Group 13 — VirCAD: bioCAD for Viral Engineering BENG 187D ABET Addendum | Alan Li | BINF Mentor: Stefan N. Lukianov

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1. Desired Needs

- Rational AAV capsid design currently requires costly, slow wet-lab iteration; a computational pre-screening tool is needed to prioritize candidate mutations before synthesis
- No accessible, modular pipeline exists for integrating point mutation generation, structure prediction, and trimer docking in a single reproducible workflow
- Variable region VIII (VR-VIII) governs receptor binding specificity but lacks systematic in silico tools for targeted mutagenesis and structural consequence prediction
- Gene therapy developers at small biotechs lack the structural biology expertise to interpret capsid engineering results; a bioCAD interface would lower this barrier

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2. Constraints

- **Safety/Regulatory:** AAV vectors are subject to FDA IND/BLA pathways; computational predictions require wet-lab validation before any clinical translation; pipeline outputs are explicitly framed as candidate prioritization, not clinical-ready designs
- **Risks:** AlphaFold structural predictions carry known error modes for novel mutations (pLDDT/PAE uncertainty); false positives could misdirect downstream experimental resources
- **Global Impact:** Open-source release democratizes capsid engineering, enabling resource-limited academic labs and global gene therapy programs to participate in AAV development
- **Manufacturability:** Pipeline implemented as modular Python codebase with version-controlled dependencies; reproducible across standard HPC and cloud computing environments
- **Quality Control/Marketability:** Structural outputs benchmarked against known AAV9/PHP.eB crystal structures via RMSD and TM-score; commercial demand exists from gene therapy CDMOs and biotech startups

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3. Engineering Standards

- PDB/mmCIF coordinate file standards for all structural inputs and outputs
- AlphaFold2 confidence metrics (pLDDT >= 70, PAE thresholds) applied as quality gates before downstream docking
- RMSD and TM-score thresholds used to define structural equivalence to wild-type capsid

- Reproducible pipeline standards: version-controlled GitHub repository, pinned dependency environment, pytest coverage for core modules

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4. Ethical, Environmental, and Societal Concerns

- **Ethical:** Capsid engineering tools carry dual-use risk; enhanced viral vectors with altered tropism could theoretically be misapplied; responsible access controls and transparent methodology documentation are necessary mitigations
- **Environmental:** Entirely computational project; environmental footprint is limited to cloud/HPC compute energy use, negligible compared to equivalent wet-lab workflows
- **Societal:** Gene therapy has historically been accessible only to well-resourced institutions; open bioCAD tooling can reduce development costs and broaden patient access, particularly for rare disease indications

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5. Active Teamwork and Leadership

- **Collaboration:** Led weekly cross-functional syncs between computational and biological team members; integrated wet-lab structural feedback to refine docking scoring criteria
- **Delegation:** Took ownership of full computational pipeline development, manuscript writing (~70% drafted), and all figure production; coordinated with teammates on experimental validation and regulatory sections
- **Goals and deadlines:** Maintained milestone-based planning tied to manuscript submission timeline and BE Day deliverables; used version control to track iterative progress
- **Constructive feedback:** Incorporated mentor feedback through iterative manuscript review cycles; revised docking methodology after peer critique identified limitations in initial scoring approach

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6. Motivating Factors

- **New knowledge:** Self-taught AlphaFold2 multimer prediction, trimer docking workflows, and APPRAISE structural scoring to address gaps no existing tool covered
- **Self-initiating:** Independently identified VR-VIII as the key mutagenesis target for LamR-binding modulation and introduced trimer docking as a methodological improvement over monomer-only analysis
- **Persisting against challenges:** Iterated from Boltz to APPRAISE as the docking scoring backend after initial approaches showed insufficient discrimination between mutant structural classes; maintained forward progress through repeated pipeline re-architecture

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7. Innovative and Entrepreneurial Ideas

- VirCAD as a SaaS platform enabling gene therapy companies to run in-house capsid engineering campaigns without deep structural biology expertise
- Pipeline architecture is vector-agnostic; near-term extension to lentiviral vectors and alternate AAV serotype switching is feasible
- Potential licensing or integration into existing bioCAD platforms serving the CDMO and gene therapy manufacturing sector