Computers in Biology and Medicine 43 (2013) 1011–1022

Contents lists available at SciVerse ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

GPU-based acceleration of an RNA tertiary structure prediction algorithm

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ARTICLE INFO

Article history:
Received 3 November 2012
Accepted 14 May 2013

Keywords:
RNA
RNA structure prediction
Parallel algorithm
Multi-core CPU
GPGPU

ABSTRACT

Experimental techniques such as X-ray crystallography and nuclear magnetic resonance have been useful for the accurate determination of RNA tertiary structures. However, high-throughput structure determination using such methods often becomes difficult, due to the need for a large quantity of pure samples. Computational techniques for the prediction of RNA tertiary structures are thus becoming increasingly popular. Most of the existing prediction algorithms are computationally intensive, and there is a clear need for acceleration. In this paper, we propose a parallelization methodology for the fragment assembly of RNA (FARNA) algorithm, one of the most effective methods for computational prediction of RNA tertiary structure. The proposed parallelization scheme exploits multi-core CPUs and GPUs in harmony to maximize their utilization. We tested our approach with a number of RNA sequences and confirmed that it allows the time required for structure prediction to be significantly reduced. With respect to the baseline architecture equipped with a single CPU core, we achieved a speedup of up to approximately 24× (roughly 4× by multi-core CPUs and 20× by GPUs). Compared with a quad-core CPU setup, the proposed approach delivers an additional 12× speedup by utilizing GPU devices. Given that most PCs these days have a multi-core CPU and a GPU card, our methodology will be very helpful for accelerating algorithms in a cost-effective manner.

1. Introduction

The role of RNA molecules in biology is amazingly diverse. They can carry and decode genetic information, work as part of protein-synthesizing machine, catalyze chemical reactions, and regulate gene expression. Such a variety is possible because RNAs can vary their tertiary structures they adopt in different conditions [1]. RNA tertiary structure determination is therefore important for understanding RNA functions and interactions. Experimental techniques such as X-ray crystallography and nuclear magnetic resonance (NMR) have been useful for the accurate determination of RNA tertiary structures, but high-throughput structure determination using such methods often becomes difficult, due to the need for a large quantity of high-purity samples [2]. Furthermore, there are a number of functionally important RNA states whose structures cannot be directly determined by high-resolution techniques [3,4]. To understand the structure–function relationships for these RNAs, we need accurate tertiary structure modeling [4].

The field of RNA structure modeling and prediction is thus receiving growing attention. There exist various approaches [5–10], and their common goal is to provide an accurate structural model of RNA and prediction methods useful for designing and verifying biological hypotheses [4]. The prediction of native-like RNA structures typically needs algorithms with high computational complexity and involves a huge number of precise floating-point number calculations [2]. The computation takes longer for a longer RNA sequence, and the prediction of a non-trivial RNA sequence can easily become prohibitively time consuming. Genomic databases are growing fast, and the need for a rapid prediction tool is becoming increasingly clear.

In this paper, we present a GPU-based parallelization scheme of the fragment assembly RNA (FARNA) algorithm [6] in the Rosetta software suite [11]. FARNA is one of the most powerful computational methods for modeling native-like RNA structural motifs with high resolution [1] and can recapitulate many non-Watson-Crick base pairs seen in native structures, which are crucial for accurate modeling. Ideally, prediction algorithms could be run on a supercomputer or a cluster of servers. Such a powerful computing environment is not available to every researcher, however, and affordable microprocessor-based PCs have been the workhorse for executing prediction algorithms in many cases. Another notable trend in computer architecture is the use of graphics processing units (GPUs) for general-purpose computing. These days, GPUs have hundreds of processing units embedded within them, and the growth in raw performance of GPUs has been outpacing

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http://dx.doi.org/10.1016/j.compbiomed.2013.05.007

that of CPUs. The many-core architectures such as GPUs are significantly more efficient in terms of arithmetic operations per units of energy or per transistor [12] and have been used for accelerating molecular modeling [13,14]. To the best of our knowledge, this paper is the first attempt to parallelize FARNA using GPUs.

2. Background

2.1. RNA structure prediction

In order to understand the function an RNA and its interaction with other molecules, it is critical to identify the tertiary structure of an RNA. However, the accurate determination of the three-dimensional structure and folding kinetics of RNAs remains challenging experimentally. It is often difficult to use X-ray crystallography or nuclear magnetic resonance for high-throughput structure determination, due to the need for the preparation of large quantities of RNA samples with high purity and technical limitations [2]. Consequently, the computational prediction of RNA tertiary structures and folding is becoming increasingly popular and important. Table 1 lists the existing computational methods for RNA tertiary prediction. In contrast to the advances made in algorithms for predicting protein folding, the computational prediction of RNA structures is still in its infancy.

There has been a great deal of interest in the modeling of 3D protein structures, and the methods developed for proteins may be useful in the context of RNA as well [15]. However, there exist key differences between RNA and protein structures, which must be considered when developing an algorithm for RNA structure prediction. Most obviously, an RNA sequence consists of only four types of bases, whereas a protein sequence can have 20 types of amino acids. Secondly, RNAs are highly negatively charged and can create strong intermolecular and/or intramolecular electrostatic interactions within and/or outside the molecules. In addition, the formation of the secondary and tertiary structures is much more clearly separated in the time domain for RNAs. Lastly, significant topological constraints can be put on the RNA molecule by the intimate intertwining of the two parts of the RNA strand.

2.2. Fragmented assembly of ribonucleic acid

The fragment assembly of RNA (FARNA) algorithm [6] was developed to predict RNA tertiary structure based on the minimum energy required to form RNA structure with great stability. FARNA was inspired by the low-resolution protein structure prediction algorithm included in the Rosetta suite [11]. The Rosetta software (https://www.rosettacommons.org) has been widely used for macromolecular modeling and includes tools for structure inference, design, and modeling of nucleic acids and proteins. For accurate modeling, it is critical to consider non-Watson–Crick pairs such as a wobble base pair and a Hoogsteen base pair [1], and FARNA cannot only reproduce canonical Watson–Crick pairs accurately but also recapitulate many of the non-Watson-Crick pairs seen in the native structures [6].

FARNA models an RNA sequence by a string of beads, each of which is assumed to be centered at a base. In this coarse-grained model, three bases are grouped together and considered at a time. Given a sequence of the target RNA, FARNA assembles short fragments from existing RNA crystal structures whose sequences match the subsequences of the target RNA. To this end, a 3D structure library is utilized. This library contains 3-nucleotide fragments taken from a large rRNA subunit, from which the torsion angles and ribose puckering parameters are extracted and stored. To assemble the fragments into native-like structures, FARNA relies on a Monte Carlo simulation, which is guided by a knowledge-based energy function that considers the backbone conformations and side-chain interactions in solved RNAs.

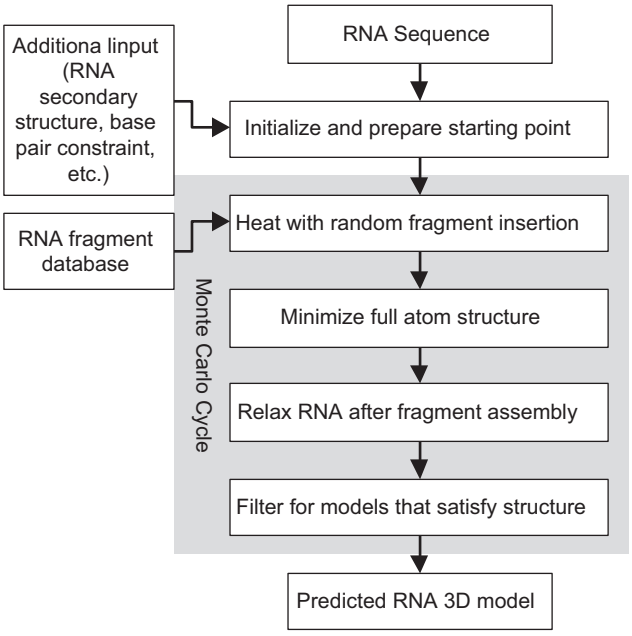

Fig. 1. Overall flow of FARNA. Given an RNA sequence and additional input such as its secondary structure and base pair constraints, the FARNA algorithm carries out a sequence of steps to predict the tertiary structure of the input sequence. The main body of the algorithm consists of four steps (random fragment insertion, atomic structure minimization, relaxation after assembly, and filtering) based on Monte Carlo simulation cycles.

Table 1
Computational methods for RNA structure modeling and prediction. The existing computational methods for RNA tertiary prediction.

Tool	Input	Model	Simulation method	Description
BARNACLE [5]	Sequence	Coarse-grained	Relica exchange, molecular dynamics	A Python library for the probabilistic sampling of RNA structures that are compatible with a given nucleotide sequence and that are RNA-like on a local length scale
FARNA [6,7]	Sequence, secondary structure	Coarse-grained	Fragment assembly, Monte Carlo	Uses 3-nt fragment library, Monte Carlo simulations and a potential function to predict the structure
iFoldRNA [8]	Sequence	Coarse-grained	Replica exchange, molecular dynamics	Uses discrete molecular dynamics and force fields to simulate RNA folding dynamics
MC-Fold/MC-Sym [9]	Sequence, secondary structure	Nucleotide cyclic motif	Fragment assembly, Las Vegas algorithm	Predicts RNA structures using free energy minimization with structure assembled using the fragment insertion by Las Vegas algorithm
NAST [10]	Secondary structure, tertiary contacts	Coarse-grained	Molecular dynamics	Performs molecular dynamics simulations guided by a knowledge-based statistical potential function