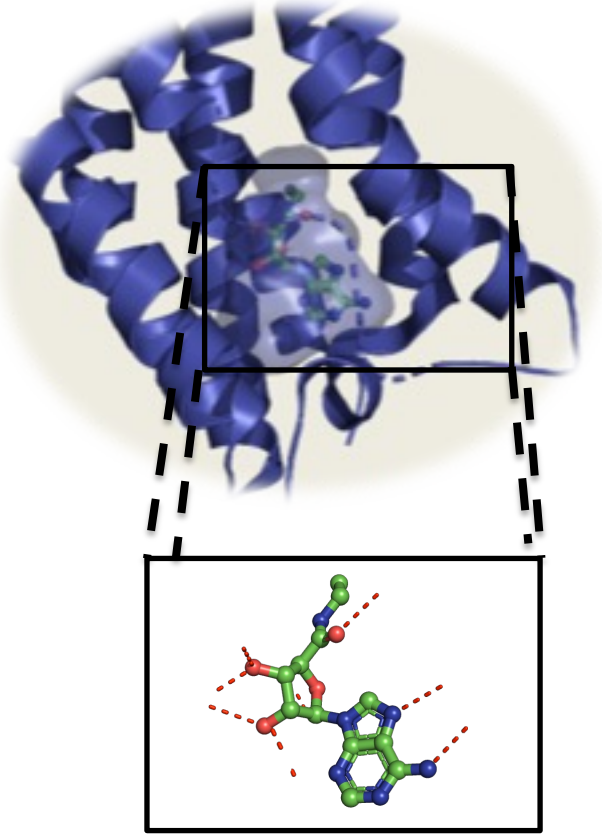
- Most important features for classification are fragments of the Ribose moiety
- Classification is based upon existence of ribose moiety
- Generalizes very badly for other chemotypes

→ Possible solution?

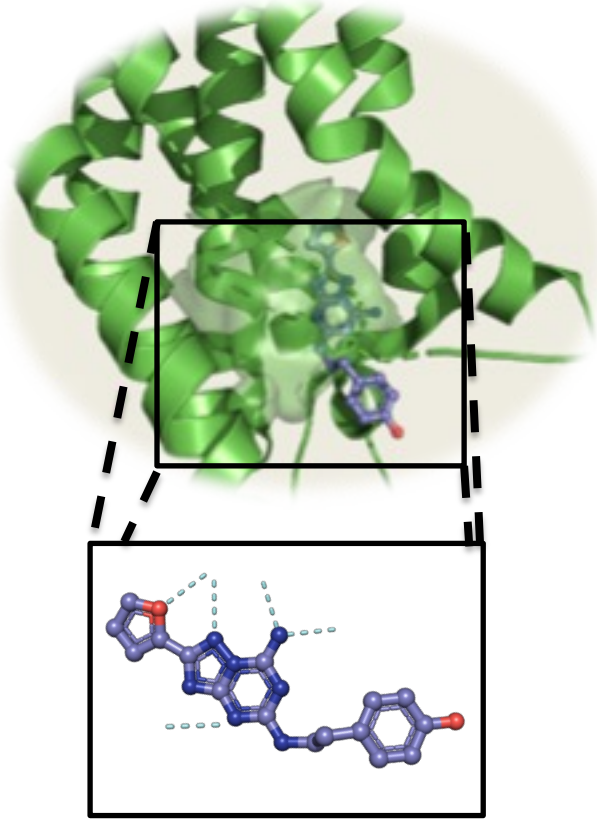
Interaction-based approach

Ligand-protein fingerprints

Agonist Crystal



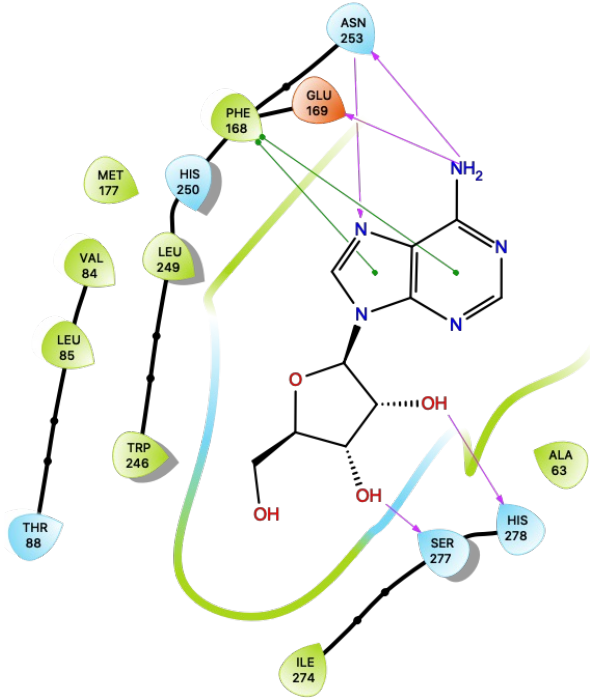
Antagonist Crystal



1011010100010010010100010001111000001010O

0101001001001111110010101011100001010100O

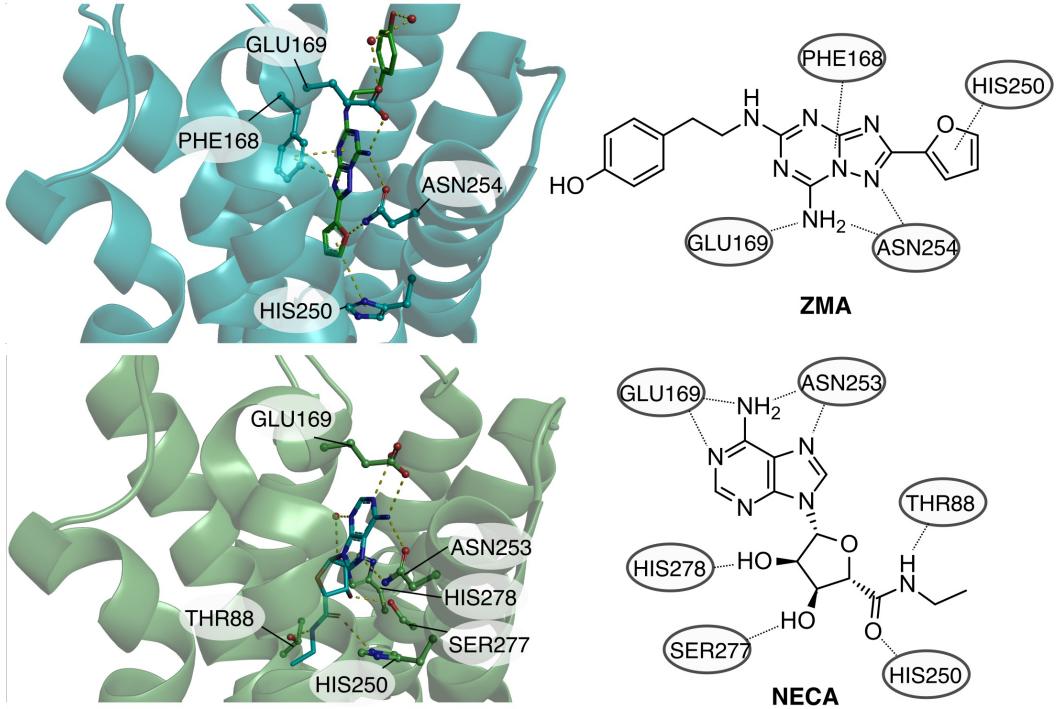
1. hydrophobic contacts
2. aromatic face to face
3. aromatic edge to face
4. hydrogen bond (protein as hydrogen bond donor)
5. hydrogen bond (protein as hydrogen bond acceptor)
6. salt bridges (protein positively charged)
7. salt bridges (protein negatively charged
8. salt bridges (ionic bond with metal ion)

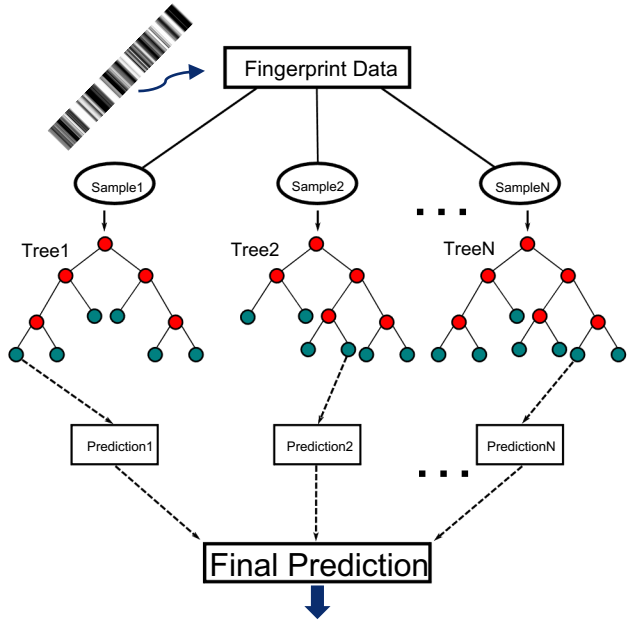


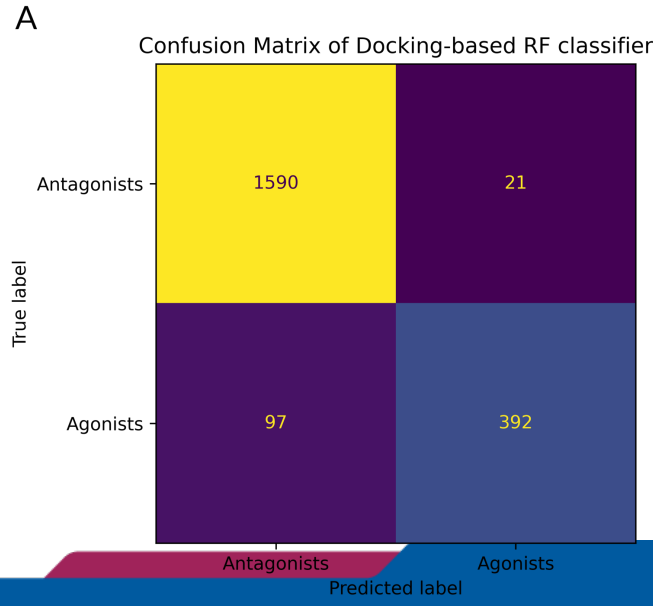
Bitwise encoded interaction pattern

Interaction-based approach

Ligand-protein fingerprints



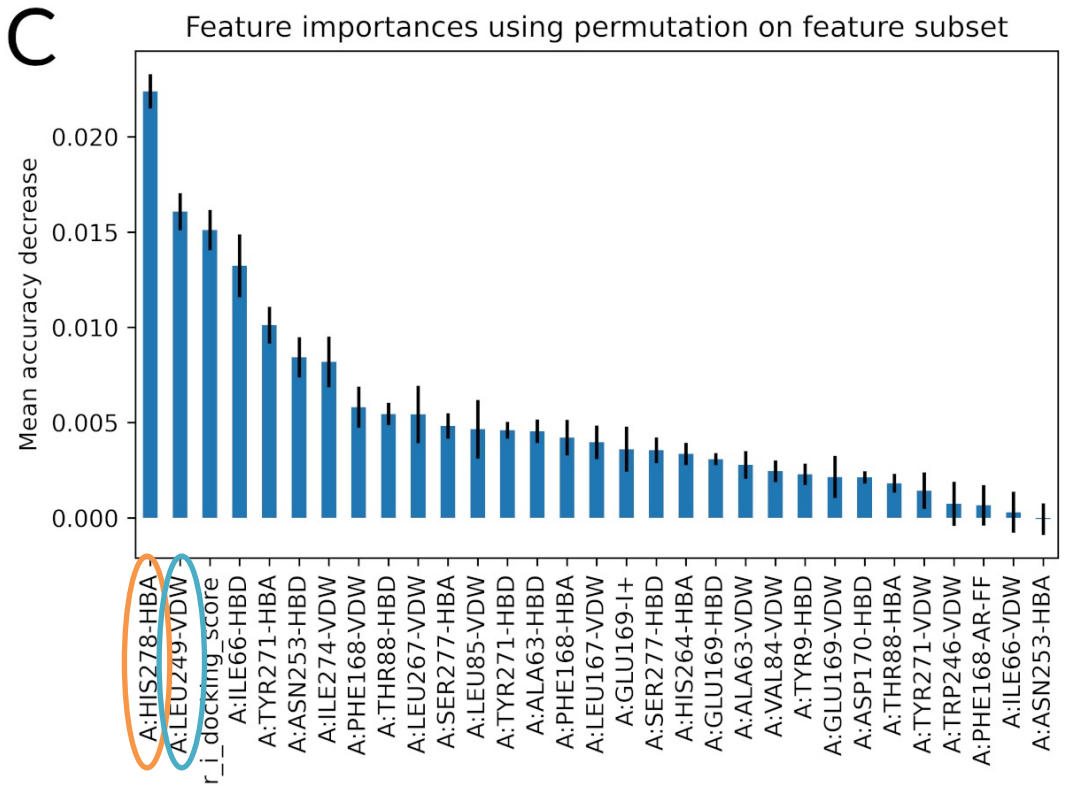


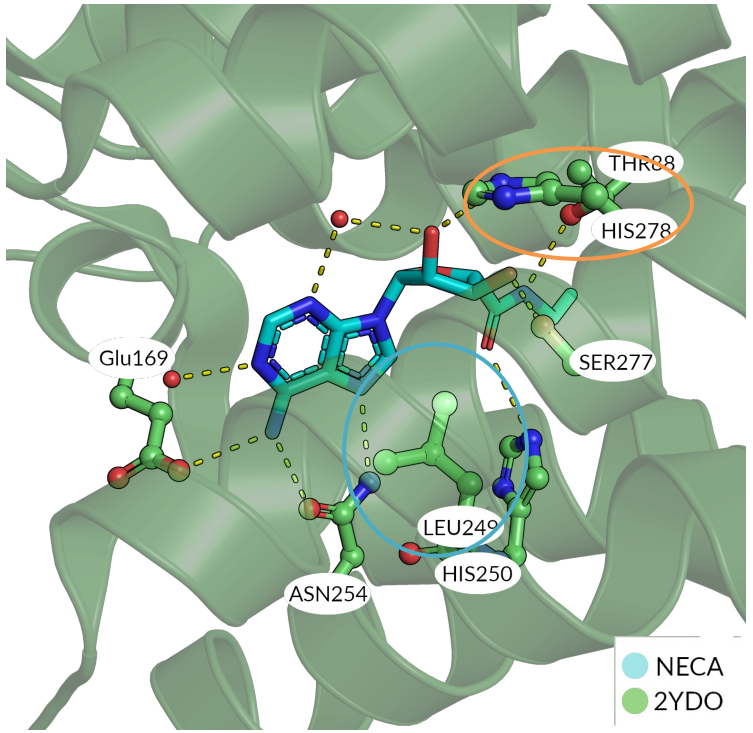


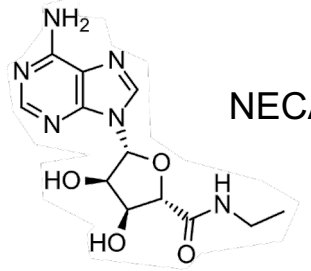
- Glide docking based classfier lead to ‘excellent’ classification (ROC AUC .97) of the holdout set

Agonist/antagonist classification

Ligand-protein fingerprints







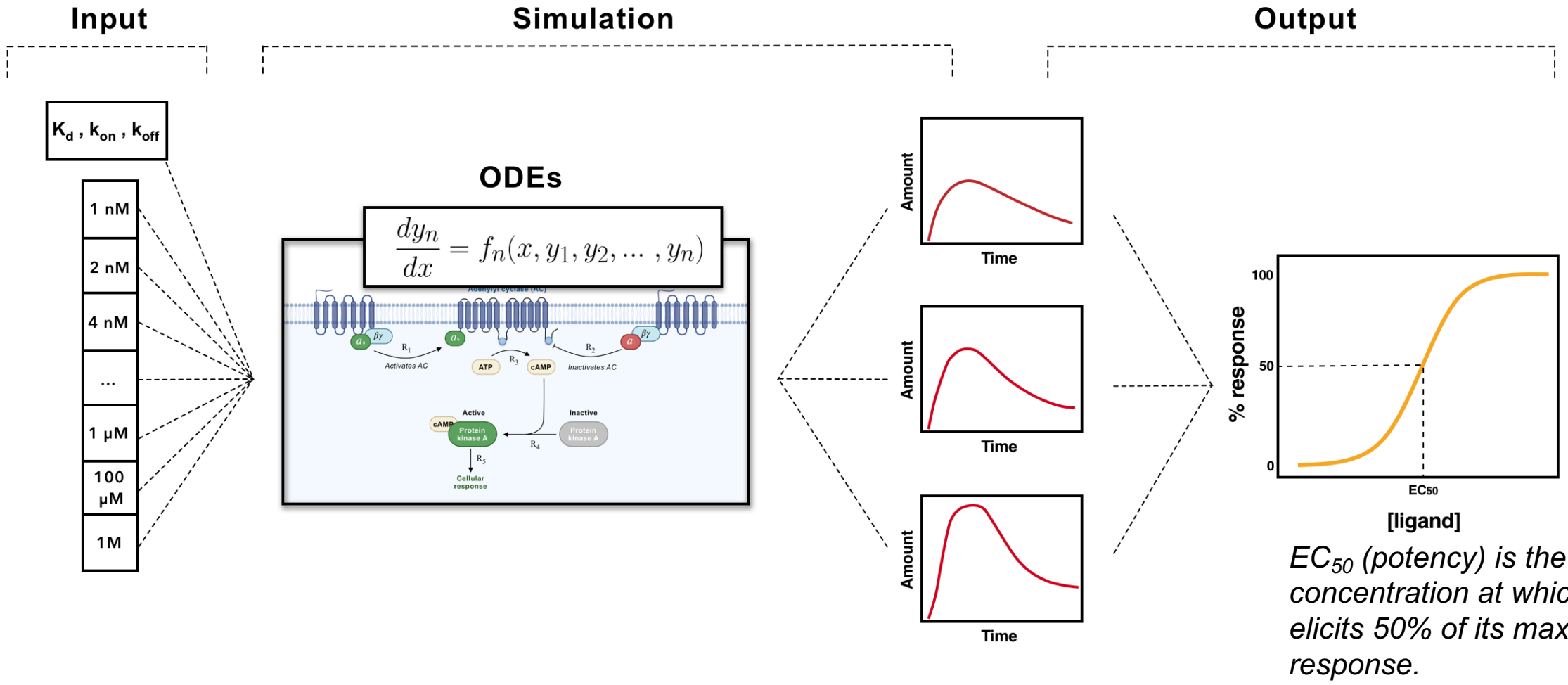
NECA

- Docking based classifier learns agonistic interaction pattern instead of common chemical scaffolds

→ More generalizable classifier working of non-ribose agonists

How pharmacological systems can be simulated?

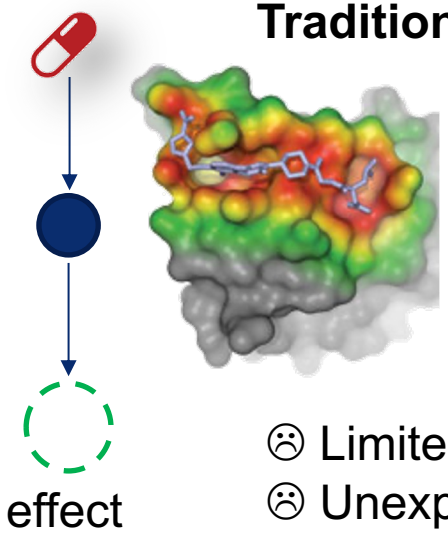
Mathematical Modeling of Biochemical Systems



EC_{50} (potency) is the concentration at which the drug elicits 50% of its maximal response.

What's Next…

Is the classifier sufficient?



Traditional drug design

'key' compounds
single-target 'lock'

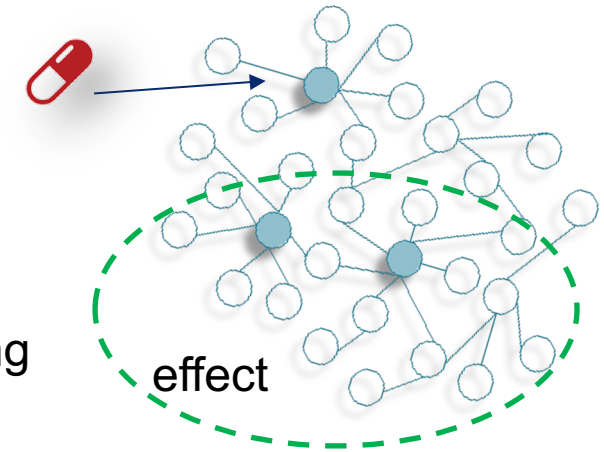
☺ High specificity
☺ Reduced side effects

☹ Limited in diseases of complex etiology
☹ Unexpected adverse effects

System Pharmacology: disease as network state

☺ Mapping of broad biological network
☺ Modeling of network dynamic: response to signals

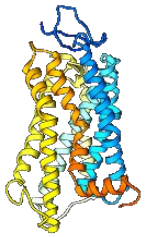
☹ Limited molecular understanding



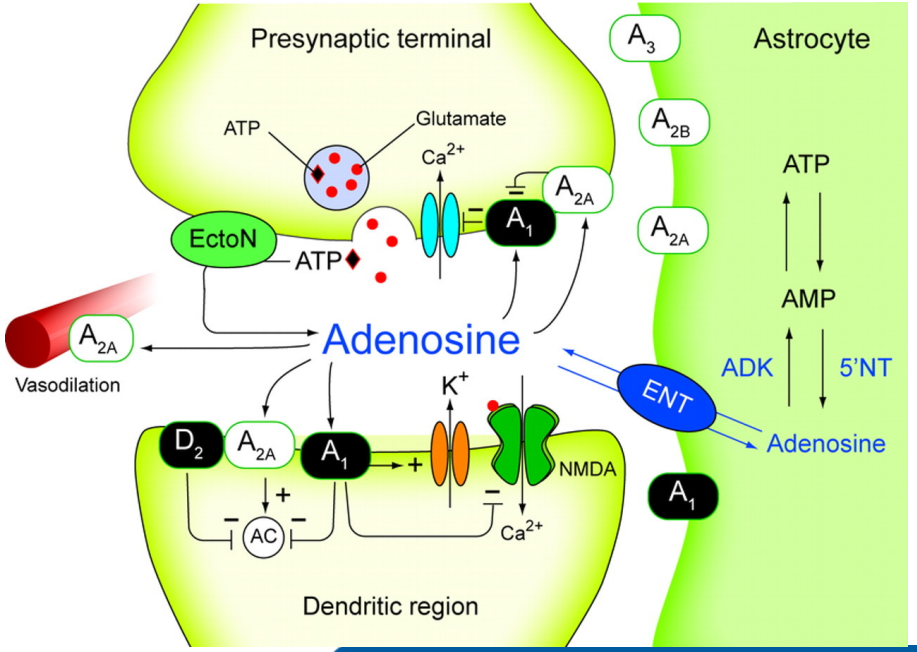
Subcellular Modeling

Function Structure

- **Structural Data**
- **Genetic Variations**
- **Post Translational Modifications (PTMs)**



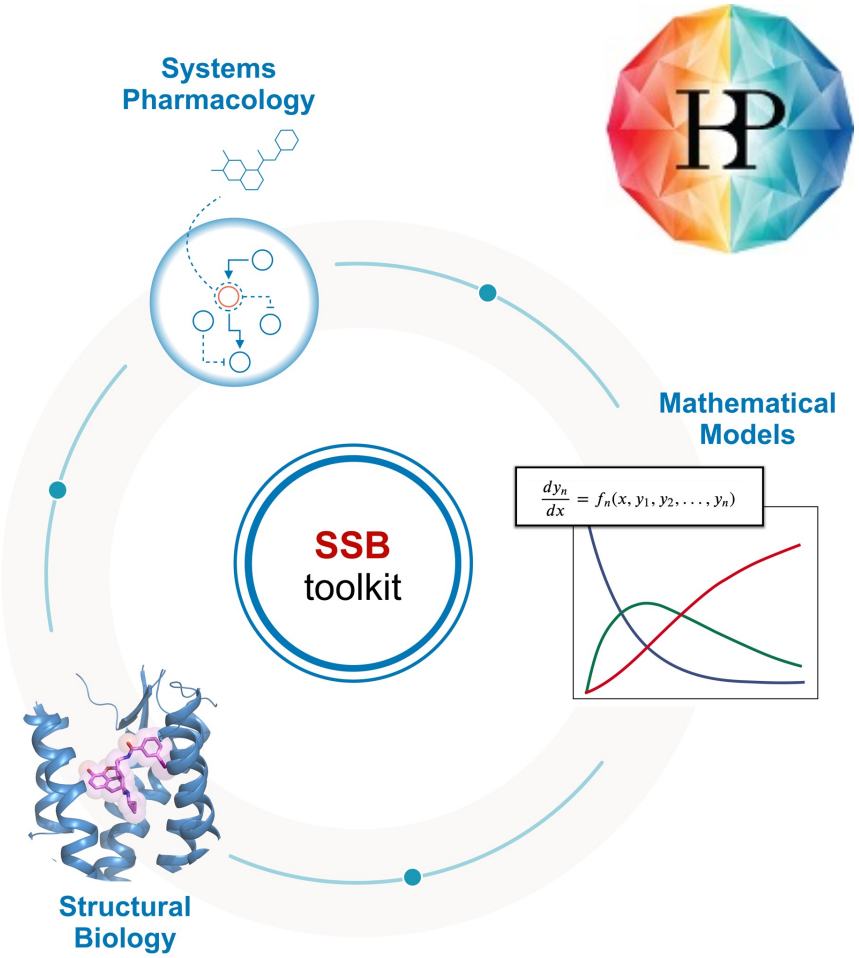
- **Functional Effects**
- **Wild type/Variants Response**
- **Dose Response**

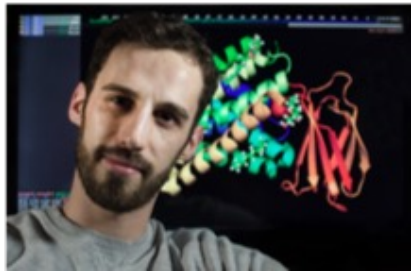


Structural System Biology

A new toolkit

- A framework to run Systems Biology simulations
- A toolkit to explore the effect of structural features on subcellular signaling dynamics
- A library of SB simulations routines to study pharmacodynamic models





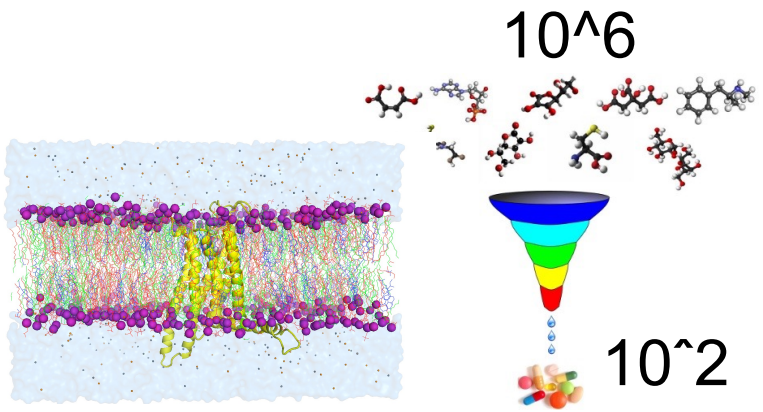
Rui Pedro Fernandes

Alejandro Giorgetti

… specifically for GPCRs

GPCRs and Drug effects

Structural System Biology (SSB)

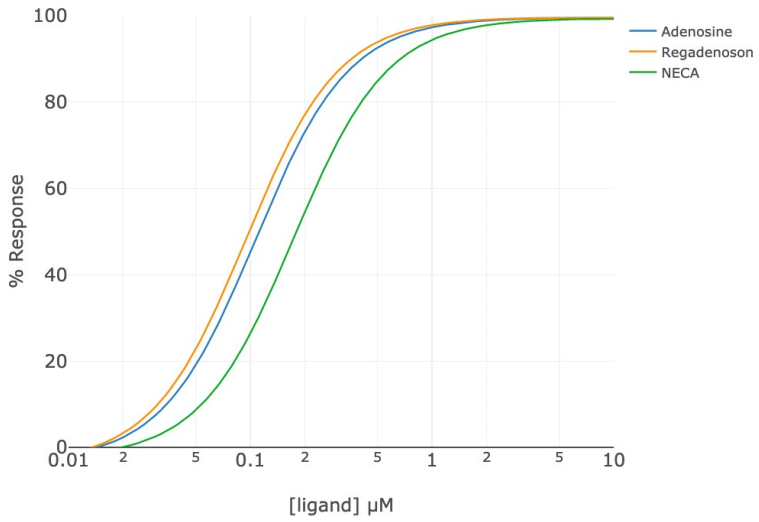


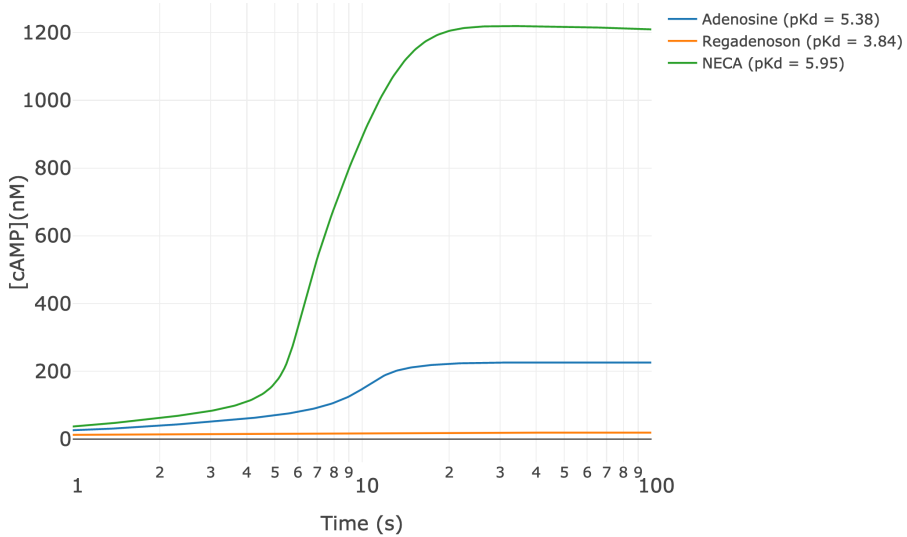
Receptor Plus Ligand

Kd prediction

Agonist/Antagonist discriminator

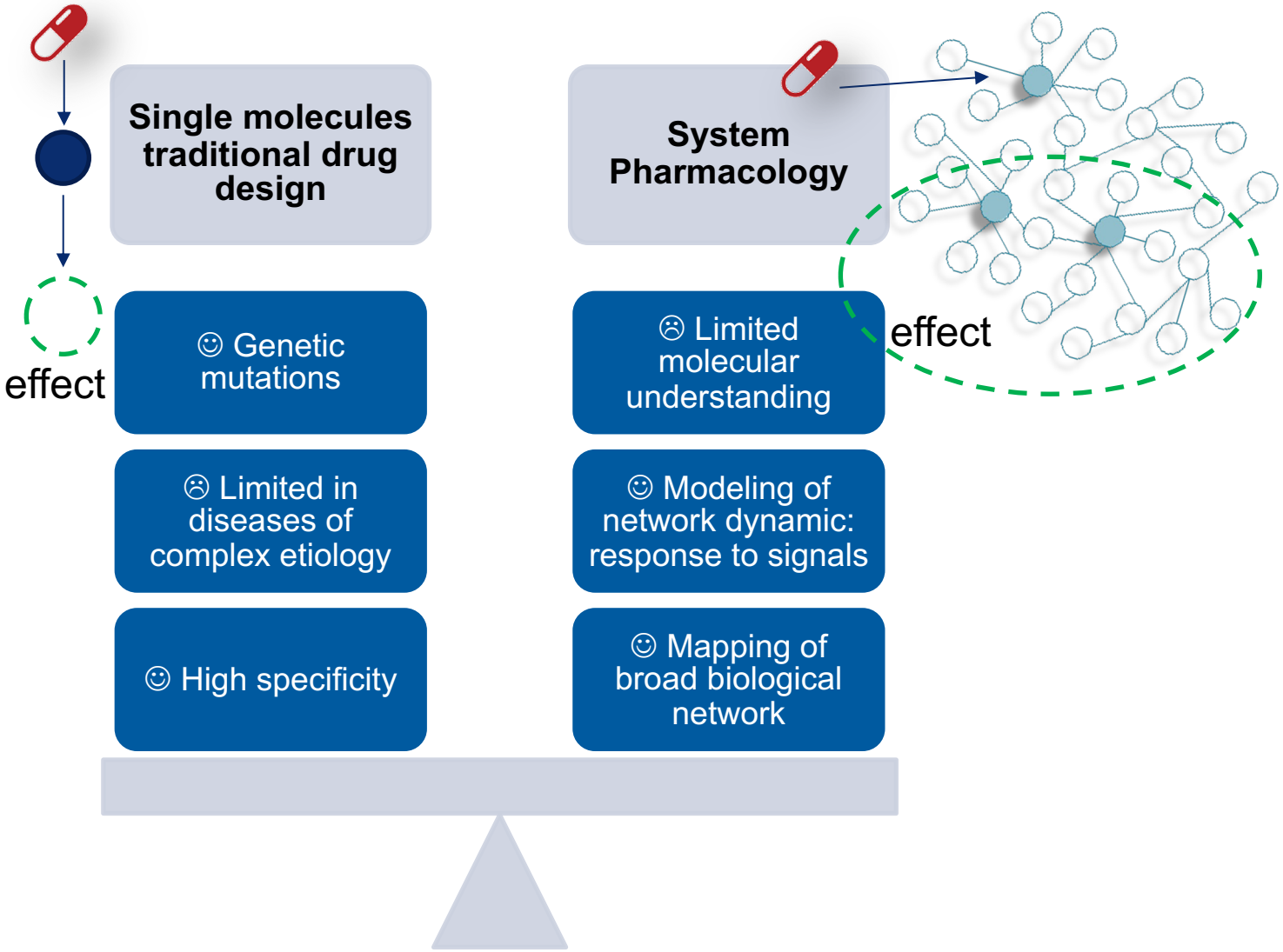
Bio-chemical network

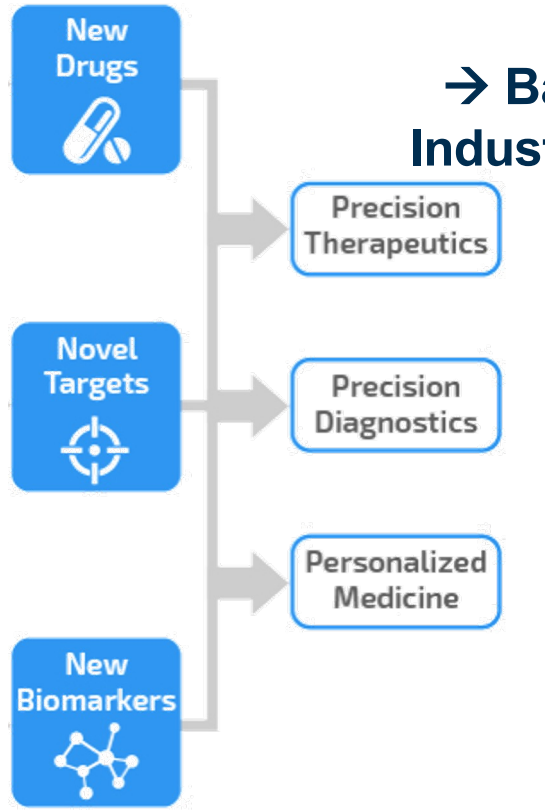




Perspectives: human complexity and Personalized Medicine

AI and Physics-based tools: The power of the combination





→ Basic Research-Industry Partnerships

Dompé

TAROS

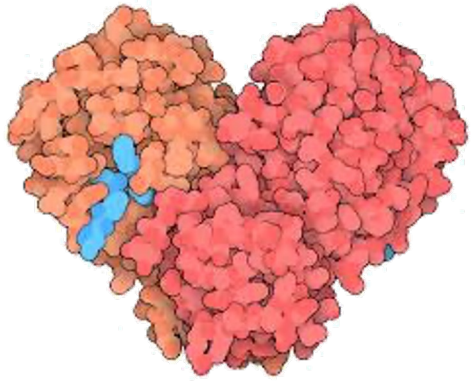
AiCuris
Anti-infective Cures

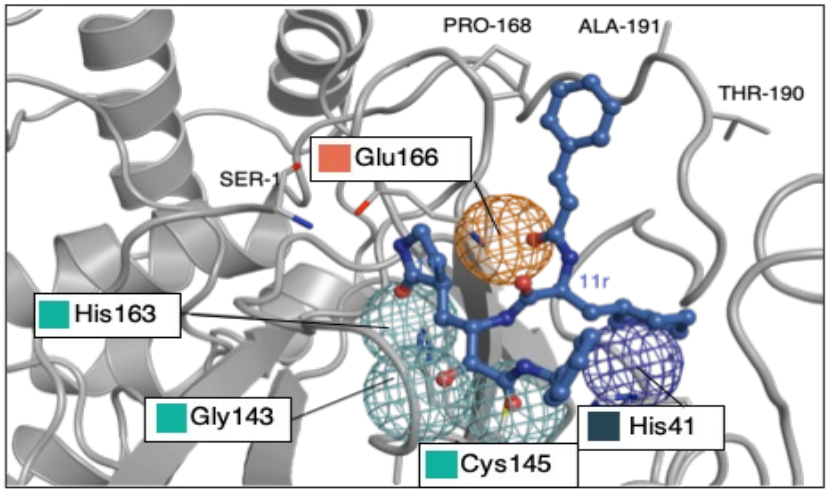
BAYER

AI and Physics-based tools for COVID19

The case of SARS-CoV-2 Mpro

EXSCALATE 4COV





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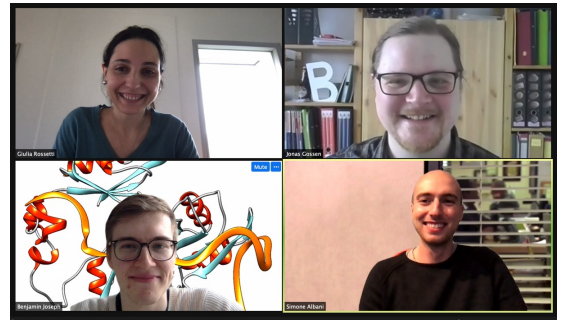

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Manelfi, C. et al. **Combining Different Docking Engines and Consensus Strategies to Design and Validate Optimized Virtual Screening Protocols for the SARS-CoV-2 3CL Protease**. Molecules **2021**

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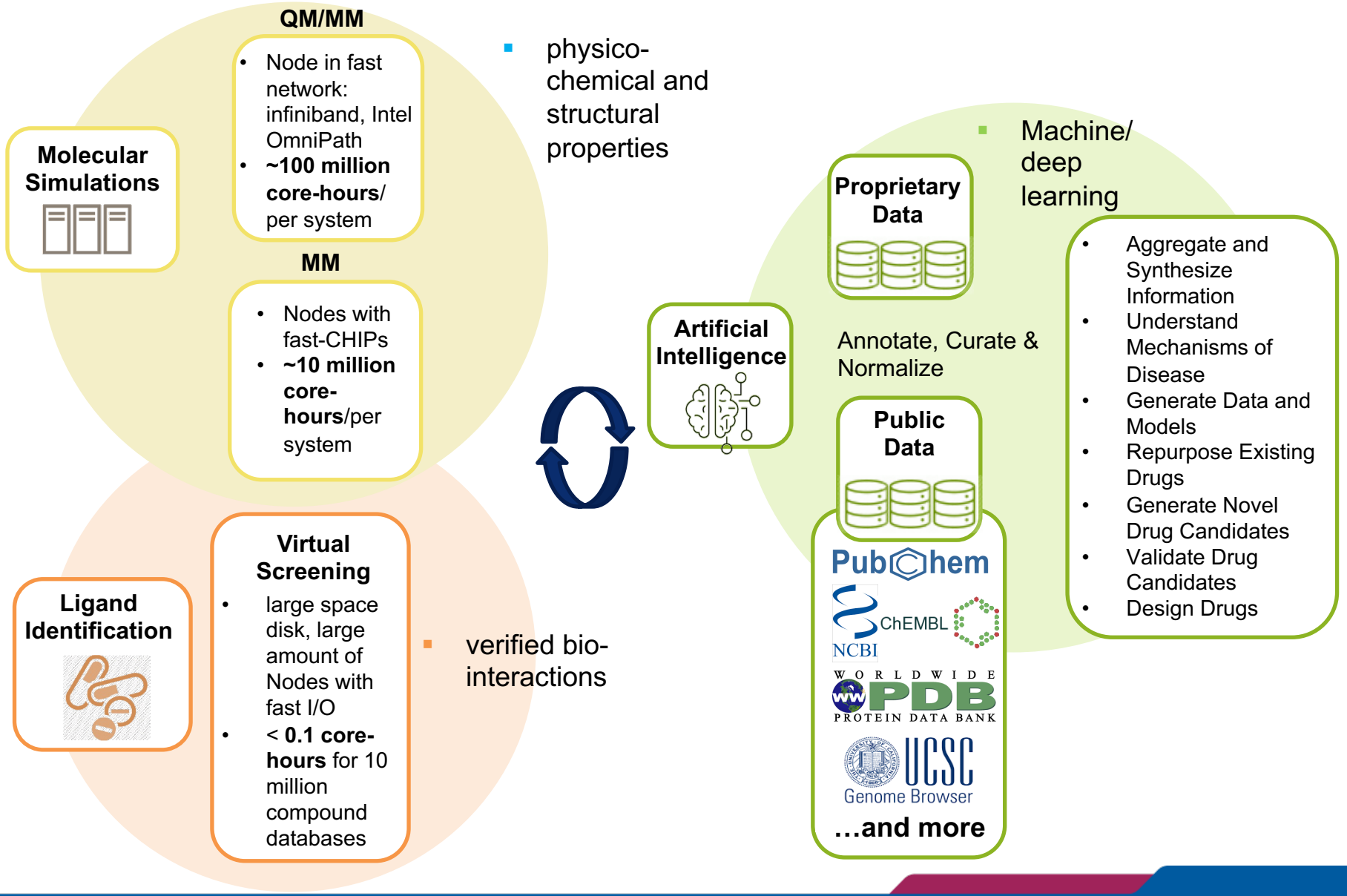
And more…

In silico Drug Design pipelines, HPC and computing modularity



Acknowledgements

Prof. Paolo Carloni
Jonas Gossen (FZJ, Germany)
Rui Pedro Fernandes (University of Verona)
Prof. Alejandro Giorgetti (FZJ/University of Verona)
Alessandro Marchetto (University of Verona)
Emiliano Ippoliti (FZJ, Germany)
Dr. Dierk Bier (FZJ, Germany)

Juelich Supercomputing Center

INM-9/IAS-5

Funding

JARA Jülich Aachen Research Alliance

SSD

MARIE CURIE ACTIONS

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EXSCALATE 4COV

IZKF Interdisziplinäres Zentrum für Klinische Forschung

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