Design of Experiments for Model Discrimination Hybridising Analytical and Data-Driven Approaches

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Pharmaceutical Applications

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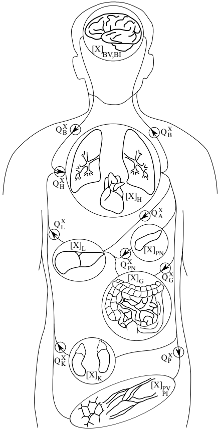
Parametric models common in pharmaceutical applications.

Examples:

- Pharmacokinetics



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Pharmaceutical Applications

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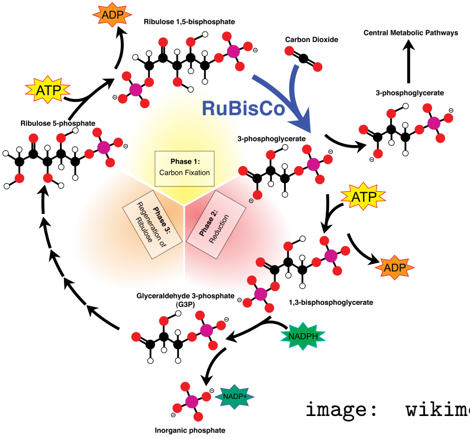
Examples:

- Pharmacokinetics
- Metabolic pathways



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Pharmaceutical Applications

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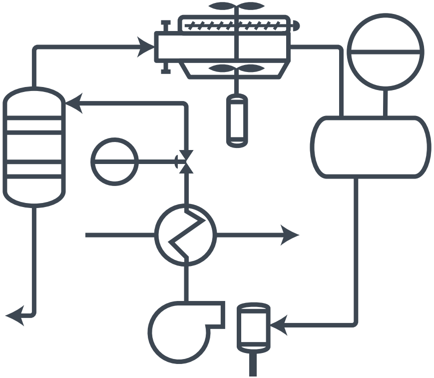
Parametric models common in pharmaceutical applications.

Examples:

- Pharmacokinetics
- Metabolic pathways
- Reaction mechanisms



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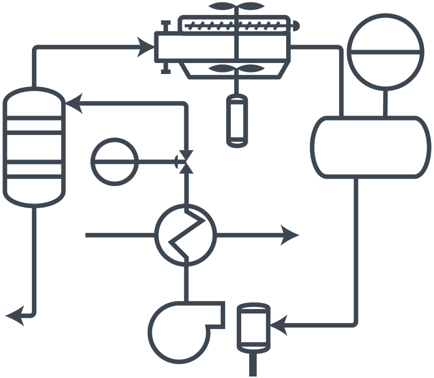
Model Discrimination

- An expensive-to-evaluate system $g : \mathbb{R}^d \to \mathbb{R}^E$.



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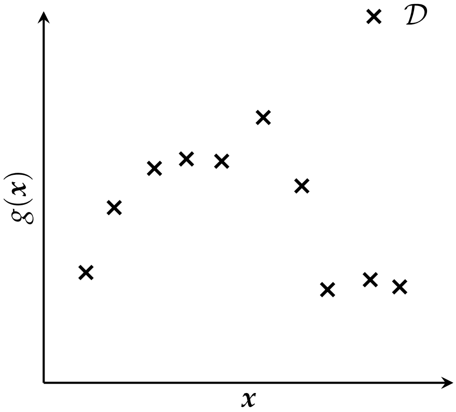
Model Discrimination

- An expensive-to-evaluate system $g : \mathbb{R}^d \to \mathbb{R}^E$.
- Collected data

$$\mathcal{D} : \boldsymbol{y} \sim \mathcal{N}\left(g(\boldsymbol{x}), \boldsymbol{\Sigma}_{\text{exp}}\right)$$



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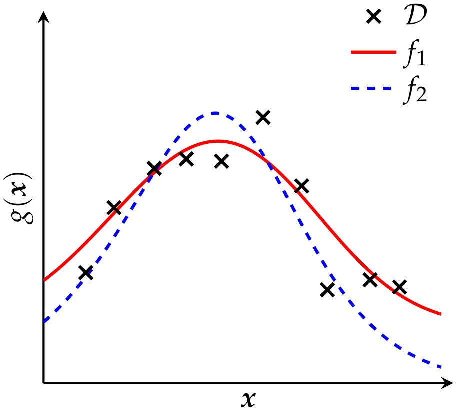

Model Discrimination

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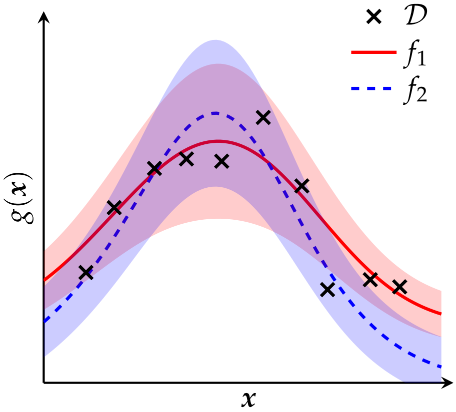

Model Discrimination

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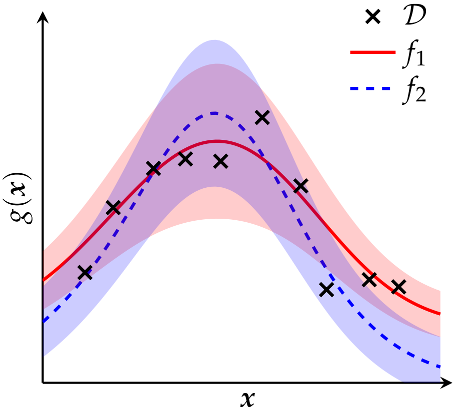
- $\forall_i : \; p(f_i \,|\, \mathcal{D}) \approx 1/M$.



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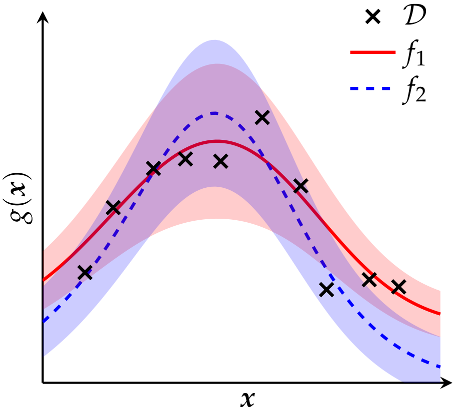

What is the optimal next experiment x^*?.

Design of Experiments for Model Discrimination

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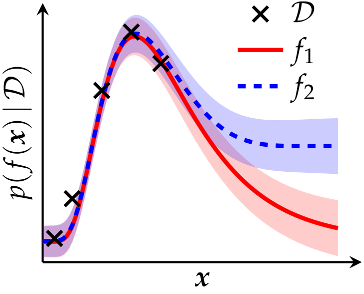
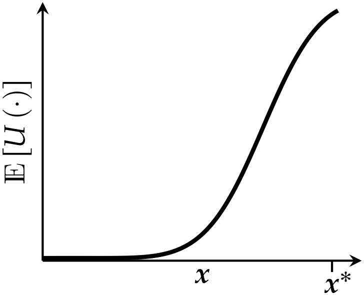
Design utility function

$$x^* = \arg\max_{x} \mathbb{E}_{\theta_1, \ldots, \theta_M \mid \mathcal{D}} \left[U_{f_1|\theta_1, \ldots, f_M|\theta_M}(x) \right]$$

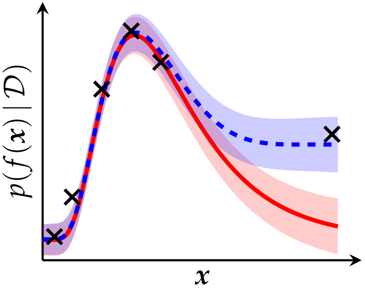
with $U(\cdot)$ some design utility given models $f_1, \ldots, f_M$ with parameters $\theta_1, \ldots, \theta_M$.



(a) $|\mathcal{D}| = 5$.



(b) Find design.



(c) $|\mathcal{D}| = 6$.

Design of Experiments for Model Discrimination

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Design utility function

$$\boldsymbol{x}^* = \arg\max_{\boldsymbol{x}} \mathbb{E}_{\boldsymbol{\theta}_1,\ldots,\boldsymbol{\theta}_M \mid \mathcal{D}} \left[U_{f_1|\boldsymbol{\theta}_1,\ldots,f_M|\boldsymbol{\theta}_M}(\boldsymbol{x}) \right]$$

with $U(\cdot)$ some design utility given models $f_1, \ldots, f_M$ with parameters $\boldsymbol{\theta}_1, \ldots, \boldsymbol{\theta}_M$.

- Hunter & Reiner (1965)
- Box & Hill (1967)
- Fedorov (1972)
- Prasad & Someswara Rao (1977)
- Buzzi-Ferraris *et al.* (1983, 1984, 1990)
- MacKay (1992)
- Chaloner & Verdinelli (1995)
- Asprey & Macchietto (2000)
- Schwaab *et al.* (2008)
- Michalik *et al.* (2010)
- Drovandi *et al.* (2014)
- Vanlier *et al.* (2014)
- Ryan *et al.* (2015, 2016)
- Woods *et al.* (2017)

Existing Approaches

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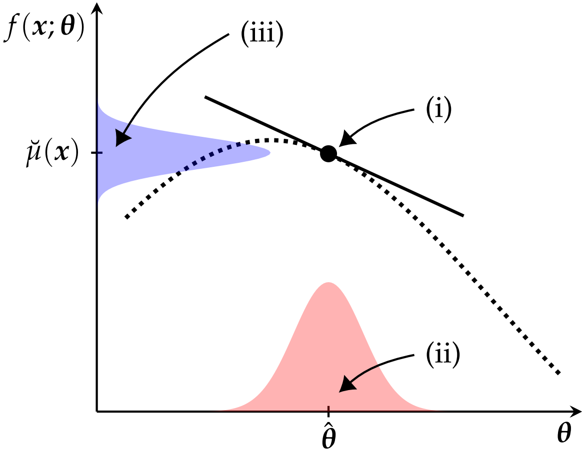
Analytical approach

(i) Linearise model around $\boldsymbol{\theta} = \hat{\boldsymbol{\theta}}$.

(ii) Assume $\boldsymbol{\theta} \sim \mathcal{N}(\hat{\boldsymbol{\theta}}, \boldsymbol{\Sigma}_\theta)$.

(iii) $p(f(\boldsymbol{x}) \mid \mathcal{D}) \approx \mathcal{N}(\breve{\mu}(\boldsymbol{x}), \breve{\Sigma}(\boldsymbol{x}))$.

(iv) Closed-form $\mathbb{E}\left[U\left(\cdot\right)\right]$.



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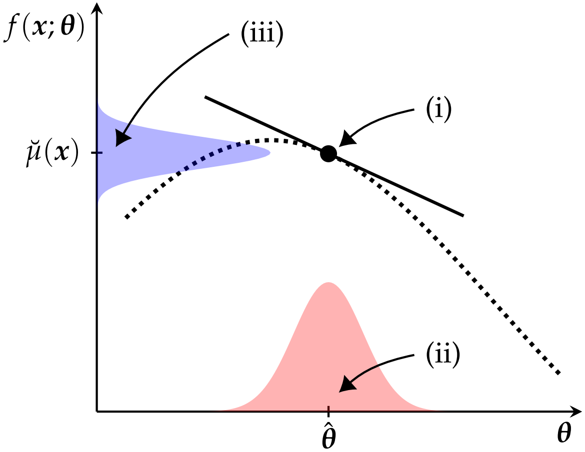

\+ Closed-form expressions, computationally cheap.

− Linearised models; requires $\partial f_i / \partial \boldsymbol{\theta}_i$.

Existing Approaches

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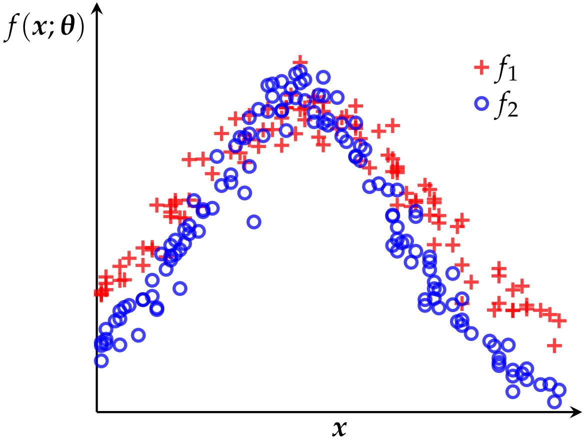
Data-driven approach

Monte Carlo-based methods to solve $\boldsymbol{x}^* = \arg\max_{\boldsymbol{x}} \mathbb{E}_{\boldsymbol{\theta}_1,\ldots,\boldsymbol{\theta}_M \mid \mathcal{D}} \left[U(\boldsymbol{x}) \right]$ by sampling from $p(\boldsymbol{\theta}_i \mid \mathcal{D})$.



Existing Approaches

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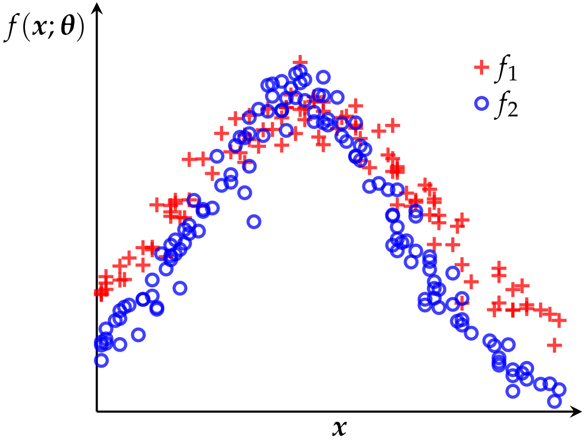
Data-driven approach

Monte Carlo-based methods to solve
$x^* = \arg\max_x \mathbb{E}_{\theta_1,\ldots,\theta_M \mid \mathcal{D}} \left[U(x)\right]$
by sampling from $p(\theta_i \mid \mathcal{D})$.

- **+** Accommodates black-box models.
- **−** Computationally costly.



Hybrid Approach

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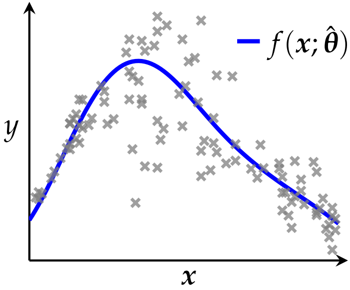
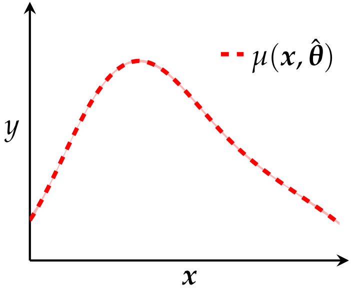
(i) Generate training data from model evaluations with sampled $\boldsymbol{x}$, $\boldsymbol{\theta}$.

(ii) Train GP surrogates.

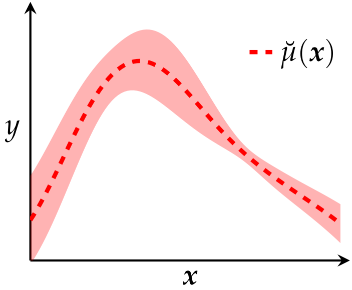
(iii) Apply analytical approach approximations on GP surrogates models.



(i) Training data



(ii) $\mathcal{N}(\mu(\boldsymbol{x}, \hat{\boldsymbol{\theta}}), \Sigma(\boldsymbol{x}, \hat{\boldsymbol{\theta}}))$



(iii) $\mathcal{N}(\breve{\mu}(\boldsymbol{x}), \breve{\Sigma}(\boldsymbol{x}))$

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(i) Generate training data from model evaluations with sampled $\boldsymbol{x}$, $\boldsymbol{\theta}$.

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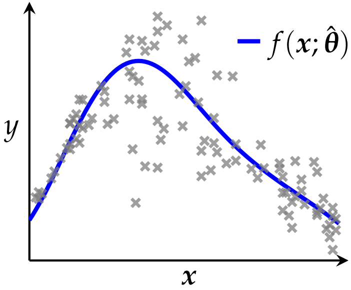
+ Computationally cheap.
+ Black-box models.
− GP scaling.



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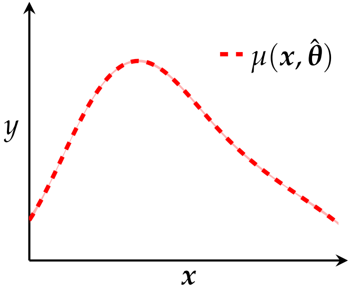

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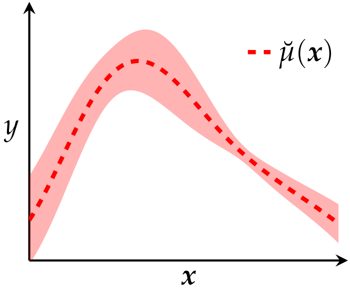

(iii) $\mathcal{N}(\breve{\mu}(\boldsymbol{x}),\breve{\Sigma}(\boldsymbol{x}))$

Results

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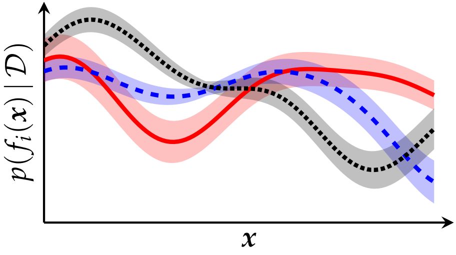
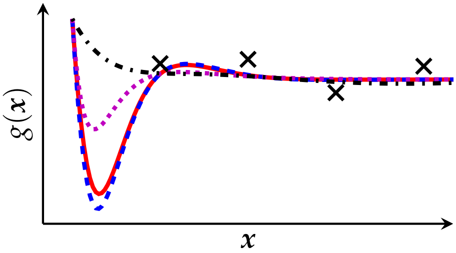


1. **Analytical case studies:** comparing to the analytical approach.



2. **Non-analytical case study:** extending the analytical approach.

Comparison to Analytical Approach

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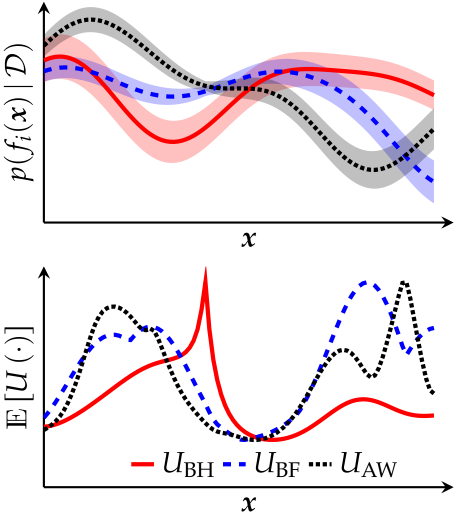
4 problems with competing models.

3 discrimination procedures.

- U_{BH}: Box & Hill (1967)
  - Upper bound on entropy change.
  - Updating Gaussian posterior.
- U_{BF}: Buzzi-Ferraris *et al.* (1990).
  - Heuristic T-statistic.
  - χ^2-test for discarding models.
- U_{AW}: Michalik *et al.* (2010).
  - Sum of Akaike weights.
  - Akaike information criterion.

$\Rightarrow$ **12 case studies**



Comparison to Analytical Approach

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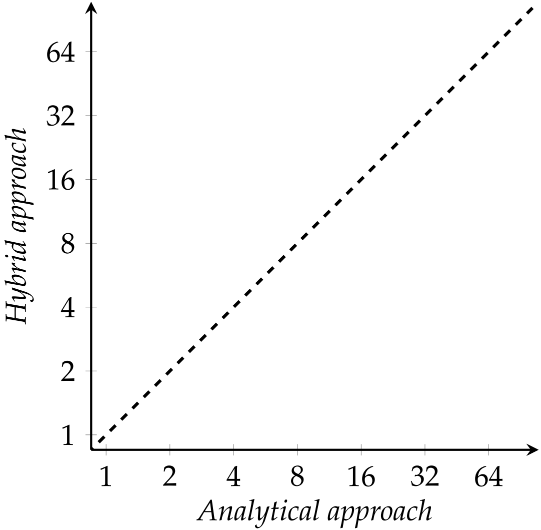
- $j = 1, \ldots, 12$ case studies.
- $\ell = 1, \ldots, N$ trials for each case study j.

$a_{j\ell}$: additional experiments needed in trial ℓ of case study j for successful model discrimination.

A_j: $\text{mean}\{a_{j1}, \ldots, a_{jN}\}$.

$\bar{\sigma}_j$: $\text{std}\{a_{j1}, \ldots, a_{jN}\}/\sqrt{N}$.



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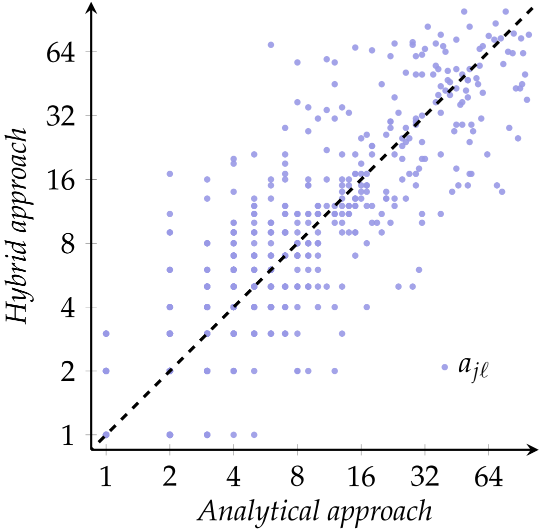

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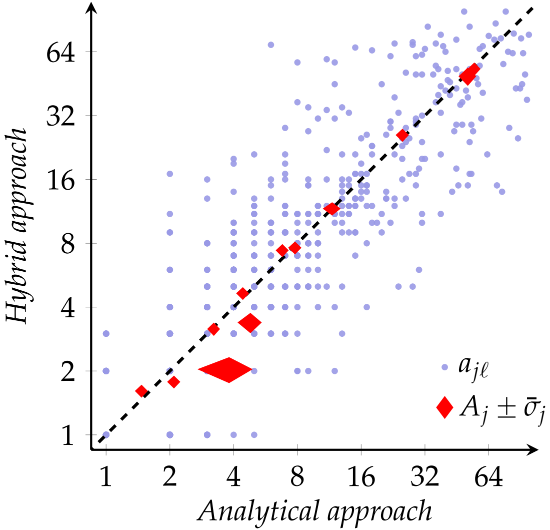

Extension to Non-Analytical Models

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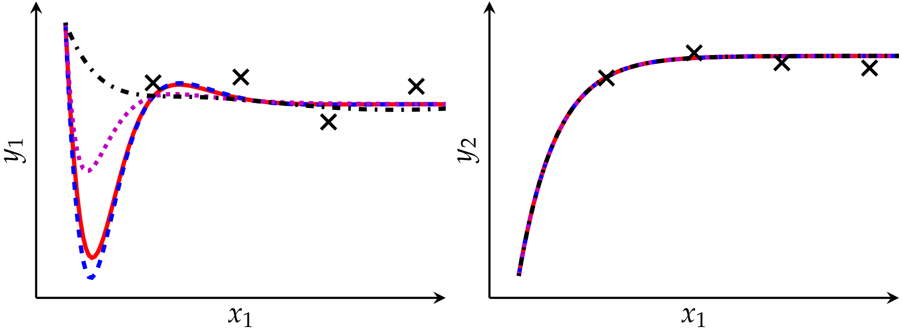
Non-analytical case study based on Vanlier *et al.* (2014)

- Four competing models.
- 20 initial observations.
- $\boldsymbol{\theta} \in \mathbb{R}^{10}$
- $\boldsymbol{x} \in \mathbb{R}^{3}$
- $\boldsymbol{y} \in \mathbb{R}^{2}$



Vanlier *et al.* (2014) Case Study

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Result	U_{BH}	U_{BF}	U_{AW}
A_j	**20.10**	**39.83**	**29.62**
$\bar{\sigma}_j$	**3.72**	**12.09**	**7.72**
Success [%]	15.9	9.5	33.3
Failure [%]	7.9	0.0	7.9
Inconclusive [%]	76.2	90.5	58.7

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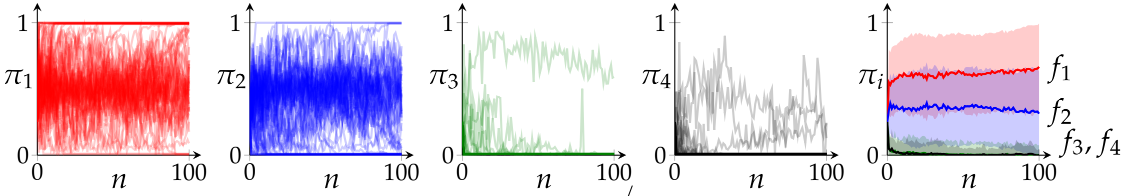
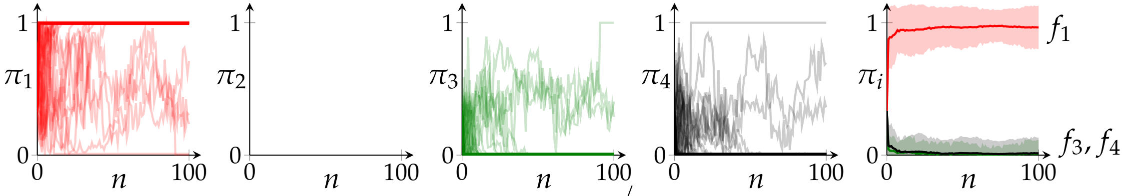


$$U_{\mathrm{AW}}: \quad \pi_i = p(f_i \mid \mathcal{D}) \Big/ \textstyle\sum_j p(f_j \mid \mathcal{D})$$

Vanlier *et al.* (2014) Case Study

	With f_2			*Without f_2*		
Result	U_{BH}	U_{BF}	U_{AW}	U_{BH}	U_{BF}	U_{AW}
A_j	20.10	39.83	29.62	15.80	21.91	9.74
$\bar{\sigma}_j$	3.72	12.09	7.72	2.05	2.52	1.70
Success [%]	**15.9**	**9.5**	**33.3**	**89.5**	**77.2**	**95.6**
Failure [%]	7.9	0.0	7.9	6.1	0.9	1.8
Inconclusive [%]	**76.2**	**90.5**	**58.7**	**4.4**	**21.9**	**2.6**



$$U_{\mathrm{AW}}: \ \ \pi_i = p(f_i \mid \mathcal{D}) \Big/ \textstyle\sum_j p(f_j \mid \mathcal{D})$$

Vanlier *et al.* (2014) Case Study

PROWLER.io the decision company

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Result	With f_2			Without f_2		
	U_{BH}	U_{BF}	U_{AW}	U_{BH}	U_{BF}	U_{AW}
A_j	20.10	39.83	29.62	15.80	21.91	9.74
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Inconclusive [%]	**76.2**	**90.5**	**58.7**	**4.4**	**21.9**	**2.6**

Approximately 1000x faster!

Conclusions

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- Hybridise analytical and data-driven approaches for design of experiments for model discrimination using Gaussian process surrogate models.
- Trade-off between accuracy and computational complexity.
- Hybridised approach performs well, and is effective in practice.

Poster #199

- `github.com/cog-imperial/GPdoemd`
- python 3.4 or higher
- Includes case studies

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