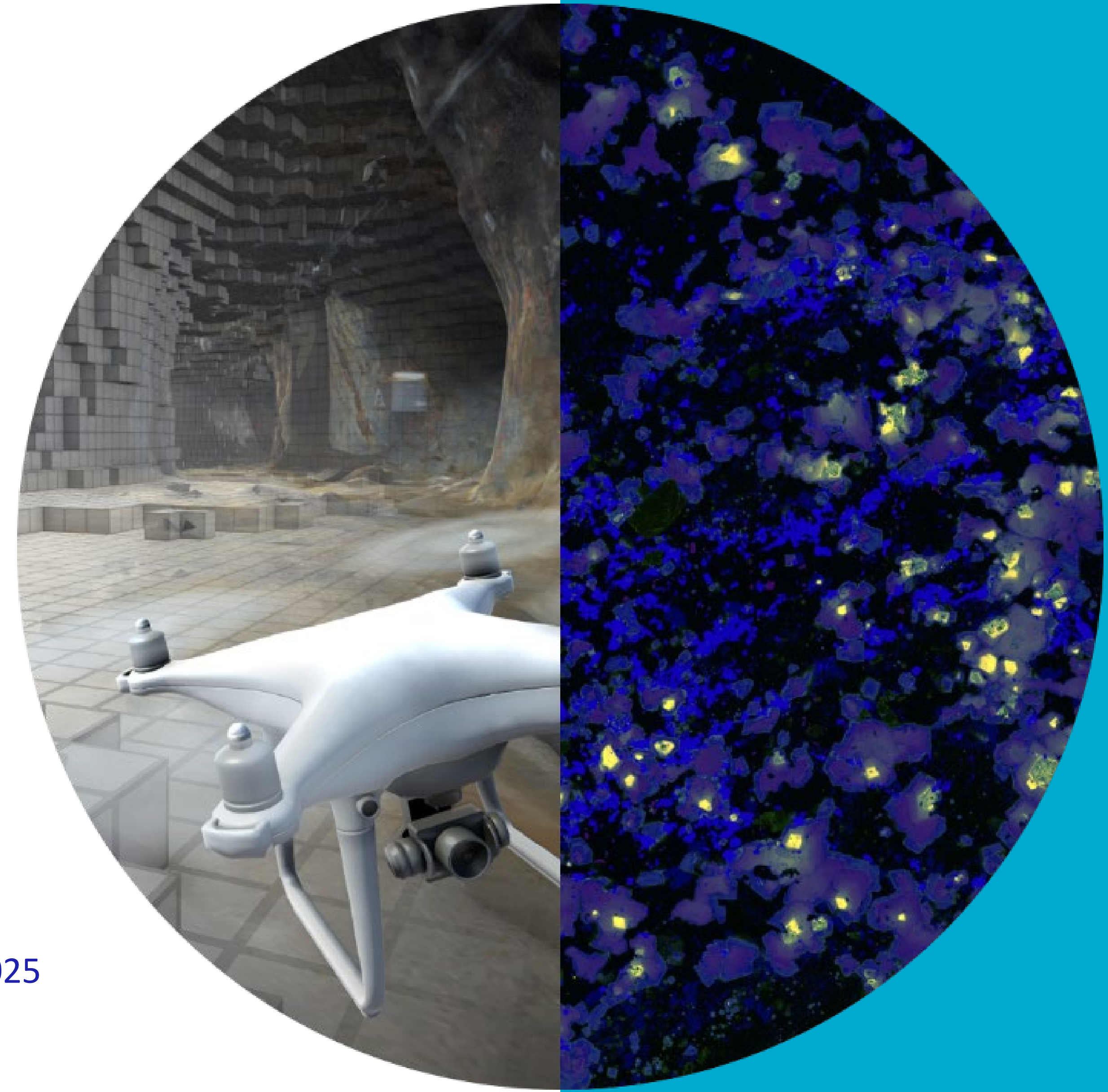
"Doing statistics is like doing crosswords except that one cannot know for sure whether one has found the solution."
– *John Tukey*

The Annals of Statistics
2002, Vol. 30, No. 6, 1535–1575

JOHN W. TUKEY: HIS LIFE AND PROFESSIONAL CONTRIBUTIONS[1]

BY DAVID R. BRILLINGER



On Finding Good Experiments (in life science)

Cheng Soon Ong,
Data61 and ANU
25 November 2025

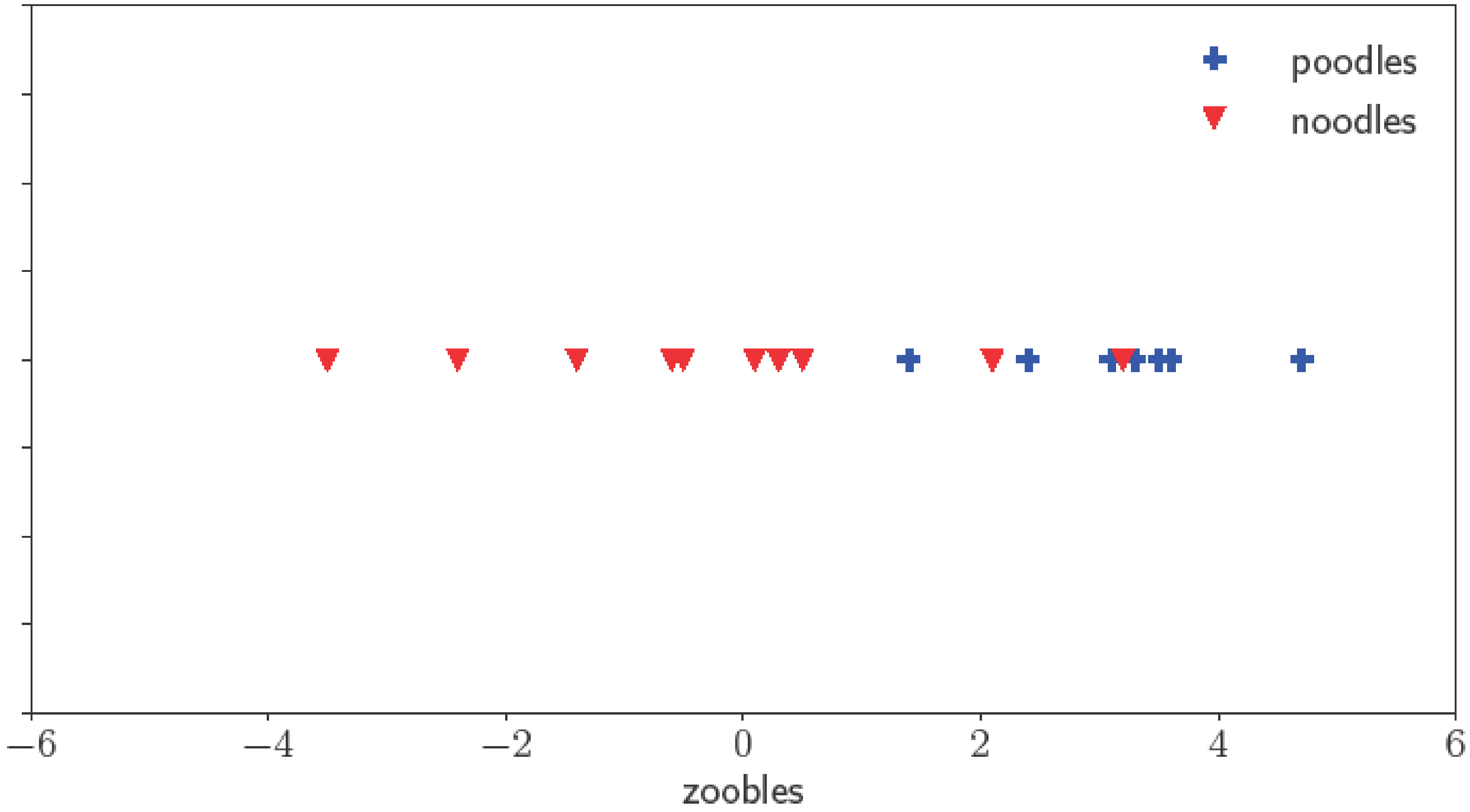
Biometrics in the Bush Capital 2025
International Biometric Society

CSIRO

I would like to acknowledge the Ngunnawal people, the traditional custodians whose ancestral lands we're meeting on today, and pay my respect to their Elders past and present.

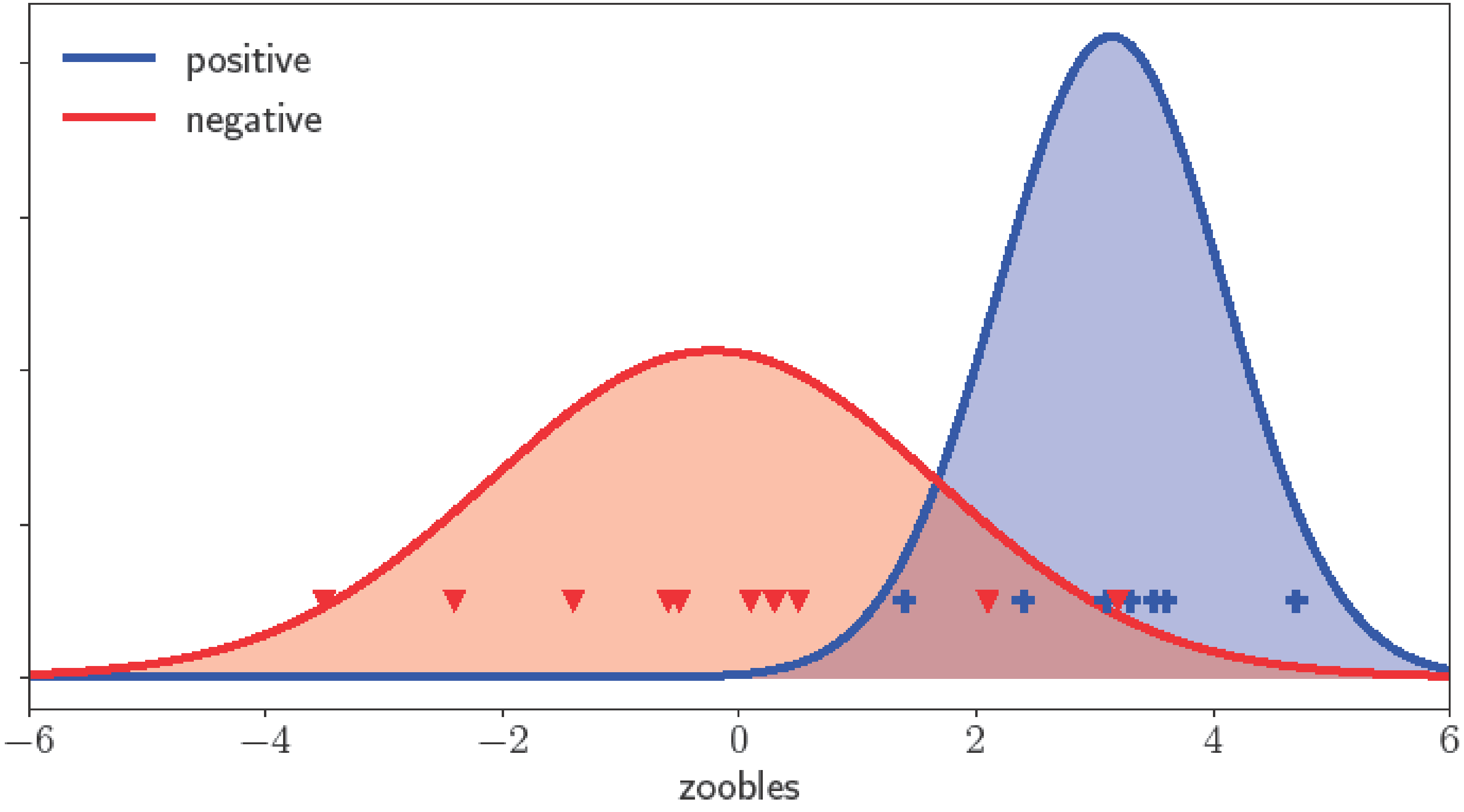
Given some data

- Classify blue plus vs red triangles, based on features



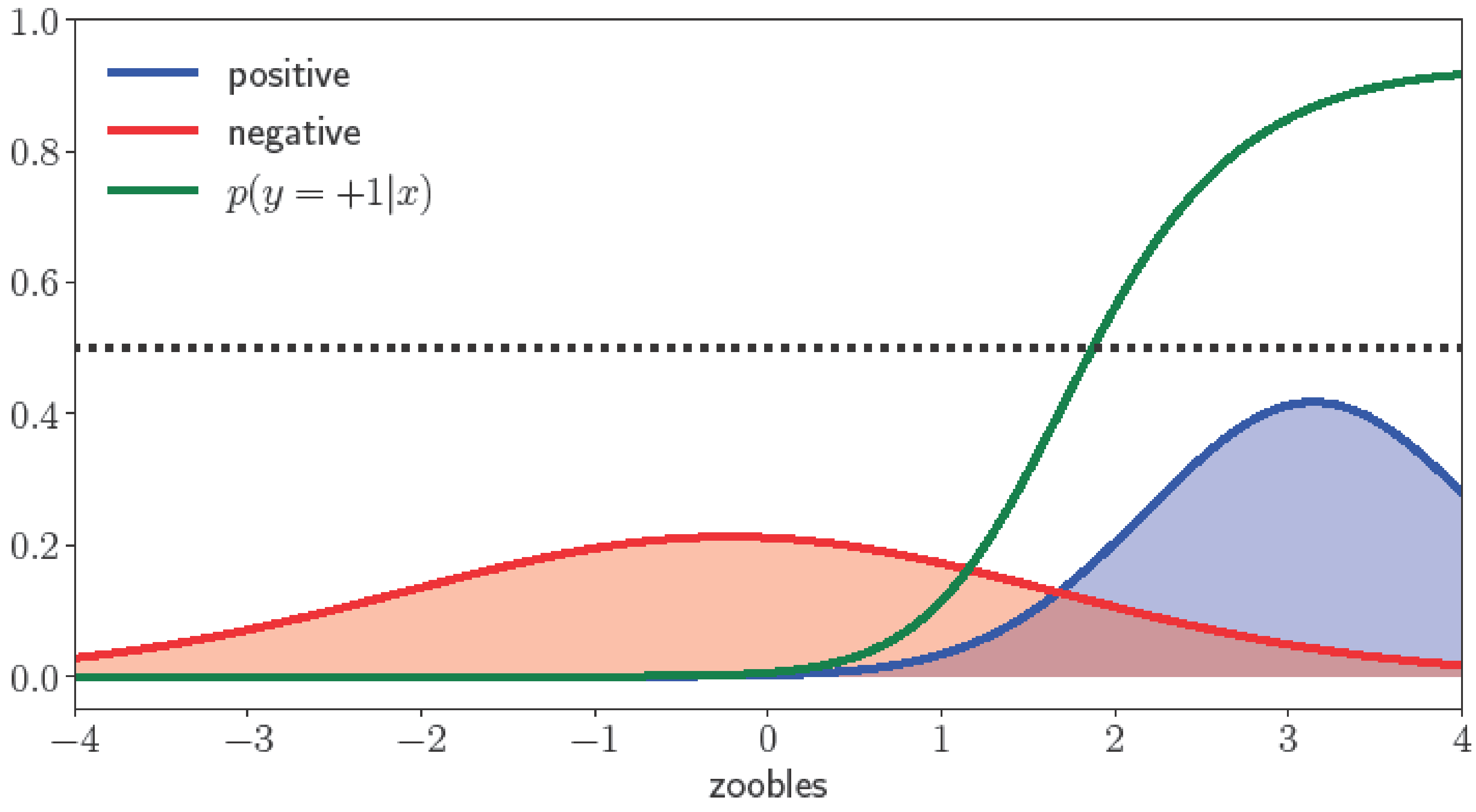
Fit a model to data

- Estimate a Gaussian for each class conditional



Build a classifier

- Compute the posterior probability of blue plus



What is machine learning?

- Mostly about prediction
  - Examples/covariates/features
  - Labels/annotations/target variables

$$x_1, \ldots, x_n \sim \mathcal{X}$$
$$y_1, \ldots, y_n \sim \mathcal{Y}$$

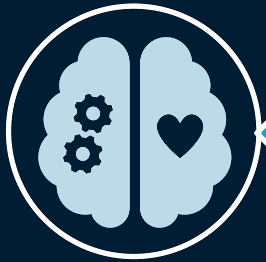
- Predictor

$$f_\theta(x) : \mathcal{X} \to \mathcal{Y}$$

- Estimate the best predictor = training = $\min_\theta \ell(f_\theta)$ (given loss)

Finding good experiments

What is an **experiment**?

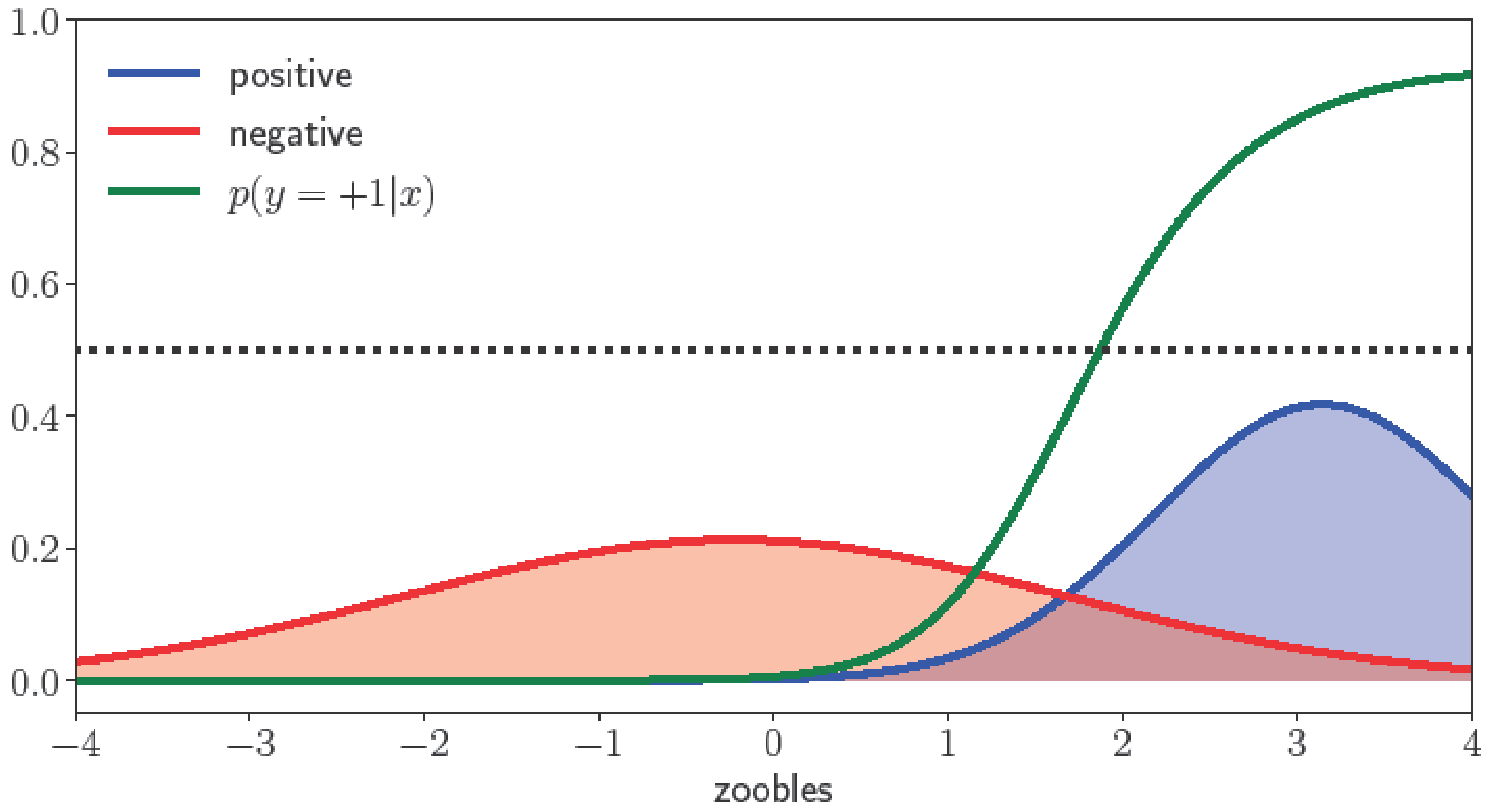


How do we **find** good experiments?

What do we mean by “**good**”?

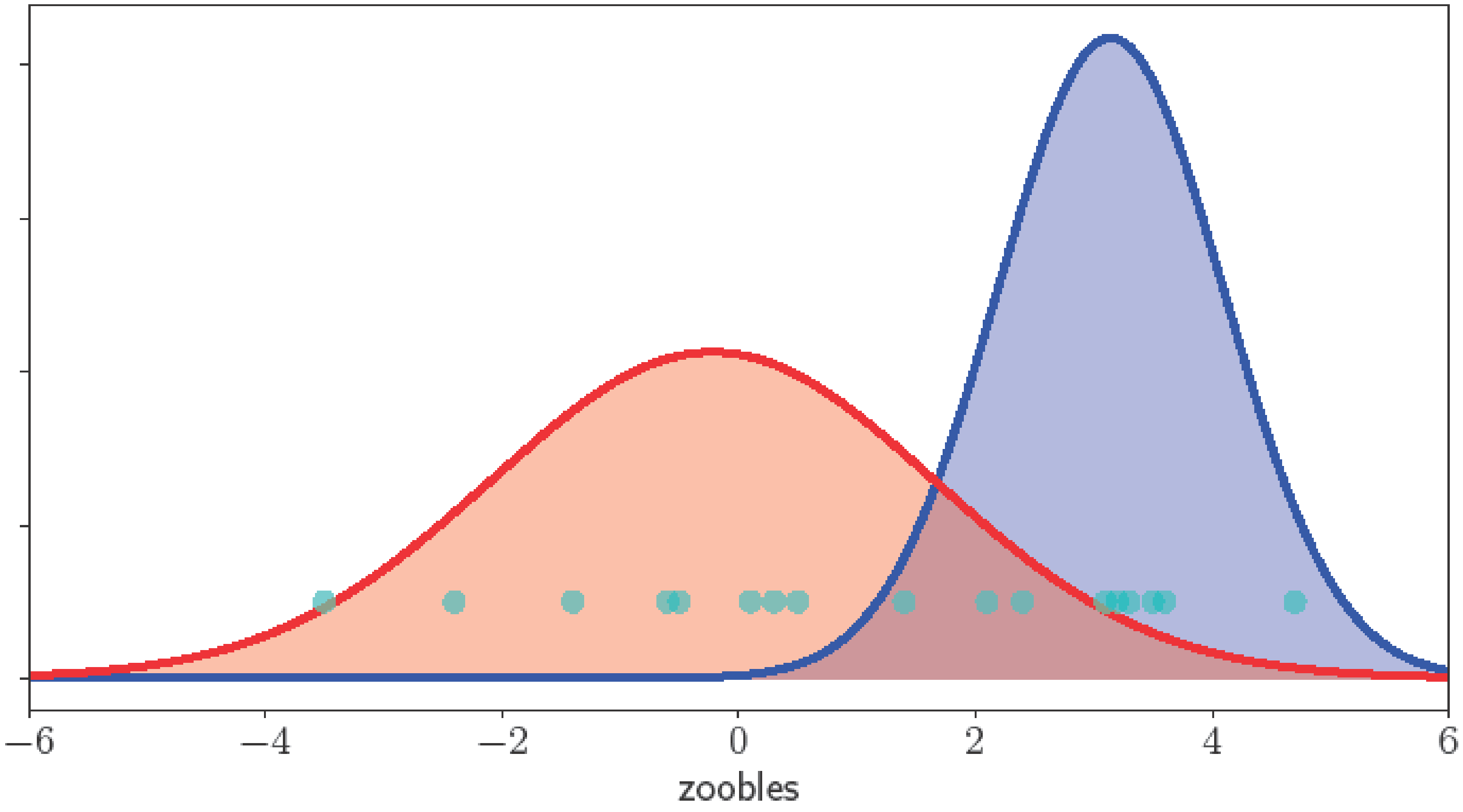
Recall what is a predictor

- Compute the posterior probability of blue plus



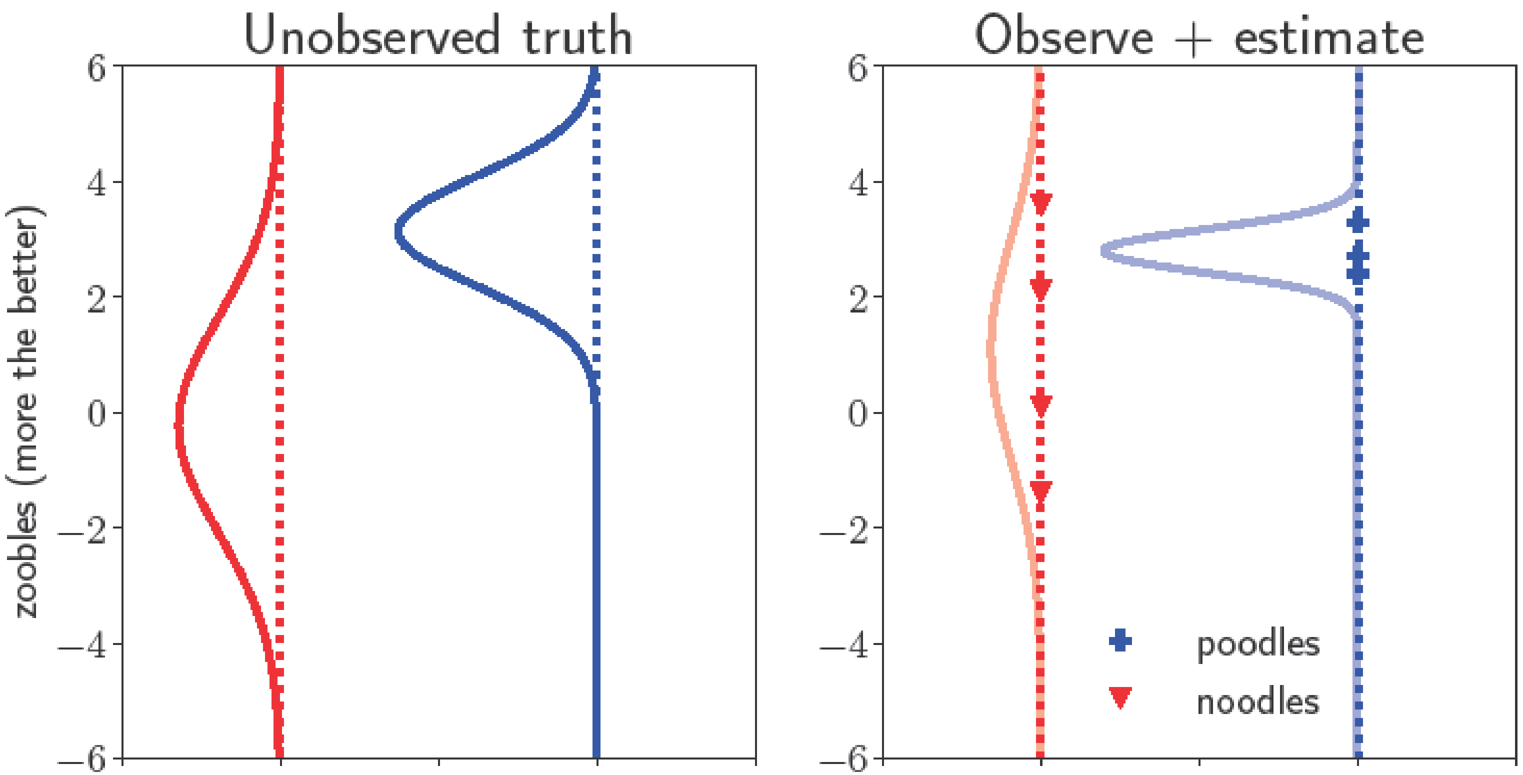
Active Learning

- Want to build a predictor without paying for a lot of labels

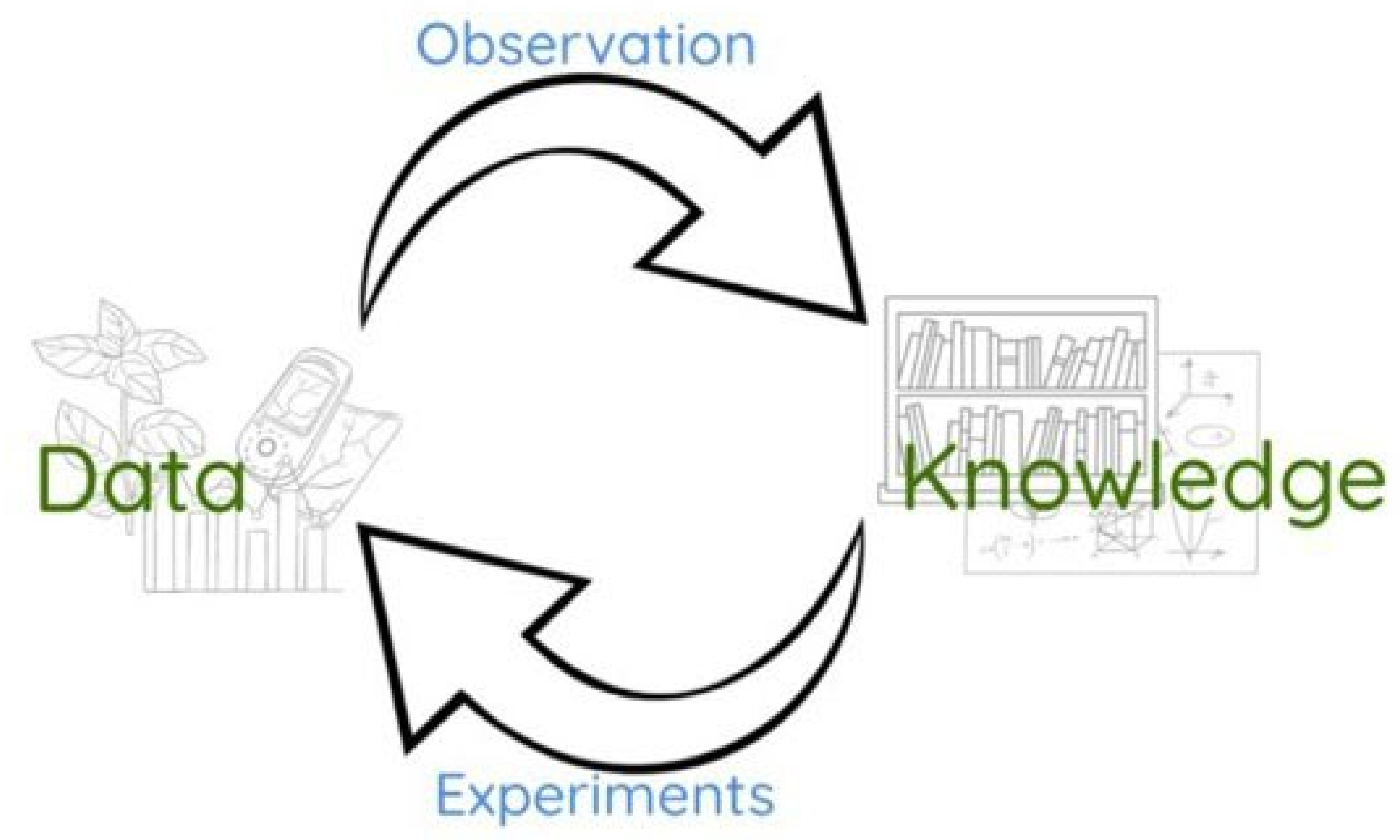


Bandits / Bayesian optimisation

- Want to maximise the outcome of different choices



The scientific method



Using a predictor to adaptively choose data

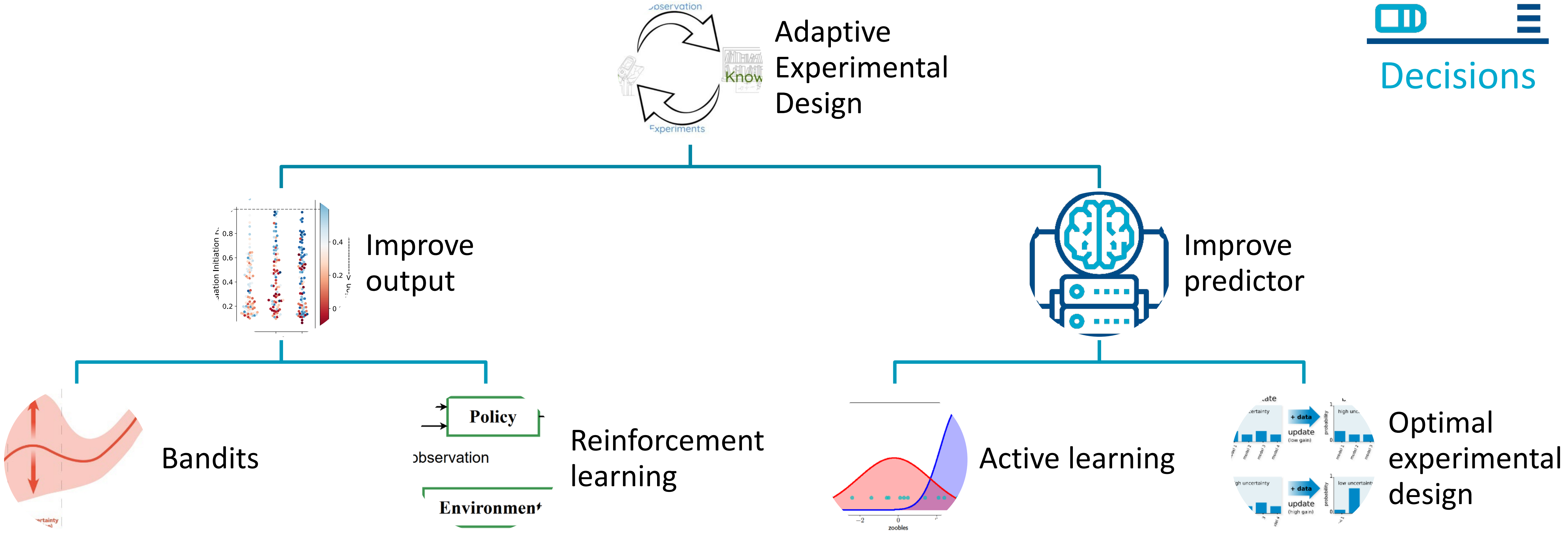
- Given a predictor

$$f_\theta(x) : \mathcal{X} \to \mathcal{Y}$$

- We could collect data (perform an experiment) to:
  - Bandits
    Improve the output of the predictor, that is better $f(x)$
  - Active Learning
    Improve the predictor/model itself, that is better θ

Decision making

Decisions



- https://researchoutreach.org/articles/adaptive-experiments-machine-learning-help-scientific-discovery/
- Chades, Blau, Ong, Machine Learning for Biological Design, Chap 19, Synthetic Biology (2nd ed), 2024

Three messages

Decisions

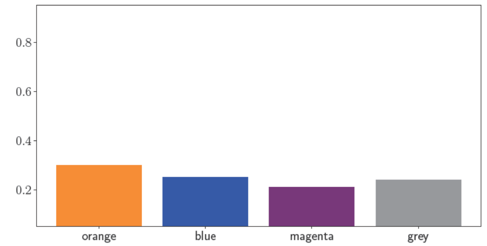
What is an experiment?

How do we find good experiments?

What do we mean by "good"?

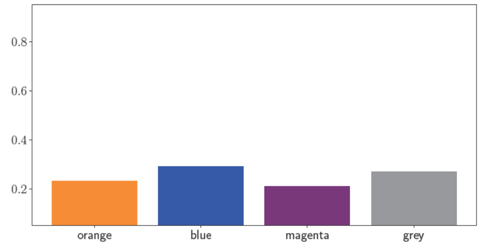
Information gain – ecological modelling

- Find experiments to improve the model's parameters



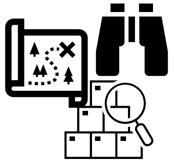
Uninformative experiment

Imagine parameters have only 4 states



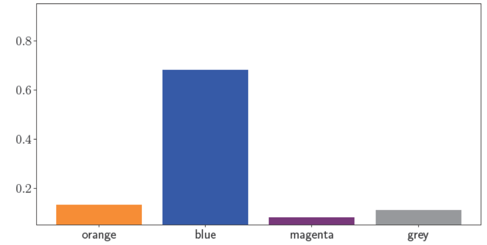
Before – prior

$$p(\theta)$$



Take a sample $\mathbf{D}$

$$p(\theta|\mathbf{D})$$



Informative experiment

$$\mathbb{E}_{\mathbf{D}\sim\mathcal{X},\mathcal{Y}} \quad \mathcal{D}[\quad p(\theta|\mathbf{D}) \quad || \quad p(\theta) \quad]$$

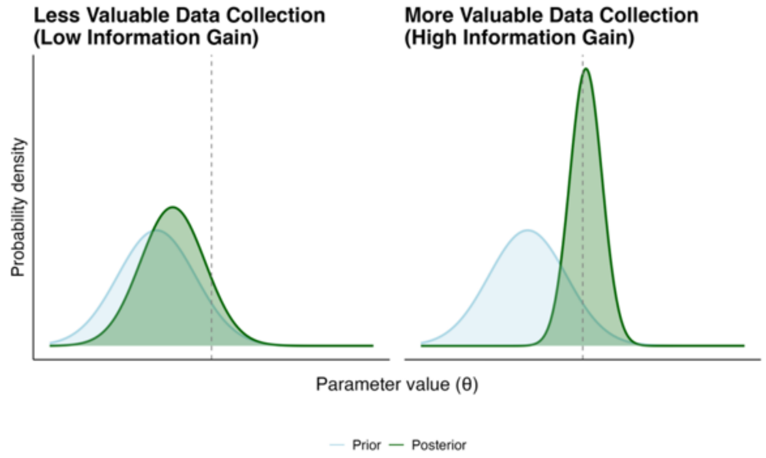
Don't know which data we're going to get

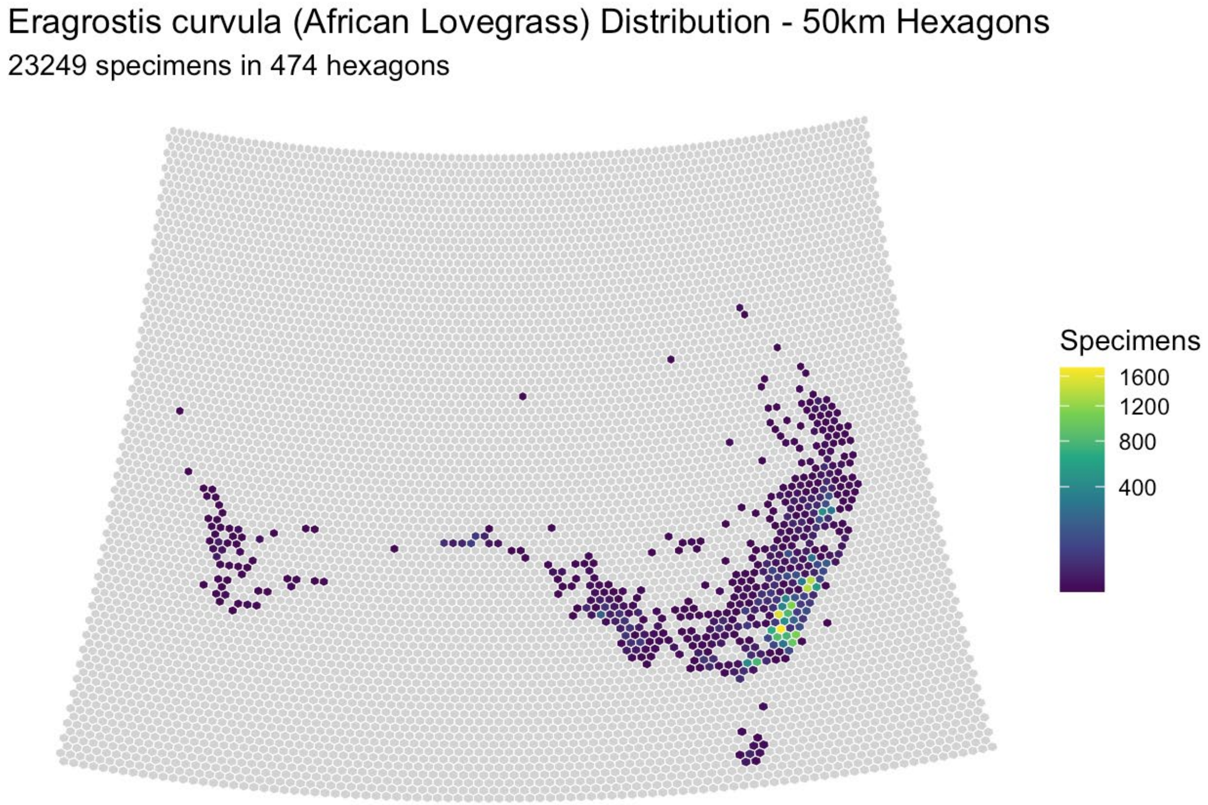
Difference between posterior and prior

UNOFFICIAL

Species distribution model

- African lovegrass
- Beta-Bernoulli presence model



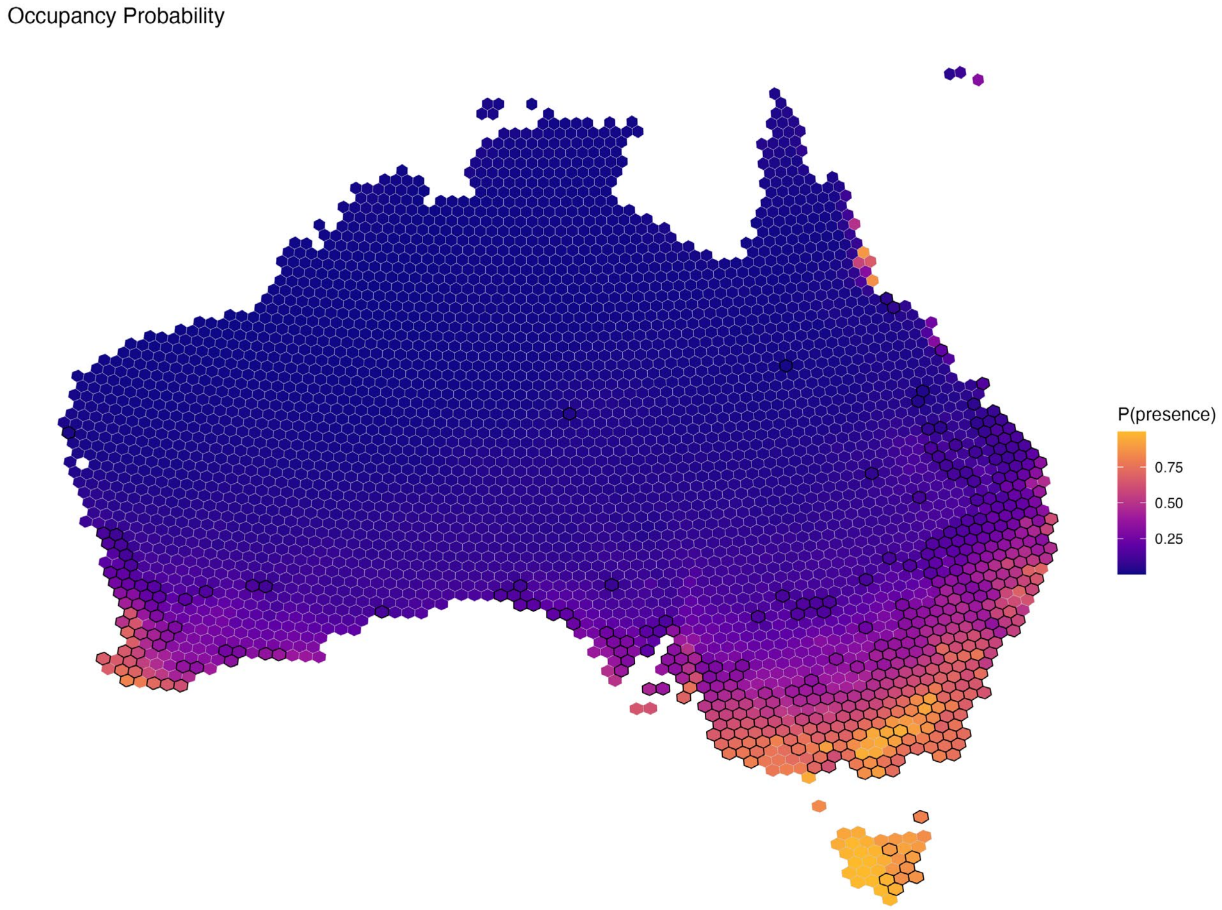


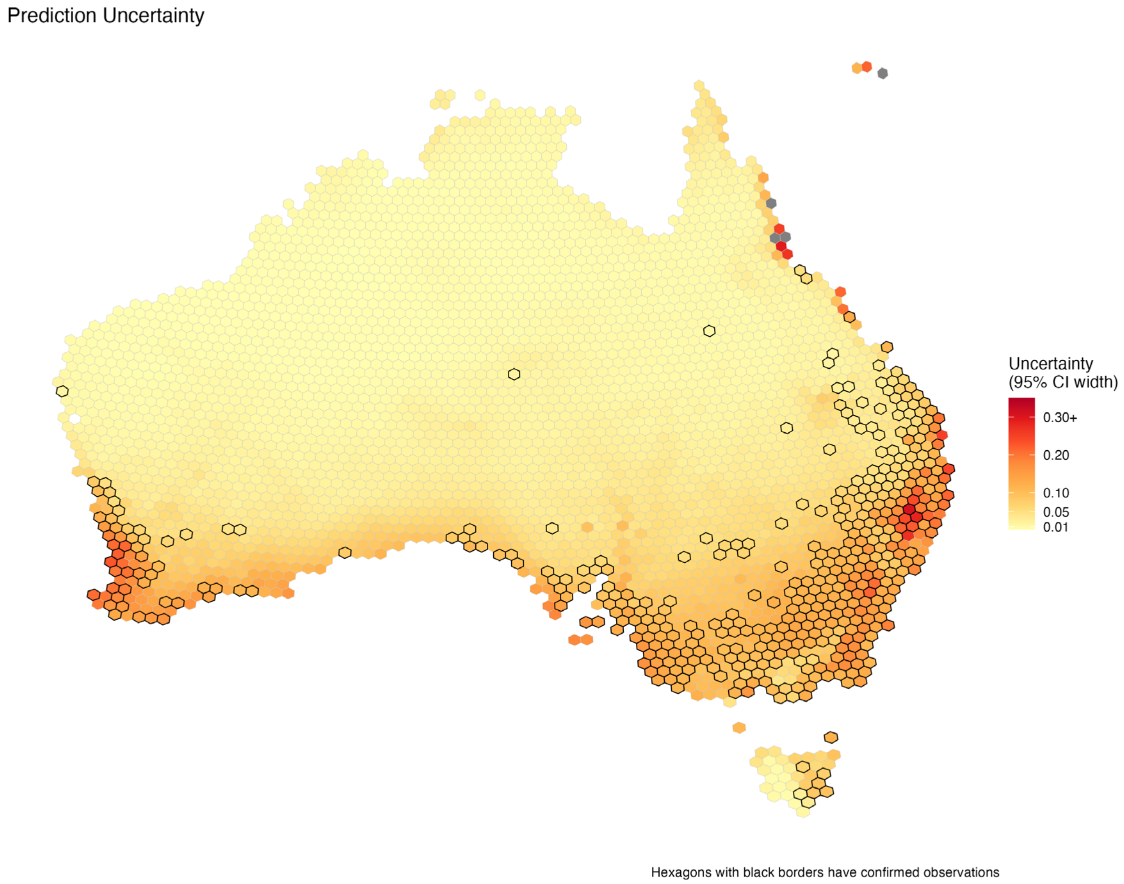
Owen Forbes

Pete Thrall

Andrew Young

Prediction and uncertainty

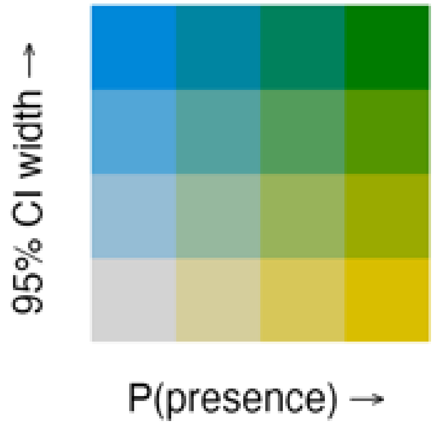




Prediction and uncertainty

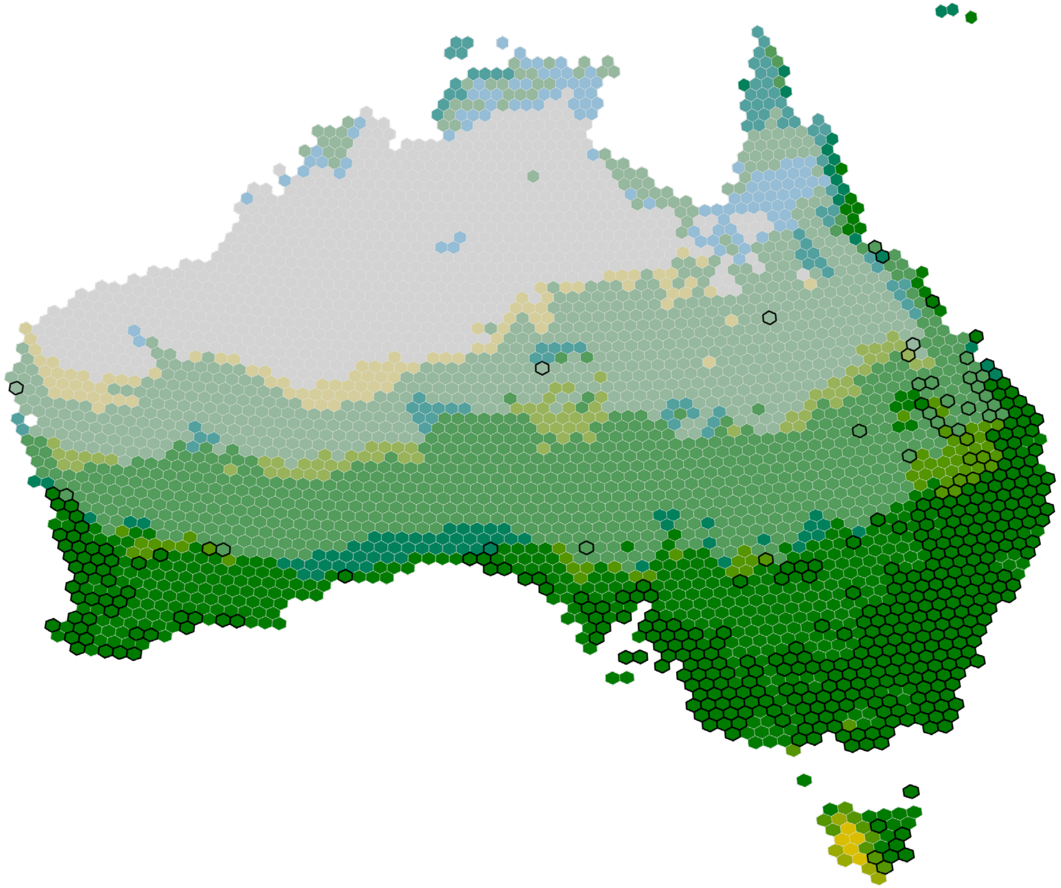
- Unify into one plot

Exploration



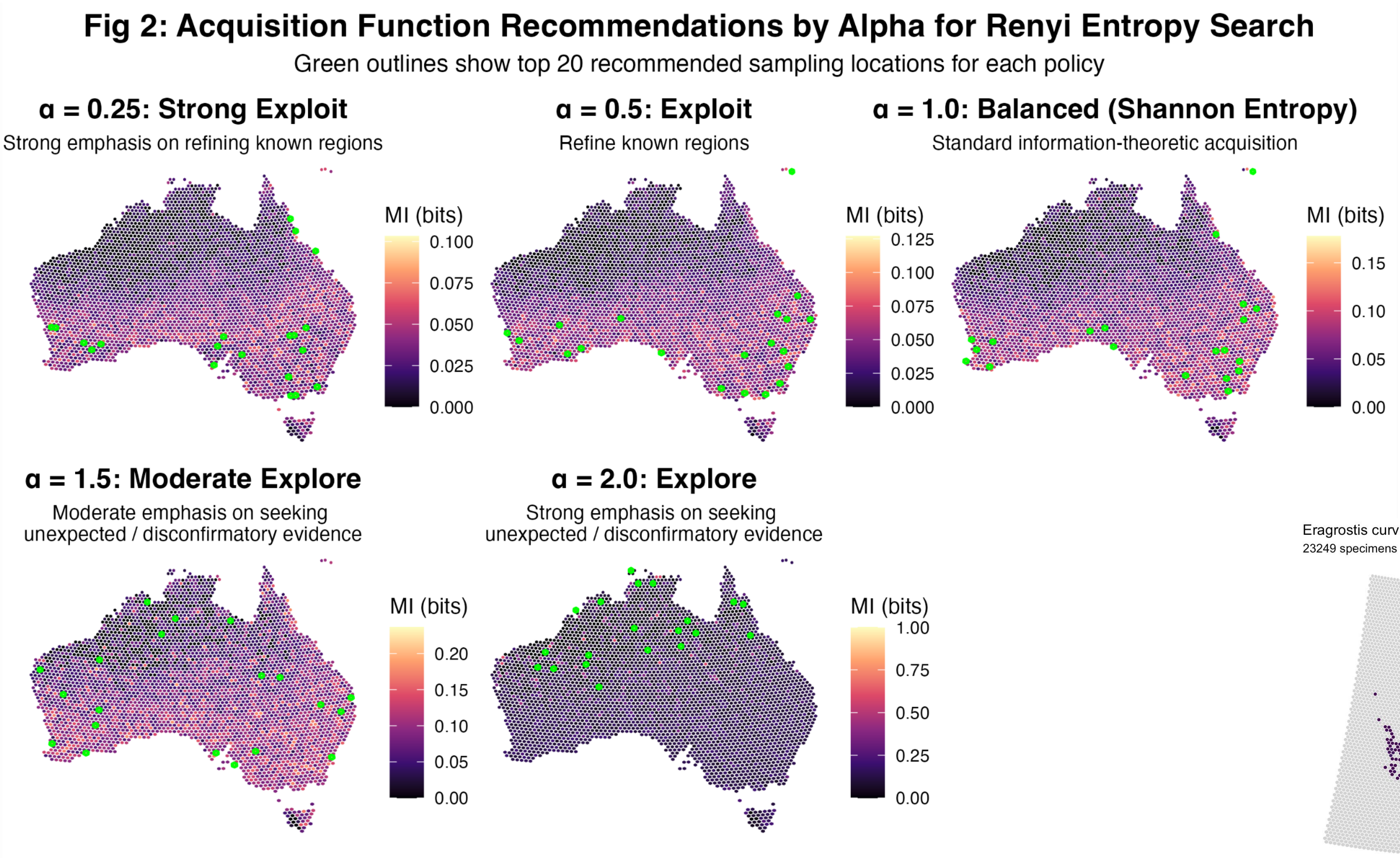
Exploitation

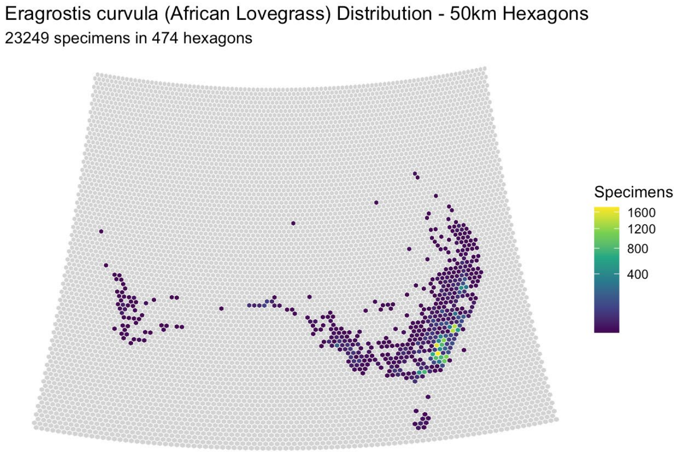
Combined: Estimate + Uncertainty



Vizumap: an R package for visualising uncertainty in spatial data
Journal of Open Source Software, 6(59), 2409, 2021

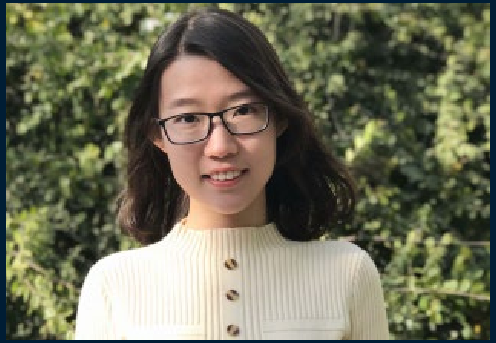
Exploration - exploitation





Higher gene expression

- Ribosomal binding site
- Given 6 letters of a genome, predict gene expression
- Sequence kernel
- Use Bayesian optimisation (GP-BUCB, kriging believer)
- 4 experimental cycles
- 35% stronger than engineered sequence



Mengyan Zhang, Oxford

Huw Hayman Zumpe,
Nourish

ACS Synthetic Biology
Volume 11, Issue 7
July 15, 2022
Pages 2221-2526

ARTICLE

Machine Learning Guided Batched Design of a Bacterial Ribosome Binding Site

View article page

Mengyan Zhang, Maciej Bartosz Holowko, Huw Hayman Zumpe and Cheng Soon Ong

CITE

https://doi.org/10.1021/acssynbio.2c00015

CSIRO's BioFoundry

- **Engineering biology:**
  *is the set of methods for **designing, building, and testing** engineered biological systems*

Hafna Ahmed

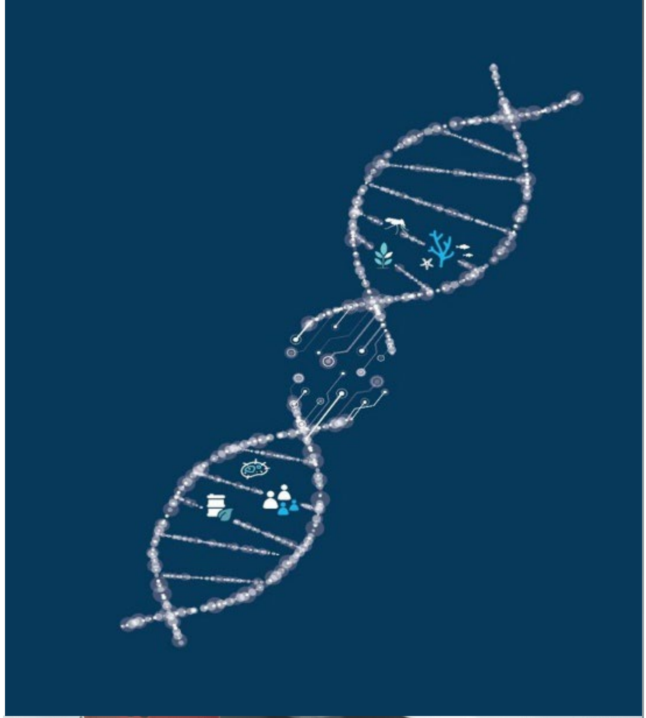
Chie Ishitate

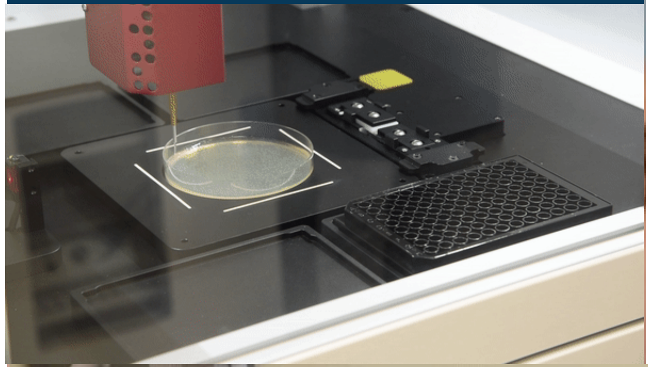
Candice Jones
MPI Marburg

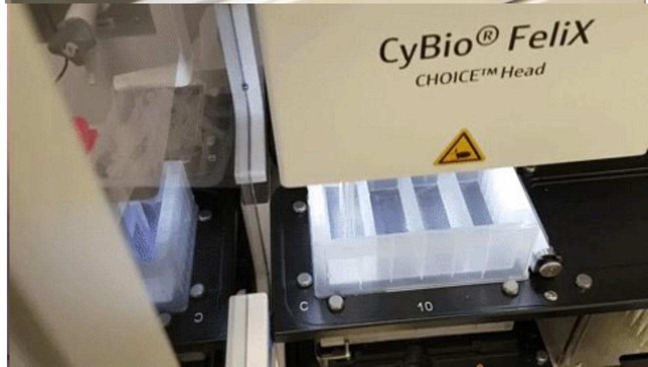
Adrian Marsh

Robert Speight

https://research.csiro.au/aeb







What's the objective?

Design Ribosome Binding Site (RBS) sequences → Optimize the protein expression level.

RBS sequence	Normalized* Protein Expression Level
TTTAAGAGTTATATATACAT	1.58
TTTAAGAATATGCTATACAT	1.42
TTTAAGACTCGGATATACAT	0.14
TTTAAGAGTTTTTTATACAT	2.88

Core part (design space): 4^6 = 4096 possibilities in total

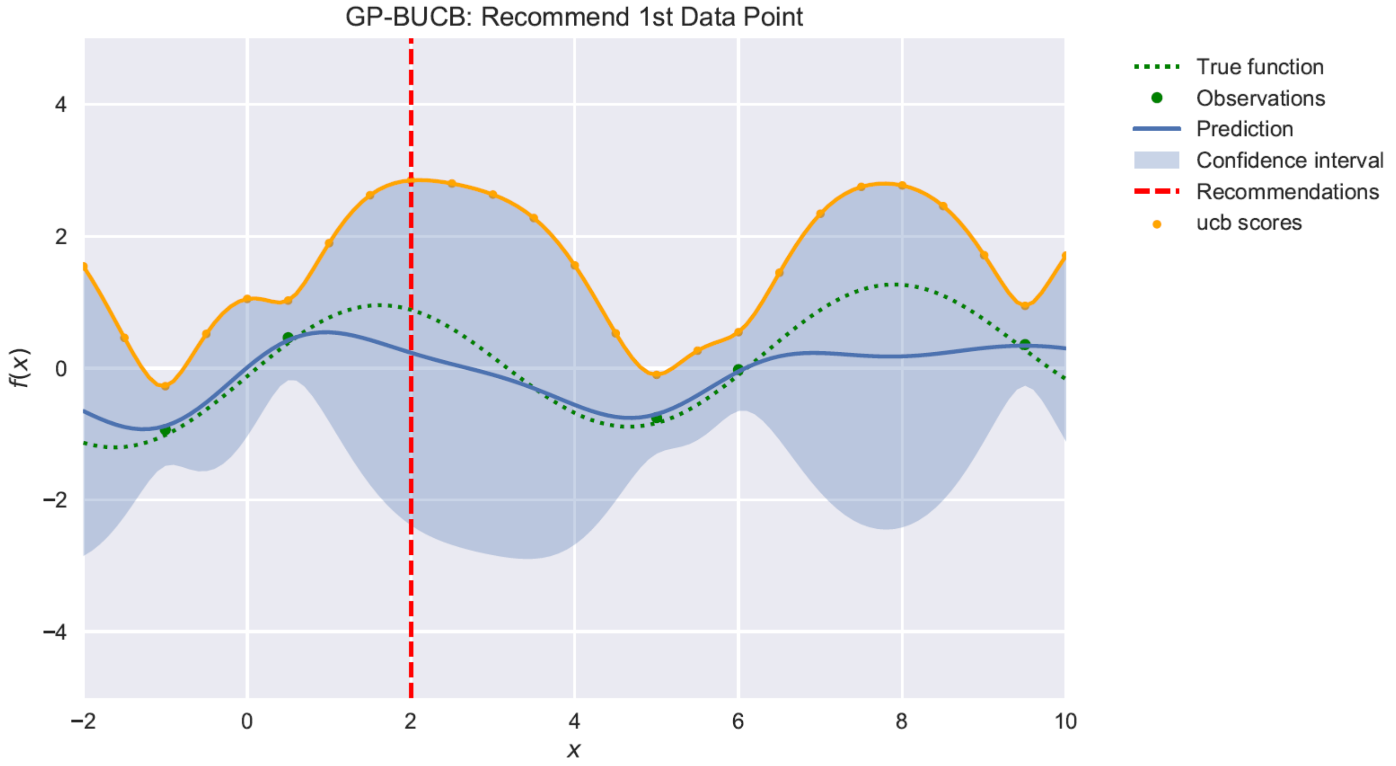
UNOFFICIAL

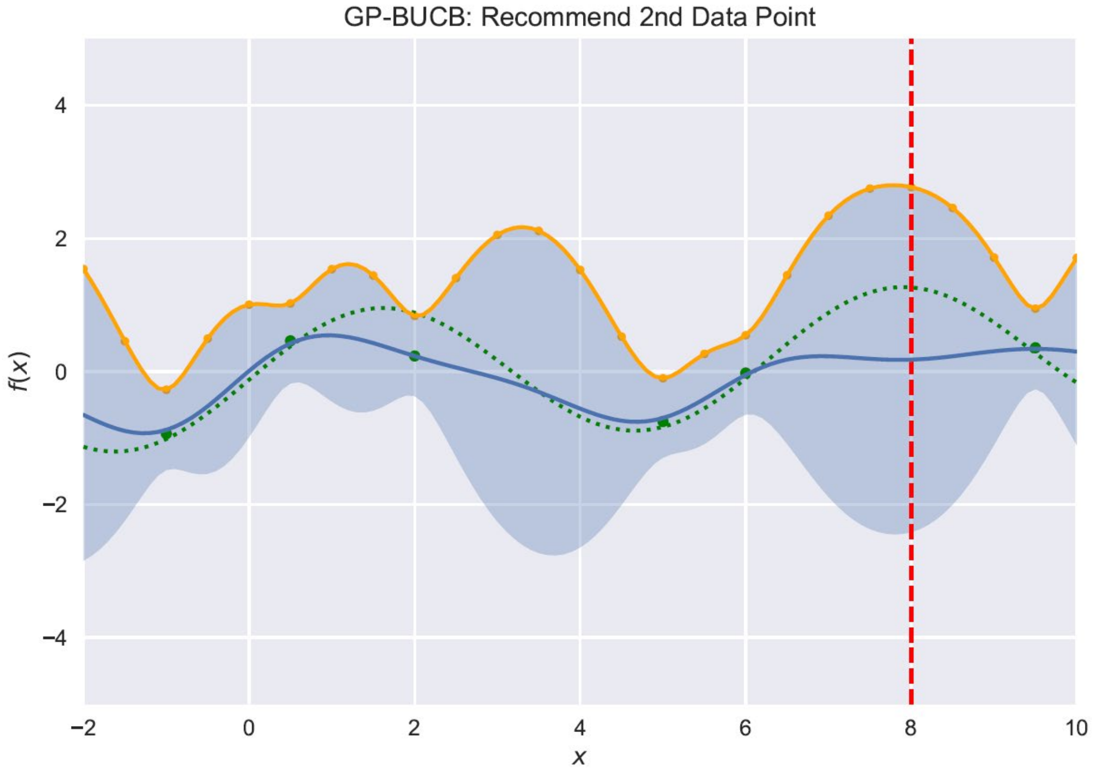
* zero mean and unit variance normalization $z = \frac{x-\mu}{\sigma}$

Upper confidence bound

A particular bandit algorithm

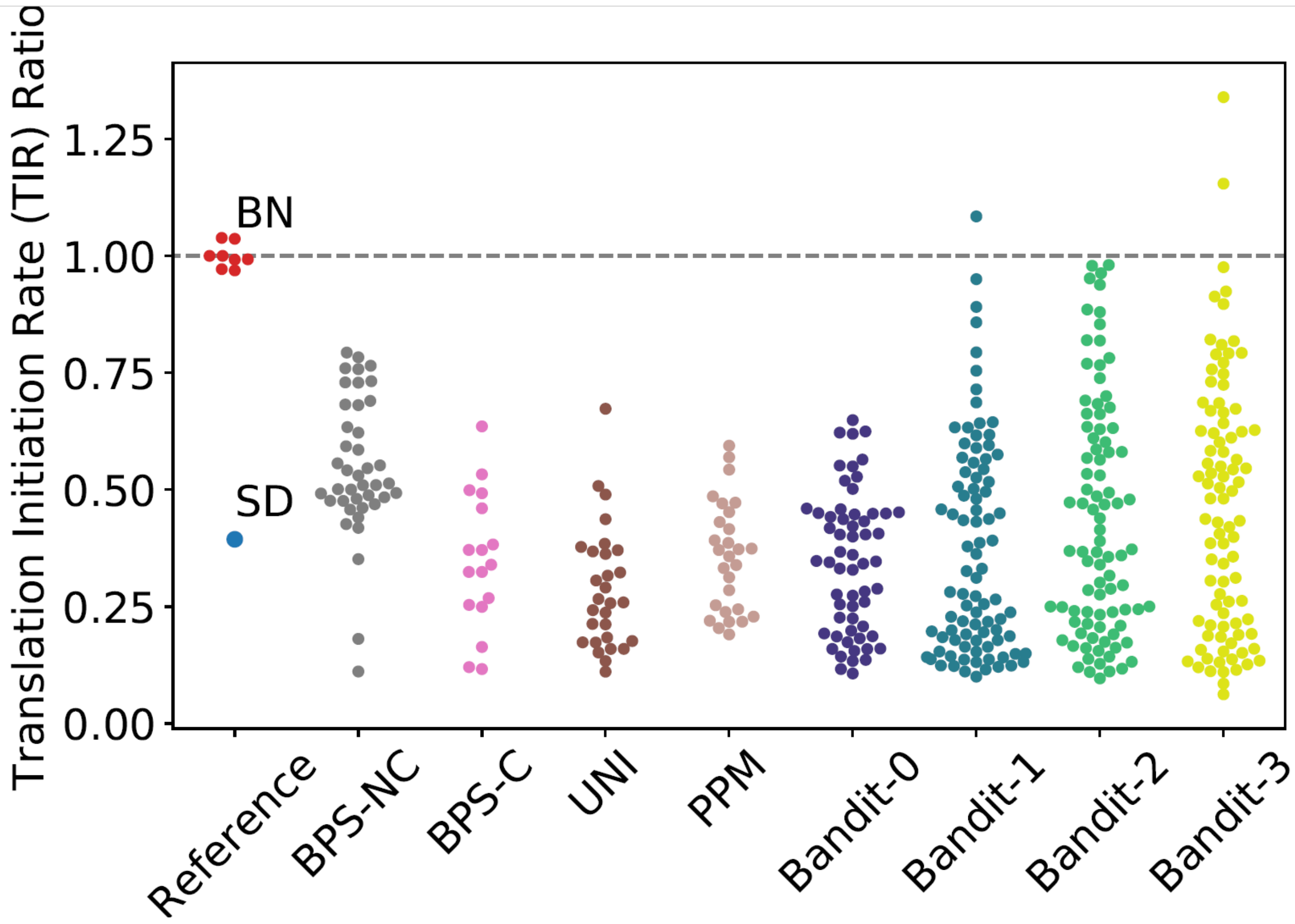
Decisions





https://distill.pub/2020/bayesian-optimization/

ML recommends good designs



TTTAAGANNNNNNTATACATATG

-20 **Feature** -1

- Hard to search by evolving sequences
- 4 experimental cycles
- 35% stronger than engineered sequence

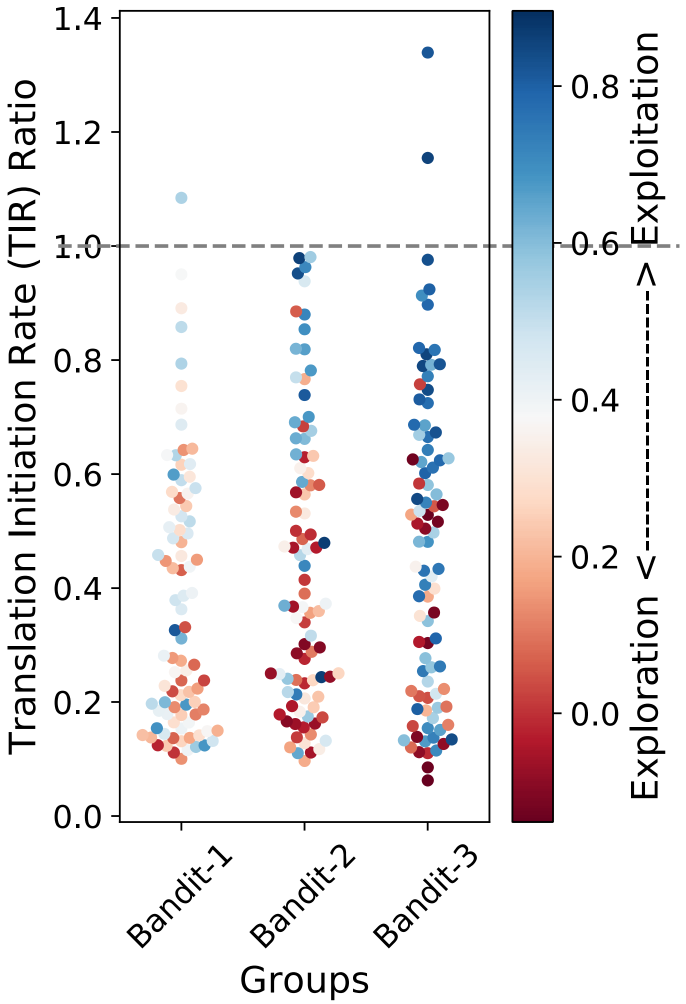
Zhang, Holowko, Hayman Zumpe, and Ong,
Machine learning guided design for ribosome binding site.
ACS Synthetic Biology, 2022

UNOFFICIAL

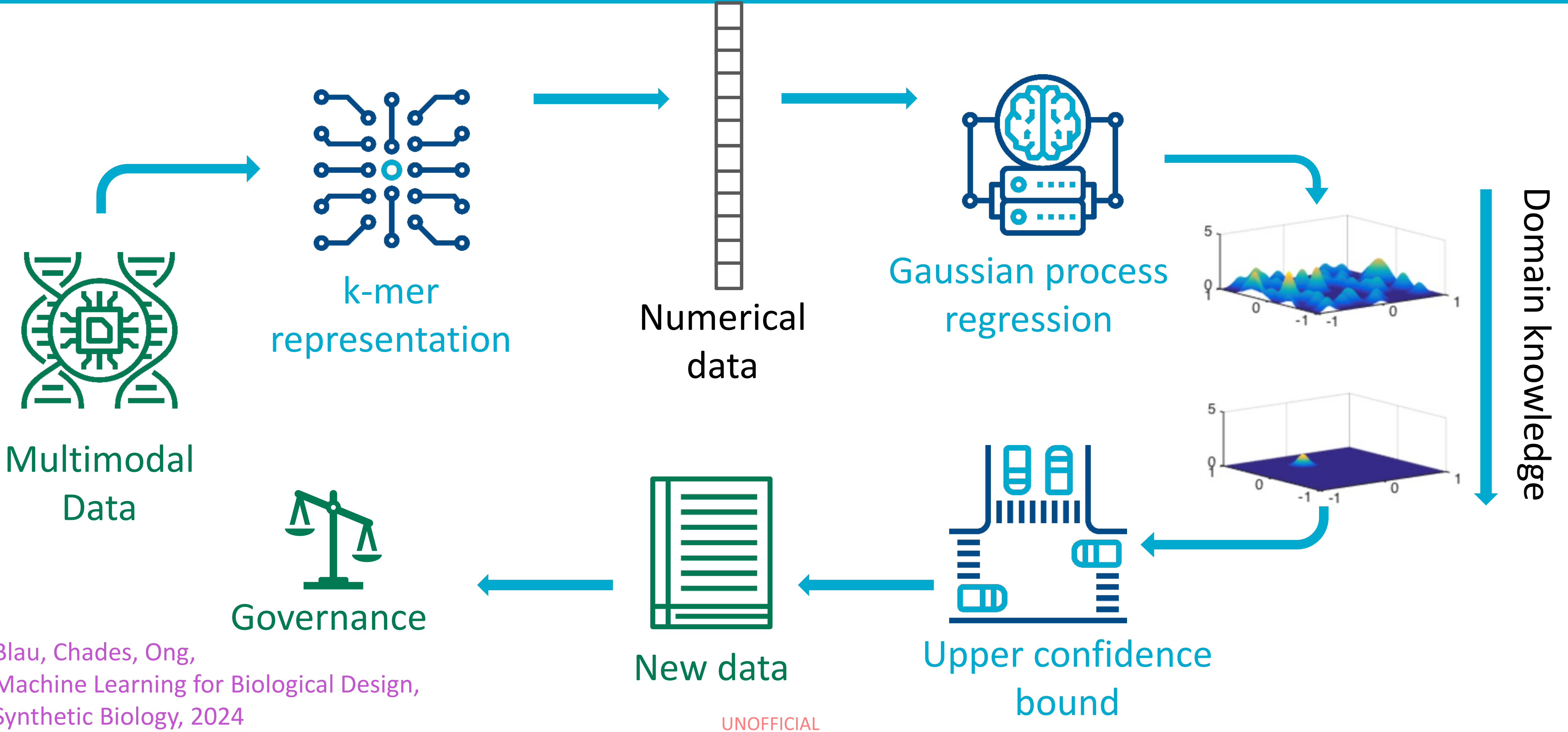
Exploration-Exploitation Trade-off

- Exploration: unknown (untested) RBS design space with potentially high label
- Exploitation: querying areas that are predicted to give relatively high labels.

Which genome should we grow?



Machine learning for genomics



Blau, Chades, Ong,
Machine Learning for Biological Design,
Synthetic Biology, 2024

Work in progress: find plastic degrading enzymes

Enzyme – a short protein sequence, acts as a catalyst for a chemical reaction. Represented as a string of amino acid letters but has a 3D form.

Aim: we want to be able to **find useful** enzymes that can digest plastic

Challenge – search space is **VAST**

Atoms in universe: 10^{80}
Seconds since Big Bang: 10^{17}

ppEST: **Aryl esterase**

MGTLLVVGDSISAAFGLDSRQGWVALLEKRLSEEGFEHSVVNASISGDTSAGGAARLSALLAEHKPELVIIELGGNDGL
RGQPPAQLQQNLASMVEQSQQAGAKVLLLGMKLPPNYGVRYTTAFAQVFTDLAEQKQVSLVPFFLEGVGGVPGM
MQADGIHPAEAAQEILLDNVWPTLKPML

20^{200} possible (substitution) variants!

Asiri Wijesinghe

Allen Zhu

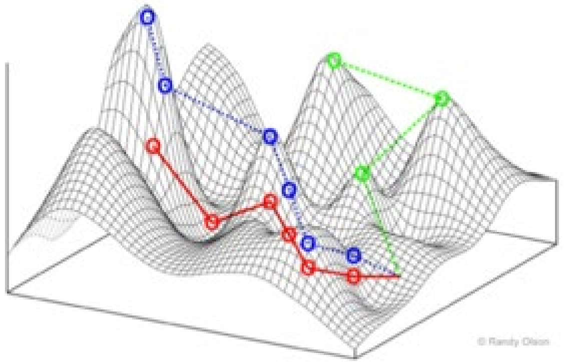
Lu Zhang

Asher Bender

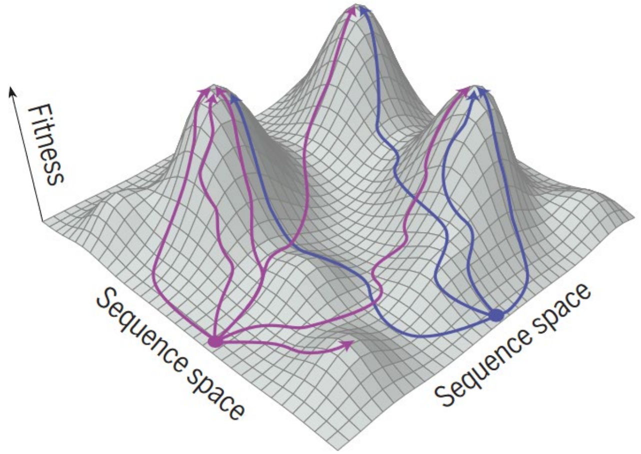
UNOFFICIAL

Fitness landscape

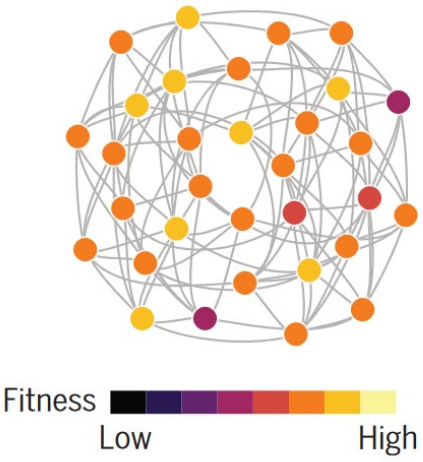
- A metaphor in evolutionary biology
- Each of the horizontal axes represents some notion of sequence variation
- The vertical axis captures some property of interest (so-called fitness)
- Open question how to represent



Wikipedia: Sewall Wright



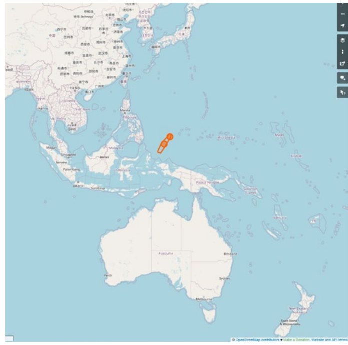
Papkou et al., Science 382, 901 (2023)



Our idea: Islands of fitness

- Desiderata: want to find only "fit" sequences
- Intuition: Many sequences are not viable, and we cannot measure their fitness

Aerial View of Seventy Islands, Micronesia, Palau by Reinhard Dirscherl



Active Generation

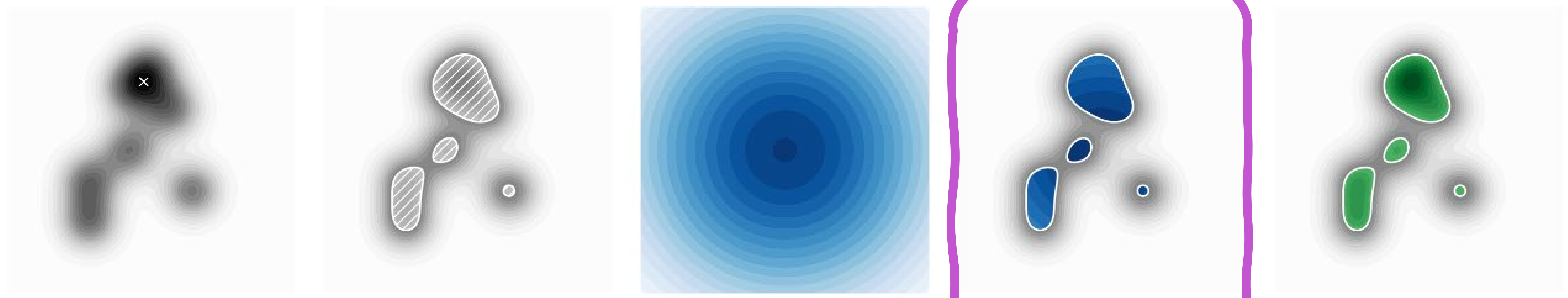
- Goal: We want to generate from a (conditional) probability density

$$p(x \mid y > \tau)$$

Where x is the space of sequences and y is the fitness value

τ is a parameter that identifies "fit" sequences

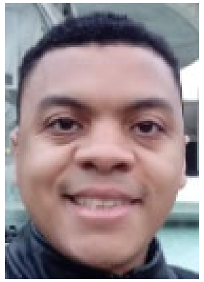
Variational Search Distributions



(a) $\mathrm{argmax}_{\mathbf{x}}\, y(\mathbf{x})$ (b) $\mathcal{S}$ (c) $p(\mathbf{x})$ (d) $p(\mathbf{x}|y > \tau)$ (e) $\mathcal{F}$

Find the fittest | Set of viable sequences | Prior | Posterior | Ground truth

Dan Steinberg



Rafael Oliveira

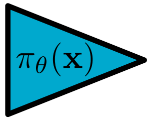
Edwin Bonilla

Steinberg, Oliveira, Ong, Bonilla,
Variational Search Distributions, ICLR 2025
https://arxiv.org/abs/2409.06142

UNOFFICIAL

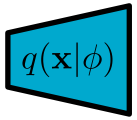
Solving active generation

- Frame online black box optimization as sequential learning of conditional generation
- In each round of the sequence, there are two steps



Fit a binary classifier (CPE), $z := \mathbf{1}[y > \tau]$ indicates “good”

$$\pi_\theta(\mathbf{x}) \approx p(z = 1|\mathbf{x})$$



Update the generative model

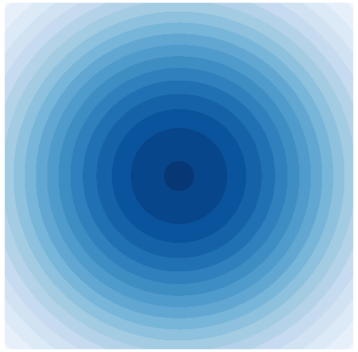
$$\phi_t^* \leftarrow \underset{\phi}{\operatorname{argmax}} \mathcal{L}_{\mathrm{ELBO}}(\phi, \theta_t^*)$$

- We choose to maximise the evidence lower bound (variational inference)

$$\mathcal{L}_{\mathrm{ELBO}}(\phi, \theta) = \mathbb{E}_{q_\phi(\mathbf{x})}[\log \pi_\theta(\mathbf{x})] - \mathbb{D}_{\mathrm{KL}}[q_\phi(\mathbf{x}) \| p(\mathbf{x}|\mathcal{D}_0)]$$

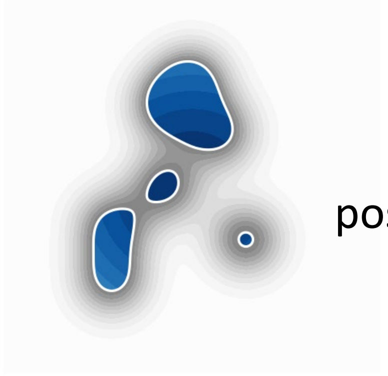
Generating unrolled images

Sample mean CPE p=0.130



prior

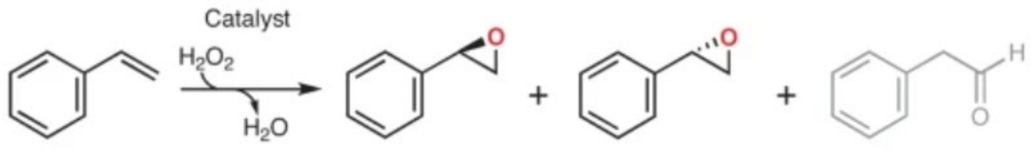
Sample mean CPE p=0.997



posterior({3,5})

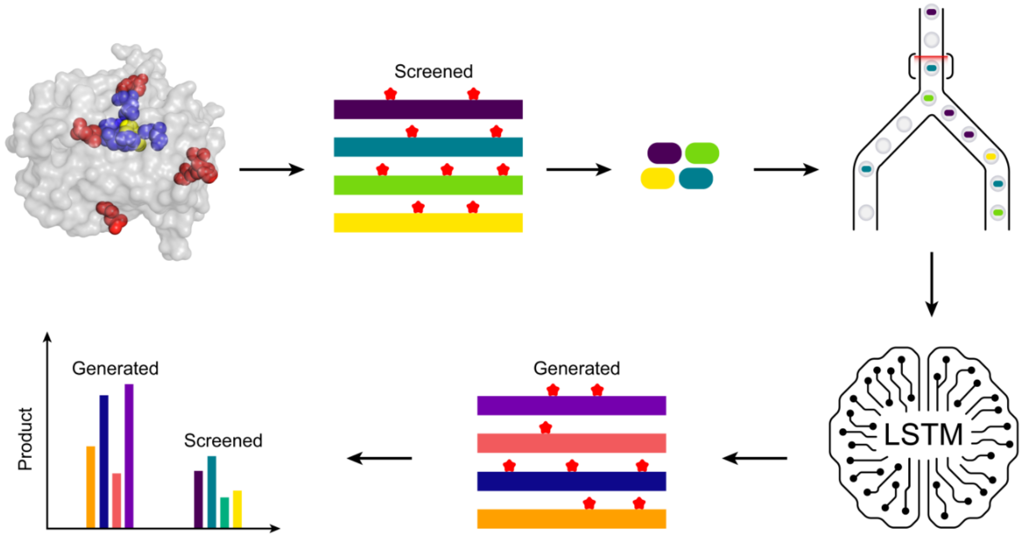
Early results - peroxygenases

- Peroxygenase is a catalyst that inserts an oxygen atom



1 (R)-2 (S)-2 3

- Want to **engineer specificity** into unspecific peroxygenase
- Enzyme library is screened using microfluidic sorting
- Active generation consistently outperformed direct selection from the same screening data



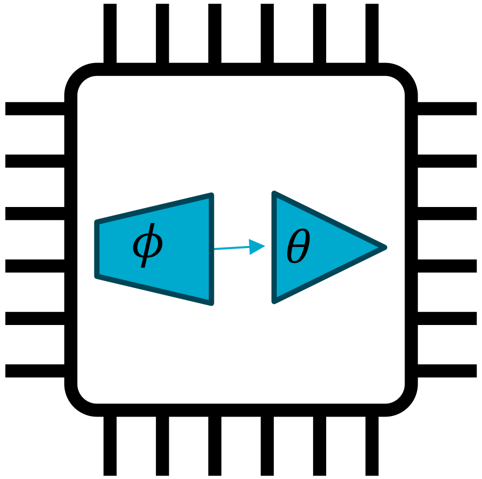
Ultrahigh throughput screening to train generative protein models for engineering specificity into unspecific peroxygenases
Nair, Steinberg, et. al.
https://www.biorxiv.org/content/10.1101/2025.11.02.685536v1

Active Generation

Active generation: find best ϕ^* for generating "good" (or best) **x**

*Can "select" from a **vast number** of enzymes (e.g. 20^{200}), since they are **generated***

** we are **not** doing latent space optimisation!



Predictor + generator learning

ϕ

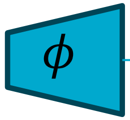
Generate good candidates instead of selecting from a list

MKTTTL...LFLVGALTQ	1.2
MKTTTL...LFLVGTLTQ	3.6
...	...
MKTTTL...LFLVGALTT	0.3

Labelled Data

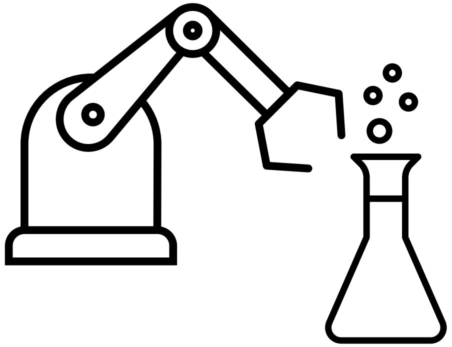
$$\pi_\theta(\mathbf{x}) \approx p(z = 1|\mathbf{x})$$

$$\phi_t^* \leftarrow \operatorname*{argmax}_{\phi} \mathcal{L}_{\mathrm{ELBO}}(\phi, \theta_t^*)$$



MKTTTL...LFLVGALTQ
MKTFTL...LFLVGTLTQ
MKTTIL...LFLVGTLTQ
MKTSTL...LFLVGTLTQ
MKTTTL...LFLVGTLTQ
...
MKTTTL...LFLVGALTT

Unlabelled data *generation*,
design is generation



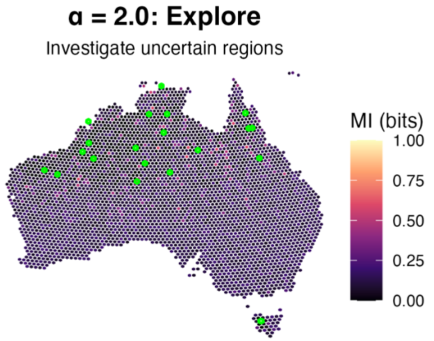
Build + Test

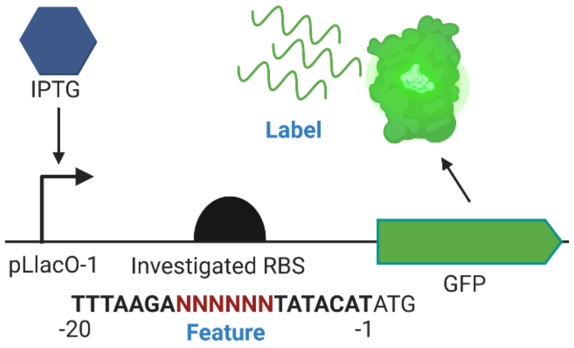
Steinberg, Wijesinghe, Oliveira, Koniusz, Ong, Bonilla
Amortized Active Generation of Pareto Sets, NeurIPS 2025

UNOFFICIAL

Data is measured for a reason

- Consider the set of all possible things to measure





- Think of the predictor output as producing features
  - Each calculated feature demonstrates the “importance” of an experiment
  - Can get multiple features by using different predictors
  - Estimate predictive uncertainty to inform decisions

- Adaptively choose the next thing to measure by maximising an objective (machine learning is about defining good objective functions)

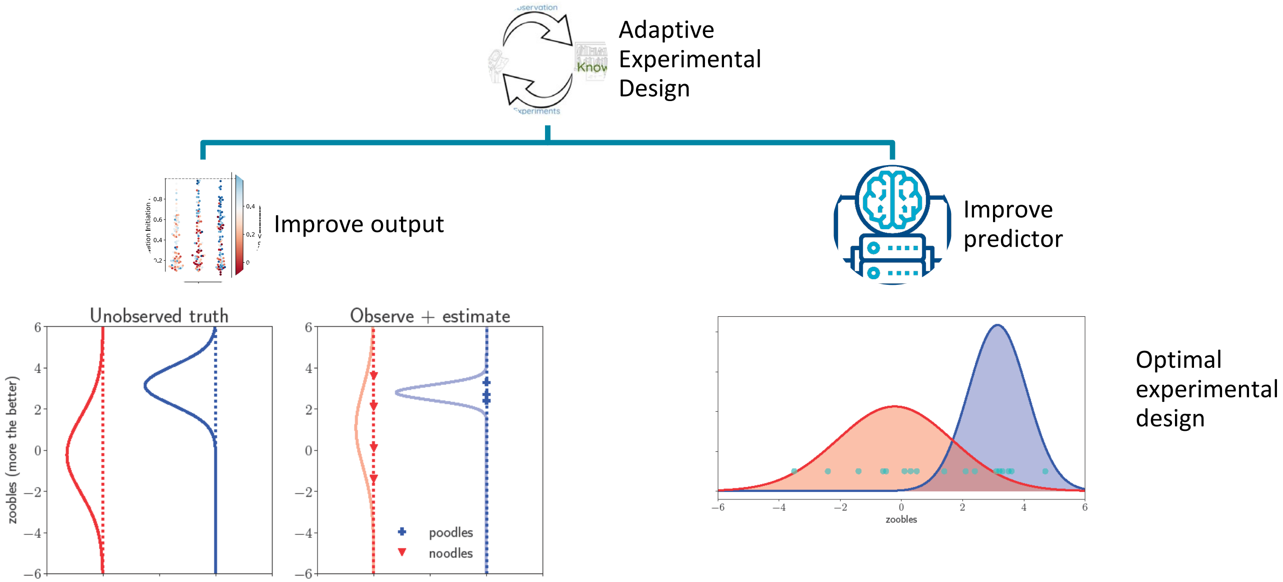
On finding good experiments

What is an experiment?

How do we find good experiments?

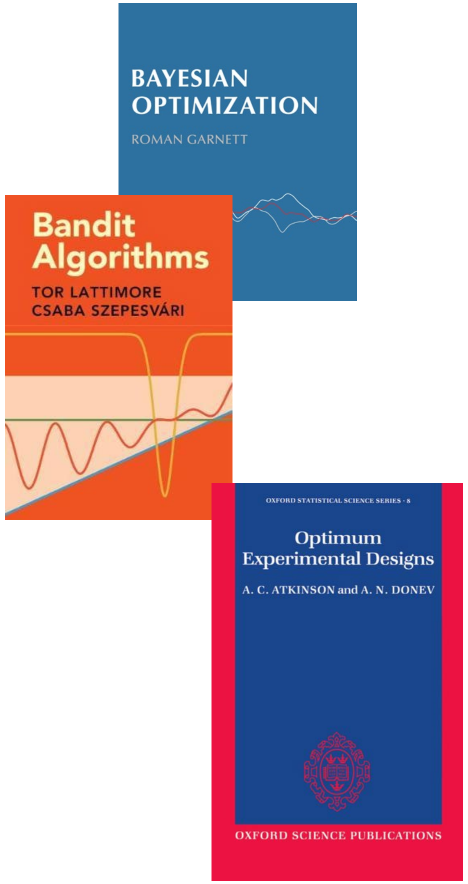
What do we mean by good?

Better measured values or better models

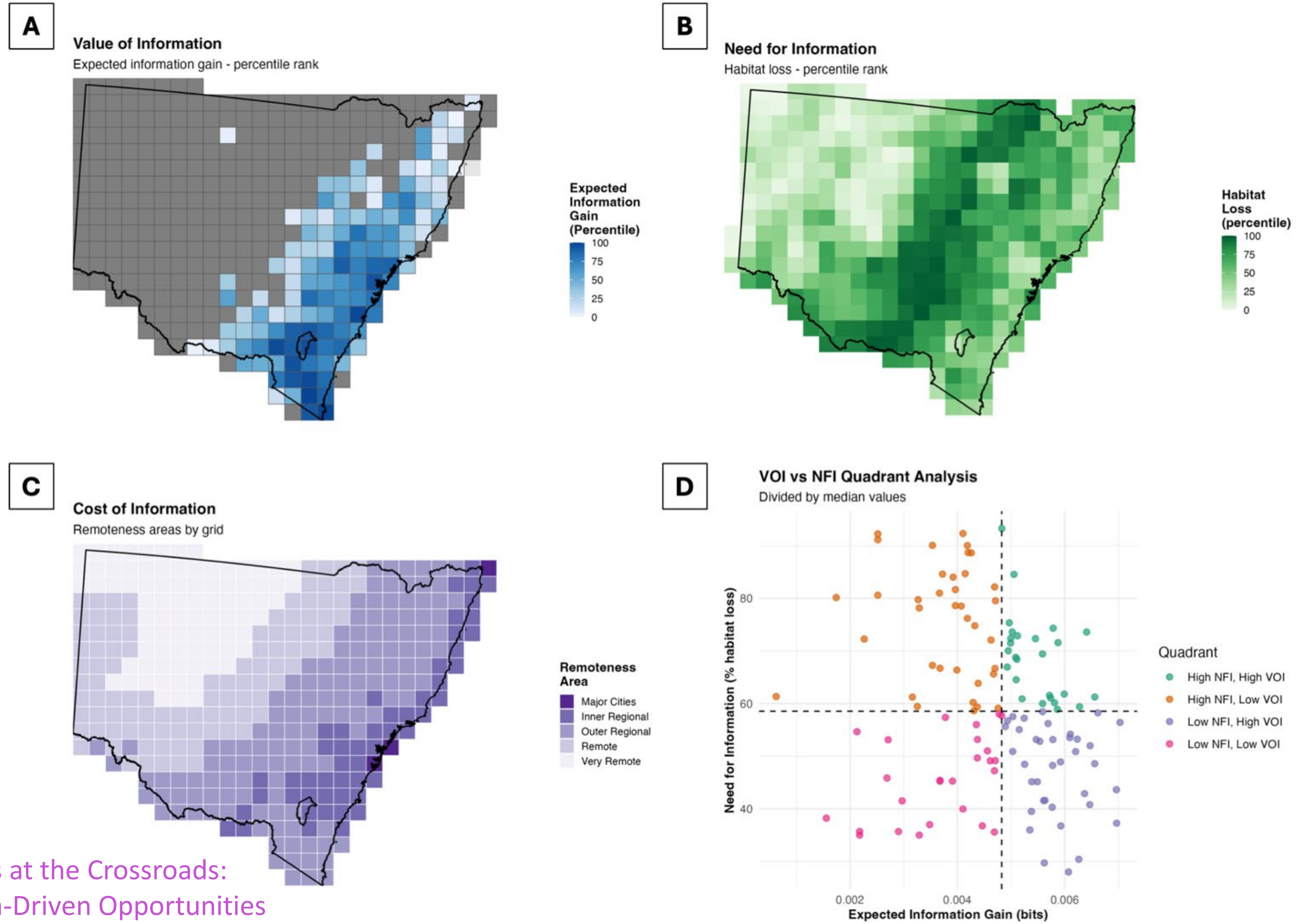


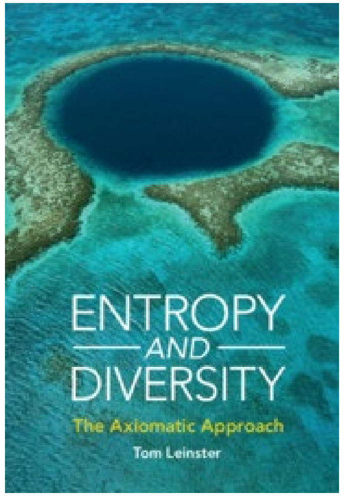
Recall that we can use a machine learning predictor in two ways:

1. The parameters of the model
2. The output values on a test set



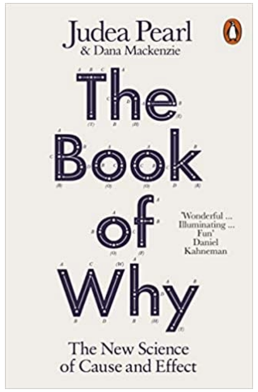
Value, need, cost



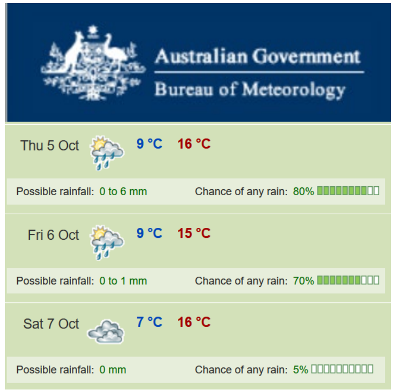


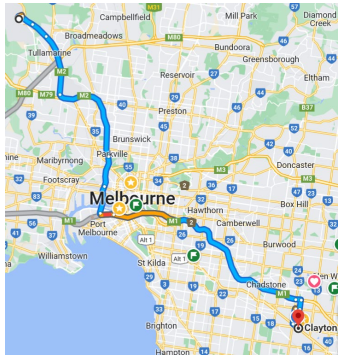
Natural History Collections at the Crossroads:
Shifting Priorities and Data-Driven Opportunities
Forbes, Thrall, Young, Ong, Ecology Letters, vol 28, no 8, 2025

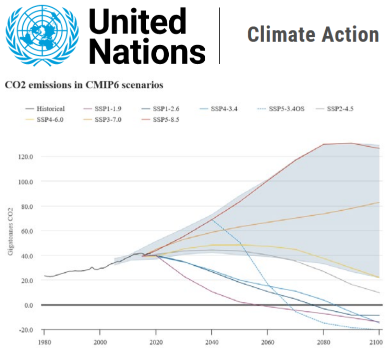
ML is **not only** about predictions



Predictions vs Decisions vs Actions







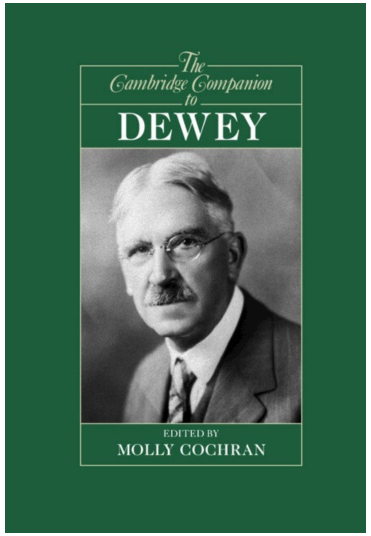
	Weather	Traffic	Climate
Predictions	Will it rain tomorrow?	Jam on M1?	Risk in 2050?
Decisions	Take umbrella?	Train or taxi?	Plan for net zero
Actions	Does not affect weather	Affects traffic!	Want wrong predictions!

When accurate prediction models yield harmful self-fulfilling prophecies, Patterns, 2025
https://doi.org/10.1016/j.patter.2025.101229

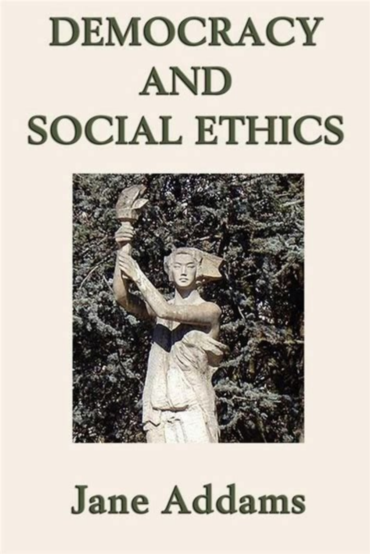
Pragmatism in International Relations

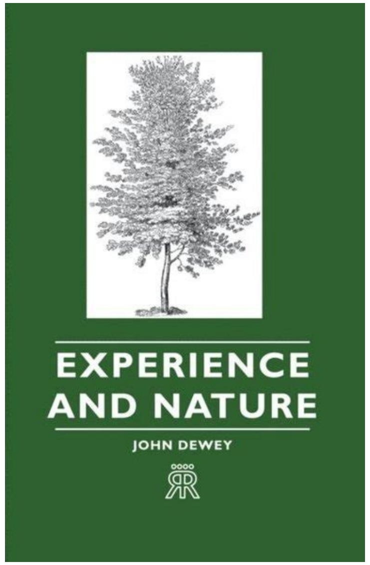
Toni Erskine, ANU

Xueyin Zha, ANU



- Need a way to say “good” and “true”

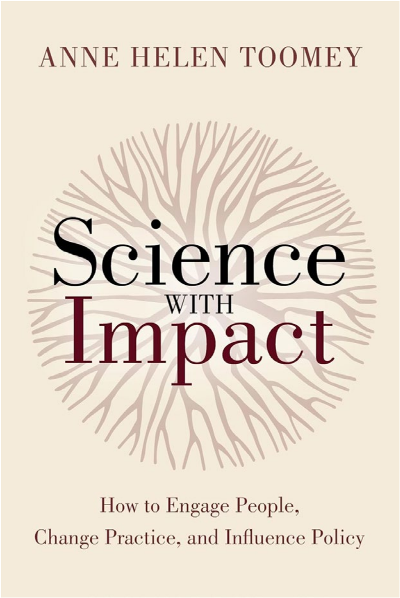




PhD thesis: Normative Truth-Seeking from the Ground Up: Experiential Pathway to Global AI Governance

We should learn from each other

- Need more than data science
- How to foster cross disciplinary projects?
- π shaped research teams



IEEE TRANSACTIONS ON TECHNOLOGY AND SOCIETY

Four Compelling Reasons to Urgently Integrate AI Development With Humanities, Social and Economics Sciences

Iadine Chades, Melanie McGrath, Erin Bohensky, Lucy Carter, Rebecca Coates, Ben Harwood, Md Zahidul Islam, Sevvandi Kandanaarachchi, Cheng Soon Ong, Andrew Reeson, Samantha Stone-Jovicich, Cécile Paris, Mitchell Scovell, Kirsty Wissing, and David M. Douglas

Position: We need responsible, application-driven (RAD) AI research

Sarah Hartman [1] Cheng Soon Ong [2,3] Julia Powles [4,5] Petra Kuhnert [1]

Opportunities and Challenges in Designing Genomic Sequences

Mengyan Zhang [1,2] Cheng Soon Ong [2,1]

https://ong-home.my

@cheng@masto.ai
@ml4x.bsky.social
chengsoon.ong@anu.edu.au

On Finding Good Experiments

- What is an experiment?
- How do we find good experiments?
- What do we mean by good?