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New generation of elastic network models

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The intrinsic flexibility of proteins and nucleic acids can be grasped from remarkably simple mechanical models of particles connected by springs. In recent decades, Elastic Network Models (ENMs) combined with Normal Model Analysis widely confirmed their ability to predict biologically relevant motions of biomolecules and soon became a popular methodology to reveal large-scale dynamics in multiple structural biology scenarios. The simplicity, robustness, low computational cost, and relatively high accuracy are the reasons behind the success of ENMs. This review focuses on recent advances in the development and application of ENMs, paying particular attention to combinations with experimental data. Successful application scenarios include large macromolecular machines, structural refinement, docking, and evolutionary conservation.

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Introduction

Almost two decades ago, Tirion was the first to realize that functional protein motions can be captured using a greatly simplified harmonic potential by Normal Mode Analysis (NMA) [1••]. Shortly afterward, several coarse-grained versions of Tirion's elastic network model (ENM) were proposed, in which a given conformation of the protein was approximated by a set of particles (e.g., residues represented by Cα atoms) interconnected by elastic springs. Two main types of ENM were established: the anisotropic network model (ANM) [2,3], which corresponds directly to the coarse-grained version of Tirion's approach, and the Gaussian network model (GNM) [4], which is a one-dimensional simplification limited to the evaluation of the mean squared displacements and cross-correlations between atomic fluctuations magnitude. From these seminal works, ENMs have proven over the years to be an effective approach to understanding the intrinsic dynamics of biomolecules [5,6•,7].

Although there are many variations to reduce the complex biomolecular structures into a network of nodes and springs, the basic assumption (and limitation) of ENMs is that the potential energy is described by a quadratic function around a minimum energy conformation:

$$V = \sum_{i<j} K_{ij}(r_{ij} - r_{ij}^0)^2 \quad (1)$$

where the superindex 0 indicates the initial conformation, r_{ij} is the distance between atoms i and j, and K_{ij} is a spring stiffness function. The intrinsic dynamics of an ENM is mostly assessed by NMA. In this classical mechanics technique, all the complex motions around an initial conformation are decoupled into a linear combination of orthogonal basis vectors, the so-called normal modes. The modes are computed solving by diagonalization the following generalized eigenvalue problem:

$$\mathbf{HU} = \boldsymbol{\lambda}\mathbf{TU} \quad \text{where} \quad \mathbf{U} = (\mathbf{u}_1, \mathbf{u}_2, ..., \mathbf{u}_N), \quad (2)$$

where $\mathbf{H}$ is the Hessian matrix (partial second derivatives of the potential energy), $\mathbf{T}$ the kinetic energy matrix, and $\boldsymbol{\lambda}$ is a diagonal matrix with the λ_k eigenvalues associated to the kth normal mode $\mathbf{u}_k$. As the frequencies ($\omega_k = \lambda_k^2/2\pi$) are directly proportional to the energy required for the movement, high frequency modes describe local motions whereas low frequency modes represent collective (large-scale) conformational changes. Most importantly, it has been widely confirmed by many studies that ENM's lowest-frequency normal modes often give a reasonable description of experimentally observed functional motions (see review articles for further methodological details including experimental validation [5,6•,8,9]). Following the structure–dynamics–function paradigm, these collective modes have been conserved during evolution as they represent the mechanical deformations of lowest energetic cost. Even though the shown usefulness, the validity of ENM–NMA fluctuations is limited to small excursions around the equilibrium conformation. However, larger deformations can be obtained by iteratively applying small displacements along the lowest modes [10].

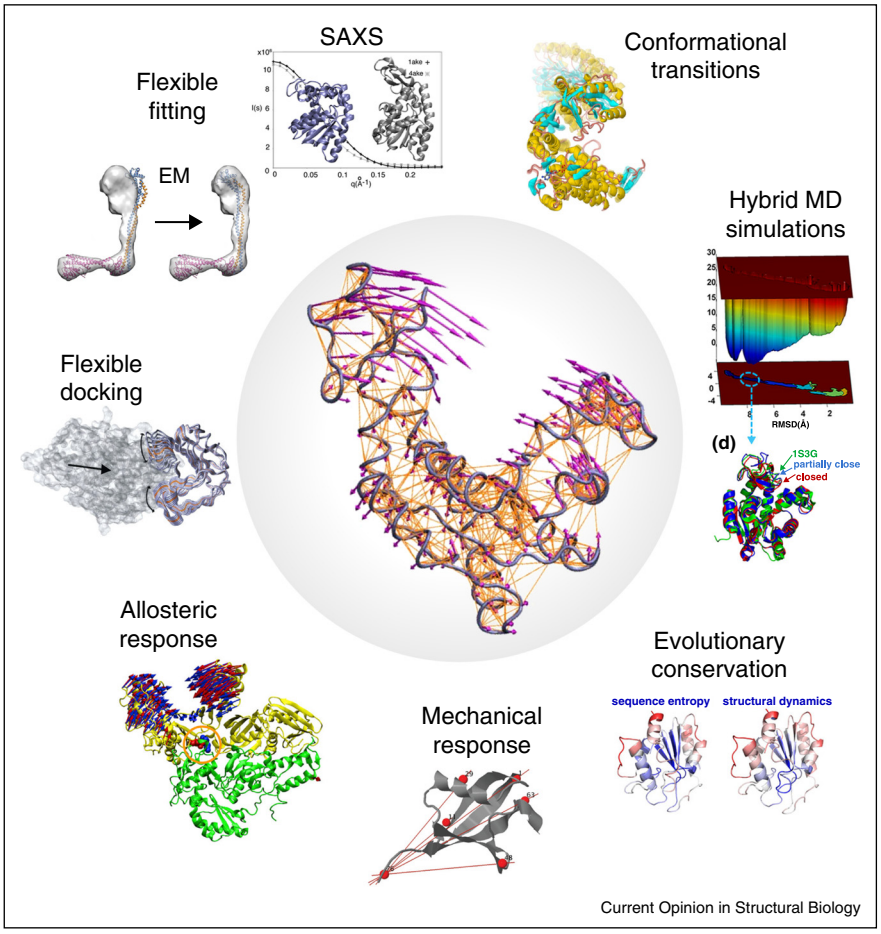
There is an overwhelming literature validating the use of ENM in multiple scenarios. This review focuses on the recent progress of ENM for characterizing macromolecular flexibility, predicting functional conformational changes, and assisting in the interpretation of structural experimental data, paying close attention to hybrid

methods that combine ENM with simulations and/or experimental data.

Trends in ENM development

The agreement between the observed functional motions and the lowest frequency modes extracted with NMA is relatively well preserved independently of model or potential details, evidencing the approach's robustness as long as the 3D contact topology is reasonably maintained. In the past, many research efforts were dedicated to further simplifying ENMs and extend the application range to larger systems. Notable reductions can be obtained by grouping atoms into clusters [11,12] or into rotational and translational blocks [13,14] without substantial loss of accuracy. Even from low-resolution 3D reconstructions, it is still possible to obtain insight into the macromolecular global flexibility [15,16], revealing the importance of the shape in determining the lowest-frequency normal modes. Other authors have used more sophisticated schemes to reduce the main computational bottleneck of the NMA, the diagonalization of the Hessian matrix, for example, by calculating only the relevant normal modes of interest [17] or considering the system symmetry [18–20]. Another elegant way to reduce the computational cost is working in internal coordinates (IC). Using dihedral angles as ICs instead of Cartesian coordinates reduces the number of degrees of freedom, leading to substantial savings in computational resources. Moreover, the implicit maintenance of the covalent structure preserves the model geometry and minimizes the potential distortions frequently observed in Cartesian approaches. Based on early works by Go and Levitt [21,22] that established the complete mathematical framework, several authors successfully developed different coarse-grained ENM approximations using torsion angles as variables [23–25]. Despite the convenience of ICs [26], the vast majority of current approaches are Cartesian-based because of their simplicity (i.e., the

Figure 1



Representative ENM application scenarios. The ENM application range is currently expanding from the prediction and analysis of biologically relevant motions to serve as a conformational sampling engine in multiple structural biology scenarios. Enclosed by different application examples, a Tirion's elastic network (orange segments) of the adenylate kinase protein (gray tube) is illustrated together with the corresponding lowest energy normal mode (pink arrows). The central image was generated using iMod [23] and VMD, and the remaining images were reproduced with permission from Refs. [23,61,69,75,77,79,86,89].