



***INVESTIGATING DRUG SYNERGY
MECHANISMS OF DISORDERED
PROTEIN-RELATED DISEASES***

Daniel Lu

Mentor: Dr. Gil Alterovitz

5th Annual PRIMES Conference

INTRO – DISORDERED PROTEINS & DISEASE

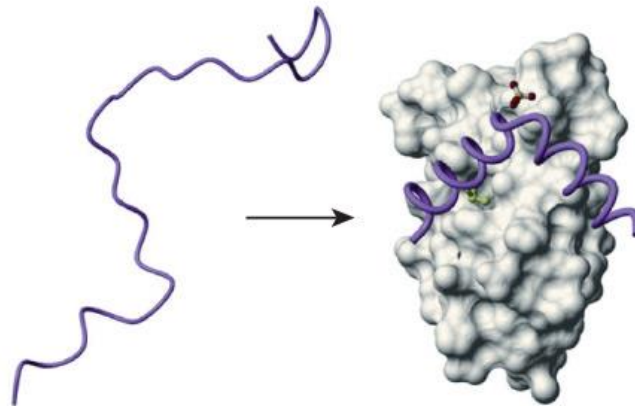
- Intrinsically Disordered Proteins (IDP's) are highly prevalent in certain diseases, especially:
 - Cancer
 - Neurodegenerative Disease
 - Cardiovascular disease (CVD)
 - Diabetes
- The Molecular Recognition Feature (MoRF) is a disordered region involved w/ binding

A 3-D model of hemagglutinin,
an IDP



INTRO – DRUG SYNERGY

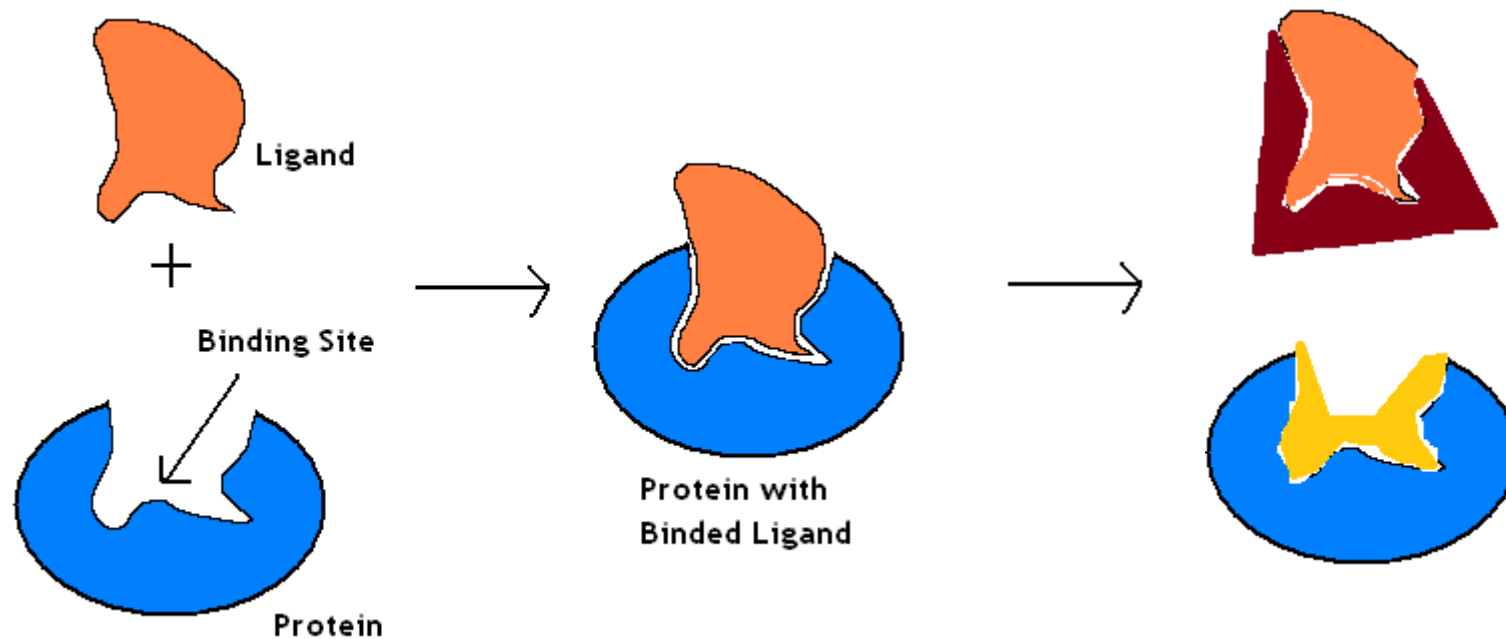
- Administering many drugs together doesn't always produce additive effect
- Drug Synergy is when two or more administered drugs have a more than additive effect.



IDP binding to ordered protein

INTRO – DRUG SYNERGY MECHANISMS

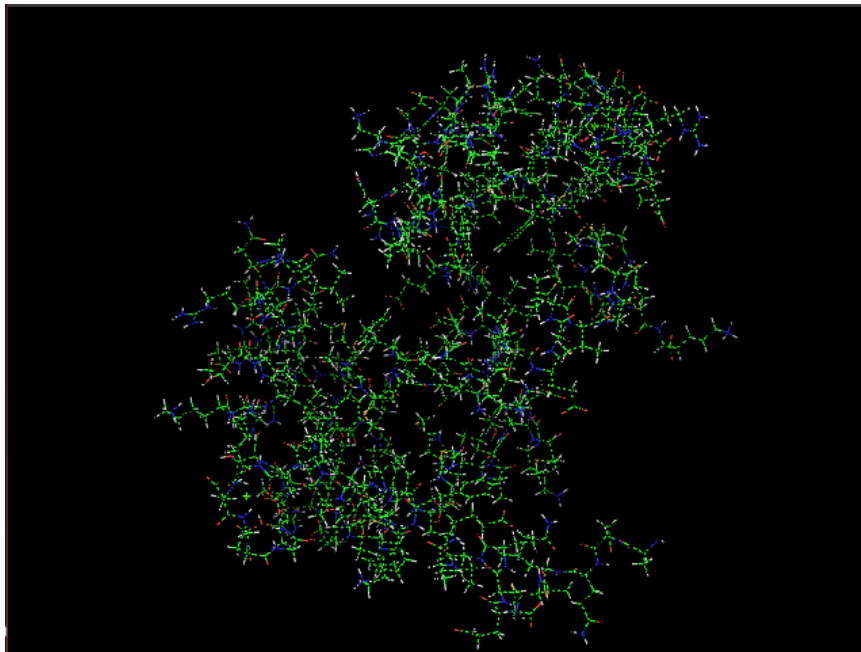
- Synergy by binding to both the MORF and its interactor



- Also by attacking different steps of the disease

METHODS – DRUGS MIMICKING MoRF

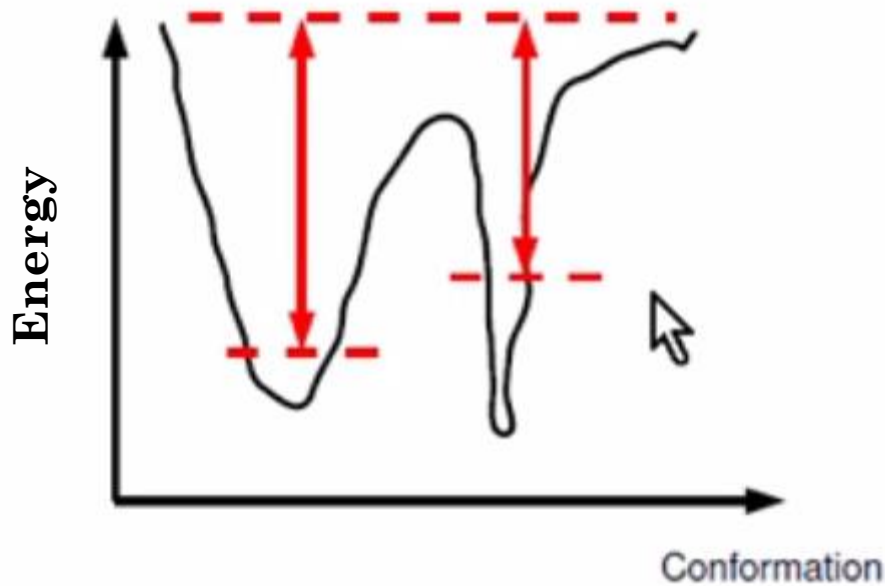
- How do you find drugs to mimic the MoRF?
 - Find 3-D Structure Model (PDB) of IDP
 - Isolate MoRF
 - Compare drugs to MoRF (Spectrophore)
 - Sort drugs as effective or ineffective (SVM)



3-D rendering of
an IDP

METHODS – AUTODOCK

- Finding strength of binding
 - Find 3-D Structure (PDB) of Protein & Drug
 - Calculate binding affinity: how much energy is released



RESULTS – HPV

- Human Papillomavirus (HPV) is a STD, cancer
- E6 is an IDP of HPV
 - Interacts with E6-AP ubiquitin-protein ligase
- Results for Synergy

Mimicking E6, binding to E6AP

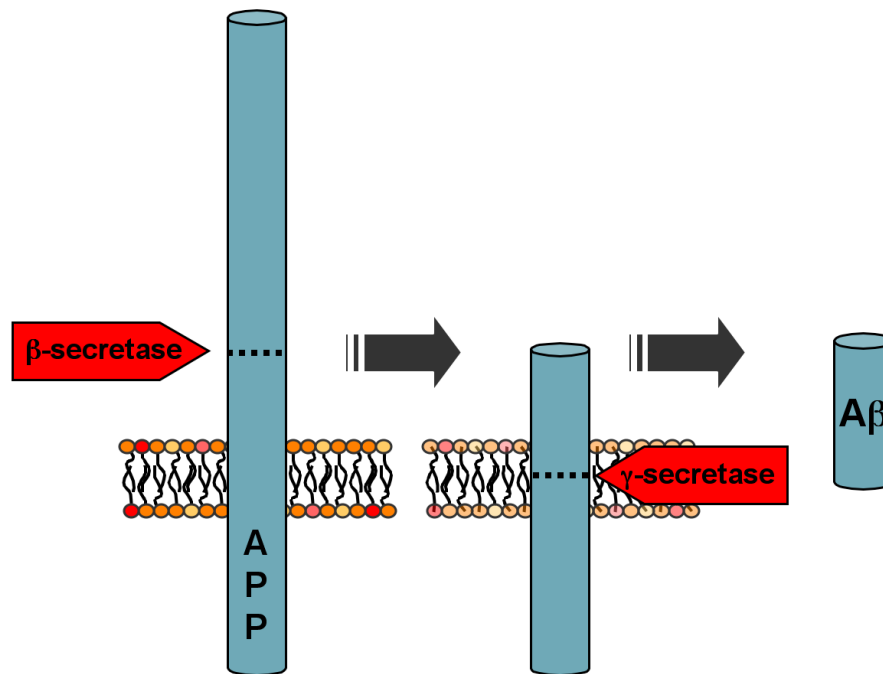
Drug Name	Predicted Similarity	Binding Affinity
RU83876	0.89398170127	-9.1

Mimicking E6AP, binding to E6

Drug ID	Predicted Similarity	Binding Affinity
ZINC_96006116	0.899067050752751	-8.2

RESULTS – ALZHEIMER’S DISEASE

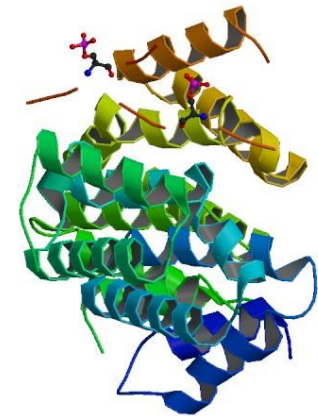
- Alzheimer’s is a neurodegenerative disease that causes memory loss
- Amyloid-beta ($A\beta$) is an IDP highly implicated



Production of Amyloid- β with β -secretase from Amyloid Precursor Protein (APP)

RESULTS – ALZHEIMER’S DISEASE

- Beta-secretase binds to GGA1 for transport
- Amyloid- β binds to leukocyte immunoglobulin-like receptor B2 (LilrB2)



Results for Synergy

Beta-secretase & GGA1

Mimicking Beta-secretase (c-terminus), binding to GGA1 VHS site

Drug Name	Predicted Similarity	Binding Affinity
Dimethylphosphonium	0.916369652124791	-3.8

Mimicking Amyloid- β , binding to LilrB2

Drug Name	Predicted Similarity	Binding Affinity
RU83876	0.90004566551	-7.5

CONCLUSION

- Ongoing Work
 - More cases of Drug Synergy

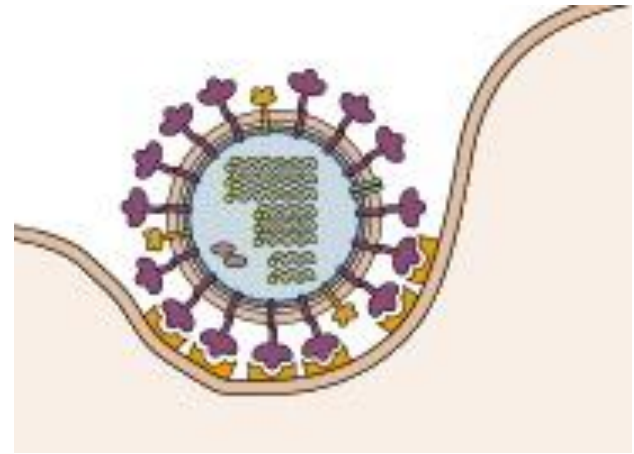


Diagram of hemagglutinin,
an IDP for influenza

- Future Work
 - Validation of synergy drug pairs

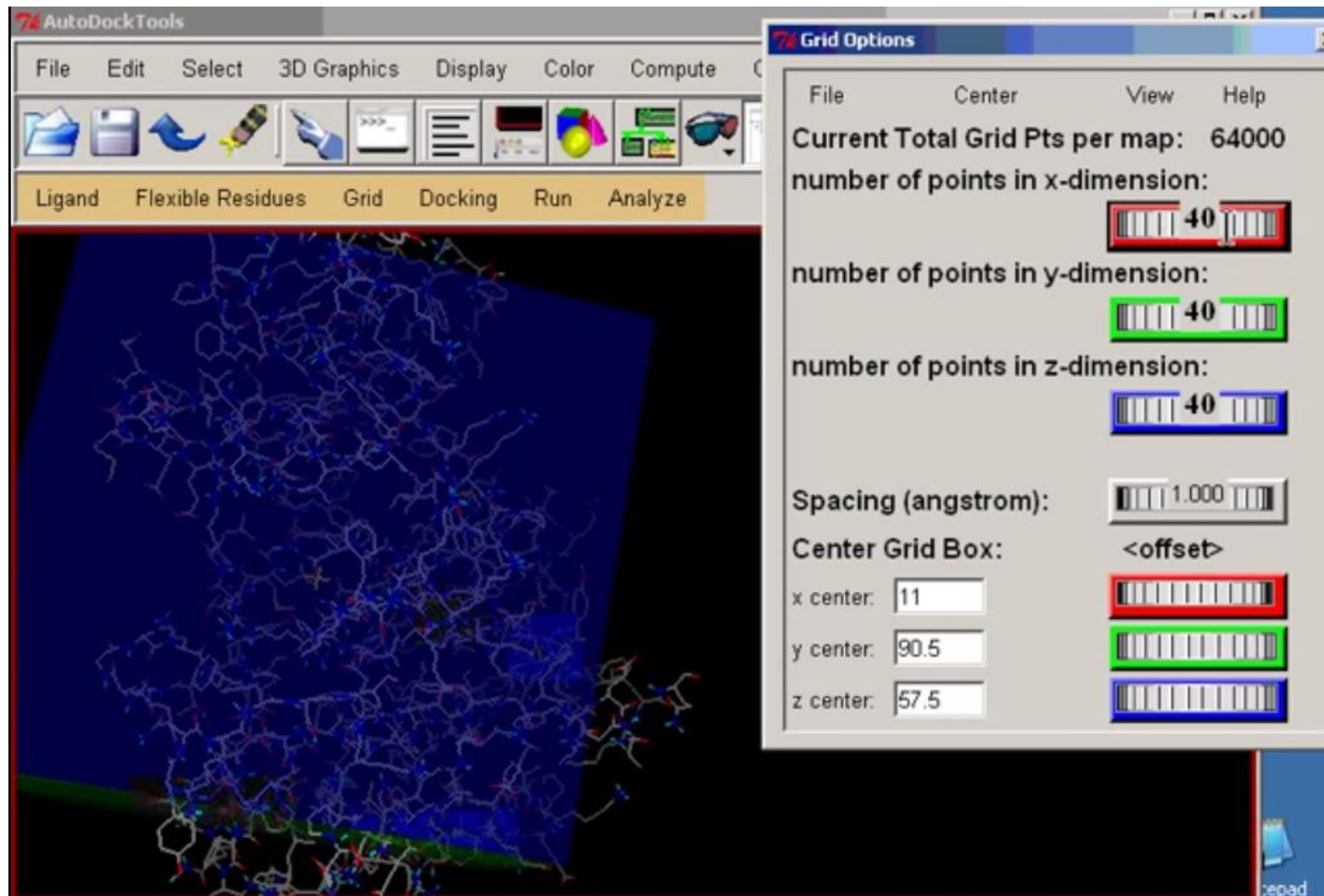
ACKNOWLEDGEMENTS

- MIT PRIMES
- Chief Research Advisor Pavel Etingof
- Program Director Slava Gerovitch
- Computer Science Section Faculty Coordinator Srini Devadas
- Mentor Dr. Gil Alterovitz
- Parents
- PRIMES & RSI alumni
- Other members of Dr. Alterovitz's PRIMES group

END

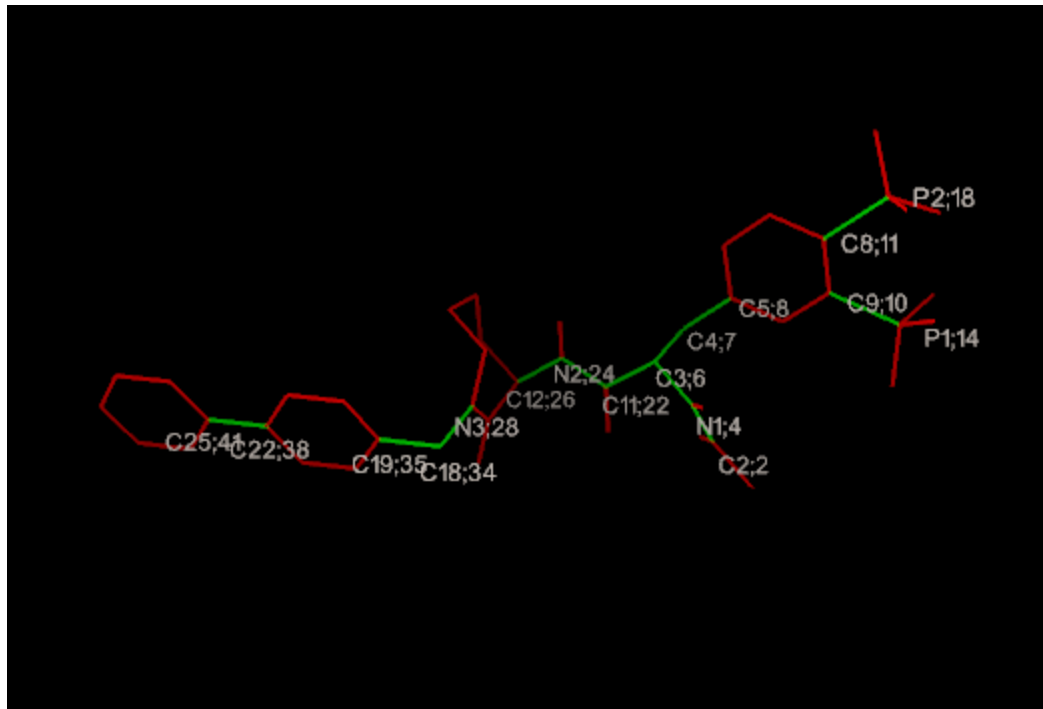
EXTRA METHODS - AUTODOCK

- Grid box determining binding region

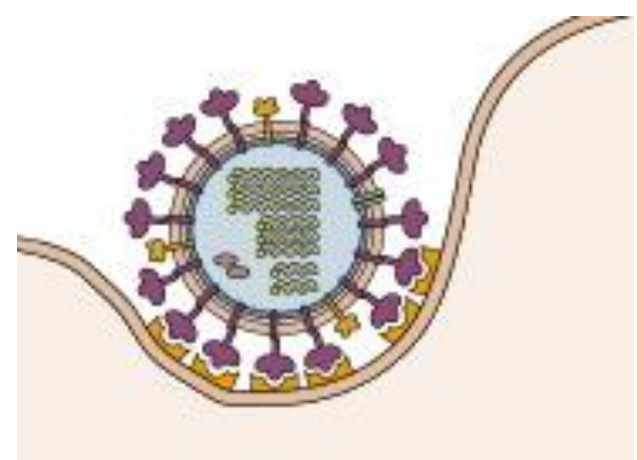


EXTRA METHODS - AUTODOCK

- Model of ZINC_53683662 with color-coded bonds
 - Green – rotatable
 - Red – unrotatable



EXTRA RESULTS – INFLUENZA



- Hemagglutinin, IDP/glycoprotein
 - Binds to cell receptors to facilitate entry of the flu
- Results for Drug Synergy

Mimicking hemagglutinin binding to sialic acid

Drug Name	Predicted Similarity	Binding Affinity
ZINC_96006030	0.84422636989	--

Mimicking antibody binding to hemagglutinin

Drug Name	Predicted Similarity	Binding Affinity
ZINC_	--	--

EXTRA RESULTS – THROMBIN & CANCER

- Thrombin is a protein that increases metastasis of tumors
 - Binds to hirudin, an IDP
- Previous work by Anvita Gupta
- Results for Drug Synergy

Mimicking hirudin, binding to thrombin (Anvita's/FDA)

Drug Name	Predicted Similarity	Binding Affinity
Dabigitran	0.8911	-6.1

Mimicking thrombin, binding to hirudin