Optimal Learning for Drug Discovery in Ewing's Sarcoma

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Outline

I. Ewing Sarcoma and Our Problem

II. Modeling Structure-Value Relationships

III. Correlated Knowledge Gradient Algorithm

IV. A First Improvement

V. A Further Improvement

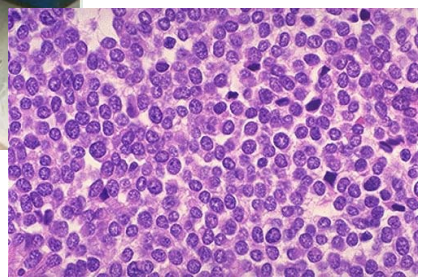
VI. Results

Ewing's Sarcoma

It is a tumor typically arising in the bones, and rarely in soft tissues, of children and adolescents.

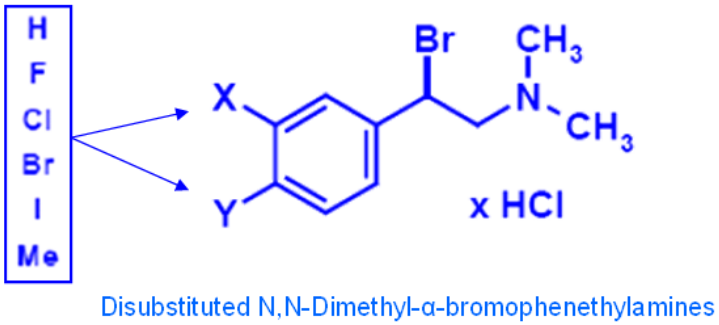
The tumor has retained the most unfavorable prognosis of all primary musculoskeletal tumors ([Iwa07])

Ewing's Sarcoma cells

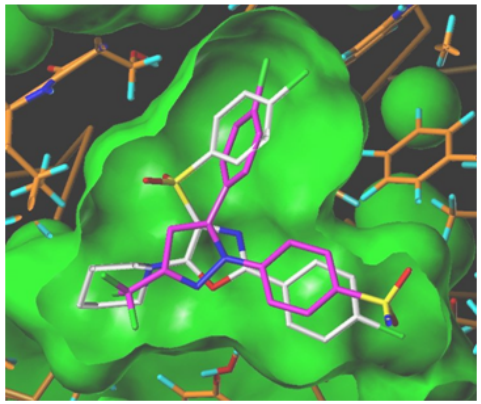


Our Problem

We have a molecule to which *substituents* can be attached at various sites $\Rightarrow$ many combinations.



Disubstituted N,N-Dimethyl-α-bromophenethylamines



Given

- measurements made so far
- possible correlations between molecules with similar structure

Can we systematically tell which compound to test next?

Modeling Structure-Value Relationships (I)

Start with a linearly additive model - Free Wilson Model.

Represent a compound as a row vector s of 0 and 1's.

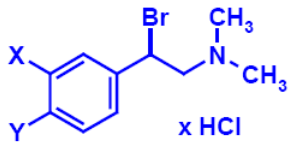
Value of a compound is

$$\vartheta = \sum_{1}^{k} a_i s_i + \zeta$$

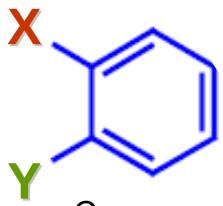
Hugo Kubinyi, www.kubinyi.de

meta (X)	para (Y)	log 1/C obs.	meta- F	Cl	Br	I	Me	para- F	Cl	Br	I	Me	log 1/C calc.
H	H	7.46											7.82
H	F	8.16						1					8.16
H	Cl	8.68							1				8.59
H	Br	8.89								1			8.84
H	I	9.25									1		9.25
H	Me	9.30										1	9.08
F	H	7.52	1										7.52
Cl	H	8.16		1									8.03
Br	H	8.30			1								8.26
I	H	8.40				1							8.40
Me	H	8.46					1						8.28
Cl	F	8.19		1				1					8.37
Br	F	8.57			1			1					8.60
Me	F	8.82					1	1					8.62
Cl	Cl	8.89		1					1				8.80
Br	Cl	8.92			1				1				9.02
Me	Cl	8.96					1		1				9.04
Cl	Br	9.00		1						1			9.05
Br	Br	9.35			1					1			9.28
Me	Br	9.22					1			1			9.30

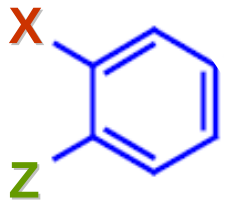
Matrix for Free Wilson Analysis



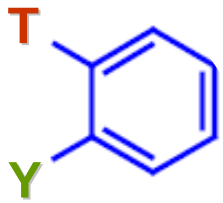
Modeling Covariance (I)



Compound 1



Compound 2



Compound 3

Model the covariance between compounds i and j as

$$\mathrm{Cov}(i,j) = \mathrm{Var}(\zeta) + \sum_{m \in \mathcal{L}_{ij}} \mathrm{Var}(a_m)$$

where $\mathcal{L}_{ij} = \{l \in \{1,...,k\} | s_l^i = s_l^j = 1\}$.

If the variance of the disubstituted molecule, $\mathrm{Var}(\zeta)$, is σ^2, then

$$\begin{aligned} \mathrm{Cov}(1,2) &= \mathrm{Var}(a_X) + \sigma^2; \\ \mathrm{Cov}(2,3) &= \sigma^2. \end{aligned}$$

Modeling Structure-Value Relationships (II)

A more general model - allow for deviations from linearity.

Value of a compound x is

$$\vartheta_x = \sum_{1}^{k} a_i s_i + \zeta + b_x.$$

where $b_1, .., b_M \sim \mathcal{N}(0, \sigma_b)$.

Hugo Kubinyi, www.kubinyi.de

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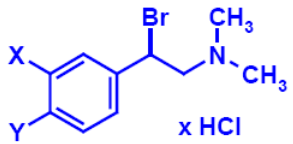
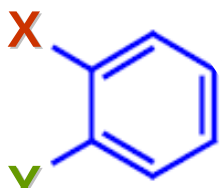


Modeling Covariance (II)



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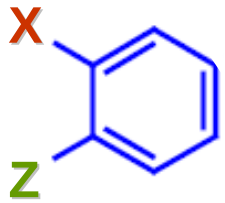
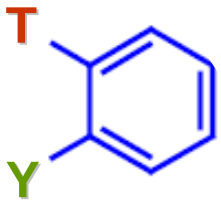


Compound 2



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\mathrm{Cov}(1,2) &= \mathrm{Var}(a_X) + \sigma^2; \\
\mathrm{Cov}(2,3) &= \sigma^2; \\
\mathrm{Cov}(1,1) &= \mathrm{Var}(a_X) + \mathrm{Var}(a_Y) + \sigma^2 + \sigma_b^2.
\end{aligned}$$

Propose: Knowledge Gradient with Correlated Beliefs (KGCB)

Make each decision so as to maximize the increase in knowledge (the gradient) from measuring a specific compound.

$$\nu^{n,KG} = \max_x \mathbb{E}_n \left[\max_i \mu_i^{n+1} | S^n = s, x^n = x \right] - \max_i \mu_i^n$$

where S^n represents the belief state at measurement n, and x is a compound.

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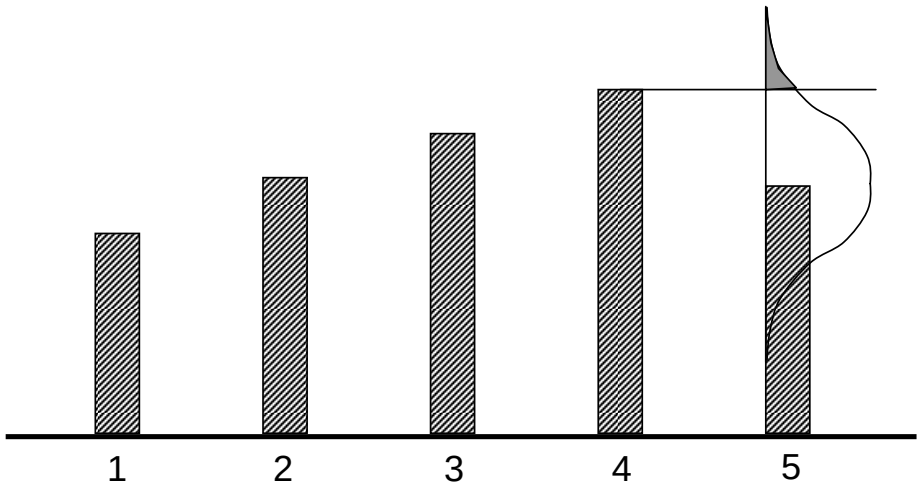

Knowledge Gradient with Correlated Beliefs (KGCB) Algorithm [FPD09]

Bayesian approach:

- Start with a belief on the values of the compounds, given by a mean vector μ^0 and a covariance matrix Σ^0;

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- Start with a belief on the values of the compounds, given by a mean vector μ^0 and a covariance matrix Σ^0;
  1. Decide what to measure and make the measurement;
  2. Update the mean vector μ and the covariance matrix Σ:

$$\begin{bmatrix} \vdots \\ \mu^{n+1} \\ \vdots \end{bmatrix} = \begin{bmatrix} \vdots \\ \mu^{n} \\ \vdots \end{bmatrix} + \alpha \begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^n & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix} \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix};$$

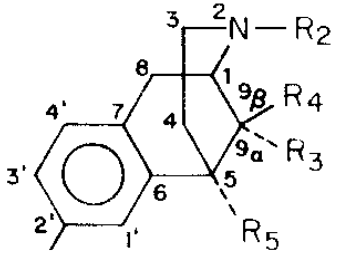
Vector of 0's with a 1 at the position of the compound that was just measured

$$\begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n+1} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix} = \begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix} + \beta \begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix} \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix}$$

- Repeat steps 1 and 2 until all measurements have been made.

A More Scalable Implementation

Consider a molecule with 5 sites, at each of which 10 substituents can be attached.



Rl

This implies $10^5 = 100,000$ compounds. Σ is too big!

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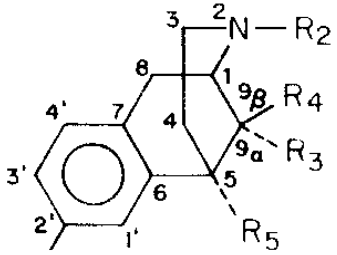

Rl

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$$\underbrace{\begin{bmatrix} \vdots \\ \mu^{n+1} \\ \vdots \end{bmatrix}}_{100{,}000} = \begin{bmatrix} \vdots \\ \mu^{n} \\ \vdots \end{bmatrix} + \alpha \begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^n & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix} \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix};$$

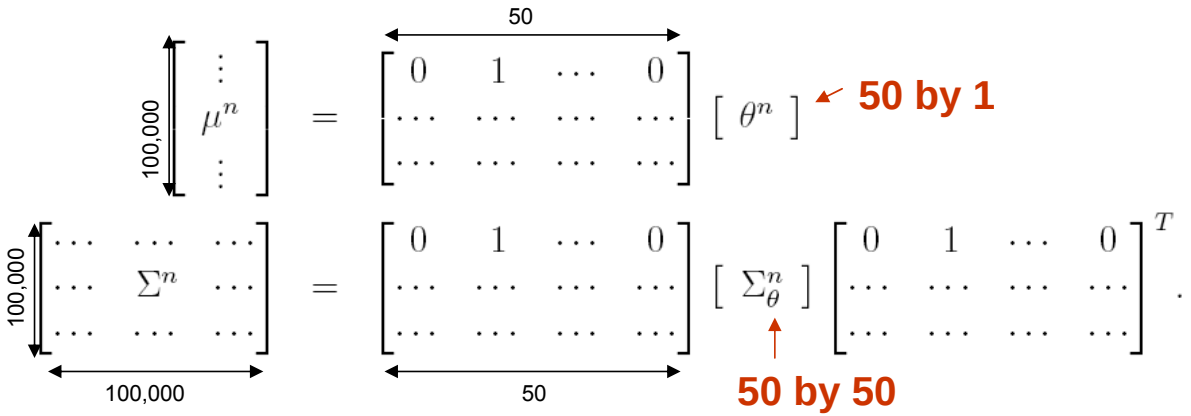
Vector of 0's with a 1 at the position of the compound that was just measured

$$\underbrace{\begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n+1} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix}}_{100{,}000 \times 100{,}000} = \underbrace{\begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix}}_{100{,}000 \times 100{,}000} + \beta \underbrace{\begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix}}_{100{,}000 \times 100{,}000} \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 0 & 1 & 0 \end{bmatrix} \underbrace{\begin{bmatrix} \cdots & \cdots & \cdots \\ \cdots & \Sigma^{n} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix}}_{100{,}000 \times 100{,}000}$$

A More Scalable Implementation

New approach: keep a belief on the *substituents* a_i.

Assume $a \sim \mathcal{N}(\theta^n, \Sigma_\theta^n)$.
For the Free-Wilson model, since $V = \Sigma a_i s_i + \zeta$,



A More Scalable Implementation

Similarly to the updates for compounds, the updates for substituents are recursive:

$$\begin{bmatrix} \theta^{n+1} \end{bmatrix} = \begin{bmatrix} \theta^{n} \end{bmatrix} - \alpha \begin{bmatrix} \Sigma_\theta^n \end{bmatrix} \begin{bmatrix} \vdots \\ x^n \\ \vdots \end{bmatrix};$$

$$\begin{bmatrix} \Sigma_\theta^{n+1} \end{bmatrix} = \begin{bmatrix} \Sigma_\theta^{n} \end{bmatrix} - \beta \begin{bmatrix} \Sigma_\theta^n \end{bmatrix} \begin{bmatrix} \vdots \\ x^n \\ \vdots \end{bmatrix} \begin{bmatrix} \dots & (x^n)^T & \dots \end{bmatrix} \begin{bmatrix} \Sigma_\theta^n \end{bmatrix}.$$

This improvement can also be implemented for the general model.

A further improvement for the Free-Wilson model

Assume an additive linear model.

Let $A(l)$ be the set of substituents that can be attached at location l, and let

$$\nu_{l,x}^{n,KG} = \max_{i \in A(l)} \mathbb{E}_n \left[\max_{k \in A(l)} a_k^{n+1} | S^n = s, x^n = x \right] - \max_{k \in A(l)} a_k^n$$

Then,

$$\nu_x^{n,KG} = \sum_l \nu_{l,x}^{n,KG}$$

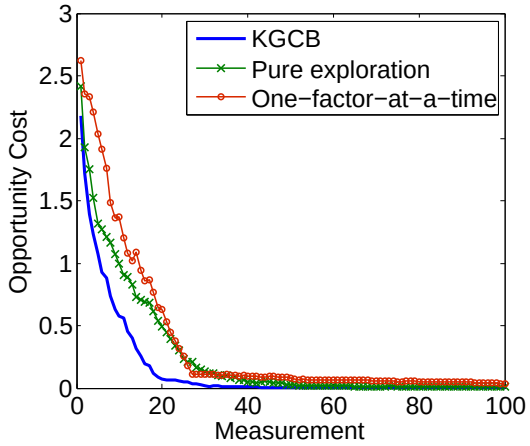
Computational Improvement

Assume there are I dimensions with M substituents at each dimension.

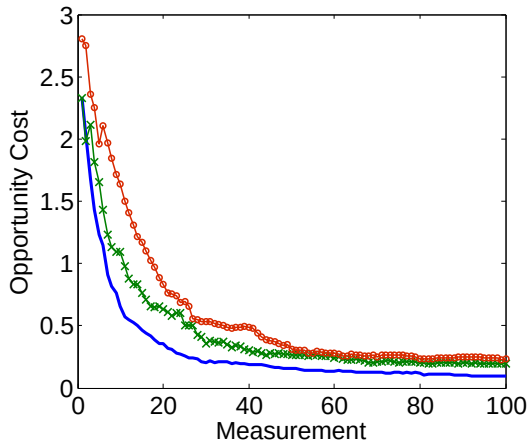
First implementations have computational complexity $O(IM^{2I} \ln M)$.

Last implementation has computational complexity $O(IM^{I+1} \ln M)$.

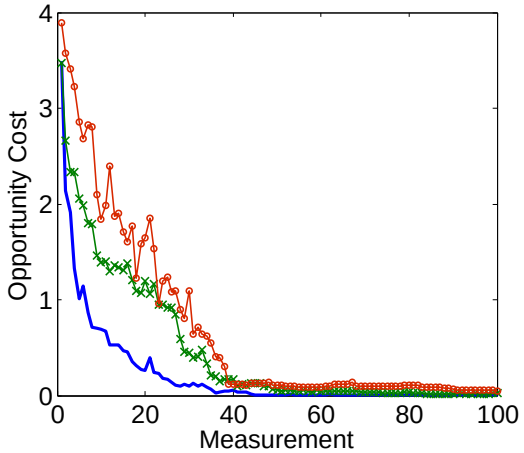
Results using various data set sizes and measurement noise values



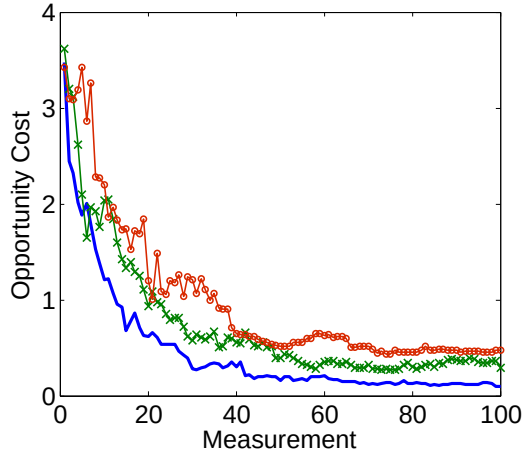
Average over 100 runs - 2640 compounds; $\sigma_{noise} = 0.1$.



Average over 100 runs - 2640 compounds; $\sigma_{noise} = 0.5$.

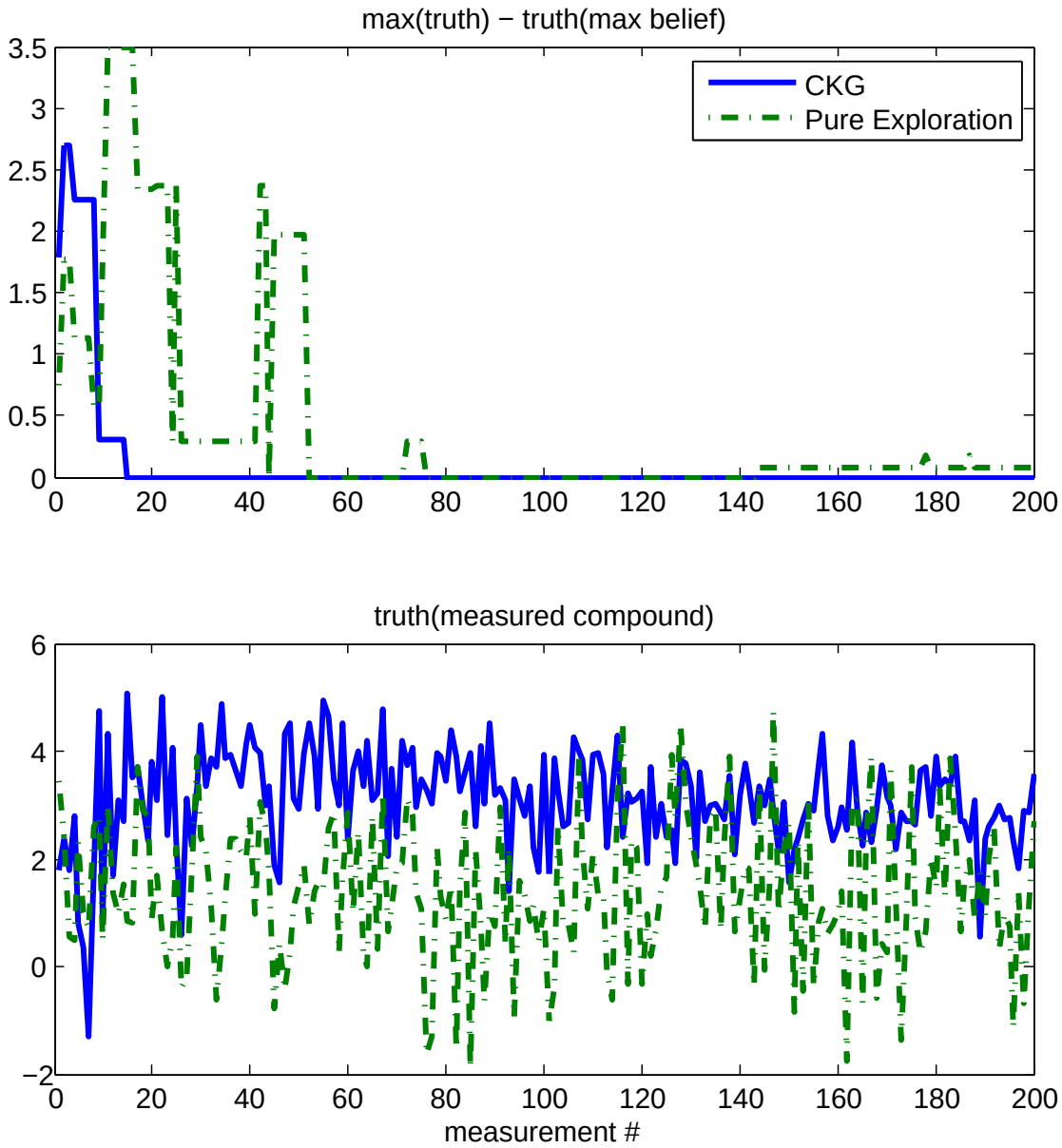


Average over 10 runs - 87120 compounds; $\sigma_{noise} = 0.1$.



Average over 10 runs - 87120 compounds; $\sigma_{noise} = 0.5$.

Results on data sets of 1,000 compounds



Results on data sets of 10,000 compounds

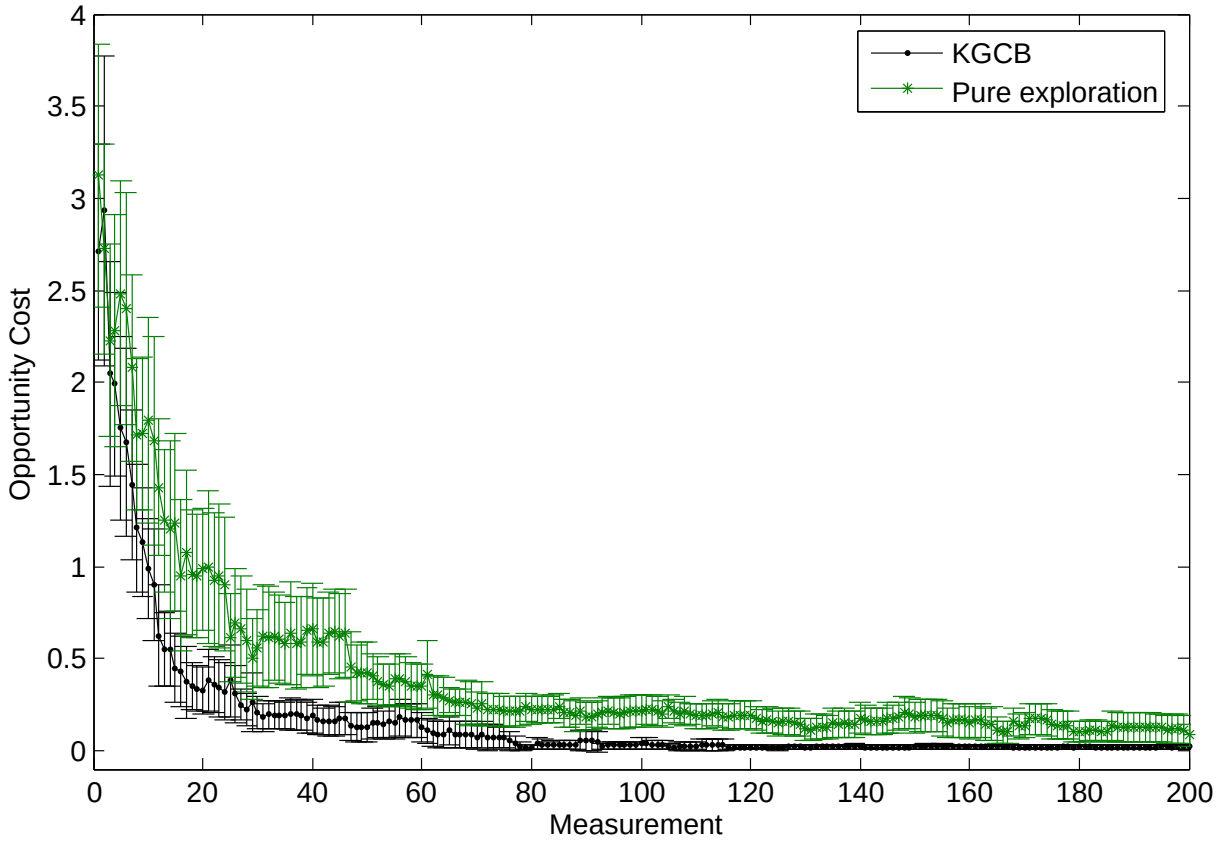


Figure: Mean and standard deviation of the mean using 15 sample paths of 10000 compounds each. $\sigma_{noise} = 0.38$.

Average performance

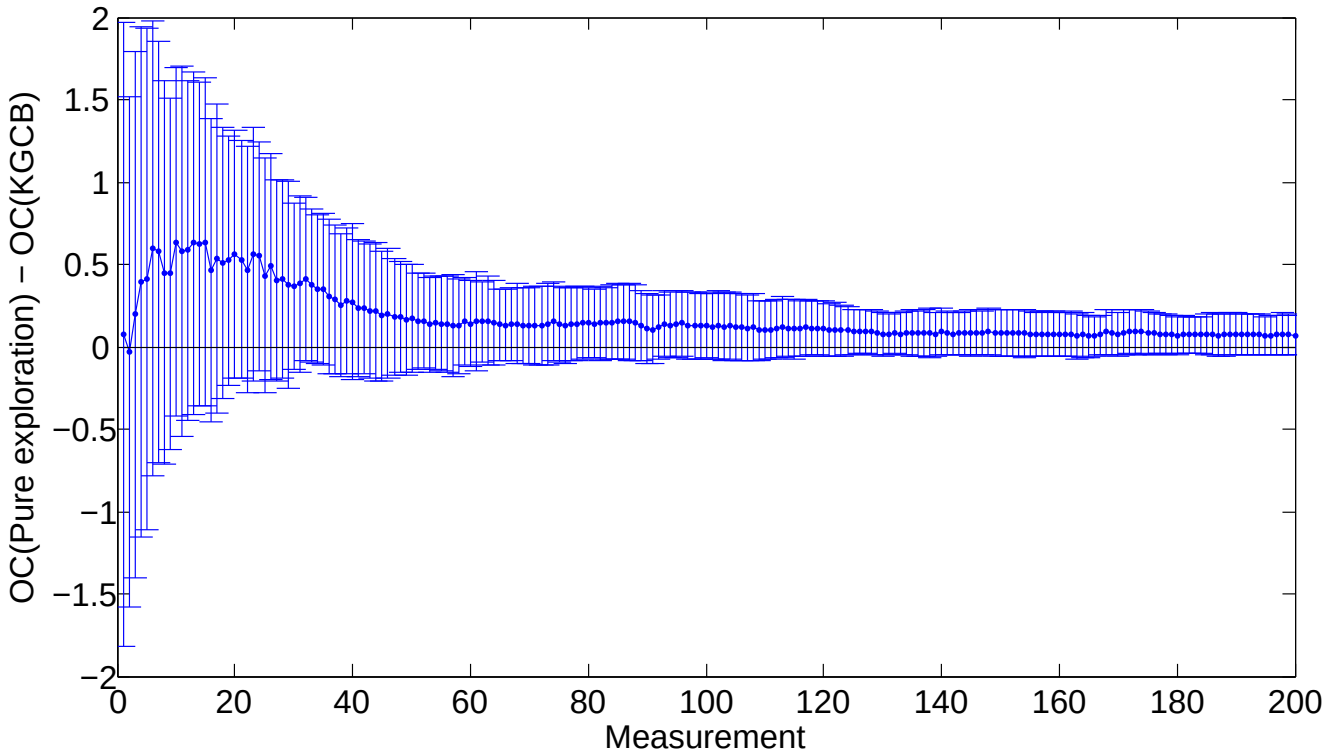


Figure: Mean and standard deviation using 75 sample paths of 10000 compounds each. $\sigma_{noise} = 0.38$.

Conclusions

- Our simulation results show that the KGCB policy reduces the number of molecules that need to be tested;
- Previous implementations of the KGCB policy require too much computational effort, but the new implementations overcome this barrier;
- The algorithm assigns a value to each compound, which researchers can use to prioritize their experiments;
- The Georgetown University team has just started to test a long sequence of compounds, and are planning to use the KGCB policy to decide which compounds to test;
- As a starting point, they have decided to use the Free-Wilson model, but further improvement might involve using a more advanced model.

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- Prof. Warren Powell
- Prof. Jeffrey Toretsky
- Prof. Sivanesan Dakshanamurthy
- Lombardi Comprehensive Cancer Center
- Go4TheGoal Foundation

References

P. Frazier, W. B. Powell, and S. Dayanik.
The knowledge-gradient policy for correlated normal rewards.
To appear in INFORMS Journal of Computing, 2009.

Y. Iwamoto.
Diagnosis and Treatment of Ewing's Sarcoma.
Japanese Journal of Clinical Oncology, 2007.

W.B. Powell and P. Frazier.
Optimal Learning.
TutORials in Operations Research, Informs, 10:213–246, 2008.

Results on data sets of 10,000 compounds

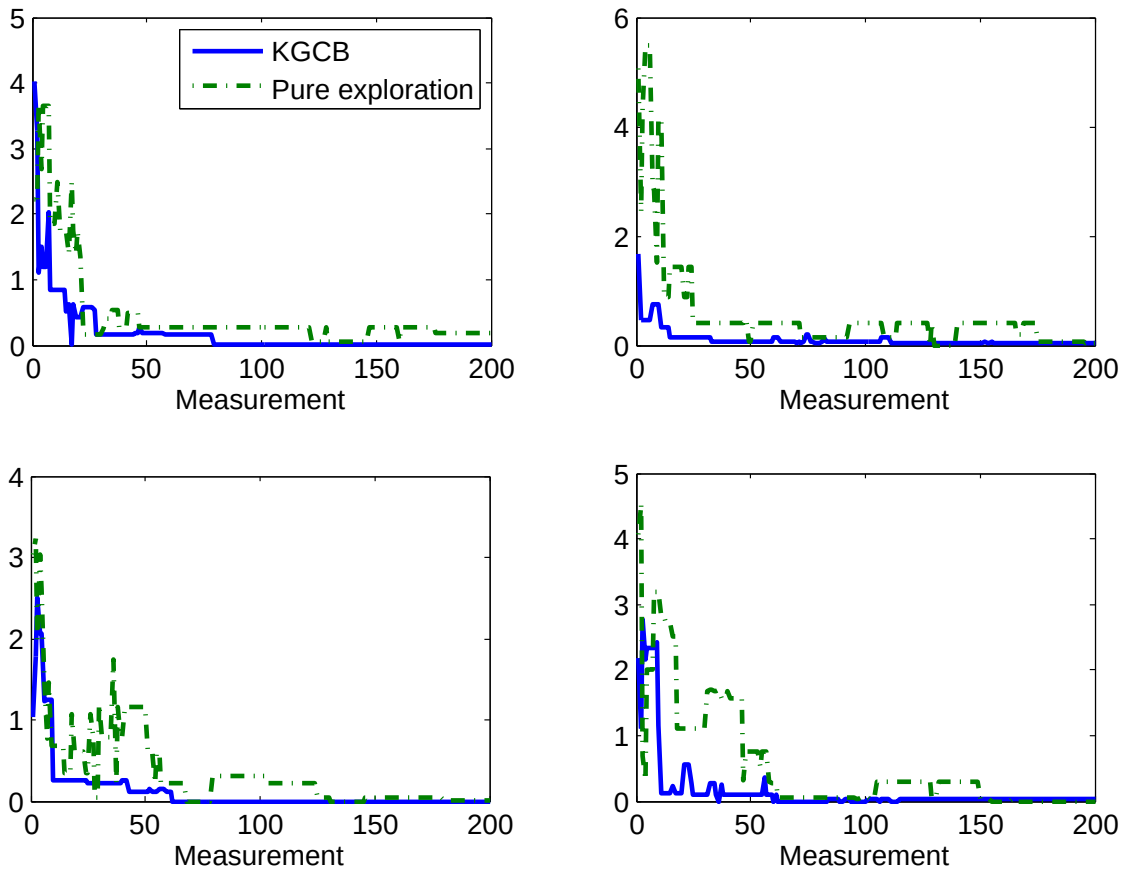

Figure: Four sample paths using data sets of 10000 compounds and a noise standard deviation of 0.38.

Results

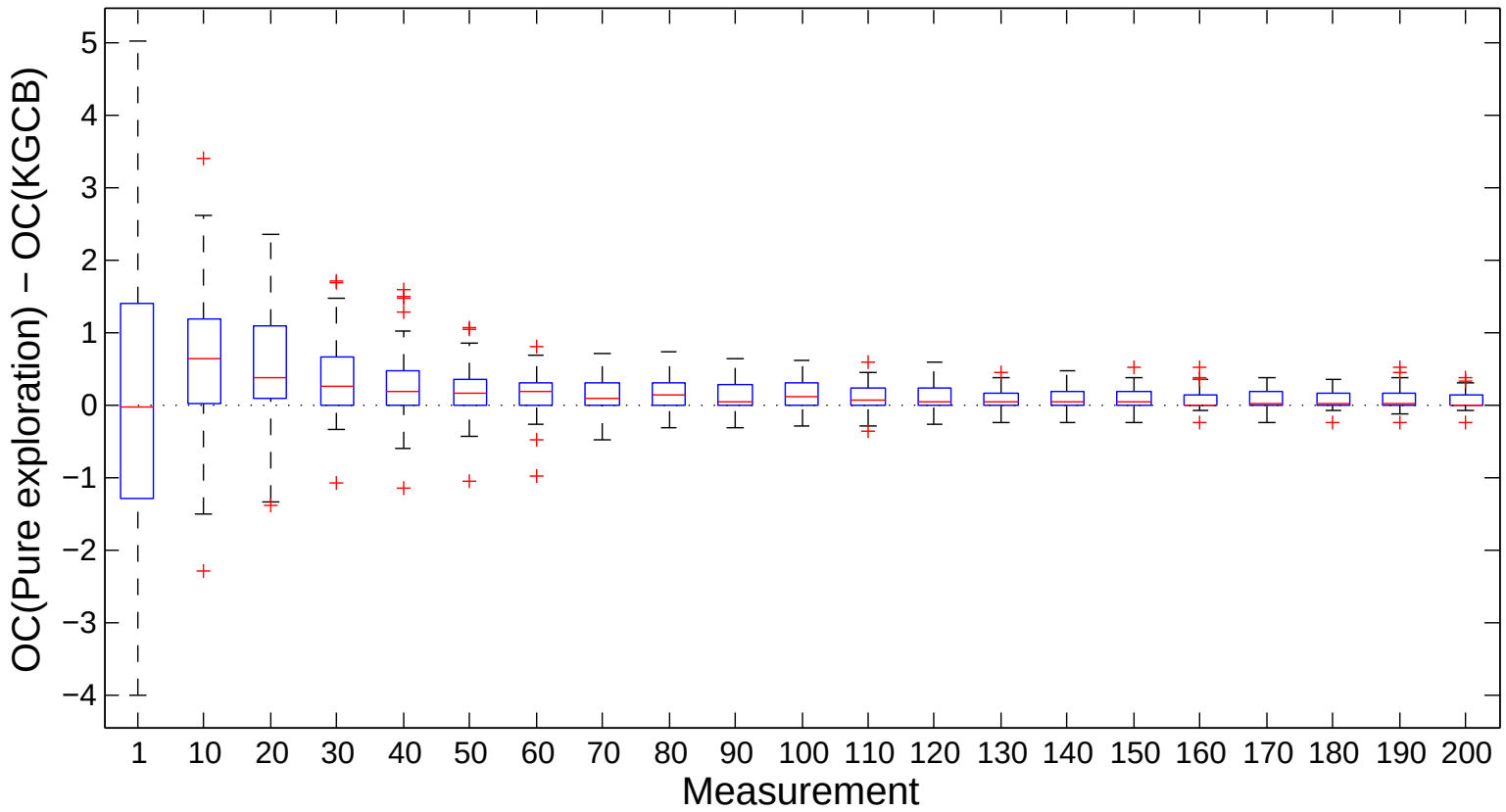

Figure: Distribution of difference between opportunity costs between pure exploration and KGCB using 75 sample paths of 10000 compounds each and a noise standard deviation of 0.38.

Results

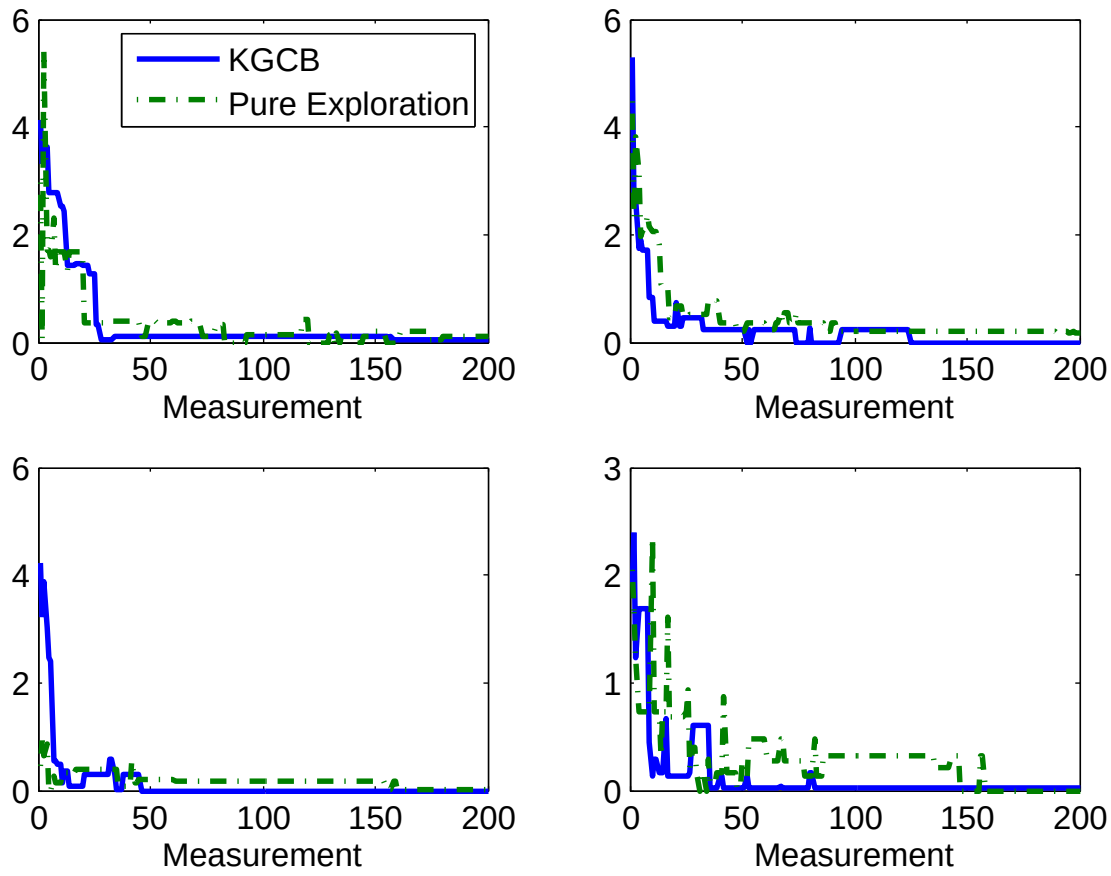

Figure: Four sample paths suing data sets of 25000 compounds and a noise standard deviation of 0.38.

Results

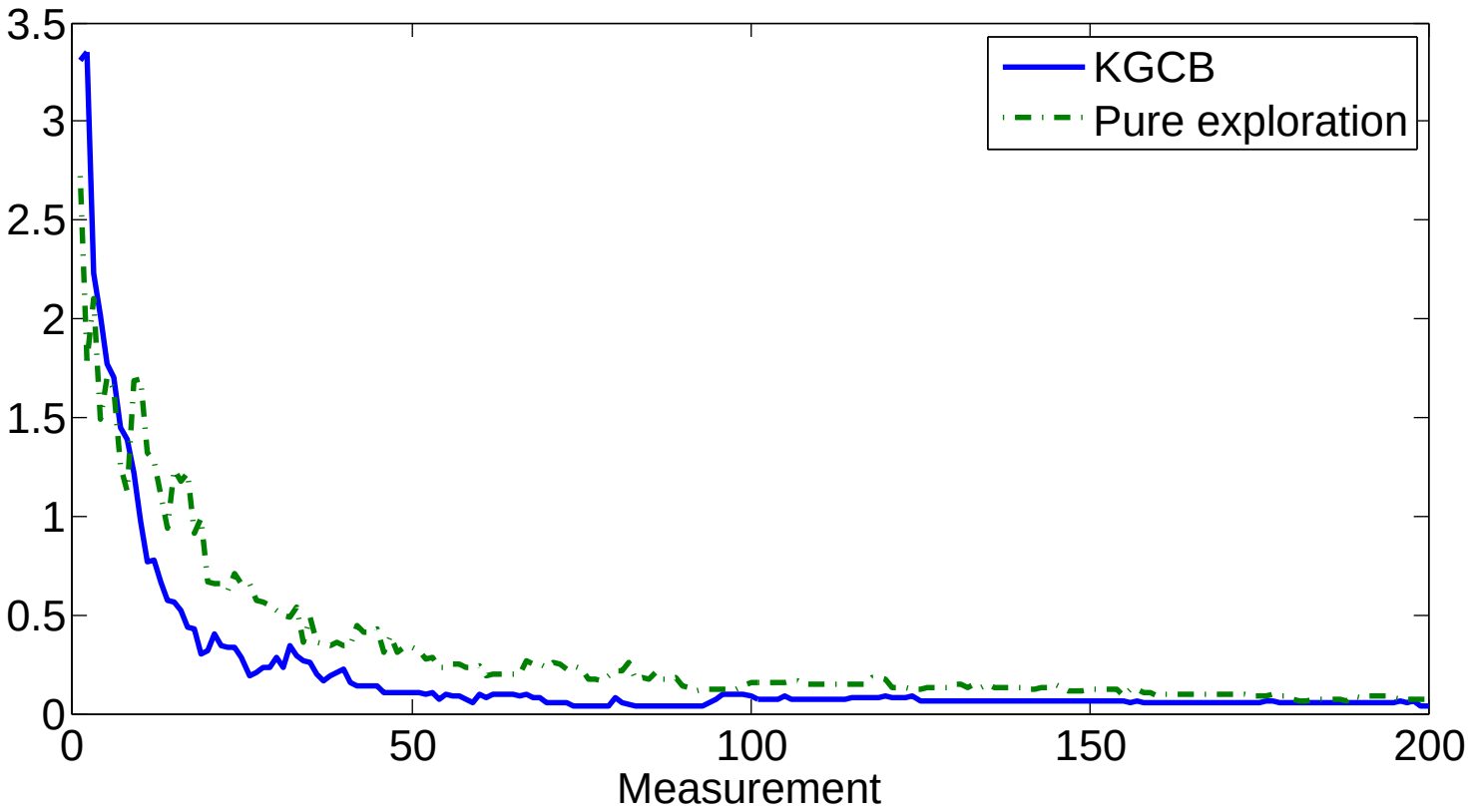

Figure: Average over nine runs of sample paths using data sets of 25000 compounds and a noise standard deviation of 0.38.