Kernel methods for *in silico* chemogenomics

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Outline

1. Introduction
   - Drug discovery
   - Chemogenomics
2. Method
   - Formalization
   - Representation of pairs
   - Kernel for ligands and targets
3. Results
4. Conclusion

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Drug discovery

Classical approach

- Imitate traditional remedies.
- Accidental discoveries.

New trend

1. Understand underlying biological process.
2. Identify targets (typically proteins).
3. Identify modulators of these targets.

Typical targets

- G-protein-coupled-receptors (GPCR).
- Enzymes.
- Ion channels.

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Virtual screening

Motivation

- Need to test a huge number of candidate molecule against a target.
- *In silico* interaction prediction is therefore a key element.

Classical paradigms

- Ligand-based : compare candidate ligand to known ligands of the target (*e.g.* using machine learning).
- Structure-based (docking) : use the 3D structure of the target to determine how well each candidate binds.

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Limits of the classical paradigms

- Ligand-based : need to know (enough) ligands of a given target to produce (accurate) predictors.
- Structure-based :
  - Time-consuming.
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Chemogenomic framework

- Idea: mine the chemical space (small molecules) against the *whole* biological space (targets).
- Similar molecules bind similar targets.
- Advantage: ligand-based approaches on targets with no (or few) known ligands can take advantage of similar targets with known ligands.

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Kernel methods for chemogenomics

- Cast the interaction problem in a joint ligand-target space (consider ligand-target pairs).
- Apply existing machine learning algorithms in this space.
- Similar to Bock and Gough (2005) and Erhan *et al.* (2006).
- Already applied to MHC-I-epitope binding prediction (Heckerman *et al.* 2005, Jacob *et al.* 2008).

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Formalization

Single-target screening

- Target t with known ligands $c_1, \ldots, c_n$.
- For each t, learn a function $f_t(c)$ from the c_i that predicts if unseen candidate c is a ligand of t.
- Linear case: given a description $\Phi(c)$ of the molecule, $f_t(c) = w_t^\top \Phi(c)$.

Chemogenomics setting

- Consider training pairs $(t, c)_i$ (known to interact or not to interact), represented by vectors $\Phi\left((t, c)_i\right)$.
- Learn a single function $f(t, c) = w^\top \Phi(t, c)$ in the joint space to predict if the candidate pair (t, c) interacts.
- How to choose the pair representation Φ?

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Vector representation of pairs

Ligand representation

- A lot of existing work to represent a molecule t by a vector $\Phi_{ligand}(c) \in \mathbb{R}^{d_c}$.
- Physico-chemical, structural properties of the molecules.

Target representation

- Similarly, much work devoted to the construction of descriptors for a given protein t by a vector $\Phi_{target}(t) \in \mathbb{R}^{d_t}$.
- Properties of the sequence, structure of the protein.

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Vector representation of pairs

Pair representation

- Use products of features of c and features of t.
- Idea (binary case): indicate that both c and t carry given features.
- May be strongly correlated with the fact that they interact.
- Set of all possible products of features of c and t is given by the tensor product:

$$\Phi(c,t) = \Phi_{ligand}(c) \otimes \Phi_{target}(t) . \tag{1}$$

- Potential issue: $d_c \times d_t$ vector, may be prohibitively large.

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Kernels for ligand-target pairs

Kernel trick

- Need to compute efficiently the inner product between pairs.
- Classical property of tensor products :

$$\begin{aligned}\Phi(c,t)^\top \Phi(c',t') &= \left(\Phi_{lig}(c) \otimes \Phi_{tar}(t)\right)^\top \left(\Phi_{lig}(c') \otimes \Phi_{tar}(t')\right) \\ &= \Phi_{lig}(c)^\top \Phi_{lig}(c') \times \Phi_{tar}(t)^\top \Phi_{tar}(t') \,.\end{aligned}$$

More generally

Denoting

$$K_{lig}(c,c') = \Phi_{lig}(c)^\top \Phi_{lig}(c'), \quad K_{tar}(t,t') = \Phi_{tar}(t)^\top \Phi_{tar}(t') \,,$$

we obtain the inner product between tensor products by:

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Kernel for ligands

2D kernel for ligands

- We chose the *Tanimoto kernel* (state-of-the-art performances in general).
- Characterizes the molecules by the occurrences of linear subgraphs of length 8 or less.

Kernels for targets: non-informative approaches

Dirac kernel

$$K_{dirac}(t, t') = \delta(t, t').$$

Equivalent to performing independant learning for each target.

Multitask kernel

$$K_{multitask}(t, t') = K_{dirac}(t, t') + 1.$$

- Naive information sharing.
- Penalize individual norm and variance among individual functions.

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Kernels for targets including biological information

Sequence-based kernels

Classical mismatch and local alignment kernel on whole sequences.

Hierarchy kernel

Use KEGG hierarchy between the targets: number of common ancestors in the corresponding hierarchy plus one.

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Data generation

- KEGG data base (Kanehisa *et al.*, 2002).
- Ligand data for GPCR, enzymes and ion channels.
- For each positive pair, generate a negative ligand-target pair (same target, random ligand among existing ligands).

Final benchmark

- 2436 pairs for enzymes, 798 for GPCR and 2330 for ion channels.
- First experiment: 10-fold cross validation (assess the incidence of using ligands from other targets on the accuracy of the learned classifier for a given target).
- Second experiment: for each t learn a classifier using only interactions that do not involve t and test on the points that involve t (simulate the behavior when making predictions for orphan targets).

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$K_{tar} \backslash$ Target	Enzymes	GPCR	Channels
Dirac	0.536 ± 0.005	0.682 ± 0.022	0.701 ± 0.017
multitask	0.874 ± 0.008	0.595 ± 0.030	0.797 ± 0.017
hierarchy	0.907 ± 0.008	0.817 ± 0.025	0.857 ± 0.015
local alignment	0.544 ± 0.007	0.696 ± 0.033	0.824 ± 0.015

Prediction accuracy for the first protocol on each dataset with various target kernels.

- Strong improvement when using data from the other targets.
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Second experiment

$K_{tar} \backslash$ Target	Enzymes	GPCR	Channels
Dirac	0.500 ± 0.000	0.500 ± 0.000	0.500 ± 0.000
multitask	0.856 ± 0.009	0.477 ± 0.025	0.636 ± 0.021
hierarchy	0.862 ± 0.009	0.776 ± 0.026	0.805 ± 0.018
local alignment	0.521 ± 0.004	0.647 ± 0.030	0.722 ± 0.019

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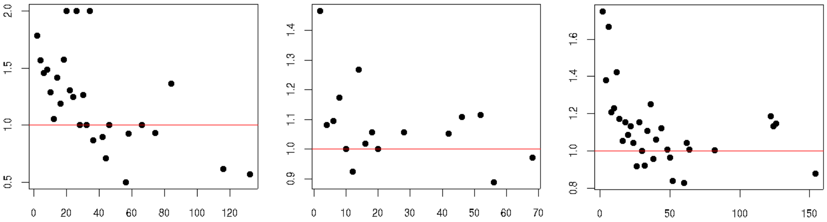

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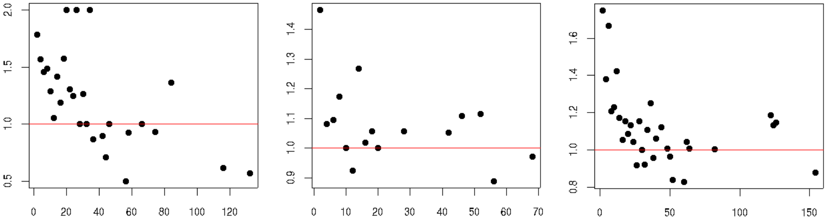

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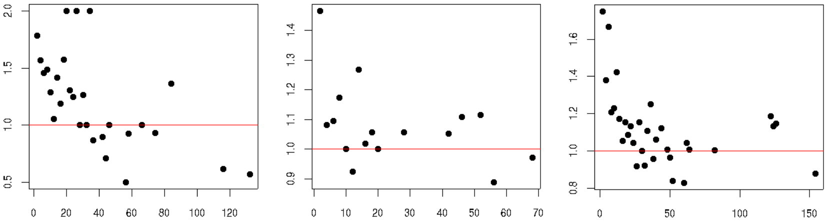

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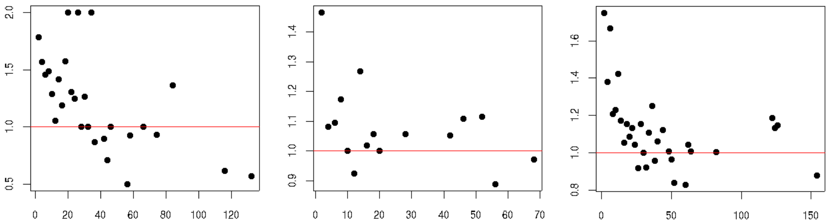

Relative improvement of the *hierarchy* kernel against the *Dirac* kernel as a function of the number of known ligands for enzymes, GPCR and ion channel datasets.

- Strong improvement when few training points available.
- After a certain point, using similar targets can deteriorates accuracy.
- Suggests that the method could be improved by learning for each target independently how much information should be shared.

Conclusion

- General method to predict interaction between any chemical compound and any biological target.
- Using target kernels allowing to share information across the targets improves the prediction.
- Accuracy improvement depends on the number of known ligands.
- Possible improvements:
  - Other kernels (using molecule 3D information or sequence/structure of targets).
  - Adapt the amount of information sharing to each target.
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