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## **Déjà Vu - Réjà Vu : on knowledge-based approaches linking ligand and target information to bioactivity**

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# Propositions

accompanying the thesis

## Déjà vu – Réjà vu

*On knowledge-based approaches linking  
ligand and target information to bioactivity*

1. The significant increase in feature space which allows proteochemometrics to model the ligand – target interaction space, also demands extensive validation, in particular output variable permutation studies (Y-Scrambling). *this thesis, in particular chapter 2*
2. Training models on a data set of combined orthologs and paralogs of a protein subfamily widens chemical space and leads to the discovery of novel ligands and more robust models compared to models trained on paralogs only. *this thesis, in particular chapter 4*
3. While the ‘molecular similarity principle’ can be used to determine the applicability domain of a structure-activity model, a proteochemometric model should also include a target similarity measure. *this thesis, in particular chapters 5 and 6*
4. When presented with a trade-off between speed and accuracy, accuracy should be preferred over speed. Speed will catch up (over less than 4 years) whereas, accuracy will not. *this thesis, in particular chapter 8*
5. A proteochemometric approach allows one to envisage receptor-ligand affinities as a surface containing both linear and non-linear components, where the ‘specificity’ part is the non-linear deviation from the linear part. *M. Lapinsh et al.; Biochim Biophys Acta; 2001, 1525 (1-2), 180-190*
6. Filling the full theoretical chemogenomic matrix implies that data on ‘unliganded’ targets should be gathered from the closest ‘liganded’ neighbouring targets, and that data on ‘untargeted’ ligands should be gathered from the closest ‘targeted’ ligands. The true question is how to measure distances between two ligands or two targets. *D Rognan; Br J Pharmacol 2007, 151 (1), 38-52*
7. Via comparison of small molecule binding to human and rat receptor orthologs it can be observed that the adenosine  $A_1$  and  $A_{2A}$  receptors display a species specific pharmacology. *Kruger and Overington; PLoS Comp Biol; 2012, 8 (1), e1002333*
8. Models yielding an error smaller than the experimental uncertainty are necessarily overtrained, it is therefore imperative to anticipate the mean error of heterogeneous public data which is estimated at 0.44 pKi units. *C Kramer et al.; J Med Chem; 2012, 55 (11), 5165-5173*

9. It's been said that a messy desk is a hallmark for a messy mind, people supporting this theory should ask themselves what an empty desk is a hallmark for.
10. In scientific literature a specificity of 95.0 % is accepted (for diagnostic tests often 99.9 %). When a government connects multiple databases and uses models on these datasets to assess say 16 million individuals and use it to identify possible criminals this corresponds to 160,000 falsely accused.
11. Traits that successfully guide us from milestone to milestone in the first years of our life (curiosity, courage and an open mind) are later lost because of conditioned behavior.
12. One intern can start more protocols than many CPUs can complete.
13. One can draw many parallels between getting a PhD and traditional hazing as it is performed within student associations.

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8 Januari 2013