

Thomas Hartung & team

ToxAlcology

- AI is the future of toxicology -

Slides available:





Toxicologist's Christmas Wish List

Human hazard

Human risk

Complex endpoints

For many chemicals

For biologicals

For mixtures

For individuals

Fast & cheap



Volume
Variety
(multi-modal)
Velocity

<https://www.e-marketing.fr/Thematique/data-1091/big-data-2223/Breves/Tout-faut-savoir-big-data-363012.htm>

AI is making Big Sense of Big Data

DATA



COMPUTING POWER

AI MODELS

Together increase
>1 billion-fold
over last 60 years

Data: +60% per year
= 90% in last three years

Computer: +40% per year
(Moore's law)

AI: +700% per year since 2010

R.E.M.
**IT'S THE END
OF THE WORLD
AS WE KNOW IT
(AND I FEEL FINE)**

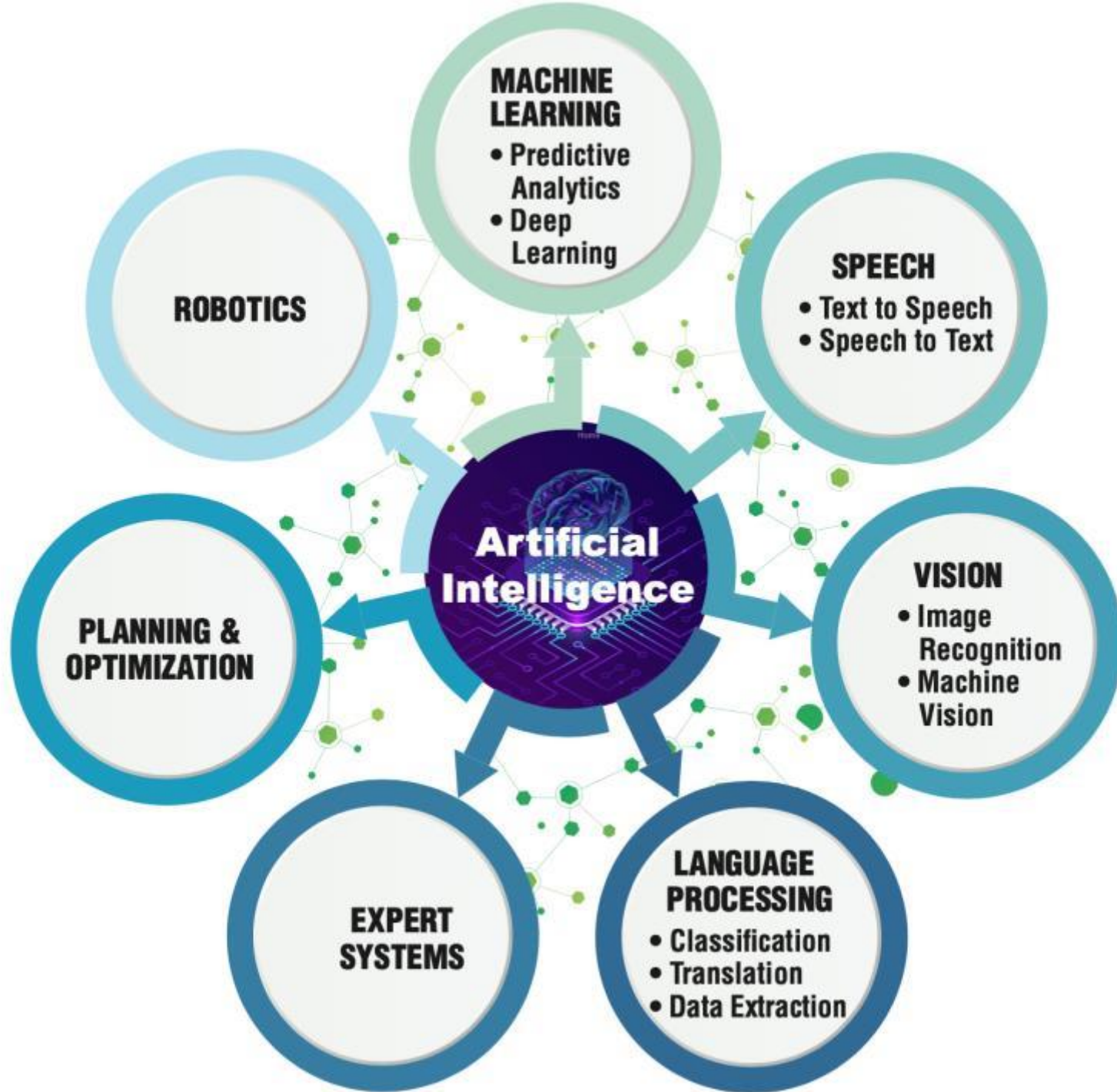


**WHY, SOMETIMES
I'VE BELIEVED
AS MANY AS
SIX IMPOSSIBLE
THINGS BEFORE
BREAKFAST.**

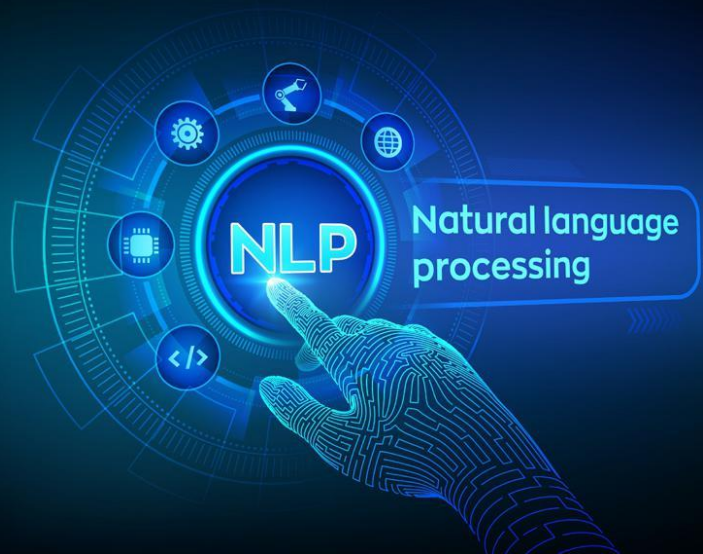
Lewis Carroll
Through the Looking-Glass

1. There is a better way to play chess
2022 DeepMind: AlphaZero
2. The structure of all proteins can be predicted from gene sequence
2022 DeepMind: AlphaFold
3. A computer is better than (most) lawyers
2023 OpenAI: GPT-4
4. A computer exceeds computational capacity of a human brain
2022 Frontier Computer exceeds 1 exaflop
5. AI can design drugs
2022 – 18 AI-first drugs in clinical trials
6. AI wins art contests
2022 Midjourney

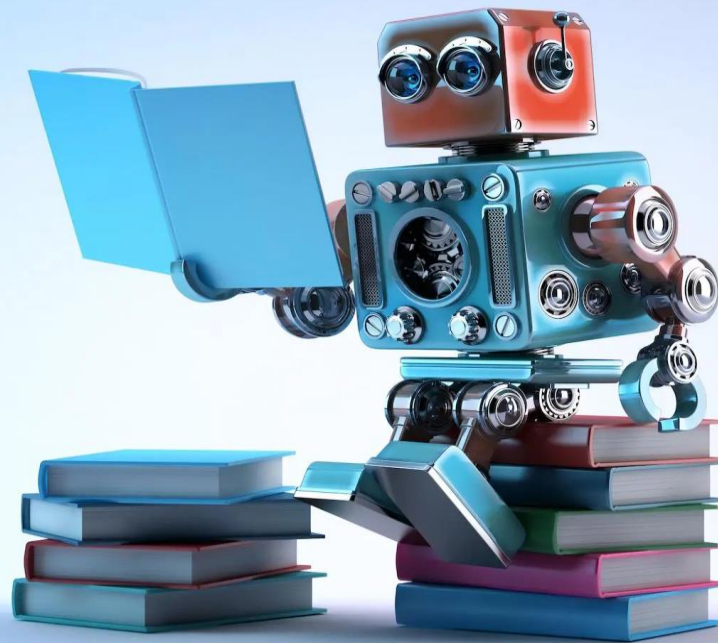




A.I. use cases



**Data extraction from
literature, reports &
databases**



Multi-modal

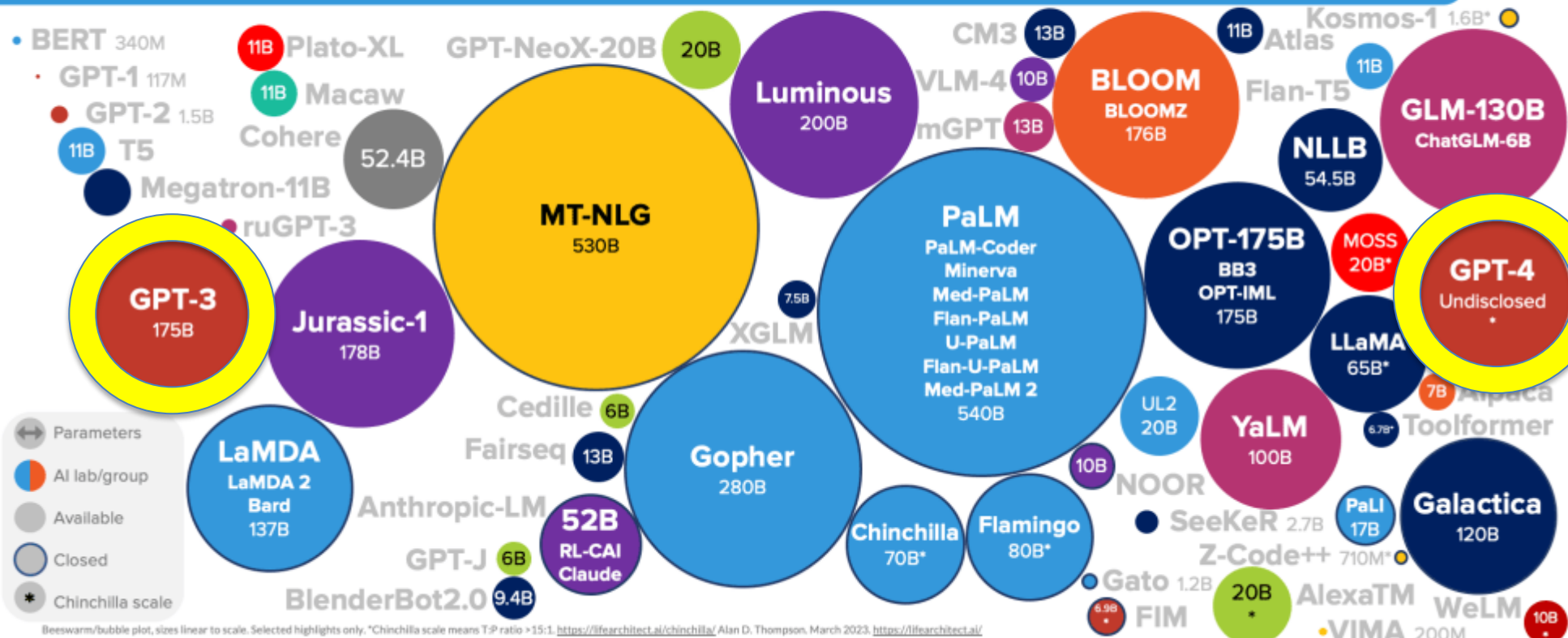
Science & Health 9%

Includes: Medical Resources, Science,
Health Care Services, Nutrition & Dieting

TOP SITES

1. journals.plos.org
2. frontiersin.org
3. link.springer.com
4. ncbi.nlm.nih.gov
5. nature.com

LANGUAGE MODEL SIZES TO MAR/2023



Variables
trained on

[LifeArchitect.ai/models](https://lifearchitect.ai/models)

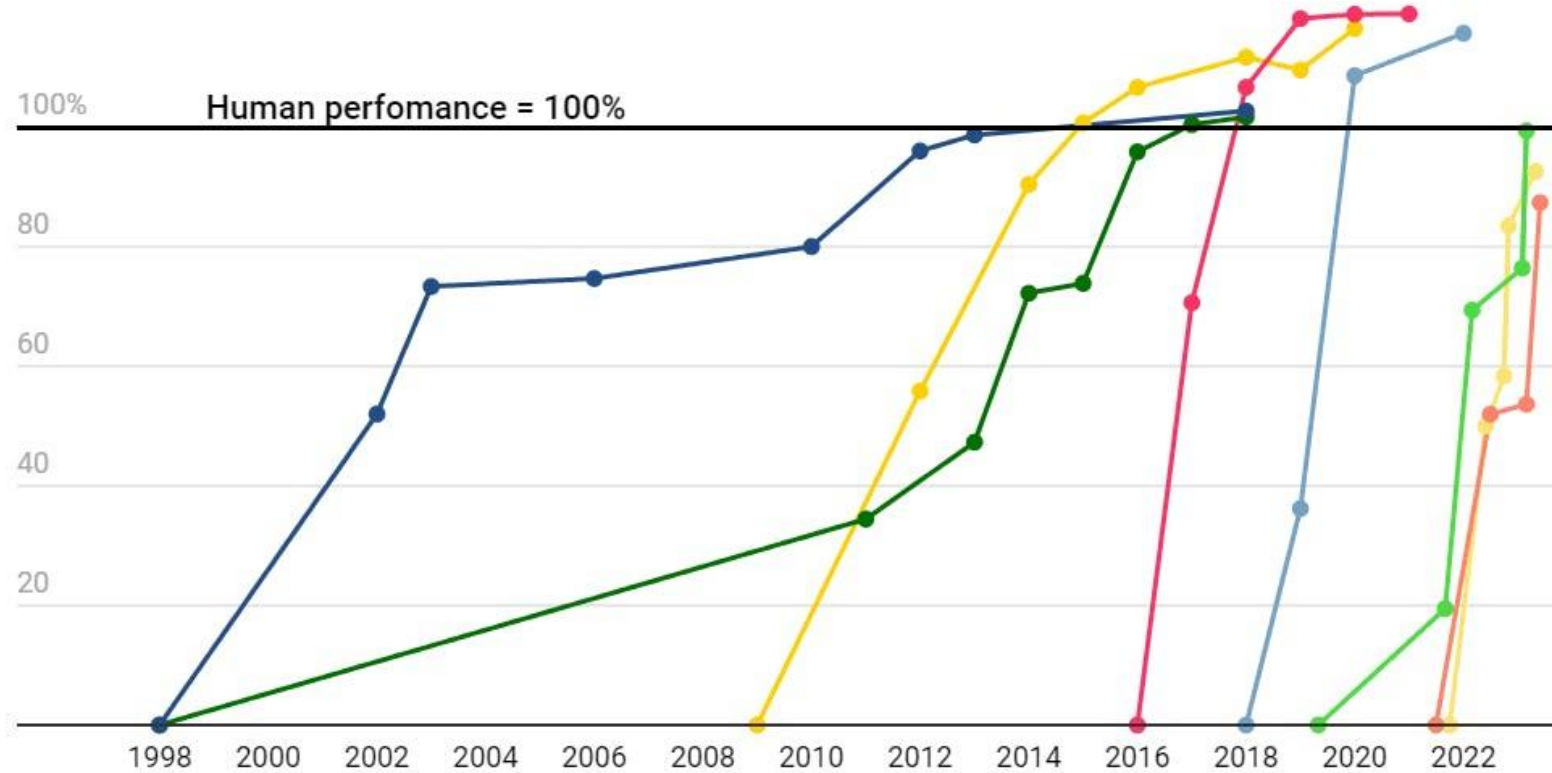
14 March 2023 Launch of GPT-4

<https://lifearchitect.ai/gpt-4/>

AI has surpassed humans at a number of tasks and the rate at which humans are being surpassed at new tasks is increasing

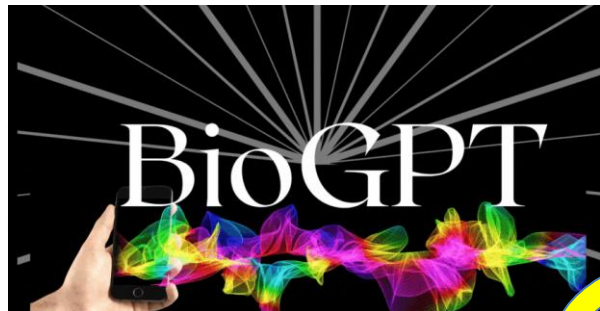
State-of-the-art AI performance on benchmarks, relative to human performance

● Handwriting recognition ● Speech recognition ● Image recognition ● Reading comprehension
● Language understanding ● Common sense completion ● Grade school math ● Code generation



GPT-4 performed at the 90th percentile on a simulated bar exam, the 93rd percentile on an SAT reading exam, and the 89th percentile on the SAT Math exam, OpenAI claimed.

For each benchmark, the maximally performing baseline reported in the benchmark paper is taken as the "starting point", which is set at 0%. Human performance number is set at 100%. Handwriting recognition = MNIST, Language understanding = GLUE, Image recognition = ImageNet, Reading comprehension = SQuAD 1.1, Reading comprehension = SQuAD 2.0, Speech recognition = Switchboard, Grade school math = GSK8k, Common sense completion = HellaSwag, Code generation = HumanEval.



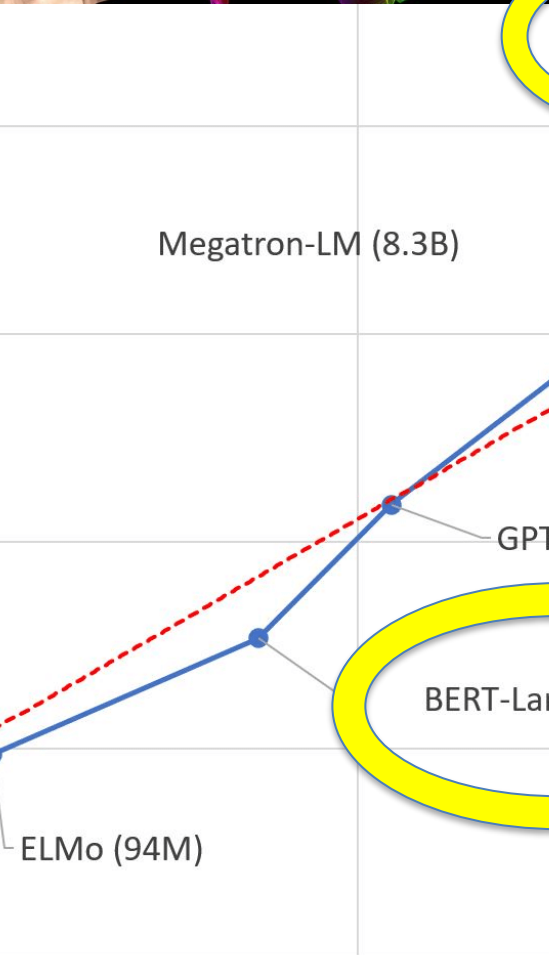
Model Size (in billions of parameters)

1000
100
10
1
0.1
0.01

2018

2019

2020



BioGPT and human annotator have comparable performance in biomedical research test

Selected performances on PubMedQA, which tests biomedical language processing

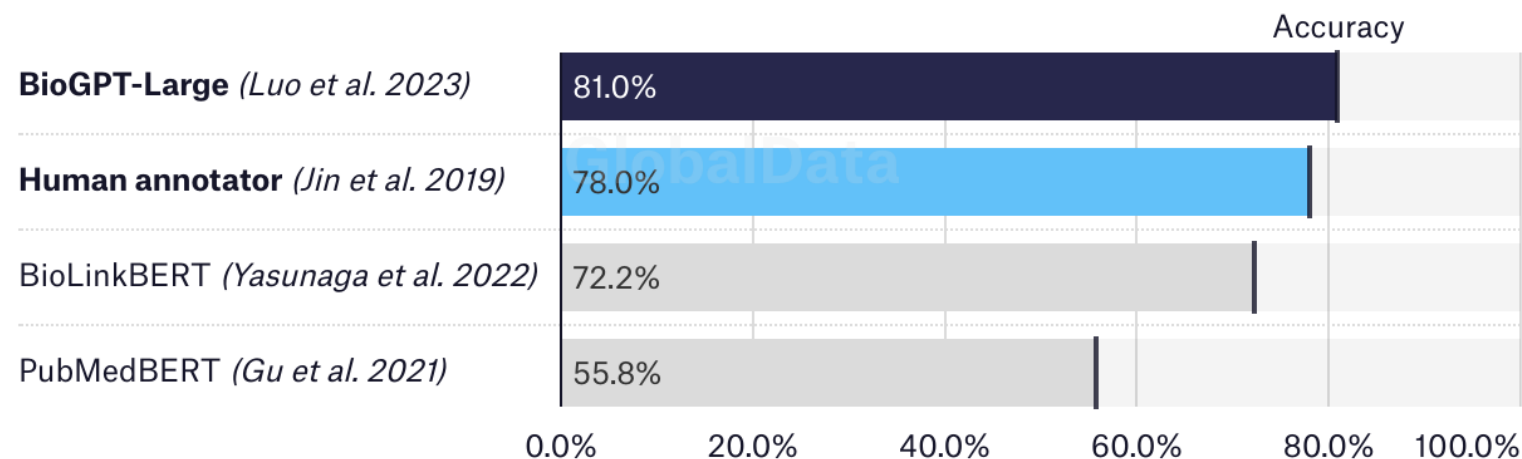
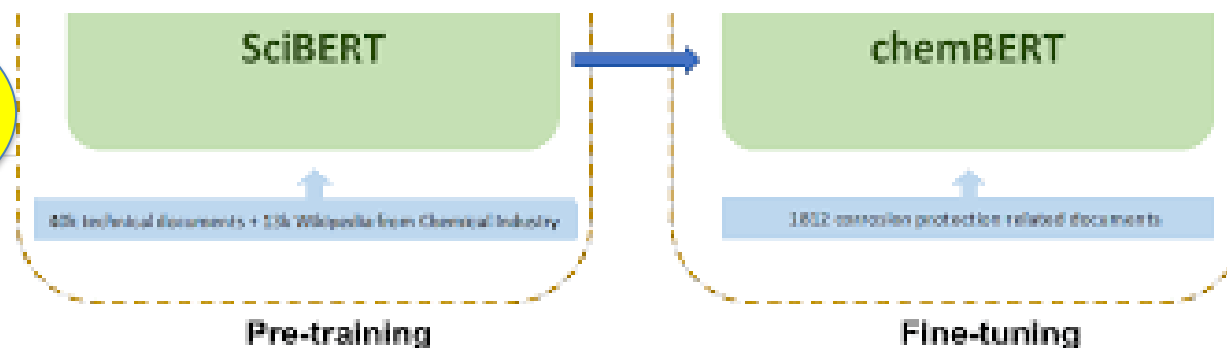


Chart: GlobalData • Source: PubMedQA



2021

2022

	PRE - 2020	2020	2022	2023?	2025?	2030?
TEXT	Spam detection Translation Basic Q&A	Basic copy writing First drafts	Longer form Second drafts	Vertical fine tuning gets good (scientific papers, etc)	Final drafts better than the human average	Final drafts better than professional writers
CODE	1-line auto-complete	Multi-line generation	Longer form Better accuracy	More languages More verticals	Text to product (draft)	Text to product (final), better than full-time developers
IMAGES			Art Logos	Mock-ups (product design, architecture, etc.)	Final drafts (product design, architecture, etc.)	Final drafts better than professional artists, designers, photographers)
				Second drafts	AI Roblox Video games and movies are personalized dreams	

</

Almost there
Ready for prime time

A personal take on science and society

Nature 20 Apr 2023

World view

Open generative AI models are a way forward for science



By Arthur Spirling

Researchers should stop using proprietary large language models and develop transparent ones to ensure reproducibility.



be the same, or even whether the technology will still be supported? GPT-3, released last November by OpenAI in San Francisco, California, has already been supplanted by GPT-4, and presumably supporting the older LLM will soon

"Can you take AI out of the wild and should you?"



Thomas Hartung

Johns Hopkins University

Field Chief Editor Frontiers in Artificial Intelligence



Test case: GPT-4 written response (included as supplement)

"summarize, praise, criticize" – very solid result

Trend "to the middle", the most probable!

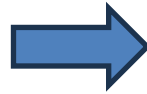
Forces us to focus on ideas, inspiration, experience, opinion...

"Food for thought"

ToxAlcology

Big Data

- High-content (~omics & imaging)
- High-throughput (Robotized testing, e.g., Tox21 & ToxCast)
- Sensors
- Literature, Internet
- Legacy studies



Big Sense

- Data retrieval
- Evidence integration (systematic reviews, risk assessments)
- Predictive toxicology
- Digital pathology
- Reporting

Big Computer

AI & Machine Learning

- Natural Language Processing (Large Language Models)
 - Blockchain
- Foundational models
- Federated Learning

ACCEPTED MANUSCRIPT

Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility



Thomas Luechtefeld, Dan Marsh, Craig Rowlands, Thomas Hartung ✉

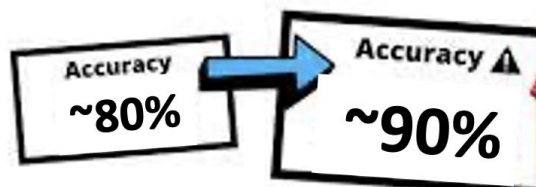
Toxicological Sciences, kfy152, <https://doi.org/10.1093/toxsci/kfy152>

Published: 11 July 2018

Uses chemical similarity
(network effect)
Uses transfer learning
(74 labels)



**TRANSFER
LEARNING**



Tom Luechtefeld

- Combining read-across with machine-learning
- Very large database
- Nine OECD test predicted
- 87% accuracy for 190,000 chemicals with known classifications
- 81% reproducibility of respective animal tests

Animal Replacement

2018: Nine most used animal tests

AI predicted 190,000 chemicals 87% correctly

Animal reproducibility 81%

2020: Human Skin Sensitization

AI predicted 506 chemicals 80% correctly

Animal 74% correct

2022: Nine most used animal tests predicted by AI

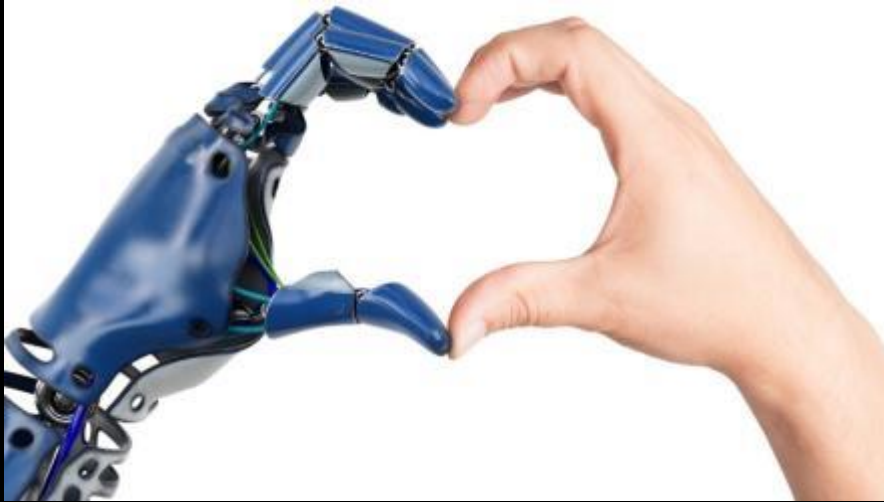
AI predicted 4700+ food chemicals 83% correctly in 1h
= 38,000 animal studies at \$250+ million

2023: Systemic toxicities

AI predicted 75% cancer risk of 950 chemicals and 82% reproductive tox of 1152 chemicals correctly

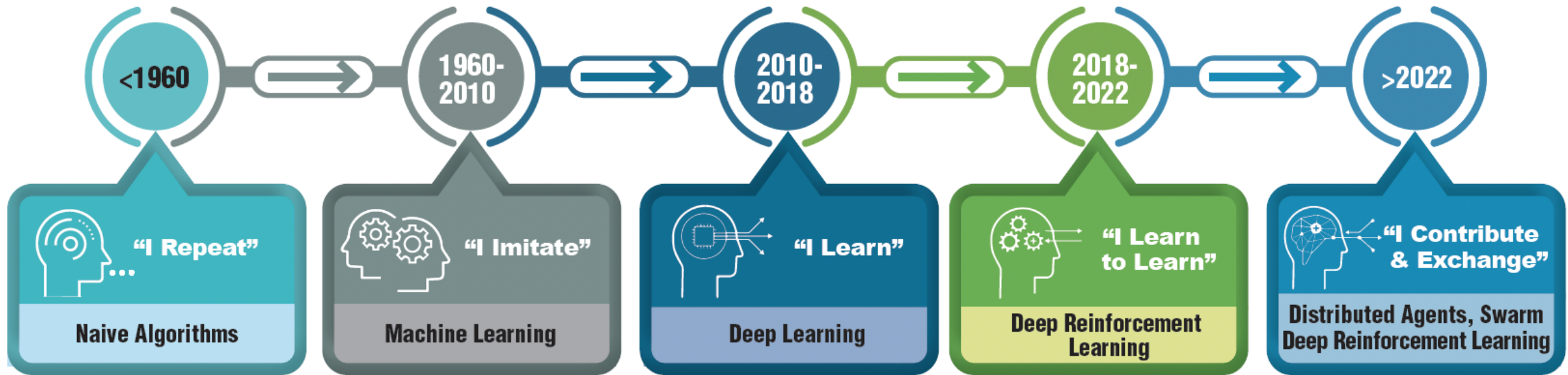
The dark side of A.I.

Humans
in the
loop



- Data and energy need
- You always get a result, whether the information is in the data or not
- Challenges: Causality, Validation,
Bias in data = bias in results

History of Machine Learning / A.I.



Emergence of...
Homogenization of...

Machine Learning

"how"
learning algorithms

Deep Learning

features
architectures

Foundation Models

functionalities
models

- Unsupervised or self-supervised learning
- Large (deep) neural networks
- Not intended for any particular end-goal
- Intended to serve as "foundation", then fine-tune
- Trained on multimodal data

Watershed moment

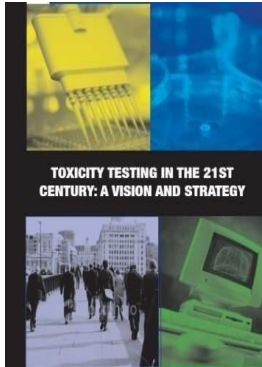
2007 NRC report



Toxicity testing in the 21st century: progress in the past decade
and future perspectives

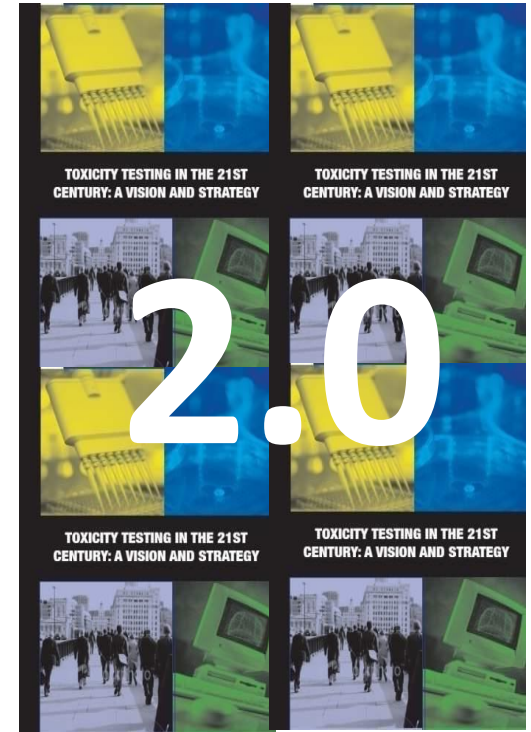
Arch Toxicol 2019

D. Krewski^{1,2,4} · M. E. Andersen³ · M. G. Tyshenko^{2,4} · K. Krishnan^{2,5} · T. Hartung^{6,13} · K. Boekelheide⁷ ·
J. F. Wambaugh⁸ · D. Jones⁹ · M. Whelan¹⁰ · R. Thomas⁸ · C. Yauk¹¹ · T. Barton-Maclaren¹¹ · I. Cote¹²



KNOWLEDGE

Doubling every
seven years





Future Directions
Workshop: Advancing
the Next Scientific
Revolution in
Toxicology

April 28-29, 2022

Thomas Hartung, Johns Hopkins University, University of Konstanz,
and Georgetown University

Ana Navas-Acien, Columbia University

Weihsueh Chiu, Texas A&M University

Prepared by:
Kate Klemic, Virginia Tech Applied Research Corporation
Matthew Peters, Virginia Tech Applied Research Corporation
Shawn Silberberg, Office of the Under Secretary of Defense
(Research & Engineering), Basic Research Office

Future Directions Workshop series
Workshop sponsored by the Basic Research Office, Office of
the Under Secretary of Defense for Research & Engineering

VT-ARC
Virginia Tech
Applied Research Corporation

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Call for a Human Exposome Project



1. Exposure-driven
2. Technology-enabled
3. Evidence-integrated

Future Directions Workshop: Advancing the Next Scientific Revolution in Toxicology

Office of the Under Secretary of Defense for Research and Engineering OUSD(R&E)

April 28–29, 2022

Arlington, VA

Food for Thought ...

ALTEX 2023

A Call for a Human Exposome Project



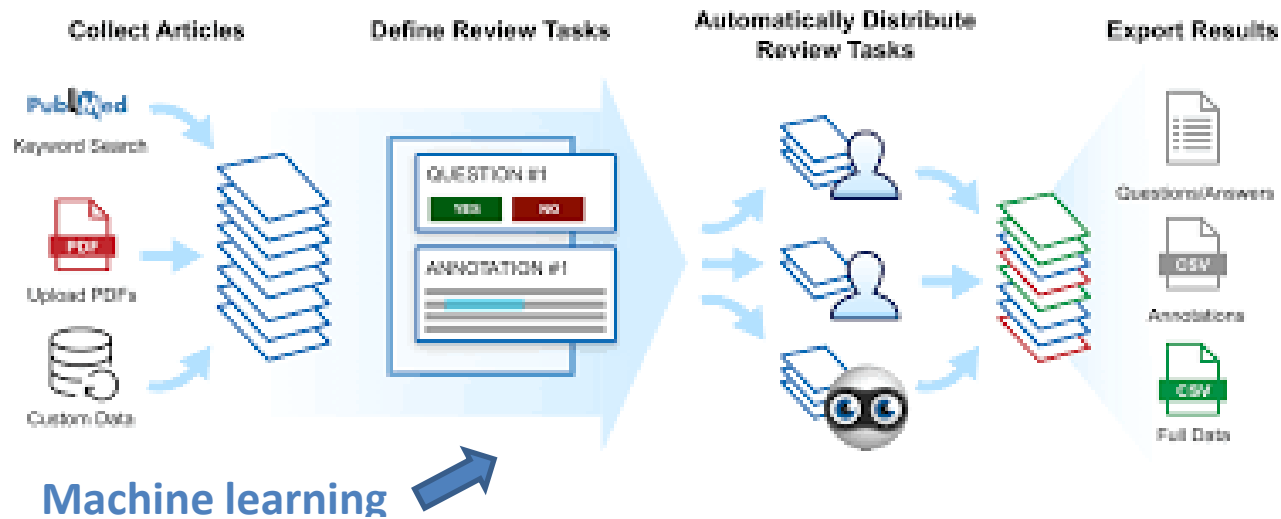
Thomas Hartung^{1,2}



EU ONTOX project (\$20 million, 2021-2026) to address liver, kidney and developing brain

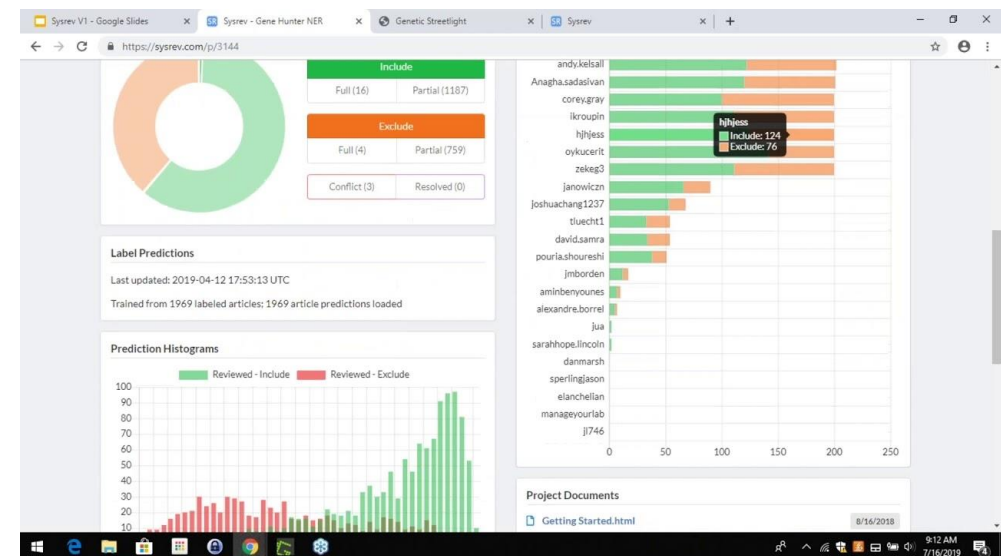


ToxTrack



Semi-automated systematic review:

- Auto-extract /annotate papers
- Auto-analyze clustering of papers
- Learn from manual inclusion / exclusion
- Automated inclusion / exclusion suggestions
- Natural Entity Recognition & Causal Relationship Extraction
- Feed into ontologies and AI
- chatGPT -> bioGPT -> toxGPT (?)



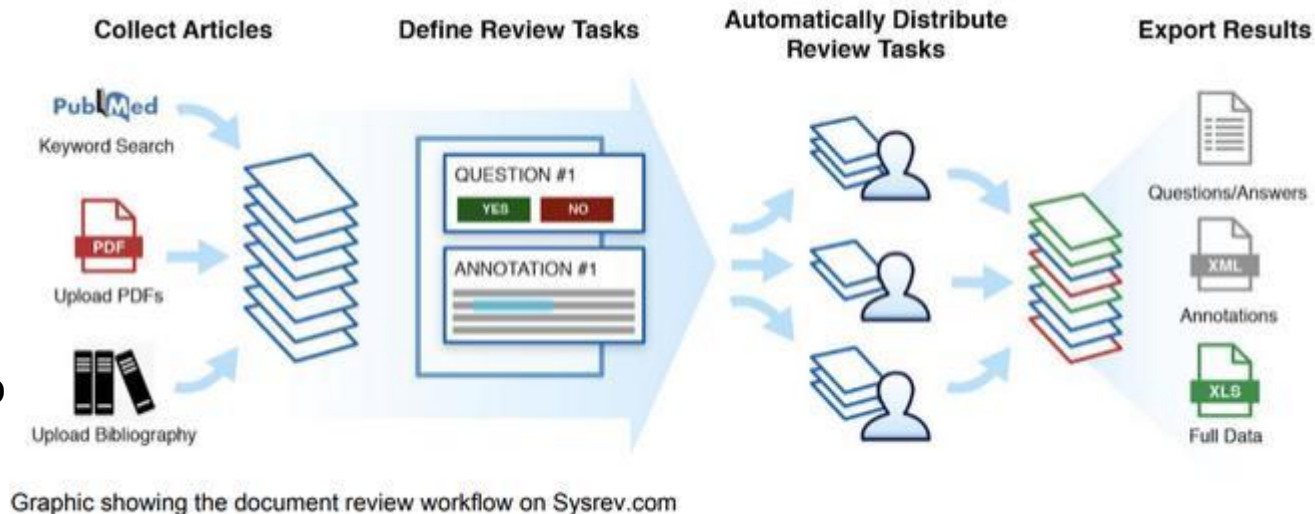
<https://www.youtube.com/channel/UCoUbMAvxBSZpOlqKjOkxNzQ/videos>



Literature



<https://www.youtube.com/c/SysRev?app=desktop>



Databases



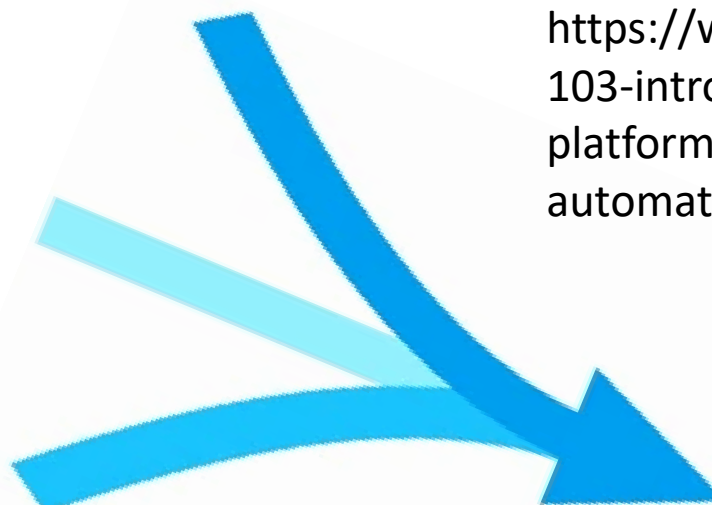
<https://www.biopharmatrend.com/post/103-introducing-sysrev-the-intelligent-platform-for-document-review-and-automated-data-extraction/>



Internet



<http://chemchart.com>

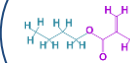


DATA

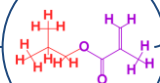
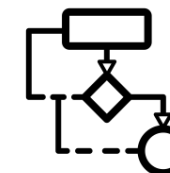
ToxTRACK

Chemchart

Synthesis and properties of poly(isobutyl methacrylatecobutanediol dimethacrylatecomethacryl polyhedral oligomeric silsesquioxane) nanocomposites (Journal of Polymer Science Part A, 2005)



MAKING CHEMISTRY SEARCHABLE



Polymer Brushes on Single-Walled Carbon Nanotubes by Atom Transfer Radical Polymerization of n-Butyl Methacrylate (Journal of the American Chemical Society, 2004)

Chemchart LabBot

"What do you need help with?"



Procurement



Synthesis



Safety



Alternatives



Testing

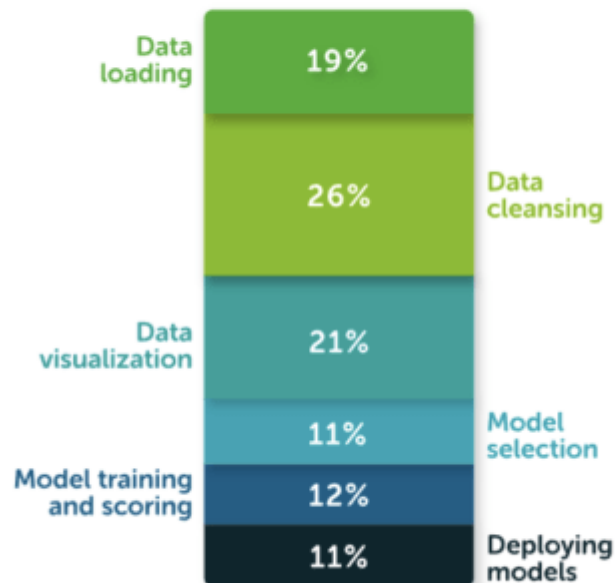


Regulation



THINKING ABOUT YOUR CURRENT JOB, HOW MUCH OF YOUR TIME IS SPENT
IN EACH OF THE FOLLOWING TASKS?

Anaconda.com - State of Data Science 2020



45% of time of data analysts
is spent loading and cleaning data

BioBricks do this
with one-line command

BioBricks.ai Faster Informatics

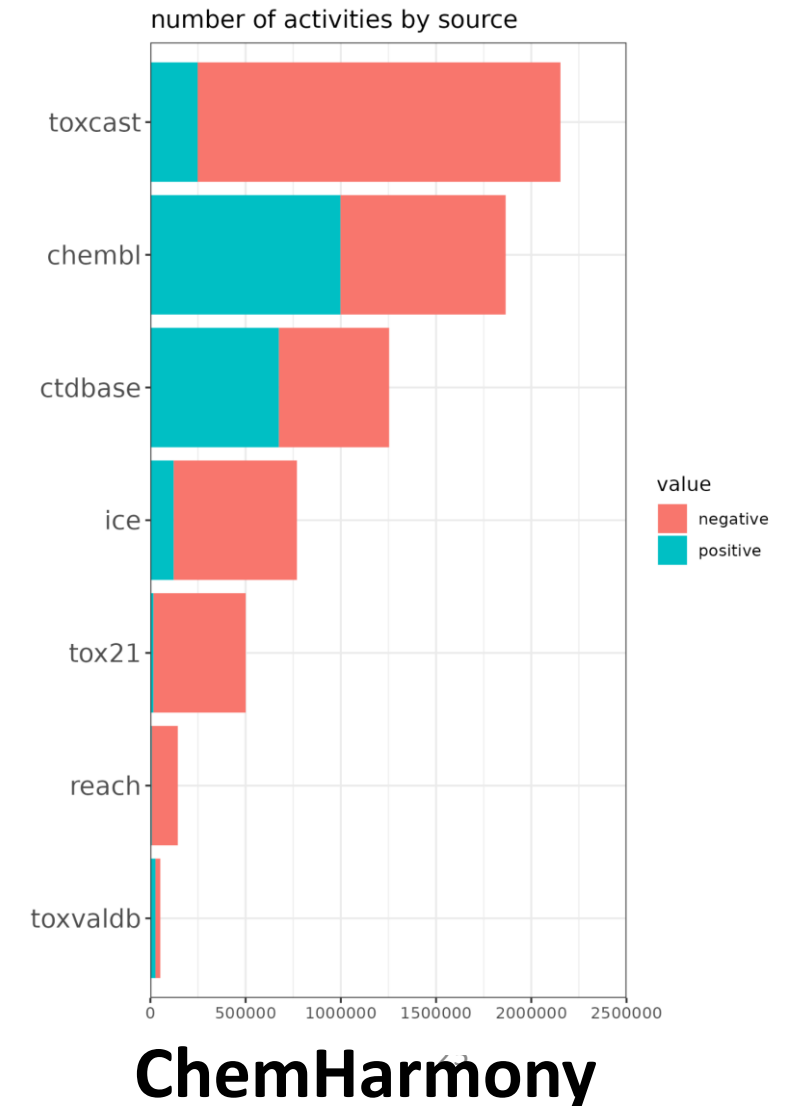
```
$ biobricks install tox21
$ python
>>> import biobricks, pandas
>>> tx21 = biobricks.load('tox21')
>>> tx21.tox21.read().load()
```

```
#      SAMPLE_ID  PROTOCOL_NAME ...      SMILES ...
# NCGC00256074-01  tox21-ache-p3 ...      OCC (=O) OCCCC ...
# NCGC00255047-01  tox21-ache-p3 ...  Nc1ccc(cc1)C(=O)OCC ...
# [2075022 rows x 19 columns]
```



Establishment of a big data platform and data gap filling for integration of collected data

- **Biobricks toolset for hosting, querying, and distributing big data for predictive tox**
- ~50 BioBricks constructed to date
- **ChemHarmony:**
integrates chembl, pubchem, ctdbase etc.:
200 million triplets of substance/property/result
- **Building querying functionality**
- **Public release of toxicology BioBricks upcoming**



Can we make a better similarity metric?

Structural similarity

(e.g., Morgan fingerprints)

Biological similarity

What is it good for?

- Chemical discovery
- Chemical clustering
- Explainable predictions
- Domain of Applicability
- QSAR
- Testing prioritization
- Database Search

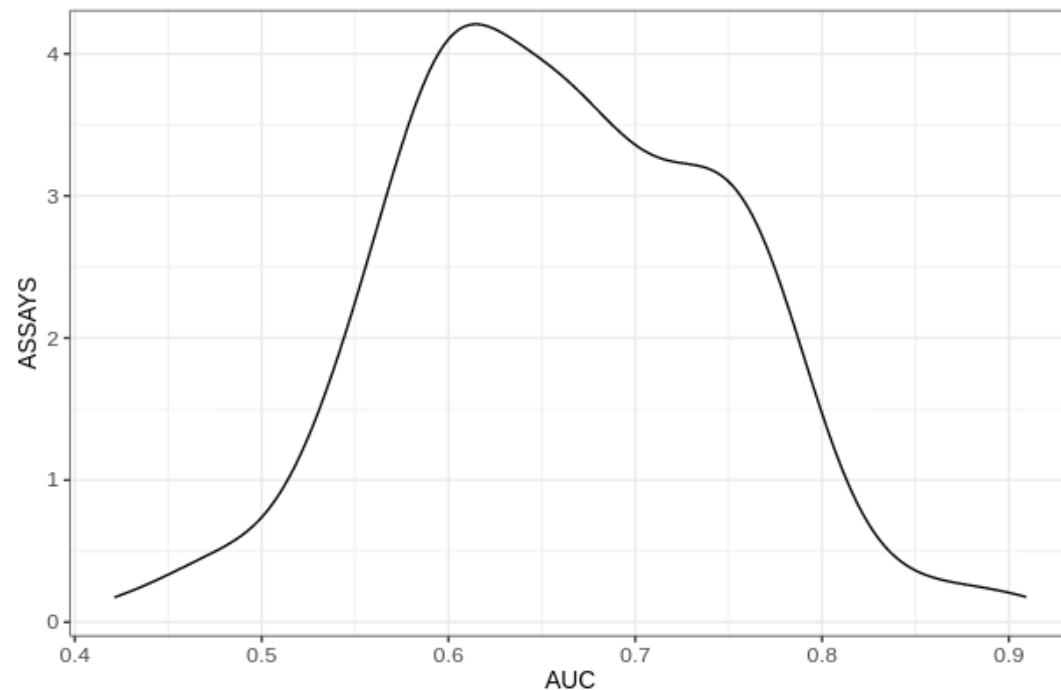


Structural similarity

Across all assays cosine similarity for Morgan fingerprints achieves **60-70% AUC**. KNN=5

Preprocessing ChemHarmony

- All INCHI mapped to smiles with rdkit
- RDKit sanitize used and error/warning instances removed
- Properties with > 10% class imbalance removed
- Top **152 properties** by unique compounds selected
- **~1.2 million activities** remain
- RDKit used to build 2048 rad 2 morgan fingerprints
- Preprocessing stage shared across branches
- 80/10/10 Train, Test and Holdout sets stratified by property



Set-up and application of machine learning/deep learning approaches to predict probability of chemical hazard and potency

We can do 1 trillion comparisons per hour on a “normal” computer!

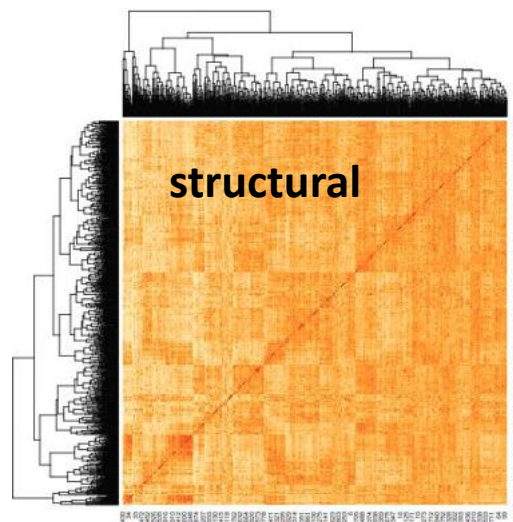


Figure 5.2A. Similarity heatmap for chembert embeddings on 1k chembl compounds
Dark red = highly similar,
White = not similar

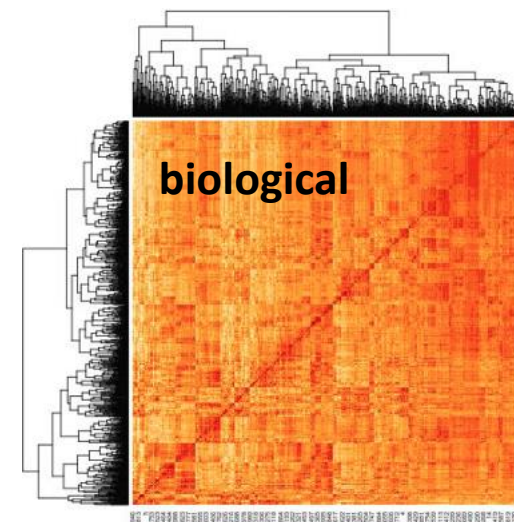


Figure 5.2B. Heatmap for inhibition assay supervised embedding
Dark red = highly similar,
White = not similar

You can form 19,999,999,900,000,000 pairs from 200 million items...
= 19,999h per property = need for supercomputer

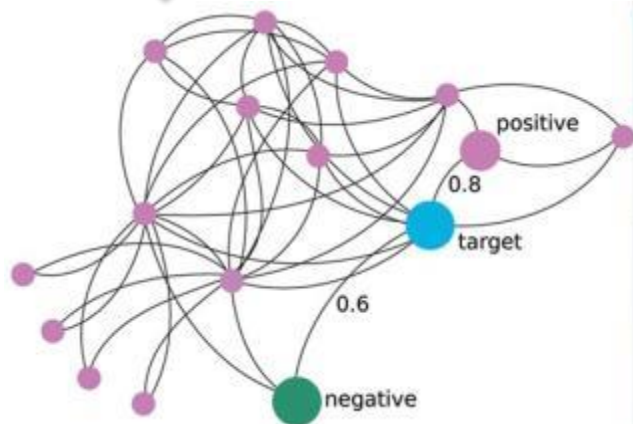
DATA

PMDEP App <https://youtu.be/YG0gjm&GD5K>



Systems Biology
Markup Language

CellDesigner™



RASAR
+ QSAR

From chemical structure and properties

From perturbation of physiology

Probability of hazard

The problem



toxic

non-toxic

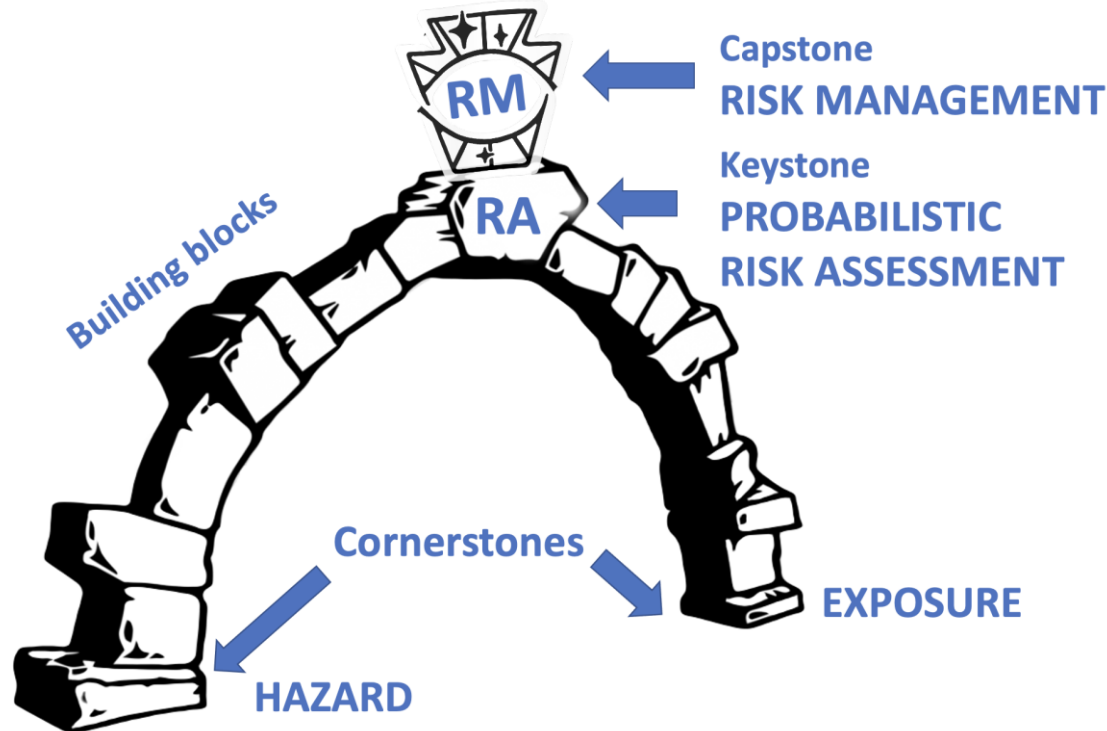


reality
= uncertainty

Food for Thought ...

Probabilistic Risk Assessment – the Keystone for the Future of Toxicology

Alexandra Maertens¹, Emily Golden¹, Thomas H. Luechtefeld^{1,2}, Sebastian Hoffmann^{1,3},
Katya Tsaoun¹ and Thomas Hartung^{1,4}



2nd Workshop 4-6 July 2023
Ranco, Italy

ToxAlcology



Big Data

- High-throughput exposure + thresholds of toxicological concern
- Perturbation of biology
- Read-across-based structure activity relationships



Big Computer

AI & Machine Learning

Big Sense

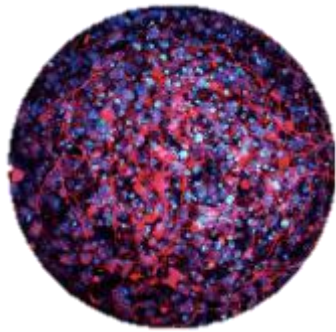
- Probabilistic risk assessment
- Information economy
- Targeted testing (MPS)

Combining MPS,
sensors and AI

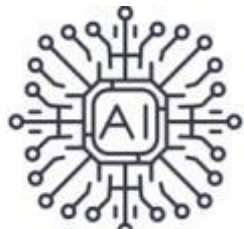
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Organoid Intelligence (OI)

- Physiology of learning
- Brain Machine Interfaces
- Tox & Drug Development
- Biological Computing



Brain
Organoid



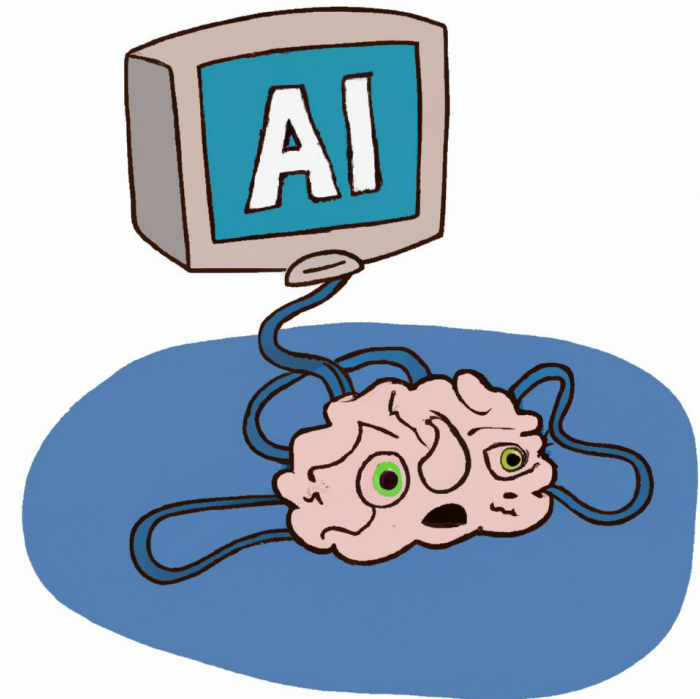
OI

AI



Input

Output





Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish

Lena Smirnova¹, Brian S. Caffo², David H. Gracias^{3,4,5,6,7,8}, Qi Huang³, Itzy E. Morales Pantoja¹, Bohao Tang², Donald J. Zack⁹, Cynthia A. Berlinicke¹⁰, J. Lomax Boyd¹¹, Timothy D. Harris^{12,13}, Erik C. Johnson¹⁴, Brett J. Kagan¹⁵, Jeffrey Kahn¹⁶, Alysson R. Muotri^{17,18}, Barton L. Paulhamus¹⁹, Jens C. Schwamborn²⁰, Jesse Plotkin¹, Alexander S. Szalay^{21,22,23}, Joshua T. Vogelstein¹², Paul F. Worley²⁴ and Thomas Hartung^{1,25*}

OPEN ACCESS

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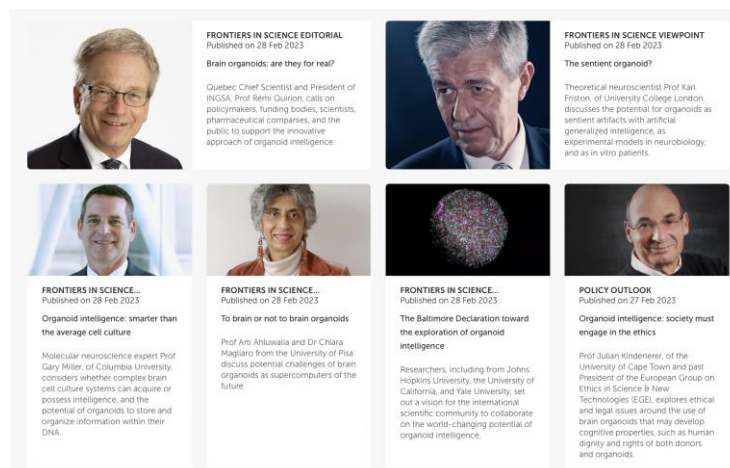
*CORRESPONDENCE

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Forming a community

- Dissemination (kid and lay versions, 600+ press hits)
- Workshop report
- US White House Bold Biotechnology Goals 3'23
- NSF "Engineering OI"
- DORI = Dementia OI Research Initiative



- Integrating Scientific Knowledge
- Accelerating Drug Development
- Optimizing Prevention
- Democratizing Healthcare Access

The Smart Path Forward

- Open access, machine readable
- Identify bias in data
- Explainable AI



Slides available: