An Assessment of Automated Quantitative Structure-Activity Relationship Modeling on Drug Discovery for Novel Treatment of Blood Disorders

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INTRODUCTION

Sickle cell disease

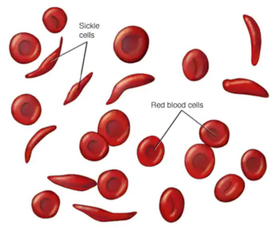


Figure 1. Healthy red blood cells compared to sickle-cells.
Source: Mayo Clinic[1]

- Inherited, lack of healthy red blood cells
- Symptoms: anemia, pain, swelling of hands and feet, and frequent infections
- >100,000 Americans have SCA
- Diagnoses and treatments → 30 year LE increase

A Novel Therapeutic Target

- HbF shown to alleviate SCA symptoms in infants
- Recruitment of the NuRD complex silences HbF production
- ETO2 recruits NuRD via MYND domain binding
- New target: disruption of a target protein domain (MYND Domain) to stop NuRD recruitment and HbF silencing

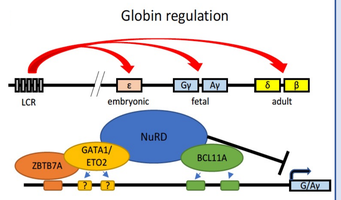


Figure 2. *Visualization of interaction between NuRD complex and ETO2 protein, as well as NuRD recruitment to globin regulation gene for silencing of HbF.*

Drug Discovery

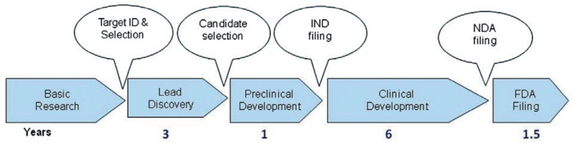
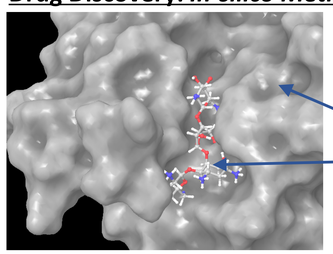


Figure 3. *From Hughes et. al. 2011: Traditional drug discovery pathway*

Drug Discovery: *In-silico Methods*



← Figure 4. *Model of in-silico docking of compounds*

Figure 5. *From Liu et. al. 2007;* 3D structure of the MYND domain (represented in orange), with its native peptide binder represented in green. →

METHODS

Library Selection
- NCI: large collection of free drug-like compounds suited for similar targets
- Enamine: more representative of large chemical spaces

Ligand Preparation
- Use of Schrödinger LigPrep Software
- 2D → 3D conversion
- Ensures chemical correctness

Docking
- Schrödinger Glide: HTVS → SP → XP
- Goes from least to most computationally expensive, filters at each stage
- Outputs docking scores for top % of initial library

Threshold Determination
- Schrödinger recommends selection a threshold for "hits" based on preliminary screening
- Threshold will be used moving forward as cutoff for binding

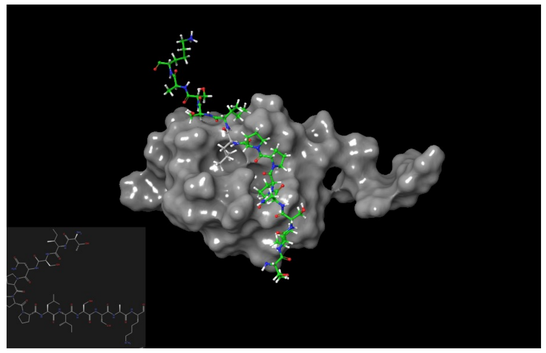


Figure 6. *Prepared protein (MYND Domain) with docked ligand for grid generation*

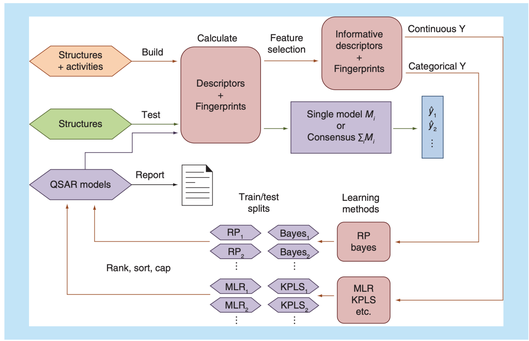


Figure 7. *From Dixon et. al. 2016 Sample schematic of QSAR workflow*

RESULTS

Preliminary Docking Study

- Docking score values range from -5.2931 to -13.569
- Threshold for "hits" ≤ -10
- 4.1% of *returned* compounds are hits
  - < 0.01% of compounds screened were hits

Data Splitting Ratios

Table 1. Summary of model comparison metrics across all 3 data splitting ratios.

	*Q^2	*RMSE	ROC-AUC	PR-AUC
Model A	0.87106	0.59421	0.92435	0.38665
Model B	0.87029	0.58852	0.92219	0.40152
Model C	0.85689	0.61476	0.91984	0.39659

→ Model A (64:16:20) was selected for remaining analysis.

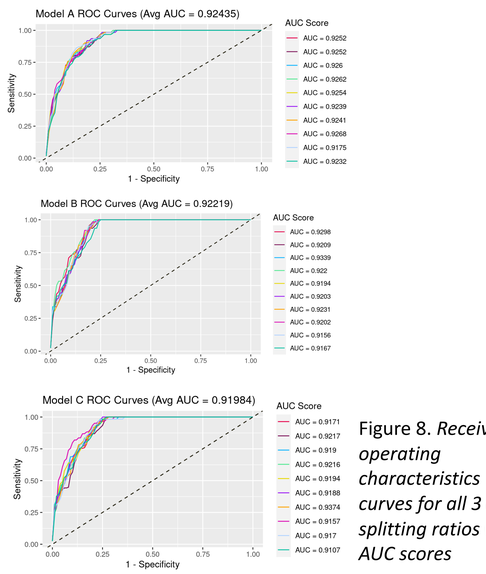


Figure 8. *Receiver operating characteristics curves for all 3 data splitting ratios with AUC scores*

RESULTS

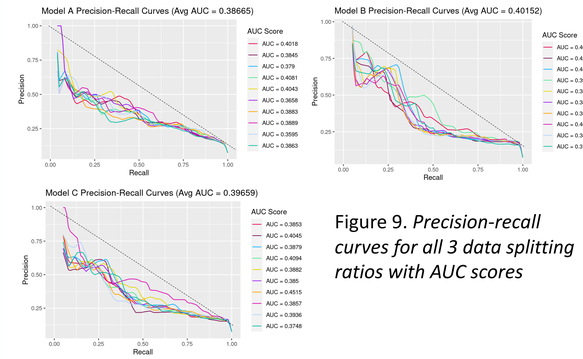


Figure 9. *Precision-recall curves for all 3 data splitting ratios with AUC scores*

Table 2. One-way ANOVA results of Q^2 across models created to test inclusion dependency

	Df	Sum Sq	Mean Sq	F value	Pr (>F)
Model	4	0.003238	0.0008096	12.79	2.52e-05
Residuals	20	0.001266	0.0000633		

Table 3. Measures of accuracy of sample prediction

RMSE		
Overall	**"Hits"**	**"Misses"**
0.59614	1.4309	0.52398
Percent Hits Captured (%)		
64.8148		

CONCLUSIONS

- AutoQSAR modeling for this protein system was unsuccessful
  - Starting structure was from NMR data, not crystallography → uncertainty in foundational information regarding the binding pocket
  - No verified drug-like binders → training set data used to build the models may have been flawed
  - High variability of models depending on specific inclusion/exclusion of binders → overfitting and descriptor patterns found across ligands was not very robust

REFERENCES

1. Sickle cell anemia - Symptoms and causes - Mayo Clinic. Accessed January 27, 2022. https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876
2. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. *Br J Pharmacol*. 2011;162(6):1239-1249. doi:10.1111/j.1476-5381.2010.01127.x
3. Liu Y, Chen W, Gaudet J, et al. Structural basis for recognition of SMRT/N-CoR by the MYND domain and its contribution to AML1/ETO's activity. *Cancer Cell*. 2007;11(6):483-497. doi:10.1016/j.ccr.2007.04.010
4. Dixon SL, Duan J, Smith E, Von Bargen CD, Sherman W, Repasky MP. AutoQSAR: an automated machine learning tool for best-practice quantitative structure-activity relationship modeling. *Future Med Chem*. 2016;8(15):1825-1839. doi:10.4155/fmc-2016-0093
5. Schrödinger, LLC. *Schrödinger Release 2022-3: Protein Preparation Wizard*. Schrödinger, LLC; 2021.
6. Schrödinger, LLC. *Schrödinger Release 2022-3: LigPrep*. Schrödinger, LLC; 2021.
7. Schrödinger, LLC. *Schrödinger Release 2022-3: Glide*. Schrödinger, LLC; 2021.
8. Schrödinger, LLC. *Schrödinger Release 2022-3: AutoQSAR*. Schrödinger, LLC; 2021.
9. Schrödinger, LLC. *Schrödinger Release 2022-3: Canvas*. Schrödinger, LLC; 2021.