AI-Driven Knowledge Management in PBPK Modeling: Challenges & Opportunities

FDA-CRCG Workshop 2025

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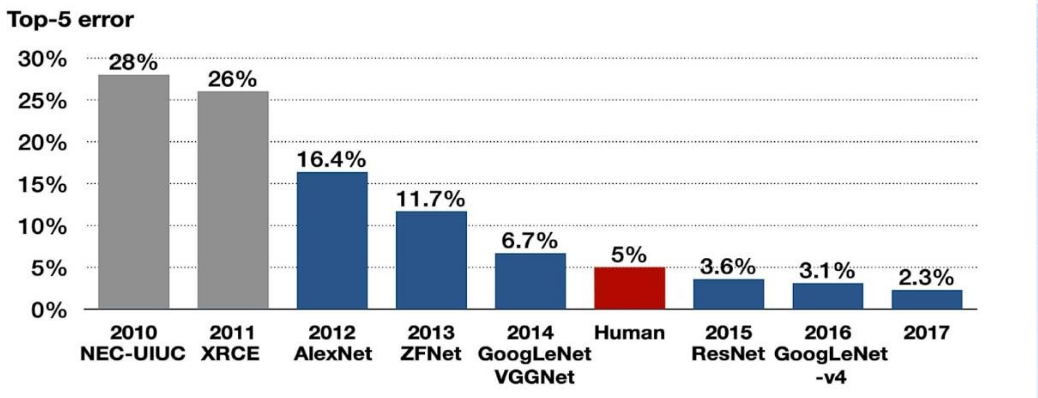
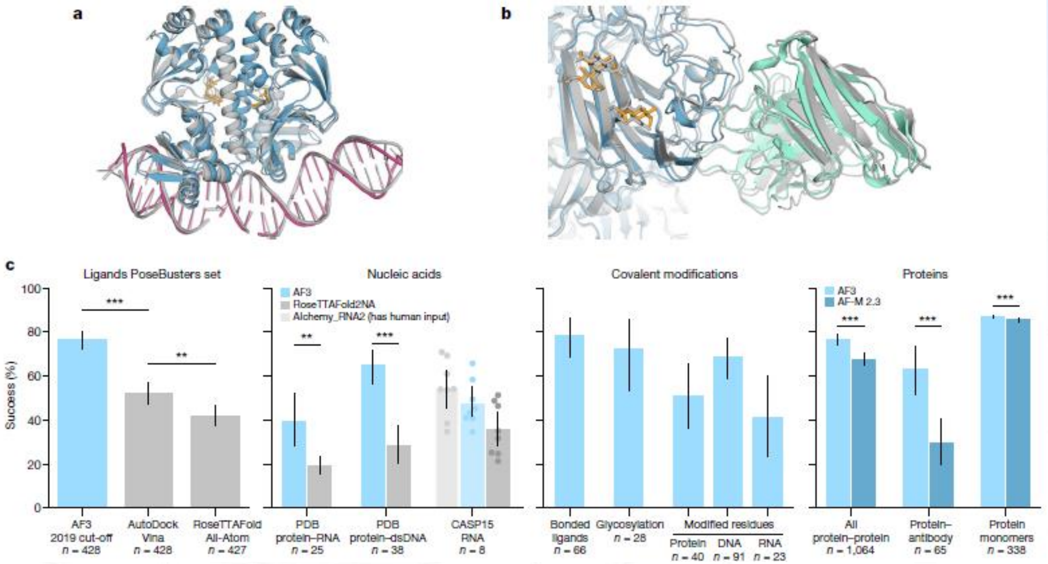
High-quality data is the foundation of every major AI advance

- **Images: Open Images V7 –** 9 mln images with extreme multi-modal annotations.
- **LLMs**: Breakthroughs fueled by massive, open internet-scale datasets.
- **AlphaFold**: Powered by decades of structural biology data in the Protein Data Bank (PDB).





References:
1. https://arxiv.org/abs/1409.0575
2. https://doi.org/10.1038/s41586-024-07487-w

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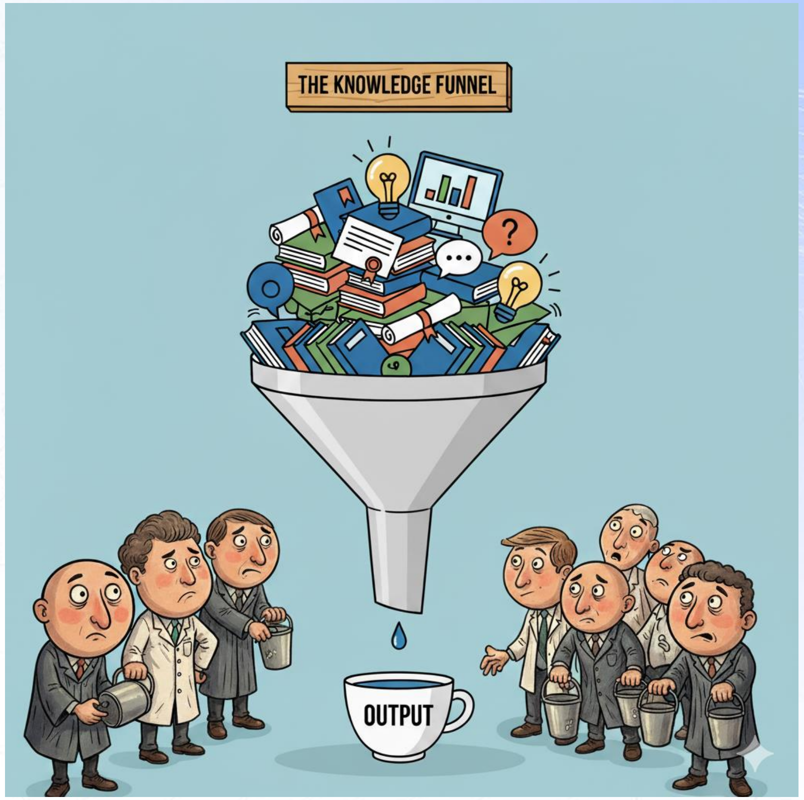
Knowledge Management

- **Centralizes** scientific and organizational knowledge
- **Ensures quality** through standards, metadata, and governance.
- **Connects** data silos via ontologies & knowledge graphs.
- **Accelerates decisions** with AI-driven insights.
- **Supports compliance**. *Regulators expect clear documentation of model assumptions and data sources.*

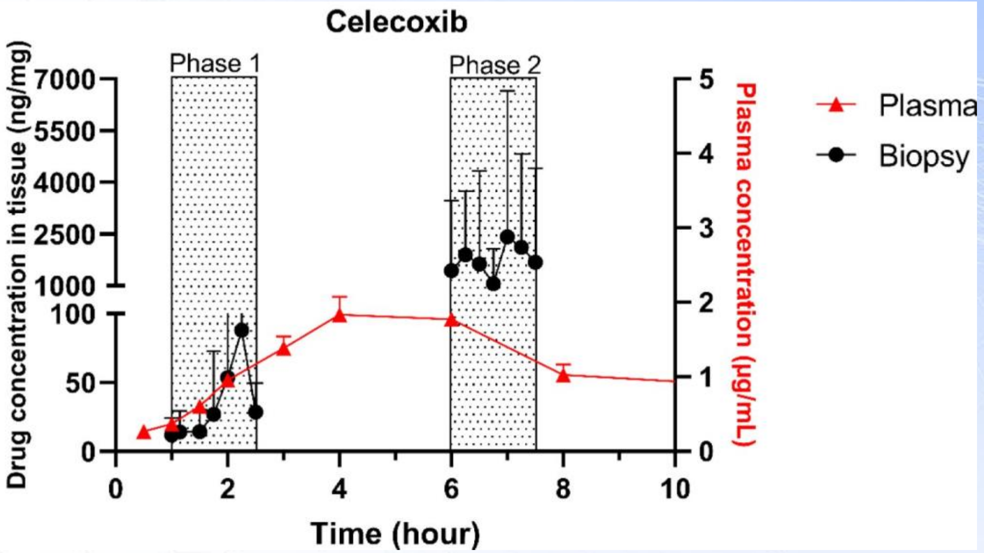


Ref: “Abstract knowledge funnel image.” AI-generated image. ChatGPT-5, OpenAI, 29 Sept. 2025, https://chat.openai.com/

*Without **knowledge management**, organizations remain trapped in a **knowledge funnel.***

AI Adoption in PBPK: Challenges

- **Diverse sources:** PBPK modeling draws on heterogeneous data sources: *in vitro* assays, clinical studies, literature data, physiological databases, etc.
- **Annotation process:** Manually gathering and reconciling these data is time-consuming and error-prone [1].
- **Curation process:** One major challenge is simply finding and curating all relevant parameters (especially for new compounds with sparse data).



Example of a complex plot as a data source from [2]

AI accelerates PBPK knowledge work, but success requires human oversight, provenance, and guardrails.

References:
1. https://doi.org/10.1007/s11095-024-03725-y
2. https://doi.org/10.3390/pharmaceutics13020161

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Interoperable Data Models: The Foundation for AI Integration

- Interoperable Data Models enable AI integration.
- There are many ways to store data models
  - SBML - Systems Biology Markup Language for physiological models
  - PharmML - Pharmacometric Modeling Language for model exchange
  - PK-Sim/MoBi - Open Systems Pharmacology Suite with XML-based model formats
- LinkML – originally YAML, but it is very easy to connect/convert to Ontologies, SQL schemas, Pydantic classes, etc.

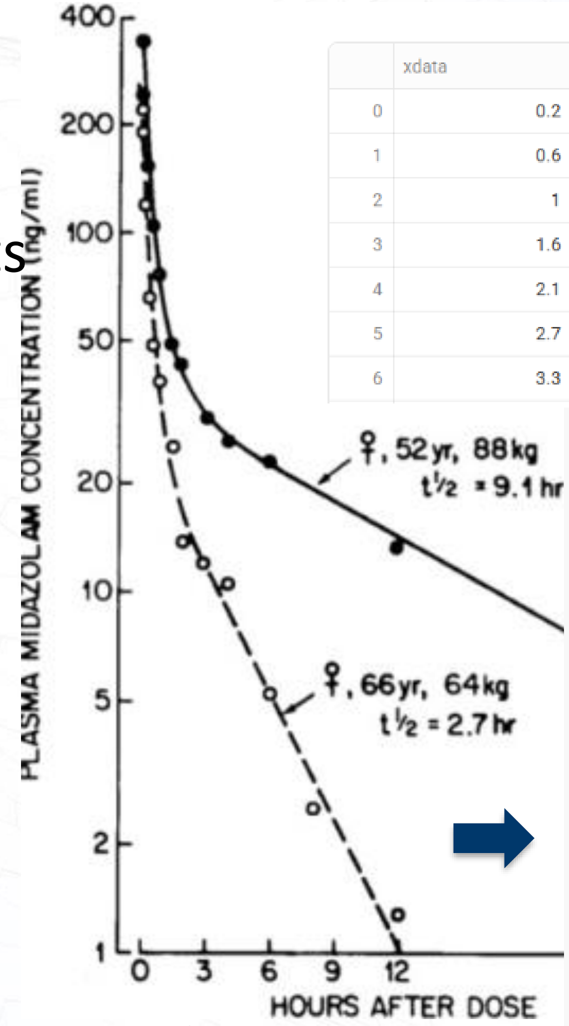

```yaml
PBPKModel:
  description: A complete PBPK model with all components
  attributes:
    model_id:
      identifier: true
      range: string
      description: Unique identifier for the model
    model_name:
      required: true
      range: string
      description: Name of the PBPK model
    description:
      range: string
      description: Description of the model purpose and scope
    compound:
      required: true
      range: Compound
      description: The compound being modeled
    subject:
      required: true
      range: Subject
      description: Subject characteristics (human, animal model, etc.)
    compartments:
      required: true
      multivalued: true
      range: Compartment
      description: List of physiological compartments in the model
    dosing_regimen:
      required: true
      range: DosingRegimen
      description: Dosing information for the simulation
    simulation_settings:
```


LinkML mockup for PBPK model

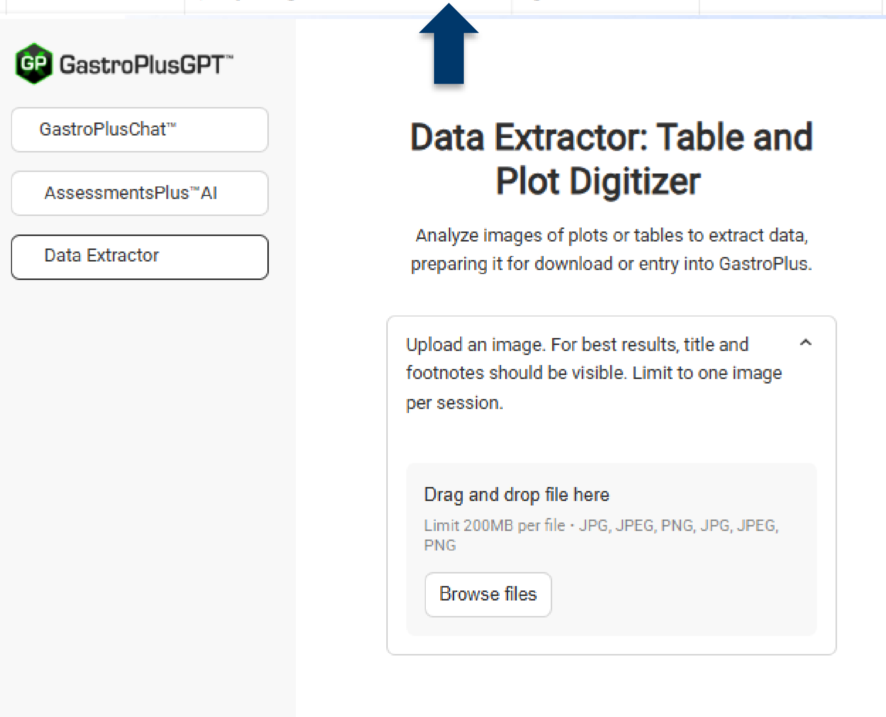
Reference: "PBPK LinkML model mock-up." AI-generated LinkML schema. ChatGPT-5, OpenAI, 30 Sept. 2025, https://chat.openai.com/

AI-driven data extraction: Opportunity

- Automates extraction from unstructured sources: documents (Word, PDF, Markdown), plots, tables.
- Improves speed over manual methods.
- Enables up-to-date, scalable knowledge ingestion.



	xdata	ydata	legend	yunits	xunits
0	0.2	210	♀, 66yr, 64kg, t½ = 2.7 hr	ng/mL	hr
1	0.6	90	♀, 66yr, 64kg, t½ = 2.7 hr	ng/mL	hr
2	1	46	♀, 66yr, 64kg, t½ = 2.7 hr	ng/mL	hr
3	1.6	22	♀, 66yr, 64kg, t½ = 2.7 hr	ng/mL	hr
4	2.1	14	♀, 66yr, 64kg, t½ = 2.7 hr	ng/mL	hr
5	2.7	9	♀, 66yr, 64kg, t½ = 2.7 hr	ng/mL	hr
6	3.3	7	♀, 66yr, 64kg, t½ = 2.7 hr	ng/mL	hr



References:

1. Simulations Plus, Inc. "GastroPlusGPT: Data Extractor – a tool to extract structured, machine-readable data from images and unstructured files." , September 29, 2025.

AI-driven data extraction: Challenges

- AI extraction is still prone to errors/hallucinations.
- E.g. OlmOCR (AllenAI) a Visual Language Model (VLM) failed to correctly convert ("OCR") a table to markdown.
- Solutions: fine tuning, and human-in-the-loop.

Ground Truth Table

Table 3. Species Comparison of Plasma-Derived PK Parameters of the Parent Drug after Single Administration of Nintedanib[a]

Species	mouse	rat[b]		cynomolgus[c]		rhesus[c]	
Method of Administration	oral	oral	i.v.	oral	i.v.	oral	i.v.
Nintedanib dose (mg/kg)	50	50	2	40	5	40	5
C_{max} [ng/mL]	547	105	124	175	1300	311	1090
$t_{1/2}$ [h]	5.15	ND	3.95	ND	5.95		
AUC [(ng·h)/mL]	2720	375	181	2390	2260		
Clearance [mL/min/kg]	NA	NA	202	NA	37.5		
MRT [h]	5.19	ND	3.25	ND	3.82		
V(ss) [L/kg]	NA	NA	41.2	NA	8.64		
Bioavailability [%]	ND	11.9	NA	13.2	NA		

[a]AUC = area under the curve; C_{max} = maximal concentration; MRT = mean residence time; NA = not applicable; ND life; V(ss) = volume of distribution at steady state. [b]Several formulations and dosages were tested. Within the dos AUC_{0-24h} and C_{max} increased proportionally with dose. [c]Single dose PK after i.v.-dosing was integrated in an o Additional dose groups were used. Only representative PK data are listed here. Linear dose dependency and no sex

Example of AI failure (OlmOCR by AllenAI)

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Bioavailability [%]	ND	11.9	NA	13.2

References
1. https://doi.org/10.1021/jm501562a
2. https://olmocr.allenai.org/

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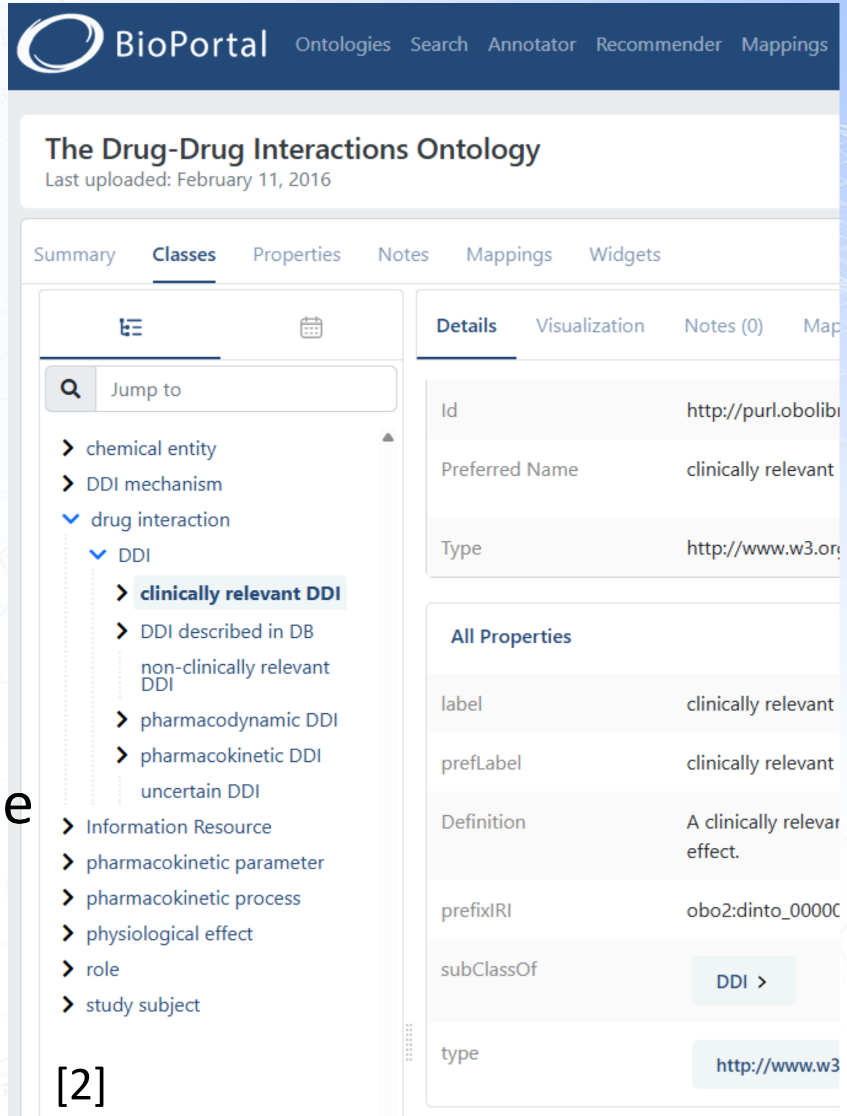
AI-Driven creation of ontologies: Opportunity

- LLMs (+NLP) mine literature, datasets, and reports [1]
- Embeddings group synonyms and normalize variants
- Relation Extraction (**RE**) identifies hierarchies
- Generative AI drafts term definitions (**NER**) and logical axioms

Human in the Loop

- Validate AI-generated terms & relationships
- Ensure regulatory and scientific accuracy
- Curate final vocabularies & ontologies for production use



[2]

References:
1. https://arxiv.org/abs/2312.10904
2. https://pubs.acs.org/doi/10.1021/acs.jcim.5b00119

AI-Driven creation of ontologies: Challenges

AI-generated ontologies are not ideal

- For example, DRAGON-AI system achieved high precision but low recall in relationship prediction, indicating that while the generated ontology term relation predictions were generally correct, a substantial number of expected relationships were not generated at all.
- DRAGON-AI doesn't generate ontologies from scratch—only individual term completions are supported.
- Solutions: reasoning models provides better results but still do not guarantee 100% success.

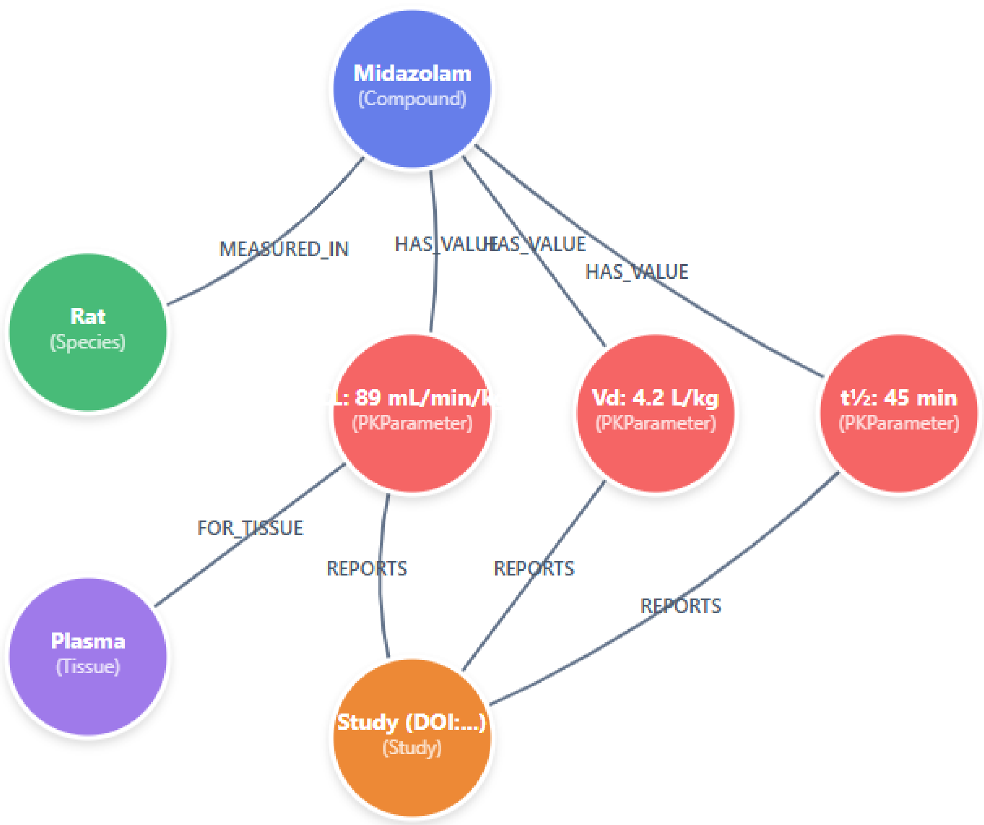
Table 4: DRAGON-AI results for relationship prediction task. We partition into two subtasks: filtered for SubClassOf, and filtered for all relationship types (heterogeneous relationship predictions). OWL Reasoning results included as baseline for SubClassOf. Note that by definition OWL reasoning is always completely precise as all entailments follow from existing axioms.

		SubClassOf Task			All Relationship Types Task		
method	model	precision	recall	F1	precision	recall	F1
DRAGON	gpt-3.5-turbo	0.831	0.352	0.494	0.746	0.392	0.514
DRAGON	gpt-4	**0.889**	**0.44**	**0.588**	**0.797**	**0.456**	**0.58**
DRAGON	nous-hermes-13b	0.68	0.273	0.39	0.597	0.292	0.392
Reasoner	n/a	*1.0**	0.337	0.504	n/a	n/a	n/a

References:
1. https://arxiv.org/abs/2312.10904

Knowledge Graph with AI: Opportunity

1. **Generate KG Schema** with AI (human validation required) grounded in **NER and/or ontology**.
2. **Extraction = schema-guided, document-type aware.**
3. **Normalize & Link**
    - Synonyms: "clearance" = "CL" = "elimination rate" → standardized term
    - Map to ChEMBL ID, convert units to standard (mL/min/kg)
    - Conflict detection: flag duplicate values → verify study conditions
4. **Query & Use**: Auto-populate PBPK models from literature using KG + AI.

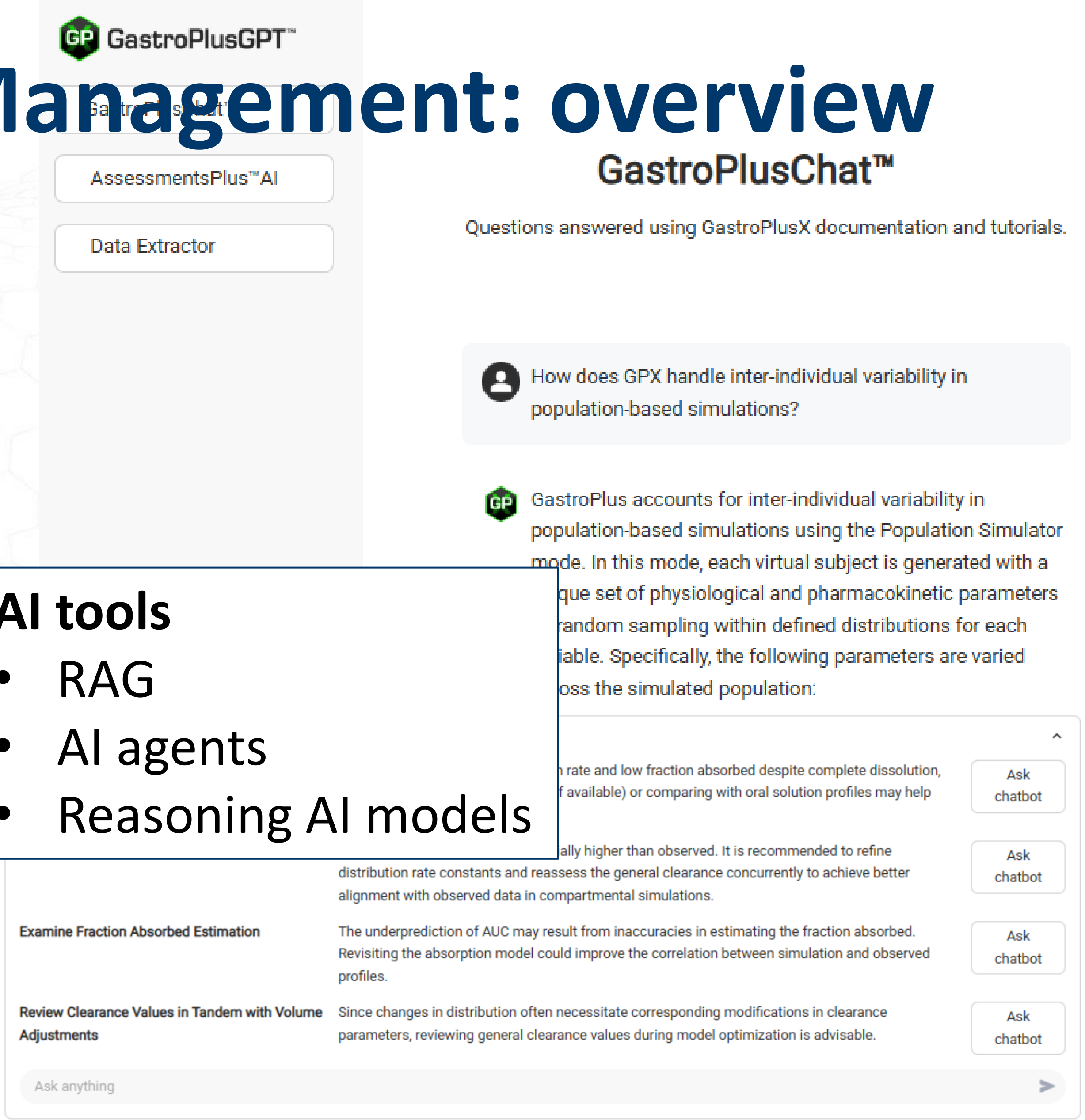


Literature → Extract → Normalize → Knowledge Graph → PBPK Model

Knowledge Graph with AI: Challenges

- **LLMs might fabricate or misread numeric values** from text and tables: "CL = **45** mL/min/kg" → LLM extracts "**54** mL/min/kg”.
- **Entity Disambiguation.** Same entity appears with multiple names, abbreviations, or identifiers across sources "midazolam" = "MDZ" = "Versed" = "dormicum“ → Which chemical ID?
- **Quality vs. Scale Trade-off.** Manual curation is high quality but slow; full automation is fast but error-prone. Solution? **Hybrid approach: AI + human validation loops.**

AI-driven Knowledge Management: overview



Data acquisition
- LLM-assisted extraction from text/tables/figures (with provenance)
- Automated de-duplication, record linkage, and QC review
- Interoperable data connectors & APIs

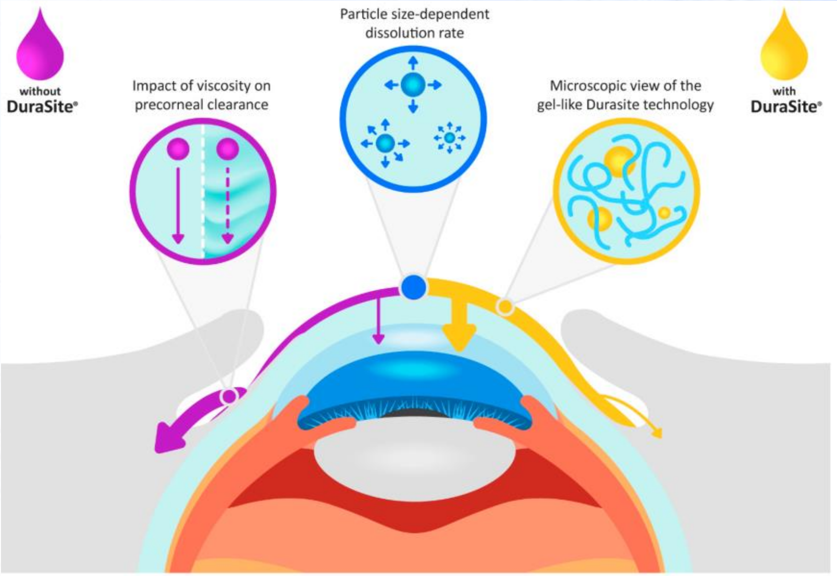
Data governance
- Provenance, lineage, and versioning (docs, prompts, models)
- Role-based access, compliance & auditability
- Continuous evaluation: coverage, groundedness, latency, user feedback

AI tools
- RAG
- AI agents
- Reasoning AI models

Case Study – Ocular PBPK Extrapolation (Rabbit → Human) with OCAT™ in GastroPlus®

Problem: Sparse human ocular PK; high inter-study variability; need for reliable rabbit → human extrapolation for generics.
Knowledge Challenges: Fragmented parameter evidence (e.g., permeability, melanin binding), heterogeneous protocols (anesthesia/tear flow effects), implicit model assumptions, and incomplete provenance.
Outcomes

- Rabbit-fitted drug parameters reused to predict human anterior-segment exposure for levofloxacin, moxifloxacin, gatifloxacin; vitreal predictions mixed—highlighting data gaps.
- Melanin binding represented via very low unbound fractions (≤1%), consistent with prolonged retention in pigmented tissues.
- Demonstrated feasibility of model-based BE support for ophthalmic solutions; identified anesthesia-mediated tear-flow as a key variability driver.



Reference: https://doi.org/10.3390/pharmaceutics16070914

Future Outlook

- **Guardrails-by-design** — safety constraints, uncertainty quantification, audit trails, human-in-the-loop approvals.
- **Evaluation at scale** - open benchmark suites, synthetic challenge sets for agents & models.
- **Interoperability & governance** - FAIR-by-default data, open standards, stable APIs into PBPK platforms.
- **Regulatory perspective** - transparent documentation, automated multi-source validation, comprehensive uncertainty analysis, and traceable, auditable evidence chains.