Proteochemometrics and Systems Biology for Drug Repositioning

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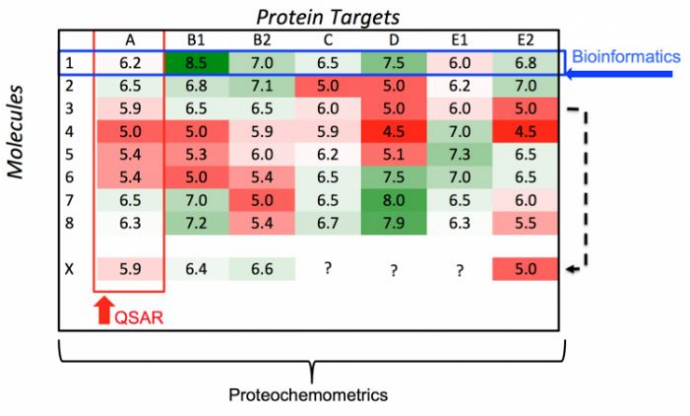
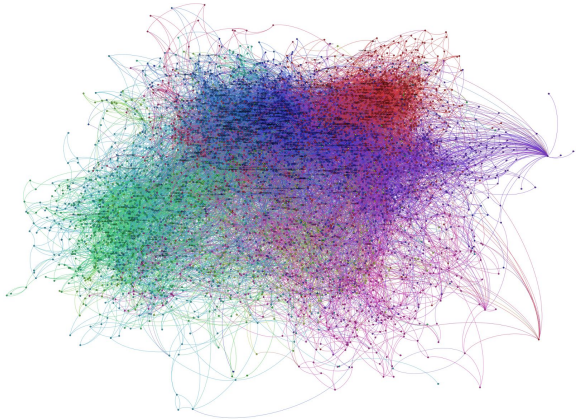
What do Chemicals do in Biological Systems?





Proteochemometrics

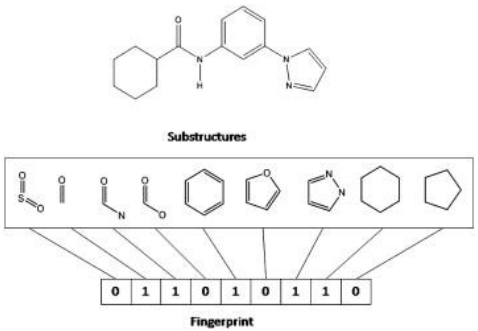
Which targets (proteins) do chemicals modulate?

Systems Biology

What are the downstream effects of proteins?

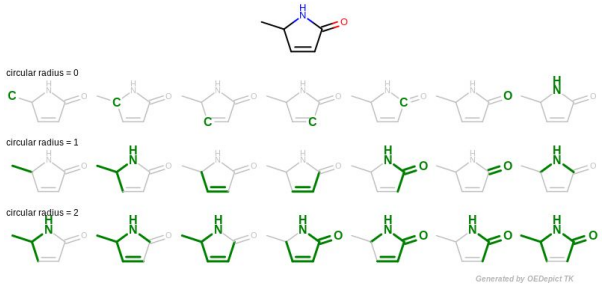
Image from https://www.universiteitleiden.nl/en/research/research-projects/science/lacdr-proteochemometrics

Feature Engineering for Chemicals



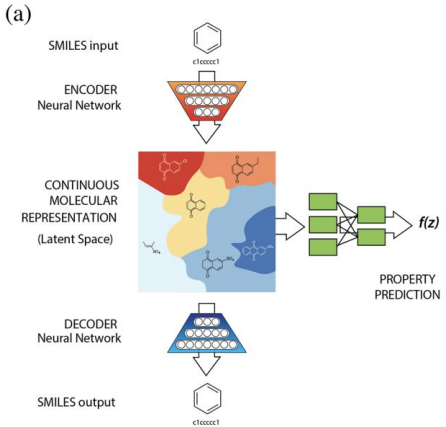
Structural fingerprints (e.g., MACCS)

https://doi.org/10.1016/j.bbapap.2013.05.010



Circular fingerprints (e.g., ECFP)

https://docs.eyesopen.com/toolkits/python/graphsimtk/fingerprint.html



Representation learning (variational autoencoders with CNN or RNN)

https://pubs.acs.org/doi/pdf/10.1021/acscentsci.7b00572

Proteochemometrics

- ~11K known drugs over ~5K targets
- Millions of drug-like molecules that have been tested over ~10K targets
- 10^{20}-10^{30} possible drug like molecules and ~20K possible targets

Data

- Sparse (chemical *x* protein) matrix
- Sequence-based chemical-chemical and protein-protein similarities

Multi-task learning used for regression task of predicting new chemical-protein assay values

Systems Biology and Drug Repurposing

- Networks are commonly used to represent biological systems in Systems biology
- Use predictions for chemicals-target values to calculate aggregate downstream effects via biological networks (e.g., heat diffusion)
- Identify drugs or combinations of drugs exerting perturbations desirable in therapeutic context by connecting proteins to biological processes and higher-order phenotypes