ROMEO: A Plug-and-play Software Platform of Robotics-inspired Algorithms for Modeling Biomolecular Structures and Motions

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ABSTRACT

Motivation: Due to the central role of protein structure in molecular recognition, great computational efforts are devoted to modeling protein structures and motions that mediate structural rearrangements. The size, dimensionality, and non-linearity of the protein structure space present outstanding challenges. Such challenges also arise in robot motion planning, and robotics-inspired treatments of protein structure and motion are increasingly showing high exploration capability. Encouraged by such findings, we debut here ROMEO, which stands for Robotics prOtein Motion ExplOration framework. ROMEO is an open-source, object-oriented platform that allows researchers access to and reproducibility of published robotics-inspired algorithms for modeling protein structures and motions, as well as facilitates novel algorithmic design via its plug-and-play architecture.

Availability and implementation: ROMEO is written in C++ and is available in GitLab (https://github.com/). This software is freely available under the Creative Commons license (Attribution and Non-Commercial).

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1 INTRODUCTION

Protein molecules regulate virtually all processes that maintain and replicate a living cell, and their tertiary structure largely determines their interactions with molecular partners [4]. A detailed understanding of the structure(s) at the disposal of a protein for biological activity and of the motions that mediate rearrangements between different structures for activity modulation is central to understanding molecular mechanisms [3]. Decades of research have shown that such understanding cannot be obtained via experimentation or computation alone; in particular, while great progress is made on modeling biomolecular structures and motions, challenges related to the size, dimensionality, and non-linearity of structure spaces associated with macromolecules, such as proteins, remain [11]. Over the past decade, great advancements in the ability to explore complex protein structure spaces have come from robotics-inspired algorithms that leverage analogies between molecular and robot configuration spaces [17].

Encouraged by such progress, we debut here ROMEO, which stands for Robotics prOtein Motion ExplOration framework. ROMEO is an open-source, object-oriented platform that allows researchers access to and reproducibility of published robotics-inspired algorithms for modeling protein structures and motions. For instance, ROMEO provides templates for popular robotics motion planning algorithms, such as the Rapidly-exploring Random Tree (RRT) and Probabilistic RoadMap (PRM), and offers disseminated adaptations of these canonical algorithms that address diverse application settings, from template-free protein structure prediction to modeling of motions that mediate re-arrangements between stable and metastable structures [1, 6, 14, 15].

2 PLUG AND PLAY DESIGN

ROMEO follows a plug-and-play architecture to facilitate novel algorithmic design and so allow researchers to further advance algorithmic research in molecular biology. ROMEO is written in C++ and its object-oriented design allows easy adaptation and expansion of its classes. These classes have been designed around a core set of components shared by many motion planning algorithms, which we summarize below (see Figure S1 for a visualization of the architecture).

Representation, Energy, and Forward Kinematics: The cfg class represents a protein configuration. Included with this initial release is an extension of this class that interfaces with the Rosetta package [5] and utilizes the coarse-grained representation known as the centroid mode, which tracks heavy backbone atoms and a side-chain centroid pseudo-atom via dihedral angles. Developers can easily extend this class to support Rosetta’s all-atom representation or others. A forward kinematics class allows projecting a configuration (under the selected representation) into Cartesian space space (retrieving Cartesian coordinates for each of the represented atoms). This class also associates an energy/fitness score with a configuration. In this initial release, ROMEO utilizes Rosetta scoring functions.

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We showcase two selected examples of how ROMEO can be utilized. The examples above illustrate the power of ROMEO’s plug-and-play via an energy threshold or dynamic techniques utilizing the Metropolis. This software can be useful in advancing algorithmic research structure and motion computation. It can also be employed in a classroom setting to allow instructors to initiate students in computational molecular biology and easily extend components of the framework.

5 ACKNOWLEDGEMENTS

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APPENDIX

ROMEO DESIGN/CLASSES

ROMEO is written in C++ and consists of a core set of components that are shared among all sampling-based robot motion planning algorithms. The object-oriented design of ROMEO allows easy adaptation and expansion of its core components, making it possible for developers to customize ROMEO for additional applications.

Figure 1 illustrates the class inheritance hierarchy of the software. The following sections summarize the purpose of each class and describe in greater detail selected member functions.

Choice of Representation

The cfg class is the base class to represent a configuration. The class stores a vector of the backbone dihedral angles of a protein structure and in doing so assumes an idealized geometry (where bond lengths and valence angles do not deviate from equilibrium values). This choice of representation is popular in template-free protein structure prediction and motion computation. We point that other applications, such as folding, necessitate extending the base class by allowing bond lengths and valence angles to deviate (thus including them in the representation) or by introducing other configuration parameters.

Since the potential energy associated with a given protein structure is used in many planning operations (for instance, when determining whether to accept a new configuration or when calculating the cost associated with moving from a current to a new configuration), energy is associated with a configuration and is also stored in the cfg class.

The class MolecularStructureRosetta provides the interface between ROMEO and the Rosetta software suite. This class, derived from the CfgForwardKinematics class offers the ability to extract a configuration from a Protein DataBank (PDB) [2] file (which is the conventional way of storing information about a tertiary structure) and to score a configuration using a selected Rosetta scoring/energy functions. Member functions are also provided to perform forward kinematics on a cfg object, that is, placing the protein in a particular configuration and obtaining the Cartesian coordinates for each atom in a given representation. ROMEO provides support for Rosetta’s centroid representation, which tracks heavy backbone atoms and a side-chain centroid pseudo-atom.

Planners

ROMEO utilizes sampling-based motion planning algorithms to explore the configuration space of a protein. Direct support is provided for two popular sampling-based planners: the Rapidly Exploring Random Tree (RRT) [10] and the Probabilistic RoadMap (PRM) [9].
As a proof of concept, to illustrate ROMEO’s plug and play architecture, the FeLTR [15] and SPRINT [14] methods have also been implemented in this release of ROMEO. By expanding the sampler classes, many variants of these planners can be implemented by other developers.

These planners all share a common set of operations or core components, such as: generating new configurations, determining the validity of a new configuration, measuring the distance between two configurations, and projecting configurations into the workspace. ROMEO abstracts these operations using a set of base classes that allow for easy “plug and play” replacements of these components.

**Samplers and Offspring Generators**

ROMEO offers two classes, one for sampling and another for offspring generation. The sampling class is employed during the generation of at-random samples/configurations. Examples include obtaining \( q_{rand} \) in the RRT planner and generating landmark configurations to populate the roadmap/graph in PRM. The offspring generator class is used to modify an existing configuration, potentially by perturbing it in a given direction. This is employed, for instance, when extending \( q_{near} \) in the direction of \( q_{rand} \) in the RRT extend step, or when connecting landmark configurations during the local planning step within the PRM planner. ROMEO extends these baseline classes to support utilizing Rosetta’s molecular fragment libraries for structure and motion computations.

Acceptors. The acceptor class is used when deciding whether a new configuration should be added to the graph or tree maintained by the planner. A simple acceptor test would be to set a maximum energy value for all configurations (thus, the acceptor verifies that new configurations are below this threshold). When studying molecular transitions, the Metropolis criterion (which utilizes differences in energy between two configurations) is commonly employed. For this reason, ROMEO also provides an acceptor class based on MMC; in particular, ROMEO implements the transition test utilized in the SPRINT [14] and Transition-based RRT (T-RRT) planners [7, 8].

Distances. Planners utilize a distance function to determine nearby configurations. ROMEO comes with basic distance classes (Euclidean distance), as well as distances commonly used in the study of proteins (such as the least root-mean-square-distance, or IRMSE[12].

**SELECTED EXAMPLES OF APPLICABILITY**

This section outlines two applications that utilize the ROMEO framework. The first example utilizes ROMEO to perform template-free protein structure prediction by implementing a robotics-inspired method known as FeLTR [15]. The second example employs RRT to compute energetically-feasible paths that connect two functionally-relevant configurations of the cyanovirin-n protein. All source code and scripts to run these examples are included with the ROMEO distribution.

**Structure Prediction**

This example showcases the FeLTR method [15] for performing template-free protein structure prediction. We summarize how ROMEO’s “plug and play” architecture is utilized to easily implement FeLTR.

As described in greater detail in [15], FeLTR employs an SNE planner that expands the search tree iteratively via selection and expansion operations and utilizes projection layers for configuration selection. The SelectionVertex function of ROMEO’s TreeSamplingBasedPlanner class is overloaded to support FeLTR’s novel node selection technique that utilizes a low-dimensional projection of a configuration. The AddVertex function is overloaded to place new vertices into FeLTR’s projection layers. Changes to the planner are limited to the addition of 100 lines of code (in addition to supporting code for computing projection coordinates from configurations). The ease with which this complex method is implemented in ROMEO highlights the advantages of its object-oriented design.

ROMEO’s distribution provides the required scripts and configuration files to run FeLTR to predict the structure of the ibeta subdomain of the mu end DNA binding domain of phage mu transposase. Figure 2 showcases the closest (in terms of IRMSE) sampled structure when compared to the native structure cataloged in the PDB. Different weighting schemes can be explored when selecting nodes from FeLTR’s low-dimensional projection, as described in [13]. Figure 3 highlights some of the behavior of each of these weighting schemes. The quad scheme utilizes a greedy strategy, selecting nodes with the lowest energies with high probability. The linear and norm (Gaussian based) schemes approach the lower IRMSE structure more gradually, and have been shown for longer executions to provide closer samples to the native structure [13].

**Motion Computation**

ROMEO can also be used to compute the motions that mediate rearrangements between two distinct functionally-relevant structures. We highlight this capability here on the cyanovirin-n protein, where we treat two distinct structures (found under PDB IDs 2EZM and 1L5E) as start and goal structures located almost 16 Å IRMSE apart from one another. We highlight here an implementation of the SPRINT method [14] with ROMEO.

We executed ROMEO for 12 hours and tested two different energy acceptors. Rosetta’s score3 energy scheme was utilized with the radius of gyration terms disabled (since this rewards more compact structures). The first acceptor limited the acceptable energy of a configuration to no higher than 60 Rosetta Energy Units (REUs). The second scheme utilized the Metropolis criterion, setting the temperature, such that an increase of 10 REUs had a 0.1 probability of being accepted. Each scheme resulted in pathways that ended with configurations (structures) within 3 Å IRMSE of the goal configuration. The energy profiles for each are shown in Figure 4. Figure 4 highlights the advantages of ROMEO’s “plug and play” architecture.

A few sample structures along the pathway computed from the MMC execution are showcased in Figure 5.

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Figure 1: In ROMEO’s plug-and-play design, all classes are derived from a common Configuration object (which can also be overloaded. All of the planner functions can also be replaced with new, derived classes.

Figure 2: The known native tertiary structure of the ibeta subdomain of the mu end DNA binding domain of phage mu transposase (found under PDB entry 2EZK) is drawn in transparent blue. The structure with the lowest LRMSD (of 3.3Å) to this native structure (among all structures computed by FeLTR during a 2-hour execution) is also shown here, drawn in red.

Figure 3: The known native tertiary structure of the ibeta subdomain of the mu end DNA binding domain of phage mu transposase (found under PDB entry 2EZK) is drawn in transparent blue. The structure with the lowest LRMSD (of 3.3Å) to this native structure (among all structures computed by FeLTR during a 2-hour execution) is also shown here, drawn in red.

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Figure 4: Two energy acceptance strategies are utilized, MMC (Metropolis Monte Carlo) and a scheme that sets the maximum energy of a structure during ROMEO’s exploration of paths connecting two distinct, known structures of the cyanovirin-n protein. The MMC scheme yields a more energetically-feasible pathway that gradually rises in energy compared to the maximum energy threshold strategy.
Figure 5: A few ROMEO-computed structures are shown along a path that illustrates the rearrangement of the cyanovirin-n protein between two distinct, known structures (with PDB IDs 2EZM and 1L5E). The computed path consists of 89 intermediate structures, of which 6 are shown here. The first structure (top left) is the one under PDB ID 2EZM. The last structure is that under PDB ID 1L5E. The other four structures are selected from the ROMEO-computed path to illustrate the rearrangement of the protein between the given start and goal structures.