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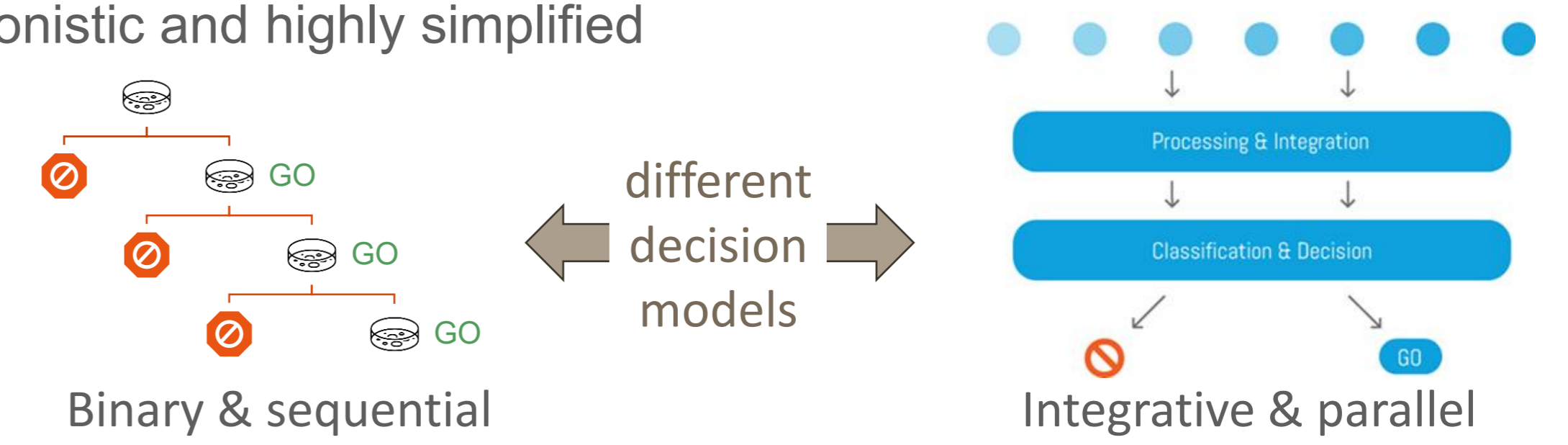
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## Introduction

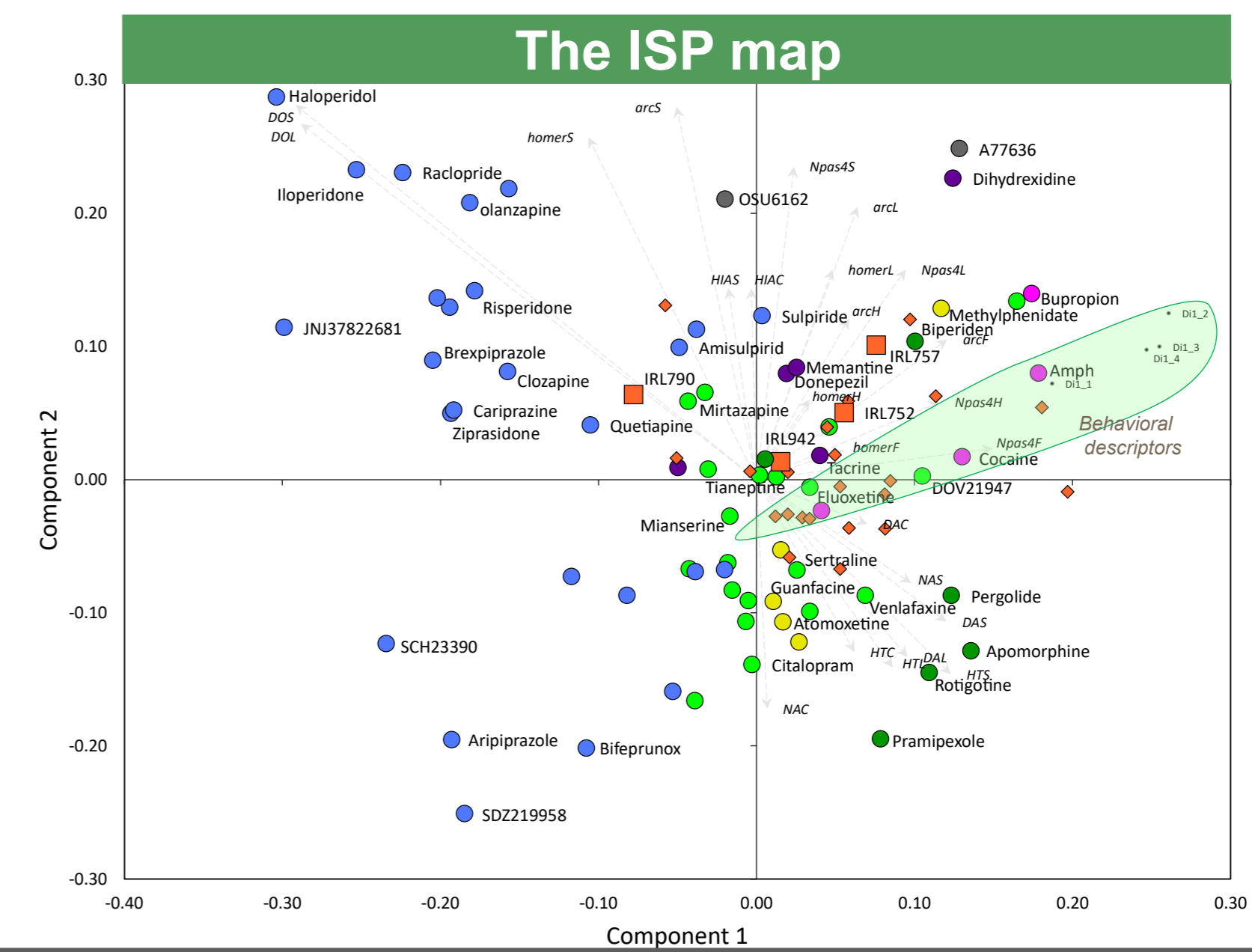
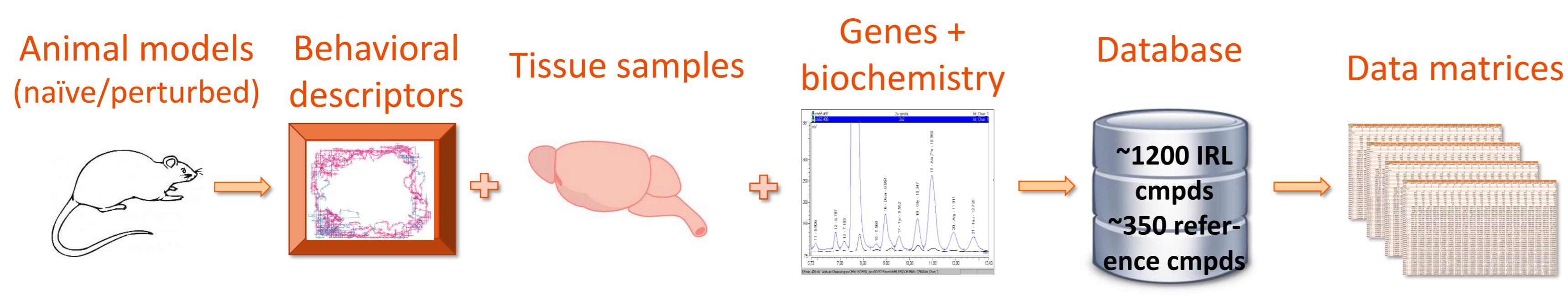
- Conventional target-based DD applies a reductionist approach (single-target optimization in *in vitro* systems with uncertain translational capacity)
- ISP<sup>1</sup> is a DD platform based on comparative *in vivo phenotypic profiling*, targeting neurotransmitter dysregulations in neurodegenerative and psychiatric disorders
- ISP allows clustering of compounds in a multivariate space by their system response profile (neurochemistry, gene expression, motor patterns)
- IRL has five drug candidates in development for PD discovered using ISP
- Here we show recent developments in AI-augmented behavioral analysis as part of ISP

## Conventional vs. ISP based drug design

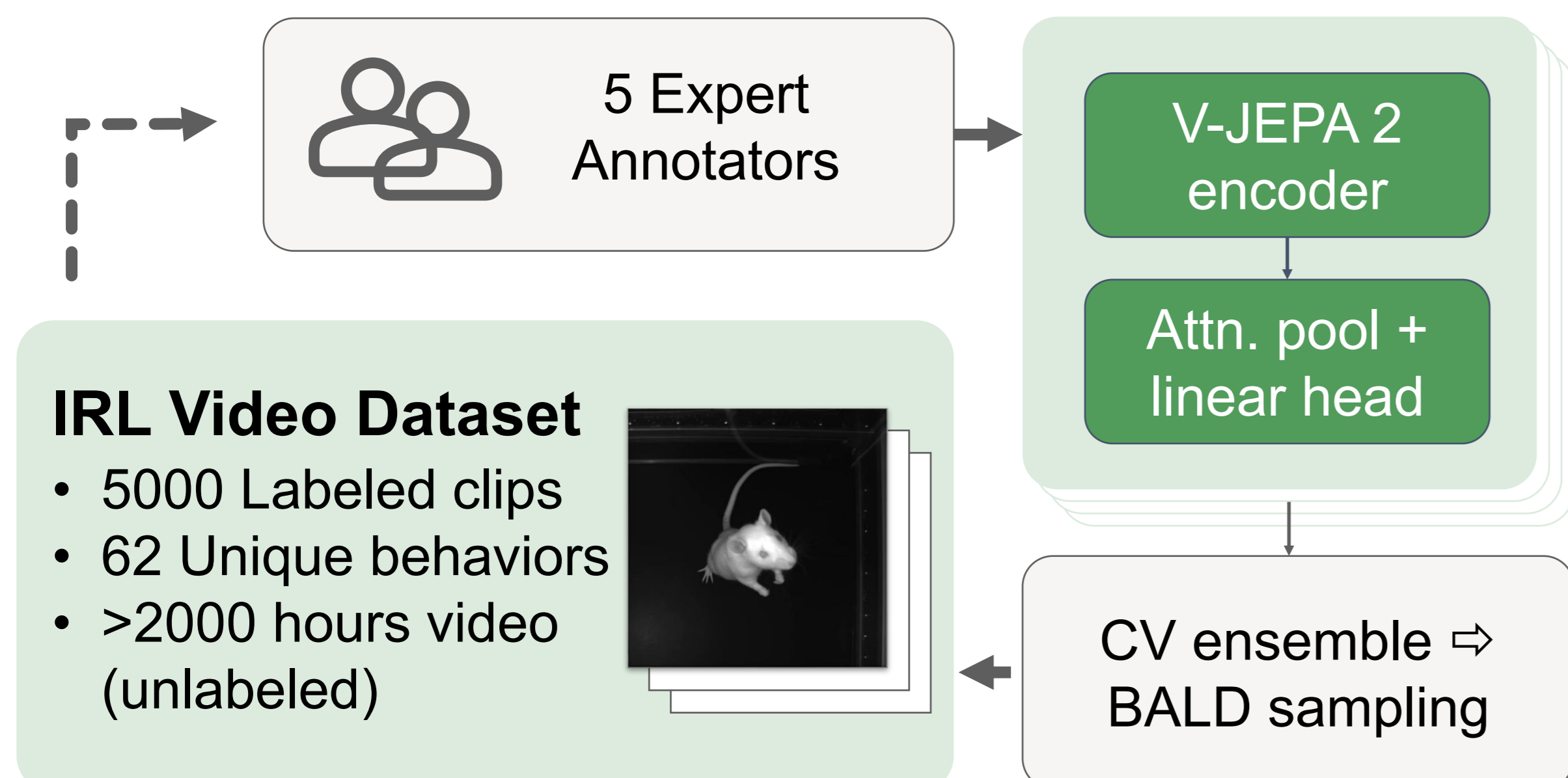
- Strategy & decisions based primarily on *in vitro* data
- Starting points from HTS - often not druggable - optimization not straight-forward
- Safety assessment late, or early with low predictivity
- Reductionistic and highly simplified
- Strategy & decisions based on high-dimensional *in vivo* phenotypic profiles
- Ideas and starting points from basic research, literature, phenotypic data...
- Safety assessment early and predictive
- Holistic – system level response to treatment



## ISP principle

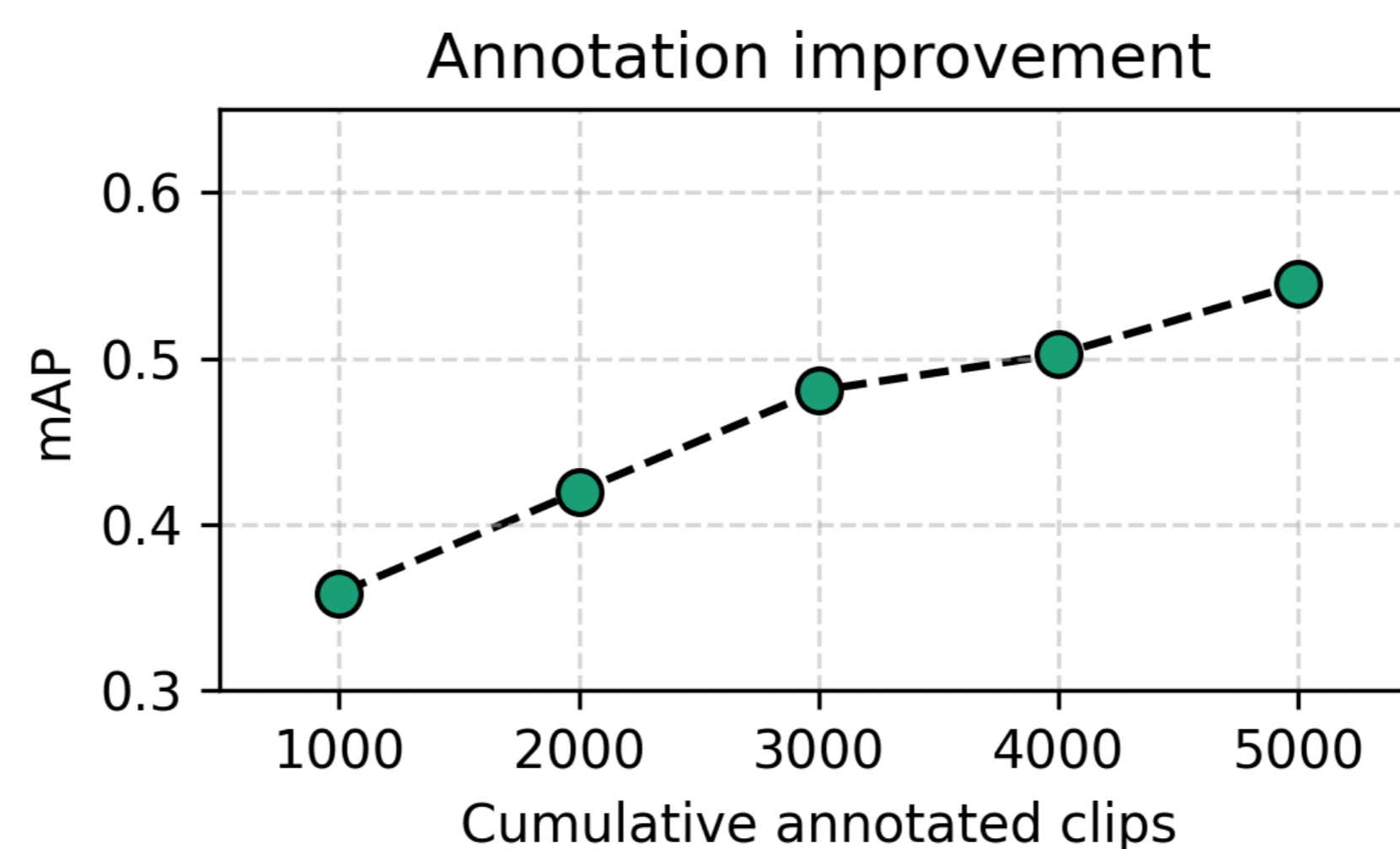


## Behavior classification - Data engine & model performance



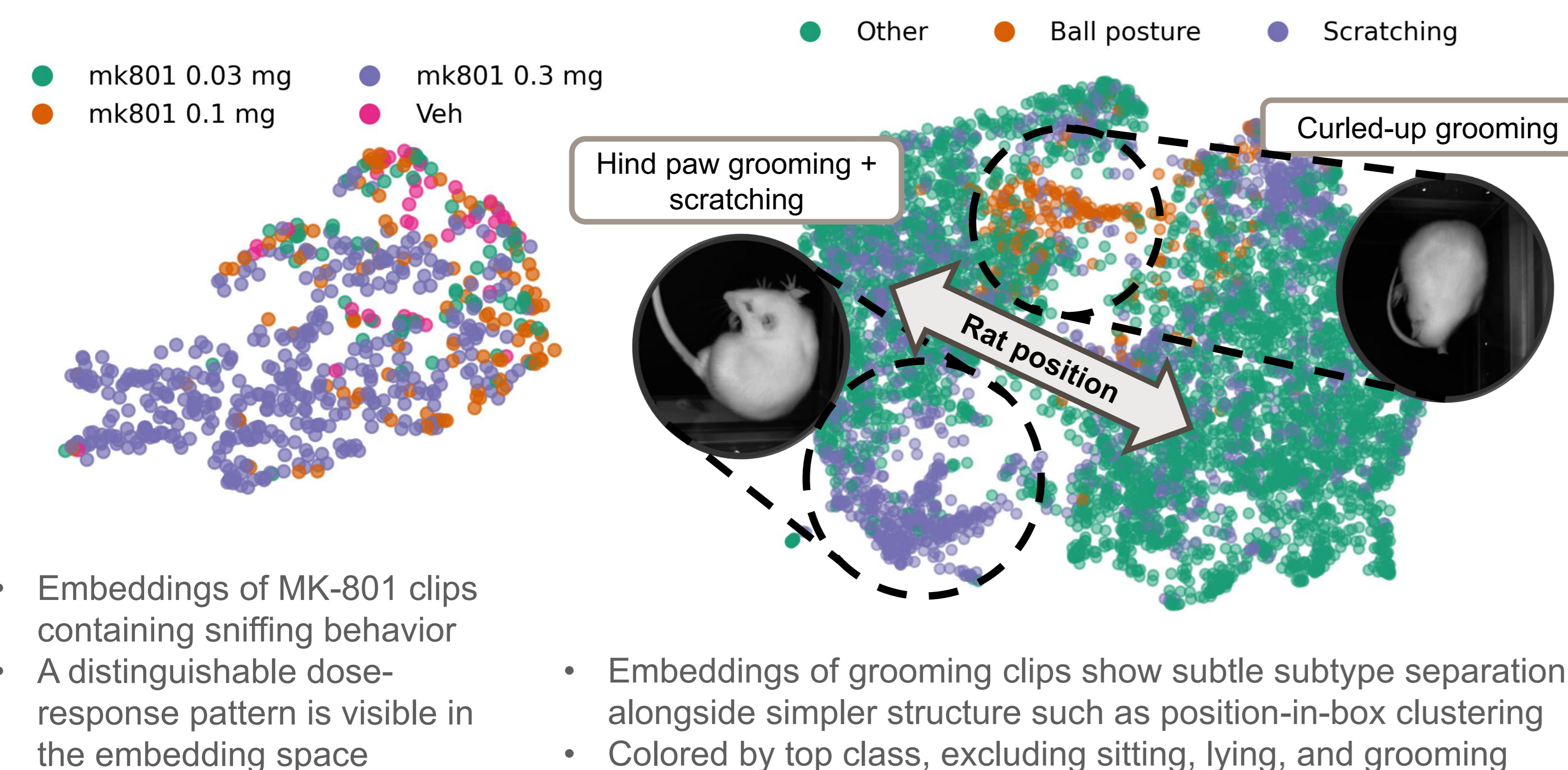
Schematic diagram of the active learning data engine and behavior classification model

- Using an in-house annotation platform to provide expert annotators with **relevant** samples selected with Bayesian disagreement-based active learning (BALD)



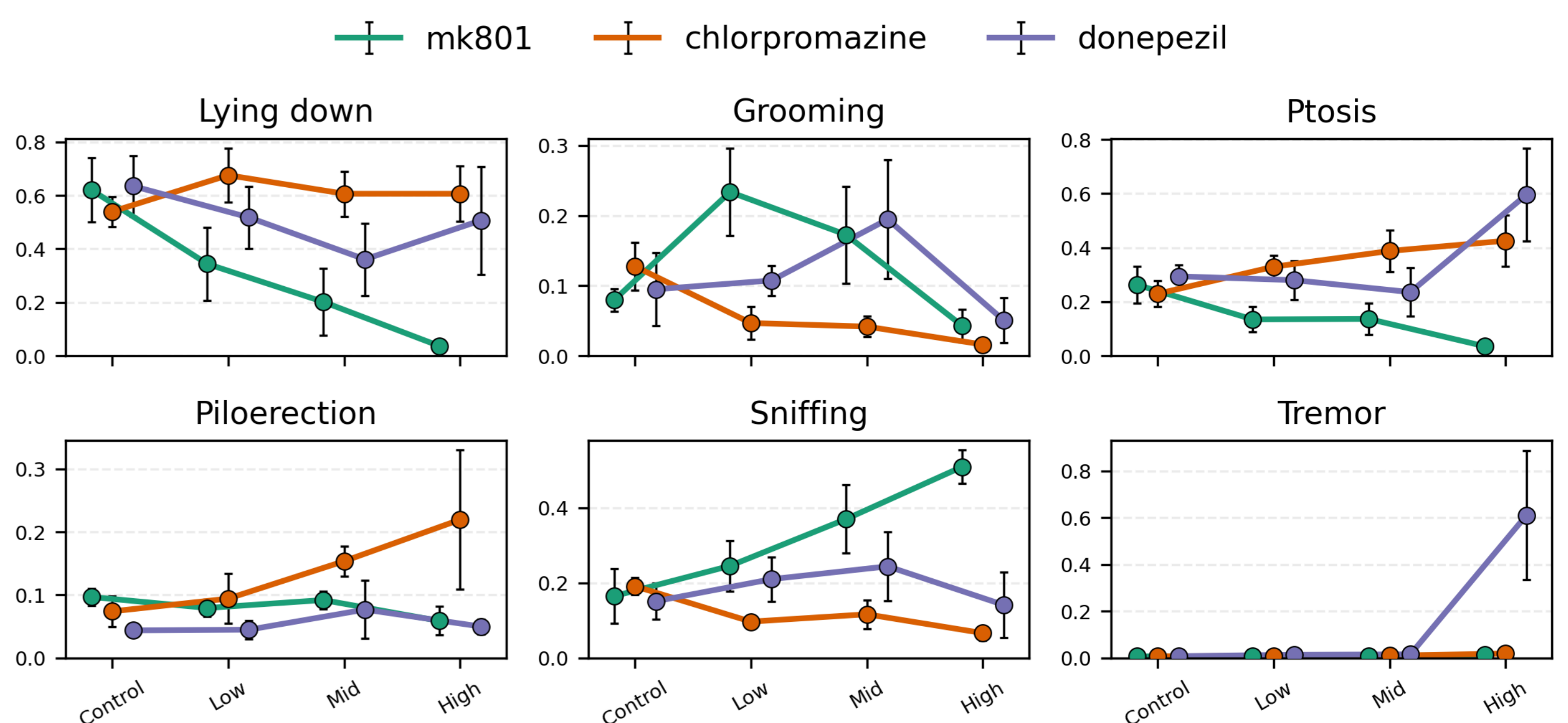
Metric	Model Performance
mAP	0.54
Classes w/ AP > 0.5	38
Classes w/ AP > 0.8	sitting, forepaw treading, abnormal posture, rotation, curled lying (ball posture), twitch, grooming, supported rearing, lying, walking, rearing, tremor, muscle twitching, anomaly
<b>Common-class performance (prevalence &gt; 10%)</b>	
mAP	0.74
<b>Rare-class performance (prevalence ≤ 1%)</b>	
mAP	0.27
Rare classes w/ AP > 0.5	digging, unsupported rearing, porphyria

## Example 1: UMAP visualization of embeddings



- Embeddings of MK-801 clips containing sniffing behavior
- A distinguishable dose-response pattern is visible in the embedding space
- Embeddings of grooming clips show subtle subtype separation alongside simpler structure such as position-in-box clustering
- Colored by top class, excluding sitting, lying, and grooming

## Example 2: Dose-response plot of selected compounds



- Dose-response comparison across a small selection of compounds and behaviors
- Behaviors are measured as mean predicted probability over the experiment

## Video modeling results

- Currently, AI/ML supported video analysis successfully classifies 38+ distinct behaviors
- Data engine with active learning sampling has led to rapid model improvement
- Enables quantification of advanced behavioral traits through-out all experiments
- Video-based behavioral analysis complements positional tracking methods, enabling an increased precision in ISP

## Summary

- The ISP approach enables effects-based DD in a multivariate space covering most CNS compound classes with well-known effects in humans
- Major leap in behavioral assessment, strengthening overall phenotyping and predictive performance in DD
- ISP enables discovery of druggable and safe first-in-class Candidate Drugs