Optimistic Games for Combinatorial Bayesian Optimization with Application to Protein Design

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The Thirteenth International Conference on Learning Representations
ICLR 2025

Combinatorial Bayesian Optimization

$$x^* \in \arg\max_{x \in \mathcal{X}} f(x),$$

where $\mathcal{X}$: combinatorial and unstructured

$$\{x^1, \ldots, x^n\}, x^i \in \mathcal{X}^{(i)}, \qquad \mathcal{X} = \prod_{i=1}^{n} \mathcal{X}^{(i)}$$

Example: Protein design

Q?F?DVF?GK??...E?PM?A → 20^{300} possibilities

300 amino acid sites

GFP protein

Combinatorial Bayesian Optimization

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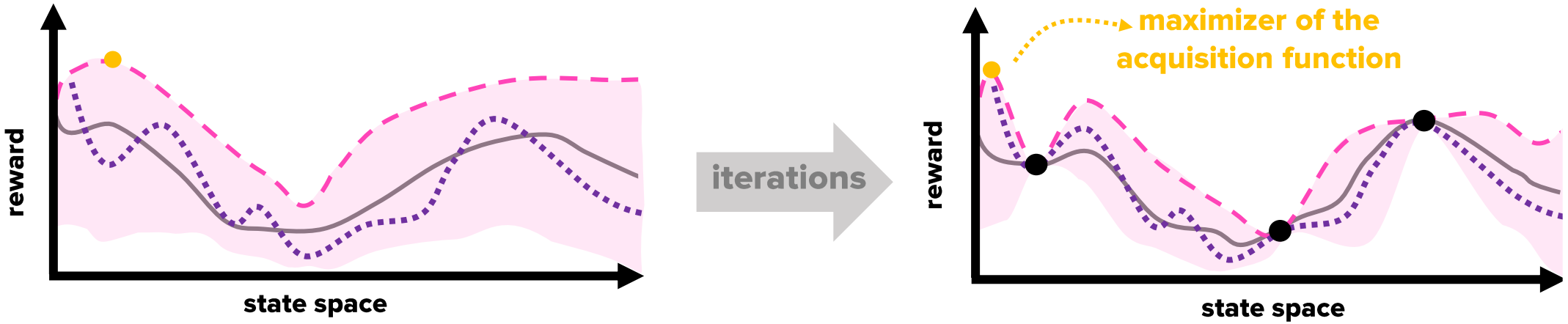
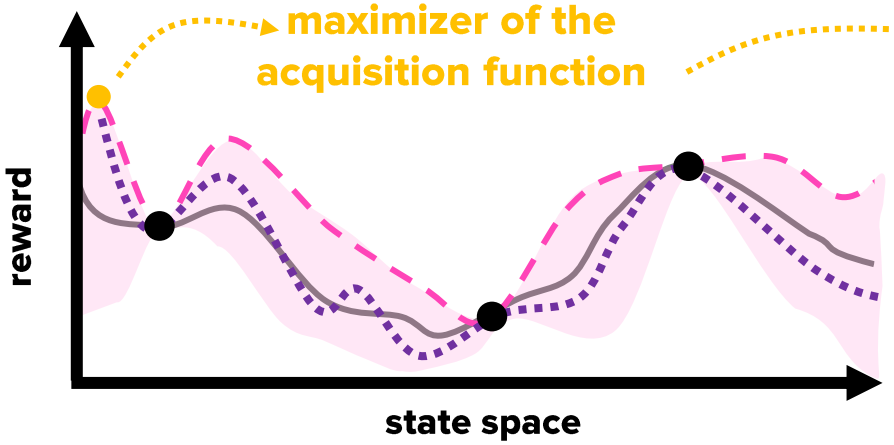
where $\mathcal{X}$: combinatorial and unstructured



acquisition function
model fit
uncertainty
true function
measurements

Combinatorial Bayesian Optimization



Q?F?DVF?GK??...E?PM?A

20^{300} possibilities

intractable

GameOpt: Optimistic Games

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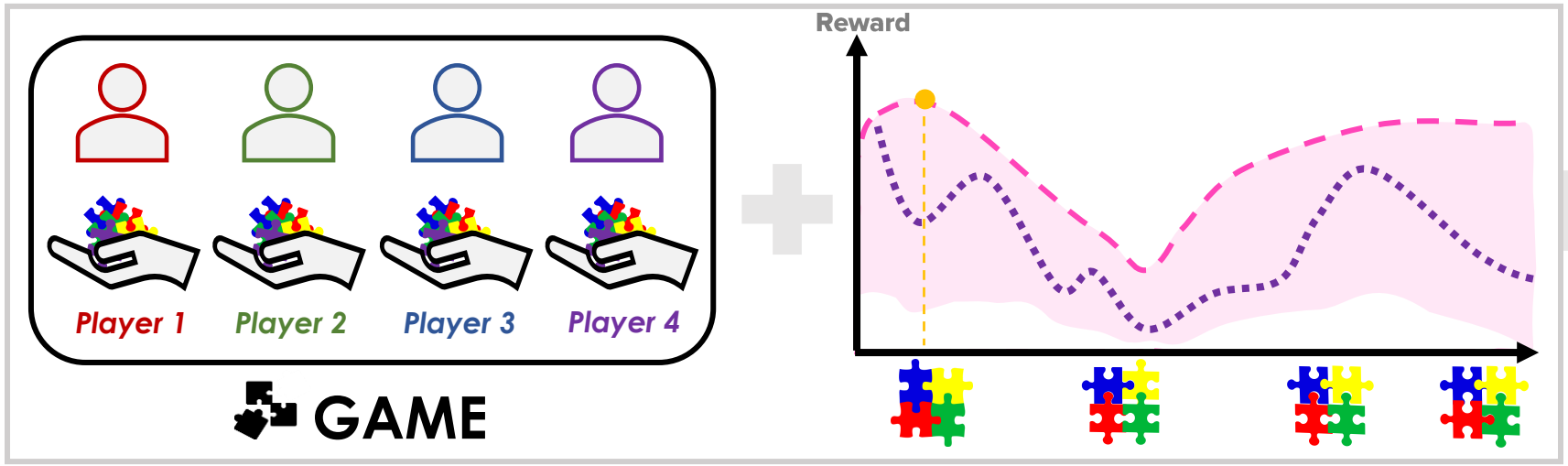
Optimistic Games - Idea

Cooperative game

Game equilibria

Maximization of acquisition function

Evaluation points



EQUILIBRIUM

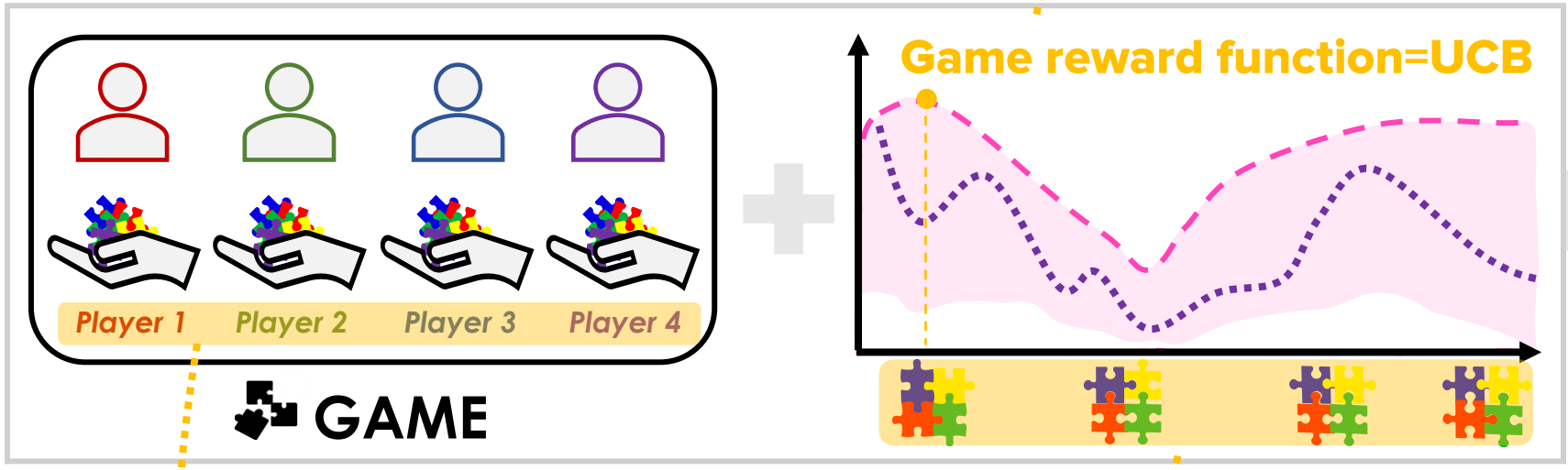
EQUILIBRIUM

Optimistic Games - Idea

$$x^* \in \arg\max_{x \in \mathcal{X}} f(x)$$

$$UCB(\mathcal{GP}, \cdot): \prod_{i=1}^{n} \mathcal{X}^{(i)} \to \mathbb{R}$$

$$UCB_t(\mathcal{GP}, x) = \mu_t(x) + \beta\sigma_t(x)$$



Candidate evaluation points

EQUILIBRIUM

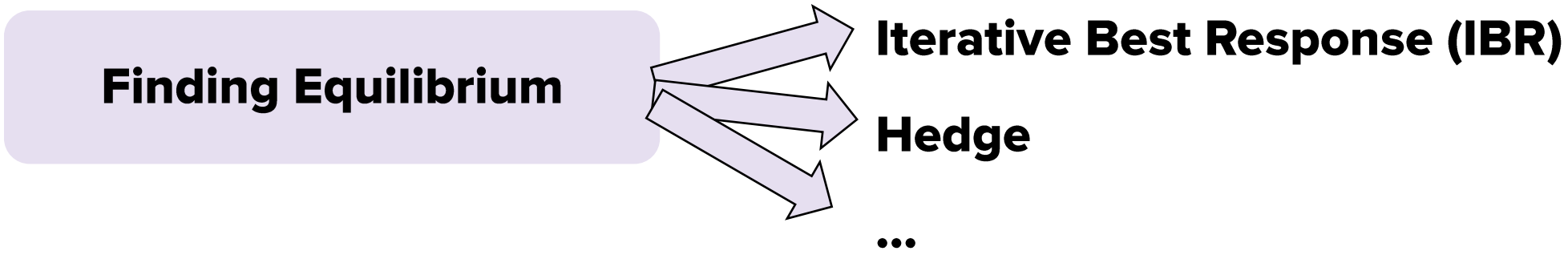
EQUILIBRIUM

$$\{x^1, \ldots, x^n\}, x^i \in \mathcal{X}^{(i)}$$

$$\mathcal{X} = \prod_{i=1}^{n} \mathcal{X}^{(i)}$$

Optimistic Games - Equilibrium Finding

The goal of players → compute (Nash) equilibria



Application to Protein Design

Application to Protein Design

Protein: QCFFDVFQGKSRPMFA → amino acid sequences

- Protein length = L
- Possible protein configurations → 20^L

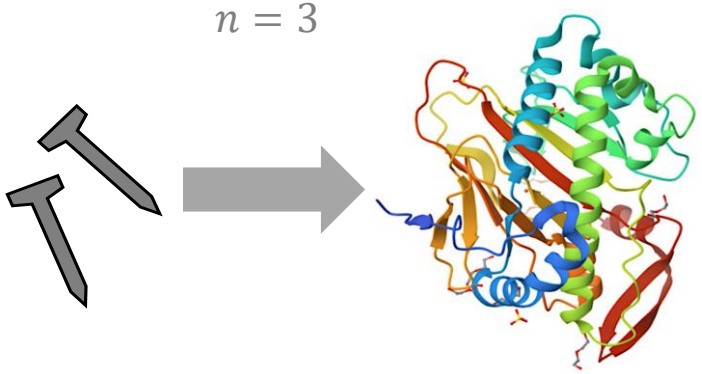
GFP protein

Goal: Find optimal amino acid sequence to maximize the functional capacity (fitness)

Application to Protein Design - Datasets

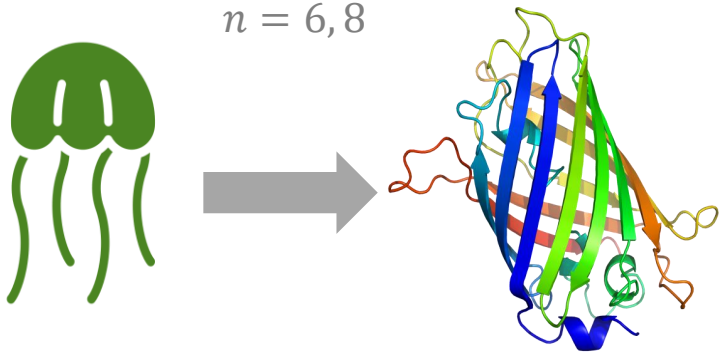
Halogenase[1], L=3

$n = 3$



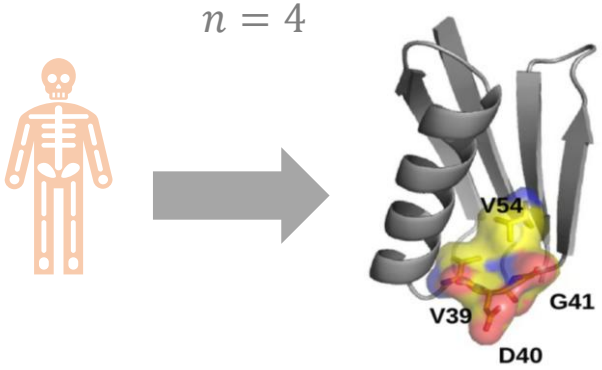
GFP[3], L=238

$n = 6,8$



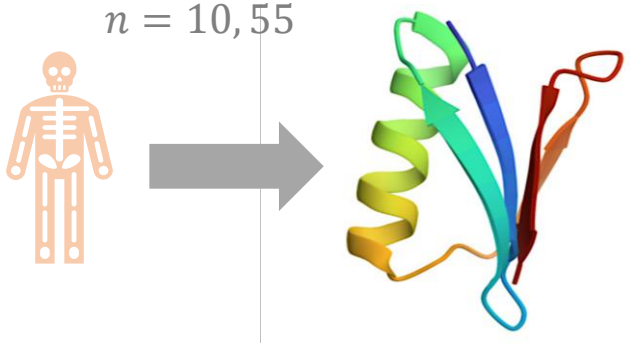
GB1(4)[2], L=4

$n = 4$



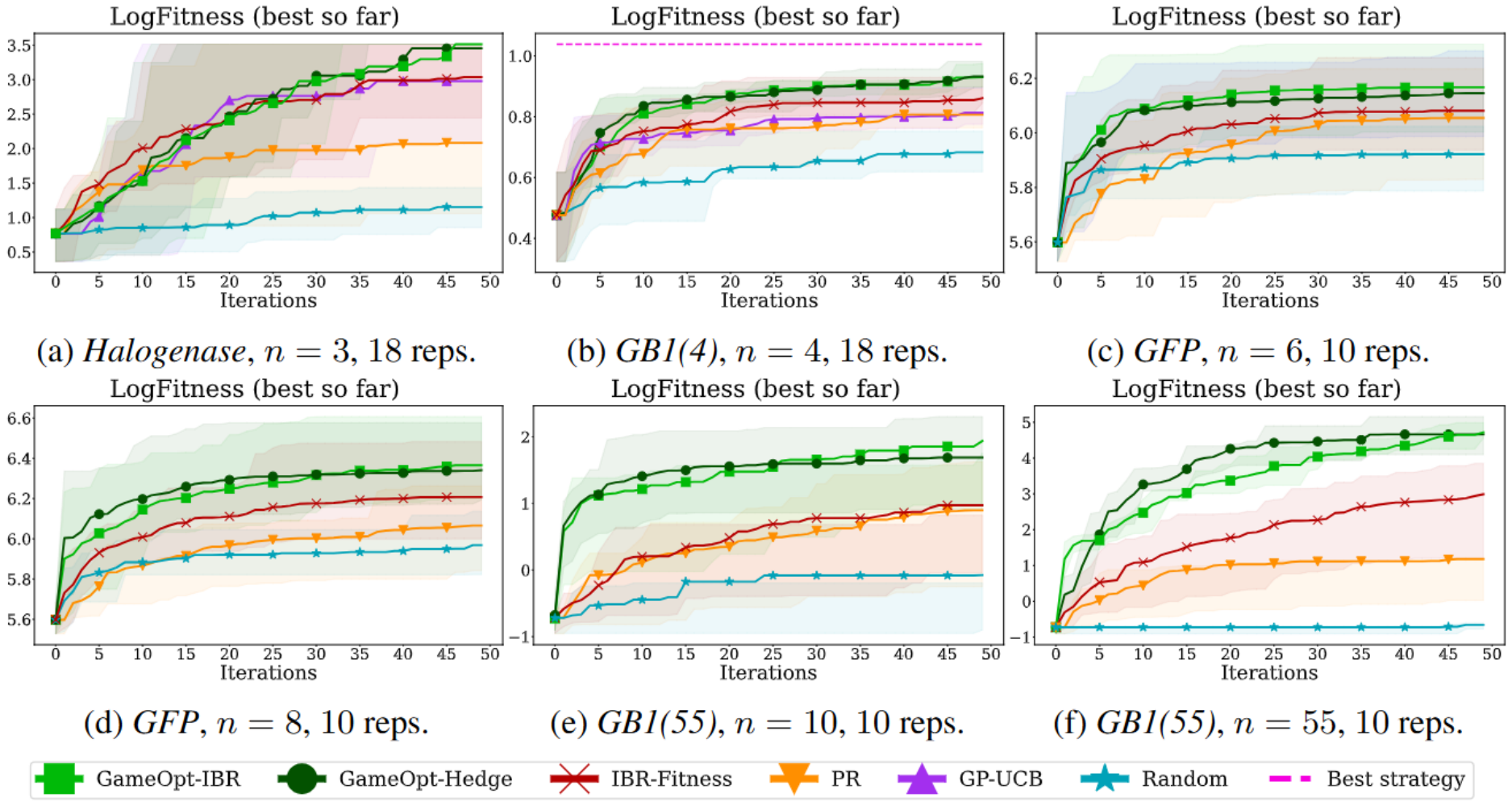
GB1(55)[4], L=55

$n = 10,55$

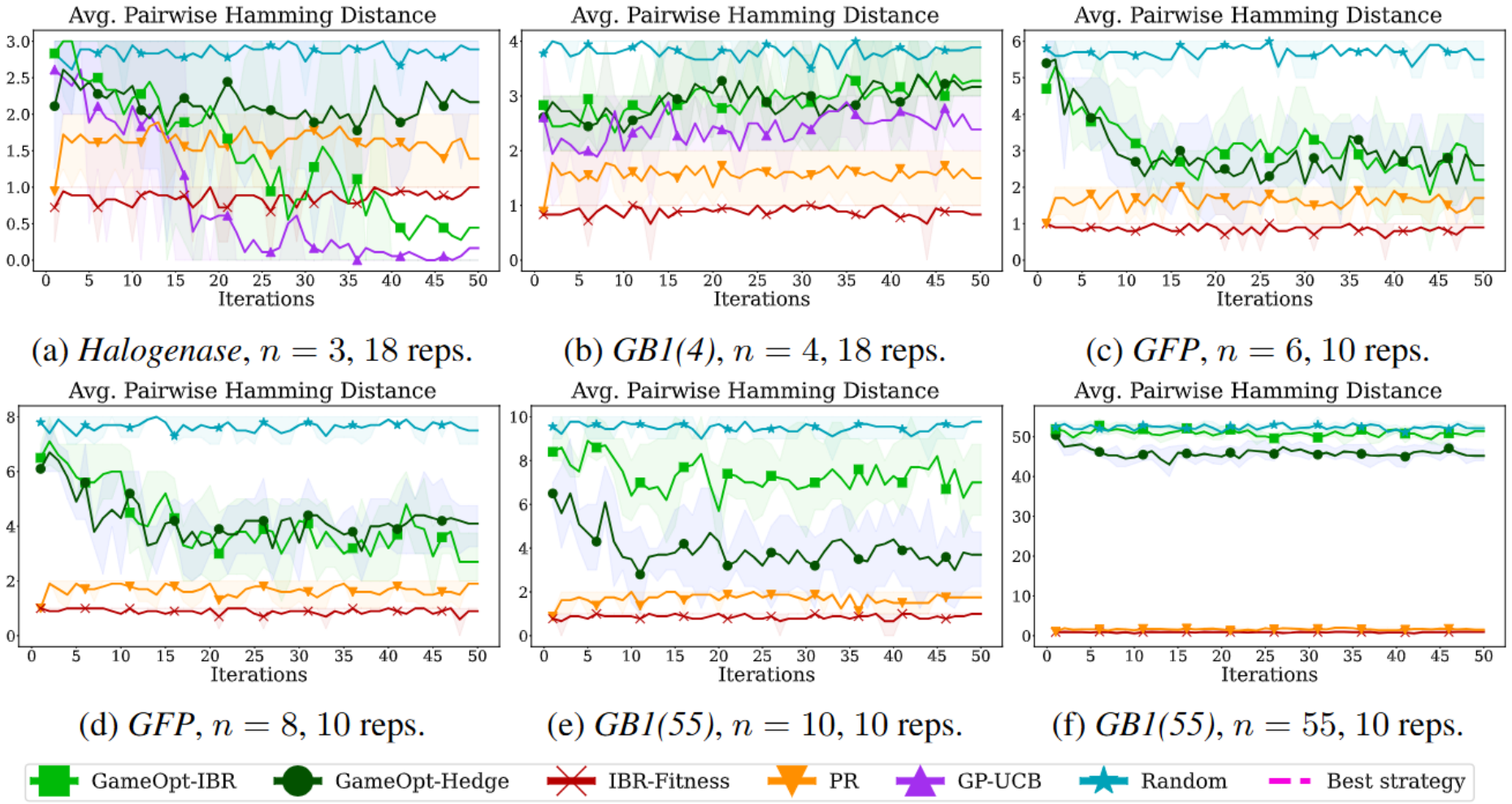


[1] Büchler, J., Malca, S. H., Patsch, D., Voss, M., Turner, N. J., Bornscheuer, U. T., Allemann, O., Le Chapelain, C., Lumbroso, A., Loiseleur, O., et al. Algorithm-aided engineering of aliphatic halogenase welo5* for the asymmetric late-stage functionalization of soraphens. Nature Communications, 2022.
[2] Wu, N. C., Dai, L., Olson, A., Lloyd-Smith, J. O., and Sun, R. Adaptation in protein fitness landscapes is facilitated by indirect paths. eLife, 2016.
[3] Biswas, S., Khimulya, G., Alley, E. C., Esvelt, K. M., and Church, G. M. Low-n protein engineering with data-efficient deep learning. Nature methods, 2021.
[4] Olson, C. A., Wu, N. C., and Sun, R. A comprehensive biophysical description of pairwise epistasis throughout an entire protein domain. Current biology, 2014.

Application to Protein Design – Convergence Speed



Application to Protein Design – Pairwise distance



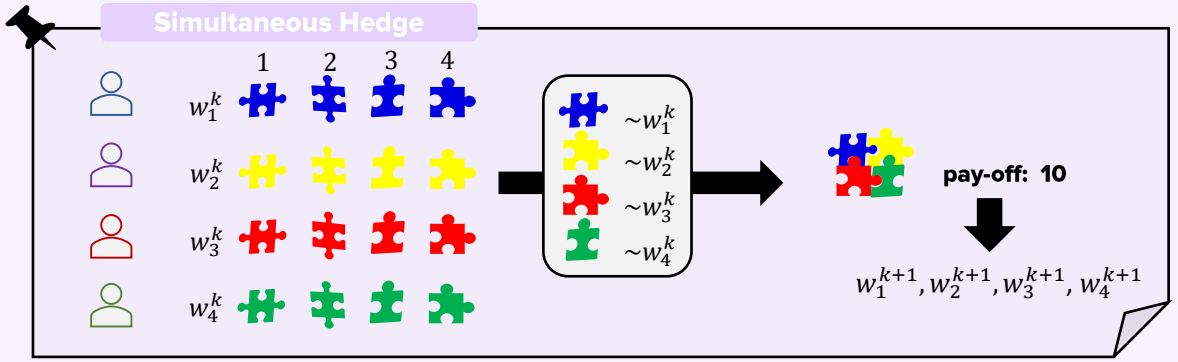
Further...

Sample complexity

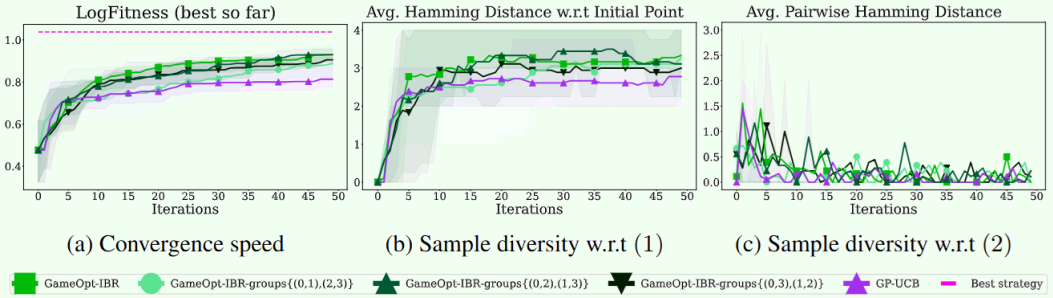
Theorem 4.2 (Sample complexity of GAMEOPT). *Assume f satisfies the regularity assumptions of Section 2, and* GAMEOPT *is run with confidence width $\beta_t = 2n \log\left(\sup_{i\in\mathcal{N}} |\mathcal{X}_i| \frac{t^2\pi^2}{6\delta}\right)$. Then, with probability at least $1-\delta$ and for a given accuracy $\epsilon \geq 0$, the strategy $x_{T^\star}$ returned by* GAMEOPT *is a ϵ-approximate Nash equilibrium when*

$$T \geq \Omega\left(\frac{\beta_T \gamma_T}{\epsilon^2}\right). \tag{4}$$

Equilibrium finding subroutines



Player grouping



(a) Convergence speed (b) Sample diversity w.r.t (1) (c) Sample diversity w.r.t (2)

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ICLR poster:
Thu 24 Apr 15:00, Poster Session #2

ArXiv

Code