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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**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).
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Limits of the classical paradigms

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Chemogenomic framework

- Idea: mine the chemical space (small molecules) against the whole biological space (targets).
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- Apply existing machine learning algorithms in this space.
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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, $f_t(c) = w_t^T \Phi(c)$.

**Chemogenomics setting**
- Consider training pairs $(t, c)_i$ (known to interact or not to interact), represented by vectors $\Phi((t, c)_i)$.
- Learn a single function $f(t, c) = w^T \Phi(t, c)$ in the joint space to predict if the candidate pair $(t, c)$ interacts.
- How to choose the pair representation $\Phi$?
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# Vector representation of pairs

## Ligand representation
- A lot of existing work to represent a molecule $t$ by a vector $\Phi_{\text{ligand}}(c) \in \mathbb{R}^{d_c}$.
- 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 $\Phi_{\text{target}}(t) \in \mathbb{R}^{d_t}$.
- Properties of the sequence, structure of the protein.
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## Pair representation

- **Use products of features of \(c\) and features of \(t\).**
- **Idea (binary case):** indicate that both \(c\) and the \(t\) 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:**

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

- **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:

\[
\Phi(c, t)^\top \Phi(c', t') = (\Phi_{\text{lig}}(c) \otimes \Phi_{\text{tar}}(t))^\top (\Phi_{\text{lig}}(c') \otimes \Phi_{\text{tar}}(t'))
\]

\[
= \Phi_{\text{lig}}(c)^\top \Phi_{\text{lig}}(c') \times \Phi_{\text{tar}}(t)^\top \Phi_{\text{tar}}(t').
\]

More generally

Denoting

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

we obtain the inner product between tensor products by:

\[
K \left( (c, t), (c', t') \right) = K_{\text{tar}}(t, t') \times K_{\text{lig}}(c, c').
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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

Dirac kernel

\[ K_{\text{dirac}}(t, t') = \delta(t, t'). \]

Equivalent to performing independent learning for each target.

Multitask kernel

\[ K_{\text{multitask}}(a, a') = K_{\text{dirac}}(a, a') + 1. \]

Naive information sharing.

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

Still possible to obtain reasonable results when no ligand is known for the target.
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<table>
<thead>
<tr>
<th>$K_{tar}$ \ Target</th>
<th>Enzymes</th>
<th>GPCR</th>
<th>Channels</th>
</tr>
</thead>
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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.

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- After a certain point, using similar targets can deteriorate accuracy.
- Suggests that the method could be improved by learning for each target independently how much information should be shared.
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