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Computational fabrication of macromolecules to enhance perception and understanding of biological mechanisms

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Abstract

We propose a fabrication technique for the fast and cheap production of 3D replicas of proteins. We leverage silicone casting with rigid molds, to produce flexible models which can be safely extracted from the mold, and easily manipulated to simulate the biological interaction mechanisms between proteins. We believe that tangible models can be useful in education as well as in laboratory settings, and that they will ease the understanding of fundamental principles of macromolecular organization.

CCS Concepts

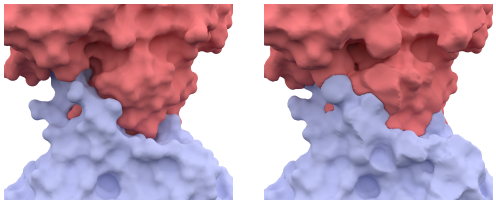
• ***Computing methodologies*** → *Shape modeling;*

1. Introduction

Interaction with physical replicas of small molecules is widely used in chemistry teaching [Fra13]. For macromolecules, however, the task is not as straightforward as assembling a combination of atoms: proteins are built by a succession of (up to hundreds of) aminoacids, each defined by N atoms (between 4 and 14, excluding Hydrogen), whose relative position can vary. Furthermore, proteins often work in complexes, and associate with other cellular or therapeutic components. Atomic or near-atomic models have proved valuable for elaborating and understanding fundamental principles of macromolecular organization [Cri74, KBD*58]. The possibility of handling physical models of objects, and of proteins in particular, fosters engagement and better understanding [HMC*06]. However, this enhanced experience comes with a cost [Kaw12]: the production of replicas is still definitely not cheap and can easily reach hundreds of euros for each custom object. Though the recent advances in 3D printing technology have offered novel tools for producing physical objects, they have not solved the problem: 3D printing devices are usually very slow, and the creation of a single moderately-sized object (up to tens of centimeters) can require more than of one day of device time. These technological and economic constraints pose significant limits in the use of physical replicas in both the teaching and the research context. Indeed, while 3D printed models have been used before to demonstrate biological features [Ols15] and in educational setting [HMC*06], the prevalent tools most frequently used, especially in research, are still based on VR [GBS*18, FNM*09], AR [BF17], and immersive structures [SDFP*16].

For all these reasons, we propose a fabrication technique based on casting that is aimed to enable the cheap production of 3D replicas of proteic polymers. The main idea is to leverage silicone casting with rigid molds. The use of silicone for casting protein models has two main practical advantages. On the one hand, the elasticity of silicone makes so the replicas can be safely extracted from the mold, and overhanging geometric details do not constitute a severe limitation. On the other hand, soft proteins models are easier to manipulate for simulating the biological mechanisms of interaction and matching. Moreover, casting is especially convenient when fabricating protein polymers, whose structure is composed of repeating subunits. We believe the method proposed in this paper may represent a step forward in facilitating the preparation and use of tangible protein models, as it is relatively straightforward, and not expensive in terms of effort, time and cost.

2. From atomic data to 3D physical models



(a) (b)

Figure 1: *(a) Non matching surfaces (b) Exactly matching surfaces*

The input to our algorithm is a macromolecular structure represented in a PDB (Protein Data Bank) record file, which lists the 3D coordinates of all atoms in the protein. We use PyMOL [Sch15] to extract the mesh representing the solvent excluded molecular

surface [LR71]. In the case of multimers, each monomer $\mathcal{M}_i$ is extracted as a single surface mesh $\mathcal{S}_i$. Since we are interested in modeling the interaction between the different monomers, we want the extracted surfaces to be exactly matching in correspondence of the interaction sites. Indeed, having matching surfaces makes it easier to detect the interaction sites and to efficaciously match the two monomers. However, extracting the surfaces $\mathcal{S}_i$ indipendently for each $\mathcal{M}_i$ often leads to difficult to match surfaces, or even to intersecting surfaces, which makes it impossible to reach a correct match (Figure 1.a). To solve this, we automatically identify the interaction sites between the monomers $\mathcal{M}_i$, and we locally interpolate a common surface between the monomers (Figure 1.b).

Given the interpolated solvent excluded surfaces of monomers, we proceed to define the geometry of the corresponding rigid molds. One of the key problems in the computational design of molds is deciding how the mold should open up to allow for the cast extraction, that is, how to place the parting surfaces which separate the different mold pieces. This is especially true for complex, free-forms shapes, such as biological entities. We use an approach based on the work from Alderighi et al. [AMG*19], which identifies valid parting surfaces robustly for objects with complex geometry and topology, making it suitable for our scenario. In [AMG*19] the authors propose to 3D print a metamold to cast a silicone mold, and then cast resin into the mold to fabricate the final object. On the contrary, we 3D print the mold itself (Figure 2), and use silicone to cast the protein replicas.

We conducted preliminary experiments on an actin filament (*PDB ID: 6ANU*, Figure 3) and human oxidized hemoglobin (*PDB ID: 1GZX*). The models were fabricated at a scale of $1 \times 10e7$, a default value perfectly suited for the study of macromolecules [Zop17]. Keeping this value allows the understanding of relative sizes for users, whether they are familiar or not with cellular dimensions, which are typically measured in Angstroms to micrometers.

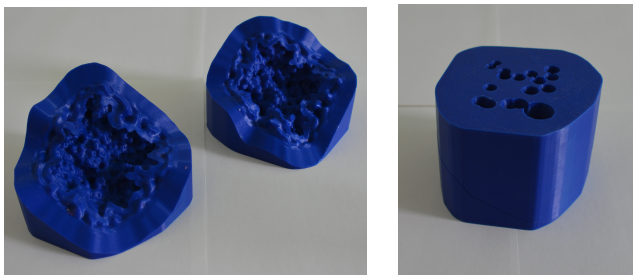


Figure 2: *(Left) The two 3D printed mold pieces. (Right) The assembled mold, ready for casting the silicone replicas.*

3. Conclusions

We have presented an ongoing work on the development of fabrication techniques for the production of 3D replicas of proteins. Our preliminary results show that silicone casting with rigid molds is a fast and cheap solution for the production of tangible models of good quality. In the future we plan to introduce new features that facilitate human interaction with the models, such as marks to identify specific functions and magnets to guide interactions. We also aim to fabricate more complex objects. Finally, we plan to perform user studies to test our technique both in the educational setting, such as in high schools and basic university courses, and in the laboratory, e.g., to assess whether fabricated models ease the problem of docking with other proteins and small molecules with therapeutic functions.

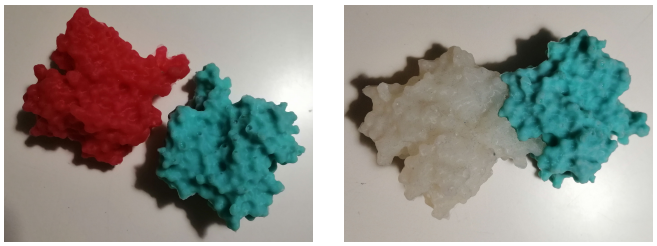


Figure 3: *(Left) Silicone replicas of an Actin monomer. (Right) The interpolated surfaces, in correspondence of interaction sites, allow for a perfect match between monomers.*

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