Insights from Lead Optimization Efforts Using KNIME in Industry

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Who We Are

- Avicenna Biosciences is first and foremost a drug development firm that generates NCEs using medicinal chemistry and machine learning
- Every machine learning scientist in Avicenna trained as either a chemist or a physicist first
- We work exclusively on solving DMPK/Tox problems to enable quality chemical matter for innovative clinical trials
- Launched in 2019, we now have multiple programs in Oncology, Neurodegeneration/Neuroinflammation and Autoimmune/Autoinflammatory indications
- Future work will move us from purely development problems to more discovery-type programs through our work on dataset augmentation with physics-based methods

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Some Difficulties in Applying ML to Drug Development

- Addressing a true drug development need is a major problem – the translation of a medicinal chemistry design point to a machine learning experiment has been a major hurdle, and the clarity of machine learning experimental design has been low in the past

- As an example, there is a miscommunication between the medicinal chemists discussing multiobjective optimization and the ML people who hear “end-to-end”

- Additionally, the process of data sourcing and curation has limited transparency and no established process for formal presentation either to internal or external audiences

- We have developed two tools that aid us in designing algorithms for our internal programs: ML experiment design diagrams and **S**chematic of **L**iterature **I**nclusion **C**riteria for **E**xperiment in ML (**SLICE** ML)

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ML Experimental Design

- The applicability domain for various ML methods is not equivalent for all methods, and some methods have limited utility for problems within chemical biology and drug development/discovery
- In our experience, there is a communication gulf between machine learning scientists and medicinal chemists/pharmacologists
- This miscommunication can result in the selection of ML methods which fail to have utility for predicting desired solutions to discovery or development problems
- A way of representing the design of machine learning experiments that is accessible to non-ML scientists would reduce miscommunication

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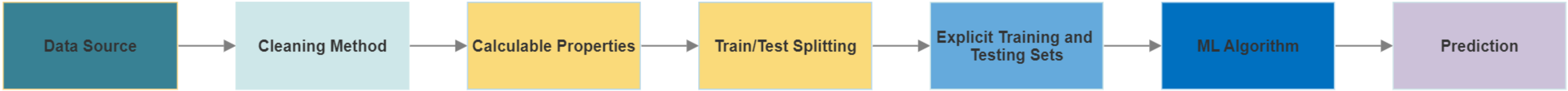
ML Experimental Design



Algorithm Type	**Random Forrest (Tree Conditions: Information Gain Ratio, Limited Tree Depth < 15, No Node Size Minimum)**
Number of Trees	200
Learning Type	Supervised Learning
Point of Run Replication	Test/Train Split
Number of Replicate Runs	Triplicate
Independent Variable	ECFP4
Dependent Variable	Active = (1,0)

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FEPML Background – Theory

- Machine learning in combination with Relative Binding Free Energy (RBFE) calculations
  - Machine learnings applicability domain is limited to the availability of data
  - How do we overcome the limitations of information poor projects?
  - RBFE has emerged as highly accurate molecular mechanics methods to predict binding affinity of similar compounds to a given target (1-2kcal/mol)
    - FEP is currently the gold standard

- Rationale
  - FEP calculations can serve as an input to ML algorithms to **partially** overcome information sparse limitations
  - Reduce time and cost associated of traditional medicinal chemistry efforts ($100-150 vs $2000-5000)

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Kaiser, T. M.; Burger, P. B., *Molecules*, **2019**, *24*, 2115

ML Experimental Design Diagrams

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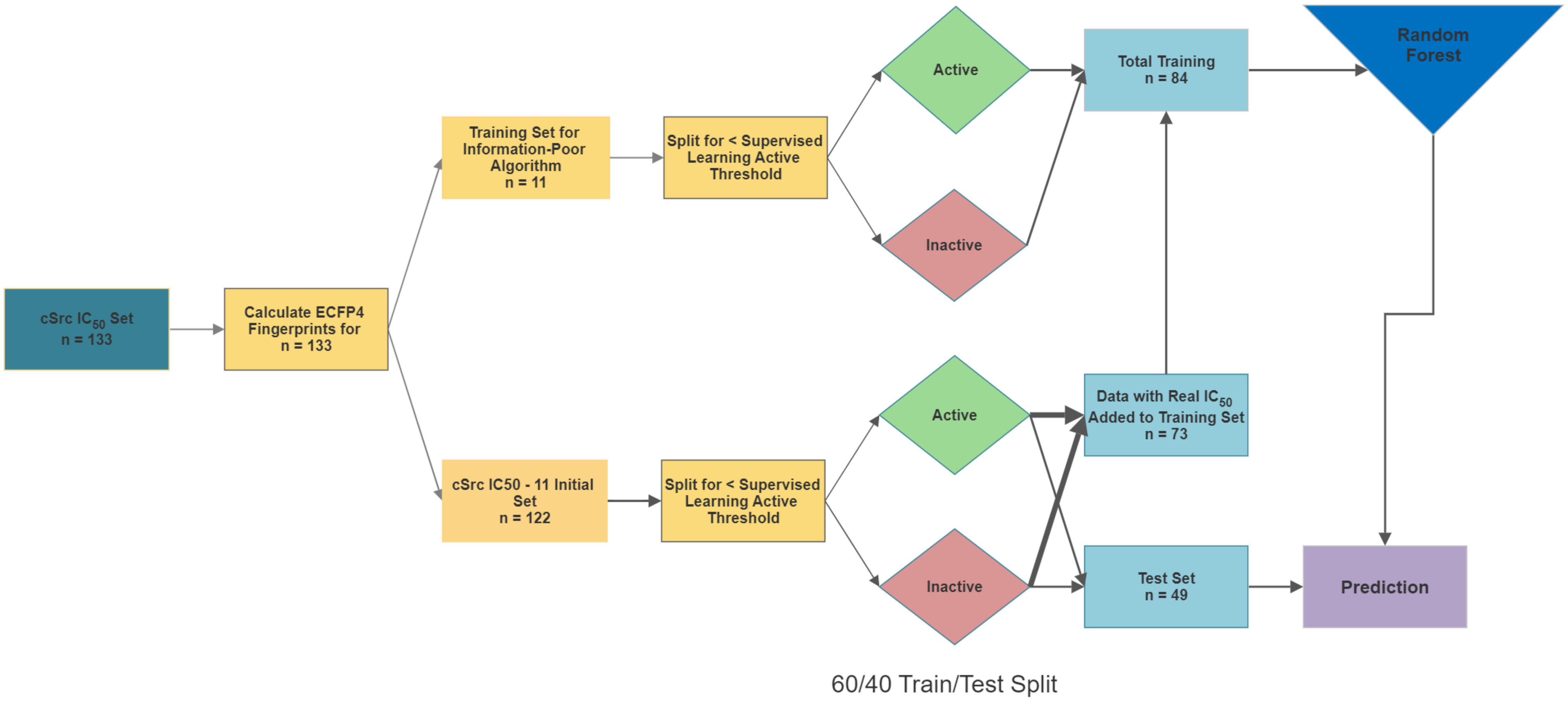
Kaiser, T. M.; Burger, P. B., *unpublished*

ML Experimental Design Diagrams



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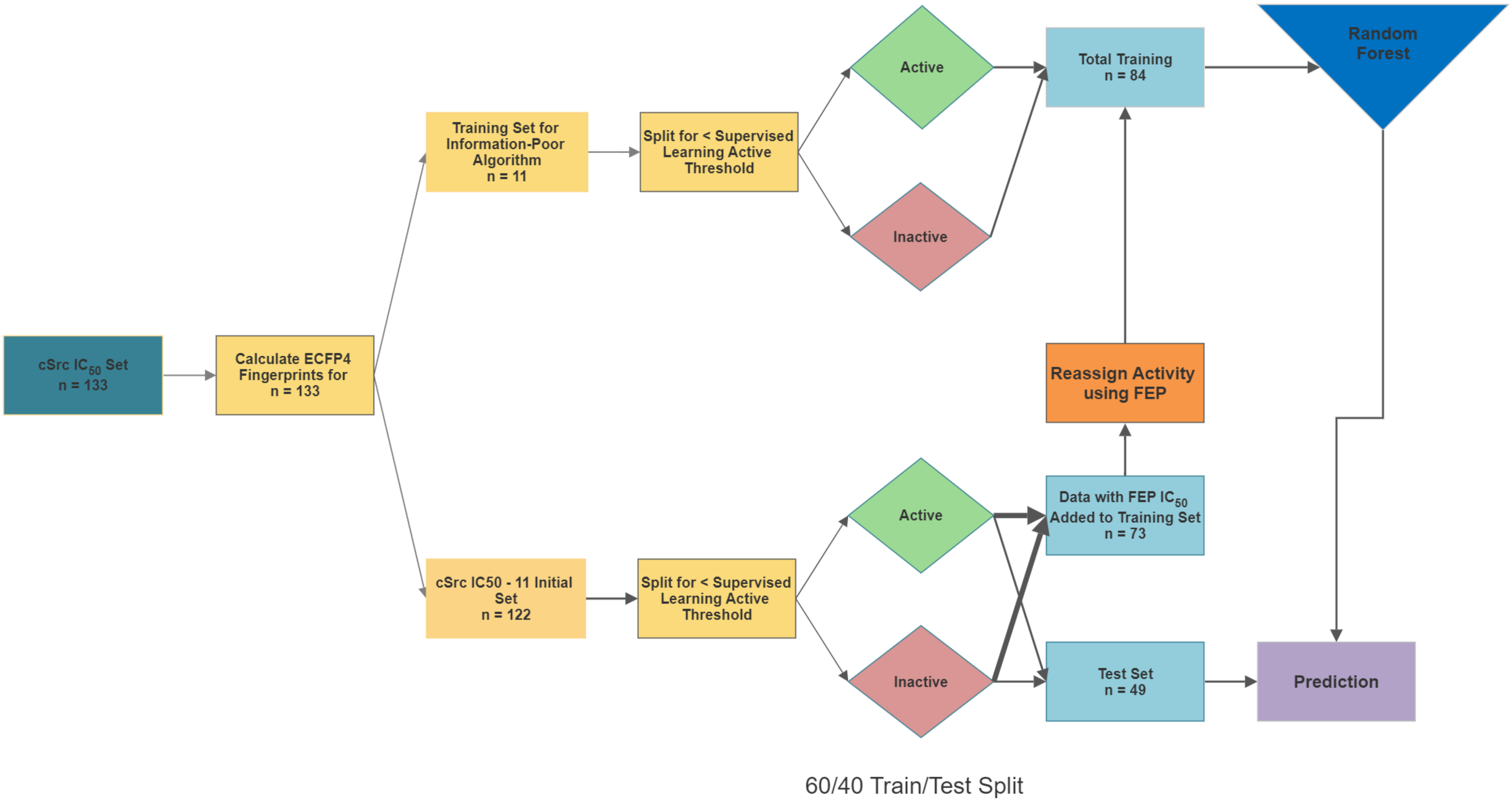
Kaiser, T. M.; Burger, P. B., *unpublished*

ML Experimental Design Diagrams



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Kaiser, T. M.; Burger, P. B., *unpublished*

ML Experimental Design Table

Algorithm Type	**Random Forest (Tree Conditions: Gini Split Criterion, No Maximum Tree Depth, No Node Size Minimum)**
Number of Trees	1000
Learning Type	Supervised Learning
Point of Run Replication	n = 11/122 partitioning
Number of Replicate Runs	10-fold
Independent Variable	ECFP4
Dependent Variable	Active = (1,0)

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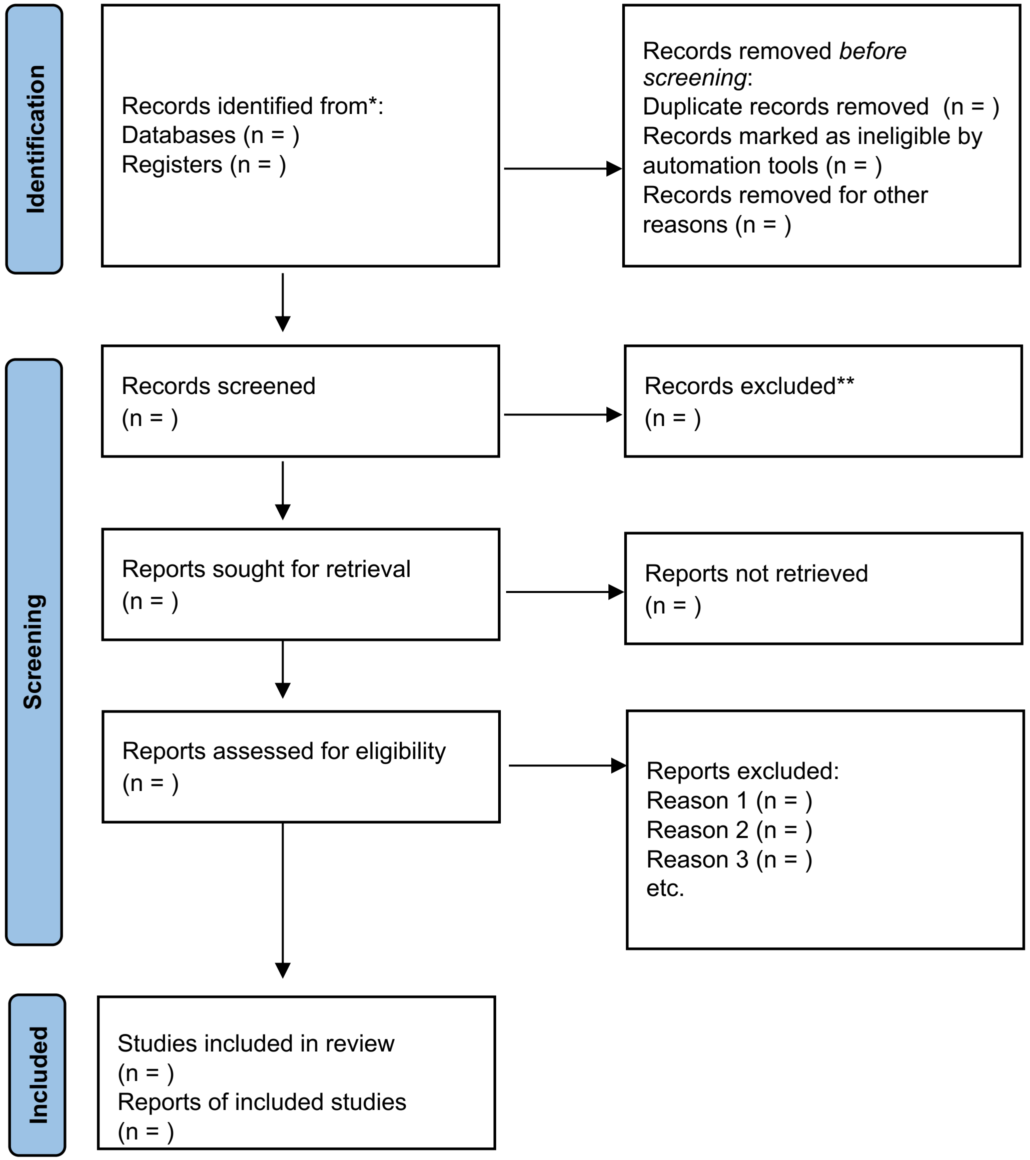
Kaiser, T. M.; Burger, P. B., *unpublished*

Lessons from Systematic Review and Meta-Analysis

- Machine learning involving multiple sets of literature and intra-organizational data is inherently a form of meta-analysis

- Medicine has explored solutions for transparency issues in experimental design for meta-analysis

- The solution most commonly employed is the use of the systematic rigor of inclusion/exclusion of data provided by the **P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses (**PRISMA**)



Page, M. J.; *et al*, *BMJ*, **2021**, *372*, n71

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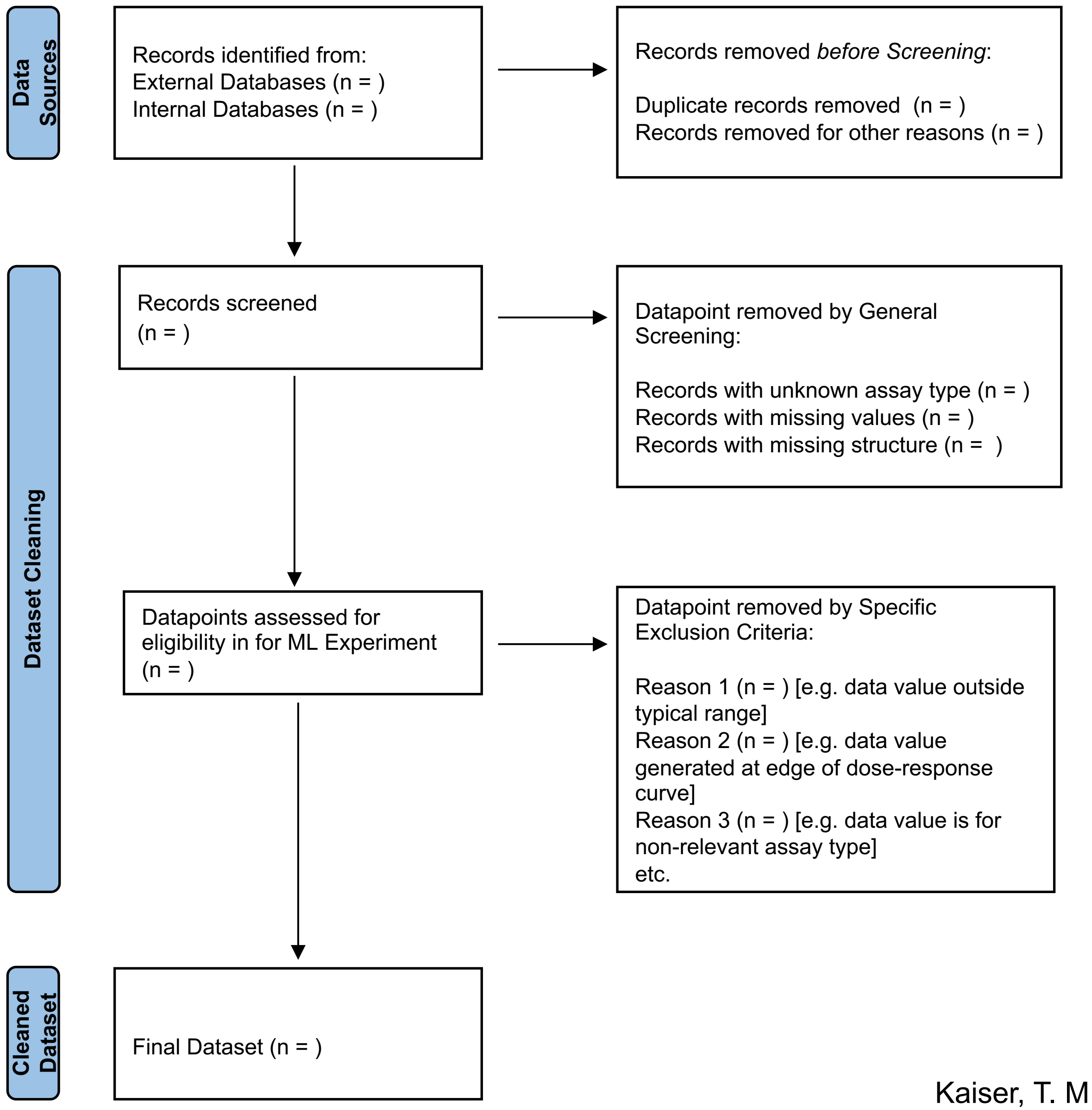
Schematic of Literature Inclusion Criteria for Experiments in Machine Learning - SLICE ML



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Kaiser, T. M.; Burger. P. B., *unpublished*

Conclusions

- We have drawn on other disciplines to generate methods for a rigorous standardization that allows machine learning, chemistry and biology to integrate into a single environment

- Clear diagrams of the machine learning experiment have enabled better translation of chemical or biological information into machine learning systems

- The formalization and transparent representation of the process of data cleaning for ML through **SLICE** ML has enabled more robust applications in our drug development process

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