Molecular Physiology

Applied Machine Learning for Drug Discovery

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Discover the world at Leiden University

Molecular Physiology

- Answer important biological and medical questions

- Focus on cancer, metabolic and brain disorders

- Design, synthesize and apply new chemical tools

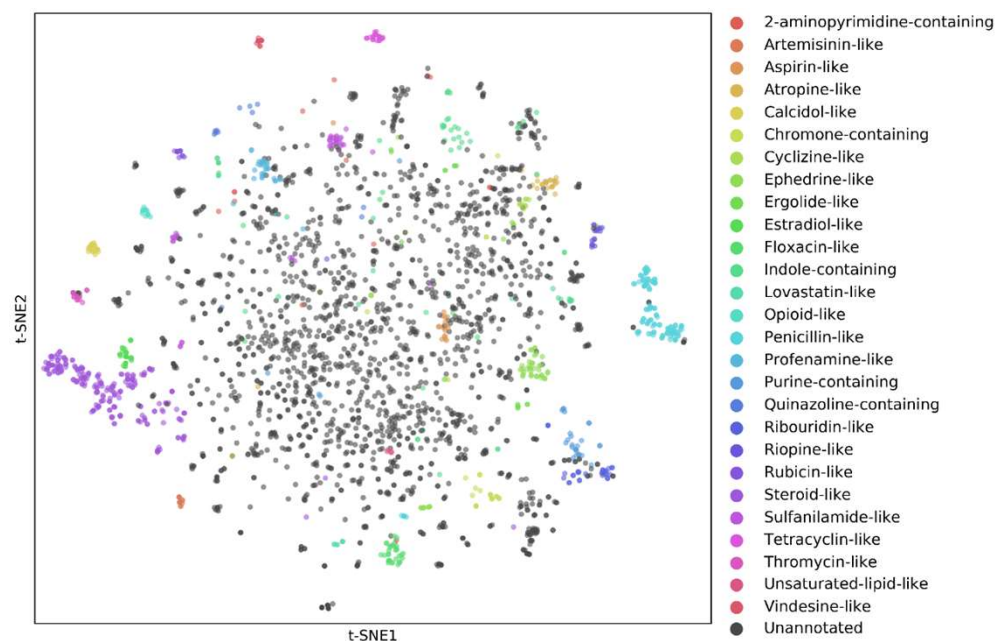- Integrate, optimize and develop machine learning tools

Cancer and ML

- Kinases are an important drug targets

- Specificity of drugs is often a problem
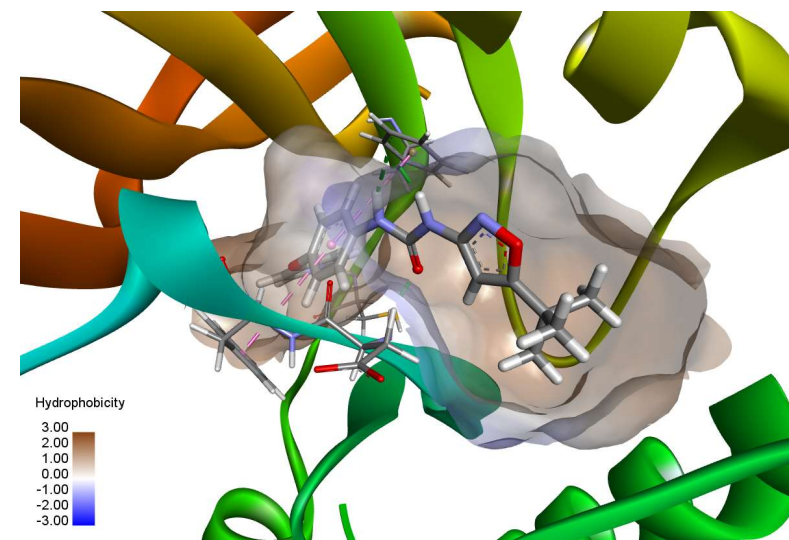
- Thanks to popularity lot of data available
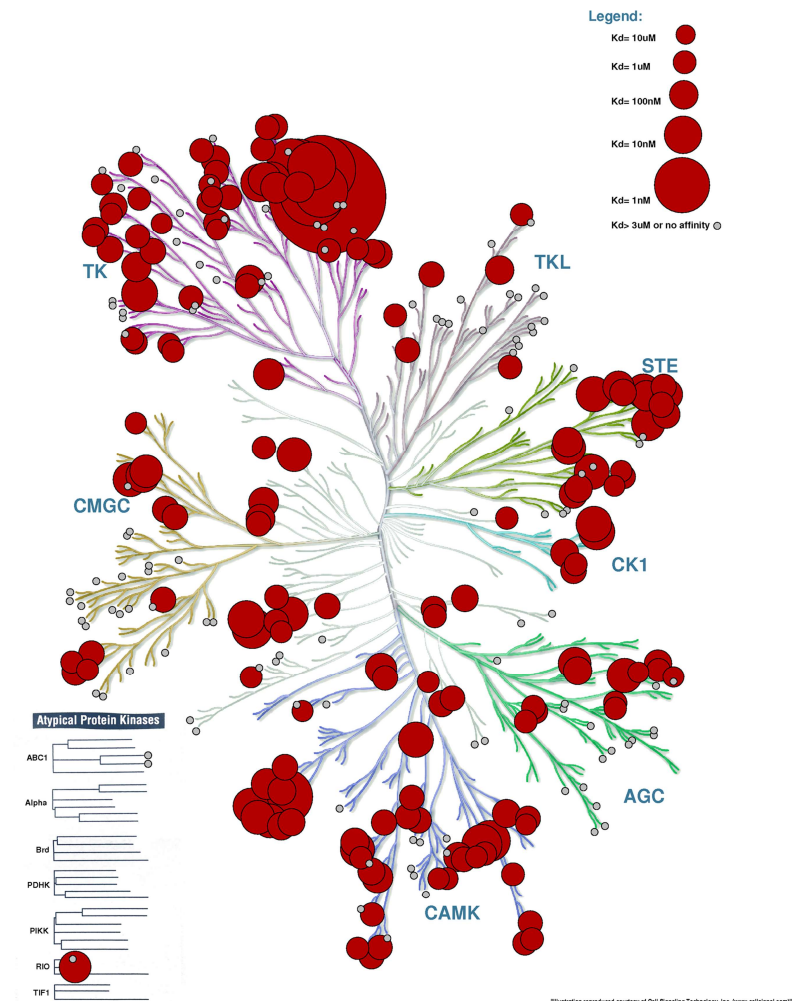
Off-target prediction using ML

- Predict (off-)targets of new molecules based on 'similarity'

- Use t-SNE as visually attractive similarity metric

Experimental validation

- Virtual screening for FLT3 resulted in 40% PPV

- Resynthesis and biological profiling revealed potent hits
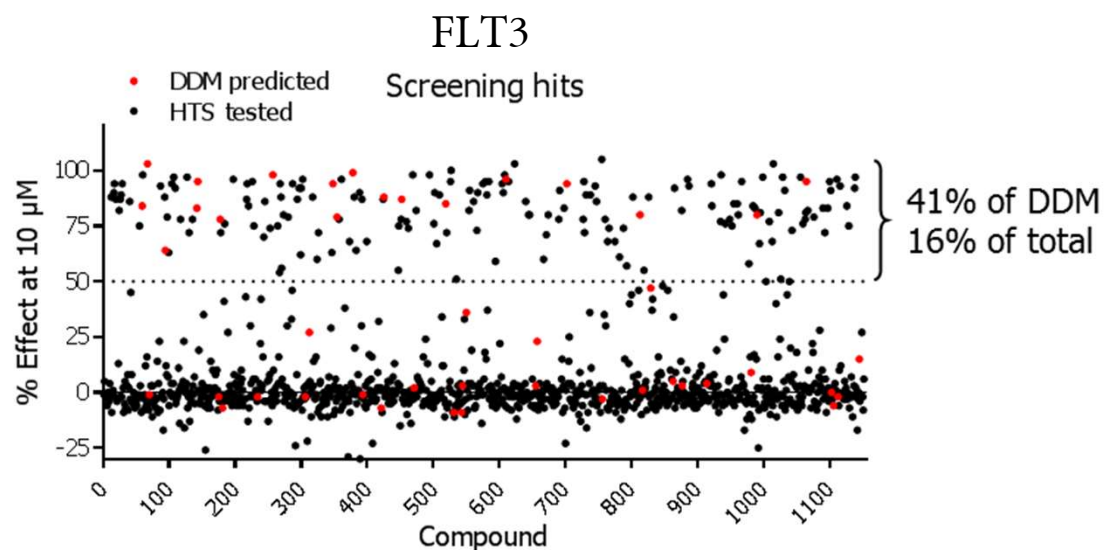
Future plans

- Learn synthetic knowledge

- Grow trainings dataset

- Implement for different target families

- Work towards automated design engine

Structure design

Synthetic route

Predict activity

Predict selectivity

Evaluate

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The scheme:

- t-SNE algorithm used for kinase inhibitor predictions

- Similarity of compounds

- Similarity of kinases

t-SNE map of inhibitors

Most similar molecules in PKIS set

Final predicted targets

PKIS Target Kinases	t-SNE found Kinases
ErbB4	FYN
ErbB2	ErbB3
EGFR	
YES	

Similar kinases through t-SNE map

Kinase targets of PKIS molecules

Kinase	1	2	3	4	5	6	7	8	9	Mean
ErbB4	63.8	68.7	94.0	85.1	94.6	79.3	79.9	94.1	99.7	84.4
ErbB2	29.9	26.3	83.0	30.9	86.6	20.0	50.9	59.0	67.7	50.5
EGFR	63.6	64.2	60.6	34.3	60.7	33.0	36.7	53.1	36.0	49.1
YES	12.3	42.0	79.9	22.9	49.8	13.1	21.9	26.2	37.0	33.9
LCK	13.5	72.2	61.1	7.1	22.6	4.5	8.2	14.4	33.0	26.3
FGR	15.5	46.2	44.2	15.5	33.3	7.6	12.6	14.9	42.2	25.8
HCK	20.5	75.1	48.5	8.3	19.9	1.9	5.7	9.6	30.6	24.5
LOK	75.4	70.1	14.2	9.2	13.9	5.4	4.0	6.2	14.4	23.6
LYN	24.3	82.4	43.4	5.6	12.0	2.2	4.3	7.6	30.4	23.6
BRK	10.3	65.5	53.2	9.4	29.2	2.4	8.3	10.9	6.4	21.7
BLK	4.0	49.0	60.8	6.3	22.6	3.7	7.8	11.5	26.3	21.3