Instruction: There are 3 problems, and you are required to solve all of them. All problems are weighted equally. Please show detailed work for full credit.

- This exam is conducted via Zoom on January 25 from 11:15 am to 1:15 pm EST.
- The entire Zoom meeting and chat messages are being recorded.
- This is a closed book, closed note exam.
- Hand calculators (or other computing devices) may not be used during the exam.
- You should join the Zoom meeting from two devices: Your computer/laptop/tablet (with webcam), and your smartphone (with camera).
- Audio should be muted and video must be kept on during the exam.
- Your computer webcam must fully show your face; your smartphone camera should show your computer monitor, your hands and workspace, with the pages of paper being used for the exam.
- At the very beginning of the exam, during set up, you will be asked to do a brief "environment scan", showing the workspace where your computer is and the desk/table/floor where you will be writing your work.
- You are required to bring enough blank pieces of paper to use for the exam. You will show the blank pages at the beginning, during the "environment scan" on Zoom.
- You are not allowed to use the internet for any searching or communication with others, with the sole exception of communication privately with the proctors via Zoom chat (which is set so that your chats only go privately to hosts, not to others).
- It is recommended that you print the exam and write your answers on it. However, you can write your answers on your blank papers if you do not have a printer with you.
- After you finish the exam, scan your pages, ordered and oriented appropriately, into a single pdf file. Email the pdf file to **robert.rizzo@stonybrook.edu** no later than 5 minutes after completion of the exam (i.e., **by 1:20 pm EST**).
- No students are allowed to leave the Zoom meeting until the exam is over.
  - If you finish the exam early, then submit your exam and remain in the Zoom meeting until the conclusion of the exam at 1:15 pm EST.
  - After submitting your exam, you can study for another exam or work on anything else, while staying in view in the Zoom meeting.
- If the answers are not submitted by 1:20 pm EST, the exam will not be graded, and a score of zero will be given.
- If you have a question during the exam, then send a chat message to the host privately.

AMS Common Exam Part B, Computational Biology Track, January Exam 2021

Name: _____ ID Num: _____

Part B: _____ / 75

Please complete ALL 3 questions which are based on AMS/CHE-535. Each question is worth 25 points.

Question 1. Note this question has multiple parts.

1a. Van der Waals (VDW) interactions in Molecular Mechanics force fields are usually computed using a Lennard-Jones potential energy function. On the axis below, sketch a curve which describes VDW interactions between two atoms A and B. Clearly label each axis and indicate the attractive and the repulsive regions of the curve as well as the point which represents the equilibrium distance between the two atoms.

1b. Describe in DETAIL how classical Molecular Mechanics force fields such as OPLS and AMBER were developed and validated. Include in your discussion the different types of experimental observables that were used and how the computational and experimental values were compared. Be detailed in your discussion.

1c. Describe in DETAIL how docking programs were developed. Include in your discussion ways in which programs can be quantitatively validated, and include in your answer known challenges for the field. Be detailed in your discussion.

Question 2. Note this question has multiple parts.

2a. Fill in the following table for the 20 naturally occurring amino acids and indicate which of the following properties best-describes each amino acid. Properties = hydrophobic, hydrophilic, aromatic ring, 5-membered ring, negatively charged, positively charged, ring in protein backbone, disulphide bonds, smallest side chain.

	Residue Name	**3 letter code**	**1 letter code**	**Residue Property**
01	glycine			
02		ALA		
03			V	
04	leucine			
05		ILE		
06			S	
07	threonine			
08		CYS		
09			M	
10	proline			
11		ASP		
12			N	
13	glutamic acid			
14		GLN		
15			K	
16	arginine			
17		HIS		
18			F	
19	tyrosine			
20		TRP		

2b. Define database enrichment as it relates to virtual screening and explain how ROC curves can be used to assess the accuracy of a given computational method or scoring function. Draw and label three examples of ROC curves with (i) poor, (ii) reasonable, and (iii) good enrichment.

2c. Define what constitutes a pharmacophore, explain the difference between a ligand-based and a receptor-based pharmacophore, and give at least four examples of features (structural or functional) that could be used.

2d. Describe in DETAIL how one would go about performing a virtual screening experiment for a newly discovered therapeutic target. Include in your answer an explanation of how you would setup the system for docking, use of docking controls, what libraries you would use for docking, how many compounds you would dock, and what strategies you would use for prioritizing compounds for purchase and subsequent experimental testing. Be detailed in your discussion.

Question 3. Note this question has multiple parts.

3a: Draw a thermodynamic cycle commonly used to compute the *absolute* free energy of binding (ΔG_{bind}) between a ligand L with a receptor target R using the Molecular Mechanics Generalized Born Surface Area (MM-GBSA) Method. Clearly label all parts and terms of your figure.

Write the simple expression which relates which legs of the thermodynamic cycle are used to computationally estimate the *absolute* free energy of binding ΔG_{bind}, which, if the calculations were exact, would be equivalent to the *absolute* experimental free energy of binding ΔG_{expt}.

Indicate which leg best corresponds to the *absolute* hydration free energy of the ligand AND provide a two-term equation commonly used to estimate ΔG_{hyd}.

3b: Write the Linear Response (LR) expression used to estimate binding free energy. Note LR is sometimes called the Linear Interaction Energy (LIE) method.

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3c: Write the more "general" Extended Linear Response (ELR) expression used to estimate binding free energy.

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3d: List four terms which could be considered as important for describing binding energy in ELR models, i.e. the "descriptors"

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3e: What is the physical meanings of the negative sign of the coefficient (-0.216) of the ΔHB_{total} term in the following ELR equation.

$$\Delta G_{calcd} = 0.100\langle EXX - C\rangle + 0.110\langle EXX - LJ\rangle - 0.216\langle \Delta HB_{total}\rangle - 1.350$$

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3f. Describe the differences between virtual screening and *de novo design*, give pros and cons of each method, and list at least three challenges associated with de novo growth of small organic molecules.