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CAAT
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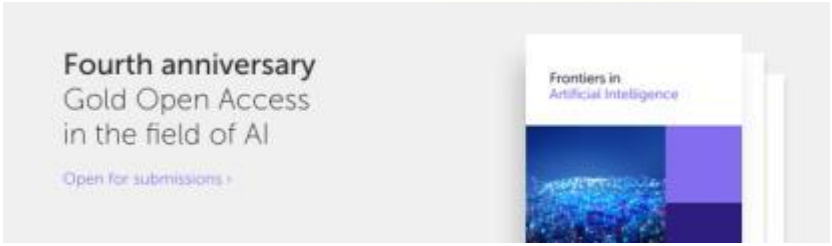

Thomas Hartung & team

ToxAIcology

- AI is the future of toxicology -

Slides available:

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frontiers in Artificial Intelligence

frontiers

We build the leading journals of the future
Frontiers in Artificial Intelligence

13 sections

759 published articles

296 Research Topics

91 days

Thomas Hartung
Field Chief Editor

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- AI in Business
- AI in Food, Agriculture and Water
- Artificial Intelligence in Finance
- Big Data and AI in High Energy Physics
- Fuzzy Systems
- Language and Computation
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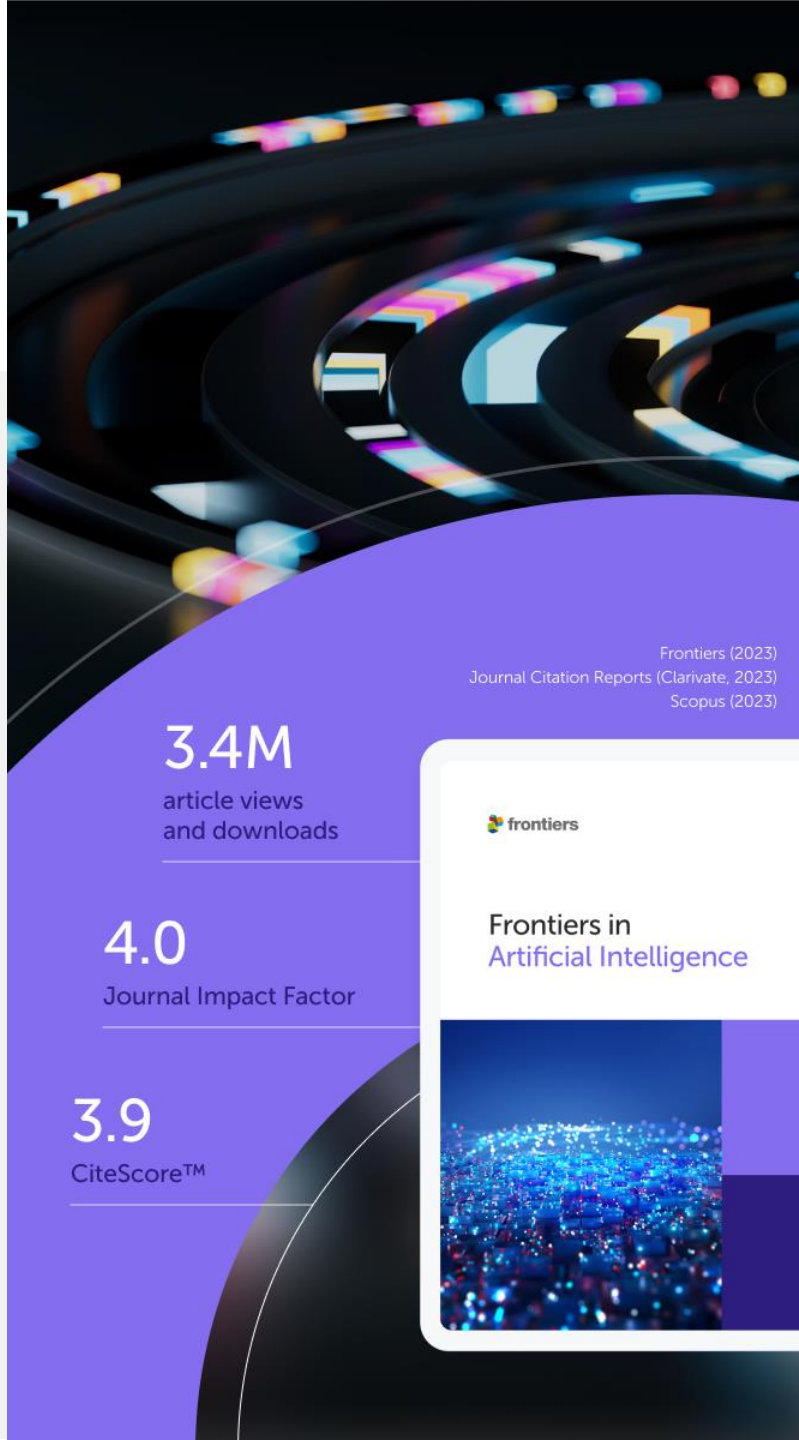
- Medicine and Public Health
- Natural Language Processing
- Organoid Intelligence NEW
- Pattern Recognition
- Technology and Law



frontiers

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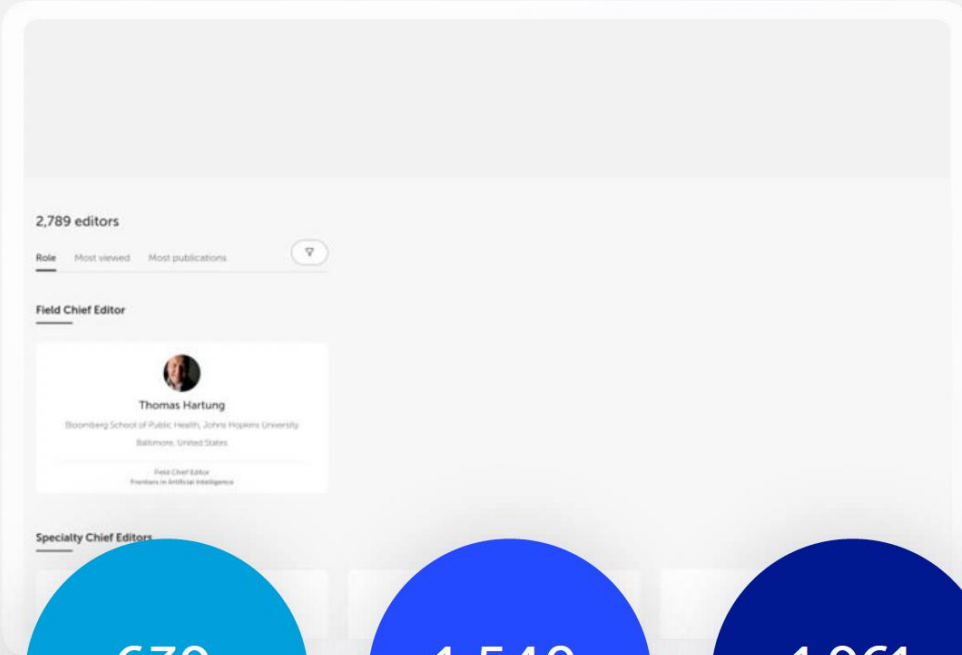
frontiers in Artificial Intelligence

editorial board



18
chief editors

382
associate editors

639
guest editors

1,540
review editors

1,961
total editors

WORLD ECONOMIC FORUM

Artificial Intelligence-Facilitated Healthcare

Curation: Frontiers Media

In Preparation

KEYSTONE SYMPOSIA
Accelerating Life Science Discovery

50 YEARS 1972-2022

AI in Healthcare

Planned 5-7 December 2023 (virtual)

Thomas Hartung

Bloomberg School of Public Health, Johns Hopkins University

Baltimore, United States

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Medicine and Public Health

Technological progress everywhere

LD_{50} test

28d study

Eye & skin test

ReproTox

Cancer bioassay

…except regulatory toxicology!

“Playing safe…”

180 million chemicals synthesized
350 thousand registered in 19 countries
>10 thousand substances in 1 biological
Metabolites and breakdown products?
Some chemicals in 50,000+ products
~3 thousand well tested substances

“Fun” facts

- 10,000+ articles BPA => ???
- 5,000+ articles glyphosate => ???
- ~45% of drug side effects predicted by rodents
- 20-80% false positive results

Animal test Cancer

18-24 months

$1 million

4-600 animals

53% positive

~57% reproducible

(rat to rat, rat to mouse)

29 trichloroethylene carcinogen risk assessments

4x “carcinogen”

19x “equivocal”

6x “non-carcinogen”

Rudén C. *Regul. Toxicol Pharmacol 2001; 34: 3-16.*

AI retrieves information

- average reference coverage **18%**
- average citation coverage of most relevant studies **80%**
- interpretation differences of most relevant studies in **27%**
- study/data quality: assessment not documented in **65%**

The different way of evidence retrieval and integration ?

Deus ex machina

Article Talk

From Wikipedia, the free encyclopedia

For other uses, see Deus ex machina (disambiguation).

Deus ex machina (/ˌdeɪəs ɛks ˈmækɪnə, ˈmɑːk-/ *DAY-əs ex-MA(H)K-in-ə*,[1] Latin: [ˈdɛ.ʊs ɛks ˈmaːkʰɪnaː]; plural: *dei ex machina*; English "god from the machine")[2][3] is a plot device whereby a seemingly unsolvable problem in a story is suddenly or abruptly resolved by an unexpected and unlikely occurrence.[4][5] Its function is generally to resolve an otherwise irresolvable plot situation, to surprise the audience, to bring the tale to a happy ending or act as a comedic device.[6]

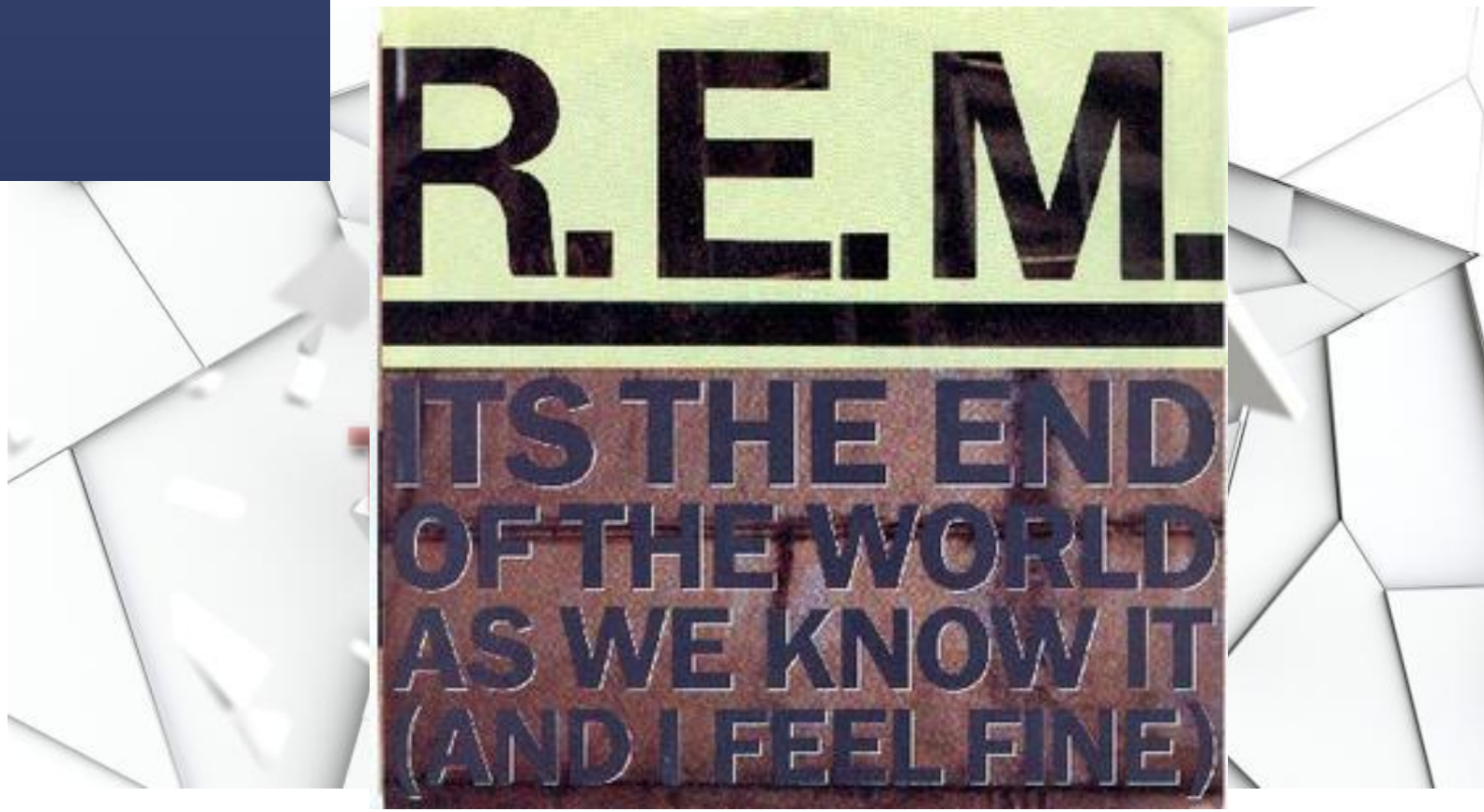
https://duiliogf.medium.com/how-to-correctly-use-a-deus-ex-machina-and-not-die-trying-85dd73166784

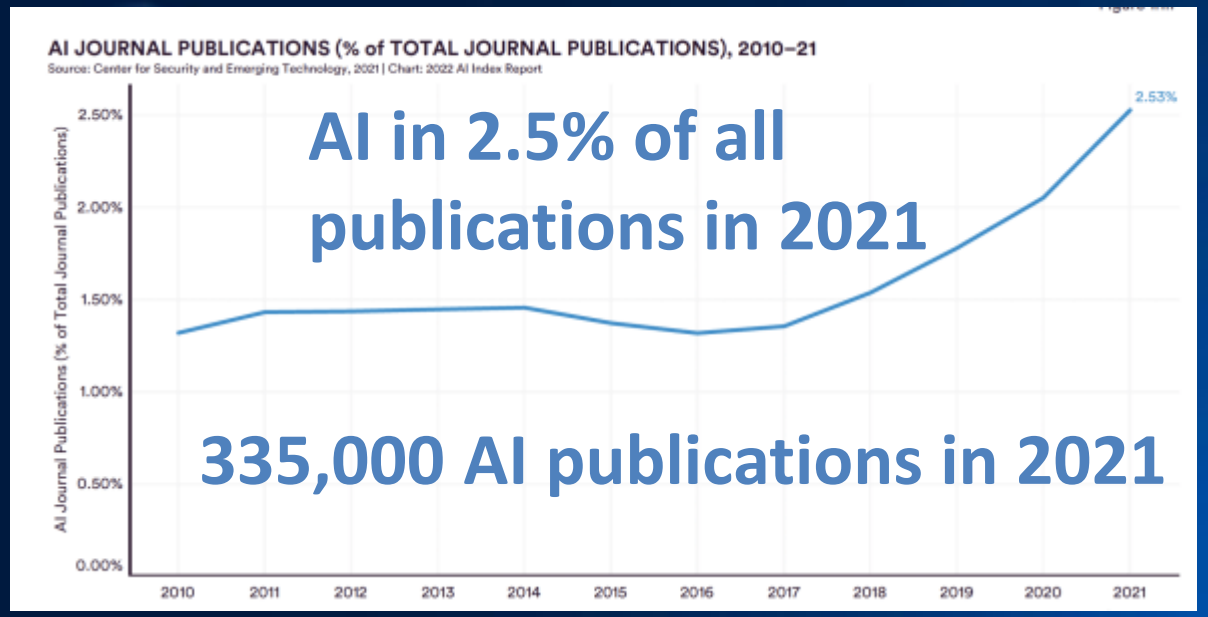
dAIus ex machina

for toxicology

Data: +60% per year
= 90% in last three years
Computer: +40% per year
(Moore's law)
AI: +700% per year since 2010

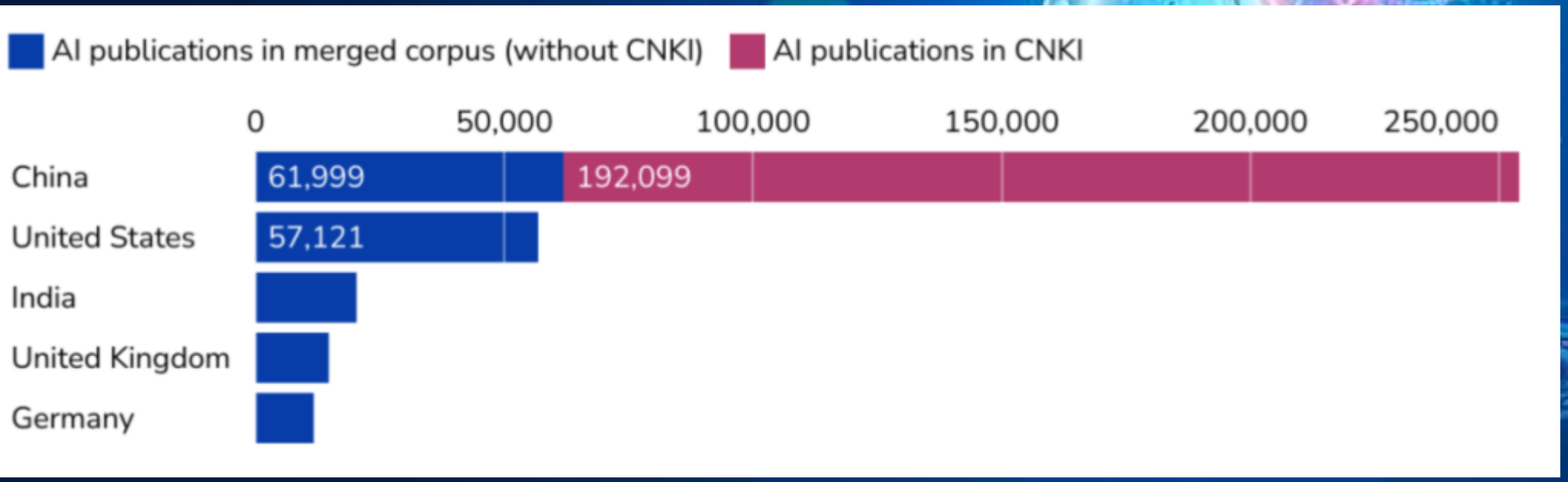
Together increase
>1 billion-fold
over last 60 years

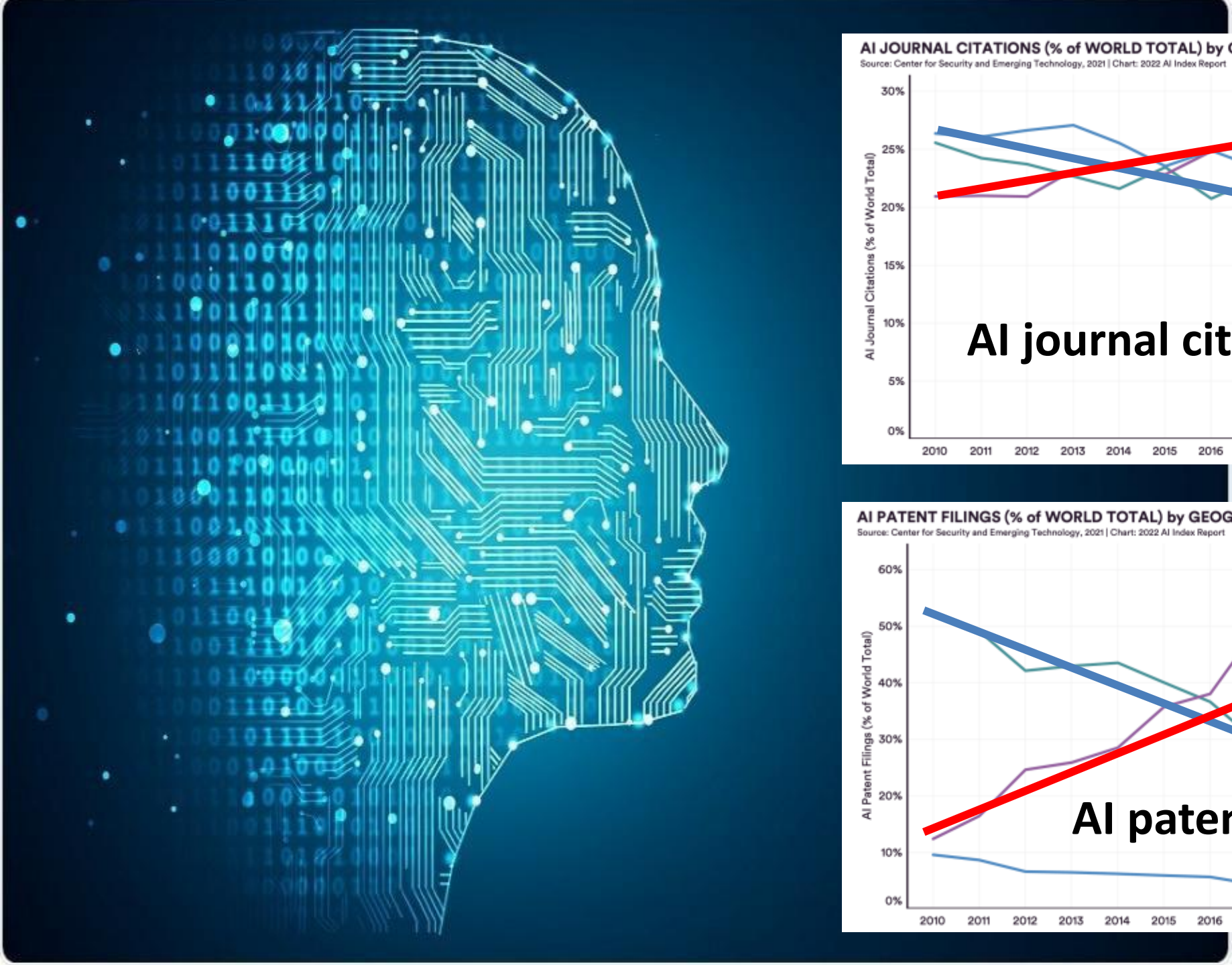


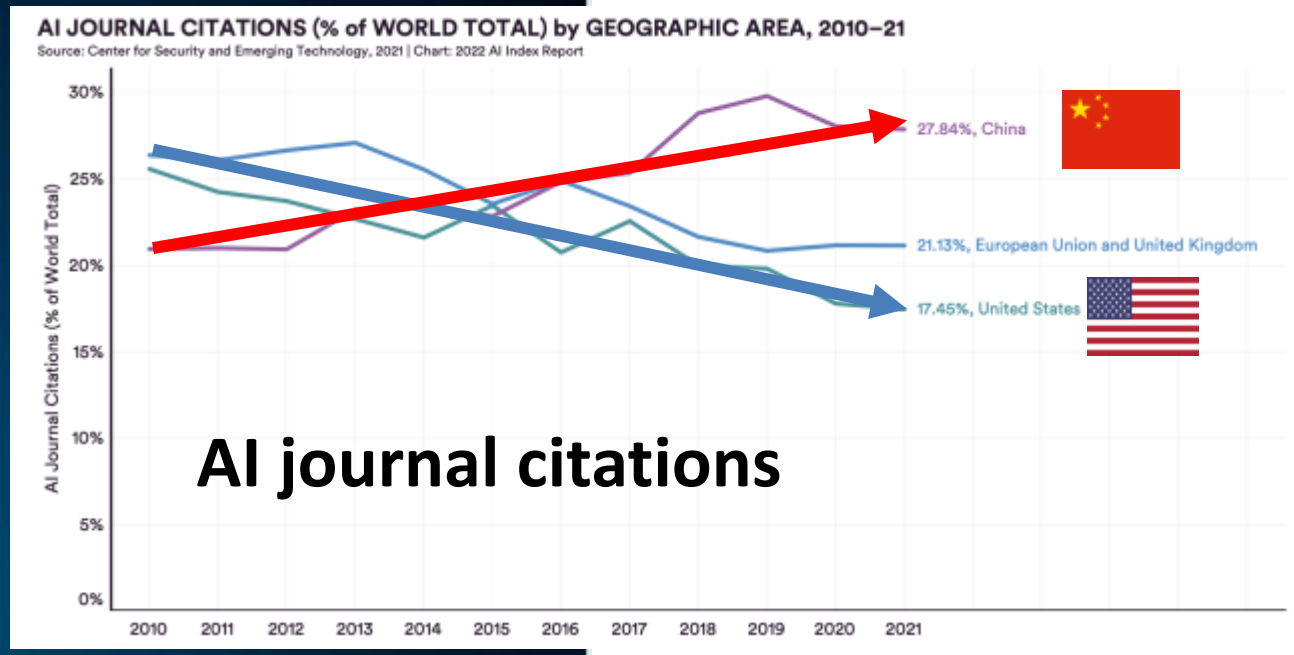


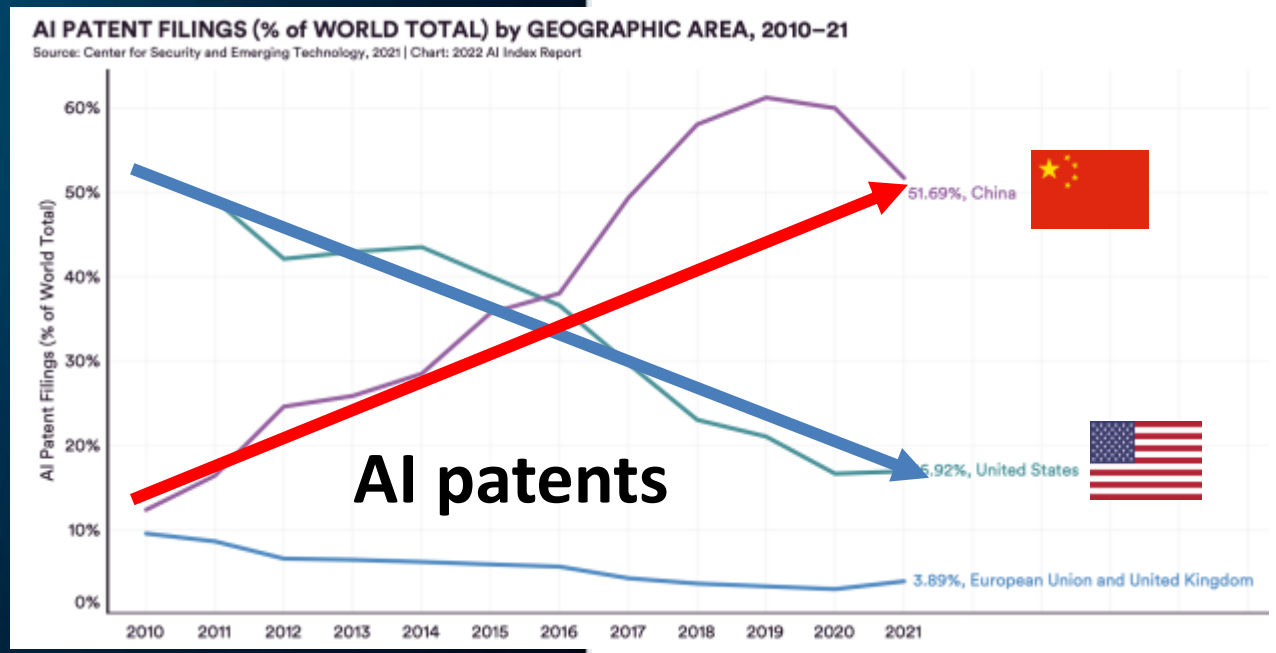
AI in 2.5% of all publications in 2021

335,000 AI publications in 2021






AI JOURNAL CITATIONS (% of WORLD TOTAL) by GEOGRAPHIC AREA, 2010–21
Source: Center for Security and Emerging Technology, 2021 | Chart: 2022 AI Index Report
AI Journal Citations (% of World Total)
30%
25%
20%
15%
10%
5%
0%
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
27.84%, China
21.13%, European Union and United Kingdom
17.45%, United States
AI journal citations


AI PATENT FILINGS (% of WORLD TOTAL) by GEOGRAPHIC AREA, 2010–21
Source: Center for Security and Emerging Technology, 2021 | Chart: 2022 AI Index Report
AI Patent Filings (% of World Total)
60%
50%
40%
30%
20%
10%
0%
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
51.69%, China
5.92%, United States
3.89%, European Union and United Kingdom
AI patents

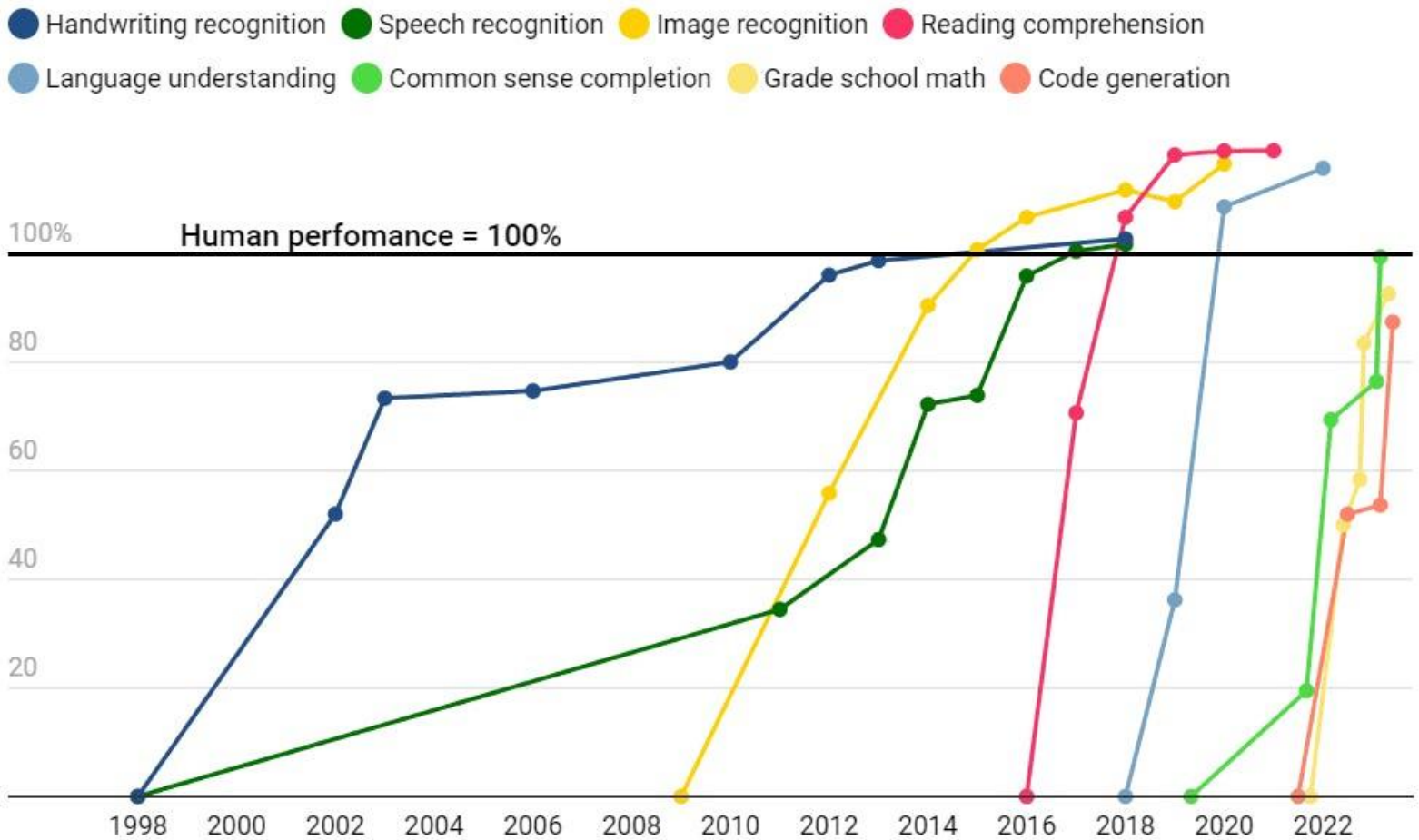
15 March 2023 Launch of GPT-4 Instantly open

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.

Variables trained on

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

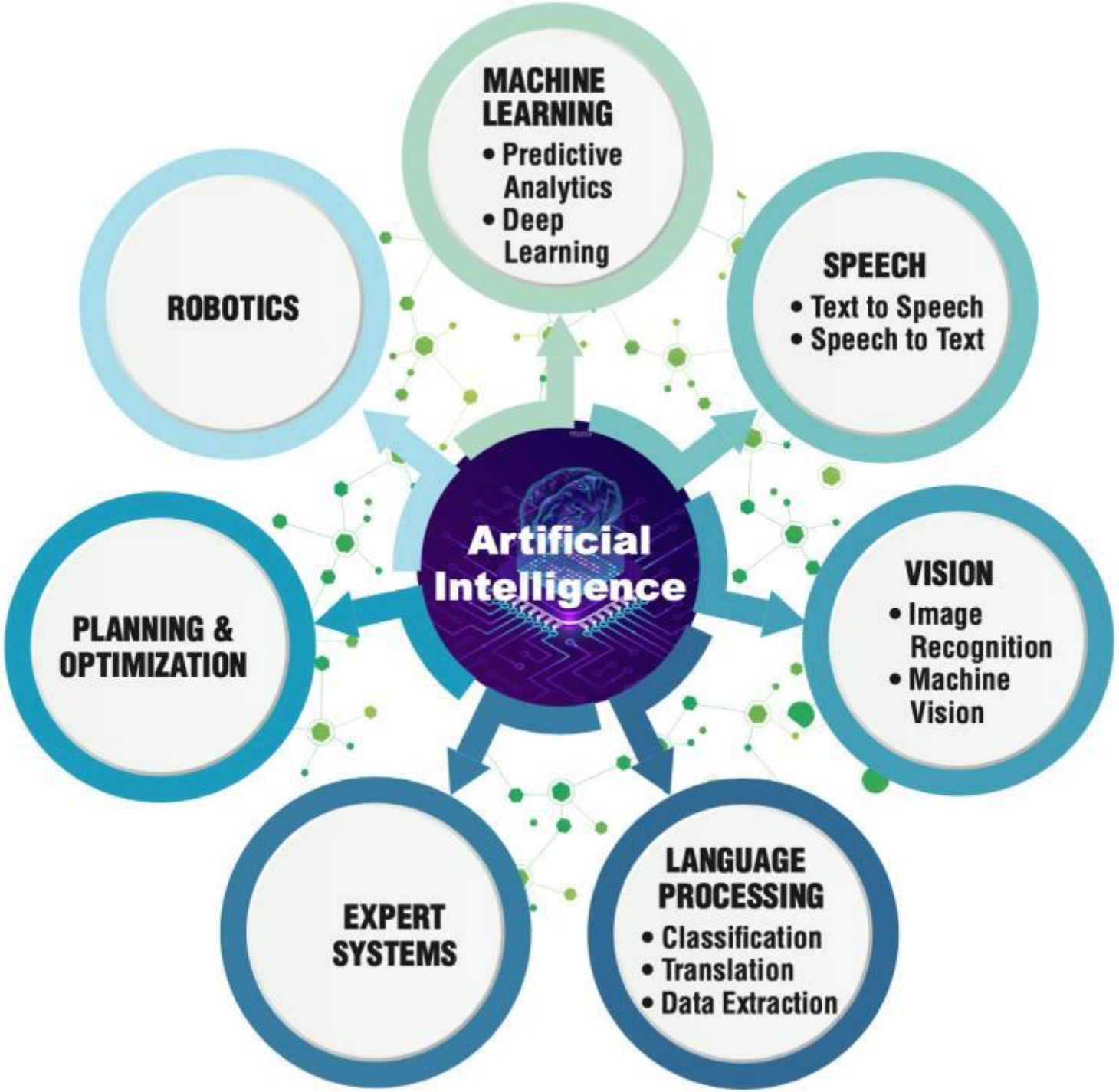
State-of-the-art AI performance on benchmarks, relative to human performance



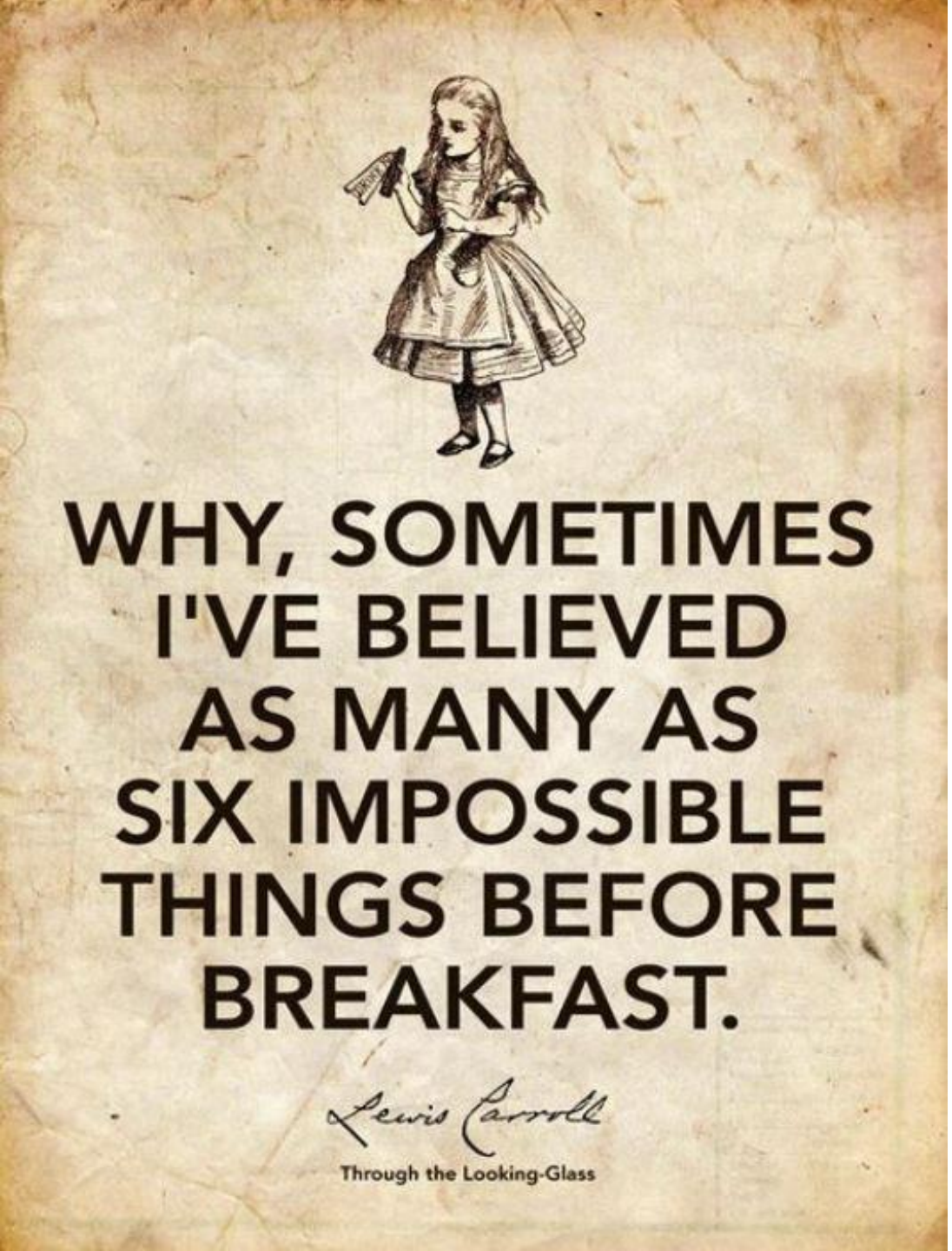
For each benchmark, the maximally performing baseline reported in the benchmark paper is taken as the "starting point", which is set at 0%. Human performance number is set at 100%. Handwriting recognition = MNIST, Language understanding = GLUE, Image recognition = ImageNet, Reading comprehension = SQuAD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

Chart: Will Henshall for TIME • Source: ContextualAI

TIME


MACHINE LEARNING
• Predictive Analytics
• Deep Learning
SPEECH
• Text to Speech
• Speech to Text
ROBOTICS
Artificial Intelligence
PLANNING & OPTIMIZATION
VISION
• Image Recognition
• Machine Vision
EXPERT SYSTEMS
LANGUAGE PROCESSING
• Classification
• Translation
• Data Extraction

A.I. use cases



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

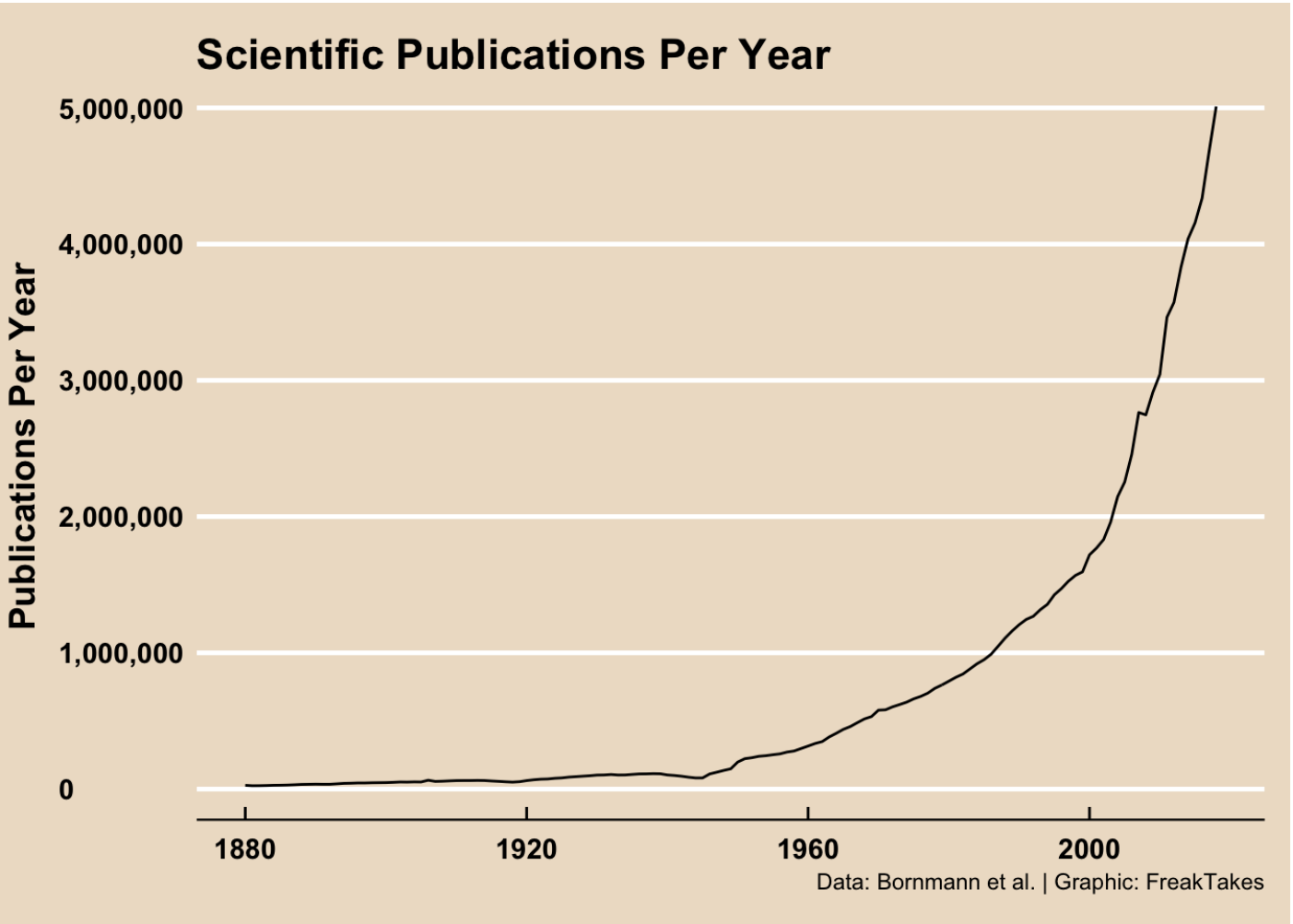
6. **AI wins art contests**
   2022 Midjourney

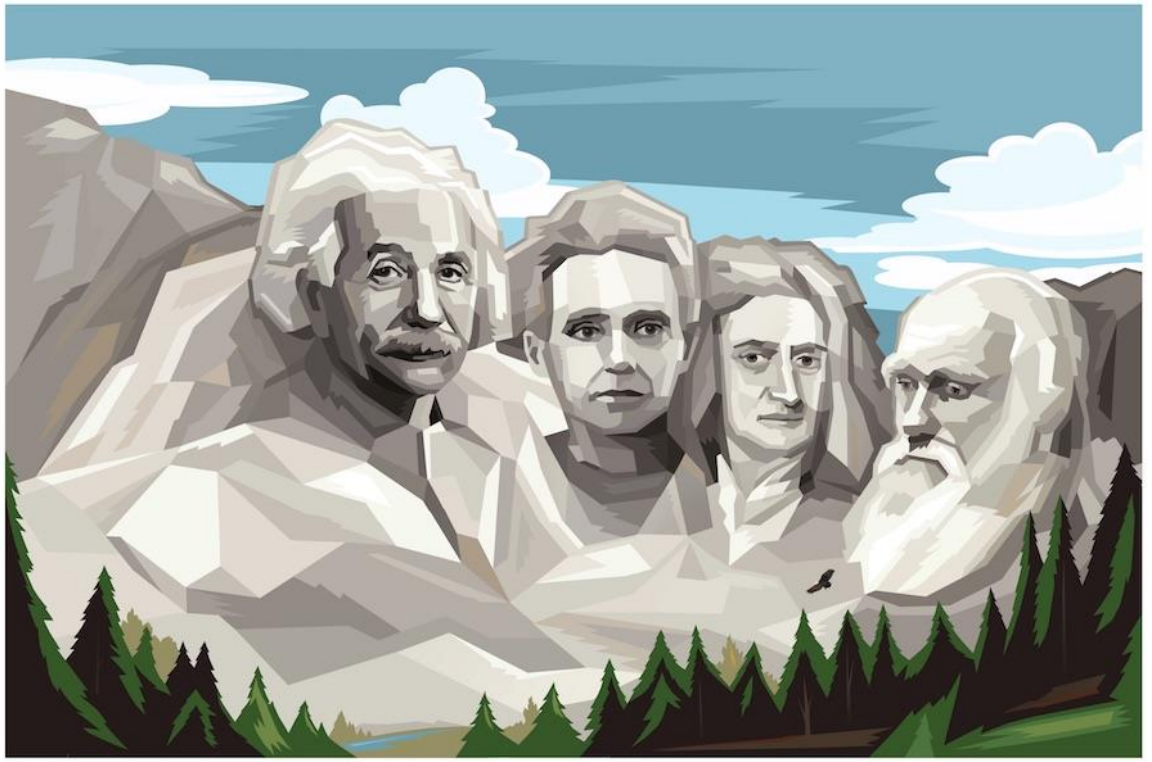
Volume
Variety
(multi-modal)
Velocity

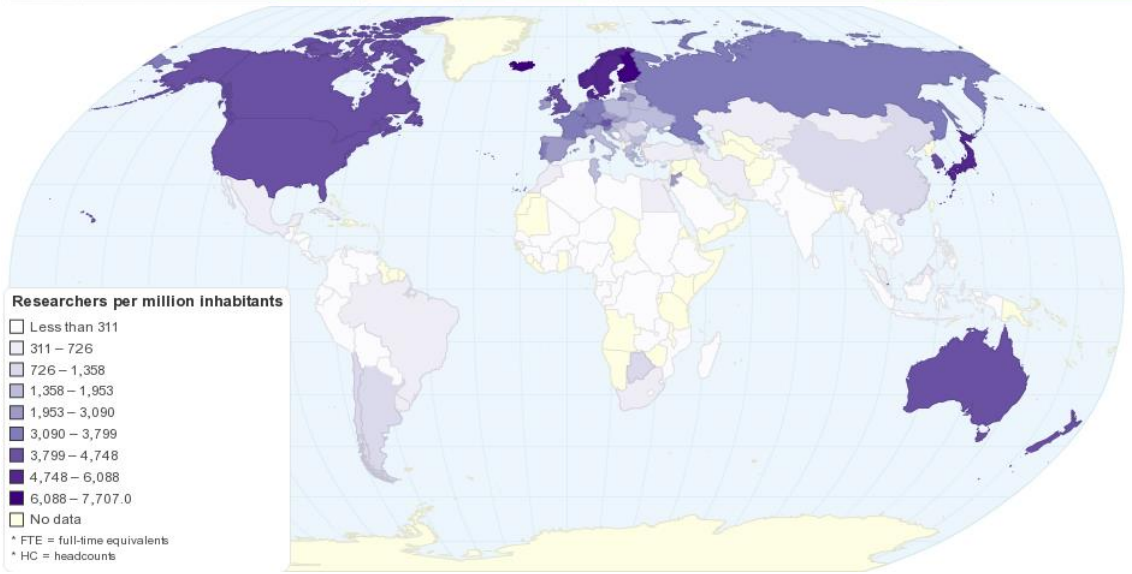
https://www.e-marketing.fr/Thematique/data-1091/big-data-2223/Breves/Tout-faut-savoir-big-data-363012.htm

AI is making Big Sense of Big Data

8.8 million researchers world-wide







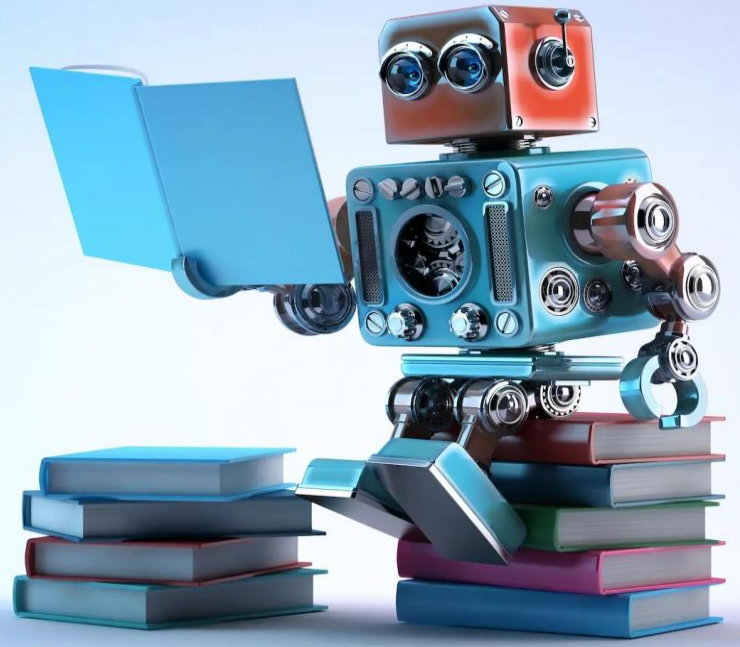
Researchers per million inhabitants

Science & Health 9%

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

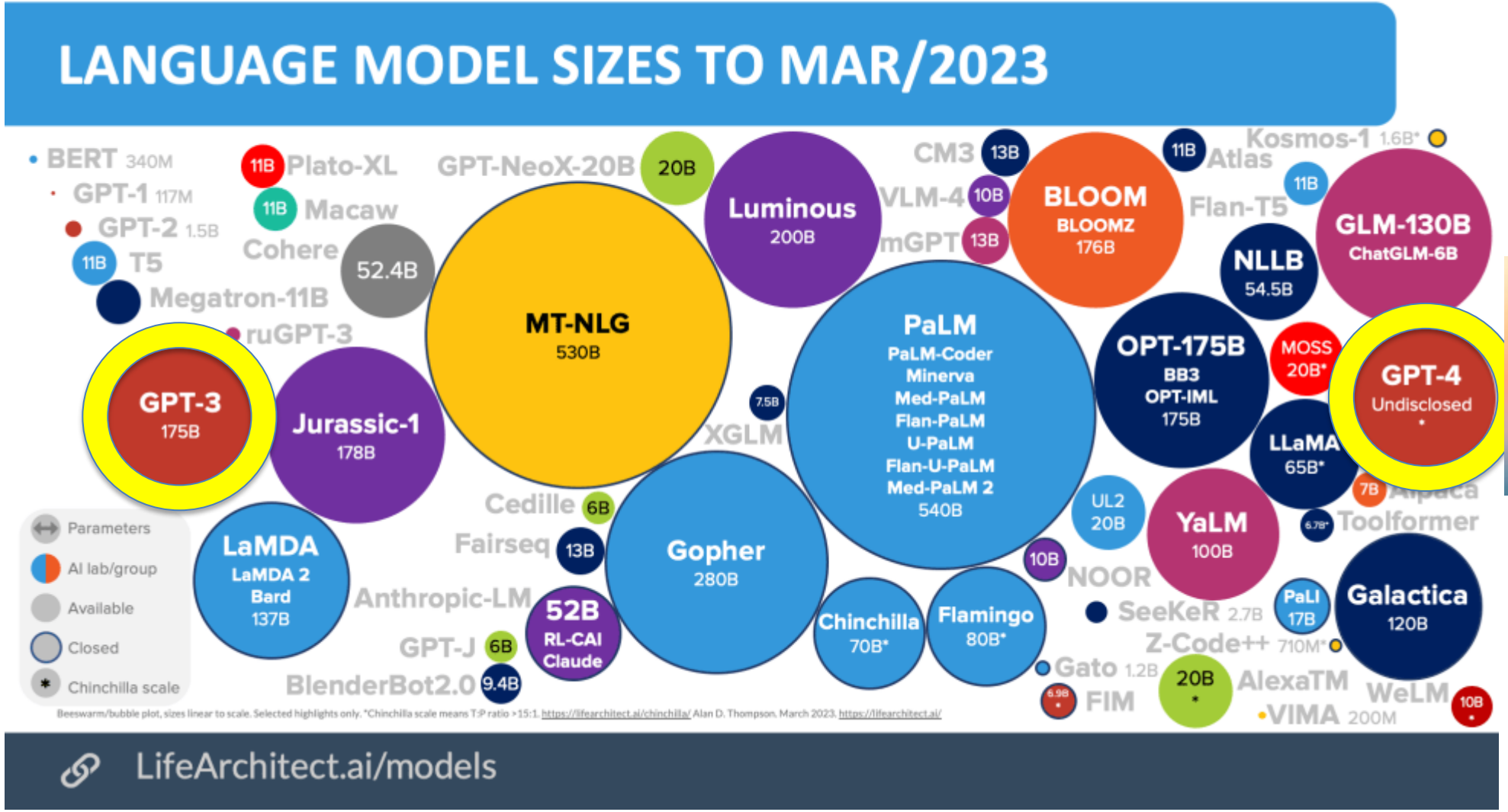
TOP SITES

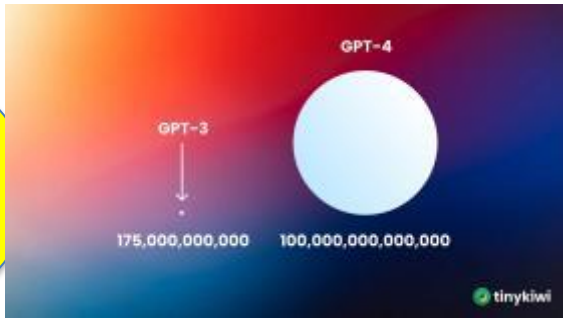
1. journals.plos.org
2. frontiersin.org
3. link.springer.com
4. ncbi.nlm.nih.gov
5. nature.com



Data extraction from literature, reports & databases

Multi-modal

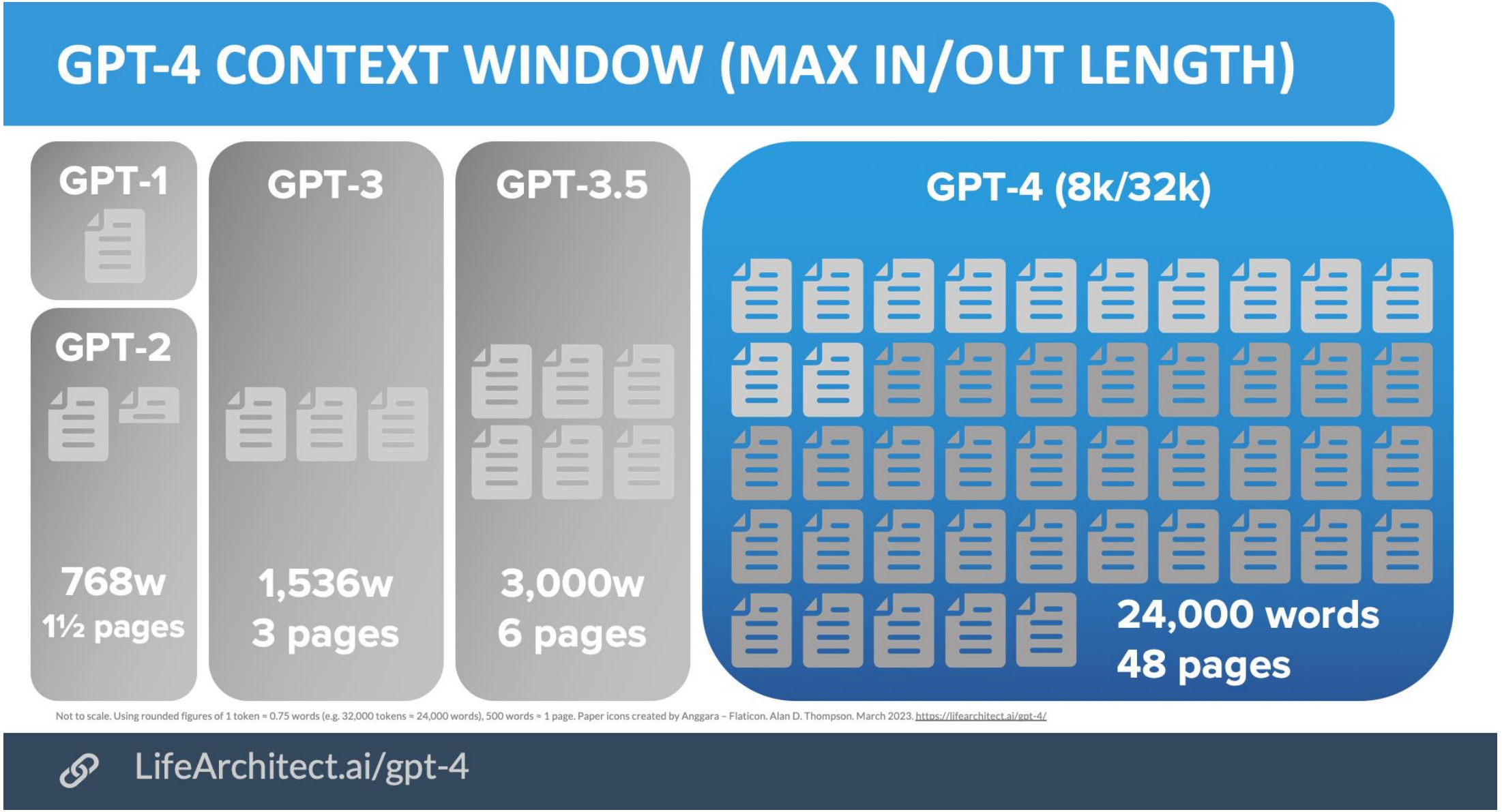




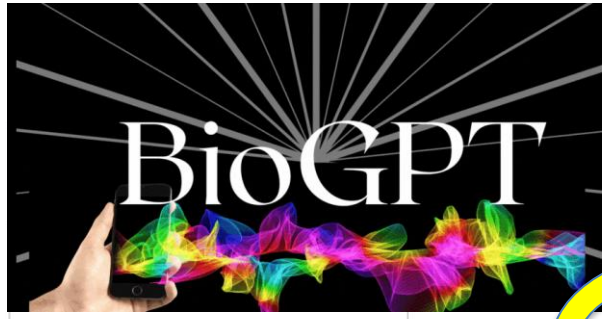
Variables trained on

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

14 March 2023 Launch of GPT-4



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



BioGPT and human annotator have comparable performance in biomedical research test

Selected performances on PubMedQA, which tests biomedical language processing

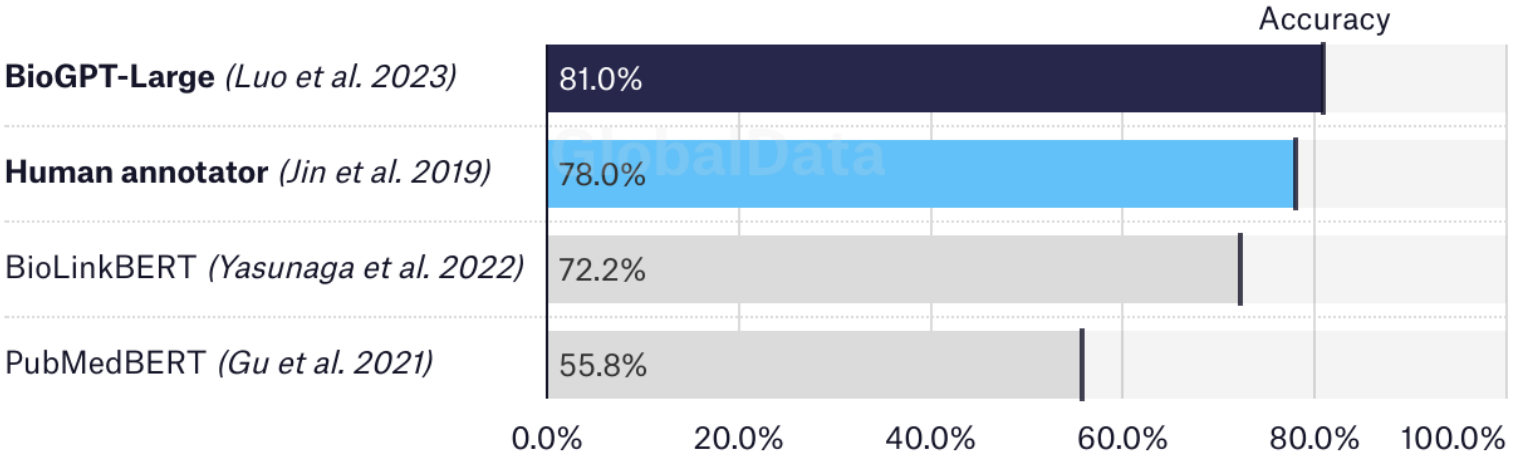
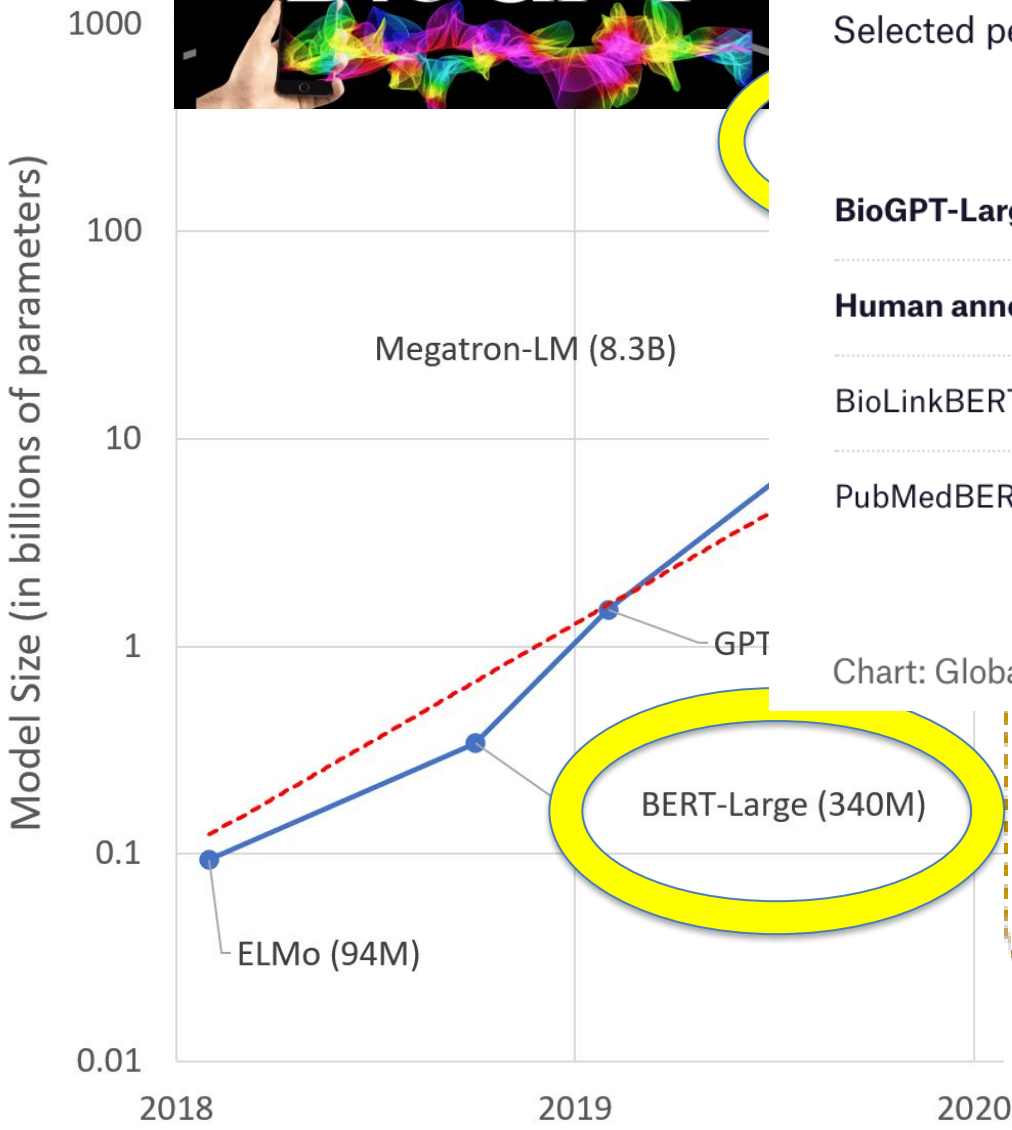
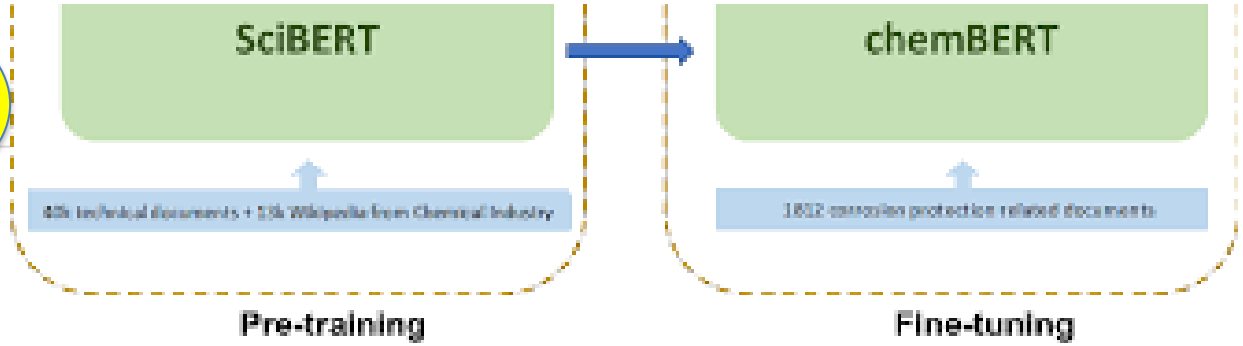


Chart: GlobalData • Source: PubMedQA





	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,	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

World view

Nature 20 Apr 2023

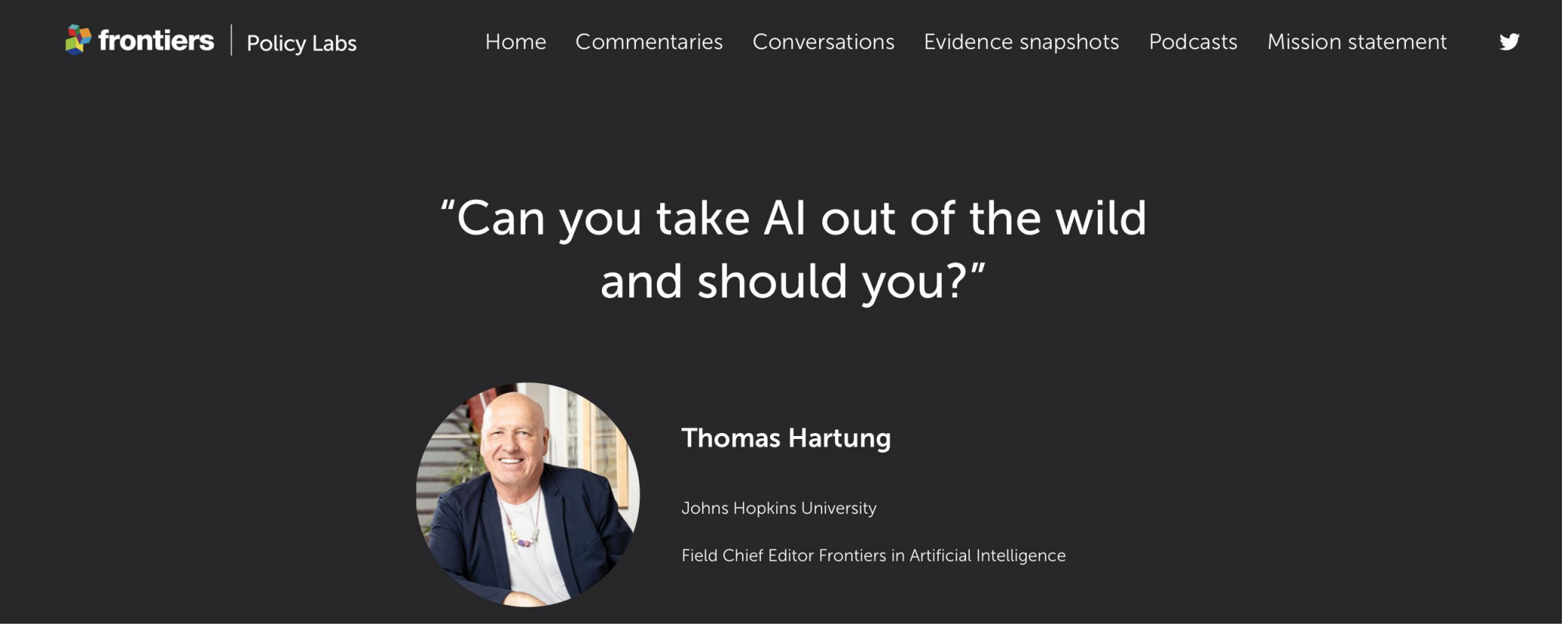
Open generative AI models are a way forward for science

By Arthur Spirling

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

“With open-source large

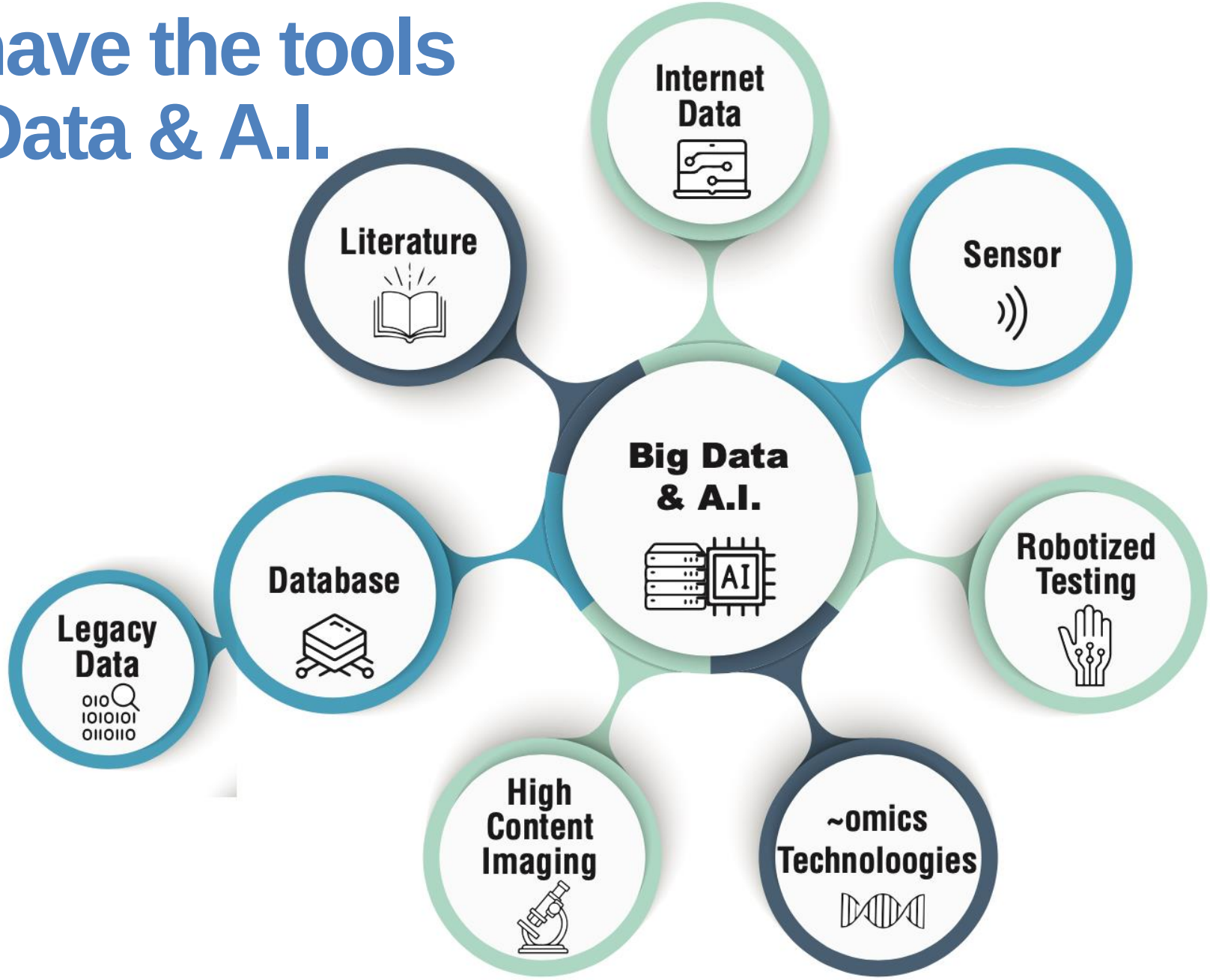
be the same, or even whether the technology will still be supported? GPT-3, released last November by OpenAI in San Francisco, California, has already been supplanted by GPT-4, and presumably supporting the older LLM will soon



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"

We have the tools
Big Data & A.I.



https://sfmagazine.com/technotes/february-2019-wipo-u-s-and-china-lead-the-world-in-ai-innovation/

9 most common toxicity tests

190,000 chemical's hazard cross-validation:

87% correct

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

Science, 12 Feb 2016

TOXICOLOGY

A crystal ball for chemical safety

By comparing new chemicals to known compounds, toxicologists seek early hazard warnings

nature

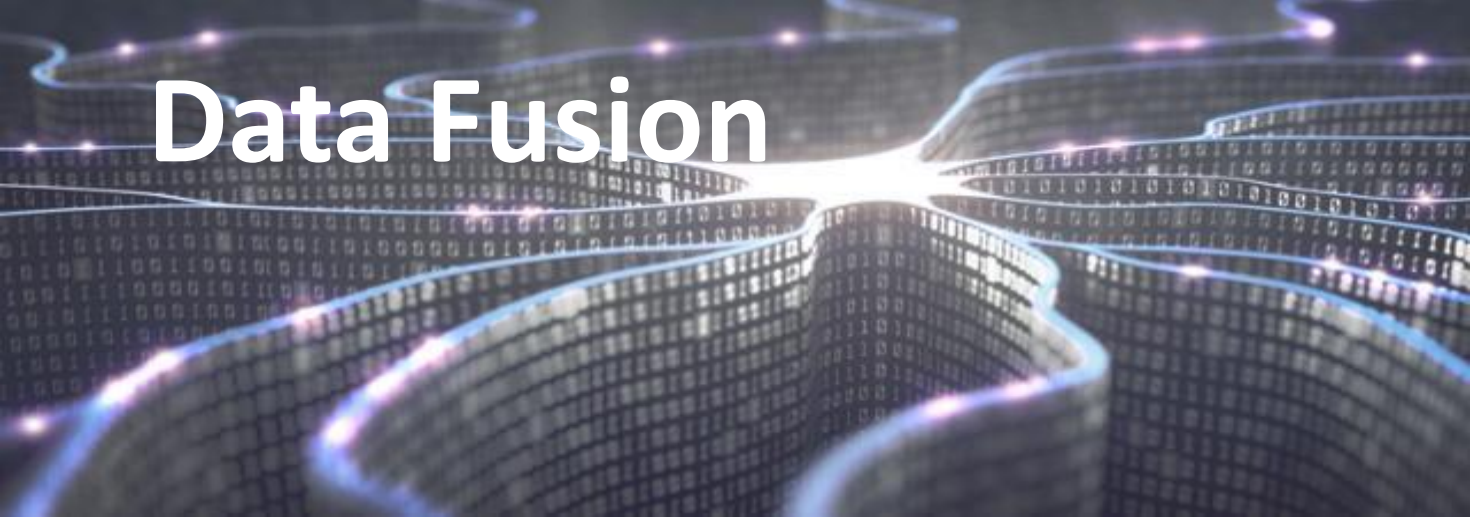
Legal tussle delays launch of huge toxicity database

nature

Software beats animal tests at predicting toxicity of chemicals

Science Home News Journals Topics Careers

New digital chemical screening tool could help eliminate animal testing



The power of transfer learning

When looking for eye irritants,
look also for neighbors' information on skin irritation, chemical reactivity etc.

AI Animal Replacement

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

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

2023: Systemic toxicities

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

Read-Across-based Structure-Activity Relationship Predictions for Reproductive Toxicity and Carcinogenicity with Deep Learning and Domain of Applicability Definition

Thomas Luechtefeld, Craig Rowlands and Thomas Hartung

Frontiers in AI, Research Topic “Leveraging Artificial Intelligence and Open Science for Toxicological Risk Assessment”

SOT 2023 NASHVILLE

#3704
Tue CompTox II

Poster Board Number **P189**
Read-Across–Based Structure-Activity Relationship Predictions for Reproductive Toxicity and Carcinogenicity with Deep Learning and Domain of Applicability Definition. *C. Rowlands*. UL Solutions, Northbrook, IL.

In preparation

Source	Descriptive Name	Sensitivity %	Specificity %	BAC %	ACC %	Coverage %
ECHA	Reproductive Toxicity 1152	82	82	82	82	81
ECHA	Carcinogenicity 950	75	80	77	78	76
OPERA	Androgen Receptor Binding 8606	100	98	99	98	99
OPERA	Androgen Receptor Agonist 8492	98	98	98	98	95
OPERA	Androgen Receptor Antagonist 8771	97	97	97	97	99

Astonishingly good prediction of complex systemic hazards

Excellent prediction of Tox21c assays

Chemical Research in Toxicology

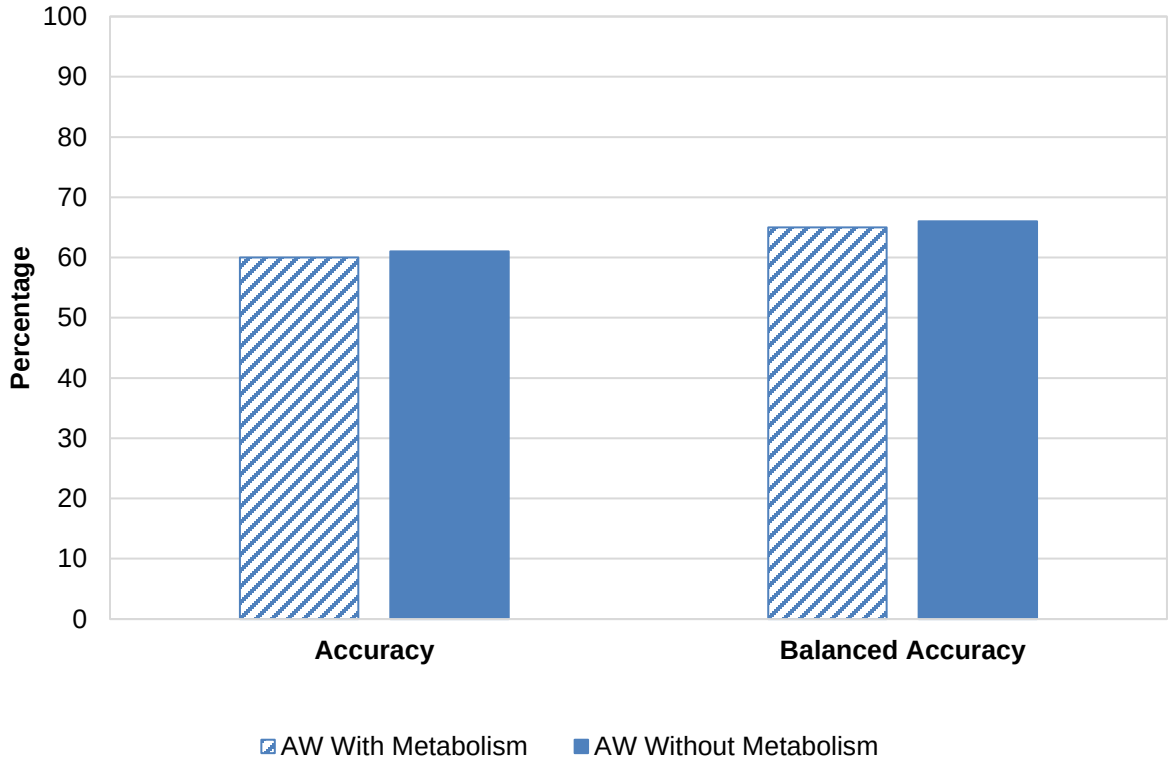
pubs.acs.org/crt

The Good, The Bad, and The Perplexing: Structural Alerts and Read-Across for Predicting Skin Sensitization Using Human Data

Emily Golden, Daniel C. Ukaegbu, Peter Ranslow, Robert H. Brown, Thomas Hartung, and Alexandra Maertens*

Metabolism Did Not Improve Model Accuracy

- **The metabolism feature for OECD QSAR Toolbox offered no improvement in accuracy for this data set**
- **Suggests there are specific areas of chemical space where metabolism is more useful than others**



frontiers

Under revision

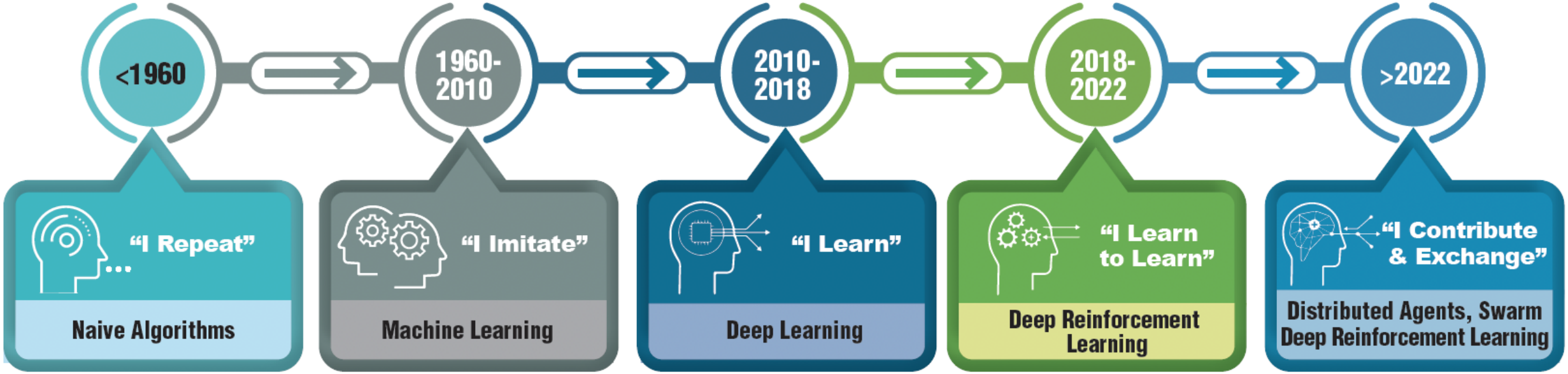
The vast majority of flame retardants (95%) and their metabolites (99%) are not present in spectral databases.

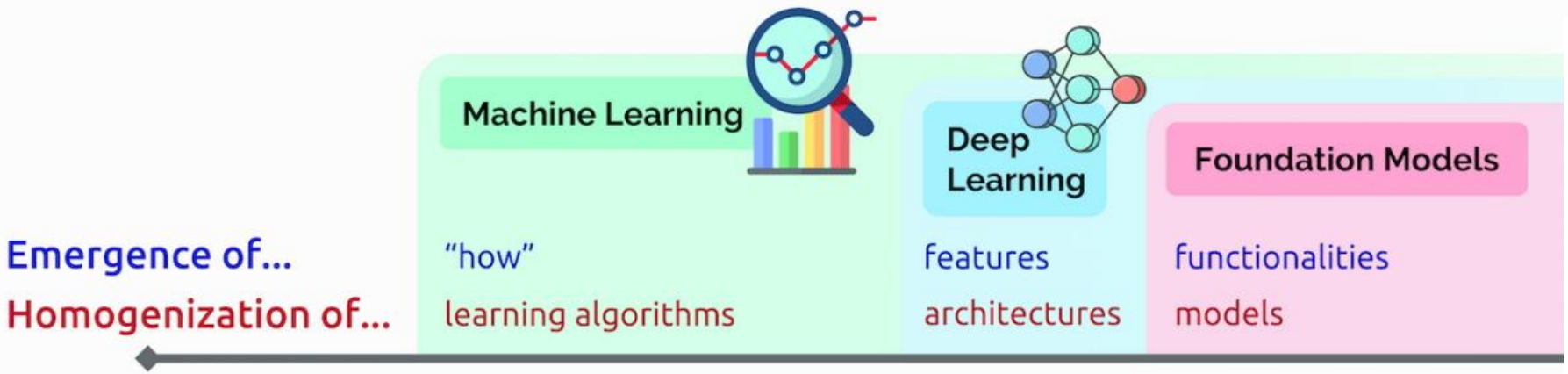
When exposures are more than the sum of their parts: using in silico tools to predict flame retardant metabolites for more informative exposomics-based approaches

Breanne Kincaid[1], Przemyslaw Piechota[1], Emiily Golden[1], Mikhail Maertens[1], Thomas Hartung[1, 2], Alexandra Maertens[1*]

In silico **tools such as metabolite prediction software, QSAR- ready structural conversion workflows, and molecular standards databases can aid in identifying novel compounds in untargeted mass spectral investigations, permitting the assessment of a more expansive pool of compounds for human health hazard.**

History of Machine Learning / A.I.





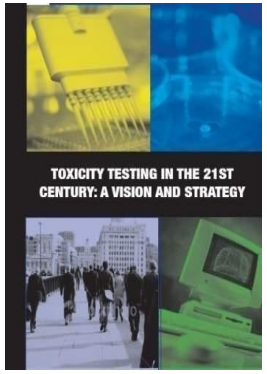
- Unsupervised or self-supervised learning
- Large (deep) neural networks
- Not intended for any particular end-goal
- Intended to serve as "foundation", then fine-tune
- Trained on multimodal data

Watershed moment
2007 NRC report

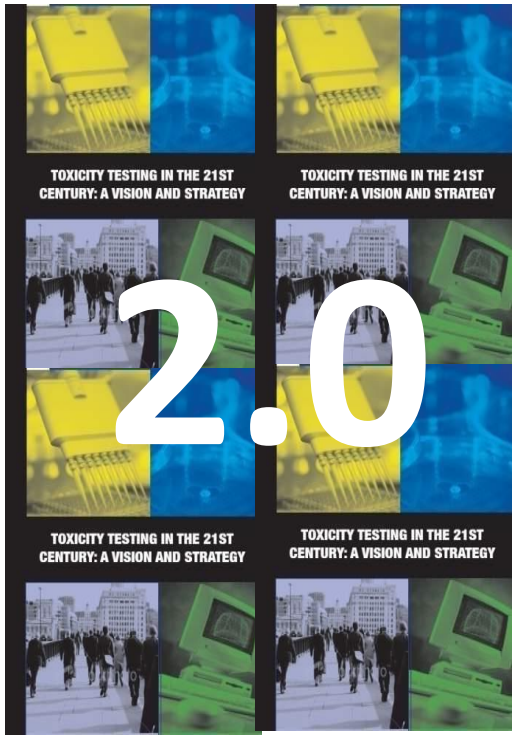
Toxicity testing in the 21st century: progress in the past decade and future perspectives

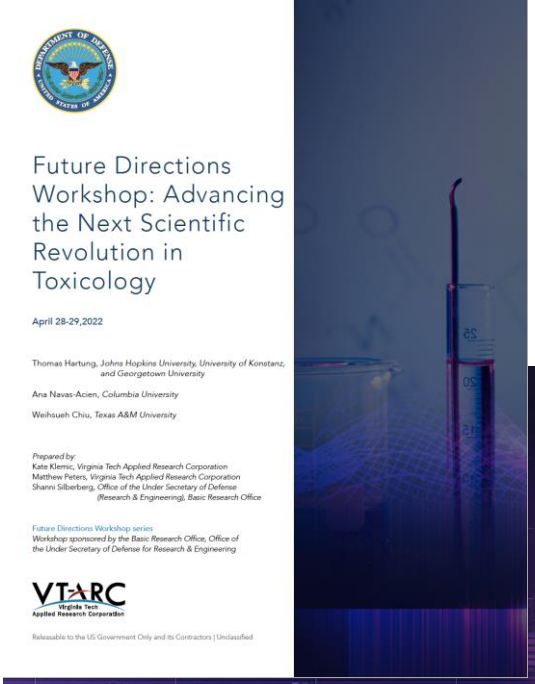
Arch Toxicol 2019

D. Krewski[1,2,4] · M. E. Andersen[3] · M. G. Tyshenko[2,4] · K. Krishnan[2,5] · T. Hartung[6,13] · K. Boekelheide[7] · J. F. Wambaugh[8] · D. Jones[9] · M. Whelan[10] · R. Thomas[8] · C. Yauk[11] · T. Barton-Maclaren[11] · I. Cote[12]



Doubling every seven years





Call for a Human Exposome Project

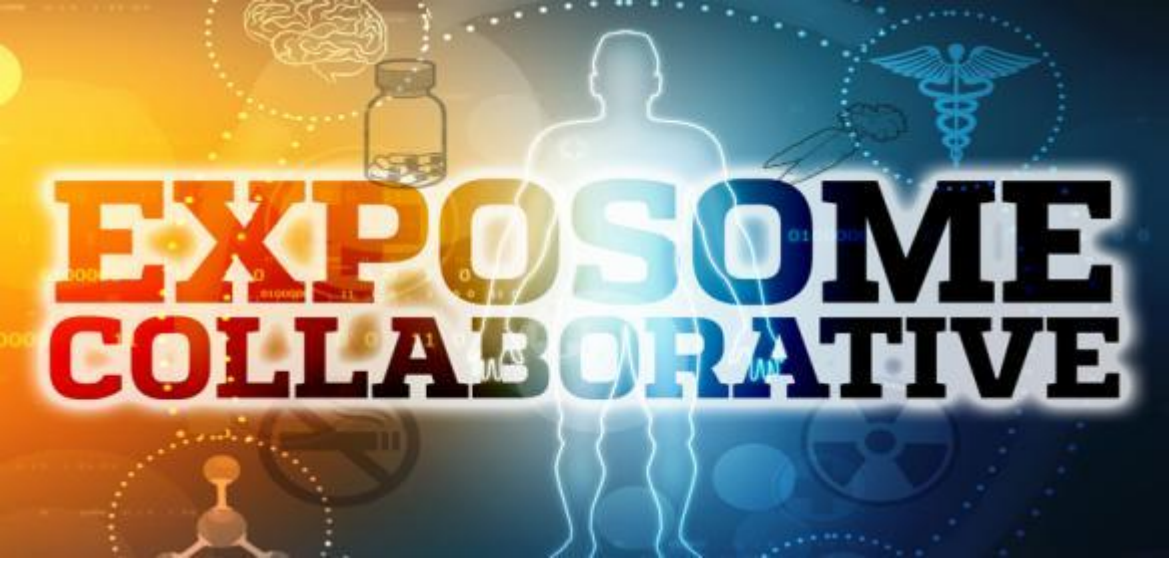
1. Exposure-driven
2. Technology-enabled
3. Evidence-integrated

Food for Thought ...

ALTEX 2023

A Call for a Human Exposome Project

Thomas Hartung[1,2]



Fenna Sillé

AI & *exposure*

ALTEX 2020, 37, 3-23

"Progress is impossible without change, and those who cannot change their minds cannot change anything."
George Bernard Shaw (1856-1950)

"If you change the way you look at things, the things you look at change."
Wayne Dyer (1940-2015)

Food for Thought ...

The Exposome – a New Approach for Risk Assessment

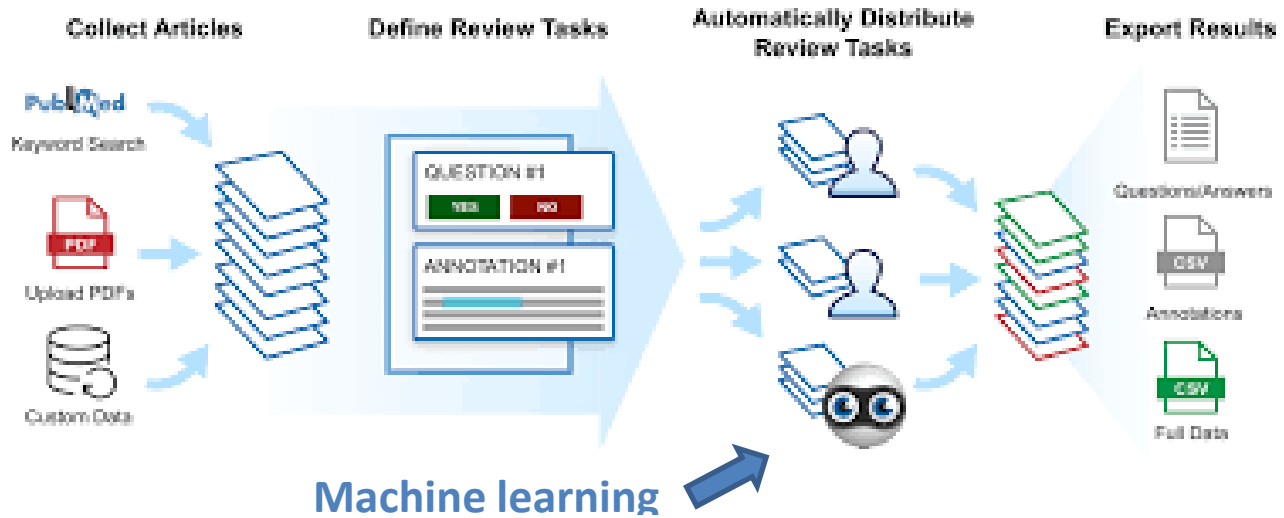
Fenna Sillé[1], Spyros Karakitsios[2], Andre Kleensang[1], Kirsten Koehler[1], Alexandra Maertens[1], Gary W. Miller[3], Carsten Prasse[1], Lesliam Quiros-Alcala[1], Gurumurthy Ramachandran[1], Stephen M. Rappaport[4], Ana M. Rule[1], Denis Sarigiannis[2,5], Lena Smirnova[1] and Thomas Hartung[1,6]

Exposome & AI = EI (Exposome Intelligence)

ONTOX

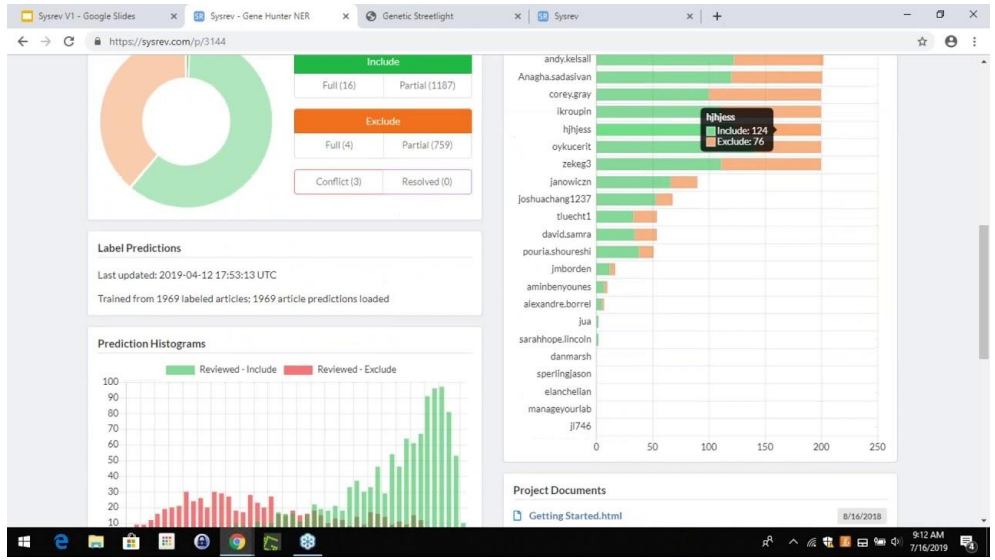
EU ONTOX project ($20 million, 2021-2026) to address liver, kidney and developing brain

ToxTrack



Semi-automated systematic review:

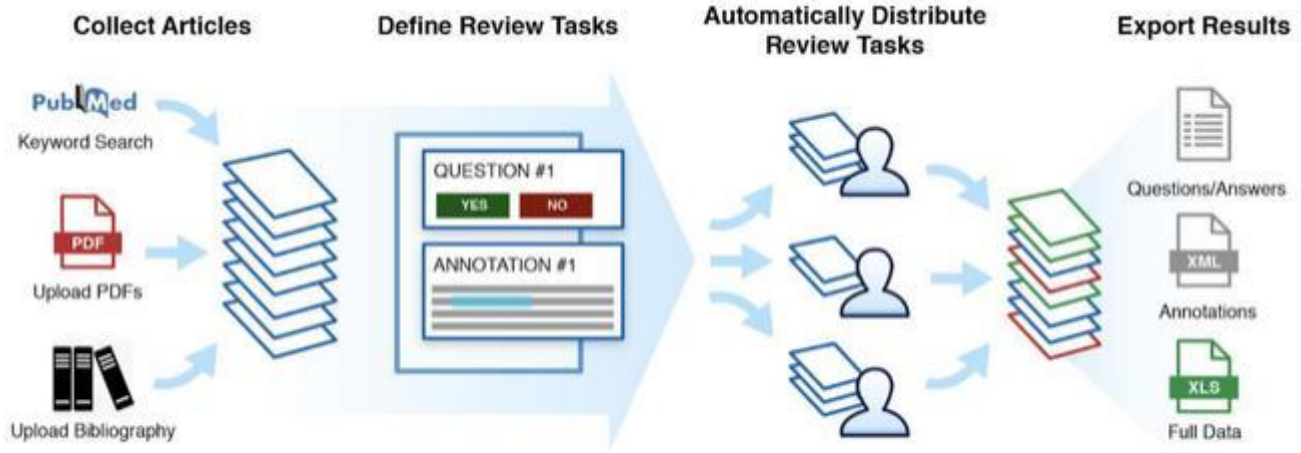
- **Auto-extract /annotate papers**
- **Auto-analyze clustering of papers**
- **Learn from manual inclusion / exclusion**
- **Automated inclusion / exclusion suggestions**
- **Natural Entity Recognition & Causal Relationship Extraction**
- **Feed into ontologies and AI**
- **chatGPT -> bioGPT -> toxGPT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



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

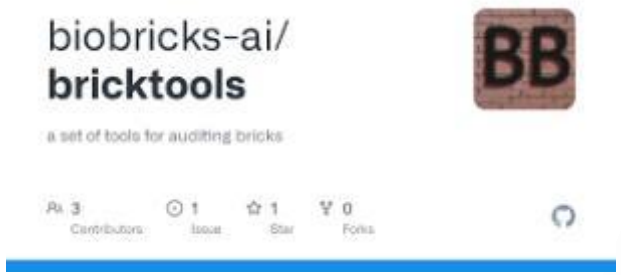
Literature

https://www.youtube.co
/c/SysRev?app=desktop



Graphic showing the document review workflow on Sysrev.com

Databases



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

Internet

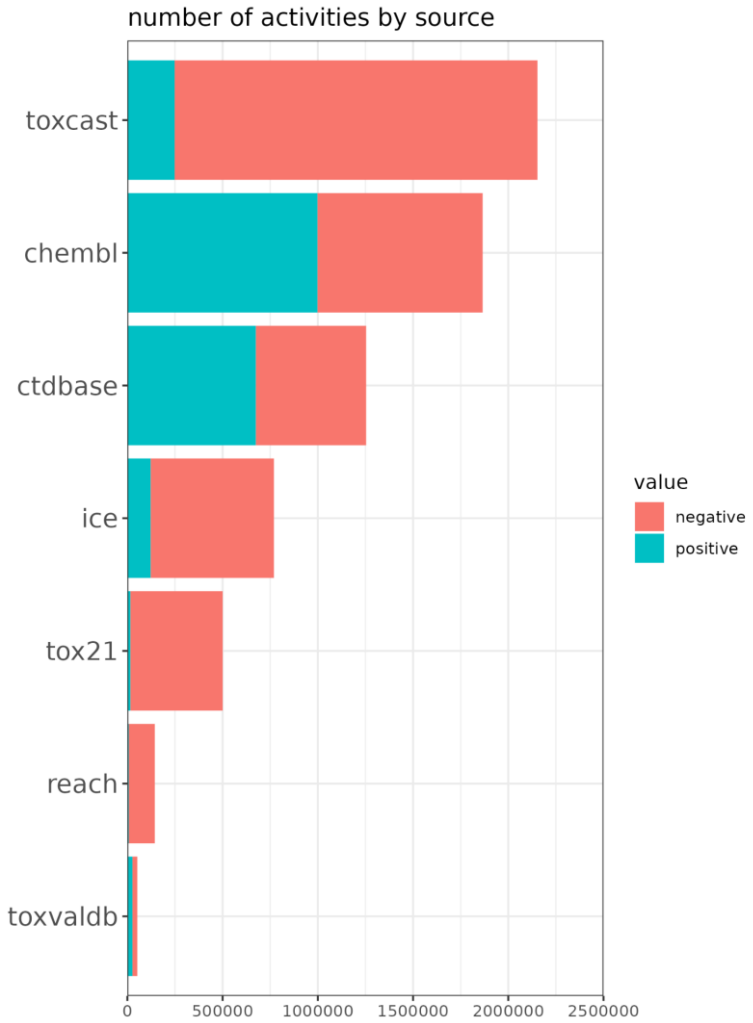
Chemchart

http://chemchart.com

DATA

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**



ChemHarmony

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!

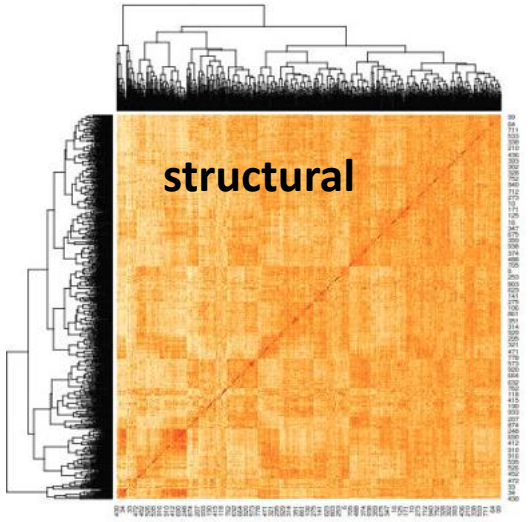


Figure 5.2A. Similarity heatmap for chembert embeddings on 1k chembl compounds
Dark red = highly similar,
White = not similar

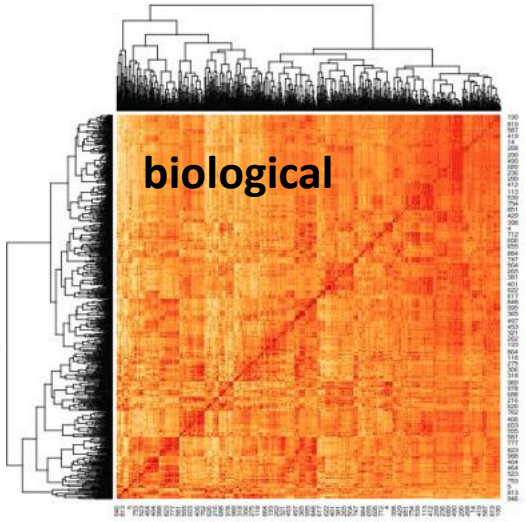


Figure 5.2B. Heatmap for inhibition assay supervised embedding
Dark red = highly similar,
White = not similar

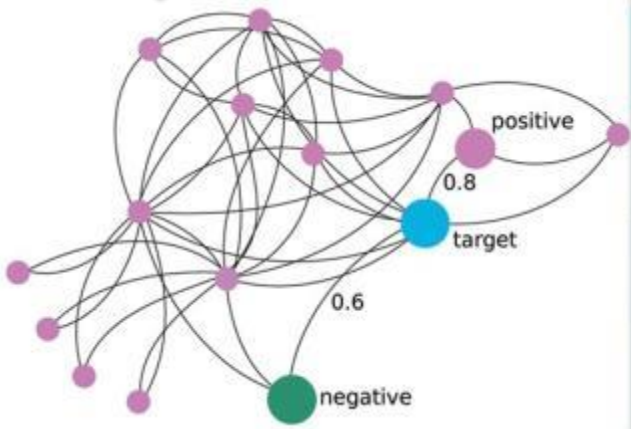
DATA

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

SBML Systems Biology Markup Language

CellDesigner™

SBtab



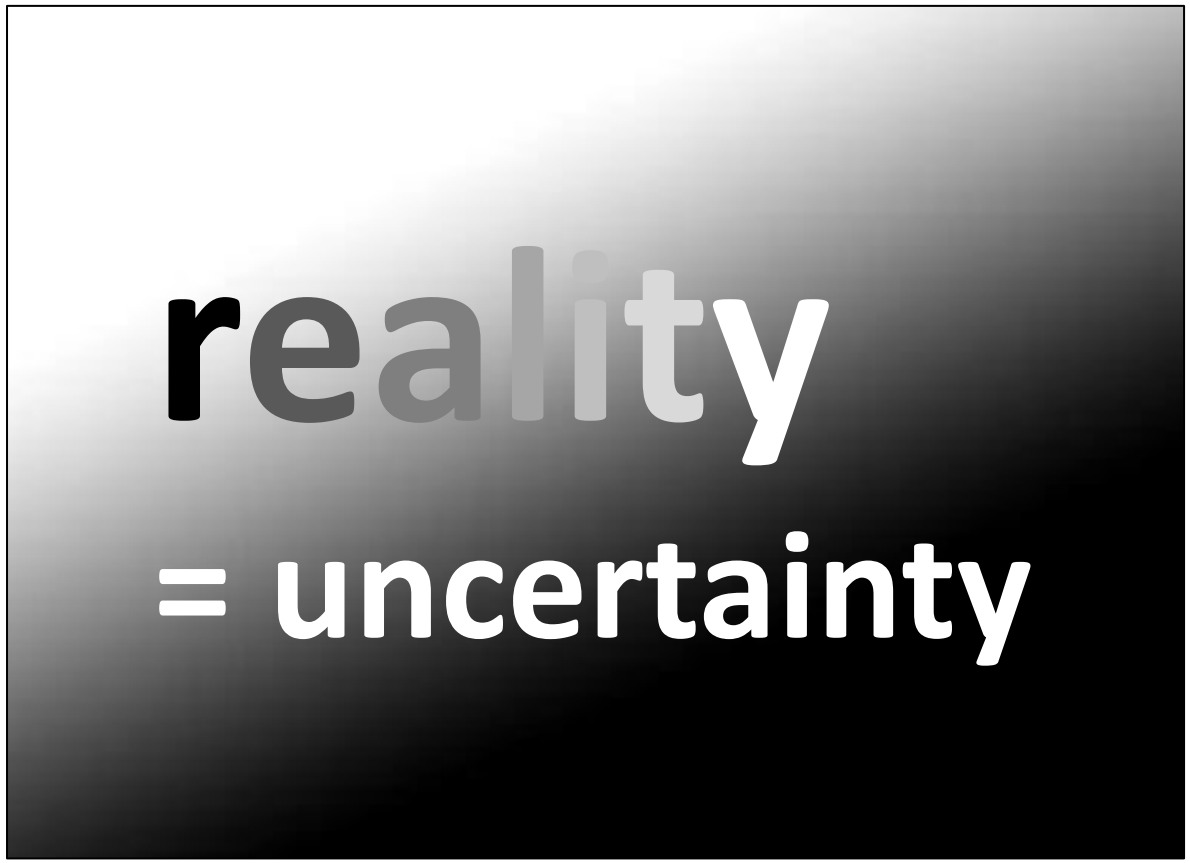
From perturbation of physiology

Probability of hazard

RASAR + QSAR

From chemical structure and properties

The problem



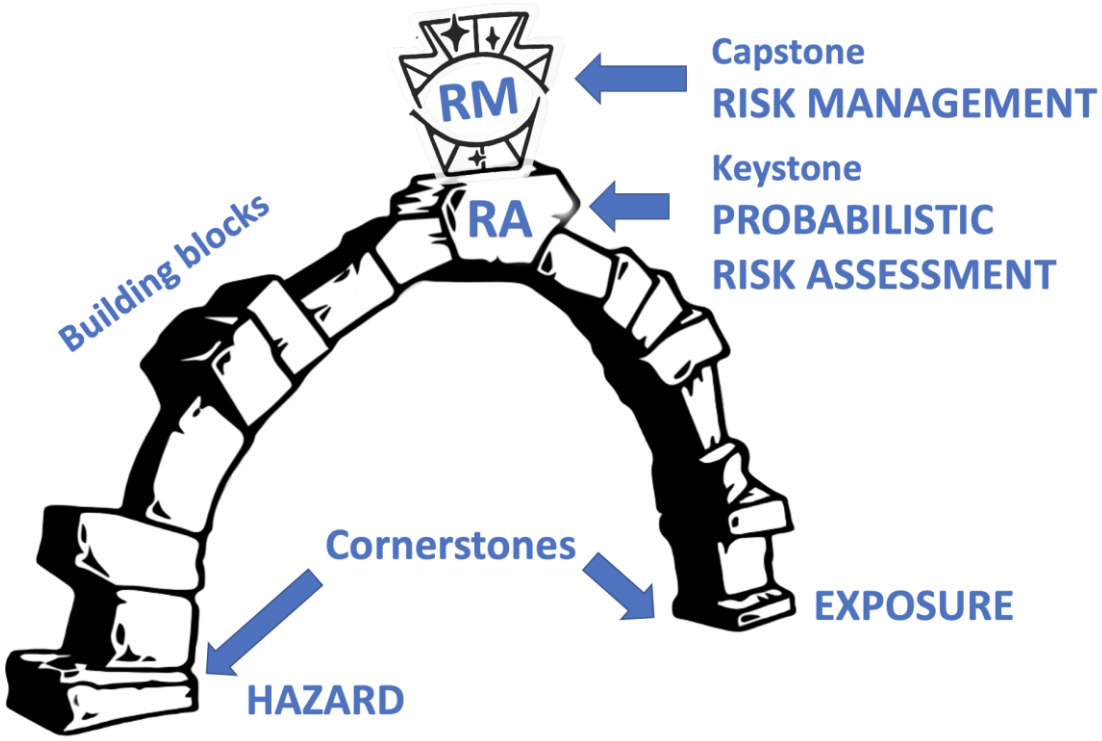
ALTEX 2022

"Probability is the very guide of life."
Cicero (106 – 43 B.C.)

Food for Thought …

Probabilistic Risk Assessment – the Keystone for the Future of Toxicology

Alexandra Maertens[1], Emily Golden[1], Thomas H. Luechtefeld[1,2], Sebastian Hoffmann[1,3], Katya Tsaioun[1] and Thomas Hartung[1,4]



transatlantic think tank for toxicology

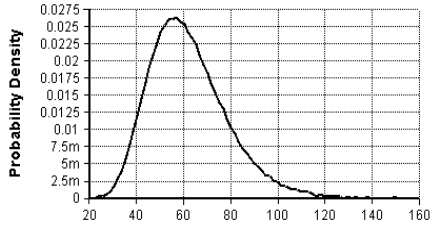
AAT

ONTOX

2nd Workshop 4-6 July 2023

Ranco, Italy

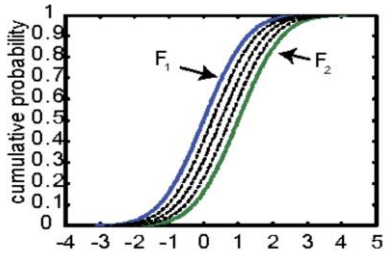
ADME testing



Exposure levels
(population given chemical)

PBPK

TTC



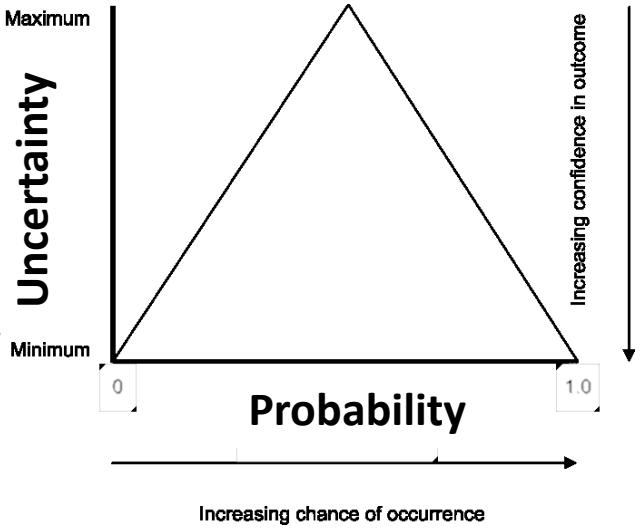
Tissue levels
(individuals)

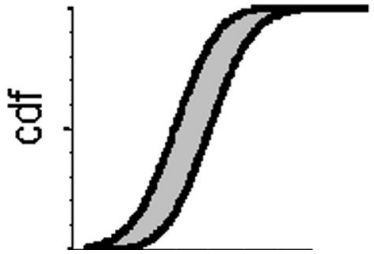
Hartung and Leist, 2008

internal
TTC

Probability
of hazard

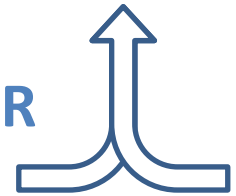
Probabilistic Risk
(individual or
cumulative population)





Concentration response

Probability hazard
(given chemical)



RASAR

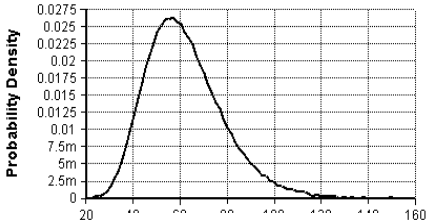
Read-across

Data

Workshop
July 2023

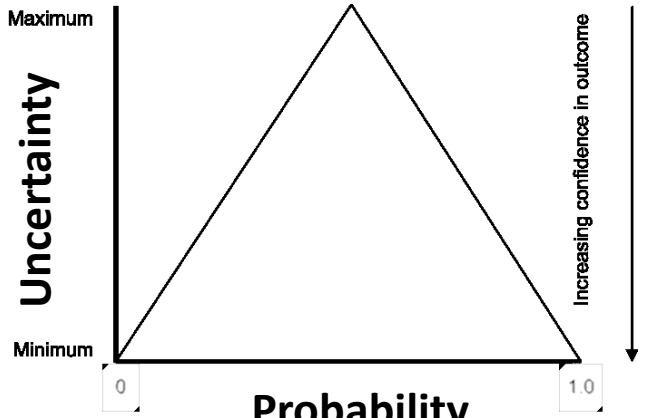
Mechanistic alerts

Probability
of exposure



Susceptibility
(individuals)

Probabilistic Risk
(individual or
cumulative population)



Minimal risk

More Testing?

Risk Management

Information economics
vs. precaution

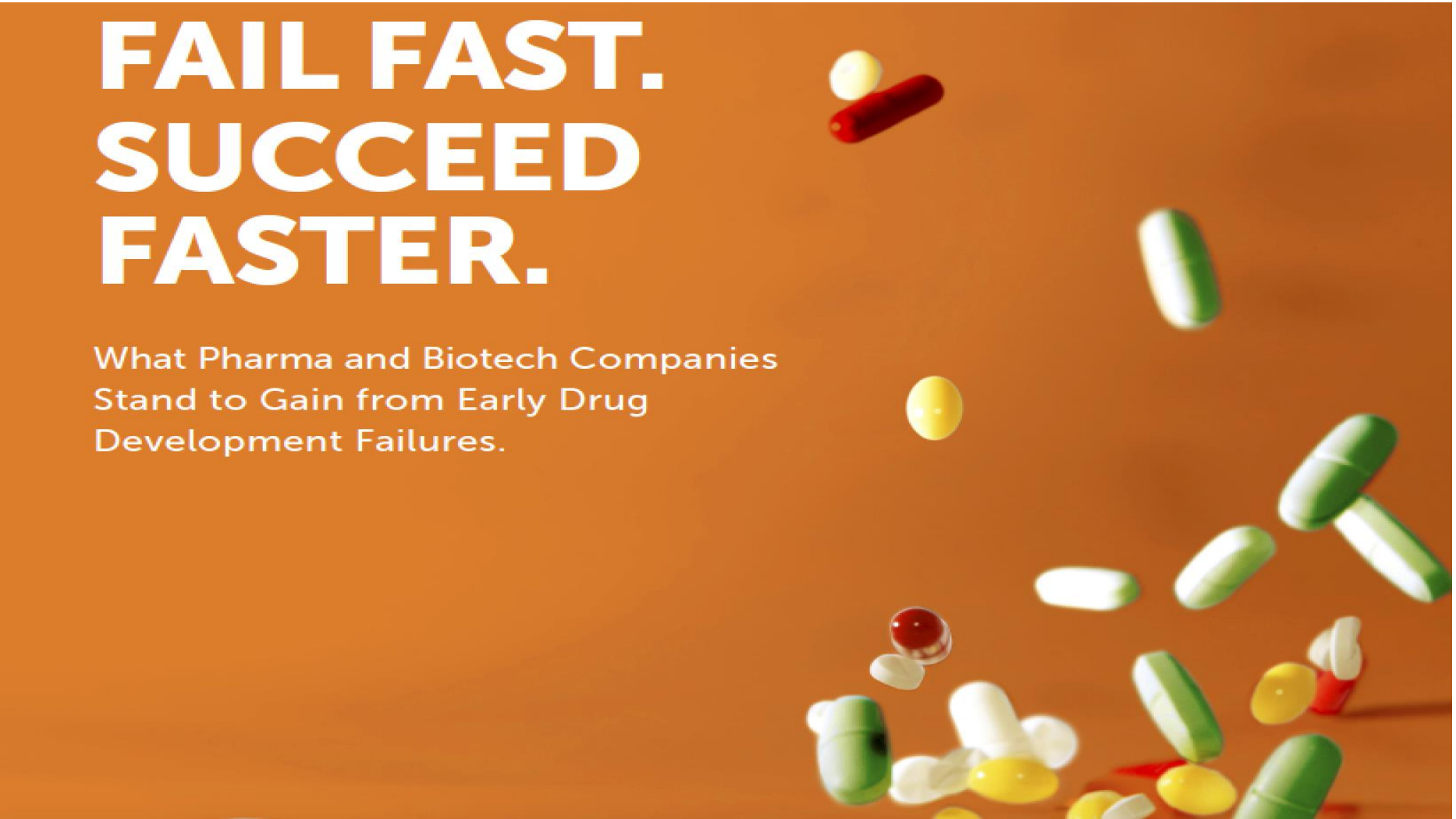
Paul Anastas and John Warner, the Fathers of Green Chemistry

Principles of Green Chemistry.

Includes toxicology

Nick Anastas, EPA, (2012): "Green Toxicology"

Concept from Pharma:
Frontloading toxicology “fail early, fail cheap”



Food for Thought ...

Green Toxicology

ALTEX 2014, 31:243-249.

Alexandra Maertens [1], *Nicholas Anastas* [3], *Pamela J. Spencer* [4], *Martin Stephens* [1], *Alan Goldberg* [1] *and Thomas Hartung* [1,2]

[1]Johns Hopkins University, Bloomberg School of Public Health, CAAT, Baltimore, MD, USA; [2]CAAT-Europe, University of Konstanz, Germany; [3]EPA Region 1, Boston, MA, USA; [4]The Dow Chemical Company, Midland, MI, USA

GREEN TOXICOLOGY

Giving screening the green light

By working with toxicologists while they're designing new compounds, chemists can avoid problems further down the chain, as Emma Davies reports

Green Toxicology

Regulatory Toxicology

Exposure-driven testing
Thresholds of Tox. Concern
Tox-21c and 3Rs

Substance Design	Research & Development	Production	Product Life Cycle
Benign Design by (Q)SAR and other *in silico*	Early testing *in chemico*, *in vitro* and lower organisms	Clean and sustainable production; Occupational hazard ↓	Exposure & waste ↓

Green toxicology

– the toxicology aspects of green chemistry

Alex Maertens

Another use of alternatives methods

Green Chemistry Series

Green Toxicology

Making Chemicals Benign by Design

Alexandra Maertens

TOXICOLOGICAL SCIENCES, 161(2), 2018, 285–289

doi: 10.1093/toxsci/kfx243
Advance Access Publication Date: December 18, 2017
Editorial

ly About and Avoid Toxic

ng*,†,1

Generated with DALL-E and LeiaPix

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

The Smart Path Forward

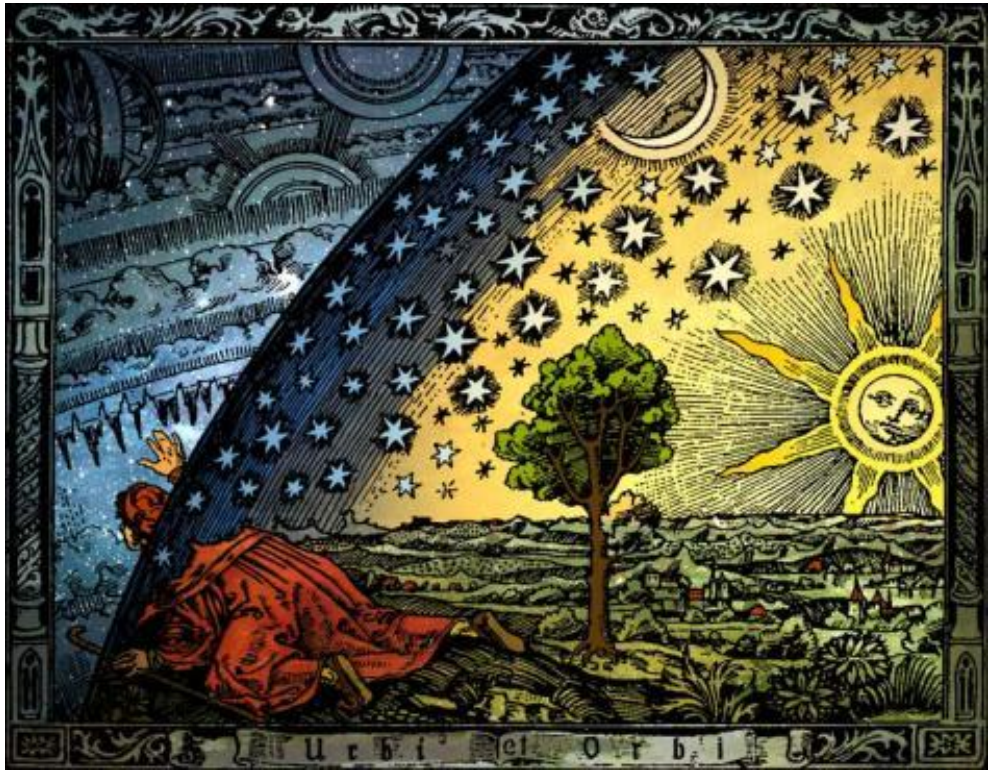
- Open access, machine readable
- Identify bias in data
- Explainable AI

The difficulty lies not in the new ideas,

but in escaping from the old ones.

John Maynard Keynes

(1883 - 1946)



Slides available: