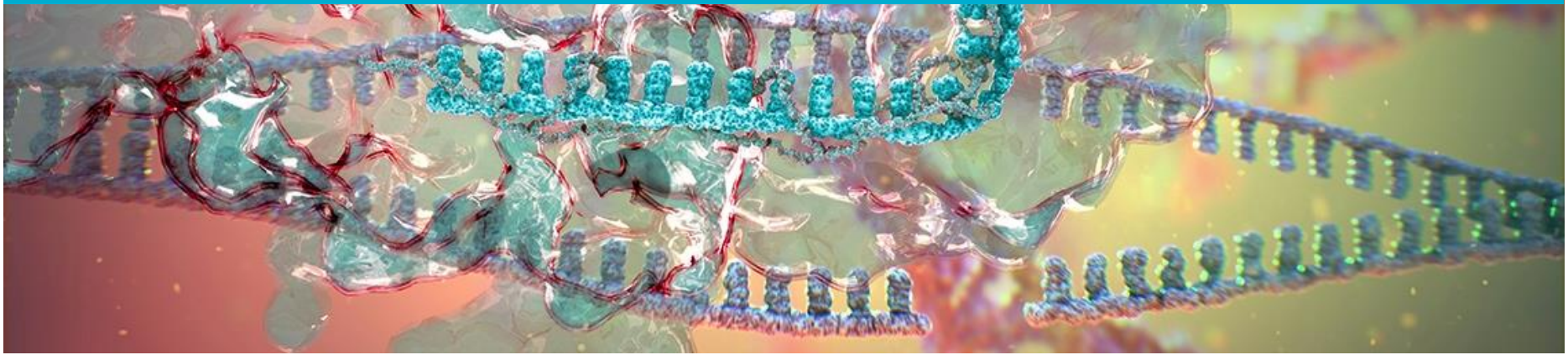
AstraZeneca
IMED Biotech Unit

How AstraZeneca is using AI to accelerate the development of novel medicines

Ola Engkvist, Hit Discovery, Discovery Sciences, R&D Biopharmaceuticals, AstraZeneca, Gothenburg, Sweden

Chalmers Lecture

May 26 2020



AstraZeneca: global dimensions

For year ending 31 December 2018

$22.1bn Total Revenue
(down 2% over 2017)

$21.1bn Product Sales
(up 4% over 2017)

$1bn Externalisation Revenue

$5.9bn invested in R&D with research across five countries

149 projects in clinical development and eight NMEs in late-stage development

23 NME approvals in 2018
(and 71 since 2014)

64.6k employees

45% of our senior roles are filled by women

29 manufacturing sites in 17 countries

Growth through innovation

> … in 2018, after the previous six years in which revenues had fallen by more than one third, we turned the corner and returned to Product Sales growth.
>
> As we enter the next phase in our journey, the fundamentals of our strategy and plans remain unchanged, with Product Sales Growth driving improved profitability and the generation of increasing levels of cash.

Pascal Soriot, CEO, AstraZeneca

Focus on three main therapy areas and across key platforms

Oncology

Cardiovascular, Renal and Metabolism

Respiratory

Combination of capabilities

SMALL MOLECULES | BIOLOGICS | IMMUNOTHERAPIES | PROTEIN ENGINEERING | OTHER EMERGING DRUG PLATFORMS | DEVICES

Three strategic R&D sites close to global bioscience clusters

AstraZeneca has extensive research and manufacturing in Sweden

- Gothenburg is one of three strategic Research & Development centers within AstraZeneca
- Södertälje is AstraZeneca's largest high-tech production and supply site
- In Sweden the AZ Nordic Marketing Company is responsible for the marketing & sales of our medicines and they have their offices in Södertälje

Gothenburg
2,400
Södertälje
+ 4,500
= 6,900

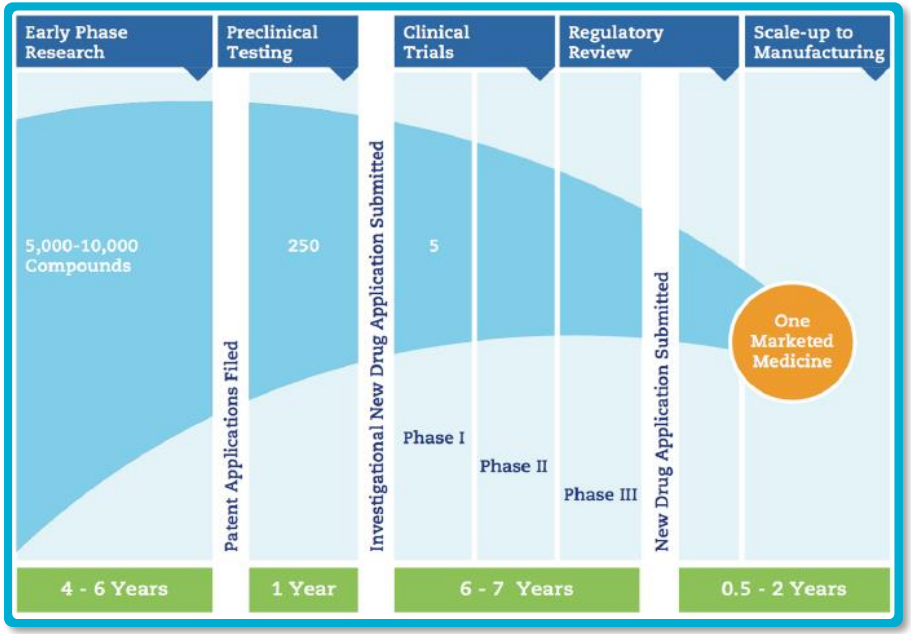
Drug Discovery is just the beginning …

Life-cycle of a medicine

We are one of only a handful of companies to span the **entire life-cycle** of a medicine from **research and development** to **manufacturing and supply**, and the **global commercialisation** of primary care and speciality care medicines

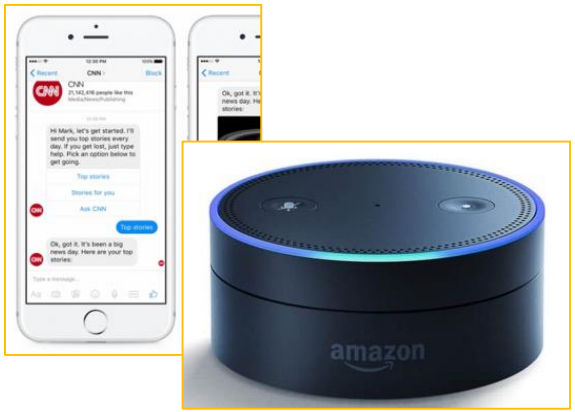
Drug Discovery & Development

- Drug discovery remains slow & expensive
- From initial screening to candidate drug
  - 4 to 7 years
  - up to $200 million
  - attrition rate of > 70%
- Genomics and Patient stratification leading to explosion in number of targets



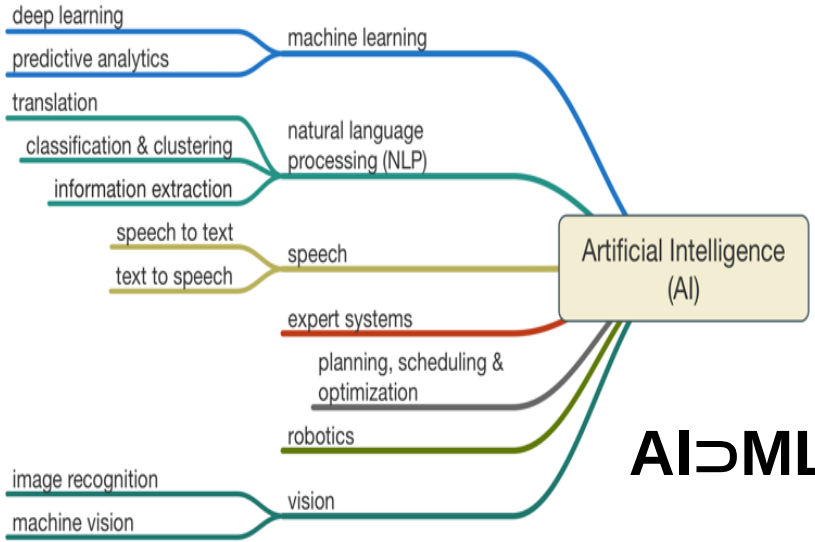
Business success requires a reduction in cycle time and costs for Lead Identification and Optimisation

Machine Learning & AI can help us improving productivity



"AI is the new electricity…just as electricity transformed industry after industry 100 years ago, I think AI will do the same."

Andrew Ng, founder of Google Brain & Coursera, former head of Baidu AI group



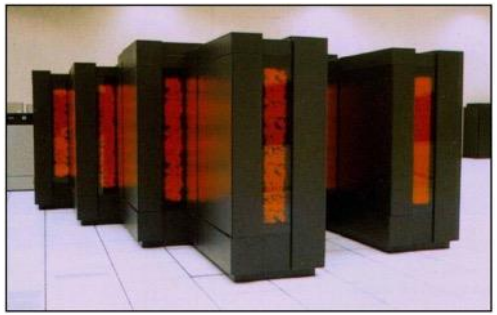
AI⊃ML⊃DL

Why now?

Advances in hardware, software and data acquisition have transformed what is possible

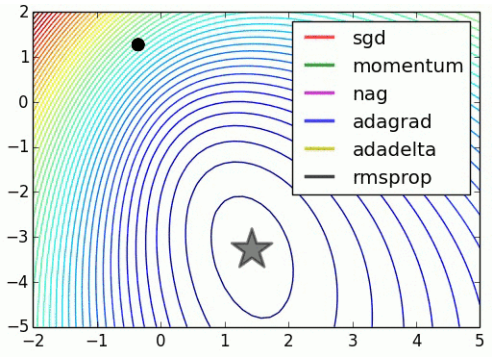
~1 million times more compute power

Algorithmic advancements



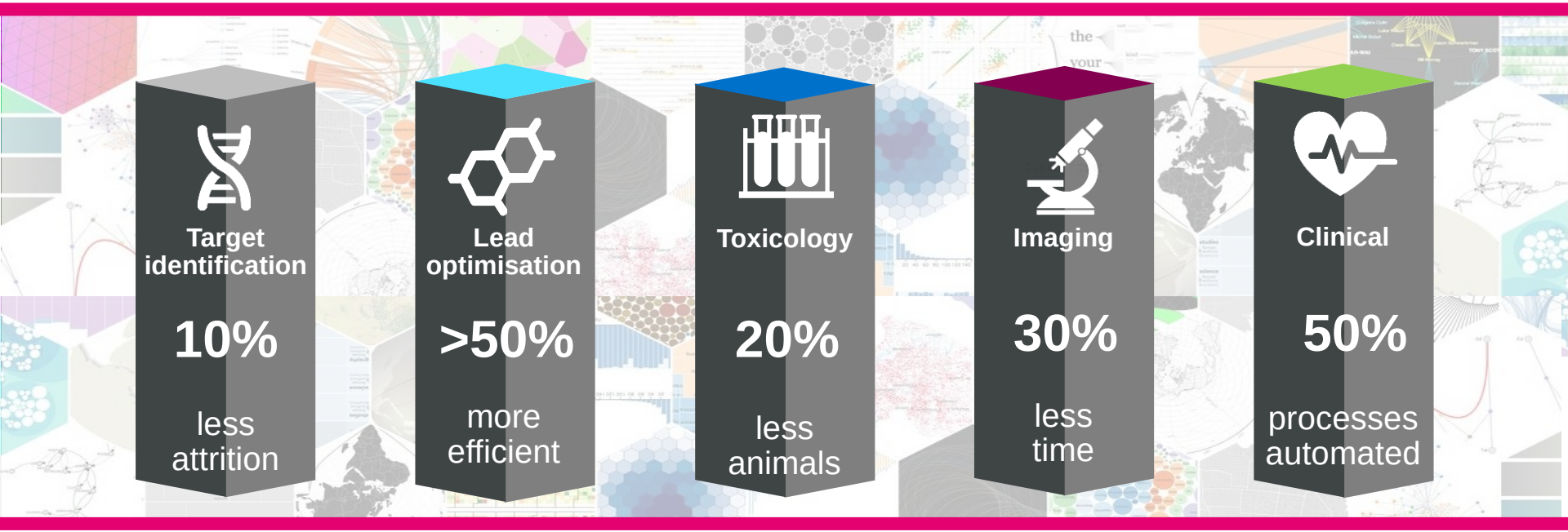
Late 1990's
~1 unit = $800K

Now
~1 unit = $1



Source: http://hduongtrong.github.io

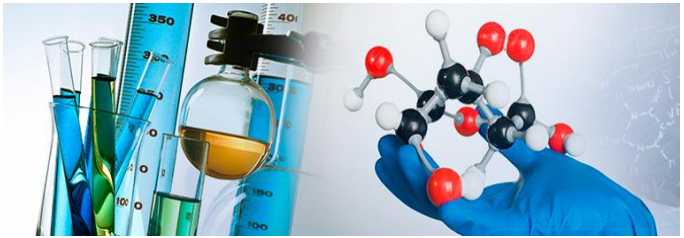
Where can AI impact our R&D units



Drug Design

What to make next?

How to make it?



De novo design
Multi-parameter scoring function

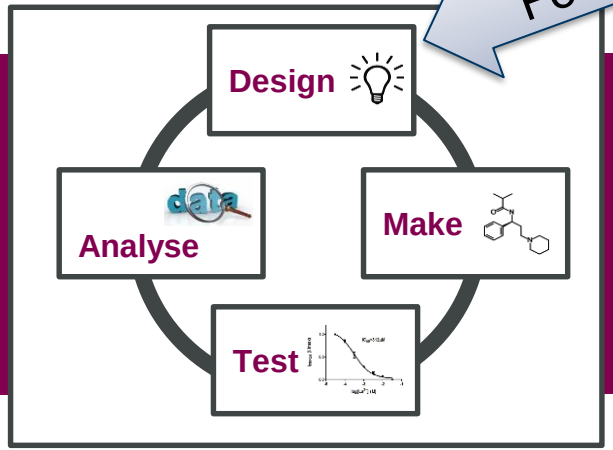
Retrosynthesis

The Design Make Test Analyze cycle in Drug Design

Drug target

Chemical starting point (“Hit”) found through HTS, DEL, fragment screening or knowledge

- Weakly active
- Target unselective
- Toxicity risk
- Low metabolic stability



Candidate drug

- Highly potent
- Effective in *in vivo* models
- Metabolically stable
- No toxicity issues

~3 years

Multiple of DMTA cycles

4-6 weeks per cycle

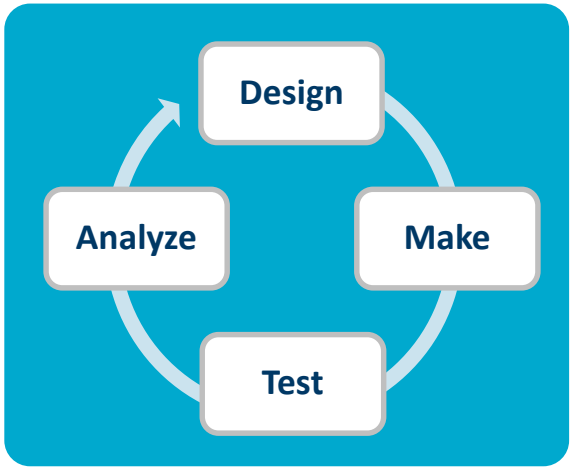
Hand-overs between multiple labs

The challenge: Find ways to speed up and improve the process using AI

Augmented Drug Discovery

How can we reduce the time to deliver a clinical candidate?

Select the most efficient synthetic route



Make more compounds in each cycle

Increase speed

Maximize learning

Three dedicated groups to build the AI/Automation capabilities

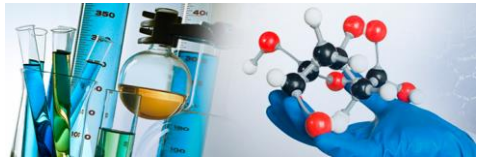
HTS/DEL

How to generate large datasets?

Molecular AI

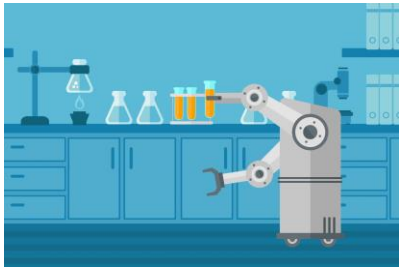
What to make next?

How to make it?



iLAB

How to synthesize, purify, quantify and test autonomously?



Key priority areas in ML/AI

- Deep learning based de novo molecular design
- Synthesis Prediction
- More accurate property predictions
- Decision making under uncertainty

+

Science @AZ

ACS central science

Research Article

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Generating Focused Molecule Libraries for Drug Discovery with Recurrent Neural Networks

Marwin H. S. Segler,[*,†] Thierry Kogej,[‡] Christian Tyrchan,[§] and Mark P. Waller[*,∥]

Commentary

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Future Medicinal Chemistry

The convergence of artificial intelligence and chemistry for improved drug discovery

Clive P Green*[,1], Ola Engkvist[2] & Garry Pairaudeau[3]

RESEARCH

Molecular De-Novo Design through Deep Reinforcement Learning

Marcus Olivecrona*, Thomas Blaschke†, Ola Engkvist† and Hongming Chen†

Application of Generative Autoencoder in *De Novo* Molecular Design

Thomas Blaschke,*[a, b] Marcus Olivecrona,[a] Ola Engkvist,[a] Jürgen Bajorath,[b] and Hongming Chen*[a]

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
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Computational prediction of chemical reactions: current status and outlook

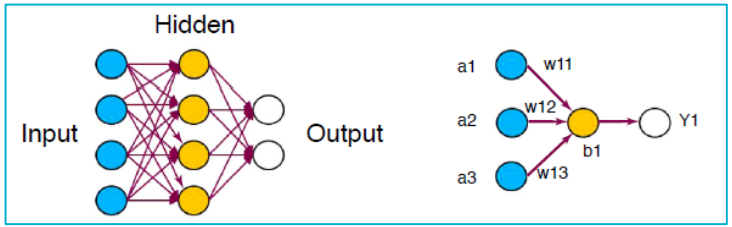
Ola Engkvist[1], Per-Ola Norrby[2], Nidhal Selmi[1], Yu-hong Lam[3], Zhengwei Peng[3], Edward C. Sherer[3], Willi Amberg[4], Thomas Erhard[4] and Lynette A. Smyth[4]

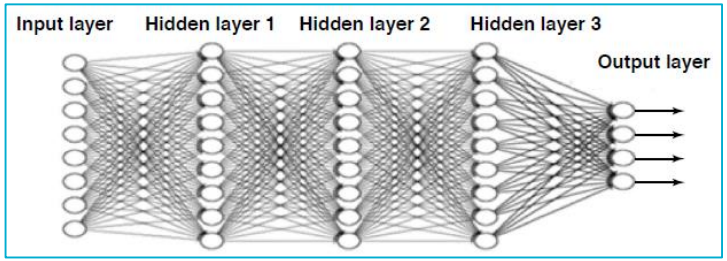
Ola Engkvist was awarded his PhD in computational chemistry by the University of Lund in 1997, and continued with postdoctoral research at

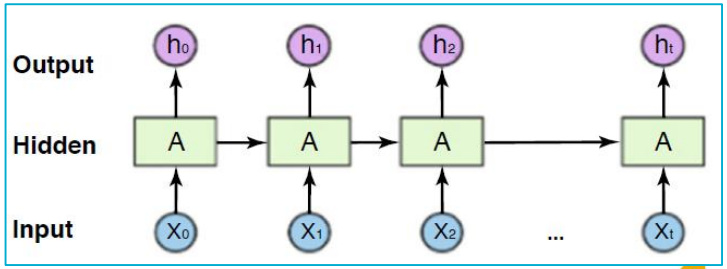
Open Source:
https://github.com/MarcusOlivecrona/REINVENT

Neural Networks & Deep Learning

- **Neural Networks known for decades**
  - Inputs, Hidden Layers, Outputs
  - Single layer NNs have been used in QSAR modelling for years
- **Recent Applications use more complex networks such as**
  - Multi-layer Feed-Forward NNs
  - Convolutional NNs
    - biological image processing
  - Auto-encoder NNs
  - Recurrent NNs
    - Trained using Maximum Likelihood Estimation to maximize the likelihood of next character







Why? Generation of Novel Compounds in the 10^{60} Chemical Space!

10^{10}-10^{12}

10^{60}

Journalist units:

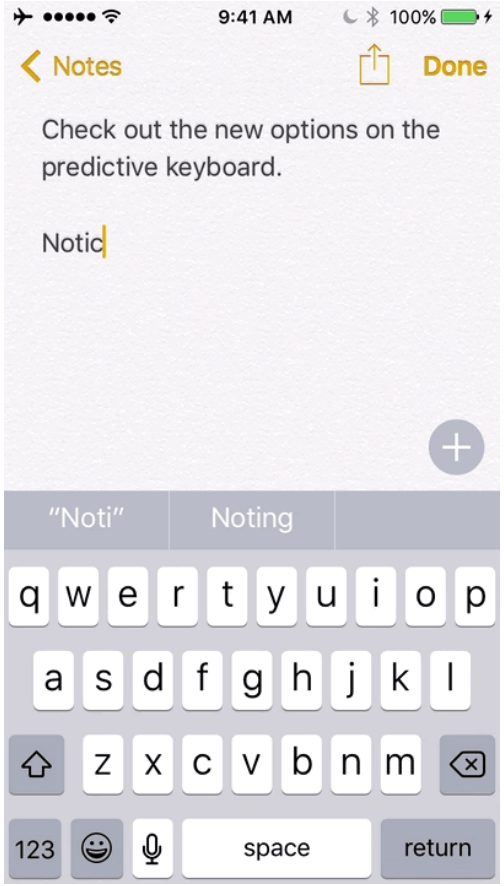
Known space: 0,00017 ng of Hydrogen atoms

Possible space: The Hydrogen atoms in 90 Suns

Where´s the impact?

- Use for de novo Molecular Design
  - Scaffold Hopping
  - Novelty
  - Virtual Screening
  - Library Design

Recurrent Neural Network & Natural language generation



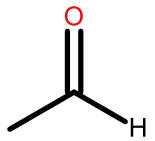
Natural language generation and molecular structure generation

- Can we borrow concepts from natural language processing and apply to SMILES description of molecular structures to generate molecules?

The → grass → is → ?

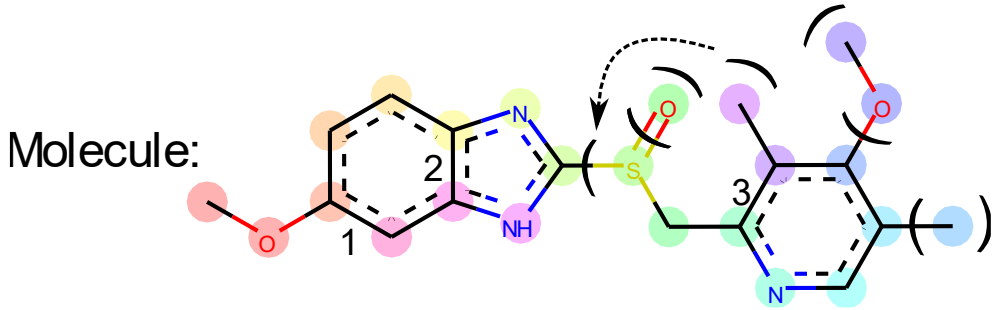
- Conditional probability distributions given context
- $P(green \mid is, grass, The)$

C → C → = → ?



- $P(O \mid =, C, C)$

Simplified Molecular Input Line Entry Specification (SMILES)



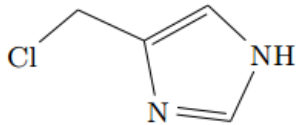
SMILES: COc1ccc2nc(S(=O)Cc3ncc(C)c(OC)c3C)[nH]c2c1

- A sequence format for molecules
- Allows us to use the progresses made with natural language processing in the recent years ☺

Tokenization of SMILES

- Tokenize combinations of characters like “Cl” or “[nH]”
- Represent the characters as one-hot vectors

Graph:

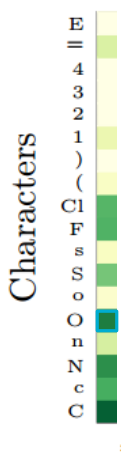


SMILES: ClCc1c[nH]cn1

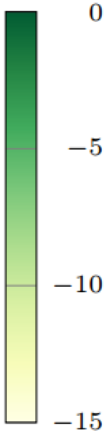
One-hot encoding:

	Cl	C	c	1	c	nH	c	n	1
C	0	1	0	0	0	0	0	0	0
c	0	0	1	0	1	0	1	0	0
n	0	0	0	0	0	0	0	1	0
1	0	0	0	1	0	0	0	0	1
nH	0	0	0	0	0	1	0	0	0
Cl	1	0	0	0	0	0	0	0	0

The generative process



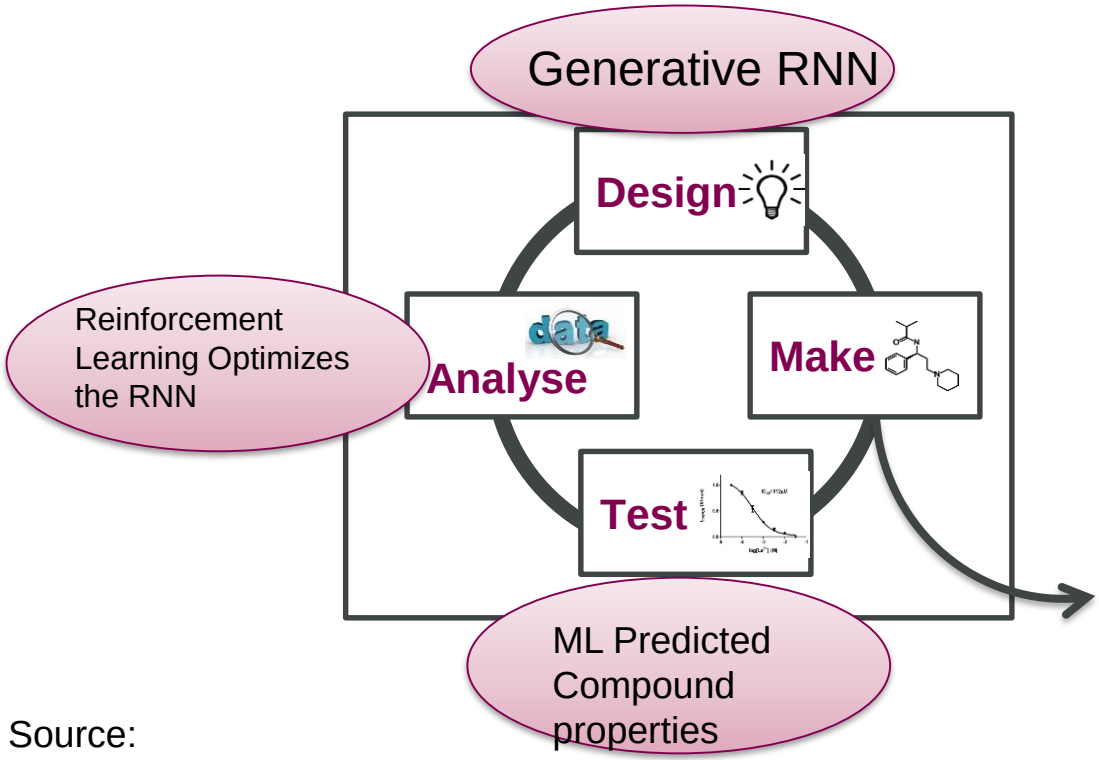
Sampled SMILES



Log P

Structure

Reinforcement Learning: An *In Silico* mini-DMTA cycle



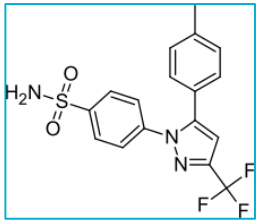
The Value:
Molecules for DMTA cycle

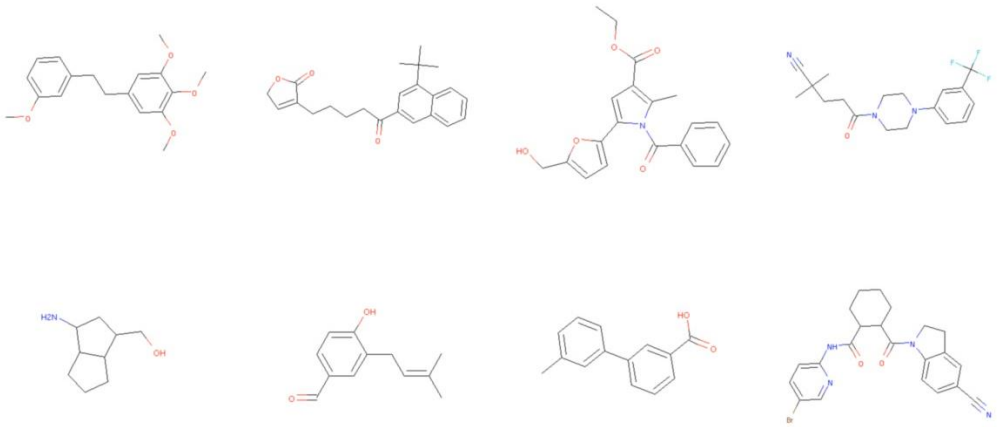
Produces novel scaffolds and improved compound suggestions for drug discovery projects

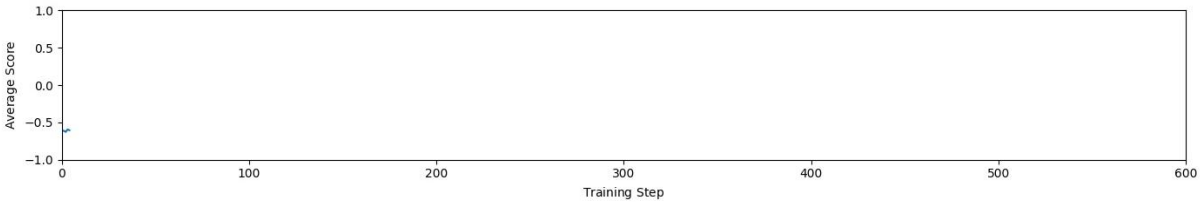
Less real world DMTA cycles => Saved time

Open Source:
https://github.com/MarcusOlivecrona/REINVENT

AI live: Create Structures Similar to Celecoxib



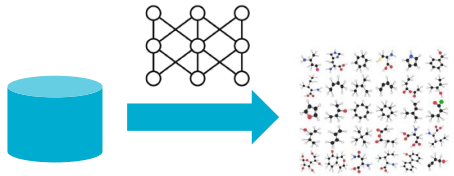




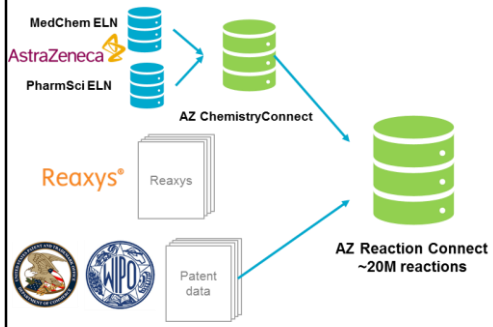
- **Key Message**
  - RNN generates structures similar to Celecoxib
  - Rapid sampling!
  - Average score describes how many learning steps are required to reach similar compounds

Artificial Intelligence Guided Drug Design Platform

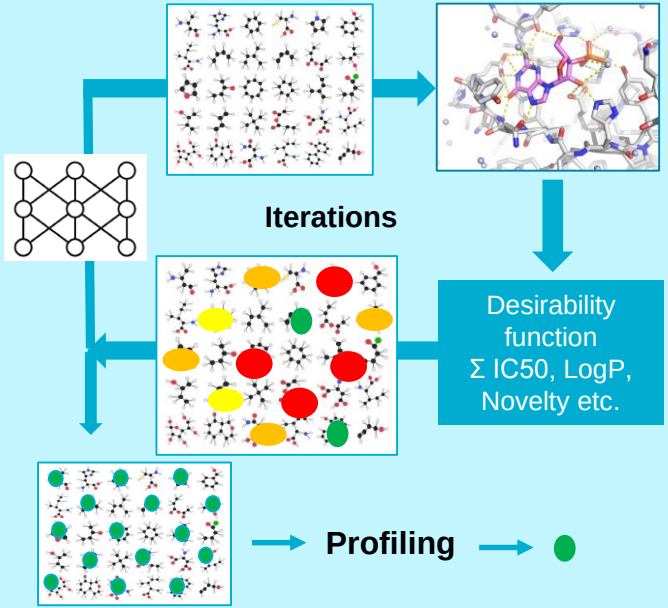
Generation of Novel Chemical Space



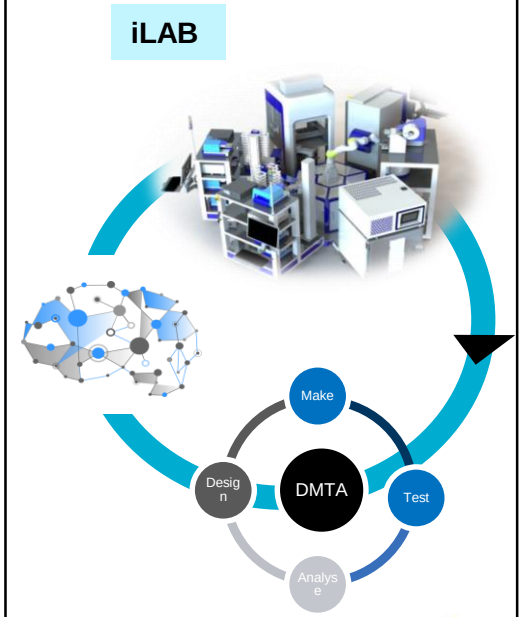
Reaction & Synthesis Prediction



AI Design Platform



Fully Automated DMTA Cycle



MACHINE LEARNING LEDGER ORCHESTRATION FOR DRUG DISCOVERY

JUNE 2019 – MAY 2022

MELLODDY

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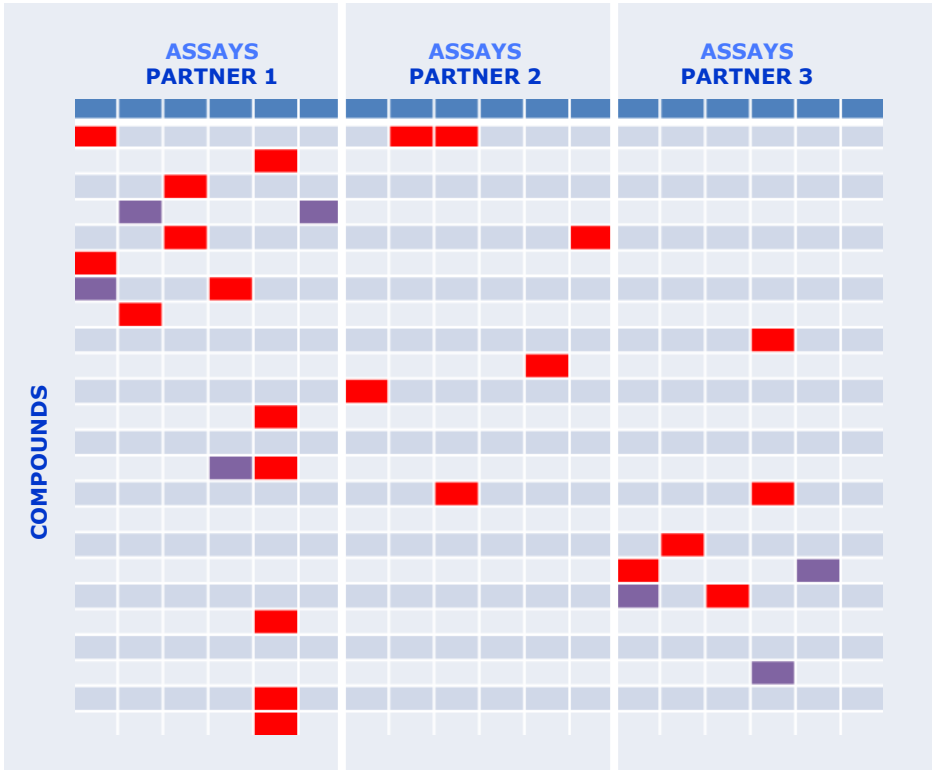
imi innovative medicines initiative · efpia

MULTI-TASK LEARNING
ACROSS PHARMA PARTNERS

Compound and activity data and assay-specific models remain under their owner's control

Multi-task approach across partners to improve predictive performance and applicability



AMGEN
astellas
AstraZeneca
BAYER
Boehringer Ingelheim
gsk
janssen
MERCK
NOVARTIS
SERVIER

What are the challenges for AI driven drug design?

- Scaling AI and chemistry automation for drug design to a whole drug discovery project portfolio including projects with low data volume
- Binding affinity and solubility predictions are major bottlenecks
- “Cambrian revolution” of new AI methods makes it difficult to assess progress
- Educational, cultural & logistical challenges besides scientific
- The bar is set high to transform drug design

Acknowledgements

Molecular AI Team

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AI Projects

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Sepp Hochreiter (Linz)
Gunther Klambauer (Linz)
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Alexander Schliep (Chalmers)
Morteza Chehreghani (Chalmers)

Have a look at the AstraZeneca Graduate Programme in Data Science & AI

https://careers.astrazeneca.com/students/programmes/imed-early-phase-drug-discovery-graduate-programme

We are always looking for Master Thesis students

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