Bayesian Optimization: recent developments and applications

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Goal of the talk

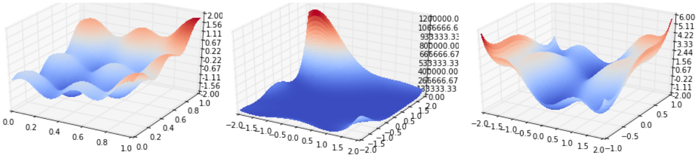
"Civilization advances by extending the number of important operations which we can perform without thinking of them."
(Alfred North Whitehead)

- To make Machine Learning completely automatic.
- To automatically design sequential experiments to optimize physical processes.

Global optimization

Consider a *well behaved* function $f : \mathcal{X} \to \mathbb{R}$ where $\mathcal{X} \subseteq \mathbb{R}^D$ is (in principle) a compact set.

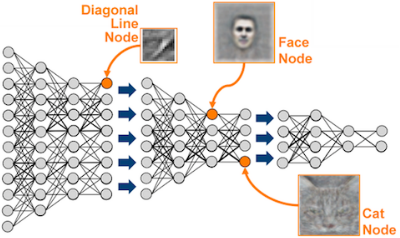
$$x_M = \arg\min_{x \in \mathcal{X}} f(x).$$



- f is explicitly unknown (computer model, process embodied in a physical process) and multimodal.
- Evaluations of f may be perturbed.
- Evaluations of f are (very) expensive.

Expensive functions, who doesn't have one?

Parameter tuning in ML algorithms.

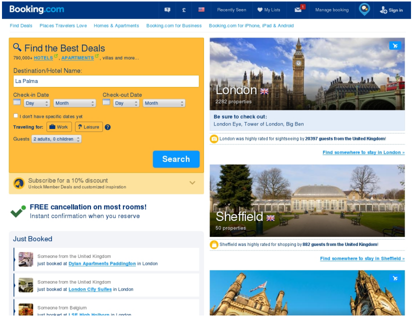


- Number of layers/units per layer
- Weight penalties
- Learning rates, etc.

Figure source: http://theanalyticsstore.com/deep-learning

Expensive functions, who doesn't have one?

Tuning websites with A/B testing



Optimize the web design to maximize sign-ups, downloads, purchases, etc.

What to do?

If f is L-Lipschitz continuous and we are in a noise-free domain to guarantee that we propose some $\mathbf{x}_{M,n}$ such that

$$f(\mathbf{x}_M) - f(\mathbf{x}_{M,n}) \leq \epsilon$$

we need to evaluate f on a D-dimensional unit hypercube:

$$(L/\epsilon)^D evaluations!$$

Example: $(10/0.01)^5 = 10e14$...
... but function evaluations are very expensive!

Regret minimization

The goal is to make a series of $x_1, \ldots, x_N$ evaluations of f such that the *cumulative regret*

$$r_N = \sum_{n=1}^{N} f(x_{M,n}) - N f(x_M)$$

is minimized.

r_N is minimized if we start evaluating f at x_M as soon as possible.

Approach

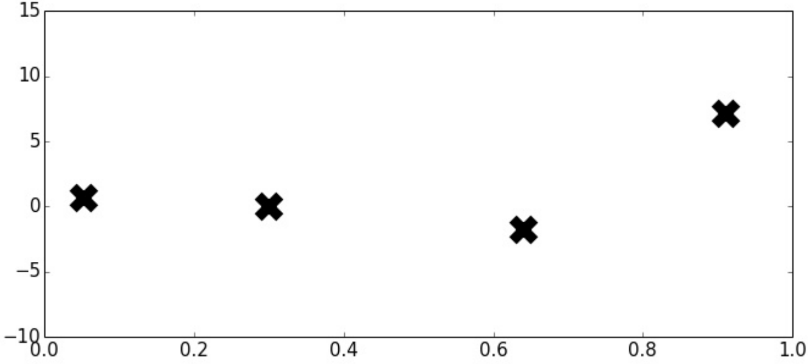
1. Minimize the regret implies to see an *optimization* problem as a *decision* problem.

2. *Decision* problems can be seen as *inference* if we take into account the *epistemic* uncertainty we have about the system we are studying.

Probability theory is the right way to model uncertainty.

Typical situation

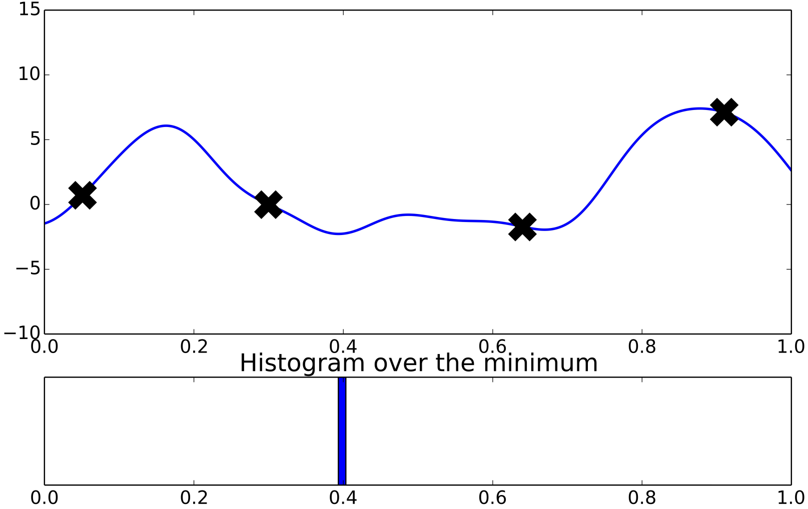
We have a few function evaluations



Where is the minimum of f?
Where should the take the next evaluation?

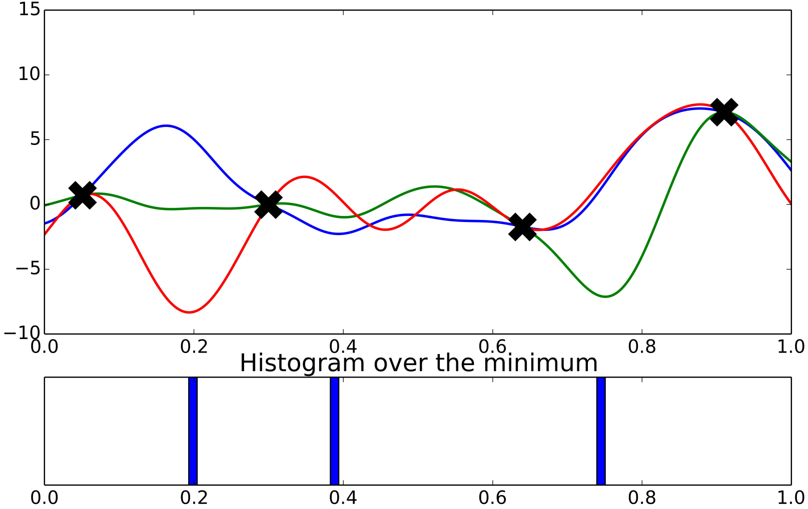
Intuitive solution

One curve



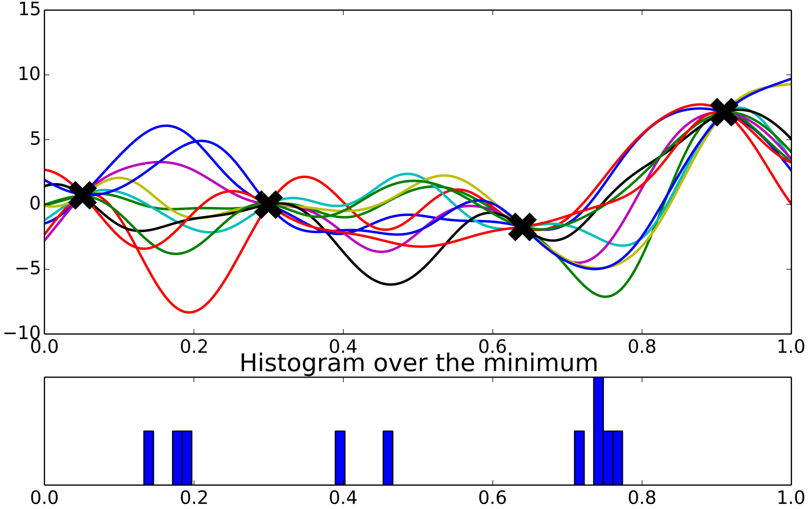
Intuitive solution

Three curves



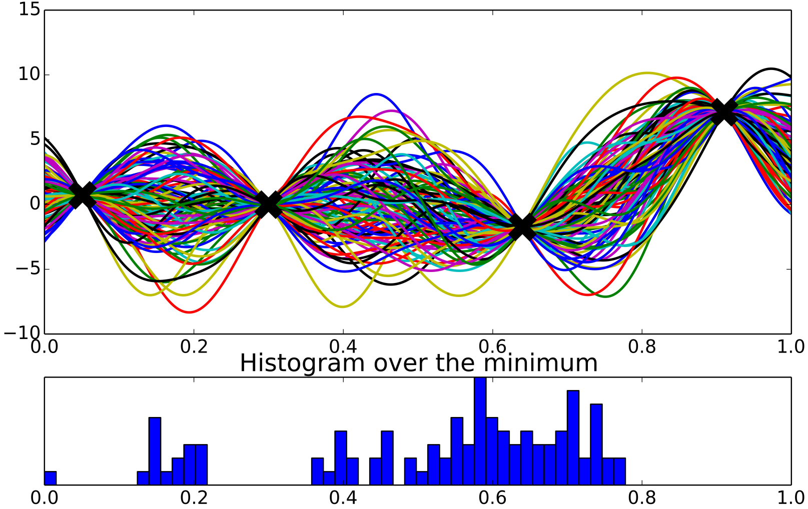
Intuitive solution

Ten curves



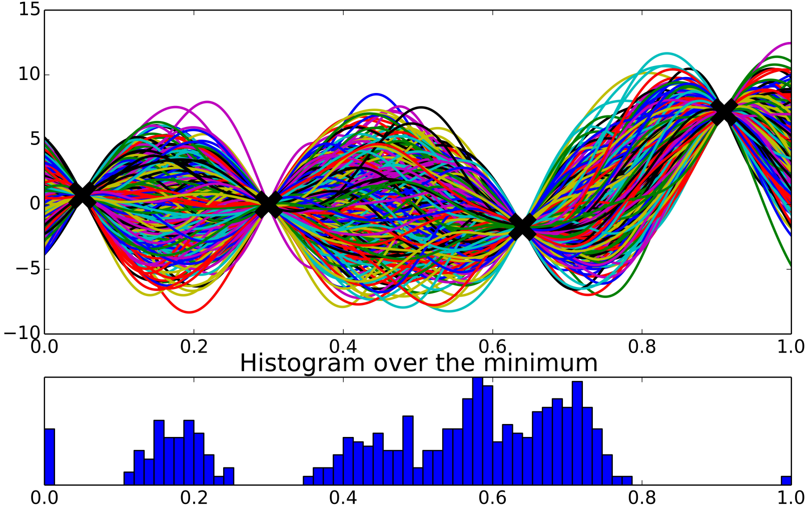
Intuitive solution

Hundred curves



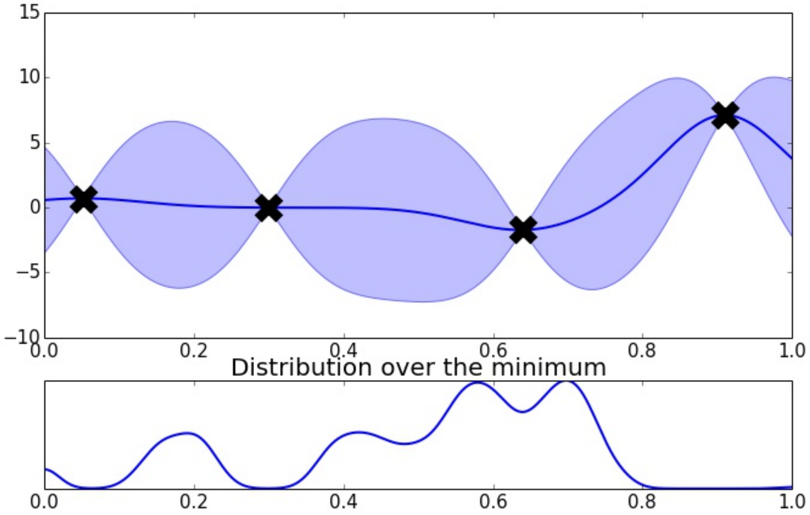
Intuitive solution

Many curves



Intuitive solution

Infinite curves



What just happened?

- We made some *prior assumptions* about our function.
- Information about the minimum is now encoded in a new function: *the probability distribution $p_{\min}$*.
- We can use $p_{\min}$ (or a functional of it) to *decide where to sample* next.
- Other functions to encode relevant information about the minimum are possible, e. g. the 'marginal expected gain' at each location.

Bayesian Optimization

Methodology to perform global optimization of multimodal black-box functions [Mockus, 1978].

1. Choose some *prior measure* over the space of possible objectives f.

2. Combine prior and the likelihood to get a *posterior* over the objective given some observations.

3. Use the posterior to decide where to take the next evaluation according to some *acquisition function*.

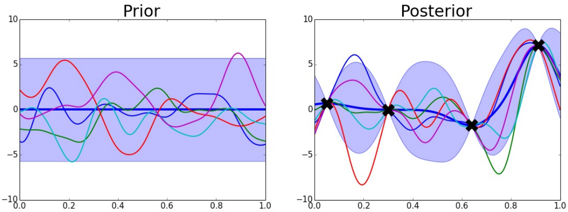
4. Augment the data.

Iterate between 2 and 4 until the evaluation budget is over.

Probability measure over functions

Default Choice: Gaussian processes [Rasmunsen and Williams, 2006]

Infinite-dimensional probability density, such that each linear finite-dimensional restriction is multivariate Gaussian.



- Model $f(x) \sim \mathcal{GP}(\mu(x), k(x, x'))$ is determined by the mean function $m(x)$ and covariance function $k(x, x'; \theta)$.
- Posterior mean $\mu(x; \theta, \mathcal{D})$ and variance $\sigma(x; \theta, \mathcal{D})$ can be computed explicitly given a dataset $\mathcal{D}$.

Acquisition functions

Making use of the model uncertainty

Here we will use Gaussian processes. GPs has marginal closed-form for the posterior mean $\mu(x)$ and variance $\sigma^2(x)$.

- **Exploration**: Evaluate in places where the variance is large.
- **Exploitation**: Evaluate in places where the mean is low.

Acquisition functions balance these two factors to determine where to evaluate next.

Exploration vs. exploitation

[Borji and Itti, 2013]

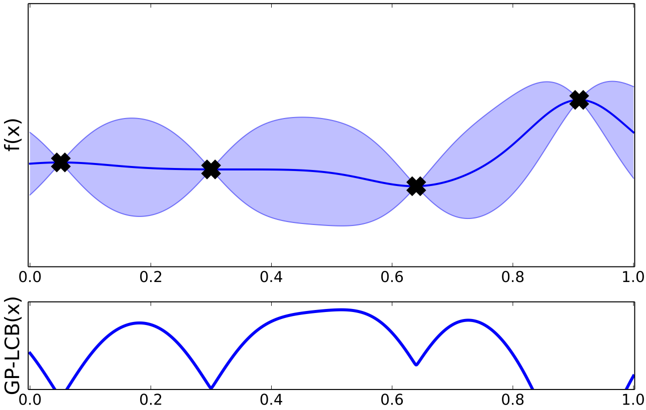
Bayesian optimization explains human active search

GP Upper (lower) Confidence Band

[Srinivas et al., 2010]

Direct balance between exploration and exploitation:

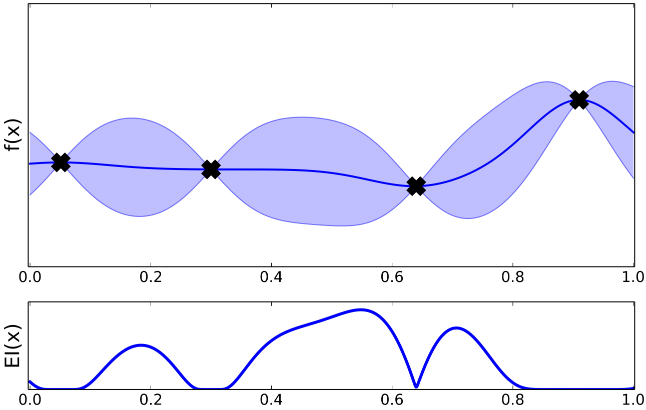
$$\alpha_{LCB}(\mathbf{x};\theta,\mathcal{D}) = -\mu(\mathbf{x};\theta,\mathcal{D}) + \beta_t\sigma(\mathbf{x};\theta,\mathcal{D})$$



Expected Improvement

[Jones et al., 1998]

$$\alpha_{EI}(\mathbf{x};\theta,\mathcal{D}) = \int_y \max(0, y_{best} - y)p(y|\mathbf{x};\theta,\mathcal{D})dy$$



Information-theoretic approaches

[Hennig and Schuler, 2013; Hernández-Lobato et al., 2014]

$$\alpha_{ES}(\mathbf{x};\theta,\mathcal{D}) = H[p(x_{min}|\mathcal{D})] - \mathbb{E}_{p(y|\mathcal{D},\mathbf{x})}[H[p(x_{min}|\mathcal{D}\cup\{\mathbf{x},y\})]]$$

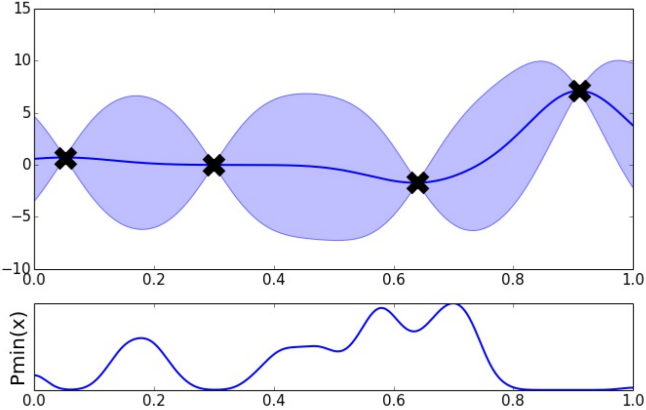
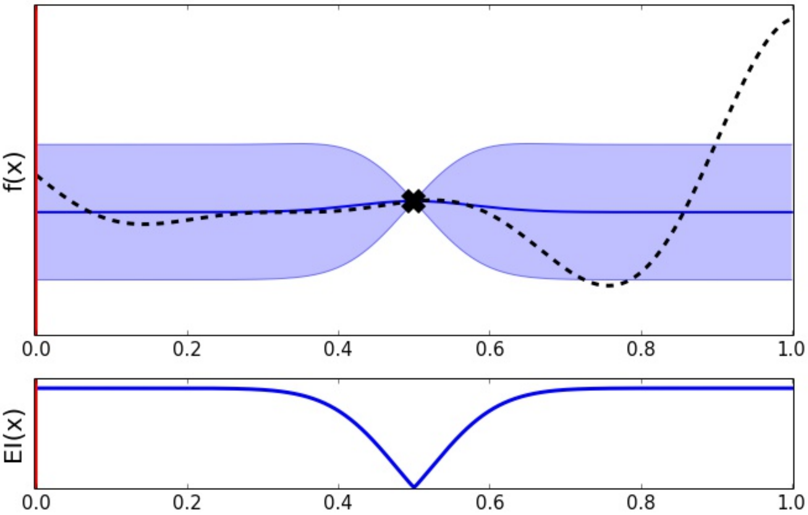


Illustration of BO



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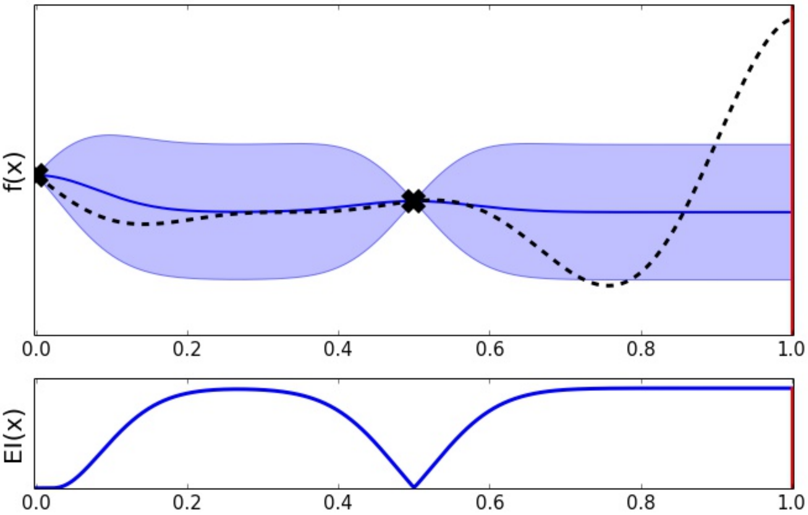

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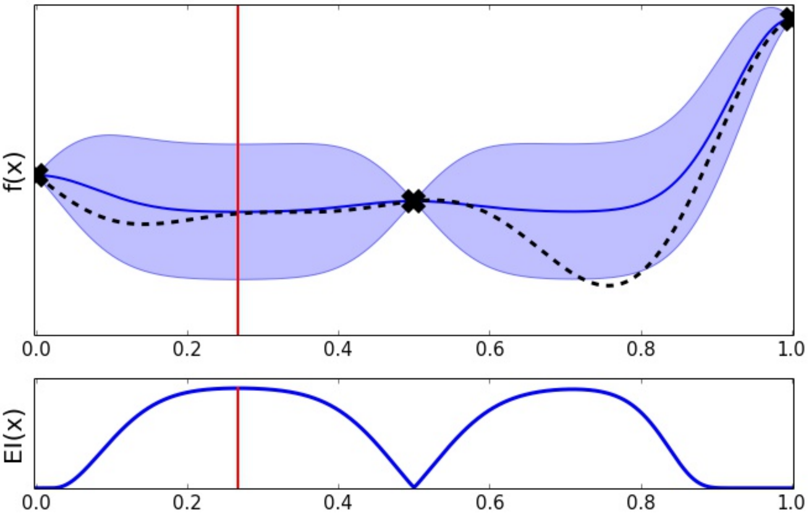

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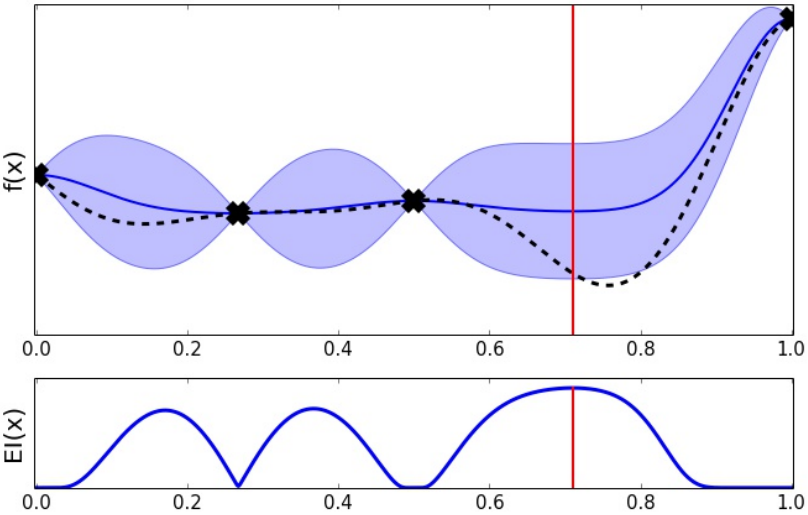

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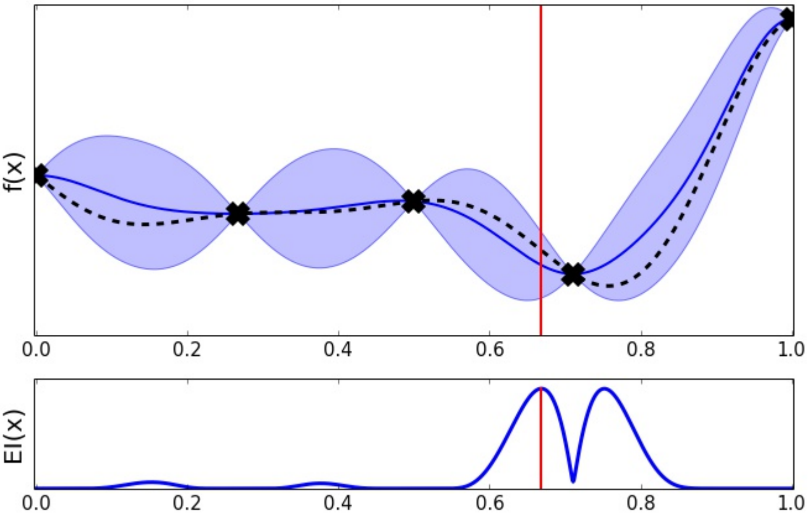

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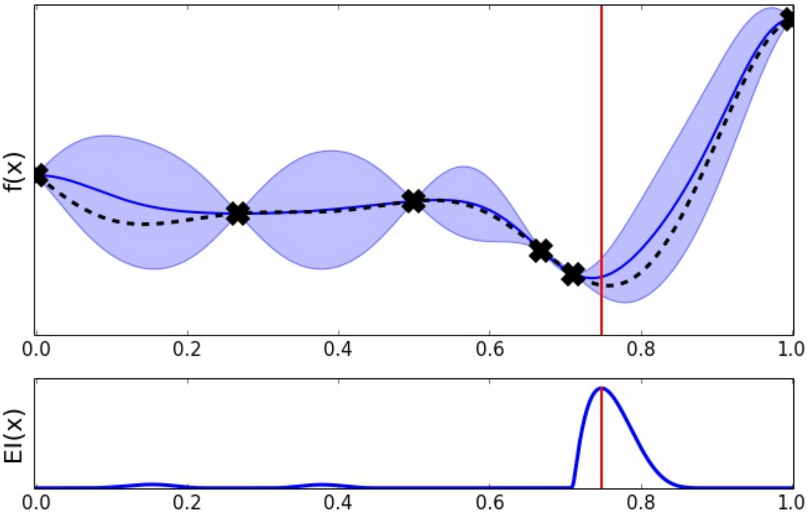

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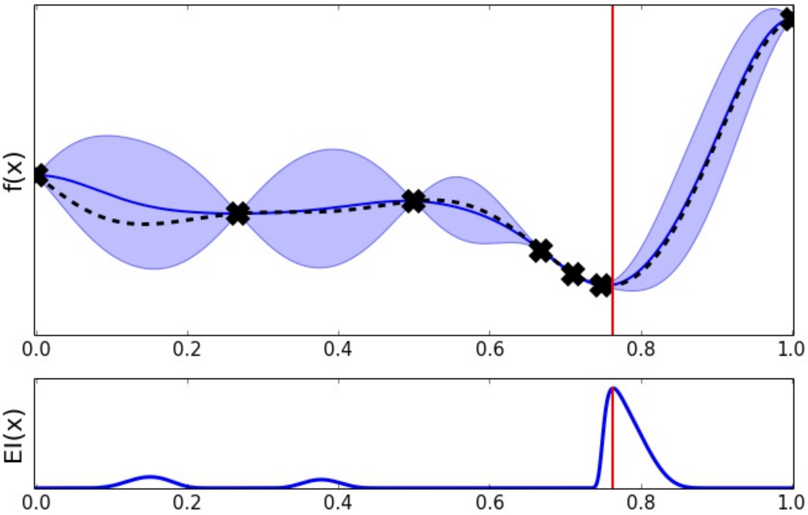

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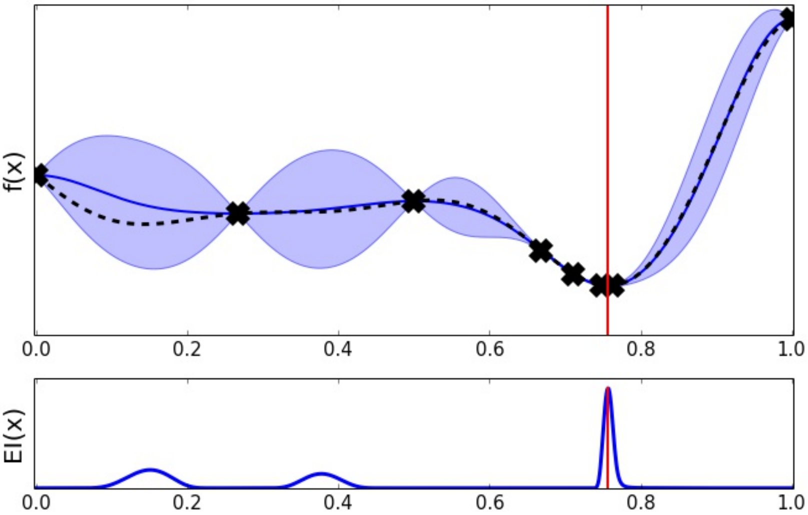

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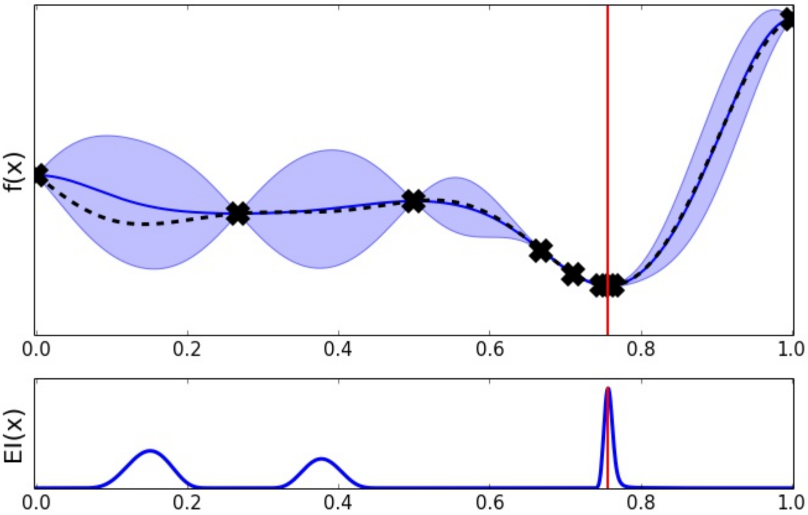


Bayesian Optimization

As a 'mapping' between two problems

BO is an strategy to transform the problem

$$x_M = \arg\min_{x \in \mathcal{X}} f(x)$$

unsolvable!

into a series of problems:

$$x_{n+1} = \arg\max_{x \in \mathcal{X}} \alpha(x; \mathcal{D}_n, \mathcal{M}_n)$$

solvable!

where now:

- $\alpha(x)$ is inexpensive to evaluate.
- The gradients of $\alpha(x)$ are typically available.
- Still need to find x_{n+1}: gradient descent, DIRECT or other heuristics.

Why these ideas have been ignored for years?

- BO depends on its own parameters.
- Lack of software to apply these methods as a black optimzation boxes.
- Reduced scalability in dimensions and number of evaluations (this is still a problem).

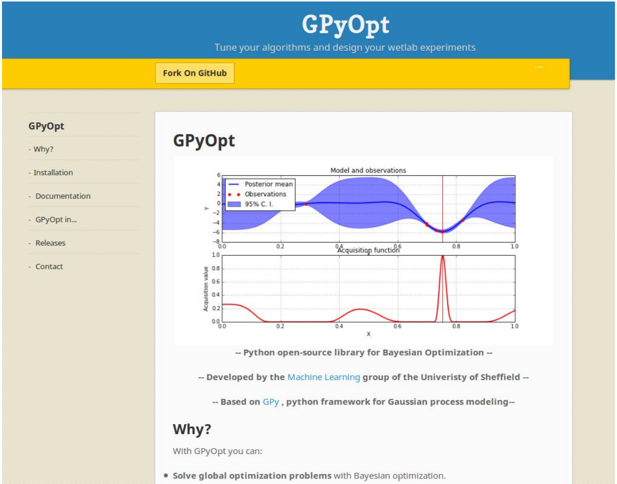
Practical Bayesian Optimisation of Machine Learning Algorithms.
Snoek, Larochelle and Adams. NIPS 2012 (Spearmint)

+

Other works of M. Osborne, P. Hennig, N. de Freitas, etc.

Open Software: GPyOpt

http://sheffieldml.github.io/GPyOpt/



Scalable BO: Parallel/batch BO

Avoiding the bottleneck of evaluating f

- Cost of $f(\mathbf{x}_n)$ = cost of $\{f(\mathbf{x}_{n,1}), \ldots, f(\mathbf{x}_{n,nb})\}$.
- Many cores available, simultaneous lab experiments, etc.

Considerations when designing a batch

- Available pairs $\{(\mathbf{x}_j, y_i)\}_{i=1}^{n}$ are augmented with the evaluations of f on $\mathcal{B}_t^{n_b} = \{\mathbf{x}_{t,1}, \ldots, \mathbf{x}_{t,nb}\}$.

- Goal: design $\mathcal{B}_1^{n_b}, \ldots, \mathcal{B}_m^{n_b}$.

Notation:

- $\mathcal{I}_n$: represents the available data set $\mathcal{D}_n$ and the $\mathcal{GP}$ structure when n data points are available.

- $\alpha(\mathbf{x}; \mathcal{I}_n)$: generic acquisition function given $\mathcal{I}_n$.

Available approaches

[Azimi et al., 2010; Azimi et al., 2011; Azimi et al., 2012; Desautels et al., 2012; Chevalier et al., 2013; Contal et al. 2013]

- Exploratory approaches, reduction in system uncertainty.
- Generate 'fake' observations of f using $p(y_{t,j}|\mathbf{x}_j, \mathcal{I}_{t,j-1})$.
- Simultaneously optimize elements on the batch using the joint distribution of $y_{t_1}, \dots y_{t,nb}$.

Bottleneck

All these methods require to iteratively update $p(y_{t,j}|\mathbf{x}_j, \mathcal{I}_{t,j-1})$ to model the iteration between the elements in the batch: $\mathcal{O}(n^3)$

How to design batches reducing this cost? BBO-LP

Goal: eliminate the marginalization step

"To develop an heuristic approximating the 'optimal batch design strategy' at lower computational cost, while incorporating information about global properties of f from the $\mathcal{GP}$ model into the batch design"

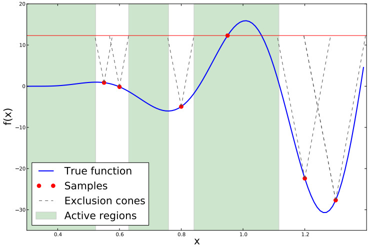
Lipschitz continuity:

$$|f(\mathbf{x}_1) - f(\mathbf{x}_2)| \leq L\|\mathbf{x}_1 - \mathbf{x}_2\|_p.$$

Interpretation of the Lipschitz continuity of f

$M = \max_{\mathbf{x} \in \mathcal{X}} f(\mathbf{x})$ and $B_{r_{x_j}}(\mathbf{x}_j) = \{\mathbf{x} \in \mathcal{X} : \|\mathbf{x} - \mathbf{x}_j\| \leq r_{x_j}\}$ where

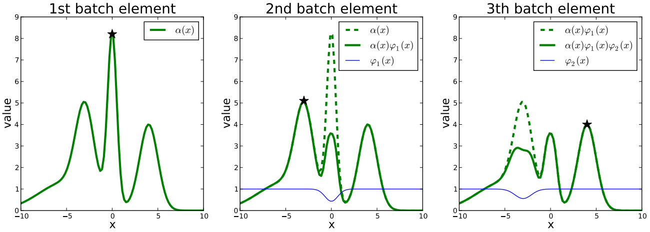
$$r_{x_j} = \frac{M - f(\mathbf{x}_j)}{L}$$



$x_M \notin B_{r_{x_j}}(\mathbf{x}_j)$ otherwise, the Lipschitz condition is violated.

Local penalization strategy

[González, Dai, Hennig, Lawrence, 2015]

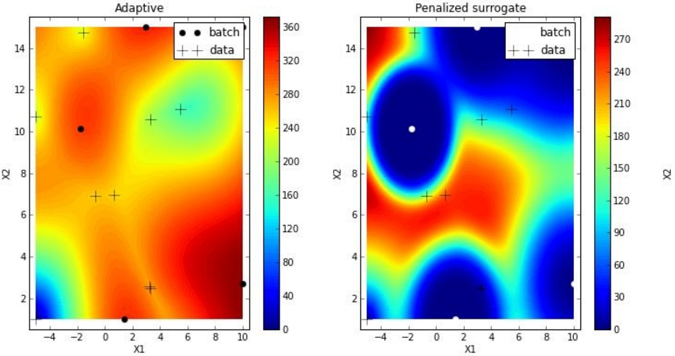


Take $\varphi(\mathbf{x};\mathbf{x}_j) = p(\mathbf{x} \notin B_{r_{\mathbf{x}_j}}(\mathbf{x}_j))$ and $\mathbf{x}_{t,k}$ as

$$\mathbf{x}_{t,k} = \arg\max_{x \in \mathcal{X}} \left\{ g(\alpha(\mathbf{x};\mathcal{I}_{t,0})) \prod_{j=1}^{k-1} \varphi(\mathbf{x};\mathbf{x}_{t,j}) \right\},$$

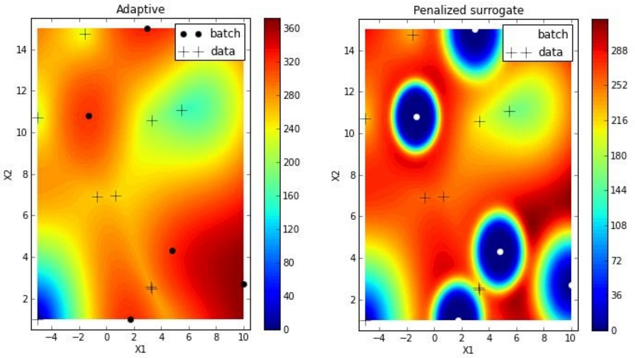
g is a transformation of $\alpha(\mathbf{x};\mathcal{I}_{t,0})$ to make it always positive.

Example for $L = 50$



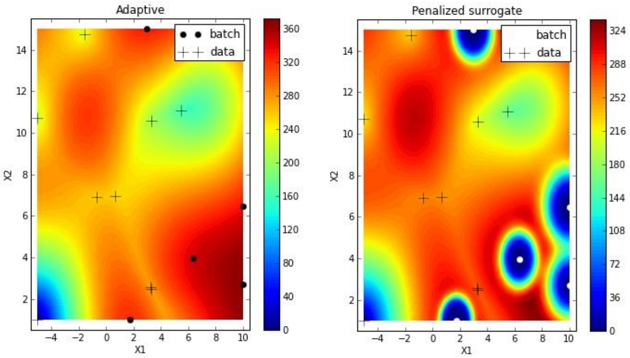
L controls the exploration-exploitation balance within the batch.

Example for $L = 100$



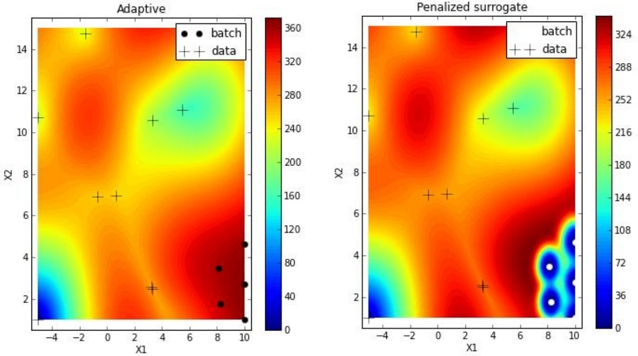
L controls the exploration-exploitation balance within the batch.

Example for $L = 150$



L controls the exploration-exploitation balance within the batch.

Example for $L = 250$



L controls the exploration-exploitation balance within the batch.

Finding an unique Lipschitz constant

The gradient of f at $\mathbf{x}^*$ is distributed as a multivariate Gaussian

$$\nabla f(\mathbf{x}^*)|\mathbf{X}, \mathbf{y}, \mathbf{x}^* \sim \mathcal{N}(\mu_\nabla(\mathbf{x}^*), \Sigma^2_\nabla(\mathbf{x}^*))$$

We choose:

$$\hat{L}_{GP-LCA} = \max_{\mathcal{X}} \|\mu_\nabla(\mathbf{x}^*)\|$$

Sobol function

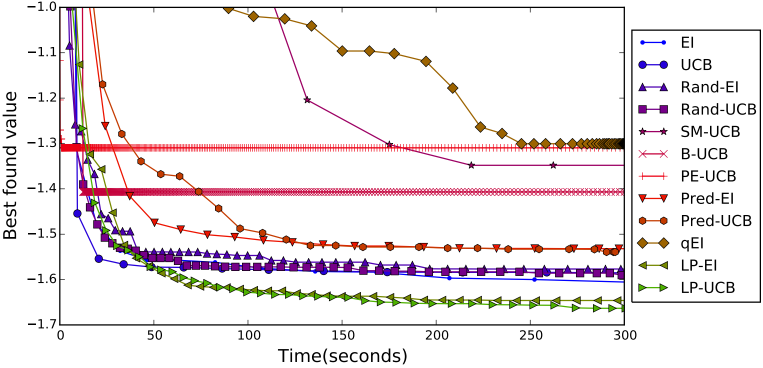
Best (average) result for some given time budget.

d	n_b	EI	UCB	Rand-EI	Rand-UCB	SM-UCB	B-UCB
2	5	0.31±0.03	0.32±0.06	0.32±0.05	**0.31±0.05**	1.86±1.06	0.56±0.03
	10			0.65±0.32	0.79±0.42	4.40±2.97	**0.59±0.00**
	20			0.67±0.31	0.75±0.32	-	0.57±0.01
5	5	8.84±3.69	11.89±9.44	9.19±5.32	10.59±5.04	137.2±113.0	**6.01±0.00**
	10			1.74±1.47	2.20±1.85	108.7±74.38	3.77±0.00
	20			2.18±2.30	2.76±3.06	-	2.53±0.00
10	5	559.1±1014	1463±1803	**690.5±947.5**	1825±2149	9e+04±7e+04	2098±0.00
	10			200.9±455.9	1149±1830	9e+04±1e+05	857.8±0.00
	20			639.4±1204	385.9±642.9	-	1656±0.00

d	n_b	PE-UCB	Pred-EI	Pred-UCB	qEI	LP-EI	LP-UCB
2	5	0.99±0.74	0.41±0.15	0.45±0.16	1.53±0.86	0.35±0.11	**0.31±0.06**
	10	0.66±0.29	1.16±0.70	1.26±0.81	3.82±2.09	0.66±0.48	0.69±0.51
	20	0.75±0.44	1.28±0.93	1.34±0.77	-	**0.50±0.21**	0.58±0.21
5	5	123.5±81.43	10.43±4.88	11.77±9.44	15.70±8.90	11.85±5.68	10.85±8.08
	10	120.8±78.56	9.58±7.85	11.66±11.48	17.69±9.04	3.88±4.15	**1.88±2.46**
	20	98.60±82.60	8.58±8.13	10.86±10.89	-	6.53±4.12	**1.44±1.93**
10	5	2e+05±2e+05	793.0±1226	1412±3032	-	1881±1176	1194±1428
	10	6e+04±8e+04	442.6±717.9	1725±3205	-	1042±1562	**100.4±338.7**
	20	5e+04±4e+04	1091±1724	2231±3110	-	1249±1570	**20.75±50.12**

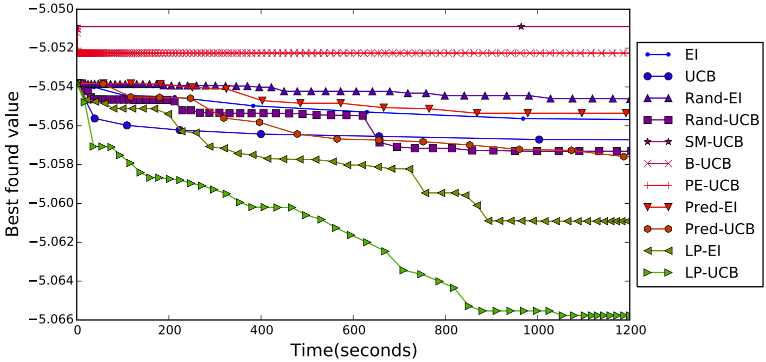
2D experiment with ‘large domain’

Comparison in terms of the wall clock time



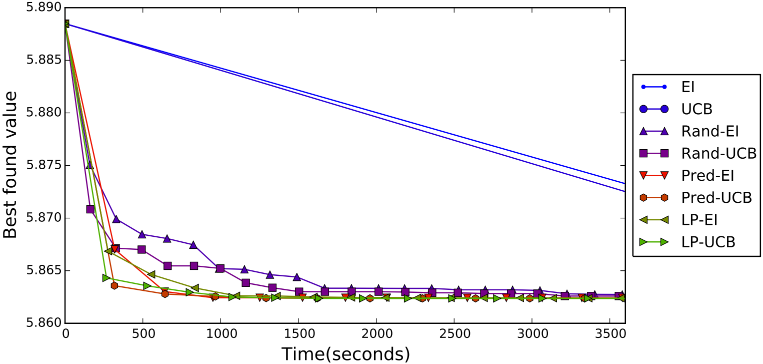
Maximizing gene translation

- Maximization of a 70 dimensional surface representing the efficiency of hamster cells producing proteins.



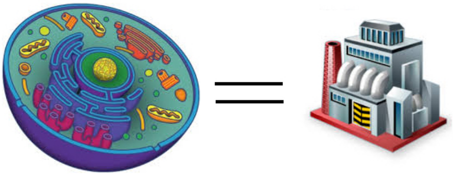
Support Vector Regression

- Minimization of the RMSE on a test set over 3 parameters.
- ’Physiochemical’ properties of protein tertiary structure?.
- 45730 instances and 9 continuous attributes.



Application: Synthetic gene design

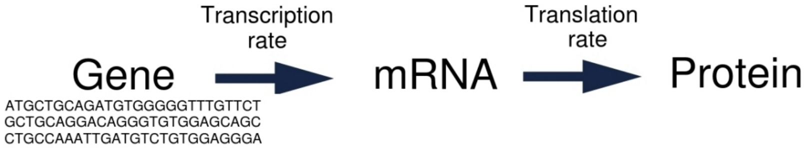
[González, Lonworth, James and Lawrence, 2014, 2015]



- Use mammalian cells to make protein products.
- Control the ability of the cell-factory to use synthetic DNA.

Optimize genes (ATTGGTUGA...) to best enable the cell-factory to operate most efficiently .

Central dogma of molecular biology



Big question

Remark: 'Natural' gene sequences are not necessarily optimized to maximize protein production.

ATGCTGCAGATGTGGGGGTTTGTTCTCTATCTCTTCCTGAC
TTTGTTCTCTATCTCTTCCTGACTTTGTTCTCTATCTCTTC...

Considerations

- Different gene sequences → same protein.
- The sequence affects the synthesis efficiency.

Which is the most efficient sequence to produce a protein?

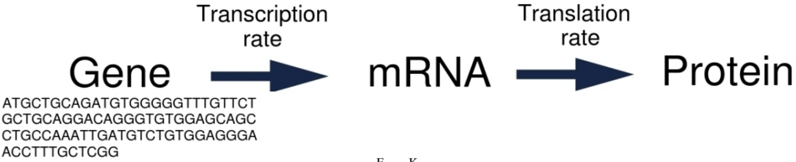
Redundancy of the genetic code

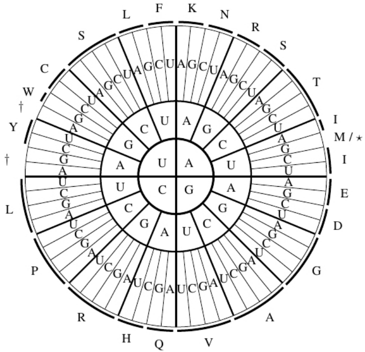
- Codon: Three consecutive bases: AAT, ACG, etc.
- Protein: sequence of amino acids.
- Different codons may encode the same aminoacid.
- ACA=ACU encodes for Threonine.

$$ATUUUG\textcolor{blue}{ACA} = ATUUUG\textcolor{red}{ACU}$$

synonyms sequences → same protein but different efficiency

Redundancy of the genetic code





How to design a synthetic gene?

A good model is crucial—: Gene sequence features → protein production efficiency.

Bayesian Optimization principles for gene design

do:

1. Build a GP model as an emulator of the cell behavior.
2. Obtain a set of gene design rules (features optimization).
3. Design one/many new gene/s coherent with the design rules.
4. Test genes in the lab (get new data).

until the gene is optimized (or the budget is over...).

Model as an emulator of the cell behavior

Model inputs
Features ($\mathbf{x}_i$) extracted gene sequences ($\mathbf{s}_i$): codon frequency, cai, gene length, folding energy, etc.

Model outputs
Transcription and translation rates $\mathbf{f} := (f_\alpha, f_\beta)$.

Model type
Multi-output Gaussian process $\mathbf{f} \approx \mathcal{GP}(\mathbf{m}, \mathbf{K})$ where $\mathbf{K}$ is a corregionalization covariance for the two-output model (+ SE with ARD).

The correlation in the outputs help!

Obtaining optimal gene design rules

Maximize the averaged EI [Swersky et al. 2013]

$$\alpha(\mathbf{x}) = \bar{\sigma}(\mathbf{x})(-u\Phi(-u) + \phi(u))$$

where $u = (y_{max} - \bar{m}(\mathbf{x}))/\bar{\sigma}(x)$ and

$$\bar{m}(\mathbf{x}) = \frac{1}{2}\sum_{l=\alpha,\beta} \mathbf{f}_*(\mathbf{x}),\ \ \bar{\sigma}^2(\mathbf{x}) = \frac{1}{2^2}\sum_{l,l'=\alpha,\beta} (\mathbf{K}_*(\mathbf{x},\mathbf{x}))_{l,l'}.$$

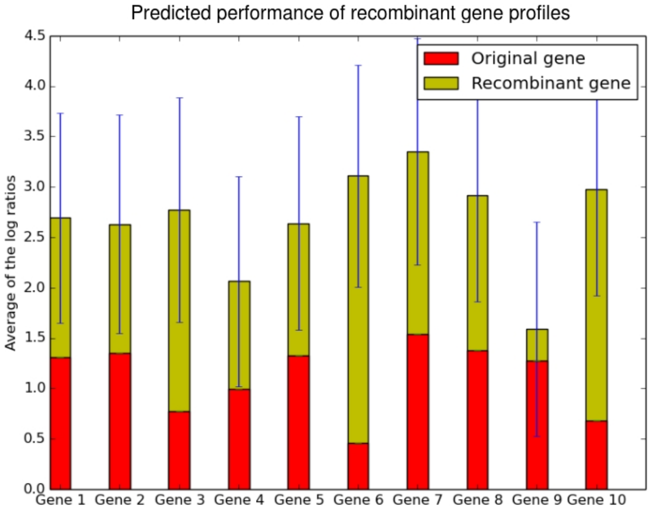
A batch method is used when several experiments can be run in parallel

Designing new genes coherent with the optimal design rules

Simulating-matching approach:

1. Simulate genes ‘coherent’ with the target (same amino-acids).
2. Extract features.
3. Rank synthetic genes according to their similarity with the ‘optimal’ design rules.

Results for 10 low-expressed genes



Wrapping up

- BO is fantastic tool for parameter optimization in ML and experimental design.
- The model and acquisition function are the two most important bits.
- Parallel approaches are the key to scale BO.
- Software available!

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Picture source: http://peakdistrictcycleways.co.uk

Use Bayesian optimization!