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Applying the enhanced Craig-Bampton method to equilibrium protein dynamics

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ABSTRACT

Finite element (FE) method has been successfully applied to analysis of equilibrium protein dynamics because of its high accuracy and computational efficiency compared with the methods based on the full atomistic force field. However, even using the FE method, analysis of macromolecular protein assemblies is still challenging due to its huge number of DOFs. In order to handle this problem, we here apply the enhanced Craig-Bampton (CB) method that was a recently developed, robust FE model reduction technique. To illustrate, its performance is investigated by analyzing the molecular structure of the Middle East Respiratory Syndrome coronavirus (MERS-CoV) 3C-like protease.

1. INTRODUCTION

The coarse-grained modeling techniques such as elastic network model (ENM) (Tirion, 1996) and finite element (FE) model (Bathe, 2008, Kim, 2011) have been successfully used for analysis of supramolecular protein assemblies. In particular, FE modeling approach offers an efficient way of incorporating the effect of externally applied mechanical forces or surrounding media (Bathe, 2008, Kim, 2011) as it models the molecular surface explicitly.

Nevertheless, analysis of supramolecular protein assemblies is still challenging even with these coarse-grained modeling approaches due to its huge number of DOFs. To address this problem, we recently proposed an automated model reduction procedure (Kim and Kim, 2015) based on component mode synthesis (CMS) that is a popular reduced order modeling (ROM) technique in structural dynamics community (Craig and

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Bampton, 1965, MacNeal, 1971, Park, Kim and Lee, 2012, Kim, Lee and Lee, 2014, Kim and Lee, 2014, Kim, Boo and Lee, 2015,). In this work, we present an improved procedure that employs the enhanced Craig-Bampton (CB) method (Kim and Lee, 2015).

First, we briefly introduce FE based protein modeling and the enhanced CB method. Then, the performance of the enhanced CB method is compared with the original CB method using numerical examples.

2. METHOD

2.1 Finite element model of proteins

Calculating the molecular surface of a protein is the first step in building the finite element protein model. Solvent-excluded surface is generally used as the molecular surface that can be computed by rolling a sphere over the Van der Waals surface. Using PMV version 1.5.6 (http://mgltools.scripps.edu/documentation/tutorial/python-molecular-viewer) which is freely available, we calculate a triangulated molecular surface of the protein. Fig. 1B represents the solvent-excluded surface of an example protein obtained using a sphere radius of 1.5 Å.

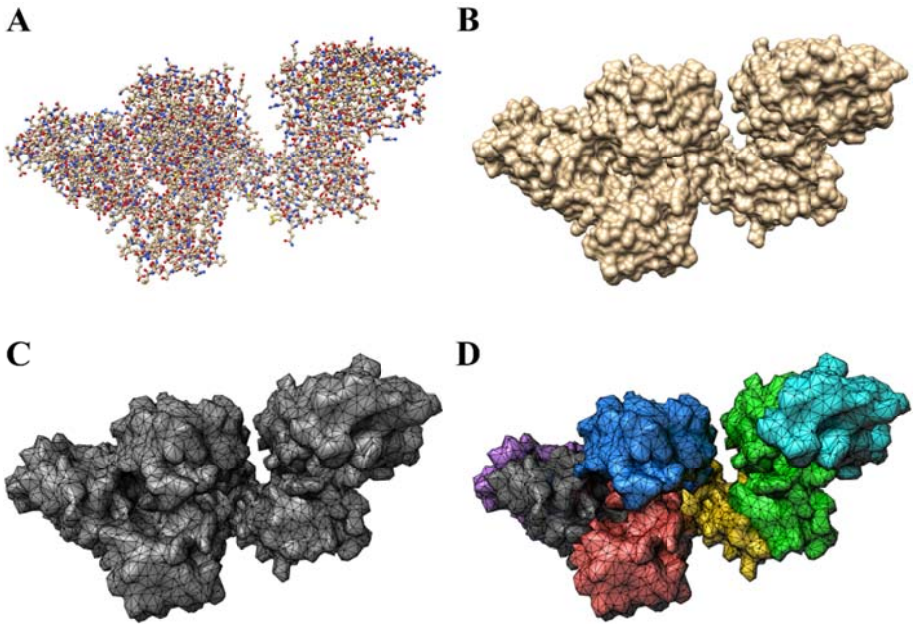

Fig. 1 (A) Atomic structure, (B) solvent-excluded surface, (C) finite element model and (D) partitioned finite element model of the Middle East Respiratory Syndrome coronavirus (MERS-CoV) 3C-like protease

From the computed molecular surface, we generate the three-dimensional volumetric finite element model using 4-node tetrahedral solid elements as shown in Fig. 1C, which is done using a commercial finite element analysis program ADINA version 9.0.7 (ADINA R&D, Inc., Watertown, MA, USA).

Finally, the constructed finite element model is partitioned into a number of substructures to be used for application of the enhanced CB method (Fig. 1D). We use METIS version 5.1.0 (http://glaros.dtc.umn.edu/gkhome/metis/metis/overview/) for partitioning of the model.

2.2 Enhanced Craig-Bampton method

The original finite element model of protein is partitioned into small substructures using METIS as in Fig. 1D, and then the matrices of the equation of motion can be expressed by

$$\mathbf{M}=\begin{bmatrix}\mathbf{M}_s & \mathbf{M}_c\\ \mathbf{M}_c{}^T & \mathbf{M}_b\end{bmatrix},\ \mathbf{K}=\begin{bmatrix}\mathbf{K}_s & \mathbf{K}_c\\ \mathbf{K}_c{}^T & \mathbf{K}_b\end{bmatrix},\ \mathbf{x}=\begin{bmatrix}\mathbf{x}_s\\ \mathbf{x}_b\end{bmatrix}, \tag{1}$$

where $\mathbf{M}$ and $\mathbf{K}$ are the mass and stiffness matrices, respectively, and $\mathbf{x}$ is displacement vector. Subscripts s, b and c denote substructural, interface boundary and coupling terms, respectively.

In the CB method, the displacement vector $\mathbf{x}$ can be approximated with the transformation matrix $\overline{\mathbf{T}}_0$ as follows

$$\mathbf{x}\approx\overline{\mathbf{x}}=\overline{\mathbf{T}}_0\begin{bmatrix}\mathbf{q}_d\\ \mathbf{x}_b\end{bmatrix},\ \overline{\mathbf{T}}_0=\begin{bmatrix}\mathbf{\Phi}_d & \mathbf{C}\\ \mathbf{0} & \mathbf{I}_b\end{bmatrix},\ \mathbf{C}=-\mathbf{K}_s^{-1}\mathbf{K}_c, \tag{2}$$

in which $\mathbf{I}_b$ is an identity matrix of interface boundary, and $\mathbf{\Phi}_d$ is a matrix consisting of the substructural dominant normal modes which are the low frequency normal modes obtained from the substructural eigenvalue problem. It should be noted that the low frequency normal modes are usually associated with important dynamic characteristics such as the conformational change of proteins.

In the CB method, the reduced matrices are constructed using $\overline{\mathbf{T}}_0$ as

$$\overline{\mathbf{M}}_p=\overline{\mathbf{T}}_0^T\mathbf{M}\overline{\mathbf{T}}_0,\ \overline{\mathbf{K}}_p=\overline{\mathbf{T}}_0^T\mathbf{K}\overline{\mathbf{T}}_0. \tag{3}$$

In the enhanced CB method, the enhanced transformation matrix $\overline{\mathbf{T}}_1$ is newly derived by considering the residual substructural mode as

$$\overline{\mathbf{T}}_1 = \overline{\mathbf{T}}_0 + \overline{\mathbf{T}}_r \,, \tag{4}$$

with

$$\overline{\mathbf{T}}_0 = \begin{bmatrix} \boldsymbol{\Phi}_d & \mathbf{C} \\ \mathbf{0} & \mathbf{I}_b \end{bmatrix}, \quad \overline{\mathbf{T}}_r = \begin{bmatrix} \mathbf{0} & \mathbf{F}_{rs}[\mathbf{M}_s\mathbf{C} + \mathbf{M}_c] \\ \mathbf{0} & \mathbf{0} \end{bmatrix} \overline{\mathbf{M}}_p^{-1} \overline{\mathbf{K}}_p \,, \quad \mathbf{F}_{rs} = \mathbf{K}_s^{-1} - \boldsymbol{\Phi}_d \boldsymbol{\Lambda}_d^{-1} \boldsymbol{\Phi}_d^T \,, \tag{5}$$

where $\mathbf{F}_{rs}$ denotes the residual flexibility, in which contains the residual mode effect.

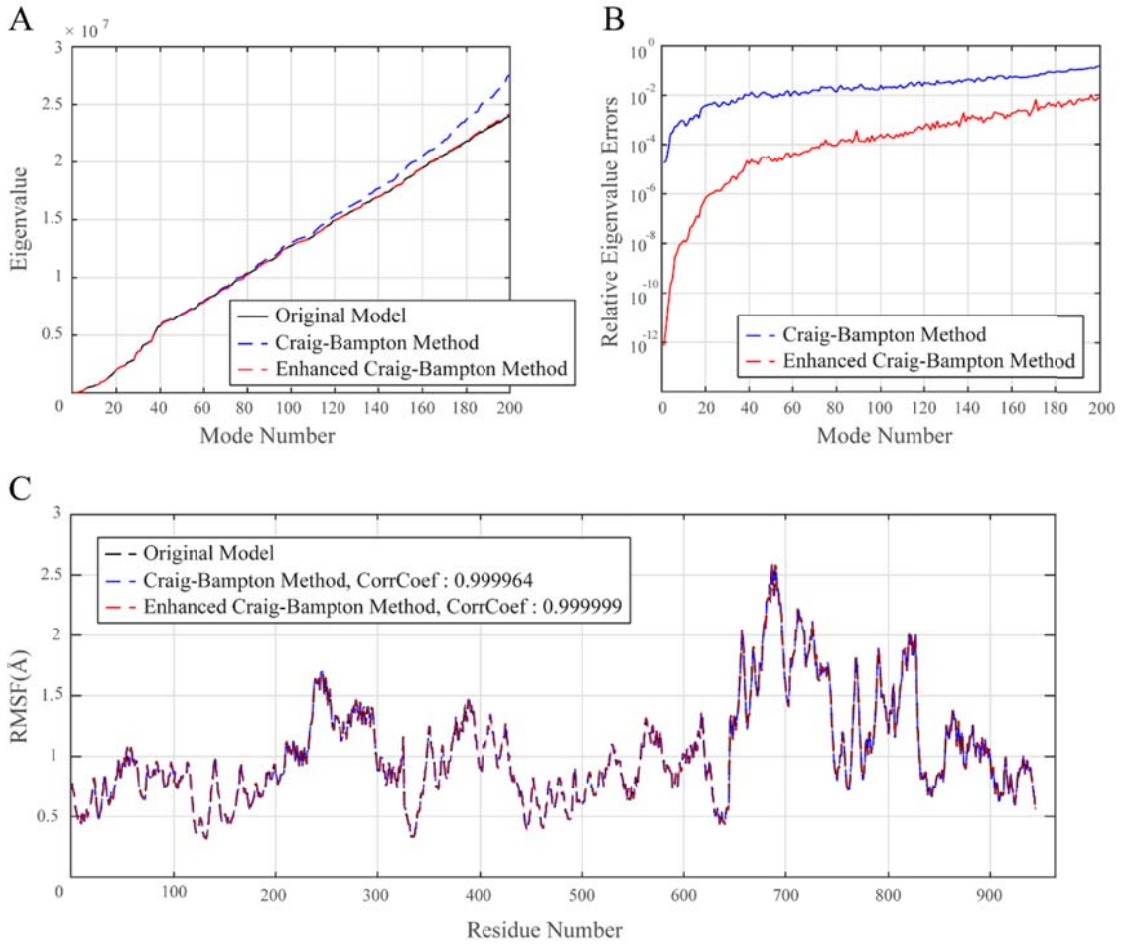

Fig. 2 Comparison between the original and enhanced CB methods. (A) eigenvalues, (B) relative eigenvalue errors and (C) RMSFs at alpha-carbons for the Middle East Respiratory Syndrome coronavirus (MERS-CoV) 3C-like protease.

Finally, the reduced matrices of the enhanced CB method are obtained as

$$\widetilde{\mathbf{M}}_p = \overline{\mathbf{T}}_1^T \mathbf{M} \overline{\mathbf{T}}_1 \,, \quad \widetilde{\mathbf{K}}_p = \overline{\mathbf{T}}_1^T \mathbf{K} \overline{\mathbf{T}}_1 \,. \tag{6}$$

Due to compensation of the residual substructural modes, the reduced matrices in Eq. (6) are much more accurate than the reduced matrices in Eq. (3).

3. RESULT AND CONCLUSION

In this section, we investigate the performance of the enhanced CB method in comparison with the original CB method. The approximated eigensolutions for the structure of Middle East Respiratory Syndrome coronavirus (MERS-CoV) 3C-like protease (RCSB Protein Data Bank, http://www.rcsb.org/, ID: 4WMF) (Needle and Lountos, 2015) are calculated by solving the eigenvalue problems using the reduced matrices in Eqs. (3) and (6).

Figs. 2A and 2C represent the eigenvalues and the relative eigenvalue errors obtained using the original and enhanced CB methods, respectively. These results clearly show that the enhanced CB method is more accurate than the original CB method. In addition, RMSFs (Root-Mean-Square-Fluctuations) at alpha-carbons are presented in Fig. 2C, which illustrates a high correlation between the results calculated using the original and enhanced CB methods.

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