Computational techniques to accelerate Drug Discovery

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Leiden Institute of Chemistry – Molecular Physiology

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Acknowledgements

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About myself

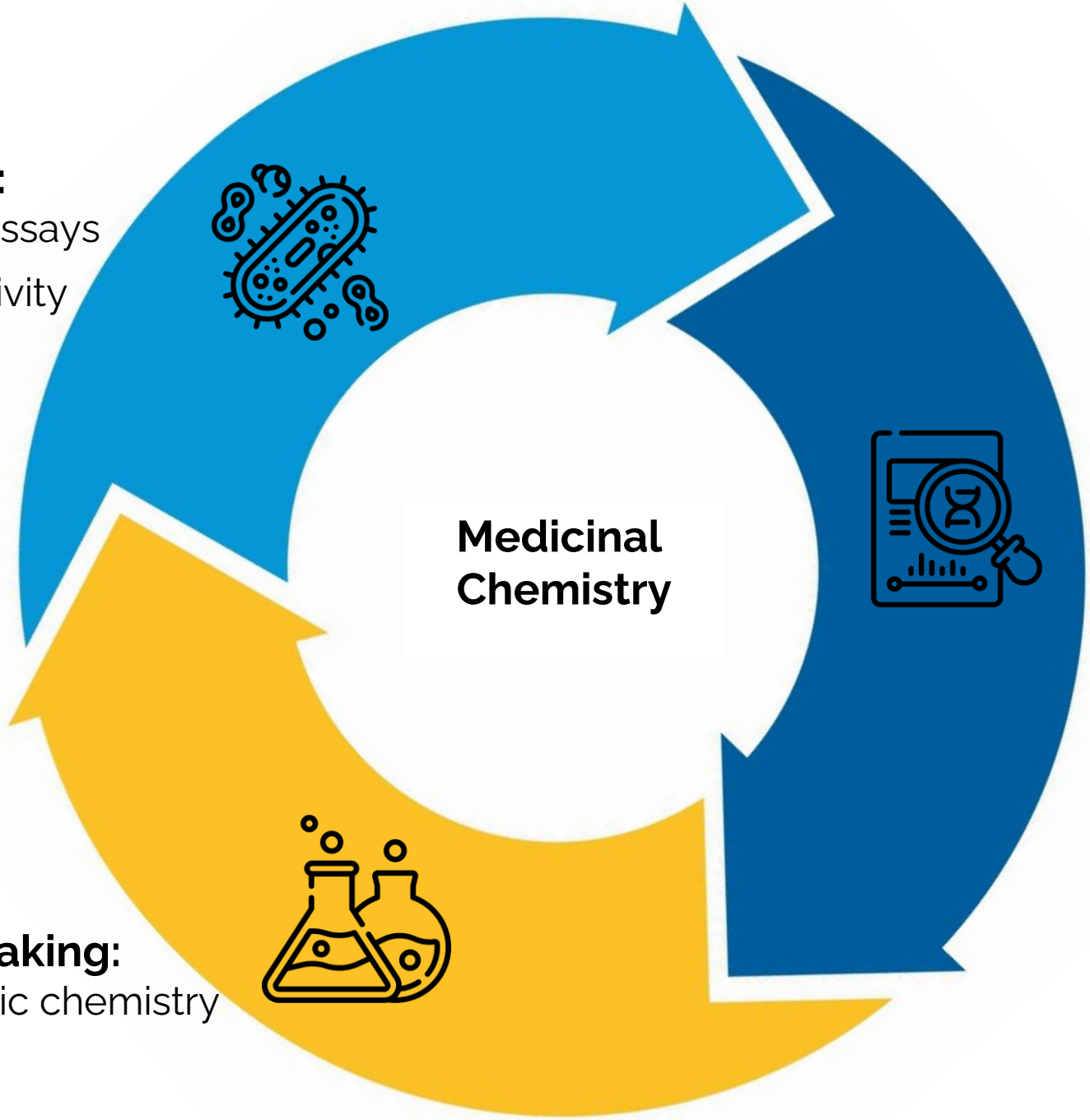
- PhD in Medicinal Chemistry
  - Molecular Physiology
- PostDoc Computational Drug Discovery
- Since 2020: Assistant Professor at LIC
- Leiden Early Drug Discovery & Development

Molecular Physiology

- Answer biological questions using chemical tools
- Strong focus on selectivity
- Utilising Chemical Biology techniques
  - Activity-based Protein Profiling
  - Bio-orthogonal (Click) Chemistry
  - Chemoproteomics

Testing:
Biochemical assays

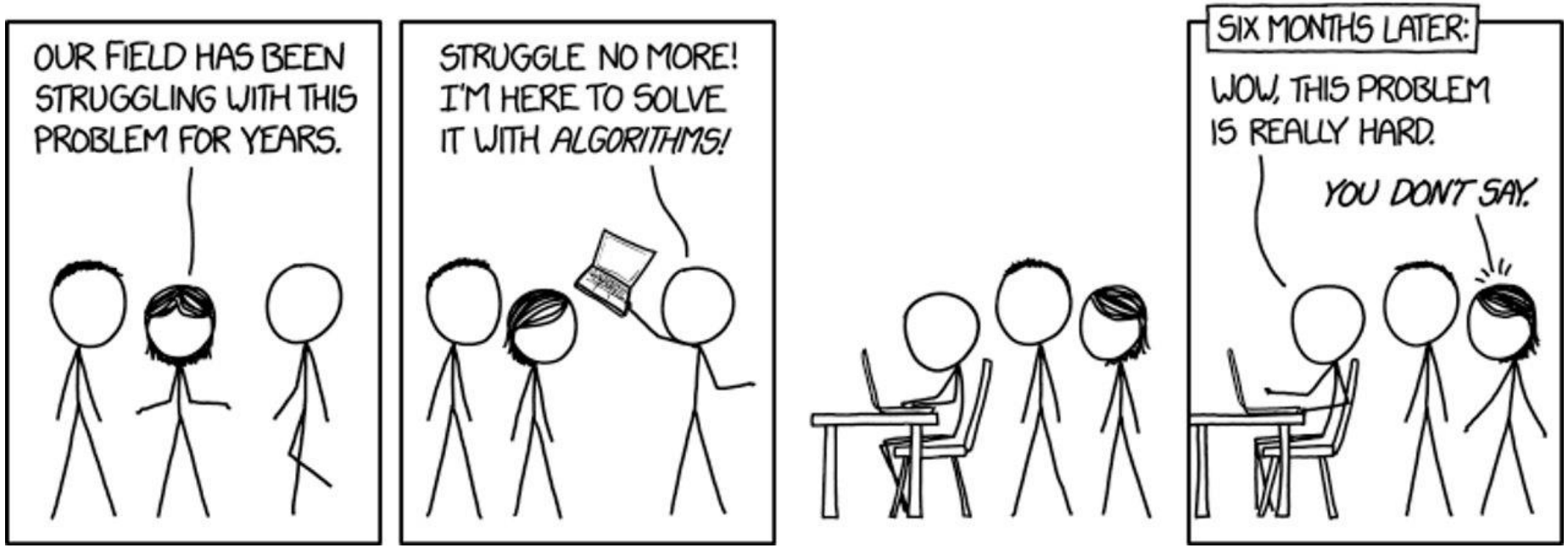
- Inhibitory activity
- Selectivity
- Stability
- Toxicity
- …



Designing:
Structure-Activity Relations

Making:
Synthetic chemistry

The *in silico* promise



XKCD 'Here to help' (2017), https://xkcd.com/1831

Testing:
Biochemical assays

***Computationally Accelerated* Medicinal Chemistry**

Designing:
Structure-Activity Relations

- Molecular docking
- *De novo* generation

Making:
Synthetic chemistry

- AI-based retro-synthesis

Testing:
Biochemical assays

***Computationally Accelerated* Medicinal Chemistry**

Designing:
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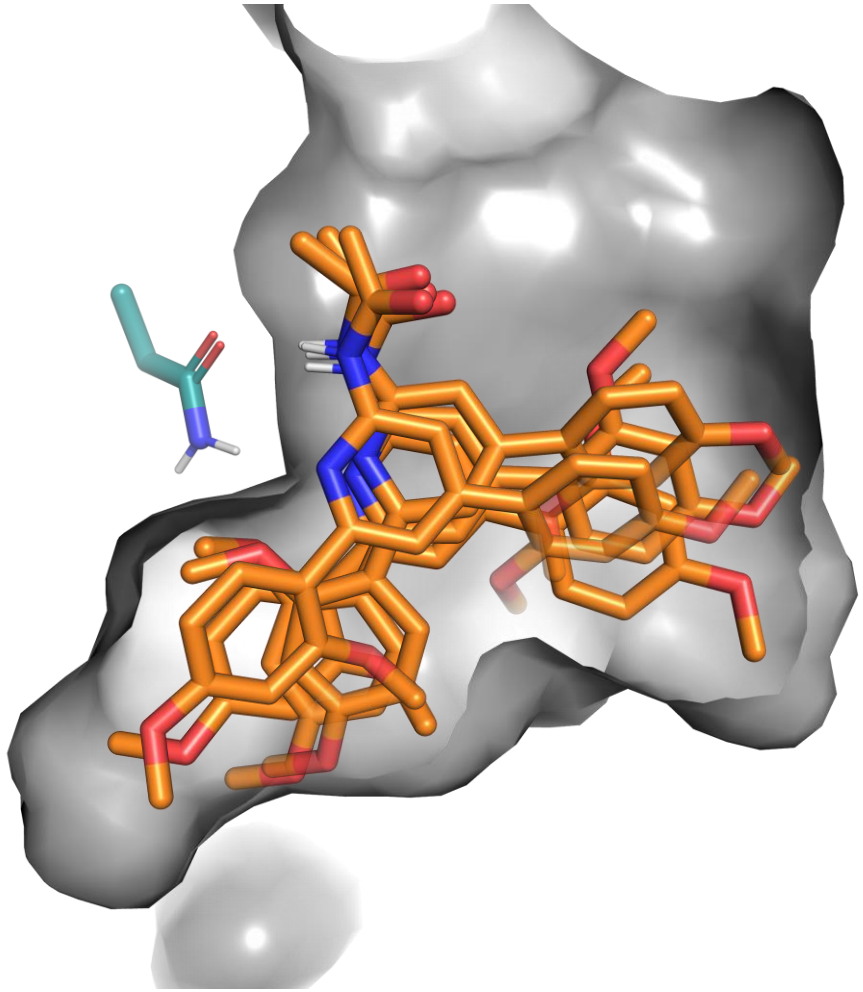
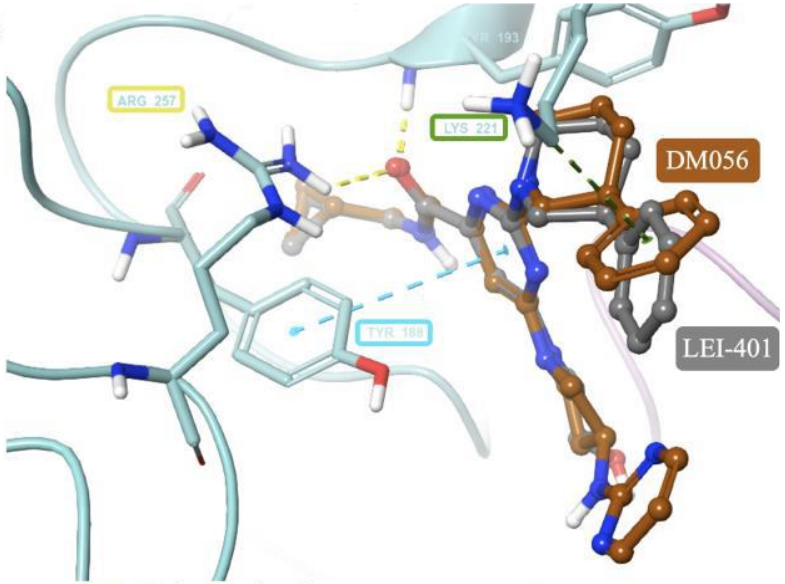
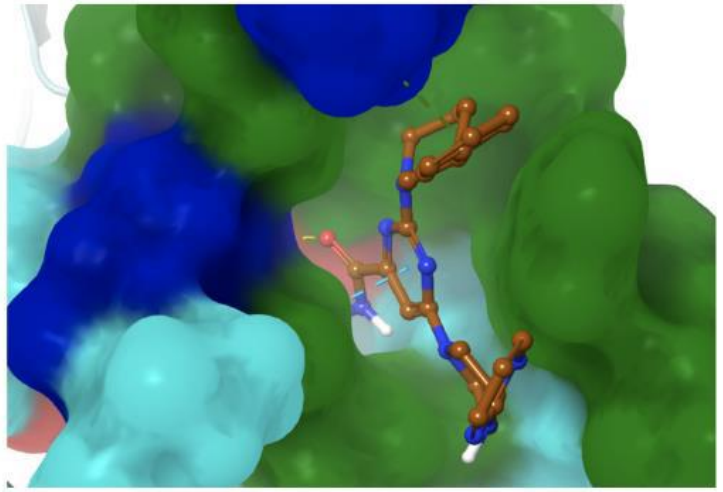
Molecular Docking

- Computer tries to fit the molecule to protein
- Predicts binding mode
- Older technique, far from perfect

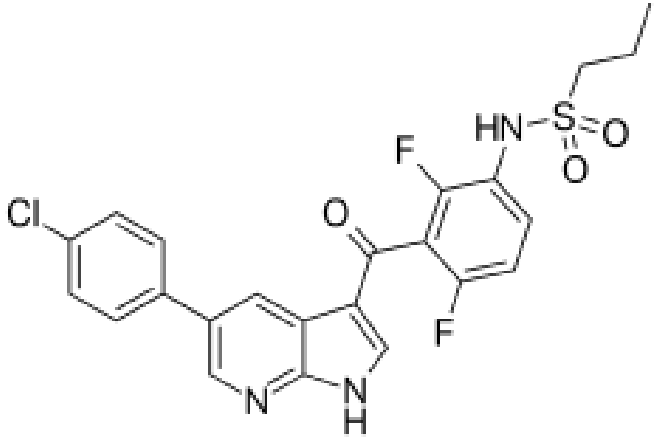






Docking: Kinases

- Family of ±500 phosphorylating enzymes
- >60 approved kinase inhibitors in clinic
- $50 bln market
- All compete with ATP

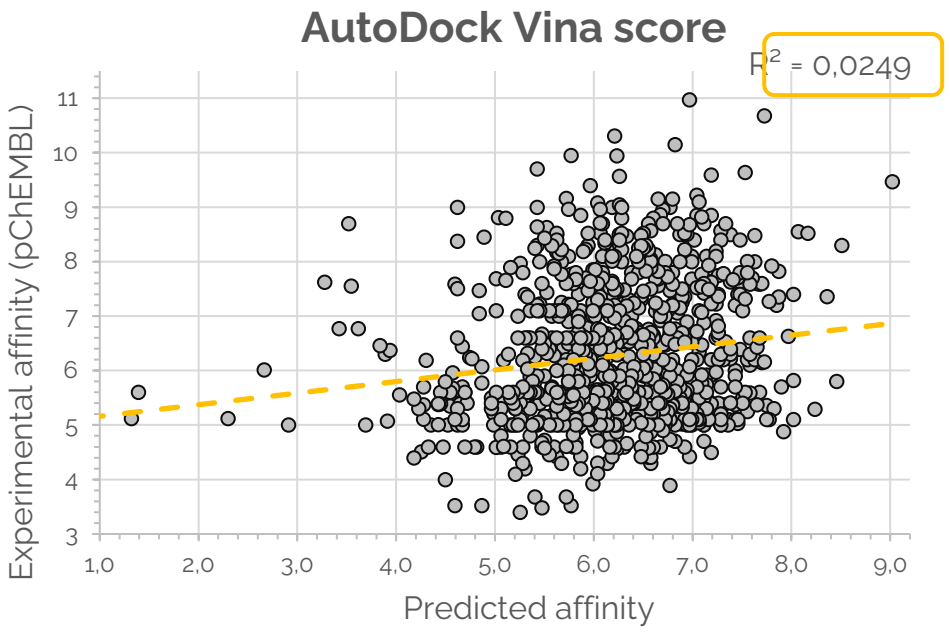


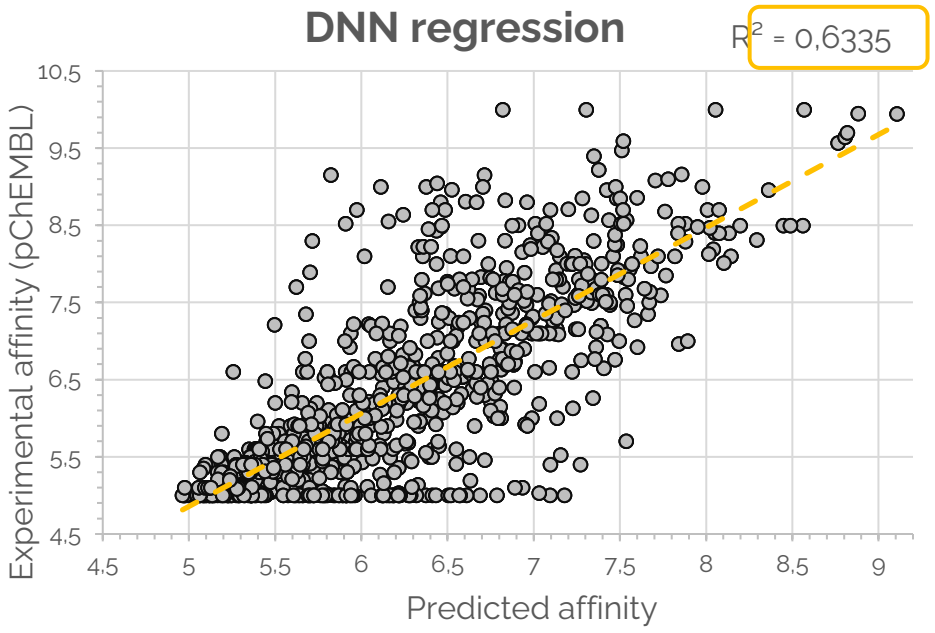
Docking: Kinases

- Collected ± 116.000 reported inhibitors
- Selected available crystal structures
- Generated docked pose for known (in)activities
- > 12 mln predicted poses

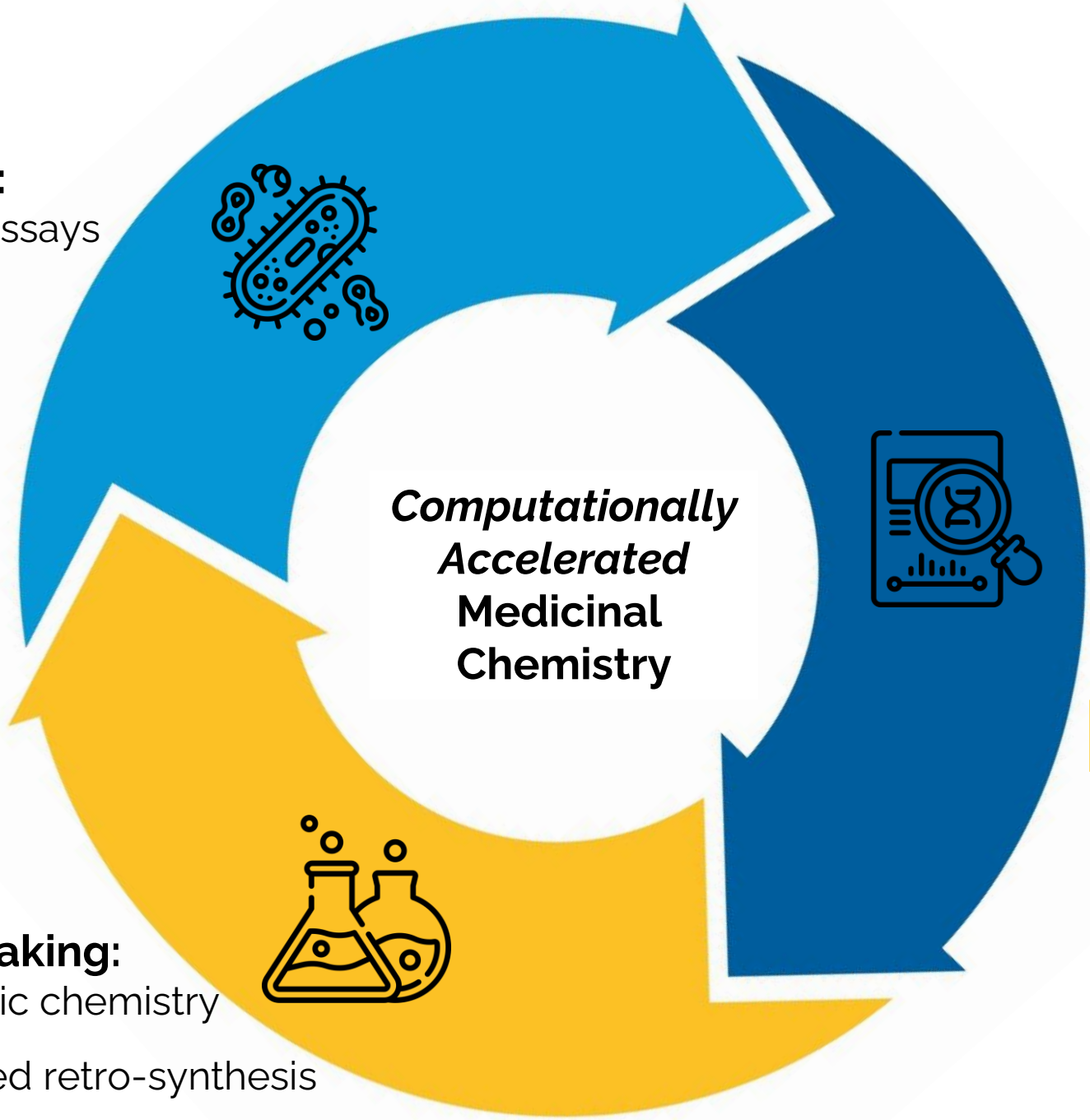
Docking: Kinases

- Predicted affinities do not correlate
- Machine learning is invoked to improve





Testing:
Biochemical assays



Designing:
Structure-Activity Relations

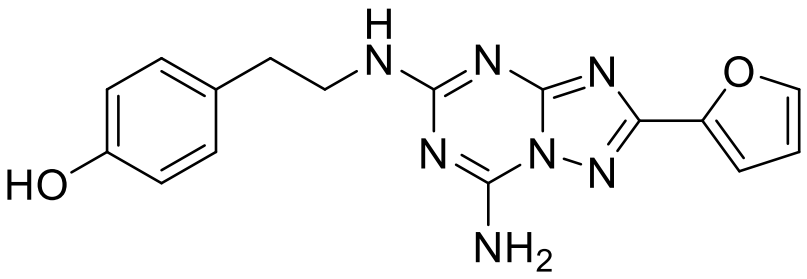
- Molecular docking
- *De novo* generation

Making:
Synthetic chemistry

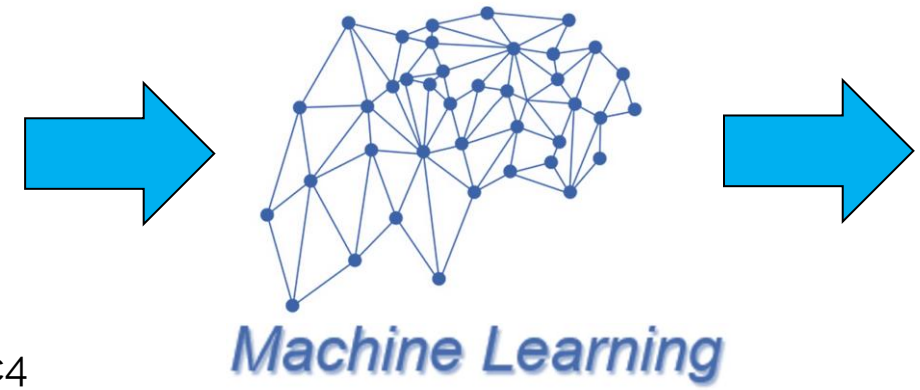
- AI-based retro-synthesis

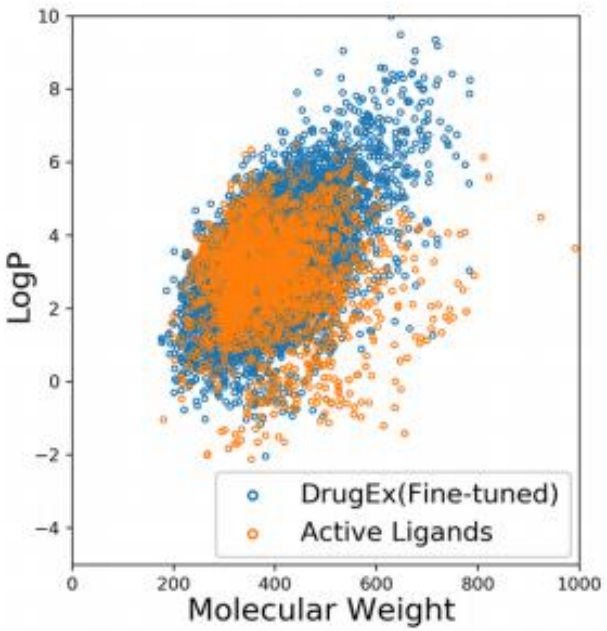
De novo generation

- AI suggests new molecules
- Language model learns chemistry
- Shown 100s-1000s of known actives



Nc1nc(NCCc2ccc(O)cc2)nc3nc(nn13)c4occc4





*Liu, et al, J Cheminf, (**2019**), 10.1186/s13321-019-0355-6*

Testing:
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***Computationally Accelerated* Medicinal Chemistry**

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Making:
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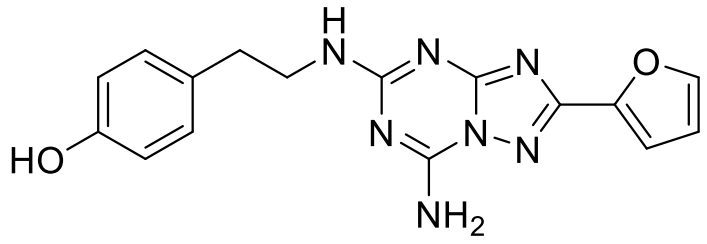
- AI-based retro-synthesis

AI for retrosynthesis

- How to make a compound?



- Working on a ‘LED3 score’ for synthesizability
- Very early days

Collaboration with A. Hassen, M. Preuss, LIACS

Conclusion

- Computationally Accelerated Medicinal Chemistry
- Combination of
  - ‘traditional’ structure-based
  - AI/Machine learning approaches
- Aimed at compound design & synthesis

Future directions

- Proteome-wide cross-library docking
  - Possible using AlphaFold
  - Covalent docking
- Enhance with Molecular Dynamics
- Integrate all aspects into pipeline

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